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Nickel-Promoted Alkylative or Arylative Carboxylation of Alkynes

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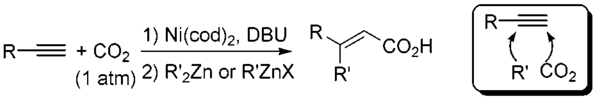
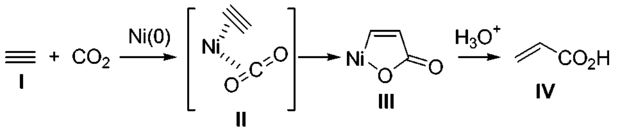
ABSTRACT



Nickel-promoted alkylative or arylative carboxylation of terminal alkynes via a carbon dioxide fixation process was investigated. In the presence of a stoichiometric amount of a zero-valent nickel complex, the reaction of alkynes with CO_2 gave a nickelacycle, which was reacted with various organozinc reagents under very mild conditions to provide β,β'-disubstituted, α,β-unsaturated carboxylic acids in a highly regio- and stereoselective manner.

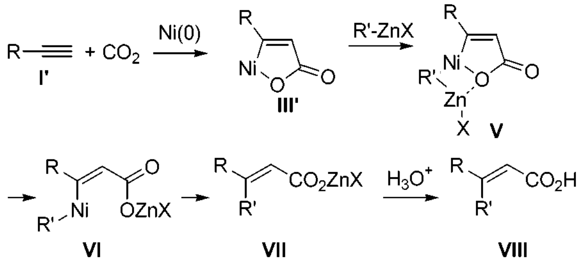
Low-valent nickel complexes have been known to be efficient mediators for the coupling of carbon dioxide (CO_2) with various unsaturated hydrocarbons.[1] For instance, oxidative coupling of alkyne with CO_2 proceeds under mild conditions in the presence of a Ni(0) complex to form oxonickelacycle **III** (Scheme 1).[2,3] Hydrolysis of **III** gives unsaturated carboxylic acid **IV**. While nickelacycle **III** still has an active nickel−Csp^2 bond which can be used for further transformation, the reactivity of **III**, other than hydrolysis, has rarely been studied. Here we report a highly regio- and stereoselective synthesis of β,β'-disubstituted unsaturated carboxylic acid utilizing a related nickel-promoted CO_2 coupling process combined with a transmetalation process.

Scheme 1. Ni-Promoted Oxidative Coupling of Alkyne with CO_2



Our plan is shown in Scheme 2. Saito and Yamamoto very recently reported a nickel-promoted regioselective coupling of terminal alkynes with CO_2 which afforded a β-substituted α,β-unsaturated acid after hydrolysis.[2d,4] They also reported that nickelacycle **III′** is an intermediate for their carboxylation process. If transmetalation of **III′** with organozinc reagents could proceed, vinyl alkyl nickel complex **VI** would be formed.[5] Succeeding reductive elimination of Ni(0) from **VI** would afford zinc carboxylate **VII**, which would be hydrolyzed to give β,β'-disubstituted unsaturated carboxylic acid **VIII**.[6]

Scheme 2



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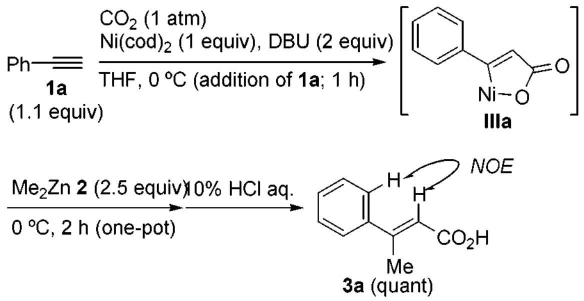
(1) Reviews: (a) Behr, A. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 661. (b) Braunstein, P. B.; Matt, D.; Nobel, D. *Chem. Rev.* **1988**, *88*, 747. (c) Gibson, D. H. *Chem. Rev.* **1996**, *96*, 2063. (d) Leitner, W. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2207.

(2) (a) Hoberg, H.; Burkhart, G. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 76. (b) Hoberg, H.; Schäfer, D. *J. Organomet. Chem.* **1982**, *238*, 383. (c) Hoberg, H.; Schäfer, D.; Burkhar, G.; Krüger, C.; Romao, M. J. *J. Organomet. Chem.* **1984**, *266*, 203. (d) Saito, S.; Nakagawa, S.; Koizumi, T.; Hirayama, K.; Yamamoto, Y. *J. Org. Chem.* **1998**, *64*, 3975.

