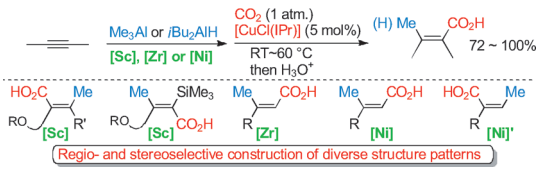

Aluminate your chemistry! Methylative and hydrogenative carboxylation of alkynes has been developed by a combination of their regio- and stereoselective methyl- and hydroalumination catalyzed by Sc, Zr, or Ni catalysts and the N-heterocyclic carbene–Cu-catalyzed carboxylation of the resulting alkenylaluminum species with CO_2 to afford α,β-unsaturated carboxylic acids (see scheme; IPr = 1,3-bis(2,6-diisopropenyl)imidazol-2-ylidene).

Synthesis

*M. Takimoto, Z. Hou** ..... ▮▮▮▮–▮▮▮▮

Cu-Catalyzed Formal Methylative and Hydrogenative Carboxylation of Alkynes with Carbon Dioxide: Efficient Synthesis of α,β-Unsaturated Carboxylic Acids

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Cu-Catalyzed Formal Methylative and Hydrogenative Carboxylation of Alkynes with Carbon Dioxide: Efficient Synthesis of α,β-Unsaturated Carboxylic Acids

Masanori Takimoto[a, b] and Zhaomin Hou*[a, b]

Abstract: The sequential hydroalumination or methylalumination of various alkynes catalyzed by different catalyst systems, such those based on Sc, Zr, and Ni complexes, and the subsequent carboxylation of the resulting alkenylaluminum species with CO_2 catalyzed by an N-heterocyclic carbene (NHC)–copper catalyst have been examined in detail. The regio- and stereoselectivity of the overall reaction relied largely on the hydroalumination or methylalumination reactions, which significantly depended on the catalyst and alkyne substrates. The subsequent Cu-catalyzed carboxylation proceeded with retention of the stereoconfiguration of the alkenylaluminum species. All the reactions could be carried out in one-pot to afford efficiently a variety of α,β-unsaturated carboxylic acids with well-controlled configurations, which are difficult to construct by previously reported methods. This protocol could be practically useful and attractive because of its high regio- and stereoselectivity, simple one-pot reaction operation, and the use of CO_2 as a starting material.

Keywords: alkynes · aluminum · carbon dioxide · carboxylation · copper

Introduction

α,β-Unsaturated carboxylic acids and derivatives, especially those with branching β-methyl groups, are important substructure motifs widely existing in biologically active natural products and medicines (Figure 1).[1] Moreover, α,β-unsaturated carboxylic acids can serve as useful building blocks in organic synthesis.[2] The α,β-unsaturated carboxyl units are usually constructed by using the Wittig reaction or the Horner–Wadsworth–Emmons reaction (HWE reaction) through condensation of aldehydes or ketones with stabilized phosphonium ylides or phosphoryl carbanions bearing a CO_2R substituent.[2] However, these reactions, though convenient, always yield a stoichiometric amount of unwanted byproducts with relatively large molecular weights, such as phosphine oxides and phosphate salts, thus limiting their synthetic utility especially in large-scale preparations.

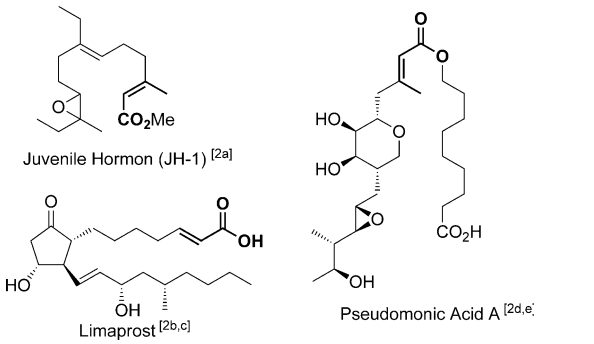

Figure 1. Some examples of biologically active compounds bearing an α,β-unsaturated carboxyl unit.

Carbon dioxide (CO_2) is a readily available, nontoxic, and inherently renewable chemical feedstock. The use of CO_2 as a building block in organic synthesis has received much current interest.[3] In principle, the hydrogenative or alkylative addition of CO_2 to alkynes could serve as an efficient synthetic route to α,β-unsaturated carboxylic acids. However, only limited success has been achieved to date in the catalytic transformation of alkynes and CO_2 into α,β-unsaturated carboxylic acids,[4–9] despite recent advances in this area.

