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Palladium-Catalyzed Imidoylative Cyclization of α-Isocyanoacetamides: Efficient Access to C2-Diversified Oxazoles

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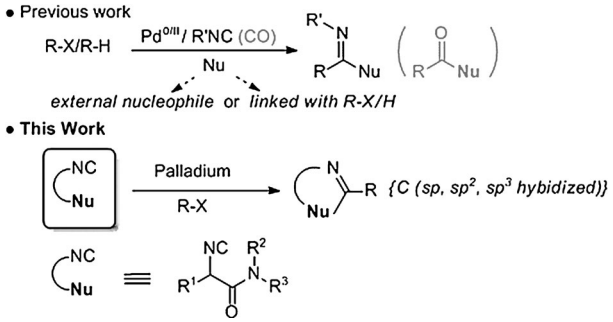
Abstract: A novel procedure for the synthesis of C2-diversified oxazoles, through palladium-catalyzed imidoylative cyclization of α-isocyanoacetamides with aryl, vinyl, alkynyl halides, or triflates, was developed. Migratory insertion of isocyanide into a C_{sp^3}-palladium(II) intermediate in a cascade process was also realized, generating alkyl-substituted oxazoles. Therefore, oxazoles functionalized at the C2 position with sp, sp^2, and sp^3 hybridized carbon atoms are accessible by applying this method.

Introduction

Compared with palladium-catalyzed carbonylation reactions,[1] the related imidoylative process using isocyanide (RNC) rather than carbon monoxide (CO) as a C1 source has received far less attention.[2] In carbonylation reactions, large excesses of toxic gaseous CO are normally required, which may limit practical applications in laboratories and industry. However, in the imidoylative reactions reported, only stoichiometric amounts of isocyanide (typically a liquid) are needed, highlighting its great advantage in this context. The key step of an imidoylative reaction involves migratory insertion of isocyanide into a palladium(II) intermediate, generated either by oxidative addition of organohalides to a Pd^0 species[3] or by Pd^{II}-catalyzed C–H activation.[4] Upon nucleophilic substitution and subsequent reductive elimination, the corresponding amidines,[3a] amides,[3b,4] ketimines,[5] imidates, or thioimidates[6] have been obtained depending on the nucleophiles used. In addition, palladium-catalyzed imidoylative cyclization provides a novel strategy to construct various highly functionalized heterocyclic compounds. By linking a nucleophile to the substrate containing the C–halogen or C–H bond to be activated, cyclic imidoylated products can be formed.[7] For example, we developed an efficient synthesis for 4-aminoquinazolines through a Pd^{II}-catalyzed C–H activation/isocyanide insertion/cyclization sequence.[7a] Recently, Maes, Orru, and Ruijter et al. reported a palladium-catalyzed aerobic oxidation reaction between bisnucleophiles and aliphatic isocyanides to produce cyclic guanidine-containing (and related) heterocycles.[8a] Cyclic (thio)imidates could also be obtained by condensation of bisnucleophiles with aryl halides in the presence of a palladium catalyst and isocyanide, in which the amino moiety in isocyanide was released as a byproduct.[9] Owing to our long-standing interest in palladium-catalyzed isocyanide insertion reactions and new synthetic methods directed towards heterocycle synthesis,[7a,10] a new class of imidoylative cyclization reactions leading to heterocycles is designed by using an isocyanide substrate containing an internal nucleophile thanks to the ability to functionalize isocyanide compared with carbon monoxide. α-Isocyanoacetamides, easily accessible by amidation of the corresponding α-isocyanoesters, salts of α-isocyanocarboxylic acid, or by dehydration of the related formamides, are ideal molecules of this kind (Scheme 1).[11]



Scheme 1. Palladium-catalyzed imidoylative reactions.

