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Catalysis |*Hot Paper*|

Cu-Catalyzed Alkylative Carboxylation of Ynamides with Dialkylzinc Reagents and Carbon Dioxide

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Abstract: Alkylative carboxylation of ynamides with CO_2 and dialkylzinc reagents using a N-heterocyclic carbene (NHC)–copper catalyst has been developed. A variety of ynamides, both cyclic and acyclic, undergo this transformation under mild conditions to afford the corresponding α,β-unsaturated carboxylic acids, which contain the α,β-dehydroamino acid skeleton. The present alkylative carboxylation formally consists of Cu-catalyzed carbozincation of ynamides with dialkylzinc reagents with the subsequent nucleophilic carboxylation of the resulting alkenylzinc species with CO_2. Dialkylzinc reagents bearing a β-hydrogen atom such as Et_2Zn and Bu_2Zn still afford the alkylated products despite the potential for β-hydride elimination. This protocol would be a desirable method for the synthesis of highly substituted α,β-dehydroamino acid derivatives due to its high regio- and stereoselectivity, simple one-pot procedure, and its use of CO_2 as a starting material.

Introduction

Carbon dioxide (CO_2) is a naturally abundant, inexpensive, and inherently renewable feed stock of low toxicity. Accordingly, its use as a C_1 building block for the synthesis of value-added chemicals has attracted increasing attention.[1] In particular, transition-metal-catalyzed or -promoted carboxylation reactions, which afford carboxylic acids or derivatives from CO_2, have been extensively studied in the past three decades.[1–6] Among these reactions, the carboxylation of alkynes with CO_2 is of great interest as various α,β-unsaturated carboxylic acids, which are valuable precursors in organic synthesis, can be synthesized efficiently. Previously, methods for the nickel-promoted hydrocarboxylation[7] and alkylative or arylative carboxylation[8] of alkynes as well as nickel-catalyzed [2+2+2] cycloaddition of alkynes with CO_2[9] have been developed. More recently, Ma and co-workers reported the nickel-catalyzed hydrogenative and methylative carboxylation of homopropargylic alcohols and related substrates.[10] In addition, Tsuji and co-workers have reported copper-catalyzed hydrogenative carboxylation,[11a] silacarboxylation,[11b] and double carboxylation of alkynes.[11c] Our group has recently shown that N-heterocyclic carbene (NHC) copper complexes can serve as excellent catalysts for the carboxylation of various organic substrates with CO_2.[5c,e,6h,7b,12,13] In this context, we have achieved the borocarboxylation of alkynes with this substrate, CO_2, and a diboron compound.[12] More recently, we developed the regio- and stereoselective formal methylative carboxylation and hydrocarboxylation of alkynes with CO_2, which afforded a variety of α,β-unsaturated carboxylic acids with well-controlled configurations.[13] Despite these recent advances, the substrate scope remains limited to relatively simple terminal- and internal alkynes. Exploration of the catalytic carboxylation of functionalized alkynes with CO_2 is therefore of obvious interest and importance.

Ynamides are a class of alkynes bearing an amide group directly connected to a C–C triple bond, which have been extensively studied as functionalized alkyne derivatives in various chemical transformations.[14] The carboxylation of ynamides with CO_2 can, in principle, provide structurally interesting nitrogen-substituted α,β-unsaturated carboxylic acid derivatives, that is, α,β-dehydro-α-amino acids (DHAAs). DHAAs are an important class of components found in several biologically active natural peptides.[15] Moreover, α,β-DHAAs and their analogues can serve as useful precursors in organic synthesis, such as in the formation of non-natural chiral α-amino acid derivatives through the catalytic enantioselective hydrogenation of α,β-DHAA esters.[15c,16,17] Therefore, much effort has been devoted to develop practical methods to synthesize α,β-DHAA derivatives. In this context, various methods, such as Erlenmyer synthesis, β-elimination from β-hydroxy-α-amino acid derivatives, condensation of α-ketocarboxylic acids with amines, and Hornor–Wadsworth–Emmons reaction of *N*-acyl dialkylphosphorylglycine esters with aldehydes, have been developed.[15c–g] However, procedures for the stereoselective synthesis of β,β′-disubstituted α,β-DHAA derivatives bearing

