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Diastereo- and Enantioselective Assembly of Spirooxindole Tetrahydroquinoline Skeletons through Asymmetric Binary Acid Catalyzed Hydride Transfer–Cyclization

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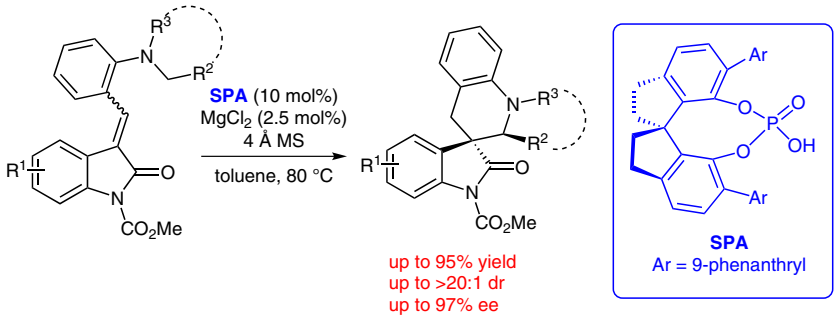

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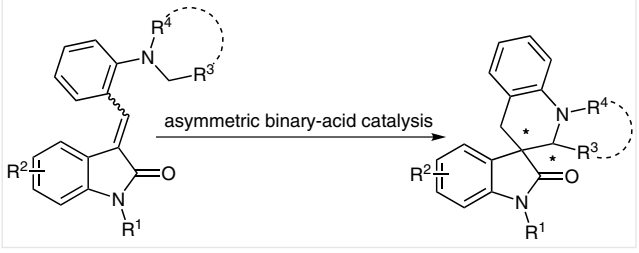
Abstract An efficient binary acid catalyzed asymmetric intramolecular tandem 1,5-hydride transfer/ring-closure reaction was achieved. The process is catalyzed by the combination of a chiral spirocyclic phosphoric acid and magnesium chloride to afford structurally diverse spirooxindole tetrahydroquinolines in good yields with high diastereo- and enantioselectivities.

Key words asymmetric catalysis, phosphoric acid, Lewis acid, spirooxindoles, quaternary stereocenter

The spirocyclic-3,3′-oxindoles as well as their analogues are important structural units that are found in natural products and a number of drug candidates.[1] Consequently, significant efforts have been devoted to the synthesis of optically enriched highly functionalized spirocyclic-3,3′-oxindoles.[2] In this context, the development of catalytic enantioselective and atom-economical methods for the efficient construction of such skeletons with all-carbon-substituted quaternary stereocenters, is a particularly compelling objective.

The intramolecular tandem 1,5-hydride transfer/ring-closure reaction represents an efficient approach to cleavage of a C(sp^3)–H bond and research in this area has made great progress.[3] Recently, the group of Yuan reported an efficient stereoselective construction of spirooxindole tetrahydroquinolines with contiguous quaternary or tertiary stereogenic carbon centers through $FeCl_3$-catalyzed intramolecular tandem 1,5-hydride shift/ring-closure.[4] They investigated an asymmetric version of this process and found that the use of many chiral ligands such as diamine, salen, bisoxazoline, and diphosphine, in combination with a number of metal salts, gave no more than 11% ee, and moderate enantioselectivity (54% ee) was obtained by using 20 mol% chiral BINOL-derived phosphoric acid[5] as the catalyst. More recently, the group of Feng showed that a chiral scandium complex of *N*,*N*′-dioxide promoted the asymmetric reactions with high levels of stereocontrol.[6] In the meantime, we also achieved an efficient asymmetric binary acid catalysis[7] for the enantioselective synthesis of spirooxindole tetrahydroquinolines through intramolecular tandem 1,5-hydride transfer/ring-closure reaction (Scheme 1). Herein, we wish to report details of the process, which was catalyzed by the combination of a chiral spirocyclic phosphoric acid[8] (Figure 1) and $MgCl_2$ to afford structurally diverse spirooxindole tetrahydroquinolines in good yields with high diastereo- and enantioselectivities.



Scheme 1 Proposed asymmetric binary acid catalysis

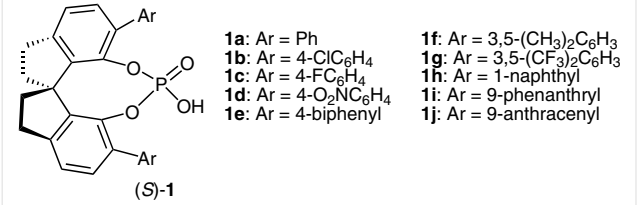
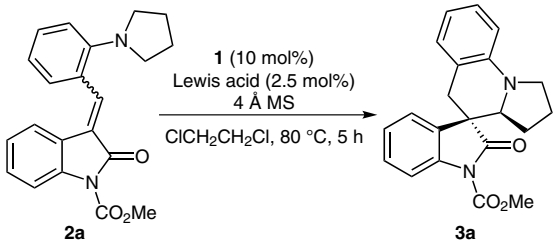


