

Asymmetric Rh-Catalyzed Intermolecular Hydroacylation of 1,5-Hexadiene with Salicylaldehyde

Yasuhiro INUI,^a Masakazu TANAKA,^{*,a,b} Masanori IMAI,^c Keitaro TANAKA,^a and Hiroshi SUEMUNE^{*,d}

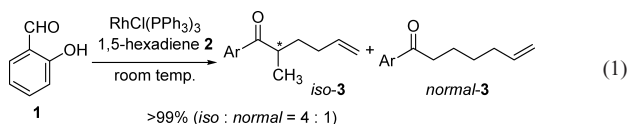
^a Graduate School of Pharmaceutical Sciences, Kyushu University; 3-1-1 Maidashi, Higashi-ku, Fukuoka 812-8582, Japan; ^b Graduate School of Biomedical Sciences, Nagasaki University; 1-14 Bunkyo-machi, Nagasaki 852-8521, Japan; and ^c Hokkaido College of Pharmacy; Hokkaido 047-0264, Japan.

Received June 19, 2009; accepted July 10, 2009; published online July 13, 2009

Asymmetric intermolecular hydroacylation between salicylaldehyde (1) and 1,5-hexadiene (2) using a combination of [RhCl(C₈H₁₄)₂] (0.10 eq), (*S*)-BINAP (0.10 eq), and ZnBr₂ (0.20 eq) afforded an enantiomerically enriched hydroacylated product *iso*-3 of 84% ee, along with an achiral product *normal*-3.

Key words rhodium; intermolecular hydroacylation; chelation; enantioselective reaction

Rh-catalyzed intramolecular^{1–7)} and intermolecular hydroacylations^{8–19)} have recently been the focus of synthetic organic and organometallic chemists. Although Rh-catalyzed asymmetric intramolecular hydroacylation (asymmetric cyclization) has been extensively studied by us,^{20–24)} and other groups,^{25–28)} Rh-catalyzed asymmetric intermolecular hydroacylation has attracted only limited attention,^{29–31)} except for asymmetric hydroformylation.^{32,33)} This may be because Rh-catalyzed intermolecular hydroacylation did not proceed under mild reaction conditions, but required vigorous reaction conditions. Recently, we have found that Rh-catalyzed intermolecular hydroacylations proceed under mild reaction conditions based on the “double chelation” of aldehyde and diene (Eq. 1).^{34–37)} Here we report enantioselective Rh-catalyzed intermolecular hydroacylation between salicylaldehyde (1) and 1,5-hexadiene (2).



The hydroacylation between salicylaldehyde (1) and 1,5-hexadiene (2, 6 eq) using RhCl(PPh₃)₃ (0.20 eq) at room temperature afforded a mixture of *iso*-hydroacylated product 3 and *normal*-hydroacylated product 3 in the ratio of 4 to 1 in quantitative yield (Eq. 1). The *iso*-hydroacylated product 3 has a chiral carbon at the α-position. Thus, we envisaged that the asymmetric induction from prochiral 1,5-hexadiene would be possible, if Rh-complex with chiral phosphine ligand were used instead of achiral RhCl(PPh₃)₃.

First, we examined the hydroacylation between salicylaldehyde (1) and 1,5-hexadiene (2) using Rh[(*R*)-BINAP]Cl (0.40 eq) at room temperature. Fortunately, the reaction afforded the mixture of *iso*-3 and *normal*-3 in the ratio of 3 to 1, and the specific rotation [α]_D of the mixture showed +9.6. This result means that the *iso*-product is not racemic but optically active, even though the chemical yield was merely 4% (entry 1 in Table 1). This result prompted us to further improve the chemical yield of the product and increase its specific rotation. We increased the amount of Rh-catalyst to 1.0 eq, but the yield of products was not improved. Several additives, such as bases, silver salts, and Lewis acids, were then examined, as shown in Table 1. We thought that the addition of base would deprotonate phenolic protons of salicyl-

aldehyde and promote hydroacylation. In contrast, the addition of silver salt would change the property of Rh-complex to a cationic species to accelerate the reaction. Unfortunately, the addition of bases, such as K₂CO₃, KOAc, and NaOAc, did not improve the yield (entries 3–5), and the addition of silver salts, such as AgClO₄ and CF₃CO₂Ag, improved the yield of products but their specific rotations were zero, meaning that the products were racemic (entries 6–8). Finally, it was found that the addition of Lewis acid improved the yield of products (entries 9–12); in particular, the addition of Zn(OTf)₂ (0.20 eq) improved the yield of product and its specific rotation showed –26° (entry 11). However, the addition of Zn(OTf)₂ and elevated temperature (50 °C) induced the migration of olefin function to produce inseparable olefin mixtures of *iso*-3, along with *normal*-3 as a by-product. Therefore, the enantiomeric excess of *iso*-3 could not be directly determined by HPLC using a chiral column. Thus, the mixture of products was hydrogenated by H₂/5% Pd–C to produce saturated hydroacylated products *iso*-4 and *normal*-4

