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Palladium-Catalyzed Decarboxylative Generation and Asymmetric Allylation of α-Imino Anions

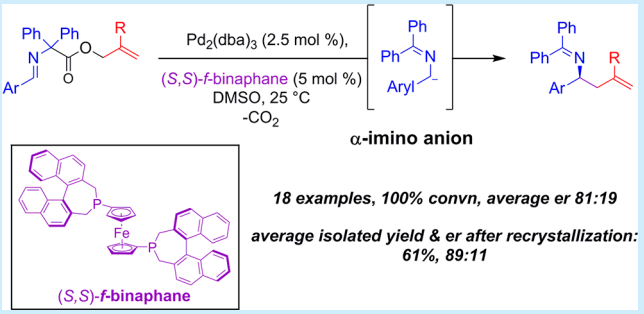
Xiaoyan Qian,[†] Pengfei Ji,[†] Chang He,[†] Jean-Olivier Zirimwabagabo,[‡] Michelle M. Archibald,[‡] Andrew A. Yeagley,[‡,§] and Jason J. Chruma*[,†]

[†]Key Laboratory of Green Chemistry & Technology, College of Chemistry, Sichuan University, Chengdu, Sichuan 610064, P. R. China

[‡]Department of Chemistry, University of Virginia, Charlottesville, Virginia 22904-4319, United States

Supporting Information

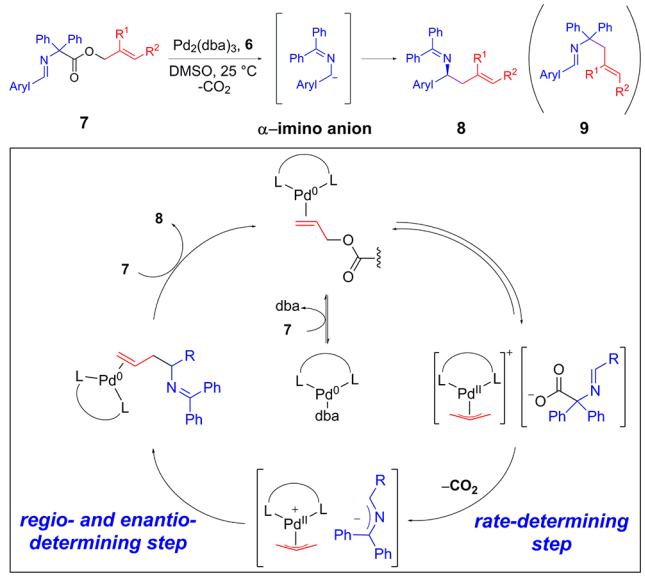
ABSTRACT: A palladium-catalyzed asymmetric decarboxylative allylic alkylation of allyl 2,2-diphenylglycinate imines using (*S,S*)-*f*-binaphane as a chiral supporting ligand has been developed. This transformation allows for decarboxylative generation and enantioselective allylation of nonenolate α-imino (2-azaallyl anions) to afford α-aryl homoallylic imines.



Interest in transition-metal-catalyzed decarboxylative allylation reactions has expanded rapidly within the past decade.[1] Since the initial reports of Tsuji[2] and Saegusa,[3] palladium catalysis has been used to concomitantly generate and allylate a variety of C-, O-, N-, and S-centered anionic nucleophiles. Despite these advances, asymmetric decarboxylative allylic alkylations (ADAA) that generate a new chirality center on the incoming nucleophilic partner have been confined predominately to reactions proceeding via conformationally defined enolates.[4−6] For Pd-catalyzed ADAA, two classes of chiral ligands have distinguished themselves: Trost's diamide bisphosphine ligands[4d−f] and the P/N Phox ligands[7] championed by Stoltz.[4a−c] Depending on ligand and substrate, the key enantiodetermining C−C bond-forming event can proceed via either an inner sphere[8] or an outer sphere mechanism in regard to the metal center.[9] Herein, we report that the ferrocenyl binaphane ligand **6** first introduced by Zhang for asymmetic hydrogenations[10] is superior for the Pd-catalyzed decarboxylative generation and asymmetric allylic alkylation of α-imino anions (2-azaallyl anions) to afford enantioenriched homoallylic imines (Scheme 1). Increasing solvent polarity resulted in improved enantioselectivity, with DMSO typically affording the best results. Overall, this represents a unique example of an ADAA involving a nonenolate nucleophile.[11]

