

## Advances in the Chemistry of Tetrahydroquinolines

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### CONTENTS

1. Introduction	7158	4.4.2. Intramolecular Cyclization of ene-C=N Moiety	7178
1.1. General	7158	4.4.3. Azomethine Ylide—Alkene Cycloaddition	7179
1.2. Scope and Organization of This Review	7159	4.4.4. Miscellaneous Reactions	7179
2. Tetrahydroquinoline-Based Natural Products and Bioactive Compounds	7159	4.5. Formation of the C <sub>4</sub> —C <sub>4a</sub> Bond	7180
2.1. Tetrahydroquinoline-Derived Natural Products	7159	4.5.1. Intramolecular Friedel—Crafts-Related Reactions	7180
2.2. Pharmacologically Relevant Tetrahydroquinolines	7160	4.5.2. Acyl Iminium Cyclization	7183
2.2.1. Tetrahydroquinolines Acting at Chemotherapeutic Targets	7161	4.5.3. Transition Metal-Catalyzed Reactions	7183
2.2.2. Tetrahydroquinolines Acting at Pharmacodynamic Targets	7162	4.5.4. Intramolecular Radical Cyclizations	7184
3. Other Applications of Tetrahydroquinolines	7165	4.5.5. Epoxide Opening	7185
3.1. Tetrahydroquinolines As Coordination Ligands	7165	4.5.6. Intramolecular Arylation	7186
3.2. Tetrahydroquinoline-Derived Dyes and Other Applications of Tetrahydroquinolines	7166	4.5.7. Miscellaneous Reactions	7187
4. Synthesis of 1,2,3,4-Tetrahydroquinolines Involving the Generation of One Bond	7166	4.6. Formation of the C <sub>8a</sub> —N Bond	7187
4.1. Introduction	7166	4.6.1. Metal-Catalyzed Intramolecular Amination	7187
4.2. Formation of the N—C <sub>2</sub> Bond	7166	4.6.2. Photochemical Reactions	7188
4.2.1. Intramolecular Allylic Amination	7166	4.6.3. Miscellaneous Reactions	7189
4.2.2. Intramolecular Hydroamination	7168	5. Synthesis of 1,2,3,4-Tetrahydroquinolines Involving the Generation of Two Bonds	7189
4.2.3. Intramolecular Aminohalogenation	7168	5.1. Introduction	7189
4.2.4. Intramolecular aza-Michael Addition	7169	5.2. Formation of the N—C <sub>2</sub> and C <sub>3</sub> —C <sub>4</sub> Bonds	7189
4.2.5. Intramolecular Nucleophilic Substitution Reactions	7170	5.2.1. Diels—Alder Related Reactions	7189
4.2.6. Intramolecular Amidation Reactions	7171	5.2.2. Tandem Michael Addition—Cyclization Sequence	7192
4.2.7. Reduction—Intramolecular Cyclization Sequences	7171	5.2.3. Miscellaneous Reactions	7193
4.2.8. Intramolecular Oxidative Cyclization/Lactamization	7174	5.3. Formation of the N—C <sub>2</sub> and C <sub>4</sub> —C <sub>4a</sub> Bonds	7194
4.2.9. Pd-Catalyzed Cross-Coupling	7175	5.3.1. Michael Addition Initiated Reactions	7194
4.2.10. Miscellaneous Reactions	7175	5.3.2. Miscellaneous Reactions	7196
4.3. Formation of the C <sub>2</sub> —C <sub>3</sub> Bond	7175	5.4. Formation of the N—C <sub>2</sub> and C <sub>2</sub> —C <sub>3</sub> Bonds	7198
4.3.1. <i>tert</i> -Amino Effect	7175	5.5. Formation of the C <sub>2</sub> —C <sub>3</sub> and C <sub>3</sub> —C <sub>4</sub> Bonds	7199
4.3.2. Conjugate Addition—Cyclization Sequence	7177	5.6. Formation of the C <sub>2</sub> —C <sub>3</sub> and C <sub>4</sub> —C <sub>4a</sub> Bonds	7200
4.3.3. Miscellaneous Reactions	7178	5.7. Formation of the C <sub>3</sub> —C <sub>4</sub> and C <sub>4</sub> —C <sub>4a</sub> Bonds	7200
4.4. Formation of the C <sub>3</sub> —C <sub>4</sub> Bond	7178	5.8. Formation of the C <sub>8a</sub> —N and C <sub>4</sub> —C <sub>4a</sub> Bonds	7200
4.4.1. Ring-Closing Metathesis	7178	5.9. Formation of the N—C <sub>2</sub> and C <sub>8a</sub> —N Bonds	7201
		6. Synthesis of 1,2,3,4-Tetrahydroquinolines Involving the Generation of Three or More Bonds	7201
		6.1. Formation of the N—C <sub>2</sub> , C <sub>2</sub> —C <sub>3</sub> , and C <sub>4</sub> —C <sub>4a</sub> Bonds: The Povarov and Related Reactions	7201

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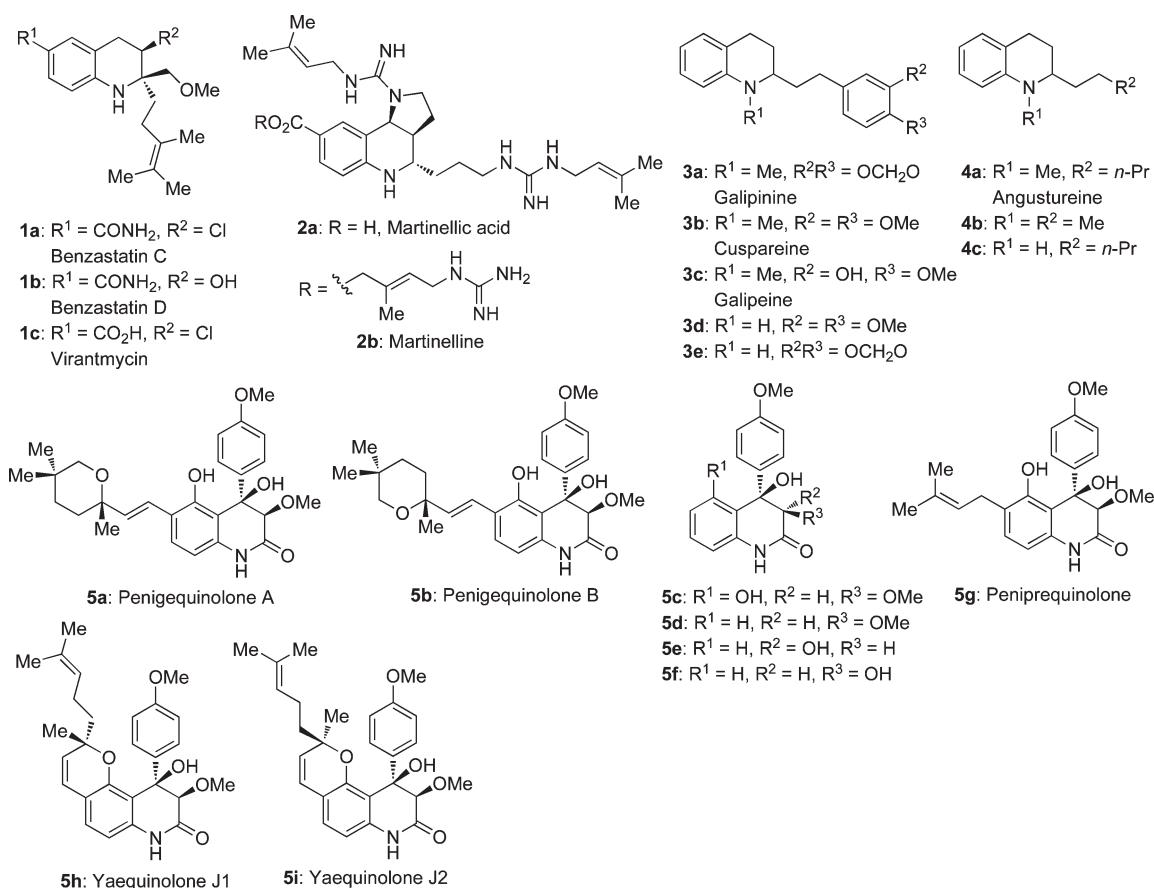
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6.1.1. Introduction	7201	10.2.3. Multicomponent Reactions and Reactions Involving the Formation of Three or More Bonds	7236
6.1.2. Mechanistic Aspects	7202	10.3. Synthesis of 5,6,7,8-Tetrahydroquinolines by Construction of the Cyclohexene Ring	7237
6.1.3. Lewis Acid-Catalyzed Reactions	7202	10.4. Synthesis of 5,6,7,8-Tetrahydroquinolines Starting from Acyclic Precursors	7238
6.1.4. Brønsted Acid-Catalyzed Reactions	7206	10.5. Synthesis of 1,4,4a,8a-Tetrahydroquinolines	7238
6.1.5. Vinylogous Povarov Reactions	7207	10.6. Synthesis of 2,3,4,4a-Tetrahydroquinolines	7238
6.1.6. Intramolecular Povarov Reactions	7208	11. Functionalization of Tetrahydroquinolines	7238
6.1.7. Enantioselective Povarov Reactions	7209	11.1. Introduction	7238
6.2. Miscellaneous Reactions Involving the Generation of N—C <sub>2</sub> , C <sub>2</sub> —C <sub>3</sub> , and C <sub>4</sub> —C <sub>4a</sub> Bonds	7210	11.2. Reactions Starting from 1,2,3,4-Tetrahydroquinolines	7239
6.3. Formation of the N—C <sub>2</sub> , C <sub>2</sub> —C <sub>3</sub> , and C <sub>3</sub> —C <sub>4</sub> Bonds	7211	11.2.1. Functionalization of the Aryl Ring	7239
6.4. Formation of More than Three Bonds	7211	11.2.2. Functionalization of the Tetrahydropyridine Ring	7240
7. Synthesis of 1,2,3,4-Tetrahydroquinolines Involving the Formation of the Aryl or Both Rings	7212	11.3. Reactions Involving 5,6,7,8-Tetrahydroquinolines	7241
8. Synthesis of 1,2,3,4-Tetrahydroquinolines Involving Rearrangement Reactions	7213	12. Transformation of Tetrahydroquinolines into Other Heterocycles	7242
9. Synthesis of 1,2,3,4-Tetrahydroquinolines Involving the Partial Reduction of Quinolines	7215	12.1. Methods that Create Additional Rings Fused to the N—C <sub>2</sub> Bond	7242
9.1. Introduction	7215	12.2. Methods that Create Additional Rings Fused to the C <sub>2</sub> —C <sub>3</sub> Bond	7243
9.2. Partial Hydrogenation of Quinolines to Racemic 1,2,3,4-Tetrahydroquinolines	7215	12.3. Methods that Create Additional Rings Fused to the C <sub>3</sub> —C <sub>4</sub> Bond	7244
9.2.1. Hydrogenation of Quinolines Catalyzed by Raney Nickel	7216	12.4. Methods that Create Additional Rings Fused to the N—C <sub>8a</sub> and C <sub>8</sub> —C <sub>8a</sub> Bonds	7244
9.2.2. Hydrogenation of Quinolines Catalyzed by Palladium or Platinum	7216	12.4.1. Creation of Five-Membered Rings	7244
9.2.3. Hydrogenation of Quinolines Catalyzed by Rhodium or Iridium	7217	12.4.2. Creation of Six-Membered Rings	7245
9.2.4. Hydrogenation of Quinolines Catalyzed by Ruthenium or Osmium	7218	12.4.3. Creation of Seven-Membered Rings	7246
9.2.5. Hydrogenation of Quinolines Catalyzed by Molybdenum	7218	12.5. Methods that Create Additional Rings Fused to the C <sub>4</sub> —C <sub>4a</sub> and C <sub>4a</sub> —C <sub>5</sub> Bonds	7247
9.2.6. Hydrogenation Reactions Involving Organocatalysts	7219	13. Concluding Remarks	7247
9.2.7. Hydrogenation Reactions Involving No Catalysts	7219	Author Information	7247
9.2.8. Miscellaneous Reactions	7219	Biographies	7247
9.3. Asymmetric Hydrogenation of Quinolines	7219	Acknowledgment	7248
9.3.1. Brønsted Acid-Catalyzed Asymmetric Hydrogenation of Quinolines	7219	References	7248
9.3.2. Asymmetric Hydrogenation of Quinolines Catalyzed by Iridium	7220		
9.3.3. Asymmetric Hydrogenation of Quinolines Catalyzed by Ruthenium and Rhodium	7228		
9.4. Synthesis of Biologically Relevant 1,2,3,4-Tetrahydroquinolines via Hydrogenation of Quinolines	7228		
9.5. Quinoline Reduction Involving the Addition of Nucleophiles	7231		
10. Synthesis of Tetrahydroquinolines with Other Hydrogenation Patterns	7232		
10.1. Introduction	7232		
10.2. Synthesis of 5,6,7,8-Tetrahydroquinolines by Construction of the Pyridine Ring	7233		
10.2.1. Formation of One Bond	7233		
10.2.2. Formation of Two Bonds	7234		

## 1. INTRODUCTION

### 1.1. General

Heterocyclic compounds, especially nitrogen heterocycles, are the most important class of compounds in the pharmaceutical and agrochemical industries, with heterocycles comprising around 60% of all drug substances. The tetrahydroquinoline ring system, in particular, is a very common structural motif and is found in numerous biologically active natural products and pharmacologically relevant therapeutic agents. Because of the significance of these scaffolds in drug discovery and medicinal chemistry the development of new methodologies for the synthesis of tetrahydroquinoline derivatives continues to be a very active field of research, as evidenced by the appearance of over 400 articles in the area during the last five years. In spite of this fast growth of tetrahydroquinoline synthesis, the last review



**Figure 1.** Alkaloids containing tetrahydroquinoline structural fragments.

on this topic, arising from the Katritzky group, was published in 1996 and covered the literature up to 1995,<sup>1</sup> although some space is devoted to tetrahydroquinolines in a general review on the chemistry of reduced heterocycles<sup>2</sup> and in a couple of reports on the synthesis of saturated nitrogen heterocycles.<sup>3</sup> Hence, in the present article we have made an effort to cover comprehensively the literature on the synthesis of tetrahydroquinoline derivatives starting from 1996 to mid-2010, giving a special emphasis to the most common system, that is, 1,2,3,4-tetrahydroquinoline. To increase the practical usefulness of our review, we have also provided an abbreviated, but comprehensive, summary of advances in the knowledge of the biological relevance of tetrahydroquinolines in the 1996–2010 period.

## 1.2. Scope and Organization of This Review

After a general introduction and two sections dealing with applications of tetrahydroquinoline derivatives, the part of our review devoted to synthetic aspects comprises four major parts, first, including the methods for the construction of the saturated tetrahydropyridine ring system of the 1,2,3,4-tetrahydroquinolines starting from aryl precursors, which have been classified as (a) methods involving the generation of one bond (section 4); (b) methods involving the generation of two bonds (section 5); (c) methods involving the generation of three or more bonds (section 6). In the second place, we discuss the methods for the creation of the benzene ring of 1,2,3,4-tetrahydroquinolines, together with their construction from acyclic precursors (section 7), or by means of rearrangement reactions (section 8). A third approach to the synthesis of tetrahydroquinolines is

based upon the partial reduction of quinoline systems, which is covered in section 9. We have devoted section 10 to the discussion of the synthesis of tetrahydroquinolines with hydrogenation patterns different from the usual 1,2,3,4-tetrahydro systems. In addition, we present two more major sections devoted to the functionalization of tetrahydroquinolines (section 11) and to the application of simple 1,2,3,4-tetrahydroquinolines as starting materials for the synthesis of other heterocyclic systems (section 12). The review ends with a Conclusion section.

## 2. TETRAHYDROQUINOLINE-BASED NATURAL PRODUCTS AND BIOACTIVE COMPOUNDS

### 2.1. Tetrahydroquinoline-Derived Natural Products

A wide variety of novel 1,2,3,4-tetrahydroquinoline-based natural products, some of which showed interesting biological activities, were reported during the 1995–2010 period<sup>4</sup> and are grouped in Figures 1 and 2. Yoo and co-workers isolated from *Streptomyces* sp. two 1,2,3,4-tetrahydroquinoline alkaloids that they called benzastatins C and D (**1a** and **1b**, Figure 1)<sup>5</sup> and that were structurally related to the previously known antiviral virantmycin **1c**.<sup>6</sup> These new alkaloids showed inhibitory activity against glutamate toxicity and lipid peroxidation and their conformational behavior was subsequently studied using semi-empirical molecular orbital calculations.<sup>7</sup>

A couple of novel pyrroloquinoline alkaloids, martinellie acid **2a** and martinelline **2b**, was isolated from the roots of the tropical plant *Martinella iquitensis*,<sup>8</sup> and they have become synthetic

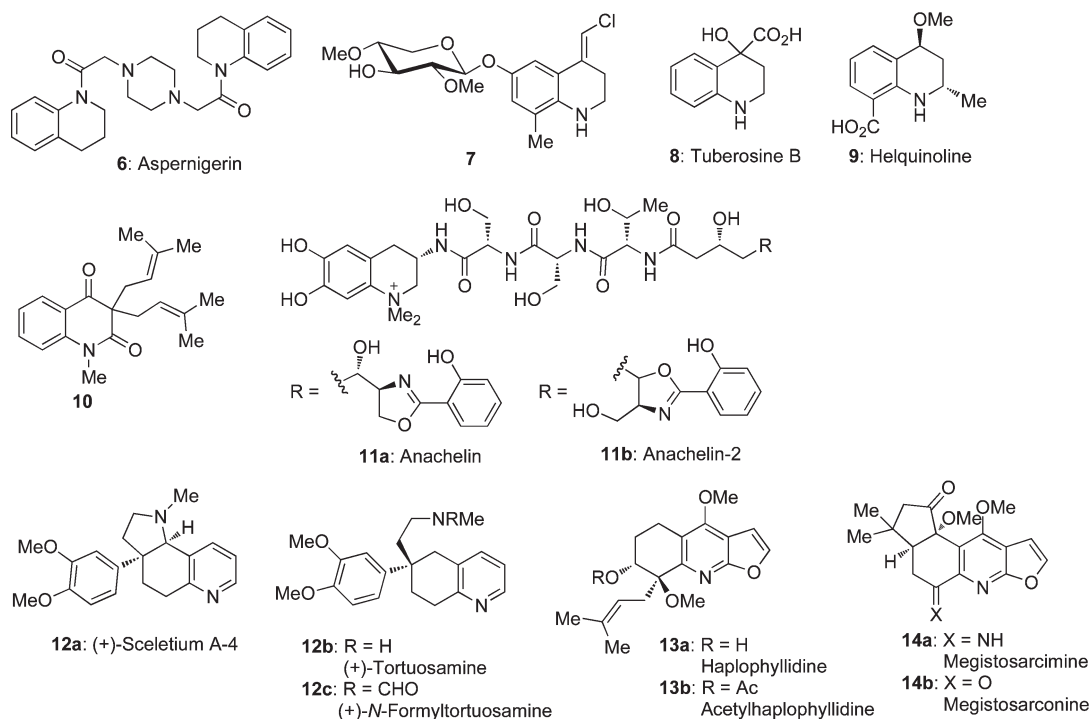


Figure 2. Some additional tetrahydroquinoline-derived natural products.

targets of many research groups.<sup>9</sup> A family of rather simple 2-substituted 1,2,3,4-tetrahydroquinoline alkaloids including galipinine **3a**,<sup>10</sup> cuspareine **3b**,<sup>11</sup> angustureine **4a**, and galipeine **3c**<sup>12</sup> were isolated from the trunk bark of the South American tree *Galipea officinalis*. After two years, a few more related tetrahydroquinoline natural products (compounds **3d**, **3e**, **4b**, and **4c**) were also isolated from the same plant<sup>13</sup> and some of these compounds were found to have antimalarial activity.<sup>14</sup>

Another interesting group of 4-(*p*-methoxyphenyl)-3,4-tetrahydroquinolin-2(1*H*)-one natural products were isolated independently by several research groups. Koshino and co-workers reported the isolation of two active pollen-growth inhibitors known as penigequinolones A and B (**5a** and **5b**) from the mycelial mats of *Penicillium* sp. No. 410.<sup>15</sup> Subsequently another Japanese group isolated the same compounds, together with two novel tetrahydroquinolones **5c** and **5d** from a culture of the fungus *Penicillium* sp. NTC-47 grown on the insoluble residue of whole soybean.<sup>16</sup> A year later the complete details of the isolation and characterization of compounds **5c** and **5d**, including their spectral and X-ray crystallographic data and also some studies on their biological activities, were described.<sup>17</sup> The Koshino group isolated from *Penicillium simplicissimum* a novel nematocidal alkaloid, namely, the peniprequinolone **5g**, together with other previously reported tetrahydroquinolone natural products,<sup>18</sup> and compound **5g** was again isolated from the fungus *Penicillium janczewskii*, obtained from the Chilean gymnosperm *Prumnopitys andina*, in 2005.<sup>19</sup> During the same period Sattler and co-workers isolated other alkaloids of the same family (compounds **5e** and **5f**) from a strain of *Penicillium janczewskii* derived from a marine sample, along with **5d** and peniprequinolone **5g**.<sup>20</sup> The insecticidal antibiotics yaequinolones J1 and J2 (**5h** and **5i**), bearing a tetrahydroquinolone skeleton with a fused pyran ring, were also isolated from *Penicillium* sp. FKI-2140<sup>21</sup> and showed toxicity against *Artemia salina* (brine shrimp).

Tan and co-workers reported the isolation of a novel cytotoxic alkaloid, aspernigerin **6** from the extract of a culture of *Aspergillus niger* IFB-E003, an endophyte in *Cyndon dactylon*, together with its total synthesis (Figure 2).<sup>22</sup> A new secondary metabolite, the tetrahydroquinoline alkaloid **7**, was discovered from a Puerto Rican collection of *Lyngbya majuscula*.<sup>23</sup> Other simple tetrahydroquinolines including tuberosine B, **8**,<sup>24</sup> helquinoline **9**,<sup>25</sup> and *N*-methyl-3,3-diprenylquinoline-2,4-dione **10**<sup>26</sup> were also isolated, respectively, from *Allium tuberosum*, *Janibacter limosus*, and *Esenbeckia almawillia* species. The isomeric siderophors anachelin **11a** and anachelin-2 **11b** were isolated from the freshwater cyanobacterium *Anabaena cylindrica* (NIES-19)<sup>27</sup> and their absolute stereochemistry was determined using the Boc-phenylglycine and Mosher's method.<sup>28</sup>

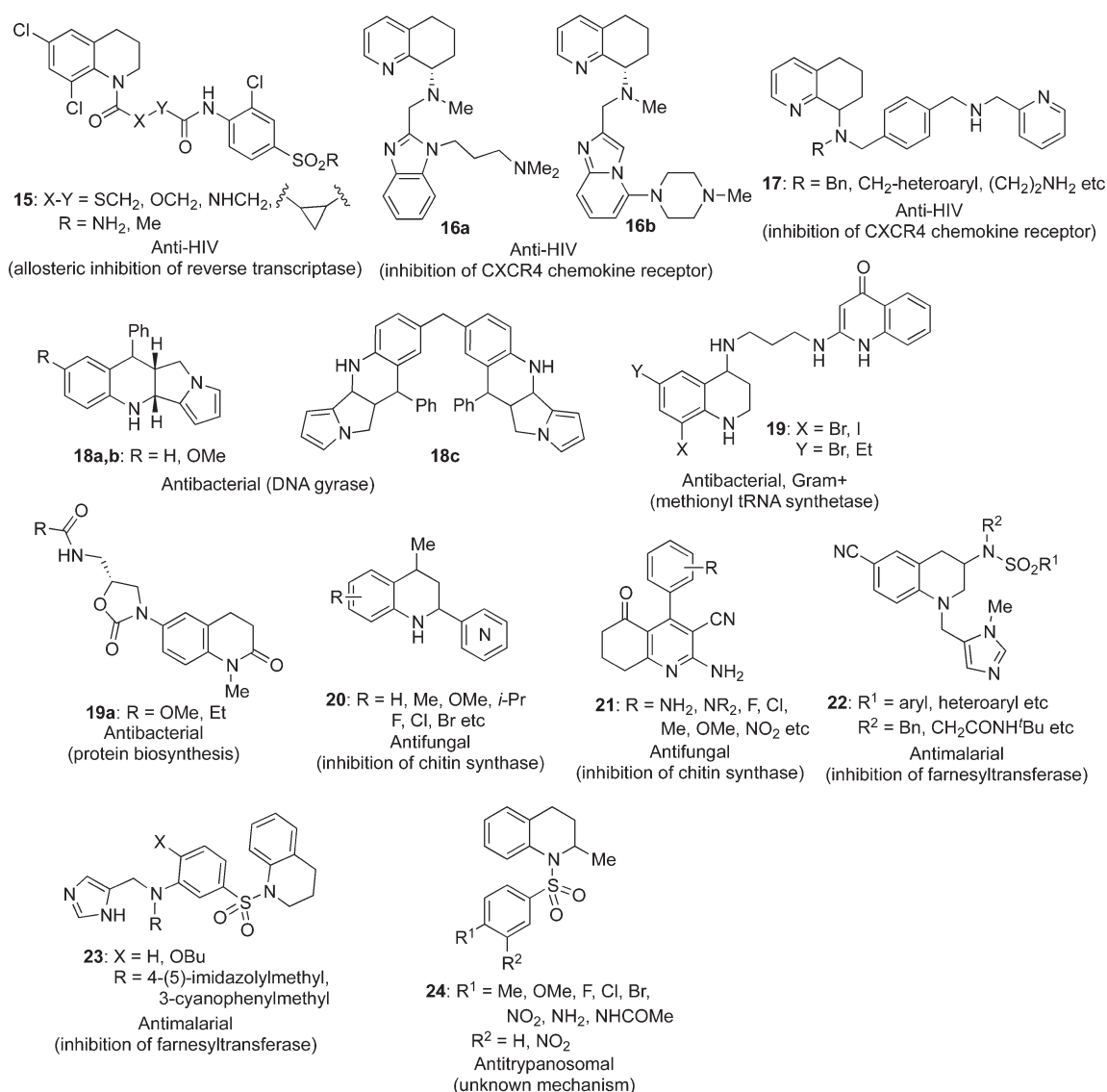
Tetrahydroquinolines having hydrogenation patterns different from the 1,2,3,4-tetrahydro-one are rarely present in natural products. Among them are notable the *Sceletium* alkaloids including (+)-sceletium A-4, **12a**, (+)-tortuosamine **12b**, and (+)-*N*-formyltortuosamine **12c**.<sup>29</sup> Haplophyllidine **13a** and its acetyl derivative **13b** were isolated from aerial parts of the central Asian plant *Haplophyllum perforatum*,<sup>30</sup> and the latter compound was previously isolated from a Brazilian plant, *Almeidia coerulia*.<sup>31</sup> Two more alkaloids of this family, that is, megistosarcimine **14a** and megistosarconine **14b**, were also isolated from the New Caledonian tree *Sarcomelicope megistophylla*.<sup>32</sup>

The synthetic aspects of these natural products will be discussed in the relevant sections.

## 2.2. Pharmacologically Relevant Tetrahydroquinolines

Because of the large number of compounds to be discussed in this section, we will divide it into two parts, where we will treat chemotherapeutic agents and pharmacodynamic agents. These data are summarized below in Figures 3 to 10.





**Figure 3.** Tetrahydroquinolines acting as antiviral, antibacterial, antimalarial, and antifungal agents.

**2.2.1. Tetrahydroquinolines Acting at Chemotherapeutic Targets.** Several tetrahydroquinoline derivatives have been found to interact with retroviral targets relevant to anti-HIV therapy. Thus, compounds **15**<sup>33</sup> were found to be potent non-nucleoside, allosteric inhibitors of reverse transcriptase, and **16**<sup>34–38</sup> and **17**<sup>39</sup> are anti-HIV compounds acting as antagonists of CXCR4, a G-protein coupled chemokine receptor that is known to behave as a coreceptor of a number of strains of HIV (Figure 3). Some 2-aryl-4-(2-oxopyrrolidin-1-yl)-1,2,3,4-tetrahydroquinolines have shown moderate activities as inhibitors of HIV transcription, probably through inhibition of the NF- $\kappa$ B and Sp1 transcription factors,<sup>40</sup> and a library of 1,2,3,4-tetrahydro-6-sulphonamide derivatives have been identified as small-molecule modifiers of hepatic microRNA function, reducing the replication of hepatitis C virus and being also active as apoptosis inducers.<sup>41</sup>

Some tetrahydroquinolines are also active against antibacterial targets, including DNA gyrase (compounds **18**)<sup>42</sup> and methionyl tRNA synthetase (**19**),<sup>43,44</sup> which has been proposed as an important target in the treatment of infections because of the

Gram-positive bacteria resistant to conventional antibiotic therapy. A few members of the oxazolidinone class of antibacterial agents that contain tetrahydroquinoline-derived side chains (compounds **19a**) have shown good activity against *Staphylococcus aureus* and *Streptococcus pneumoniae*, and act by disrupting bacterial protein synthesis.<sup>45</sup> Some simple tetrahydroquinoline derivatives where the heterocyclic nitrogen is part of a urea moiety have shown activity against Gram-positive and Gram-negative bacteria, and also against some fungi.<sup>46</sup>

In the course of a study on the antifungal activity of several series of homoallylamines and their analogues, compounds **20**<sup>47–49</sup> were shown to have antifungal activity, which was attributed mainly to chitin synthase inhibition, a property that was subsequently found also in compounds **21**.<sup>50</sup> The imidazole substituted tetrahydroquinoline derivatives **22**<sup>51–58</sup> and **23**<sup>59</sup> have received much attention as antimalarial agents, since they are highly cytotoxic to *Plasmodium falciparum* because of inhibition of farnesyltransferase of the parasite, while 1-benzenesulfonyl derivatives **24**<sup>60</sup> were shown to have good activity against *Trypanosoma cruzi*.

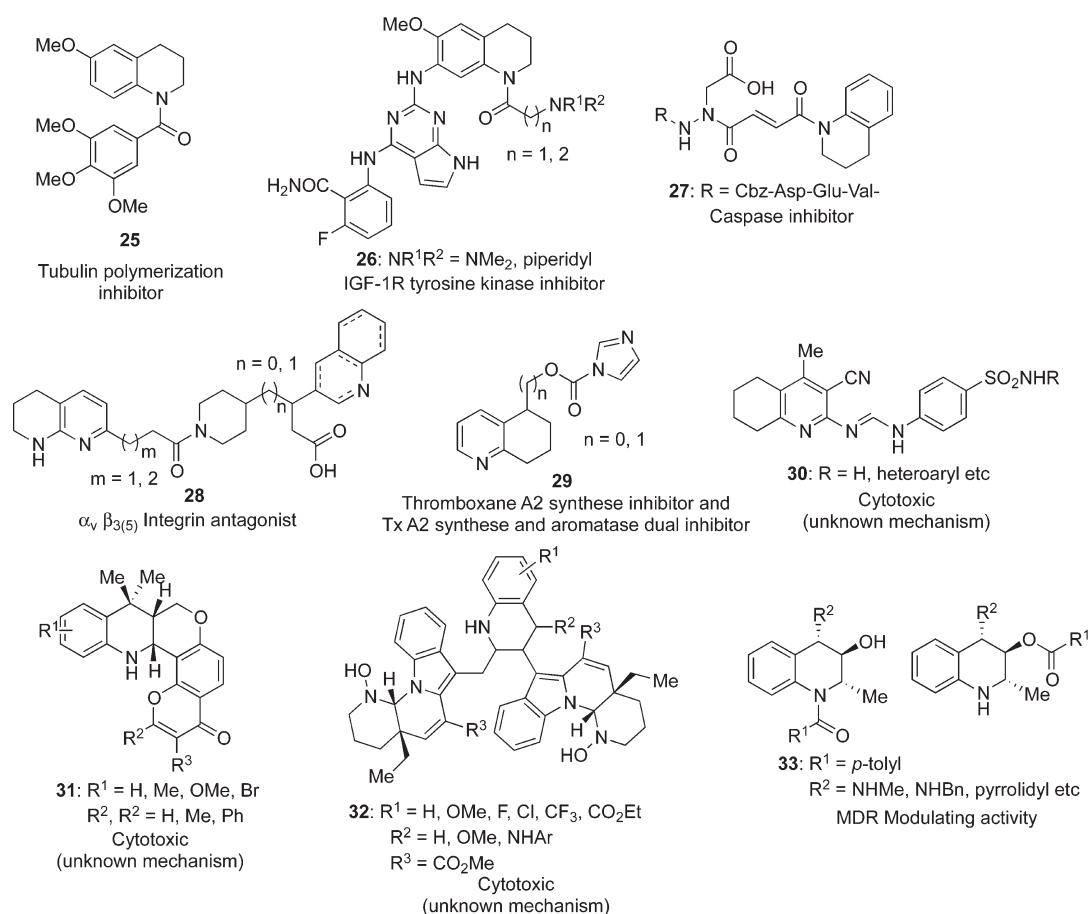


Figure 4. Tetrahydroquinolines with antitumor activity.

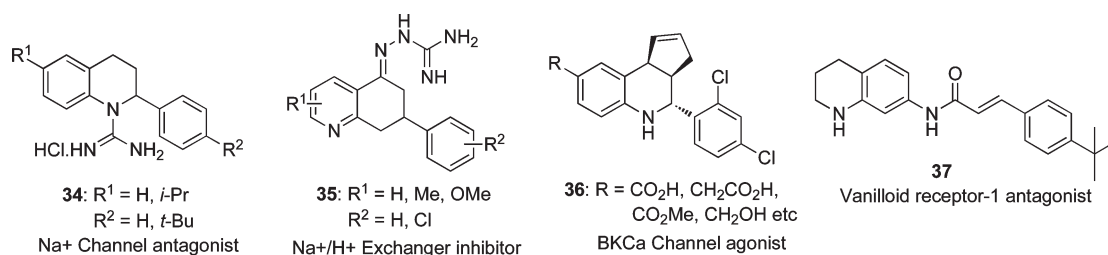
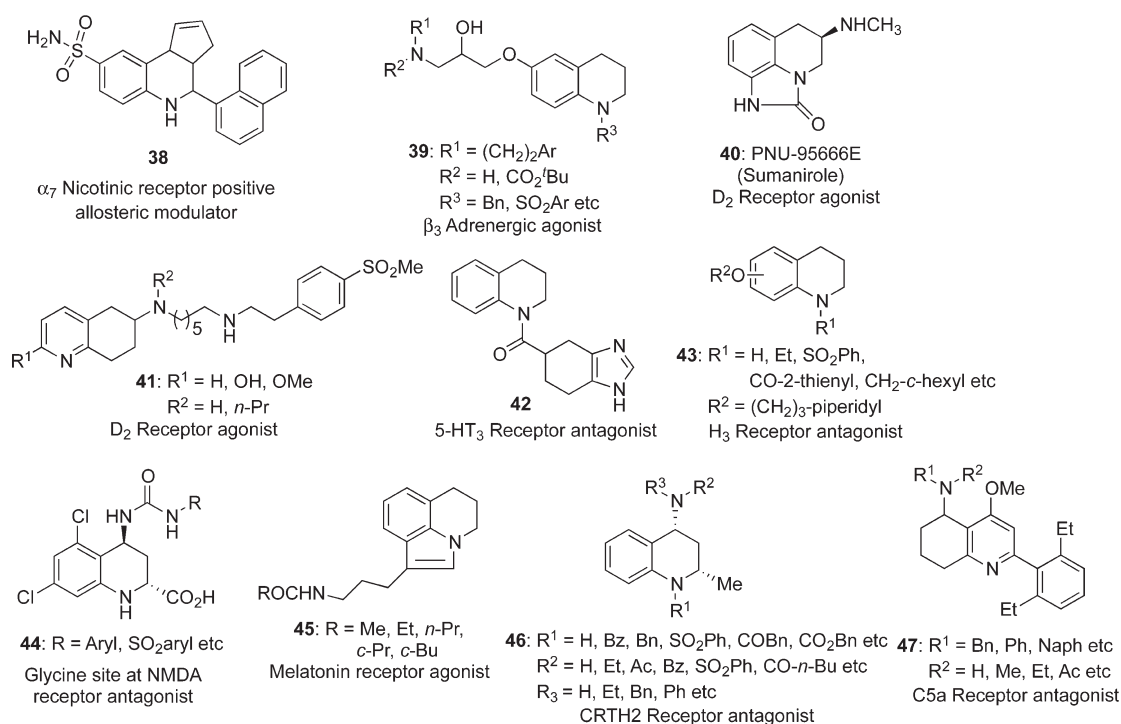


Figure 5. Bioactive tetrahydroquinolines acting on ion channels.

Regarding cancer chemotherapy, compound **25**<sup>61</sup> has cytotoxic activity and was shown to act as an inhibitor of tubulin polymerization (Figure 4). Some tetrahydroquinoline derivatives are inhibitors of potential anticancer targets, although their cytotoxicity has not been studied. They include compounds **26**,<sup>62</sup> which inhibit IGF-1R tyrosine kinase, **27**,<sup>63</sup> which are caspase inhibitors, **28**,<sup>64–66</sup> which are integrin  $\alpha_v\beta_{3(5)}$  antagonists, and **29**,<sup>67,68</sup> which is an inhibitor of thromboxane  $\text{A}_2$  synthase (P450  $\text{TxA}_2$ ) or dual inhibitors of  $\text{TxA}_2$  and the related enzyme aromatase.<sup>69</sup> Some tetrahydroquinolines, including compounds **30**,<sup>70</sup> **31**,<sup>71</sup> and **32**,<sup>72,73</sup> have shown in vitro cytotoxicity, but its mechanism has not been determined, although in the latter case it has been hypothesized to involve CDK inhibition. The 2-methyl tetrahydroquinoline derivatives **33**<sup>74</sup> were also found to have moderate to high modulating activity in multidrug

resistance (MDR), which is considered as one of the main obstacles in successful anticancer chemotherapy. Some aminotetrahydroquinoline-based scaffolds have been used for the in silico and NMR-based development of inhibitors of apoptosis factors such as Mcl-1 and Bcl- $\text{X}_\text{L}$ .<sup>75,76</sup>

**2.2.2. Tetrahydroquinolines Acting at Pharmacodynamic Targets.** Some tetrahydroquinoline derivatives have interesting activities on ion channels (Figure 5). Thus, tetrahydroquinolines whose  $\text{N} - 1$  atom belongs to a guanidine moiety (compounds **34**)<sup>77</sup> are antagonists of neuronal  $\text{Na}^+$  channels. Another type of tetrahydroquinoline-derived guanidine compounds (**35**)<sup>78</sup> are inhibitors of the  $\text{Na}^+/\text{H}^+$  exchanger, an important target in the prevention of ischemia-reperfusion injury following a myocardial infarction. Compounds **36**,<sup>79</sup> derived from Povarov chemistry, were identified as agonists of the



**Figure 6.** Tetrahydroquinoline derivatives acting on membrane receptors.

large-conductance calcium-activated potassium channel (BKCa), one of which was shown to reduce neuronal excitability by inducing membrane hyperpolarization following a large potassium ion efflux. The vanilloid receptor-1 (VR1, TRPV1), a member of the transient receptor potential family of ion channels that is considered as a promising target in the management of pain, is antagonized by some tetrahydroquinoline derivatives (compound 37).<sup>80</sup>

The structures of some tetrahydroquinoline derivatives acting on neurotransmitter receptors and other membrane receptors are collected in Figure 6. Thus, compound 38<sup>81,82</sup> is positive allosteric modulator of the α<sub>7</sub> nicotinic acetylcholine receptor, 39<sup>83</sup> are agonists of β<sub>3</sub> adrenergic receptors, 40 (sumanirole)<sup>84,85</sup> and 41<sup>86</sup> are agonists of dopaminergic D<sub>2</sub> receptors, 42<sup>87</sup> is antagonist of the serotonin 5-HT<sub>3</sub> receptor and 43<sup>88</sup> are antagonists of histamine H<sub>3</sub> receptors. Compounds with structure 44<sup>89–95</sup> are well-known antagonists of the glycine site at the NMDA receptor, and have received much attention as potential candidates for the treatment of nicotine craving. Other membrane receptors that are targeted by tetrahydroquinoline derivatives include melatonin receptors (compounds 45),<sup>96</sup> CRTH2 (chemoattractant receptor-homologous molecule expressed on Th2 cells, compounds 46)<sup>97</sup> and receptors for anaphylatoxin C5a, a potent pro-inflammatory mediator that arises by proteolysis of complement component 5 (compounds 47).<sup>98,99</sup> Other tetrahydroquinoline derivatives bearing a similar structural core of compound 45 were identified as platelet activation factor (PAF) inhibitors<sup>100</sup> and antiepileptic or antiobesity active compounds.<sup>101</sup>

Tetrahydroquinoline derivatives can also act at steroid hormone receptors. Compounds 48<sup>102</sup> behave as estrogen receptor modulators (SERMs), where the 6-hydroxy-2-phenyl-1,2,3,4-tetrahydroquinoline system plays the same role as the stilbene core in traditional SERMs (Figure 7). A related 3-aryl-7-hydroxy-1,2,3,4-tetrahydroquinoline system is the key structural fragment

of 49,<sup>103</sup> a family of agonists of β estrogen receptor. Compound 50a<sup>104–108</sup> was identified as the first agonist of GPR30, an estrogen-activated G protein-coupled receptor that mediates many aspects of cellular signaling ranging from calcium mobilization to EGFR transactivation to gene regulation. The tetrahydroquinoline system has also served as the structural basis for progesterone receptor antagonists like compound 51<sup>109</sup> and androgen receptor antagonists (52).<sup>110</sup> It was subsequently found that the substitution pattern in the tetrahydropyridine fragment was crucial for activity, and in fact androgen receptor agonists (e.g., 53, LG 121071)<sup>111–114</sup> resulted by simple changes in this part of the molecule. The tetrahydroquinoline 54<sup>115</sup> was found to have selective androgen receptor (SARM) modulating properties that led to a potent anabolic activity. The 6-(7-indolyl)-1,2,3,4-tetrahydroquinoline derivatives 55,<sup>116</sup> which are potent glucocorticoid receptor (GR) ligands, were found to have good E-selectin transrepression activity.

Cholesteryl ester transfer protein (CETP) is a plasma glycoprotein that mediates the transfer of cholesteryl esters from the cardioprotective high density lipoprotein cholesterol (HDL-C) to the proatherogenic low density lipoprotein cholesterol (LDL-C), and hence its inhibition is an important goal in cardiovascular therapy. A tetrahydroquinoline derivative, namely, compound 56 (torcetrapib),<sup>117–120</sup> has been under clinical trials as an anti-hypercholesterolemia drug, although it was later withdrawn, and has served as the stimulus to the preparation of other families of analogues (compounds 57 and 58).<sup>121,122</sup>

Regarding interaction with nonsteroidal hormone receptors, compounds 59<sup>123</sup> were found to be antagonists of vasopressin receptors in the micromolar range, with some V<sub>2</sub>/V<sub>1a</sub> selectivity (Figure 8). Ring-expanded analogues derived from the benzazepine system were subsequently found to have much higher potency, and hence higher selectivities, in favor of the V<sub>2</sub> receptor and 6-amino-4-phenyl-1,2,3,4-tetrahydroquinoline derivatives

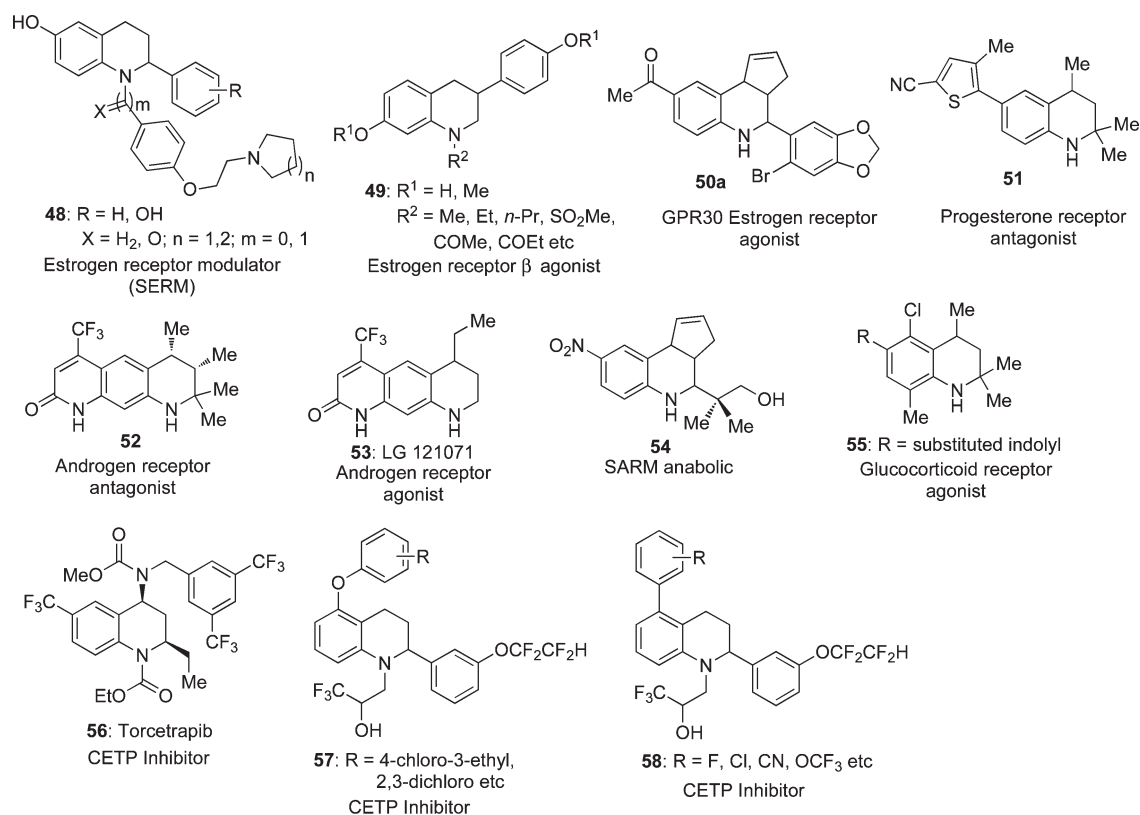


Figure 7. Tetrahydroquinoline derivatives acting on steroid hormone receptors.

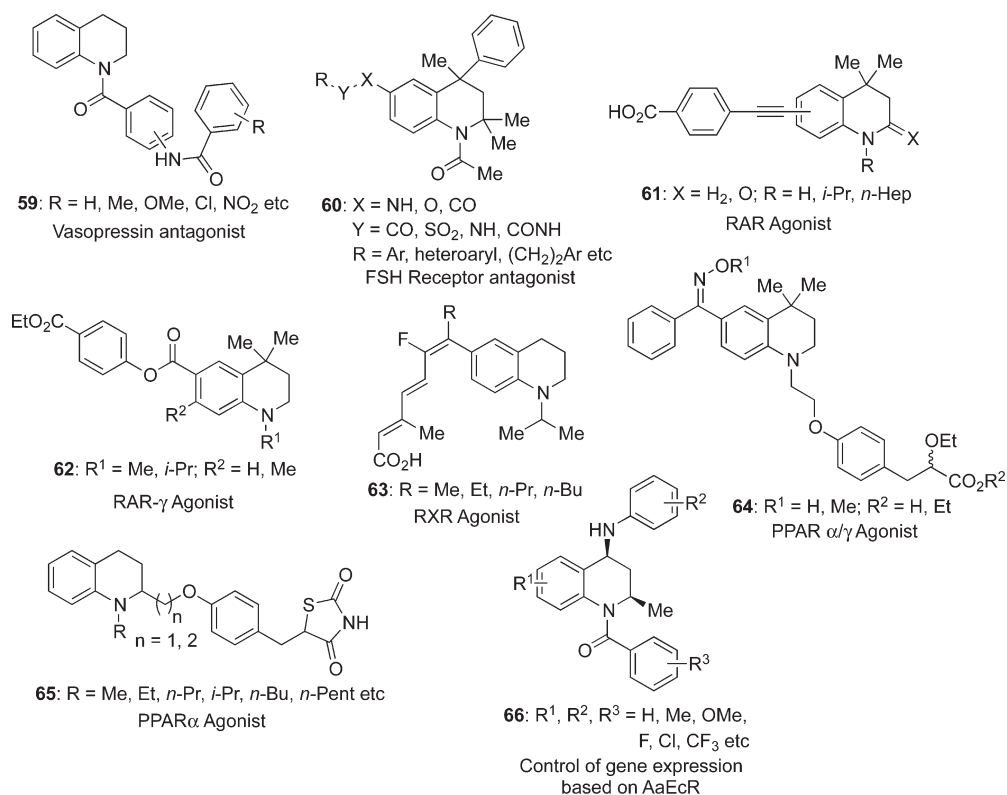


Figure 8. Tetrahydroquinoline derivatives acting on nonsteroidal hormone receptors.

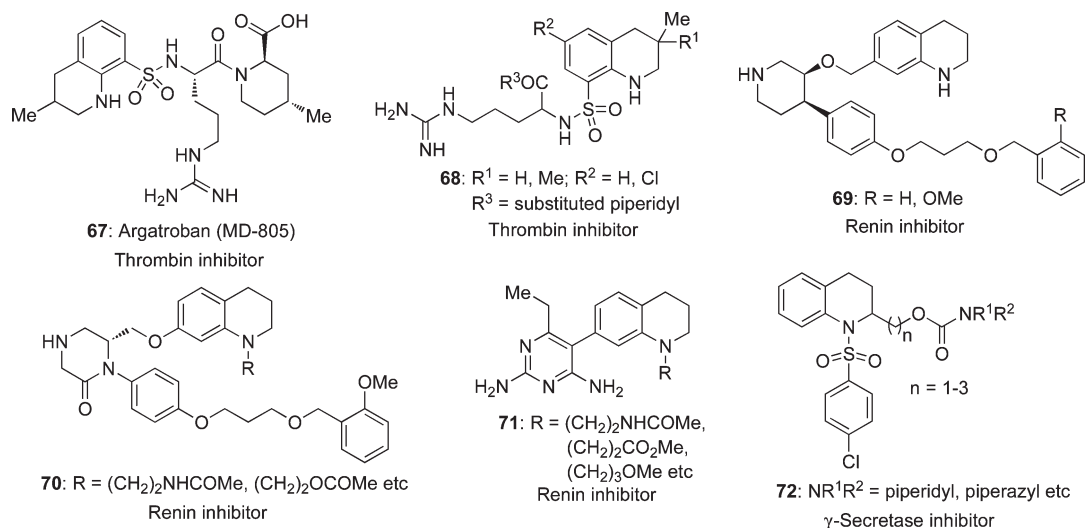


Figure 9. Enzyme inhibitors derived from tetrahydroquinolines.

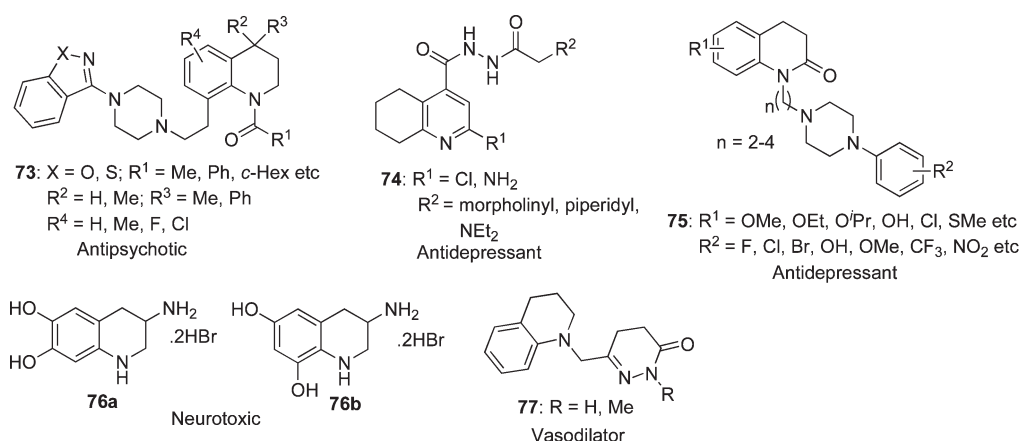


Figure 10. Bioactive tetrahydroquinolines acting at unknown targets.

**60**<sup>124,125</sup> were identified as potent (nM) antagonists for the receptor of follicle-stimulating hormone (FSH). Other intracellular receptors that can interact with tetrahydroquinoline derivatives include retinoid A receptors (RAR, compounds **61**<sup>126</sup> and **62**<sup>127</sup>), retinoid X receptors (RXR, compounds **63**<sup>128</sup>) and peroxysome proliferator activated receptors (PPAR, compounds **64**<sup>129,130</sup> and **65**<sup>131</sup>). We will also mention compounds **66**,<sup>132</sup> which are interesting because of their ability to control expression of the gene involved in the production of the ecdysone receptor (EcR) in *Aedes aegypti* (AaEcR), which is a nuclear hormone receptor that has a pivotal role in insect metabolism.

A number of compounds containing tetrahydroquinoline frameworks behave as inhibitors of therapeutically relevant enzymes. On the basis of the structure of argatroban **67**,<sup>133</sup> a commercial antithrombotic drug acting as a thrombin inhibitor, a series of analogues **68**<sup>134</sup> has been prepared, some of which were superior to the reference compound in some situations. Some families of tetrahydroquinoline derivatives, including compounds **69**,<sup>135</sup> **70**,<sup>136,137</sup> and **71**<sup>138</sup> are inhibitors of renin, a very important target in antihypertensive drug development. Compounds **72**<sup>139,140</sup> are inhibitors of enzyme that constitute an important target in the therapy for Alzheimer's disease, namely,  $\gamma$ -secretase (Figure 9).

Some tetrahydroquinolines have interesting biological properties that are addressed at unknown targets, as summarized in Figure 10. They include antipsychotic compounds, like **73**,<sup>141,142</sup> antidepressants (**74**<sup>143</sup> and **75**<sup>144</sup>), neurotoxicity accompanied by serotonin depletion (**76**),<sup>145</sup> and vasodilator activity (**77**).<sup>146</sup> Furthermore, some simple tetrahydroquinoline derivatives have been tested for antioxidant activity.<sup>147,148</sup>

### 3. OTHER APPLICATIONS OF TETRAHYDROQUINOLINES

#### 3.1. Tetrahydroquinolines As Coordination Ligands

Some tetrahydroquinoline-derived chiral ligands have found application in asymmetric synthesis. Thus, the phosphine/phosphoramidite derivatives **78** have been identified as suitable chiral ligands for the Rh-catalyzed hydrogenation of acrylates and aminoacrylates in >99% ee,<sup>149</sup> and a similar iridium complex of the phosphoramidite ligand **79** was found to be useful in asymmetric Friedel–Crafts reactions of indoles (Figure 11).<sup>150</sup> The related phosphinites **80**<sup>151–153</sup> were also useful in iridium-catalyzed asymmetric hydrogenations, including that of purely alkyl olefins.<sup>153</sup> In another application, vanadium complexes of the chiral 8-hydroxy-5,6,7,8-tetrahydroquinolines **81** were found



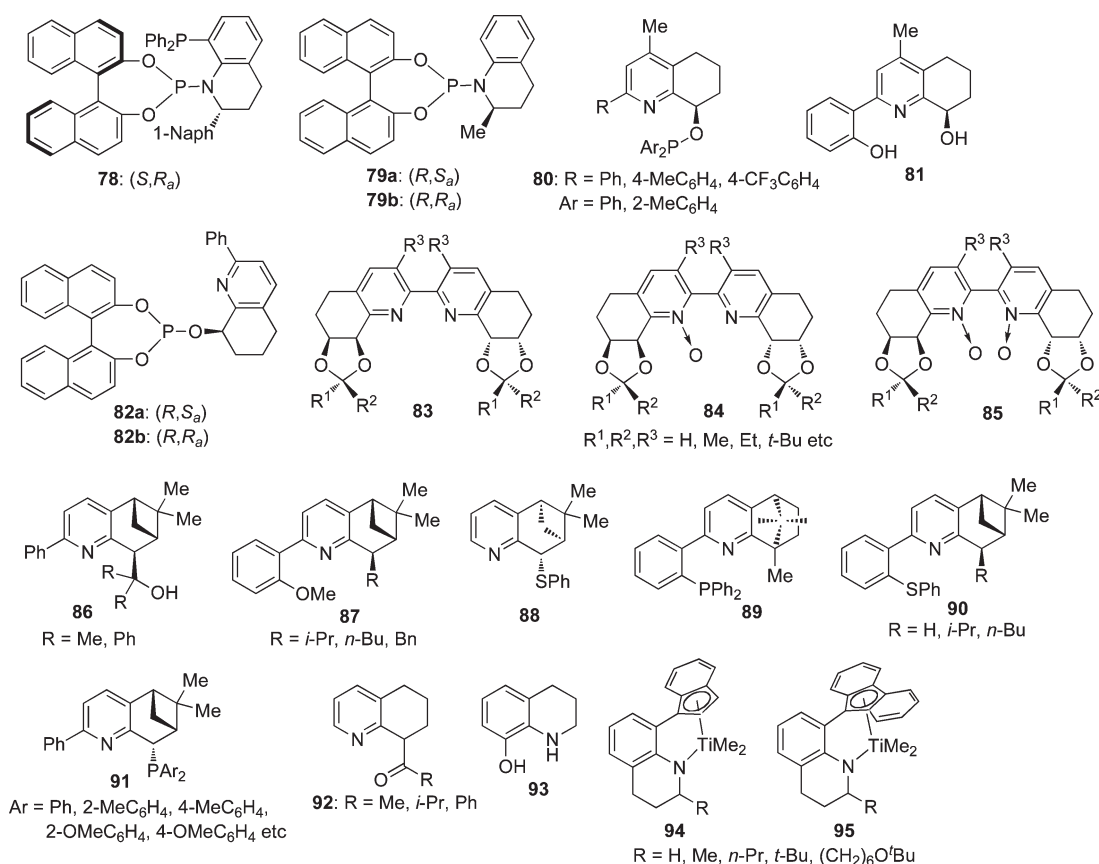


Figure 11. Tetrahydroquinolines acting as coordination ligands.

to allow the preparation of chiral sulfoxides from sulfides in around 70% *ee* when combined with hydrogen peroxide as an oxidant.<sup>154</sup> Copper catalysts generated from tetrahydroquinoline-derived chiral phosphites (compounds 82) were found to promote the conjugated addition of diethylzinc onto acyclic enones in excellent yields and *ee* about 90%.<sup>155</sup> Chiral 2,2'-bis-tetrahydroquinolines and their *N*-oxides (83–85) were applied as catalysts in the asymmetric aminolysis of epoxides and the asymmetric allylation of aldehydes.<sup>156</sup> Other asymmetric reactions where chiral 5,6,7,8-tetrahydroquinoline ligands 86–91 are involved include the enantioselective addition of diethylzinc to arylaldehydes,<sup>157–159</sup> palladium-catalyzed enantioselective allylic alkylation of 1,3-diphenylprop-2-enyl acetate with dimethyl malonate,<sup>160–163</sup> and iridium-catalyzed asymmetric hydrogenation of alkenes.<sup>164,165</sup>

Some 8-acyl-5,6,7,8-tetrahydroquinolines 92<sup>166,167</sup> and 8-hydroxy-1,2,3,4-tetrahydroquinoline 93<sup>168</sup> are good ligands for copper-catalyzed reactions and have been employed as catalysts for a variety of *N*-arylation reactions. Tetrahydroquinoline-based titanium complexes 94 and 95 were found to be good catalysts for ethylene/1-octene copolymerization reactions, showing some advantages over previously known catalysts.<sup>169</sup> A few other tetrahydroquinoline complexes of tantalum,<sup>170</sup> palladium,<sup>171</sup> iridium<sup>172</sup> and rhenium,<sup>173</sup> and also some ( $\eta^6$ -arene)tricarbonylmetal complexes,<sup>174</sup> have been synthesized and characterized, without any specific synthetic application being mentioned for them.

### 3.2. Tetrahydroquinoline-Derived Dyes and Other Applications of Tetrahydroquinolines

Some dyes containing a tetrahydroquinoline unit as the electron donor and a cyanoacrylic acid moiety as the electron

acceptor (compounds 96–98) were prepared for their use in dye-sensitized solar cells (DSSC).<sup>175</sup> The tetrahydroquinoline derivative 99 and related compounds were studied as sensitizers for alkali-developable photopolymerization systems.<sup>176</sup> Other families of dyes containing a tetrahydroquinoline structural fragment include monoazo dyes 100, 101,<sup>177,178</sup> and 102<sup>179</sup> (Figure 12). The tetrahydroquinoline derivatives 103 were prepared as molecular glasses and their thermal and photochemical properties were studied.<sup>180</sup>

## 4. SYNTHESIS OF 1,2,3,4-TETRAHYDROQUINOLINES INVOLVING THE GENERATION OF ONE BOND

### 4.1. Introduction

The 1,2,3,4-tetrahydroquinoline ring can be constructed by creating one new bond starting from precursors containing a benzene ring. In this section, we will discuss the synthetic methodologies involving the generation of one new bond as the key step. We have organized the section according to the numbers of the positions of the new bond in the final product, namely N–C<sub>2</sub>, C<sub>2</sub>–C<sub>3</sub>, C<sub>3</sub>–C<sub>4</sub>, C<sub>4</sub>–C<sub>4a</sub>, and C<sub>8a</sub>–N (Figure 13).

### 4.2. Formation of the N–C<sub>2</sub> Bond

**4.2.1. Intramolecular Allylic Amination.** The intramolecular asymmetric allylic amination of allyl acetate 104a in the presence of a chiral phosphine (9-PBN) and Pd(dba)<sub>2</sub> afforded a diastereomeric mixture of tetrahydroquinolines 105 in moderate yields and enantioselectivities. The same reaction furnished the racemic *cis* product 105a in excellent yield (92%) in a substrate-controlled manner with tributylphosphine, an achiral phosphine.

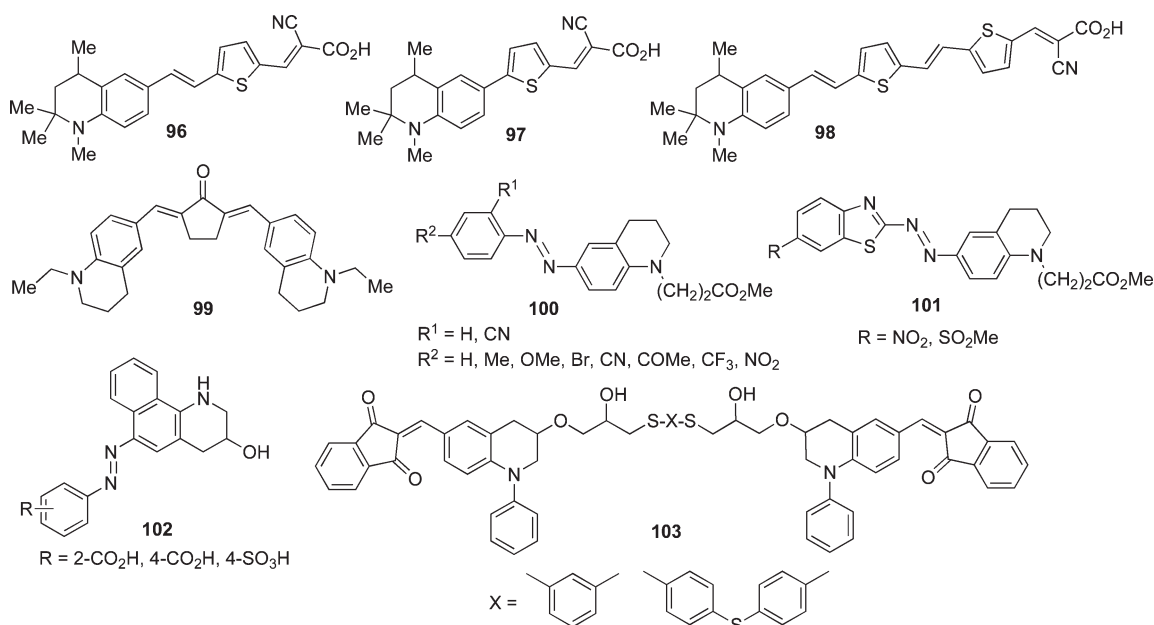


Figure 12. Tetrahydroquinolines with miscellaneous applications.

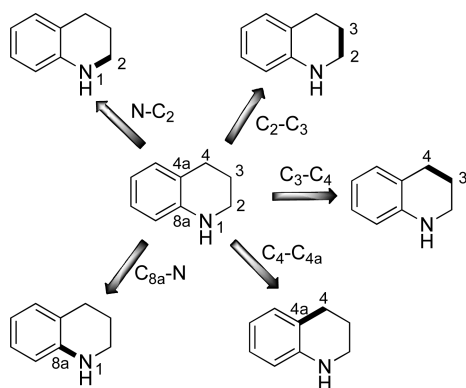


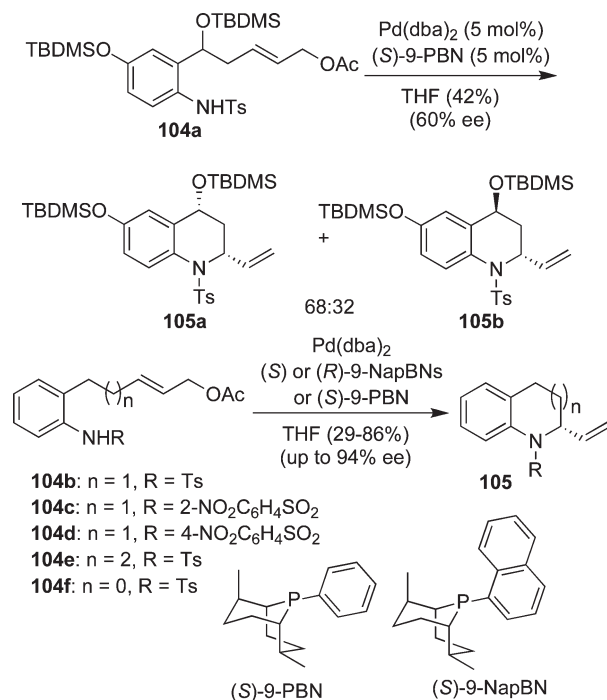
Figure 13. Disconnections of the tetrahydroquinoline framework discussed in section 4.

The starting compound **104a** was prepared from 5-hydroxyanthranilic acid in a route having a Reformatsky reaction as the key step.<sup>181</sup> A few years later the authors extended their intramolecular allylic amination procedure to a variety of substrates (**104b–f**) and achieved enantioselectivities up to 94% using (S)- and (R)-9-NapBNs as chiral ligands (Scheme 1).<sup>182</sup>

The postfunctionalization of the *N*-tosyl-6-benzyloxy-4-hydroxy-2-vinyl-1,2,3,4-tetrahydroquinoline **106** afforded the pyrrolo[3,2-*c*]quinoline skeleton of the martinelline natural products.<sup>183</sup> The PDC oxidation of **106** followed by treatment with formaldehyde in the presence of *N*-methylaniline trifluoroacetate and KCN/AcOH furnished the *trans*-2,3-disubstituted tetrahydroquinolone **107** in good yield, which was subsequently converted into the pyrrolo[3,2-*c*]quinoline **108** by the Raney nickel reduction of the nitrile group followed by reduction of the cyclic imine with NaBH<sub>3</sub>CN (Scheme 2).

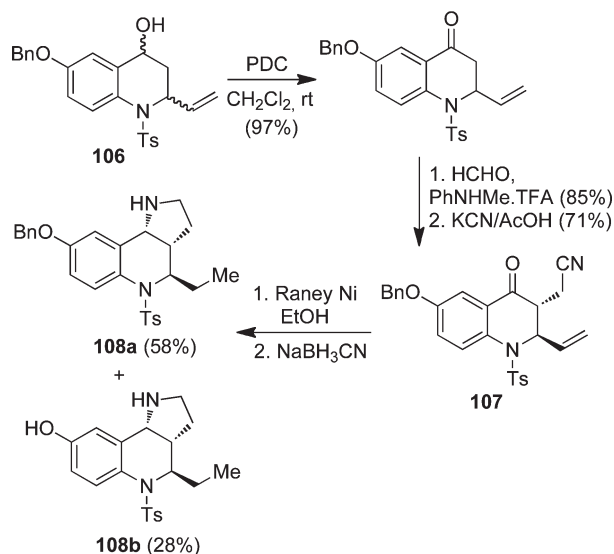
The application of gold catalysts in organic synthesis is a remarkably active topic, as evidenced by the appearance of numerous articles and reviews in this field.<sup>184</sup> In this context,

Scheme 1. Synthesis of Tetrahydroquinolines via Pd-Catalyzed Intramolecular Asymmetric Allylic Amination Reaction

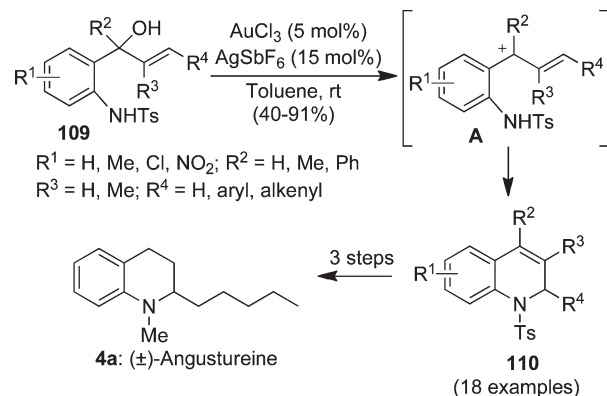


Chan and co-workers demonstrated an AuCl<sub>3</sub>/AgSbF<sub>6</sub>-catalyzed synthesis of 1,2-dihydroquinolines **110** through an intramolecular allylic amination of 2-tosylaminophenylprop-1-en-3-ols **109** and its application to the synthesis of the tetrahydroquinoline natural product angustureine **4a**.<sup>185</sup> The reaction was successful for a wide range of substrates containing electron-donating, electron-withdrawing, and sterically hindered substituents. The authors proposed a mechanism where gold acts as a Lewis acid, coordinating with the hydroxyl group to generate a carbocation

Scheme 2. Synthesis of the Skeleton of the Martinellines



Scheme 3. Synthesis of (±)-Angustureine (4a) Based on Gold-Catalyzed Intramolecular Allylic Amination

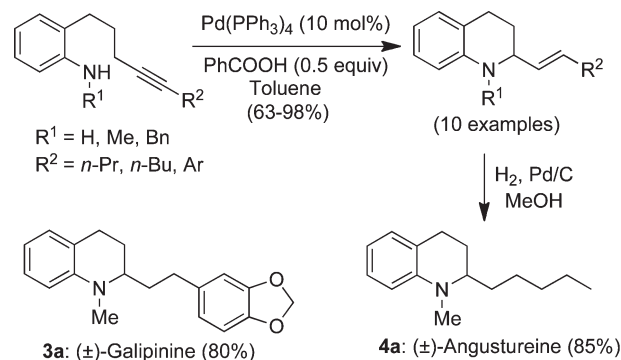


intermediate **A**, which subsequently undergoes intramolecular allylic amination to furnish the dihydroquinolines (Scheme 3).

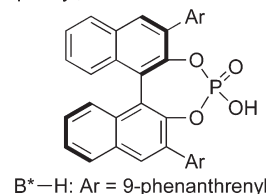
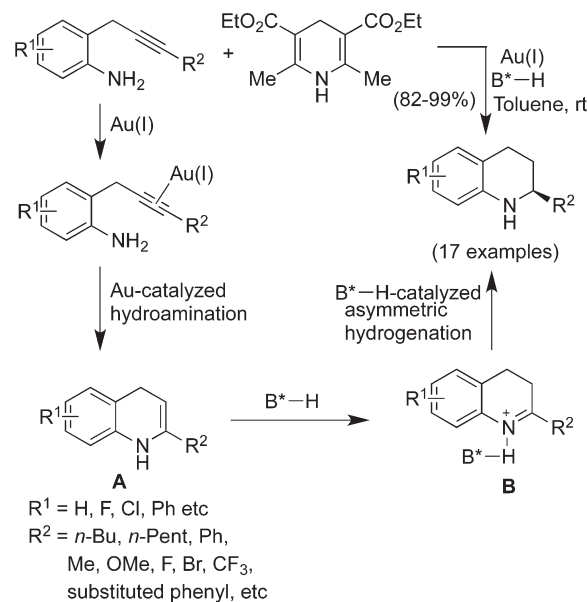
**4.2.2. Intramolecular Hydroamination.** Yamamoto and co-workers reported the synthesis of 2-alkenyl-1,2,3,4-tetrahydroquinolines through the intramolecular hydroamination of anilinoalkynes catalyzed by  $\text{Pd}(\text{PPh}_3)_4/\text{PhCOOH}$ . A wide variety of aminoalkynes, having a free amino group or electron-donating group on the N-atom, afforded the corresponding tetrahydroquinolines in good to excellent yields. However, the presence of electron-withdrawing groups, such as Boc, Ts, or Nf groups, on the nitrogen led to failure of the reaction. The use of (R,R)-2,3-bis(diphenylphosphino)norbormane (RENORPHOS)/ $\text{Pd}_2(\text{dba})_3$  catalytic system furnished the products with good enantioselectivities (up to 78% *ee*), and the methodology was subsequently applied to the synthesis of the alkaloids galipinine **3a** and angustureine **4a** (Scheme 4).<sup>186</sup>

Brønsted acid-catalyzed intramolecular hydroamination of *N*-arylsulfonyl-2-allylanilines afforded indolines and tetrahydroquinolines in high yields. Although sulphuric acid gave good conversion in toluene, triflic acid was found to be superior.<sup>187</sup> A consecutive asymmetric hydroamination/asymmetric transfer

Scheme 4. Synthesis of (±)-Galipinine (3a) and (±)-Angustureine (4a) via Pd-Catalyzed Intramolecular Hydroamination of Anilinoalkynes



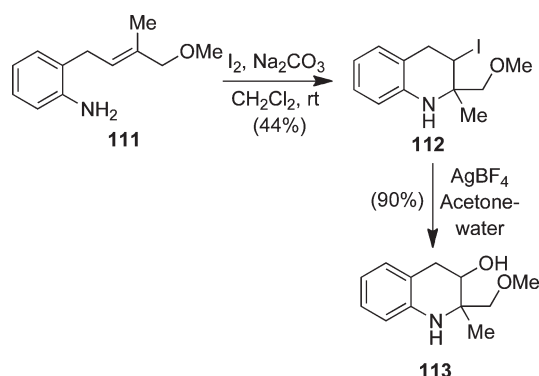
Scheme 5. Gold Complex/Chiral Brønsted Acid-Catalyzed Synthesis of Optically Active Tetrahydroquinolines



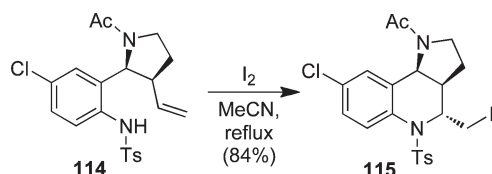
hydrogenation of 2-(2-propynyl)anilines in the presence of an achiral gold complex/chiral Brønsted acid allowed the synthesis of optically active 2-substituted tetrahydroquinolines.<sup>188</sup> The proposed mechanism for the synthesis of enantiopure tetrahydroquinolines includes the gold catalyst-initiated hydroamination to furnish the 1,4-dihydroquinoline intermediate **A**, which subsequently isomerized to 3,4-dihydroquinolinium complex **B** by the chiral Brønsted acid. Intermediate **B** then underwent asymmetric transfer hydrogenation with Hantzsch ester to afford enantiopure tetrahydroquinolines (Scheme 5).

