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Rhodium-Catalyzed Kinetic Resolution of Tertiary Homoallyl Alcohols via Stereoselective Carbon–Carbon Bond Cleavage

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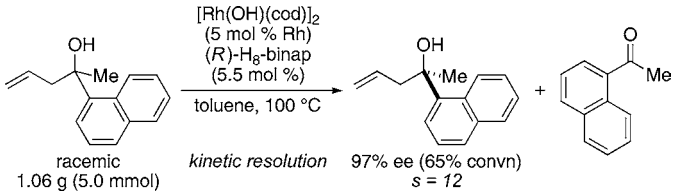
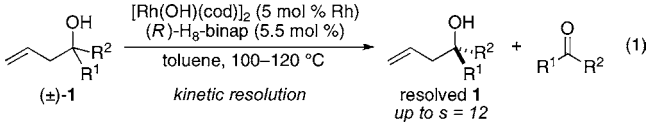
ABSTRACT



A nonenzymatic kinetic resolution of tertiary homoallyl alcohols has been developed through a rhodium-catalyzed retro-allylation reaction under simple conditions. Selectivity factors of up to 12 have been achieved by employing (*R*)-H$_8$-binap as the ligand, and the reaction can be conducted on a preparative scale.

Nonenzymatic kinetic resolution of racemic secondary alcohols has been extensively investigated in the past few decades and has reached its mature stage.[1,2] In contrast, the corresponding kinetic resolution of tertiary alcohols has been much less studied, and to the best of our knowledge, there are only two effective nonenzymatic catalyst systems available to date. Thus, Miller developed peptide-based organocatalysts for enantioselective acylation of tertiary alcohols bearing an acetamido group at the β-carbon,[3] and Matsunaga and Shibasaki recently described the use of mixed La/Li heterobimetallic catalysts for the kinetic resolution of tertiary alcohols having a nitro group at the β-carbon through a retro-nitroaldol reaction.[4] To remedy this methodological deficiency, we envisioned that efficient kinetic resolution might be achieved by late transition metal-catalyzed stereoselective cleavage of an α,β-carbon−carbon bond in racemic tertiary alcohols. In particular, here we focus on utilizing the retro-allylation approach under transition-metal catalysis,[5,6] and we demonstrate that a Rh/(*R*)-H$_8$-binap complex can effectively catalyze kinetic resolution of tertiary homoallyl alcohols under simple reaction conditions (eq 1).



In an initial investigation, we employed racemic 2-phenyl-4-penten-2-ol (**1a**) as a model homoallyl alcohol and con-

(1) For reviews, see: (a) Kagan, H. B.; Fiaud, J. C. *Top. Stereochem.* **1988**, *18*, 249. (b) Vedejs, E.; Jure, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 3974. (c) Robinson, D. E. J. E.; Bull, S. D. *Tetrahedron: Asymmetry* **2003**, *14*, 1407. See also: (d) Fu, G. C. *Acc. Chem. Res.* **2000**, *33*, 412.

(2) For recent progress, see: (a) Rendler, S.; Auer, G.; Oestreich, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 7620. (b) Birman, V. B.; Li, X.; Jiang, H.; Uffman, E. W. *Tetrahedron* **2006**, *62*, 285. (c) MacKay, J. A.; Vedejs, E. *J. Org. Chem.* **2006**, *71*, 498. (d) Mazet, C.; Roseblade, S.; Köhler, V.; Pfaltz, A. *Org. Lett.* **2006**, *8*, 1879. (e) Li, Y.-Y.; Zhang, X.-Q.; Dong, Z.-R.; Shen, W.-Y.; Chen, G.; Gao, J.-X. *Org. Lett.* **2006**, *8*, 5565.

(3) (a) Jarvo, E. R.; Evans, C. A.; Copeland, G. T.; Miller, S. J. *J. Org. Chem.* **2001**, *66*, 5522. (b) Angione, M. C.; Miller, S. J. *Tetrahedron* **2006**, *62*, 5254.

(4) Tosaki, S.; Hara, K.; Gnanadesikan, V.; Morimoto, H.; Harada, S.; Sugita, M.; Yamagiwa, N.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2006**, *128*, 11776.

(5) Rhodium catalysis: (a) Takada, Y.; Hayashi, S.; Hirano, K.; Yorimitsu, H.; Oshima, K. *Org. Lett.* **2006**, *8*, 2515. (b) Jang, M.; Hayashi, S.; Hirano, K.; Yorimitsu, H.; Oshima, K. *Tetrahedron Lett.* **2007**, *48*, 4003.

