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Zinc- and Indium-Promoted Conjugate Addition−Cyclization Reactions of Ethenetricarboxylates with Propargylamines and Alcohol: Novel Methylenepyrrolidine and Methylenetetrahydrofuran Syntheses

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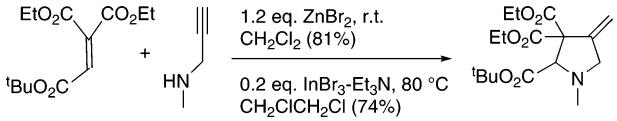

A new zinc- and indium-promoted conjugate addition−cyclization reaction to afford nitrogen- and oxygen-containing five-membered heterocycles has been developed. Reaction of ethenetricarboxylates with propargylamines (1 equiv) in the presence of $ZnBr_2$ or $InBr_3$ afforded methylenepyrrolidines in high yields. The stoichiometric use of $ZnBr_2$ or $InBr_3$ at room temperature and the catalytic use of $InBr_3$−Et_3N at 80 °C were effective. Reaction of ethenetricarboxylates with propargyl alcohol in the presence of $ZnBr_2$ or $InBr_3$ afforded methylenetetrahydrofurans.

Introduction

Nitrogen- and oxygen-containing five-membered heterocycles such as pyrrolidines, including proline and related amino acids, and tetrahydrofurans are important core structures in organic chemistry because of their presence in many natural products and their biological activity.[1,2] For this reason, mild and efficient processes for the one-step construction of functionalized pyrrolidines[3] and tetrahydrofurans[4] are highly desirable. Recently, *n*BuLi, NaH/Pd, and Cu-promoted one-pot reactions with propargylamines or allylamines leading to pyrrolidines have been reported.[5] In these examples, most substrates were arylidenemalonates and the use of a primary propargylamine was unsuccessful. *n*BuLi/Pd, Cu-promoted,[6] and Zn-promoted[7] reactions of alkylidenemalonates with excess amounts of propargyl alcohol to give methylenetetrahydrofurans also have been reported. Ethenetricarboxylate derivatives have been shown to be highly electrophilic C=C components in Lewis acid-promoted cycloadditions.[8] Lewis acid-promoted intramolecular

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(2) For examples of tetrahydrofurans, see: Dean, F. M.; Sargent, M. V. In *Comprehensive Heterocyclic Chemistry*; Katrizky, A. R., Rees, C. W., Eds.; Pergamon: Oxford, UK, 1984; Vol. 4, p 531.

(3) For examples of syntheses of pyrrolidines, see: (a) Felpin, F.-X.; Girard, S.; Vo-Thanh, G.; Robins, R. J.; Villiéras, J.; Lebreton, J. *J. Org. Chem.* **2001**, *66*, 6305. (b) Xu, Y.-z.; Choi, J.; Calaza, M. I.; Turner, S. C.; Rapoport, H. *J. Org. Chem.* **1999**, *64*, 4069. (c) Turner, S. C.; Zhai, H.; Rapoport, H. *J. Org. Chem.* **2000**, *65*, 861. (d) Knight, D. W.; Salter, R. *Tetrahedron Lett.* **1999**, *40*, 5915. (e) Schlummer, B.; Hartwig, J. F. *Org. Lett.* **2002**, *4*, 1471.

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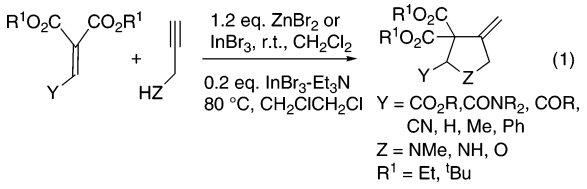
TABLE 1. Stoichiometric Reaction of 1a (Y = $CO_2{}^tBu$) with *N*-Methylpropargylamine 2a (R = Me)[a]

entry	MX_n	**3a** (yield/%)	**4a** (yield/%)
1	$ZnBr_2$	81	
2	$ZnCl_2$	75	
3	ZnI_2	78	
4	$Zn(OTf)_2$	73	
5	$InBr_3$	78	
6	$InCl_3$	65	
7	$In(OTf)_3$	67	
8	$Cu(OTf)_2$	22	
9	$AlCl_3$		76
10	$GaCl_3$		72
11	$FeCl_3$		75
12	$SnCl_4$	*b*	
13	$Sn(OTf)_2$		94
14	$Sc(OTf)_3$		86
15	$TiCl_4$	*b*	
16	$ZrCl_4$		97

[a] Reactions were carried out with 0.5 mmol of **1a**, 0.5 mmol of **2a**, and 1.2 equiv (0.6 mmol) of MX_n and at 0.56 M for **1a** in CH_2Cl_2 for 17−20 h at room temperature. [b] Decomposition.

