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Palladium-Catalyzed Cross-Coupling Reaction of Azides with Isocyanides

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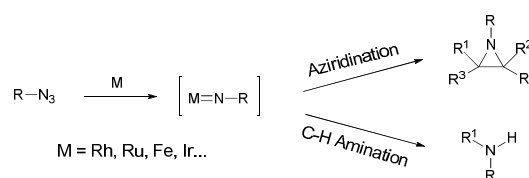
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An efficient palladium-catalyzed cross-coupling reaction of azides with isocyanides is developed, providing a general synthetic route to unsymmetric carbodiimides with excellent yields. This method shows broad substrate scope, including not only aryl azides, but also unactivated benzyl and alkyl azides. Furthermore, from readily available substrates, Pd-catalyzed coupling with tandem amine insertion cascade to obtain unsymmetric trisubstituted guanidines has been achieved in a one-pot fashion.

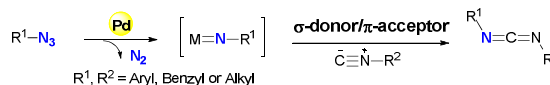
With the rapid development of nitrene chemistry, organic azides, as convenient amino sources and efficient nitrene precursors, have been explored for C-N bond formations.¹ Conventional transformations involve C-H amination and aziridination, which are usually catalyzed by Rh², Ru³, Fe⁴, Ir⁵, etc⁶ (Scheme 1). However, though acting as the stable and common catalysts for various cross-coupling reactions, palladium complexes have seldom been used in nitrene transformations.⁷ On the other hand, Pd-catalyzed coupling reaction of carbene/nitrene precursors with σ -donor/ π -acceptor ligands is an efficient route to active unsaturated intermediates. Although Pd-catalyzed carbene transfer reactions with carbon monoxide⁸, alkynes⁹, and isonitriles¹⁰ to form ketenes, allenes, and ketenimines have been developed, direct Pd-catalyzed nitrene transformation with σ -donor/ π -acceptor ligands has rarely been explored.^{7a,b,e} Thus, we have paid much attention to Pd-catalyzed cross-coupling reaction of azides with isocyanides, which would be a high efficient strategy to access unsymmetric carbodiimides.

Functionalized unsymmetric carbodiimides are one of the most common precursors to multi-substituted guanidines¹¹ and N-containing heterocycles^{11c,12}, which serve as important building blocks for compounds of high utility in pharmaceuticals, agrochemicals and materials chemistry.¹³

Conventional transition metal-catalyzed nitrene transformation:



This work:



Scheme 1 Transition metal-catalyzed nitrene transformation.

Conventional synthetic approaches to unsymmetric carbodiimides¹⁴ mainly involve dehydration of ureas¹⁵, desulfurization of thioureas¹⁶, and aza-Wittig reaction of phosphinimines with isocyanates,¹⁷ which either need specialized substrates or produce much waste. An alternative strategy involving transition-metal-catalyzed oxidative coupling of amines with isocyanides has been studied.¹⁸ However, the requirement of stoichiometric external oxidants limits reaction efficiency and substrate scope. Transition-metal, such as Fe¹⁹, Ni²⁰, Cu²¹, and Co²², catalyzed carbodiimides formation *via* nitrene transformation has also been sporadically documented. For example, Fe(CO)₃ was employed to catalyzed alkyl carbodiimides formation in an early report.^{19a} In recent years, N-heterocyclic carbenes / β -diketiminates stabilized Fe and Ni species catalyzed reactions of azides with isocyanides have also been reported.¹⁹⁻²⁰ Nonetheless, these methods tend to require rigorous experimental environment or suffer from limited the substrate scope due to the instability and sensitivity of metal catalyst bearing bulky or complicated ligands. Herein we report a general and efficient Pd(PPh₃)₄-catalyzed expeditious synthesis of unsymmetric carbodiimides from azides *via* nitrene transfer to isocyanides under redox-free and environmentally friendly conditions (N₂ as the only byproduct). It is worth mentioning that this protocol covers not only common aryl azides, but also

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Table 1 Examination of reaction conditions^a

