Remote amide-directed palladium-catalyzed benzylic C–H amination with *N*-fluorobenzenesulfonimide†

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Received 29th June 2010, Accepted 26th July 2010
DOI: 10.1039/c0cc02175j

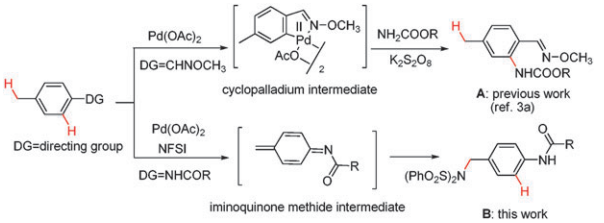
An unprecedented remote amide-directed palladium-catalyzed intermolecular highly selective benzylic C–H amination with *N*-fluorobenzenesulfonimide is developed, which represents the first direct benzylic C–H amination with a non-nitrene nitrogen source. This methodology provides a novel approach to circumvent the common *ortho* aromatic C–H selectivity in directed palladium catalyzed C–H functionalization.

Transition metal catalyzed direct carbon–hydrogen bond functionalization appears highly appealing especially if high selectivity for a unique C–H bond can be achieved.[1] Accordingly, directed metallation,[1,2] is a powerful approach for selective functionalization of C–H bonds in complex substrates. All previously reported directed palladium catalyzed C–H functionalization of arenes provided *ortho*-C(sp)^2–H functionalized products *via* an *ortho*-arene substituted cyclopalladium intermediate (Scheme 1A, with C–H to C–N[3] as an example[3a]), which may restrict their potential synthetic application. Therefore, development of a new directing paradigm overriding the common *ortho* aromatic C–H selectivity to realize remote *meta*/*para* aromatic or benzylic C–H activation remains a challenge.[4] Recently, a remarkably interesting amide group[5] directed copper-catalyzed *meta* aromatic C–H arylation reaction was reported by Gaunt and Phipps.[4a] In this communication, an unprecedented amide directed Pd(OAc)$_2$ catalyzed benzylic C(sp^3)–H[6] amination with *N*-fluorobenzenesulfonimide (NFSI) was realized and a novel iminoquinone methide was proposed as the key intermediate (Scheme 1B).

Nitrogen functionality is prevalent in synthetic and natural small molecules with significant biological activities.[7] Recently, the area of catalytic C–H amination has led to significant results both arising from the discovery of simple efficient nitrene transfers[8,9] and the combination of transition metal catalyzed C–H activation with C–N bond formation.[8] However, to date, benzylic C–H activation amination with a non-nitrene nitrogen source had never been realized. Most recently, the works of Michael[10a,b] and Liu[10c] showed that NFSI could be efficiently utilized as nitrogen source as well as oxidant. Combining with our continuing interest in the synthesis of heterocyclic compounds from amide substrates,[11] we have attempted the amide directed palladium catalyzed C–H amination of arenes with NFSI.

Initial studies focused on the amination reaction of *N*-*p*-tolylpivalamide (**1a**) with NFSI. With Pd(OAc)$_2$ (0.1 equiv.) as catalyst, the reaction of **1a** (0.4 mmol) and NFSI (2.5 equiv.) was conducted at 90 °C in 1,2-dichloroethane (DCE) for 1.5 h, surprisingly, instead of the usually formation of C(sp^2)–H amination product (Scheme 1A), a benzyl C(sp^3)–H amination product **2a** was generated in 73% yield (Table 1, entry 1) and 17% *N*-(phenylsulfonyl)benzenesulfonamide was obtained.‡§ However, when NBS was used instead of NFSI, the normal C(sp^2)–H bromination[2] product *N*-(2-bromo-4-methylphenyl)-pivalamide was obtained in 92% yield. When additive KF (4.0 equiv.) was added, **2a** was obtained in 86% yield with a relatively longer reaction time (entry 2). No reaction occurred in the absence of palladium catalyst (entry 3). $NaHCO_3$ was as effective as KF (entry 4). With solvents such as acetonitrile, DMA, DMF and DMSO, no desired **2a** was obtained. Other solvents such as 1,4-dioxane, C_6H_5Cl and mesitylene were not as effective as DCE (entries 5–7). In addition, the use of Pd(TFA)$_2$ as catalyst gave **2a** in 72% yield (entry 8). With Pd(dba)$_2$ as catalyst, after 24 h, the reaction of **1a** and NFSI gave **2a** in 23% yield, and 63% **1a** was recovered (entry 9). Whereas, the reaction employing catalyst $Pd(PPh_3)_2Cl_2$ gave no desired **2a** and 80% **1a** was recovered (entry 10). It should be noted that the transformation from **1a** to **2a** represents the first direct benzylic C–H amination with a non-nitrene nitrogen source. In our experiment, starting from substrates *N*-*o*-tolylpivalamide and *N*-*m*-tolylpivalamide, no reaction occurred. On the contrary to benzylic C–H amination of nitrenes,[8,9] high selectivity toward benzylic C–H *para* to the directed amide group of the present study is desirable.