The oxidative cycloaddition of CO_2 and the C–C triple bond of alkynes to low-valent transition-metal species, such as Ni^0 or Ti^{II}, was reported to give the corresponding metallacyclic α,β-unsaturated carboxylates, which on hydrolysis afforded α,β-unsaturated carboxylic acids.[4] However, a stoichiometric amount of transition-metal reagents was usually required in such transformations. Electrochemical reduction of a nickel metallacycle on a Mg-anode was reported to lead to catalytic formation of the α,β-unsaturated carboxylic acid products, but this reaction generally suffered from poor regioselectivity.[6]

Recently, Tsuji and co-workers reported the catalytic hydrogenative carboxylation of alkynes with CO_2 by using a Cu^I salt as a catalyst and hydrosilane as a hydrogen sour-

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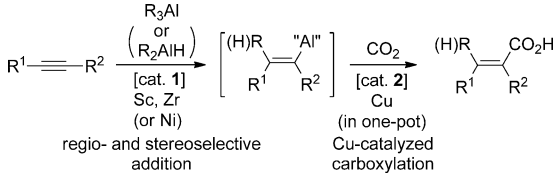
ce.[7a] Ma and co-workers found that the analogous hydrogenative carboxylation reactions could also be realized by using a nickel catalyst with diethylzinc as a hydride source.[7b,c] In both cases, the substrate scope was limited to internal alkynes, while terminal alkynes are not applicable.

In contrast to hydrogenative carboxylation of alkynes, which adds a hydrogen atom and CO_2 to a C–C triple bond to give α,β-unsaturated carboxylic acids without a substituent on the β-carbon atom, alkylative carboxylation of alkynes leads to simultaneous addition of both an alkyl group and CO_2 to afford tetrasubstituted olefinic units. However, studies on the alkylative carboxylation of alkynes with CO_2 were even scarcer. In 2005, Mori and co-workers achieved the methylative caroboxylation of alkynes with CO_2 by using Me_2Zn as a methyl source to react with a nickel metallacycle intermediate.[9a] This reaction required a large excess amount of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) and usually yielded a regioisomeric mixture of the α,β-unsaturated carboxylic acid products. Very recently, Ma and co-workers reported the Ni-catalyzed methylative carboxylation of homopropargylic alcohols through a methylzincation/carboxylation cascade.[9b] In this reaction, a hydroxyl group in the alkyne substrates served as a directing group to enhance the regioselectivity and the reactivity. Similar to the hydrogenative carboxylation mentioned above, all of these alkylative carboxylation reactions were limited to internal alkynes, whereas terminal alkynes are not suitable.

It is well known that the hydroalumination and methylalumination of terminal and internal alkynes can be achieved in a regio- and stereospecific fashion by choosing an appropriate catalyst.[10,11] Various alkenylaluminum species with well-controlled configurations could be generated in this way. We envisioned that if the alkenylaluminum species could be added to CO_2 in a stereospecific manner,[12–15] α,β-unsaturated carboxylic acids with the desired structural patterns would be efficiently synthesized from alkynes and CO_2. We have recently reported that N-heterocyclic carbene (NHC)–copper complexes can serve as an excellent catalyst for the carboxylation of various substrates with CO_2.[15] In this paper, we report the regio- and stereospecific, formal methylative and hydrogenative carboxylation of alkynes with CO_2 by combination of the catalytic methylalumination and hydroalumination of various alkynes with the Cu-catalyzed carboxylation of the resulting alkenyl (Scheme 1). A variety of α,β-unsaturated carboxylic acids, which were difficult to prepare previously, could be obtained efficiently by using this protocol.

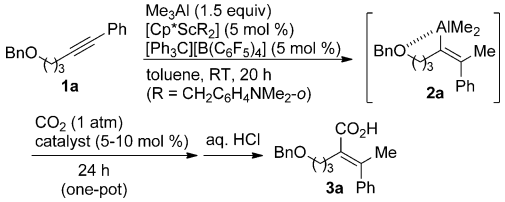


Scheme 1. Formal carboxylation of alkynes by a carboalumination (or hydroalumination)/carboxylation cascade.

Results and Discussion

Regio- and stereospecific formal methylative carboxylation of internal alkynes by using a Sc/Cu catalyst combination: At first, we examined the carboxylation of the alkenylaluminum species **2a** prepared by the scandium-catalyzed methylalumination of an internal alkyne containing a tethered ether group (**1a**) (Table 1). In the presence of a catalytic amount of $[Sc(CH_2C_6H_4NMe_2\text{-}o)_2(Cp^*)]/[Ph_3C][B(C_6F_5)_4]$ (Cp^* = pentamethylcyclopentadienyl), the reaction of **1a** with Me_3Al afforded the trisubstituted alkenylalmuminum **2a** regio- and stereoselectively, as reported previously.[11e] The alkenylaluminum **2a** alone did not react with CO_2 (1 atm), even at 70 °C (Table 1, entry 1). To our delight, in the presence of a catalytic amount of the copper complex [CuCl(IPr)] (5 mol %) (IPr = 1,3-bis(2,6-diisopropenyl)imidazol-2-ylidene), the carboxylation of **2a** with CO_2 proceeded smoothly to give the carboxylic acid product **3a** after hydrolysis workup. A quantitative formation of **3a** from **2a** and CO_2 was achieved at room temperature in 24 h (Table 1, entry 3). It is also noteworthy that the carboxylation of **2a** did not require an additional base, in contrast with the carboxylation of organoboron compounds reported previously.[13a,e–f,15a,b] CuCl or IPr alone gave a much lower yield under similar conditions (Table 1, entries 4 and 5). Nickel- and palladium-based catalysts previously used in the carboxylation of organozinc species[8a,13d] did not work well in the present carboxylation of **2a** (Table 1, entries 6 and 7).

