Asymmetric Catalysis

DOI: 10.1002/ange.201102069

# Catalytic Asymmetric Conjugate Addition/Oxidative Dearomatization Towards Multifunctional Spirocyclic Compounds**

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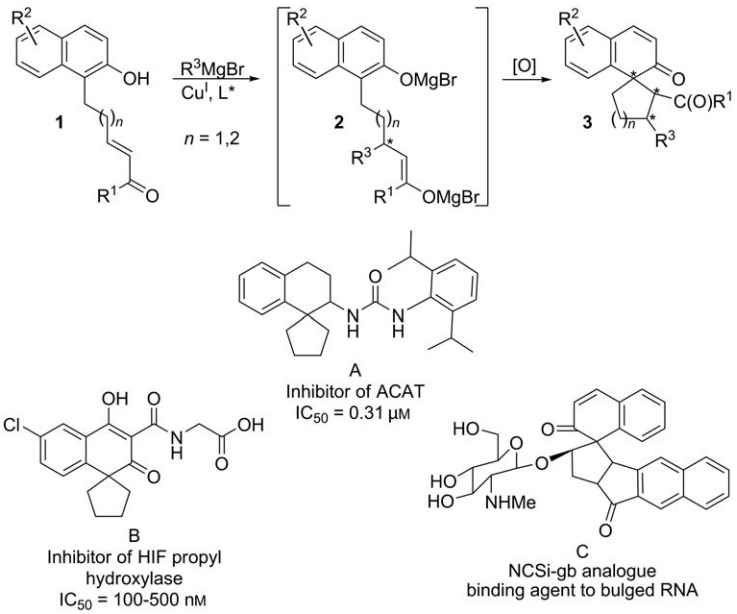
The copper-catalyzed asymmetric conjugate addition of Grignard reagents to α,β-unsaturated carbonyl compounds has established itself as a reliable and efficient method for the preparation of chiral building blocks that contain a new carbon–carbon bond and a single stereogenic center.[1] The resultant magnesium enolate formed during this process lends itself towards the development of sequential processes, where trapping of the enolate leads to the formation of two or more stereocenters in a one-pot procedure.[2] This strategy is particularly attractive as a high degree of structural and stereochemical complexity can be achieved in a sequential process using small amounts of a chiral catalyst.[2b,3]

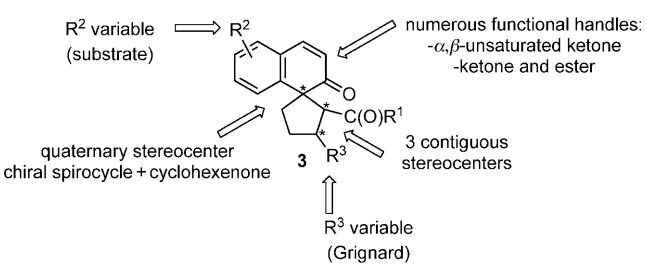
To develop new sequential transformations compatible with the copper-catalyzed conjugate addition of Grignard reagents, we explored the synthetic utility of oxidative dearomatization processes of phenol and naphthol compounds.[4] Oxidative dearomatization is an important pathway in the biosynthesis of many natural products[5] and likewise, it is a method regularly used in their laboratory synthesis.[6] During the oxidative dearomatization event, the phenol reactivity changes from nucleophilic to electrophilic. Subsequent nucleophilic addition can afford chiral products from substrates that once featured planar structures.[4b] Recently, the research groups of Gaunt[7] and Jørgensen[8] employed an oxidative dearomatization strategy of phenols in conjunction with enamine catalysis for the synthesis of chiral phenol derivatives.

Our proposed reaction scheme comprises a naphthol (**1**) bearing an *ortho*-tethered α,β-unsaturated carbonyl group (Scheme 1). Conjugate addition to afford enolate **2**, and subsequent intramolecular oxidative coupling, involving a naphtholate and an enolate, would yield a chiral spirocyclic five- or six-membered ring compound (**3**).

