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Borrowing Hydrogen/Chiral Enamine Relay Catalysis Enables Diastereo- and Enantioselective β-C−H Functionalization of Alcohols

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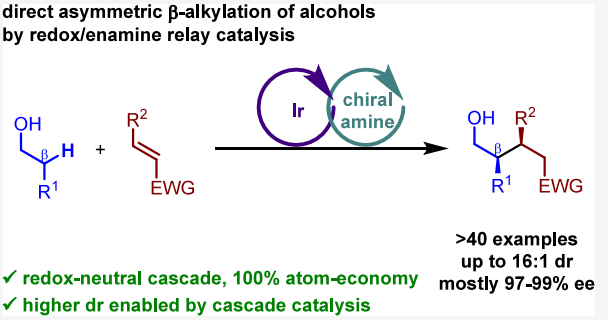
ABSTRACT: We report herein an unprecedented borrowing hydrogen/chiral enamine relay catalysis strategy that enables a highly efficient enantioselective formal β-alkylation of simple alcohols using electron-deficient alkenes and especially nitroalkenes. A variety of 1,4-difunctional products such as nitro alcohols are readily accessible in one waste-free step from feedstock alcohols in excellent levels of stereoselectivity. It is important to note that the products are formed in much higher diastereoselectivity than the enamine catalysis step alone under identical conditions, highlighting the unique advantage of cascade borrowing hydrogen catalysis in achieving high efficiency, economy, and stereoselectivity.

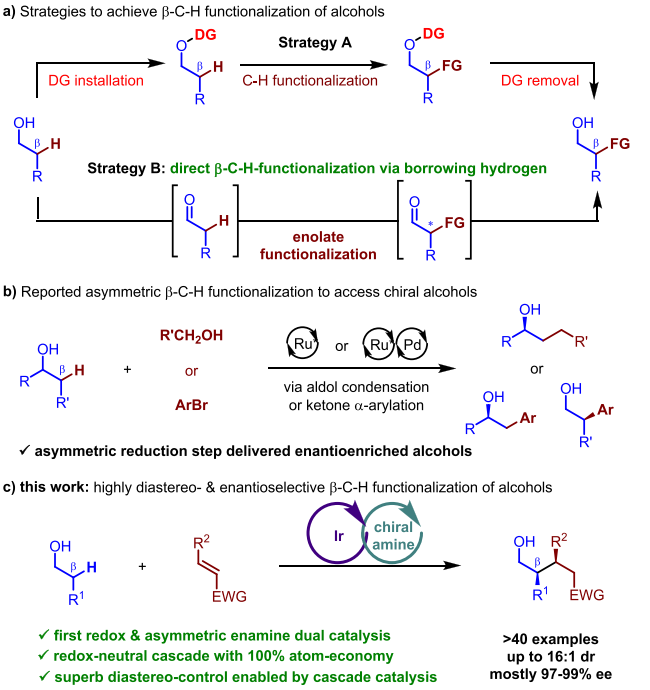


INTRODUCTION

Alcohols are readily available feedstock molecules and serve as important building blocks to access value-added fine chemicals and pharmaceuticals. Most classical transformations of alcohols either take place right on the hydroxyl unit or require prior alcohol activation to enable bond construction at other sites (e.g., oxidation of alcohols to access diverse carbonyl chemistry). The achievement of direct sp^3 C−H functionalization of alcohols is highly desirable for effective access to functionalized alcohols, with much room for further downstream derivatization. In the past few decades, significant advances have been made for α-C−H bond functionalization of alcohols,[1] which is elegantly exemplified by the Krische allylation reaction that has changed the paradigm of polyketide synthesis.[2] In sharp contrast, direct functionalization of the unactivated β-C−H bond of alcohols still represents a formidable challenge. The current state-of-the-art methods on this topic necessitate the use of a directing group and therefore a multistep procedure including installation and removal of such units onto the alcohol functionality (strategy A,Scheme 1a).[3] Notably, an elegant example of enantioselective β-amination of alcohols was reported by the Nagib group using this strategy through an asymmetric 1,5-HAT process.[4]

Borrowing hydrogen catalysis has been established as a highly economical strategy for achieving direct formal substitution of alcohols to deliver valuable products.[5] The majority of these methods involve condensation of the carbonyl intermediate, followed by reaction with a nucleophile. In contrast, utilizing the enolate chemistry of the carbonyl intermediate, generated in a borrowing hydrogen process, can lead to highly attractive redox-neutral formal β-C−H functionalization of feedstock alcohols (strategy B,Scheme

