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Pinacol rearrangement for constructing asymmetric centers adjacent to heterocycles

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Abstract—Stereospecific pinacol-type 1,2-shift of electron-rich heterocycles was achieved under organoaluminum-promoted conditions to afford optically pure ketones or alcohols possessing these heterocycles. The method was applied to the asymmetric formal total synthesis of indolmycin. © 2002 Elsevier Science Ltd. All rights reserved.

Asymmetric center adjacent to heterocyclic structures is a motif shared by various biologically active natural/unnatural products[1–4] (Fig. 1). In many cases, the lack of an appropriate synthetic handle renders the construction of such asymmetric centers a challenge.

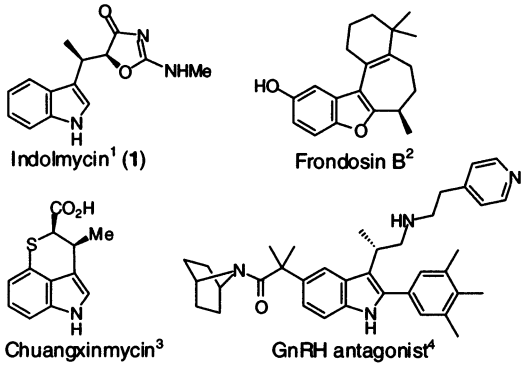
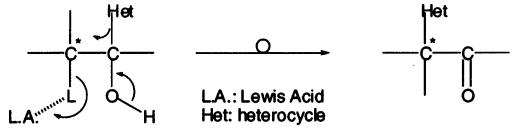


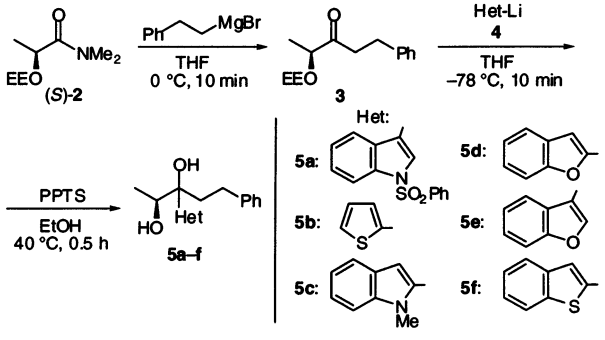
Figure 1.

We have previously described the efficient and stereoselective construction of asymmetric centers by Lewis acid-promoted pinacol-type rearrangement of mesylates and epoxides.[5] It was unclear, however, if similar conditions could be developed for the stereo- and regioselective rearrangement of electron-rich aromatic heterocycles for constructing such structures via the 1,2-shift of heterocycles (Eq. (1)), where the presence of additional coordinating groups could potentially interfere with the Lewis acid-mediated process. We now report the successful development of conditions for the pinacol-type rearrangement of heterocycles in the chiral lactate-derived mesyloxy alcohols, which is nicely promoted by organoaluminum Lewis acids.



(1)

Scheme 1 shows the preparation of starting materials for the 1,2-shift of heterocycles. For instance, diol **5a**, having a 3-indolyl group, was prepared as a 7/3 diastereomeric mixture by successive introduction of a 2-phenylethyl group and a 3-indolyl group[7a] to the chiral lactamide, (*S*)-**2**,[8] followed by acidic removal of the ethoxyethyl protecting group. Other diols **5b–5f** were also prepared by introducing the respective lithiated heterocycle.[7]



Scheme 1.

