Organic Letters
Letter
pubs.acs.org/OrgLett

EtAlCl$_2$/2,6-Disubstituted Pyridine-Mediated Carboxylation of Alkenes with Carbon Dioxide

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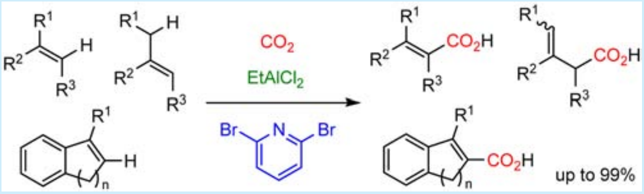
Supporting Information

ABSTRACT: α-Arylalkenes and trialkyl-substituted alkenes undergo carboxylation with CO$_2$ in the presence of EtAlCl$_2$ and 2,6-dibromopyridine to afford the corresponding α,β- and/or β,γ-unsaturated carboxylic acids. This reaction is suggested to proceed via the electrophilic substitution of EtAlCl$_2$ with the aid of the base, followed by the carbonation of the resulting ate complex. This reaction can be applied to terminal dialkylalkenes by using a mixture of 2,6-di-*tert*-butylpyridine and 2,6-dibromopyridine.



Recently, increasing attention has been paid to the development of methods to prepare carboxylic acids using CO$_2$. Remarkable advances have been made in the transition-metal-catalyzed carboxylation of unsaturated compounds.[1−7] Although the carboxylation of alkenes with CO$_2$ is one of the most attractive methods to prepare vinylcarboxylic acids from the perspective of atom economy, such a transformation via the cleavage of a vinyl C−H bond with a transition metal catalyst is difficult. This is because a C=C bond is easily inserted into various M−X bonds of transition metal complexes, whereas it is difficult to add a vinyl C−H bond oxidatively to low-valent transition metals.[6] Therefore, α,β-unsaturated carboxylic acids have been prepared via addition reactions to alkynes, which allow only limited access to multisubstituted vinylcarboxylic acids.[7] Ethylene is converted into sodium acrylate using a Ni complex via Ni-mediated oxidative coupling of ethylene with CO$_2$ to form a nickelalactone, followed by the abstraction of an α-hydrogen of the carboxy group with sodium *tert*-butoxide.[8,9] Recently, this reaction was applied to some other alkenes; however, the yields of the corresponding acids based on the starting alkenes were moderate (<40%).[8c]

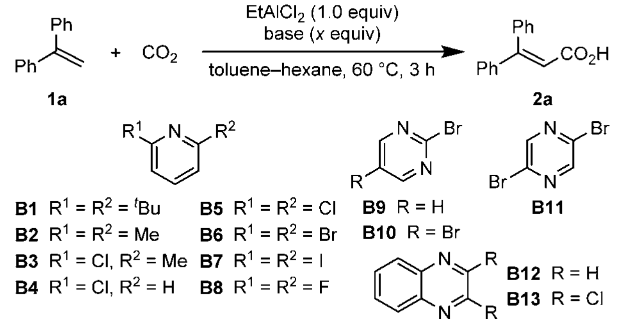
In our continuing efforts to develop Lewis-acid-mediated carboxylation reactions of aromatic compounds with CO$_2$,[10,11] we succeeded in the carboxylation of 1-methylindoles using Me$_2$AlCl. Mechanistic studies revealed that the reaction proceeds via the electrophilic aromatic substitution of a substrate with Me$_2$AlCl, followed by the carbonation of the resulting indolylaluminum ate complex.[10d] Because alkenes are more susceptible to electrophilic attacks than aromatic compounds, an Al-based Lewis acid such as Me$_2$AlCl adds to an alkene to form a zwitterionic species. Although the species should rather react with nucleophiles (e.g., the substrate) than eliminate a proton at the α-position to the Al,[11] we considered that the latter substitution pathway would predominate if the α-proton is abstracted by the addition of a base without deactivating the Lewis acid.[12,13] In this study, we have found such a base and achieved the carboxylation of alkenes.

