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# VIP $Pd^{II}$-Catalyzed Intermolecular Amination of Unactivated $C(sp^3)$–H Bonds

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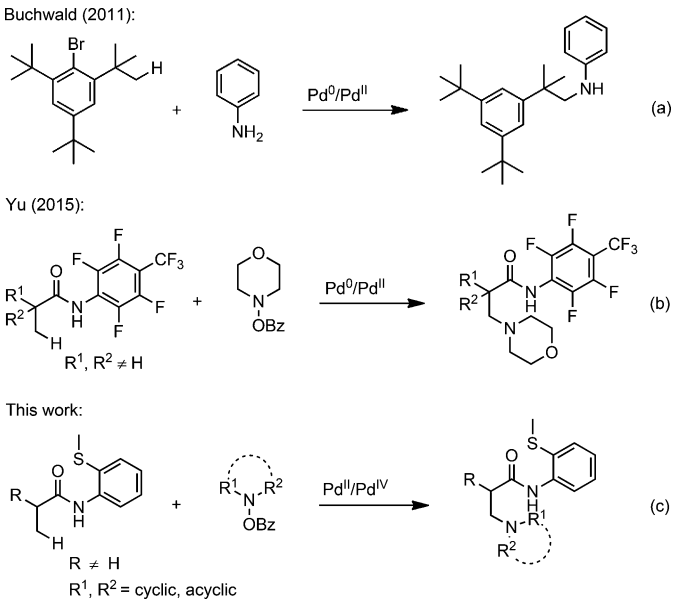
**Abstract:** $Pd^{II}$-catalyzed intermolecular amination of unactivated $C(sp^3)$–H bonds has been successfully developed for the first time. This method provides a new way to achieve the challenging intermolecular amination of unactivated $C(sp^3)$–H bonds, producing a variety of unnatural $\beta^2$-amino carboxylic acid analogues. This $C(sp^3)$–H amination protocol is demonstrated with a broad substrate scope, good functional-group tolerance, and chemoselectivity. It is operated without use of phosphine ligand or external oxidant.

The construction of C–N bonds is a highly important field since nitrogenated compounds are widely present in pharmaceuticals, agricultural chemicals, and natural products.[1] The importance of this field has led to the rapid development of C–N bond-forming reactions. Particularly notable among these reactions are Ullman–Goldberg-[2] and Buchwald–Hartwig-type[3] amination/amidation reactions, which involve metal-catalyzed coupling of preactivated (hetero)aryl (pseudo)halides with amines or amides. Despite these advances, recent years have seen significant progress in direct C–H activation/C–N bond-forming reactions since this strategy eliminates the step of substrate preactivation and, therefore, shortens the synthetic route. Nevertheless, the C–H activation/C–N bond-forming reactions are primarily focused on $C(sp^2)$–H amination/amidation catalyzed by diverse metals.[4–10] Development of intermolecular amination/amidation of unactivated $C(sp^3)$–H bonds is challenging and still in its infancy. Recently, several examples of intermolecular amidation of unactivated $C(sp^3)$–H bonds have appeared in the literature.[11] In comparison, intermolecular amination of unactivated $C(sp^3)$–H bonds is rare,[12] although the intramolecular version of this reaction has been reported.[13] Until now, only two examples of $Pd^0$-catalyzed intermolecular amination of unactivated $C(sp^3)$–H bonds were individually reported by Buchwald[12a] and Yu[12b] (Scheme 1a,b), and these represent a major breakthrough in this challenge. In Buchwald's protocol, the nitrogen source was limited to aryl amines. Yu's method was operated under the assistance of a monodentate fluorinated aniline and was successful in the preparation of only $\beta^{2,2}$-amino carboxylic acid derivatives. Development of new methods for intermolecular amination of unactivated $C(sp^3)$–H bonds to expand the current limitations is in high demand. Herein, we report the first example of $Pd^{II}$-catalyzed intermolecular amination of unactivated $C(sp^3)$–H bonds (Scheme 1c). This method works under the assistance of a bidentate directing group, 2-aminothioether,[14] and offers a different method to achieve the intermolecular amination of unactivated $C(sp^3)$–H bonds. This reaction produces a variety of unnatural and functional $\beta^2$-amino carboxylic acid analogues, a set of compounds that have wide biological and medicinal applications.[15]




