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Asymmetric Relay Catalysis

Step-Economical Synthesis of Tetrahydroquinolines by Asymmetric Relay Catalytic Friedländer Condensation/Transfer Hydrogenation**

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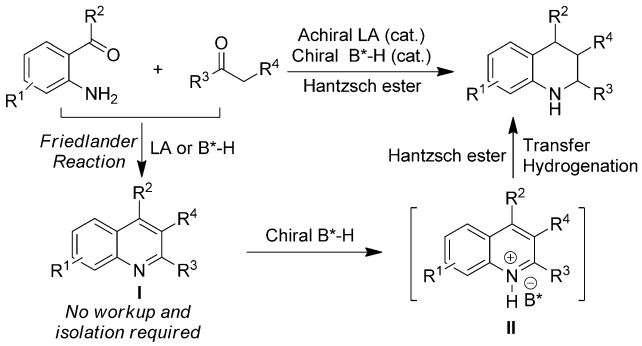
Chiral 1,2,3,4-tetrahydroquinoline derivatives have found widespread application in the preparation of naturally occurring alkaloids and pharmaceutically relevant molecules.[1] Their great synthetic importance has stimulated a boom in the development of asymmetric synthetic methods.[2,3] The most common access to this structural motif is the asymmetric reduction of quinolines.[3] Although it is straightforward, this approach requires preformed quinoline derivatives and thereby suffers from moderate step economy. The direct and enantioselective conversion of readily available precursors of quinolines into the 1,2,3,4-tetrahydroquinolines would provide a more elegant approach, but such methods remain extremely rare. Herein we describe a new relay catalytic reaction to produce 1,2,3,4-tetrahydroquinolines in high levels of enantiopurity by using easily accessible 2-aminobenzaldehydes and enolizable carbonyl-containing compounds as reagents.

Step economy is a preeminent concept in contemporary organic synthesis.[4] It has been accepted as an ultimate goal to construct pharmaceutical compounds and complex natural products. Recently, the combined use of organocatalysts and metal complexes in relay and cooperative catalysis has led to the creation of new enantioselective protocols.[5–14] More significantly, asymmetric relay catalysis (ARC) has been proven to enable the discovery of unprecedented step-economical transformations.[5] Successful relay catalysis relies on the compatibility and more importantly, on the synergism of metal complexes and organocatalysts. The binary organo/metal catalyst systems disclosed so far include the combination of transition-metal complexes based on Pd,[6,7] Au,[8] Rh,[9,10] Ru,[11,12] and other transition metals[13,14] with chiral organocatalysts. In contrast, combinations of Lewis acids and phosphoric acids have rarely found application in asymmetric relay catalysis.[15]

The Friedländer condensation has long been recognized as a reliable and preparatively straightforward route to quinolines.[16] Either Brønsted or Lewis acids are able to efficiently promote this transformation. On the other hand, chiral phosphoric acids[17] have been excellent catalysts for the asymmetric transfer hydrogenation of quinolines with Hantzsch esters.[3a,18] Encouraged by these elegant achievements, we proposed a sequence consisting of a Friedländer condensation and transfer hydrogenation catalyzed by a combination of an achiral Lewis acid and a chiral Brønsted acid for the direct conversion of 2-aminobenzaldehydes and enolizable compounds containing carbonyl groups into highly optically active 1,2,3,4-tetrahydroquinoline derivatives (Scheme 1).



Scheme 1. Proposed strategy for the one-pot synthesis of enantiomerically enriched tetrahydroquinolines. LA = Lewis acid, B*–H = chiral Brønsted acid.

Our initial study began with the reaction of 2-aminobenzaldehyde (**1a**) and ethyl acetoacetate (**2a**) with Hantzsch ester **3a** catalyzed by phosphoric acid **5a** (10 mol%) in toluene at 35 °C. Encouragingly, the reaction proceeded with high diastereoselectivity in favor of the *anti* diastereomer and with 90% *ee* for the major product; however, the yield was poor because the reaction was slow (Table 1, entry 1). The same reaction went to completion in the presence of 10 mol% of **5a** combined with 10 mol% of $Mg(OTf)_2$,[19] giving the desired product in 83% yield, and more significantly, the stereoselectivity remained high (Table 1, entry 2). However, in the absence of the phosphoric acid, an incomplete Friedländer condensation occurred to give a quinoline derivative of type **I** in 41% yield while the desired tetrahydroquinoline **4aa** was not detected (Table 1, entry 3). These results indicated that the Friedländer condensation can be catalyzed by either the phosphoric acid or the Lewis acid while the transfer hydrogenation is accelerated solely by the chiral Brønsted acid. We surveyed phosphoric acids **5** (Figure 1) and found that **5a** is the optimal catalyst in terms of enantioselectivity (Table 1, entries 4–8). The evaluation of Hantzsch esters revealed that the methyl Hantzsch ester **3b** provides the

