Letter

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ACS Catal., **Just Accepted Manuscript** • DOI: 10.1021/acscatal.6b03571 • Publication Date (Web): 17 Jan 2017

Copper-Catalyzed Carboxylation of Hydroborated Disubstituted Alkenes and Terminal Alkynes with Cesium Fluoride

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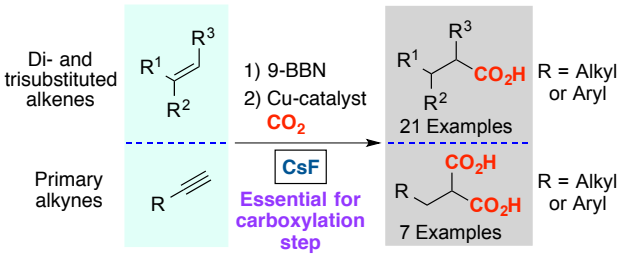
Supporting Information Placeholder

ABSTRACT: A protocol for the hydrocarboxylation of disubstituted alkenes and terminal alkynes providing access to different secondary carboxylic acids and malonic acid derivatives has been developed. This methodology relies on an initial hydroboration using 9-BBN followed by carboxylation with carbon dioxide in the presence of a copper catalyst and the additive, cesium fluoride. Different cyclohexene, styrene and stilbene derivatives could be utilized, and alkynes could be transformed into their corresponding dicarboxylic acids in good yields. Finally, six different terpenoids were carboxylated using the developed procedure.



KEYWORDS: *copper catalysis, carbon dioxide, hydroboration, carboxylic acid, disubstituted alkenes*

Carboxylic acids are a common structural motif in a variety of bioactive molecules[1] (Figure 1), as well as being useful precursors for accessing alcohols,[2] esters,[3] amides[4] and acid chlorides.[5] Carbon dioxide is widely abundant and has been utilized as a useful C1-building block for synthesizing benzoic derivatives by employing phenoxides[6] or organometallic reagents, such as aryl lithium species and Grignard reagents.[7] Milder conditions involving the carboxylation of aryl halides and aryl boronic esters have recently been reported by the groups of Martin,[8] Tsuji,[9] Daugulis,[10] Hou,[11] and Iwasawa,[12] respectively. However, these methodologies are limited to the formation of vinylic- and benzoic acids. Martin and co-workers have later extended the methodology to include benzylic and aliphatic electrophiles with focus on the preparation of benzylic and alkyl carboxylic acids, respectively.[13]

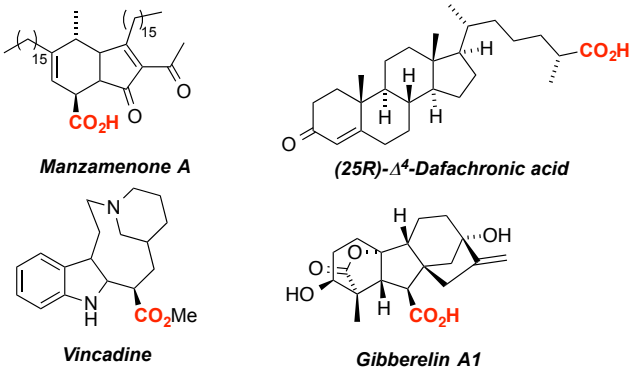
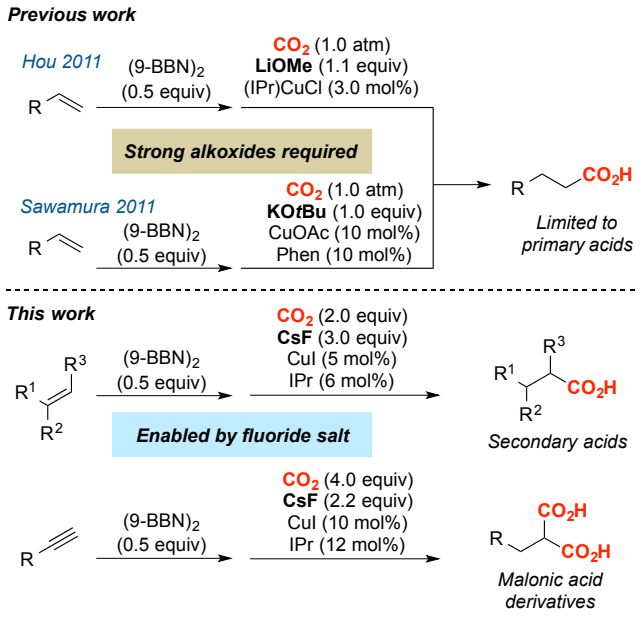


Figure 1. Bioactive molecules containing secondary carboxylic acid groups and derivatives thereof.