Table 1. Effect of Additive on Asymmetric Intermolecular Hydroacylation

Entry	Additive (eq)	Temp. (°C)	Time (h)	3: Yield % (i : n)	[α] _D ^d
1	—	rt ^b	120	4 (3 : 1)	+9.6
2 ^c	—	rt	120	5 (3 : 1)	— ^d
3	K ₂ CO ₃ (0.4) ^e	rt	120	2 (2 : 1)	— ^d
4	K ₂ CO ₃ (0.4) ^f	40	120	13 (2 : 1)	— ^d
5	KOAc (0.4) ^f	40	120	16 (3 : 1)	— ^d
6	AgClO ₄ (0.4)	40	120	23 (3 : 1)	0
7	AgClO ₄ (0.4), NaOAc (0.4) ^f	50	14	90 (2 : 1)	0
8	CF ₃ CO ₂ Ag (0.4), NaOAc (0.4) ^f	50	72	88 (4 : 1)	0
9	Mg(OTf) ₂ (0.2) ^f	50	72	22 (2 : 1)	–1.8
10	MgCl ₂ (0.2) ^f	50	72	Trace	— ^d
11	Zn(OTf) ₂ (0.2) ^f	50	48	85 (3 : 1)	–26.8 ^g
12	Cu(OTf) ₂ (0.2) ^f	50	72	17 (1 : 1)	–1.8

a) Specific rotation of the mixture of products. b) Reaction at 50 °C afforded a mixture of products in 15% yield. c) 1.0 eq of Rh-complex was used. d) Not measured. e) NaOAc was also examined. f) 5% EtOH in CICH₂CH₂Cl was used as a solvent. g) Enantiomeric excess of *iso*-3 was 68% ee.

* To whom correspondence should be addressed. e-mail: matanaka@nagasaki-u.ac.jp

in quantitative yield, and the enantiomeric excess of *iso-4* was determined by HPLC using a chiral column. The enantiomeric excess of *iso-4* in entry 11 was determined to be 68% ee.

Next, we studied the effect of chiral bidentate phosphine ligand on the enantiomeric excess of product. The results are summarized in Table 2. We examined hydroacylation using Rh(ligand)Cl (0.20 eq) and Zn(OTf)₂ (0.10 eq) at 50 °C. In these conditions, where a reduced amount of Rh-catalyst was used, the yield of products generally decreased, except for the (*R,R*)-Me-BPE ligand, and enantiomeric excesses fell. Even using Rh[(*S*)-BINAP]Cl (0.20 eq), the enantiomeric excess of *iso-3* decreased to 53% ee (entry 1). Thus, we have not found a phosphine ligand which showed better enantiomeric excess than the (*S*)-BINAP ligand.

We optimized the reaction conditions of Rh-catalyzed hydroacylation in the presence of zinc salts (Table 3). Hydroacylation by Rh[(*S*)-BINAP]Cl (0.20 eq) in the presence of Zn(OTf)₂ and K₂CO₃ did not efficiently proceed at room temperature (entry 1). The equivalence of Zn(OTf)₂ was tested (entries 2–4), and when 0.10–0.20 eq Zn(OTf)₂ was added, the reaction afforded *iso-3* of 53–54% ee (entries 3, 4), but the decrease of Zn(OTf)₂ to 0.05 eq was disadvantageous for the enantiomeric excess of the product. Furthermore, addition of a base was detrimental to the enantiomeric excess (entry 5). When ZnBr₂ (0.10 or 0.20 eq) was added as a zinc salt, the best enantiomeric excess (78% ee) of *iso-3* was attained (entries 6–9), although the ratio of *iso/normal* (2 : 1) was not good.