**4.2.3. Intramolecular Aminohalogenation.** Intramolecular aminohalogenation of *o*-allylanilines is of interest because it

**Scheme 6. Synthesis of the 3-Hydroxy Tetrahydroquinoline Core (113) of the Benzastatin Natural Products**



**Scheme 7. Construction of the Martinelline Core via Intramolecular Aminoiodination Reaction**



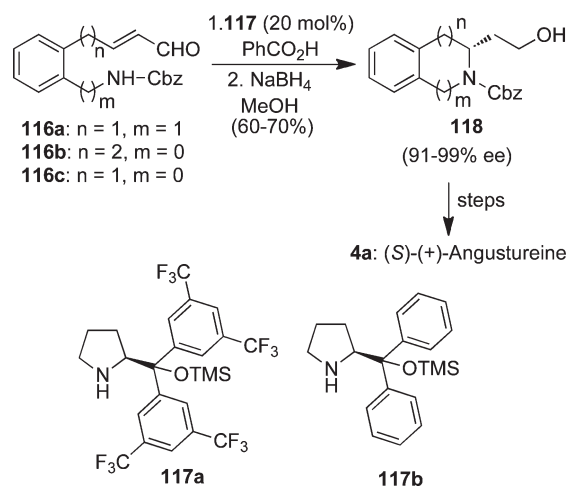
allowed the construction of tetrahydroquinoline ring system bearing a halogen substituent, which could be useful for further functionalization to achieve complex derivatives. Treatment of arylamine **111** with molecular iodine and sodium carbonate afforded the 3-iodotetrahydroquinoline derivative **112** in moderate yield through intramolecular aminoiodination.<sup>189</sup> The 3-iodo substituent was subsequently replaced by hydroxyl group by  $\text{AgBF}_4$  in acetone–water to furnish the 3-hydroxy tetrahydroquinoline core (**113**) of the benzastatin natural products (Scheme 6). A related method based on a selenoamination approach was found to give 1:1 mixtures of dihydroindoles and tetrahydroquinolines.<sup>190</sup>

Frank and Aupé illustrated a novel intramolecular aminoiodination reaction to construct the pyrroloquinoline ring system during their study toward the synthesis of the tricyclic core of the martinelline natural products.<sup>191</sup> Intermediate **114**, synthesized from the corresponding 2-aminoarylaldehyde in few steps, afforded pyrroloquinoline **115** diastereoselectively in 84% yield upon treatment with iodine. Similarly the *N*-unprotected analogue of **114** gave the aminoiodination product in moderate yield (Scheme 7).

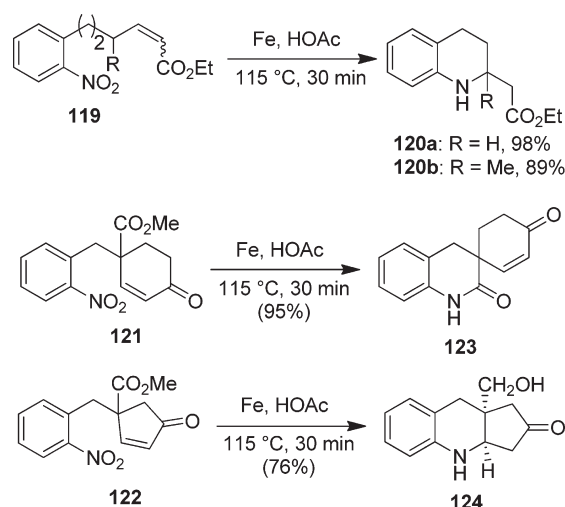
Chemler and co-workers demonstrated the first intramolecular aminobromination and aminochlorination of *N*-substituted-*ortho*-allylanilines in the presence of catalytic amount of a palladium reagent and excess of copper(II) halides. For instance, *N*-tosyl-*ortho*-allylaniline reacted with 10 mol % of  $\text{Pd}(\text{OCOCF}_3)_2$  and copper(II) bromide (3 equiv) to afford quantitative conversion of *N*-tosyl-2-(bromomethyl)indoline and *N*-tosyl-3-bromo-1,2,3,4-tetrahydroquinoline in 3:1 ratio. A mechanism was proposed involving a  $\text{Pd}(\text{II})/\text{Pd}(\text{IV})$  catalytic cycle, where copper(II) was involved in the oxidation of  $\text{Pd}(\text{II})$  to  $\text{Pd}(\text{IV})$ .<sup>192</sup>

**4.2.4. Intramolecular aza-Michael Addition.** The organocatalytic enantioselective intramolecular aza-Michael reaction of *N*-protected amines **116** in the presence of diarylprolinols **117**

**Scheme 8. Enantioselective Organocatalyzed Intramolecular aza-Michael Reaction**



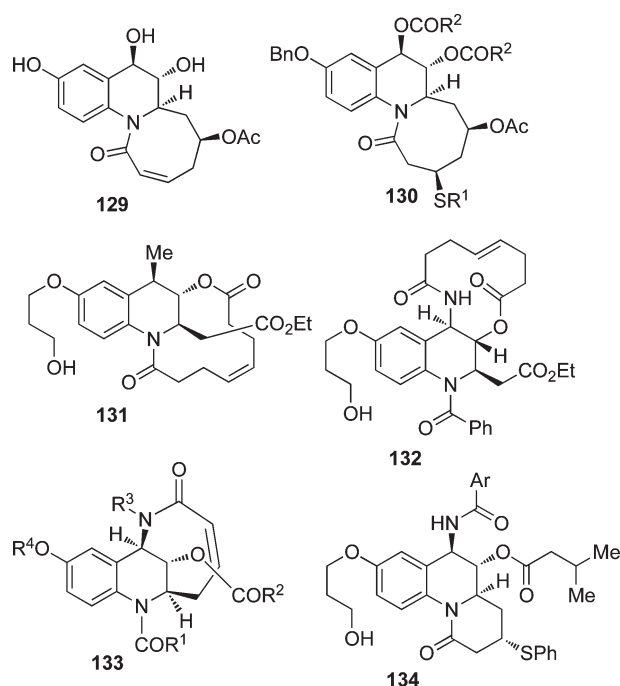
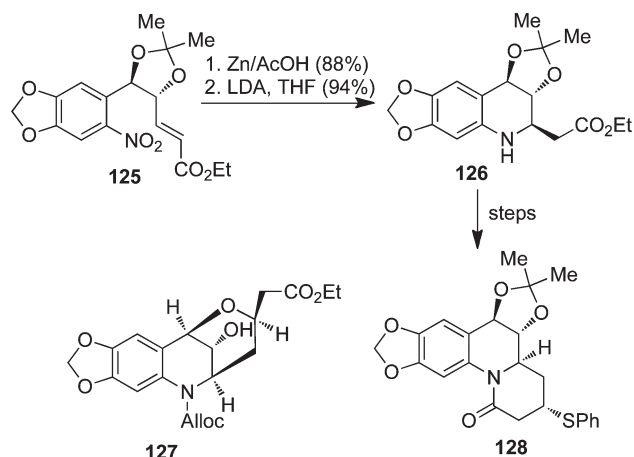
**Scheme 9. Synthesis of Tetrahydroquinolines Starting from Nitro Precursors**



allowed the construction of 1,2,3,4-tetrahydroquinolines and 1,2,3,4-tetrahydroisoquinolines **118** in good yields and excellent enantioselectivities.<sup>193</sup> The methodology was further extended for the enantioselective synthesis of the alkaloid (*S*)-(+)-angustureine **4a** (Scheme 8).

A tandem reduction-Michael addition reaction sequence was developed for the synthesis of tetrahydroquinoline-2-acetic esters.<sup>194</sup> The 2-nitro-substituted substrates **119** reacted with 6 equivalents of iron powder in glacial acetic acid to afford tetrahydroquinoline derivatives **120** in high yields through a reductive cyclization. Recently the same group extended their methodology for the synthesis of fused and spiro-tetrahydroquinolines **123** and **124** starting from nitro compounds **121** and **122** (Scheme 9).<sup>195</sup> The cyclohexenone derivative **121** did not afford the expected reduction-Michael adduct, and instead the spiro compound **123** was isolated in 95% yield. However, cyclopentenone **122** underwent smoothly the reduction-Michael addition sequence to afford the expected tetrahydroquinoline **124**.

**Scheme 10.** Synthesis of Natural Product-like Tetrahydroquinoline Libraries through Reduction-Michael Addition Sequence

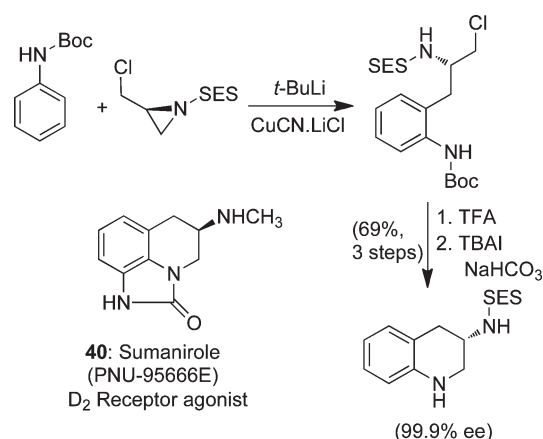


**Figure 14.** Selected examples of structurally diverse tetrahydroquinolines synthesized by the Arya group.

The reduction-Michael addition strategy was also employed by Arya and co-workers for the construction of natural product-like tetrahydroquinoline libraries through a diversity-oriented solution and solid-phase synthesis. For instance, the enantiopure tetrahydroquinoline derivative **126** was synthesized from the suitable nitro precursor **125** by a Zn/AcOH mediated reduction-Michael addition sequence in high yield and the product was then modified into structurally complex tetrahydroquinolines **127** and **128** (Scheme 10).<sup>196</sup>

The same group published a series of subsequent reports describing the synthesis of a large variety of structurally diverse tetrahydroquinoline derivatives containing medium to macrocyclic ring skeletons, where the key step was the reduction-

**Scheme 11.** Synthesis of Chiral 3-Amino-1,2,3,4-tetrahydroquinoline (Core Structure of Sumanirole, PNU-95666E, **40**)



Michael addition sequence. Some selected examples are given in Figure 14, where compounds **129** and **130**<sup>197</sup> possess an eight-membered ring while compounds **131** and **132**<sup>198</sup> have a 12-membered ring. The synthesis of tetrahydroquinolines **133**<sup>199</sup> and **134**<sup>200</sup> was also reported.

**4.2.5. Intramolecular Nucleophilic Substitution Reactions.** 3-Amino-1,2,3,4-tetrahydroquinoline constitutes the core structure of sumanirole (PNU-95666E, **40**), a dopamine D<sub>2</sub> receptor agonist that is considered as a candidate drug for the treatment of Parkinson's disease. This compound was synthesized with 99.9% *ee* by means of an aziridine ring-opening-cyclization sequence (Scheme 11).<sup>201</sup> For alternative approaches to this compound, see section 4.6.3 and ref 202.

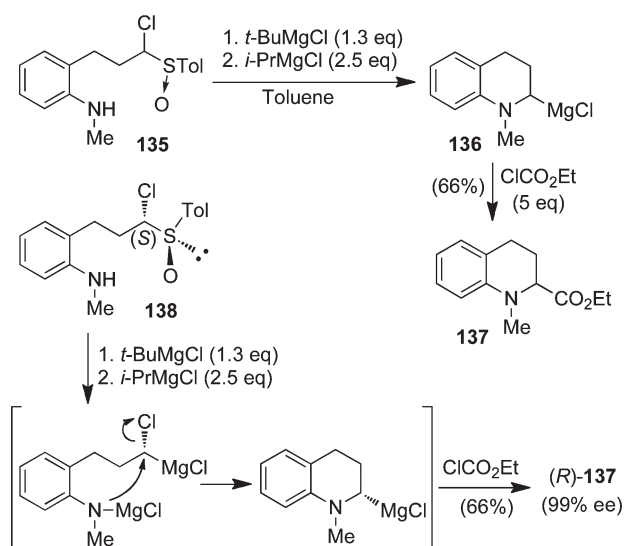
Cyclic  $\alpha$ -amino acid derivatives, for instance, ethyl 1,2,3,4-tetrahydroquinoline-2-carboxylate **137**, were synthesized by the intramolecular reaction of a magnesium carbenoid with *N*-magnesium arylamine. The sulfoxide **135** reacted with *t*-BuMgCl and *i*-PrMgCl in toluene to afford intermediate **136**, which was then converted into the tetrahydroquinoline derivative **137** in 66% yield (Scheme 12).<sup>203</sup> Recently, the same group reported the asymmetric synthesis of **137** starting from chiral sulfoxide **138** using the same methodology.<sup>204</sup> The cyclization occurred through an inversion of configuration at the carbenoid carbon, which was supported by the earlier observation of Hoffmann<sup>205</sup> (Scheme 12).

Enantiopure 2,2-disubstituted-4-hydroxy-1,2,3,4-tetrahydroquinolines were synthesized from readily available chiral homoallylic alcohols via a vanadium-catalyzed epoxidation-acid-mediated intramolecular epoxide opening sequence. The epoxidation of the homoallylic alcohols **139** was effected in the presence of catalytic amount of VO(acac)<sub>2</sub> and excess of *t*-butyl hydroperoxide. An intramolecular epoxide opening-cyclization process of compound **140** afforded the tetrahydroquinolines **141** as 1:1 diastereomeric mixtures, in moderate yields but with good enantioselectivities (Scheme 13).<sup>206</sup>

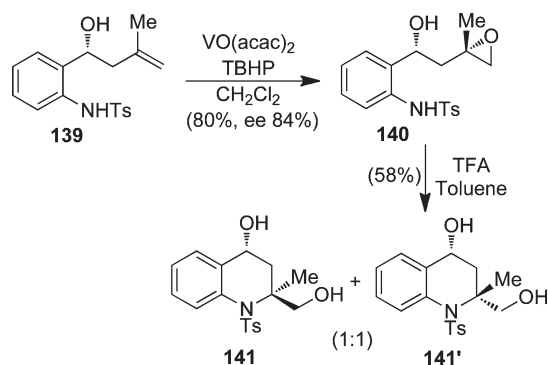
During the enantioselective synthesis of (+)-virantmycin **1c** the construction of the tetrahydroquinoline core was achieved through a trifluoroacetic acid-mediated intramolecular epoxide opening reaction.<sup>207</sup> The chiral epoxide **142**, obtained from the Sharpless asymmetric epoxidation, afforded the tetrahydroquinoline derivative **143** in 67% yield upon treatment with two equivalents of trifluoroacetic acid, which was then transformed into (+)-virantmycin **1c** (Scheme 14).



Scheme 12. Synthesis of Tetrahydroquinoline 137 Starting from Sulfoxide



Scheme 13. Synthesis of Tetrahydroquinolines 141 via Vanadium-Catalyzed Epoxidation-Acid-Mediated Intramolecular Epoxide Opening Sequence

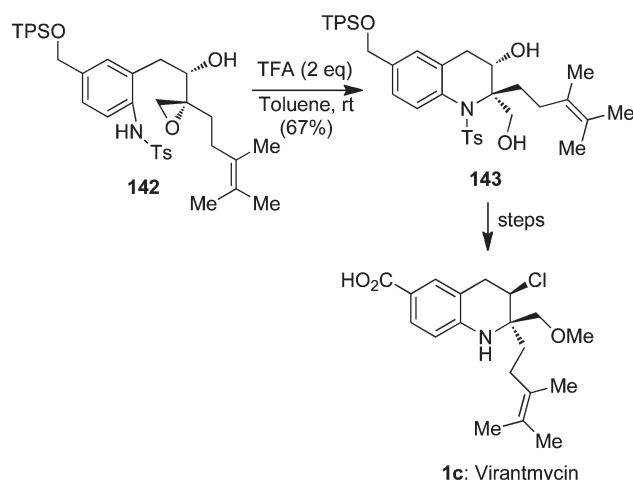


**4.2.6. Intramolecular Amidation Reactions.** The asymmetric synthesis of 3,4-disubstituted 1,2,3,4-tetrahydroquinolines **145** was effected through an acid-catalyzed intramolecular cyclization of enantiopure 2-aminoaryl compounds **144**, which were readily prepared by (–)-sparteine-mediated dynamic thermodynamic resolution of 2-( $\alpha$ -lithiobenzyl)-*N*-pivaloylaniline.<sup>208</sup> A temperature and concentration controlled epimerization-substitution sequence was utilized for the synthesis of highly enantiopure benzyl-substituted *N*-pivaloylanilines **144** (*ee* 99%) (Scheme 15).

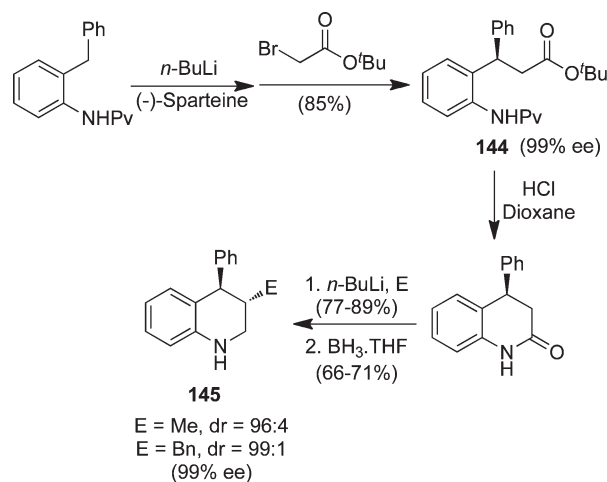
#### 4.2.7. Reduction–Intramolecular Cyclization Sequences.

Bunce and co-workers also developed a tandem reduction-reductive amination procedure for the construction of tetrahydroquinolines from 2-nitroaryl compounds bearing a carbonyl group in the side chain.<sup>209</sup> The starting compounds **146** were simply prepared from methyl (2-nitrophenyl)acetate by alkylation with allyl halides. A one-pot ozonolysis-reduction-reductive amination reaction series provided the *N*-methyl-2-substituted-1,2,3,4-tetrahydroquinoline-4-carboxylic esters **147** in good yields. The isolated ozonolysis products **148** also afforded the final tetrahydroquinolines without

Scheme 14. Synthesis of Virantmycin 1c through Acid-Mediated Intramolecular Epoxide Opening Reaction



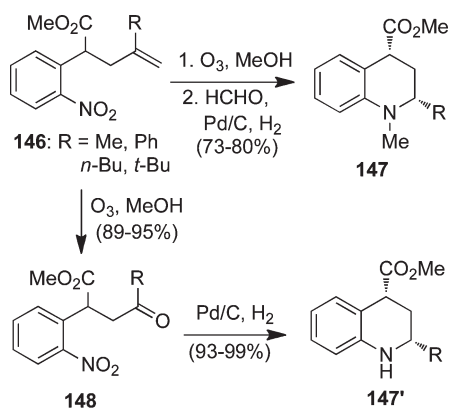
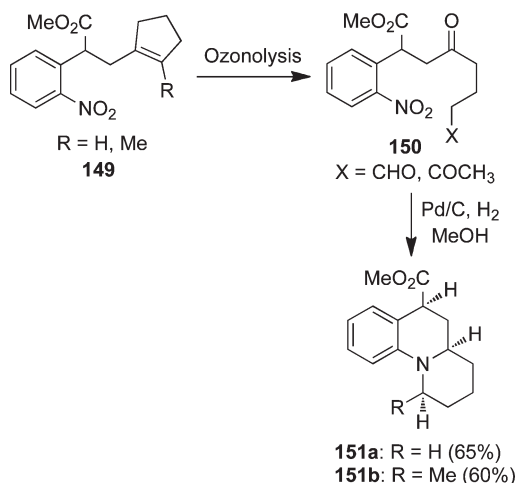
Scheme 15. Synthesis of Enantiopure Tetrahydroquinolines via Intramolecular Amidation Reaction



*N*-substitution in almost quantitative yields by hydrogenation with Pd/C/H<sub>2</sub> (Scheme 16). Furthermore, the procedure was extended to the synthesis of the angular-fused tricyclic benzo[*c*]quinolizine-6-carboxylic esters **151** through the reduction-reductive cyclization reaction of the tricarbonyl precursor **150**, which was previously generated by ozonolysis of the cyclopentene derivative **149** (Scheme 17). A few years later the same group broadened the scope of their procedure for the diastereoselective synthesis of 2,3-disubstituted tetrahydroquinolines (dr up to 16:1).<sup>210,211</sup>

The product obtained in the organocatalytic enantioselective Michael addition of malonates to  $\alpha,\beta$ -unsaturated enones was successfully converted into an optically active tetrahydroquinoline derivative.<sup>212</sup> Michael addition of malonates in the presence of 10 mol % of a chiral imidazolidine catalyst derived from phenylalanine to  $\alpha,\beta$ -unsaturated carbonyl compounds furnished the adducts in excellent yields and enantioselectivities. A suitably substituted enantiopure product **152** was transformed into the chiral tetrahydroquinoline **153** using previously

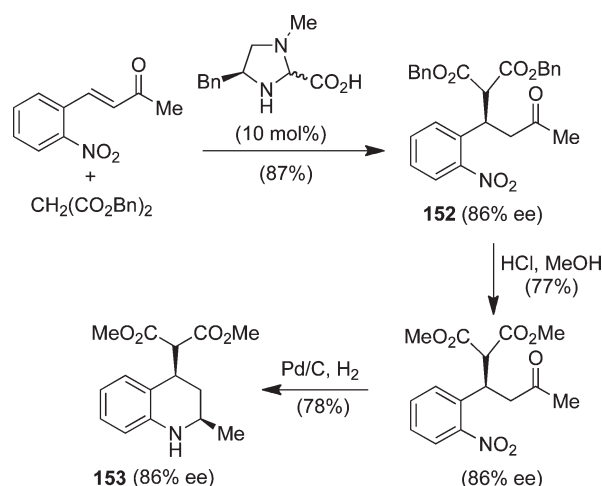
Scheme 16. Tandem Reduction-Reductive Amination Sequence Developed by Bunce

Scheme 17. Synthesis of Angular-Fused Tricyclic Benzo[*c*]quinolizine-6-carboxylic Esters 151

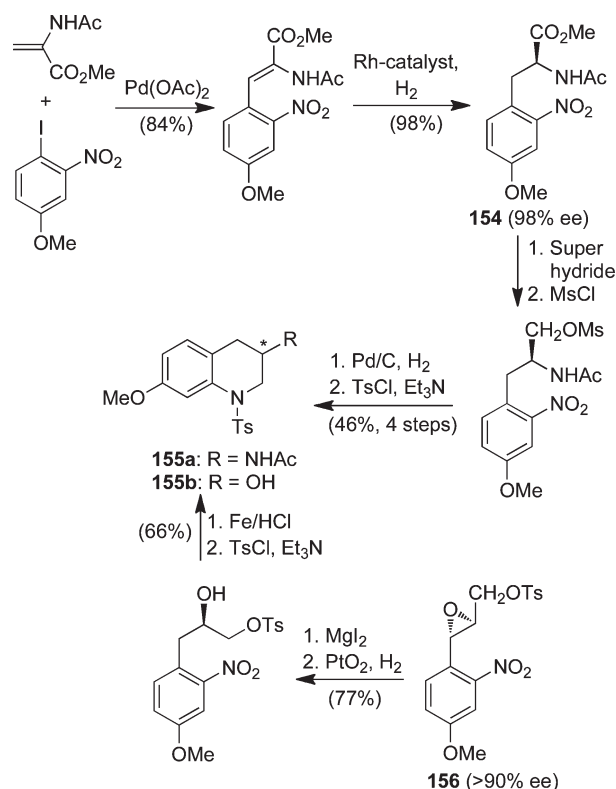
described reduction-reductive amination procedure in 78% yield and 86% *ee* (Scheme 18). A similar strategy was used for the synthesis of 7-amino-1,2,3,4-tetrahydroquinoline, a potential precursor for the orally available vanilloid receptor-1 antagonists, starting from methyl 3-(2,4-dinitrophenyl)acrylate.<sup>80</sup> Recently, 2-aryl-1,2,3,4-tetrahydroquinolines were synthesized from *ortho*-nitrochalcones through Pd/C catalyzed reductive cyclization.<sup>213</sup>

Highly enantiopure functionalized 1,2,3,4-tetrahydroquinolines were synthesized from 2-nitroaryl compounds using Rh-catalyzed asymmetric hydrogenation-reductive cyclization strategies. The precursor **154** was prepared from 4-methoxy-2-nitroiodobenzene through a Pd-catalyzed asymmetric Heck reaction followed by Rh-catalyzed asymmetric hydrogenation with excellent enantioselectivity (>98% *ee*). The final cyclization step was achieved by Pd/C-catalyzed hydrogenation to afford the unstable 3-acetamido-1,2,3,4-tetrahydroquinoline, which was subsequently transformed into the stable tosyl derivative **155a**. The synthesis of chiral tetrahydroquinoline **155b** was alternatively attained through a regioselective opening of enantiopure epoxide **156** by MgI<sub>2</sub> followed by Fe/HCl-mediated reductive cyclization, again with high enantioselectivity (Scheme 19).<sup>214</sup> It is also relevant to mention that the reduction of suitably

Scheme 18. Chiral Synthesis of 2,4-Disubstituted Tetrahydroquinoline 153



Scheme 19. Synthesis of Chiral Tetrahydroquinolines 155

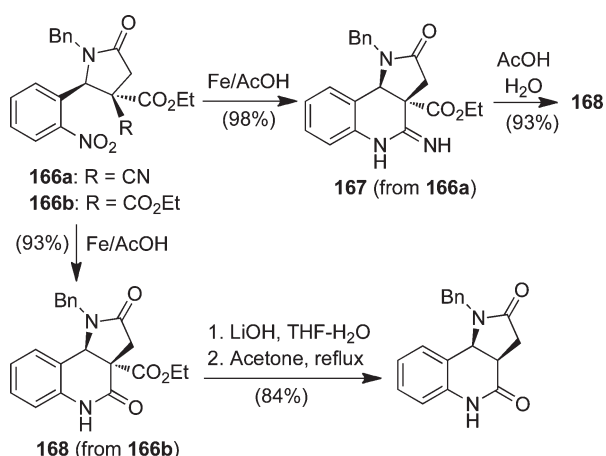


substituted 2-nitroarenes with zinc powder in near-critical water afforded quinolines in good yields together with small amounts of the corresponding 1,2,3,4-tetrahydroquinolines.<sup>215</sup>

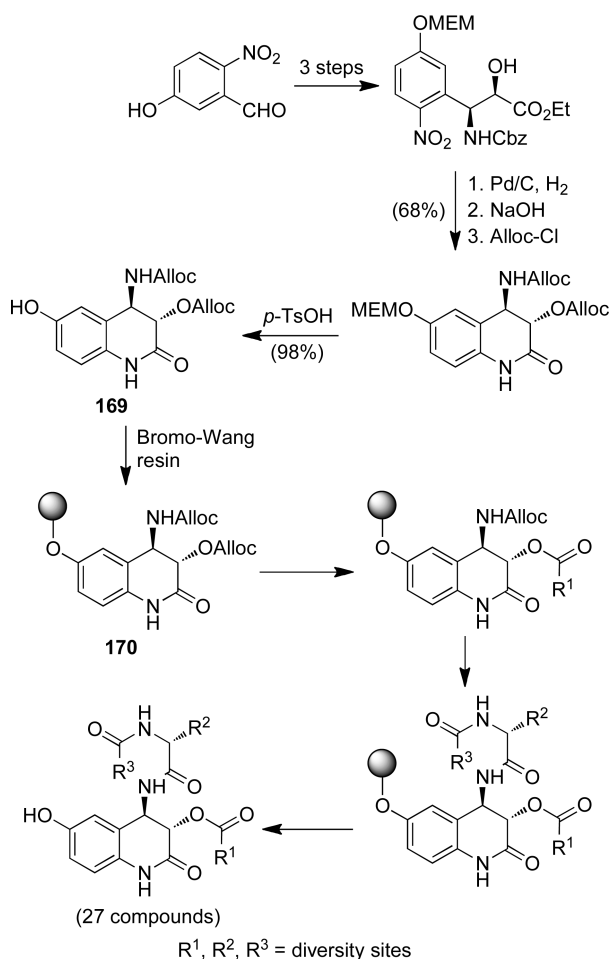
3-Amino-6,7-dimethoxy-1,2,3,4-tetrahydroquinoline **159**, an intermediate in the synthesis of the natural product anachelin **11** (see the Introduction), was synthesized in three steps starting from the corresponding nitro compound **157**.<sup>216</sup> The reductive cyclization was achieved by treatment with Fe/AcOH to afford the tetrahydroquinolone derivative **158** in high yield. However, an attempt to reduce the amide functionality with borane led only



Scheme 23. Comesse's Reductive Cyclization Route to the Synthesis of Martinelline Core

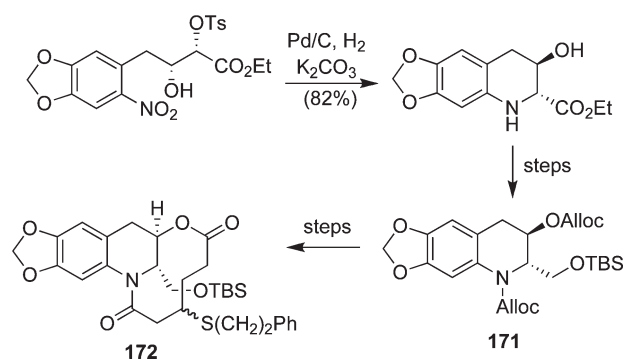


Scheme 24. Synthesis of a Library of Enantiopure Tetrahydroquinolines via Reduction–Cyclization Sequence

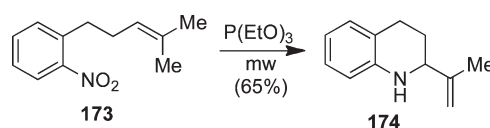


Subsequently the same group synthesized polycyclic tetrahydroquinoline derivatives containing a ten-membered ring using the previously described solution and solid-phase approach where the key step was again the reduction of a nitro group

Scheme 25. Synthesis of Polycyclic Tetrahydroquinoline Derivative Containing a Ten-Membered Ring



Scheme 26. Microwave-Assisted Synthesis of Tetrahydroquinoline 174



followed by cyclization. The 1,2,3-trisubstituted tetrahydroquinolines **171** were transformed into the macrocyclic compounds **172** using a RCM reaction (Scheme 25).<sup>224</sup>

The application of the methodology developed by Beifuss and co-workers for the synthesis of N-heterocycles starting from *ω*-nitroalkenes in the presence of triethyl phosphite was extended to the synthesis of a single example of 1,2,3,4-tetrahydroquinoline.<sup>225,226</sup> The starting *ω*-nitroalkene **173**, in the presence of excess of triethyl phosphite under microwave irradiation, furnished the tetrahydroquinoline derivative **174** in 65% yield (Scheme 26). Although the mechanism of this reaction was not described, it can be presumed to have a nitrene as an intermediate, and the method was found to be general and highly effective to synthesize other heterocycles, such as tetrahydroquinoxalines and benzoxazines.

Lemaire and co-workers reported a novel synthesis of tetrahydroquinolines starting from 2-(2-nitroaryl)-3-aryl-benzo[*b*]thiophene **175** involving a nickel-catalyzed reduction–cyclization–desulfurization sequence.<sup>227</sup> Treatment of the benzo[*b*]thiophene derivatives **175** with hydrogen in the presence of Raney nickel or Ni<sub>2</sub>B afforded the corresponding 2,3-diaryltetrahydroquinolines **176** in moderate to good yields (Scheme 27).

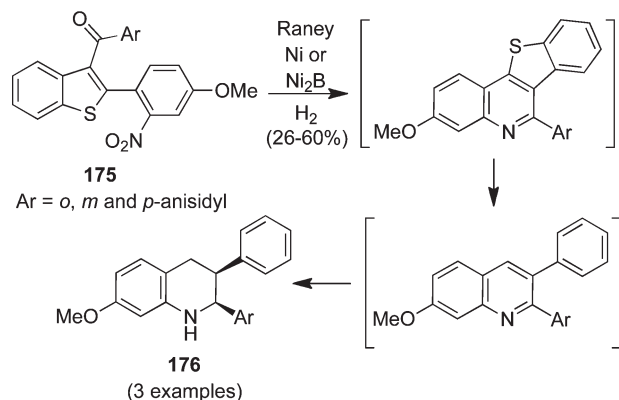
**4.2.8. Intramolecular Oxidative Cyclization/Lactamization.** An iridium-catalyzed oxidative cyclization of aromatic amino alcohols to indoles and 1,2,3,4-tetrahydroquinolines was demonstrated by Fujita and co-workers. Ir[Cp\*IrCl<sub>2</sub>]<sub>2</sub>/K<sub>2</sub>CO<sub>3</sub> was identified as the best catalytic system after systematic screening experiments. A broad variety of 3-(2-aminophenyl)propanols bearing substituents on the aryl ring and the side chain afforded 1,2,3,4-tetrahydroquinolines in the presence of 5 mol % of the catalyst in very good yields.<sup>228</sup> A couple of years later, the authors noticed that the use of a Cp\*Rh catalyst in acetone for the previous reaction allowed the intramolecular lactamization instead of N-alkylation (Scheme 28).<sup>229</sup>

A plausible mechanism was proposed involving an initial catalytic oxidation of alcohol to generate the aldehyde intermediate

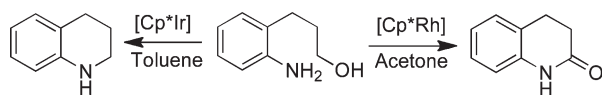
A and an iridium-hydride species (Scheme 29).<sup>230</sup> Subsequently, intermediate A undergoes a noncatalytic intramolecular cyclization to give aminal B and then imine C, which reacts with the iridium-hydride species to furnish the amido iridium intermediate D. This intermediate then reacts with another molecule of the starting amino alcohol to complete the catalytic cycle, leading to the final 1,2,3,4-tetrahydroquinoline. The mechanism proposed for the rhodium-catalyzed intramolecular lactamization of the amino alcohols involves the reaction of B with the rhodium catalyst and a molecule of acetone to give E, which then evolves to the observed product and regenerates the catalyst.

**4.2.9. Pd-Catalyzed Cross-Coupling.** The palladium-catalyzed cross-coupling reaction between *o*-allylic or *o*-vinyl anilines **177** and vinylic halides or triflates **178** afforded tetrahydroquinolines or indolines **179**.<sup>231</sup> It was found that the nature of the substituent on the nitrogen played a vital role in the reaction, with *N*-tosyl-substituted substrates generally giving higher yields. The reactions probably proceed through the  $\sigma$ -

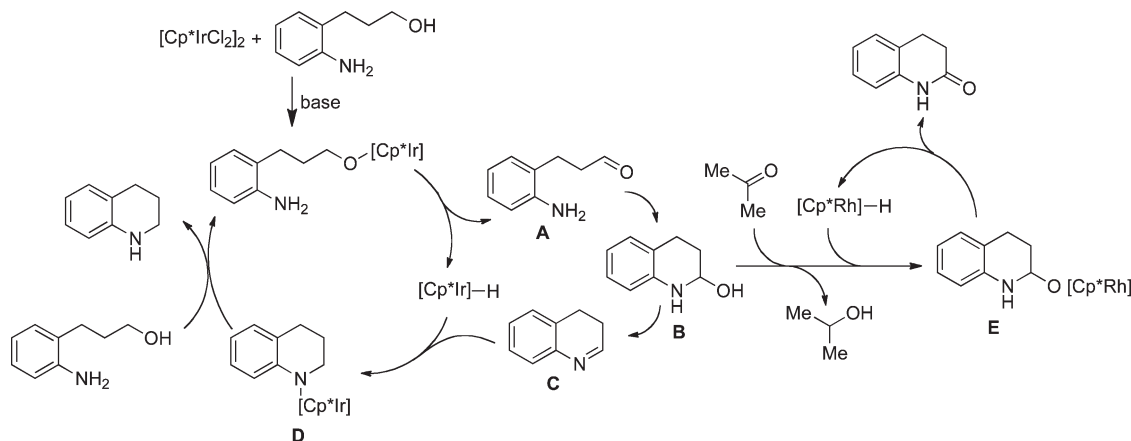
**Scheme 27. Ni-Catalyzed Reduction–Cyclization–Desulfurization Sequence**



**Scheme 28. Ir-Catalyzed Oxidative Cyclization and Rh-Catalyzed Intramolecular Lactamization**



**Scheme 29. Proposed Mechanism for the Oxidative Cyclization and Intramolecular Lactamization Reactions**



alkylpalladium and  $\pi$ -allylpalladium intermediates A and C. The drawback of this methodology is the irreversible elimination of palladium hydride from complex B, which is presumably responsible for the formation of side product **180** (Scheme 30). The extension of this methodology to the synthesis of dihydroquinolines and a full paper elaborating these results subsequently appeared in the same year.<sup>232</sup>

**4.2.10. Miscellaneous Reactions.** Yang and co-workers reported a simple and convenient procedure for the synthesis of 3-aryl-1,2,3,4-tetrahydroquinoline derivatives **182** in moderate to good yield starting from 2-aryl-3-(2-nitrophenyl)-propionitrile **181**, derived from 2-nitroarylaldehydes, through an intramolecular reductive cyclization.<sup>233</sup> Some of the compounds thus obtained were transformed into the estrogen receptor  $\beta$ -agonists **49** (Scheme 31).<sup>103</sup>

Solé, Bonjoch, and co-workers reported an unusual conversion of  $\alpha$ -(2-nitrophenyl) enones to bridged tetrahydroquinolines in the presence of TBAF in DMF-HMPA.<sup>234</sup> Thus, the  $\alpha$ -(2-nitrophenyl) enone **183** reacted with TBAF to furnish a mixture of tetrahydroquinoline derivative **184** and the protodesilylation product **185** in low yields. The authors proposed a mechanism for the formation of compound **184** considering compound **185** as the intermediate, where the initial step involves a nucleophilic attack of the enolate on the nitro group followed by formylation with DMF to give intermediate A. Subsequent elimination of CO<sub>2</sub> furnishes the hydroxylamine intermediate **186**, which undergoes a second formylation-reduction sequence to afford tetrahydroquinoline **184** (Scheme 32).

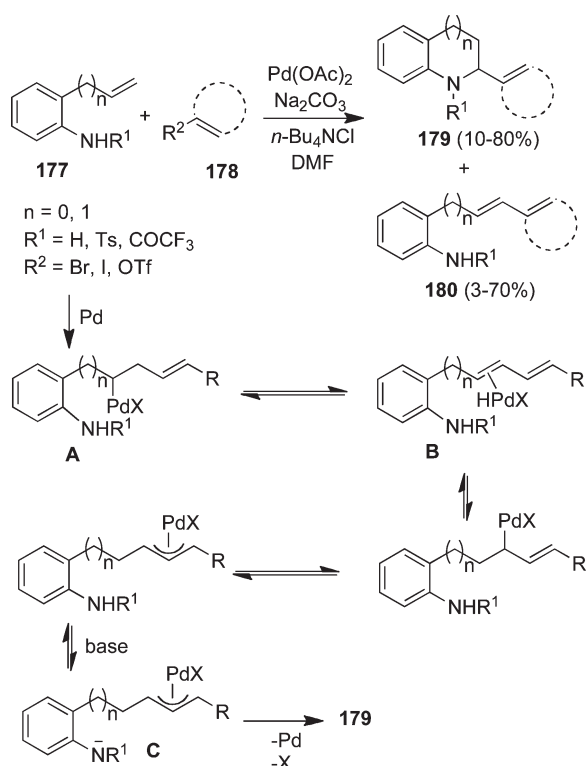
Perumal and co-workers demonstrated the efficiency of the indium(III) chloride-SiO<sub>2</sub> catalytic system for the microwave-assisted cyclization of 2-aminochalcones to 2-aryl-2,3-dihydroquinolin-4(1H)-ones through an intramolecular aza-Michael reaction.<sup>235</sup> *N*-Isopropyl and *N*-benzyl-2-(2-cyclohexenyl)anilines reacted with iodine under basic conditions to afford 1-iodo-hexahydrocarbazoles which underwent quantitative isomerization into 3-iodo-2,4-propano-1,2,3,4-tetrahydroquinolines.<sup>236</sup>

### 4.3. Formation of the C<sub>2</sub>–C<sub>3</sub> Bond

**4.3.1. *tert*-Amino Effect.** The synthesis of 1,2,3,4-tetrahydroquinolines by constructing the C<sub>2</sub>–C<sub>3</sub> bond is atypical, and the few examples that are illustrated in the literature are normally rooted in the *tert*-amino effect, an unusual cyclization reaction of some *ortho*-substituted tertiary anilines to afford fused ring systems (see also section 5.5).<sup>237</sup> This reaction involves a 1,5-hydride shift-ring



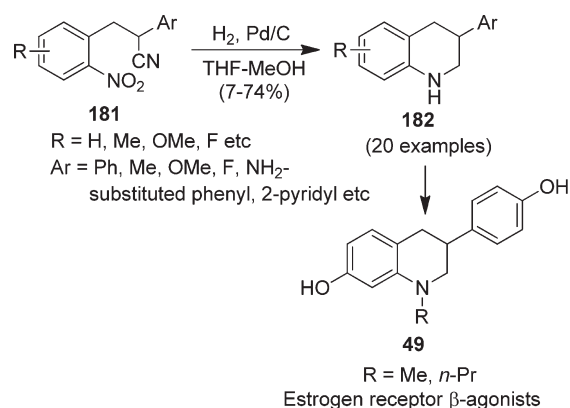
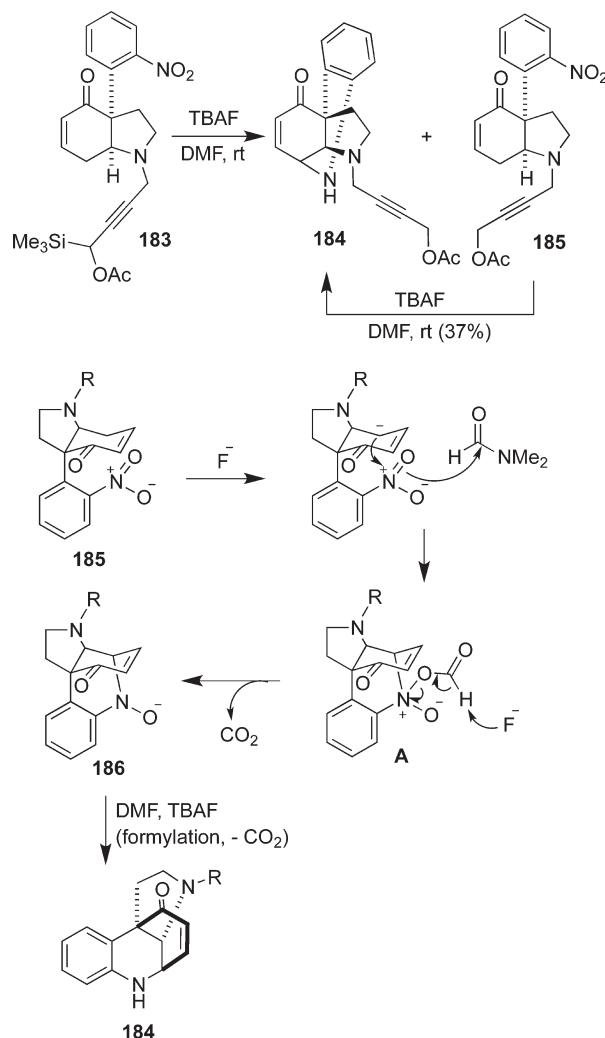
Scheme 30. Pd-Catalyzed Cross-Coupling Reactions for the Synthesis of Tetrahydroquinolines



closure sequence from tertiary anilines that can be considered as an intramolecular redox process. In Reinhoubt's original report<sup>238</sup> for the synthesis of tetrahydroquinoline derivatives involving *tert*-amino effect, the reaction was carried out under thermal conditions but Seidel and co-workers have recently demonstrated the use of Lewis acid catalysts for the transformation of compounds **187** into the products **188** under mild conditions at room temperature.<sup>239</sup> Among the tested Lewis acids, scandium triflate was highly effective but gadolinium triflate was found to be superior, and was assumed to activate the substrates by coordinating with malonate unit thereby inducing the 1,5-hydride shift-cyclization sequence. This protocol allowed the synthesis of a large number of simple and fused tetrahydroquinolines based on the nature of substituents on the nitrogen atom (Scheme 33). Subsequently, an asymmetric variation of this reaction for the synthesis of optically active ring-fused tetrahydroquinolines in high enantioselectivities was also described, using chiral catalysts that combined metal salts and oxazolinine-derived chiral ligands.<sup>240</sup>

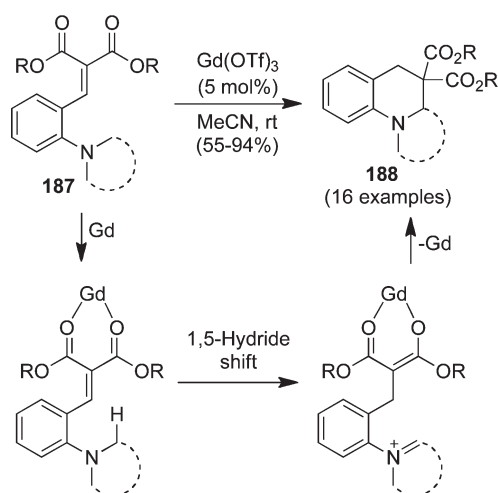
The synthesis of 1,2,3,4-tetrahydroquinoline-3-carboxylic acids **190** was achieved in one-pot fashion in good yields starting from *ortho*-dialkylaminoaldehydes **189** and Meldrum's acid in the presence of chlorotrimethylsilane in DMF.<sup>241</sup> Mechanistically speaking, compounds **189** were assumed to react with Meldrum's acid to afford spiro compounds **A**, which were then converted into the observed carboxylic acid derivatives under the acidic reflux conditions prevalent in the reaction medium. This mechanism was confirmed by isolation of the proposed intermediates **A** (Scheme 34).

Other examples of the use of *tert*-amino effect for the synthesis of tetrahydroquinoline derivatives include the synthesis of 1,2,3,4-tetrahydroquinoline-2-spirocycloalkanes,<sup>242</sup> and barbituric acid

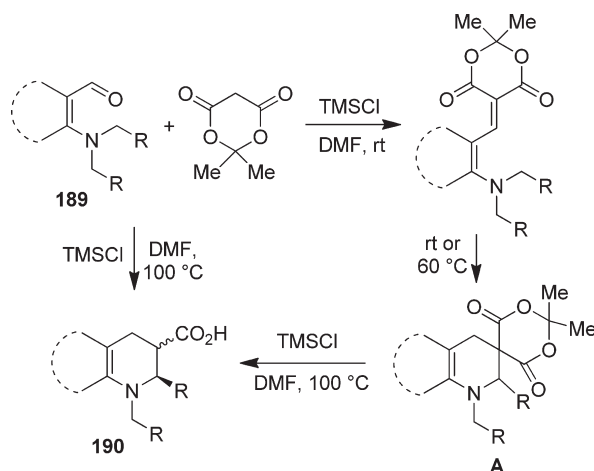
Scheme 31. Synthesis of Estrogen Receptor  $\beta$ -Agonists **49** via Intramolecular Reductive Cyclization ReactionScheme 32. Solé and Bonjoch's Synthesis of Tetrahydroquinoline **184** and Their Proposed Mechanism

attached 3-spiro-tetrahydroquinolines.<sup>243,244</sup> Other advances in this reaction are the use of microwave assistance for cyclization reactions carried out in solution<sup>245</sup> and also under solvent-free conditions.<sup>246</sup>

**Scheme 33.** Gd(OTf)<sub>3</sub>-Catalyzed Synthesis of Tetrahydroquinolines **188** Involving *tert*-Amino Effect



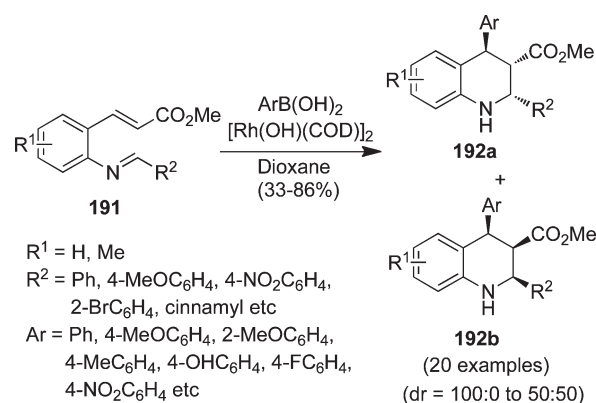
**Scheme 34.** TMSCl-Mediated Synthesis of 1,2,3,4-Tetrahydroquinoline-3-carboxylic acids **190**



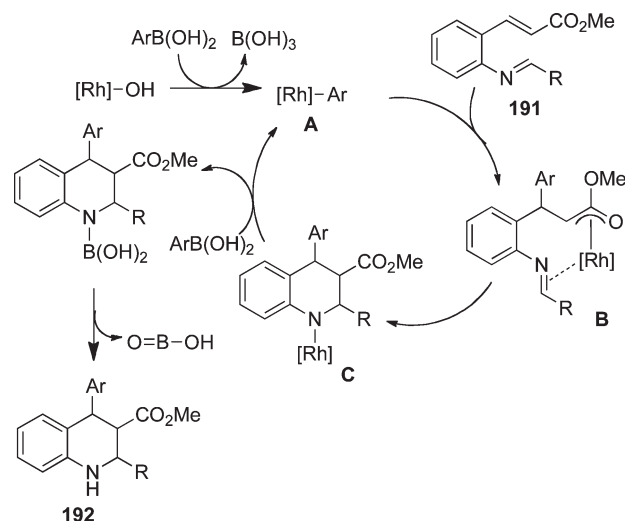
**4.3.2. Conjugate Addition—Cyclization Sequence.** The next method to be discussed that involves the creation of the C<sub>2</sub>–C<sub>3</sub> bond is the intramolecular cyclization of imine-substituted electron-deficient alkenes. Youn and co-workers demonstrated a rhodium-catalyzed domino conjugate addition–Mannich cyclization sequence of compound **191** for the synthesis of 2,3,4-trisubstituted-1,2,3,4-tetrahydroquinolines **192**. The starting materials reacted with arylboronic acids in the presence of [Rh(OH)(COD)]<sub>2</sub> to give diastereomeric mixtures of the tetrahydroquinolines in good yields (Scheme 35).<sup>247</sup>

The authors suggested a mechanism based on the one proposed for related Rh-catalyzed domino cyclizations triggered by conjugate addition with organoboronic acids.<sup>248</sup> The initial step of the reaction was proposed to be the generation of organorhodium(I) species **A** from transmetalation of the Rh-catalyst with the starting arylboronic acid. The conjugate addition of species **A** to the substrate **191** affords the (oxa- $\pi$ -allyl)rhodium(I) intermediate **B**, which subsequently undergoes intramolecular nucleophilic addition to form intermediate **C**. Another molecule of the arylboronic acid reacts with the latter to

**Scheme 35.** Rh-Catalyzed Domino Conjugate Addition–Mannich Cyclization Sequence



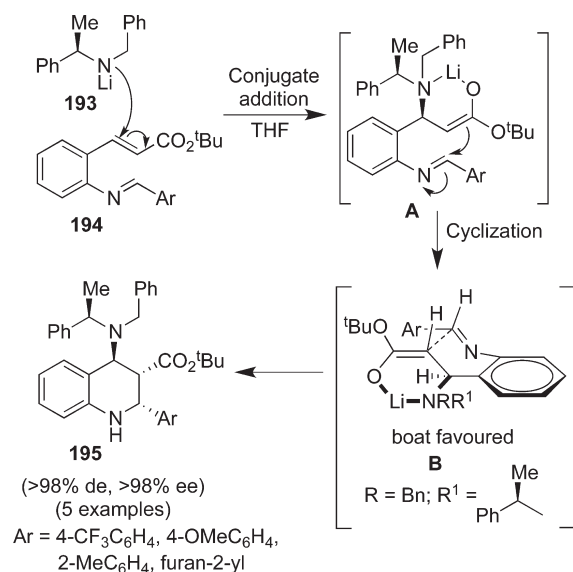
**Scheme 36.** Mechanistic Proposal for the Formation of Tetrahydroquinolines **192**



furnish the product **192** and the organorhodium(I) species **A**, thus closing the catalytic cycle (Scheme 36).

A procedure that can be considered as rather similar to the previous one, although with potential advantages, was developed recently for the synthesis of chiral 4-amino-1,2,3,4-tetrahydroquinolines substituted at C-2 and C-3. This method involves the tandem conjugate addition–cyclization of lithium (*R*)-*N*-benzyl-*N*-( $\alpha$ -methylbenzyl)amide **193** to aromatic imines, **194**, bearing an electron-deficient alkene substituent in the *ortho* position to give 2-aryl-4-aminotetrahydroquinoline-3-carboxylic acid derivatives **195** in excellent diastereo- and enantioselectivities (Scheme 37),<sup>249</sup> which could be explained through the formation of highly rigid intermediates **A** and **B**. Conjugate addition of the optically pure lithium amide gives the lithium (*Z*)- $\beta$ -amino enolate intermediate **A**, fixing the C-4 stereocenter. The next cyclization of the intermediate **A** proceeds in an excellent *anti*-selectivity because of the reaction of the lithium–nitrogen chelated enolate on the least hindered face through the boat-like intermediate **B**. Subsequently, the substituents on the C-4 nitrogen were successfully removed by Pd(OH)<sub>2</sub>/C-catalyzed hydrogenation to give the free amino group, while maintaining

Scheme 37. Tandem Conjugate Addition–Cyclization Sequence

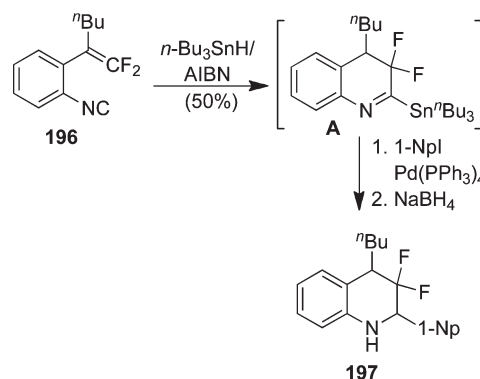
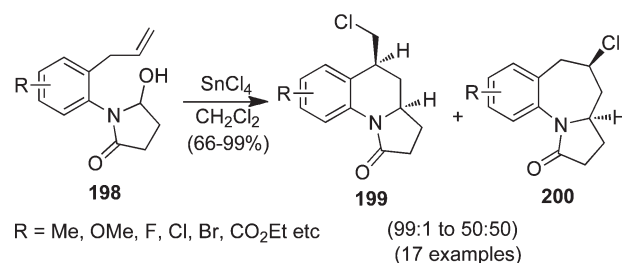


the diastereo- and enantiopurities, affording materials that may be used as intermediates for the synthesis of some tetrahydroquinoline natural products.

**4.3.3. Miscellaneous Reactions.** Mori and Ichikawa reported an interesting one-pot synthesis of 4-*n*-butyl-3,3-difluoro-2-naphthyl-1,2,3,4-tetrahydroquinoline **197** based on a tin-mediated radical cyclization of the *ortho*-isocyanostyrene derivative **196** followed by a substitution-reduction sequence.<sup>250</sup> Treatment of the starting compound **196** with *n*-Bu<sub>3</sub>SnH in the presence of AIBN triggered a 6-endo-trig radical cyclization that afforded the 2-stannyl intermediate **A**, which was subsequently transformed into the corresponding 2-(1-naphthyl) derivative through a palladium-catalyzed Stille coupling. The final sodium borohydride reduction of the dihydroquinoline intermediate furnished 1,2,3,4-tetrahydroquinoline **197** in overall 50% yield starting from **196** (Scheme 38). This procedure was also employed for the synthesis of 2-aryl-3-fluoroquinoline derivatives through a Stille coupling, followed by dehydrofluorination of the 2-stannyl intermediate **A**.

Recently, the synthesis of pyrroloquinoline derivatives **199** was achieved involving a SnCl<sub>4</sub>-mediated cyclization of the 1-aryl- $\gamma$ -hydroxylactams **198**.<sup>251</sup> A broad variety of compounds **198** reacted with SnCl<sub>4</sub> to afford pyrroloquinolines **199** in high yields together with small amounts of the pyrrolobenzazepine derivatives **200**. A number of protic and Lewis acids including TFA, formic acid, TiCl<sub>4</sub>, ZnCl<sub>2</sub>, AlCl<sub>3</sub>, FeCl<sub>3</sub>, and SnCl<sub>4</sub> were tested for the cyclization and the latter one was found to be superior. The reaction was proposed to proceed through a *N*-acyliminium ion<sup>252</sup> intermediate involving a 7-endo-trig cyclization followed by a cationic rearrangement (Scheme 39).

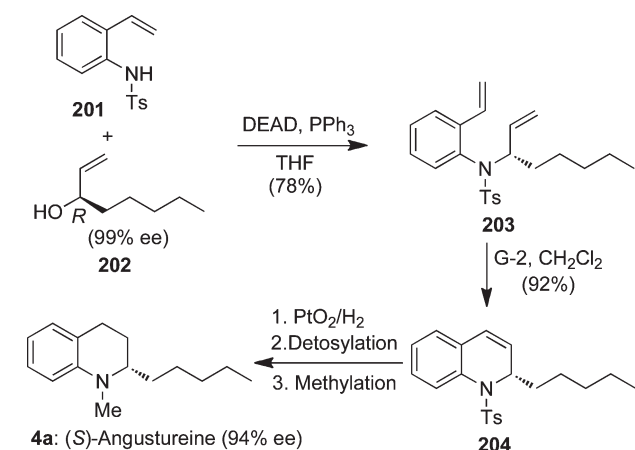
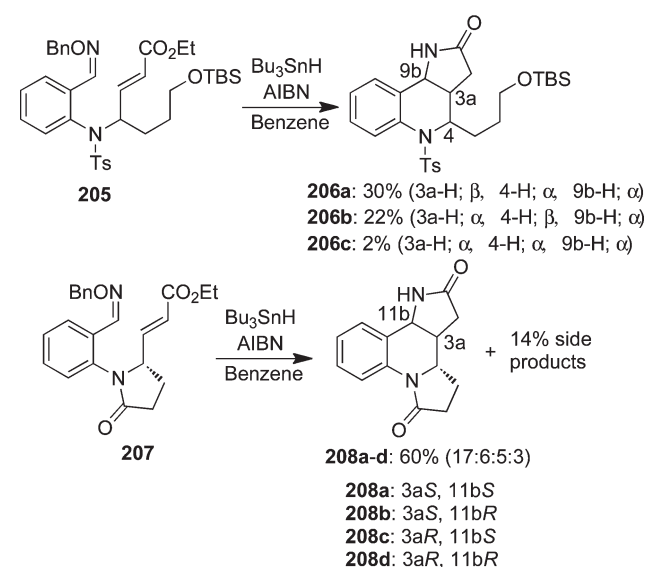
Although cannot be considered a general method for the synthesis of tetrahydroquinolines, it should be mentioned here that the thermal intramolecular annulation of *N*-(2-alkenyl-phenyl)amino-substituted Fischer chromium carbenes gave a mixture of indoles, quinolines and 1,2,3,4-tetrahydroquinolines, depending on the reaction conditions. In a few cases, the tetrahydroquinolines were the major products with yields up to 70%.<sup>253</sup>

Scheme 38. Bu<sub>3</sub>SnH/AIBN-Mediated Radical Cyclization–Pd-Catalyzed Stille Coupling–NaBH<sub>4</sub> Reduction SequenceScheme 39. SnCl<sub>4</sub>-Mediated Cyclization of 1-Aryl- $\gamma$ -hydroxylactams **198**

#### 4.4. Formation of the C<sub>3</sub>–C<sub>4</sub> Bond

**4.4.1. Ring-Closing Metathesis.** The naturally occurring (+)-(*S*)-angustureine **4a** was synthesized using Mitsunobu and ring-closing metathesis reactions as key steps and its absolute configuration was also determined.<sup>254</sup> The intermediate 2-vinyl-*N*-tosylaniline **201** was synthesized from 2-nitrobenzaldehyde in three steps, and was subsequently treated with the readily available chiral secondary alcohol **202** (available in 99% *ee*) under Mitsunobu conditions to afford the metathesis precursor **203**. The RCM reaction was achieved using Grubbs second generation catalyst to allow the creation of the C<sub>3</sub>–C<sub>4</sub> bond of a dihydroquinoline derivative (compound **204**), which was then converted into the enantiomer of the natural product in a completely stereodefined manner by hydrogenation, detosylation, and methylation reactions (Scheme 40). The natural product was thus found to have the *R* configuration. A year later the authors published a detailed article summarizing their previous achievements on the use of RCM for the synthesis of natural products including quinolines and tetrahydroquinolines.<sup>255</sup>

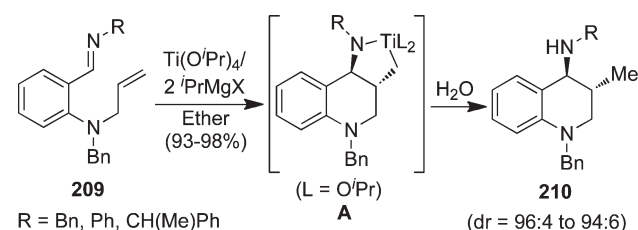
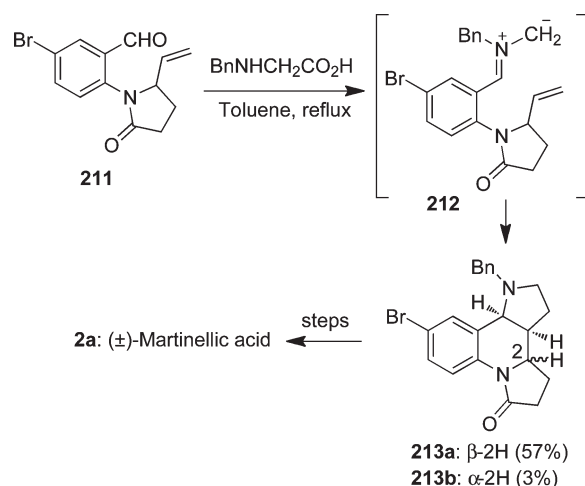
**4.4.2. Intramolecular Cyclization of ene-C=N Moiety.** A Bu<sub>3</sub>SnH-promoted radical addition–cyclization–elimination (RACE) strategy was developed for the construction of the pyrroloquinoline moiety in the formal total synthesis of the natural product martinelline **2b**,<sup>256</sup> which was further extended to the asymmetric total synthesis of (–)-martinelline acid **2a**.<sup>257</sup> Oxime ethers **205** afforded a mixture of diastereomers **206a–c** upon treatment with Bu<sub>3</sub>SnH and AIBN in refluxing benzene in a 15:11:1 ratio, where the diastereomer **206b**, required for the total synthesis of the natural product, was minor. However, an oxime ether bearing a 2-pyrrolidone moiety (compound **207**) gave

**Scheme 40. Synthesis of (+)-(S)-Angustureine 4a Involving Mitsunobu and RCM Reactions****Scheme 41. Bu<sub>3</sub>SnH-Promoted Radical Addition—Cyclization—Elimination (RACE) Sequence**

tetrahydroquinoline **208**, again as a diastereomeric mixture, but this time the desired diastereomer was the major one (Scheme 41).

Okamoto and co-workers reported a novel synthesis of 1,2,3,4-tetrahydroquinoline derivatives through a cyclization of  $\omega$ -vinylimines with  $\text{Ti}(\text{O-}i\text{-Pr})_4/i\text{-PrMgX}$ .<sup>258</sup> Treatment of the enimes **209** with the titanium reagent followed by addition of water afforded the 3,4-disubstituted tetrahydroquinolines **210** through intermediate **A** in excellent yields and diastereoselectivities (Scheme 42). The reaction allowed the introduction of other substituents, such as hydroxyl and iodo groups at the C-3 methyl group by the addition of oxygen or iodine, respectively, after treatment with the titanium reagent.

**4.4.3. Azomethine Ylide—Alkene Cycloaddition.** Snider and co-workers developed a novel intramolecular [3 + 2] azomethine ylide cycloaddition for the construction of the pyrroloquinoline ring system of martinellie acid **2a**,<sup>259</sup> which

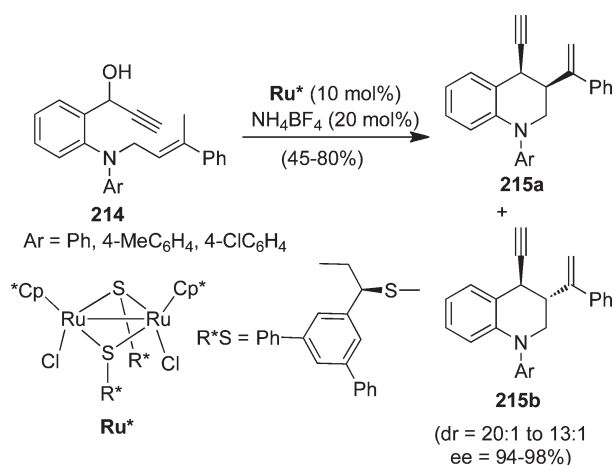
**Scheme 42. Cyclization of  $\omega$ -Vinylimines with  $\text{Ti}(\text{O-}i\text{-Pr})_4/i\text{-PrMgX}$** **Scheme 43. Synthesis of ( $\pm$ )-Martinellie Acid 2a Involving Intramolecular [3 + 2] Azomethine Ylide Cycloaddition**

was then successfully employed for its total synthesis.<sup>260</sup> The suitably substituted aryl aldehyde **211** was treated with *N*-benzylglycine to generate the azomethine ylide **212**, through an iminium salt, which then underwent an intramolecular cycloaddition to afford the pyrroloquinoline **213** in acceptable yield (Scheme 43).

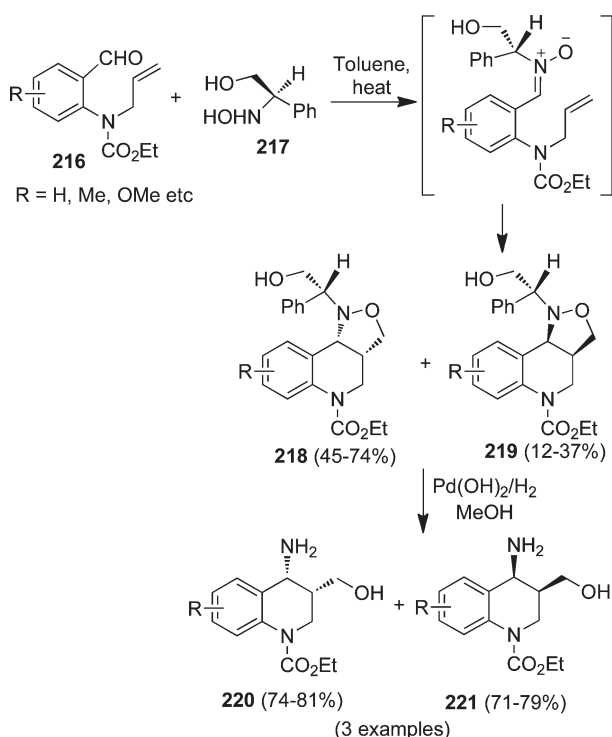
Concurrently, Lovely and co-workers reported their findings on the construction of pyrroloquinoline moiety of martinellie acid using similar cycloaddition strategy.<sup>261</sup> Subsequent developments on Lovely's investigation include the introduction of bromo and ester substituents at the C-7 carbon,<sup>262</sup> creation of a carbonyl function at C-2,<sup>263</sup> and further structural manipulations to achieve the formal total synthesis of martinellie acid **2a**,<sup>264</sup> which was subsequently followed by its synthesis in enantiopure form.<sup>265</sup>

**4.4.4. Miscellaneous Reactions.** Nishibayashi and co-workers illustrated a ruthenium catalyzed enantioselective synthesis of chromane, thiochromane, and tetrahydroquinoline derivatives. For instance, the reactions of propargylic alcohols, **214**, bearing an allylic amine moiety with 10 mol % of an optically active thiolate-bridged diruthenium complex and 20 mol % of  $\text{NH}_4\text{BF}_4$  furnished the corresponding tetrahydroquinolines **215** in good yields and excellent enantioselectivities (Scheme 44).<sup>266</sup>

The enantioselective synthesis of 4-amino-3-hydroxymethyl-1,2,3,4-tetrahydroquinolines **220** and **221** was attained through a strategy based on the intramolecular 1,3-dipolar cycloaddition of nitrones. The procedure involved the synthesis of 2-(*N*-allyl)-arylaldehydes **216** using the Vilsmeier reaction followed by

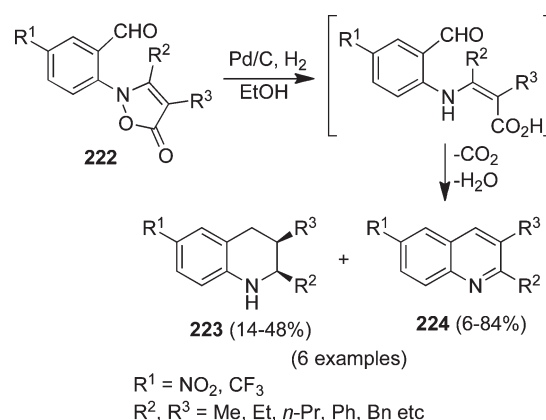
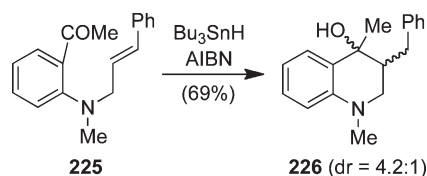
Scheme 44. Ru-Catalyzed Enantioselective Synthesis of Tetrahydroquinolines **215**

Scheme 45. Synthesis of Tetrahydroquinolines via 1,3-Dipolar Cycloaddition of Nitrones



intramolecular cycloaddition of the *N*-allyl group with nitrone moiety, generated in situ from the reaction between the aldehyde and chiral hydroxylamine **217**. The final ring-opening of the isoxazolidine intermediates **218** and **219** with Pd(OH)<sub>2</sub>/H<sub>2</sub> system afforded the final products **220** and **221** (Scheme 45).<sup>267</sup>

In a report related to the synthesis of quinolines **224** through catalytic hydrogenation of 2-(2-formylphenyl)isoxazolin-5(2*H*)-ones **222**, the corresponding tetrahydroquinolines **223** were also obtained in poor to moderate yields (Scheme 46).<sup>268</sup> The substrates bearing a nitro group on the aryl ring were also reduced to the corresponding amino derivatives.

Scheme 46. Synthesis of Tetrahydroquinolines via Catalytic Hydrogenation of **222**Scheme 47. Bu<sub>3</sub>SnH/AIBN-Mediated Cyclization of Aryl Amine **225**

The Bu<sub>3</sub>SnH/AIBN-mediated cyclization of aryl amine **225** derived from *N*-methyl-2-aminoacetophenone and cinnamyl bromide afforded 1,2,3,4-tetrahydroquinoline **226** in 69% yield as a 4.2:1 inseparable mixture of diastereomers. The procedure was also used for the synthesis of tetrahydroquinolones, tetrahydrofurans, tetrahydropyrans, chromanols, and related compounds (Scheme 47).<sup>269</sup>

Procter and co-workers disclosed a novel procedure for the synthesis of tetrahydroquinolones involving an intramolecular cyclization of  $\alpha$ -sulfonyl amides.<sup>270</sup> Thus, the sulfones of  $\alpha$ -sulfonyl amides **227**, derived from the corresponding *ortho*-bromo derivatives via Heck coupling followed by oxidation, underwent intramolecular cyclization to provide tetrahydroquinolones **228** in the presence of K<sub>2</sub>CO<sub>3</sub>. The sulfone unit was then removed successfully by treatment with SmI<sub>2</sub>. Interestingly, introduction of substituents at the sulfur-attached carbon of compound **228** and subsequent removal of the sulfone moiety allowed the access to less common 3-substituted tetrahydroquinoline derivatives **229**. A solid-phase approach to the same reaction was also developed starting from a benzylthiol resin (Scheme 48).

