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Palladium-Catalyzed Four-Component Carbonylative Cyclization Reaction of Trifluoroacetimidoyl Chlorides, Propargyl Amines, and Diaryliodonium Salts: Access to Trifluoromethyl-Containing Trisubstituted Imidazoles

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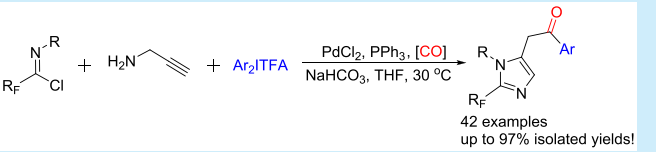
ABSTRACT: A palladium-catalyzed four-component carbonylative cyclization reaction for the expeditious construction of trifluoromethyl-containing trisubstituted imidazoles has been achieved. With readily accessible trifluoroacetimidoyl chlorides, propargyl amines, and diaryliodonium salts as the starting materials, the carbonylative transformation proceeds smoothly under mild conditions to enable the formation of multifunctionalized imidazole molecules in a one-pot, one-step manner. Diaryliodonium salts serve as both oxidants and aryl sources in the reaction.



Multicomponent reactions (MCRs) have been recognized as an appealing and powerful approach for the assembly of a wide variety of valuable chemical scaffolds, especially structurally complicated heterocycles, exhibiting a huge advantage over traditional synthetic methods.[1] The major challenge of MCRs lies in the control of the subtle balance between reactivity and selectivity with multiple reactive components.[2] The issue becomes more serious with an increase in the number of reaction reagents and reactive sites. Consequently, the development of new MCRs to access multifunctionalized azaheterocycles is of great significance and is still highly desirable.

On the other hand, palladium-catalyzed carbonylative transformations have emerged as an expeditious route to the synthesis of diverse carbonyl-containing molecules.[3,4] In these protocols, the highly reactive and nonstable acyl−palladium complex is formed through the insertion of CO into the C−Pd bond, which could be identified as the key intermediate. Then the coupling of the acyl−palladium complex with different nucleophiles gave rise to a series of desired carbonyl-containing compounds.

Additionally, imidazoles are some of the highly privileged heterocyclic scaffolds and have found wide applications in pharmaceutical fields, ligand chemistry, and materials science.[5] Numerous methods have been developed for the synthesis of imidazoles over the past several decades.[6] Among these, isocyanide "C═N" bond [3+2] cycloaddition reactions have emerged as a mainstream synthetic route to imidazoles.[7] In 2012, Wu and co-workers disclosed a gold(I)-catalyzed synthesis of 2-fluoroalkyl imidazoles from a 5-*exo*-*dig* cyclization of fluorinated propargyl amidines, and imidazole-5-carbaldehyde was produced in the presence of the electrophile NIS.[8] Arndtsen and co-workers achieved a novel palladium-catalyzed carbonylative synthesis of (hetero)aryl-substituted imidazoles from aryl halides and imines, as well.[9] The reaction proceeds effectively under CO pressure (4 bar). As a continuation of our ongoing pursuit of the construction of structurally diverse nitrogen-containing heterocycles,[10] we report a palladium-catalyzed four-component carbonylative cyclization reaction for preparing trifluoromethyl- and benzoyl-substituted imidazoles. Here, the challenges for this novel MCRs are how to circumvent troublesome issues such as the direct aminoarylation without CO insertion, the direct carbonylative reaction of trifluoroacetimidoyl chlorides and propargyl amines, the quite unstable alkenyl−palladium complex formed *in situ*, etc. It is noteworthy that the pendent trifluoromethyl group can significantly influence the properties of the azaheterocycles, such as the increased electronegativity, bioavailability, metabolic stability, and lipophilicity.[11] In addition, the manipulation of toxic and flammable carbon monoxide gas is avoided here, as demonstrated via application of formic acid as the CO source via an *in situ*-generated formic acetic anhydride in an *In-Ex* reaction tube.[12]

We initially chose *N*-[4-(*tert*-butyl)phenyl]-2,2,2-trifluoroacetimidoyl chloride **1g**, propargyl amine **2a**, and diphenyliodonium tetrafluoroborate as the model substrates for the multicomponent carbonylative reaction (Table 1). The trifluoroacetimidoyl chlorides could be easily prepared[13] and were frequently applied as versatile trifluoromethyl-containing

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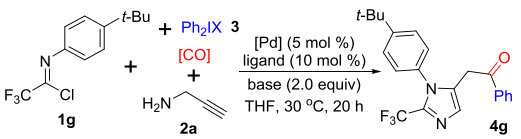
Table 1. Optimization of Reaction Conditions[a]



