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Chiral imidates as a new class of nitrogen-based chiral ligands: synthesis and catalytic activity in asymmetric aziridinations and diethylzinc additions

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ABSTRACT

Chiral imidates were efficiently synthesized in one step and with high yields (seven examples). These chiral imidates were used as ligands in the Cu(I)-catalyzed asymmetric aziridination of methyl cinnamate and in the asymmetric diethylzinc additions to benzaldehyde as a proof of principle. The imidate catalyst system showed high catalytic activities and induced encouraging selectivities. An X-ray structure analysis of an imidate-Cu(I) complex is included, showing a distorted tetrahedral arrangement with two bidentate ligand molecules surrounding the metal.

1. Introduction

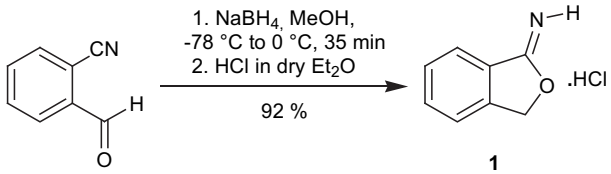
The dramatic growth of enantioselective catalysis calls for a permanent search for new chiral ligands. Although phosphane ligands are the most widely used ligands, nitrogen-containing ligands have several distinct advantages.[1] First, they are widely available in enantiomerically pure form from the chiral pool. Second, the production of chiral amines from the resolution of racemates is probably one of the easiest methods of enantiomer separation. Third, nitrogen-containing ligands may be used in asymmetric catalysis with other transition metals, less expensive than noble metals, e.g., cobalt complexes.[2] Finally, they turn out to be suitable for heterogeneous catalysis, which is one of their main advantages over phosphane ligands. As a result, a lot of attention has been devoted to the design, synthesis, and application of a wide variety of nitrogen-containing ligands such as oxazolines,[3] diimines,[4] semicorrins,[5] 2,2′-bipyridines,[6] pyrrolyl-, pyrrolidinyl-, and pyridyloxazolines,[7] benzoxazines,[8] amidines,[9] and sulfoximines.[10]

Imidates are esters of the hypothetical imidic acids.[11] These compounds are known to be very useful synthetic building blocks[12] and pharmacophores,[13] explaining the interest in their preparation. The classical method for synthesizing imidates is the Pinner reaction.[14] Hereby, a nitrile is condensed with an alcohol under anhydrous conditions in the presence of hydrogen chloride or hydrogen bromide at 0 °C. Since the pioneering work of Pinner, several new methods to synthesize imidate esters have been developed, e.g., a base-catalyzed reaction of nitriles with alcohols,[15] the reaction of amines with orthoesters,[16] a modified Staudinger ligation,[17] a three-component coupling of terminal alkynes, sulfonyl azides, and an alcohol in the presence of a copper catalyst,[18] a palladium-catalyzed insertion of isonitriles into *ortho* bromo arylalcohol,[19] and a three-component coupling using arynes, isonitriles, and aldehydes.[20]

Chiral imidates have, to the best of our knowledge, never been used as ligands in asymmetric catalysis. This is probably due to their presumed instability. In this paper we wish to present our results concerning the synthesis and application of both monodentate C_1- and bidentate C_2- symmetrical imidates as stable ligands for asymmetric catalysis.

2. Results and discussion

The literature describes the synthesis of imidate **1** via a Pinner reaction starting from *ortho*-cyanobenzylalcohol.[21] Surprisingly, we found that the cyclic imidate was formed immediately upon treatment of 2-cyanobenzaldehyde with $NaBH_4$ in EtOH (Scheme 1). This



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Scheme 1. Synthesis of imidate **1**.

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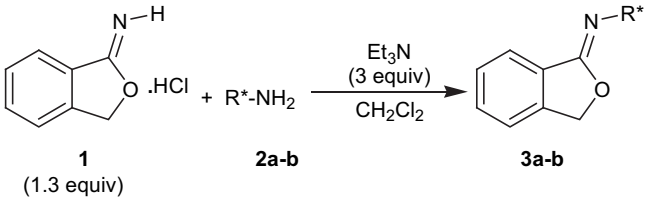
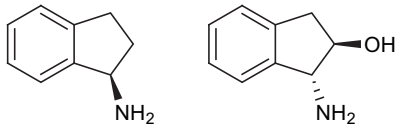
Table 1
Synthesis of monoimidates (**2a**–**b**)



R*-NH_2:

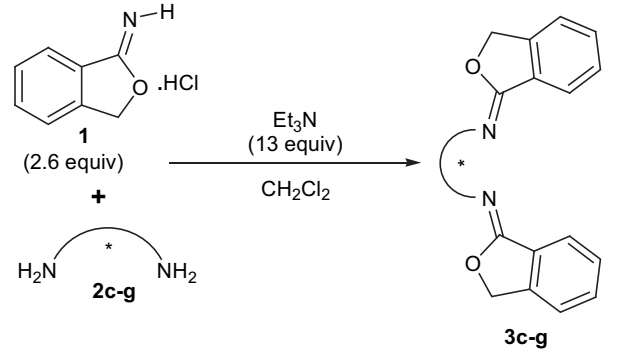


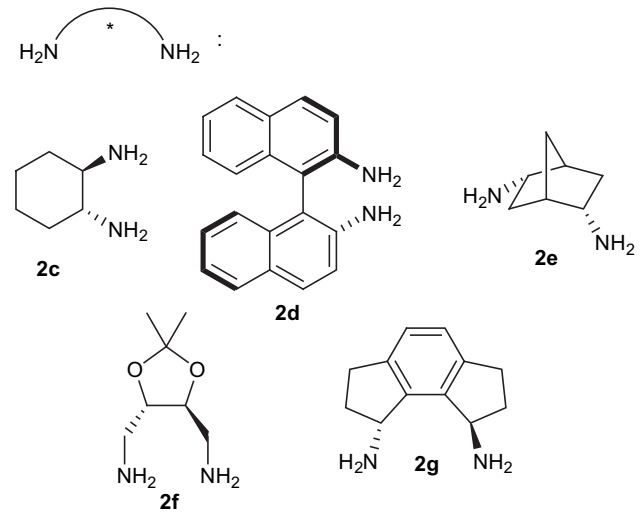
2a **2b**

Entry	Monoamine	Yield[a] (%)
1	*R*-(−)-aminoindane (**2a**)	74 (**3a**)
2	(1*R*,2*R*)-(−)-*trans*-1-amino-2-indanol (**2b**)	91 (**3b**)

[a] Isolated yield.

