

Palladium-Catalyzed, Enantioselective Heine Reaction

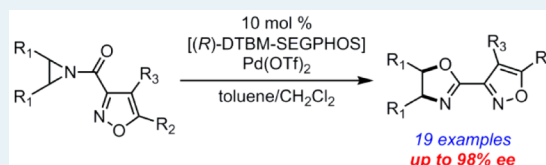
Molly Punk, Charlotte Merkley, Katlyn Kennedy, and Jeremy B. Morgan*

Department of Chemistry and Biochemistry, University of North Carolina Wilmington, Dobo Hall, Wilmington, North Carolina 28403, United States

S Supporting Information

ABSTRACT: Aziridines are important synthetic intermediates for the generation of nitrogen-containing molecules. *N*-Acylaziridines undergo rearrangement by ring expansion to produce oxazolines, a process known as the Heine reaction. The first catalytic, enantioselective Heine reaction is reported for *meso*-*N*-acylaziridines where a palladium(II)–diphosphine complex is employed. The highly enantioenriched oxazoline products are valuable organic synthons and potential ligands for transition-metal catalysis.

KEYWORDS: enantioselective, aziridine, palladium, heterocycles, desymmetrization



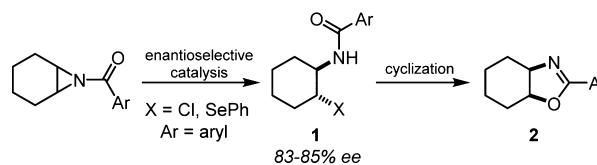
Nonracemic oxazolines are highly valued structures in organic synthesis.^{1–4} The five-membered heterocycles are employed as functionalized building blocks for the production of biologically active molecules and ligands for enantioselective catalysis.^{5–8} Typically enantioenriched oxazolines are synthesized from 1,2-amino alcohols available from the chiral pool.^{2,9–14} The enantioselective synthesis of oxazolines from alkenes can be performed with stoichiometric chiral modifiers;^{15–17} however, a catalytic, enantioselective synthesis of oxazolines from achiral starting materials is not available.^{18–23} Herein we report the first example of an enantioselective Heine reaction, catalyzed by palladium(II)–diphosphine complexes,^{24,25} as a new strategy for generating enantioenriched oxazolines that might be otherwise difficult to access.

Heine and co-workers were the first to utilize *N*-acylaziridines as synthetic precursors to oxazolines under Lewis acid catalysis.²⁶ Subsequently, Heine's group also explored mild Lewis base catalysts for the rearrangement reaction that now bears his name.^{27–30} Chiral *N*-acylaziridines can undergo stereospecific rearrangement to enantioenriched oxazolines under Lewis acid catalysis,^{19,31–34} and a mechanism for this process has been proposed.^{35,36} *Meso*-*N*-Acylaziridines offer the opportunity to control the absolute stereochemistry during oxazoline formation by enantioselective catalysis; however, only racemic oxazolines have been produced by a direct Lewis acid-catalyzed Heine reaction.¹⁹ Two methods for enantioenriched oxazoline formation from aziridine desymmetrization intermediates are known (Scheme 1).^{37,38} In both examples, the ring-opened intermediate (**1**) was isolated with varying levels of enantiomeric excess, and only one substrate was cyclized to the oxazoline **2**. The current work accomplishes a direct catalytic, highly enantioselective aziridine rearrangement to oxazoline (**3** → **4**, Scheme 1).

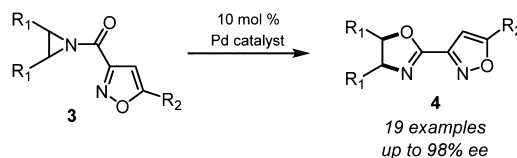
Our research group has been interested in novel synthetic methods that incorporate *N*-acylaziridines.^{34,39} The majority of enantioselective processes incorporating *N*-acylaziridines have

Scheme 1. Enantioselective Synthesis of Oxazolines by *N*-Acylaziridine Desymmetrization

Previous Work:^{37,38}



This Work:



