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Enantioselective Organocatalytic C−H Bond Functionalization via Tandem 1,5-Hydride Transfer/Ring Closure: Asymmetric Synthesis of Tetrahydroquinolines

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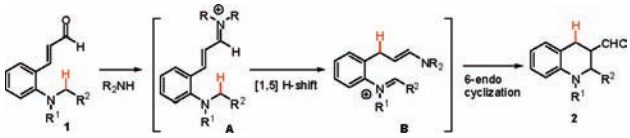
Abstract: The first organocatalytic enantioselective intramolecular 1,5-hydride transfer/ring closure reaction is described. This redox neutral reaction cascade allows for the efficient formation of ring-fused tetrahydroquinolines in high enantioselectivities.

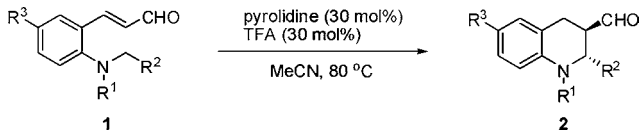
The development of direct C−H bond functionalization has now become an area of intense interest in synthetic organic chemistry because such reactions offer new strategies for the synthesis of complex organic targets.[1] The Lewis or Brønsted acid mediated activation of an unreactive C−H bond was recently reported by Sames and other groups.[2] This protocol includes the initial cleavage of a C−H bond in the context of a 1,5-hydride transfer and subsequent ring closure. The *tert*-amino effect and related 1,5-hydride transfer/subsequent ring closure have attracted much attention due to its unique features to afford tetrahydroquinolines.[3,4] Although the C−H functionalization was mostly promoted by a transition metal catalyst, this methodology is limited in terms of the reaction conditions employed. Enantiopure tetrahydroquinolines have great synthetic importance in the preparation of pharmaceuticals and agrochemicals, as well as in material sciences.[5] Furthermore, many natural products, particularly alkaloids, consist of this structural key element.[6] Recently, Seidel's group reported the asymmetric synthesis of ring-fused tetrahydroquinolines via a Lewis acid catalyzed enantioselective intramolecular hydride transfer/ring closure reaction.[7] Although, an enantioselective tandem 1,5-hydride transfer reaction catalyzed by chiral organocatalysts remains elusive, if successfully promoted with a practically accessible chiral catalyst, it could provide a highly attractive, convergent approach toward optically active tetrahydroquinolines. Recently, chiral amines have emerged as new and powerful catalysts for enantioselective organocatalytic reactions.[8]

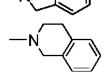
Scheme 1. Concept of the Organocatalytic Intramolecular Redox Reaction



As part of the research program related to the development of synthetic methods for the enantioselective construction of stereogenic carbon centers,[9] we recently reported the organocatalytic asymmetric conjugate addition reaction to α,β-unsaturated carbonyl compounds.[10] Herein, we describe the first organocatalytic synthesis of tetrahydroquinoline derivatives via 1,5-hydride transfer/ring closure sequences (Scheme 1). To the best of our knowledge, there are no reports of organocatalytic intramolecular redox reactions.

Table 1. Organocatalytic Hydride Transfer/Ring Closure



entry	1,	-NR^1(CH$_2$R^2)	R^3	time (d)	yield (%)[a]	dr (%)[b]
1	**1a**		H	2	95	87/13
2	**1b**		CF_3	4	90	77/23
3	**1c**		Br	3	90	77/23
4	**1d**		H	3	65	78/22
5	**1e**		H	1	90	70/30
6	**1f**		H	2 h	95	77/23
7	**1g**		CF_3	2 h	90	80/20
8	**1h**		Br	2 h	90	75/25
9	**1i**		H	1.5 h	87	77/23
10	**1j**		H	1	67	90/10
11	**1k**		H	1	98	59/41

