Organic LETTERS
Letter
pubs.acs.org/OrgLett

Cadmium Iodide Mediated Allenylation of Terminal Alkynes for the Synthesis of Methyl-Substituted Allenes

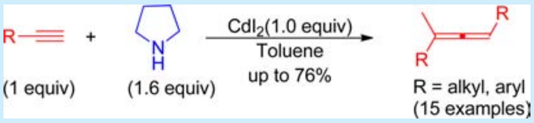
Xinjun Tang,[†] Yulin Han,[†] and Shengming Ma*[,†,‡]

[†]State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 345 Lingling Lu, Shanghai 200032, P. R. China

[‡]Department of Chemistry, Fudan University, 220 Handan Road, Shanghai 200433, P. R. China

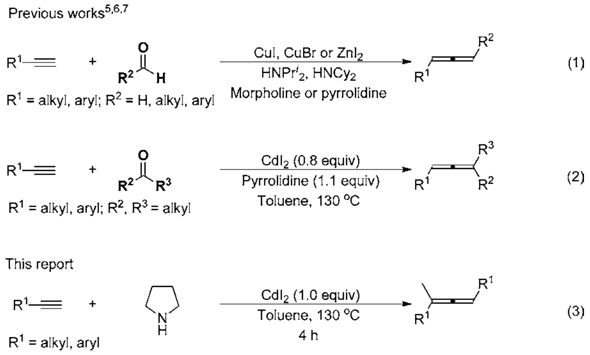
Ⓢ *Supporting Information*

ABSTRACT: A cadmium iodide mediated tandem reaction involving amine and two molecules of terminal alkynes for the synthesis of trisubstituted allenes has been developed. By applying this protocol, methyl-substituted allenes may be obtained easily from two molecules of terminal alkynes and pyrrolidine via methyl ketoniminium and propargylic amine formation, 1,5-hydride transfer and β-elimination.



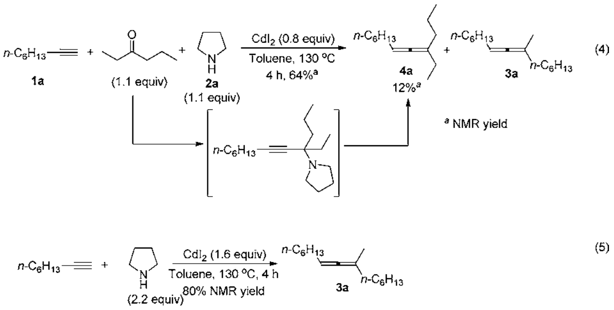
Allenes are important and useful building blocks in organic synthesis.[1,2] Many natural products and bioactive compounds containing allene moieties have been identified.[3] In the past decades, much effort has been focused toward the efficient synthesis of allenes.[4] By using the allenylation of terminal alkynes (ATA) reaction, mono-,[5] 1,3-di-,[6] and trisubstituted[7] allenes may now be easily prepared from readily available chemicals in any chemical laboratory, i.e., terminal alkynes, aldehydes or ketones, and amines (Scheme 1).

Scheme 1. Synthesis of Allenes by Using ATA Reaction



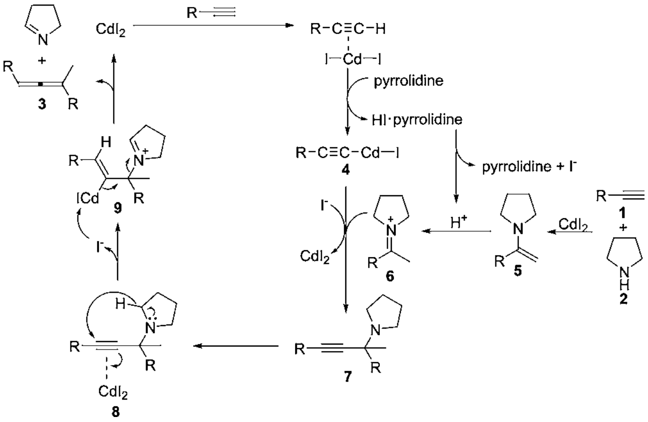
During our studies on the synthesis of trisubstituted allenes,[7] the reaction of 1-octyne **1a**, hexan-3-one, and pyrrolidine, the normal allene product **4a** (12% by NMR) was contaminated with the formation of an unexpected product **3a**, which was later identified as 7-methylpentadeca-7,8-diene in 64% NMR yield. This product must be formed from two molecules of the terminal alkyne (Scheme 2, eq 4). In order to investigate the origin of this product, we conducted the same reaction in the absence of 3-hexanone. To our delight, the unexpected methyl-substituted allene **3a** could be formed successfully in 80% NMR yield (Scheme 2, eq 5).

