JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY
Communication
pubs.acs.org/JACS

Enantioselective Rhodium-Catalyzed Allylic Alkylation of Prochiral α,α-Disubstituted Aldehyde Enolates for the Construction of Acyclic Quaternary Stereogenic Centers

Timothy B. Wright and P. Andrew Evans*

Department of Chemistry Queen's University, 90 Bader Lane, Kingston, Ontario K7L 3N6, Canada

Supporting Information

ABSTRACT: A highly enantioselective rhodium-catalyzed allylic alkylation of prochiral α,α-disubstituted aldehyde enolates with allyl benzoate is described. This protocol provides a novel approach for the synthesis of acyclic quaternary carbon stereogenic centers and it represents the first example of the direct enantioselective alkylation of an aldehyde enolate *per se*. The versatility of the α-quaternary aldehyde products is demonstrated through their conversion to a variety of useful motifs applicable to target-directed synthesis. Finally, mechanistic studies indicate that high levels of asymmetric induction are achieved from a mixture of prochiral (*E*)- and (*Z*)-enolates, which provides an exciting development for this type of transformation.

The asymmetric synthesis of acyclic α-quaternary functionalized aldehydes is a very challenging endeavor for modern synthetic chemistry.[1,2] Although asymmetric enolate alkylation provides a conceptually straightforward approach toward accessing this motif,[3] the propensity for aldehydes to undergo competing reactions, such as aldol condensations, makes them especially demanding substrates in this regard. Furthermore, the enantioselective alkylation of enolates tends to be optimal for geometrically defined systems,[4] which are particularly difficult to control in acyclic α,α-disubstituted carbonyl derivatives.[5] While recent advances in organocatalysis[6] have resulted in several elegant methods for the asymmetric α-alkylation of aldehydes to prepare ternary[7] stereogenic centers, there are relatively few methods that facilitate the construction of the corresponding quaternary substituted derivatives (Scheme 1A).[8] Alternatively, the enantioselective formation of α-quaternary aldehydes can also be accomplished via dual organo- and transition metal catalysis (Scheme 1B).[9] Although recent reports have illustrated the success of these approaches for the alkylation of α-methyl benzylic aldehydes, the ability to extend these methodologies beyond substrates that contain a simple methyl substituent has proven particularly challenging, which thus limits their potential synthetic utility.[10]

We envisaged that the direct asymmetric allylic alkylation of an aldehyde enolate would facilitate a significant expansion in scope, while providing a straightforward solution to the challenging aldehyde α-alkylation process. In a program directed toward the development of rhodium-catalyzed allylic substitution reactions,[11−13] we recently reported the direct enantioselective allylic alkylation of α-alkoxy ketone enolates using Wilkinson's catalyst and a chiral monodentate phosphite ligand.[14] We anticipated a similar approach could be applied to the asymmetric allylic alkylation of aldehydes, albeit controlling the enolate geometry would be significantly more challenging in the absence of chelation assistance. Herein, we now describe the first direct and highly enantioselective rhodium-catalyzed allylic alkylation of enolates derived from the α-alkyl benzylic aldehydes **1** with allyl benzoate (**2**) to afford the chiral nonracemic α-quaternary aldehydes **3** (Scheme 1C).

Scheme 1. Inspiration and Challenges with Previous Approaches for the Enantioselective Alkylation of α-Substituted Benzylic Aldehydes

