# Cooperative Pd/Cu Catalysis: Multicomponent Synthesis of Tetrasubstituted Imidazolones from Methyl α-Isocyanoacetates, Primary Amines, and Aryl(vinyl) Iodides

Antonin Clemenceau, Qian Wang, and Jieping Zhu*[iD]

Laboratory of Synthesis and Natural Products, Institute of Chemical Sciences and Engineering, Ecole Polytechnique Fédérale de Lausanne, EPFL-SB-ISIC-LSPN, BCH 5304, 1015 Lausanne, Switzerland

S *Supporting Information*

ABSTRACT: Three-component reaction of methyl α,α-disubstituted α-isocyanoacetates, primary amines, and aryl(vinyl) halides in the presence of $Pd(OAc)_2$ (0.05 equiv) and Cu_2O (1.0 equiv) provided 2,3,5,5-tetrasubstituted imidazolones via the formation of three chemical bonds. A copper-mediated migratory insertion of the isocyano group into the N−H bond of the amine followed by lactamization and Pd-catalyzed cross-coupling of the in situ generated amidinyl copper species with aryl(vinyl) halides accounted for the reaction outcome.


R^1, R^2 = alkyl, aryl, R^3 = alkyl, R^4 = aryl, alkenyl, X = I, Br
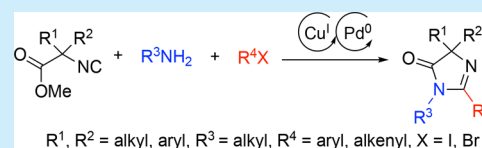
Imidazolone, a nonaromatic heterocycle, is found in bioactive natural products[1] and is a key structural element responsible for the luminescent properties of green fluorescent proteins (GFP).[2] It is a core structure of a number of pharmaceuticals displaying potent inhibitory activities against fatty acid synthases[3] and angiotensin II receptor antagonists.[4] For example, irbesartan, a marketed drug for the treatment of hypertension, contains this heterocycle.[5] Different synthetic methods toward the substituted imidazolones[6] have been developed including, mainly: (a) the transformation of the Erlenmeyer azlactones;[7] (b) the cyclization of the amino acid derived formamidines,[8] α-amidoamides,[9] and α-isocyanoacetamides;[10] and (c) the functionalization of the simple imidazolones.[11] Recently, Hoarau, Bischoff, and co-workers reported a Pd-catalyzed direct C−H functionalization of imidazolones **1** for the synthesis of the C-2 functionalized counterpart **2** (Scheme 1a).[12] Pirali et al. developed a synthesis of the C-2 arylated imidazolones by reaction of the α-isocyanoacetamides with benzynes (Scheme 1b).[13]

Metal-catalyzed domino processes initiated by isocyanide insertion reaction has recently been developed into a powerful tool for the rapid construction of heterocycles.[14−17] In connection with our research program aimed at exploiting the diverse reactivities of the isocyano group,[18] we reported a silver nitrate-catalyzed synthesis of the 3,5,5-trisubstituted imidazolones **1** from methyl α-isocyanoacetates **3** and primary amines **4**.[19] As a continuation of this research topic, we describe herein a three-component synthesis of 2,3,5,5-tetrasubstituted imidazolones **2** by a Pd/Cu-catalyzed reaction of methyl α,α-disubstituted α-isocyanoacetates **3** with primary amines **4** and aryl(vinyl) halides **5** (Scheme 1c).

Methyl α,α-dibenzyl α-isocyanoacetates (**3a**, $R^1 = R^2$ = Bn), benzylamine (**4a**), and 4-iodotoluene (**5a**) were chosen as test substrates to evaluate the feasibility of our approach. Combining $AgNO_3$, the optimum metal salt for catalyzing the reaction between **3a** and **4a**, with Pd catalyst afforded only an intractable

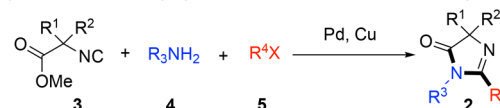## Scheme 1. Synthesis of Tetrasubstituted Imidazolones

a) Hoarau, Bischoff and co-workers: C-H arylation of imidazolones
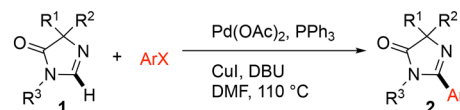
b) Pirali and co-workers: α-addition of α-isocyanoacetamides to benzynes
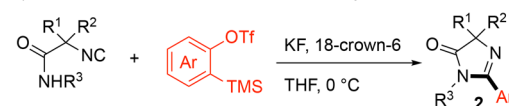
c) This work: one-step synthesis of imidazolones from α-isocyanoacetates