The groups of Hou[14] and Sawamura[15] independently reported on a hydroboration-carboxylation sequence of terminal olefins using copper catalysis and alkoxides as additives to form aliphatic, linear carboxylic acids (Scheme 1). The 9-BBN dimer was exploited for the hydroboration step. Interestingly, in this work, 1,2-disubstituted olefins were not included for the formation of carboxylic acids. Given our interest in CO_2 consuming reactions,[16,17] we set out to identify the appropriate parameters for expanding the two-step hydrocarboxylation procedure to include these more elaborately substituted olefins as well as primary alkynes (Scheme 1). In this report, we demonstrate a viable protocol for accessing carboxylic acids from cyclohexenes, stilbenes, and styrenes. Furthermore, terminal alkynes are able to undergo a double carboxylation leading to malonic acid derivatives. Finally, the developed conditions for the two-step hydrocarboxylation were tested on a number of simple terpene-based natural products displaying either internal or exocyclic C=C double bonds.



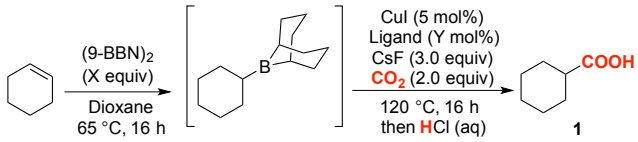
Scheme 1. Previous Results on the Hydroboration-Carboxylations of Olefins

Based on the previous results by Hou[14] and Sawamura[15], we sought to develop a hydroboration-carboxylation for functionalizing internal alkenes. Cyclohexene was chosen as the test substrate and hydroboration of the double bond was obtained in the presence of 9-BBN at 65 °C in dioxane. Optimization of the ensuing carboxylation is depicted in Table 1. The previous work of Hou and Sawamura relied on alkoxides (LiOMe and KO*t*Bu) as additives to promote the necessary σ-bond metathesis. However, employing alkoxides for the hydrocarboxylation of cyclohexene did not lead to the formation of carboxylic acid **1** even after raising the reaction temperature to 120 °C (See Supporting Information).

As in the case of the Suzuki-Miyaura reaction, such strong basic additives can be replaced by a milder fluoride source.[18] With this in mind, the carboxylation step was examined with cesium fluoride, 2 equiv. of CO_2 and 5 mol% of CuI in the presence of different ligands (Table 1). In the absence of ligand or with the two different phosphine ligands tested even at 120 °C, we did not observe any carboxylation (entries 1–3). Resorting to 1,10-phenanthroline, previously utilized by Sawamura, proved also futile (entry 4).[15] On the other hand, the NHC ligands IPr, ICy and BICy allowed for the isolation of the desired carboxylic acid **1** with similar efficiencies in a yield of approx 65% (entries 5–7). Lowering the reaction temperature led to reduced yields of the carboxylic acid, while no product was formed upon omission of CuI (entry 8). However, when the hydroboration step was carried out with 1 equiv. of the 9-BBN dimer, the formation of **1** could be achieved in an excellent 94% isolated yield (entry 9).