Owing to the strong electron-donating nature of the amino group in α-isocyanoacetamide, the carbonyl oxygen atom of the amide is nucleophilic enough to attack the intramolecular nitrilium intermediate generated by initial nucleophilic addition of the terminal carbon of isocyanide to imines or aldehydes in Ugi- or Passerini-type reactions, respectively. In pioneering work by Zhu et al. in 2001, 2-aminoalkyl oxazole derivatives were prepared by using α-isocyanoacetamides in a Ugi-type three-component reaction.[12] Later on, the same group successfully applied the strategy to the enantioselective synthesis

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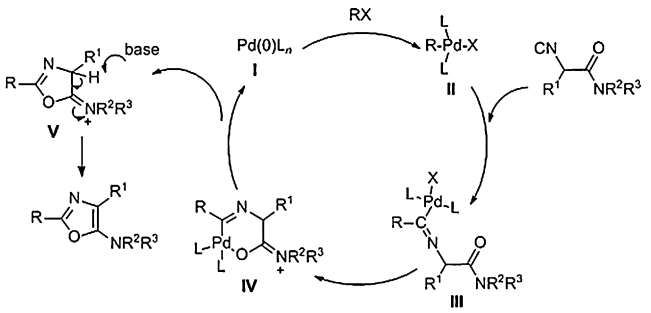
of 2-aminoalkyl oxazoles[13] and its cascade reactions using the in situ generated oxazoles as key intermediates.[14] Very recently, Zhu et al. reported a $ZnBr_2$ promoted reaction of α-isocyanoacetamides with tertiary propargyl amines, used as synthetic equivalents of vinyl cations, for the synthesis of 2-alkenyl oxazoles.[15] We thus envisioned that α-isocyanoacetamides could also participate in palladium-catalyzed imidoylative cyclization reactions, affording a novel approach to multisubstituted oxazoles. As shown in Scheme 2, an initial oxidative addition of organohalides to Pd^0, and a subsequent migratory insertion of the isocyanide moiety to the palladium(II) intermediate **II** gives an imidoyl palladium(II) intermediate, **III**. Nucleophilic substitution of the intramolecular carbonyl oxygen atom on palladium(II) generates a key six-membered palladacycle, **IV**. Following this, reductive elimination and deprotonative aromatization delivers 2,4,5-trisubstituted oxazoles. Theoretically, various palladium(II) intermediates in the form of R–Pd–X can be applied in this strategy, giving tremendous diversity to the C2 position of the oxazole products. Herein, we report a general method for the synthesis of C2-diversified multisubstituted oxazoles by palladium-catalyzed imidoylative cyclization of α-isocyanoacetamides with aryl, vinyl, alkynyl halides, and triflates. Furthermore, the C_{sp^3}-palladium(II) intermediate generated from carbopalladation of alkenes could also be applied in this process, leading to diversified oxazoles, which are ubiquitous in natural products, pharmaceutical agents, and functional materials (Figure 1).[16]



Scheme 2. Proposed scenario of Pd-catalyzed imidoylative cyclization of α-isocyanoacetamides.

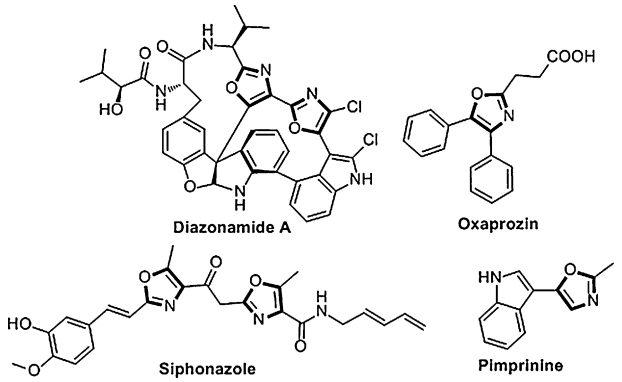


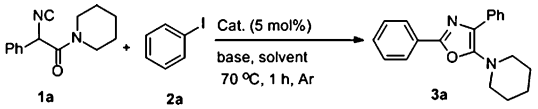
Figure 1. Oxazole-containing natural and bioactive molecules.

Results and Discussion

Optimization studies

The study was initiated by investigating the reaction between 2-isocyano-2-phenyl-1-(piperidin-1-yl)ethanone, **1a**, and iodobenzene, **2a**, in MeCN (Table 1). When a range of inorganic and organic bases were screened, the desired C2-phenylated oxazole **3a** was indeed formed, albeit in no more than 10% yield in the presence of $[Pd(PPh_3)_4]$ (entries 1–3). Other catalysts such as $[Pd(PPh_3)_2Cl_2]$ gave lower yields. These low yields were due to the decomposition of starting material **1a** in the reaction mixture. The yield of **3a** was increased to 26% by adding a MeCN solution of **1a** over 30 min with Et_3N as a base (entry 5). The cyclization efficiency was further improved in the presence of DIPEA (diisopropylethylamine; entry 6, 59%). Other solvents, such as DMSO, DMF, and DMA, gave similar or worse results (entry 7–9). Satisfyingly, when a solution of **1a** was added with a syringe pump within 1 h, **3a** was obtained in 96% yield.

