ChemPubSoc Europe
DOI: 10.1002/cctc.201600279
CHEMCATCHEM
Communications

Synthesis of Vinyl Carboxylic Acids using Carbon Dioxide as a Carbon Source by Iron-Catalyzed Hydromagnesiation

Rajagopal Santhoshkumar+,[a] Ya-Chun Hong+,[a] Ching-Zong Luo,[a] Yun-Ching Wu,[a] Chen-Hsun Hung,[a] Kuen-Yuan Hwang,[b] An-Pang Tu,[b] and Chien-Hong Cheng*[a]

An iron-catalyzed synthesis of α,β-unsaturated carboxylic acids from alkynes and carbon dioxide was developed. This reaction proceeds through hydromagnesiation of alkynes followed by carbon dioxide insertion under atmospheric pressure and ambient temperature in the presence of iron and a Grignard reagent as a catalyst and hydride source, respectively. Several symmetrical and unsymmetrical alkynes were transformed into the corresponding acids in good to excellent yields. The methodology provides an efficient route to the synthesis of vinyl carboxylic acids.

The utilization of carbon dioxide (CO_2) for the synthesis of high-value-added products and iron-catalyzed reactions have undergone explosive growth over the last decade.[1,2] Iron and CO_2 are attractive in organic synthesis owing to their low cost, abundance, nontoxicity, and environmentally benign nature. However, the activation of thermodynamically and kinetically stable raw materials is highly challenging. Thus, the efficient transition-metal-catalyzed conversion of CO_2 is highly attractive. Illustrative examples are cycloaddition[3] and the direct carboxylation of organometallics[4] and unsaturated compounds such as alkynes,[5] alkenes,[6] allenes,[7] and dienes.[8] Besides these reactions, CO_2 insertion into carbon–halogen,[9] carbon–oxygen,[10] and activated C–H bonds[11] has been studied. In a similar manner, iron-catalyzed reactions provide an ideal economic as well as ecological alternative to typical transition metals. In 2012, Hayashi and co-workers reported the carbometalation of alkynes with alkyl Grignard reagents.[12a] Later, Greenhalgh and Thomas demonstrated the hydrocarboxylation of styrene derivatives,[6d] and Nakamura et al. developed the hydromagnesiation of diarylalkynes,[12b] which was proposed to involve hydrometalation as the key step.

Catalytic hydrocarboxylation of alkynes by employing CO_2 was developed in the presence of Cu[5d] or Ni[5e] as a catalyst. These reactions are very interesting, but they require pyrophoric diethylzinc as a reducing reagent or N-heterocyclic carbene ligands. Recently, Martin et al.[5f] demonstrated the Ni-catalyzed hydrocarboxylation of alkyne by using simple alcohols as a proton source, which resulted in exceptional chemoselectivity. However, the development of a method for the ligand-free, nontoxic-metal-catalyzed hydrocarboxylation of alkynes under mild reaction conditions is highly desirable. Our continued interest in first-row transition-metal-catalyzed reductive coupling reactions of different π components[13] motivated us to extend the reactions of alkynes with CO_2. Herein, we wish to report the iron-catalyzed synthesis of α,β-unsaturated carboxylic acids from alkyne by using CO_2 as the carbon source.

Initially, diphenylacetylene (**1a**) was treated with ethylmagnesium bromide in diethyl ether as the hydride source in the presence of 5 mol% $FeCl_2$ by using diethyl ether as the solvent at ambient temperature for 15 min, and this was followed by trapping with CO_2. The reaction gave desired carboxylic acid **2a** in 90% yield with high (*E*) stereoselectivity. The effects of different solvents were tested (see the Supporting Information). We observed that ether solvents such as Et_2O and THF were highly effective, whereas 1,4-dioxane was less effective. Hydride sources other than EtMgBr, such as *i*PrMgBr, CyMgBr (Cy = cyclohexyl), CpMgBr (Cp = η^5-cyclopentadienyl), and Et_2Zn gave lower yields or the starting material remained unchanged. Furthermore, the addition of 5 mol% *N*,*N*,*N*′,*N*′-tetramethylethylenediamine, tri(*n*-butyl)phosphine, 2,2′:6′,2′′-terpyridine, and bidentate phosphine ligands completely retarded the catalytic reaction. A control experiment revealed that the reaction did not proceed without $FeCl_2$ or EtMgBr, and the use of other transition metals in place of iron failed to provide the desired product.

