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Palladium-Catalyzed Regioselective and Stereospecific Ring-Opening Suzuki-Miyaura Arylative Cross-Coupling of 2-Arylazetidines with Arylboronic Acids

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Abstract: We have developed a palladium-catalyzed regioselective and enantiospecific ring-opening Suzuki–Miyaura arylative cross-coupling of *N*-tosyl-2-arylazetidines to give enantioenriched 3,3-diarylpropylamines. This reaction represents an example of transition-metal-catalyzed ring-opening cross-coupling using azetidines as a non-classical alkyl electrophile. Density functional theory rationalized the mechanism of the full catalytic cycle, which consists of the selectivity-determining ring opening of the azetidine, reaction with water, rate-determining transmetalation, and reductive elimination. Transition states of the selectivity-determining ring-opening step were systematically determined by the multi-component artificial force induced reaction (MC-AFIR) method to explain the regioselectivity of the reaction.

Keywords: Azetidine; Cross-Coupling; Palladium; Ring Opening; Computational Chemistry

Introduction

Azetidines, a family of four-membered saturated N-heterocycles, are found in natural products, and they serve as unique pharmacophores[1] and as useful building blocks in organic synthesis.[2] Azetidines accommodates a large ring strain energy (ca. 25 kcal mol^{-1}), which is slightly smaller than that of the one-carbon-less N-heterocyclic analogues (i.e., aziridines) (ca. 27 kcal mol^{-1}).[3] Using an analogy from the high reactivities of aziridines toward nucleophiles driven by the release of ring strain,[4] one would surmise that regioselective ring-opening substitution of azetidines with a variety of nucleophiles should constitute a useful synthetic method for γ-functionalized alkylamines. In reality, the ring-opening functionalization of azetidines is more limited when compared with those using aziridines. For example, ring-opening substitution with heteroatomic nucleophiles (i.e., ROH, RSH, and RNH_2),[5] formal [4+2] cycloaddition with nitriles[6] or aldehydes,[7] the Friedel-Crafts-type arylation,[8] the Hosomi-Sakurai-type allylation,[9] and ring-opening nucleophilic substitution with organotrifluoroborates[10] have been reported. However, these reactions exclusively require the activation of the azetidines by Lewis acids (LAs) and/or Brønsted acids (BAs) to cleavage the C–N bond. Moreover, the stereochemistry of azetidines is lost through these reactions, due to S_N1-like mechanisms exerted under acidic conditions.

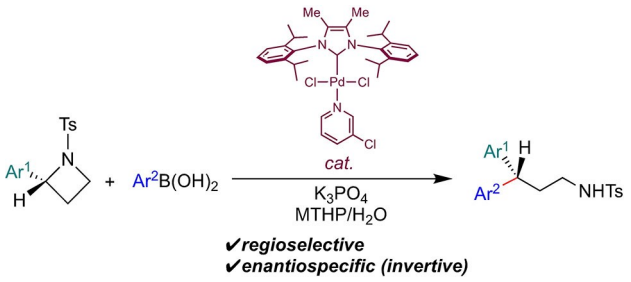
Over the last several years, various transition-metal-catalyzed ring-opening cross-coupling of aziridines has been extensively developed to form a C–C,[11–16] C–B,[17,18] and C–Si bond.[19,20] The significant features of these ring-opening cross-couplings include the high regioselectivity governed by the oxidative addition event. In contrast to the flourishing cross-coupling chemistry of aziridines, transition met-

al-catalyzed ring-opening cross-couplings of azetidines have not yet been developed. Given that such cross-coupling would offer new synthetic routes to medicinally-important γ-functionalized propylamines,[21] it is important to develop cross-couplings using azetidines as a non-classical alkyl electrophile. As relevant reactions, Pd- and Co-catalyzed regioselective and stereospecific ring-expansive reactions of azetidines with CO[22] and heterocumulenes, by making use of a rapid migratory insertion process, have been reported.[23] Herein, we disclose a Pd/N-heterocyclic carbene (NHC)-catalyzed enantiospecific (stereo-invertive) and regioselective ring-opening cross-coupling of an enantiopure 2-arylazetidine with arylboronic acids to give enantioenriched 3,3-diarylpropylamine derivatives (Scheme 1).

Results and Discussion

Reaction Optimization and Synthetic Studies

To develop cross-coupling reaction using azetidines, we selected arylboronic acids and their derivatives as the nucleophilic partner, as they are readily accessible, bench-stable, low-toxic, and storable to easily handle in laboratory. Initially, we applied the optimal reaction conditions for the Pd/SIPr-catalyzed regioselective cross-coupling of *N*-tosyl-2-arylaziridines with arylboronic acids to the coupling of *N*-tosyl-2-phenylazetidine (**1a**) with $PhB(OH)_2$ (**2a**).[11a] However, it turned out that only azetidine substrate **1a** was recovered without giving any desired cross-coupled products. This distinct difference in reactivities between the three- and four-membered N-heterocycles under the similar cross-coupling conditions prompted us to explore the appropriate reaction conditions for the cross-coupling of **1a** with **2a**. As the results of extensive screening of reaction conditions (for the details of the screening, see the SI), in the presence of PEPPSI-^{Me}IPr catalyst (8 mol%) and inorganic base (K_3PO_4) in the MTHP/H_2O mixed solvent heated at 100 °C, the cross-coupling of **1a** with **2a** proceeded regioselectively at

