

Copper-Catalyzed Reaction of α -Aryldiazoesters with Terminal Alkynes: A Formal [3 + 2] Cycloaddition Route Leading to Indene Derivatives

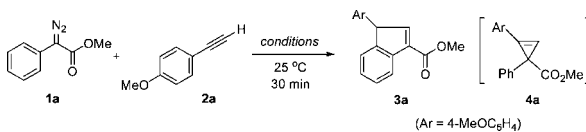
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α -Diazocarbonyl compounds have long been used as a versatile precursor of carbenes in organic synthesis leading to various applications.¹ Attributing to their ease of preparation and handling, a diverse range of reactivities of α -diazocarbonyls has been extensively investigated under thermolytic, photolytic, or transition metal-employed conditions.² Representative examples among those are cyclopropanation, ylide transformation, or X–H insertion (X = O, N, S, C, Si, etc.)³ which have been elegantly utilized in the synthesis of complex molecules.⁴ Reaction of alkynes with carbenoids normally affords cyclopropene compounds⁵ which are versatile synthetic building blocks.⁶ However, we recently observed a notable outcome from the Cu(NHC)-catalyzed [NHC: *N*-heterocyclic carbene] reaction of terminal alkynes with α -aryldiazoesters leading to indenenes, representing the first example of Cu-catalyzed formal [3 + 2] cycloaddition between those two components.⁷ Since indene derivatives have received a great attention from pharmaceutical and materials chemistry,⁸ we further investigated the scope and mechanistic details of the reaction, which are described herein.⁹

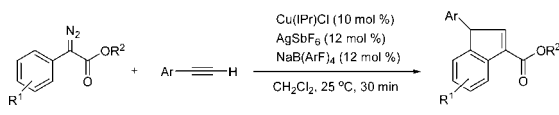
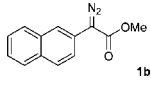
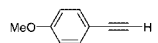
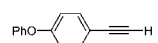
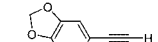
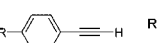
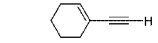
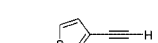
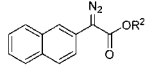
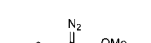
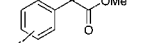
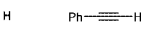
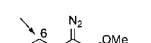
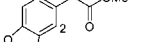
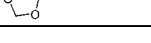
Table 1. Optimization of the Reaction Conditions^a

			
entry	catalyst system	solvent	yield (%) ^b
1	CuCl	CH ₂ Cl ₂	<1 (95)
2	CuCl/AgSbF ₆	CH ₂ Cl ₂	44 (40)
3	Cu(IPr)Cl	CH ₂ Cl ₂	<1 (<1)
4	Cu(IPr)Cl/AgSbF ₆	CH ₂ Cl ₂	75 (14)
5	Cu(IPr)Cl/AgSbF ₆ /NaB(ArF) ₄	CH ₂ Cl ₂	90 (<1)
6	Cu(IMes)Cl/AgSbF ₆ /NaB(ArF) ₄	CH ₂ Cl ₂	48 (8)
7	Cu(IPr)Br/AgSbF ₆ /NaB(ArF) ₄	CH ₂ Cl ₂	84 (10)
8	Cu(IPr)Cl/AgSbF ₆ /NaB(ArF) ₄	CH ₃ CN	41 (27)
9	Au(IPr)Cl/AgSbF ₆ /NaB(ArF) ₄	CH ₂ Cl ₂	30 (10)

^a **1a** (0.2 mmol), **2a** (0.6 mmol), catalyst (10 mol %), AgSbF₆ (12 mol %), NaB(ArF)₄ (12 mol %) in solvent (2.0 mL) at 25 °C for 30 min. ^b NMR yield of **3a** and number in parenthesis is NMR yield of **4a**.

When methyl α -diazophenylacetate (**1a**) was reacted with (4-methoxyphenyl)acetylene (**2a**) in the presence of CuCl catalyst, a cyclopropene compound (**4a**) was exclusively obtained (Table 1, entry 1).¹⁰ Quite surprisingly, upon the use of cationic copper species, 3*H*-indene-1-carboxylate (**3a**) was produced along with **4a** in similar ratio (entry 2). Although a copper catalyst alone such as Cu(IPr)Cl¹¹ [IPr: 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene] was ineffective (entry 3), a silver additive significantly increased conversion and selectivity, giving **3a** as a major adduct (entry 4). Interestingly, certain additives such as NaB(ArF)₄ [ArF: 3,5-bis(trifluoromethyl)phenyl] offered further improvement of the reaction efficiency and selectivity under the mild conditions (entry

Table 2. Catalytic Reaction of α -Aryldiazoesters with 1-Alkynes^a

			
Entry	α -Aryldiazoester	Alkyne	Yield (%) ^b
1	 1b	 2a	81
2	1b	 2a	70
3	1b	 2a	49
4	1b	 2a R = Me	51
5	1b	 2a <i>t</i> -Bu	57
6	1b	 2a Br	23
7	1b	 2a	64
8	1b	 2a	52
9	 1b	R ² = <i>t</i> -Bu 2a	70
10	 1b	Bn 2a	85
11	 1b	R ¹ = H  2a	45
12	 1b	H 2a	89
13	 1b	4-Br 2a	85
14	 1b	4-Me 2a	85
15	 1b	4-OMe 2a	59
16	 1b	2-Br 2a	46
17	 1b	2-Me 2a	58
18	 1b	2a	63 (6/2 = >99:1)

^a Conditions: α -aryldiazoester (0.5 mmol), 1-alkyne (1.5 mmol), Cu(IPr)Cl (10 mol %), AgSbF₆ (12 mol %), NaB(ArF)₄ (12 mol %) in CH₂Cl₂ (5.0 mL) at 25 °C for 30 min. ^b Isolated yield.