Next, we examined the scope of the reaction under the standard reaction conditions. Various symmetrical diarylalkynes **1a–h** containing electron-withdrawing groups (EWGs) and electron-donating groups (EDGs) were successfully transformed into the corresponding acids with high stereoselectivity (Table 1, entries 1–8). For example, substrates **1b–d** containing a methyl substituent at the *ortho*, *meta*, and *para* positions of the benzene ring afforded vinylic acids **2b–d** in yields of 44, 61, and 82%, respectively. In a similar manner, electron-rich bis(4-methoxyphenyl)acetylene (**1e**) also underwent the CO_2 insertion reaction. Fluoro- and chloro-substituted alkynes **1f** and **1g** were tolerated under the reaction conditions and provided vinyl carboxylic acids **2f** and **2g**, whereas the bromo- and iodo-substituted alkynes gave trace amounts of the dehalogenation products only. Thiophen-2-yl-substituted alkyne **1h**

---

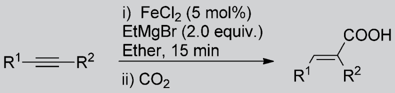
[a] R. Santhoshkumar,+ Y.-C. Hong,+ C.-Z. Luo, Y.-C. Wu, C.-H. Hung,
Prof. Dr. C.-H. Cheng
Department of Chemistry
National Tsing Hua University
Hsinchu, 30013 (Taiwan)
Fax: (+886) 3572-4698
E-mail: chcheng@mx.nthu.edu.tw

[b] K.-Y. Hwang, A.-P. Tu
Chang Chun Plastics Co., LTD
Hsinchu 30013 (Taiwan)

[+] These authors contributed equally to this work.

Supporting Information for this article can be found under http://dx.doi.org/10.1002/cctc.201600279.

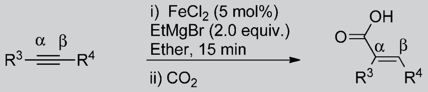
Table 1. Iron-catalyzed hydrocarboxylation of symmetrical diarylalkynes **1a–h** with CO_2[a]

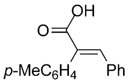
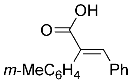
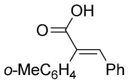
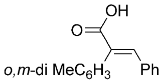
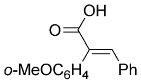
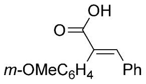
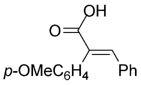
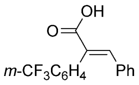


Entry	1	$R^1=R^2$	2	Yield[b] [%]
1	**1a**	Ph	**2a**	90
2	**1b**	*p*-MeC_6H_4	**2b**	82
3	**1c**	*m*-MeC_6H_4	**2c**	61
4	**1d**	*o*-MeC_6H_4	**2d**	44
5	**1e**	*p*-$MeOC_6H_4$	**2e**	80
6	**1f**	*p*-FC_6H_4	**2f**	41
7	**1g**	*p*-ClC_6H_4	**2g**	45
8	**1h**	2-thienyl	**2h**	70

[a] Reaction conditions: alkyne **1** (0.30 mmol), $FeCl_2$ (5.0 mol%), EtMgBr (0.60 mmol), Et_2O (1.50 mL), RT, 15 min. [b] Yield of isolated product.

Table 2. Iron-catalyzed hydrocarboxylation of unsymmetrical alkynes **1i–p** with CO_2[a]

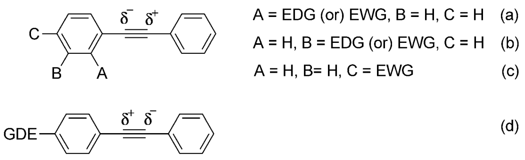


Entry	1	2		Ratio (α/β)	Yield[b] [%]
1	**1i**		**2i**	40:60	53
2	**1j**		**2j**	55:45	52
3	**1k**		**2k**	84:16	60
4	**1l**		**2l**	68:32	35
5	**1m**		**2m**	100:0	86
6	**1n**		**2n**	50:50	60
7	**1o**		**2o**	10:90	58
8	**1p**		**2p**	100:0	89

[a] Reaction conditions: alkyne **1** (0.30 mmol), $FeCl_2$ (5.0 mol%), EtMgBr (0.60 mmol), Et_2O (1.50 mL), RT, 15 min. [b] Yield of isolated product.