Table 2
Synthesis of bidentate bisimidates (**2c**–**g**)





Entry	Diamine	Yield[a] (%)
1	(1*R*,2*R*)-(−)-Diaminocyclohexane (**2c**)	85 (**3c**)
2[b]	(*R*)-(+)-1,1′-Binaphtyl-2,2′-diamine (**2d**)	71 (**3d**)
3	(1*S*,2*S*,4*S*,5*S*)-2,5-Diaminonorbornane (**2e**)	56 (**3e**)
4	(4*S*,5*S*)-4,5-Di(aminomethyl)-2,2-dimethyldioxolane (**2f**)	92 (**3f**)
5	(1*R*,8*R*)-1,2,3,6,7,8-Hexahydro-*as*-indacene-1,8-diamine (**2g**)	93 (**3g**)

[a] Isolated yield.
[b] The reaction was performed in refluxing MeOH.

was confirmed by IR spectroscopy of **1** where no absorption characteristic for a nitrile functionality could be detected. The free imidate base was a—slightly impure—brownish oil, which upon treatment with HCl in dry Et_2O was transformed into a highly pure crystalline HCl salt **1**.

Chiral imidates can be efficiently obtained in a single step as shown in Tables 1 and 2. Condensation of **1** with (*R*)-aminoindane **2a** and (1*R*,2*R*)-*trans*-1-amino-2-indanol **2b** resulted in the formation of monoimidates (**3a**–**b**) in high yields (Table 1). When diamines were used (**2c**–**g**), the corresponding chiral bidentate bisimidates (**3c**–**g**) were obtained in excellent yields. It should be noted that these ligands were perfectly stable for a long period at room temperature.[22]

Bisimidate **3c** showed for the alfa-protons on the cyclohexane ring two small vicinal coupling constants (dd, J=3.9, 4.7 Hz) suggesting an equatorial position of the imidate groups. The potential for bisimidate **3c** to act as a bidentate ligand was investigated by treatment of **3c** with $Cu(CH_3CN)_4PF_6$ in CH_3CN. Suitable crystals for X-ray diffraction were grown from a solution of the complex in MTBE/CH_3CN. An X-ray structure was obtained, shown in Figure 1. This revealed that in the complex the opposite chair conformation was adopted with the imidate groups in equatorial position and hence suitable for complexation with Cu(I). The Cu(I) complex shows a tetrahedral arrangement with two ligands surrounding the metal. The Cu–N bond lengths are 2.07 Å and 2.05 Å for both ligands. The angles between N(2)–Cu(1)–N(9) and N(28)–Cu(1)–N(35) are, respectively, 84.0° and 84.4°. The imidate groups clearly possess the *Z*-geometry dissecting the space around the metal effectively in a C_2-fashion.

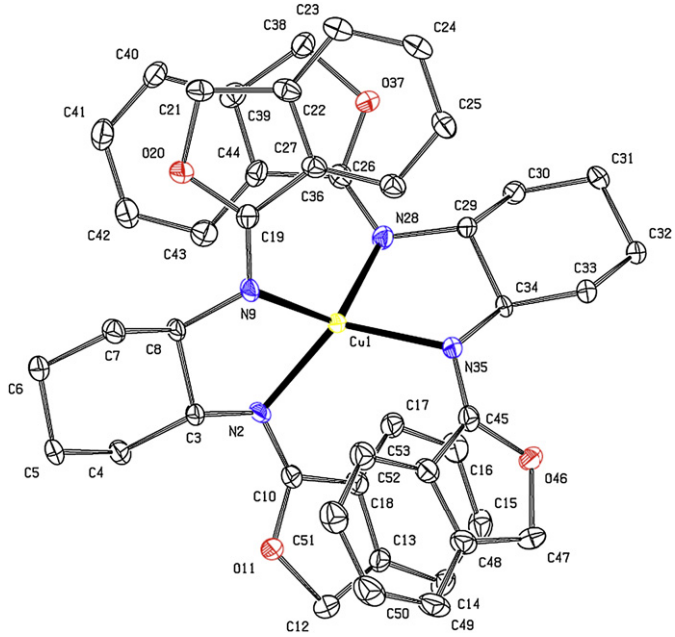
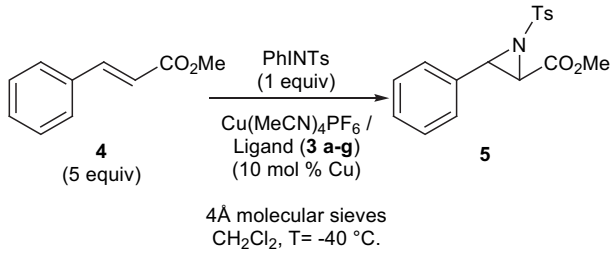


Figure 1. X-ray structure of $Cu(\mathbf{3c})_2 \cdot PF_6$. Hydrogens and PF_6 are omitted for clarity. Selected distances, bond angles, and torsion angles: Cu(1)–N(2) 2.065 Å, Cu(1)–N(9) 2.054 Å, Cu(1)–N(28) 2.078 Å, Cu(1)–N(35) 2.046 Å; N(2)–Cu(1)–N(9) 84.02°, N(2)–Cu(1)–N(28) 127.49°, N(2)–Cu(1)–N(35) 120.08°, N(9)–Cu(1)–N(28) 117.70°, N(9)–Cu(1)–N(35) 128.75°, N(28)–Cu(1)–N(35) 84.41°, N(2)–C(3)–C(8)–N(9) −49.6°, N(28)–C(29)–C(34)–N(35)−46.7°.