**Scheme 1.** Intermolecular amination of unactivated $C(sp^3)$–H bonds.

In a program directed to develop new C–H activation reactions,[16] we became interested in the investigation of direct amination of β-$C(sp^3)$–H bonds of α-monosubstituted propionic acid derivatives. If successful, this transformation could produce a variety of unnatural $\beta^2$-amino carboxylic acid analogues in a straightforward manner. Amination of substrate **1a** by aminating reagent **2a**, *O*-benzoyl hydroxylmorpholine,[17] was chosen as the model reaction to begin the optimization (Table 1). After screening a variety of $Pd^{II}$ catalysts with $Cs_2CO_3$ as the base and benzene as the solvent (Table 1, entries 1–5), we quickly identified $PdCl_2$ as an optimal catalyst which afforded the amination product **3aa** in 85% yield (entry 5). $Pd^0$ cata-

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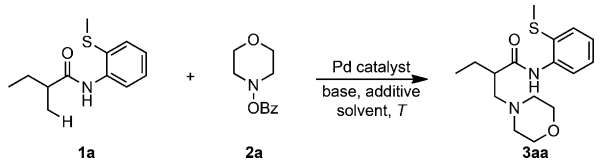
**Table 1.** Optimization of reaction conditions.[a]




1a 2a 3aa

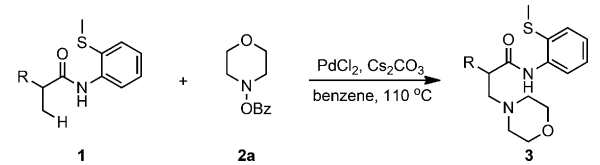
| Entry | Pd catalyst | Base | Solvent | Yield [%][b] |
|---|---|---|---|---|
| 1 | $Pd(OAc)_2$ | $Cs_2CO_3$ | benzene | 61 |
| 2 | $[Pd(tfa)_2]$ | $Cs_2CO_3$ | benzene | 26 |
| 3 | $[Pd(MeCN)_4(BF_4)_2]$ | $Cs_2CO_3$ | benzene | 20 |
| 4 | $[PdCl_2(cod)]$ | $Cs_2CO_3$ | benzene | 72 |
| 5 | $PdCl_2$ | $Cs_2CO_3$ | benzene | 85 |
| 6[c] | $[Pd_2(dba)_3]$ | $Cs_2CO_3$ | benzene | 0 |
| 7[c] | $[Pd(PPh_3)_4]$ | $Cs_2CO_3$ | benzene | 0 |
| 8[d] | $PdCl_2$ | $Cs_2CO_3$ | benzene | 0 |
| 9[e] | $PdCl_2$ | $Cs_2CO_3$ | benzene | 0 |
| 10 | $PdCl_2$ | $K_2CO_3$ | benzene | 28 |
| 11 | $PdCl_2$ | CsOAc | benzene | 6 |
| 12 | $PdCl_2$ | $Cs_2CO_3$ | toluene | 69 |
| 13 | $PdCl_2$ | $Cs_2CO_3$ | dioxane | 0 |
| 14 | $PdCl_2$ | $Cs_2CO_3$ | *t*-AmylOH | 0 |
| 15 | $PdCl_2$ | $Cs_2CO_3$ | DMF | 0 |
| 16[f] | $PdCl_2$ | $Cs_2CO_3$ | benzene | 92 |

[a] General procedure: **1a** (0.20 mmol), **2a** (0.40 mmol), Pd catalyst (10 mol%), and base (0.40 mmol) in solvent (1.0 mL) under 110 °C for 24 h. [b] Determined by $^1H$ NMR spectroscopic analysis of the crude product using $CH_2Br_2$ as an internal standard. [c] Reaction under rigorous $N_2$ protection. [d] Reaction with 20 mol% $PPh_3$ under rigorous $N_2$ protection [e] Reaction with 20 mol% BINAP under rigorous $N_2$ protection. [f] 2.5 equiv of **2a** was used. cod = 1,5-cyclooctadiene; tfa = trifluoroacetic acid.