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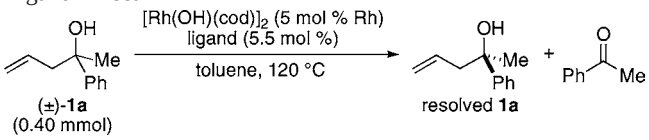
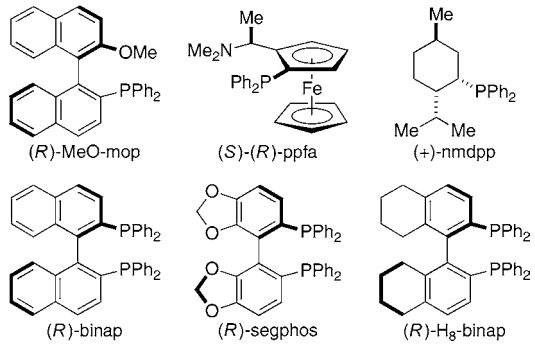
ducted a rhodium-catalyzed retro-allylation reaction with various chiral phosphine ligands (Table 1). On the basis of

Table 1. Rhodium-Catalyzed Kinetic Resolution of (±)-**1a**: Ligand Effect



entry	ligand	time (h)	ee of resolved **1a**[a]	s[b]
1[c]	(*R*)-MeO-mop	0.5	17% ee (*S*) (49% convn)	1.7
2[c]	(*S*)-(*R*)-ppfa	1.5	1% ee (*S*) (66% convn)	1.0
3[c]	(+)-nmdpp	1.5	25% ee (*S*) (70% convn)	1.5
4	(*R*)-binap	17	51% ee (*R*) (49% convn)	5.3
5	(*R*)-segphos	17	52% ee (*R*) (46% convn)	6.8
6	(*R*)-H_8-binap	17	89% ee (*R*) (67% convn)	7.0

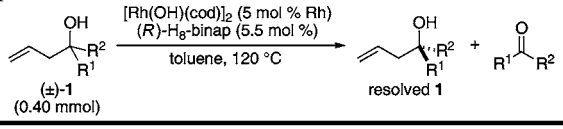
[a] The ee was determined by chiral HPLC after purification and the conversion was dermined by crude ^{1}H NMR against internal standard (1,4-dimethoxybenzene). [b] $s = \ln\{(1 - c)(1 - ee)\}/\ln\{(1 - c)(1 + ee)\}$ where c is the conversion of **1a** and *ee* is the ee of remaining **1a**. [c] 11 mol % of ligand was used.

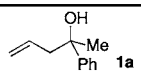
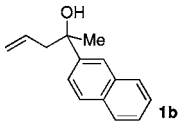
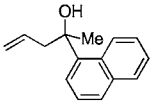
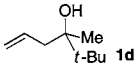
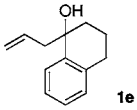
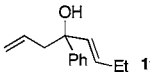


the report by Yorimitsu and Oshima where monodentate phosphines are effective ligands on rhodium catalysts for retro-allylation,[5] we started our study by using chiral monodentate phosphine ligands, such as (*R*)-MeO-mop,[7] (*S*)-(*R*)-ppfa,[8] and (+)-nmdpp.[9] As expected, retro-allylation of (±)-**1a** smoothly proceeded in the presence of 5 mol % of rhodium/monophosphine catalyst in toluene at 120 °C, reaching 49−70% conversions within 90 min (entries 1−3). Unfortunately, however, these chiral ligands could not effectively distinguish between the two enantiomers of **1a**, resulting in almost nonselective processes ($s = 1.0-1.7$). In contrast, we found that the use of (*R*)-binap,[10] a chiral bisphosphine ligand, induced higher enantioselectivity ($s =$ 5.3), albeit in lower reactivity (49% conversion after 17 h; entry 4). The change of (*R*)-binap to its analogues, (*R*)-segphos[11] and (*R*)-H_8-binap,[12] led to further improvement of stereoselectivity ($s = 6.8$ and $s = 7.0$, respectively; entries 5 and 6). The absolute configuration of remaining **1a** in entry 6 (89% ee) was determined to be (*R*) by comparison of the optical rotation with the reported value in the literature.[13]

Under these conditions with (*R*)-H_8-binap as a ligand, several tertiary homoallyl alcohols can be kinetically resolved through retro-allylation (Table 2). Thus, 2-(2-naphthyl)-4-

Table 2. Rhodium-Catalyzed Kinetic Resolution of (±)-**1**: Scope



entry	substrate	time (h)	ee of resolved **1**[a]	s[b]
1	 **1a**	9	89% ee (*R*) (67% convn)	7.0
2	 **1b**	9	88% ee (*R*) (68% convn)	6.4
3	 **1c**	9	94% ee (*R*) (67% convn)	8.8
4[c]		24	94% ee (*R*) (64% convn)	11
5	 **1d**	9	84% ee (*R*) (70% convn)	5.1
6	 **1e**	6	71% ee (*R*) (61% convn)	5.4
7	 **1f**	5	70% ee (*S*) (67% convn)	4.0

[a] The ee was determined by chiral HPLC after purification and the conversion was dermined by crude ^{1}H NMR against internal standard (1,4-dimethoxybenzene). [b] $s = \ln\{(1 - c)(1 - ee)\}/\ln\{(1 - c)(1 + ee)\}$ where c is the conversion of **1** and *ee* is the ee of remaining **1**. [c] The reaction was conducted at 100 °C.

