Alkynylation

A Mild Method for the Preparation of γ-Hydroxy-α,β-Acetylenic Esters**

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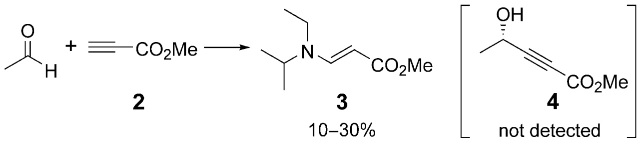
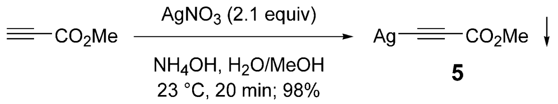
The alkynylation of a carbonyl compound is a powerful reaction for forming a carbon–carbon σ bond. Highly functionalized γ-hydroxy-α,β-acetylenic esters $\mathrm{RCH(OH)C{\equiv}C{-}CO_2Me}$ (**A**) are promising synthetic intermediates that can be used as precursors to a variety of complex molecules.[1] Since the procedure was reported by Midland et al.,[2] alcohols **A** have mainly been prepared by the treatment of aldehydes with the lithium acetylide $\mathrm{Li{-}C{\equiv}C{-}CO_2Me}$ (**1**). The acetylide **1** can be generated in situ by the addition of *n*-butyllithium to methyl propiolate (**2**). Because *n*-butyllithium is itself a nucleophile toward aldehydes and ketones, the amount of base used must be controlled carefully. Furthermore, as a result of these strongly basic conditions access to **A** is mostly limited to base-stable compounds. As this widely used method requires a stringent balance in the stoichiometry of the reagents, one of which is moisture sensitive, it is often difficult to obtain satisfactory results. Therefore, a milder and more robust synthetic method with broader scope is needed for the preparation of alcohols **A**.

A recent development in the enantioselective addition of a terminal alkyne to an aldehyde, pioneered by Carreira and co-workers, involves the in situ generation of a zinc acetylide in the presence of a tertiary amine.[3] However, this method did not enable us to couple acetaldehyde with **2** to form the corresponding methyl pentynoate **4** (Scheme 1). Instead, we isolated compound **3** as the major product. We attributed this undesired reaction to the facile conjugate addition of the tertiary amine to **2**, followed by loss of one *i*Pr group. These results prompted us to develop alternative reaction conditions under which an aldehyde would undergo condensation with **2** in the absence of a base.



Scheme 1. Reagents and conditions: $\mathrm{Zn(OTf)_2}$ (1.0 equiv), $i\mathrm{Pr_2NEt}$ (1.05 equiv), (−)-*N*-methylephedrine (1.05 equiv), $\mathrm{CH_2Cl_2}$, 0→23 °C. Tf = trifluoromethanesulfonyl.

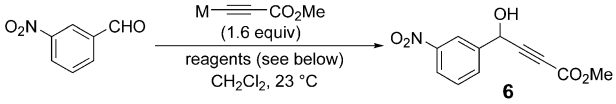
The preparation of metal acetylides $\mathrm{M{-}C{\equiv}C{-}R}$ (M = Li, Sn, Si, B) often involves the use of a strong base. In contrast, the silver acetylide **5**[4] can be readily prepared in nearly quantitative yield by a known mild protocol on an ~8-g scale, and this solid material can be stored at ambient temperature in a vial for many months in the dark without any precaution to avoid moisture (Scheme 2).[5]



Scheme 2. Preparation of the silver acetylide **5**.

Various silver acetylides are known to react with acid chlorides to generate alkyl 4-oxo-2-alkynoates.[6] However, in the absence of an additive, compound **5** failed to react with 3-nitrobenzaldehyde to afford the alcohol **6** (Table 1, entry 1).

Table 1: $[\mathrm{Cp_2ZrCl_2}]$-promoted alkynylation.



Entry	M	Reagents	*t* [h]	Yield [%][a]
1	Ag	none	30	0
2	Ag	$[\mathrm{Cp_2ZrCl_2}]$ (1.2 equiv)	30	73
3	Ag	$[\mathrm{Cp_2ZrCl_2}]$ (1.2 equiv)+AgOTf (0.2 equiv)	5	95
4	H	$[\mathrm{Cp_2ZrCl_2}]$ (1.2 equiv)	30	0

[a] Yield of isolated product.

