Asymmetric Catalysis

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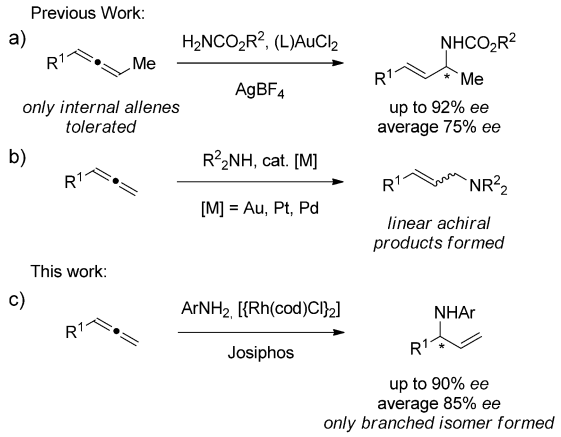
Enantioselective Rhodium-Catalyzed Synthesis of Branched Allylic Amines by Intermolecular Hydroamination of Terminal Allenes**

*Michael L. Cooke, Kun Xu, and Bernhard Breit**

α-Chiral allylic amines are an important, versatile class of building blocks for organic synthesis that can be employed in the formation of a diverse array of nitrogen-containing molecules, and many strategies for their enantioselective synthesis have been developed.[1] Several of the most general methods (for example, allylic substitution, the Overman rearrangement, or imine vinylation) require either activated substrates and/or stoichiometric amounts of either a leaving group or an organometallic reagent, which makes them less attractive in terms of atom and/or step economy.[2,3] Catalytic enantioselective intermolecular hydroamination is a highly attractive, atom economical approach for the synthesis of non-racemic amines and their derivatives, and has been the subject of much attention.[4] Despite extensive effort, efficient methods for catalytic enantioselective intermolecular hydroamination are rare.[5] Although the enantioselective intermolecular hydroamination of allenes would be an efficient method for the synthesis of α-chiral allylic amines,[6,7] only one example has been reported, which requires internal allenes, has a limited scope, and provides only moderate levels of enantioselectivity (Scheme 1 a).[8,9] To date, the enantioselective intermolecular hydroamination of mono-substituted allenes has not been reported, owing to the propensity of many hydroamination catalysts to form achiral products (either imines or linear allylic amines) from such substrates (Scheme 1 b).[10] Herein, we report the first example of the enantioselective intermolecular hydroamination of mono-substituted allenes, producing versatile branched allylic amines with perfect regioselectivity, high yield and good enantioselectivity (Scheme 1 c).

During the course of our investigations into the atom-economic functionalization of terminal alkynes and allenes,[11] we identified a rhodium-catalyzed method to access valuable, enantioenriched branched allylic esters from terminal allenes and carboxylic acids.[11b] We hypothesized that an appropriate nitrogen nucleophile could permit the synthesis of branched allylic amines in an analogous manner.[12]



Scheme 1. Intermolecular hydroamination of allenes. For the structure of Josiphos, see Table 1. cod = 1,5-cyclooctadiene, L = ligand.