Scheme 1. Synthetic Strategies for Selective β-C−H Functionalization of Alcohols



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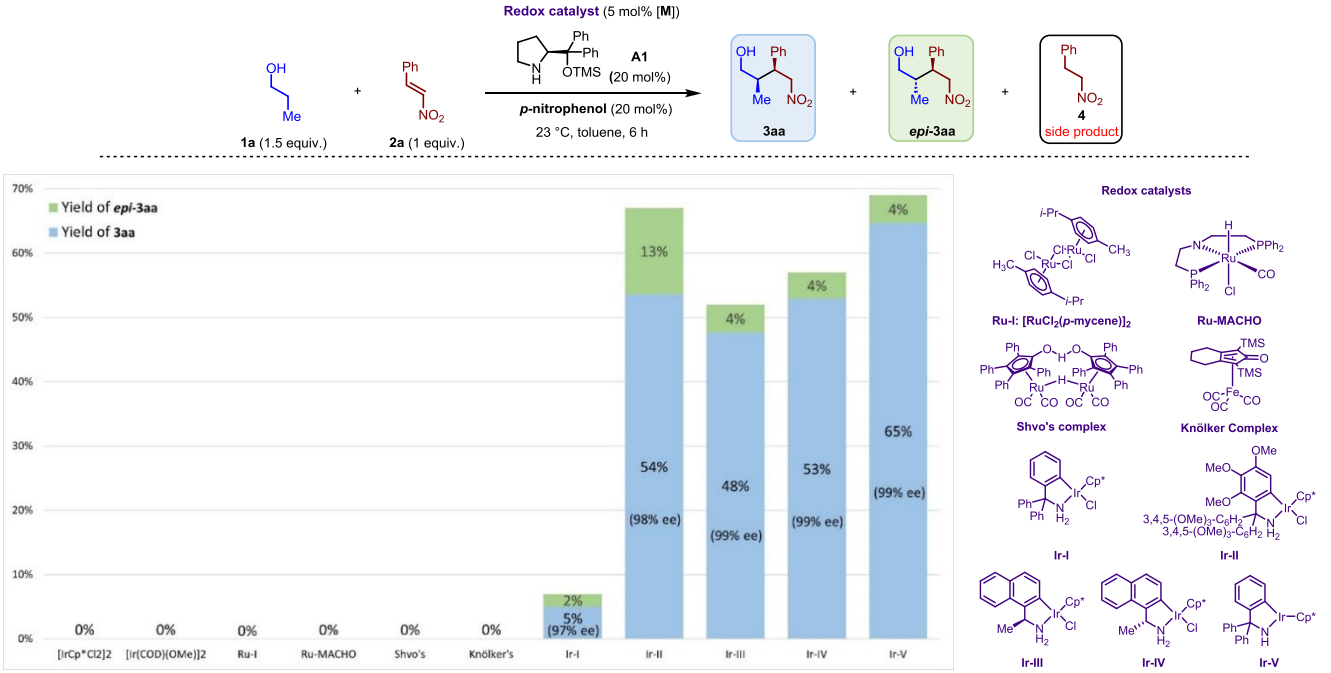
Scheme 2. Optimization of Diastereo- and Enantioselective β-Alkylation of Alcohol Using Nitroalkene



[a]The reactions were carried out using 1 equiv. **2a**, 1.5 equiv. **1a**, 5 mol % redox catalyst, 20 mol % **A1**, and 20 mol % *p*-nitrophenol at ambient temperature in toluene for 6 h. See the Supporting Information for details.

1a). An elegant demonstration of this concept is the Guerbet reaction that has found much industrial application.[6] However, achieving enantioselectivity in this type of complicated cascade transformations presents a formidable challenge.[7] Only limited examples are known for alcohol β-C−H alkylation/arylation to deliver enantioenriched monofunctional alcohols (Scheme 1b). These transformations involve either a base-promoted aldol condensation[8] or Pd-catalyzed α-arylation of aldehydes[9] as the intermediate step, and all of them rely on a Ru-catalyzed asymmetric hydrogenation step to set the enantioselectivity.