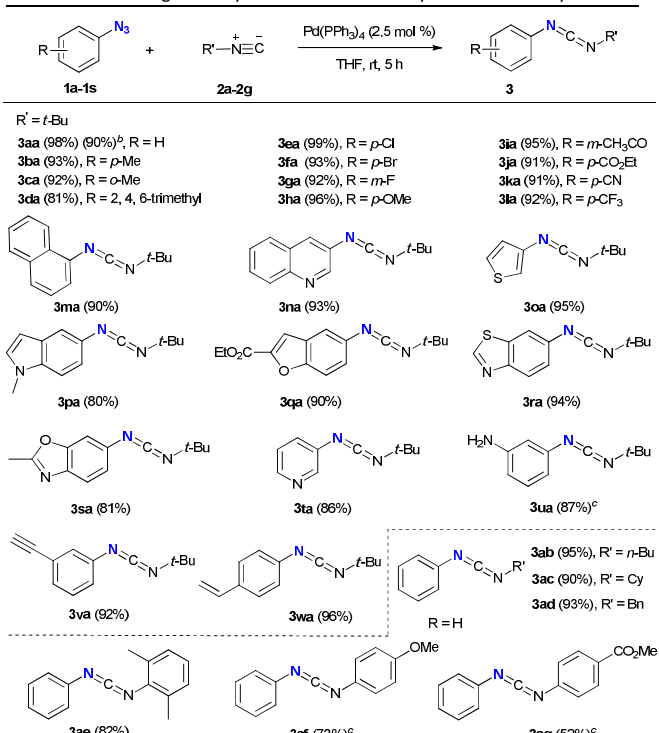
Entry	[Pd] (mol%)	Solvent	<i>t</i> (h)	<i>T</i> (°C)	Yield (%) ^b
1	Pd ₂ (dba) ₃ (2.5)	PhMe	8	50	85
2	Pd(PPh ₃) ₄ (5)	PhMe	5	50	91
3	PdCl ₂ (5)	PhMe	10	50	trace
4	Pd(OAc) ₂ (5)	PhMe	10	50	15
5	Pd(PPh ₃) ₄ (5)	THF	5	rt	99
6	Pd(PPh ₃) ₄ (5)	DCE	14	rt	90
7	Pd(PPh ₃) ₄ (5)	MeCN	14	rt	89
8	----	THF	24	50	0
9	Pd(PPh₃)₄(2.5)	THF	5	rt	98 (90)^c

^a Reaction conditions: **1a** (0.15 mmol), **2a** (0.18 mmol), 2 mL of solvent. ^b Determined by ¹H NMR using mesitylene as internal standard. ^c Isolated yield.

unactivated benzyl and alkyl azides, which remain a challenge in nitrene transformations.²³ In addition, the tandem amine insertion achieved in a one-pot fashion also provides a valuable route to unsymmetric trisubstituted guanidines.

At the outset of our investigation, we selected the model reaction of azidobenzene (**1a**) and 2-isocyano-2-methylpropane (**2a**) as substrates under N₂. To our delight, when the reaction was performed using Pd₂(dba)₃ as catalyst at 50 °C in PhMe, **3aa** was directly obtained in excellent yield. This result encouraged us to screen diverse Pd catalysts. Consequently, comparison experiments were implemented between Pd(II) and Pd(0) for their efficiency, showing the superior activity of Pd(0) complex (Table 1, entries 3 and 4). In further explorations, we examined various solvents. When reactions were carried out in DCE and MeCN, comparable yields were obtained (90% and 89%, respectively, Table 1, entries 6 and 7); almost equivalent yield was obtained when the experiment was carried out in THF by using Pd(PPh₃)₄ as catalyst, even at ambient temperature for 5 h (Table 1, entry 5). Finally, the catalyst loading was reduced to 2.5 mol%, which provided 98% NMR yield and 90% isolated yield (Table 1, entry 9). Notably, the expected product couldn't be accessed in the absence of Pd catalysts (Table 1, entry 8).

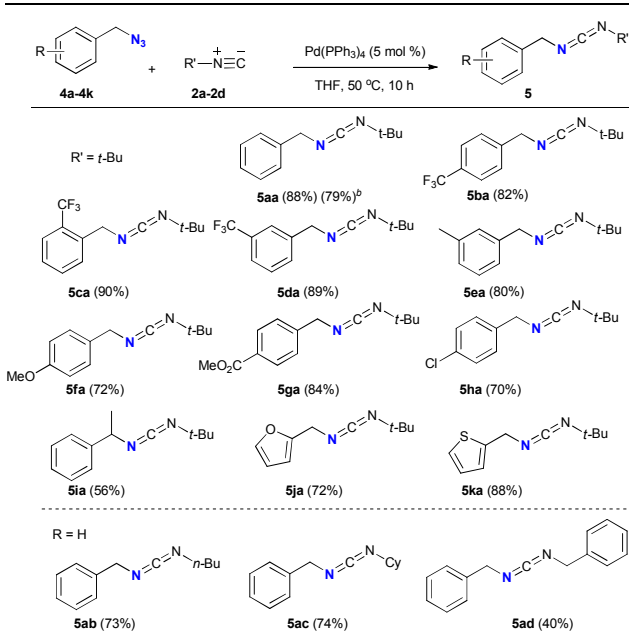
Under the optimized reaction conditions described above, an array of functionalized aryl azides and isocyanides were subjected to this reaction in order to investigate the substrate scope (Table 2). Generally, the transformation of substrates bearing electron-donating groups resulted in good yields, albeit slightly decreased due to steric hindrance of **1d**. Substrates containing strongly electron-withdrawing groups such as COMe, CO₂Me (while direct CO₂H was not succeeded), CN and CF₃ groups in **1i–l** are also compatible. In addition, halogen, amino, alkenyl and alkynyl substituents were well-tolerated on the aromatic ring (**3ea–3ga**, **3ua–3wa**), thus offering a handle for further synthetic transformations. Importantly, reactions of azide-substituted naphthalene and a

