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Asymmetric Synthesis of Axially Chiral Anilides by Enantiotopic Lithiation of Tricarbonyl(*N*-methyl-*N*-acyl-2,6-dimethylanilide)chromium Complex

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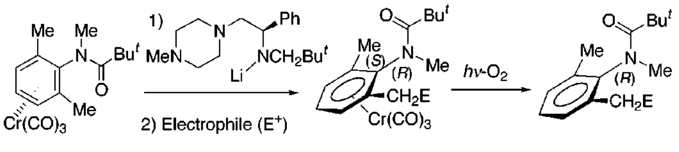
ABSTRACT



1

2 up to 97% ee

14

Axially chiral *N*-methylanilides were synthesized by enantioselective lithiation of prochiral tricarbonyl(*N*-methyl-*N*-pivaloyl-2,6-dimethylaniline)-chromium (1) with the lithium amide of the 4-methylpiperazinylethylamine derivative 13 followed by electrophilic quenching up to 97% ee in good yields. The resulting axially chiral chromium-complexd anilides 2 were oxidized under air to give the axially chiral anilides 14 in enantiomerically active form without axial bond rotation at room temperature.

There are very few examples of non-biaryl axial chiral compounds being used as chiral ligands or chiral auxiliaries in asymmetric reactions; axially chiral biaryl compounds are normally used. Atropisomers due to a rotational barrier about the C(aryl)−C(carbonyl) bond of *N*,*N*-dialkyl *o*-substituted aromatic carboxamides and the C(aryl)−N bond of *o*-substituted anilides and related compounds are well-known.[1,2] Recently, axially chiral anilide derivatives were developed for the stereoselective reaction. However, in these reactions, racemic or achiral axial anilides have been used almost exclusively.[2] The chromatographic separation of some racemates to optically active axial aromatic carboxamides or anilides has been achieved by using HPLC on a chiral stationary phase.[3] Simpkins et al. attempted to prepare an optically enriched anilide through kinetic resolution of racemic *N*-propionyl-*o*-*tert*-butylanilide by treatment with chiral lithium amide, but the chiral anilide was obtained in very poor yield.[2b] In addition, the absolute configuration of this anilide could not be determined. Taguchi et al. have reported that the axially chiral anilides were prepared by separation of a diastereomer derived from (*S*)-*O*-acetyllactic acid with high enantiomeric purity.[4] The axially chiral cyclic *N*-*o*-*tert*-butylphenylpyrrolidinone[5a,b] or atropisomeric quinazolinone derivative with a diphenylphosphino group[5c,d] is

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(1) Some representative axially chiral naphth- or benzamides: (a) Clayden, J. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 949. (b) Clayden, J.; Westlund, N.; Wilson, F. X. *Tetrahedron Lett.* **1999**, *40*, 3329. (c) Clayden, J.; Lai, L. W. *Angew. Chem., Int. Ed.* **1999**, *38*, 2556. (d) Ahmed, A.; Bragg, R. A.; Clayden, J.; Lai, L. W. McCarthy, C.; Pink, J. H.; Westlund, N.; Yasin, S. A. *Tetrahedron* **1998**, *54*, 13277. (e) Mikata, Y.; Hayashi, K.; Mizukami, K.; Matsumoto, S.; Yano, S.; Yamazaki, N.; Ohno, A. *Tetrahedron Lett.* **2000**, *41*, 1035.

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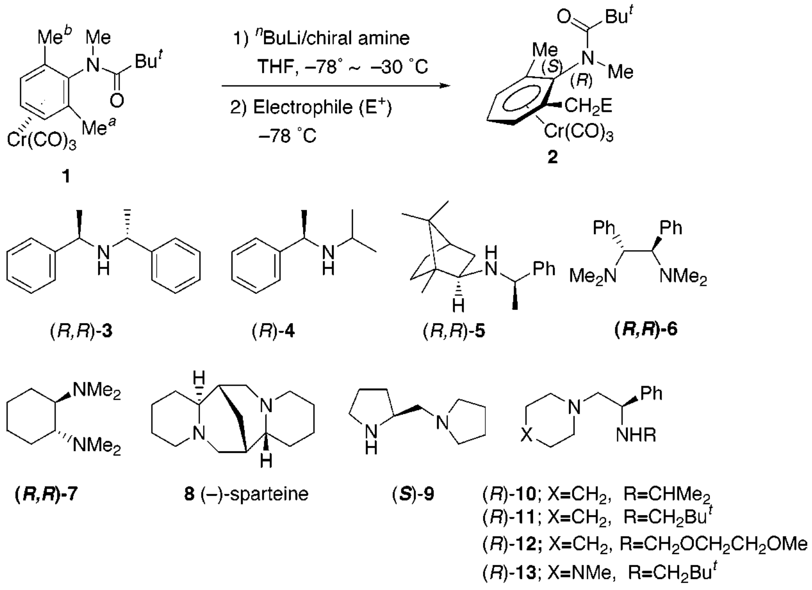
Scheme 1