Table 1. Optimization of the reaction conditions.[a]

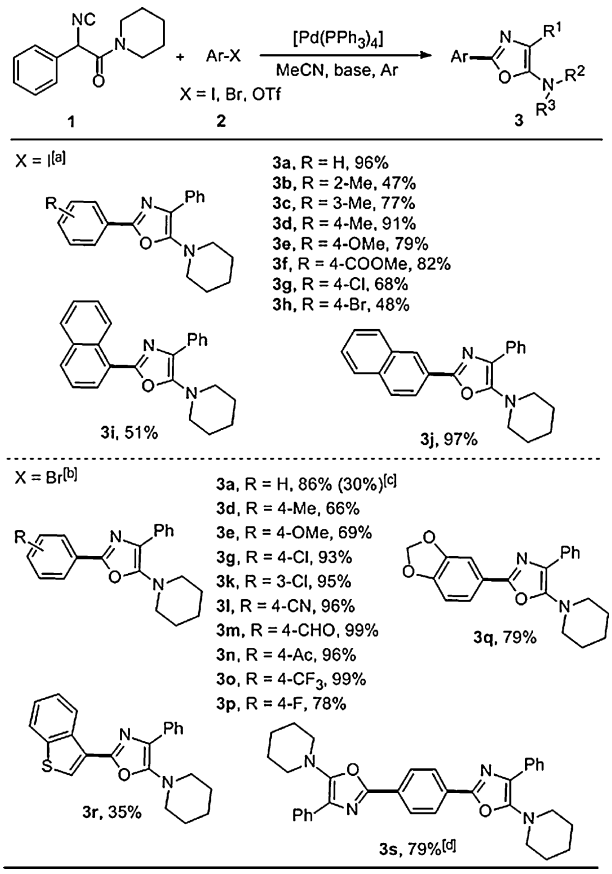


Entry	Solvent	Base	Catalyst	Yield (%)[b]
1	MeCN	Cs_2CO_3	$[Pd(PPh_3)_4]$	<10
2	MeCN	K_2CO_3	$[Pd(PPh_3)_4]$	<10
3	MeCN	Et_3N	$[Pd(PPh_3)_4]$	10
4	MeCN	Et_3N	$[Pd(PPh_3)_2Cl_2]$	6
5[c]	MeCN	Et_3N	$[Pd(PPh_3)_4]$	26
6[c]	MeCN	DIPEA	$[Pd(PPh_3)_4]$	59
7[c]	DMSO	DIPEA	$[Pd(PPh_3)_4]$	56
8[c]	DMF	DIPEA	$[Pd(PPh_3)_4]$	53
9[c]	DMA	DIPEA	$[Pd(PPh_3)_4]$	30
10[d]	**MeCN**	**DIPEA**	**$[Pd(PPh_3)_4]$**	**96**

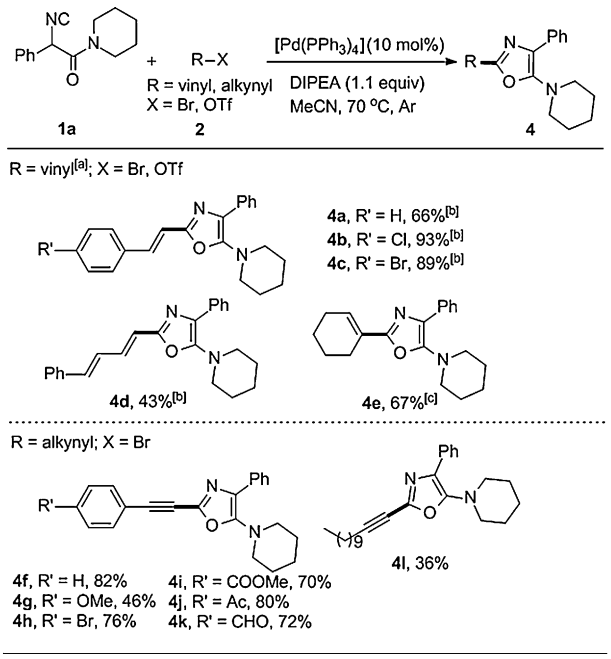
[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.30 mmol), $[Pd(PPh_3)_4]$ (0.01 mmol, 5 mol%), base (0.22 mmol), solvent (2 mL), 70 °C, 1 h, under Ar. [b] Isolated yield. [c] A solution of **1a** in solvent (1 mL) was added slowly over 30 min. [d] A solution of **1a** in solvent (1 mL) was added by syringe pump within 1 h.