With the optimized conditions in hand, the scope and limitations of this hydrocarboxylation sequence was investigated employing different internal alkenes (Scheme 2). Using BICy as ligand instead of IPr allowed for the carboxylation of the tri-substituted 1-methylcyclohex-1-ene to give carboxylic acid **2**. Only the *anti*-isomer was observed, originating from the *syn*-addition of the borane. Norbornene could be carboxylated to give **3** as the *exo*-isomer. Disubstituted styrenes were attempted as reaction partners, resulting in carboxylation of the α-position, which is similar to the Ni-catalyzed carboxylation of styrenes reported by Rovis (carboxylic acids **4–8**).[19] Methyl-substituted styrene-derivatives coupled smoothly whereas having an

Table 1. Optimization of Conditions for Carboxylation of Secondary Olefins

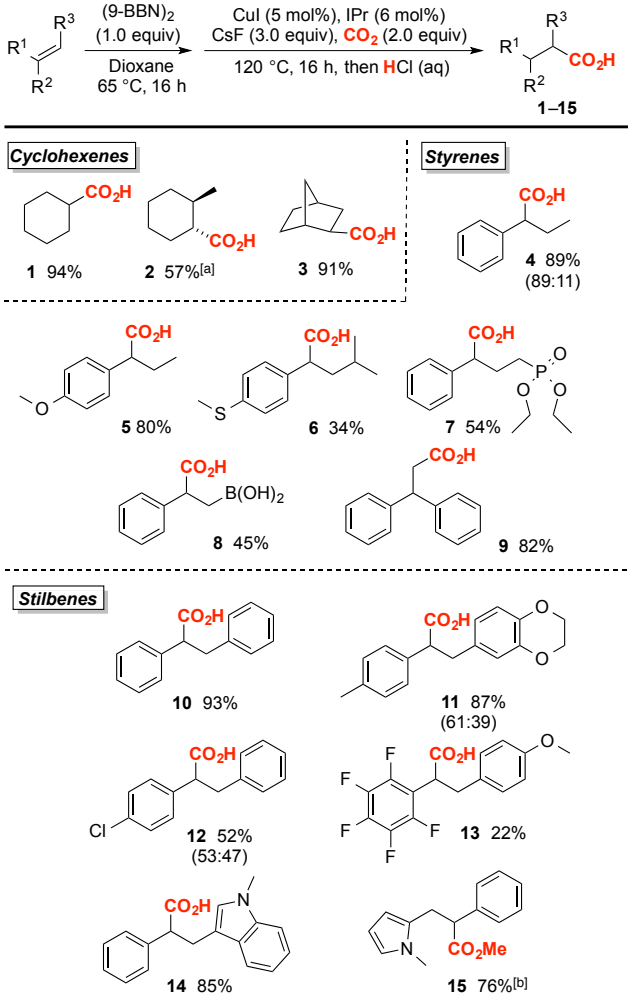


Entry	Ligand (mol%)	(9-BBN)2 (equiv)	Yield **1** (%)[a]
1	-	0.5	-
2	PPh_3 (5)	0.5	-
3	BINAP (5)	0.5	-
4	Phen (5)	0.5	-
5	IPr (6)[b]	0.5	65
6	ICy (6)[b]	0.5	65
7	BICy (6)[b]	0.5	68
8[c]	IPr (6)[b]	0.5	-
9	IPr (6)[b]	1.0	94

General conditions: Reactions were carried out in a 10 mL glass tube. Hydroboration step: Cyclohexene (41 μL, 0.4 mmol), 9-BBN dimer (X equiv) and dioxane (1.0 mL). Carboxylation step: CuI (3.8 mg, 5 mol%), ligand (Y mol%), CsF (182 mg, 3.0 equiv), CO_2 (20 mL, 2.0 equiv) and dioxane (1.0 mL). Quenched with 1 M HCl (6.0 mL). [a]Isolated yields. [b]Prepared *in situ* from the HCl salt using NaO*t*Bu (2.3 mg, 6 mol%). [c]No CuI. BINAP (2,2′-bis(diphenylphosphino)-1,1′-binapthalene), Phen (1,10-phenanthroline), IPr (1,3-bis(2,6-diisopropylphenyl)-1,3-dihydro-2*H*-imidazol-2-ylidene), ICy (1,3-dicyclohexyl-1,3-dihydro-2*H*-imidazol-2-ylidene), BICy (1,3-dicyclohexyl-1,3-dihydro-2*H*-benzimidazol-2-ylidene).

