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Palladium-Catalyzed Cross-Coupling Reactions of Electron-Deficient Alkenes with *N*-Tosylhydrazones: Functional-Group-Controlled C–C Bond Construction

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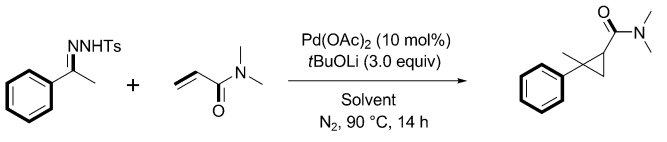
Due to the versatility of the cyclopropane unit in organic synthesis and the occurrence of a number of important cyclopropane-containing natural products and synthetic materials, the synthesis of cyclopropanes has drawn considerable attention.[1] The most commonly used route is the transition-metal-catalyzed decomposition of diazo compounds in the presence of an alkene, in which a formal [2+1] cycloaddition of metal–carbene complexes to alkenes proceeds rapidly[2] and excellent stereoselectivity can be achieved in many cases.[3] Nevertheless, in consideration of the stability and operability of diazo compounds without an electron-withdrawing group, *N*-tosylhydrazones are readily prepared from carbonyl compounds and are likely to have remarkable synthetic potential as an in situ source of diazo compounds.[4] This possibility extends the current methods for the modification of carbonyl compounds.

After decades of development, palladium-catalyzed carbon–carbon bond-forming reactions can be recognized as one of the cornerstones in current organic synthetic chemistry.[5] The impressive selectivity, availability, and functional-group tolerance illustrates the tremendous enabling ability of these modern synthetic tools.[6] Moreover, sequential transformations and multifarious coupling partners, ranging from traditional organic reagents to organometallic reagents, also promote the efficiency and application in total synthesis of this type of reaction.[7]

Recently, great efforts have been made to develop Pd-catalyzed carbene cross-coupling reactions based on *N*-tosylhydrazones due to these advantages.[8] With relation to our interest in palladium chemistry,[9] we envisioned the possibility of exploring a Pd-catalyzed, new, intermolecular cross-coupling reaction between *N*-tosylhydrazones and functionalized terminal alkenes.

At the outset of this investigation, we explored the Pd-catalyzed reaction between *N*-tosylhydrazone (**1a**) and acrylamide (**2a**; Scheme 1) because in comparison with Rh, Ru, Co, and Cu metal–carbenes, Pd metal–carbenes are optimal for reactions involving electron-deficient rather than electron-rich alkenes.[10] Only a trace amount of the cyclopropane-containing product **3a** was detected when an anhydrous solvent was used. After extensive screening of the reaction conditions, the yield rose to about 30% when a hydrous solvent was used. This implied that the product yield was dependent on the concentration of water in the reaction. Initial studies elucidated that the electron-deficient terminal alkenes could be effectively cyclopropanated by using the Pd–carbene catalyst when 2.0 equivalents of water were added.[11]



Scheme 1. Initial studies of water concentration.

The investigation of different catalysts convinced us that the palladium catalyst could not be neglected in this reaction (Table 1, entry 1). A dramatic suppression effect caused by extra ligands resulted in lower yields (Table 1, entries 2–8). As a consequence, palladium acetate was chosen to catalyze this cross-coupling reaction.

With the optimized reaction conditions, we then studied the scope of this reaction by using various *N*-tosylhydrazones and acrylamides. As illustrated in Table 2, the cross-

Table 1. Investigation of the catalyst.[a]

Entry	Catalyst	Yield[b] [%]
1	–	0
2	$Pd(OAc)_2$	73 (68)
3	$PdCl_2$	45
4	$Pd(OAc)_2$[c]	42
5	$[PdCl_2(PPh_3)_2]$	55
6	$[PdCl_2(CH_3CN)_2]$	32
7	$[Pd(dba)_2]$	35
8	$[Pd(PPh_3)_4]$	50

[a] Reaction conditions: **1a** (0.25 mmol), **2a** (0.25 mmol), a catalyst (10 mol%), H_2O (2.0 equiv), and *t*BuOLi (3.0 equiv) in CH_3CN (3 mL, distilled) for 14 h under N_2. [b] Determined by GC, number in parentheses is isolated yield. [c] PPh_3 (25 mol%) was added.