In 2007, we introduced the Pd-catalyzed decarboxylative allylation of allyl diphenylglycinate imines **7** to afford the corresponding racemic homoallylic imines **8**, with the regioisomers **9** occasionally produced as minor side products.[12a] The regioisomeric ratio (**8**:**9**) demonstrated a positive linear Hammett correlation and could be improved by increasing solvent polarity. Empirical and computational studies suggest that the rate-determining step of this transformation is the decarboxylation of a solvent-separated ion pair, whereas the regio- and enantiodetermining event is a later-stage outer sphere attack of an α-imino anion onto a π-allylPd(II) cationic intermediate (Scheme 1, inset).[12b] In an attempt to identify an enantioselective variant of this process,[11] we initiated a screen of several chiral mono- and bidentate ligands for the Pd-catalyzed

Scheme 1. Pd-Catalyzed ADAA of Imines 7



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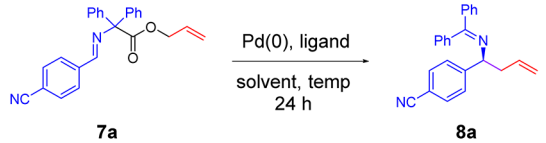
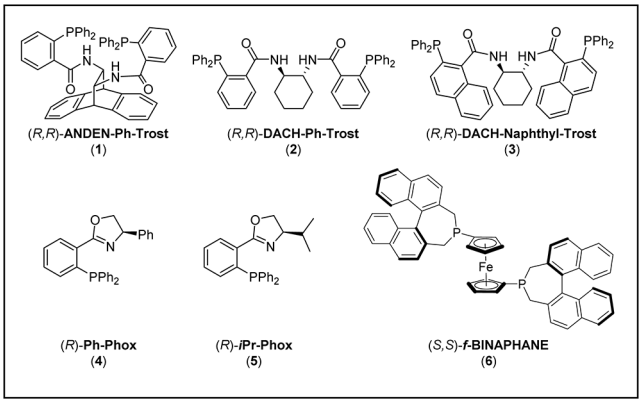
ADAA of *p*-cyanobenzaldimine **7a** (Table 1).[13] Conversion was determined by ^{1}H NMR analysis of the concentrated reaction mixture, and the resultant enantiomeric ratios (er) were determined by chiral HPLC analysis after column chromatography.[14] The P/N ligands **4** and **5** both provided essentially racemic product in varying amounts (entries 1 and 2). The Trost ligands, on the other hand, showed more promise (entries 3–6), particularly when **1** was used with $Pd(dba)_2$ in toluene (entry 6). Unfortunately, these reaction conditions provided highly variable and inconsistent results in our hands.[15] A more forgiving and general alternative was found using 5 mol % of ferrocenyl binaphane **6** with 2.5 mol % of $Pd_2(dba)_3$ in THF at 20 °C (entry 7). Cooling the reaction mixture to −5 °C resulted in a moderately improved er (entry 8). More importantly, the er of the final product could be increased to essentially homochirality by preferentially crystallizing out the racemate from cold hexanes (entry 9).

Having identified suitable reaction conditions, we next applied them to a selection of aryl and heteroaryl imine substrates **7** (Scheme 2). The overall sense of chirality for the products **8** was determined to be (*S*) by conversion of the 3-pyridinyl **8m** to scalemic (*S*)-nornicotine and comparison with reported optical rotation values (Scheme 3).[16] A general trend observed was a corresponding decrease in enantioselectivity upon increasing the electron-donating nature of the arylimine substituent in **7**.[17] This

Table 1. Selected Examples from Chiral Ligand Screen[13,14]



