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Effect of Ester on Rhodium-Catalyzed Intermolecular [5 + 2] Cycloaddition of 3-Acyloxy-1,4-enynes and Alkynes

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Abstract

We systematically examined the effect of different esters for the rhodium-catalyzed intermolecular [5 + 2] cycloaddition of 3-acyloxy-1,4-enynes and alkynes with a concomitant 1,2-acyloxy migration. Significant rate acceleration was observed for benzoate substrates bearing an electron-donating substituent. The cycloaddition can now be conducted at much more practical conditions for most terminal alkynes.

Cycloaddition is one of the most efficient means to construct cyclic compounds by forming at least two bonds in one operation. The importance of the seven-membered ring as a basic structural motif in natural products and pharmaceutical agents continues to inspire the development of novel cycloaddition reactions.¹ An important breakthrough in this area is the discovery of vinylcyclopropane (VCP) **1** as a 5-carbon building block by Wender's group for Rh-catalyzed [5+2] cycloadditions with alkynes, alkenes, and allenes (Scheme 1).² Research groups of Trost,³ Louie,⁴ and Fürstner⁵ developed different metal catalysts for the [5+2] cycloaddition of VCPs and alkynes. Computational studies by Wender, Houk, and Yu elucidated the detailed mechanism for these cycloadditions.⁶ Recently, new 5-carbon building blocks embedded in substrates **2** and **3** were developed for [5+2] cycloadditions by Yu's⁷ and Mukai's⁸ groups. The Rh-catalyzed hetero-[5+2] cycloadditions were also realized by Wender⁹ and Zhang¹⁰ using cyclopropyl imines and vinyloxydes, respectively. We recently developed a Rh(I)-catalyzed intramolecular [5+2] cycloaddition of 3-acyloxy-1,4-enyne (ACE) and a tethered alkyne in compound **4** with a concomitant 1,2-acyloxy migration.¹¹ Subsequently, the intermolecular [5+2] cycloaddition of ACE **5** and various different alkynes was realized (eq 1).¹² A highly functionalized seven-membered ring **6** could be prepared in as few as two steps from commercially available starting materials. This intermolecular reaction, however, often requires high loading of rhodium catalyst (10 mol%) and excess alkynes to achieve good yields.

Although extensive studies have been conducted in the area of transition metal-catalyzed 1,2-acyloxy migration of propargylic esters, the effect of ester has not been systematically investigated.¹³ Pivalate was employed in most previous studies including ours.

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Occasionally, acetate and benzoate were examined. We herein report our systematic study on the effect of the ester in Rh-catalyzed intermolecular [5+2] cycloaddition of ACEs and alkynes. This investigation has led to the discovery of a new 5-carbon building block that undergoes intermolecular [5+2] cycloaddition with alkynes under much more practical conditions.

Pivalate **5a**, acetate **5b**, and benzoates **5c–5h** containing an electron-donating or electron-withdrawing group were prepared from commercially available 3-methyl-1-penten-4-yn-3-ol by esterification (Table 1). We then examined the rate of intermolecular [5+2] cycloaddition of all ACEs and propargylic alcohol **7** at room temperature using Wilkinson's catalyst in CDCl₃ (eq 2).¹⁴ The rate for pivalate **5a** was comparable to *p*-methyl benzoate **5e** (entries 1 and 5). The rate for acetate **5b** was comparable to non-substituted benzoate **5f** (entries 2 and 6). By increasing the electron donating ability from methyl, to methoxy, and to dimethylamino group for benzoates, the reaction rate increased dramatically, peaking at dimethylaminobenzoate **5c** with a rate about 46 times faster than the non-substituted benzoate **5f** (entries 3–6). The yield of product **6c** was nearly quantitative after 4h, suggesting no other competing pathways. The rate was also increased slightly after going towards the more electron withdrawing groups (entries 7 and 8). The ¹H NMR spectra of crude products, however, appeared to be very complex for substrates **5g** and **5h**, suggesting that other competing pathways became dominant. We therefore did not examine more benzoates with electron-withdrawing groups.

Previously, at least 2.0 equiv of propargylic alcohol **7** and 10 mol % of catalysts were required for the isolation of 81% yield of the cycloaddition product **6a** at 65 °C. When *p*-dimethylaminobenzoate **5c** was employed as the new 5-carbon building block, a 97% isolated yield of product **6c** could be obtained with just a slightly excess of propargylic alcohol and 0.5 mol % of Wilkinson's catalyst at 50 °C (entry 1, Table 2). Only one isomer was obtained for cycloaddition products **6c**.

We have examined the intermolecular cycloaddition of ACE **5a** and various alkynes in our previous study.¹² Some representative alkynes were selected to further test the efficiency of the [5+2] cycloaddition using ACE **5c** (Table 2). In the presence of only 0.5 mol% of catalyst, most functionalized terminal alkynes underwent cycloaddition with ACE **5c** to afford products in excellent yields and regioselectivity (eq 3 and entries 1–6). The functional group on the propargylic position of these terminal alkynes can be primary alcohol, tertiary alcohol, ether, sulphonamide, or acetonitrile. The efficiency of the cycloaddition was decreased for conjugated enyne **8f** (entry 7). Non-functionalized alkyne **8g** also participated in the cycloaddition, albeit under higher catalyst loading (entry 8).

