Asymmetric Catalysis

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Asymmetric Three-Component Inverse Electron-Demand Aza-Diels–Alder Reaction: Efficient Synthesis of Ring-Fused Tetrahydroquinolines**

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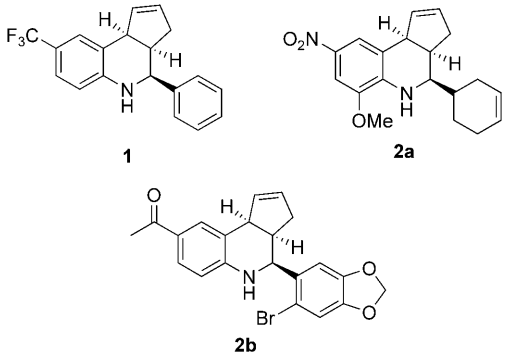
Tetrahydroquinoline derivatives have attracted considerable attention because of their important biological activities.[1] For their construction, one of the most powerful strategies is the inverse electron-demand aza-Diels–Alder (IEDDA) reaction of N-arylimines with electron-rich alkenes (dienophiles).[2–8] In 1996, the first catalytic asymmetric IEDDA reaction, using cyclopentadiene and vinylethers as dienophiles, was reported by Kobayashi and Ishitani using chiral binaphthol–ytterbium complexes.[6a] Subsequently, aminodiol–titanium complexes[6b] and chiral phosphoric acids[7] have been developed for the stereoselective IEDDA reactions, and great breakthroughs in reactivity and enantioselectivity had been made with vinylethers,[7a] enecarbamates,[7b] and vinylindoles[7c] as dienophiles. However, with cyclopentadiene as the dienophile, the asymmetric IEDDA reaction has been less well-developed, especial the three-component version,[9] and a combination of high enantioselectivities and good yield have not yet been obtained simultaneously. In contrast to those heteroatom-containing dienophiles, it is relatively difficult to find an efficient catalyst for cyclopentadiene, which contains only carbon atoms. As the ring-fused tetrahydroquinoline derivatives, such as **1**, exhibit potential biological activities in treating tumors,[10a] and **2a**, **2b** in preventing some diseases,[10b] an effective catalyst for this IEDDA transformation is highly desirable.

Using the excellent chiral *N*,*N*′-dioxides scaffolds,[11] herein, we report an asymmetric three-component IEDDA reaction with cyclopentadiene as the dienophile, promoted by 5 mol% of an *N*,*N*′-dioxide–$Sc(OTf)_3$ complex, to afford ring-fused tetrahydroquinoline derivatives in high yields, excellent diastereoselectivities (up to >99:1 d.r.), and enantioselectivities (90 to over 99% *ee*). Notably, the asymmetric reaction affords ring-fused tetrahydroquinolines with three contiguous stereocenters in a one-pot manner under mild conditions.



Initially, we examined the three-component reaction between benzaldehyde, 2-aminophenol, and cyclopentadiene, promoted by *N*,*N*′-dioxide **L1** with various metals. As shown in Table 1, $La(OTf)_3$, $Y(OTf)_3$ and $Yb(OTf)_3$ gave racemic ring-fused tetrahydroquinoline **6a** in trace yield with good diastereoselectivities (Table 1, entries 1–3). Only $Sc(OTf)_3$ afforded the desired **6a** with improved results (36% yield, 92:8 d.r., 41% *ee*; Table 1, entry 4). Encouraged by the results, a series of *N*,*N*′-dioxides that contained different sterically hindered amide substituents were tested (Table 1, entries 4–6). *N*,*N*′-dioxide **L3**, which contained bulkier isopropyl group at the *ortho* positions of aniline groups, was more successful (99% yield, 94:6 d.r., 93% *ee*; Table 1, entry 6 versus entries 4 and 5). As for the amino acid backbone, L-ramipril-acid-derived *N*,*N*′-dioxide **L5** exhibited superior enantioselectivity (98%) and lower diastereoselectivity (81:19) compared with those derived from L-proline and L-pipecolic acid (Table 1, entry 8 versus entries 6 and 7). To our delight, improved diastereoselectivity (96:4) was observed when the molar ratio of ligand to central metal was changed to 2:1 (Table 1, entry 9). Furthermore, when the catalyst loading was decreased to 5 mol%, excellent results could also be obtained by increasing the substrate concentration (90% yield, 96:4 d.r., 97% *ee*; Table 1, entry 10). Furthermore, when the catalyst loading was further lowered to 2.5 mol%, similar results could still be obtained with longer reaction time (Table 1, entry 11). This process is also tolerant to air and moisture. However, when aniline or 2-methoxyaniline were tested, only trace amounts of the products were obtained, which indicated that the hydroxy group on the aniline was essential for the reaction to proceed (Table 1, entries 12–13).

