Bismuth-catalyzed Intramolecular Hydro-oxycarbonylation of Alkynes

Kimihiro Komeyama,* Keita Takahashi, and Ken Takaki*
Department of Chemistry and Chemical Engineering, Graduate School of Engineering, Hiroshima University,
1-4-1 Kagamiyama, Higashi-Hiroshima 739-8527

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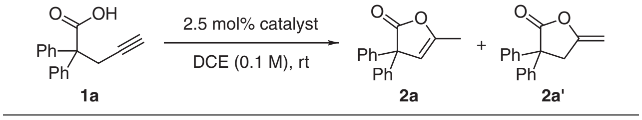
$Bi(OTf)_3$ was found to be a good catalyst for intramolecular addition of carboxylic acids to alkynes (hydro-oxycarbonylation), which afforded the corresponding 5- and 6-membered lactones in moderate to good yields under mild conditions.

Heterocycles are common structures of a wide range of natural and biological active molecules. Therefore, the development of new and efficient methodologies for the synthesis of heterocyclic compounds is of central importance in organic synthesis.[1] Of the attractive process recently developed, transition-metal-catalyzed addition of the heteroatom–hydrogen bond (X–H) across the carbon–carbon multiple bond could be recognized as the most atom-economical method.[2] However, due to a number of inherent factors including low reactivity of X–H bond and alkyne, effective transition-metal-catalyzed protocols for the transformation with heteroatom nucleophiles remain scarce.

Previously, we have demonstrated that environmentally benign iron salts were effective catalysts for the intramolecular hetero-functionalization of unactivated olefins with amines, alcohols, and carboxylic acids to yield the corresponding heterocycles, wherein the iron could activate both the heteroatoms and the carbon–carbon double bonds in a dual mode.[3] However, the catalyst showed lower activity for the addition to alkynes. Thus, we searched other catalysts, and then discovered a high activity of bismuth catalyst for the alkyne-functionalization. Herein, we report a new method for intramolecular cyclization of alkynyl carboxylic acids by use of $Bi(OTf)_3$ catalyst.

As an initial investigation, we examined a catalytic ability of various transition metals for the cyclization of 2,2-diphenylpent-4-ynoic acid (**1a**) as a model substrate. These results are summarized in Table 1. When the acid **1a** was treated with an early transition metal catalyst like $Sc(OTf)_3$ at room temperature in dichloroethane (DCE), no consumption of the substrate was observed (Entry 1). Late transition metals such as $PdCl_2$ and $PtCl_2$ were greatly effective for the cyclization (Entries 2 and 3), especially, $PtCl_2$ exclusively afforded 5-membered vinylidene–lactone **2a**′ in excellent yield (Entry 3). $Ni(OTf)_2$ and $Cu(OTf)_2$ showed a sluggish susceptibility for the reaction to leave most of **1a** unchanged (Entries 4 and 5). In sharp contrast, different behavior was observed when the borderline-metal catalysts,[4] $Fe(OTf)_3$ and $Bi(OTf)_3$, were employed in the cyclization. Thus, these catalysts exhibited a good to high catalytic performance and a drastic change of the product structure: exclusive formation of *endo*-lactone **2a** (Entries 6 and 7).[5] Utilization of the bismuth catalyst particularly made the cyclization complete quickly (0.5 h). The counter ion of the bismuth catalysts also had effect on the reaction. With ClO_4 and BF_4, the reactions were less effective than OTf (Entries 7–9). Of course, the cyclization did not proceed without these catalysts.

