HHS Public Access

Author manuscript

Angew Chem Int Ed Engl. Author manuscript; available in PMC 2020 March 26.

Published in final edited form as:

Angew Chem Int Ed Engl. 2019 March 26; 58(14): 4705–4709. doi:10.1002/anie.201900545.

Dynamic Kinetic Resolution of Aldehydes by Hydroacylation

Zhiwei Chen,
Department of Chemistry, University of California, Irvine, Irvine, California 92697 (United States)

Yusuke Aota,
Department of Chemistry, University of California, Irvine, Irvine, California 92697 (United States)

Department of Chemistry, Graduate School of Sciences, Kyoto University, Sakyo, Kyoto 606-8502 (Japan)

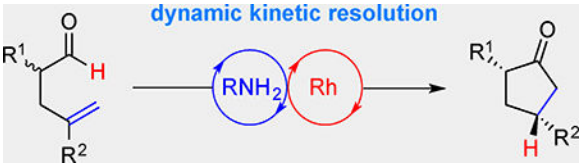
Hillary M. H. Nguyen, and
Department of Chemistry, University of California, Irvine, Irvine, California 92697 (United States)

Vy M. Dong
Department of Chemistry, University of California, Irvine, Irvine, California 92697 (United States)

Abstract

We report a dynamic kinetic resolution (DKR) of chiral 4-pentenals by olefin hydroacylation. A primary amine racemizes the aldehyde substrate via enamine formation and hydrolysis. Then, a cationic Rh-catalyst promotes hydroacylation to generate α,γ-disubstituted cyclopentanones with high enantio- and diastereoselectivities.

Graphical Abstract



Dynamic duo: Racemic α-allyl aldehydes undergo stereoconvergent hydroacylation to generate α,γ-disubstituted cyclopentanones with high diastereo- and enantioselectivities. In this dynamic kinetic resolution, a primary amine catalyst racemizes the aldehyde substrate via enamine formation and hydrolysis, while a Rh-catalyst promotes cyclization.

Keywords

dynamic kinetic resolution; hydroacylation; dual catalysis; C–H activation; rhodium

* dongv@uci.edu.

Conflict of interest
The authors declare no conflict of interest.

By merging epimerization with asymmetric catalysis, chemists have developed powerful ways to convert racemic reagents into enantiopure precursors, including those used for making natural products and medicinal targets.[1] While most dynamic kinetic resolutions (DKR's) feature hydrogenation[2a–c] or acylation,[2d,e] variants that exploit C–C bond formation remain rare.[3] Olefin hydroacylation is an atom-economical[4] route to ketones that achieves both C–H bond activation and C–C bond formation.[5] Herein, we disclose a DKR strategy to prepare α,γ-disubstituted cyclopentanones by intramolecular hydroacylation.

The first kinetic resolution of an α-chiral aldehyde was fortuitously discovered by James in 1983. While attempting to develop an enantioselective decarbonylation, the authors observed that 2-methyl-2-phenylpent-4-enal underwent intramolecular hydroacylation to furnish the corresponding cyclopentanone in up to 69% *ee* (Figure 1a).[6a,b] Fu described a parallel kinetic resolution of racemic 4-alkynals to generate a mixture of enantioenriched cyclopentenones and cyclobutanones.[6c] Most recently, Willis disclosed an kinetic resolution of β-thio aldehydes by intermolecular alkyne hydroacylation.[6d] Aldehydes bearing either α- or β-stereocenters undergo kinetic resolution. These early studies contribute to emerging kinetic resolutions that occur by C–H bond activation,[7] however, the theoretical yield for the enantiopure ketone products is limited to fifty percent. Despite the first resolution over three decades ago, the DKR of aldehydes by hydroacylation had yet to be achieved. In light of this challenge, we imagined combining aldehyde racemization with formyl C–H bond functionalization to invent DKR's via hydroacylation.[8]

We propose using an amine organocatalyst and a Rh-catalyst in tandem to produce α,γ-disubstituted cyclopentanones, a motif not yet accessible by hydroacylation (Figure 1b). Given that branched aldehydes readily undergo epimerization,[9] we reasoned a DKR variant of hydroacylation would be feasible. Since the substrate and product have similar acidities, one challenge would be to identify a catalyst that would rapidly and selectively epimerize the aldehyde reagent, in preference to the ketone product. If successful, this DKR by C–C bond formation would complement Buchwald's DKR of cyclopentenones by asymmetric reduction.[10]

To test our hypothesis, we investigated the cyclization of aldehyde **1a** (Table 1). Our initial studies included various bases, such as alkoxides and tertiary amines. The use of pyridine **A1** and a Segphos-derived ligand (Segphos = 5,5'-bis(diphenylphosphino)-4,4'-bi-1,3-benzodioxole) provided an early lead (Table 1a), where bulkier phosphine substituents afforded higher reactivity (**L2** and **L3**), presumably due to increased dispersive interactions.[11] The combination of **L3** and **A1** led to cyclopentanone **2a** in 33% yield with high stereoselectivities (>20:1 *dr*, 94% *ee*). Aldehydes are known to form enamines with primary amines, and this reactivity has been used by List to achieve a DKR by reductive amination using aniline **A2**.[9b] We found that **A2** promoted the hydroacylation with excellent reactivity (96%) but gave only 4:1 *dr*. However, aliphatic primary amines provided higher diastereocontrol with increased steric bulk: *n*-butylamine (**A3**) (65%, 10:1 *dr*), cyclohexylamine (**A4**) (50%, 16:1 *dr*), and 1-adamantylamine (**A5**) (73%, 14:1 *dr*). By using a lower loading of **A5** (10 mol%) and switching the catalyst counter-ion to SbF_6, **2a** was obtained in high yield and stereocontrol (94%, >20:1 *dr*, >99% *ee*). The absolute

