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# Mild-Condition Synthesis of Allenes from Alkynes and Aldehydes Mediated by Tetrahydroisoquinoline (THIQ)

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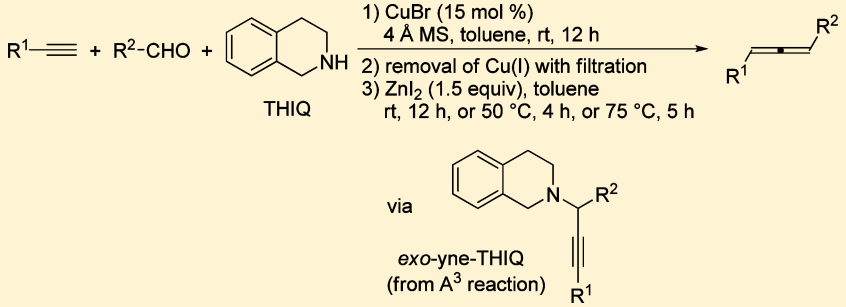
Supporting Information




**ABSTRACT:** A practical 1,2,3,4-tetrahydroisoquinoline (THIQ)-mediated synthesis of 1,3-disubstituted allenes from terminal alkynes and aldehydes under mild conditions in the presence of CuBr first and then $ZnI_2$ was reported. This telescoped allene synthesis reaction includes three consecutive steps and two reactions: first, a room-temperature CuBr-catalyzed synthesis of propargylamines, *exo*-yne-THIQs, from terminal alkynes, aldehydes, and THIQ, then filtration of the CuBr catalyst, and finally the $ZnI_2$-mediated allene synthesis from the generated *exo*-yne-THIQs under mild conditions (either at room temperature or heating at 50 or 75 °C). A wide range of aliphatic or aromatic aldehydes and terminal alkynes are tolerated, affording the allene products in up to 92% yield. Especially, temperature-sensitive aldehydes can be used in the reaction system. Preliminary exploration of the asymmetric allene synthesis has also been conducted, and a moderate enantioselectivity has been achieved. Finally, the relative reactivities of several secondary amines were compared with THIQ, showing that THIQ is the best of these amines in the synthesis of allenes under mild reaction conditions.

## INTRODUCTION

Allenes are very useful building blocks and functional groups that are widely applied for many transformations in organic synthesis.[1,2] Allene moieties have also been found in natural products, pharmaceuticals, and molecular materials.[3] Because of these, developing efficient reactions for the synthesis of allenes from simple and readily available organic compounds is very important. Until now numerous synthetic methodologies have been developed to access allenes.[4,5] One of the methods that are appealing to synthetic chemists for the synthesis of allenes is the secondary amine-mediated allene synthesis from alkynes and aldehydes in the presence of metal promoters (Scheme 1).[6−11] This transformation was originally reported by Crabbé and co-workers for the generation of monosubstituted allenes by a three-component reaction of terminal alkynes, paraformaldehyde, and diisopropylamine in the presence of substoichiometric CuBr (reaction *a*, Scheme 1).[6] Reaction *a* is now recognized as Crabbé homologation, and several modifications have been reported.[7] Ma has significantly improved the Crabbé homologation reaction by replacing both CuBr and diisopropylamine by CuI and dicyclohexylamine respectively, showing that the reaction yield can be improved dramatically and many functional groups can be tolerated in this new protocol.[7d] However, a limitation in both the original and modified Crabbé homologation is that the reaction is restricted to paraformaldehyde, and no allene was formed when other aldehydes were used. Recently, Ma and co-workers have reported a breakthrough, achieving a one-pot synthesis of 1,3-disubstituted allenes from terminal alkynes, normal aldehydes, and morpholine in the presence of $ZnI_2$ at high temperature (reaction *b*, Scheme 1).[8,9] Later on, Ma and Periasamy's groups independently developed the asymmetric versions of this reaction by using either chiral ligands or chiral secondary amines (reactions *c*−*e*, Scheme 1).[10] Meanwhile, Che and co-workers have also reported a two-step process for the synthesis of axially chiral allenes at 40 °C, including first gold(III) salen complex-catalyzed synthesis of chiral propargylamines via a three-component coupling reaction of terminal alkynes, aldehydes, and amines, and then gold- or silver-mediated highly enantioselective synthesis of chiral allenes (reaction *f*, Scheme 1).[11]

We were especially attracted by the allene synthesis developed by Ma and Periasamy because of their efficient synthesis of allenes in one pot and the use of cheap mediators. However, these synthetic methods require very high temperature (some reactions

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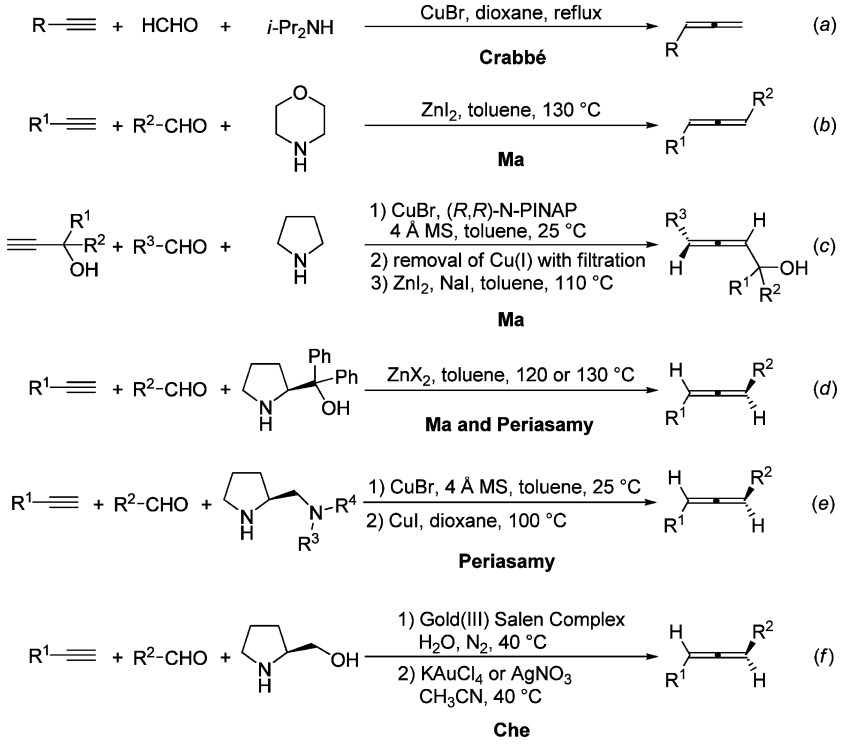
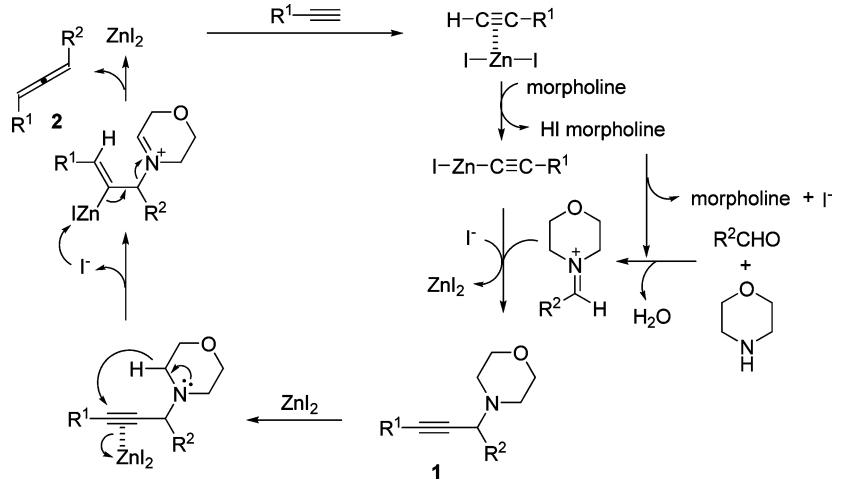
**Scheme 1. Previous Reports on the Secondary Amine-Mediated Allene Synthesis**




**Scheme 2. Mechanism for the Allene Synthesis Proposed by Ma**




were carried out at 130 °C), and we believe that this can limit the use of these methods in organic synthesis. For instance, some aldehydes or alkynes are not stable at high temperature, and consequently they cannot be used for the synthesis of allenes using Ma and Periasamy's methods. This could become a serious problem for multistep synthesis if any precursor for the three-component allene synthesis is sensitive to high temperature because of the lability of specific functional groups. Moreover, high temperature could be detrimental to the reaction yield. Also for achieving asymmetric synthesis of allenes, high temperature may result in low enantioselectivity because the energy difference between two transition states leading to enantiomers becomes smaller at higher temperature. In addition, racemization of the generated allenes could take place in the reaction system, further diminishing the enantioselectivity. Actually when we applied Ma's protocol in synthesizing allenes using temperature-sensitive substrates, we did not get the desired products.[12] Therefore, developing allene synthesis under milder conditions is highly desired.

The proposed mechanism by Ma for the allene synthesis is shown in Scheme 2.[8] The whole procedure involves two parts: the generation of the propargylamine intermediate **1** via the nucleophilic attack of the 1-alkynyl zinc species to the iminium ion formed in situ from an aldehyde and morpholine,[13,14] and the $ZnI_2$-mediated formation of allene **2** through [1,5]-hydride transfer[15,16] and $\beta$-elimination.

