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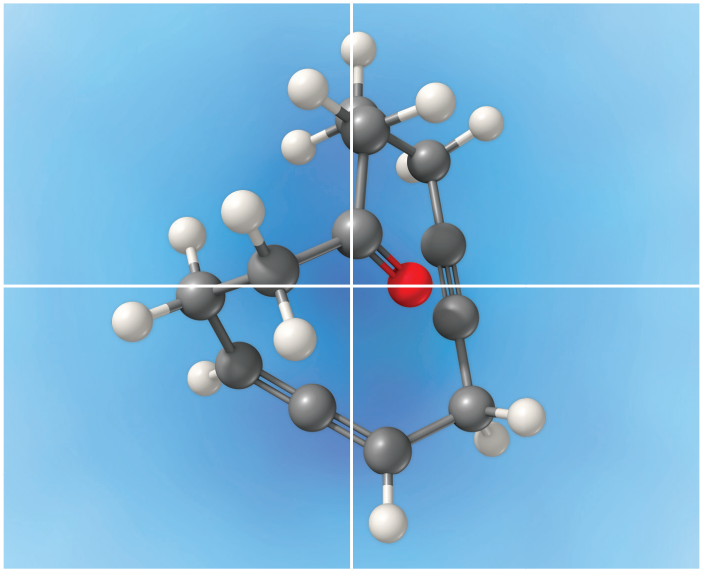

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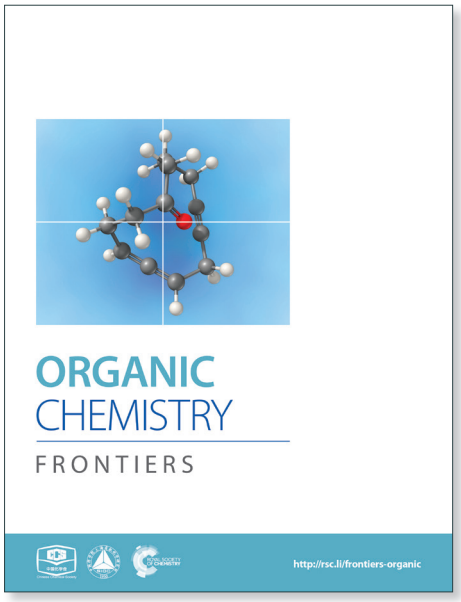

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A Room-Temperature Synthesis of 2, 2'-Bisoxazoles through Palladium-Catalyzed Oxidative Coupling of α-Isocyanoacetamides

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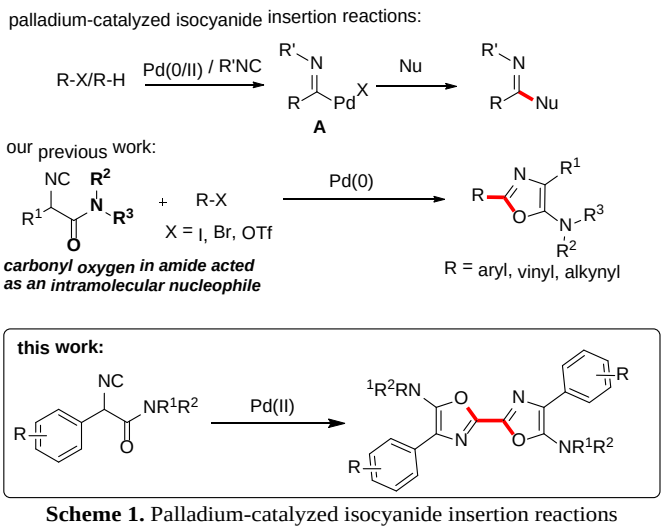
A palladium-catalyzed synthesis of symmetric and unsymmetric 2, 2'-bisoxazoles starting from readily available α-isocyanoacetamides was developed. The reaction was performed at room temperature in air which acted as the sole oxidant of $Pd^{(0)}$. Mechanistic studies suggested that double isocyanide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

Acting as 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 aiming at construction of heterocycles by linking a nucleophile to 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 details.