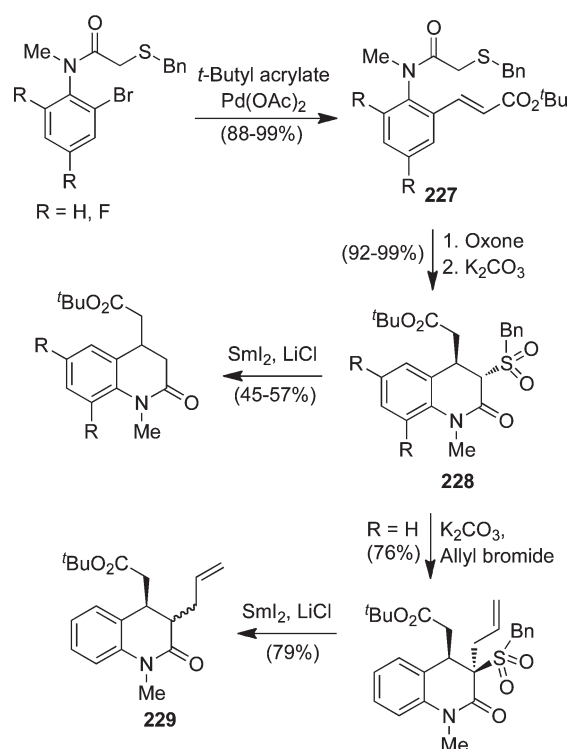
It is also relevant to mention here that some fused tetrahydroquinoline derivatives were synthesized based on an ethylenediamine diacetate-catalyzed one-pot domino Knoevenagel/hetero-Diels–Alder reaction sequence starting from 1,3-dicarbonyl compounds and which creates a new C<sub>3</sub>–C<sub>4</sub> bond.<sup>271</sup> The synthesis of a set of novel heterocycles including pyrrolizines and indolizines bearing a tetrahydroquinoline fragment was achieved via intramolecular [3 + 2] cycloaddition.<sup>272</sup>

#### 4.5. Formation of the C<sub>4</sub>–C<sub>4a</sub> Bond

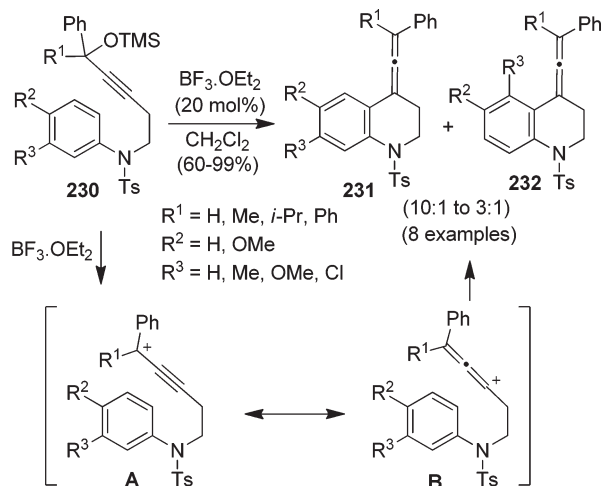
**4.5.1. Intramolecular Friedel–Crafts-Related Reactions.** Ishikawa and co-workers developed an expedient method



**Scheme 48. Tetrahydroquinoline Synthesis Involving Intramolecular Cyclization of  $\alpha$ -Sulfonyl Amides**



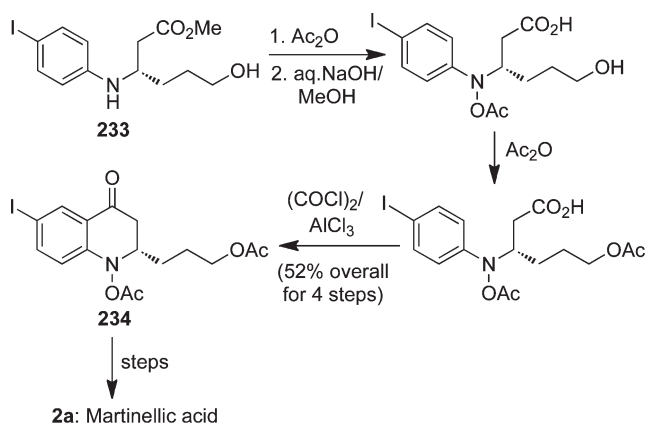
**Scheme 49. Ishikawa's Tetrahydroquinoline Synthesis Based on Lewis Acid-Catalyzed Intramolecular Friedel–Crafts Reaction**



for the synthesis of 4-vinylidenetetrahydroquinolines based on a Lewis acid-catalyzed intramolecular Friedel–Crafts reaction. A variety of  $N$ -tosyl propargyl silyl ethers **230** were smoothly transformed into the corresponding tetrahydroquinolines, through the cationic intermediates **A** and **B**, as a mixture of two possible regioisomers **231** and **232**, in good to excellent yields in the presence of 20 mol % of  $\text{BF}_3 \cdot \text{OEt}_2$  (Scheme 49).<sup>273</sup>

The first total synthesis of martinelllic acid **2a** was established by Ma, where the key reaction for the construction of the

**Scheme 50. Ma's First Total Synthesis of Martinelllic Acid **2a****

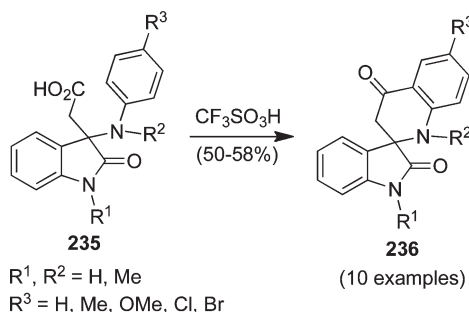


tetrahydroquinoline moiety was an intramolecular Friedel–Crafts acylation. The  $N$ -aryl  $\beta$ -amino ester **233** was transformed into compound **234**, a martinelllic acid intermediate, in four steps that included protection, hydrolysis, reprotection and  $\text{AlCl}_3$ -catalyzed acylation reactions in 52% overall yield (Scheme 50).<sup>274</sup> A couple of years later the authors extended their study giving a special emphasis to the  $\text{CuI}$ -catalyzed coupling route to martinelllic acid, there again the tetrahydroquinoline ring was created through an intramolecular acylation reaction.<sup>275</sup> This protocol was also utilized for an efficient synthesis of optically pure (*S*)-2-functionalized 1,2,3,4-tetrahydroquinoline derivatives from  $N$ -aryl  $\beta$ -amino acids<sup>276</sup> and to synthesize a library of 4-spirotetrahydroquinolines.<sup>277</sup> A similar intramolecular Friedel–Crafts acylation strategy was also used for the synthesis of tetrahydroquinoline-based CRTH2 antagonists.<sup>97</sup>

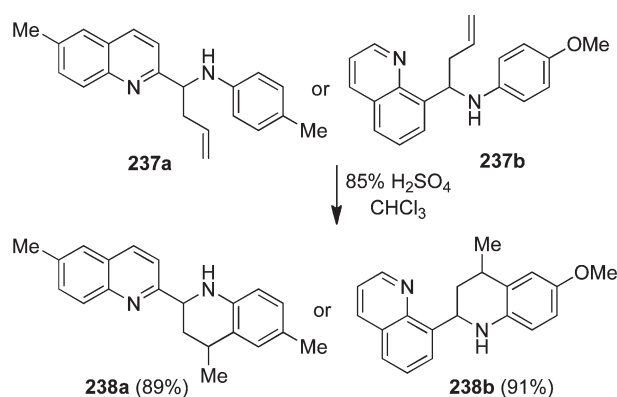
It is interesting to note that a wide variety of oxindoles **235** underwent an intramolecular cyclodehydration reaction to afford spiro-tetrahydroquinolines **236** in the presence of triflic acid in moderate yields.<sup>278</sup> The precursors were synthesized from isatin in three straightforward steps, namely, base-catalyzed condensation with malonic acid,  $\text{HBr}$  addition, and substitution of arylamines (Scheme 51).

Recently, Kouznetsov and co-workers demonstrated the synthesis of biquinoline derivatives based on a sulfuric acid-catalyzed intramolecular cyclization of homoallyl amines, which were readily prepared from the corresponding quinolinecarboxaldehydes and primary amines, in excellent yields. For instance, the homoallyl amines **237** afforded the corresponding tetrahydroquinolines **238** in excellent yields in the presence of sulphuric acid (Scheme 52).<sup>279</sup> The Povarov reaction, which will be discussed in section 6.1 in detail, was also employed for the construction of the tetrahydroquinoline ring. A similar approach was also used for the synthesis of simple antifungal 1,2,3,4-tetrahydroquinolines<sup>47,48,280</sup> and 2-spirotetrahydroquinolines.<sup>281</sup>

The acid-catalyzed cyclization of 1-allyl-1- $N$ -arylamino-cyclohexanes afforded spiro-tetrahydroquinolines together with an unexpected product obtained through an intramolecular *ipso*-substitution–alkylation sequence. For instance, the *o*-ethylphenyl amine **239** afforded a 65:25 mixture of isomeric tetrahydroquinolines **240** and **241** upon acid treatment. The formation of **241** could be explained by attack of the carbocation generated by the acid to the ethyl substituted *ipso*-carbon followed by a 1,2-shift of the ethyl group (Scheme 53).<sup>282,283</sup>

Scheme 51. Synthesis of *spiro*-Tetrahydroquinolines 236

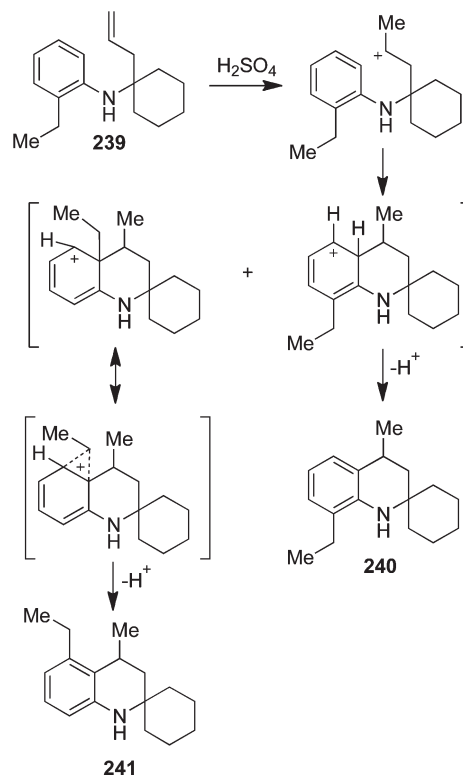
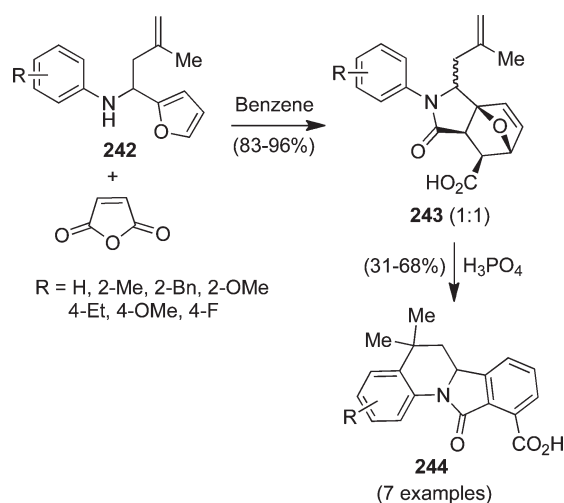
Scheme 52. Kouznetsov's Synthesis of Tetrahydroquinolines Bearing a Quinoline Moiety



Zubkov and co-workers demonstrated an efficient synthesis of tetrahydroquinolines containing an isoindolo[2,1-*a*]quinoline skeleton in two steps starting from homoallylamines, based on a [4 + 2] cycloaddition followed by acid-catalyzed intramolecular cyclization.<sup>284,285</sup> The furyl substituted homoallylamines **242** underwent N-acylation and a subsequent intramolecular Diels–Alder reaction to afford the carboxylic acid derivatives **243** in excellent yields, which were further treated with phosphoric acid to obtain tetrahydroquinoline derivatives **244** through a dehydration-intramolecular cyclization sequence (Scheme 54). Subsequently the procedure was extended to the synthesis of halogenated tetrahydroquinoline analogues.<sup>286</sup>

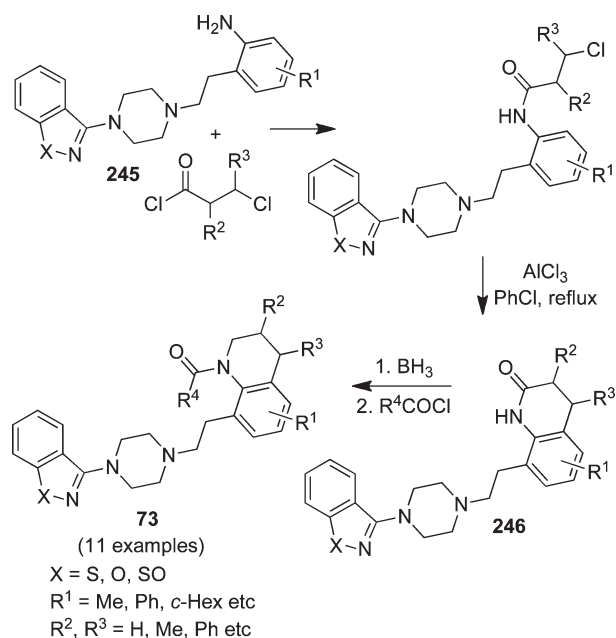
A library of novel potent dopamine subtype 2 (DA D<sub>2</sub>) active tetrahydroquinolines with serotonin subtype 2A (5-HT<sub>2A</sub>) selectivity was synthesized by means of an intramolecular Friedel–Crafts cyclization.<sup>141</sup> The arylamine precursors **245** were synthesized from commercially available aryl acetic acids in four steps, which underwent further N-acylation and AlCl<sub>3</sub>-catalyzed cyclization reactions to afford tetrahydroquinolones **246**. The subsequent BH<sub>3</sub> reduction–N-acylation sequence furnished the corresponding tetrahydroquinolines derivatives **73**, which showed potential in vitro affinity to DA D<sub>2</sub> and 5-HT<sub>2A</sub> receptors (Scheme 55).

The key step for the synthesis of *N*-alkyl tetrahydroquinolines **62**, which are potent retinoid A receptor (RAR $\gamma$ ) agonists, was the AlCl<sub>3</sub>-catalyzed intramolecular Friedel–Crafts cyclization.<sup>127</sup> The starting compounds **247** and **249**, derived from the corresponding arylamines, were treated with AlCl<sub>3</sub> at elevated temperatures to afford the corresponding tetrahydroquinolones,

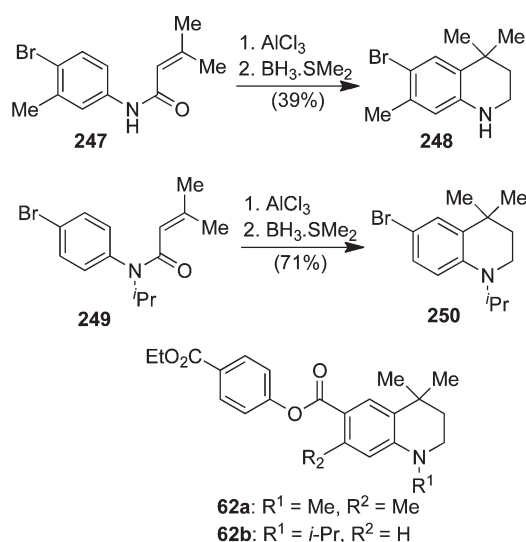
Scheme 53. Formation of Unexpected Tetrahydroquinoline 241 via Intramolecular *ipso*-Substitution–Alkylation SequenceScheme 54. Synthesis of Tetrahydroquinolines Bearing Isoindolo[2,1-*a*]quinoline Skeleton

which were subsequently reduced to tetrahydroquinoline derivatives **248** and **250** using borane-dimethyl sulfide complex. Further structural manipulation of these compounds afforded the biologically important tetrahydroquinolines **62** (Scheme 56). A rather similar procedure was also used for the synthesis of 4,4-dimethyl-1,2,3,4-tetrahydroquinoline, a precursor for the tetrahydroquinoline-derived peroxisome proliferator activated receptor (PPAR $\alpha/\gamma$ ) agonists.<sup>129</sup>

**Scheme 55. Synthesis of Dopamine Subtype 2 (DA D<sub>2</sub>) Active Tetrahydroquinolines 73**



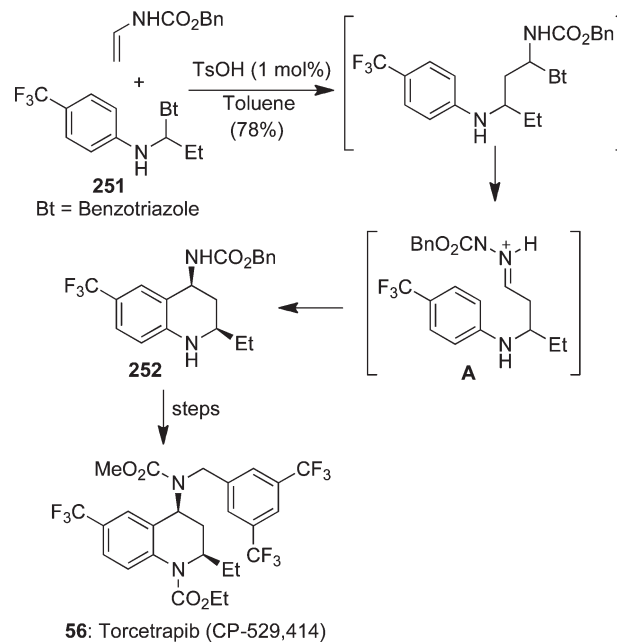
**Scheme 56. Synthesis of Retinoid A Receptor (RAR $\gamma$ ) Agonists 62**



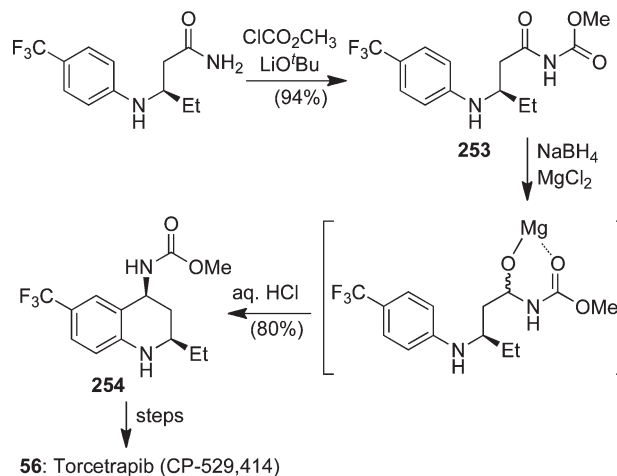
**4.5.2. Acyl Iminium Cyclization.** A multikilogram scale synthesis of torcetrapib (CP-529,414, **56**), an inhibitor of cholesteryl ester transfer protein (CETP), was established through an intramolecular acyl iminium cyclization reaction to construct the tetrahydroquinoline core. Since the simple Povarov reaction gave low conversion and purity, the authors synthesized the benzotriazole adduct of the imine **251**,<sup>287</sup> which reacted smoothly with the vinyl carbamate in the presence of catalytic amount of TsOH to afford the corresponding tetrahydroquinoline **252** via the acyl iminium cation intermediate **A** (Scheme 57).<sup>288</sup>

Simultaneously, the same group developed an efficient route for the synthesis of enantiopure torcetrapib **56**, again in

**Scheme 57. Multikilogram Scale Synthesis of Cholesteryl Ester Transfer Protein (CETP) Inhibitor Torcetrapib (CP-529,414, **56**)**

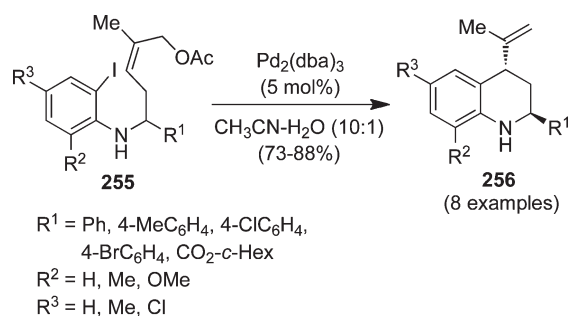


**Scheme 58. Synthesis of Enantiopure Torcetrapib 56 (Multikilogram Scale)**



multikilogram scale, where the tetrahydroquinoline intermediate **254** was obtained from the chiral precursor **253** through a NaBH<sub>4</sub>/MgCl<sub>2</sub>-mediated cyclization. The amide carbonyl was reduced by NaBH<sub>4</sub>, and the resulting intermediate was subsequently cyclized with the help of the magnesium salt (Scheme 58).<sup>289</sup> Hii and co-workers also explored the synthesis of the chiral acyclic precursors through an enantioselective aza-Michael reaction and utilized the NaBH<sub>4</sub>/MgCl<sub>2</sub>-mediated cyclization procedure for the synthesis of enantiopure torcetrapib.<sup>290</sup>

**4.5.3. Transition Metal-Catalyzed Reactions.** A Pd-catalyzed intramolecular coupling between aryl iodides and allyl moieties was explored for the diastereoselective synthesis of

Scheme 59. Pd-Catalyzed Synthesis of *trans*-2,4-Disubstituted Tetrahydroquinolines

2,4-disubstituted 1,2,3,4-tetrahydroquinolines. For instance, allyl acetates **255** underwent cyclization in the presence of 5 mol % of  $\text{Pd}_2(\text{dba})_3$  to afford *trans*-tetrahydroquinolines **256** in very good yields. The reaction tolerated both electron-donating and electron-withdrawing groups on the aryl ring (Scheme 59).<sup>291</sup>

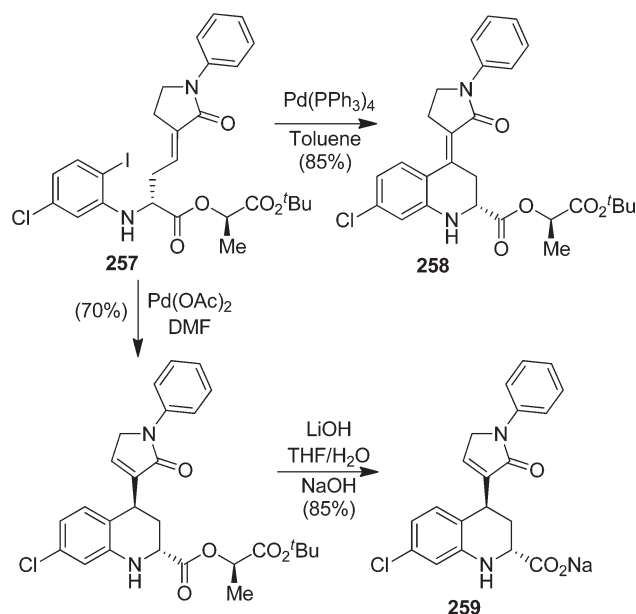
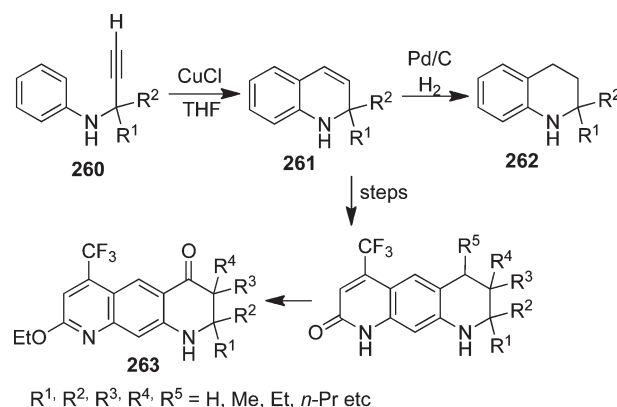
Di Fabio and co-workers reported a direct access to biologically relevant tetrahydroquinoline derivatives involving intramolecular Heck-type cyclization. The 2-iodo-*N*-arylamine **257** was effectively converted into tetrahydroquinoline **258** in good yield in the presence of  $\text{Pd}(\text{PPh}_3)_4$ .<sup>292,94</sup> Subsequently, the methodology was extended to the enantioselective synthesis of some tetrahydroquinoline-based antagonists of the glycine binding site associated to NMDA receptors including compound **259** (Scheme 60).<sup>293</sup> The reaction allowed the stereoselective synthesis of C-2  $\alpha$ -amino acid derivatives using lactate as a commercially available, low-cost chiral auxiliary. Recently, the procedure was improved to allow the synthesis of more than 300 kg of the final product with 99.9% purity.<sup>95</sup> In an article describing the general procedure for the synthesis of heterocycles such as indolines, dihydrobenzofurans, chromans, isochromanes and tetrahydroisoquinolines from acyclic precursors via ligand-free Pd-catalyzed reductive Heck cyclizations, a single example of a 1,2,3,4-tetrahydroquinoline derivative was reported in 96% yield.<sup>294</sup>

A CuCl-catalyzed intramolecular hydroarylation of *N*-propargyl anilines was described by Hamann and co-workers for the synthesis of intermediates en route to biologically relevant nonsteroidal, peripherally selective tetrahydroquinoline androgen receptor (AR) antagonists.<sup>110</sup> The *N*-propargyl anilines **260** reacted with catalytic amount of CuCl in THF under reflux conditions to afford the dihydroquinolines **261**, which were subsequently hydrogenated to the corresponding tetrahydroquinolines **262**. Further structural manipulation allowed a set of tricyclic tetrahydroquinoline derivatives **263** possessing potential AR antagonist activity (Scheme 61).<sup>112</sup> The same group<sup>112</sup> and the one of Dorey<sup>147</sup> again used the CuCl-catalyzed cyclization strategy for the synthesis of novel AR antagonist and antioxidant tetrahydroquinolines. Moreover, Ward and co-workers reported the synthesis of 3-, 4-, and 3,4-function-alized 2,2-dimethyl-1,2,3,4-tetrahydroquinolines<sup>295</sup> and virantmycin-related tetrahydroquinolines<sup>296</sup> using similar methodology.

A related method was reported by Ryu for the synthesis of (+)-(*S*)-angustureine **4a** using  $\text{PtCl}_4$  as a catalyst. The intermediate dihydroquinoline obtained was successfully converted into the natural product through a hydrogenation-*N*-Ms deprotection-*N*-methylation sequence.<sup>297</sup>

**4.5.4. Intramolecular Radical Cyclizations.** The  $\text{Bu}_3\text{SnH}/\text{Et}_3\text{B}$ -mediated radical cyclization of chiral *N*-allyl-*N*-*o*-iodoacrylamides **264** afforded a mixture of indolines **265** (from 5-*exo*-trig

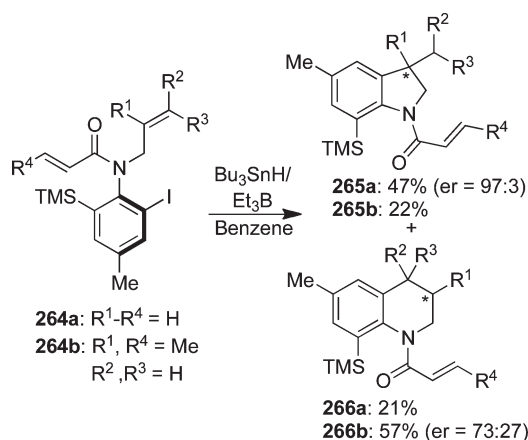
Scheme 60. Synthesis of Tetrahydroquinoline-Based Antagonists of the Glycine Binding Site Associated to NMDA Receptors

Scheme 61. CuCl-Catalyzed Intramolecular Hydroarylation of *N*-Propargyl Anilines

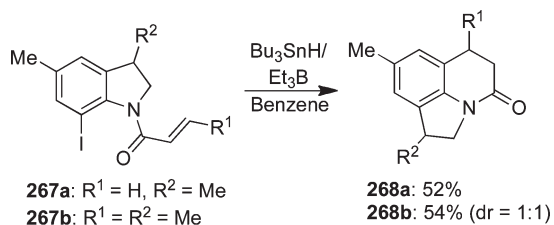
cyclization) and 1,2,3,4-tetrahydroquinolines **266** (from 6-*endo*-trig cyclization) with good chirality transfer (Scheme 62).<sup>298</sup> The synthesized racemic precursors **264** were resolved on a semipreparative chiral HPLC and the enantiopure compounds were cyclized in the presence of the tin reagent. For instance, the cyclization of **264a** ( $R^1\text{--}R^4 = \text{H}$ ) gave 47% of **265a** with excellent chirality transfer ( $er = 97:3$ ) and 21% of **266a** as a racemic product. However, cyclization of the *N*-crotyl-*N*-crotonyl derivative **264b** afforded 22% of **265b** as a racemic compound and 57% of **266b** with significant chirality transfer ( $er = 73:27$ ). The authors claimed that this was the first report of chirality transfer from a chiral axis to a stereocenter in a radical hydrogen transfer reaction.

Pyrroloquinolones **268** were prepared in moderate yields by cyclization under similar conditions of 7-iodoindolines **267**, obtained from **265** by ICl treatment. If the substituent  $R^1$  is other than hydrogen, the products were isolated as a 1:1 diastereomeric mixture (Scheme 63).

**Scheme 62.** Bu<sub>3</sub>SnH/Et<sub>3</sub>B-Mediated Radical Cyclization of Chiral *N*-Allyl-*N*-*o*-iodoacrylamides **264**



**Scheme 63.** Synthesis of Pyrroloquinolones **268**



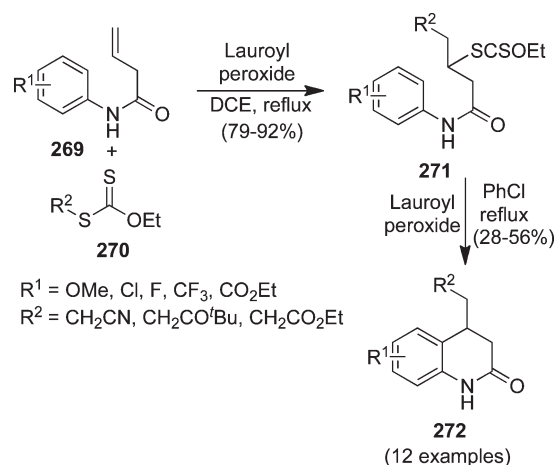
Binot and Zard developed an unusual radical cyclization of secondary amides containing a xanthate moiety for the synthesis of tetrahydroquinolones. The unprotected butenylanilides **269** reacted with xanthates **270** to afford compounds **271** through a radical addition mechanism, which subsequently underwent cyclization in the presence of stoichiometric amounts of lauroyl peroxide to furnish tetrahydroquinolones **272** in moderate yields (Scheme 64).<sup>299</sup>

Recently, the same group demonstrated the addition of unactivated alkenes to xanthates **273**, derived from the corresponding anilines, to obtain adducts **274**, which in turn underwent cyclization in the presence of lauroyl peroxide to afford tetrahydroquinolones **275**. The methodology was further extended to the synthesis of tricyclic compounds **277**, starting from the corresponding xanthate **276** (Scheme 65).<sup>300</sup> A one-pot variation of the reaction was also achieved, with improved overall yields, without isolating the intermediate adducts **274**.

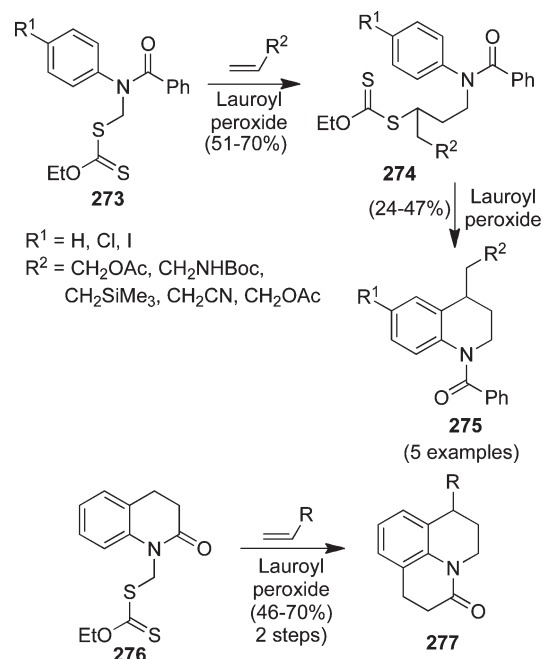
The syntheses of several types of nitrogen heterocycles, including 1,2,3,4-tetrahydroquinolines, dihydroindoles, and benz-fused azepines, was demonstrated based on a Bu<sub>3</sub>SnH/AIBN induced formal radical cyclization strategy.<sup>301</sup> The precursors, namely, cross-conjugated ketones **278**, were synthesized in very good yields from the corresponding 4-aminophenols by a PhI(OAc)<sub>2</sub>-mediated oxidative addition of methanol. The radical cyclization of **278** in the presence of Bu<sub>3</sub>SnH/AIBN followed by acid treatment afforded tetrahydroquinolones **279**, again in high yields (Scheme 66). Under similar experimental conditions, suitably modified substrates gave a variety of tetrahydroquinolones and other heterocycles such as indoles and azepines.

In a somewhat related reaction, *N*-(2-haloalkanoyl) derivatives of anilines afforded a mixture of oxindoles and tetrahydroquinolones

**Scheme 64.** Binot and Zard's Synthesis of Tetrahydroquinolin-2-ones Involving Radical Cyclization



**Scheme 65.** Addition of Unactivated Alkenes to Xanthates: Application to the Synthesis of Tetrahydroquinolines



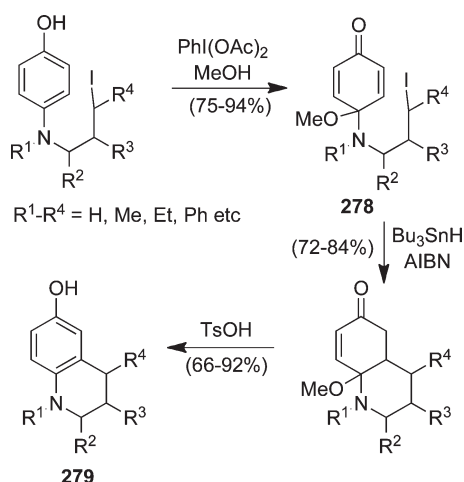
under photochemical conditions. A mechanism was proposed for this transformation assuming that it proceeded through radical intermediates.<sup>302</sup>

**4.5.5. Epoxide Opening.** The intramolecular thermal ring-opening of *N*-(2,3-epoxypropyl)diphenylamine afforded 3-hydroxy-*N*-phenyl-1,2,3,4-tetrahydroquinoline in 53% yield.<sup>303</sup> Furthermore, the same group demonstrated the synthesis of bis-tetrahydroquinoline **281** starting from epoxide **280** by treatment with dilute hydrochloric acid and subsequent heating.<sup>304</sup> Other developments in this procedure include the synthesis of compounds **282**<sup>305</sup> and **283**<sup>306</sup> from the corresponding epoxides (Scheme 67).

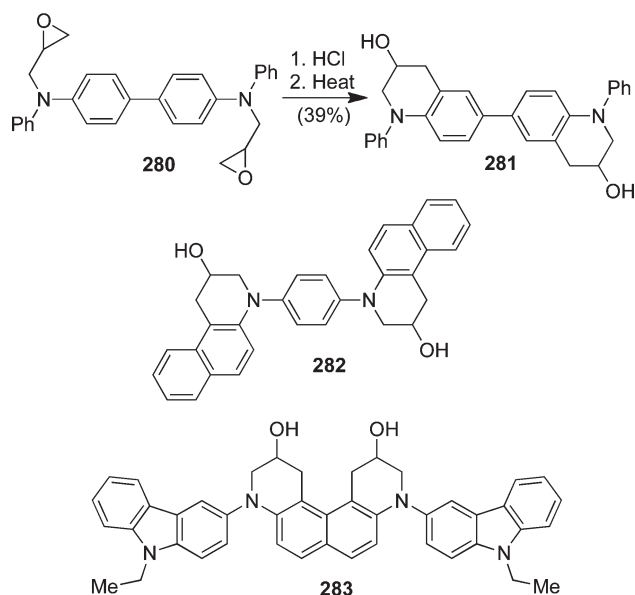
Wipf and Maciejewski observed that the Cp<sub>2</sub>TiCl<sub>2</sub>/Mn system was effective to catalyze the reductive cyclization of the epoxides of *N*-allylanilines to indolines and tetrahydroquinolones, where



Scheme 66. Synthesis of 6-Hydroxytetrahydroquinolines 279



Scheme 67. Synthesis of Tetrahydroquinolines via Intramolecular Epoxide Ring-Opening

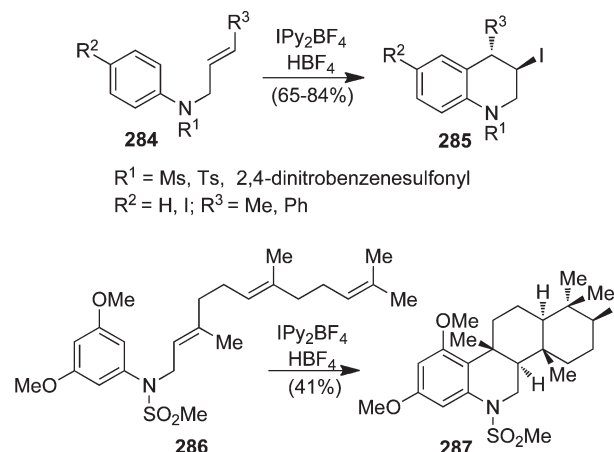


the latter were isolated as minor products, and then optimized the reaction to give exclusively indolines.<sup>307</sup>

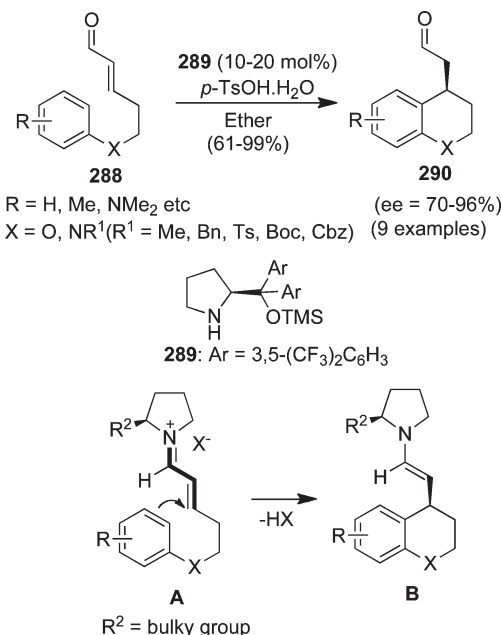
**4.5.6. Intramolecular Arylation.** Barluenga and co-workers established a novel intramolecular arylation of alkenes in the presence of iodonium ion ( $\text{IPy}_2\text{BF}_4$ ) for the synthesis of chromans and tetrahydroquinolines.<sup>308</sup> For instance, the *N*-protected-*N*-allylaniline derivatives **284** were smoothly converted into 3-iodo-1,2,3,4-tetrahydroquinolines **285** in good yields. Interestingly, compound **286** underwent polycyclization diastereoselectively to afford tetrahydroquinoline **287** in a single step and in 41% yield (Scheme 68). A mechanism was proposed involving the coordination of the iodonium ion to the double bond, followed by cyclization.

A rather similar report appeared subsequently dealing with Lewis acid-catalyzed intramolecular halo-arylation of tethered alkenes using *N*-halosuccinimides as the halogen source.<sup>309</sup>

Scheme 68. Barluenga's Intramolecular Arylation of Alkenes

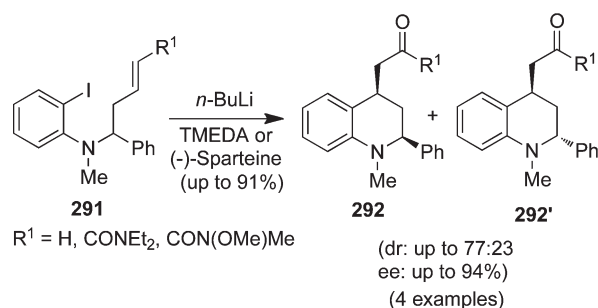
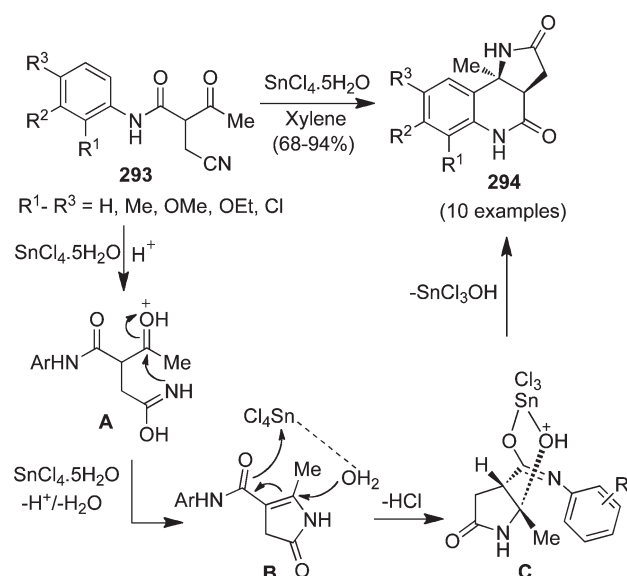


Scheme 69. Organocatalyzed Asymmetric Intramolecular Hydroarylation of 288



A number of Lewis acids were tested to activate the substrate, and  $\text{Sm}(\text{OTf})_3$  was found to be the best one. The substrates tested were similar to compounds **284**, but *N*-protected *N*-aryl cinnamic acid amides also underwent halo-cyclization and gave the corresponding tetrahydroquinolone-2-ones in excellent yields.

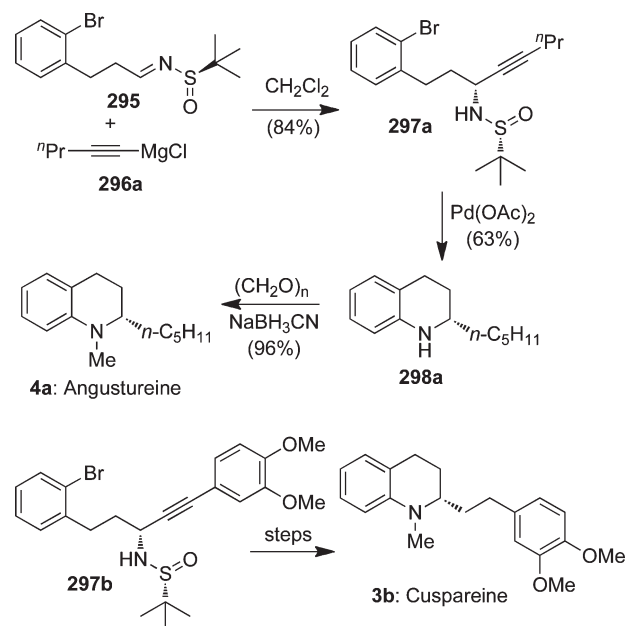
The asymmetric intramolecular hydroarylation of electron-rich phenol and aniline derivatives bearing an  $\alpha,\beta$ -unsaturated aldehyde moiety afforded chroman and tetrahydroquinoline derivatives in high yields and enantioselectivities in the presence of a chiral organocatalyst.<sup>310</sup> The phenol and aniline-derived enals **288**, in the presence of 10–20 mol % of the catalyst **289**, gave cyclized products **290** (Scheme 69). A mechanism was proposed involving the formation of iminium ion intermediate **A**, similar to the one commonly accepted for proline-catalyzed reactions,<sup>311</sup> by coordinating the enal with the chiral catalyst **289**. Since the Si face of the activated alkene of the intermediate **A**

**Scheme 70. Enantioselective Synthesis of Tetrahydroquinolines Involving Carbolithiation Process****Scheme 71. Liu's Diastereoselective Synthesis of Tricyclic Pyrroloquinoline Core (294) of Martinellines**

was shielded by the bulky groups of the catalyst, the electron-rich aryl ring attacked from the *Re* face of the alkene to generate cyclic intermediate **B**, which furnished the product **290** after hydrolysis of the enamine moiety.

**4.5.7. Miscellaneous Reactions.** One of the best methods to synthesize functionalized five-membered carbo- and heterocyclic systems include the carbolithiation of alkenes and alkynes. Lete and co-workers described the synthesis of 4-substituted-2-phenyl-tetrahydroquinolines **292** as mixtures of two diastereomers from *N*-alkenyl substituted 2-iodoanilines **291** using the carbolithiation process (Scheme 70).<sup>312</sup> The reaction rate and selectivity were found to depend on several factors including the lithium source, solvent system, additives, and reaction temperature. *n*-Butyllithium was identified as the best lithiation agent and TMEDA was the best additive, nevertheless, only a maximum diastereomeric ratio of 77:23 in favor of the *cis* isomer was achieved. When (–)-sparteine was used as a chiral ligand, the major product was the *trans* isomer and up to 94% *ee* was observed.

The high-yielding and diastereoselective synthesis of the tricyclic pyrroloquinoline core **294** of martinellid acid **2a** was achieved by Liu and co-workers based on a  $\text{SnCl}_4 \cdot 5\text{H}_2\text{O}$ -mediated cyclization of 2-(cyanomethyl)-3-oxo-*N*-arylbutanamides **293**. A mechanism

**Scheme 72. Wang's Asymmetric Synthesis of Natural Products (+)-Angustureine 4a and (–)-Cuspareine 3b**

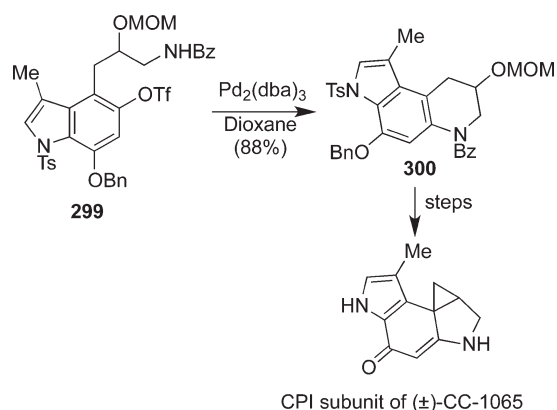
was proposed involving a consecutive hydrolysis of the cyano group followed by a double annulation sequence (Scheme 71).<sup>313</sup> Hydrolysis of the cyano group of **293** and a proton-catalyzed aza-annulation-dehydration, where the protons were generated from the hydrolysis of  $\text{SnCl}_4$ ,<sup>314</sup> gave the pyrrolinone intermediate **B**. The  $\text{SnCl}_4$ -mediated Michael addition of water to **B** generated the *cis*-fused ring intermediate **C** and its subsequent intramolecular annulation afforded the final product **294**.

#### 4.6. Formation of the $\text{C}_{8a}$ –N Bond

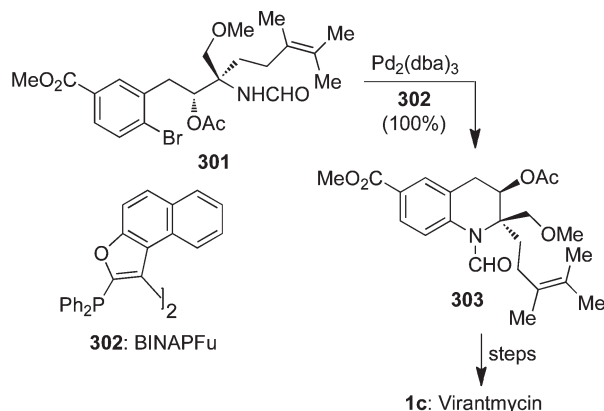
**4.6.1. Metal-Catalyzed Intramolecular Amination.** Reagents based on transition metals, including Pd, Cu, Ni, and others, effectively catalyzed intramolecular amination reactions that furnished tetrahydroquinolines by creating the  $\text{C}_{8a}$ –N bond. Wang and co-workers recently developed an efficient procedure for the asymmetric synthesis of natural products (+)-angustureine **4a** and (–)-cuspareine **3b** based on the addition of alkynylmagnesium reagents to *N*-*tert*-butanesulfinyl aldimines followed by a Pd-catalyzed Buchwald–Hartwig amination.<sup>315</sup> Grignard addition of **296a** to aldimine **295** afforded the adduct **297a** in 84% yield, which then underwent an intramolecular *N*-arylation in the presence of  $\text{Pd(OAc)}_2$  to give tetrahydroquinoline **298a**, whose subsequent *N*-methylation furnished the natural product angustureine **4a** in 96% yield. A similar procedure was also employed for the synthesis of cuspareine **3b** involving addition of a suitable Grignard reagent to **295** to give adduct **297b**. The key cyclization step was again achieved using  $\text{Pd(OAc)}_2$ , following replacement of the *N*-sulfinamide group by *N*-Boc (Scheme 72). Jackson and co-workers also reported a Pd-catalyzed cyclization of similar *N*-Boc protected substrates to the corresponding indolines and tetrahydroquinolines in high yields.<sup>316</sup>

The Buchwald–Hartwig amination was also employed for the synthesis of pyrrolo[3,2-*f*]tetrahydroquinoline **300**, a precursor for the synthesis of the cyclopropa[*c*]pyrrolo[3,2-*e*]indole (CPI) subunit of the antitumor natural product (±)-CC-1065.<sup>317</sup>

**Scheme 73.** Pd-Catalyzed Synthesis of Pyrrolo[3,2-*f*]tetrahydroquinoline **300**



**Scheme 74.** Pd-Catalyzed Synthesis of Precursor (**303**) of the Antiviral Agent Virantmycin **1c**

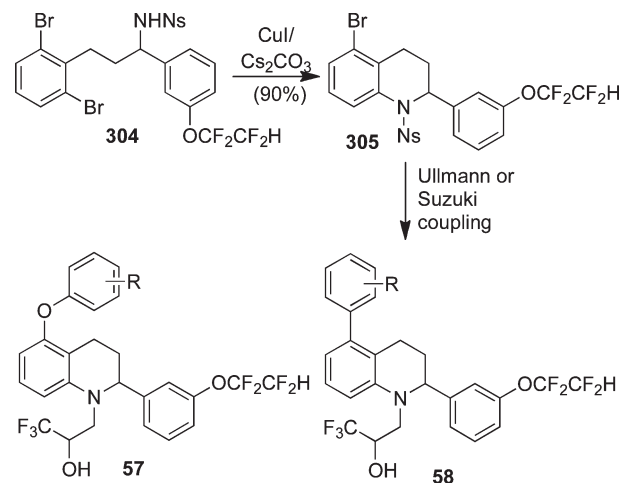


Thus, indole **299**, synthesized in several steps using a [4 + 2] cycloaddition as the key reaction, was treated with  $\text{Pd}_2(\text{dba})_3$  to afford an excellent yield of pyrroloquinoline **300**, which was then transformed into the CC-1065 CPI subunit (Scheme 73).

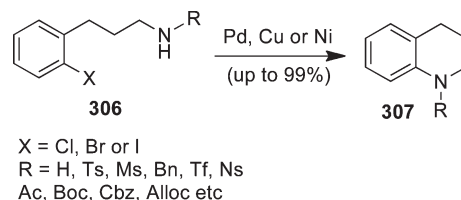
Back and Wulff reported the synthesis of virantmycin **1c** employing a Buckward–Hartwig aryl amination to construct the tetrahydroquinoline skeleton in the key step.<sup>318</sup> The formamide derivative **301**, synthesized in several steps starting from methyl 4-bromo-3-bromomethylbenzoate, was transformed quantitatively into the tetrahydroquinoline **303** by treatment with  $[\text{Pd}_2(\text{dba})_3]$  in the presence of the Keay ligand BINAPFu **302**,<sup>319</sup> and subsequent manipulation led to the antiviral agent virantmycin **1c** (Scheme 74).

The cholesteryl ester transfer protein (CETP) inhibitors **57** and **58** were efficiently synthesized through intramolecular Buckward–Hartwig N-arylation of compound **304** in the presence of  $\text{CuI}/\text{Cs}_2\text{CO}_3$  followed by Ullmann or Suzuki couplings.<sup>121,122</sup> The dibromo compound **304**, prepared from 2,6-dibromobenzylbromide, was treated with copper iodide and cesium carbonate in DMSO to furnish 5-bromo tetrahydroquinoline derivative **305** in 90% yield, which was subsequently converted into the CETP inhibitors **57** and **58** under Ullmann or Suzuki conditions, respectively (Scheme 75). The  $\text{CuI}/\text{Cs}_2\text{CO}_3$

**Scheme 75.** Synthesis of Cholesteryl Ester Transfer Protein (CETP) Inhibitors (**57** and **58**) through Intramolecular Buckward–Hartwig N-Arylation



**Scheme 76.** Metal-Catalyzed Cyclization of N-Substituted Aryl Halides **306**

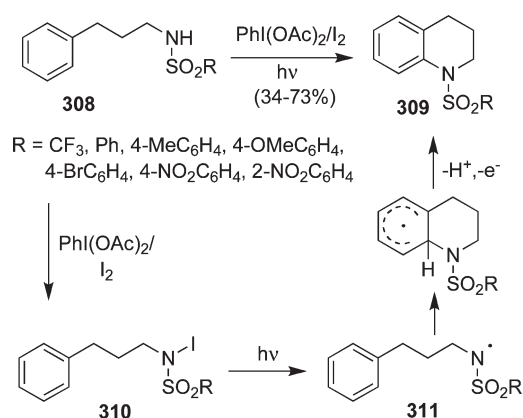


procedure was also used to prepare an intermediate for the total synthesis of the natural product yatakemycin.<sup>320</sup>

In the context of a general report on Pd-catalyzed N-arylation reactions in supercritical carbon dioxide, the cyclization of N-substituted aryl halide **306** was performed to afford the corresponding tetrahydroquinolines **307** in moderate to good yields (Scheme 76).<sup>321</sup> Other reagents involved in the cyclization of substrates **306** with different N-substituents include  $\text{CuI}/\text{CsOAc}$ ,<sup>322</sup>  $\text{CuI}$ ,<sup>323</sup>  $\text{CuI}/\text{Cs}_2\text{CO}_3$ ,<sup>324,325</sup>  $\text{CuOAc}/\text{K}_3\text{PO}_4$ ,<sup>326</sup> and  $\text{Ni}(0)$ .<sup>327</sup> Fort and co-workers also reported a palladium-catalyzed synthesis of N-aryl heterocycles, including N-aryl-1,2,3,4-tetrahydroquinolines, starting from 3-(2-chlorophenyl)propan-1-amine and chlorobenzenes, through sequential intra- and intermolecular N-arylation processes.<sup>328</sup>

**4.6.2. Photochemical Reactions.** Sulfonamides of primary amines **308** bearing an aryl ring at the  $\gamma$ -position reacted with  $\text{PhI}(\text{OAc})_2$  and  $\text{I}_2$  under photochemical conditions, affording the corresponding tetrahydroquinolines **309** in good yields.<sup>329</sup> The reactivity of the substrates depends on the nature of the substituents on the nitrogen atom. A mechanism was proposed based on the formation of N-iodo intermediate **310**, followed by homolytic cleavage of the N–I bond under the irradiation conditions to generate the sulfonamidyl radical **311**, which undergoes final oxidative aromatization to afford the final tetrahydroquinolines (Scheme 77). Recently, the same group reported a similar cyclization strategy using 1,3-diiodo-5,5-dimethylhydantoin (DIH) and iodine under photochemical conditions with improved yields and substrate scope.<sup>330</sup>

**Scheme 77. Synthesis of Tetrahydroquinolines via Photoinduced Cyclization of Sulfonamides 308**



**4.6.3. Miscellaneous Reactions.** The 3-(*N*-methylamino)-1,2,3,4-tetrahydroquinoline derivative **313**, an intermediate for the synthesis of the previously mentioned dopamine D<sub>2</sub> receptor agonist sumanirole (PNU-95666E, **40**),<sup>331</sup> was obtained through the cyclization of *N*-methoxyamide **312** using  $\text{PhI}(\text{CO}_2\text{CF}_3)_2$  followed by  $\text{BH}_3$  reduction (Scheme 78).<sup>85</sup> The cyclization step needed 3 equivalents of trifluoroacetic acid, which presumably increased the electrophilicity of the *N*-methoxy-*N*-acylnitronium ion intermediate.

In another tetrahydroquinoline synthesis employing iodonium reagents, we will mention an article that contains a single example of tetrahydroquinoline in 58% yield<sup>332</sup> in the context of a rather general synthesis of heterocycles such as indoles, quinolines, and phenanthridines from orthoquinol acetates, which were in turn generated from phenols by phenyliodine(III) diacetate-mediated oxidation.

Narasaka and co-workers demonstrated the synthesis of 8-hydroxy-1,2,3,4-tetrahydroquinolines **315** in good yields by cyclization of 3-hydroxyphenethyl ketone *O*-2,4-dinitrophenyloximes **314** using sodium hydride and sodium cyanoborohydride.<sup>333,334</sup> Although the mechanism was not discussed in detail, the authors mentioned that the reaction could proceed through an alkylideneaminyl radical intermediate generated by an intramolecular electron transfer (Scheme 79).

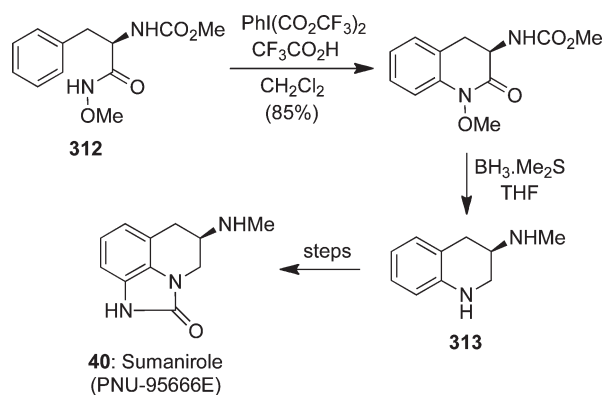
Gademann and Bethuel demonstrated a biomimetic route for the synthesis of the peptide alkaloid anachelin **11** involving an oxidative aza annulation process for the creation of the key tetrahydroquinoline framework. Treatment of compound **316** with dianisyltellurium oxide, followed by protection of the free hydroxy groups afforded in good yield the quaternary ammonium salt **317**, an intermediate in the synthesis of the natural product **11** (Scheme 80).<sup>335</sup>

## 5. SYNTHESIS OF 1,2,3,4-TETRAHYDROQUINOLINES INVOLVING THE GENERATION OF TWO BONDS

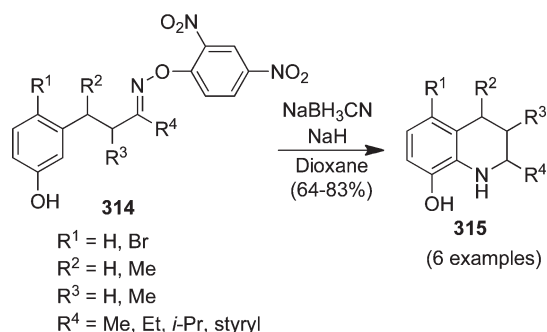
### 5.1. Introduction

The synthesis of 1,2,3,4-tetrahydroquinolines from an aromatic substrate and an acyclic precursor by creating two bonds simultaneously in the key step will be discussed in this Section. It has been divided into several subheadings for better understanding, discussing the creation of  $\text{N}-\text{C}_2$  and  $\text{C}_3-\text{C}_4$ ,  $\text{N}-\text{C}_2$  and  $\text{C}_4-\text{C}_{4a}$ ,  $\text{N}-\text{C}_2$  and  $\text{C}_2-\text{C}_3$ ,  $\text{C}_2-\text{C}_3$  and  $\text{C}_3-\text{C}_4$ ,  $\text{C}_2-\text{C}_3$

**Scheme 78. Synthesis of Intermediate 313 of Sumanirole (PNU-95666E, 40)**



**Scheme 79. Narasaka's Synthesis of 8-Hydroxy-1,2,3,4-tetrahydroquinolines 315**



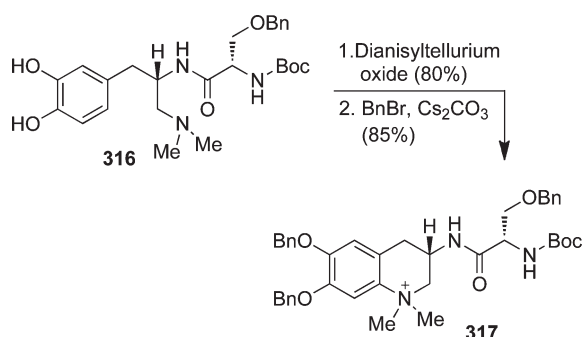
and  $\text{C}_4-\text{C}_{4a}$ ,  $\text{C}_3-\text{C}_4$  and  $\text{C}_4-\text{C}_{4a}$ ,  $\text{C}_{8a}-\text{N}$  and  $\text{C}_4-\text{C}_{4a}$ , and  $\text{N}-\text{C}_2$  and  $\text{C}_{8a}-\text{N}$  bonds (Figure 15).

### 5.2. Formation of the $\text{N}-\text{C}_2$ and $\text{C}_3-\text{C}_4$ Bonds

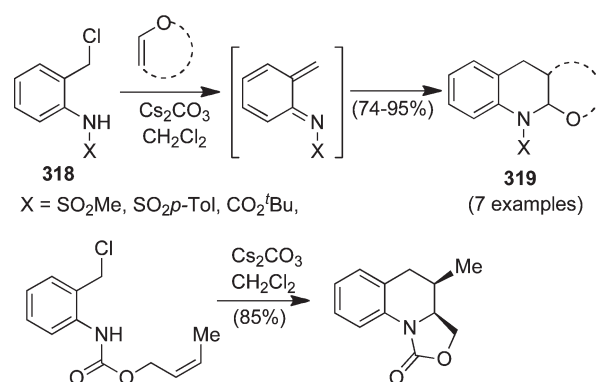
**5.2.1. Diels–Alder Related Reactions.** The construction of the tetrahydroquinoline moiety can be achieved by creating the  $\text{N}-\text{C}_2$  and  $\text{C}_3-\text{C}_4$  bonds in unison starting from *o*-substituted anilines and a  $\text{C}_2-\text{C}_3$  fragment. The cycloaddition of *o*-azaxylylenes with suitable dienophiles is a straightforward method for the generation of tetrahydroquinolines and related heterocycles.<sup>336</sup> For instance, Corey and Steinhagen established an efficient procedure for the synthesis of tetrahydroquinolines through a  $[4 + 2]$  cycloaddition of in situ generated *o*-azaxylylenes from chloromethylaniline derivatives and electron-rich dienophiles.<sup>337</sup> The *o*-azaxylylenes generated from chloromethyl anilines **318** in the presence of  $\text{Cs}_2\text{CO}_3$  were trapped with a number of cyclic and noncyclic vinyl ethers to afford the corresponding tetrahydroquinolines **319** in excellent yields. An intramolecular version of the reaction was also developed, which furnished the products stereospecifically by a suprafacial (cis) cycloaddition (Scheme 81).

Subsequently, the authors extended their intramolecular strategy for the synthesis of the natural antiviral agent virantmycin **1c**. The intermediate **320** was synthesized starting from 2-amino-5-iodobenzyl alcohol in a few steps, and the  $\text{Cs}_2\text{CO}_3$  mediated intramolecular cycloaddition allowed access to the virantmycin precursor **321**, which was then transformed into the final product

Scheme 80. Synthesis of Intermediate 317 of the Peptide Alkaloid Anachelin 11



Scheme 81. Corey's Tetrahydroquinoline Synthesis Involving [4 + 2] Cycloaddition



Scheme 82. Synthesis of Intermediate 321 of Virantmycin 1c

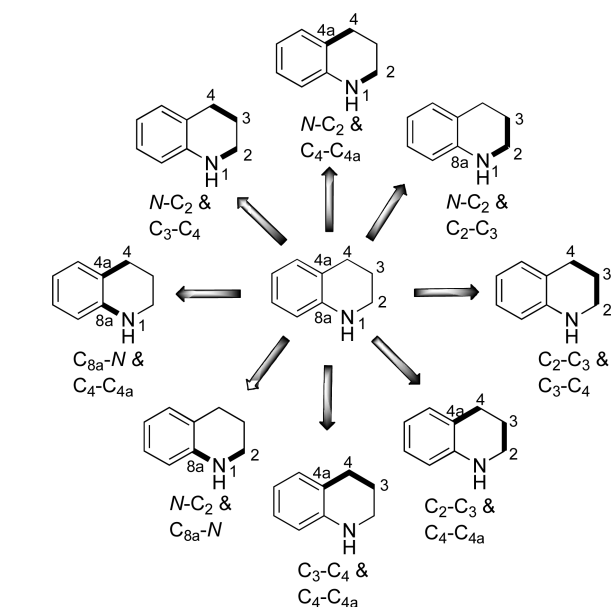
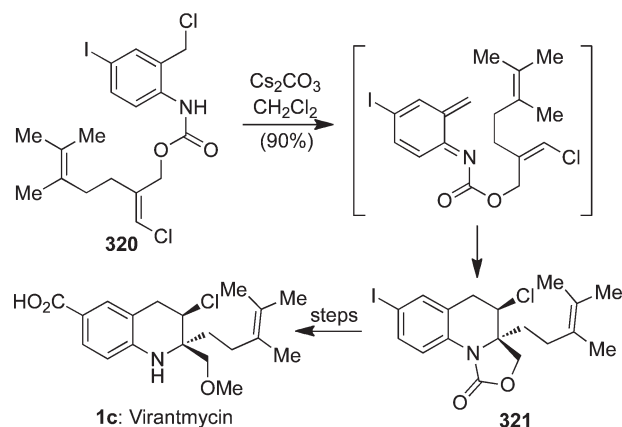


Figure 15. Disconnections of the tetrahydroquinoline framework discussed in section 5.

in four additional steps (Scheme 82).<sup>338</sup> Bräse and co-workers also reported a rather similar procedure for the synthesis of tetrahydroquinoline 321.<sup>339</sup>

An example of the use of carbonates as leaving groups was reported by Kubo and co-workers, wherein the generation of *o*-azaxylylenes from *N,O*-diethoxycarbonyl-*o*-aminobenzyl alcohols under thermal conditions and subsequent trapping with dienophiles were described.<sup>340</sup> Bräse and co-workers also demonstrated a similar strategy for the construction of the tetrahydroquinoline moiety starting from 2-aminobenzyl alcohol in two steps and its application to the total synthesis of the alkaloids angustureine 4a and 1-methyl-2-propyltetrahydroquinoline 4b through intermediates 322.<sup>341</sup> Treatment of 2-aminobenzyl alcohol with excess of allocCl or 3-butenyl chloroformate followed by Cs<sub>2</sub>CO<sub>3</sub> gave a good yield of the tetrahydroquinoline derivatives 322, which were then transformed into the natural products. The same reaction was also achieved in three steps through a benzyl chloride intermediate (Scheme 83).

The first asymmetric total synthesis of (–)-martinelline 2b and the second total synthesis of (–)-martinellacid 2a were achieved by Iwabuchi and co-workers and involved the

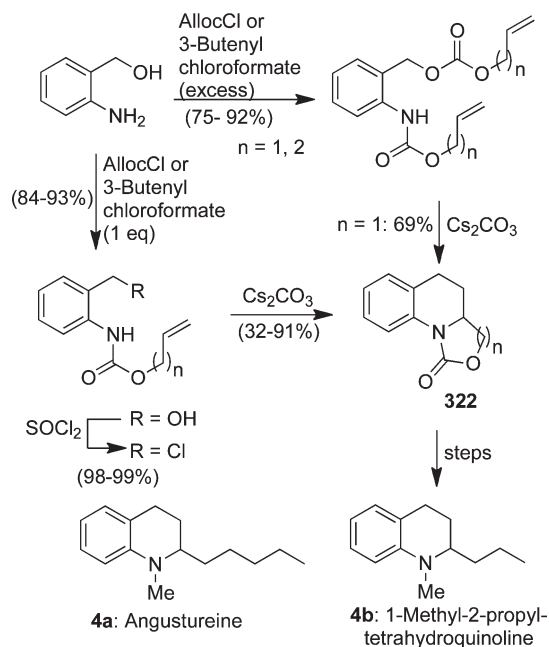
construction of the pyrroloquinoline core of the natural products through a Lewis acid-catalyzed intramolecular [4 + 2] cycloaddition. Substrate 325 was readily accessed from *o*-aminoarylaldehyde 323 and chiral amine 324. The BF<sub>3</sub>·OEt<sub>2</sub> mediated intramolecular cycloaddition of 325 furnished pyrroloquinolines 326 as a 4.2:1 mixture of diastereomers and the major isomer was separated and transformed into the natural products in further steps (Scheme 84).<sup>342</sup>

Funk and Crawley demonstrated the construction of the tetrahydroquinoline ring system of the cytotoxic natural product communesin B (331) based on an intramolecular cycloaddition involving an *o*-quinone methide intermediate. Ring-opening of epoxide 327 with benzazepine 328 afforded intermediate 329 in good yield as a 9:1 regioisomeric mixture and the subsequent thermolysis of the major isomer gave compound 330, which contains the hexacyclic core of communesin B, as a single diastereomer through the cycloaddition of the in situ generated diene with the indole heterodienophile (Scheme 85).<sup>343</sup>

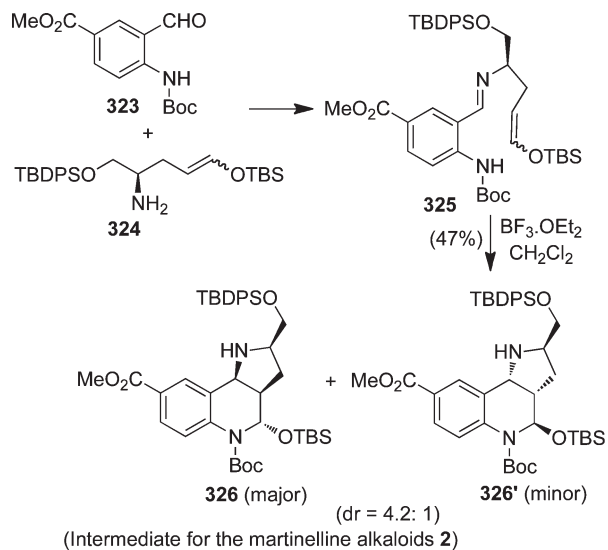
A few years later the same authors developed an alternative route to achieve the synthesis of the communesin ring system via the ring-opening of 2-(2-acylamino-phenyl)aziridines. The *trans*-aziridine 332 was synthesized from *N*-methyltryptamine in good yield and treated with bis[(trifluoromethyl)sulfonyl]imine (HNTf<sub>2</sub>). This reaction provided the cycloadduct 333a with an unexpected migration of the ethoxycarbonyl group to the aziridine nitrogen (Scheme 86).<sup>344</sup> A plausible mechanism was



**Scheme 83. Bräse's Synthesis of Angustureine 4a and 1-Methyl-2-propyltetrahydroquinoline 4b**



**Scheme 84. Synthesis of Intermediates for the First Asymmetric Total Synthesis of (–)-Martinelline 2b and the Second Total Synthesis of (–)-Martinelliacid 2a**

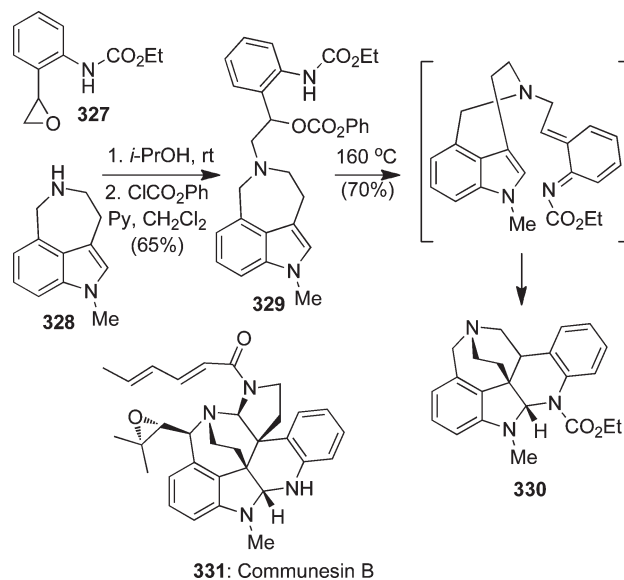


proposed involving the generation of the diene component **A** through intermediates **B** and **C** generated by an acid-catalyzed transfer of the acyl group to the aziridine nitrogen, followed by ring-opening.

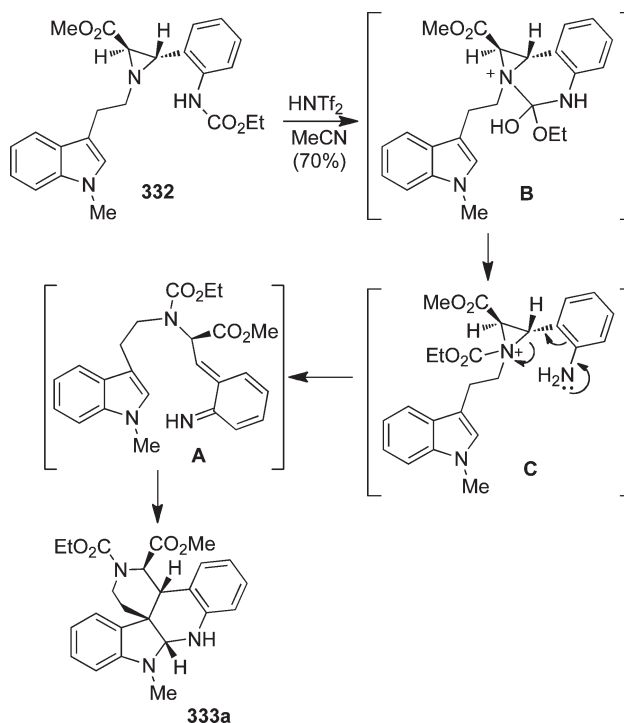
The reaction was also achieved through a fluoride-promoted ring-opening of TEOC substituted aziridine **334** to give compound **333b**, bearing no substituent on the piperidine nitrogen, which was then converted into the hexacyclic core (**335**) of communesin B using a  $\text{AuCl}(\text{PPh}_3)/\text{AgOTf}$  catalytic system (Scheme 87).

