Heterocycle Synthesis

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Catalytic Asymmetric Synthesis of Substituted Morpholines and Piperazines**

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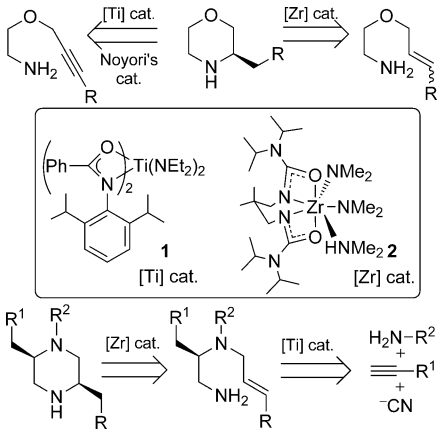
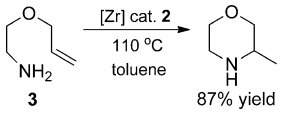
Hydroamination is a powerful C–N bond forming reaction that has been used for over two decades in the preparation of heterocyclic compounds.[1–5] Indeed, various pyrrolidine and piperidine alkaloids, and derivatives thereof, have been prepared using a broad range of hydroamination reaction conditions.[6] However, the extension of such strategies to biologically active heterocycles with more than one heteroatom, such as morpholines and piperazines, has only recently been achieved using late transition metal intramolecular hydroamination or carboamination catalysts.[7] Early transition and lanthanide metals, to the best of our knowledge, have never been reported for intramolecular transformations demanding such functional group tolerance. Herein, we disclose a one-pot enantioselective synthesis of 3-substituted morpholines and a modular diastereoselective synthesis of 2,5-substituted piperazines (Scheme 1) using recently developed inexpensive and easily accessed early transition metal amidate[8] (**1**) and/or ureate[9] (**2**) complexes for the assembly of the C–N bonds in these heterocycles. Most importantly, the synthetic approach adopted generates desirable biologically active heterocyclic products[10] in a modular fashion with high atom economy and excellent stereoselectivity with minimal protection/deprotection protocols.



Scheme 1. Hydroamination with N,O-chelated group 4 precatalysts for the synthesis of 3-substituted morpholines and 2,5-substituted piperazines. Noyori's cat. = [{(*S*,*S*)-Ts-dpen}(*p*-cymene)RuCl].

The morpholine moiety is a common structural motif in medicinal chemistry. Although it is a very popular building block for the pharmaceutical industry, the number of commercially available, enantiopure substituted morpholines is quite limited. Established synthetic routes to these compounds generally involve the stepwise synthesis of enantioenriched β-amino alcohols,[11] which are typically derived from naturally occurring chiral amino acids or asymmetric methods, such as the Sharpless aminohydroxylation.[12] Enantioenriched 2-substituted morpholines can be assembled using Pd-catalyzed allylic substitution reactions with good *ee* values (up to 90%).[13] More recently, diastereoselective Pd-catalyzed routes for disubstituted morpholines have been achieved by the carboamination or hydroamination of ether containing aminoalkenes.[7,11f,14] Through the use of enantioenriched β-amino alcohols, chiral morpholines could be obtained with excellent *ee* values (up to 99% *ee*).[11c–e,g] However, there are no reported catalytic enantioselective syntheses of 3-substituted morpholines using prochiral substrates with hydroamination as the key C–N bond forming step.

Although late transition metal catalysts are noted for their functional group tolerance,[7c,11f] initial experiments in our program focused on the use of group 4 precatalysts, which are known to be oxophilic. Gratifyingly, the simple ether-containing aminoalkene **3** could be cyclized with previously reported Zr–ureate precatalyst **2** in high yield (Scheme 2). To the best of our knowledge, such aminoalkene cyclohydroamination substrates with heteroatoms in the backbone have not been reported to react with early transition or rare earth metal hydroamination precatalysts. Unfortunately, efforts to realize asymmetric hydroamination of **3** with a previously reported chiral version of **2** resulted in only traces of product.[15,16]



Scheme 2. Synthesis of 3-methyl morpholine.

