DOI: 10.1002/ejoc.201000877

Catalytic Asymmetric Additions of Carbon-Centered Nucleophiles to Nitrogen-Containing Aromatic Heterocycles

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Keywords: Nitrogen heterocycles / Asymmetric catalysis / Nucleophilic addition / Bifunctional catalysis

Nearly a century after the first report of the Reissert reaction the first catalytic, asymmetric example was published. Since then there have been a small number of reports of similar reaction types: activation of nitrogen-containing aromatic rings through alkylation or acylation, followed by the addition of a carbon-centered nucleophile to the ring. These reactions place great demands on catalyst design; many of the catalysts are bifunctional, simultaneously activating both nucleophiles and electrophiles. The structures obtained from such reactions may easily be derivatized into natural products or drug-like structures. Despite the elegance of the known examples, there are still many reaction types that have not been reported.

Introduction

The addition of cyanide ion to quinoline in the presence of an acylating agent is commonly known as the Reissert reaction.[1] Since the first report over a century ago, there have been many modifications to this reaction[2] leading to its widespread use in synthesis.[3] A heterocycle reacts under these conditions since the ring is activated by covalent bond formation between the ring nitrogen and the acylating agent, permitting attack of the nucleophile to generate the new C–C bond.[4] Activation of azaaromatics (which should be taken to mean pyridines, quinolines and isoquinolines) by acylation, alkylation or *N*-oxide formation, followed by attack of a nucleophile on the ring, operate by related mechanisms which may be grouped together as "Reissert-like chemistry."[5] This review summarizes all reports of reactions involving the attack of carbon-centered nucleophiles[6] on activated aromatic nitrogen heterocycles, but specifically those cases that generate enantioenriched products catalytically (Scheme 1). The focus is on catalytic construction of the relevant stereocenters; a destructive kinetic resolution via conversion of one enantiomer of a Reissert compound to the achiral isoquinoline was reported,[7] and there have been several reports of Reissert[8] or Reissert-like[9] processes employing chiral auxiliaries.[10] The review will not deal with processes involving substrates that are

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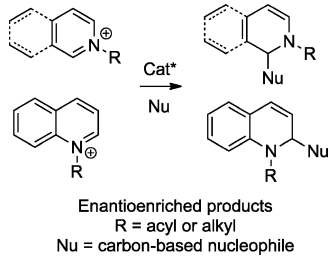
not fully aromatic such as imines[11] or dihydroisoquinolines[12] nor such substrates that are generated oxidatively in situ[13] since the challenge of the addition to azaaromatic compounds is precisely because of the extended aromaticity. The emphasis of this review is also on addition to azaaromatic systems that have been covalenty pre-activated via reaction with the ring nitrogen, since these substrates are positively charged and therefore exert specific demands on catalyst design; Alexakis has shown that it is possible to achieve catalytic, enantioselective alkylation and arylation of isoquinoline[14a] and quinoline[14b–14c] using sparteine (or other diamines) and bisoxazoline catalysts. Organolithium reagents were found to be able to add directly to the ring without addition of an activating agent, whereas other reagents such as Grignard, aluminum or zinc reagents required pre-addition of chloroformates before reaction could be observed.

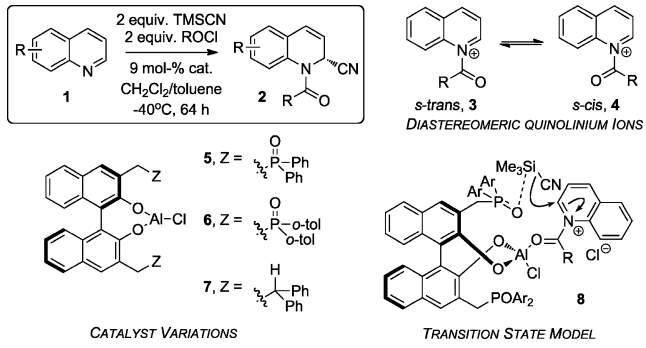


Scheme 1. Scope of this review.

