Enantioselective *ortho*-Lithiation of Substituted Ferrocenes

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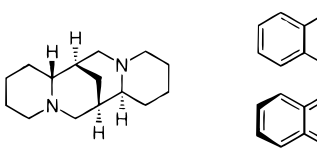
Ferrocene and its derivatives are widely used as structural units for the construction of unusual compounds and components in material science.[1] Moreover, ferrocenes with planar chirality are of increasing importance as chiral ligands in transition metal-catalyzed asymmetric organic synthesis, and the stereochemical capabilities of chiral ferrocenes have been widely investigated.[2] Ferrocenes with planar chirality have so far been obtained by only two methods: the optical resolution of racemic ferrocenes and the diastereoselective *ortho*-lithiation of chiral ferrocenes.[3] In the latter case, it is necessary to have a preestablished chiral center on the side chain of the ferrocene ring. Very recent reports on the enantioselective *ortho*-lithiation of prochiral tricarbonyl(η^6-arene)chromium complexes[4] prompted us to apply this method to substituted ferrocenes. We now report the first example of the preparation of ferrocenes with planar chirality via the enantioselective *ortho*-lithiation of substituted ferrocenes.

Treatment of ((*N*,*N*-dimethylamino)methyl)ferrocene (**1**; R = NMe_2) (0.4 mmol) with *n*-butyllithium (0.6 mmol) in ether (1 mL) at 0 °C in the presence of *N*,*N*,*N*′,*N*′-tetramethyl-1(*R*),2(*R*)-cyclohexanediamine (**2**) (0.8 mmol) followed by the addition of chlorodiphenylphosphine (0.6 mmol) afforded (*R*)-1-((*N*,*N*-dimethylamino)methyl)-2-(diphenylphosphino)ferrocene (**3**; R = NMe_2)[5] in 49% chemical yield with 62% ee (Scheme 1). The absolute configuration of this compound was *R*, as deduced from its optical rotation. The use of a slight excess of **2** relative to *n*-BuLi was necessary to achieve higher selectivity. As for the lithium reagent, *n*-BuLi was the most effective in this enantioselective lithiation. When (−)-sparteine (**4**) was employed as a chiral ligand in place of **2**, the ferrocenylphosphine **3** (R = NMe_2) was obtained in only a trace amount, while with *N*,*N*,*N*′,*N*′-tetramethyl-1,1′-binaphthyl-2,2′-diamine (**5**) **3** was obtained in 40% yield, but without enantioselectivity. The use of tetrahydrofuran (THF) and toluene instead of ether as the solvent decreased the yield of **3**. Typical results are shown in Table 1. The optimum conditions entailed the use of *n*-BuLi (1.5 equiv to **1**) and the chiral diamine **2** (2.0 equiv to **1**) in ether at 0 °C. The maximum enantioselectivity obtained by lithiation of **1** was only 62% ee, but after two recrystallizations from dry EtOH almost optically pure (*R*)-**3** (R = NMe_2) was obtained in 25% isolated yield.



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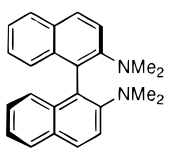

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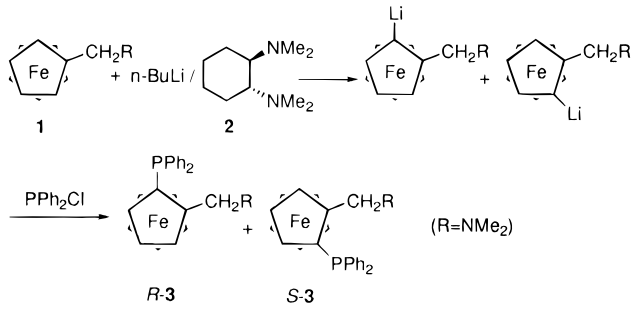
Scheme 1



Next, to examine the effect of the bulkiness of an amino moiety on the side chain of the ferrocene and also to widen the utility of this reaction, various (aminomethyl)ferrocenes (**1**) were lithiated in the presence of the chiral diamine **2** and quenched by DMF (dimethylformamide) instead of PPh_2Cl (Scheme 2). The isolated products were the corresponding aldehydes of *R*-configuration with up to 80% ee. Typical results are shown in Table 2. The changing of the substituent from NMe_2 to pyrrolidinyl to morpholinyl decreased the ee value only slightly. With N(*i*-Pr)$_2$ no reaction took place, probably due to the bulkiness of the two isopropyl groups. This result reveals the importance of coordination of the lithium of a chiral lithium reagent to the nitrogen of **1** for *ortho*-lithiation of the ferrocenes.