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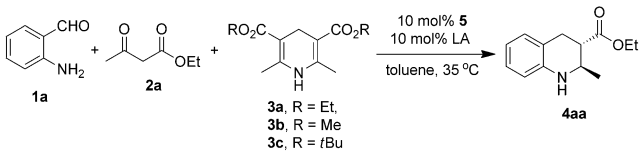
Table 1: Optimization of reaction conditions.[a]



Entry	5	LA	3	Yield [%][b]	d.r.[c]	*ee* [%][d]
1	**5a**	none	**3a**	35	10:1	90
2	**5a**	$Mg(OTf)_2$	**3a**	83	12:1	90
3[e]	—	$Mg(OTf)_2$	**3a**	–	–	–
4	**5b**	$Mg(OTf)_2$	**3a**	99	3.5:1	7(6)
5	**5c**	$Mg(OTf)_2$	**3a**	70	16:1	88
6	**5d**	$Mg(OTf)_2$	**3a**	97	3.2:1	22(5)
7	**5e**	$Mg(OTf)_2$	**3a**	68	6.5:1	51(18)
8	**5f**	$Mg(OTf)_2$	**3a**	52	7:1	86(45)
9	**5a**	$Mg(OTf)_2$	**3b**	76	>20:1	94
10	**5a**	$Mg(OTf)_2$	**3c**	51	7:1	80
11	**5a**	$Zn(OTf)_2$	**3b**	49	>20:1	89
12	**5a**	$Yb(OTf)_3$	**3b**	64	>20:1	90
13	**5a**	$Mg(ClO_4)_2$	**3b**	61	>20:1	94
14	**5a**	$FeCl_3$	**3b**	37	18:1	92
15	**5a**	$NaAuClO_4$	**3b**	17	13:1	93
16	**5a**	$Sc(OTf)_3$	**3b**	30	17:1	90

[a] The reaction of **1a** (0.2 mmol), **2a** (1.0 mmol), and **3** (0.46 mmol) was conducted in toluene (1.0 mL) with 3 Å molecular sieves (200 mg) at 35 °C for 36 h. [b] Yield of isolated **4aa**. [c] Determined by ^{1}H NMR analysis of the crude product. [d] Major (minor) diastereomer, determined by HPLC on a chiral stationary phase. [e] Only quinoline (41 % yield) was isolated. Tf = trifluoromethanesulfonyl.

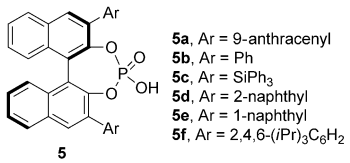
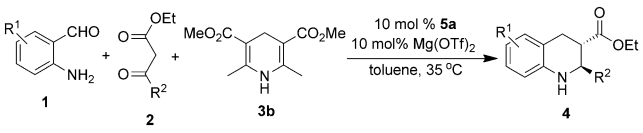


Figure 1. Phosphoric acid derivatives surveyed.

highest level of stereoselectivity (>20:1 d.r., 94 % *ee*; Table 1, entry 9). A variety of Lewis acids, which have been applied to the Friedländer condensation, were examined in combination with **5a** (Table 1, entries 11–16). Basically, the reaction conversion and diastereoselectivity depend highly on the Lewis acid co-catalysts while the enanatioselectivity appears to be less sensitive. The use of either zinc triflate or ytterbium triflate gave high diastereoselectivities, but both the yield and enantioselectivity were lower than those obtained with magnesium triflate (Table 1, entries 11 and 12). Magnesium perchlorate gave results comparable to those with magnesium triflate (Table 1, entry 13). However, other Lewis acids that have shown high catalytic activity for Friedländer condensation, including $FeCl_3$,[20] $NaAuCl_4$,[21] and $Sc(OTf)_3$,[22] led to an incomplete cascade reaction in combination with **5a**, although the stereoselectivity was maintained in most cases (Table 1, entries 14–16).