Since there were already some reports on the generation of propargylamines from terminal alkynes, aldehydes, and secondary amines ($A^3$ reactions) carried out at room temperature,[17] we hypothesized that the [1,5]-hydride transfer process in Ma and Periasamy's protocols could be the rate-determining step in the allene synthesis and this step might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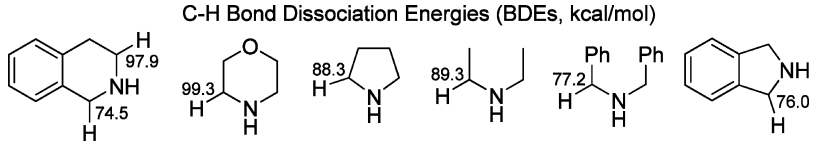
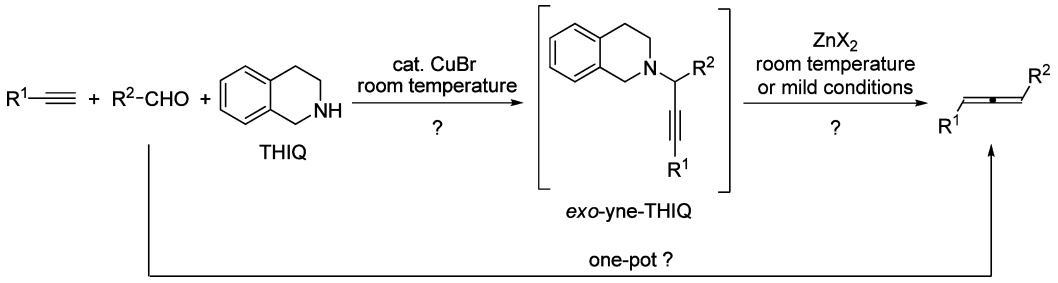
**Scheme 3. (U)B3LYP/6-31G(d) Computed C−H Bond Dissociation Energies (BDEs)**



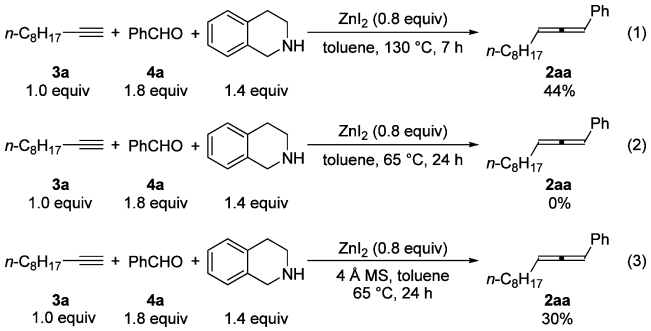

**Scheme 4. Target Allene Synthesis of the Present Investigation**




require high temperature. We envisioned that if a secondary amine with a benzylic H atom adjacent to the reactive N atom can be used, the [1,5]-hydride transfer could become easier because of the weaker benzylic C−H bond. Once this step becomes easier, the allene synthesis could be carried out at lower temperature. We computed the C−H bond dissociation energies (BDE) of several secondary amines, finding that the benzylic C−H bond adjacent to the reactive N atom in the commercially available 1,2,3,4-tetrahydroisoquinoline (THIQ) is the weakest among the C−H bonds in all calculated secondary amines (Scheme 3).[18,19] Therefore, we hypothesized that the allene synthesis mediated by THIQ could be achieved under mild conditions through room-temperature formation of propargylamines (*exo*-yne-THIQs) and [1,5]-hydride transfer also at room temperature or under mild conditions (Scheme 4). This hypothesis was encouraged by the discovery of Helaja, who showed that *exo*-yne-THIQs can give allenes using Au catalysts.[20] However, only very special *exo*-yne-THIQs (enyne-THIQs) had been investigated by Helaja and co-workers, and the reported yields of allenes were not satisfactory. Because of this, we wanted to test whether cheap promoters such as $ZnX_2$ can convert *exo*-yne-THIQs to allenes under mild conditions. In addition, *exo*-yne-THIQs used by Helaja were not synthesized by the $A^3$ reaction.[21] Therefore, realization of the hypothesized allene synthesis using THIQ as the mediator will provide a general and efficient strategy to achieve allene synthesis from common aldehydes and alkynes, via either a stepwise fashion or a one-pot fashion. Here we report our development of THIQ-mediated synthesis of 1,3-disubstituted allenes from terminal alkynes and aldehydes under mild conditions.

## RESULTS AND DISCUSSION

**1. Reaction Optimization of Allene Synthesis Mediated by THIQ.** We initially carried out the allene synthesis using 1-decyne **3a**, benzaldehyde **4a**, THIQ, and $ZnI_2$ in toluene under Ma's reaction conditions[8] at 130 °C (eq 1). To our delight, a 44% yield could be reached within 7 h, although it was lower than that using morpholine as the secondary amine in Ma's standard conditions. The dimeric coupling product (**3a**−**3a**, structure is given in Table 1) of 1-decyne **3a** was also obtained using THIQ, and then a test was conducted to determine whether a lower temperature could promote this allene synthesis. It was found that the reaction of 1.0 equiv of 1-decyne **3a** with 1.8 equiv of benzaldehyde **4a**, 1.4 equiv of THIQ, and 0.8 equiv of $ZnI_2$ in toluene at 65 °C did not give any allene product at all (eq 2). We reasoned that the in situ generated water, originating from the formation of iminium ion between aldehyde and amine, might affect the reaction at low temperature, while it could be excluded from the reaction mixture at 130 °C in Ma's protocol. Therefore, a portion of 4 Å molecular sieves (MS) was added to the reaction system. In this case, the reaction took place smoothly, affording allene **2aa** in 30% yield at 65 °C (eq 3). Since there were still lots of starting materials left in the reaction system, further efforts on the optimization of the reaction conditions were pursued. Unfortunately, it was found that the reaction yield did not increase significantly. We then decided to optimize the formation of the propargylamine intermediate *exo*-yne-THIQ and the [1,5]-hydride transfer process separately. Once both steps were optimized, we could then combine them together to get one-pot synthesis of allene.




Stimulated by previous studies of $A^3$ reactions,[17] first of all, we screened the reaction conditions for the formation of **5aa** (Table 1). A series of copper salts, zinc triflate, and gold tribromide were tested (entries 1−7). Usage of CuCl gave the propargylamine intermediate *exo*-yne-THIQ in 71% yield together with a coupling product of 1-decyne **3a** in 23% yield (entry 1). Astonishingly, a side *endo*-yne-THIQ product **5aa′**, which was not reported so far to our knowledge, can be obtained when CuBr was employed (entry 2). Side product **5aa′** could be furnished as the major product triggered by CuI as the catalyst (entry 3). Some other catalysts gave low conversion with poor chemoselectivity (entries 4 and 7), while CuCN, $Zn(OTf)_2$ led to nothing (entries 5 and 6). To get rid


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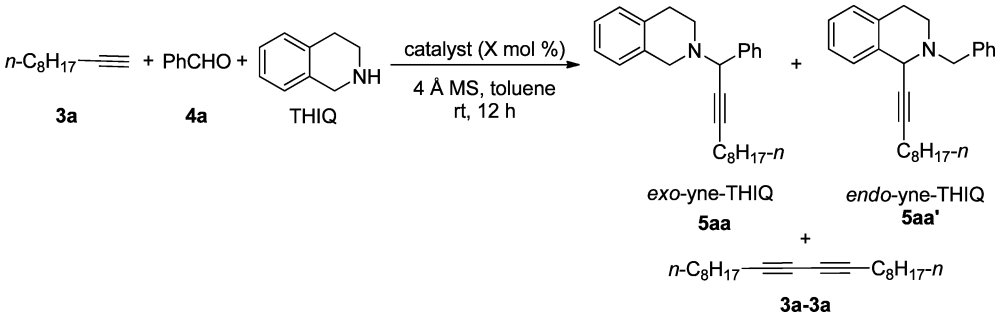
**Table 1. Optimization of the Formation of Propargylamine Intermediate *exo*-Yne-THIQ[a]**



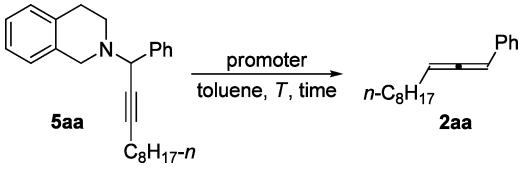

| entry | catalyst (X mol %) | ratio (3a/4a/THIQ) | yield (%)[b] 5aa + 5aa′ (ratio)[c] | yield (%)[b] 3a−3a |
|---|---|---|---|---|
| 1 | CuCl (10) | 1/1.2/1.2 | 71 (1/0) | 23 |
| 2 | CuBr (10) | 1/1.2/1.2 | 80 (6/1) | 14 |
| 3 | CuI (10) | 1/1.2/1.2 | 96 (0/1) | 0 |
| 4 | CuOTf (10) | 1/1.2/1.2 | 12 (2/1) | 66 |
| 5 | CuCN (10) | 1/1.2/1.2 | NR | NR |
| 6 | $Zn(OTf)_2$ (10) | 1/1.2/1.2 | NR | NR |
| 7[d] | $AuBr_3$ (10) | 1/1.2/1.2 | 42 (1/1.2) | 7 |
| 8 | CuBr (10) | 1/1.8/1.4 | 86 (4.4/1) | trace |
| **9** | **CuBr (20)** | **1/1.2/1.2** | **87 (1/0)** | **3** |

[a]The reactions were carried out on 0.5 mmol scale in 2.0 mL of toluene using 300 mg of 4 Å MS. [b]Isolated yield. [c]The value in the parentheses is the ratio of isomers **5aa** and **5aa**′ determined by $^1$H NMR. [d]This is the second example of Au(III)-catalyzed Glaser coupling in homogeneous system.[23]

of the coupling product **3a**−**3a**, an increased equivalent of **4a** and THIQ was also tested, finding that a combined reaction yield of 86% and a ratio of 4.4/1 for two yne-THIQs can be obtained (entry 8). As **5aa**′ cannot give the final allene product, then we concentrated here on finding the optimal conditions for the formation of **5aa**. Study of the scope of the formation of **5aa**′ will be reported in another paper.[22] Fortunately, it indicated that with 20 mol % of CuBr as the catalyst, the reaction of 1-decyne with 1.2 equiv of benzaldehyde, 1.2 equiv of THIQ in toluene at room temperature afforded the desired product **5aa** in 87% yield (entry 9).