One-pot transformations to yield chiral small molecules displaying a high degree of skeletal complexity, diversity, and functionality are a mainstay of diversity oriented synthesis.[9] Our proposed process would provide, besides the spirocyclic framework, two new carbon–carbon bonds and three contiguous stereocenters—including one quarternary stereocenter—in a single transformation (Scheme 2). The products are architecturally complex, possessing optically active cyclohexenone and spirocyclic moieties, both of which have been used as intermediates in the synthesis of natural products and pharmaceuticals (see Scheme 1).[10,11] Substituents $R^2$ and $R^3$ are easily varied, depending on the substrate or Grignard reagent employed. Product **3** also contains a number of functional groups, including an α,β-unsaturated ketone and two carbonyl units, which are amenable to further transformations such as [4+2] cycloadditions as well as 1,4- and 1,2-additions.




***Scheme 1.*** Proposed conjugate addition/oxidative dearomatization of naphthols and targets accessible from this approach.




***Scheme 2.*** Features of product **3**.

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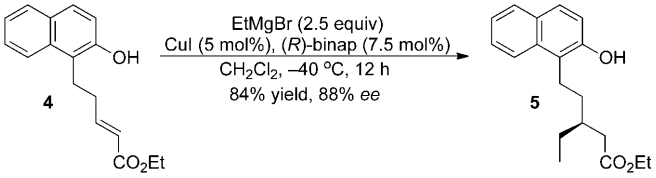
[**] We thank T. D. Tiemersma-Wegman and M. J. Smith for technical support (HPLC and MS analysis) and Dr. T. den Hartog for useful discussions. Financial support from NWO-CW is gratefully acknowledged.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201102069.

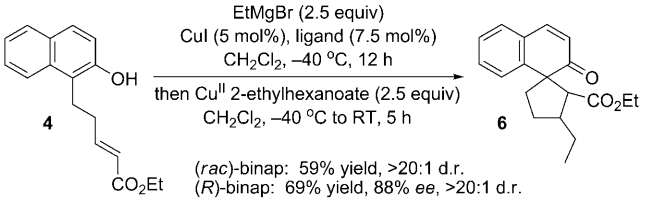
Despite existing strategies for the synthesis of chiral molecules through oxidative dearomatization/nucleophilic addition,[12] to the best of our knowledge, this is the first method to use the enolate intermediate of a catalytic asymmetric conjugate addition of Grignard reagents.[13]

Our initial investigations focused on 2-naphthol-based substrate **4** (Scheme 3). We first needed to optimize the reaction conditions for the copper-catalyzed conjugate addition of EtMgBr to **4**. Under slightly modified conditions, **5** was isolated in 84% yield and 88% *ee*, with an *S* configuration at the stereocenter (see below).[14–16]




***Scheme 3.*** Optimized conditions for the conjugate addition of EtMgBr to substrate **4**. binap = 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl.

Our preliminary experiments for the sequential conjugate addition/oxidative cyclization reaction gave highly promising results (Scheme 4).

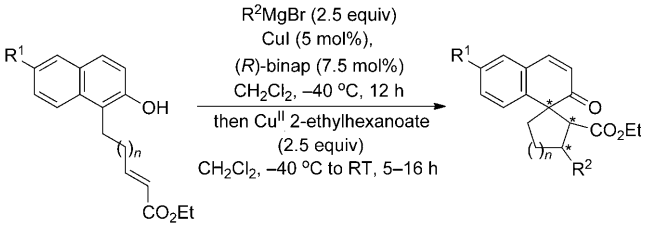



***Scheme 4.*** Initial result for the sequential conjugate addition/oxidative cyclization reaction.

Under racemic reaction conditions, the conjugate addition of EtMgBr to **4** was followed by the addition of copper(II) 2-ethylhexanoate as an oxidant,[13a–d,17] in the same pot (Scheme 4). The desired spirocyclic product **6** was obtained in 59% yield upon isolation, as a single diastereomer. Under the asymmetric reaction conditions employing (*R*)-binap as the chiral ligand, the same transformation afforded product **6** with high yield (69%) and 88% *ee*. Further screening of oxidizing reagents (other sources of $Cu^{II}$, $Fe^{III}$, phenyliodine-(III) diacetate, and phenyliodine (III) bis(trifluoroacetate)) did not improve on these results. The enantiomeric excess of **6** matches exactly that of **5** obtained under the same reaction conditions for the conjugate addition (see Scheme 3). The high diastereoselectivity (> 20:1 d.r.) achieved in the cyclization to **6** suggests that once the first stereocenter is established during the conjugate addition, it controls the formation of the two subsequent stereocenters.