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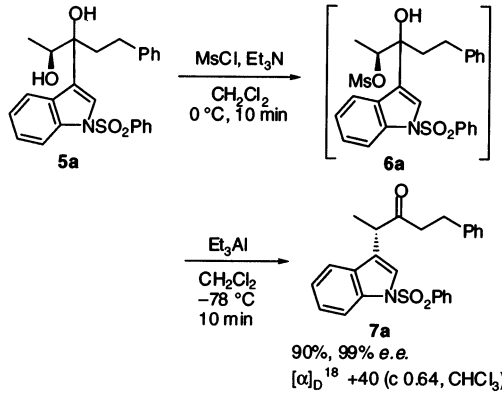
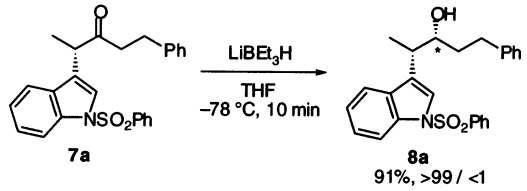
Scheme 2 exemplifies the pinacol-type shift of a 3-indolyl group (**5a**→**7a**).[6] Methanesulfonylation of **5a** with MsCl and Et_3N (CH_2Cl_2, 0°C, 10 min) proceeded regioselectively at the *sec*-hydroxy group to give mesyloxy alcohol **6a**, which, without isolation, was successively treated with Et_3Al (3.0 equiv.) at −78°C for 10 min.[9] The indolyl group underwent smooth 1,2-shift, giving chiral ketone **7a** in 90% yield. The stereospecificity of the 1,2-shift was confirmed by the enantiomeric purity of **7a** (99% *e.e.*) by the chiral HPLC analysis[10] (DAICEL CHIRALCEL OD-H, *i*-PrOH/hexane = 1/9), reflecting the *e.e.* of the starting lactate (99% *e.e.*).[11]



Scheme 2.

*The experimental procedure for the rearrangement of **5a** to **7a** is as follows*: to a solution of diol **5a** (500 mg, 1.15 mmol) in CH_2Cl_2 (5 mL) was added Et_3N (240 μL, 1.72 mmol), and MsCl (107 μL, 1.38 mmol) at 0°C. After stirring for 10 min, the mixture was chilled to −78°C, to which was added a hexane solution (0.92 mmol/mL) of Et_3Al (3.7 mL, 3.4 mmol). After 10 min, the mixture was poured into aqueous $KHSO_4$, and the products were extracted with Et_2O. The combined organic layer was washed with water and brine, dried ($MgSO_4$), and concentrated. Purification with silica gel column chromatography (EtOAc/hexane = 1/6) afforded ketone **7a** (430 mg, 90%).[6]



Scheme 3.

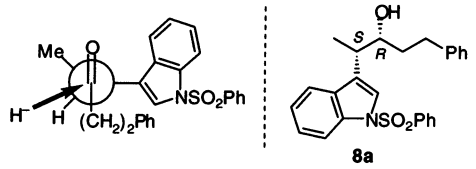


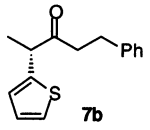
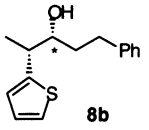
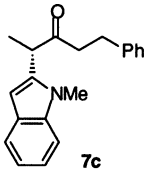
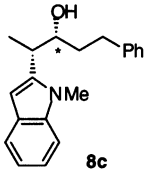
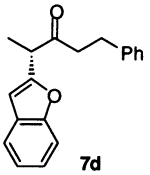
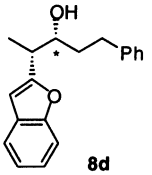
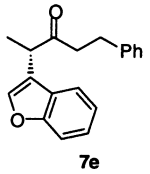
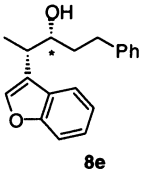
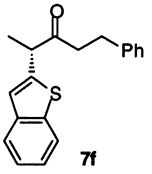
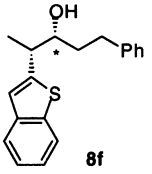
Figure 2.

Furthermore, reduction of ketone **7a** with $LiBEt_3H$ (THF, −78°C, 10 min) proceeded in excellent selectivity to give alcohol **8a**[6] as a sole product (Scheme 3). The stereostructure of **8a** was deduced from the Felkin–Anh model[12] applied to the reduction process of **7a** with the indolyl group serving as a large group (Fig. 2). This assignment was verified by the (*R*) absolute configuration of the alcohol center according to the Mosher–Kusumi method.[13] The (*S*) chirality at the adjacent center resulted from the inversive 1,2-shift.