isopropyl group present lowered the efficiency of the reaction (compounds **4–6**). A phosphonate group was well-tolerated and even a boronic acid derivative could be isolated in a moderate yield (compounds **7**, **8**). The carboxylic acid **8** is particularly interesting as no additional carboxylation or protodeboration was observed. Furthermore, **8** is set up for an ensuing Suzuki-Miyaura cross-coupling.[20] In the previous work by Hou and Sawamura, 1,1-diphenylethylene was tested as a coupling partner with varying degrees of success (0% and 54%, respectively). However, an improved yield of **9** (82%) could be secured using our modified conditions reported here. Stilbene also proved to be a suitable candidate for the reaction as the hydrocarboxylated product **10** was formed in a high yield. Other stilbenes were competent substrates furnishing the corresponding carboxylic acids in good to moderate yields as a mixture of α- and β-isomers (compounds **11** and **12**). This is due to the similar electronic property of the two

aryl rings. Employing a stilbene equipped with an electron-deficient and an electron-rich aryl ring allowed for the formation of the α-regioisomer **13** as the sole product, albeit in a low yield.

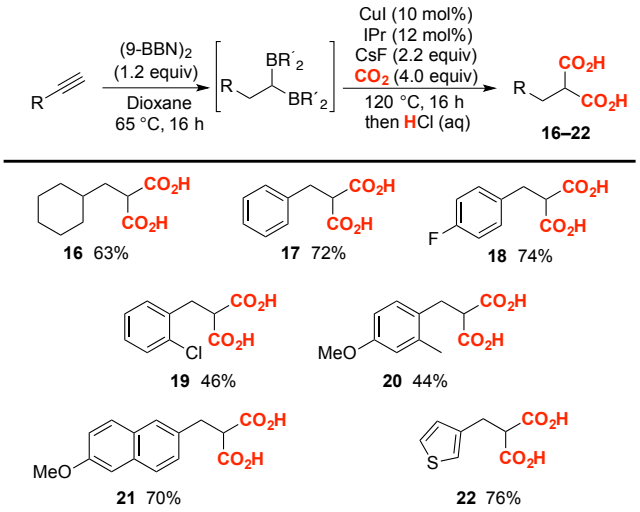


General conditions: Reactions were carried out in a 10 mL glass tube. Hydroboration step: Olefin (0.4 mmol), 9-BBN dimer (97.6 mg, 1.0 equiv) and dioxane (1.0 mL). Carboxylation step: CuI (3.8 mg, 5 mol%), IPr·HCl (10.2 mg, 6 mol%), NaO*t*Bu (2.3 mg, 6 mol%), CsF (182 mg, 3.0 equiv), CO_2 (20 mL, 2.0 equiv) and dioxane (1.0 mL). Quenched with 1 M HCl (6.0 mL). Isolated yields. [a] 9-BBN (58.6 mg, 0.6 mmol), BICy·HCl (7.7 mg, 6 mol%) employed instead of IPr·HCl. [b] 2.0 M $TMSCH_2N_2$ in diethyl ether (1.0 mL, 5.0 equiv).

Scheme 2. Cu-Catalyzed Carboxylation of Different Disubstituted Olefins

Finally, stilbenes constructed with heteroaromatic rings such as an indole and a pyrrole could be exploited for this transformation as illustrated for the products **14** and **15**. Interestingly, the corresponding benzylic boron compounds derived from the styrene and stilbene entries could be carboxylated in the absence of copper, albeit in a lower yield (42% for **4**).[21]

Alkynes are known to react with CO_2 to form acrylic acid derivatives.[22] However, when employing the optimized conditions for the carboxylation of internal olefins to terminal alkynes, we observed the formation of the corresponding malonic acid. This approach for accessing these synthetically useful substrates through a double hydroboration generating a 1,1-gem-diboryl intermediate,[23] has been reported earlier in the presence of *n*-BuLi.[24] Interestingly, Hou and co-workers reported on the use of similar conditions for carboxylation of alkynes using B_2pin_2 to generate boralactones and not malonic acids.[25]

