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Palladium-catalyzed intermolecular amination of unactivated C(sp^3)-H bonds *via* cleavable directing group

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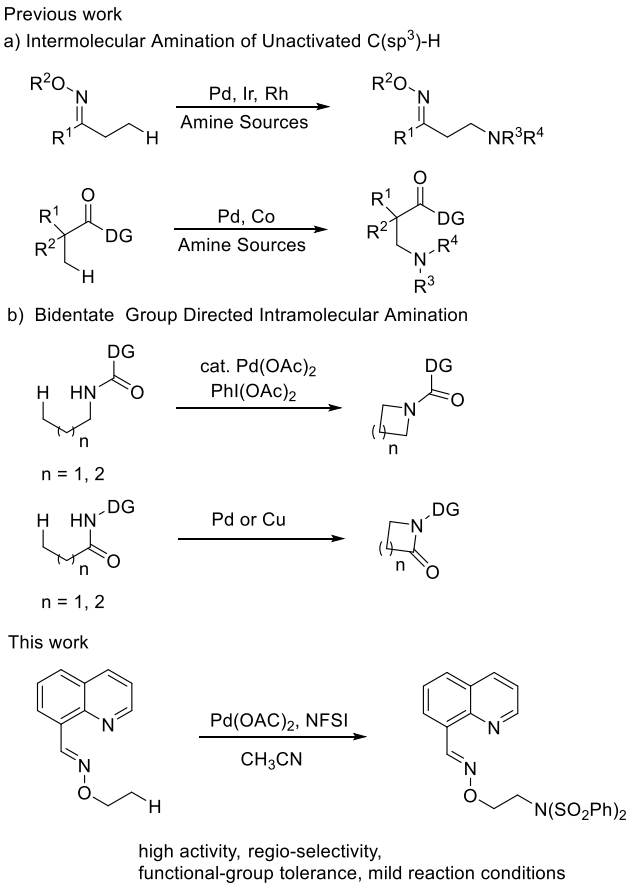
A palladium-catalyzed intermolecular amination of unactivated C(sp^3)-H bond was developed. Through NFSI as both the amino source and the oxidant, this protocol operates under mild conditions with excellent terminal selectivity and a broad substrate scope. Moreover, the directing group can be easily removed to produce 1,2-amino alcohols.

Nitrogen-containing compounds are abundant in both natural products and synthetic molecules and their importance in biology and drug discovery have been widely documented.[1] Therefore, development of efficient and selective methods for C–N bond formation is highly attractive in synthetic chemistry. Even though directed intermolecular sp^2 C–N bond formation have been well-established such as Ullmann and Buchwald-Hartwig couplings,[2] intermolecular amination of unactivated C(sp^3)–H bonds remains challenging. Developing amination protocols *via* C-H activation would be highly desirable.

Recently, notable achievements have been made in metal-catalyzed C(sp^3)–H amination via nitrene transfer through using reactive metal-imido/nitrene species.[3] However, these catalytic systems are only suitable for methylene C–H bonds at allylic, benzylic or α-heteroatomic positions in order to generate synthetic utility. Besides the nitrene-involved C-H functionalization, another promising strategy is *via* metal-catalyzed C-H bond activation with the assistance of directing groups.[4,5,6,7] Despite these elegant precedents, most of them mainly focus on functionalizing either C(sp^2)-H or benzylic C-H bonds. To our knowledge, only a few examples of directed intermolecular amination of unactivated C(sp^3)-H bonds have been reported (Scheme 1a).[8] In 2005, the use of bidentate directing groups for the catalyzed C(sp^3)-H functionalization was highlighted by Daugulis and co-workers.[9] This strategy has widely been used to promote the directed aliphatic C-H activation because of the stability, coordinating capacity, and reactivity of the chelation groups.[10] However, only intramolecular amination products were obtained, as most of the bidentate directing groups were connected with amide bond (Scheme 1b).[11] Herein, we report a palladium-catalyzed



Scheme 1 Transition-metal-catalyzed amination of unactivated C(sp^3)-H bonds.