The enantioselective *ortho*-lithiation of the related sulfonylferrocenes **7** was also examined (Scheme 3), as it is known that the oxygen of a sulfonyl group can coordinate strongly with the lithium of BuLi to give *ortho*-lithiated aromatic compounds.[6] Under the above-mentioned optimum conditions, the lithiation took place smoothly with **7** (R = *t*-Bu) to give a good yield of the products (*R*)- and (*S*)-**8** but, unfortunately, without enantioselectivity even at −78 °C. From **7** (R = *p*-tolyl), the corresponding compounds **8** were formed in lower yields and could not be isolated in pure form because many substitution products were also produced due to the lability of the *ortho*-positions of the tolyl group.

In conclusion, we have demonstrated for the first time the enantioselective *ortho*-lithiation (up to 80% ee) of substituted ferrocenes. This method can be applied to prepare optically pure ferrocenes with planar chirality from nonchiral ferrocenes.

Experimental Section

General. ^{1}H (270 MHz) and ^{13}C NMR (67.5 MHz) samples were measured as solutions in $CDCl_3$. Melting points are uncorrected. Column chromatographies on Al_2O_3 or SiO_2 were

(1) For a review: Togni, A.; Hayashi, T. *Ferrocenes*; VCH: Weinheim, 1995 and references therein.

(2) For an example: Sawamura, M.; Ito, Y. *Chem. Rev.* **1992**, *92*, 867.

(3) Diastereoselective lithiation of chiral ferrocenes. (a) Marquarding, D.; Klusacek, H.; Gokel, G.; Hoffmann, P.; Ugi, I. *J. Am. Chem. Soc.* **1970**, *92*, 5389. (b) Riant, O.; Samuel, O.; Kagan, H. B. *J. Am. Chem. Soc.* **1993**, *115*, 5835. (c) Rebiere, F.; Riant, O.; Ricard, L.; Kagan, H. B. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 568. (d) Richards, C. J.; Damalidis, T.; Hibbs, D. E.; Hursthouse, M. B. *Synlett* **1995**, 74. (e) Sammakia, T.; Latham, H. A.; Schaad, D. R. *J. Org. Chem.* **1995**, *60*, 10. (f) Nishibayashi, Y.; Uemura, S. *Synlett* **1995**, 79.

(4) (a) Price, D.; Simpkins, N. S. *J. Org. Chem.* **1994**, *59*, 1961. (b) Price, D.; Simpkins, N. S.; MacLeod, A. M.; Watt, A. P. *Tetrahedron Lett.* **1994**, *35*, 6159. (c) Uemura, M.; Hayashi, Y.; Hayashi, Y. *Tetrahedron: Asymmetry* **1994**, *5*, 1427.

(5) Hayashi, T.; Mise, T.; Fukushima, M.; Kagotani, M.; Nagashima, N.; Hamada, Y.; Matsumoto, A.; Kawakami, S.; Konishi, M.; Yamamoto, K.; Kumada, M. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 1138.

(6) For an example: Snieckus, V. *Chem. Rev.* **1990**, *90*, 879.

0022-3263/96/1961-1172$12.00/0

Table 1. Enantioselective *ortho*-Lithiation of 1 (R = NMe_2)[a]

run	solvent	BuLi (equiv)	diamine (equiv)	time[b] (h)	yield in **3**,[c] (%)	ee[d] (%)
1	Et_2O	*n*-BuLi (1.5)	**2** (1.5)	5	26	43
2	Et_2O	*n*-BuLi (1.5)	**2** (2.0)	5	49	62
3	Et_2O	*n*-BuLi (3.0)	**2** (3.0)	5	31	57
4	Et_2O	*s*-BuLi (1.5)	**2** (1.5)	3	38	48
5[e]	Et_2O	*t*-BuLi (1.5)	**2** (1.5)	1	trace	
6	THF	*n*-BuLi (1.5)	**2** (1.5)	5	10	
7	toluene	*n*-BuLi (1.5)	**2** (1.5)	5	12	19
8	Et_2O	*n*-BuLi (1.5)	**4** (2.0)	5	trace	
9	Et_2O	*n*-BuLi (1.5)	**5** (2.0)	5	40	0

