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Asymmetric Synthesis of Axially Chiral Benzamides and Anilides by Enantiotopic Lithiation of Prochiral Arene Chromium Complexes

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Axially chiral benzamides and anilides were prepared by enantiotopic lithiation at the distinguished benzylic methyl of prochiral tricarbonylchromium complexes of *N*,*N*-diethyl 2,6-dimethylbenzamide (**1**) and *N*-methyl-*N*-acyl 2,6-dimethylaniline (**14** and **21**) with a chiral lithium amide base followed by electrophilic substitution in good yields with high optical purity. The resulting axially chiral chromium-complexed benzamides and anilides were oxidized under air to give chromium-free axially chiral benzamides and anilides in an enantiomerically active form without axial bond rotation at room temperature.

Introduction

There are relatively few molecules for nonbiaryl atropisomeric compounds, while axially chiral biaryls are of significant importance as a chiral ligand or an auxiliary in asymmetric reactions and some biologically active natural products. The presence of atropisomers due to the rotational barrier about the C(aryl)−C(carbonyl) bond of *N*,*N*-dialkyl 2,6-disubstituted aromatic carboxamides[1] or the C(aryl)−N bond of *N*-alkyl anilide[2] derivatives possessing a sterically bulky ortho substituent is well-known. The chromatographic separation of some racemates to optically active axial aromatic carboxamides and anilides has been achieved using HPLC on a chiral stationary phase.[3] The axially chiral benzamides and anilides were recently employed in stereoselective reactions, e.g., cyclic addition, alkylation, radical-mediated cyclization, and catalytic allylic alkylation, and so on.[1,2,4] Furthermore, antagonistic activity at the NK$_1$ receptor is found to be largely dependent on the axially chiral amide configuration in 1,7-naphthyridene-6-carboxamide derivatives.[5] Therefore, the preparation of enantiopure axially chiral nonbiaryl compounds is significantly important for the asymmetric reaction and biological activity. There are relatively few reports on the asymmetric

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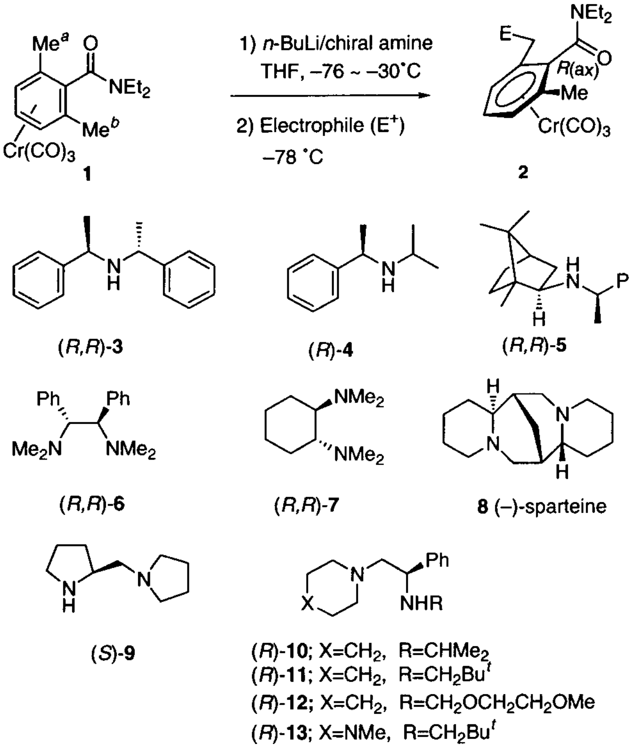
synthesis of nonbiaryl axially chiral benzamides and anilides. Beak reported an asymmetric deprotonation of *N*,*N*-dialkyl 1-naphthamides with a combination of butyllithium/(−)-spartein followed by quenching with alkyl halides to afford axially chiral *N*,*N*-dialkyl 2-alkyl-1-naphthamides.[6] However, the optical purity of the axial aromatic carboxamides obtained by this asymmetric deprotonation is moderate. Simpkins et al. attempted to prepare an optically enriched anilide through kinetic resolution of racemic *N*-propionyl-*o*-*tert*-butylanilide by treatment with a chiral lithium amide, but the yield of the chiral anilide was very low.[7] In addition, the absolute configuration of this axial anilide could not be determined. Taguchi et al. reported that the axially chiral anilides were prepared by separation of the diastereomer derived from (*S*)-*O*-acetyl lactic acid with high enantiomeric purity, and these anilides have been developed for many asymmetric reactions.[8] The axially chiral cyclic *N*-*o*-*tert*-butylphenyl pyrrolidinone[9a,b] or atropisomeric quinazolinone derivative having a diphenylphosphino group[9c,d] was obtained in enatiomerically active form by using chiral auxiliary or optical resolution with a chiral palladium(II) reagent, respectively. Recently, Clayden et al. reported that axially chiral 2-substituted naphthamides were obtained in high optical purity by reaction with a chiral proline-derived aniline through a dynamic resolution.[10] A new synthetic strategy for enantiopure axially chiral nonbiaryl compounds is still highly demanded for the development of asymmetric reactions. To the best of our knowledge, there is no previous report on the asymmetric synthesis of axially chiral nonbiaryl compounds in an *enantiomerically pure form*. As part of our asymmetric synthetic exploration of planar chiral (arene)chromium complexes, we report herein the asymmetric synthesis of the axially chiral *N*,*N*-diethyl 2,6-disubstituted benzamides and *N*-methyl-*N*-acyl 2,6-disubstituted anilides by kinetically discriminated lithiation at the benzylic position with a chiral lithium amide base.[11]

Scheme 1. Enantiotopic Lithiation of Prochiral Benzamide Chromium Complex 1



Results and Discussion

Asymmetric Synthesis of Axially Chiral Benzamide Chromium Complexes. We have already reported that planar chiral *N*,*N*-diethyl *o*-substituted benzamide chromium complexes could be converted to the axially chiral 2,6-disubstituted benzamide chromium complexes via ortho lithiation and subsequent electrophilic quenching.[12] Thus, the introduction of a sterically bulky substituent at the ortho position of planar chiral *N*,*N*-dialky 2-substituted benzamide chromium complexes could induce axial chirality. On the basis of this stereochemical result, we initially focused on an enantiotopic deprotonation between two ortho hydrogens of tricarbonyl(*N*,*N*-dialkyl benzamide)chromium giving the planar chiral *o*-substituted benzamide chromium complexes directed toward the induction of axial chirality. Simpkins et al. reported[13] the enantiotopic ortho lithiation of a benzamide chromium complex for the preparation of planar chiral chromium complexes. Thus, tricarbonyl(*N*,*N*-diisopropyl benzamide)chromium was treated with lithium (*R*,*R*)-bis-α-phenylethylamide in the presence of Me_3SiCl in THF to give (−)-(*o*-trimethylsilylbenzamide)chromium in 87% yield. However, the enantiomeric purity of the product was unfortunately moderate (48% enantiomeric excess (ee)). We also investigated this type of enantiotopic ortho lithiation of *N*,*N*-diethyl benzamide chromium complex by using other types of chiral lithium amides, but the optical purity of the products was still unsatisfactory. Therefore, we next turned our attention to a discriminating lithiation between two enantiotopic benzyl methyls of prochiral tricarbonyl(*N*,*N*-diethyl 2,6-dimethylbenzamide)chromium (**1**) (Scheme 1). The reaction was performed with a combination of *n*-BuLi/chiral amine[14] 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 monoamines gave a reasonable result with respect to the optical purity, while *N*,*N*,*N*′,*N*′-tetraalkyl

