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Palladium-Catalyzed Cascade Process Consisting of Isocyanide Insertion and Benzylic C(sp^3)–H Activation: Concise Synthesis of Indole Derivatives

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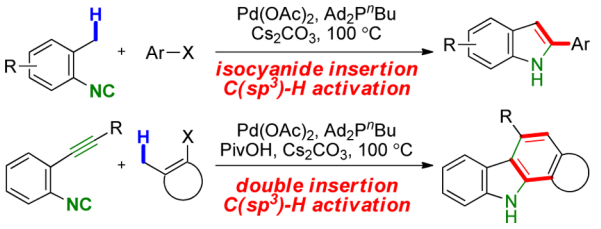
ABSTRACT



Synthesis of the indole skeleton was achieved using a Pd-catalyzed cascade process consisting of isocyanide insertion and benzylic C(sp^3)–H activation. It was found that slow addition of isocyanide is effective for reducing the amount of catalyst needed and Ad_2P^nBu is a good ligand for C(sp^3)–H activation. The construction of the tetracyclic carbazole skeleton was also achieved by a Pd-catalyzed domino reaction incorporating alkyne insertion.

C(sp^3)–H functionalization, the transformation with cleavage of an sp^3-C–H bond, is one of the most direct and effective approaches for the construction of molecules.[1] Much effort has been focused on the development of C(sp^3)–H activation, and methods using palladium catalysts have been developed by many groups, including ours.[2−5] Generally, palladium-catalyzed C(sp^3)–H activation can be divided into three catalytic systems: Pd(0)/(II),[2,3] Pd(II)/Pd(0),[4] and Pd(II)/Pd(IV).[5] The Pd(0)/Pd(II) catalyst system initiated by oxidative addition to aryl halides is expected to be very useful because it enables cascade processes. Cascade processes combining many steps are powerful tools for the concise syntheses of complicated frameworks.[6] However, almost all reactions in previous reports involving C(sp^3)–H activation can be categorized as simple C(sp^3)–H functionalizations consisting of oxidative addition, C(sp^3)–H activation, and reductive elimination (Scheme 1a). To the best of our

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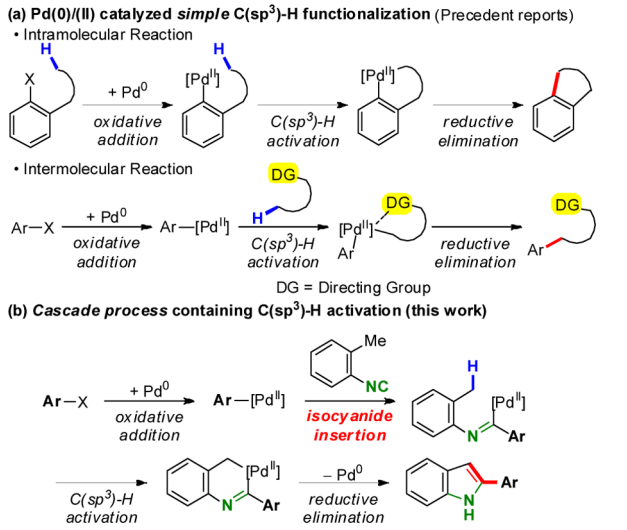
knowledge, palladium-catalyzed cascade reactions containing a C(sp^3)–H activation step have not been investigated, despite its potential usefulness; there is only one specific example using insertion into the olefin bond of norbornene.[2r]

Scheme 1. Strategy for Single and Multiple C–C Bond Formation via C(sp^3)–H Activation