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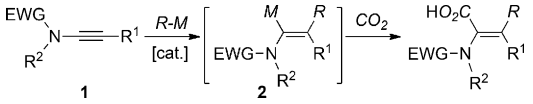
two different β-substituents have been very limited. Wandless and co-workers reported a method using a stereospecific β-elimination of cyclic sulfanamidates, which were readily prepared from β-hydroxy-α-amino acid derivatives and thionyl chloride.[18a] Although one of the β-substituents is limited to the trifluoromethyl group, (*Z*)-selective condensation of isocyanate with trifluoromethylkentones has been achieved.[18b] A method involving stereoselective β-halogenetion of β-monosubstituted DHAA derivatives along with the subsequent stereospecific Suzuki–Miyaura coupling with arylboronic acids has also been reported.[17c,18c] More recently, related methods using a combination of stereoselective tosylation of β-keto-α-amino acid derivatives followed by the subsequent Suzuki–Miyaura coupling have appeared.[17e] In this paper, we report our studies on the copper-catalyzed alkylative carboxylation of ynamides, which provide α,β-DHAA derivatives bearing two different β-substituents with well-controlled configuration.

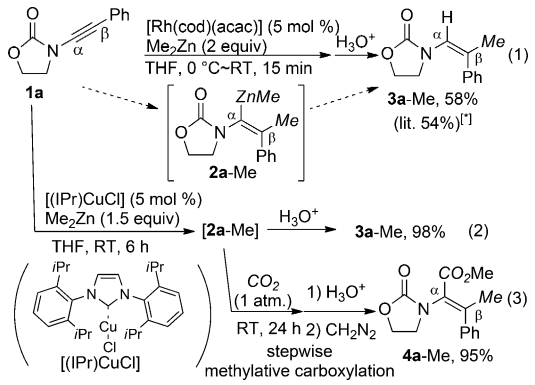
Results and Discussion

Our initial concept is illustrated in Scheme 1. We envisioned that alkylative carboxylation could be achieved by a combination of carbometalation of ynamide **1** with alkylmetal reagents (R–M) and the subsequent nucleophilic addition of the generated alkenylmetal species **2** to CO_2. We first screened alkylating reagents and reaction conditions suitable for the former carbometalation process.



Scheme 1. Carboxylation of ynamides by the carbometalation process.

Initially, we tried carbometalation of ynamide **1a** by using Me_3Al as the alkylating reagent as we have previously demonstrated for the formal methylative carboxylation of alkynes.[13] However, such attempts failed possibly due to the high reactivity of Me_3Al towards the carbonyl group of ynamide **1a** providing complex reaction mixtures. In contrast, the reaction of **1a** with Me_2Zn using a rhodium catalyst, which was developed by Lam and co-workers[19] proceeded rapidly; however, the yield of the desired product **3a**-Me was not sufficient to apply to the subsequent carboxylation process (Scheme 2, Eq. (1)). Fortunately, [(IPr)CuCl] (IPr = 1,3-bis(2,6-diisopropenyl)imidazol-2-ylidene) serves as an excellent catalyst for this carbozincation process under mild conditions. In the presence of [(IPr)CuCl] (5 mol%), the reaction of ynamide **1a** with Me_2Zn (1.5 equiv) in THF at room temperature occurred smoothly in six hours to afford enamide **3a**-Me in 98% yield following protonolysis of the corresponding alkenylzinc species, **2a**-Me (Scheme 2, Eq. (2)). In addition, exposure of a crude reaction mixture containing **2a**-Me to CO_2 (1 atm.) allowed the isolation of the carboxylated product **4a**-Me in 95% yield after hydrolysis and subsequent diazomethane esterification (Scheme 2, Eq. (3)). NOE experiments on **4a**-Me confirmed that the double bond



Scheme 2. Methylzincation and sequential methylative carboxylation of **1a**.

has a (*Z*)-configuration and that the methyl group is introduced to the β-position of **1a** (Figure 1), indicating a retention of configuration upon carboxylation of **2a**-Me.