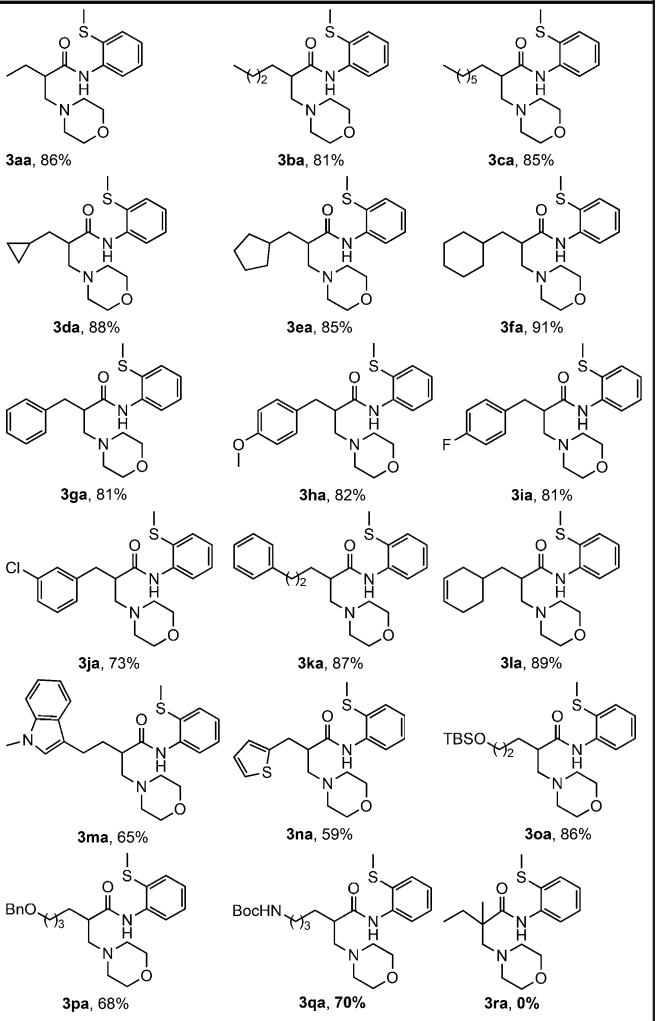
lysts, such as $[Pd_2(dba)_3]$ (dba = dibenzylideneacetone) or $[Pd(PPh_3)_4]$ were not effective (entries 6–7). Addition of phosphine ligands ($PPh_3$ or BINAP) (BINAP = (2,2′-bis(diphenylphosphino)-1,1′-binaphthyl)) to $PdCl_2$ completely inhibited the reaction (entries 8–9). Further investigation of bases revealed that $Cs_2CO_3$ was optimal. Other bases with different cation or anions from $Cs_2CO_3$ were inferior (entries 10–11). Solvent effects on the reaction were significant. We found that nonpolar solvents were tolerated in general. For example, besides benzene, toluene also afforded **3aa** in a useful 69% yield (entry 12). On the contrary, polar solvents were not effective (entries 13–15). Gratifyingly, when the amount of **2a** was used in 2.5 equivalents, the yield of **3aa** was further increased to 92% (entry 16).

With the optimal reaction conditions in hand, we explored the scope of the carboxylic acid derivatives. Various α-monosubstituted propionic acid derivatives were examined. It was delightful to find that the reaction conditions tolerated wide substrate scope as illustrated in Table 2. Substrates substituted by simple aliphatic chains were well tolerated to deliver the amination products in excellent yields (**3aa**–**ca**). Substrates containing cyclic aliphatic chains including cyclopropyl, cyclopentyl, and cyclohexanyl groups also underwent the amination reactions smoothly (**3da**–**fa**). In addition, benzyl analogues regardless of their electronic properties afforded the corresponding products in good yields (**3ga**–**ja**). Aryl substitution can be further extended to the δ-position without any problem (**3ka**).