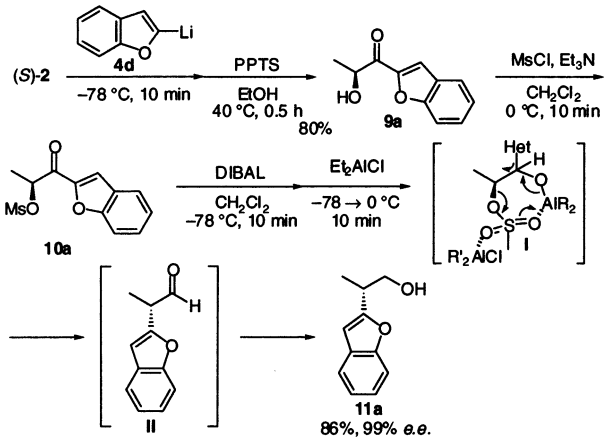
These conditions for stereoselective 1,2-shifts were directly applicable to a variety of heterocyclic structures, and results are summarized in Table 1. Migration of 2-thienyl, 1-methyl-2-indolyl, 3-benzofuranyl, and 2-benzothiophenyl groups proceeded smoothly, and optically pure ketones **7b**, **7c**, **7e**, and **7f** were obtained in high yields.[6,14] The single exception in these attempts was the sluggishness of the 1,2-shift of 2-benzofuranyl group, resulting in a low yield of **7d** with considerable racemization, although the reason is not clear. The inherent migratory aptitude of 2-benzofuranyl group is not low, judging from the successful conversion of **10a**→**11a** (vide infra), and work is in progress for clearing this issue.

In all cases listed, subsequent reduction with $LiBEt_3H$ (THF, −78°C) proceeded diastereoselectively to afford alcohols **8b**–**f**.[6,15]

Table 1.

run	product	yield/%, / % *e.e.*	product	yield/%, / % *d.s.*
1	 **7b**	93, 99	 **8b**	95, 96
2	 **7c**	85, 99	 **8c**	94, 88
3	 **7d**	41, 80	 **8d**	99, 94
4	 **7e**	96, 99	 **8e**	99, 94
5	 **7f**	90, 99	 **8f**	97, 97

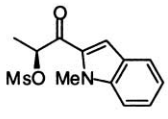
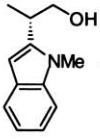
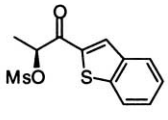
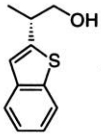
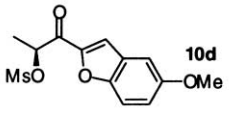
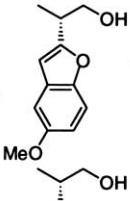
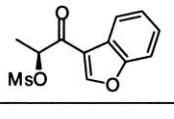
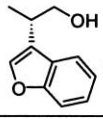
The reductive version of such 1,2-shift[5c] proved also viable in stereospecific manner, as illustrated by the reductive shift of 2-benzofuranyl group (Scheme 4). Thus, mesyloxy ketone **10a** was prepared by the reaction of 2-benzofuranyllithium **4d** with the lactamide (*S*)-**2** followed by deprotection to give α-keto alcohol **9a**, which was converted into the corresponding mesylate. After simple extractive workup and drying, **10a** was dissolved in CH_2Cl_2, to which was added DIBAL (3 mol equiv.) and Et_2AlCl (1.5 mol equiv.) at −78°C followed by warming to 0°C in 10 min. By this procedure, the carbonyl reduction in **10a** occurred to generate the aluminum alkoxide **I** in situ, which underwent 1,2-shift of the 2-benzofuranyl group by activation with Et_2AlCl[16] to give the aldehyde **II**, which was reduced by the excess DIBAL to give **11a**[6,17] in 99% *e.e.*



Scheme 4.

