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Organocatalytic Transfer Hydrogenation of Cyclic Enones

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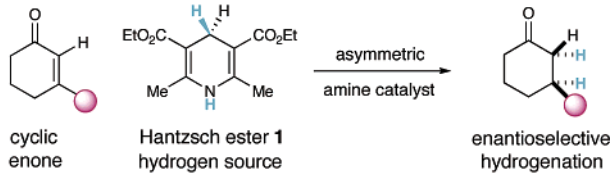
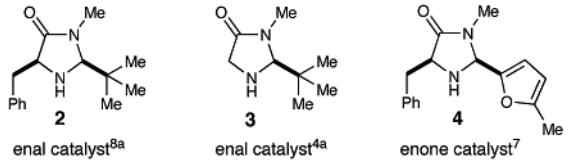
Over the last 50 years, the field of enantioselective catalysis has focused great attention on the invention of hydrogenation technologies.[1] While these powerful transformations have relied mainly on the use of organometallic catalysts,[2] recent studies have demonstrated that organocatalytic transfer hydrogenations can be accomplished with α,β-unsaturated aldehydes using the conceptual blueprints of biochemical reduction, wherein enzymes and NADH cofactors[3] are replaced by small molecule amine catalysts and Hantzsch ester pyridines.[4] Given that stereogenically complex carbocycles are among the most broadly represented synthons found in natural products and medicinal agents, we recently questioned whether the enantio- and chemoselective reduction of cyclic enones could also be addressed using this biomimetic activation mode (eq 1). In this paper, we report the successful execution of these ideals and present the first asymmetric organocatalytic transfer hydrogenation of α,β-unsaturated ketones, an operationally trivial protocol that allows rapid access to enantioenriched cycloalkenones using an aerobically stable catalyst, wet solvents, and an inexpensive hydride source.

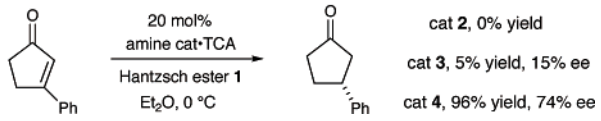
Enantioselective Organocatalytic Transfer Hydrogenation (eq 1)



Imidazolidinone Iminium–Activation Catalysts (Cat)

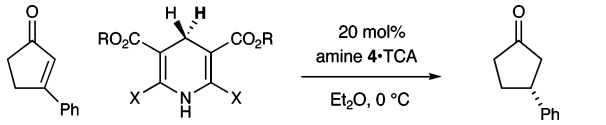


Organocatalytic Enone Reduction: Preliminary Results (eq 2)



The proposed enantioselective enone hydrogenation was first examined using 3-phenyl-2-cyclopentenone, ethyl Hantzsch ester **1**,[5] and a series of imidazolidinone catalysts **2**−**4** (eq 2). Notably, this conjugate reduction strategy was unsuccessful with imidazolidinone salts that have previously been identified[4a] as useful catalysts for enal hydrogenation, an appreciable outcome given that ketones are sterically and electronically deactivated toward iminium formation in comparison to aldehydic carbonyls (catalyst **2**, 0% yield; catalyst **3**, 5% yield). With this in mind, we next examined the furyl imidazolidinone catalyst **4**,[6] an amine that has previously enabled enantioselective Diels−Alder reactions with cyclic enones[7] via an iminium activation platform.[8] As revealed in eq 2, the *cis*-2,5-furylbenzyl disubstituted amine **4** did indeed effect the organocatalytic hydrogenation of 3-phenyl-2-cyclopentenone with excellent reaction efficiency and moderate enantiocontrol (eq 2, catalyst **4**, 96% yield, 74% ee).

Table 1. Effect of Hantzsch Ester Substituents on Enantioselectivity



	Hantzsch Ester				
entry	CO_2R	X	time (h)	% conversion[a]	% ee[b]
1	CO_2Et	Me	3	96	74
2	CO_2Et	Et	4	76	82
3	CO_2Et	H	3	93	73
4	CO_2Me	*i*-Pr	24	57	86
5	CO_2*i*-Pr	Me	3	78	78
6	CO_2*t*-Bu	Me	6	86	91

[a] Conversion determined by GLC analysis. [b] Enantiomeric excess determined by chiral GLC analysis (Bodman Γ-TA).

Heartened by these preliminary results, we next performed structure−selectivity relationship studies on the dihydropyridine transfer hydrogenation reagent[9] (Table 1). There appears to be a trend toward improved enantiocontrol as the steric demand at the 2,6-dialkyl position increases (cf. entries 1−3, X = H, 73% ee; X = Me, 74% ee; X = Et, 82% ee). Furthermore, the relative size of the ester moieties at the 3,5-dihydropyridine site correlates directly with the observed selectivities (entries 1, 5, and 6, R = Et, 74% ee; R = *i*-Pr, 78% ee; R = *t*-Bu, 91% ee). Most importantly, a dramatic improvement in asymmetric induction was achieved using the bis(*tert*-butyl) ester Hantzsch system to afford the reduced cyclopentanone in 91% ee (entry 6). The superior levels of induction and efficiency exhibited by the TCA of amine **4** in Et_2O at 0 °C to afford (*R*)-3-phenylcyclopentanone in 91% ee and 86% conversion prompted us to select these conditions for further exploration.

