Chiral Amidophosphane–Rhodium(I)-Catalyzed Asymmetric Conjugate Arylation of Acyclic Enones with Arylboronic Acids

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A catalytic asymmetric conjugate arylation of acyclic α,β-unsaturated ketones with arylboronic acids was catalyzed by 3 mol% of chiral amidomonophosphane 1–rhodium(I) in the presence of potassium hydroxide in a mixture of 1,4-dioxane and water at 70 °C to afford 1,4-conjugate arylated acyclic ketones with high enantiomeric excess in high chemical yield. Thirteen examples of the reaction demonstrate the general applicability of the catalytic system.

Key words catalytic asymmetric reaction; arylation; arylboronic acid; conjugate addition; α,β-unsaturated ketone

The carbon–carbon bond forming catalytic asymmetric conjugate addition reaction of α,β-unsaturated carbonyl compounds with organometallic reagents has been the significant milestone of catalytic asymmetric reactions.[1—5] Tremendous efforts on the discovery of efficient chiral sources for the reaction with carbon- and hetero-nucleophiles provided a fruit of chiral sources like phosphorous compounds.[6] A touchstone for the evaluation of chiral sources has been the asymmetric reaction of cyclohexenone **2** with diorganozinc–copper(I),[7,8] Grignard reagent–copper(I)[9,10] or arylboronic acid–rhodium(I)[11—18] reagent–catalyst combinations. We have also engaged in this fascinating challenge and fortunately succeeded in the development of chiral amidophosphane **1**-based catalytic asymmetric conjugate addition reaction of **2** with organometallic reagents, especially, Grignard reagents[19—21] and diorganozincs.[22—26] Especially, **1**–rhodium(I) catalyzed asymmetric conjugate arylation of **2** with arylboronic acids gave **3** with excellently high ee of up to 99% (Chart 1).[27—30] However, there has been known the presence of a large gap in reaction efficiency between the arylation of cyclic and acyclic enones probably due to *s-trans* and *s-cis* conformation differences of enones. Now we describe a catalytic asymmetric arylation of acyclic enones **7** with arylboronic acids **5** yielding arylation products **8** with relatively high ee.

Acyclic Enones as Good Acceptors for Conjugate Phenylation At the beginning of this arylation study 4-methylbenzylidenemalonate **4**[31,32] was examined with its acceptor ability by treating with phenylboronic acid (**5a**) in a 10 : 1 mixture of 1,4-dioxane and water under the catalysis of **1**–rhodium(I). Unfortunately, the starting **4** was recovered almost quantitatively without detectable production of adduct **6** (Chart 2). This disaster was overcome by the selection of enone **7** as an acceptor for the conjugate arylation.

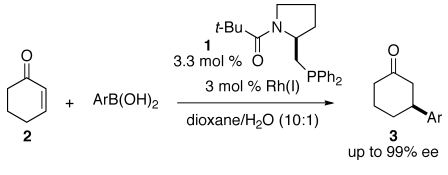


Chart 1. Catalytic Asymmetric Conjugate Arylation of Cyclohexenone

Non-3-ene-2-one (**7a**) was then selected as the second acceptor because of the simple methyl ketone structure (Table 1). The phenylation of **7a** with 5 eq of phenylboronic acid (**5a**) was catalyzed by 3 mol% of **1**–rhodium(I) in a 10 : 1 mixture of 1,4-dioxane and water.[27] Although the chemical yield was not high under the catalysis of **1**–acetylacetonatobis(diethylene)rhodium(I), the desired ketone **8aa**[12,33] with 56% ee was obtained in 35% isolated yield (Table 1, entry 1). Enantioselectivity (ee%) was determined by HPLC with chiral stationary phase (Daicel Chiralcel OB-H, hexane/2-propanol = 100/1, 0.5 ml/min, 254 nm) as described in Experimental. Other two *N*-Boc-valine-connected amidophosphanes **9** and **10**[34] (Fig. 1) exhibited the same level of performance to give **8aa** with 65% and 61% ees, respectively (entries 2, 3). The sense of asymmetric induction was controlled by the pyrrolidine part of the ligands and not by the stereochemistry of the valine moiety; **8aa** of the same ab-

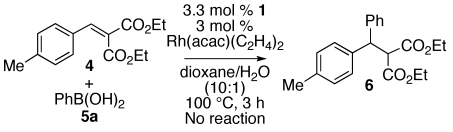
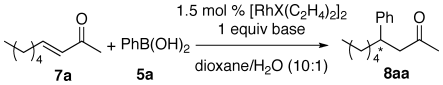


