JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

Article

pubs.acs.org/JACS

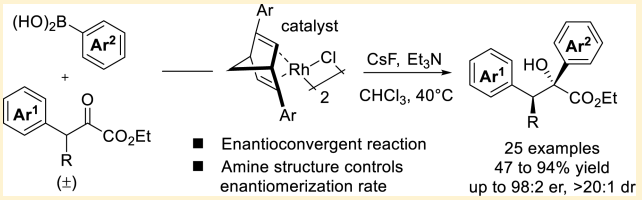
Synthesis of Complex Tertiary Glycolates by Enantioconvergent Arylation of Stereochemically Labile α-Keto Esters

Samuel L. Bartlett, Kimberly M. Keiter, and Jeffrey S. Johnson*

Department of Chemistry, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina 27599-3290, United States

Supporting Information

ABSTRACT: Enantioconvergent arylation reactions of boronic acids and racemic β-stereogenic α-keto esters have been developed. The reactions are catalyzed by a chiral (diene)Rh(I) complex and provide a wide array of β-stereogenic tertiary aryl glycolate derivatives with high levels of diastereo- and enantioselectivity. Racemization studies employing a series of sterically differentiated tertiary amines suggest that the steric nature of the amine base additive exerts a significant influence on the rate of substrate racemization.



INTRODUCTION

The conversion of racemic α-stereogenic ketones to enantiomerically enriched alcohol building blocks through transformation of the carbonyl functionality is an enabling chemical transformation.[1] Transition-metal-catalyzed dynamic kinetic hydrogenation reactions, pioneered by Noyori, have been widely employed for the production of enantioenriched secondary alcohols (Scheme 1A).[2] The synthesis of tertiary alcohols through the enantioconvergent addition of stabilized carbon nucleophiles to configurationally labile electrophiles is comparatively less common.[3] Reported examples employ basic catalysts or additives to promote simultaneous activation of the pro-nucleophile and enantiomerization of the electrophile. Considering this dual role of base in the context of designing other stereoconvergent processes, the transition-metal-catalyzed addition of nonstabilized carbon nucleophiles to ketones emerged as a compelling opportunity to generate complex tertiary alcohols not accessible through other methods (Scheme 1B). The Hayashi−Miyaura-type reactions typically rely on the base promoted transmetalation of an organoboron or organosilicon pro-nucleophile to a chiral metal complex.[4] As an example, the enantioselective addition of arylboronic acids to carbonyl derivatives, including α-keto esters, has been widely developed (Scheme 1C).[5] Considering their chemical stability, ease of handling, and broad commercial availability,[6] we envisioned that the deployment of arylboronic acids in an enantioconvergent addition to racemic α-keto ester electrophiles would facilitate the production of diverse, stereochemically complex glycolate architectures. The purpose of this article is to convey experimental findings related to the dynamic kinetic 1,2-addition of arylboronic acids to racemic α-keto esters (Scheme 1D).

Carbonyl electrophiles and their derivatives lacking electron withdrawing functionality (i.e., ketone, ester, or halogen) at the chiral α center are underutilized in dynamic kinetic resolutions (DKR). List and Zhao have reported dynamic kinetic reductive aminations employing α-alkyl, aryl branched imines that presumably racemize via enamine intermediates.[7] The cyclohexanecarboxaldehyde derivatives utilized by Ward and co-workers likely racemize via an analogous pathway.[3e] Dynamic kinetic hydrogenations of nonactivated aldehydes and ketones have been shown to occur in the presence of *tert*-butoxide bases.[8] Nevertheless, with the consideration that facile racemization is essential, the execution of DKRs employing compounds of lower acidity is more challenging.[9] However, in this context the use of less activated substrates would allow access to heretofore unknown glycolate architectures.