Experiments to probe the scope of the cyclic enone component have revealed that a wide range of carbocycles and β-olefin substituents are tolerated in this enantioselective transfer hydrogenation[10] (Table 2). For example, high levels of stereocontrol are obtained with ring systems that incorporate β-alkyl groups of broad steric demand, (cf. entries 1 and 6, Me = 72% yield, 95% ee; *c*-hex = 85% yield, 96% ee). Indeed, even the severe steric constraints of the *tert*-butyl adduct are readily accommodated at 0 °C (entry 2, 81% yield, 96% ee), a substrate that, to date, has not been useful for analogous metal-mediated reductions. Moreover, variation in the electronic nature of the ketone component has little influence on the inherent enantiocontrol. For example, good levels of asymmetric induction are available with enones that do not readily participate in iminium formation (entries 7 and 8, R = COMe, 78% yield, 91% ee, R = CO_2Me, 83% yield, 90% ee), as well as

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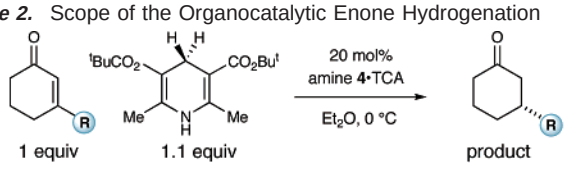
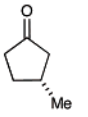
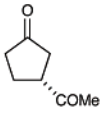
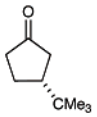
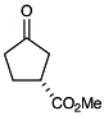
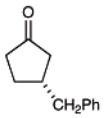
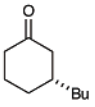
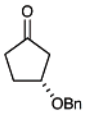
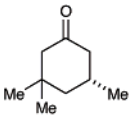
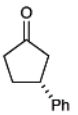
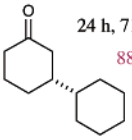
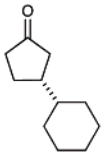
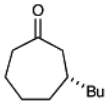
Table 2. Scope of the Organocatalytic Enone Hydrogenation



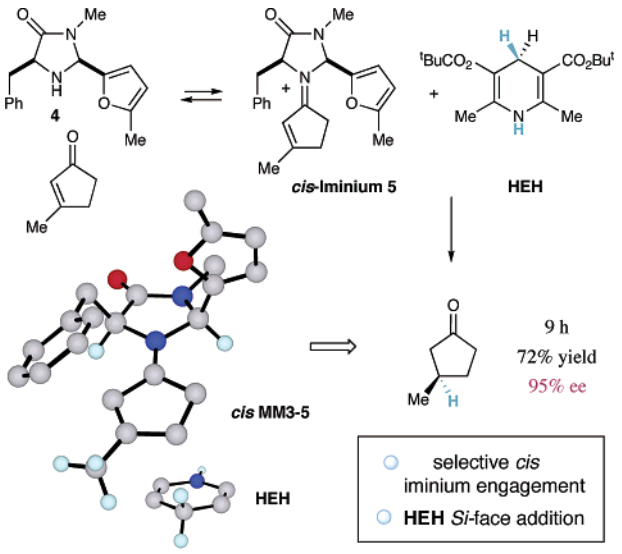
entry	product	time (h) yield, % ee[a]	entry	product	time (h) yield, % ee[a]
1		9 h 72% yield[b] 95% ee	7		1 h 78% yield 91% ee
2		6 h 81% yield[b] 96% ee	8		1 h 83% yield 90% ee
3		11 h 78% yield 90% ee	9		25 h 82% yield 90% ee
4		13 h 89% yield[c] 91% ee	10		40 h 66% yield 98% ee
5		9 h 73% yield 91% ee	11		24 h, 71% yield 88% ee
6[d]		8 h 85% yield 96% ee	12		9 h 70% yield 92% ee

[a] Enantiomeric excess determined by chiral GLC analysis. [b] Yield determined by NMR. [c] Performed with 1.3 equiv of Hantzsch ester. [d] Performed with 1.1 equiv of ethyl Hantzsch ester **1**.

unsaturated systems that provide stable iminium intermediates (entry 5, R = Ph, 73% yield, 91% ee). Interestingly, the 3-benzyloxy-2-cyclopentenyl system is a suitable substrate for this reduction protocol, a surprising result given the anticipated stability of the corresponding iminium adduct and the capacity of the subsequent enamine intermediate to undergo β-benzyloxy elimination (entry 4, 89% yield, 91% ee). Importantly, this enantioselective transfer hydrogenation appears to be suitable for a diverse range of ring sizes, including cyclopentenyl, cyclohexenyl, and cycloheptenyl architecture (cf. entries 1, 9, and 12, 70−82% yield, 90−95% ee). This protocol has also been validated with enones that incorporate alkyl substituents at other ring positions, an important consideration with respect to natural product synthesis (e.g., entry 10, *gem*-dimethyl, 66% yield, 98% ee).

The sense of asymmetric induction observed in all cases is consistent with selective engagement of the Hantzsch ester reductant with the *Si* face of the *cis*-iminium isomer **5** (**MM3**−**5**). This result is in complete accord with our previous Diels−Alder studies involving cyclic enones and furanyl imidazolidinone **4**.

In summary, we have developed the first enantioselective organocatalytic transfer hydrogenation involving cyclic enones, an



operationally simple reaction that allows the rapid and chemoselective access to β-substituted cycloalkenones. Full details of this survey will be disclosed shortly.

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

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(6) Furyl imidazolidinone **4** is now commercially available from Aldrich Chemical Co., Milwaukee, WI.

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(10) Representative procedure: To a flask containing the α,β-unsaturated ketone (1 equiv) in Et_2O (0.5 M) at 0 °C was added catalyst **3** (20 mol %), followed by *tert*-butyl Hantzsch ester (1.1 equiv), then trichloroacetic acid (20 mol %). The resulting mixture was stirred at 0 °C until complete consumption of the unsaturated ketone was determined by TLC analysis. The reaction mixture was then passed through a plug of silica gel with the aid of Et_2O and then purified by silica gel chromatography.

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