The Synthesis of New C_2-Symmetric Chiral 1,4-Diamino Motif and Application in Catalytic Asymmetric Alkynylation of meso-Epoxides

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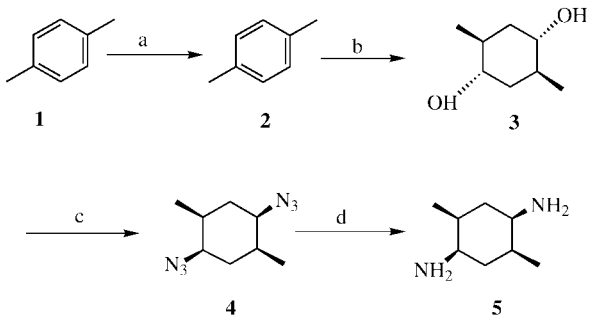
Received 29 October 2003

Abstract: The efficient asymmetric preparation of the C_2-symmetric chiral 1,4-diamine, (1*R*,2*S*,4*R*,5*S*)-1,4-diamino-2,5-dimethylcyclohexane (**5**), and its salen ligands is described. With the Mitsunobu reaction as the key step, the overall yield of the four-step synthesis of **5** is 45%. The enantioselective alkynylation of meso-epoxides catalyzed by chiral gallium complexes is also achieved.

Key words: 1,4-diamine, salen ligand, alkynylation, gallium complex, asymmetric synthesis

The development of novel chiral ligands is crucial to the advancement of asymmetric catalysis.[1] Diamine ligands are one of the most common types of nitrogen-containing ligands which are becoming applicable for catalytic asymmetric synthesis, and enantiomerically pure diamines are constituents of many natural compounds and commonly used in various areas, particularly in pharmaceutical and medicinal chemistry.[2] It has been reported that chiral 1,4-diamine have served as key intermediate in the synthesis of potent HIV protease inhibitors.[3] Although numerous studies describing the enantioselective synthesis and the applications in catalytic asymmetric synthesis of 1,2-diamines have been performed, there are only a few examples involving 1,4-diamine have been reported in literature.[4] This prompted us towards the development of new chiral 1,4-diamine ligands, which can be applicable to miscellaneous asymmetric reactions. We envisaged that the ligands derived from 1,4-diamine with cyclohexane backbone could provide a better face or site discrimination in asymmetric reactions. Very recently, Berkessel reported that the chiral 1,4-diamine (*endo,endo*-2,5-diamino-norborane) based salen ligands promoted efficient and highly enantioselective catalytic Nozaki–Hiyama–Kishi reactions.[5] Here we wish to report the synthesis of a new C_2-symmetric chiral ligand, (1*R*,2*S*,4*R*,5*S*)-1,4-diamino-2,5-dimethylcyclohexane, and the application of its salen ligands to the asymmetric alkynylation reaction of meso epoxides catalyzed by gallium complexes.

As outlined in Scheme 1, the asymmetric synthesis of **5** started with the conversion of 1,4-dimethylbenzene (**1**) into 1,4-dimethylcyclohexadiene (**2**) by a modified Birch reduction in up to 96% yield.[6] Following the established procedure,[7] exposure of **2** to excess enantiomerically pure monoisopinocampheylborane [from (1*R*)-(+)-α-pinene] followed by oxidation with basic hydrogen peroxide, gave the enantiomerically pure diol **3**, (1*S*,2*S*,4*S*,5*S*)-1,4-dihydroxy-2,5-dimethylcyclohexane, in 66% yield after separation by silica gel chromatography and recrystallization.[8] The absolute configuration was determined by comparison of the optical rotation with its enantiomer which was formed from (1*S*)-(–)-α-pinene.[7b]



Scheme 1 Synthesis of 1,4-diamine **5**. *Reagents and conditions*: (a) Li/NH_3 (l)–EtOH, –40 °C, 96%; (b) (i) $IpcBH_2$, Et_2O, –25 °C; (ii) H_2O_2, NaOH, 66%; (c) $(PhO)_2P(O)N_3$, Ph_3P, $EtO_2CN{=}NCO_2Et$, THF, 85%; (d) (i) $LiAlH_4$, THF, 0 °C; (ii) NaF, H_2O; (iii) HCl (g), THF, 83%.