We next focused our efforts on the scope of the reaction (Table 1). Linear alkyl Grignard reagents provided the desired products in good to excellent yields (entries 1–3) and good *ee* (entries 1–3, 5, and 6). The addition of *i*PrMgBr proceeded in good yield, but with lower enantioselectivity,

***Table 1:*** Reaction scope of substituted 2-naphthols.




**4**: $R^1$ = H, *n* = 1 **15**: $R^1$ = OMe, *n* = 1
**13**: $R^1$ = Br, *n* = 1 **17**: $R^1$ = H, *n* = 2

**6–12, 14, 16, 18**

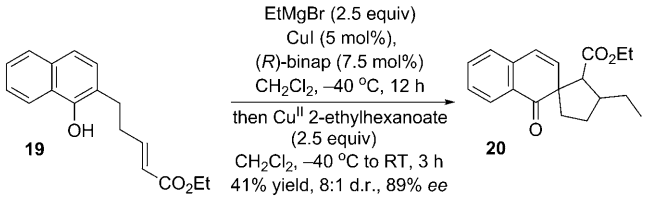
| Entry[a] | Substrate | $R^2$ | Product (d.r.[b]) | Yield [%][c] | *ee* [%][d] |
|---|---|---|---|---|---|
| 1 | **4** | Et | **6** (> 20:1) | 69 | 88 |
| 2 | **4** | hexyl | **7** (> 20:1) | 84 | 80 |
| 3 | **4** | $CH_2CH_2Ph$ | **8** (> 20:1) | 51 | 80 |
| 4 | **4** | *i*Pr | **9** (> 20:1) | 70 | 54 |
| 5 | **4** | but-3-enyl | **10** (> 20:1) | 20 | 87 |
| 6 | **4** | Me | **11** (> 20:1) | 32 | 82 |
| 7 | **4** | Ph | **12** (> 20:1) | 8 | 0 |
| 8 | **13** | Et | **14** (> 20:1) | 63 | 83 |
| 9 | **15** | Et | **16** (> 20:1) | 63 | 89 |
| 10 | **17** | Et | **18** (> 20:1) | 13 | 94 |

[a] Reaction conditions: **4** (0.25 mmol) in $CH_2Cl_2$ (0.8 mL) was added over 1 h to a solution of CuI (5 mol%), (*R*)-binap (7.5 mol%), and Grignard reagent (2.5 equiv) in $CH_2Cl_2$ (0.4 mL) at −40°C. The reaction mixture was stirred at −40°C for 4–12 h, and solid copper(II) 2-ethylhexanoate (2.5 equiv) was added to the reaction mixture and warmed to RT. [b] Determined by $^1H$ NMR analysis of the crude reaction mixture. [c] Yield of isolated product. [d] Determined by HPLC on a chiral stationary phase.

which is common for this particular Grignard reagent in the copper-catalyzed asymmetric conjugate addition reaction (entry 4). Electron-withdrawing (entry 8) or electron-donating (entry 9) groups in the 6 position of the naphthol core were both compatible under the reaction conditions, and gave the cyclized products in good yields and enantioselectivities. The use of a Grignard reagent bearing a terminal olefin (entry 5), MeMgBr (entry 6),[18] and PhMgBr (entry 7)[19] afforded the products in lower yields either as a result of the reactivity of the Grignard reagent (entries 6 and 7) or instability towards the oxidative conditions (entry 5). Low or no enantioselectivity with PhMgBr in conjugate addition reactions is also common.[1] Finally, cyclization of substrate **17** to afford a six-membered spirocyclic ring proceeded in a lower yield than the formation of a five-membered ring, but with the highest enantioselectivity (94%) achieved with this method (entry 10). Although it would appear at first glance that yields could be improved in a few cases, the high degree of structural and stereochemical complexity introduced in a single-pot operation makes this method highly valuable. Furthermore, current oxidative dearomatization processes are difficult, prone to side reactions, and are generally lower yielding.[20]