It is well known that the compounds derived from azaaromatics are extremely important in medicinal and natural products research.[15] The first example of catalytic, asymmetric addition of a nucleophile to an azaaromatic was the addition of an allylzinc reagent to an acylpyridinium salt in the presence of a bisoxazoline ligand, but the product was generated with an *ee* of only 5.3%.[12a] Since then a small number of powerful methods have been invented. If there is one message this review makes clear it is this: given the importance of the structures generated by this class of reactions, it is surprising that there are still so few examples of these processes.

Shibasaki's Bifunctional Catalysis of the Reissert Reaction

In 2000 Shibasaki reported the catalytic, asymmetric Reissert reaction, 95 years after the original report of the racemic version (Scheme 2).[16] The two challenges of achieving a catalytic, asymmetric version of this reaction were noted in this seminal paper. First the reactive acylating agents employed could irreversibly derivatize any ligand (including via transfer from the reactive acylated intermediate[17]). Secondly, and more subtly, a catalyst must be able to effect an enantioselective transformation despite there being potentially two diastereomers (rotamers) of the acylated heterocycle in equilibrium, the *s-trans* (**3**) and the *s-cis* (**4**) forms.

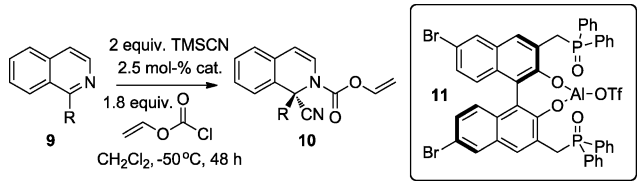


Scheme 2. Shibasaki's catalytic, asymmetric Reissert reaction.

In this case a BINOL-derived catalyst **5**, formed in situ, was found to be effective in the reaction between a range of substituted quinolines, isoquinolines and acyl chlorides with TMSCN. The catalyst is bifunctional[18] in that the Lewis acidic aluminium atom coordinates the carbonyl of the acylated heterocycle, further activating the ring to nucleophilic attack by the TMSCN which is itself activated by coordination from the Lewis basic oxygen of the phosphane oxide.[19] A range of substituents on the isoquinoline was found to be compatible with the reaction. The best acylating agent was the electron-rich (and hence less reactive) 2-furoyl chloride – presumably because this reduces the rate of the background reaction. Chemical yield and enantioselectivity were found to improve by the use of the more bulky and more Lewis-basic di-*o*-tolylphosphane oxide (**6**), while worse results were obtained with a ligand lacking Lewis basic character (**7**). These results led to the suggested dual activation mode shown (**8**), where the *s-trans* isomer of the isoquinolinium ion positions the relevant groups well for the reaction to proceed, while the *s-cis* isomer does not, allowing the catalyst to distinguish between these interconverting forms. Under optimized conditions yields and enantioselectivities were as high as 99 and 91%, respectively. Mechanistic studies suggested that the catalyst accelerates the attack of cyanide and not the acylquinolinium ion formation. While most of the studies on this catalyst system were carried out with a 9 mol-% catalyst loading, it was found as part of a synthesis of the NMDA receptor antagonist L-689,560 that the loading could be reduced to 1 mol-%. A solid-supported version of the catalyst was also shown to be approximately as effective as the homogeneous equivalent, and could be recycled three times.

