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Asymmetric Synthesis of γ-Secondary Amino Alcohols via a Borrowing-Hydrogen Cascade

Yupeng Pan,[†] Yipeng You,[†] Dongxu He, Fumin Chen, Xiaoyong Chang, Ming Yu Jin,* and Xiangyou Xing*

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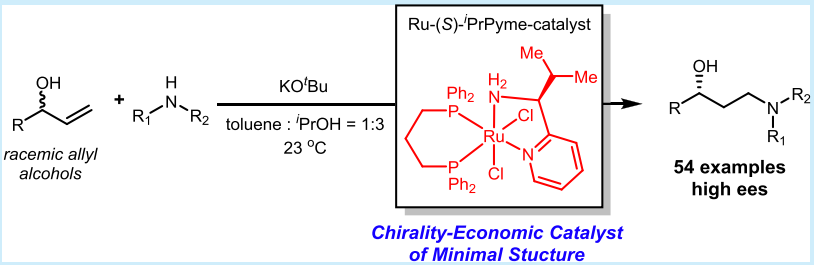

ABSTRACT: The borrowing-hydrogen (or hydrogen autotransfer) process, where the catalyst dehydrogenates a substrate and formally transfers the H atom to an unsaturated intermediate, is an atom-efficient and environmentally benign transformation. Described here is an example of an asymmetric borrowing-hydrogen cascade for the formal anti-Markovnikov hydroamination of allyl alcohols to synthesize optically enriched γ-secondary amino alcohols. By exploiting the Ru-(*S*)-^{i}PrPyme catalyst with minimal stereogenicity, a cascade process including dehydrogenation, conjugate addition, and asymmetric reduction was developed. The mild conditions, functional group tolerance, and broad substrate scope (54 examples) demonstrate the synthetic practicality of the catalytic system.

The borrowing-hydrogen[1] (or hydrogen autotransfer) process, which falls under the broader field of transfer hydrogenation,[2] typically starts with the catalyst-mediated abstraction of hydrogen from the starting reagent and ends with the incorporation of the abstracted hydrogen into the final product. Featuring operational simplicity and no net hydrogen loss or gain, this process is sustainable, environmentally benign, and markedly atom-efficient, with a high proportion of material incorporated into the product.[1] Of particular interest to our group, this strategy has been applied to the indirect, formal anti-Markovnikov addition of carbon- or nitrogen-based nucleophiles to allyl alcohols (Figure 1A).[3] Such "one-pot" relay cascades dehydrogenate allyl alcohols to give the corresponding α,β-unsaturated carbonyl intermediates, followed by the subsequent conjugate addition of nucleophiles onto the intermediates to afford the β-functionalized carbonyl compounds, which are finally hydrogenated with the metal hydride to provide γ-functionalized alcohols. To date, such processes have been independently reported by Williams,[3a,b] Rodriguez,[3c] Oe,[3d] Wang,[3e] and Dydio.[3f] However, to the best of our knowledge, enantioselectivity at the alcohol carbons was not generated in these γ-functionalized alcohol products.

Contemplating enantioselectivity in such reactions, we considered our recently developed Ru catalysts that have significant chirality economy with only one stereogenic element and yet are capable of effecting asymmetric transfer hydrogenation over a broad scope of ketone substrates (Figure 1B).[4] We envisioned that given their strong dehydrogenation ability and excellent reactivity in the asymmetric transfer hydrogenation, these catalysts could effect the asymmetric version of the aforementioned borrowing-hydrogen cascade to generate optically enriched γ-secondary amino alcohols that are featured extensively in the preparations of various antidepressants.[5]

Here we report that under chirality-economy catalysis, an array of racemic allyl alcohols and amines undergo a formal anti-Markovnikov hydroamination that includes a cascade process of dehydrogenation/conjugate addition/asymmetric reduction to afford γ-secondary amino alcohols with high enantioselectivity (Figure 1D). This catalytic protocol not only serves as a powerful new extension of the asymmetric borrowing-hydrogen methodology[6,3c] but also provides an appealing alternative approach to access γ-secondary amino alcohols that is distinct from widely used methods, such as the asymmetric hydrogenation of β-amino ketones or the one-pot,