**Table 2.** Substrate scope of carboxylic acid derivatives.[a,b]




1 2a 3

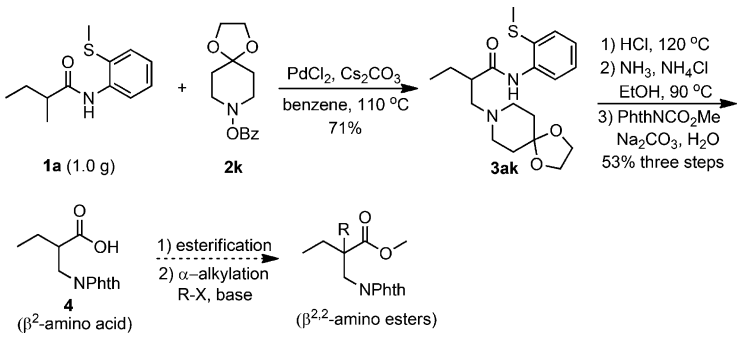



[a] Optimal reaction conditions: **1** (0.20 mmol), **2a** (0.50 mmol), $PdCl_2$ (10 mol%), and $Cs_2CO_3$ (0.40 mmol) in benzene (1.0 mL) under 110 °C for 24–34 h. [b] Isolated yield.

Further exploration revealed that complex substrates such as olefine (**3la**), indole (**3ma**), and thiophene (**3na**) analogues also survived under the reaction conditions. The success of these substrates revealed the high chemselectivity of this method in the activation of $C(sp^3)$–H over $C(sp^2)$–H bonds. Moreover, it was remarkable that other functional groups such as TBS ether (**3oa**), benzyl ether (**3pa**), and *tert*-butyloxycarbonyl (Boc)-protected amine (**3qa**) were also well tolerated without incident. It is worth noting that these functional groups could be utilized as handles for further transformations to diversify the product portfolio. Interestingly, tertiary substrate **1r** derived from 2,2-dimethylbutanoic acid did not

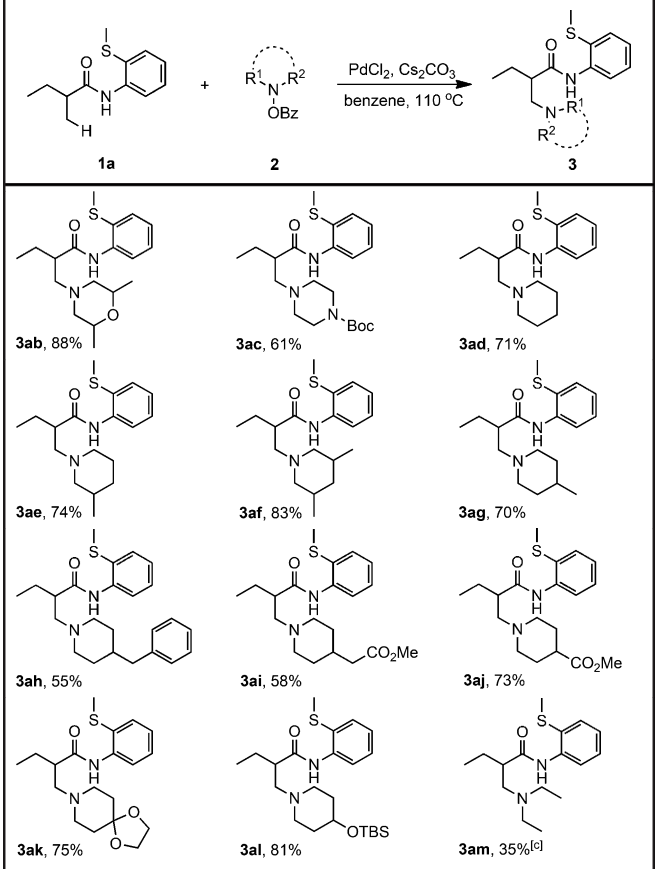
afford amination product **3ra** under the reaction conditions presumably due to the steric factor (Table 2).

