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Pd/NHC-Catalyzed Enantiospecific and Regioselective Suzuki–Miyaura Arylation of 2-Arylaziridines: Synthesis of Enantioenriched 2-Arylphenethylamine Derivatives

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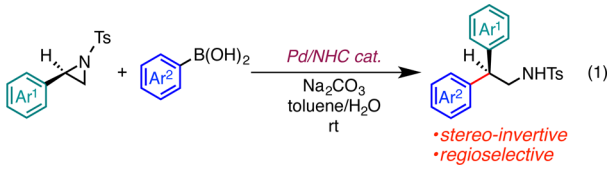
Supporting Information

ABSTRACT: A palladium-catalyzed stereospecific and regioselective cross-coupling of enantiopure 2-arylaziridines with arylboronic acids under mild conditions to construct a tertiary stereogenic center has been developed. N-heterocyclic carbene (NHC) ligands efficiently promote the coupling, suppressing β-hydride elimination. The enantiospecific cross-coupling allowed us for preparation of a series of biologically important 2-arylphenethylamine derivatives in an enantiopure form.

The construction of stereogenic centers through metal-catalyzed cross-coupling in a highly stereocontrolled manner has remained a big challenge in organic synthesis.[1] An excellent approach toward achieving this involves enantioconvergent cross-coupling of racemic secondary alkyl electrophiles[2] or alkylmetals[3] with the aid of a chiral catalyst through dynamic kinetic resolution. Another comprises stereospecific cross-coupling employing either enantioenriched α-chiral secondary alkylmetals[4] or alkyl halides[5] with an achiral catalyst, through which the stereochemical information on substrates is efficiently translated into products (retention or inversion). Meanwhile, the past decade has seen a significant growth in stereospecific cross-coupling of α-chiral nonclassical secondary alkyl electrophiles bearing a $*C_{sp^3}$–O or $*C_{sp^3}$–N bond ($*C_{sp^3}$: stereogenic carbon; O = OSO_2R,[6] OR,[7] and OC(O)R;[8] N = $^+NMe_3(^-OTf)$[9] and NTs_2[10]): α-chiral alcohols and amines are widely accessible by established methods,[11] and their derivatives are highly stable, less toxic and exhibit orthogonal reactivities compared with classical alkyl halides. In this connection, stereospecific cross-coupling using α-chiral nonclassical electrophiles would provide great opportunity for diverse access to chiral complex molecules that are otherwise difficult to synthesize by conventional methodologies. Herein we disclose a Pd/NHC-catalyzed stereospecific and regioselective cross-coupling of enantiopure 2-arylaziridines with arylboronic acids to produce a series of completely stereoinverted 2-arylphenethylamine derivatives (eq 1).



(1)

The 2-arylphenethylamine scaffold constitutes a pharmacologically important motif in dopamine receptor agonists, thereby serving as potential candidates for the treatment of disorders of the central nervous system such as schizophrenia and Parkinson disease.[12] Not surprisingly, they often exhibit biological enantiospecificity.[13] Therefore, the asymmetric construction of such a skeleton is important in terms of the exploration of structurally related bioactive agents and pharmaceuticals. However, the asymmetric construction of this privileged structure has been mainly limited to Lewis acid-catalyzed stereospecific Friedel–Crafts-type ring-opening of enantiopure 2-arylaziridines[14] and to a sequence of enantioselective Michael-addition of arylmetals to β-nitrostyrenes and following reduction.[15] The former intrinsically requires electron-rich arenes as an aryl reactant, and the latter suffers from difficulty in controlling enantioselectivity of products. Recognizing that enantioenriched 2-arylaziridines are accessible by various methods,[16] we assumed that enantiospecific and regioselective cross-coupling of 2-arylaziridines with an arylmetals would allow for an efficient, functional-tolerant, and diverse route to enantioenriched 2-arylphenethylamine derivatives (eq 1).