5).¹² Catalysts having NHC ligands other than IPr were less effective (entry 6). Modification of the copper species or change of solvent resulted in detrimental effects (entries 7–8). In addition, Au(IPr)Cl catalyst displayed lower efficiency when compared to that of the corresponding Cu species (entry 9).

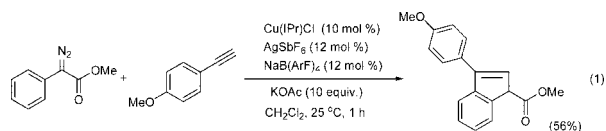
To explore the substrate scope, a range of alkynes and α -diazooesters bearing various functional groups were then examined (Table 2). It was found that electronic property of alkynes has

profound effects on the reaction efficiency, consistent with the mechanistic proposal that alkyne initially inserts onto carbenoid.

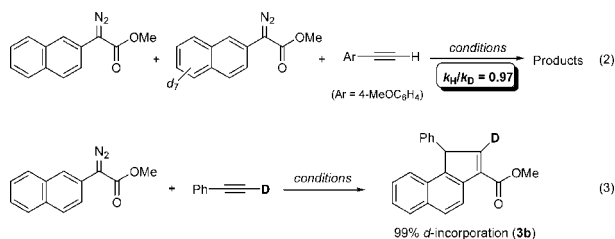
In fact, phenylacetylenes bearing electron-donating groups react more readily, in general, with α -aryldiazoesters under the optimized conditions as compared to electron-deficient alkynes. Structure of the obtained indenenes was confirmed by an X-ray crystallographic analysis of one product (entry 6).¹³

Although aliphatic alkynes were inert under the conditions, alkynes conjugated with vinyl or bearing a thienyl moiety readily participated in the reaction (entries 7–8).¹⁴ Variation of alkoxy groups in diazoesters did not affect the reaction efficiency (entries 9–10). Interestingly, electronic alternation on α -diazoesters showed little effects on the reaction efficiency when compared to the alkyne counterpart (entries 12–17). In addition, the reaction was highly regioselective (entry 18), in that an unsymmetric aryldiazoester reacts exclusively at the less hindered site.

Interestingly, when the reaction was carried out in the presence of a base such as potassium acetate, regioisomeric 1*H*-indene compounds could be isolated, which can be attributed to the base-mediated rearrangement of initially formed 3*H*-isomers (eq 1).¹⁵



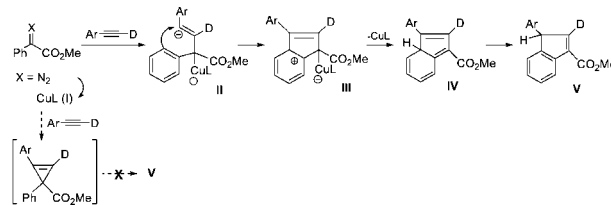
To gain insight into the reaction mechanism, we performed kinetic isotope effect studies (eq 2). Experiments revealed that this cyclization exhibits no *intermolecular* kinetic isotope effects ($k_H/k_D = 0.97$). When phenylacetylene-*d* was allowed to react, the deuterium atom was exclusively incorporated with high extent (99%) at the 2-position of 1-phenyl-1*H*-benzindene-3-carboxylate (**3b**, eq 3).



On the basis of the above experiments and precedent reports,² a plausible mechanistic pathway is presented in Scheme 1. Electron-rich acetylene is proposed to insert into an initially formed copper carbenoid (**I**) to afford zwitterionic species **II**.¹⁶ Subsequent intramolecular electrophilic attack on the aromatic ring of **II** leads to isoindene **IV** via **III** upon the release of copper species.¹⁷ Isomerization of **IV** to a more favorable structure will provide 3*H*-indene product **V**. When an isolated cyclopropene species **4a** was subjected to the reaction conditions of copper catalysts, the corresponding indene **3a** was not generated, but **4a** was recovered quantitatively. Thus, the possibility of Cu-catalyzed isomerization of arylcyclopropenes to indenenes can be clearly excluded although the rearrangement was revealed to proceed by rhodium catalysts.¹⁸

In summary, we have developed the first example of a novel type of Cu-catalyzed intermolecular formal [3 + 2] cycloaddition

Scheme 1. Mechanistic Proposal of the Formal [3 + 2] Cyclization



between terminal alkynes and α -aryldiazoesters, thus allowing for selective synthesis of indene derivatives under mild conditions.

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Supporting Information Available: Experimental procedures, analytical data, copies of NMR spectra of products, and a CIF file. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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