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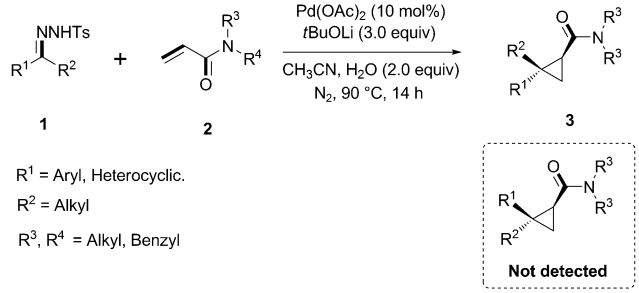
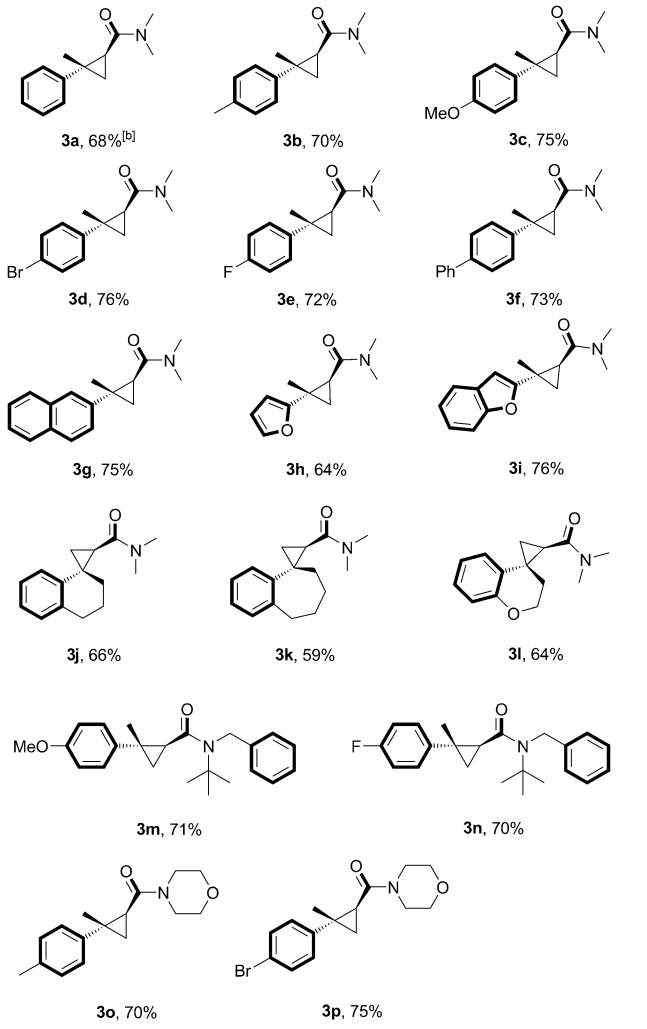
coupling reaction proceeds smoothly with a wide range of substrates to provide moderate to good yields. The cross-coupling reaction of aromatic *N*-tosylhydrazones containing electron-withdrawing or electron-donating groups gave the desired products **3a**–**3f** (Table 2). The naphthyl *N*-tosylhydrazone was also a suitable substrate for this reaction (**3g**). Heterocyclic *N*-tosylhydrazones, such as those based on furan and benzofuran, also reacted smoothly with acrylamide under similar conditions (**3h** and **3i**). Notably, cyclic *N*-tosylhydrazones performed well and gave the corresponding products (**3j**–**3l**) in moderate yield. The steric hindrance of *N*-benzyl-*N*-(*tert*-butyl)acrylamide implied that it would not be a useable substrate; however, it reacted well with substrates containing either electron-withdrawing or -donating groups to give the products **3m** and **3n**. Remarkably, the formation of **3m** was completely stereoselective, and the structure was confirmed by X-ray diffraction (Scheme 2). An acrylamide substrate containing a morpholine fragment was also found to be a reasonable coupling partner (**3o** and **3p**). Encouraged by these initial findings, the α,β-unsaturated ketones were examined to provide a more extensive scope of the electron-deficient terminal alkenes that suit this strategy. The coupling reactions between *N*-tosylhydrazones and the ketones proceeded effectively and a series of chain products, shown in Table 3, were obtained. The reaction was not significantly affected by the substituents on the aromatic ring of the *N*-tosylhydrazones. Electron-donating and -withdrawing groups were tolerated under the reaction conditions (**5a**–**5d**). Naphthyl, cyclic, and heterocyclic *N*-tosylhydrazones also underwent smooth reactions to afford the corresponding products (**5e**–**5g**) in good yields. The ketone substrate containing a long aliphatic carbon chain was also a good coupling partner (**5h**). The reactions of both alkyl- and aryl-substituted *N*-tosylhydrazones were performed in a highly stereoselective manner to produce compounds **5i** and **5j**; however, the reaction results were more complicated when other aryl-substituted ketone substrates were treated.[11] In these cases, yields were low or only trace amounts were obtained, and mixtures of chain and cyclopropane product were detected.

