Organic Letters

Letter

pubs.acs.org/OrgLett

Copper-Catalyzed Stereodefined Construction of Acrylic Acid Derivatives from Terminal Alkynes via CO_2 Insertion

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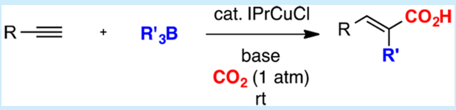
Supporting Information

ABSTRACT: IPrCuCl catalyzes the CO_2 insertion reaction undergone by a dialkylvinylborane intermediate derived from alkynyltrialkylborate by a 1,2-alkyl group migration to afford α-alkyl acrylic acids with excellent regio- and stereoselectivities.

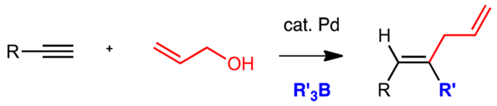


CO_2 fixation is among the most straightforward synthetic methodologies for the construction of carboxylic acids.[1] Specifically, Cu- and Ni-catalyzed multicomponent coupling reactions with alkynes, organoaluminum, or organozinc regents under a CO_2 atmosphere that provide β-substituted acrylic acids are promising strategies for efficient modern organic synthesis.[2] CO_2 insertion into the unsaturation in enynes,[3] dienes,[4] allenes,[5] and allylating substrates[6] is utilized for the convenient and selective formation of unsaturated carboxylic acids. Notably, among direct C−C bond transformations, significant attention has been paid to the activation of sp^2 carbon atoms via transition-metal-catalyzed C−H activation and the incorporation of CO_2 to form aromatic carboxylic acids[7] and unsaturated carboxylic acids in recent years.[8]

Alkenyl organoboranes are important and useful key intermediates in organic synthesis, especially cross-coupling reactions.[9] In general, alkenyl organoboranes are prepared from hydroborations of alkynes with organoboranes and bis(pinacolate)diborane.[10] Although some examples of the formation of alkenyl organoboranes via alkynyl ate comlexes have been reported so far,[11] synthetic utilities of alkynylborates have so far been limited.[12]

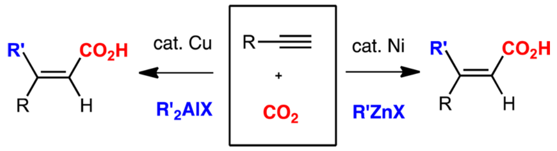
From this point of view, we previously developed a Pd-catalyzed regio- and stereoselective three-component coupling reaction of a terminal alkyne, a trialkylborane, and allylic alcohols to provide trisubstituted alkenes involving alkynyl ate complexes (Scheme 1).[13] In this case, the terminal alkyne reacted with the trialkylborane to give the alkynyltrialkylborate, which was followed by the 1,2-alkyl migration process; then the transmetalation of alkenylborane with π-allylpalladium species provided the stereodefined trisubstituted alkenes. Furthermore, similar multicomponent coupling reactions involving conjugated dienes with terminal alkynes in the presence of a Pd catalyst and Et_3N as a base could be applicable for the tandem dimerization of conjugated dienes to form 1,4,9-decatrienes.[14]

Scheme 1. Pd-Catalyzed Stereoselective Allylation of Terminal Alkyne To Form 1,4-Pentadiene



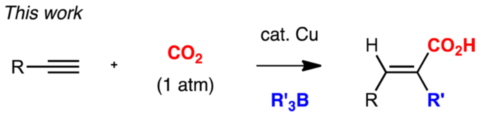
Based on the results of these multicomponent coupling reactions, we envisaged the use of CO_2 as an electrophilic reagent instead of π-allylpalladium in the presence of trialkylboranes and transition-metal catalysts. We could thus succeed in the three-component coupling reaction of an alkyne, a trialkylborane, and CO_2 to yield α-substituted acrylic acids as a single product. In contrast to the previously reported results of Ni- and Cu-catalyzed coupling reactions with terminal alkynes and organometalloids such as organoaluminum and organozinc reagents with CO_2 (Scheme 2), the present coupling reaction offers regioselectivity. Herein, we discuss the scope and limitations of Cu-catalyzed highly regio- and stereoselective formations of α-substituted acrylic acids by coupling reactions of terminal alkynes and trialkylboranes under CO_2 at atmospheric pressure through the 1,2-alkyl migration of alkynyltrialkylborate as a key intermediate (Scheme 3).