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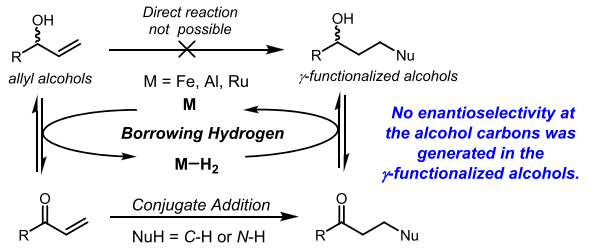
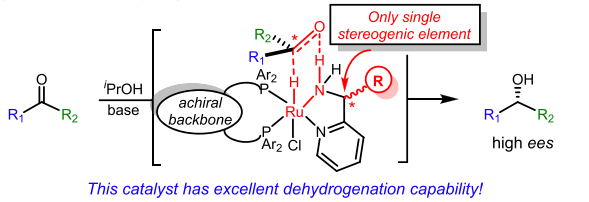
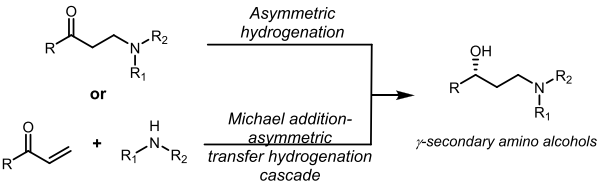
A. Borrowing-hydrogen strategy in the formal anti-Markovnikov addition to allyl alcohols.



B. Our previous work: Ru-catalysts of minimal stereogenicity and simplified structure in asymmetric transfer hydrogenation.



C. Previous work: Asymmetric synthesis of chiral γ-secondary amino alcohols.



D. This work: Asymmetric synthesis of γ-secondary amino alcohols through borrowing-hydrogen catalysis.

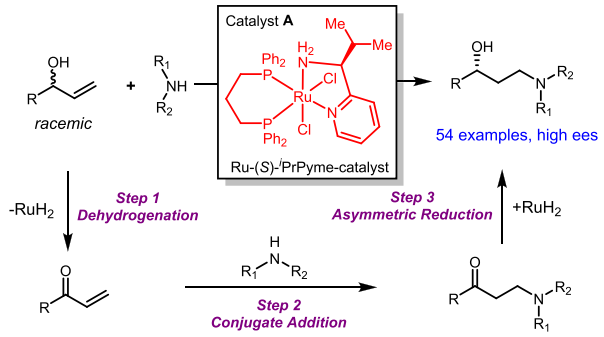
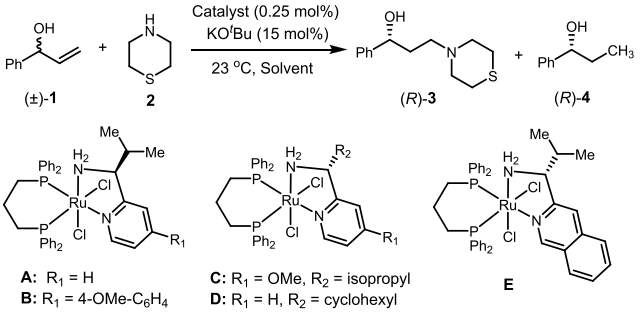


Figure 1. Asymmetric borrowing-hydrogen cascade for the formal anti-Markovnikov hydroamination of allyl alcohols.

highly efficient transformation of enones and amines via a Michael addition–asymmetric transfer hydrogenation cascade process (Figure 1C).[7]

Our studies began by conducting the reaction with (±)-1-phenylallyl alcohol (**1**) and thiomorpholine (**2**) as model substrates in the presence of 0.25 mol % loading of Ru-catalyst **A** and KO^{t}Bu (15 mol %) in CH_2Cl_2 at 23 °C (Table1, entry 1). To our delight, we obtained a 9:1 ratio of γ-amino alcohol **3** and the fully reduced side product **4**, and the desired product **3** was produced in 79% yield with 60% ee. Subsequent screening of various parameters revealed that the solvent plays an important role in the overall reaction outcomes (Table 1, entries 2–4). When ^{i}PrOH, which serves as a hydrogen donor in the general transfer hydrogenation, was used as the solvent,[2,4] an apparent increase in the enantioselectivity was observed, probably because ^{i}PrOH prohibits reversible dehydrogenation of the product **3**, and thus its high ee was maintained. ^{i}PrOH also inhibits the formation of the side product **4**, providing a 13:1 ratio of **3**/**4** (Table 1, entry 4). It is worth noting that due to the reversibility of the transfer

