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Efficient synthesis of chiral C_2-symmetric diamines via allylboration of bis-*N*,*N*′-metallodiimines

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ABSTRACT

An enantioselective synthesis of C_2-symmetric bis-homoallylic aromatic and heteroaromatic diamines in 54–89% yields, in 73–94% de and ⩾98% ee has been achieved via the allylboration of the corresponding *N*,*N*′-bis(trimethylsilyl)dialdimines and *N*,*N*′-bis(diisobutylalumino)dialdimines with *B*-allyldiisopinocampheylborane in the presence of methanol, followed by alkaline hydrogen peroxide workup. One-pot synthesis of stable *N*,*N*′-bis(benzaldimine–triethylborane) complexes and subsequent allylboration to afford benzene diamines is also described.

1. Introduction

The development of new chiral ligands for stereoselective reactions is of critical importance in the realm of asymmetric synthesis.[1] A vast number of the successful ligands that are extensively used in asymmetric reactions possess C_2-symmetry since they reduce the number of possible diastereomeric transition states and thus impart a beneficial effect on stereocontrol by eliminating less selective pathways.[2,3] Chiral C_2-symmetric ligands with oxygen-, nitrogen-, and phosphorus electron-donor atoms are regarded as some of the most effective ones in transition metal-catalyzed asymmetric reactions.[4] In our efforts to prepare chiral C_2-symmetric ligands, we had described the asymmetric reduction of diacylbenzenes and diacylpyridines with (−)-*B*-chlorodiisopinocampheylborane [(−)-DIP-Chloride™, **1**] providing the corresponding C_2-symmetric diols in 70% to ⩾99% de and 81% to ⩾99% ee (Scheme 1)[5] and the allylboration of dicarboxaldehydes with (−)-*B*-allyldiisopinocampheylborane [(−)-Ipc$_2$BAll, **2**] affording C_2-symmetric bis-homoallylic diols in 88–98% de and ⩾98% ee (Scheme 2).[6]

The extensive application of optically active C_2-symmetric diamines as chiral inducers in a vast number of asymmetric processes[7] prompted us to examine the allylboration of bis-*N*,*N*′-metallodiimines for the synthesis of bis-homoallylic diamines. Although a few racemic bis-homoallylic diamines have been reported[8], to the best of our knowledge, the chiral molecules have not been reported.

We had reported that *N*-trimethylsilylarylaldimines can be allylborated, in the presence of stoichiometric amount of water or methanol, with **2** to provide the corresponding homoallylic amines in 69–90% yield and 81–94% ee.[9] The reaction proceeds via the rapid liberation of free NH aldimine intermediate as an allylborane complex, followed by the allyl transfer via a six-membered chair-like transition state to an amino-dialkylborane intermediate, which upon workup provides the homoallylamine (Scheme 3). We also synthesized a series of *N*-aluminoimines by the partial reduction of a series of representative aromatic and aliphatic nitriles with DIBAL-H, followed by the allylboration with **2** to obtain the corresponding homoallylic amines (Scheme 3).[10,11] In this case also, 1 equiv of methanol was added as an indispensable ingredient for the methanolysis of N–Al bond resulting in the formation of the same intermediate for subsequent allylboration with Ipc$_2$BAll. Recently, we had also reported the preparation of stable aldimine–triethylborane complexes by the partial reduction of nitriles with Super-Hydride® (LiEt$_3$BH), followed by the addition of stoichiometric methanol and subsequent one-pot allylboration with Ipc$_2$BAll to afford chiral homoallylic amines in high yield and enantioselectivity.[12]

We sought to extend these reactions to aromatic diimines. Accordingly, we prepared a series of aromatic *N*,*N*′-bis(trimethylsilyl)dialdimines (**4a–e**) from benzene-1,2-dicarboxaldehyde (**3a**), benzene-1,3-dicarboxaldehyde (**3b**), benzene-1,4-dicarboxaldehyde (**3c**), 2,5-thiophenedicarboxaldehyde (**3d**), and 2,6-pyridinedicarboxaldehyde (**3e**) following the same procedure for the preparation of *N*-trimethylsilylbenzaldimine.[13] Treatment of benzene-1,4-dicarboxaldehyde **3c** with lithium bis(trimethylsilyl)amide at −50 °C in ether and subsequent purification by vacuum distillation afforded