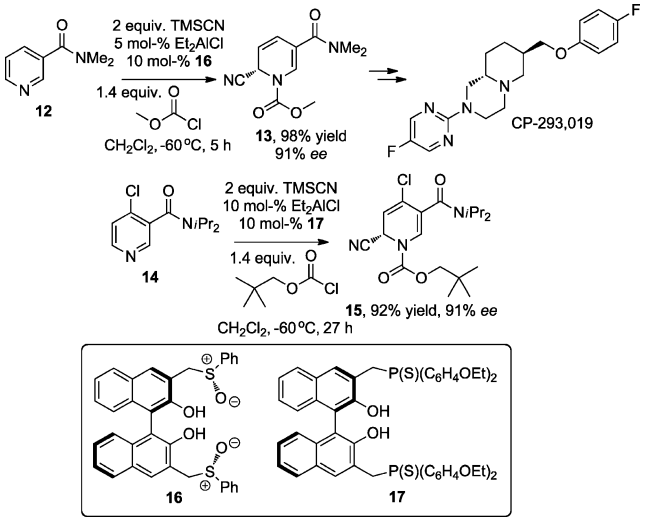
The catalytic system described above was also shown to work well with a single example of an isoquinoline, albeit one containing a methyl group in the 3 position in order to bias the position of equilibrium of the iminium ion isomers in favour of the *s-trans*, without which the enantioselectivity was low. In later studies, however, a similar catalyst system (**11**) was shown to be effective in Reissert reactions of a range of 1-substituted isoquinolines when chloroformates were employed in place of acyl halides (Scheme 3).[20] Attachment of electron-withdrawing halides to the 6,6′-positions of the BINOL moiety gave improved results, presumably through increasing the Lewis acidity of the aluminium.

Improvements could also be effected by modification of the aluminium counterion, but it was found that the use of highly electron-withdrawing counterions such as NTf_2^- or BF_4^- may promote a racemic reaction because of ion exchange: cyanide may transfer to aluminium, yielding a highly Lewis acidic silicon species that could effect a racemic Reissert reaction off the BINOL catalyst. Triflate was found to be the optimal counterion in these studies, giving products in excellent yields and enantioselectivities and the resulting methodology was used in the first asymmetric synthesis of several pharmaceutically important compounds.



Scheme 3. Asymmetric Reissert reaction of 1-substituted isoquinolines.

A related BINOL-derived bifunctional catalyst was employed for the Reissert-like reaction of pyridines.[21] The previously-employed catalysts described above did not work well with this alternative substrate, but modification of the Lewis base in the catalyst to a sulfoxide (in **16**) gave greatly improved results for the nicotinic amide substrates (e.g. **12**, Scheme 4), with good yields, enantioselectivities and regioselectivities (1,2- vs. 1,6-addition). One of the products of this process was taken on to the enantioenriched dopamine antagonist CP-293,019. The stoichiometry of metal/ligand employed in the Reissert step was explored and it was found that catalysts composed of metal/ligand ratios greater than unity were more effective – in the case shown bimetallic complexes composed of 5 mol-% Et_2AlCl and 10 mol-% ligand **16** were found to be very effective. However, for other substrates containing a halogen in the 4-position (designed

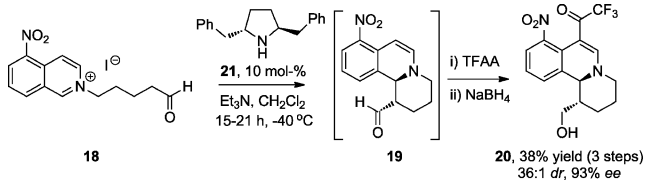


Scheme 4. Catalytic, enantioselective Reissert reaction of pyridines.

for further synthetic elaboration) a ligand containing a phosphane sulfide in a 1:1 ratio with added metal was found to be optimal, generating product **15** very efficiently.

