Hydroamination Reactions Hot Paper

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Anti-Markovnikov Hydroamination of Racemic Allylic Alcohols to Access Chiral γ-Amino Alcohols

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Abstract: *A ruthenium-catalyzed formal anti-Markovnikov hydroamination of allylic alcohols for the synthesis of chiral γ-amino alcohols is presented. Proceeding via an asymmetric hydrogen-borrowing process, the catalysis allows racemic secondary allylic alcohols to react with various amines, affording enantiomerically enriched chiral γ-amino alcohols with broad substrate scope and excellent enantioselectivities (68 examples, up to > 99 % ee).*

Chiral γ-amino alcohols serve as key intermediates for the synthesis of many drug and biologically active molecules. Examples are seen in the drug molecules (*S*)-Duloxetine, (*R*)-Atomoxetine and Fluoxetine (Figure 1 a).[1] They can also be employed as chiral auxiliaries and ligands for asymmetric synthesis and catalysis.[2] A number of methods have been developed for the synthesis of enantiomerically enriched chiral γ-amino alcohols,[3] with asymmetric hydrogenation of β-amino ketones[4] being one of the most favored choices. Asymmetric hydroamination of allylic alcohols provides another ideal atom-economic approach to access chiral γ-amino alcohols, as pioneered by Buchwald and co-workers.[5] However, the traditional hydroamination[6] of allylic alcohols could only produce chiral γ-amino alcohols with the stereogenic center adjacent to the nitrogen atom (Figure 1 b).[5]

A different approach for asymmetric γ-functionalization of allylic alcohols is via hydrogen-borrowing catalysis.[7] Quintard[8] and Dydio[9] have elegantly demonstrated that primary allylic alcohols could react with carbon nucleophiles via hydrogen-borrowing to afford γ-chiral primary alcohols,[10] in which an achiral hydrogen-borrowing catalyst is cascaded with a chiral C–C coupling catalyst (Figure 1 c). Oe[11] and more recently we[12] have shown that the hydrogen-borrowing strategy could be employed for the formal anti-Markovnikov hydroamination of allylic alcohols to give racemic γ-amino alcohols. This finding could offer a new pathway for chiral γ-amino alcohols, departing from the common asymmetric hydroamination strategy. Specifically, if a viable chiral hydrogen-borrowing catalyst can be identified that enables the dehydrogenation of a racemic secondary allylic alcohol as well as the subsequent asymmetric hydrogenation of the resulting amino ketone intermediate, chiral γ-amino alcohols with the stereogenic center adjacent to the OH group could be obtained (Figure 1 d). Herein, we report that a chiral Ru-diamine-diphosphine complex catalyzes the formal anti-Markovnikov hydroamination of racemic secondary allylic alcohols to give enantiomerically enriched chiral γ-amino