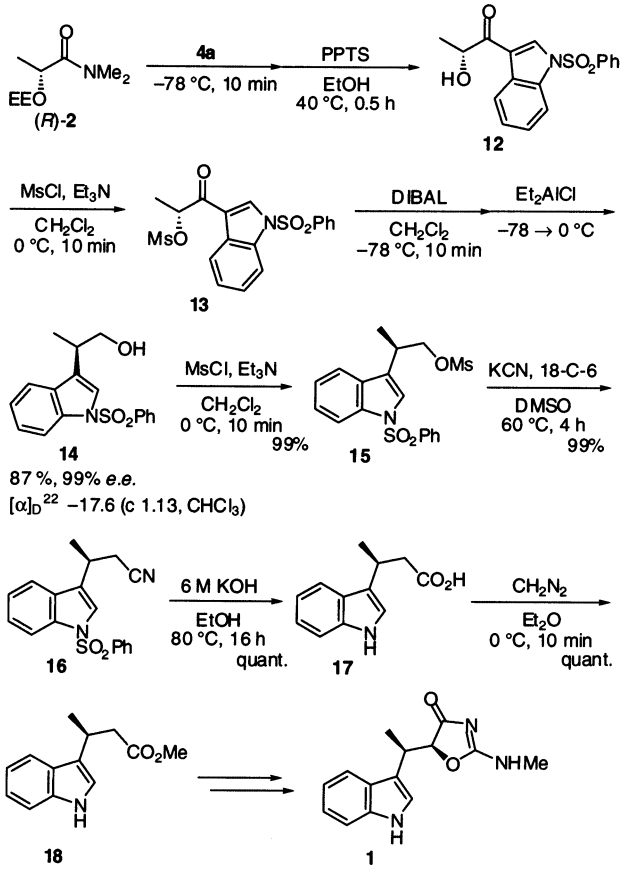
1-Methyl-2-indolyl, 2-benzothiophenyl, 5-methoxy-2-benzofuranyl,[7b] and 3-benzofuranyl groups also shifted stereospecifically to give chiral alcohols **11b**, **11c**, **11d** and **11e**, respectively[6,17] (Table 2).

Table 2.

run	mesyloxy ketone		product		yield/ %	% *e.e.*
1		**10b**		**11b**	86	99
2		**10c**		**11c**	98	99
3		**10d**		**11d**	70	99
4		**10e**		**11e**	88	99

Scheme 5 shows the application of this process to the formal total synthesis of indolmycin (**1**). Treatment of the enantiomeric lactamide (*R*)-**2** with 3-lithioindole **4a** (vide supra) cleanly gave the corresponding ketone, and removal of the ethoxyethyl group afforded hydroxy ketone **12**. Mesylation of **12** smoothly gave mesyloxy ketone **13**, which was successively treated with DIBAL (3 equiv.) and Et_2AlCl (1.5 equiv.) at −78°C. The 1,2-reduction occurred immediately, and was followed by the 1,2-shift of the indolyl group and reduction of the resulting aldehyde to give the chiral alcohol **14**[18] in 87% yield. The enantiomeric excess of **14** was assessed by HPLC analysis (DAICEL CHIRALCEL OD-H, *i*-PrOH/hexane = 1/9), showing the stereochemical integrity of the whole sequence.

The 1,2-shift proved to be stereospecific with inversion of the chiral center, as shown by the absolute configuration of the known ester **18**, the key intermediate of Takeda's synthesis of indolmycin.[1a] Thus, mesylation of **14** to give mesylate **15**, which was then treated with KCN to afford cyanide **16**. Basic hydrolysis of **16** followed by treatment of the resulting acid **17** with diazomethane gave methyl ester **18** {$[\alpha]_D^{22}$ +11.1 (*c* 1.17, C_6H_6), lit.[1a] $[\alpha]_D^{22}$ +10.9 (*c* 2.12, C_6H_6)}. The enantiomeric excess of **18** (99% *e.e.*) was further verified by HPLC analysis[19] (DAICEL CHIRALCEL OJ-H, EtOH/hexane = 1/4).



