

Bismuth-Catalyzed Intramolecular Carbo-oxycarbonylation of 3-Alkynyl Esters

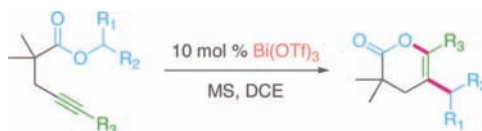
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ABSTRACT



Borderline metal complexes, especially $\text{Bi}(\text{OTf})_3$, efficiently catalyze the carbo-oxycarbonylation of alkynyl esters to form multisubstituted lactones in moderate to high yields.

Transition-metal-catalyzed addition of heteroatoms across carbon–carbon unsaturated bonds has attracted significant interest, particularly in the intramolecular reaction, because the heterocycles provide the core and key structures of natural products and organic materials. Thus, many metal catalysts have been explored for the efficient transformation. On their survey, there are two activation modes of the substrates by the catalysts: σ - and π -activations (**A** and **B** in Figure 1,

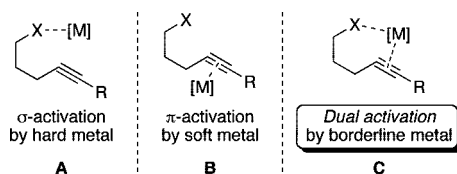


Figure 1. Activation modes of heteroatom (X) and $\text{C}\equiv\text{C}$ with metal catalysts ($[\text{M}]$) in the intramolecular heterofunctionalization.

respectively). According to the HSAB theory, the mode is dependent on the affinity of the reaction site of the substrate with the metals.¹ In the σ -activation, hard metals (e.g., group 3 and 4 metals), having relatively higher LUMO energy, interact strongly with heteroatoms (donor) followed by the metalation of heteroatom–hydrogen bonds to yield reactive

intermediates like amide, imide, and alkoxide species.² On the other hand, soft metals (e.g., Au, Pt, Hg, Ag, and Pd), with lower LUMO energy, provide π -complexes with carbon–carbon multiple bonds (acceptor).³ Although these catalysts reveal excellent capacity in the area, their substitution by air-stable, inexpensive, and environmentally benign metal is desired for practical production.

For the development of a new catalyst system, we investigated the activity of borderline metals,^{1b} based on the following working hypothesis. Their LUMO energy should be laid in the middle of those of hard and soft metals, and therefore, they can interact with both heteroatoms and carbon–carbon multiple bonds as depicted (**C**) in Figure 1. Consequently, dual activation of donor and acceptor, i.e., σ - and π -activation, could be expected with the borderline catalysts, which would guarantee a good catalytic performance in the reaction.⁴ Moreover, the interaction may bring the two reaction sites close. In spite of these possibilities, their application to the heteroatom-cyclization had been

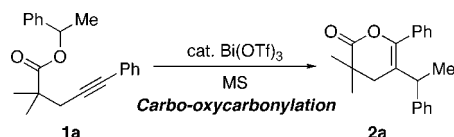
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scarcely developed. Recently, this idea proved to work well by our studies on hydroamination, hydroalkoxylation, and hydro-oxycarbonylation of unactivated alkenes and alkynes using iron and bismuth as representative borderline catalysts.⁵ During our investigation along this line, we found that intramolecular carbo-oxycarbonylation of alkyne⁶ takes place readily on treatment of alkynyl benzylic esters with Bi(OTf)₃ catalyst⁷ (Scheme 1). We report herein these results.