First, the carboxylation of 1,1-diphenylethene (**1a**) was investigated using various bases (1.0 molar equiv) under CO$_2$ pressure (3.0 MPa) in the presence of EtAlCl$_2$ (1.0 molar equiv) in toluene at 60 °C (Table 1). The use of Hunig's base, DBU, *N*,*N*-dimethylaniline, and triphenylamine gave no carboxylic acid. The use of a pyridine-type base, 2,6-di-*tert*-butylpyridine (**B1**), which is often used as a proton scavenger under Lewis acidic conditions,[14] also failed (entry 1). However, less sterically bulky 2,6-lutidine (**B2**) afforded a small amount (3%) of the desired acid **2a** (entry 2). We then investigated the suitability of 2-mono- and 2,6-disubstituted pyridines, as well as related heterocyclic amines, using the pK_a of the conjugate acid[15,16] and the sum of the *A* values of the substituents as the clues (Figure 1); *A* value is used to estimate the steric bulkiness of substituents.[17] Reducing the basicity of 2,6-lutidine (**B2**) by replacing one of the methyl groups of **B2** with a chloro group (**B3**) slightly improved the yield of the acid (entry 3). However, the removal of the other methyl group (**B4**) completely inhibited the reaction (entry 4), indicating that 2,6-disubstituted pyridines are promising. In fact, the use of 2,6-dichloropyridine (**B5**) significantly improved the yield (entry 5). Better yields were obtained by using 2,6-dibromopyridine (**B6**) and 2,6-diiodopyridine (**B7**), which have a similar steric bulk as dichloride **B5** but a slightly higher basicity (entries 6 and 7). On the other hand, less bulky and less basic difluoride **B8** decreased the yield and worsened the mass balance (entry 8). A similar trend for the effects of the steric bulkiness and basicity on the yield of the acid was also observed for other heterocyclic amines. A good yield was obtained for 2,3-dichloroquinoxaline (**B13**), whose bulkiness and basicity are similar to those of dihalopyridines **B5**−**B7** (entry 13). On the

Received: March 31, 2016
Published: May 17, 2016

DOI: 10.1021/acs.orglett.6b00918
Org. Lett. 2016, 18, 2576−2579

Table 1. Carboxylation of 1,1-Diphenylethene (1a) in the Presence of Various Bases[a]



entry	base	*x*	**2a** (%)[b]	**1a** (%)[b]
1	**B1**	1.0	nd	24
2	**B2**	1.0	3	91
3	**B3**	1.0	7	93
4	**B4**	1.0	nd	>99
5	**B5**	1.0	58	42
6	**B6**	1.0	87	5
7	**B7**	1.0	71	28
8	**B8**	1.0	19	48
9	**B9**	1.0	5	95
10	**B10**	1.0	1	99
11	**B11**	1.0	nd	>99
12	**B12**	1.0	nd	>99
13	**B13**	1.0	71	29
14[c]	**B6**	1.0	96 (95)	2
15	**B6**	0.5	83	trace
16	**B6**	0.1	53	nd

[a]Reaction conditions: **1a** (0.50 mmol), $EtAlCl_2$ (1.0 molar equiv, used as a 1.0 M hexane solution), base (*x* molar equiv), CO_2 (3 MPa), toluene (1.0 mL), 60 °C, 3 h. [b]^1H NMR yield determined using CH_2Br_2 as the internal standard. Isolated yield is shown in parentheses. [c]$EtAlCl_2$ (2.0 molar equiv) was used.

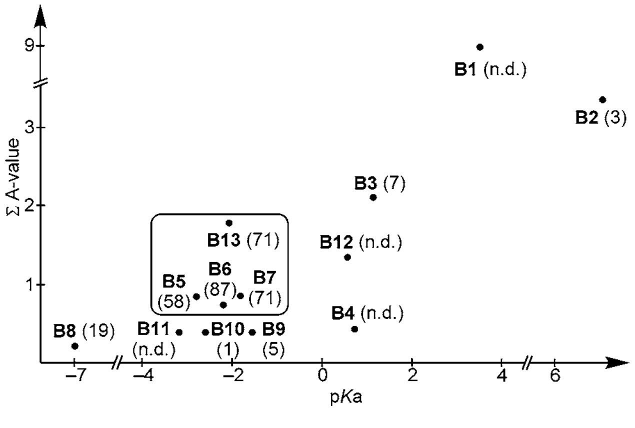
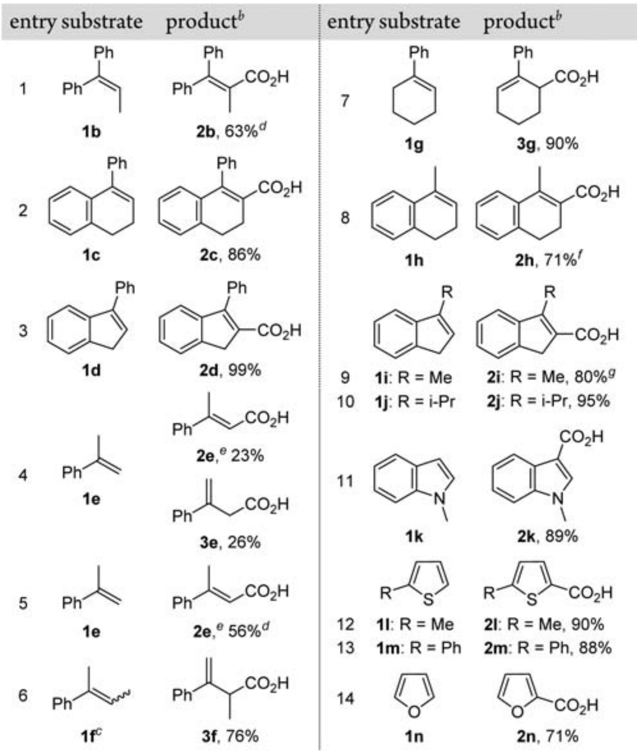


