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Scandium Triflate–Promoted Addition of Organozinc Reagents to Benzaldiminetricarbonylchromium Derivatives

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Abstract: The reaction of benzaldiminetricarbonylchromium derivatives with organozinc reagents in the presence of scandium triflate afforded a single diastereomer of the corresponding amine complex exclusively. Even in the case of benzaldiminetricarbonylchromium having an *m*-substituent of the aromatic ring, one diastereomer was obtained using the *o*-TMS-protected chromium complex. The TMS group and the chromium moiety were easily removed and the benzyl group was deprotected using HOOH and Pd to afford the corresponding amine.

Keywords: imines, organozinc reagents, stereocontrol

Stereoselective nucleophilic addition to benzaldiminetricarbonylchromium derivatives that have a planar chiral moiety[1–3] is an important transformation for constitiution of chiral amines, because the bulkiness of the tricarbonylchromium moiety plays an important role promoting the reaction with quite high facial selectivities, and the tricarbonylchromium moiety is easily removed by air and sunlight. Recently, we reported diastereoselective addition of organozinc reagents to the benzaldiminetricarbonylchromium derivatives in the presence of $BF_3 \cdot Et_2O$.[4] Though the reaction of the

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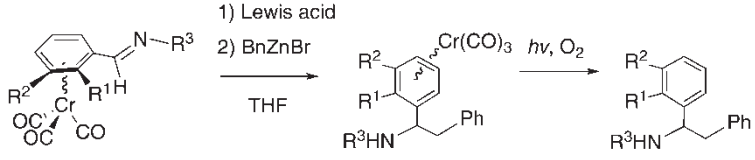
chromium complex having a *m*-substituted aromatic ring at the α-position of the benzaldimine moiety gave both diastereomers (62% de), single diastereomers were observed in the case of the complexes having an *o*-substituted aromatic ring. Herein, we describe the diastereoselective reaction of the benzaldiminetricarbonylchromium derivatives having an N-benzyl group with organozinc reagents in the presence of $Sc(OTf)_3$ to give one diastereomer of the corresponding chromium complex, even in the case of the chromium complex having an *m*-substituted aromatic ring. Deprotection of the tricarbonylchromium moiety and the N-benzyl group of the products afforded the corresponding amines, which would be useful for synthesis of natural products.[5]

We first examined the reaction of benzaldiminetricarbonylchromium derivatives[6] with benzylzinc bromide using various Lewis acids (Scheme 1). Many examples using the chromium complexes having an N-aryl group have been reported;[7] however, there are few reports on the reactions of the complexes having N-alkyl or other functional groups. We tried the reactions of the complexes (**1a**–**1c**) having an N-TMS, N-tosyl, or N-methyl group, but no product was detected by ^1H NMR under the various reaction conditions. Fortunately, the use of an N-benzyl group gave the corresponding chromium complex in the presence of $SnCl_4$ or $Sc(OTf)_3$ (Table 1, entries 2–7). Removal of the tricarbonylchromium moiety of the complex by using air and sunlight led to the secondary amine. Using $Sc(OTf)_3$ (2 equiv. to the chromium complex) afforded excellent de of the product in 99% yield (entry 3). A catalytic amount of $Sc(OTf)_3$ (0.5 equiv. to the chromium complex) produced 50% yield of the product (entry 4). We also examined the reaction of *o*- or *m*-substituted benzaldiminetricarbonylchromium derivatives in the presence of $Sc(OTf)_3$ (entries 5–7). A single diastereomer was obtained using the chromium complex having an *o*-substituted aromatic



1a : R^1 = Me, R^2 = H, R^3 = TMS
1b : R^1 = Me, R^2 = H, R^3 = Ts
1c : R^1 = Me, R^2 = H, R^3 = Me
1d : R^1 = Me, R^2 = H, R^3 = Bn
1e : R^1 = MeO, R^2 = H, R^3 = Bn
1f : R^1 = TMS, R^2 = H, R^3 = Bn
1g : R^1 = H, R^2 = Me, R^3 = Bn

Scheme 1. Addition of benzylzinc bromide to benzaldiminetricarbonylchromium derivatives.