To determine how water promotes this cross-coupling reaction, two deuterium-labeling experiments were carried out (Scheme 3). Under the optimized conditions, 2.0 equivalents of D_2O were added to the reaction instead of H_2O (Scheme 3, a). Similarly, the deuterated substrate [D_3]-**1a** was reacted with **2a** (Scheme 3, b). The results suggest that the cyclopropane products might not directly originate from a metallacyclobutane intermediate.[11]

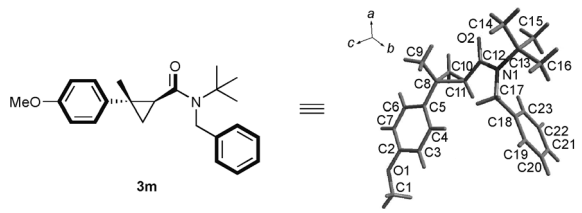
The desired chain or cyclopropane product was not detected when the *N*-tosylhydrazone derived from benzaldehyde (**6a**) was subjected to reactions with the functionalized terminal alkenes (Scheme 4), indicating that the *β*-hydrogen atoms may participate in the reaction processes. Although

Table 2. Palladium-catalyzed cross-coupling of various *N*-tosylhydrazones and acrylamides.[a]



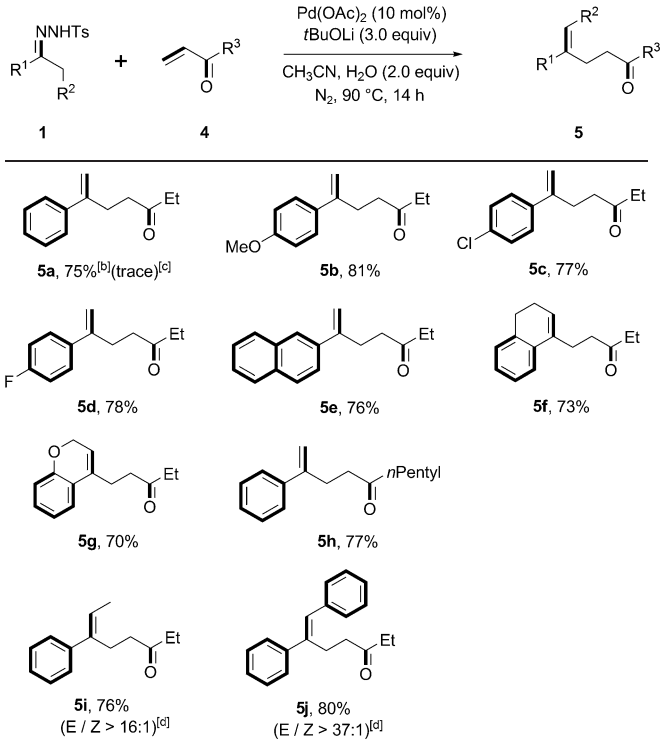


[a] Reaction conditions: **1** (0.25 mmol), **2** (0.25 mmol), $Pd(OAc)_2$ (10 mol%), H_2O (2.0 equiv), and *t*BuOLi (3.0 equiv) in CH_3CN (3 mL, distilled) for 14 h under N_2. [b] Isolated yield.