Scope and limitations

With the optimized reaction conditions in hand, we first screened the scope of aryl iodides (Scheme 3). Aryl iodides containing various substituents were converted smoothly to give the corresponding arylated products in moderate to excellent yields. *ortho*-Methyl iodobenzene gave a much lower yield than its *meta*- and *para*-methyl iodobenzene counterparts (**3b** vs. **3c** and **3d**), indicating that the reaction was sensitive to the steric hindrance of aryl iodides. Ester (**3f**) and bromide (**3h**), valuable functionalities for further transformations, survived the reaction conditions.



Scheme 3. Scope of reactions with aryl halides/triflates. Reaction conditions: **1** (0.20 mmol), **2** (0.30 mmol), $[Pd(PPh_3)_4]$ (0.01 mmol, 5 mol%), base (0.22 mmol), MeCN (2 mL), Ar, syringe pump addition within 1 h. [a] base = DIPEA, 70 °C. [b] base = CsF, 90 °C. [c] 0.5 equiv of 1,4-dibromobenzene. [d] X = OTf, 10 mol% of $[Pd(PPh_3)_4]$ (0.02 mmol), base = DIPEA, 70 °C.



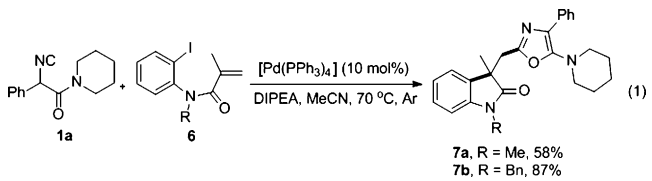
Scheme 4. Scope of reaction with vinyl/alkynyl halides/triflates. Reaction conditions: **1** (0.20 mmol), **2** (0.30 mmol), $[Pd(PPh_3)_4]$ (0.01 mmol), base (0.22 mmol), MeCN (2 mL), Ar, syringe pump addition within 1 h. [a] Vinyl bromides are mixtures of *E,Z*-isomers. The *E*/*Z* ratio ranged from 1:1 to 10:1. The equivalent of **2** was based on *E*-isomer. [b] X = Br. [c] X = OTf.

No desired product was obtained with aryl bromides as the coupling partner at 70 °C. When the reaction temperature was raised to 90 °C, **3a** was generated with DIPEA as a base, albeit in relatively low yield (72%). After a screening a series of bases, CsF was found to be the optimal base, producing **3a** in 86% yield. Aryl bromides substituted with electron-neutral or -donating groups provided the same products in lower yields than the corresponding aryl iodides (Scheme 3, **3a**, **3d**, and **3e**). Electron-withdrawing substituents on aryl bromides, such as chloro (**3g**, **3k**), cyano (**3l**), formyl (**3m**), acetyl (**3n**), trifluoromethyl (**3o**), and fluoro groups (**3p**), generated excellent yields in most cases. Heterocycles, including benzodioxole (**3q**) and benzothiophene (**3r**), could also be introduced into the C2 position of oxazole by using the corresponding bromides. To our delight, when 1,4-dibromobenzene was used as the coupling partner, double imidoylative cyclization took place to produce a highly conjugated symmetric molecule, **3s**, in good yield. In addition, phenyl triflate could also be used as an electrophile in this process, although it gave a relatively low yield (30%).