$C(sp^2)$-$C(sp^2)$ 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 oganometallic 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, method 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 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.

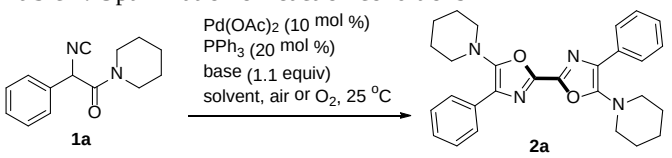


Scheme 1. Palladium-catalyzed isocyanide insertion reactions

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 (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 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 during 0.5 h to a mixture containing $Pd(OAc)_2$, PPh_3, Cs_2CO_3 and 1 mL of MeCN, the yield of **2a** was increased slightly to 74% (entry 8).

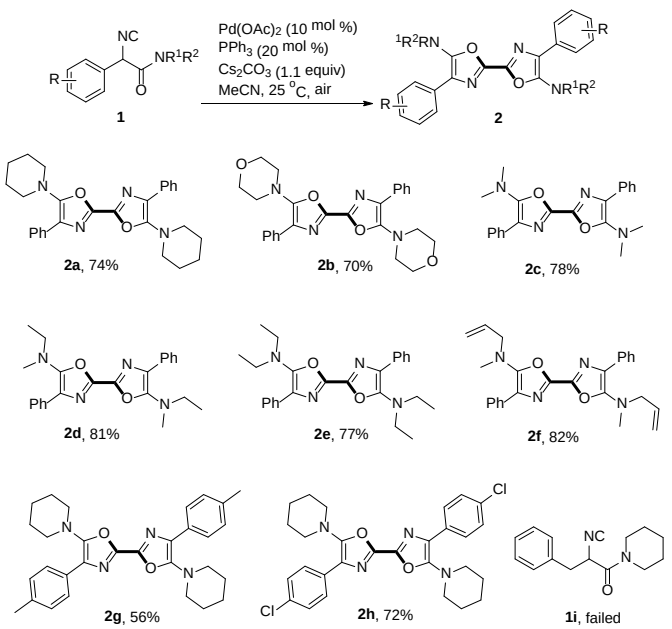
Table 2. Optimization of reaction conditions[a]



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	LiOtBu	PPh_3	air	50%
8[d]	**MeCN**	**Cs_2CO_3**	**PPh_3**	**air**	**74%**

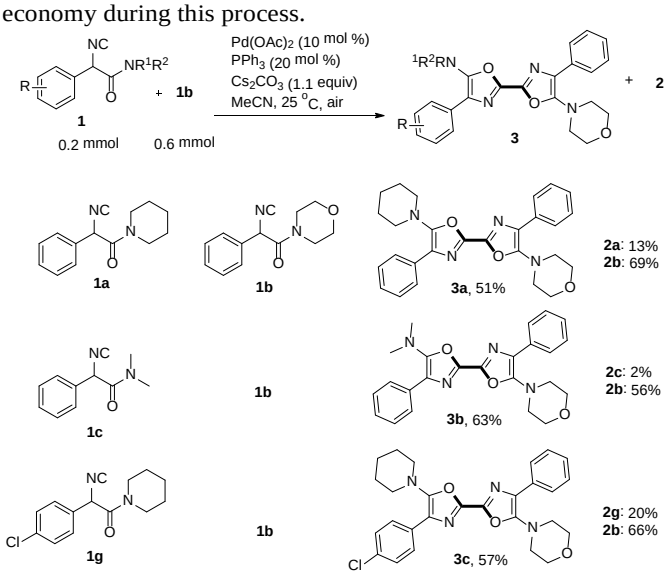
[a] Reaction conditions: **1a** (0.2 mmol), $Pd(OAc)_2$ (10 mol %), base (0.22 mmol, 1.1 equiv), PPh_3 (20 mol %), solvent (2 mL), in air, 25 °C, 0.5 h. [b]Isolated yield. [c]2.0 h. [d]A solution of **1a** in MeCN (1 mL) was added to the reaction mixture via a syringe pump within 0.5 h.