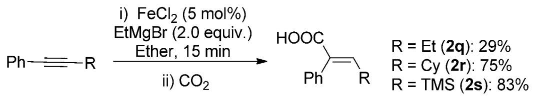
was also suitable for the hydrocarboxylation reaction, and it afforded product **2h** in good yield.

The present catalytic reaction was successfully extended to a variety of unsymmetrical diarylalkynes containing *ortho*, *meta*, and *para* substituents on the phenyl ring; this has not been studied in previous hydrocarboxylation protocols (Table 2). The regioselectivity of the products imitates Alami's work on the *ortho*-directing effect for the palladium-catalyzed hydrostannylation of internal alkynes, in which the regioselectivity is controlled by the *ortho* substituent at the aromatic ring, irrespective of the electronic nature of the substituent (Scheme 1a).[14] Our results are also in accord with Helaja's report on electronic regioselectivity of *para*- and *meta*-substituted diarylalkynes in the cobalt-mediated Pauson–Khand reaction (Scheme 1b–d).[15]



Scheme 1. Electronic nature of the unsymmetrical diarylalkynes.

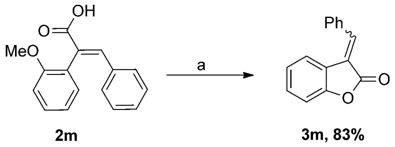
Thus, alkyne **1i** containing a *para*-methyl group on one of the phenyl rings gave a mixture of substituted vinylic acids **2i**-α and **2i**-β in 53% combined yield with the latter as the major product. In contrast, for *ortho*-methyl- and *meta*-methyl-substituted alkynes **1j–l**, the corresponding α-regioisomers with the carboxylic group near the methyl-substituted phenyl ring were observed in moderate yields. Complete regioselectivity for the hydrocarboxylation of 2-methoxy-substituted alkyne **1m** gave α-regioisomer **2m** in 86% yield. In a similar manner, 3- and 4-methoxyphenylalkynes **1n** and **1o** underwent the CO_2 insertion reaction to afford a mixture of regioisomeric products **2n** and **2o** in good yields. For substrate **1n**, the α- and β-regioisomers were equally formed, but for **1o**, the β-regioisomer became the major species with an α/β ratio of 1:9. Alkyne **1p** containing an electron-withdrawing CF_3 group at the *meta* position was also a suitable candidate for the regioselective hydrocarboxylation reaction, and it provided only product **2p**-α in 89% yield. For 1-phenyl-1-butyne (**1q**), the hydride was regioselectively added to the carbon atom near the alkyl group to afford product **2q**, albeit in low yield. The presence of β-hydrogen atoms in **1q** leading to the rearrangement of the alkyne to an allene likely accounts for the low product yield owing to the fact that under the reaction conditions the allene group does not undergo hydrocarboxylation (Scheme 2). Gratifyingly, alkyne **1r** with a cyclohexyl group afforded corresponding acid **2r** in 75% yield with a regioisomeric ratio of 83:17.[16] Alkyne **1s** containing a trimethylsilyl group



Scheme 2. Hydrocarboxylation of unsymmetrical alkynes. For product **2r**, the ratio of regioisomers was 83:17. For product **2s**, *E*/*Z* = 68:32.

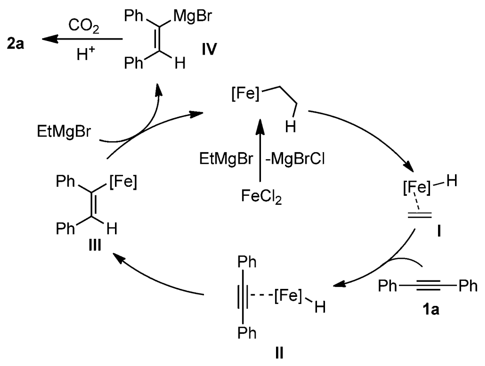
was also suitable for the reaction, and it gave vinylic acid **2s** in 83% yield with an *E/Z* ratio of 68:32.