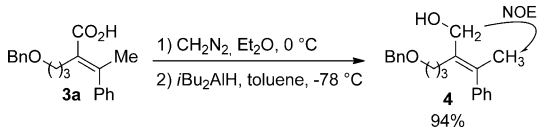
Table 1. One-pot sequential methylalumination/carboxylation of an internal alkyne.[a]



Entry	Catalyst	T [°C][b]	**3a** [%][c]
1	none	70	0
2	[CuCl(IPr)][d]	70	86
3	[CuCl(IPr)][d]	RT	100
4	CuCl[d]	70	8[e]
5	IPr[d]	70	28[e]
6	$[Ni(cod)_2]/Cs_2CO_3$[f]	RT	29
7	$Pd(OAc)_2/PCy_3$[g]	RT	5[e]

[a] The reaction was carried out in "one-pot" by addition of a THF solution of [CuCl(IPr)] to a toluene solution of **2a** prepared by reaction of **1a** with Me_3Al in the presence of $[Sc(Cp^*)(R)_2]/[Ph_3C][B(C_6F_5)_4]$, and the resulting mixture was then stirred under CO_2 (1 atm) for 24 h, unless otherwise noted. [b] Temperature for the carboxylation reaction. [c] Isolated yield based on **1a**. [d] 5 mol %. [e] Isolated yield of the methyl ester product prepared by reaction of **3a** with CH_2N_2. [f] 10 mol % of $[Ni(cod)_2]$ (cod = 15-cyclooctadiene) and 20 mol % of Cs_2CO_3. [g] 10 mol % of $Pd(OAc)_2$ and 20 mol % of PCy_3.

An NOE analysis of compound **4**, which was obtained by methylation of **3a** with CH_2N_2 followed by reduction of the

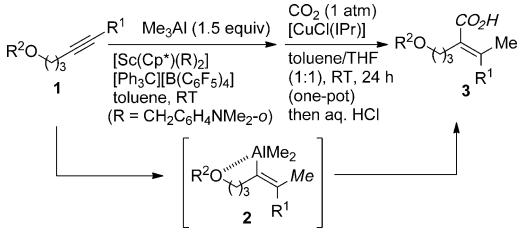


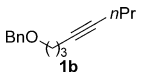
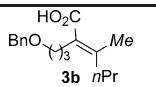
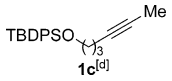
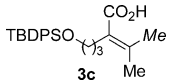
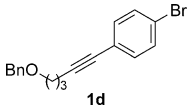
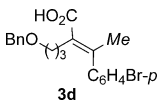
Scheme 2. Transformation of the carboxyl group in **3a** to a hydroxymethyl unit for stereochemistry confirmation.

resulting ester with iBu$_2$AlH (Scheme 2), indicated that the methyl group and the carboxyl group in **3a** should be on the same side of the C=C double bond (*cis* configuration). These results suggest that the carboxylation of the alkenylaluminum **2a** with CO_2 occurred in a stereospecific manner with retention of the stereoconfiguration.

The sequential methylalumination/carboxylation of other internal alkynes containing an ether tether group, such as **1b–d**, could also be achieved by using the combination of the scandium and copper catalysts to give the corresponding β-methyl-α,β-unsaturated carboxylic acids **3b–d** containing a configurationally well-defined tetrasubstituted olefin moiety in high yields (Table 2). Both siloxy and alkoxy groups could

Table 2. One-pot formal methylative carboxylation of internal alkynes containing an ether tether group.[a]

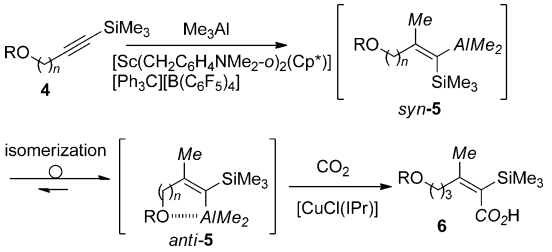


Entry	Alkyne	Product	Yield [%][b]
1	 **1b**	 **3b** *n*Pr	92[c]
2	 **1c**[d]	 **3c**	86
3	 **1d**	 **3d**	92

[a] The reaction was carried out in "one-pot" by addition of a THF solution of [CuCl(IPr)] to a toluene solution of **2** pre-prepared by reaction of **1** with Me_3Al in the presence of [Sc(Cp*)(R)$_2$]/[Ph$_3$C][B(C$_6$F$_5$)4], and the resulting mixture was then stirred under CO_2 (1 atm) for 24 h, unless otherwise noted. [b] Isolated yield based on **1**. [c] Carboxylation was carried out for 12 h. [d] TBDPS = tBu(Ph)$_2$Si–. [e] Methylalumination was carried out at 40 °C.

serve as a directing group to lead the carboxylation (or alumination) taking place at the proximal position and the methylation at the distal position in a regio- and stereospecific (*cis*) fashion. The aromatic C–Br bond is compatible with the catalytic reaction conditions.[16]