Our preliminary studies in this area focused on the identification of an appropriate nitrogen nucleophile. After testing a range of nucleophiles and conditions (see the Supporting Information for details), we were pleased to identify that a mixture of $[\{Rh(cod)Cl\}_2]$ (cod = 1,5-cyclooctadiene) and DPEphos (**3**; see Table 1 for structure) in a mixture of 1,2-dichloroethane (DCE) and ethanol (1:2) effectively catalyzed the hydroamination of cyclohexylallene with aniline, affording the desired branched allylic amine **2a** exclusively in 69% yield (Table 1, entry 1). With an effective method for the racemic intermolecular hydroamination in hand, we then tested a range of chiral bidentate phosphine ligands in the reaction (entries 2–12). Whereas most of the ligands tested resulted in poor yield and/or enantioselectivity (entries 2–4), Josiphos ligand **7a** afforded **2a** in a promising 33% yield and 66% *ee* (entry 5). Other Josiphos ligands were tested and, pleasingly, **7c** afforded **2a** in 83% yield with 78% *ee* (entry 7). We were able to reduce the catalyst loading to 1 mol% in combination with 3 mol% of the ligand without significant detriment to either the yield or enantioselectivity of the reaction (entry 8). Further screening revealed that a 9:1 ratio of DCE:EtOH is optimal (entry 9). In contrast to the reaction using ligand **3**, the reaction does proceed in the absence of EtOH with **7c**, although with reduced yield and enantioselectivity. We determined that the ratio of allene to aniline can be reduced to 1.2:1 (entry 11), with no detrimental effects. Although the reaction still proceeds with only 0.1 mol% of the catalyst precursor, the yield and enantiomeric excess are somewhat reduced (entry 12). A single recrystallization of the HCl salt allows **2a** to be obtained in

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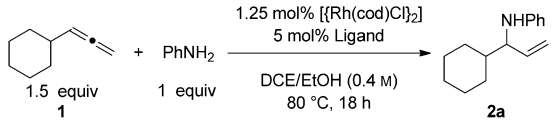
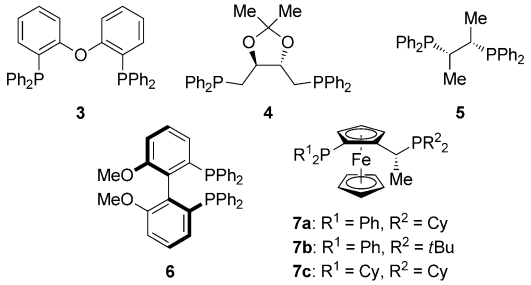
Table 1: Optimization of enantioselective hydroamination.



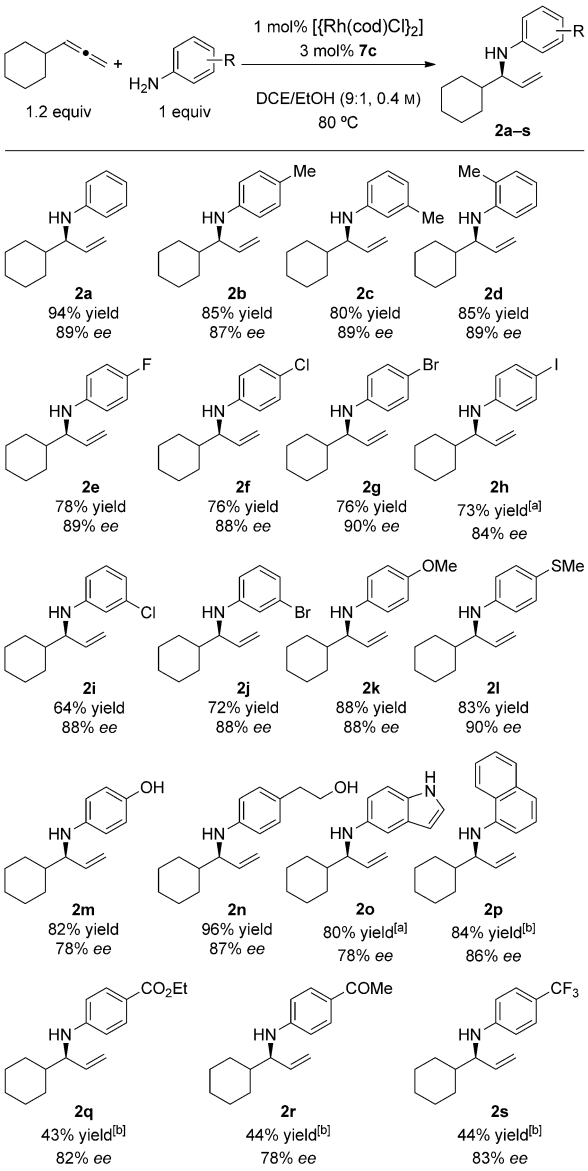
Entry	Ligand	DCE/EtOH	Yield [%][a]	*ee* [%][b]
1	**3**	1:2	69	–
2	**4**	1:2	26	54
3	**5**	1:2	11	33
4	**6**	1:2	55	32
5	**7a**	1:2	33	66
6	**7b**	1:2	0	–
7	**7c**	1:2	83	78
8[c]	**7c**	1:2	85	74
9[c]	**7c**	9:1	95	89
10	**7c**	1:0	63	84
11[c,d]	**7c**	9:1	94	89
12[d,e]	**7c**	9:1	50	80(98)[f]