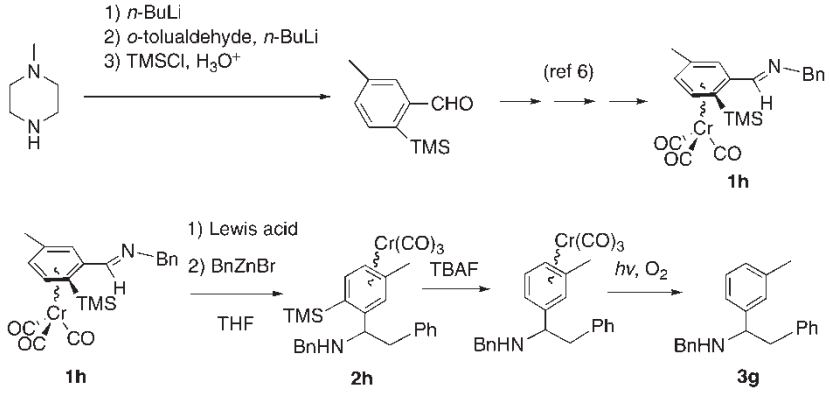
Table 1. Reaction of the Chromium complexes in the presence of Lewis acids

Entry	Chromium complex	Lewis acid (equiv to complex)	De (%) of **2**[a]	Isolated yield of **3** (%)[b]
1	**1d**	$BF_3 \cdot Et_2O$ (2 equiv)	—	0
2	**1d**	$SnCl_4$ (2 equiv)	—	<30
3	**1d**	Sc $(OTf)_3$ (2 equiv)	>95	99
4	**1d**	Sc $(OTf)_3$(0.5 equiv)	>95	50
5	**1e**	Sc $(OTf)_3$ (2 equiv)	>95	88
6	**1f**	Sc $(OTf)_3$ (2 equiv)	>95	90
7	**1g**	Sc $(OTf)_3$ (2 equiv)	48	72

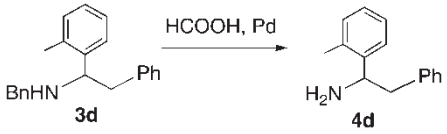
[a]Determined by ^{1}H NMR of the crude product.
[b]Yields after column chromatography.

ring; however, two diastereomers were observed in the case of the chromium complex **1 g** having an *m*-tolyl group (48% de, entry 7) where rotation between the carbon atom of the C═N bond and the α-carbon of the aldimine might decrease the diastereoselectivities.

To circumvent the problem, we used the TMS group at the *ortho* position of the aromatic ring of the chromium complex,[8] which would lead to a dramatic increase in diastereoselectivities. The chromium complex **1h** was prepared as shown in Scheme 2, starting from *o*-tolualdehyde.[9] As expected, the reaction using the complex **1h** selectively gave single diastereomer **2h**. The result indicated that using benzaldiminetricarbonylchromium derivatives with an *o*-TMS-protected aromatic ring afforded one diastereomer exclusively even though the complexes have *m*-substituents. After removal of the chromium moiety, deprotection of the TMS group of the corresponding product using tetrabutylammonium (TBAF) or aqueous HCl solution under



Scheme 2. Preparation of benzaldiminetricarbonylchromium derivative **1 h** and its reaction.



Scheme 3. Deprotection of the benzyl group in **3d**.

various conditions resulted in recovery of the starting materials. However, TMS deprotection of the complex **2h** and then removal of the tricarbonylchromium moiety gave 82% yield of the product **3g**.[8b] Deprotection of the N-benzyl group in **3d** was carried out using Pd and HCOOH in MeOH[10] to give the corresponding amine in quantitative yield (Scheme 3).

In conclusion, we have developed diastereoselective reaction of benzaldiminetricarbonylchromium derivatives having *o*- and *m*-substituents of the aromatic ring with organozinc reagents. Further studies to investigate the chiral reactions and applications are now in progress.

EXPERIMENTAL

Typical Experimental Procedure for Reaction of Benzaldiminetricarbonylchromium Derivatives

To a stirred solution of benzaldiminetricarbonylchromium derivatives (0.24mmol) and scandium trifluoromethanesulfonate (0.47 g, 0.48 mmol) in dry THF (5 mL), 1.5 ml (0.75 mmol) of benzylzinc bromide (0.5 M THF solution) were added at room temperature. The solution was stirred at rt for 18 h, and the mixture was quenched with water. The mixture was extracted with ether (20 mL × 3), and the combined organic layers were dried over $NaSO_4$. The precipitates were filtered off, and the solvent was evaporated to give the crude chromium product. The diastereomeric ratio was determined by ^{1}H NMR. To the crude chromium product, dichloromethane (60 mL) was added, and the mixture was exposed to air and sunlight for 1 h. The solvent was evaporated, and ether was added to the mixture. The precipitates were filtered off, and the solvent was evaporated to give the crude amine, which was purified by flash-column chromatography on SiO_2 (*n*-hexane/EtOAc = 3/1). Isolated yields were measured after the chromatography.

