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Highly Selective Nickel-Catalyzed Methyl-Carboxylation of Homopropargylic Alcohols for α-Alkylidene-γ-butyrolactones

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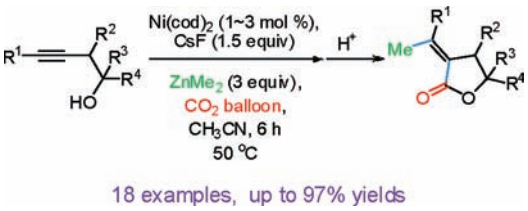
ABSTRACT



A first practical Ni(0)-catalyzed highly stereoselective methyl-carboxylation of homopropargylic alcohols with $ZnMe_2$ and CO_2 for the efficient synthesis of α-alkylidene-γ-butyrolactones is described. The reaction may be applied to other alkynols.

During the last 10 years, there have been tremendous developments in CO_2 activation. Mainly three types of transition-metal-catalyzed CO_2 activation reactions forming new carbon–carbon bonds have been developed:[1] (1) the carboxylation of organometallic reagents (Sn,[2] B,[3] Zn[4]), aryl bromides,[5] arenes,[6] or terminal C–H bonds of alkynes[7] affording carboxylic acids (Scheme 1, eq 1); (2) the carboxylation of unsaturated hydrocarbons such as

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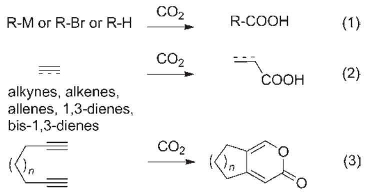
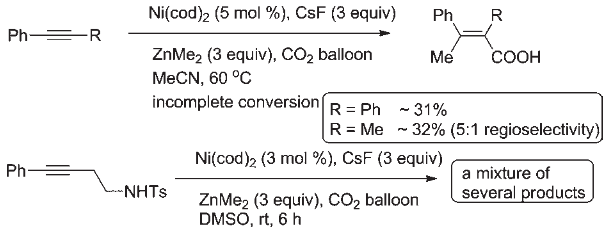
alkynes,[8,9] alkenes,[10] 1,3-dienes,[11] bis-1,3-dienes,[12] and allenes[13] also affording carboxylic acids (Scheme 1, eq 2); and (3) the cycloaddition of CO_2 and diynes affording pyrones (Scheme 1, eq 3).[14] Thus, activation of CO_2 is still mostly limited to the simple substrates for preparation of simple carboxylic acids except for those noted in ref 14.

Scheme 1. Transition-Metal-Catalyzed CO_2-Activation Forming C−C Bonds



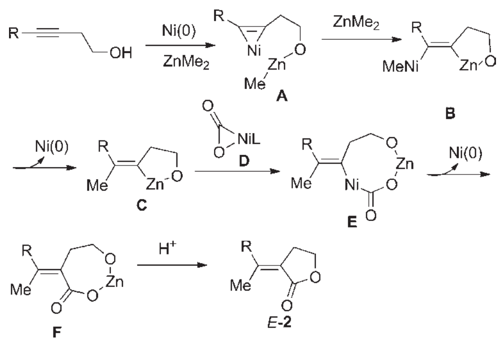
In 2005, Mori et al. reported catalytic alkylative carboxylation of alkynes by using 20 mol % of $Ni(cod)_2$ and 10 equiv of DBU with moderate regioselectivity via a cyclometalation mechanism.[8] However, to the best of our knowledge, alkyl-carboxylation, which would be very efficient for the synthesis of stereodefined fully substituted α,β-unsaturated alkenoic acids, has not been well established. Recently, we have developed a hydrocarboxylation of alkynes with a unique mechanism by using $ZnEt_2$ as the hydride source via β-elimination.[9a] We reasoned that the protocol may be easily extended to methylcarboxylation by following the established reaction conditions for alkynes in MeCN and 3-butynyl tosylamides in DMSO reported in ref 9a. However, as shown in Scheme 2, the methylcarboxylation of phenyl-substituted alkynes in MeCN or 4-phenylbutynyl tosylamide in DMSO all yielded the corresponding carboxylic acids in unsatisfactory yields and poor regioselectivity (for further results, see Table S1 in the Supporting Information).