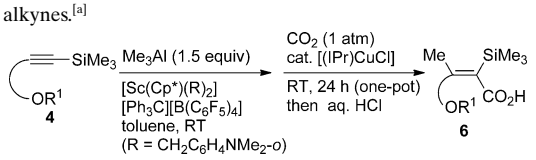
***Anti*-selective formal methylative carboxylation of SiMe$_3$-substituted internal alkynes by using a Sc/Cu catalyst combination**: The Sc-catalyzed methylalumination of trimethylsilyl-substituted alkynes (TMS-alkynes) containing a tethered ether group,[11e] such as **4**, could give the corresponding alkenylaluminum species in an *anti* configuration (Scheme 3).[17] We then decided to see if the TMS-containing *anti*-alkenylaluminum species (*anti*-**5**) could be carboxylated with CO_2 in the presence of the [CuCl(IPr)] catalyst.

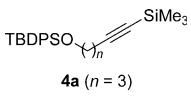
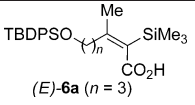
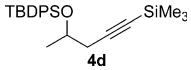
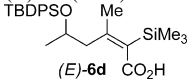


Scheme 3. Formal *anti*-methylative carboxylation of TMS-substituted alkynes by using a Sc/Cu catalyst combination.

The methylalumination of **4a** with Me_3Al was carried out in the presence of a catalytic amount of [Sc(CH$_2$C$_6$H$_4$NMe$_2$-*o*)$_2$(Cp*)]/[Ph$_3$C][B(C$_6$F$_5$)$_4$] and, subsequently, the resulting alkenylaluminum species was allowed to react with CO_2 (1 atm) at room temperature in the presence of [CuCl(IPr)] (5 mol%). The (*E*)-α-silyl-β-methyl-α,β-unsaturated carboxylic acid **6a** was obtained in 74% yield after hydrolysis (Table 3, entry 1). The carboxylation (or alumination) took

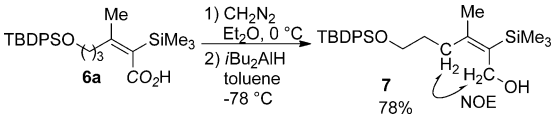
Table 3. One-pot *anti*-methylative carboxylation of TMS-substituted internal alkynes.[a]



Entry	Alkyne	Product	Yield [%][b]
1	 **4a** (n = 3)	 (*E*)-**6a** (n = 3)	74
2	**4b** (n = 2)	(*E*)-**4b** (n = 2)	94
3	**4c** (n = 1)	(*E*)-**4b** (n = 1)	97
4	 **4d**	 (*E*)-**6d**	100

[a] The reaction was carried out in "one-pot" by addition of a THF solution of [CuCl(IPr)] to a toluene solution of **5** pre-prepared by reaction of **4** with Me_3Al in the presence of [Sc(Cp*)(R)$_2$]/[Ph$_3$C][B(C$_6$F$_5$)$_4$], and the resulting mixture was then stirred under CO_2 (1 atm) for 24 h, unless otherwise noted. [b] Isolated yield based on **4**.

place at the distal position from the ether group, and the methyl group was introduced to the proximal position in a regioselective manner.[18] An NOE analysis of compound **7**, which was prepared by methylation of **6a** followed by reduction (Scheme 4), indicated that the methyl group and the



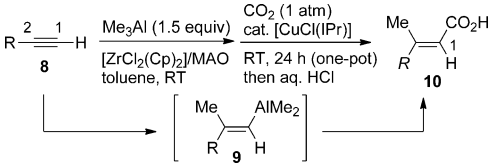
Scheme 4. Transformation of the carboxyl group in **6a** to a hydroxymethyl unit for stereochemistry confirmation.

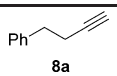
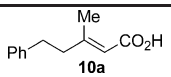
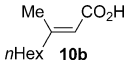
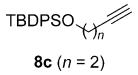
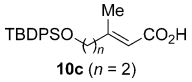
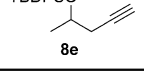
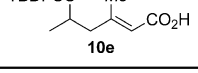
carboxyl group in **6a** should be on the *anti* side of the C=C double bond. The regio- and stereoselective methylative carboxylation of TMS alkynes containing an ether group with different tether lengths, such as **4b** and **4c**, could also be achieved similarly (Table 3, entries 2 and 3). An alkyne with a secondary *tert*-butyldiphenylsilyl ether (**4d**) is also suitable for this reaction (Table 3, entry 4).[16] As far as we are aware, this is the first example of *anti*-selective methylative carboxylation of alkynes.

