Multi-component Reactions

Palladium-Catalyzed Cascade Reactions of α-Halo-N-Tosylhydrazones, Indoles, and Aryl Iodides

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Abstract: α-Halo-N-tosylhydrazones are explored as reagents for the multiple carbon–carbon bond formations in palladium-catalyzed three-component reactions. A strategy has been designed for this transformation by using a nucleophile to react with the azoalkene intermediate formed in situ from the α-halo-N-tosylhydrazone to generate the diazo intermediate, which is further subjected to palladium-catalyzed C—C bond forming reactions with aryl iodides.
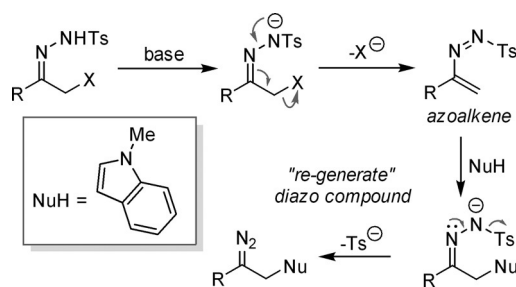
Scheme 1. Generation of the diazo intermediate from α-halo N-tosylhydrazone.

N-Tosylhydrazones, which are easily prepared by condensation of aldehydes or ketones with N-tosylhydrazide, have been widely utilized in recent years as reliable precursors for the in situ generation of diazo compounds (Bamford–Stevens reaction).[1] This method is particularly valuable for access to non-stabilized diazo compounds, which lack the stabilization from electron-withdrawing substituents.[2] In general, under basic conditions, the N-tosylhydrazone moiety is first smoothly converted into a diazo group, which is subsequently applied to various transformations in situ.[2, 3] However, azoalkenes will be formed instead of the diazo compounds in the presence of base when the N-tosylhydrazones derived from α-halo-ketones or α-halo-aldehydes are employed (Scheme 1). This transformation has been explored as an efficient access to azoalkenes, which have aroused considerable attention as reactive intermediates for the synthesis of various heterocyclic compounds through [4+1], [4+2], and [4+3] annulations in recent years.[4]

Notably, the azoalkenes formed in situ from α-halo-N-tosylhydrazones are highly susceptible to conjugate additions. So, the diazo compound could be generated by introducing a nucleophile through the process shown in Scheme 1. With this strategy, we reported the transition-metal-free cascade reaction of α-halo-N-tosylhydrazones, indoles, and arylboronic acids recently.[5] It indicates that the α-halo-N-tosylhydrazone is a powerful tool for multiple bond formations. As a continuation of our interest in carbene-based couplings as well as in developing multi-component reactions,[5, 6] we report herein the cascade reaction using indole as the nucleophile to regenerate the diazo intermediate from α-halo-N-tosylhydrazone, which is further used to undergo the following transformations: 1) Pd-catalyzed reaction with aryl iodides; 2) Cu[I]-catalyzed 1,2-H shift reactions (Scheme 2).
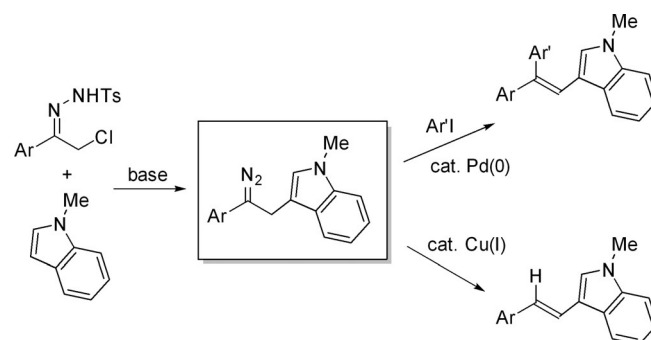
Scheme 2. Transformations through the diazo intermediate with palladium and copper catalysts.