configuration of **2a** was determined to be (2*R*,4*R*) by X-ray crystallography.[12] To demonstrate the scalability of this DKR, we cyclized **1a** on a gram-scale and obtained **2a** in high yield and stereocontrol (89%, >20:1 *dr*, >99% *ee*).

We next examined the cyclization of various α-alkyl aldehydes (Table 2). These branched aldehydes undergo DKR with moderate to high reactivity (**2b–2k**, 52–94%), diastereocontrol (11–>20:1 *dr*), and enantiocontrol (82–>99% *ee*). This hydroacylation is chemoselective for the terminal olefin as styrenyl olefins (**1g**) and internal alkynes (**1h**), remain intact to afford cyclopentanones **2g** and **2h** (11–>20:1 *dr*, 94–95% *ee*). Placing bulkier alkyl substituents on the olefin led to diminished reactivity and diastereoselectivity (**2j**, 21%, 1:1 *dr*, 88% *ee*). However, high reactivity and stereoselectivities were restored by using JoSPOphos (**L4**) as the chiral ligand (89%, >20:1 *dr*, >99% *ee*). We also prepared a monosubstituted cyclic ketone (**2k**, 52%, 82% *ee*). A substrate containing an internal olefin (**1l**) failed to cyclize.

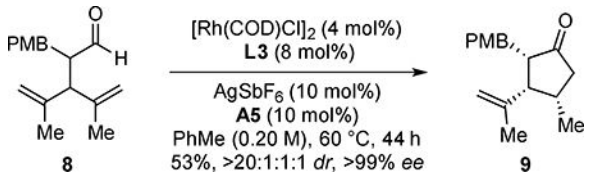
Aldehydes with styrenyl olefins (e.g. **3a**) were slow to react with ligand **L3** (Table 3). To overcome this limitation, we used amine **A5** and ligand **L4**. This combination enabled the resolution of chiral aldehydes bearing a range of styrenyl olefins with excellent stereocontrol (**4a**–**4h**, >20:1 *dr*, 74–>99% *ee*). The absolute configuration of **4a** is analogous to that of **2a**, as determined by X-ray crystallography.[12a]

In contrast to the previous aldehydes, we found that the DKR of α-aryl aldehydes **5** requires an aniline co-catalyst (Table 4). Using **A5** and **L3**, **5a** transformed into cyclopentanone **6a** with high selectivity (>20:1 *dr*, >99% *ee*), albeit with low yield (24%). Switching to other biaryl ligand scaffolds produced similar results. In contrast, changing the amine to 2,6-disubstituted anilines **A7** and **A8** resulted in improved reactivity and diastereocontrol (78–80%, 13–14:1 *dr*).[13] Aniline **A9**, which is more sterically hindered, provided higher diastereocontrol (16:1 *dr*) but lower yield (68%). Using **A8**, we found that Garphos-derived ligand **L5** promoted the formation of **6a** in 87% yield with high stereoselectivities (>20:1 *dr*, >99% *ee*) (Garphos = 2,2’-bis(diphenylphosphino)-4,4’,6,6’-tetramethoxybiphenyl).

We found that **6a** epimerizes on silica and decomposes to form hydroxyketone **6aa** and keto acid **6ab**, which we isolated as the methyl ester (Scheme 1).[12a] This observation is consistent with those reported by Houminer and others that α-aryl cyclopentanones undergo oxidation via a hydroperoxide intermediate.[14] To circumvent this oxidation, we treat the reaction mixture with L-Selectride® to produce the all-*syn* cyclopentanol **7a** with high diastereoselectivity (>20:1:1:1 *dr*) (Table 5). The absolute configuration of **7a** was determined by X-ray crystallography after derivatization to the corresponding 3,5-dinitrobenzoic ester.[12a]

With this two-step protocol, various cyclopentanols can be prepared (**7a**–**7j**, >20:1:1:1 *dr*, 95–>99% *ee*) (Table 5). Cyclopentanols containing aryl halides (**7e**–**7g**) can be accessed with high stereoselectivities (>20:1:1:1 *dr*, 98–>99% *ee*). Electron-deficient (**7g**) and electron-rich arenes (**7h** and **7i**) are tolerated. Cyclopentanols bearing heterocycles (**7j**) are obtained with excellent stereocontrol (>20:1:1:1 *dr*, >99% *ee*). By merging DKR with desymmetrization,[15] the α,β,γ-trisubstituted cyclopentanone **9** can be generated in 53%

yield as a single stereoisomer (>20:1:1:1 *dr*, >99% *ee*) [Eq. (1)]. This example illustrates enantioselective construction of three contiguous stereocenters via a single C–H oxidation.