Scheme 2. Unexpected Formation of Trisubstituted Allene 3a



Based on the above results and the recent reports of ATA reactions, a plausible mechanism for this reaction was proposed as shown in Scheme 3.[6,7] Different from the classical ATA

Scheme 3. Proposed Mechanism for the Formation of 3



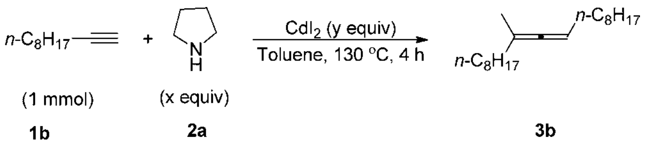
Received: January 13, 2015
Published: February 12, 2015

DOI: 10.1021/acs.orglett.5b00105
Org. Lett. 2015, 17, 1176–1179

reactions in the presence of the ketone,[7] the ketoniminium **6** was generated from hydroamination of alkyne **1** in this protocol.[8] It is worth noting that the hydroamination followed Markovnikov's rule to afford enamine **5** only,[9] which may isomerize to ketoniminium **6** easily. This in situ generated intermediate would react with 1-alkynyl cadmium species **4**, which was generated from a terminal alkyne in the presence of pyrrolidine, to give the corresponding propargylic amine **7**. With the mediation of CdI_2, the trisubstituted allene **3** would be formed via 1,5-hydride transfer and β-elimination.[7] Herein, we wish to report our observations on this new ATA reaction for the synthesis of trisubsitituted allenes through cadmium iodide mediated tandem amine–alkyne–alkyne reaction.

Our optimization work began with 1-decyne **1b** and pyrrolidine **2a** under the mediation of CdI_2. After numerous trials, we were happy to find that the reaction of **1b** (1 mmol), **2a** (1.6 equiv), and CdI_2 (1.6 equiv) in 5 mL of toluene with stirring at 130 °C for 4 h afforded the trisubstituted allene **3b** in 82% yield (Table 1, entry 3)! Further reducing the loading of pyrrolidine **2a** gave a lower yield of the corresponding allene **3b** (Table 1, entry 4); reducing the loading of CdI_2 also led to a lower yield of the allene product (Table 1, entries 5–7). Considering the amount of CdI_2, we chose conditions of entry 6 for further study. Then, the concentration of the reaction was considered (Table 1, entries 8 and 9). As shown in the table, the reaction at a concentration of 0.5 M yielded the highest yield of 81% (Table 1, entry 8).

Table 1. Optimization of the Reaction Conditions for the ATA Reaction[a]

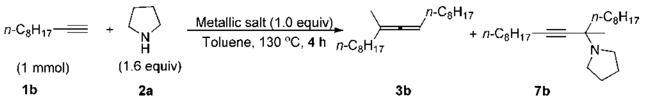


entry	*x* (equiv)	*y* (equiv)	**3b**, yield (%)[b]
1	2.2	1.6	80
2	1.8	1.6	82
3	1.6	1.6	82
4	1.4	1.6	78
5	1.6	1.2	80
6	1.6	1.0	78
7	1.6	0.8	65
8[c]	1.6	1.0	81
9[d]	1.6	1.0	68

[a] The reaction was conducted using alkyne **1b** (1 mmol), amine **2a**, and CdI_2 at 130 °C in 5 mL of toluene for 4 h. [b] Determined by ^1H NMR analysis using CH_3NO_2 as the internal standard. [c] The concentration of the reaction was 0.5 M. [d] The concentration of the reaction was 0.125 M.

We also examined the effect of other metal mediators. To our surprise, only $CdBr_2$ could mediate the formation of allene **3b**, although the NMR yield was only 17%, together with a 40% NMR yield of propargylic amine **7b** (Table 2, entry 1). Other metallic salts in groups 11 and 12, such as CuI,[5,10] ZnI_2,[6] AgI,[11] AuI,[12] and $HgCl_2$, all failed to promote the reaction (Table 2, entries 2–6), indicating the unique effect of cadmium halide in the formation of allene. When CuI was used as the mediator, the Glasser-type coupling product was not detected. Thus, **1b** (1 mmol), **2a** (1.6 equiv), and CdI_2 (1.0 equiv) in 2 mL of toluene with stirring at 130 °C for 4 h were defined as the optimized reaction conditions for further study.