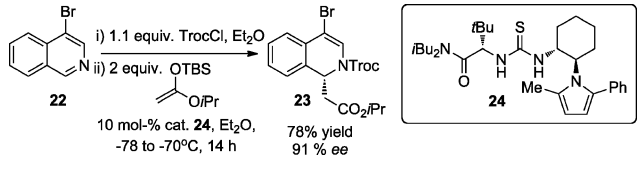
Organocatalytic Addition Reactions

An organocatalytic intramolecular nucleophilic addition of aldehydes to isoquinolinium ions was reported by Jørgensen in 2005 (Scheme 5).[22] The asymmetric step was mediated by a chiral pyrrolidine derivative **21**, and the initially-formed aldehydes **19** were transformed into isolable species **20** through reaction of the enamine and reduction of the aldehyde. A range of substituents in the isoquinoline was tolerated (with the exception of electron-donating methoxy groups), and the optimal results were obtained after careful refinement of catalyst and base giving products with sometimes excellent *ee* and *dr*. An intermolecular version of this reaction had earlier proven to be intractable. A mechanism for the intramolecular process was proposed that relied on a stabilizing cation-π interaction between isoquinolinium ion and a phenyl group in the catalyst (tethered as part of the reactive enamine) in the transition state.

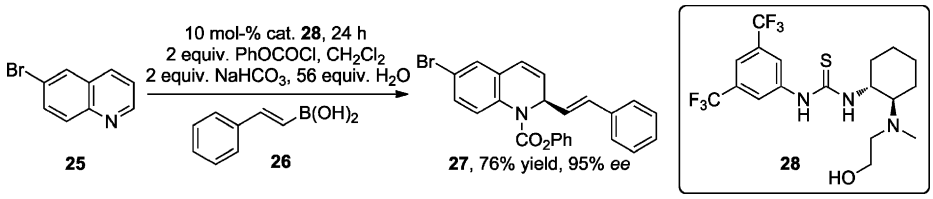


Scheme 5. An example of Jørgensen's intramolecular, organocatalysed addition of aldehyde-derived enamines to activated isoquinolines (the stereochemistry shown is by inference from related example).

An intermolecular, organocatalytic addition of enolates to *N*-acylisoquinolines was discovered by Jacobsen (Scheme 6).[23] Thioamide **24** was found to catalyze the addition of a silyl ketene acetal to acylated isoquinolines in good to excellent yields and enantioselectivities; the *ee* values obtained were sensitive to the nature of the solvent and acylating agent, with chloroformates performing better than acetyl chloride. It was found that the double bond in the resulting dihydroisoquinoline derivatives could be easily reduced and the carbamate cleaved to gain 1-substituted tetrahydroisoquinolines with no loss of enantiomeric excess. It was speculated that the catalyst acts by hydrogen bonding interactions with the carbonyl group of the substrate, which potentially exists as a neutral chloroamide structure rather



Scheme 6. Jacobsen's thioamide-catalyzed addition of enolates to acylated isoquinolines.



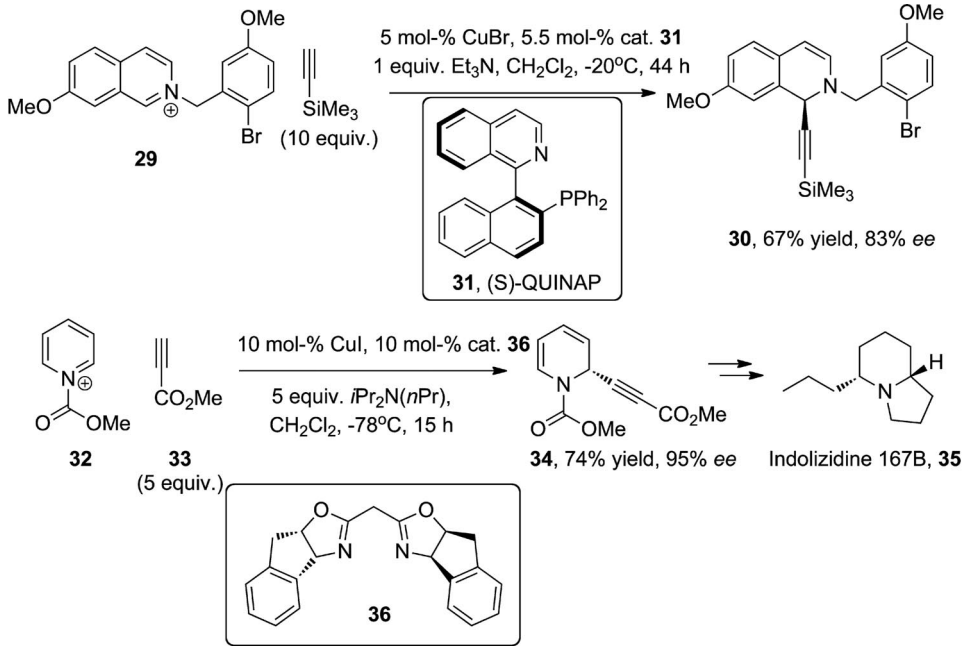
Scheme 7. Takemoto's catalytic, asymmetric Petasis reaction on quinolines.