Hillhouse[17] and Wolfe[18] independently reported that 2-alkylaziridines smoothly undergo oxidative addition to Ni(0) and Pd(0) complexes at the less hindered C–N bond in a S_N2 fashion to give isolable azametallacyclobutanes, respectively. After several years of their pioneering works, the Doyle group opened up the way to the utilization of aziridines as a nonclassical alkyl electrophile in metal-catalyzed cross-coupling by demonstrating Ni-catalyzed Negishi coupling of 2-aryl and 2-alkylaziridines.[19] Until then, metal-catalyzed transformations of nonvinylic aziridines were limited to the insertion of unsaturated components like CO[20a–c] and heterocumullenes,[20d,e] which outcompete β-hydride elimination. Despite their elegant works, the general prediction of stereoconfiguration of products in the Ni-catalyzed systems is difficult, probably due to the involvement of single-electron-transfer (SET) mechanism. More recently, Michael et al. reported a Pd/phosphine-catalyzed regioselective cross-coupling of 2-alkylaziridines with arylboronic acids which exclusively gives linear coupled products.[21] The stereo-inversion at the less hindered aziridine carbon showed good agreement with S_N2 oxidative addition mechanism. However, Pd-catalyzed branch-selective cross-coupling of aziridines to construct a

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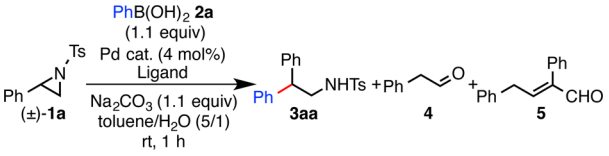
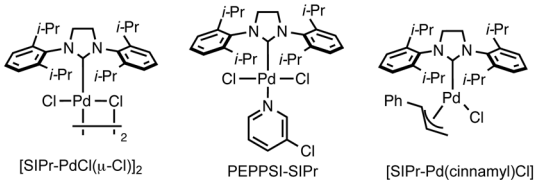
Table 1. Effect of Pd Catalysts in the Cross-Coupling[a]



entry	Pd cat.	ligand (mol%)	yield (%)[b] 3aa	4	5
1	$Pd(PPh_3)_4$	–	0	28	1
2	$Pd(PCy_3)_2$	–	6	35	2
3	$Pd(dba)_2$	P(*t*-Bu)$_3$ (8)	0	24	1
4	$Pd(dba)_2$	IPr (4)	17	0	0
5	$Pd(dba)_2$	SIPr (4)	21	0	0
6	$Pd(dba)_2$	SIMes (4)	3	0	0
7	[SIPr-PdCl(μ-Cl)]$_2$	–	81	0	0
8	PEPPSI-SIPr	–	23	0	0
9	**[SIPr-Pd(cinnamyl)Cl]**	–	**96** (93)[c]	**0**	**0**



[a]Reaction conditions: **1a** (0.2 mmol), **2a** (0.22 mmol), Pd catalyst (8 μmol), ligand, and Na_2CO_3 (0.22 mmol) in toluene/H_2O (1.2 mL, *v*/*v* 5:1) at room temperature under N_2 atmosphere for 1 h. [b]Determined with GC. [c]Isolated yield.

tertiary stereogenic center in a highly stereocontrolled manner has not yet been reported (eq 1).

We began by identifying the catalytic system capable of efficient C−C bond formation in the cross-coupling of racemic 2-phenylaziridine [(±)-**1a**] with phenylboronic acid (**2a**) as a model reaction (Table 1). Since stereochemical scrambling was of special concern,[19] we chose Pd catalysts as an alternative option. In terms of synthetic diversity, readily available and easily handled arylboronic acids were selected as a nucleophilic partner. Screening of privileged Pd catalysts[22] revealed that Pd/PR_3 systems typically suffered from production of **4** and **5**, which were probably derived through β-hydride elimination (entries 1−3, Table 1).[23,24] In sharp contrast, the use of NHCs as an adventitious ligand facilitated the regioselective formation of coupled product **3aa** without forming regioisomeric product, **4**, and **5**, albeit in low yields (entries 4−6). After extensive screening, NHC-ligated Pd precatalysts were found highly effective for the coupling (entries 7−9), and among tested, a bench-stable catalyst [SIPr-Pd(cinnamyl)Cl][25] gave **3aa** in an excellent yield even at room temperature (entry 9).

