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Cadmium iodide-mediated allenylation of terminal alkynes with ketones

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Allenes are important building blocks in organic synthesis and have attracted much attention from researchers worldwide. So far, mono- and 1,3-disubstituted allenes can be prepared easily by applying the allenylation of terminal alkynes reaction of aldehydes. However, trisubstituted allenes have never been reported using this reaction due to the extremely low reactivity of ketones. Here, we report the one-pot synthesis of trisubstituted allenes from terminal alkynes and ketones utilizing cadmium iodide as the mediator. With this protocol, a series of different allenes, including 1,5-bisallenes and optically active allenols, which are especially important in synthetic chemistry, have been successfully prepared.

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Allene moieties have been found in many natural products and pharmaceuticals[1–4]. Due to the unique reactivities, allenes have also been demonstrated as useful and important starting materials in organic synthesis[5–25]. Thus, efficient methods for the synthesis of allenes from simple and readily available chemicals are highly desirable[26–36]. For such a reaction, the most straight forward method is using the allenylation of terminal alkynes (ATA) reaction due to the fact that all the starting materials, that is, terminal alkynes, amines, carbonyl compounds (aldehydes and ketones), are common chemicals in any chemical laboratory[37–41]. However, so far this ATA reaction may only be applied to paraformaldehyde (with Cu^{I})[37–40] and aldehydes (with Zn^{II} or Cu(I))[41] for the synthesis of mono- and 1,3-disubstituted allenes. The synthesis of trisubstituted allenes from this approach using ketones is still not possible (Fig. 1)[42,43].

In this paper, we report a method for the synthesis of trisubstituted allenes using a CdI_2 (refs 44,45)-mediated ATA reaction of ketones (Fig. 1). With the use of CdI_2, a series of trisubstituted allenes can be prepared easily in a one-pot synthesis. By applying this protocol, 1,5-bisallenes and optically active allenols, which are useful in organic synthesis, can also be prepared successfully.

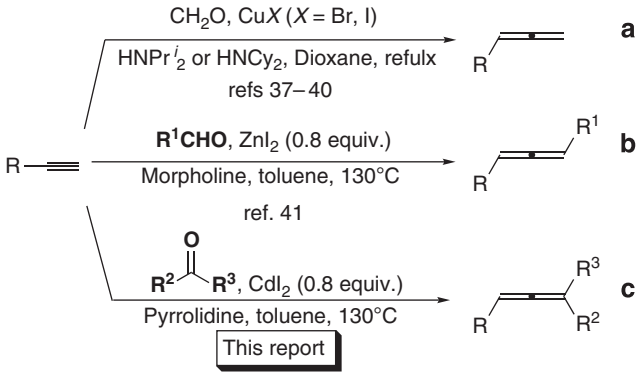


Figure 1 | Approaches to allenes from terminal alkynes. (**a**) Allenylation using formaldehyde. (**b**) Allenylation using aldehydes. (**c**) Synthesis of trisubstituted allenes using ketones.

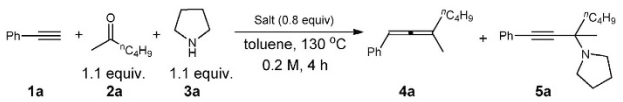
Results

Different inorganic metallic salts for the ATA reaction. Our initial work began with commercially available starting materials: phenylacetylene **1a**, 2-hexanone **2a** and pyrrolidine **3a** under the mediation of different groups 11 and 12 inorganic metallic salts (Table 1). After systematic trials, we were happy to find that the ATA reaction of **1a** (1.0 mmol) and **2a** (1.1 mmol) in the presence of pyrrolidine **3a** (1.1 mmol) with **CdI_2** (0.8 mmol) in 5 ml of toluene with stirring at 130 °C for 4 h afforded the trisubstituted allene **4a** in 57% yield (Table 1, entry 4)! Other metallic salts in groups 11 and 12, such as CuI (refs 37–40,46), ZnI_2 (ref. 41), AgI (ref. 47), AuI (ref. 48) and $HgCl_2$, afforded only a trace amount of the expected trisubstituted allene **4a** (Table 1, entries 1–3, 5 and 6).

Optimization of the ATA reaction. The reaction was sensitive to the concentration of the substrates (Table 2, entries 1–3). With 0.6 equiv. of CdI_2, the yield dropped dramatically (Table 2, entry 4). We also examined the solvent effect, with toluene still being the best (Table 2, entry 5). The yield of trisubstituted allene **4a** with $CdBr_2$ was only 7% (Table 2, entry 6). Thus, **1a** (1.0 mmol), **2a** (1.1 mmol), **3a** (1.1 mmol) and CdI_2 (0.8 mmol) in 5 ml of toluene with stirring at 130 °C for 4 h were defined as the optimized reaction conditions for further study, as the same reaction at 120 °C gave a lower yield (46%).

Substrate scope. With the optimal reaction conditions in hand, we then investigated the scope of the reaction by applying various terminal alkynes and ketones (Table 3). First, differently substituted terminal aryl-substituted alkynes were examined. Phenylacetylene **1a** and the analogues substituted with *p*-MeO, *p*-Br, *m*-Br and *o*-Cl groups all afforded good yields of the products, providing further opportunity of elaboration (Table 3, entries 1–5). Heteroaryl-substituted acetylene **1f** was also suitable for this reaction with 41% yield (Table 3, entry 6). The reaction may also be extended to terminal alkyl-substituted alkynes such

Table 1 | Group 11 or 12 metal salts for ATA reaction*.