Our group has had a continuous interest in stereoselective borrowing hydrogen catalysis[10] and achieved a series of catalytic redox-neutral formal substitution of alcohols to deliver enantioenriched chiral amines,[11] *N*-heterocycles,[12] and ketones.[13] During our efforts toward economical chiral alcohol preparation, we were attracted to the possibility of borrowing hydrogen/asymmetric enamine relay catalysis strategy. While this approach can open up vast opportunities to deliver enantiopure multifunctional alcohols from feedstock alcohols, it has remained elusive in the literature. It is also interesting to note that in many reports of enamine catalysis using aldehyde substrates, the functionalized aldehyde products are routinely reduced to the corresponding alcohols as the preferred stable products, which requires an additional reduction step.[14] Thus, the borrowing hydrogen/asymmetric enamine relay catalysis can provide a highly attractive alternative for alcohol functionalization with excellent atom and step economy.

Herein, we report the first successful demonstration of such a strategy in a highly efficient enantioselective formal β-alkylation of simple alcohols using electron-deficient alkenes and especially nitroalkenes (Scheme 1c). This system adopts dual iridium and chiral enamine catalysts, proceeds in a redox-neutral fashion without the formation of any stoichiometric byproduct, and produces versatile valuable 1,4-nitroalcohols bearing contiguous stereocenters with excellent diastereo- and enantioselectivities. Importantly, these products are formed in much higher diastereoselectivity (mostly >10:1 dr) than the enamine catalysis step alone under identical conditions (typically <3:1 dr), highlighting the unique advantage of cascade borrowing hydrogen catalysis in achieving high efficiency as well as stereoselectivity.

RESULTS AND DISCUSSION

We initiated our investigation using propanol **1a** and nitrostyrene **2a** as the model substrates (Scheme 2). Our reaction optimization was carried out with the choice of ambient temperature, which proved critical for the enamine catalysis step to operate in high stereoselectivity.[14] Preliminary exploration identified Jørgensen−Hayashi chiral amine catalyst **A1**[15] and *p*-nitrophenol as a good starting point. The key challenge was to identify a suitable redox catalyst that is compatible with the chiral amine catalyst and effective for the redox steps to achieve formal β-C−H functionalization. Representative redox catalysts that were screened are listed in Scheme 2 (see Figure S1 in the SI for more details). Disappointingly, a series of commercially available complexes including $[IrCp^*Cl_2]_2$, Ru-MACHO, and Shvo's and Knölker's complexes, which have been established as effective redox catalysts in other systems, failed to deliver the desired product **3aa** in any noticeable amount. A significant side product nitroalkane **4** was identified in all of the reactions, resulting from a competing transfer hydrogen of nitroalkene by the alcohol substrate. This further imposed a formidable chemoselectivity to overcome for the desirable borrowing hydrogen pathway. To our excitement, a breakthrough with the formation of a small amount of the desired **3aa** was finally achieved with the use of iridacycle **Ir-I**, which was originally reported by the Ikariya group for ATH of ketones[16] and has shown superior reactivity in our previous explorations of