Table 1. Screening of catalysts for hydro-oxycarbonylation of **1a**



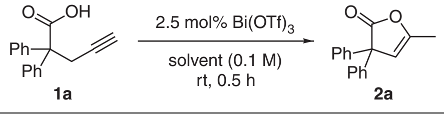
Entry	Catalyst	Time/h	Yield (**2a**/**2a**′)/%[a]	Conv./%[a]
1	$Sc(OTf)_3$	24	no reaction	—
2	$PdCl_2$	22	67 (0/100)	67
3	$PtCl_2$	9	95 (0/100)	100
4	$Ni(OTf)_2$	24	10 (0/100)	16
5	$Cu(OTf)_2$	24	9 (0/100)	9
6	$Fe(OTf)_3$	24	45 (100/0)	100
7	$Bi(OTf)_3$	0.5	83 (100/0)	100
8	$Bi(ClO_4)_3$	0.5	79 (100/0)	100
9	$Bi(BF_4)_3$	0.5	52 (100/0)	100

[a]Determined by ^1H NMR.

The catalytic activity strongly depended on the solvent used (Table 2). In non-polar solvents, the bismuth catalyst showed a high catalytic performance. That is, **2a** was given in high yield in DCE and toluene, whereas polar solvents such as acetonitrile and 1,4-dioxane resulted in low or negligible conversions of the substrate, respectively. Most of the substrate **1a** remained unchanged in hexane solvent because of its insolubility.

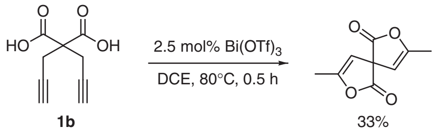
Other $Bi(OTf)_3$-catalyzed cyclizations of alkynyl carboxylic acids to lactones succeeded as shown in eqs 1–3. The acid **1b**, bearing two terminal alkynyl and carboxylic moieties in a molecule, converted directly into spiro-cyclic lactone in 33% yield (eq 1). Although the transformation of the long chain acid **1c** proceeded smoothly to give 6-membered lactone via exo-cyclization mode in 91% NMR yield, a part of the product was spontaneously hydrated by a workup procedure to give the keto-carboxylic acid in 22% isolated yield (eq 2). It is remarkable that the Bi catalyst took part in the cyclization of alkyne rather than that of olefin (eq 3).[6]

Table 2. Solvent effect for $Bi(OTf)_3$-catalyzed hydro-oxycarbonylation

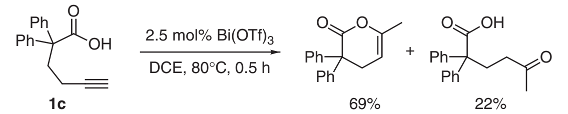


Entry	Solvent	Yield/%[a]	Conv./%[a]
1	DCE	83	100
2	Toluene	80	100
3	MeCN	35	46
4	1,4-dioxane	0	7
5	Hexane	0	2

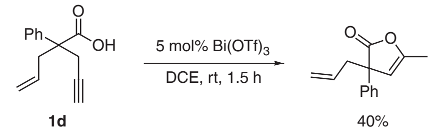
[a]Determined by ^1H NMR.



(1)

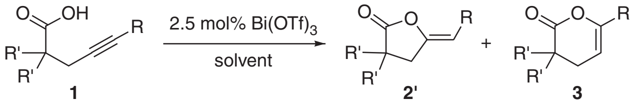


(2)



(3)

Table 3.



Entry	Alkynyl carboxylic acid **1**			Temp /°C	Time /h	Total yield /%[a]	Ratio (**2**′/**3**) /%[b]
	R	R′					
1	Ph	Ph	**1e**	80	3.0	95	(28/72)
2	4-MeOC$_6$H$_4$	Ph	**1f**	rt	1.5	54	(0/100)
3	3-MeC$_6$H$_4$	Ph	**1g**	80	3.0	73	(0/100)
4	4-BrC$_6$H$_4$	Ph	**1h**	80	0.5	83	(0/100)
5	Ph	Me	**1i**	80	0.5	92[b]	(12/88)
6	4-MeOC$_6$H$_4$	Me	**1j**	rt	0.5	100[b]	(0/100)
7	4-MeC$_6$H$_4$	Me	**1k**	rt	8.0	93[b]	(0/100)
8	3-MeC$_6$H$_4$	Me	**1l**	80	0.5	98[b]	(6/94)
9	4-BrC$_6$H$_4$	Me	**1m**	80	1.5	99[b]	(24/76)

[a]Isolated yield. [b]Determined by ^{1}H NMR.