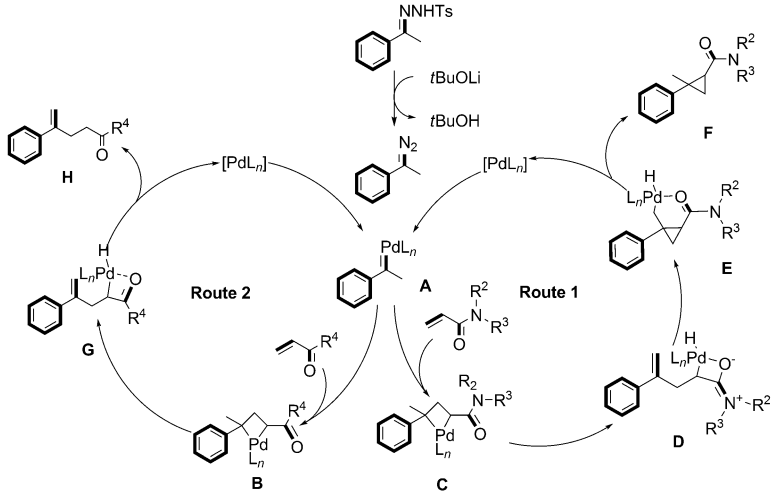
Scheme 2. X-ray crystal structure of **3m**.

Table 3. Palladium-catalyzed cross-coupling of various *N*-tosylhydrazones and ketones.[a]

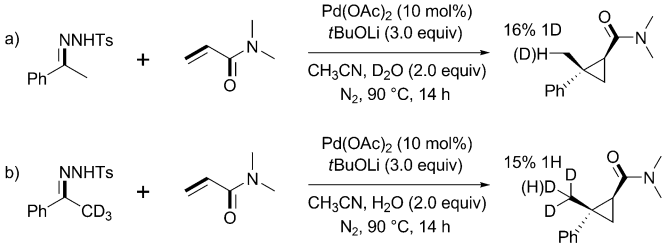


[a] Reaction conditions: **1** (0.25 mmol), **4** (0.35 mmol), $Pd(OAc)_2$ (10 mol%), H_2O (2.0 equiv), and *t*BuOLi (3.0 equiv) in CH_3CN (3 mL, distilled) for 14 h under N_2. [b] Isolated yield. [c] No water was added. [d] The *E*/*Z* selectivity was determined by ^1H NMR spectroscopy.

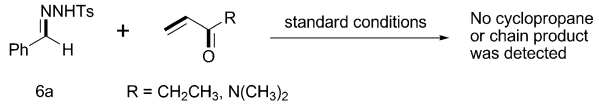
the desired cyclopropane products were not synthesized when ketones were applied, this result would be helpful for understanding the mechanism of this reaction system. A feasible mechanism derived from the acquired results was conceived (Scheme 5).



Scheme 5. Proposed reaction mechanism.



Scheme 3. Deuterium-labeling experiments.

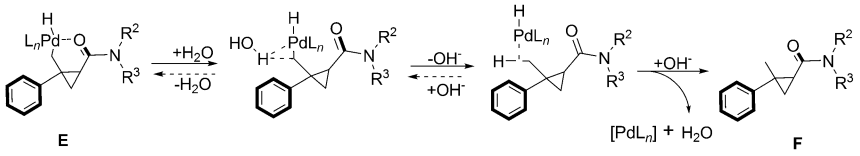


Scheme 4. Control experiments.

Decomposition of the diazo compound, which is generated in situ from *N*-tosylhydrazone in the presence of base, by a palladium catalyst leads to the palladium–carbene **A**.[4] Cycloaddition of carbene **A** to an electron-deficient terminal alkene affords a metallacyclobutane intermediate, **B** or **C**. Intermediate **D** would be produced from **C** by a β-hydrogen elimination process (Scheme 5, route 1).[12] The second β-hydrogen elimination might be suppressed by a stronger coordination effect resulting from resonance isomerization.[13] Amide intermediates **D** then undergo an alkene insertion to give cyclopropane structures.[14] A conceivable steric state (**E**) may be responsible for the complete stereoselectivity of the reaction. Considering the deuterium-labeling experiments (Scheme 2), reductive elimination and protonolysis[15] are expected to work together to finish the last procedure and form compound **F** (Scheme 6).

