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Synthesis of new chiral auxiliaries for 6π-azaelectrocyclization: 4- and 7-alkyl substituted *cis*-1-amino-2-indanols

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Abstract—The synthesis of new chiral auxiliaries, 7-alkyl substituted *cis*-1-amino-2-indanol derivatives, was established by the Diels–Alder reaction of 1-substituted dienes with cyclopentenone followed by the asymmetric epoxidation of the resulting indene derivatives and then the Ritter reaction. These bulky *cis*-aminoindanol derivatives are very effective as chiral auxiliaries and nitrogen sources in the asymmetric 6π-azaelectrocyclization. The corresponding 4-alkyl derivative was also prepared using a similar method.

Chiral *cis*-1-amino-2-indanol has been recognized as a satisfactory chiral auxiliary and ligand for advanced asymmetric reactions.[1] Both its sterically bulky indane structure and the conformationally restricted *cis*-aminoalcohol moiety, compared with a simple amino alcohol such as 2-phenylglycinol, create an effective chiral discriminative environment, in which a highly diastereo- or enantioselective reaction could be achieved.

Recently, we have been evaluating the promising chiral amines, which achieve highly stereoselective asymmetric 6π-azaelectrocyclization via the reaction with (*E*)-3-carbonyl-2,4,6-trienal compounds under quite mild conditions.[2] This facile 6π-azaelectrocyclization was based on the remarkable orbital interaction between the HOMO and LUMO of 1-azatrienes resulting from the combination of substituent effects, that is the C4-ester and C6-alkenyl or phenyl substituents (Fig. 1).[3]

After many trials using the commercially available chiral amines, we finally found that *cis*-1-amino-2-indanol **A** provided excellent stereoselectivity in the reaction with the sterically hindered trienal **1** (Fig. 2). However, from the reaction with a more general aldehyde **2**, **A** had the moderate selectivity of 3:1, and therefore, as shown in Figure 1, the more bulky 4- and 7-alkyl substituted *cis*-aminoindanol derivatives such as **B**–**D** were investigated. 4-Methyl substituted *cis*-aminoindanol **B** afforded a 3:1 diastereoselectivity by the reaction with the aldehyde **2**, the selectivity of which is similar to that obtained by employing the simple aminoindanol **A**. In contrast, a remarkably high diastereoselectivity was also observed using the 7-alkyl substituted aminoindanols; the methyl derivative **C** produced the corresponding piperidine derivative with a 12:1 diastereoselectivity, and the isopropyl substituted aminoindanol **D** with a 24:1 diastereoselectivity at room temperature. Moreover, the

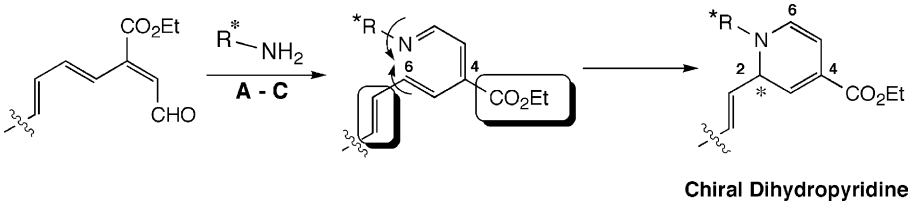

Figure 1.