Internal alkyne **8h** worked smoothly in the presence of only 0.5 mol% metal catalyst (eq 4 and entry 9). We were pleased to find that sensitive substrate such as dimethyl acetylenedicarboxylate **8i** also produced the desired cycloaddition product, though the catalyst loading need to be increased to 10 mol% (entry 10). Non-symmetric internal alkyne **8j** afforded a mixture of two isomers in a ratio of 5:1 (entry 11). The reaction of **5c** and internal alkynes **8k** or **8l** led to low yield of desired products and large amount of unidentified by products under various conditions.

Previously, product **11a** was obtained in only 16% yield from pivalate **10a** derived from a secondary alcohol using Wilkinson's catalyst or [Rh(COD)Cl]₂ (5 mol %) and (*p*-CF₃C₆H₄)₃P (30 mol %) at 70 °C in CHCl₃ (eq 5).¹² Longer reaction time or higher temperature did not improve the yield. After switching to substrate **10b**, we were able to isolate 53% yield of the desired product **11b** in the presence of [Rh(COD)Cl]₂ (5 mol %)

and (*p*-CF₃C₆H₄)₃P (30 mol %). No improvement was observed for substrate **10b** over **10a** when Wilkinson's catalyst was employed.

(5)

As we proposed previously,¹² the intermolecular [5+2] cycloaddition could be initiated by a Rh-promoted 1,2-acyloxy migration of the propargylic ester in metal complex **13** to form intermediate **14** (Scheme 2). Metallacyclohexadiene **15** could be derived from direct cyclization of metal complex **14**, or through carbene **16** via a 6- π electrocyclicization. Insertion of alkyne to metallacycle **15** followed by reductive elimination of metallacyclooctatriene **17** would then produce cycloheptatriene product **18** as the major isomer.¹² The electron-donating ester may facilitate the reaction in the first nucleophilic attack step from intermediate **13** to **14** or last reductive elimination step from intermediate **17** to product **18**. In a gold-catalyzed bis-1,2-acyloxy migration of 1,4-bis-propargylic acetates, the migration aptitude of *p*-nitrobenzoate was found to be greater than benzoate.¹⁵ This suggests that the electron-donating ester likely facilitated the reductive elimination step.¹⁶

To further understand the 1,2-migration step, we carried out the cross-over experiment for the cycloadditions between ACE **5i**¹² or **5c** and propargylic alcohol **7** (eq 6). No crossover product was observed. This suggests that the acyloxy group in intermediate **13** does not dissociate from the enyne.

(6)

In summary, dramatic rate acceleration was observed for the intermolecular [5+2] cycloaddition of ACEs and alkynes when the ACE bearing a *p*-dimethylaminobenzoate was employed as the 5-carbon building block. High yields of cycloaddition products could be obtained at a much lower catalyst loading and with less excess of alkynes. The electronic effect of the ester we observed for intermolecular [5+2] cycloaddition not only shed light on the mechanism of the cycloaddition reaction but also have potential broad implications for other transformations involving transition metal-catalyzed 1,2-acyloxy migration of propargylic esters.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Scheme 1.

Five-Carbon Building Blocks for Rh-Catalyzed [5 + 2] Cycloadditions

Scheme 2.
Proposed Mechanism for Rh-Catalyzed Intermolecular [5 + 2] Cycloaddition of ACE and Alkyne

Table 1Rates of Rh-catalyzed [5+2] Cycloaddition of **5** and propargylic alcohol **7**

(2)

Entry	Ester	Initial rate ^{a,b} (min ⁻¹)	Ratio of rates 5/5f
1	5a	4.05	2.72
2	5b	1.01	0.68
3	5c	69.0	46.3
4	5d	9.38	6.30
5	5e	3.09	2.07
6	5f	1.49	1.00
7	5g	1.80	1.21
8	5h	2.78	1.87

^a rate = % yield/time,^b MeNO₂ was used as internal standard.

Table 2

Rh-Catalyzed [5 + 2] Cycloaddition of **5c** and Alkynes (Ar = *p*-Me₂NC₆H₄)^a

(3)

(4)

Entry	Alkyne Substrates	Yield	Ratio of (9: 9')
1	7	6c , 97%	only 6c
2	8a ,	9a , 87%	only 9a
3	8b ,	9b , 89%	>20:1
4	8c ,	9c , 95%	only 9c
5	8d ,	9d , 96%	17:1
6	8e ,	9e , 74%	only 9e

(3)

(4)

Entry	Alkyne Substrates	Yield	Ratio of (9: 9')
7 ^b	8f , 	9f , 58%	>20:1
8 ^c	8g , 	9g , 77%	8:1
9	8h , 	9h , 82%	-
10 ^c	8i , MeO ₂ C-C≡C-CO ₂ Me	9i , 89%	-
11 ^b	8j , (R = CH ₂ OH, R' = Me)	9j , 77%	5:1
12	8k , EtO ₂ C-C≡C-Me (R = CO ₂ Et, R' = Me)	complex mixture	
13	8l , <i>n</i> -Pr-C≡C- <i>n</i> -Pr	complex mixture	

^a Conditions: [Rh(PPh₃)₃Cl] (0.5 mol %), alkyne **7** or **8** (1.1 equiv), CHCl₃ (0.4 M), 50 °C, 24h unless noted otherwise. Isomeric ratios were determined by ¹H NMR of crude products.

^b [Rh(PPh₃)₃Cl] (2 mol %)

^c [Rh(PPh₃)₃Cl] (10 mol %)