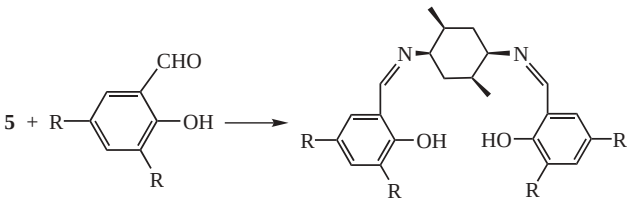
For the conversion of the diol **3** to the diamine **5**, we initially attempted to introduce the azide functionality by displacement of the tosylate or triflate of **3** with sodium or lithium azide.[9] Unexpectedly, both the tosylate and triflate of **3** are unreactive to those reagents. After other several unsuccessful attempts had been tried, we based our strategy for the synthesis of the diamine on the Mitsunobu reaction,[10] which proved to be the best key step in terms of the yields and simplicity. Substitution of the diol **3** with diphenylphosphoryl azide under Mitsunobu condition in the presence of triphenylphosphine and diethyl azodicarboxylate in tetrahydrofuran gave the diazide **4** in 85% yield.[11] Compound **4** was then reduced with $LiAlH_4$ in tetrahydrofuran at 0 °C to give 1,4-diamino-2,5-dimethylcyclohexane,[12] which was then treated with dry hydrogen chloride provided dihydrochloride salt of **5** (83% yield from **4**) for easy purification and higher stability.[13] The absolute configuration of 1,4-diamino-2,5-dimethylcyclo-

SYNLETT 2004, No. 3, pp 0465–0468
Advanced online publication: 12.01.2004
DOI: 10.1055/s-2004-815401; Art ID: U22403ST

hexane was determined as (1*R*,2*S*,4*R*,5*S*), since the stereospecific conversion of the stereocenters during Mitsunobu reaction. It could be expected that this new chiral motif could be derivatized in a broad range to serve as variable stereo directing reagents or ligands in miscellaneous asymmetric synthesis.

The desymmetrization of meso epoxides via the enantioselective addition of nucleophiles is an efficient strategy for asymmetric synthesis since it simultaneously establishes two contiguous stereogenic centers.[14] This type of reaction has been successfully accomplished with various nucleophiles.[15] The oxirane ring cleavage by metal acetylides forms *trans*-β-hydroxyacetylenes, which could be one of the very useful synthons for the synthesis of a variety of optically active compounds. Tomioka and coworkers have reported the enantioselective reaction of cyclohexene oxide with phenylethynyl lithium using stoichiometric amount of $BF_3{\cdot}OEt_2$ in very poor enantioselectivity.[16] Given that trimethylgallium, a remarkably effective catalyst for the ring opening reaction of oxiranes with alkylnyl lithium,[17] we considered the asymmetric alkynylation reaction of meso-epoxide catalyzed by chiral gallium complexes with **5** based salen ligands.

Following the procedure established in the literature,[18] the chiral salen ligands **6** and **7** were readily prepared by the reaction of dihydrochloride salt of **5** with salicylaldehyde or its derivative 3,5-di-*tert*-butyl-2-hydroxybenzaldehyde in ethanol in the yield of 86% and 89%, respectively (Scheme 2).[19]

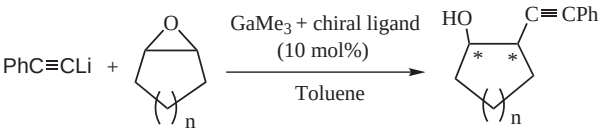


6 R = H

7 R = *t*-Bu

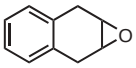
Scheme 2 Synthesis of salen ligands **6** and **7**. *Reagents and conditions*: K_2CO_3, EtOH, 80 °C.