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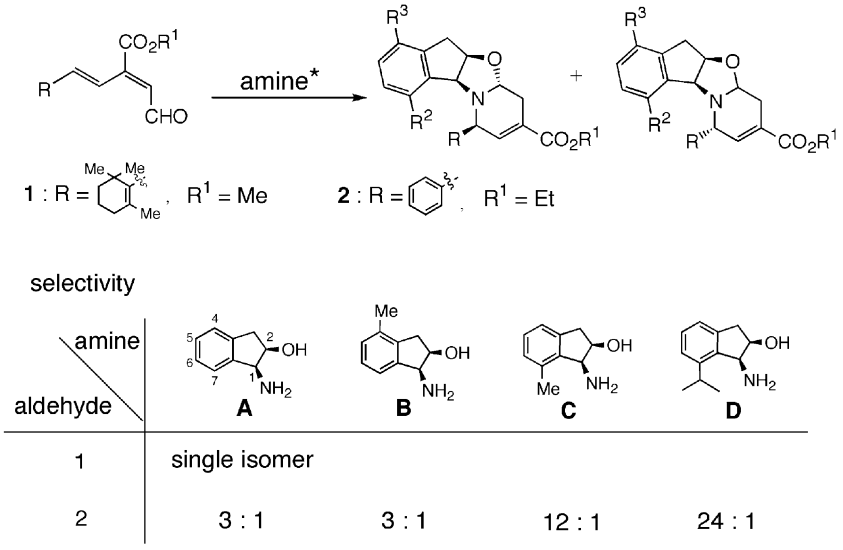
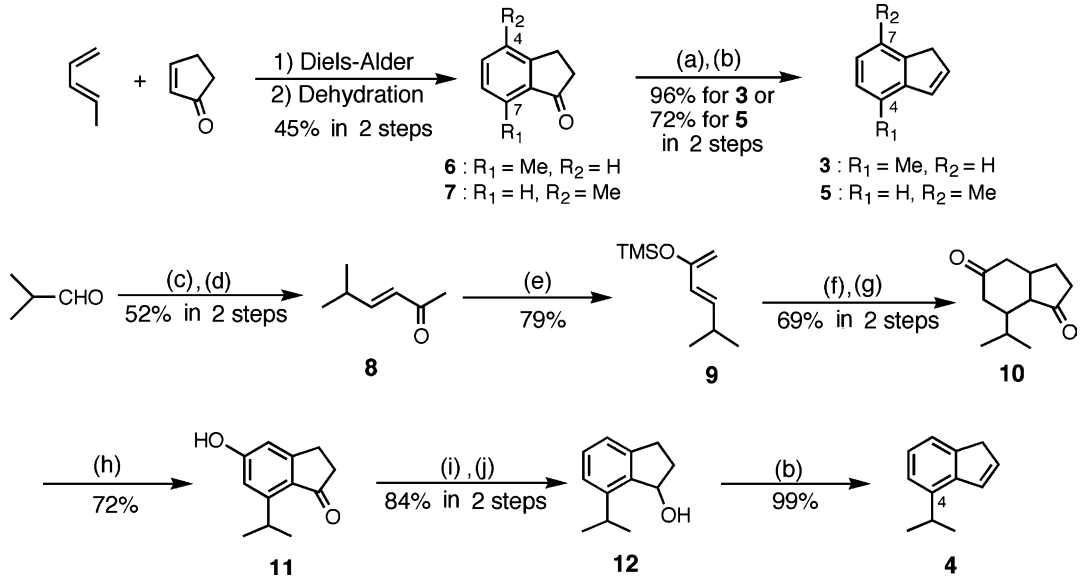


Figure 2.

isopropyl derivative **D** provided an almost single isomer at a lower temperature of 13 °C. Thus, we achieved a highly stereoselective azaelectrocyclization by utilizing the more bulky 7-alkyl substituted aminoindanols **C** and **D**.[4] Herein, we report the synthesis of these chiral *cis*-1-amino-2-indanol derivatives **B**–**D**, which would also be useful as chiral auxiliaries and ligands for metal catalyzed asymmetric reactions (Fig. 2).

The synthesis of chiral 4- and 7-substituted *cis*-1-amino-2-indanols **B**–**D** was followed by the procedure of the commercially available **A** developed by Merck's group.[5] This procedure involved the asymmetric epoxidation of the indene derivatives and the modified Ritter reaction of the resulting indene oxides. Therefore, the 4- and 7-substituted indene derivatives **3**–**5** were needed (Scheme 1). Thus, 4-methylindene **3** was prepared on a 50 g scale starting from the Diels–Alder reaction between 1,3-pentadiene and cyclopentenone according to the method of House and Rasmusson.[6] Aromatization of the D–A adduct via treatment with Pd/C at 200 °C produced 7-methylindanone **6** in 50% yield, which was reduced by $LiAlH_4$ and then dehydrated via treatment with a catalytic amount of *p*-toluenesulfonic acid at 80 °C to give the desired product **3** in 96% yield in two steps. The 7-substituted indene **5** was prepared from commercially available 4-methylindanone **7** in 72% yield by a sequence of LAH reduction and acid treatment. The synthesis of 4-isopropyl substituted indene **4** then occurred. Unfortunately, various attempts in preparing a large quantity

