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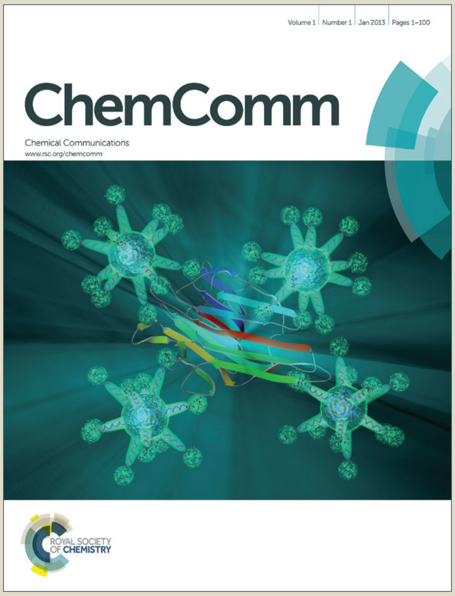

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ARTICLE TYPE

Palladium-catalyzed three-component reaction of *N*-tosyl hydrazones, isonitriles and amines leading to amidines†

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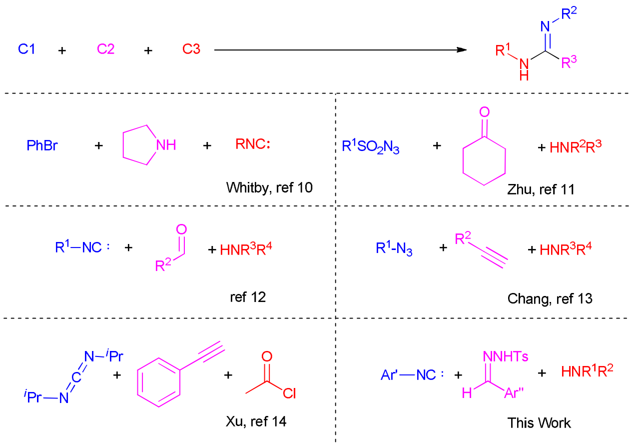
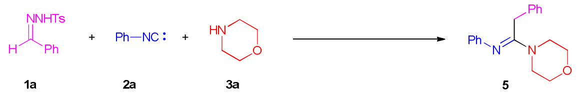
A palladium-catalyzed three-component reaction between *N*-tosyl hydrazone, aryl isonitrile and amine was developed, leading to amidines in moderate to good yields. This procedure features with the rapid construction of amidine framework with high diversity and complexity. Ketenimine serves as intermediate, which encounters a nucleophilic attack by amine to produce amidines.

Amidines are ubiquitous in bioactive natural products,[1] pharmaceutical compounds,[2] synthetic intermediates,[3] neonicotinoid insecticides,[4] and ligands in coordinate chemistry.[5] Moreover, they serve as super base[6] and nucleophilic catalysts[7] in organic synthesis. However, except some recent developed methods catalyzed by transition metal,[8] the traditional pathways towards amidines were limited to the transformation of the simple precursors such as amides, nitriles and oximes.[9] The increasing demand on the diversity and complexity spurred the chemist to develop the MCRs leading to amidine (Scheme 1). Whitby reported the combination of ArBr, isonitrile and amine were efficient to construct amidine frameworks.[10] Consequently, Zhu developed the reaction between amine, cyclic ketone and fluoroalkanesulfonyl azide leading to such a structure.[11] The MCRs between isonitrile, amine and aldehyde was well developed towards α-amino amidines.[12] Recently, Chang demonstrated the copper-catalyzed MCRs of azide, alkyne and amine towards amidine.[13] Very recently, Xu developed the access of amidine between terminal alkyne, acid chloride and carbodiimides.[14] Recently, Cai disclosed that isonitriles can react with Pd-carbenes to form ketenimines, which can be transformed into amides in the presence of water.[15] However, the ketenimine intermediate failed to be trapped with amines in their procedure, which would be a potencially facile pathway leading to amidines. Occasionally, we observed the formation of the *N*-nucleophilic product when using phenyl isonitrile rather than *tert*-butyl isonitrile. This inspired us to further investigate the MCRs between *N*-Ts hydrazone, isonitrile and amine, allowing to rapid access amidine with high diversity and complexity, which was beneficial to combinatorial chemistry.



