Pergamon

Tetrahedron Letters 40 (1999) 3443–3446

TETRAHEDRON LETTERS

Axially Chiral Benzamides: Diastereoselective Nucleophilic Additions to Planar Chiral (*N,N*-Diethyl-2-Acyl-6-Methylbenzamide)Chromium Complexes

Hiroshige Koide[a] and Motokazu Uemura*[a,b]

a; Department of Chemistry, Faculty of Integrated Arts and Sciences, Osaka Prefecture University, Sakai, Osaka 599-8531, Japan

b; Research Institute for Advanced Science and Technology, Osaka Prefecture University, Sakai, Osaka 599-8570, Japan

Received 5 February 1999; revised 3 March 1999; accepted 5 March 1999

Abstract: Axially chiral *N,N*-diethyl-2-methyl-6-α-hydroxyalkylbenzamides were prepared as an enantiomerically pure form by nucleophilic additions to the planar chiral tricarbonylchromium-complexed 2-acyl (or formyl)-6-methylbenzamides.

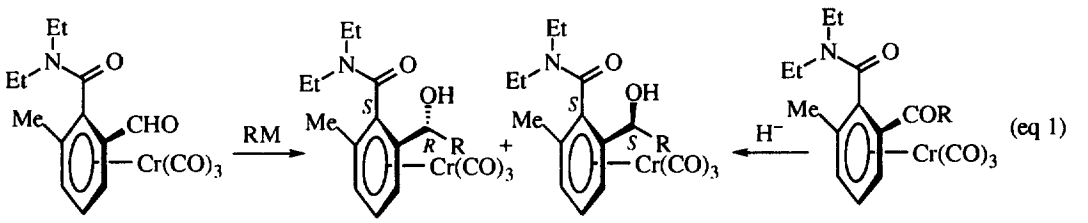
Keywords: atropisomerism, benzenes, chromium and compounds, complexes

Atropisomers due to a rotational barrier around the C(aryl)–C(carbonyl) bond of *N,N*-dialkyl-2,6-disubstituted aromatic carboxamides are well known,[1] and the chromatographic separation of some racemates to optically active axial aromatic carboxamides has been achieved by using HPLC on a chiral stationary phase.[2] Clayden and co-workers have recently reported[3] the synthesis of diastereomeric atropisomers as *racemate* by reaction of *N,N*-dialkyl-2-formyl-1-naphthamides with carbon nucleophiles, or reduction of *N,N*-dialkyl-2-acyl-1-naphthamides. To the best of our knowledge, there is no previous report of the synthesis of *enantiomerically pure N,N*-dialkyl 2,6-disubstituted aromatic carboxamides.[4] The enantiomerically pure axial benzamides or anilides with (or without) a chiral center would be expected to be new-type chiral auxiliaries for the asymmetric reaction,[1d,3f] and design of simple molecular devices.[5] As part of our exploration of the asymmetric synthesis of planar chiral arene chromium complexes to the axially chiral benzamides,[6] we wish to report our investigation on diastereoselective synthesis of axially chiral benzamides having a secondary alcohol as *optically pure* form.

The enantiomerically pure (*N,N*-diethyl-2-methyl-6-formylbenzamide)$Cr(CO)_3$ (**1**) ($[\alpha]_D^{26}$ –454.0 (*c* 0.1, $CHCl_3$)) was easily obtained by quenching of *ortho* lithiated intermediate of (+)-tricarbonyl(*N,N*-diethyl-2-methylbenzamide)chromium with DMF. The formyl group of **1** was converted to a diastereomeric secondary alcohol by an addition of a carbon nucleophile for inhibition of the axial bond rotation (eq 1). The diastereoselectivity at the newly created benzylic center was found to be controlled by the nature of nucleophile as shown in Table 1. Methylmagnesium bromide was treated with the complex **1** in THF at –78 °C to give easily a separable diastereomeric mixture in a ratio of 98 : 2 (entry 1). The stereochemistry of major product **2** (R = Me; $[\alpha]_D^{26}$ –30.5 (*c* 0.2, $CHCl_3$)) was determined by X-ray crystallography and found to be (S_p,S_{ax},*R*)-configuration.[7] The corresponding (*R*)-axial isomers could not be detected in the reaction with **1**. The *N,N*-diethylamino part of the complex **2** is oriented *anti* to the $Cr(CO)_3$ fragment by steric repulsion, and the N-C=O