We then screened the reaction conditions to obtain a mild-condition [1,5]-hydride transfer reaction from *exo*-yne-THIQ **5aa** (Table 2). When we subjected **5aa** to 0.8 equiv of $ZnI_2$ in toluene at 65 °C, the reaction finished in 4 h and afforded the allene product **2aa** in 83% yield (entry 1). To our delight, the reaction could be carried out at room temperature, even though it gave the allene in a lower yield (39%) and with a longer reaction time (entry 2). As the starting materials were not totally consumed after 12 h, we increased the amount of $ZnI_2$ (entries 3−5). When 1.5 equiv of $ZnI_2$ was used, the propargylamine **5aa** was almost fully converted to the allene product **2aa** in 88% yield (entry 4). Further increasing the amount of $ZnI_2$ to 1.8 equiv did not shorten the reaction time but decreased the reaction yield (entry 5), maybe because of the lability of the generated allene under these reaction conditions. When $ZnI_2$ was changed to $ZnBr_2$, the reaction yield decreased sharply (entry 6). We also tested Che's system using $KAuCl_4$ or $AgNO_3$ as promoter,[11b,c] but the allene product was isolated in only 20 and 23% yields, respectively (entries 7 and 8). Therefore, for the transformation from **5aa** to **2aa**, the best reaction conditions include using 1.5 equiv of $ZnI_2$ as promoter, toluene as solvent, and carrying out the reaction at room temperature for 12 h (entry 4). Here we want to point out that after the reaction, we could not isolate the byproduct 3,4-dihydroisoquinoline. This could be attributed to the lability of 3,4-dihydroisoquinoline in the present reaction system.[24]

**Table 2. Optimization of the [1,5]-Hydride Transfer Reaction[a]**




| entry | promoter | equiv | T (°C) | time (h) | yield (%)[b] |
|---|---|---|---|---|---|
| 1 | $ZnI_2$ | 0.8 | 65 | 4 | 83 |
| 2 | $ZnI_2$ | 0.8 | rt | 12 | 39 |
| 3 | $ZnI_2$ | 1.0 | rt | 12 | 45 |
| 4 | $ZnI_2$ | 1.5 | rt | 12 | 88 |
| 5 | $ZnI_2$ | 1.8 | rt | 12 | 72 |
| 6 | $ZnBr_2$ | 1.5 | rt | 12 | 51 |
| 7[c] | $KAuCl_4$ | 0.1 | 40 | 24 | 20 |
| 8[c] | $AgNO_3$ | 0.5 | 40 | 24 | 23 |

[a]The reactions were carried out on 0.5 mmol scale in 2.5 mL of toluene unless specified. [b]Isolated yield. [c]The reactions were carried out on 0.1 mmol scale in 2.0 mL of $CH_3CN$.

The successes of room-temperature synthesis of *exo*-yne-THIQ **5aa** and its easy transformation to the allene product **2aa** promoted us to combine these two steps in one pot using both CuBr and $ZnI_2$ as the mediators. Unfortunately, all endeavors to this aim failed because these two reaction systems were not compatible to each other. Therefore, we decided to use a three-step procedure, which was developed by Ma in the asymmetric synthesis of allenes (reaction *c*, Scheme 1).[10a] We carried out the propargylamine synthesis and [1,5]-hydride transfer process separately, and the two procedures were connected by a simple filtration through a short pad of silica gel to remove Cu(I) catalyst from the first step. After screening the reaction conditions (Table 3), we were happy to find that the best


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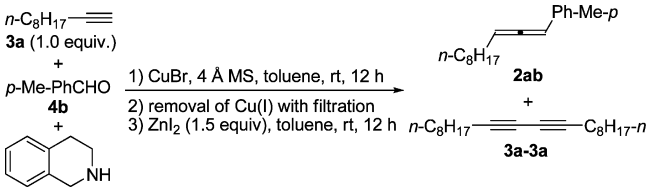
**Table 3. Screening of the Reaction Conditions**[a]




| entry | 4b (equiv) | THIQ (equiv) | CuBr (mol %) | 4 Å MS (mg) | yields (2ab, 3a−3a) (%)[b] |
|---|---|---|---|---|---|
| 1 | 1.2 | 1.2 | 20 | 300 | 50, 9 |
| 2 | 1.8 | 1.8 | 20 | 300 | 58, 5 |
| 3 | 1.8 | 1.8 | 20 | 150 | 64, trace |
| 4 | 1.5 | 1.5 | 20 | 150 | 52, 5 |
| 5 | 1.8 | 1.8 | 15 | 150 | 70, trace |
| 6 | 1.8 | 1.8 | 10 | 150 | 67, 6 |
| 7 | 1.8 | 1.4 | 15 | 150 | 73, trace |

[a]The reactions were carried out on 0.5 mmol scale in 2.0 mL of toluene for the first step and 2.5 mL of toluene for the third step. [b]Because of the fact that **2ab** and **3a−3a** have the same $R_f$, the mixture of **2ab** and **3a−3a** was separated by column chromatography, and the separate yields were determined by $^1$H NMR.

conditions for allene synthesis are those given in entry 7 of Table 3.

**2. Scope of Allene Synthesis Mediated by THIQ.** We then investigated the scope of the reaction (Table 4). In the presence of THIQ, CuBr, and then $ZnI_2$, 1-decyne reacted with various substituted benzaldehydes **4** at room tempersature to give the corresponding allenes **2** in good to excellent yields (60−92%), not influenced by the substitution patterns and the electronic natures of the substituents (entries 2−8). The heterocyclic aryl-substituted aldehyde can also be used in the reaction, but heating at 50 °C was required in the third step to give product **2ci** in 51% yield (entry 9). To our delight, the temperature-sensitive aldehydes, such as *trans*-cinnamaldehyde and *trans*-3-cyclopropylacrylaldehyde, which were not suitable substrates by using Ma's method at 130 °C, can be subjected to our reaction system when these reactions were carried out at 50 or 75 °C for the [1,5]-hydride transfer step, giving the desired products **2bj** and **2bk** in 33 and 24% yields, respectively (entries 10 and 11).[12] The relative lower yields may be due to the lability of the generated allenes under the reaction conditions (highly polar and inseparable mixture was observed in the reaction systems). The aliphatic cyclohexanecarboxaldehyde, valeraldehyde, and isobutyraldehyde are less reactive compared with aromatic aldehydes because their reactions with 4-phenyl-1-butyne to afford allenes **2bl**, **2bm**, and **2bn** had to be conducted at 50 °C for the [1,5]-hydride transfer step, instead of room temperature (entries 12−14).

In addition to 1-decyne, the used alkynes can have different substituents (for example, phenyl, chloro, cyano, and vinyl groups, entries 15−18). Furthermore, the low-boiling 1-heptyne and aromatic phenylacetylene can also react with benzaldehyde to give allenes **2fa** and **2ga** in 76 and 70% yields, respectively (entries 19 and 20). To further demonstrate the practicality of this methodology in synthesizing 1,3-disubstituted allenes, the reaction of 1-decyne, benzaldehyde, and THIQ was conducted on a scale of 10 mmol, and allene **2aa** was obtained in a slightly higher yield, 67% (entry 1). We also tried to use this method to synthesize terminal allenes using paraformaldehyde. Unfortunately, only a trace amount of the allene product was observed.

**3. Preliminary Test of Asymmetric Allene Synthesis Mediated by THIQ and Its Analogues.** After the successful development of THIQ-mediated synthesis of 1,3-disubstituted allenes under mild conditions, we then explored its asymmetric version. We added chiral ligands to the reaction system in the first step of the standard three-step procedure, but we found that either the reaction systems became complex or no reaction took place at all (Scheme 5).

We then explored the asymmetric allene synthesis by using chiral THIQ derivatives, readily prepared from naturally abundant phenylalanine derivatives (Scheme 6). It was found that **6a**, **6c**, and **6d**[25b] cannot mediate the allene synthesis. Fortunately, **6b**[25a] gave a moderate yield (53%) and ee value (65%) of the chiral allene ***R*-2aa** (its absolute chirality was assigned on the basis of previous studies).[10b] If we purified the *exo*-yne-THIQ **7** from the first step of A$^3$ reaction and then subjected the purified **7** to allene synthesis, the final reaction yield (68%) and ee (72%) value of obtained allene ***R*-2aa** can be improved. The chirality transfer from pure *exo*-yne-THIQ **7** (75% ee from the first step A$^3$ reaction using **6b**) to allene ***R*-2aa** (72% ee) was satisfactory, but this was decreased by 10% in the three-step sequence (from 75 to 65% ee), suggesting that possibly some side products from the A$^3$ step were detrimental to [1,5]-hydride transfer step if the used *exo*-yne-THIQ **7** was not purified.

**4. Comparison of Reactivities of THIQ and Other Amines in Allene Synthesis.** Finally, we tested whether other secondary amines can also mediate the allene synthesis under mild conditions, which have not been investigated by Ma and Periasamy previously (Table 5). When we treated different amines with the similar conditions used for THIQ-mediated allene synthesis, we found that, in all cases, the propargylamine intermediates can be generated in the presence of CuBr at room temperature, with good or poor yield. However, the reaction conditions of the $ZnI_2$-mediated transformations from the propargylamine intermediates to the allene products varied and depended on amine substrates. For morpholine or dibenzylamine, no allene product was observed when the reaction mixture of the first step (after removal of Cu(I) with filtration) was treated with 1.5 equiv of $ZnI_2$ at room temperature. Only when the reaction temperature was increased to 50 °C, allene **2aa** was isolated in 20 and 52% total yields, respectively (entries 2 and 5). When pyrrolidine and diethylamine were used as the secondary amines in the allene synthesis, the $ZnI_2$-mediated transformations from the propargylamine intermediates to the allene product could take place at room temperature, but affording allene **2aa** in low yields, 13 or 36%, respectively (entries 3 and 4). When isoindoline was used to mediate the allene synthesis, only a trace amount of the allene product was observed (entry 6). This may be due to the lability of isoindoline and the corresponding propargylamine intermediate. The above comparison shows that THIQ is the best to mediate the allene synthesis under mild reaction conditions. When we carried out the synthesis of allene in a stepwise fashion by isolating the A$^3$ products first and then running $ZnI_2$-mediated allene synthesis separately, THIQ still had the best performance.