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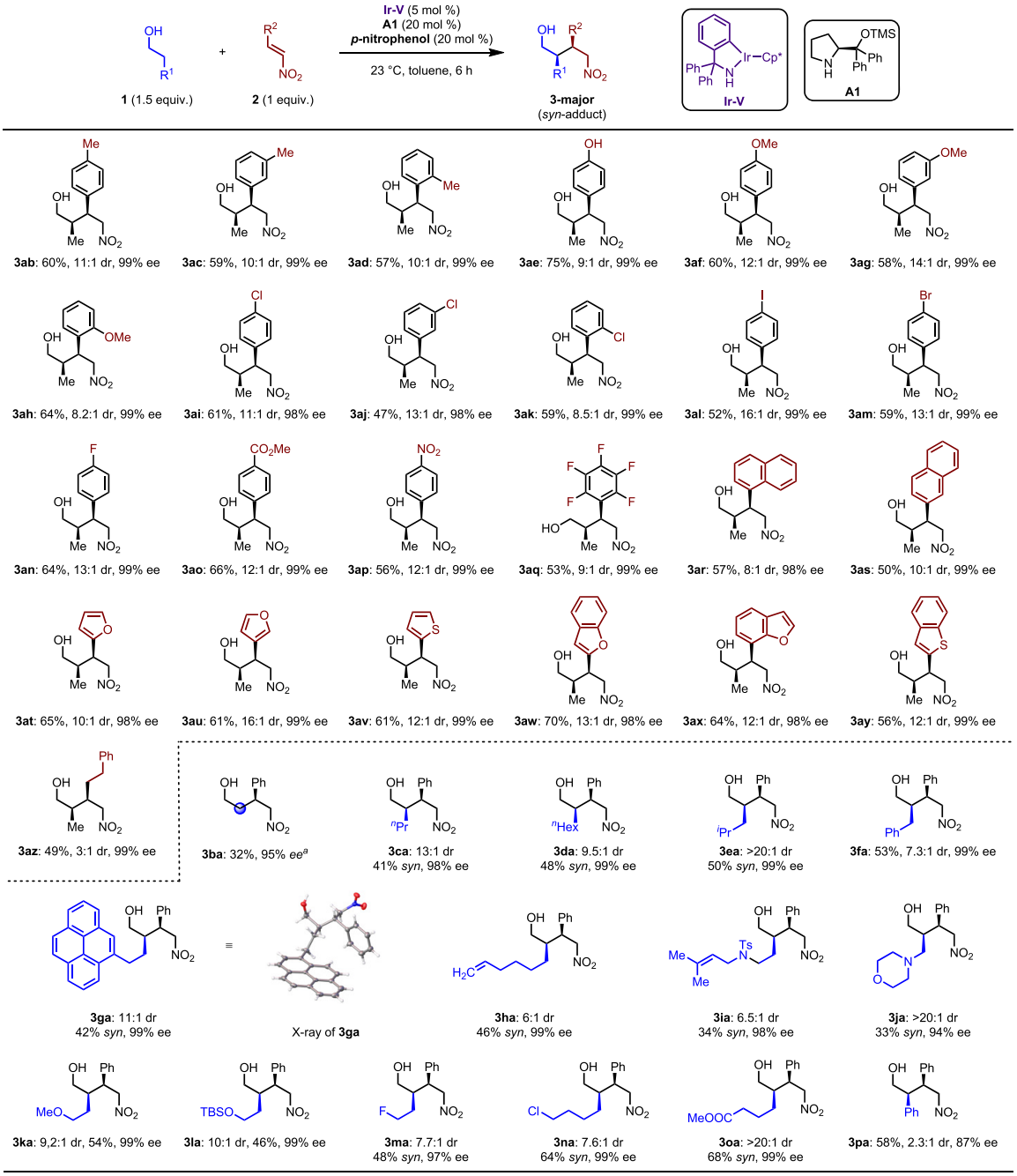
Scheme 3. Scope of Nitroalkenes and Alcohols for β-Alkylation of Alcohols[a]



[a]The reactions were carried out using 1 equiv. **2**, 1.5 equiv. **1**, 5 mol % **Ir-V**, 20 mol % **A1**, and 20 mol % *p*-nitrophenol at ambient temperature in toluene for 6 h. See the Supporting Information for details. [b]Reaction time 3 h.

asymmetric borrowing hydrogen processes.[8a,12a] We then carried out a focused screening of analogous iridacycle complexes, including the more electron-rich **Ir-II** and chiral iridium complexes exemplified by the two isomeric **Ir-III** and **Ir-IV**. Unfortunately, the levels of diastereoselectivity or chemo-selectivity were not improved to a significant amount using these catalysts. After extensive experimentation, we identified that using the preformed 16-electron complex **Ir-V** (by removing the HCl component from **Ir-1**) yielded **3aa** in a good 69% isolated yield in 15:1 dr and 99% ee. At this stage, further screening of an array of chiral amine catalysts including various pyrrolidine- and cinchona alkaloid-derived ones still proved **A1** as the optimal choice (see Table S1 in the SI). A similar observation was made for the evaluation of Brønsted acids; phenol-type additives were shown to be essential for satisfactory yield and diastereoselectivity, with *p*-nitrophenol as the best choice (see Table S2 in the SI).