We next addressed reaction optimization with respect to various *N*-*p*-tolylamide derivatives **1b–e** (Table 2). We found that changing the nature of the acyl group had a large effect on the yield of the reaction without compromising the benzyl C–H selectivity (entries 2–4). In addition, the reaction works with carbamate (entry 5), although the yield was only moderate. With the defined efficient directing group (Table 2, entry 1), the scope of benzyl C–H amination reaction was explored. As described in Table 3, *N*-*p*-tolylpivalamide derivatives **1f–j** were



Scheme 1 Directed palladium catalyzed C–H amination.

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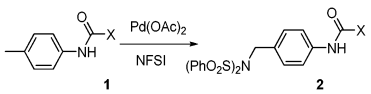
† Electronic supplementary information (ESI) available: Experimental procedures, full characterization data, copies of ^{1}H and ^{13}C NMR spectra for all the new compounds. CCDC 779680. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c0cc02175j

Table 1 Benzylic C–H amination of **1a** with NFSI[a]

Entry	Catalyst	Solvent	Additive (4.0 equiv.)	Time/h	Yield of **2a**[b] (%)
1	$Pd(OAc)_2$	DCE	None	1.5	73
2	$Pd(OAc)_2$	DCE	KF	5.5	86
3	None	DCE	KF	24.0	0
4	$Pd(OAc)_2$	DCE	$NaHCO_3$	3.5	83
5	$Pd(OAc)_2$	1,4-dioxane	KF	3.0	17
6	$Pd(OAc)_2$	C_6H_5Cl	KF	5.0	64
7	$Pd(OAc)_2$	Mesitylene	KF	1.0	23
8	$Pd(TFA)_2$	DCE	KF	8.0	72
9	$Pd(dba)_2$	DCE	KF	24.0	23
10	$Pd(PPh_3)_2Cl_2$	DCE	KF	8.0	Trace

[a] Reactions were carried out with **1** (0.4 mmol), 10 mol% palladium catalyst, NFSI (2.5 equiv.) in solvent (4 mL) at 90 °C. [b] Yield of the isolated product.

Table 2 $Pd(OAc)_2$ catalyzed benzylic C–H amination of **1a–e** with NFSI[a]



Entry	Substrate	X	Time/h	Product **2**[b] (%)
1	**1a**	*t*-Bu	5.5	86
2	**1b**	Me	11.0	71
3	**1c**	Ph	15.5	59
4	**1d**	$PhCH_2$	10.0	57
5	**1e**	$OC(CH_3)_3$	3.3	51[c]

[a] Reactions were carried out with **1** (0.4 mmol), 10 mol% $Pd(OAc)_2$, NFSI (2.5 equiv.) and KF (4 equiv.) in DCE (4 mL) at 90 °C. [b] Yield of the isolated product. [c] Without adding additive.

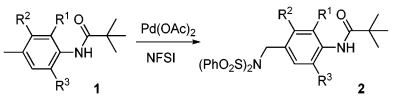
successfully reacted with NFSI to afford **2f–j** in 72–83% yield (entries 1–5) and **1g–i** with strong electron donating OR group needed a relatively shorter reaction time (entries 2–4). Interestingly, starting from biphenyl derivatives **1k–m**, the desired benzylic C–H amination products **2k–m** could also be obtained without the formation of carbazole derivatives *via* possible intramolecular competing C–N formation reaction[5a,c] (entries 6–8). From substrate **1n** with both OMe and phenyl at aromatic ring, **2n** was obtained in 94% yield (entry 9).

Although the mechanistic details of this transformation are not clear at the moment,[12] we propose the possible catalytic cycle as shown in Scheme 2. The suggested initial step is the formation of intermediate **A** with an O–Pd(II) bond.[13] Oxidative addition of NFSI[10a,b] to intermediate **A** generates Pd(IV) species **B**. The next elimination of benzenesulfonimide gives a key iminoquinone methide intermediate **C**[14] and regenerates the active Pd(II) species. Finally, the nucleophilic amination[10b,15] of intermediate **C** and benzenesulfonimide leads to the products **2**.[16]

In conclusion, an unprecedented remote amide-directed palladium-catalyzed intermolecular highly selectively benzylic C–H amination with NFSI is developed. This methodology provides a novel approach to circumvent the common *ortho* aromatic C–H selectivity in directed palladium catalyzed C–H functionalization, although currently, this chemistry has narrow scope limited to *N*-*p*-tolylamide derivatives. Further studies of these transformations may lead to new paths for developing efficient C–H activation methodologies.