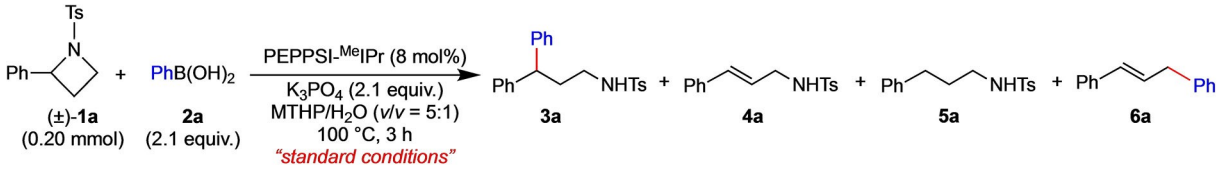


Scheme 1. Palladium-catalyzed regioselective and enantiospecific ring-opening Suzuki–Miyaura arylative cross-coupling of *N*-tosyl-2-arylazetidines.

the C2-position of **1a** to produce 3,3-diphenylpropylamide **3a** in 65% yield (denoted as "standard conditions", entry 1, Table 1). Cinnamyl amide **4a** (22%) and a trace amounts of **5a** (2%) and **6a** (3%) were obtained as byproducts. Amide **4a** would be produced through β-hydride elimination from the oxidative adduct, and the generated Pd–H could serve as a hydride source for reduction of **1a** to give **5a**. On one hand, 1,3-diphenylpropene (**6a**) could be produced through a cross-coupling of **4a** with **2a** via η^3-allyl Pd intermediate generated by the C–N cleavage.[24] In fact, **6a** was formed by the treatment of **4a** with a stoichiometric amount of $PhB(OH)_2$ in similar catalytic conditions (for the details, see Scheme S1 and S2 in the SI). Representative results to show the effect of reaction parameters on the product distribution are listed in Table 1. The NHC ligand (entry 2), inorganic base (entry 3), solvent (entries 4 and 5), and water (entries 6 and 7) are indispensable for effective progress of the coupling. As the coupling nucleophilic partner, phenylboronic neopentyl glycol ester PhB(neop) **2a'** was found an alternative choice for the cross-coupling (entry 8).

To investigate the generality of the reaction conditions and the stereochemical outcome of the reaction, cross-coupling using an enantiopure azetidine (*R*)-**1a** with a variety of arylboronic acids **2** or neopentyl glycol esters **2'** was explored (Table 2). The cross-coupling of (*R*)-**1a** with 2-naphthylboronic acid proceeded regioselectively at 100 °C in three hours (*conditions A*) to give enantioenriched coupled product **3b** (86% es, which was determined by chiral high performance liquid chromatography (HPLC) analysis) in a moderate yield. The X-ray crystallographic analysis of the single crystal of **3b** grown from a Et_2O/*n*-hexane solution revealed its absolute stereochemistry as *S* configuration (the inset figure in Table 2). This result confirmed the net inversion of the stereochemistry of the starting azetidine substrate through the cross-coupling.[25] This is consistent with our previous reports,[11] although the slight decrease in the enantiomeric excess (ee) of the coupled product implied the existence of minor racemization pathways. The couplings of (*R*)-**1a** with arylboronic acids or their neopentyl glycol esters having a substituent at the *p*-position (i.e., Me, Ac, F, and CF_3) gave the corresponding cross-coupled products (**3c**, **3d**, **3e**, and **3f**, respectively) in moderate yields with high enantiospecificities (Table 2). Also, the coupling with *m*-amide-substituted arylboronic acid gave the coupled product **3g** in a good yield with high es. It is noted that the other enantiomer (*R*)-**3g** was synthesized by applying the other enantiomer (*S*)-**1a** as the substrate (see, the SI). The cross-coupling of **1a** with arylboronic acids having an electron-deficient functionality such as Ac and CF_3 group allowed for the preparation of the 3,3-diarylpropylamines otherwise difficult to synthesize

Table 1. Effect of reaction parameters on the cross-coupling of **1a** with **2a**.[a]



Entry	Alternations from the "standard conditions"	Yield (%)[b]				Recovery of **1a** (%)[b]
		3a	**4a**	**5a**	**6a**	
1	None	65 (47)[c]	22	2	3	0
2	PEPPSI-SIPr[d] in place of PEPPSI-^{Me}IPr	0	16	5	Trace	67
3	Na_2CO_3 in place of K_3PO_4	8	47	3	5	36
4	Toluene in place of MTHP	10	35	3	4	47
5[e]	THF in place of MTHP	27	31	4	3	34
6	without H_2O	0	7	0	0	93
7	MeOH in place of H_2O	0	13	0	0	73
8[e]	PhB(neop)[f] (**2a'**) in place of $PhB(OH)_2$	60	37	0	3	0

[a] Standard conditions: (±)-**1a** (0.20 mmol), $PhB(OH)_2$ (0.42 mmol), (4,5-dimethyl-1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene)(3-chloropyridyl)palladium(II) dichloride (PEPPSI-^{Me}IPr) (16 μmol), K_3PO_4 (0.42 mmol), 4-methyltetrahydropyrane (MTHP)/H_2O (1.2 mL, 5:1 *v/v*), 100 °C, 3 h.
[b] Determined by the ^{1}H NMR analysis of the crude product.
[c] Isolation yield.
[d] PEPPSI-SIPr: (1,3-bis(2,6-diisopropylphenyl)imidazolidene)(3-chloropyridyl)palladium(II) dichloride.
[e] The reaction was run at 60 °C for 12 h.
[f] PhB(neop): phenylboronic acid neopentyl glycol ester.