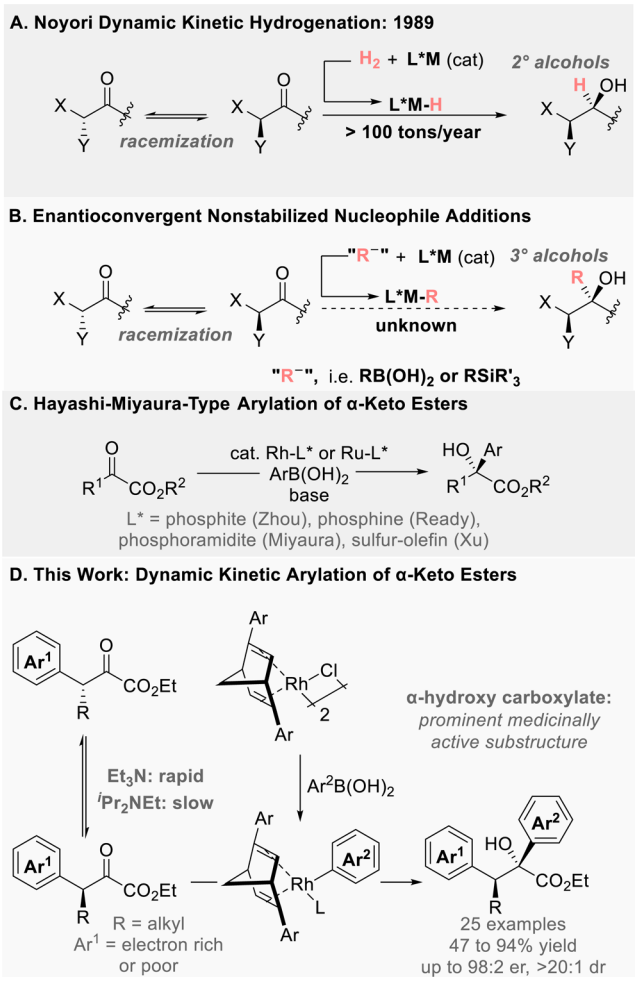
RESULTS AND DISCUSSION

In light of the considerations described above, the β-alkyl, aryl-substituted α-keto ester derivative **1a** was chosen as a model substrate for this transformation (Table 1). Our group has previously developed dynamic kinetic resolutions of α-keto esters that occur in the presence of tertiary amines;[2l−n,3a] therefore, we reasoned that an amine base would promote substrate racemization. Sterically hindered Hünig's base ($^{i}Pr_2NEt$) was initially selected in an effort to minimize interference with the Rh(I)-catalyst through nonproductive binding. A substoichiometric quantity of potassium hydroxide was employed because analogous conditions promote the Hayashi−Miyaura arylation of isatins and **1a** is sensitive to stoichiometric hydroxide base.[10] An initial evaluation of ligands revealed that the Ph-substituted norbornadiene derived ligand **A** developed by Hayashi and co-workers[11] provided promising levels of enantioselectivity, although low conversion was observed under these conditions (entry 1). Further screening showed that the 4-$CF_3C_6H_4$- and 3,5-$(CF_3)_2C_6H_3$-substituted analogues **B** and **C** provided higher levels of enantioselection; however, conversion remained low (entries 2 and 3). The

Received: January 27, 2017

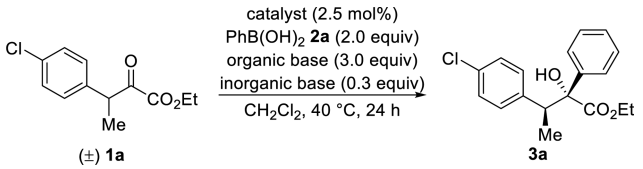
DOI: 10.1021/jacs.7b00943
J. Am. Chem. Soc. XXXX, XXX, XXX−XXX

Scheme 1. Background and Proposed Enantioconvergent Arylation

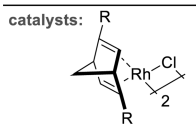


supposed low acidity of these substrates caused us to wonder if a simple kinetic resolution was occurring under these conditions, but this possibility was ruled out by isolation of racemic unreacted **1a** from entry 3. Interestingly, the benzyl-substituted ligand **D** provided low enantioselectivity slightly in favor of the opposite enantiomer, while also exhibiting drastically lower levels of diastereocontrol over the formation of **3a** (entry 4). Switching the inorganic base promoter from potassium hydroxide to CsF while increasing the loading to 3.0 equiv allowed for full conversion to the desired aryl glycolate, albeit with a striking drop in enantioselectivity (entry 5). Simply replacing Hünig's base with triethylamine restored the previously observed levels of enantioselectivity (entry 6). Further increasing the amount of triethylamine to 6.0 equiv provided higher levels of enantioselectivity (entry 7), although a longer reaction time was necessary to achieve full conversion under these conditions. Satisfactory levels of enantioselectivity were achieved when chloroform was used as solvent in place of methylene chloride (entry 8). At this stage of optimization it was noted that both the 4-$CF_3C_6H_4$- and 3,5-$(CF_3)_2C_6H_3$-substituted norbornadiene ligands **B** and **C** provided identical levels of enantioselectivity (entries 8 and 9). Running the reaction at 60 °C does not influence the enantio- or diastereoselectivity of the process (entry 10). Substituting the ethyl ester of **1a** with bulkier ^{t}Bu or Bn groups (entries 11 and 12, respectively) did not result in improved enantioselectivity.

