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Formal [4 + 1]-Cycloaddition of Homopropargyl Alcohols to Diazo Dicarbonyl Compounds Giving Substituted Tetrahydrofurans

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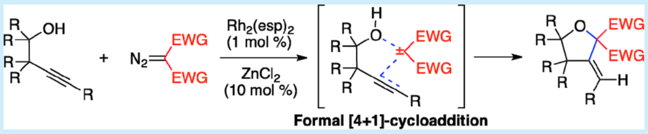
S *Supporting Information*

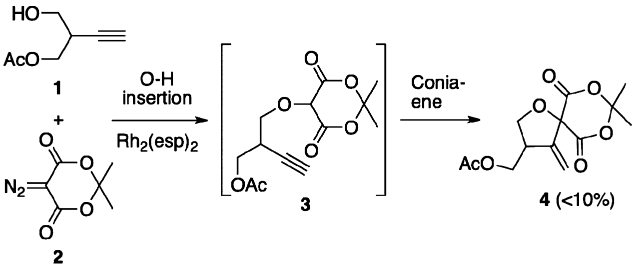
ABSTRACT: A novel formal [4 + 1]-cycloaddition of readily available homopropargyl alcohols with diazo dicarbonyl compounds is described, which involves tandem O−H insertion/Conia-ene cyclization under cooperative Rh(II)/Zn(II) catalysis. This reaction provides easy access to various substituted tetrahydrofurans and exhibits complete *E*-selectivity in the case of nonterminal alkynes.



Tetrahydrofurans are ubiquitous structural elements found in numerous biologically active natural products.[1] Among the many approaches toward their synthesis,[2,3] cycloaddition reactions[4] provide us with powerful and efficient strategies. Recently, in the course of our campaign directed toward the synthesis of natural products utilizing an In(OTf)$_3$-catalyzed Conia-ene reaction,[5] we discovered a new methodology for the synthesis of tetrahydrofurans which consists of formal [4 + 1]-cycloaddition of homopropargyl alcohols to diazo dicarbonyl compounds.

During the examination of Rh(II)-catalyzed O−H insertion of **1** onto **2**, we unexpectedly found that the cyclized product **4** was directly formed possibly via Rh(II)-catalyzed Conia-ene reaction of **3** although the yield was less than 10% (Scheme 1).

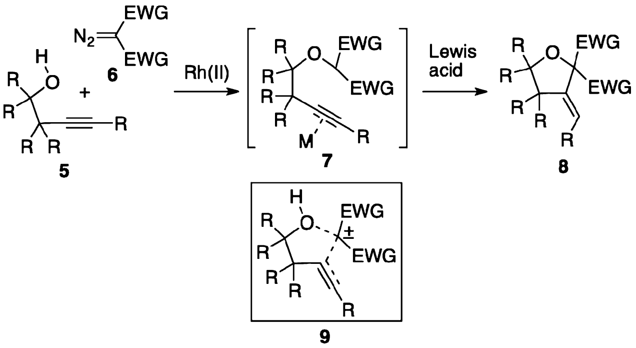
Scheme 1. Formation of 4 via a O−H Insertion/Conia-Ene Process



This observation allowed us to envisage that, provided the second cyclization step is facilitated by the addition of an appropriate Lewis acid,[6−12] the O−H insertion reaction of **5** with **6** and the following cyclization reaction of **7** could be achieved in a cascade manner[13] to directly produce tetrahydrofuran **8** (Scheme 2). To our knowledge, this type of transformation, formally regarded as a [4 + 1]-cycloaddition[14] as depicted in **9**, has not been reported to date.

To assess the feasibility of our envisaged tetrahydrofuran synthesis, we first surveyed Lewis acids as an additive in the reaction of **5a** and **6a** using the Rh$_2$(esp)$_2$ catalyst[15] in CH$_2$Cl$_2$ at room temperature (Table 1). It was observed that the cyclization step was very slow in the absence of a Lewis acid although tetrahydrofuran **8aa** was produced directly in very poor yield (Table 1, entry 1). As a result, among the additives examined, In(OTf)$_3$[5,8c] and ZnCl$_2$[9c] were found to effectively promote the cyclization to provide **8aa** in acceptable yields (Table 1, entries 2 and 3). Since the In(OTf)$_3$-catalyzed conditions were found to exhibit a limited substrate scope,[16] the conditions using ZnCl$_2$ were selected for further optimization.

