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A room-temperature synthesis of 2,2′-bisoxazoles through palladium-catalyzed oxidative coupling of α-isocyanoacetamides†

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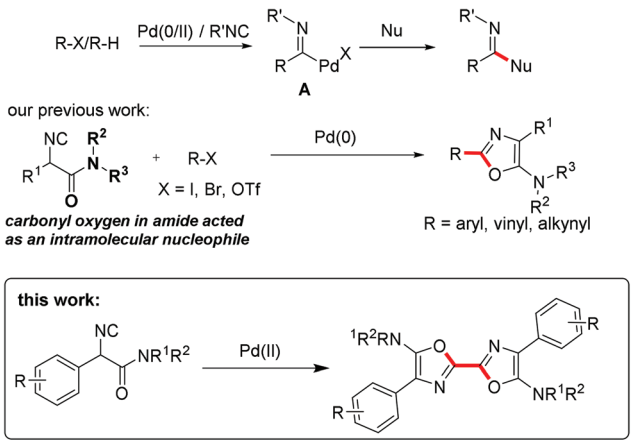
A palladium-catalyzed synthesis of symmetric and unsymmetric 2,2′-bisoxazoles starting from readily available α-isocyanoacetamides was developed. The reaction was performed at room temperature in air which acted as the sole oxidant of $Pd^{(0)}$. Mechanistic studies suggested that double isocyanide insertion into the $Pd^{(II)}$–O bond was involved.

Acting as an isoelectronic equivalent of carbon monoxide, isocyanide has shown its great potential in palladium-catalyzed isocyanide insertion reactions.[1] Imidoyl palladium(II) complex **A** was considered as a general intermediate in reaction with various nucleophiles followed by reductive elimination, generating amidines,[2] amides,[3] ketimines,[4] imidates, thioimidates[5] and aldehydes[6] correspondingly (Scheme 1). Functionalized heterocycles could be generated by linking a nucleophile to substrates R–X/R–H ready for imidoyl palladium(II) intermediate formation upon oxidative addition or C–H bond activation and isocyanide insertion.[7] Another strategy for heterocycle construction involving isocyanide insertion as a key step employs bisnucleophiles and isocyanides under oxidative conditions.[8] For instance, Orru and co-workers reported an efficient synthesis of cyclic guanidine derivatives and related heterocycles *via* palladium-catalyzed isocyanide insertion with diamines or amino alcohols.[8a] Recently, our group developed a different strategy aimed at construction of heterocycles by linking a nucleophile to an isocyanide substrate. α-Isocyanoacetamides, in which the carbonyl oxygen in the amide moiety acted as an intramolecular nucleophile, reacted with aryl, vinyl, or alkynyl halides under palladium catalysis to provide C2-diversified oxazoles.[9] During the optimization of reaction conditions, a symmetric 2,2′-bisoxazole byproduct was identified, albeit in very low yield (Scheme 1). In this novel process, two oxazole rings are formed in one pot through multiple bond formation including two C–O bonds and one C–C bond starting from acyclic substrates. This unprecedented and unexpected transformation intrigued us to investigate it in detail.



Scheme 1 Palladium-catalyzed isocyanide insertion reactions.

C(sp^2)–C(sp^2) direct linked bisheterocycles are of vital importance in pharmaceuticals, natural products, and functional materials.[10] Traditional approaches to these compounds are mostly based on heteroaryl (pseudo)halides and organometallic reagents.[11] In recent years, more step-efficient and atom-economic strategies employing oxidative coupling of existing heterocyclic skeletons through C–H bond activation were developed.[12] For instance, methods directed towards 2,2′-bisoxazoles were successfully developed by transition metal catalyzed coupling of dual C–H bonds.[13] However, limitations of these methods, including high reaction temperatures, using a stoichiometric or excess amount of Cu/Ag-based oxidant, still exist. Herein, we report a novel palladium-catalyzed synthesis of symmetric and unsymmetric 2,2′-bisoxazoles by oxidative homo- and cross-coupling of readily available α-isocyanoacetamides.[14] This reaction occurs smoothly at room temperature and uses air as the sole oxidant.