With the optimal conditions in hand, we next studied the generality of this catalytic diastereo- and enantioselective β-alkylation of primary alcohols using nitroalkenes. As illustrated in Scheme 3, methyl substituents on the *para-*, *meta-*, or *ortho*-position of the phenyl ring were all tolerated to yield the corresponding products **3ab**−**3ad** in 57−60% yield with excellent, >10:1 dr, and uniform 99% ee. Electron-donating

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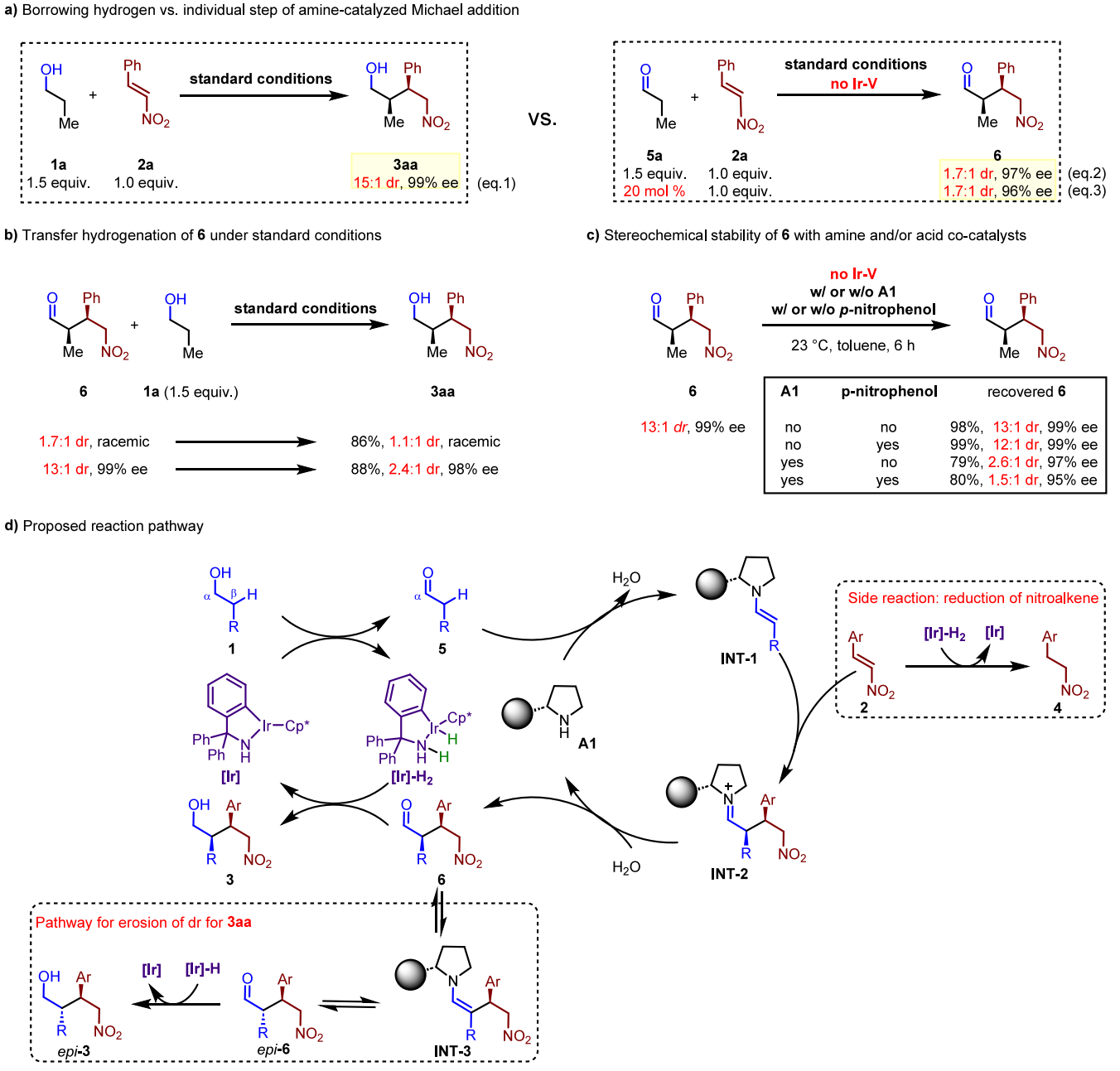
Scheme 4. Mechanistic Investigation of Highly Diastereoselective Formation of 3aa and Proposed Reaction Pathways



substituents including both phenol and methoxy on *para*-, *meta*-, and *ortho*-positions were also well tolerated to afford **3ae**−**3ah** in 58−75% yield, up to 14:1 dr, and all in 99% ee. Electron-withdrawing substituents including halogen (**3ai**−**3an**), ester (**3ao**), and even the very electron-deficient nitro (**3ap**) and pentafluorophenyl (**3aq**) also participated in the reaction smoothly to afford the corresponding products in good yield, dr, and excellent ee. Naphthyls (**3ar**, **3as**) as well as a series of heteroarenes (**3at**−**3ay**) also worked well to afford the corresponding product in 50−70% yield, 8:1−16:1 dr, 98−99% ee. Alkyl-substituted nitroalkenes also worked to produce **3az** with excellent ee, albeit with much lower dr and a moderate yield.