Chart 2. Attempted Arylation of 4-Methylbenzylidenemalonate **4**

Table 1. Catalytic Asymmetric Conjugate Phenylation of **7a**



Entry	Ligand	X	Base	Temp. (°C)	Time (h)	Yield (%)	ee (%)
1	**1**	acac	none	100	3	35	56
2	**9**	acac	none	100	1	58	65
3	**10**	acac	none	100	1	61	61
4	**1**	Cl	KOH	100	7	96	76
5	**1**	Cl	K_3PO_4	100	15	90	72
6	**1**	Cl	Et_3N	100	15	70	75
7	**9**	Cl	KOH	100	31	82	63
8	**1**	Cl	KOH	70	20	90	81
9	**1**	Cl	KOH	50	23	37	67

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solute configuration was obtained in the similar level of enantioselectivity.

The reaction was much more improved by using **1**–chlorobis(ethylene)rhodium(I) complex in the presence of potassium hydroxide at 100 °C for 7 h to give **8aa** with 76% ee in 96% yield (entry 4). Other bases, potassium phosphate and triethylamine, also gave the similar level of efficiency (entries 5, 6). *N*-Boc-L-valine-connected amidophosphane **9** was not a better ligand than **1** to give **8aa** with 63% ee (entry 7). Best efficiency was obtained at 70 °C reaction temperature for 20 h to give **8aa** with 81% ee in 90% yield (entries 8, 9).

Generality in Catalytic Asymmetric Conjugate Arylation The established conditions above were applied to the catalytic asymmetric conjugate arylation of six acyclic enones **7a**—**f** with five arylboronic acids **5a**—**e** under the catalysis of **1**–rhodium(I) in the presence of one equiv of potassium hydroxide in a 10 : 1 mixture of 1,4-dioxane and water at 70 °C as has been summarized in Table 2.

The similar level of relatively high enantioselectivity, 76% and 78% ees, were obtained with the use of substituted phenylboronic acids bearing electron-donating methoxy and withdrawing phenyl groups (Table 2, entries 1, 2). Relatively bulky isopropyl substituent at the reaction site of enone **7b** did not disturb the reaction to give the arylation products with 76—86% ee (entries 3—6). A phenyl group bearing an electron-withdrawing trifluoromethyl substituent was introduced in the best enantioselectivity of 86% (entry 5). The phenyl group at the reaction site of **7c** was deleterious to the enantioselectivity to give arylation products with 65% and 60% ees (entries 7, 8). Although ethylketone **7d** was usable as an acceptor with 72% and 74% enantioselectivity, phenylketones **7e** and **7f** were the worst acceptors giving 51% selectivity (entries 9, 10). The sense of asymmetric induction was determined as indicated by the comparison of the sign of the specific rotation of **8da** and **8fa** with those reported. The absolute stereochemistry of other products **8** was presented by analogy.

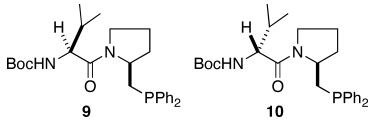


Fig. 1. *N*-Boc-L- and D-Valine Connected Amidophosphanes **9** and **10**

Conclusion

The combination of a chiral amidophosphane, chlorobis(ethylene)rhodium dimer, and potassium hydroxide was proven to be a good chiral catalyst for the asymmetric conjugate arylation of acyclic enones with arylboronic acid in a 10 : 1 mixture of 1,4-dioxane and water. It is important to note that not only cyclic enones of *s-trans* conformation but also acyclic enones of possible *s-cis* conformation are the substrate for the present catalytic asymmetric conjugate arylation with arylboronic acids, although the enantioselectivity is not so high. Further studies towards higher enantioselectivity are the current focus of our efforts.