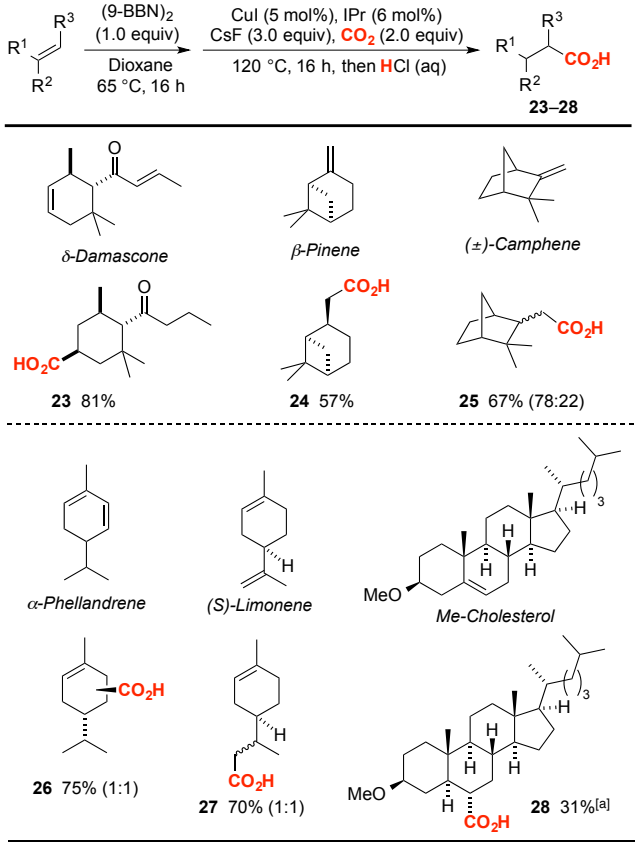


General conditions: Reactions were carried out in a 10 mL glass tube. Hydroboration step: Alkyne (0.2 mmol), 9-BBN (117.2 mg, 1.2 equiv) and dioxane (1.0 mL). Carboxylation step: CuI (7.6 mg, 10 mol%), IPr·HCl (20.4 mg, 12 mol%), NaO*t*Bu (4.6 mg, 12 mol%), CsF (133.7 mg, 2.2 equiv), CO_2 (40 mL, 4.0 equiv) and dioxane (1.0 mL). Quenched with 1 M HCl (6.0 mL). Isolated yields.

Scheme 3. Cu-Catalyzed Double Carboxylation of Alkynes

After a small optimization study (See Supporting Information), conditions were obtained that allowed for the dicarboxylation of a cyclohexyl acetylene giving **16** in a good yield (Scheme 3). Phenylacetylene and a 4-fluoro derivative also provided the malonic acid products **17** and **18** after column chromatography. The presence of *ortho*-substituents reduced the efficiency of the reaction as seen for compounds **19** and **20**, however, an electron-rich naphthylacetylene proved to be effective with the generation of malonic acid **21**. Finally, 2-ethynylthiophene provided the desired diacid **22** in a good yield.

Having examined the reactivity of different internal olefins, we turned to investigate whether the developed methodology could be applied to the carboxylation of olefin-containing natural products (Scheme 4). δ-Damascone, a well-known fragrance agent, was selectively carboxylated at the unactivated double bond providing the carboxylic



General conditions: Reactions were carried out in a 10 mL glas tube. Hydroboration step: Olefin (0.4 mmol), 9-BBN (97.6 mg, 1.0 equiv) and dioxane (1.0 mL). Carboxylation step: CuI (3.8 mg, 5 mol%), IPr·HCl (10.2 mg, 6 mol%), NaO*t*Bu (2.3 mg, 6 mol%), CsF (182 mg, 3.0 equiv), CO_2 (20 mL, 2.0 equiv) and dioxane (1.0 mL). Quenched with 1 M HCl (6.0 mL). Isolated yields. [a]Hydroboration conducted at 90 °C.

Scheme 4. Cu-Catalyzed Carboxylation of Common Natural Products

acid **23** in a good isolated yield (81%) as a single regioisomer. A *trans*-relationship was observed for the acyl group and the corresponding β-methyl substituent with a coupling constant between the two diaxial protons of 11.0 Hz. The carboxylic acid occupies an equatorial position as measured from the coupling constants for the α-proton (dddd at 2.6 ppm with a two similar *trans*-couplings (J = 12.8 Hz) and two equal *cis*-couplings (J = 2.6 Hz). Nevertheless, the activated double bond was reduced during the hydroboration step.