The enantioselective Cu(I)-catalyzed aziridination was chosen as the first catalytic test reaction in order to determine the efficiency of the new ligand system. Aziridines are very versatile building blocks in organic chemistry and they exhibit a similar reactivity pattern as epoxides.[23] In sharp contrast with these epoxides, the methods for asymmetric aziridine formation are scarce.

Table 3
Cu(I)-catalyzed asymmetric aziridination of methyl cinnamate (**4**)

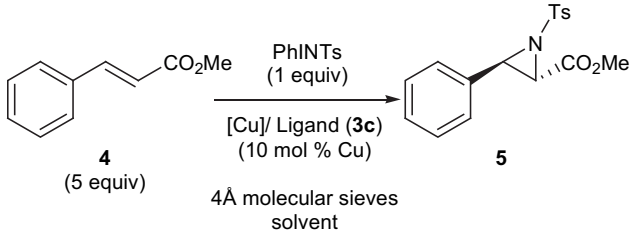


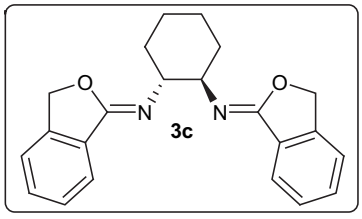
Entry	Ligand	Time (h)	Yield[a] (%)	% ee[b]	Configuration[c]
1[d]	**3a**	21	18	11	(2*S*,3*R*)
2	**3b**	24	24	16	(2*S*,3*R*)
3	**3c**	22	90	45	(2*S*,3*R*)
4	**3d**	21	22	26	(2*S*,3*R*)
5	**3e**	22	90	37	(2*S*,3*R*)
6	**3f**	23	97	3	n.d.
7	**3g**	21	87	<1	n.d.

[a] Isolated yield, calculated on PhINTs as a limiting reagent.
[b] Determined by HPLC analysis with a chiral stationary phase column (Chiralcel OD-H).
[c] Assigned by the sign of the optical rotation.
[d] Because **3a** is a monodentate ligand 22 mol % was used.

An interesting methodology to obtain these chiral aziridines is the Cu(I)-catalyzed asymmetric aziridination of alkenes. There are only a few ligand types appropriate for use in the asymmetric Cu(I)-catalyzed aziridination,[24] the two most important families being bisoxazolines[25] and diimines.[26] We evaluated the catalytic activity of the newly synthesized imidate ligands in this type of reaction.

Table 4
Cu(I)-catalyzed asymmetric aziridination of methyl cinnamate (**4**): variation of several reaction parameters with ligand **3c**





Entry	[Cu]	Solvent	Temp (°C)	Time (h)	Yield[a] (%)	% ee[b]
1	CuOTf	CH_2Cl_2	−40	24	18	42
2	$Cu(MeCN)_4BF_4$	CH_2Cl_2	−40	24	21	42
3	$Cu(MeCN)_4OTf$	CH_2Cl_2	−40	24	44	46
4	$Cu(OTf)_2$	CH_2Cl_2	−40	24	n.d.	—
5	$Cu(MeCN)_4PF_6$	Toluene	−40	48	<5	<1
6	$Cu(MeCN)_4PF_6$	CH_3CN	−40	24	31	28
7	CuOTf	Toluene	−40	24	n.d.	—
4	CuOTf	Benzene	25	24	56	14
5	$Cu(MeCN)_4PF_6$	$(CH_2Cl)_2$	−30	24	87	33
6	$Cu(MeCN)_4PF_6$	CH_2Cl_2	25	24	64	27
7	$Cu(MeCN)_4PF_6$	CH_2Cl_2	−78	24	58	51

[a] Isolated yield, calculated on PhINTs as a limiting reagent.
[b] Determined by HPLC analysis with a chiral stationary phase column (Chiralcel OD-H).

The catalytic asymmetric aziridination of methyl cinnamate was carried out with (*N*-(*p*-toluenesulfonyl)imino)phenyliodinane (PhINTs) as a nitrene precursor in dichloromethane at −40 °C. With monodentate imidate (**3a**) and imidate alcohol (**3b**) as a chiral ligand, low yields were obtained (Table 3, entries 1 and 2). We observed excellent yields for all bisimidates (Table 3, entries 3 and 5–7) except for imidate **3d** derived from binaphtyldiamine **2d** (Table 3, entry 4). The enantioselectivities were low (Table 3, entries 1–2 and 6–7) to moderate (Table 2, entries 3–5). Nevertheless, the result obtained with ligand **3c** was promising (Table 3, entry 3).[24]

With ligand **3c**, we tried to optimize the reaction conditions by varying different reaction parameters (Table 4). Changing the copper source resulted in a lower yield and comparable selectivities (Table 4, entries 1–3). With a copper (II) species, the reaction was sluggish and almost no conversion was observed (Table 4, entry 4). Changing the solvent led to very slow reactions (Table 4, entries 5–8). Dichloroethane as a solvent afforded a good yield but lower enantioselectivity than dichloromethane (Table 4, entry 9). The highest enantioselectivity was observed at a temperature of −78 °C (51% ee) (Table 4, entry 11).