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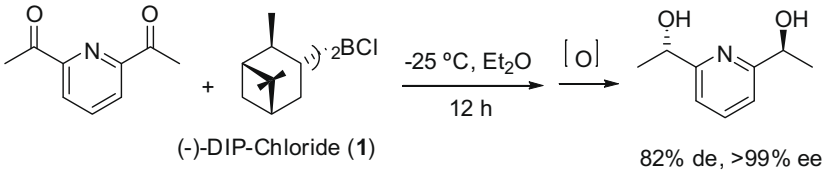
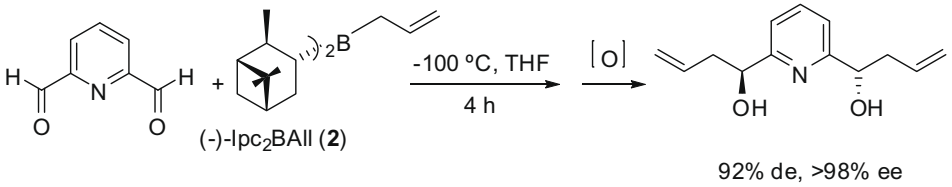


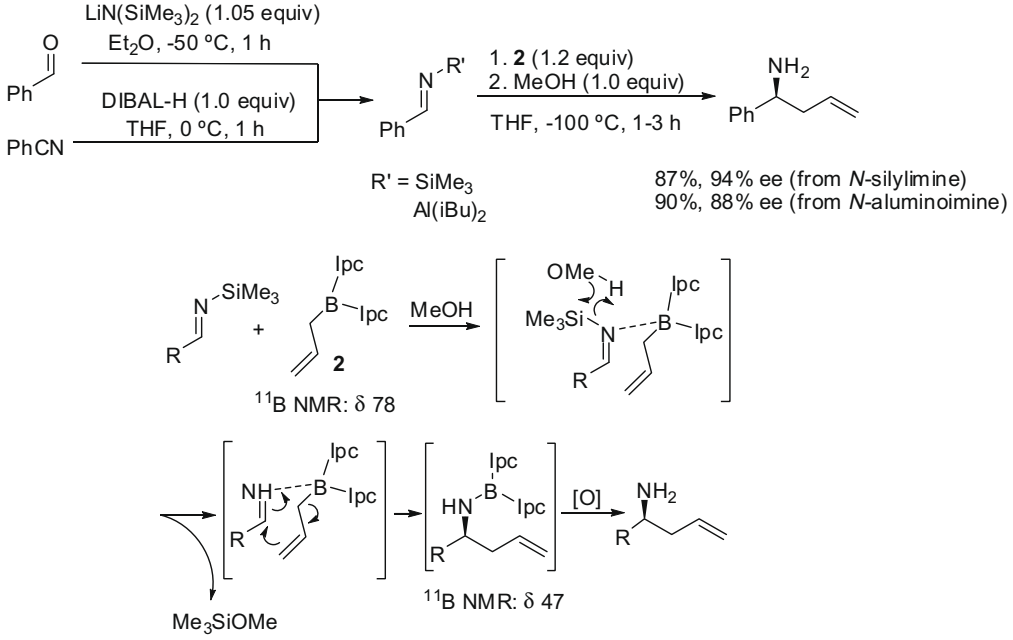
(-)-DIP-Chloride (**1**)

Scheme 1. Asymmetric reduction of diacylpyridines with (−)-DIP-chloride.



(-)-Ipc$_2$BAll (**2**)

Scheme 2. Allylboration of pyridinedicarboxyaldehyde with (−)-Ipc$_2$BAll.

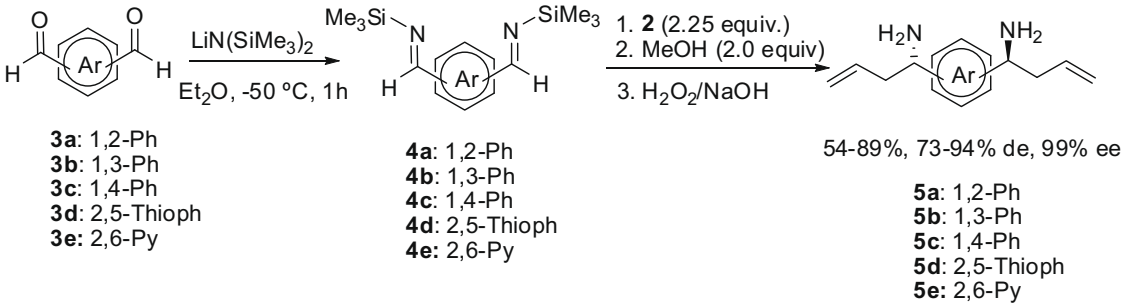


Scheme 3. Allylboration of *N*-trimethylsilyl- and *N*-aluminobenzaldimine with Ipc$_2$BAll.