Treatment of the ligands with equal equivalents of trimethyl gallium gave the catalysts, which were not isolated, and directly used. Toluene was chosen as the solvent according to the literature.[16] Asymmetric ring openings of cyclohexene oxide, cyclopentene oxide and 1,4-dihydronaphthalene oxide with phenylethynyl lithium were examined in the presence of chiral gallium catalysts with various kinds of ligands.[20] As summarized in Table 1, the expected β-phenylethynyl hydrins have been obtained in yields varying from 34% to 60%, with the enantioselectivity varying from 27% to 55% depending on the nature of the catalyst used. The reaction of cyclohexene oxide with phenylethynyl lithium using ligand **7** afforded the product in 55% ee (entry 1), which is much higher than that provided by equivalent $BF_3{\cdot}OEt_2$ system using tridentate oxygen-containing chiral ligand (22% ee).[16] Comparing entries 1 and 2, 5 and 6, it can be found that the steric bulkiness of *t*-Bu substituents in the salicylidene component induced a positive effect in the enantioselectivity of the reaction. By the way, the addition of 4Å molecular sieves did not improve the reactivity or selectivity for this reaction. To our best knowledge, this is the first example of asymmetric alkynylation reaction of meso-epoxides catalyzed by chiral gallium complexes (Scheme 3).



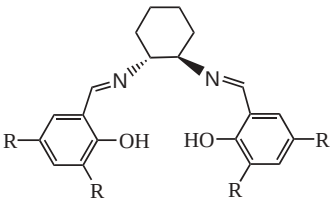
Scheme 3 Enantioselective phenylethynylation of meso-epoxides.

Table 1 Results of Enantioselective Ring Opening of meso-Epoxides with Phenylethynyl Lithium Catalyzed by Chiral Gallium Complexes

Entry	Epoxide	Ligand	Temp (°C)	Time (h)	Yield (%)[a]	Ee (%)[b]
1		**6**	0	48	54	34
2		**7**	0	48	60	55
3		**8**	0	48	50	30
4		**9**	0	48	57	47
5		**6**	0	60	46	27
6		**7**	0	60	42	45
7		**9**	0	60	45	38
8		**7**	Reflux	72	34	41

[a] Isolated yields.

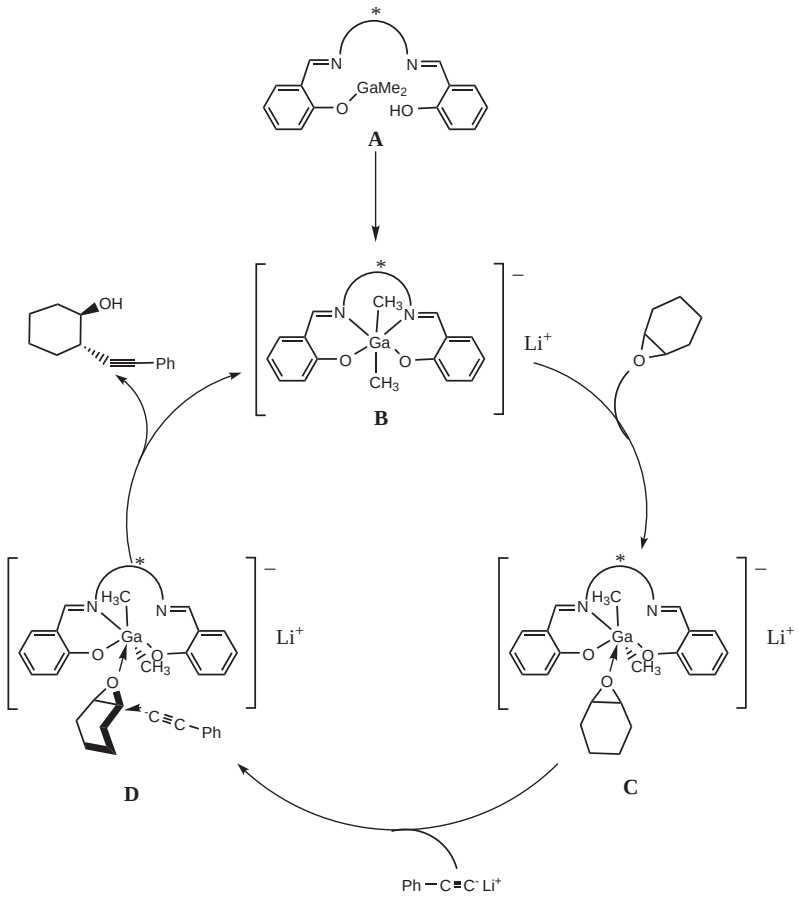
[b] Enantioselectivity excess values were determined by HPLC analysis using a DAICEL CHIRAL OD-H column.