The first Lewis acid catalyzed generation of *o*-quinone methide imines starting from *o*-aminobenzyl alcohols and their

**Scheme 85. Funk and Crawley's Synthesis of the Hexacyclic Core (330) of the Cytotoxic Natural Product Communesin B (331)**

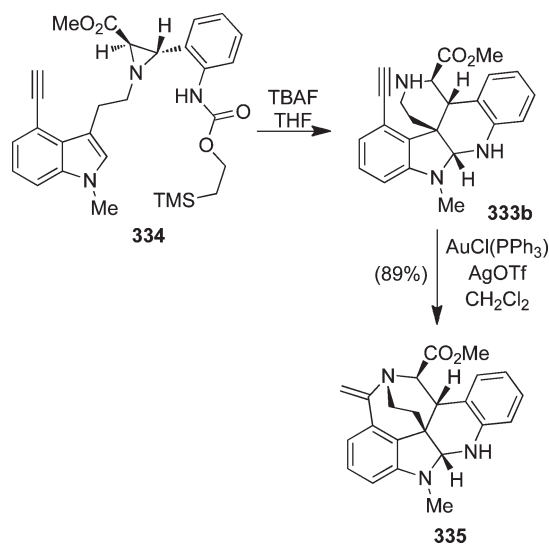


**Scheme 86. Alternative Route Reported by Funk and Crawley for the Construction of Communesin B (331) Core**



subsequent Diels–Alder reaction to afford tetrahydroquinolines was reported by Lau.<sup>345,346</sup> A variety of *o*-aminobenzyl alcohols **336**, in the presence of  $\text{BF}_3 \cdot \text{OEt}_2$  under mild conditions, generated effectively the heterodienes **A** which underwent [4 + 2] cycloaddition with a number of dienophiles to give the corresponding tetrahydroquinolines **337** in good to excellent yields. The intramolecular version of the reaction was

**Scheme 87. Third Approach to Communesin B (331) Ring Skeleton Involving a Fluoride-Promoted Ring-Opening of Aziridine 334**



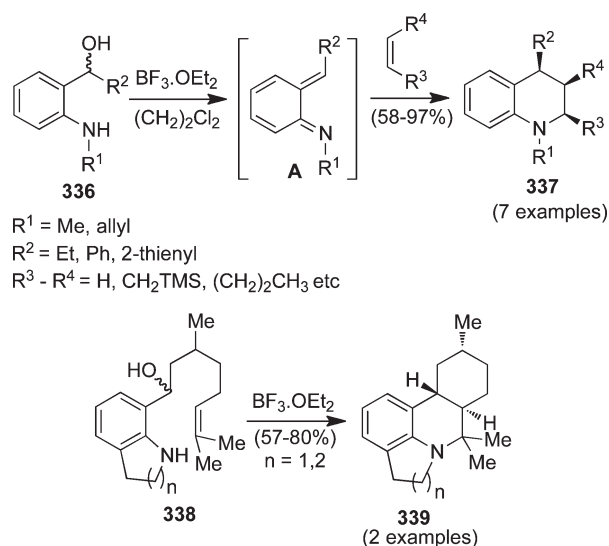
also successful, and allowed ready access to polycyclic tetrahydroquinoline derivatives **339** starting from compounds **338** (Scheme 88).

Martin and co-workers proved that *o*-quinone methide imines generated from *o*-aminobenzyl alcohols **336** were effectively trapped by fullerene  $C_{60}$  to give the corresponding cycloadducts bearing a tetrahydroquinoline moiety **340** (Scheme 89).<sup>347</sup> On the basis of detailed NMR studies, a boat conformation was assigned to the tetrahydropyridine ring where the H-4 hydrogen is in a pseudoequatorial position and the phenyl (R) group in a flagpole position, which was then conformed by theoretical calculations at the semiempirical PM3 level.

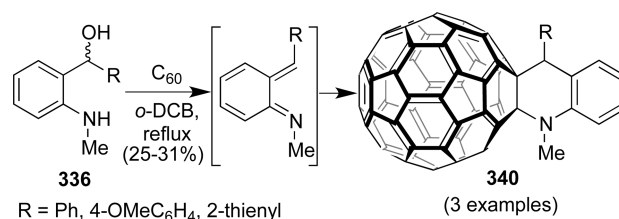
1,4-Dihydro-2*H*-3,1-benzoxazin-2-ones were also found to be efficient precursors for the generation of 1,3-heterodienes after elimination of a molecule of carbon dioxide under reflux conditions, without any catalyst. For instance, compounds **341** reacted with *N*-phenylmaleimide to provide the corresponding tetrahydroquinolines **342** in good yields (Scheme 90).<sup>348</sup> Ohno and co-workers also extended this procedure to the synthesis of fullerene-tetrahydroquinolines in moderate yields.<sup>349</sup>

Asymmetric decarboxylative cycloaddition of vinyl benzoxazinones **343** with benzylidene malononitriles **344** furnished tetrahydroquinolines **345** in excellent yields and selectivities in the presence of  $Pd(PPh_3)_4$  and a chiral ligand through a palladium-polarized aza-*o*-xylylene intermediate.<sup>350</sup> Among the tested ligands, the anthracenyl diamine, a Trost-ligand, was highly effective and allowed excellent enantioselectivity. The reaction tolerated a variety of substituents including electron-releasing and electron-withdrawing groups on both the diene and dienophile components. Although the origin of the stereoselectivity was not clear, the authors proposed a mechanism based on the generation of intermediate **A** and a subsequent enantioselective aza-Michael addition to the activated olefin to afford the second intermediates **B** and **C**, which then cyclized to afford the final products. The most favored species **C** underwent fast cyclization to the observed major diastereomer (Scheme 91). A year later, the scope of reaction was studied in more detail and the results were summarized as a full paper.<sup>351</sup>

**Scheme 88. Lau's Approach to Tetrahydroquinolines Involving [4 + 2] Cycloaddition of *o*-Quinone Methide Imines**



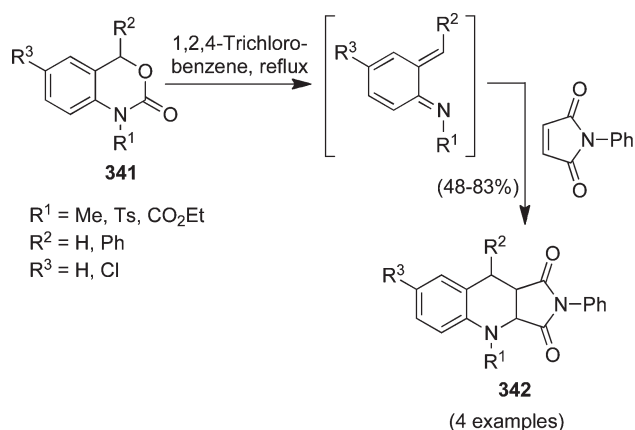
**Scheme 89. Synthesis of Tetrahydroquinolines Bearing a Fullerene Moiety**



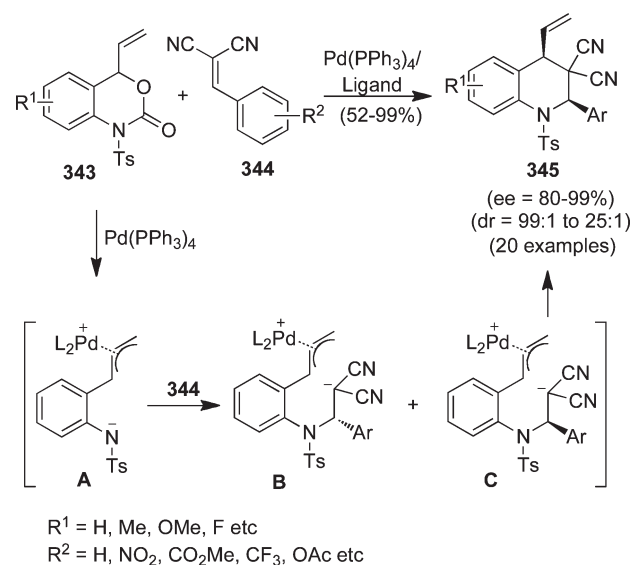
**5.2.2. Tandem Michael Addition–Cyclization Sequence.** Magnesium bis(diisopropyl)amide (MBDA), generated in situ from diisopropylamine and ethylmagnesium bromide, mediated the Michael addition of 2-(alkylamino)-phenyl ketones **346** with  $\alpha,\beta$ -unsaturated carbonyl compounds **347** followed by aldol-type cyclization to give tetrahydroquinolines **348** in good yields.<sup>352</sup> Other bases such as LDA led to poor conversion, and NaH was totally inactive. The trans stereochemistry of the products was assigned based on the coupling constants between the  $H_2$ – $H_3$  protons. The products were subsequently converted into the corresponding dihydroquinolines by treatment with  $SOCl_2$  and pyridine in high yields (Scheme 92). Lee and co-workers found that DABCO was also effective to achieve a similar Michael addition–cyclization reaction, giving 4-hydroxy-tetrahydroquinoline derivatives.<sup>353</sup> The procedure was extended to the synthesis of tetrahydroquinolin-4-ones through a magnesium bis(diisopropyl)amide-mediated sequential conjugate addition–Claisen-type condensation between methyl 2-(methylamino)benzoate and  $\alpha,\beta$ -unsaturated carbonyl compounds.<sup>354</sup>

Hamada and co-workers developed an efficient procedure for the synthesis of tetrahydroquinolines based on a tandem Michael-aldol sequence under basic conditions.<sup>355,356</sup> The *N*-protected *o*-aminobenzaldehyde **349** reacted with  $\alpha,\beta$ -unsaturated carbonyl compounds **350** in the presence of a quaternary ammonium salt (benzyltriethylammonium chloride,  $BnNEt_3Cl$ ) and sodium

**Scheme 90. Generation of Tetrahydroquinolines 342 Starting from 1,4-Dihydro-2*H*-3,1-benzoxazin-2-ones via [4 + 2] Cycloaddition**



**Scheme 91. Pd-Catalyzed Enantioselective Synthesis of Tetrahydroquinolines 345**

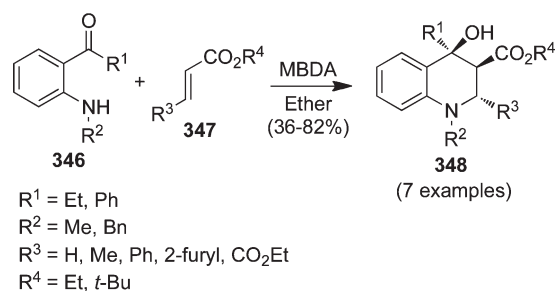


bicarbonate to afford the corresponding tetrahydroquinoline derivatives **351** in excellent yields. One of these compounds (**351**) was then converted into the martinelline skeleton **353** in a few steps through intermediate **352** (Scheme 93).

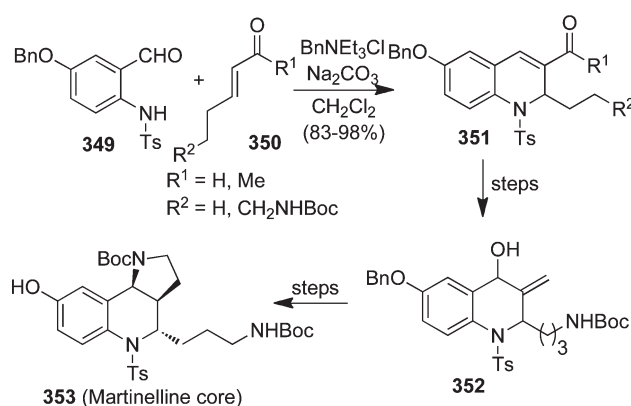
A sequential process comprising a Pd-catalyzed allylic amination/thiazolium salt-catalyzed Stetter reaction sequence allowed the synthesis of tetrahydroquinolin-4-ones starting from simple *o*-aminoarylaldehydes.<sup>357</sup> Treatment of 2-aminoarylaldehydes **354** with  $\gamma$ -acetoxy  $\alpha,\beta$ -unsaturated esters **355** in the presence of  $\text{Pd}(\text{OAc})_2$  afforded intermediates **356**, which subsequently underwent an intramolecular Stetter reaction with a catalytic amount of the thiazolium salt **357** to furnish the final tetrahydroquinoline derivatives **358** in almost quantitative yields. The reaction was found to be efficient for both electron-rich and electron-deficient arylaldehydes (Scheme 94).

Bridged tetrahydroquinolines **361** were synthesized in high yields through a novel reaction between 2-(trimethylsilyl)ethynylanilines

**Scheme 92. Magnesium Bis(diisopropyl)amide (MBDA)-Mediated Michael Addition—Cyclization Sequence**



**Scheme 93. Hamada's Tetrahydroquinoline Synthesis Based on a Tandem Michael Addition-Aldol Sequence**

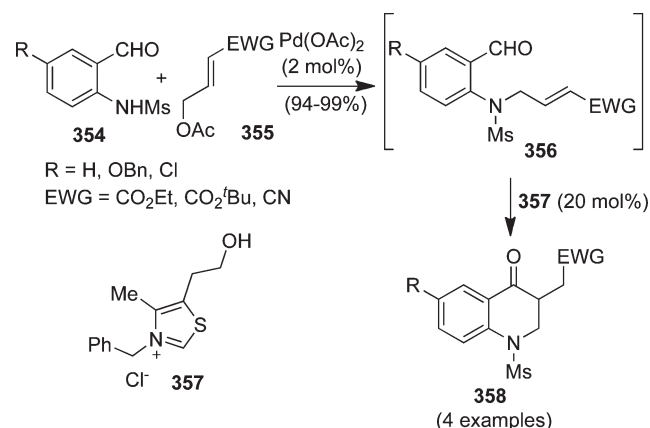


**359** and ethenetricarboxylate **360** in the presence of zinc triflate.<sup>358</sup> The initial Lewis acid-catalyzed conjugate addition of **359** to **360** afforded intermediate **A**, which was activated by the catalyst to give intermediate **B** bearing a free carboxylic acid group. A subsequent intramolecular cyclization furnished tetrahydroquinolines **361** (Scheme 95).

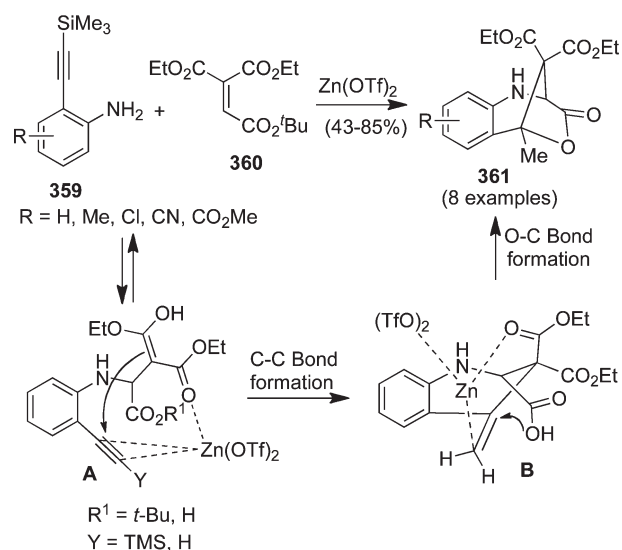
Recently, the same authors described the diastereoselective synthesis of 2,3,4-trisubstituted tetrahydroquinolines through a zinc triflate-catalyzed cyclization of 2-aminoarylaldehydes and ethenetricarboxylate derivatives with very good yields.<sup>359</sup> The reaction afforded tetrahydroquinolines **362** at room temperature in dichloromethane while the bridged analogues **363** were isolated at elevated temperature. A mechanism was proposed involving a Michael addition—cyclization sequence to form compound **362**, followed by a zinc triflate-activated second cyclization to give the bridged tetrahydroquinoline **363**. This mechanism was supported by the fact that isolated compounds **362** were successfully converted into **363** under similar experimental conditions (Scheme 96).

**5.2.3. Miscellaneous Reactions.** Croce and co-workers reported a simple route for the synthesis of 2-hydroxy-1,2,3,4-tetrahydroquinolines **365** starting from *N*-(2-bromomethylphenyl)benzenesulfonamides **364** and 1,3-dicarbonyl compounds in the presence of sodium hydride.<sup>360</sup> The reaction proceeded through an initial deprotonation of the 1,3-dicarbonyl compound followed by a nucleophilic displacement of the benzylic bromine atom to give intermediate **A**, which was subsequently cyclized through intermediate **B** to afford tetrahydroquinolines **365** (Scheme 97). A similar methodology was employed for the

**Scheme 94.** Pd-Catalyzed Allylic Amination/Thiazolium Salt-Catalyzed Stetter Reaction Sequence for the Synthesis of Tetrahydroquinolin-4-ones



**Scheme 95.** Zinc Triflate-Catalyzed Synthesis of Bridged Tetrahydroquinolines 361

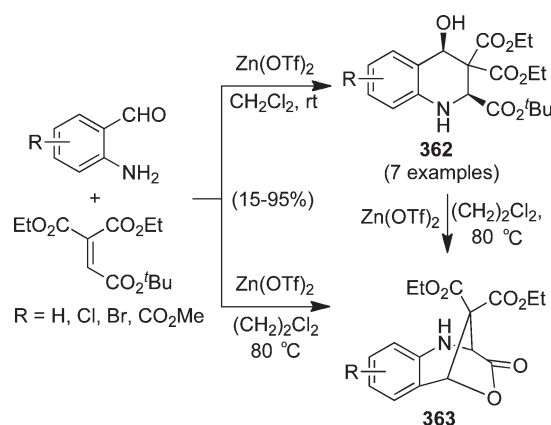


synthesis of a set of tetrahydroquinolones possessing protein farnesyltransferase (*Pf*-PFT) inhibitory activity, where the key step was the NaH-mediated construction of the tetrahydroquinolone ring system from 2-(*N*-substituted-amino)benzyl chlorides and diethyl acetamidomalonate.<sup>57</sup>

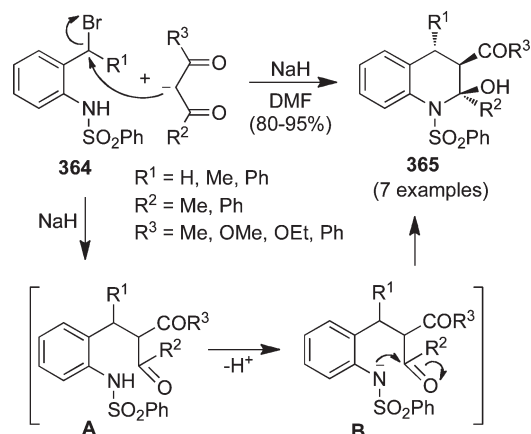
The reaction between 2-aminoarylaldehydes 366, bearing both electron-releasing and electron-donating groups, and alkenyl trifluoroborates 367 in the presence of TMSCl and Et<sub>3</sub>N furnished the corresponding dihydroquinolines 368 in moderate to good yields through intermediate A, and one of the products was then hydrogenated quantitatively to a tetrahydroquinoline derivative (Scheme 98).<sup>361</sup> While the reaction starting from 2-arylviny, 2-alkenylviny and 2-alkylalkenyl trifluoroborates proceeded well, the unsubstituted vinyltrifluoroborate furnished the corresponding quinoline derivative in poor yield.

Gurjar and co-workers reported an interesting procedure involving the palladium-catalyzed arylation of dihydropyrrole derivatives for the synthesis of pyrroloquinolones.<sup>362</sup> For

**Scheme 96.** Temperature and Solvent-Dependent Synthesis of Tetrahydroquinolines 362 and 363



**Scheme 97.** Croce's Synthesis of 2-Hydroxy-1,2,3,4-tetrahydroquinolines 365

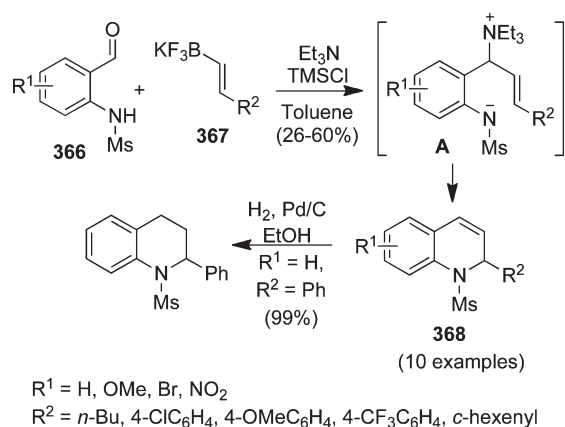


instance, 2-iodoanilines 369 reacted with *N*-substituted 3-carbethoxy-4,5-dihydropyrroles 370 in the presence of Pd(OAc)<sub>2</sub> to furnish tricyclic compounds 371, which gave pyrroloquinolones 372 after catalytic hydrogenation (Scheme 99).

### 5.3. Formation of the N–C<sub>2</sub> and C<sub>4</sub>–C<sub>4a</sub> Bonds

**5.3.1. Michael Addition Initiated Reactions.** Yadav and co-workers demonstrated the diastereoselective synthesis of enantiopure tetrahydroquinolines 373 based on the InBr<sub>3</sub>-catalyzed reaction between arylamines and D-glucal, L-rhamnal, and D-xylal.<sup>363</sup> A variety of arylamines bearing both electron-donating and electron-withdrawing groups afforded the tetrahydroquinolines in very good yields. Among the tested catalysts including InBr<sub>3</sub>, InCl<sub>3</sub>, CeCl<sub>3</sub>·7H<sub>2</sub>O, YCl<sub>3</sub>, YbCl<sub>3</sub>, Sc(OTf)<sub>3</sub>, Bi(OTf)<sub>3</sub>, Yb(OTf)<sub>3</sub>, Ce(OTf)<sub>3</sub>, Sm(OTf)<sub>3</sub>, and TMSOTf, stoichiometric amount of TMSOTf and catalytic InBr<sub>3</sub> were found to be the best. A mechanism was proposed involving intermediates A and B, based on the isolation of the deuterated compounds 373a when the reaction was carried out in D<sub>2</sub>O (Scheme 100). Dodecatungstocobaltate, K<sub>5</sub>CoW<sub>12</sub>O<sub>40</sub>·3H<sub>2</sub>O, was also found to catalyze the same reaction.<sup>364</sup>

In subsequent work, the Yadav group studied the use of the CeCl<sub>3</sub>·7H<sub>2</sub>O/NaI system to catalyze the same reaction.<sup>365</sup> In

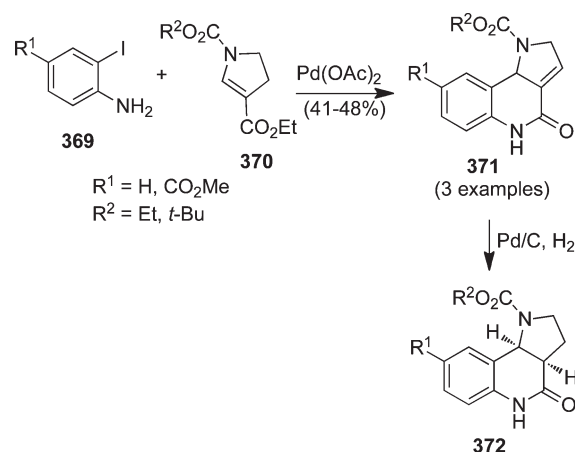
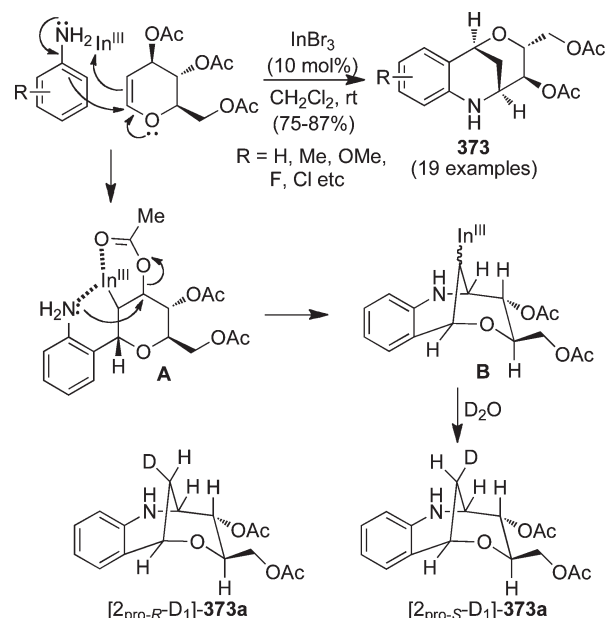
Scheme 98. Synthesis of *N*-Mesyl-2-phenyl-1,2,3,4-tetrahydroquinoline

this case, they proposed that the catalyst promotes opening of the starting materials to give a Michael acceptor **374**, which then reacts with the starting aniline through a tandem Michael addition-intramolecular Friedel–Crafts cyclization sequence (see the detailed mechanism in Scheme 101). Perhaps on the basis of this finding, later work by the same group on the same transformation is based on the reaction between arylamines and chiral  $\alpha,\beta$ -unsaturated aldehydes bearing a  $\delta$ -hydroxy group. In one of their reports of this variation of their method, they identified 5 mol %  $\text{Bi}(\text{OTf})_3$  as a good catalyst, allowing the use of mono-, di-, and trisubstituted arylamines with compounds **374** to give the corresponding tetrahydroquinolines **373** as single diastereoisomers and in high yields (Scheme 101).<sup>366</sup> Other metal triflates such as  $\text{In}(\text{OTf})_3$ ,  $\text{Ce}(\text{OTf})_3$ , and  $\text{Yb}(\text{OTf})_3$  were found to be less active. Simultaneously, the authors published another article using  $\text{InCl}_3$  as a catalyst for the same reaction without any significant improvement.<sup>367</sup> A few years later, another group reported a similar protocol with improved yields using lanthanum(III) nitrate as a catalyst.<sup>368</sup>

Montmorillonite clay was identified as an excellent catalyst for the reaction between arylamines and 2-deoxy-D-ribose to afford sugar-derived enantiopure tetrahydroquinolines.<sup>369</sup> For instance, substituted anilines reacted with  $\alpha,\beta$ -unsaturated aldehydes **376**, generated in situ from 2-deoxy-D-ribose **375** in the presence of montmorillonite KSF clay under mild conditions to give 1:1 mixtures of tetrahydroquinolines **377** and **378** in very good yields. The initial Michael addition, followed by a Friedel–Crafts cyclization, afforded intermediate **A**, which subsequently underwent a second cyclization to furnish tetrahydroquinolines **377** and **378** (Scheme 102).  $\text{InCl}_3$  was also found to be effective to achieve this transformation, and, interestingly, in this case the reaction was carried out in water.<sup>370</sup>

In an article dealing mainly with the synthesis of optically active chromanes using a tandem Michael addition–Friedel–Crafts reaction sequence, a single example was reported of the synthesis of tetrahydroquinoline **379** starting from *m*-methoxy-*N*-methylaniline and a  $\beta,\gamma$ -unsaturated  $\alpha$ -ketoester in the presence of a chiral ligand and magnesium triflate.<sup>371</sup> Although the product was obtained as a single diastereoisomer in quantitative yield, no enantioselectivity was achieved (Scheme 103).

A set of tetrahydroquinolines acting as human androgen receptor (hAR) antagonists were synthesized starting from anilines and  $\alpha,\beta$ -unsaturated carboxylic acids. The synthesis

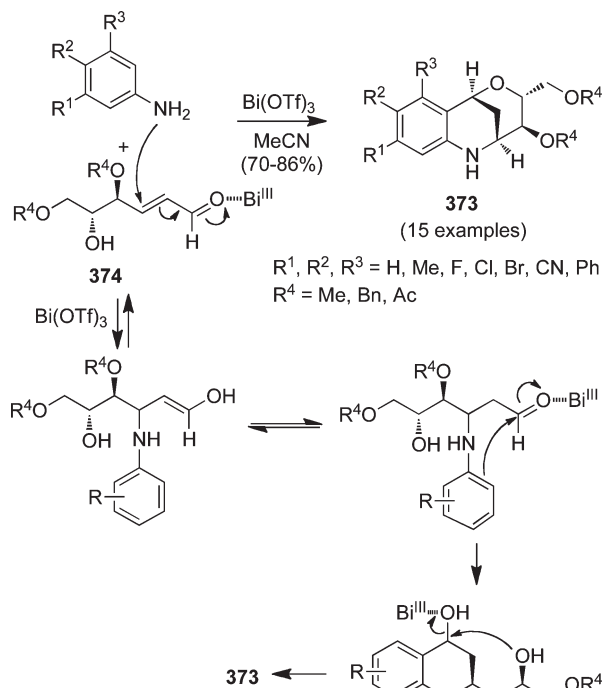
Scheme 99. Gurjar's Pd-Catalyzed Synthesis of Pyrroloquinolones **372**Scheme 100.  $\text{InBr}_3$ -Catalyzed Diastereoselective Synthesis of Enantiopure Tetrahydroquinolines **373**

was straightforward and the simple tetrahydroquinolin-4-ones **380** thus obtained were further manipulated into the structurally complex tricyclic tetrahydroquinoline derivatives **382** through the intermediacy of 7-amino-1,2,3,4-tetrahydroquinolines **381**.<sup>113</sup> All the synthesized compounds were tested for their human androgen receptor antagonist activity and many of them showed interesting activity (Scheme 104). Subsequently, the same group extended their studies in an effort to develop more active analogs, and again they used a similar strategy for the construction of the tetrahydroquinoline moiety.<sup>114</sup>

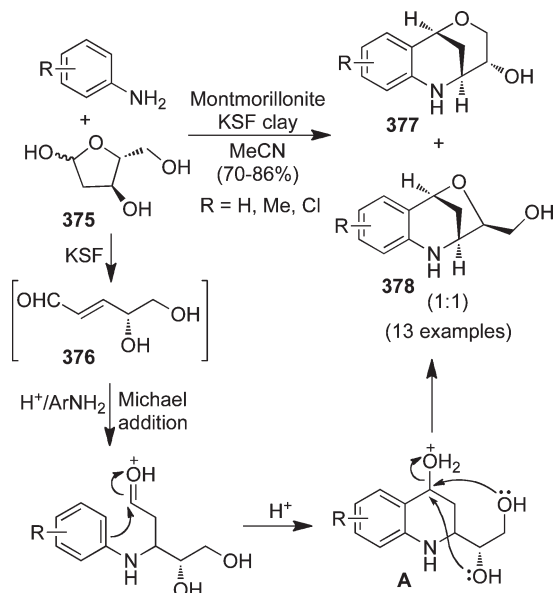
The 6-amino-1,2,3,4-tetrahydroquinoline derivative **384**, an intermediate for the preparation of tetrahydroquinoline-derived follicle-stimulating hormone receptor antagonists **60**, was synthesized in two steps involving a iodine-catalyzed Skraup reaction<sup>372</sup> between a monoprotected *p*-phenylenediamine and mesityl oxide to give dihydroquinoline **383**. Its *N*-acetylation



**Scheme 101. Formation of Tetrahydroquinolines 373 via Tandem Michael Addition–Intramolecular Friedel–Crafts Cyclization Sequence**



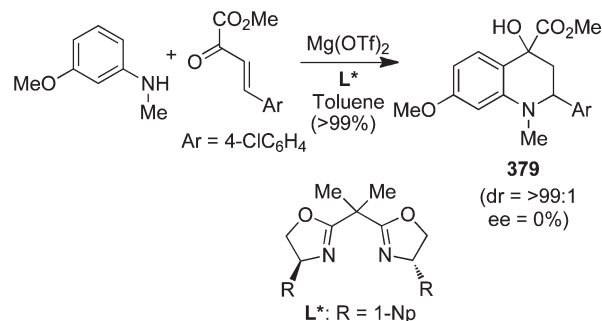
**Scheme 102. Montmorillonite Clay-Catalyzed Synthesis of Sugar-Derived Enantiopure Tetrahydroquinolines**



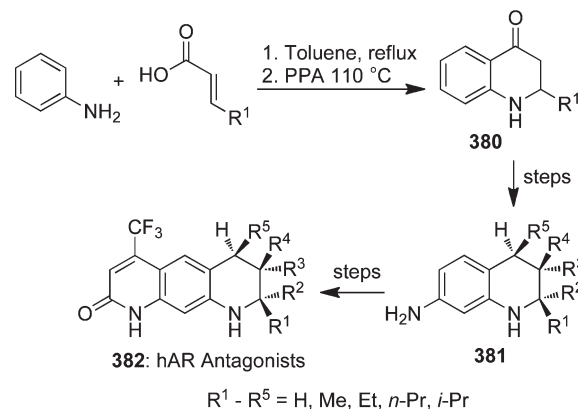
followed by  $\text{AlCl}_3$ -catalyzed Friedel–Crafts alkylation with benzene gave **384**, and further derivatization of the amino group furnished the bioactive compounds **60**<sup>124</sup> (Scheme 105).

Similarly, Roach and co-workers synthesized a set of 1,2,3,4-tetrahydroquinolines bearing an indole moiety, designed as potential glucocorticoid receptor ligands, through a molecular

**Scheme 103. Tandem Michael Addition–Friedel–Crafts Reaction Sequence for the Synthesis of Tetrahydroquinoline 379**



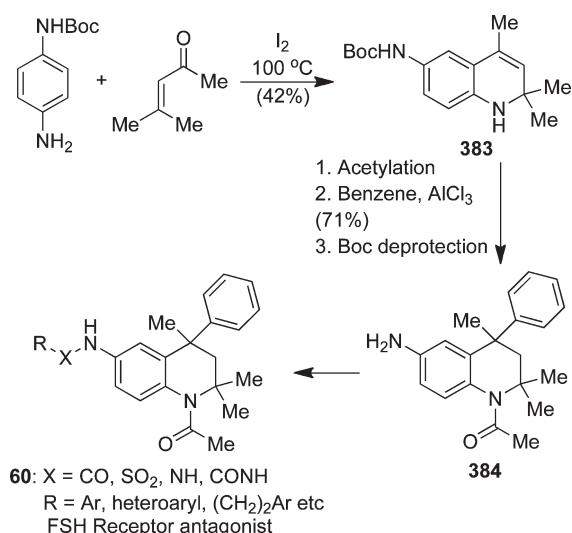
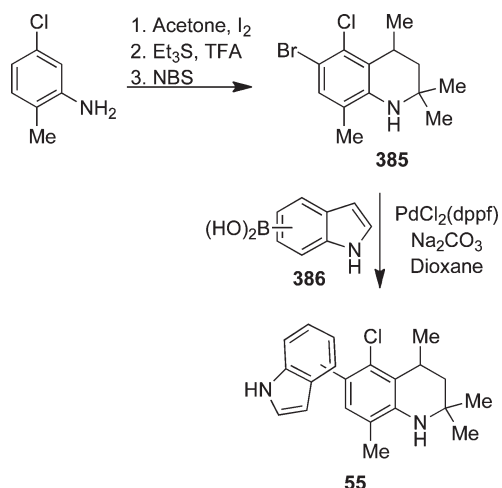
**Scheme 104. Synthesis of Human Androgen Receptor (hAR) Antagonists 382**



iodine-catalyzed reaction between arylamines and mesityl oxide, generated in situ by dimerization of acetone.<sup>116</sup> Treatment of 2-methyl-5-chloroaniline with acetone afforded the corresponding dihydroquinoline through the Skraup reaction, and this compound was then transformed into a 6-bromo tetrahydroquinoline derivative **385** through hydrogenation-bromination steps. A subsequent palladium-catalyzed Suzuki coupling with indoleboronic acids **386** furnished the glucocorticoid receptor ligands **55** (Scheme 106). In a closely related transformation, 2,2,4,7-tetramethyl-1,2,3,4-tetrahydroquinoline, a potential antioxidant, was synthesized through a molecular iodine-catalyzed reaction between *m*-toluidine and 4-hydroxy-4-methyl-pent-2-one, followed by catalytic hydrogenation.<sup>373</sup>

**5.3.2. Miscellaneous Reactions.** Getautis and co-workers reported the synthesis of some tetrahydroquinolines having application in materials science starting from diphenylamine and epichlorohydrin. The 3-hydroxy-1-phenyl-1,2,3,4-tetrahydroquinoline **387** was synthesized in 62% yield using epoxide opening-cyclization steps, and they were subsequently transformed into the hole-transporting materials **388** in five straightforward steps (Scheme 107).<sup>374</sup>

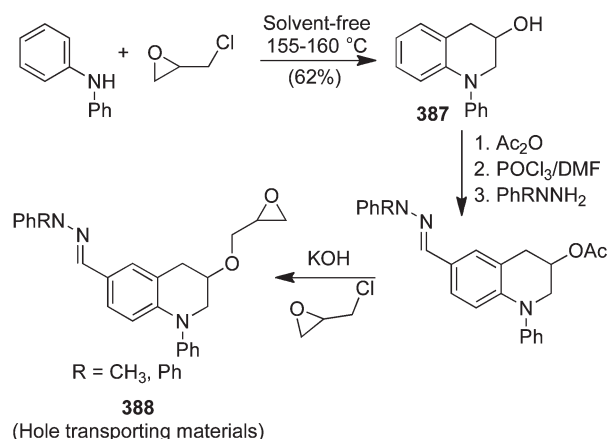
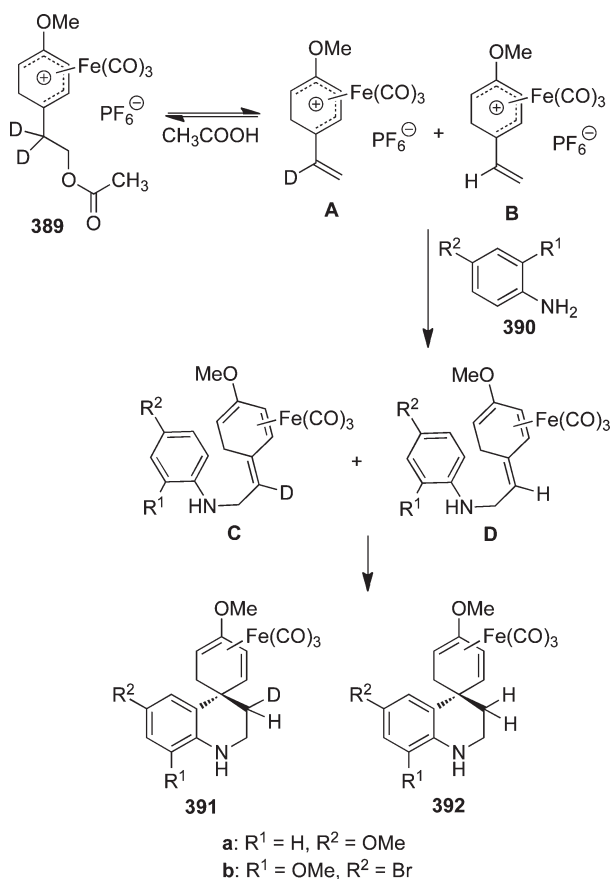
A revised mechanism has been proposed for the reaction between cationic 1-substituted ( $\eta^5$ -4-methoxycyclohexadienyl)-(tricarbonyl)iron complexes with anilines for the synthesis of spiro-tetrahydroquinoline derivatives.<sup>375</sup> The reaction of bideuterated complex **389** with anilines **390** afforded the 3-azaspiro[5,5]undecane derivatives as a mixture of mono- and

**Scheme 105. Synthesis of Follicle-Stimulating Hormone Receptor Antagonists 60****Scheme 106. Roach's Synthesis of Glucocorticoid Receptor Ligands 55**

nondeuterated compounds **391** and **392**. On the basis of this observation, a mechanism was proposed involving the vinylogous intermediates **A** and **B**. The nondeuterated cation **B** could be generated from the monodeuterated species **A** by successive addition–elimination reactions of the nucleophile present in the reaction mixture. Intermediates **A** and **B** reacted with anilines to give the final products **391** and **392** through the second set of intermediates **C** and **D** (Scheme 108).

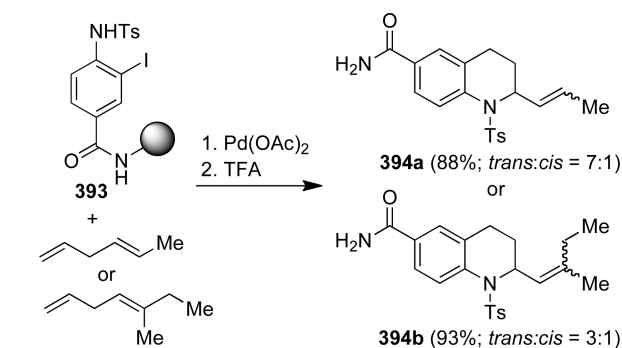
Wang and Huang reported the synthesis of 1,2,3,4-tetrahydroquinolines through a palladium-catalyzed reaction between solid-phase linked *N*-tosyl-2-iodoanilines and 1,4-dienes. For instance, the aniline derivative **393** reacted with 1,4-pentadiene or 5-methyl-1,4-heptadiene in the presence of Pd(OAc)<sub>2</sub> and furnished the corresponding 2-alkenyl-1,2,3,4-tetrahydroquinolines **394** in excellent yields after removal of the solid support by TFA (Scheme 109).<sup>376</sup>

Recently, Waibel and Cramer demonstrated a novel protocol for the synthesis of some types of nitrogen heterocycles,

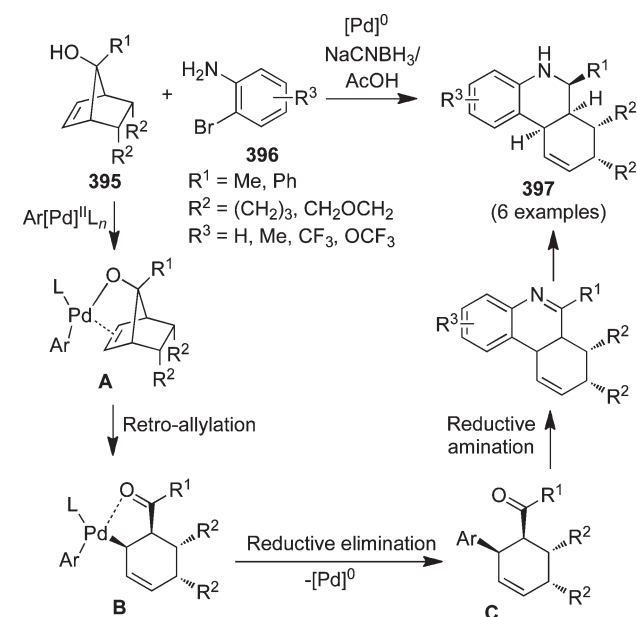
**Scheme 107. Synthesis of Tetrahydroquinoline-Based Hole Transporting Materials****Scheme 108. Revised Mechanism for the Reaction between Cationic Complex 389 and Arylamines**

including fused tetrahydroquinolines, involving a Pd(0)-catalyzed domino cyclization between *o*-bromoanilines and norbornenols.<sup>377</sup> A broad variety of norbornenols **395** underwent arylative ring-opening with *o*-bromoanilines **396** in the presence of a palladium catalyst followed by NaCNBH<sub>3</sub> reduction to afford the fused tetrahydroquinolines **397** in good yields. The reaction could proceed through intermediate **A**, generated

Scheme 109. Wang and Huang's Pd-Catalyzed Synthesis of Tetrahydroquinolines



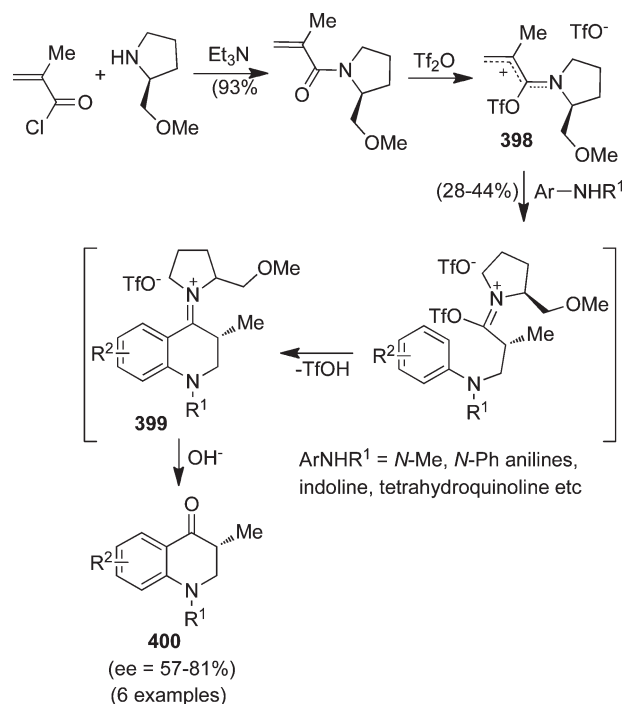
Scheme 110. Synthesis of Fused Tetrahydroquinolines Reported by Waibel and Cramer



by coordination of the Pd species with both the hydroxy group and the double bond of **395**, which could be transformed into the Pd(II) intermediate **B** through a retro-allylation process. Reductive elimination of **B** would give ketone **C**, which would then undergo intramolecular condensation followed by hydride reduction to provide the final tetrahydroquinoline derivatives **397** (Scheme 110).

Only a limited number of procedures are known for the synthesis of 3-substituted tetrahydroquinolines. For this reason, the method developed by Nenajdenko and co-workers, which allowed the enantioselective synthesis of 3-methyltetrahydroquinolin-4-ones starting from anilines, is significant. The *N*-methacryloyl-(*S*)-2-methoxymethyl pyrrolidine-triflic anhydride complex **398**, prepared by acylation of (*S*)-2-methoxymethyl pyrrolidine with methacryloyl chloride followed by treatment with  $\text{TiF}_2\text{O}$ , reacted with secondary aromatic amines to afford the corresponding tetrahydroquinolones **400** after hydrolysis of the enamine intermediate **399** (Scheme 111).<sup>378</sup>

In another report, 6-ethyl-2,3-dihydroquinolin-4(1*H*)-one, a precursor for the synthesis of tetrahydroquinoline-based

Scheme 111. Synthesis of Chiral 3-Methyltetrahydroquinolin-4-ones **400**

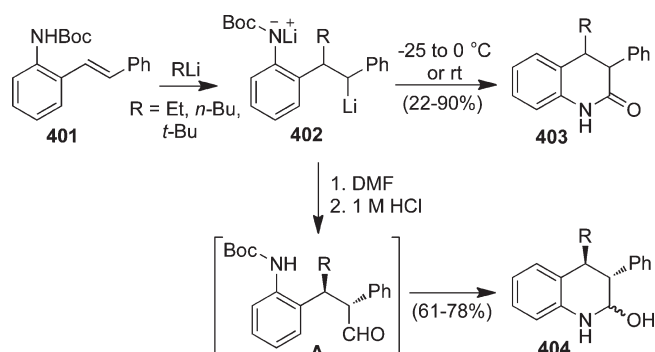
antibacterial agents, was prepared through the reaction between 4-ethylaniline and propiolactone. Treatment of the intermediate obtained with  $\text{P}_2\text{O}_5$ /polyphosphoric acid at elevated temperature afforded the tetrahydroquinoline derivative and subsequent structural modifications led to biologically important compounds.<sup>43</sup> It is relevant to mention here that tetrahydroquinoline-2,4-diones were synthesized, by condensation of arylamines and diethyl benzylmalonate, followed by oxidation with peroxyacetic acid, and their reactivity was also subsequently studied.<sup>379</sup>

#### 5.4. Formation of the N–C<sub>2</sub> and C<sub>2</sub>–C<sub>3</sub> Bonds

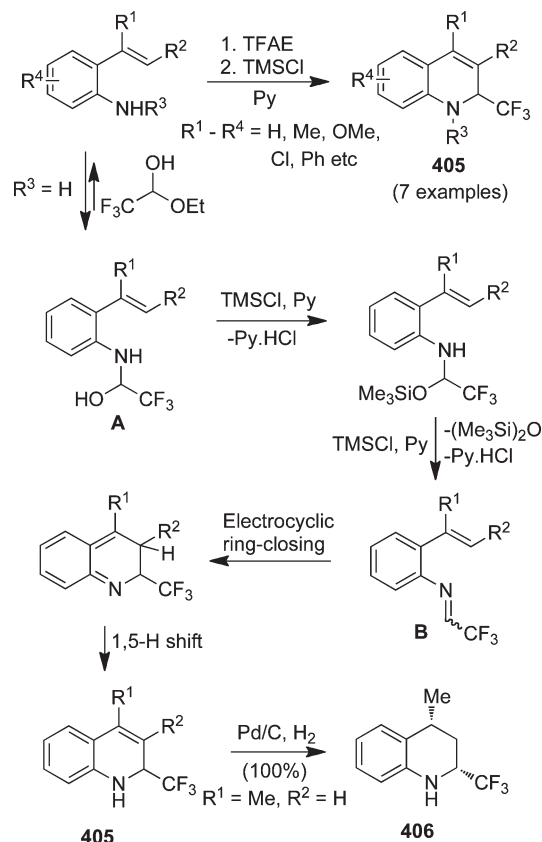
2-Amino-(*E*)-stilbenes were effectively converted into 1,2,3,4-tetrahydroquinoline derivatives through a regioselective carbolithiation process.<sup>380</sup> The *N*-Boc-protected *o*-aminostilbenes **401** gave lithiated intermediates **402** upon treatment with alkyl-lithium reagents at low temperature, which afforded the corresponding tetrahydroquinolin-2-ones **403** during gradual increase of the reaction temperature to 0 °C. On the other hand, the lithiated intermediates **402** reacted with DMF followed by acid treatment to furnish 2-hydroxy-tetrahydroquinolines **404** as a mixture of two diastereoisomers in good yields via the aldehyde intermediate **A** (Scheme 112). A year later, the authors published a full article elaborating their preliminary results of the carbolithiation processes.<sup>381</sup>

Taguchi and co-workers developed an efficient procedure for the synthesis of fluorinated 1,2-dihydroquinolines **405** by the reaction between 2-vinylanilines and trifluoroacetaldehyde ethyl hemiacetal (TFAE) in the presence of TMSCl in pyridine.<sup>382</sup> One of the compounds **405** was then hydrogenated quantitatively into *cis*-tetrahydroquinoline **406** (Scheme 113). A mechanism was proposed assuming that TMSCl and pyridine accelerate the formation of an imine **B** through the *N,O*-hemiacetal intermediate **A**. The electrocyclic ring-closing of imine **B** followed by a 1,5-hydrogen shift afforded the 1,2-dihydroquinolines **405**.

**Scheme 112. Tetrahydroquinoline Synthesis Involving Regioselective Carbolithiation Process**



**Scheme 113. Taguchi's Synthesis of Fluorinated 1,2-Dihydroquinolines**

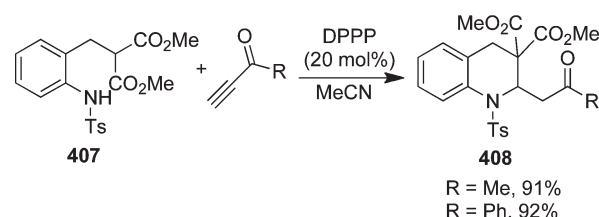


In a general article describing the synthesis of indolines, dihydropyrrolopyridines, benzimidazolines, tetrahydroisoquinolines, dihydrobenzo-1,4-oxazines, and dihydrobenzo-3,1-oxazines based on a diphenylphosphinopropane (DPPP)-catalyzed C- and N-double-Michael reaction, the preparation of 1,2,3,4-tetrahydroquinolines **408** from aniline derivative **407** was also reported (Scheme 114).<sup>383</sup>

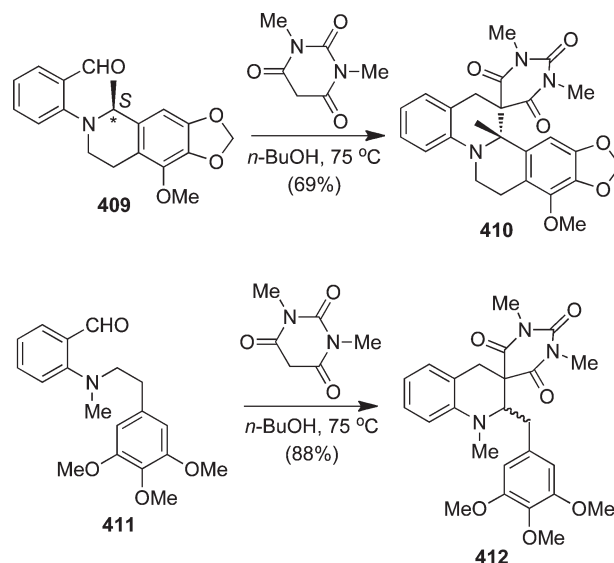
### 5.5. Formation of the C<sub>2</sub>–C<sub>3</sub> and C<sub>3</sub>–C<sub>4</sub> Bonds

A number of complex tetrahydroquinoline-based heterocycles were synthesized starting from naturally occurring chiral starting materials through a strategy that involved the application of the

**Scheme 114. Diphenylphosphinopropane (DPPP)-Catalyzed Synthesis of Tetrahydroquinolines **408****



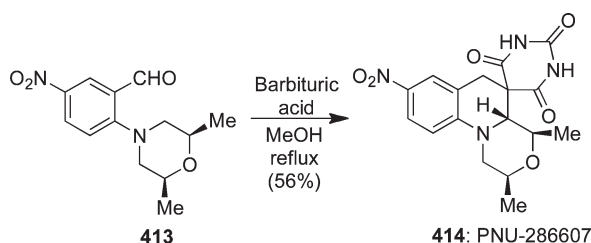
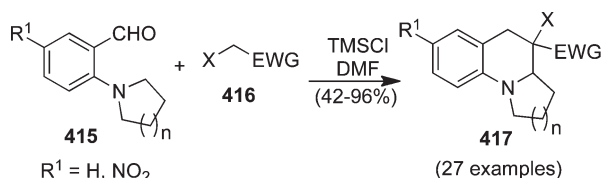
**Scheme 115. Synthesis of Barbituric Acid-Derived Spiro-Tetrahydroquinolines Involving *tert*-Amino Effect**



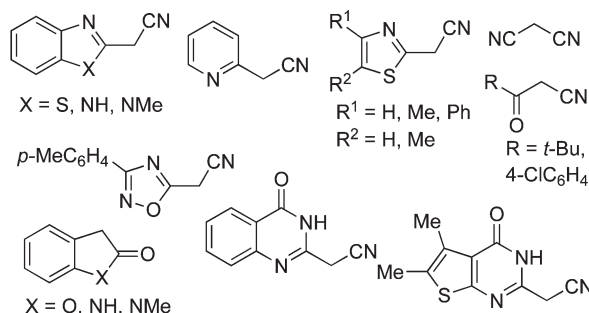
*tert*-amino effect (see also section 4.3.1). For instance, the derivative of (–)-anhalonine **409** reacted with *N,N*-dimethylbarbituric acid to give spiro-tetrahydroquinoline **410** as a single diastereoisomer by creating the C<sub>2</sub>–C<sub>3</sub> and C<sub>3</sub>–C<sub>4</sub> bonds simultaneously. Similarly, *N*-methylmescaline derivative **411** underwent regioselective cyclization to afford compound **412** (Scheme 115).<sup>384</sup> Meldrum's acid was also used instead of barbituric acid and the products derived from Meldrum's acid were transformed into the corresponding tetrahydroquinoline-3-carboxylic acids by acid treatment. Other *N*-piperidine and *N*-pyrrolidine substrates were also used for the construction of tetrahydroquinoline derivatives. Recently, a similar procedure was used for the synthesis of 3-spiro-tetrahydroquinolines from arylaldehydes and *N*-monoalkyl barbituric acids.<sup>385</sup>

The antibacterial tetrahydroquinoline derivative PNU-286607 (**414**)<sup>386</sup> was also synthesized by a route that involved the application of the *tert*-amino effect. Treatment of the *meso*-aldehyde **413** with barbituric acid in methanol under reflux conditions without any catalyst furnished compound **414** in good yield.<sup>387</sup> Subsequently the asymmetric synthesis of the (–)-enantiomer of **414** was achieved, again in high yields (Scheme 116).

Another application of the *tert*-amino effect to the synthesis of complex fused tetrahydroquinolines was reported by Volochnyuk and co-workers, who established the synthesis of pyrrolo- and pyrido- tetrahydroquinolines **417** starting from aryl dialkylaminoaldehydes **415** and a wide variety of active

**Scheme 116.** Synthesis of Antibacterial Tetrahydroquinoline Derivative PNU-286607 (**414**)**Scheme 117.** Volochnyuk's Synthesis of Pyrrolo- and Pyrido-Tetrahydroquinolines **417**

Selected examples of **416**:

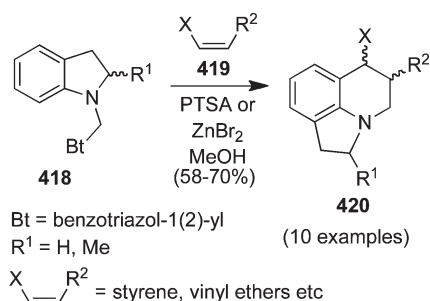
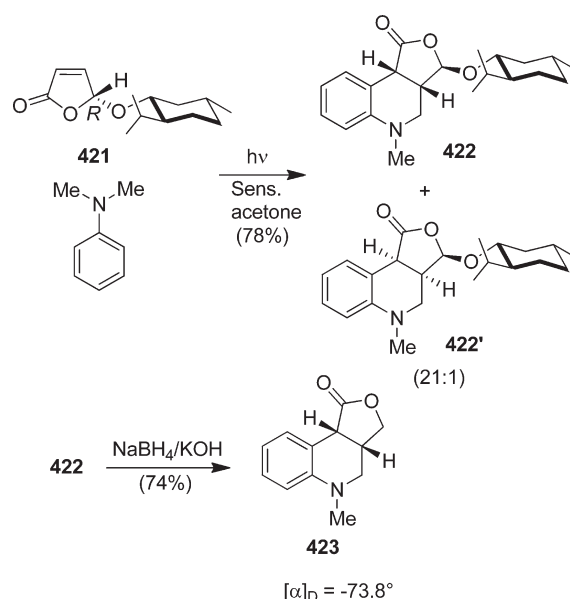


methylene compounds **416** in the presence of TMSCl in DMF<sup>388,389</sup> (Scheme 117).

### 5.6. Formation of the C<sub>2</sub>–C<sub>3</sub> and C<sub>4</sub>–C<sub>4a</sub> Bonds

Katritzky's benzotriazole methodology has found application to the synthesis of pyrrolo-tetrahydroquinolines. The benzotriazolyl derivatives of indolines **418** reacted with unactivated and electron-rich alkenes **419**, including styrene and vinyl ethers, in the presence of a catalytic amount of *p*-toluenesulfonic acid to afford the corresponding tetrahydroquinoline derivatives **420** in high yields (Scheme 118).<sup>390</sup> A similar procedure was employed by the original authors for the synthesis of tetrahydroquinoline derivatives bearing carbazole<sup>391</sup> and benzodiazepinone<sup>392</sup> fragments. In a related procedure, unactivated alkenes were also used for the synthesis of 4-, 2,4-, 3,4-substituted 1,2,3,4-tetrahydroquinolines.<sup>393</sup>

Hoffmann and co-workers illustrated the synthesis of tetrahydroquinolines **422** in moderate yields through a domino radical reaction between *N,N*-dimethylaniline and furanone **421** in the presence of catalytic amount of Michler's ketone as a sensitizer under photochemical conditions.<sup>394</sup> A few years later the reaction was improved to give higher yield (78%) and diastereoselectivity (21:1) using acetone as the photosensitizer. The chiral auxiliary of compound **422** was removed by NaBH<sub>4</sub> reduction to afford the enantiopure tetrahydroquinoline **423** (Scheme 119).<sup>395</sup> It is also relevant to mention here that the

**Scheme 118.** Synthesis of Pyrrolo-tetrahydroquinolines Involving Katritzky's Benzotriazole Methodology**Scheme 119.** Hoffmann's Synthesis of Tetrahydroquinolines under Photochemical Conditions

*N,N*-dimethylaniline hydroperoxide, obtained through a radical reaction between the corresponding aniline and the NHPI/Co(OAc)<sub>2</sub>/O<sub>2</sub> system, was effectively converted into tetrahydroquinoline derivatives by treatment with alkenyl ethers in the presence of BF<sub>3</sub>·OEt<sub>2</sub>.<sup>396</sup>

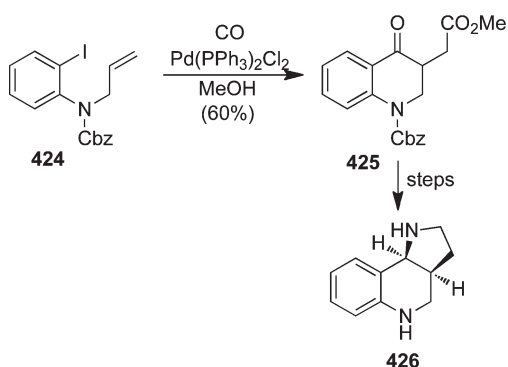
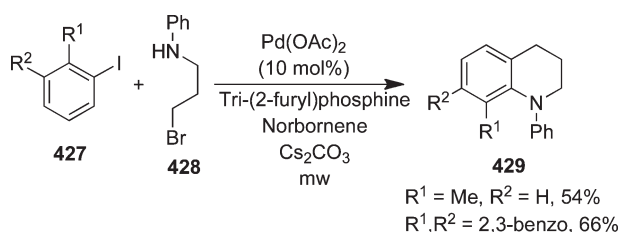
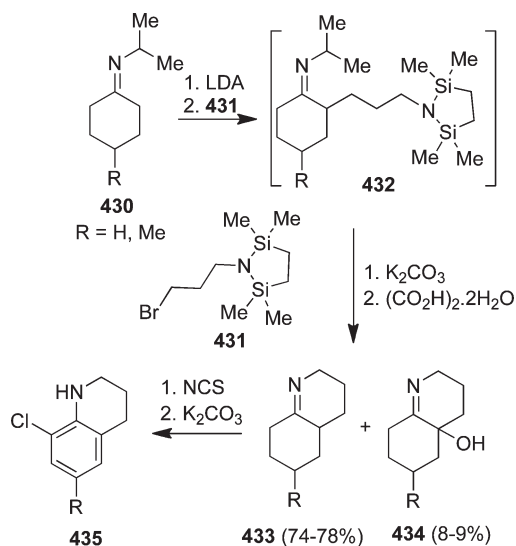
### 5.7. Formation of the C<sub>3</sub>–C<sub>4</sub> and C<sub>4</sub>–C<sub>4a</sub> Bonds

The only available report for the synthesis of tetrahydroquinolines **422** involving the creation of the C<sub>3</sub>–C<sub>4</sub> and C<sub>4</sub>–C<sub>4a</sub> bonds is the palladium-catalyzed carbonylative cyclization of *N*-allyl-2-iodoaniline.<sup>397</sup> During the enantioselective synthesis of the pyrroloquinoline core of the martinelline alkaloids **2**, Nieman and Ennis synthesized tetrahydroquinolin-4-one **425**, precursor for the synthesis of pyrroloquinoline **426**, starting from the Cbz protected *N*-allyl-2-iodoaniline **424** and carbon monoxide in the presence of a palladium catalyst in methanol by employing a modified procedure developed by Negishi.<sup>398</sup> The tetrahydroquinolin-4-one **425** was subsequently transformed into pyrroloquinoline **426** in six additional steps (Scheme 120).

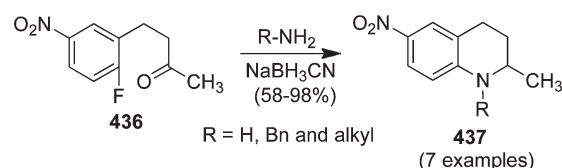
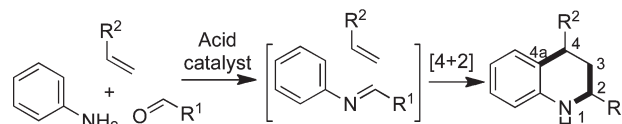
### 5.8. Formation of the C<sub>8a</sub>–N and C<sub>4</sub>–C<sub>4a</sub> Bonds

The palladium-catalyzed C–C and C–N bond formation of bromoalkylamines and functionalized aryl iodides allowed the



**Scheme 120. Pd-Catalyzed Carbonylative Cyclization Reaction****Scheme 121. Synthesis of Tetrahydroquinolines via Pd-Catalyzed C–C and C–N Bond Formation Reactions****Scheme 122. Tetrahydroquinoline Synthesis via  $\alpha$ -Lithiation of Cyclohexanone Imines**

synthesis of tetrahydroquinoline derivatives.<sup>399</sup> For instance, *N*-phenyl bromopropylamine **428** reacted with aryl iodides **427** in the presence of 10 mol % of  $\text{Pd}(\text{OAc})_2$ , norbornene, tri-(2-furyl)phosphine and  $\text{Cs}_2\text{CO}_3$  under microwave irradiation furnished *N*-phenyl-1,2,3,4-tetrahydroquinolines **429** in good yields (Scheme 121). A mechanism was proposed based on an initial ortho-alkylation followed by Buchwald–Hartwig reaction involving  $\text{Pd}(0)/\text{Pd}(\text{IV})$  species.

**Scheme 123. Bunce's Reductive Amination- $\text{S}_{\text{N}}\text{Ar}$  Reaction Sequence for the Synthesis of Tetrahydroquinolines****Scheme 124. Povarov Reaction**

$\alpha$ -Lithiation of cyclohexanone imines **430**, followed by addition of primary halide **431**, which contains a masked primary amino group, afforded compounds **432**. *N*-Desilylation with potassium carbonate led to mixtures of octahydroquinolines **433** via a transimination of an intermediate  $\delta$ -aminoimine, together with their air-oxidation products **434**. Chlorination of the mixtures of **433** and **434** with *N*-chlorosuccinimide, followed by base-induced elimination, afforded tetrahydroquinolines **435**<sup>400</sup> (Scheme 122).

### 5.9. Formation of the N–C<sub>2</sub> and C<sub>8a</sub>–N Bonds

Bunce and co-workers developed a novel procedure for the synthesis of 6-nitro-1,2,3,4-tetrahydroquinoline derivatives based on a reductive amination– $\text{S}_{\text{N}}\text{Ar}$  reaction sequence.<sup>401,402</sup> The starting compound **436** was prepared in three steps from *t*-butyl acetoacetate and 2-fluoro-5-nitrobenzyl bromide. Treatment of ketone **436** with a wide variety of primary amines in the presence of  $\text{NaBH}_3\text{CN}$  afforded tetrahydroquinoline derivatives **437** in good to excellent yields (Scheme 123). However, the corresponding aldehydes gave the tetrahydroquinolines together with small amounts of the hydroamination products.

## 6. SYNTHESIS OF 1,2,3,4-TETRAHYDROQUINOLINES INVOLVING THE GENERATION OF THREE OR MORE BONDS

This Section will cover the methods that allow the synthesis of 1,2,3,4-tetrahydroquinolines by creating three or more bonds in a single operation starting from a benzene derivative and two or more  $\text{C}_2$ – $\text{C}_3$ – $\text{C}_4$  fragments.

### 6.1. Formation of the N–C<sub>2</sub>, C<sub>2</sub>–C<sub>3</sub>, and C<sub>4</sub>–C<sub>4a</sub> Bonds: The Povarov and Related Reactions

**6.1.1. Introduction.** The acid-catalyzed inverse electron demand formal  $[4 + 2]$  cycloaddition reaction between *N*-arylimines and electron-rich dienophiles to give 1,2,3,4-tetrahydroquinolines, normally classified among aza-Diels–Alder or imino-Diels–Alder reactions, was developed by the Russian chemist Povarov in 1960s, and is now popularly known as the Povarov reaction.<sup>403</sup> The reaction can also be performed in three-component fashion using the in situ generated *N*-arylimines starting from suitable arylamines and aldehydes, and a dienophile. The three-component Povarov reaction allows the creation of three bonds, that is, N–C<sub>2</sub>, C<sub>2</sub>–C<sub>3</sub> and C<sub>4</sub>–C<sub>4a</sub> bonds in a

Table 1. Catalysts Used for the Povarov Reaction

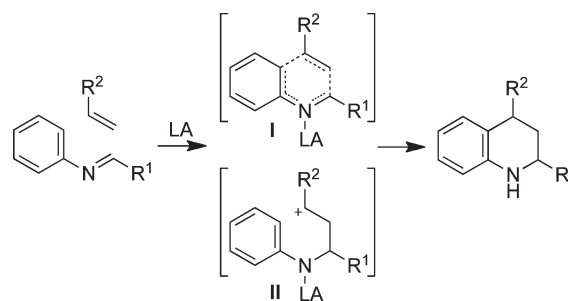
Lewis acids and metal salt-related catalysts	Brønsted acids and others
BF <sub>3</sub> ·OEt <sub>2</sub>	CF <sub>3</sub> COOH
Ln(OTf) <sub>3</sub> Ln = La, Pr, Nd, Sm, Eu, Gd, Dy, Ho, Er, Tm, Yb, and Lu	(CF <sub>3</sub> ) <sub>2</sub> CHOH
	CF <sub>3</sub> CH <sub>2</sub> OH
	CF <sub>3</sub> SO <sub>3</sub> H
	HCl
Sc(OTf) <sub>3</sub> , Y(OTf) <sub>3</sub>	TsOH
Yb(OTf) <sub>3</sub> /(R)-(+)-BINOL	PPA
	NH <sub>2</sub> SO <sub>3</sub> H
CAN	phosphomolybdic acid
I <sub>2</sub> , SmI <sub>2</sub>	polymer-supported $\pi$ -acid
CuBr <sub>2</sub>	(poly-DCKA-1)
ZnCl <sub>2</sub> , ZnCl <sub>2</sub> /SiO <sub>2</sub>	camphorsulfonic acid (CSA)
TiO <sub>2</sub> /h $\nu$	
BiCl <sub>3</sub> , InCl <sub>3</sub>	photoinduced electron transfer (PET)
TiCl <sub>3</sub> , TiCl <sub>4</sub> –PPh <sub>3</sub>	
GdCl <sub>3</sub> , SbCl <sub>3</sub>	molecular sieves
FeCl <sub>3</sub> , ZrCl <sub>4</sub>	ionic liquids
SnCl <sub>4</sub> , TiCl <sub>4</sub> –PPh <sub>3</sub>	selenium ionic liquid salts
Et <sub>2</sub> AlCl	
EtAlCl <sub>2</sub> , MeAlCl <sub>2</sub>	montmorillonite KSF
LiClO <sub>4</sub>	2,4,6-triphenylpyrylium
Et <sub>3</sub> N–AlCl <sub>3</sub>	tetrafluoroborate (TPT)
Ar <sub>3</sub> N <sup>+</sup> ·SbCl <sub>6</sub> <sup>−</sup>	
PPh <sub>3</sub> ·HClO <sub>4</sub>	resin AG50W-X2
Ph <sub>3</sub> PO·Tf <sub>2</sub> O	Fe <sup>3+</sup> –K-10 clay
KHSO <sub>4</sub>	Co <sub>2</sub> (CO) <sub>8</sub>
ABDDP–TiCl <sub>2</sub>	TMSCl

single operation. Although the two-component version of the reaction involving the use of isolated *N*-arylimines for the construction of tetrahydroquinolines by creating the C<sub>2</sub>–C<sub>3</sub> and C<sub>4</sub>–C<sub>4a</sub> bonds in the key step is also widely used, for the sake of a better organization we will present both the two- and three-component Povarov reactions together in this Section (Scheme 124).

The synthetic applications of the Povarov reaction were reviewed almost simultaneously, but independently, by Glushkov<sup>404</sup> and Kouznetsov.<sup>405</sup> Since the latter review covers the literature up to September 2008, we will discuss here a short summary of the previous reports as background information, together with the recent advances of the Povarov and related reactions from the mentioned date. The appearance of more than 70 articles involving the use of the Povarov reaction during the mid-2008 to mid-2010 period proves the enormous importance, scope, and synthetic applications of this transformation.

The Povarov reaction can be catalyzed by a variety of reagents, including Lewis acids, Brønsted acids, and metal salts, which are listed in Table 1.<sup>405</sup> Moreover, the reaction permits a huge diversity in substrate selection, allowing the use of a variety of electron-rich and electron-deficient arylamines and aldehydes in the diene component and vinyl ethers, vinyl sulfides, silyl enol ethers, vinyl enamides, enamines, alkenes, and alkynes as dienophiles. Chiral versions of the reaction have also been achieved, leading to the synthesis of enantiopure tetrahydroquinolines in the presence of enantioselective catalysts. In addition, a wide

Scheme 125. Concerted and Stepwise Mechanisms of the Povarov Reaction



variety of intramolecular versions of the Povarov reaction have been developed for the synthesis of polycyclic, natural product-like tetrahydroquinolines.

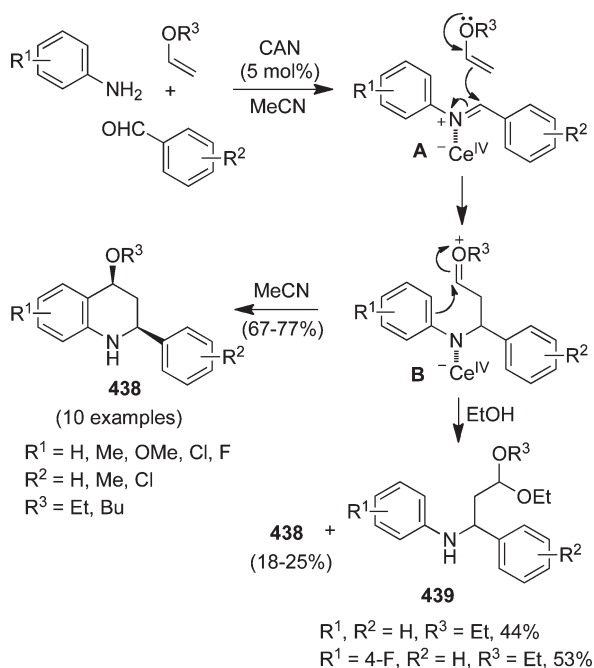
**6.1.2. Mechanistic Aspects.** Regarding the mechanism of the Povarov reaction,<sup>406</sup> initially it was believed that it could proceed through a concerted process involving a cyclic transition state I similar to the one proposed for the traditional [4 + 2] Diels–Alder cycloaddition reaction. However, recent developments involving the trapping of reaction intermediates proved that the reaction is stepwise and it proceeds through the cationic intermediate II (Scheme 125).

