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Synthesis of cyclopropanes by Pd-catalyzed activation of alkyl C–H bonds

Qinhua Huang, Richard C. Larock *

Department of Chemistry, Iowa state University, Ames, IA 50011, United States

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ABSTRACT

A novel synthesis of cyclopropanes has been developed via palladium-catalyzed C–H activation in which two new carbon–carbon bonds are formed in a single step. This method involves palladium-catalyzed activation of normally unreactive secondary alkyl C–H bonds and provides an efficient way to access cyclopropapyrrolo[1,2-*a*]indoles, analogues of mitomycin and cyclopropamitosenes.

The ability of palladium to activate C–H bonds has been used extensively in organic synthesis.[1] In recent years, palladium-catalyzed C–H activation has received considerable attention due to a wide variety of reactions this metal will catalyze. For instance, catalytic amounts of Pd salts have been used to effect the addition of C–H bonds of electron-rich arenes to alkenes and alkynes, and to effect the carbonylation.[2] We[3] and others[4] have reported that intramolecular C–H activation in organopalladium intermediates derived from *o*-halobiaryls leads to 1,4-palladium migration (Scheme 1). These migration reactions provide an alternate way to introduce a palladium moiety into organic molecules and have been found to be quite general. Recently, aryl to aryl,[3,4] vinylic to aryl,[5] alkyl to aryl,[6] aryl to alkyl,[7] vinylic to aryl to allylic,[8] benzylic to aryl,[9] aryl to benzylic,[10] aryl to imidoyl,[11] and aryl to acyl[12] migrations have been reported to be a useful tool for the synthesis of a variety of carbocyclic and heterocyclic ring systems. Herein, we wish to report a novel C–H activation using palladium chemistry to synthesize cyclopropanes,[13] especially cyclopropapyrrolo[1,2-*a*]indoles, analogues of the mitomycin antibiotics[14] and anticancer cyclopropamitosenes.[15]

During our investigation of Pd-catalyzed aryl to aryl migration chemistry,[3c] iodoindole **1** was allowed to react under our standard palladium migration conditions [5 mol % $Pd(OAc)_2$, 5 mol % bis(diphenylphosphino)methane (dppm), 2 equiv of CsO_2CCMe_3 (CsPiv) and DMF as the solvent], and only trace amounts of the desired migration/arylation product **2** were detected (Scheme 2). Surprisingly, compound **3** was isolated in a 42% yield. As shown in Scheme 2, the indolylpalladium iodide **A**, formed by palladium migration from the 2 position of the phenyl group to the 2 position of the indole ring, apparently reacts with the carbon–carbon double bond to generate an alkyl intermediate **B**. Instead of forming a new carbon–carbon bond at the 2 position of the phenyl group to form pentacyclic compound **2**, the alkylpalladium iodide apparently activates a normally unreactive alkyl C–H bond through a four-membered palladacycle **C** intermediate to generate cyclopropane **3**. Due to our interest in Pd-catalyzed activation of unreactive alkyl C–H bonds and the substantial biological activities of cyclopropapyrrolo[1,2-*a*]indoles,[15] we have investigated this novel Pd-catalyzed C–H activation and examined its scope by employing various substrates.

Our initial studies focused on achieving optimal reaction conditions for this novel palladium-catalyzed C–H activation process employing the isomeric iodoindole **4** (Table 1).

