ChemPubSoc Europe

DOI: 10.1002/chem.201403093

CHEMISTRY
A European Journal
Communication

Catalysis

Palladium-Catalyzed Intramolecular Reductive Cross-Coupling of Csp^2–Csp^3 Bond Formation

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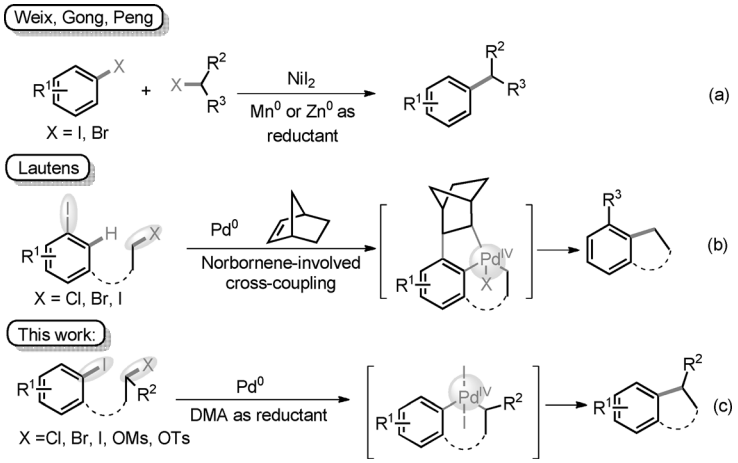
Abstract: A Pd-catalyzed efficient reductive cross-coupling reaction without metallic reductant to construct a Csp^2–Csp^3 bond has been reported. A Pd^{IV} complex was proposed to be a key intermediate, which subsequently went through double oxidative addition and double reductive elimination to produce the cross-coupling products by involving $Pd^{0/II/IV}$ in one transformation. The oxidative addition from Pd^{II} to Pd^{IV} was partially demonstrated to be a radical process by self-oxidation of substrate without additional oxidants. Furthermore, the solvent was proved to be the reductant for this transformation through XPS analysis.

Transition-metal-catalyzed cross-coupling reactions have emerged as a tremendously powerful synthetic tool in organic chemistry.[1] According to coupling partners, three types of coupling were classified: traditional coupling,[2] oxidative coupling,[3] and reductive coupling (Scheme 1), in which reductive cross-coupling was less intensively studied. The Ullmann reaction, initially reported in 1901, is one of the most efficient reductive cross-coupling reactions used in constructing carbon—carbon bonds between two aryl halides using stoichiometric copper.[4] Much milder conditions were obtained by combining Ni^0 and reductant (such as zinc) or electrochemical reduction regenerating the catalytically active species.[5] Palladium-catalyzed reductive coupling, which was reported by Shimizu et al. in 1993,[6] has been proved to be an effective protocol in the preparation of the Csp^2–Csp^2 bond as well.[7] However, these products were restricted to homocoupling ones. The research on the formation of the Csp^2–Csp^3 bond by the reductive cross-coupling reaction is relatively rare due to the β-hydrogen elimination in palladium chemistry. Since Fu's pioneering work on cross-couplings involving the Csp^3–X bond,[8] the reductive cross-coupling of the Csp^2–Csp^3 bond has provoked more attention in the last decade. Efficient nickel-catalyzed reductive cross-couplings between Csp^2–X and Csp^3–X using Zn or Mn as the reductant have been reported by Weix[9a–c] and others[9d–f] (Scheme 1a). The Lautens group reported a series of palladium-catalyzed Csp^2–Csp^3 bond formations by means of an original strategy of Pd^{IV} formation with the help of norbornene (Scheme 1b).[10] In connection with our goal in the transition-metal-catalyzed transformations of Csp^3–X,[11] we demonstrate a novel palladium-catalyzed intramolecular cross-coupling of Csp^2–I and Csp^3–X bonds through double oxidative addition and reductive elimination via a Pd^{IV} intermediate (Scheme 1c).



Scheme 1. Reductive cross-coupling protocols in the construction of the Csp^2–Csp^3 bond.

