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Catalytic One-Pot Synthesis of Trisubstituted Allenes from Terminal Alkynes and Ketones

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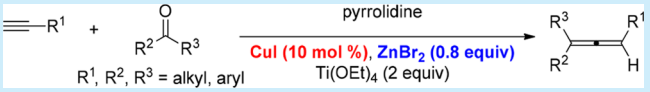
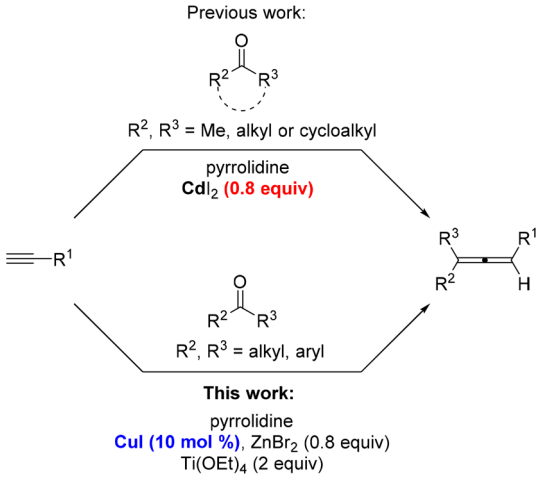
Supporting Information

ABSTRACT: An efficient one-pot synthesis of trisubstituted allenes from readily available terminal alkynes and ketones is realized. A wide range of trisubstituted allenes may be synthesized efficiently via this method. Preliminary mechanistic studies revealed that CuI and $Ti(OEt)_4$ are in charge of the formation of propargylic amine, while $ZnBr_2$ is responsible for the transformation from propargylic amine to allene.



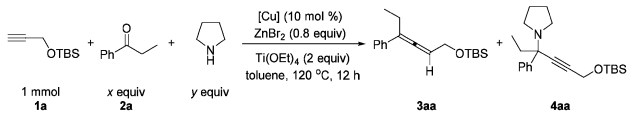
Allenes are not only important structural motifs in natural products, drugs, and molecular materials[1] but also useful intermediates in organic synthesis.[2] Differences in steric and electronic effects between the two cumulated double bonds are helpful for solving selectivity problems in organic transformation. Therefore, great efforts have been directed toward the synthesis of this type of compounds,[3−7] such as transition-metal-catalyzed coupling reaction of propargylic derivatives,[4] [3,3]-sigmatropic rearrangement,[3e,5] coupling of terminal alkynes with diazo compounds,[6] and conjugate addition to enynes.[7] However, convenient and straightforward methods for synthesizing trisubstituted allenes from readily available starting materials are very rare. In 2013, our group reported that the CdI_2-mediated allenylation of terminal alkynes (ATA) reaction realized the one-pot synthesis of trisubstituted allenes from terminal alkynes and ketones (Scheme 1).[8] However, further study in this group revealed that the substrate scope of ketones is quite narrow: only *cyclic* ketones and *methyl* alkyl ketones work well. Moreover, CdI_2 is not environmentally friendly. Herein, we report an efficient and practical one-pot synthesis of trisubstituted allenes from the ATA reaction with ketones under the catalysis of CuI with the help of $ZnBr_2$ and $Ti(OEt)_4$.

Scheme 1. Allenylation of Terminal Alkynes Using Ketones



We initiated our study with the reaction of TBS-protected propargyl alcohol **1a** (1 mmol), propiophenone **2a** (1.4 equiv), pyrrolidine (1.1 equiv), $ZnBr_2$ (0.8 equiv), and $Ti(OEt)_4$ (2 equiv) in toluene. After screening different copper catalysts, we discovered that when 10 mol % of CuI was used, the desired allene product **3aa** was formed in 56% yield (entry 4, Table 1). Increasing the loading of ketone **2a** improved the yield of **3aa** to 60% (entry 5, Table 1). When the reaction time was prolonged from 12 to 18 h, the yield of propargylic amine **4aa**

Table 1. Optimization of the Reaction Conditions[a]



entry	*x*/*y* (equiv)	[Cu]	yield of **3aa**[b] (%)	yield of **4aa**[b] (%)
1[c]	1.4/1.1		0	8
2	1.4/1.1	$CuBr_2$	45	7
3	1.4/1.1	CuCl	45	2
4	1.4/1.1	CuI	56	14
5	1.6/1.1	CuI	60 (55[d])	14
6[e]	1.6/1.1	CuI	42	7

[a]The reaction was carried out on a 1 mmol scale in 5 mL of toluene. [b]Determined by ^1H NMR analysis with mesitylene or CH_2Br_2 as the internal standard. [c]The reaction time was 10 h. [d]Isolated yield. [e]The reaction time was 18 h.