Figure 1 Chiral spirocyclic phosphoric acids (SPAs)

We selected oxindole derivative **2a** as a model substrate to examine the asymmetric intramolecular hydride transfer–cyclization reaction. Previously, the groups of Akiyama and Gong reported that the reaction of acyclic tertiary amines could be achieved with good enantioselectivity through the sole use of chiral phosphoric acid as the catalyst.[9] Thus, we started with chiral phosphoric acid **1a** alone to catalyze the reaction. Unfortunately, almost no reaction occurred (Table 1, entry 1). The combination of $MgCl_2$ and chiral spirocyclic phosphoric acid **1** was then examined in 1,2-dichloroethane at 80 °C, and we were pleased to find that all reactions proceeded quite smoothly (entries 2–11). To our delight, The combination of $MgCl_2$ and **1i**, with 6,6′-bis(9-phenanthryl) moieties, gave the desired product **3a** in quantitative conversion with an encouraging 71% ee (entry 10). In addition, the reaction using the combination of **1i** and other Lewis acids, such as MgF_2, $Mg(SO_3CF_3)_2$, or $FeCl_3$ also proceeded well to afford the corresponding product **3a**, albeit in slightly reduced enantioselectivity, without compromising the conversion (entries 12–14).

Table 1 Catalyst Optimization[a]



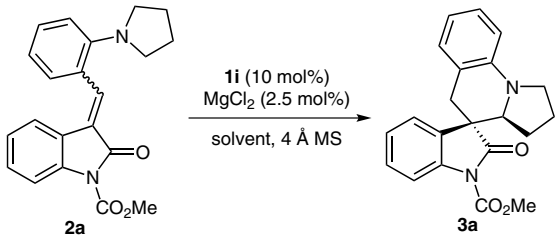
2a **3a**

Entry	Phosphoric acid	Lewis acid	Conv. (%)[b]	ee (%)[c,d]
1	**1a**	–	trace	–
2	**1a**	$MgCl_2$	quant.	2
3	**1b**	$MgCl_2$	quant.	24
4	**1c**	$MgCl_2$	quant.	8
5	**1d**	$MgCl_2$	80	13
6	**1e**	$MgCl_2$	60	2
7	**1f**	$MgCl_2$	quant.	13
8	**1g**	$MgCl_2$	80	40
9	**1h**	$MgCl_2$	85	6
10	**1i**	$MgCl_2$	quant.	71
11	**1j**	$MgCl_2$	90	55
12	**1i**	MgF_2	quant.	65
13	**1i**	$Mg(SO_3CF_3)_2$	quant.	54
14	**1i**	$FeCl_3$	quant.	65

[a] Reaction conditions: **2a** (0.05 mmol), phosphoric acid **1** (10 mol%, 0.005 mmol), Lewis acid (2.5 mol%, 0.00125 mmol), MS 4Å (15 mg), $ClCH_2CH_2Cl$ (0.7 mL), 80 °C under Ar.
[b] Conversions were determined by ^1H NMR spectroscopic analysis.
[c] Up to 20:1 d.r. was obtained in all cases as determined by ^1H NMR spectroscopic analysis.
[d] Determined by chiral HPLC analysis.

A survey of solvents was then conducted in the presence of 2.5 mol% $MgCl_2$ and 10 mol% **1i** (Table 2, entries 1–7). Toluene turned out to be the best solvent for this process, and the spirooxindole tetrahydroquinoline product **3a** was obtained in quantitative conversion and 90% ee at 80 °C for 5 h (entry 7). The enantioselectivity declined slightly when the reaction was conducted at reduced temperature (entry 8). Different molar ratios of **1i**/$MgCl_2$ were also examined, and the optimal ratio in terms of enantioselectivity was found to be 4:1 (entries 9 and 10 versus 7). Thus, the most suitable reaction conditions for the model reaction were established (entry 7).