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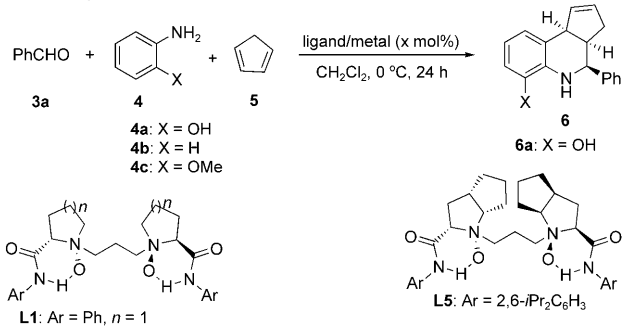
Table 1: Optimization of the reaction conditions.[a]



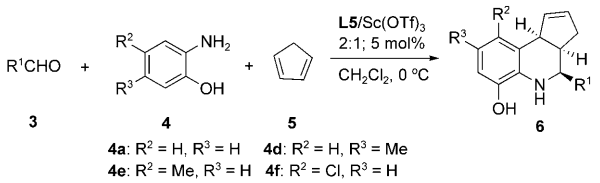
Entry	Ligand	Metal	4	x [mol%]	Yield [%][b]	cis/trans[c]	ee [%][c]
1	**L1**	$La(OTf)_3$	**4a**	10	trace	91:9	0
2	**L1**	$Y(OTf)_3$	**4a**	10	trace	91:9	0
3	**L1**	$Yb(OTf)_3$	**4a**	10	4	93:7	0
4	**L1**	$Sc(OTf)_3$	**4a**	10	36	92:8	41
5	**L2**	$Sc(OTf)_3$	**4a**	10	99	97:3	79
6	**L3**	$Sc(OTf)_3$	**4a**	10	99	94:6	93
7	**L4**	$Sc(OTf)_3$	**4a**	10	48	88:12	84
8	**L5**	$Sc(OTf)_3$	**4a**	10	90	81:19	98
9[d]	**L5**	$Sc(OTf)_3$	**4a**	10	79	96:4	99
10[d,e]	**L5**	$Sc(OTf)_3$	**4a**	5	90	96:4	97
11[d,e,f]	**L5**	$Sc(OTf)_3$	**4a**	2.5	83	96:4	97
12[d,e]	**L5**	$Sc(OTf)_3$	**4b**	5	trace	90:10	0
13[d,e]	**L5**	$Sc(OTf)_3$	**4c**	5	trace	n.d.[g]	n.d.[g]

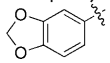
[a] Unless otherwise noted, all reactions were carried out with **L**/metal (1:1), **3a** (0.11 mmol), **4** (0.1 mmol), **5** (150 μL), and 4 Å M.S. (10.0 mg) in CH_2Cl_2 (1.0 mL) under N_2 at 0°C for 24 hours. [b] Yield of isolated product. [c] Determined by chiral HPLC analysis, the *cis* isomer was confirmed by ^{1}H NMR spectroscopy and the *ee* value refers to the *cis* isomer. [d] The molar ratio of **L**/$Sc(OTf)_3$ was 2:1. [e] 0.3 mL CH_2Cl_2 was used. [f] Reaction time: 42 hours. [g] n.d. = not determined. Tf = trifluoromethylsulfonyl.