We then examined the scope of aminating reagents in the coupling with **1a** (Table 3). We were delighted to find that the reaction conditions tolerated various amine partners. In addition to unsubstituted morpholine, sterically hindered 2,6-dimethylmorpholine also afforded the amination product **3ab** in 88% yield. Other medicinally useful amine partners including piperazine and piperidine also delivered the corresponding products without a problem (**3ac**–**ad**). The scope of the amine partners can be further extended to a variety of functional piperidines. Not only simple alkyl substitutions (**3ae**–**ah**), remarkably various functional groups including ester (**3ai**–**aj**), ketal (**3ak**), and TBS ether (**3al**) on the piperidines were also reserved under the reaction conditions. These functional piperidines could be further derivatized to synthesize other biologically active compounds. In particular, acyclic dialkylamine also underwent the amination reaction, albeit in moderate yield (**3am**). It is worth noting that for the first time acyclic dialkylamine was successful as an amine partner in the amination of unactivated C($sp^3$)–H bonds. Intriguingly, similar to the early $Pd^0$-catalyzed protocol,[12b] we found that pyrrolidine was not an effective amine partner under our reaction conditions.




**Scheme 2.** Preparation of β-amino acid.

**Table 3.** Substrate scope of aminating reagents.[a,b]

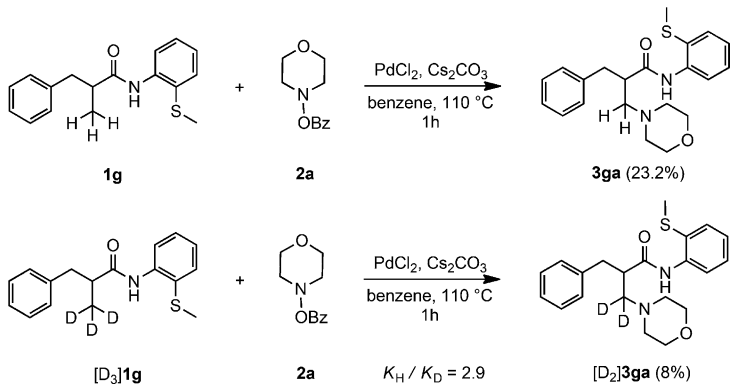



[a] Optimal reaction conditions: **1a** (0.20 mmol), **2** (0.50 mmol), $PdCl_2$ (10 mol%), and $Cs_2CO_3$ (0.40 mmol) in benzene (1.0 mL) under 110 °C for 24–34 h. [b] Isolated yield. [c] Unreacted **1a** was recovered in 55% yield.

The utility of the method was demonstrated in Scheme 2. Amination of **1a** by **2k** can be conducted on a gram scale to afford **3ak** in 71% yield. Following the literature procedure,[18] the directing group and piperidone unit of **3ak** were removed sequentially to deliver the free $\beta^2$-amino carboxylic acid, which was then converted to Phth-protected $\beta^2$-amino carboxylic acid **4** in 53% overall yield. The α-proton of **4** could be manipulated to introduce an additional substitution group for the preparation of diverse $\beta^{2,2}$-amino carboxylic esters.[19]

