Synthetic Methods

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Synthesis of Isocoumarins through Three-Component Couplings of Arynes, Terminal Alkynes, and Carbon Dioxide Catalyzed by an NHC–Copper Complex**

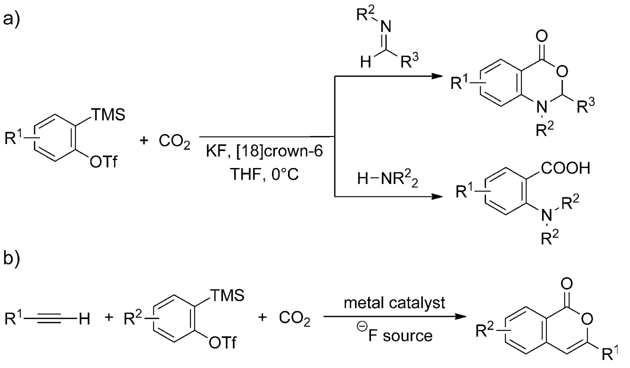
*Woo-Jin Yoo, Thanh V. Q. Nguyen, and Shū Kobayashi**

Abstract: *A copper-catalyzed multicomponent coupling reaction between in situ generated ortho-arynes, terminal alkynes, and carbon dioxide was developed to access isocoumarins in moderate to good yields. The key to this CO_2-incorporating reaction was the use of a versatile N-heterocyclic carbene/copper complex that was able to catalyze multiple transformations within the three-component reaction.*

Isocoumarins are an important class of lactones that are found in numerous natural products with a wide range of biological activities.[1] As such, there is continued interest in the development of new synthetic strategies to prepare these materials in an expedient manner.[2] One of the most prevalent methods to construct the isocoumarin ring structure is the intramolecular cyclization of *ortho*-alkynylbenzoic acid derivatives.[3] The major limitation of this strategy is the multistep synthetic route required to obtain these 2-alkynylbenzoic acids. The development of a multicomponent coupling reaction would thus allow access to these heterocycles in rapid and modular fashion.

The chemical utilization of carbon dioxide (CO_2) as a C1 feedstock and a reaction medium to access value-added materials and fuels is attractive, as CO_2 is a safe, inexpensive, and readily available gas.[4] However, because of its intrinsic kinetic and thermodynamic stability, the use of CO_2 in synthetic organic chemistry is challenging and limited. In order to overcome these barriers, the strategic use of highly energetic starting materials and/or intermediates, in conjugation with a catalyst, allows the development of useful synthetic methodologies that can incorporate CO_2 into complex organic materials.

Arynes are highly unstable species that have found use as reactive intermediates in a variety of multicomponent carbon–carbon and carbon–heteroatom bond formation processes.[5] In most cases, these multicomponent coupling reactions take advantage of the highly electrophilic nature of *ortho*-arynes to undergo nucleophilic addition with a variety of nucleophiles, followed by the subsequent interception of the aryl anion intermediate with various electrophiles, to generate 1,2-disubstituted arenes. Based on the highly energetic nature of the aryne intermediate, it should be well suited to serve as a key intermediate for multicomponent coupling reactions involving CO_2. For example, Yoshida et al. reported CO_2 incorporation reactions using arynes, with imines[6] and amines[7] as nucleophilic partners to generate benzoxazinones and anthranilic acid, respectively (Scheme 1). Despite these seminal reports, very few examples of multicomponent coupling reactions involving benzynes and CO_2 have been disclosed thus far.[8]



Scheme 1. Multicomponent coupling reactions with a) arynes and CO_2 (Yoshida et al. **2006**[6], **2008**[7]), and b) terminal alkynes, arynes, and CO_2 (this work). TMS = trimethylsilyl, OTf = trifluoromethanesulfonate.

In order to expand the synthetic possibilities of incorporating CO_2 with reactive aryne intermediates, our strategy involves the use of transition-metal catalysts to broaden the choice for potential nucleophilic partners in these multicomponent coupling reactions. Herein, we report an N-heterocyclic carbene (NHC) copper complex as a catalyst for the three-component coupling reaction of 2-(trimethylsilyl)aryl triflates, terminal alkynes, and CO_2 to generate isocoumarins in an efficient manner (Scheme 1).