Scheme 2. Formal [4 + 1]-Cycloaddition Giving Tetrahydrofurans



After the experiments shown in Table 2 were conducted, we identified the reaction conditions listed in entry 3 to be optimum. Thus, when **6a** was reacted with 1 equiv of **5a** using 1 mol % of Rh$_2$(esp)$_2$ and 10 mol % of ZnCl$_2$ in CH$_2$Cl$_2$ at room temperature, the cycloaddition completed within 4 h to give **8aa** in 83% yield. When ZnCl$_2$ was reduced to 5 mol % or less, the cyclization became very sluggish (Table 2, entries 1−4). Toluene, THF, and MeCN were found to be inferior to CH$_2$Cl$_2$ as solvent (Table 2, entries 5−7).

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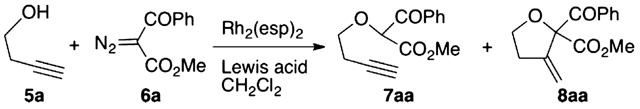
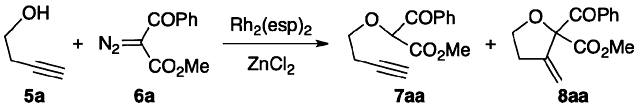
Table 1. Reaction of **5a** and **6a**[a]



entry	Lewis acid	time (h)	yield (%)[b]	
			7aa	**8aa**
1	none	72	80	4
2	$In(OTf)_3$	3	0	93
3	$ZnCl_2$	6	16	68
4	$AuCl(PPh_3)$, AgOTf	6	78	1
5	$Pd(OAc)_2$	3	81	13
6	AgOTf	6	64	20
7	$Ni(acac)_2$	4	23	22
8	CuOTf·1/2PhH	6	21	43
9	$FeCl_3$	6	73	15

[a] Reaction conditions: **5a** (10 equiv), **6a** (1 equiv), $Rh_2(esp)_2$ (1 mol %), Lewis acid (5 mol %), 4 Å MS (30 mg/mL), CH_2Cl_2 (0.5 M), rt. [b] **7aa** and **8aa** were inseparable, and the yields were calculated by their ratio determined by ^1H NMR.

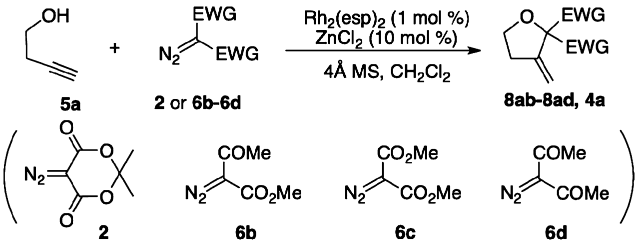
Table 2. Optimization of the Synthesis of **8aa**[a]

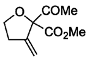
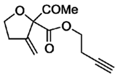
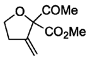
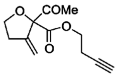
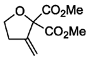
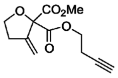
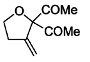
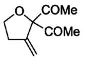
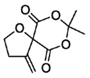


entry	**5a** (equiv)	$ZnCl_2$ (mol %)	solvent	time (h)	yield (%)[b]	
					7aa	**8aa**
1	10	5	CH_2Cl_2	6	16	68
2	10	20	CH_2Cl_2	7	0	86
3	1	10	CH_2Cl_2	4	0	83
4	1	1	CH_2Cl_2	96	47	47
5	1	10	toluene	18	37	22
6	1	10	MeCN	19	57	4
7	1	10	THF	23	0	20

[a] Reaction conditions: **5a** (indicated amount), **6a** (1 equiv), $Rh_2(esp)_2$ (1 mol %), $ZnCl_2$ (indicated amount), 4 Å MS (30 mg/mL), solvent (0.5 M), rt. [b] **7aa** and **8aa** were inseparable, and the yields were calculated by their ratio determined by ^1H NMR.

Table 3. Substrate Scope of Diazo Dicarbonyl Compounds[a]