through the Friedel-Crafts ring-opening arylation of azetidines.[8] Arylboronic acid having a sterically-demanding substituent at the *o*-position was also applicable to the reaction conditions to give enantioenriched 3,3-diarylpropylamine **3h** in a stereospecific manner (Table 2). As for the variation of nucleophilic partner, some other boronic acid derivatives such as *n*-butylboronic acid and allylboronic acid pinacol ester were examined, but no reaction occurred.

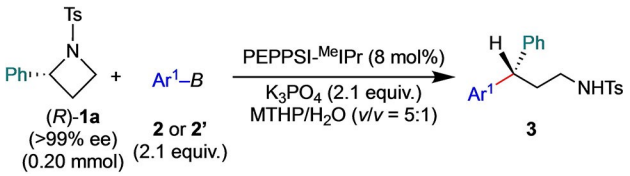
Then, the scope of azetidines was examined using phenylboronic acid (**2a**) or its neopentyl glycol ester **2a'** as the nucleophile (Table 3). Since the asymmetric synthetic methods for 2-arylazetidines have not been established, racemic azetidines were applied for the reaction. The cross-coupling of 2-arylazetidines having an electron-donating (i.e., Me, OMe) and an electron-withdrawing functional group (i.e., F, CF_3) at the *p*-position with **2a** or **2a'** proceeded regioselectively to afford the corresponding 3,3-diarylpropylamines in low to moderate yields. Azetidines that have an extended π-moiety as the 2-aryl substituent was also cross-coupled with phenylboronic acid to provide the coupling products **3b**, **3j**, and **3k** (Table 3). In contrast, the coupling using *N*-tosyl-2-(*o*-tolyl) azetidine (**1b**) gave the corresponding coupled product **3h** in less than 5% (Table 3). Also, in the case of an azetidine having a non-aromatic substituent (Me) at the 2-position, any reaction did not proceed at all (Table 3). These results would support the oxidative addition of azetidine via the pre-coordination of arene unit to Pd, as indicated in the computational studies (*vide infra*). In the case of non-aromatic substituted azetidine, the absence of π-unit that can coordinate to the Pd center does not allow for the oxidative addition step, which is the starting point of the catalytic cycle.

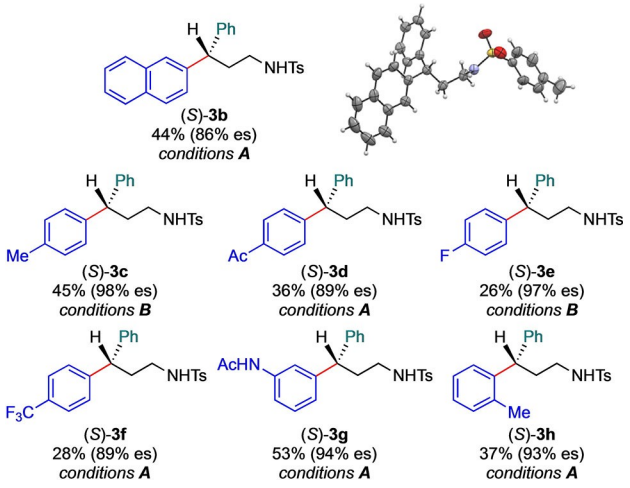
Computational Studies

Computational methods. All structure optimizations were performed using the density functional theory (DFT) as implemented in the Gaussian16 programme (Version C.01).[26] The B3LYP[27] method, employing the D3 version of Grimme's dispersion with Becke-Johnson damping,[28] was used. The SDD[29] basis sets and the associated effective core potential were applied for Pd, and the 6-31G(d)[30] basis sets were used for the other atoms. The polarizable continuum model (PCM)[31] was employed as the implicit solvent model with the dielectric constant of 7.4257 (tetrahydrofuran). Vibrational frequency calculations were performed at 298.15 K and 1 atm to confirm the nature of the stationary points [i.e. no imaginary frequency for a local minimum (LM) and one imaginary frequency for a transition state (TS)], and to calculate zero-point energy. Potential energy of the fully optimized LMs and TSs was calculated as the single-point energy using the SDD basis sets for Pd and cc-pVTZ[32] basis sets for the other atoms.