We then applied the optimized conditions to the cascade reaction of various 2-aminobenzaldehydes and β-keto esters (Table 2). Substitution on the 2-aminobenzaldehyde was

Table 2: Generality of the reaction for 2-aminobenzaldehydes and β-keto esters.[a]



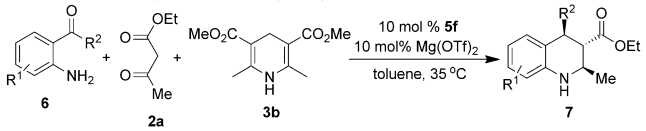
Entry	1, R^1	2, R^2	4	Yield [%][b]	*ee* [%][c,d]
1	**1b**, 5-AcO	**2a**, Me	**4ba**	91	92
2	**1c**, 5-MeO	**2a**, Me	**4ca**	65	92
3	**1d**, 5-F	**2a**, Me	**4da**	65	92
4	**1e**, 5-Cl	**2a**, Me	**4ea**	76	90
5	**1f**, 5-Br	**2a**, Me	**4fa**	81	90
6	**1g**, 4-Cl	**2a**, Me	**4ga**	55	95
7	**1a**, H	**2b**, *n*-Pr	**4ab**	63	91
8[e]	**1a**, H	**2c**, Ph	**4ac**	72	91
9[e]	**1a**, H	**2d**, 4-MeC_6H_4	**4ad**	71	96
10[e]	**1a**, H	**2e**, 4-FC_6H_4	**4ae**	64	96
11[e]	**1a**, H	**2f**, 4-ClC_6H_4	**4af**	61	97
12[e]	**1a**, H	**2g**, 4-$NO_2C_6H_4$	**4ag**	67	96
13[e]	**1a**, H	**2h**, 2-Naphthyl	**4ah**	73	97

[a] The reaction of **1** (0.2 mmol), **2** (1.0 mmol), and **3b** (0.46 mmol) was conducted in toluene (1.0 mL) with 3 Å molecular sieves (200 mg) at 35 °C. [b] Yield of isolated product. [c] Determined by HPLC on a chiral stationary phase. [d] d.r. >20:1, determined by ^{1}H NMR analysis of crude product. [e] **1**/**2**/**3b** = 1:1.2:2.3.

nicely tolerated: the introduction of electron-donating substituents resulted in high levels of enantioselectivity (92 % *ee*; Table 2, entries 1 and 2). Halogenated 2-aminobenzaldehydes participated in the reaction giving the expected product in high yields and enantioselectivities (Table 2, entries 3–6). In the reactions of **1e** and **1g** we found that the position of the substituent exerts a considerable effect on the enantioselectivity (Table 2, entry 4 versus entry 6). More interestingly, the reaction conditions were amenable to a wide scope of β-keto esters and gave high levels of stereochemical control (Table 2, entries 7–13). In addition to ethyl acetoacetate (**2a**), other aliphatic analogues also underwent smooth reaction with high enantioselectivity as exemplified by ethyl butyrylacetate (**2b**; Table 2, entry 7). More significantly, aromatic β-keto esters proved to be reactive components and provided excellent levels of enantioselectivity (91–97 % *ee*; Table 2, entries 8–13). The configuration of **4fa** was assigned by X-ray analysis (see the Supporting Information).

2,3,4-Trisubstituted tetrahydroquinolines hold great potential in organic synthesis and show important bioactivity;[1d] however, only a limited number of enantioselective catalytic protocols have been available to prepare these molecules.[23] Thus, a further investigation on the substrate scope was focused on the 2-aminophenyl ketones. However, the extension of the optimized reaction conditions to 1-(2-aminophenyl)ethanone (**6a**) provided **7aa** in moderate yield and 85 % *ee* (Table 3, entry 1). We therefore re-evaluated the phosphoric acid catalysts and found that **5f** delivered high yield and excellent enantioselectivity (98 % *ee*; Table 3, entry 2). The application of the optimized conditions to 1-(5-methyl-2-aminophenyl)ethanone (**6b**) provided **7ab** in 90 % yield and 96 % *ee* (Table 3, entry 3). More interestingly, (2-aminophenyl)(aryl)methanones were also successful sub-

Table 3: The scope of 2-aminophenyl ketones **6**.[a]



6 **2a** **3b** **7**

Entry	**6**, R^1, R^2	**7**	Yield [%][b]	d.r.[c]	*ee* [%][d]
1[e]	**6a**, H, Me	**7aa**	64	>20:1	85
2	**6a**, H, Me	**7aa**	88	>20:1	98
3	**6b**, 5-Me, Me	**7ab**	90	>20:1	96
4	**6c**, H, Ph	**7ac**	96	>20:1	95
5	**6d**,H, 4-MeC_6H_4	**7ad**	97	>20:1	91
6	**6e**, 5-Cl, Ph	**7ae**	70	>20:1	93
7	**6f**, 5-F, Ph	**7af**	72	>20:1	95
8	**6g**, 5-BnO, Ph	**7ag**	76	>20:1	92

[a] The reaction of **6** (0.1 mmol), **2a** (0.5 mmol), and **3b** (0.23 mmol) was conducted in toluene (1.0 mL) with 3 Å molecular sieves (100 mg) at 35 °C. [b] Yield of isolated product. [c] Determined by ^{1}H NMR analysis of crude product. [d] Determined by HPLC on a chiral stationary phase. [e] Phosphoric acid **5a** was used.

strates and participated in the relay catalytic reaction to give the tetrahydroquinoline products in high yields and excellent levels of enantioselectivity (Table 3, entries 4–8). The presence of either electron-withdrawing or -donating substituents on the aryl rings was tolerated, and tetrahydroquinolines bearing three continuous stereogenic centers were obtained in high yields and with excellent stereoselectivities (Table 3, entries 5–8). The configuration of the product was confirmed by X-ray analysis after derivatization (see the Supporting Information).