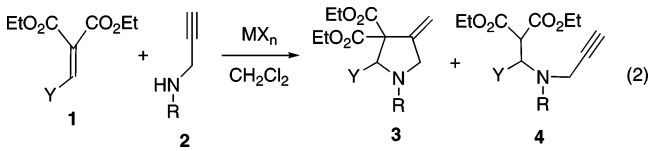
cyclization of ethenetricarboxylate esters also has been studied.[9] We have studied the reaction of highly reactive ethenetricarboxylate derivatives and related compounds with propargyl substrates in this work. We have discovered stoichiometric (at room temperature) and catalytic (at higher temperature) zinc- and indium-promoted formal [3+2] cycloadditions of ethenetricarboxylates with 1 equiv of propargylamines (*N*-methyl and primary) and propargyl alcohol to afford nitrogen- and oxygen-containing five-membered rings (eq 1). No requirement for an excess of the propargyl substrates and the mild conditions are valuable features of this reaction.



(1)

Results and Discussion

At first, reactions involving stoichiometric amounts of Lewis acids (1.2 equiv) and substrates (1 equiv) were examined. Triester **1a** (Y = $CO_2{}^tBu$) and *N*-methylpropargylamine (**2a**) reacted in the presence of $ZnBr_2$ (1.2 equiv) in CH_2Cl_2 at room temperature overnight to afford five-membered proline derivative **3a** in 81% yield (eq 2, Table 1, entry 1). Various metal



(2)

halides and triflates were examined. Interestingly, $AlCl_3$, $FeCl_3$, $GaCl_3$ $Sn(OTf)_2$, $Sc(OTf)_3$, and $ZrCl_4$ gave exclusively 1,4-adduct **4a** (Y = $CO_2{}^tBu$, R = Me).[10] The reaction of **1a** and **2a** in the absence of metal halides and triflates also gave **4a** quantitatively.[11] Cyclization only occurred when zinc, indium, and copper salts were used at room temperature, although copper triflate gave **3a** in lower yield. Treatment of the noncyclic adduct **4a** with 1.2 equiv of $ZnBr_2$ or $InBr_3$ gave **3a** in 60% and 66% yields, respectively.

TABLE 2. Reaction of 1a (Y = $CO_2{}^tBu$) with *N*-Methylpropargylamine 2a (R = Me) in Various Solvents

entry	solvent	MX_n	**3a** (yield/%)	**4a** (yield/%)
1	CH_2Cl_2	$ZnBr_2$	81[a]	
2	CH_2Cl_2	$InBr_3$	78[a]	
3	THF	$ZnBr_2$		96
4	toluene	$ZnBr_2$	32[b]	65[b]
5	toluene	$InBr_3$	87	
6	CH_2ClCH_2Cl	$ZnBr_2$	95	
7	CH_2ClCH_2Cl	$InBr_3$	81	
8	no solvent	$ZnBr_2$	18[b]	73[b]
9	no solvent	$InBr_3$	31[b]	61[b]

[a] Results in Table 1. [b] NMR yield.

Various solvents were examined for the reaction of **1a** and **2a** in the presence of $ZnBr_2$ and $InBr_3$ (1.2 equiv) at room temperature (Table 2). Dichloromethane and 1,2-dichloroethane are better solvents for formation of **3a**.