Recently, several groups reported the cascade process containing palladium-catalyzed isocyanide insertion and C(sp^2)–H activation for consice syntheses of carbo- and heterocycles.[7] While Jones and co-workers described the indole formation from 2,6-disubstituted isocyanide via Ru-catalyzed C(sp^3)–H activation,[8] there is no synthesis of heterocycles using *a combination of palladium-catalyzed isocyanide insertion and C(sp^3)–H activation*. We believed that this combination would enable concise syntheses of various nitrogen-containing heterocycles and initially designed the following cascade process based on this concept (Scheme 1b). *o*-Methylphenyl isocyanide and an aryl halide in the presence of a palladium catalyst would be transformed into a 2-arylindole via a cascade consisting of oxidative addition to the aryl halide, isocyanide insertion, C(sp^3)–H activation at the benzylic position, and reductive elimination. Upon comparison with other synthetic methods for the indole skeleton,[9] which is an important nitrogen-containing heterocycle in pharmaceutical sciences, our strategy has several advantages: (1) the divergent synthesis of 2-arylindoles can be achieved by changing the coupling partners; (2) the synthetic method involving formation of a C–C bond between the 2- and 3-positions of the indole is unique,[10] particularly in palladium-catalyzed syntheses;[11] (3) the starting materials are simple. To realize our idea, it was essential to overcome the problem of isocyanide coordination to palladium, which would hamper the palladium-catalyzed cascade process, including C(sp^3)–H activation. Here we report the use of a combination of palladium-catalyzed isocyanide insertion and C(sp^3)–H activation as an effective procedure for the construction of the heterocycles including the indole skeleton, with multibond formation.

Our initial efforts focused on optimization of the reaction conditions using 2,6-dimethylphenyl isocyanide **1a** and iodobenzene **2a** as test substrates (Table 1). Treatment of **1a** and **2a** with stoichiometric amounts of palladium acetate, tricyclohexylphosphine, which is known to be effective for C(sp^3)–H activation,[2] and Cs_2CO_3 in DMF at 100 °C gave the desired product **3a** in 66% yield (entry 1). When the amount of catalyst was decreased to 20 mol %, the reaction proceeded to give **3a** in 46% yield (entry 2). Next, several ligands, including the bidentate ligand (DPPF), the biphenyl-type ligand (biphPCy$_2$), and bulkier ligands (P^tBu_3 and Ad_2P^nBu[12]), were screened, and it was found that Ad_2P^nBu effectively increased the yield (entries 3–6).[3] However, lowering the amount of catalyst had a negative impact on the yield (entry 7). Some reports on the use of isocyanides have shown that an excess of isocyanide deactivates the catalyst by forming palladium clusters.[13] We assumed that the low conversions in the reactions were

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(10) For selected examples on the syntheses of indoles with the formation of C–C bond between 2- and 3-position, see: (a) Seong, C. M.; Park, C. M.; Choi, J.; Park, N. S. *Tetrahedron Lett.* **2009**, *50*, 1029. (b) Lee, S.; Lee, W.-M.; Sulikowski, G. A. *J. Org. Chem.* **1999**, *64*, 4224. (c) Tokuyama, H.; Yamashita, T.; Reding, M. T.; Kaburagi, Y.; Fukuyama, T. *J. Am. Chem. Soc.* **1999**, *121*, 3791. (d) Fürstner, A.; Hupperts, A. *J. Am. Chem. Soc.* **1995**, *117*, 4468. (e) Fukuyama, T.; Chen, X.; Peng, G. *J. Am. Chem. Soc.* **1994**, *116*, 3127. (f) Ito, Y.; Kobayashi, K.; Seko, N.; Saegusa, T. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 73. (g) Houlihan, W. J.; Parrino, V. A.; Uike, Y. *J. Org. Chem.* **1981**, *46*, 4511. (h) Ito, Y.; Kobayashi, K.; Saegusa, T. *J. Am. Chem. Soc.* **1977**, *99*, 3532. (i) Jones, C. D. *J. Org. Chem.* **1972**, *37*, 3624.

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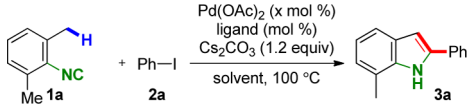
caused by such catalyst deactivation, so slow addition of isocyanide was adopted as a standard procedure (entries 8–12). As a result, catalyst loadings as low as 5 mol % were sufficient for complete conversion (entry 10). Further screening revealed that toluene was the best solvent (entry 12).

