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Communications

Pd(II)-Catalyzed C-H Amination for *N*-Heterocyclic Synthesis

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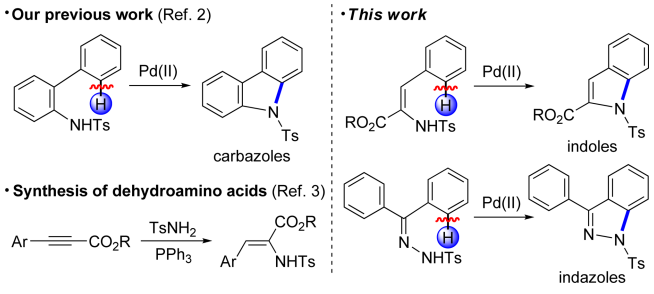
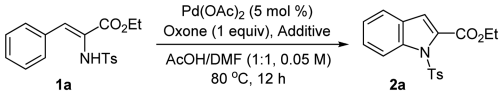
Owing to the prevalence of *N*-heterocycles in agrochemicals, pharmaceuticals, and many other biologically active compounds, the development of new synthetic protocols for the formation of *N*-heterocycles continues to be an active area of research. In particular, direct C-H amination without prefunctionalization of simple starting materials to the corresponding organic (pseudo)halides has emerged as a powerful, atom-economic, and environmentally benign tool for the synthesis of a wide range of *N*-heterocycles.[1] Recently, our group reported a Pd-catalyzed oxidative C-H amination of *N*-Ts-2-arylanilines for the synthesis of carbazoles (Scheme 1).[2] Considering the skeletal similarity of their structures to those of *N*-Ts-2-arylanilines, we were interested in investigating whether the readily available substrates, *i.e.*, (*Z*)-*N*-Ts-dehydroamino acid esters[3] and *N*-Ts-hydrazones, could also undergo the similar Pd-catalyzed oxidative C-H amination to afford the corresponding indole-2-carboxylic acid esters and indazoles, respectively (Scheme 1). Herein we disclose the realization of this proposal.[4]

In light of our recent success in Pd-catalyzed oxidative C-H amination of *N*-Ts-2-arylanilines,[2] we began our studies on the proposed oxidative C-H amination reaction using (*Z*)-*N*-Ts-dehydroamino acid ester (**1a**) as the test substrate (Table 1). Similar to our previous work,[2] it was revealed that $Pd(OAc)_2$, Oxone, and acid/DMF cosolvent system were the catalyst, oxidant, and solvent of choice, respectively, for this transformation. In contrast to our previous work using PivOH, however, AcOH as a cosolvent proved superior among all the acids examined. In addition, the use of molecular sieve 4 Å and/or K_2CO_3 as an additive further improved the yield



Scheme 1. C-H amination for heterocyclic synthesis.

Table 1. Optimization studies



Entry	Additive (equiv)	Yield (%)[a]	Entry	Additive (equiv)	Yield (%)[a]
1	-	53	8[e]	K_2CO_3 (1)	(45)
2[b]	-	47	9[f]	K_2CO_3 (1)	(35)
3[c]	MS 4A (600 mg/mmol)	68 (63)	10[g]	K_2CO_3 (1)	59
4[c]	MS 4A (600 mg/mmol), K_2CO_3 (1)	65	11[h]	K_2CO_3 (1)	39
5[c]	K_2CO_3 (1)	61 (56)	12[i]	K_2CO_3 (1)	31
6	K_2CO_3 (2)	31	13[j]	K_2CO_3 (1)	(52)
7[d]	K_2CO_3 (1)	44	14[k]	K_2CO_3 (1)	(54)

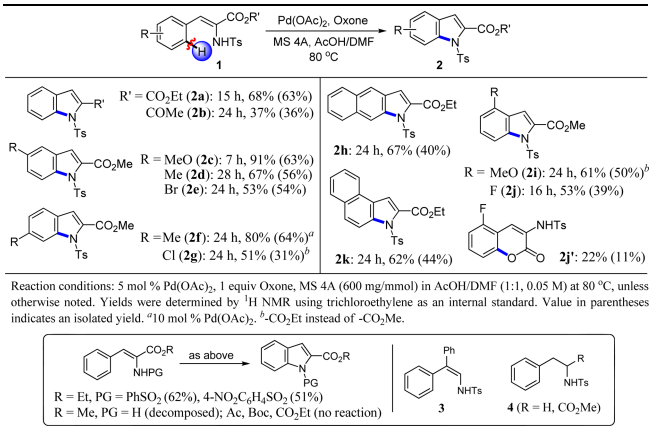
[a]Determined by ^{1}H NMR using trichloroethylene as an internal standard. Value in parentheses indicates an isolated yield. [b]In 0.1 M AcOH/DMF (1:1). [c]For 15 h. [d]Using PivOH instead of AcOH. [e]10 mol % $Pd(OAc)_2$ for 24 h. [f]2 mol % $Pd(OAc)_2$ for 24 h. [g]2 equiv Oxone. [h]In 0.05 M AcOH/DMF (1:2). [i]In 0.05 M AcOH/DMF (2:1). [j]At 100 °C. [k]At 60 °C for 20 h.