[a] Yield of isolated product. [b] Determined by HPLC analysis on a chiral stationary phase. [c] Using [{Rh(cod)Cl}$_2$] (1 mol%) and ligand (3 mol%). [d] Allene/amine ratio was 1.2:1. [e] Using [{Rh(cod)Cl}$_2$] (0.1 mol%) and ligand (0.3 mol%). [f] Value in parentheses is the *ee* obtained after a single recrystallization of the HCl salt.



98% *ee*, which demonstrates the utility of this method for the synthesis of enantiopure allylic amines.

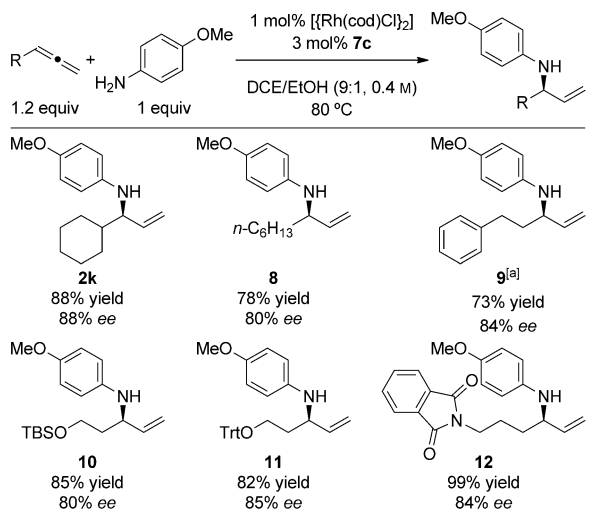
Following the establishment of optimized conditions, we investigated the scope of anilines in the enantioselective intermolecular hydroamination reaction (Scheme 2). A wide range of substituted anilines were suitable substrates for the reaction, with good to excellent yields and good enantiomeric excesses observed in most cases. Alkyl substituents were well tolerated in all positions (**2b–d**). A range of halide-substituted anilines could be coupled, providing allylic amines suitable for a range of cross-coupling reactions (**2e–j**). A variety of other *para*-substituted anilines were also compatible, including *p*-anisidine, the product of which (**2k**) can be readily deprotected to afford the free allylic amine.[13] Unprotected alcohols and phenols are also compatible with this method (**2m**,**n**), although slightly reduced enantioselectivity was observed for phenol **2m**. Other aromatic amines were also suitable substrates for the reaction, with 5-aminoindole and 1-naphthylamine affording the corresponding allylic amines **2o** and **2p** in good yields and enantiomeric excesses. Electron-deficient anilines are more challenging substrates and require slightly elevated temperatures (100°C vs. 80°C); however, products bearing esters, ketones, and trifluoromethyl groups (**2q–s**) can be obtained in moderate yields with slightly reduced enantiomeric excesses.



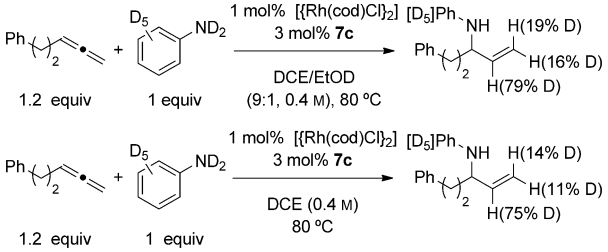
Scheme 2. Scope of anilines in the enantioselective rhodium-catalyzed hydroamination. [a] Reaction carried out at 70°C. [b] Reaction carried out at 100°C.