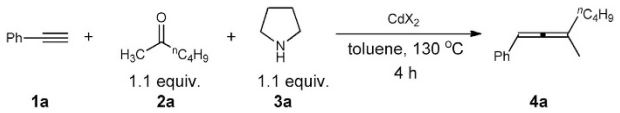


Entry	Salt	Yield of 4a/5a (%)†
1	CuI	Trace/73
2	ZnI_2	Trace/trace
3	AgI	Trace/13
4	**CdI_2**	**57/trace**
5	AuI	4/2
6	$HgCl_2$	Trace/trace

Group 11	Group 12
29 **Cu** Copper 63.546	30 **Zn** Zinc 65.39
47 **Ag** Silver 107.8682	48 **Cd** Cadmium 112.411
79 **Au** Gold 196.96655	80 **Hg** Mercury 200.59

*The reaction was conducted using alkyne **1a** (1.0 mmol), ketone **2a** (1.1 mmol) and pyrrolidine (1.1 mmol) in 5 ml of toluene for 4 h.
†Determined by ^{1}H NMR analysis with nitromethane as the internal standard.

Table 2 | Optimization of ATA reaction conditions*.

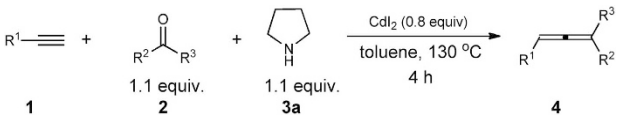


1a 2a 3a 4a

Entry	CdX_2 (equiv.)	c (mmol ml^{-1})	Yield of 4a (%)†
1	I (0.8)	0.33	49
2	**I (0.8)**	**0.2**	**57**
3	I (0.8)	0.125	51
4	I (0.6)	0.2	35
5‡	I (0.8)	0.2	32
6	Br (0.8)	0.2	7
7§	I (0.8)	0.33	46

*The reaction was conducted using alkyne **1a** (1.0 mmol), ketone **2a** (1.1 mmol) and pyrrolidine (1.1 mmol) in toluene for 4 h.
†Determined by ^{1}H NMR analysis with mesitylene or nitromethane as the internal standard.
‡5 ml of benzene was used instead of toluene at 110 °C.
§The reaction was conducted at 120 °C.

Table 3 | The scope of terminal alkynes and ketones*.



1 2 3a 4

Entry	R^1	R^2, R^3	Isolated yields of 4 (%)
1	Ph (**1a**)	$-(CH_2)_5-$ (**2b**)	78 (**4b**)
2	4-$MeOC_6H_4$ (**1b**)	$-(CH_2)_5-$ (**2b**)	75 (**4c**)
3†	4-BrC_6H_4 (**1c**)	$-(CH_2)_5-$ (**2b**)	76 (**4d**)
4	3-BrC_6H_4 (**1d**)	$-(CH_2)_5-$ (**2b**)	75 (**4e**)
5	2-ClC_6H_4 (**1e**)	$-(CH_2)_5-$ (**2b**)	66 (**4f**)
6	2-thienyl (**1f**)	$-(CH_2)_5-$ (**2b**)	41 (**4g**)
7	*n*-C_6H_{13} (**1g**)	$-(CH_2)_5-$ (**2b**)	82 (**4h**)
8	*n*-C_8H_{17} (**1h**)	$-(CH_2)_5-$ (**2b**)	80 (**4i**)
9	Ph (**1a**)	Me, *n*-C_4H_7 (**2a**)	55 (**4a**)
10	Ph (**1a**)	Me, *n*-C_6H_{13} (**2c**)	40 (**4j**)
11	*n*-C_6H_{13} (**1g**)	Me, *n*-C_6H_{13} (**2c**)	63 (**4k**)
12	*n*-C_8H_{17} (**1h**)	Me, CH_2CH_2Ph (**2d**)	54 (**4l**)

*The reaction was conducted using alkyne (1.0 mmol), ketone (1.1 mmol), pyrrolidine **3a** (1.1 mmol) and CdI_2 (0.8 mmol) in 5 ml of toluene at 130 °C for 4 h.
†The reaction time is 5 h.

as 1-octyne **1g** and 1-decyne **1h**, which gave trisubstituted allenes **4h** and **4i** in 82% and 80% yields, respectively (Table 3, entries 7 and 8). Next, we turned to investigate the ATA reaction with different ketones. 2-Hexanone **2a** reacted with phenylacetylene **1a** to give the corresponding allene **4a** in 55% yield (Table 3, entry 9); 2-octanone **2c** and 4-phenyl-2-butanone **2d** worked well with 1-octyne **1g** and 1-decyne **1h** to afford the corresponding allenes **4k** and **4l** in 63% and 54% yields, respectively (Table 3, entries 11 and 12).

Synthesis of 1,5-bisallenes. As we know, 1,5-bisallenes are useful starting materials in organic synthesis[20,49]. With this methodology, 1,5-bisallenes **4m** and **4n** could be easily prepared in 69% and 72% yields (Fig. 2).

Synthesis of acetyl-protected α- and β-allenols. Recently, allenols have been proven as versatile building blocks in organic synthesis[5,50–53]. By applying this protocol, acetate-protected trisubstituted α- and β-allenols could be obtained in moderate to good yields (Fig. 3).

Preparation of trisubstituted allene on gram scale. It is easy to conduct the reaction on a 1-g scale to afford **4r** in 50% yield, which could be easily deprotected by its treatment with K_2CO_3 in MeOH and H_2O to afford the corresponding allenol **4s** in 96% yield, indicating the potential synthetic utility of this method (Fig. 4).

Trisubstituted allenes with central and/or axial chirality. When we used the *tert*-butyldimethylsilyl ether of chiral alkynol (*S*)-**1m** (>99% ee) as the starting material, optically active *tert*-butyldimethylsilyl-protected α-allenol (*S*)-**4t** was also afforded in 87% yield with 99% ee (Fig. 5a). Nonsymmetrical ketone **2a** was also suitable for this reaction yielded a pair of diastereoisomers (d.r. = 1:1) in 69%, indicating that there is no 1,2-chiral induction of the propargylic central chirality on the *in situ* formed axial chirality (Fig. 5b).