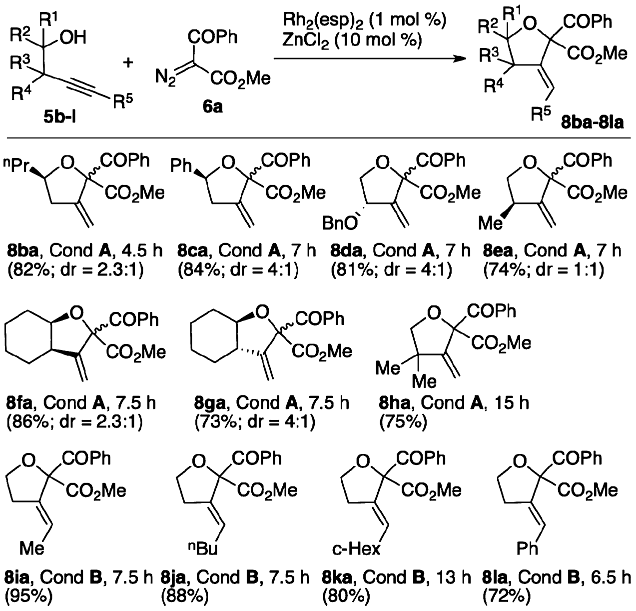
entry	conditions	products and yield[b]
1	**6b** (1 equiv), **5a** (1 equiv), $Rh_2(esp)_2$ (1 mol %), $ZnCl_2$ (10 mol %), rt, 8 h	  **8ab** (49%) **8ab'** (16%)
2	**6b** (1 equiv), **5a** (1.5 equiv), $Rh_2(esp)_2$ (1 mol %), $ZnCl_2$ (10 mol %), rt, 8 h	  **8ab** (70%) **8ab'** (13%)
3	**6c** (1 equiv), **5a** (1.5 equiv), $Rh_2(esp)_2$ (1 mol %), $ZnCl_2$ (10 mol %), rt, 35 min, then reflux, 4 h	  **8ac** (66%) **8ac'** (24%)
4	**6d** (1 equiv), **5a** (1 equiv), $Rh_2(esp)_2$ (1 mol %), $ZnCl_2$ (1 mol %), rt, 7.5 h	 **8ad** (80%)
5[c]	**6d** (1 equiv), **5a** (10 equiv), $Rh_2(esp)_2$ (1 mol %), rt, 27 h	 **8ad** (56%)
6[c,d]	**2** (1 equiv), **5a** (1 equiv), $Rh_2(esp)_2$ (1 mol %), rt, 7 d	 **4a** (16%)

[a] The reactions were conducted using 4 Å MS (30 mg/mL) in CH_2Cl_2 (0.5 M). [b] Isolated yield. [c] $ZnCl_2$ was not employed. [d] Addition of $ZnCl_2$ (10 mol %) led to the complex mixture.

Having established optimized reaction conditions, we next evaluated the substrate scope with the diazo dicarbonyl compounds (Table 3). It was found that compounds **6b**−**d** similarly underwent a cycloaddition reaction with **5a** to afford the corresponding cyclized products **8ab**−**8ad** in moderate to good yields. However, in the cases of **6b** and **6c**, side products **8ab**′ and **8ac**′ were also formed via an ester exchange reaction while the corresponding ester exchange product was not observed for **6a** (Table 3, entries 1−3). Hence, 1.5 equiv of **5a** was necessarily employed to obtain **8ab** and **8ac** in acceptable yields (entries 2 and 3). Reaction of O−H insertion product **7ab**[17] with **5a** under the same conditions using $Rh_2(esp)_2$, $ZnCl_2$, and 4 Å molecular sieves in CH_2Cl_2 did not afford **8ab**′, indicating that the ester exchange reaction occurred prior to O−H insertion. In the case of more reactive **6d**, $ZnCl_2$ could be reduced to 1 mol %, and **8ad** was still obtained in good yield (Table 3, entry 4). Furthermore, the cyclization proceeded even in the absence of $ZnCl_2$ to give **8ad** in moderate yield (Table 3, entry 5). Reaction of **5a** with diazo compound **2** also afforded the cyclized product **4a** directly under the conditions using $Rh_2(esp)_2$ alone as seen in the reaction of Scheme 1 although the yield was very low. However, the addition of $ZnCl_2$ caused the formation of a complex mixture possibly due to the reactivity of the cyclic malonic ester functionality under Lewis acidic conditions (Table 3, entry 6).

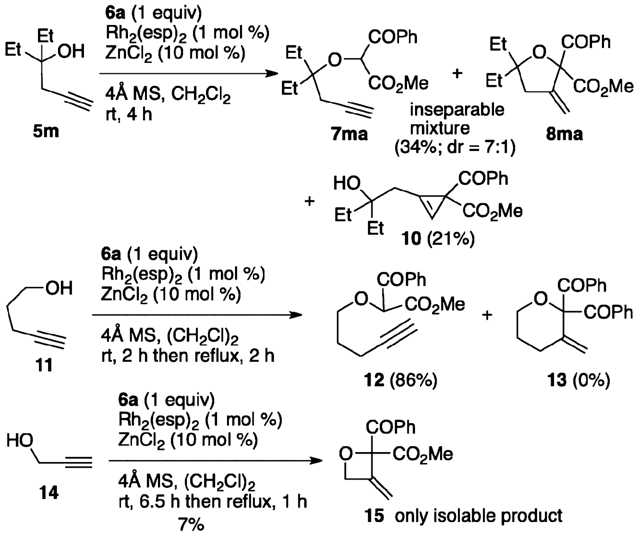
Scheme 3 illustrates the substrate scope with alkynols in the reaction with **6a**. This cycloaddition method is applicable to various substituted homopropargyl alcohols. The presence of a substitutent at the C1 or C2 position did not negatively affect the cyclization, and tetrahydrofurans **8ba**−**8ea** were obtained in good yields, albeit moderate diastereoselectivities.[18] *cis-*/*trans-*Octahydrobenzofuran derivatives **8fa** and **8ga** were also obtained in good yields as a diastereoisomeric mixture.[18] Furthermore, **8ha** could be synthesized in good yield from **5h** having gem-methyl groups next to the alkynic triple bond. It is noteworthy that, in the cases of nonterminal alkynes **5i**−**5l**, the cyclization proceeded with complete *E*-selectivity to produce **8ia**−**8la** in good to excellent yields. Scheme 4 shows the limitation of this method. In the case of tertiary alcohol **5m**, the O−H insertion step was so slow that either **7ma** or **8ma** could not be produced effectively. Instead, **5m** underwent competitive cycloaddition of **6a** to the triple bond to give cyclopropene **10**.

