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Synthetic Methods

Palladium-Catalyzed Amidation by Chemoselective C(sp^3)–H Activation: Concise Route to Oxindoles Using a Carbamoyl Chloride Precursor**

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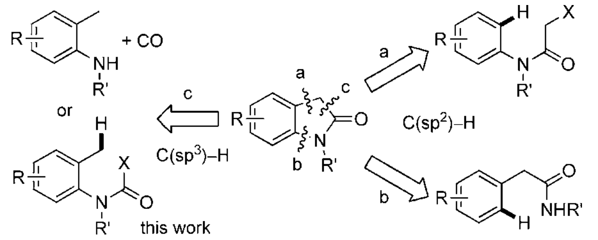
As oxindole forms the core of many complex natural products and is an important pharmacophore, its structure has attracted attention for over a century.[1] The oxindole structure has been constructed by the formation of a lactam from aniline,[1a] Wolff–Kishner-like reduction of isatin,[1b] oxidation of indole,[1c] transition metal catalyzed intramolecular amidation,[1d–f] and the Heck reaction.[1g,h] However, a concise method is still required for ready access to the various oxindoles.

Recent research has focused on C–H bond activation after C–C bond formation because the syntheses are straightforward and atom-economical. While catalytic C(sp^2)–H activation and subsequent C–C bond formation have been studied by many groups, the corresponding C(sp^3)–H fuctionalization is less developed.[2] With palladium(0)-catalyzed C(sp^3)–H activation of a methyl group, Baudoin and co-workers reported the synthesis of cyclobutenes,[3a–d] and several groups[3e–6] described intramolecular cyclization of a five-membered ring. Yu and co-workers also achieved Pd^0/PR_3-catalyzed intermolecular arylation of C(sp^3)–H bonds.[7] C(sp^3)–H bond activation of methyl and methylene groups and subsequent C–C bond formation is challenging.[8,9] As discussed by Fagnou and co-workers[4a] and Glorius and co-workers,[9b] C(sp^2)–H activation proceeds selectively in the presence of the competitive C(sp^3)–H bond. Thus, the selectivity for C(sp^3)–H activation also needs to be addressed for its application to constructing complex molecules.

Oxindole could be readily synthesized using C–H activation chemistry. As shown in Scheme 1, there are three possible synthetic routes: a) palladium(0)-catalyzed C(sp^2)–H bond activation after C–C bond formation at the *ortho* position of aniline, b) palladium(II)-catalyzed C(sp^2)–H bond amidation, and c) C(sp^3)–H bond activation after insertion of carbon monoxide (CO) or C(sp^3)–H bond amidation. Routes a) and b) have been developed by the groups of Buchwald,[10] Yu,[11] and Murakami[12] independently. Although route c) would be a complementary method, it has not been reported, presumably because of the difficulty of C(sp^3)–H activation compared to C(sp^2)–H activation.[13] In the course of our research, we have used carbamoyl chloride in palladium-catalyzed reactions.[14] It is a useful intermediate for preparing lactam moieties, and earlier reports suggest that it could be applied to C–H activation chemistry. Herein we describe a new strategy for the preparation of various oxindoles from a carbamoyl chloride precursor using C–H activation chemistry. Selective C(sp^3)–H activation in the presence of a C(sp^2)–H bond is discussed.



Scheme 1. Synthetic strategies for oxindole based on C–H activation.

