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Construction of Arene-Fused-Piperidine Motifs by Asymmetric Addition of 2-Trityloxymethylaryllithiums to Nitroalkenes: The Asymmetric Synthesis of a Dopamine D1 Full Agonist, A-86929

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Chiral arene-fused-piperidine **1** is one of the representative structural motifs often observed in biologically active compounds such as naturally occurring phenanthridine and isoquinoline alkaloids[1,2] as well as artificial pharmaceuticals.[3] A straightforward synthetic way toward **1** is the conjugate addition of 2-hydroxymethylaryllithiums **2** to nitroalkenes **3** and subsequent reduction of the nitro group to an amino group and cyclization to construct piperidine motifs **1** (Figure 1).[4] The first asymmetric alkyllithium addition to nitroalkenes was developed by the mediation of a chiral ligand, giving the β-alkyl nitroalkanes in moderate enantioselectivity.[5] The catalytic asymmetric additions of dialkylzinc[6] and arylboronic acid[7] were impressive recent successes. However, there have been only few that achieve asymmetric addition of 2-hydroxymethylaryl or its equivalent nucleophiles to nitroalkenes. A spectacular exception was the sparteine-mediated conjugate addition of the lithiated *N*-Boc allylic and benzylic amines to nitroalkenes, which provided an efficient way to the synthesis of simple piperidines in high enantioselectivities.[8] We describe the straightforward construction of chiral arene-fused-piperidines **1** by a highly enantioselective addition of 2-trityloxymethylaryllithiums **2** (R = CPh_3) to cyclic and acyclic nitroalkenes **3**.[9,10] The versatility of the process was proven by the first asymmetric synthesis of a dopamine D1 full agonist, A-86929 (**20**).[3a,b]

We began our studies with the reaction of a cyclic nitroalkene **3a** with 2-hydroxymethylphenyllithiums **2**, generated from the corresponding aryl bromides by treatment with butyllithium in the presence of chiral ligands **5**−**8** in toluene at −78 °C for 0.5 h, to find an efficient chiral mediator from our stocks.[10] Although the reaction of **3a** with nonprotected dianion **2a** did not give **4a** (R = H) in satisfactory chemical yield and enantioselectivity (at most 26% yield and 5% ee), the reaction of protected aryllithiums **2** seemed promising. Thus, the reaction of TBDMS-protected monoanion **2b** was mediated by the ligands **5**−**7**, giving **4b** (R = TBDMS) in 52−84% yields. However, the enantioselectivity was at most 21% ee by using **5** (Table 1, entries 1−3). Improvement in enantioselectivity was realized when the trityl group-protected aryllithium **2c** was used as a carbonucleophile, giving **4c** (R = CPh_3) in higher 42% ee (entry 4). More improvement was realized by using chiral aminodiether ligand **7**[10c] at −95 °C to give **4c** in 81% ee (entry 6). Satisfactorily high 98% yield and 95% ee were realized by using chiral aminodiether **8**[10f] as a ligand at −95 °C (entry 7).[11] A trans/cis-mixture of **4c** was readily isomerized to the thermodynamically stable *trans*-**4c** quantitatively. It is also important to note that **8** was recovered nearly quantitatively and reused.

Under the mediation of **8**, **2c** was an excellent nucleophile, reacting with cyclic **9** gave **12c** in 99% yield with *cis*-**12c** of 90% ee as a major isomer (Table 2, entry 1). The reaction with linear **10** and **11** gave **13c** and **14c** in 93% and 66% yields with 85% and 91% ee, respectively (entries 4 and 5).[12]