Encouraged by these results, we next examined the alkylative carboxylation of ynamide **1a** in a one-pot manner, that is, by mixing the substrate, catalyst, Me_2Zn, and CO_2 together at once (Table 1). To our delight, the one-pot reaction of **1a** with Me_2Zn (1.5 equiv) and CO_2 (1 atm.) in the presence of [(IPr)CuCl] (5 mol%) proceeded smoothly and cleanly at room temperature to provide the same carboxylated product (**4a**-Me) in 86% yield (Table 1, entry 1). When the reaction was repeated at 50 °C, the yield of **4a**-Me was improved to 93% (entry 2). The use of CuCl or [Rh(cod)(acac)] (acac = acetylacetonate; cod = 1,5-cyclooctadiene) as the precatalyst resulted in significantly lower yields (entries 3 and 4). The [(IPr)CuCl] catalyst

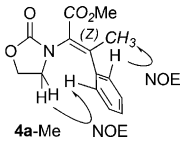
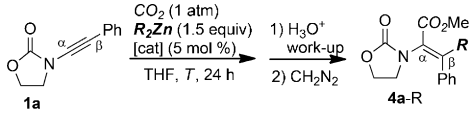


Figure 1. ^{1}H NMR spectroscopic NOE studies on **4a**-Me.

Table 1. One-pot alkylative carboxylation of **1a** under various conditions.



1a 4a-R

Entry	Cat.	R_2Zn	*T* [°C]	Product, **4a**-R (yield [%])[a]
1	[(IPr)CuCl]	Me_2Zn	RT	**4a**-Me (86%)
2	[(IPr)CuCl]	Me_2Zn	50	**4a**-Me (93%)
3	CuCl	Me_2Zn	RT	**4a**-Me (52%)
4	[Rh(cod)(acac)]	Me_2Zn	RT	**4a**-Me (38%)
5	[(IPr)CuCl]	Et_2Zn	50	**4a**-Et (92%)
6	[(IPr)CuCl]	Bu_2Zn	50	**4a**-Bu (92%)

[a] Yield of isolated product.

may also play a role in accelerating the nucleophilic addition of the alkenylzinc intermediate, such as **2a**-Me, toward CO_2.

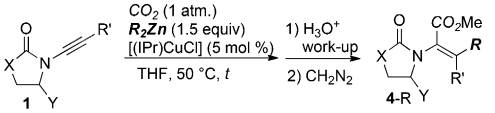
With the optimized reaction conditions in hand (Table 1, entry 2), the scope of dialkylzinc reagents was examined using ynamide **1a** as the substrate (entries 5 and 6). When dialkylzinc reagents bearing a β-hydrogen atom are used, the corresponding alkylated product is still formed with no evidence of β-hydride elimination. For example, when Et_2Zn was used in the alkylative carboxylation of **1a**, the desired ethylated product **4a**-Et was obtained in 92% yield (entry 5). This result contrasts the previously reported carboxylation of alkynes using Et_2Zn in which β-hydride elimination takes place to provide only hydrogenative carboxylation products.[10a,c] Similarly, when Bu_2Zn is used instead under similar conditions, the butylated carboxylation product **4a**-Bu could be obtained in 93% yield (Table 1, entry 6). As seen for Me_2Zn, both reactions took place in a *syn*-selective manner introducing the alkyl group to the β-position of the ynamides and the carboxyl group to the α-position, regioselectively.