We commenced with our study by investigating *N*-(2-iodoethyl)-*N*-(2-iodophenyl)-4-methylbenzene-sulfonamide (**1aa**). The reaction was first performed in the presence of [$PdCl_2$(dppf)] and Cs_2CO_3 at 110 °C in MeCN, which generated the desired product **2a** in 33% yield (Table 1, entry 1). Due partially to starting material recovery, a higher temperature was used (entries 2 and 3). To stabilize the catalyst, 10 mol% of additional ligand TFP was added, which increased the yield to 70% (en-

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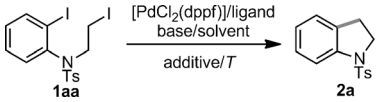
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201403093.

Table 1. Optimization of reaction conditions.[a]



Entry	Ligand [mol%]	Base	Solvent	Additive [equiv]	T [°C]	t [h]	Yield[%][b]
1	–	Cs_2CO_3	MeCN	–	110	16	33
2	–	Cs_2CO_3	MeCN	–	130	16	35
3	–	Cs_2CO_3	MeCN	–	150	16	45
4	dppf[c] (5)	Cs_2CO_3	MeCN	–	150	16	49
5	PPh_3 (10)	Cs_2CO_3	MeCN	–	150	16	36
6	PCy_3[d] (10)	Cs_2CO_3	MeCN	–	150	16	64
7	TFP[e] (10)	Cs_2CO_3	MeCN	–	150	16	70
8	TFP (20)	Cs_2CO_3	MeCN	–	150	16	68
9	TFP (10)	Cs_2CO_3	PhCl	–	150	24	26
10	TFP (10)	Cs_2CO_3	PhMe	–	150	12	8
11	TFP (10)	Cs_2CO_3	Dioxane	–	150	12	12
12	TFP (10)	Cs_2CO_3	DMF	–	150	12	15
13	TFP (10)	Cs_2CO_3	DMSO	–	150	10	trace
14	TFP (10)	Cs_2CO_3	DMA	–	150	6	75
15	TFP (10)	K_2CO_3	DMA	–	150	12	35
16	TFP (10)	K_3PO_4	DMA	–	150	12	41
17	TFP (10)	Ag_2CO_3	DMA	–	150	6	trace
18	TFP (10)	KO*t*Bu	DMA	–	150	6	ND
19	TFP (10)	Cs_2CO_3	DMA	LiCl (2.0)	150	6	80
20	**TFP (10)**	**Cs_2CO_3**	**DMA**	**LiBr (2.0)**	**150**	**6**	**88**
21	TFP (10)	Cs_2CO_3	DMA	LiBr (0.3)	150	6	80
22	TFP (10)	Cs_2CO_3	DMA	LiBr (1.0)	150	6	81
23	TFP (10)	Cs_2CO_3	DMA	LiBr (3.0)	150	6	84
24	TFP (10)	Cs_2CO_3[f]	DMA	LiBr (2.0)	150	6	68
25	TFP (10)	Cs_2CO_3[g]	DMA	LiBr (2.0)	150	6	87

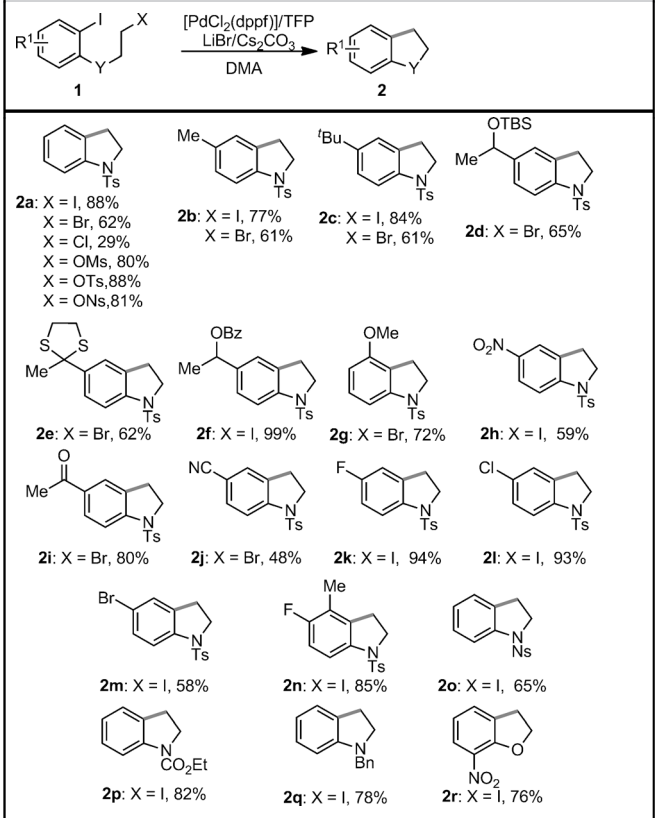
[a] Reaction Conditions: **1aa** (0.1 mmol), $[PdCl_2(dppf)]$ (0.01 mmol), base (0.3 mmol), solvent (1.0 mL). [b] Isolated yields. [c] dppf = 1,1′-bis(diphenylphosphino)ferrocene. [d] PCy_3 = tricyclohexyl-phosphine. [e] TFP = tri(2-furyl)phosphine. [f] 2.0 equiv of Cs_2CO_3 was used. [g] 4.0 equiv of Cs_2CO_3 was used.