(1)

We propose a mechanism involving two catalysts (Scheme 2). The primary amine catalyst condenses with aldehyde **1** to form an achiral enamine (**A**) that then undergoes hydrolysis. The *R*-enantiomer ((*R*)-**1**) undergoes oxidative addition with the Rh-catalyst to generate the Rh-acyl-hydride **B**. Subsequent migratory insertion makes metallacycle **C**, which undergoes reductive elimination to afford cyclopentanone **2**. When **1a** was subjected to the Rh-catalyst *in the absence of amine* ***A5***, we observed hydroacylation with the same diastereo- and enantiocontrol (>20:1 *dr*, >99% *ee*), although in lower yield as expected (38%) (Scheme 3a). This experiment points to the aldehyde as being the substrate for hydroacylation, as opposed to the imine intermediate.[16] In the absence of aldehyde, **2a** can be epimerized. When **2a** (>20:1 *dr*) was subjected to the standard reaction conditions with **L3** and **A5**, it was recovered with lower diastereoselectivity (14:1 *dr*). (Scheme 3b). When treated with *n*-butylamine (**A3**), **2a** epimerized more rapidly (5:1 *dr*). Due to unfavorable steric interactions, enamine formation with the product should be more challenging with bulky amines. Moreover, the bulky amine should favor the less substituted enamine **2ab** to avoid allylic strain (Scheme 3c).

An isotope labeling experiment with **1a**-*d* showed that the deuterium label is fully incorporated at the γ-position (Scheme 4a). This result is consistent with a highly regioselective olefin insertion step. We reason that reductive elimination is the turnover-limiting step. When a 1:1 mixture of **1a** and **1a**-*d* was used for the reaction, no primary kinetic isotope effect (KIE) was observed (Scheme 4b), which suggests that oxidative addition and migratory insertion are not turnover-limiting.[17]

By using tandem catalysis,[18] we have added a dynamic twist to hydroacylation. The empirical trends we observed for catalyst choice provides a useful guide for accessing a wide range of enantiopure cyclopentanones that are relatively unique.[19] Our study contributes to a growing class of DKR's that feature aldehyde racemization.[9] The identification of an efficient amine-catalyst for racemization will impact future studies that feature DKR of aldehydes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

Funding provided by UC Irvine and the National Institutes of Health (R35GM127071). Z.C. and H.M.H.N. are grateful for Allergan Fellowships. We thank Kyle B. Brook and Alexander Y. Jiu for help with initial studies and characterization data. We acknowledge Dr. Curtis Moore and Dr. Arnold Rheingold (UC San Diego) for X-ray crystallographic analysis.

References

[1]. a)For selected reviews on dynamic kinetic resolution, see: Bhat V, Welin ER, Guo X, Stoltz BM, Chem. Rev 2017, 117, 4528–4561; [PubMed: 28164696] b)Nakano K, Kitamura M in Separation of Enantiomers: Synthetic Methods (Ed. Todd M), Wiley-VCH: Weinheim, 2014, pp. 161–216;c)Verho O, Bäckvall J-E, J. Am. Chem. Soc 2015, 137, 3996–4009; [PubMed: 25730714] d)Pàmies O, Bäckvall J-E, Chem. Rev 2003, 103, 3247–3262. [PubMed: 12914497]

[2]. a)For selected examples using hydrogenation, see: Steward KM, Gentry EC, Johnson JS, J. Am. Chem. Soc 2012, 134, 7329–7332; [PubMed: 22509806] b)Wang DS, Chen Q-A, Li W, Yu C-B, Zhou Y-G, Zhang X, J. Am. Chem. Soc 2010, 132, 8909–8911; [PubMed: 20552968] c)Xie J-H, Liu S, Kong W-L, Bai W-J, Wang X-C, Wang L-X, Zhou Q-L, J. Am. Chem. Soc 2009, 131, 4222–4223. [PubMed: 19267434] d)For selected examples using acylation, see:Piotrowski DW, Kamlet AS, Dechert-Schmitt A-MR, Yan J, Brandt TA, Xiao J, Wei L, Barrila MT, J. Am. Chem. Soc 2016, 138, 4818–4823; [PubMed: 27003237] e)Lee SY, Murphy JM, Ukai A, Fu GC, J. Am. Chem. Soc 2012, 134, 15149–15153. [PubMed: 22934603]

[3]. For a review of C–C bond formations using DKR, see Bartlett SL, Johnson JS, Acc. Chem. Res 2017, 50, 2284–2296. [PubMed: 28817258] Also, see Doyle AG, Jacobsen EN, Angew. Chem. Int. Ed 2007, 46, 3701–3705.