We initiated our study with α-halo-N-tosylhydrazone **1a**, N-methyl indole **2a** (as the nucleophile), and phenyl iodide **3a** to optimize the reaction conditions. To our delight, with the Pd(OAc)$_2$/PPh$_3$ catalytic system, the three-component reaction worked to give the desired product in 15% isolated yield at 100°C in toluene with K$_2$CO$_3$ as base (Table 1, entry 1). Encour-

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Table 1. Optimization of the three-component reaction.[a]

Entry	Base	Solvent	Additive	Yield [%][b]
1	K_2CO_3	PhMe	–	15
2	Cs_2CO_3	PhMe	–	21
3	Na_2CO_3	PhMe	–	trace
4	LiO*t*Bu	PhMe	–	no reaction
5	Cs_2CO_3	PhMe	H_2O (50 µL)	28
6	Cs_2CO_3	dioxane	H_2O (50 µL)	24
7	Cs_2CO_3	MeCN	H_2O (50 µL)	17
8	Cs_2CO_3	PhMe	H_2O (50 µL)	20
9	Cs_2CO_3	PhMe	*i*PrOH (50 µL)	38
10	Cs_2CO_3	PhMe	*i*PrOH (100 µL)	34

[a] Reaction conditions: **1a** (0.1 mmol), **2a** (0.1 mmol), **3a** (0.1 mmol), base (0.2 mmol), 4 h. [b] Isolated yield.

Table 2. Optimization of the three-component reaction.[a]

Entry	Pd (mmol%)	Ligand	Ratio (**1a**/**3a**/**2a**)	Yield [%][b]
1	Pd(OAc)$_2$ (5)	dppf	1:1:1	43
2	Pd(OAc)$_2$ (5)	Xphos	1:1:1	11
3	Pd(OAc)$_2$ (5)	P(2-furyl)$_3$	1:1:1	32
4	Pd(OAc)$_2$ (5)	P(o-tol)$_3$	1:1:1	36
5	Pd(OAc)$_2$ (5)	L[c]	1:1:1	37
6	Pd(PPh$_3$)$_2$Cl$_2$ (5)	dppf	1:1:1	32
7	Pd(MeCN)$_2$Cl$_2$ (5)	dppf	1:1:1	32
8	Pd(PPh$_3$)$_2$OAc$_2$ (5)	dppf	1:1:1	32
9	Pd$_2$(dba)$_3$ (2.5)	dppf	1:1:1	no reaction
10	Pd(OAc)$_2$ (10)	dppf	1:1:1	50
11	Pd(OAc)$_2$ (10)	dppf	1.5:1.5:1	64
12	Pd(OAc)$_2$ (10)	dppf	1.2:1.5:1	60
13	Pd(OAc)$_2$ (10)	dppf	1.7:1.5:1	68
14	Pd(OAc)$_2$ (10)	dppf	1.7:1.5:1	74[d]
15	Pd(OAc)$_2$ (5)	dppf	1.7:1.5:1	56

[a] Reaction conditions: **2a** (0.3 mmol), base (2 equiv of **1a**), [P]/[Pd] = 2:1. [b] Isolated yield. [c] L = P[(3,5-bis(trifluoromethyl)phenyl)]$_3$. [d] With 100 mg of 4 Å MS.