Table 1. Reaction Optimization



entry[a]	cat.	org. base	inorg. base	conv (%)[b]	dr[b]	er[c]
1	A	DIPEA	KOH	59	>20:1	80:20
2	B	DIPEA	KOH	56	>20:1	90:10
3	C	DIPEA	KOH	40	>20:1	90:10
4[d]	D	DIPEA	KOH	61	2.7:1	43:57
5[e]	C	DIPEA	CsF	>95	>20:1	70:30
6[e]	C	Et_3N	CsF	>95	20:1	89:11
7[e,f]	C	Et_3N	CsF	85	>20:1	92:8
8[e,f,g,h]	C	Et_3N	CsF	>95	>20:1	94:6
9[e,f,g,h]	B	Et_3N	CsF	>95	>20:1	94:6
10[e,f,g,h,i]	B	Et_3N	CsF	>95	>20:1	94:6
11[j,k,e,f,g,h]	C	Et_3N	CsF	>95	>20:1	93:7
12[j,l,,e,f,g]	C	Et_3N	CsF	>95	14:1	91:9
13[e,g,h,j]	E	Et_3N	CsF	trace	-	-
14[e,g,h,j]	F	Et_3N	CsF	trace	-	-



[a]All reactions were conducted on a 0.10 mmol scale. [b]Determined by ^{1}H NMR analysis of the crude reaction mixture. [c]Determined by HPLC using a chiral stationary phase. [d]Reaction time = 36 h. [e]3.0 equiv CsF. [f]6.0 equiv of Et_3N. [g]$CHCl_3$ as solvent. [h]Reaction time = 48 h. [i]Reaction was run at 60 °C. [j]3.0 equiv $PhB(OH)_2$. [k]Substrate ester = ^{t}Bu. [l]Substrate ester = CH_2Ph

Finally, although phosphine[5b] and phosphite[5a] ligands have been utilized in Hayashi–Miyaura-type arylation reactions of α-keto esters, a complex of triphenylphosphite (**E**, entry 13) as well as hydroxy[(*S*)-BINAP]rhodium(I) dimer (**F**, entry 14) failed to catalyze this transformation.

At this juncture we sought to understand the large contribution to product enantioselectivity associated with the superficially similar structure of the amine base additive. We hypothesize that this difference might arise from a faster rate of starting material racemization under the action of triethylamine. Using Hünig's base in conjunction with low inorganic base concentration resulted in high levels of product enantioselectivity, and the unreacted starting material recovered from the reaction was not enantioenriched (entry 3, Table 1), suggesting

DOI: 10.1021/jacs.7b00943
J. Am. Chem. Soc. XXXX, XXX, XXX–XXX

that an efficient dynamic kinetic resolution is occurring under these conditions. We postulate that under conditions of low inorganic base concentration the arylation reaction is slow relative to Hünig's base promoted racemization ($k_{rac} > k_{fast}$)[9] resulting in a dynamic kinetic resolution. However, in entry 5 the higher loading of CsF results in a faster arylation reaction for both substrate enantiomers, presumably due to higher rates of transmetalation, while the rate of racemization by Hünig's base occurs too slowly for efficient dynamic kinetic resolution.[12] To gain further insight into this phenomenon and to provide support for our hypothesis we studied the rate of racemization of **1a** using an array of tertiary amine bases (Figure 1). At room temperature racemization with triethyl-

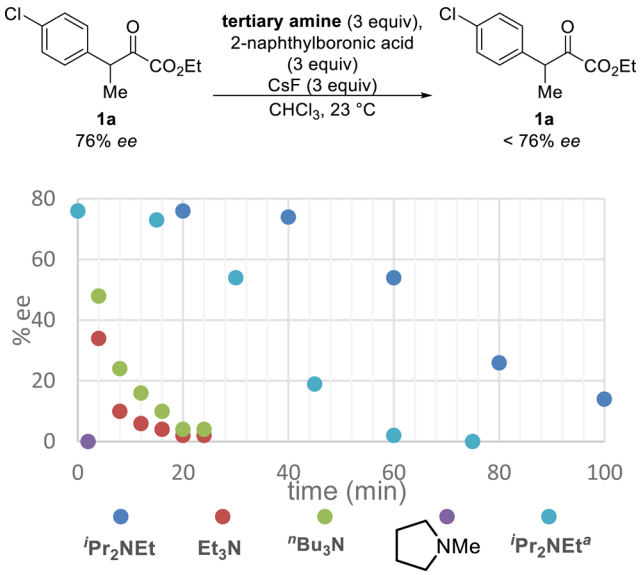


Figure 1. Influence of base structure on racemization rate. Superscript a indicates trial conducted at 40 °C, with 6.0 equiv of Hünig's base.

