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Silver-Catalyzed Carbon Dioxide Fixation on Alkynylindenes

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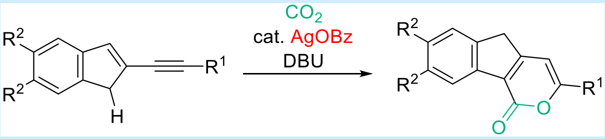
ABSTRACT: The synthesis of polycyclic indene derivatives via silver-catalyzed carbon dioxide fixation on 2-alkynylindene derivatives was achieved by nucleophilic addition of the indenyl anion to carbon dioxide involving carbon−carbon bond formation and subsequent intramolecular cyclization to the alkyne part activated by a silver catalyst. This cascade process could be applied to various substrates to obtain the corresponding products in high yields. The *endo*/*exo* selectivity of the cyclization could be controlled by the steric or electronic effect of the substituents on the substrates, and 6-*endo*-selective cyclization was realized to afford α-pyrone-fused indenes.



Carbon dioxide is an attractive C_1 source for molecular construction in terms of nontoxicity, low-cost availability, and easy handling.[1] However, the thermodynamic stability of CO_2 has made it difficult to fix carbon dioxide into an organic substrate, and thus, reactions with strong nucleophiles are often required in order to suppress decarboxylation from a CO_2 adduct.[2] For this problematic concern, the CO_2 incorporation reaction based on base-mediated deprotonation and subsequent nucleophilic addition to CO_2—sequential intramolecular cyclization with an alkyne activated by transition metal catalysts[3]—is a reliable solution that has been widely applied to various heterocycle syntheses.[4] While silver-catalyzed CO_2 incorporation into propargyl alcohols and alkynyl anilines based on this strategy has been reported,[3a] carbon nucleophiles, such as alkynyl ketones[5] and ynones,[6] involving C−H carboxylation[7] through generation of an enolate were more recently achieved for these reactions. Therefore, the achievement of carboxylative cyclization involving carbon−carbon bond formation with CO_2 is one of the attractive tasks in CO_2 chemistry and might allow for rapid access to the target molecules.

The development of efficient methods for the synthesis of polycyclic indene derivatives has been considered an important issue in organic synthesis because indenes have many promising applications, such as pharmaceutical agents showing unique biological activities, building blocks for functional materials,[8] and ligand precursors of indenyl−metal complexes.[9] An interesting characteristic of indene is its relatively high acidity (pK_a = 20.1 in DMSO)[10] originating from the cyclopentadiene structure containing a benzylic position, and a base-mediated deprotonation reaction can occur to generate an indenyl anion, which can be applied for further reactions with some electrophiles. However, the applicable electrophiles have been limited because a strong base has been used for the generation of the indenyl anion.[11] We envisioned that the indenyl anion generated from deprotonation of a 2-alkynylindene could capture carbon dioxide to give the carboxylate intermediate, which could be followed by intramolecular cyclization into the alkyne part activated by a silver catalyst and protonation of the vinylsilver intermediate to afford the polycyclic indene (Scheme 1). We now report a new method for the synthesis of polycyclic indenes by silver-catalyzed CO_2 incorporation into 2-alkynylindenes.

A catalyst screening was conducted using 2-alkynylindene derivative **1a**. The reaction was carried out using DBU as a base in toluene under CO_2 at a pressure of 2 MPa (Table 1). Without a transition metal salt, no cyclized product was obtained, and **1a** was recovered (entry 1). Metal salts such as