To explore the synthesis of different spirocyclic architectures using this method, we employed 1-naphthol substrate **19**, with the pendant α,β-unsaturated ester in the 2-position. The desired product **20** was obtained in 41% yield and with a diastereoselectivity of 8:1 (Scheme 5). The enantioselectivity toward the major isomer was 89% *ee*.[21]




***Scheme 5.*** Reaction of 1-naphthol-based substrate bearing a pendant α,β-unsaturated ester.

To determine the absolute configuration of the spirocyclic products, we converted the ethyl ester of bromo-substituted product **14** into the corresponding carboxylic acid **22**. Slow diffusion of hexanes into a solution of **22** in ethyl acetate gave crystals suitable for X-ray diffraction, which established the absolute configuration of **22** (Figure 1).[22]

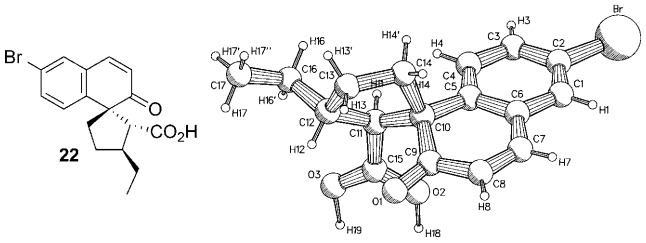



***Figure 1.*** Ball-and-stick structure of **22**. (One half of a dimeric species shown.)

The X-ray crystal structure of **22** verifies the *trans* configuration between the ethyl and carboxylic acid substituents on the five-membered ring. The vicinal proton coupling constant measured for the *trans* substituents on the cyclopentane ring of **22** is $J = 9.4$ Hz. The analogous coupling constant for **14** (the ester precursor of **22**) is $J = 9.8$ Hz. Similarly, the vicinal coupling constant of these two protons for all the spirocyclic products (**6**–**12** and **16**) have values between $J = 9.8$–$10.0$ Hz. Owing to the similarity between the NMR spectra, we assume the absolute configuration to be the same for all products **6**–**12** and **16**.

The stereoselectivity in the formation of the quaternary center can be rationalized by comparison of the three-dimensional structures of **14** and its diastereomer **23** (Figure 2). Compound **14** (Figure 2) depicts the same absolute configuration as compound **22** (Figure 1). The three-dimensional structure of **14** shows the ester substituent positioned under the aromatic ring, where minimal interaction between all substituents can be achieved. This is the preferred diastereomer from the ring-closing reaction. In contrast, the three-dimensional structure of compound **23** clearly shows that if this diastereomer were to form, there would be both an electronic and steric clash between the carbonyl oxygen atom of the ethyl ester and the carbonyl unit of the cyclohexenone moiety.

The precise mechanism of the transformation described in here is not yet known. The oxidative coupling or dimerization of enolates with copper(II) 2-ethylhexanoate has been shown by Baran and co-workers to operate via a single-electron

