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Catalytic Enantioselective Intramolecular Redox Reactions: Ring-Fused Tetrahydroquinolines

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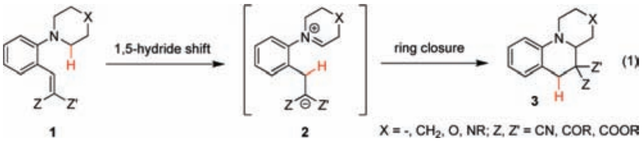
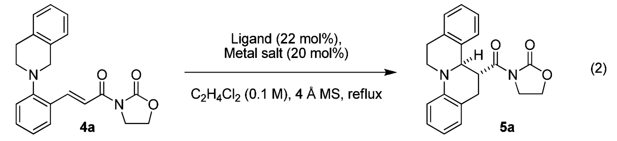
The functionalization of relatively unreactive C−H bonds via intramolecular hydride shift/ring closure sequences offers intriguing opportunities for the rapid buildup of molecular complexity (e.g., eq 1). Such transformations represent redox-neutral processes distinctly different from oxidative C−H bond functionalizations.[1,2] Exciting advances in this field have recently been achieved by application of catalytic approaches as a means of lowering activation barriers.[3,4] However, a catalytic enantioselective variant of this process has remained elusive. Here we report the first successful realization of such a reaction in the context of tetrahydroquinoline synthesis (eq 2).[5]



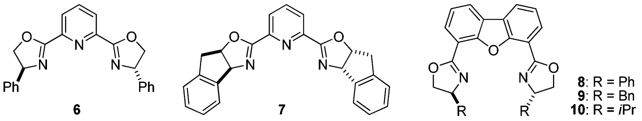
1 2 3

Reactions of the type outlined in eq 1 have been classified under the term *tert*-amino effect.[6,7] These transformations have been known for some time and are typically promoted thermally. As part of a program that focuses on the development of hydride shift processes,[8] we have recently reported that gadolinium triflate efficiently catalyzes the rearrangement of compounds **1** (Z, Z′ = COR, COOR) to **3** at room temperature.[8c] Unfortunately, attempts to develop a catalytic enantioselective variant of this reaction have met with limited success. Although thermally promoted rearrangements of compounds **1** typically require the presence of two activating groups,[9] we speculated that Lewis acid catalysis could overcome this limitation. We thus decided to investigate substrates bearing an acyl oxazolidinone (e.g., **4a**) as an alternative acceptor moiety capable of chelation to a chiral metal complex.[10] Initial attempts to promote rearrangement of readily available **4a**[11] to **5a** using scandium or gadolinium triflate in combination with ligand **6** or **7** led to disappointing results (Table 1, entries 1−5). Only trace formation of product **5a** in low ee was observed in one instance (entry 1). Gratifyingly, the use of nickel perchlorate in combination with DBFox[12] ligand **8** led to the formation of **5a** in good diastereo- and enantioselectivity (entry 6). In the absence of molecular sieves, lower selectivities were observed (entry 7). The use of nickel tetrafluoroborate or nickel hexafluoroantimonate led to inferior results (entries 8 and 9). Whereas zinc perchlorate catalyzed the reaction less efficiently (entry 10), magnesium salts in combination with ligand **8** led to excellent conversions (entries 11−13). The best result was obtained with magnesium triflate (entry 13). While the diastereoselectivity in this case was slightly lower than that in the nickel perchlorate catalyzed process, the overall yield and enantioselectivity were improved. The use of DBFox ligand **9** or **10** in combination with various nickel or magnesium salts led to no further improvement (entries 14−17). It is important to note that 1,2-dichloroethane is uniquely effective as a solvent.[13] No or very sluggish product formation was observed when performing the reaction at temperatures lower than 84 °C (reflux).

Table 1. Evaluation of Reaction Parameters[a]



4a 5a



6 7

entry	ligand	metal salt	time [h]	yield [%][b]	dr [%][c]	ee [%][d]
1	**6**	$Sc(OTf)_3$	48	15[f]	ND	19/ND
2	**6**	$Gd(OTf)_3$	48	trace	ND	ND
3	**6**	$Mg(ClO_4)_2\cdot 6H_2O$	72	trace	ND	ND
4	**7**	$Sc(OTf)_3$	48	trace	ND	ND
5	**7**	$Gd(OTf)_3$	48	trace	ND	ND
6	**8**	$Ni(ClO_4)_2\cdot 6H_2O$	12	68	89:11	90/85
7[e]	**8**	$Ni(ClO_4)_2\cdot 6H_2O$	12	70	83:17	89/81
8	**8**	$Ni(BF_4)_2\cdot 6H_2O$	48	68	88:12	83/85
9	**8**	$Ni(SbF_6)_2$	72	28[f]	ND	71/ND
10	**8**	$Zn(ClO_4)_2\cdot 6H_2O$	72	30[f]	ND	58/ND
11	**8**	$Mg(ClO_4)_2\cdot 6H_2O$	12	89	75:25	87/91
12	**8**	$Mg(NTf_2)_2$	12	75	81:19	77/77
13	**8**	$Mg(OTf)_2$	30	88	74:26	94/85
14	**9**	$Ni(ClO_4)_2\cdot 6H_2O$	48	29[f]	ND	54/ND
15	**9**	$Mg(OTf)_2$	48	18[f]	ND	44/ND
16	**10**	$Ni(ClO_4)_2\cdot 6H_2O$	12	80	81:19	75/73
17	**10**	$Mg(OTf)_2$	72	35[f]	ND	45/ND
18[g]	**8**	$Mg(OTf)_2$	72	50	70:30	61/60

[a] Reactions were performed on a 0.12 mmol scale. The ee's were determined by HPLC analysis. [b] Combined yield of both diastereomers. [c] Determined by ^1H NMR. [d] Major/minor diastereomer. [e] Reaction performed without molecular sieves. [f] Isolated yield of major diastereomer, reaction did not proceed to completion. [g] Reaction performed in CH_3NO_2.