tries 4–7). More TFP did not give a better result (entry 8). After screening of the solvents, *N*,*N*-dimethylacetamide displayed an irreplaceable role for providing the reductive atmosphere (entries 9–14). Cs_2CO_3 is also a crucial base compared to others (entries 15 and 16). Ag_2CO_3, which was supposed to accelerate this transformation by precipitating iodide anion, however, could not promote this reaction (entry 17). When KO*t*Bu was used, no desired product **2a** was detected (entry 18). Notably, the yield was increased to 88% by using two equivalents of LiBr as an additive, which might further prohibit the β-hydrogen elimination of the Csp^3–X bond (entries 19–23).[12] Compound **2aa** was obtained in 68% yield with 22% of **1aa** recovered when the amount of Cs_2CO_3 decreased to two equivalents (entry 24). No big improvement was achieved when more Cs_2CO_3 was launched (entry 25).

Indolines are highly valuable building blocks for medicinal chemistry and organic synthesis. Some elegant strategies have been developed in the past, such as through the reduction of indoles,[13a] C–H bond activation,[13b,c] and cross-couplings.[13d,e] The difficulties in the synthesis of substrates limits the application of these strategies. However, the substrates in this novel protocol could be obtained from substituted aniline efficiently. Moreover, not only substituted indoline could be synthesized efficiently, but also substituted 2,3-dihydrobenzofuran, tetrahydropyridine, and pyrrole derivatives could also be achieved.

The results shown in Table 2 demonstrate that the protocol has a great functional-group tolerance. Both electron-rich and -deficient substrates in the cases could be efficiently trans-

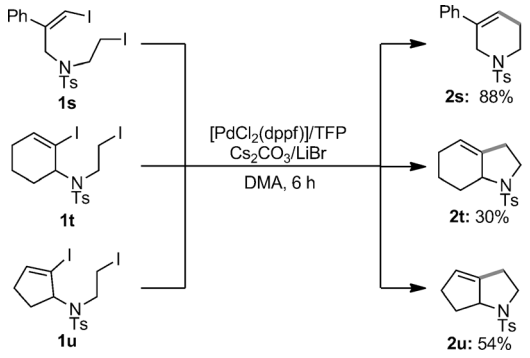
Table 2. Pd-catalyzed cross-coupling of Csp^2–I and Csp^3–X bonds.[a]



[a] Reaction conditions: **1** (0.1 mmol), $[PdCl_2(dppf)]$ (0.01 mmol), TFP (0.01 mmol), Cs_2CO_3 (0.3 mmol), LiBr (0.2 mmol), DMA (1.0 mL), 150 °C, 6 h.

formed to the corresponding products in good to excellent yields (**2a**–**j**). Notably, the sulfur-containing substrate **1e** proceeds well in this system without poisoning the catalyst Pd. Fluoro-, chloro-, and bromo-substituted substrates **1k**, **1l**, and **1m** could survive in these conditions, leading to **2k** (94%), **2l** (93%), and **2m** (58%), respectively. Multisubstituted product 5-fluoro-4-methyl-1-tosylindoline **2n** could be obtained in 85% yield. Substrates with different protecting groups on the nitrogen, such as *N*-(4-nitrobenzene-1-sulfonyl), COOEt, and Bn, could offer the corresponding products in good yields as well (**2o**–**q**). The oxygen-tethered substrate **1r** provided 7-nitro-2,3-dihydrobenzofuran in 76% yield.