Scheme 2. Methylcarboxylation of Phenyl-Substituted Alkynes or 4-Phenyl-3-butynyl Tosylamide



We reasoned that the OH group in the readily available homopropargylic alcohols may be acting as the directing group to increase the regioselectivity because of the intramolecular transmetalation of intermediate **A** in the presence of $ZnMe_2$, forming intermediate **B** (Scheme 3). In addition, the cyclic structure of intermediate **C** may also increase the reactivity of its C−Zn bond with the Aresta's complex **D** because of the release of the ring strain to form α-alkylidene-γ-butyrolactones *E*-**2** efficiently via lactonization.

Scheme 3. Concept for the Synthesis of γ-Butyrolactones based on the Previous Mechanistic Study Reported in Ref 9a



As we know, α-methylene- or alkylidene-γ-butyrolactone is a commonly observed structural unit in many biologically active natural products (Figure 1)[15] showing anticancer, antimalarial, antiviral, antibacterial, antifungal, and anti-inflammatory activities.[16,17] The exo-cyclic double bond is not only responsible for their interesting biological properties but also serves as a functional group for further manipulations in organic synthesis.[18] In this paper, we report our recent realization of such a concept.

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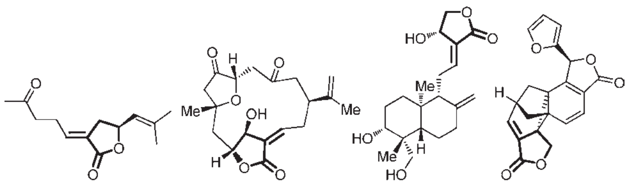
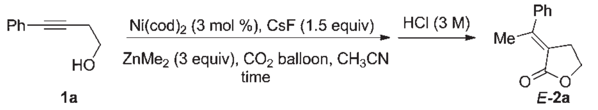


Heteroplexisolide E Scabrolide E Andrographolide Salvileucalin B

Figure 1. Natural products bearing the α-alkylidene-γ-butyrolactone substructure.

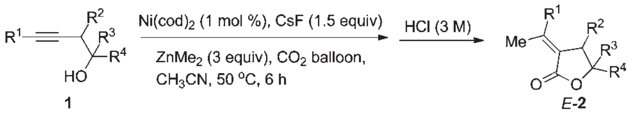
Table 1. Optimization of Conditions for Methyl-Lactonization of **1a**[a]



entry	Ni(cod)$_2$ (mol %)	time/h	temp/°C	yield of *E*-**2a** (%)[b]
1[c]	3	14	50	28
2[d]	3	2.0	50	57
3[e]	3	2.0	50	55
4	3	2.0	50	76
5	3	16	30	72
6	3	3.5	40	67
7	3	1.5	60	73
8	3	0.75	70	73
9[f]	3	2.0	50	54
10[g]	3	2.0	50	75
11[h]	3	2.0	50	71
12[i]	3	2.0	50	67
13	5	1.5	50	67
14	1	6.0	50	80
15[j]	0.25	17.3	50	78

[a] Reaction conditions: The reaction was carried out with 0.5 mmol of **1a**, the indicated amount of Ni(cod)$_2$, 1.5 equiv of CsF, 3 equiv of ZnMe$_2$ (1.20 M in toluene, 1.25 mL), and a balloon of CO$_2$ (about 1 L) in 3 mL of CH$_3$CN at the indicated temperature. [b] NMR yield. [c] DMSO was used as the solvent, and **1a** was recovered in 37% NMR yield. [d] DMF was used as the solvent. [e] NMP was used as the solvent. [f] 2 equiv of ZnMe$_2$ were used, and **1a** was recovered in 24% NMR yield. [g] 4 equiv of ZnMe$_2$ were used. [h] 3.0 equiv of CsF were used. [i] 1.0 equiv of CsF was used. [j] **1a** was recovered in 5% NMR yield.