Having optimized reaction conditions, we then probed stereochemical outcomes of the reaction by applying both enantiomers of aziridine **1a** separately to the coupling with boronic acid **2b** (Scheme 1). Analysis of the coupled product obtained from (*R*)-**1a** and **2b** with HPLC equipped with a chiral column revealed that the product was enantiomerically pure (99% ee).[26] The absolute configuration of the product was unambiguously determined by X-ray crystallography of its single crystal to be *R*,[26] confirming the complete stereo-inversion at the benzylic carbon of aziridine. As predicted, the other enantiomeric product (*S*)-**3ab** was obtained by the coupling of (*S*)-**1a** with **2b**.

To investigate the scope of this enantiospecific coupling, enantiopure (*R*)-**1a** was coupled with a variety of arylboronic acids (Table 2). The coupling with $ArB(OH)_2$ bearing an electron-donating and a neutral group at the *p*-position

Scheme 1. Enantiospecificity of the Cross-Coupling

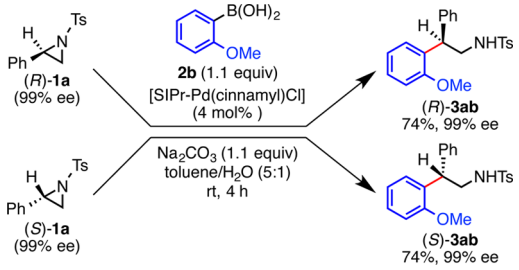
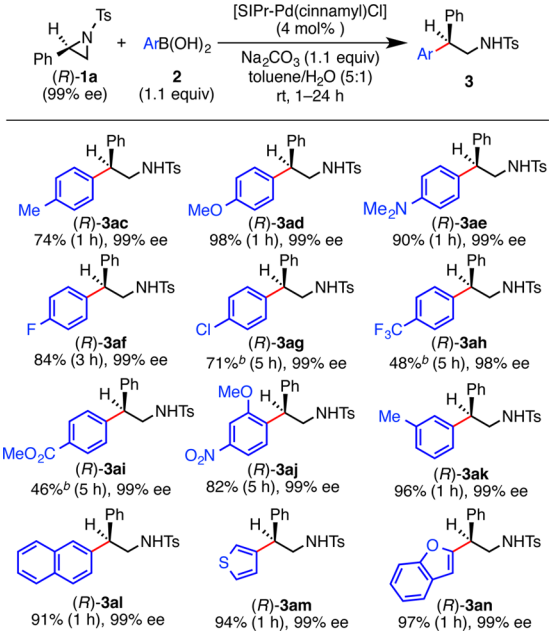


Table 2. Pd-Catalyzed Enantiospecific Cross-Coupling of (*R*)-1a with $ArB(OH)_2$[a]



[a]Reaction Conditions: (*R*)-**1a** (1.0 mmol), **2** (1.1 mmol), and Na_2CO_3 (1.1 mmol) in toluene/H_2O (6 mL, *v*/*v* 5:1) at room temperature; enantiomeric excess (ee) was determined by chiral HPLC analysis. [b][SIPr-Pd(allyl)Cl] was used as an alternative catalyst.