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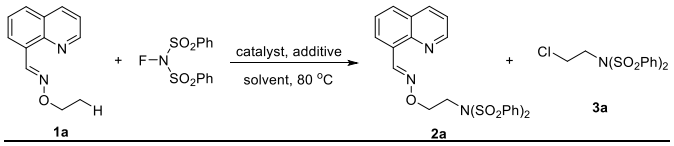
intermolecular amination of unactivated C(sp^3)-H bond with a bidentate directing group which was connected with imine bond. This amination reaction employs NFSI (N-fluorobis (phenylsulfonyl)-imide) as the amino source under mild conditions with high terminal C(sp^3)-H bond selectivity, excellent functional group tolerance, and a broad substrate scope. Furthermore, the bidentate directing group can be easily cleaved to give 1,2-amino alcohols, which represent one types of versatile intermediate in organic synthesis.

Initially, we searched for optimized intermolecular amination reaction conditions by employing (*E*)-quinoline-8-carbaldehyde *O*-ethyl oxime (**1a**) as model substrate. A series of nitrogen sources were screened (see Supporting Information, Table S1). By treating **1a** (0.2 mmol) with nitrogen sources such as *p*-toluenesulfonyl azide, *O*-benzoyl hydroxylmorpholine, amide/oxidant, 3-phenyl-1,4,2-dioxazol-5-one (0.4 mmol) in the presence of $Pd(OAc)_2$ in DCE (1,2-dichloroethane) at 80 °C for 12 h, no desired product was detected. When NFSI was used as nitrogen source, the corresponding amination product (**2a**) was obtained in 12% yield and by-product (**3a**) which formed through the SN2 nucleophilic reaction between NFSI and 1,2-dichloroethane was also detected in 5% yield (entry 1, table 1). Further addition of 1 equiv of AcOH dramatically improved the amination yield to 48% (entry 2) and similarly high yields were realized using PivOH and Ac_2O (entries 3, 4). A screening of solvents indicated that CH_3CN was the best solvent, while other solvents were less effective (entries 5-10). Only acetoxylated product (43%) were observed when the reaction was carried out in AcOH (entry 11). By

Table 1 Optimization of the reaction conditions[a]



1a 2a 3a

Entry	Cat.	Additive	Solvent	Yield (%)[b]
1	$Pd(OAc)_2$	--	DCE	12 (5)[c]
2	$Pd(OAc)_2$	AcOH	DCE	48
3	$Pd(OAc)_2$	PivOH	DCE	36
4	$Pd(OAc)_2$	Ac_2O	DCE	26
5	$Pd(OAc)_2$	AcOH	CH_3CN	56
6	$Pd(OAc)_2$	AcOH	toluene	0
7	$Pd(OAc)_2$	AcOH	1,4-dioxane	0
8	$Pd(OAc)_2$	AcOH	MeOH	0
9	$Pd(OAc)_2$	AcOH	DMF	5
10	$Pd(OAc)_2$	AcOH	chlorobenzene	14
11	$Pd(OAc)_2$	AcOH	AcOH	43[d]
12[e]	$Pd(OAc)_2$	AcOH	CH_3CN	5
13[f]	$Pd(OAc)_2$	AcOH	CH_3CN	95
14	--	AcOH	CH_3CN	0
15	$[RhCp^*Cl_2]_2$/ $AgNTf_2$	AcOH	CH_3CN	0
16	$[IrCp^*Cl_2]_2$/ $AgNTf_2$	AcOH	CH_3CN	0
17	$CoCp^*(CO)I_2$/ $AgSbF_6$	AcOH	CH_3CN	0

[a] Reaction conditions: **1a** (0.2 mmol), NFSI (0.4 mmol), catalyst (10 mol %), additive (1 equiv), solvent (2 mL), 80 °C, N_2, 12 h. [b] ^1H NMR yield determined by analysis of the crude reaction mixture using CH_2Br_2 as the internal standard. [c] ^1H NMR yield of **3a**. [d] ^1H NMR Yield of acetoxylated product. [e] 60 °C. [f] 4 equiv of AcOH.