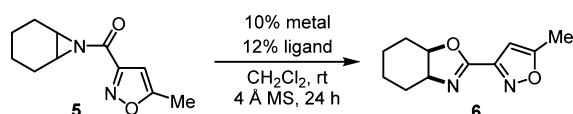
been Lewis acid-catalyzed desymmetrization of *meso*-aziridines by ring opening reactions with nucleophiles.^{37,38,40–54} Benzoyl-protected aziridines have proven to be the most successful in these desymmetrization reactions; however, early efforts in our group to develop an enantioselective Heine reaction using these aziridines were completely nonselective despite evidence for metal catalysis. We considered the strategy of transition-state organization by 2-point binding as a solution. While *N*-(2-picolinoyl)-aziridines have been successfully employed for ring opening desymmetrization,^{48–54} we identified 3-acylisoxazoles as a novel directing group (**3**, Scheme 1). The isoxazole structure is highly modular at the C4 and C5 positions which enables tuning of reaction yield and enantioselectivity.

Aziridine **5** was produced from the corresponding *N*-tosylaziridine for a catalyst survey (Table 1). Commercially available metal triflate salts and ligands (Figure 1) were

Received: May 18, 2016

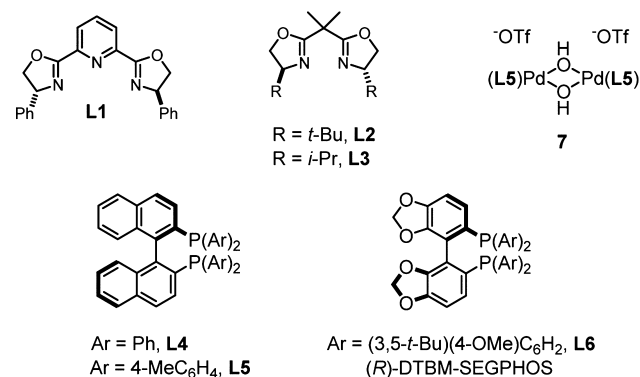
Revised: June 13, 2016

Published: June 15, 2016

Table 1. Catalyst Discovery for an Enantioselective Heine Reaction^a

entry	metal	ligand	conversion (%) ^b	ee (%) ^b
1	Cu(OTf) ₂	L1	12	28
2	La(OTf) ₃	L1	24	-33
3	Cu(OTf) ₂	L2	95	39
4	Cu(OTf) ₂	L3	93	82
5	Ni(OTf) ₂	L3	23	-35
6	Pd(OTf) ₂	L3	41	60
7	Pd(OTf) ₂	L4	29	85
8	Pd(OTf) ₂	L5	27	95
9	7	—	0	—
10	Pd(OTf) ₂	L6	33	92
11 ^c	Pd(OTf) ₂	L6	79	94
12 ^c	Pd(ClO ₄) ₂	L6	60	76
13	Pd(BF ₄) ₂	L6	0	—
14 ^{c,d}	Pd(OTf) ₂	L6	89	88

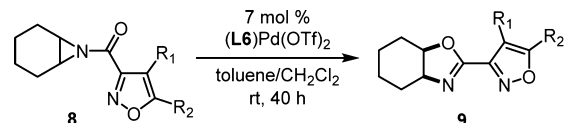
^aReaction conditions: aziridine **5** (0.1 mmol) and 50 mg of 4 Å powdered molecular sieves were added to the preformed catalyst (0.01 mmol of metal and 0.012 mmol of ligand) in CH₂Cl₂ (0.2 M) at room temperature for 24 h. ^bDetermined by HPLC peak area ratios of **5** and **6** at 250 nm using the CHIRALCEL OJ column. ^cReaction solvent was toluene. ^dReaction performed with 5 mol % catalyst.