proceeded smoothly to give stereo-inverted products (*R*)-**3ac**, **3ad**, **3ae**, and **3af** in good to high yields as the single enantiomer. In contrast, the couplings with electron-deficient boronic acids (*p*-Cl, CF_3, and CO_2Me) were rather sluggish and gave low yields (20−50%) of the corresponding products under the optimized conditions. As the results of modifying conditions,[22] precoordinated allylic ligands on the Pd center were found to significantly affect the reaction efficiencies,[22] and [SIPr-Pd(allyl)Cl] gave the best result. It is noteworthy that electron-deficient arylboronic acids were coupled with aziridines under such mild conditions because such products are difficult to access by conventional Friedel−Crafts methods.[14] The generality of this stereospecific coupling was also confirmed by the reactions with *m*-tolyl-, naphthyl-, and heteroaromatic boronic acids, although the reactions with N-heterocyclic aromatic boronic acids like 3-pyridyl- and *N*-Boc-2-pyrrole boronic acids did not work under the optimal conditions.

Functionalized 2-arylaziridines and 2,3-disubstituted aziridines were applicable to the stereospecific coupling to give perfectly stereo-inverted products in a regioselective manner (Table 3). Notably, enantiopure aziridines bearing an electron-withdrawing aryl moiety [(*R*)-**1i**, (*S*)-**1g**, (*S*)-**1o**] were smoothly cross-

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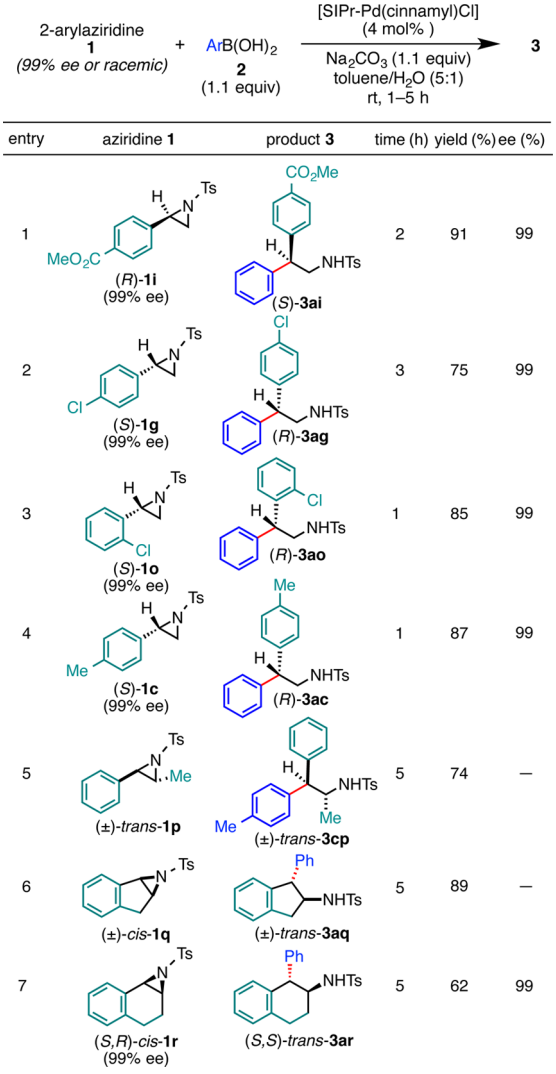
Table 3. Scope of Aziridine Substrates[a]

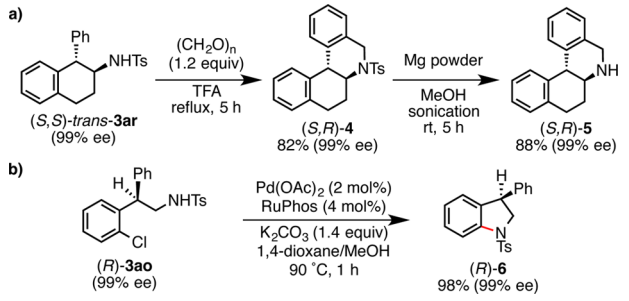


[a]Reaction Conditions: **1** (1.0 mmol), $ArB(OH)_2$ (1.1 mmol), and Na_2CO_3 (1.1 mmol) in toluene/H_2O (6 mL, *v*/*v* 5:1) at room temperature for the time indicated.