Using the optimized conditions, the scope of the reaction was explored (Chart 1). Various substitution patterns on the basic substrate framework are well tolerated (products **5a**−**e**). Starting materials derived from β-carboline and *N*-Me-β-carboline underwent the rearrangement successfully and gave rise to products **5f** and **5g** in good yields and high levels of stereoselectivity. Products **5h** and **5i** which incorporate seven- or eight-membered azacycles were formed in good yields but with reduced levels of enantio- and diastereoselectivity.

The absolute configuration of products **5b** and **5e** was determined by X-ray crystallographic analysis.[11] Figure 1 shows a proposed transition state that accounts for the formation of the major product enantiomer. Formation of the opposite enantiomer would suffer from severe interactions between the substrate and the phenyl residue of the ligand, a fact that helps to explain the observed high levels of enantioselectivity at this relatively high reaction temperature. The

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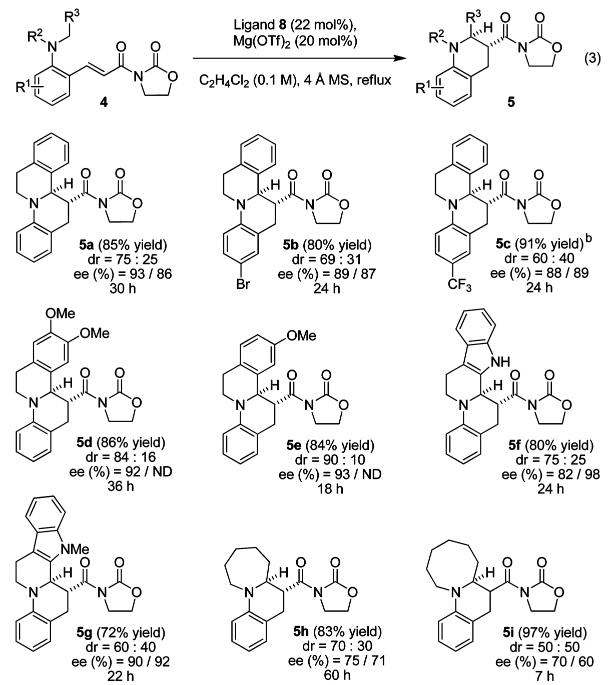
Chart 1. Scope of the Reaction[a,b]



[a] Reactions were performed on a 0.3 mmol scale. The ee's were determined by HPLC analysis, and dr's by ^{1}H NMR. [b] $Ni(ClO_4)_2\cdot 6H_2O$ was used instead of Mg(OTf)$_2$.

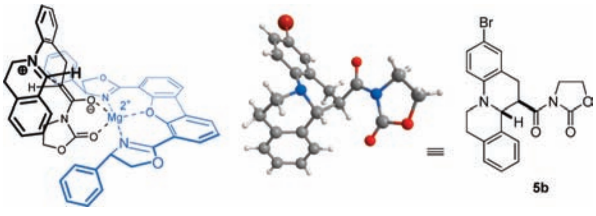
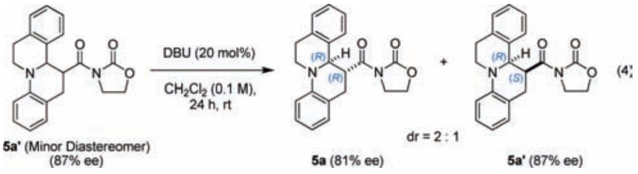


Figure 1. Proposed transition state leading to major diastereomer. Absolute configuration of **5b** (X-ray).

proposed trigonal bipyramidal coordination geometry for the magnesium DBFox complex has previously been suggested by Kanemasa et al.[12d]

The absolute configuration of the minor diastereomer **5a′** was determined as outlined in eq 4. Upon exposure to DBU, partial equilibration to the major diastereomer **5a** with slight erosion of ee was observed. Compound **5a** was recovered as the same enantiomer (*R*,*R*) that is formed in the catalytic reaction as revealed by HPLC correlation.[11] This established the absolute configuration of **5a′** as shown.[14]



In summary, we have described the first example of a catalytic enantioselective hydride shift/ring closure reaction cascade. Ring-fused tetrahydroquinolines are obtained in good yields and with high levels of enantioselectivity. It is anticipated that this communication will set the stage for a variety of other catalytic enantioselective processes involving hydride shift triggered reaction cascades.

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Supporting Information Available: Additional discussion, experimental procedures, and characterization data including X-ray crystal structures of **5b** and **5e**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) For additional experiments regarding the interconversion between **5a** and **5a′** under the reaction conditions, see the Supporting Information.

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