As an example of the type of reasoning employed to study the mechanism of the Povarov reaction, we will discuss here the CAN-catalyzed<sup>407</sup> three-component reaction between arylamines, aromatic aldehydes and vinyl ethers for the diastereoselective synthesis of 4-alkoxy-2-ary-1,2,3,4-tetrahydroquinolines.<sup>408</sup> The one-pot reaction proceeded in less than one hour in acetonitrile and gave tetrahydroquinolines **438** in good yields (67–77%) with excellent diastereoselectivity (*dr* = 92:8 to 97:3), regardless of the nature of the substituents on the *N*-aryl ring (Scheme 126). Interestingly, when the reaction was carried out in ethanol, acetals **439** were isolated as the major products together with small amounts of tetrahydroquinolines **438**. It was clear from this observation that the vinyl ethers added to the Lewis acid (CAN)-activated *N*-aryl imine **A** to generate the oxonium species **B**, which subsequently underwent an intramolecular electrophilic substitution reaction to afford tetrahydroquinolines **438**. On the other hand, when the reaction was performed in ethanol, the oxonium species **B** was trapped by the nucleophilic solvent to furnish acetals **439**, which confirmed the generation of the carbocation intermediate and hence the stepwise mechanism (Scheme 126).<sup>409</sup>

The origin of the diastereoselectivity can be explained based on the configuration of the oxonium intermediate **B**. The major *cis* tetrahydroquinoline may be derived from the less-hindered chair-like transition state **B1** where the alkoxy and aryl groups occupy the equatorial positions, allowing minimum interaction between the substituents. The minor *trans* product would arise from the more hindered, less favored transition state **B2** (Scheme 127). It must be pointed out, however, that these assumptions, although logical, have not been confirmed by computational studies.<sup>410</sup>

**6.1.3. Lewis Acid-Catalyzed Reactions.** The SnCl<sub>4</sub> and BF<sub>3</sub>·OEt<sub>2</sub>-catalyzed, one-pot, three-component reaction between *N*-methylaniline, paraformaldehyde, and nonactivated alkenes, leading to the synthesis of 2-unsubstituted 1,2,3,4-tetrahydroquinolines in high yields. The reaction was proposed to proceed through a cationic intermediate derived from the

**Scheme 126.** Menéndez's Evidence for the Stepwise Mechanism of the CAN-Catalyzed Povarov Reaction



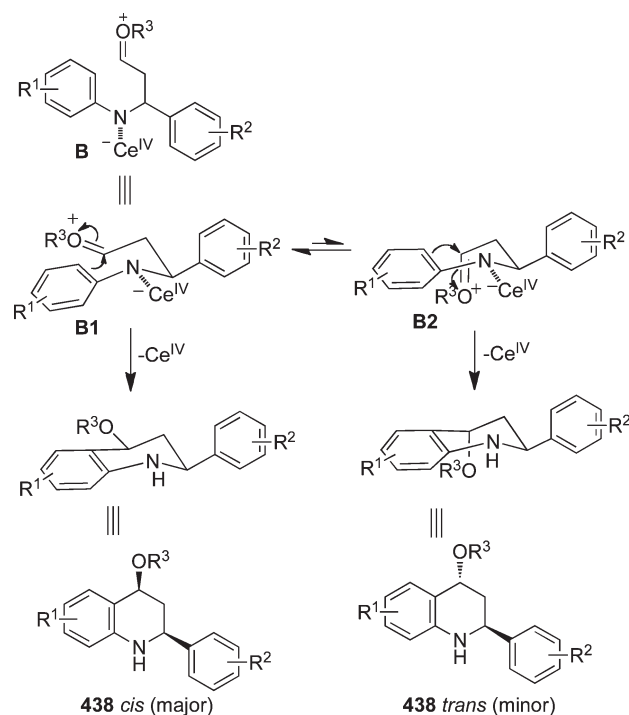
reaction between *N*-methylaniline and formaldehyde.<sup>411</sup> Recently, Kouznetzov, one of the main contributors to Povarov chemistry, used a similar procedure for the synthesis of 4-aryl-3-methyltetrahydroquinolines.<sup>412</sup> The cationic intermediate **A**, generated from the starting *N*-benzylanilines **440** and formaldehyde, reacted with *trans*-anethole **441a** and *trans*-isoeugenol **441b** in the presence of  $\text{BF}_3 \cdot \text{OEt}_2$  and afforded the *trans*-3,4-disubstituted tetrahydroquinolines **442** in good yields (Scheme 128). The *N*-protection was successfully removed under catalytic hydrogenation conditions. It should be mentioned here that the intermediates of type **A** had been previously generated from *N*-substituted *N*-(ethoxymethyl)anilines and 2-(phenylamino)acetonitriles in the presence of Lewis acids.<sup>413</sup>

The diastereoselective synthesis of 2-spiro-tetrahydroquinoline derivatives **444** was achieved in moderate yields based on a  $\text{BF}_3 \cdot \text{OEt}_2$ -catalyzed reaction between 3-*N*-aryliminoisatins **443** and isoeugenol **441b** (Scheme 129).<sup>414</sup> Almost simultaneously, Raghunathan and co-workers reported a  $\text{InCl}_3$ -catalyzed version of the same reaction using 3,4-dihydro-2*H*-pyran as the dienophile.<sup>415</sup> Although the latter reaction proceeded in higher yields, the products were isolated as mixtures of two separable diastereomers.

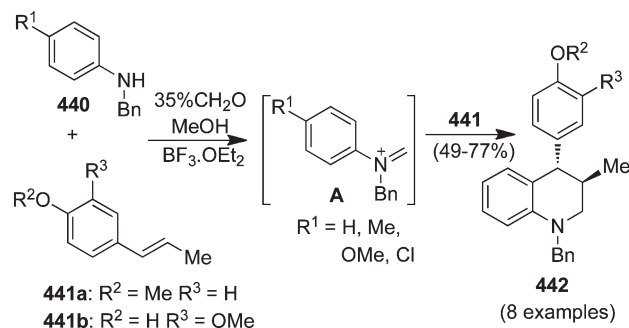
*N*-Vinylpyrrolidin-2-one was an interesting dienophile for the solvent-free, microwave-assisted, three-component synthesis of 2-aryl-1,2,3,4-tetrahydroquinolines **445** from arylamines and arylaldehydes in the presence of 20 mol % of  $\text{BiCl}_3$ . A library of 24 compounds was synthesized in good to excellent yields (78–95%) irrespectively of the nature of substituents on both aryl rings (Scheme 130).<sup>416</sup> Similarly,  $\text{SbCl}_3$ <sup>417</sup> and  $\text{CuPy}_2\text{Cl}_2$ <sup>418</sup> were also used as catalysts for the three-component Povarov reaction.

The  $\text{BF}_3 \cdot \text{OEt}_2$ -catalyzed synthesis of 2-furyl-4-(2-oxopyrrolidinyl)-substituted tetrahydroquinolines from the corresponding imines and *N*-vinylpyrrolidin-2-one was also reported recently.<sup>419</sup> Viologens, such as *N,N'*-dicyanomethyl-4,4'-bipyridinium  $\cdot 2\text{PF}_6$ , were also effective to catalyze the reaction

**Scheme 127.** Explanation for the Origin of the Diastereoselectivity



**Scheme 128.** Kouznetzov's Synthesis of 4-Aryl-3-methyltetrahydroquinolines

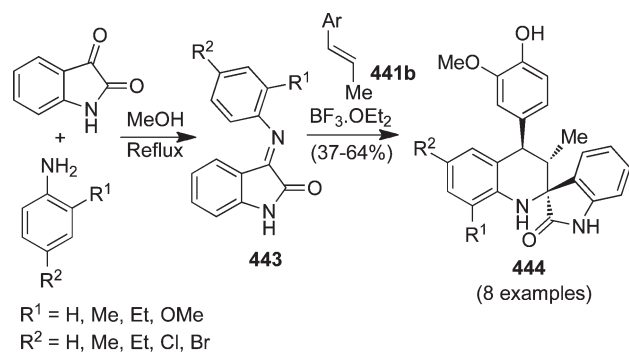


between *N*-arylimines and *N*-vinylpyrrolidin-2-one or *N*-vinylcarbazole to allow the diastereoselective synthesis of tetrahydroquinoline derivatives in high yields. The catalyst was proposed to act as a Lewis acid to activate the imine substrate.<sup>420</sup>

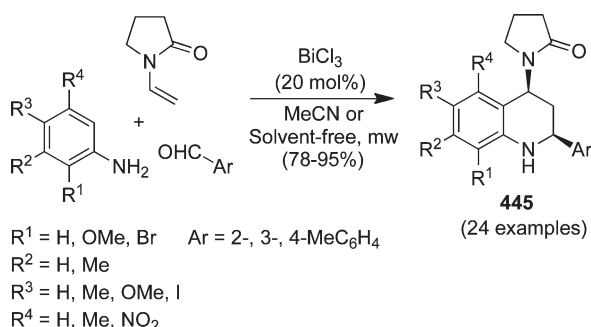
The reaction between arylamines and cyclic enol ethers in the presence of a catalytic amount of  $\text{BiBr}_3$  (5 to 20 mol %) afforded tetrahydroquinoline derivatives in moderate to good yields.<sup>421</sup> The arylamines reacted with one equivalent of enol ethers to give the corresponding *N*-arylimines **446**, which underwent [4 + 2] cycloaddition with another equivalent of the enol ether in the presence of  $\text{BiBr}_3$  to afford tetrahydroquinolines **447** as a diastereomeric mixture (Scheme 131). We have previously described the diastereoselective synthesis of 2-methyl-1,2,3,4-tetrahydroquinolines starting from arylamines and vinyl ethers, using CAN as a catalyst, through a similar mechanism.<sup>422</sup>

Lavilla and co-workers recently illustrated the use of unsaturated lactams with endo- and exocyclic C–C double bonds as

Scheme 129. Synthesis of 2-Spiro-tetrahydroquinolines



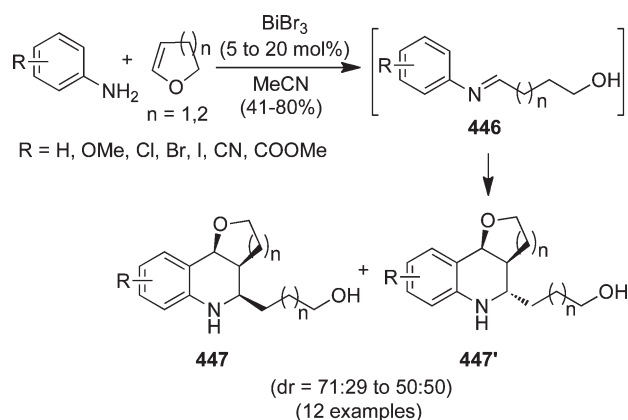
Scheme 130. Microwave-Assisted, Solvent-Free Synthesis of 2-Aryltetrahydroquinolines



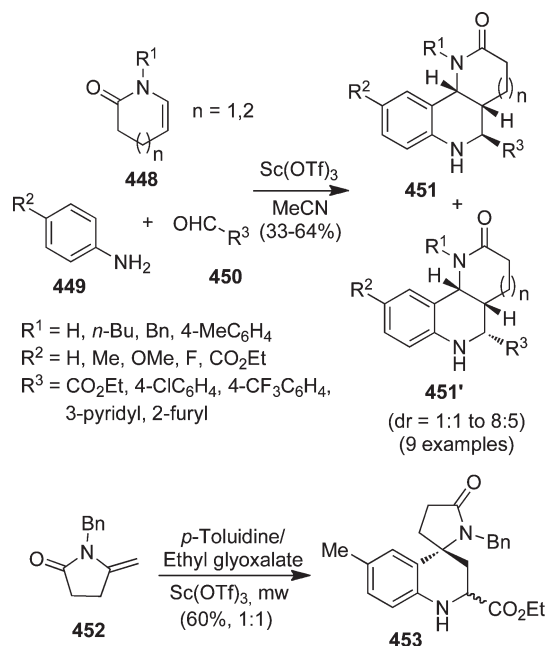
dienophiles for the  $\text{Sc}(\text{OTf})_3$ -catalyzed, three-component Povarov reaction.<sup>423</sup> The six- and seven-membered lactams **448** reacted with a wide variety of arylamines **449** and aliphatic, aryl and heteroaryl aldehydes **450** in the presence of  $\text{Sc}(\text{OTf})_3$  to afford tetrahydroquinoline derivatives **451** in moderate yields. Although the overall diastereoselectivity of the reaction was poor ( $dr = 1:1\text{--}8:5$ ), a single diastereomer was isolated in the case of the 2-furyl-substituted system. The pyrrolidone derivative bearing an exocyclic double bond **452** was used as a dienophile for the synthesis of 4-spiro-tetrahydroquinolines **453**, again as diastereomeric mixtures, under microwave irradiation (Scheme 132). It is also relevant to mention here the related preparation of spiro-tetrahydroquinolines as intermediates for the synthesis of glycosylidene-based quinolines starting from an exoglycal and *N*-arylimines in the presence of  $\text{Sc}(\text{OTf})_3$ .<sup>424</sup>

The Lavilla group has also pioneered the use of dihydropyridines as the dienophile component in Povarov reactions.<sup>425</sup> On this basis, we have recently explored the synthesis of tetrahydroquinolines **456** through a  $\text{Yb}(\text{OTf})_3$ -catalyzed reaction between *N*-arylimines and *N*-alkyl-1,4-dihydropyridines **455**.<sup>426</sup> The starting 1,4-dihydropyridines **455** were obtained using a novel Lewis acid ( $\text{CAN}$  or  $\text{InCl}_3$ )-catalyzed, four-component reaction between primary amines, 1,3-dicarbonyl compounds,  $\alpha,\beta$ -unsaturated aldehydes, and alcohols to prepare 6-alkoxy tetrahydropyridines **454**,<sup>427,428</sup> followed by elimination of a molecule of alcohol (Scheme 133).<sup>429</sup> This approach avoids the use of pyridines as starting materials and allows the preparation of previously inaccessible substitution patterns in compounds **456**.

The first G protein-coupled estrogen receptor GPR 30-selective agonist **50a** (G-1),<sup>104</sup> and its analogs were synthesized

Scheme 131.  $\text{BiBr}_3$ -Catalyzed, Three-Component Synthesis of Tetrahydroquinolines **447**

Scheme 132. Lavilla's Synthesis of Fused Tetrahydroquinolines

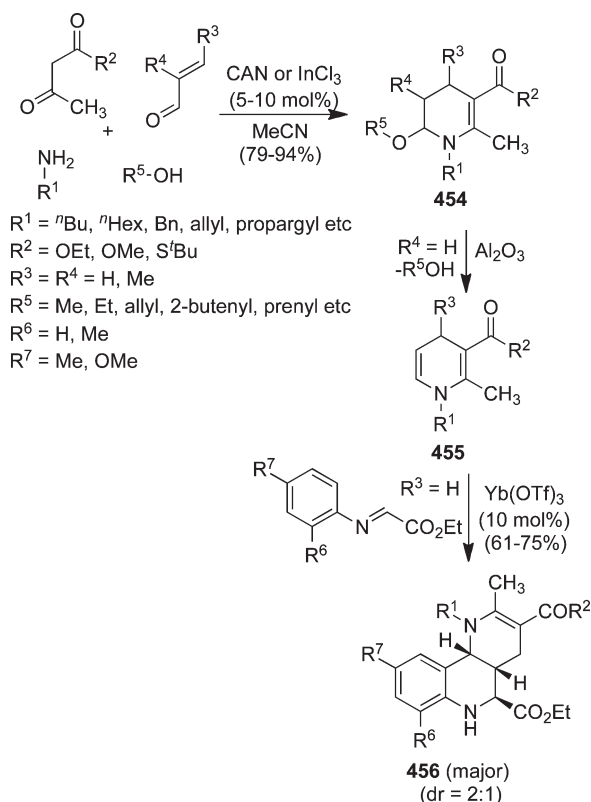


in excellent yields and diastereoselectivities using a simple  $\text{Sc}(\text{OTf})_3$ -catalyzed Povarov reaction, and the structure of G-1 was confirmed by single crystal X-ray analysis.<sup>106</sup> The reaction between 6-bromopiperonal, 4-aminoacetophenone, and cyclopentadiene in the presence of 10 mol % of  $\text{Sc}(\text{OTf})_3$  in acetonitrile afforded tetrahydroquinoline **50a** in nearly quantitative yield with a diastereomeric ratio of 94:6. The procedure was extended to the synthesis of 14 analogues of **50a**, again in high yields (Scheme 134). Additional work on tetrahydroquinoline-derived GPR30 agonists was also based on  $\text{Sc}(\text{OTf})_3$ -catalyzed, three-component Povarov reactions.<sup>105,107</sup>

A similar methodology involving the use of Yb and Sc triflates as catalysts for the synthesis of tetrahydroquinolines in acetonitrile or in an ionic liquid was also described recently.<sup>430</sup> Mahajan and co-workers demonstrated the synthesis of quinoline-tethered pyrimidinone derivatives through the corresponding



Scheme 133. Menéndez's Tetrahydropyridine Synthesis and Its Application to Povarov Chemistry

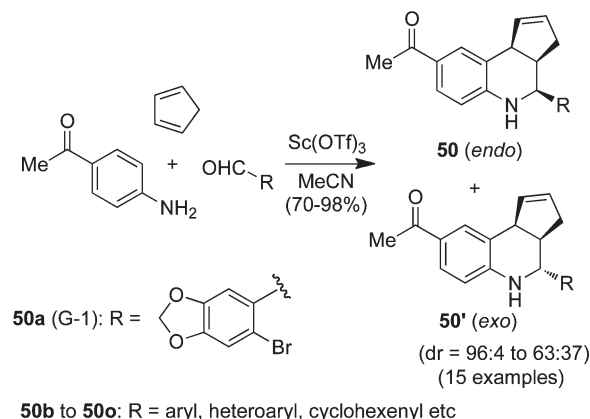
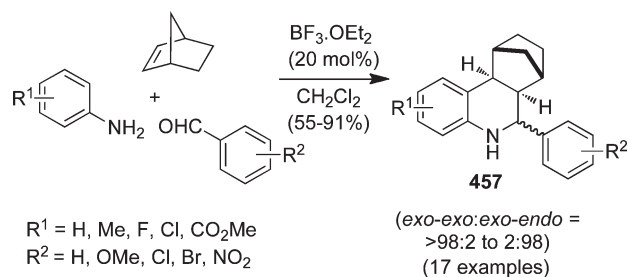


tetrahydroquinoline intermediates based on the triflate (Yb and Sc) and nontriflate ( $\text{MgBr}_2$ ,  $\text{ZnCl}_2$ , and  $\text{InCl}_3$ ) Lewis acid catalyzed Povarov reaction between *N*-aryl imines and 5-vinyl and 5-isopropenyl-pyrimidines.<sup>431</sup>

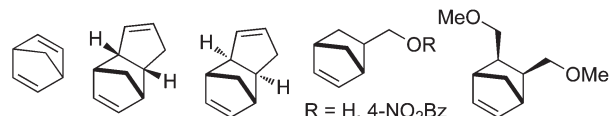
Batey and co-workers demonstrated the power of the  $\text{BF}_3 \cdot \text{OEt}_2$ -catalyzed reaction between *N*-arylimines and strained norbornene-derived dienophiles for the diastereoselective synthesis of bridged tetrahydroquinolines.<sup>432</sup> The three-component reaction between arylamines, arylaldehydes, and norbornene in the presence of 20 mol % of  $\text{BF}_3 \cdot \text{OEt}_2$  in dichloromethane gave the corresponding tetrahydroquinoline derivatives **457** in good to excellent yields. Although the electronic nature of the aniline ring did not affect the formation of the reaction products, the position of the substituents on the arylamine ring played a vital role on the diastereoselectivity. Almost in all cases, *exo*-facial selectivity on the norbornene ring was observed exclusively. A number of norbornene derivatives **458** were effectively used as dienophiles and the highly reactive ethyl glyoxalate-derived imines were also used as dienes (Scheme 135).

Other recent Lewis acid-catalyzed, three-component straightforward Povarov-type tetrahydroquinoline syntheses include the  $\text{BF}_3 \cdot \text{OEt}_2$ -catalyzed reaction between arylamines, pyridine-2-carbaldehyde, and indene,<sup>433</sup> the  $\text{Sc}(\text{OTf})_3$ -catalyzed reaction between arylamines, ethyl glyoxalate, and indole,<sup>434</sup> the preparation of polycyclic tetrahydroquinoline derivatives through a  $\text{BF}_3 \cdot \text{OEt}_2$ -catalyzed Povarov reaction in 2,2,2-trifluoroethanol,<sup>435</sup> and the molecular iodine-catalyzed reaction between *N*-arylimines and electron-rich dienophiles in 2,2,2-trifluoroethanol<sup>436</sup> or acetonitrile,<sup>437</sup> and also under solvent-free conditions.<sup>438</sup> In addition, antimony(III) sulfate was also found to be a good

Scheme 134. Synthesis of G Protein-Coupled Estrogen Receptor GPR 30-Selective Agonist 50a (G-1) and Its Analogs

Scheme 135.  $\text{BF}_3 \cdot \text{OEt}_2$ -Catalyzed Synthesis of Tetrahydroquinoline Derivatives **457**

Other norbornene derivatives **458** used as dienophiles:

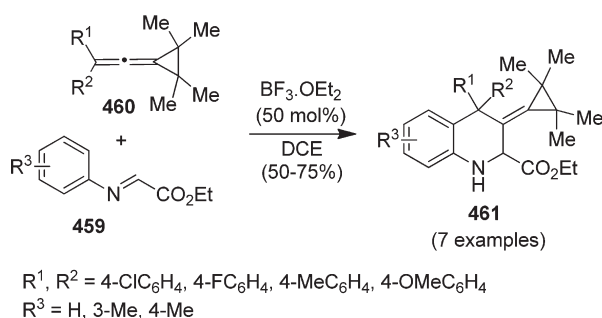
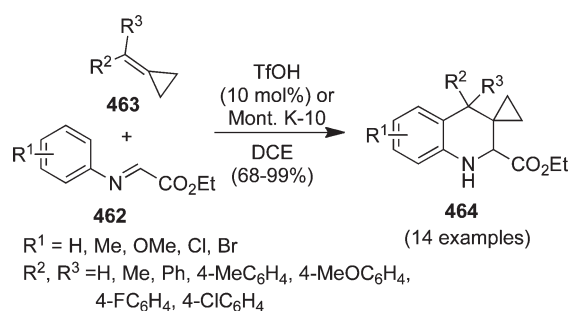


catalyst to drive the Povarov reaction, although the role of the catalyst was not well described.<sup>439</sup> A set of pyrano[3,2-*c*]quinoline derivatives were also synthesized through a  $\text{Y}(\text{OTf})_3$ - or  $\text{Sc}(\text{OTf})_3$ -catalyzed three-component reaction between arylamines, arylaldehydes, and 3,4-dihydro-2*H*-pyran and tested for their acetylcholinesterase (AChE) inhibitory activity.<sup>440</sup>

The  $\text{BF}_3 \cdot \text{OEt}_2$ -catalyzed reaction between *N*-arylimines derived from electron-rich arylamines and arylvinylidenecyclopropanes allowed a novel synthesis of 1,2,3,4-tetrahydroquinolines. For instance, treatment of imines **459** and allenes **460** with 50 mol % of  $\text{BF}_3 \cdot \text{OEt}_2$  afforded the polysubstituted tetrahydroquinoline derivatives **461** bearing an exocyclic double bond at C-3 position in good yields and under mild experimental conditions (Scheme 136).<sup>441</sup> A mechanism was also proposed involving carbocation intermediates and the study was subsequently elaborated as a full paper.<sup>442</sup>

Povarov products have often been transformed into the corresponding fully aromatic quinoline derivatives. Thus, polyfunctionalized 2-(hetero)arylquinolines having in vitro antifungal properties were synthesized from the corresponding 4-(2-oxopyrrolidinyl)tetrahydroquinolines prepared through a  $\text{BiCl}_3$ -catalyzed Povarov reaction.<sup>443</sup>

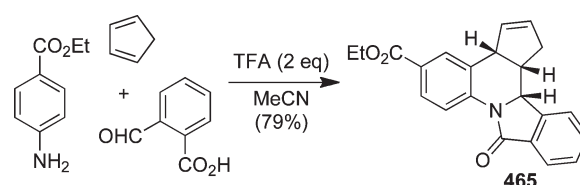
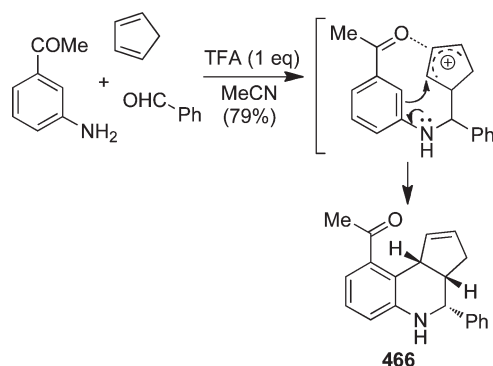


**Scheme 136. Povarov Reaction Involving Allenes As Dienophiles****Scheme 137. Triflic Acid or Montmorillonite K-10 Clay-Catalyzed Tetrahydroquinoline Synthesis**

**6.1.4. Brønsted Acid-Catalyzed Reactions.** Parallel to Lewis acid catalysts, Brønsted acids were also found to catalyze the Povarov reaction effectively. For instance, treatment of a wide variety of imines **462**, derived from arylamines and ethyl glyoxalate, and a number of methylenecyclopropanes **463** with a catalytic amount of triflic acid ( $\text{TfOH}$ ) or the acidic clay montmorillonite K-10 afforded good to excellent yields of tetrahydroquinolines **464** bearing a cyclopropane ring at the 3-position (Scheme 137). Although Lewis acids, including  $\text{BF}_3 \cdot \text{OEt}_2$ , Yb, Cu, Sn, La, Zr, and Zn triflates, gave good yields for this transformation, triflic acid was identified as the best catalyst. The reaction showed some limitations, and thus the 2-chloroaryl methylenecyclopropane starting material did not give the expected tetrahydroquinoline, presumably because of steric hindrance, and the reaction also failed when bis(alkyl)-substituted methylenecyclopropanes were employed, probably because the cationic intermediate generated in the Povarov reaction could not be sufficiently stabilized by the alkyl groups.<sup>444</sup>

Natural supramolecular carbohydrate scaffolds including cellulose and starch sulfonic acids effectively catalyzed the reaction between arylamines and cyclic enol ethers to give the corresponding tetrahydroquinolines in excellent yields.<sup>445</sup> Likewise, 4-nitrophthalic acid was used as a catalyst for the three-component synthesis of 2-methyl-1,2,3,4-tetrahydroquinolines starting from two equivalents of *N*-vinylpyrrolidin-2-one and one equivalent of arylamines.<sup>446</sup> The mechanism of these reactions is similar to the one described in Scheme 131.

Khadem and co-workers developed a one-pot synthesis of isoindolo[2,1-*a*]quinoline derivative **465** based on a trifluoroacetic acid (TFA)-mediated reaction between ethyl-4-amino- benzoate, 2-carboxybenzaldehyde and cyclopentadiene as a

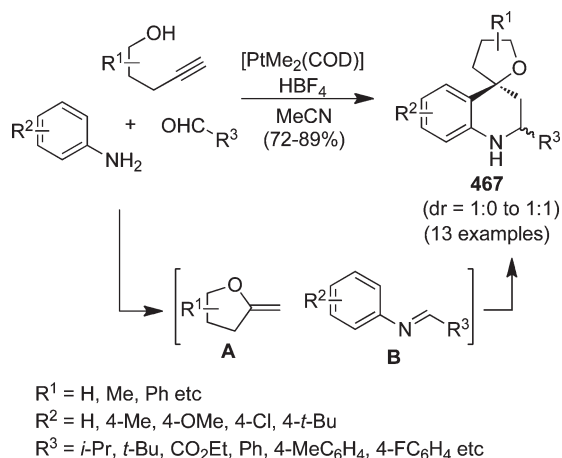
**Scheme 138. Khadem's Synthesis of Isoindolo[2,1-*a*]quinoline 465****Scheme 139. Regioselective Synthesis of Fused Tetrahydroquinoline 466**

single diastereomer through a Povarov-cyclocondensation domino sequence (Scheme 138).<sup>447</sup> It is also interesting to note that the reaction between 3-aminoacetophenone, benzaldehyde, and cyclopentadiene with 1 equiv of TFA furnished tetrahydroquinoline **466** as a single regioisomer. This observation was explained by the assumption that the carbocation intermediate generated during the reaction could be stabilized by the adjacent carbonyl group (Scheme 139).

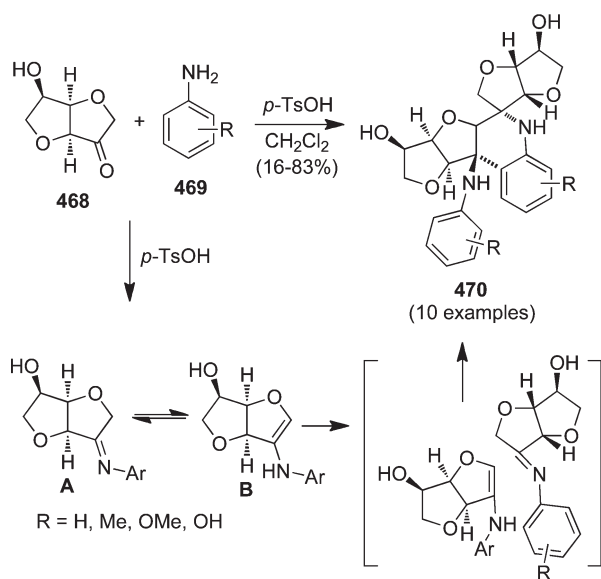
A three-component domino process was developed by Barluenga and co-workers for the synthesis of 4-spiro-tetrahydroquinolines **467**, with Pt(II) being used as the catalyst for the first part of the cascade, namely, the generation of exocyclic enol ethers **A** starting from alkynols through an intramolecular hydroalkoxylation reaction. This was followed by a proton-catalyzed Povarov-type reaction with *N*-arylimines **B**, generated in situ from the corresponding arylamines and aldehydes (Scheme 140).<sup>448</sup> Takasu and co-workers established the synthesis of tetrahydroquinolines and quinoline derivatives involving a cascade Povarov reaction-hydrogen transfer process in the presence of  $\text{Tf}_2\text{NH}$ .<sup>449</sup> The tetrahydroquinolines obtained from the Povarov reaction between *N*-arylimines and electron-rich olefins underwent hydrogen transfer with two equivalents of the *N*-arylimines to afford the corresponding quinolines and the reduced *N*-arylimines in a single operation.

The asymmetric synthesis of polycyclic spiro-tetrahydroquinolines **470** was achieved starting from the keto sugar **468** and arylamines **469** in the presence of *p*-TsOH.<sup>450</sup> The reaction involved the condensation of the starting materials to generate imine **A**, which is in equilibrium with its enamine form **B**. The Povarov-type [4 + 2] cycloaddition between imine **A** and enamine **B** in the presence of the acid catalyst afforded high yields of tetrahydroquinoline derivatives **470**, which showed in vitro immunobiological activity and cytotoxicity (Scheme 141). A rather similar reaction was also previously described for the

**Scheme 140. Pt-Catalyzed, Three-Component Domino Synthesis 4-Spiro-tetrahydroquinolines 467 Developed by Barluenga**



**Scheme 141. Chiral Synthesis of Immunobiological Active and Cytotoxic Polycyclic Spiro-Tetrahydroquinolines 470**

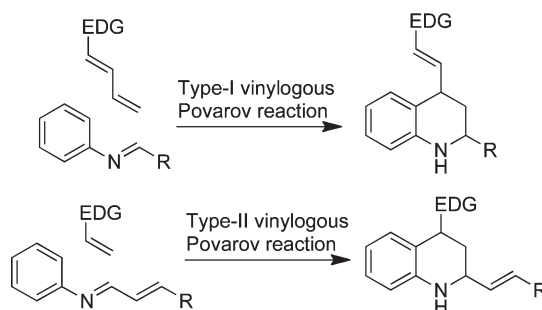


synthesis of 2-methyl-4-arylamino-1,2,3,4-tetrahydroquinolines from arylamines and acetaldehyde.<sup>132</sup>

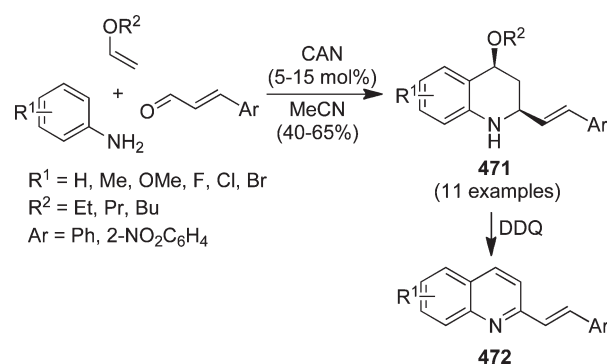
The preparation of simple tetrahydroquinoline derivatives by means of the Povarov reaction was again achieved using HClO<sub>4</sub>-SiO<sub>2</sub>,<sup>451</sup> tungstophosphoric acid,<sup>452</sup> 4-nitrophthalic acid,<sup>453</sup> hexafluoro-2-propanol,<sup>454</sup> TFA,<sup>79,455</sup> and proline triflate (derived from L-proline and trifluoromethanesulfonic acid)<sup>456</sup> as catalysts, without significant synthetic novelty. Some of the compounds obtained from the TFA-catalyzed reaction showed interesting activity as agonists of the large-conductance calcium-activated potassium channel. The synthesis of tetrahydroquinolines and quinolines was also achieved starting from nitroaromatic compounds in the presence of TiO<sub>2</sub> and *p*-toluenesulfonic acid under photochemical conditions.<sup>457</sup>

**6.1.5. Vinylogous Povarov Reactions.** We have previously classified the vinylogous versions of the Povarov reaction into

**Scheme 142. Classification of the Vinylogous Povarov Reactions**



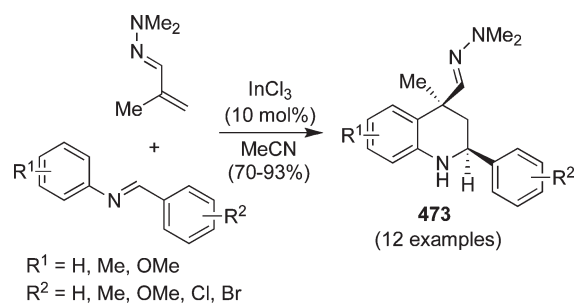
**Scheme 143. CAN-Catalyzed Synthesis of 2-Styryl-1,2,3,4-tetrahydroquinolines and Their Aromatization**



two types for better systemization of this field. The use of butadiene derivatives bearing an electron-releasing group as dienophiles for the synthesis of tetrahydroquinolines having alkene functionality at C-4 carbon is termed as Type-I vinylogous Povarov reaction. On the other hand, the Type-II version of the reaction involves the use of *N*-arylimines derived from  $\alpha,\beta$ -unsaturated aldehydes and result in an alkene functionality at the C-2 position of the tetrahydroquinolines (Scheme 142).<sup>458</sup>

The CAN-catalyzed, three-component reaction between arylamines, cinnamaldehydes, and cyclic and acyclic enol ethers afforded the corresponding 2-styryl-1,2,3,4-tetrahydroquinolines 471 in moderate to good yields.<sup>459</sup> It was interesting to note that the enol ether attacked the azomethine carbon of the Lewis acid activated unsaturated imine while the  $\gamma$ -carbon with respect to the nitrogen atom remained unaffected. Although cyclic enol ethers gave 1:1 mixtures of diastereomers, the acyclic vinyl ethers furnished the corresponding *cis* products exclusively, together with small amounts of 2-methyl-1,2,3,4-tetrahydroquinolines, generated as side products from the reaction between arylamines and two equivalents of vinyl ethers. These products were successfully transformed into biologically relevant 2-styrylquinolines 472 through a DDQ oxidation. A stepwise mechanism was also proposed based on experimental evidence pointing at the generation of an oxonium cation intermediate (Scheme 143).

We have also developed a novel vinylogous type-I Povarov reaction involving the use of  $\alpha,\beta$ -unsaturated hydrazones as the dienophiles.<sup>460</sup> Treatment of a wide variety of *N*-arylimines with methacrolein *N,N*-dimethylhydrazone in the presence of 10 mol % of InCl<sub>3</sub> furnished 1,2,3,4-tetrahydroquinolines 473 bearing a hydrazone unit at the C-4 carbon as a single diastereomer in high

**Scheme 144. Vinylogous Type-I Povarov Reaction Involving the Use of  $\alpha,\beta$ -Unsaturated Hydrazones as the Dienophiles**


yields (Scheme 144).  $\alpha,\beta$ -Unsaturated *N,N*-dimethylhydrazones have found widespread use as dienes in aza-Diels–Alder reactions,<sup>461</sup> but this was the first report of their use as dienophiles in this type of chemistry.

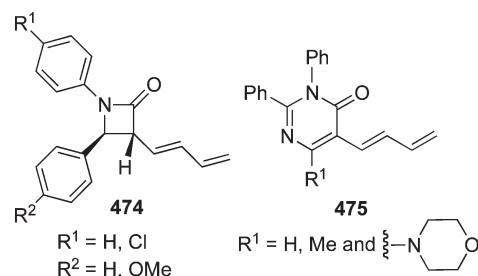
The Lewis acid-catalyzed reaction between *N*-arylimines and 3-dienyl-2-azetidinones **474**<sup>462</sup> or 5-dienyl pyrimidinones **475**<sup>463,464</sup> afforded the corresponding 4-alkenyl-substituted quinoline derivatives through the corresponding tetrahydroquinoline intermediates (Figure 16). A number of Lewis acids, including  $\text{MgBr}_2$ ,  $\text{ZnCl}_2$ ,  $\text{InCl}_3$ ,  $\text{AlCl}_3$ , and the triflates of yttrium and scandium, were also tested for the reaction, which in most cases proceeded in good conversions.

**6.1.6. Intramolecular Povarov Reactions.** The synthetic applications of a variety of intramolecular versions of the Povarov reaction were discussed in detail in the previous review by Kouznetsov.<sup>405</sup> Herein we summarize the recent developments of the intramolecular methodology, mainly contributed by Raghunathan and co-workers. Treatment of *N*-prenyl aldehydes **476** with arylamines in the presence of 20 mol % of  $\text{InCl}_3$  in acetonitrile furnished a diastereomeric mixture of the pyrrolo-[3,4-*b*]quinolines **477** in excellent yields. The in situ generated imine was trapped intramolecularly by the *N*-tethered prenyl moiety to afford the corresponding fused tetrahydroquinoline derivatives (Scheme 145).<sup>465</sup>

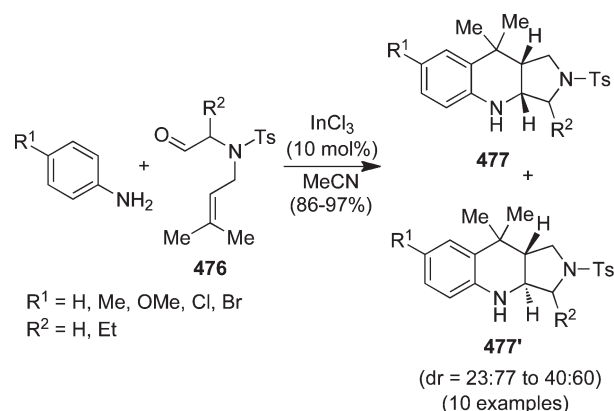
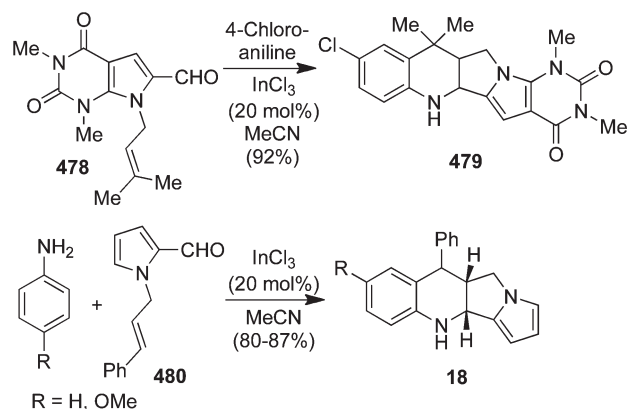
Raghunathan and co-workers also reported the synthesis of antibacterial tetrahydroquinolines **479** and **18** starting from arylamines and *N*-prenyl pyrrolopyrimidine-6-carbaldehyde **478** or 1-cinnamyl-1*H*-pyrrole-2-carbaldehyde **480**, both of them involving  $\text{InCl}_3$ -catalyzed intramolecular Povarov reactions (Scheme 146).<sup>42</sup> Bis-tetrahydroquinolines were also synthesized from the corresponding diamines, and the  $\text{InCl}_3$ /silica gel-catalyzed synthesis of pyrano/thiopyranoquinolines was also achieved through intramolecular Povarov reactions under microwave irradiation.<sup>466</sup>

Nagaiah and co-workers recently reported the synthesis and antiproliferative activity studies of tetrahydrochromeno[4,3-*b*]quinolines **31**. The compounds were synthesized through intramolecular Povarov reaction between the in situ-generated imine from arylamines and the 7-*O*-prenyl derivatives of 8-formyl-2,3-disubstituted chromenones **481** in the presence of a catalytic amount of  $\text{Yb}(\text{OTf})_3$ .<sup>71</sup> The reaction was completely diastereoselective and afforded exclusively the *cis* isomers in excellent yields (Scheme 147). The synthesized compounds were tested for their antiproliferative activity against MDA-MB-231 and MCF-7 breast cancer cell lines, with some of them showing significant activity in MCF-7 breast cell lines and one of them displaying activity comparable to tamoxifen on both cell lines.

Recently, a library of pyrimidine-fused tetrahydroquinolines **484** were synthesized, using intramolecular Povarov reaction as



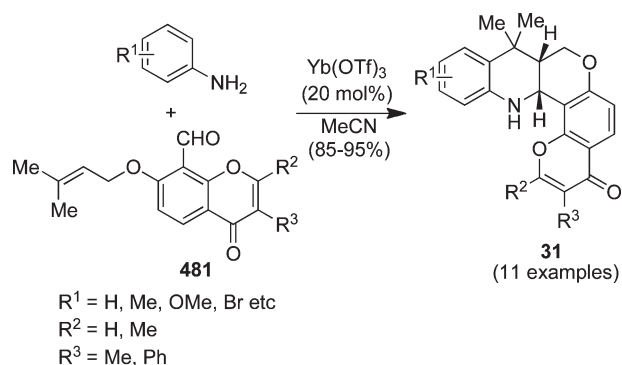
**Figure 16.** Dienophiles used in the vinylogous Povarov reactions.

**Scheme 145. Raghunathan's Synthesis of Pyrrolo[3,4-*b*]-quinolines Involving Intramolecular Povarov Reaction**

**Scheme 146. Synthesis of Antibacterial Tetrahydroquinolines **479** and **18** via Intramolecular Povarov Reaction**


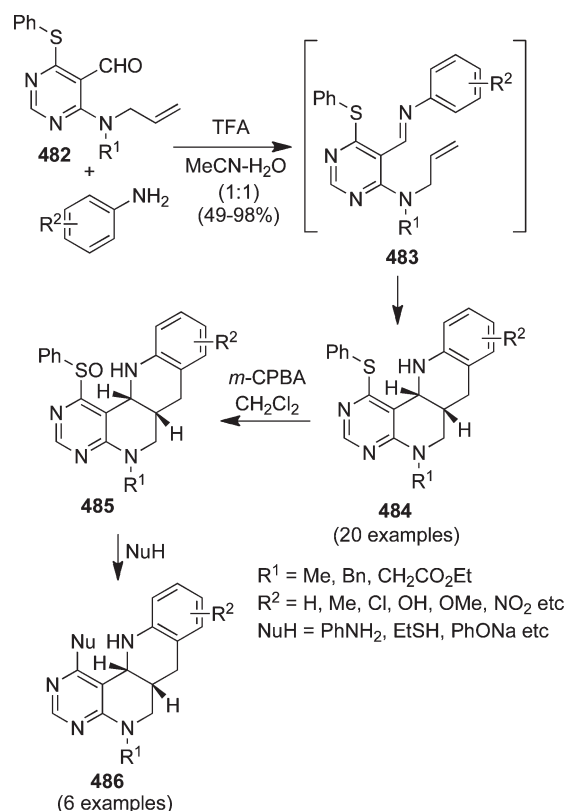
the key step, starting from arylamines and allylaminopyrimidinealdehydes **482** bearing a phenylthio group, through intermediate **483**, in the presence of trifluoroacetic acid.<sup>467</sup> Interestingly, the phenylthio moiety was oxidized to the corresponding sulfoxide **485** and subsequently replaced by a number of nucleophiles including amines, thiols and alkoxides to give compounds **486** (Scheme 148).

Zhou and Magomedov demonstrated an interesting intramolecular Povarov reaction for the asymmetric synthesis of tetrahydroquinoline derivative **488**,<sup>468</sup> an intermediate for the synthesis of the natural products isoschizogamine **489a** and

**Scheme 147.** Nagaiah's Synthesis of Antiproliferative Tetrahydrochromeno[4,3-*b*]quinolines **31**



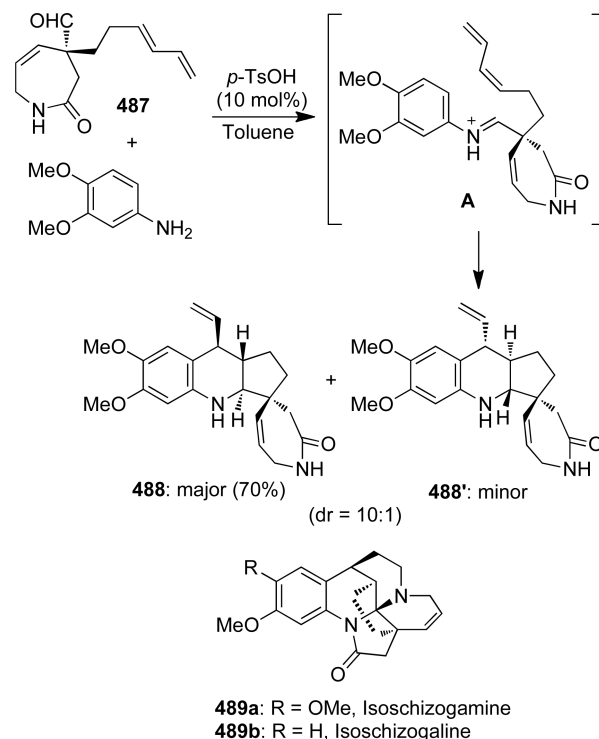
**Scheme 148.** Synthesis of Pyrimidine-Fused Tetrahydroquinoline Library



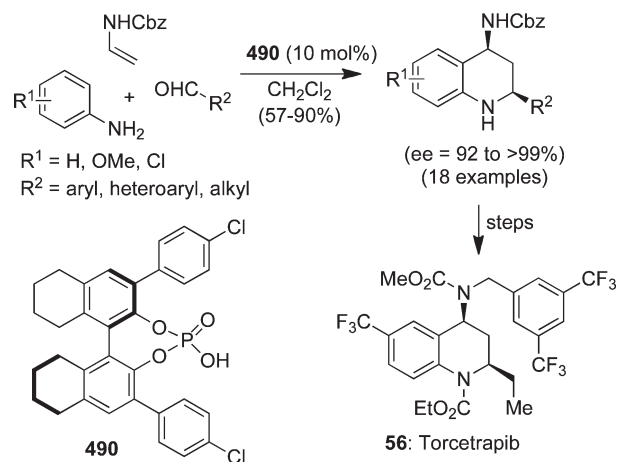
isoschizogaline **489b**.<sup>469</sup> The chiral aldehyde **487**, obtained in several steps from an enantiopure aziridine derivative, reacted with 3,4-dimethoxyaniline in the presence of *p*-TsOH to give directly and diastereoselectively the spirotetrahydroquinolines **488** through the intermediacy of imine **A** (Scheme 149).

**6.1.7. Enantioselective Povarov Reactions.** Although the Povarov reaction is one of the simplest and best methods for the rapid synthesis of polysubstituted tetrahydroquinoline derivatives, the enantioselective version of the reaction was not well established until very recently. There were only three methodologies developed before 2008, including reactions

**Scheme 149.** Synthesis of Intermediate (**488**) of the Natural Products Isoschizogamine **489a** and Isoschizogaline **489b**



**Scheme 150.** Zhu's Chiral Brønsted Acid-Catalyzed Enantioselective Synthesis of Tetrahydroquinolines

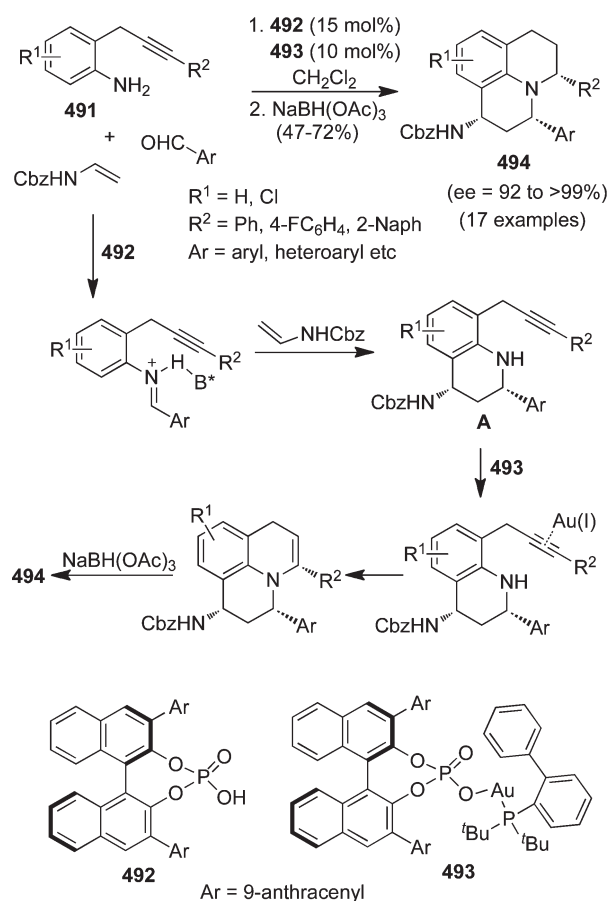


catalyzed by a BINOL-lanthanide complex,<sup>470</sup> an aminodiol-titanium(IV) complex<sup>471</sup> and a chiral Brønsted acid.<sup>472</sup>

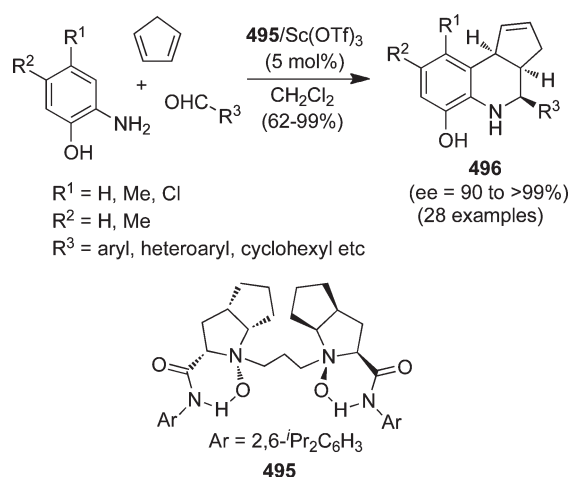
Zhu and co-workers demonstrated recently an excellent procedure for the synthesis of enantiopure tetrahydroquinolines involving a chiral Brønsted acid catalyzed three-component reaction between arylamines, aldehydes, and enecarbamates in high yields and excellent enantioselectivities.<sup>473</sup> The BINOL-derived phosphoric acid **490** was found to catalyze the reaction in dichloromethane, affording the *cis*-2,4-disubstituted tetrahydroquinolines with greater than 99% enantiomeric excess. A number of arylamines and aldehydes, including aliphatic ones, afforded



**Scheme 151. Chiral Phosphoric Acid–gold(I) Complex-Catalyzed Enantioselective Synthesis of Julolidine Derivatives**

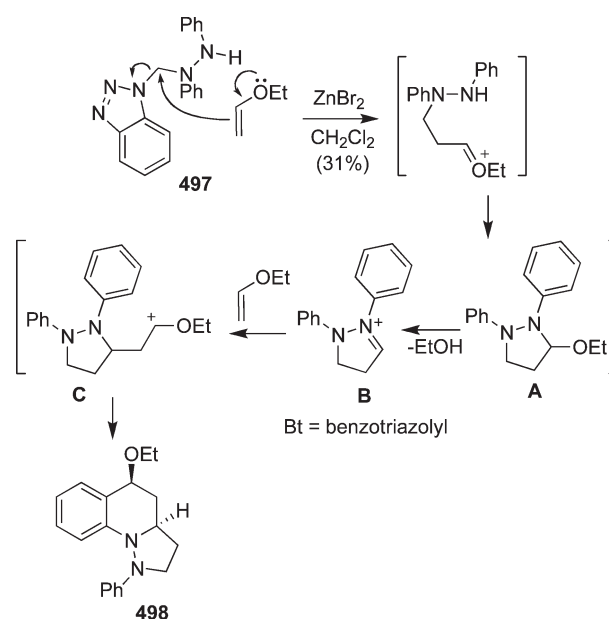


**Scheme 152. Enantioselective Synthesis of Fused 8-Hydroxytetrahydroquinolines**



the desired products without any significant difference in yields and selectivities. The procedure was successfully extended to the enantioselective synthesis of the antihypercholesterolemic drug candidate torcetrapib **56** (Scheme 150). Ricci and co-workers also developed a related chiral phosphoric acid as a catalyst for the Povarov reaction, again in excellent enantioselectivities,

**Scheme 153. Katritzky's Tetrahydroquinoline Synthesis Starting from the Benzotriazole Derivative 497**



employing 2- and 3-vinylindoles as dienophiles to afford enantiopure 4-indolyl-substituted tetrahydroquinolines.<sup>474</sup>

A highly enantioselective synthesis of julolidine derivatives was achieved through a three-component enantioselective Povarov reaction-intramolecular hydroamination cascade, catalyzed by a chiral phosphoric acid, and a gold(I) complex.<sup>475</sup> Treatment of 2-(2-propynyl)anilines **491** with arylaldehydes and an enecarbamate in the presence of 15 mol % of the chiral phosphoric acid **492** and 10 mol % of the gold complex **493** afforded the highly enantiopure tricyclic products **494** after reduction of the enamine moiety by sodium triacetoxyborohydride (Scheme 151). The reaction was proposed to proceed through an initial chiral Brønsted acid-catalyzed Povarov reaction to generate the enantioselective tetrahydroquinoline intermediate **A**, which subsequently underwent a gold(I)-catalyzed intramolecular hydroamination to give the julolidine derivatives.

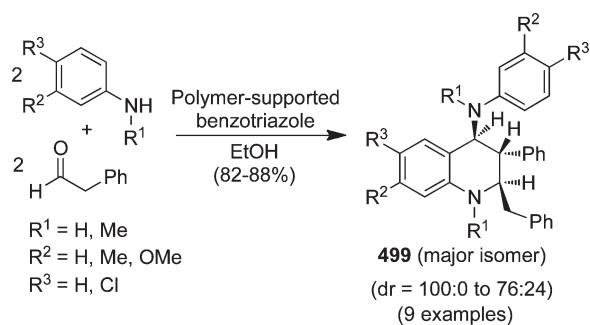
More recently, Jacobsen and co-workers established an efficient synthesis of chiral tetrahydroquinoline derivatives in the presence of chiral ureas and strong Brønsted acids through enantioselective Povarov reactions.<sup>476</sup> A detailed mechanism was also proposed describing the role of the ligands and possible intermediates were supported by theoretical calculations. The use of a chiral  $N,N'$ -dioxide- $\text{Sc}(\text{OTf})_3$  complex as a catalyst for the enantioselective Povarov reaction was also reported recently. The three-component reaction between 2-aminophenols, aldehydes and cyclopentadiene in the presence of 5 mol % of  $N,N'$ -dioxide **495** and  $\text{Sc}(\text{OTf})_3$  afforded the corresponding tetrahydroquinoline derivatives **496** in excellent yields and diastereo- and enantioselectivities (Scheme 152).<sup>477</sup> The enantioselectivity dropped in the absence of a 2-hydroxy group on the arylamines, which proved the essential role of this group in coordinating with the ligand to induce enantioselectivity.

## 6.2. Miscellaneous Reactions Involving the Generation of $N\text{--C}_2$ , $\text{C}_2\text{--C}_3$ , and $\text{C}_4\text{--C}_{4a}$ Bonds

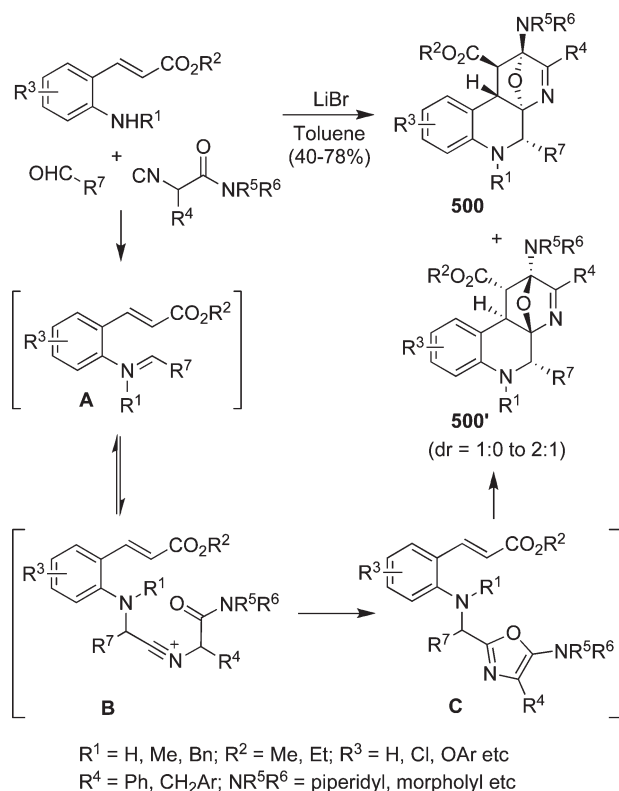
Katritzky and co-workers reported the application of  $N$ -(1-benzotriazolylalkyl)- $N,N'$ -disubstituted hydrazines for the



**Scheme 154. Polymer-Supported Benzotriazole Catalyzed Synthesis of 4-Arylamino Tetrahydroquinolines**



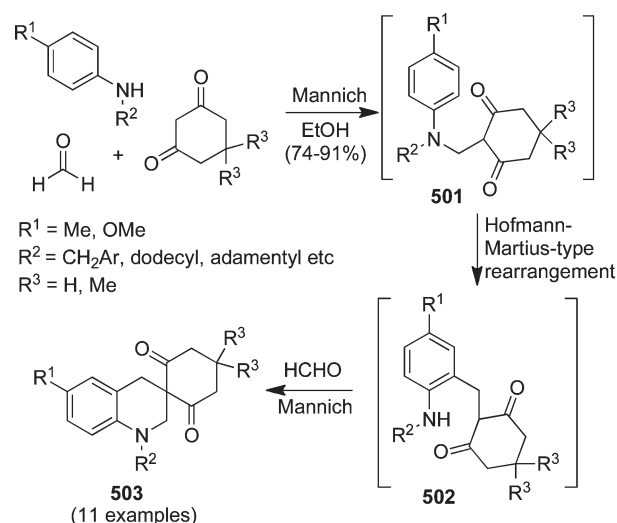
**Scheme 155. Zhu's Synthesis of Oxa-Bridged Tetrahydroquinolines**



synthesis of tetrahydroquinolines. For instance, the benzotriazole derivative **497** reacted with excess of ethyl vinyl ether in the presence of  $\text{ZnBr}_2$  to afford the corresponding tetrahydroquinoline **498** in 31% yield.<sup>478</sup> A Povarov-like mechanism was proposed involving a carbocation intermediate as depicted in Scheme 153. The starting compound **497** reacted with one equivalent of ethyl vinyl ether followed by elimination of the benzotriazole moiety to give intermediate **A**, which subsequently lost a molecule of ethanol to generate iminium cation **B**, an active Povarov diene. The second equivalent of ethyl vinyl ether underwent a Povarov-type cycloaddition with **B** to furnish tetrahydroquinoline **498**.

2,3,4-Trisubstituted tetrahydroquinolines were synthesized through a reaction between arylamines and phenylacetaldehyde,

**Scheme 156. Synthesis of 3-Spiro-tetrahydroquinolines via Mannich/Hofmann–Martius–Mannich Sequence**



catalyzed by a polymer-supported benzotriazole that was prepared by linking 5-(hydroxymethyl)benzotriazole and benzotriazole-5-carboxylic acid with Wang resin, Merrifield resin, or (monomethoxy)poly(ethylene glycol). The two-pair coupling reactions of arylamines and aldehydes bearing an active methylene group in the presence of 20 mol % of the catalyst afforded 4-arylamino tetrahydroquinolines **499** in high yields with good diastereoselectivity (Scheme 154).<sup>479</sup> In a related article, aniline hydrochloride reacted with enolizable aldehydes in the presence of sodium cyanoborohydride to afford 2,3-disubstituted 1,2,3,4-tetrahydroquinolines in moderate yields.<sup>480</sup> It is also interesting to note that tetrahydroquinolines were also synthesized, albeit in poor yields, through a photochemical reaction between *m*-nitrocinnamic acid and alcohols.<sup>481</sup>

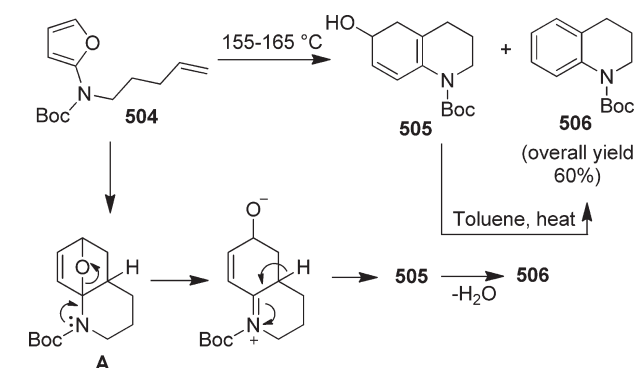
### 6.3. Formation of the N–C<sub>2</sub>, C<sub>2</sub>–C<sub>3</sub>, and C<sub>3</sub>–C<sub>4</sub> Bonds

A couple of reports by Zhu and co-workers described the synthesis of oxa-bridged tetrahydroquinolines, involving the creation of the N–C<sub>2</sub>, C<sub>2</sub>–C<sub>3</sub>, and C<sub>3</sub>–C<sub>4</sub> bonds in a single operation. The three-component reaction between *ortho*-aminocinnamates,  $\alpha$ -isocyanoacetamides and aldehydes in the presence of LiBr afforded a separable diastereomeric mixture of oxa-bridged tetrahydroquinolines **500** by creating one C–N, one C–O, and three C–C bonds in a single operation (Scheme 155).<sup>482</sup> The reaction proceeded through the oxazole intermediate **C**, as evidenced by the fact that it was isolated in some occasions, which could be generated from the iminium and nitrilium ion intermediates **A** and **B**. A few years later the scope of the reaction was extended to the synthesis of 4,6-phenanthroline derivatives.<sup>483</sup>

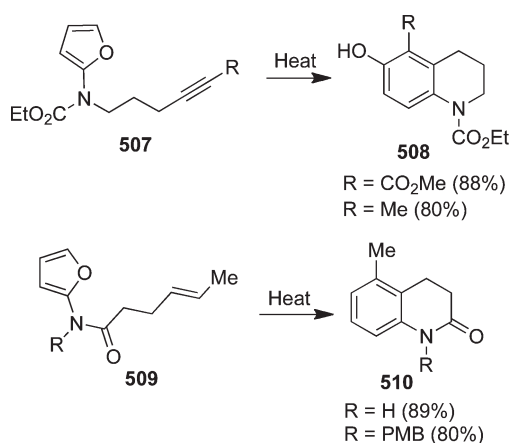
### 6.4. Formation of More than Three Bonds

The synthesis of 3-spiro-substituted 1,2,3,4-tetrahydroquinolines was achieved based on a three-component reaction between arylamines, formaldehyde, and  $\beta$ -diketones by creating the N–C<sub>2</sub>, C<sub>2</sub>–C<sub>3</sub>, C<sub>3</sub>–C<sub>4</sub>, and C<sub>4</sub>–C<sub>4a</sub> bonds in a single operation through a domino sequence.<sup>484</sup> The reaction involved an initial Mannich reaction between the starting materials to give the Mannich base **501**, which underwent a Hofmann–Martius-type rearrangement to generate aminodiketone **502**. Intermediate **502** then reacted with formaldehyde to afford the final spiro-tetrahydroquinoline **503** through a second intramolecular

**Scheme 157. Padwa's Tetrahydroquinoline Synthesis Based on the Intramolecular Diels–Alder Reaction of 2-Substituted Aminofurans**



**Scheme 158. Tetrahydroquinolines from Furan Derivatives Bearing Alkyne Side Chain and Furanamides**



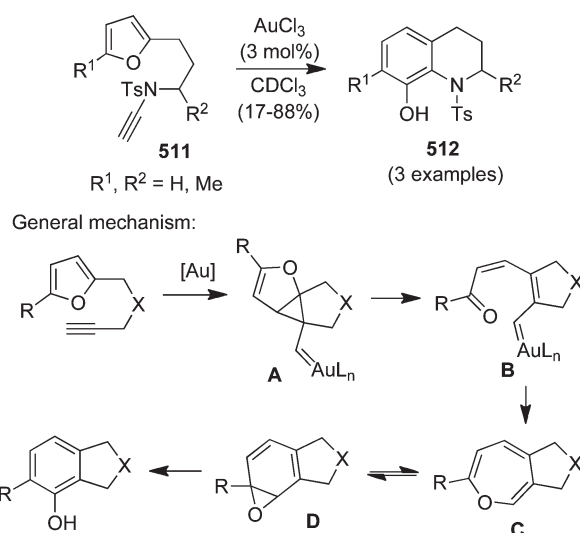
Mannich reaction (Scheme 156). Subsequently, this procedure was extended by the same group to the synthesis of benz-fused tetrahydroquinolines using naphthylamine.<sup>485</sup>

## 7. SYNTHESIS OF 1,2,3,4-TETRAHYDROQUINOLINES INVOLVING THE FORMATION OF THE ARYL OR BOTH RINGS

As we discussed in the previous sections, most of the existing methods for the synthesis of 1,2,3,4-tetrahydroquinoline derivatives are based on the formation of the dihydropyridine ring starting from an aryl precursor. Nevertheless, a few procedures are available for the construction of the aryl ring starting from a piperidine derivative or for the creation of both rings from completely acyclic precursors or from substrates bearing a furan moiety as a benzene ring precursor, and these protocols will be discussed in this section.

Padwa and co-workers developed an interesting methodology for the synthesis of indolines and tetrahydroquinolines by means of an intramolecular Diels–Alder reaction of 2-substituted aminofurans (IMDAF).<sup>486</sup> The *N*-Boc protected furan derivative **504**, obtained from 2-furoic acid, gave a mixture of hexahydroquinoline **505** and tetrahydroquinoline **506** under thermal conditions. The former compound was then quantitatively

**Scheme 159. Hashmi's Gold-Catalyzed Synthesis of 8-Hydroxytetrahydroquinolines**



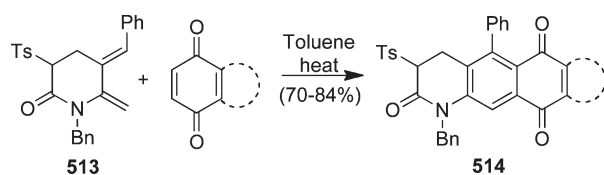
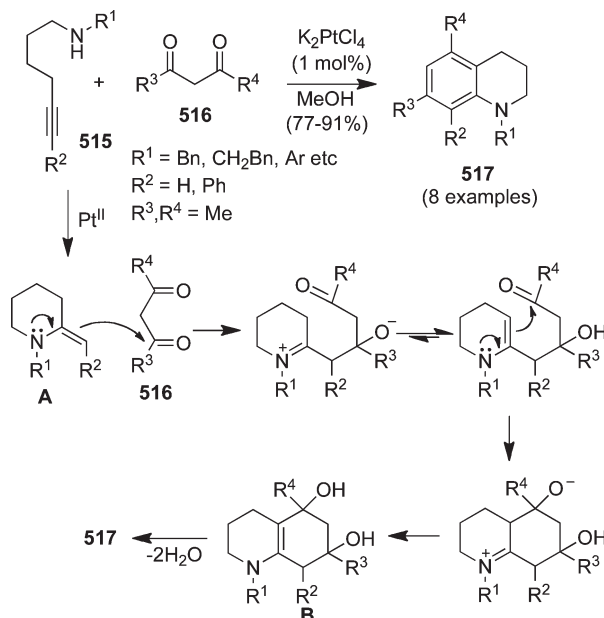
converted into tetrahydroquinoline **506** upon further heating in toluene and the overall yield of the product **506** was 60%.<sup>487</sup> The initial step of the reaction was an intramolecular [4 + 2] cycloaddition of compound **504** to generate the oxa-bridged intermediate **A**, which then underwent nitrogen-assisted ring-opening to give hexahydroquinoline **505** and a subsequent thermal dehydration that afforded tetrahydroquinoline **506** (Scheme 157).

Interestingly, furan derivatives bearing an alkyne side chain **507** also furnished the corresponding tetrahydroquinolines **508** in high yields. Similar reactions starting from 2-substituted furanamides **509** were also successful and gave tetrahydroquinolin-2-ones **510**, again in high yields (Scheme 158). The same group also reported some additional related procedures for the synthesis of heterocycles including tetrahydroquinolines.<sup>488,489</sup> Li and Hsung recently described a similar protocol for the synthesis of a tetrahydroquinoline derivative as an application of their Rh-catalyzed synthesis of 2-amino-substituted furans.<sup>490</sup>

Hashmi and co-workers reported a novel synthesis of benz-fused heterocycles including chromans, dihydrobenzofurans, dihydroindoles, and tetrahydroquinolines based on a gold-catalyzed reaction. For instance, treatment of the furan derivatives **511** with 3 mol % of AuCl<sub>3</sub> afforded the corresponding tetrahydroquinolines **512** in good yields.<sup>491</sup> The reaction may be initiated by a gold-catalyzed ene-yne cyclization to give the cyclopropyl carbenoid intermediate **A**, which could be then transformed into the final products through intermediates **B–D**, as demonstrated previously in literature (Scheme 159).<sup>492</sup>

A Diels–Alder approach was developed for the synthesis of tetrahydroquinolin-2-ones and their fused analogues. For instance, the exodiene lactam **513** reacted with *p*-quinones to afford the fused tetrahydroquinolin-2-ones **514** in good yields. The procedure was also extended to the synthesis of hexahydro- and dihydroquinoline derivatives (Scheme 160).<sup>493</sup>

Liu and Che demonstrated a novel synthesis of indolines and tetrahydroquinolines starting from aminoalkynes and 1,3-diketones in the presence of a platinum(II) catalyst. A broad variety of 1,5-aminoalkynes **515** were treated with 1,3-diketones **516** under mild conditions with 1 mol % of K<sub>2</sub>PtCl<sub>4</sub> to afford the corresponding tetrahydroquinolines **517** in high yields.<sup>494</sup>

**Scheme 160.** Synthesis of Fused Tetrahydroquinolin-2-ones via Diels–Alder Reaction**Scheme 161.** Pt-Catalyzed Synthesis of Tetrahydroquinolines Developed by Liu and Che

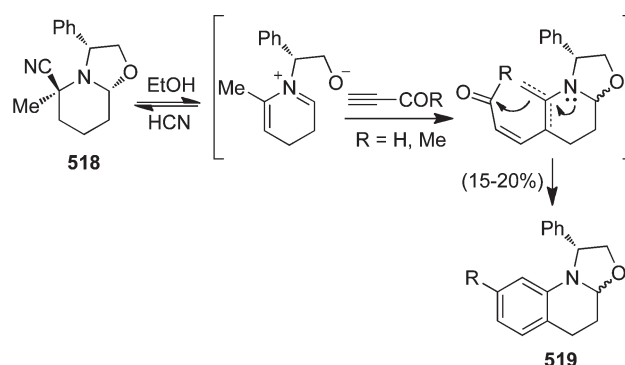
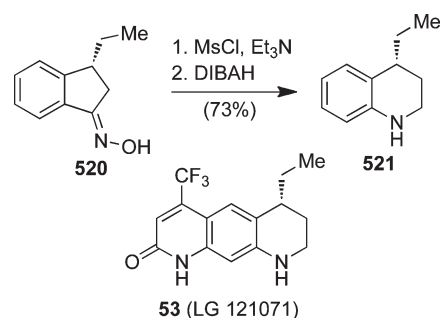
A mechanism was proposed for this domino reaction involving an initial Pt-catalyzed intramolecular hydroamination<sup>495</sup> of the starting compound **515** to afford intermediate **A**. The nucleophilic attack of **A** to compound **516** followed by cyclization furnished the diol intermediate **B**, which was then transformed into the final product after elimination of two molecules of water (Scheme 161).