Scheme 1 MCRs towards amidine

Table 1 Screening the optimized reaction conditions[a,]

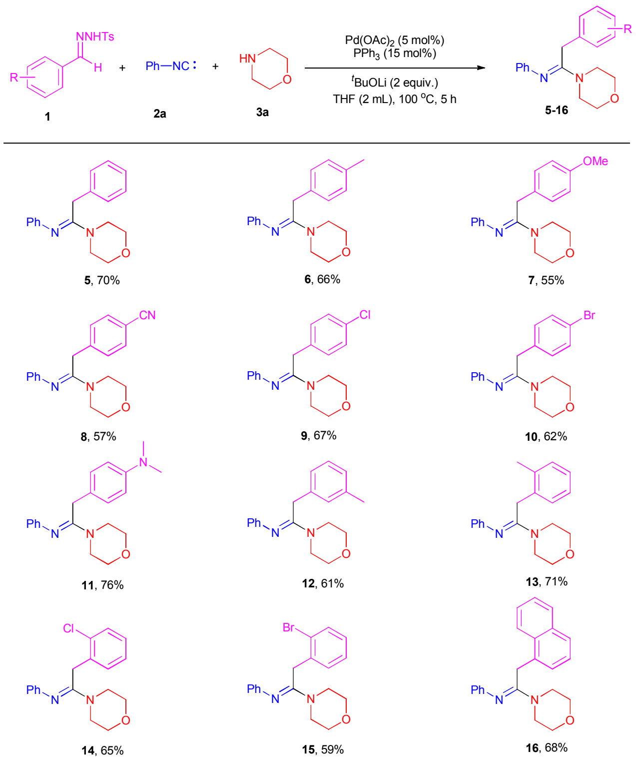


Entry	Cat. (mol%)	Solvent	T (°C)	Yield (%)[b]
1	$PdCl_2(dppf)$	THF	100	49
2	$PdCl_2$	THF	100	68
3	$Pd(OAc)_2$	THF	100	74, 0[c], 63[d]
4	$Pd(PPh_3)_4$	THF	100	61
5	$Pd(OAc)_2$	THF	80	49
6	$Pd(OAc)_2$	THF	120	68
7	$Pd(OAc)_2$	1,4dioxane	100	53
8	$Pd(OAc)_2$	CH_3CN	100	45
9	$Pd(OAc)_2$	acetone	100	66
10	$Pd(OAc)_2$	EA	100	51
11	$Pd(OAc)_2$	THF	100	63[e], 48[f]
12	$Pd(OAc)_2$	THF	100	59[g], 70[h]

[a] Reaction conditions: under air, **1a** (0.3 mmol), **2a** (0.3 mmol), **3a** (0.2 mmol), LiO^tBu (0.4 mmol), indicated palladium (5 mol%), PPh_3 (15 mol%), solvent (2 mL) at the indicated temperature for 5 h in sealed tube. [b] Isolated Yields. [c] Indicated reaction conditions without Pd. [d] Indicated reaction conditions without PPh_3. [e] K_2CO_3 (0.4 mmol). [f] Cs_2CO_3 (0.4 mmol). [g] **1a** (0.2 mmol). [h] **1a** (0.2 mmol), **2a** (0.4 mmol).

We initially test the reaction between benzaldehyde *N*-Ts hydrazone, phenyl isonitrile and morpholine in the presence of PdCl$_2$(dppf), PPh$_3$, and LiO^{t}Bu in THF under air at 100 ^{o}C. To our delight, the amidines was isolated in 49% yield (Table 1, entry 1). Replacing PdCl$_2$(dppf) with PdCl$_2$ slightly increased the yield to 68% (Table 1, entry 2). Among the palladium tested, Pd(OAc)$_2$ was the best (74%, Table 1, entry 3); while Pd(PPh$_3$)$_4$ worked to some extent (61%, Table 1, entry 4). Palladium was essential for this transformation indicated by the blank experiments (Table 1, entry 3). The reaction efficiency decreased at 80 and 120 ^{o}C (Table 1, entries 5 and 6). Some solvents, such as dioxane, acetonitrile, acetone, ethyl acetate were tested but they were all inferior to THF (Table 1, entries 7-10). Switching the base to K$_2$CO$_3$ and Cs$_2$CO$_3$ slightly decreased the reaction efficiency (63% and 48%, Table 1, entry 11). The ratio of the three components had some effect on this transformation (Table 1, entry 12). The configuration of C=N in **5** was confirmed to be *E* by single crystal test (for details, see Supporting Information).[16]