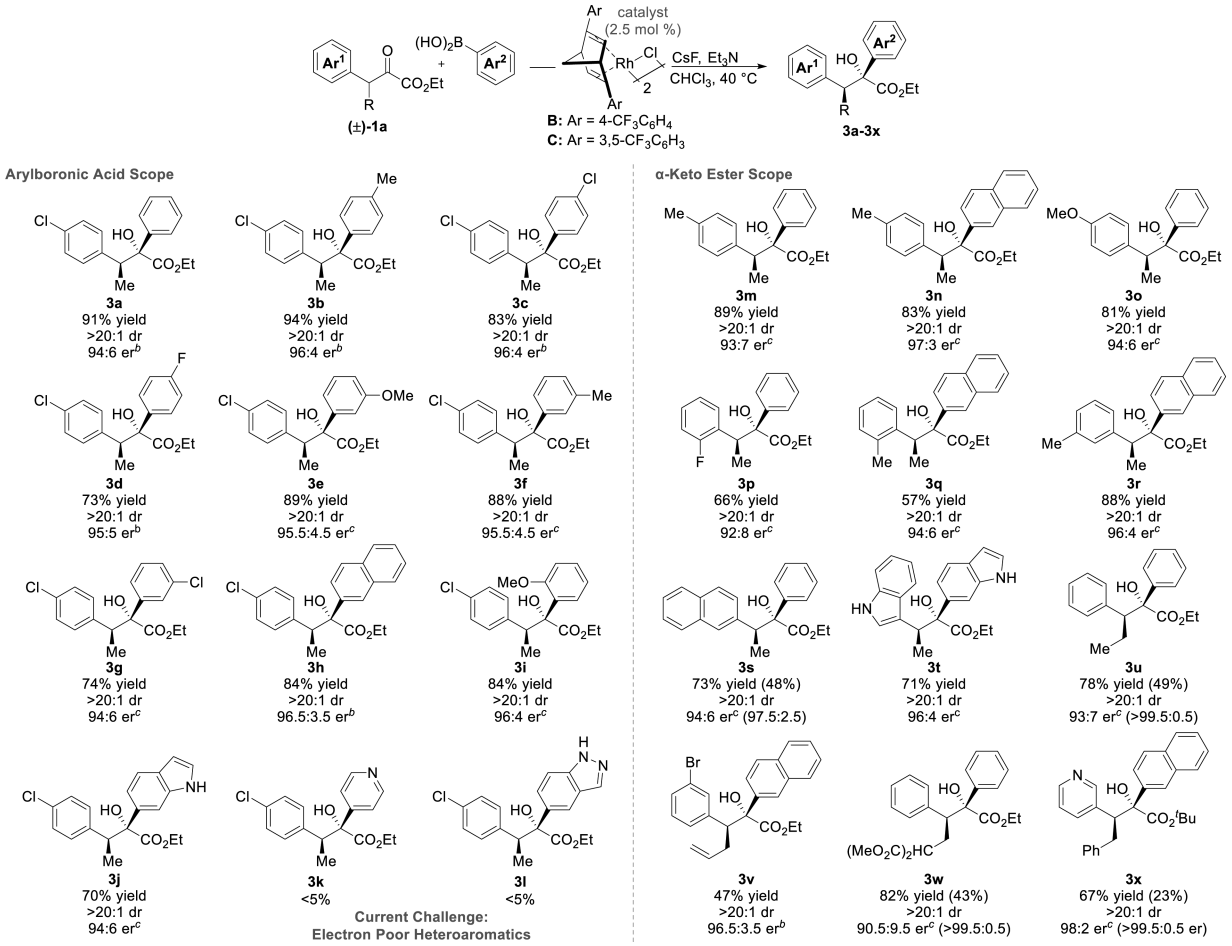
amine was rapid; within 8 min the extent of racemization had reached 87%, and complete racemization occurred after 20 min. Tri-*n*-butylamine exhibited a noticeably slower racemization profile, but was still nearly complete within 20 min. In contrast to triethylamine and tri-*n*-butylamine, the alkyl branched Hünig's base displayed a slow racemization profile, and **1a** was still measurably enriched after approximately 1.7 h at room temperature. When studied at 40 °C in the presence of 6 equiv of Hünig's base, racemization of **1a** was enhanced, but complete racemization only occurred after 1 h. Thus, although Hünig's base exhibits greater thermodynamic basicity than triethylamine, it is less effective at promoting the racemization of **1a**.[13] Finally, *N*-methylpyrroldine, which possesses lower thermodynamic basicity than triethylamine,[14] displayed the fastest racemization profile, promoting complete racemization of **1a** in under 2 min. The observed trend suggests the kinetic basicity of the tertiary amine exerts a larger influence on the racemization of **1a** than its thermodynamic basicity. This observation may prove to be generally important in the *de novo* design of novel dynamic kinetic resolutions involving enolizable carbonyl substrates.