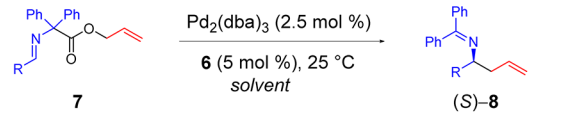
7a **8a**



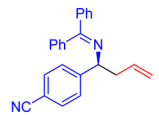
entry	conditions	convn[a] (%)	er[b]
1	$Pd(dba)_2$ (10 mol %), **4** (10 mol %), THF (0.2 M), 20 °C	>95	51:49
2	$Pd(dba)_2$ (10 mol %), **5** (10 mol %), THF (0.2 M), 20 °C	33	48.5:51.5
3	$Pd(dba)_2$ (10 mol %), **2** (10 mol %), MeCN (0.2 M), 20 °C	>95	27.5:72.5
4	$Pd(dba)_2$ (10 mol %), **3** (10 mol %), MeCN (0.2 M), 20 °C	>95	40:60
5	$Pd(dba)_2$ (10 mol %), **1** (10 mol %), THF (0.2 M), 20 °C	22	15.5:84.5
6	$Pd(dba)_2$ (10 mol %), **1** (10 mol %), $PhCH_3$ (0.2 M), 20 °C	81[c]	12.5:87.5[c]
7	$Pd_2(dba)_3$ (2.5 mol %), **6** (5 mol %), THF (0.2 M), 20 °C	>95	90:10
8	$Pd_2(dba)_3$ (2.5 mol %), **6** (5 mol %), THF (0.2 M), −5 °C[d]	60	95.5:4.5
9	$Pd(dba)_2$ (5 mol %), **6** (5 mol %), CH_2Cl_2 (0.2 M), 20 °C; *crystallized racemate from hexanes*[d]	75[e]	>99.9:0.1

[a]Conversion determined by ^{1}H NMR analysis of concentrated reaction mixture. [b]The enantiomeric ratio (er) of **8a** was determined by chiral HPLC. The ratios are listed corresponding to the order of elution. [c]Conversion ranged from 52 to >95%, and er varied from 32:68 to 5:95 under these conditions. [d]Only performed once. [e]Isolated yield after removal of crystalline racemate.

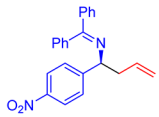
Scheme 2. Pd-Catalyzed ADAA of Imines 7 Using Ligand 6[a,b]



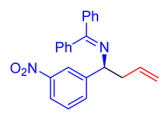
7 (*S*)–**8**



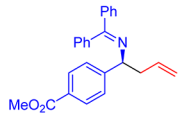
8a
THF: *er* 90.5:9.5
DMF: *er* 90:10
DMSO: *er* 93.5:6.5
(88%, 98:2)[c]



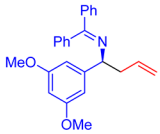
8b
THF: *er* 90:10
DMF: *er* 91:9
DMSO: *er* 94.5:5.5
(quant)[d]



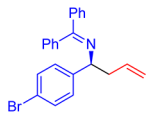
8c
THF: *er* 71:29
DMF: *er* 85:15
DMSO: *er* 82:18
(96%)[d]



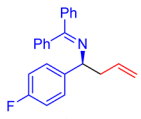
8d
THF: *er* 84.5:15.5
DMF: *er* 89.5:10.5
DMSO: *er* 94:6
(73%, 97.5:2.5)[c]



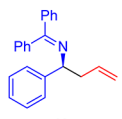
8e
THF: *er* 76:24
DMF: *er* 85.5:14.5
DMSO: *er* 89.5:10.5
(88%)[d]



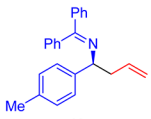
8f
THF: *er* 85.5:14.5
DMF: *er* 86:14
DMSO: *er* 90:10
(76%, 92:8)[c]



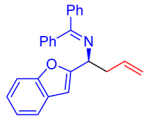
8g
THF: *er* 70:30
DMF: *er* 83.5:16.5
DMSO: *er* 87:13
(48%, 97:3)[c]



8h
THF: *er* 67.5:32.5
DMF: *er* 82:18
DMSO: *er* 86:14
(78%, 89.5:10.5)[d]

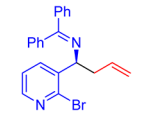


8i
THF: *er* 70.5:29.5
DMF: *er* 86.5:13.5
DMSO: *er* 89.5:10.5
(37%, 95:5)[c]



