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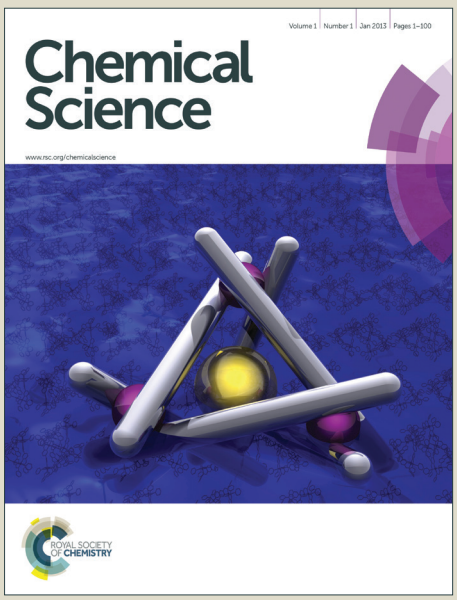

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ARTICLE

Palladium-Catalyzed Benzo[*d*]isoxazole Synthesis by C-H Activation/[4+1] Annulation

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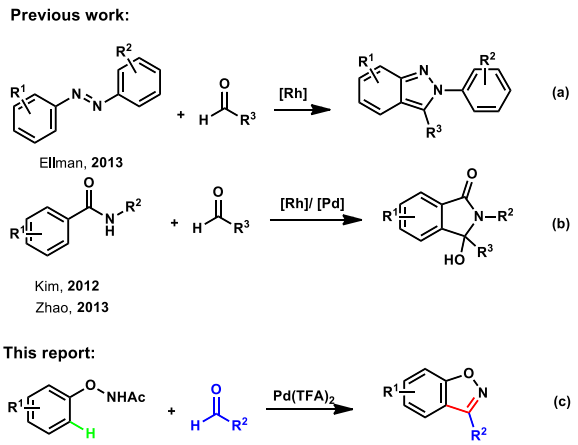
We report a palladium-catalyzed intermolecular [4+1] annulation of N-phenoxyacetamides with aldehydes to form 1,2-benzisoxazoles. By activating the C-H bonds ortho to phenol-derived O-N bonds, the method enables the simultaneous construction of C-C and C=N bonds in 1,2-benzisoxazoles with the O-N bonds intact. The method has been successfully applied to the synthesis of the active pharmaceutical intermediates, such as risperidone.

Introduction

Transition metal-catalyzed C-H activation/annulation reaction has become one of the most important and powerful methods in organic synthesis.[1] The direct insertion of unsaturated molecules via C-H bond transformation offers many efficient syntheses in an atom-economic fashion. Thanks to their commercial availability and low cost, aldehydes are widely used as coupling partners in metal-catalyzed C-H functionalizations.[2] Several recent reports utilized aldehydes in directed transition metal-catalyzed annulations (Scheme 1), which enabled simultaneous formation of C-C and C-heteroatom bonds.[3] Specifically, there are three reports highlighting a [4+1] annulation strategy involving aldehydes. Ellman et al. demonstrated a highly efficient Rh(III)-catalyzed reaction between azobenzenes and aldehydes to yield substituted N-aryl-2H-indazoles (Scheme 1a).[3a] Kim et al. reported the synthesis of 3-Hydroxyisoindolin-1-ones via a Rh(III)–catalyzed cascade reaction.[3b] Zhao and co-workers recently reported improved Pd(II)-catalyzed reaction conditions (Scheme 1b).[3c]

Many natural products and pharmaceuticals, such as risperidone and zonisamide, contain 1,2-benzisoxazoles as a key fragment.[4] We hypothesized that N-phenoxyacetamides[5] might react with aldehydes to form 1,2-benzisoxazoles using a catalytic [4+1] annulation strategy (Scheme 1c). Herein we report the first example that introduces Pd(II)-catalyzed intermolecular C-H activation route for the simultaneous construction of C-C and C=N bonds in 1,2-benzisoxazoles.

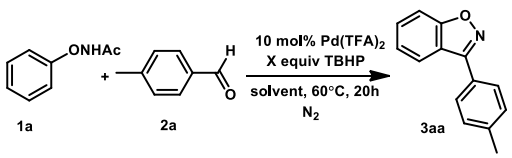


Scheme 1 Heterocycle formation through [4+1] annulation.