obtained in an enatiomerically active form by using a chiral auxiliary or optical resolution with a chiral palladium(II) reagent, respectively. To the best of our knowledge, there is no previous report on asymmetric synthesis of acyclic axially chiral anilides in optically pure form.

As part of our asymmetric synthetic exploration of the planar chiral (arene)chromium complexes, we have developed an asymmetric synthesis of the axially chiral *N*,*N*-diethyl 2,6-disubstituted benzamides.[6] In this paper, we wish to report the asymmetric synthesis of axially chiral *N*-methyl-*N*-acyl 2,6-disubstituted anilides through a kinetically discriminating lithiation between two enantiotopic benzyl methyls of prochiral 2,6-dimethylanilide chromium complexes with a chiral lithium amide base (Scheme 1).

The reaction was performed by treatment of *N*-methyl-*N*-pivaloyl-2,6-dimethylaniline chromium complex **1** with a combination of chiral amine and *n*-BuLi in THF followed by quenching with electrophiles, and the results are summarized in Table 1. Among the various chiral monoamines or diamines examined, the lithium amides derived from bis-α-phenylethylamine and the related chiral monoamines gave moderate enantioselectivities by quenching with methyl iodide (entries 1−3), while use of *N*,*N*,*N*′,*N*′-tetraalkyl diamines such as **6**, **7**, and (−)-sparteine led to a racemic compound (entries 4−6). These results indicate that the chiral versions of LDA could discriminate the enantiotopic benzyl methyls of anilide chromium complex **1** for the asymmetric deprotonation. For the achievement of high enantioselectivity, we next examined the enantio-discriminated lithiation by using the bidentate chiral lithium amides which could exist as five-membered chelated structures. Chiral lithium amide derived from (*S*)-2-(1-pyrrolidinylmethyl)pyrrolidine (**9**) increased the enantioselectivity slightly, although the chemical yield was moderate. Employment of 1-phenyl-2-piperidinoethylamine derivatives **10** and **11** resulted in higher yields and enantioselectivities (entries 8 and 9), and the

Table 1. Enantiotopic Lithiation of Tricarbonyl(*N*-methyl-*N*-pivaloyl-2,6-dimethyl)chromium (**1**) with Chiral Lithium Amide

entry	chiral amine	E$^+$ (electrophile)	**2** (%)	% ee	$[\alpha]_D$ (CHCl$_3$)
1	**3**	MeI	50	44	
2	**4**	MeI	51	72	
3	**5**	MeI	86	42[a]	
4	**6**	MeI	35	0	
5	**7**	MeI	24	0	
6	**8**	MeI	50	0	
7	**9**	MeI	44	78	
8	**10**	MeI	60	65	
9	**11**	MeI	80	79	
10	**13**	MeI	90	95	−29.4
11	**11**	$C_6H_5CH_2Br$	78	80	
12	**12**	$C_6H_5CH_2Br$	48	89	
13	**13**	$C_6H_5CH_2Br$	90	97	−19.5
14	**13**	$CH_2{=}CHCH_2Br$	81	92	−25.9
15	**13**	$MeC{\equiv}CCH_2Br$	86	96	−38.5
16	**13**	$PhC{\equiv}CCH_2Br$	84	96	−51.1
17	**13**	benzophenone	73	96	−75.7
18	**13**	cyclohexanone	58	96	−77.3
19	**13**	PhCOCl	31	97	−15.0

[a] Enantiomer of **2**.

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(4) (a) Kitagawa, O.; Izawa, H.; Taguchi, T.; Shiro, M. *Tetrahedron Lett.* **1997**, *38*, 4447. (b) Kitagawa, O.; Izawa, H.; Sato, K.; Dobashi, A.; Taguchi, T. *J. Org. Chem.* **1998**, *63*, 2634. (c) Fujita, M.; Kitagawa, O.; Izawa, H.; Dobashi, A.; Fukaya, H.; Taguchi, T. *Tetrahedron Lett.* **1999**, *40*, 1949. (d) Hughes, A. D.; Simpkins, N. S. *Synlett* **1998**, 967.