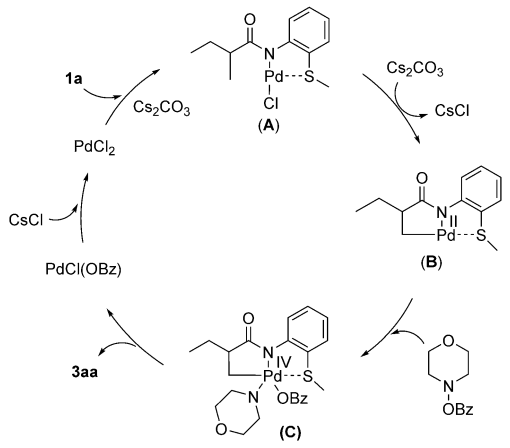
The significance of this method is worth noting in the following points. Firstly, the reaction shows broad substrate scope demonstrated by the β-amination of a variety of functional secondary carboxylic amides in Table 2. Additionally, the resulting secondary $\beta^2$-amino carboxylic amide products can be further derivatized to prepare tertiary $\beta^{2,2}$-amino carboxylic acid analogues by utilizing the α-proton as a handle, as illustrated in Scheme 2. Overall, not only was it applicable to directly prepare the secondary $\beta^2$-amino carboxylic acid analogues, but also the tertiary $\beta^{2,2}$-amino carboxylic acid analogues after additional transformation. The broad functional-group tolerance and strategic flexibility of this method was not seen in the early $Pd^0$-catalyzed protocol reported by Yu, which was restricted to the preparation of only tertiary $\beta^{2,2}$-amino carboxylic acid analogues.[12b] Secondly, this method avoids the use of phosphine as a ligand, which was necessary in the early $Pd^0$-catalyzed protocol.[12b] Essentially, this phosphine ligand-free method utilizes a bidentata 2-aminothioether as the directing group to achieve broader C($sp^3$)–H bond aminations than the early $Pd^0$-catalyzed protocol using a monodentata fluorinated aniline as the directing group.

We conducted kinetic isotope experiments to probe the reaction mechanism (Scheme 3). The result (parallel intermolecular KIE = 2.9) suggested that the cleavage of the β-C($sp^3$)–H bond of the substrate occurred as the rate-limiting step. Amination of chiral substrate (*S*)-**1a** (95% *ee*) with **2a** produced (*R*)-**3aa** (95% *ee*) without erosion of chirality (see the Supporting Information). This result implied that the reaction pathway did not involve the α-proton of the substrate. We have shown that $Pd^0$ or in situ-generated $Pd^0$ catalysts[20] were not effective




**Scheme 3.** Kinetic isotope experiments.

for this reaction (see Table 1, entries 6–7 and 8–9). Based on these observations, we exclude the involvement of a $Pd^0/Pd^{II}$ catalytic cycle for the reaction. Although additional solid evidence remains to be obtained, we propose a $Pd^{II}/Pd^{IV}$ catalytic cycle for this reaction.[4b–d] As shown in Scheme 4, under the assistance of 2-aminothioether and $Cs_2CO_3$, substrate **1a** can coordinate with $PdCl_2$ to form intermediate **A** as the initial step. Further activation of the β-C($sp^3$)–H bond generates $Pd^{II}$ intermediate **B**. Oxidative addition of *O*-benzoyl hydroxylmorpholine into **B** takes place to form $Pd^{IV}$ intermediate **C**, which eventually affords product **3aa** after reductive elimination. The catalytic cycle is restored after ligand exchange of $Pd^{II}$ catalyst.




**Scheme 4.** Proposed reaction mechanism.

In summary, we have successfully developed the first example of $Pd^{II}$-catalyzed intermolecular amination of unactivated C($sp^3$)–H bonds. This C($sp^3$)–H amination protocol produces diverse unnatural and functional β$^2$-amino carboxylic acid analogues. This method is demonstrated with broad substrate scope, good functional-group tolerance, and chemselectivity. In addition, this reaction is scalable on a gram scale. It is operated without use of phosphine ligand or external oxidant. Further investigation of the detailed reaction mechanism and an expansion of the reaction scope is currently in progress.

## Experimental Section

### General method

A 10 mL teflon-capped vial was charged with **1** (0.20 mmol), **2** (0.50 mmol), $PdCl_2$ (10 mol%), $Cs_2CO_3$ (0.40 mmol), and benzene (1.0 mL) under an air atmosphere. The vial was then tightly capped. The mixture was stirred at RT for 1 min for proper mixing of the reactants, and was then heated at 110 °C with vigorous stirring for 24–34 h. After this time, the vial was cooled to RT, diluted with ethyl acetate and filtered through a short pad of Celite. The filtrate was concentrated in vacuo and the residue was purified by flash chromatography on silica gel (ethyl acetate/petroleum ether) to afford the desired product **3**.

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**Keywords:** amination · C($sp^3$)–H activation · cross-coupling · palladium · β-amino acids

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