Figure 1. Correlation chart between the properties of base **B** and the yield of acid **2a** in the carboxylation of alkene **1a** (Table 1). The *x*- and *y*-axes indicate the pK_a of the conjugate acid of base **B** and the steric bulkiness of base **B** estimated from the sum of the *A* values of its substituents, respectively. The yield of acid **2a** is indicated in parentheses.

other hand, less bulky (**B9–11**) or more basic (**B12**) heterocycles were ineffective, even though either the bulkiness or basicity was similar to that of the dihalopyridines (entries 9–12). On the basis of these observations, it can be concluded that the suitable amines for this reaction should have two ortho substituents, with the sum of *A* values in an approximate range of 0.7–1.8, and exhibit a basicity (pK_a) of approximately −2; they fall within the area shown by a rounded rectangle in Figure 1. The reaction conditions were investigated further using dibromide **B6** as the base. An increase in the amount of $EtAlCl_2$ to 2 molar equiv increased the yield to 96% (entry 14). Interestingly, a reduction in the amount of the base to 0.5 molar equiv did not significantly affect the yield (entry 15). The acid was still obtained in a moderate yield even by reducing the amount to 0.1 molar equiv; however, the conversion of the alkene to the acid decreased (entry 16). These results indicate that the amine can serve as a catalyst, but its stoichiometric use is effective in achieving a high yield by suppressing side reactions. We also investigated the combined use of dibromide **B6** with other Al-based Lewis acids under the conditions used in entry 6, which was adopted as a standard thereafter, but the acid yield did not increase that obtained in entry 6.[18]

The carboxylation of diverse α-arylalkenes was investigated under standard conditions (Table 2). An internal alkene, 1,1-diphenylpropene (**1b**), afforded the corresponding vinylcarboxylic acid **2b** in a yield lower than that of **2a** obtained in the reaction of 1,1-diphenylethane (entry 1 vs entry 6 in Table 1), indicating that the steric hindrance caused by the methyl group prevented the proton abstraction from the zwitterionic intermediate generated by the addition of $EtAlCl_2$ to the alkene. Indeed, less bulky cyclic diarylalkenes, **1c** and **1d**, were converted to the corresponding acids in good to excellent yields (entries 2 and 3). Styrene gave cinnamic acid in a low yield (5%) because of

Table 2. Carboxylation of α-Arylalkenes and Heteroaromatics[a]



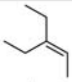
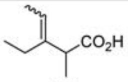
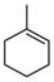
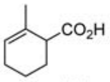
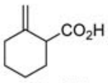
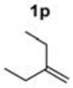
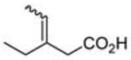
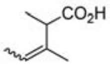
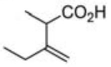
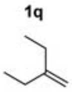
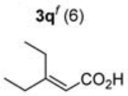
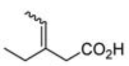
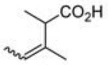
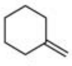
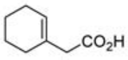
[a]Reaction conditions: **1** (0.50 mmol), $EtAlCl_2$ (1.0 molar equiv, used as a 1.0 M hexane solution), **B6** (1.0 molar equiv), CO_2 (3 MPa), toluene (1.0 mL), 60 °C, 3 h. [b]Isolated yield. [c]**1f** (*E*/*Z* = 95:5) was used. [d]24 h. [e]*E* only. [f]1-Methylene-1,2,3,4-tetrahydronaphthalene-2-carboxylic acid (**3h**, 2%) was also isolated. [g]1 h.