Table 2 Optimization of the Reaction Conditions[a]



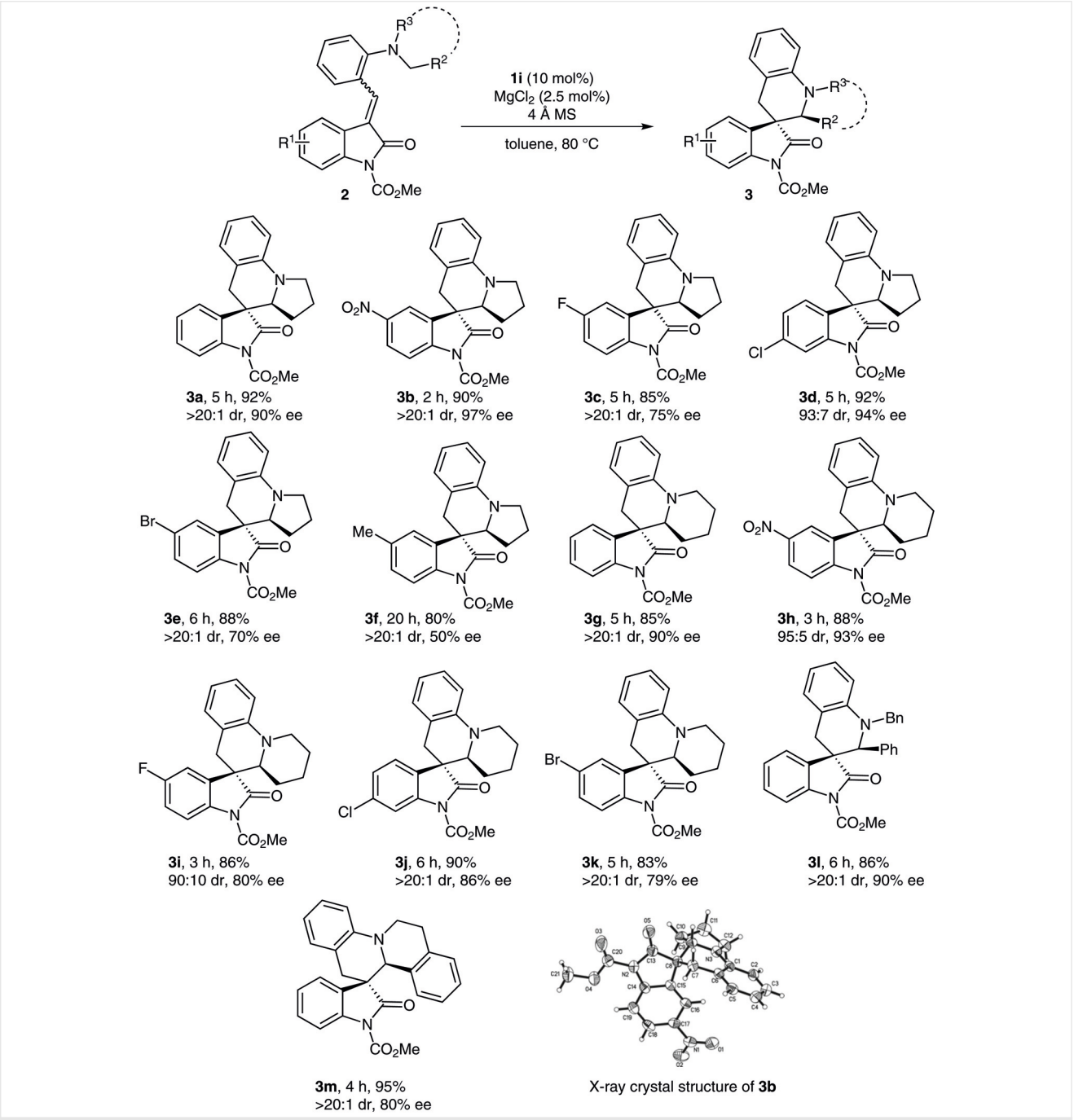
2a **3a**

Entry	Solvent	Temp. (°C)	Conv. (%)[b]	ee (%)[c,d]
1	$ClCH_2CH_2Cl$	80	quant.	71
2	CH_2Cl_2	reflux	50	58
3	$CHCl_3$	reflux	80	67
4	CCl_4	reflux	95	85
5	MeCN	80	90	66
6	benzene	80	quant.	85
7	toluene	80	quant.	90
8	toluene	60	quant.	85
9[e]	toluene	80	quant.	87
10[f]	toluene	80	quant.	83

[a] Reaction conditions: **2a** (0.05 mmol), phosphoric acid **1i** (10 mol%, 0.005 mmol), $MgCl_2$ (2.5 mol%, 0.00125 mmol), MS 4Å (15 mg), solvent (0.7 mL), 5 h under Ar.
[b] Conversions were determined by ^1H NMR spectroscopic analysis.
[c] Up to 20:1 d.r. was obtained in all cases as determined by ^1H NMR spectroscopic analysis.
[d] Determined by chiral HPLC analysis.
[e] Molar ratio of **1i**/$MgCl_2$ was 3:1.
[f] Molar ratio of **1i**/$MgCl_2$ was 2:1.