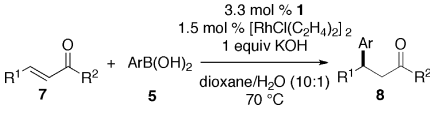
Experimental

General Procedure. (*R*)-4-Phenylnonan-2-one (8aa)[12] (Table 1, Entry 8) 1,4-Dioxane (2.5 ml), 4 M aqueous KOH (0.25 ml), and **7a** (140 mg, 1.0 mmol) were added to a mixture of $[RhCl(C_2H_4)_2]_2$ (5.8 mg, 0.015 mmol), **1** (11.6 mg, 0.033 mmol), and **5a** (610 mg, 5.0 mmol) under argon. The mixture was stirred at 70 °C for 20 h. After dilution with EtOAc (40 ml), the mixture was washed with 10% NaOH (10 ml) and brine (20 ml), and then dried over Na_2SO_4. Concentration and silica gel column chromatography (hexane/AcOEt=30/1) gave **8aa** (90%) as colorless oil: $[\alpha]_D^{20}$ −15.1 (*c*=1.1, $CHCl_3$). 81% ee (HPLC: Daicel Chiralcel OB-H, hexane/*i*-PrOH=100/1, 0.5 ml/min, 254 nm; major 16.7 min, minor 13.4 min). ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 0.82 (t, *J*=7.0 Hz, 3H), 1.10—1.23 (m, 6H), 1.55—1.63 (m, 2H), 2.01 (s, 3H), 2.69 (dd, *J*=7.3, 16.2 Hz, 1H), 2.73 (dd, *J*=7.6, 16.2 Hz, 1H), 3.10 (m, 1H), 7.16—7.31 (m, 5H). ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 14.0, 22.4, 27.0, 30.6, 31.7, 36.4, 41.3, 50.9, 126.2, 127.4, 128.4, 144.6, 208.1. IR (neat) cm^{-1}: 1710. MS *m/z*: 218 (M^+).

(*R*)-4-(3-Methoxyphenyl)nonan-2-one (8ab)[14] (Table 2, Entry 1) Eluent, hexane/AcOEt=40/1. Colorless oil. $[\alpha]_D^{20}$ −13.9 (*c*=1.05, $CHCl_3$). 76% ee (OB-H, hexane/*i*-PrOH=100/1, 0.5 ml/min, 254 nm; major 38.1 min, minor 23.4 min). ^{1}H-NMR δ: 0.82 (t, *J*=7.0, 3H), 1.17—1.24 (m, 6H), 1.52—1.62 (m, 2H), 2.03 (s, 3H), 2.67 (dd, *J*=7.0, 16.0, 1H), 2.72 (dd, *J*=7.4, 16.0, 1H), 3.07 (m, 1H), 3.79 (s, 3H), 6.72—6.78 (m, 3H), 7.20 (dd, *J*=8.0, 8.0, 1H). ^{13}C-NMR δ: 13.9, 22.4, 27.0, 30.6, 31.7, 36.3, 41.3, 50.8, 55.1, 111.2, 113.5, 119.9, 129.4, 146.4, 159.7, 208.1. IR (neat): 1716. MS *m/z*: 248 (M^+).

(*R*)-4-(4-Phenylphenyl)nonan-2-one (8ae) (Entry 2) Eluent, hexane/AcOEt=50/1. White solid. mp 46—48 °C. $[\alpha]_D^{20}$ −11.7 (*c*=0.99, $CHCl_3$). 78% ee (AD-H, hexane/*i*-PrOH=100/1, 0.5 ml/min, 254 nm; major 18.7 min, minor 20.6 min). ^{1}H-NMR δ: 0.84 (t, *J*=7.6, 3H), 1.16—1.25 (m, 6H), 1.55—1.65 (m, 2H), 2.04 (s, 3H), 2.72 (dd, *J*=7.0, 16.2, 1H), 2.76 (dd, *J*=7.4, 16.2, 1H), 3.16 (m, 1H), 7.24 (d, *J*=8.0, 2H), 7.32 (t, *J*=7.5, 1H),

Table 2. Catalytic Asymmetric Conjugate Arylation of Acyclic Enones **7**



Entry	**7**	R_1	R_2	**5**	Ar	Time (h)	**8**	Yield (%)	ee (%)
1	**7a**	*n*-Pen	Me	**5b**	3-$MeOC_6H_4$	11	**8ab**	87	76
2	**7a**	*n*-Pen	Me	**5e**	4-PhC_6H_4	17	**8ae**	82	78
3	**7b**	*i*-Pr	Me	**5a**	Ph	21	**8ba**	83	76
4	**7b**	*i*-Pr	Me	**5b**	3-$MeOC_6H_4$	21	**8bb**	80	77
5	**7b**	*i*-Pr	Me	**5c**	4-$CF_3C_6H_4$	22	**8bc**	81	86
6	**7b**	*i*-Pr	Me	**5e**	4-PhC_6H_4	26	**8be**	95	79
7	**7c**	Ph	Me	**5d**	4-$MeOC_6H_4$	26	**8cd**	88	65
8	**7c**	Ph	Me	**5e**	4-PhC_6H_4	5	**8ce**	94	60
9	**7d**	Me	Et	**5a**	Ph	10	**8da**	92	72*R*
10	**7d**	Me	Et	**5e**	4-PhC_6H_4	24	**8de**	99	74
11	**7e**	*n*-Pen	Ph	**5a**	Ph	22	**8ea**	71	51
12	**7f**	Me	Ph	**5a**	Ph	7	**8fa**	75	51*R*