Table 2 Substrate scope[a,b]

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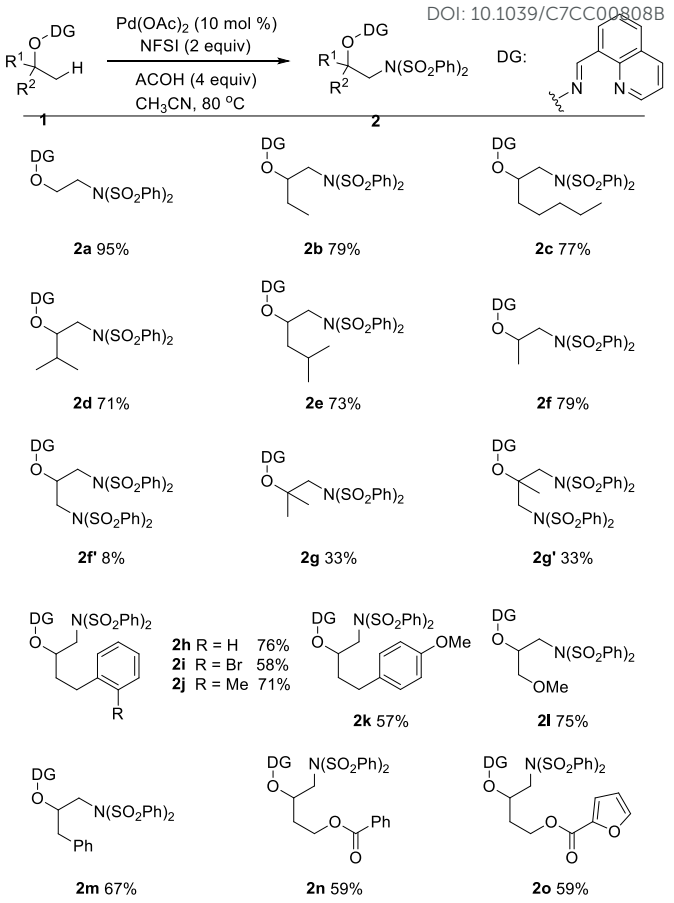
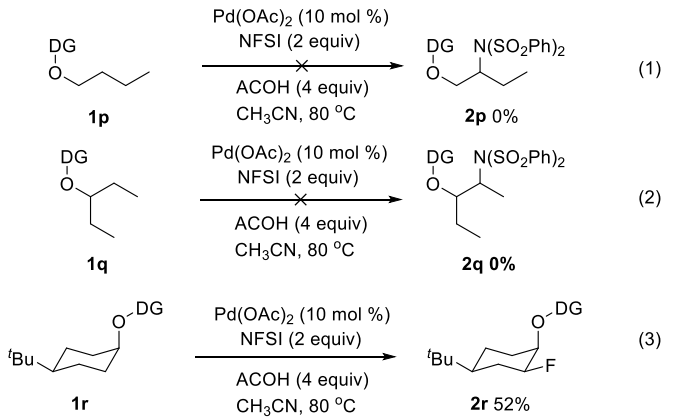
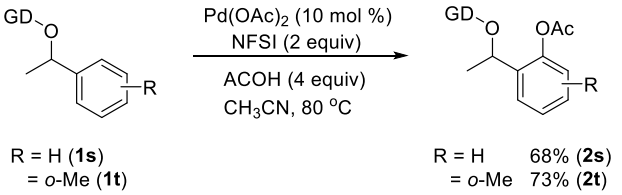


[a] Reaction conditions: **1** (0.2 mmol), NFSI (0.4 mmol), $Pd(OAc)_2$ (10 mol %), AcOH (0.8 mmol), CH_3CN (2 mL), 80 °C, N_2, 12 h. [b] Isolated yields.