Table 1. Investigation of Reaction Conditions

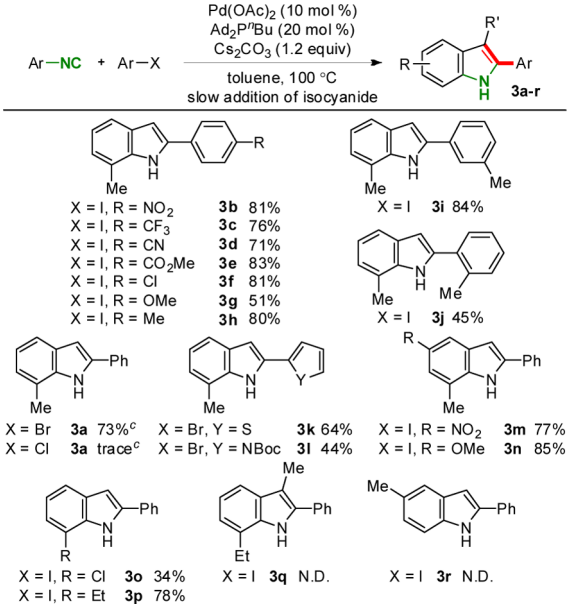


entry	x	ligand (mol %)	solvent	yield[a]
1	100	PCy_3•HBF_4(200)	DMF	66%
2[b]	20	PCy_3•HBF_4(40)	DMF	(46%)
3	20	DPPF(20)	DMF	N.D.
4	20	biphPCy_2(40)	DMF	N.D.
5[b]	20	P^{t}Bu$_3$•HBF_4(40)	DMF	trace
6	20	Ad_2P^nBu(40)	DMF	(54%)
7	10	Ad_2P^nBu(20)	DMF	trace
8[c]	20	Ad_2P^nBu(40)	DMF	(65%)
9[c]	10	Ad_2P^nBu(20)	DMF	(62%)
10[c]	5	Ad_2P^nBu(10)	DMF	54%
11[c]	5	Ad_2P^nBu(10)	1,4-dioxane	54%
12[c]	**5**	**Ad_2P^nBu(10)**	**toluene**	**81%**

[a] Isolated yield (GC yield in parentheses). [b] 1.6 equiv of Cs_2CO_3 was used. [c] Isocyanide **1a** was added dropwise to the solution of PhI, $Pd(OAc)_2$, Ad_2P^nBu, and Cs_2CO_3 by using syringe pump. biph = 2-biphenyl, Ad = 1-adamantyl, N.D. = Not detected.

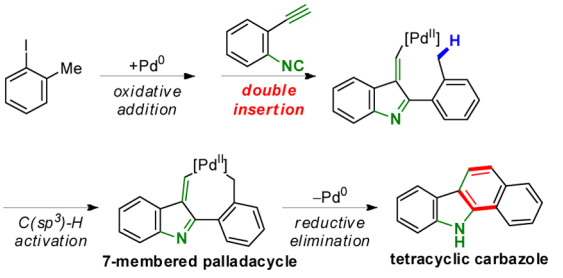
We investigated the substrate scope of the reaction under the optimal conditions (Scheme 2). Initially, various aryl halides were used as the coupling partner. The reactions of aryl iodides bearing a variety of electron-withdrawing and -donating groups at the *para* position gave the desired products **3b**–**h** in moderate to good yields. Introducing a methyl group at the *meta* position maintained a high yield, but methyl substitution at the *ortho* position decreased the yield (**3i** and **3j**). Bromobenzene was also successfully transformed to the indole **3a** in 73% yield, but chlorobenzene did not react. Not only a benzene ring but also heteroaromatic rings, such as thiophenes and pyrroles, could be introduced at the 2-position of indoles **3k** and **3l**. Then the reaction was performed using various aryl isocyanides. The reactions of isocyanides bearing nitro and methoxy groups gave **3m** and **3n** in 77% and 85% yields, respectively. When one methyl group at the *ortho* position of the isocyanide was replaced by other groups such as chloro and ethyl groups, a C–H bond of the methyl group selectively reacted to give the desired products **3o** and **3p** as single products. In contrast, diethylphenyl isocyanide did not give indole **3q** via C–H activation of methylene. Use of a substrate with no substituent at one side of the *ortho* position of the isocyanide (i.e., 2,4-dimethylphenyl isocyanide) resulted in no reaction, probably because of the instability of less hindered isocyanides[7a,14] and the flexible conformation of the reaction intermediate (**3r**).