Table 2. Synthesis of α-Alkylidene-γ-butyrolactones by Methyl-Lactionization of Homopropargylic Alcohols[a]



entry	R^1/R^2/R^3/R^4	yield of *E*-**2** (%)[b]
1	Ph/H/H/H (**1a**)	71 (*E*-**2a**)
2	*p*-MeOC$_6$H$_4$/H/H/H (**1b**)	82 (*E*-**2b**)
3	*p*-EtO$_2$CC$_6$H$_4$/H/H/H (**1c**)	71 (*E*-**2c**)
4	*p*-BrC$_6$H$_4$/H/H/H (**1d**)	52 (*E*-**2d**)
5	α-naphthyl/H/H/H (**1e**)	82 (*E*-**2e**)
6	2-thienyl/H/H/H (**1f**)	64 (*E*-**2f**)
7[c]	^{n}C$_5$H$_{11}$/H/H/H (**1g**)	61 (*E*-**2g**)
8	(*E*)-1-hexenyl/H/H/H (**1h**)	54 ((*E*, *E*)-**2h**)
9	Ph/Ph/H/H (**1i**)	77 (*E*-**2i**)
10	Ph/H/Me/H (**1j**)	74 (*E*-**2j**)
11	Ph/H/Et/H (**1k**)	78 (*E*-**2k**)
12	Ph/H/Ph/H (**1l**)	90 (*E*-**2l**)
13	*p*-MeOC$_6$H$_4$/H/Ph/Me (**1m**)	90 (*E*-**2m**)
14	Ph/H/Me/Me (**1n**)	68 (*E*-**2n**)

[a] Reaction conditions: The reaction was carried out with 0.5 mmol of **1**, 1 mol % of Ni(cod)$_2$ (1.4 mg, 0.005 mmol), 1.5 equiv of CsF (113.9 mg, 0.75 mmol), 3 equiv of ZnMe$_2$ (1.2 M in toluene, 1.25 mL), and a balloon of CO$_2$ (about 1 L) in 3 mL of CH$_3$CN at 50 °C. [b] Isolated yield. [c] 2 mol % of Ni(cod)$_2$ was used, and the reaction time was 13 h.

We initiated this study by using 4-phenyl-3-butynol **1a** as the starting point. Interestingly, the slow methyl-lactonization reaction of alkynol **1a** in DMSO[9a] did afford *E*-**2a**, albeit in 28% yield (Table 1, entry 1). However, the regio- and stereoselectivity are excellent. Optimization on the solvent (Table 1, entries 2–4), temperature (Table 1, entries 5–8), amount of ZnMe$_2$ (Table 1, entries 9–10), CsF (Table 1, entries 11–12), and catalyst loading (Table 1, entries 13–15) was then conducted with the optimal conditions being established as follows: homopropargylic alcohol **1a** was treated with 1 mol % Ni(cod)$_2$, 1.5 equiv of CsF, and 3.0 equiv of ZnMe$_2$ in CH$_3$CN in 50 °C to afford *E*-**2a**, indicating a dramatic solvent effect (Table 1, entry 14).[9a] It deserves to be mentioned that the lactonization was complete after the concentration of the crude product and the regioselectivity of methylative carboxylation of alkynols was very high (≥97:3, if any on the basis of the ^{1}H NMR analysis of the crude products after lactonization).

Next, the scope of the reaction was examined (Table 2). Aryl substituted homopropargylic alcohols gave moderate to excellent yields of *E*-**2** (Table 2, entries 1–6 and 9–14), whereas *n*-pentyl- and (*E*)-1-hexenyl-substituted alkynols produced moderate yields of *E*-**2g** and *E*-**2h** (Table 2, entries 7 and 8). Ester- (Table 2, entry 3), conjugated ene- (Table 2, entry 8), and *p*-Br-substituted phenyl (Table 2, entry 4) homopropargylic alcohols may all be successfully applied to afford *E*-**2c**, *E*-**2h**, and *E*-**2d** in moderate to good yields.

