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$AlBr_3$-Mediated Tandem Cyclization–Carboxylation of Allenylbenzenes with CO_2 in the Presence of Pyridines

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$AlBr_3$-Mediated Tandem Cyclization–Carboxylation of Allenylbenzenes with CO_2 in the Presence of Pyridines

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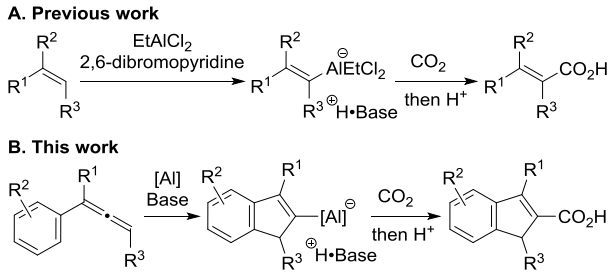
Abstract

Indene-2-carboxylic acids are prepared from allenylbenzenes and CO_2 by an $AlBr_3$-mediated tandem reaction consisting of intramolecular Friedel-Crafts alkylation of allenylbenzenes and subsequent carbonation of the resulting indenylaluminum species. The reaction requires 2,6-di-*tert*-butylpyridine or 2,6-diiodopyridine to neutralize an acidic byproduct without deactivating the Lewis acid.

Indene is an important framework often found in biologically active compounds,[1] functional materials,[2] and ligands for transition metals.[3] As the carboxy group is one of the most important resorts for elaborating various functional groups, the development of a facile method for the preparation of indenecarboxylic acids, especially the 2-regioisomers,[4] is important in organic synthesis. Although indene-2-carboxylic acids have been prepared from the corresponding haloindenes,[5] this route requires multistep reactions. Intramolecular Friedel-Crafts cyclization of allenylbenzenes is an efficient method for the preparation of indenes.[6–10] We envisaged that indene-2-carboxylic acids would be prepared by a tandem reaction of allenylbenzenes with CO_2 with the aid of an Al-based Lewis acid (Scheme 1B). The initial step of the tandem reaction is the intramolecular Friedel-Crafts alkylation of the aluminated allenylbenzene generated *in situ* by the addition of the Lewis acid to the allenyl moiety of a substrate,[10] which is followed by the carbonation of the resulting indenylaluminum species. Our concern was that a protonic acid generated during the reaction might cause decomposition and/or polymerization of the starting allenylbenzene. Therefore, it seemed that the success of this synthesis would depend on the choice of a base, which can prevent such side reactions without deactivating the Lewis acid. In relation to this, we recently succeeded in the carboxylation of alkenes with CO_2 with the aid of $EtAlCl_2$ and 2,6-dibromopyridine (Scheme 1A).[11] This reaction was realized by a careful choice of a base, which can prevent the decomposition and/or polymerization of a starting alkene without deactivating the Lewis acid and abstract a proton from the intermediate generated by the addition of $EtAlCl_2$ to the alkene. In this study, we investigated the tandem cyclization–carboxylation of allenylbenzenes by the combined use of an Al-based Lewis acid and a pyridine-type base (Scheme 1B).

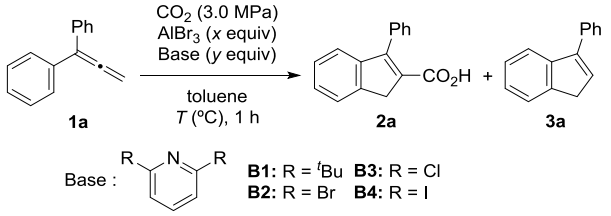


Scheme 1. Carboxylation of alkenes and tandem cyclization–carboxylation of allenylbenzenes by the combined use of an Al-based Lewis acid and a pyridine-type base.