Table 1. Optimization of Conditions[a]



Entry	catalyst	Solvent [ratio]	Yield of **3** [%][b]	Ratio of [**3**:**4**][c]	*ee* of **3** [%][d]
1	**A**	CH_2Cl_2	79	9:1	60
2	**A**	THF	45	3:1	45
3	**A**	Toluene	41	4:1	76
4	**A**	^{i}PrOH	53	13:1	92
5	**A**	CH_2Cl_2 : iPrOH [1:3]	45	9:1	94
6	**A**	Toluene:^{i}PrOH [1:3]	63	16:1[e]	93
7	**B**	Toluene:^{i}PrOH [1:3]	60	12:1	91
8	**C**	Toluene:^{i}PrOH [1:3]	41	20:1	-90
9	**D**	Toluene:^{i}PrOH [1:3]	54	11:1	-91
10	**E**	Toluene:^{i}PrOH [1:3]	60	10:1	-93
11[f]	**A**	Toluene:^{i}PrOH [1:3]	34	11:1	96
12[g]	**A**	Toluene:^{i}PrOH [1:3]	78	5:1	83

[a]General conditions: (±)-1-phenylallyl alcohol **1** (0.2 mmol), thiomorpholine **2** (0.4 mmol), catalysts **A**–**E** (0.25 mol %), KO^{t}Bu (15 mol %), toluene/^{i}PrOH 1:3 (2.0 mL), 23 °C, 4–12 h. [b]Yields were determined by ^{1}H NMR using 1,4-dinitrobenzene as the internal standard. [c]Ratio was determined by crude ^{1}H NMR. [d]ee values were determined by HPLC. [e]Side product **4** was obtained in 4% yield with 81% ee. [f]Reaction was performed at 0 °C for 12 h. [g]Reaction was performed at 50 °C for 12 h.

hydrogenation, longer reaction times resulted in higher conversions and yields but erosion of the enantioselectivity.[8] Therefore, in exchange for good enantioselectivity, the yield of product **3** is moderately limited. When CH_2Cl_2 is used as the cosolvent in combination with ^{i}PrOH, the ee increases to 94%, whereas the yield and ratio of **3**/**4** decrease. The yield and enantioselectivity of **3** were further improved when toluene was used as the cosolvent in combination with ^{i}PrOH (Table 1, entry 5). A variety of Ru catalysts of minimal stereogenicity developed by us were surveyed, and all of them show surprisingly good performances in generating enantioselectivity in the desired product **3** (Table 1, entries 6–9). Although both the enantioselectivity of **3** and the ratio of **3**/**4** were maintained at 0 °C, a lower yield of **3** was obtained (Table 1, entry 10). In contrast, increasing the reaction temperature to 50 °C led to a higher yield of **3**, albeit with a lower enantioselectivity and a poor ratio of **3**/**4** (Table 1, entry 11).

With the optimal conditions in hand (Table 1, entry 5), we then investigated whether they could be extended to a broader family of substrates. As summarized in Table 2A, the catalyst **A** was shown to be capable of effecting the cascade process of

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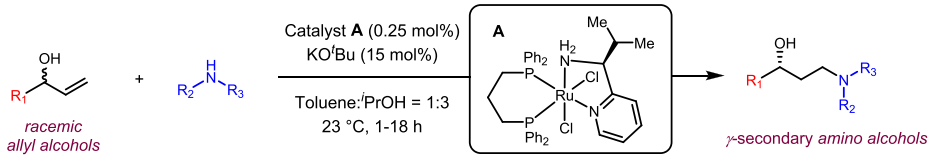
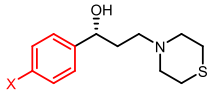
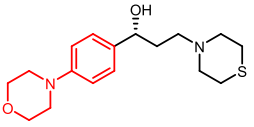
Table 2. Asymmetric Synthesis of γ-Secondary Amino Alcohols: Scope of Racemic Allyl Alcohols and Amines[a]



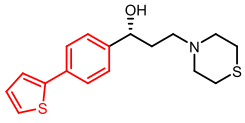
A. Scope of racemic allyl alcohols:



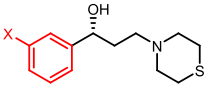
5, X = F, 67% yield, **92% ee**
6, X = Cl, 58% yield, **91% ee**
7, X = Br, 66% yield, **92% ee**
8, X = CF_3, 59% yield, **90% ee**
9, X = COO^{i}Pr, 63% yield, **91% ee**
10, X = OCF_3, 57% yield, **93% ee**
11, X = OPh, 62% yield, **92% ee**
12, X = OBn, 71% yield, **92% ee**
13, X = SMe, 65% yield, **93% ee**
14, X = NMe_2, 55% yield, **88% ee**
15, X = Me, 57% yield, **92% ee**
16, X = *t*-Bu, 54% yield, **93% ee**
17, X = Ph, 69% yield, **91% ee**



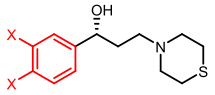
18, 68% yield, **90% ee**



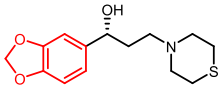
19, 76% yield, **90% ee**



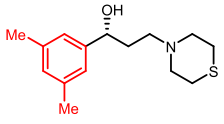
20, X = Cl, 59% yield, **91% ee**
21, X = Br, 60% yield, **92% ee**
22, X = OMe, 69% yield, **93% ee**



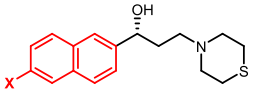
23, X = F, 57% yield, **90% ee**
24, X = OMe, 55% yield, **92% ee**



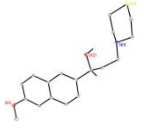
25, 62% yield, **90% ee**



26, 57% yield, **94% ee**



27, X = H, 54% yield, **93% ee**
28, X = OMe, 61% yield, **93% ee**



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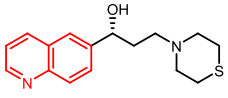
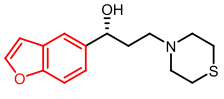
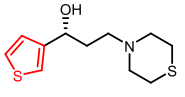


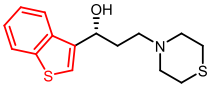
29[b], 64% yield, **90% ee**



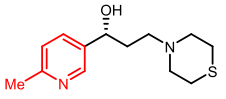
30, 52% yield, **90% ee**



31, 65% yield, **90% ee**

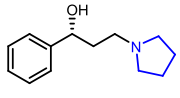


32, 54% yield, **91% ee**

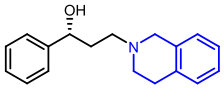


33[b], 54% yield, **88% ee**

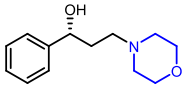
B. Scope of amines:



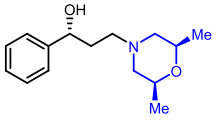
34, 59% yield, 83% ee



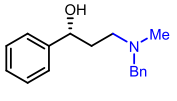
35, 72% yield, 88% ee



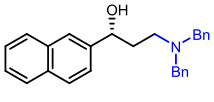
36, 62% yield, 91% ee



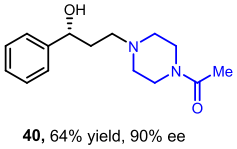
37, 62% yield, 94% ee



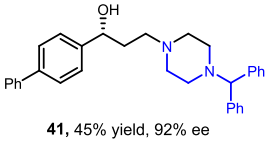
38, 51% yield, 90% ee



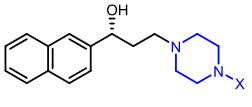
39, 57% yield, 90% ee



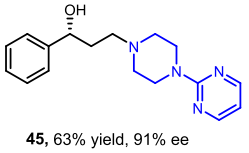
40, 64% yield, 90% ee



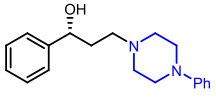
41, 45% yield, 92% ee



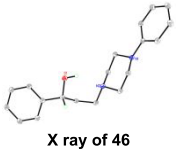
42, X = Me, 66% yield, 94% ee
43, X = Boc, 63% yield, 93% ee
44, X = Ph, 55% yield, 91% ee