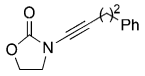
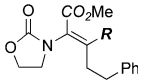
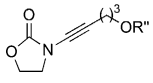
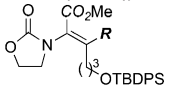
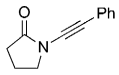
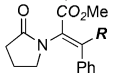
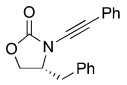
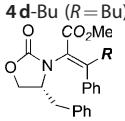
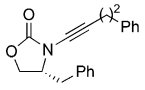
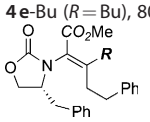
Next, the scope of ynamide substrates was explored (Table 2). Ynamides bearing an alkyl substituent (Table 2, entries 1–9) were found to be excellent substrates in this catalytic process. The reaction of ynamide **1b** bearing a phenethyl substituent with Me_2Zn and CO_2 afforded **4b**-Me in 96% yield (entry 1). Both Et_2Zn and Bu_2Zn could also be used to give **4b**-Et (96%) and **4b**-Bu (88%), respectively (entries 2 and 3). Substrates bearing a tethered siloxy group (TBDPSO-, TBDPS = *t*BuPh$_2$Si) could be tolerated giving **4c**-Me in 70% yield, though 16% of **1c** was also recovered (entry 4). When the methylative carboxylation of **1c** was carried out in a stepwise manner, that is, performing the methylzincation (50 °C, 24 hr) under a N_2 atmosphere before the subsequent carboxylation process (50 °C, 24 hr), the yield of isolated product could be improved to 92% (entry 5). In this regard, the yield of the one-pot procedure could be improved by increasing the number of equivalents of the dialkylzinc reagent (entries 6 and 7). Hence, when two equivalents of Me_2Zn were used (50 °C, 48 h), the yield of **4c**-Me was slightly improved (74%, entry 6); however, when the reaction was carried out with three equivalents of Me_2Zn, the desired product was obtained in 96% yield (entry 7). In contrast, the alkylative carboxylation of **1c** by using Et_2Zn and Bu_2Zn proceeded smoothly when using the one-pot method even with 1.5 equivalents of the dialkylzinc reagents to give **4c**-Et and **4c**-Bu in high yields (entries 8 and 9). These results suggest that coordination of the sterically less hindered Me_2Zn to the siloxy group interferes with the methylzincation process, leading to the recovery of unreacted starting material.

Despite bearing relatively acidic protons next to the carbonyl group of its pyrrolidine-2-one moiety, ynamide **1d** cleanly underwent alkylative carboxylation with Me_2Zn, Et_2Zn, and Bu_2Zn under the standard one-pot conditions, to give **4d**-Me (83%), **4d**-Et (83%), and **4d**-Bu (85%), respectively (Table 2, entries 10–12). Ynamides **1e** and **1f** bearing Evans' chiral oxazolidin-2-one moiety were also suitable substrates in this reaction; the desired products **4e**-Me, **4e**-Et, and **4e**-Bu, along with **4f**-Me, **4f**-Et, and **4f**-Bu were obtained in high yields, (80–97%, entries 13–18). However, prolonged reaction times (48 h) were often required, possibly due to the steric hindrance imposed by the proximal benzyl group. These products have potential applications in asymmetric reactions due to the presence of a chiral auxiliary moiety.[23]

Acyclic *tert*-butoxycarbonyl (Boc)-protected ynamides also undergo alkalytive carboxylation. When a substrate bearing a benzyl group on the nitrogen atom is used, such as **1g**, the reaction is strongly dependant on the nature of the dialkylzinc reagents. For example, when Me_2Zn is used under the standard one-pot reaction conditions, the expected product was not observed and 80% of the starting material **1g** was recovered. A similar result occurred when the reaction was repeated under the sequential methylzincation/carboxylation protocol

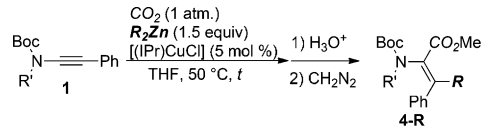
Table 2. One-pot alkylative carboxylation of various cyclic ynamides.