[a] All the reactions were carried out in the presence of diamine at 0 °C followed by addition of Ph_2PCl (1.5−3.0 equiv). [b] Lithiation time. [c] Isolated yield of **3** (R = NMe_2). [d] By optical rotation: the configuration is *R*. [e] The reaction was carried out at −78 °C.

Scheme 2

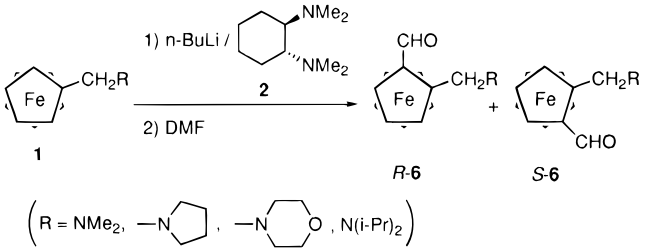
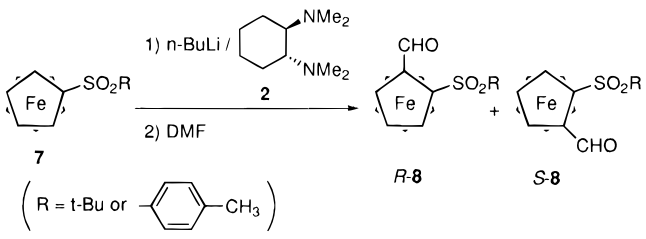


Table 2. Effect of an Amino Moiety (R) of 1 upon Lithiation[a]

run	R	yield in **6** (%)[b]	ee(%)[c]
1	—NMe_2	41	80
2	—N	40	73
3	—N O	42	67
4	—N(i-Pr)$_2$	trace	-

[a] All the reactions were carried out in the presence of diamine (**2**) (0.80 mmol) with substituted ferrocene (0.40 mmol) and *n*-BuLi (0.60 mmol) in Et_2O at 0 °C for 5 h followed by addition of excess DMF. [b] Isolated yield of substituted ferrocenecarboxaldehyde (**6**). [c] By ^{1}H-NMR (see Experimental Section).

Scheme 3



performed with ICN Alumina N, Akt. I or Wakogel C-300 (hexane and hexane/ethyl acetate as eluents), respectively. Elemental analyses were performed at the Microanalytical Center of Kyoto University. Solvents were distilled from CaH_2 or $LiAlH_4$ and stored over molecular sieves 4 Å under N_2. Commercial *m*-chloroperbenzoic acid (*m*-CPBA) (70% purity) was used without further purification. Di-*tert*-butyl disulfide, di-*p*-tolyl disulfide, *n*-, *s*-, and *t*-BuLi (hexane solution), Eu(hfc)$_3$, and the inorganic compounds are commercial products. 1(*R*),2(*R*)-Cyclohexanediamine, (−)-sparteine (**4**), and (*R*)-1,1′-binaphthyl-2,2′-diamine were purchased, and the corresponding tetramethyldiamines (**2** and **5**) were prepared by treating them with formaldehyde in formic acid.[7] ((*N*,*N*-Dimethylamino)methyl)ferrocene (**1**; R = NMe_2) was a commercial reagent, while other various substituted ferrocenes (**1** and **7**) were prepared as described below.

Preparation of Aminoferrocenes 1. A typical experimental procedure for preparation of (pyrrolidinomethyl)ferrocene (**1**, R = pyrrolidinyl) is as follows. To a solution of the ferrocene **1** (R = NMe_2) (3.50 g, 14.3 mmol) in acetonitrile (20 mL) was added 25 mL of methyl iodide, and the mixture was stirred at room temperature for 2 h during which time the solution turned from homogeneous to heterogeneous. It was then evaporated to leave a brown ammonium salt.