Figure 1 Substrate scope of aldehydic hydrazone

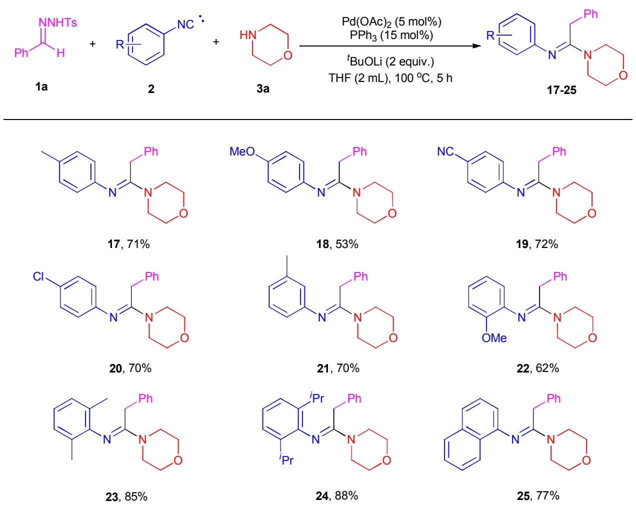


Reaction conditions: under air, **1** (0.2 mmol), **2a** (0.4 mmol), **3a** (0.2 mmol), LiO^{t}Bu (0.4 mmol), Pd(OAc)$_2$ (5 mol%), PPh$_3$ (15 mol%), THF (2 mL), 100 ^{o}C in sealed tube, 5 h.

After the establishment of the reaction conditions, the scope of *N*-Ts hydrazone was tested, as shown in Figure 1. To our delight, the procedure tolerated some functional group, such as bromo, chloro, cyano and *N,N*-dimethylamino, which provided handles for further functionalization. We also tested a variety of *N*-tosylhydrazones, such as alkyl aldehyde, alkenyl aldehyde and ketone analogues, but they didn't work in our system.

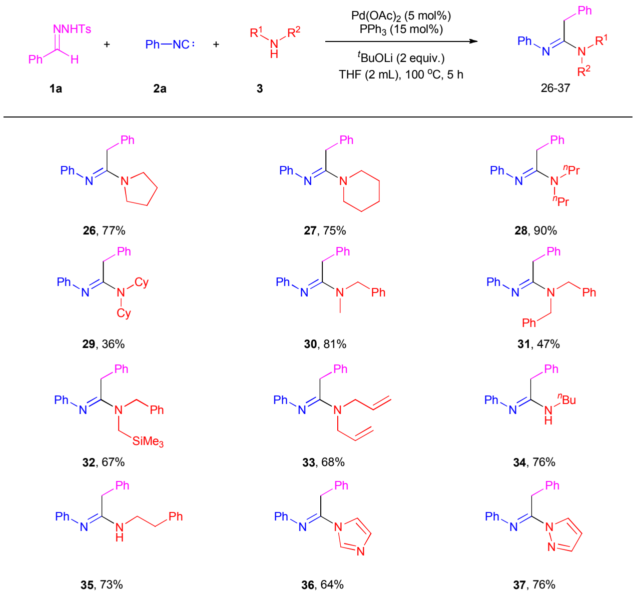
Next, the scope of isonitrile was studied, as shown in Figure 2. As expected, all substrate ran smoothly under the procedure. Notably, the crowded 2,6-disubstitued phenyl isonitrile provided the MCRs product **23** and **24** in excellent yields (85% and 88%). Disappointingly, alkyl isonitriles such as *tert*-butyl isonitrile didn't work in our system.