Scheme 1



When alkynyl ester **1a** was treated with 2.5 mol % of Bi(OTf)₃ and molecular sieves in dichloromethane (DCE) at room temperature for 6 h, 3,4-dihydropyran-2-one **2a** was obtained in 69% yield together with 2,2-dimethyl-5-phenylpent-4-ynoic acid (**3**) (18%), a hydrolysis product of **1a** (Table 1, entry 1). Molecular sieves played important roles in repressing the formation of the carboxylic acid **3** and in reducing reaction time (entry 2). However, its excess use caused a decrease of the catalytic performance (entries 3 and 4). More loading of the catalyst increased the reaction rate, although the yield of **2a** was almost unchanged (entries 5 and 6). The present reaction did not proceed with molecular sieves alone or without the bismuth catalyst (entries 7 and 8). Employment of other borderline metals, such as Fe(OTf)₂, Cu(OTf)₂, Zn(OTf)₂, and Ni(OTf)₂, were similarly effective, albeit with slightly lower yields (entries 9–13). PtCl₂ and PdCl₂, soft π -acids, also gave the product **2a**, but the reaction rate was very slow (20–24% yield, 24 h) (entries 14 and 15). In sharp contrast, TfOH and Sc(OTf)₃, a hard Brønsted acid and Lewis acid, exclusively provided the carboxylic acid **3** as a single product (entries 16 and 17). Hexane, toluene, and MeNO₂ were suitable solvents as well as DCE, whereas 1,4-dioxane, tetrahydrofuran, and acetonitrile prevented the reaction.

(4) σ - π Chelation of typical metals was reported by Yamamoto et al.; see: Asao, N.; Asano, T.; Ohishi, T.; Yamamoto, Y. *J. Am. Chem. Soc.* **2000**, *122*, 4817.

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(6) Fürstner has reported similar reactions using platinum and gold catalysts; see ref 3b and: Fürstner, A.; Davies, P. W. *J. Am. Chem. Soc.* **2005**, *127*, 15024.

(7) The behavior of Bi(OTf)₃/MPF₆ (M = K or Cu) systems as σ - and π -acids was postulated by Shibasaki and Matsunaga et al.: Qin, H.; Yamagiwa, N.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2006**, *128*, 1611.

(8) In previous work,^{5d} we found that the iron- and the bismuth-catalyzed addition of heteroatom to alkynes seems to mainly proceed at the alkynyl carbon attached with aryl group. Furthermore, treatment of product **2r'** with NaOH (5 equiv) for 3 h in methanol provided 2-(2-benzhydrylhexanoyl)benzoic acid in 47% yield.

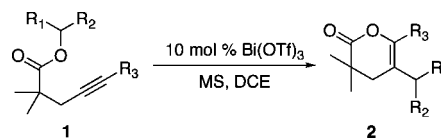
Table 1. Optimization of Conditions in Carbo-oxycarbonylation of Alkynyl Ester **1a** in the Presence of Various Catalysts and MS^a

entry	catalyst (mol %)	MS (mg)	time (h)	yield of 2^b (%)	conv of 1^b (%)
1	Bi(OTf) ₃ (2.5)	100	6	69	100
2	Bi(OTf) ₃ (2.5)	none	10	41	100
3	Bi(OTf) ₃ (2.5)	150	24	56	82
4	Bi(OTf) ₃ (2.5)	200	24	57	77
5	Bi(OTf) ₃ (5.0)	100	3	61	100
6	Bi(OTf) ₃ (10.0)	100	3	62 (60)	100
7	none	none	10	n.r.	
8	none	100	10	n.r.	
9	Fe(OTf) ₂ (10.0)	100	7	50	100
10	Fe(OTf) ₃ (10.0)	100	7	55	100
11	Cu(OTf) ₂ (10.0)	100	7	51	100
12	Zn(OTf) ₂ (10.0)	100	7	45	100
13	Ni(OTf) ₂ (10.0)	100	7	40	98
14	PdCl ₂ (10.0)	100	24	20	21
15	PtCl ₂ (10.0)	100	24	24	25
16	Sc(OTf) ₃ (10.0)	100	7	trace	100
17	TfOH (10.0)	100	7	trace	100

^a **1a** (50 mg, 0.16 mmol) was used at room temperature in DCE (0.1 M). ^b Determined by ¹H NMR with mesitylene as a internal standard. Value in parentheses indicates isolated yield.

