VIP Heterocycle Synthesis

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Synthesis of Indolines and Tetrahydroisoquinolines from Arylethylamines by Pd^{II}-Catalyzed C–H Activation Reactions**

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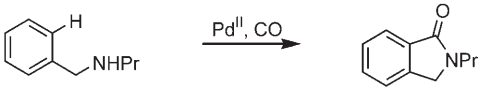
Owing to the prevalence of heterocyclic compounds in medicinal chemistry, the development of new transition-metal-catalyzed reactions for the formation of heterocycles continues to be an active area of research.[1,2] Construction of such ring systems by means of C–H activation followed by C–N bond formation is a complementary approach to the remarkably powerful Buchwald–Hartwig amination reaction.[3] For instance, Orito et al. developed a C–H activation/carbonylation process for the preparation of benzolactams [Eq. (1)].[4] Buchwald and co-workers reported a Pd-

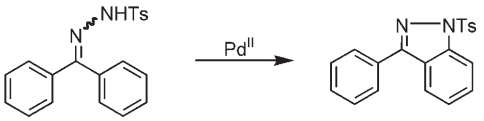


(1)

catalyzed formation of a carbazole ring from acetylated 2-phenylaniline [Eq. (2)].[5] Hiroya, Inamoto, and co-workers developed a protocol for making indazole rings from hydra-

(2)

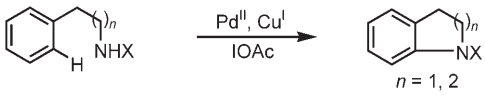
zones [Eq. (3), Ts = toluenesulfonyl].[6] Despite these important pioneering studies, a method for making indolines and



(3)

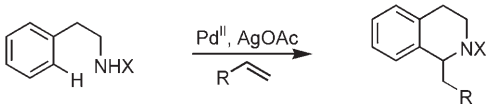
tetrahydroisoquinolines from readily available phenylethylamines and phenylpropylamines by C–H activation remains an unsolved problem owing to sluggish reactions proceeding via six- and seven-membered palladacycles.[7]

Herein we report a tandem C–H bond iodination/amination route for the preparation of indolines using Pd^{II}/Cu^{I} catalysts [Eq. (4)]. This reaction can also be modified to



(4)

prepare tetrahydroquinolines [Eq. (4)] and tetrahydroisoquinolines by using different substrates and reaction conditions [Eq. (5)].



(5)

Prompted by our recently developed iodination reaction for compounds with unactivated C–H bonds using a Pd^{II} catalyst and IOAc as the stoichiometric oxidant,[8] we envisioned that a tandem C–H bond-iodination/C–N bond-forming reaction using a combination of Pd^{II} and Cu^{I} catalysts could lead to an effective protocol for heterocycle synthesis. Thus, our first challenge was to develop an effective iodination reaction of C–H bonds using an amine as the directing group, which can subsequently react directly with the iodide to form the C–N bond. The aforementioned amino groups[4–6] and phenylsulfonamides[9] employed as directing groups for C–H activation reactions illustrate the feasibility of the proposed approach. However, none of these directing groups were effective for the type of substrates shown in Equations (4) and (5) owing to the reduced reactivity of six- and seven-membered palladacycles. We began to study a wide range of amino functionalities as directing groups to assist C–H activation. In order to form indolines, acetyl-, trifluoroacetyl-, Boc-, and Troc-protected 2-phenylethylamines were selected as substrates to develop a tandem iodination/amination reaction (Scheme 1). Substrates **1**–**4** were subjected to our previously developed iodination conditions.[8] The results are consistent with the hypothesis that the acidity of the NH moiety is crucial in promoting the C–H activation, presumably owing to formation of Pd–N bond while sufficient electrophilicity of Pd^{II} center is maintained. We therefore tested other phenylsulfonamide substrates. Notably, while benzenesulfonyl-protected 2-phenylaniline[9] was previously observed to undergo C–H activation/Heck coupling,[10] no significant improvement was observed with substrates **5**–**7**.