We were initially inspired by the copper-catalyzed multicomponent coupling reactions of arynes with terminal alkynes and various electrophiles.[9] The common reactive intermediate among these multicomponent reactions is the transient *ortho*-alkynylaryl/copper complex **1**. We anticipated that such an intermediate could be intercepted by CO_2[10] to generate copper carboxylate **2** or undergo an additional 5-*exo*-dig or 6-

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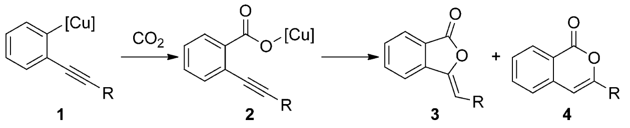
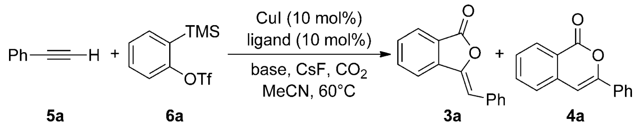


Scheme 2. Assumed reaction of copper intermediate **1** with CO_2.

endo-dig cyclization to furnish phthalides **3** or isocoumarins **4**, respectively (Scheme 2).

The starting point for our optimization studies was based on the work by Zhang and co-workers,[9a] who accomplished the multicomponent coupling reaction of arynes, terminal alkynes, and allylic chlorides by using catalytic amounts of copper iodide, 1,2-bis(diphenylphosphino)ethane (dppe), and stoichiometric amounts of K_2CO_3 and CsF in MeCN at 60 °C. We thus attempted the three-component coupling of phenylacetylene (**5a**) and benzyne precursor **6a** as the model reaction (Table 1).

Table 1: Initial study of the copper-catalyzed three-component coupling of terminal alkyne **5a**, 2-(trimethylsilyl)phenyl triflate (**6a**), and CO_2.[a]

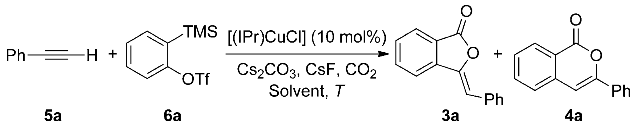


Entry	Ligand	Base	CO_2 [atm]	Yield [%][b]	
				3a	**4a**
1	dppe	K_2CO_3	1	n.d.	
2	dppe	K_2CO_3	25	2	5
3	dppe	Cs_2CO_3	25	3	13
4	$P(nBu)_3$	Cs_2CO_3	25	8	19
5	$P(Cy)_3$	Cs_2CO_3	25	10	4
6	$P(tBu)_3$	Cs_2CO_3	25	13	18

[a] Reaction conditions: alkyne **5a** (0.25 mmol), aryne precursor **6a** (0.38 mmol), CuI (0.025 mmol, 10 mol%), ligand (0.025 mmol, 10 mol%), base (1.25 mmol), CsF (0.75 mmol) in MeCN (1 mL) at 60 °C under CO_2 pressure. [b] Yields based on **5a** and determined by ^{1}H NMR analysis using 1,1,2,2-tetrachloroethane as an internal standard. n.d. = not detected.

Initially, when we performed the three-component coupling reaction, the expected product was not obtained. Instead, we found 1,2-diphenyl alkyne, derived from the copper-catalyzed addition of terminal acetylene **5a** to the in situ generated benzyne, as the major product (Table 1, entry 1). Based on this result, we assumed that one atmosphere of CO_2 was insufficient to induce carboxylation. By increasing the CO_2 pressure to 25 atm, the desired cyclized products **3a** and **4a** were obtained (Table 1, entry 2). Motivated by our previous experience with carboxylation reactions,[11] we changed the base from K_2CO_3 to Cs_2CO_3, which slightly improved the three-component coupling reaction (Table 1, entry 3). Under the assumption that the carboxylation reaction would be favored with electron-rich copper complexes, we surveyed various electron-rich phosphine ligands, which slightly improved the yields of the desired carboxylated products (Table 1, entries 4–6). Fortuitously, when we examined [(IPr)CuCl][12] (IPr = 1,3-bis(diisopropyl)-phenylimidazol-2-ylidene) as the catalyst, we obtained the desired heterocyclic compounds in moderate yield with isocoumarin **4a** as the major product (Table 2, entry 1). We conducted the further optimization with [(IPr)CuCl] as the catalyst and a reduced amount of base, and found that using a mixed solvent system composed of MeCN and THF improved the reaction (Table 2, entries 2–5). We also varied the reaction temperature and found that at 90 °C, the selectivity toward the six-membered heterocycle **4a** was improved (Table 2, entries 6–8). In addition, we examined the effect of CO_2 pressure, and the multicomponent carboxylation reaction occurred smoothly even at 15 atm (Table 2, entries 9–11). Finally, we examined various N-heterocyclic carbene/copper complexes, but found no significant improvements over the commercially available catalyst [(IPr)-CuCl].[13]