many unidentified byproducts. However, introduction of a methyl group to the *α*-position (**1e**) furnished the product in a moderate yield (entry 4). In this reaction, both *α*,*β*- and *β*,*γ*-unsaturated acids (**2e** and **3e**, respectively) were obtained in similar yields, but they converged to the former by prolonging the reaction time (entry 5). The time course of the change in the yield indicated that nonconjugated acid **3e** was formed initially and then isomerized to more stable conjugated acid **2e**.[18] The initial formation of **3e** is rationalized by the selective proton abstraction from the zwitterionic intermediate at the *γ*-position to the Al that is less crowded than the *α*-position (vide infra). Under the standard conditions, *α*,*β*-dimethyl-substituted styrene (**1f**) and 1-phenylcyclohexene (**1g**) selectively produced the corresponding *β*,*γ*-unsaturated acids (entries 6 and 7), whereas dihydronaphthalene **1h** and indenes **1i** and **1j** afforded the corresponding *α*,*β*-unsaturated acids (entries 8−10). The product selectivity seems to depend on the easiness of the isomerization from the nonconjugated to conjugated acids. Indeed, in the reaction of dihydronaphthalene **1h**, shortening the reaction time to 1 h provided the corresponding *β*,*γ*-unsaturated acid in 27% yield at the expense of *α*,*β*-unsaturated acid **2h** (51%). Furthermore, this reaction could be applied to heteroaromatics. We previously reported that 1-substituted indoles and thiophenes were carboxylated using Me_2AlCl and $EtAlCl_2$, respectively.[10d,b] Indole **1k** was carboxylated in a yield comparable to that obtained by the reaction using Me_2AlCl (86%), instead of $EtAlCl_2$ and **B6** under the same conditions (entry 11). Thiophenes **1l** and **1m** were carboxylated in high yields (entries 12 and 13); notably, the addition of **B6** made the reaction conditions milder and increased the yields of the acids.[10b] Moreover, furan (**1n**), which could not be carboxylated using any Al-based Lewis acid in the absence of a base, afforded the corresponding 2-carboxylic acid in a good yield (entry 14). However, a vinyl ether, 2,3-dihydrofuran, was not carboxylated under the standard conditions.

In general, the electrophilic substitution of alkenes is difficult, except when a cationic intermediate formed by the addition of an electrophile benefits from the resonance stabilization by a substituent such as an aryl, amino, or alkoxy group attached to the *β*-position to the newly introduced substituent, and/or the intermediate has a structure that can easily release a proton at the *α*-position.[19] Gratifyingly, this reaction could be applied to trialkyl-substituted alkenes **1o** and **1p** (entries 1 and 2 in Table 3); the products were only *β*,*γ*-unsaturated acids **3**. On the other hand, terminal alkene **1q** underwent isomerization prior to the carboxylation to afford *β*,*γ*-unsaturated acids **4qa** and **4qb**, corresponding to the resulting internal alkene, in preference to *β*,*γ*-unsaturated acid **3q**, corresponding to the original alkene (entry 3). To investigate this isomerization, alkene **1q** was heated with 1.0 molar equiv each of $EtAlCl_2$ and **B6** in toluene-d_8 at 60 °C. Under the conditions, the terminal alkene was gradually isomerized to the internal alkene; the molar ratio reached 98:2 (internal/terminal) after 3 h, as evidenced by ^1H NMR analysis.[18] This indicates that the isomerization proceeds via the electrophilic addition of $EtAlCl_2$ to the alkene, followed by the abstraction of a hydrogen at the *γ*-position to the Al by the base and subsequent protonolysis of the resulting allylaluminum ate complex with the conjugate acid of **B6**. We envisioned that the isomerization would be suppressed by the addition of a strong and bulky base that can receive a proton from the conjugate acid of **B6** and tightly hold it without deactivating the Lewis acid. We found that 2,6-di-*tert*-butylpyridine (**B1**) is such a suitable base. By the combined use of **B1** and **B6** in the presence of an excess of $EtAlCl_2$, the desired *β*,*γ*-unsaturated acid **3q** was obtained as the major product from the terminal alkene **1q**, along with its *α*,*β*-unsaturated isomer **2q** and a trace amount of undesired **4qa** (entry 4). The molar equivalences of **B1**, **B6**, and $EtAlCl_2$ to the substrate were optimized to be 1.4, 0.5, and 2.5, respectively.[18] Under the same conditions, another terminal alkene **1r** was also successfully carboxylated (entry 5).