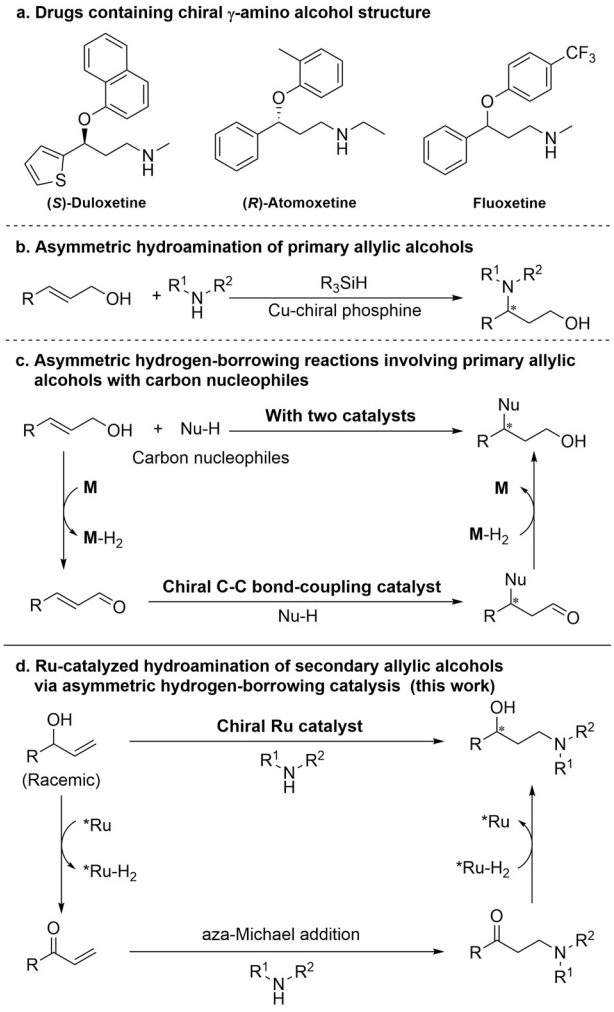

Figure 1. Drugs containing chiral γ-amino alcohol units and methods for asymmetric γ-functionalization of allylic alcohols.

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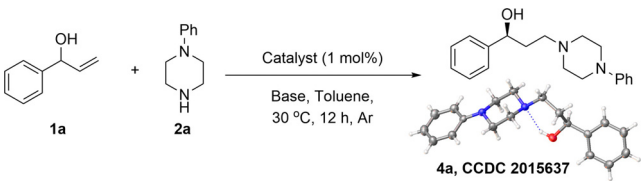
alcohols with the stereogenic center adjacent to the OH group.[13] Note that this kind of chiral γ-amino alcohols is otherwise impossible to get via the normal asymmetric hydroamination[5] (Figure 1b), and the selectivity pattern realized is different from the previously reported γ-functionalization of allylic alcohols[7–8] (Figure 1c).

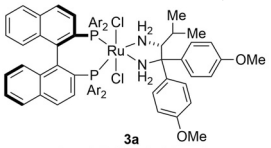
We recently showed the feasibility of formal anti-Markovnikov hydroamination of allylic alcohols with an achiral iron catalyst via hydrogen borrowing.[12] Our further work using a similar approach has revealed that the Guerbet reaction can be made enantioselective with a chiral Ru-diamine-diphosphine catalyst, in which an intermediary ketone is reduced to a chiral alcohol product.[10q] We envisioned that such chiral Ru-diamine-diphosphine catalysts could be utilized for the formal hydroamination of racemic secondary allylic alcohols, which would produce chiral γ-amino alcohols (Figure 1d). Thus, we commenced our study by investigating the reaction between the racemic 1-phenylprop-2-en-1-ol **1a** with 1-phenylpiperazine **2a** using Ru-diamine-diphosphine catalysts. According to our previous study,[12] 1.5 equivalent of **1a** (relative to **2a**) was used. The initial results are indeed encouraging. With the Noyori catalyst[14] **3a** (1 mol%), which was used for the asymmetric cross coupling of alcohols in our previous study,[10q] the desired product **4a** was obtained in 97% *ee*, albeit with a low yield of 10%, in the presence of 0.5 equivalent of K_3PO_4 in toluene at 30°C for 12 h under Ar (Table 1, entry 1). Similar results were obtained with another Noyori catalyst **3b**[14] (Table 1, entry 2). A sharp increase of activity was observed with catalyst **3c**, which was developed by Ohkuma[15] and commercialized by Takasago (Table 1, entry 3). The diamine ligand is essential for the activity observed, as demonstrated with complex **3d** (Table 1, entry 4). The yield could be improved to 94% by increasing the amount of K_3PO_4 to 1.5 equivalents without adversely affecting the enantioselectivity (Table 1, entry 5). Control experiments showed that both the catalyst and the base were indispensable for the transformation (Table 1, entries 6 and 7). The absolute configuration of **4a** was determined to be *S* by X-ray crystallography. The solid state structure indicates that there exists a hydrogen bonding interaction between the OH moiety and the γ-N atom (The O–H···N distance is 2.080 Å), which, along with the enhanced steric bulkiness in the product, may explain why the reverse dehydrogenation of the product appears to be negligible, unlike the Guerbet reaction.[10q]