Furthermore, the α,β-unsaturated carboxylic acids were easily transformed into the corresponding benzofuran-2-one skeletons, which are present in various natural products and bioactive molecules (Scheme 3).[17] Notably, crude product **2m** was directly converted into **3m** in 83% yield with the aid of BBr_3.



Scheme 3. Synthesis of fused lactone **3m**. Reagents and conditions: a) acid **2m** (0.20 mmol), BBr_3 (0.30 mmol), CH_2Cl_2, 0 °C to RT, 12 h.

On the basis of literature reports,[6d,12a] a plausible mechanism is proposed, as shown in Scheme 4. The reaction is initiated by alkylation of the iron catalyst with ethylmagnesium bromide, which is followed by β-hydrogen elimination to afford hydride intermediate **I**. Coordination of alkyne **1a** to **I** gives iron alkyne hydride species **II**. Hydrometalation of the alkyne gives intermediate **III**, which then undergoes transmetalation with the Grignard reagent to afford vinylmagnesium bromide **IV** with regeneration of the ironalkyl species for the next cycle. Finally, insertion of CO_2 with **IV** takes place to provide desired product **2a**.



Scheme 4. A plausible catalytic cycle.

In conclusion, we developed a naturally abundant and inexpensive iron-catalyzed protocol for the hydrocarboxylation of alkynes for the synthesis of α,β-unsaturated carboxylic acids by using CO_2 as a carbon source with high stereoselectivity under mild reaction conditions. Various unsymmetrical diarylalkynes bearing electron-donating and electron-withdrawing groups were successfully transformed into acids with good yields and regioselectivity; these substrates have not been previously studied in hydrocarboxylation reactions. Notably, the hydrocarboxylation of *ortho*-ethynylanisole gave regio- and stereodefined acids that could be further converted into benzofuranone.

Experimental Section

Synthesis of vinyl carboxylic acid 2a

A sealed tube containing $FeCl_2$ (1.9 mg, 0.015 mmol, 5 mol%) and diphenylacetylene (**1a**; 53.5 mg, 0.30 mmol) was evacuated and purged with nitrogen gas (3×). Then, freshly distilled diethyl ether (1.50 mL) and a solution of ethylmagnesium bromide in diethyl ether (0.2 mL, 3 M in Et_2O, 0.6 mmol) were added to the mixture by syringe under a nitrogen atmosphere. The mixture was stirred at ambient temperature for 15 min and then carbon dioxide was bubbled through the mixture for 15 min. The reaction was quenched with 1 N HCl solution (2.0 mL), and the aqueous layer was extracted with dichloromethane (2×5 mL). The combined organic phase was concentrated under vacuum, and the residue was purified by chromatography (silica gel, *n*-hexane/isopropyl alcohol) to afford desired product **2a** (61 mg, 90%).

Acknowledgements

We thank the Ministry of Science and Technology of the Republic of China (MOST-103–2622-E-007—025) for support of this research.

Keywords: carbon dioxide fixation · carboxylic acids · Grignard reagents · hydrocarboxylation · iron

[1] a) L. Zhang, Z. Hou, *Chem. Sci.* **2013**, *4*, 3395–3403; b) Y. Tsuji, T. Fujihara, *Chem. Commun.* **2012**, *48*, 9956–9964; c) M. Cokoja, C. Bruckmeier, B. Rieger, W. A. Herrmann, F. E. Kuhn, *Angew. Chem. Int. Ed.* **2011**, *50*, 8510–8537; *Angew. Chem.* **2011**, *123*, 8662–8690; d) K. Huang, C.-L. Sun, Z.-j. Shi, *Chem. Soc. Rev.* **2011**, *40*, 2435–2452; e) R. Martín, A. W. Kleij, *ChemSusChem* **2011**, *4*, 1259–1263; f) T. Sakakura, J. C. Choi, H. Yasuda, *Chem. Rev.* **2007**, *107*, 2365–2387.