than as an ion pair *N*-acyliminum ion. The nature of the substrate, and the catalyst's interactions with it, are important considerations for future rational catalyst design.

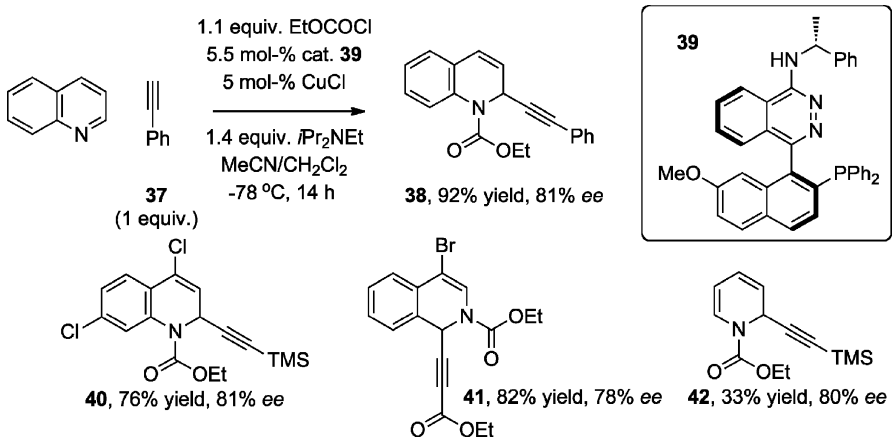
Another thiourea catalyst containing a pendant hydroxy moiety was discovered by Takemoto that accelerated an enantioselective Petasis reaction (Scheme 7).[24] Here the nucleophile attacking the activated aromatic ring comes from a boronate that is generated in situ. The ability of the hydroxyl of the catalyst **28** to deliver the vinyl group by forming the boronate probably accounts for the lack of any competing 1,4-addition to the quinlione ring. When a similar catalyst lacking the hydroxy group was employed, a low yield was obtained of nearly racemic product. Once again chloroformates were found to be effective activating agents for the ring. Electronic substitution of the aromatic ring of the boronic acid had a substantial effect on the rate of reaction, but not the stereoselectivity of reaction. In general across a wide range of substrates the levels of stereocontrol achieved were very high.

Addition of Alkynes

The first report of the catalytic, asymmetric addition of terminal alkynes to azaaromatics was a single example described by Schreiber employing a QUINAP catalyst (**31**) with copper(I) bromide in the addition of trimethylsilylacetylene to an alkylated isoquinoline (Scheme 8).[25] The report is mainly concerned with similar additions to dihydroisoquinolines, which proceed more quickly than for the fully aromatic substrate, and frequently with improved yields and enantioselectivities. The first catalytic, enantioselective addition of terminal alkynes to acylated azaaromatics was also a copper-catalyzed process, reported by Ma in 2007.[26] Bidentate bisoxazoline ligands such as **36** gave good stereoinduction in the reaction between ethyl propiolate and acylpyridinium salts derived from chloroformates, with yields which depended heavily on the nature of the chloroformate used. Five equivalents of chloroformate and alkyne were required for good results to be



Scheme 8. Copper-catalyzed additions of terminal alkynes to alkylisoquinolinium and acylpyridinium salts (the stereochemistry shown for compound **30** is by inference from related example).