## ■ CONCLUSION

In summary, we have developed a practical 1,2,3,4-tetrahydroisoquinoline (THIQ)-mediated synthesis of 1,3-disubstituted allenes from terminal alkynes and aldehydes under mild conditions in the presence of CuBr first and then $ZnI_2$. This telescoped allene synthesis has wide scope, including several


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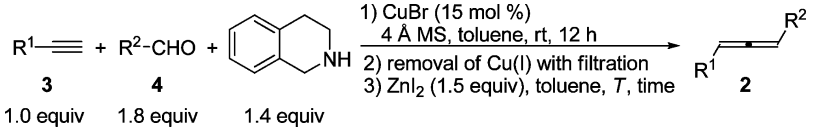
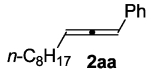
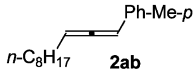
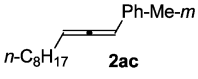
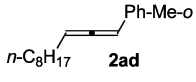
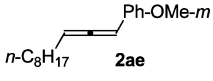
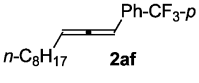
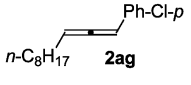
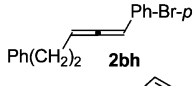
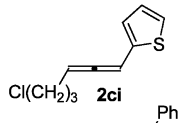
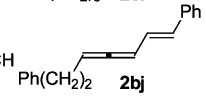
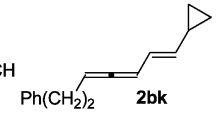
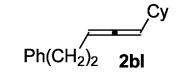
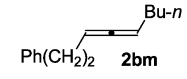
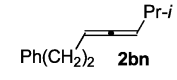
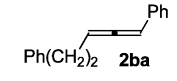
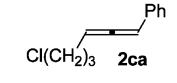
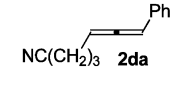
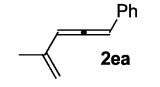
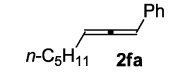
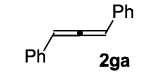
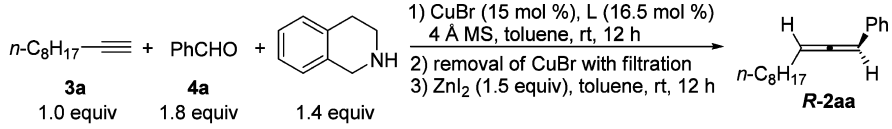
**Table 4. Scope of the Allene Synthesis**[a,b]

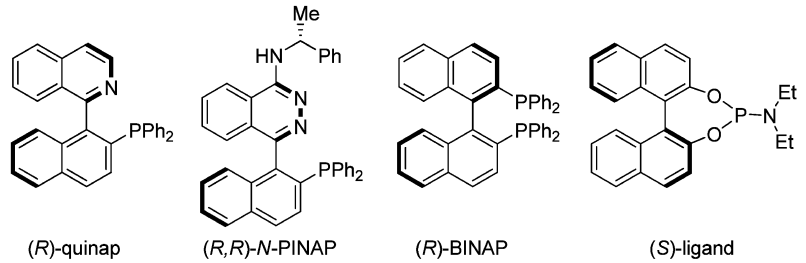



| entry | $R^1$/$R^2$ | 2 | T (°C) | time (h) | yield (%)[c] |
|---|---|---|---|---|---|
| 1 | $R^1$ = *n*-$C_8H_{17}$<br>$R^2$ = Ph |  **2aa** | rt | 12 | 63 (67)[d,e] |
| 2 | $R^1$ = *n*-$C_8H_{17}$<br>$R^2$ = *p*-Me-Ph |  **2ab** | rt | 12 | 73 |
| 3 | $R^1$ = *n*-$C_8H_{17}$<br>$R^2$ = *m*-Me-Ph |  **2ac** | rt | 12 | 77 |
| 4 | $R^1$ = *n*-$C_8H_{17}$<br>$R^2$ = *o*-Me-Ph |  **2ad** | rt | 12 | 92 |
| 5 | $R^1$ = *n*-$C_8H_{17}$<br>$R^2$ = *m*-MeO-Ph |  **2ae** | rt | 12 | 60 |
| 6 | $R^1$ = *n*-$C_8H_{17}$<br>$R^2$ = *p*-$CF_3$-Ph |  **2af** | rt | 12 | 69 |
| 7 | $R^1$ = *n*-$C_8H_{17}$<br>$R^2$ = *p*-Cl-Ph |  **2ag** | rt | 12 | 67[e,f] |
| 8 | $R^1$ = $Ph(CH_2)_2$<br>$R^2$ = *p*-Br-Ph |  **2bh** | rt | 12 | 66 |
| 9 | $R^1$ = $Cl(CH_2)_3$<br>$R^2$ = 2-thiophenyl |  **2ci** | 50 | 4 | 51 |
| 10 | $R^1$ = $Ph(CH_2)_2$<br>$R^2$ = *trans*-PhCH=CH |  **2bj** | 50 | 4 | 33 |
| 11[g] | $R^1$ = $Ph(CH_2)_2$<br>$R^2$ = *trans*-CypCH=CH |  **2bk** | 75 | 5 | 24 |
| 12 | $R^1$ = $Ph(CH_2)_2$<br>$R^2$ = Cy |  **2bl** | 50 | 4 | 49 |
| 13 | $R^1$ = $Ph(CH_2)_2$<br>$R^2$ = *n*-Bu |  **2bm** | 50 | 4 | 42 |
| 14 | $R^1$ = $Ph(CH_2)_2$<br>$R^2$ = *i*-Pr |  **2bn** | 50 | 4 | 42 |
| 15 | $R^1$ = $Ph(CH_2)_2$<br>$R^2$ = Ph |  **2ba** | rt | 12 | 86 |
| 16 | $R^1$ = $Cl(CH_2)_3$<br>$R^2$ = Ph |  **2ca** | rt | 12 | 63 |
| 17 | $R^1$ = $NC(CH_2)_3$<br>$R^2$ = Ph |  **2da** | 50 | 4 | 62 |
| 18 | $R^1$ = 1-Methylvinyl<br>$R^2$ = Ph |  **2ea** | rt | 12 | 72 |
| 19 | $R^1$ = *n*-$C_5H_{11}$<br>$R^2$ = Ph |  **2fa** | rt | 12 | 76 |
| 20 | $R^1$ = Ph<br>$R^2$ = Ph |  **2ga** | 50 | 4 | 70 |

[a]The reactions were carried out on 0.5 mmol scale in 2.0 mL of toluene using 150 mg of 4 Å MS for the first step and 2.5 mL of toluene for the third step. [b]For a comparative purpose, a list of selected examples including the results of the THIQ method with previous ones from Ma and Periasamy groups was given in Table S1 of the Supporting Information, which shows that the present method gives reaction yields usually comparable to those obtained by Periasamy's method but are higher than those obtained by Ma's method. [c]Isolated yield. [d]The value in the parentheses is the yield when the reaction was conducted on a 10 mmol scale using 3.0 g of 4 Å MS. [e]We found that the reactions under Ma's standard conditions at 130 °C using THIQ gave lower yields (44 and 16% for entries 1 and 7, respectively), suggesting that THIQ-mediated allene synthesis is not good at high temperature. [f]The yield is much higher than that using Ma's protocol. [g]Cyp = Cyclopropyl.

**Scheme 5. Preliminary Exploration of Asymmetric Allene Synthesis Using Chiral Ligands**




| | (*R*)-quinap | (*R,R*)-*N*-PINAP | (*R*)-BINAP | (*S*)-ligand |
|---|---|---|---|---|
| Result: | complex mixture | no reaction | complex mixture | complex mixture |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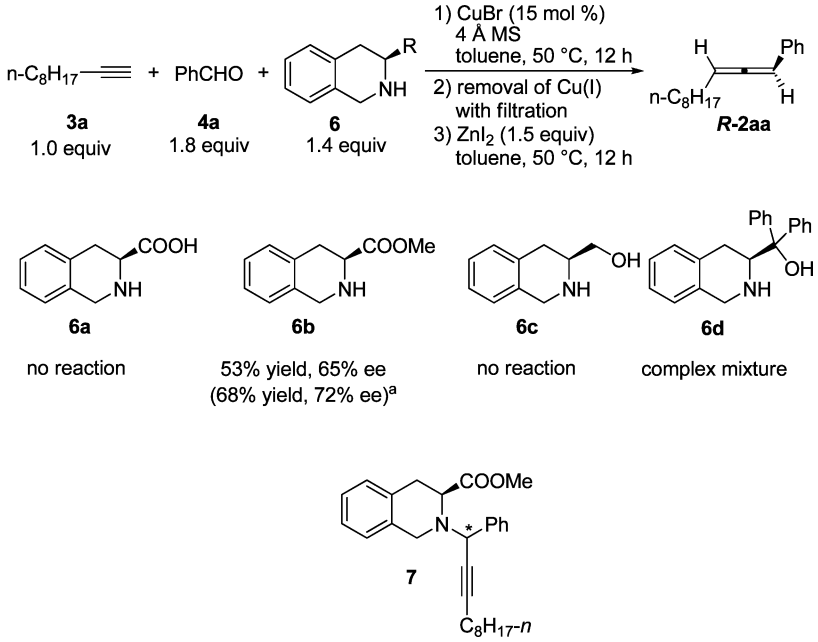
**Scheme 6. Preliminary Exploration of Asymmetric Allene Synthesis Using Chiral THIQ Derivatives**




[a]Yield and ee values in parentheses were obtained when the *exo*-yne-THIQ from the $A^3$ reaction was purified first and then subjected this intermediate to $ZnI_2$-mediated allene synthesis. [b]"No reaction" means that the first $A^3$ reaction did not take place.

examples using unprecedented labile substrates, and good to excellent yields. A promising asymmetric allene synthesis with moderate enatioselectivity was also achieved by using a chiral THIQ derivative readily prepared from naturally abundant phenylalanine. Finally, we compared the reactivities of selected secondary amines with THIQ, showing the obvious advantage of THIQ as the mediator in allene synthesis. Further study of using DFT calculations to understand how different substituents affect the [1,5]-hydride transfer and $\beta$-elimination processes is ongoing and will be disclosed in due course.

## EXPERIMENTAL SECTION

**General Information.** Toluene was dried over Na before use. The reaction course was followed by TLC. For chromatographic purifications, 200−300 mesh silica gel was employed. $^1$H NMR (400 MHz) and $^{13}$C NMR (100 MHz) spectra were recorded in parts per million using tetramethylsilane (TMS) as the internal standard. IR spectra were reported in wavenumbers ($cm^{-1}$). HRMS were performed under ESI ionization technique using FT-ICR analyzer. PE = petroleum ether, EA = ethyl acetate.

**Experimental Notes.** The commercially available $ZnI_2$ was used in the synthesis. But sometimes the purchased $ZnI_2$ was not pure, and the reaction yield of allene synthesis was low at room temperature. In this case, sublimed $ZnI_2$ can be used to reproduce the reaction yield reported in Table 2. Also the first step of formation of *exo*-yne-THIQs is sensitive to air and must be conducted under $N_2$ or Ar atmosphere. The $ZnI_2$-mediated synthesis of allene is also sensitive to moisture. We also found that the reported reaction can be performed under $N_2$ atmosphere, and there is no need to use glovebox (in our lab, CuBr and $ZnI_2$ purchased were stored in the glovebox, so we measured these reagents within the glovebox).