Regio- and stereospecific methylative carboxylation of terminal alkynes by using a Zr/Cu catalyst combination: In contrast to internal alkynes, the methylative carboxylation of terminal alkynes has not been reported previously. It was well known that the methylalumination of terminal alkynes could be achieved in a regiospecific fashion by the use of a Zr catalyst.[11a–d]

The carboxylation of the resulting alkenylaluminum species with CO_2 was then examined in the presence of the Cu catalyst. As shown in Table 4, the methylalumination of 4-phenylbutyne **8a** with Me_3Al was first carried out in the presence of $[ZrCl_2(Cp)_2]$ (10 mol%) and methylaluminoxane (MAO) (10 mol%) in toluene at room temperature to give the alkenylaluminum species **9** ($R = C_2H_4Ph$).[11d,19] Subsequently, the carboxylation reaction with CO_2 (1 atm) was conducted in the presence of [CuCl(IPr)] (5 mol%). The overall one-pot reaction afforded the (*E*)-β-methyl-α,β-unsaturated carboxylic acid **10a**, quantitatively, after hydrolysis (Table 4, entry 1). In the same manner, the methylative carboxylation of 1-octyne **8b** and terminal alkynes containing a siloxy group, such as **8c–e**, could also be achieved to give the corresponding (*E*)-β-methyl-α,β-unsaturated carboxylic acids **10b–e** in high yields (Table 4, entry 2–5).[16] In all of these reactions, the carboxyl group was introduced to the less hindered C_1-position and the methyl group was bonded to the C_2-carbon atom. The addition of these two groups was completely controlled in a *syn* fashion, reflecting the high stereoselectivity both in the Zr-catalyzed methyl-alumination reaction and in the Cu-catalyzed carboxylation reaction.

Table 4. One-pot formal methylative carboxylation of terminal alkynes.[a]



Entry	Alkyne	Product	Yield [%][b]
1	 **8a**	 **10a**	100
2	 **8b**	 **10b**	85
3	 **8c** ($n = 2$)	 **10c** ($n = 2$)	88
4	**8d** ($n = 3$)	**10d** ($n = 3$)	87
5	 **8e**	 **10e**	78[c]

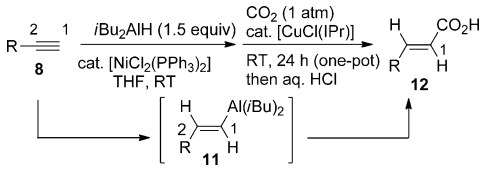
[a] The reaction was carried out in "one-pot" by addition of a THF solution of [CuCl(IPr)] to a toluene solution of **9** pre-prepared by reaction of **8** with Me_3Al in the presence of $[ZrCl_2(Cp)_2]$ (10 mol%) and MAO (10 mol%), and the resulting mixture was then stirred under CO_2 (1 atm) for 24 h, unless otherwise noted. [b] Isolated yield based on **8**. [c] Carboxylation was performed at 50 °C.

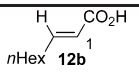
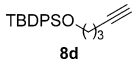
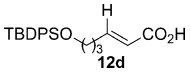
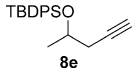
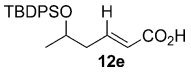
The above Zr/Cu-catalyzed transformations represent the first example of methylative carboxylation of terminal alkynes. Moreover, the high *E* selectivity of this protocol could make it highly attractive in organic synthesis.[20] For example, the carboxylic acid **10c** (Table 4, entry 3) was previously reported as a synthetic precursor of a *trans*-fusarininne derivative, which is a side chain commonly found in fungal siderophores.[21] The previously reported synthesis of **10c** required four-step reactions from the alkyne **8c**, and the separation of the *E*/*Z* isomers was also necessary. In contrast, our present method afforded **10c** with complete *E* selectivity in 88% yield in one-pot from the same starting material **8c**.

Regio- and stereospecific formal hydrogenative carboxylation of termninal alkynes by using a Ni/Cu catalyst combination: The Ni-catalyzed hydroalumination of terminal alkynes with iBu_2AlH reported recently by Hoveyda and co-workers[10c] could also be efficiently combined with the Cu-catalyzed carboxylation reaction. As shown in Table 5, the hydroalumination of 1-octyne **8b** with iBu_2AlH catalyzed by $[NiCl_2(PPh_3)_2]$ (5 mol%) and the subsequent carboxylation with CO_2 (1 atm) in the presence of [CuCl(IPr)] (5 mol%) at room temperature afforded (*E*)-α,β-unsaturated carboxylic acid **12b** in 78% yield after hydrolysis workup (Table 5, entry 1).[19] Similarly, the formal hydrogenative C_1-carboxylation of alkynes **8d** and **8e** could also be performed efficiently (Table 5, entries 2 and 3).[16] In all the cases, the carboxylation took place at the C_1-position and the hydride was added to the C_2-position in a regio- and stereospecific (*cis*) fashion. These reactions represent the first example of (formal) catalytic hydrocarboxylation of terminal alkynes with CO_2.