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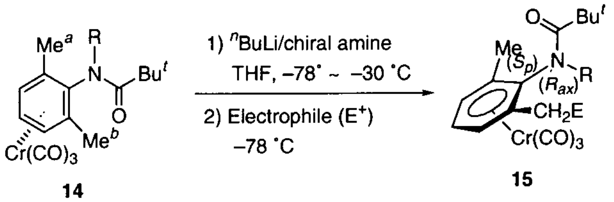
Table 1. Enantiotopic Lithiation of Prochiral Benzamide Chromium Complex 1 with Chiral Lithium Amide

entry	chiral amine	E^+ (electrophile)	% yield	% ee of **2**
1	**3**	MeI	85	86
2	**4**	MeI	82	51
3	**5**	MeI	15	21
4	**6**	MeI	43	3
5	**7**	MeI	40	5
6	**8**	MeI	40	17
7	**9**	MeI	18	27
8	**11**	MeI	41	6
9	**12**	MeI	10	44
10	**3**	$PhCH_2Br$	41	83
11	**3**	$CH_2{=}CHCH_2Br$	52	83

Scheme 2



a: R = Me, **b:** R = Et, **c:** R = CH_2OMe

Table 2. Enantiotopic Lithiation of Tricarbonyl(*N*-alkyl-*N*-pivaloyl 2,6-dimethylaniline)chromium (14)

entry	complex **14**	chiral amine	E^+ (electrophile)	% yield **15**	% ee **15**	$[\alpha]_D$
1	**14a**	**3**	MeI	50	44	
2	**14a**	**4**	MeI	51	72	
3	**14a**	**5**	MeI	86	42	
4	**14a**	**6**	MeI	35	0	
5	**14a**	**7**	MeI	24	0	
6	**14a**	**8**	MeI	50	0	
7	**14a**	**9**	MeI	44	78	
8	**14a**	**10**	MeI	60	65	
9	**14a**	**11**	MeI	80	79	
10	**14a**	**13**	MeI	90	95	−29.4
11	**14a**	**11**	$C_6H_5CH_2Br$	78	80	
12	**14a**	**12**	$C_6H_5CH_2Br$	48	89	
13	**14a**	**13**	$C_6H_5CH_2Br$	90	97	−19.5
14	**14a**	**13**	$CH_2{=}CHCH_2Br$	81	92	−25.9
15	**14a**	**13**	$MeC{\equiv}CCH_2Br$	86	96	−38.5
16	**14a**	**13**	$PhC{\equiv}CCH_2Br$	84	96	−51.1
17	**14a**	**13**	benzophenone	73	96	−75.7
18	**14a**	**13**	cyclohexanone	58	96	−77.3
19	**14a**	**13**	PhCOCl	31	97	−15.0
20	**14b**	**13**	MeI	83	98	−25.0
21	**14b**	**13**	$PhCH_2Br$	71	99	−27.0
22	**14c**	**13**	MeI	73	96	−18.2
23	**14c**	**13**	$PhCH_2Br$	78	94	−13.7

diamines such as **6**−**8** led to unsatisfactory results. Especially, a chiral lithium amide of bis-(*R*,*R*)-α-phenylethylamine (**3**) showed high optical purity in the asymmetric lithiation. Thus, the lithiation of prochiral benzamide chromium complex **1** with the chiral lithium amide of **3** gave (+)-tricarbonyl(*N*,*N*-diethyl 2-ethyl-6-methylbenzamide)chromium (**2**) (E = Me) by trapping with methyl iodide with 86% ee in 85% yield (entry 1). The optical purity was increased to >97% ee by a single recrystallization. The effects of other solvents and the presence of an additive, e.g., LiCl, were not observed to enhance the enantiomeric excess. The axial configuration of **2** (E = Me) was assigned as the (*R*)-configuration by comparison with the optical rotation of an authentic compound.[12] With other electrophiles, e.g., benzyl bromide or allyl bromide, the corresponding (*R*)-axial benzamide chromium complexes were obtained with comparable optical purity (entries 10 and 11). In this way, the enantiotopic deprotonation at the benzylic methyl of prochiral *N*,*N*-diethyl 2,6-dimethylbenzamide chromium complex (**1**) afforded the axially chiral benzamides with high optical purity.

Asymmetric Synthesis of Axially Chiral *N*-Pivaloyl Aniline Chromium Complexes. We further developed the kinetically discriminated lithiation for asymmetric synthesis of axially chiral *N*-methyl 2,6-disubstituted anilides. At first, the *N*-methyl-*N*-pivaloyl 2,6-dimethylaniline chromium complex (**14**) was examined for the enantiotopic lithiation (Scheme 2, Table 2). In analogy with the enantiotopic lithiation of benzamide chromium complex **1**, the chiral versions of LDA could discriminate the enantiotopic benzyl methyls of anilide chromium complex **14** for the asymmetric deprotonation, while the chiral lithium amides derived from *N*,*N*,*N*′,*N*′-tetraalkyl diamines resulted in a racemic compound after quenching with methyl iodide (entries 4−6). Since the chiral lithium amides of monoamines resulted in moderate optical purity for methyl iodide quenching (entries 1−3), we next examined the enantio-discriminated lithiation by using the bidentate chiral lithium amides, which could exist as five-membered chelated structures. The chiral lithium amide derived from (*S*)-2-(1-pyrrolidinylmethyl)pyrrolidine (**9**) increased the enantioselectivity, although the chemical yield was moderate (entry 7). 1-Phenyl-2-piperidinoethylamine derivatives **10** and **11** resulted in higher yields (entries 8 and 9). The optical purity was determined by HPLC with chiralpack AS. Fortunately, the use of 4-methylpiperazinylethylamine derivative **13** containing an additional nitrogen atom increased substantially both the enantioselectivity and the chemical yield. Thus, treatment of **14** 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 **15** (E = Me) in 90% yield with 95% ee (entry 10). The absolute stereochemistry of (−)-**15a** (E = Me) was determined to be of the (S_p,R_{ax})-configuration by X-ray crystallography.[15] The pivaloyl group is exo to the tricarbonylchromium fragment, and the amide oxygen is trans to the *N*-methyl group. Similarly, other electrophiles such as benzyl-, allyl bromides, or carbonyl compounds could be easily trapped to give the corresponding (*R*)-axially chiral anilide chromium complexes **15** via lithiation at the $CH_3{}^b$ group among two benzyl methyls with high enantioselectivity (entries 13−19). Interestingly, the prochiral anilide **14** gave the (*R*)-axially chiral