Scheme 1. Background and Representative Concepts of the Present Work

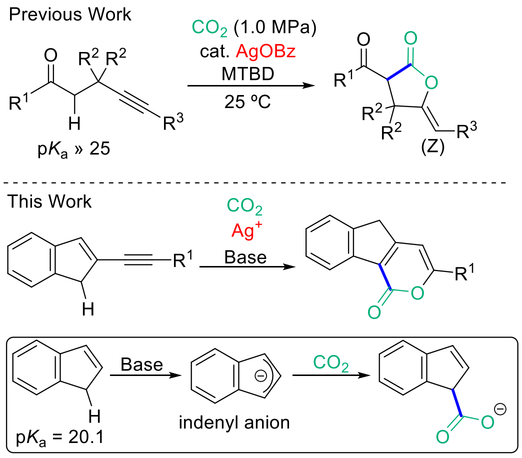


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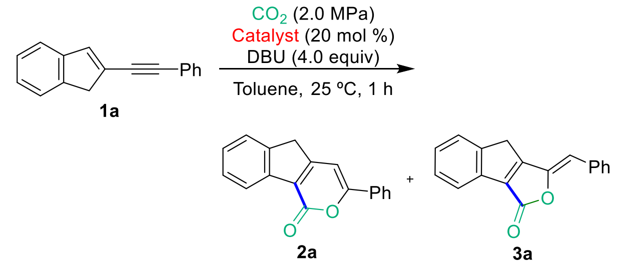
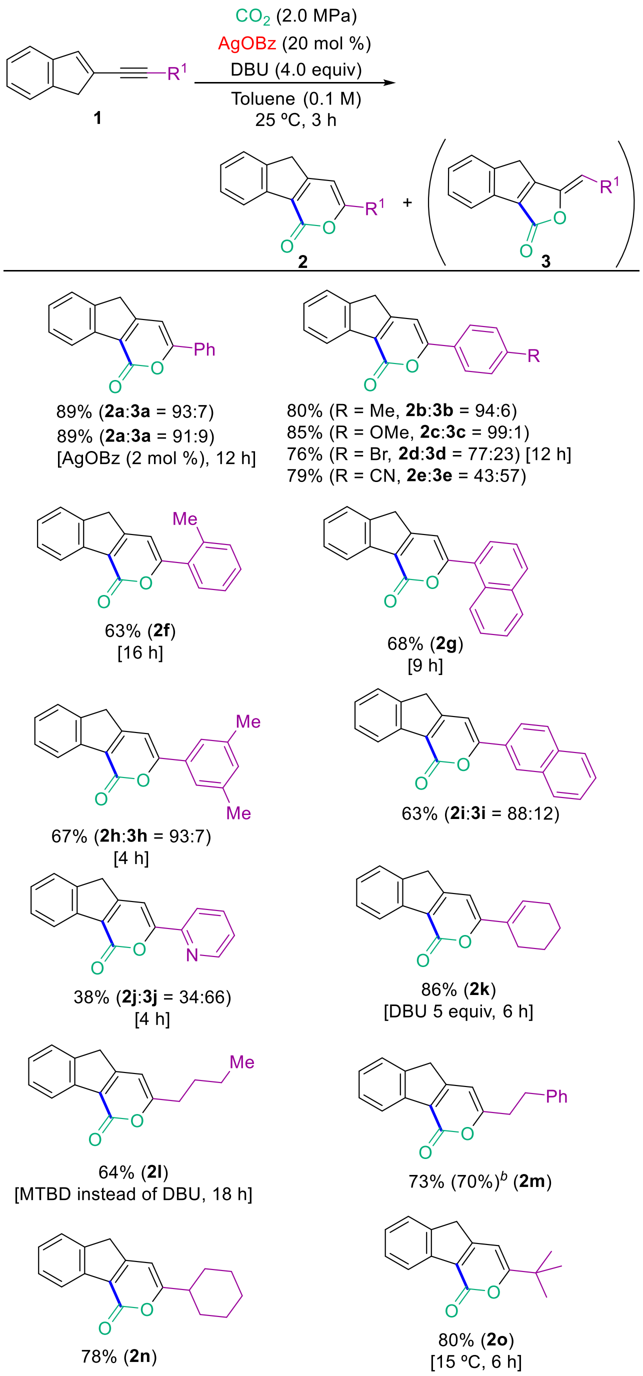
Table 1. Examination of the Reaction Conditions[a]



entry	catalyst	RSM (%)	yields (%)[b] 2a	3a
1	none	97	0	0
2	AuCl	97	0	0
3	$Pt(acac)_2$	97	0	0
4	$Pd(OAc)_2$	97	0	0
5	AgOBz	11	74	9
6[c]	AgOBz	0	86	10
7	AgF	83	10	2
8	AgO	23	62	6
9	$AgNO_3$	10	68	13
10[d]	AgOBz	0	58	11
11[e]	AgOBz	0	62	10
12[f]	AgOBz	0	53	12

[a] Conditions: **1a** (0.1 mmol) and the catalyst (20 mol %) in toluene (1.0 mL) at 25 °C under CO_2 at a pressure of 2 MPa. [b] NMR yields. [c] The reaction time was 3 h. [d] In DMF. [e] In CH_3CN. [f] In DMSO.