Intermediates. It is observed that the reaction of phenylacetylene **1a**, 2-octanone **2c** and pyrrolidine **3a** at a lower temperature, 100 °C, for 1 h afforded the corresponding propargylic amine **5j** in 24% isolated yield with 3% ^{1}H NMR yield of allene **4j**. Then propargylic amine **5j** was converted to allene **4j** in 82% yield

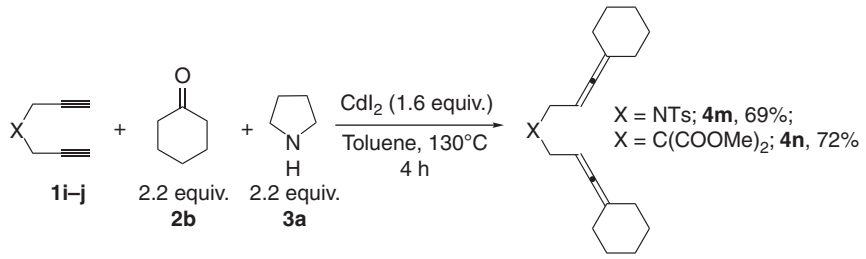


Figure 2 | Synthesis of 1,5-bisallenes with ATA reaction. 1,5-Bisallenes were synthesized by applying this protocol, which are not easily prepared by other methods. NTs = *N*-tosyl.

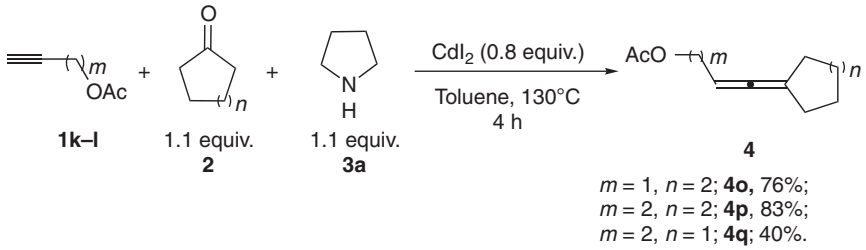


Figure 3 | Synthesis of acetyl-protected trisubstituted α- and β-allenols. Easily available acetyl-protected propargyl alcohols could be converted to trisubstituted allenes using ATA reaction.

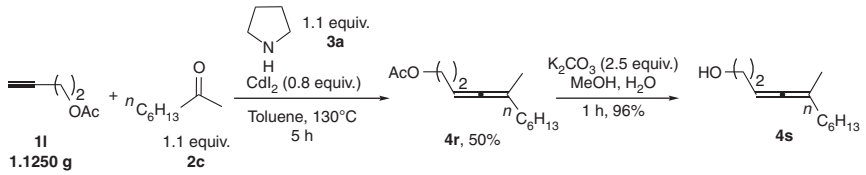


Figure 4 | Gram-scale synthesis of 5,5-disubstituted allenol 4r. The reaction could be conducted on a 1-g scale to afford acetyl-protected trisubstituted allene, which could be converted to allenol easily.

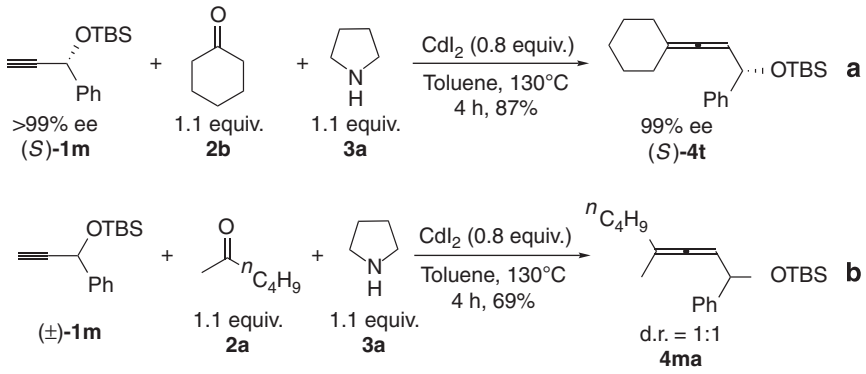


Figure 5 | ATA reaction with protected terminal propargylic alcohols. (**a**) When TBS-protected chiral alkynol was used, the chirality was kept in the allene product. (**b**) When nonsymmetrical keone **2a** reacted with alkynol (±)−**1m**, a pair of diastereoisomers were observed (d.r. = 1:1). TBS, *tert*-butyldimethylsilyl.

under the standard reaction conditions, indicating the intermediacy of **5j**-type propargylic amine in this type of reaction. What is more, the propargylic amines **5u–5x** may be converted to the corresponding allenes **4u–4x** in 45–88% yields in the presence of CdI_2 in toluene at 130 °C within 4 h (Fig. 6).

Discussion

From the results in Table 1, it should be noted that only in the case of CuI, propargylic amine **5a** was formed in 73% yield, which could not be converted to allene **4a** under the mediation of CuI (Table 1, entry 1), demonstrating that only CdI_2 is working for both the propargylic amine and allene formation steps. In fact, with this notion that CuI could mediate the formation of propargylic amine **5a**, which was considered as the intermediate, a number of metallic salts, such as ZnI_2, AgI, AuI and $HgCl_2$, were tried in this reaction in the presence of CuI (Table 4). Unfortunately, none of these mixed systems could mediate the formation of allene **4a** in decent yield, indicating the unique effect of **CdI_2** on this ATA reaction.