**Figure 1.** Ligand structures surveyed for the catalytic, enantioselective Heine reaction.

complexed in dichloromethane with 4 Å molecular sieves prior to the addition of aziridine **5**. A large variety of catalysts produced oxazoline **6** as a single diastereomer, with a relevant sample shown in Table 1. Interestingly, oxazoline-based ligands gave the best initial hits with lanthanide and copper triflates (entries 1–4). The copper(II)–BOX complexes were promising with high conversion and good enantioselectivity, but adjustment of reaction parameters could not improve selectivity above 82% ee (entry 4). While considering other late transition metals with BOX ligands (entries 5–6), we discovered that palladium(II)–BINAP derived catalysts produced very good ee with reduced conversion (entries 7–8). The μ -hydroxy dimeric palladium(II) catalyst^{55,56} (**7**) was inactive (entry 9). Further investigation of diphosphine ligands revealed DTBM-SEGPHOS as the optimal choice following a solvent switch to toluene (entries 10–11).^{57–60} Alternative noncoordinating anions were inferior to triflate (entry 12–13), and lowering the

catalyst loading to 5 mol % was possible, albeit with diminished enantioselectivity (entry 14).

The effect of isoxazole structure on the reaction outcome was investigated (**8**, Table 2). Slight modifications to reaction

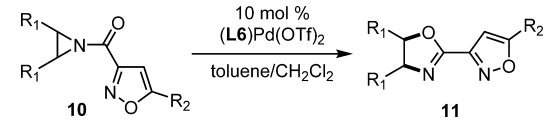
Table 2. Isoxazole Substituent Effects on the Enantioselective Heine Reaction^a

entry	R ₁	R ₂	yield (%) ^b	ee (%) ^c
1	H	H	61	86
2	H	methyl	81	92
3	H	ethyl	82	89
4	H	isopropyl	74	90
5	H	cyclopropyl	69	83
6	H	<i>tert</i> -butyl	75	95
7	H	phenyl	62	91
8	I	methyl	68	85
9	–CH ₂ CH ₂ CH ₂ CH ₂ –	–	63	89

^aReaction conditions: aziridine (0.2 mmol), [(*R*)-DTBM-SEGPHOS]-Pd(OTf)₂ (0.014 mmol), and 100 mg of 4 Å powdered molecular sieves in 9:1 toluene/CH₂Cl₂ (0.2 M) at room temperature for 40 h. ^bIsolated yield; average of two or more runs. ^cDetermined by HPLC.

conditions were employed with 7 mol % of [DTBM-SEGPHOS]Pd(OTf)₂ producing adequate yield and enantioselectivity after 40 h at room temperature. Adjusting the steric size of the 5-isoxazole substituent (R₂) had only a slight effect on yield and enantioselectivity (entries 1–6). The trend was not linear, with methyl (entry 2) and *tert*-butyl (entry 6) producing the highest enantioselectivities. A 5-phenyl substituent suppressed the yield but generated high levels of enantioselectivity (entry 7). Aziridines containing a 4-isoxazole substituent resulted in similar yields and enantioselectivities (entries 8–9). The 4-iodo derivative is an interesting compound for further functionalization.

meso-Aziridines with structurally diverse backbones were synthesized as both the 5-methyl and 5-*tert*-butyl-3-acylisoxazole derivatives (**10**, Table 3). The changes in aziridine structure led to significant decreases in turnover for most substrates at room temperature. To combat slower reactions, catalyst loading was increased to 10 mol %, and reaction temperature was optimized for yield and enantioselectivity of oxazoline **11**. Under the modified standard conditions, substrates containing a 6-membered ring carbocyclic aziridine backbone gave high yields and excellent ee values (entries 1–2, Table 3). Decreasing the ring size gave comparable results (entry 3) where incorporation of the 5-*tert*-butyl isoxazole produced a decrease in yield, but the highest ee observed in the study (entry 4). A 7-membered carbocyclic backbone resulted in significant issues with conversion though enantioselectivity remained high (entries 5–6). After 7 days at 30 °C, only 40% and 44% yields could be isolated for the two isoxazole variations. When accounting for recovered starting material, high yield was observed for the *tert*-butyl derivative (entry 6). Incorporation of oxygen in the aziridine backbone was possible utilizing a dioxepine ring (entry 7) or tetrahydrofuran ring (entry 8), albeit with reduced enantioselectivity and yield. An acyclic *meso*-aziridine was a very good substrate when