We then investigated the scope of the allene coupling partner (Scheme 3). The terminal allenes used were readily prepared in one or two steps from commercially available starting materials (see the Supporting Information for details). As well as α-branched allenes, linear alkyl-substituted allenes were suitable substrates (**8** and **9**). Protected alcohols were also tolerated in the reaction (**10** and **11**), although slightly lower enantiomeric excess was observed with TBS protected alcohol (**10**). A phthalimide bearing allene was also compatible, affording differentially protected diamine **12** in excellent yield and good enantiomeric excess.

Isotopic labeling experiments were carried out with [D_7]aniline (Scheme 4).[14] In accordance with our observations on the addition of carboxylic acids to allenes,[11b] deuterium incorporation was observed at all positions of the alkene.

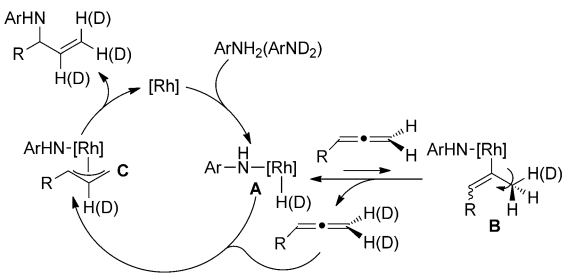


Scheme 3. Scope of allenes in the enantioselective rhodium-catalyzed hydroamination. [a] Absolute configuration determined by comparison with known compound. TBS = *tert*-butyldimethylsilyl, Trt = triphenylmethyl.



Scheme 4. Isotopic labeling experiments with [D_7]aniline. DCE = 1,2-dichloroethane.

On the basis of these observations, a plausible mechanism is as follows (Scheme 5). Oxidative addition of Rh^I to aniline can generate Rh^{III} complex **A**.[12,15] Hydrometalation of the terminal allene double bond to afford σ-vinyl-Rh species **B**, followed by β-hydride elimination could explain the deuterium incorporation at the terminal positions. Hydrometalation of the more substituted double bond could generate π-allyl-Rh complex **C**, which, after reductive elimination (or external aniline attack), could generate the observed branched allylic amine. The regioselectivity of this step is in accordance with that observed previously for other π-allylrhodium complexes.[16]



Scheme 5. Proposed mechanism for the rhodium-catalyzed allene hydroamination.

In summary, we have developed the first method for the enantioselective intermolecular hydroamination of terminal allenes with anilines. A broad range of valuable branched allylic amines can be isolated in excellent yields and good enantioselectivities in an atom-economic manner using a catalyst derived from a commercially available rhodium source and a Josiphos ligand. Further studies will focus on mechanistic investigations and the extension of this method to other nucleophiles.

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Communications

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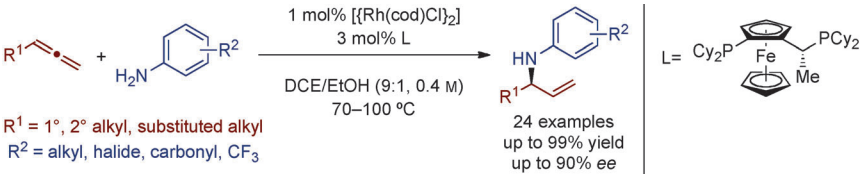

Branching out: The rhodium-catalyzed enantioselective hydroamination of monosubstituted allenes with anilines permits the atom-economic synthesis of valuable branched allylic amines. In contrast to previous linear selective allene hydroaminations, a Rh^{I}/Josiphos catalyst system (see scheme) allows branched allylic amines to be obtained with perfect regioselectivity, high yield, and good enantioselectivity.