Scheme 2. Substrate Scope[a,b]



[a] Isolated yield. [b] Isocyanides were added dropwise to the solution of ArX, $Pd(OAc)_2$, Ad_2P^nBu, and Cs_2CO_3 by using syringe pump. [c] 5 mol % of $Pd(OAc)_2$ and 10 mol % of Ad_2P^nBu were used. Ad = 1-adamantyl, N.D. = Not detected.

Scheme 3. Domino Reaction Using *o*-Alkynylphenyl Isocyanide



To extend the synthetic scope of the cascade process via palladium-catalyzed isocyanide insertion and C(sp^3)–H activation, we attempted the following domino reaction (Scheme 3). *o*-Alkynylphenyl isocyanide and iodo-2,6-dimethylbenzene in the presence of a palladium catalyst would couple to give a tetracyclic carbazole via a cascade process consisting of oxidative addition to iodobenzene, sequential insertions of isocyanide and alkyne, C(sp^3)–H activation at the benzylic position, and reductive elimination. Under the optimal conditions, using $Pd(OAc)_2$, Ad_2P^nBu, and Cs_2CO_3 in toluene at 100 °C, this reaction gave the desired product **4a** but the conversion was low

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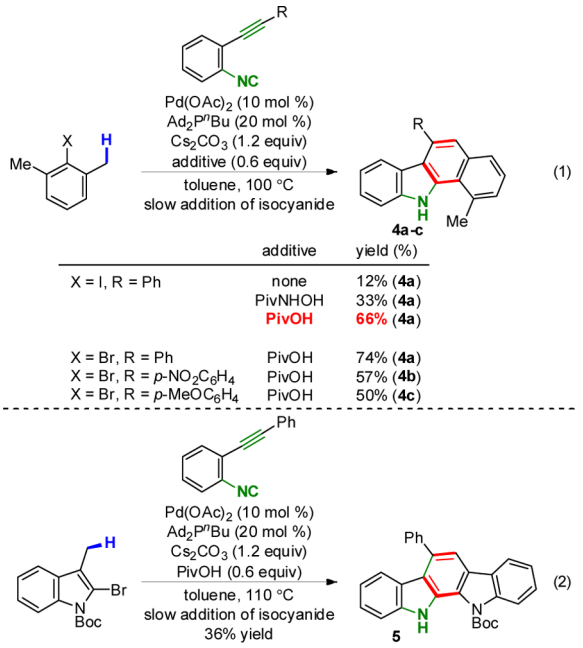
Scheme 4. Investigation of Domino Reaction



(Scheme 4, eq 1). This is probably because the reaction proceeded via a seven-membered palladacycle, which is less favored than five- or six-membered palladacycles. In contrast, the addition of catalytic amounts of PivOH and PivNHOH, which have been reported to promote C(sp^3)–H activation,[2m,3] effectively accelerated the reaction, and when PivOH was used, tetracyclic carbazole **4a** was obtained in 66% yield. The structure of carbazole **4a** was determined using X-ray crystallography.[15]

In this reaction, bromo-2,6-dimethylbenzene (X = Br), instead of iodo-2,6-dimethylbenzene (X = I), can be used as the substrate; the electronic state of the alkyne did not significantly influence the yields of carbazoles **4a**–**c** (R = Ph, $NO_2C_6H_4$, $MeOC_6H_4$) (Scheme 4, eq 1). Furthermore, this strategy can be applied to the synthesis of indolo[2,3-*a*]carbazole derivatives, which have interesting biological effects.[16] Using 1-Boc-2-bromoskatole as the substrate, the desired carbazole **5** was obtained in 36% yield (eq 2). These results were the first example of a palladium-catalyzed domino reaction containing a C(sp^3)–H activation step.

In summary, we have developed a palladium-catalyzed cascade process involving C(sp^3)–H activation and isocyanide insertion for the construction of 2-arylindoles and polycyclic nitrogen-containing compounds such as benzo- and indolo-carbazoles. In the reaction, formation of two or three C–C bonds was achieved by avoiding deactivation of the Pd catalyst. We are currently extending this strategy to give a comprehensive approach to the synthesis of nitrogen-containing polycycles.

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Supporting Information Available. Experimental procedures and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

(15) See Supporting Information.

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