When $[NiCl_2(dppp)]$ (dppp = 1,3-bis(diphenylphosphino)-propane) instead of $[NiCl_2(PPh_3)_2]$ was used as a catalyst for the hydroalunination reaction,[10c] the C_2 (rather than C_1) carboxylation of terminal alkynes could be achieved selectively in a similar manner. As shown in Table 6, the combination of the hydroalumination of **8b** with *i*BuAlH by $[NiCl_2(dppp)]$ and the subsequent carboxylation of the resulting alkenylaluminum species with CO_2 (1 atm) in the

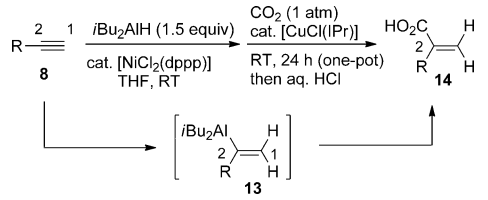
Table 5. One-pot formal hydrogenative C_1-carboxylation of terminal alkynes.[a]

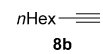
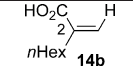
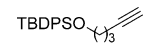
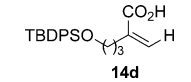
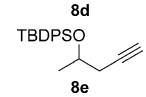
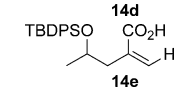


Entry	Alkyne	Product	Yield [%][b]
1	 **8b**	 **12b**	78
2	 **8d**	 **12d**	79
3	 **8e**	 **12e**	72

[a] The reaction was carried out in "one-pot" by addition of a THF solution of [CuCl(IPr)] to a THF solution of **11** prepared by reaction of **8** with iBu$_2$AlH in the presence of [NiCl$_2$(PPh$_3$)$_2$], and the resulting mixture was then stirred under CO_2 (1 atm) for 24 h, unless otherwise noted. [b] Isolated yield based on **8**.

Table 6. One-pot formal hydrogenative C_2-carboxylation of terminal alkynes.[a]

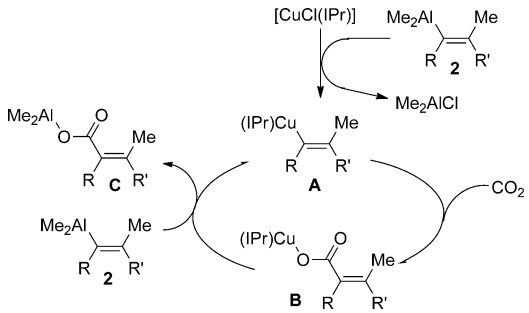


Entry	Alkyne	Product	Yield [%][b]
1	 **8b**	 **14b**	75
2	 **8d**	 **14d**	85
3	 **8e**	 **14e**	78

[a] The reaction was carried out in "one-pot" by addition of a THF solution of [CuCl(IPr)] to a THF solution of **13** pre-prepared by reaction of **8** with iBu$_2$AlH in the presence of [NiCl$_2$(dppp)], and the resulting mixture was then stirred under CO_2 (1 atm) for 24 h, unless otherwise noted. [b] Isolated yields based on **8**.

presence of [CuCl(IPr)] afforded the branched carboxylation product **14b** in 75% yield (Table 6, entry 1).[19] Similarly, the siloxy-substituted terminal alkynes, such as **8d** and **8e**, could also undergo the hydrocarboxylation with the same regioselectivity to give the corresponding α-methylene carboxylic acids **14d** and **14e** (Table 6, entries 2 and 3).[16] In all of these reactions, the carboxyl group was selectively introduced to the internal carbon (C_2) and the hydrogen atom was added to the terminal carbon of the alkynes, in contrast to what was observed in the [NiCl$_2$(PPh$_3$)$_2$]/[CuCl(IPr)] catalyst combination (see Table 5).

Reaction mechanism: A possible reaction mechanism of the present catalytic carboxylation of alkenylaluminum species with CO_2 is illustrated in Scheme 5. The transmetalation reaction between [CuCl(IPr)] and an alkenylaluminum species, such as **2**, would give the copper alkenyl species **A**,



Scheme 5. A possible catalytic carboxylation pathway.

which on reaction with CO_2, should afford the copper carboxylate **B**.[15a] The transmetalation between **B** and the alkenylaluminum species **2** could release the aluminum carboxylate **C** and regenerate the copper alkenyl species **A**, thus completing the catalytic cycle.

Conclusion

We have demonstrated that the combination of the hydroalumination or methylalumination of various alkynes with the carboxylation of the resulting alkenylaluminum species with CO_2 can serve as a useful protocol for the synthesis of a variety of α,β-unsaturated carboxylic acids with well-controlled regio- and stereoselectivity. The NHC–copper complex [CuCl(IPr)], acting as an excellent catalyst for the carboxylation reactions, matches well with various catalyst systems for the hydroalumination or methylalumination reactions. In all the cases, the carboxylation proceeds in a stereospecific manner with retention of the stereoconfiguration of the alkenylaluminum species and, therefore, the regio- and stereoselectivity of the overall reaction is determined solely by the methylalumination or hydroalumination process. In view of the high regio- and stereoselectivity, simple one-pot reaction operation, and the use of CO_2 as a starting material, this protocol should be a practically useful and attractive method for the synthesis of various α,β-unsaturated carboxylic acids with desired configurations.

Experimental Section

General information: Unless otherwise noted, all manipulations were performed under a dry nitrogen atmosphere by using standard Schlenk-type glasswares on a dual-manifold vacuum/nitrogen line. The scandium complex [Sc(CH$_2$C$_6$H$_4$NMe$_2$-*o*)$_2$(Cp*)][22] and the copper–NHC complex [CuCl(IPr)][23] were prepared according to literature methods. All other chemicals commercially available were purchased and purified when nec-

essary by using standard procedures. Silica gel column chromatography was performed with Merck Silica Gel 60 (0.040–0.063 mm). NMR spectroscopic data were recorded on a JEOL AL-400 or JEOL ECS-400 spectrometer.