0040-4039/99/$ - see front matter
PII: S0040-4039(99)00511-0

plane is almost perpendicular to the chromium-complexed arene ring. On the other hand, the reaction with methyl lithium gave the diastereoisomeric complex **3** (R = Me; $[\alpha]_D^{27}$ –49.0 (*c* 0.5, $CHCl_3$)) with (*S*)-benzylic alcohol as the major product in a ratio of 71 : 29 (entry 2). Reaction with $MeCeCl_2$ reagent[8] resulted in a moderate predominance of **2**. Similarly, ethyl lithium produced the corresponding complex **3** as the major product, while ethylmagnesium bromide gave a reduced compound without formation of the addition products.



1 **2** **3** **4**

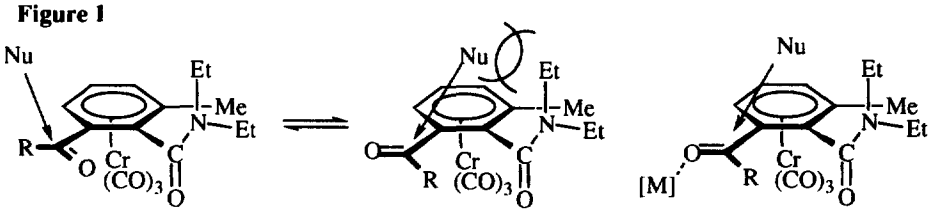
Table 1. Addition of Nucleophiles to (Arene)chromium Complexes 1 and 4

Entry	Complex 1 or 4	Nucleophile (RM or H^-)	Yield (%)	Ratio of 2 : 3
1	**1**	MeMgBr	83	98 : 2
2	**1**	MeLi[c]	70	29 : 71
3	**1**	MeLi, $MgBr_2 \cdot OEt_2$	76	55 : 45
4	**1**	$MeCeCl_2$	78	61 : 39
5[a]	**1**	EtMgBr	0	- : -
6	**1**	EtLi[c]	65	25 : 75
7	**1**	$EtCeCl_2$	75	48 : 52
8[b]	**4** (R = Me)	$NaBH_4$	96	96 : 4
9	**4** (R = Me)	$LiAlH_4$	99	90 : 10
10	**4** (R = Me)	DIBAL-H	91	9 : 91
11[b]	**4** (R = Et)	$NaBH_4$	94	93 : 7
12	**4** (R = Et)	$LiAlH_4$	98	91 : 9
13	**4** (R = Et)	DIBAL-H	88	10 : 90

a; A reduced product, tricarbonyl(*N*,*N*-diethyl-2-methyl-6-hydroxymethylbenzamide)chromium was obtained in 57 % yield.
b, Reaction temperature was 0 °C in MeOH. Other reactions were performed at –78 °C in THF.
c, An alkyllithium contains lithium salt in a solution.

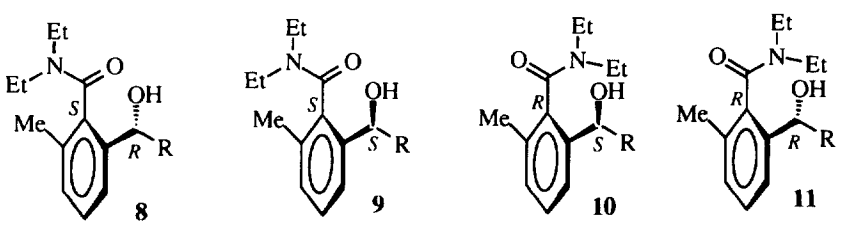
We next turned to the diastereoselectivity in hydride reduction of (+)-tricarbonyl(*N*,*N*-diethyl-2-acyl-6-methylbenzamide)chromium complexes **4** (R = Me, Et) which were prepared by oxidation of the mixtures of diastereoisomeric alcohols obtained by the reaction of *ortho*-lithiated (+)-tricarbonyl(*N*,*N*-diethyl-2-methylbenzamide)chromium with aldehydes. The reduction of **4** (R = Me, Et) with sodium borohydride in MeOH at 0 °C afforded predominantly the (*R*)-benzylic alcohol complexes **2** with high selectivities (entries 8,11), while diisobutylalminium hydride reduction resulted in the predominant formation of (*S*)-benzyl alcohols **3** with a reversed selectivity (entries 10,13). Thus, both diastereomers **2** and **3** were easily prepared by complementary routes from the complexes **1** and **4**. The corresponding (*R*)-axially chiral benzamide chromium complexes having a secondary alcohol were prepared starting from the planar antipode (–)-(*N*,*N*-diethyl-2-methylbenzamide)$Cr(CO)_3$ complex under same reaction conditions.