(5) (a) Fujita, M.; Kitagawa, O.; Izawa, H.; Dobashi, A.; Fukaya, H.; Taguchi, T. *Tetrahedron Lett.* **1999**, *40*, 1949. (b) Fujita, M.; Kitagawa, O.; Yamada, Y.; Izawa, H.; Hasegawa, H.; Taguchi, T. *J. Org. Chem.* **2000**, *65*, 1108. (c) Dai, X.; Wong, A.; Virgil, S. C. *J. Org. Chem.* **1998**, *63*, 2597. (d) Dai, X.; Virgil, S. *Tetrahedron Lett.* **1999**, *40*, 1245.

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optically purity was determined by HPLC with Chiralpack AS. Fortunately, 4-methylpiperazinylethylamine derivative **13**, containing an additional nitrogen atom, increased both the enantioselectivity and chemical yield extremely. Thus, treatment of **1** with the chiral lithium amide prepared from amine **13** and *n*-BuLi in THF at −78 °C followed by quenching with methyl iodide produced the axially chiral anilide chromium complex **2** (E = Me) ($[\alpha]^{30}_{D}$ −29.4) in 90% yield with 95% ee (entry 10). The absolute stereochemistry of (−)-**2** (E = Me) was determined to be (S_p,R_{ax})[7] by X-ray crystallography.[8] The pivaloyl group is *exo* to the tricarbonylchromium fragment due to steric effects, and the amide oxygen is *trans* to the *N*-methyl group (Figure 1).

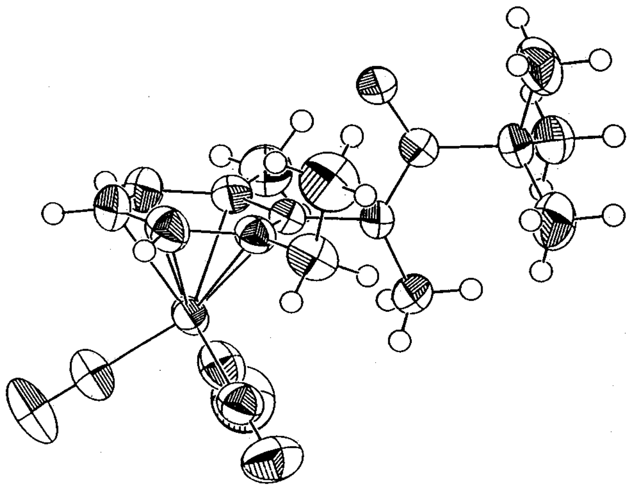


Figure 1. Crystallographic structure of (−)-**2** (R = Me).

Similarly, other electrophiles such as benzyl and allyl bromides or carbonyl compounds could be easily trapped to give the corresponding (*R*)-axially chiral anilide chromium complexes **2** via lithiation at the CH_3[a] group between two benzyl methyls with high enantioselectivities (entries 13−19).[9] The highly stereoselective deprotonation could be attributed to a conformation of the prochiral chromium complex **1**, where the amido carbonyl oxygen is oriented *trans* to the *N*-methyl group, resulting in a closely facing orientation with chromium-complexed phenyl ring. Predominat existence as the *trans*-rotamer between the *N*-methyl and the amide carbonyl oxygen of **1** was also observed in ^{1}H NMR.[10] Interestingly, the corresponding tricarbonylchromium-complexed *N*,*N*-diethyl-2,6-dimethylbenzamide was enantioselectively lithiated at an *alternative* benzyl methyl with the chiral lithium amides derived from (*R*,*R*)-**3**, (*R*)-**4**, or (*S*)-**9** to give the (R_p,R_{ax})-benzamide chromium complexes after quenching with electrophiles.[6b] The differentiated benzyl methyl position in the enantiotopic lithiation between the tricarbonylchromium-complexed 2,6-dimethylanilide **1** and *N*,*N*-diethyl-2,6-dimethylbenzamide with identical chiral lithium amides would contribute to the conformation of C(=)O−NR in the tricarbonylchromium fragment. Thus, the amide carbonyl oxygen of the *N*,*N*-diethyl-2,6-dimethylbenzamide chromium complex is found to be *syn*-oriented with respect to the tricarbonylchromium fragment from X-ray crystallography, while the corresponding carbonyl oxygen of anilide complex **1** is *anti* due to a stereoelectronic effect. At the present time, the precise mechanism for the enantiotopic lithiation at the differentiated benzylic position between tricarbonylchromium-complexed anilide **1** and benzamide is not clear, although the lithiation would be initiated by a coordination of the chiral lithium atom with the amido carbonyl. As the coordination structure seems to be essential for the reaction mechanism, we are investigating further the enantiotopic lithiation of other *N*-acylanilides such as *N*-acetyl, benzoyl, or *N*,*N*-dialkyl analogues.