The weaker coordination effect of the ketone intermediates **G** is likely to make an alkene insertion unachievable, instead leading to chain products **H** (Scheme 5, route 2).[16] Probably, the water acts as an additional proton source and ligand to restrain the β-hydrogen elimination process.[17]

In conclusion, we have uncovered an alternative protocol for the Pd-catalyzed intermolecular cross-coupling reaction of electron-deficient terminal alkenes and *N*-tosylhydrazones. Notably, the presence of water substantially promotes both cascade reaction routes, by which diverse C–C bonds could be created as a result of variations in the the electron-withdrawing group of the alkenes. Further mechanistic studies and the application of this strategy to the selective synthesis of C–C bonds, de-



Scheme 6. Water-promoted protonolysis procedure.

pending on the electronic nature of substrates, are currently under investigation.

Experimental Section

General procedure for the reaction of *N*-tosylhydrazone (1a) and *N*,*N*-dimethylacrylamide (2a): $Pd(OAc)_2$ (5.6 mg, 0.025 mmol), CH_3CN (3 mL), *N*-tosylhydrazone (72 mg, 0.25 mmol), *N*,*N*-dimethylacrylamide (25 mg, 0.25 mmol), water (9 mg, 0.5 mmol), and *t*BuOLi (60 mg, 0.75 mmol) were added successively to a Schlenk tube. After stirring for 14 h at 90 °C under a nitrogen atmosphere, the mixture was cooled to room temperature. Ethyl acetate and brine were added sequentially and the layers were separated. The aqueous phase was extracted twice with ethyl acetate. The combined organic layers were purified by flash column chromatography on silica gel by using light petroleum ether/ethyl acetate (2:1, v/v) as the eluent, which furnished the desired product **3a** as a yellow oil (35 mg, 68%). IR (KBr): $\tilde{\nu}_{max}$ = 3061, 2927, 1643, 1505, 1457, 1387, 697 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.27–7.32 (m, 4H), 7.19–7.23 (m, 1H), 3.10 (s, 3H), 3.02 (s, 3H), 1.99 (dd, J = 8.3, 6.0 Hz, 1H), 1.58 (dd, J = 5.8, 4.9 Hz, 1H), 1.41 (s, 3H), 1.38 ppm (dd, J = 8.4, 4.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.37, 145.80, 128.53, 126.12, 37.49, 35.63, 29.68, 27.59, 19.46, 19.09 ppm; HRMS (ESI): *m*/*z* calcd for $C_{13}H_{17}NO$: 204.1383 [M+H^+]; found: 204.1388.

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Keywords: alkenes · domino reactions · cyclopropanes · electron-deficient compounds · *N*-tosylhydrazones · palladium

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Cross-Coupling Reactions

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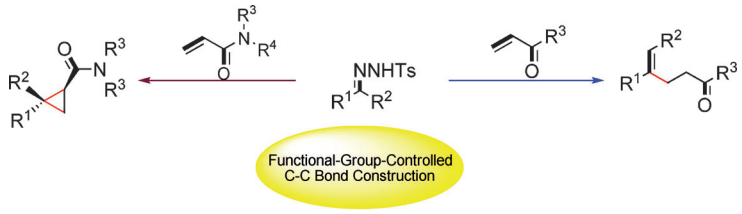
Palladium-Catalyzed Cross-Coupling Reactions of Electron-Deficient Alkenes with *N*-Tosylhydrazones: Functional-Group-Controlled C–C Bond Construction



In the zone: A palladium-catalyzed cross-coupling reaction of electron-deficient alkenes with *N*-tosylhydrazones, which affords diverse C–C bonds resulting from the functional-group-controlled effect, is reported (see scheme). These cascade transformations present remarkable stereoselectivity and a high synthetic potential. The presence of water substantially promotes both reaction routes.