We then explored the scope of primary alcohols. First, we were excited to observe that even ethanol worked out under our catalytic conditions, despite much complication from a double alkylation under the standard reaction condition (6 h). Fortunately, shortening reaction time to 3 h suppressed the over-alkylation and delivered the desired product **3ba** in 32% yield with 95% ee. Considering the significant challenge for enamine catalysis using acetaldehyde,[17] our method provides a practical alternative solution to this issue. A range of aliphatic primary alcohols were examined next; all underwent this transformation smoothly, furnishing **3ca**−**3ea** in useful yields and excellent diastereo- and enantioselectivities. Phenyl- and pyrenyl-containing alcohols also participated in this reaction to deliver **3fa**, **3ga** in excellent ee, useful dr, and yields. A wide range of functionalities, including alkene, sulfonamide, ether, silyl ether, halogen, and ester, were all well tolerated (**3ha**−**3ia**, **3ka**−**3oa**). Morpholine-containing alcohols gave the desired product **3ja** in excellent stereoselectivity, albeit in low yield. In comparison, *β*-aryl-substituted alcohols resulted in lower

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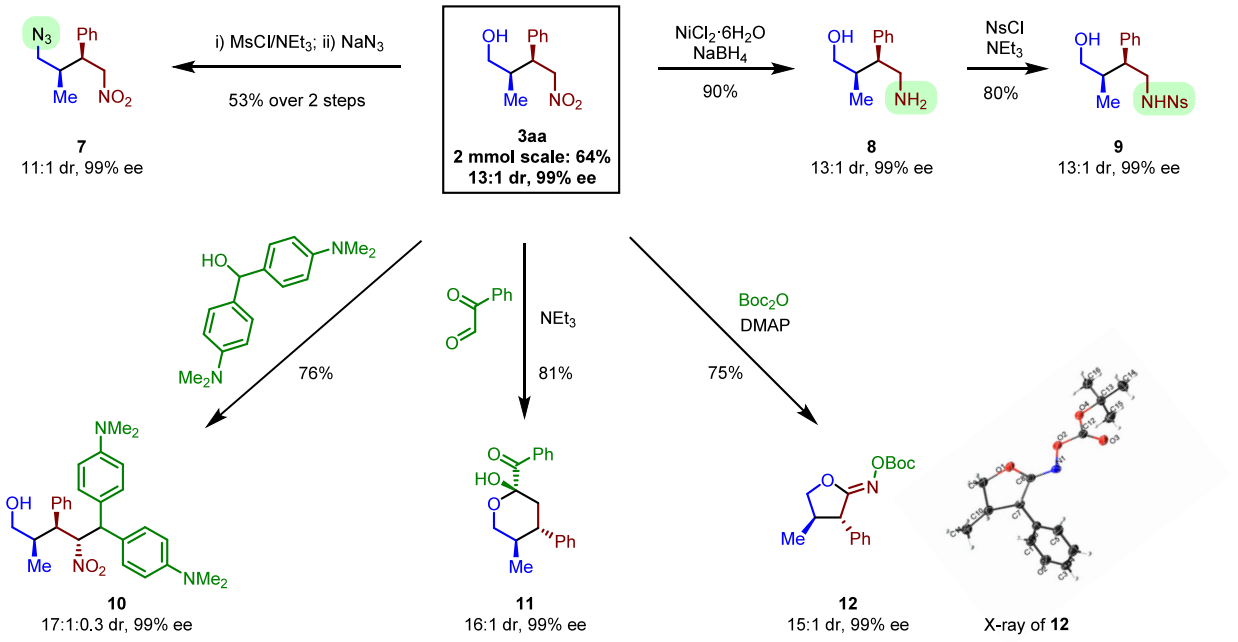
Scheme 5. Product Derivatizations



stereoselectivity (**3pa**), representing a current limitation for this catalytic system.[18]