7.42 (dd, J=7.5, 8.0, 2H), 7.52 (d, J=8.0, 2H), 7.57 (d, J=8.0, 2H). ^{13}C-NMR δ: 13.9, 22.4, 27.0, 30.6, 31.7, 36.4, 40.8, 50.8, 126.96, 127.07, 127.14, 127.9, 128.7, 139.2, 140.9, 143.8, 208.1. IR (KBr): 1713. MS m/z: 294 (M^+). *Anal.* Calcd for $C_{21}H_{26}O$: C, 85.67; H, 8.90. Found: C, 85.43; H, 8.99.

(*S*)-5-Methyl-4-phenylhexan-2-one (8ba)[12] **(Entry 3)** Eluent, hexane/AcOEt=50/1. Colorless oil. $[\alpha]_D^{20}$ −25.7 (c=1.2, $CHCl_3$). 76% ee (OD-H, hexane/*i*-PrOH=50/1, 0.5 ml/min, 254 nm; major 26.4 min, minor 23.1 min). ^{1}H-NMR δ: 0.74 (d, J=6.7, 3H), 0.93 (d, J=6.7, 3H), 1.83 (m, 1H), 1.98 (s, 3H), 2.75—2.83 (m, 2H), 2.91 (m, 1H), 7.13—7.20 (m, 3H), 7.25—7.29 (m, 2H). ^{13}C-NMR δ: 20.2, 20.6, 30.5, 33.2, 47.6, 48.0, 126.3, 128.2, 128.3, 143.3, 208.5. IR (neat): 1716. MS m/z: 190 (M^+).

(*S*)-4-(3-Methoxyphenyl)-5-methylhexan-2-one (8bb)[14] **(Entry 4)** Eluent, hexane/AcOEt=30/1. Colorless oil. $[\alpha]_D^{20}$ −21.8 (c=1.16, $CHCl_3$). 77% ee (OD-H, hexane/*i*-PrOH=100/1, 0.5 ml/min, 254 nm; major 33.1 min, minor 25.0 min). ^{1}H-NMR δ: 0.74 (d, J=6.7, 3H), 0.93 (d, J=6.7, 3H), 1.82 (m, 1H), 1.99 (s, 3H), 2.75—2.80 (m, 2H), 2.89 (m, 1H), 3.79 (s, 3H), 6.69—6.75 (m, 3H), 7.19 (dd, J=8.0, 8.0, 1H). ^{13}C-NMR δ: 20.3, 20.6, 30.5, 33.2, 47.6, 48.1, 55.1, 111.2, 114.4, 120.7, 129.1, 145.1, 159.5, 208.4. IR (neat): 1717, 1601. MS m/z: 220 (M^+).

(*S*)-4-(4-(Trifluoromethyl)phenyl)-5-methylhexan-2-one (8bc) (Entry 5) Eluent, hexane/AcOEt=50/1. Colorless oil. $[\alpha]_D^{20}$ −9.5 (c=1.12, $CHCl_3$). 86% ee (AD-H, hexane/*i*-PrOH=100/1, 0.5 ml/min, 254 nm; major 24.6 min, minor 22.3 min). ^{1}H-NMR δ: 0.74 (d, J=6.8, 3H), 0.93 (d, J=6.4, 3H), 1.84 (m, 1H), 2.01 (s, 3H), 2.80 (dd, J=9.5, 16.6, 1H), 2.86 (dd, J=5.0, 16.6, 1H), 3.02 (m, 1H), 7.26 (d, J=8.0, 2H), 7.53 (d, J=8.0, 2H). ^{13}C-NMR δ: 20.2, 20.5, 30.4, 33.0, 47.1, 47.5, 124.3 (q, $^1J_{CF}$=270), 125.1 (q, $^3J_{CF}$=3.1), 128.53 (q, $^2J_{CF}$=31.9), 128.57, 147.8, 207.4. IR (neat): 1717. MS m/z: 258 (M^+). *Anal.* Calcd for $C_{14}H_{16}F_3O$: C, 65.10; H, 6.63. Found: C, 64.95; H, 6.63.