It is noteworthy that the cross-coupling of vinyl iodide and alkyl iodide were successfully achieved in moderate to good yields (Scheme 2). The six-membered 1,2,3,6-tetrahydropyridine derivate **2s** could also be formed in excellent yield. The five-membered hexahydro-1*H*-indole derivate **2t** and hexahydrocyclopenta[*b*]pyrrole derivate **2u** are both valuable cores in or-



Scheme 2. Reductive cross-coupling of vinyl iodide with Csp^3–I.

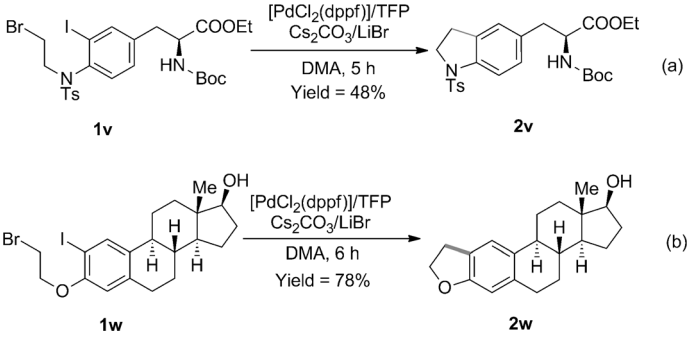
ganic synthesis,[14] which could be achieved in moderate yields by this protocol (**2t** and **2u**).

To extend the application of reductive cross-coupling in organic synthesis, two natural molecules were examined. For example, L-phenylalanine derivate **1v** was converted to indoline **2v** in 48% yield (Scheme 3a). Notably, a more complex structure **1w**, based on natural product estradiol, was subjected to standard conditions giving the corresponding products **2w** in 78% yield, which was hard to achieve through late-stage modification strategies (Scheme 3b).

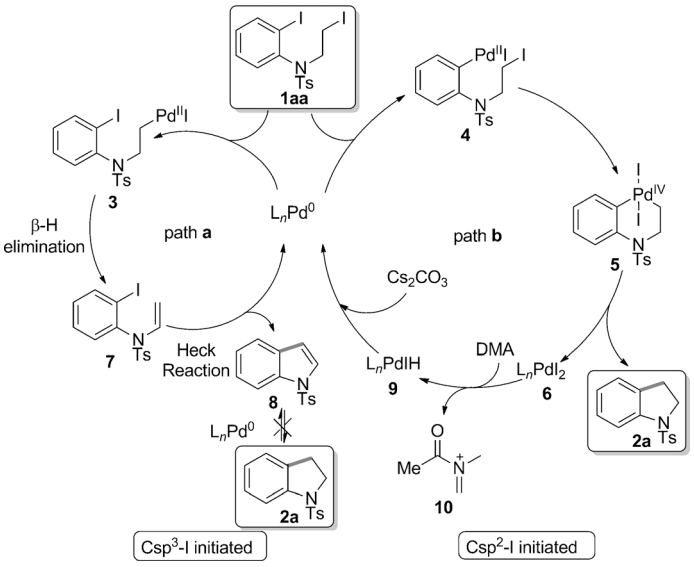
To gain mechanistic insight into this reductive cross-coupling, two possible pathways were taken into consideration (Scheme 4). Though Csp^2–I oxidative addition exhibited superiority to Csp^3–X, which indicated that path b is a favorable route,[15] path a which was initiated from the Csp^3–I bond was still a competitive route owing to the observation of compounds **7** and **8** under the conditions listed in Table 1, entry 8 (Scheme 4). To demonstrate this hypothesis, compound **7** was subjected to the same conditions, producing **8** in 89% yield; however, no product **2a** was observed (Scheme 5). On the other hand, product **2a** could not be converted to compound **8** either, which indicated path a in Scheme 4 could be responsible for this side transformation (Scheme 5). The above results showed the reductive cross-coupling product **2a** could not be obtained through path a in Scheme 4.

To investigate path b in Scheme 4 initiated from the Csp^2–I bond, a stoichiometric reaction of $[Pd_2(dba)_3]/PPh_3$ with **1q** was conducted under a N_2 atmosphere in the absence of Cs_2CO_3 and LiBr (Scheme 6). A palladium complex **1q-A** was obtained in 65% yield, which was confirmed by X-ray crystallography. Treating the complex **1q-A** with Cs_2CO_3 and LiBr in DMA at 100 °C for 1 h gave the desired product **2q** in 88% yield, which indicated that the palladium complex **1q-A** should be a key intermediate in this transformation. According to path b in Scheme 4, a palladium(IV) intermediate should be generated. When complex **1q-A** was heated to 100 °C in benzene, no intermediate **1q-B** was detected, but the coupling product **2q** was formed in 79% yield after 5 h (there was no transformation under 100 °C), which indicated the reductive elimination of palladium(IV)
intermediate was a faster process than oxidative addition of palladium(II).