8 R = H

9 R = *t*-Bu

Figure 1



Scheme 4 Possible mechanism for the ring opening of meso epoxide with phenylethynyl lithium catalyzed by chiral Ga-complex.

For comparison of the ligand effect, salen ligands **8** and **9** (Figure 1), which were derivatized from (1*R*,2*R*)-1,2-diaminocyclohexane, were also examined in this reaction (entries 3, 4 and 7), and provided lower selectivity than that of corresponding 1,4-analogues. This result preliminarily demonstrates that 1,4-diamino motifs are more efficient on the enantioselectivity in the alkynylation reaction than that of 1,2-diamino analogues.

A proposal mechanism for the catalytic asymmetric epoxide opening is shown in Scheme 4. The salen ligand reacted with trimethylgallium gave a monometallic open chain compound **A** as a precatalyst.[21,22] Ring closure ate complex **B**, which was the de facto catalytic species in the catalytic cycle, was most possibly formed as **A** was treated with phenylethynyl lithium.[23] The gallium metal appeared to function as a Lewis acid, activating epoxide and also controlling the orientation of epoxide due to coordination of an axial lone pair, allowing for the cleavage of C–O bond by backside attack. The catalyst derived from 1,4-diamino ligand with the cyclohexene backbone as a 'chiral wall', can provide a better site discrimination around the center metal than that of 1,2-diamino counterpart, in which the chiral centers are just in the plane with the center metal.

In summary, the synthesis of new chiral C_2-symmetric 1,4-diamino-2,5-dimethylcyclohexane, based on the Mitsunobu reaction, was efficiently accomplished. We also achieved the first enantioselective alkynylation of meso epoxides catalyzed by chiral gallium complexes. Although the enantioselectivity of the present reaction is modest, an obvious improvement of our new ligand than that of 1,2-diaminocyclohexane was observed. Further studied on the application of 1,4-diamino-2,5-dimethylcyclohexane on other asymmetric reaction are now in progress in our research group.

Acknowledgment

We gratefully acknowledge the National Natural Science Foundation of China, the 863 High Technology Program, Science Foundation of Jiangsu Province and the Key Laboratory of Fine Petrochemical Technology of Jiangsu Province for their financial support.