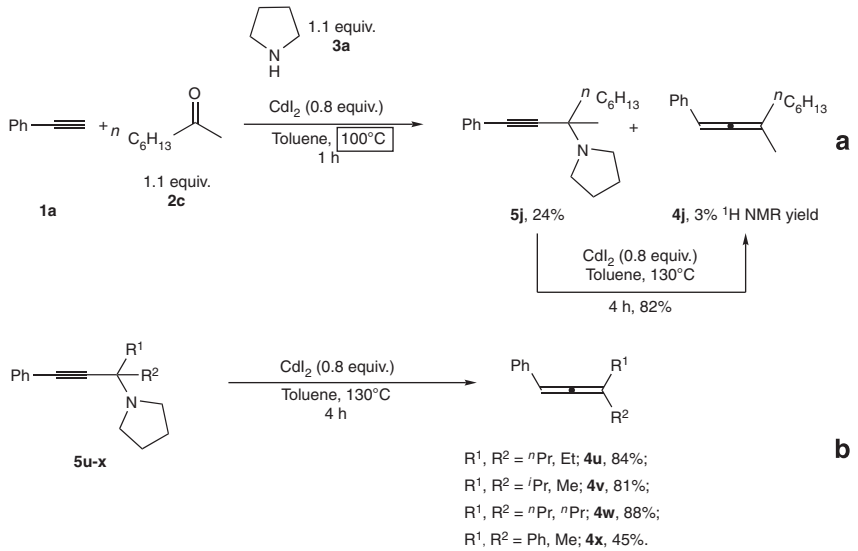
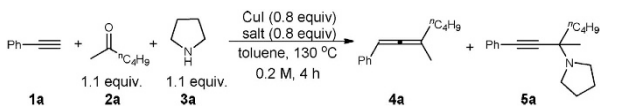


Figure 6 | Synthesis of allenes from propargylic amines. (**a**) The intermediate, propargylic amine **5j**, was synthesized at 100 °C and then converted to the allene successfully. (**b**) Allenylation of propargylic amines.

Table 4 | Mixed metal salts for ATA reaction*.



Entry	Salt added	Yield of 4a/5a (%)†
1	ZnI_2	2/trace
2	AgI	Trace/76
3	AuI	Trace/46
4	$HgCl_2$	Trace/trace

*The reaction was conducted using alkyne (1.0 mmol), ketone (1.1 mmol) and pyrrolidine (1.1 mmol) in 5 ml of toluene for 4 h.
†Determined by ^{1}H NMR analysis with nitromethane as the internal standard.

Based on the above data and recent reports of this type of reactions[41,47], we proposed a plausible mechanism for the ATA reaction (Fig. 7): Alkynyl cadmium species **6**, generated from terminal alkyne in the presence of pyrrolidine, would react with the ketoniminum **7** formed *in situ* from ketone and pyrrolidine, to give the corresponding propargylic amine **5**. The carbon–carbon triple bond in propargylic amine **5** coordinates to CdI_2 forming complex **8**, which would be followed by 1,5-hydride transfer and β-elimination to afford the corresponding trisubstituted allene **4**.

In conclusion, we have developed an efficient CdI_2-mediated ATA reaction to synthesize trisubstituted allenes from commercially available alkynes and ketones. This protocol is operationally simple and all the starting materials are basic chemicals readily available, showing the potential synthetic utility of this method. Further studies including the asymmetric version of this reaction and the application of these allenes are being conducted in our laboratory.

Methods

Materials. Chloroform-*d* (Cambridge Isotope Ltd.) for ^{1}H and ^{13}C NMR spectroscopy was used as received. CdI_2 (99.5%) was purchased from Aladdin and kept in a glove box. Toluene was dried over sodium wire with benzophenone as indicator and distilled freshly before use. Other reagents were used without further treatment.

General spectroscopic methods. ^{1}H NMR spectra were obtained at 27 °C using an Agilent spectrometer operating at 400 MHz. ^{13}C NMR spectra were obtained at 27 °C using an Aglient spectrometer operating at 100 MHz. ^{1}H NMR, ^{13}C NMR and HPLC spectra are supplied for all compounds: see Supplementary Figures S1–S56. See Supplementary Methods for the characterization data of compounds not listed in this part.

Synthesis of 1-phenyl-3-methyl-1,2-heptadiene 4a. To a dried Schlenk tube was added CdI_2 (293.4 mg, 0.8 mmol) inside a glove box. The Schlenk tube was then taken out and dried under vacuum with a heating gun until the white CdI_2 turned to yellow green. **1a** (101.5 mg, 1 mmol)/toluene (2.5 ml), **2a** (109.8 mg, 1.1 mmol)/toluene (2.5 ml) and **3a** (92.0 µl, d = 0.852 g ml^{-1}, 78.3 mg, 1.1 mmol) were then added sequentially under Ar atmosphere. The Schlenk tube was then equipped with a condenser and placed in a pre-heated oil bath of 130 °C with stirring for 4 h. After cooling to room temperature, the crude reaction mixture was filtrated through a short pad of silica gel eluted with ether (20 ml). After evaporation, the residue was purified by chromatography on silica gel to afford **4a** (ref. 54) (102.7 mg, 55%) (eluent: petroleum ether) as a liquid: thin-layer chromatography (TLC) (petroleum ether): R_f = 0.92; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 – 7.23 (m, 4H, Ar – H), 7.19 – 7.11 (m, 1H, Ar – H), 6.07 – 6.01 (m, 1H, CH = C), 2.12 – 2.02 (m, 2H, CH_2), 1.79 (d, J = 2.8 Hz, 3H, CH_3), 1.52 – 1.29 (m, 4H, 2 × CH_2), 0.89 (t, J = 7.2 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.6, 136.1, 128.4, 126.5, 126.3, 103.7, 93.7, 33.8, 29.7, 22.4, 18.8, 13.9; MS (EI) *m*/*z* (%) 186 (M^+, 1.61), 129 (100); IR (neat): ν = 2957, 2927, 2858, 1951, 1598, 1496, 1462, 1259, 1071, 1025 cm^{-1}.