In the aforementioned reactions, the neutral Rh-complex Rh[(*R*)-BINAP]Cl was prepared *in situ* by mixing [RhCl(C₈H₁₄)₂]₂ (0.10 eq, 0.20 eq as Rh-metal) with bidentate phosphine ligand (*S*)-BINAP (0.2 eq) in 5% EtOH of CICH₂-CH₂Cl solution,³⁸ and then the ratio of [RhCl(C₈H₁₄)₂]₂ and BINAP ligand was checked. The results are summarized in Table 4. A reduced amount of (*S*)-BINAP ligand to 0.10 eq, that is to say, the ratio of Rh-metal/ligand is 2/1, enhanced the enantiomeric excess of *iso*-(–)-**3** to 84% ee, although the ratio of *iso/normal* decreased (entry 2). However, the use of further reduced (*S*)-BINAP ligand (0.05 eq) was detrimental to the reaction and the enantiomeric excess (entry 3). Enantiomeric (*R*)-BINAP ligand afforded the enantiomeric (+)-product (entry 4). To improve the enantiomeric excess, the reaction was performed at 40 °C, but a lower temperature was disadvantageous, and the enantiomeric excess of *iso-3* decreased to 71% ee (entry 5). The best enantiomeric excess (84% ee) of *iso-3* was attained in entries 2 and 4 of Table 4, although under these reaction conditions a mixture of *iso*- and *normal-3* in the ratio of 1 to 1 was obtained, and the migration of olefin in the products was observed.

The reaction mechanisms, such as the role of zinc salt, and the enantio-face selection are unclear. We considered that zinc salt as Lewis acid may coordinate the carbonyl function of aldehyde and promote the reaction. The best enantiomeric excess of *iso-3* (84% ee as a hydrogenated *iso-4*) was attained when the reaction was performed using the ratio of 2 to 1 of Rh-metal and BINAP ligand; thus, the real Rh-catalyst may be dimeric Rh-complexes, such as η⁶-Ph-bi-Rh-complexes and μ₂-ligand-Rh-complexes.

In summary, we developed asymmetric intermolecular hydroacylation between salicylaldehyde **1** and 1,5-hexadiene **2**

Table 2. Effect of Phosphine Ligand on Asymmetric Hydroacylation

Entry	Ligand ^{a)}	Time (h)	Yield % (i : n)	<i>iso-3</i> % ee
1	(<i>S</i>)-BINAP	72	68 (2 : 1)	53
2	(<i>S</i>)-Tol-BINAP	72	65 (1 : 1)	53
3	(<i>R,R</i>)-Me-BPE	48	85 (1 : 2)	6
4	(<i>R,R</i>)-Me-DUPHOS	72	18 (1 : 2)	17
5	(<i>R,R</i>)-DIOP	72	50 (4 : 1)	0
6	(<i>S</i>)-(<i>R</i>)-PPFA	72	45 (2 : 1)	0

a) Abbreviations: (*S*)-BINAP: (*S*)-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl; (*S*)-Tol-BINAP: (*S*)-2,2'-bis(di-*p*-tolylphosphino)-1,1'-binaphthyl; (*R,R*)-Me-BPE: 1,2-bis-((2*R*,5*R*)-2,5-dimethylphospholano)ethane; (*R,R*)-Me-DUPHOS: 1,2-bis((2*R*,5*R*)-2,5-dimethylphospholano)benzene; (*R,R*)-DIOP: (4*R*,5*R*)-4,5-bis(diphenylphosphinomethyl)-2,2-dimethyl-1,3-dioxolane; (*S*)-(*R*)-PPFA: (*R*)-*N,N*-dimethyl-1-[(*S*)-2-(diphenylphosphino)ferrocenyl]ethylamine.

Table 3. Effect of Zinc Salts and Reaction Conditions on Intermolecular Hydroacylation

Entry	Zinc salt (eq)	Yield % (i : n)	<i>iso-3</i> % ee
1	Zn(OTf) ₂ (0.2), K ₂ CO ₃ (0.2) ^{a)}	5 (2 : 1)	— ^{b)}
2	Zn(OTf) ₂ (0.05)	84 (2 : 1)	44
3 ^{c)}	Zn(OTf) ₂ (0.1)	68 (2 : 1)	53
4	Zn(OTf) ₂ (0.2)	78 (2 : 1)	54
5	Zn(OTf) ₂ (0.1), K ₃ PO ₄ (0.1)	82 (2 : 1)	8
6	ZnCl ₂ (0.1)	96 (2 : 1)	62
7	ZnBr ₂ (0.1)	81 (1 : 1)	77
8	ZnBr ₂ (0.2)	83 (2 : 1)	78
9	ZnI ₂ (0.1)	75 (2 : 1)	60

a) Reaction was carried out at room temperature. b) Not measured. c) Entry 3 is same as entry 1 in Table 2.