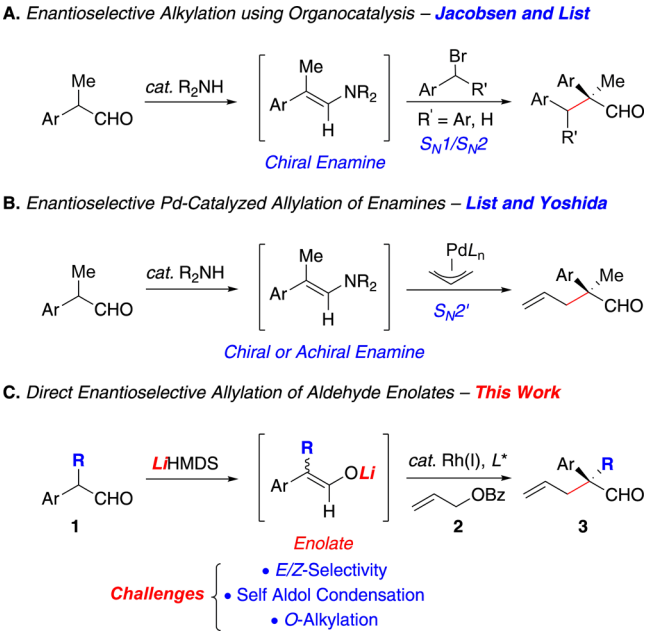
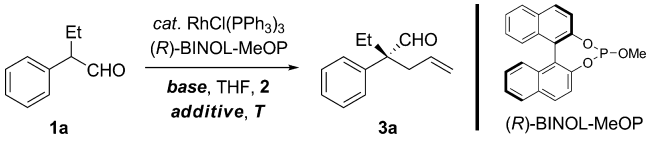


Table 1 outlines the preliminary studies for the development of an enantioselective rhodium-catalyzed allylic alkylation reaction using an aldehyde enolate. Treatment of allyl benzoate (**2**) with the lithium enolate of 2-phenylbutanal (**1a**) in the presence of the chiral complex derived from $RhCl(PPh_3)_3$ and (*R*)-BINOL-MeOP at −10 °C afforded aldehyde **3a** in 37% yield and with excellent enantiomeric excess (entry 1). While the level of enantioselectivity was very encouraging, we elected

Received: September 26, 2016
Published: November 18, 2016

DOI: 10.1021/jacs.6b10099
J. Am. Chem. Soc. 2016, 138, 15303−15306

Table 1. Optimization of the Enantioselective Rhodium-Catalyzed Allylic Alkylation Using 2-Phenylbutanal (1a)[a]



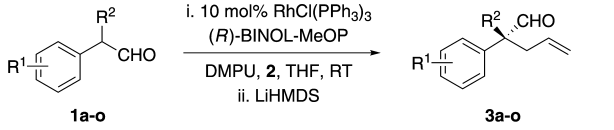
entry	base	T (°C)	additive	yield of **3a** (%)[b]	*ee* (%)[c]
1	LiHMDS	−10	–	37	93
2	LDA	”	–	34	14
3	LiTMP	”	–	32	34
4	LiDPA[d]	”	–	23	22
5	LiHMDS	”	LiCl[e]	27	80
6	”	”	12-crown-4[e]	55	84
7	”	”	DMPU[e]	45	87
8	”	0	”	54	90
9	”	RT	”	51	92
10[f]	***LiHMDS***	***RT***	***DMPU***	***77 (74)***[g]	***92***