Gram-scale synthesis of acetyl-protected β-allenol 4r. To a dried three-necked bottle was added CdI_2 (2.9307 g, 8 mmol) inside a glove box. The three-necked bottle was then taken out and dried under vacuum with a heating gun until the white CdI_2 turned to yellow-green. **1l** (1.1250 g, 10 mmol)/toluene (20 ml), **2c** (1.4100 g, 11 mmol)/toluene (20 ml) and **3a** (0.7839 g, 11 mmol)/toluene (10 ml) were then added sequentially under Ar atmosphere. The three-necked bottle was then equipped with a condenser and placed in a pre-heated oil bath of 130 °C with stirring. After 5 h, the reaction was complete as monitored by TLC, the resulting mixture was cooled to room temperature and filtrated through a short pad of silica gel eluted with ether (100 ml). After evaporation, the residue was purified by chromatography on silica gel to afford **4r** (1.1283 g, 50%) (eluent: petroleum ether/ethyl ether = 30/1) as a liquid: TLC (petroleum ether:ethyl acetate, 10:1 v/v): R_f = 0.80; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.03 – 4.94 (m, 1H, CH = C = C), 4.10 (t, J = 6.8 Hz, 2H, OCH_2), 2.28 (q, J = 6.7Hz, 2H, CH_2), 2.04 (s, 3H,CH_3), 1.91 (td, J = 7.4 Hz, 2.5 Hz, 2H, CH_2), 1.66 (d, J = 2.4 Hz, 3H, CH_3), 1.44 – 1.22 (m, 8H, 4 × CH_2), 0.88 (t, J = 7.0 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.9, 171.0, 100.3, 85.6, 63.8, 33.8, 31.7, 28.9, 28.6, 27.4, 22.6, 20.9, 19.1, 14.0; MS (EI) *m*/*z* (%) 224 (M^+, 1.01), 94 (100); IR (neat): ν = 2956, 2926, 2856, 1966, 1742,

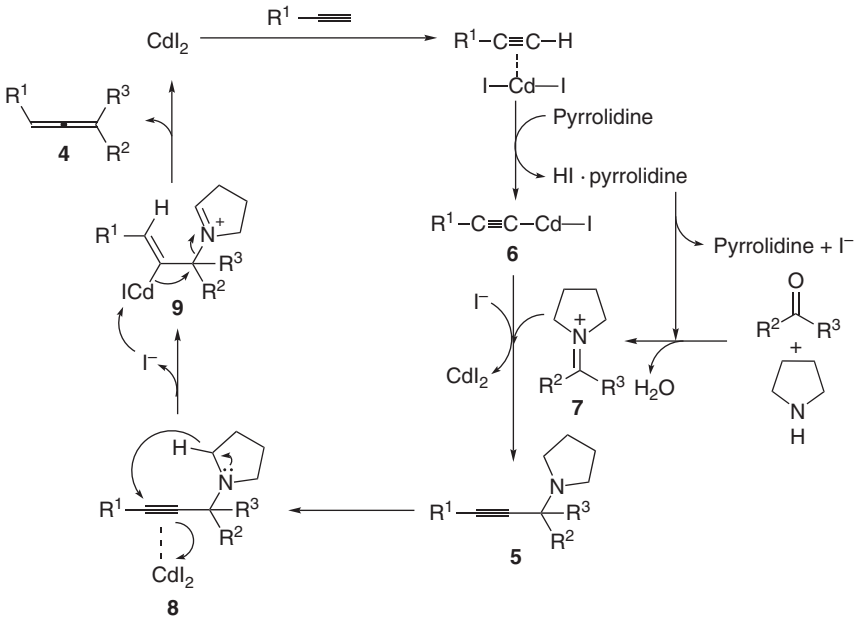


Figure 7 | Proposed mechanism for the ATA reaction of ketones. The key step of propargylic amine formation followed by 1,5-hydride transfer and β-elimination. The intermediate, propargylic amine **5j**, was synthesized at a lower temperature and could be converted to the allene successfully.

1459, 1383, 1364, 1231, 1035 cm^{-1}; HRMS (*m/z*): $[M]^+$ calcd. for $C_{14}H_{24}O_2$, 224.1776; found, 224.1779.

Synthesis of optically active allene (*S*)-4t from chiral alkyne. Following the synthesis procedure of **4a**: The reaction of CdI_2 (293.7 mg, 0.8 mmol), (*S*)-**1m** (246.6 mg, 1 mmol)/toluene (2.5 ml), **2b** (108.6 mg, 1.1 mmol)/toluene (2.5 ml) and **3a** (92.0 µl, $d = 0.852$ g/ml, 78.3 mg, 1.1 mmol) afforded (*S*)-**4t** (285.1 mg, 87%) (eluent: petroleum ether) as a liquid: TLC (petroleum ether): $R_f = 0.93$; 99% ee (HPLC conditions: Chiralcel OJ − H column, CO_2/*i*-PrOH = 98/2, 1.5 ml/min, $\lambda = 214$ nm, t_R(major) = 7.2 min, t_R(minor) = 6.9 min); $[\alpha]_D^{21.7} = +132.7$ ($c = 1.01$, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (d, $J = 7.6$ Hz, 2H, Ar − H), 7.30 (t, $J = 7.6$ Hz, 2H, Ar − H), 7.21 (t, $J = 7.2$ Hz, 1H, Ar − H), 5.21 (d, $J = 7.2$ Hz, 1H, OCH), 5.12-5.04 (m, 1H, CH = C = C), 2.16 − 2.07 (m, 4H, 2 × CH_2), 1.63 − 1.46 (m, 6H, 3 × CH_2), 0.93 (s, 9H, 3 × CH_3), 0.11 (s, 3H, CH_3), 0.07 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.6, 144.8, 127.9, 126.7, 125.7, 104.1, 94.7, 74.6, 31.4, 31.1, 27.3, 27.2, 26.0, 25.9, 18.3, −4.4, −4.9; MS (EI) *m/z* (%) 328 (M^+, 1.01), 221 (100); IR (neat): $\nu = 2928$, 2887, 2855, 1966, 1492, 1469, 1447, 1252, 1084, 1062, 1006 cm^{-1}; HRMS (*m/z*): $[M]^+$ calcd. for $C_{21}H_{32}OSi$, 328.2222; found, 328.2225.