Scheme 5.

In conclusion, the stereospecific pinacol-type shift of some π-electron-rich heterocycles could be effected under organoaluminum-promoted conditions, and should find various utility in the selective construction of asymmetric centers adjacent to heterocycles.

References

1. Asymmetric synthesis of indolmycin: (a) Takeda, T.; Mukaiyama, T. *Chem. Lett*. **1980**, 163; (b) Akita, H.; Kawaguchi, T.; Enoki, Y.; Oishi, T. *Chem. Pharm. Bull*. **1990**, *38*, 323; (c) Bando, T.; Shishido, K. *Heterocycles* **1997**, *46*, 111; (d) Hasuoka, A.; Nakayama, Y.; Adachi, M.; Kamiguchi, H.; Kamiyama, K. *Chem. Pharm. Bull*. **2001**, *49*, 1604. Synthesis of (±)-indolmycin: (e) Dhue, Y.-K. *Tetrahedron Lett*. **1996**, *37*, 6447.
2. (a) Inoue, M.; Frontier, A.; Danishefsky, S. J. *Angew. Chem., Int. Ed*. **2000**, *39*, 761; (b) Appendino, G.; Casiraghi, G.; Zanardi, F. *Chemtracts* **2000**, *13*, 741; (c) Inoue, M.; Carson, M. W.; Frontier, A. J.; Danishefsky, S. J. *J. Am. Chem. Soc*. **1878**, *123*, 2001.
3. (a) Kozikowski, A. P.; Greco, M. N. *J. Am. Chem. Soc*. **1980**, *102*, 1165; (b) Guo, X.; Zhang, Z. *Yaoxue Xuebao* **1987**, *22*, 671; (c) Matsumoto, M.; Watanabe, N. *Heterocycles* **1987**, *26*, 1743; (d) Dickens, M. J.; Mowlem, T. J.; Widdowson, D. A.; Slawin, A. M. Z.; Williams, D. J. *J. Chem. Soc., Perkin Trans. 1* **1992**, 323; (e) Kato, K.; Ono, M.; Akita, H. *Tetrahedron Lett*. **1805**, *38*, 1997; (f) Kato, K.; Ono, M.; Akita, H. *Tetrahedron* **2001**, *57*, 10055.
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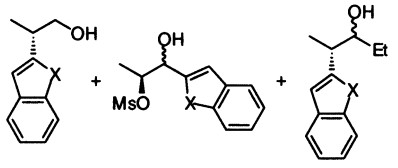
5. (a) Suzuki, K.; Katayama, E.; Tsuchihashi, G. *Tetrahedron Lett*. **1983**, *24*, 4997; (b) Suzuki, K.; Katayama, E.; Tsuchihashi, G. *Tetrahedron Lett*. **1817**, *25*, 1984; (c) Suzuki, K.; Katayama, E.; Matsumoto, T.; Tsuchihashi, G. *Tetrahedron Lett*. **1984**, *25*, 3715; (d) Tsuchihashi, G.; Tomooka, K.; Suzuki, K. *Tetrahedron Lett*. **1984**, *25*, 4253; (e) Suzuki, K.; Ohkuma, T.; Tsuchihashi, G. *Tetrahedron Lett*. **1985**, *26*, 861; (f) Suzuki, K.; Tomooka, K.; Matsumoto, T.; Katayama, E.; Tsuchihashi, G. *Tetrahedron Lett*. **1985**, *25*, 3711; (g) Suzuki, K.; Tomooka, K.; Shimazaki, M.; Tsuchihashi, G. *Tetrahedron Lett*. **1985**, *26*, 4781; (h) Suzuki, K.; Ohkuma, T.; Miyazawa, M.; Tsuchihashi, G. *Tetrahedron Lett*. **1986**, *27*, 373; (i) Suzuki, K.; Tomooka, K.; Katayama, E.; Matsumoto, T.; Tsuchihashi, G. *J. Am. Chem. Soc*. **1986**, *108*, 5221; (j) Suzuki, K. *J. Synth. Org. Chem. Jpn*. **1988**, *46*, 365; (k) Nagasawa, T.; Taya, K.; Kitamura, M.; Suzuki, K. *J. Am. Chem. Soc*. **1996**, *118*, 8949.
6. All new compounds were fully characterized by spectroscopic means and combustion analysis.
7. (a) 3-Indolyllithium and 3-benzofuranyllithium were generated by halogen–lithium exchange of the corresponding bromide (*n*-BuLi, THF, −78°C, 1 min); (b) 2-Thienyllithium, 2-benzothiophenyllithium, 2-benzofuranyllithium, and 5-methoxy-2-benzofuranyllithium were generated by hydrogen–lithium exchange (*n*-BuLi, THF, −78→25°C, 30 min); (c) 1-Methyl-2-indolyllithium was generated by hydrogen–lithium exchange in the presence of TMEDA (*n*-BuLi, THF, −78→25°C, 30 min).