reaction mixture (entry 1, Table 1). Screening other cocatalysts (entries 2−11) indicated that Cu_2O formed the most productive couple with Pd leading to the desired three-component adduct **2a** in 72% isolated yield (entry 7). The impact of base on the reaction outcome was also examined. Among the two best copper copromoters, addition of a base increased the product yield in the case of CuI (entries 4 vs 5), but exerted a deleterious effect on the reaction mediated by Cu_2O (entries 7 vs 12−14). The reaction temperature of 130 °C seemed optimum as the reaction carried out at other temperatures led to the product with diminished yields (entries 7 vs 15, 16). Performing the reaction in DMSO (entry 17) or with reduced loading of Cu_2O (entries 18, 19) resulted in low yields of **2a**. However, reaction proceeded smoothly in the absence of phosphine ligand to provide **2a**, albeit with reduced yield (entries 21).[20] Finally, performing the reaction with Pd or Cu alone afforded **2a** in much reduced

Table 1. Synthesis of 2,3,5,5-Tetrasubstituted Imidazolones 2a: Survey of Reaction Conditions[a]

3a　　　4a　　　5a　　　　　　　　　　　　　　　2a Ar = 4-MeC$_6$H$_4$
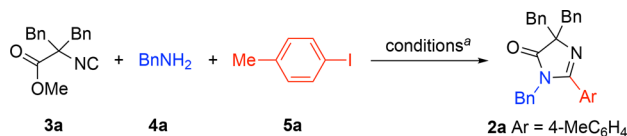
entry	Pd/ligand	Lewis acid	base	yield (%)[b]
1	Pd(OAc)$_2$/PPh$_3$	AgNO$_3$	DBU	degradation
2	Pd(OAc)$_2$/PPh$_3$	AgOTf	DBU	33
3	Pd(OAc)$_2$/PPh$_3$	Yb(OTf)$_3$	DBU	23
4	Pd(OAc)$_2$/PPh$_3$	CuI	DBU	68
5	Pd(OAc)$_2$/PPh$_3$	CuI		57
6	Pd(OAc)$_2$/PPh$_3$	CuCl		55
7	Pd(OAc)$_2$/PPh$_3$	Cu$_2$O		75(72)[h]
8	Pd(OAc)$_2$/PPh$_3$	CuOTf		58
9	Pd(OAc)$_2$/PPh$_3$	CuOAc		21
10	Pd(OAc)$_2$/PPh$_3$	[(MeCN)$_4$Cu]BF$_4$		50
11	Pd(OAc)$_2$/PPh$_3$	Cu(OTf)$_2$		6
12	Pd(OAc)$_2$/PPh$_3$	Cu$_2$O	DBU	28
13	Pd(OAc)$_2$/PPh$_3$	Cu$_2$O	Et$_3$N	57
14	Pd(OAc)$_2$/PPh$_3$	Cu$_2$O	Cs$_2$CO$_3$	27
15[c]	Pd(OAc)$_2$/PPh$_3$	Cu$_2$O		66
16[d]	Pd(OAc)$_2$/PPh$_3$	Cu$_2$O		66
17[e]	Pd(OAc)$_2$/PPh$_3$	Cu$_2$O		41
18[f]	Pd(OAc)$_2$/PPh$_3$	Cu$_2$O		34
19[g]	Pd(OAc)$_2$/PPh$_3$	Cu$_2$O		54
20	Pd(dba)$_2$	Cu$_2$O		66
21	Pd(OAc)$_2$	Cu$_2$O		62
22		Cu$_2$O		43[i]
23	Pd(OAc)$_2$/PPh$_3$			21

[a]Standard conditions: **3a** (0.1 mmol), **4a** (0.15 mmol), **5a** (0.2 mmol), Lewis acid (1.0 equiv), Pd catalyst (5 mol %), ligand (10 mol %), base (1.0 equiv), DMF (1.0 mL), 130 °C. [b]NMR yield using CH$_2$Br$_2$ as an internal standard. [c]110 °C. [d]150 °C. [e]Reaction was performed in DMSO. [f]10 mol % of Cu$_2$O was used. [g]25 mol % of Cu$_2$O was used. [h]Yield of isolated product in parentheses. [i]Yield referred to C2-unsubstituted imidazolone resulting from the Cu-promoted amination/lactamization sequence (cf. ref 19).

yield indicating a strong synergistic effect of these two metals in catalyzing/mediating this transformation (entries 22, 23). Overall, the optimum conditions found consisted of performing the reaction in DMF at 130 °C in the presence of Pd(OAc)$_2$ (5 mol %), PPh$_3$ (10 mol %), and Cu$_2$O (1.0 equiv). Under these conditions, imidazolone **2a** was isolated in 72% yield. The reaction was chemoselective since direct N-arylation of primary amine **4a** by aryl iodide was not observed under these conditions.