Deprotection of N-Benzyl Group in 3d[11]

To a stirred solution of **3d** (1.5 g, 0.5 mmol) and Pd (0.8 g, 7.7 mmol) in dry MeOH (5 mL), 0.22 mL of HCOOH was added. The mixture was stirred at rt for 2 h, then monitored by thin-layer chromatography (TLC). Pd (0.8 g, 7.7 mmol) and HCOOH (0.22 mL) were further added to the solution and

stirred for 1 h. The mixture was quenched with sat. $NaHCO_3$ solution and extracted with ether. The combined organic layers were dried over Na_2SO_4, and the mixture was filtered off. The solvent was evaporated to give 1.08 g (100%) of the corresponding product **4d**.

The products were identified by the following data.

Data

3d: ^{1}H NMR (500 MHz, $CDCl_3$); δ 2.11 (s, 3H), 2.80–2.84 (m, 1H), 2.91 (m, 1H), 3.43 (d, 1H, $J = 13.4$ Hz), 3.65 (d, 1H, $J = 13.4$ Hz), 4.14–4.16 (m, 1H), 7.08–7.28 (m, 13H), 7.66–7.67 (m, 1H). HRMS-FAB(M^+): Obsd. m/z 301.1843. Calcd. for $C_{22}H_{23}$ N: 301.1830.

3e: ^{1}H NMR (300 MHz, $CDCl_3$); δ 2.79–2.92 (m, 2H), 3.40 (d, 1H, $J = 13.5$ Hz), 3.60 (d, 1H, $J = 13.5$ Hz), 3.70 (s, 3H), 3.77–3.82 (m, 1H), 6.98–7.22 (m, 14H). HRMS-FAB($M + H)^+$: Obsd. m/z 318.1874. Calcd. for $C_{22}H_{24}NO$: 318.1858.

3f: ^{1}H NMR (300 MHz, $CDCl_3$); δ 0.36 (s, 9H), 2.81 (dd, 1H, $J = 13.8$, 9.8 Hz), 3.08 (dd, 1H, $J = 13.8$, 3.7 Hz), 3.50–3.53 (m, 2H), 4.34 (dd, 1H, $J = 9.8$, 3.7 Hz), 7.01–7.31 (m, 14H). HRMS-FAB(M^+): Obsd. m/z 359.2059. Calcd. for $C_{24}H_{29}NSi$: 359.2069.

3g: ^{1}H NMR (500 MHz, $CDCl_3$); δ 2.28 (s, 3H), 2.76–2.90 (m, 2H), 3.37 (d, 1H, $J = 13.6$ Hz), 3.58 (d, 1H, $J = 13.6$ Hz), 3.74–3.79 (m, 1H), 6.99–8.28 (m, 14H). HRMS-FAB(M^+): Obsd. m/z 301.1815. Calcd. for $C_{22}H_{23}$ N: 301.1830.

3h: ^{1}H NMR (500 MHz, $CDCl_3$); δ 0.26 (s, 9H), 2.31 (s, 3H), 2.73 (dd, 1H, $J = 14.0$, 9.9 Hz), 3.00 (dd, 1H, $J = 14.0$, 3.9 Hz), 3.46–3.51 (m, 2H), 4.24 (dd, 1H, $J = 9.9$, 3.9 Hz), 7.09–7.60 (m, 13H). HRMS-FAB(M^+): Obsd. m/z 373.2216. Calcd. for $C_{25}H_{31}NSi$: 373.2226.

4d: ^{1}H NMR (500 MHz, $CDCl_3$); δ 2.20 (s, 3H), 2.65 (dd, 1H, $J = 13.3$, 8.9 Hz), 2.89 (dd, 1H, $J = 13.3$, 4.5 Hz), 4.33 (dd, 1H, $J = 8.9$, 4.5 Hz), 7.06–7.21 (m, 9H). HRMS-FAB(M^+): Obsd. m/z 211.1365. Calcd. for $C_{15}H_17$ N: 211.1361.

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