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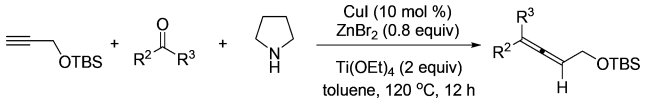
dropped from 14% to 7%, whereas the yield of **3aa** also dropped from 60% to 42% (entry 6, Table 1).[9] Thus, **1a** (1 mmol), **2a** (1.6 equiv), pyrrolidine (1.1 equiv), CuI (10 mol %), $ZnBr_2$ (0.8 equiv), and $Ti(OEt)_4$ (2 equiv) in toluene at 120 °C for 12 h (entry 5, Table 1) were defined as the optimized reaction conditions for further study.

With the optimized conditions in hand, we began to investigate the scope of the method. At first, different kinds of ketones were tested. Cyclic ketones from 5-membered ring **2b** to 12-membered ring **2f** all could afford trisubstituted allenes **3ab**–**af** in 45–77% yields (entries 1–6, Table 2). The reaction could also be extended to acyclic aliphatic ketones, such as nonmethyl hexan-3-one **2h** and methyl 2-phenylethyl ketone **2i** (entries 7 and 8, Table 2). Even the sterically hindered α-substituted ketones **2g** and **2j** yielded the corresponding products in 69% (dr = 2.5:1) and 60% yield, respectively (entries 6 and 9, Table 2). As for the aromatic ketones, long-chain alkyl aromatic ketone **2k** was also suitable for this reaction, with a yield of 44% (entry 10, Table 2). Propiophenone analogues with *m*-Br, *p*-Cl, *p*-F, and *m*-MeO substituents all afforded 48–51% yields of the corresponding products (entries 11–14, Table 2).

Table 2. Scope of Ketones[a]



1 mmol **1a** | 1.6 equiv **2** | 1.1 equiv | **3**

entry	R^2, R^3	isolated yield of **3** (%)
1	$-(CH_2)_4-$ (**2b**)	54 (**3ab**)
2	$-(CH_2)_5-$ (**2c**)	77 (**3ac**)
3	$-(CH_2)_6-$ (**2d**)	67 (**3ad**)
4	$-(CH_2)_7-$ (**2e**)	45 (**3ae**)
5	$-(CH_2)_{11}-$ (**2f**)	60 (**3af**)
6	$-CH(CH_3)(CH_2)_4-$ (**2g**)	69 (**3ag**)[b]
7	*n*-Pr, Et (**2h**)	65 (**3ah**)
8	$PhCH_2CH_2$, Me (**2i**)	66 (**3ai**)
9	*i*-Pr, Me (**2j**)	60 (**3aj**)
10	Ph, *n*-Bu (**2k**)	44 (**3ak**)
11	*m*-BrC_6H_4, Et (**2l**)	48 (**3al**)
12	*p*-ClC_6H_4, Et (**2m**)	50 (**3am**)
13	*p*-FC_6H_4, Et (**2n**)	48 (**3an**)
14	*m*-$MeOC_6H_4$, Et (**2o**)	51 (**3ao**)

[a]The reaction was carried out on a 1 mmol scale in 5 mL of toluene. [b]dr = 2.5:1.

This method can also be utilized in a relatively complex substrate, such as tropinone **2p** (Scheme 2, eq 1). The acid-sensitive functional group ketal **2q** can be tolerated under the reaction conditions (Scheme 2, eq 2).

Even with acetone **2r** with a low boiling point, the yield of **3br** was 55% with 23% of **1b** recovered (entry 1, Table 3). A wide range of different alkynes were examined. Secondary propargyl alcohol derivatives (**1b** and **1c**) afforded **3bc** and **3cc** in 85% and 84% yields, respectively (entries 2 and 3, Table 3), and TBS-protected homopropargyl alcohol **1d** could also produce **3dc** in 56% yield (entry 4, Table 3). The phthalimide **1e** could also be applied in this reaction to afford the trisubstituted allenes **3ec** and **3ea** in 49% and 51% yields, respectively (entries 5 and 6, Table 3). In addition, 4-ethynylanisole **1f** afforded 43% of product **3fc** (entry 7, Table 3). The terminal alkyl-substituted alkyne, 1-octyne **1g**, could also react smoothly, forming products **3gs** and **3gc** (entries 8 and 9, Table 3).