Table 2: Optimization of reaction conditions with [(IPr)CuCl] as a catalyst.[a]

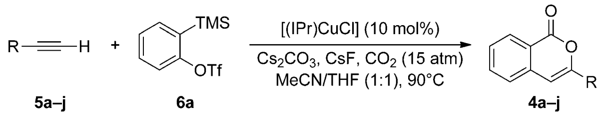


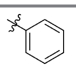
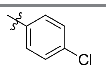
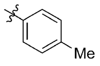
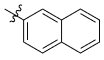
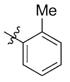
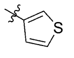
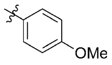
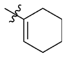
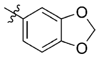
Entry	Solvent	*T* [°C]	CO_2 [atm]	Yield [%][b]	
				3a	**4a**
1	MeCN	60	25	2	49
2	MeCN, MePh	60	25	traces	
3	MeCN, DCM	60	25	5	39
4	MeCN, DME	60	25	5	50
5	MeCN, THF	60	25	4	66
6	MeCN, THF	40	25	5	45
7	MeCN, THF	90	25	1	68
8	MeCN, THF	110	25	2	40
9	MeCN, THF	90	1	n.d.	
10	MeCN, THF	90	15	1	70
11	MeCN, THF	90	40	2	64

[a] Reaction conditions: alkyne **5a** (0.25 mmol), aryne precursor **6a** (0.38 mmol), [(IPr)CuCl] (0.025 mmol, 10 mol%), Cs_2CO_3 (0.75 mmol), CsF (0.75 mmol) in solvent (1:1, 1 mL) at various temperatures under CO_2 pressure. [b] Yields based on **5a** and determined by ^{1}H NMR analysis using 1,1,2,2-tetrachloroethane as an internal standard.

With the optimized conditions in hand, we examined the substrate scope for the three-component coupling reaction of terminal alkynes **5a–j**, 2-(trimethylsilyl)phenyl triflate (**6a**), and CO_2 (Table 3). In general, the copper-catalyzed carboxylation reaction occurred relatively smoothly with various substituted terminal alkynes bearing electron-donating moieties, furnishing the desired isocoumarins **4a–e** in good yields (Table 3, entries 2–5); the exception was the reaction with *ortho*-substituted alkyne **5c** (entry 3). When the electron-deficient alkyne **5f** was examined as a nucleophile, the yield was only modest (Table 3, entry 6). Other terminal alkynes, bearing a naphthyl group (Table 3, entry 7), a heteroaromatic substituent (entry 8), and a vinyl moiety (entry 9), were also suitable coupling partners for the three-component reaction with CO_2. While terminal alkynes substituted by sp^2-hybridized carbon atoms provided the desired carboxylated product

Table 3: Substrate scope of the copper-catalyzed coupling reaction of terminal alkynes **5a-j** and 2-(trimethylsilyl)phenyl triflate (**6a**) under CO_2 pressure (15 atm).[a]



Entry	R	Yield [%][b]	Entry	R	Yield [%][b]
1		72 (**4a**)	6		52 (**4f**)
2		81 (**4b**)	7		74 (**4g**)
3		43 (**4c**)	8		55 (**4h**)
4		70 (**4d**)	9		69 (**4i**)
5		68 (**4e**)	10[c]	C_6H_{13}	33 (**4j**)