Synthesis of the intermediate 5j. To a dried Schlenk tube was added CdI_2 (293.8 mg, 0.8 mmol) inside a glove box. The Schlenk tube was then taken out and dried under vacuum with a heating gun until the white CdI_2 turned to yellow green. **1a** (102.6 mg, 1 mmol)/toluene (2.5 ml), **2c** (141.3 mg, 1.1 mmol)/toluene (2.5 ml) and **3a** (92.0 µl, d = 0.852 g ml^{-1}, 78.3 mg, 1.1 mmol) were then added sequentially under Ar atmosphere. The Schlenk tube was then equipped with a condenser and placed in a pre-heated oil bath of 100 °C with stirring for 1 h. After cooling to room temperature, the crude reaction mixture was filtrated through a short pad of silica gel eluted with acetone (20 ml). After evaporation, to the residue was added 27.0 µl of CH_3NO_2 as the internal standard for ^{1}H NMR analysis (29% ^{1}H NMR yield of **5j** and 3% ^{1}H NMR yield of **4j**) and then purified by chromatography on silica gel to afford **5j** (67.5 mg, 24%) (eluent:petroleum ether/ethyl acetate = 200:2 ml to 200:4 ml, then 20:1, finally petroleum ether/ethyl acetate/Et_3N = 500 ml/50 ml/0.5 ml was applied to get the pure product) as a liquid:TLC (petroleum ether:ethyl acetate, 10:1 v/v): $R_f = 0.20$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 − 7.38 (m, 2H, Ar − H), 7.33 − 7.23 (m, 3H, Ar − H), 2.85 − 2.73 (m, 4H, CH_2NCH_2), 1.83 − 1.72 (m, 5H, 2 × CH_2 + one proton of CH_2), 1.71 − 1.61 (m, 1H, one proton of CH_2), 1.59 − 1.41 (m, 5H, CH_2 + CH_3), 1.37 − 1.28 (m, 6H, 3 × CH_2), 0.89 (t, $J = 6.4$ Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 131.7, 128.1, 127.6, 123.6, 91.3, 84.3, 57.9, 47.7, 41.5, 31.8, 29.7, 25.8, 24.3, 23.6, 22.6, 14.1; MS (ESI) *m/z* 284 ($M + H^+$), 213 ($M + H^+$-pyrrolidine); IR (neat): $\nu = 2954$, 2928, 2857, 2808, 1598, 1489, 1463, 1443, 1370, 1253, 1193, 1143, 1101, 1070, 1026 cm^{-1}; HRMS (*m/z*):$[M + H]^+$ calcd. for $C_{20}H_{30}N$, 284.2373; found, 284.2373.

Synthesis of allene 4j from propargylic amine. To a dried Schlenk tube was added CdI_2 (293.5 mg, 0.8 mmol) inside a glove box. The Schlenk tube was then taken out and dried under vacuum with a heating gun until the white CdI_2 turned to yellow green. **5j** (284.1 mg, 1 mmol) and toluene (5 ml) were then added under Ar atmosphere. The Schlenk tube was then equipped with a condenser and placed in a pre-heated oil bath of 130 °C with stirring for 4 h as monitored by TLC. After cooling to room temperature, the crude reaction mixture was filtrated through a short pad of silica gel eluted with ether (20 ml). After evaporation, the residue was purified by chromatography on silica gel to afford **4j** (176.9 mg, 82%) (eluent: petroleum ether) as a liquid: TLC (petroleum ether): $R_f = 0.94$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 − 7.25 (m, 4H, Ar − H), 7.20 − 7.12 (m, 1H, Ar − H), 6.07 − 6.01 (m, 1H, CH = C = C), 2.07 (td, $J = 7.4$ Hz, 2.5 Hz, 2H, CH_2), 1.80 (d, $J = 2.8$ Hz, 3H, CH_3), 1.52 − 1.44 (m, 2H, CH_2), 1.38 − 1.21 (m, 6H, 3 × CH_2), 0.86 (t, $J = 7.0$ Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.7, 136.1, 128.4, 126.5, 126.3, 103.7, 93.8, 34.1, 31.7, 29.1, 27.5, 22.7, 18.8, 14.0.