The multi-component artificial force induced reaction (MC-AFIR) method,[33] implemented in the

Table 2. Pd-catalyzed cross-coupling of enantiopure (*R*)-**1 a** with **2** or **2'**.[a,b]

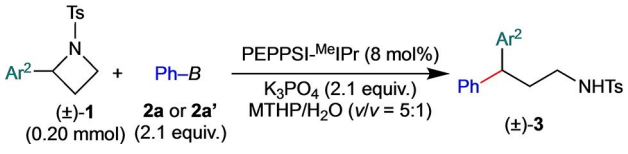


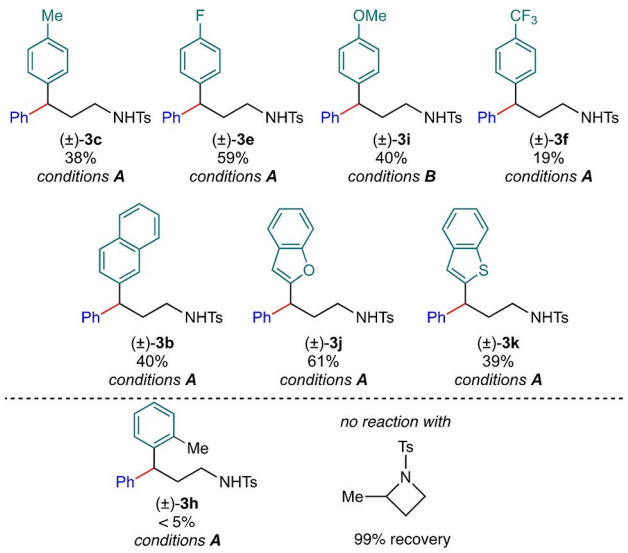


[a] *conditions A*: (*R*)-**1 a** (0.20 mmol), $Ar^1B(OH)_2$ **2** (0.42 mmol), PEPPSI-^{Me}IPr (16 µmol), K_3PO_4 (0.42 mmol), MTHP/H_2O (1.2 mL, 5:1 *v/v*), 100 °C, 3 h; *conditions B*: (*R*)-**1 a** (0.20 mmol), Ar^1B(neop) **2'** (0.42 mmol), PEPPSI-^{Me}IPr (16 µmol), K_3PO_4 (0.42 mmol), MTHP/H_2O (1.2 mL, 5:1 *v/v*), 60 °C, 12 h.

[b] The yields indicate isolation yields; The enantiospecificity (es) was determined by chiral HPLC analysis.

Table 3. Pd-catalyzed cross-coupling of **1** with **2 a** or **2 a'**.[a]





[a] *conditions A*: (±)-**1** (0.20 mmol), $PhB(OH)_2$ **2 a** (0.42 mmol), PEPPSI-^{Me}IPr (16 µmol), K_3PO_4 (0.42 mmol), MTHP/H_2O (1.2 mL, 5:1 *v/v*), 100 °C, 3 h; *conditions B*: (±)-**1** (0.20 mmol), PhB(neop) **2a'** (0.42 mmol), PEPPSI-^{Me}IPr (16 µmol), K_3PO_4 (0.42 mmol), MTHP/H_2O (1.2 mL, 5:1 *v/v*), 60 °C, 12 h.

[b] The yields indicate isolation yields;

GRRM17 programme,[34] was used for searching reaction paths of the ring-opening step. The two-layer ONIOM[35] method was used for calculating potential energy and derivatives for the MC-AFIR search (Figure 1a). The B3LYP–D3 method and the SDD basis sets for Pd, and 3-21G basis sets for the other atoms were applied for the ONIOM high-layer. The PM6-D3[36] method was used for the ONIOM low-layer. The artificial force parameter (γ) of 1000 kJ/mol was applied between Pd and the azetidine ring, as shown in Figure 1b, which is suitable for determining the ring-opening reaction paths. The resulting AFIR paths were inspected, and approximate TSs were identified. Then, all approximate TSs were fully optimized, and the Boltzmann distribution of all fully optimized TSs was used for calculating the regioselectivity of the ring-opening step.

Energy decomposition analysis (EDA)[37] was performed for the important transition states that lead to the desired or undesired products (Figure 2). For this purpose, TS structure was separated into two fragments, specifically catalyst (A) and substrate (B).

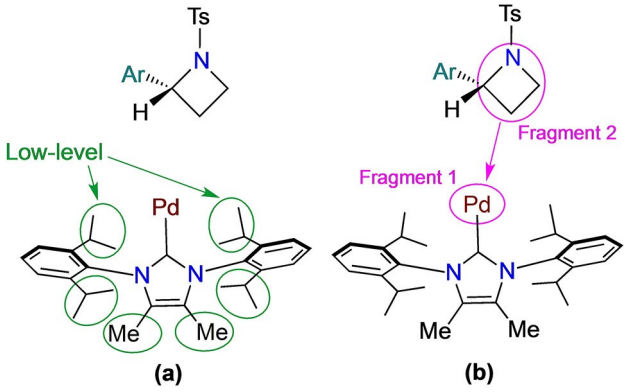


Figure 1. (a) Partitioning of the molecular system for two-layer ONIOM calculations. (b) Adding of the artificial force between the two fragments.

Then, the interaction energy (INT_{AB}) and deformation energy (DEF_{AB}) were calculated. The INT_{AB} is defined as the interaction energy between A and B at the TS geometry. The DEF_{AB} is the energy of A and B at the TS compared to the optimized structures of the isolated

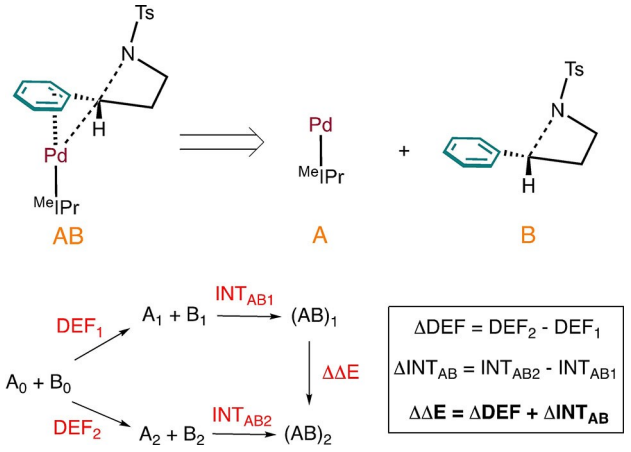


Figure 2. Energy decomposition analysis (EDA) for two transition states, $(AB)_1$ and $(AB)_2$.