Scheme 2. CO_2 Insertion into Terminal Alkyne Using Organozinc and Organoaluminum



The reaction was carried out in the presence of 0.05 mmol of a CuCl catalyst with various carbene ligands, 2.0 mmol of base,

Scheme 3. Cu-Catalyzed CO_2 Insertion into Terminal Alkyne Using Organoboranes

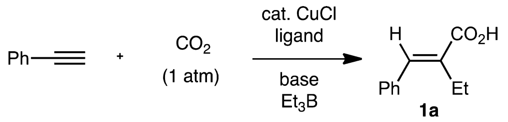


Received: December 27, 2016

DOI: 10.1021/acs.orglett.6b03860
Org. Lett. XXXX, XXX, XXX−XXX

and 1.0 mmol of Et_3B at room temperature under CO_2 atmosphere for 24 h. The crude mixture was subjected to silica gel column chromatography to obtain the corresponding acrylic acid as a single product. The results summarized in Table 1 indicate that the choice of base dramatically affected the product yields. *t*-BuOK provided the desired product **1a** in 38% yield (entry 1, Table 1). In contrast, similar sodium and lithium *tert*-butoxide bases were ineffective for the coupling reactions, and the expected product was not obtained at all (entries 2 and 3, Table 1). Low product yields were observed according to the low conversion of terminal alkynes, and (*Z*)-1-phenyl-1-butene was generated as a byproduct. The use of EtOK as a base provided the desired product in 50% yield (entry 4). Further inspection of the bases revealed that MeOK was the most efficient base for the three-component coupling reactions. In particular, in the presence of 3.0 mmol of Et_3B and 2.0 mmol of MeOK, the reaction mixture resulted in the formation of product **1a** in the highest yield in 1,4-dioxane. Diminishing the amount of base was ineffective, and other solvents such as THF, DMA, toluene, and hexane were not beneficial (entries 7−10, Table 1). Although various kinds of carbene ligands besides IPr were investigated, such as ^{Cl}IPr, ^{Me}IPr, IPr*, and IMes (entries 11−14, Table 1), the reaction with a combination of the IPr ligand and MeOK in dioxane provided the best results. Product **1a** was obtained as a single isomer with almost complete regio- and stereoselectivities.[15]

Table 1. Cu-Catalyzed CO_2 Insertion into Phenylacetylene[a]

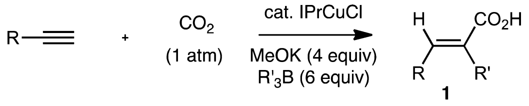


entry	catalyst	base	solvent	yield (%)
1	IPrCuCl	*t*-BuOK	dioxane	38 (*E* only)
2	IPrCuCl	*t*-BuONa	dioxane	NR
3	IPrCuCl	*t*-BuOLi	dioxane	NR
4	IPrCuCl	EtOK	dioxane	50 (*E* only)
5	IPrCuCl	MeOK	dioxane	61 (*E* only)
6[b]	IPrCuCl	MeOK	dioxane	78 (*E* only)
7[b]	IPrCuCl	MeOK	THF	61 (*E* only)
8[b]	IPrCuCl	MeOK	DMA	NR
9[b]	IPrCuCl	MeOK	toluene	57 (*E* only)
10[b]	IPrCuCl	MeOK	hexane	66 (*E* only)
11[b]	^{Cl}IPrCuCl	MeOK	dioxane	70 (*E* only)
12[b]	^{Me}IPrCuCl	MeOK	dioxane	73 (*E* only)
13[b]	IPr*CuCl	MeOK	dioxane	trace
14[b]	IMesCuCl	MeOK	dioxane	NR

[a] Entries 1−5: phenylacetylene (0.5 mmol), base (2.0 mmol), and Et_3B (1.0 mmol) in the presence of CuCl catalyst (0.05 mmol) in dioxane (3 mL) at rt for 24 h under CO_2 (1 atm). [b] Entries 6−14: phenylacetylene (0.5 mmol), base (2.0 mmol), and Et_3B (3.0 mmol) in the presence of CuCl catalyst (0.05 mmol) in solvent (3 mL) at rt for 24 h under CO_2 (1 atm).