β-Pinene displays an exocyclic double bond, which could be carboxylated to form **24** in 57% yield with hydroboration occurring from the *Re*-face due to the *gem*-dimethyl group.[26] Similarly camphene could undergo carboxylation to **25** in a good yield (67%) with the *exo*-isomer as the major product.[27] α-Phellandrene displays both a di- and a tri-substituted double bond, which enables the less-substituted double bond to be selectively carboxylated, providing the carboxylic acid **26** (75%) as a 1:1 regioisomeric mixture with the acid group positioned *trans* to the isopropyl group. Likewise, (*S*)-limonene can be selectively functionalized generating the terminal carboxylic acid **27** in a 70% yield. In an earlier experiment, a trisubstituted alkene was carboxylated as demonstrated with compound **2** (Scheme 1) under slightly modified conditions. However, carboxylation of both double bonds in (*S*)-limonene proved unfruitful (result not shown). Cholesterol displays a tri-substituted C=C double bond in the B-ring. Gratifyingly, the methyl ether of cholesterol could be carboxylated to compound **28** in a 31% yield with complete control at the two new stereogenic carbon centers. A double double doublet at 2.30 ppm with two *trans*-couplings (J = 12.0 Hz) and a *cis*-coupling (J = 3.2 Hz), corresponding to the α-hydrogen to the carboxylic acid, confirming the relative stereochemistry.

A proposed mechanistic cycle for the hydroboration-carboxylation methodology is depicted in Figure 2,[28] similar to that presented by Hou and Sawamura though with alkoxide activation.[14,15] The active IPr-ligated copper-fluoride species **A** is generated *in situ* from CuI, IPr and cesium fluoride.[29] **A** can then undergo a σ-bond metathesis reaction with the preformed alkylborane species to form the alkyl-copper complex **B**. This complex can then insert CO_2 to generate complex **C**, which can liberate **A** and a cesium carboxylate finally generating the desired carboxylic acid after an acidic quench.

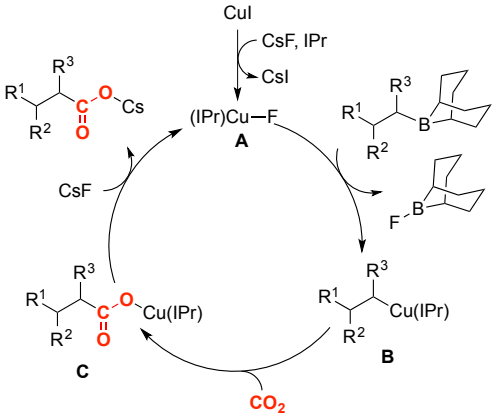


Figure 2. Possible catalytic cycle for the carboxylation of disubstituted olefins.

In conclusion, we have developed an efficient methodology for accessing secondary carboxylic acids through a hydroboration-carboxylation sequence of internal olefins. This could be extended to different cyclic olefins, stilbenes and styrenes in moderate to good yields. Furthermore, terminal alkynes underwent a double carboxylation enabling the formation of the corresponding malonic acid derivatives. Finally, a range of different natural products was submitted to the optimized conditions, which allowed for carboxylation of di- and trisubstituted double bonds. Future work on expanding the developed methodology is currently underway in our laboratories.

ASSOCIATED CONTENT

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Notes

The authors declare no competing financial interest. M. J. and S.L.R.L have contributed equally to this work.

Supporting Information

Experimental details and spectroscopic data. This material is available free of charge via the Internet at http://pubs.acs.org.

ACKNOWLEDGMENT

We are deeply appreciative of the generous financial support from the Danish National Research Foundation (Grant No. DNRF118) and Aarhus University for generous financial support.

REFERENCES

(1) McGrath, N. A.; Brichacek, M.; Njardarson, J. T. *J. Chem. Ed.* **2010**, *87*, 1348–1349.

(2) Kanth, J. V. B.; Periasamy, M. *J. Org. Chem.* **1991**, *56*, 5964–5965.