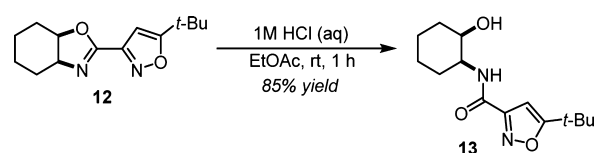
Table 3. Substrate Scope for *meso*-Aziridine Desymmetrization by Enantioselective Rearrangement^a


entry	aziridine	temp (°C)	time (h)	yield (%) ^[b]	ee (%) ^[c]	
1 ^[d]		40	24	74	94	
2 ^[d]		40	24	91	93	
3 ^[d]		R ₂ = Me	40	24	94	92
4		R ₂ = <i>t</i> -Bu	40	24	77	98
5		R ₂ = Me	30	168	40(68)	92
6		R ₂ = <i>t</i> -Bu	30	168	44(88)	92
7 ^[e]		25	168	56	66	
8		40	72	48(96)	32	
9		R ₂ = Me	25	48	64(78)	90
10		R ₂ = <i>t</i> -Bu	25	48	61(87)	83

^aReaction conditions: aziridine (0.2 mmol), [(*R*)-DTBM-SEGPHOS]-Pd(OTf)₂ (0.02 mmol), and 100 mg of 4 Å powdered molecular sieves in 2:1 toluene/CH₂Cl₂ (0.2 M). ^bIsolated yield for an average of two or more runs. Yield in parentheses is based on recovered starting material (bmrs). ^cDetermined by HPLC. ^dReaction solvent was 1:1 toluene/CH₂Cl₂. ^eReaction solvent was CH₂Cl₂.

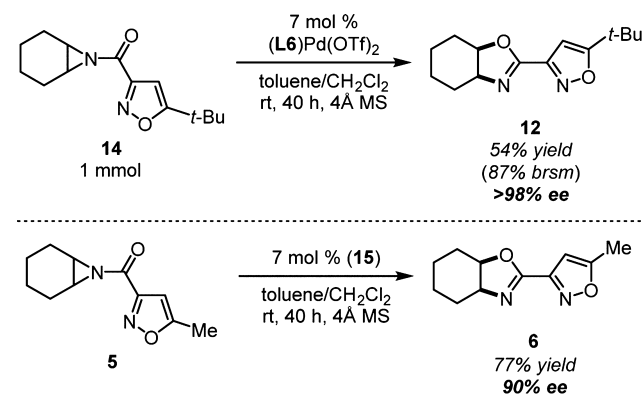
performed at room temperature where enantioselectivities were highest (entries 9–10).

Aqueous HCl in ethyl acetate rapidly converts oxazoline **12** to 1,2-hydroxyamide **13** by ring opening (Scheme 2). Such rapid hydrolysis of **12** was not surprising as certain purified oxazolines produced by rearrangement hydrolyzed during

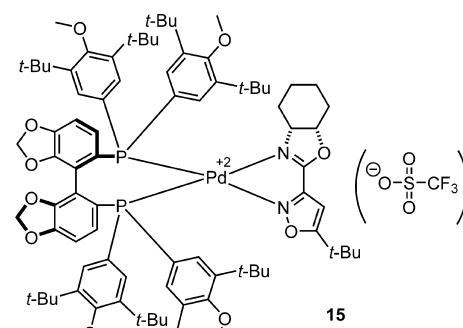
Scheme 2. Hydrolysis of Enantioenriched Oxazoline **12**

storage under ambient conditions. Independent synthesis of amide **13** proved the absolute configuration of oxazoline **12** to be 4*S*,*S**R* when the *R* catalyst was employed.

The enantioselective rearrangement of aziridine **14** was scaled to 1 mmol with reduced yield, but an increase in ee (Scheme 3). Following the reaction, the catalyst mixed with 4 Å

Scheme 3. Enantioselective Heine Reaction Scale-Up

mol sieves was collected by filtration before purification of oxazoline **12** by column chromatography. The recovered catalyst was a single diastereomer by ¹H NMR and has a structure consistent with **15** by HRMS (Figure 2). Con-

