Synthesis of axially chiral *N,N*-diethyl 2,6-disubstituted benzamides utilizing planar chiral (arene)chromium complexes

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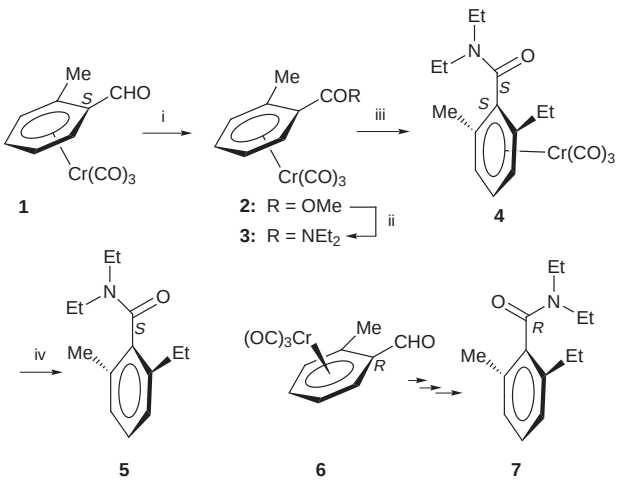
Axially chiral *N,N*-diethyl 2,6-disubstituted benzamides are prepared stereoselectively in an optically active form from a planar chiral (arene)chromium complex.

The tertiary arylamides with 2,6-disubstituents are a class of atropisomeric compounds[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 reported[3] the synthesis of *diastereomeric* atropisomers by reaction of *N,N*-dialkyl 2-lithio-1-naphthamides with the aldehydes, or reduction of *N,N*-dialkyl-2-acyl-1-naphthamides, or laterally lithiation of *N,N*-dialkyl 2-alkyl-1-naphthamides followed by eletrophilic quenching. The asymmetric deprotonation of *N,N*-dialkyl-1-naphthamides with a combination of butyllithium/(−)-sparteine followed by quenching with alkylhalides giving the axially chiral *N,N*-dialkyl 2-alkyl-1-naphthamides in an optically active form has been recently reported by Beak.[4] However, the optical purity of the axial aromatic carboxamides obtained by this asymmetric deprotonation with the chiral base is moderate. To the best of our knowledge, there is no previous report of asymmetric synthesis of *N,N*-dialkyl 2,6-disubstituted aromatic carboxamides in an *enantiomerically pure form*.

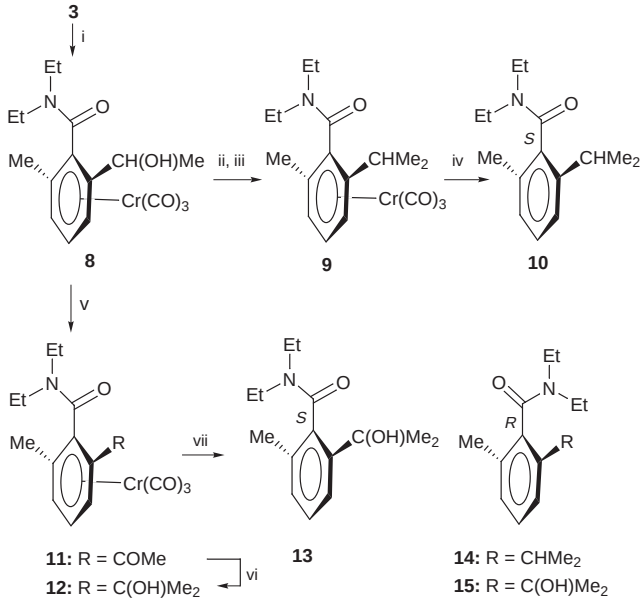
We wish to report the asymmetric synthesis of axially chiral *N,N*-dialkyl 2,6-disubstituted benzamides in an *enantiomerically pure form* by using a planar chiral arene chromium complex.