With optimal reaction conditions in hand we began to study the scope of the process with respect to the arylboronic acid component (Table 2). It should be noted that while catalysts **B** and **C** provide identical levels of selectivity for product **3a**, in certain cases it was found that one catalyst was more selective for a particular substrate. Ultimately, electron-rich arylboronic acids were found to be suitable reaction partners as the *p*-tolyl adduct **3b** was formed in high yield with high levels of diastereo- and enantiocontrol. Electron-poor arylboronic acids could also be used; however, in the case of *p*-fluoro- and *p*-chlorophenylboronic acid, a larger excess was required to achieve good yields. Nevertheless, high levels of diastereo- and enantioselectivity were still observed for addition products **3c** and **3d**. Substitution of the arylboronic acid at the *m*-position was also tolerated. For instance, the *m*-methoxy and *m*-tolyl adducts **3e** and **3f** were obtained in good yield, with high levels of stereocontrol. Electron withdrawing substituents were also tolerated at this position, and the use of *m*-chlorophenylboronic acid afforded the desired arylation product **3g** in good yield with high levels of stereocontrol. Polyaromatic boronic acids were also suitable substrates for this transformation, as the 2-naphthyl adduct **3h** could be obtained in good yield with similarly high levels of diastereo- and enantiocontrol. The sterically demanding *o*-methoxy adduct **3i** was formed in good yield with high levels of enantiocontrol, although in this instance a relatively large excess of the boronic acid substrate was required to achieve full conversion. Finally, we found that even unprotected 6-indoylboronic acid could be employed, furnishing adduct **3j**, while maintaining reaction efficiency. It should be noted that at this stage of optimization certain electron-poor arylboronic acid substrates cannot be used, as the 4-pyridyl and 5-indazole adducts **3k** and **3l** were not detected. In addition, the reaction with 2-thienylboronic acid only reached 11% conversion after 36 h under the optimized reaction conditions (not shown). Efforts to address these limitations are currently underway in our laboratory.

Next, we explored the scope of the reaction with respect to the α-keto ester reaction partner (Table 2). Substrates bearing electron donating substituents at the *para*-position of the aryl ring were suitable reaction partners. For example, the *p*-tolyl-substituted product **3m** was obtained in good yield with high levels of stereocontrol. Higher levels of enantioselectivity were observed with this substrate when 2-naphthylboronic acid was employed as a nucleophile furnishing addition product **3n**. Apparently, the electron-rich *p*-methoxy-substituted substrate was subject to facile racemization under the reaction conditions, as product **3o** could also be obtained in good yield with high levels of stereocontrol. An *o*-F-substituted α-keto ester was subject to phenylboronic acid addition, producing **3p** in acceptable yield and high diastereoselectivity and decent levels of enantiocontrol. The *o*-tolyl product **3q** was afforded in 57% yield, and 94:6 er, while the *m*-tolyl product **3r** was formed in 88% yield with 96:4 er, suggesting that the steric nature of the α-keto ester aryl component has a slight impact on reaction efficiency and enantioselectivity. A 2-naphthyl-substituted α-keto ester could also be used, affording addition product **3s** with high levels of enantio- and diastereoselectivity. Product **3s** could be enriched to 97.5:2.5 er following a single crystallization. Notably, arylation of an unprotected 3-indole-substituted α-keto ester with 6-indoleboronic acid afforded bis(indole) adduct **3t** in good yield with high levels of selectivity. The use of 2-naphthyl and *m*-tolylboronic acid was also successful with this α-keto ester (see Supporting Information). Larger alkyl substituents at the β-position were tolerated, and the β-ethyl-substituted product **3u** was obtained in good yield with acceptable levels of enantiocontrol. Product **3u** could be obtained as a single enantiomer in acceptable yield following a single recrystallization. The arylation reaction

DOI: 10.1021/jacs.7b00943
J. Am. Chem. Soc. XXXX, XXX, XXX−XXX

Table 2. Scope of Dynamic Kinetic Arylation Reaction[a]

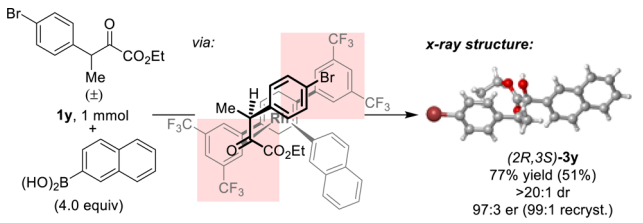


[a]Reactions run on 0.1 mmol scale for 48 or 60 h (see SI for individual reaction times and boronic acid equivalents); reported yields and er values are averages of two runs. Values in parentheses represent recrystallized yields and enantiomeric ratios. [b]Catalyst **B** employed. [c]Catalyst **C** employed.

exhibited functional group chemoselectivity in the presence of competing functionality as the bromoaryl- and β-allyl-substituted product **3v** was obtained in acceptable yield with high levels of stereocontrol. Notably, less than 10% of Heck-type coproducts[15] were observed during formation of **3v**. Additionally, no Suzuki-type products are observed in this process. The branched diester product was formed in excellent yield. Although lower levels of enantiocontrol were observed in this reaction, product **3w** can be accessed as a single enantiomer in acceptable yield following a single crystallization. Finally, although pyridine containing boronic acids are not successful reaction partners at this stage of optimization, a 3-pyridyl-substituted α-keto ester was tolerated under the reaction conditions and afforded arylation product **3x** in good yields with high diastereo- and enantiocontrol. Product **3x** could also be recovered as a single enantiomer, albeit in lower yield, after a single crystallization. Substrates bearing only aliphatic substitution at the β-position have not been tested at this juncture; presumably, these substrates are less acidic and would be challenging to implement under the present reaction conditions.