10.1021/ol016585z CCC: $20.00

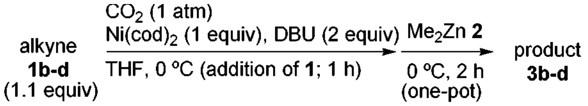
Initially, we tried a nickel-promoted reaction of **1a** with CO_2 and dimethylzinc **2** (Scheme 3). When alkyne **1a** (1.1 equiv) was reacted with CO_2 (1 atm) in the presence of a stoichiometric amount of $Ni(cod)_2$ (1.0 equiv) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, 2 equiv) according to Yamamoto's procedure, nickelacycle **IIIa** is formed. Dimethylzinc **2** (2.5 equiv) was added to this solution at 0 °C, and the mixture was stirred at 0 °C for 2 h. Hydrolysis of the reaction mixture with a 10% aqueous HCl solution afforded β-methylcinnamic acid **3a** in quantitative yield.[7] The results of an NOE experiment showed that the configuration of the double bond in **3a** is *E*. These results indicated that stereoselective *cis*-addition of CO_2 and a methyl group to the alkyne moiety of **1a** occurred in a highly regioselective manner and that the reaction proceeded via transmetalation of nickelacycle **IIIa** with dimethylzinc **2** as shown in Scheme 2.

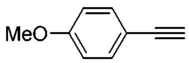
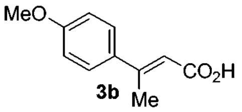
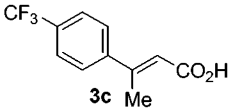
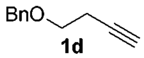
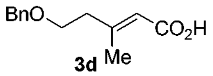
Scheme 3



To investigate the generality of this methylative carboxylation, various terminal alkynes were examined (Table 1).

Table 1. Methylative Carboxylation of Various Alkynes



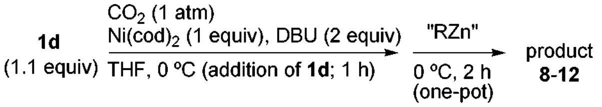
entry	alkyne	yield (%)[a]	product
1[b]	 **1b**	78	 **3b**
2[c]	 **1c**	53	 **3c**
3[c]	 **1d**	81	 **3d**

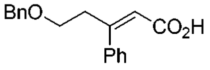
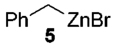
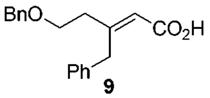
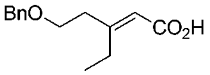
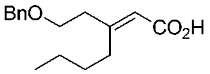
[a] Isolated yield based on $Ni(cod)_2$. [b] 2.5 equiv of **2** was used. [c] 1.5 equiv of **2** was used.

In each case, the desired β-methylated carboxylic acid **3b**−**d** was obtained as a sole product. The yields were generally good, but an electron-withdrawing subsituent on a conjugated aromatic ring slightly reduced the yield (entry 2). Aliphatic alkyne **1d** also gave a β,β'-disubstituted unsaturated acid in a highly regio- and stereoselective manner (entry 3).

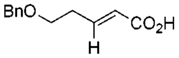
We next examined the alkylative or arylative carboxylation of **1d** with various organozinc reagents (Table 2).[8,9] Reactions using phenylzinc chloride **4** and benzylzinc bromide **5** afforded the desired carboxylic acids **8** and **9b**, respectively, in good yields (entries 1 and 2). However, the reaction using diethylzinc **6** gave β-ethylated product **10** in only 9% yield. In this reaction, the major product was carboxylic acid **12**, which possessed no ethyl group originating from the zinc reagent **6**. This reaction should also proceed via the same mechanism (Scheme 4). Transmetalation of nickelacycle **IIId** with **6** affords ethyl vinyl nickel complex **IX**, which then undergoes β-hydride elimination to form hydride nickel

Table 2. Carboxylation of **1d** with Various Organozinc Reagents



entry	"RZn"	equiv	yield (%)[a]	product
1	PhZnCl **4**	2	69	 **8**
2	 **5**	1.5	81	 **9**
3	Et_2Zn **6**	1.5	9[b]	 **10**
4	BuZnI **7**	3	68	 **11**

[a] Isolated yield based on $Ni(cod)_2$. [b] Compound **12** was also obtained in 78% yield.



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Scheme 4. β-Hydride Elimination Pathway

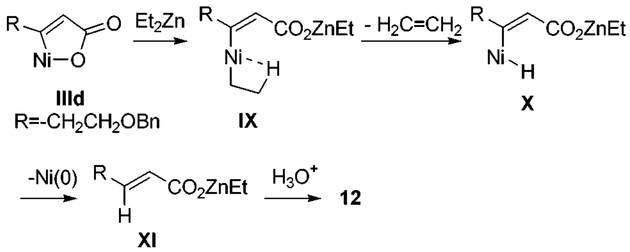
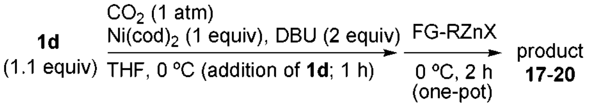
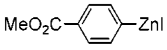
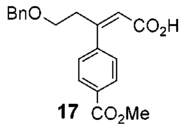
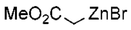
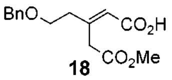
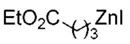
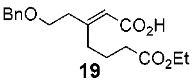
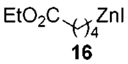
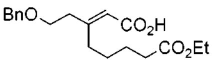


Table 3. Carboxylation of **1d** with Functionalized Organozinc Reagents



entry	FG-RZnX	equiv	yield (%)[a]	product
1	 **13**	2	70	
2	 **14**	3	33	
3	 **15**	3	81	
4	 **16**	3	82	 **20**

[a] Isolated yield based on Ni(cod)$_2$.

intermediate **X**. Reductive elimination of Ni(0) from **X** would afford **XI**, which would be hydrolyzed to give **12**. It was very interesting that the use of butylzinc iodide **7** instead of **6** afforded the desired β-alkylated product **11** in good yield, although the alkyl group of **7** possesses β-hydrogen atoms.