References

1. Hoffmann-Röder, A. & Krause, N. Synthesis and properties of allenic natural products and pharmaceuticals. *Angew. Chem. Int. Ed.* **43,** 1196–1216 (2004).
2. Lyakhova, E. G. *et al.* Structures and absolute stereochemistry of nipponallene and neonipponallene, new brominated allenes from the red alga *Laurencia nipponica*. *Tetrahedron Lett.* **47,** 6549–6552 (2006).
3. Hu, G., Liu, K. & Williams, L. J. The brosimum allene: a structural revision. *Org. Lett.* **10,** 5493–5496 (2008).
4. Kim, M. J., Sohn, T., Kim, D. & Paton, R. S. Concise substrate-controlled asymmetric total syntheses of dioxabicyclic marine natural products with 2,10-dioxabicyclo-[7.3.0]dodecene and 2,9-dioxabicyclo[6.3.0]undecene skeletons. *J. Am. Chem. Soc.* **134,** 20178–20188 (2012).
5. Ma, S. Transition metal-catalyzed/mediated reaction of allenes with a nucleophilic functionality connected to the α-carbon atom. *Acc. Chem. Res.* **36,** 701–712 (2003).
6. Ma, S. Some typical advances in the synthetic applications of allenes. *Chem. Rev.* **105,** 2829–2871 (2005).
7. Ma, S. Recent advances in the chemistry of allenes. *Aldrichimica Acta* **40,** 91–102 (2007).
8. Ma, S. Electrophilic addition and cyclization reactions of allenes. *Acc. Chem. Res.* **42,** 1679–1688 (2009).
9. Yu, S. & Ma, S. Allenes in catalytic asymmetric synthesis and natural product syntheses. *Angew. Chem. Int. Ed.* **51,** 3074–3112 (2012).
10. Ma, S. Pd-catalyzed coupling reactions involving propargylic/allenylic species. *Eur. J. Org. Chem.* 1175–1183 (2004).
11. Wang, K. K. Cascade radical cyclizations via biradicals generated from enediynes, enyne-Allenes, and enyne-ketenes. *Chem. Rev.* **96,** 207–222 (1996).
12. Zimmer, R., Dinesh, C. U., Nandanan, E. & Khan, F. A. Palladium-catalyzed reactions of allenes. *Chem. Rev.* **100,** 3067–3125 (2000).
13. Hashmi, A. S. K. New and selective metal catalyzed reactions of allenes. *Angrew. Chem. Int. Ed.* **39,** 3590–3593 (2000).