[a] Reaction conditions: alkyne **5a–j** (0.25 mmol), aryne precursor **6a** (0.38 mmol), [(IPr)CuCl] (0.025 mmol, 10 mol%), Cs_2CO_3 (0.75 mmol), CsF (0.75 mmol) in MeCN/THF (1:1, 1 mL) at 90 °C under 15 atm of CO_2 pressure. [b] Yields of isolated products **4a–j** based on **5a–j**. [c] [(TPr)CuCl] (0.025 mmol) was used as the catalyst. TPr = 1,4-bis(2,6-diisopropylphenyl)-3-methyl-1,2,3-triazol-5-ylidene.

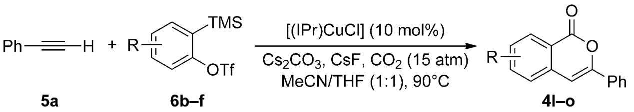
in good to modest yields, the use of aliphatic terminal alkynes, such as **5j**, led to a low yield (Table 3, entry 10).[14]

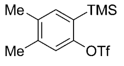
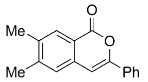
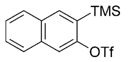
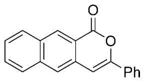
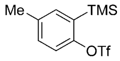
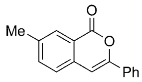
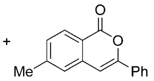
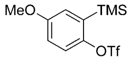
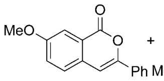
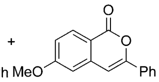
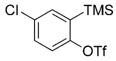
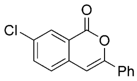
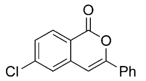
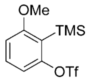
Next, we investigated the copper-catalyzed multicomponent carboxylation with phenylacetylene (**5a**) and various substituted 2-(trimethylsilyl)aryl triflates **6b–f** (Table 4). When 4,5-disubstituted aryne precursors **6b,c** were utilized as substrates, the expected isocoumarins **4k,l** were generated in good yields (Table 4, entries 1 and 2). In addition, the nucleophilic addition to the unsymmetrical *ortho*-aryne intermediate showed poor regioselectivity, providing 4-substituted silyl triflates **4m–4o** and **4m′–o′** as mixtures of regioisomers with modest to good yields (Table 4, entries 3–5). In order to improve the regioselectivity of the three-component coupling reaction, we screened C6-substituted silyl aryl triflate **6g** (Table 4, entry 6). However, the desired carboxylated product was not detected, presumably because of the poor nucleophilicity of the expected sterically hindered 2,6-disubstituted copper intermediate.

In order to demonstrate the synthetic utility of the three-component coupling reaction of 2-(trimethylsilyl)aryl triflates, terminal alkynes, and CO_2, we also performed this copper-catalyzed carboxylation reaction on a gram scale (Scheme 3).

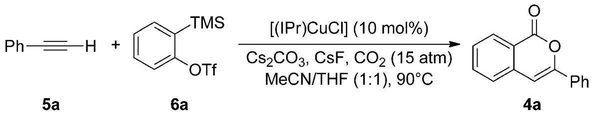
Based on previous reports on multicomponent coupling reactions with *ortho*-aryne intermediates,[9] a tentative mechanism is proposed in Scheme 4. Initially, the in situ formed NHC–copper hydroxide or carbonate deprotonates terminal alkyne **5** to generate copper acetylide **A**. Concurrently, the fluoride-induced silyl elimination of **6** provides the reactive *ortho*-benzyne **B**, and this electrophilic intermediate reacts with **A** to furnish *ortho*-alkynyl copper complex **C**. Such intermediates have been previously proposed for multicomponent coupling reactions involving terminal alkynes and 2-(trimethylsilyl)aryl triflates, and under our optimized reaction conditions in the absence of CO_2 led to the formation of diphenylacetylene [Scheme 5, Eq. (1)]. Although the nucleophilic addition of **A** to CO_2 has been reported,[15] we speculate that this unproductive pathway is disfavored because of the strong electrophilicity of **B**. Next, *ortho*-alkynyl aryl copper complex **C** can undergo nucleophilic addition to CO_2 to generate copper carboxylate **D**,[12] which would be followed by a 6-*endo*-dig cyclization to form endocyclic copper heterocycle **E**. In order to validate the proposed carboxylation–cyclization steps, the [(IPr)CuCl]-catalyzed carboxylation of *ortho*-alkynylarylboronic ester **7** was performed [Eq. (2)]. This copper-catalyzed reaction, which also involves **C** as an intermediate,[16] provided the

