Enantioselective NiH/Pmrox-Catalyzed 1,2-Reduction of α,β-Unsaturated Ketones

Fenglin Chen, Yao Zhang, Lei Yu, and Shaolin Zhu*

In memory of Xiaozeng You

Abstract: The enantioselective 1,2-reduction of α,β-unsaturated ketones was achieved using a NiH catalyst in the presence of pinacolborane. This mild process represents a general method to access a wide variety of structurally diverse α-chiral allylic alcohols in excellent yields and enantioselectivity, as well as very high levels of ambidoselectivity for 1,2-over 1,4-reduction. Furthermore, for reactions on a 10 mmol scale, catalyst loadings as low as 0.5 mol% could be employed to deliver product without any detrimental effect on the yield, enantio-, or ambidoselectivity.

As a privileged structural element, α-chiral allylic alcohols are commonly found in pharmaceuticals and natural products (Figure 1). In addition, they are valuable synthetic intermediates that permit a wide variety of downstream synthetic manipulations.[1] Asymmetric 1,2-reduction of α,β-unsaturated ketones constitutes an efficient and straightforward approach for their construction. However, these transformations are generally complicated by competing 1,2- and 1,4-reduction processes.[2] The two main enantioselective approaches are catalytic hydrogenation[3] and Corey–Bakshi–Shibata (CBS) reduction.[4,5]

Over the past two decades, the use of first-row transition metals in catalytic metal hydride chemistry has attracted increasing attention owing to their low cost and sustainability. In particular, copper and iron hydride based catalysts have become powerful tools for hydrofunctionalization chemistry.[3] Although great progress has been demonstrated for the use of first-row transition-metal hydrides in asymmetric reduction, several challenges still exist. For example, while a highly enantioselective method for enantioselective 1,2-reduction of enones using a CuH catalyst has been reported by Lipshutz, a substituent at the α-position is needed to obtain high levels of 1,2-selectivity (Figure 2A).[6a] Moreover, the chiral phosphate ligands associated with CuH catalysts are generally prepared through expensive, lengthy multistep synthetic procedures, although some are now commercially available. A general asymmetric 1,2-reduction of enones that employs only simple, inexpensive ligands as the source of chirality would be advantageous, especially if previously challenging substitution patterns can be accommodated.

Compared to CuH chemistry, enantioselective reactions involving NiH are not well explored,[8] despite the utility of nickel in a range of chemoselective reductive processes.[9] In this work, we report the ambid- and enantioselective NiH-catalyzed 1,2-reduction of α,β-unsaturated ketones as a convenient and general method for the synthesis of α-chiral...
allyl alcohols (Figure 2B). Specifically, we demonstrate that, by employing the novel, easily prepared chiral oxazoline ligand t-Bu-Pmrox (L1), highly efficient and selective 1,2-reduction of a large collection of enones can be achieved by NiH catalysis.  

We began our study by optimizing the conditions for the reduction of (E)-4-phenylbut-3-en-2-one (S1). Investigation of a range of parameters showed that the desired 1,2-adduct could be obtained in excellent yield (99%) and ee (> 99% ee) within 40 min (Table 1, entry 1). Ligand L1 (t-Bu-Pmrox) was found to be the most effective for this reaction. t-Bu-Pmrox is easily accessible in one step from the corresponding chiral amino alcohol and was readily prepared on a decagram scale (Figure 2B, see the Supporting Information for synthetic details). Although the use of the known ligand t-Bu-Pyrox (L2) led to a comparable result (entry 2), it was subsequently found that L1 provided high 1,2- and enantioselectivity for a broader range of substrates. On the other hand, poor yields were obtained when Box and phosphine ligands were used (entries 3, 4). Conducting the reaction at RT instead of -25 °C led to somewhat lower 1,2-selectivity (entry 5). Furthermore, lower levels of 1,2-selectivity and enantioselectivity were observed in the absence of DABCO as an additive (entry 6). Control experiment showed that HBpin slowly reduced S1 in the absence of Ni and ligand. The addition of DABCO inhibited this background reaction, which accounts for the role of this additive in improving overall levels of selectivity (entries 7, 8). Additionally, other hydride sources (like hydrosilanes) were comparatively ineffective (entry 9). Finally, THF was also found to be a suitable solvent for this reaction (entry 10).

With our optimized conditions, we next examined the substrate scope. As illustrated in Table 2a, an array of β-aryl substituted enones could be converted into secondary allylic alcohol in a highly enantio- and 1,2-selective manner. A wide variety of substituents on the β-aryl ring, including electron-withdrawing (2-7) and electron-donating (8-11) substitutents were well-tolerated. It is noteworthy that, under these exceptionally mild reaction conditions, potentially sensitive functional groups, including a boronic acid pinacol ester (4), an aryl chloride (5), a bromide (6), an iodide (7), and a triflate (11), were left intact. An α,β-unsaturated amide (12) was also compatible, thus highlighting the excellent chemoselectivity of the reaction. Under these conditions, an unprotected phenol could also be used as a substrate (10) if an additional equivalent of pinacolborane was included. The phenol hydroxy group is presumably transformed into the corresponding boronate ester, which then undergoes the desired 1,2-reduction to give the desired α-chiral allylic alcohol product upon chromatographic purification. In addition, heteroaromatic substrates, such as those containing a furan (13) or an indole (14), were also suitable for this reaction. Moreover, chalcone, a substrate bearing an aryl substituent on the carbonyl, also underwent reduction in high conversion and enantioergic excess, although the ambidoselectivity was somewhat diminished compared to α-alkyl substrates (15).