Results and discussion

The initial reaction of N-phenoxyacetamide (**1a**) and *p*-tolualdehyde (**2a**) was carried out in the presence of 10 mol% $Pd(TFA)_2$ and 4 equiv *tert*-butyl hydroperoxide (TBHP) at 80℃ in THF under N_2 atmosphere, affording the desired product **3aa** in 31% yield (Table 1, entry 1). The crystal structure of product **3aa** is shown in Table 2.[6] Other oxidants such as Ag salts, $K_2S_2O_8$ and $Cu(OAc)_2$ did not promote the desired reaction (see Table S1). We also examined different additives and found that acids and bases did not improve the reaction yield (see Table S1). A variety of solvents were screened. DMSO improved the yield to 59% (entry 3) and *t*-AmOH proved to be the most effective solvent, affording the product in 75% yield (entry 5), indicating that solvent played a key role in the reaction. Gratifyingly, by lowering the reaction temperature to 60℃, the yield was improved to 85% (entry 6). Lowering the catalyst loading from 10 mol% to 5 mol%, the yield reduced obviously from 85% to 73% (entry 7). The yield had no obvious impact when 2.5 equiv TBHP was used in place of 4 equiv TBHP (entry 9). In the absence of TBHP, there was no product observed (entry 10). Eventually we set the standard reaction conditions to be $Pd(TFA)_2$ (10 mol%) and TBHP (2.5 eq) in *t*-AmOH under nitrogen at 60℃.

Table 1 Optimization of Reaction Conditions[a,b]

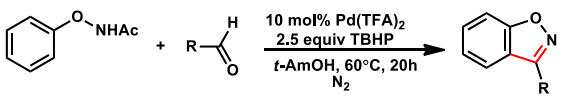


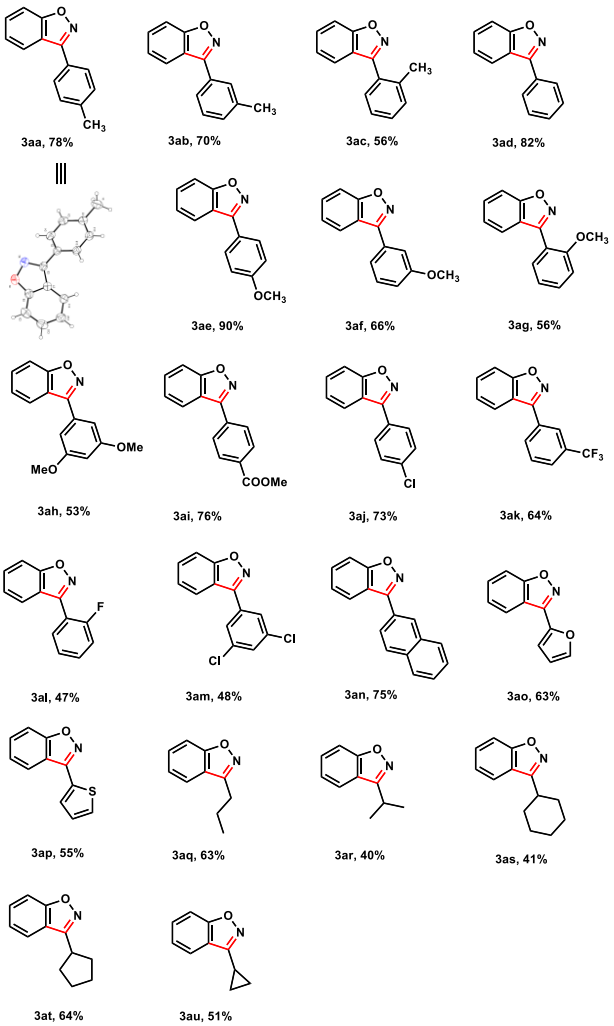
Entry	Solvent	X	Yield[%]
1[c]	THF	4	31
2[c]	1,4-dioxane	4	46
3[c]	DMSO	4	59
4[c]	*t*-BuOH	4	46
5[c]	*t*-AmOH	4	75
6	t-AmOH	4	85
7[d]	*t*-AmOH	4	73
8	*t*-AmOH	3	80
9	*t*-AmOH	2.5	88
10	*t*-AmOH	-	N.R.

[a]Determined by GC analysis using mesitylene as an internal standard. [b]All reactions were kept in dark place. [c]reaction at 80℃. [d]5 mol% $Pd(TFA)_2$.