Table 2 Substrate generality of the reactions of aryl azides and isocyanides.^a

^a Reaction conditions: **1** (0.2 mmol), **2** (0.24 mmol), 2.5 mol% Pd(PPh₃)₄, 2 mL of THF, rt, 5 h. Yields were determined by ¹H NMR using mesitylene as internal standard. ^b Isolated yield. ^c 40 °C for 12 h, 5 mol% Pd(PPh₃)₄.

wide range of heterocycles, including thiophene, pyridine, quinoline, indole, etc., proceed smoothly to give the corresponding products in high yields (**3ma–3ta**). For further inspection of the reaction, the scope of isocyanides was then examined in the transformation with phenyl azide. 1-Isocyanobutane, isocyanocyclohexane and (isocyanomethyl)-benzene worked equally well (**3ab–3ad**). Regarding different aryl isocyanides, *N,N'*-diarylsubstituted carbodiimides were obtained in moderate to good yields.

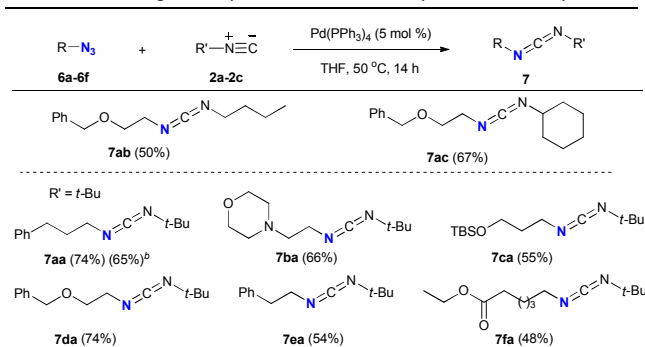
Although we have presented broad substrate generality of aryl azides with a high level of functional group tolerance, further applications of this method in organic synthesis require even broader generality. The installation of benzyl- and alkyl-substituted imino groups was envisioned to be highly desirable. Compared with aryl azides, benzyl and alkyl azides demonstrated poorer reactivity.²³ However, the reaction could furnish the desired carbodiimides in acceptable to high yields, when properly prolonging reaction time to 10 h and increasing the loading of Pd(PPh₃)₄ to 5 mol% and the reaction temperature to 50 °C.²⁴ Encouraged by this result, the scope of benzyl azides was subsequently investigated (Table 3). To our delight, the anticipated products were obtained in high yields when a trifluoromethyl group was substituted at the 2-, 3- or 4-position of the arene moiety. Reactions of benzyl azides bearing both electron-donating substituents (Me, OMe), and electron-withdrawing substituents (CO₂Me) or halogens on the aryl ring afforded the desired products (**5ea–5ha**), respectively, in good yields (80%, 72%, 84%, 70%). More

Table 3 Substrate generality of the reactions of ArCH(R)N₃ and isocyanides.^a

^a Reaction conditions: **4** (0.2 mmol), **2** (0.24 mmol), 5 mol% Pd(PPh₃)₄, 2 mL of THF, 50 °C, 10 h. Yields were determined by ¹HNMR using mesitylene as internal standard. ^b Isolated yield.

importantly, substrates containing heterocycles and other alkyl isocyanides were found to be compatible with this protocol. However, presumably owing to steric effect and weak reactivity of benzyl isocyanides, the carbodiimides **5ia** and **5ad** were obtained in moderate yields.