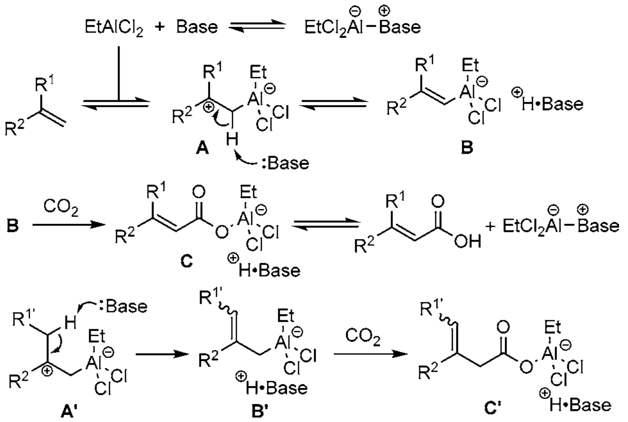
A feasible mechanism for the carboxylation is shown in Scheme 1. First, $EtAlCl_2$, which is in an equilibrium state with its pyridine salt, electrophilically attacks an alkene to generate zwitterion **A**. Then, the base abstracts a proton at the *α*- or *γ*-position to the Al (**A** and **A′**, respectively), affording ate complex **B** or **B′**. Apparently, a sterically bulky and less basic amine favors the dissociation of the Al-pyridine salt, whereas a sterically undemanding and highly basic amine favors the proton abstraction. The balance between these conflicting demands seems to determine the amines suitable for this reaction, as shown in Figure 1. The ate complex **B** or **B′** is then carbonated to

Table 3. Carboxylation of Aliphatic Alkenes[a]

entry	substrate	yield[b]	products (distribution)[c]
1	 **1o**	66%	 **3o**[e]
2	 **1p**	85%	 **3pa** (79)  **3pb** (21)
3	 **1q**	79%	 **3q**[f] (6)  **4qa**[g] (73)  **4qb** (21)
4[d]	 **1q**	69%	 **2q** (12)  **3q**[h] (88)  **4qa**[i] (trace)
5[d]	 **1r**	59%	 **3r**

[a] Reaction conditions: **1** (0.50 mmol), $EtAlCl_2$ (1.0 molar equiv, used as a 1.0 M hexane solution), **B6** (1.0 molar equiv), CO_2 (3 MPa), toluene (1.0 mL), 60 °C, 3 h. [b] Isolated yield. [c] The ratio was determined by ^1H NMR. [d] $EtAlCl_2$ (2.5 molar equiv), **B6** (0.5 molar equiv), **B1** (1.4 molar equiv) were used. [e] *E*/*Z* = 32:68. [f] *E*/*Z* = 58:42. [g] *E*/*Z* = 69:31. [h] *E*/*Z* = 57:43. [i] *E*/*Z* could not be determined.

Scheme 1. Feasible Mechanism for the Carboxylation of Alkenes



afford aluminum carboxylate **C** or **C**′, respectively. Because the $\mathrm{p}K_a$ of the conjugate acid of the pyridine base (approximately −2) is far less than that of the carboxylic acid (∼5), the aluminum carboxylate liberates the free acid, regenerating the Al-pyridine salt. Hence, the base can serve as a catalyst. On the other hand, it is necessary to use $EtAlCl_2$ stoichiometrically because it is deactivated by coordinating to the carboxylic acid.

In conclusion, alkenes were carboxylated with CO_2 by the combined use of $EtAlCl_2$ and 2,6-dibromopyridine. This is the first example of the displacement of vinyl hydrogen atoms with the carboxy group in practical yields. This will provide useful insights for the development of methodologies to react alkenes with a strong Lewis acid and to compatibly use a Lewis acid and Lewis base. Further studies along these lines are in progress.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00918.

Supplemental data, experimental procedures, characterization data, and NMR spectral charts (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

T.H. thanks Kazuo Tanaka (the Koheleth private foundation) for financial support.

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