[4]. Trost BM, Science 1991, 254, 1471–1477. [PubMed: 1962206]

[5]. a)For selected reviews, see: Murphy SK, Dong VM, Chem. Commun 2014, 50, 13645–13649;b)Willis MC, Chem. Rev 2010, 110, 725–748. [PubMed: 19873977]

[6]. a) James BR, Young CG, J. Chem. Soc., Chem. Commun 1983, 1215–1216;b)James BR, Young CG, J. Organomet. Chem 1985, 285, 321–332;c)Tanaka K, Fu GC, J. Am. Chem. Soc 2003, 125, 8078–8079; [PubMed: 12837058] d)González-Rodríguez C, Parsons SR, Thompson AL, Willis MC, Chem. Eur. J 2010, 16, 10950–10954. [PubMed: 20715218]

[7]. a)For selected examples of kinetic resolutions by C–H functionalization, see: Xiao K-J, Chu L, Chen G, Yu J-Q, J. Am. Chem. Soc 2016, 138, 7796–7800; [PubMed: 27249208] b)Zheng J, You S-L, Angew. Chem. Int. Ed 2014, 53, 13244–13247;c)Chu L, Xiao K-J, Yu J-Q, Science 2014, 346, 451–455; [PubMed: 25342799] d)Larrow JF, Jacobsen EN, J. Am. Chem. Soc 1994, 116, 12129–12130.

[8]. For a dynamic kinetic asymmetric transformation (DYKAT) of 1,3-disubstituted allenes using hydroacylation, see Osborne JD, Randell-Sly HE, Currie GS, Cowley AR, Willis MC, J. Am. Chem. Soc 2008, 130, 17232–17233. [PubMed: 19053453]

[9]. a)For selected dynamic kinetic resolutions of aldehydes, see: Xie J-H, Zhou Z-T, Kong W-L, Zhou Q-L, J. Am. Chem. Soc 2007, 129, 1868–1869; [PubMed: 17263537] b)Hoffmann S, Nicoletti M, List B, J. Am. Chem. Soc 2006, 128, 13074–13075; [PubMed: 17017786] c)Cheng X, Goddard R, Buth G, List B, Angew. Chem. Int. Ed 2008, 47, 5079–5081;d)Lee A, Michrowska A, Sulzer-Mosse S, List B, Angew. Chem. Int. Ed 2011, 50, 1707–1710.

[10]. Jurkauskas V, Buchwald SL, J. Am. Chem. Soc 2002, 124, 2892–2893. [PubMed: 11902878]

[11]. For a review of London dispersion, see Wagner JP, Schreiner PR, Angew. Chem. Int. Ed 2015, 54, 12274–12296.

[12]. a) See the Supporting Information for more details; b) CCDC 1869120 contains the supplementary crystallographic data for **2a**.

[13]. Sterically encumbered anilines are also effective for racemizing α-alkyl aldehydes. Using L3 and A8, 1a cyclized to 2a with high diastereo- and enantioselectivity (86%, >20:1 dr, 96% ee).

[14]. a) Houminer Y, J. Org. Chem. 1985, 50, 786–789;b)For selected additional reports, see:Schröder K, Join B, Amali AJ, Junge K, Ribas X, Costas M, Beller M, Angew. Chem. Int. Ed 2011, 50, 1425–1429;c)Paju A, Kanger T, Pehk T, Lopp M, Tetrahedron 2002, 58, 7321–7326.

[15]. a)For selected examples of desymmetrizations using olefin hydroacylation, see: Park J-W, Kou KGM, Kim DK, Dong VM, Chem. Sci 2015, 6, 4479–4483; [PubMed: 26508999] b)Phan DHT, Kou KGM, Dong VM J. Am. Chem. Soc 2010, 132, 16354–16355; [PubMed: 21028819] c)Tanaka M, Imai M, Fujio M, Sakamoto E, Takahashi M, Eto-Kato Y, Wu XM, Funakoshi K, Sakai K, Suemune H, J. Org. Chem 2000, 65, 5806–5816. For an example using alkyne hydroacylation, see: [PubMed: 10970327] d)Tanaka K, Fu GC, J. Am. Chem. Soc 2002, 124, 10296–10297. [PubMed: 12197729]

[16]. a)For selected examples of an olefin hydroacylation via an imine intermediate, see: Beletskiy EV, Sudheer C, Douglas CJ, J. Org. Chem 2012, 77, 5884–5893; [PubMed: 22775578] b)Jun C-H, Lee D-Y, Lee H, Hong J-B, Angew. Chem. Int. Ed 2000, 39, 3070–3072;c)Jun C-H, Lee H, Hong J-B, J. Org. Chem 1997, 62, 1200–1201

[17]. Simmons EM, Hartwig JF, Angew. Chem. Int. Ed. 2012, 51, 3066–3072.

[18]. a)For selected reviews on tandem catalysis, see: Lohr TL, Marks TJ, Nat. Chem 2015, 7, 477–482; [PubMed: 25991525] b)Wasilke J-C, Obrey SJ, Baker RT, Bazan GC, Chem. Rev 2005, 105, 1001–1020; [PubMed: 15755083] c)Fogg DE, dos Santos EN, Coord. Chem. Rev 2004, 248, 2365–2379.

[19]. We evaluated each model aldehyde (**1a**, **3a**, and **5a**) using each of the ligand and amine combinations. See the Supporting Information for more details.