While the reaction of compound **1** generated a 42% yield of the desired cyclopropane **3** (Scheme 2), the reaction of compound **4** under the same reaction conditions afforded cyclopropane **3** in a 62% yield and compound **2** in a 15% yield (Table 1, entry 1). Omitting dppm as the ligand, the yield dropped from 62% (entry 1) to 37% (entry 2). When the organic base Bu_3N was used, cyclopropane **3** was isolated in only a 15% yield (entry 3). When the reaction was carried out at 100 °C, the yield dropped to 55% and a longer reaction time was required to reach completion (entry 4). Compared to the reaction using dppm as the ligand (entry 1), when bis(dicyclohexylphosphino)methane (dcpm), a more electron-donating ligand, was employed, the C–H activation process was much faster and reached completion in 1.5 h (entry 5). However, the yield decreased to 47% from 62% (entry 1). The bases NaOAc, Na_2CO_3, Cs_2CO_3, and KO-*t*-Bu have also been employed and the desired cyclopropane **3** has been obtained in yields of 36%, 26%, 52%, and a trace amount, respectively (entries 6–9). When $Pd(PPh_3)_4$ was employed as the catalyst with and without the addition of dppm, the reactions were very sluggish and compound **3** was produced in 30% and 27% yields, respectively (entries 10 and 11). Thus, we chose the following conditions as our 'optimal' reaction conditions: 0.50 mmol of the substrate, 5 mol % $Pd(OAc)_2$, 5 mol % dppm, 2 equiv of CsPiv in DMF (4 mL), stirred at 110 °C under an Ar atmosphere.

Using our optimal reaction conditions,[16] the scope of this novel Pd-catalyzed C–H activation process has been explored using a variety of substrates carefully selected in order to establish the generality of the process and its applicability to commonly encountered synthetic problems (Table 2). While the reaction of

* Corresponding author. Tel.: +1 515 294 4660; fax: +1 515 294 0105.
E-mail address: larock@iastate.edu (R.C. Larock).

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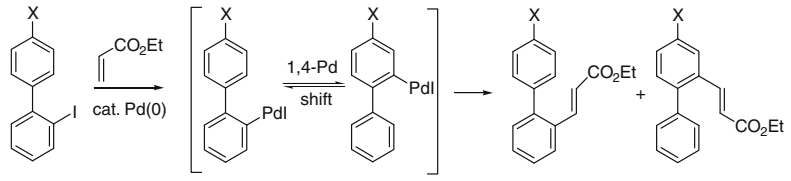
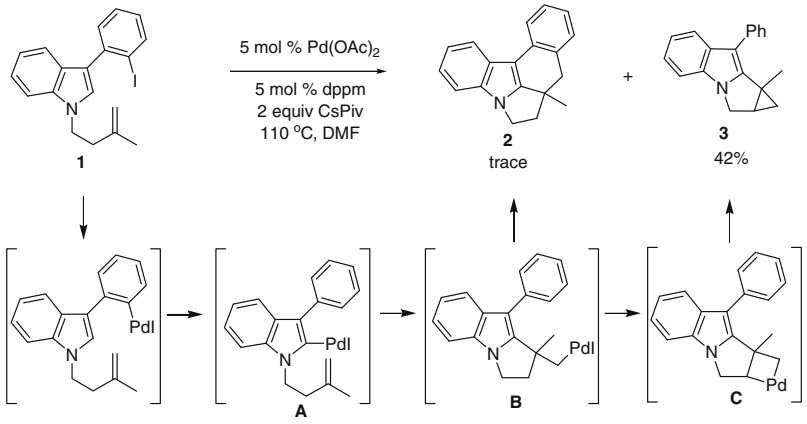
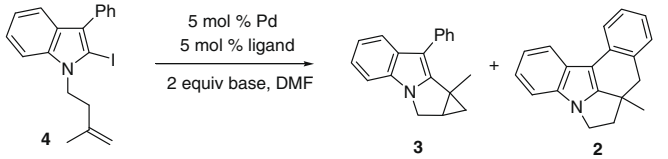


Scheme 1.



Scheme 2.

Table 1
Optimization reactions for the synthesis of compound **3**[a,b]



Entry	Catalyst	Ligand	Base	*T* (°C)	Time (h)	Yield of **3** (%)
1	$Pd(OAc)_2$	dppm	CsPiv	110	6	62[c,d]
2		—	CsPiv	110	12	37[c]
3		—	Bu_3N	110	72	15[c]
4		dppm	CsPiv	100	24	55[e]
5		dcpm	CsPiv	110	1.5	47[e]
6		dppm	NaOAc	115	24	36[e]
7		dppm	Na_2CO_3	110	72	26[e]
8		dppm	Cs_2CO_3	115	48	52[e]
9		dppm	KO^{t}Bu	115	0.5	Trace
10	$Pd(PPh_3)_4$	dppm	Na_2CO_3	110	72	30[e]
11	$Pd(PPh_3)_4$	—	Na_2CO_3	110	72	27[e]