Table 2. Groups 11 and 12 Metallic Salts for the ATA Reaction[a]



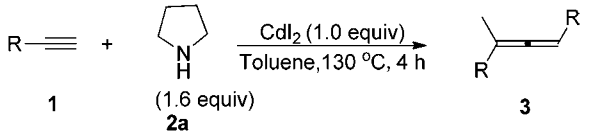
entry	metallic salt	**3b**, yield (%)[b]	**7b**, yield (%)[b]
1	$CdBr_2$	17	40
2	CuI	0	14
3	ZnI_2	0	–
4	AgI	0	–
5	AuI	0	–
6	$HgCl_2$	0	9

[a] The reaction was conducted using alkyne **1b** (1 mmol), amine **2a** (1.6 equiv), and metallic salt (1.0 equiv) at 130 °C in 2 mL of toluene for 4 h. [b] Determined by ^1H NMR analysis using CH_3NO_2 as the internal standard.

With the optimal reaction conditions in hand, we first examined the reactivity of different terminal alkyl-substituted alkynes (Table 3). 1-Decyne **1b** and shorter chain alkynes **1a** and **1c** all afforded decent yields of the corresponding allene products (Table 3, entries 1–3). Functionalized alkyl alkynes were also suitable for this ATA reaction (Table 3, entries 4–9): interestingly, the ethyl and methyl ester of dodec-11-ynoic acids **1d** and **1e** gave the products **3d** and **3e** in the same yield of 58% (Table 3, entries 4 and 5), while dodec-11-ynoic acid did not work under the standard reaction conditions. However, undec-10-yn-1-ol **1f** reacted well in the presence of pyrrolidine to afford allene **3f** in a moderate yield (Table 3, entry 6). Moreover, the TBS and TIPS protected propargyl alcohols **1g** and **1h** could also be applied in this ATA reaction yielding allenes **3g** and **3h** in 36% and 42% yields, respectively (Table 3, entries 7 and 8). The cyano group could also be tolerated to form functionalized allene **3i** in 23% yield (Table 3, entry 9).

Then we turned to investigate the scope of aryl-substituted terminal alkynes (Scheme 4): Phenylacetylene **1j** and its analogues substituted by *p*-MeO, *p*-Br, *m*-Br, *o*-Cl, and 3,5-

Table 3. Scope of Alkyl-Substituted Terminal Alkynes[a]

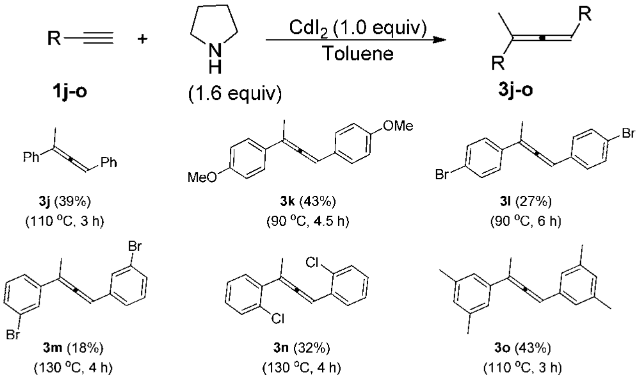


entry	R	**3**, yield (%)[b]
1	*n*-C_6H_{13} (**1a**)	**3a**, 68
2	*n*-C_8H_{17} (**1b**)	**3b**, 76
3	*n*-C_5H_{11} (**1c**)	**3c**, 59
4	$(CH_2)_9CO_2C_2H_5$ (**1d**)	**3d**, 58
5	$(CH_2)_9CO_2CH_3$ (**1e**)	**3e**, 58
6	$(CH_2)_9OH$ (**1f**)	**3f**, 50
7	CH_2OTBS (**1g**)	**3g**, 36
8	CH_2OTIPS (**1h**)	**3h**, 42
9	$(CH_2)_3CN$ (**1i**)	**3i**, 23

[a] The reaction was conducted using alkyne (1 mmol), amine (1.6 equiv), and CdI_2 (1.0 equiv) at 130 °C in 2 mL of toluene for 4 h. [b] Isolated yield.

DOI: 10.1021/acs.orglett.5b00105
Org. Lett. 2015, 17, 1176–1179

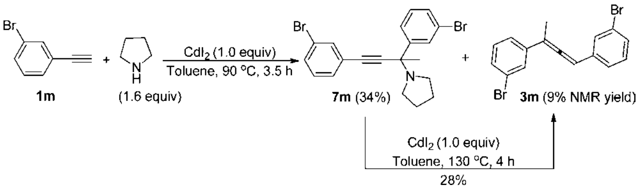
Scheme 4. Scope of Aromatic Alkynes



dimethyl groups were examined in this ATA reaction to afford the allene products **3j**–**o** successfully in somewhat lower yields.