Table 4: Substrate scope of the copper-catalyzed coupling of phenylacetylene (**5a**) and 2-(trimethylsilyl)aryl triflates **6b–f** under CO_2 pressure (15 atm).[a]



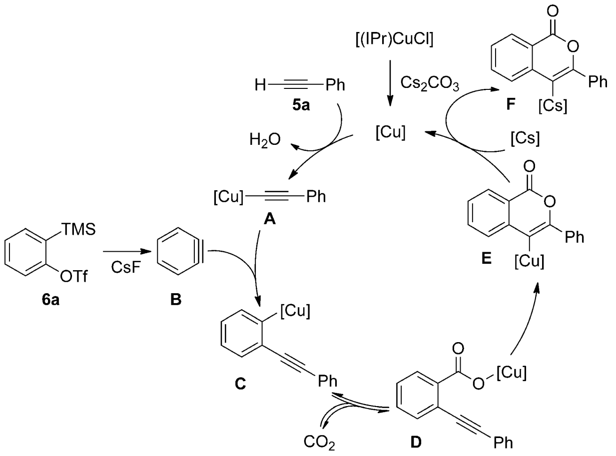
Entry	Pre-arynes **6b–f**	Isocoumarins **4l–o**	Yield [%][b] (**4**:**4′**)[c]
1	 **6b**	 **4k**	84
2	 **6c**	 **4l**	80
3	 **6d**	 +  **4m** **4m'**	71 (1:1.1)
4	 **6e**	 +  **4n** **4n'**	66 (1:1)
5	 **6f**	 +  **4o** **4o'**	48 (1:1)
6	 **6g**	n.d.	

[a] Reaction conditions: alkyne **5a** (0.25 mmol), aryne precursor **6b–f** (0.38 mmol), [(IPr)CuCl] (0.025 mmol, 10 mol%), Cs_2CO_3 (0.75 mmol), CsF (0.75 mmol) in MeCN/THF (1:1, 1 mL) at 90 °C under 15 atm of CO_2 pressure. [b] Yields of isolated products **4k–o** based on **5a**. [c] Regioisomeric ratios determined by ^{1}H NMR analysis.

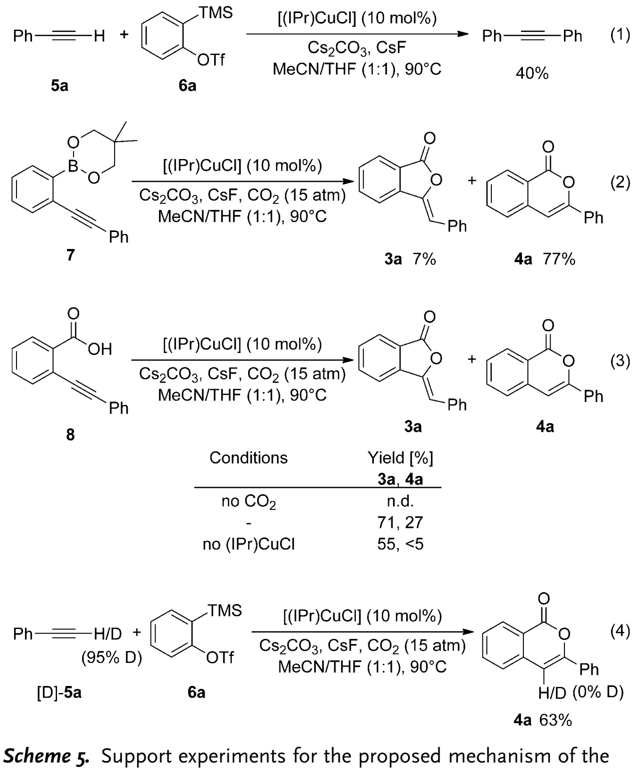


10.0 mmol 1.50 g, 68% yield

Scheme 3. Gram-scale synthesis of 3-substituted isocoumarin **4a**.