the 1,4-[*N*,*N*′-bis(trimethylsilyl)]dibenzaldimine **4c** in high yield. The allylboration of **4c** was carried out with **2** at −78 °C in the presence of 2 equiv of methanol. The completion of the reaction was monitored by ^{11}B NMR spectroscopy, and alkaline oxidative workup , followed by column chromatography provided the desired C_2-symmetric diamine **5c** in 85% yield with 75% de and 99% ee (Scheme 4). The de was determined by either the ^{1}H or the ^{19}F NMR spectroscopy of the bis-MTPA amides derived from the diamines. Lowering the reaction temperature to −100 °C improved the de to 85% establishing a direct correlation between the temperature and the diastereoselectivity for the allylboration of bis-(trimethylsilyl)diimines (Table 1, entries 4 and 5). Allylboration of 1,2-[*N*,*N*′-bis(trimethylsilyl)]dibenzaldimine (**4a**) and 1,3-[*N*,*N*′-bis(trimethylsilyl)]dibenzaldimine (**4b**) with **2** at −78 °C provided the corresponding bis-homoallylic diamines **5a** and **5b** in 57% yield, 88% de, ⩾99% ee and 88% yield, 75% de, 99.6% ee, respectively (Table 1, entries 1 and 2).

Heteroaromatic bis-homoallylic diamines **5d** and **5e** were also prepared from the corresponding dialdimines (**4d** and **4e**) at −78 °C and −100 °C in 74–81% yield, 72–94% de, and ⩾98% ee. The results are summarized in Table 1. Upon successful preparation of bis-homoallylic diamines by allylboration of pure **4a–e**, we also attempted a one-pot allylboration of the in situ-generated 1,4-[*N*,*N*′-bis(trimethylsilyl)]dibenzaldimine (**4c**) with **2**. Preparation of **4c** by the treatment of benzene-1,4-dicarboxaldehyde (**3c**) with lithium bis(trimethylsilyl)amide, followed by the addition of **2** and methanol at −78 °C in the same pot afforded **5c** in 54% yield, 72% de, and ⩾99% ee (Table 1, entry 6). The low yield of the reaction could probably be attributed to the presence of impurities in the in situ-generated bis-(trimethylsilyl)diimine.

Allylboration of *N*-aluminoimines has significant practical advantages over that of *N*-silylimines due to the ease of preparation, ready availability of the starting nitriles, and relatively higher stability of both aromatic and aliphatic *N*-aluminoimines. In an effort to develop a generalized protocol for the preparation of C_2-symmetric bis-homoallylic diamines starting from different classes of *N*-metaloimines, we extended our *N*-aluminoimine-based protocol[11] for the preparation of selected diamines (**5a**, **c**, and **e**) by the partial reduction of 1,2-dicyanobenzene (**6a**), 1,4-dicyanobenzene

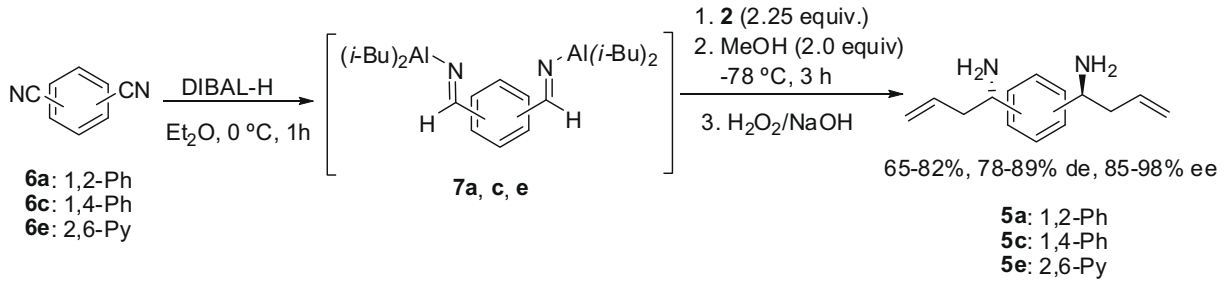


Scheme 4. Allylboration of *N*,*N*′-bis(trimethylsilyl)dibenzaldimines with (−)Ipc$_2$BAll.