lowering the reaction temperature, the yield was reduced dramatically (entry 12). We also screened the amounts of $Pd(OAc)_2$,NFSI and AcOH (Table S2). We found the reaction of **1a** with NFSI (2 equiv) in the presence of 4 equiv AcOH catalyzed by 10 mol % $Pd(OAc)_2$ in acetonitrile at 80 ˚C gave the desired amination product **2a** in 95 % yield (entry 13). No acetoxylated and fluorinated products were detected under the reaction condition. Other transition metals



Scheme 2 Reaction conditions: **1** (0.2 mmol), NFSI (0.4 mmol), $Pd(OAc)_2$ (10 mol %), AcOH (0.8 mmol), CH_3CN (2 mL), 80 °C, N_2, 12 h.

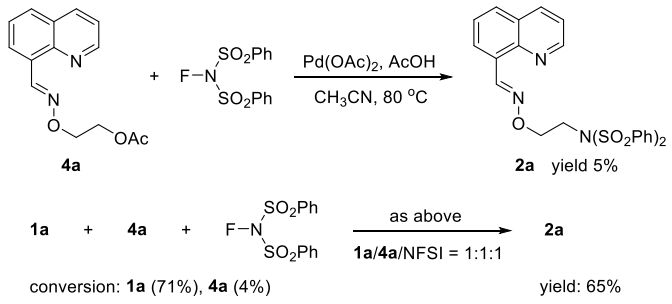


Scheme 3 Reaction conditions: **1** (0.2 mmol), NFSI (0.4 mmol), $Pd(OAc)_2$ (10 mol %), AcOH (0.8 mmol), CH_3CN (2 mL), 80 °C, N_2, 12 h.

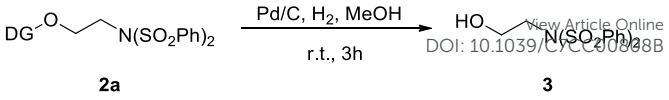
such as $[RhCp^*Cl_2]_2$, $[IrCp^*Cl_2]_2$ or $CoCp^*(CO)I_2$ were ineffective for the direct amination reaction (entries 14−17). The structure of **2a** is *E*-style, which was determined by the NOE effect between H on methylene and H on imine.

With the optimized conditions in hand, we next investigated the scope and limitations of this reaction using NSFI as the amino source (Table 2). The reaction proceeded smoothly with NSFI in the presence of $Pd(OAc)_2$ to afford corresponding $C(sp^3)$-amidated products in moderate to excellent yields with excellent site selectively at the *β*-methyl group. Various methyl C−H bonds at the *β*-position of primary, secondary and tertiary alcohols can be efficiently amidated (**2a** - **2g**). That amination of the *γ*- or *δ*-methyl group were not observed indicated that the formation of a five-membered ring intermediate in the cyclometalation step is predominantly favoured over the six or seven-membered ring intermediate (**2b** and **2e**). Diamidated products were also observed as minor products for substrates with more than one available methyl group (**2f'** and **2g'**). Substrates with aromatic rings, including electron-donating or electron-withdrawing substituents, give the corresponding products in moderate to good yields (**2h** - **2k**). Surprisingly, the amination reactions showed excellent *β*-methyl selectivity, even in the substrates with more activated methylene C−H bonds such as benzylic or *α*-heteroatomic hydrogens. Only *β*-methyl amination products were obtained under this catalytic system (**2l** and **2m**). Our protocol is different from the bidentate directed intramolecular amination systems,[11] in which the intramolecular benzylic C−H amidation was the predominant pathway. Ester (**2n**) and heteroarene (**2o**) were both tolerated well for the aminations.

Furthermore, it was found that β-methyl group is required for this reaction since substrates **1p** and **1q** with unactivated methylene C−H bonds failed to provide the desired products (Scheme 2, Eq. 1 and 2). Interestingly a competing fluorination reaction occurred in 52% yield for cyclic methylene substrate



Scheme 4 Control experiments.