[a] All reactions were carried out under the following reaction conditions: 0.25 mmol of compound **4**, 5 mol % Pd catalyst, 5 mol % ligand, 2 equiv of base in 4 mL of DMF at the indicated temperature under an Ar atmosphere.
[b] Along with cyclopropane **3**, another cyclopropane product, generated by having the palladium intermediate close onto the methyl group, has been obtained in a 5–10% yield.
[c] Isolated yield.
[d] Compound **2** was isolated in a 15% yield.
[e] The yield is based on gas chromatographic analysis.

compound **4** afforded cyclopropane **3** in a 62% yield (entry 2), the reaction of iodoindole **5** generated cyclopropane **6** in a 46% yield (entry 3). Iodoindole **7**, with no substituent in the 3 position of the indole ring, has been allowed to react under our optimal reaction conditions, but only a trace amount of the desired product was detected. It is quite possible that the alkylpalladium intermediate first produced undergoes palladium migration to the 3 position of the indole ring circumventing cyclopropane formation, although we failed to isolate any recognizable products (Scheme 3).[17] This type of alkyl to aryl palladium migration has been observed previously in our research group under the same reaction conditions.[6]

To test if the C–H activation process occurs when forming a new six-membered ring, we have prepared compounds **9** and **11** and carried out the corresponding reactions under our optimal reaction conditions (entries 5 and 6). Although the yields are a little lower, the anticipated new fused six-membered ring systems can be generated by this Pd-catalyzed alkyl C–H activation chemistry.

Is the indole nitrogen essential to this C–H activation process? To answer this question, compounds **13** and **15** were employed under our optimal reaction conditions. Unfortunately, only trace amounts of the desired cyclopropane products **14** and **16** were detected by GC analysis (entries 7 and 8). It appears that the indole ring system is critical to formation of the cyclopropanes by this Pd-catalyzed C–H activation process. Consistent with this observation is the fact that the reaction of compound **17** afforded none of the desired cyclopropane product. It is quite possible that compound **17** under our reaction conditions may generate a π-allylpalladium intermediate, which circumvents cyclopropane formation. When compound **19** was employed, the reaction again failed to produce any cyclopropane product. However, 2-iodo-3-phenylindole was isolated in a 72% yield (entry 10). This product probably arises by simple decomposition of the *N*-(alkoxycarbonyl)indole. When, aryl bromide **21** was allowed to react under our optimal reaction conditions, none of the desired cyclopropane product was detected (entry 11).

In conclusion, a novel palladium-catalyzed activation of simple alkyl C–H bonds has been investigated as a unique new way to form polycyclic cyclopropanes. Our experiments indicate that the indole ring is apparently critical to this activation process, although the reason for this is not clear. This method provides a facile method to access cyclopropapyrrolo[1,2-*a*]indoles and cyclopropapiperido[1,2-*a*]indoles.

Table 2
Pd-catalyzed cyclopropanation through C–H activation[a,b]