aged by this result, we proceeded to further optimize the reaction conditions. First, the effect of base was examined. The yield was slightly increased with Cs_2CO_3, whereas nearly no product was observed with Na_2CO_3 and LiO*t*Bu (entries 2–4). Water as an additive was found to slightly improve the reaction, giving 28% yield (entry 5). Under similar reaction conditions, the effect of solvents was then examined. The reactions with dioxane, MeCN, and dichloroethene (DCE) as the solvent all gave the desired product, but with diminished yields (entries 6–8). We found that *i*PrOH facilitated the reaction and best result was obtained with 50 µL *i*PrOH as an additive (entries 9–10).
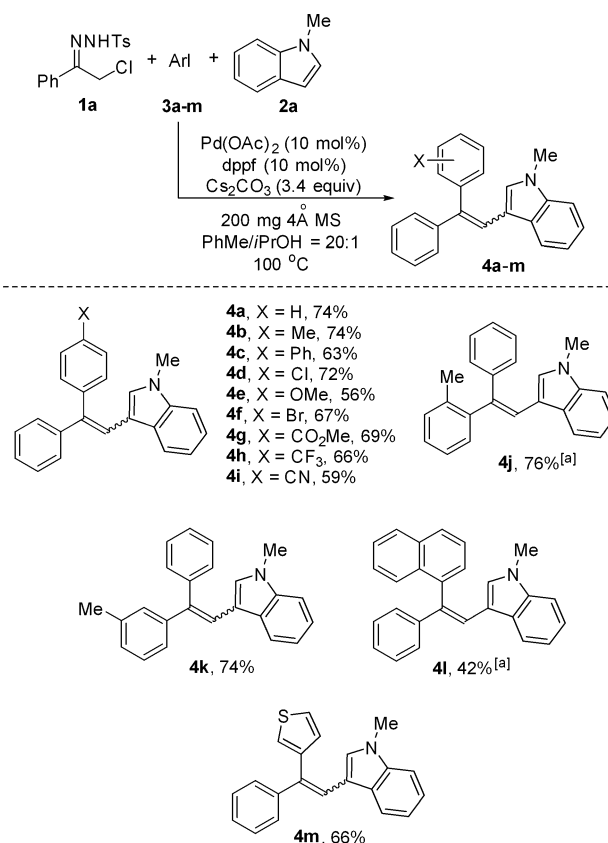
With these results, various palladium catalysts and ligands were examined for further reaction conditions optimization. As summarized in Table 2, the 1,1′-bis(diphenylphosphino)ferrocene (dppf) ligand turned out to be the most effective, giving 43% yield; other tri-aryl phosphine ligands gave similar results as PPh$_3$, and although Xphos was the best ligand in previous works,[7] it resulted in diminished yields in the current reaction (entries 1–5). Next, a survey of other palladium catalysts indicated that the Pd^{II} catalysts, such as Pd(PPh$_3$)$_2$Cl$_2$, Pd(MeCN)$_2$Cl$_2$, and Pd(PPh$_3$)$_2$OAc$_2$, all gave decreased yields and no product was obtained when using Pd$_2$(dba)$_3$ (entries 6–9). Further improvement was achieved by increasing the catalyst loading, and the yield could be improved to 50% with 10 mol% of Pd(OAc)$_2$ (entry 10). Finally, after a judicious screening of the ratio of the reactants and additives, a satisfactory result of 74% yield was given with 4 Å molecular sieves (MS) as an extra additive (entries 11–14). Under these reaction conditions, we also tried to reduce the catalyst loading, but the yield was slightly diminished (entry 15).

With the optimized experimental conditions in hand, we next proceeded to examine the substrate scope. First, various aryl iodides were submitted to the palladium-catalyzed three-component coupling reaction (Scheme 3). It was observed that aryl iodides bearing different substituents on the aromatic ring afforded the corresponding compounds **4a–l** in 42–76%

Scheme 3. Palladium-catalyzed three-component reaction with various aryl iodides. Reaction conditions: **1a** (0.51 mmol), **2a** (0.3 mmol), **3a–m** (0.45 mmol), Cs_2CO_3 (1.02 mmol), Pd(OAc)$_2$ (0.03 mmol), dppf (0.03 mmol) in 3 mL PhMe/*i*PrOH (20:1) at 100 °C for 4 h. Except for the cases of **4a**, **4j**, **4l**, the product was isolated as an approximate 1:1 mixture of *E/Z* isomers. [a] The *Z* configuration was confirmed according to ref. [2a].