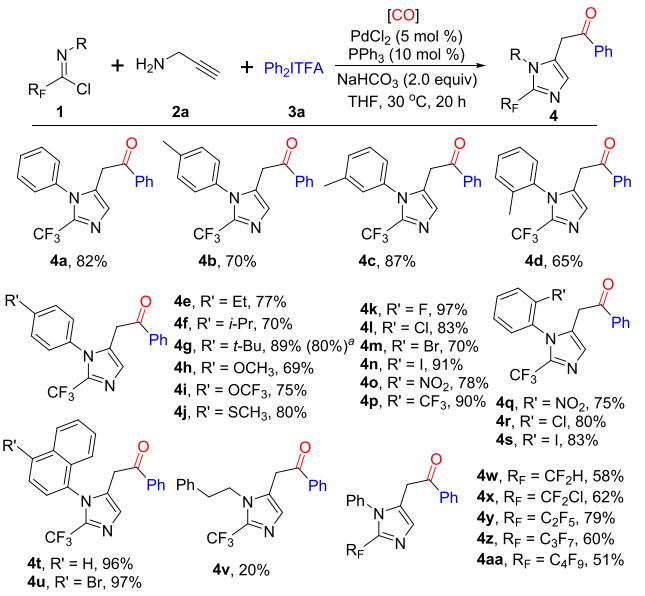
entry	X	[Pd]	ligand	base	yield (%)[b]
1	BF_4	$Pd(OAc)_2$	PPh_3	$NaHCO_3$	63
2	BF_4	$PdCl_2$	PPh_3	$NaHCO_3$	77
3	BF_4	$Pd(TFA)_2$	PPh_3	$NaHCO_3$	59
4	BF_4	$Pd(acac)_2$	PPh_3	$NaHCO_3$	55
5	OTf	$PdCl_2$	PPh_3	$NaHCO_3$	64
6	OTs	$PdCl_2$	PPh_3	$NaHCO_3$	trace
7	Cl	$PdCl_2$	PPh_3	$NaHCO_3$	51
8	TFA	$PdCl_2$	PPh_3	$NaHCO_3$	92 (89)[c]
9	TFA	$Pd(OAc)_2$	PPh_3	$NaHCO_3$	82
10	TFA	$Pd(TFA)_2$	PPh_3	$NaHCO_3$	83
11	TFA	$Pd(acac)_2$	PPh_3	$NaHCO_3$	75
12	TFA	$PdCl_2$	$P(p\text{-}OMePh)_3$	$NaHCO_3$	71
13	TFA	$PdCl_2$	Sphos	$NaHCO_3$	82
14	TFA	$PdCl_2$	Xantphos	$NaHCO_3$	82
15	TFA	$PdCl_2$	dppm	$NaHCO_3$	72
16	TFA	$PdCl_2$	dppf	$NaHCO_3$	81
17	TFA	$PdCl_2$	PPh_3	Na_2CO_3	90
18	TFA	$PdCl_2$	PPh_3	Cs_2CO_3	69
19	TFA	$PdCl_2$	PPh_3	NEt_3	65
20	TFA	$PdCl_2$	PPh_3	$NaHCO_3$	48−84[d]

[a]Reaction conditions: **1a** (0.3 mmol), **2a** (0.2 mmol), **3** (0.3 mmol), [Pd] (5 mol %), ligand (10 mol % for monodentate ligands, 5 mol % for bidentate ligands), [CO] (Ac_2O + HCO_2H, 2 mmol), and base (2.0 equiv) in THF (2.0 mL) at 30 °C for 20 h. Abbreviations: OTf, $-OSO_2CF_3$; OTs, $-OSO_2$-4-Me-Ph; TFA, $-O_2CCF_3$. [b]Yields determined by GC analysis using *n*-dodecane as an internal standard. [c]Isolated yields. [d]The solvent of the reaction was 1,4-dioxane (71%), DMF (38%), DMSO (48%), or CH_3CN (84%).

