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Enantioselective Organocatalytic Hydride Reduction

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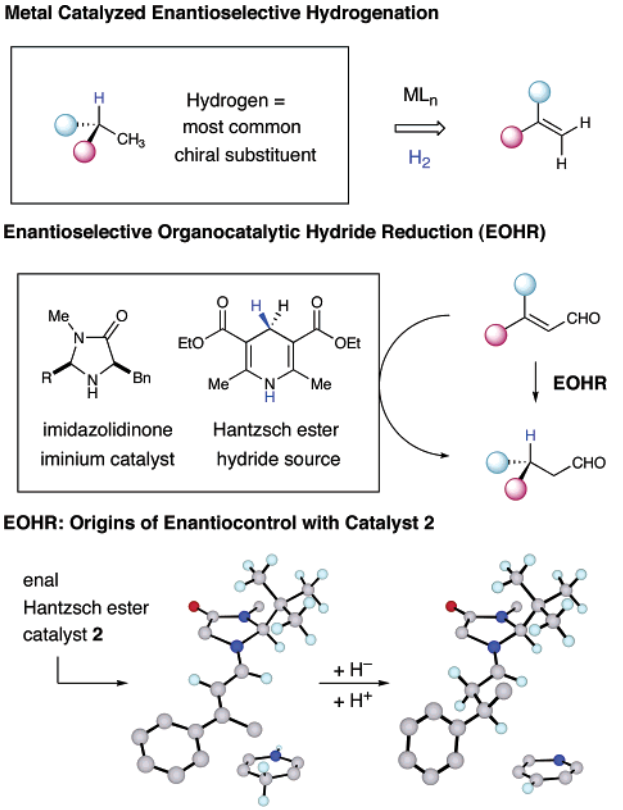
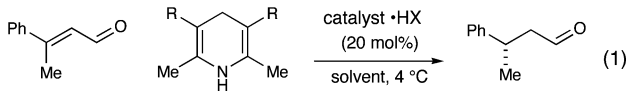
Within the vast architectural subclass known as stereogenicity, hydrogen is found to be the most common substituent. Not surprisingly, therefore, the field of enantioselective catalysis has focused great attention on the invention of hydrogenation technologies over the last 50 years.[1] While these powerful transformations rely mainly on the use of organometallic catalysts and hydrogen gas, it is intriguing to consider that the large majority of hydrogen bearing stereocenters are created in biological cascade sequences involving enzymes and hydride-reduction cofactors such as NADH or $FADH_2$.[2] On this basis, we recently questioned whether the conceptual blueprints of biochemical hydride addition might be employed in a chemical reduction wherein enzymes and cofactors are replaced by small molecule organocatalysts and dihydropyridine analogues. In this context, we report the development of the first enantioselective organocatalytic hydride reduction (EOHR),[3] a bio-inspired protocol that formally allows the enantioselective transfer of hydrogen from Hantzsch esters to enal-olefins using amine catalysts.[4]



Our laboratory has reported that the LUMO-lowering activation of α,β-unsaturated aldehydes via the reversible formation of iminium ions is a useful platform for the development of enantioselective cycloadditions[5a] and π-nucleophile alkylations.[5b] On this basis, we began to consider that the enantioselective reduction of α,β-unsaturated aldehydes[6] might be accomplished using dihydropyridine analogues[7] in the presence of iminium catalysts. As revealed in Table 1, exposure of 3-methyl-(*E*)-cinnamaldehyde to ethyl Hantzsch ester[8] in the presence of L-proline resulted in inefficient and nonselective reduction (entry 1). In contrast, a dramatic increase in enantioselectivity and reaction efficiency was achieved using our imidazolidinone catalysts **1** and **2** (entries 2−8, ≥75% ee). A survey of reaction media for this organocatalytic hydride delivery revealed that $CHCl_3$ provides the highest levels of enantiocontrol at subambient temperatures (entry 7, 93% ee). The superior levels of asymmetric induction and efficiency exhibited by amine salts **2**·TFA or **2**·TCA in $CHCl_3$ at −30 °C to afford (*S*)-3-phenylbutanal in ≥92% ee prompted us to select these conditions for further exploration.