Scheme 4. Proposed mechanism for the [(IPr)CuCl]-catalyzed three-component reaction between alkynes, 2-(trimethylsilyl)aryl triflates, and CO_2.



Conditions	Yield [%] 3a, 4a
no CO_2	n.d.
-	71, 27
no (IPr)CuCl	55, <5

Scheme 5. Support experiments for the proposed mechanism of the copper-catalyzed carboxylation reaction to access 3-substituted isocoumarins.

expected isocoumarin **4a** as the major product. In addition, we examined *ortho*-alkynylbenzoic acid **8** as a model substrate for the intramolecular cyclization reaction [Eq. (3)], and found that the expected cyclic lactone **4a** was not detected. Under the assumption that the interconversion between **C** and **D** is reversible, we repeated the cyclization reaction of **8** under CO_2 atmosphere and found that the heterocyclic compounds were obtained in an excellent yield, albeit with phthalide **3a** as the major product. This result suggested that the origin of the product distribution is a result of the competition between the base-mediated 5-*exo*-dig and the copper-catalyzed 6-*endo*-dig cyclization reactions of metalated *ortho*-alkynylbenzoates. Indeed, the control experiment in the absence of [(IPr)CuCl] showed that the base-mediated cyclization reaction of **8** provides **3a** as the major regioisomer. Finally, we examined the three-component coupling reaction with a deuterium-enriched alkyne **[D]-5a** as a substrate and found that deuterium was not incorporated into isocoumarin **4a**. This result suggested that the regeneration of the copper catalyst is most likely a result of transmetalation between endocyclic copper heterocycle **E** and the cesium salts found in the reaction mixture.

In conclusion, we have developed an efficient copper-catalyzed three-component coupling reaction of terminal alkynes, 2-(trimethylsilyl)aryl triflates, and CO_2. We found that a single NHC–copper complex possessed the ability to facilitate multiple transformations within the multicomponent reaction to deliver a wide range of substituted isocoumarins in good yields. Further investigations into the synthetic utility of *ortho*-arynes as reactive intermediates for CO_2-incorporating reactions are ongoing in our group.

Experimental Section

General procedure for the three-component coupling reaction between terminal alkynes, *ortho*-aryne precursors, and CO_2: In a glove box with an inert atmosphere (Ar), [IPrCuCl] (12.0 mg, 0.025 mmol, 10 mol%), CsF (114.0 mg, 0.75 mmol), and Cs_2CO_3 (244.0 mg, 0.75 mmol) were weighed and placed into a stainless-steel high-pressure reactor. Concurrently, a solution composed of 1-alkyne **5** (0.25 mmol) and 2-(trimethylsilyl)aryl triflate **6** (0.38 mmol) in MeCN/THF (1 mL, 1:1 *v*/*v*) was prepared in a screw-capped vial (5 mL). After capping the high-pressure reactor with a rubber septum, both the reaction vessel and the MeCN/THF solution were removed from the glove box. The solution containing **5** and **6** was transferred to the stainless steel reactor by syringe through the rubber septum. The septum was quickly replaced with a stainless steel gas line, and the reaction vessel was heated to 90 °C under 15 atm of CO_2 for 24 h with magnetic stirring. Next, the high-pressure reactor was allowed to cool to room temperature and the excess CO_2 was vented. After the addition of CH_2Cl_2 (20 mL) and a saturated NH_4Cl solution (10 mL) to the reaction mixture, the aqueous phase was extracted twice with CH_2Cl_2 (2 × 10 mL) and the combined organic phase was dried over Na_2SO_4. The solvent was removed under reduced pressure and the crude mixture was purified using preparative TLC or column chromatography (*n*-hexane/EtOAc, 10:1 *v*/*v*) to afford isocoumarins **4** as light-yellow solids.

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[14] When [(IPr)CuCl] was used as a catalyst, **4j** was obtained in only 24% yield, based on **5j** and determined by ^{1}H NMR analysis using 1,1,2,2-tetrachloroethane as an internal standard.

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