Use of catalytic amounts of $ZnBr_2$, $InBr_3$, and $In(OTf)_3$ at room temperature gave **4a** exclusively (entries 1, 3, and 4, Table 3). Catalytic amounts of $Zn(OTf)_2-NEt_3$[6] at room temperature gave the mixture of **3a** and **4a** (entry 2). With 1,2-dichloroethane as a solvent, the catalytic reaction at higher temperature (80 °C) was examined. With 0.2 equiv of $ZnBr_2$, $InBr_3$, $ZnBr_2-Et_3N$, or $Zn(OTf)_2-Et_3N$, lower yields of **3a** compared to stoichiometric reactions at room temperature were obtained along with small amounts of **4a** and the starting material **1a** (entries 5−7, 9, and 10). With 0.2 equiv of $InBr_3-Et_3N$ for 4 h, the yield of **3a** was increased up to 74% (entry 8).[12] The reaction of **4a** with $InBr_3-Et_3N$ (0.2 equiv) at 80 °C for 4 h or with $Zn(OTf)_2$ (0.2 equiv) at 80 °C for 16 h gave **3a** in 61% and 71% yields, along with **1a** (13% and 21%), respectively.

The reaction of **1a** and *N*-propargylamine **2b** with $ZnBr_2$ or $InBr_3$ (1.2 equiv) also gave **3b** (Y = $CO_2{}^tBu$, R = H) as a major product (Table 4). The reaction of **1a** and *N*-propargylamine **2b** in the absence of $ZnBr_2$ or $InBr_3$ or by their catalytic use (0.2 equiv) at room temperature gave **4b** exclusively. The reaction of **1a** and **2b** in the presence of catalytic $InBr_3-Et_3N$ (0.2 equiv) at 80 °C for 4 h gave **3b** in 75% yield (entry 5).

The reaction of various ethenetricarboxylate and related ketone derivatives **1** with *N*-propargylamines **2** proceeded to give proline derivatives (Table 5). Both stoichiometric (at room temperature) and catalytic (at 80 °C) conditions are shown.

Other substrates, di-*tert*-butyl methylenemalonate (**5**),[13] diethyl ethylidenemalonate (**6**), and diethyl benzylidenemalonate

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(10) **4a** is somewhat unstable to column chromatography (SiO_2). Partial decomposition of **4a** to **1a** possibly by retroconjugate addition was observed. The instability is consistent with the reported results. (a) Bartoli, G.; Bartolacci, M.; Giuliani, A.; Marcantoni, E.; Massaccesi, M.; Torregiani, E. *J. Org. Chem.* **2005**, *70*, 169. (b) Bartoli, G.; Bosco, M.; Marcantoni, E.; Petrini, M.; Sambri, L.; Torregiani, E. *J. Org. Chem.* **2001**, *66*, 9052. (c) Toda, F.; Takumi, H.; Nagami, M.; Tanaka, K. *Heterocycles* **1998**, *47*, 467.

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(12) The reaction also proceeds without Et_3N. Et_3N or unreacted propargylamines may capture the transiently generated HBr in situ.

TABLE 3. Catalytic Reaction of 1a (Y = $CO_2{}^tBu$) with *N*-Methylpropargylamine 2a (R = Me)[a]

entry	solvent	reaction conditions	MX_n (0.2 equiv)	**3a**[b] (yield/%)	**4a** (yield/%)	**1a** (yield/%)
1	CH_2Cl_2	rt, 16 h	$ZnBr_2$		96[b]	
2	CH_2Cl_2	rt, 16 h	$Zn(OTf)_2-Et_3N$[d]	35	41[c]	15[c]
3	CH_2Cl_2	rt, 16 h	$InBr_3$		quant[b]	
4	CH_2Cl_2	rt, 16 h	$In(OTf)_3$		98[b]	
5	CH_2ClCH_2Cl	80 °C, 16 h	$ZnBr_2$	14	19[c]	14[c]
6	CH_2ClCH_2Cl	80 °C, 4 h[e]	$InBr_3$	55	3[c]	10[c]
7	CH_2ClCH_2Cl	80 °C, 16 h	$ZnBr_2-Et_3N$[d]	38	19[c]	14[c]
8	CH_2ClCH_2Cl	80 °C, 4 h[e]	$InBr_3-Et_3N$[d]	74		
9	CH_2ClCH_2Cl	80 °C, 4 h	$Zn(OTf)_2-Et_3N$[d]	45	4[c]	13[c]
10	CH_2ClCH_2Cl	80 °C, 16 h	$Zn(OTf)_2-Et_3N$[d]	45		21[c]