synthons for the construction of trifluoromethyl-substituted N-heterocycles.[10b,14] To our delight, the desired carbonylative reaction proceeded smoothly to give the target imidazole product **4g** in 63% yield using the combination of $Pd(OAc)_2$ (5 mol %) and PPh_3 (10 mol %) as the catalyst under a CO (2 mmol) atmosphere in THF at 30 °C for 20 h (Table 1, entry 1). Then, different palladium catalysts were examined, and $PdCl_2$ could enable the highest yield (Table 1, entries 2−4). The nature of the diaryliodonium salt counterion has an obvious influence on the reaction outcome. Diverse diaryliodonium salts were tested, and the corresponding triflate and chloride salts afforded the desired product in 51−64% yields without reactivity of the tosylate salt (Table 1, entries 5−7). It is noteworthy that the best result was obtained with respect to trifluoroacetate salt, where imidazole **4g** could be obtained in 89% isolated yield (Table 1, entry 8). By defining trifluoroacetate as the diaryliodonium salt counterion, we screened the palladium catalysts again, and $PdCl_2$ was the best choice (Table 1, entries 9−11). The effect of ligands was also surveyed, and a series of phosphine ligands were examined for the reaction. The results revealed that a comparable reactivity of other phosphine ligands was observed, which was slightly inferior to that of PPh_3 (Table 1, entries 12−16). Further investigation of different bases, including Na_2CO_3, Cs_2CO_3, and NEt_3, suggested that $NaHCO_3$ proved to be the best choice (Table 1, entries 17−19, respectively). Screening of the solvents indicated that THF was the optimal solvent. When the reaction was conducted in DMF or DMSO, the yields decreased to 38% or 48%, respectively. 1,4-Dioxane and CH_3CN could give a reduced yield compared with that of THF (Table 1, entry 20).

With the optimal reaction conditions in hand, the scope and limitation of the palladium-catalyzed multicomponent carbonylative reaction were investigated (Scheme 1). A wide range of

Scheme 1. Scope of Fluorinated Imidoyl Chlorides[b]



[a]The reaction was run on a 1 mmol scale in the presence of 2.5 mol % $PdCl_2$ and 5 mol % PPh_3. [b]Reaction conditions: **1** (0.3 mmol), **2a** (0.2 mmol), **3a** (0.3 mmol), $PdCl_2$ (5 mol %), PPh_3 (10 mol %), [CO] (Ac_2O + HCO_2H, 2 mmol), and $NaHCO_3$ (2.0 equiv) in THF (2.0 mL) at 30 °C for 20 h, isolated yields.

N-aryltrifluoroacetimidoyl chlorides bearing electron-donating or -withdrawing groups were tested under the standard conditions, and good to excellent efficiencies could be observed in most cases (**4a−r**). In general, the electronic nature (**4a−r**) and steric hindrance (**4b−d**, **4q**, and **4r**) of the aryl ring had a marginal effect on the reaction, as verified by the comparable yields of these substrates. The halogen substitutions could be quite compatible with the current reaction conditions, affording the synthetic handle for further derivatization (**4k−n**, **4r**, and **4s**). The transformation could be scaled up on a 1 mmol scale with a reduced amount of catalyst and ligand, and product **4g** was obtained in 80% yield along with a 13% yield of coupling product amidine isomers (**7** and **7′**) intact. Apart from halogen groups, some trifluoroacetimidoyl chlorides with strongly electron-withdrawing groups, including nitro and trifluoromethyl, were amenable substrates under the optimized conditions (**4o−q**), which highlighted the good functional group compatibility of the protocol. Furthermore, naphthalene rings were smoothly incorporated into corresponding imidazole products in 96−97% yields (**4t** and **4u**). Notably, trifluoroacetimidoyl chloride derived from aliphatic amine was also applied as a viable substrate, albeit a relatively low yield was obtained for product **4v**. Gratifyingly, a series of other fluorinated imidoyl chlorides could successfully participate in the transformation to lead to the diverse fluoroalkyl-substituted imidazoles in moderate to good yields (**4w−aa**). The exact structure of imidazole **4l** was unambiguously confirmed by single-crystal X-ray diffraction analysis (CCDC 1973692).[15]

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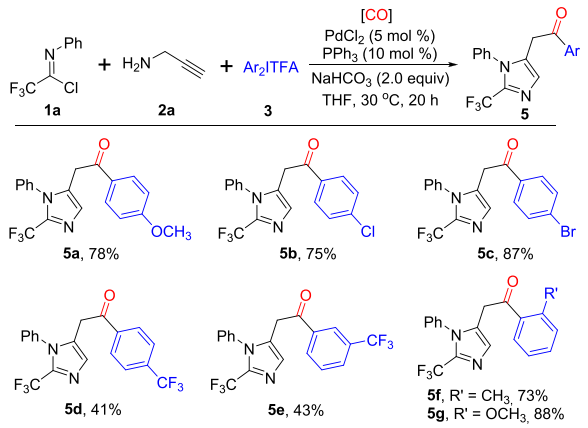
The generality of the protocol was next explored by employing a variety of symmetrical diaryliodonium salts (Scheme 2). The diaryliodonium trifluoroacetate salts bearing