8j
THF: *er* 63:37
DMF: *er* 69:31
DMSO: *er* 79.5:20.5
(55%, 82:18)[c]

8k
THF: *er* 48.5:51.5
DMF: *er* 56.5:43.5
DMSO: *er* 60:40
(33%, 81:19)[c]



8l
THF: *er* 71:29
DMF: *er* 77.5:22.5
DMSO: *er* 82:18
(85%, 84:16)[c]

[a]All reactions proceeded to complete conversion as judged by TLC. [b]Er determined by chiral HPLC with the first number referring to the initially eluted (*S*) enantiomer; see ref 14. [c]Isolated yield (200 mg scale in DMSO) and er after recrystallization from hexane. [d]Isolated yield (200 mg scale in DMSO) of liquid product after chromatography.

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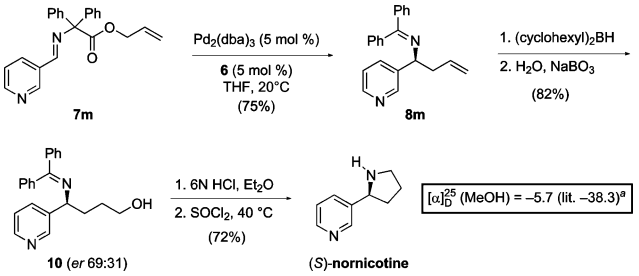
Scheme 3. Synthesis of Scalemic (*S*)-Nornicotine



[a]See ref 16a.

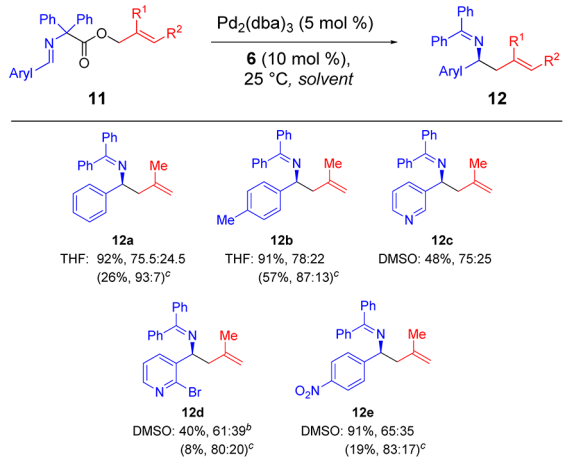
is consistent with our previous mechanistic analysis which suggests that the enantiodetermining step is an outer-sphere process involving an ion pair between a resonance-stabilized α-imino anion and an η^3-π-allylPd(II) cationic electrophile (in contrast to a nonionic inner sphere process).[12b] Reaction conditions that better stabilize the ion-pair intermediate should result in improved enantioselectivity.[18] Switching the reaction medium from THF to more polar acetonitrile proved fruitless due to the poor solubility of the **6**–Pd complex in the latter solvent. Changing the solvent to DMF, however, did provide higher average er values for almost every substrate investigated. Increasing the solvent polarity further by using DMSO consistently generated our best results. These conditions are most appropriate for *para* monosubstituted benzaldimines, affording an average er just over 90:10 prior to recrystallization. Alternatively, heteroarylimino substrates, particularly the smaller thiazole **7k**, tend to afford poorer enantioselectivities.

In addition to improved overall er values, the use of DMF or DMSO as solvent offers significant technical advantages. For example, the product can be separated from any remaining starting material and catalyst simply by selective extraction from the reaction mixture with hexane. After concentration of the combined hexane fractions, ^{1}H NMR analysis indicated that they only contain **8** and occasionally the regioisomer **9**. As noted in our previous studies, the undesired minor product **9** can be removed by selective hydrolysis on slightly acidified silica gel prior to chromatography through a short plug of silica gel.[12a,19] In most cases, the enantiopurity of the homoallylic imine product **8** can be enriched by recrystallization from hexane; in several circumstances (e.g., **8a**, **8e**, **8j**, and **8k**), the racemate preferentially crystallizes out and the mother liquor is enantioenriched.