14. Sydnes, L. K. Allenes from cyclopropanes and their use in organic synthesis-recent developments. *Chem. Rev.* **103,** 1133–1150 (2003).
15. Tius, M. A. Cationic cyclopentannelation of allene ethers. *Acc. Chem. Res.* **36,** 284–290 (2003).
16. Wei, L.-L., Xiong, H. & Hsung, R. P. The emergence of allenamides in organic synthesis. *Acc. Chem. Res.* **36,** 773–782 (2003).
17. Brandsma, L. & Nedolya, N. A. Allenic compounds and isothiocyanates as key building units in the synthesis of heterocycles. *Synthesis* 735–745 (2004).
18. Brasholz, M., Reissig, H.-U. & Zimmer, R. Sugars, alkaloids, and heteroaromatics: exploring heterocyclic chemistry with alkoxyallenes. *Acc. Chem. Res.* **42,** 45–56 (2009).
19. Schreiber, S. L. & Kiessling, L. L. Synthesis of the bicyclic core of the esperamicin/calichemicin class of antitumor agents. *J. Am. Chem. Soc.* **110,** 631–633 (1988).
20. Ma, S. *et al.* What can a metal catalyst do with allenes? One-step formation of steroid scaffolds from readily available starting materials. *Angew. Chem. Int. Ed.* **44,** 5275–5278 (2005).
21. Ghosh, P., Zhang, Y., Emge, T. J. & Williams, L. J. Modeling a macrocyclic bis[spirodiepoxide] strategy to erythronolide A. *Org. Lett.* **11,** 4402–4405 (2009).
22. Jiang, X., Fu, C. & Ma, S. A concise synthesis of (–)- and (+)-*trans*-whisky lactones. *Eur. J. Org. Chem.* 687–693 (2009).
23. Kong, W., Fu, C. & Ma, S. General Au-catalyzed benzannulation towards naturally occurring carbazole alkaloids from methoxypropadiene. *Chem. Eur. J.* **17,** 13134–13137 (2011).
24. Zeng, R., Fu, C. & Ma, S. Highly selective mild stepwise allylation of *N*-methoxybenzamides with allenes. *J. Am. Chem. Soc.* **134,** 9597–9600 (2012).
25. Zhu, C., Zhang, X., Lian, X. & Ma, S. One-pot approach to installing eight-membered rings onto indoles. *Angew. Chem. Int. Ed.* **51,** 7817–7820 (2012).
26. Krause, N. & Hoffmann-Röder, A. Synthesis of allenes with organometallic reagents. *Tetrahedron* **60,** 11671–11694 (2004).
27. Brummond, K. M. & DeForrest, J. E. Synthesizing allenes today (1982–2006). *Synthesis* 795–818 (2007).
28. Ogasawara, M. Catalytic enantioselective synthesis of axially chiral allenes. *Tetrahedron: Asymmetry* **20,** 259–271 (2009).
29. Yu, S. & Ma, S. How easy are the syntheses of allenes? *Chem. Commun.* **47,** 5384–5418 (2011).
30. Fürstner, A. & Méndez, M. Iron-catalyzed cross-coupling reactions: efficient synthesis of 2,3-allenol derivatives. *Angew. Chem. Int. Ed.* **42,** 5355–5357 (2003).
31. Nakamura, H., Kamakura, T., Ishikura, M. & Biellmann, J.-F. Synthesis of allenes via palladium-catalyzed hydrogen-transfer reactions: propargylic amines as an allenyl anion equivalent. *J. Am. Chem. Soc.* **126,** 5958–5959 (2004).
32. Deutsch, C., Lipshutz, B. H. & Krause, N. Small but effective: copper hydride catalyzed synthesis of α-hydroxyallenes. *Angew. Chem. Int. Ed.* **46,** 1650–1653 (2007).
33. Pu, X. & Ready, J. M. Direct and stereospecific synthesis of allenes via reduction of propargylic alcohols with $Cp_2Zr(H)Cl$. *J. Am. Chem. Soc.* **130,** 10874–10875 (2008).
34. Liu, H., Leow, D., Huang, K.-W. & Tan, C.-H. Enantioselective synthesis of chiral allenoates by Guanidine-catalyzed isomerization of 3-alkynoates. *J. Am. Chem. Soc.* **131,** 7212–7213 (2009).
35. Kolakowski, R. V., Manpadi, M., Zhang, Y., Emge, T. J. & Williams, L. J. Allene synthesis via C-C fragmentation: method and mechanistic insight. *J. Am. Chem. Soc.* **131,** 12910–12911 (2009).
36. Bolte, B., Odabachian, Y. & Gagosz, F. Gold(I)-catalyzed rearrangement of propargyl benzyl ethers: a practical method for the generation and *in situ* transformation of substituted allenes. *J. Am. Chem. Soc.* **132,** 7294–7296 (2010).
37. Crabbé, P., Fillion, H., André, D. & Luche, J.-L. Efficient homologation of acetylenes to allenes. *J. Chem. Soc., Chem. Commun.* 859–860 (1979).
38. Crabbé, P., Nassim, B. & Robert-Lopes, M.-T. One-step homologation of acetylenes to allenes: 4-hydroxynona-1,2-diene. *Org. Synth.* **63,** 203–204 (1985).
39. Kuang, J. & Ma, S. An efficient synthesis of terminal allenes from terminal 1-alkynes. *J. Org. Chem.* **74,** 1763–1765 (2009).
40. Luo, H. & Ma, S. CuI-catalyzed synthesis of functionalized terminal allenes from 1-alkynes. *Eur. J. Org. Chem.* 3041–3048 (2013).
41. Kuang, J. & Ma, S. One-pot synthesis of 1,3-disubstituted allenes from 1-alkynes, aldehydes, and morpholine. *J. Am. Chem. Soc.* **132,** 1786–1787 (2010).
42. Lavallo, V., Frey, G. D., Kousar, S., Donnadieu, B. & Bertrand, G. Allene formation by gold catalyzed cross-coupling of masked carbenes and vinylidenes. *Proc. Natl Acad. Sci. USA* **104,** 13569–13573 (2007).
43. Xiao, Q., Xia, Y., Li, H., Zhang, Y. & Wang, J. Coupling of *N*-tosylhydrazones with terminal alkynes catalyzed by copper(I): synthesis of trisubstituted allenes. *Angew. Chem. Int. Ed.* **50,** 1114–1117 (2011).
44. Raghuvanshi, D. S. & Singh, K. N. Highly efficient cadmium-catalyzed three-component coupling of an aldehyde, alkyne, and amine via C–H activation under microwave conditions. *Synlett.* **3,** 373–377 (2011).
45. Laskar, D. D., Prajapati, D. & Sandhu, J. S. Chemoselective dithioacetalisation of carbonyl compounds under solvent-free conditions. *J. Chem. Research (S)* 313–315 (2001).
46. Kuang, J., Luo, H. & Ma, S. Copper (I) iodide-catalyzed one-step preparation of functionalized allenes from terminal alkynes: amine effect. *Adv. Synth. Catal.* **354,** 933–944 (2012).
47. Lo, V. K.-Y., Zhou, C.-Y., Wong, M.-K. & Che, C.-M. Silver(I)-mediated highly enantioselective synthesis of axially chiral allenes under thermal and microwave-assisted conditions. *Chem. Commun.* **46,** 213–215 (2010).
48. Lo, V. K.-Y., Zhou, C.-Y. & Che, C.-M. Gold-catalyzed highly enantioselective synthesis of axially chiral allenes. *Org. Lett.* **10,** 517–519 (2008).
49. Jiang, X. & Ma, S. *trans*-$RhCl(CO)(PPh_3)_2$-catalyzed monomeric and dimeric cycloisomerization of propargylic 2,3-dienoates. establishment of α,β-unsaturated δ-lactone rings by cyclometallation. *J. Am. Chem. Soc.* **129,** 11600–11607 (2007).
50. Yoneda, E., Kaneko, T., Zhang, S.-W., Onitsuka, K. & Takahashi, S. Ruthenium-catalyzed cyclic carbonylation of allenyl alcohols. selective synthesis of γ- and δ-lactones. *Org. Lett.* **2,** 441–443 (2000).
51. He, J.-Q., Shibata, D., Ohno, C. & Okamoto, S. Two-step allylic carbon insertion between ketone carbonyl and α carbons giving a-quaternary α-vinyl ketones. *Tetrahedron Lett.* **49,** 6724–6727 (2008).
52. Cheng, J., Tang, X., Yu, Y. & Ma, S. $FeCl_3$-catalyzed cyclization of α-sulfonamido-allenes with aldehydes—the substituent effect. *Chem. Commun.* **48,** 12074–12076 (2012).
53. Cheng, J., Tang, X. & Ma, S. Highly Selective $FeCl_3$-Catalyzed Cyclization of β-Sulfonamidoallenes or β-Allenols and Aldehydes. *ACS Catal.* **3,** 663–666 (2013).
54. Ting, C.-M., Hsu, Y.-L. & Liu, R.-S. Gold-catalyzed isomerization of unactivated allenes into 1,3-dienes under ambient conditions. *Chem. Commun.* **48,** 6577–6579 (2012).

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Author contributions

S.M. directed the research and developed the concept of the ATA reaction. X.T. performed the experiments and data analysis. C.Z. performed some experiments and important control studies. T.C., J.K., W.L., S.N. and J.Z. contributed equally in helping collecting some experimental data and their names are shown in alphabetical order. The paper was written by X.T. and S.M. with assistance from the other authors.

Additional information

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