Table 4. Effect of Ratio of RhCl[(C₈H₁₄)₂]₂ and Phosphine Ligand BINAP

Entry	BINAP (eq)	Yield % (i : n)	<i>iso-3</i> % ee	[α] _D ^{c)}
1 ^{d)}	(<i>S</i>)-BINAP (0.2)	83 (2 : 1)	78	–30.8
2	(<i>S</i>)-BINAP (0.1)	86 (1 : 1)	84	–26.7
3	(<i>S</i>)-BINAP (0.05)	68 (1 : 2)	61	–15.8
4	(<i>R</i>)-BINAP (0.1)	81 (1 : 1)	84	+24.8
5 ^{e)}	(<i>S</i>)-BINAP (0.1)	89 (1 : 1)	71	–21.2

a) 0.2 eq as Rh-metal. b) 5% EtOH in CICH₂CH₂Cl was used as a solvent, and the reaction was performed at 50 °C. c) Specific rotation of mixture of *iso*- and *normal-3*. d) Entry 1 is the same as entry 8 in Table 3. e) Reaction was performed at 40 °C.

using a combination of [RhCl(C₈H₁₄)₂]₂, (*S*)-BINAP, and ZnBr₂. The reaction afforded an enantiomerically enriched hydroacylated *iso-3* of 84% ee (as a hydrogenated *iso-4*), along with an achiral *normal-3* in 86% yield.³⁹⁾

Experimental

Typical Procedure A solution of [RhCl(C₈H₁₄)₂]₂ (72 mg, 0.10 mmol, 0.20 mmol as Rh-metal) and (*S*)-BINAP (62.3 mg, 0.10 mmol) in 5% EtOH

of $\text{CICH}_2\text{CH}_2\text{Cl}$ (4 ml) was stirred at room temperature for 1 h under Ar atmosphere. Then, salicylaldehyde (**1**, 122 mg, 1.0 mmol), 1,5-hexadiene (**2**, 493 mg, 6.0 mmol), and ZnBr_2 (45 mg, 0.20 mmol) were added, and the solution was stirred at 50 °C under Ar atmosphere. After being stirred for 48 h, Et_2O was added, and the resulting precipitate was filtered off. After removal of the solvent, the residue was purified by column chromatography on silica gel (10% EtOAc in hexane) to give a 1:1 mixture of *iso*-**3** and *normal*-**3** (176 mg, 86%) as a colorless oil. $[\alpha]_D^{25} -26.7$ ($c=1.0$, CHCl_3).

1-(2-Hydroxyphenyl)-2-methylhexan-1-one (iso-4) and 1-(2-Hydroxyphenyl)heptan-1-one (normal-4) A mixture of *iso*-**3** and *normal*-**3** (50 mg, 0.245 mmol) and 5% Pd-C (50 mg) in MeOH (5 ml) was rigorously stirred under H_2 atmosphere at room temperature for 4 h. Then, the Pd-catalyst was filtered off, and the filtrate was evaporated *in vacuo*. The residue was purified by column chromatography on silica gel (10% EtOAc in hexane) to leave *iso*-**4** and *normal*-**5** (50 mg, quantitative) as a colorless oil. Both isomers could be separated by preparative TLC. *iso*-**4**: a colorless oil; IR (neat) cm^{-1} : 3045, 2959, 2932, 1638; $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ : 12.6 (1H, s), 7.76 (1H, br d, $J=8$ Hz), 7.43 (1H, br t, $J=8$ Hz), 6.97 (1H, br d, $J=8$ Hz), 6.87 (1H, br t, $J=8$ Hz), 3.48 (1H, sestet, $J=6.5$ Hz), 1.80 (1H, m), 1.39 (1H, m), 1.28 (2H, m), 1.19–1.20 (5H, m), 0.86 (3H, t, $J=6.5$ Hz) ppm; FAB-MS m/z : 207 $[(M+1)^+]$. *normal*-**4**: a colorless oil; IR (neat) cm^{-1} : 3039, 2955, 2929, 1639; $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ : 12.4 (1H, s), 7.74 (1H, br d, $J=8$ Hz), 7.43 (1H, br t, $J=8$ Hz), 6.95 (1H, br d, $J=8$ Hz), 6.87 (1H, br t, $J=8$ Hz), 2.96 (2H, t, $J=7.4$ Hz), 1.72 (2H, quintet, $J=7.4$ Hz), 1.19–1.39 (6H, m), 0.88 (3H, t, $J=6.5$ Hz) ppm; FAB-MS m/z : 207 $[(M+1)^+]$.

Determination of the Enantiomeric Excess of iso-3 The enantiomeric excess of *iso*-**3** was determined by HPLC, after conversion of *iso*-**3** into *iso*-**4** by hydrogenation. HPLC conditions: column: CHIRALCEL OB-H, 0.46 $\text{cm}\phi\times 25$ cm; detection: UV 254 nm; eluent: 0.1% *iso*-PrOH in hexane; flow rate: 0.5 ml/min; retention time (t_R): (–)-*iso*-**4**, 9.8 min, (+)-*iso*-**4**, 11.8 min, *normal*-**4**, 15 min.

Acknowledgements This work was supported in part by a Grant-in-Aid for Young Scientists (B) from the Japan Society for the Promotion of Science.

References and Notes

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