Scheme 2. Substrate Scope of Silver-Catalyzed CO_2 Fixation[a]



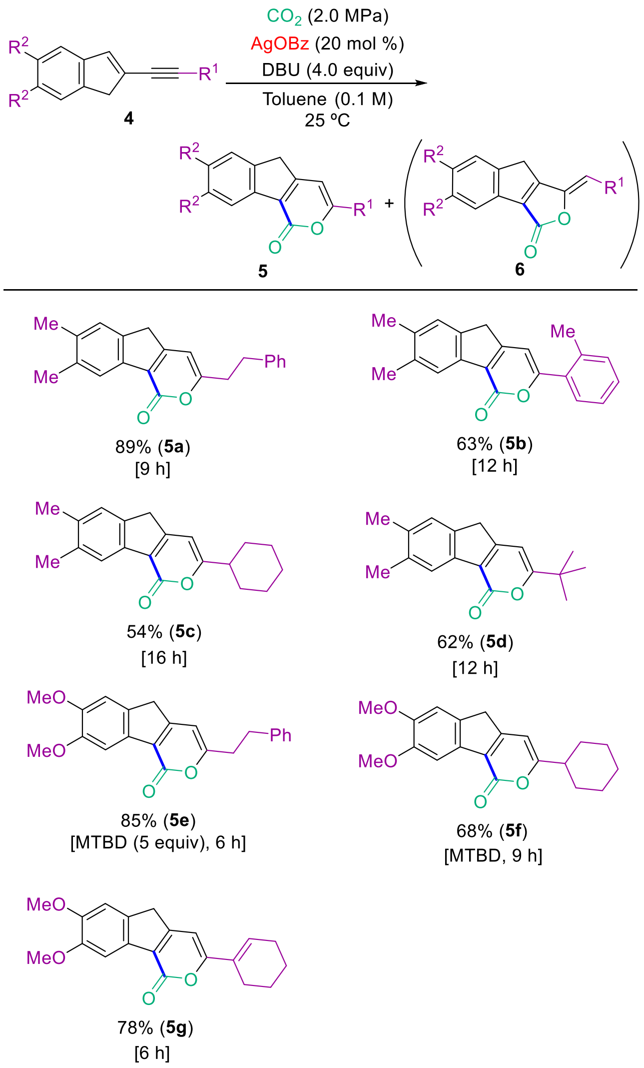
[a] Conditions: starting material **1** (0.1 mmol) and AgOBz (20 mol %) in toluene (1.0 mL) at 25 °C under CO_2 at a pressure of 2 MPa (details in the Supporting Information). Isolated yields are shown. MTBD = 7-methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene. [b] **1m** (1 mmol) was used.

Au, Pt, and Pd, which were expected to activate the alkyne moiety, were proved not to be effective for this reaction (entries 2–4). Interestingly, silver benzoate was employed for this reaction and gave the 6-*endo*-cyclized product **2a** in 74% yield along with the 5-*exo*-cyclized product **3a** in 9% yield (entry 5). The yield of **2a** was further improved by a longer reaction time (entry 6). Although other silver salts were evaluated to improve the yield and the selectivity, no catalyst surpassed AgOBz (entries 7–9). The reaction solvent was also investigated, and it was found that the use of polar solvents such as DMF, CH_3CN, and DMSO did not have a positive effect on the yield of **2a** (entries 10–12).[12] The optimal reaction conditions were established as follows: AgOBz (20 mol %), DBU (4 equiv), CO_2 (2.0 MPa), toluene, 25 °C, 3 h.

The substrate scope was explored. The catalyst loading for the reaction of **1a** could be reduced to 2 mol % without any decreased yield of **2a**. Investigation of the effect of the R^1 substituent (Scheme 2) showed an increase in the yield of **2** with **1b** and **1c**, which contained an electron-donating group (EDG) on the benzene ring, to afford **2b**/**3b** and **2c**/**3c** in 80% and 85% yield, respectively. On the other hand, an electron-withdrawing group (EWG) on R^1 (**1d**, **1e**) resulted in decreased yields (**2d**/**3d**, 76% yield; **2e**/**3e**, 79%) and 5-*exo*/6-*endo* selectivity. The use of a 2-tolyl group (**1f**) and a 1-naphthyl group (**1g**), which could have a larger steric influence around the alkyne moiety, showed a positive effect, and selective 6-*endo* cyclization was realized to afford **2f** and **2g** in 63% and 68% yield, respectively. Substrates bearing other aromatics at the alkyne terminus, such as 3,5-xylyl (**1h**), 2-naphthyl (**1i**), and 2-pyridyl (**1j**), were also suitable for this method and gave the corresponding 6-*endo*-cyclized products. Substrate **1k** containing the cyclohexene unit at R^1 was selectively converted into the 6-*endo*-cyclized product **2k** in 64% yield. Next, the reactions of alkyl-substituted substrates were examined. Substitution with primary (*n*-butyl (**2l**), phenethyl (**2m**)), secondary (cyclohexyl (**2n**)), and tertiary (*tert*-butyl (**2o**)) alkyl groups realized the 6-*endo*-selective cyclization to afford the corresponding products in good yields.