The reaction conditions were screened with 2-isocyano-2-phenyl-1-(piperidin-1-yl)ethanone **1a** as a test substrate catalyzed by $Pd(OAc)_2$ (10 mol%) in air at room temperature

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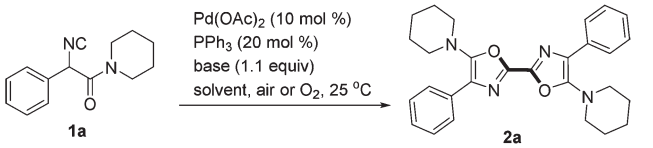
Table 1 Optimization of reaction conditions[a]



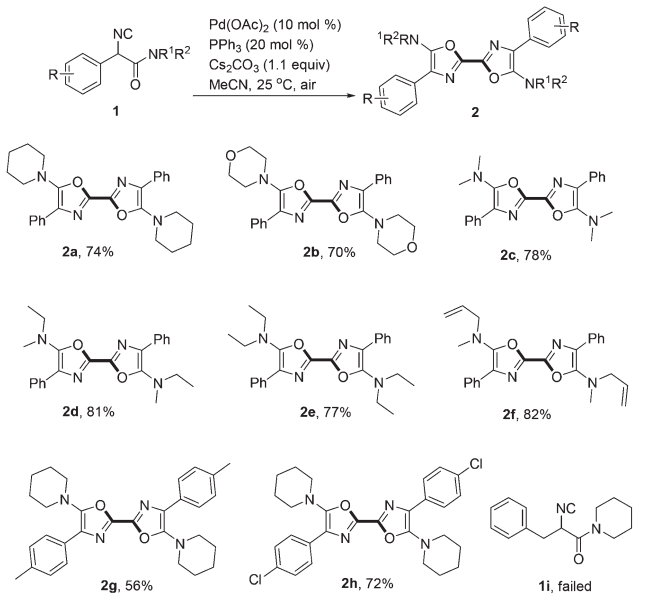
Entry	Solvent	Base	Ligand	Atmosphere	Yield[b]
1	DMF	Cs_2CO_3	PPh_3	Air	26%
2	DCM	Cs_2CO_3	PPh_3	Air	66%
3	Dioxane	Cs_2CO_3	PPh_3	Air	44%
4	MeCN	Cs_2CO_3	PPh_3	Air	70%
5	MeCN	Cs_2CO_3	PPh_3	O_2	44%
6[c]	MeCN	Cs_2CO_3	—	Air	51%
7	MeCN	LiO*t*Bu	PPh_3	Air	50%
8[d]	MeCN	Cs_2CO_3	PPh_3	Air	74%

[a] Reaction conditions: **1a** (0.2 mmol), $Pd(OAc)_2$ (10 mol%), base (0.22 mmol, 1.1 equiv.), PPh_3 (20 mol%), solvent (2 mL), in air, 25 °C, 0.5 h. [b] Isolated yield. [c] 2.0 h. [d] A solution of **1a** in MeCN (1 mL) was added to the reaction mixture *via* a syringe pump within 0.5 h.

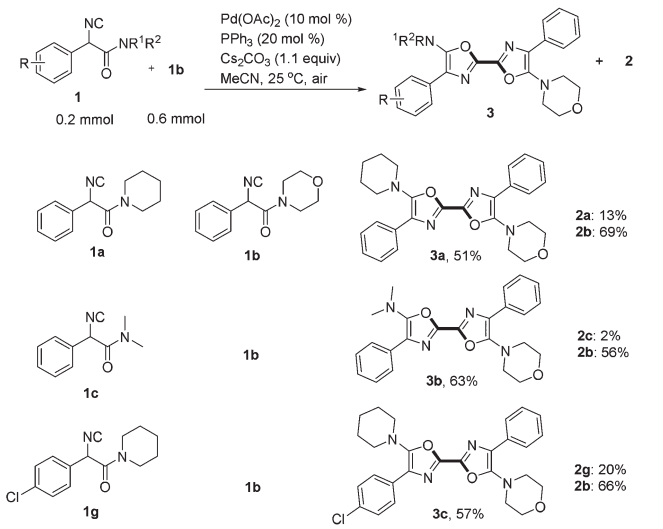
(Table 1). Among various solvents tested, the reaction performed best in MeCN in the presence of Cs_2CO_3 (1.1 equiv.) and PPh_3 (20 mol%), delivering the desired symmetric 2,2′-bisoxazole **2a** in 70% yield (entries 1–4). Further investigations including changing the reaction atmosphere from air to pure O_2 or replacing the base from Cs_2CO_3 to LiO*t*Bu gave lower yields of **2a** (entries 5 and 7). In the absence of PPh_3, the transformation was much less efficient (51% yield, entry 6). When a solution of **1a** in MeCN (1.0 mL) was added slowly *via* a syringe pump over 0.5 h to a mixture containing $Pd(OAc)_2$, PPh_3, Cs_2CO_3 and 1 mL of MeCN, the yield of **2a** increased slightly to 74% (entry 8).