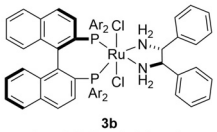
With optimal conditions in hand, the generality of the method was evaluated (Figure 2). The reaction time was prolonged to 48 h in most cases and 2 mol% of **3c** was used in some cases, to ensure maximum yields. Isolated yields were obtained for all the products. The reaction of various racemic allylic alcohols with **2a** was first examined (Figure 2, **4a**–**4ab**). Both electron-donating and -withdrawing substituents on the *meta*- and *para*-positions of the phenyl ring of allylic alcohols could be well tolerated, the corresponding γ-amino alcohols being obtained with good yields and excellent enantioselectivities (**4d**–**4p**). However, low activities were observed for *ortho*-substituted substrates (**4b**, **4c**), suggesting that the reaction is sensitive to steric hindrance. Allylic alcohols with

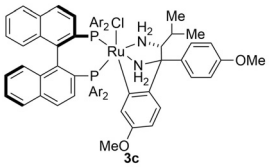
Table 1: Optimization of reaction conditions.

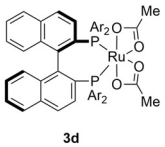


Entry[a]	Catalyst	Base (equiv)	Yield [%][b]	*ee* [%][c]
1	**3a**	K_3PO_4 (0.5)	10	97
2	**3b**	K_3PO_4 (0.5)	20	98
3	**3c**	K_3PO_4 (0.5)	85	98
4	**3d**	K_3PO_4 (0.5)	0	–
5	**3c**	K_3PO_4 (1.5)	94	98
6	**3c**	–	0	–
7	–	K_3PO_4 (1.5)	0	–







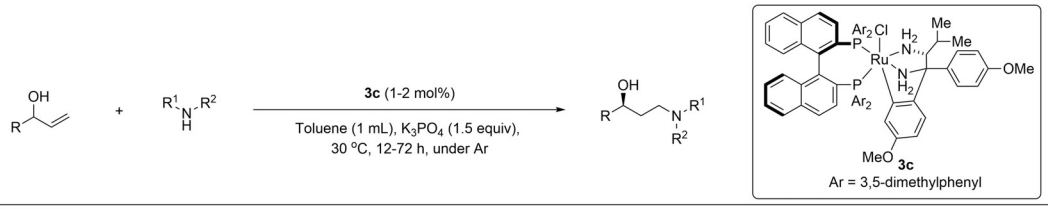


[a] Reaction conditions: **1a** (0.375 mmol), **2a** (0.25 mmol), catalyst (1 mol%), base, toluene (1 mL), 30°C, under Ar, 12 h. [b] Determined by ^{1}H NMR analysis with 1,3,5-trimethoxybenzene as an internal standard. [c] The enantiomeric excess (*ee*) was determined by HPLC analysis of pure isolated product, and the absolute configuration of **4a** was determined to be *S* by X-ray crystallography.

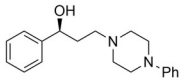
naphthyl, di-substituted phenyl, and heterocyclic groups are all viable (**4s**–**4y**), albeit with low yield for **4u**. A limitation of the protocol is that the enantioselectivities for allylic alcohols with benzyl or aliphatic groups adjacent to the alcohol carbon are quite low (**4z**–**4ab**). X-ray structures were obtained for products **4j**, **4n** and **4o**, confirming their absolute configuration to be *S*. As with **4a**, for almost all the X-ray structures determined, hydrogen bonds between the OH group and its γ-nitrogen atom are observed.

The substrate scope for amines were then investigated with 1-(4-bromophenyl)prop-2-en-1-ol (Figure 2, **5a**–**5aj**). Excellent enantioselectivities were obtained for all the cyclic secondary amines, including both six and five membered rings (**5a**–**5x**). The structures of **5g** and **5l** were confirmed by X-ray crystallography. Acyclic secondary amines could also be employed as substrates (**5y**–**5ah**). However, low yields were obtained for acyclic secondary aromatic amines (**5af**–**5ah**). The low activities could be due to their low nucleophilicity and relatively large steric hindrance. Almost no reaction took place for primary aromatic amines, although moderate yield and good *ee* were observed for an example of primary aliphatic amine (**5ai**).