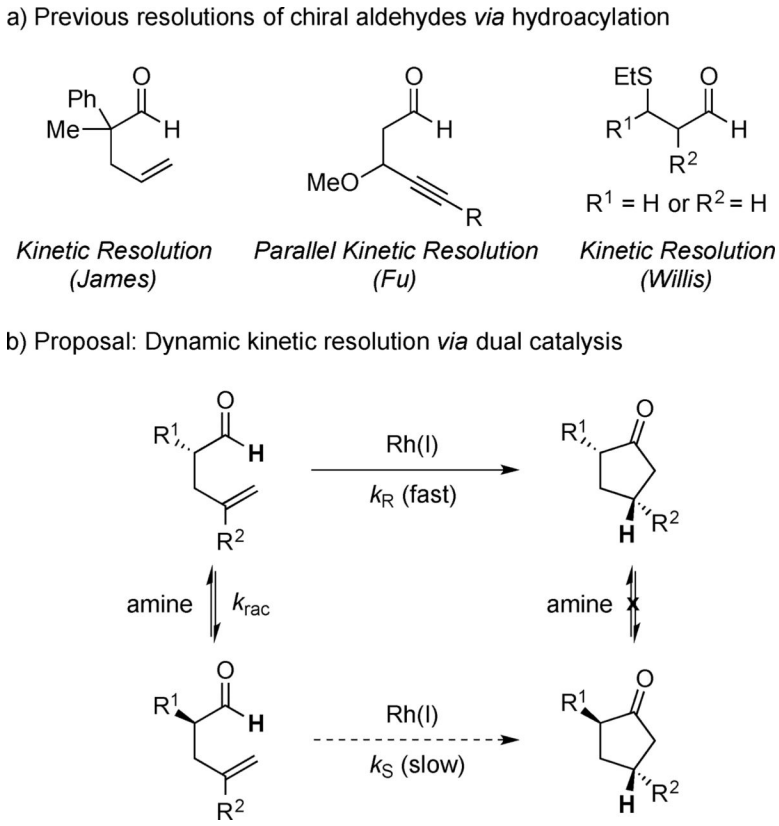
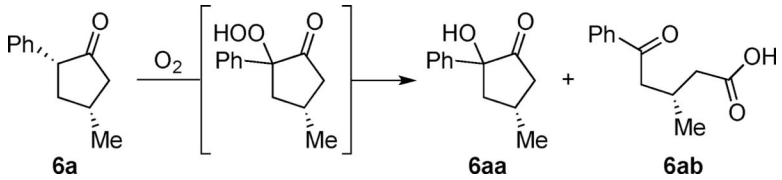
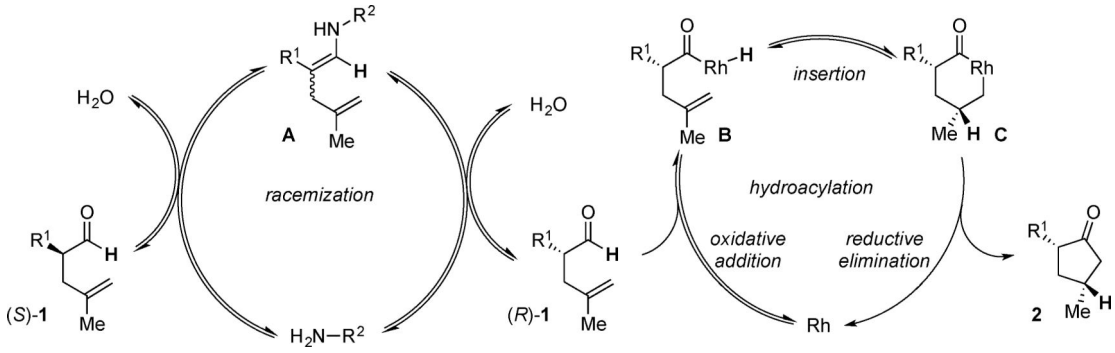


Figure 1.
Resolutions of chiral aldehydes by hydroacylation.

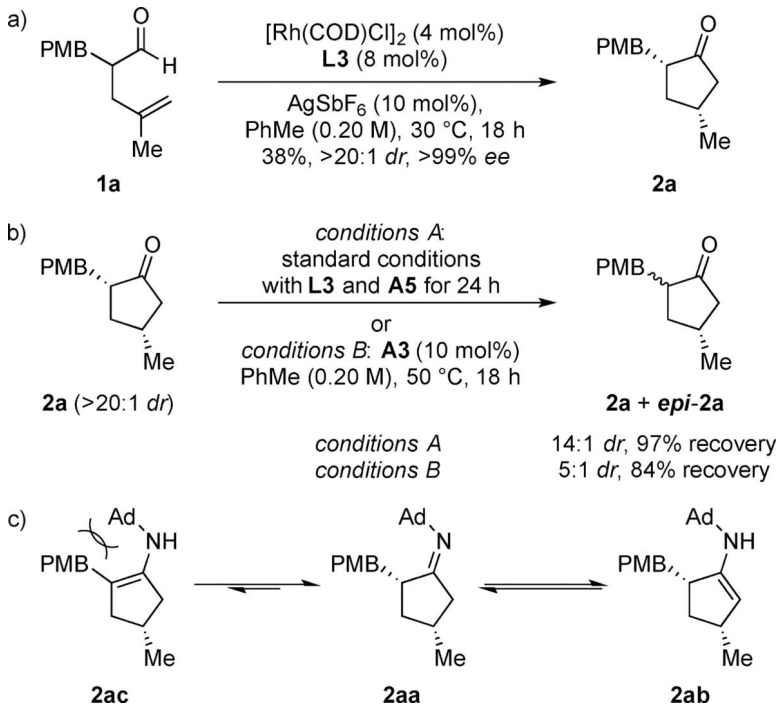


Scheme 1.
Decomposition of **6a**.