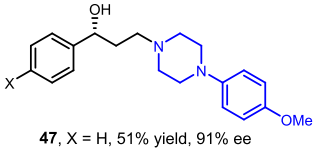
45, 63% yield, 91% ee



46, 65% yield, 85% ee

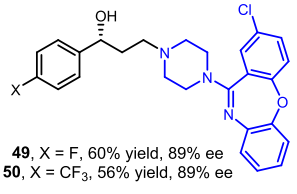


X ray of 46

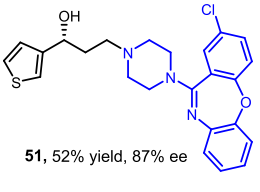


47, X = H, 51% yield, 91% ee
48, X =  , 70% yield, 87% ee

Amoxapine derivatives

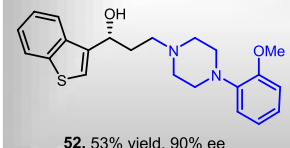


49, X = F, 60% yield, 89% ee
50, X = CF_3, 56% yield, 89% ee

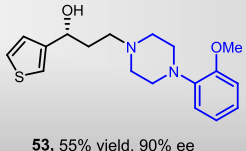


51, 52% yield, 87% ee

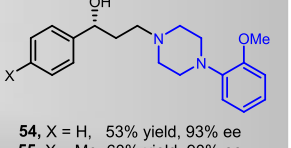
Antidepressant agents:



52, 53% yield, 90% ee

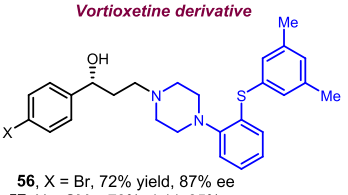


53, 55% yield, 90% ee



54, X = H, 53% yield, 93% ee
55, X = Me, 60% yield, 90% ee

Vortioxetine derivative



56, X = Br, 72% yield, 87% ee
57, X = SMe, 73% yield, 85% ee

[a]General conditions: allyl alcohol (0.2 mmol), thiomorpholine **2** (0.4 mmol), catalyst **A** (0.25 mol %), KO^{t}Bu (15 mol %), toluene/^{i}PrOH 1:3, total volume of solvents = 2.0 mL, 23 °C. Yields of isolated products are given. The ee values were determined by HPLC. [b]Reaction was performed at 50 °C for 12 h.

various racemic aryl-substituted allyl alcohols with thiomorpholine (**2**) with generally good enantiomeric excess (88−94% ee). para-Substitution on the aryl ring by halogen (F, Cl, Br), trifluoromethyl (CF_3), ester (COO^{i}Pr), alkoxy (OCF_3, OPh,

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OBn), methylthio (SMe), dimethylamino (NMe_2), morpholinyl, alkyl (Me, ^{t}Bu), phenyl or thienyl groups, which are either electron-donating or -withdrawing in nature, is all well tolerated, leading to 88−93% ee in γ-amino alcohol products **5**−**19**. Racemic aryl allyl alcohols bearing a meta-substitution, including halogen (Cl, Br) and electron-donating methoxyl (OMe) groups, were also transformed to the corresponding alcohols with 91 to 93% ee (**20**−**22**). Allyl alcohols with 3,4-or 3,5-disubsitution on the aryl rings were investigated, and good enantioselectivities (90−94% ees) were obtained in these cases (**23**−**26**). Substrates with extended conjugation, such as naphthalenyl-substituted allyl alcohols, were smoothly converted to give γ-amino alcohol products **27** and **28** with 93% ee, respectively. The structure of **28** was verified by X-ray crystallography, which unambiguously confirmed the absolute stereochemistry assignment. Finally, racemic allyl alcohols with heteroaromatic substituents, such as quinoline, benzofuran, benzothiophene, thiophene, and methylpyridine, were all remarkably reactive to form the corresponding γ-amino alcohols (**29**−**33**) with 88−91% ee.