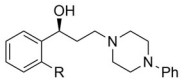
As many natural products and drugs contain secondary amine structures, this protocol could be used for the



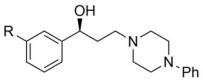
Scope of secondary alcohols



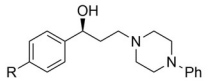
4a, 90% yield, 98% *ee*



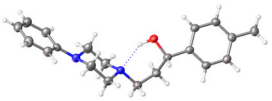
4b, R = Me, 34% yield, 92% *ee*
4c, R = F, 40% yield, 97% *ee*



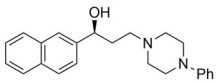
4d, R = Me, 76% yield, 99% *ee*
4e, R =OMe, 82% yield, 99% *ee*
4f, R = F, 87% yield, 97% *ee*
4g, R = Cl, 85% yield, 98% *ee*
4h, R = Br, 92% yield, 99% *ee*
4i, R = CF_3, 89% yield, 97% *ee*



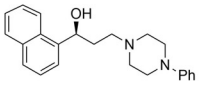
4j, R = Me, 84% yield, 96% *ee*
4k, R = OMe, 77% yield, 97% *ee*
4l, R = *i*Bu, 77% yield, 98% *ee*
4m, R = F, 95% yield, 98% *ee*
4n, R = Cl, 93% yield, 98% *ee*
4o, R = Br, 94% yield, 98% *ee*
4p, R = CF_3, 97% yield, 99% *ee*



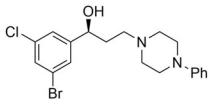
4j, CCDC 2015642



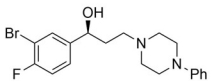
4q, 93% yield, 98% *ee*



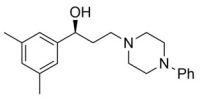
4r, 71% yield, 99% *ee*



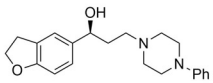
4s, 99% yield, 96% *ee*



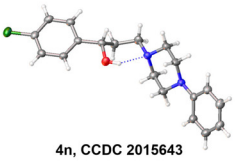
4t, 99% yield, 99% *ee*



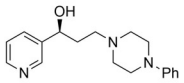
4u, 23% yield, 82% *ee*



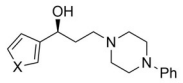
4v,60% yield, 98% *ee*



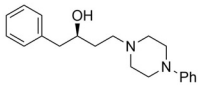
4n, CCDC 2015643



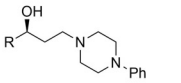
4w, 89% yield, 98% *ee*



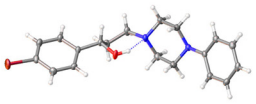
4x, X = O, 83% yield, 98% *ee*
4y, X = S, 95% yield, 99% *ee*



4z, 77% yield,16% *ee*

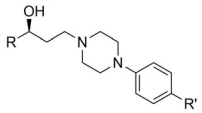


4aa, R = Et, 60% yield, 11% *ee*
4ab, R = Me, 87% yield, 6% *ee*

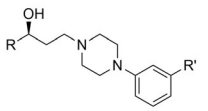


4o, CCDC 2015644

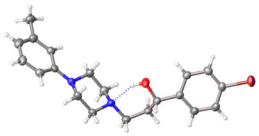
Scope of amines, R = *p*-bromophenyl



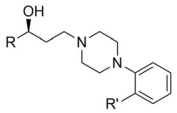
5a, R' = Me, 80% yield, 97% *ee*
5b, R' = OMe, 87% yield, 99% *ee*
5c, R' = F, 87% yield, 97% *ee*
5d, R' = Cl, 83% yield, 99% *ee*
5e, R' = Br, 87% yield, 99% *ee*
5f, R' = CF_3, 70% yield, 98% *ee*