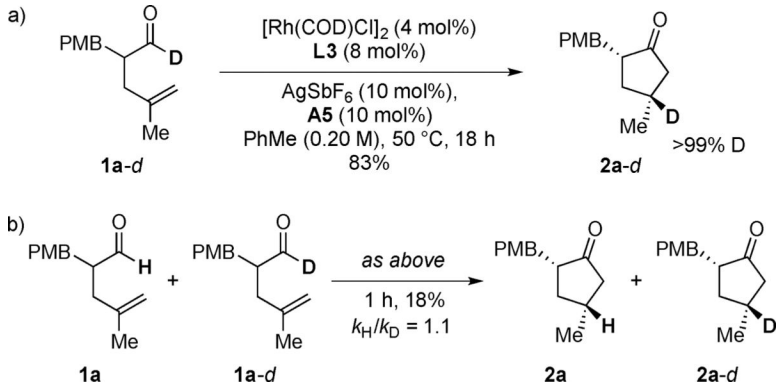
Scheme 2.

Amine-catalyzed racemization and Rh-catalyzed hydroacylation



Scheme 3.

Amine-free hydroacylation and product epimerization.

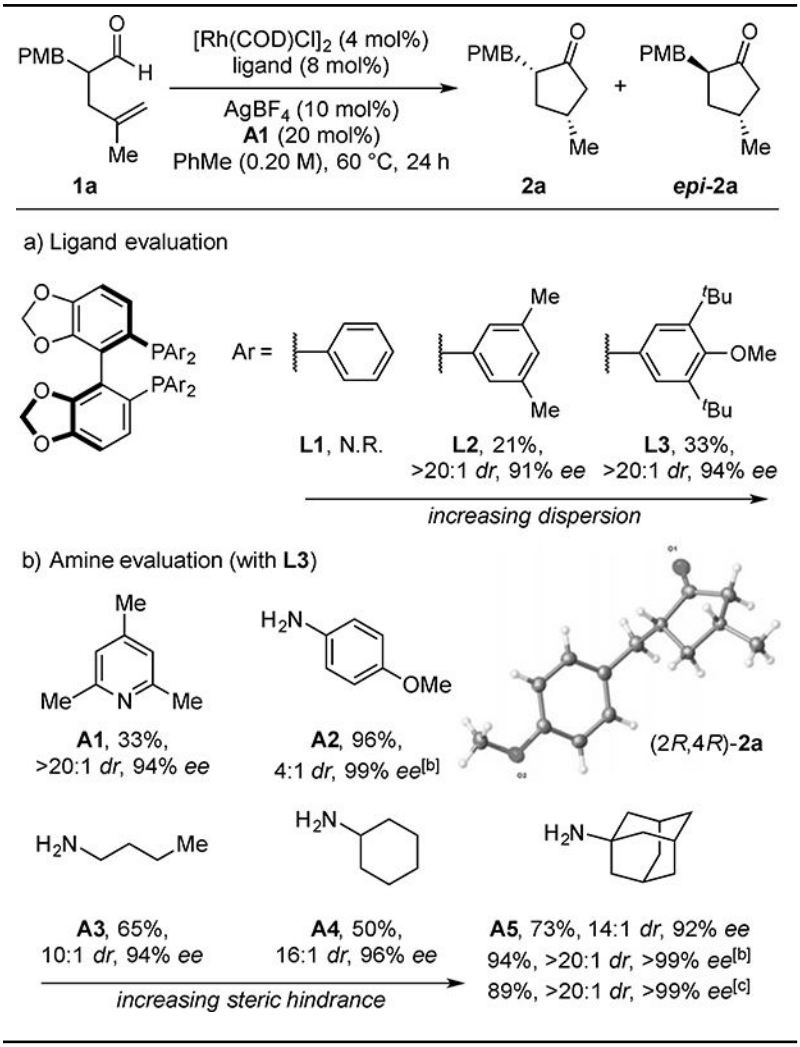


Scheme 4.

Isotopic labeling and KIE experiments.

Table 1.

Ligand and Amine Evaluation with α-Alkyl Aldehyde **1a**[a]