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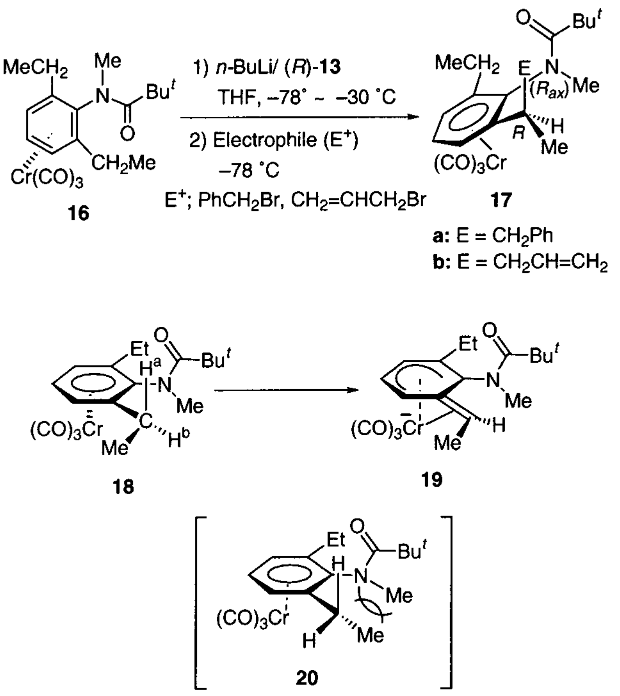
[15] Crystal data for optically active compound **15a** (E = Me): empirical formula = $C_{18}H_{23}NO_4Cr$, M = 369.38, yellow prismatic, monoclinic, space group, $P2_1$ (#4), a = 7.880(1), b = 11.640(2), c = 10.206(1) Å, β = 91.33(1)°, V = 935.9(2) Å^3, Z = 2, D_c = 1.311 g/cm^3, $F(000)$ = 388.00, μ(Mo Kα) = 6.31 cm^{-1}, $R_1(R_W)$ = 0.031 (0.037). A total of 2415 data of reflections were collected (using w scans with 22.1 < 2θ < 25.0°), of which 2259 were unique (R_{int} = 0.016). Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with Cambridge Crystallographic Data Center as supplementary publication no. CCDC-170561 for **15a** (E = Me), CCDC-170560 for **17a** (E = CH_2Ph), and CCDC-170559 for **21b**.

anilide chromium complexes **15** via lithiation at the CH$_3^b$ group with the chiral lithium amides derived from (*R*,*R*)-**3**, (*R*)-**4**, or (*S*)-**9** after quenching with electrophiles, while tricarbonylchromium-complexed *N*,*N*-diethyl 2,6-dimethylbenzamide (**1**) was enantioselectively lithiated at the *alternative* benzyl CH$_3^a$ group with the same absolute chiral lithium amides as shown in Table 1. The highly enantioselective deprotonation at the differentiated benzyl methyl between the tricarbonylchromium-complexed *N*,*N*-diethyl 2,6-dimethylbenzamide **1** and 2,6-dimethyl anilide **14** with the identical chiral lithium amide would be contributed to the conformation of C(=)O–NR to the tricarbonylchromium fragment. In the prochiral chromium complex **14**, the amido carbonyl oxygen is oriented trans to the *N*-methyl group and is oriented anti to the tricarbonylchromium fragment due to a steric effect; as a result, it closely faces the chromium-complexed phenyl ring. The predominant existence as the trans rotamer between the *N*-methyl and amide carbonyl oxygen of **14** was also observed in ^{1}H NMR.[16] On the other hand, the amide carbonyl oxygen of the *N*,*N*-diethyl 2,6-dimethylbenzamide chromium complex (**1**) was found to be oriented syn to the tricarbonylchromium fragment. At the present time, the precise mechanism for the enantiotopic lithiation at the differentiated benzylic position between tricarbonylchromium-complexed benzamide **1** and anilide **14** is not clear, but the lithiation would be initiated by a coordination of the chiral lithium atom with the amido carbonyl.

We further investigated the enantiotopic lithiation at the discriminated benzyl positions of prochiral 2,6-diethyaniline chromium complex **16**. The treatment of **16** with the lithium amide of **13** followed by quenching with benzyl bromide or allyl bromide gave product **17** in good yields (Scheme 3). Although the obtained chromium complexes **17** have an additional stereocenter at the newly created benzylic position, only the single diastereomer **17** was obtained. The benzylic stereocenter of **17a** was found to be of the (*R*)-configuration by X-ray crystallography.[17] The formation of **17** as a single isomer could be explained as follows. The chiral lithium amide of **13** would selectively deprotonate a proton H^a in the sterically favored conformation **18** from the exo side to generate a configurationally stable carbanion intermediate, which implies the exo cyclic double-bond character of **19** due to an overlap of the p-orbital of the benzylic carbon with the d-orbital of the chromium.[18] Thus, rotation of the C$_\alpha$–C$_{ipso}$ bond would be inhibited, and the electrophiles attack from the opposite face to the chromium fragment to give **17** as a single diastereomer.

Asymmetric Synthesis of Axially Chiral *N*-Benzoyl Aniline Chromium Complexes. The enantiotopic lithiation of the corresponding *N*-aroyl 2,6-dimethylaniline chromium complex **21** instead of the *N*-pivaloyl group was further examined (Scheme 4, Table 3). With *N*-benzoyl aniline complex **21a**, the chiral versions of LDA could also discriminate the enantiotopic benzyl methyls. The chiral lithium amides derived from (*R*,*R*)-bis-α-phenylethylamine (**3**) or the bidentate chiral lithium