The imidate ligands were further tested in 1,2-additions of diethylzinc to benzaldehyde. This reaction has become a classical test in the design of new ligands. Amino alcohols are the ligands of choice in this type of reaction.[27] It is known that bisoxazolines without

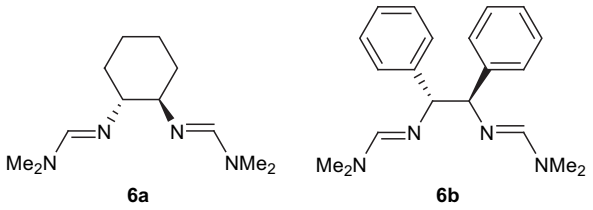
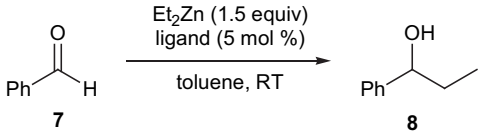


Figure 2. Bisamidine ligands.

Table 5
Additions of Et_2Zn to benzaldehyde in the presence of ligands **3a–d** and **6a–b**



Entry	Ligand	Time (h)	Yield[a] (%)	% ee[b]	Configuration[c]
1	**3a**	24	23	4	(*R*)
2[d]	**3b**	24	14	36	(*S*)
3	**3c**	48	80	11	(*S*)
4	**3d**	24	83	75	(*R*)
5	**3e**	24	87	14	(*R*)
6	**3f**	24	38	<1	n.d.
7	**3g**	24	42	5	(*R*)
8	**6a**	24	87	4	(*S*)
9	**6b**	3	95	24	(*S*)
10[d,e]	**3d**	24	87	64	(*R*)
11[d,f]	**3d**	24	73	54	(*R*)
12[d,g]	**3d**	24	77	46	(*R*)
13[d,h]	**3d**	72	18	59	(*R*)
14[i]	**3d**	48	70	75	(*R*)
15[h,i]	**3d**	48	71	76	(*R*)

[a] Isolated yield.
[b] Determined by HPLC analysis with a chiral stationary phase column (Chiralcel OD-H).
[c] Assigned by the sign of the optical rotations.
[d] 2.5 mol% ligand was added.
[e] 2.5 mol % Ti (^{i}OPr)$_4$ was added.
[f] 20 mol % Ti (^{i}OPr)$_4$ was added.
[g] 30 mol % Ti (^{i}OPr)$_4$ was added.
[h] Reaction temperature=0 °C.
[i] 10 mol % of ligand **3b**.

a hydroxyl substituent give rather low enantioselectivities.[28] We also compared our bisimidate ligands with bisamidine ligands **6a**–**b** (Fig. 2).[9]

The monodentate imidate ligands **3a** and **3b** gave slower reactions (Table 5, entries 1–2). Again we observed excellent yields with all bisimidate ligands, except for ligand **3f** and **3g** (Table 5, entries 3–7). The bisamidines **6a** and **6b** also gave very good yields (Table 5, entries 8–9). However the enantioselectivities were in general low for both bisimidates and bisamidines, with one exception: ligand **3d** afforded the product in good yield and good enantioselectivity (83%, 75% ee) (Table 4, entry 4). With ligand **3d**, we tried to optimize the reaction conditions (Table 5, entries 10–15). Addition of Ti (^{i}OPr)$_4$ resulted in lower selectivities (Table 5, entries 10–12). Decreasing the temperature resulted in a much slower reaction and a lower selectivity (Table 5, entry 13). Increasing the amount of ligand resulted in a selectivity comparable to our first experiment with ligand **3d** and a slight decrease in yield (Table 5, entries 14–15).

3. Conclusion

In summary, we introduced chiral imidates (**3a**–**g**) as a new class of chiral ligands, readily obtained via an efficient one-step synthesis starting from imidate **1** and chiral amines **2a**–**g**. As a proof of principle, high yields and moderate to good enantioselectivities were obtained in both asymmetric aziridinations and Et_2Zn additions. Current studies are focused on expanding the imidate family, taking advantage of its modular design and easy synthesis, and exploring the scope of this new ligand family. Results will be reported in due course.

4. Experimental

4.1. General

All reactions, unless otherwise stated, were carried out under argon atmosphere in dry solvents under anhydrous conditions. Benzaldehyde was passed through basic alumina. All other reagents were purchased and used without purification, unless otherwise noted. (1*S*,2*S*,4*S*,5*S*)-2,5-Diaminonorbornane (**2e**),[29] PhINTs,[30] bisamidines[9] **6a** and **6b** were synthesized according to literature procedures. Analytical TLC was performed using silica plates containing a UV_{254} indicator. Flash chromatography was carried out over silicagel (0.040–0.063 mm). ^{1}H NMR spectra were recorded at 300 or 500 MHz, ^{13}C NMR spectra at 75.4 or 125.7 MHz, as indicated. Chemical shifts are reported in ppm relative to TMS, using the residual solvent signal as a standard. ^{13}C NMR spectra were recorded using the attached proton test. IR-spectra were recorded on an FT-IR spectrometer equipped with a Horizontal Attenuated Total Reflectance (HATR) module. LC–MS analysis was performed on an HPLC with quaternary pump, DAD, and single quadrupole MS detector with an API-ES source, using a Phenomenex Luna C18(2) column (250×4.6 mm, particle size 5 μm). Analytical chiral HPLC separations were performed on an HPLC system with DAD detection. Exact molecular masses were measured on a Kratos MS50TC mass spectrometer. Melting points were measured with a Kofler melting point apparatus.