On the basis of an earlier report, we first examined the reaction of (2,6-dimethylphenyl)(methyl)carbamoyl chloride **1a**, which was prepared from the corresponding aniline **2a** in 84 % yield, with $Pd(OAc)_2$ (3 mol %), $PCy_3{\cdot}HBF_4$ (6 mol %), and Cs_2CO_3 (1.1 equiv) in mesitylene at 135 °C under argon.[4a] 1,7-Dimethylindolin-2-one (**3a**) was obtained in an approximately 10 % yield along with a large amount of **2a** (Table 1, entry 1). As Fagnou et al. reported, addition of pivalic acid (PivOH) gave a better yield,[4a] but **2a** was still obtained as a major product (entry 2). Interestingly, the reaction without PivOH under a CO atmosphere gave a comparable yield (entry 3). It is noteworthy that addition of PivOH was compatible with the CO atmosphere, and the reaction under these reaction conditions proceeded smoothly to give **3a** in good yield (entry 4). Next, the reaction temperature, and several additives and ligands were examined. The reaction at 120 °C had a comparable yield (entry 5) to that obtained at 135 °C. Although the Ac_2NH and $PivNH_2$ additives had little or no effect on the yield, *N*-hydroxypivalamide (PivNHOH)[15] was a good additive and the cyclized product **3a** was obtained in 84 % yield (entries 6–8). Addition of a bulky alkyl ligand, such as $t\mathrm{Bu}_3\mathrm{P}{\cdot}\mathrm{HBF}_4$[16] or $t\mathrm{Bu}_2\mathrm{PPh}$, was not effective (entries 9 and 10). The ligand Ad_2PBu[17] (entry 11; optimum reaction conditions) gave better results than $PCy_3{\cdot}HBF_4$. We also tried to reduce the amount of the palladium catalyst and the reaction with 1 mol % of $Pd(OAc)_2$ and 2 mol % of Ad_2PBu gave **3a** in 80 % yield, but additional

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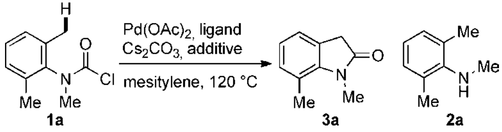
Table 1: Investigation of the reaction conditions.[a]



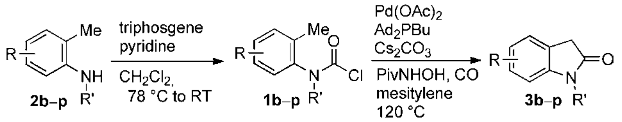
Entry	Ligand	Additive and atmosphere	Yield [%][b]	
			3a	**2a**
1[c]	$Cy_3P\cdot HBF_4$	none, Ar	ca.10	10
2[c]	$Cy_3P\cdot HBF_4$	PivOH, Ar	32	48
3[c]	$Cy_3P\cdot HBF_4$	none, CO	35	1
4[c]	$Cy_3P\cdot HBF_4$	PivOH, CO	67	9
5	$Cy_3P\cdot HBF_4$	PivOH, CO	72	1
6	$Cy_3P\cdot HBF_4$	Ac_2NH, CO	52	3
7	$Cy_3P\cdot HBF_4$	$PivNH_2$, CO	28	11
8	$Cy_3P\cdot HBF_4$	PivNHOH, CO	84	10
9	$t Bu_3P\cdot HBF_4$	PivNHOH, CO	7	6
10	$t Bu_2PPh$	PivNHOH, CO	27	35
11	Ad_2PBu	PivNHOH, CO	88	6

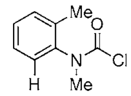
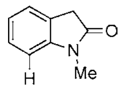
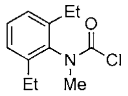
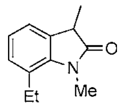
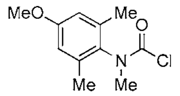
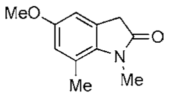
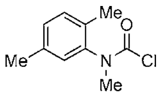
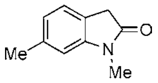
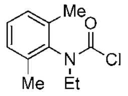
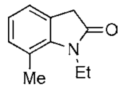
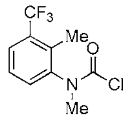
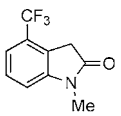
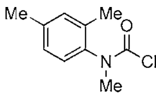
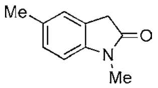
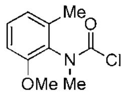
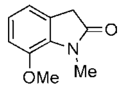
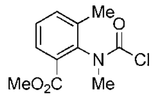
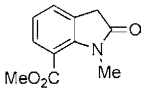
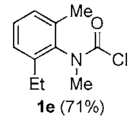
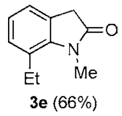
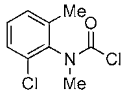
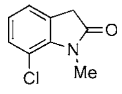
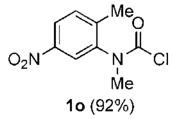
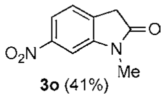
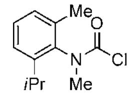
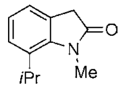
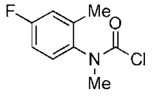
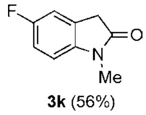
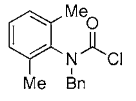
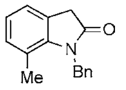
[a] The mixture of **1a** was treated with the palladium catalyst (3 mol%), ligand (6 mol%), base (1.1 equiv), and additives in mesitylene at 120°C. [b] Yield of isolated product. [c] The reaction was performed at 135°C. Ad = adamantyl, Piv = pivaloyl.