8. Honda, Y.; Ori, A.; Tsuchihashi, G. *Bull. Chem. Soc. Jpn*. **1987**, *60*, 1027.
9. This one-pot procedure is particularly suitable for the case when the intermediary mesylate was unstable. Details for the comparison of this protocol with the two-pot protocol[5a,b] we previously employed will be disclosed elsewhere.
10. An authentic sample of (±)-**7a** was prepared from (±)-ethyl lactate along the same lines.
11. The *e.e.* of the ethyl (*S*)-lactate was determined to be 99% by 400 MHz ^{1}H NMR analysis of the (−)-MTPA ester.[12a]
12. (a) Chérest, M.; Felkin, H.; Prudent, N. *Tetrahedron Lett*. **1968**, 2201; (b) Anh, N. T.; Eisenstein, O. *Nouv. J. Chim*. **1977**, *1*, 61.
13. The (*R*) absolute configuration of the alcohol center was deduced by the Mosher–Kusumi method based on the chemical shifts of the corresponding (+)- and (−)-MTPA esters. (a) Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc*. **1973**, *95*, 512; (b) Kusumi, T.; Ohtani, I.; Inoue, Y.; Kakisawa, H. *Tetrahedron Lett*. **1988**, *29*, 4731.
14. The enantiomeric excess was determined as follows. For **7b**: ketone **7b** was reduced with DIBAL to give the diastereomeric alcohols (ca. 1/1), which were converted to the corresponding (+)-MTPA esters. For comparison, the alcohols derived from (±)-ethyl lactate were converted to the (+)-MTPA esters. For **7c–f**: by the chiral HPLC analysis (DAICEL CHIRALCEL OD-H, *i*-PrOH/hexane = 1/9) of the chiral ketones and (±)-ketones.
15. The diastereomers of **8b–8f** were inseparable on TLC, respectively. Each of the ratio was assessed by ^{1}H NMR, and the configurations of alcoholic center are based on the analogy with **8a**.
16. In this reductive version of rearrangement, the second organoaluminum (Et_2AlCl) is crucial for the smooth 1,2-shift to occur, as noted previously.[5c] In its absence, the rearrangement was much slower, and higher temperature was necessary (see also Refs. 5d and 5g). In the case where Et_3Al was used as the second Lewis acid instead, the yield was somewhat lower, and some byproducts were produced, including the one from ethylation of the aldehyde intermediate.



X	yield / %	yield / %	yield / %
NMe	78	7	-
O	47	9	15
S	57	-	38

17. The enantiomeric excess was determined by the chiral HPLC analysis (DAICEL CHIRALCEL OD-H, *i*-PrOH/hexane = 1/9).
18. Although compound **14** was previously reported by Bando et al. (Ref. 1c) in their formal total synthesis of indolmycin via enzymatic transformation, the specific rotation was not reported. Thus the $[\alpha]_D$ value of the corresponding methyl ester **18** was compared with that of **18** reported by Takeda (Ref. 1a).
19. An authentic sample of (±)-**18** was prepared from (±)-ethyl lactate along the same lines.