Both enantiomers of the axially chiral 2-ethyl-6-methylbenzamide were synthesized as shown in Scheme 1. Enantiomerically pure (−)-tricarbonyl(*o*-methylbenzaldehyde)chromium (**1**)[5] was oxidized to the corresponding (−)-methyl benzoate chromium complex **2** ($[\alpha]_D^{26}$ −100.0)† with active manganese dioxide and sodium cyanide in acetic acid and methanol in 85% yield. Conversion of the methyl ester to the corresponding (+)-*N,N*-diethylamide complex **3** ($[\alpha]_D^{26}$ +8.4) was achieved by treatment with lithium diethylamide in THF at −78 °C in 80% yield. Directed *ortho* lithiation[6] of *N,N*-diethyl *o*-methylbenzamide complex **3** with Bu^{t}Li in the presence of TMEDA followed by quenching with ethyl iodide gave the axially chiral (−)-(S_{Ar},S_{ax})[7]-tricarbonyl(*N,N*-diethyl 2-ethyl-6-methylbenzamide)chromium (**4**) ($[\alpha]_D^{25}$ −31.0) in 36% yield, along with 15% yield of tricarbonyl(*N,N*-diethyl 2-propylbenzamide)chromium *via* benzyl methyl lithiation. In this *ortho* lithiation, the *N,N*-diethyl benzamide complex **4** was obtained as a single axially chiral compound without formation of the corresponding (*R*)-axial isomer. The stereochemistry of the axially chiral benzamide complex **4** was determined by X-ray crystallography,‡ and the axial chirality was found to be the (*S*)-configuration in which the diethylamino part was oriented in an *anti*-conformation to the tricarbonylchromium moiety, and the amide carbonyl oxygen is in a *syn*-orientation. The X-ray crystal structure shows that the dihedral angle between the plane of the amide and the aryl ring is approximately perpendicular. The formation of **4** as the single axial isomer by electrophilic quenching of the *ortho*-lithiated intermediate may be attributed to the stereoelectronic repulsion between the tricarbonylchromium and diethylamino fragments. After producing the axially chiral *N,N*-diethyl 2-ethyl-6-methylbenzamide chromium complex **4**, we next investigated an oxidative demetalation giving a chromium free axially chiral *N,N*-diethyl 2-ethyl-6-methylbenzamide. Thus, a solution of (−)-**4** in ether was exposed to sunlight at 0 °C until the yellow color of the solution disappeared. The demetalation product, *N,N*-diethyl 2-ethyl-6-methylbenzamide (**5**) has a positive optical rotation value ($[\alpha]_D^{26}$ +14.0). Similarly, the corresponding axially chiral antipode (−)-*N,N*-diethyl 6-ethyl-2-methylbenzamide (**7**) ($[\alpha]_D^{26}$ −13.0) was obtained from the antipode (+)-tricarbonyl(2-methylbenzaldehyde)chromium (**6**)[5] by following the same reaction sequence. The optical purities of the axial *N,N*-diethyl 2-ethyl-6-methylbenzamides, **5** and **7**, were found to be ~94% ee.[8] However, the optical rotation values of these chromium free axial benzamides slowly decreased on standing at room temperature.

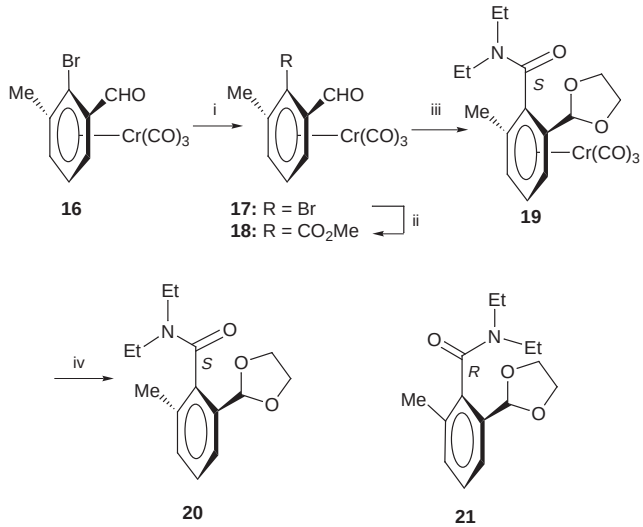


Scheme 1 i, MnO_2, NaCN, AcOH, MeOH, 85%; ii, $LiNEt_2$, THF, −78 °C, 80%; iii, Bu^{t}Li, TMEDA, THF, −78 °C, then EtI, 36%; iv, *hv*, O_2, diethyl ether, 0 °C, 90%.

Since the *N,N*-diethyl 2-ethyl-6-methylbenzamide underwent slow racemization at room temperature,[9] the sterically bulky substituent was next introduced at the *ortho*-position to inhibit the axial isomerization (Scheme 2). The *o*-lithiated intermediate derived from **3** was trapped with acetaldehyde to produce a diastereomeric mixture of **8** at the newly created benzylic center in a ratio of 54 : 46 in 44% yield. The diastereomeric mixture **8** was acetylated, and then treated with triethylaluminium to give tricarbonyl(*N,N*-diethyl 2-methyl-6-isopropylbenzamide)chromium (**9**) ($[\alpha]_D^{24}$ −54.0) *via* a tricarbonylchromium-stabilized benzylic carbocation intermediate[10] in 60% yield. Alternatively, the hydroxide of diastereoisomeric complex **8** was oxidized with acetic anhydride and DMSO to afford acetophenone complex **11** which was further converted to tertiary-alcohol complex **12** ($[\alpha]_D^{25}$ +37.0) by treatment with $MeCeCl_2$



Scheme 2 i, Bu^{s}Li, TMEDA, THF, −78 °C, then MeCHO, 44%; ii, Ac_2O, pyridine, DMAP; iii, Me_3Al, CH_2Cl_2, −78 °C, 60% from **8**; iv, *hν*, O_2, diethyl ether, 0 °C, 98%; v, DMSO, Ac_2O, 88%; vi, $MeCeCl_2$, THF, −78 °C, 94%; vii, *hν*, O_2, diethyl ether, 0 °C, 90%.