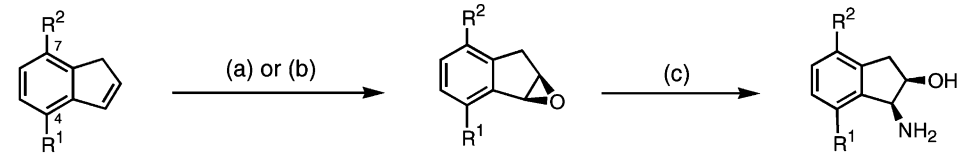


Scheme 1. Reagents and conditions: (a) LAH, ether; (b) *p*-TsOH (0.1 equiv), benzene, gradually to 80 °C; (c) 2.5 M NaOH aq acetone, 0 °C, 2.5 h (2 mol scale); (d) *p*-TsOH (0.005 equiv), Na_2SO_4, benzene, 80 °C; (e) TMSCl, $LiN(TMS)_2$, toluene:THF (2:1), −78 °C; (f) 2-cyclopentenone, 2,5-di-*tert*-butylhydroquinone, benzene, 200 °C, 72 h; (g) *p*-TsOH, acetone; (h) 10% Pd/C, *p*-cymene, 200 °C, 48 h; (i) TsCl, NaH, THF; (j) $NiCl_2$ (1.0 equiv), $NaBH_4$ (30 equiv), MeOH, 0 °C.

of the corresponding isopropyl substituted 1,3-dienes proved unsuccessful using the same method, which gave a mixture of regio- and stereoisomers. Therefore, we selected the corresponding 2-siloxy-4-isopropyl-1,3-pentadiene as a partner for the D–A reaction with cyclopentenone, as shown in Scheme 1. Thus, more than 200 g of isobutylaldehyde was treated with a 2.5 M solution of sodium hydroxide in acetone to give the corresponding aldol product in 69% yield, which was then dehydrated by treatment with *p*-toluenesulfonic acid to provide the (*E*)-α,β-unsaturated ketone **8** with 75% yield on 200 g scale. The treatment of **8** with chlorotrimethylsilane and solid lithium bis(trimethylsilyl)amide in a mixed solvent system of THF and toluene (1:2) at −78 °C provided the desired siloxydiene **9** in 79% yield. The purification of all the products so far was successfully done by distillation that enabled us to easily prepare the siloxydiene **9** on a >100 g scale. The siloxydiene **9** was then reacted with cyclopentenone in the presence of 2,5-di-*tert*-butylhydroquinone in benzene at 200 °C for 72 h to give the desired cycloadduct, which was hydrolyzed immediately without further purification, by treatment with *p*-toluenesulfonic acid in acetone to provide the diketone **10** with 69% yield in two steps. This diketone consisted of two stereoisomers based on ^{1}H NMR analysis. The oxidative aromatization was successfully achieved by treatment of the diketones **10** with 10% Pd/C in *p*-cymene at 200 °C for 2 days to produce the phenol **11** in 72% yield. In order to remove the phenolic hydroxy group of **11**, the nickel catalyzed reductive deoxygenation by sodium borohydride was successfully employed. Thus the tosylate, prepared by treatment of the phenol **11** with *p*-toluenesulfonyl chloride and sodium hydride, was reacted with 30 equiv of sodium borohydride in the presence of 1 equiv of nickel(II) chloride hexahydrate in methanol to give the desired alcohol **12** in 84% yield in two steps, accompanied by the simultaneous reduction of the ketone group.[7] As previously described, the alcohol **12** was quantitatively dehydrated by a reaction with *p*-toluenesulfonic acid to provide the 4-isopropyl indene **4**.