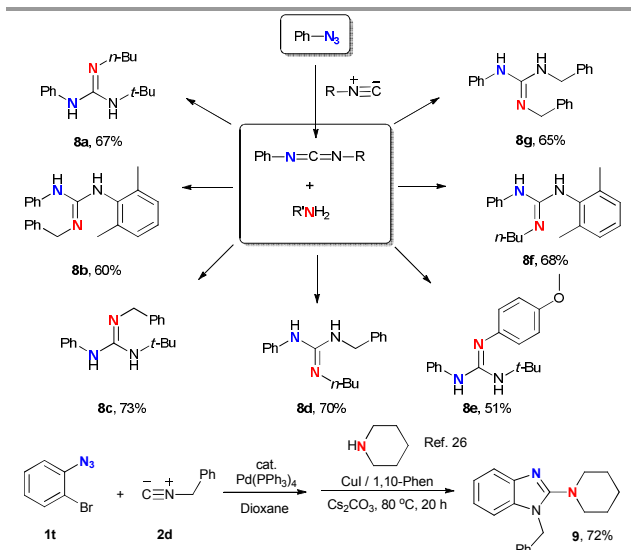
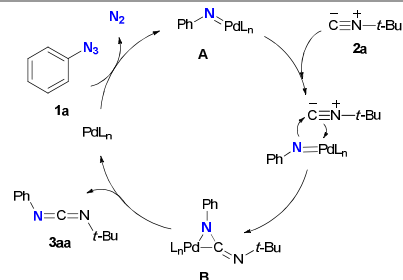
Having successfully surveyed aryl and benzyl azides, we considered expanding the methodology to aliphatic azides. As shown in Table 4, the reaction could be carried out with a series of substituted aliphatic azides, affording the corresponding primary, secondary, and tertiary alkyl substituted unsymmetric carbodiimides in moderate to good yields. Even more, some special functional groups like morpholine and TBS moiety were well-tolerated. Besides, the transformation of 1-isocyanobutane and isocyanocyclohexane (**7ab**, **7ac**) proceed smoothly in 50%, 67% yield, respectively.

Table 4 Substrate generality of the reactions of alkyl azides and isocyanides.^a

^a Reaction conditions: **6** (0.2 mmol), **2** (0.26 mmol), 5 mol% Pd(PPh₃)₄, 2 mL of THF, 50 °C, 14 h. Yields were determined by ¹HNMR using mesitylene as internal standard. ^b Isolated yield.

As mentioned above, unsymmetric carbodiimide is an important partner in a two-component synthetic route to guanidines. Although a large body of works have been published for the preparation of the guanidine scaffold,^{9,23} the discovery of a facile method to synthesize unsymmetric *N,N,N'*-trisubstituted guanidines from simple and available substrates through concise and convenient steps is still needed. In the following investigation, we successfully implemented a one-pot Pd-catalyzed three-component reaction of azides, isocyanides and amines (Scheme 2). Generally, phenyl azide as well as different substituted isocyanides (**2a**, **2d**, **2e**) were selected to give desired unsymmetric carbodiimides. Then, diverse amines as another nitrogen source were added for the next transformation at 90 °C for another 18 h. Interestingly, a diversity of symmetric and unsymmetric *N,N',N''*-trisubstituted guanidines were obtained in 51%-73% overall yields from the one-pot synthesis. Furthermore, when 1-azido-2-bromobenzene (**1t**) was treated with (isocyanomethyl)benzene (**2d**) and piperidine in the presence of Pd and Cu complexes, 1-benzyl-2-(piperidin-1-yl)-1*H*-benzo[d]imidazole (**9**) was produced in 72% total yield without isolation of the carbodiimide intermediate. Derivatives of **9** were widely studied for potential antistaphylococcal activities.²⁵

On the basis of palladium nitrene intermediate as stated earlier⁷, a plausible mechanism was proposed in Scheme 3.²⁷ First, the probable palladium nitrene species **A** is formed from

**Scheme 2** One-pot synthesis of *N,N,N'*-trisubstituted guanidines and *N*-containing heterocycles.

Scheme 3 Proposed mechanism.

1a simultaneously with the release of N₂. Subsequently, insertion of isocyanide (**2a**) into Pd-nitrene species **A** occurred to give intermediate **B**. Finally, reductive elimination of intermediate **B** affords the product carbodiimide **3aa** and regenerates the Pd(0)-catalyst.

In conclusion, under a robust and redox-free condition, we have developed a novel Pd-catalyzed cross-coupling reaction of azides with isocyanides, which is a general and efficient route to unsymmetric carbodiimides. All of aryl, benzyl, and alkyl azides/isocyanides were selectively transformed in high yields with excellent functional group tolerance. Moreover, based on this mild protocol, a series of unsymmetric *N,N',N''*-trisubstituted guanidines were easily prepared in an efficient one-pot fashion from simple and readily available starting materials. This work amply demonstrates that Pd-catalyzed nitrene reactions using organic azides as convenient precursors show great potential in C-N bond construction. Exploration of reaction mechanism and further applications of this chemistry are currently under way in our laboratory.

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