Substitution on the 2-position of the allyl moiety was tolerated but required higher catalyst loading. Even so, both conversion and er values were still significantly reduced (Scheme 4). Moreover, electron-neutral (**11a**) or electron-rich (**11b**) benzaldimines converted to the corresponding homoallylic imines **12a** and **12b**, respectively, in THF but not in DMSO. This was not an issue for the other imino esters investigated (**11c**–**e**).

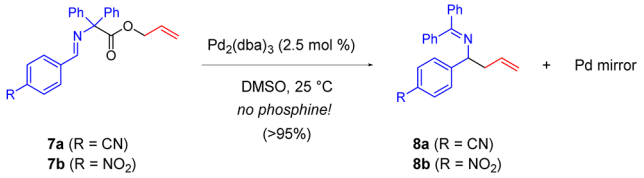
Given that sulfoxides typically are not innocent spectators in Pd-catalyzed processes,[20] we investigated the conversion of both **7a** and **7b** at 25 °C overnight in DMSO with $Pd_2(dba)_3$ but without any bisphosphine **6** (Scheme 5). In the absence of phosphine ligand, complete conversion to the corresponding racemic products **8** was observed for both substrates in addition to formation of a palladium mirror on the walls of the reaction vials. No conversion was observed in the absence of phosphine when THF was employed as solvent. Likewise, no palladium

Scheme 4. Pd-Catalyzed ADAA with Substituted Allyls[a,b]



[a]Unless otherwise indicated, all yields and er values are an average of at least two runs on a 200 mg scale. [b]Reaction conducted at 40 °C. [c]Values in parentheses indicate isolated yield and er after recrystallization.

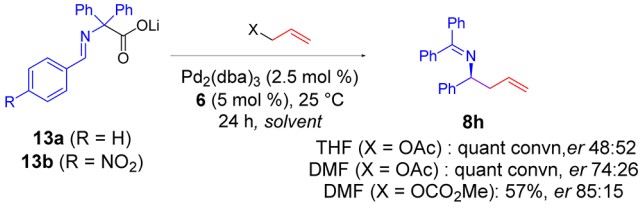
Scheme 5. Phosphine-Free Decarboxylative Allylation



mirrors formed in DMSO when ligand **6** was included in the reaction mixture. The exact role of sulfoxide in our reaction is still under investigation.

Very recently, Zhao reported an "intermolecular" variant of our decarboxylative allylation reaction.[21] Specifically, relatively stable lithium diphenylglycinate imines will readily decarboxylate to the corresponding α-imino anions upon dissolution in aprotic solvents and react with in situ-generated π-allylPd(II) electrophiles. Given the increased simplicity that this modification offers, we sought to determine if it also could be made enantioselective by using chiral ligand **6** (Scheme 6). While

Scheme 6. "Intermolecular" ADAA of Carboxylate 13a



benzaldimine **13a** was converted quantitatively into the corresponding homoallylic imine **8h** in THF using **6** as ligand, the product was essentially racemic. Performing the reaction in DMF improved the resulting er, but it remained significantly lower in comparison to our "intramolecular" option (74:26 versus 82:18). Given that both reactions should proceed via the same 2-azaallyl anion intermediate species, the presence of lithium acetate is the presumed culprit for the reduced enantioselectivity.[18] Indeed, changing the leaving group to a carbonate improved the enantioselectivity dramatically, albeit at

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a lower overall yield.[22] A more serious issue, however, is that the highly electron-withdrawing *p*-nitrobenzaldimine **13b** could not be prepared due to premature decarboxylation both in the solid state and in methanolic solutions. A one-pot imine formation/decarboxylation/allylation tactic is not a likely option since highly electron-withdrawing aryl aldehydes are known to intercept the incipient 2-azaallyl anion intermediate prior to allylation.[12a] Since benzaldimines with strongly electron-withdrawing substituents, e.g., **7b**, afford the best enantioselectivies, this represents a significant advantage of our "intramolecular" process over the otherwise more convenient "intermolecular" variant.