**Figure 2. Structure of recovered catalyst from reaction scale-up.**

firmation of **15** was obtained following treatment with pyridine to free the oxazoline portion for analysis. A crossover experiment was performed by subjecting aziridine **5** to rearrangement conditions with 7 mol % of **15** (Scheme 3). Oxazoline **6** was produced in nearly identical yield and enantioselectivity as standard conditions (entry 2, Table 2). This experiment suggests that the active catalyst is formed in situ from **15**.⁶¹

A proposed reaction mechanism is provided in Figure 3. The anhydrous, premade catalyst⁵⁸ (**16**) coordinates the aziridine (**17**) by 2-point binding. We favor binding to both nitrogen atoms to form intermediate **18** based on the azaphilic nature of palladium. Bond reorganization directly to the product bound catalyst **19** occurs in the enantiodetermining step. We propose that the *cis*-oxazoline product is generated exclusively by C–O bond construction via an S_Ni mechanism leading to retention of stereochemistry.³⁶ The orientation of **18** would project substituents on the aziridine backbone toward the chiral ligand. The requirement of a triflate counterion may suggest a double inversion mechanism involving triflate, which has not been ruled out. Intermediate **19** releases the product, likely by

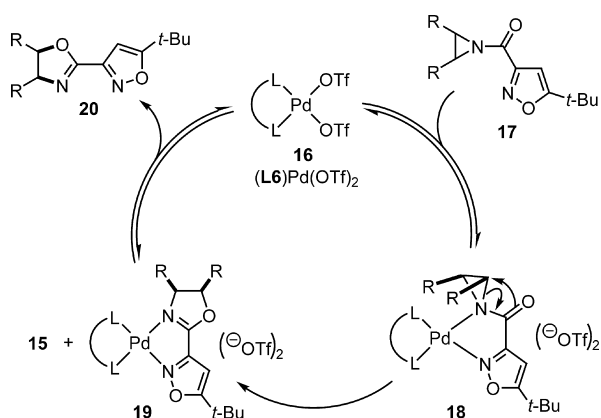


Figure 3. Proposed mechanism for the palladium-catalyzed, enantioselective Heine reaction.

dissociative substitution, to turn over the catalytic cycle. Slow release of product (**20**) by intermediate **19** may explain the requirement for higher catalyst loading. The recovered catalyst **15** appears to be a low energy intermediate that can be formed directly from **18**, but re-enter the catalytic cycle.

The first example of a catalytic, enantioselective Heine reaction has been described. A cationic palladium(II)–diphosphine catalyst produces highly enantioenriched oxazoline products with good to excellent yields across a series of structural modifications. The application of the isoxazole-based oxazoline products as synthetic intermediates and ligands for catalysis is currently being explored. Efforts are underway to discern the reaction mechanism and apply this catalyst system to new aziridine ring-opening reactions.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acscatal.6b01400.

Detailed experimental procedures and analytical data (PDF)

NMR data for all new compounds (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: morganj@uncw.edu.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The authors are grateful to the National Institute of General Medical Sciences of the National Institutes of Health (R15GM114766) for financial support. The HRMS data was collected from a Bruker MicrOTOF-Q II instrument purchased with funds from the National Science Foundation (CHE-1039784) and University of North Carolina Wilmington. The 600 MHz NMR data was obtained using a Bruker instrument purchased with funds from the National Science Foundation (CHE-0821552).

■ REFERENCES

- (1) Frump, J. A. *Chem. Rev.* **1971**, *71*, 483.
- (2) Gant, T. G.; Meyers, A. I. *Tetrahedron* **1994**, *50*, 2297.
- (3) Meyers, A. I. *J. Org. Chem.* **2005**, *70*, 6137.
- (4) Hoogenboom, R. *Angew. Chem., Int. Ed.* **2009**, *48*, 7978.