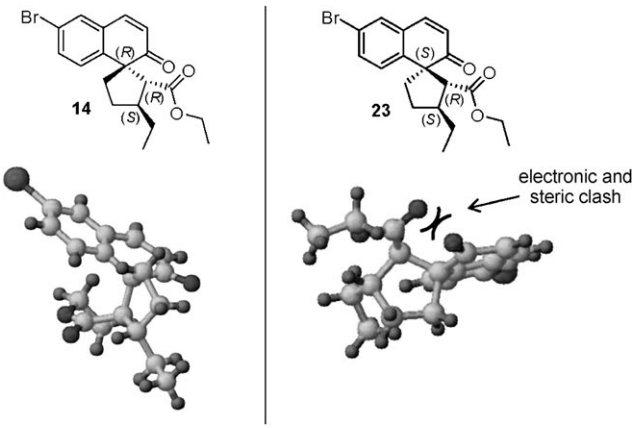



***Figure 2.*** Comparison of the 3D structures of **14** and diastereomer **23**.

transfer (SET) mechanism, where both enolates may be bound to a single copper(II) atom.[13d] Recent work by Roithová and Milko on the oxidative dimerization of naphthol, mediated by copper(II), indicates that it occurs via dinuclear clusters, where both naphthol units are activated towards dimerization by binding to their own copper(II) center through the phenoxy group.[23] On the other hand, for the oxidation and dearomatization of phenols, an ionic mechanism was proposed by Quideau and co-workers in which an oxocyclohexadienylium cation is the intermediate at which nucleophilic substitution occurs.[4b] So far, we are unable to distinguish between an ionic or radical mechanism for this reaction.

The benzofused spirocyclic cyclohexenone framework produced by this new method is present in a variety of pharmacologically active compounds (Scheme 1) such as potential ACAT inhibitors (**A**),[24] inhibitors of HIF propyl hydroxylase (**B**),[25] and RNA binding agents (**C**), which may have potential in developing therapeutic agents for HIV.[26] Our method would allow for easy access to chiral analogues of these compounds, which now either are devoid of chirality or require numerous synthetic steps to access them.

In summary, we have developed a sequential asymmetric conjugate addition/oxidative cyclization of naphthol compounds for the synthesis of highly functionalized benzofused spirocyclic cyclohexenones. A high degree of molecular complexity was achieved in this one-pot transformation, along with the formation of three contiguous stereocenters. The chiral catalyst controls the configuration of the first stereocenter, achieving *ee* values of up to 94% and the subsequent two stereocenters are formed with high diastereoselectivity (up to $>20$:1), which is governed by the first stereocenter.

## Experimental Section

General procedure for the copper(I)-catalyzed asymmetric conjugate addition/oxidative dearomatization reaction (Table 1): In an oven-dried Schlenk tube under nitrogen, CuI (2.38 mg, 13 μmol, 5 mol%) and (*R*)-binap (6.38 mg, 19 μmol, 7.5 mol%) in $CH_2Cl_2$ (0.4 mL) were stirred at RT for 15–30 min until a clear yellow solution resulted. The catalyst solution was cooled to −40°C and to this, ethylmagnesium

bromide (0.63 mmol, 2.5 equiv) was added. The reaction mixture was stirred at −40 °C for an additional 10 min before a solution of the naphthol substrate (0.25 mmol, 1.0 equiv) in $CH_2Cl_2$ (0.8 mL) was added slowly to the reaction mixture over 1 h by syringe pump. The resulting reaction mixture was stirred at −40 °C for 4–16 h until the reaction was complete (as evident by TLC). Copper(II) 2-ethylhexanoate (220 mg, 0.63 mmol, 2.5 equiv) was added to the reaction mixture in one portion at −40 °C. The mixture was further diluted with $CH_2Cl_2$ (0.5–2.0 mL) if necessary, allowed to warm to RT and stirred at RT for an additional 5–16 h. The reaction was quenched with saturated aqueous ammonium chloride (5 mL) and the organic layer was separated. The aqueous phase was extracted with $CH_2Cl_2$ (2 × 5 mL). The combined organic layers were washed with a 10% aqueous ammonia solution and brine, separated, dried over $MgSO_4$, filtered, and the solvent removed under reduced pressure. The crude product was purified by column chromatography on silica gel using pentane/diethyl ether. The *ee* value was determined by HPLC on a chiral stationary phase.

Received: March 23, 2011
Published online: May 12, 2011

**Keywords:** asymmetric catalysis · conjugate addition · dearomatization · oxidation · spiro compounds

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[19] A by-product of compound **12**, where 1,2-addition of PhMgBr has occurred on the ethyl ester moiety to afford the aryl ketone, accounts for an additional 16% of the reaction mixture.

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