In conclusion, we have presented a Pd-catalyzed ADAA of allyl diphenylglycinate imines **7** to afford enantioenriched α-arylhomoallylic imines **8**. These results represent the first examples of bisphosphine **6** as a chiral ligand for any transition metal-catalyzed asymmetric C−C bond-forming reaction. Moreover, they provide the first examples of highly enatioselective ADAAs involving nonenolate nucleophilic intermediate.[6,11] Future studies will involve the application of this method toward the synthesis of homochiral peptidomimetics and an exploration into the impact of chiral ligand **6** and related analogues on other Pd-catalyzed decarboxylative alkylation processes.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, complete chiral ligand studies, preliminary Hammett plot analysis, and characterization of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: chruma@scu.edu.cn.

Present Address

[§]Longwood University, Department of Chemistry & Physics, Farmville, VA 23909.

Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) For recent reviews, see: (a) Weaver, J. D.; Recio, A., III; Grenning, A. J.; Tunge, J. A. *Chem. Rev.* **2011**, *111*, 1846. (b) Mohr, J. T.; Stoltz, B. M. *Chem.—Asian J.* **2007**, *2*, 1476. (c) Braun, M.; Meier, T. *Angew. Chem., Int. Ed.* **2006**, *45*, 6952. (d) Trost, B. M.; Crawley, M. L. *Chem. Rev.* **2003**, *103*, 2921. (e) You, S.-L.; Dai, L.-X. *Angew. Chem., Int. Ed.* **2006**, *45*, 5236.

(2) Shimizu, I.; Yamada, T.; Tsuji, J. *Tetrahedron Lett.* **1980**, *21*, 3199.

(3) Tsuda, T.; Chujo, Y.; Nishi, S.; Tawara, K.; Saegusa, T. *J. Am. Chem. Soc.* **1980**, *102*, 6381.

(4) (a) Behenna, D. C.; Stoltz, B. M. *J. Am. Chem. Soc.* **2004**, *126*, 15044. (b) Reeves, C. M.; Behenna, D. C.; Stoltz, B. M. *Org. Lett.* **2014**, *16*, 2314. (c) Bennett, N. B.; Duquette, D. C.; Kim, J.; Liu, W.-B.; Marziale, A. N.; Behenna, D. C.; Virgil, S. C.; Stoltz, B. M. *Chem.—Eur. J.* **2013**, *19*, 4414. (d) Trost, B. M.; Xu, J. *J. Am. Chem. Soc.* **2005**, *127*, 2846. (e) Trost, B. M.; Xu, J.; Schmidt, T. *J. Am. Chem. Soc.* **2009**, *131*, 18343. (f) Fournier, J.; Lozano, O.; Menozzi, C.; Arseniyadis, S.; Cossy, J. *Angew. Chem., Int. Ed.* **2013**, *52*, 1257.

(5) For Pd-catalyzed asymmetric allylic alkylations (AAA) not involving decarboxylation, see: (a) Hayashi, T.; Kanehira, K.; Hagihara, T.; Kumada, M. *J. Org. Chem.* **1988**, *53*, 113. (b) Sawamura, M.; Nagata, H.; Sakamoto, H.; Ito, Y. *J. Am. Chem. Soc.* **1992**, *114*, 2586. (c) Kuwano, R.; Ito, Y. *J. Am. Chem. Soc.* **1999**, *121*, 3236. (d) Kuwano, R.; Uchida, K.-i.; Ito, Y. *Org. Lett.* **2003**, *5*, 2177. (e) Trost, B. M.; Radinov, R.; Grenzer, E. M. *J. Am. Chem. Soc.* **1997**, *199*, 7879. (f) Trost, B. M.; Thaisrivongs, D. A. *J. Am. Chem. Soc.* **2008**, *130*, 14092. (g) You, S.-L.; Hou, X.-L.; Dai, L.-X.; Zhu, X.-Z. *Org. Lett.* **2001**, *2*, 149. (h) Curto, J. M.; Dickstein, J. S.; Berritt, S.; Kozlowski, M. C. *Org. Lett.* **2014**, *16*, 1948.

(6) For the Pd-catalyzed asymmetric α-arylation of aliphatic α-imino anions, see: Zhu, Y.; Buchwald, S. L. *J. Am. Chem. Soc.* **2014**, *136*, 4500.

(7) (a) Pfaltz, A. *Acta Chem. Scand. B* **1996**, *50*, 189. (b) Williams, J. M. J. *Synlett* **1996**, 705.