Scheme 2. ATA Reaction with Ketone 2p and 2q

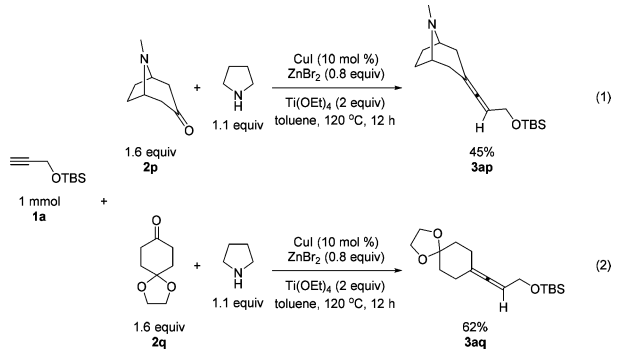
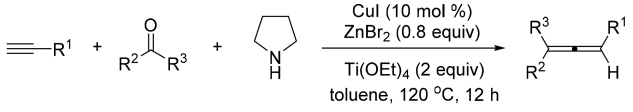


Table 3. Scope of Terminal Alkynes and Ketones[a]

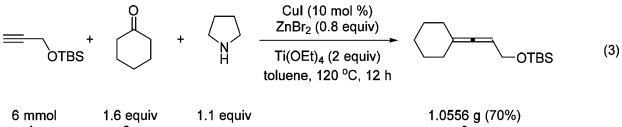


1 mmol **1** | 1.6 equiv **2** | 1.1 equiv | **3**

entry	R^1	R^2, R^3	isolated yield of **3** (%)
1[b]	CH(Ph)OTBS (**1b**)	Me, Me (**2r**)	55 (**3br**)[c]
2	CH(Me)OTBS (**1c**)	$-(CH_2)_5-$ (**2c**)	84 (**3cc**)
3	CH(Ph)OTBS (**1b**)	$-(CH_2)_5-$ (**2c**)	85 (**3bc**)
4	CH_2CH_2OTBS (**1d**)	$-(CH_2)_5-$ (**2c**)	56 (**3dc**)
5	CH_2NPhth (**1e**)	$-(CH_2)_5-$ (**2c**)	51 (**3ec**)
6	CH_2NPhth (**1e**)	Ph, Et (**2a**)	49 (**3ea**)
7	*p*-$MeOC_6H_4$ (**1f**)	$-(CH_2)_5-$ (**2c**)	43 (**3fc**)
8	*n*-C_6H_{13} (**1g**)	Me, CH(Me)OBn (**2s**)	46 (**3gs**)[d]
9	*n*-C_6H_{13} (**1g**)	$-(CH_2)_5-$ (**2c**)	40 (**3gc**)

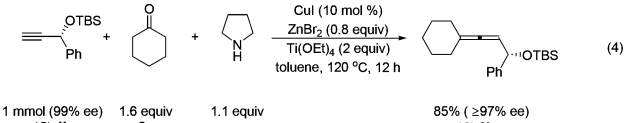
[a]The reaction was carried out on a 1 mmol scale in 5 mL of toluene. [b]3 equiv of acetone was used. [c]23 mol % of **1b** was recovered. [d]dr = 1:1.

The reaction may be easily conducted on a 1-g scale, affording the trisubstituted allene **3ac** in 70% yield (eq 3).



6 mmol **1a** | 1.6 equiv **2c** | 1.1 equiv | 1.0556 g (70%) **3ac**

For the TBS-protected chiral alkynol (*S*)-**1b**, optically active TBS-protected α-allenol (*S*)-**3bc** was afforded in 85% yield with ≥97% ee (eq 4).



1 mmol (99% ee) (*S*)-**1b** | 1.6 equiv **2c** | 1.1 equiv | 85% (≥97% ee) (*S*)-**3bc**

To investigate the role of CuI, $ZnBr_2$, and $Ti(OEt)_4$ in the reaction, control experiments were conducted (Scheme 3). When the reaction was carried out with 0.8 equiv of $ZnBr_2$ and 2 equiv of $Ti(OEt)_4$ in the absence of CuI at 120 °C for 12 h,