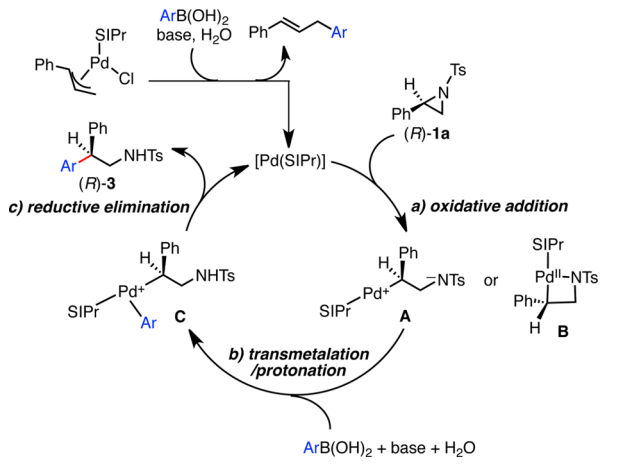
coupled with $PhB(OH)_2$ (**2a**) to afford the corresponding products (*S*)-**3ai**, (*R*)-**3ag**, and (*R*)-**3ao** in good to high yields (entries 1−3): these products were obtained in poor yields when electron-neutral aziridine **1a** was coupled with electron-deficient boronic acids under the same conditions (Table 2). Racemic *trans*-**1p** and *cis*-**1q** were successfully arylated in a regioselective and stereospecific manner to give *trans*-**3cp** and *trans*-**3aq** as the single diastereomer, respectively (entries 5 and 6). Furthermore, enantiopure **1r** was converted into stereo-inverted product (*S*,*S*)-**3ar** (entry 7).[27]

Making use of the excellent enantiospecificity, coupled products were transformed into cyclic amine derivatives (Scheme 2). Enantiopure **3ar** was efficiently transformed into fused tetracyclic amine (*S*,*R*)-**5**, keeping the ee intact through Pictet−Spengler reaction and Ts-deprotection (Scheme 2a). Such tetracyclic amine scaffold is a ubiquitous motif in dopamine D_1 agonists.[12] Furthermore, (*R*)-**3ao** was smoothly cyclized under the modified Pd-catalyzed intramolecular amination conditions[28] to give enantiopure indoline (*R*)-**6** in a quantitative yield (Scheme 2b). Such three-substituted indoline motif is also often found in natural products and structurally related drugs.[29]

Scheme 2. Derivatization of Coupling Products



Scheme 3. A Plausible Catalytic Cycle



A plausible catalytic cycle is illustrated in Scheme 3. Since the stoichiometric reaction of [SIPr-Pd(cinnamyl)Cl] with $PhB(OH)_2$ in the absence of aziridine gave 1,3-diphenylpropene as a major product (53% yield) along with a small amount of cinnamyl alcohol (8% yield), we postulate that activation of the precatalyst would mainly occur through direct nucleophilic attack of $ArB(OH)_2$ on the cinnamyl position or transmetalation/reductive elimination.[30] Oxidative addition of enantiopure aziridine to the resulting singly ligated [(SIPr)-Pd(0)] complex would proceed in a S_N2 manner to form stereoinverted alkylpalladium **A** or **B**. The regioselectivity could be facilitated by the precoordination of aryl moiety of aziridines to Pd(0) center[31] or the contribution of π-benzyl palladium species.[19] Transmetalation and simultaneous protonation of amide anion by boronic acid or water would form T-shaped Pd complex **C**, which undergoes reductive elimination to give **3**. Stereoretention through transmetalation and reductive elimination is well established.[32] Since prereduction of Pd(II) to Pd(0) with a catalytic amount of phenylboronic acid as a sacrificial reductant did not improve the yield of **3ah** (18%), the low reaction efficiencies of the coupling using electron-deficient boronic acids could be ascribed to slow transmetalation and/or reductive elimination. Although the precise roles of SIPr ligand are unclear at this point, we conjecture that (i) the strong σ-donating nature of SIPr would allow the Pd center for smooth oxidative addition; (ii) weak interaction operating between methyl hydrogen atoms of *i*-Pr groups of SIPr and the Pd center could suppress β-hydride elimination through coordinatively saturating the Pd center with multiple methyl hydrogens;[33] (iii) the steric bulk of SIPr would facilitate reductive elimination.