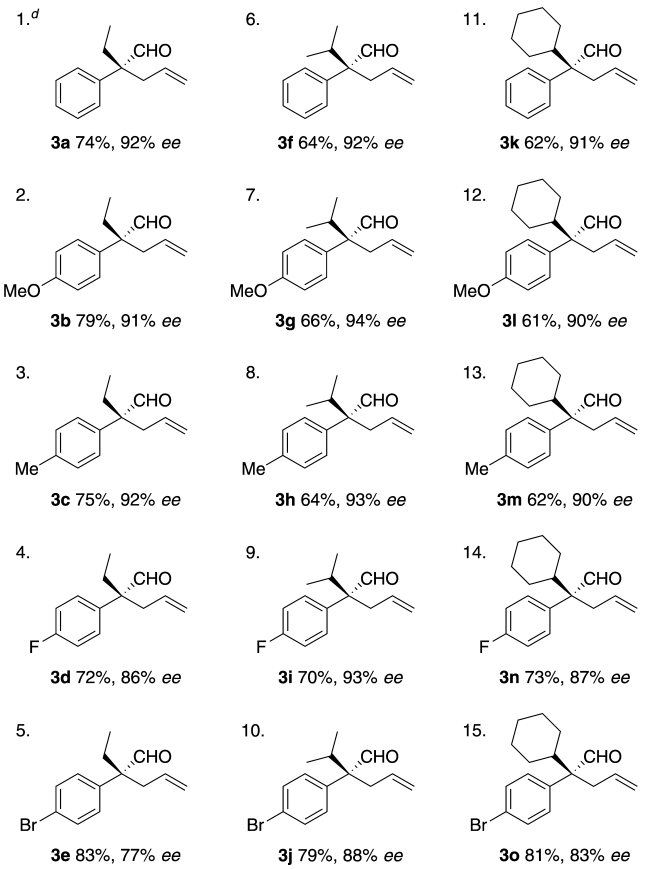
[a]All reactions were performed on a 0.25 mmol scale using 10 mol % $RhCl(PPh_3)_3$, 40 mol % (*R*)-BINOL-MeOP, 2.0 equiv **1a**, and 1.9 equiv of base in THF (2.5 mL) for *ca.* 16 h. [b]GC yields of **3a**. [c]Determined by chiral HPLC analysis on the corresponding alcohol. [d]DPA = diphenylamine. [e]1.9 equiv of additive. [f]LiHMDS was added dropwise over a period of 30 min. [g]Isolated yield of **3a**.

to investigate other lithium amide bases, which we envisioned could impact the enolate reactivity. Remarkably, the lithium enolates generated by deprotonation with LDA, LiTMP, and LiDPA provided aldehyde **3a** in similar yield but with significantly reduced enantioselectivity (entries 2−4). Hence, the silyl amide lithium base is a critical component for attaining high levels of asymmetric induction in this reaction.[15] Nevertheless, the poor yield prompted the examination of deaggregating agents in an effort to enhance the reactivity of the enolate. To this end, the addition of lithium chloride reduced the efficiency and enantioselectivity, whereas 12-crown-4 provided a significant improvement in yield (entries 5 vs 6). However, given the cost and toxicity of the crown ether, we examined the impact of DMPU, which provided **3a** in similar yield and with slightly higher enantiomeric excess (entry 7 vs 6). In the next phase of this study, we elected to investigate the effect of temperature, which afforded further improvement in the selectivity of the reaction upon elevation from −10 °C to room temperature (entries 7−9). Finally, in order to address the rather modest yield, we examined dropwise addition of the base using a syringe-pump to minimize the side-reactions associated with aldehyde enolates. Gratifyingly, the dropwise addition of base over 30 minutes provided **3a** in an improved 74% isolated yield and with 92% enantiomeric excess (entry 10). Importantly, the ability to employ a commercially available base and precatalyst with a readily available chiral ligand[14] at room temperature makes this a simple protocol for the asymmetric construction of acyclic α-quaternary aldehydes.

Table 2 summarizes the application of the optimized reaction conditions (Table 1, entry 10) to a variety of α-branched benzylic aldehydes.[16,17] Interestingly, the reaction is tolerant of both electron-rich and electron-deficient aryl systems, albeit with slightly lower enantioselectivity for aldehydes with electron-withdrawing substituents (entries 1−5). An important feature with this trend is its complementarity relative to our previous work on the enantioselective rhodium-catalyzed allylic alkylation of benzyl nitrile anions.[18] For instance, the current

Table 2. Scope of the Enantioselective Rhodium-Catalyzed Allylic Alkylation of α-Alkyl Benzylic Aldehyde Enolates[a,b,c]





