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Metal catalyzed C(sp^3)–H bond amination of 2-alkyl azaarenes with diethyl azodicarboxylate†

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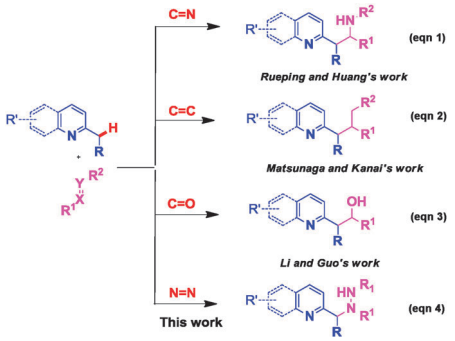
Metal-catalyzed direct C(sp^3)–H bond amination of 2-alkyl azaarenes with N═N double bonds has been developed, which expands the scope of C(sp^3)–H bond activation reactions and provides a new access to medicinally important azaarene derivatives.

Ubiquity of the nitrogen-containing compounds among biologically active molecules continues to drive the development of new C–N bond-forming reactions.[1] Transition-metal-catalyzed direct amination of unactivated C(sp^3)–H bonds without prefunctionalized substrates is a desirable process to construct C–N bonds in organic synthesis.[2,3] Particularly, the addition of 2-alkyl azaarenes to azodicarboxylates is of great importance due to the usefulness of benzylic amines *via* deprotection in pharmaceutical synthesis.[4] Azodicarboxylates are mainly used as an amination reagent for the α-amination of aldehydes or ketones,[5] but there is no report on the metal-catalyzed benzylic C(sp^3)–H amination with azodicarboxylates.

Recently, the direct C(sp^3)–H bond functionalization of 2-alkyl-substituted azaarenes catalyzed by palladium or Lewis acid without an activating group has been developed.[6] For example, Huang and Rueping *et al.* reported the addition of 2-alkyl azaarenes to the C═N double bond of *N*-sulfonyl aldimines[7] (eqn 1, Scheme 1). Matsunaga and Kanai *et al.* reported the direct addition of alkyl-substituted azaarenes to the C═C double bond of enones promoted by Lewis acids[8] (eqn 2, Scheme 1). Li and Guo *et al.* developed Brønsted acid or Lewis acid catalyzed 2-methyl azaarenes addition to the C═O double bond of isatins or aldehyde-ester[9] (eqn 3, Scheme 1). To the best of our knowledge, the addition of 2-alkyl azaarenes to the N═N double bond has not been developed. According to the reported results, we postulated that palladium or copper catalyzed addition of 2-alkyl azaarenes to diethyl azodicarboxylate *via* direct C(sp^3)–H activation might be feasible, which will expand the substrate scope of the direct C(sp^3)–H bond functionalization of 2-alkyl-substituted azaarenes. Herein, we report the successful addition of 2-alkyl azaarenes to the N═N double bond of azodicarboxylates *via* metal-catalyzed benzylic C–H amination.



Scheme 1 C(sp^3)–H bond functionalization with different double bonds containing electrophiles.

In order to test the practicality of our hypothesis, 2-methyl quinoline **1a** and diethyl azodicarboxylate **2a**[10] were initially chosen as model substrates (Table 1). When the reaction was performed in THF at 120 °C under a N_2 atmosphere catalyzed by palladium acetate in the presence of 1,10-phenanthroline in a sealed reaction vessel according to the reported conditions by Huang *et al.*,[7a] the anticipated hydrazide was not observed. Considering that diethyl azodicarboxylate would decompose under high pressure at high temperature with a metal catalyst, the high boiling solvent DMF was used as the solvent to reduce the pressure, and the desired product was given in 43% yield as well as an unexpected diaminated product (entry 1). To enhance the selectivity of the monoamination product, we then screened the influence of the reaction temperature. We were pleased to find that the monoamination product was obtained in 67% isolated yield when the reaction temperature was reduced from 120 °C to 90 °C (entry 3). Further decreasing the reaction temperature to 80 °C led to a lower yield of 53% (entry 4). Then, the effect of solvents was examined. The reaction was found to proceed much better in polar solvents than in nonpolar ones, and DMSO was found to be an optimal selection (entries 10–15). A screening of potential catalysts, including $Cu(OTf)_2$, $Cu(OAc)_2$, CuI, $PdCl_2$ and $Ni(acac)_2{\cdot}2H_2O$, showed that palladium acetate was still to be the most efficient catalyst