A and B (denoted as A_0 and B_0). The energy difference between the two transition states (ΔΔE) can be defined as the sum of the interaction energy difference (ΔINT) and deformation energy difference (ΔDEF). The ΔINT term was further separated into electrostatic interactions (ΔE_{elstat}), Pauli repulsion (ΔE_{Pauli}), orbital interaction (ΔE_{oi}), dispersion energy (ΔE_{disp}), and solvation energy (ΔE_{sol}).[38] EDA was performed using the B3LYP–D3BJ method in the ADF programme (Version 2020.101).[39] The TZ2P[40] basis sets were used for all electrons in the system, and the relativistic Scalar ZORA[41] approach was used for Pd. The COSMO[42] method was used as the implicit solvent model, where tetrahydrofuran was used as the solvent.

Catalytic cycle. For the mechanistic survey, we have used ^{Me}IPr–Pd as the catalyst, and **1a** as the substrate. Computed free energy profile is shown in Figure 3. When ^{Me}IPr–Pd encounters **1a**, a π-coordinated adduct (**I1**) is formed, which is −14.2 kcal/mol stable compared to the free energy sum of the isolated ^{Me}IPr–Pd and **1a**. Then, we have searched TSs for the ring-opening (*vide infra*). In the lowest energy TS (**TS1**), the ring opening occurs at the benzylic carbon position of **1a**, leading to the desired product of the reaction. The computed free energy barrier for the ring-opening process is 14.9 kcal/mol, which is a larger barrier than that for the ring-opening process for *N*-tosyl-2-phenylaziridine (7.4 kcal/mol), a three-membered ring system.[11c] Since the ring component atoms of the azetidines have higher sp^3-hybrized character than those of aziridines, the reacting point in the ring-opening process of azetidine (i.e., the C(2) atom) is more sterically hindered, and the bond dissociation

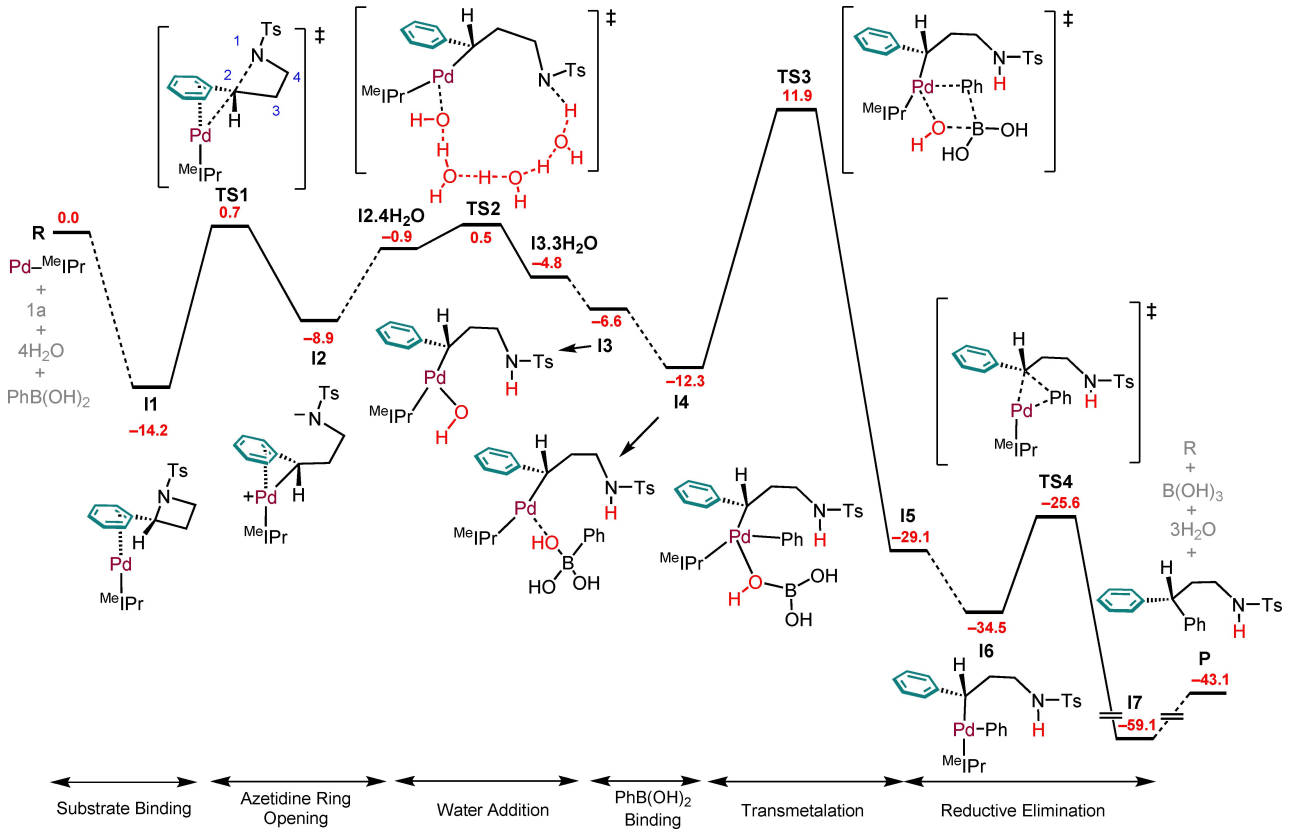


Figure 3. Computed free energy (kcal/mol) profile for the reaction of ^{Me}IPr–Pd with **1a** and $PhB(OH)_2$.