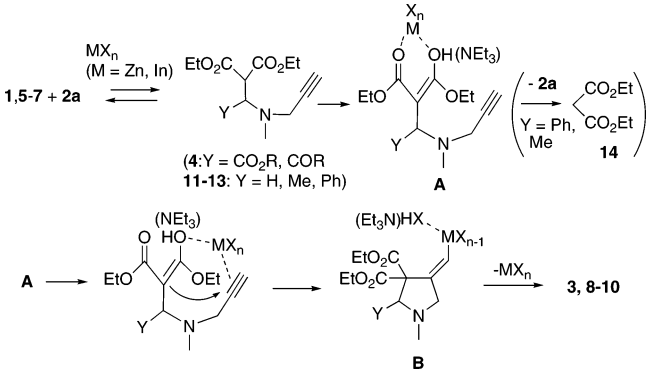
[a] Reactions were carried out with 0.5 mmol of **1a**, 0.5 mmol of **2a**, and 0.2 equiv (0.1 mmol) of $MX_n-(Et_3N)$ and at 0.56 M for **1a** in CH_2Cl_2 or CH_2ClCH_2Cl. [b] Isolated yield. [c] NMR yield. [d] Et_3N (0.2 equiv) was added. [e] Longer reaction times decreased the yield.

TABLE 4. Reaction of 1a (Y = $CO_2{}^tBu$) with *N*-Propargylamine 2b (R = H)

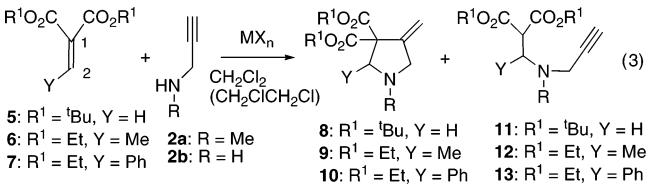
entry	reaction conditions[a]	MX_n	equiv	**3b** (yield/%)	**4b** (yield/%)
1	rt, 16 h	$ZnBr_2$	1.2	54	
2	rt, 16 h	$InBr_3$	1.2	82	
3	rt, 16 h	$ZnBr_2$	0.2		82
4	rt, 16 h	$InBr_3$	0.2		71
5	80 °C, 4 h[b]	$InBr_3-Et_3N$[c]	0.2	75	

[a] CH_2Cl_2 was used as solvent at rt and CH_2ClCH_2Cl was used at 80 °C. [b] Longer reaction time decreased the yield. [c] Et_3N (0.2 equiv) was added.

SCHEME 1

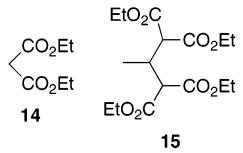


(**7**) were investigated to examine the effect of 2-substituents (eq 3). Catalytic reaction of **5** with **2a** proceeded even at room



temperature (entries 6−8, Table 6). Treatment of the noncyclic adduct **11a** in CH_2ClCH_2Cl with $InBr_3-Et_3N$ (0.2 equiv) at 80 °C for 4 h gave **8a** in 73% yield. For the reaction of **6** and **7**, byproducts **14** and **15** (for **7**) formed. The reaction of **7** with **2a** at 80 °C under the catalytic conditions gave a cyclized product **10a** in 49% yield (entry 23).

The probable mechanism for formation of the five-membered rings **3** and **8**−**10** is shown in Scheme 1. Conjugate addition of nitrogen of **2** to **1** and **5**−**7** leading to 1,4-adduct (**4** and **11**−**13**) and simultaneous zinc (or indium) coordination to the diester moiety gives intermediate **A**.[14] Zinc (or indium) transfer to alkyne and the following cyclization leads to intermediate **B**. Protonation of the intermediate **B** furnishes the five-membered rings **3** and **8**−**10**. The successful cyclization by zinc and indium



salts can be rationalized by the dual activation of the carbonyl and alkyne moieties.[15] The reversibility of the first 1,4-addition step is suggested as follows. The B3LYP/6-31G* calculated ΔG_{298} of **4** (R = Me, Y = CO_2Et) in the gas phase is 5 kcal/mol less stable relative to **1b** and **2a**.[16,17] ΔG_{298} of **13a** (R = Me, Y = Ph) is 12.0 kcal/mol less stable relative to **7** and **2a**.[18] For the reaction of **7** (Y = Ph), the reverse 1,4-addition seems to be more preferred because of conjugation with the Ph group.[19] The higher reactivity of ethenetricarboxylate **1** arises from activation of the 2-position of **1** by the electron-withdrawing ester group in the addition step.