Scheme 3



Scheme 4

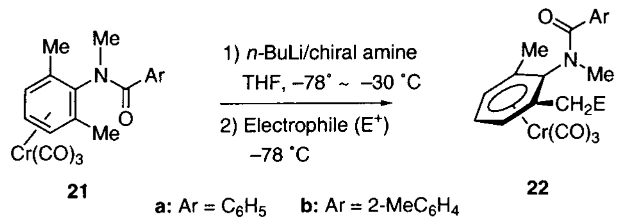


Table 3. Enantiotopic Lithiation of Prochiral Tricarbonyl(*N*-methyl-*N*-aroyl 2,6-dimethylaniline)chromium (21)

entry	complex **21**	chiral amine	E$^+$ (electrophile)	% yield **22**	% ee **22**	[α]$_D$ (CHCl$_3$)
1	**21a**	**3**	$C_6H_5CH_2Br$	26	35	
2	**21a**	**4**	$C_6H_5CH_2Br$	63	67	
3	**21a**	**9**	$C_6H_5CH_2Br$	41	22	
4	**21a**	**13**	$C_6H_5CH_2Br$	25	36	
5	**21b**	**3**	MeI	48	99	−32.0
6	**21b**	**3**	$C_6H_5CH_2Br$	58	94	−14.5
7	**21b**	**4**	$C_6H_5CH_2Br$	62	81	
8	**21b**	**9**	$C_6H_5CH_2Br$	76	61	
9	**21b**	**13**	$C_6H_5CH_2Br$	48	8	
10	**21b**	**3**	$CH_2{=}CHCH_2Br$	52	94	−26.5
11	**21b**	**3**	cyclohexanone	67	91	−58.9

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(16) NOE (5.7%) between *N*-Me and Me of Bu^t groups in *N*-pivaloyl aniline chromium complex **14a** was observed. The ratio of trans and cis rotamers was >12:1. The *N*-methyl singlet and three methyls of the *tert*-butyl group of the trans rotamer were observed at a lower field than those of the cis rotamer: trans rotamer δ 1.37 (C*Me*$_3$), 3.55 (*NMe*) ppm; cis rotamer δ 1.06, 3.33 ppm. The predominant trans rotamer in the chromium-complexed anilides is in sharp contrast to the tricarbonylchromium-free *N*-methyl anilides; see: refs 3e and 21.

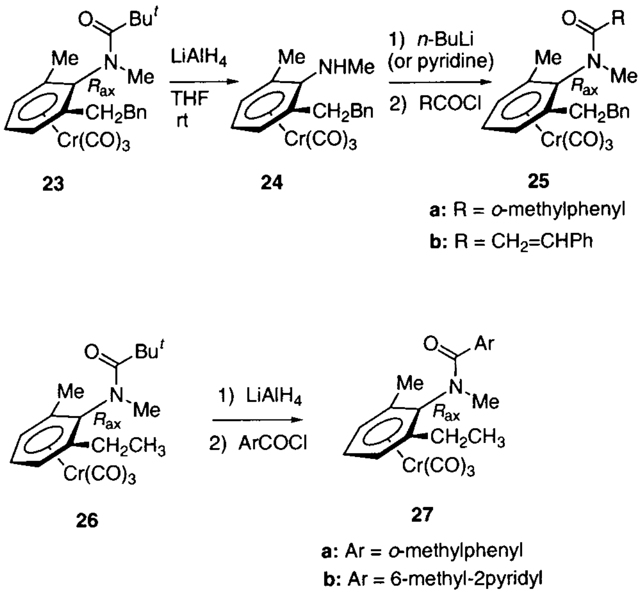
(17) Crystal data for racemic **17a** (E = CH$_2$Ph): empirical formula = $C_{26}H_{31}NO_4Cr$, M = 473.53, yellow prismatic, monoclinic, space group, $P2_1/c$ (#14), a = 10.629(4), b = 21.393(2), c = 10.722(1) Å, β = 92.86(1)°, V = 2435(1) Å^3, Z = 4, D_c = 1.292 g/cm^3, $F(000)$ = 1000.00, μ(Mo Kα) = 5.01 cm^{-1}, $R_1(R_W)$ = 0.045 (0.034). A total of 5863 data of reflections were collected (using w scans with 25.3 < 2θ < 29.5°), of which 5575 were unique (R_{int} = 0.046).

(18) (a) Collman, J. P.; Hegedus, L. S.; Norton, J. R.; Finke, R. G. *Principles and Applications of Organotransition Metal Chemistry*; University Science Books: Mill Valley, CA, 1987; p 921. (b) Solladié-Cavallo In *Advances in Metal-Organic Chemistry*; Liebeskind, L. S., Ed.; JAI Press: Greenwich, CT, 1989; Vol. 1, p 99. (c) Davies, S. G.; Coote, S. J.; Goodfellow, C. L. In *Advances in Metal-Organic Chemistry*; Liebeskind, L. S., Ed.; JAI Press: Greenwich, CT, 1991: Vol. 2, p 1. (d) Uemura, M. In *Advances in Metal-Organic Chemistry*; Liebeskind, L. S., Ed.; JAI Press: Greenwich, CT, 1991: Vol. 2, p 195. (e) Davies, S. G.; McCarthy, T. M. In *Comprehensive Organometallic Chemistry II*; Wilkinsons, G., Stone, P. G. A., Abel, E. W., Eds.; Pergamon Press: Oxford, 1995; Vol. 12, p 1039.

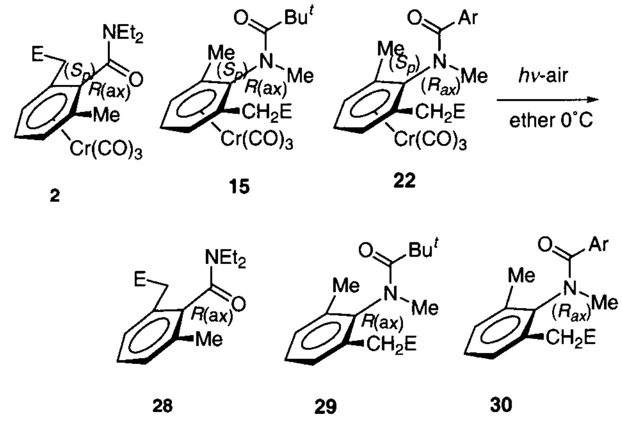
amides of **6** and **13** resulted in moderate enantioselectivity and low chemical yield. The lithium amide of (*R*)-α-phenylethyl isopropylamine (**4**) resulted in higher enantioselectivity and chemical yield (entry 2), but the enantiomeric excess (67% ee) was still unsatisfactory. These moderate enantioselectivities would be attributed to an equilibration between the trans and cis rotamers of the *N*-methyl group with the amide carbonyl oxygen in a solution. Indeed, the ^{1}H NMR spectrum of **21a** indicates a pair of signals in a 1:1 ratio.[19] Therefore, we next turned our attention to the corresponding *N*-*o*-methylbenzoyl analogue **21b** for a shift to a single rotamer by introduction of a methyl group at the ortho position of the *N*-benzoyl arene ring. As expected, the ^{1}H NMR spectrum of the *o*-methyl-substituted anilide complex **21b** shows predominantly one rotamer (>12:1 ratio of trans and cis rotamers).[19] The amido carbonyl oxygen of **21b** was also found to be oriented trans to the *N*-methyl group by X-ray crystallography.[20] As expected, high enantioselectivity was obtained in the discriminated lithiation/substitution of **21b** by treatment with chiral lithium amides. Especially, lithium (*R,R*)-bis-α-phenylethylamide resulted in superior enantioselectivity by quenching with some electrophiles (entries 5, 6, 10, and 11). In this way, the chiral lithium amide for the achievement of high enantiotopic lithiation was largely dependent upon the substituent of the *N*-acyl part of the chromium-complexed *N*-methyl anilines. With *N*-pivaloyl 2,6-dimethylaniline chromium complex **14**, the chiral lithium amide derived from 1-phenyl-2(4′-methylpiperazinyl)ethylamine derivative **13** gave excellent selectivity for the discriminated lithiation at the benzylic methyls, while *N*-*o*-methylbenzoyl complex **21b** was lithiated in high enantioselectivity with the chiral lithium amide of **3**.