To obtain insight into the reaction process, we investigated the kinetics of each individual reaction. As shown in Figure 2, both $Mg(OTf)_2$ and Brønsted acid **5a** showed catalytic activity for the Friedländer condensation, but $Mg(OTf)_2$ was somewhat more effective. Interestingly, in the presence of a mixture of **5a** and $Mg(OTf)_2$, the Friedländer condensation proceeded even faster, implying a synergistic effect of the metal complex and Brønsted acid. This type of synergism was not observed in the transfer hydrogenation, however, because the reactions catalyzed by **5a** and $Mg(OTf)_2$ together and by **5a** alone gave similar results (Figure 3). Thus, in this relay catalytic process, Lewis and Brønsted acids cooperatively catalyze the Friedländer condensation while the chiral Brønsted acid acts as the sole catalyst for the asymmetric transfer hydrogenation.

In conclusion, we have developed a relay reaction consisting of a catalytic Friedländer condensation and a transfer hydrogenation by using a combination of an achiral Lewis acid and a chiral Brønsted acid. This concise step-economical protocol provides access to highly substituted tetrahydroquinoline derivatives with concomitant generation of multiple stereogenic centers in excellent levels of stereochemical control. In this cascade reaction, the Friedländer condensation is catalyzed either by Lewis acid or the chiral phosphoric acid while the asymmetric transfer hydrogenation is promoted solely by the chiral Brønsted acid. More importantly, the synergism of the Lewis acid and the chiral Brønsted acid occurs in the catalytic process. The compatibility and synergism of the Lewis acid and chiral Brønsted acid may provide a new reaction mode potentially amenable to disclosing other relay catalytic asymmetric transformations.

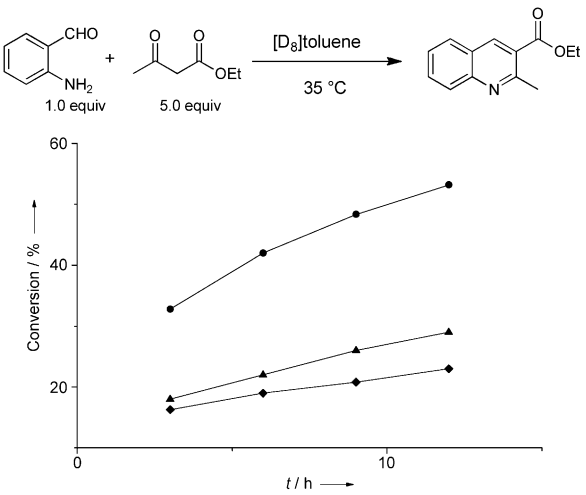


Figure 2. Course of the Friedländer condensation catalyzed by 5 mol% $Mg(OTf)_2$ and 5 mol% **5a** (●), by 10 mol% $Mg(OTf)_2$ (▲), and by 10 mol% **5a** (◆).

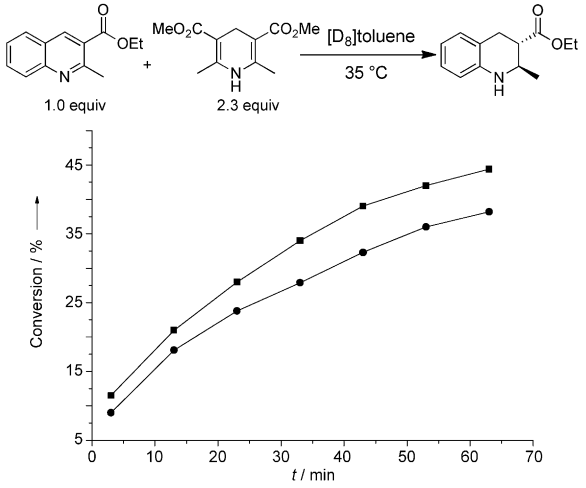


Figure 3. Course of the transfer hydrogenation catalyzed by 10 mol% $Mg(OTf)_2$ and 10 mol% **5a** (■), and catalyzed by 10 mol% **5a** (●).

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