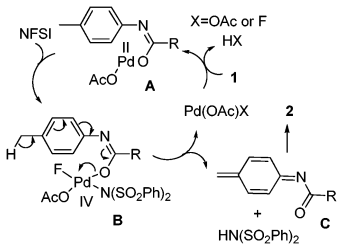
Financial support of this research by the NCET-08-0756, NNSFC (20772015 and 20972028), NENU-STC07006, JLSDP (20080547 and 20082212) is greatly acknowledged.

Table 3 $Pd(OAc)_2$ catalyzed benzylic C–H amination of **1f–n** with NFSI[a]



Entry	Substrate **1**	R^1	R^2	R^3	Time/h	Yield of **2**[b] (%)
1	**1f**	Me	H	H	19.0	75
2	**1g**	OMe	H	H	1.0	83
3	**1h**	OEt	H	H	0.5	77
4	**1i**	OCH_2Ph	H	H	0.3	73
5	**1j**	H	Me	H	20.0	72
6	**1k**	H	H	Ph	0.5	70
7	**1l**	H	H	4-MeC_6H_4	0.6	81
8	**1m**	H	Me	Ph	13.0	58[c]
9	**1n**	H	Ph	OMe	4.0	94

[a] Reactions were carried out with **1** (0.4 mmol), 10 mol% $Pd(OAc)_2$, NFSI (2.5 equiv.) and $NaHCO_3$ (4 equiv.) in DCE (4 mL) at 90 °C. [b] Yield of the isolated product. [c] With 15% $HN(SO_2Ph)_2$ obtained.



Scheme 2 Proposed mechanism for formation of **2**.

Notes and references

‡ General procedure for the preparation of **2** (with **2a** as an example): To a solution of the *N*-*p*-tolylpivalamide (**1a**, 0.40 mmol) in 1,2-dichloroethane (4.0 ml) was added the *N*-fluorobenzenesulfonimide (315 mg, 1.0 mmol), KF (93 mg, 1.6 mmol) and $Pd(OAc)_2$ (9.0 mg, 0.04 mmol). The reaction was stirred for the 5.5 h at 90 °C under air. After completion of the reaction (TLC monitoring) the mixture was poured onto ice–water and extracted with dichloromethane (3 × 15 mL). The combined organic layers were dried (Na_2SO_4), filtered over Celite, evaporated *in vacuo*, and the residue was purified by column chromatography to give the compound *N*-(4-((*N*-(phenylsulfonyl)-phenylsulfonamido)methyl)phenyl)pivalamide (**2a**, 167 mg, 86%).
§ Selected data for **2a**: White solid. mp: 151 °C; ^{1}H NMR (500 MHz; $CDCl_3$): δ = 1.34 (s, 9H), 4.88 (s, 2H), 7.30 (s, 1H), 7.33 (d, J = 8.5 Hz, 2H), 7.41–7.47 (m, 6H), 7.59 (t, J = 7.5 Hz, 2H), 7.80 (d, J = 7.5 Hz, 4H). ^{13}C NMR (125 MHz; $CDCl_3$): δ = 27.6, 39.7, 51.9, 119.7, 128.1, 128.9, 129.9, 130.2, 133.7, 137.9, 139.8, 176.6. IR (KBr, cm^{-1}): 1676, 1394, 1170, 788, 582. MS calcd m/z 486.6036, $[M]^+$ found 486.6041; Anal. Calcd for: $C_{24}H_{26}N_2O_5S_2$: C, 59.24; H, 5.39; N, 5.76. Found: C, 59.27; H, 5.34; N, 5.75%.

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13 No reaction occurred starting from substrate *N*-methyl-*N*-*p*-tolylacetamide. In addition, high yields could be achieved by adding base such as $NaHCO_3$ or KF to facilitate proton abstraction. These results may support the formation of anionic-typecoordination intermediate **A**.
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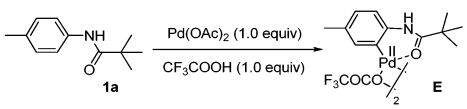
16 An *ortho*-substituted cyclopalladium (II) intermediate **E** was prepared from **1a** (eqn (1)). No desired **2a** was obtained when the reaction of **E** and NFSI was performed under identical conditions described in Table 2, entry 1. For preparation and X-ray diffraction analysis of intermediate **E** (CCDC-776890), please see Supporting Information†



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