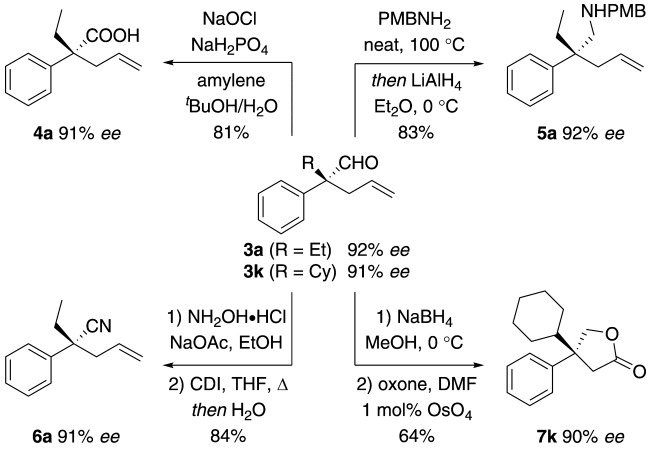
[a]All reactions were performed on a 0.5 mmol scale using 10 mol % $RhCl(PPh_3)_3$, 40 mol % (*R*)-BINOL-MeOP, 2.0 equiv of **1**, 1.9 equiv of LiHMDS, and 1.9 equiv of DMPU in THF (5 mL) for *ca.* 16 h. [b]Isolated yields. [c]Enantiomeric excess was determined by chiral HPLC analysis on the corresponding alcohol. [d]78% yield and 91% *ee* on a 10 mmol (1.6 g) scale using 5 mol % $RhCl(PPh_3)_3$ and 20 mol % (*R*)-BINOL-MeOP.

work provides excellent enantioselectivity for aryl groups that had proven challenging in the asymmetric alkylation of α-alkyl benzyl nitriles. Furthermore, the ability to alkylate sterically encumbered aldehydes offers a direct approach to products that have not been accessible using the current organocatalytic methods. For example, aldehydes with an α-isopropyl group provided excellent levels of enantiomeric excess, despite a slight reduction in efficiency for electron-rich aryl systems (entries 6−10). Additionally, substrates bearing an α-cyclohexyl substituent afforded comparable yields and selectivities to the isopropyl series (entries 11−15). Finally, the reaction proceeds with similar yield and enantioselectivity on gram-scale, which highlights the utility of this process for target-directed synthesis (entry 1). *Overall, this work offers a convenient procedure for the enantioselective construction of acyclic quaternary carbon stereogenic centers.*

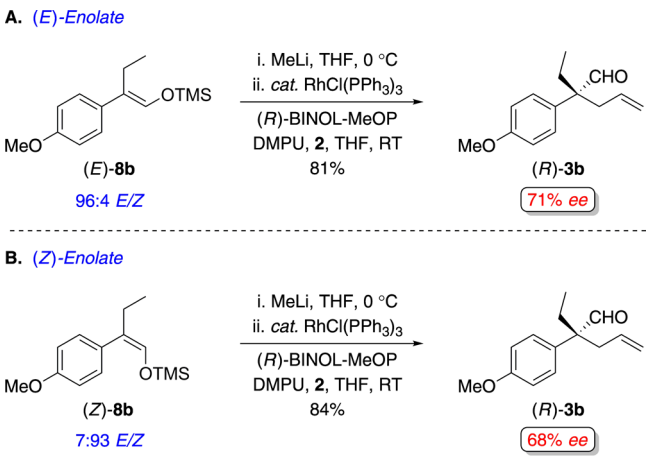
Scheme 2 outlines a series of transformations on the enantioenriched α-quaternary aldehydes **3a** and **3k** to further

DOI: 10.1021/jacs.6b10099
J. Am. Chem. Soc. 2016, 138, 15303−15306

Scheme 2. Transformations of Enantiomerically Enriched Aldehydes 3a and 3k



Scheme 3. Stereochemical Outcome of the (*E*)- and (*Z*)-Enolate Isomers of Aldehyde 1b