Having learned the scope of the DKR arylation process, we sought to examine the effect of increasing the scale of the reaction while simultaneously decreasing the catalyst loading (Scheme 2). The 4-bromo-substituted α-keto ester **1y** underwent arylation with 2-naphthylboronic acid on a 1 mmol scale

Scheme 2. Millimole Scale Arylation and Stereochemical Model



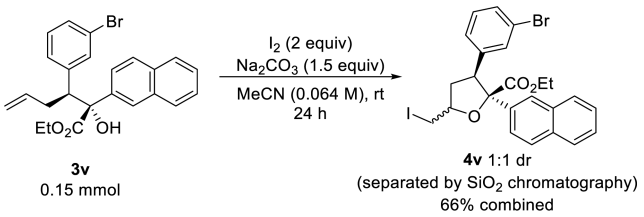
using 0.5 mol % of the catalyst (1 mol % Rh) to afford **3y** in good yield with high levels of diastereo- and enantiocontrol. Product **3y** could be recrystallized to 99:1 er allowing the absolute stereochemistry of **3y** to be determined via X-ray crystallography. The configuration of the other arylation products **3a**−**3x** were assigned by analogy.[16] The observed stereochemistry can be attributed to the C_2-symmetric nature of (*R*,*R*)-catalyst **C** which enforces high levels of enantiocontrol in this reaction by effectively blocking the shaded quadrants in the stereochemical model shown in Scheme 2; the bulky sp^3 center is guided to the top left quadrant. The diastereoselectivity of this transformation is in accord with the Felkin−Ahn model.[17]

DOI: 10.1021/jacs.7b00943
J. Am. Chem. Soc. XXXX, XXX, XXX−XXX

Aromatic interactions appear to be important for achieving high levels of enantio- and diastereoselectivity as evidenced by the inferior results using the benzyl-substituted catalyst **D**.

Finally, considering the sterically encumbered nature of the tertiary alcohol installed in the arylation reaction, we wondered if this functionality could be leveraged in downstream transformations. Preliminary findings have been promising. For instance, unsaturated alcohol **3v** undergoes iodoetherification to tetrahydrofuran **4v** in 66% yield albeit without diastereoselectivity (Scheme 3). The diastereomers of **4v** were easily separated by silica gel column chromatography.

Scheme 3. Iodoetherification of 3v



CONCLUSION

In summary, we have developed an enantioconvergent arylation of racemic β-alkyl-substituted α-keto esters catalyzed by a chiral rhodium-diene complex. A wide range of complex aryl glycolate derivatives could be obtained in good yields with high levels of stereocontrol. Notably, despite the longstanding use of transition metal catalysts in dynamic kinetic hydrogenations, the title reaction is a rare case of installing C−C bonds in dynamic kinetic additions to carbonyl electrophiles. With consideration of the substantial number of commercially available arylboronic acid derivatives and the well-recognized biological activity of the glycolic acid substructure,[18] this chemistry opens the door to a diverse array of interesting building blocks. Although racemization rate is central to efficient dynamic kinetic resolutions,[9] it is rarely discussed or studied in detail; here, we have shown that the racemization of less acidic β-alkyl/aryl-substituted α-keto esters is strongly linked to the steric size of a tertiary amine additive. Preliminary results show that the products of this reaction can be utilized in additional downstream transformations including the synthesis of valuable tetrahydrofuran derivatives. Extension of this work to other classes of nonstabilized carbon centered nucleophiles is currently underway in our laboratory and will be reported in due course.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.7b00943.

Crystallographic data for $C_{22}H_{21}O_3Br$ (CIF)
Crystallographic data for $C_{46}H_{24}Cl_2F_{24}Rh_2$ (CIF)
Crystallographic data for $C_{42}H_{28}Cl_2F_{12}Rh_2$ (CIF)
Experimental procedures, and spectral and analytical data (PDF)

AUTHOR INFORMATION

Corresponding Author

*jsj@unc.edu

ORCID

Jeffrey S. Johnson: 0000-0001-8882-9881

Notes

The authors declare no competing financial interest.