With the optimized reaction conditions in hand, the scope of α-isocyanoacetamides was then screened (Scheme 2). Besides piperidinyl amide, a cyclic morpholino analogue of **1a** also generated the corresponding product **2b** smoothly in 70% yield. Other α-isocyanoacetamides derived from acyclic secondary amines including *N*,*N*-dimethylamine (**1c**), *N*-methyl-*N*-ethylamine (**1d**), *N*,*N*-diethylamine (**1e**) and *N*-methylallylamine (**1f**) all homo-coupled efficiently to produce the corresponding symmetric 2,2′-bisoxazoles (**2c**–**2f**) in good yields. It is noteworthy that the terminal alkene in **2f** survived the reaction well. Methyl and chloro substituted 2,2′-bisoxazoles **2g** and **2h** were obtained in 56% and 72% yields respectively. Unfortunately, isocyanoacetamide bearing a benzyl group rather than an aryl one at the α-position was not a suitable substrate in this transformation (**1i**).

When two different α-isocyanoacetamides were present, an unsymmetric 2,2′-bisoxazole product derived from cross-coupling together with two homo-coupling products was obtained (Scheme 3). For example, addition of a solution of **1a** (0.2 mmol, 1 equiv.) and **1b** (3 equiv.) in 4 mL of MeCN to an open reaction tube containing the catalyst, ligand, base and CH_3CN (1 mL) *via* a syringe pump in 1 h generated an unsymmetric 2,2′-bisoxazole product **3a** in synthetically useful yield

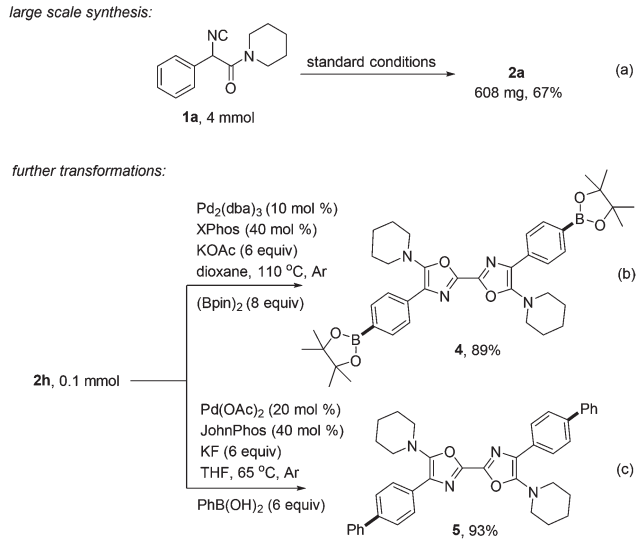


Scheme 2 Scope of symmetric 2,2′-bisoxazoles. Reaction conditions: a solution of **1a** (0.20 mmol) in MeCN (1 mL) was added to the reaction mixture containing $Pd(OAc)_2$ (0.02 mmol, 10 mol%), PPh_3 (0.04 mmol, 20 mol%), Cs_2CO_3 (0.22 mmol, 1.1 equiv.) and MeCN (1 mL) *via* a syringe pump within 0.5 h at 25 °C in air.



Scheme 3 Scope of unsymmetric 2,2′-bisoxazoles. Reaction conditions: a solution of **1** (0.20 mmol) and **1b** (0.6 mmol) in MeCN (4 mL) was added to the reaction mixture containing $Pd(OAc)_2$ (0.02 mmol, 10 mol%), PPh_3 (0.04 mmol, 20 mol%), Cs_2CO_3 (0.22 mmol, 1.1 equiv.) and MeCN (1 mL) *via* a syringe pump within 1 h at 25 °C in air. Isolated yields of **2b** are based on **1b**. Other yields are based on another reactant **1**.