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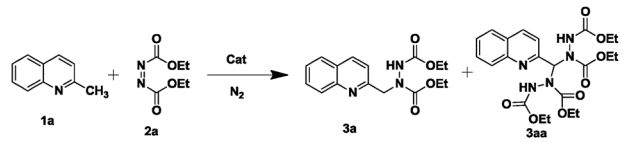
† Electronic supplementary information (ESI) available: Experimental procedures, compound characterizations, and the copies of ^{1}H NMR and ^{13}C NMR spectra. See DOI: 10.1039/c2cc35309a

Table 1 Optimization of the reaction conditions[a]



Entry	Catalyst	Ligand	Solvent	T/°C	Yield[b]/%
1	$Pd(OAc)_2$	1,10-Phenanthroline	DMF	120	43/13[c]
2	$Pd(OAc)_2$	1,10-Phenanthroline	DMF	100	54/8[c]
3	$Pd(OAc)_2$	1,10-Phenanthroline	DMF	90	67[d]
4	$Pd(OAc)_2$	1,10-Phenanthroline	DMF	80	53
5	$PdCl_2$	1,10-Phenanthroline	DMF	90	61
6	$Ni(acac)_2$	None	DMF	90	28
7	$Cu(OTf)_2$	1,10-Phenanthroline	DMF	90	38
8	$Cu(OAc)_2$	1,10-Phenanthroline	DMF	90	30
9	CuI	1,10-Phenanthroline	DMF	90	0
10	$Pd(OAc)_2$	1,10-Phenanthroline	Dioxane	90	58
11	$Pd(OAc)_2$	1,10-Phenanthroline	Toluene	90	13
12	$Pd(OAc)_2$	1,10-Phenanthroline	DCE	90	50
13	$Pd(OAc)_2$	1,10-Phenanthroline	THF	90	17
14	$Pd(OAc)_2$	1,10-Phenanthroline	*i*-PrOH	90	0
15	$Pd(OAc)_2$	1,10-Phenanthroline	DMSO	90	72[d]
16	$Pd(OAc)_2$	DPPP	DMSO	90	63
17	$Pd(OAc)_2$	None	DMSO	90	18

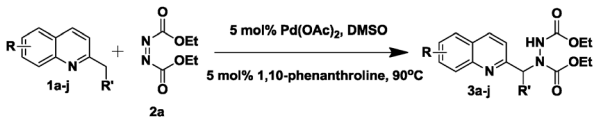
[a] Unless otherwise stated, all reactions were carried out with **1a** (0.75 mmol), **2a** (0.3 mmol), catalyst (5 mol%), ligand (5 mol%), solvent (1.5 mL), 18 h. [b] Yield of **3a** was determined by HPLC. [c] Monoaminated product/diaminated product. [d] Isolated yield of **3a**.

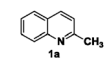
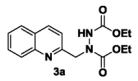
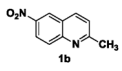
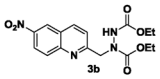
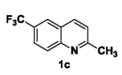
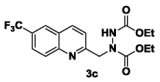
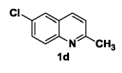
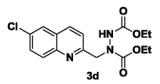
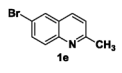
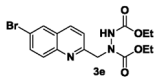
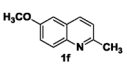
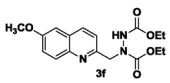
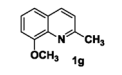
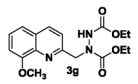
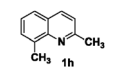
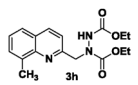
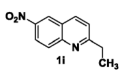
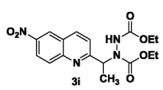
(entries 5–9). And 1,10-phenanthroline was essential to this transformation (entry 17).

With the optimal conditions in hand, the scope of various 2-alkyl quinolines with electron-neutral, electron-donating or electron-withdrawing groups, such as OCH_3, CH_3, NO_2, CF_3, Br or Cl, was examined (Table 2). The results revealed that the reaction was tolerant of a wide variety of functional groups. Obviously, the reaction was greatly affected by the electronic nature of the functional groups. When the H atom at the C6 of quinoline was substituted with electron-withdrawing groups (such as NO_2, CF_3, Br, Cl), the reaction proceeded smoothly and provided the corresponding products in good yields (73–84%, entries 2–5). However, replacement of H by an electron-donating group (OCH_3) at the C6 made the reaction sluggish with 41% yield (entry 6). Then, the influence of the substituents at the C8 position was also investigated. Unfortunately, when the C8 position of the 2-alkyl quinolines was substituted with an electron-withdrawing group such as nitro group (NO_2), no expected product was formed, and the substrates with electron-donating substituents at the C8 gave relatively lower yields (42–48%, entries 7–8). Generally, the C6-substituted 2-methyl quinolines gave higher yields than C8-substituted 2-methyl quinolines, which might be caused by not only electronic effect but also steric interference of the C8 substituents which might affect the coordination of metal catalyst to the nitrogen atom of quinolines. And 2-ethyl-6-nitroquinoline was also examined and 54% yield was obtained (entry 9).