With the optimized reaction conditions in hand, the scope of α-isocyanoacetamides was then screened (Scheme 2). Besides piperidinyl amide, 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**).



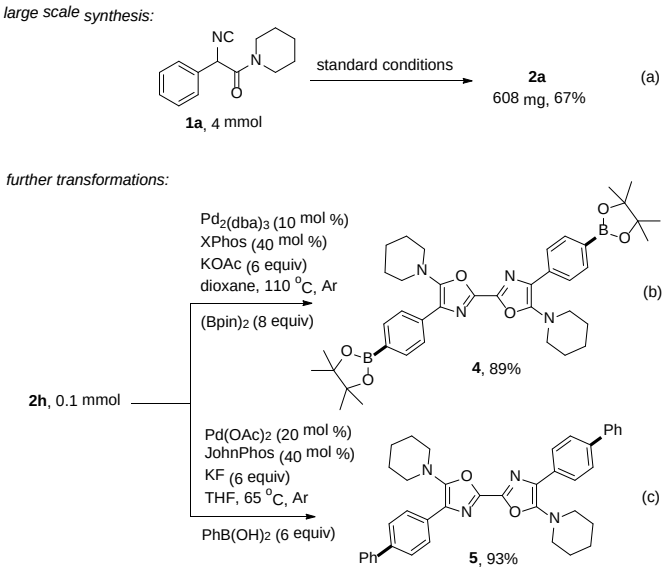
Scheme 2. Scope of symmetric 2, 2'-bisoxazoles. Reaction conditions: A solution of **1a** (0.20 mmol) in MeCN (1 mL) was added to the reaction mixture containing $Pd(OAc)_2$ (0.02 mmol, 10 mol %), PPh_3 (0.04 mmol, 20 mol %), Cs_2CO_3 (0.22 mmol, 1.1 equiv) and MeCN (1 mL) via a syringe pump within 0.5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

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 a solution of **1a** (0.2 mmol, 1 equiv) and **1b** (3 equiv) in 4 mL of MeCN to an open reaction tube containing 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 (51%) after careful chromatography 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 functionality 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.



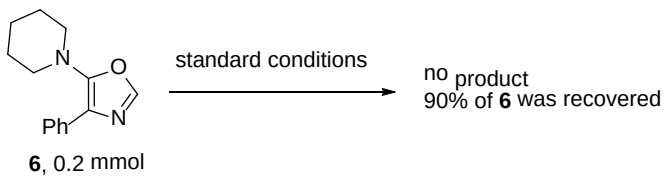
Scheme 3. Scope of unsymmetric 2, 2'-bisoxazoles. Reaction conditions: A solution of **1** (0.20 mmol) and **1b** (0.6 mmol) in MeCN (4 mL) was added to the reaction mixture containing $Pd(OAc)_2$ (0.02 mmol, 10 mol %), PPh_3 (0.04 mmol, 20 mol %), Cs_2CO_3 (0.22 mmol, 1.1 equiv) and MeCN (1 mL) via 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**.

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]

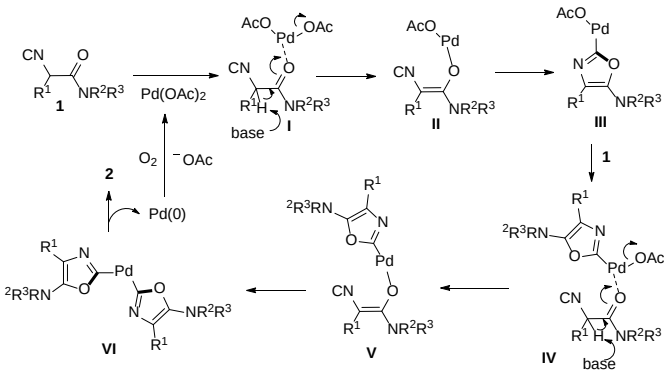


Scheme 4. Large scale synthesis and further transformations.

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 unlikely a 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 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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Notes and references

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