Next, we explored the substrate scope for aldehydes (Table 2). The reaction went well for diverse substrates including aromatic, heterocyclic, and aliphatic aldehydes. When benzaldehyde derivatives were used as the starting materials, electron-donating substitution groups such as methyl (**2a**, **2b**, **2c**) and methoxyl (**2e**, **2f**, **2g**) afforded the corresponding products in moderate to high yields ranging from 56% to 90%, while electron-withdrawing groups such as ester (**2i**), trifluoromethyl (**2k**) and naphthyl (**2n**) also gave products in yields ranging from 64% to 76%. With the same substitution group, the yield was typically highest when the para-positions of the phenyl ring was occupied, and lowest for the ortho-substitituted benzaldehyde (**3aa**>**3ab**>**3ac**, **3ae**>**3af**> **3ag**). This trend held true for different substitution groups of the same electron withdrawing category on the phenyl ring (**3ai**, **3aj**>**3ak**>**3al**), indicating that steric hindrance might play a key role in the reaction. This transformation tolerated dual-substitution, such that 3,5-dimethoxybenzaldehyde (**2h**) and 3,5-dichlorobenzaldehyde (**2m**) proceeded smoothly to afford products in 53% and 48% yield, respectively. Heterocyclic aldehydes such as furfural (**2o**) and 2-thiophenecarboxaldehyde (**2p**) proceeded smoothly in moderate yields. Various aliphatic aldehydes could also form the desired products under standard condition. Simple aliphatic aldehydes, such as butyraldehyde (**2q**) offered the desired product in 63% yield and the branched isobutyraldehyde (**2r**) gave the corresponding product in 40% yield. The cycloalkane carboxaldehydes such as cyclohexanecarboxaldehyde (**2s**) and cyclopentanecarboxaldehyde (**2t**) participated in the coupling reaction to furnish products in 41% and 64% yield, respectively. The coupling reaction was facile enough that the cyclopropyl ring was kept intact when cyclopropanecarboxaldehyde (**2u**) reacted with N-phenoxyacetamide to afford the 3-cyclopropyl-1,2-benzisoxazole in 51% yield.

Table 2 Scope of Aldehydes[a,b]

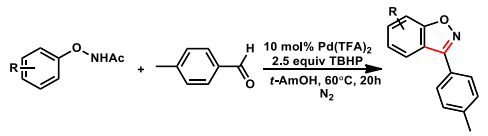


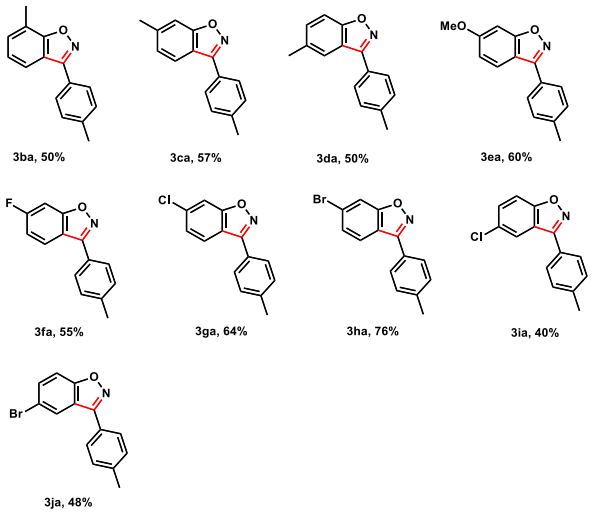


[a]Reaction conditions: 1a (0.2 mmol), 2 (0.4 mmol), *t*-AmOH (1 ml). [b]isolated yields.

The scope of the substituents on N-phenoxyacetamide was also investigated (Table 3). N-phenoxyacetamides with either electron-rich or electron-deficient substituents proceeded smoothly. A variety of functionalities including methoxyl, fluoro, chloro and bromo groups were tolerable. The meta-substituted N-phenoxyacetamides were annulated only at the less hindered ortho position. The complete regiospecificity suggested again that steric effect is important (**3ca**, **3ea**-**3ha**). When the substitutes on N-phenoxyacetamides were para (**3ga**, **3ha**) to the newly formed carbon-carbon bond, the yields were higher than that when substitutes were meta (**3ia**, **3ja**), and it might be attributed to the competing inductive effect and resonance stabilization， which could also explain the tendency of yield, **3ha**>**3ga**>**3fa**.