To further increase the acidity of the NH moiety and hence facilitate formation of the Pd–N bond, the trifluoro-

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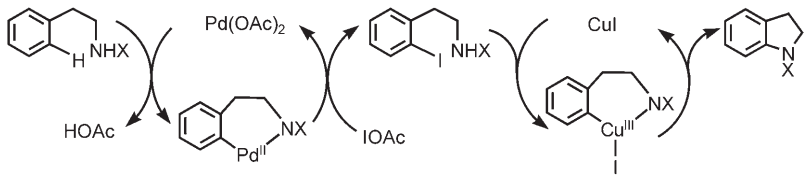
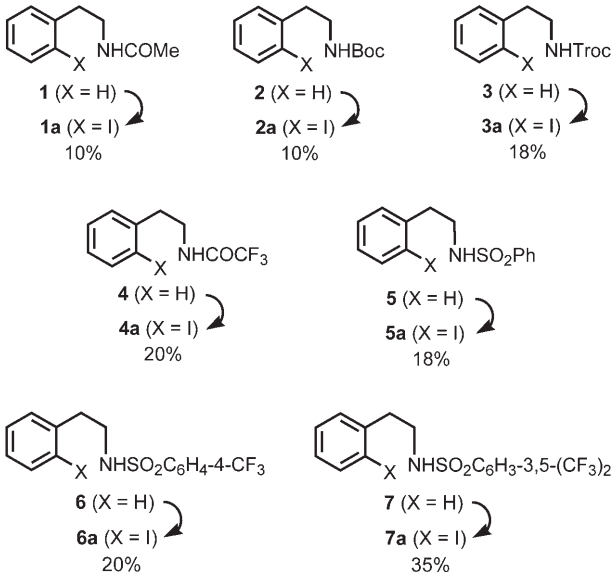
methylsulfonamide (triflamide, NHTf) derivative **8** of 2-*para*-tolylethylamine was prepared to test the iodination reaction. We found that the diiodinated product was obtained in synthetically useful yields (59% yield of isolated product) along with the monoiodinated products (10–20% by ^{1}H NMR analysis) (Table 1). Gratifyingly, triflamides of the natural amino acids phenylalanine and tyrosine are reactive under the same conditions (entries 3 and 4, Table 1). These products are valuable chiral building blocks for heterocycle synthesis. Iodination of triflamide **12** through a seven-membered cyclopalladation process also occurs, albeit giving lower yield (entry 5, Table 1). The iodination products are obtained in excellent yield with the mono-*ortho*-substituted substrates (entries 6 and 7, Table 1).

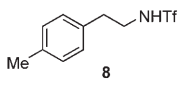
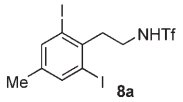
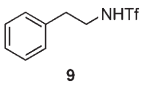
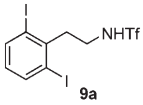
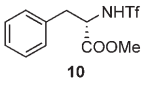
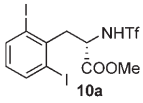
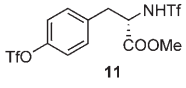
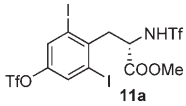
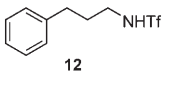
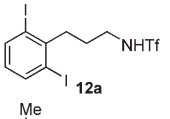
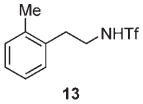
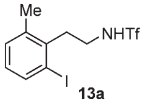
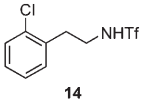
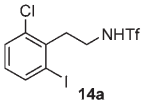


Scheme 2. Catalytic cycle for tandem C–H iodination/amination.



Scheme 1. C–H activation directed by acidic amides for the iodination of substrates **1**–**7**. Boc = *tert*-butyloxycarbonyl, Troc = 2,2,2-trichloroethoxycarbonyl.

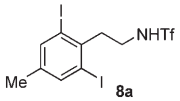
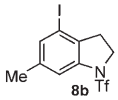
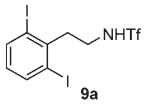
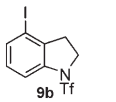
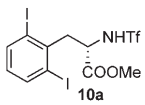
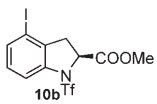
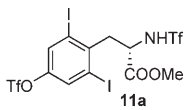
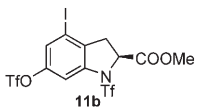
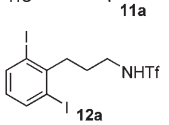
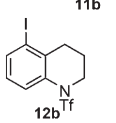
Table 1: Pd(OAc)$_2$-catalyzed iodination.[a]

Entry	Substrate	Product	Yield [%]
1			59
2			56
3			68
4			52
5			31[b]
6			91
7			85

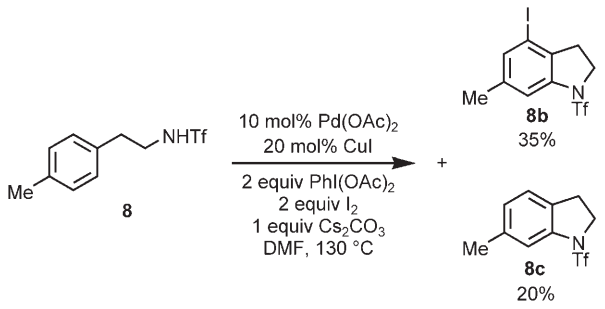
[a] Reaction conditions: 10 mol% Pd(OAc)$_2$, 2 equiv $C_6H_5I(OAc)_2$, 2 equiv I_2, 1 equiv $NaHCO_3$, DMF, 130°C, 72 h. [b] 15 mol% Pd(OAc)$_2$.