Typical procedure for formal *syn*-methylative carboxylation of internal alkyne 1a (Table 1, entry 3; synthesis of 3a): In a glovebox, a Schlenk (20 mL) flask with a PTFE J. Young valve was charged with $[Sc(CH_2C_6H_4NMe_2\text{-}o)_2(Cp^*)]$ (4.5 mg, 0.01 mmol) and toluene (0.5 mL). A solution of $[Ph_3C][B(C_6F_5)_4]$ (9.2 mg, 0.01 mmol) was slowly added to this in toluene (1.0 mL). After 1 min, a mixture of alkyne **1a** (50 mg, 0.20 mmol) and Me_3Al (2.0 M in toluene, 150 μL, 0.30 mmol) in toluene (1.0 mL) was added. After 20 h at room temperature, a solution of [CuCl(IPr)] (4.8 mg, 0.01 mmol) in THF (2.5 mL) was added to the resulting reaction mixture and the flask was taken out from the glovebox. The Schlenk flask was evacuated and refilled with CO_2 several times. The PTFE valve was closed and then the mixture was stirred at room temperature for 24 h. The reaction mixture was hydrolyzed with 10% aqueous solution of HCl at 0 °C, and the mixture was extracted with Et_2O. The organic layer was washed with brine and dried over Na_2SO_4. After removal of the solvent, the residue was purified by silica gel column chromatography (hexane/AcOEt 2:3) to afford compound **3a** (colorless viscous oil, 62 mg, 100%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.20–7.39 (m, 8H), 7.12 (d, J = 6.9 Hz, 2H), 4.38 (s, 2H), 3.35 (t, J = 6.4 Hz, 2H), 2.31 (s, 3H), 2.27 (t, J = 7.3 Hz, 2H), 1.73 ppm (tt, J = 7.3, 6.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.9, 148.8, 143.2, 138.3, 128.9, 128.4, 128.2, 127.5, 127.4, 127.1, 126.7, 72.5, 69.8, 29.1, 27.7, 23.9 ppm; IR (neat): $\tilde{\nu}$ = 3600–2400 (br), 3059, 3028, 2926, 2856, 2644, 1950, 1978, 1810, 1682, 1620, 1597 cm^{-1}; HRMS (EI): m/z: calcd for $C_{20}H_{22}O_3$: 310.1569 [M^+]; found: 310.1570.

An example of formal *anti*-methylative carboxylation of TMS-alkyne 4a (Table 3, entry 1: synthesis of 6a): According to the typical procedure mentioned above, alkyne **4a** (50 mg, 0.20 mmol) was reacted with Me_3Al (2.0 M in toluene, 95 μL, 0.19 mmol) in toluene (2.0 mL) at room temperature for 6 h by using $[Sc(CH_2C_6H_4NMe_2\text{-}o)_2(Cp^*)]$ (2.8 mg, 0.0063 mmol) and $[Ph_3C][B(C_6F_5)_4]$ (5.8 mg, 0.0063 mmol) as the catalysts. After addition of [CuCl(IPr)] (2.5 mg, 0.0063 mmol) in THF (2.0 mL) to the resulting mixture, it was stirred at room temperature for 24 h under an atmosphere of CO_2. A crude material, which was obtained after a similar workup procedure, was purified by silica gel column chromatography (hexane/AcOEt 5:1) to afford compound (*E*)-**6a** (colorless oil, 42 mg, 74%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.63–7.67 (m, 4H), 7.32–7.43 (m, 6H), 3.64 (t, J = 6.4 Hz, 2H), 2.25 (t, J = 7.8 Hz, 2H), 1.82 (s, 3H), 1.71 (tt, J = 7.8, 6.4 Hz, 2H), 1.03 (s, 9H), 0.18 ppm (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 178.0, 153.5, 135.5, 133.9, 131.3, 129.5, 127.6, 63.7, 35.1, 31.2, 26.8, 21.6, 19.2, −0.3 ppm; IR (neat): $\tilde{\nu}$ = 3500–2400 (br), 3070, 3049, 2956, 2931, 2896, 2858, 2617, 1958, 1888, 1824, 1677, 1613 cm^{-1}; HRMS (ESI): m/z: calcd for $C_{26}H_{38}NaO_3Si_2$: 477.2257 [M+Na$^+$]; found 477.2243.