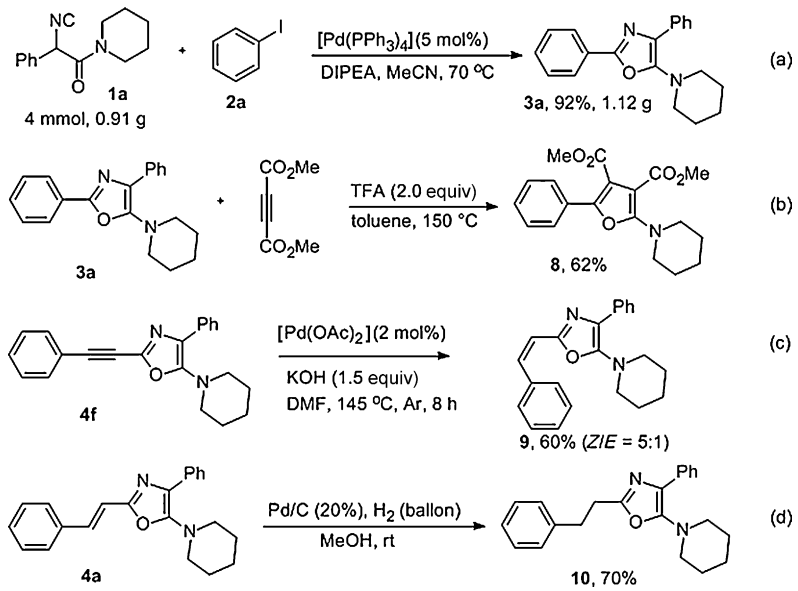
Vinyl and alkynyl bromides were also suitable reactants for this coupling reaction under higher catalyst-loading conditions, furnishing C2-alkenylated and -alkynylated oxazoles, respectively (Scheme 4). It is worth noting that when mixtures of *E*- and *Z*-vinyl bromides (*E*/*Z* = 1:1 to 10:1) were used as starting materials, only the *E*-isomers reacted, affording the corresponding *E*-alkenylated products in good yields. The *Z*-vinyl bromides remained unreacted. For example, a 1:1 mixture of (*E*/*Z*)-(2-bromovinyl)benzene reacted with **1a** to deliver the desired (*E*)-4-phenyl-5-(piperidin-1-yl)-2-styryloxazole, **4a**, in 66% yield as the only product. Electron-withdrawing Cl and Br substituents on the phenyl ring enhanced the reactivity of vinyl bromides, providing **4b** and **4c** in 93% and 89% yields, respectively. It was intriguing that during the formation of **4c**, the bromo group on the phenyl ring remained unreacted, demonstrating excellent chemoselectivity in favor of the vinyl bromide over the aromatic bromide. The reaction is also applicable to conjugated dienyl bromide. Thus, ((*1E,3E*)-4-bromobuta-1,3-dien-1-yl)benzene gave the desired product in moderate yield (**4d**). Cyclohexenyl-substituted oxazole **4e** was also accessible from the corresponding vinyl triflate, which was easily accessible from cyclohexanone (67%). Furthermore, alkynyl bromides were another class of substrates suitable for this imidoylative cyclization reaction. Functionalities including OMe, Br, COOMe, Ac, and CHO on the phenyl ring of (bromoethynyl)-benzene were compatible with the reaction conditions, giving the corresponding alkynylated oxazoles **4f**–**4k** in moderate to good yields. Again, the alkynyl bromide reacted preferentially over the aromatic bromide (**4h**). Alkyl-substituted alkynyl bromide was also compatible with this process, affording the product **4l** in 36% yield. To the best of our knowledge, migratory insertion of isocyanide to a C_{sp}–Pd^{II} intermediate is unprecedented.

Changing the piperidinyl group in α-isocyanoacetamide **1a** to other amino groups, such as pyrrolidinyl, dimethylamino, *N*-methylethylamino, and diethylamino, all resulted in moderate to good yields (**5a–5d**). Altering the phenyl group in **1a** to a benzyl group (**5e**) gave an excellent yield of 91%. Unfortunately, secondary α-isocyanoacetamide failed to form the corresponding cyclized product **5f** (Scheme 5).

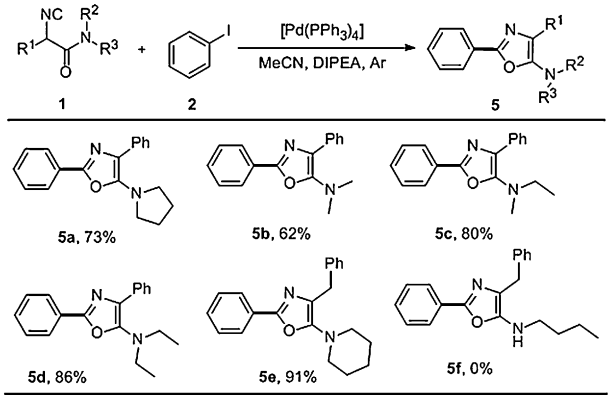
A domino process involving oxidative addition of *N*-(2-iodophenyl)methacrylamide derivative **6** to Pd^0, intramolecular alkene insertion, and imidoylative cyclization of the resulting C_{sp^3}–Pd^{II} intermediate with α-isocyanoacetamide **1a**, was realized to install an oxindole moiety on the oxazole with a methylene tether (Equation 1, **7a** and **7b**). Isocyanide insertion into a C_{sp^3}–Pd^{II} intermediate is rare.[3b]