Using the optimized conditions (Table 1, entry 10), the substrate scope of the three-component IEDDA reaction was then examined (Table 2). Regardless of the electronic properties or steric hindrance of the substituents on the aromatic ring of aldehydes, ring-fused tetrahydroquinolines were obtained in good to excellent yields with high diastereoselectivities (up to 98:2) and enantioselectivities (90- > 99%; Table 2, entries 1–18). In the case of fused-ring aromatic aldehydes, the catalyst was also efficient (Table 1, entries 19–20). Furthermore, the heteroaromatic aldehydes were competent candidates for the IEDDA reaction, affording their corresponding cyclization products in high yields and 95–98% *ee* (Table 2, entries 21–23). Moreover, aliphatic aldehydes were also suitable substrates to afford the ring-fused adducts in 94–99% *ee* (Table 2, entries 24–25). Substituted anilines also worked well to give the desired adducts in moderate to high yields and 90–98% *ee* (Table 2, entries 26–28). Other alkenes, including cyclohexa-1,3-diene, ethyl vinyl ether and 2,3-dihydrofuran were also explored as dienophiles, but the results were poor.[12]

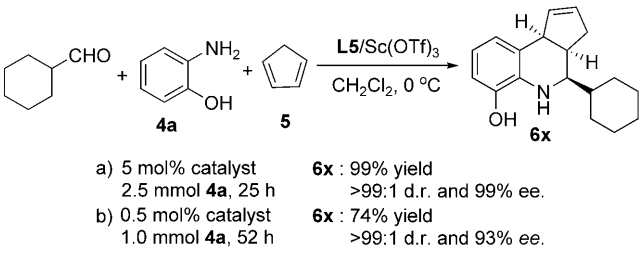
To further evaluate the synthetic potential of the catalyst system, a large-scale synthesis of chiral ring-fused tetrahydroquinoline **6x** were performed. As shown in Scheme 1, by treatment of 2.5 mmol starting material under the optimized reaction conditions, 0.69 g of the corresponding adduct **6x** was obtained without any loss of reactivity, diastereo-, or enan-

Table 2: Substrate scope of the asymmetric three-component IEDDA reactions.[a]



Entry	R^1	4	Yield [%][b]	cis/trans[c]	ee [%][c]
1	Ph	**4a**	90 (**6a**)	96:4	97
2	2-MeC_6H_4	**4a**	62 (**6b**)	92:8	92
3	3-MeC_6H_4	**4a**	82 (**6c**)	95:5	98
4	4-MeC_6H_4	**4a**	87 (**6d**)	95:5	98
5	2-ClC_6H_4	**4a**	99 (**6e**)	96:4	90
6	3-ClC_6H_4	**4a**	93 (**6f**)	96:4	93
7	4-ClC_6H_4	**4a**	99 (**6g**)	95:5	96
8[d]	2,4-$Cl_2C_6H_3$	**4a**	95 (**6h**)	92:8	94
9[d]	3,4-$Cl_2C_6H_3$	**4a**	99 (**6i**)	92:8	94
10	3-BrC_6H_4	**4a**	87 (**6j**)	95:5	92
11	4-BrC_6H_4	**4a**	92 (**6k**)	96:4	96
12	4-FC_6H_4	**4a**	82 (**6l**)	96:4	97
13	4-$CF_3C_6H_4$	**4a**	97 (**6m**)	96:4	95
14[d]	4-$NO_2C_6H_4$	**4a**	99 (**6n**)	92:8	94
15	4-CNC_6H_4	**4a**	93 (**6o**)	98:2	92
16[d]	4-$MeOC_6H_4$	**4a**	63 (**6p**)	90:10	> 99
17	4-PhC_6H_4	**4a**	72 (**6q**)	95:5	> 99
18	3-$PhOC_6H_4$	**4a**	90 (**6r**)	96:4	95
19	1-naphthyl	**4a**	85 (**6s**)	96:4	95
20[d]		**4a**	71 (**6t**)	91:9	> 99
21	3-furyl	**4a**	82 (**6u**)	98:2	95
22[d]	2-thienyl	**4a**	93 (**6v**)	96:4	98
23	3-thienyl	**4a**	93 (**6w**)	98:2	98
24	cyclohexyl	**4a**	99 (**6x**)	> 99:1[e]	99
25[d]	Et_2CH	**4a**	62 (**6y**)	> 95:5[e]	94
26	Ph	**4d**	85 (**6z**)	96:4	98
27	Ph	**4e**	70 (**6aa**)	92:8	96
28	Ph	**4f**	96 (**6ab**)	92:8	90