< Ineffective (or less effective) reaction parameters >
- Oxidants: $K_2S_2O_8$, $CuCl_2$, $Cu(OAc)_2$, AgOAc, Ag_2O, Ag_2CO_3, benzoquinone, $PhI(OAc)_2$
- Solvents: DMSO, *t*BuOH, 1,2-dichloroethan, THF, 1,4-dioxane, MeCN, toluene
- Acids: PivOH, CF_3CO_2H, *p*TsOH, TfOH, 1-AdCO$_2$H, $PhCO_2H$, *conc.* HCl
- Pd catalysts: $Pd(O_2CCF_3)_2$, $PdCl_2$, $PdCl_2(MeCN)_2$, $PdCl_2(PhCN)_2$, $PdCl_2(PPh_3)_2$, $PdCl_2$(dppf)
- Additives: Na_2CO_3, Cs_2CO_3, K_3PO_4, NaOAc, NaOH, benzoquinone, *p*TsOH, H_2O

(entries 3-5). Subsequently, we screened other parameters (amounts of additive, catalyst, and oxidant; solvent ratio; temperature; other acid cosolvent) to find more effective reaction conditions (entries 6-14). Finally, an optimal reaction conditions was established as entry 3 in Table 1, giving **2a** in 63% isolated yield.

With the optimized conditions in hand, we examined the effect of *N*-protecting groups. As expected, the acidity of NH group had a great influence on the chemical reactivity, an observation that is in line with the protecting group effect described in our previous work and other related reports.[2,4e,4l,4n] The effectiveness of sulfonyl, especially *p*-toluenesulfonyl (Ts), as the preferred group for this reaction was immediately apparent.[2,4d,4i,4l,4n-o] Next, we set out to explore the substrate scope of this process (Table 2). Replacing the ester group with a ketone moiety, the desired indole **2b** was uneventfully obtained, albeit in only moderate yield. A variety of (*Z*)-*N*-Ts-dehydroamino acid esters underwent C-H amination smoothly to afford the corresponding indoles irrespective of the aryl substitution, showing little electronic and/or steric dependence. Both electron-donating and -with-

Table 2. Substrate scope: Synthesis of indoles



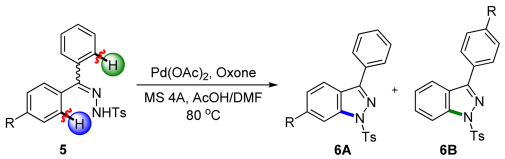
Reaction conditions: 5 mol % $Pd(OAc)_2$, 1 equiv Oxone, MS 4A (600 mg/mmol) in AcOH/DMF (1:1, 0.05 M) at 80 °C, unless otherwise noted. Yields were determined by ^{1}H NMR using trichloroethylene as an internal standard. Value in parentheses indicates an isolated yield. [a]10 mol % $Pd(OAc)_2$. [b]-CO_2Et instead of -CO_2Me.

drawing substituents were well tolerated. *m*-Substituted substrates showed remarkable regioselectivity, leading to products originating from activation of the less hindered C-H bond (**2c-e** and **2h**). Compared to other substrates, the reaction of *m*-MeO-substituted substrate proceeded relatively fast (**2c**), presumably supporting the electrophilic nature of this process. Particularly noteworthy is that halogenated substrates afforded products with the halogen substituents remaining intact, where the formation of dehalogenated products was not observed (**2e**, **2g**, and **2j**). While a clear mechanism is elusive at this juncture, interestingly, the reaction of 2-fluoro-substituted substrate gave a small amount of coumarin derivative **2j'** along with the desired indole product **2j**. On the other hand, enamine **3** led to a complicated mixture and no reaction occurred with phenethylamine **4**, observations that are consistent with the significant influence of a substitution pattern on the chemical reactivity described in the previous related works.[5]

Subsequently, we investigated the Pd-catalyzed C-H amination using a series of benzophenone *N*-Ts-hydrazones **5** for the formation of indazoles **6** (Table 3). The corresponding reaction proceeded smoothly under the same reaction conditions as the earlier one. In the cases of **5b-c** and (*E*)-**5d** (entries 2-4), product ratios (**6A**:**6B**) were similar to those of starting materials (*Z*:*E*), suggesting the relatively slow rate of hydrazone isomerization compared to that of cyclization ((*Z*)-**5** → **6A**, (*E*)-**5** → **6B**). In sharp contrast, when more electron-deficient aromatic ring resides proximate to the NHTs group (*e.g.*, (*Z*)-**5d** and **5e**, entries 5-6), the isomerization of hydrazones seems to precede a cyclization.[4i] *E*/*Z* mixture **5e** bearing a strong electron-withdrawing group (*i.e.*, NO_2) afforded only **6eB** resulting from the regioselective cyclization at the non-substituted benzene ring (entry 6), further evidence in support of the electrophilic nature of this process.

In summary, we have developed the Pd-catalyzed oxidative C-H amination of the readily available (*Z*)-*N*-Ts-de-

Table 3. Synthesis of indazoles



Entry	R (*Z*:*E*)	*t* (h)	Yield (%, **6A**:**6B**)[a]	Entry	R (*Z*:*E*)	*t* (h)	Yield (%, **6A**:**6B**)[a]
1	H (**5a**)	3	52 (45) (**6a**)	4	Cl (0:1) (**5d**)	4	46 (37) (**6d**, 0:1)
2	MeO (0.9:1) (**5b**)	4	65 (38) (**6b**, 0.9:1)	5	Cl (1:0) (**5d**)	4	49 (32) (**6d**, 1:1)
3	Me (1:1) (**5c**)	3	57 (48) (**6c**, 1:0.8)	6	NO_2 (0.4:1) (**5e**)	6	49 (35) (**6e**, 0:1)

Reaction conditions: 5 mol% $Pd(OAc)_2$, 1 equiv Oxone, MS 4A (600 mg/mmol) in AcOH/DMF (1:1, 0.05 M) at 80 °C. [a]Yield and ratio were determined by ^{1}H NMR using trichloroethylene as an internal standard. Value in parentheses indicates an isolated yield.

hydroamino acid esters and *N*-Ts-hydrazones to afford a variety of indole-2-carboxylic acid esters and indazoles, respectively. Further investigations to expand the scope of this reaction are currently underway in our laboratory.

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