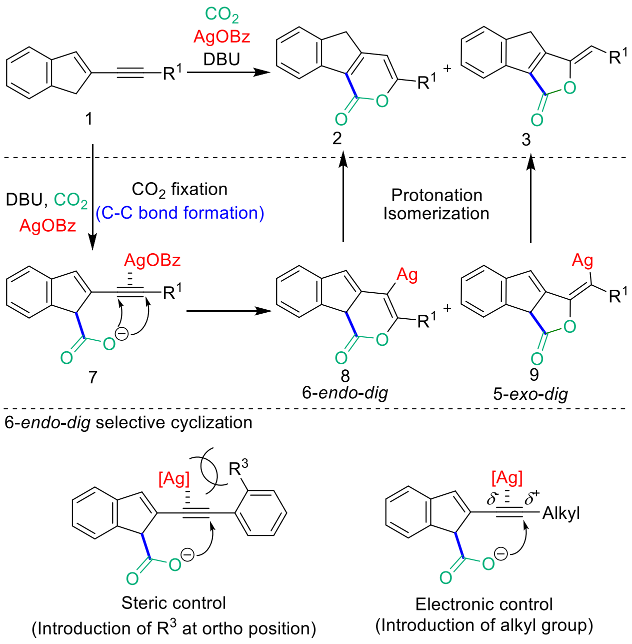
Next, the effect of substituents on the indene was investigated (Scheme 3). Substrates having a 5,6-dimethylindene structure (**4a** and **4b**) were employed for this reaction to

Scheme 3. Substrate Scope of Silver-Catalyzed CO$_2$ Fixation[a]



[a]Conditions: starting material **4** (0.1 mmol) and AgOBz (20 mol %) in toluene (1.0 mL) at 25 °C under CO$_2$ at a pressure of 2 MPa (details in Supporting Information). Isolated yields are shown.

Scheme 4. Plausible Reaction Mechanism



give the corresponding products **5a** and **5b** in 89% and 63% yield, respectively, without the 5-*exo*-cyclized product. Cyclohexyl- and *tert*-butyl-substituted **4c** and **4d** were also converted into **5c** and **5d** in 54% and 62% yield, respectively. Substrates containing a 5,6-dimethoxyindene moiety (**4e**−**h**) were found to form the corresponding products bearing phenethyl (**5e**), cyclohexyl (**5f**), and cyclohexenyl (**5g**) groups in good yields.

A plausible reaction mechanism is shown in Scheme 4. CO$_2$ is incorporated onto substrate **1** in the presence of the silver catalyst with DBU by means of carbon−carbon bond formation to afford π complex 7.[13]Sequential intramolecular cyclization of the carboxylate on the activated alkyne part occurs to give the six- and five-membered vinylsilver intermediates **8** and **9**, respectively. Finally, the polycyclic indenes are obtained through protonation and isomerization of the vinylsilver intermediates. Although the 6-*endo* cyclization pathway proceeds mainly, the selectivity of the cyclization could be perfectly controlled by the introduction of a substituent at the *ortho* position of the benzene ring and alkyl groups at the alkyne terminus, giving only **2**. In the former case, it could be considered that the repulsion between R^3 and the silver coordinated to the alkyne causes a bias in coordination to the alkyne, and as a result, the 6-*endo* cyclization proceeds selectively. In the latter case, the alkyl substitution induces a polarization between the two alkyne carbons, and the 6-*endo* cyclization occurs at the positively charged alkyne carbon substituted by the alkyl group.[14]

In summary, the synthesis of polycyclic indenes was accomplished by carbon dioxide fixation and sequential silver-catalyzed intramolecular cyclization of 2-alkynylindene derivatives as substrates. It is worth noting that this process involves carbon−carbon bond formation with CO$_2$ based on C−H functionalization under mild reaction conditions. Various substrates were suitable for this method, and the 6-*endo* cyclization mainly proceeded to give α-pyrone-fused indenes in good yields. Further investigation of the reaction mechanism and application of the reaction to the synthesis of more complex molecules are underway.

■ ASSOCIATED CONTENT

SI Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c03250.

Experimental procedures, characterization details, NMR spectra of new compounds and reaction products (PDF)

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Notes

The authors declare no competing financial interest.

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