In conclusion, we have developed a Pd-catalyzed enantiospecific and regioselective cross-coupling of 2-arylaziridines with

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arylboronic acids. The reaction was drastically promoted by a NHC-ligated Pd complex, outcompeting β-hydride elimination. The stereospecific coupling allowed for preparation of configurationally defined 2-arylphenethylamine derivatives that are otherwise difficult to access in a simple operation by conventional methods. Investigations into mechanistic aspects and further exploration of the Pd/NHC catalytic system for the development of new transformations of aziridines are underway.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details and spectroscopic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Malinakova, H. C. *Chem.—Eur. J.* **2004**, *10*, 2636. (b) Rudolph, A.; Lautens, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 2656. (c) Jarvo, E.; Taylor, B. *Synlett* **2011**, 2761. (d) Jana, R.; Pathak, T. P.; Sigman, M. S. *Chem. Rev.* **2011**, *111*, 1417.

(2) (a) Fischer, C.; Fu, G. C. *J. Am. Chem. Soc.* **2005**, *127*, 4594. (b) Saito, B.; Fu, G. C. *J. Am. Chem. Soc.* **2008**, *130*, 6694. (c) Lou, S.; Fu, G. C. *J. Am. Chem. Soc.* **2010**, *132*, 1264. (d) Lu, Z.; Wilsily, A.; Fu, G. C. *J. Am. Chem. Soc.* **2011**, *133*, 8154.

(3) (a) Hayashi, T.; Konishi, M.; Fukushima, M.; Mise, T.; Kagotani, M.; Tajika, M.; Kumada, M. *J. Am. Chem. Soc.* **1982**, *104*, 180. (b) Cordier, C. J.; Lundgren, R. J.; Fu, G. C. *J. Am. Chem. Soc.* **2013**, *135*, 10946.

(4) Sn: (a) Labadie, J. W.; Stille, J. K. *J. Am. Chem. Soc.* **1983**, *105*, 6129. (b) Ye, J.; Bhatt, R. K.; Falck, J. R. *J. Am. Chem. Soc.* **1994**, *116*, 1. (c) Li, L.; Wang, C.-Y.; Huang, R.; Biscoe, M. R. *Nat. Chem.* **2013**, *5*, 607. Si: (d) Hatanaka, Y.; Hiyama, T. *J. Am. Chem. Soc.* **1990**, *112*, 7793. B: (e) Ridgway, B. H.; Woerpel, K. A. *J. Org. Chem.* **1998**, *63*, 458. (f) Imao, D.; Glasspoole, B. W.; Laberge, V. S.; Crudden, C. M. *J. Am. Chem. Soc.* **2009**, *131*, 5024. (g) Sandrock, D. L.; Jean-Gérard, L.; Chen, C.-Y.; Dreher, S. D.; Molander, G. A. *J. Am. Chem. Soc.* **2010**, *132*, 17108. (h) Ohmura, T.; Awano, T.; Suginome, M. *J. Am. Chem. Soc.* **2010**, *132*, 13191. (i) Lee, J. C. H.; McDonald, R.; Hall, D. G. *Nat. Chem.* **2011**, *3*, 894. Mg: (j) Hölzer, B.; Hoffmann, R. W. *Chem. Commun.* **2003**, 732. Zn: (k) Campos, K. R.; Klapars, A.; Waldman, J. H.; Dormer, P. G.; Chen, C.-Y. *J. Am. Chem. Soc.* **2006**, *128*, 3538.