Table 3 Scope of N-Phenoxyacetamides[a,b]

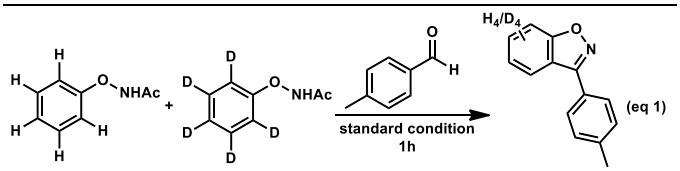




[a]Reaction conditions: 1 (0.2 mmol), 2a (0.4 mmol), *t*-AmOH (1 ml). [b]Isolated yield.

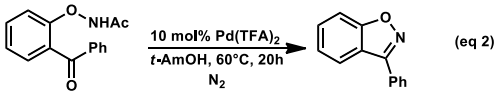
Mechanism

The kinetic isotope effect experiment was carried out between equimolar amounts of deuterio-**1a** and N-phenoxyacetamide **1a** with aldehyde **2a** under our standard conditions for one hour. It gave a K_H/K_D ratio of 3.2, indicating that the C-H bond cleavage was involved in the product determining step (eq 1).[7]



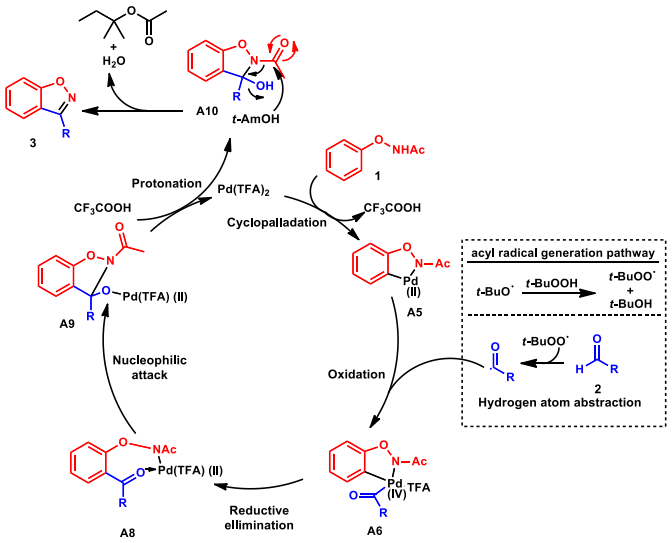
K_H/K_D=3.2

To probe the catalytic mechanism, we carried out the model reaction with 10 mol% $Pd(TFA)_2$ or 1 equiv $Pd(TFA)_2$ in the absence of TBHP, no desired product was detected, demonstrating that Pd(II)/Pd(IV)/Pd(II) catalytic cycle instead of the Pd(II)/Pd(0)/Pd(II) cycle. When we added a radical scavenger, such as 2,2,6,6-tetramethylpiperidin-1-oxyl (TEMPO),[8] to the reaction, the reaction rate was suppressed in a dose-dependent manner from GC analysis. Thus radical intermediates might be involved in the mechanism. When the substrate (**1k**) was treated with 10 mol% $Pd(TFA)_2$ in *t*-AmOH at 60℃ under N_2, it was exclusively converted to the corresponding product **3ad,** indicating that **1k** was likely the intermediate in the process of the reaction (eq 2) (see the Supporting Information for mechanism study in detail).