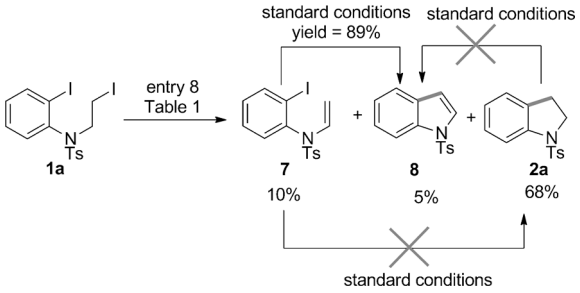
The key Pd^{IV} intermediate **5**, which was proposed in Scheme 4,[10,17] was generated from intramolecular oxidative addition of alkyl iodide to intermediate **4** according to the research of Lautens[10] and Chen.[18] To investigate the mechanism of the oxidative addition (OA) process of Csp^3–I in this system, the chiral substrate **1x** was tested under the standard conditions (Scheme 7, Eq. (1)). Substrate **1x** (*ee* = 98%) was converted to **2x** in 57% yield with only 5% *ee* remaining. This demonstrated that the OA from Pd^{II}(**1x-A**) to Pd^{IV}(**1x-B**) might be a radical mechanism in this process (Scheme 7, Eq. (1)). Then the first reductive elimination of **5** led to the desired product **2a** and complex $[PdI_2L_n]$ **6** through C–C bond reductive elimination, which could produce Pd^0 by the second reductive elimination of $[PdI_2L_n]$ in the presence of Cs_2CO_3 and *N*,*N*-dimethy-



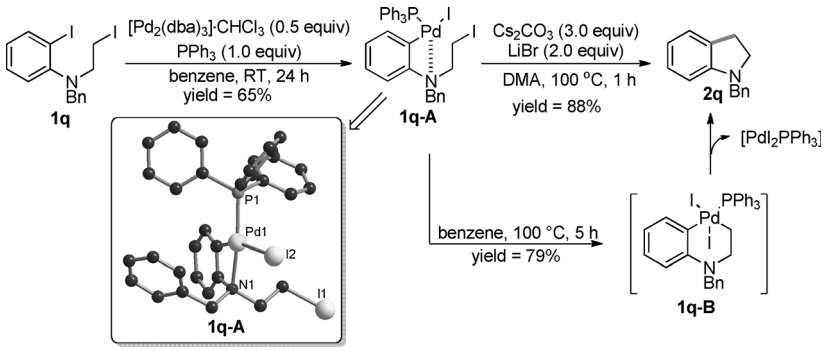
Scheme 3. Modification of natural molecules by reductive cross-coupling.



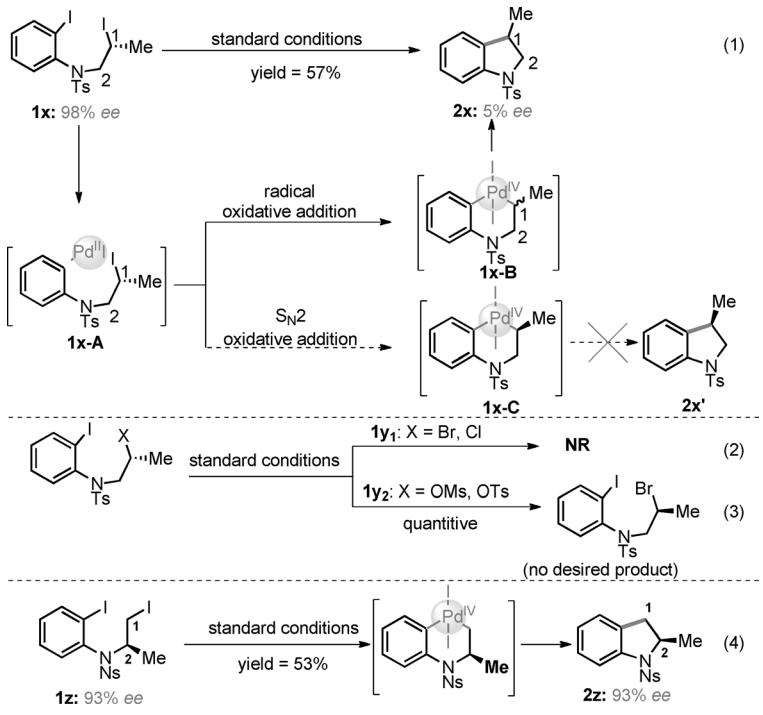
Scheme 4. Proposed mechanism.