After screening several additives, we found that the desired alcohol **6** was produced in 73 % yield after 30 h at 23 °C in the presence of $[\mathrm{Cp_2ZrCl_2}]$ (Table 1, entry 2). Although the use of $\mathrm{ZnBr_2}$, $[\mathrm{Cp_2TiCl_2}]$, and $\mathrm{ZrCl_4}$ led to the alcohol **6** in 4, ~30, and 51 % yield, respectively, neither $\mathrm{BF_3{\cdot}OEt_2}$ nor $\mathrm{Cu(OTf)_2}$ promoted the condensation reaction. Based on these preliminary studies, this alkynylation appears to be facilitated by zirconium reagents. Of the solvents that we employed for the coupling reaction ($\mathrm{CH_2Cl_2}$, THF, MeCN), the use of $\mathrm{CH_2Cl_2}$ gave the highest yield.

Although we have not characterized any intermediates in the coupling reaction, we hypothesized that $[\mathrm{Cp_2(Cl)Zr{-}C{\equiv}C{-}CO_2Me}]$ might be the reactive species.[7] The observations by Jordan et al. and Suzuki and co-workers that silver salts facilitate the coupling between $[\mathrm{Cp_2(Cl)Zr{-}R}]$ ($\mathrm{R = CH_3}$ and R = alkenyl, respectively) and an aldehyde or a ketone prompted us to examine whether our $[\mathrm{Cp_2ZrCl_2}]$-promoted coupling could be further accelerated by AgOTf.[8] Thus, AgOTf (0.2 equiv) was used together with $[\mathrm{Cp_2ZrCl_2}]$ (1.2 equiv). This modification accelerated the coupling reac-

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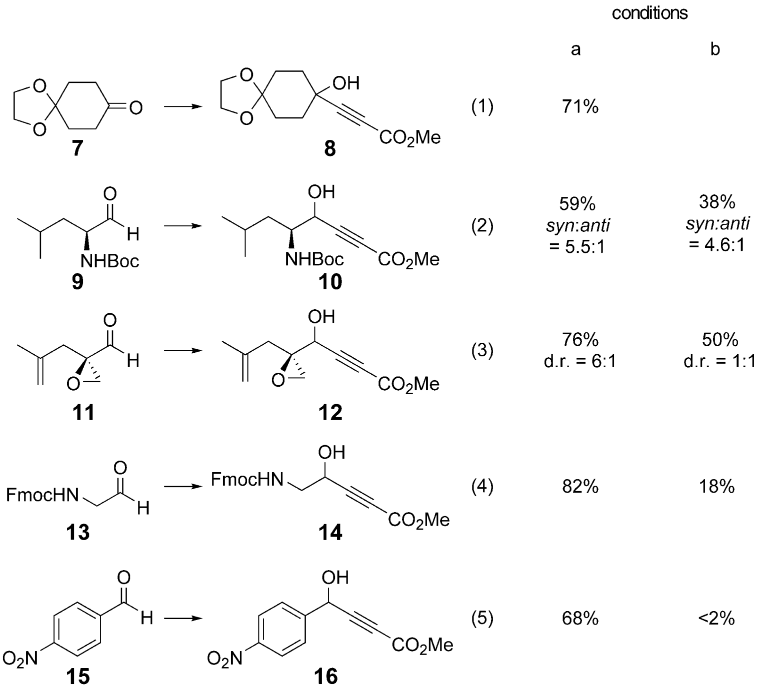
tion dramatically; the reaction was complete after 5 h (95 % yield) rather than the 30 h required in the absence of AgOTf (Table 1, entry 3). The necessity of the silver acetylide **5** was demonstrated by using **2** in the presence of [Cp_2ZrCl_2], which did not produce the alcohol **6** (Table 1, entry 4).

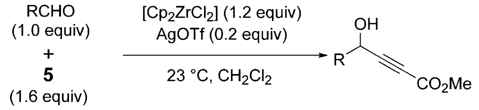
We then screened a variety of aldehydes to test the scope of the zirconium-promoted alkynylation reaction (Table 2). Both electron-deficient and electron-rich aromatic aldehydes reacted with **5** to form the corresponding alcohols in 76–95 % yield (Table 2, entries 1–3). Cinnamaldehyde reacted in a 1,2-addition fashion to form the corresponding alcohol in 93 % yield (Table 2, entry 4). The reactions of aliphatic aldehydes, including easily enolizable phenylacetaldehyde, also afforded the corresponding alcohols in 53–78 % yield (Table 2, entries 5–8).