Scheme 3 i, $HO(CH_2)_2OH$, *p*-TsOH, MeCN, $MgSO_4$, 84%; ii, Bu^{n}Li, TMEDA, diethyl ether, then ClCOOMe, 83%; iii, $LiNEt_2$, THF, −78 °C, 60%; iv, *hν*, O_2, diethyl ether, 0 °C, 90%.

in 74% overall yield. These tricarbonylchromium-complexed axially chiral benzamides **9** and **12** gave the (*S*)-axially chiral benzamides **10** ($[\alpha]_D^{23}$ +9.8) and **13** ($[\alpha]_D^{27}$ +63.2) in >99% ee[8] by oxidative demetalation, in which the optical purities of these compounds did not change after prolong standing (36 h) at room temperature. On the other hand, the corresponding (*R*)-axially chiral 2-methyl-6-substituted benzamides **14** ($[\alpha]_D^{23}$ −9.8) and **15** ($[\alpha]_D^{27}$ −63.2) with its optical antipode were prepared from **6** by the same reaction sequence. Thus, axially chiral *N*,*N*-diethyl 2,6-disubstituted benzamides were stereoselectively prepared in enantiomerically pure form by *ortho* lithiation of the planar chiral (benzamide)chromium complex.

Furthermore, the enantiomerically pure axially chiral *N*,*N*-diethyl 2,6-disubstituted benzamide was also stereoselectively prepared by conversion of the methyl ester of planar chiral tricarbonyl(methyl 2,6-disubstituted benzoate)chromium to the diethylamide group as follows (Scheme 3). Thus, the enantiomerically pure (−)-tricarbonyl(2-bromo-3-methylbenzaldehyde)tricarbonylchromium (**16**) ($[\alpha]_D^{27}$ −752.6) was converted to the corresponding tricarbonylchromium complex of methyl 2,6-disubstituted benzoate **18** ($[\alpha]_D^{27}$ −10.4) by usual method. Complex **18** was treated with lithium diethylamide at −78 °C in THF to produce stereoselectively (−)-*N*,*N*-diethyl benzamide **19** ($[\alpha]_D^{25}$ −75.2) with (*S*)-axial configuration as a single isomer in which the stereochemistry was determined by X-ray crystallography.‡ No diastereoisomeric (*R*)-axial benzamide chromium complex was obtained in this reaction. It is reasonable to assume that the sterically bulky diethylamino group approached from the *exo*-side to the tricarbonylchromium moiety. Complex **19** was exposed to sunlight to produce the enantiomerically pure[8] axially chiral benzamide **20** ($[\alpha]_D^{27}$ +33.7). The corresponding (−)-(*R*)-axial benzamide **21** ($[\alpha]_D^{27}$ −33.2) was also prepared from the antipode (+)-(3-methyl-2-bromobenzaldehyde)tricarbonylchromium by the same reaction sequence. This axially chiral compound **20** is stable against axial isomerization at room temperature.

In conclusion, we have demonstrated that axially chiral *N*,*N*-diethyl 2,6-disubstituted benzamides can be prepared with high optical purities by using planar chiral tricarbonyl(arene)chromium complexes.

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Notes and references

† All optical rotation values were measured in $CHCl_3$ solution.

‡ *Crystal data* for racemic **4**: empirical formula $C_{17}H_{21}NO_4Cr$, M = 355.35, yellow prismatic, monoclinic, space group $P2_1$, a = 7.363(1), b = 17.4258(7), c = 13.8120(9) Å, β = 96.490(8)°, V = 1760.7(3) Å^3, Z = 4, D_c = 1.340 g cm^{-3}, $F(000)$ = 744.00, μ(CuKα) = 55.12 cm^{-1}, $R(R_W)$ = 0.041 (0.058). A total of 2661 data were collected (using ω scans with 58.58 < 2θ < 59.87°), of which 2443 were unique (R_{int} = 0.014). For racemic **19**: empirical formula $C_{18}H_{21}NO_6Cr$, M = 399.36, yellow prismatic, monoclinic, space group $P2_1/n$, a = 7.487(2), b = 19.806(1), c = 12.905(2) Å, β = 104.93(2)°, V = 1849.0(6) Å^3, Z = 4, D_c = 1.435 g cm^{-3}, $F(000)$ = 832.00, μ(MoKα) = 6.52 cm^{-1}, $R(R_W)$ = 0.039 (0.052), A total of 4559 data were collected (using ω scans with 29.64 < 2θ < 30.00°), of which 4246 were unique (R_{int} = 0.029). CCDC 182/1037.

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5 Enantiomerically pure compound was obtained by optical resolution of diastereomers obtained from L-valinol; see S. G. Davies and C. L. Goodfellow, *J. Chem. Soc., Perkin Trans. 1*, 1990, 393.

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7 First symbol *S* indicates the configuration of the tricarbonylchromium-complexed arene carbon substituted by the diethylamido group, the second *S* shows the axial chirality.

8 The optical purities of axial chiral benzamides were determined by ^{1}H NMR spectroscopy in the presence of chiral shift reagent, Eu(tfc)$_3$.

9 The optical purity of compound **5** decreased with time of standing at room temperature; 86% ee after 6 h, 70% ee after 24 h.

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