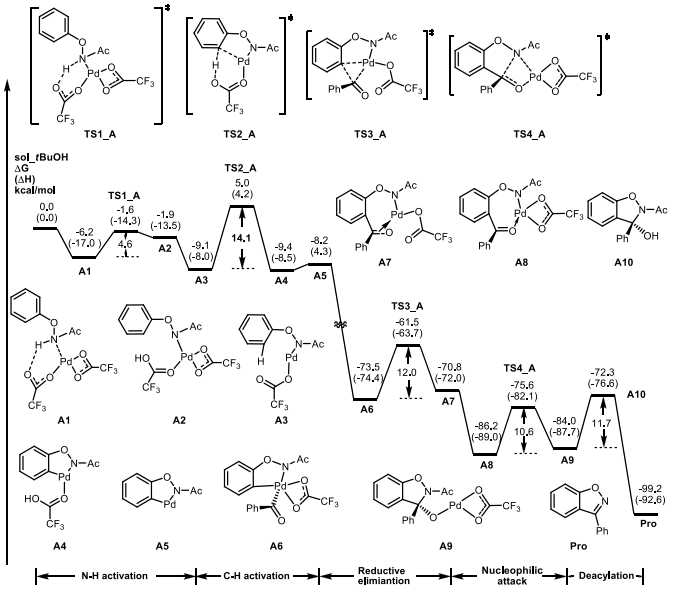


1k 3ad
conversion=100%
Yield (GC)=86%

On the basis of these observations, a possible mechanism was proposed as shown in Scheme 2. Density functional theory (DFT) studies were conducted to further elucidate the mechanism (Scheme 3). The catalyst $Pd(TFA)_2$ and substrate N-phenoxyacetamides were taken as the reference point. The catalytic cycle started from $Pd(TFA)_2$, which was first ligated to compound **1** with concomitant loss of two molecules of trifluoroacetic acid. The N-H activation step via **TS1_A** had a very low barrier (4.6 kcal/mol), which contributed to the deprotonated N-phenoxyacetamide in intermediate **A2**. Next, we proposed that intermediate **A4** was obtained via C-H activation pathway through a concerted metalation-deprotonation (CMD) transition state (**TS2_A**). The CMD step had an activation energy of about 14.1 kcal/mol, which is the rate-determining step. Subsequently, the trifluoroacetic acid ligand dissociated and produced Pd(II) complex **A5**. The oxidative addition of the intermediate **A5** with acyl radical, which was generated from aldehyde via hydrogen atom abstraction by *t*-BuOO·[9] from TBHP, would generate a Pd(IV) intermediate **A6**. This process was calculated to be very exergonic (ΔG=-65.3 kcal/mol). Reductive elimination from intermediate **A6** via **TS3_A** ($\Delta G^{\ddagger}$= 12.0 kcal/ mo1) allowed for the C-C bond formation and delivered intermediate **A8**. Intramolecular nucleophilic attack occurred via **TS4_A** to form a palladium alkoxide **A9**, which was protonated by trifluoroacetic acid to afford the corresponding organic intermediate **A10**. Finally, de-acylation and dehydration yielded the desired product **3** and regenerated the palladium catalyst. The other two possible mechanisms, aldehyde insertion mechanism[2c] and nitrogen radical initiation mechanism[3c] were also studied and found to be unfavorable (see **SI**).

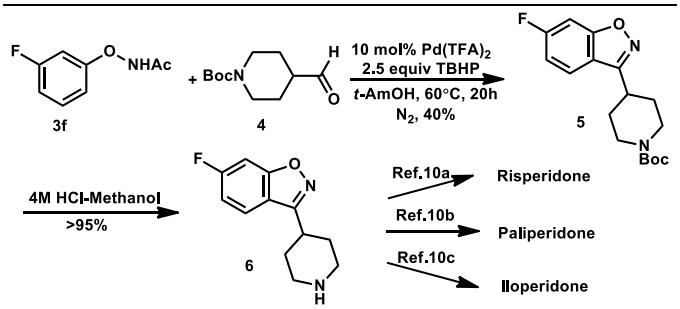


Scheme 2 Proposed mechanism of 1,2-benzisoxazole synthesis.



Scheme 3 The M06 free energy profile for the palladium-catalyzed benzo[*d*]isoxazole synthesis. Enthalpies are given in parentheses.

The synthetic applicability of our methodology was further illustrated by the assembly of a 1,2-benzisoxazole compound **6** (Scheme 4). The desired product **5** was obtained conveniently in 40% yield in a single step under our standard reaction condition. Compound **5** was further deprotected in nearly quantitative yield (>95%). Compound **6** was the key intermediate in the synthesis of pharmaceuticals of risperidone, paliperidone and iloperidone.[10]



Scheme 4 The catalytic synthesis of key intermediate 6.

Conclusions

Taken together, we have developed a novel Pd(II)-catalyzed intermolecular [4+1] annulation for the synthesis of 1,2-benzisoxazoles utilizing N-phenoxyacetamides and aldehydes as starting materials. Interestingly, Lu and co-workers recently reported Rh-catalyzed directed C-H bond activations on N-phenoxyacetamides. Their ingenious work suggested that the O-N functionality acted as an internal oxidant as well as a directing group.[5] In contrast, the O-N bonds were kept intact and became part of the 1,2-benzisoxazole products in our Pd-catalyzed system. DFT calculations on our Pd-catalyzed reaction supported a Pd(II)/Pd(IV)/Pd(II) catalytic cycle involving a concerted metalation-deprotonation process. Investigations on developing a wider scope of metal-catalyzed [4+1] annulation to furnish interesting heterocycles are underway and will be reported in due course.

Acknowledgements

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Notes and references

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†Electronic supplementary information (ESI) available: Experimental procedures, characterization data for all new compounds. CCDC 963147. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/b000000x/

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6 CCDC 963147 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc. cam.ac.uk/data_request/cif.

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