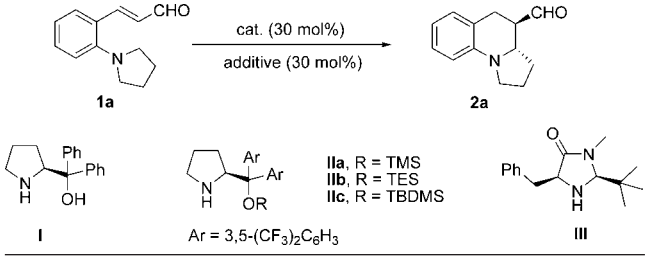
[a] Combined yield of both diastereomers. [b] Diastereomeric ratio is determined by ^{1}H NMR spectroscopic analysis.

We thus decided to investigate the use of organocatalysts for the transformation of **1** to **2**. We speculated that cinnamaldehyde derivatives **1** represent ideal acceptors that are susceptible to activation by secondary amine catalysts capable of forming iminium ion **A**. This iminium ion activation is expected to increase the hydride transfer to alkene.

In an attempt to validate the feasibility of the proposed organocatalytic intramolecular redox reactions, *o*-dialkylamino-substituted cinnamaldehydes **1** were reacted in the presence of pyrrolidine (30 mol %) as an organocatalyst and trifluoroacetic acid (30 mol %) as an additive in CH_3CN at 80 °C. The results of a representative selection of intramolecular redox reactions with cinnamaldehydes **1** are summarized in Table 1. The corresponding cinnamaldehydes **1e**−**i** containing seven- to nine-membered amine donors readily afforded to the corresponding products with high yields (entries 5−9). Isoindoline- and tetrahydroisoquinoline-substituted cinnamaldehydes **1j**−**k** were also readily rearranged to **2j**−**k**.

Based on preliminary results, we performed the enantioselective organocatalytic intramolecular redox reactions using *o*-*N*-pyrrolidinyl-substituted cinnamaldehydes **1a** (Table 2). Initially, chiral secondary amine catalysts **I**−**III** (entries 1−3) were screened for activity in the presence of trifluoroacetic acid as additives in acetonitrile at 80 °C. The reaction proceeded (80−95% conversion after 12 h) and afforded the product **2a** in low enantioselectivity (9−17% for major diastereomer). To address the need for enhanced enantioselectivity, we screened various solvents (entries 4−6) and additives (entries 7−11).

Table 2. Optimization of Reaction Conditions for Catalytic Enantioselective Hydride Transfer/Ring Closure[a]



entry	cat.	additive	solvent	temp (°C)	time	yield (%)[b]	dr (%)[c]	ee (%)[d]
1	**I**	TFA	MeCN	80	12 h	95	83/17	9/3
2	**IIa**	TFA	MeCN	80	12 h	95	83/17	9/9
3	**III**	TFA	MeCN	80	12 h	80	92/8	17/27
4	**IIa**	TFA	DCE	45	62 h	57	85/15	29/17
5	**IIa**	TFA	DCM	45	62 h	53	86/14	35/17
6	**IIa**	TFA	TCE	45	62 h	59	82/18	37/12
7	**IIa**	HCl	TCE	45	36 h	72	89/11	69/9
8	**IIa**	HBr	TCE	45	20 h	59	83/17	50/9
9	**IIa**	TfOH	TCE	45	20 h	95	83/17	30/35
10	**IIa**	DNBS	TCE	45	24 h	95	86/14	59/19
11	**IIa**	(−)-CSA	TCE	45	48 h	66	82/18	72/15
12	**IIa**	(−)-CSA	TCE	rt	8 d	45	93/7	82/83
13	**IIb**	(−)-CSA	TCE	rt	10 d	44	83/17	89/79

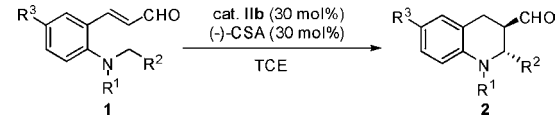
[a] Reactions were performed in a 0.1 M solution of solvent. [b] Combined yield of both diastereomers. [c] Diastereomeric ratio is determined by ^{1}H NMR spectroscopic analysis. [d] Enantiomeric excess determined by chiral HPLC analysis.