[2] a) C. Bolm, J. Legros, J. Le Paih, L. Zani, *Chem. Rev.* **2004**, *104*, 6217–6254; b) M. D. Greenhalgh, A. S. Jones, S. P. Thomas, *ChemCatChem* **2015**, *7*, 190–222; c) S. Enthaler, K. Junge, M. Beller, *Angew. Chem. Int. Ed.* **2008**, *47*, 3317–3321; *Angew. Chem.* **2008**, *120*, 3363–3367; d) C. Bolm, *Nat. Chem.* **2009**, *1*, 420; e) I. Bauer, H.-J. Knölker, *Chem. Rev.* **2015**, *115*, 3170–3387; f) R. B. Bedford, *Acc. Chem. Res.* **2015**, *48*, 1485–1493; g) E. Negishi, C. Copéret, S. Ma, S.-Y. Liou, F. Liu, *Chem. Rev.* **1996**, *96*, 365–394; h) I. Ojima, M. Tzamarioudaki, Z. Li, R. J. Donovan, *Chem. Rev.* **1996**, *96*, 635–662.

[3] a) T. Tsuda, S. Morikawa, R. Sumiya, T. Saegusa, *J. Org. Chem.* **1988**, *53*, 3140–3145; b) J. Louie, J. E. Gibby, M. V. Farnworth, T. N. Tekavec, *J. Am. Chem. Soc.* **2002**, *124*, 15188–15189.

[4] a) H. Ochiai, M. Jang, K. Hirano, H. Yorimitsu, K. Oshima, *Org. Lett.* **2008**, *10*, 2681–2683; b) T. Ohishi, M. Nishiura, Z. Hou, *Angew. Chem. Int. Ed.* **2008**, *47*, 5792–5795; *Angew. Chem.* **2008**, *120*, 5876–5879.

[5] a) S. Saito, S. Nakagawa, T. Koizumi, K. Hirayama, Y. Yamamoto, *J. Org. Chem.* **1999**, *64*, 3975–3978; b) M. Takimoto, K. Shimizu, M. Mori, *Org. Lett.* **2001**, *3*, 3345–3347; c) M. Aoki, M. Kaneko, S. Izumi, K. Ukai, N. Iwasawa, *Chem. Commun.* **2004**, 2568–2569; d) T. Fujihara, T. Xu, K. Semba, J. Terao, Y. Tsuji, *Angew. Chem. Int. Ed.* **2011**, *50*, 523–527; *Angew. Chem.* **2011**, *123*, 543–547; e) S. Li, W. Yuan, S. Ma, *Angew. Chem. Int. Ed.* **2011**, *50*, 2578–2582; *Angew. Chem.* **2011**, *123*, 2626–2630; f) X. Wang, M. Nakajima, R. Martin, *J. Am. Chem. Soc.* **2015**, *137*, 8924–8927.

[6] a) Y. Hoberg, Y. Peres, C. Krüger, Y.-H. Tsay, *Angew. Chem. Int. Ed. Engl.* **1987**, *26*, 771–773; *Angew. Chem.* **1987**, *99*, 799–800; b) H. Hoberg, Y. Peres, A. Milchereit, *J. Organomet. Chem.* **1986**, *307*, C38–C40; c) C. M. Williams, B. Jeffrey, J. B. Johnson, T. Rovis, *J. Am. Chem. Soc.* **2008**, *130*,

14936 – 14937; d) M. D. Greenhalgh, S. P. Thomas, *J. Am. Chem. Soc.* **2012**, *134*, 11900 – 111903.

[7] a) M. Takimoto, M. Kawamura, M. Mori, *Org. Lett.* **2003**, *5*, 2599 – 2601; b) M. Aoki, S. Izumi, M. Kaneko, K. Ukai, J. Takaya, N. Iwasawa, *Org. Lett.* **2007**, *9*, 1251 – 1253; c) J. Takaya, N. Iwasawa, *J. Am. Chem. Soc.* **2008**, *130*, 15254 – 15255.

[8] a) M. Takimoto, M. Mori, *J. Am. Chem. Soc.* **2001**, *123*, 2895 – 2896; b) M. Takimoto, Y. Nakamura, K. Kimura, M. Mori, *J. Am. Chem. Soc.* **2004**, *126*, 5956 – 5957; c) J. Takaya, K. Sasano, N. Iwasawa, *Org. Lett.* **2011**, *13*, 1698 – 1701.