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(18) ΔG_{298} for **3c** (R = Me, Y = CO_2Et) relative to **1b** and **2a** is −35.3 kcal/mol and ΔG_{298} for **10a** (R = Me) relative to **7** and **2a** is −25.9 kcal/mol.

(19) Without Lewis acid, the reaction of **7** and **2a** in CH_2Cl_2 at room temperature for 17 h gave a ca. 1:1 mixture of **7** and a probable amine adduct **13a**. **13a** could not be isolated and decomposed to give **7** by column chromatography.

TABLE 5. Reaction of 1 with *N*-Propargylamines 2a (R = Me) and 2b (R = H)

entry	1	2	reaction conditions[a,b]	MX_n	equiv	3 (yield/%)
1	**1b** (Y = CO_2Et)	**2a**	rt	$ZnBr_2$	1.2	**3c** (91)
2	**1b** (Y = CO_2Et)	**2a**	rt	$InBr_3$	1.2	**3c** (64)
3	**1b** (Y = CO_2Et)	**2a**	80 °C, 4 h	$InBr_3-Et_3N$[c]	0.2	**3c** (64)
4	**1b** (Y = CO_2Et)	**2b**	rt	$ZnBr_2$	1.2	**3d** (96)
5	**1b** (Y = CO_2Et)	**2b**	rt	$InBr_3$	1.2	**3d** (88)
6	**1b** (Y = CO_2Et)	**2b**	80 °C, 4 h	$InBr_3-Et_3N$[c]	0.2	**3d** (53)
7	**1c** (Y = CO_2CH_2Ph)	**2a**	rt	$ZnBr_2$	1.2	**3e** (81)
8	**1c** (Y = CO_2CH_2Ph)	**2a**	rt	$InBr_3$	1.2	**3e** (79)
9	**1c** (Y = CO_2CH_2Ph)	**2a**	80 °C, 4 h	$InBr_3-Et_3N$[c]	0.2	**3e** (65)
10	**1c** (Y = CO_2CH_2Ph)	**2b**	rt	$InBr_3$	1.2	**3f** (80)
11	**1c** (Y = CO_2CH_2Ph)	**2b**	80 °C, 4 h	$InBr_3-Et_3N$[c]	0.2	**3f** (45)
12	**1d** (Y = $CONMeCH_2C{\equiv}CH$)	**2a**	rt	$ZnBr_2$	1.2	**3g** (43)
13	**1d** (Y = $CONMeCH_2C{\equiv}CH$)	**2a**	rt	$InBr_3$	1.2	**3g** (60)
14	**1d** (Y = $CONMeCH_2C{\equiv}CH$)	**2a**	80 °C, 4 h	$InBr_3-Et_3N$[c]	1.2	**3g** (53)
15	**1e** (Y = $CON-(CH_2)_5-$)	**2a**	rt	$ZnBr_2$	1.2	**3h** (62)
16	**1e** (Y = $CON-(CH_2)_5-$)	**2a**	rt	$InBr_3$	1.2	**3h** (74)
17	**1e** (Y = $CON-(CH_2)_5-$)	**2b**	rt	$InBr_3$	1.2	**3i** (69)
18	**1f** (Y = COPh)	**2a**	rt	$ZnBr_2$	1.2	**3j** (92)
19	**1f** (Y = COPh)	**2a**	rt	$InBr_3$	1.2	**3j** (68)
20	**1f** (Y = COPh)	**2a**	80 °C, 4 h	$InBr_3-Et_3N$[c]	1.2	**3j** (69)
21	**1g** (Y = CN)	**2a**	rt	$InBr_3$	1.2	**3k** (56)

[a] CH_2Cl_2 was used as a solvent at rt and CH_2ClCH_2Cl was used at 80 °C. [b] Reaction time is 15−17 h unless otherwise stated. [c] Et_3N (0.2 equiv) was added.