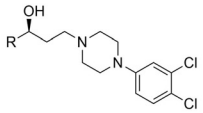
5g, R' = Me, 89% yield, >99% *ee*
5h, R' = OMe, 81% yield, 97% *ee*



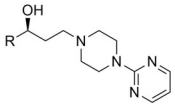
5g, CCDC 2015645



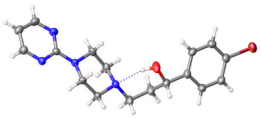
5i, R' = Me, 95% yield, 98% *ee*
5j, R' = OMe, 83% yield, 98% *ee*



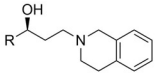
5k, 89% yield, 99% *ee*



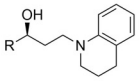
5l, 92% yield, 99% *ee*



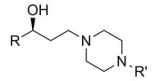
5l, CCDC 2015646



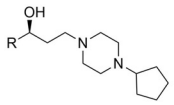
5m, 82% yield, 98% *ee*



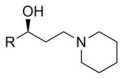
5n,54% yield, 97% *ee*



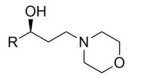
5o, R' = Et, 90% yield, >99% *ee*
5p, R' = *i*Pr, 87% yield, 97% *ee*



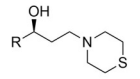
5q, 56% yield, 95% *ee*



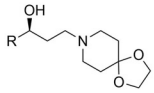
5r, 77% yield, 98% *ee*



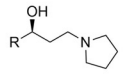
5s, 87% yield, 98% *ee*



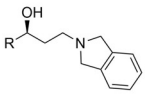
5t, 91% yield, 99% *ee*



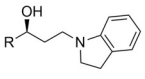
5u, 80% yield, 99% *ee*



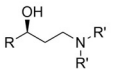
5v, 76% yield, 95% *ee*



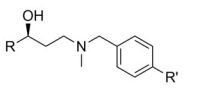
5w, 81% yield, 99% *ee*



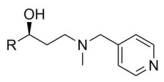
5x, 70% yield, 97% *ee*



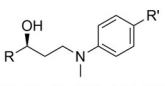
5y, R' = Bn, 70% yield, 97% *ee*
5z, R' = Et, 56% yield, >99% *ee*
5aa, R' = Me, 82% yield, >99% *ee*



5ab, R' = H, 89% yield, 98% *ee*
5ac, R' = CH_3, 74% yield, 92% *ee*
5ad, R' = CF_3, 75% yield, >99% *ee*



5ae, 83% yield, 95% *ee*



5af, R' = H, 40% yield, 98% *ee*
5ag, R' = CH_3, 41% yield, 98% *ee*
5ah, R' = F, 38% yield, 98% *ee*

5ai, 53% yield, 89% *ee*

Cytisine
5aj, 91% yield, 99% *ee*

Amoxapine
5ak, 89% yield, 95% *ee*

Figure 2. Substrate scope for the formal asymmetric hydroamination of allylic alcohols. General reaction conditions: allylic alcohol (0.375 mmol), amine (0.25 mmol), K_3PO_4 (0.375 mmol), **3c** (1–2 mol%), toluene (1 mL), 30°C, under Ar, isolated yield. See the Supporting Information for detailed conditions for each product.

modification of natural products and drugs. This is demonstrated by the functionalization of Cytisine and Amoxapine, leading to **5aj** and **5ak** (Figure 2). The utility of the reaction is further demonstrated by a gram-scale preparation of the key intermediate (**6**, X-ray structure obtained) for the synthesis of a potential analgesic agent[16] (Figure 3a), and intermediates for the synthesis of (*S*)-Fluoxetine (**7**)[3q,t] (Figure 3b), an antidepressant (sold in racemate), and (*S*)-Duloxetine (**8**)[3q,t] (Figure 3c), an antidepressant and anxiolytic. Notably, the enantioselectivities remained excellent for these relatively large-scale reactions.