Figure 1



5 *syn*- (C=O/CONEt$_2$) **6** *anti*- (C=O/CONEt$_2$) **7**

The diastereoselectivity at the newly created benzylic position can be explained by a transition state in which the reagents attack the carbonyl in the conformations as shown in Figure 1. It is well known[9] that the nucleophilies attack the carbonyl in an *anti*-conformer **6** (R = H) from an opposite face of the Cr(CO)$_3$ fragment in the *o*-alkoxy and *o*-methylbenzaldehyde chromium complexes, regardless of the nature of carbanions. However, X-ray crystal structure[10] of **1** is found to be a *syn*-conformer **5** (R = H), in which the plane of H-C=O is nearly coplanar, and the N-C=O plane is almost perpendicular to the aromatic ring, respectively. Therefore, the major product **3** derived from addition of alkyllithiums seems to proceed via an *exo*-attack to the carbonyl in the *syn*-conformer **5** (R = H). In the reaction with Griganard reagent, however, the first step of this reaction is a coordination of Grignard reagent to the carbonyl oxygen. An equilibrium between the conformers would be rapidly established, and the rate-limiting step of this reaction is presumably the addition of nucleophile.[11] Consequently, the major products **2** would be formed by attack of the Grignard reagent to the carbonyl of coordinated *anti*-conformer **7**, since the corresponding coordinated structure of *syn* conformer **5** with Lewis acidic reagent is strongly destabilized by increasing steric size. To confirm this proposal, we added MgBr$_2$·OEt$_2$ to the reaction media of **1** with MeLi. The diastereomers were formed with reduced selectivity, consistent with an increased preference for the coordinated *anti* transition state (entry 3). The transition states for diastereoselective reduction of the acyl complex **4** would be analogous. Thus, the reducing agent such as NaBH$_4$ and LiAlH$_4$ attacks the ketone in *syn*-conformer **5** (R = alkyl), while diisobutylaluminium hydride approaches the carbonyl in the coordinated *anti*-conformer **7**, giving the diastereomer **3** with reversed selectivity. Thus, the nucleophiles approach from the *exo*-side of the Cr(CO)$_3$ fragment to the carbonyl in a preferable conformer depending on the nature of the reagents, while the diastereoselectivity in the chromium-free benzamides could be induced by the stereogenic axis of rotationally restricted tertiary naphthamides.[3b,f]



8 **9** **10** **11**

Oxidative demetalation of (–)-**2** (R = Me) by exposure to sunlight in ether at 0 °C afforded the chromium-free (*S*$_{ax}$,*R*)-*N*,*N*-diethyl-2-methyl-6-(α-hydroxyethyl)benzamide **8** (R = Me; [α]$_D^{27}$ +70.0 (*c* 0.35, CHCl$_3$))[12] with >99% ee[13] in a quantitative yield, and the diastereoisomeric complex (–)-**3** (R = Me) gave the enantiomerially pure (*S*$_{ax}$,*S*)-**9** (R = Me, [α]$_D^{25}$ –12.0 (*c* 0.10, CHCl$_3$)).[12,13] These chiral benzamides are stable for the axial bond rotation at room temperature.[14] Similarly, the corresponding (*R*)-axial benzamides

possessing a chiral secondary alcohol, **10** and **11**, were obtained from planarly isomeric (+)-(*N,N*-diethyl 2-methyl-6-formylbenzamide)$Cr(CO)_3$ under the same reaction conditions.

In conclusion, we have demonstrated that the axially chiral benzamides with a secondary alcohol can be prepared in *enantiomerically pure* form by diastereoselective nucleophilic additions to the carbonyl function of planar chiral tricarbonyl(arene)chromium complexes. We are now investigating the elaboration of the asymmetric reaction utilizing these axial chiral benamides as chiral auxiliary.

Acknowledgment: This work was supported by a Grant-in Aid for Scientific Research from The Ministry of Education, Science, Sports and Culture of Japan. M.U. thanks The Asahi Glass Foundation for financial support.