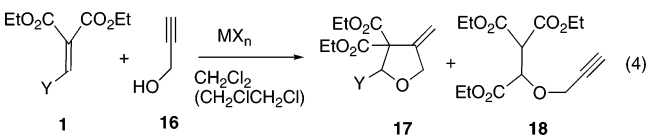
TABLE 6. Reaction of 5−7 with *N*-Propargylamines 2 (R = Me, H)

entry	substrate	2	reaction conditions[a,b]	MX_n	equiv	product (yield/%)[c]	
1	**5**	**2a**	rt	$ZnBr_2$	1.2	**8a** (89)	
2	**5**	**2a**	rt	$ZnBr_2$	0.2		**11a** (86)
3	**5**	**2a**	rt	$ZnBr_2-Et_3N$[e]	0.2		**11a** (89)
4	**5**	**2a**	rt	$InBr_3$	1.2	**8a** (63)	
5	**5**	**2a**	rt, 37 h	$InBr_3$	1.2	**8a** (65)	
6	**5**	**2a**	rt	$InBr_3$	0.2	**8a** (51)	**11a** (38)
7	**5**	**2a**	rt, 46 h	$InBr_3$	0.2	**8a** (64)	**11a** (22)
8	**5**	**2a**	rt	$InBr_3-Et_3N$[e]	0.2	**8a** (47)	**11a** (39)
9	**5**	**2a**	80 °C, 4 h	$InBr_3-Et_3N$[e]	0.2	**8a** (73)	
10	**5**	**2b**	rt	$ZnBr_2$	1.2	**8b** (96)[f]	
11	**5**	**2b**	rt 4 h[d]	$InBr_3$	1.2	**8b** (100)[f]	
12	**5**	**2b**	80 °C, 4 h	$InBr_3-Et_3N$[e]	0.2	**8b** (100)[f]	
13	**6**	**2a**	rt	$ZnBr_2$	1.2	**9a** (72)	
14	**6**	**2a**	rt	$InBr_3$	1.2	**9a** (73)	
15	**6**	**2a**	80 °C, 4 h	$InBr_3-Et_3N$[e]	0.2	**9a** (46)	
16	**6**	**2b**	rt	$ZnBr_2$	1.2	**9b** (37)[f,g]	**15** (63)
17	**6**	**2b**	rt	$InBr_3$	1.2	**9b** (47)[f,g]	**14** (50)
18	**6**	**2b**	80 °C, 4 h	$InBr_3-Et_3N$[e]	0.2	**9b** (38)[f,g]	**14** (5)[g], **15** (3)[g]
19	**7**	**2a**	rt	$ZnBr_2$	1.2		**14** (43), **7** (57)
20	**7**	**2a**	rt	$InBr_3$	1.2	**10a** (22)	**7** (65)
21	**7**	**2a**	80 °C	$InBr_3$	1.2	**10a** (34)	**7** (19)
22	**7**	**2a**	80 °C	$Zn(OTf)_2-Et_3N$[e]	0.2		**14** (47)[g], **7** (47)[g]
23	**7**	**2a**	80 °C, 4 h	$InBr_3-Et_3N$[e]	0.2	**10a** (49)	**14** (12), **7** (38)

[a] CH_2Cl_2 was used as a solvent at rt and CH_2ClCH_2Cl was used at 80 °C. [b] Reaction time is 15−17 h unless otherwise stated. [c] Isolated yield unless otherwise stated. [d] Longer reaction time decreased the yield. [e] Et_3N (0.2 equiv) was added. [f] Unstable to column chromatography. [g] NMR yield.

Formation of byproduct **14** in the reaction of **6** and **7** arises from the reverse Knoevenagel reaction. Formation of **15** arises from the conjugate addition reaction of **14** generated in situ toward **6**.