With a sufficient amount of indenes **3**–**5** in hand, the Jacobsen's asymmetric epoxidation and the Ritter reaction were examined as the key steps towards the substituted aminoindanols **B**–**D**. Thus, according to the procedure developed by Merck's group,[5] indene **3** was treated with 3.9 equiv of sodium hypochlorite solution in the presence of 1.2 mol% of (*S*,*S*)-(+)-*N*,*N*′-bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediaminomanganese(III) chloride and 6.0 mol% of 4-phenylpyridine *N*-oxide at 0 °C for 7 h to provide the desired indene oxide **13** in 67% yield and 85% ee[8] after rapid chromatography on alumina. Quite fortunately, the compound **13** thus obtained was recrystallized from a mixture of ether and hexane to give the enantiomerically pure (+)-indene oxide **13**, $[\alpha]_D^{24}$ +2.6 (*c* 0.9, $CHCl_3$). Epoxide **13** was then reacted with fuming sulfuric acid (30% of SO_3) in acetonitrile to give the intermediary oxazoline derivative, which was hydrolyzed without purification in H_2O at 100 °C to provide the desired (−)-7-methyl-*cis*-1-amino-2-indanol **C** [99% ee, $[\alpha]_D^{22}$ −110.8 (*c* 0.6, $CHCl_3$)] in 52% yield in two steps.

Meanwhile, the application of the same reaction conditions as Jacobsen's epoxidation (mentioned previously) towards the 4-isopropyl substituted indene **4** disappointedly gave the indene oxide **14** in both a lower chemical yield (~50%) and enantioselectivity (~50% ee). Therefore, we attempted the improved Jacobsen's epoxidation protocol under anhydrous and lower temperature conditions.[9] Indene **4** was treated with 2 equiv of *m*-chloroperbenzoic acid and 5 equiv of *N*-methylmorpholine *N*-oxide in the presence of 5 mol% of (*S*,*S*)-(+)-*N*,*N*′-bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediaminomanganese(III) chloride at −78 °C to provide the indene oxide **14** in 86% yield and 56% ee. Unfortunately, recrystallization did not effectively isolate the enantiomerically pure epoxide **14**. The indene oxide **14** was then directly subjected to the Ritter reaction followed by hydrolysis of the oxazoline intermediate using the same procedure as that utilized for **13** to provide the isopropyl substituted compound **D** in 77% yield in two steps (39% yield after recrystallization). The enantiomerically homogeneous (−)-**D** [99% ee, $[\alpha]_D^{20}$ −114.2 (*c* 0.5, $CHCl_3$)] was successfully obtained by recrystallization from toluene. The obtained enantiomeric excess of (−)-**D** was analyzed by chiral HPLC.[10]



3 : R^1=Me, R^2=H	67% yield, 85 % *ee*	**13** : R^1=Me, R^2=H	52% in 2 steps	**C** : $[\alpha]^{22}_D$ -110.8 (*c* 0.6, $CHCl_3$)
4 : R^1=*i*Pr, R^2=H	86% yield, 56 % *ee*	**14** : R^1=*i*Pr, R^2=H	77% in 2 steps (39% yield after recrystallization)	**D** : $[\alpha]^{20}_D$ -114.2 (*c* 0.5, $CHCl_3$)
5 : R^1=H, R^2=Me	73% yield, 88 % *ee*	**15** : R^1=H, R^2=Me	56% in 2 steps	**B** : $[\alpha]^{24}_D$ -30.7 (*c* 0.9, $CHCl_3$)

Scheme 2. Reagents and conditions: (a) 1.8 M NaClO aq (4.0 equiv), (*S*,*S*)-(+)-*N*,*N*-bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexane-diaminomanganese(III) chloride (1.2 mol%), 4-phenylpyridine *N*-oxide (6 mol%), CH_2Cl_2, rt; (b) *m*-CPBA (2 equiv), NMO (5 equiv), *S*,*S*-(+)-*N*,*N*-bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediaminomanganese(III) chloride (5 mol%), CH_2Cl_2, −78 °C; (c) fuming H_2SO_4, CH_3CN, rt, 30 min, then H_2O, 100 °C, 2 h.

Similarly, Jacobsen's improved epoxidation of indene **5** provided the indene oxide **15** in 73% yield and 88% ee. The obtained **15** was then converted into **B** with 56% yield in two steps, from which the enantiomerically homogeneous (−)-**B** [99% ee, $[\alpha]_D^{24}$ −30.7 (*c* 0.9, $CHCl_3$)], was successfully obtained by recrystallization from toluene. Thus, a sufficient amount of chiral 7-methyl and 7-isopropyl substituted *cis*-aminoindanol **C** and **D** along with 4-methyl substituted compound **B** were produced[11](Scheme 2).