Next, we investigated the reactions of various kinds of terminal alkynes and organoboranes (Table 2). Irrespective of the kinds of substituents on the aromatic terminal alkynes, a similar coupling reaction proceeded in moderate to good yields under optimized conditions, as elucidated in Table 1. *p*-Methoxy- and *o*-methoxyphenyl-substituted alkynes resulted in the formation of *α*-ethyl-*β*-aryl acrylic acids **1b** and **1c** as a single isomer in moderate to good yields, and the CO_2 insertion reaction proceeded with high *E*-stereoselectivity (entries 2 and 3, Table 2). Halogenated aromatic compounds could participate in the reaction to form the desired products **1e** and **1f** as (*E*)-isomers (entry 5 and 6, Table 2). Although heteroaromatic substitutents took part in the coupling reactions as well as phenyl groups, alkylated substituents were not suitable for the reactions.[16]

Table 2. Cu-Catalyzed CO_2 Insertion into Terminal Acetylene[a]



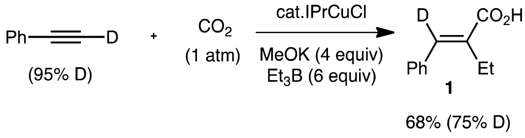
entry	alkyne R	R'_3B	yield of **1** (%)
1	Ph	Et_3B	**1a** (78)
2	*p*-OMePh	Et_3B	**1b** (62)
3	*o*-OMePh	Et_3B	**1c** (73)
4	*p*-C_5H_{11}Ph	Et_3B	**1d** (56)
5	*p*-ClPh	Et_3B	**1e** (68)
6	*o*-ClPh	Et_3B	**1f** (59)
7	2,4,5-MePh	Et_3B	**1g** (83)
8	2-thiophene-yl	Et_3B	**1h** (53)
9	CH_2OBn	Et_3B	**1i** (24)
10	Ph	*n*-Bu_3B	**1j** (43)
11	Ph	(*t*-$BuC_2H_4)_3B$	**1k** (23)

[a] Conditions: alkyne (0.5 mmol), MeOK (2.0 mmol), and organoborane (3.0 mmol) in the presence of IPrCuCl (0.05 mmol) in 1,4-dioxane (3 mL) at rt for 24 h under CO_2 (1 atm).

As in the case of tri-*n*-butylborane, a similar coupling reaction proceeded to form product **1j** as a single isomer as well as triethylborane (entry 10, Table 2). Tris(3,3-dimethylbutyl)-borane, which was prepared via the hydroboration of 3,3-dimethyl-1-butene, could take part in the coupling reaction to afford the desired product **1k** (entry 11, Table 2). Therefore, the three-component coupling reaction with terminal alkynes under CO_2 could be achieved not only with commercially available trialkylboranes but also with organoboranes prepared from hydroboration of alkenes for the synthesis of stereo-defined *α*,*β*-substituted acrylic acid derivatives.[17]

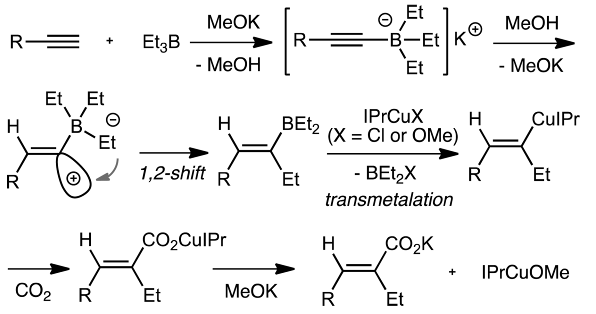
To investigate the mechanistic aspects of the catalytic process, a deuterium-labeling experiment was performed. 1-Deuteriophenylacetylene (95% D) underwent the coupling reaction via treatment with MeOK and Et_3B in the presence of IPrCuCl as the catalyst in 1,4-dioxane under CO_2 atmosphere (Scheme 4). The product incorporated a deuterium atom at the vinylic position, affording (75% D) in a reasonable yield. Although the reason for the incomplete incorporation of deuterium is currently unclear, this result suggests that the origin of the proton source at the vinylic position might be attributed to the acetylenic terminal proton atom, giving rise to the trisubstituted alkenes with high regio- and stereo-selectivities.[18]