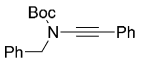
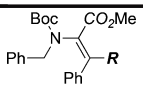
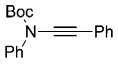
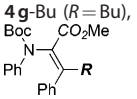


Entry	Ynamide **1**	R_2Zn	*T* [h]	Product **4**, yield[a]
				
1	**1b**	Me_2Zn	19	**4b**-Me (*R* = Me), 96%
2	**1b**	Et_2Zn	24	**4b**-Et (*R* = Et), 96%
3	**1b**	Bu_2Zn	24	**4b**-Bu (*R* = Bu), 88%
				
4	**1c** (R″ = TBDPS)	Me_2Zn	19	**4c**-Me (*R* = Me), 70%[b]
5[d]	**1c**	Me_2Zn	48[c]	**4c**-Me, 92%
6	**1c**	Me_2Zn[d]	48	**4c**-Me, 74%
7	**1c**	Me_2Zn[e]	48	**4c**-Me, 96%
8	**1c**	Et_2Zn	24	**4c**-Et (*R* = Et), 97%
9	**1c**	Bu_2Zn	30	**4c**-Bu (*R* = Bu), 94%
				
10	**1d**	Me_2Zn	24	**4d**-Me (*R* = Me), 83%
11	**1d**	Et_2Zn	24	**4d**-Et (*R* = Et), 83%
12	**1d**	Bu_2Zn	20	**4d**-Bu (*R* = Bu), 85%
				
13	**1e**	Me_2Zn	48[f]	**4e**-Me (*R* = Me), 97%
14	**1e**	Et_2Zn	48[f]	**4e**-Et (*R* = Et), 90%
15	**1e**	Bu_2Zn	48[f]	**4e**-Bu (*R* = Bu), 80%
				
16	**1f**	Me_2Zn	48[e]	**4f**-Me (*R* = Me), 93%
17	**1f**	Et_2Zn	24	**4f**-Et (*R* = Et), 95%
18	**1f**	Bu_2Zn	24	**4f**-Bu (*R* = Bu), 92%

[a] Yield of isolated product. [b] 16% of ynamide **1c** was recovered. [c] The reaction was carried out in a stepwise manner; the reaction of **1c** with Me_2Zn (1.5 equiv) was performed at 50 °C for 24 h, and then the resulting mixture was treated with CO_2 (1 atm.) for 24 h. [d] 2 equiv of Me_2Zn was used. [e] 3 equiv of Me_2Zn was used. [f] After 24 h, the flask was refilled with CO_2.

Table 3. Alkylative carboxylation of acyclic ynamides.

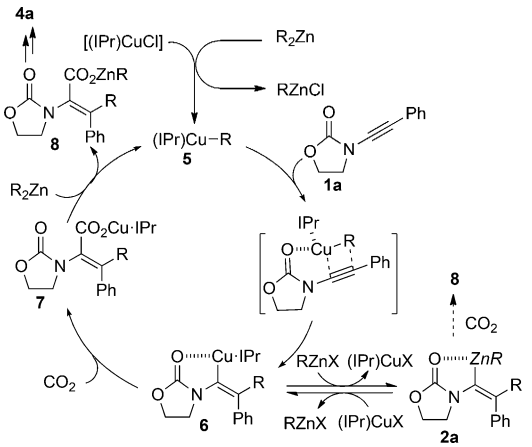


Entry	Ynamide **1**	R_2Zn	*t* [h]	Product **4**, yield[a]
				
1	**1g**	Me_2Zn	48	–[b]
2	**1g**	Et_2Zn	48	**4g**-Et (*R* = Et), 76%
3	**1g**	Bu_2Zn	24	**4g**-Bu (*R* = Bu), 75%
				
4	**1h**	Me_2Zn	48	–[c]
5	**1h**	Et_2Zn	30	**4h**-Et (*R* = Et), 79%
6	**1h**	Bu_2Zn	36	**4h**-Bu (*R* = Bu), 83%

[a] Yield of isolated product. [b] 80% of **1g** was recovered. [c] 80% of **1h** was recovered.

indicating that methylzincation is not occurring under these conditions. In contrast to these results, ethylative and butylative carboxylation of **1g** proceeds smoothly under the one-pot protocol to give the desired products **4g**-Et (76%) and **4g**-Bu (75%) in good yields (Table 3, entries 2 and 3). Similarly, ynamide **1h** undergoes alkylative carboxylation under similar conditions when Et_2Zn or Bu_2Zn are used to give **4h**-Et (79%) or **4h**-Bu (83%) (entries 5 and 6), whilst the reaction using Me_2Zn only returned unreacted **1h** (entry 4). At present, the reason for the differing reactivity when Me_2Zn is used is unclear. However, coordination of the sterically unsaturated Me_2Zn to the Boc group may hinder methylzincation in a similar manner as that described for **1c**.