Mechanistic Studies. An important observation was made during our development of this methodology: our cascade reaction resulted in significantly higher diastereomeric ratio for **3aa** (15:1 dr, eq 1 in Scheme 4a) than the corresponding individual step of amine-catalyzed Michael addition of aldehyde **5a** to **2a**, which produced the nitro-aldehyde **6** with only 1.7:1 dr under identical conditions except for the redox catalyst **Ir-V** (eq 2 in Scheme 4a). Considering that nitro-aldehyde **6** is the key intermediate that is present only in a low catalytic amount in our borrowing hydrogen procedure, we also attempted the Michael addition step using a catalytic amount of **5a** (20 mol %) vs nitroalkene **2a**. Yet, a similarly low 1.7:1 dr was observed for **6** (eq 3 in Scheme 4a). Notably, the ee of **6** remained the same for all of these cases.

We proposed two scenarios to rationalize the enhanced diastereoselectivity in our dual catalytic system to form **3aa**: either the relatively low diastereomeric ratio of aldehyde **6** formed in the enamine catalysis step was enhanced in the hydrogenation step, or undesired epimerization of intermediate **6** was suppressed in our borrowing hydrogen conditions to preserve the high dr when **6** was reduced to **3aa**. To test the first hypothesis, transfer hydrogenation of aldehyde **6** was attempted under the standard catalytic conditions. As shown in Scheme 4b, transfer hydrogenation of **6** (*syn:anti* 1.5:1, racemic) resulted in 86% **3aa** with an even lower 1.1:1 dr. When a diastereo- and enantioenriched **6** (*syn:anti* 13:1, 98% ee) was used instead, **3aa** was also formed with a much lower 2.4:1 dr but the same 98% ee. These results clearly ruled out the hypothesis of enhancement of diastereoselectivity in the reduction step, leading to **3aa**.

Alternatively, we subjected enantiopure **6** (*syn:anti* 13:1, 98% ee) to a series of catalytic conditions in the absence of iridium catalyst but with or without the chiral amine/acid cocatalysts (Scheme 4c). In the absence of all catalysts, recovered **6** remained diastereo- and enantioenriched as expected. In the presence of either chiral amine **A1** or *p*-nitrophenol, partial epimerization was observed for **6**, with **A1** being the dominant factor. The presence of both **A1** and *p*-nitrophenol led to a significant decrease in the dr of **6** (1.5:1). These results supported the partial epimerization of **6** under enamine catalysis conditions. We hypothesize that the borrowing hydrogen process, by effectively reducing the catalytic amount of aldehyde intermediate **6** to **3aa**, manages to preserve the diastereoselectivity of the final product at a high level. This clearly highlights the unique advantage of cascade borrowing hydrogen catalysis in achieving high efficiency as well as stereoselectivity in the formation of functionalized alcohol products, particularly for challenging substrates that are prone to epimerization in their aldehyde form.[19]

Based on the above observations, we propose a catalytic pathway shown in Scheme 4d. The relay of a redox cycle and an enamine-catalyzed Michael addition cycle works smoothly to achieve the direct conversion of simple alcohol **1** to the diastereo- and enantioenriched 1,4-nitroalcohol **3**. It is important to note that a significant side reaction pathway, transfer hydrogenation of **2** to **4**, provides a key challenge to overcome. Furthermore, aldehyde intermediate **6** can undergo epimerization promoted by the amine catalyst through enamine **INT-3**. Such a pathway is effectively diminished under the catalytic borrowing hydrogen conditions due to formation of **6** in low concentrations in combination with efficient reduction to the desired product **3**.

A scale-up synthesis (with identical efficiency and stereoselectivities) and various derivatizations of **3aa** were performed to showcase the synthetic utility of the direct stereoselective *β*-alkylation of alcohols (Scheme 5). First, azidation yielded **7** in 53% yield over two steps smoothly; alternatively, Ni-catalyzed hydrogenation of the nitro group produced *δ*-aminoalcohol **8**, which was protected as sulfonamide **9** with both dr and ee preserved. Next, the S_N1-type alkylation of the nitroalkane moiety in **3aa** afforded **10** in excellent diastereoselectivity.[20] A Henry reaction/E1cB-type HNO_2-elimination cascade with phenylglyoxal also worked out efficiently to deliver the