illustrate the synthetic utility of these intermediates. For example, Pinnick oxidation of aldehyde **3a** provides efficient access to the carboxylic acid **4a** with excellent stereochemical fidelity. Alternatively, condensation of aldehyde **3a** with 4-methoxybenzylamine under solvent-free conditions, followed by reduction of the intermediary imine with lithium aluminum hydride furnished the secondary amine **5a**. Aldehyde **3a** was also converted to a nitrile with conservation of stereochemical information by treatment with hydroxylamine hydrochloride to afford the oxime, which upon heating with 1,1′-carbonyldiimidazole provides nitrile **6a**. Hence, the interchangeable nature of the aldehyde and nitrile groups permits access to highly enantiomerically enriched quaternary benzylic stereogenic centers regardless of the electronic nature of the aryl group (*vide supra*). In order to further illustrate the synthetic utility of the homoallylic aldehyde adducts and to establish the absolute configuration of the products, aldehyde **3k** was converted to the known γ-lactone **7k**[19] in 64% overall yield (two steps). Overall, the ability to convert the aldehyde products into an array of important intermediates with retention of stereochemistry highlights the potential application of this process to target-directed synthesis.

In order to delineate the origin of the excellent enantioselectivity, we elected to probe the impact of enolate geometry. In general, controlling the enolate geometry is a critical component for attaining asymmetric induction,[5,14,20] albeit the equilibration of a mixture of enolate isomers to facilitate the stereoselective α-alkylation of carbonyls via a dynamic kinetic resolution mechanism is also possible.[21] Experiments probing the geometrical selectivity of enolate formation under the optimized conditions (Table 1, entry 10) indicates the presence of a mixture of (*E*)- and (*Z*)-enolates.[22] Hence, in order to determine the impact of geometry on the mechanism of asymmetric induction, we subjected stereodefined enolates to the optimized reaction conditions. To this end, alkylation of the (*E*)-lithium enolate, generated by treatment of the silyl enol ether (*E*)-**8b** with methyllithium, furnished the aldehyde (*R*)-**3b** in 81% yield and with 71% enantiomeric excess (Scheme 3A). Surprisingly, alkylation of the lithium enolate derived from (*Z*)-**8b** proceeded with similar yield and selectivity, providing aldehyde **3b** with the same absolute configuration (Scheme 3B). These results suggest that both geometrical isomers are reactive under the optimized conditions and that asymmetric induction occurs by alkylation of the mixture of (*E*)- and (*Z*)-enolates to provide to same enantiomer.[23] Moreover, the level of stereocontrol is lower than the observed value for the alkylation of aldehyde **1b**, which further highlights the importance of the silyl amide base that is absent under these conditions.[24] Additional studies are currently ongoing to elucidate the origin of this interesting phenomenon.

In conclusion, we have developed a direct and highly enantioselective rhodium-catalyzed allylic alkylation of α-alkyl benzylic aldehydes with allyl benzoate. This is a significant development, given that it represents the first example of the direct asymmetric alkylation of an α,α-disubstituted aldehyde enolate to furnish an acyclic quaternary stereogenic center. The reactive nature of the enolate nucleophile permits the alkylation of more hindered α-alkyl benzylic aldehydes, to facilitate the preparation of enantiomerically enriched α-quaternary aldehydes that have been previously inaccessible through related methodologies. In addition, the conversion of the homoallylic aldehydes to several functionalized derivatives illustrates the utility of these intermediates for target-directed synthesis. Finally, the study indicates that both the (*E*)- and (*Z*)-isomers provide the same sense of asymmetric induction, which circumvents the need to control the enolate geometry thereby making this a simple and practical synthetic method. To the best of our knowledge, this constitutes the first example of a highly enantioselective alkylation of a geometrical mixture of enolates that does not involve a dynamic kinetic resolution of the enolate isomers.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b10099.

Experimental procedures, spectral data, and NMR spectra for all compounds including pertinent NOEs, GC and HPLC traces (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*Andrew.Evans@chem.queensu.ca

Notes

The authors declare no competing financial interest.

DOI: 10.1021/jacs.6b10099
J. Am. Chem. Soc. 2016, 138, 15303−15306

■ ACKNOWLEDGMENTS

We sincerely thank the National Sciences and Engineering Research Council (NSERC) for a *Discovery Grant* and Queen's University for generous financial support. NSERC is also thanked for supporting a *Tier 1 Canada Research Chair* (P.A.E.). We also acknowledge the Government of Ontario for an *Ontario Graduate Scholarship* (T.B.W.).