Scheme 4. Deuterium-Labeling Experiment for Cu-Catalyzed CO_2 Insertion of Phenylacetylene-*d*



Although it is premature to speculate on the reaction mechanism based on the deuterium-labeling experiment, a plausible reaction mechanism with terminal alkyne, Et_3B, and CO_2 might be proposed, as illustrated in Scheme 5. At first, the acetylide was generated from the abstraction of the terminal proton of alkyne by MeOK as a base to react with Et_3B, thus providing alkynyltriethylborate.[19] This alkynyltriethylborate ate complex then underwent protonation at the β-carbon position to yield a vinylic cation intermediate, which then experienced [1,2] an ethyl group migration reaction to the empty p orbital of the vinylic carbocation with excellent stereoselectivity to form the vinyldiethylborane intermediate.[11] Then, transmetalation with a carbene−copper species affords a vinylcopper intermediate. The nucleophilic addition of vinylcopper to CO_2 might have yielded a carboxylate salt, which then reacted with MeOK to regenerate the carbene−copper species.

Scheme 5. Plausible Reaction Mechanism for Cu-Catalyzed CO_2 Insertion into Terminal Alkynes



In summary, a Cu-catalyzed CO_2 insertion reaction involving a dialkylvinylborane intermediate derived from alkynyltrialkylborate by a 1,2-alkyl group migration was carried out to afford α-alkylated acrylic acids with excellent regio- and stereoselectivities. This CO_2 insertion is in contrast to the previously developed methods utilizing Cu- and Ni-catalyzed multicomponent coupling, which prepared α-substituted acrylic acids from the terminal alkynes.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b03860.

Experimental procedures, characterization data, NMR spectra, an dX-ray data for **1a** (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We gratefully acknowledge funding from a Grant-in-Aid for Scientific Research (B) (26288052) from the Ministry of Education, Culture, Sports and Technology (MEXT), Japan.

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(15) CCDC 1517933 contains the supplementary crystallographic data for **1a**. This data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

(16) Under similar conditions, 1-octyne could not provide the desired products at all, irrespective of the kinds of bases. Although it is premature to rationalize the reason nonarylated terminal alkynes could not participate in the expected reactions, the exquisite balance of the acidity of alkynes and the basicity of bases seems to be most effective for the protonation process and regeneration of Cu active species.

(17) *n*-Octyl-9-BBN and Ph-9-BBN could not work as alkylating and arylating agents, respectively. The present reaction is limited to the use of trialkylboranes.

(18) It has been reported the protonation of lithium or sodium alkynyltrialkylborates provided the *E*/*Z* mixture of alkenylboranes; see: (a) Miyaura, N.; Yoshinari, T.; Itoh, M.; Suzuki, A. *Tetrahedron Lett.* **1974**, *15*, 2961−2964. (b) Binger, P.; Köster, R. *Tetrahedron Lett.* **1965**, *6*, 1901−1906. In the present case, the products were obtained with excellent stereoselectivity. This highly selective process might be attributed to Cu-catalyzed stereocontrolled protonation with methanol.

(19) Cu catalyst might act as a promoter for the formation of alkynyltrialkylborates from terminal alkynes and trialkylboranes; IPrCuCl seems to serve as a Lewis acid to enhance the acidity of terminal alkynes via the π-alkyne complex. A similar assumption of the Cu-catalyzed enhancement of the acidity of terminal alkyne has been reported; see: Gooßen, L. J.; Rodriguez, N.; Manjolinho, F.; Lange, P. P. *Adv. Synth. Catal.* **2010**, *352*, 2913−2917.