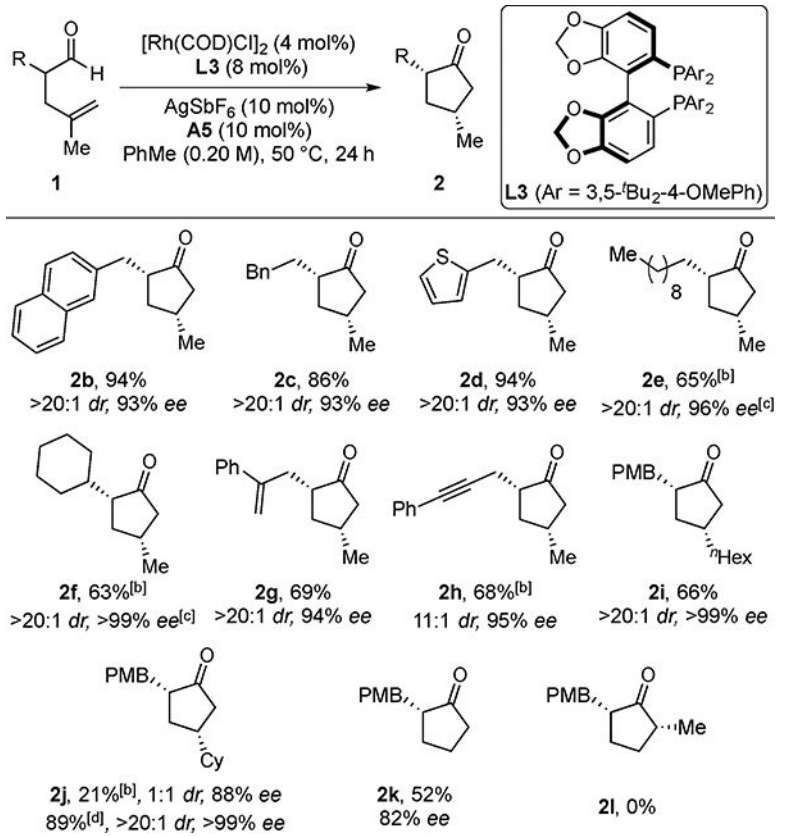


[a]With 0.050 mmol of **1a**.

Yields and diastereoselectivities were determined by ^{1}H NMR analysis of the unpurified reaction mixture using triphenylmethane as an internal standard. Enantioselectivities (*ee*'s) were determined by chiral SFC analysis. [b] With 0.10 mmol of **1a**. Reaction performed at 50 °C using $AgSbF_6$ (10 mol%) and 10 mol% of the amine. [c] Isolated yield of **2a** (4.6 mmol scale) using 2 mol% $[Rh(COD)Cl]_2$, 4 mol% **L3**, 10 mol% $AgSbF_6$, and 10 mol% **A5** for 48 h. PMB = *p*-methoxybenzyl. COD = 1,5-cyclooctadiene.

Table 2.

Hydroacylation Scope with α-Alkyl Aldehydes[a]

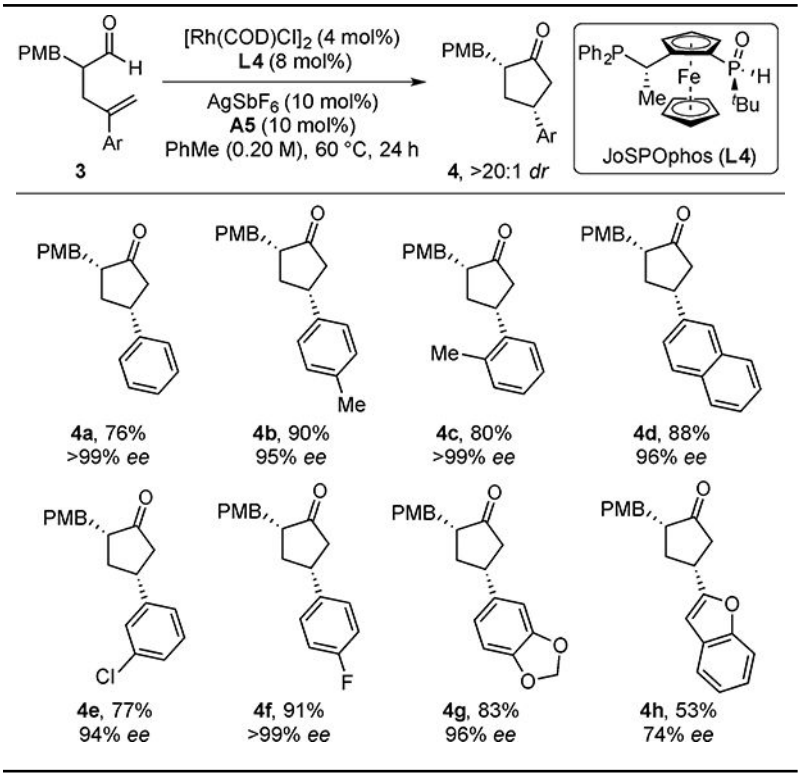


[a]With 0.10 mmol of **1**.

Isolated yields are given. Diastereoselectivities were determined by ^{1}H NMR analysis of the unpurified reaction mixture. Enantioselectivities (*ee*'s) were determined by chiral SFC analysis. [b] Reaction performed at 60 °C. [c] SFC analysis performed with the tertiary alcohol after treatment with PhMgBr. [d] Reaction performed with **L4** at 60 °C.

Table 3.

Hydroacylation Scope with Styrenyl Olefins[a]