Since we have prepared the tricarbonylchromium-complexd anilides possessing both planar and axial chiralities with high enantioselectity, we next focused our attention on the chromium-free axially chiral *N*-methyl 2,6-disubstituted anilides (Scheme 2). Exposure of **2** (E = Me) in ether at 0 °C to sunlight gave *N*-methyl-*N*-pivaloyl-2-ethyl-6-methylaniline **14** (E = Me, ($[\alpha]_D$ −4.9)) (Table 2, entry 1). The

Scheme 2

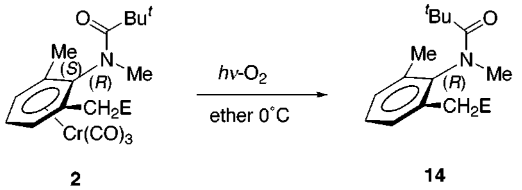
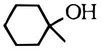


Table 2. Preparation of Axially Chiral *N*-Methylanilide **14** by Photooxidation

entry	E	**14** (%)	$[\alpha]_D$[a]	% ee[b]
1	Me	98	−4.9	95
2	CH_2Ph	95	−11.9	97[c]
3	$CH_2CH{=}CH_2$	96	−9.4	92
4	$CH_2C{\equiv}CCH_3$	95	−27.3	96
5	$CH_2C{\equiv}CPh$	95	−47.1	96
6	$C(OH)Ph_2$	96	+78.1	96
7	 OH	96	+9.0	96
8	COPh	94	−40.9	97

[a] Optical rotaions were measured in $CHCl_3$. [b] Enantiomeric excess was determined by ^{1}H NMR in the presence of Eu(tfc)$_3$. [c] Enantiomeric excess was determined by HPLC with Chiralpak AS.

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(7) The first symbol S_p indicates the absolute configuration at the chromium-complexed arene carbon substituted with the amido group, and the second symbol R_{ax} shows the axial chirality.

(8) All crystallographic data will be deposited in the Cambridge Structural Database.

(9) The slightly different ee's of the axially chiral anilides **2** were obtained with different electrophiles even by using same lithium amide. It is not clear if these are within experimental error or a rapid equilibration between the chromium-complexed benzyllithium intermediates.

optical purity of freshly obtained chromium-free anilide **14** (E = Me) was determined to be ∼95% ee without a decrease in optical purity of the chromium-complexed anilide **2** (E = Me) by ^{1}H NMR in the presence of chiral shift reagent Eu(tfc)$_3$. Furthermore, no axial bond rotation of the chromium-free chiral anilide **14** was observed after standing at room temperature for 24 h. Other chiral chromium-complexed anilides **2** were also oxidized to give the chromium-free axially chiral anilides **14** with high enantiopurity.

In conclusion, we have developed an asymmetric synthesis of the axially chiral *N*-methylanilides by desymmetrization of prochiral tricarbonylchromium-complexed *N*-methyl-2,6-dimethylanilide via enantioselective deprotonation at the benzylic methyls by treatment with chiral lithium amides followed by electrophilic quenching with highly optical purities. We are now investigating asymmetric reactions utilizing these axially chiral anilides.

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Supporting Information Available: General experimental details and characterization data for chromium-complexed and chromium-free axially chiral anilides **2**, **14**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) The *trans*-rotamer in the chromium-complexed anilide **2** is in sharp contrast to the tricarbonylchromium-free *N*-methyl-*N*-acylanilides, in which *N*-methyl is preferentially *cis*-oriented to the carbonyl oxygen in both the crystalline state and solution. See 3e and following references: (a) Itai, A.; Toriumi, Y.; Tomioka, N.; Kagechika, H.; Azumaya, I.; Shudo, K. *Tetrahedron Lett.* **1989**, *30*, 6177. (b) Itai, A.; Toriumi, Y.; Saito, S.; Kagechika, H.; Shudo, K. *J. Am. Chem. Soc*. **1992**, *114*, 10649. (c) Azumaya, I.; Yamaguchi, K.; Okamoto, I.; Kagechika, H.; Shudo, K. *J. Am. Chem. Soc*. **1995**, *117*, 9083.