Figure 2 Substrate scope of isonitriles



Reaction conditions: under air, **1a** (0.2 mmol), **2** (0.4 mmol), **3a** (0.2 mmol), LiO^{t}Bu (0.4 mmol), Pd(OAc)$_2$ (5 mol%), PPh$_3$ (15 mol%), THF (2 mL), 100 ^{o}C in sealed tube, 5 h.

Figure 3 Substrate scope of amine



Reaction conditions: under air, **1a** (0.2 mmol), **2a** (0.4 mmol), **3** (0.2 mmol), LiO^{t}Bu (0.4 mmol), Pd(OAc)$_2$ (5 mol%), PPh$_3$ (15 mol%), THF (2 mL), 100 ^{o}C in sealed tube, 5 h.

Besides the cyclic amines, this procedure was applicable for acyclic aliphatic analogues and hetero aromatic amines. For example, **28**, **30** and **35** were isolated in 90%, 81% and 73% yields, respectively. Notably, hetero aromatic amine produced the

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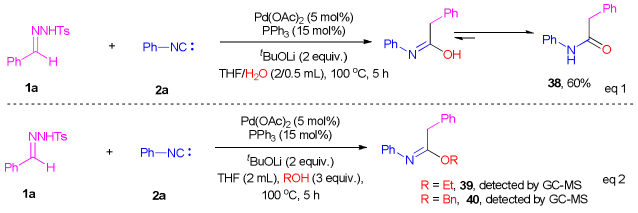
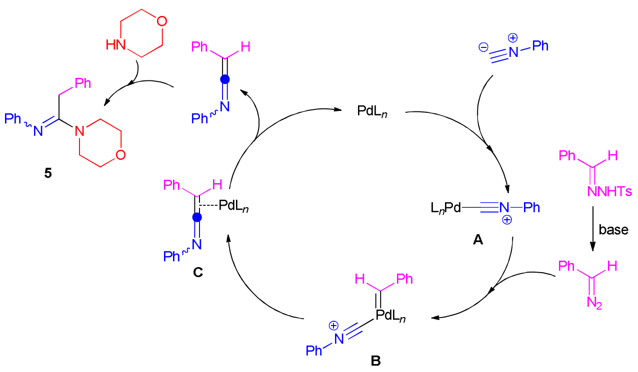
MCRs products **36** and **37** in 64% and 76% yields respectively. However, aniline failed to work under the standard procedure. Particularly, diallyl amine worked well under the procedure, providing **33** in 68% yield. Importantly, the procedure was applicable for primary amine, as butyl amine delivered **34** in 76% yield.

Some experiments were conducted to some insights into the mechanism. Replacing amine with water, product **38** was isolated in 60% yield, which derived from the nucleophilic attack of intermediate by H_2O (Scheme 2, eq 1). This result was consistent with Cai's report.[15] Moreover, the intermediate was captured by EtOH and BnOH, as confirmed by the formation of products **39** and **40** detected by GC-MS (Scheme 2, eq 2). Notably, during the reaction between isonitrile and *N*-Ts hydrazone, a species with molecular weight 193, probably assigned to ketenimine, was detected by GC-MS (For details, see Supporting Information).



Scheme 2 Preliminary mechanism study

Base on the property of isonitrile[15] and reported literatures,[17] similar with Cai's report, a tentative mechanism was outlined in Scheme 3. Firstly, the complex **A** of palladium coordinated with isonitrile was formed. Then, under basic conditions, detosylation took place to form a diazo compound, which reacted with palladium to produce a palladium carbene **B**. After that, the reaction between palladium carbene and isonitrile provided ketenimine intermediate **C** via migratory insertion. Finally, amine attacked ketenimine to produce the final MCRs product amidines.



Scheme 3 Tentative mechanism.

In conclusion, we have developed a palladium-catalyzed MCRs between *N*-tosyl hydrazone, aryl isonitrile and amine, leading to diverse amidines in moderate to excellent yields. The procedure proceeded with ketenimine intermediate derived from the reaction between palladium carbene and isonitrile via migratory insertion.

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Notes and references

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† Electronic supplementary information (ESI) available: Detailed synthetic procedures and characterization of new compounds. See DOI: 10.1039/ b000000x

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