Next, under the optimized conditions we investigated the intramolecular addition of carboxylic acid to aromatic alkyne moiety. These results are listed in Table 3. The reaction of **1e** with Bi(OTf)$_3$ catalyst mainly afforded **3e** in 68% yield with benzylidene–lactone **2e**′[7] in 27% yield (Entry 1). It is noteworthy that late transition-metal-catalyzed cyclization of 4-pentynoic acids generally leads 5-exo-dig manner to furnish mainly the vinylidene–lactones, except for a few examples.[8] Indeed, exposure of the acid **1e** with PtCl$_2$ (2.5 mol %) at 80 °C (DCE) for 19 h yielded 82% of **2e**′ along with 9% of the endocyclic one **3e**, in contrast with the present result. Moreover, replacement of substituent at terminal phenyl group resulted in an exclusive formation of the 6-membered lactone. Thus, reaction of **1f** with the bismuth catalyst gave 54% yield of **3f** without any other isomers (Entry 2). Similar regiospecificity were also observed in the case of **1g** and **1h**, leading to only **3g** and **3h** in 73% and 83% yields, respectively (Entries 3 and 4). Similar predominant formation of 6-membered lactones was achieved in the reaction of 2,2-dimethyl-4-pentynoic acid derivatives **1i**–**1m** (Entries 5–9).[9]

In summary, we have disclosed a bismuth-catalyzed intramolecular hydro-oxycarbonylation of alkynes, giving rise to 5- and 6-membered lactones in high yields and selectivity under mild conditions.[10] In comparison with other transition-metal catalysts, the bismuth catalyst is helpful for the transformation owing to its easy handling and commercial availability. Although the actual role of the bismuth catalyst is not yet clear, we thought that the bismuth might act as a dual activator of both carboxylic and alkyne function like our previous finding.[3] Studies on scope and limitation of the system and on details of the reaction mechanism are currently in progress.

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References and Notes

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5 When **2a′** was treated with Bi(OTf)$_3$ catalyst, quantitative yield of **2a** was formed. The result would indicate the vinylidene–lactone was reconstructed to the endocyclic one via olefinic isomerization under the conditions.

6 The same selectivity was accomplished by Au^I catalyst. E. Genin, P. Y. Toullec, S. Antoniotti, C. Brancour, J.-P. Genêt, V. Michelet, *J. Am. Chem. Soc.* **2006**, *128*, 3112.

7 The olefinic isomerization, described in Table 1, was not observed in the reaction of the aromatic alkynes due to thermodynamic stability of benzylidene-form.

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9 These product yields were determined by NMR measurement for the crude product with dimethyl terephthalate as an internal standard because the products **3f**–**3j** were somewhat labile.

10 Representative procedure for the Bi-catalyzed cyclization of alkynyl carboxylic acid: A solution of **1a** (50 mg, 0.20 mmol) and Bi(OTf)$_3$ (3.3 mg, 5 µmol) in DCE (2 mL) was stirred under the suitable conditions with TLC monitoring. After complete, the reaction mixture was passed through a short silica-gel column with ether. Concentration of the filtrate gave the crude product, which afforded 82% (41 mg) of 3,3-diphenyl-5-methyl-2(3H)-furanone (**2a**) by silica-gel column chromatography. **2a**: Colorless oil; R_f (Hexane/EtOAc = 5:1) = 0.51; ^{1}H NMR (CDCl$_3$, 270.05 MHz) δ 2.10 (3H, d, $J = 1.3$ Hz), 5.70 (1H, br s), 7.22–7.38 (10H, m); ^{13}C NMR (CDCl$_3$, 67.8 MHz) δ 14.0, 61.5, 109.6, 127.5, 127.6, 128.7, 140.4, 151.3, 177.6; EI-MS m/z 250 (M$^+$), 221 (46), 207 (83), 179 (100).