To this compound (1.30 g, 3.4 mmol) suspended in acetonitrile (20 mL) was added pyrrolidine (25 g, 352 mmol), and the resulting mixture was stirred at reflux temperature for 20 h. After the solvent was removed under reduced pressure, the residue was treated with saturated Na_2CO_3 (100 mL) and then extracted with CH_2Cl_2 (50 mL × 3). The extract was dried over $MgSO_4$ and evaporated to leave a brown solid of (pyrrolidinomethyl)ferrocene which was purified by column chromatography on alumina with *n*-hexane/ethyl acetate (7/3) as eluent: 432 mg, 1.60 mmol; 47% yield; mp 52−53 °C; ^{1}H NMR δ 1.69−1.77 (m, 4H), 2.42−2.49 (m, 4H), 3.43 (s, 2H), 4.09 (t, 2H, J = 2 Hz), 4.11 (s, 5H), 4.19 (t, 2H, J = 2 Hz); ^{13}C NMR δ 23.3 (t), 53.8 (t), 55.5 (t), 67.9 (d), 68.4 (d), 69.8 (d), 84.3 (s). Anal. Calcd for $C_{15}H_{19}FeN$: C, 66.93; H, 7.11; N, 5.20. Found: C, 66.75; H, 7.07; N, 5.08.

Spectroscopic and analytical data and isolated yield of other aminoferrocenes **1** are as follows.

(Morpholinomethyl)ferrocene (1; R = morpholinyl): yellow solid; 79% yield; mp 77- 78 °C; ^{1}H NMR δ 2.38−2.42 (m, 4H), 3.35 (s, 2H), 3.64−3.68 (m, 4H), 4.12 (s, 5H), 4.12 (t, 2H, J = 2 Hz), 4.17 (t, 2H, J = 2 Hz); ^{13}C NMR δ 53.2 (t), 58.8 (t), 66.9 (t), 68.1 (d), 68.5 (d), 70.3 (d), 82.3 (s). Anal. Calcd for $C_{15}H_{19}FeNO$: C, 63.18; H, 6.72; N, 4.91. Found: C, 63.40; H, 6.82; N, 4.86.

((*N*,*N*-Diisopropylamino)methyl)ferrocene (1; R = diisopropylamino): brown oil; 43% yield; ^{1}H NMR δ 1.00 (d, 12H, J = 7 Hz), 3.04 (sept, 2H, J = 7 Hz), 3.45 (s, 2H), 4.05 (t, 2H, J = 2 Hz), 4.10 (s, 5H), 4.19 (t, 2H, J = 2 Hz); ^{13}C NMR δ 20.8 (q), 44.0 (t), 47.4 (d), 67.2 (d), 68.4 (d), 69.5 (d), 88.7 (s). Anal. Calcd for $C_{15}H_{25}FeN$: C, 68.24; H, 8.42; N, 4.68. Found: C, 68.23; H, 8.23; N, 4.46.

Preparation of Sulfonylferrocenes 7. A typical experimental procedure for preparation of **7** (R = *t*-Bu) is as follows. To a dry tetrahydrofuran (THF) (50 mL) solution of ferrocene (9.30 g, 51 mmol) was added *t*-BuLi (hexane solution; 40 mmol) by syringe at 0 °C for 1 h under N_2 with stirring. To the mixture was added di-*tert*-butyl disulfide (8.20 g, 46 mmol) in THF (20 mL) at 0 °C by syringe, and the resulting mixture was stirred at room temperature for 3 h. The mixture was treated with brine (100 mL) and then extracted with CH_2Cl_2 (100 mL × 3). The extract was dried over $MgSO_4$ and evaporated to leave a brown solid of *tert*-butyl ferrocenyl sulfide which was purified by column chromatography on SiO_2 with *n*-hexane/ethyl acetate (9/1) as eluent: 4.80 g, 17.4 mmol; 34% yield.