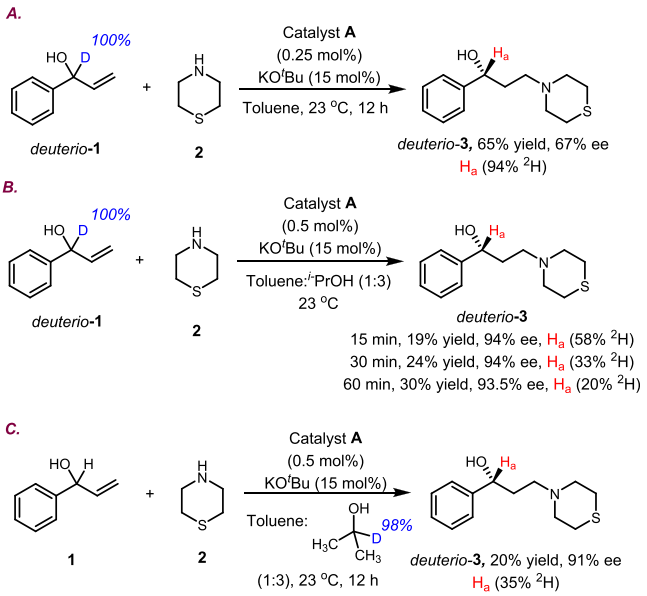
To demonstrate the generality of this method, numerous secondary amines were then successfully accommodated, affording a range of γ-amino alcohols **34**−**57** in 45−72% yields with 83−94% ee. As shown in Table 2B, cyclic secondary amines, such as pyrrolidine, tetrahydroisoquinoline, and morpholines, were readily reacted with (±)-1-phenylallyl alcohol to give the corresponding alcohols **34**−**37** in 59−62% yields with 83−94% ee. Acyclic secondary amines coupled to both (±)-1-phenylallyl alcohol and (±)-2-(2-naphthyl)allyl alcohol, affording the desired alcohols **38** and **39** with 90% ee, respectively. A series of piperazine derivatives that are significant pharmaceutical structures[9] were than investigated, and the alcohol products **40**−**48** were obtained with 85−94% ee. The absolute configuration of **46** was also assigned as (R)-configuration by X-ray analysis.

Gratifyingly, the 2-methoxyphenyl-substituted piperazine furnished the antidepressant agents **52**−**55** in 53−60% yields with 90−93% ee.[5a] We note that drug molecules, such as amoxapine and vortioxetine, were smoothly coupled to racemic allyl alcohols to deliver the alcohol products **49**−**51** and **56**−**57** with 85−89% ee.[10]

Finally, deuterium labeling experiments were investigated (Scheme 1). As illustrated in Scheme 1A, the reaction of the fully deuterium-incorporated substrate (±)-*deuterio*-**1** and **2** in the presence of catalyst **A**, KO^{t}Bu, and toluene without ^{i}PrOH was explored, and 94% deuterium incorporation was observed at the benzylic position of the γ-amino alcohol *deuterio*-**3**, indicating a typical borrowing-hydrogen cascade where the D atom in (±)-*deuterio*-**1** was transferred into the product *deuterio*-**3**. When the reaction of (±)-*deuterio*-**1** with **2** in the presence of ^{i}PrOH was conducted, the D atom was partially transferred to *deuterio*-**3**, and deuterium incorporation also varied according to the reaction times, suggesting that the γ-amino alcohols undergo a dedeuteration/hydrogenation sequence. (Scheme 1B). Additionally, the reaction of (±)-**1** and -**2** in the presence of a combination of toluene/2-D-^{i}PrOH enables 35% deuterium incorporation into the γ-amino alcohol *deuterio*-**3** at its benzylic position (Scheme 1C). All together, these results strongly support the notion that both the racemic allyl alcohols and ^{i}PrOH were involved as hydride donors in this asymmetric borrowing-hydrogen cascade.

In conclusion, we report a method catalyzed by the chirality-economic Ru-(*S*)-^{i}PrPyme for the direct conversion of a variety of racemic allyl alcohols to valuable γ-amino alcohols that occurs with high levels of enantioselectivity. This borrowing-hydrogen process represents the first protocol for the formal anti-Markovnikov reaction of racemic allyl alcohols to generate high enantioselectivity at alcohol carbons in the γ-functionalized alcohol products. Deuterium labeling studies indicate that both the allyl alcohols and ^{i}PrOH serve as hydrogen donors in the cascade process. We believe that this work represents a useful application of our chiral Ru catalysts, demonstrating a high level of efficiency in asymmetric induction.

Scheme 1. Deuterium Labeling Experiments



■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c02614.

Experimental procedures and characterization data (^{1}H and ^{13}C NMR, HRMS) for all new compounds (PDF)

Accession Codes

CCDC 1977820−1977821 and 2009257 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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