This novel three-component reaction displayed a broad application scope (Scheme 2). Aryl iodides bearing electron-donating (Me, OMe) and electron-withdrawing groups (F, CF$_3$, NO$_2$) at different positions were appropriate substrates for this reaction. Various alkyl amines, linear, branched, and function-alized, such as tryptamine (**2m**), participated well in this reaction. However, aniline failed to participate in this reaction. Reactions involving chiral amines (**2e**, **2f**) and α-amino ester (**2u**) afforded the three-component adducts in good yields without racemiza-tion. The α,α-disubstituted α-isocyanoacetates bearing different substituents reacted with amines and aryl iodide to afford the adducts, including spiroimidazolones (**2o**, **2p**), without event. The protocol can also be applied to complex natural products. Thus, reaction of 3α-amino-5-cholestene[21,22] with 4-iodotoluene (**5a**) and methyl α,α-diisobutyl isocyanoacetate afforded **2v** in 52% yield. The α-nonsubstituted and α-monosubstituted α-isocyanoacetates[23] and methyl 2-isocyanobenzoate failed to undergo the three-component coupling reaction. Finally,

performing the reaction of **3a**, **4a**, and **5a** at 1.0 mmol scale afforded the three-component adduct **2a** in 90% isolated yield.

Vinyl bromides, including the 1,2-disubstituted, 1,1-disub-stituted, and tetrasubstituted ones, reacted smoothly with **3** and **4** to provide the 2-vinyl substituted imidazolones (**2w−2y**) in good yields (Scheme 3a). Based on this novel three-component reaction, more complex domino process can be designed for the one-pot synthesis of the polyheterocyclic compounds. For example, reaction of ortho-bromobenzylamine (**6**) with methyl isocyanoacetates **3** furnished the tricyclic compounds **7a** and **7b**, respectively (Scheme 3b).

To gain insight on the reaction mechanism, the following control experiments were carried out (Scheme 4a). The reaction of the presynthesized 3,5,5-trisubstituted imidazolone **1a** with iodide **5a** under our optimized conditions led only to the recovery of **1a**.[24] In accordance with Hoarau and Bischoff's observation on the importance of the base on the C2−H arylation of imidazolones, the same reaction performed in the presence of benzylamine (1.5 equiv) afforded indeed **2a**, albeit in only 26% yield. The low yield of **2a** indicated nevertheless that the formation of transient imidazolone **1a** followed by C−H arylation, although feasible, was not the main reaction pathway under our reaction conditions. Taking into consideration the above results, a possible reaction sequence leading to imidazolone **2** is depicted in Scheme 4b. Coordination of the isocyano and the amino groups to the copper affording complex **A**. Migratory insertion from **A** would afford **B**. Intramolecular