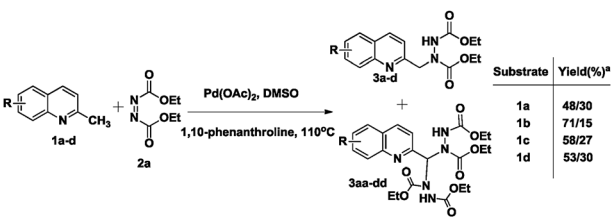
In addition, it was found that the reaction of 2-methyl quinolines (**1a–1d**) also gave the corresponding diamines **3aa–3dd** in moderate to good yields under a relatively simple modification of the optimal conditions (Scheme 2). When the amount of diethyl azodicarboxylate was enhanced to 3.0 equivalents at 110 °C promoted by 10 mol% of $Pd(OAc)_2$ and 10 mol% of

Table 2 Substrate scope of 2-alkyl quinolines[a]



Entry	Substrate	Time/h	Product	Yield[b]/%
1		18		72
2		12		84
3		18		78
4		18		75
5		18		73
6		24		41
7		24		48
8		24		42
9		24		54

[a] Unless otherwise stated, all reactions were carried out with **1a** (0.75 mmol), **2a** (0.3 mmol), $Pd(OAc)_2$ (5 mol%), 1,10-phenanthroline (5 mol%), DMSO (1.5 mL), 90 °C. [b] Isolated yield.

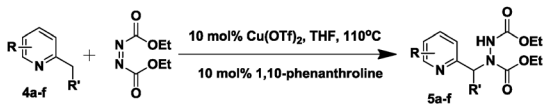


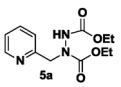
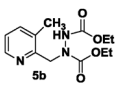
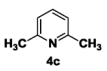
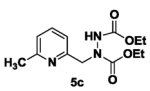
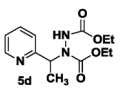
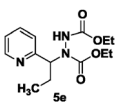
Scheme 2 The palladium-catalyzed diamination reaction.

1,10-phenanthroline, the reaction afforded the diamine products in 48–71% yields (Scheme 2). The successful diamination of 2-methyl quinolines provides a simple access to benzylic diamines which are difficult to obtain by the conventional methods.

Prompted by the successful C(sp^3)–H amination of 2-alkyl-quinolines, we next investigated the scope of the 2-alkyl pyridines. The optimal conditions for quinolines were not applicable to 2-alkyl pyridines due to their different properties. Then we made a modification of the reaction conditions, and relatively satisfactory yields (45–63%) were obtained at 110 °C within 12 h by using 10 mol% of $Cu(OTf)_2$ as the catalyst and 10 mol% of 1,10-phenanthroline as the ligand (entries 2–5, Table 3).

Table 3 Substrate scope of 2-alkyl pyridines[a]



Entry	Substrate	Product	Yield[b] (%)
1			63[c]
2			54
3			58
4			51
5			45

[a] Unless otherwise stated, all reactions were carried out with **4b–f** (0.75 mmol), **2a** (0.3 mmol), $Cu(OTf)_2$ (10 mol%), 1,10-phenanthroline (10 mol%), THF (1.5 mL), 110 °C, 12 h. [b] Isolated yield. [c] The reactions were carried out with **4a** (0.75 mmol), **2a** (0.3 mmol), $Pd(OAc)_2$ (5 mol%), 1,10-phenanthroline (5 mol%), DMSO (1.5 mL), 110 °C, 18 h.

2-Methyl pyridine gave the corresponding product in good yield when the reaction was conducted at 110 °C for 18 h in DMSO by using $Pd(OAc)_2$ as the catalyst (entry 1).

In conclusion, we have developed a novel metal-catalyzed benzylic C(sp^3)–H amination of 2-alkyl azaarenes with diethyl dicarboxylates, which expands the substrate scope of the direct C(sp^3)–H bond functionalization of 2-alkyl-substituted azaarenes. The present work is a highly selective and practical methodology for the synthesis of amines and alkyl hydrazides. More detailed mechanistic studies and applications of this method in the synthesis of heterocyclic compounds are underway.

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