reduction in the amount of catalyst and ligand decreased the yield. For example, with 0.3 mol% of $Pd(OAc)_2$ the yield was 60% (data not shown).

To investigate the scope of the reaction we applied the optimum reaction conditions to several carbamoyl chlorides, **1b–p**, having various substituents on the aromatic ring and the nitrogen atom. The substrates **1b–p** were obtained from the corresponding anilines **2b–p** in moderate to excellent yield by treatment with triphosgene and pyridine; the exceptions being **1i** and **1n**. These low yields were presumably a result of the instability of the products. Treatment of **1b**, which has no substituent on the aromatic ring (R = H), with $Pd(OAc)_2$ (3 mol%), Ad_2PBu (6 mol%), and Cs_2CO_3 (1.1 equiv) in mesitylene at 120°C gave the cyclized product **3b** in 62% yield (Table 2, entry 1). The reactions of **1c** and **1d**, having methyl groups at the C4- and C5-positions gave oxindoles **3c** and **3d**, respectively (entries 2 and 3). These results indicate that the substituent at the C6-position is not essential, and starting materials with substituents at other positions can be used. The reactions of **1e** and **1f** gave oxindoles **3e** and **3f**, respectively, with excellent chemoselectivity (entries 4 and 5). The desired product **3g** was not obtained and degradation to aniline **2g** (81%) was observed in the case of (2,6-diethylphenyl)(methyl)carbamoyl chloride **1g** (entry 6). Under these reaction conditions, C–H activation of the methyl group only occurred to form a five-membered ring. The reaction of substrate **1h** with an ethyl group on the nitrogen atom proceeded smoothly to give oxindole **3h** in 79% yield (entry 7). Several functional groups, such as

Table 2: Reaction scope and limitations.[a,b]

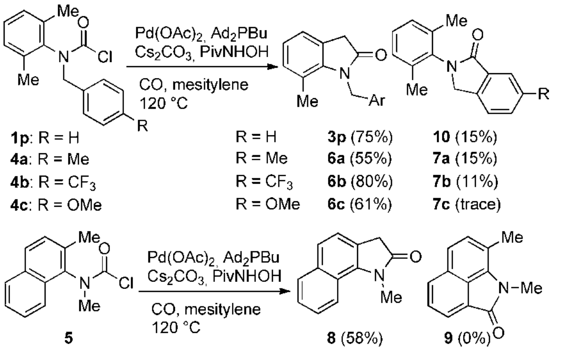


Entry	Carbamoyl chloride (**1**)	Oxindole (**3**)	Entry	Carbamoyl chloride (**1**)	Oxindole (**3**)	Entry	Carbamoyl chloride (**1**)	Oxindole (**3**)
1	 **1b** (81%)	 **3b** (62%)	6	 **1g** (90%)	 **3g** (0%)	11	 **1l** (86%)	 **3l** (81%)
2	 **1c** (78%)	 **3c** (60%)	7	 **1h** (77%)	 **3h** (79%)	12	 **1m** (96%)	 **3m** (70%)
3	 **1d** (83%)	 **3d** (49%)	8	 **1i** (38%)	 **3i** (88%)	13	 **1n** (44%)	 **3n** (67%)
4	 **1e** (71%)	 **3e** (66%)	9	 **1j** (84%)	 **3j** (64%)	14	 **1o** (92%)	 **3o** (41%)
5	 **1f** (83%)	 **3f** (64%)	10	 **1k** (91%)	 **3k** (56%)	15	 **1p** (93%)	 **3p** (75%)[c]

[a] A solution of **1** in mesitylene was treated with $Pd(OAc)_2$ (3 mol%), Ad_2PBu (6 mol%), Cs_2CO_3 (1.1 equiv), and PivNHOH (0.3 equiv) under CO at 120°C. [b] Yield of isolated product indicated within parentheses. [c] $Pd(OAc)_2$ (5 mol%), and Ad_2PBu (10 mol%) were used.