The reaction was also tolerant of a broad array of β-alkyl-substituted enones. As shown in Table 2b, a variety of functional groups were again readily accommodated, including a secondary carbamate (18), ethers (19, 20), an alkene (22), and a silane (23). Moreover, α-substituents other than a methyl group were handled without incident (17, 18, 21). Moreover, the configuration of a conjugated double bond was retained during the reaction (21), and the presence of extended conjugation in β-ionone did not interfere with the 1,2-reduction (22). Finally, a β-silylated enone also underwent 1,2-reduction to afford highly enantioenriched allylic alcohol containing a γ-silicon substituent (23) suitable for subsequent electrophilic functionalization.

The broad scope of this 1,2-reduction method was further demonstrated using a range of less reactive and more challenging β,β-disubstituted enones[1e-11] (Table 2c). Indeed, both β-aryl-β-alkyl-substituted and β,β-dialkyl-substituted enones were found to work well. Moreover, substrates containing electron-donating (25) or electron-withdrawing (26) substitutients on the β-aryl ring both proved compatible, maintaining both high yield and excellent enantioergic excess. In addition, a heteroaromatic substrate based on thiophene (27) could be successfully applied in this reaction, again delivering the corresponding chiral alcohol in high yield and ee. Notably, α-substitution with an alkyl group other than methyl was tolerated without issue (28). In the case of β,β-dialkyl-substituted enone 29, high enantioselectivity was obtained, although the reaction rate was somewhat attenuated compared to β-aryl-β-alkyl-substituted enones.

Enantioenriched protected allylic alcohols are valuable synthetic intermediates. To show the utility of this method in
preparing compounds of this type, we developed a method to prepare the acetyl-protected allylic ester in one-pot procedure. The desired allylic acetate was produced in good yield, with the high enantioselectivity of the 1,2-reduction maintained (Scheme 1).

Finally, to demonstrate the applicability of this process to gram-scale synthesis, two sets of 10.0 mmol reactions were conducted: first with a β-aryl enone and then with a β-alkyl enone. A catalyst loading of 0.5 mol% proved sufficient for both of these reactions, providing the desired products in excellent yield and enantioselectivity and illustrating the high catalytic efficiency and convenience of the developed method (Scheme 2).

In summary, we have described a catalytic asymmetric selective 1,2-reduction process for α,β-unsaturated ketones. Most notably, this versatile method tolerated an unprecedented variety of substitution patterns on the enones. Moreover, the functional-group tolerance of the method was excellent. The use of an abundant first-row transition metal and easily prepared ligand (t-Bu-Pmrox) renders this method suitable for larger-scale applications. Furthermore, in this context, the amount of catalyst required could be further reduced. The application of this method to the synthesis of

| Table 2: NiH-catalyzed asymmetric 1,2-reduction of α,β-unsaturated ketones.^[abc]
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<tr>
<td>α,β-unsaturated ketone</td>
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<tr>
<td>1 R = COOMe, 99% yield, &gt;99% ee</td>
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<tr>
<td>2 R = COOMe, 99% yield, &gt;99% ee</td>
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<tr>
<td>3 R = CN, 96% yield, &gt;99% ee</td>
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<tr>
<td>9 99% yield, &gt;99% ee</td>
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<tr>
<td>11 R = H, 99% yield, &gt;99% ee</td>
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<td>13 99% yield, 99% ee</td>
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<td>15 92% yield, 99% ee</td>
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<td>17 99% yield, 98% ee</td>
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<td>24 99% yield, 95% ee</td>
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<td>26 93% yield, 92% ee</td>
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<td>28 99% yield, 94% ee</td>
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[a] Yield of isolated product on 0.20 mmol scale; unless otherwise noted, the 1,2/1,4 ratios determined by crude ^1^H NMR spectroscopy were always >25:1. [b] Absolute configuration was assigned by chemical correlation or analogy. [c] Enantioselectivities were determined by chiral HPLC analysis.

[d] 2.2 equiv HBpin, 3.0 equiv DABCO. [e] 12 h, [f] 24 h.
pharmaceutical agents and natural products is currently being investigated.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: α,β-unsaturated ketones · 1,2-reduction · asymmetric catalysis · nickel · synthetic methods

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A CuH/phosphine complex has been used for the asymmetric reduction of β,δ-disubstituted enones, but relative lower selectivities and activities were observed. See Ref. [6b].

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