**Synthesis of 2-(1-Phenylundec-2-ynyl)-1,2,3,4-tetrahydroisoquinoline (5aa).** To a flame-dried pear-shaped flask (10 mL) was added CuBr (14.4 mg, 0.1 mmol) and newly activated 4 Å molecular sieves (300 mg) inside a glovebox. Toluene (2 mL) was then added under nitrogen atmosphere outside of the glovebox, followed by benzaldehyde **4a** (55.4 mg, 0.522 mmol), THIQ (71.1 mg, 0.534 mmol), and 1-decyne **3a** (61.0 mg, 0.441 mmol). The reaction mixture was stirred at room temperature (25 °C) for 12 h. After completion of the reaction, the mixture was filtered through a thin pad of silica gel. The filter cake was washed with PE/EA (10/1), and the combined filtrate was concentrated. The crude product was purified by flash column chromatography on silica gel (eluted with PE/EA = 50/1) to afford propargylamine **5aa** (141.3 mg, 87%). Pale yellow oil: TLC $R_f$ = 0.71 (PE/EA = 20/1); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.65 (d, $J$ = 7.4 Hz, 2H), 7.34 (t, $J$ = 7.4 Hz, 2H), 7.28 (t, $J$ = 7.3 Hz, 1H), 7.12−7.06 (m, 3H), 7.01−6.97 (m, 1H), 4.81 (s, 1H), 3.76 (d, $J$ = 16.8 Hz, 1H), 3.72 (d, $J$ = 15.2 Hz, 1H), 2.96−2.83 (m, 2H), 2.82−2.68 (m, 2H), 2.31 (td, $J$ = 7.0, and 2.0 Hz, 2H), 1.63−1.50 (m, 2H), 1.48−1.37 (m, 2H), 1.33−1.20 (m, 8H), 0.87 (t, $J$ = 6.8 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 139.0, 135.5, 134.5, 128.7, 128.5, 128.1, 127.5, 126.7, 125.9, 125.5, 88.9, 75.3, 61.2, 52.1, 47.1, 31.9, 29.7, 29.3, 29.1, 29.0, 22.7, 18.8, 14.1; IR (neat) 2925, 2854, 1491, 1449, 1141 $cm^{-1}$; HRMS (ESI) calcd for $C_{26}H_{34}N$ $(M + H)^+$ 360.26858, found 360.26810.

**Synthesis of 2-Benzyl-1-(dec-1-yn-1-yl)-1,2,3,4-tetrahydroisoquinoline (5aa′).** To a flame-dried pear-shaped flask (10 mL) was added CuI (9.5 mg, 0.05 mmol) and newly activated 4 Å molecular sieves (300 mg) inside a glovebox. Toluene (2 mL) was then added under nitrogen atmosphere outside of the glovebox, followed by benzaldehyde **4a** (65.5 mg, 0.617 mmol), THIQ (80.4 mg, 0.604 mmol), and 1-decyne **3a** (70.5 mg, 0.510 mmol). The reaction mixture was stirred at room temperature (25 °C) for 12 h. After completion of the reaction, the mixture was filtered through a thin pad of silica gel. The filter cake was washed with PE/EA (10/1), and the combined filtrate was concentrated. The crude product was purified by flash column chromatography on silica gel (eluted with PE/EA = 50/1) to afford propargylamine **5aa′** (176.2 mg, 96%). Pale yellow oil: TLC $R_f$ = 0.60 (PE/EA = 20/1); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.43 (d, $J$ = 7.1 Hz, 2H), 7.32 (t, $J$ = 7.3 Hz, 2H), 7.27 (d, $J$ = 7.2 Hz, 1H), 7.21−7.17 (m, 1H), 7.15−7.11 (m, 2H), 7.11−7.05 (m, 1H), 4.55 (s, 1H), 3.89 (d, $J$ = 13.1 Hz, 1H), 3.80 (d, $J$ = 13.1 Hz, 1H), 3.06−2.88 (m, 2H), 2.82−2.65 (m, 2H), 2.23 (td, $J$ = 7.0, and 2.0 Hz, 2H), 1.58−1.48 (m, 2H), 1.47−1.36 (m, 2H), 1.34−1.19 (m, 8H), 0.88 (t, $J$ = 6.7 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 138.6, 136.4, 133.9, 129.2, 128.9, 128.2, 127.7, 127.1, 126.7, 125.7, 87.2, 77.9, 59.5, 54.1, 45.6, 31.9, 29.3, 29.11, 29.06, 29.00, 28.9, 22.7, 18.9, 14.1; IR (neat) 2929, 2858, 1499, 1458, 1138 $cm^{-1}$; HRMS (ESI) calcd for $C_{26}H_{34}N$ $(M + H)^+$ 360.26858, found 360.26874.

**General Procedure for THIQ-Mediated Synthesis of 1,3-Disubstituted Allenes from Terminal Alkynes and Aldehydes.** To a flame-dried pear-shaped flask (10 mL) was added CuBr (10.8 mg, 0.075 mmol) and newly activated 4 Å molecular sieves (150 mg) inside


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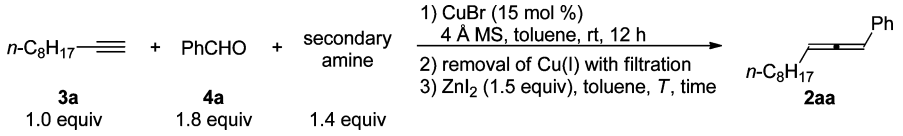
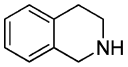
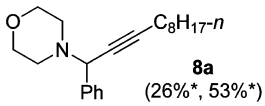
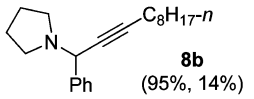
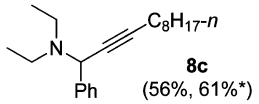
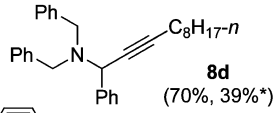
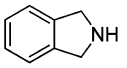
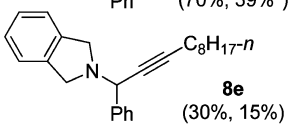
**Table 5. Comparison of the Reactivities of THIQ and Other Secondary Amines in Allene Synthesis**[a]




**3a** 1.0 equiv | **4a** 1.8 equiv | secondary amine 1.4 equiv | **2aa**

| entry | secondary amine | propargyl amine [a,b] | T (°C) | time (h) | yield (%)[c] |
|---|---|---|---|---|---|
| 1 |  | **5aa** (93%, 88%) | rt | 12 | 63 |
| 2 |  |  **8a** (26%*, 53%*) | 50[d] | 12 | 20 |
| 3 |  |  **8b** (95%, 14%) | rt | 12 | 13 |
| 4 |  |  **8c** (56%, 61%*) | rt | 12 | 36 |
| 5 |  |  **8d** (70%, 39%*) | 50[d] | 24 | 52 |
| 6 |  |  **8e** (30%, 15%) | rt | 12 | trace |

[a]The reactions were carried out on 0.5 mmol scale in 2.0 mL of toluene using 150 mg of 4 Å MS for the first step and 2.5 mL of toluene for the third step. [b]Yields in the parentheses are results of the first step of $A^3$ coupling and the second step of [1,5]-hydride transfer of purified propargyl amines, respectively, which are both carried out at room temperature. Yields with star marks were carried out at 50 °C, and in these cases, room temperature reactions are not satisfactory. [c]Isolated yield using the three-step procedure. [d]No allene product was observed when the temperature was lowered to room temperature.

a glovebox. Toluene (2 mL) was then added under nitrogen atmosphere outside of the glovebox, followed by aldehyde **4** (0.9 mmol), THIQ (93.2 mg, 0.7 mmol), and terminal alkyne **3** (0.5 mmol). The reaction mixture was stirred at room temperature (25 °C) for 12 h. After completion of the reaction, the mixture was filtered through a thin pad of silica gel. The filter cake was washed with PE/EA, and the combined filtrate was concentrated. The crude product was used in the next step without further treatment. To another flame-dried pear-shaped flask (10 mL) was added $ZnI_2$ (239.4 mg, 0.75 mmol) inside a glovebox, and then the flask was taken out. The above crude product was dissolved in toluene (2.5 mL) and transferred to the flask via a syringe under nitrogen atmosphere. After stirring at the indicated temperature for the indicated reaction time (at room temperature for 12 h, or at 50 °C for 4 h, or at 75 °C for 5 h; see these in Table 4), the reaction was stopped, the reaction mixture was filtered through a thin pad of silica gel, and the filter cake was washed with PE (except for the synthesis of allene **2da**, where PE/EA = 10/1 was used as the eluting solvent). After evaporation, the residue was purified by flash column chromatography on silica gel (eluted with PE/EA = 10/1 for allene **2da** and PE for other allenes) to afford the corresponding allene product **2**. Also this procedure was applied for the three-step synthesis of allene shown in Table 5, except that THIQ was replaced by the corresponding secondary amines.

The structures of allene molecules **2aa**,[8] **2ab**,[10b] **2ac**,[10b] **2ae**,[10b] **2af**,[10b] **2ag**,[8] **2bh**,[10b] **2ci**,[10b] **2bj**,[26] **2bl**,[27] **2bm**,[27] **2bn**,[28] **2ba**,[10b] **2ca**,[10b] **2da**,[10b] **2ea**,[11c] **2fa**,[10b] **2ga**[11b] and ***R*-2aa**,[10b] which were confirmed by $^1H$ and $^{13}C$ NMR spectra, are consistent with those reported previously.

*1-(2-Methylphenyl)undeca-1,2-diene (**2ad**).* Following the general procedure above, 1-decyne (71.4 mg, 0.516 mmol), 2-methylbenzaldehyde (110.8 mg, 0.922 mmol), and THIQ (91.1 mg, 0.684 mmol) were converted to the allene product **2ad** (114.8 mg, 92% yield). Colorless oil: TLC $R_f$ = 0.93 (PE); $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.37 (d, $J$ = 7.5 Hz, 1H), 7.20−7.03 (m, 3H), 6.33−6.27 (m, 1H), 5.56−5.48 (m, 1H), 2.36 (s, 3H), 2.16−2.08 (m, 2H), 1.54−1.43 (m, 2H), 1.40−1.19 (m, 10H), 0.88 (t, $J$ = 6.8 Hz, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 205.9, 134. 8, 133.3, 130.4, 127.0, 126.5, 126.0, 94.2, 91.7, 31.9, 29.4, 29.3, 29.2, 28.9, 22.7, 19.8, 14.1; IR (neat) 2925, 2854, 1465, 1262 $cm^{-1}$; HRMS (ESI) calcd for $C_{18}H_{27}$ $(M + H)^+$ 243.21073, found 243.21071.