Table 1. Effect of Catalyst and Solvent on EOHR[a]



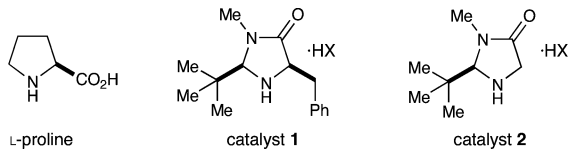
entry	catalyst	HX	solvent	time (h)	% conversion[b]	% ee[c]
1	L-proline	TFA	toluene	5	47	15
2	**1**	TFA	toluene	1	96	75
3	**2**	TFA	toluene	1	95	88
4	**1**	HCl	toluene	8	70	81
5	**2**	HCl	toluene	31	19	87
6	**2**	TFA	$CHCl_3$	1	99	85
7	**2**	TFA	$CHCl_3$	24	90[d]	93
8	**2**	TCA	$CHCl_3$	23	91[d]	93

[a] R = CO_2Et. [b] Conversion determined by GLC analysis. [c] Enantiomeric excess determined by chiral GLC analysis (Bodman Γ-TA). [d] At −30 °C.

Table 2. Effect of Dihydropyridine Component on EOHR[a]

entry	hydrogen source	time (h)	% conversion[b]	% ee[c]
1	NADH	24	–	–
2	*N*-Bn-nicotanamide	26	15	88
3	R = CO_2Et	7	92	92
4	R = CO_2Bn	7	94	88
5	R = CO_2Me	26	57	89
6	R = COPh	24	54	80
7	R = COMe	26	45	86

[a] Experiment as shown in eq 1 at −30 °C. [b] Conversion by GLC analysis. [c] Enantiomeric excess by chiral GLC analysis (Bodman Γ-TA).



The utility of various dihydropyridine reagents has been investigated (Table 2, eq 1). To our surprise, NADH was not a viable reagent, whereas *N*-benzylnicotinamide was quite selective (entry 2, 88% ee). While a range of reduced pyridines that incorporate electron withdrawing groups is useful, the ethyl Hantzsch ester proved to be superior (entry 3, 93% ee).

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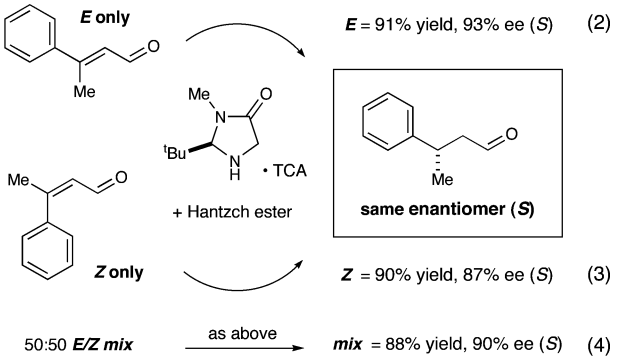
We next examined the influence of the aldehyde olefin geometry on the sense of asymmetric induction. As shown in eqs 2 and 3, we were surprised to find that isomerically pure *E*- and *Z*-olefin substrates *converge to the same (S)-enantiomer*. As such, implementation of the corresponding *E*:*Z* olefin mixture provides excellent levels of enantiocontrol (eq 4, 90% ee). This result stands in marked contrast to most metal-mediated hydrogenations wherein olefin geometry dictates enantiospecific reductions.[9] Preliminary studies have shown that the origin of stereoconvergence in our case arises from catalyst accelerated *E*−*Z* isomerization prior to selective hydride delivery to the *E*-olefin isomer. We anticipate that the capacity to tolerate starting materials of low geometric purity will greatly enhance the general utility of this operationally simple asymmetric reduction.



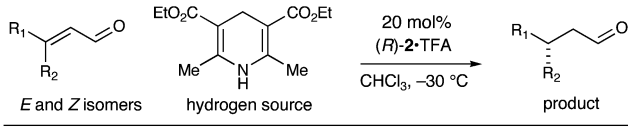
Experiments that probe the scope of the α,β-unsaturated aldehyde component are summarized in Table 3. Given the capacity of catalyst **2** to rapidly isomerize disubstituted enals, we were surprised to find that this asymmetric hydride reduction can accommodate β,β-olefin substituents of similar steric demand (entries 1−6, R_1 = Me, Et; R_2 = Ar, c-hex). For example, high levels of enantiocontrol are obtained with the ethyl−cyclohexyl combination (entry 6, 95% yield, 91% ee), a transformation that can differentiate the geometric location of methine and methylene substituents in a dynamic kinetic resolution. Moreover, the presence of a silyloxy group allows selective partitioning of a similar methylene−methyl relationship (entry 8, 74% yield, 90% ee). Variation in the electronic nature of the aldehyde component has little influence on the inherent enantiocontrol. Indeed, good levels of asymmetric induction are available with enals that do not readily participate in iminium formation (entry 7, R_1 = CO_2Me, 83% yield, 91% ee), as well as aldehydes that provide stable iminium intermediates (entry 2, R_1 = Ph, 91% yield, 93% ee). The severe steric constraints of the *tert*-butyl adduct are rapidly overcome at 23 °C (entry 9, 97% ee, 95% yield, 5 min). Importantly, this mild hydride-delivery method is compatible with functional groups that are often susceptible to reduction (e.g., aldehydes and halogens, entry 4, 92% yield, 97% ee).