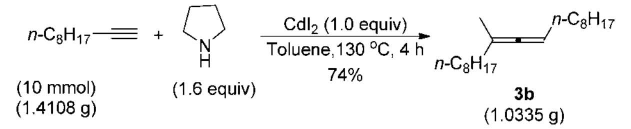
In order to support the reaction mechanism shown in Scheme 3, *m*-bromophenylacetylene **1m** was reacted with pyrrolidine **2a** in the presence of CdI_2 at a lower temperature (90 °C), for 3.5 h. The corresponding intermediate propargylic amine **7m** was isolated in 34% yield with a 9% NMR yield of allene product **3m**. Then this amine **7m** was reacted under the standard reaction conditions to afford **3m** in 28% isolated yield with 10% of **7m** being recovered (Scheme 5). These data supported the proposed mechanism.

Scheme 5. Mechanistic Study



It is easy to conduct the reaction on 1-g scale to afford **3b** in 74% yield (Scheme 6).

Scheme 6. Gram-Scale Synthesis of Trisubstituted Allene 3b



In conclusion, we have developed a new ATA reaction to synthesize trisubstituted allenes from terminal alkynes and pyrrolidine. The easy availability of the starting materials, the operational simplicity of the protocol, and the tolerance of functional groups show the potential synthetic utility of this method. Further studies including applying different terminal alkynes and the asymmetric version of this reaction are being conducted in our laboratory.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Detailed experimental procedures and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: masm@sioc.ac.cn.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Financial support from National Basic Research Program (2015CB856600) and National Natural Science Foundation of China (21232006). We thank Mr. Dengke Ma of our research group for reproducing the results of entries 2 and 8 in Table 3 and **3k** in Scheme 4.

■ REFERENCES

(1) For reviews, see: (a) Ma, S. *Acc. Chem. Res.* **2003**, *36*, 701. (b) Ma, S. *Chem. Rev.* **2005**, *105*, 2829. (c) Ma, S. *Aldrichimica Acta* **2007**, *40*, 91. (d) Ma, S. *Acc. Chem. Res.* **2009**, *42*, 1679. (e) Yu, S.; Ma, S. *Angew. Chem., Int. Ed.* **2012**, *51*, 3074. (f) Ma, S. *Eur. J. Org. Chem.* **2004**, 1175. (g) Wang, K. K. *Chem. Rev.* **1996**, *96*, 207. (h) Zimmer, R.; Dinesh, C. U.; Nandanan, E.; Khan, F. A. *Chem. Rev.* **2000**, *100*, 3067. (i) Hashmi, A. S. K. *Angew. Chem., Int. Ed.* **2000**, *39*, 3590. (j) Sydnes, L. K. *Chem. Rev.* **2003**, *103*, 1133. (k) Tius, M. *Acc. Chem. Res.* **2003**, *36*, 284. (l) Wei, L.-L.; Xiong, H.; Hsung, R. P. *Acc. Chem. Res.* **2003**, *36*, 773. (m) Brandsma, L.; Nedolya, N. A. *Synthesis* **2004**, 735. (n) Brasholz, M.; Reissig, H.-U.; Zimmer, R. *Acc. Chem. Res.* **2009**, *42*, 45.

(2) For selected examples, see: (a) Schreiber, S. L.; Kiessling, L. L. *J. Am. Chem. Soc.* **1988**, *53*, 1623. (b) Ma, S.; Lu, P.; Lu, L.; Hou, H.; Wei, J.; He, Q.; Gu, Z.; Jiang, X.; Jin, X. *Angew. Chem., Int. Ed.* **2005**, *44*, 5275. (c) Ghosh, P.; Zhang, Y.; Emge, T. J.; Williams, L. J. *Org. Lett.* **2009**, *11*, 4402. (d) Jiang, X.; Fu, C.; Ma, S. *Eur. J. Org. Chem.* **2009**, 687. (e) Kong, W.; Fu, C.; Ma, S. *Chem.—Eur. J.* **2011**, *17*, 13134. (f) Zeng, R.; Fu, C.; Ma, S. *J. Am. Chem. Soc.* **2012**, *134*, 9597. (g) Zhu, C.; Zhang, X.; Lian, X.; Ma, S. *Angew. Chem., Int. Ed.* **2012**, *51*, 7871.

(3) For reviews, see: (a) Hoffmann-Röder, A.; Krause, N. *Angew. Chem., Int. Ed.* **2004**, *43*, 1196. (b) Kim, H.; Williams, L. J. *Curr. Opin. Drug Discovery Dev.* **2008**, *11*, 870.