References and Notes

1 (a) Ackerman, J. H.; Laidlaw, G. M. *Tetrahedron Lett.* **1969**, 4487-4488; *Ibid.* **1970**, 2381-2384; (b) Bastiaansen, L. A. M.; Kanters, J. A.; van der Steen, F. H.; de Graaf, J. A. C.; Buck, H. M. *J. Chem. Soc. Chem. Commun.* **1986**, 536-537; (c) Gallo, R.; Roussel, C.; Berg, U. *Adv. Heterocyclic Chem.* **1988**, *43*, 173-299; (d) Clayden, J. *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 949-951.

2 Cuyegkeng, M. A.; Mannschreck, A. *Chem. Ber.* **1987**, *120*, 803-809; Pirkle, W. H.; Welch, C. J.; Zych, A. J. *J. Chromatogr.* **1993**, *648*, 101-109.

3 (a) Bowles, P.; Clayden, J.; Tomkinson, M. *Tetrahedron Lett.* **1995**, *36*, 9219-9222; (b) Clayden, J.; Westlund, N.; Wilson, F. X. *Tetrahedron Lett.* **1996**, *37*, 5577-5580; (c) Clayden, J.; Pink, J. H. *Tetrahedron Lett.* **1997**, *38*, 2565-2568; (d) Clayden, J.; Darbyshire, M.; Pink, J. H.; Westlund, N.; Wilson, F. X. *Tetrahedron Lett.* **1997**, *38*, 8587-8590; (e) Clayden, J.; Pink, J. H.; Yasin, S. A. *Tetrahedron Lett.* **1998**, *39*, 105-108. (f) Clayden, J. *Synlett* **1998**, 810-816.

4 Axial *N,N*-dihexyl-2-alkyl-1-naphthamides were obtained with modest optical purity in a low yield by deprotonation under a combination of *s*-butyllithium and (-)-sparteine: Thayumanavan, S.; Beak, P.; Curran, D. P. *Tetrahedron Lett.* **1996**, *37*, 2899-2902.

5 Clayden, J.; Pink, J. H. *Angew. Chem. Int. Ed. Engl.* **1998**, *37*, 1937-1939.

6 Koide, H.; Uemura, M. *Chem. Commun.* **1998**, 2483-2484.

7 The first symbol S_p indicates the absolute configuration of the $Cr(CO)_3$-complexed aromatic carbon substituted with the amido function, and the second symbol S_{ax} shows the axial chirality.

8 The organocerium reagents were prepared by the following literature method: Imamoto, T.; Sugiura, Y.; Takiyama, N. *Tetrahedron Lett.* **1984**, *25*, 4233-4236.

9 Some reviews; Solladié-Cavallo, A.; *Advances in Metal-Organic Chemistry*, Ed. by L. S. Liebeskind, JAI Press, Greenwich, 1989, vol. 1. p. 99; Davies, S. G.; McCarthy, T. D. *Comprehensive Organometallic Chemistry* II, Eds. by Abel, E. W.; Stone, F. G.; Wilkinson, G. Elsevier, 1995, vol. 12, p. 1039.

10 The carbonyl oxygen is oriented upper side to the chromium-complexd arene with 4° incline, and the angle between N-C=O plane and the ring is 91°.

11 In the reactions of tricarbonylchromium-complexed benzaldehydes a possessing bulky *ortho* triisopropylsilyl substituent with alkyl lithium and Grignard reagents, the diastereomers were selectively obtained via two conformers depending on the nature of nucleophile: Davies, S. G.; Goodfellow, C. L. *Synlett*, **1989**, 59-62.

12 Optical rotation values (in $CHCl_3$) of the other enantiomerically pure axial benzamides **8**, **9**, **10** and **11** are as follows: **8** (R = Et) +67.5 (*c* 0.27); **9** (R = Et) –14.0 (*c* 0.20); **10** (R = Me) –69.0 (*c* 0.30); **10** (R = Et) –67.2 (*c* 0.27); **11** (R = Me) +12.0 (*c* 0.10); **11** (R = Et) +14.0 (*c* 0.20).

13 Enantiomeric excess was determined by HPLC with Chiralpack OD-H.

14 Thermal interconversion of **2** (R = Et) to the corresponding atropisomer reached equilibration along with the formation of 3-ethyl-7-methylphthalide under heating at 90 °C in $Cl_2CDCDCl_2$.