First, the reaction of propa-1,2-diene-1,1-diyldibenzene (**1a**) was examined (Table 1). Compound **1a** was treated with 1 molar equiv each of $AlBr_3$ and 2,6-di-*tert*-butylpyridine (**B1**) in toluene under CO_2 pressure (3.0 MPa) at 60 °C for 3 h to give the desired acid **2a** in a low yield (24%), accompanied by the formation of indene **3a** (entry 1). Replacement of $AlBr_3$ with other Al-based Lewis acids did not improve the yield of the acid.[12] In the absence of **B1**, almost no acid (<10%) was obtained with many unidentifiable byproducts, which was ascribed to the decomposition and/or polymerization of the substrate. The yield of **2a** was improved with increasing the temperature to reach the maximum (47%) at 100 °C, and was reduced at a higher temperature (entries 1–4). The yield was further improved by increasing the amount of $AlBr_3$ to 1.5 molar equiv (entry 5). Shortening the reaction time to 1 h did not affect much on the yield (entry 6). We assumed that a reaction path consisting of the formation of indene **3a** and subsequent carboxylation of **3a** with CO_2 (vide infra) is involved in the present reaction besides the above-mentioned cyclization–carbonation path (Scheme 1B). Our previous study (Scheme 1A) suggested that 2,6-dibromopyridine (**B2**) is a suitable base for the carboxylation of **3a**.[11] However, because of its weak basicity, **B2** might not prevent the destructive side reaction(s) of the starting allene. In order to promote the carboxylation of **3a**, the reaction was then carried out using **B1** and **B2** simultaneously, but the yield of acid **2a** was decreased (entry 7). However, we have found that the reaction proceeds even by using only dibromide **B2** (entry 8). Screening of the performance of other dihalopyridines revealed that

2,6-diiodopyridine (**B4**) is effective, giving the desired acid in a comparable yield to that obtained using **B1** (entries 9 and 10). These results indicate that despite their low basicities,[13] the dihalopyridines suppress the decomposition and/or polymerization of allene **1a** by neutralizing superacid $HAlBr_4$ generated *in situ* from HBr and $AlBr_3$ (Scheme 2); however, the dihalopyridines were not effective for the reaction of most of other allenylarenes (vide infra). The molar ratios of $AlBr_3$ and diiodide **B4** to allene **1a** were optimized to be 1:3:2 (**1a**:$AlBr_3$:**B4**) (entries 11–13), thereby achieving the best yield of **2a** (81%) (entry 13). Replacing the diiodide with stronger base **B1**, while maintaining the molar ratios, did not improve the yield (entry 14).

Table 1. Tandem cyclization–carboxylation of allenediyldibenzene **1a** with the aid of $AlBr_3$ and various bases.[a]

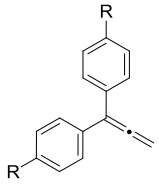
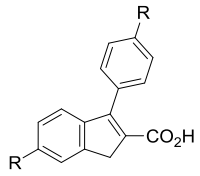
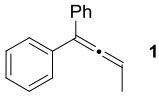
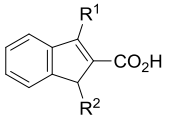
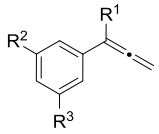
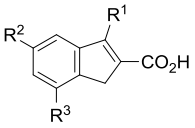
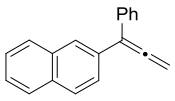
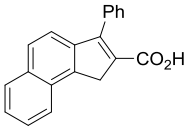


entry	*x*	Base	*y*	*T* (°C)	**2a** (%)[b]	**3a** (%)[b]
1[c]	1.0	**B1**	1.0	60	24	22
2[c]	1.0	**B1**	1.0	80	30	19
3[c]	1.0	**B1**	1.0	100	47	21
4[c]	1.0	**B1**	1.0	120	43	32
5[c]	1.5	**B1**	1.0	100	59	n.d.
6	1.5	**B1**	1.0	100	56	n.d.
7	1.5	**B1, B2**	1.0, 1.0	100	39	n.d.
8	1.5	**B2**	1.0	100	33	19
9	1.5	**B3**	1.0	100	24	n.d.
10	1.5	**B4**	1.0	100	49	14
11	2.0	**B4**	1.0	100	65	n.d.
12	2.5	**B4**	1.5	100	67	n.d.
13	3.0	**B4**	2.0	100	81	n.d.
14	3.0	**B1**	2.0	100	61	n.d.

[a] Reaction conditions: **1a** (0.40 mmol), $AlBr_3$ (*x* molar equiv), base (*y* molar equiv), CO_2, (3.0 MPa), toluene (2 mL), 60–120 °C, 1 h. [b] ^1H NMR yield determined using CH_2Br_2 as the internal standard. [c] 3 h.