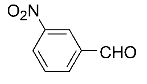
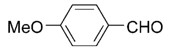
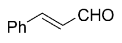
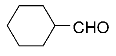
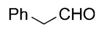
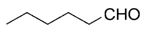


Scheme 3. Conditions: a) **5** (1.6 equiv), [Cp_2ZrCl_2] (1.2 equiv), AgOTf (0.2 equiv), CH_2Cl_2, 23 °C, 2–7 h; b) **2** (1.6–2 equiv), *n*BuLi or LiN(TMS)$_2$ (1.4–1.6 equiv), −78 °C, 1 to 30 min. Boc = *tert*-butoxycarbonyl, Fmoc = 9-fluorenylmethoxycarbonyl, TMS = trimethylsilyl.

This method could be used to couple **5** with the ketone **7**, even in the presence of the cyclic ketal, to afford the corresponding alcohol **8** [Eq. (1), Scheme 3]. To test 1,2-asymmetric induction in this alkynylation method, we prepared the aldehyde **9** according to the published protocol.[9] We chose this aldehyde because the stereoselectivity in the addition of **1** is known (38 % yield, *syn*:*anti* = 4.6:1).[10] The aldehyde **9** was converted into the alcohol **10** under our conditions in 59 % yield with a *syn*:*anti* ratio of 5.5:1 [Eq. (2), Scheme 3]. This result shows the higher efficiency and comparable degree of 1,2-asymmetric induction of our alkynylation method at room temperature relative to a widely-used alkynylation method with **1** at −78 °C. A spiroepoxide was also found to be compatible with this Zr-promoted alkynylation. Thus, the alcohol **12** was produced in 77 % yield with a diastereomeric ratio of 6:1 from the aldehyde **11** [Eq. (3), Scheme 3; relative configuration not determined]. In contrast, the treatment of **11** with **1** gave the alcohol **12** in 50 % yield with a diastereomeric ratio of 1:1. The base-sensitive *N*-Fmoc-protected aldehyde **13** was subjected to the same reaction conditions [Eq. (4), Scheme 3]. The corresponding propargylic alcohol **14** was isolated in 82 % yield, whereas the addition of **1** to the same aldehyde afforded the desired alcohol in only 18 % yield. The Zr-promoted alkynylation was also effective for the preparation of the base-sensitive compound **16** from **15** in 68 % yield [Eq (5), Scheme 3]. In contrast, the coupling of **15** with **1** generated **16** in less than 2 % yield. These examples indicate that the Zr-promoted alkynylation method can be used for substrates that can not be prepared under conventional conditions. The results shown in Equations (2) and (4) also demonstrate that this reaction is compatible with the relatively acidic carbamate protons -N*H*CO$_2$R. Although the same products were formed in all these reactions whether AgOTf was present or not, we found that AgOTf accelerated the reactions and led to the formation of the products in higher yields. The quantity of AgOTf used could be reduced to 5 mol % without a decrease in yield (data not shown).

Table 2: [Cp_2ZrCl_2]/AgOTf-promoted alkynylation of aldehydes.



Entry	RCHO	*t* [h]	Yield [%][a]
1		5	95
2		3	76
3	PhCHO	10	84
4		2.5	93
5	CH_3CHO	4	53
6		1	78
7		3.5	61
8		4	78

[a] Yield of isolated product.

In summary, we have developed a novel method for the coupling of aldehydes or ketones with alkyl propiolates in the absence of a base. Because the reagents involved in this coupling reaction are easier to handle than *n*-butyllithium and **1**, these reaction conditions can be employed on a small scale (~ 0.5 mmol) or on a 6 mmol scale without a decrease in yield. We have also demonstrated that various functional groups are compatible with these alkynylation conditions. Additionally, **5**, [Cp_2ZrCl_2], and AgOTf can be stored at room temperature without paying particular attention to the exclusion of moisture. The synthetic use of silver acetylides has been limited until now to only a few reaction types.[11] This study suggests that the formation of silver acetylides of electron-deficient alkynes is a powerful method for the conversion of non-nucleophilic alkynes into reactive species toward aldehydes and ketones. Studies into the scope and limitation (note: the silver acetylide of the acetylenic ketone Ag-C≡C-C(=O)CH_3 was found to be shock-sensitive) of these reaction conditions with other electrophiles and nucleophiles are in progress in our laboratory.

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