The absolute stereochemistry of the anilide chromium complex **22b** obtained by the enantiotopic lithiation of **21b** was determined by comparison with the *N*-*o*-benzoyl aniline complex derived from stereochemically defined (S_p,R_{ax})-*N*-pivaloyl aniline chromium complex **23** (Scheme 5). Reductive cleavage of **23** ([α]$^{30}_{D}$ −19.5, 97% ee) with $LiAlH_4$ gave the planar chiral *N*-methyl aniline chromium complex **24** in 58% yield. The chromium complex **24** was converted to *N*-methyl-*N*-*o*-methylbenzoyl aniline complex **25a** ([α]$^{24}_{D}$ −15.0), which was identical with **22b** (E = Me) derived from **21b** in all respects of the spectra data, including optical rotation. Therefore, the prochiral tricarbonylchromium-complexed *N*-methyl-*N*-*o*-methylbenzoyl 2,6-dimethylaniline (**21b**) was selectively lithiated at the benzyl Me^b by treatment with the chiral lithium amide of **3**. Furthermore, *N*-acylation of the chromium complex **24** took place stereoselectively to give a single anilide complex with an induction of axial chirality. This stereoselective N-acylation could be applied to the preparation of other axially chiral *N*-acyl complexes **25b** and **27** having a heteroaromatic or α,*β*-unsaturated amide in good yield. These axially chiral anilide complexes would be further utilized as a chiral auxiliary or a chiral ligand in an asymmetric reaction.

Scheme 5



Scheme 6



Chromium-Free Axially Chiral Benzamides and Anilides. Since we have prepared the tricarbonylchromium-complexed axially chiral benzamides and anilides with high optical purity, our attention was next focused on the chromium-free axially chiral nonbiaryl compounds (Scheme 6, Table 4). An ether solution of (+)-*N,N*-diethyl 2-ethyl-6-methylbenzamide chromium complex (**2**) (E = Me) was exposed to sunlight at 0 °C until the yellow color disappeared. The optically active *N,N*-diethyl 2-ethyl-6-methylbenzamide (**28**) (E = Me, [α]$^{26}_{D}$ −13.0) was obtained. The optical purity of freshly obtained axially chiral *N,N*-diethyl 2-ethyl-6-methylbenzamide (**28**) (E = Me) was determined by ^{1}H NMR spectroscopy in the presence of a chiral shift reagent, Eu(tfc)$_3$, and was nearly identical with that of the chromium-complexed benzamide **2** (E = Me). However, the optical rotation of the chromium-free axial benzamide decreased slowly on standing at room temperature. Thus, the optical purity of the axially chiral *N,N*-diethyl 2-ethyl-6-methylbenzamide **28** (E = Me) decreased to 70% ee after 24 h. However, the axial chiral benzamides having sterically bulky substituents at the ortho position were found to be stable against the axial isomerization at room temperature.[12] Similarly, the axially chiral *N*-methyl anilides

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(19) The *N*-Me signal of **21a** appeared at 3.36 and 3.49 ppm as 1:1 ratio, while the corresponding methyl signal of **21b** appeared at 3.21 ppm as a single rotamer.

(20) Crystal data for **21b**: empirical formula = $C_{20}H_{19}NO_4Cr$, M = 389.37, yellow prismatic, monoclinic, space group, $P2_1/n$ (#14), a = 12.716(3), b = 11.153(2), c = 14.768(3) Å, β = 113.90(1)°, V = 1914.9(6) Å^3, Z = 4, D_c = 1.351 g/cm^3, F(000) = 808.00, μ(Mo Kα) = 6.21 cm^{-1}, $R_1(R_W)$ = 0.086 (0.155). A total of 4798 data of reflections were collected (using w scans with $29.5 < 2\theta < 30.0°$), of which 4395 were unique (R_{int} = 0.016).

Table 4. Preparation of Axially Chiral Benzamides and Anilides by Photo-Oxidation

entry	**28**, **29**, **30**	% yield	$[\alpha]_D$[c]	% ee[d]	cis/trans **29**, **30**
1[a]	**28** (E = Me)	90	−13.0	94	
2[b]	**28** (E = CHMe$_2$)	93	−9.8	99	
3	**29** (E = Me)	98	−4.9	95	6/1
4	**29** (E = CH$_2$Ph)	95	−11.9	97[e]	6/1
5	**29** (E = CH$_2$CH═CH$_2$)	96	−9.4	92	4/1
6	**29** (E = CH$_2$C≡CMe$_{)}$	95	−27.3	96	5/1
7	**29** (E = CH$_2$C≡CPh$_{)}$	95	−47.1	96	4/1
8	**29** (E = C(OH)Ph$_{2)}$	96	+78.1	96	1/2.5
9	**29** (E = 1-cyclohexanol)	96	+9.0	96	1/1.5
10	**29** (E = COPh)	94	−40.9	97	2/1
11	**30** (E = Me)	97	+2.3	97	2/1
12	**30** (E = CH$_2$Ph)	98	+10.8	98	2.5/1
13	**30** (E = 1-cyclohexanol)	96	+16.8	96	6/1

[a] Starting material **2** (E = Me) with >97% ee was used. [b] See ref 12. [c] Optical rotations were measured in CHCl$_3$. [d] Optical purity was determined by ^{1}H NMR in the presence of Eu(tfc)$_3$ unless otherwise noted. [e] Optical purity was determined by HPLC with a chiralpak AS column.