CCDC 1502349, CCDC 1502350, and CCDC 1529845 contain the supplementary crystallographic data for this paper. This data can be obtained free of charge from the Cambridge Crystallographic Date Centre via www.ccdc.cam.ac.uk/data_request/cif.

ACKNOWLEDGMENTS

The project described was supported by Awards R01 GM103855 and R35 GM118055 from the National Institute of General Medical Sciences. K.M.K. gratefully acknowledges support from the Matthew Neely Jackson Undergraduate Research Fellowship. X-ray crystallography was performed by Dr. Peter White.

REFERENCES

(1) Reviews on dynamic kinetic resolution: (a) Caddick, S.; Jenkins, K. *Chem. Soc. Rev.* **1996**, *25*, 447−456. (b) Huerta, F. F.; Minidis, A. B. E.; Bäckvall, J. E. *Chem. Soc. Rev.* **2001**, *30*, 321−331. (c) Pellissier, H. *Tetrahedron* **2003**, *59*, 8291−8327. (c) Pellissier, H. *Tetrahedron* **2011**, *67*, 3769−3802. (d) Bhat, V.; Welin, E. R.; Guo, X.; Stoltz, B. M. *Chem. Rev.* **2017**, DOI: 10.1021/acs.chemrev.6b00731.

(2) For select literature examples, see: (a) Kitamura, M.; Tokunaga, M.; Noyori, R. *J. Am. Chem. Soc.* **1993**, *115*, 144−152. (b) Noyori, R.; Tokunaga, M.; Kitamura, M. *Bull. Chem. Soc. Jpn.* **1995**, *68*, 36−55. (c) Eustache, F.; Dalko, P. I.; Cossy, J. *Org. Lett.* **2002**, *4*, 1263−1265. (d) Ros, A.; Magriz, A.; Dietrich, H.; Lassaletta, J. M.; Fernández, R. *Tetrahedron* **2007**, *63*, 7532−7537. (e) Ros, A.; Magriz, A.; Dietrich, H.; Ford, M.; Fernández, R.; Lassaletta, J. M. *Adv. Synth. Catal.* **2005**, *347*, 1917−1920. (f) Ding, Z.; Yang, J.; Wang, T.; Shen, Z.; Zhang, Y. *Chem. Commun.* **2009**, 571−573. (g) Huang, X.-F.; Zhang, S.-Y.; Geng, Z.-C.; Kwok, C.-Y.; Liu, P.; Li, H.-Y.; Wang, X.-W. *Adv. Synth. Catal.* **2013**, *355*, 2860−2872. (h) Cheng, T.; Ye, Q.; Zhao, Q.; Liu, G. *Org. Lett.* **2015**, *17*, 4972−4975. (i) Son, S.-M.; Lee, H.-K. *J. Org. Chem.* **2014**, *79*, 2666−2681. (j) Cartigny, D.; Püntener, K.; Ayad, T.; Scalone, M.; Ratovelomanana-Vidal, V. *Org. Lett.* **2010**, *12*, 3788−3791. (k) Steward, K. M.; Gentry, E. C.; Johnson, J. S. *J. Am. Chem. Soc.* **2012**, *134*, 7329−7332. (l) Steward, K. M.; Corbett, M. T.; Goodman, C. G.; Johnson, J. S. *J. Am. Chem. Soc.* **2012**, *134*, 20197−20206. (m) Corbett, M. T.; Johnson, J. S. *J. Am. Chem. Soc.* **2013**, *135*, 594−597. (n) Goodman, C. G.; Do, D. T.; Johnson, J. S. *Org. Lett.* **2013**, *15*, 2446−2449. (0) Bao, D.-H.; Gu, S.-H.; Xie, J.-H.; Zhou, Q.-L. *Org. Lett.* **2017**, *19*, 118−121.

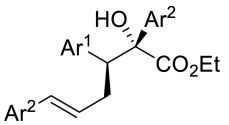
(3) Known examples: (a) Corbett, M. T.; Johnson, J. S. *Angew. Chem., Int. Ed.* **2014**, *53*, 255−259. (b) Goodman, C. G.; Johnson, J. S. *J. Am. Chem. Soc.* **2014**, *136*, 14698−14701. (c) Goodman, C. G.; Walker, M. M.; Johnson, J. S. *J. Am. Chem. Soc.* **2015**, *137*, 122−125. (d) Cohen, D. T.; Eichman, C. C.; Phillips, E. M.; Zarefsky, E. R.; Scheidt, K. A. *Angew. Chem., Int. Ed.* **2012**, *51*, 7309−7313. (e) Ward, D. E.; Jheengut, V.; Akinnusi, O. T. *Org. Lett.* **2005**, *7*, 1181−1184. (f) Bergeron-Brlek, M.; Teoh, T.; Britton, R. *Org. Lett.* **2013**, *15*, 3554−3557. (g) Yang, J.; Wang, T.; Ding, Z.; Shen, Z.; Zhang, Y. *Org. Biomol. Chem.* **2009**, *7*, 2208−2213. (h) Calter, M. A.; Phillips, R. M.; Flaschenriem, C. *J. Am. Chem. Soc.* **2005**, *127*, 14566−14567. (i) Calter, M.; Li, N. *Org. Lett.* **2011**, *13*, 3686−3689. (j) Wu, Z.; Li, F.; Wang, J. *Angew. Chem., Int. Ed.* **2015**, *54*, 1629−1633.