Based on our previous studies[10q,12] and the literature,[11] the mechanism of this asymmetric hydroamination may be similar to that of the previously reported formal anti-Markovnikov hydroamination of allylic alcohols.[11–12] As illustrated in Figure 1d, the chiral Ru catalyst is likely to dehydrogenate the allylic alcohol to afford a Ru hydride complex and an α,β-unsaturated ketone intermediate, which undergoes aza-Michael addition to give a β-amino ketone intermediate. The β-amino ketone is then reduced by the chiral Ru hydride, affording the chiral γ-amino alcohol product. Preliminary mechanistic studies were carried out to corroborate the reaction pathway. Hydrogen gas was detected under the standard hydroamination conditions of the model reaction with or without the amine substrate (Supporting Information, Section 6.1). No reaction took place when the OH group of **1a** was replaced with a OAc group (Supporting Information, Section 6.2), and when the deuterium labelled **1a′** was used as substrate, no deuterium atom was found in the product, indicative of fast H/D exchange during dehydrogenation/hydrogenation (Supporting Information, Figure S1a, Section 6.3). These observations all support the involvement of a Ru-catalyzed dehydrogenation/hydrogenation process. Furthermore, the dehydrogenated α,β-unsaturated ketone intermediate **9** underwent aza-Michael addition with **2a** to give the intermediate **10** in the absence of the Ru catalyst (Supporting Information, Figure S1b, Section 6.4). Still further, under the catalysis of **3c**, **10** was reduced to **4a** with either the allylic alcohol **1a** or H_2 as the hydrogen source, with enantiomeric excess identical to the model reaction (Supporting Information, Figure S1c, Section 6.5; Table 1). Taken together, these studies suggest that the hydroamination proceeds via a Ru-catalyzed dehydrogenation/hydrogenation process in cooperation with a catalyst-free, aza-Michael addition step.

A 1:1 substrate ratio experiment of the model reaction under the standard reaction conditions afforded product **4a** in over 50% yield (67% yield, 99% *ee*), and the recovered unreacted starting alcohol **1a** had an *ee* value of 29%, suggesting the existence of both kinetic resolution and dynamic kinetic resolution during the reaction (Supporting Information, section 6.6). Racemization experiment with the enantioenriched **4a** and the time course of yield and *ee* of the model reaction under the standard reaction conditions suggest that the amino alcohol products are stable under the reaction conditions and do not racemize (Supporting Information, section 6.7), which might be due to the intramolecular hydrogen bonding and the increased steric bulkiness in the products (see above) and the competing dehydrogenation of allylic alcohol substrates with the products.

In conclusion, we have developed a Ru-catalyzed formal anti-Markovnikov asymmetric hydroamination of allylic alcohols via a hydrogen borrowing mechanism. For the first time, racemic secondary allylic alcohols are hydroaminated with various secondary amines to afford chiral γ-amino alcohols with broad substrate scope, good yields and excellent enantioselectivities. The protocol can be performed on a gram scale and could potentially be used for the synthesis of drug molecules.

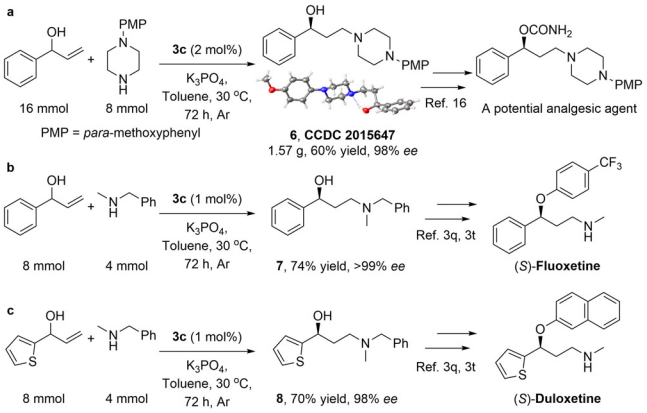


Figure 3. Gram-scale reaction and synthetic applications.

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Conflict of interest

Some of this research has been included in a Chinese patent (patent application number: 202010234438.1).

Keywords: allylic alcohol · amino alcohol · asymmetric catalysis · hydrogen borrowing · ruthenium catalyst

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