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(8) (1*S*,2*S*,4*S*,5*S*)-(+)-1,4-dihydroxy-2,5-Dimethylcyclohexane(**3**): white solid, mp 120–121 °C. $[\alpha]_D^{25}$ +32.7 (*c* 1.0, CH_2Cl_2). ^1H NMR (300 MHz, $CDCl_3$): δ = 3.51–3.57 (m, 2 H), 1.87–1.93 (m, 2 H), 1.68–1.78 (m, 4 H), 1.53–1.59 (m, 2 H), 1.01 (d, *J* = 6.9 Hz, 6 H) ppm. IR (KBr): ν_{OH} = 3313.8 cm^{-1}. MS (EI): *m/z* (%) = 144.1 (4) [M^+], 126.0 (4), 111.1 (10), 72 (100). Anal. Calcd for $C_8H_{16}O_2$: C, 66.63; H, 11.18. Found: C, 66.34; H, 11.22.
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(11) (1*R*,2*S*,4*R*,5*S*)-(–)-1,4-diazido-2,5-dimethylcyclohexane(**4**): yellow oil. $[\alpha]_D^{25}$ –44.6 (*c* 0.2, THF). ^1H NMR (300 MHz, $CDCl_3$): δ = 3.59–3.64 (m, 2 H), 1.95 (br. s, 2 H), 1.83 (ddd, *J* = 13.5, 7.5, 4.2 Hz, 2 H), 1.64 (ddd, *J* = 13.5, 7.5, 4.2 Hz, 2 H), 1.11 (d, *J* = 7.0 Hz, 6 H) ppm. IR (KBr): ν (-N_3) = 2097.9 cm^{-1}. MS (EI): *m/z* (%) = 194.0 (1) [M^+], 166.1 (1), 141.0 (1), 109.1 9 (7), 81.0 (20), 42 (100). Anal. Calcd for $C_8H_{14}N_6$: C, 49.47; H, 7.27; N, 43.27. Found: C, 49.32; H, 7.23, N 43.41.
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(19) Spectroscopic data for compound **6** and **7**: For **6**: yellow crystals, mp 154–156 °C. $[\alpha]_D^{25}$ +21.6 (*c* 2.0, CH_2Cl_2). ^1H NMR (300 MHz, $CDCl_3$): δ = 13.57 (s, 2 H), 8.40 (s, 2 H), 7.28–7.36 (m, 4 H), 6.88–7.02 (m, 4 H), 3.50 (d, *J* = 3.0 Hz, 2 H), 2.00–2.08 (m, 4 H), 1.81–1.85 (m, 2 H), 1.06 (d, *J* = 6.6 Hz, 6 H) ppm. IR (KBr): $\nu_{C=N}$ = 1627.6 cm^{-1}. MS (EI): *m/z* (%) = 350.2 (100) [M^+], 335.1 (3), 320.1 (2), 229.1 (43), 188.1 (57), 122.1 (78). Anal. Calcd for $C_{22}H_{26}N_2O_2$: C, 75.40; H, 7.48; N, 7.99. Found: C, 75.21; H, 7.44; N, 7.83. For **7**: yellow solid, mp >210 °C. $[\alpha]_D^{25}$ +17.5 (*c* 2.0, CH_2Cl_2). ^1H NMR (300 MHz, $CDCl_3$): δ = 13.78 (s, 2 H), 8.42 (s, 2 H), 7.42 (d, *J* = 2.1 Hz, 2 H), 7.14 (d, *J* = 2.1 Hz, 2 H), 3.43–3.46 (m, 2 H), 2.01–2.07 (m, 4 H), 1.82–1.88 (m, 2 H), 1.49 (s, 18 H), 1.36 (s, 18 H), 1.06 (d, *J* = 5.9 Hz, 6 H) ppm. IR (KBr): $\nu_{C=N}$ = 1628.8 cm^{-1}. MS (EI): *m/z* (%) = 574.2 (100) [M^+], 559.3 (17), 544.3 (2), 341.3 (29), 272.1 (32), 69.0 (100). Anal. Calcd for $C_{38}H_{58}N_2O_2$: C, 79.39; H, 10.17; N, 4.87. Found: C, 79.30; H, 10.23; N, 4.72.