(8) (a) Keith, J. A.; Behenna, D. C.; Sherden, N.; Mohr, J. T.; Ma, S.; Marinescu, S. C.; Nielsen, R. J.; Oxgaard, J.; Stoltz, B. M.; Goddard, W. A., III. *J. Am. Chem. Soc.* **2012**, *134*, 19050. (b) Keith, J. A.; Behenna, D. C.; Mohr, J. T.; Ma, S.; Marinescu, S. C.; Oxgaard, J.; Stoltz, B. M.; Goddard, W. A., III. *J. Am. Chem. Soc.* **2007**, *129*, 11876.

(9) (a) Steinhagen, H.; Reggelin, M.; Helmchen, G. *Angew. Chem., Int. Ed.* **1997**, *36*, 2108. (b) Butts, C. P.; Filali, E.; Lloyd-Jones, G. C.; Norrby, P.-O.; Sale, D. A.; Schramm, Y. *J. Am. Chem. Soc.* **2009**, *131*, 9945.

(10) Xiao, D.; Zhang, X. *Angew. Chem., Int. Ed.* **2001**, *40*, 3425.

(11) Following a complimentary method, Burger and Tunge reported that use of (*R*)-BINAP as a chiral ligand for the Pd-catalyzed ADAA of allyl *N*-(diphenylmethyleneimino)phenylglycinate at 100 °C in dioxane afforded the corresponding homoallylic imine in 30% ee: Burger, E. C.; Tunge, J. A. *J. Am. Chem. Soc.* **2006**, *128*, 10002.

(12) (a) Yeagley, A. A.; Chruma, J. J. *Org. Lett.* **2007**, *9*, 2879. (b) Li, Z.; Jiang, Y.-Y.; Yeagley, A. A.; Bour, J. P.; Liu, L.; Chruma, J. J.; Fu, Y. *Chem.—Eur. J.* **2012**, *18*, 14527.

(13) See the Supporting Information for a complete synopsis of our ligand studies.

(14) Unless otherwise noted, all reported values represent an average of at least three trials.

(15) This may be a result of competition between the highly selective monomeric and the less selective polymeric forms of the Pd−ligand complex at the catalyst concentrations investigated, see ref 9b.

(16) (a) Kisaki, T.; Janaki, E. *Arch. Biochem. Biophys.* **1961**, *92*, 351. (b) Späth, E.; Zaijc, E. *Chem. Ber.* **1935**, *68*, 1667.

(17) See the Supporting Information for a preliminary Hammett plot analysis of the enatiomeric ratios.

(18) Evans, L. A.; Fey, N.; Harvey, J. N.; Hose, D.; Lloyd-Jones, G. C.; Murray, P.; Orpen, A. G.; Osborne, R.; Owen-Smith, G. J. J.; Purdie, M. *J. Am. Chem. Soc.* **2008**, *130*, 14471.

(19) Yeagley, A. A.; Lowder, M. A.; Chruma, J. J. *Org. Lett.* **2009**, *11*, 4022.

(20) (a) Chen, M. S.; White, M. C. *J. Am. Chem. Soc.* **2004**, *126*, 1346. (b) Chen, M. S.; Prabagaran, N.; Labenz, N. A.; White, M. C. *J. Am. Chem. Soc.* **2005**, *127*, 6970. (c) Steinhoff, B. A.; Fix, S. R.; Stahl, S. S. *J. Am. Chem. Soc.* **2002**, *124*, 766. (d) Grennberg, H.; Gogoll, A.; Bäckwall, J.-E. *J. Org. Chem.* **1991**, *56*, 5808. (e) Kitching, W.; Rappoport, Z.; Winstein, S.; Young, W. G. *J. Am. Chem. Soc.* **1966**, *88*, 2054. (f) Trost, B. M. *Acc. Chem. Res.* **1980**, *13*, 385.

(21) Ding, L.; Chen, J.; Hu, Y.; Xu, J.; Gong, X.; Xu, D.; Zhao, B.; Li, H. *Org. Lett.* **2014**, *16*, 720.

(22) See the Supporting Information for related experiments.