Selective Reduction

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Change of Direction: Enantioselective CuH-Catalyzed 1,2-Reduction of α,β-Unsaturated Ketones

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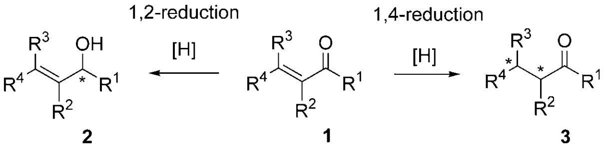
The reduction of α,β-unsaturated ketones generally can give rise to a variety of products: apart from the synthetically useful chiral allylic alcohols (1,2-reduction) and saturated ketones (1,4-reduction), the reaction can also lead to saturated alcohols (consecutive 1,4- and 1,2-reductions) and, under certain circumstances, further to alkenes and alkanes. Therefore, over the years efforts have been directed at developing and refining practical methods to tackle the issues of regio- and chemoselectivity with a particular focus on selective 1,2- and 1,4-reduction manifolds (Scheme 1).[1]



Scheme 1. Regioselectivity in the reduction of unsaturated ketones.

For substrates with the appropriate substitution pattern, both reactions shown in Scheme 1 will generate new stereogenic centers. A modern paradigm for stereochemical thinking dictates that in such cases the regioselectivity has to be complemented by a high level of enantiocontrol, preferably delivered in the catalytic manner. As a result, a number of highly efficient catalytic systems have been introduced to promote either 1,2-reduction (Scheme 1, **1**→**2**)[2] or conjugate reduction (**1**→**3**)[3] of α,β-unsaturated ketones. However, a particular value is attributed to the methods that are competent in both 1,2- and 1,4-reduction manifolds, where the regioselectivity can be predictably controlled by altering electronic and steric properties of the catalytic system or the substrate or both.

One such emerging methodology involves Lewis base catalyzed reduction of unsaturated ketones with trichlorosilane.[4] Here, strong Lewis bases such as hexamethylphosphoramide (HMPA) and triphenylphosphine oxide favor 1,4-reduction, whereas the weaker Lewis base *N*,*N*-dimethylformamide (DMF) promotes the addition of hydride in a 1,2-fashion. With the chiral phosphine oxide catalyst BINAPO, the conjugate reduction proceeded in high enantioselectivity (up to 97% *ee*) and was further extended to the reductive aldol reaction.[4] However, despite some success in the asymmetric reduction of simple ketones and the 1,2-reduction of conjugated imines,[5] the respective asymmetric 1,2-reduction manifold of conjugated ketones is yet unexplored.

In the array of asymmetric reduction methods, the hydrosilylation of carbon–carbon and carbon–heteroatom double bonds employing chiral CuH complexes occupies a privileged position because of the excellent record shown in application to a variety of substrate classes. Copper hydride coordinated to a chiral ligand provided useful enantioselectivity in the conjugate reduction of various Michael acceptors and in the 1,2-reduction of prochiral ketones and ketimines.[6] As far as unsaturated ketones are concerned, the inherent tendency of Cu to coordinate to C–C double bonds renders 1,4-addition the preferred mode of action. This led to development of a number of highly efficient enantioselective protocols.[7] However, in spite of some earlier observations that the natural 1,4-regioselectivity of the CuH systems can be switched to 1,2-selectivity by careful tuning of the steric and electronic properties of the ligands,[8] the asymmetric version remained on chemists' wish list.

Therefore, the recent publication from the group of Lipshutz[9] on the asymmetric 1,2-reduction of α,β-unsaturated ketones can be heralded as this missing piece in the jigsaw puzzle of enantio- and regioselective methodology based on CuH catalysis (Scheme 2). The main features of the new methodology are as follows: In the general structure of the substrate ketones **4**, α substitution is the prerequisite for 1,2-selectivity. High enantioselectivity on the level of 90% *ee* was attained with the chiral ligands **L1** and **L2**. Diethoxymethylsilane (DEMS) was the best of the stoichiometric reducing reagents, delivering the highest enantioselectivity. Diethyl ether as the solvent and a reaction temperature of −25 °C completed the set of optimal reaction conditions.