(4) For reviews on the synthesis of allenes, see: (a) Krause, N.; Hoffmann-Röder, A. *Tetrahedron* **2004**, *60*, 11671. (b) Brummond, K. M.; DeForrest, J. E. *Synthesis* **2007**, 795. (c) Ogasawara, M. *Tetrahedron: Asymmetry* **2009**, *20*, 259. (d) Yu, S.; Ma, S. *Chem. Commun.* **2011**, *47*, 5384. (e) Ye, J.; Ma, S. *Org. Chem. Front.* **2014**, *1*, 1210.

(5) (a) Crabbé, P.; Fillion, H.; André, D.; Luche, J.-L. *J. Chem. Soc., Chem. Commun.* **1979**, 859. (b) Ma, S.; Hou, H.; Zhao, S.; Wang, G. *Synthesis* **2002**, 1643. (c) Kazmaier, U.; Lucas, S.; Klein, M. *J. Org. Chem.* **2006**, *71*, 2429. (d) Nakamura, H.; Sugiishi, T.; Tanaka, Y. *Tetrahedron Lett.* **2008**, *49*, 7230. (e) Kuang, J.; Ma, S. *J. Org. Chem.* **2009**, *74*, 1763. (f) Chen, B.; Wang, N.; Fan, W.; Ma, S. *Org. Biomol. Chem.* **2012**, *10*, 8465. (g) Luo, H.; Ma, S. *Eur. J. Org. Chem.* **2013**, 3041. (h) Kuang, J.; Xie, X.; Ma, S. *Synthesis* **2013**, *45*, 592. (i) Huang, X.; Fu, C.; Ma, S. *Synthesis* **2014**, *46*, 2917.

(6) For ZnX_2-mediated reactions, see: (a) Kuang, J.; Ma, S. *J. Am. Chem. Soc.* **2010**, *132*, 1786. (b) Ye, J.; Li, S.; Chen, B.; Fan, W.; Kuang, J.; Liu, J.; Liu, Y.; Miao, B.; Wan, B.; Wang, Y.; Xie, X.; Yu, Q.; Yuan, W.; Ma, S. *Org. Lett.* **2012**, *14*, 1346. (c) Ye, J.; Fan, W.; Ma, S. *Chem.—Eur. J.* **2013**, *19*, 716. (d) Ye, J.; Lü, R.; Fan, W.; Ma, S. *Tetrahedron* **2013**, *69*, 8959. (e) Lü, R.; Ye, J.; Cao, T.; Chen, B.; Fan, W.; Lin, W.; Liu, J.; Luo, H.; Miao, B.; Ni, S.; Tang, X.; Wang, N.; Wang, Y.; Xie, X.; Yu, Q.; Yuan, W.; Zhang, W.; Zhu, C.; Ma, S. *Org. Lett.* **2013**, *15*, 2254. (f) Zhang, X.; Qiu, Y.; Fu, C.; Ma, S. *Org. Chem. Front.* **2014**, *1*, 247. For CuI-mediated reactions, see: (g) Kitagaki, S.; Komizu, M.; Mukai, C. *Synlett* **2011**, *8*, 1129. (h) Kuang, J.; Luo, H.; Ma, S. *Adv. Synth. Catal.* **2012**, *354*, 933.

(7) Tang, X.; Zhu, C.; Cao, T.; Kuang, J.; Lin, W.; Ni, S.; Ma, S. *Nat. Commun.* **2013**, *4*, 2450 DOI: 10.1038/ncomms3450.

(8) (a) Pohlki, F.; Doye, S. *Chem. Soc. Rev.* **2003**, *32*, 104. (b) Alonso, F.; Beletskaya, I. P.; Yus, M. *Chem. Rev.* **2004**, *104*, 3079.

(9) (a) Zhou, L.; Shuai, Q.; Jiang, H.-f.; Li, C.-J. *Chem.—Eur. J.* **2009**, *15*, 11668. (b) Zhou, L.; Bohle, D. S.; Jiang, H.-f.; Li, C.-J. *Synlett.* **2009**, *6*, 937. (c) Zhou, L.; Jiang, H.-f.; Li, C.-J. *Adv. Synth. Catal.* **2008**, *350*, 2226.

(10) Kuang, J.; Luo, H.; Ma, S. *Adv. Synth. Catal.* **2012**, *354*, 933.

(11) Lo, V. K.-Y.; Zhou, C.-Y.; Wong, M.-K.; Che, C.-M. *Chem. Commun.* **2010**, *46*, 213.

(12) Lo, V. K.-Y.; Zhou, C.-Y.; Che, C.-M. *Org. Lett.* **2008**, *10*, 517.