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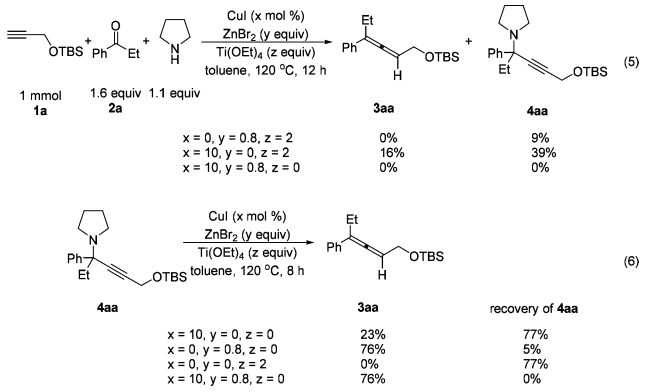
no allene product **3aa** was detected, and only propargylic amine **4aa** was formed in 9% NMR yield. But when the reaction was carried out with 10 mol % of CuI and 2 equiv of $Ti(OEt)_4$, **3aa** and **4aa** were produced in 16% and 39% NMR yield, respectively. However, when the reaction was carried out with both 0.8 equiv of $ZnBr_2$ and 10 mol % of CuI in the absence of $Ti(OEt)_4$, no **3aa** or **4aa** was formed. These results suggested that $Ti(OEt)_4$ is necessary, and CuI was more efficient than $ZnBr_2$ in promoting the formation of propargylic amine **4aa** as the first step.

When the isolated propargylic amine **4aa** was reacted with 10 mol % of CuI for 8 h, allene **3aa** was obtained in 23% yield, with 77% of **4aa** being recovered. On the contrary, with 0.8 equiv of $ZnBr_2$, 76% of the **3aa** was obtained and 5% of **4aa** was recovered, and when **4aa** was treated with 10 mol % of CuI and 0.8 equiv of $ZnBr_2$, the yield of **3aa** is the same as that when only $ZnBr_2$ was used with a complete conversion of **4aa** (Scheme 3). These data indicate $ZnBr_2$ is more effective in converting propargylic amine **4aa** to allene **3aa** than CuI in the second step. In addition, no allene **4aa** was detected when only $Ti(OEt)_4$ was used. Thus, $Ti(OEt)_4$ did not participate in the second step.

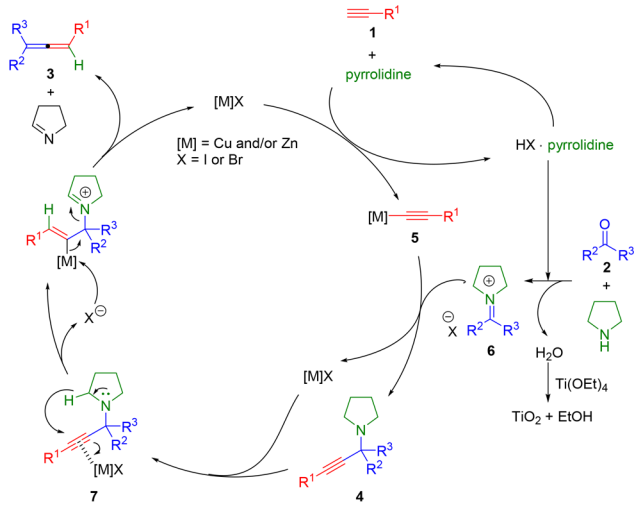
Scheme 3. Control Experiments



Based on the above data and related reports on this field,[10,11] we proposed a plausible mechanism for the current protocol of ATA reaction: The alkynylmetal species **5**, generated from terminal alkyne in the presence of CuI, $ZnBr_2$, pyrrolidine, reacted with ketoniminum **6** formed in situ from ketone, pyrrolidine, and $Ti(OEt)_4$ to form the corresponding propargylic amine **4** (Scheme 4). Zn(II) and/or Cu(I) coordinated to the carbon−carbon triple bond in the propargylic amine **4** to form complex **7**, which then underwent an intramolecular 1,5-hydride transfer and β-elimination to afford the corresponding trisubsituted allene **3**.

In summary, we have developed an efficient one-pot ATA reaction to synthesize trisubstituted allenes from readily available alkynes and ketones using environmentally friendly metallic catalyst and reagents. This method has a much broader substrate scope. Control experiments suggested that each of them, CuI, $ZnBr_2$, and $Ti(OEt)_4$, played a crucial and different role in this transformation. Further studies, including the asymmetric version of this reaction, are being conducted in our laboratory.

Scheme 4. Plausible Mechanism



■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b02443.

Experimental procedure, spectroscopic data, and ^1H, ^{13}C, and ^{19}F NMR spectra for all the products (PDF)

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Notes

The authors declare no competing financial interest.

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