(*S*)-4-(4-Phenylphenyl)-5-methylhexan-2-one (8be) (Entry 6) Eluent, C_6H_6/AcOEt=200/1. White solid. mp 66—68 °C. $[\alpha]_D^{20}$ −19.9 (c=1.07, $CHCl_3$). 79% ee (OD-H, hexane/*i*-PrOH=100/1, 0.5 ml/min, 254 nm; major 21.6 min, minor 20.2 min). ^{1}H-NMR δ: 0.78 (d, J=6.7, 3H), 0.95 (d, J=6.7, 3H), 1.86 (m, 1H), 2.01 (s, 3H), 2.82—2.84 (m, 2H), 2.97 (m, 1H), 7.21 (d, J=8.0, 2H), 7.32 (t, J=7.5, 1H) , 7.42 (dd, J=7.5, 8.0, 2H) , 7.50 (d, J=8.0, 2H), 7.57 (d, J=8.0, 2H). ^{13}C-NMR δ: 20.3, 20.6, 30.5, 33.2, 47.5, 47.6, 126.8, 126.9, 127.1, 128.66, 128.7, 139.1, 140.9, 142.4, 208.3. IR (neat): 1717. MS m/z: 266 (M^+). *Anal.* Calcd for $C_{19}H_{22}O$: C, 85.67; H, 8.32. Found: C, 85.57; H, 8.33.

(*S*)-4-(4-Methoxyphenyl)-4-phenylbutan-2-one (8cd)[35] **(Entry 7)** Eluent, hexane/AcOEt=20/1. Colorless oil. $[\alpha]_D^{20}$ −0.72 (c=0.97, $CHCl_3$). 65% ee (OD-H, hexane/*i*-PrOH=50/1, 1.0 ml/min, 254 nm; major 37.4 min, minor 44.7 min). ^{1}H-NMR δ: 2.07 (s, 3H), 3.14 (d, J=7.7, 2H), 3.76 (s, 3H), 4.54 (t, J=7.7, 1H), 6.81 (d, J=8.9, 2H), 7.12—7.28 (m, 7H). ^{13}C-NMR δ: 30.6, 45.2, 49.8, 55.1, 114.0, 126.4, 127.6, 128.6, 128.7, 136.0, 144.2, 158.1, 207.1. IR (nujol): 1709, 1605. MS m/z: 254 (M^+).

(*S*)-4-(4-Phenylphenyl)-4-phenylbutan-2-one (8ce) (Entry 8) Eluent, C_6H_6/AcOEt=100/1. White solid. mp 117—119 °C. $[\alpha]_D^{20}$ +6.6 (c=0.96, $CHCl_3$). 60% ee (OD-H, hexane/*i*-PrOH=50/1, 1.0 ml/min, 254 nm; major 19.6 min, minor 23.3 min). ^{1}H-NMR δ: 2.11 (s, 3H), 3.22 (d, J=7.3, 2H), 4.64 (t, J=7.3, 1H), 7.19 (m, 1H), 7.26—7.33 (m, 7H), 7.41 (dd, J=7.8, 7.8, 2H), 7.50 (d, J=8.0, 2H), 7.54 (d, J=7.6, 2H). ^{13}C-NMR δ: 30.6, 45.6, 49.6, 126.5, 127.0, 127.1, 127.3, 127.7, 128.1, 128.6, 128.7, 139.3, 140.8, 143.0, 143.8, 206.8. IR (KBr): 1713. MS m/z: 300 (M^+). EI-MS m/z: 300.1504 (Calcd for $C_{22}H_{20}O$: 300.1514).