Typical procedure for formal *syn*-methylative carboxylation of terminal alkyne 8a (Table 4, entry 1: synthesis of 10a): In a glovebox, a 20 mL Schlenk flask with a PTFE J. Young valve was charged with $[ZrCl_2(Cp)_2]$ (11 mg, 0.038 mmol) and toluene (1.0 mL). Me_3Al (2.0 M in toluene, 288 μL, 0.57 mmol) was slowly added to this mixture and after 1 min, MAO (1.25 M in toluene, 31 μL, 0.038 mmol) was added followed by alkyne **8a** (50 mg, 0.38 mmol) in toluene (1.0 mL). After 15 h at room temperature, a solution of [CuCl(IPr)] (7.4 mg, 0.019 mmol) in THF (2.0 mL) was added to the mixture and the flask was taken out from the glovebox. The Schlenk flask was evacuated and refilled with CO_2 several times. The PTFE valve was closed and the mixture was stirred at room temperature for 24 h. The reaction mixture was hydrolyzed with a 10% aqueous solution of HCl at 0 °C, and then the mixture was extracted with Et_2O. The organic layer was washed with brine and dried over Na_2SO_4. After removal of the solvent, the residue was purified by silica gel column chromatography (hexane/AcOEt 3:1) to afford compound **10a** (colorless viscous oil, 77 mg, 100%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.26 (dd, J = 6.8, 6.8 Hz, 2H), 7.11–7.22 (m, 3H), 570 (s, 1H), 2.78 (t, J = 8.2 Hz, 2H), 2.46 (t, J = 8.2 Hz, 2H), 2.20 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 172.4, 162.1, 140.8, 128.4, 128.2, 126.1, 115.6, 42.9, 33.8, 19.2 ppm; IR (neat): $\tilde{\nu}$ = 2400–3400 (br), 3085, 3063, 3024, 2944, 2884, 2559, 2583, 1948, 1869, 1805, 1686, 1638 cm^{-1}; HRMS (EI): m/z: calcd for $C_{12}H_{14}O_2$: 190.0993 [M^+]; found: 190.1033.

Typical procedure for formal hydrogenative C1-carboxylation of terminal alkyne 8b (Table 5, entry 1: synthesis of 12b): In a glovebox, a Schlenk flask (20 mL) with a PTFE J. Young valve was charged with $[NiCl_2(PPh_3)_2]$ (4.5 mg, 0.01 mmol) and THF (0.5 mL). *i*Bu_2AlH (1.0 M in toluene, 680 μL, 0.68 mmol) was slowly added to this mixture and after 1 min, alkyne **8b** (50 mg, 0.45 mmol) in THF (1.5 mmol) was added. After 16 h at room temperature, a solution of [CuCl(IPr)] (8.8 mg, 0.023 mmol) in THF (1.5 mL) was added to the reaction mixture and the flask was taken out from the glovebox. The Schlenk flask was evacuated and refilled with CO_2 several times. The PTFE valve was closed, and then the mixture was stirred at room temperature for 24 h. The reaction mixture was hydrolyzed with a 10% aqueous solution of HCl at 0 °C, and the mixture was extracted with Et_2O. The organic layer was washed with brine and dried over Na_2SO_4. After removal of the solvent, the residue was purified by silica gel column chromatography (hexane/AcOEt 3:1) to afford compound **12b** (colorless viscous oil, 56 mg, 78%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.08 (dt, J = 15.6, 7.3 Hz, 1H), 5.82 (d, J = 15.6 Hz, 1H), 2.23 (dt, J = 7.3, 7.3 Hz, 2H), 1.41–1.52 (m, 2H), 1.21–1.37 (m, 6H), 0.88 ppm (t, J = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.1, 152.4, 120.5, 32.4, 31.6, 28.9, 27.9, 22.6, 14.1 ppm; IR (neat): $\tilde{\nu}$ = 3500–2400 (br), 2957, 2929, 2858, 2678, 2550, 1697, 1651 cm^{-1}; HRMS (EI): m/z: calcd for $C_9H_{16}O_2$: 156.1150 [M^+]; found: 156.1140.

An example of formal hydrogenative C2-carboxylation of terminal alkyne 8b (Table 6, entry 1: synthesis of 14b): According to the above-mentioned typical procedure for the synthesis of **12b** mentioned above, alkyne **8b** (50 mg, 0.45 mmol) was reacted with *i*Bu_2AlH (1.0 M in toluene, 680 μL, 0.68 mmol) in THF (2.0 mL) at room temperature for 6 h by using $[NiCl_2(dppp)]$ (12.3 mg, 0.023 mmol) as the catalyst. After the addition of [CuCl(IPr)] (8.8 mg, 0.023 mmol) in THF (1.5 mL) to the resulting mixture, it was stirred at room temperature for 24 h under an atmosphere of CO_2. A crude material, which was obtained after a similar workup procedure, was purified by silica gel column chromatography (hexane/AcOEt 4:1) to afford compound **14b** (colorless oil, 52 mg, 75%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.67 (d, J = 6.0 Hz, 4H), 7.35–7.45 (m, 6H), 6.29 (s, 1H), 5.63 (s, 1H), 3.69 (t, J = 6.4 Hz, 2H), 2.42 (t, J = 7.3 Hz, 2H), 1.75 (tt, J = 7.3, 6.4 Hz, 2H), 1.06 ppm (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 172.7, 139.7, 135.6, 133.9, 129.6, 127.6, 127.3, 63.0, 31.2, 27.9, 26.8, 19.2 ppm; IR (neat): $\tilde{\nu}$ = 3400–2400 (br), 3070, 3048, 2956, 2930, 2894, 2857, 2640, 1695, 1627; HRMS (EI): m/z: calcd for $C_9H_{16}O_2$: 156.1150 [M^+]; found 156.1153.

Acknowledgements

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