Although enantioselective alkene hydroamination is a long-standing challenge in the field, asymmetric imine reduction of readily accessible cyclic imines could be an attractive option.[17] By using sequential regioselective alkyne hydroamination and asymmetric transfer hydrogenation in

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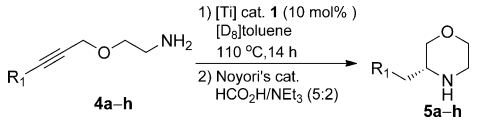
a one-pot synthesis, the targeted chiral 3-substituted morpholines can be prepared. Herein, we show that Ti-amidate precatalyst **1** can be used for regioselective intramolecular hydroamination with functionalized ether-containing aminoalkynes, and we also demonstrate that this N,O-chelated catalyst is suitable for applications in sequential, one-pot catalytic approaches using the Noyori–Ikariya transfer hydrogenation catalyst, [{(*S*,*S*)-Ts-dpen}(η^6-*p*-cymene)RuCl] (Ts-dpen = (1*S*,2*S*)-*N*-*p*-toluenesulfonyl-1,2-diphenylethanediamine).[17] Using this approach, 3-substituted morpholines (**5**) can be obtained in good yield with excellent enantiomeric excesses (Table 1).

Table 1: One-pot enantioselective synthesis of 3-substituted morpholines.

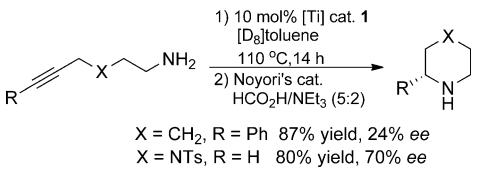


Entry	R^1	Product	Yield [%][a]	*ee* [%][b]
1	H	**5a**	65%	>99%[c]
2	Et	**5b**	78%	97%[c]
3	$BnO(CH_2)_2$	**5c**	79%	97%
4	*t*Bu	**5d**	74%	74%[c]
5	Ph	**5e**	78%	98%
6	*p*-BrC_6H_4	**5f**	80%	97%[e]
7	C_6F_5	**5g**	77%	98%
8	2-Py	**5h**	66%[d]	99%

[a] Yield of crude isolated product (>95% pure by NMR spectroscopy). [b] Determined by supercritical fluid chromatography. [c] Determined after derivatization with *p*-toluenesulfonyl chloride. [d] Yield of isolated product after flash chromatography. [e] *ee* values can be increased to >99% *ee* by recrystallization of the oxalate salt. Bn = benzyl, Noyori's cat. = [{(*S*,*S*)-Ts-dpen}(*p*-cymene)RuCl], Py = pyridyl.

For example, using the simplest aminoalkyne **4a** in combination with precatalyst **1** (10 mol%), regioselective cyclohydroamination proceeds smoothly at 110°C overnight to give the desired imine intermediate and its enamine isomer. Using a one-pot method, the crude reaction mixture is then treated with a dimethylformamide (DMF) solution of [{(*S*,*S*)-Ts-dpen}(η^6-*p*-cymene)RuCl] (1 mol%)[17] and subsequently a solution of formic acid in NEt_3 is added. The reaction mixture is left to stir overnight before isolating the crude product using a simple aqueous wash of the acidified morpholine product, followed by treatment with base before extraction of the desired product with ethyl acetate. Upon removal of volatiles, product **5a** was obtained in good yield (65%, reduced yield owing to volatility of the product) as a crude product with 98% *ee* (Table 1, entry 1). Using this same general procedure, substrate scope was explored and good yields and high enantioselectivities were obtained in almost all cases. Notably, alkyl substituents with varying steric bulk are tolerated (entries 2–4) and most importantly, further functional groups can be incorporated (entry 3). Aryl substituted substrates are particularly well suited for this method (entries 5–8). Entry 6 highlights an advantage of early transition metal catalysts: a substrate containing an aryl bromide is used and yields a morpholine product that could be further derivatized using Pd-catalyzed cross-coupling methods. Medicinally relevant fluorinated substituents can be incorporated (entry 7) and even strong electron-donor/hydrogen-bonding substituents, such as the pyridine moiety of entry 8, do not inhibit these catalyst systems.