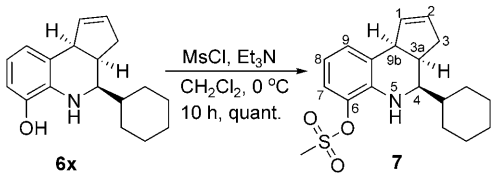
[a] Unless otherwise noted, all reactions were carried out with 5 mol% **L5**/$Sc(OTf)_3$, **3** (0.11 mmol), **4** (0.1 mmol), **5** (150 μL), and 4 Å M.S. (10.0 mg) in CH_2Cl_2 (0.3 mL) under N_2 at 0°C for 18–69 hours. [b] Yield of isolated product. [c] Determined by chiral HPLC analysis, the *cis* isomer was confirmed by ^{1}H NMR and the *ee* value refers to the *cis* isomer. [d] The reaction was performed at 25°C. [e] Ratio of *cis*/*trans* was determined by ^{1}H NMR spectroscopy.

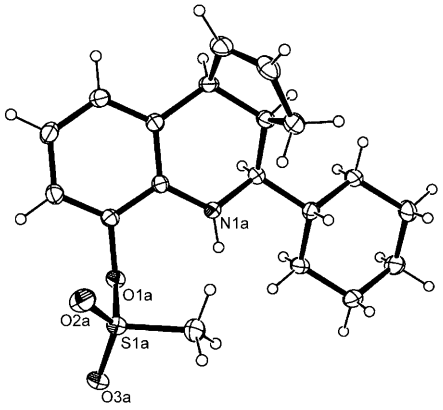


Scheme 1. a) The large-scale asymmetric synthesis of **6x**. b) The catalyst loading was reduced to 0.5 mol%.

tioselectivity. Meanwhile, when the reaction was performed at 0.5 mol% catalyst loading, tricyclic adduct **6x** was also obtained in 74% yield, >99:1 d.r., and 93% *ee* (Scheme 1).

The absolute configuration of the ring-fused tetrahydroquinoline **6x** was unambiguously determined to be (3a*R*, 4*R*, 9b*S*) by single-crystal X-ray diffraction analysis of the methanesulfonyl-protected tetrahydroquinoline **7** (Scheme 2).[13]