With optimal conditions in hand, we examined the scope of the Bi(OTf)₃-catalyzed carbo-oxycarbonylation with various alkynyl esters (Table 2). Lower temperature improved the product yield of **2a** up to 81%, albeit for longer reaction time (entry 2). With respect to the substituent effect of the

Table 2. Bismuth-Catalyzed Carbo-oxycarbonylation of Various Alkynyl Esters **1^a**

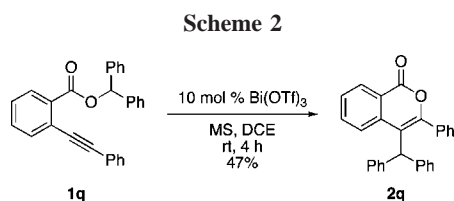


alkynyl esters **1**

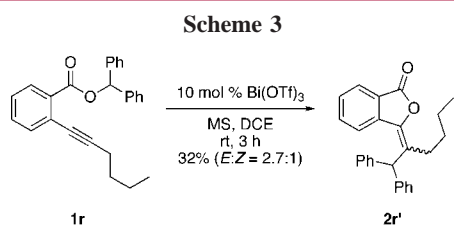
entry	R ¹	R ²	R ³	T (°C)	time (h)	yield of 2 (%) ^b
1	1a , Ph	Me	Ph	rt	3	60
2	1a , Ph	Me	Ph	0	44	81
3	1b , Ph	Et	Ph	rt	5	45
4	1c , 4-ClC ₆ H ₄	Me	Ph	rt	7	70
5	1d , 4-MeC ₆ H ₄	Me	Ph	-15	19	67
6 ^c	1e , 4-MeOC ₆ H ₄	Me	Ph	rt	1	37
7	1f , Ph	Ph	Ph	rt	7	87
8	1g , 4-ClC ₆ H ₄	4-ClC ₆ H ₄	Ph	rt	3	92
9	1h , 4-MeC ₆ H ₄	4-MeC ₆ H ₄	Ph	0	2	69
10	1i , 4-MeOC ₆ H ₄	4-MeOC ₆ H ₄	Ph	0	2	34
11	1j , Ph	2-naphthyl	Ph	rt	1	58
12	1k , Ph	cyclopropyl	Ph	0	7	45
13	1l , Ph	C≡C ⁿ Bu	Ph	rt	2	78
14	1m , Ph	Ph	4-BrC ₆ H ₄	rt	2	83
15	1n , Ph	Ph	4-MeOC ₆ H ₄	rt	1	93
16	1o , Ph	Ph	4-MeC ₆ H ₄	rt	2	95
17	1p , Ph	Ph	3-MeC ₆ H ₄	rt	1	98

^a Conditions: **1** (0.16 mmol), MS (100 mg), Bi(OTf)₃ (10 mol %), DCE (0.1 M). ^b Isolated yield. ^c Carried out in MeNO₂ solvent.

ester moieties (R^1), the electron-deficient aryl of **1c** provided a slightly better yield than the electron-rich ones of **1d** and **1e** (entries 4–6). Moreover, diarylmethyl esters **1f–h** were more reactive than the corresponding monoarylethyl esters **1a**, **1c**, and **1d**, wherein electron-deficient aryls also facilitated the reaction (entries 8 vs 9, 10). A bulky naphthyl group did not prevent the cyclization (entry 11). It is noteworthy that the present reaction permitted labile substituents like alkynyl and cyclopropyl groups to take part in the transformation (entries 12 and 13). However, other alkynyl esters such as allyl, 2-cyclohexenyl, bezyl, fluorenyl, and 2,2,2-trifluoro-1-phenylethyl esters were unchanged and did not provide the desired products. These findings might indicate that the cleavage of C(O)O–C bond of esters is a key step of the present carbo-oxycarbonylation. Electronic property of terminal aryl substituents (R^3) did not influence the reactivity to afford the dihydropyran-2-ones **2m–p** in excellent yields (entries 14–17). Additionally, the procedure could be applied to the synthesis of multisubstituted isocoumarin **2q** (Scheme 2). In contrast, in the case of terminal



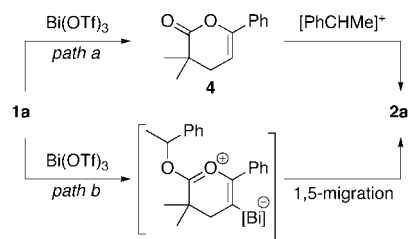
alkyl substituent **1r**, *exo*-type cyclization mainly proceeded to afford 5-membered lactone **2r'** with two stereoisomers (Scheme 3).⁸