were obtained without a decrease in the optical purity by an oxidative demetalation of **15** and **22**. No axial bond rotation of the chromium-free chiral anilides was observed after standing at room temperature for 24 h. The chromium-free axially chiral *N*-methyl-*N*-acyl anilines **29** and **30** exist as an equilibrium of trans and cis rotamers between the *N*-methyl and the amido carbonyl oxygen group in a CDCl$_3$ solution. The cis rotamer preference is well-known in both the crystalline state and solution for *N*-methyl anilides.[3e,21] The *N*-methyl signal for the major rotamer of **29** (R = Me) appeared at 3.11 ppm, while the corresponding signal for the minor rotamer was observed at 3.34 ppm. Since the downfield *N*-Me singlet of the *N*-methyl-*N*-acyl anilides was assigned to the trans rotamers,[3e] the major rotamer of **29** could be assigned to the cis conformer. Furthermore, the major cis rotamers of **29** (R = Me, CH$_2$Ph, CH$_2$C≡CMe, CH$_2$C≡CPh) were observed by 0.40−0.45 ppm high-field shifts of three methyls of the *tert*-butyl group compared with those of the corresponding minor rotamer. These shifts are attributed to the cis conformation, where the *tert*-butyl group is located closely facing the phenyl ring plane. Similarly, the axially chiral *N*-methyl-*N*-*o*-methylbenzoyl anilines **30** were found to exist predominantly as the cis rotamer. However, the trans rotamer is the predominant conformer for the axially chiral anilides **29** possessing a hydroxy group on the side chain, probably due to an intramolecular hydrogen bond with the amido carbonyl (entries 8 and 9).

In conclusion, we have developed an asymmetric synthesis of the axially chiral *N*,*N*-diethyl benzamides and *N*-methyl anilides by desymmetrization of prochiral tricarbonylchromium complexes of *N*,*N*′-diethyl 2,6-dimethylbenzamide and *N*-methyl-*N*-acyl 2,6-dimethylanilide via enantioselective deprotonation at the benzylic methyls by treatment with chiral lithium amides followed by electrophilic quenching with high optical purity. We are now investigating asymmetric reactions such as alkylation, conjugate addition, and catalytic allylic alkylation utilizing these axially chiral anilides.

Experimental Section

All manipulations involving organometallics were carried out under an atmosphere of nitrogen or argon with inert gas/vacuum double-manifold techniques. All melting points were determined on a Yanagimoto MPJ-2 micro melting point apparatus and were uncorrected. ^{1}H NMR spectra were measured on a JEOL EX-270 apparatus. All NMR spectra were recorded in a CDCl$_3$ solvent with tetramethylsilane as an internal reference. IR spectra were determined on a JASCO A-100 spectrometer. Diethyl ether and tetrahydrofuran were distilled from sodium/benzophenone ketyl immediately before use. Methylene chloride was distilled over P$_2$O$_5$ before use. Optical rotations were measured on a JASCO DIP-370 automatic polarimeter at 589 nm (sodium D line) using a 0.5 dm cell.

Preparation of Tricarbonyl(*N*,*N*-diethyl 2,6-dimethylbenzamide)chromium (1). To a solution of tricarbonyl(*N*,*N*-diethyl 2-methylbenzamide)chromium[12] (982 mg, 3.0 mmol) and TMEDA (418 mg, 0.75 mmol) in dry THF (30 mL) was added *s*-BuLi (1.0 M in cyclohexane, 3.6 mL, 3.6 mmol) at −78 °C under argon, and the resulting mixture was stirred for 1 h. Methyl iodide (1.28 g, 9.0 mmol) was added to the reaction mixture at −78 °C, and the mixture was warmed to 0 °C over 2 h. The reaction mixture was quenched with saturated aqueous NH$_4$Cl and extracted with ether. The extract was washed with brine, dried over MgSO$_4$, and evaporated in vacuo. The residue was purified by silica gel column chromatography (hexane/ethyl acetate; 2/1) to give 768 mg (75%) of **1**: mp 153 °C; ^{1}H NMR (CDCl$_3$) δ 1.09 (t, 3H, J = 7.3 Hz), 1.22 (t, 3H, J = 7.3 Hz), 2.20 (s, 6H), 3.24 (q, 2H, J = 7.3 Hz), 3.53 (q, 2H, J = 7.3 Hz), 4.93 (d, 2H, J = 6.3 Hz), 5.36 (t, 1H, J = 6.3 Hz); IR (CHCl$_3$) 1970, 1890, 1630 cm^{-1}. Anal. Calcd for C$_{16}$H$_{19}$NO$_4$Cr: C, 56.31; H, 5.61; N, 4.10. Found: C, 56.53; H, 5.35; N, 3.85.

Preparation of Tricarbonyl(*N*-methyl-*N*-pivaloyl 2,6-dimethylaniline)chromium (14a). To a solution of tricarbonyl(*N*-methyl 2,6-dimethylaniline)chromium (1.0 g, 3.7 mmol) in dry THF (30 mL) was added *n*-BuLi (1.6 M in hexane, 3.5 mL, 5.52 mmol) at −78 °C under argon, and the resulting mixture was stirred for 1 h. Pivaloyl chloride (7.4 mmol, 0.9 g) was added to the reaction mixture at −78 °C, and the mixture was warmed to room temperature over 2 h. The reaction mixture was quenched with saturated aqueous NH$_4$Cl and extracted with ether. The extract was washed with brine, dried over MgSO$_4$, and evaporated in vacuo. The residue was purified by silica gel column chromatography (hexane/ethyl acetate; 3/1) to give 1.0 g (76%) of **14a**: mp 178 °C; ^{1}H NMR (CDCl$_3$) δ 1.37 (s, 9H), 2.09 (s, 6H), 3.55 (s, 3H), 4.95 (d, 2H, J = 6.3 Hz), 5.54 (t, 1H, J = 6.3 Hz); IR (CHCl$_3$) 1970, 1880, 1630 cm^{-1}. Anal. Calcd for C$_{17}$H$_{21}$NO$_4$Cr: C, 57.46; H, 5.96; N, 3.94. Found: C, 57.72; H, 5.89; N, 3.97.

Tricarbonyl(*N*-methyl-*N*-*o*-methylbenzoyl 2,6-dimethylaniline)chromium (21b): mp 140 °C dec; ^{1}H NMR (CDCl$_3$) δ 2.30 (s, 6H), 2.36 (s, 3H), 3.21 (s, 3H), 5.04 (d, 2H, J = 6.3 Hz), 5.59 (t, 1H, J = 6.3 Hz), 7.15−7.37 (m, 4H); IR (CHCl$_3$) 1970, 1880, 1640, 1410 cm^{-1}. Anal. Calcd for C$_{20}$H$_{19}$NO$_4$Cr: C, 61.69; H, 4.92; N, 3.60. Found: C, 61.95; H, 4.65; N, 3.35.