As documented in Table 3, various organozinc reagents having an ester group as a functional group were also applicable to this reaction.[10] High yields were generally obtained except for the case of Reformatsky reagent **14**.[14] Reactions using linear alkylzinc reagents **15** and **16** afforded the desired products **19** and **20**, respectively, in high yields without the occurrence of β-hydride elimination.

In summary, we succeeded in the alkylative or arylative carboxylation of terminal alkynes. The remarkable feature of this reaction is that the reaction proceeds under very mild conditions in a highly regio- and stereoselective manner. Not only aromatic but also aliphatic terminal alkynes gave β,β'-disubstituted unsaturated carboxylic acid in high yields. Various organozinc reagents, including functionalized aryl- or alkylzinc reagents, could be used. Further studies on applications of this carboxylation reaction and the development of a catalytic process are now in progress.

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Supporting Information Available: Information on experimental procedures, spectral data for substrate **1d**, and spectral data for compounds **3a−d**, **8−12**, and **17−20**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(3) Recent reports of catalytic reactions involving a related coupling process: (a) Inoue, Y.; Itoh, Y.; Kazama, H.; Hashimoto, H. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 3329. (b) Tsuda, T.; Morikawa, S.; Hasegawa, N.; Saegusa, T. *J. Org. Chem.* **1990**, *55*, 2978. (d) Dèrien, S.; Clinet, J.-C.; Duñach, E.; Pèrichon, J. *J. Am. Chem. Soc.* **1991**, *113*, 8447.

(4) Duñach also reported a nickel-catalyzed electrochemical carboxylation of terminal alkynes which afforded α-substituted-α,β-unsaturated acid in a reverse regioselectivity. (a) Duñach, E.; Pèrichon, J. *J. Organomet. Chem.* **1988**, *352*, 239. (b) Duñach, E.; Pèrichon, J. *J. Organomet. Chem.* **1990**, *385*, C43. See also ref 3d.

(5) Transmetalation processes of structurally related oxanickelacycles with organozinc reagents were already reported by Montgomery. (a) Oblinger, E.; Montgomery, J. *J. Am. Chem. Soc.* **1997**, *119*, 9065. (b) Montgomery, J. *Acc. Chem. Res.* **2000**, *33*, 467.

(6) We recently reported a cross-coupling reaction of nickel complexes generated from 1,3-diene and CO$_2$ with organozinc reagents which was based on a similar concept. Takimoto, M.; Mori, M. *J. Am. Chem. Soc.* **2001**, *123*, 2895.

(7) The actual yield based on used Ni(cod)$_2$ was 110%, which exceeded the amount of the limiting reagent. This result suggested that zero-valent nickel species regenerated and that the reaction could proceed by a catalytic amount of nickel complex. However, our initial attempt at a catalytic experiment using 25 mol % of Ni(cod)$_2$ was unsuccessful and **3a** was obtained in only 30% yield.

(8) For the preparation of benzylzinc bromide, see: Berk, S. C.; Knochel, P.; Yeh, M. C. P. *J. Org. Chem.* **1988**, *53*, 5789.

(9) Butylzinc iodide was prepared from butyl iodide and metallic zinc according to a method described in the following report. Knochel, P.; Yeh, M. C. P.; Berk, S. C.; Talbert, J. *J. Org. Chem.* **1988**, *53*, 2390.

(10) Reviews for functionalized zinc reagents: (a) Knochel, P.; Singer, R. D. *Chem. Rev.* **1993**, *93*, 2117. (b) Rieke, R. D. *Aldrichimica Acta* **2000**, *33*, 52. For the preparation of specific zinc reagents that appear in Table 3, see refs 11−13.

(11) Arylzinc iodide **13**: Zhu, L.; Wehmeyer, R. M.; Rieke, R. D. *J. Org. Chem.* **1991**, *56*, 1445.

(12) Reformatsky reagent **14**: (a) Curé, J.; Gaudemar, M. *Bull. Soc. Chim. Fr.* **1968**, *8*, 3224. (b) Curé, J.; Gaudemar, M. *Bull. Soc. Chim. Fr.* **1969**, *9*, 2471.

(13) For the preparation of organozinc reagents **15** and **16**, see ref 9.

(14) It is not clear yet why the yield of the reaction using **14** was low. We have tentatively speculated that **14** was lost by the reaction with CO$_2$, since the nucleophilicity of **14** is higher than that of other organozinc reagents.