Thienyl- and furanyllithium bearing trityloxymethyl substituents

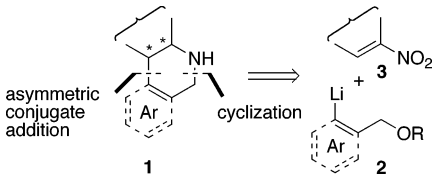
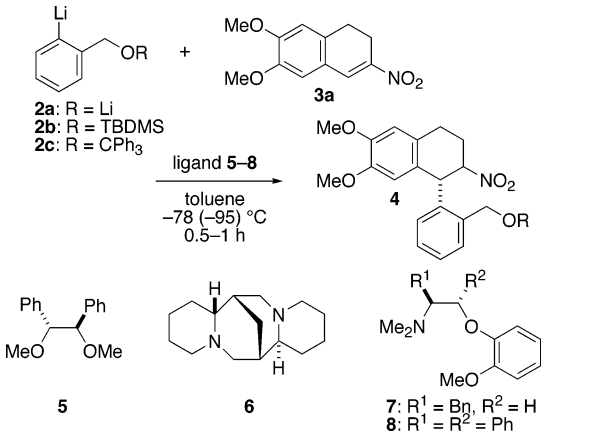


Figure 1. A straightforward construction of chiral arene-fused-piperidine motif **1** by the asymmetric addition of 2-hydroxymethylaryllithium **2** to nitroalkene **3**.

Table 1. Asymmetric Addition of Aryllithiums **2** to Nitroalkene **3a** by the Mediation of Chiral Ligands **5**−**8**



entry	ArLi	5–8	4	yield (%)	trans:cis[a]	ee[b]
1	**2b**	**5**	*ent*-**4b**	52	75:25	21
2	**2b**	**6**	*ent*-**4b**	87	98:2	7
3	**2b**	**7**	**4b**	84	83:17	12
4	**2c**	**5**	*ent*-**4c**	40	56:44	42
5	**2c**	**6**	*ent*-**4c**	74	59:41	5
6[c]	**2c**	**7**	**4c**	94	77:23	81
7[c,d]	**2c**	**8**	**4c**	98	69:31	95

[a] Determined by ^{1}H NMR of the crude product. [b] Determined after conversion to *trans*-**4a** (R = H) (**4b**, TBAF, THF; **4c**, $NaHCO_3$, EtOH, reflux; concentrated HCl−MeOH). [c] At −95 °C. [d] **2c** (1.5 equiv) and **8** (2.1 equiv).

2d and **2e** satisfactorily reacted with **9** to give **12d** and **12e** in 94% and 99% yields with the cis-isomer of 94% and 91% ee as a major diastereomer, respectively (entries 2 and 3). It was also exciting to find that **2d** reacted with **3a** to produce **15**, a key synthetic intermediate for A-86929 (**20**),[3a,b] in 92% yield with 97% ee (entry 6). These cis-major mixtures were quantitatively isomerized to trans-products (>96:4) by treatment with sodium bicarbonate in refluxing ethanol.

The trityl group in **2c**−**e** plays critical roles in protection and efficiency control[13] and was not replaceable by a triphenylsilyl or diphenylmethylsilyl group. The reactions of the corresponding silyl-

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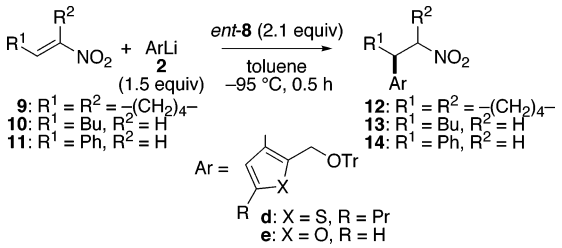
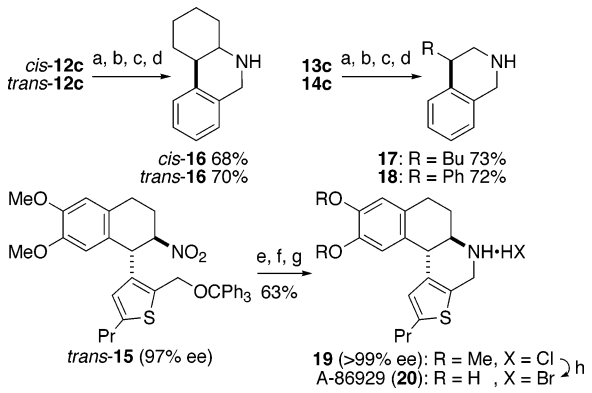
Table 2. Asymmetric Addition of Aryllithiums **2** to Nitroalkenes **3a**, **9**−**11**