Table 1
Allylboration of *N*,*N*′-bis(trimethylsilyl)dialdimines with (-)-Ipc$_2$BAll

Entry	Dialdimines		Bis-homoallylic diamines							
			Temp (°C)	#	Yield[a] (%)	*S*,*S*	*R*,*R*	*R*,*S*	de[b] (%)	ee[b] (%)
1	**4a**	1,2-Ph	−78	**5a**	57	94	0	6	88	⩾99
2	**4b**	1,3-Ph	−78	**5b**	89	87.5	0.2	12.3	~75	⩾98
3	**4b**	1,3-Ph	−100	**5b**	82	97	0	3	94	⩾99
4	**4c**	1,4-Ph	−78	**5c**	85	87.3	0.5	12.2	~75	99
5	**4c**	1,4-Ph	−100	**5c**	78	92.3	0	7.7	~85	⩾99
6	**4c**	1,4-Ph	−78[c]	**5c**	54	86.3	0	13.7	73	⩾99
7	**4d**	2,5-Thioph	−78	**5d**	81	86.2	0.7	13.1	72	⩾98
8	**4d**	2,5-Thioph	−100	**5d**	79	95	0	5	90	⩾99
9	**4e**	2,6-Py	−78	**5e**	77	89.4	0	10.6	~79	⩾99
10	**4e**	2,6-Py	−100	**5e**	74	97	0	3	94	⩾99

[a] Isolated yield after chromatography.
[b] Determined by analysis of ^{1}H or ^{19}F NMR of bis-Mosher amide.
[c] One-pot reaction without purification of **4c**.



Scheme 5. Allylboration of *N*,*N*′-bis(diisobutylalumino)dialdimines with (−)-Ipc$_2$BAll.

(**6c**), and 2,6-pyridinedicarbonitrile (**6e**) with DIBAL-H to obtain the corresponding *N*,*N*′-bis(diisobutylalumino)dialdimines (**7a**, **c**, and **e**), followed by the allylboration with **2** in the presence of 2 equiv of methanol at −78 °C for 3 h (Scheme 5). The reaction proceeded well and the desired bis-homoallylic diamines (**5a**, **c**, and **e**) were obtained in 69–82% yield with 80–90% de and ⩾98% ee. The results are summarized in Table 2. Due to our interest in fluoro-organic chemistry, we included a fluorinated diimine as well. Thus, the preparation of 1,4-[*N*,*N*′-bis(diisobutylalumino)]-2,3,5,6-tetrafluorobenzaldimine (**7f**) from 1,4-dicyano-2,3,5,6-tetrafluorobenzene (**6f**) and allylboration with **2** provided the corresponding bis-homoallylic amine (**5f**) in 94% de and the major diastereomer was obtained in ⩾99% ee (Scheme 6).

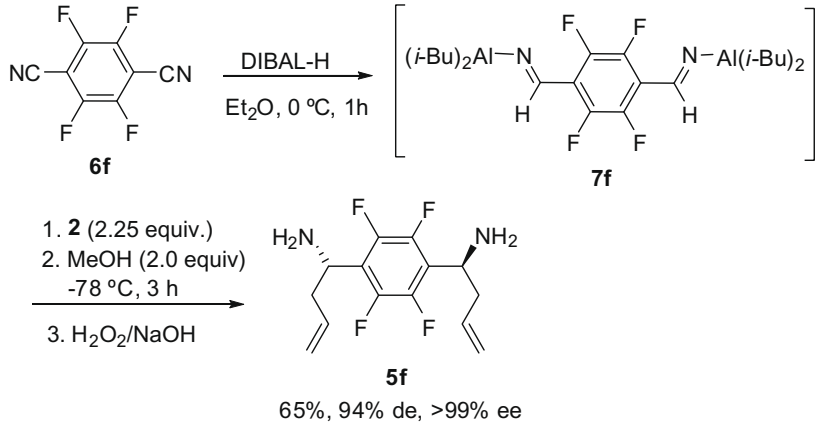
Subsequently, we also developed a methodology to prepare diimines from imine–borane adducts, *N*,*N*′-bis(benzaldimine–triethylborane) complexes (**8b** and **c**), derived by the partial reduction of 1,3-dicyanobenzene (**6b**) and 1,4-dicyanobenzene (**6c**), respectively, with 2 equiv of LiEt$_3$BH, followed by the addition of 2 equiv of methanol. One-pot allylboration of these in situ-generated *N*,*N*′-bis(benzaldimine–triethylborane) complexes with **2** at −78 °C for 6 h afforded the desired diamines (**5b** and **c**) in 72–79% yield, 78–82% de, and ⩾99% ee (Scheme 7).