To a dry CH_2Cl_2 (50 mL) solution of *tert*-butyl ferrocenyl sulfide (4.70 g, 17.4 mmol) was added dropwise *m*-CPBA (70% purity; 10.1 g, 42.9 mmol) at 0 °C, and the resulting mixture was stirred at the temperature for 8 h. The mixture was poured into a saturated Na_2CO_3 solution (100 mL) and extracted with CH_2Cl_2 (100 mL × 3). The extract was dried over $MgSO_4$ and evaporated to leave a yellow solid of **7** (R = *t*-Bu) which was purified by column chromatography on SiO_2 with *n*-hexane/ethyl acetate (9/1) as eluent: 3.30 g, 9.33 mmol; 54% yield; mp 134−135 °C; ^{1}H NMR δ 1.28 (s, 9H), 4.44 (t, 2H, J = 2 Hz), 4.45 (s, 5H), 4.62 (t, 2H, J = 2 Hz); ^{13}C NMR δ 23.5 (q), 58.7 (s), 70.7 (d), 71.0 (d), 71.4 (d), 82.9 (s). Anal. Calcd for $C_{14}H_{18}FeSO_2$: C, 54.92; H, 5.93. Found: C, 54.76; H, 5.71.

Similarly, **7** (R = *p*-tolyl) was prepared using di-*p*-tolyl disulfide in place of di-*tert*-butyl disulfide: yellow solid; 23% yield; mp 179−180 °C; ^{1}H NMR δ 2.36 (s, 3H), 4.38 (t, 2H, J = 2 Hz), 4.49 (s, 5H), 4.66 (t, 2H, J = 2 Hz), 7.23 (d, 2H, J = 8 Hz), 7.72 (d, 2H, J = 8 Hz); ^{13}C NMR δ 21.5 (q), 69.1 (d), 70.7 (d), 71.0 (d), 90.7 (s), 126.7 (d), 129.6 (d), 140.3 (s), 143.4 (s).

(7) Moore, M. L. *Org. React.* **1949**, *5*, 323.

Anal. Calcd for $C_{17}H_{16}FeSO_2$: C, 60.02; H, 4.74. Found: C, 59.92; H, 4.74.

Asymmetric Synthesis of 3 (R = NMe_2) by Enantioselective Lithiation of 1 (R = NMe_2). To an ether (1 mL) solution of the diamine **2** (2.00 mmol) was added n-BuLi (hexane solution; 1.50 mmol) by syringe at 0 °C under N_2. The ferrocene **1** (R = NMe_2) (243 mg, 1.00 mmol) in ether (1 mL) was then added to the solution, and the mixture was stirred at 0 °C for 5 h. Chlorodiphenylphosphine (330 mg, 1.50 mmol) was next added, and the resulting mixture was warmed to room temperature and then heated at reflux temperature for 16 h. It was treated with saturated Na_2CO_3 (50 mL) and extracted with CH_2Cl_2 (20 mL × 3). The extract was dried over $MgSO_4$ and evaporated to leave a yellow solid of **3** (R = NMe_2) which was purified by column chromatography on alumina with *n*-hexane/ethyl acetate (7/3) as eluent; 210 mg (0.49 mmol); $[\alpha]^{30}_D$ +200° (*c* 0.56, $CHCl_3$). The enantiomeric excess was determined by optical rotation in comparison with the reported value ((*R*)-FcPN: lit.[5] $[\alpha]^{25}_D$ +324° (*c* 0.5, $CHCl_3$)). The configuration of **3** (R = NMe_2) was *R*.

Asymmetric Synthesis of ((*N*,*N*-Dimethylamino)methyl)-2-formylferrocene [6 (R = NMe_2)] by Enantioselective Lithiation of 1 (R = NMe_2). A typical experimental procedure for preparation of **6** (R = NMe_2) is as follows. After lithiation of the ferrocene **1** (R = NMe_2) (100 mg, 0.40 mmol) with *n*-BuLi (0.60 mmol) in the presence of the diamine **2** (0.80 mmol) by the above-described method, dimethylformamide (DMF) (0.5 mL) was added by syringe at 0 °C. The mixture was warmed to room temperature and then stirred for 2 h. It was treated with saturated Na_2CO_3 (50 mL) and extracted with CH_2Cl_2 (20 mL × 3). The extract was dried over $MgSO_4$ and evaporated to leave an orange oil of **6** (R = NMe_2) (43 mg, 0.16 mmol) which was purified by column chromatography on alumina with *n*-hexane/ethyl acetate (7/3) as eluent: 41% yield; ^{1}H NMR δ 2.21 (s, 6H), 3.34 (d, 1H, J = 13 Hz), 3.83 (d, 1H, J = 13 Hz), 4.22 (s, 5H), 4.55 (m, 1H), 4.61 (m, 1H), 4.78 (m, 1H), 10.10 (s, 1H); ^{13}C NMR δ 44.8 (q), 56.7 (t), 70.2 (d), 70.4 (d), 72.9 (d), 75.9 (d), 77.8 (s), 86.6 (s), 193.3 (s). Anal. Calcd for $C_{14}H_{17}FeNO$: C, 62.02; H, 6.32; N, 5.17. Found: C, 61.77; H, 6.53; N, 4.97. The ee value was determined by ^{1}H-NMR from integrals of the nonsubstituted cyclopentadienyl ring protons in the presence of Eu(hfc)$_3$ after reduction of **6** with $LiAlH_4$ at 0 °C to the corresponding alcohol.