(5) (a) Rodríguez, N.; Ramírez de Arellano, C.; Asensio, G.; Medio-Simón, M. *Chem.—Eur. J.* **2007**, *13*, 4223. (b) López-Pérez, A.; Adrio, J.; Carretero, J. C. *Org. Lett.* **2009**, *11*, 5514.

(6) (a) Netherton, M. R.; Fu, G. C. *Angew. Chem., Int. Ed.* **2002**, *41*, 3910. (b) He, A.; Falck, J. R. *J. Am. Chem. Soc.* **2010**, *132*, 2524.

(7) (a) Taylor, B. L. H.; Swift, E. C.; Waetzig, J. D.; Jarvo, E. R. *J. Am. Chem. Soc.* **2010**, *133*, 389. (b) Greene, M. A.; Yonova, I. M.; Williams, F. J.; Jarvo, E. R. *Org. Lett.* **2012**, *14*, 4293. (c) Taylor, B. L. H.; Harris, M. R.; Jarvo, E. R. *Angew. Chem., Int. Ed.* **2012**, *51*, 7790.

(8) (a) Legros, J.-Y.; Toffano, M.; Fiaud, J.-C. *Tetrahedron* **1995**, *51*, 3235. (b) Harris, M. R.; Hanna, L. E.; Greene, M. A.; Moore, C. E.; Jarvo, E. R. *J. Am. Chem. Soc.* **2013**, *135*, 3303. (c) Zhou, Q.; Srinivas, H. D.; Dasgupta, S.; Watson, M. P. *J. Am. Chem. Soc.* **2013**, *135*, 3307.

(9) Maity, P.; Shacklady-McAtee, D. M.; Yap, G. P. A.; Sirianni, E. R.; Watson, M. P. *J. Am. Chem. Soc.* **2013**, *135*, 280.

(10) Li, M.-B.; Tang, X.-L.; Tian, S.-K. *Adv. Synth. Catal.* **2011**, *353*, 1980.

(11) (a) *Classics in Stereoselective Synthesis*; Carreira, E. M., Kvaerno, L., Eds.; Wiley-VCH: Weinheim, 2009. (b) *Chiral Amine Synthesis; Methods, Developments and Applications*; Nugent, T. C., Ed.; Wiley-VCH: Weinheim, 2010.

(12) (a) Zhang, A.; Neumeyer, J. L.; Baldessarini, R. J. *Chem. Rev.* **2007**, *107*, 274. (b) Zhang, J.; Xiong, B.; Zhen, X.; Zhang, A. *Med. Res. Rev.* **2009**, *29*, 272.

(13) Michaelides, M. R.; Hong, Y.; DiDomenico, S., Jr.; Bayburt, E. K.; Asin, K. E.; Britton, D. R.; Lin, C. W.; Shiosaki, K. *J. Med. Chem.* **1997**, *40*, 1585.

(14) (a) Farr, R. N.; Alabaster, R. J.; Chung, J. Y.; Craig, B.; Edwards, J. S.; Gibson, A. W.; Ho, G.-J.; Humphrey, G. R.; Johnson, S. A.; Grabowski, E. J. J. *Tetrahedron: Asymmetry* **2003**, *14*, 3503. (b) Pineschi, M.; Bertolini, F.; Crotti, P.; Macchia, F. *Org. Lett.* **2006**, *8*, 2627. (c) Kaiser, H. M.; Zenz, I.; Lo, W. F.; Spannenberg, A.; Schröder, K.; Jiao, H.; Gördes, D.; Beller, M.; Tse, M. K. *J. Org. Chem.* **2007**, *72*, 8847. (d) Hajra, S.; Maji, B.; Mal, D. *Adv. Synth. Catal.* **2009**, *351*, 859.

(15) (a) Yamashita, M.; Yamada, K.-I.; Tomioka, K. *J. Am. Chem. Soc.* **2004**, *126*, 1954. (b) Wang, Z.-Q.; Feng, C.-G.; Zhang, S.-S.; Xu, M.-H.; Lin, G.-Q. *Angew. Chem., Int. Ed.* **2010**, *49*, 5780.