Next, we sought to develop conditions conducive for subsequent intramolecular amination. Since the iodination proceeds through Pd^{II}/Pd^{IV} catalysis,[8] a subsequent Pd^0-catalyzed Buchwald–Hartwig intramolecular amination would not be compatible. However, a Cu^I-catalyzed intramolecular amination[11] could, in principle, be accomplished under the same conditions if the C–H activation step is not adversely affected by Cu^I salts (Scheme 2). Thus, the diiodinated products were treated with CuI and Cs_2CO_3 in the same solvent (DMF) as that used for the iodination reaction. The intramolecular amination reaction is extremely effective affording the indolines (entries 1–4, Table 2) and tetrahydroquinoline (entry 5, Table 2) in excellent yields.[12] The remaining 5-iodo group in the products is a versatile functional group for further transformation, especially through Pd-catalyzed coupling reactions. Removal of the iodide can also be achieved by stirring with Pd/C under hydrogen atomosphere.

Table 2: CuI-catalyzed intramolecular amination.[a]

Entry	Substrate	Product	Yield [%]
1			96
2			95
3			92[b]
4			91[b]
5			92

[a] Reaction conditions: 0.5 equiv CuI, 1 equiv Cs_2CO_3, DMF, 130°C, 24 h. [b] 1 equiv CuI, 1 equiv $NaHCO_3$, DMF, 130°C, 24 h.

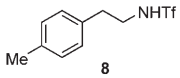
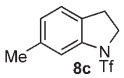
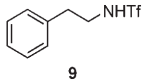
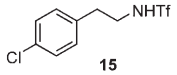
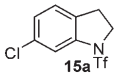
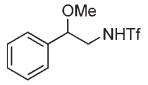
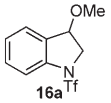
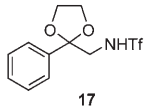
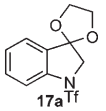
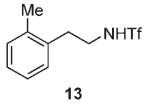
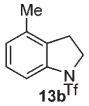
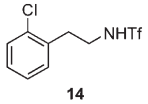
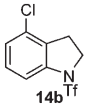


Scheme 3. One-pot iodination–amination of C–H bonds.

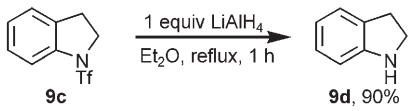
With the triflamide-directed iodination and amination procedures in hand, we subjected substrate **8** to reaction conditions for both of these transformations simultaneously. The tandem iodination/amination reaction proceeded to give a mixture of products **8b** and **8c** (Scheme 3). We reasoned that formation of **8b** from the diiodinated precursor could be minimized by using more CuI to accelerate the amination reaction of the monoiodinated precursor. Indeed, the use of 1 equiv of CuI significantly improved the selectivity in favor of the formation of indolines from the monoiodinated precursors (Table 3). Although the ester groups in substrates **10** and **11** are partially hydrolyzed in the presence of Cs_2CO_3, the tolerance of halides, benzylic methoxyl and acid-labile ketal groups (entries 3–5 and 7, Table 3) illustrates the potential utility of this new route for the preparation of indolines. Notably, the 5-chloroindoline **14b** is a valuable precursor for the preparation of 5-substituted analogues. The triflamide group can be readily removed by Hendrickson's procedure (Scheme 4).[13] The obtained indolines can also be oxidized to indoles by treating with MnO_2 at 40 °C.[14]

We envisioned that the triflamide-directed C–H activation could also be combined with a Heck coupling to give precursors from which tetrahydroisoquinolines could be prepared by an intramolecular metal-catalyzed addition of the sulfonamide to the olefin using recently reported procedures.[15] A wide range of substrates were subjected to conditions similar to those of the iodination reactions. The monoalkenylated products were obtained in 50–65% yield along with dialkenylated products in 10–20% yield (Table 4).