- (5) Johnson, J. S.; Evans, D. A. *Acc. Chem. Res.* **2000**, *33*, 325.
- (6) McManus, H. A.; Guiry, P. J. *Chem. Rev.* **2004**, *104*, 4151.
- (7) Desimoni, G.; Faita, G.; Jorgensen, K. A. *Chem. Rev.* **2006**, *106*, 3561.
- (8) Desimoni, G.; Faita, G.; Jorgensen, K. A. *Chem. Rev.* **2011**, *111*, PR284.
- (9) Bansal, S.; Halve, A. K. *Int. J. Pharm. Sci. Res.* **2014**, *5*, 4601.
- (10) For additional methods not covered in ref 9, see refs 11–14.
- (11) Winstein, S.; Boschan, R. *J. Am. Chem. Soc.* **1950**, *72*, 4669.
- (12) Wipf, P.; Miller, C. P. *Tetrahedron Lett.* **1992**, *33*, 907.
- (13) Phillips, A. J.; Uto, Y.; Wipf, P.; Reno, M. J.; Williams, D. R. *Org. Lett.* **2000**, *2*, 1165.
- (14) Crosignani, S.; Young, A. C.; Linclau, B. *Tetrahedron Lett.* **2004**, *45*, 9611.
- (15) Tiecco, M.; Testaferri, L.; Santi, C.; Tomassini, C.; Marini, F.; Bagnoli, L.; Temperini, A. *Eur. J. Org. Chem.* **2000**, *2000*, 3451.
- (16) Minakata, S.; Nishimura, M.; Takahashi, T.; Oderaotoshi, Y.; Komatsu, M. *Tetrahedron Lett.* **2001**, *42*, 9019.
- (17) Nishimura, M.; Minakata, S.; Takahashi, T.; Oderaotoshi, Y.; Komatsu, M. *J. Org. Chem.* **2002**, *67*, 2101.
- (18) For racemic examples, see refs 19–23.
- (19) Ferraris, D.; Drury, W. J.; Cox, C.; Lectka, T. *J. Org. Chem.* **1998**, *63*, 4568.
- (20) Yeung, Y. Y.; Gao, X. R.; Corey, E. J. *J. Am. Chem. Soc.* **2006**, *128*, 9644.
- (21) Minakata, S.; Morino, Y.; Ide, T.; Oderaotoshi, Y.; Komatsu, M. *Chem. Commun.* **2007**, 3279.
- (22) Hajra, S.; Bar, S.; Sinha, D.; Maji, B. *J. Org. Chem.* **2008**, *73*, 4320.
- (23) Scholz, S. O.; Farney, E. P.; Kim, S.; Bates, D. M.; Yoon, T. P. *Angew. Chem., Int. Ed.* **2016**, *55*, 2239.
- (24) Sodeoka, M.; Hamashima, Y. *Chem. Commun.* **2009**, 5787.
- (25) Sheshenev, A. E.; Smith, A. M. R.; Hii, K. K. *Nat. Protoc.* **2012**, *7*, 1765.
- (26) Heine, H. W.; Proctor, Z. *J. Org. Chem.* **1958**, *23*, 1554.
- (27) Heine, H. W.; Fetter, M. E.; Nicholson, E. M. *J. Am. Chem. Soc.* **1959**, *81*, 2202.
- (28) Heine, H. W. *Angew. Chem., Int. Ed. Engl.* **1962**, *1*, 528.
- (29) Heine, H. W. *Mech. Mol. Migr.* **1971**, *3*, 145.
- (30) Kurti, L.; Czako, B. *Strategic Applications of Named Reactions in Organic Synthesis*; Elsevier Academic Press: San Diego, 2005.
- (31) Nishiguchi, T.; Tochio, H.; Nabeya, A.; Iwakura, Y. *J. Am. Chem. Soc.* **1969**, *91*, 5841.
- (32) Nabeya, A.; Shigemoto, T.; Iwakura, Y. *J. Org. Chem.* **1975**, *40*, 3536.
- (33) Cardillo, G.; Gentilucci, L.; Mohr, G. P. *Eur. J. Org. Chem.* **2001**, *2001*, 3545.
- (34) Cockrell, J.; Wilhelmsen, C.; Rubin, H.; Martin, A.; Morgan, J. B. *Angew. Chem., Int. Ed.* **2012**, *51*, 9842.
- (35) Nishiguchi, T.; Tochio, H.; Nabeya, A.; Iwakura, Y. *J. Am. Chem. Soc.* **1969**, *91*, 5835.
- (36) Hori, K.; Nishiguchi, T.; Nabeya, A. *J. Org. Chem.* **1997**, *62*, 3081.
- (37) Mita, T.; Jacobsen, E. N. *Synlett* **2009**, *2009*, 1680.
- (38) Senatore, M.; Lattanzi, A.; Santoro, S.; Santi, C.; Della Sala, G. *Org. Biomol. Chem.* **2011**, *9*, 6205.
- (39) Martin, A.; Casto, K.; Morris, W.; Morgan, J. B. *Org. Lett.* **2011**, *13*, 5444.
- (40) Mita, T.; Fujimori, I.; Wada, R.; Wen, J.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2005**, *127*, 11252.
- (41) Fujimori, I.; Mita, T.; Maki, K.; Shiro, M.; Sato, A.; Furusho, S.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2006**, *128*, 16438.
- (42) Fukuta, Y.; Mita, T.; Fukuda, N.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2006**, *128*, 6312.
- (43) Rowland, E. B.; Rowland, G. B.; Rivera-Otero, E.; Antilla, J. C. *J. Am. Chem. Soc.* **2007**, *129*, 12084.
- (44) Della Sala, G.; Lattanzi, A. *Org. Lett.* **2009**, *11*, 3330.
- (45) Larson, S. E.; Baso, J. C.; Li, G. L.; Antilla, J. C. *Org. Lett.* **2009**, *11*, 5186.