In conclusion, we have developed a convenient, highly stereoselective general procedure for the preparation of C_2-symmetric bis-homoallylic diamines via the allylboration of a series of aromatic dialdimines. We successfully prepared *N*,*N*′-bis(trimethylsilyl)dialdimines from dialdehydes, *N*,*N*′-bis(diisobutylalumino)dialdimines, and *N*,*N*′-bis(aldimine–triethylborane) complexes from dinitriles

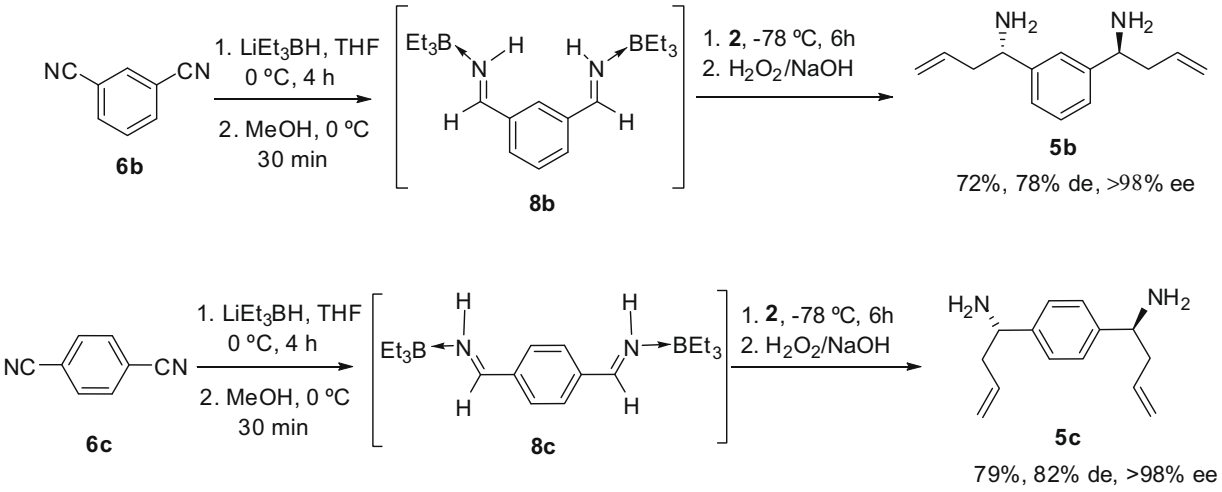
Table 2
Allylboration of *N*,*N*′-bis(diisobutylalumino)dialdimines with (−)-Ipc$_2$BAll

Entry	Dialdimines		Bis-homoallylic diamines						
			#	Yield[a] (%)	*S*,*S*	*R*,*R*	*R*,*S*	de[b] (%)	ee[b] (%)
1	**7a**	1,2-Ph	**5a**	79	95	0	5	90	⩾99
2	**7c**	1,4-Ph	**5c**	82	90	1	9	80	⩾98
3	**7e**	2,6-Py	**5e**	69	91	0	9	82	⩾99

[a] Isolated yield after chromatography.
[b] Determined by analysis of ^{1}H or ^{19}F NMR of bis-Mosher amide.



Scheme 6. Allylboration of 1,4-[*N*,*N*′-bis(diisobutylalumino)-2,3,5,6-tetrafluoro-benzaldimine with (−)-Ipc$_2$BAll.



Scheme 7. Allylboration of *N*,*N*′-bis(benzaldimine–triethylborane) complexes.

and achieved the allylboration of both isolated and in situ-generated dialdimines. We are currently exploring to extend this methodology to synthesize aliphatic diamines.