Scheme 2. Scope of Symmetrical Diaryliodonium Salts[a]

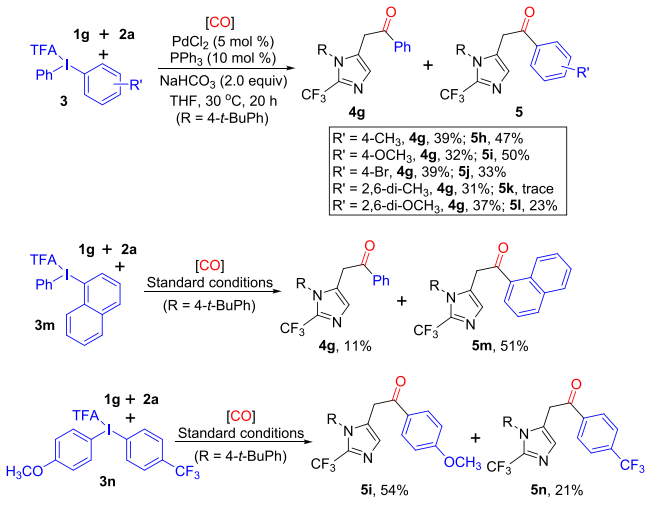


[a]Reaction conditions: **1a** (0.3 mmol), **2a** (0.2 mmol), **3** (0.3 mmol), $PdCl_2$ (5 mol %), PPh_3 (10 mol %), [CO] (Ac_2O + HCO_2H, 2 mmol), and $NaHCO_3$ (2.0 equiv) in THF (2.0 mL) at 30 °C for 20 h, isolated yields.

diverse functional groups at different positions of the phenyl ring reacted well to afford the desired imidazole products (**5a**–**g**). With respect to the strongly electron-withdrawing trifluoromethyl group, moderate reactivity was observed under the current catalytic system (**5d** and **5e**). In general, the electron-rich diaryliodonium salts showed better reactivity.

To further demonstrate the compatibility and applicability of the transformation, an array of unsymmetrical diaryliodonium salts were examined (Scheme 3). The reaction of the electronically differentiated diaryliodonium salts revealed a slightly preferred transfer of the more electron-rich aryl moiety (**5h** and **5i**) over the phenyl group or the phenyl group over the

Scheme 3. Scope of Unsymmetrical Diaryliodonium Salts[a]



[a]Reaction conditions: **1g** (0.3 mmol), **2a** (0.2 mmol), **3** (0.3 mmol), $PdCl_2$ (5 mol %), PPh_3 (10 mol %), [CO] (Ac_2O + HCO_2H, 2 mmol), and $NaHCO_3$ (2.0 equiv) in THF (2.0 mL) at 30 °C for 20 h. Yields determined by NMR analysis using 1,3,5-trimethoxybenzene as an internal standard.

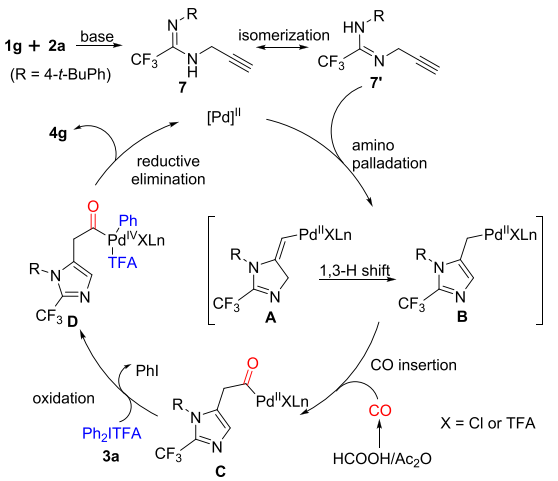
more electron-deficient aryl moiety (**5j**). In the case of the sterically differentiated diaryliodonium salts, the steric hindrance exerted an obvious impact on the reaction (**5k** and **5l**). The obtained 23% yield of **5l** could presumably be attributed to the comprehensive effect of the electronic nature and steric hindrance. With respect to phenyl(naphthyl)-iodonium salt **3m**, the naphthalene moiety dominated the reaction with 4.6:1 selectivity. In particular, the transformation with unsymmetrical diaryliodonium salt **3n** afforded the desired products (**5i** and **5n**) with a distinct electron-rich preference, which agreed with the preliminary observations.