In summary, we established the synthesis of new chiral auxiliaries, 7-methyl and 7-isopropyl substituted *cis*-1-amino-2-indanol derivatives **C** and **D**, which proved to be very effective as chiral auxiliaries and nitrogen sources. We also prepared the corresponding 4-alkyl derivative **B**. These bulky *cis*-aminoindanol derivatives are considered to be new, effective chiral auxiliaries and/or ligands for a variety of asymmetric reactions.

Acknowledgements

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References and notes

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10. The enantiomeric excess of **C** was determined by reacting **C** with 2,4-dinitrofluorobenzene in CH_2Cl_2. The yellow solution was diluted with ethanol (1:10), and then analyzed by HPLC on an OD column, 10% isopropanal in hexane, with 27 min for the first eluted isomer (major product) and 41 min for the second eluted isomer.
11. Spectral data of aminoindanol derivatives: 4-Methyl-*cis*-1-amino-2-indanol **B**: $[\alpha]_D^{24}$ −30.7 (*c* 0.9, $CHCl_3$); IR (KBr disk, cm^{-1}) 3349 (br), 1601, 1476, 1335, 1026; ^1H NMR (400 MHz, $CDCl_3$) δ 2.26 (s, 3H), 2.88 (dd, 1H, $J = 16.6$, 2.7 Hz), 3.01 (dd, 1H, $J = 16.6$, 5.6 Hz), 4.33 (d, 1H, $J = 5.4$ Hz), 4.39 (ddd, 1H, $J = 5.6$, 5.4, 2.7 Hz), 7.06 (d, 1H, $J = 7.0$ Hz), 7.11–7.19 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.8, 38.0, 58.6, 72.1, 121.1, 127.1, 128.8, 134.8, 139.7, 143.5; EI HRMS *m*/*e* calcd for $C_{10}H_{13}NO$ (M^+) 163.0997, found 163.0989.
7-Methyl-*cis*-1-amino-2-indanol **C**: $[\alpha]_D^{22}$ −110.8 (*c* 0.6, $CHCl_3$); IR (KBr disk, cm^{-1}) 3314–2571 (br), 1593, 1474, 1346, 1098; ^1H NMR (400 MHz, $CDCl_3$) δ 2.19 (br s, 3H), 2.39 (s, 3H), 2.81 (dd, 1H, $J = 15.9$, 7.6 Hz), 3.13 (dd, 1H, $J = 15.9$, 7.3 Hz), 4.22 (d, 1H, $J = 6.6$ Hz), 4.35 (ddd, 1H, $J = 7.1$, 7.1, 7.1 Hz), 7.00–7.03 (m, 2H), 7.14 (dd, 1H, $J = 7.6$, 7.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.4, 39.3, 55.6, 71.2, 122.7, 128.26, 128.32, 134.5, 140.7, 142.6; EI HRMS *m*/*e* calcd for $C_{10}H_{13}NO$ (M^+) 163.0996, found 163.1001.
7-Isopropyl-*cis*-1-amino-2-indanol **D**: $[\alpha]_D^{20}$ −114.2 (*c* 0.5, $CHCl_3$); IR (KBr disk, cm^{-1}) 3194 (br), 1586, 1480, 1451, 1383, 1333, 1094; ^1H NMR (400 MHz, $CDCl_3$) δ 1.25 (d, 3H, $J = 6.8$ Hz), 1.31 (d, 3H, $J = 6.8$ Hz), 2.31 (br s, 3H), 2.80 (dd, 1H, $J = 15.6$, 8.3 Hz), 3.14 (dd, 1H, $J = 15.6$, 7.6 Hz), 3.13–3.21 (m, 1H), 4.29 (br d, 1H, $J = 6.6$ Hz), 4.34–4.38 (m, 1H), 7.03 (d, 1H, $J = 7.3$ Hz), 7.14 (d, 1H, $J = 7.8$ Hz), 7.23 (dd, 1H, $J = 7.6$, 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.9, 24.2, 30.0 39.3, 55.0, 71.4, 122.7, 123.6, 128.8, 140.6, 141.3, 145.8; CI HRMS *m*/*z* calcd for $C_{12}H_{18}$ $(M+H)^+$ 192.1387, found 192.1383.