With the optimized reaction conditions in hand, we next turned our attention to assessing the substrate scope; the results are summarized in Scheme 2. In all cases, the expected intramolecular tandem 1,5-hydride transfer/ring-closure reaction proceeded smoothly to afford the corresponding products with excellent diastereoselectivities (90:10 to > 20:1 d.r.). The nature of the substituent on the oxindole aromatic ring had a dramatic effect on enantioselectivity, although the yields remained good (**3a**–**f**; Scheme 2). The reaction involving a substrate with a strong electron-withdrawing group, such as NO_2, proceeded smoothly to

give the corresponding product **3b** in 90% yield with 97% ee and up to >20:1 d.r. The incorporation of an electron-rich substituent, such as CH_3, on the oxindole aromatic ring appeared to have a remarkably negative effect on the enantioselectivity of the reaction (**3f**; Scheme 2). The method was not limited to pyrrolidine-derived substrates **2a**–**f**: the reactions with piperidine-derived substrates also occurred smoothly to afford the desired products **3g**–**k** in good yields with high diastereo- and enantioselectivities under the optimal conditions. Subsequently, an acyclic tertiary amine derived substrate was examined and the reaction was also found to proceed efficiently to produce **3l** in 86% yield with



Scheme 2 Scope of the reaction. *Reagents and conditions*: **2** (0.05 mmol), **1i** (10 mol%, 0.005 mmol), $MgCl_2$ (2.5 mol%, 0.00125 mmol), MS 4Å (15 mg), toluene (0.7 mL), 80 °C under Ar. Yields given are of the isolated major isomer. Diastereomeric ratios were determined by ^1H NMR spectroscopic analysis. The ee values were determined by chiral HPLC analysis.

90% ee and >20:1 d.r. In addition, the tetrahydroisoquinoline-derived oxindole also furnished the desired prodct **3m** in high yield with good diastereo- and enantioselectivity. A single-crystal X-ray analysis of **3b** determined its absolute configuration as (3*S*, 3a′*S*).[10]

In summary, we have developed an efficient enantioselective intramolecular tandem 1,5-hydride transfer/ring-closure reaction through the application of chiral phosphoric acid-$MgCl_2$ combined binary acid catalysis.[11] By following this methodology, a series of structurally diverse spirooxindole tetrahydroquinolines were obtained in good yields with high diastereo- and enantioselectivities. Further application of this method for the preparation of new bioactive heterocycles is underway.

Acknowledgment

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0035-1560198.

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(10) CCDC-1059197 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB21EZ, UK; fax: +44(1223)336033; or deposit@ccdc.cam.ac.uk].

(11) **General Procedure for the Synthesis of 3**: Phosphoric acid catalyst **1i** (10 mol%, 3.3 mg), a solution of $MgCl_2$ in EtOH (2.5 mol%, 0.12 mg, 0.1 mL, 1.2 mg/mL), and 4 Å molecular sieves (15 mg) were added to a Schlenk-type flask and the mixture was dried under vacuum. Toluene (0.3 mL) was then added and the resulting mixture was stirred for 1 h under Ar. A solution of **2** in toluene (0.05 mmol, 0.4 mL) was added and the resulting mixture was heated to 80 °C until the starting material disappeared. The product was purified by silica gel column chromatography (EtOAc–PE, 1:4) to afford the desired product **3**.

Compound 3a: Yield: 92%; off-white solid; m.p. 149–150 °C; HPLC analysis: 90% ee {Chiralpak AD-H (hexane–*i*-PrOH, 90:10; 0.8 mL/min): t_R = 12.4 (major), 16.8 (minor) min}; $[\alpha]_D^{20}$ 42.9 (*c* = 1.2, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.96 (d, *J* = 8.0 Hz, 1 H), 7.29–7.20 (m, 2 H), 7.02 (d, *J* = 7.6 Hz, 1 H), 6.96–6.92 (m, 1 H), 6.67–6.63 (m, 1 H), 6.59 (d, *J* = 8.0 Hz, 1 H), 6.45 (dd, *J* = 7.6, 1.2 Hz, 1 H), 4.05 (s, 3 H), 3.77 (q, *J* = 9.6 Hz, 1 H), 3.54–3.44 (m, 1 H), 3.26–3.20 (m, 1 H), 2.75 (d, *J* = 15.6 Hz, 1 H), 1.92–1.81 (m, 3 H), 0.93–0.88 (m, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.26, 151.34, 143.46, 139.02, 129.64, 128.39, 128.11, 127.99, 124.95, 124.51, 117.83, 115.90, 114.51, 110.26, 62.88, 53.94, 47.09, 46.79, 37.76, 27.04, 23.24. IR (film): 2965, 1760, 1738, 1604, 1479, 1462, 1360, 1287, 1243, 1160, 1072, 746 cm^{-1}. HRMS (EI-TOF): *m*/*z* calcd for $C_{21}H_{20}N_2O_3$: 348.1474; found: 348.1476.