Furthermore, to our delight, the scope of substrates is not just limited to linear homopropargaylic alcohols; fused bicyclic α-alkylidene-γ-butyrolactones (*trans*,*E*)-**2o** could also be synthesized through this method efficiently (Scheme 4, eq 1). A similar strategy may also be applied to

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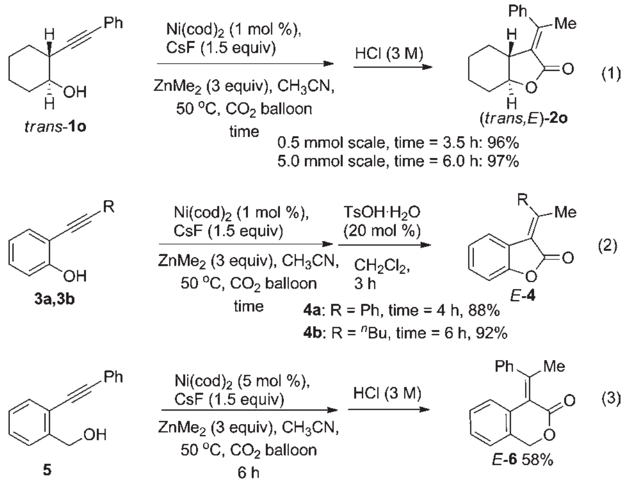
o-ethynylphenols **3a** and **3b** for the synthesis of 2(3*H*)-benzofuranones *E*-**4a** and *E*-**4b** in good to excellent yields (Scheme 4, eq 2). (*E*)-4-(1-Phenyl ethylidene)-3-isochromanone *E*-**6** was produced in 58% yield from (2-(phenylethynyl)phenyl)methanol (**5**) (Scheme 4, eq 3). To check the practicality, this reaction was scaled up to 1 g (5 mmol) of **1o** affording *E*-**2o** in 97% yield (Scheme 4, eq 1).

Scheme 4. Synthesis of Fused Lactones



In conclusion, we have successfully developed the first example of transition-metal-catalyzed highly regio- and stereoselective alkylative carboxylation of alkynes with CO_2 under the catalysis of just 1−2 mol % of Ni(cod)$_2$.[8] For the unique character of the directing OH group, we reasoned that the deprontonation of this functionality with the zinc reagent makes the interaction between the oxygen atom and Zn much stronger than that of tosylamide with Zn;[9a] thus, the OH group acts as a much better activating/directing group for the yield of CO_2 fixation as well as the regioselectivity (see Scheme 3). For the role of CsF, we reasoned that it is increasing the reactivity of the alkenyl zinc intermediate toward CO_2.[19] Because of the ready availability of various homopropargylic alcohols, excellent catalytic activity, high regio- and stereoselectivity, and good compatibility of various functional groups, this transformation will be a useful and practical method for highly selective synthesis of natural and unnatural lactones with synthetic or biological potentials, which opens new and efficient ways for CO_2 activation. However, it should be noted that such nonmethyl alkyl- or arylative is still a challenge.[20] Further studies in this area are being pursued in this laboratory.[21]

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Supporting Information Available. Spectroscopic data, general procedure, and $^1H/^{13}C$ NMR spectra of all the products. This material is available free of charge via the Internet at http://pubs.acs.org.

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[20] When $ZnEt_2$ was used instead of $ZnMe_2$ in the reaction with **1a** under the standard conditions presented in entry 14 of Table 1, only 20% of ethyl-carboxylation products were obtained together with 69% of the hydro-carboxylation products on the basis of ^1H NMR analysis.

[21] The terminal alkynes do not work well in this catalytic system.