(51%) after careful chromatographic isolation. Symmetric 2,2′-bisoxazoles **2a** and **2b** generated from homo-coupling were also obtained in 13% and 69% yields, respectively. The selectivity for cross-coupling was better in a reaction of **1c** and **1b**, generating unsymmetric product **3b** in 63% yield. Unsymmetric 2,2′-bisoxazole **3c** containing an aromatic chloride func-

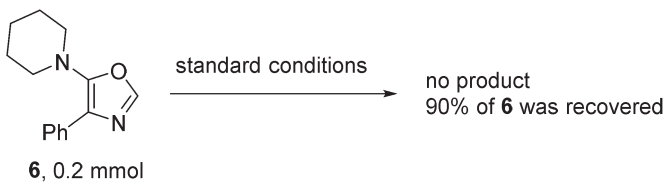


Scheme 4 Large scale synthesis and further transformations.

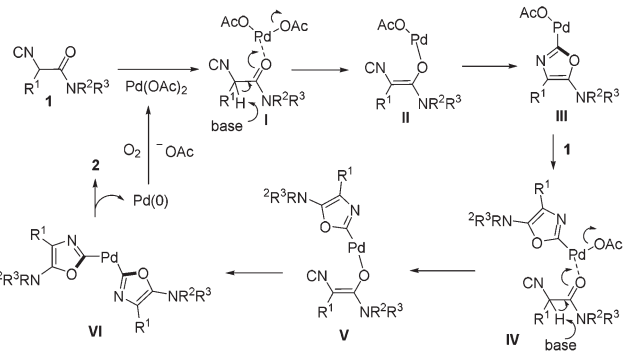
tionality was also isolated in 57% yield. The current strategy provides an efficient approach to both symmetric and unsymmetric 2,2′-bisoxazoles in one step starting from simple acyclic α-isocyanoacetamides. It is notable that two heterocyclic rings are constructed simultaneously at ambient temperature in open air. Three chemical bonds including two C–O bonds and one C–C bond are formed with 100% atom-economy during this process.

This reaction was scalable, as exemplified by sub-gram preparation of **2a** with equal efficiency (a, Scheme 4). Further diversification of the obtained oxazole product **2h** was also performed. Transforming the chloride moiety to boronic acid ester through palladium catalysis was realized in 89% yield. The product **4** containing two aromatic boronic acid ester moieties is expected to be a useful precursor for more complicated symmetric 2,2′-bisoxazole synthesis (b).[15] Suzuki coupling of **2h** with phenyl boronic acid also performed smoothly, giving highly conjugated product **5** in high yield (c).[16]

To verify the reaction pathway, C2 unsubstituted oxazole **6** was treated under the standard aerobic conditions. Most of the starting material **6** was recovered with no homo-coupling product **2a** being detected, which suggested that **6** was an unlikely reaction intermediate. Although the role of triphenyl phosphine was not fully understood, it may facilitate the process of reductive elimination and stabilize the Pd(0) species before being oxidized to $Pd^{(II)}$ by O_2 in air.



A plausible reaction mechanism was proposed in Scheme 5. Coordination of the carbonyl oxygen in α-isocyanoacetamide **1** with $Pd(OAc)_2$ affords intermediate **I**. Deprotonation and the subsequent isocyanide insertion to the Pd–O bond forms the first oxazole ring in intermediate **III**. Repeating the same process furnishes the key bisoxazole ligated palladium(II) intermediate **VI**. Reductive elimination releases the homo-coupling product **2** and the $Pd^{(0)}$ species which is reoxidized to $Pd^{(II)}$ by O_2 in air. It is also possible that isocyanide insertion to the Pd–O bond in $Pd(OAc)_2$ takes place before its coordination with the carbonyl oxygen.



Scheme 5 Proposed mechanism.

In summary, we have developed a novel palladium-catalyzed synthesis of symmetric and unsymmetric 2,2′-bisoxazoles starting from readily available acyclic α-isocyanoacetamides. Double isocyanide insertion was believed as a key step in this transformation. The reaction was performed at room temperature in air which acted as the sole oxidant of Pd(0). The resulting symmetric or unsymmetric products were highly π-conjugated, showing their great potential in functional material synthesis.

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