Methylenetetrahydrofuran Formation. These zinc- and indium salt-promoted conditions were also found to be suitable for methylenetetrahydrofuran formation. The reactions of ethenetricarboxylate derivatives with propargyl alcohol **16** were examined (eq 4, Table 7). The reaction of *tert*-butyl ester **1a**



and **16** in the presence of $ZnBr_2$ or $InBr_3$ did not give the expected methylenetetrahydrofuran, probably because *tert*-butyl cation generated in situ reacts with intermediates.[20] On the other hand, the reaction of triethyl ester **1b** and **16** in the presence of $ZnBr_2$ or $InBr_3$ (1.2 equiv) gave methylenetetrahydrofuran **17b** in 64% and 89% yields, respectively. The reaction of **1b** and **16** in the presence of catalytic amounts of $InBr_3$ with and without Et_3N at 80 °C gave **17b** in 66% and 73% yields, respectively (entries 6 and 7). The reaction of **1b** and **16** without $ZnBr_2$ or $InBr_3$ did not proceed. The different reactivity of propargylamines and alcohol arises from the difference of nucleophilicity of nitrogen and oxygen. The use of catalytic amounts of $InBr_3$

(20) Yamazaki, S.; Ohmitsu, K.; Ohi, K.; Otsubo, T.; Moriyama, K. *Org. Lett.* **2005**, *7*, 759.

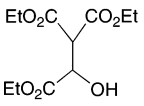
TABLE 7. Reaction of 1 with Propargyl Alcohol 16

entry	1	Y	reaction condition[a,b]	MX_n	equiv	product (yield)
1	**1b**	CO_2Et	rt	$ZnBr_2$	1.2	**17b** (64%) **18** (trace) **19** (23%)
2	**1b**	CO_2Et	rt	$Zn(OTf)_2-Et_3N$[c]	0.2	**18** (63%) recovered **1b** (21%)
3	**1b**	CO_2Et	80 °C	$Zn(OTf)_2-Et_3N$[c]	0.2	**17b** (38%) recovered **1b** (57%)
4	**1b**	CO_2Et	rt	$InBr_3$	1.2	**17b** (89%)
5	**1b**	CO_2Et	rt	$InBr_3$	0.2	**18** (65%) **19** (8%)
6	**1b**	CO_2Et	80 °C	$InBr_3$	0.2	**17b** (66%)
7	**1b**	CO_2Et	80 °C, 4 h	$InBr_3-Et_3N$[c]	0.2	**17b** (73%)[d]
8	**1d**	$CONMeCH_2C{\equiv}CH$	rt	$ZnBr_2$	1.2	**17d** (60%) **20** (7%)
9	**1e**	$CON-(CH_2)_5-$	rt	$ZnBr_2$	1.2	**17e** (64%)
10	**1e**	$CON-(CH_2)_5-$	rt	$InBr_3$	1.2	**17e** (63%)
11	**1e**	$CON-(CH_2)_5-$	80 °C	$InBr_3$	0.2	**17e** (88%)
12	**1f**	COPh	rt	$ZnBr_2$	1.2	**17f** (78%)
13	**1f**	COPh	rt	$InBr_3$	1.2	**17f** (91%)
14	**1f**	COPh	80 °C	$InBr_3$	0.2	**17f** (78%)

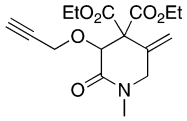
[a] CH_2Cl_2 was used as a solvent at rt and CH_2ClCH_2Cl was used at 80 °C. [b] Reaction time was 16−18 h unless otherwise stated. [c] 0.2 equiv of Et_3N was added. [d] A small amount of impurity could not be removed. Longer reaction times increased the impurity.

(0.2 equiv) at room temperature leads to the formation of 1,4-adduct **18** in 65% yield as a main product, along with the H_2O adduct **19** (8%) (entry 5).[21] Formation of **18** is different from the reported reaction of **7** with propargyl alcohol in the presence of catalytic $Zn(OTf)_2-Et_3N$.[7] Stoichiometric use of propagyl alcohol is sufficient to lead to the satisfactory yields, in contrast to the reaction of **7**. These results arise from the high reactivity of **1** toward propargyl alcohol as described for the reaction with propargylamines similarly in the first 1,4-addition step, and the reverse 1,4-addition is less favored than in the reaction of **7**.