yields. The electronic nature and the substituents at different positions of the aromatic ring did not show any significant effect on the reaction. For instance, the reaction proceeded smoothly with aryl iodides bearing electron-donating groups at different positions (*para*, *meta*, *ortho*) to afford the corresponding compounds in 74–76% yields (**4b**, **4j**, **4k**). It should be noted that the aryl iodides bearing chloro- or bromo-substituents on the aromatic ring reacted smoothly and gave the products **4d** and **4f** in 72% and 67% yields, respectively, thus providing the opportunity for further transformation with transition-metal catalysis. The aryl iodides containing electron-withdrawing groups, such as ester groups, were also good coupling partners, giving the desired products in moderate yields (**4i**–**k**). Finally, we found that 3-iodothiophene could also be used as a reactant in this coupling process, leading to the desired product **4m** in 66% yield.
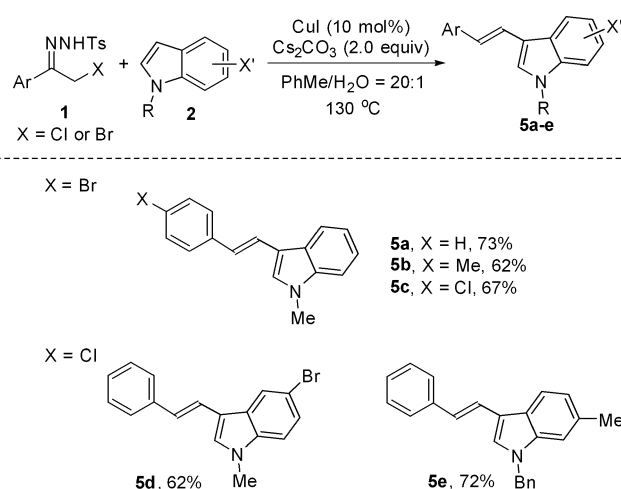
We then evaluated the substrate scope with respect to the α-halo-*N*-tosylhydrazones and indoles; the results are summarized in Scheme 4. Most reactions proceeded smoothly and were complete within four hours to give the products in moderate to good yields (47–89%). The electronic properties and the substitution pattern of the substituents on the aromatic ring of the α-halo-*N*-tosylhydrazones were found to influence the reaction marginally. The cascade reaction proceeded well
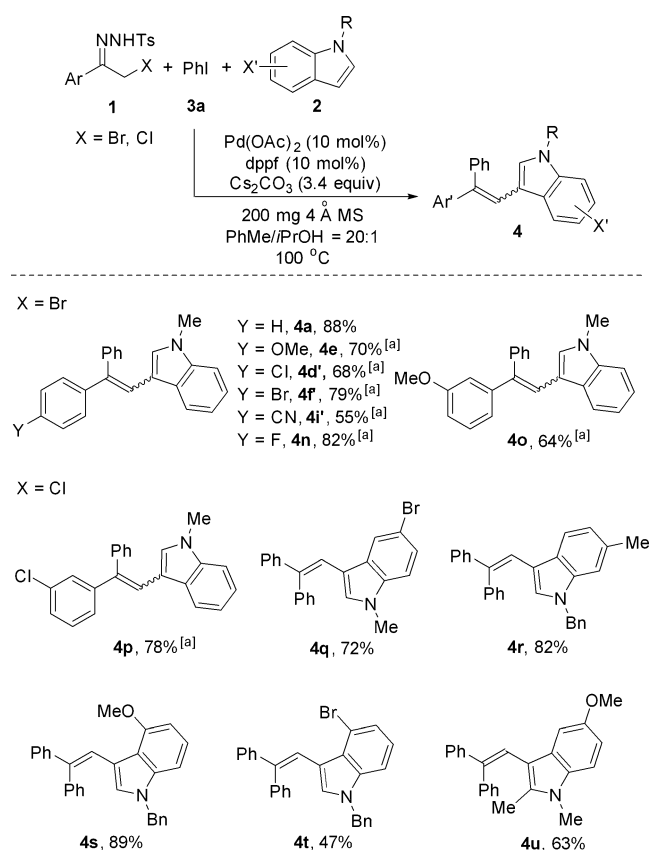
with both electron-donating groups such as methyl and methoxy (**4a**, **4e**) and electron-withdrawing groups (**4f'**–**4i'**). The results indicated that these α-halo-*N*-tosylhydrazones are amenable to the reaction conditions for palladium-catalyzed three-component reactions.