(3) Ishihara, K.; Nakagawa, S.; Sakakura, A. *J. Am. Chem. Soc.* **2005**, *127*, 3407–3410.

(4) Ishihara, K.; Ohara, S.; Yamamoto, H. *J. Org. Chem.* **1996**, *61*, 4196–4197.

(5) Hardee, D. J.; Kovalchuke, L.; Lambert, T. H. *J. Am. Chem. Soc.* **2010**, *132*, 5002–5003.

(6) Lindsey, A. S.; Jeskey, H. *Chem. Rev.* **1957**, *57*, 583–620.

(7) Correa, A.; Martin, R. *Angew. Chem. Int. Ed.* **2009**, *48*, 6201–6204.

(8) Correa, A.; Martin, R. *J. Am. Chem. Soc.* **2009**, *131*, 15974–15975.

(9) Fujihara, T.; Nogi, K.; Xu, T.; Terao, J.; Tsuji, Y. *J. Am. Chem. Soc.* **2012**, *134*, 9106–9109.

(10) Tran-Vu, H.; Daugulis, O. *ACS Catal*. **2013**, *3*, 2417–2420.

(11) Ohishi, T.; Nishiura, M.; Hou, Z. *Angew. Chem. Int. Ed.* **2008**, *47*, 5792–5795.

(12) Takaya, J.; Tadami, S.; Ukai, K.; Iwasawa, N. *Org. Lett.* **2008**, *10*, 2697–2700.

(13) (a) Liu, Y.; Cornella, J.; Martin, R. *J. Am. Chem. Soc.* **2014**, *136*, 11212–11215. (b) Börjesson, M.; Moragas, T.; Martin, R. *J. Am. Chem. Soc.* **2016**, *138*, 7504–7507. (c) Moragas, T.; Gaydou, M.; Martin, R. *Angew. Chem. Int. Ed.* **2016**, *55*, 5053-5057. (d) Börjesson, M.; Moragas, T.; Gallego, D.; Martin, R. *ACS Catal.* **2016**, *6*, 6739–6749.

(14) Ohishi, T.; Zhang, L.; Nishiura, M.; Hou, Z. *Angew. Chem. Int. Ed.* **2011**, *50*, 8114–8117.

(15) Ohmiya, H.; Tanabe, M.; Sawamura, M. *Org. Lett.* **2011**, *13*, 1086–1088.

(16) (a) Lescot, C.; Nielsen, D. U.; Makarov, I. S.; Lindhardt, A. T.; Daasbjerg, K.; Skrydstrup, T. *J. Am. Chem. Soc.* **2014**, *136*, 6142–6147. (b) Xin, Z.; Lescot, C.; Friis, S. D.; Daasbjerg, K.; Skrydstrup, T. *Angew. Chem. Int. Ed.* **2015**, *54*, 6862–6866. (c) Lian, Z.; Nielsen, D. U.; Lindhardt, A.; Daasbjerg, D.; Skrydstrup, T. *Nat. Commun.* **2016**, *7*, 13782–13788.

(17) For examples on the valorization of CO_2 see: (a) Arresta, M.; Dibenedetto, A.; Angelini, A. *Chem. Rev.* **2014**, *114*, 1709–1742. (b) Yu, D.; Teong, S. P.; Zhang, Y. *Coord. Chem. Rev.* **2015**, *293*, 279–291. (c) Huang, K.; Sun, C.-L.; Shi, Z.-J. *Chem. Soc. Rev.* **2011**, *40*, 2435–2452.

(18) Amatore, C.; Jutand, A.; Le Duc, G. *Angew. Chem. Int. Ed.* **2012**, *51*, 1379–1382.

(19) Williams, C. M.; Johnson, J. B.; Rovis, T. *J. Am. Chem. Soc.* **2008**, *130*, 14936–14937.

(20) (a) Chemler, S. R.; Trauner, D.; Danishefsky, S. D. *Angew. Chem. Int. Ed.* **2001**, *40*, 4544–4568. (b) Saito, B.; Fu, G. C. *J. Am. Chem. Soc.* **2007**, *129*, 9602–9603.