Scheme 3. Substrate Scope of Alkynols[a]

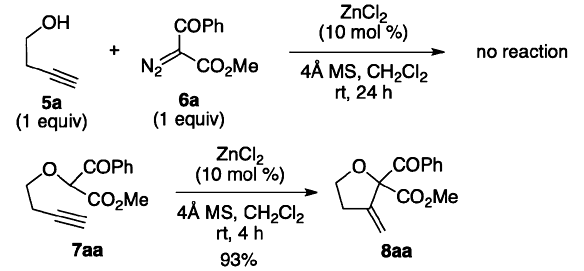


[a]Condition **A**: **5b**−**h** (1 equiv), **6a** (1 equiv), $Rh_2(esp)_2$ (1 mol %), $ZnCl_2$ (10 mol %), 4 Å MS (30 mg/mL), CH_2Cl_2 (0.5 M), rt; Condition **B**: **5i**−**l** (1 equiv), **6a** (1 equiv), $Rh_2(esp)_2$ (1 mol %), $ZnCl_2$ (10 mol %), 4 Å MS (30 mg/mL), $(CH_2Cl)_2$ (0.5 M), rt 30 min, then reflux.

Scheme 4. Limitation of the Cycloaddition Method



Scheme 5. Control Experiments

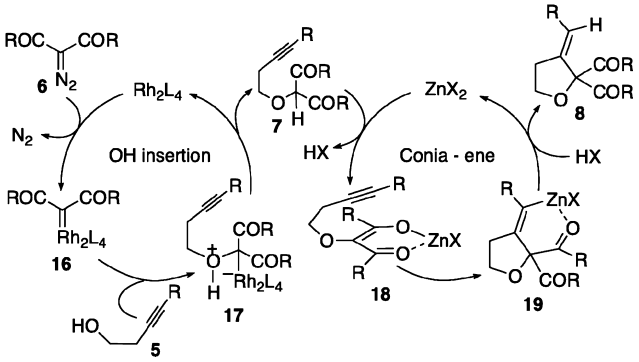


In addition, this method cannot be applied to the synthesis of tetrahydropyrans and oxetanes as observed in the reactions of alkynols **11** and **14** with **6a**.

In order to probe the reaction mechanism, control experiments were carried out as shown in Scheme 5. When the reaction of **5a** with **6a** was conducted using 10 mol % of $ZnCl_2$ alone, no reaction occurred and **6a** was recovered quantitatively. On the other hand, **7aa** smoothly underwent the cyclization reaction under the conditions using 10 mol % of $ZnCl_2$ to produce **8aa** in high yield. These results and the result listed in entry 1 of Table 1 suggest that (i) $Rh_2(esp)_2$ participates in the O−H insertion step while it does not promote the cyclization effectively; (ii) $ZnCl_2$ catalyzes the cyclization step effectively while it does not promote the O−H insertion.

These observations allowed us to propose the reaction mechanism depicted in Scheme 6 where Rh(II) and Zn(II) catalysts worked independently without exerting a deleterious influence on each other. Namely, Rh(II) reacts with diazo dicarbonyl compound **6** to form Rh carbenoid **16** which in turn undergoes the O−H insertion reaction with alkynol **5** via **17** to generate **7**.[19] Then intermediate **7** is involved in the Zn(II)-mediated Conia-ene reaction giving tetrahydrofuran **8** with an *E*-configuration via carbometalation of Zn enolate **18** to **19**.[9a] This mechanism explains the highly selective production of the *E*-isomers **8ia**−**8la**.

Scheme 6. Proposed Reaction Mechanism



In conclusion, we have developed a novel formal [4 + 1]-cycloaddition of readily available homopropargyl alcohols with diazo dicarbonyl compounds, which features broad applicability as well as atom economical efficiency and operational simplicity. The present work provides new entry to tetrahydrofurans.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, characterization data, ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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