Chiral tetrahydroquinolines **519** were prepared in low yields by the reaction between the enantiopure oxazolo[3,2-*a*]pyridine derivative **518** and 3-buten-2-one or propionaldehyde in the presence of  $\text{Al}_2\text{O}_3$  and the proposed mechanism is depicted in Scheme 162.<sup>496</sup>

In a report mainly related to the synthesis of hexahydroquinolines through a carbo-[3 + 3] annulation process, starting from a piperidine derivative, two examples of tetrahydroquinolines were isolated as minor products during the DDQ-mediated aromatization of the hexahydroquinolines to the corresponding quinolines.<sup>497</sup>

## 8. SYNTHESIS OF 1,2,3,4-TETRAHYDROQUINOLINES INVOLVING REARRANGEMENT REACTIONS

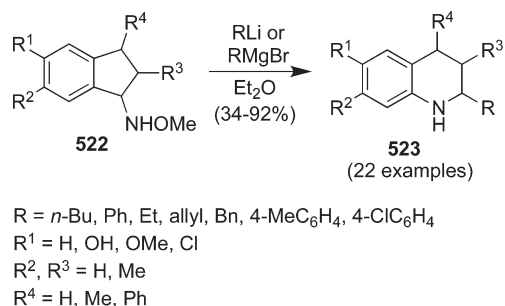
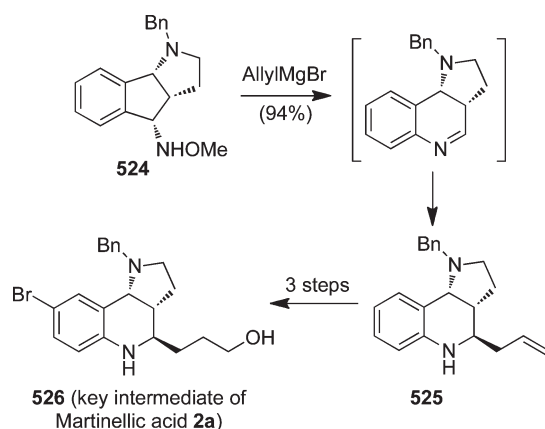
There are only a few reports describing the synthesis of 1,2,3,4-tetrahydroquinolines through rearrangement reactions starting from aryl precursors and they are summarized in this section.

**Scheme 162.** Synthesis of Tetrahydro-oxazolo[3,2-*a*]-quinolines **519****Scheme 163.** Synthesis of Chiral Tetrahydroquinoline **521** (Intermediate for LG 121071, **53**) via Beckmann Rearrangement

A modified Beckmann rearrangement was employed for the synthesis of chiral (*R*)-4-ethyl-1,2,3,4-tetrahydroquinoline **521**, which is a potential intermediate for the synthesis of the androgen receptor modulator LG 121071 (**53**). The mesylate of the enantiopure oxime **520**, derived from ethyl 3-phenylpent-2-enoate, was treated with DIBAH to afford the chiral tetrahydroquinoline derivative **521** in 73% yield (Scheme 163).<sup>498</sup> The rearrangement of *O*-triisopropylsilyl (TIPS) oximes of 2,3-dihydro-1*H*-inden-1-ones also furnished the corresponding tetrahydroquinolines upon reduction with  $\text{BH}_3\text{--SMO}_2/\text{BF}_3\cdot\text{OEt}_2$  system in good to excellent yields.<sup>499</sup>

A novel procedure for the synthesis of 2-substituted 1,2,3,4-tetrahydroquinolines was reported involving a tandem reaction sequence. Treatment of *N*-indanyl(methoxy)amines **522** with Grignard or organolithium reagents afforded the corresponding tetrahydroquinolines **523** in high yields by elimination of the methoxy group and rearrangement of the aryl ring, followed by the addition of the organolithium or magnesium reagent (Scheme 164).<sup>500</sup> A large number of Grignard reagents including the ethyl, phenyl, allyl, benzyl, and aryl magnesium bromides and organolithium reagents (*n*-BuLi, PhLi) furnished the final products in very short reaction times at room temperature.

Subsequently, the protocol was utilized for the formal total synthesis of (±)-martinellic acid **2a**. The tricyclic methoxyamine **524**, synthesized from 2-bromobenzaldehyde acetal, was treated with allylmagnesium bromide to give 2-allylpyrroloquinoline **525** in 94% yield, which was then transformed into compound **526**,

Scheme 164. Synthesis of Tetrahydroquinolines **523**Scheme 165. Synthesis of Martinellie Acid Intermediate **526**

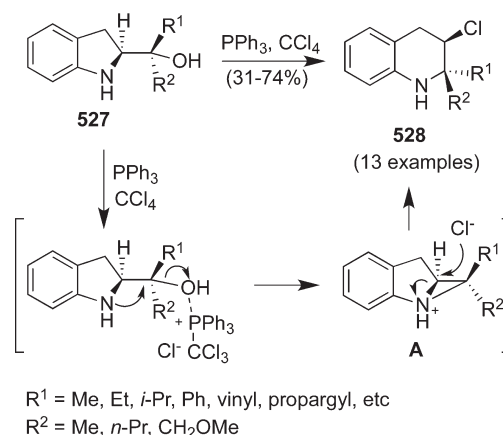
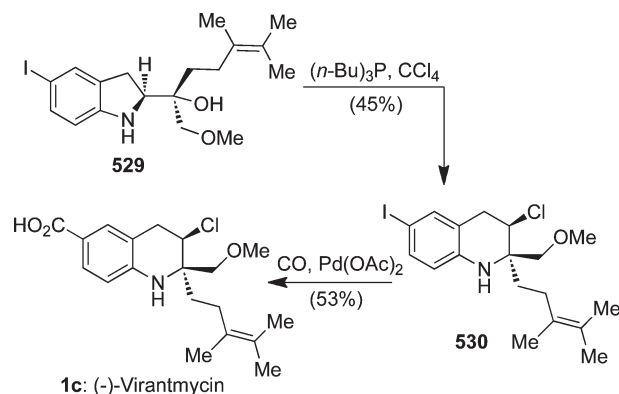
the key intermediate for the synthesis of the natural product (Scheme 165).<sup>260</sup>

Kogen and co-workers illustrated a novel rearrangement of indoline-2-methanol derivatives for the synthesis of 3-chloro-1,2,3,4-tetrahydroquinolines bearing a quaternary C-2 carbon.<sup>501</sup> A broad variety of  $\alpha,\alpha$ -disubstituted indoline-2-methanols **527** were treated with triphenylphosphine (3 equiv) and CCl<sub>4</sub> (10 equiv) under reflux conditions to afford the corresponding 3-chloro tetrahydroquinolines **528** in good yields. The mechanism of the reaction is depicted in Scheme 166 and involved the formation of an aziridine intermediate **A** from the starting materials, followed by ring-opening by chloride ion to give the final products. A similar ring-opening of aziridines by chloride ion to give the virantmycin core was previously described by Morimoto and co-workers.<sup>502</sup>

Subsequently, this methodology was extended to an efficient total synthesis of (–)-virantmycin **1c**. Substrate **529** was synthesized in a few steps starting from the commercial (S)-(–)-indoline-2-carboxylic acid and underwent an aziridine formation-ring-opening process under standard reaction conditions to afford the tetrahydroquinoline derivative **530**. A final carboxylation with carbon monoxide in the presence of a palladium catalyst furnished the natural product **1c** (Scheme 167). The authors then published the details of the process together with its extension to other cases as a full paper.<sup>503</sup>

The reaction between *N*-(4-methoxyphenyl)azetidin-2-ones **531** and LiAlH<sub>4</sub>/AlCl<sub>3</sub> afforded a mixture of the corresponding reduction products, namely azetidines **532** and **533**, together with the unexpected 1,2,3,4-tetrahydroquinolines **534**.<sup>504</sup> The

Scheme 166. Rearrangement of Indoline-2-methanol Derivatives to 3-Chloro-1,2,3,4-tetrahydroquinolines

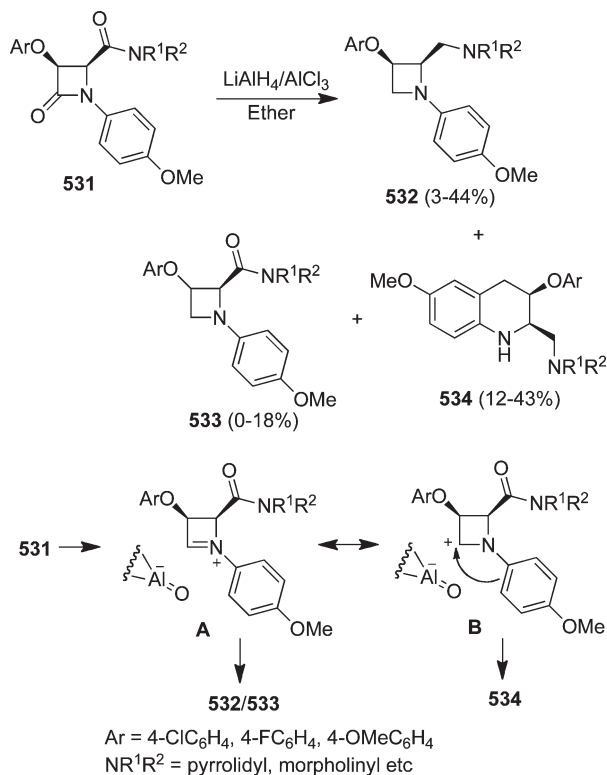
Scheme 167. Total Synthesis of (–)-Virantmycin **1c** Involving a Rearrangement Reaction

formation of compound **534** could be explained through the intermediacy of **A** and **B** (Scheme 168).

The palladium-catalyzed ring expansion of indoles with alkynes afforded polysubstituted 1,2,3,4-tetrahydroquinolines in high yields under mild conditions. A number of substituted indole derivatives **535** reacted with alkynes **536** in the presence of Pd(OAc)<sub>2</sub> under an oxygen atmosphere to afford the corresponding tetrahydroquinolines **537** through a novel rearrangement (Scheme 169).<sup>505</sup> On the basis of several deuterium labeled experiments, a plausible mechanism was proposed involving an initial electrophilic palladation of indoles at C-3 position<sup>506</sup> to give intermediate **A**, which subsequently afforded **B** after the successive insertion of two alkyne molecules. The next intramolecular 5-exo-dig cyclization gave the spiro intermediate **C**, which afforded the final product **537** by either of the two routes shown in Scheme 169. In the first route, intermediate **C** was trapped by a second molecule of indole to furnish **D**, which subsequently gave the final product through a reductive elimination-rearrangement sequence. The Pd(0) formed was then reoxidized to Pd(II) by oxygen. In the second route, intermediate **C** underwent a rearrangement to afford the tetrahydroquinoline species **E**, and the subsequent electrophilic palladation of a second molecule of indole followed by reductive elimination gave the final product **537**.

The 5,6,7,8-tetrahydroquinoline derivative **539**, an intermediate for the synthesis of unsymmetrically bridged terpyridines, was prepared by the thermal rearrangement of cyclohexanone

**Scheme 168.** Reactivity of *N*-(4-Methoxyphenyl)Azetidin-2-ones **531** with  $\text{LiAlH}_4/\text{AlCl}_3$



oxime *O*-allyl ether **538**, followed by loss of water and dehydrogenation.<sup>507</sup> The mechanism of this unusual reaction had been previously described in the literature and was found to involve a [2,3]-sigmatropic rearrangement.<sup>508</sup> Similarly, 6-amino-5,6,7,8-tetrahydroquinoline, a precursor for the synthesis of tetrahydroquinolines showing dopaminergic activity, was also synthesized from the corresponding oxime *O*-allyl ether by a route involving this rearrangement<sup>86</sup> (Scheme 170).

## 9. SYNTHESIS OF 1,2,3,4-TETRAHYDROQUINOLINES INVOLVING THE PARTIAL REDUCTION OF QUINOLINES

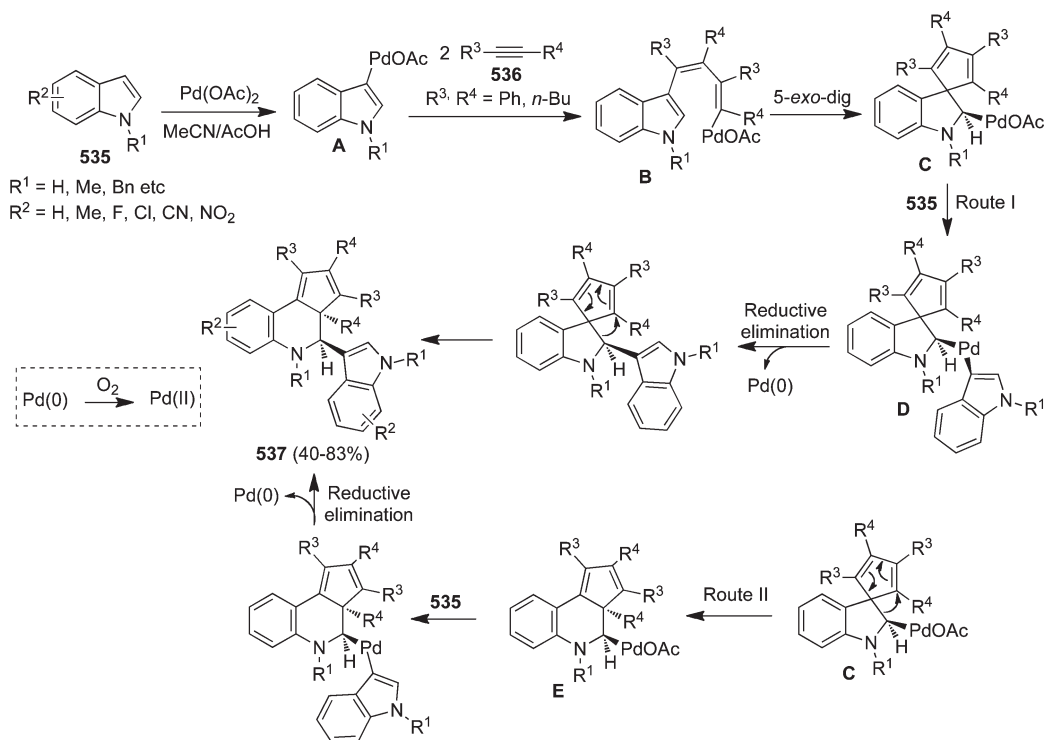
### 9.1. Introduction

The partial hydrogenation of quinoline derivatives is a straightforward method for the synthesis of 1,2,3,4-tetrahydroquinolines. The traditional procedures for this reduction include platinum, palladium, and cobalt-catalyzed hydrogenations, metals in acids ( $\text{Sn}/\text{HCl}$ ,  $\text{Zn}/\text{HCOOH}$ ,  $\text{Zn}/\text{CH}_3\text{COOH}$ , etc), and hydride reduction, where early developments have been discussed in a previous review.<sup>1</sup> In this section, we will demonstrate recent work on the partial reduction of quinolines to 1,2,3,4-tetrahydroquinolines, giving a special emphasis to the asymmetric version of this process.

### 9.2. Partial Hydrogenation of Quinolines to Racemic 1,2,3,4-Tetrahydroquinolines

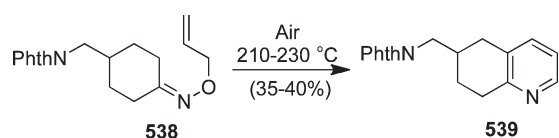
This section will discuss the methodologies developed for the partial hydrogenation of quinolines excluding the chiral versions, which will be treated under a separate heading. Transition metals, such as Ni, Pd, Pt, Rh, Ir, Ru, Os, and Mo, and their complexes were successfully employed as catalysts for the hydrogenation of quinolines and other heteroaromatic compounds. Moreover, organocatalysts were also found to be useful for the partial

**Scheme 169.** Pd-Catalyzed Ring Expansion of Indoles with Alkynes

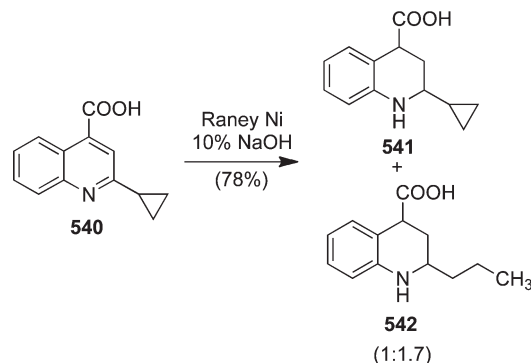




**Scheme 170.** Thermal Rearrangement of Cyclohexanone Oxime *O*-Allyl Ether **538**



**Scheme 171.** Hydrogenation of 2-Cyclopropylquinoline-4-carboxylic Acid **540** in the Presence of Raney Nickel



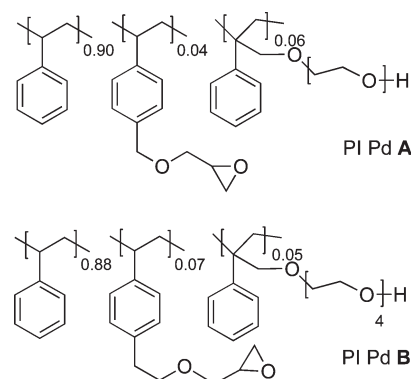
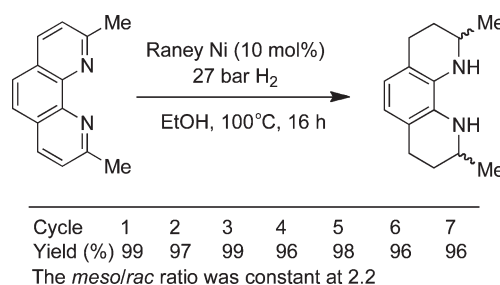
hydrogenation of quinolines. A detailed account on the recent developments of the reactivity and selectivity of these catalysts are summarized in the following subheadings.

**9.2.1. Hydrogenation of Quinolines Catalyzed by Raney Nickel.** Zhuravleva and co-workers reported a new methodology for the reduction of quinoline carboxylic acids employing Raney nickel as a catalyst. The suitable reaction conditions were found to be dependent on the nature of the substituents. For instance, 2-cyclopropylquinoline-4-carboxylic acid **540** was reduced by Raney nickel in aqueous alkali to a mixture of tetrahydroquinolines **541** and **542** (Scheme 171).<sup>509</sup>

Similarly, a variety of phenanthroline derivatives were quantitatively reduced by Raney nickel in ethanol and the “stir bar supported” catalyst was easily recovered with a pair of tweezers, washed with ethanol, and reused several times. The efficiency of the recycled catalyst was tested for the hydrogenation of a single example and gave excellent yields for several cycles, as shown in Scheme 172. 8-Hydroxyquinoline was also reduced to 8-hydroxy-1,2,3,4-tetrahydroquinoline in 88% yield using the same methodology.<sup>510</sup>

**9.2.2. Hydrogenation of Quinolines Catalyzed by Palladium or Platinum.** The role of palladium in organic synthesis is unique, and no other transition metal can offer such versatile methods for bond-forming reactions.<sup>511</sup> Furthermore, the use of palladium on carbon, alumina, or other supports as catalysts for hydrogenation processes is one of the most frequently employed reactions in academic research, as well as in industry. Some palladium catalysts that have found use in the hydrogenation of quinolines include Pd/TiO<sub>2</sub>,<sup>512</sup> polymer incarcerated palladium (PI Pd),<sup>513</sup> silica sol–gel entrapped Pd–[Rh(COD)Cl]<sub>2</sub>,<sup>514</sup> palladium nanoparticles supported on hyperbranched aromatic polyamides,<sup>515</sup> and subnanometer palladium clusters.<sup>516</sup> Among these Pd catalysts, polymer incarcerated palladium (PI Pd) had the highest synthetic interest (Figure 17). It was found to be an excellent catalyst for the hydrogenation of quinolines, olefins, alkynes, and nitro compounds under mild experimental conditions.

**Scheme 172.** Hydrogenation of 2,9-Dimethyl-1,10-phenanthroline

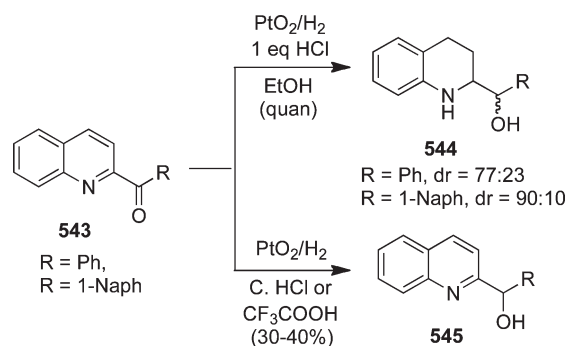


**Figure 17.** Structures of PI Pd catalysts.

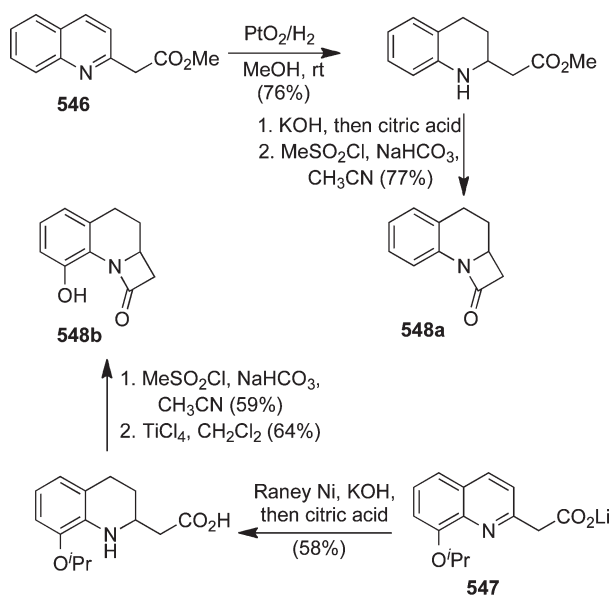
The traditional Pd catalysts continue to have widespread application, and thus it is interesting to note that hydrogenation of 2-methylquinoline in the presence of Pd/C in trifluoroacetic acid afforded 2-methyl-5,6,7,8-tetrahydroquinoline in almost quantitative yield.<sup>517</sup> Similarly, quinoline derivatives bearing a phosphonate moiety were also hydrogenated effectively in the presence of Pd/C and excess of ammonium formate to afford the corresponding 1,2,3,4-tetrahydroquinolines.<sup>518</sup> In a recent article, it was reported that the hydrogenation of polysubstituted quinoline derivatives in the presence of Pd/C or Pd(OH)<sub>2</sub> afforded the corresponding 1,2,3,4-tetrahydroquinolines.<sup>519</sup>

Kobayashi and co-workers also developed a polymer incarcerated platinum (PI Pt) catalyst similar to the Pd-containing one previously discussed. The catalyst was prepared from PtCl<sub>2</sub>–(COD) or H<sub>2</sub>PtCl<sub>6</sub>·6H<sub>2</sub>O and styrene copolymers based on the reduction of a Pt source with triethylamine, coacervation, and cross-linking strategies.<sup>520</sup> A small amount of this catalyst (1 mol %) was sufficient to reduce quinoline to 1,2,3,4-tetrahydroquinoline in 82% yield under atmospheric pressure of hydrogen.

The reduction of a number of quinoline derivatives was demonstrated using the PtO<sub>2</sub>/H<sub>2</sub> system. The nature of the products strongly depended on the experimental conditions. For example, the presence of a carbonyl-containing function at the 2-position of quinolines **543** allowed the reduction of both the heterocyclic ring and the carbonyl group with PtO<sub>2</sub>/H<sub>2</sub> and one equivalent of HCl (compound **544**), whereas the use of PtO<sub>2</sub>/H<sub>2</sub> and concentrated hydrochloric acid or trifluoroacetic acid furnished product **545** from reduction of the carbonyl group (Scheme 173).<sup>521</sup> In a related procedure, hydrogenation with PtO<sub>2</sub>/H<sub>2</sub> in trifluoroacetic acid of quinolines bearing acetamido substituents at a variety of positions afforded a mixture of both

Scheme 173.  $\text{PtO}_2$ -Catalyzed Hydrogenation of Quinolines 543

Scheme 174. Synthesis of Azetidinones 548 via Partial Reduction of Quinolines

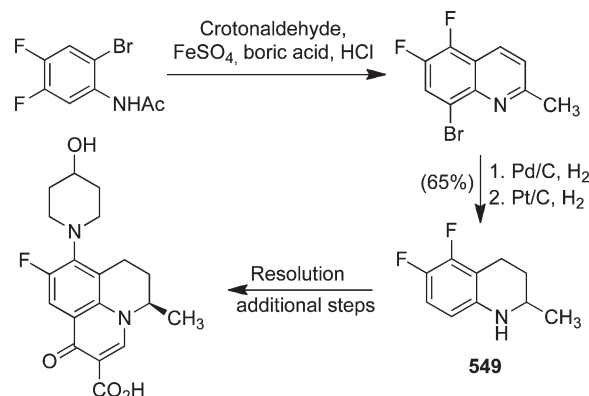


1,2,3,4- and 5,6,7,8-tetrahydroquinolines, the latter being the major products.<sup>522</sup> The reduction by this method of quinolines bearing an oxazolidinone chiral auxiliary unit at C-2 has been used as the basis for the preparation of enantiomerically pure decahydroquinoline systems.<sup>523</sup>

The hydrogenation of halogen-containing substrates is a challenging process since it is often accompanied by reductive dehalogenation. Zhadarev and co-workers demonstrated a selective partial hydrogenation of halogen-containing 8-hydroxyquinolines to 8-hydroxy-1,2,3,4-tetrahydroquinolines avoiding or at least diminishing the hydrodehalogenation products by using a  $\text{Pt}/\text{Al}_2\text{O}_3/\text{H}_2$  system.<sup>524</sup>

Gilchrist and Rahman reported the synthesis of azetidinones **548** via the partial hydrogenation of quinolines using  $\text{PtO}_2/\text{H}_2$  or Raney nickel.<sup>525</sup> Quinolinecarboxylic acids **546** or their lithium salts **547** were hydrogenated directly in good yields in the presence of  $\text{PtO}_2$  and Raney nickel, respectively, and the hydrogenated products were subsequently transformed into the final azetidinones **548** by addition of sodium bicarbonate and methanesulfonyl chloride (Scheme 174). The  $\text{PtO}_2/\text{H}_2$  reduction

Scheme 175. Synthesis of Antibacterial Compound (S)-(-)-Nadifloxacin 550 via Catalytic Hydrogenation of Quinoline Derivative



system was also found to be appropriate for the reduction of quinolines in the presence of other heterocyclic ring systems<sup>526</sup> and functionalities such as carboxylic acid,<sup>142,527–529</sup> hydroxy,<sup>156</sup> and amino<sup>530</sup> groups.

(S)-(-)-Nadifloxacin **550**, an antibacterial agent that shows potent activity against *Propionibacterium acnes*, was synthesized from 2-methyl-5,6-difluoro-1,2,3,4-tetrahydroquinoline **549**.<sup>531</sup> Treatment of the *N*-acetyl derivative of 2-bromo-4,5-difluoroaniline with crotonaldehyde afforded the corresponding 2-methylquinoline derivative. The quinoline moiety was hydrogenated in the presence of  $\text{Pt}/\text{C}$ , which was followed by removal of the bromine atom in the presence of the  $\text{H}_2/\text{Pd}/\text{C}$  system. Optical resolution of the racemic tetrahydroquinoline **549** and further structural manipulation afforded (S)-(-)-nadifloxacin **550** in good yield (Scheme 175).

**9.2.3. Hydrogenation of Quinolines Catalyzed by Rhodium or Iridium.** A broad variety of substituted quinolines were effectively hydrogenated by  $\text{Rh}/\text{Al}_2\text{O}_3/\text{H}_2$  reduction system and the reaction was found to be solvent-dependent. Methanol was found to be the best solvent to obtain 1,2,3,4-tetrahydroquinolines, while hexafluoro-2-propanol gave the corresponding decahydroquinoline derivatives.<sup>532</sup> Bianchini and co-workers reported the synthesis of polymer-supported rhodium catalyst ( $[\text{Rh}(\text{COD})(\text{POLYDIPHOS})]\text{PF}_6$ ) and its use for the hydrogenation of quinolines (Figure 18).<sup>533</sup> The reduction of quinoline using this catalyst afforded a mixture of 1,2,3,4-tetrahydroquinoline, as the major product, and small amounts of 5,6,7,8-tetrahydroquinoline and decahydroquinoline.

Subsequently, the same group demonstrated the use of rhodium catalysts modified with a tripodal polyphosphine ligand  $\text{MeC}(\text{CH}_2\text{PPh}_2)_3$  for the selective hydrogenation of quinolines. The authors carried out a set of kinetic and isotopic labeling studies, and proposed a detailed mechanism for the reaction.<sup>534</sup> The chiral 2-cyano-1,2-dihydroquinolines derived from the asymmetric Reissert-type reaction were reduced to the corresponding 2-cyano-1,2,3,4-tetrahydroquinolines by  $\text{Rh}/\text{C}/\text{H}_2$  in acetic acid.<sup>535,536</sup> The rhodium bipyridine compound  $\text{cis}[\text{Rh}(\text{bipy})_2\text{Cl}_2]\text{Cl}\cdot 2\text{H}_2\text{O}$  was also found to be a good catalyst for the transfer hydrogenation of different unsaturated compounds including quinoline.<sup>537</sup>

Iridium complexes have a significant role in the hydrogenation of heteroaromatic compounds. Fujita and co-workers described a

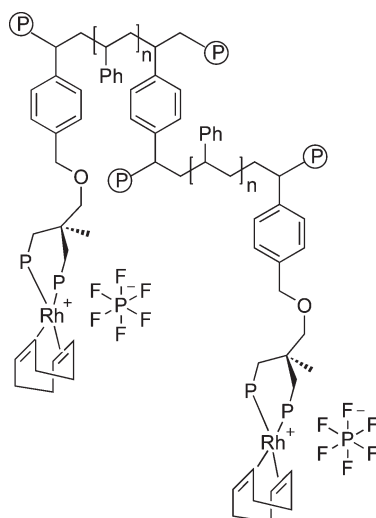
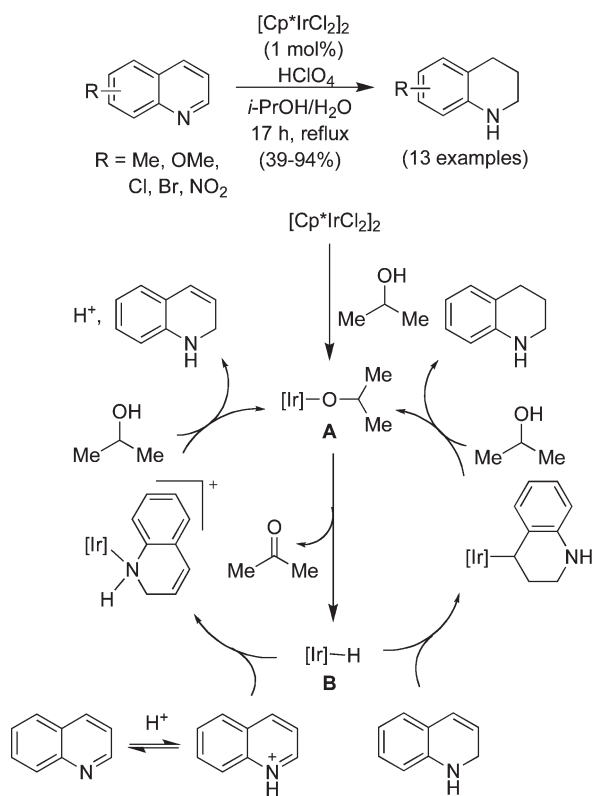


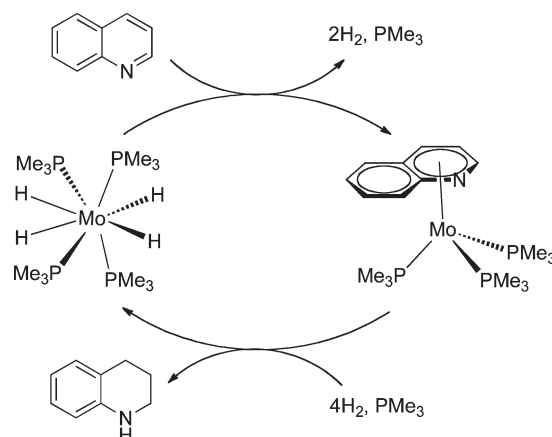
Figure 18. Structure of  $[\text{Rh}(\text{COD})(\text{POLYDIPHOS})]\text{PF}_6$ .

**Scheme 176. Fujita's Ir-Catalyzed Hydrogenation of Quinolines and the Proposed Mechanism**



new catalytic system involving a pentamethylcyclopentadienyl ( $\text{Cp}^*$ ) iridium complex  $[\text{Cp}^*\text{IrCl}_2]_2$  for the regio- and chemo-selective transfer hydrogenation of quinolines.<sup>538</sup> After systematic screening experiments, the authors identified  $\text{HClO}_4$  (10 mol %) as the best additive and 2-propanol as a suitable hydrogen source. A plausible mechanism for the hydrogenation process was also proposed, as depicted in Scheme 176, involving the generation of iridium isopropoxide **A** and iridium hydride **B** as intermediates, by reaction between the catalyst and 2-propanol. Species **B** would attack the carbon–nitrogen bond of the

**Scheme 177. Catalytic Cycle for the Hydrogenation of Quinoline in the Presence of  $\text{Mo}(\text{PMe}_3)_4\text{H}_4$**

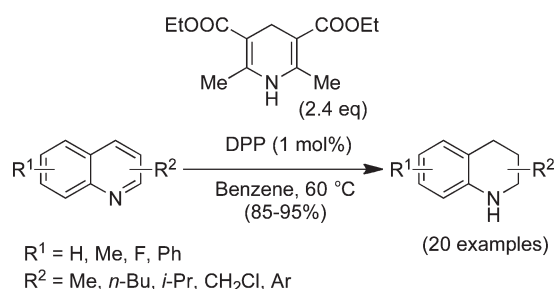
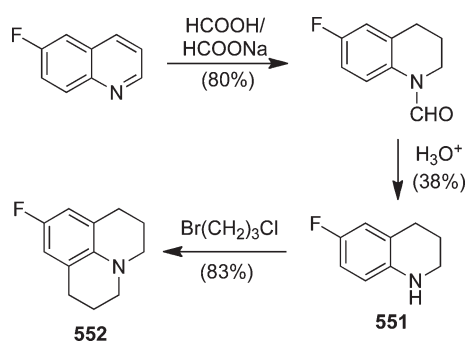


quinolinium ion generated by protonation of the quinoline nitrogen to give the dihydroquinoline intermediate, which would again react with another molecule of **B** to furnish 1,2,3,4-tetrahydroquinoline after protonolysis. Although the intermediate 1,2-dihydroquinoline was not detected during the course of the reaction, the isolation of 1,2,3,4-tetrahydroquinoline in 87% yield starting from pure 1,2-dihydroquinoline, in a separate experiment but under identical experimental conditions, supported the proposed mechanism.

Other catalysts for the hydrogenation of quinolines include iridium (or Rh) nanoparticles entrapped in aluminum oxyhydroxide nanofibers,<sup>539</sup>  $\text{Ir}[(\text{COD})\text{Cl}]_2$  stabilized with the tris-pyrazolyl borate ligands,<sup>540</sup> Ir (or Rh) complexes containing mono-, di-, and tridentate phosphine ligands<sup>541</sup> and  $[\text{Ir}(\text{COD})(\text{NHC})\text{PPh}_3]\text{BF}_4$ , where NHC = 1-neopentyl-4-*n*-butyltriazole-5-ylidene<sup>542</sup> etc. The latter catalyst was used for the transfer hydrogenation of quinoline (67% yield) using 2-propanol and potassium carbonate with a turnover number (TON) of 67.

**9.2.4. Hydrogenation of Quinolines Catalyzed by Ruthenium or Osmium.** Zhou and co-workers explored  $[\text{Ru}(p\text{-cymene})\text{Cl}_2]_2/\text{I}_2$  as an efficient catalytic system for the hydrogenation of quinoline derivatives to 1,2,3,4-tetrahydroquinolines.<sup>543</sup> It was found that THF, EtOAc, and EtOH were effective solvents and that the role of iodine as an additive was essential. The reaction was excellent even in a substrate-to-catalyst (S/C) ratio of 20 000/1 in THF. Other versions of ruthenium and osmium catalysts for the hydrogenation of quinolines include the ruthenium nanoparticles immobilized on poly(4-vinylpyridine),<sup>544</sup> Ru(II) species containing water-soluble phosphine TPPTS (tris-*meta*-sulfonatophenylphosphine) ligands,<sup>545</sup> Ru(II) mesoporous catalyst  $(\text{Ru-MOC})$ ,<sup>546</sup> dihydride ruthenium complexes,<sup>547</sup>  $\text{MH}(\text{CO})(\kappa^3\text{-OCOR})(\text{PPh}_3)_2$  [ $\text{M} = \text{Ru}, \text{Os}$ ;  $\text{R} = \text{CH}_3, \text{CH}_2\text{Cl}, \text{Ph}, \text{CH}(\text{CH}_3)_2$ ],<sup>548</sup> and  $[\text{OsH}(\text{CO})(\text{NCMe})_2(\text{PPh}_3)_2]\text{BF}_4$ ,<sup>549</sup> etc. These articles describe mainly the synthesis and properties of the catalysts and demonstrate their application to the hydrogenation of quinolines.

**9.2.5. Hydrogenation of Quinolines Catalyzed by Molybdenum.** The first molybdenum-based catalyst developed for the hydrogenation of heteroaromatic compounds, including quinolines, is  $\text{Mo}(\text{PMe}_3)_4\text{H}_4$ .<sup>550</sup> Although this catalyst promotes the hydrogenation of heteroaromatics, the efficiency of the catalytic cycle was low. The rationale for its preparation was based on the conversion of the complex  $(\eta^6\text{-NHetH})\text{Mo}(\text{PMe}_3)_3$

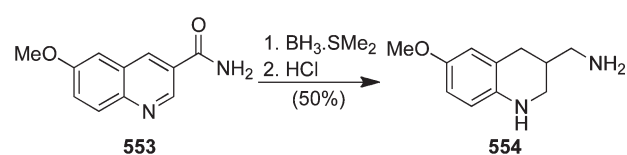
**Scheme 178.** Rueping's Brønsted Acid-Catalyzed Transfer Hydrogenation Process for the Reduction of Quinolines**Scheme 179.** Synthesis of Fluorinated 1,2,3,4-Tetrahydroquinolines

to its isomers in which the carbocyclic ring coordinates with the molybdenum, and these isomers are less reactive toward hydrogenation. The catalytic cycle for the hydrogenation of quinolines to 1,2,3,4-tetrahydroquinolines in the presence of the molybdenum catalyst is given in Scheme 177.

**9.2.6. Hydrogenation Reactions Involving Organocatalysts.** The first Brønsted acid-catalyzed transfer hydrogenation process for the reduction of quinolines to 1,2,3,4-tetrahydroquinolines in the presence of Hantzsch ester was developed by Rueping in 2006.<sup>551</sup> Although all the tested Brønsted acids, namely, camphorsulfonic acid (CSA), TFA, HBF<sub>4</sub> and diphenyl phosphate (DPP), gave excellent results, DPP was found to be superior since 1 mol % of the catalyst was sufficient to allow almost quantitative conversions under mild conditions (Scheme 178).

A couple of years later, haloperfluoroalkanes (10 mol %) were also found to be efficient catalysts for the partial reduction of 2-substituted quinolines, and here again Hantzsch ester was used as the hydride donor.<sup>552</sup> The ability of highly fluorinated alkanes to make strong halogen bonds to sp<sup>2</sup> nitrogen activates the substrates for the hydrogenation process. Perfluorinated iodoalkanes were more active than the corresponding bromo derivatives.

**9.2.7. Hydrogenation Reactions Involving No Catalysts.** In a procedure mainly dealing with the microwave-assisted, solvent-free reduction of Schiff bases by trimethylammonium formate/formic acid system, quinoline was also successfully reduced to 1,2,3,4-tetrahydroquinoline in 81% yield just in 10 min.<sup>553</sup> Gawinecki and co-workers reported the synthesis of fluorinated 1,2,3,4-tetrahydroquinolines **551** and **552** based on a formic acid/sodium formate reduction of 6-fluoroquinoline (Scheme 179).<sup>554</sup> The synthesis of N-substituted 1,2,3,4-tetrahydroquinolines in good yields was also reported by reaction

**Scheme 180.** Borane-Dimethyl Sulfide Reduction of Quinoline **553**

between quinolines, acyl/benzyl/allyl/alkyl halides, and Hantzsch dihydropyridine esters in the absence of any catalyst.<sup>555</sup>

**9.2.8. Miscellaneous Reactions.** The synthesis of 6-methoxy-3-aminomethyl-1,2,3,4-tetrahydroquinoline **554**, a novel lead structure for 5-HT<sub>4</sub> receptor ligands, was achieved by borane-dimethyl sulfide reduction of the corresponding quinoline **553** (Scheme 180).<sup>556</sup> In another study, a mixture of NaBH<sub>3</sub>CN and boron trifluoride etherate was found to be the best combination for the partial hydrogenation of quinolines to 1,2,3,4-tetrahydroquinolines in good to excellent yields.<sup>557</sup> Sodium cyanoborohydride alone was also utilized for the hydrogenation of 2-cyclohexylquinoline, an intermediate for the preparation of CB1 cannabinoid agonists<sup>558</sup> and 1,10-phenanthrolines.<sup>559</sup>

Metallic indium and ammonium chloride in aqueous ethanol was an effective reduction system for the partial hydrogenation of heterocyclic compounds including quinolines, isoquinolines, and quinoxalines.<sup>560,561</sup> This reagent was found to selectively hydrogenate the quinoline ring in the presence of other functional groups like amide.

Grignon–Dubois and co-workers reported a novel Zn/AcOH promoted synthesis of fused tetrahydroquinoline derivatives based on a cascade reaction of dihydroquinoline derivatives. They found that, when treated with Zn/AcOH, a number of commercially available monosubstituted quinoline derivatives afforded the pentacyclic compounds **555** or **556** and **557** in good yields depending on the nature of the substituents. For instance, quinoline and 6-methylquinoline afforded only compound **555** as a diastereomeric mixture, while 3- or 4-substituted quinolines furnished mixtures of compounds **555**, **556**, and **557**. This dimerization–cyclization cascade allowed the formation of two C–C bonds and four to five stereogenic centers (Scheme 181).<sup>562</sup>

Radiyov and co-workers developed recently a novel protocol for the reduction of polycyclic aromatic and heteroaromatic compounds, including quinolines, in the presence of cobalt or manganese nanoparticles generated in situ from CoCl<sub>2</sub>·6H<sub>2</sub>O or MnCl<sub>2</sub>·2H<sub>2</sub>O.<sup>563</sup>

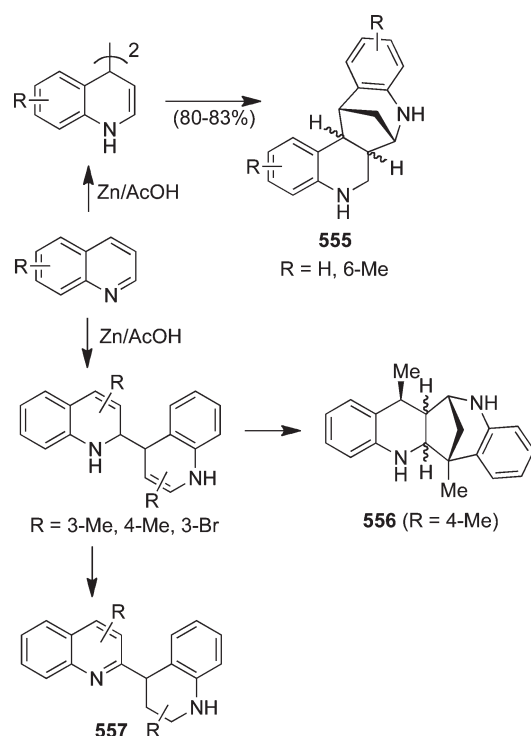
### 9.3. Asymmetric Hydrogenation of Quinolines

Asymmetric synthesis remains a challenge to synthetic chemists as the demand for enantiomerically pure compounds continues to increase. Many groups working in chemical synthesis and drug discovery are striving to find new methods for asymmetric synthesis that allow the development of new chiral molecules. Asymmetric hydrogenation of quinoline derivatives is the best and easiest way to access enantiopure 1,2,3,4-tetrahydroquinolines in a single operation. This chemistry was developed in the 2000 decade, mainly by Chinese groups (Zhou, Chan, and others), and is based mainly on the use of iridium catalysts, although other metal and Brønsted acid catalysts have also been developed simultaneously.

**9.3.1. Brønsted Acid-Catalyzed Asymmetric Hydrogenation of Quinolines.** Chiral Brønsted acids have recently materialized as excellent catalysts for many synthetically



Scheme 181. Zn/AcOH-Promoted Synthesis of Fused Tetrahydroquinoline Derivatives



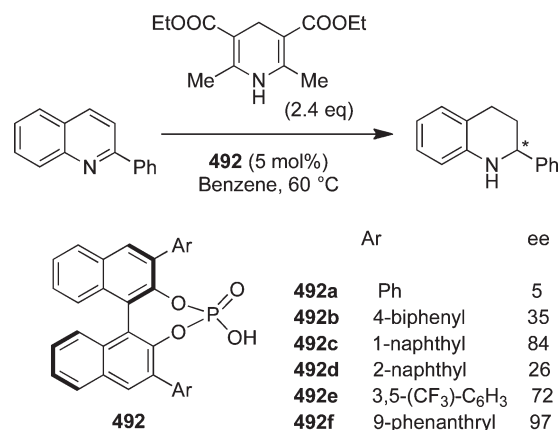
important asymmetric transformations.<sup>564</sup> The first chiral Brønsted acid-catalyzed asymmetric transfer hydrogenation process of quinolines was again developed by Rueping.<sup>565–567</sup> After a systematic catalyst survey, the authors identified the chiral phosphoric acids **492** as the ideal choice for the asymmetric hydrogenation. As shown in Scheme 182, sterically crowded chiral acid **492f** afforded the best enantioselectivity, among the tested catalysts, for the hydrogenation of 2-phenylquinoline to 2-phenyl-1,2,3,4-tetrahydroquinoline. Halomethane derivatives ( $\text{CH}_2\text{Cl}_2$ ,  $\text{CHCl}_3$ , and  $\text{CCl}_4$ ), and aromatic hydrocarbons (benzene and toluene) were found to be the best solvents to improve enantioselectivity.

A variety of 2-substituted quinolines were hydrogenated enantioselectively in the presence of **492f**, and the methodology was subsequently adapted to the synthesis of some biologically active tetrahydroquinoline alkaloids, such as galipinine **3a**, cuspareine **3b**, and angustureine **4a** (Scheme 183).

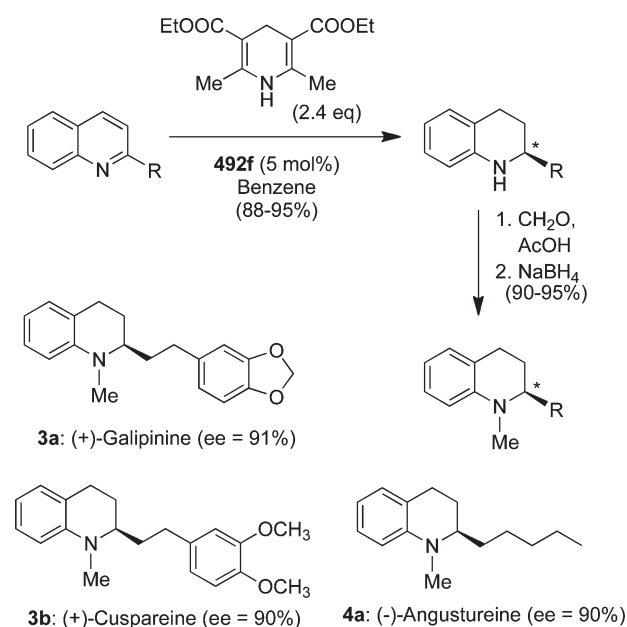
The authors proposed a mechanism based on the protonation of quinoline by catalyst **492** to generate iminium intermediate **A**, which undergoes a subsequent hydride transfer with the Hantzsch ester to give enamine **B** and pyridinium species **C**. The latter intermediate then undergoes a proton transfer to regenerate the catalyst leaving a molecule of Hantzsch pyridine, while the former reacts with the catalyst to produce iminium species **D** in a second cycle. The second hydride transfer of the Hantzsch ester to **D** gives the tetrahydroquinoline product and pyridinium intermediate **C**, which regenerates the catalyst after affording the second molecule of pyridine through a hydride transfer (Scheme 184).

This procedure furnished excellent enantioselectivities (up to 99%) for the 2-aryl-substituted quinolines, but not for the case of the 2-alkyl derivatives. To overcome this drawback, Du and co-workers developed a novel family of double axially chiral

Scheme 182. First Chiral Brønsted Acid-Catalyzed Asymmetric Transfer Hydrogenation of Quinolines Developed by Rueping



Scheme 183. Asymmetric Synthesis of Tetrahydroquinoline Natural Products via Transfer Hydrogenation Process

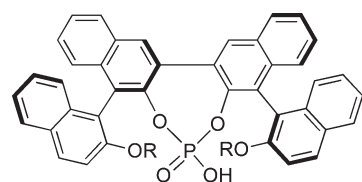
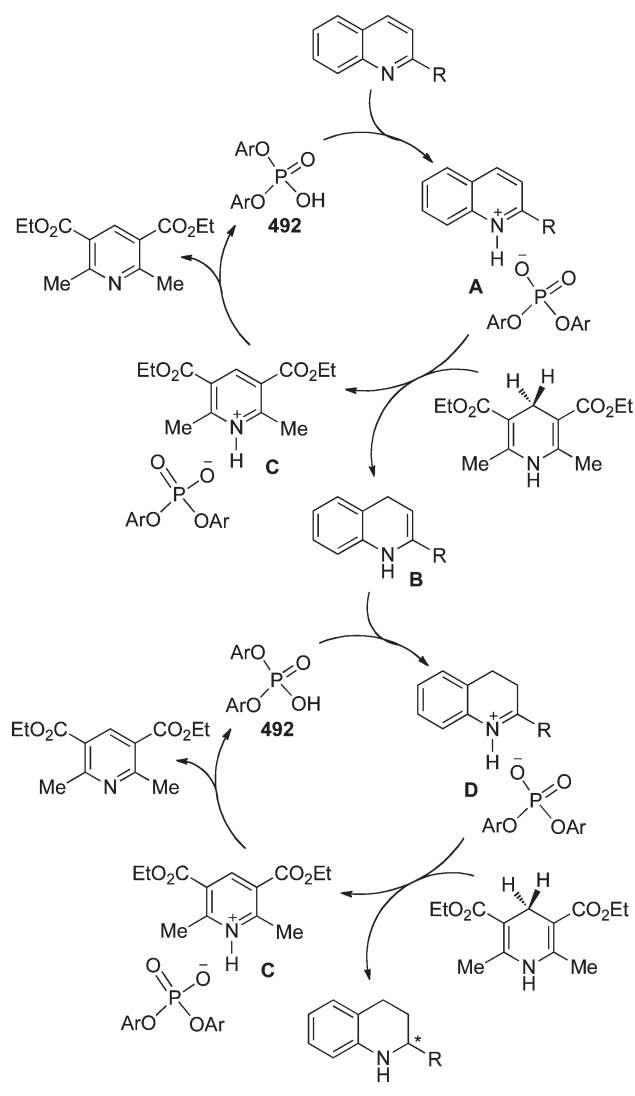


phosphoric acid catalysts **558** and achieved improved enantioselectivities for the hydrogenation of 2-alkylquinolines (Figure 19).<sup>568</sup> These starting materials were reduced under mild conditions with just 0.2 mol % of catalyst in diethyl ether. 2,3-Disubstituted quinolines also gave excellent enantio- and diastereoselectivities (dr up to 20:1). A comparative account of the yields and enantioselectivities obtained with the catalysts **492** and **558** is summarized in Table 2. The catalysts developed by Rueping (compounds **492d** and **492f**) were also used by Metallinos and co-workers for the enantioselective hydrogenation of 2- and 2,9-substituted 1,10-phenanthrolines in good yields and enantioselectivities.<sup>569</sup> Recently, the use of chiral Brønsted acids was also reported for the asymmetric hydrogenation of fluoroquinolines in very high enantioselectivities.<sup>570</sup>

**9.3.2. Asymmetric Hydrogenation of Quinolines Catalyzed by Iridium.** The iridium-catalyzed asymmetric



Scheme 184. Proposed Mechanism for the Asymmetric Transfer Hydrogenation of Quinolines



558a: R = Me  
 558b: R = *i*-Pr  
 558c: R = *n*-Bu  
 558d: R = *c*-Hex (higher ee was observed)

Figure 19. Structure of Double Axially Chiral Phosphoric Acid Catalysts.

hydrogenation<sup>571</sup> of quinolines has received great attention in recent years, and it has proved to be the best method to access enantiopure 1,2,3,4-tetrahydroquinolines, as evidenced by the fact that around 70% of articles in this field deal with the iridium catalysts. The primary report on the use of an iridium catalyst for the hydrogenation of quinolines was published by Zhou and co-workers in 2003.<sup>572</sup> These authors found that the best conditions involved the use of the  $[\text{Ir}(\text{COD})\text{Cl}]_2/\text{MeO-Biphep}/\text{I}_2$  catalytic

Table 2. Comparison of Catalysts 492 and 558 for the Enantioselective Hydrogenation of 2-Substituted Quinolines

entry	R	catalyst (492f)		catalyst (558d)	
		yield (%)	ee (%)	yield (%)	ee (%)
1	Ph	92	97	99	96
2	2-Naphthyl	93	>99	99	97
3	2-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	54	91	52	86
4	4-CF <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	91	>99	99	98
5	<i>n</i> -Pentyl	88	90	99	92
6	<i>n</i> -Butyl	91	87	99	94
7	<i>n</i> -Propyl	-	-	99	94
8	PhCH <sub>2</sub> CH <sub>2</sub>	90	90	99	93

Table 3. Scope of the  $[\text{Ir}(\text{COD})\text{Cl}]_2/\text{MeO-Biphep}/\text{I}_2$ -Catalyzed Hydrogenation of Quinolines (Selected Examples)

(R)-MeO-Biphep

entry	R <sup>1</sup>	R <sup>2</sup>	yield (%)	ee (%)
1	H	Me	94	94 (R)
2	H	<i>n</i> -propyl	92	93 (R)
3	H	3-butenyl	91	92 (R)
4	Me	Me	91	91 (R)
5	H	Ph	95	72 (S)
6	F	Me	88	96 (R)
7	H	CH <sub>2</sub> OCOCH <sub>3</sub>	90	87 (S)
8	H	CH <sub>2</sub> OH	83	75 (S)

system in toluene with 700 psi hydrogen pressure at room temperature with a substrate/[Ir]/ligand/ $\text{I}_2$  ratio of 100:0.5:1.1:10 (Table 3). The role of iodine as an additive was essential, and all attempts to use other additives, such as *n*-Bu<sub>4</sub>NI, BiI<sub>3</sub>, phthalimide, benzylamine, etc., were unsuccessful. Toluene was the best choice among the tested solvents (others were CH<sub>2</sub>Cl<sub>2</sub>, (CICH<sub>2</sub>)<sub>2</sub>, MeOH, *i*-PrOH, THF, and benzene). The methodology thus developed was successfully employed for the synthesis of the tetrahydroquinoline natural products galipinine 3a, cuspareine 3b, and angustureine 4a in excellent yields and selectivities. Recently, the iridium-catalyzed hydrogenation of quinolines in the presence of piperidine.TfOH as activator was also reported.<sup>573</sup>

Subsequently, the authors extended their procedure for the first enantioselective total synthesis of the naturally occurring alkaloid (–)-galipeine 3c starting from isovanillin in seven steps

### Scheme 185. First Enantioselective Total Synthesis of (–)-Galipeine 3c

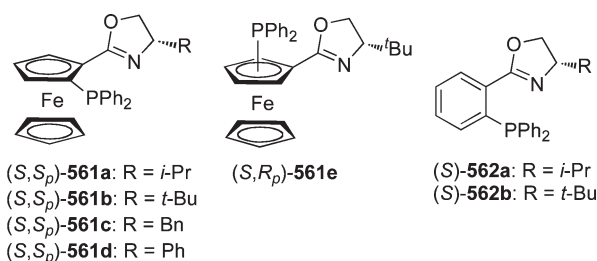
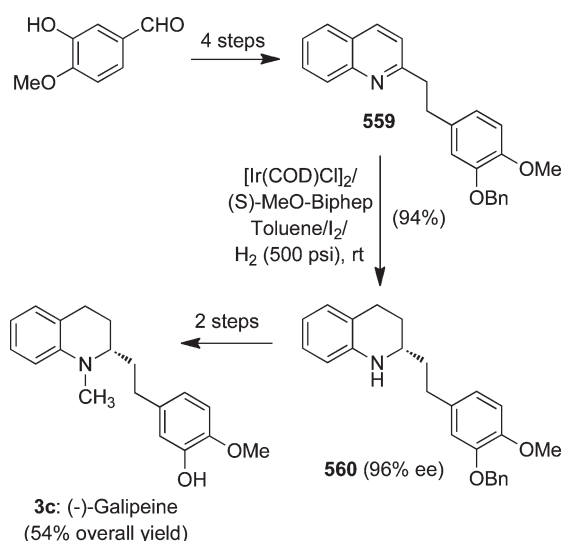


Figure 20. Structures of chiral ferrocenyloxazoline and oxazoline ligands.

with 54% overall yield (Scheme 185).<sup>574</sup> The intermediate quinoline **559** was synthesized in four steps and was then hydrogenated enantioselectively to the corresponding 1,2,3,4-tetrahydroquinoline derivative **560** in 94% yield and 96% ee employing the previous procedure. The natural product (–)-galipeine **3c** was obtained after two further N-methylation and deprotection steps.

The same group further reported an iridium/ferrocenyloxazoline derived *N,P*-ligand-based catalytic system for the asymmetric hydrogenation of quinolines.<sup>575,576</sup> One of the advantages of this method includes the easy preparation of the ligands starting from commercially available optically pure amino acids.<sup>577</sup> The chiral ferrocenyloxazoline ligands involved in this study are listed in Figure 20. The *t*-butyl substituted ligand **561b** was superior in terms of enantioselectivity to other less sterically hindered analogues. Ligands **562**, having no ferrocenyl substituent, showed lower enantioselectivity compared to the ferrocenyloxazoline ligands **561a** and **561b**. Ligand **561e**, with the same central chirality and opposite planar chirality to **561b**, gave an absolute configuration (*S*,*R*<sub>p</sub>) similar to the product obtained by using **561b** for the hydrogenation of 2-methylquinoline but proceeded in lower enantioselectivity. This indicates that the absolute configuration of the product is mainly determined by the central chirality of the oxazoline ring. The mismatched nature of the (*R*) planar chirality and the (*S*) central chirality of the ligand **561e** could be the reason for the observed lower enantioselectivity.

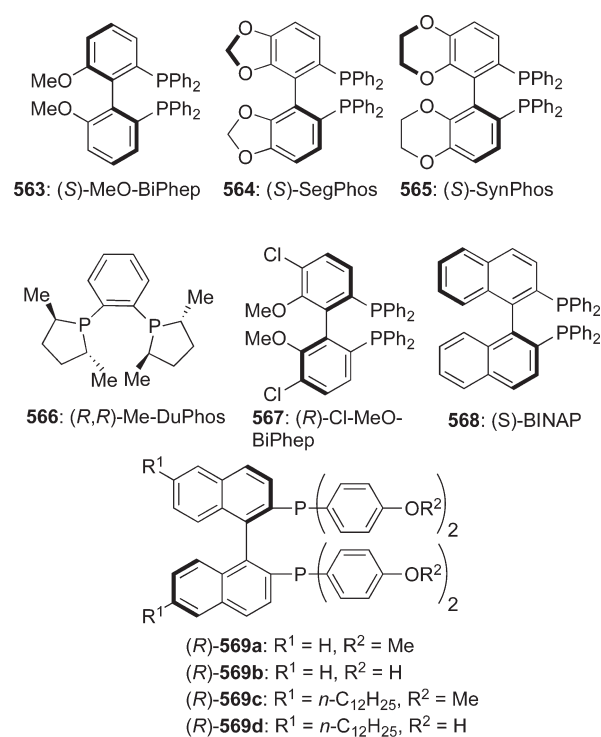


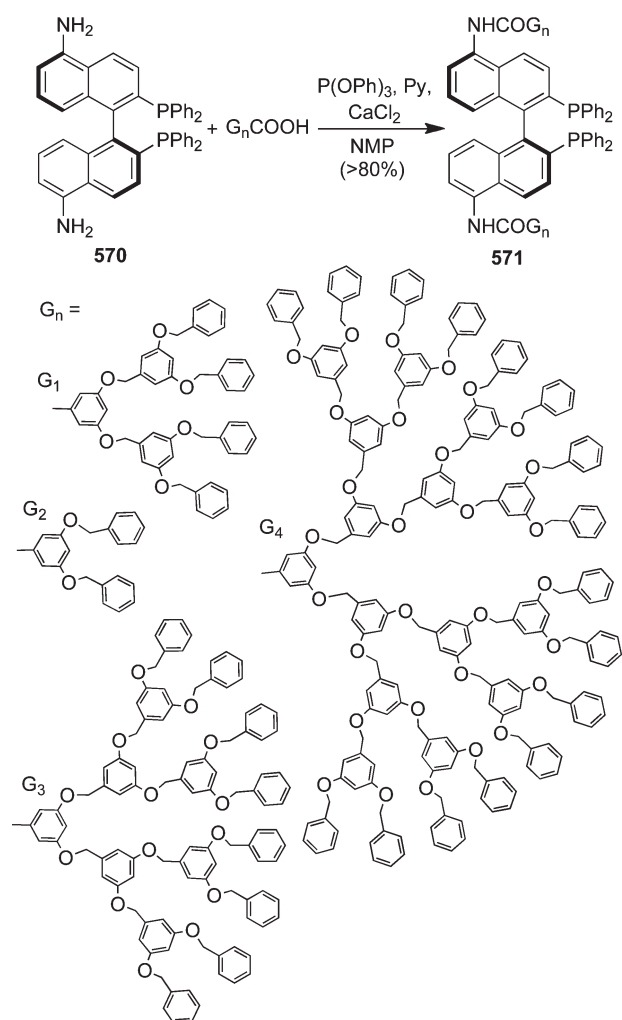
Figure 21. Ligands used for the asymmetric hydrogenation of quinolines reported by Zhou and Lamaire.

The best conditions for the hydrogenation reaction were the use of 0.5 mol % of the catalyst, 1.1 mol % of the ligand, and 10 mol % of iodine as additive in toluene with 600 psi hydrogen pressure at room temperature. The scope of the reaction was demonstrated by carrying out the hydrogenation of several 2- and 6-substituted quinolines, which afforded up to 95% yields and 92% ee. The catalytic efficiency was further evaluated by studying the substrate-to-catalyst (S/C) ratio. The hydrogenation of 2-methylquinoline proceeded smoothly with S/C ratios of 100/1 (95%, 90% ee), 500/1 (95%, 88% ee) and 1000/1 (95%, 86% ee), but with a 2000/1 ratio both the yield and ee were lower (67%, 82% ee) with ligand **561b**. This procedure was later on used for the synthesis of 2-methyl-1,2,3,4-tetrahydroquinoline-derived phosphoramidites, potential ligands for the iridium-catalyzed Friedel–Crafts reaction of indoles.<sup>150</sup>

Next, the authors studied the use of Hantzsch esters as hydrogen donors for the iridium-catalyzed asymmetric hydrogenation of quinolines in the presence of (S)-MeO-Biphep **563**, (S)-SegPhos **564**, (S)-SynPhos **565**, (R,R)-Me-DuPhos **566**, (R)-Cl-MeO-Biphep **567**, and (S)-BINAP **568** ligands.<sup>578</sup> Although most of these ligands gave good to excellent yields, (S)-SegPhos **564** was identified as the one that furnished the highest enantioselectivities (up to 88%, Figure 21). Lamaire and co-workers synthesized a few electronically enriched chiral ligands **569** starting from (*R*)-BINOL and tested their catalytic activity combined with Ir and Ru complexes for the asymmetric hydrogenation of α-ketoesters and 2-methylquinoline. Although the catalytic system worked well for the reduction of α-ketoesters, 2-methylquinoline gave only moderate enantioselectivity (Figure 21).<sup>579</sup>

The well-defined molecular architecture of dendrimers allowed the possibility of fine-tuning the catalytic activity of their

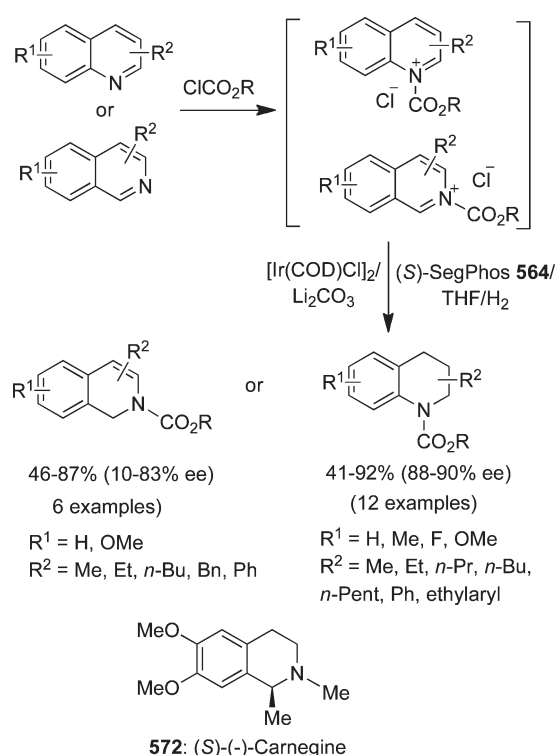
Scheme 186. Synthesis of Chiral Dendritic Ligands 571 Reported by Fan



metal complexes. Accordingly, a variety of organometallic dendrimers with different catalytic sites were developed recently.<sup>580</sup> Fan and co-workers synthesized four chiral dendritic catalysts **571** originated from BINAP, which showed excellent catalytic activities (TON up to 43 000 and TOF up to  $3450 \text{ h}^{-1}$ ) and high enantioselectivities (up to 93%) for the hydrogenation of quinoline derivatives (Scheme 186).<sup>581</sup> The dendrimer ligands ( $G_n\text{Den-BINAP}$ ) were synthesized from the dendritic wedges  $G_n\text{COOH}$  and (*S*)-5,5'-diamino BINAP **570** in more than 80% yields in the presence of triphenylphosphite, pyridine, and calcium chloride in NMP.<sup>582</sup> The  $G_n\text{Den-BINAP}/[\text{Ir}(\text{COD})\text{Cl}]_2$  catalytic system showed excellent activity and a TON of 43 000 was observed, which is the highest TON reported so far. Furthermore, the catalysts were recovered and reused at least four times without any significant loss in the reactivity in terms of yield and enantioselectivity.

The aforementioned catalytic systems are excellent for the asymmetric hydrogenation of quinolines, but nevertheless efforts to develop new methods continued since most of the above procedures were not suitable for the reduction of other heterocycles, including isoquinolines. Zhou and co-workers invented a new catalytic system suitable for the hydrogenation of quinolines and isoquinolines based on the activation of these substrates by

Scheme 187. Chloroformate Activated Hydrogenation of Quinolines and Isoquinolines Developed by Zhou



chloroformates.<sup>583</sup> It was found that  $[\text{Ir}(\text{COD})\text{Cl}]_2$ , in the presence of equimolar amounts of chloroformates,  $\text{Li}_2\text{CO}_3$ , and the (*S*)-Segphos ligand **564**, reduced quinolines and isoquinolines to the corresponding tetrahydroquinolines and dihydroisoquinolines, respectively, in high yields and enantioselectivities (Scheme 187). The substituent on the nitrogen atom was effectively removed by the  $\text{Pd}/\text{C}/\text{H}_2$  system without affecting the enantioselectivity. This chloroformate-activated procedure was then applied to the synthesis of the tetrahydroquinoline natural products cuspareine **3b**, angustureine **4a** and also the tetrahydroisoquinoline natural product carnegine **572**. Zhou also published a general account, summarizing his results, dealing with the asymmetric hydrogenation of heteroaromatic compounds.<sup>584</sup> It is relevant to mention here that the enantioselective addition of alkyl and aryllithium reagents to quinolines in the presence of methylchloroformate and bisoxazoline ligands afforded the corresponding 2-substituted 1,2-dihydroquinolines in good yields and moderate enantioselectivities, and these materials were subsequently hydrogenated to the 1,2,3,4-tetrahydroquinoline derivatives using a  $\text{Pd}/\text{C}$  catalyst.<sup>585</sup>

Chan and co-workers also reported a diphosphinite H8-BINAPO ligand derived from H8-BINOL, combined with iridium, for the asymmetric hydrogenation of quinolines that gave 1,2,3,4-tetrahydroquinolines with up to 97% enantioselectivity.<sup>586</sup> In this case, (*S*)-H8-BINAPO **573a** and (*R*)-BINAPO **573b** were tested as ligands, with the former being found to furnish higher enantioselectivity (Figure 22). The screening experiments showed that the best source for iridium was  $[\text{Ir}(\text{COD})\text{Cl}]_2$  and that iodine was the best additive. These conclusions were similar to the ones previously reported using Zhou's methodology.

The Chan group also developed an air-stable, reusable iridium-dipyridylphosphine ligand (P-Phos, **574**) catalyst,<sup>587,588</sup> which

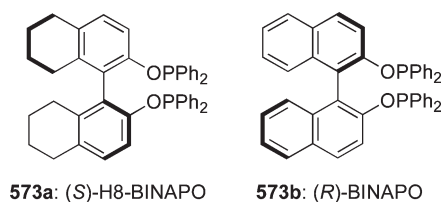
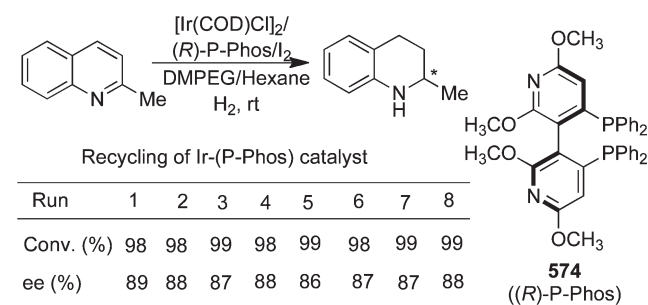
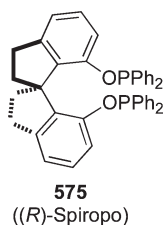


Figure 22. Structures of diphosphinite ligands.

Scheme 188. Asymmetric Hydrogenation of 2-Methylquinoline in the Presence of Ir-Dipyridylphosphine Catalyst 574

Table 4. Hydrogenation of 2-Methylquinoline in the Presence of 575- $[\text{Ir}(\text{COD})\text{Cl}]_2$  catalyst

solvent	S/C ratio	conversion (%)	ee (%)
THF	100	100	92
toluene	100	100	89
Et <sub>2</sub> O	100	100	91
CH <sub>2</sub> Cl <sub>2</sub>	100	72	71
MeOH	100	10	16
THF	500	100	92
THF	1000	100	92
THF	2000	100	92
THF	5000	91	92

can be immobilized in polyethylene glycol dimethyl ether (DMPEG). The resulting species was identified as an eco-friendly, relatively low-cost liquid polymer for the asymmetric hydrogenation of quinolines.<sup>589</sup> Hydrogenation of 2-methylquinoline in the presence of this catalyst was excellent in terms of conversion (up to 99%) and enantioselectivity (up to 92%) and the products were easily isolated from the reaction mixture by simple hexane extraction and the catalyst was reused several times without any loss in yield and enantioselectivity (Scheme 188). The authors then studied the role of a few more chiral ligands for the hydrogenation of quinolines in a DMPEG/hexane biphasic system. The role of ionic liquids as

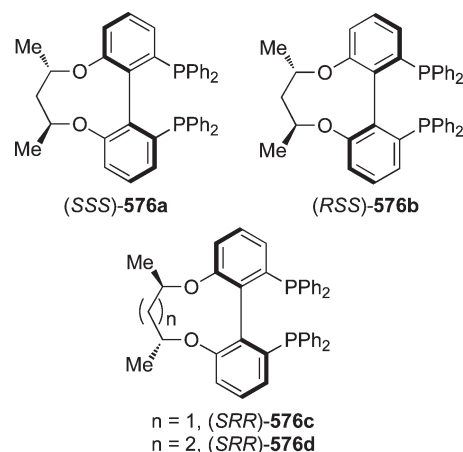


Figure 23. Structures of the chiral-bridged atropisomeric diphosphine ligands 576.

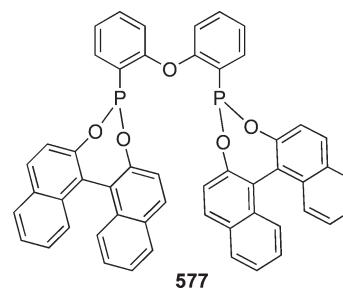


Figure 24. BINOL-derived diphosphonite ligand 577 reported by Reetz and Li.