- (46) Wu, B.; Gallucci, J. C.; Parquette, J. R.; RajanBabu, T. V. *Angew. Chem., Int. Ed.* **2009**, *48*, 1126.
- (47) Xu, Y. J.; Lin, L. Q.; Kanai, M.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2011**, *133*, 5791.
- (48) Hayashi, M.; Shiomi, N.; Funahashi, Y.; Nakamura, S. *J. Am. Chem. Soc.* **2012**, *134*, 19366.
- (49) Kalow, J. A.; Doyle, A. G. *Tetrahedron* **2013**, *69*, 5702.
- (50) Li, J.; Liao, Y. T.; Zhang, Y. L.; Liu, X. H.; Lin, L. L.; Feng, X. M. *Chem. Commun.* **2014**, *50*, 6672.
- (51) Yang, D. X.; Wang, L. Q.; Han, F. X.; Li, D.; Zhao, D. P.; Cao, Y. M.; Ma, Y. X.; Kong, W. D.; Sun, Q. T.; Wang, R. *Chem. - Eur. J.* **2014**, *20*, 16478.
- (52) Li, D.; Wang, L. Q.; Yang, D. X.; Zhang, B. Z.; Wang, R. *ACS Catal.* **2015**, *5*, 7432.
- (53) Wang, L. Q.; Yang, D. X.; Han, F. X.; Li, D.; Zhao, D. P.; Wang, R. *Org. Lett.* **2015**, *17*, 176.
- (54) Wang, L. Q.; Yang, D. X.; Li, D.; Wang, R. *Org. Lett.* **2015**, *17*, 3004.
- (55) Fujii, A.; Hagiwara, E.; Sodeoka, M. *J. Am. Chem. Soc.* **1999**, *121*, 5450.
- (56) Hagiwara, E.; Fujii, A.; Sodeoka, M. *J. Am. Chem. Soc.* **1998**, *120*, 2474.
- (57) Hamashima, Y.; Yagi, K.; Takano, H.; Tamas, L.; Sodeoka, M. *J. Am. Chem. Soc.* **2002**, *124*, 14530.
- (58) Corkey, B. K.; Toste, F. D. *J. Am. Chem. Soc.* **2005**, *127*, 17168.
- (59) Corkey, B. K.; Toste, F. D. *J. Am. Chem. Soc.* **2007**, *129*, 2764.
- (60) Brazeau, J. F.; Zhang, S. Y.; Colomer, I.; Corkey, B. K.; Toste, F. D. *J. Am. Chem. Soc.* **2012**, *134*, 2742.
- (61) The active catalyst likely contains a palladium(II)–diphosphine core structure. NMR of the reaction over time shows multiple ^{31}P signals, but no indication of the precatalyst or free diphosphine ligand. Also, the rearrangement of **5** with a product-derived catalyst, (6)Pd(OTf)₂, produced **6** in 40% yield and 17% ee.