■ REFERENCES

(1) (a) For a recent review on the asymmetric synthesis of α-functionalized carbonyl compounds, see: MacMillan, D. W. C.; Watson, A. J. B. In *Science of Synthesis: Stereoselective Synthesis 3*; de Vries, J. G., Evans, P. A., Molander, G. A., Eds.; Thieme: Stuggart, Germany, 2011; pp 675−745. For a recent review on the asymmetric α-alkylation of aldehydes, see: (b) Hodgson, D. M.; Charlton, A. *Tetrahedron* **2014**, *70*, 2207.

(2) For recent reviews on the catalytic enantioselective construction of quaternary carbon stereogenic centers, see: (a) Corey, E. J.; Guzman-Perez, A. *Angew. Chem., Int. Ed.* **1998**, *37*, 388. (b) Trost, B. M.; Jiang, C. *Synthesis* **2006**, 369. (c) Das, J. P.; Marek, I. *Chem. Commun.* **2011**, *47*, 4593. (d) Quasdorf, K. W.; Overman, L. E. *Nature* **2014**, *516*, 181.

(3) For a recent review on asymmetric enolate alkylation, see: Stoltz, B. M.; Mohr, J. T. In *Science of Synthesis: Stereoselective Synthesis 3*; de Vries, J. G., Evans, P. A., Molander, G. A., Eds.; Thieme: Stuggart, Germany, 2011; pp 615−674.

(4) (a) Imai, M.; Hagihara, A.; Kawasaki, H.; Manabe, K.; Koga, K. *J. Am. Chem. Soc.* **1994**, *116*, 8829. (b) Trost, B. M.; Schroeder, G. M. *J. Am. Chem. Soc.* **1999**, *121*, 6759. (c) Behenna, D. C.; Stoltz, B. M. *J. Am. Chem. Soc.* **2004**, *126*, 15044. (d) Doyle, A. G.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2005**, *127*, 62.

(5) For recent review on the importance of enolate geometry on stereocontrol for the construction of acyclic quaternary stereogenic centers, see: Minko, Y.; Marek, I. *Chem. Commun.* **2014**, *50*, 12597.

(6) For recent reviews on organocatalysis, see: (a) Mukherjee, S.; Yang, J. W.; Hoffmann, S.; List, B. *Chem. Rev.* **2007**, *107*, 5471. (b) Vesely, J.; Rios, R. *ChemCatChem* **2012**, *4*, 942. (c) MacMillan, D. W. C. In *Science of Synthesis: Asymmetric Organocatalysis 1*; List, B., Maruoka, A., Eds.; Thieme: Stuggart, Germany, 2012; pp 271−307.

(7) For selected examples, see: (a) Vignola, N.; List, B. *J. Am. Chem. Soc.* **2004**, *126*, 450. (b) Beeson, T. D.; Mastracchio, A.; Hong, J.-B.; Ashton, K.; MacMillan, D. W. C. *Science* **2007**, *316*, 582. (c) Nicewicz, D. A.; MacMillan, D. W. C. *Science* **2008**, *322*, 77. (d) Shih, H.-W.; Vander Wal, M. N.; Grange, R. L.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2010**, *132*, 13600.

(8) (a) Brown, A. R.; Kuo, W.-H.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2010**, *132*, 9286. (b) List, B.; Čorić, I.; Grygorenko, O. O.; Kaib, P. S. J.; Komarov, I.; Lee, A.; Leutzsch, M.; Chandra Pan, S.; Tymtsunik, A. V.; van Gemmeren, M. *Angew. Chem., Int. Ed.* **2014**, *53*, 282.

(9) (a) Mukherjee, S.; List, B. *J. Am. Chem. Soc.* **2007**, *129*, 11336. (b) Jiang, G.; List, B. *Angew. Chem., Int. Ed.* **2011**, *50*, 9471. (c) Yoshida, M.; Terumine, T.; Masaki, E.; Hara, S. *J. Org. Chem.* **2013**, *78*, 10853. (d) Yoshida, M.; Masaki, E.; Terumine, T.; Hara, S. *Synthesis* **2014**, *46*, 1367. For an example of stereodivergent dual catalysis using secondary allylic alcohols, see: (e) Krautwald, S.; Sarlah, D.; Schafroth, M. A.; Carreira, E. M. *Science* **2013**, *340*, 1065.