Scheme 5. Exclusion of the formation of **2a** through path a (Scheme 4).



Scheme 6. Insight into path b (Scheme 4) through isolation, X-ray analysis, and transformation of the key palladium intermediate **1q-A**.[16]



Scheme 7. Investigation of the transformation from Pd^{II} to Pd^{IV}.

lacetamide (Scheme 4, path b).[19] The reaction of substrates with chiral Csp^3–Br, Cl, OMs, and OTs were also subjected to the standard conditions; however, no reaction occurred for substrates $\mathbf{1y_1}$ (X = Br, Cl) (Scheme 7, Eq. (2)) and $\mathbf{1y_2}$ were converted to $\mathbf{1y_2}$-Br by S_N2 replacement (Scheme 7, Eq. (3)), which might be due to the difficulties of radical formation from the Csp^3–X (X = Br, Cl, OMs, OTs) compared to the Csp^3–I bond. When the substrate **1z** (*ee* = 93%) was examined, **2z** was obtained in 53% yield with 93% *ee* under the standard conditions (Scheme 7, Eq. (4)), which indicated that no β-hydrogen elimination occurred from the Pd^{IV} intermediate during this transformation.[12]

As no additional reductant was added to this transformation, *N*,*N*-dimethylacetamide was supposed to act as a reductant to regenerate the Pd^0 by sequent ligand exchange, β-hydrogen elimination, and reductive elimination from complex **6** (Scheme 4). The oxidative states of the [Pd] under *N*,*N*-dimethylacetamide conditions was investigated through X-ray photoelectron spectroscopic (XPS) techniques (Figure 1). Curve A showed the identical binding energy ($Pd3d_{5/2}$ 338.1 eV, $Pd3d_{3/2}$ 343.2 eV) of [$PdCl_2$(dppf)], a characteristic binding energy for the Pd^{II} species. After [$PdCl_2$(dppf)] was treated with *N*,*N*-dimethylacetamide and Cs_2CO_3 in one hour, the binding energy shifted to $Pd3d_{5/2}$ 337.4 eV and $Pd3d_{3/2}$ 342.6 eV (62%), which indicated that the Pd^{II} complex has been reduced to the Pd^0 active species through *N*,*N*-dimethylacetamide.[20] Meanwhile, the binding energy of the partial catalyst (38%) shifted to $Pd3d_{5/2}$ 336.2 eV and $Pd3d_{3/2}$ 341.5 eV, which might be the palladium black.[20c] Similar results were obtained when [$PdCl_2$-(dppf)] was treated with MeCN and Cs_2CO_3 ($Pd3d_{5/2}$ 337.4 eV and $Pd3d_{3/2}$ 342.6 eV for 67%), which demonstrated the generation of the Pd^0 active species (See part V in the Supporting Information).

In conclusion, we have developed a Pd-catalyzed efficient reductive cross-coupling reaction to construct Csp^2–Csp^3 bonds without metallic reductant. A Pd^{IV} complex was proposed to be a key intermediate, which went through double oxidative addition and double reductive elimination to produce the cross-coupling products; this method utilized palladium chemistry by involving $Pd^{0/II/IV}$ in one transformation. The oxidative addition from Pd^{II} to Pd^{IV} was partially demonstrated to be a radical process by self-oxidation of substrate without additional oxidants. Furthermore, the solvent was proved to be the reductant for this transformation through XPS analysis. Meanwhile, this methodology could provide a remarkably straightforward means for the late-stage modification of drugs. Synthetic applications will be reported in due course.