(20) **A Typical Procedure for the Ring Opening of meso Epoxides by Phenylethynyl Lithium:** $GaMe_3$ (0.2 mL, 0.1 mmol, 0.5 M in toluene) was added dropwise to the toluene solution of ligand **7** (57 mg, 0.10 mmol) under argon atmosphere. The mixture was stirred for 2 h at r.t. to form the salen–Ga complex. The toluene solution of phenylethynyl lithium, which was prepared from the reaction of *n*-BuLi (1.6 mmol in 1 mL hexane) and phenylacetylene (153 mg, 1.5 mmol) at –78 °C before use, was transferred to above solution of salen-Ga complex at 0 °C and stirred for another 1 h. Then the cyclohexene oxide (101 μL, 1.0 mmol) was added slowly to the mixture using a syringe at 0 °C. The resulting mixture was stirred for 48 h at the same temperature before being quenched with a sat. NH_4Cl solution and extracted with EtOAc. The organic phase was dried over Na_2SO_4, and removed the solvent. After being separated by preparative silica gel TLC, 2-(2-phenylethynl)-1-cyclohexanol (120 mg) was obtained as yellow oil in the yield of 60% with 55% ee. $[\alpha]_D^{25}$ –57.2 (*c* 0.7, $CHCl_3$). The ee value was determined by HPLC analysis (DAICEL CHIRAL OD-H column, hexane/*i*-PrOH = 30:1, 0.5 mL/min, 254 nm): t_R = 22.35 min, 23.77 min. ^1H NMR[16] (300 MHz, $CDCl_3$): δ = 7.39–7.48 (m, 2 H), 7.30–7.39 (m, 3 H), 3.53–3.60 (m, 1 H), 2.46–2.48 (m, 1 H), 1.24–2.11 (m, 9 H) ppm. IR(neat): ν = 3429.4, 2229.8 cm^{-1}.
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(22) Identification of the pre-catalysts. Analytical data of the complex formed from ligand **6** and $GaMe_3$ (1:1 molar ration at r.t. in toluene): ^1H NMR (300 MHz, $CDCl_3$): δ = 13.43 (s, 1 H), 8.36 (s, 1 H), 8.11 (s, 1 H), 7.30–7.39 (m, 4 H), 6.73–7.01 (m, 4 H), 3.90–3.94 (m, 1 H), 3.38–3.44 (m, 1 H), 2.37–2.39 (m, 1 H), 2.20–2.24 (m, 2 H), 1.93–2.20 (m, 2 H), 1.59–1.63 (m, 1 H), 1.00–1.02 (d, *J* = 7.3 Hz, 6 H), –0.21 (s, 3 H), –0.31 (s, 3 H) ppm. MS (EI): *m/z* (%) = 434.9 (6) (M^+ – 15), 417.0 (100), 333.0 (2), 222.9 (5), 188.9 (8), 122.0 (7), 109.0 (3), 68.9 (12). Anal. Calcd for $C_{24}H_{31}N_2O_2Ga$: C, 64.17; H, 6.95; N, 6.24. Found: C, 64.35; H, 7.10; N, 6.38. Analytical data of the complex formed from ligand **7** and $GaMe_3$ (1:1 molar ration at r.t. in toluene): ^1H NMR (300 MHz, $CDCl_3$): δ = 13.55 (s, 1 H), 8.11 (s, 1 H), 8.08 (s, 1 H), 7.42–7.43 (d, *J* = 2.3 Hz, 1 H), 7.13–7.14 (d, *J* = 2.3 Hz, 1 H), 7.03–7.04 (d, *J* = 2.5 Hz, 1 H), 6.90–6.91 (d, *J* = 2.5 Hz, 1 H), 3.50–3.51 (m, 1 H), 3.37–3.39 (m, 1 H), 1.51–2.42 (m, 6 H), 1.48 (s, 9 H), 1.48 (s, 9 H) 1.33 (s, 9 H), 1.31 (s, 9 H), 0.99–1.02 (d, *J* = 6.3 Hz, 6 H), –0.21 (s, 3 H), –0.36 (s, 3 H). MS (EI): *m/z* (%) = 657.4 (14) (M^+ – 15), 642.4 (100), 321.6 (5), 313.8 (10), 68.9 (9). Anal. Calcd for $C_{40}H_{63}N_2O_2Ga$: C, 71.32; H, 9.43; N, 4.16. Found: C, 71.54; H, 9.52; N, 3.98.
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