(10) R = Et (Scheme 1C) has been previously attempted; see ref 9b−d.

(11) For reviews on transition metal-catalyzed allylic substitution reactions, see: (a) Trost, B. M.; Van Vranken, D. L. *Chem. Rev.* **1996**, *96*, 395. (b) Crawley, M. L. In *Science of Synthesis: Stereoselective Synthesis 3*; de Vries, J. G., Evans, P. A., Molander, G. A., Eds.; Thieme: Stuggart, Germany, 2011; pp 403−442. For the use of enolates and enolate equivalents, see: (c) Braun, M.; Meier, T. *Synlett* **2006**, 661. (d) Oliver, S.; Evans, P. A. *Synthesis* **2013**, *45*, 3179.

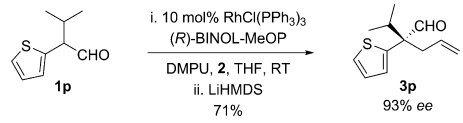
(12) Evans, P. A.; Leahy, D. K. In *Modern Rhodium-Catalyzed Organic Reactions*; Evans, P. A., Ed.; Wiley-VHC: Weinheim, Germany, 2005; Chapter 10, pp 191−214.

(13) For a related example of the regio- and stereospecific rhodium-catalyzed allylic substitution with achiral pronucleophiles, see: Evans, P. A.; Nelson, J. D. *J. Am. Chem. Soc.* **1998**, *120*, 5581.

(14) Evans, P. A.; Clizbe, E. A.; Lawler, M. J.; Oliver, S. *Chem. Sci.* **2012**, *3*, 1835.

(15) The use of LiDPTMDS (DPTMDS = 1,3-Diphenyl-1,1,3,3-tetramethyldisilazane) under analogous conditions to Table 1, entries 1−4 afforded aldehyde **3a** in 39% yield with 81% *ee*.

(16) α-Heteroaromatic aldehydes are also compatible substrates. For example, the allylation of 3-methyl-2-(thiophen-2-yl)butanal (**1p**) proceeds in 71% yield and with 93% *ee*.



(17) The use of α,α′-dialkyl aldehydes proceeds with lower efficiency and selectivity. For example 2-cyclohexylpropanal gives the allylation product in 26% yield and with 50% *ee*.

(18) Turnbull, B. W. H.; Evans, P. A. *J. Am. Chem. Soc.* **2015**, *137*, 6156.

(19) Oliveira, C. C.; Pfaltz, A.; Correia, C. R. D. *Angew. Chem., Int. Ed.* **2015**, *54*, 14036.

(20) For selected examples, see: (a) Yan, X.-X.; Liang, C.-G.; Zhang, Y.; Hong, W.; Cao, B.-X.; Dai, L.-X.; Hou, X.-L. *Angew. Chem., Int. Ed.* **2005**, *44*, 6544. (b) Trost, B. M.; Xu, J. *J. Am. Chem. Soc.* **2005**, *127*, 17180.

(21) For an example using an *E*/*Z* mixture of tin-enolates, see: Doyle, A. G.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2007**, *46*, 3701.

(22) Trapping the enolate with TMSCl under the reaction conditions afforded a 4:1 mixture of *E*/*Z*-isomers by 500 MHz ^{1}H NMR.

(23) Although a dynamic kinetic resolution of the *E*- and *Z*-enolates cannot be completely ruled out, our studies strongly support the alkylation of both isomers.

(24) Using the HMDS enamine of **1b** or the silyl enol ethers (*E*)-**8b**/(*Z*)-**8b** did not provide any of the allylation product **3b** by 500 MHz ^{1}H NMR under the optimized conditions.

DOI: 10.1021/jacs.6b10099
J. Am. Chem. Soc. 2016, 138, 15303−15306