2. Experimental

2.1. General procedure for the allylboration of *N*,*N*′-bis(trimethylsilyl)dialdimines

Compound **4c** (1.41 g, 5.1 mmol) was added to a stirred solution of (−)-*B*-allyldiisopinocampheylborane (**2**; 1 M in THF; 11.48 mL, 11.48 mmol), prepared from **1** and allylmagnesium bromide,[14] diluted with THF (7 mL), and cooled to −78 °C, followed by the slow addition of methanol (0.33 g, 10.2 mmol). The reaction mixture was stirred at −78 °C for 3 h when the reaction was complete (^{11}B NMR spectral peak shift from δ 79 ppm to 47 ppm). The reaction was slowly oxidized with H_2O_2 (30% in H_2O; 4.6 mL) in the presence of NaOH (3 M in H_2O; 7.6 mL) and was left stirred under positive N_2 pressure while it slowly warmed to rt. The product was extracted with EtOAc (3 × 15 mL), the combined organic layer was washed with saturated brine solution and dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure, and the crude product was purified on silica gel (dichloromethane/methanol/triethylamine 95:4.5:0.5) to afford 0.94 g (4.33 mmol, 85% yield) of **5c**. Analysis of the bis-MTPA amide using ^{19}F NMR spectroscopy showed the diamine to be of 75% de. The major diastereomer was obtained in 99% ee. ^{1}H NMR: (300 MHz, $CDCl_3$) δ 7.41–7.27 (m, 4H), 5.79–5.64 (m, 2H), 5.12–4.99 (m, 4H), 3.96 (dd, *J* = 5.2 Hz, *J* = 7.7 Hz, 2H), 2.47–2.28 (m, 4H), 1.80 (br s, 4H); ^{13}C NMR: (75 MHz, $CDCl_3$) δ 144.4, 135.5, 126.5, 117.7, 55.1, 44.1.

2.2. General procedure for the allylboration of *N*,*N*′-bis(diisobutylalumino)dialdimines

DIBAL-H (1.44 g, 1.82 mL, and 10.2 mmol) was added to a solution of 1,4-dicyanobenzene (**6c**; 0.65 g, 5.1 mmol) in THF (5 mL) cooled to 0 °C and the mixture was stirred for 1 h to obtain the corresponding *N*,*N*′-bis(alumino)diimine (**7c**). The reaction mixture was cooled to −78 °C and was transferred via a cannula to a stirred solution of (−)-*B*-allyldiisopinocampheylborane (**2**; 1 M in THF; 11.48 mL, and 11.48 mmol) diluted with THF (7 mL) and cooled to −78 °C, followed by the slow addition of methanol (0.326 g, 10.2 mmol). The reaction mixture was stirred at −78 °C for 3 h when the reaction was complete (^{11}B NMR spectral peak shift from δ 79 ppm to 47 ppm). The reaction was slowly oxidized with H_2O_2 (30% in H_2O; 4.6 mL) in the presence of NaOH (3 M in H_2O; 7.6 mL) and was left stirred under positive N_2 pressure while it slowly warmed to rt. The product was extracted with EtOAc (3 × 15 mL), the combined organic layer was washed with saturated brine solu-

tion and dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure, and the crude product was purified on silica gel (dichloromethane/methanol/triethylamine 95:4.5:0.5) to afford 0.902 g (4.18 mmol, 82% yield) of **5c**. Analysis of the bis-MTPA amide using ^{19}F NMR spectroscopy showed the diamine to be of 80% de. The major diastereomer was obtained in $\geqslant$98% ee.

2.3. General procedure for the allylboration of *N,N′*-bis(benzaldimine–triethylborane) complexes

Lithium triethylborohydride (1 M in THF; 10.2 mL, and 10.2 mmol) was added to a solution of 1,4-dicyanobenzene (**6c**; 0.65 g, 5.1 mmol) in THF (5 ml) at 0 °C and the solution was stirred for 4 h. Methanol (0.326 g, 10.2 mmol) was added to the reaction mixture and stirred for an additional 30 min. The reaction mixture was cooled to −78 °C and slowly transferred via a cannula to a stirring solution of (−)-*B*-allyldiisopinocampheylborane (**2**; 1 M in THF; 11.48 mL, 11.48 mmol) diluted with THF (7 mL) and cooled to −78 °C. The reaction mixture was stirred at −78 °C for 6 h when the reaction was complete. The reaction was slowly oxidized with H_2O_2 (30% in H_2O; 4.6 mL) in the presence of NaOH (3 M in H_2O; 7.6 mL) and was left stirred under positive N_2 pressure while it slowly warmed to rt. The product was extracted with EtOAc (3 × 15 mL), the combined organic layer was washed with saturated brine solution and dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure, and the crude product was purified on silica gel (dichloromethane/methanol/triethylamine 95:4.5:0.5) to afford 0.87 mg (4.02 mmol, 79% yield) of **5c**. Analysis of the bis-MTPA amide using ^{19}F NMR spectroscopy showed the diamine to be of 82% de. The major diastereomer was obtained in $\geqslant$99% ee.

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