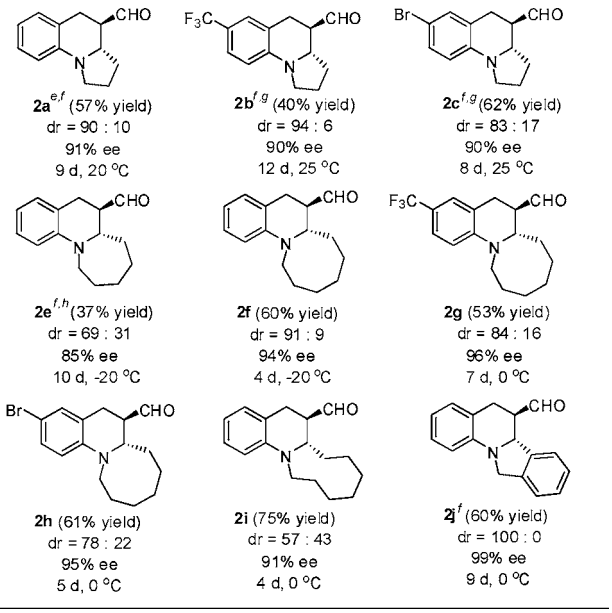
Accordingly, in an initial proof of concept, we found tetrahydroquinoline adduct **2a** was afforded in an encouraging 72% ee when 30 mol % of catalyst **IIa** was employed with 30 mol % of (−)-camphorsulfonic acid (CSA) in 1,1,2-tichloroethane (TCE) as solvent (entry 11). Anticipating that a prevalent background reaction would operate under these conditions, we used silicon-based bulky amino organocatalyst **IIb** at room temperature. Gratifyingly, the cyclization adduct was formed in 89% ee (entry 13, Table 2).

With optimal reaction conditions in hand, the scope of the reaction was explored (Table 3). As demonstrated, organocatalyst **IIb**-catalyzed enantioselective intramolecular redox reactions of **1** proved to be a general approach for the synthesis of versatile chiral tetrahydroquinolines **2**. Notably, high to excellent enantiomeric excess was obtained (up to 99% ee). High enantioselectivities were observed for a range of substituted cinnamaldehydes (90−91% ee, **2a**−**c**). Products **2e**−**i** which incorporated seven- to nine-membered azacycles were formed with excellent enantioselectivities (85−96%). The starting material derived from tetrahydroisoquinoline underwent the rearrangement successfully and afforded product **2j** in excellent enantio- and diastereoselectivity (99% ee, 100:0 dr).

In summary, we have presented the first example of a organocatalytic enantioselective hydride transfer/ring closure reaction

Table 3. Catalytic Enantioselective Hydride Transfer/Ring Closure[a−d]





[a] Reactions were performed at a 0.1 mmol scale in TCE (0.5 M). [b] Combined yield of both diastereomers. [c] Diastereomeric ratio is determined by ^{1}H NMR spectroscopic analysis. [d] Enantiomeric excess of major diastereomer is determined by chiral HPLC analysis. [e] Cat. **IIc** was used instead of cat. **IIb**. [f] Isolated yield of major diasteromer. [g] Cat. **IIa** was used instead of cat. **IIb**. [h] See the Supporting Information for determination of the absolute configuration of **2e**.

cascade. The synthetically useful ring-fused tetrahydroquinoline derivatives were obtained in moderate yields and high levels of enantioselectivity. Further investigations for organocatalytic hydride transfer are ongoing and will be reported in due course.

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Supporting Information Available: General experimental procedures, ^{1}H and ^{13}C NMR spectra, characterization data, and HPLC assays. This material is available free of charge via the Internet at http://pubs.acs.org.

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