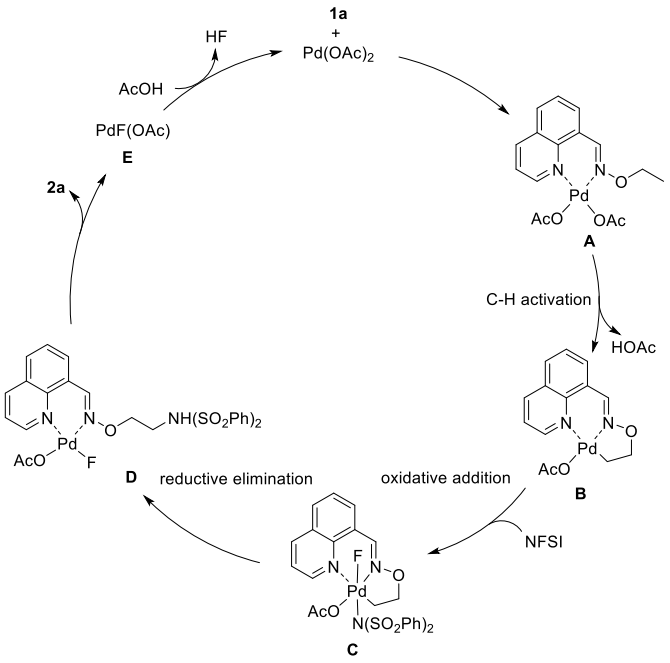
Scheme 5 Cleavage of the DG.

(Scheme 2, Eq. 3). The reason for this may be due to the relative easier dissociation of bis(phenylsulfonyl)-imino group than fluorine when reacting with methyl C-H bonds. In regards of methylene C-H bonds, steric hinderance decreases the accessibility of the bis(phenylsulfonyl)-imino group approach to the bulkier cyclic methylene than the methyl group. More efforts on fluorination reactions and detailed mechanistic studies are underway in our laboratory.

Substrates (**1s** and **1t**) with the 1-phenyl-substitute under the same reaction conditions can not be amidated , and instead, the acetoxylation of aromatic C-H bonds were formed in 68 and 73% yield (Scheme 3).

The control experiments were conducted to explore the plausible reaction pathway (Scheme 4). When acetoxylated compound **4a** was employed as substrate, only trace amount of product **2a** was obtained under the standard reaction conditon. Intermolecular competition reactions between **1a** and **4a** was also carried out. By treating **1a** (0.2 mmol) and **4a** (0.2 mmol) with NFSI (0.2 mmol) catalyzed by $Pd(OAc)_2$ at 80 °C for 12 h, the conversions of **1a** and **4a** were 71 and 4% , respectively, and **2a** was observed in 65% yield base on **1a**. It indicated that the amination product was derived from C-H bond activation.

To further evaluate the synthetic application of this methodology, removal of the DG was carried out under mild conditions. The Pd/C-catalysed hydrogenation condition can chemoselectively cleave the oxime N−O bond to give 1,2-amino alcohol in 90% yield with a H_2 balloon (Scheme 5).



Scheme 6 Proposed mechanism.

On the basis of the above observation and the previous reports,[12] a plausible catalytic cycle of this transformation is depicted in Scheme 6. First, **1a** coordinated with palladium to form intermediate **A**. Then through the activation of the C(sp^3)-H bond, intermediate **B** was generated. Next, Pd(IV)intermediate **C** was formed *via* oxidative addition of NFSI towards **B**. Subsequent reductive elimination of **C** followed by a ligand dissociation occurs to form product **2a** and a Pd(II) specie **E**. Following anion exchange, $Pd(OAc)_2$ was regenerated.

In conclusion, we have developed the Pd-catalyzed direct amination of unactivated C(sp^3)-H bond under mild reaction conditions using NFSI as amino source and oxidant. This protocol shows excellent chemoselectivity, functional group tolerance, and a broad substrate scope. Furthermore, the bidentate directing group can be easily cleaved to give 1,2-amino alcohols in excellent yield.

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