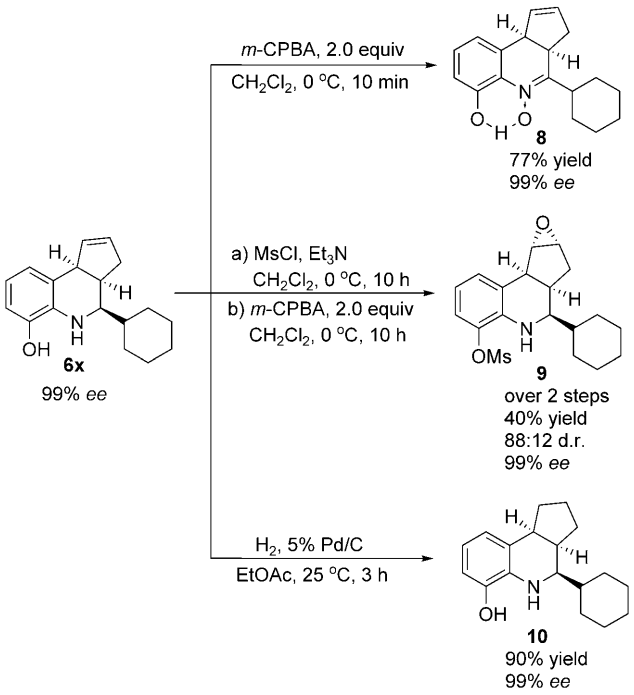




Scheme 2. Derivatization of **6x** and the structure of **7** determined by X-ray analysis. Ellipsoids set at 30% probability.

Because of the potential biological activities exhibited by the ring-fused tetrahydroquinolines,[10] structural elaboration of the tricyclic core is extremely important (Scheme 3). Considering that the epoxide of **6x** is an useful intermediate for forming different ring-fused tetrahydroquinolines by nucleophilic substitution reactions,[14] the synthesis of the epoxide was attempted. Surprisingly, oxidation of **6x** by *m*-CPBA did not afford the expected epoxide, but rather rapidly gave dihydroquinoline *N*-oxide **8**, in which a six-membered ring containing an intramolecular hydrogen bond was observed.[15] To avoid forming the intramolecular hydrogen bond, the hydroxy group of **6x** was protected by a methanesulfonyl group and the corresponding product **7** (Scheme 2) was obtained in quantitative yield. The desired epoxide **9** was then obtained by oxidation of **7** with good diastereoselectivity. Furthermore, hydrogenation of **6x** smoothly generated a tricyclic tetrahydroquinoline **10** in excellent yield (90%) without loss of diastereo- and enantioselectivity, which might also exhibit potential biological activity.[10]

In summary, we have developed an efficient asymmetric three-component inverse electron-demand aza-Diels–Alder reaction, with cyclopentadiene as the dienophile, catalyzed by 0.5–5 mol% of a *N*,*N*′-dioxide–Sc(OTf)$_3$ complex. A wide variety of ring-fused tetrahydroquinolines that contained



Scheme 3. Preparation of different ring-fused tetrahydroquinoline derivatives.

three contiguous stereocenters were obtained in a one-pot manner in good to high yields and excellent diastereo- (up to >99:1) and enantioselectivities (up to >99% *ee*). Moreover, through simple transformation, different ring-fused tetrahydroquinoline derivatives, which may also have biological activity, could be obtained under mild conditions with excellent enantioselectivities. Further application of the catalyst to other reactions is currently investigation.

Experimental Section

General procedure: Sc(OTf)$_3$ (2.5 mg, 0.005 mmol), the *N*,*N*′-dioxide ligand **L5** (7.1 mg, 0.01 mmol), aldehyde (0.11 mmol), 2-aminophenol (10.9 mg, 0.1 mmol), and 4 Å molecular sieves (10.0 mg) were stirred in 0.3 mL CH_2Cl_2 under nitrogen for 0.5 hours at 25 °C. Subsequently, cyclopentadiene (150 μL) was added at 0 °C, and the reaction mixture was stirred until 2-aminophenol was completely consumed (determined by TLC). The residue was purified by flash chromatography on silica gel to afford the desired product.

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[12] The results were listed as follows: cyclohexa-1,3-diene: 5% yield, *cis*/*trans*: 99:1, 45% *ee* (*cis* isomer); ethyl vinyl ether: 42% yield, *cis*/*trans*: 65:35, 24% *ee* (*cis* isomer); 2,3-dihydrofuran: 66% yield, *cis*/*trans*: 39:61, 84% *ee* (*cis* isomer).

[13] CCDC 763201 (**7**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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