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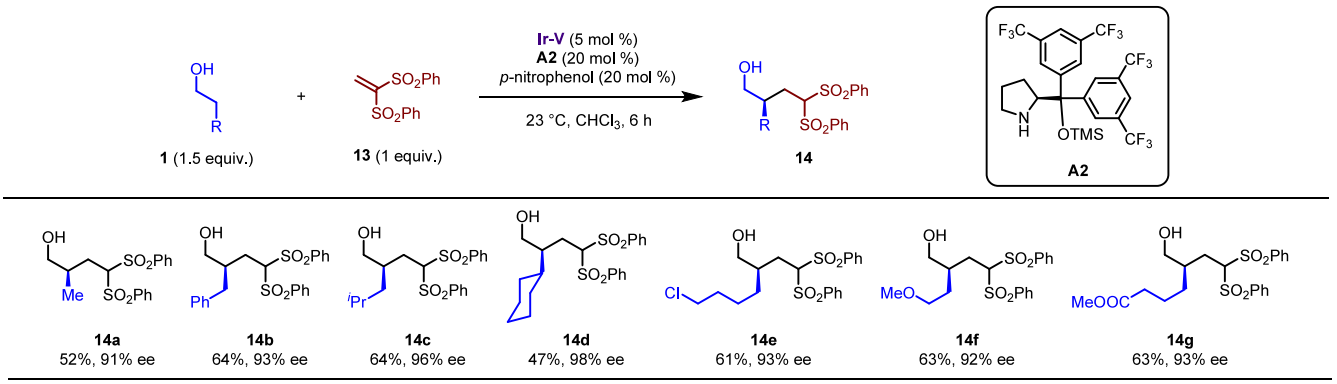
Scheme 6. β-Alkylation of Alcohol Using Vinyl Sulfones[a]



[a]The reactions were carried out using 1 equiv. **2**, 1.5 equiv. **1**, 5 mol % **Ir-V**, 20 mol % **A2**, and 20 mol % *p*-nitrophenol at ambient temperature in chloroform for 6 h. See the Supporting Information for details.

enantioenriched cyclic hemiketal **11**.[21] Oxime carbonate **12** was also formed via Boc_2O-mediated cyclization, which can serve as a useful precursor to chiral butyrolactone natural products.[22]

As another significant extension, we tried to apply this hydrogen-enamine relay catalysis borrowing to Michael acceptors beyond nitroalkenes. As shown in Scheme 6, when vinyl bis-sulfone **13** was used as the formal alkylating reagent, chiral amine catalyst **A2** was identified to be the optimal. Under such conditions, a range of primary alcohols **1** possessing either linear or branched structures or bearing different functionalities participated in β-alkylation smoothly. The 1,4-sulfonyl alcohols **14a**−**14g** were obtained in useful 47−64% yield with uniformly high enantioselectivities ranging from 91 to 98% ee.

CONCLUSIONS

We have achieved a highly efficient, selective, and general β-alkylation of primary alcohols using nitroalkenes through an unprecedented dual catalysis of borrowing hydrogen and enamine Michael addition process. A wide range of densely functionalized 1,4-nitroalcohol products with two contiguous stereogenic centers are formed in good yield (up to 75%), high dr (up to 16:1), and excellent ee (up to 99%). This catalytic β-alkylation of alcohols was also successfully extended to the synthesis of 1,4-sulfonyl alcohols with excellent enantioselectivities. This dual catalysis process is redox-neutral, atom-economical, and step-economical with no stoichiometric waste. Furthermore, we discovered that the borrowing hydrogen cascade delivers the product in higher diastereoselectivity than the enamine catalysis step alone due to an efficient conversion of the catalytically formed substituted aldehyde intermediate to the functionalized alcohol product. We believe our achievement opens diverse opportunities for direct, stereoselective β-C−H functionalization of alcohols that can find wide application in chemical synthesis. Efforts toward that goal are ongoing in our laboratories and will be reported in due course.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.4c17355.

Experimental procedures and characterization data for all the substrates, catalysts, and products (PDF)

Accession Codes

Deposition Numbers 2361825 and 2361832 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via the joint Cambridge Crystallographic Data Centre (CCDC) and Fachinformationszentrum Karlsruhe Access Structures service.

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Notes

The authors declare no competing financial interest.

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