In terms of the substrate scope, α-methyl cinnamyl derivatives (**4**, $R^3 = $ aryl, $R^2 = $ Me or Et) all produced the respective allylic alcohols in high yields (93–97%) and good enantioselectivities (62–95% *ee*). Homologues with, for example, ethyl and *n*-pentyl instead the α-methyl group,

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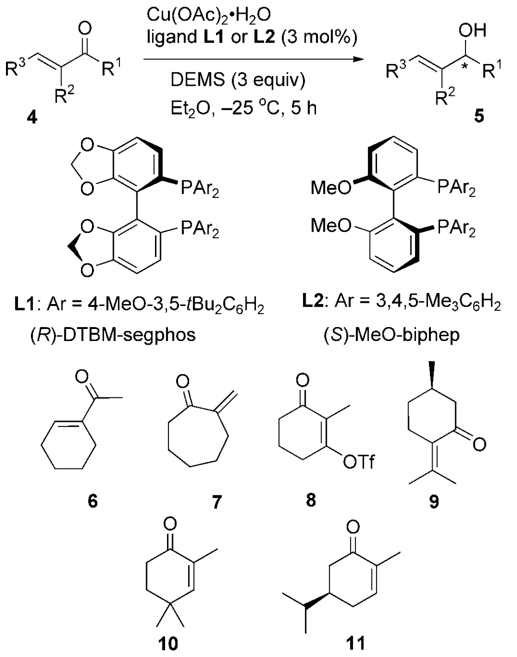

Scheme 2. Enantioselective 1,2-reduction of unsaturated ketones.

behaved in the same way; however, somewhat lower selectivity (76–77 % *ee*) was observed for substrates with α-phenyl and α-bromo substituents. Reduction of cyclic substrates **6–10** followed the same pattern of regio- and enantiocontrol.

Several important observations are worth noting. The crucial role of α substitution in the substrate ketone is further illustrated by the reduction of exocyclic enone **7**: even in the absence of any steric bias at the β position, only the carbonyl function is reduced. Mild reaction conditions allowed for a clean 1,2-reduction of ketone **8** bearing an additional vinyl triflate functionality, which with harsher reducing reagents suffered extensive decomposition. In the reduction of (*R*)-pulegone (**9**), the sense of the asymmetric induction was shown to be controlled by the chiral ligand. Thus the complex of CuH with (R_{ax})-**L1** produced the *cis* isomer, whereas the catalyst based on (S_{ax})-**L1** gave rise to the respective, less common *trans* product.

The results of this investigation demonstrated that to promote 1,2-regioselectivity in the asymmetric reduction of unsaturated ketones catalyzed by chiral CuH complexes, α substitution in the substrates appears to be a necessary condition; however, it is certainly not a sufficient one. Thus, with *o*-bis-(diphenylphosphino)benzene as a ligand and α-methyl cinnamyl derivative **4** ($R^3 = Ph$; R^1, $R^2 = Me$) as a substrate, conjugate reduction was the predominant process. Further, while the [(R_{ax})-**L1**]CuH system led exclusively to the 1,2-reduction of **10**, complex [$(Ph_3P)CuH$] in the reduction of similar ketone **11** resulted in 1,4-selectivity.[7b] Clearly, the ligands with their specific electronic and steric properties also have an important role to play. Future mechanistic and computational investigations should shed more light on the nature of this intriguing switch in regioselectivity.

In conclusion, the new methodology developed by Lipshutz and co-workers has a twofold significance. First, it demonstrates that, at least for an extended subset of substrates, it is possible to override the natural 1,4-reactivity of CuH complexes towards conjugated ketones and switch it to the normally less favorable 1,2-reaction manifold by carefully tuning the electronic and steric properties of the catalytic system, though the exact nature of these effects remains obscure at the moment. Secondly, the new methodology gives practical access to chiral nonracemic allylic alcohols, a valuable class of stereochemically defined synthetic building blocks.

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