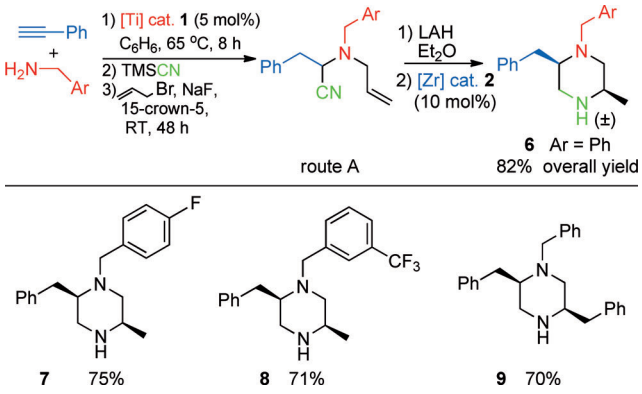
The described method, which avoids column chromatography, yields 3-substituted morpholines as yellow-brown oils. Further derivatization of these crude products to the oxalate salt allows for recrystallization, which removes any trace impurities and also increases the *ee* from 97% to 99.8% (entry 6).[15] Thus, this method results in the one-pot synthesis, isolation, and purification of 3-substituted morpholines with excellent *ee* values while avoiding chromatographic separations. Remarkably, the outstanding stereoselectivity observed is in contrast to previous literature reports for similar simple cyclic imines.[18] Indeed, our one-pot synthetic method can be used to prepare piperidines and piperazines to give heterocycles in high yield, but only low to modest *ee* values are observed (Scheme 3). The mechanistic rationale for the outstanding *ee* values obtained specifically for morpholines is an area of ongoing investigation.



Scheme 3. Enantioenriched heterocycle synthesis. Noyori's cat. = [{(*S*,*S*)-Ts-dpen}(*p*-cymene)RuCl].

The synthesis of the requisite aminoalkyne starting materials requires multistep syntheses, as has been previously reported for diastereoselective late transition metal approaches.[19] However, with proof of concept established for the use of Ti–amidate precatalyst **1** in one-pot reactions, as well as the successful ring closure of oxygen-tethered aminoalkenes with Zr–ureate precatalyst **2**, a novel strategy that takes advantage of these attractive reactivity features in the synthesis of disubstituted piperazines was envisaged (Scheme 4). This efficient approach uses commercially available benzylamines, allyl bromides, and alkyne starting materials to assemble 2,5-substituted piperazines, while avoiding the use of amino acid derivatives and protection/deprotection sequences during synthesis.

2,5-Asymmetrically substituted piperazines are traditionally prepared from amino acids to give diketopiperazines, which, upon reduction, yield the desired heterocyclic compounds.[20] Although attractive for the preparation of heterocycles derived from naturally occurring amino acids, this approach requires sequential protection/deprotection steps and stoichiometric amino acid coupling reagents.[21] Furthermore, these approaches do not facilitate the assembly of heterocycles with a broad range of substituents that may be desired for exploring structure/biological activity relationships. Herein, we take advantage of our previously reported strategy for a one-pot, modified Strecker reaction with

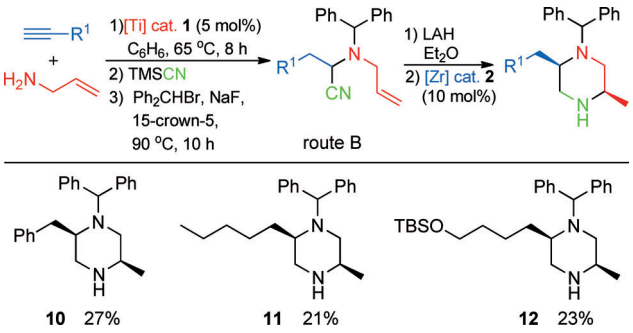


Scheme 4. Modular, diastereoselective synthesis of 2,5-disubstituted piperazines from commercially available starting materials. Yields shown are overall yields of isolated product using alkyne as the limiting reagent. LAH = lithium aluminum hydride, TMS = trimethylsilyl.

TMSCN,[22] to give TMS-protected α-aminonitriles within 12 h. Regioselective alkyne hydroamination with Ti–amidate precatalyst **1** is used to form the reactive aldimine intermediate in situ[8a] before C–C bond formation with a $^{-}$CN nucleophile and subsequent one-pot installation of an allyl group in excellent yield (Scheme 4). This 3-step, one-pot synthetic sequence results in the preparation of protected α-aminonitriles in excellent yield (83–89%), before selective nitrile reduction to give the desired substituted diaminoalkene substrates required for ring-closure using Zr–ureate intramolecular aminoalkene hydroamination precatalyst **2**.