(21) Grigg, R. D.; Rigoli, J. W.; van Hoveln, R.; Neale, S.; Schomaker, J. M. *Chem. Eur. J.* **2012**, *18*, 9391–9396.

(22) (a) Wang, X.; Nakajima, M.; Martin, R. *J. Am. Chem. Soc.* **2015**, *137*, 8924–8927. (b) Fujihara, T.; Xu, T.; Semba, K.; Terao, J.; Tsuji, Y. *Angew. Chem. Int. Ed.* **2011**, *50*, 523–527. (c) Yu, B.; Diao, Z.-F.; Guo, C.-X.; He, L.-N. *J. CO_2 Util.* **2013**, *1*, 60–68. (d) Burkhart, G.; Hoberg, H. *Angew. Chem. Int. Ed.* **1981**, *21*, 76. (e) Saito, S.; Nakagawa, S.; Koizumi, T.; Hirayama, K.; Yamamoto, Y. *J. Org. Chem.* **1999**, *64*, 3975–3978. (f) Aoki, M.; Kaneko, M.; Izumi, S.; Ukai, K.; Iwasawa, N. *Chem. Commun.* **2004**, 2568–2569. (g) Takimoto, M.; Shimizu, K.; Mori, M. *Org. Lett.* **2001**, *3*, 3345–3347. (h) Shimizu, K.; Takimoto, M.; Mori, M. *Org. Lett.* **2003**, *5*, 2323–2325. (i) Shimizu, K.; Takimoto, M.; Sato, Y.; Mori, M. *Org. Lett.* **2005**, *7*, 195–197. (j) Shimizu, K.; Takimoto, M.; Mori, M.; Sato, Y. *Synlett.* **2006**, *18*, 3182–3184. (k) Zhou, C.; Larock, R. C. *J. Org. Chem.* **2005**, *70*, 3765–3777.(l) Li, S.; Yuan, W.; Ma, S. *Angew. Chem. Int. Ed.* **2011**, *50*, 2578–2582.

(23) (a) Brown, H. C.; Scouten, C. G.; Liotta, R. *J. Am. Chem. Soc.* **1979**, *101*, 96–99. (b) Pasto, D. J. *J. Am. Chem. Soc.* **1964**, *86*, 3039–3047. (c) Brown, H. C.; Ravindran, N. *J. Am. Chem. Soc.***1976**, *98*, 1785–1798. (d) Brown, H. C.; Ravindran, N. *J. Am. Chem. Soc.* **1976**, *98*, 1798–1806. (e) Lee, S.; Li, D.; Yun, J. *Chem. Asian. J.* **2014**, *9*, 2440–2443. (f) Marek, I.; Normant, J.-F. *Chem. Rev.* **1996**, *96*, 3241–3267. (g) Endo, K.; Hirokami, M.; Shibata, T. *Synlett*, **2009**, *8*, 1331–1335.

(24) Cainelli, G.; Dal Bello, G.; Zubiani, G. *Tetrahedron Lett.* **1965**, *6*, 3429–3432.

(25) Zhang, L.; Cheng, J.; Carry, B.; Hou, Z. *J. Am. Chem. Soc.* **2012**, *134*, 14314–14317.

(26) Midland, M. M.; Greer, S.; Tramontano, A.; Zderic, S. A. *J. Am. Chem. Soc.* **1979**, *101*, 2352–2355.

(27) The stereochemistry was determined by NMR analysis and by comparison with the outcome of the hydrosilylation of camphene with $HSiMe_2Cl$. Beckmann, J.; Dakter-

nieks, D.; Duthie, A.; Floate, S. L.; Foitzik, R. C.; Schiesser, C. H. *J. Organomet. Chem.* **2004**, *689*, 909–916.

(28) Dang, L.; Lin, Z.; Marder, T. B. *Organometallics,* **2010**, *29*, 917–927.

(29) (a) Herron, J. R.; Ball, Z. T. *J. Am. Chem. Soc.* **2008**, *130*, 16486–16487. (b) Dang, H.; Mailig, M.; Lalic, G. *Angew. Chem. Int. Ed.* **2014**, *53*, 6473–6476.