energy of the C(2)–N(1) is larger than that of aziridines. Given these differences in the three- and four-membered ring systems, the S_N2 type oxidative addition of the azetidine is reasonably higher than that for aziridines.

The resulting intermediate (**I2**, −8.9 kcal/mol) interacts with water molecules in the solution to initiate the consecutive proton and hydroxy anion transfer to the N atom and the Pd center of the oxidative adduct, respectively. Calculated free energy barrier for this process is 9.4 kcal/mol. When the resulting Pd-hydroxo intermediate (**I3**, −6.6 kcal/mol) encounters $PhB(OH)_2$ in the solution, a relatively stable intermediate (**I4**, −12.3 kcal/mol) is formed. It is important to note that the concentration of $PhB(OH)_2$ in the solution is large. Thus, **I4** in solution is stabilized, allowing the transmetalation with an overall free energy barrier of 24.2 kcal/mol, giving rise to **I5** (−29.1 kcal/mol). After removing $B(OH)_3$ from the metal coordination sphere of **I5**, a more stable intermediate **I6** (−34.5 kcal/mol) can be formed. Finally, the reductive elimination occurs with a free energy barrier of 8.9 kcal/mol (**TS4**), lending to the product (**P**). At the same time, the catalyst (^{Me}IPr–Pd) for the next catalytic cycle is recovered.

Based on the computed free energy profile, we concluded that the selectivity-determining step of the mechanism is the ring opening of the azetidine (i.e., the oxidative addition), and the rate-determining step of the mechanism is the transmetalation. The overall free energy barrier for the transmetalation is 26.1 kcal/mol (i.e. free energy difference between **TS3** and **I1**), which can be achieved under the reaction conditions. When *N*-tosyl-2-arylaziridine was used as the substrate (i.e., a three-membered ring system), the overall free energy barrier for the rate-determining step (i.e. transmetalation) was relatively lower (20.9 kcal/mol).[11c] Compared to the three-membered ring system, the four-membered ring system is sterically-demanding for the transmetalation step that requires for the association of an oxidative adduct and phenylboronic acid. Thus, the entropic penalty to overcome the barrier for the transmetalation is larger in the four-membered system. As a result, the four-membered ring-opening cross-coupling reaction rate would be lower than that of the three-membered ring-opening cross-coupling reactions. To accelerate the desired coupling reaction of azetidines, a higher reaction temperature than aziridines is requried. This concomitantly allowed for side reactions that lead to byproducts such as **4a**, **5a**, and **6a** through β-hydride elimination. As a result, moderate yield of the desired cross-coupled products was observed.

Regioselectivity. We have searched reaction paths for the regioselectivity-determining ring-opening step using an MC-AFIR search. Calculated TSs were categorized into eight groups (Figure 4). Group A

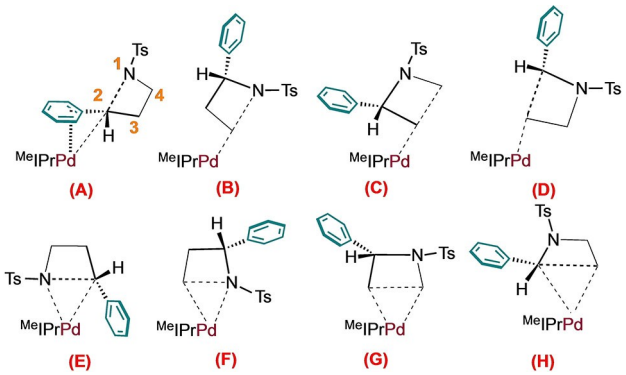


Figure 4. Transition state groups for the ring-opening step.

represents the ring-opening through the C(2)–N(1) bond cleavage with stereoinversion in an S_N2 fashion, giving rise to the cross-coupling product. In Group B, ring opening through the C(4)–N(1) bond cleavage gives the regioisomeric cross-coupled product. The enantiomer of the product and its regioisomeric coupled product can be formed through the TSs in the Group E and Group F, respectively, where stereochemistry is retained. Group C/G and Group D/H represent the ring opening through the C(3)–C(4) and C(2)–C(3) bonds, respectively.

Fully optimized TSs, their relative free energies, and existence probabilities are summarized in Table 4. The lowest energy transition state, **TSa** (=**TS1**) in Group A, contributes to 58.8% of the cross-coupling product formation, and **TSb** (21.3%), **TSc** (18.0%), and **TSd** (1.0%) also give some contributions. **TSe** (0.7%) and **TSf** (0.1%) are the lowest energy transition states in Group F, leading to the regioisomeric cross-coupling product. However, their contributions are very low (0.8% in total). Thus, concentration of the subsequent intermediates or the rate of the formation of the regioisomeric cross-coupling product would be very low. The existence probabilities of the TSs in Group C, D, G, and H are zero. Therefore, the ring openings through C(3)–C(4) and C(2)–C(3) are unlikely to occur. This prediction is consistent with the experimental results. By considering all TSs, the computed regioselectivity (99:1) is in good agreement with the experimental results (100:0).