Next, the reaction of various allenylarenes was investigated under the conditions of entry 6 (method I) and entry 13 (method II) in Table 1 using **B1** and **B4**, respectively (Table S1).[12] Table 2 shows some selected results. For most allenylarenes tested, method I gave better yields than method II. Introduction of a substituent into each benzene ring of **1a** at the *para*-position to the allenyl moiety decreased the acid yield, regardless of the electronic properties of the substituent (entries 1 and 2): The electron-donating methyl group (**1b**) decreases the electrophilicity of the allyl cation generated by the addition of $AlBr_3$ to the substrate, while the electron-withdrawing chloro group (**1c**) deactivates the benzene ring toward the electrophilic substitution. Therefore, both substituents seem to have retarded the intramolecular Friedel-Crafts reaction. Introduction of a methyl group into the terminal methine group of **1a** (**1d**) also decreased the yield (entry 3); in this reaction, two regioisomers with regard to the double bond, **2da** and **2db**, were obtained. Mono-aryl-substituted buta-1,2-dienes **1e**–**1g** gave the corresponding acids in moderate yields, despite our anticipation that replacing a phenyl group of **1a** with a methyl group would increase the tendency toward the side reaction(s) (entries 4–6). Unsymmetrically diarylated allenes **1h** and **1i** were exclusively cyclized on the aromatic rings more susceptible to the electrophilic aromatic substitution (entries 7 and 8); further, **1i** was cyclized at the most reactive position of the aromatic ring. Similar observations have been made in other indene ring formation reactions,[7a,8c,16] but we cannot rule out the possibility that the bulkier aromatic ring is disposed *anti* to Al in the allyl cation intermediate, from which the cyclization takes place.

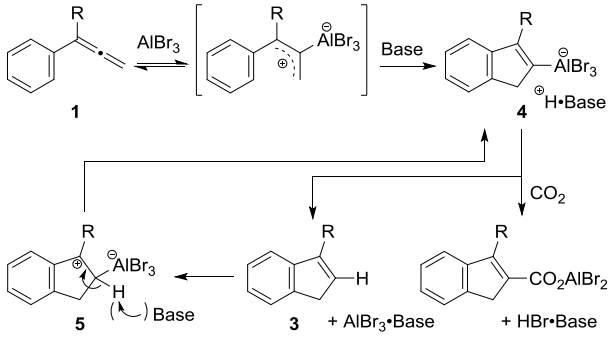
Table 2. Tandem cyclization–carboxylation of various allenylarenes.[a]

entry	substrate	product, yield (method)[b]
1	 **1b:** R = Me	 **2b:** R = Me, 53% (II)
2	**1c:** R = Cl	**2c:** R = Cl, 11% (I)
3	 **1d**	 **2da:** R^1 = Ph, R^2 = Me; **2db:** R^1 = Me, R^2 = Ph } 24% (I)[c]
4	 **1e:** R^1 = Me, R^2 = R^3 = H	 **2e:** R^1 = Me, R^2 = R^3 = H, 49% (I)
5	**1f:** R^1 = R^2 = Me, R^3 = H	**2fa:** R^1 = R^2 = Me, R^3 = H; **2fb:** R^1 = R^3 = Me, R^2 = H } 32% (I)[d]
6	**1g:** R^1 = R^2 = R^3 = Me	**2g:** R^1 = R^2 = R^3 = Me, 25% (I)
7	**1h:** R^1 = Ph, R^2 = R^3 = Me	**2h:** R^1 = Ph, R^2 = R^3 = Me, 46% (I)
8	 **1i**	 **2i**,34% (I)

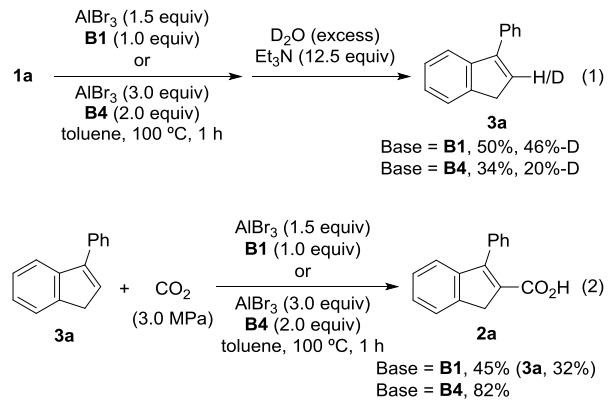
[a] Reaction conditions: **1** (0.40 mmol), CO_2 (3.0 MPa), $AlBr_3$ (1.5 molar equiv)/**B1** (1.0 molar equiv) (method I) or $AlBr_3$ (3.0 molar equiv)/**B4** (2.0 molar equiv) (method II), toluene (2 mL), 100 °C, 1 h. [b] Isolated yield. [c] **2da**/**2db** = 84/16. [d] **2fa**/**2fb** = 59/41.