A possible reaction mechanism for the alkylative carboxylation of **1a** is illustrated in Scheme 3. Transmetallation between [(IPr)CuCl] and a dialkylzinc reagent would form an alkylcopper species, **5**. The carbonyl group on the ynamide moiety would act as a directing group in the subsequent carbocupration process, forming the alkenylcopper species **6** in a regioselective manner.[19–21] Transmetalation between **6** and an alkylzinc species would provide an alkenylzinc species **2a**, which could regenerate **6** by a reversible process. Although a pathway through direct nucleophilic carboxylation of **2a** cannot be ruled out,[3c] we currently speculate that carboxylation would take place by CO_2 insertion into the Cu–C bond in the alkenylcopper species **6** to afford the corresponding copper carboxylate **7**. Finally, transmetalation between the copper carboxylate **7** and the dialkylzinc reagent would provide zinc carboxylate **8** regenerating alkylcopper species **5**.



Scheme 3. Possible catalytic cycle.

Conclusion

In summary, we have developed a highly efficient NHC–Cu-catalyzed regioselective alkylative carboxylation of ynamides using CO_2 and dialkylzinc reagents. This three-component coupling reaction can be carried out easily in one pot under mild conditions to form various nonsymmetric β-β′-disubstituted α,β-dehydroamino acid derivatives in good to high yields. The reaction appears to proceed by the Cu-catalyzed carbozincation of ynamides and alkenyl copper species may play an important role in facilitating the subsequent carboxylation process. In view of the high regio- and stereoselectivity for the formations of nonsymmetrical β,β′-disubstituted α, β-dehydro-α-amino acid derivatives with well-defined configurations, a simple one-pot reaction operation, and the use of CO_2 as a starting material, this protocol is a practically useful and attractive method for use in synthetic organic chemistry.

Experimental Section

Typical Procedure: Synthesis of methyl (2*Z*)-2-(2-oxooxazolidin-3-yl)-3-phenylbut-2-enoate (4a-Me) (Table 1, entry 2)

In a Schlenk flask equipped with a PTFE J. Young valve and a magnetic stirring bar, [(IPr)CuCl] (6.5 mg, 0.013 mmol) and ynamide **1a** (50 mg, 0.27 mmol) were added and dissolved in THF (2.7 mL). A solution of Me_2Zn (2.0 M in toluene, 200 μL, 0.40 mmol) was added to this mixture at 0 °C. The flask was evacuated and CO_2 was quickly introduced. The same gas-substitution procedure was repeated several times before the flask was sealed. After the mixture had been stirred at 50 °C for 24 h, it was hydrolyzed with a 10% aqueous solution of HCl at 0 °C. The organic materials were extracted into ethyl acetate and the resulting extract was washed with water and brine, and then dried over anhydrous Na_2SO_4. After evaporation of the solvents, the residue was dissolved in AcOEt (1 mL) and treated with CH_2N_2 in Et_2O. The reaction mixture was worked-up according to the standard procedure. The obtained crude material was purified by silica gel column chromatography (hexane/EtOAc = 2:1) to afford ester **4a**-Me as a colorless solid (68 mg, 93%).

Spectral data for 4a-Me

IR (in $CHCl_3$): $\tilde{\nu}$ = 3040, 3030, 3020, 3013, 3017, 1725 (br), 1724, 1629, 1478 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.32–7.41 (m, 3H), 7.26–7.30 (m, 2H), 4.08 (t, *J* = 7.8 Hz, 2H), 3.82 (s, 3H), 3.27 (t, *J* = 7.8 Hz, 2H), 2.49 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.7, 157.7, 153.4, 140.5, 128.4, 128.4, 126.4, 123.2, 62.6, 52.1, 45.7,

21.7 ppm; HRMS (ESI): *m/z*: calcd for $C_{14}H_{15}NNaO_4$: 214.0893 $[M+Na]^+$; found: 214.0891.

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