Asymmetric Lithiation of Prochiral Arene Chromium Complexes with Chiral Lithium Amide. The typical procedure is as follows. To a solution of (*R*,*R*)-bis-α-phenylethylamine (**3**) (101 mg, 0.45 mmol) in dry THF (1.5 mL) was added *n*-BuLi (1.6 M in hexane, 0.23 mL, 0.36 mmol) at −78 °C under argon, and the mixture was stirred for 30 min. To the mixture was added a solution of *N*,*N*-diethyl 2,6-dimethylbenzamide chromium complex (**1**) (102 mg, 0.30 mmol) in THF (1.5 mL) at −78 °C, and the mixture was warmed to −30 °C over 1 h. The reaction mixture was again cooled to −78 °C, and then a solution of MeI (90 mg, 0.60 mmol) in THF (0.5 mL) was added to the reaction mixture. The mixture was warmed to −30 °C, quenched with saturated aqueous NH$_4$Cl, and extracted with

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[21] (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.; Kagechika, H.; Fujiwara, Y.; Itoh, M.; Yamaguchi, K.; Shudo, K. *J. Am. Chem. Soc.* **1991**, *113*, 2833. (d) Saito, S.; Toriumi, Y.; Tomioka, N.; Itai, A. *J. Org. Chem.* **1995**, *60*, 4715. (e) Azumaya, I.; Yamaguchi, K.; Okamoto, I.; Kagechika, H.; Shudo, K. *J. Am. Chem. Soc.* **1995**, *117*, 9083.

ether. The organic layer was washed with brine, dried over $MgSO_4$, and evaporated under reduced pressure. The residue was purified by silica gel column chromatography to give 90 mg (85%) of (+)-*N*,*N*-diethyl 2-ethyl-6-methylbenzamide chromium complex **2**: mp 99 °C; $[\alpha]^{26}_{D}$ +27.0 (*c* 0.2, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.12 (t, 3H, *J* = 7.3 Hz), 1.21 (t, 3H, *J* = 7.3 Hz), 1.22 (t, 3H, *J* = 7.3 Hz), 2.20 (s, 3H), 2.46−2.64 (m, 2H), 3.22−3.29 (m, 2H), 3.50−3.59 (m, 2H), 4.96 (d, 1H, *J* = 6.3 Hz), 5.02 (d, 1H, *J* = 6.3 Hz), 5.37 (t, 1H, *J* = 6.3 Hz); IR ($CHCl_3$) 1970, 1890, 1630 cm^{-1}. Anal. Calcd for $C_{17}H_{21}NO_4Cr$: C, 57.46; H, 5.96; N, 3.94. Found: C, 57.30; H, 5.92; N, 3.93. The optical purity was determined to be 86% ee by chiral HPLC with a Chiralcell OJ-H column eluted with 1:1 hexane/2-propanol; flow rate, 0.5 mL/min; column temperature, 40 °C; UV detector, 254 nm; retention time, 13.5 and 17.2 min.

15a (E = Me): mp 108 °C; $[\alpha]^{30}_{D}$ −29.4 (*c* 1.8, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.16 (t, 3H, *J* = 7.6 Hz), 1.36 (s, 9H), 2.07 (s, 3H), 2.41 (dq, 1H, *J* = 15.0, 7.6 Hz), 2.44 (dq, 1H, *J* = 15.0, 7.6 Hz), 3.55 (s, 3H), 4.97 (d, 1H, *J* = 6.3 Hz), 4.98 (d, 1H, *J* = 6.3 Hz), 5.58 (t, 1H, *J* = 6.3 Hz); IR ($CHCl_3$) 1970, 1890, 1640 cm^{-1}. Anal. Calcd for $C_{18}H_{23}NO_4Cr$: C, 58.53; H, 6.28; N, 3.79. Found: C, 58.81; H, 6.37; N, 3.77. The enantiomeric excess was determined by chiral HPLC with a Chiralpak AS column eluted with 20:1 hexane/2-propanol; flow rate, 1 mL/min; column temperature, 40 °C; UV detector, 254 nm; retention time, 7.6 and 8.8 min.

15a (E = CH_2Ph): mp 118 °C; $[\alpha]^{31}_{D}$ −19.5 (*c* 2.1, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.37 (s, 9H), 2.09 (s, 3H), 2.48−2.91 (m, 4H), 3.57 (s, 3H), 4.75 (d, 1H, *J* = 6.3 Hz), 4.96 (d, 1H, *J* = 6.3 Hz), 5.50 (t, 1H, *J* = 6.3 Hz), 7.15−7.31 (m, 5H); IR ($CHCl_3$) 1970, 1890, 1640 cm^{-1}. Anal. Calcd for $C_{24}H_{27}NO_4Cr$: C, 64.71; H, 6.11; N, 3.14. Found: C, 64.68; H, 6.14; N, 3.10. Retention time, 8.0 and 10.9 min.

15b (E = Me): mp 114 °C; $[\alpha]^{25}_{D}$ −25.0 (*c* 0.2, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.14 (t, 3H, *J* = 7.3 Hz), 1.37 (s, 9H), 1.50 (t, 3H, *J* = 7.3 Hz), 2.06 (s, 3H), 2.29−2.47 (m, 2H), 3.79−4.00 (m, 2H), 5.00 (d, 1H, *J* = 6.3 Hz), 5.02 (d, 1H, *J* = 6.3 Hz), 5.62 (t, 1H, *J* = 6.3 Hz); IR ($CHCl_3$) 1970, 1880, 1640 cm^{-1}. Anal. Calcd for $C_{19}H_{25}NO_4Cr$: C, 59.52; H, 6.57; N, 3.65. Found: C, 59.76; H, 6.29; N, 3.40. The enantiomeric excess was determined by chiral HPLC with a Chiralpak AS column eluted with 40:1 hexane/2-propanol; flow rate, 0.5 mL/min; column temperature, 40 °C; UV detector, 254 nm; retention time, 15.7 and 17.1 min.

15c (E = Me): $[\alpha]^{22}_{D}$ −18.2 (*c* 1.7, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.12 (t, 3H, *J* = 7.7 Hz), 1.38 (s, 9H), 2.13 (s, 3H), 2.36−2.58 (m, 2H), 3.39 (s, 3H), 3.61−3.74 (m, 4H), 4.94 (d, 2H, *J* = 6.3 Hz), 5.09 (d, 1H, *J* = 9.9 Hz), 5.24 (d, 1H, *J* = 9.9 Hz), 5.63 (t, 1H, *J* = 6.3 Hz); IR ($CHCl_3$) 1970, 1880, 1640 cm^{-1}; MS (relative intensity) *m*/*z* 443 (M^+, 14), 359 (100), 301 (31), 285 (36); HRMS calcd for $C_{21}H_{29}NO_6Cr$ 443.1400, found 443.1405; retention time, 5.2 and 5.8 min.

