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.

socoumarins 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

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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 CO₂. For example, Yoshida et al. reported CO₂ incorporation reactions using arynes, with imines^[6] and amines^[7] as nucleophilic partners to generate benzoxazinones anthranilic acid. respectively and (Scheme 1). Despite these seminal reports, very few examples of multicomponent coupling reactions involving benzynes and CO₂ 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 Nheterocyclic 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 CO2.

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 K₂CO₃ 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 CO₂.^[a]

Ph	-H +	f Cul (10 m ligand (10 base, CsF MeCN, 6	$ \begin{array}{c} \text{mol\%})\\ \text{mol\%})\\ \hline \\ \hline \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\$		O U O Ph	
5a	6a			3a	4a	
Entry	Ligand	Base	CO ₂ [at	tm] Yie	Yield [%] ^[b]	
				3 a	4 a	
1	dppe	K ₂ CO ₃	1		n.d.	
2	dppe	K ₂ CO ₃	25	2	5	
3	dppe	Cs ₂ CO ₃	25	3	13	
4	$P(nBu)_3$	Cs ₂ CO ₃	25	8	19	
5	P(Cy) ₃	Cs ₂ CO ₃	25	10	4	
6	P(tBu) ₃	Cs ₂ CO 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 CO₂ pressure. [b] Yields based on **5a** and determined by ¹H 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 CO₂ 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

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

Ph	-H + TMS OTf 6a	[(IPr)CuCl] (10 m Cs ₂ CO ₃ , CsF, (Solvent, <i>T</i>		0 +	O O Ph 4a	
Entry	Solvent	T [°C] CO ₂ [atm]		Yield	Yield [%] ^[b]	
				3 a	4a	
1	MeCN	60	25	2	49	
2	MeCN, MePh	60	25	tr	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	r	ı.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%), Cs₂CO₃ (0.75 mmol), CsF (0.75 mmol) in solvent (1:1, 1 mL) at various temperatures under CO₂ pressure. [b] Yields based on **5a** and determined by ¹H NMR analysis using 1,1,2,2-tetrachloroethane as an internal standard.

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]

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 carboxvlation 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 electrondeficient alkyne 5 f 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 CO₂. While terminal alkynes substituted by sp²-hybridized carbon atoms provided the desired carboxylated product

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Table 3: Substrate scope of the copper-catalyzed coupling reaction of terminal alkynes **5 a-j** and 2-(trimethylsilyl)phenyl triflate (**6 a**) under CO₂ pressure (15 atm).^[a]

R—≡	≕н +	TMS [(IF OTf Cs ₂ CC Me	Pr)CuCl] (10 m D ₃ , CsF, CO ₂ (CN/THF (1:1),	01%) 15 atm) 90°C	U O R
5a	њj	6a		4	a–j
Entry	R	Yield [%] ^[b]	Entry	R	Yield [%] ^[b]
1	X ²	72 (4 a)	6	3 ² CI	52 (4 f)
2	Me	81 (4b)	7	X	74 (4g)
3	Me	43 (4c)	8	S	55 (4 h)
4	3 OMe	70 (4 d)	9	X C	69 (4 i)
5		68 (4e)	10 ^[c]	^{يخ} C ₆ H ₁₃	33 (4 j)

[a] Reaction conditions: alkyne **5a–j** (0.25 mmol), aryne precursor **6a** (0.38 mmol), [(IPr)CuCl] (0.025 mmol, 10 mol%), Cs₂CO₃ (0.75 mmol), CsF (0.75 mmol) in MeCN/THF (1:1, 1 mL) at 90 °C under 15 atm of CO₂ 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 silvl 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 threecomponent 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 threecomponent 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 multicom-

Table 4: Substrate scope of the copper-catalyzed coupling of phenylacetylene (**5 a**) and 2-(trimethylsilyl)aryl triflates **6 b**–**f** under CO₂ pressure (15 atm).^[a]



[a] Reaction conditions: alkyne **5a** (0.25 mmol), aryne precursor **6b–f** (0.38 mmol), [(IPr)CuCl] (0.025 mmol, 10 mol%), Cs₂CO₃ (0.75 mmol), CsF (0.75 mmol) in MeCN/THF (1:1, 1 mL) at 90 °C under 15 atm of CO₂ pressure. [b] Yields of isolated products **4k–o** based on **5a**. [c] Regioisomeric ratios determined by ¹H NMR analysis.



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

ponent 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*alknyl 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

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



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 CO₂ 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 coppercatalyzed three-component coupling reaction of terminal alkynes, 2-(trimethylsilyl)aryl triflates, and CO₂. 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 CO₂incorporating reactions are ongoing in our group.

Experimental Section

General procedure for the three-component coupling reaction between terminal alkynes, ortho-aryne precursors, and CO₂: 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 Cs₂CO₃ (244.0 mg, 0.75 mmol) were weighed and placed into a stainlesssteel high-pressure reactor. Concurrently, a solution composed of 1alkyne 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 CO₂ for 24 h with magnetic stirring. Next, the high-pressure reactor was allowed to cool to room temperature and the excess CO₂ was vented. After the addition of CH2Cl2 (20 mL) and a saturated NH4Cl 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 Na₂SO₄. 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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Communications

Synthetic Methods

W.-J. Yoo, T. V. Q. Nguyen, S. Kobayashi* _____ IIII - IIII

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

$$R^1 \longrightarrow H + R^2 \longrightarrow TMS + CO_2 \longrightarrow IPrCuCl OOTf + CO_2 CsF, Cs_2CO_3 \qquad R^2 \longrightarrow R^1 \longrightarrow R^1$$

A facile synthetic protocol to isocoumarins consists of a three-component coupling reaction between 1-alkynes, 2-(trimethylsilyl)aryl triflates, and CO_2 (see scheme). The key to this reaction was the use of a versatile N-heterocyclic carbene/ copper complex that was able to catalyze multiple transformations within the three-component reaction.

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