*trans-1-Cyclopropyl-7-phenylhepta-1,3,4-triene (**2bk**).* Following the general procedure above, 4-phenyl-1-butyne (65.0 mg, 0.5 mmol), *trans*-3-cyclopropylacrylaldehyde (86.0 mg, 0.9 mmol), and THIQ (93.2 mg, 0.7 mmol) were converted to the allene product **2bk** (25.0 mg, 24% yield). Colorless oil: TLC $R_f$ = 0.81 (PE); $^1H$ NMR (400 MHz, $C_6D_6$; the singlet peak at 7.15 was used as the standard) $\delta$ 7.20−7.11 (m, 2H), 7.10−7.01 (m, 3H), 5.99 (dd, $J$ = 14.8 and 10.6 Hz, 1H), 5.91−5.82 (m, 1H), 5.28 (q, $J$ = 5.9 Hz, 1H), 4.97 (dd, $J$ = 15.0 and 8.8 Hz, 1H), 2.61 (t, $J$ = 7.6 Hz, 2H), 2.28−2.17 (m, 2H), 1.24−1.13 (m, 1H), 0.53−0.42 (m, 2H), 0.24−0.15 (m, 2H); $^{13}C$ NMR (100 MHz, $C_6D_6$; the triplet peaks at 128.0 were used as the standard) $\delta$ 206.7, 141.9, 136.1, 128.8, 128.6, 126.1, 123.9, 95.2, 92.0, 35.6, 31.0, 14.4, 7.3; IR (neat) 2934, 2858, 1944, 1497, 1454 $cm^{-1}$; HRMS (ESI) calcd for $C_{16}H_{19}$ $(M + H)^+$ 211.14813, found 211.14823.

**General Procedure for Attempts of Asymmetric Allene Synthesis Using Chiral Ligands.** Similar to the general procedure for THIQ-mediated allene synthesis, terminal alkyne and aldehyde were converted into 1,3-disubstituted allene via a three-step sequence. Corresponding chiral ligand (0.083 mmol) was added into the flask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inside a glovebox prior to the addition of substrates. Reactions were monitored by TLC.

**General Procedure for Attempts of Asymmetric Allene Synthesis Using Chiral THIQs.** Similar to the general procedure for THIQ-mediated allene synthesis, terminal alkyne and aldehyde were converted into 1,3-disubstituted allene via a three-step sequence. The first and third steps were carried out at 50 °C instead of room temperature for 12 h. Reactions were monitored by TLC.

**Synthesis of Allene *R*-2aa[10b] in One Pot via a Three-Step Sequence.** Following the general procedure for allene synthesis, THIQ-ester **6b** (264.3 mg, 0.6 mmol), benzaldehyde **4a** (87.5 mg, 0.8 mmol), and 1-decyne **3a** (53.6 mg, 0.4 mmol) were finally converted into allene product **2aa** (47.2 mg, 0.2 mmol, 53%). The ee value of allene was determined by HPLC using an OD-H chiral column with hexane as eluent. The ee value turned out to be 65%. $[\alpha]_D^{25}$ −150.2 ($c$ = 0.50, $CHCl_3$).

**Stepwise Synthesis of Allene *R*-2aa: Synthesis of *exo*-Yne-THIQ 7 and Subsequent Chiral Allene Synthesis Using Chiral THIQ 6b.** Similar to the synthesis of *exo*-yne-THIQ **5aa**, THIQ-ester **6b** (114.7 mg, 0.6 mmol), benzaldehyde **4a** (53.0 mg, 0.5 mmol), and 1-decyne **3a** (83.0 mg, 0.6 mmol) were converted into *exo*-yne-THIQ **7** (186.7 mg, 0.447 mmol, 89%). Purification was by silica gel, PE/EA = 100/1. The ee value of **7** was determined by HPLC using an AD-H chiral column with 99/1 hexane/*i*PrOH as eluent. The measured ee value was 75% according to the HPLC profile (the absolute configuration of the stereogenic center was not determined). Subsequently, **7** (108.4 mg, 0.260 mmol) was applied to the general procedure for the allene synthesis from *exo*-yne-THIQ; allene **2aa** (45.3 mg, 0.198 mmol, 76%) was obtained. The measured ee value was 72%.

*(3S)-Methyl 2-(1-phenylundec-2-yn-1-yl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (**7**).* Colorless oil: TLC $R_f$ = 0.40 (PE/EA = 30/1); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.63 (d, $J$ = 7.3 Hz, 2H), 7.34 (t, $J$ = 7.3 Hz, 2H), 7.30−7.24 (m, 1H), 7.11−7.02 (m, 3H), 6.88 (d, $J$ = 6.6 Hz, 1H), 5.01 (s, 1H), 4.12 (t, $J$ = 5.7 Hz, 1H), 3.73 (s, 2H), 3.72 (s, 3H), 3.25−3.10 (m, 2H), 2.25 (td, $J$ = 7.0, 2.0 Hz, 2H), 1.58−1.46 (m, 2H), 1.44−1.34 (m, 2H), 1.34−1.18 (m, 8H), 0.87 (t, $J$ = 6.8 Hz, 3H); $^{13}$C NMR (101 MHz, $CDCl_3$) $\delta$ 173.7, 139.4, 134.7, 132.4, 128.5, 128.3, 128.1, 127.7, 126.4, 126.1, 126.0, 89.3, 75.9, 58.8, 58.7, 51.7, 48.0, 33.0, 31.9, 29.3, 29.1, 28.94, 28.90, 22.7, 18.9, 14.2; IR (neat) 2927, 2854, 1742, 1451, 1195, 1173 cm$^{-1}$; HRMS (ESI) calcd for $C_{28}H_{36}NO_2$ $(M + H)^+$ 418.27406, found 418.27404.

Synthesis of **8a**−**8e** followed the similar procedure of synthesis of **5aa**

*4-(1-Phenylundec-2-yn-1-yl)morpholine (**8a**).* Similar to the synthesis of **5aa**, under 50 °C, morpholine (110.7 mg, 1.27 mmol), benzaldehyde (113.5 mg, 1.07 mmol), and 1-decyne (175.2 mg, 1.27 mmol) were converted to propargyl amine product **8a** (88.3 mg, 26% yield). Colorless oil: TLC $R_f$ = 0.30 (PE/EA = 10/1); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.56 (d, $J$ = 7.2 Hz, 2H), 7.36−7.30 (m, 2H), 7.29−7.24 (m, 1H), 4.52 (s, 1H), 3.75−3.63 (m, 4H), 2.59−2.46 (m, 4H), 2.31 (td, $J$ = 6.9, and 1.8 Hz, 2H), 1.63−1.52 (m, 2H), 1.49−1.38 (m, 2H), 1.37−1.21 (m, 8H), 0.88 (t, $J$ = 6.7 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 138.5, 128.6, 128.1, 127.5, 88.8, 75.4, 67.2, 61.7, 49.8, 31.8, 29.2, 29.1, 29.04, 28.97, 22.7, 18.8, 14.1; IR (neat) 2926, 2854, 1451, 1321, 1117 cm$^{-1}$; HRMS (ESI) calcd for $C_{21}H_{32}NO$ $(M + H)^+$ 314.24784, found 314.24723.

*1-(1-Phenylundec-2-yn-1-yl)pyrrolidine (**8b**).* Similar to the synthesis of **5aa**, under 25 °C, pyrrolidine (267.7 mg, 3.76 mmol), benzaldehyde (393.2 mg, 3.71 mmol), and 1-decyne (416.7 mg, 3.01 mmol) were converted to propargyl amine product **8b** (850.3 mg, 95% yield). Colorless oil: TLC $R_f$ = 0.16 (PE/EA = 10/1); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.48−7.41 (m, 2H), 7.26−7.20 (m, 2H), 7.19−7.14 (m, 1H), 4.53 (s, 1H), 2.57−2.46 (m, 4H), 2.19 (td, $J$ = 7.0, and 2.1 Hz, 2H), 1.72−1.63 (m, 4H), 1.52−1.42 (m, 2H), 1.40−1.30 (m, 2H), 1.29−1.12 (m, 8H), 0.80 (t, $J$ = 6.8 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 140.2, 128.2, 128.1, 127.3, 87.1, 77.018, 58.8, 50.2, 31.9, 29.3, 29.1, 29.0, 28.9, 23.5, 22.7, 18.8, 14.1; IR (neat) 2928, 2856, 1451, 1268, 1136, 1030 cm$^{-1}$; HRMS (ESI) calcd for $C_{21}H_{32}N$ $(M + H)^+$ 298.25293, found 298.25224.

*N,N-Diethyl-1-phenylundec-2-yn-1-amine (**8c**).* Similar to the synthesis of **5aa**, under 25 °C, diethylamine (487.1 mg, 6.66 mmol), benzaldehyde (514.6 mg, 4.85 mmol), and 1-decyne (805.3 mg, 5.82 mmol) were converted to propargyl amine product **8c** (818.3 mg, 56% yield). Yellow oil: TLC $R_f$ = 0.60 (PE/EA = 10/1); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.62 (d, $J$ = 7.6 Hz, 2H), 7.31 (t, $J$ = 7.5 Hz, 2H), 7.24 (t, $J$ = 7.2 Hz, 1H), 4.80 (s, 1H), 2.60−2.49 (m, 2H), 2.49−2.38 (m, 2H), 2.30 (td, $J$ = 6.9, and 1.9 Hz, 2H), 1.62−1.51 (m, 2H), 1.50−1.40 (m, 2H), 1.38−1.23 (m, 8H), 1.03 (t, $J$ = 7.1 Hz, 6H), 0.88 (t, J = 6.6 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 140.6, 128.4, 127.9, 127.0, 87.5, 76.0, 56.5, 44.5, 31.9, 29.3, 29.14, 29.11, 28.9, 22.7, 18.8, 14.1, 13.6; IR (neat) 2929, 2856, 1450, 1382, 1196 cm$^{-1}$; HRMS (ESI) calcd for $C_{21}H_{34}N$ $(M + H)^+$ 300.26858, found 300.26820.