4.2. Synthesis of 1,3-dihydro-iminoisobenzofuran hydrochloride (3A)

2-Formylbenzonitrile (7.0 g, 53.4 mmol) was dissolved in absolute ethanol (420 mL) and cooled to −78 °C. $NaBH_4$ was added and the reaction mixture was allowed to heat to 0 °C in 30 min. The reaction mixture was poured into H_2O and extracted with CH_2Cl_2 (3×1000 mL). The organic phases were dried over Na_2SO_4 and concentrated in vacuo. The resulting orange oil was dissolved in CH_2Cl_2 (165 mL) and dry HCl in Et_2O (65 mL) was added. The resulting suspension was filtrated and the white crystals were washed with dry THF. This resulted in 8.3 g (92%) of imidate ester hydrochloride (**3A**). ^{1}H NMR (300 MHz, CD_3OD) δ 5.99 (s, 2H), 7.76 (t, *J*=7.8 Hz, 1H), 7.84 (d, *J*=7.8 Hz, 1H), 7.98 (t, *J*=7.8 Hz, 1H), 8.33 (d, *J*=7.8 Hz, 1H). ^{13}C NMR (75.4 MHz, CD_3OD): δ 81.0 (CH_2), 123.9 (CH), 124.6 (C), 126.5 (CH), 131.1 (CH), 138.1 (CH), 148.9 (C), 178.4 (C). IR (HATR): 3422, 3357, 3062, 3036, 2924, 2806, 2717, 2628, 1676, 1617, 1592, 1560, 1486, 1446, 1330, 1318, 1222, 1080, 938, 794, 739 cm^{-1}. EIMS *m*/*z* (rel intensity %): 133 ((M$^+$−HCl), 50), 104 (100), 89 (15), 77 (44), 63 (14), 51 (20), 43 (7). ES-MS: 134 [M−Cl$^-$]$^+$. Mp decomposition. HRMS (EI) calcd for C_8H_7ON: 133.0528; found: 133.0533.

4.3. Synthesis of imidate ligands (3a–g)

*4.3.1. Synthesis of (R)-indan-1-yl-(3H-isobenzofuran-1-ylidene)-amine (**3a**).* A suspension of (*R*)-(−)-1-indanylamine (**2a**) (100 mg, 0.75 mmol) and imidate **1** (178.0 mg, 1.05 mmol) in dry CH_2Cl_2 (5 mL) was cooled in an ice bath. Et_3N (0.31 mL, 2.25 mmol) was added and the resulting suspension was stirred for 24 h at room temperature. Evaporation in vacuo and purification by flash chromatography over silicagel (toluene/Et_2O, 6/4, +1% Et_3N) resulted in **3a** as a white solid, 138 mg (74%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.09–2.21 (m, 1H), 2.59–2.64 (m, 1H), 2.93–3.04 (m, 1H), 3.11–3.20 (ddd, *J*=3.2, 8.8, 15.7 Hz, 1H), 5.42 (s, 2H), 5.57 (dd, *J*=7.5, 7.5 Hz, 1H), 7.20–7.45 (m, 5H), 7.48 (d, *J*=7.5 Hz, 1H), 7.55 (t, *J*=7.5 Hz, 1H), 7.96 (d, *J*=7.5 Hz, 1H). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 30.8 (CH_2), 34.6 (CH_2), 61.2 (CH), 72.0 (CH_2), 121.2 (CH), 123.6 (CH), 124.2 (CH), 124.4 (CH), 126.2 (CH), 126.8 (CH), 128.3 (CH), 130.5 (C), 131.1 (CH), 143.1 (C), 143.4 (C), 145.8 (C), 160.1 (C). IR (HATR): 3018, 2957, 2931, 2859, 1689, 1470, 1456, 1361, 1331, 1289, 1073, 1024, 1015, 1002, 781, 776, 766, 740, 726, 700, 670 cm^{-1}. EIMS *m*/*z* (rel intensity %): 249 (M$^+$, 20), 234 (11), 220 (13), 134 (100), 118 (64), 90 (80), 76 (16), 63 (27), 51 (21). $[\alpha]_D^{20}$ +123.5 (*c* 0.78, $CHCl_3$). Mp 79–80 °C. HRMS (EI) calcd for $C_{17}H_{15}NO$: 249.1154; found: 249.1154.

*4.3.2. Synthesis of (1R,2R)-trans-1-(3H-isobenzofuran-1-ylidene-amino)-indan-2-ol (**3b**).* A suspension of (1*R*, 2*R*)-(−)-*trans*-1-amino-2-indanol (**2b**) (100.0 mg, 0.67 mmol) and imidate **1** (125.0 mg, 0.74 mmol) in CH_2Cl_2 was cooled in an ice bath. Et_3N (0.28 mL, 2.0 mmol) was added and the reaction mixture was stirred for 48 h at room temperature. Evaporation in vacuo and recrystallization from CH_2Cl_2 resulted in **3b** as a white solid, 161 mg (91%). ^{1}H NMR (300 MHz, DMSO): δ 2.74 (dd, *J*=7.0, 15.6 Hz, 1H), 3.18 (dd, *J*=7.0, 15.6 Hz, 1H), 4.33 (m, 1H), 5.12 (d, *J*=5.6 Hz, 1H), 5.16 (d, *J*=5.2 Hz, 1H), 5.44 (d, *J*=14.9 Hz, 1H), 5.50 (d, *J*=14.9 Hz, 1H), 7.05–7.20 (m, 4H), 7.44–7.49 (m, 1H), 7.56–7.63 (m, 2H), 7.70 (d, *J*=7.6 Hz, 1H). ^{13}C NMR+HSQC[31] (75.4 MHz, DMSO): δ 39.3 (CH_2), 68.3 (CH), 72.1 (CH_2), 79.5 (CH), 122.2 (CH), 122.8 (CH), 124.3 (CH), 124.5 (CH), 126.4 (CH), 127.1 (CH), 128.4 (CH), 129.7 (C), 131.5 (CH), 140.2 (C), 143.2 (C), 143.8 (C), 160.1 (C). IR (HATR): 3189, 1680, 1467, 1419, 1369, 1298, 1225, 1200, 1084, 1028, 998, 777, 747, 730, 703, 675 cm^{-1}. EIMS *m*/*z* (rel intensity %): 265 (M$^+$, 20), 247 (4), 237 (17), 218 (5), 146 (15), 134 (23), 118 (100), 104 (50), 90 (97), 63 (19), 49 (43). ES-MS: 266 [M+H]$^+$. $[\alpha]_D^{20}$ −304.8 (*c* 0.81, DMSO). Mp 236 °C. HRMS (EI) calcd for $C_{17}H_{15}NO_2$: 265.1103; found: 265.1107.