Gratifyingly, as observed by ^{1}H NMR spectroscopy, diastereoselective ring-closure results in only one product, piperazine **6**.[15] For example, upon ring closure only one diagnostic doublet for the methyl substituent α to the nitrogen atom is observed at a chemical shift of approximately 1.1 ppm, while the respective olefinic proton signals at 6.0 ppm are lost. No other signals are observed for the alternative diastereomer and the formation of a single diastereomer has been further confirmed by GC-MS analysis of the final reaction mixture. Piperazine **6** is then isolated and purified by column chromatography as a pale yellow oil in 92% yield from the intermediate α-aminonitrile. Thus, from commercially available benzyl amine, phenylacetylene, and allyl bromide in only five steps and with three purifications piperazine **6** is prepared in 82% overall yield. This compares favorably with optimized traditional syntheses from commercially available protected amino acid precursors requiring five steps and four purifications (including coupling and deprotection steps with substantial by-product formation) to give products in 40–50% overall yield.[20a,23] Furthermore, we envisage that this general strategy can be extended to stereospecific syntheses and more highly substituted piperazines by using substituted allylic starting materials.

To verify the potential broader application of this modular approach, we needed to carry out preliminary functional group tolerance investigations of our N,O-chelated precatalysts **1** and **2.** Modular route A (Scheme 4) can accommodate fluorinated substituents (compounds **7** and **8**), which are commonly targeted in medicinal chemistry. Most importantly, compound **9** shows that this route is not limited to the synthesis of α-methyl substituted piperazines, and more challenging internal alkenes can be used for the cyclohydroamination reaction.[9a] Attempts to prepare *N*-benzhydryl substituted piperazines **10**–**12**, a common substituent for application in medicinal chemistry, using route A could not be achieved owing to ineffective alkylation with the allylbromide electrophile in the last step of the one-pot α-aminonitrile synthesis. Presumably, this is due to the increased steric bulk of the benzhydryl substituted amine versus the nucleophilic benzyl-substituted amine intermediate implicated in Scheme 4. However, the flexible and modular approach featuring the use of functional-group-tolerant and regioselective Ti-amidate precatalyst **1**[8a] can be used to advantage (Scheme 5). In route B, allyl amines rather than benzyl



Scheme 5. Flexible, modular, diastereoselective synthesis of *N*-benzhydryl substituted 2,5-substituted piperazines from commercially available starting materials. Yields shown are overall yields of isolated product using alkyne as the limiting reagent. LAH = lithium aluminum hydride, TBS = *tert*-butyldimethylsilyl, TMS = trimethylsilyl.

amines are used as hydroamination substrates,[24] and the benzhydryl substituent rather than the allyl moiety is installed through nucleophilic substitution. Thus, the more sterically demanding targeted benzhydryl α-aminonitrile intermediates can be assembled, albeit in reduced yields (23–29%). Gratifyingly, the change in the *N*-substituent does not affect the diastereoselectivity of the ring closure step, as was verified by the synthesis of piperazine **6** by both routes A and B.[25] As shown, route A is the higher yielding approach, whereas route B permits the incorporation of benzhydryl protecting groups, simple alkyl chains, and even protected alcohol substituents (**11** and **12**). Notably, compounds **11** and **12** cannot be derived from naturally occurring amino acids and thus this route permits facile diastereoselective preparation of these otherwise challenging heterocyclic targets.

The relative stereochemistries of 2,5-substituents on the piperazine scaffold are known to be difficult to conclusively assign by NMR spectroscopy.[7b,26] To rigorously assign the relative stereochemistry of the final product, X-ray quality crystals were obtained for the solid product 2-benzyl-5-methyl-*N*-(*p*-fluorobenzyl)piperazine (**7**). Analysis of these crystals confirmed the *cis* orientation of the 2,5-substituents.[15]

Whereas all products are assigned a *cis* orientation by analogy to structurally characterized compound **7**, further evidence supporting this assignment has been obtained through the independent syntheses of *cis*-piperazines **6**, **9**, and **10** using commercially available amino acid precursors and published diketopiperazine methods.[15]

In summary, we have shown that group 4 catalysts, which are often overlooked for application in organic synthesis owing to their perceived lack of functional group tolerance, can be used for the efficient preparation of heterocycles common to the medicinal chemistry community. Using Ti catalyst **1** for intramolecular hydroamination, coupled with enantioselective reduction using the Noyori–Ikariya catalyst, chiral 3-substituted morpholines were isolated in high yield with excellent enantioselectivities. We have also developed a flexible and modular approach for the diastereoselective synthesis of 2,5-asymmetrically substituted piperazines from readily available terminal alkynes, primary amines, and allyl or benzyl bromides. Synthetic advances, mechanistic insights, and applications in medicinal chemistry will be disclosed in due course.

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