On the other hand, with regard to the scope of indoles, the electronic properties of the substituents on the aromatic ring affect the reactivity of the indoles, which function as the nucleophiles to initiate the reaction. The indole derivatives with methyl and benzyl as the *N*-protected groups proceeded successfully to afford the corresponding products with moderate yields. However, no product was obtained when the indole substrate bearing phenyl as the *N*-protecting group was employed, presumably owing to the decreased electron density of the indole substrate. Compared with **4q**, indoles containing bromine at the C4 position gave **4t** in low yield owing to the decreased electron density. Notably, the steric effect at C2 and C4 of the indole derivatives has little influence on the results, giving products **4u** and **4s** with 63% and 89% yields, respectively. It is also worth mentioning that the bromo- and chloro-substituents are compatible with the current reaction; and the products could be employed for further transformations.

Furthermore, we also explored the 1,2-H shift reaction of the diazo intermediate by using copper(I) iodide as the catalyst. As summarized in Scheme 5, the reaction proceeded smoothly and afforded only *E*-configured olefins with good yields.[8]

Scheme 4. Palladium-catalyzed three-component reactions with α-halo-*N*-tosylhydrazones and indoles. Reaction conditions: **1** (0.51 mmol), **2** (0.3 mmol), **3** (0.45 mmol), Cs_2CO_3 (1.02 mmol), Pd(OAc)$_2$ (0.03 mmol,), dppf (0.03 mmol) in 3 mL PhMe/*i*PrOH (20:1) at 100°C for 4 h. [a] The product was isolated as an approximate 1:1 mixture of *E/Z* isomers.

Scheme 5. Cu^I-catalyzed 1,2-H shift reaction. Reaction conditions: **1** (0.375 mmol), **2a** (0.3 mmol), CuI (0.03 mmol), Cs_2CO_3 (0.6 mmol), in 2 mL PhMe/H_2O (20:1) at 130°C for 4 h.

In summary, by employing the diazo intermediates generated in situ by nucleophilic addition of indoles to the azoalkenes formed from α-halo-*N*-tosylhydrazones, we have developed a procedure for multiple carbon–carbon bond formations through palladium or copper-catalyzed processes. Further studies toward the exploration of α-halo-*N*-tosylhydrazones as diazo precursors for multi-component transformations and synthetic applications are underway in our laboratory.

Experimental Section

General procedure for the palladium-catalyzed reactions

α-Halo-*N*-tosylhydrazones **1** (0.51 mmol), indoles **2** (0.3 mmol), aryl iodides **3** (0.45 mmol), cesium carbonate (1.02 mmol), Pd(OAc)$_2$ (0.03 mmol), 1,1′-bis(diphenylphosphino)ferrocene (0.03 mmol), and 4 Å molecular sieves (200 mg) were added into a Schlenk tube, which was subjected to three vacuum evacuation/nitrogen backfill cycles. Then, toluene (3 mL) and isopropanol (150 μL) were added into the mixture. The mixture was stirred at 100 °C in an oil bath. After 4 h, the mixture was cooled to room temperature, and the solvent was removed in vacuo to leave the crude product, which was purified by column chromatography on silica gel to afford the product.

General procedure for the copper-catalyzed 1,2-H shift

α-Halo-*N*-tosylhydrazones **1** (0.375 mmol), indoles **2** (0.3 mmol), copper iodide (0.03 mmol), and cesium carbonate (0.6 mmol) were added into a Schlenk tube, which was subjected to three vacuum evacuation/nitrogen backfill cycles. Then, toluene (2 mL) and water (100 μL) were added into the mixture. The mixture was stirred at 130 °C for 4 h. After the mixture was cooled to room temperature, the solvent was removed to leave the crude product, which was purified by column chromatography on silica gel to afford the product **5**.

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