Table 3: One-pot intramolecular amination catalyzed by $Pd(OAc)_2$ and CuI.[a]

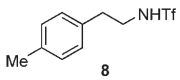
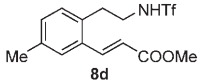
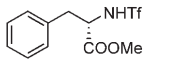
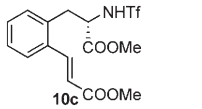
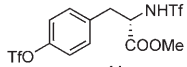
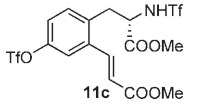
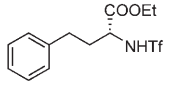
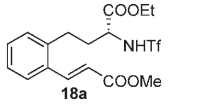
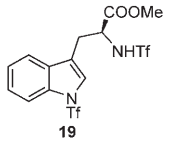
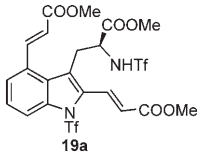
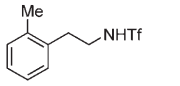
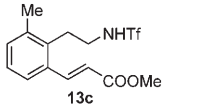
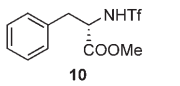
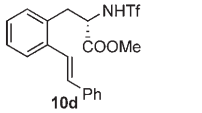
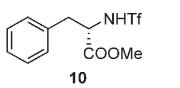
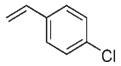
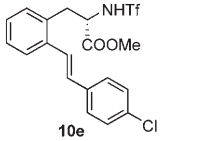
Entry	Substrate	Product	Yield [%]
1	 8	 8c	59[b]
2	 9	 9c	58[b]
3	 15	 15a	50[b]
4	 16	 16a	49[b]
5	 17	 17a	46[b]
6	 13	 13b	81[c]
7	 14	 14b	82[c]

[a] Reaction conditions: 10 mol% $Pd(OAc)_2$, 2 equiv $C_6H_5I(OAc)_2$, 2 equiv I_2, 1 equiv Cs_2CO_3, 1 equiv CuI, DMF, 130 °C, 96 h. [b] 5-Iodoindolines were isolated in 7—10% yield . [c] 0.5 equiv CuI.



Scheme 4. Deprotection of trifluorosulfonamide.

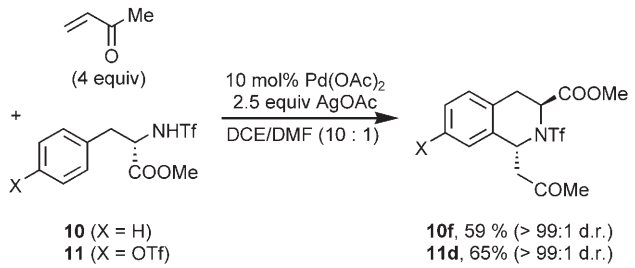
Table 4: $Pd(OAc)_2$-catalyzed alkenylation reactions.[a]

Entry	Substrate	Olefin	Product	Yield [%][b]
1	 8		 8d	50
2	 10		 10c	61[c]
3	 11		 11c	65[c]
4	 18		 18a	39
5	 19		 19a	58[d]
6	 13		 13c	87
7	 10		 10d	51[e]
8	 10		 10e	56[e]

[a] Reaction conditions: 10 mol% $Pd(OAc)_2$, 2.5 equiv AgOAc, 4 equiv olefin, 0.1 mL DMF, 2 mL dichloroethane, 130 °C, 72 h. [b] Dialkenylated products also formed in 10–20% yield. [c] 1 equiv NaH_2PO_4 was added to decrease the formation of the dialkenylated products. [d] Reaction was stopped after 85 h. [e] Reaction was stopped after 48 h.

Both electron-deficient and electron-rich olefins are reactive. While the formation of dialkenylated products reduced the efficiency of this reaction, the alkenylation of the *ortho*-substituted substrate **13** afforded **13c** in exceedingly high yield (entry 6, Table 4).

Notably, a tandem C–H alkenylation and aza-Michael addition proceeds to give the desired tetrahydroisoquinolines in high diastereoselectivity when vinyl ketones are used. Among the strategies for constructing isoquinoline rings, the Pictet–Spengler condensation and the Bischler–Napieralski cyclization are most widely used.[16] However, both of these methods often require two electron-donating groups on the aryl rings. The results in Scheme 5 show that our cyclization



Scheme 5. One-pot synthesis of tetrahydroisoquinoline.

reaction does not require electron-donating groups on the aryl rings. Trifluoromethylsulfonate at the *para* position does not retard the reaction (entry 3, Table 4). As shown in the tandem iodination and amination reaction, the electron-withdrawing chloro group is also tolerated (entries 3, 7, Table 3). In addition, various olefins are inexpensive reagents for introducing diversified substitutions at C1.

In summary, we have developed a promising C–H activation route for the preparation of indolines and tetrahydroisoquinolines from arylethylamines. The natural amino acids phenylalanine, tyrosine, and tryptophan can be converted into various heterocycles using this method.[17] We are currently exploiting this method to access medicinally relevant heterocycle libraries.

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