As mentioned above, we supposed that the present reaction would proceed *via* the formation of a zwitterionic species by the electrophilic addition of $AlBr_3$ to an allene, followed by its intramolecular Friedel-Crafts alkylation and subsequent carbonation of the resulting indenylaluminum ate complex **4** (Scheme 2). The by-production of indene **3** is attributable to the protonolysis of complex **4** with the counter ion. Electrophilic addition of $AlBr_3$ to indene **3** and subsequent deprotonation of the resulting zwitterionic species **5** may regenerate complex **4**; this is essentially the same reaction path as that proposed for the metallation step of α-arylalkenes with $EtAlCl_2$ with the aid of 2,6-dibromopyridine in the carboxylation of α-arylalkenes (Scheme 1A).[11] In order to examine this mechanism, we fist investigated the formation of the indenylaluminum species **4** by deuteration experiments. Compound **1a** was treated with $AlBr_3$ and **B1** under the conditions of method I except that nitrogen was used as the atmospheric gas instead of CO_2, and the mixture was quenched

with D_2O containing an excess amount of triethylamine (eq. 1). The reaction gave indene **3a** deuterated at the 2-position with a deuteration ratio of 46% in 50% yield. A similar treatment of **1a** with $AlBr_3$ and **B4** gave **3a** with a deuteration ratio of 20% in 34% yield. These observations clearly indicate the formation of an inden-2-ylaluminum species. Both the yield and deuteration ratio of **3a** were higher in the former reaction, which can be rationalized by the difference in the basicities of **B1** and **B4**. Thus, stronger base **B1** can suppress the side reaction(s) more efficiently than **B4** to increase the recovery of **3a**, while the weaker conjugate acid of **B1** has a lower ability to protonate the indenylaluminum species than that of **B4**, resulting in the increase in the deuteration ratio of **3a**. We next investigated whether indene **3** is metallated with $AlBr_3$ under the conditions of methods I and II. The treatment of **3a** with $AlBr_3$ under these conditions gave acid **2a** in 45% (method I) and 82% yields (method II) (eq. 2), indicating the formation of an inden-2-ylaluminum species. However, **B1** bearing bulky *tert*-butyl groups near the nitrogen atom is not likely to be able to abstract a proton from the zwitterionic species **5** because of steric hindrance.[11] Therefore, in this case, the deprotonation seems to have occurred spontaneously in favor of the side reaction(s) because the positive charge of **5** is highly stabilized by the indan benzene ring.



Scheme 2. Feasible mechanism for the tandem cyclization–carboxylation



In conclusion, we have developed tandem cyclization–carboxylation of allenylbenzenes with CO_2 mediated by $AlBr_3$. The reaction required a base to trap *in situ*-generated superacid $HAlBr_4$ without deactivating $AlBr_3$. Highly bulky and highly basic 2,6-di-*tert*-butylpyridine (**B1**) and less bulky and less basic 2,6-diiodopyridine (**B4**) were suitable as such a base. In the presence of these bases, the tandem reaction competed well with the decomposition and/or polymerization of the substrates, despite the presence of strong acids such as $AlBr_3$ and 2,6-diiodopyridinium.

Supporting Information

Supporting Information: Supplemental data, experimental procedures, characterization data, and NMR spectral charts. This material is available on http://dx.doi.org/10.1246/bcsj.***.

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11. S. Tanaka, K. Watanabe, Y. Tanaka, T. Hattori, *Org. Lett.* **2016**, *18*, 2576.
12. See supporting Information
13. The p*K*a values of conjugate acids were calculated to be 5.5 (**B1**), −2.2 (**B2**), −2.8 (**B3**), and −1.9 (**B4**), using ACE and JChem acidity and basicity calculator (https://epoch.uky.edu/ace/public/pKa.jsp).

Graphical Abstract

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<Summary>
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<Diagram>