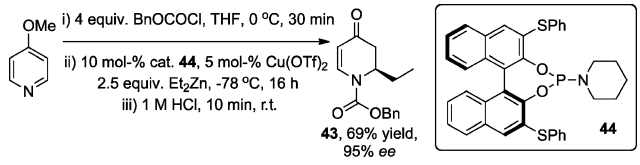
Scheme 9. Copper-catalyzed enantioselective addition of terminal alkynes to pyridines, quinolines and isoquinolines.

obtained. A conjugated carbonyl group (i.e. position 3 of the terminal alkyne) was found to be required for high enantioselectivity. In no cases was competing 1,4-addition observed. Two of the addition products were further elaborated into enantioenriched piperidine-based alkaloids, such as **35**.

A similar reaction was reported by Arndtsen in which the catalytic, enantioselective addition of terminal alkynes was performed on a wider range of substrates, and with a more favourable stoichiometry of the reagents (Scheme 9).[27] Chloroformates were once again employed as the activating agent, with copper(I) mediating the addition of both electron withdrawing and electron donating alkynes. Several ligands were evaluated, with QUINAP and PINAP ligands providing good results, but the authors synthesized new ligands based on the latter scaffold, with ligand **39** giving the optimal results. Notably 1,4-addition was never observed, even when the starting material contained a halogen in that position (to give products **40** and **41**, for instance). Pyridines, quinolines and isoquinolines generally all reacted well under the optimized conditions.

Addition of Organozinc Reagents

Broadening the scope of copper-catalyzed asymmetric additions to activated pyridines, the direct alkylation of the ring was recently reported, employing organozinc reagents and phosphoramidite ligands (Scheme 10).[28] A number of different parameters were explored in these reactions, with the use of benzyl chloroformate, THF as solvent and copper(II) triflate as copper source proving optimal. As with Ma's reaction, an excess of chloroformate and organozinc (2.5 equiv.) were found to be necessary to give good results. The temperature of the reaction was a key variable, in that room temperature reactions gave improved results over low-temperature reactions, but a compromise of 0 °C with excess chloroformate gave the highest yields and enantioselectivities, presumably because these conditions pushed the position of equilibrium in the pyridine acylation towards the pyridinium salt. The best results were obtained by the addition of the salt to a solution of catalyst. Several organozinc reagents were shown to be effective in this reaction (the exception being dimethylzinc) and a short formal synthesis of (*R*)-coniine was demonstrated.



Scheme 10. Direct catalytic, asymmetric alkylation of pyridines.

Conclusions

Several powerful methods have been developed for the catalytic, asymmetric addition of nucleophiles to pyridines, quinolines and isoquinolines that have been pre-activated through covalent bond formation by the ring nitrogen atom. Although several carbon-centered nucleophiles have been employed, there is still limitation in the scope of such nucleophiles. While there have been reports of alkylzinc reagents as nucleophiles there are no reports of sp^2-centered (e.g. aromatic) organometallic nucleophiles. There are reports of enolate equivalents and cyanide being used, but no reports to date of nitroalkanes being employed in Henry-type reactions. There is only one report of an intramolecular addition reaction. There is also significant limitation in the nature of the electrophile, both in terms of the aromatic heterocycle employed (few examples of pyridines, and no examples of related rings such as pyrazines) and in terms of the activating group (which in almost all cases needs to be a chloroformate for high yields and enantioselecivities).

In many, possibly all, cases, catalysts are bifunctional, in that further activation of the cation takes place with concomitant activation of the nucleophile. While this places extra demands on catalyst design, it is likely that such systems

lead to the best results through suppression of competing reaction pathways, such as (the usually undesired) 1,4-addition. The relatively small number of successful catalytic systems discovered to date is perhaps testament to the difficulty of controlling the reactivity of what are relatively strong electrophiles and nucleophiles in one pot without catalyst degradation. Given the synthetic utility of the structures generated, it is likely this area will see continued expansion in the near future.

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Received: June 17, 2010
Published Online: September 3, 2010