*4.3.3. Synthesis of (1R,2R)-N,N′-bis-(3H-isobenzofuran-1-ylidene)-cyclohexane-1,2-diamine (**3c**).* A suspension of (1*R*,2*R*)-(−)-diaminocyclohexane (**2c**) (119 mg, 1.04 mmol) and imidate **1** (450 mg, 2.65 mmol) in dry CH_2Cl_2 (5 mL) was cooled in an ice bath. Et_3N (1 mL, 13.6 mmol) was added and the resulting suspension was refluxed for 24 h. The reaction mixture was passed through a short pad of silicagel and eluted with EtOAc. Evaporation in vacuo and

purification by flash chromatography over silicagel (toluene/Et_2O, 6/4, +1% Et_3N) resulted in **3c** as a white solid, 308 mg (85%). ^1H NMR (500 MHz, $CDCl_3$): δ 1.47 (m, 2H) 1.60 (m, 2H), 1.80 (m, 2H), 1.92 (m, 2H), 3.98 (dd, J=3.9, 4.7 Hz, 2H), 5.16 (d, J=14.3 Hz, 2H), 5.23 (d, J=14.3 Hz, 2H), 7.23 (td, J=0.7, 7.5 Hz, 2H), 7.3 (dt, J=0.7, 7.5 Hz, 2H), 7.38 (dt, J=0.9, 7.5 Hz, 2H), 7.76 (d, J=7.5 Hz, 2H). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 24.9 (CH_2), 32.5 (CH_2), 61.0 (CH), 71.7 (CH_2), 121.1 (CH), 123.4 (CH), 128.0 (CH), 130.6 (CH), 130.9 (C), 143.1 (C), 158.9 (C). IR (HATR): 3040, 2927, 2873, 2854, 1689, 1614, 1468, 1448, 1360, 1288, 1227, 1093, 1015, 951, 863, 775, 726, 702, 670 cm^{-1}. EIMS m/z (rel intensity %): 346 (M^+, 22), 213 (22), 186 (10), 160 (30), 146 (20), 118 (70), 104 (46), 90 (100), 63 (15), 41 (12). ES-MS: 347 $[M+H]^+$. $[\alpha]_D^{20}$ +84.8 (c 1.12, $CHCl_3$). Mp: 146 °C. HRMS (EI) calcd for $C_{22}H_{22}N_2O_2$: 346.1681; found: 346.1680.

*4.3.4. Synthesis of (R)-(+)-N,N′-bis-(3H-isobenzofuran-1-ylidene)-1,1′-binaphthyl-2,2′-diamine (**3d**).* A suspension of (*R*)-(+)-1,1′-binaphthyl-2,2′-diamine (**2d**) (99 mg, 0.35 mmol) and imidate **1** (179 mg, 1.06 mmol) in MeOH (5 mL) was cooled in an ice bath. Et_3N (0.32 mL, 2.3 mmol) was added and the resulting suspension was refluxed for five days. Evaporation in vacuo and purification by flash chromatography over silicagel (toluene/EtOAc, 7/3, +1% Et_3N) resulted in **3d** as a white solid, 127.8 mg (71%). ^1H NMR (300 MHz, $CDCl_3$): δ 4.07 (d, J=14.6 Hz, 2H), 4.84 (d, J=14.6 Hz, 2H), 7.10–7.56 (m, 16H), 7.85 (m, 4H). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 71.8 (CH_2), 120.8 (CH), 122.9 (CH), 123.9 (CH), 124.6 (CH), 125.6 (CH), 126.5 (C), 126.9 (CH), 127.5 (CH), 127.6 (CH), 128.4 (CH), 130.5 (C), 130.7, 131.4 (CH), 133.8 (C), 143.2 (C), 144.3 (C), 158.3 (C). IR (HATR): 3050, 2357, 1687, 1614, 1589, 1502, 1466, 1361, 1291, 1262, 1206, 1408, 1004, 942, 826, 770, 727 cm^{-1}. EIMS m/z (rel intensity %): 516 (M^+, 16), 382 (29), 284 (12), 266 (18), 149 (32), 118 (31), 90 (83), 45 (100). ES-MS: 517 $[M+H]^+$. $[\alpha]_D^{20}$ +596.6 (c 1.01, $CHCl_3$). Mp: 216–218 °C. HRMS (EI) calcd for $C_{36}H_{24}N_2O_2$: 516.1838; found: 516.1837.