[9] a) T. Fujihara, K. Nogi, T. Xu, J. Terao, Y. Tsuji, *J. Am. Chem. Soc.* **2012**, *134*, 9106 – 9109; b) H. Tran-Vu, O. Daugulis, *ACS Catal.* **2013**, *3*, 2417 – 2420; c) A. Correa, R. Martin, *J. Am. Chem. Soc.* **2009**, *131*, 15974 – 15975.

[10] a) A. Correa, T. Leon, R. Martin, *J. Am. Chem. Soc.* **2014**, *136*, 1062 – 1069; b) K. Nogi, T. Fujihara, J. Terao, Y. Tsuji, *Chem. Commun.* **2014**, *50*, 13052 – 13055.

[11] a) L. Ackermann, *Angew. Chem. Int. Ed.* **2011**, *50*, 3842; *Angew. Chem.* **2011**, *123*, 3926; b) I. I. F. Boogaerts, S. P. Nolan, *J. Am. Chem. Soc.* **2010**, *132*, 8858 – 8859.

[12] a) E. Shirakawa, D. Ikeda, S. Masui, M. Yoshida, T. Hayashi, *J. Am. Chem. Soc.* **2012**, *134*, 272 – 279; b) L. Ilies, T. Yoshida, E. Nakamura, *J. Am. Chem. Soc.* **2012**, *134*, 16951 – 16954.

[13] a) C.-C. Wang, P.-S. Lin, C.-H. Cheng, *J. Am. Chem. Soc.* **2002**, *124*, 9696 – 9697; b) S. Bhuvaneswari, M. Jeganmohan, C.-H. Cheng, *Chem. Commun.* **2008**, 5013 – 5015; c) S. Mannathan, M. Jeganmohan, C.-H. Cheng, *Angew. Chem. Int. Ed.* **2009**, *48*, 2192 – 2195; *Angew. Chem.* **2009**, *121*, 2226 – 2229; d) P.-S. Lin, M. Jeganmohan, C.-H. Cheng, *Chem. Eur. J.* **2008**, *14*, 11296 – 11299; e) P. Gandeepan, A. K. Parthasarathy, T. H. Su, C.-H. Cheng, *Adv. Synth. Catal.* **2012**, *354*, 457 – 468; f) R. Santhoshkumar, S. Mannathan, C.-H. Cheng, *Org Lett* **2014**, *16*, 4208 – 4211.

[14] M. Alami, F. Liron, M. Gervais, J.-F. Peyrat, J.-D. Brion, *Angew. Chem. Int. Ed.* **2002**, *41*, 1578 – 1580; *Angew. Chem.* **2002**, *114*, 1648 – 1650.

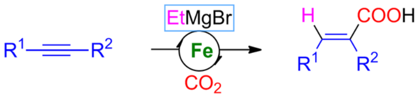
[15] a) E. Fager-Jokela, M. Muuronen, M. Patzschke, J. Helaja, *J. Org. Chem.* **2012**, *77*, 9134 – 9147.

[16] CCDC 1417115 (**2r**), and 1417116 (**2r'**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge crystallographic Data Centre.

[17] a) N. T. Dat, X. Jin, Y.-S. Hong, J. J. Lee, *J. Nat. Prod.* **2010**, *73*, 1167 – 1169; b) P. Lin, S. Li, S. Wang, Y. Yang, J. Shi, *J. Nat. Prod.* **2006**, *69*, 1629 – 1632; c) Y. S. Rao, *Chem. Rev.* **1976**, *76*, 625 – 694; d) E.-i. Negishi, M. Kotora, *Tetrahedron* **1997**, *53*, 6707 – 6738.

Received: March 12, 2016
Revised: April 15, 2016

Iron fist: The ever-growing demand for energy has led to a concomitant increase in the concentration of CO_2 in the atmosphere, and this has become a key global environmental threat. Hence, the utilization of CO_2 to synthesize useful products is an excellent way to scavenge it. Herein, the most abundant transition metal, iron, is used as a catalyst for the hydrocarboxylation of alkynes by CO_2.



*R. Santhoshkumar, Y.-C. Hong, C.-Z. Luo, Y.-C. Wu, C.-H. Hung, K.-Y. Hwang, A.-P. Tu, C.-H. Cheng**

■■ – ■■

Synthesis of Vinyl Carboxylic Acids using Carbon Dioxide as a Carbon Source by Iron-Catalyzed Hydromagnesiation