17a: mp 154 °C; $[\alpha]^{24}_{D}$ −9.9 (*c* 2.2, EtOH); ^1H NMR ($CDCl_3$) δ 1.23 (t, 3H, *J* = 7.3 Hz), 1.24 (d, 3H, *J* = 6.9 Hz), 1.40 (s, 9H), 2.38−2.51 (m, 3H), 2.82−3.00 (m, 2H), 3.60 (s, 3H), 4.86 (d, 1H, *J* = 6.3 Hz), 5.10 (d, 1H, *J* = 6.3 Hz), 5.55 (t, 1H, *J* = 6.3 Hz), 7.05−7.27 (m, 5H); IR ($CHCl_3$) 1960, 1870, 1640 cm^{-1}. Anal. Calcd for $C_{26}H_{31}NO_4Cr$: C, 65.95; H, 6.60; N, 2.96. Found: C, 66.15; H, 6.52; N, 3.01. Chiralpak AS column eluted with 20:1 hexane/2-propanol; flow rate, 1 mL/min; column temperature, 40 °C; UV detector, 254 nm; retention time, 5.2 and 6.2 min.

22b (E = Me): mp 155 °C; $[\alpha]^{24}_{D}$ −32.0 (*c* 0.7, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.32 (t, 3H, *J* = 7.3 Hz), 2.30 (s, 3H), 2.40 (s, 3H), 2.51 (dq, 1H, *J* = 15.0, 7.3 Hz), 2.66 (dq, 1H, *J* = 15.0, 7.3 Hz), 3.21 (s, 3H), 5.06 (d, 2H *J* = 6.3 Hz), 5.64 (t, 1H, *J* = 6.3 Hz), 7.15−7.37 (m, 4H). IR ($CHCl_3$) 1960, 1880, 1640 cm^{-1}. Anal. Calcd for $C_{21}H_{21}NO_4Cr$: C, 62.53; H, 5.25; N, 3.47. Found: C, 62.80; H, 5.18; N, 3.26. retention time, 14.2 and 17.2 min.

Conversion of 23 to 25b: To a suspension of $LiAlH_4$ (55.0 mg, 1.45 mmol) in THF (3 mL) was added a solution of **23** (216 mg, 0.48 mmol) in THF (7 mL) at room temperature and stirred for 3 h. The reaction was quenched with aqueous 2 M NaOH (0.06 mL). After filtration and washing with ether, the organic layer was dried over $MgSO_4$ and evaporated in vacuo. The resulting yellow oil (101 mg) was dissolved in CH_2Cl_2 (5 mL). Then, (*E*)-cinnamoyl chloride (139 mg, 0.84 mmol) and pyridine (44.0 mg) were added to the above solution, and the reaction mixture was stirred at room temperature for 3 h. Usual workup and purification with SiO_2 column chromatography gave 83.0 mg (60%) of **25b**: mp 139 °C; $[\alpha]^{26}_{D}$ −91.0 (*c* 0.2 $CHCl_3$); ^1H NMR ($CDCl_3$) δ 2.17 (s, 3H), 2.64−2.92 (m, 4H), 3.49 (s, 3H), 4.84 (d, 1H, *J* = 6.2 Hz), 5.02 (d, 1H *J* = 6.2 Hz), 5.58 (t, 1H, *J* = 6.2 Hz), 6.30 (d, 1H, *J* = 15.0 Hz), 6.96−7.41 (m, 10H), 7.79 (d, 1H, *J* = 15.0 Hz); IR ($CHCl_3$) 1970, 1890, 1620, 1430 cm^{-1}. Anal. Calcd for $C_{28}H_{25}NO_4Cr$: C, 68.42; H, 5.13; N, 2.85. Found: C, 68.20; H, 5.09; N, 2.75.

Preparation of Chromium-Free Axially Chiral Benzamide and Anilides by Photo-Oxidative Demetalation. The typical reaction is as follows. A solution of **15** (E = Me) (260 mg, 0.71 mmol) in ether (5 mL) was exposed to sunlight at 0 °C until the yellow color disappeared. A precipitate was filtered and washed with ether. The ether layer was evaporated under reduced pressure to give 161 mg (98%) of **29** (E = Me) as a colorless crystal. Optical purity was determined by ^1H NMR spectrum in the presence of Eu(tfc)$_3$: mp 33 °C; $[\alpha]^{24}_{D}$ −4.9 (*c* 3.0 $CHCl_3$); ^1H NMR ($CDCl_3$) major cis rotamer δ 0.97 (s, 9H), 1.23 (t, 3H, *J* = 7.6 Hz), 2.24 (s, 3H), 2.58 (q, 2H, *J* = 7.6 Hz), 3.11 (s, 3H), 7.05−7.22 (m, 3H); minor trans rotamer δ 1.20 (t, 3H, *J* = 7.6 Hz), 1.42 (s, 9H), 2.15 (s, 3H), 2.58 (q, 2H, *J* = 7.6 Hz), 3.34 (s, 3H), 7.05−7.22 (m, 3H); IR ($CHCl_3$) 1610, 1420 cm^{-1}. Anal. Calcd for $C_{15}H_{23}NO$: C, 77.21; H, 9.93; N, 6.00. Found: C, 77.31; H, 10.10; N, 5.79.

29 (E = CH_2Ph): mp 43 °C; $[\alpha]^{30}_{D}$ −11.9 (*c* 1.3 $CHCl_3$); ^1H NMR ($CDCl_3$) major cis rotamer δ 0.96 (s, 9H), 2.23 (s, 3H), 2.86−2.93 (m, 4H), 3.00 (s, 3H), 7.10−7.30 (m, 8H); minor trans rotamer δ 1.41 (s, 9H), 2.16 (s, 3H), 2.86−2.93 (m, 4H), 3.25 (s, 3H), 7.10−7.30 (m, 8H); IR ($CHCl_3$) 1620, 1460 cm^{-1}. Anal. Calcd for $C_{21}H_{27}NO$: C, 81.51; H, 8.79; N, 4.53. Found: C, 81.80; H, 9.07; N, 4.42.

30 (E = Me): $[\alpha]^{21}_{D}$ +2.3 (*c* 2.1, $CHCl_3$); ^1H NMR ($CDCl_3$) major cis rotamer δ 1.31 (t, 3H, *J* = 7.6 Hz), 2.36 (s, 3H), 2.48 (s, 3H), 2.58−2.81 (m, 2H), 3.02 (s, 3H), 6.70−7.35 (m, 7H); minor trans rotamer δ 1.18 (t, 3H, *J* = 7.6 Hz), 2.25 (s, 3H), 2.49 (s, 3H), 2.58−2.81 (m, 2H), 3.33 (s, 3H), 6.70−7.35 (m, 7H); IR ($CHCl_3$) 1630, 1420 cm^{-1}; MS (relative intensity) *m*/*z* 267 (M^+, 100), 238 (28), 148 (33), 132 (41), 119 (89); HRMS calcd for $C_{18}H_{21}NO$ 267.1609, found 267.1616.

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Supporting Information Available: Experimental procedures and characterization data of products. This material is available free of charge via the Internet at http://pubs.acs.org.

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