Energy decomposition analysis. In order to get some insights into the origin of the selectivity of the reaction between ^{Me}IPr–Pd and **1a**, an EDA was performed (Table 5) using the lowest energy transition sates that lead to the major product (**TSa**) and the minor product (**TSe**). Geometries of the optimized **TSa** and **TSe** are shown in Figure 5. Computed free energy difference ($\Delta\Delta G$) between **TSa** and **TSe** is 2.6 kcal/mol, while the potential energy difference ($\Delta\Delta E$) is 2.3 kcal/mol. Thus, $\Delta\Delta E$ is the key to the origin of the selectivity, and the entropy plays a minor role. For the

Table 4. Groups, relative free energies (kcal/mol), and existence probabilities (%) of the TSs for the ring opening.

TS	TS Groups	ΔG	$\Delta\Delta G$	%
TSa (= TS1)	A	0.7	0.0	58.8
TSb	A	1.3	0.6	21.3
TSc	A	3.1	2.4	18.0
TSd	A	1.4	0.7	1.0
TSe	F	3.3	2.6	0.7
TSf	F	4.5	3.8	0.1
TSg	F	6.6	5.9	0.0
TSh	F	7.8	7.1	0.0
TSi	F	8.5	7.8	0.0
TSj	H	12.1	11.4	0.0
TSk	H	12.3	11.6	0.0
TSl	H	12.9	12.2	0.0
TSm	G	14.8	14.1	0.0
TSn	H	15.4	14.7	0.0
TSo	H	16.0	15.3	0.0
TSp	B	17.5	16.8	0.0
TSq	B	17.5	16.8	0.0
TSr	B	25.6	24.9	0.0
TSs	F	33.3	32.6	0.0
TSt	C	34.6	33.9	0.0
TSu	C	36.7	36.0	0.0
TSv	C	38.9	38.2	0.0
TSw	B	45.8	45.1	0.0

Table 5. Energy decomposition analysis.

TS	DEF (DE-F_A,DEF_B)	INT (E_{Pauli}, E_{elstat}, E_{oi}, E_{disp}, E_{sol})
TSa	45.8 (4.7, 41.2)	−63.4 (131.9, −92.9, −57.0, −26.2, −19.2)
TSe	42.9 (3.5, 39.5)	−54.7 (139.5, −104.0, −49.4, −11.5, −29.4)
	ΔDEF (ΔDEF_A, ΔDEF_B)	ΔINT (ΔE_{elstat}, ΔE_{Pauli}, ΔE_{oi}, ΔE_{disp}, ΔE_{sol})
TSa	–	–
TSe	2.9 (1.2, 1.7)	−8.7 (−7.6, 11.1, −7.6, −14.7, 10.2) $\Delta\Delta E = \Delta DEF + \Delta INT$
TSa		–
TSe		−5.8

EDA, we have used the B3LYP–D3(BJ)/TZ2P/ZORA/COSMO level of theory as implemented in the ADF program, where the computed $\Delta\Delta E$ is relatively high (5.8 kcal/mol).

According to EDA, deformation of the catalyst ($\Delta DEF_A = 1.2$ kcal/mol) and deformation of the substrate ($\Delta DEF_B = 1.7$ kcal/mol) equally contributed to the ΔDEF (2.9 kcal/mol). Computed ΔINT is −8.7 kcal/mol, and it contributes mainly to the $\Delta\Delta E$ that stabilizes **TSa** over **TSe** to achieve the complete

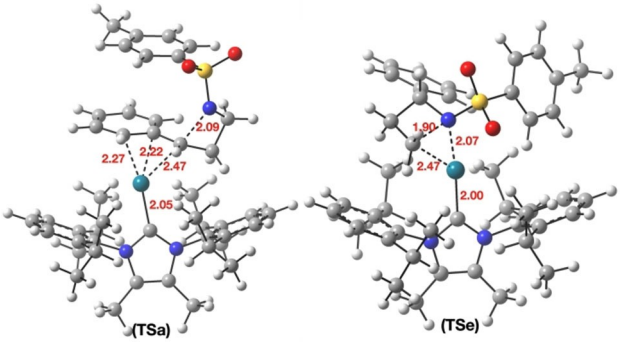


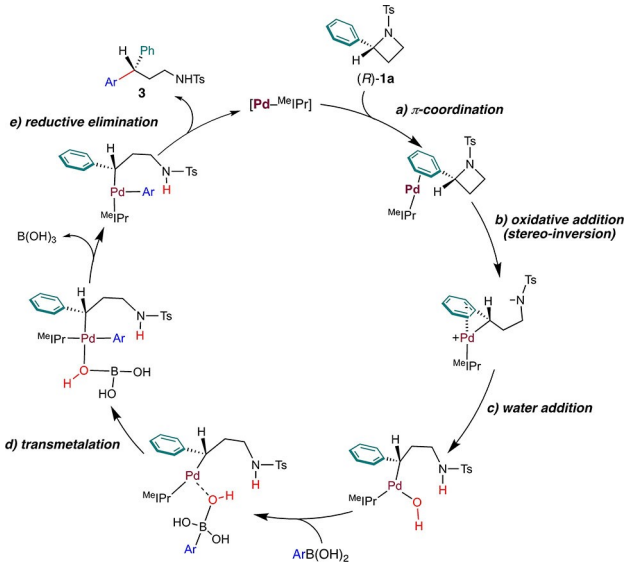
Figure 5. Geometries of the optimized **TSa** and **TSe**. Bond distances are shown in Å.