The reactivity of substituted propargyl amines was also investigated under the catalytic system described herein (for details, see the Supporting Information). With regard to 3-phenylprop-2-yn-1-amine **2b**, the corresponding five-membered imidazole product **5o** and six-membered 1,4-dihydropyrimidine **6a** were generated in 30% isolated yields. Nevertheless, only traces of cyclized products (**5p** and **6b**) could be detected by GC-MS analysis when but-2-yn-1-amine **2c** was used as the coupling reagent. Notably, no reaction occurred when 2-methylbut-3-yn-2-amine **2d** was employed. The observation data also shed light on the mechanism of the reaction, implying the extreme instability of alkenyl–palladium complex **A** derived from substrate **2c** or **2d** in the proposed catalytic cycle.

To gain more insights into the mechanism, a series of control experiments were performed (for details, see the Supporting Information). From the results, we found that a typical Pd^0/Pd^{II} catalytic cycle might not be involved in the reaction and the reaction did not proceed via a pathway involving a radical. We also synthesized the coupling product amidine isomers **7** and **7′** between trifluoroacetimidoyl chloride **1g** and propargyl amine **2a** and applied them to react with diaryliodonium salt **3a** under the standard conditions. As expected, target imidazole product **4g** was isolated in 90% yield, indicating the intermediacy of compounds **7** and **7′**.

On the basis of the results from the preliminary mechanistic study of the multicomponent carbonylative reaction and in previous reports,[5,16] a plausible mechanism was proposed as depicted in Scheme 4. It was considered that a Pd^{II}/Pd^{IV} catalytic cycle was involved in the reaction to a larger extent, although a Pd^0/Pd^{II} catalysis could not be entirely excluded.[5,17] At first, the coupling of trifluoroacetimidoyl chloride **1g** and propargyl amine **2a** in the presence of a base could deliver

Scheme 4. Plausible Reaction Mechanism



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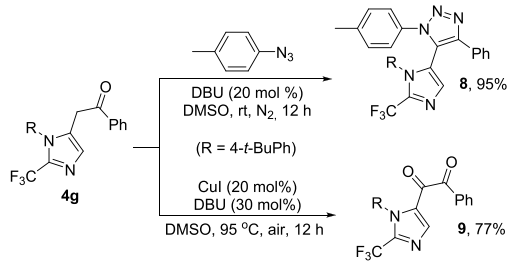
fluorinated propargyl amidine **7**, which underwent a 1,3-H shift to form isomer **7′**. Then, the nucleophilic amino-palladation of compound **7′** occurred to give alkenyl−palladium intermediate **A**, followed by another 1,3-H shift to isomerize it to the more stable alkyl−palladium species **B**. Subsequently, coordination and insertion of CO into alkyl−palladium **B** afforded acyl−palladium intermediate **C**. The oxidation of **C** by diaryliodonium salt **3a** furnished Pd^{IV} complex **D**, which provided the final imidazole product **4g** after reductive elimination with the release of the Pd^{II} catalyst to fulfill the catalytic cycle. In the transformation, diaryliodonium salt **3a** served as both the aryl source and the oxidant.

To further illuminate the synthetic utility of the methodology presented here, serval chemical transformations of the imidazole products were conducted (Scheme 5). Imidazole molecule **4g** could undergo [3+2] cycloaddition with an organic azide in the presence of catalytic DBU to give functionalized (1*H*-imidazol-5-yl)-1*H*-1,2,3-triazole framework **8** with high efficiency. In addition, (1*H*-imidazol-5-yl)-1,2-dione derivative **9** was delivered in 77% yield under copper-catalyzed aerobic oxidative conditions.

Scheme 5. Synthetic Transformations of the Obtained Imidazole Molecules



In conclusion, we have developed a new palladium-catalyzed four-component carbonylative cyclization reaction for the rapid assembly of multifunctionalized imidazoles. The reaction proceeded smoothly at room temperature in the absence of external oxidants and allowed general access to the formation of multiple new bonds and CO insertion in one pot. A range of imidazoles with trifluoromethyl and benzoyl groups were directly constructed in good yields. This method featured mild conditions, a broad substrate scope, and scalability, with no manipulation of CO gas or additional oxidants, which made it suitable for the late-stage functionalization of complex molecules. A reaction mechanism has been proposed on the basis of our control experiments and detected key intermediates.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c00328.

General comments, optimization details, procedures for substrate preparation, analytic data for substrates and products, and NMR spectra for substrates and products (PDF)

Accession Codes

CCDC 1973692 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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