We envisioned two possible reaction paths, inter- and intramolecular alkyl migrations, for the present cyclization as illustrated in Scheme 4. In the intermolecular process (path a), the ester **1a** would be converted to the primary product **4**^{5d} by the fast hydrolysis of the C(O)O–benzyl bond followed by hydro-oxycarbonylation, which is then benzylated with the $[PhCHMe]^+$ equivalent derived from another molecule of **1a** to afford the product **2a**. Alternatively, direct cyclization of **1a** leading to the metalated intermediate and subsequent intramolecular 1,5-migration of the alkyl group⁹ would yield **2a** (path b). Path a seems to be less likely

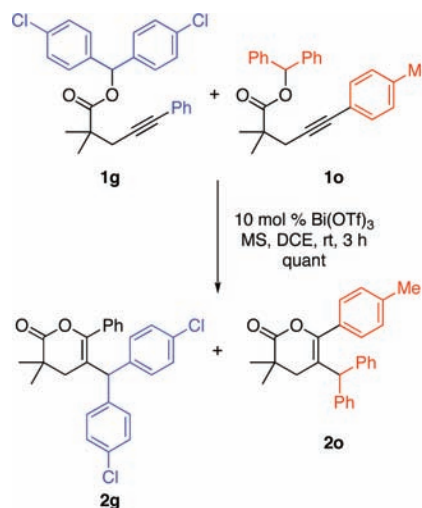
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Scheme 4. Inter- vs. Intramolecular Reaction



because the postulated product **4** was not detected under various conditions. In addition, although bismuth complexes have been known to catalyze the benzylation of aromatic rings with benzylic alcohols,¹⁰ the compound **4** prepared separately was recovered unchanged in the reaction with 1-phenylethanol and its acetate using $Bi(OTf)_3$. Furthermore, evidence to support the intramolecular reaction was obtained by the crossover experiment (Scheme 5). Treatment of an

Scheme 5. Crossover Reaction of **1g** and **1o**

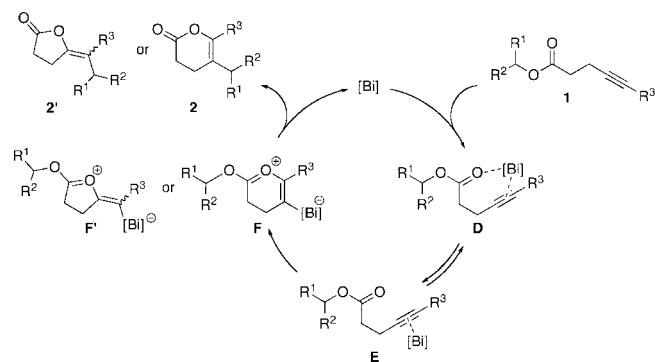


equimolar mixture of **1g** and **1o** with 10 mol % of $Bi(OTf)_3$ gave **2g** and **2o** in quantitative yields, respectively, without any crossover products.

On the basis of these results, we propose the reaction mechanism in Scheme 6. The borderline bismuth would coordinate not only to the ester moiety but also to the triple bond of **1**, leading to dually activated species **D**, in which the activated mode would make two reaction sites (ester and alkyne) close. Subsequent cyclization of **D** takes place readily through nucleophilic addition of the carbonyl oxygen to the bismuth-coordinated alkyne **E** to yield the zwitterionic intermediates **F** or **F'**. Then, intramolecular 1,5-migration of the benzyl group to the metalated sp^2 -carbon liberates the products **2** or **2'** and the catalyst.

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Scheme 6. Plausible Reaction Mechanism



In conclusion, we have developed a novel bismuth-catalyzed intramolecular carbo-oxycarbonylation of alkynyl benzylic esters, which mainly afforded multisubstituted 6-membered lactones **2** in good to high yields under mild

conditions. The excellent catalyst activity of the borderline metals, particularly of bismuth, observed in this cyclization would be attributable to their unique activation mode. Furthermore, these results suggest that inexpensive and tractable bismuth has a good potentiality to substitute a part of the conventional transition metal catalysts and to provide new reaction pathways in organic synthesis. We are currently exploring the detail of mechanism and developing other functionalizations of the carbon-carbon multiple bonds with the borderline metals.

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Supporting Information Available: Experimental procedures and product characterization. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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