*4.3.5. Synthesis of (1S,2S,4S,5S)-bis-(3H-isobenzofuran-1-ylidene)-bicyclo[2.2.1]heptane-2,5-diamine (**3e**).* A suspension of (1*S*,2*S*,4*S*,5*S*)-2,5-diaminonorbornane (**2e**)[29] (410 mg, 3.26 mmol) and imidate **1** (1.60 g, 9.46 mmol) in dry CH_2Cl_2 (30 mL) was cooled in an ice bath. Et_3N (2.5 mL, 18 mmol) was added and the resulting suspension was stirred for 16 h at room temperature. Evaporation in vacuo and purification by flash chromatography over silicagel (toluene/Et_2O, 6/4, 1% Et_3N) resulted in a white solid. This contained 90% of **3c** and 10% of *endo–exo* bisimidate. Recrystallization in CH_2Cl_2/hexane afforded **3e** as a pure product, 654.3 mg (56%). ^1H NMR (500 MHz, $CDCl_3$): δ 1.59 (s, 2H), 1.93 (m, 2H), 1.95 (m, 2H), 2.38 (s, 2H), 4.18 (m, 2H), 5.29 (s, 4H), 7.31 (d, J=7.6 Hz, 2H), 7.35 (t, J=7.6 Hz, 2H), 7.44 (t, J=7.6 Hz, 2H), 7.87 (d, J=7.6 Hz, 2H). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 29.8 (CH_2), 38.1 (CH_2), 43.2 (CH), 58.2 (CH), 72.1 (CH_2), 121.1 (CH), 123.8 (CH), 128.5 (CH), 130.6 (C), 131.0 (CH), 143.0 (C), 160.0 (C). IR (HATR): 3023, 2963, 2860, 2368, 2324, 1679, 1468, 1447, 1362, 1337, 1286, 1062, 1042, 1002, 936, 850, 780, 723 cm^{-1}. EIMS m/z (rel intensity %): 358 (M^+, 9), 317 (9), 239 (9), 225 (24), 198 (24), 184 (32), 159 (23), 134 (27), 118 (69), 90 (100). ES-MS: 359 $[M+H]^+$. $[\alpha]_D^{20}$ −54.6 (c 1.24, $CHCl_3$). Mp: 108 °C. HRMS (EI) calcd for $C_{23}H_{22}N_2O_2$: 358.1681; found: 358.1682.

*4.3.6. Synthesis of (4S,5S)-4,5-di[(3H-isobenzofuran-1-ylidene)aminomethyl]-2,2-dimethyl-1,3-dioxolane (**3f**).* A suspension of (4*S*,5*S*)-4,5-di(aminomethyl)-2,2-dimethyl-1,3-dioxolane (**2f**) (105.0 mg, 0.66 mmol) and imidate **1** (307 mg, 1.81 mmol) in CH_2Cl_2 was cooled in an ice bath. Et_3N (0.48 mL, 3.4 mmol) was added and the reaction mixture was stirred for 16 h at room temperature. Evaporation in vacuo and recrystallization from EtOAc resulted in **3f** as a white solid, 236.6 mg (92%). ^1H NMR (300 MHz, $CDCl_3$): δ 1.49 (s, 6H), 3.81 (m, 4H), 4.24 (t, J=3.5 Hz, 2H), 5.25 (s, 4H), 7.31 (d, J=7.5 Hz, 2H), 7.37 (t, J=7.5 Hz, 2H), 7.46 (dt, J=1.0, 7.5 Hz, 2H), 7.83 (d, J=7.5 Hz, 2H). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 27.3 (CH_3), 49.8 (CH_2), 72.1 (CH_2), 79.8 (CH), 109.1 (C), 121.2 (CH), 123.7 (CH), 128.3 (CH), 130.4 (C), 131.1 (CH), 143.2 (C), 160.7 (C). IR (HATR): 2903, 1692, 1367, 1293, 1251, 1166, 1073, 998, 724, 664 cm^{-1}. EIMS m/z (rel intensity %): 392 (M^+, <1), 377 (2), 260 (5), 246 (17), 201 (29), 188 (46), 160 (17), 146 (100), 118 (28), 91 (58). ES-MS: 393 $[M+H]^+$. $[\alpha]_D^{20}$ −47.0 (c 1.00, $CHCl_3$). Mp: 204 °C. HRMS (EI) calcd for $C_{23}H_{24}N_2O_4$: 392.1736; found: 392.1737.

*4.3.7. (1R,8R)-N,N′-Bis-(3H-isobenzofuran-1-ylidene)-1,2,3,6,7,8-hexahydro-as-indacene-1,8-diamine (**3g**).* (1*R*,8*R*)-1,2,3,6,7,8-hexahydro-*as*-indacene-1,8-diamine hydrochloride (**2g**)[32] (10.9 mg, 0.0417 mmol) and imidate **1** (20.3 mg, 0.1197 mmol) was suspended in dry CH_2Cl_2 (0.75 mL) and cooled in an ice bath. Et_3N (32 μL, 0.230 mmol) was added and the resulting suspension was stirred for 24 h at room temperature. The reaction mixture was passed through a short pad of silicagel and eluted with EtOAc. Evaporation in vacuo and purification by flash chromatography over silicagel (cyclohexane/EtOAc, 2/1) resulted in **3g** as a white solid, 16.3 mg (93%). ^1H NMR (300 MHz, C_6D_6): δ 2.20 (dddd, J=8.0, 8.5, 8.5, 12.1 Hz, 2H), 2.64 (dddd, J=2.2, 8.0, 8.5, 12.1 Hz, 2H), 2.86 (ddd, J=8.5, 8.5, 15.0 Hz, 2H), 3.01 (ddd, J=2.2, 8.5, 15.0 Hz, 2H), 3.44 (d, J=14.2 Hz, 2H), 4.28 (d, J=14.2 Hz, 2H), 6.23 (t, J=8.0 Hz, 2H), 6.37–6.45 (m, 2H), 6.85–6.98 (m, 4H), 7.18 (s, 2H), 7.94–8.01 (m, 2H). ^{13}C NMR (75.4 MHz, C_6D_6): δ 31.4 (CH_2), 34.7 (CH_2), 60.8 (CH), 71.0 (CH_2), 120.7 (CH), 123.5 (CH), 123.9 (CH), 127.8 (CH), 130.2 (CH), 131.9 (C), 142.2 (C), 143.5 (C), 143.7 (C), 158.2 (C). IR (HATR): 2952, 2936, 2874, 2844, 1695, 1468, 1364, 1338, 1290, 1228, 1152, 1078, 1025, 1016, 775, 726 cm^{-1}. EIMS m/z (rel intensity %): 421 (M^+, <1), 287 (100), 258 (11), 154 (20), 90 (21). ES-MS: 421 $[M+H]^+$. $[\alpha]_D^{20}$ −157.3 (c 0.56, $CHCl_3$). Mp: 184–186 °C. HRMS (EI) calcd for $C_{28}H_{24}N_2O_2$: 420.1838; found: 420.1830.