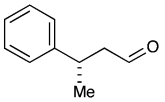
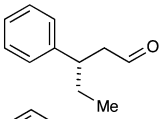
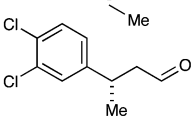
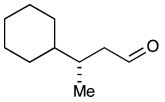
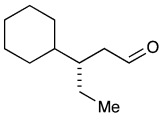
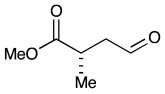
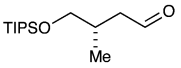
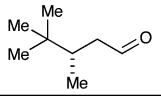
In summary, we have developed the first organocatalytic hydride reduction, an operationally simple reaction that allows the enantio- and chemoselective transfer of hydrogen from Hantzsch esters to geometrically impure enals. Full details of this survey along with catalytic procedures for cyclic and acyclic enone reduction will be described shortly.

Acknowledgment. Financial support was provided by the NIHGMS (R01 GM66142-01) and kind gifts from Amgen, Lilly, and Merck. S.G.O. is grateful for an NSERC fellowship.

Supporting Information Available: Experimental procedures, structural proofs, and spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

Table 3. Effect of Aldehyde Substituents on EOHR



entry	*E*:*Z* substrate	product	time (h)	% yield	% ee[a]
1	> 20:1		23	91	93[b]
2	> 20:1		48	79	94[b,c]
3	> 20:1		16	74	94
4	> 20:1		16	92	97
5	5:1		10	91	96[b]
6	3:1		23	95	91[c]
7	> 20:1		26	83[d]	91[f]
8	> 20:1		72	74	90
9	> 20:1		0.5	95[d]	97[e]

[a] Enantiomeric excess determined by chiral GLC analysis. [b] Performed at −45 °C. [c] Using 10 mol % catalyst. [d] Yield determined by NMR. [e] Using 5 mol % catalyst at 23 °C. [f] Performed at −50 °C.

References

(1) (a) Akabori, S.; Sakurai, S.; Izumi, Y.; Fujii, Y. *Nature* **1956**, *178*, 323. (b) Ohkuma, T.; Kitamura, M.; Noyori, R. In *Catalytic Asymmetric Synthesis*, 2nd ed.; Ojima, I., Ed.; Wiley-VCH: New York, 2000. (c) Noyori, R. *Angew. Chem., Int. Ed.* **2002**, *41*, 2008.

(2) Alberts, B.; Bray, D.; Lewis, J.; Raff, M.; Roberts, K.; Watson, J. D. *Molecular Biology of the Cell*, 3rd ed.; Garland: New York & London, 2002.

(3) This complete study was first presented orally at the Lilly Grantee Symposium, Indianapolis, IN, March 1, 2003.

(4) The conjugate reduction of Wieland−Miescher ketone has previously been accomplished with Hantzsch ester: (a) Pandit, U. K.; Mas Cabré, F. R.; Gase, R. A.; de Nie-Sarink, M. J. *J. Chem. Soc., Chem. Commun.* **1974**, 627. (b) de Nie-Sarink, M. J.; Pandit, U. K. *Tetrahedron Lett.* **1979**, *26*, 2449

(5) (a) Ahrendt, K. A.; Borths, C. J.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2000**, *122*, 4243. (b) Austin, J. F.; MacMillan, D. W. C. *J Am. Chem. Soc.* **2002**, *124*, 1172.

(6) Keinan, E.; Greenspoon, N. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 8, Chapter 3.5, p 523.

(7) (a) Stout, D. M.; Meyers, A. I. *Chem. Rev.* **1982**, *82*, 223. (b) Lavilla, R. *J. Chem. Soc., Perkin Trans. 1* **2002**, 1141.

(8) Hantzsch, A. *Justus Liebigs Ann. Chem.* **1882**, *215*, 1.

(9) (a) Miyashita, A.; Yasuda, A.; Takaya, H.; Toriumi, K.; Ito, T.; Souchi, T.; Noyori, R. *J. Am. Chem. Soc.* **1980**, *102*, 7932. (b) Lipshutz, B. H.; Servesko, J. M. *Angew. Chem., Int. Ed.* **2003**, *41*, 4789.

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