*N,N-Dibenzyl-1-phenylundec-2-yn-1-amine (**8d**).* Similar to the synthesis of **5aa**, under 25 °C, dibenzylamine (1.1934 g, 6.05 mmol), benzaldehyde (505.5 mg, 4.76 mmol), and 1-decyne (827.5 mg, 5.99 mmol) were converted to propargyl amine product **8d** (1.4137 g, 70% yield). Colorless oil: TLC $R_f$ = 0.21 (PE); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.67 (d, J = 7.8 Hz, 2H), 7.40 (d, $J$ = 7.4 Hz, 4H), 7.34−7.25 (m, 6H), 7.20 (q, $J$ = 7.0 Hz, 3H), 4.69 (s, 1H), 3.70 (d, $J$ = 13.5 Hz, 2H), 3.44 (d, $J$ = 13.5 Hz, 2H), 2.42 (td, $J$ = 6.9, and 2.0 Hz, 2H), 1.71−1.62 (m, 2H), 1.60−1.50 (m, 2H), 1.43−1.25 (m, 8H), 0.89 (t, $J$ = 6.9 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 140.03, 139.96, 129.0, 128.44, 128.35, 128.1, 127.4, 127.0, 88.9, 74.9, 55.8, 54.7, 32.0, 29.5, 29.4, 29.3, 29.2, 22.9, 19.0, 14.3; IR (neat) 2928, 2853, 1494, 1452, 1117 cm$^{-1}$; HRMS (ESI) calcd for $C_{31}H_{38}N$ $(M + H)^+$ 424.29988, found 424.30106.

*2-(1-Phenylundec-2-yn-1-yl)isoindoline (**8e**).* Similar to the synthesis of **5aa**, under 25 °C, isoindoline (718.5 g, 6.03 mmol), benzaldehyde (530.1 mg, 4.99 mmol), and 1-decyne (830.9 mg, 6.01 mmol) were converted to propargyl amine product **8e** (510.6 mg, 30% yield). Dark red oil: TLC $R_f$ = 0.64 (PE/EA = 10/1); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.67−7.61 (m, 2H), 7.39−7.32 (m, 2H), 7.31−7.26 (m, 1H), 7.15 (s, 4H), 4.91 (s, 1H), 4.05 (d, $J$ = 11.2 Hz, 2H), 3.97 (d, $J$ = 11.1 Hz, 2H), 2.27 (td, $J$ = 7.0, and 2.0 Hz, 2H), 1.57−1.48 (m, 2H), 1.43−1.34 (m, 2H), 1.31−1.19 (m, 8H), 0.87 (t, $J$ = 6.9 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 140.0, 139.6, 128.23, 128.21, 127.5, 126.6, 122.4, 89.5, 76.3, 58.3, 55.3, 31.8, 29.2, 29.1, 29.0, 28.9, 22.7, 18.8, 14.1; IR (neat) 2928, 2854, 1465, 1343, 1272 cm$^{-1}$; HRMS (ESI) calcd for $C_{25}H_{32}N$ $(M + H)^+$ 346.25293, found 346.25385.

## ■ ASSOCIATED CONTENT

### Supporting Information

Copies of $^1$H and $^{13}$C spectra for all products, HPLC analysis profile of ***R*-2aa**, **7**, comparison of different allene synthesis methods, and computational details. This material is available free of charge via the Internet at http://pubs.acs.org.

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### Notes

The authors declare no competing financial interest.

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reaction yield. We thank Prof. Ma for this great help also. We also thank Dr. Lei Jiao and Prof. Thorsten Bach from Technische Universität München, Mr. Zhe Dong and Prof. Guangbin Dong from University of Texas, Austin, and Mr. Yaocheng Shi from Peking University, for repeating the experiment of the synthesis of **2aa**. We are grateful to Prof. Zuqiang Bian of Peking University for helping us get sublimed $ZnI_2$.

## REFERENCES

(1) For recent monographs, see: (a) *Modern Allene Chemistry*; Krause, N., Hashmi, A. S. K., Eds.; Wiley-VCH: Weinheim, 2004; Vols. *1* and *2*. (b) Ma, S. Palladium-catalyzed two- or three-component cyclization of functionalized allenes. In *Palladium in Organic Synthesis*; Tsuji, J., Ed.; Springer: Berlin, 2005; pp 183−210.

(2) For reviews on the chemistry of allenes, see: (a) Wang, K. K. *Chem. Rev.* **1996**, *96*, 207. (b) Marshall, J. A. *Chem. Rev.* **2000**, *100*, 3163. (c) Hashmi, A. S. K. *Angew. Chem., Int. Ed.* **2000**, *39*, 3590. (d) Zimmer, R.; Dinesh, C. U.; Nandanan, E.; Khan, F. A. *Chem. Rev.* **2000**, *100*, 3067. (e) Lu, X.; Zhang, C.; Xu, Z. *Acc. Chem. Res.* **2001**, *34*, 535. (f) Bates, R. W.; Satcharoen, V. *Chem. Soc. Rev.* **2002**, *31*, 12. (g) Ma, S. *Acc. Chem. Res.* **2003**, *36*, 701. (h) Brandsma, L.; Nedolya, N. A. *Synthesis* **2004**, 735. (i) Tius, M. A. *Acc. Chem. Res.* **2003**, *36*, 284. (j) Wei, L. L.; Xiong, H.; Hsung, R. P. *Acc. Chem. Res.* **2003**, *36*, 773. (k) Ma, S. *Chem. Rev.* **2005**, *105*, 2829. (l) Ma, S. *Aldrichimica Acta* **2007**, *40*, 91. (m) Brasholz, M.; Reissig, H.-U.; Zimmer, R. *Acc. Chem. Res.* **2009**, *42*, 45. (n) Ma, S. *Acc. Chem. Res.* **2009**, *42*, 1679. (o) Alcaide, B.; Almendros, P.; Campo, T. M. d. *Chem.—Eur. J.* **2009**, *15*, 1901. (p) Alcaide, B.; Almendros, P.; Campo, T. M. d. *Chem.—Eur. J.* **2010**, *16*, 5836. (q) Aubert, C.; Fensterbank, L.; Garcia, P.; Malacria, M.; Simonneau, A. *Chem. Rev.* **2011**, *111*, 1954. (r) Krause, N.; Winter, C. *Chem. Rev.* **2011**, *111*, 1994. (s) Inagaki, F.; Kitagaki, S.; Mukai, C. *Synlett* **2011**, 594. (t) López, F.; Mascareñas, J. L. *Chem.—Eur. J.* **2011**, *17*, 418. (u) Alcaide, B.; Almendros, P.; Luna, A.; Cembellín, D.-C. S.; Arnó, M.; Domingo, L. R. *Chem.—Eur. J.* **2011**, *17*, 11559. (v) Yu, S.; Ma, S. *Angew. Chem., Int. Ed.* **2012**, *51*, 3074. (w) Alcaide, B.; Almendros, P.; Cembellín, S.; del Campo, T. M.; Fernández, I. *Chem. Commun.* **2013**, *49*, 1282. (x) Alcaide, B.; Almendros, P.; Alonso, J. M.; Fernández, I. *J. Org. Chem.* **2013**, *78*, 6688.

(3) For a review on the natural products and pharmaceuticals containing allene unit(s), see: (a) Hoffmann-Röder, A.; Krause, N. *Angew. Chem., Int. Ed.* **2004**, *43*, 1196. For a review on the molecular materials containing allene unit(s), see: (b) Rivera-Fuentes, P.; Diederich, F. *Angew. Chem., Int. Ed.* **2012**, *51*, 2818.

(4) For reviews on the synthesis of allenes, see: (a) Sydnes, L. K. *Chem. Rev.* **2003**, *103*, 1133. (b) Krause, N.; Hoffmann-Röder, A. *Tetrahedron* **2004**, *60*, 11671. (c) Brummond, K. M.; Deforrest, J. E. *Synthesis* **2007**, 795. (d) Krause, N.; Belting, V.; Deutsch, C.; Erdsack, J.; Fan, H.; Gockel, B.; Hoffmann-Röder, A.; Morita, N.; Volz, F. *Pure Appl. Chem.* **2008**, *80*, 1063. (e) Ogasawara, M. *Tetrahedron: Asymmetry* **2009**, *20*, 259. (f) Yu, S.; Ma, S. *Chem. Commun.* **2011**, *47*, 5384.

(5) For selected recent reports on the synthesis of allenes, see: (a) Ahmed, M.; Arnauld, T.; Barrett, A. G. M.; Braddock, D. C.; Flack, K.; Procopiou, P. A. *Org. Lett.* **2000**, *2*, 551. (b) Nakamura, H.; Kamakura, T.; Ishikura, M.; Biellmann, J.-F. *J. Am. Chem. Soc.* **2004**, *126*, 5958. (c) Karunakar, G. V.; Periasamy, M. *J. Org. Chem.* **2006**, *71*, 7463. (d) Deutsch, C.; Lipshutz, B. H.; Krause, N. *Angew. Chem., Int. Ed.* **2007**, *46*, 1650. (e) Lavallo, V.; Frey, G. D.; Kousar, S.; Donnadieu, B.; Bertrand, G. *Proc. Natl. Acad. Sci. U. S. A.* **2007**, *104*, 13569. (f) Pu, X.; Ready, J. M. *J. Am. Chem. Soc.* **2008**, *130*, 10874. (g) Tang, M.; Fan, C.-A.; Zhang, F.-M.; Tu, Y.-Q.; Zhang, W.-X.; Wang, A.-X. *Org. Lett.* **2008**, *10*, 5585. (h) Maity, P.; Lepore, S. D. *J. Org. Chem.* **2009**, *74*, 158. (i) Liu, H.; Leow, D.; Huang, K.-W.; Tan, C.-H. *J. Am. Chem. Soc.* **2009**, *131*, 7212. (j) Ogasawara, M.; Okada, A.; Nakajima, K.; Takahashi, T. *Org. Lett.* **2009**, *11*, 177. (k) Kolakowski, R. V.; Manpadi, M.; Zhang, Y.; Emge, T. J.; Williams, L. J. *J. Am. Chem. Soc.* **2009**, *131*, 12910. (l) Zhao, X.; Zhong, Z.; Peng, P.; Zhang, W.; Wang, J. *Chem. Commun.* **2009**, 2535. (m) Bolte, B.; Odabachian, Y.; Gagosz, F. *J. Am. Chem. Soc.* **2010**, *132*, 7294. (n) Xiao, Q.; Xia, Y.; Li, H.; Zhang, Y.; Wang, J. *Angew. Chem., Int. Ed.* **2011**, *50*, 1114. (o) Hossain, M. L.; Ye, F.; Zhang, Y.; Wang, J. *J. Org. Chem.* **2013**, *78*, 1236. (p) Hashimoto, T.; Sakata, K.; Tamakuni, F.; Dutton, M. J.; Maruoka, K. *Nat. Chem.* **2013**, *5*, 240.