4.4. Synthesis of $Cu(3c)_2PF_6$

N,*N*′-Bis-(3*H*-isobenzofuran-1-ylidene)-cyclohexane-(1*R*,2*R*)-diamine (**3c**) (31.0 mg, 89.5 μmol) and $Cu(MeCN)_4PF_6$ (29.4 mg, 78.9 μmol) were dissolved in acetonitrile (2 mL). The resulting yellow suspension was filtrated and evaporated in vacuo. The resulting yellow solids were recrystallized from benzene. This resulted in pure $Cu(\mathbf{3c})_2PF_6$ as a yellow solid, 40.3 mg (quantitative yield). ^1H NMR (300 MHz, CD_3CN): δ 1.20 (m, 8H), 1.68 (m, 4H), 2.31 (d, J=10.4 Hz, 4H), 3.20 (br s, 4H), 4.83 (d, J=15.4 Hz, 4H), 5.23 (d, J=15.4 Hz, 4H), 7.42 (m, 8H), 7.58 (t, J=7.5 Hz, 4H), 8.27 (d, J=7.5 Hz, 4H). ^{13}C NMR (75.4 MHz, CD_3CN): δ 26.0 (CH_2), 31.7 (CH_2), 64.0 (CH), 75.2 (CH_2), 122.8 (CH), 125.4 (CH), 129.3 (CH), 130.0 (C), 133.5 (CH), 144.8(C), 167.0 (C). IR (HATR): 2937, 2861, 1644, 1470, 1452, 1364, 1298, 1102, 1095, 1040, 1020, 998, 953, 832, 776, 726, 673 cm^{-1}. ES-MS: 755 $[Cu(\mathbf{3c})_2]^+$, 450 $[Cu(\mathbf{3c})\ CH_3CN]^+$, 409 $[Cu(\mathbf{3c})]^+$, 347 $[\mathbf{3c}+H]^+$. $[\alpha]_D^{20}$ −387.3 (c 0.79, CH_3CN). Mp: decomposition.

4.5. General procedure for the Cu(I)-catalyzed asymmetric aziridination of methyl cinnamate

Bisimidate (**3c**) (7.6 mg, 0.022 mmol) and $Cu(MeCN)_4PF_6$ (7.5 mg, 0.020 mmol) were dissolved in CH_2Cl_2 (2 mL) and stirred for 45 min at room temperature under argon. To this reaction mixture was added 4 Å molecular sieves (100 mg) and methyl cinnamate (162 mg, 1.0 mmol). The resulting suspension was cooled to −40 °C. Subsequently, PhINTs (74.6 mg, 0.2 mmol) was added and stirred for 21 h. The reaction mixture was passed through a short pad of silicagel and eluted with EtOAc. Evaporation in vacuo and purification by flash chromatography over silicagel (gradient elution with hexane/EtOAc, 90/10 to hexane/EtOAc, 80/20) resulted in **5**, 59.3 mg (90%, 45% ee). The adduct **5** was fully characterized by comparing its spectral data with those reported in

the literature.[25] Conditions for chiral HPLC analysis: Chiralcel OD-H column (250×4.6 mm, particle size 10 μm), solvent: *n*-hexane/EtOH (90/10), flow rate = 1 mL/min, $T = 35$ °C, retention times: 10.7 min for (2*R*,3*S*)-**5** and 16.4 min for (2*S*,3*R*)-**5**.

4.6. General procedure for the addition of Et_2Zn to benzaldehyde

Bisimidate (**3d**) (6.0 mg, 0.012 mmol) was dissolved in toluene (2 mL). Et_2Zn (0.75 mL, 1 M in hexane) was added and the resulting yellow solution was stirred for 20 min at room temperature under argon atmosphere. Next, benzaldehyde was added (50 mL, 0.49 mmol) and the reaction was stirred for another 24 h. The reaction was quenched with 1 mL saturated NH_4Cl solution. The reaction was added to 25 mL H_2O and extracted with EtOAc (3×25 mL). The combined organic phases were dried on Na_2SO_4 and evaporated in vacuo. Purification by flash chromatography over silicagel (pentane/EtOAc, 90/10) resulted in **8**, 55.7 mg (83%, 75% ee). The adduct **8** was fully characterized by comparing its spectral data with those reported in the literature.[33] Conditions for chiral HPLC analysis: Chiralcel OD-H column, solvent: *n*-hexane/EtOH (97/3), flow rate=1 mL/min, T=35 °C, retention times: 7.8 min for *R*-(+)-**8** and 9.0 min for *S*-(−)-**8**.

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Supplementary data

A procedure for **2e**, crystal data and parameters for $Cu(\mathbf{3c})_2 \cdot PF_6$ and the ^1H NMR and APT-spectra of all new compounds can be found in the online version.

Crystallographic data (excluding structure factors) for $Cu(\mathbf{3c})_2 \cdot PF_6$ have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 738785. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 lEZ, UK [fax: +44(0) 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk]. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2009.08.028.

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