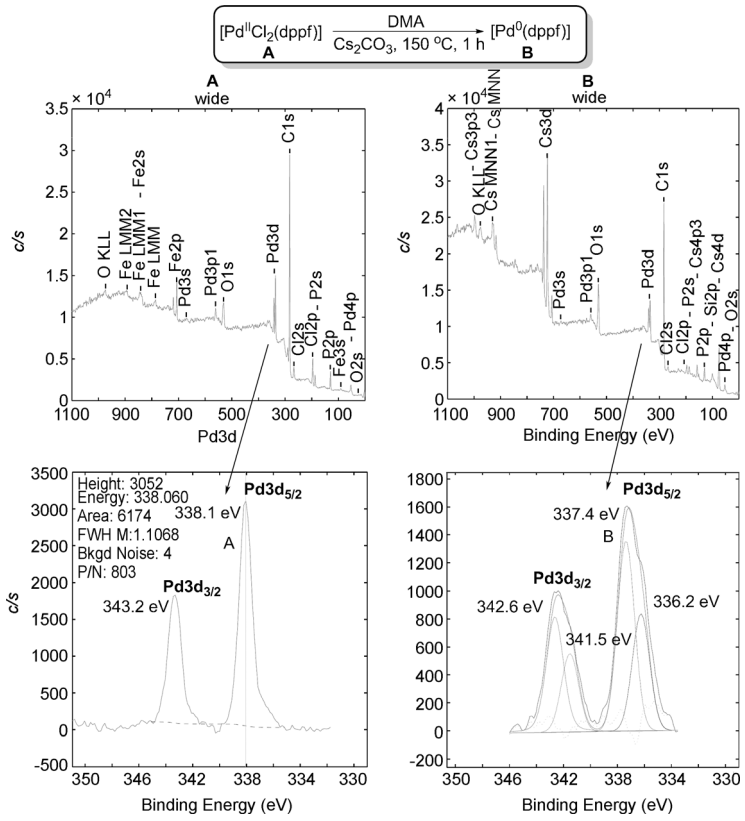


Figure 1. X-ray photoelectron spectra of [Pd]. Conditions for A: [$PdCl_2$(dppf)]; conditions for B: [$PdCl_2$(dppf)] in *N*,*N*-dimethylacetamide at 150 °C for 1.0 h.

Experimental Section

General method

In a 25 mL sealed tube, the air was exchanged with N_2 for three times. Then the mixture of substrate **1** (0.1 mmol), [$PdCl_2$(dppf)] (0.01 mmol), TFP (0.01 mmol), Cs_2CO_3 (0.3 mmol), and LiBr (0.2 mmol) was dissolved in DMA (1 mL). The system was heated to 150 °C for 6 h. When the reaction was finished, the mixture was cooled to RT. and directly subjected to silica gel column chromatography to give product **2**.

Acknowledgements

Financial support was provided by NSFC (21272075, 21302057), NCET (120178), DFMEC (20130076110023), Fok Ying Tung Education Foundation (141011), "Shanghai Pujiang Program" (12J1402500), program for Professor of Special Appointment (Eastern Scholar) at Shanghai Institutions of Higher Learning, and program for Changjiang Scholar and Innovative Research Team in University.

Keywords: catalysis · C–C bond formation · cross-coupling · Csp^3–X bond · palladium

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Received: April 14, 2014
Published online on ■■ ■■, 0000

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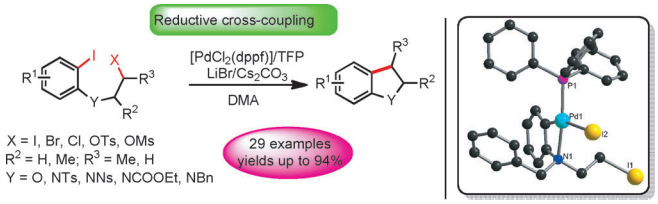

Radical chemistry: A palladium-catalyzed reductive cross-coupling reaction to construct Csp^2–Csp^3 bonds was developed (see scheme). Palladium ($Pd^{0/II/IV}$) was involved in one transformation, in which the oxidative addition from Pd^{II} to Pd^{IV} by Csp^3–X was proved to be a radical process. Solvent *N*,*N*-dimethylacetamide (DMA) was proved to be the reductant in this catalytic cycle by XPS examination.

Catalysis

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Palladium-Catalyzed Intramolecular Reductive Cross-Coupling of Csp^2–Csp^3 Bond Formation