entry	nitroalkene	ArLi	product	yield (%)	trans:cis[a]	ee
1	**9**	**2c**	**12c**	99	12:88	89/90[b]
2	**9**	**2d**	**12d**	94	6:94	95/94[b]
3	**9**	**2e**	**12e**	99	11:89	91/91[b]
4	**10**	**2c**	**13c**	93		85
5	**11**	**2c**	**14c**	66		91
6[c]	**3a**	**2d**	**15**[d]	92	37:63	97[e]

[a] Determined by ^{1}H NMR of the crude product. [b] Trans/cis. [c] With **8**. [d] See Scheme 1. [e] Determined after conversion to a trans-derivative. See Supporting Information.

Scheme 1. Construction of Chiral Arene-Fused-Piperidines and Asymmetric Synthesis of Dopamine D1 Full Agonist A-86929 (**20**)[a]



[a] (a) Concentrated HCl, MeOH−THF; (b) H_2, Raney-Ni, EtOH; (c) concentrated HCl, dioxane, reflux; (d) K_2CO_3, *t*-BuOH, reflux; (e) Zn, HOAc−THF, 96%; (f) concentrated HCl, THF, 99%; (g) CBr_4, PPh_3, CH_2Cl_2; HCl, EtOH; recrystallization (MeOH−EtOAc), 67%; (h) BBr_3, CH_2Cl_2, −78 to 0 °C, quant.

protected aryl bromides with butyllithium turned out to give a silyl group migration to produce hydroxymethylbenzenes silylated at the ortho position.

Stereospecific construction of piperidine motifs **1** was readily achievable from the addition products (Scheme 1). Both *cis*- and *trans*-**12c**, which were easily separated by column chromatography, were converted to *cis*- and *trans*-phenanthridine **16** in 68% and 70% overall yields, respectively, through removal of the trityl group, reduction of the nitro group, conversion to amino-chlorides, and cyclization without any loss of stereochemical integrity. By the same procedure, **13c** and **14c** were converted to isoquinoline motifs **17** and **18** in 73% and 72% overall yields, respectively.

A-86929 (**20**) is a dopamine D1 full agonist developed by Abbott Laboratories, and its diacetate is under clinical trial for cocaine addiction.[3a,b] The first asymmetric synthesis of **20** was achieved starting from *trans*-**15**. Reduction of the nitro group with zinc followed by detritylation gave the corresponding amino alcohol. Cyclization via the alkoxyphosphonium salt[14] and enantioenrichment by recrystallization from MeOH−AcOEt gave optically pure **19**. Demethylation of the two methoxy groups furnished **20** in 58% overall yield in seven steps from **3a**.

In conclusion, we have developed the efficient and straightforward synthesis of arene-fused-piperidine motifs through the highly enantioselective addition of 2-trityloxymethylaryllithiums to nitroalkenes using the chiral aminodiether ligand.

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Supporting Information Available: Additional entries with other aryllithiums, the experimental procedure, characterization data, NMR spectra, and HPLC traces (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) The procedure for Table 1, entry 7: a hexane solution of BuLi (0.75 mmol) was added to a solution of aryl bromide (0.75 mmol) and a chiral ligand **8** (1.1 mmol) in toluene (5 mL) at −78 °C. The solution was stirred for 0.5 h at −78 °C. A solution of **3a** (0.5 mmol) in toluene (2.5 mL) was dropwise added to the solution at −95 °C. The whole mixture was stirred at −95 °C for 0.5 h and then quenched with MeOH and then saturated NH_4Cl.

(12) The shown absolute configurations of **4a**−**c**, **14c**, and **15** were determined by conversion to known compounds. See Supporting Information.

(13) The reactions of other aryllithiums having a bulky substituent at the ortho position also gave products in good selectivities. See Supporting Information.

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