penten-2-ol (**1b**) gave the resolved alcohol in 88% ee at 68% conversion ($s = 6.4$; entry 2) and 2-(1-naphthyl)-4-penten-2-ol (**1c**) gave 94% ee at 67% conversion ($s = 8.8$; entry 3). Somewhat better selectivity factor ($s = 11$) was observed when **1c** was resolved at 100 °C (entry 4). In addition to these 2-aryl-4-penten-2-ols, alkyl-substituted alcohol **1d** was also resolved with reasonably high efficiency ($s = 5.1$; entry 5). Other homoallyl alcohols such as cyclic alcohol **1e** and aryl alkenyl carbinol **1f** were employed as well, achieving $s = 5.4$ and $s = 4.0$, respectively (entries 6 and 7). It is worth

(6) Ruthenium catalysis: (a) Kondo, T.; Kodoi, K.; Nishinaga, E.; Okada, T.; Morisaki, Y.; Watanabe, Y.; Mitsudo, T. *J. Am. Chem. Soc.* **1998**, *120*, 5587. Palladium catalysis: (b) Hayashi, S.; Hirano, K.; Yorimitsu, H.; Oshima, K. *J. Am. Chem. Soc.* **2006**, *128*, 2210. (c) Iwasaki, M.; Hayashi, S.; Hirano, K.; Yorimitsu, H.; Oshima, K. *J. Am. Chem. Soc.* **2007**, *129*, 4463.

(7) (a) Hayashi, T. *Acc. Chem. Res.* **2000**, *33*, 354. (b) Uozumi, Y.; Tanahashi, A.; Lee, S.-Y.; Hayashi, T. *J. Org. Chem.* **1993**, *58*, 1945.

(8) 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.

(9) Morrison, J. D.; Masler, W. F. *J. Org. Chem.* **1974**, *39*, 270.

(10) Takaya, H.; Mashima, K.; Koyano, K.; Yagi, M.; Kumobayashi, H.; Taketomi, T.; Akutagawa, S.; Noyori, R. *J. Org. Chem.* **1986**, *51*, 629.

(11) Saito, T.; Yokozawa, T.; Ishizaki, T.; Moroi, T.; Sayo, N.; Miura, T.; Kumobayashi, H. *Adv. Synth. Catal.* **2001**, *343*, 264.

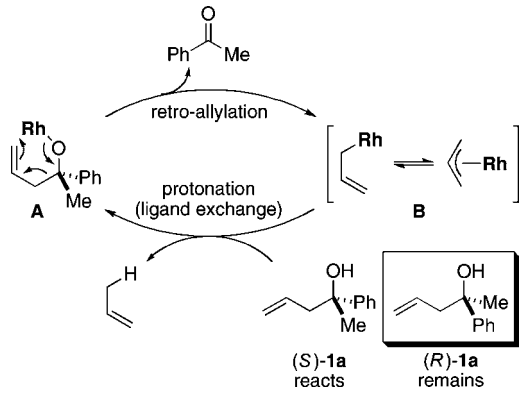
(12) Zhang, X.; Mashima, K.; Koyano, K.; Sayo, N.; Kumobayashi, H.; Akutagawa, S.; Takaya, H. *Tetrahedron Lett.* **1991**, *32*, 7283.

(13) Soai, K.; Ishizaki, M.; Yokoyama, S. *Chem. Lett.* **1987**, 341.

noting that the results shown here represent rare examples where significantly high enantioselectivity is observed in the asymmetric reactions at as high as 120 °C.

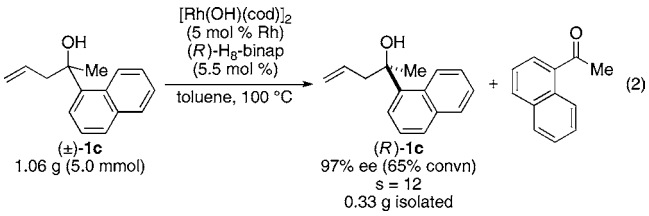
On the basis of the absolute configuration of the unreacted alcohol, a proposed catalytic cycle of this process with substrate **1a** is illustrated in Scheme 1. Thus, alkoxorhodium

Scheme 1. Proposed Catalytic Cycle for the Rhodium-Catalyzed Kinetic Resolution of (±)-**1a** (**Rh** = Rh((*R*)-H_8-binap)).



species **A** derived from (*S*)-**1a** preferentially undergoes retro-allylation to give acetophenone and allylrhodium species **B**. The allyl-moiety of intermediate **B** is then protonated through ligand exchange with (*S*)-**1a**, regenerating alkoxorhodium **A** and leaving (*R*)-**1a** behind.

Of course, the present catalysis can be easily scaled up as shown in eq 2. Thus, 5.0 mmol of (±)-**1c** was subjected to the Rh/(*R*)-H_8-binap-catalyzed retro-allylation at 100 °C, giving resolved **1c** in 97% ee at 65% conversion ($s = 12$).



In summary, we have developed a rhodium-catalyzed kinetic resolution of tertiary homoallyl alcohols under simple reaction conditions. High selectivity factors have been achieved by employing (*R*)-H_8-binap as the ligand and the reaction can be conducted on a preparative scale. Future studies will explore further improvement of the reaction conditions and expansion of the substrate scope.

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Supporting Information Available: Experimental procedures and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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