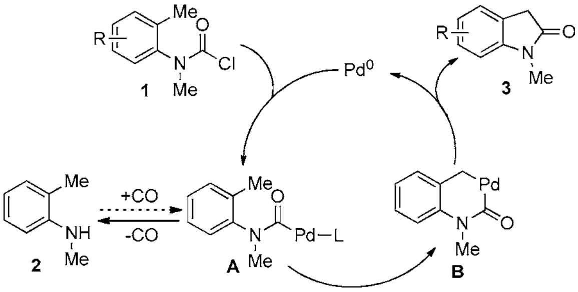
methoxy, chlorine, fluorine, ester, and trifluoromethyl, were tolerated under these reaction conditions. The reactions of **1i–n** gave the corresponding oxindoles **3i–n** in moderate to good yield (entries 8–13). In some cases, the corresponding aniline **2** was observed as a by-product. The reaction of carbamoyl chloride **1o** with a nitro group gave the desired oxindoles **3o** along with a large amount of aniline **2o** in approximately 20% yield (entry 14). Surprisingly, the reaction of **1p** gave the oxindole **3p** as the major product and a small amount of by-product (15%) derived from C(sp^2)–H activation, which is a more favorable process than C(sp^3)–H activation.[4a,6] Our conditions could be applied to substrates with various functional groups to prepare oxindoles.

Because selective C(sp^3)–H activation was observed, we investigated to see whether or not the selectivity could be controlled by changing the electron density of the aromatic ring. Compounds **4a–c** and **5** were designed and treated under the same reaction conditions (Scheme 2). The reactions of **4a** and **4b** (R = Me and CF$_3$) gave oxindoles **6a** and **6b**, respectively, each derived from C(sp^3)–H activation, and a small amount of the isomers **7a** and **7b** (11–15%), which were derived from C(sp^2)–H activation. Interestingly, with the methoxy group as a substituent, the reaction of **4c** proceeded smoothly and the competitive C(sp^2)–H activation was mostly suppressed. The reaction of **5**, having a naphthalene moiety, gave only oxindole **8**. Additionally, when carbamoyl chloride **1p** was treated under the previously reported reaction conditions (Pd(OAc)$_2$ (3 mol%), Cy$_3$P·HBF$_4$ (6 mol%) and Cs$_2$CO$_3$ (1.1 equiv) in mesitylene at 135°C),[4a] no selectivity was observed and **3p** (24%), **10** (23%), and the corresponding aniline (36%) were obtained (data not shown). These results indicate that C(sp^3)–H activation is more favorable than C(sp^2)–H activation under these reaction conditions. To the best of our knowledge, this is a first example of a chemoselective palladium(0)-catalyzed C(sp^3)–H activation.



Scheme 2. Investigation of the reaction conditions.

The proposed mechanism is shown in Scheme 3. The reaction commences with oxidative addition of Pd^0 to give the intermediate **A**. Under the optimum reaction conditions, CO elimination from **A** was suppressed by performing the reaction under a CO atmosphere. The formation of a six-membered transition state[3b,c,4] led to C(sp^3)–H activation to give the intermediate **B**, which was converted into oxindole along with the production of Pd^0. The effect of PivNHOH is not clear, but we assume that it assists in benzylic C(sp^3)–H activation from **A**.



Scheme 3. Possible reaction mechanism.

In summary, a new strategy using C(sp^3)–H activation was investigated for rapid access to various oxindoles using carbamoyl chloride precursors. The reaction with Ad$_2$PBu as a ligand and PivNHOH as an additive under CO was effective. Under the developed reaction conditions, selective C(sp^3)–H activation occurred in the presence of the competitive C(sp^2)–H bond. These results will be helpful in synthesis of complex molecules using C(sp^3)–H activation. Further mechanistic studies and synthetic application are in progress.

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Keywords: C–H activation · chemoselectivity · heterocycles · palladium · synthetic methods

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