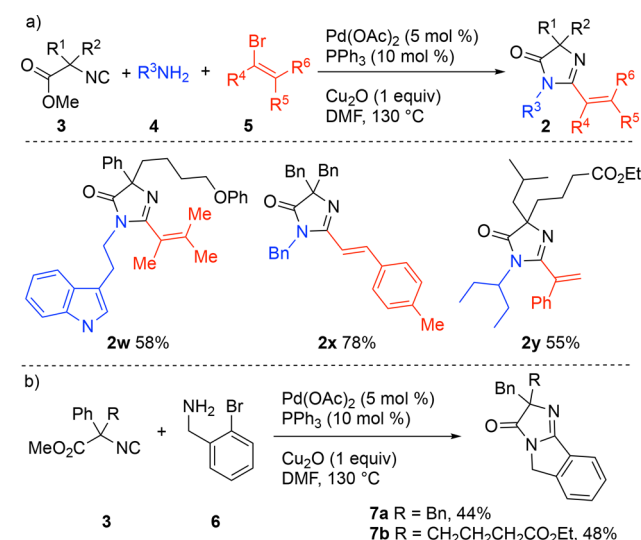## Scheme 2. Three-Component Synthesis of 2-Aryl Substituted Imidazolones 2
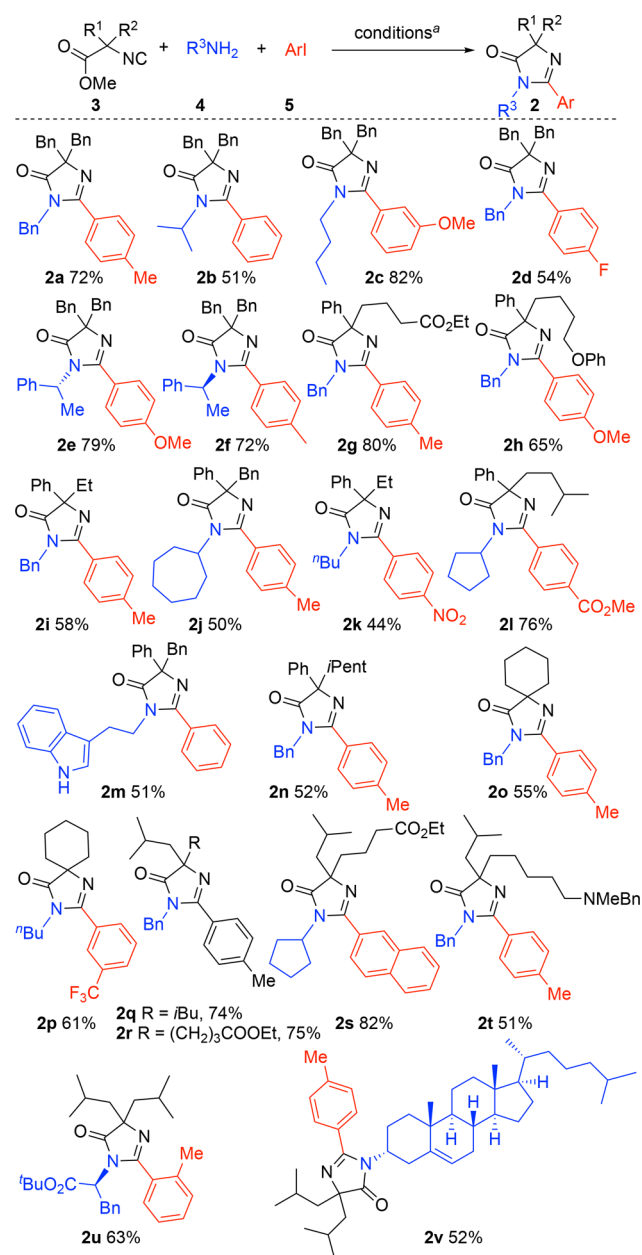
^{a}Conditions: **3** (0.1 mmol), **4** (0.15 mmol), **5** (0.2 mmol), Cu$_2$O (1.0 equiv), Pd(OAc)$_2$ (5 mol %), PPh$_3$ (10 mol %), DMF (1.0 mL), 130 °C.

Scheme 3. Three-Component Synthesis of 2-Vinyl Substituted Imidazolones and Tricyclic Compounds

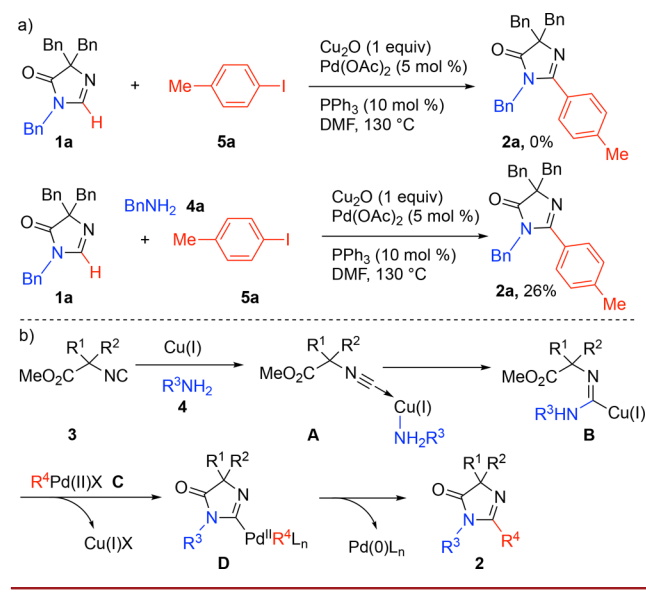## Scheme 4. Possible Reaction Pathway and Control Experiments

amidation followed by transmetalation of the organocopper species with R^{4}Pd(II)X **C** (R^4 = aryl, vinyl), generated in situ by oxidative addition of **5** to Pd(0), would produce complex **D**.[25] Reductive elimination would then furnish imidazolone **2** with concurrent regeneration of the palladium(0) catalyst.

In summary, we have developed a palladium-catalyzed, Cu$_2$O-mediated three-component reaction of methyl α,α-disubstituted α-isocyanoacetates **3** with primary amines **4** and aryl(vinyl) iodides **5**. Three chemical bonds were created in this process leading to diversely substituted 2,3,5,5-tetrasubstituted imidazolones **2** in good yields. This multicomponent reaction, applicable to a wide range of substrates, constitutes novel access to this medicinally important nonaromatic heterocycle.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b03479.

Experimental procedures, product characterization data, and ^{1}H and ^{13}C NMR spectra for new compounds (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: jieping.zhu@epfl.ch.

ORCID Ⓘ

Jieping Zhu: 0000-0002-8390-6689

Notes

The authors declare no competing financial interest.

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