(16) *Aziridines and Epoxides in Organic Synthesis*; Yudin, A. K., Ed.; Wiley-VCH: Weinheim, 2006.

(17) Lin, B. L.; Clough, C. R.; Hillhouse, G. L. *J. Am. Chem. Soc.* **2002**, *124*, 2890.

(18) Ney, J. E.; Wolfe, J. P. *J. Am. Chem. Soc.* **2006**, *128*, 15415.

(19) (a) Huang, C.-Y.; Doyle, A. G. *J. Am. Chem. Soc.* **2012**, *134*, 9541. (b) Nielsen, D. K.; Huang, C.-Y.; Doyle, A. *J. Am. Chem. Soc.* **2013**, *135*, 13605.

(20) (a) Alper, H.; Urso, F.; Smith, D. J. H. *J. Am. Chem. Soc.* **1983**, *105*, 6737. (b) Calet, S.; Urso, F.; Alper, H. *J. Am. Chem. Soc.* **1989**, *111*, 931. (c) Piotti, M. E.; Alper, H. *J. Am. Chem. Soc.* **1996**, *118*, 111. (d) Baeg, J.-O.; Alper, H. *J. Org. Chem.* **1992**, *57*, 157. (e) Baeg, J.-O.; Bensimon, C.; Alper, H. *J. Am. Chem. Soc.* **1995**, *117*, 4700.

(21) Duda, M. L.; Michael, F. E. *J. Am. Chem. Soc.* **2013**, *135*, 18347.

(22) For the details, see the SI.

(23) Wolfe, J. P.; Ney, J. E. *Org. Lett.* **2003**, *5*, 4607.

(24) Pd-catalyzed Aldol condensation of **4** to give **5** has been reported: Kim, J.-H.; Kulawiec, R. J. *J. Org. Chem.* **1996**, *61*, 7656.

(25) Marion, N.; Navarro, O.; Mei, J.; Stevens, E. D.; Scott, N. M.; Nolan, S. P. *J. Am. Chem. Soc.* **2006**, *128*, 4101.

(26) For the details of chiral HPLC analysis and X-ray crystallography, see the SI.

(27) Unfortunately, 2,2-disubstituted aziridines such as 2-methyl-2-phenylaziridine did not give coupled product. Instead, β-hydride elimination proceeded exclusively to form allylic amine in this case. Although the coupling of *N*-tosyl-2-*n*-butylaziridine with **2a** was attempted under the optimized conditions, no coupled product was obtained with a quantitative recovery of the aziridine substrate.

(28) Panteleev, J.; Zhang, L.; Lautens, M. *Angew. Chem., Int. Ed.* **2011**, *50*, 9089.

(29) Boger, D. L.; Boyce, C. W.; Garbaccio, R. M.; Goldberg, J. A. *Chem. Rev.* **1997**, *97*, 787.

(30) Allylic alkoxylation pathway is also known for the activation of [(NHC)Pd(allyl)Cl] with a strong base (*t*-BuOK) in a polar solvent (DME): Viciu, M. S.; Germaneau, R. F.; Navarro-Fernandez, O.; Stevens, E. D.; Nolan, S. P. *Organometallics* **2002**, *21*, 5470.

(31) Green, J. C.; Herbert, B. J.; Lonsdale, R. *J. Organomet. Chem.* **2005**, *690*, 6054.

(32) Stille, J. K. *Oxidative Addition and Reductive Elimination. In The Chemistry of the Metal—Carbon Bond*; Hartley, F. R., Patai, S., Eds.; John Wiley & Sons, Ltd.: New York, 1985; Vol. 2, p 625.

(33) Chass, G. A.; O'Brien, C. J.; Hadei, N.; Kantchev, E. A. B.; Mu, W.-H.; Fang, D.-C.; Hopkinson, A. C.; Csizmadia, I. G.; Organ, M. G. *Chem.—Eur. J.* **2009**, *15*, 4281.