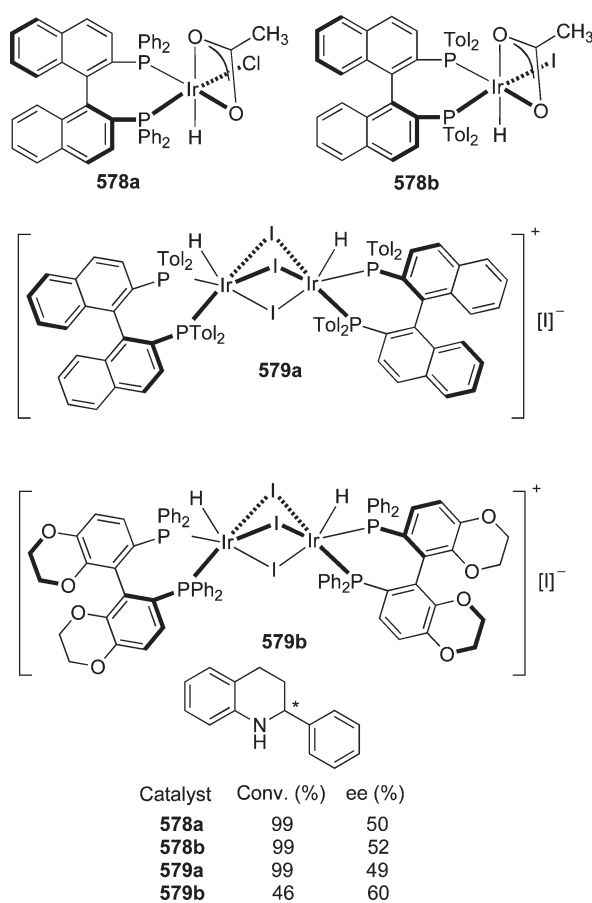
solvents and the possibility of recycling the catalyst were also studied.<sup>590</sup>

A catalytic system based on  $[\text{Ir}(\text{COD})\text{Cl}]_2$  and a phosphinite ligand derived from (*R*)-1,1'-spirobiindane-7,7'-diol (Spiro, 575) was developed for the hydrogenation of quinolines, which afforded excellent catalytic activity, with substrate/catalyst (S/C) ratio up to 5000, and normally good enantioselectivity (Table 4).<sup>591</sup> THF was identified as the best solvent for the hydrogenation of 2-methylquinoline, and the reaction allowed complete conversion with 92% ee in a S/C ratio of 2000. The increase of the S/C ratio to 5000 maintained the ee, although the conversion went down to 91% under similar conditions. A number of substituted quinolines were successfully hydrogenated with higher enantioselectivities using the lowest catalyst load. The less polar DMPEG–hexane solvent system was also found to be a good substitute for THF.

The same group further synthesized a set of chiral-bridged atropisomeric diphosphine ligands 576 through selective Ullmann coupling and ring-closure reactions and tested their role in the iridium-catalyzed asymmetric hydrogenation of quinolines (Figure 23).<sup>592</sup> Quinolines, 2-methylquinoxalines, and 2,3,3-trimethylindolenine were successfully hydrogenated by combining the synthesized ligands with an iridium complex and an additive in toluene, with good enantioselectivities.

The search for new ligands for the asymmetric hydrogenation of quinolines still continued, and Reetz and Li reported a BINOL-derived diphosphonite ligand 577 for this purpose (Figure 24). The ligand 577 allowed the enantioselective synthesis of a set of 1,2,3,4-tetrahydroquinoline derivatives in the





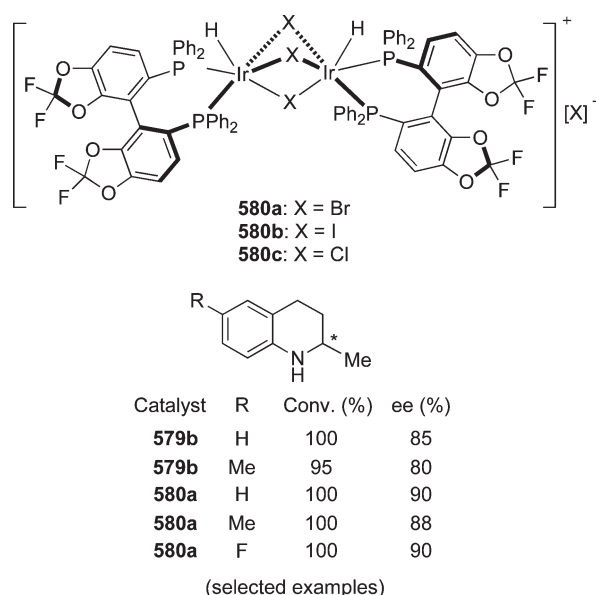
**Figure 25.** Mono- and dinuclear iridium(III) complexes developed by Genet and Mashima.

presence of 0.5 mol % of Ir catalyst in excellent yields and enantioselectivity.<sup>593</sup>

A group of mononuclear halide-carboxylate iridium(III) complexes and cationic triply halogen-bridged dinuclear iridium(III) complexes of BINAP, *p*-TolBINAP, and SynPhos (**578** and **579**) were synthesized by a novel one-pot protocol and their application for the asymmetric hydrogenation of 2-phenylquinoline was demonstrated (Figure 25). The catalysts showed excellent reactivity and a moderate enantioselectivity. The catalytic activity of the cationic iodo-dinuclear BINAP complex was higher than that of the corresponding chloro and bromo complexes.<sup>594</sup>

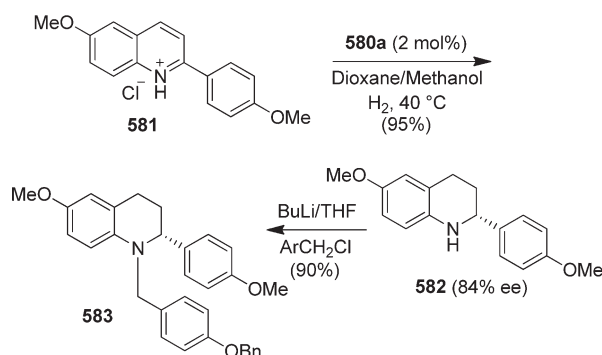
A year later the same group extended their study to synthesize a DifluorPhos-iridium catalyst **580a**–**c** and compared the catalytic activity of the previously obtained **579b** and **580a** for the hydrogenation of 2-substituted quinolines (Figure 26). Both types of catalysts allowed the hydrogenation of 2-methylquinolines with high enantioselectivities (ee up to 92%).<sup>595</sup>

Most of the previously discussed methodologies are excellent, in general, for the asymmetric hydrogenation of quinolines to 1,2,3,4-tetrahydroquinolines. Nonetheless, many of them failed to give high enantioselectivities for 2-aryl quinolines. Mashima and co-workers employed the iridium catalyst **580a** and **580c**, shown in Figure 26, for the hydrogenation of hydrogen halide salts of 2-aryl-substituted quinolines. Interestingly, these quinoline salts furnished almost quantitative conversions and excellent enantioselectivities (ee up to 95%) with 30 bar hydrogen pressure in a 1,4-dioxane/methanol solvent system (Scheme 189). This



**Figure 26.** DifluorPhos-iridium catalysts for the asymmetric hydrogenation of quinolines.

### Scheme 189. Asymmetric Hydrogenation of Quinoline Hydrochloride **581**



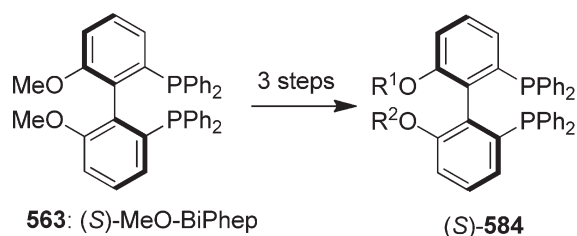
compound was subsequently applied to the enantioselective synthesis of selective estrogen receptor modulators.<sup>596</sup> The hydrogenation of 2-(4-methoxyphenyl)-7-methoxyquinoline hydrochloride **581** using catalyst **580a** afforded the 1,2,3,4-tetrahydroquinoline derivative **582** in 95% yield and 84% ee, which was then N-alkylated by BuLi and 1-(benzyloxy)-4-(chloromethyl)benzene. The N-alkyl derivative **583** was finally converted into the biologically active compound by employing the methodology<sup>102</sup> previously reported by Wallace.

Zhou and Wank reported the synthesis of seventeen tunable axial chiral bisphosphine ligands (**584**) starting from (*S*)-MeO-Biphenyl **563** and their application to the iridium-catalyzed hydrogenation of quinolines. All the ligands assayed gave enantiomeric excess around 90%, and the MeO-PEG-(1600) supported ligand **584k** was subsequently used to hydrogenate a set of substituted quinolines. The catalyst was recovered and reused up to five cycles with the same yield and only slight loss in selectivity (Scheme 190).<sup>597</sup>

The chiral diamine-based catalysts are more air-stable and easily available compared to the chiral phosphorus ligand-containing catalysts, which are rapidly and irreversibly oxidized by



**Scheme 190.** Synthesis of Tunable Axial Chiral Bisphosphine Ligands (584) Reported by Zhou and Wank

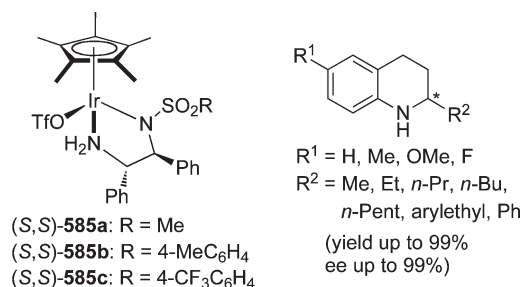


- 584a:**  $R^1 = n\text{-C}_{16}\text{H}_{33}$ ,  $R^2 = n\text{-C}_{16}\text{H}_{33}$   
**584b:**  $R^1 = n\text{-C}_6\text{H}_{13}$ ,  $R^2 = n\text{-C}_{16}\text{H}_{33}$   
**584c:**  $R^1 = n\text{-C}_{16}\text{H}_{33}$ ,  $R^2 = \text{Bn}$   
**584d:**  $R^1 = n\text{-C}_6\text{H}_{13}$ ,  $R^2 = \text{Bn}$   
**584e:**  $R^1 = n\text{-C}_4\text{H}_9$ ,  $R^2 = \text{Bn}$   
**584f:**  $R^1 = \text{Me}$ ,  $R^2 = \text{MeO-PEG-(1600)}$   
**584g:**  $R^1 = \text{Et}$ ,  $R^2 = \text{MeO-PEG-(1600)}$   
**584h:**  $R^1 = n\text{-C}_4\text{H}_9$ ,  $R^2 = \text{MeO-PEG-(1600)}$   
**584i:**  $R^1 = n\text{-C}_6\text{H}_{13}$ ,  $R^2 = \text{MeO-PEG-(1600)}$   
**584j:**  $R^1 = n\text{-C}_8\text{H}_{17}$ ,  $R^2 = \text{MeO-PEG-(1600)}$   
**584k:**  $R^1 = n\text{-C}_{12}\text{H}_{25}$ ,  $R^2 = \text{MeO-PEG-(1600)}$   
**584l:**  $R^1 = n\text{-C}_{16}\text{H}_{33}$ ,  $R^2 = \text{MeO-PEG-(1600)}$   
**584m:**  $R^1 = \text{Bn}$ ,  $R^2 = \text{MeO-PEG-(1600)}$   
**584n:**  $R^1 = \text{CH}_2=\text{CH-CH}_2$ ,  $R^2 = \text{MeO-PEG-(1600)}$   
**584o:**  $R^1 = \text{MeO-PEG-(1600)}$ ,  $R^2 = \text{MeO-PEG-(1600)}$   
**584p:**  $R^1 = n\text{-C}_{12}\text{H}_{25}$ ,  $R^2 = \text{MeO-PEG-(1100)}$   
**584q:**  $R^1 = n\text{-C}_{12}\text{H}_{25}$ ,  $R^2 = \text{MeO-PEG-(5000)}$

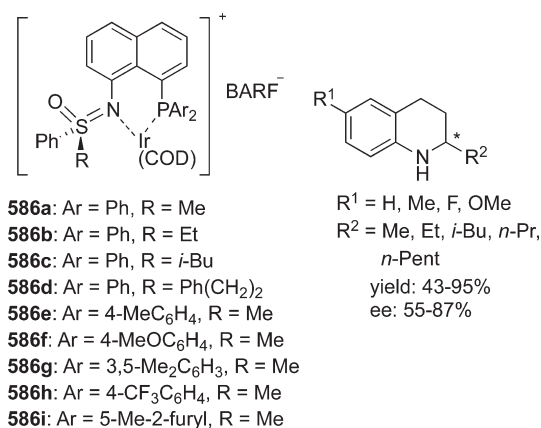
oxygen.<sup>598</sup> Consequently, asymmetric hydrogenations catalyzed by such catalysts need extremely oxygen-free conditions as evidenced by the previously mentioned reports. A highly air-stable, phosphine-free iridium catalyst  $\text{Cp}^*\text{Ir}(\text{OTf})(\text{CF}_3\text{TsDPEN})$  **585** was recently developed by Fan group for the asymmetric hydrogenation of quinolines ( $\text{CF}_3\text{TsDPEN} = N\text{-(}p\text{-trifluoromethylbenzenesulfonyl)-1,2-diphenylethylenediamine}$ ).<sup>599,600</sup> The catalyst **585c** was extremely reactive and selective, and afforded up to 99% ee in a substrate/catalyst ratio as high as 1000 with 10 mol % of  $\text{CF}_3\text{COOH}$  as additive. The catalyst gave a similar enantioselectivity even in an undegassed solvent and in the presence of air. Protic solvents such as methanol, ethanol and 2-propanol were found to be the best for conversion and enantioselectivities in contrast to the aprotic solvents  $\text{CH}_2\text{Cl}_2$ , toluene and THF (Figure 27).

Lu and Bolm developed a novel sulfoximine based naphthalene-bridged  $P,N$ -type ligands and their iridium complexes **586** for the asymmetric hydrogenation of quinolines (Figure 28).<sup>601</sup> These ligands were as good as the previously reported chiral ligands and furnished excellent yields and enantioselectivities. Increasing steric bulkiness on the alkyl substituents of the sulfoximido moiety decreased the selectivity.

The first homogeneous, oxidant-free catalytic system, derived from  $\text{Cp}^*\text{Ir}$  complexes, for the reversible dehydrogenation–hydrogenation reactions of 1,2,3,4-tetrahydroquinoline–quinoline system was recently reported.<sup>602</sup> The authors developed a set of  $\text{Cp}^*\text{Ir}$  catalysts **587** containing 2-pyridonate units as functional ligands, which effectively dehydrogenated the 1,2,3,4-tetrahydroquinolines in the presence of 5 mol % of the catalyst in  $p$ -xylene under

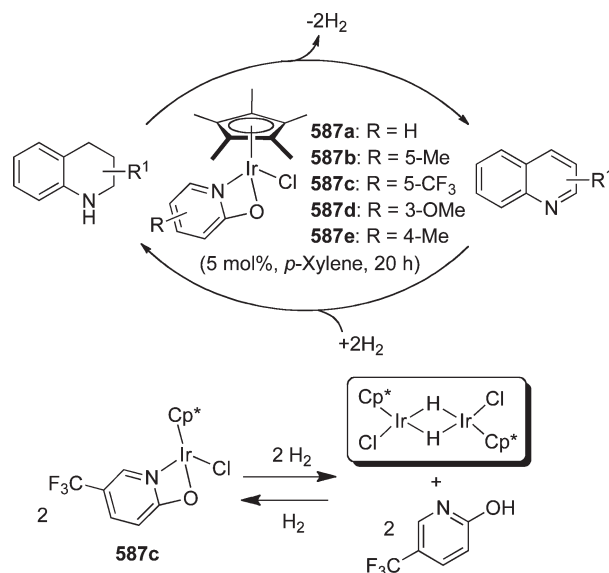


**Figure 27.** Phosphine-free iridium catalysts **585** developed for the asymmetric hydrogenation of quinolines by Fan.

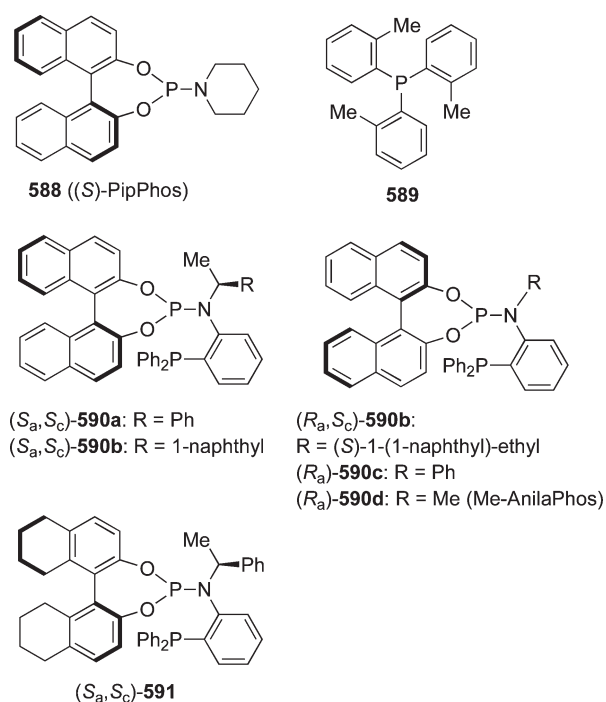


**Figure 28.** Lu and Bolm's sulfoximine based naphthalene-bridged  $P,N$ -type ligands used for the asymmetric hydrogenation of quinolines.

**Scheme 191.** Reversible Dehydrogenation–Hydrogenation Reactions of 1,2,3,4-Tetrahydroquinoline–Quinoline System Catalyzed by  $\text{Cp}^*\text{Ir}$  Complexes



reflux conditions (Scheme 191). The evolution of hydrogen in the dehydrogenation of 1,2,3,4-tetrahydroquinoline reaction was confirmed by connecting the reaction flask to another one containing 1-decene as a hydrogenation substrate in the presence of a rhodium



**Figure 29.** Phosphoramidite and phosphine-phosphoramidite ligands involved in the asymmetric hydrogenation of quinolines.

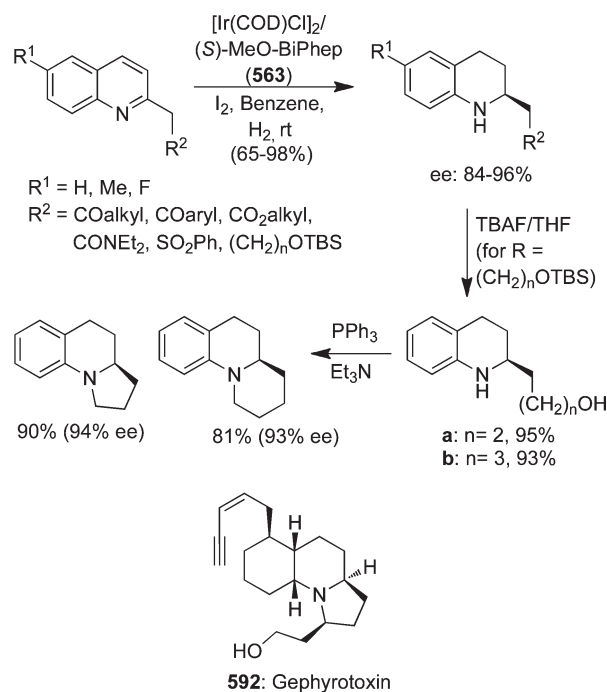
catalyst. After completion of the dehydrogenation of tetrahydroquinoline, 94% of decane was observed in the second reaction flask, which confirmed that hydrogen gas was formed in the dehydrogenation reaction. The catalysts also efficiently catalyzed the hydrogenation of quinolines to 1,2,3,4-tetrahydroquinolines in the presence of hydrogen and the reactive species for both the hydrogenation and dehydrogenation processes were identified on the basis of experimental evidence (Scheme 191).

The next improvements in this field included the use of monodentate BINOL-derived phosphoramidites<sup>603</sup> and phosphine-phosphoramidite ligands<sup>604</sup> for the asymmetric hydrogenation of quinolines. The iridium complex of the phosphoramidite ligand (*S*)-PipPhos, **588** in the presence of 10 mol % of piperidine hydrochloride and tri-*O*-tolylphosphine, **589** in toluene or dichloromethane hydrogenated quinolines in excellent yields and enantioselectivities. The phosphine-phosphoramidite ligands **590** and **591** also showed excellent reactivity in the enantioselective hydrogenation of 2-substituted quinolines (Figure 29).

As evidenced by the previous discussion, almost all of the reported methodologies, except Xu's procedure,<sup>568</sup> described the hydrogenation of simple 2-methylquinoline and 2,6-disubstituted quinoline derivatives. 2,3-Disubstituted quinolines and 2-functionalized quinolines are interesting substrates since the products are synthetic intermediates for many biologically active alkaloids. For this reason, Zhou and co-workers studied the hydrogenation of 2-benzyl and other 2-functionalized quinolines using iridium catalyst in the presence of (*S*)-MeO-BiPhep ligand **563**.<sup>605</sup> The system tolerated ketone, ester, amide, benzenesulfonyl, and TBS protected hydroxy groups. The application of this protocol was demonstrated by the synthesis of model compounds for a formal synthesis of the alkaloid gephyrotoxin **592**<sup>606</sup> in high yield and selectivity (Scheme 192).

A mechanism for the iridium-catalyzed asymmetric hydrogenation was proposed on the basis of experimental evidence. The role

**Scheme 192.** Asymmetric Hydrogenation of 2-Functionalized Quinolines

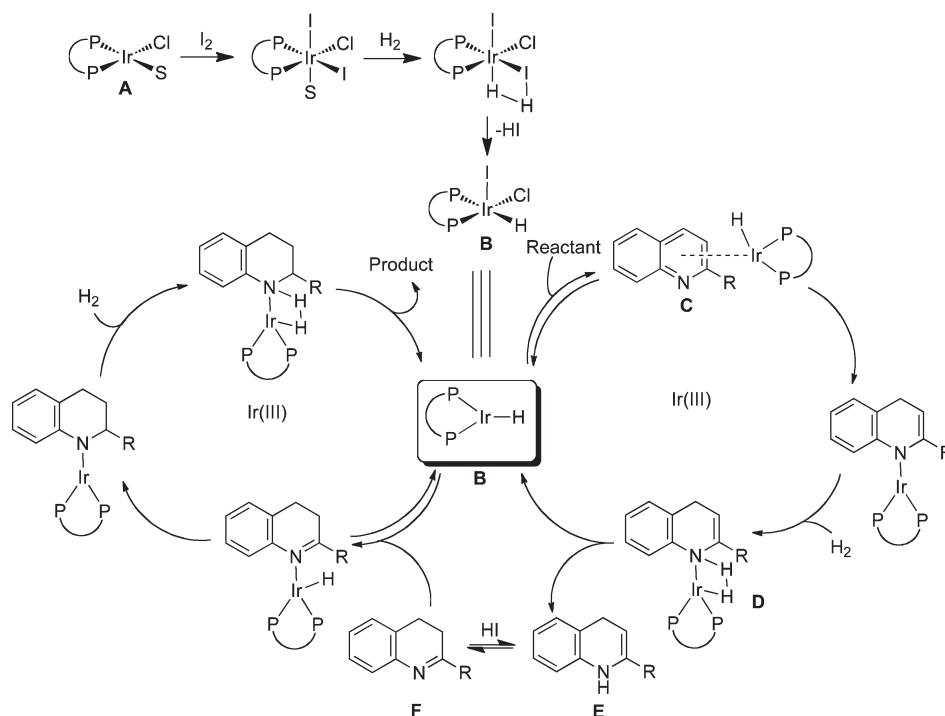


of iodine is important as an additive in most of the procedures reported so far. The complex obtained by the reaction between 2-methylquinoline and iodine did not undergo hydrogenation in the presence of iridium catalysts, thus ruling out the possibility of substrate activation by iodine. On the other hand, a catalytic mixture containing both chloride and iodide anions, obtained by the reaction between  $[\text{Ir}(\text{COD})\text{Cl}]_2/(\text{S})\text{-SegPhos} **564** and iodine in  $\text{CH}_2\text{Cl}_2$  after 12 h gave the hydrogenated product in excellent yield with 93% ee, which confirmed that iodine activates the catalyst. Additional experiments proved the mode of hydrogenation process, that is, the first step is the 1,4-hydrogenation followed by isomerization and 1,2-addition. The proposed mechanism is given in Scheme 193, which includes the initial oxidative addition of iodine to the iridium(I) complex **A** to generate the iridium(III) species and subsequent heterolytic cleavage of  $\text{H}_2$  to create the  $\text{Ir(III)-H}$  species **B**. The quinoline substrate then coordinates with **B**, followed by 1,4-hydride transfer to give intermediate **D**, which affords enamine **E** after heterolytic cleavage of hydrogen. Intermediate **E** then undergoes isomerization to imine **F**, catalyzed by the generated Brønsted acid  $\text{HI}$ , which coordinates again with the catalyst and reacts with another molecule of hydrogen to furnish the 1,2,3,4-tetrahydroquinoline final product, thus completing the catalytic cycle (Scheme 193). The kinetics and mechanism of the metal catalyzed hydrogenation of quinolines was also discussed in a recent article.<sup>607</sup>$

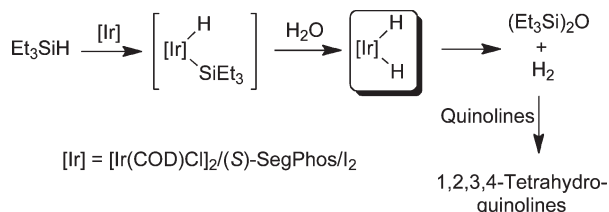
The latest developments in this area include the use of ligands containing bulky substituents on the coordinating phosphorus atom to avoid the formation of inactive dimers and trimers through hydride-bridged bonds in the presence of hydrogen.<sup>608</sup> Introduction of bulky *t*-butyl groups in the 3- and 5-positions of the phenyl rings attached to the phosphorus atom of **561**, **563**, and **564** (Figures 20 and 21) improved the catalytic efficiency of the system with a substrate/catalyst ratio up to 5000.

Another advance in the asymmetric hydrogenation of quinolines is the use of water/silane as the hydrogen source.<sup>609</sup> The

Scheme 193. Mechanistic Proposal for the Ir-Catalyzed Asymmetric Hydrogenation of Quinolines Reported by Zhou and Li



Scheme 194. Asymmetric Hydrogenation of Quinolines Involving Water/Silane as the Hydrogen Source



reaction between triethylsilane and water in the presence of iridium complexes generates hydrogen gas which was used for the asymmetric hydrogenation of quinolines with good enantioselectivity (Scheme 194).

**9.3.3. Asymmetric Hydrogenation of Quinolines Catalyzed by Ruthenium and Rhodium.** Although iridium is the most widely used metal for the asymmetric hydrogenation of quinolines to generate enantiopure 1,2,3,4-tetrahydroquinolines, other transition metals such as ruthenium and rhodium were also used as catalysts in the presence of suitable chiral ligands. A recyclable phosphine-free chiral cationic ruthenium catalyst Ru/Ts-dpen **593** (Ts-dpen = *N*-(*p*-toluenesulfonyl)-1,2-diphenylethylenediamine) in an ionic liquid was found to be excellent for the asymmetric hydrogenation of quinolines, which allowed almost quantitative conversions and enantioselectivities up to 99%.<sup>610</sup> The catalysts were highly stable in ionic liquids, maintained the same activity even after exposure to air for 30 days, and they could be recovered and reused at least six times without any loss in yield and selectivity. A year later the same group achieved the same reaction under solvent-free conditions in high yields and enantioselectivities.<sup>611</sup>

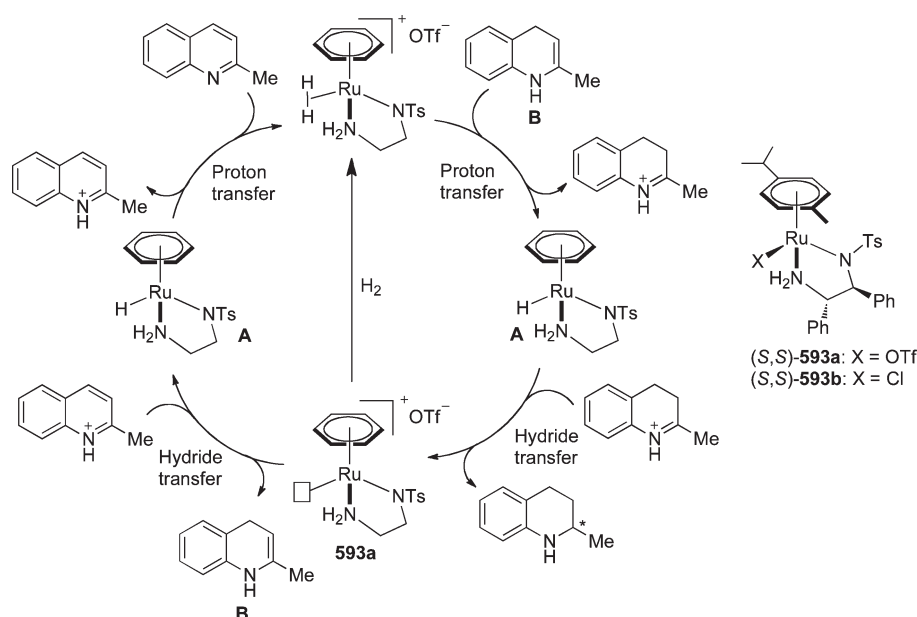
A mechanism was also proposed based on the observations that (i) 2-methylquinoline did not react with the hydride complex **A**, while the protonated 2-methylquinoline gave the hydrogenated product in moderate yields with high enantioselectivity; (ii) in the presence of a tetrahydroquinoline salt as a proton source, the protonated 2-methylquinoline reacted with **A** to give the hydrogenated product in 95% yield and 99% *ee*. On the basis of these studies the authors proposed that the first step of the mechanism could be the coordination of hydrogen to catalyst **593a**, which is subsequently deprotonated by the substrate to afford the hydride complex **A**.<sup>612</sup> A 1,4-hydride transfer regenerates the catalyst and the enamine **B**, which could be activated by protonation, and a 1,2-hydride transfer gives the hydrogenated product and the regenerated catalyst (Scheme 195).

The rhodium-catalyzed asymmetric transfer hydrogenation (ATP) of quinolines in water was the first economical and environmentally benign procedure developed in this area of asymmetric hydrogenation.<sup>613</sup> The reaction was performed in the presence of Rh-Ts-dpen, similar to **593**, and 10 equiv of sodium formate at pH 5. A broad range of substrates, including some that were problematic for other catalytic systems, were effectively hydrogenated with excellent enantioselectivities and yields. The ruthenium and rhodium-catalyzed asymmetric transfer hydrogenation of quinolines to afford enantiopure 1,2,3,4-tetrahydroquinoline derivatives in the presence of formic acid/triethylamine was also reported recently.<sup>614</sup>

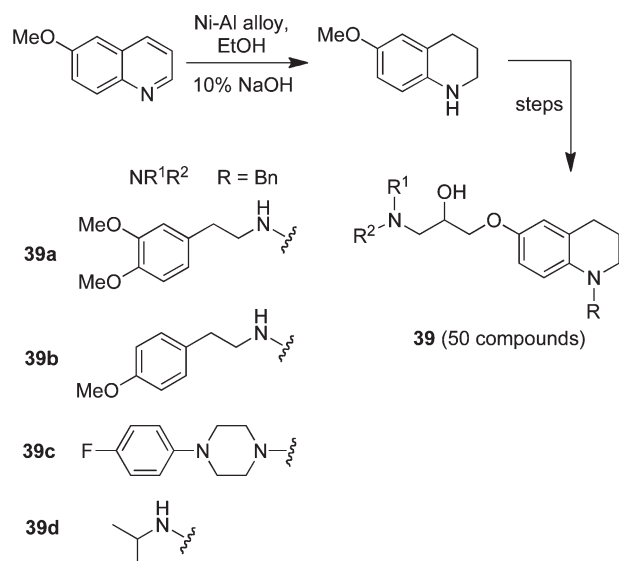
#### 9.4. Synthesis of Biologically Relevant 1,2,3,4-Tetrahydroquinolines via Hydrogenation of Quinolines

As demonstrated in the introduction part, suitably functionalized tetrahydroquinolines possess a number of interesting biological activities. In this section the synthesis of such bioactive tetrahydroquinoline derivatives, where the hydrogenation of quinoline moiety is the key step, will be discussed.

**Scheme 195.** Proposed Mechanism for the Ru/Ts-dpen (593)-Catalyzed Asymmetric Hydrogenation of Quinolines Reported by Fan and Chan

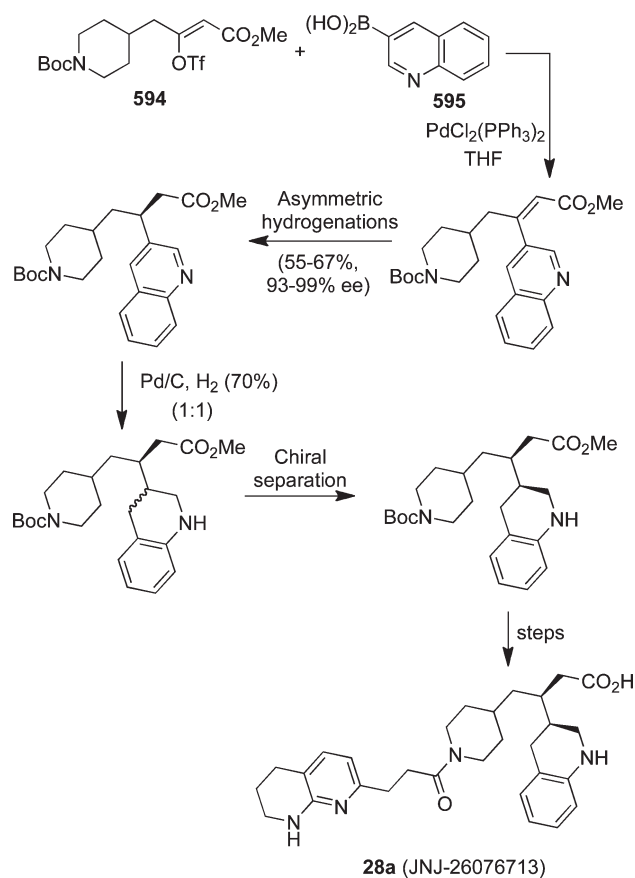


**Scheme 196.** Synthesis of  $\beta_3$ -Adrenergic Receptor Agonists **39** via Hydrogenation of 6-Methoxyquinoline

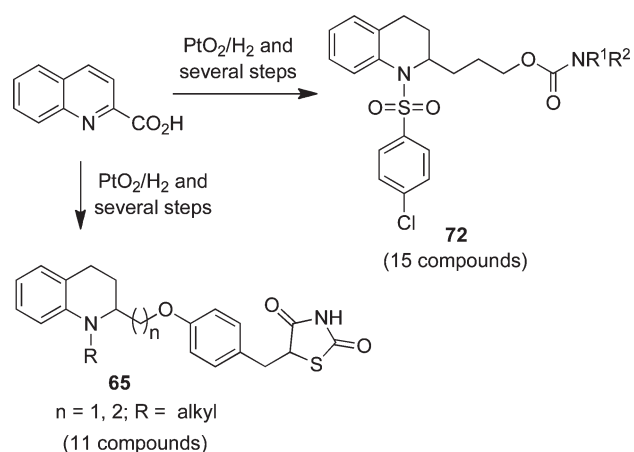
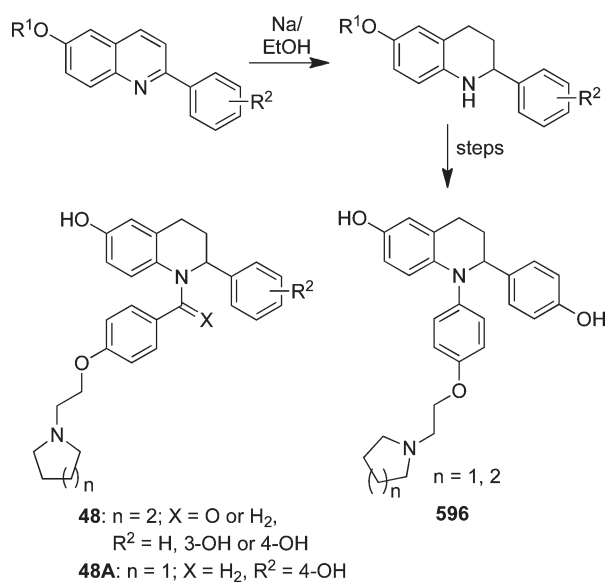


The synthesis and antiparasitic activity of a new class of 1-benzenesulfonyl-2-methyl-1,2,3,4-tetrahydroquinolines **24** were reported recently, wherein the 2-methyl-1,2,3,4-tetrahydroquinoline was obtained by the reduction of 2-methylquinoline by  $NaBH_4/NiCl_2 \cdot 6H_2O$  in methanol.<sup>60</sup> The compounds thus synthesized demonstrated interesting activity against *Trypanosoma cruzi* with low cytotoxicity and also against *Plasmodium falciparum*. A library of 1,2,3,4-tetrahydroquinolin-6-yloxypropanes active as  $\beta_3$ -adrenergic receptor agonists were synthesized via a Raney nickel reduction of quinolines.<sup>83</sup> Among the synthesized compounds the *N*-benzyl derivatives were found to be superior to the *N*-arylsulfonyl analogues. Compounds **39a–d**

**Scheme 197.** Enantioselective Scaled-up Synthesis of JNJ-26076713 (**28a**)



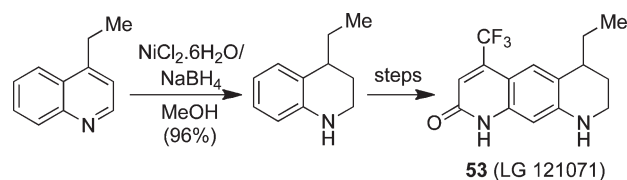
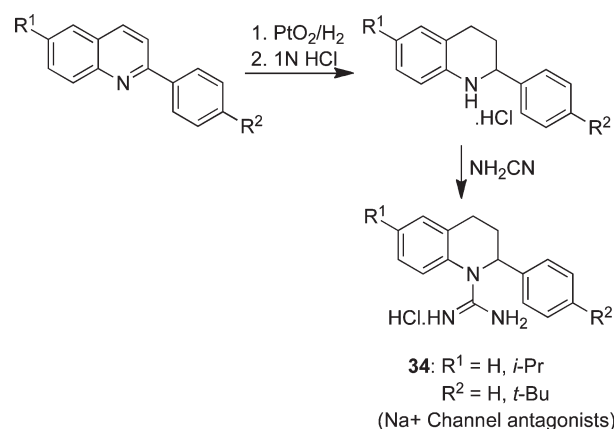
showed very good  $\beta_3$ -adrenergic receptor agonistic  $IC_{50}$  values, which are the possible leads for further development of

**Scheme 198.** Synthesis of Biologically Relevant Tetrahydroquinolines **65** and **72****Scheme 199.** Wallace's Synthesis of Selective Estrogen Receptor Modulators (SERMs) **48** and **596**

$\beta_3$ -adrenergic receptor agonists for the treatment of obesity and Type-II diabetes (Scheme 196).

The enantioselective scaled-up synthesis of JNJ-26076713, **28a**, an orally active 1,2,3,4-tetrahydroquinoline acting as a  $\alpha_v\beta_3/\alpha_v\beta_5$  integrin antagonist, was achieved starting from compounds **594** and **595**, using a sequence comprising a Suzuki–Miyaura coupling, asymmetric reduction of the double bond and hydrogenation of the quinoline ring by Pd/C/H<sub>2</sub> as the key steps (Scheme 197).<sup>615,65,66</sup>

A group of tetrahydroquinoline sulfonamides **72**, which inhibits  $\gamma$ -secretase, a key enzyme involved in the production of  $\beta$ -amyloid peptides which are important in the onset and progression of Alzheimer's disease (AD), were synthesized from quinoline-2-carboxylic acid.<sup>139,140</sup> Likewise, tetrahydroquinoline-linked thiazolidinediones **65** containing peroxisome proliferator activated receptor- $\gamma$  (PPAR $\gamma$ ) agonistic activity were synthesized starting from quinoline-2-carboxylic acid (Scheme 198).<sup>131</sup> The

**Scheme 200.** Synthesis of Human Androgen Receptor (hAR) Agonist **53** (LG 121071) via NiCl<sub>2</sub>·6H<sub>2</sub>O/NaBH<sub>4</sub> Reduction of 4-Ethylquinoline**Scheme 201.** Maillard's Synthesis of Neuronal Na<sup>+</sup> Channel Antagonists **34**

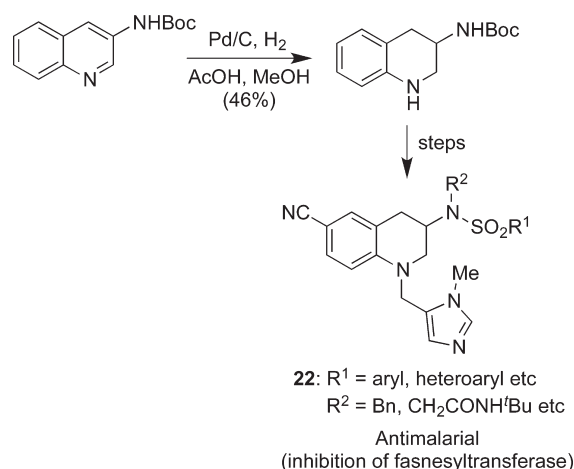
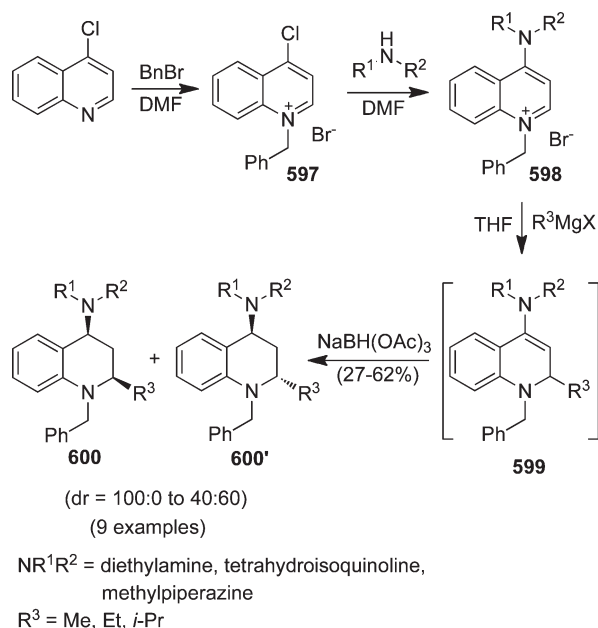
partial reduction of some substituted quinolines by PtO<sub>2</sub>/H<sub>2</sub> allowed the corresponding 1,2,3,4-tetrahydroquinoline derivatives which were subsequently used as precursors for the synthesis of a library of compounds acting as antagonists of the human and rat H<sub>3</sub> receptors.<sup>88</sup>

Wallace and co-workers demonstrated the synthesis of tetrahydroquinoline-based selective estrogen receptor modulators (SERMs) **48** and **596** starting from 2-arylquinolines.<sup>102</sup> The binding affinity and functional activity of the synthesized tetrahydroquinolines in MCF-7 cells were tested. Compounds containing an amide linker between the core and basic side chain showed weaker binding and functional activities and compound **48A** was the most potent inhibitor of MCF-7 proliferation of the synthesized series (Scheme 199).

An orally active nonsteroidal human androgen receptor (hAR) agonist **53** (LG 121071) was synthesized from 4-ethylquinoline via a NiCl<sub>2</sub>/NaBH<sub>4</sub> reduction and a subsequent nitration-reduction-cyclization sequence (Scheme 200).<sup>111</sup> Similarly, a set of nonsteroidal human progesterone receptor (hPR) antagonists was synthesized from 1,2-dihydroquinolineboronic acid through a palladium-catalyzed Suzuki reaction, followed by Pd/H<sub>2</sub> reduction.<sup>109</sup> In an article related to the synthesis of tetrahydroquinoline derivatives **69**, inhibitors of renin, the quinoline moiety was reduced by NiCl<sub>2</sub>/NaBH<sub>4</sub> reduction system.<sup>135</sup>

Maillard and co-workers reported the synthesis of a series of N-substituted 2-aryl-1,2,3,4-tetrahydroquinolines **34**, which were identified as potent inhibitors of neuronal Na<sup>+</sup> channels, based on the hydrogenation of 2-arylquinolines in the presence of PtO<sub>2</sub>. The suitably substituted 2-arylquinolines were synthesized from the corresponding quinolines through arylation using aryllithium reagents. The PtO<sub>2</sub>-catalyzed hydrogenation,

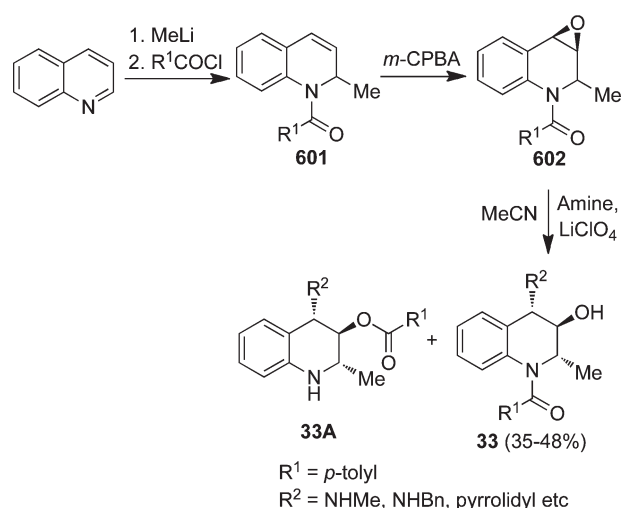


**Scheme 202.** Synthesis of Farnesyltransferase Inhibitors **22** via Hydrogenation of 3-Aminoquinoline**Scheme 203.** Synthesis of 4-Amino-2-alkyl-1,2,3,4-tetrahydroquinolines Starting from 4-Chloroquinoline

followed by the treatment with cyanamide, afforded the bioactive guanidines **34** (Scheme 201).<sup>77</sup> Similarly tetrahydroquinoline-based farnesyltransferase inhibitors **22**, were synthesized from 3-aminoquinoline, where the quinoline ring was partially hydrogenated in the presence of Pd/C to allow the corresponding tetrahydroquinoline derivative (Scheme 202).<sup>52</sup> Leeper and co-workers reported the synthesis of 6-methoxy-1-methyl-1,2,3,4-tetrahydroquinoline-3-methanol, a precursor for the synthesis of biologically relevant hapten, starting from 6-methoxyquinoline where the key step was a partial hydrogenation.<sup>616</sup>

### 9.5. Quinoline Reduction Involving the Addition of Nucleophiles

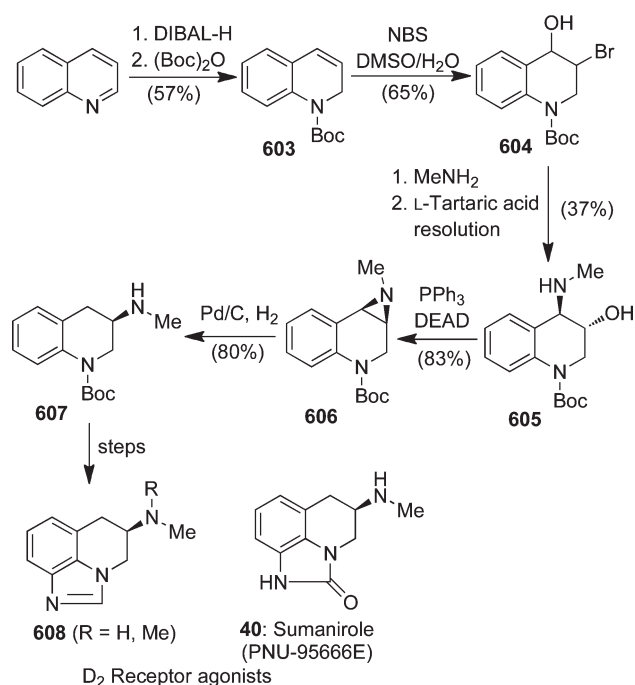
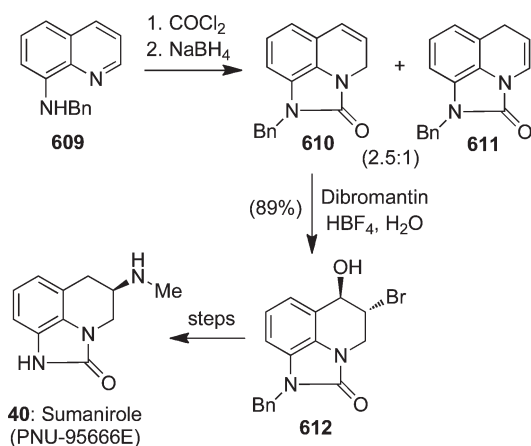
4-Amino-1,2,3,4-tetrahydroquinolines are important molecules because of their use in medicinal chemistry, but their

**Scheme 204.** Synthesis of Trisubstituted Tetrahydroquinolines

preparation is rather difficult. Bazin and Kuhn described an interesting procedure for the preparation of 4-amino-2-alkyl-1,2,3,4-tetrahydroquinolines starting from 4-chloroquinoline through *N*-arylation and Grignard addition reactions.<sup>617</sup> Treatment of 4-chloroquinolinium salt **597** with a number of secondary amines afforded intermediate **598**, which subsequently reacted with Grignard reagents to give dihydroquinoline derivatives **599** that were then reduced in situ with sodium triacetoxyborohydride to furnish the corresponding tetrahydroquinolines **600** as a mixture of diastereomers (Scheme 203). A solid-phase protocol was also developed for the same synthesis using the quinolinium salt derived from 4-chloroquinoline and bromo-Wang resin.<sup>618</sup>

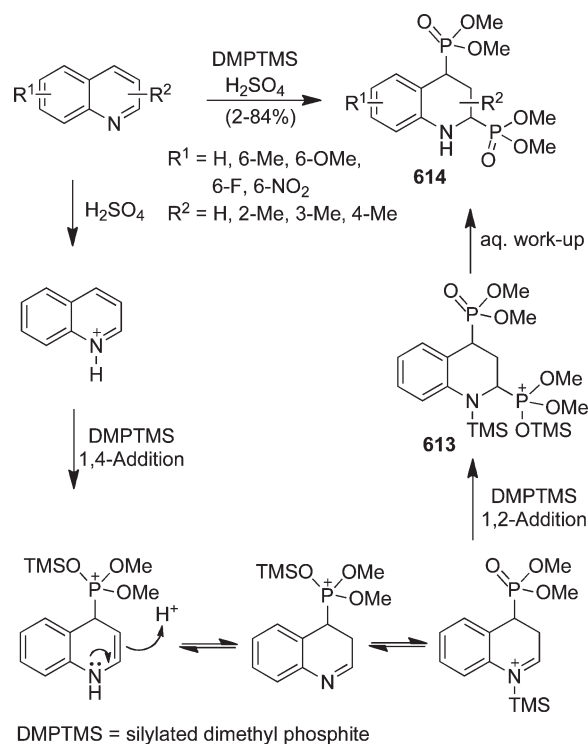
The reductive 2-alkylation of quinoline with organolithium reagents, followed by *N*-acylation allowed the synthesis of 2-alkyl-1,2-dihydroquinolines **601**, which were then transformed into tetrahydroquinoline derivatives having modulating activity in multidrug resistance (MDR). Thus, epoxide **602**, obtained by oxidation of the C<sub>3</sub>–C<sub>4</sub> double bond of compound **601** with *m*-CPBA, was opened with a number of amine nucleophiles in the presence of LiClO<sub>4</sub> to afford the corresponding tetrahydroquinolines **33** (Scheme 204).<sup>74</sup> Migration of the acyl group from nitrogen to the hydroxy group was also observed, depending on the basicity of the amine used, to give compounds **33A**. In another report, the same group demonstrated ring-opening of epoxides **602** with a number of nucleophiles including H<sub>2</sub>O, MeOH, and AcOH to furnish tetrahydroquinolines **33** bearing different substituents at C-4.<sup>619</sup>

The partial reduction of quinoline with DIBAL-H gave 1,2-dihydroquinoline, and subsequent structural manipulation at the C<sub>3</sub>–C<sub>4</sub> double bond allowed the synthesis of a number of biologically relevant 3-amino-1,2,3,4-tetrahydroquinoline derivatives.<sup>84</sup> Treatment of *N*-Boc-1,2-dihydroquinoline **603** with NBS and water furnished the corresponding bromohydrin **604**, which was then transformed into amino alcohol **605** through epoxide formation followed by ring-opening with methylamine and resolution with tartaric acid. The formation of aziridine **606**, followed by its reductive ring-opening furnished the 3-amino derivative **607**, as shown in Scheme 205. Compound **607** was used as a precursor for the synthesis of some D<sub>2</sub> receptor agonists **608** and sumanirole (PNU-95666E, **40**).

Scheme 205. Synthesis of D<sub>2</sub> Receptor Agonists **608** and Sumanirole (PNU-95666E, **40**)Scheme 206. Wuts's Synthesis for Sumanirole **40**

Wuts and co-workers developed another practical synthesis for sumanirole **40**, where the key step was the reaction between 8-N-benzylaminoquinoline **609** and phosgene, followed by a subsequent sodium borohydride reduction to afford a mixture of isomeric dihydroquinoline derivatives **610** and **611**. Treatment of compound **610** with dibromantin and water in the presence of tetrafluoroboric acid afforded the 3-bromo-4-hydroxytetrahydroquinoline derivative **612**, which was then transformed into the desired sumanirole **40** in several steps (Scheme 206).<sup>620</sup> It is also relevant to mention here that alcohols were added successfully to the C<sub>3</sub>–C<sub>4</sub> double of 1,2-dihydroquinoline derivatives under photochemical conditions to give the corresponding 4-alkoxy-1,2,3,4-tetrahydroquinolines.<sup>621</sup>

Another interesting synthesis of tetrahydroquinoline derivatives starting from quinolines involves the consecutive addition

Scheme 207. Synthesis of 2,4-Diphosphono-1,2,3,4-tetrahydroquinolines **614**

of two molecules of a phosphorus nucleophile to quinolines. Trialkyl and silylated dialkyl phosphites were found to be good nucleophiles to achieve a domino 1,4- and 1,2- addition to quinolines to afford the corresponding 2,4-diphosphono-1,2,3,4-tetrahydroquinolines **614** in good yields under acidic conditions, through intermediate **613** (Scheme 207).<sup>622</sup>

Partially oxidized derivatives of the natural products angustureine **4a**, galipinine **3a**, and cuspareine **3b** were effectively hydrogenated to the corresponding natural products in the presence of Pd/C.<sup>623</sup> The key reaction of this protocol consisted of a novel sequential domino reaction between organolithium reagents, quinoline, and electrophiles involving the addition of a variety of organolithium reagents to quinoline, followed by the addition of suitable electrophiles to afford the dihydroquinoline precursors of the natural products, which were subsequently hydrogenated. For instance, treatment of quinoline with *n*-pentyllithium and methyl iodide followed by hydrogenation of the C<sub>3</sub>–C<sub>4</sub> double bond furnished the natural product angustureine **4a** (Scheme 208).

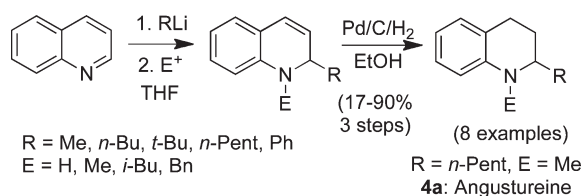
The synthesis of two other natural products, namely galipinine **3a** and cuspareine **3b**, started from vinyl bromides **615**, which were transformed into the corresponding lithium species by halogen–lithium exchange upon treatment with *t*-butyllithium. These lithiated species were then treated with quinoline and methyl iodide to afford the natural products in good yields after hydrogenation of the two double bonds (Scheme 209).

## 10. SYNTHESIS OF TETRAHYDROQUINOLINES WITH OTHER HYDROGENATION PATTERNS

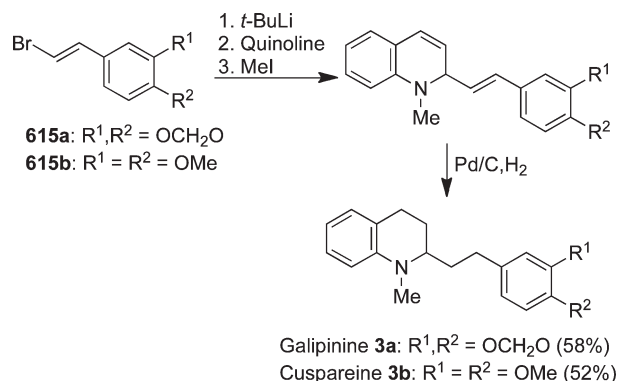
### 10.1. Introduction

Although 1,2,3,4-tetrahydroquinolines are the most common tetrahydroquinoline system, a considerable number of reports

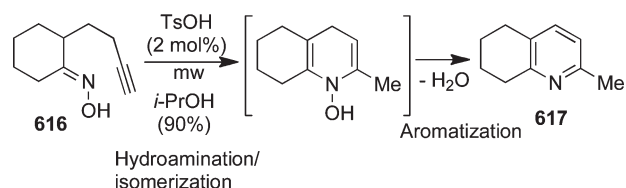
Scheme 208. Synthesis of Angustureine 4a Starting from Quinoline



Scheme 209. Synthesis of Galipinine 3a and Cuspareine 3b



Scheme 210. Microwave-Assisted Synthesis of 2-Methyl-5,6,7,8-tetrahydroquinoline 617

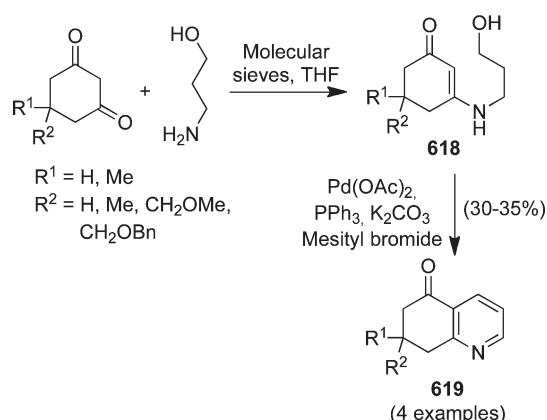


are available for the synthesis of 5,6,7,8-tetrahydroquinoline derivatives, which will be treated in this Section. We will also discuss the synthesis of tetrahydroquinolines with other hydrogenation patterns.

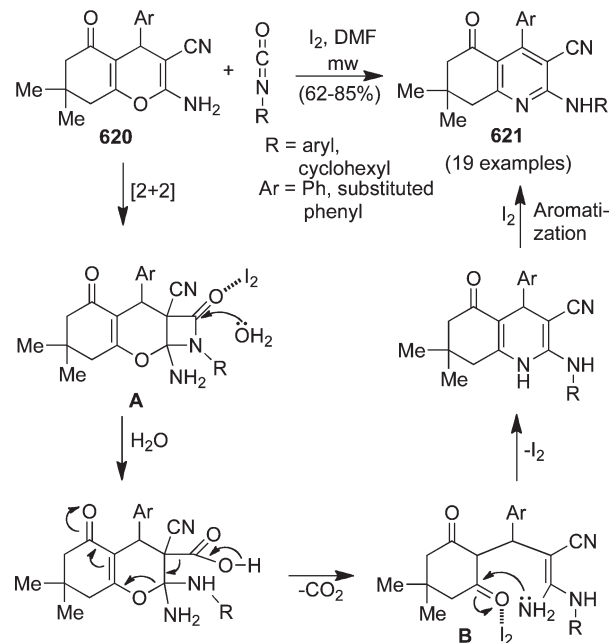
## 10.2. Synthesis of 5,6,7,8-Tetrahydroquinolines by Construction of the Pyridine Ring

**10.2.1. Formation of One Bond.** Beauchemin and co-workers established a novel synthesis of pyridines starting from acyclic alkynyl oximes under microwave irradiation in the presence of 2 mol % of TsOH. The reaction proceeded through an initial acid-catalyzed intramolecular hydroamination reaction followed by a tandem isomerization-dehydrative aromatization sequence. The application of this procedure was extended to the synthesis of 2-methyl-5,6,7,8-tetrahydroquinoline **617** from the corresponding cyclohexanone oxime **616** in 90% yield (Scheme 210).<sup>624</sup>

The palladium-catalyzed oxidation of  $\gamma$ -hydroxy-enaminones **618** allowed the synthesis of 5,6,7,8-tetrahydroquinolin-5-ones **619** in moderate yields.<sup>625</sup> The starting  $\gamma$ -hydroxy-enaminones **618** were prepared from cyclic 1,3-dicarbonyl compounds and  $\gamma$ -amino alcohols under mild conditions in the presence of molecular sieves. The best conditions for the Pd-catalyzed

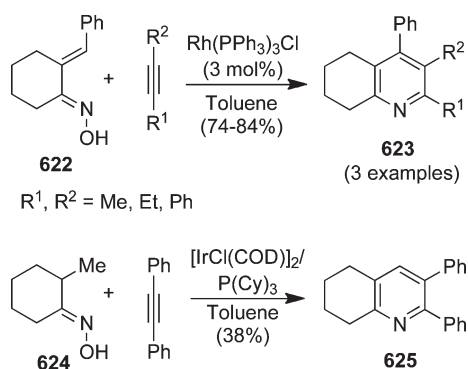
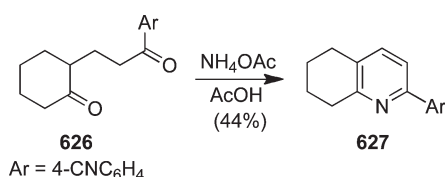
Scheme 211. Pd-Catalyzed Oxidation of Cyclic  $\gamma$ -Hydroxy-enaminones

Scheme 212. Iodine-Promoted Domino Ring-Opening/Recyclization Reaction of 2-Aminochromene-3-carbonitrile 620



reaction consisted of the use of a catalytic amount of Pd(OAc)<sub>2</sub>, mesityl bromide as oxidant and triphenylphosphine as cocatalyst. The role of K<sub>2</sub>CO<sub>3</sub> was also found to be essential for the reaction to proceed effectively (Scheme 211).

Tu and co-workers recently demonstrated the synthesis of N-substituted 2-aminochromene-3-carbonitriles **621** in high yields through an interesting iodine-promoted ring-opening/recyclization domino reaction of 2-aminochromene-3-carbonitrile **620** with isocyanates under microwave heating.<sup>626</sup> The reaction was proposed to proceed through a [2 + 2] cycloaddition between the starting material **620** and the isocyanide to generate the  $\beta$ -lactam intermediate **A**, which would subsequently undergo ring-opening followed by elimination of a molecule of CO<sub>2</sub> to give intermediate **B**. The intramolecular cyclization/aromatization of **B** would finally afford the tetrahydroquinoline derivatives **621** (Scheme 212). Similarly, the synthesis of

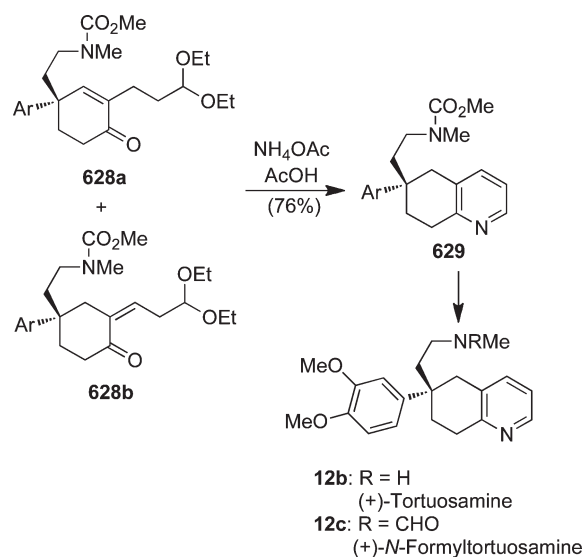
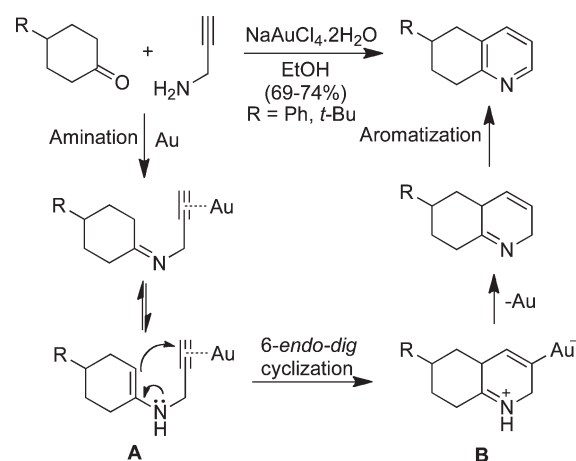
**Scheme 213.** Parthasarathy and Cheng's Synthesis of 5,6,7,8-Tetrahydroquinolines**Scheme 214.** Synthesis of 2-(4-Cyanophenyl)-5,6,7,8-tetrahydroquinoline **627**

5,6,7,8-tetrahydroquinoline salts was recently achieved by a reaction involving a diethylamine-mediated intramolecular cyclization of tetracyanoethylene-cyclohexanone adducts.<sup>627</sup>

**10.2.2. Formation of Two Bonds.** Parthasarathy and Cheng reported a novel rhodium-catalyzed reaction between ketoximes possessing an exocyclic double bond and alkynes for the synthesis of 5,6,7,8-tetrahydroquinoline derivatives.<sup>628</sup> For instance, 2-benzylidene-1-cyclohexanone oxime **622** reacted with a variety of alkynes in the presence of 3 mol % of  $\text{Rh(PPh}_3)_3\text{Cl}$  in toluene and afforded the corresponding tetrahydroquinolines **623** in high yields, with unsymmetrical alkynes furnishing an equimolar amount of the two regioisomers (Scheme 213). Interestingly, a catalytic amount of the iridium complex,  $[\text{IrCl(COD)}]_2$ , together with  $\text{P(Cy)}_3$ , was effective to activate the  $\text{sp}^3\text{C-H}$  bond of 2-methylcyclohexanone oxime **624** to afford the 4-unsubstituted tetrahydroquinoline derivative **625**.

It is also interesting to note a report by Pfaltz and co-workers describing the synthesis of chiral 8-hydroxy-2-phenyl-5,6,7,8-tetrahydroquinoline, a potential ligand for the iridium-catalyzed asymmetric hydrogenation of olefins and furan derivatives. Its preparation involved the reaction between 2-(3-oxo-3-phenylpropyl)cyclohexanone and hydroxylamine hydrochloride.<sup>152</sup> A rather similar approach was previously demonstrated for the synthesis of 2-(4-cyanophenyl)-5,6,7,8-tetrahydroquinoline **627** starting from the corresponding 1,5-diketone **626** using ammonium acetate as the nitrogen source (Scheme 214).<sup>507</sup>

Yamada and Ogasawara reported the asymmetric synthesis of sceletium alkaloids including (+)-tortuosamine **12b** and (+)-*N*-formyltortuosamine **12c**, where the intermediate **629** was synthesized from the  $\delta$ -ketoacetal **628**.<sup>29</sup> In the multistep total synthesis, the key reaction was the construction of the pyridine ring from a mixture of the isomeric cyclohexenone derivatives **628** and ammonium acetate in acetic acid at high temperature. The deprotection of the acetal moiety followed by cyclization of

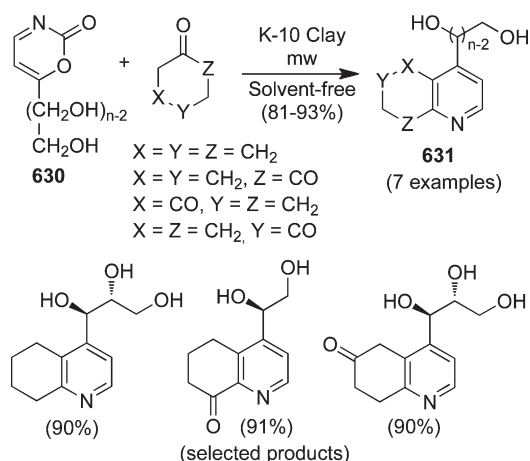
**Scheme 215.** Yamada and Ogasawara's Synthesis of (+)-Tortuosamine **12b** and (+)-*N*-Formyltortuosamine **12c****Scheme 216.** Gold-Catalyzed Domino Amination–Cyclization–Aromatization Sequence

the 1,5-dicarbonyl compound with ammonia gave a good yield of tetrahydroquinoline **629**, which was then transformed into the natural products (Scheme 215).

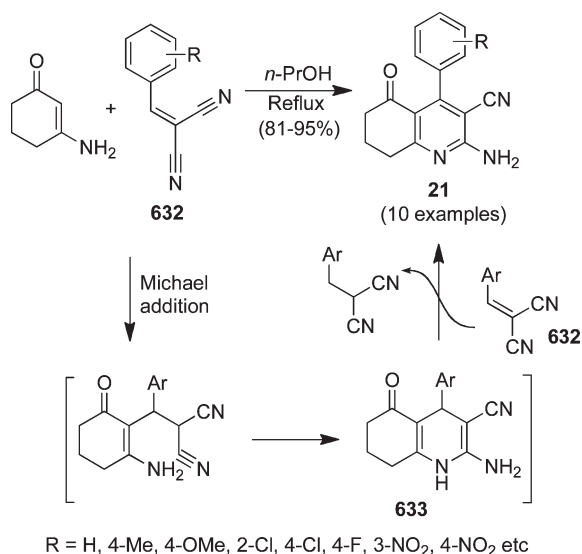
The  $\text{NaAuCl}_4 \cdot 2\text{H}_2\text{O}$ -catalyzed reaction between cyclohexanone derivatives and propargylamine afforded 5,6,7,8-tetrahydroquinolines in high yields through a domino amination–cyclization–aromatization reaction sequence.<sup>629,630</sup> The reaction may be initiated by the metal salt-catalyzed reaction between cyclohexanones and propargylamine to give enamines **A** via the corresponding imines, which subsequently underwent regioselective 6-endo-dig nucleophilic intramolecular cyclization to afford the organometallic intermediate **B**. The final protonolysis of the C–M bond of intermediate **B**, followed by aromatization of the hexahydroquinoline derivative would furnish the tetrahydroquinolines (Scheme 216). This procedure was then employed successfully to the reaction between propargylamine and a wide variety of carbonyl compounds including aldehydes, simple and polycyclic ketones bearing an active methylene group for the synthesis of



**Scheme 217. Microwave-Assisted, Solvent-Free Synthesis of 4-Polyhydroxyalkyltetrahydroquinolines**



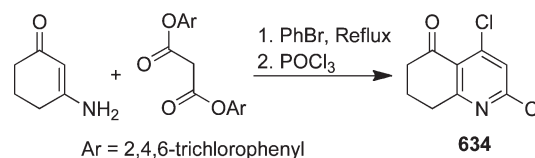
**Scheme 218. Synthesis of Antifungal Tetrahydroquinolines 21 via Michael Addition—Cyclization—Aromatization Sequence**



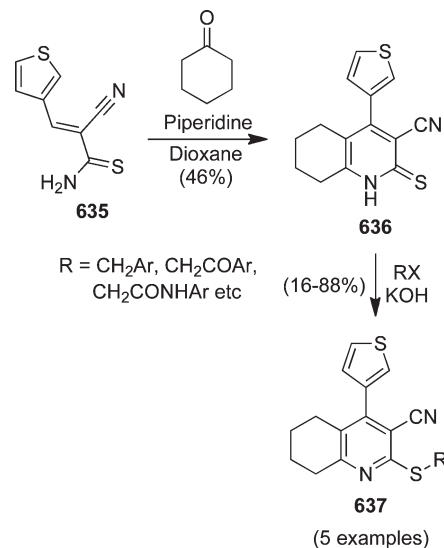
pyridine or fused pyridine derivatives. This methodology was recently used for the synthesis of 5,6,7,8-tetrahydroquinolin-8-one, an intermediate for the synthesis of tetrahydroquinoline CXCR4 antagonists, starting from cyclohexa-1,2-dione.<sup>36</sup> Fukumoto and co-workers also reported the synthesis of 4-methyl-7-aryl-5,6,7,8-tetrahydroquinolin-5-one, precursors for the tetrahydroquinoline-based Na<sup>+</sup>/H<sup>+</sup> exchanger inhibitors, based on the cyclization of the enamines derived from cyclohexa-1,3-diones and but-2-yn-1-amine under thermal conditions.<sup>78</sup>

K-10 clay was found to be an excellent catalyst for the synthesis of 4-polyhydroxyalkylquinolines from 1,3-oxazin-2-ones and cyclic ketones under solvent-free microwave irradiation conditions.<sup>631</sup> The starting materials, 1,3-oxazin-2-ones **630**, were synthesized from D-glucose or D-xylose and semicarbazide through a microwave-assisted, acid-catalyzed, domino cycloisomerization—dehydration—dehydration sequence. Microwave irradiation of compound **630** and cyclohexanone or

**Scheme 219. Synthesis of 2,4-Dichloro-5,6,7,8-tetrahydroquinolin-5-one 634 (Intermediate for the C5a Receptor Antagonists)**



**Scheme 220. Synthesis of Tetrahydroquinolines 637**



cyclohexadiones afforded the corresponding tetrahydroquinoline derivatives **631** in the presence of K-10 clay in excellent yields. The decarboxylative ring transformation reaction that leads to the observed products could be initiated by a Michael-type nucleophilic attack of the enol form of the cyclic ketone to the C-6 electrophilic center of the oxazine ring (Scheme 217).