(4) (a) Sakai, M.; Ueda, M.; Miyaura, N. *Angew. Chem., Int. Ed.* **1998**, *37*, 3279−3281. (b) Takaya, Y.; Ogasawara, M.; Hayashi, T.; Sakai, M.; Miyaura, N. *J. Am. Chem. Soc.* **1998**, *120*, 5579−5580. (c) Tian, P.; Dong, H.-Q.; Lin, G.-Q. *ACS Catal.* **2012**, *2*, 95−119.

(5) (a) Duan, H.-F.; Xie, J.-H.; Qiao, X.-C.; Wang, L.-X.; Zhou, Q.-L. *Angew. Chem., Int. Ed.* **2008**, *47*, 4351−4353. (b) Cai, F.; Pu, X.; Qi, X.; Lynch, V.; Radha, A.; Ready, J. M. *J. Am. Chem. Soc.* **2011**, *133*, 18066−18069. (c) Yamamoto, Y.; Shirai, T.; Watanabe, M.; Kurihara,

DOI: 10.1021/jacs.7b00943
J. Am. Chem. Soc. XXXX, XXX, XXX−XXX

K.; Miyaura, N. *Molecules* **2011**, *16*, 5020−5034. (d) Zhu, T.-S.; Jin, S.-S.; Xu, M.-H. *Angew. Chem., Int. Ed.* **2012**, *51*, 780−783. (e) Zhu, T.−S.; Xu, M.-H. *Chin. J. Chem.* **2013**, *31*, 321−328.
(6) Greater than 1000 boronic acids are available from Sigma-Aldrich.
(7) (a) Hoffmann, S.; Nicoletti, M.; List, B. *J. Am. Chem. Soc.* **2006**, *128*, 13074−13075. (b) Rong, Z.− Q.; Zhang, Y.; Chua, R. H. B.; Pan, H.− J.; Zhao, Y. *J. Am. Chem. Soc.* **2015**, *137*, 4944−4947.
(8) Xie, J.− H.; Zhou, Q.- L. *Aldrichimica Acta* **2015**, *48*, 33−39.
(9) Walsh, P. J.; Kozlowski, M. C. *Fundamentals of Asymmetric Catalysis*; University Science Books: CA, 2009; p 272.
(10) (a) Shintani, R.; Inoue, M.; Hayashi, T. *Angew. Chem., Int. Ed.* **2006**, *45*, 3353−3356.
(11) (a) Hayashi, T.; Ueyama, K.; Tokunaga, N.; Yoshida, K. *J. Am. Chem. Soc.* **2003**, *125*, 11508−11509. (b) Berthon-Gelloz, G.; Hayashi, T. *J. Org. Chem.* **2006**, *71*, 8957−8960.
(12) Rovis and co-workers noted a similar effect during the development of an asymmetric glyoxamidation of alkylidene malonates: Liu, Q.; Perreault, S.; Rovis, T. *J. Am. Chem. Soc.* **2008**, *130*, 14066−14067.
(13) Scherrer, R. A.; Donovan, S. F. *Anal. Chem.* **2009**, *81*, 2768−2778.
(14) Stoimenovski, J.; Izgorodina, E.− I.; MacFarlane, D.− R. *Phys. Chem. Chem. Phys.* **2010**, *12*, 10341−10347.
(15) For preparation of the racemic standards for β-allyl-substituted products such as **3v**, significant amounts of the Heck product shown below was observed:



(16) CCDC 1502349, CCDC 1502350, and CCDC 1529845 contain the supplementary crystallographic data for this paper. This data can be obtained free of charge from the Cambridge Crystallographic Date Centre via www.ccdc.cam.ac.uk/data_request/cif.
(17) (a) Chérest, M.; Felkin, H.; Prudent, N. *Tetrahedron Lett.* **1968**, *9*, 2199−2204. (b) Anh, N. T.; Eisenstein, O. *Tetrahedron Lett.* **1976**, *17*, 155−158.
(18) Kiefel, M. J.; von Itzstein, M. *Chem. Rev.* **2002**, *102*, 471−490.

DOI: 10.1021/jacs.7b00943
J. Am. Chem. Soc. XXXX, XXX, XXX−XXX