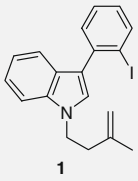
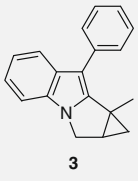
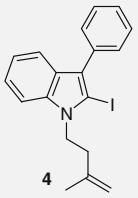
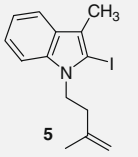
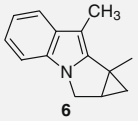
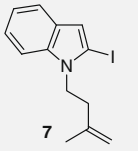
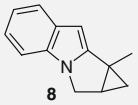
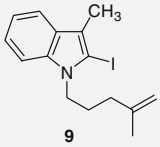
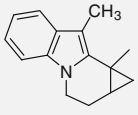
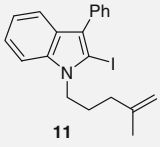
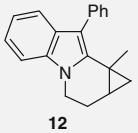
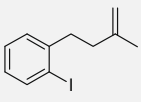
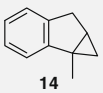
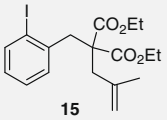
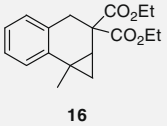
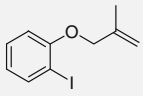
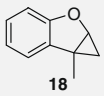
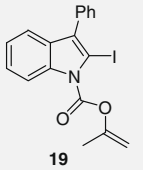
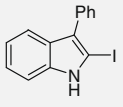
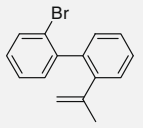
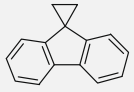
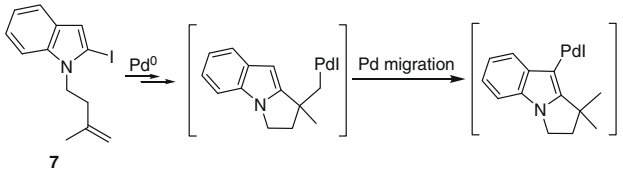
Entry	Aryl iodide	Time (h)	Product	% Yield[c]
1	 **1**	8	 **3**	42
2	 **4**	6	**3**	62
3	 **5**	12	 **6**	40 (46[d])
4	 **7**	12	 **8**	Trace
5	 **9**	16	 **10**	31[d]
6	 **11**	18	 **12**	42
7	 **13**	3	 **14**	<5%
8	 **15**	12	 **16**	Trace

Table 2 (*continued*)

Entry	Aryl iodide	Time (h)	Product	% Yield[c]
9	 **17**	12	 **18**	0
10	 **19**	12	 **20**	72
11	 **21**	24	 **22**	Trace

[a] All reactions were carried out under the following reaction conditions, unless otherwise specified: 0.5 mmol of the substrate, 5 mol % $Pd(OAc)_2$, 5 mol % dppm, 2 equiv of CsPiv in 4 mL of DMF at 110 °C under an Ar atmosphere.
[b] For entries 1–3, 5, and 6, along with the desired cyclopropane derivative, another cyclopropane product has been detected in 5–10% yields, in which the palladium closes onto the methyl group.
[c] Isolated yield.
[d] The yield was determined by gas chromatographic analysis.



Scheme 3.

Acknowledgments

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16. *Representive Pd-catalyzed cyclopropanation procedure (entry 2,* Table 2): To a 6 dram vial were added $Pd(OAc)_2$ (6.0 mg, 0.025 mmol), dppm (9.2 mg, 0.025 mmol), CsPiv (234 mg, 1.0 mmol), compound **4** (0.50 mmol), and dry DMF (4 mL). The reaction mixture was stirred at 25 °C under an Ar atmosphere for 5 min, and was then stirred at 110 °C for 6 h to reach completion. The reaction mixture was allowed to cool to 25 °C, diluted with Et_2O (20 mL), and washed with brine (20 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was subjected to purification by chromatography to afford 80 mg of the desired cyclopropane **3** in a 62% yield as a white solid; mp 158–160 °C; ^{1}H NMR ($CDCl_3$) δ 1.01–1.03 (m, 1H), 1.28 (dd, J = 4.8, 8.0 Hz, 1H), 1.46 (s, 3H), 2.08–2.10 (m, 1H), 4.05 (d, J = 6.4 Hz, 1H), 4.24 (dd, J = 5.6, 10.4 Hz, 1H), 7.06–7.17 (m, 3H), 7.25–7.29 (m, 1H), 7.42–7.46 (m, 2H), 7.61 (dd, J = 0.8, 8.0 Hz, 1H), 7.71 (d, J = 8.0 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 17.5, 23.6, 24.2, 28.8, 46.5, 108.4, 109.2, 119.3, 119.7, 121.2, 125.6, 128.4, 129.5, 131.3, 132.8, 135.2, 145.7; IR ($CHCl_3$, cm^{-1}) 3018, 2930, 1602, 1478, 1460, 1216; HRMS calcd for $C_{19}H_{17}N$: 259.1361. Found: 259.1365.
17. For compounds **4** (entry 2) and **5** (entry 3), the 3-position of the indole ring is blocked; therefore, 1,4 alkyl to aryl migration is prohibited.