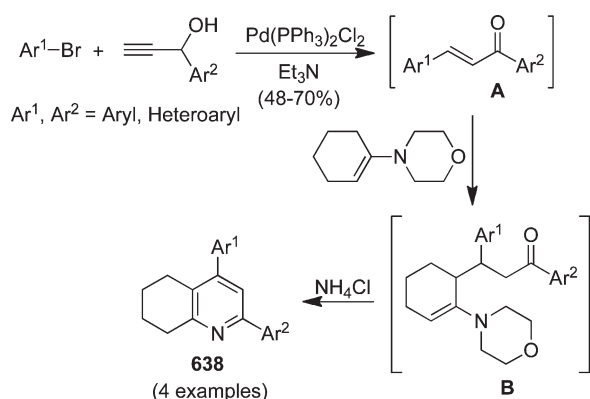
A set of antifungal 2-amino-3-cyano-4-aryl-5,6,7,8-tetrahydroquinolin-5-one derivatives **21** was synthesized in excellent yields by the reaction between 3-amino-2-cyclohexen-1-one and an excess of arylidenemalononitriles **632** through a Michael addition—cyclization—aromatization sequence.<sup>50</sup> This novel protocol gave hexahydroquinoline intermediates **633**, which subsequently underwent aromatization by transferring hydrogen to the arylidenemalononitriles **632** under the same experimental conditions without the need for any catalyst (Scheme 218). A rather similar procedure was also developed for the synthesis of 2,3,4-unsubstituted 5,6,7,8-tetrahydroquinoline derivatives based on the reaction between an enaminone derived from a substituted cyclohexa-1,3-dione and acrolein<sup>632</sup> or propionaldehyde.<sup>67</sup>

2,4-Dichloro-5,6,7,8-tetrahydroquinolin-5-one **634**, an intermediate for the synthesis of tetrahydroquinoline-derived C5a receptor antagonists, was prepared by cyclocondensation of 3-amino-2-cyclohexen-1-one and malonic acid bis(2,4,6-trichlorophenyl) ester, followed by chlorination with POCl<sub>3</sub> (Scheme 219).<sup>98</sup> This intermediate was subsequently transformed into the bioactive compounds using a Suzuki coupling and further functional group modifications.

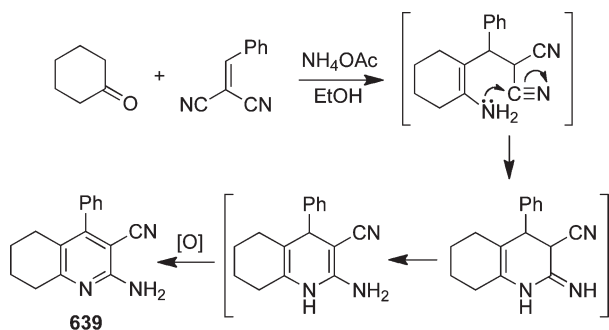
The piperidine-promoted reaction between cyclohexanone and compound **635**, obtained through a Knoevenagel reaction,



Scheme 221. Müller's Pd-Catalyzed Sequential Four-Component Synthesis of Tetrahydroquinolines



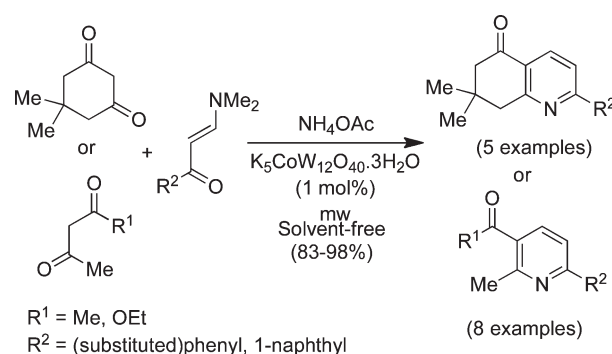
Scheme 222. Tetrahydroquinoline Synthesis via Enamine Formation—Michael Addition—Cyclization—Oxidation Sequence



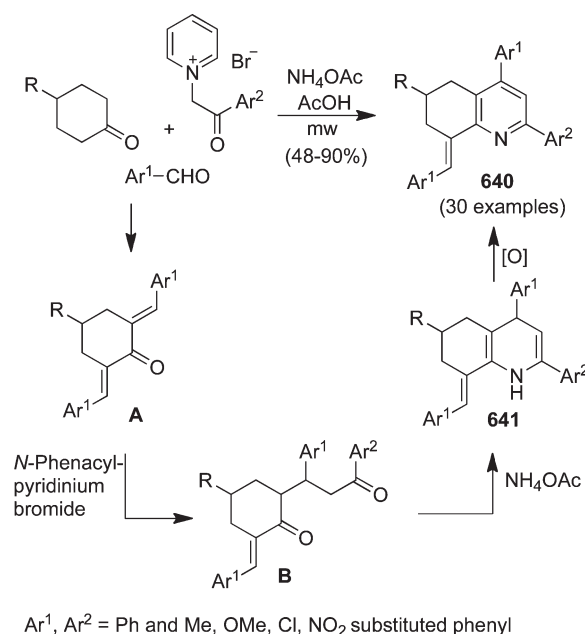
gave thiolactams **636**, probably through a Michael-initiated mechanism. This compound was then *S*-alkylated to afford tetrahydroquinolines **637** (Scheme 220).<sup>633</sup>

**10.2.3. Multicomponent Reactions and Reactions Involving the Formation of Three or More Bonds.** Müller and co-workers reported an interesting one-pot, three-step, four-component sequential reaction between aryl halides, propargyl alcohols, cyclic *N*-morpholino alkenes and ammonium chloride in the presence of a palladium catalyst for the synthesis of pyridines and tetrahydroquinolines.<sup>634</sup> This reaction involves an initial Pd-catalyzed Sonogashira coupling between aryl halides and propargyl alcohols, followed by isomerization to give the chalcone intermediate **A**, which affords the Michael adduct **B** upon reaction with *N*-morpholino alkenes. The intermediate **B** then reacts with ammonium chloride to furnish the final tetrahydroquinolines **638** through a cyclocondensation reaction (Scheme 221). Subsequently, the same authors elaborated their studies to include a number of additional substrates and published the details of their coupling—*isomerization*—*enamine addition*—*cyclocondensation* reaction strategy as a full paper.<sup>635</sup> It is relevant to add here that Dyachenko and Chernega reported the synthesis of 2-thio-substituted tetrahydroquinolines starting from cyclohexanone enamine and the product of the Knoevenagel reaction between isovaleraldehyde and cyanothioacetamide, involving an intermediate of type **A**.<sup>636</sup> Dyachenko also reported the synthesis of some fused tetrahydroquinoline derivatives through cross-recyclization of 2,6-diamino-4*H*-thiopyran-3,5-dicarbonitriles with enamines.<sup>637</sup>

Scheme 223. Microwave-Assisted, Three-Component, Solvent-Free Synthesis of Tetrahydroquinolines and Pyridines



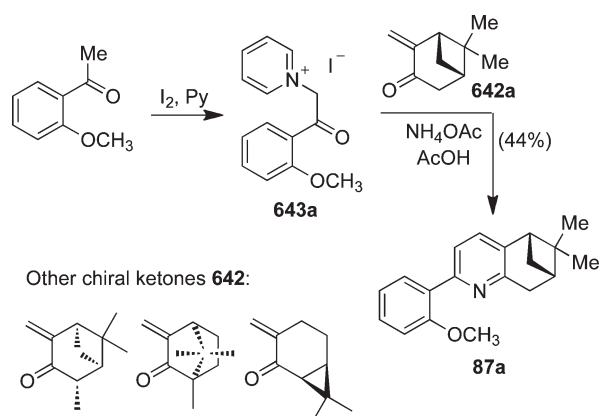
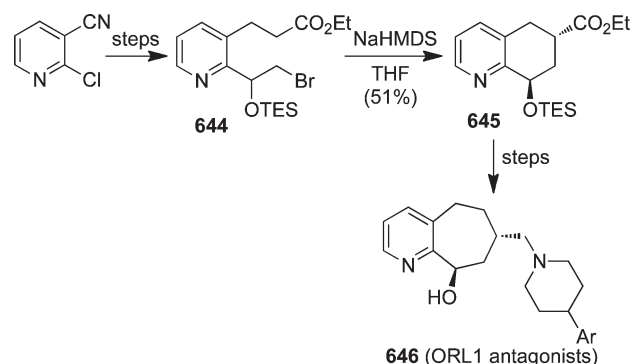
Scheme 224. Yan's Four-Component Tetrahydroquinoline Synthesis



The synthesis of 2-amino-4-phenyl-5,6,7,8-tetrahydroquinoline-3-carbonitrile **639** was achieved by the reaction between cyclohexanone, 2-benzylidenemalononitrile and ammonium acetate. A mechanism was proposed for this reaction that involved the initial formation of an enamine, followed by a Michael addition—cyclization—oxidation sequence (Scheme 222).<sup>638</sup> The compound thus synthesized was used for the preparation of a variety of heterocycles including pyrimidines, thiourea derivatives and pyrimidoquinolines. A similar strategy was recently employed for the synthesis of precursors for anticancer tetrahydroquinoline derivatives.<sup>70</sup>

A number of pyridine and tetrahydroquinoline derivatives were synthesized based on the microwave-assisted, three-component reaction between cyclic and acyclic 1,3-dicarbonyl compounds, ammonium acetate and enaminoketones in the presence of the unusual catalyst K<sub>5</sub>CoW<sub>12</sub>O<sub>40</sub>·3H<sub>2</sub>O. The mechanism of the reaction was similar to the previous one, involving enamine formation, Michael addition and cyclization steps (Scheme 223).<sup>639</sup> Similar products were accessible through a related protocol using α,β-unsaturated ketones instead of enaminoketones, although in

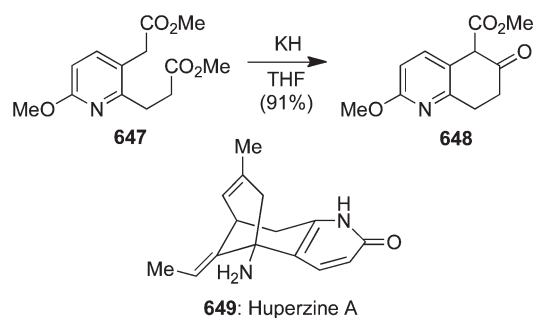
Scheme 225. Synthesis of Tetrahydroquinoline-Based Chiral Ligands

Scheme 226. Synthesis of Intermediate (**645**) of the ORL1 Antagonists **646**

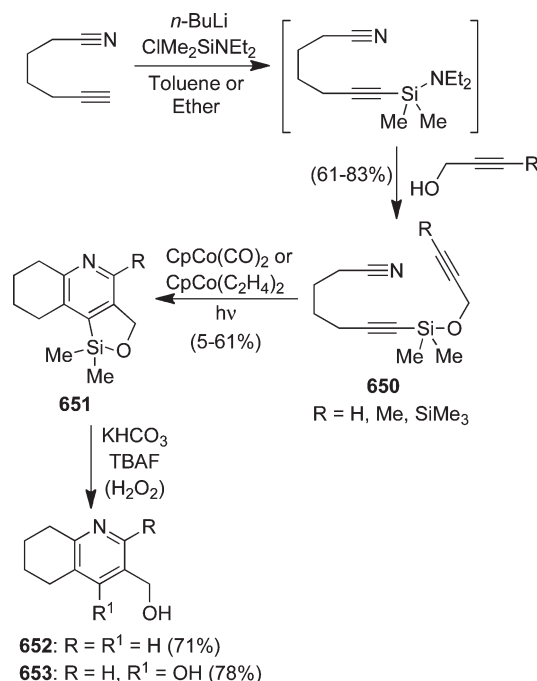
this case a final dehydrogenation step was needed.<sup>640</sup> Similarly, the enamines generated in situ from dimedone and ammonium acetate reacted with 3-substituted ( $\text{CF}_3\text{CO}$ ,  $\text{CHO}$ , and  $\text{CN}$ ) chromones to give the corresponding 5,6,7,8-tetrahydroquinolines in moderate yields.<sup>641</sup>

Yan and co-workers discovered a four-component synthesis of tetrahydroquinolines starting from cyclohexanones, arylaldehydes, *N*-phenacylpyridinium bromide, and ammonium acetate under microwave irradiation in good yields.<sup>642</sup> The reaction was found to be general and tolerated a number of electron-rich and electron-deficient substituents on both aryl rings. A reaction mechanism was proposed based on the initial formation of 2,6-bis-(arylidene)cyclohexanone **A** from the ammonia-catalyzed reaction between cyclohexanones and arylaldehydes. The subsequent Michael addition of the pyridinium salt to intermediate **A** would then afford the 1,5-dicarbonyl derivative **B**, which would then react with ammonium acetate to afford the final tetrahydroquinolines **640** via the hexahydroquinoline intermediate **641** (Scheme 224). The authors then extended their procedure to the synthesis of tetrahydroquinolin-2-ones starting from cyclohexanone, arylaldehydes, *N*-ethoxycarbonylmethylpyridinium chloride, and ammonium acetate.<sup>643</sup> Zhou and co-workers also reported a four-component synthesis of tetrahydroquinolines involving a modified Hantzsch reaction followed by dehydrogenation.<sup>644</sup>

Some tetrahydroquinoline-related chiral ligands useful in asymmetric synthesis were prepared from chiral ketones **642**,

Scheme 227. Tetrahydroquinoline Synthesis via Dieckmann Condensation of **647**

Scheme 228. Cobalt-Catalyzed Synthesis of 5,6,7,8-Tetrahydroquinolines Starting from Acyclic Precursors

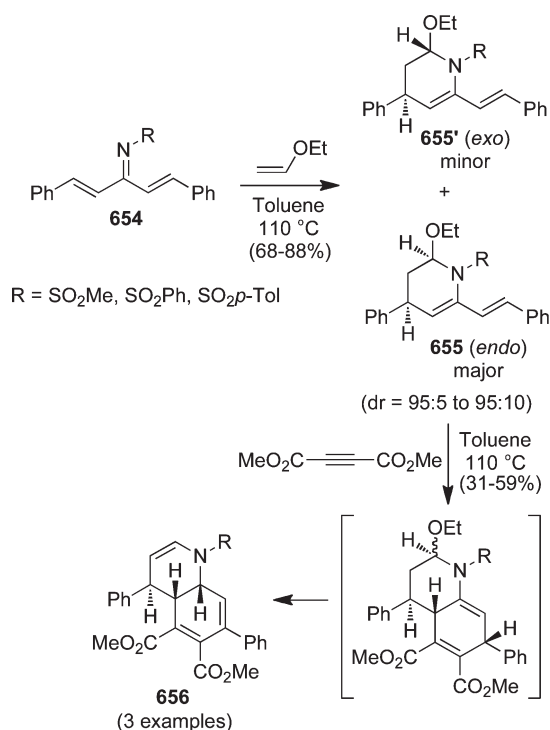


ammonium acetate and 1-phenacylpyridinium iodides **643**, generated in situ from acetophenone derivatives and pyridine. For instance, 1-phenacylpyridinium iodide **643a**, derived from 2-methoxyacetophenone, reacted with (–)-pinocarvone **642a** and ammonium acetate in acetic acid to afford the chiral tetrahydroquinoline **87a** in 44% yield (Scheme 225).<sup>161</sup> For the synthesis of related compounds, see also refs 157–165.

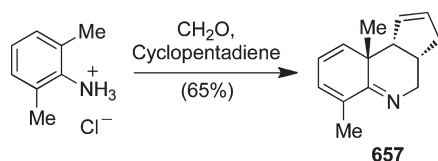
### 10.3. Synthesis of 5,6,7,8-Tetrahydroquinolines by Construction of the Cyclohexene Ring

A set of 6,7,8,9-tetrahydro-5*H*-cyclohepta[*b*]pyridine derivatives **646** were found to be potent and selective opioid receptor-like 1 (ORL1) antagonists, and were obtained from the corresponding 6,8-disubstituted 5,6,7,8-tetrahydroquinoline derivative **645**.<sup>645</sup> Compound **645** was in turn synthesized from 2-chloro-3-cyanopyridine in several steps, where the key reaction was the diastereoselective base-promoted cyclization of pyridine derivative **644** (Scheme 226).

Scheme 229. Synthesis of 1,4,4a,8a-Tetrahydroquinolines via Sequential Diels–Alder Reactions



Scheme 230. Synthesis of 2,3,4,4a-Tetrahydroquinoline 657

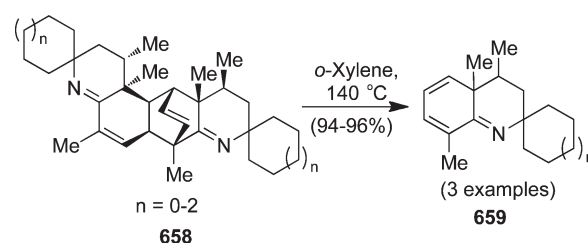


The tetrahydroquinoline derivative **648** is a potential precursor for the alkaloid huperzine A (**649**), a potent inhibitor of acetylcholinesterase, and was synthesized in 91% yield from the pyridine derivative **647** through Dieckmann condensation in the presence of potassium hydride. The starting compound **647** was readily prepared from 2-methyl-6-methoxypyridine (Scheme 227).<sup>646</sup>

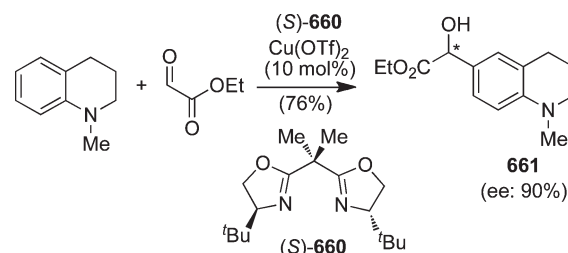
#### 10.4. Synthesis of 5,6,7,8-Tetrahydroquinolines Starting from Acyclic Precursors

The creation of both rings of 5,6,7,8-tetrahydroquinoline in a single step starting from acyclic precursors is rare, and the only report of this type of transformation in the literature is the cobalt-catalyzed synthesis of 5,6,7,8-tetrahydroquinolines from diynenitriles.<sup>647</sup> Diynenitriles **650** were synthesized from heptynenitrile by treatment with ClMe<sub>2</sub>SiNEt<sub>2</sub> followed by addition of propynylalcohols in the presence of BuLi. The intramolecular cyclization of diynenitriles **650**, to afford the tetrahydroquinoline derivatives **651**, was achieved in the presence of a catalytic amount of CpCo(CO)<sub>2</sub> or CpCo(C<sub>2</sub>H<sub>4</sub>)<sub>2</sub> under photochemical conditions. Compounds **651a** (R = H) gave tetrahydroquinoline **652** upon treatment with KHCO<sub>3</sub> and TBAF, while the dihydroxy derivative **653** was isolated in the presence of hydrogen peroxide as an oxidant (Scheme 228). The procedure was also extended to substrates containing the indole moiety.

Scheme 231. Synthesis of Compounds 659 via Thermal Retro Diels–Alder Reaction



Scheme 232. Jørgensen's Asymmetric Friedel–Crafts Type Reaction of N-Methyl-1,2,3,4-tetrahydroquinoline



#### 10.5. Synthesis of 1,4,4a,8a-Tetrahydroquinolines

1,4,4a,8a-Tetrahydroquinolines are readily available using a diene-transmissive Diels–Alder strategy. Thus, azatrienes **654**, derived from dibenzylideneacetone, were used as the diene partner in imino Diels–Alder reactions to give tetrahydropyridines **655**, which were in turn employed as dienes in Diels–Alder reactions with dimethyl acetylenedicarboxylate that afforded 1,4,4a,8a-tetrahydroquinoline derivatives **656** (Scheme 229).<sup>648</sup>

#### 10.6. Synthesis of 2,3,4,4a-Tetrahydroquinolines

Povarov reactions starting from 2,6-dimethylaniline afford tetrahydroquinoline derivatives with a 2,3,4,4a-tetrahydro hydrogenation pattern (compound **657**), which cannot be transformed into the more stable 1,2,3,4-tetrahydro one, having an aromatic ring, because of the presence of a methyl group at the ring fusion (Scheme 230).<sup>649</sup>

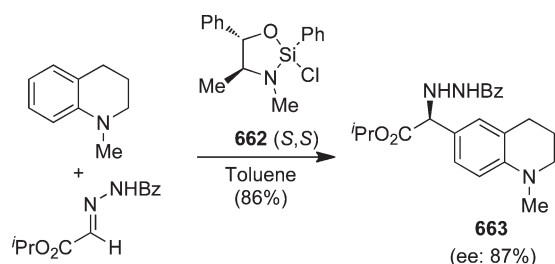
Compounds **658**, previously mentioned as side products of the synthesis of 2-spiro 4,5,8-tetramethyl-1,2,3,4-tetrahydroquinoline derivatives<sup>282,283</sup> from *ortho*-dimethyl homoallylic aromatic amines, (see section 4.5.1), were shown to undergo a thermal retro Diels–Alder reaction to give compounds **659**, which were subsequently employed as the diene partner in a number of [4 + 2] cycloaddition reactions (Scheme 231).<sup>650</sup>

### 11. FUNCTIONALIZATION OF TETRAHYDROQUINOLINES

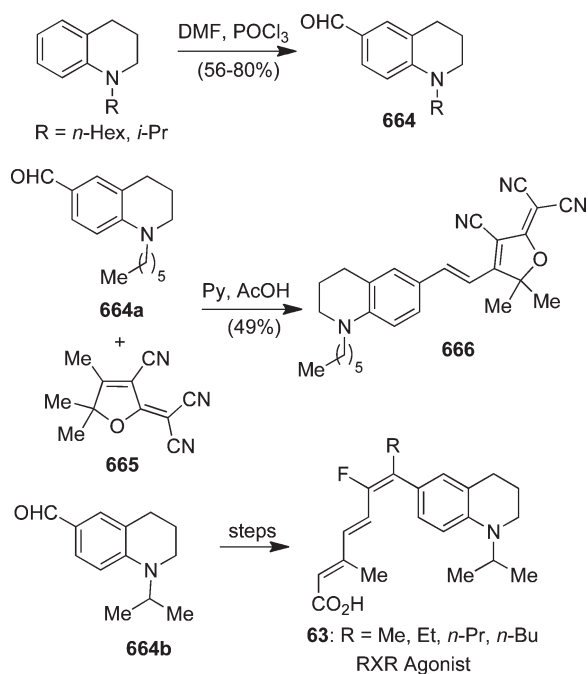
#### 11.1. Introduction

Although the primary intention of this review is to explore the synthesis of tetrahydroquinolines, we have considered pertinent, for the sake of completeness, to discuss the procedures that involve the functionalization of tetrahydroquinoline derivatives. For this reason, in the following two sections we will discuss, respectively, the methodologies developed for the functionalization of tetrahydroquinolines and the synthesis of other,

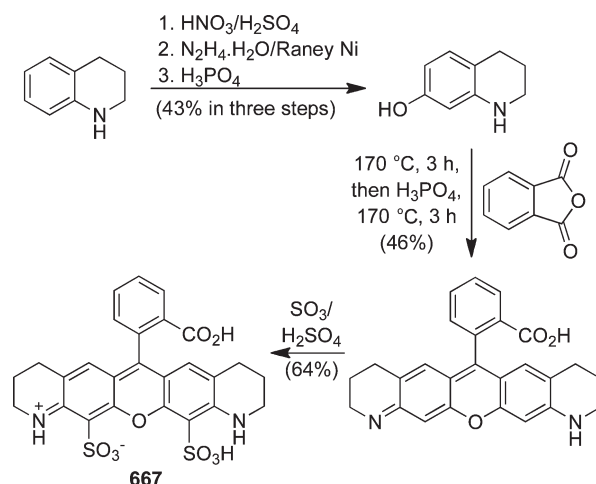
**Scheme 233.** Leighton's Enantioselective Friedel–Crafts Alkylation of *N*-Methyl-1,2,3,4-tetrahydroquinoline



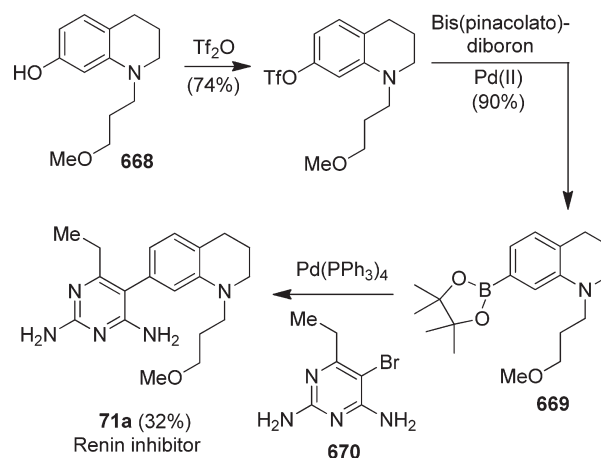
**Scheme 234.** Synthesis of Tetrahydroquinoline-Based Fluorophores **666** and the Retinoid X Receptor (RXR) Agonists **63**



**Scheme 235.** Synthesis of Water-Soluble Fluorescent Dye **667**



**Scheme 236.** Synthesis of Tetrahydroquinoline-Based Renin Inhibitor **71a** via Suzuki Coupling



normally more complex, heterocycles starting from simple tetrahydroquinolines.

## 11.2. Reactions Starting from 1,2,3,4-Tetrahydroquinolines

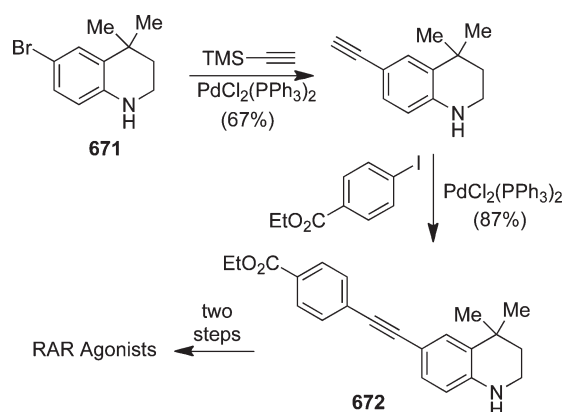
**11.2.1. Functionalization of the Aryl Ring.** The reactions that involve functionalization of the aryl ring of 1,2,3,4-tetrahydroquinolines disclosed in this section are normally relatively straightforward reactions of their benzene ring, which in many cases were carried out in the presence of chiral catalysts. In the first example that we will discuss, Jørgensen and co-workers developed a chiral bisoxazoline–copper(II) complex-catalyzed asymmetric Friedel–Crafts reaction of aryl compounds with ethyl glyoxalate to afford enantiopure mandelic acid esters.<sup>651</sup> For instance, *N*-methyl-1,2,3,4-tetrahydroquinoline afforded the corresponding 6-substituted derivative **661**, in good yield and enantioselectivity, upon treatment with 10 mol % of the copper complex of the bisoxazoline ligand **660** (Scheme 232).

Leighton and co-workers reported an interesting enantioselective Friedel–Crafts alkylation of electron-rich aromatic and heteroaromatic compounds with benzoylhydrazones in the

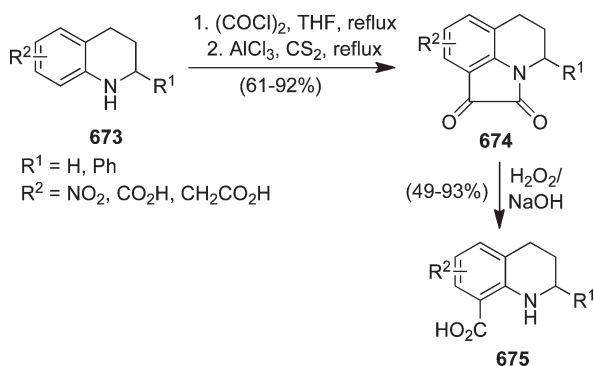
presence of easily accessible chiral silane derivative **662**.<sup>652</sup> For instance, *N*-methyl-1,2,3,4-tetrahydroquinoline reacted with the benzoylhydrazone of isopropyl glyoxalate to afford the corresponding glycine derivative **663** in 86% yield and 87% ee (Scheme 233). It was proposed that the Lewis acidity of the catalyst drives the reaction, and also that its ability to coordinate with the hydrazone group blocks the access of the back (*re*) face of the molecule and allows the arene to approach from the front (*si*) face to afford preferentially a single enantiomer.

Tetrahydroquinoline-based dicyanomethylenedihydrofuran (DCDHF) fluorophores **666**<sup>653</sup> were synthesized starting from simple tetrahydroquinolines, and the key reaction was the formylation at the C-6 carbon under Vilsmeier conditions. Some fused tetrahydroquinoline derivatives, prepared from the corresponding arylamines and 1,3-bromochloropropane, were also formylated under similar conditions. The tetrahydroquinoline-6-carbaldehyde **664a** thus obtained was coupled with compound **665**, derived from 3-hydroxy-3-methylbutan-2-one and malononitrile, to afford fluorophores **666**. Similarly, aldehyde **664b** was also transformed into the retinoid X receptor

Scheme 237. Synthesis of Intermediate (672) for the Agonists of Retinoid A Receptors (RAR)



Scheme 238. Synthesis of Tetrahydroquinoline-8-carboxylic Acids



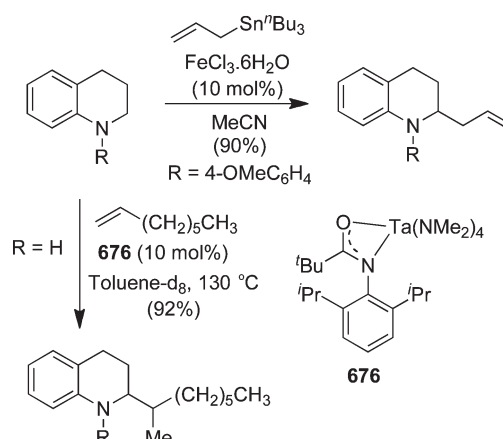
(RXR) agonists **63** in a few additional, straightforward steps (Scheme 234).<sup>128</sup>

7-Hydroxy-1,2,3,4-tetrahydroquinoline, an intermediate for the synthesis of water-soluble fluorescent dyes, was prepared from 1,2,3,4-tetrahydroquinoline by nitration, reduction and treatment of the resulting amino compound with phosphoric acid. A subsequent reaction with phthalic anhydride followed by sulfonation ortho to the tetrahydroquinoline nitrogens afforded the water-soluble dyes **667** (Scheme 235).<sup>654</sup>

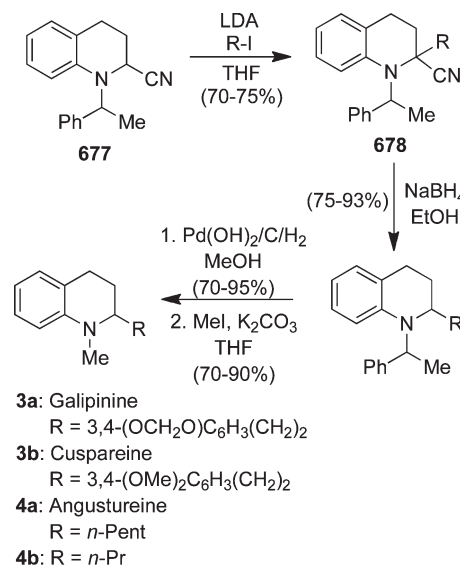
The tetrahydroquinoline-derived renin inhibitor **71** was synthesized from the corresponding 7-hydroxy-1,2,3,4-tetrahydroquinoline derivative **668**.<sup>138</sup> The triflate of compound **668** was transformed into the boronate ester **669** through a palladium-catalyzed reaction with bis(pinacolato)diboron and its subsequent Suzuki reaction with 5-bromo-6-ethyl-2,4-diaminopyrimidine **670** afforded the final renin inhibitor **71a** (Scheme 236). Interestingly, C–H functionalization by borylation of nonfunctionalized 1,2,3,4-tetrahydroquinoline was also possible with bis(pinacolato)diboron in 40% yield in the presence of an iridium catalyst, and took place at its C-8 position.<sup>655</sup>

A set of tetrahydroquinoline-based agonists of retinoid A receptors (RAR) were synthesized through functionalization of bromo-substituted tetrahydroquinolines. A consecutive double palladium-catalyzed coupling of (trimethylsilyl)-acetylene with 6-bromo-1,2,3,4-tetrahydroquinoline derivative **671** and ethyl 4-iodobenzoate furnished compounds **672**, the

Scheme 239. C-2 Functionalization of 1,2,3,4-Tetrahydroquinolines



Scheme 240. Hurvois's Synthesis of Tetrahydroquinoline Natural Products



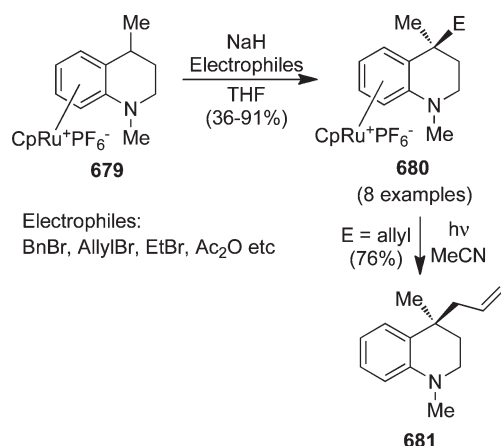
precursors for the final products with RAR agonist activity (Scheme 237).<sup>126</sup>

Tetrahydroquinoline derivatives **673** were carboxylated at their C-8 position by *N*-acylation with oxalyl chloride followed by an intramolecular Friedel–Crafts acylation to give the corresponding isatin derivatives **674**. Oxidative cleavage of these compounds in the presence of hydrogen peroxide under basic conditions afforded the tetrahydroquinoline-8-carboxylic acid derivatives **675** in good overall yields (Scheme 238).<sup>656</sup>

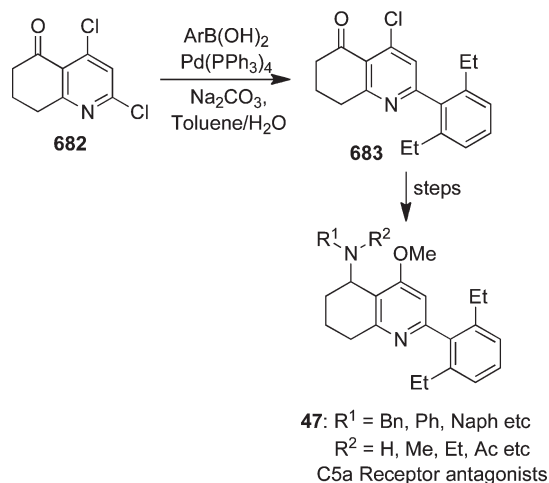
**11.2.2. Functionalization of the Tetrahydropyridine Ring.** The protocols available for the functionalization of the C-2 position of 1,2,3,4-tetrahydroquinoline derivatives include FeCl<sub>3</sub>-catalyzed oxidative allylation,<sup>657</sup> tantalum-amidate complex (**676**)-catalyzed hydroaminoalkylation,<sup>658</sup> 2-lithiation of 2-cyano tetrahydroquinolines in the presence of LDA, followed by alkylation<sup>659</sup> and 2-silylation.<sup>660</sup> The first two methodologies are general and can be employed for the allylation and hydroaminoalkylation of a variety of secondary amines,



Scheme 241. Creation of C-4 Quaternary Center of Tetrahydroquinoline 679



Scheme 242. Synthesis of C5a Receptor Antagonists 47

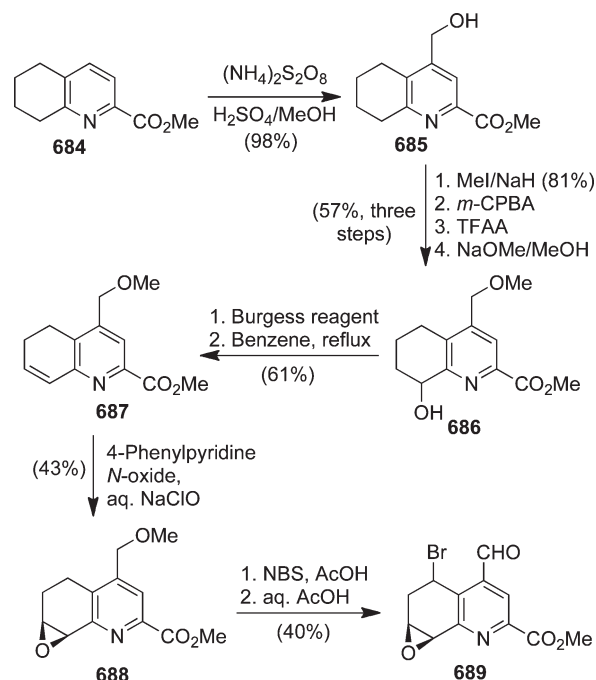


including tetrahydroquinolines, tetrahydroisoquinolines, pyrrolidines, piperidines, morpholines, and *N*-methyl arylamines (Scheme 239).

The 2-lithiation-based methodology developed by the Hurvois group allowed a facile synthesis of the tetrahydroquinoline alkaloids galipinine **3a**, cuspareine **3b**, angustureine **4a** and compound **4b**, derived from *Galipea officinalis*.<sup>659</sup> The starting  $\alpha$ -amino nitrile **677**, prepared in good yield from 1,2,3,4-tetrahydroquinoline using an electrochemical reaction as the key step, was treated with suitable alkyl iodides in the presence of LDA to furnish the corresponding 2-alkyl derivatives **678**. The reductive decyanation of these compounds with sodium borohydride, followed by reductive cleavage of the *N*-benzyl bond in the presence of Pearlman's catalyst and a subsequent *N*-methylation afforded the natural products (Scheme 240).

Pigge and co-workers established a novel procedure for the functionalization of the C-4 position of the ruthenium complexes of 1,4-dimethyl-1,2,3,4-tetrahydroquinolines **679**. This method allowed the creation of a quaternary center at C-4 by the addition of a variety of electrophiles in the presence of sodium hydride. The removal of the ruthenium unit of compounds **680** to obtain the metal-free tetrahydroquinoline derivative **681** was also

Scheme 243. Functionalization of Tetrahydroquinoline 684



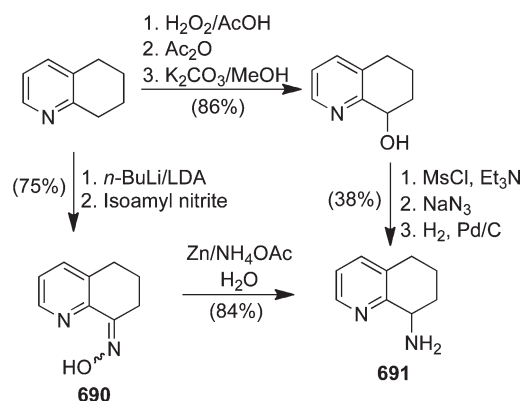
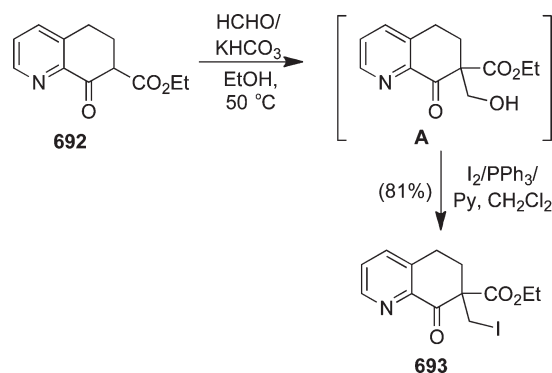
demonstrated under photochemical conditions, although for a single example (Scheme 241).<sup>661</sup>

Other methods allowing the functionalization of 1,2,3,4-tetrahydroquinolines are oxidation at the C-2 position with hydrogen peroxide/bromine<sup>662</sup> and potassium permanganate.<sup>663</sup> Tetrahydroquinolin-2-ones were easily reduced in excellent yields to the corresponding *N*-alkyl-1,2,3,4-tetrahydroquinoline derivatives using boranes.<sup>664</sup>

### 11.3. Reactions Involving 5,6,7,8-Tetrahydroquinolines

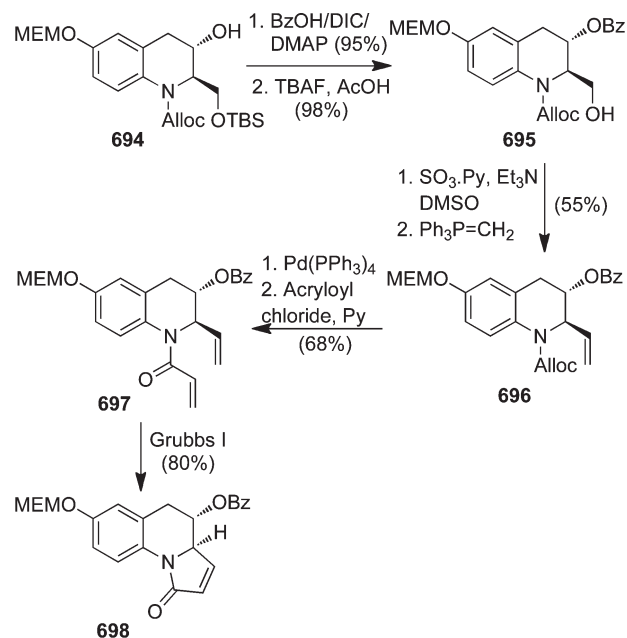
A few reports are available for the functionalization of both rings of 5,6,7,8-tetrahydroquinoline derivatives. For instance, the tetrahydroquinoline-derived compounds **47**, which were identified as antagonists of the complement component 5a (C5a) receptor, were synthesized from 2,4-dichloro-5,6,7,8-tetrahydroquinolin-5-one **682** and the corresponding arylboronic acid via Suzuki coupling through the intermediate ketone **683** (Scheme 242).<sup>99</sup>

In the course of the construction of fragments for the total synthesis of the natural product siomycin A,<sup>665</sup> Hashimoto and co-workers reported the synthesis of tetrahydroquinoline-based epoxide **689** starting from a simple 5,6,7,8-tetrahydroquinoline derivative.<sup>666,667</sup> The starting step of this synthesis was the introduction of a hydroxymethyl group at C-4 position of compound **684** by treatment with (NH<sub>4</sub>)<sub>2</sub>S<sub>2</sub>O<sub>8</sub> in acidic aqueous methanol to give the corresponding hydroxymethyl derivative **685**. Subsequently, a hydroxy group was introduced at C-8 position, to furnish compound **686**, by means of a three-step reaction sequence, that is, *N*-oxidation with *m*-CPBA, a modified Boekelheide rearrangement,<sup>668</sup> induced by acylation of the *N*-oxide in the presence of trifluoroacetic anhydride, and final treatment with sodium methoxide. The successive dehydration of **686** in the presence of the Burgess reagent furnished compound **687** with a double bond between C-7 and C-8. Further epoxidation and functionalization afforded intermediate **688** and then compound **689**, an intermediate for the synthesis of the natural product siomycin A (Scheme 243).

Scheme 244. Synthesis of 8-Amino-5,6,7,8-tetrahydroquinoline **691**Scheme 245. Iodomethylation of Compound **692**

In another report, 8-amino-5,6,7,8-tetrahydroquinoline **691** was synthesized from 5,6,7,8-tetrahydroquinoline through the corresponding 8-hydroxy derivative. The hydroxy group was installed at the C-8 position in good yield by means of a Boelkeheide rearrangement, but the subsequent transformation of the hydroxy group into amino gave only 38% yield.<sup>669</sup> For this reason, the same group subsequently developed an improved procedure for the synthesis of the same target molecule starting from 5,6,7,8-tetrahydroquinoline. The C-8 lithiation of 5,6,7,8-tetrahydroquinoline with *n*-BuLi/LDA, followed by treatment with isoamyl nitrite, afforded oxime **690**, which was then reduced to the corresponding 8-amino derivative **691** with Zn/NH<sub>4</sub>OAc (Scheme 244).<sup>670</sup> It is interesting to note that Uenishi and Hamada disclosed an efficient procedure for the synthesis of enantiopure 8-hydroxy-5,6,7,8-tetrahydroquinoline (>99% ee) through a lipase-catalyzed kinetic acetylation of the corresponding racemic compound followed by hydrolysis,<sup>671</sup> and this compound was then transformed into the chiral 8-amino- and 8-thio-derivatives without any significant loss in enantioselectivity.

5,6,7,8-Tetrahydroquinoline derivative **692**, bearing a  $\beta$ -dicarbonyl fragment, was effectively iodomethylated at the  $\alpha$ -position through a one-pot, two-step process.<sup>672</sup> Treatment of compound **692** with aqueous formaldehyde in the presence of a base afforded the corresponding hydroxymethyl derivative **A**, which was then exposed to molecular iodine, PPh<sub>3</sub>, and pyridine to give the iodomethyl derivative **693** in 81% overall yield (Scheme 245).

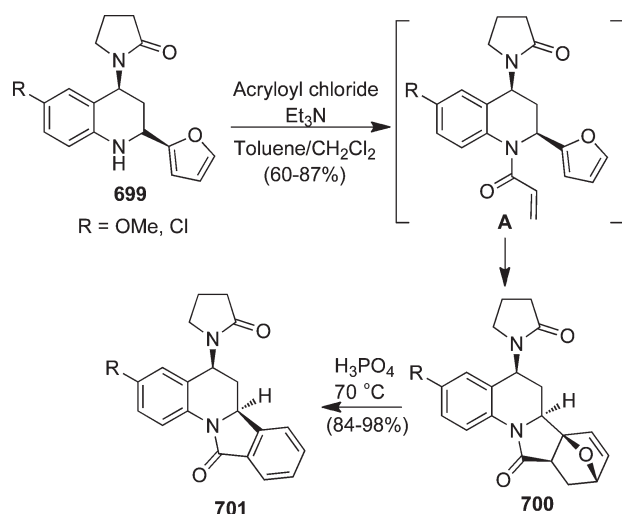
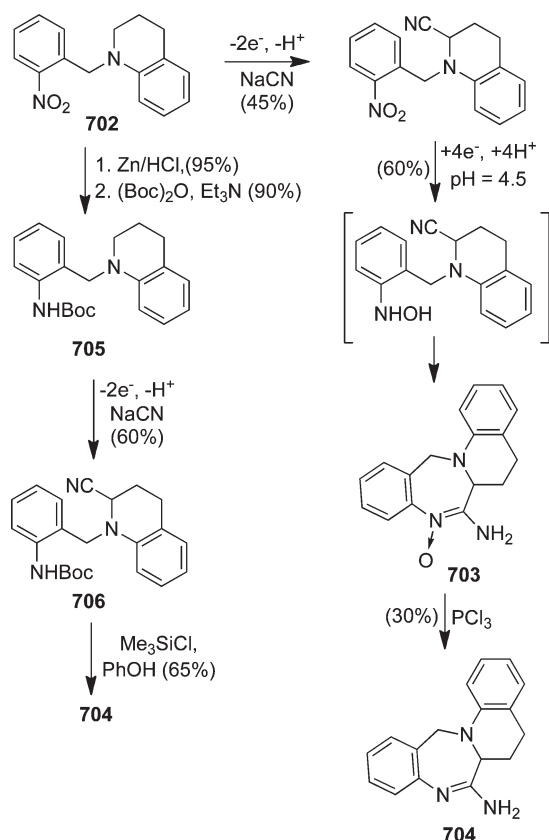
Scheme 246. Synthesis of Pyrrolo[1,2-*a*]quinoline **698**

## 12. TRANSFORMATION OF TETRAHYDROQUINOLINES INTO OTHER HETEROCYCLES

In the previous sections, we have thoroughly discussed the construction of tetrahydroquinolines and their fused analogues starting from a wide variety of simple precursors. We will now describe the application of tetrahydroquinolines as starting materials for the synthesis of other heterocycles, normally with fused frameworks. A significant number of reports have been published documenting the creation of additional rings fused to either the tetrahydropyridine ring (N–C<sub>2</sub>, C<sub>2</sub>–C<sub>3</sub>, or C<sub>3</sub>–C<sub>4</sub> bonds) or the ring junction between both rings (N–C<sub>8a</sub> and C<sub>8</sub>–C<sub>8a</sub> or C<sub>4</sub>–C<sub>4a</sub> and C<sub>4a</sub>–C<sub>5</sub> bonds) of tetrahydroquinolines.

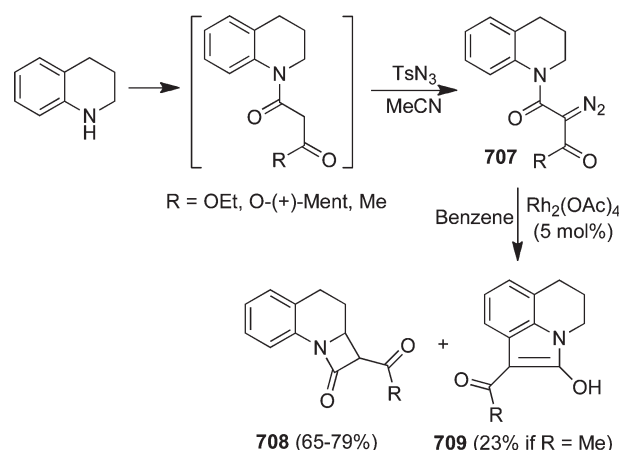
### 12.1. Methods that Create Additional Rings Fused to the N–C<sub>2</sub> Bond

The creation of additional rings fused to the N–C<sub>2</sub> bond of the 1,2,3,4-tetrahydroquinoline system has been generally achieved by introducing suitable substituents on the nitrogen atom, followed by their subsequent reaction with the C-2 carbon or with substituents at C-2. For instance, Khadem and co-workers recently demonstrated a novel solution- and solid-phase synthesis of pyrrolo[1,2-*a*]quinolines starting from previously known tetrahydroquinoline **694**.<sup>224</sup> The first step of the sequence was the benzoyl protection of the secondary alcohol and the deprotection of the TBS group in the presence of TBAF to afford primary alcohol **695**. Further oxidation of this alcohol followed by Wittig olefination furnished 2-vinyl tetrahydroquinoline **696** in moderate yield. Palladium(0)-catalyzed removal of the alloc group and *N*-acylation gave the metathesis precursor **697**, which was then converted into the pyrrolo[1,2-*a*]quinoline derivative **698** in good yield by ring-closing metathesis in the presence of the Grubbs first generation catalyst (Scheme 246).<sup>673</sup> For other procedures involving the synthesis of complex heterocycles starting from simple 1,2,3,4-tetrahydroquinolines developed by the Arya group, see refs 196–200.

Scheme 247. Transformation of the Povarov Adducts **699** in to the Tetracyclic Compounds **701**Scheme 248. Synthesis of Tetrahydroquinoline-Fused Benzodiazepine **704**

The 2-furyl tetrahydroquinoline derivatives **699**, derived from a Povarov reaction, were found to be interesting substrates for the synthesis of fused pentacyclic tetrahydroquinolines **700**.<sup>674</sup> *N*-Acylation of compounds **699** with acryloyl chloride in the presence of triethylamine afforded the corresponding, nonisolated, *N*-acyl intermediate **A**, which subsequently

Scheme 249. Rh-Catalyzed Functionalization of Tetrahydroquinolines



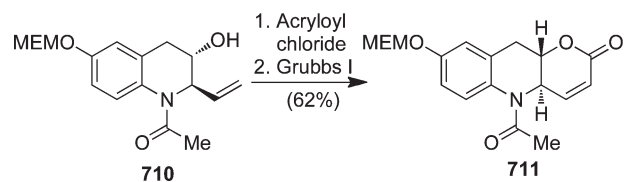
underwent a [4 + 2] intramolecular cycloaddition reaction with the furyl diene to give compounds **700**; their treatment with phosphoric acid provided the tetracyclic compounds **701** through a ring-opening-aromatization sequence (Scheme 247). A similar strategy was subsequently described by Zubkov and co-workers.<sup>675</sup>

The tetrahydroquinoline-fused benzodiazepine **704** was prepared from the readily available tetrahydroquinoline derivative **702**, the key step being the cyanation at C-2 position under electrochemical conditions.<sup>676</sup> The benzodiazepine *N*-oxide **703** was obtained in two successive electrochemical reactions, that is, 2-cyanation and partial reduction of the nitro group followed by intramolecular cyclization. The subsequent reduction of the *N*-oxide with PCl<sub>3</sub> afforded the final product **704** in 30% yield. Alternatively, benzodiazepine **704** was also obtained from the *N*-Boc derivative **705**, which in turn was prepared from compound **702** in two simple steps. An additional electrochemical 2-cyanation of **705** furnished compound **706**, which was then converted into the final product upon treatment with Me<sub>3</sub>SiCl (Scheme 248).

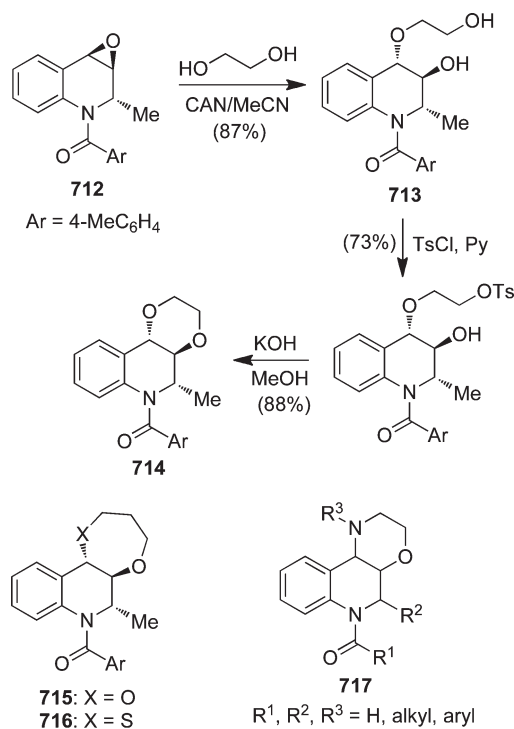
Rhodium-catalyzed intramolecular carbene insertion of diazoamides **707**, prepared from simple 1,2,3,4-tetrahydroquinoline through diazo transfer reaction of the corresponding amides, afforded tetrahydroquinoline-fused  $\beta$ -lactams **708** in good yields.<sup>677</sup> The use of (+)-menthol as a chiral auxiliary to induce chirality at the newly generated C-2 asymmetric center was also demonstrated. Interestingly, compound **707c** (R = Me) gave a mixture of **708c** and pyrroloquinoline **709** in a 3:1 ratio (Scheme 249). Simultaneously, a similar Rh-catalyzed synthesis of  $\beta$ -lactams of type **708** bearing a diethylphosphonate moiety was also reported.<sup>678</sup>

## 12.2. Methods that Create Additional Rings Fused to the C<sub>2</sub>–C<sub>3</sub> Bond

The previously mentioned metathesis protocol developed by Khadem and co-workers was also employed for the creation of an additional ring fused to the C<sub>2</sub>–C<sub>3</sub> bond.<sup>673</sup> Acylation of the secondary alcohol **710** with acryloyl chloride followed by a ring-closing metathesis reaction in the presence of Grubbs first generation catalyst afforded the pyrano[3,2-*b*]-quinoline **711** in good yields (Scheme 250) (see also refs 196–200).

Scheme 250. Synthesis of Pyrano[3,2-*b*]quinoline 711

Scheme 251. Regioselective Nucleophilic Ring-Opening Tosylation—Base-Promoted Cyclization Sequence of Epoxide 712

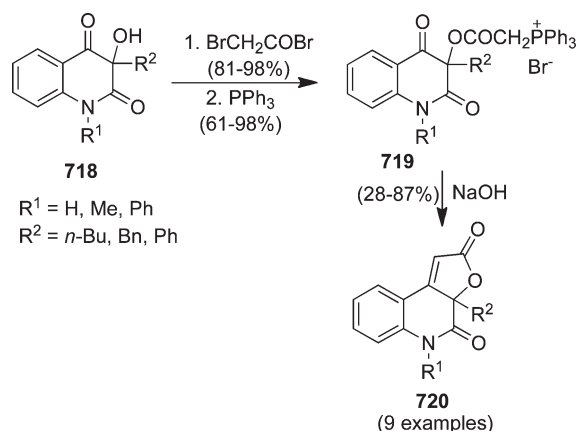
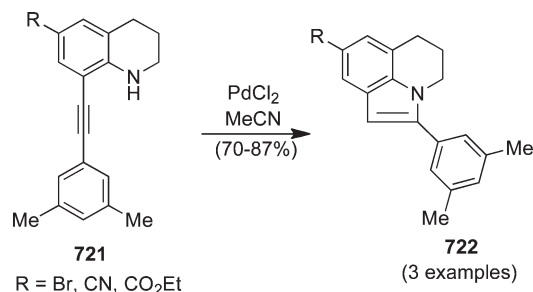


### 12.3. Methods that Create Additional Rings Fused to the C<sub>3</sub>–C<sub>4</sub> Bond

The regioselective nucleophilic ring-opening of the readily available epoxide **712**<sup>679,619</sup> with alcohols in the presence of CAN afforded diastereoselectively the tetrasubstituted 1,2,3,4-tetrahydroquinoline derivative **713**. Subsequent tosylation of the primary alcohol group, followed by a base-promoted cyclization, furnished the C<sub>3</sub>–C<sub>4</sub>-fused tetrahydroquinoline **714**.<sup>680</sup> A similar protocol was also utilized for the synthesis of compounds **715** and **716** using suitable nucleophiles. It is also relevant to mention here that the same group had previously demonstrated the synthesis of compounds **717** based on a similar strategy (Scheme 251).<sup>681</sup>

Klásek and Kafka established the synthesis of the tricyclic compounds **720** starting from tetrahydroquinoline-2,4-diones **718** through a three-step procedure, as summarized in Scheme 252.<sup>682</sup> Treatment of compounds **718** with bromoacetyl bromide, followed by triphenylphosphine, afforded the salts **719**, which were then transformed into the final products **720** under basic conditions. The same group had previously demonstrated the preparation of similar compounds as minor products from **718** through a Wittig reaction followed by intramolecular cyclization.<sup>683</sup>

Scheme 252. Klásek and Kafka's Synthesis of Compounds 720

Scheme 253. Pd-Catalyzed Synthesis of Pyrrolo[3,2,1-*ij*]quinolines 722

### 12.4. Methods that Create Additional Rings Fused to the N–C<sub>8a</sub> and C<sub>8</sub>–C<sub>8a</sub> Bonds

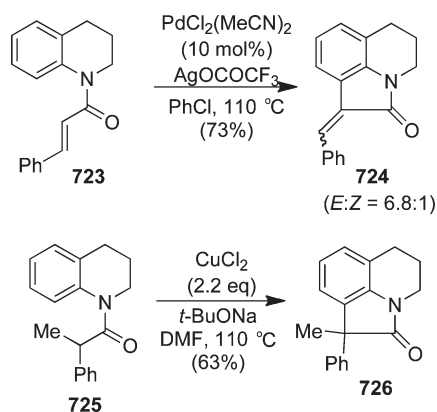
**12.4.1. Creation of Five-Membered Rings.** The palladium-catalyzed ring-closure of 2-alkynylanilines is an efficient methodology to obtain indole derivatives.<sup>684</sup> This protocol was successfully employed for the creation of an additional ring fused to the N–C<sub>8a</sub> and C<sub>8</sub>–C<sub>8a</sub> bonds of tetrahydroquinolines. Thus, 8-alkynyl-1,2,3,4-tetrahydroquinolines **721**, prepared from the corresponding 8-iodo-derivatives via Sonogashira coupling, afforded the corresponding pyrrolo[3,2,1-*ij*]quinolines **722** in good yields upon treatment with palladium chloride (Scheme 253).<sup>685</sup> Recently, a similar transformation was also achieved in the presence of copper iodide in good to excellent yields.<sup>686</sup>

Nagasawa and co-workers illustrated recently a novel palladium-catalyzed C–H functionalization/intramolecular alkenylation of *N*-cinnamoyl-*N*-arylamines for the synthesis of oxindoles. For instance, treatment of *N*-cinnamoyl-1,2,3,4-tetrahydroquinoline **723** with 10 mol % of a palladium catalyst provided the tricyclic compound **724** in 73% yield.<sup>687</sup> In another report, as an application of CuCl<sub>2</sub>-mediated synthesis of oxindoles from *N*-arylamides, *N*-acyl-1,2,3,4-tetrahydroquinoline **725** reacted with 2.2 equiv of CuCl<sub>2</sub> to furnish compound **726** (Scheme 254).<sup>688</sup>

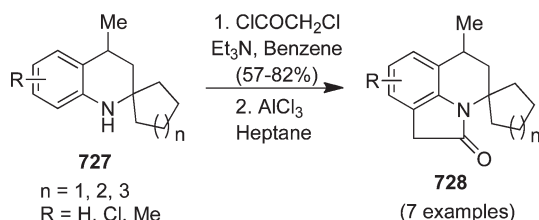
*N*-Acylation of 1,2,3,4-tetrahydroquinoline with a suitable acid chloride followed by an intramolecular Friedel–Crafts alkylation was found to be an efficient methodology for the creation of an additional ring between nitrogen and C-8 positions. Thus, treatment of 2-spiro-4-methyl-1,2,3,4-tetrahydroquinoline derivatives **727** with chloroacetyl chloride afforded the



**Scheme 254.** Pd-Catalyzed and Cu-Mediated Functionalization of C-8 Position via Intramolecular Cyclization



**Scheme 255.** Synthesis of Pyrrolo[3,2,1-*ij*]quinolines via *N*-Acylation–Intramolecular Friedel–Crafts Alkylation Sequence

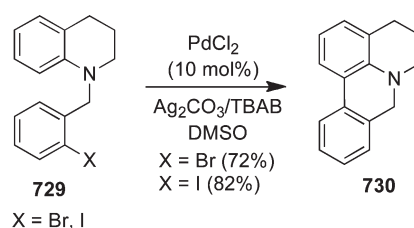


corresponding *N*-acyl derivatives. The successive  $\text{AlCl}_3$ -catalyzed intramolecular alkylation furnished pyrrolo[3,2,1-*ij*]quinolines 728 (Scheme 255).<sup>689,690</sup> It is also relevant to mention here that some simple 1,2,3,4-tetrahydroquinoline derivatives gave the corresponding tricyclic compounds in poor yields upon reaction with phenacyl bromide via a *N*-alkylation–cyclization sequence.<sup>691</sup> Furthermore, the Fischer indole cyclization of *N*-amino-1,2,3,4-tetrahydroquinolines with suitable aldehydes or ketones also allowed the synthesis of pyrrolo[3,2,1-*ij*]quinolines.<sup>96,100,101</sup>

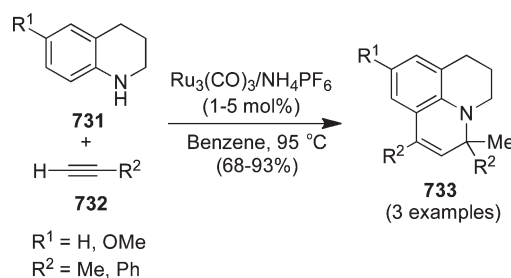
**12.4.2. Creation of Six-Membered Rings.** The palladium-catalyzed intramolecular diaryl coupling of *N*-(2-halobenzyl)-1,2,3,4-tetrahydroquinolines 729 in the presence of  $\text{Ag}_2\text{CO}_3$  as a base and TBAB as an additive afforded the corresponding benzannulated pyrido[3,2,1-*ij*]quinoline derivative 730 in good yields together with a small amount of the dehalogenated product.<sup>692</sup> A similar procedure was also employed for the intramolecular coupling reaction of *N*-(2-iodobenzoyl)-1,2,3,4-tetrahydroquinoline, where a variety of phosphine derivatives were used as ligands (Scheme 256).<sup>693</sup>

A ruthenium-catalyzed C–H bond activation/hydroamination process was developed for the synthesis of tricyclic nitrogen heterocycles, using indolines or tetrahydroquinolines and terminal alkenes as starting materials.<sup>694</sup> For instance, 1,2,3,4-tetrahydroquinolines 731 reacted with excess of alkynes 732 in the presence of 1 to 5 mol % of  $\text{Ru}_3(\text{CO})_3/\text{NH}_4\text{PF}_6$  to furnish high yields of the corresponding tricyclic pyrido[3,2,1-*ij*]quinolines 733, having the structural core of the julolidine alkaloids (Scheme 257). A mechanism for the reaction was also proposed involving cationic intermediates, which was confirmed by the isolation of one of these intermediates.

**Scheme 256.** Pd-Catalyzed Intramolecular Diaryl Coupling of *N*-(2-Halobenzyl)-1,2,3,4-tetrahydroquinolines 729



**Scheme 257.** Ru-Catalyzed C–H Bond Activation–Hydroamination Sequence of Tetrahydroquinolines with Alkynes



Kouznetsov and co-workers adapted a previously described procedure<sup>689</sup> (see Scheme 255) to the construction of spiroannulated julolidines. A *N*-acylation–intramolecular Friedel–Crafts sequence starting from compounds 727 and a suitable acid chloride allowed the synthesis of julolidine derivatives 734.<sup>695,696</sup> These authors also described an alternative route for the construction of julolidine framework through *N*-alkylation of 727 with ethyl 2-bromoacetate to obtain the compounds 735 in good yields. Their subsequent treatment with polyphosphoric acid at elevated temperature afforded the unexpected tricyclic products 736 (Scheme 258),<sup>695,697</sup> whose structure was confirmed by the independent preparation of 736 through reduction of the carbonyl group in 734.

The formation of 736 was explained by a mechanism involving an initial nucleophilic attack of the hydroxy group of PPA to the ester carbonyl of 735 to give a molecule of ethanol and intermediate **A**, which subsequently eliminates dihydrogenphosphate and  $\text{CO}_2$  to afford iminium cation **B**. In the presence of PPA, the previously liberated ethanol would produce ethylene, which would then react with intermediate **B** to furnish a carbocation that would be trapped by dihydrogenphosphate to generate the next intermediate **C**. Finally, the intramolecular cyclization of **C** would afford the observed product 736 (Scheme 259).

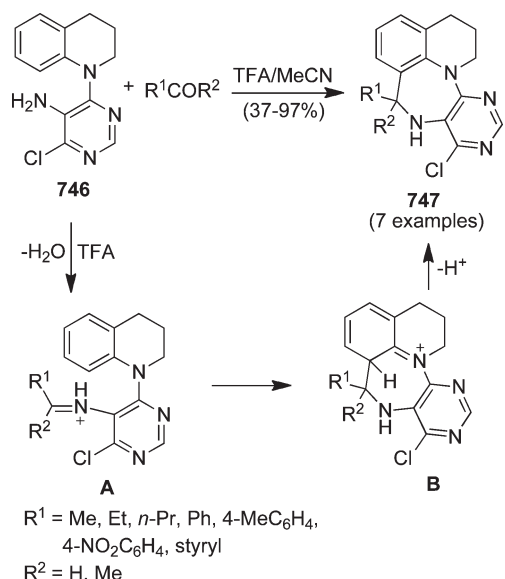
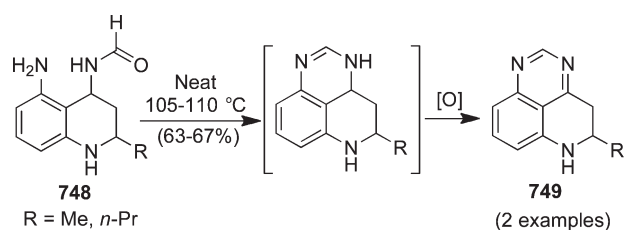
The julolidine framework was also constructed through the reaction between 1,2,3,4-tetrahydroquinoline and methanetricarboxylic acids under thermal conditions, without the need for any catalyst (Scheme 260).<sup>698</sup> Interestingly, further functionalization of the ester group of compounds 737 with suitable arylamines afforded the corresponding amide derivatives 738, which were found to have antitubercular activity.<sup>699,700</sup>

Flumequine 742, an antibacterial agent, was synthesized from 6-fluoro-2-methyl-1,2,3,4-tetrahydroquinoline 739 using the traditional route for the preparation of 4-quinolone antibacterial agents. The initial step was the preparation of compound 740 by

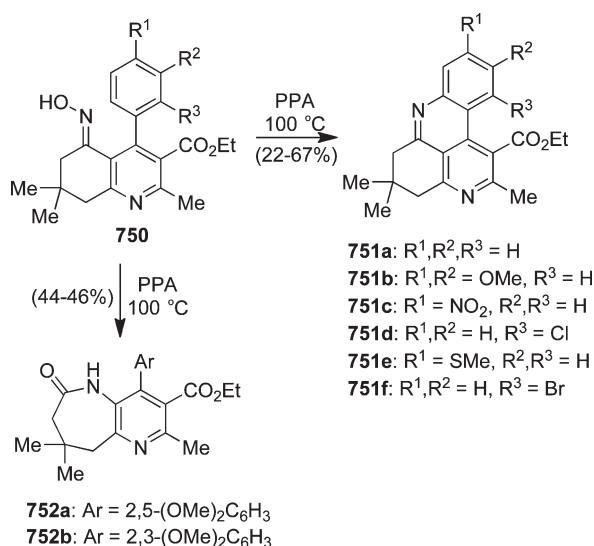




Scheme 263. Synthesis of Fused Tetrahydroquinolines 747

Scheme 264. Solvent-Free Synthesis of Pyrido[4,3,2-*de*]quinazolines 749

Scheme 265. Polyphosphoric Acid-Mediated Synthesis of Compounds 751 and 752



between compound **746** and the carbonyl compounds, to afford intermediate **B**. Subsequent loss of a proton from intermediate **B** furnished the final product **747** (Scheme 263).

## 12.5. Methods that Create Additional Rings Fused to the C<sub>4</sub>–C<sub>4a</sub> and C<sub>4a</sub>–C<sub>5</sub> Bonds

The 5-amino-substituted 1,2,3,4-tetrahydroquinoline **748** obtained from catalytic hydrogenation of the corresponding nitro derivative, in turn prepared from *m*-nitroaniline through Katritzky's benzotriazole Povarov-like protocol, was heated at 105–110 °C under solvent-free conditions to afford pyrido[4,3,2-*de*]quinazolines **749** in good yields, through a sequence of condensation and oxidation reactions (Scheme 264).<sup>705</sup>

The 4-aryl-5,6,7,8-tetrahydroquinolin-5-one oximes **750** furnished tetracyclic compounds **751** or the Beckmann rearrangement products **752** in low yields upon treatment with polyphosphoric acid at high temperature, depending on the nature of substituents on the 4-aryl ring.<sup>706</sup> The formation of compounds **751** was explained by the generation of a nitrenium cation intermediate followed by its attack to the 4-aryl ring (Scheme 265).

## 13. CONCLUDING REMARKS

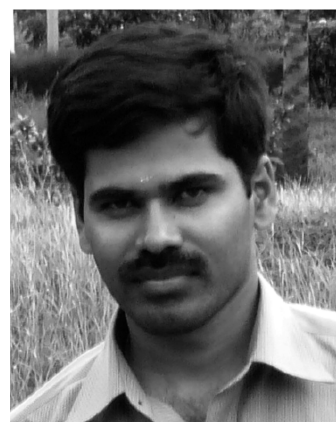
We hope to have conveyed to the readers of this review the current interest of the synthetic community in the preparation of tetrahydroquinoline derivatives. Work in this topic is certain to continue in the near future, and it can be anticipated that two of the areas that will probably experience the fastest growth will be the development of step- and atom-economic methods based on the use of multicomponent and domino strategies, and the study of reactions leading to enantiomerically pure tetrahydroquinolines.

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## BIOGRAPHIES



Vellaisamy Sridharan was born in Tamil Nadu, India. He received his M.Sc degree in Chemistry, together with a Gold medal for university first rank, from Madurai Kamaraj University, Madurai, India. He then started his doctoral studies in the Department of Organic Chemistry of the same university, with a CSIR-NET/JRF fellowship, under the joint guidance of Professors S. Muthusubramanian and S. Sivasubramanian. After obtaining his Ph.D degree in 2005, he joined the group of Professor José Carlos Menéndez in the Complutense University, Spain, as a postdoctoral associate to work on the development of new synthetic methodologies and multicomponent reactions for

the synthesis of biologically relevant molecules and natural products. He took a temporary break from Madrid to spend one year postdoctoral stay in the University of Paul Cézanne, Marseille, France, during 2008–2009, to work with Professor Jean Rodriguez on sulfoximine chemistry. Recently he has been awarded the Japan Society for the Promotion of Science (JSPS) fellowship for another postdoctoral stay in the Osaka University, Japan. He has coauthored around 40 international publications, including a previous article in *Chemical Reviews*.



Padmakar Apparao Suryavanshi was born in Parbhani, Maharashtra, India. He received his M. Sc. in Organic Chemistry in 2004 from Swami Ramanand Teerth Marathwada University, Nanded, India. Subsequently, he gained two years research experience in organic synthesis from the National Chemical Laboratory (NCL) and the Sai Advantium Pharmaceutical Company, Pune. At present, he is working for his Ph.D thesis under the guidance of Dr. V. Sridharan and Professor J. C. Menéndez in the Complutense University, Madrid, Spain. His research interests include the development of new synthetic methodologies using CAN as a catalyst and the synthesis of biologically important heterocycles.



José Carlos Menéndez was born in Madrid (1960) and obtained degrees in Pharmacy from Universidad Complutense at Madrid, UCM (1982) and Chemistry from UNED (1985) followed by a Ph. D. in Pharmacy from UCM in 1988, under the supervision of Dr. Mónica M. Söllhuber. In August 1988, he joined the group of Professor Steven V. Ley at Imperial College, London, where he worked on the total synthesis of the natural ionophoric antibiotic routienocin. In September 1989 he

returned as a Profesor Titular to the Organic and Medicinal Chemistry Department at UCM, where he has pursued his teaching and research career ever since, having obtained Habilitation as a Full Professor in 2010. He has varied research interests, mostly related to synthetic work related to the development of new antitumour drugs, including heterocyclic quinones, antitumour marine natural products and MDR reversors and, more recently, ligands of prion protein. Other projects pursued in his group place more emphasis on the development of new synthetic methodology, including work on hetero Diels–Alder reactions, microwave-assisted organic synthesis, CAN as a catalyst for organic synthesis, and new domino and multicomponent reactions for the preparation of biologically relevant bicyclic systems and nitrogen heterocycles. This work has been documented in about 170 research papers, reviews, and chapters and 9 patents. He has also some long-standing collaborations with several chemical and pharmaceutical Spanish companies. Additionally, he has coauthored two textbooks in Medicinal Chemistry for McGraw-Hill Interamericana (*Introducción a la Química Farmacéutica*, 2nd ed., 2001, and *Ejercicios de Química Farmacéutica*, 1997), and a third one for Elsevier (*Medicinal Chemistry of Anticancer Drugs*, 2008). He is the head of the Organic Microanalysis service at UCM since its creation in 1991. He was a Visiting Professor at Université Paul Cézanne (Aix-Marseille III) in 2007. Since 2004, he is a Corresponding Member of the Spanish Royal Academy of Pharmacy.

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