The $ZnBr_2$-promoted reaction of amide derivative **1d** with **16** gave methyleneterahydrofuran **17d** in 60% yield, along with δ-lactam **20** in 7% yield formed by internal propargyl amide



19



20

participation, which we have reported previously (entry 8).[22] The reaction of piperidine amide **1e** and ketone derivative **1f** with **16** in the presence of $ZnBr_2$ or $InBr_3$ (1.2 equiv) at room temperature and $InBr_3$ (0.2 equiv) at 80 °C (entries 9−14) also gave methylenetetrahydrofurans **17e−f** in 63−91% yield.

In summary, zinc- and indium-promoted reactions of ethenetricarboxylate derivatives **3** with *N*-propargylamines and alcohols afford nitrogen- and oxygen-containing five-membered rings. Stoichiometric and catalytic conditions were examined. The present reaction to utilize highly electrophilic substrates provided an efficient cyclization method. Because the obtained highly functionalized heterocycle skeletons are biologically of interest, further transformation of the products to potentially useful compounds is ongoing.

Experimental Section

Typical Experimental Procedure. A (Table 1, Entry 1): To a solution of **1a** (137 mg, 0.5 mmol) in dichloromethane (0.92 mL) was added *N*-methylpropargylamine (35 mg, 43 μL, 0.5 mmol) and $ZnBr_2$ (130 mg, 0.58 mmol) at 0 °C. The mixture was allowed to warm to room temperature and stirred overnight (17 h). The reaction mixture was quenched by water (1.5 mL) and then saturated aqueous $NaHCO_3$. The mixture was extracted with dichloromethane and the organic phase was washed with water, dried (Na_2SO_4), and evaporated in vacuo. The residue was purified by column chromatography over silica gel with hexanes−ether as eluent to give **3a** (138 mg, 81%).

B (Table 3, Entry 1): To a solution of **1a** (133 mg, 0.49 mmol) in 1,2-dichloroethane (0.9 mL) was added *N*-methylpropargylamine (34 mg, 41 μL, 0.49 mmol), Et_3N (9.9 mg, 14 μL, 0.098 mmol) and $InBr_3$ (35 mg, 0.098 mmol). The mixture was heated to 80 °C for 4 h. The reaction mixture was cooled to room temperature and quenched by water (1.5 mL) and then saturated aqueous $NaHCO_3$. The mixture was extracted with dichloromethane and the organic phase was washed with water, dried (Na_2SO_4), and evaporated in vacuo. The residue was purified as above to give **3a** (124 mg, 74%).

3a: R_f 0.8 (ether); pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.26 (t, J = 7.1 Hz, 3H), 1.27 (t, J = 7.1 Hz, 3H), 1.47 (s, 9H), 2.46 (s, 3H), 3.39 (dt, J = 13.0, 2.1 Hz, 1H), 3.67 (dt, J = 13.0, 2.1 Hz, 1H), 4.02 (s, 1H), 4.08−4.30 (m, 4H), 5.27 (t, J = 1.9 Hz, 1H), 5.46 (t, J = 2.4 Hz, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 13.89 (q), 13.94 (q), 28.1 (q), 39.1 (q), 59.1 (t), 61.8 (t), 62.2 (t), 66.7 (s), 72.9 (d), 81.7 (s), 111.5 (t), 143.1 (s), 167.1 (s), 168.2 (s), 168.4 (s). Selected HMBC correlations are between δ 4.02 ($CHCO_2{}^tBu$) and δ 59.1 (NCH_2), 66.7 ($C(CO_2Et)_2$), and 143.1 ($C{=}CH_2$); IR (neat) 1742 cm^{-1}; MS (FAB) m/z 342 $(M + H)^+$; exact mass $(M + H)^+$ 342.1920 (calcd for $C_{17}H_{28}NO_6$ 342.1917). Anal. Calcd for $C_{17}H_{27}NO_6$: C, 59.81; H, 7.97; N, 4.10. Found: C, 59.77; H, 8.11; N, 4.09.

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Supporting Information Available: Additional experimental procedures, spectral data, and computational data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(21) The formation of **19** presumably arises from participation of adventitious water in situ.[20]

(22) Yamazaki, S.; Inaoka, S.; Yamada, K. *Tetrahedron Lett.* **2003**, *44*, 1429.