Gram-scale preparation of **3a** was equally efficient (Scheme 6a). Further diversifications of the obtained functionalized oxazole products were also performed. For example, a Diels–Alder reaction of oxazole **3a** with dimethyl but-2-ynedioate afforded tetra-substituted furan **8** in 62% yield (Scheme 6b).[17] (*Z*)-4-Phenyl-5-(piperidin-1-yl)-2-styryloxazole **9**, a configurational isomer of **4a**, was accessed as a major product through the palladium-catalyzed partial hydrogenation of **4f** (Scheme 6c).[18] This transformation provides a complementary approach to current imidoylative cyclizations with vinyl bromides to configurationally defined alkenylated oxazoles. Generally, C2-alkyl-substituted oxazoles could be synthesized easily by hydrogenation of alkenylated derivatives, as exemplified by the synthesis of **10** from **4a** (Scheme 6d).



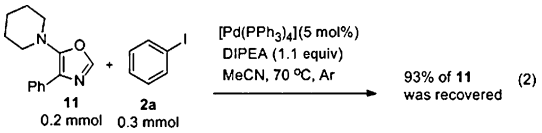
Scheme 6. Large scale synthesis and further transformations.



Scheme 5. Scope of reaction with isocyanides. Reaction conditions: **1** (0.20 mmol), **2a** (0.30 mmol), $[Pd(PPh_3)_4]$ (0.01 mmol, 5 mol%), DIPEA (0.22 mmol), MeCN (2 mL), Ar, syringe pump addition within 1 h.

Mechanistic study

A control reaction between 4-phenyl-5-(piperidin-1-yl)oxazole, **11**, and iodobenzene under the standard conditions resulted in no formation of the desired product, with 93% of **11** recovered (Equation 2). A possible pathway involving direct arylation of in situ generated oxazole was thus ruled out. Therefore, isocyanide insertion into Pd^{II} intermediates is believed to be the key step of this reaction, as shown in Scheme 3.



Conclusion

We have developed a novel procedure for the synthesis of C2-functionalized oxazoles through palladium-catalyzed imidoylative cyclizations of α-isocyanoacetamides with the corresponding aryl, vinyl, alkynyl halides, or triflates. Migratory insertion of isocyanide into a C_{sp}–palladium(II) intermediate is reported for the first time, affording C2-alkynylated oxazoles. Both *E*- and *Z*-isomers of alkenylated oxazoles can be accessed by the current imidoylative cyclization with vinyl bromides or by selective hydrogenation of alkynylated precursors, respectively. Migratory

insertion of isocyanide into a C_{sp^3}–palladium(II) intermediate in a cascade process was also realized, generating alkyl-substituted oxazoles. Therefore, oxazoles functionalized at the C2 position with sp, sp^2, and sp^3 hybridized carbon atoms are accessible by this method. Further studies on extending this transformation and the evaluation of the biological activity of these compounds are currently underway in our laboratory.

Experimental Section

Representative procedure

An oven-dried 25 mL Schlenk tube was charged with $[Pd(PPh_3)_4]$ (0.01 mmol, 11.6 mg), and was evacuated and refilled with Ar three times. A solution of DIPEA (0.22 mmol, 38.4 μL) and iodobenzene (**2a**, 0.3 mmol) in MeCN (1.0 mL) was added by syringe and the tube was placed in an oil bath at 70 °C. A solution of 2-isocyano-2-phenyl-1-(piperidin-1-yl)ethanone (**1a**, 0.2 mmol) in MeCN (1.0 mL) was added to the reaction mixture with a syringe pump within 1 h. The crude reaction mixture was extracted with CH_2Cl_2 (20 mL × 3) and washed with brine (20 mL). The organic phase was concentrated in vacuo and the purified product **3a** was isolated as a white solid by flash chromatography using petroleum ether and ethyl acetate (50:1 to 15:1) as the eluent.

Acknowledgements

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Keywords: heterocycles · imidoylative cyclization · α-isocyanoacetamide · oxazoles · palladium

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