Spectroscopic and analytical data and the isolated yield of other **6** are as follows.

(Pyrrolidinomethyl)-2-formylferrocene (6; R = pyrrolidinyl): orange oil; 40% yield; ^{1}H NMR δ 1.73 (m, 4H), 2.49 (m, 4H), 3.55 (d, 1H, J = 13 Hz), 3.95 (d, 1H, J = 13 Hz), 4.22 (s, 5H), 4.55 (m, 1H), 4.64 (m, 1H), 4.77 (m, 1H), 10.12 (s, 1H); ^{13}C NMR δ 23.3 (t), 52.7 (t), 53.7 (t), 70.0 (d), 70.2 (d), 71.9 (d), 75.6 (d), 78.0 (s), 87.6 (s), 193.4 (s). Anal. Calcd for $C_{16}H_{19}FeNO$: C, 64.67; H, 6.44; N, 4.71. Found: C, 64.40; H, 6.73; N, 4.69.

(Morpholinomethyl)-2-formylferrocene (6; R = morpholinyl): brown oil; 42% yield; ^{1}H NMR δ 2.38−2.50 (m, 4H), 3.41 (d, 1H, J = 13 Hz), 3.63−3.66 (m, 4H), 3.93 (d, 1H, J = 13 Hz), 4.23 (s, 5H), 4.56 (m, 1H), 4.60 (m, 1H), 4.78 (m, 1H), 10.10 (s, 1H); ^{13}C NMR δ 53.0 (t), 56.1 (t), 66.9 (t), 70.3 (d), 70.5 (d), 71.9 (d), 76.0 (d), 77.9 (s), 85.7 (s), 193.3 (s). Anal. Calcd for $C_{16}H_{19}FeNO_2$: C, 61.36; H, 6.12; N, 4.47. Found: C, 61.11; H, 6.31; N, 4.23.

Enantioselective Lithiation of 7. A typical experimental procedure for preparation of **8** (R = *t*-Bu) is as follows. After lithiation of **7** (R = *t*-Bu) (95 mg, 0.30 mmol) with *n*-BuLi (0.32 mmol) in the presence of the diamine **2** (0.34 mmol) in THF (3 mL) at −78 °C for 6 h under nitrogen, DMF (0.5 mL) was added at −78 °C. The mixture was warmed to room temperature and then stirred for 2 h. The mixture was then treated with saturated Na_2CO_3 (50 mL) and extracted with CH_2Cl_2 (20 mL × 3). The extract was dried over $MgSO_4$ and evaporated to leave a brown oil of **8** (R = *t*-Bu) (17 mg, 0.05 mmol) which was purified by column chromatography on SiO_2 with *n*-hexane/ethyl acetate (7/3) as eluent: 16% yield; ^{1}H NMR δ 1.31 (s, 9H), 4.57 (s, 5H), 4.86 (m, 1H), 4.97 (m, 1H), 5.19 (m, 1H), 10.36 (s, 1H); ^{13}C NMR δ 23.5 (q), 59.2 (d), 71.3 (d), 72.6 (d), 73.7 (d), 77.7 (d), 80.0 (s), 85.0 (s), 193.4 (s). Anal. Calcd for $C_{15}H_{18}FeO_3S$: C, 53.91; H, 5.43. Found: C, 54.00; H, 5.67. The ee value of the product was determined by HPLC using Daicel Chiralcel OJ (eluent; 2% *i*-PrOH/*n*-hexane) at 40 °C.

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