(*R*)-5-Phenylhexan-3-one (8da)[36] **(Entry 9)** Eluent, hexane/AcOEt=30/1. Colorless oil. $[\alpha]_D^{22}$ −64.2 (c=1.3, C_6H_6); lit. $[\alpha]_D^{22}$ −56.4 (c=1.0, C_6H_6) for *R*. 72% ee (AD-H, hexane/*i*-PrOH=100/1, 0.5 ml/min, 254 nm; major 11.8 min, minor 10.6 min). ^{1}H-NMR δ: 0.98 (t, J=7.4, 3H), 1.26 (d, J=7.0, 3H), 2.26—2.38 (m, 2H), 2.63 (dd, J=8.0, 16.2, 1H), 2.72 (dd, J=6.7, 16.2, 1H), 3.32 (m, 1H), 7.17—7.30 (m, 5H). ^{13}C-NMR δ: 7.5, 21.8, 35.4, 36.6, 50.7, 126.3, 126.8, 128.5, 146.3, 210.5. IR (neat): 1713. MS m/z: 176 (M^+).

(*R*)-5-(4-Phenylphenyl)hexan-3-one (8de) (Entry 10) Eluent, hexane/AcOEt=20/1. White solid. mp 54—56 °C. $[\alpha]_D^{20}$ −36.6 (c=1.0, $CHCl_3$). 74% ee (AD-H, hexane/*i*-PrOH=100/1, 0.5 ml/min, 254 nm; major 24.0 min, minor 18.7 min). ^{1}H-NMR δ: 1.00 (t, J=7.3, 3H), 1.30 (d, J=6.7, 3H), 2.29—2.40 (m, 2H), 2.67 (dd, J=8.0, 16.2, 1H), 2.76 (dd, J=6.7, 16.2, 1H), 3.37 (m, 1H), 7.28 (d, J=8.0, 2H), 7.33 (t, J=7.5, 1H), 7.42 (dd, J=7.5, 8.0, 2H), 7.52 (d, J=8.0, 2H), 7.57 (d, J=8.0, 2H). ^{13}C-NMR δ: 7.5, 21.9, 35.0, 36.6, 50.7, 127.0, 127.1, 127.19, 127.21, 128.7, 139.2, 140.9, 145.5, 210.4. IR (neat): 1713. MS m/z: 252 (M^+). *Anal.* Calcd for $C_{18}H_{20}O$: C, 85.67; H, 7.99. Found: C, 85.48; H, 8.00.

(*R*)-1,3-Diphenyloctan-1-one (8ea)[37] **(Entry 11)** Eluent, hexane/AcOEt=20/1. White solid. mp 63—64 °C. $[\alpha]_D^{20}$ +1.3 (c=1.1, $CHCl_3$). 51% ee (AD, hexane/*i*-PrOH=100/1, 0.5 ml/min, 254 nm; major 19.1 min, minor 15.0 min). ^{1}H-NMR: 0.82 (t, J=6.4, 3H), 1.19—1.26 (m, 6H), 1.60—1.72 (m, 2H), 3.20—3.35 (m, 3H), 7.17 (t, J=7.5, 1H), 7.22 (d, J=7.5, 2H), 7.28 (dd, J=7.5, 7.5, 2H), 7.43 (dd, J=7.5, 7.5, 2H), 7.53 (t, J=7.5, 1H), 7.89 (d, J=7.5, 2H). ^{13}C-NMR: 13.9, 22.4, 27.1, 31.7, 36.2, 41.1, 45.9, 126.2, 127.6, 128.0, 128.4, 128.5, 132.9, 137.3, 145.0, 199.3. IR (neat): 1680. MS m/z: 280 (M^+).

(*R*)-1,3-Diphenylbutan-1-one (8fa)[38] **(Entry 12)** Eluent, hexane/AcOEt=50/1. White solid. mp 50—51 °C. $[\alpha]_D^{25}$ −7.8 (c=2.65, CCl_4); lit. $[\alpha]_D^{25}$ −14.6 (c=1.8, CCl_4) for *R*. 51% ee (AD, hexane/*i*-PrOH=100/1, 0.5 ml/min, 254 nm; major 10.7 min, minor 8.6 min). ^{1}H-NMR: 1.33 (d, J=7.0, 3H), 3.19 (dd, J=8.3, 16.5, 1H), 3.30 (dd, J=5.5, 16.5, 1H), 3.50 (m, 1H), 7.20 (m, 1H), 7.26—7.32 (m, 4H), 7.44 (dd, J=7.5, 7.5, 2H), 7.55 (t, J=7.5, 1H), 7.92 (d, J=7.5, 2H). ^{13}C-NMR: 21.8, 35.5, 47.0, 126.3, 126.9, 128.1, 128.56, 128.59, 133.0, 137.2, 146.6, 199.2. IR (neat): 1682. MS m/z: 224 (M^+).

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