regioselectivity. In the case of **TSa**, the benzylic carbon of **1a** approaches the Pd center (Figure 5), while in the case of **TSe**, the N atom of **1a** approaches the Pd center. Among the negative components of the ΔINT, dispersion interactions ($\Delta E_{disp} = -14.4$ kcal/mol) of **TSa** is dominant, compared to electrostatic interaction ($\Delta E_{elstat} = -7.6$ kcal/mol) or orbital interactions ($\Delta E_{oi} = -7.6$ kcal/mol). These interactions together overcome the Pauli repulsion ($\Delta E_{Pauli} = 11.1$ kcal/mol) and solvation energy ($\Delta E_{sol} = 10.2$ kcal/mol).

Conclusion

In conclusion, we have developed a Pd/NHC-catalyzed regioselective and steroinvertive Suzuki-Miyaura arylation of 2-arylazetidines to afford medicinally important enantioenriched 3,3-diarylpropylamines. The developed reaction represents an example of transition metal-catalyzed C–C cross-coupling using azetidines as a non-classical alkyl electrophile. In contrast to traditional Brønsted or Lewis acid-catalyzed C(2)-selective ring-opening arylations, the developed reaction allows for the preparation of biologically-important enantio-enriched 3,3-diarylpropylamines.

Computational studies rationalize the mechanism of the full catalytic cycle that involves the selectivity-determining ring opening (oxidative addition), reaction with water, rate-determining transmetalation, and reductive elimination (Scheme 2). A systematic survey on the TSs for the selectivity-determining step was performed using an MC-AFIR search, and the lowest energy TSs contributing to the selectivity of the reaction were identified. Computed regioselectivity reproduced the experimental results. EDA indicated that interactions between the catalyst and the substrate is the key to achieve the regioselectivity of the reaction. Our combined experimental and computational study would give important mechanistic insights to develop ring-opening cross-coupling reactions of saturated N-heterocyclic compounds in a selective fashion.



Scheme 2. Catalytic cycle for the Pd-catalyzed cross-coupling of **1a** with arylboronic acids.

Experimental Section

Typical Procedures for the Pd-Catalyzed Cross-Coupling of 2-Arylazetidines with Arylboronic Acids

Conditions A: To a 3 mL vial with a magnetic stir bar (10 mm), were added **1a** (57.5 mg, 0.20 mmol), phenylboronic acid (51.2 mg, 0.42 mmol, 2.1 equiv.), K_3PO_4 (89.2 mg, 0.42 mmol, 2.1 equiv.), and PEPPSI-^{Me}IPr (11.3 mg, 16 µmol, 8 mol%). The vial was capped with a hole cap and Teflon®/rubber septum, evacuated under vacuum, and refilled with N_2 gas for 3 cycles. MTHP (1.0 mL) and deionized H_2O (0.20 mL) were added through the septum under a stream of N_2 gas, and the resulting mixture was stirred at 100 °C on an aluminum heating block for 3 h. The reaction mixture was filtrated through the Celite pad (2.0 cm), and the residue was washed with Et_2O (10 mL × 3). The filtrate was dried by evaporating the solvents under vacuum. Yields of products were estimated based on ^{1}H NMR integration of the crude product using 1,1,1,2-tetrachloroethane as an internal standard. The crude product was purified by flash column chromatography on silica gel followed by gel permeation chromatography (GPC) to give coupling product.

Conditions B: To a 3 mL vial with a magnetic stir bar (10 mm), were added **1a** (57.5 mg, 0.20 mmol), phenylboronic acid neopentyl glycol ester (79.8 mg, 0.42 mmol, 2.1 equiv.), K_3PO_4 (89.2 mg, 0.42 mmol, 2.1 equiv.), and PEPPSI-^{Me}IPr (11.3 mg, 16 µmol, 8 mol%). The vial was capped with a hole cap and Teflon®/rubber septum, evacuated under vacuum, and refilled with N_2 gas for 3 cycles. MTHP (1.0 mL) and deionized H_2O (0.20 mL) were added through the septum under a stream of N_2 gas, and the resulting mixture was stirred at 60 °C on an aluminum heating block for 12 h. The reaction mixture was filtrated through the Celite pad (2.0 cm), and the residue was washed with Et_2O (10 mL × 3). The filtrate was dried by evaporating the solvents under vacuum. Yields of products were estimated based on ^{1}H NMR integration of the crude product using 1,1,1,2-tetrachloroethane as an internal standard. The crude product was purified by flash column chromatography on silica gel followed by GPC to give coupling product.

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FULL PAPER

Palladium-Catalyzed Regioselective and Stereospecific Ring-Opening Suzuki-Miyaura Arylative Cross-Coupling of 2-Arylazetidines with Arylboronic Acids

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