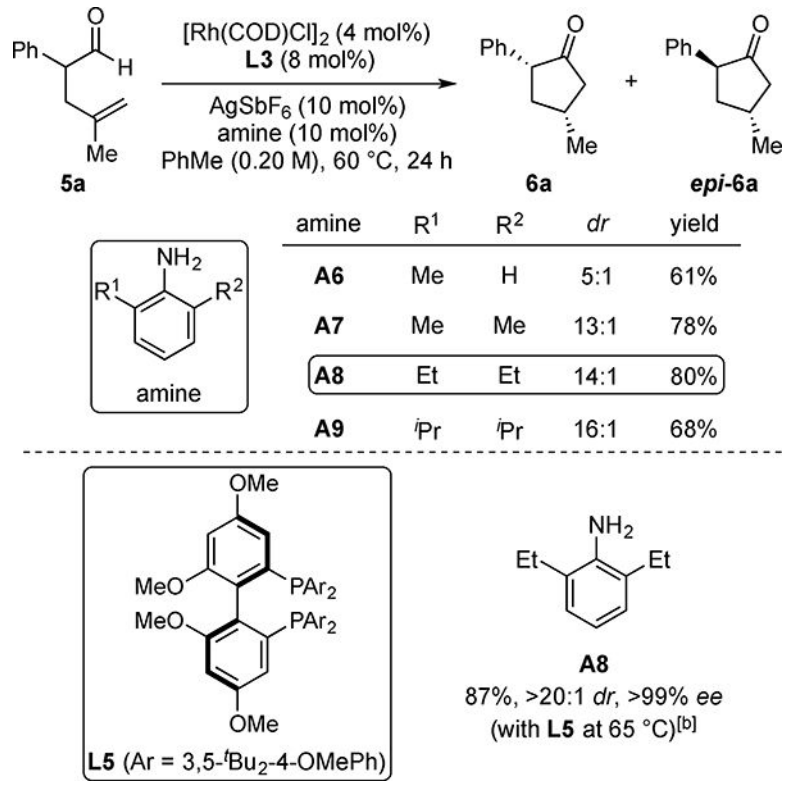


[a]With 0.10 mmol of **3**.

With 0.10 mmol of **3**. Isolated yields are given. Diastereoselectivities were determined by ^{1}H NMR analysis of the unpurified reaction mixture. Enantioselectivities (*ee*'s) were determined by chiral SFC analysis. (Rp)-1-[(*S*)-*tert*-Butylphosphinoyl]-2-[(*S*)-1-(diphenylphosphino)ethyl]ferrocene (**L4**) is abbreviated as JoSPOphos.

Table 4.

Ligand and Amine Evaluation with α-Aryl Aldehyde **5a**[a]



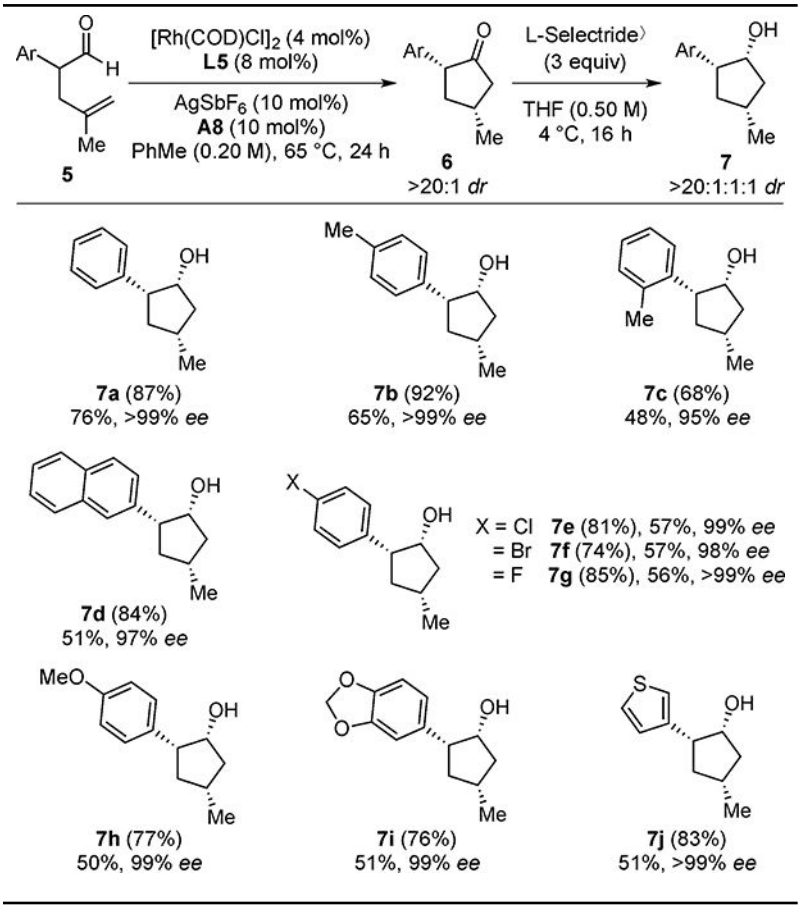
amine	R^1	R^2	*dr*	yield
A6	Me	H	5:1	61%
A7	Me	Me	13:1	78%
A8	Et	Et	14:1	80%
A9	^{i}Pr	^{i}Pr	16:1	68%

[a]With 0.050 mmol **5a**.

Yields and diastereoselectivities were determined by ^{1}H NMR analysis of the unpurified reaction mixture using triphenylmethane as an internal standard. Enantioselectivities (*ee*'s) were determined by chiral SFC analysis. [b] Using 0.10 mmol of **5a**.

Table 5.

Hydroacylation Scope with α-Aryl Aldehydes[a]



[a]With 0.10 mmol of **5**.

^{1}H NMR yields of **6** are given in parentheses. Isolated yields over two steps are given of **7**. Diastereoselectivities of each step were determined by ^{1}H NMR analysis of the unpurified reaction mixture. Enantioselectivities (*ee*'s) were determined by chiral SFC analysis.