(6) (a) Rona, P.; Crabbé, P. *J. Am. Chem. Soc.* **1969**, *91*, 3289. (b) Dollat, J.-M.; Luche, J.-L.; Crabbé, P. *J. Chem. Soc., Chem. Commun.* **1977**, 761. (c) Crabbé, P.; Fillion, H.; André, D.; Luche, J.-L. *J. Chem. Soc., Chem. Commun.* **1979**, 859. (d) Crabbé, P.; André, D.; Fillion, H. *Tetrahedron Lett.* **1979**, 893. (e) Searles, S.; Li, Y.; Nassim, B.; Lopes, M.-T. R.; Tran, P. T.; Crabbé, P. *J. Chem. Soc., Perkin Trans. 1* **1984**, 747.

(7) (a) Ma, S.; Hou, H.; Zhao, S.; Wang, G. *Synthesis* **2002**, 1643. (b) Kazmaier, U.; Lucas, S.; Klein, M. *J. Org. Chem.* **2006**, *71*, 2429. (c) Nakamura, H.; Sugiishi, T.; Tanaka, Y. *Tetrahedron Lett.* **2008**, *49*, 7230. (d) Kuang, J.; Ma, S. *J. Org. Chem.* **2009**, *74*, 1763. (e) Kuang, J.; Xie, X.; Ma, S. *Synthesis* **2013**, *45*, 592.

(8) Kuang, J.; Ma, S. *J. Am. Chem. Soc.* **2010**, *132*, 1786.

(9) For recently reported CuI promoted one-pot synthesis of 1,3-disubstituted allenes, see: (a) Kitagaki, S.; Komizu, M.; Mukai, C. *Synlett* **2011**, 1129. (b) Kuang, J.; Luo, H.; Ma, S. *Adv. Synth. Catal.* **2012**, *354*, 933.

(10) (a) 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. (b) Periasamy, M.; Sanjeevakumar, N.; Dalai, M.; Gurubrahamam, R.; Reddy, P. O. *Org. Lett.* **2012**, *14*, 2932. (c) Ye, J.; Fan, W.; Ma, S. *Chem.—Eur. J.* **2013**, *19*, 716. (d) Gurubrahamam, R.; Periasamy, M. *J. Org. Chem.* **2013**, *78*, 1463. (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) Periasamy, M.; Reddy, P. O.; Sanjeevakumar, N. *Eur. J. Org. Chem.* **2013**, *18*, 3866.

(11) (a) Lo, V. K.-Y.; Liu, Y.; Wong, M.-K.; Che, C.-M. *Org. Lett.* **2006**, *8*, 1529. (b) Lo, V. K.-Y.; Wong, M.-K.; Che, C.-M. *Org. Lett.* **2008**, *10*, 517. (c) Lo, V. K.-Y.; Zhou, C.-Y.; Wong, M.-K.; Che, C.-M. *Chem. Commun.* **2010**, *46*, 213.

(12) We tried to synthesize allene **2bk** (Table 4) and its analogues to investigate their Rh-catalyzed isomerization for synthesis of seven-membered carbocycles. However, using Ma's protocol could not give the desired product **2bk**. The isomerization of the analogues of **2bk** was later realized by Tang's group, and we stopped our further investigation. See: (a) Li, X.; Zhang, M.; Shu, D.; Robichaux, P. J.; Huang, S.; Tang, W. *Angew. Chem., Int. Ed.* **2011**, *50*, 10421. (b) Yao, Z.-K.; Li, J.; Yu, Z.-X. *Org. Lett.* **2011**, *13*, 134.

(13) For recent reviews on the synthesis of propargylamines from terminal alkynes and aldehydes in the presence of amines, see: (a) Zani, L.; Bolm, C. *Chem. Commun.* **2006**, 4263. (b) Feng, J.; Li, C.-J. *Sci. Synth.* **2009**, *40a*, 579. (c) Blay, G.; Monleón, A.; Pedro, J. R. *Curr. Org. Chem.* **2009**, *13*, 1498. (d) Yoo, W. J.; Zhao, L.; Li, C.-J. *Aldrichimica Acta* **2011**, *44*, 43.

(14) For a recent report on mechanistic investigation of oxidative Mannich reaction, see: Ratnikov, M. O.; Doyle, M. P. *J. Am. Chem. Soc.* **2013**, *135*, 1549.

(15) For selected reports on the reactions involving the [1,5]-hydride transfer processes, see: (a) Nijhuis, W. H. N.; Verboom, W.; Reinhoudt, D. N. *J. Am. Chem. Soc.* **1987**, *109*, 3136. (b) Pastine, S. J.; McQuaid, K. M.; Sames, D. *J. Am. Chem. Soc.* **2005**, *127*, 12180. (c) Pastine, S. J.; Sames, D. *Org. Lett.* **2005**, *7*, 5429. (d) Zhang, C.; Murarka, S.; Seidel, D. *J. Org. Chem.* **2009**, *74*, 419. (e) Murarka, S.; Zhang, C.; Konieczynska, M. D.; Seidel, D. *Org. Lett.* **2009**, *11*, 129. (f) Jurberg, I. D.; Odabachian, Y.; Gagosz, F. *J. Am. Chem. Soc.* **2010**, *132*, 3543. (g) Alajarin, M.; Bonillo, B.; Sanchez-Andrada, P.; Vidal, A. *J. Org. Chem.* **2010**, *75*, 3737. (h) Kang, Y. K.; Kim, S. M.; Kim, D. Y. *J. Am. Chem. Soc.* **2010**, *132*, 11847. (i) Cao, W.; Liu, X.; Wang, W.; Lin, L.; Feng, X. *Org. Lett.* **2011**, *13*, 600. (j) Sugiishi, T.; Nakamura, H. *J. Am. Chem. Soc.* **2012**, *134*, 2504. (k) Han, Y.-Y.; Han, W.-Y.; Hou, X.; Zhang, X.-M.; Yuan, W.-C. *Org. Lett.* **2012**, *14*, 4054. (l) Chen, L.;

Zhang, L.; Lv, J.; Cheng, J.-P.; Luo, S. *Chem.—Eur. J.* **2012**, *18*, 8891. (m) Vadola, P. A.; Carrera, I.; Sames, D. *J. Org. Chem.* **2012**, *77*, 6689.
(16) For selected reports on the computational studies of the [1,5]-hydride transfer processes, see: (a) Vrček, V.; Vrček, I. V.; Siehl, H.-U. *J. Phys. Chem. A* **2006**, *110*, 1868. (b) refs 15g and 15l.
(17) (a) Gommermann, N.; Koradin, C.; Polborn, K.; Knochel, P. *Angew. Chem., Int. Ed.* **2003**, *42*, 5763. (b) Knöpfel, T. E.; Aschwanden, P.; Ichikawa, T.; Watanabe, T.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2004**, *43*, 5971. (c) Gommermann, N.; Knochel, P. *Chem. Commun.* **2005**, 4175. (d) Gommermann, N.; Knochel, P. *Chem.—Eur. J.* **2006**, *12*, 4380. (e) Zhao, Y.; Zhou, X.; Okamura, T.-a.; Chen, M.; Lu, Y.; Sun, W.-Y.; Yu, J.-Q. *Dalton Trans.* **2012**, *41*, 5889. (f) refs 10a and 10d. For the synthesis of optically active propaygylamines using 4-piperidone hydrochloride hydrate as the amine, see: (g) Aschwanden, P.; Stephenson, C. R. J.; Carreira, E. M. *Org. Lett.* **2006**, *8*, 2437.
(18) (a) Cheng, Y.-H.; Zhao, X.; Song, K.-S.; Liu, L.; Guo, Q.-X. *J. Org. Chem.* **2002**, *67*, 6638. (b) Song, K.-S.; Liu, L.; Guo, Q.-X. *J. Org. Chem.* **2003**, *68*, 262. (c) Feng, Y.; Liu, L.; Wang, J.-T.; Zhao, S.-W.; Guo, Q.-X. *J. Org. Chem.* **2004**, *69*, 3129. (d) Chong, S.-S..; Fu, Y.; Liu, L.; Guo, Q.-X. *J. Phys. Chem. A* **2007**, *111*, 13112.
(19) The computed bond dissociation energies (BDE) are very close to those experimental measured ones (computational details are given in the Supporting Information). For example, the BDEs of the C−H bond adjacent to the N atom in pyrrolidine and diethylamine are 87.0−90.1 and 87.0−88.6 kcal/mol, respectively, according to different experimental measuring methods. See: (a) Wayner, D. D. M.; Clark, K. B.; Rauk, A.; Yu, D.; Armstrong, D. A. *J. Am. Chem. Soc.* **1997**, *119*, 8925. (b) Kranenburg, M.; Ciriano, M. V.; Cherkasov, A.; Mulder, P. *J. Phys. Chem. A* **2000**, *104*, 915. (c) Lalevée, J.; Allonas, X.; Fouassier, J.-P. *J. Am. Chem. Soc.* **2002**, *124*, 9613.
(20) Melchionna, M.; Nieger, M.; Helaja, J. *Chem.—Eur. J.* **2010**, *16*, 8262.
(21) (a) Hattori, G.; Matsuzawa, H.; Miyake, Y.; Nishibayashi, Y. *Angew. Chem., Int. Ed.* **2008**, *47*, 3781. (b) Hattori, G.; Sakata, K.; Matsuzawa, H.; Tanabe, Y.; Miyake, Y.; Nishibayashi, Y. *J. Am. Chem. Soc.* **2010**, *132*, 10592. (c) Dyatkin, A. B.; Rivero, R. A. *Tetrahedron Lett.* **1998**, *39*, 3647. (d) Kabalka, G. W.; Venkataiah, B.; Dong, G. *Tetrahedron Lett.* **2004**, *45*, 729. (e) ref 17e.
(22) Zheng, Q.-H.; Meng, W.; Jiang, G.-J.; Yu, Z.-X. *Org. Lett.* **2013**, DOI: 10.1021/ol402517e.
(23) (a) Only one example of Glaser coupling product was given in this report: González-Arellano, C.; Abad, A.; Corma, A.; García, H.; Iglesias, M.; Sánchez, F. *Angew. Chem., Int. Ed.* **2007**, *46*, 1536. For heterogeneous Au-catalyzed Glaser coupling, see: (b) Gao, H.-Y.; Franke, J.-H.; Wagner, H.; Zhong, D.-Y.; Held, P.-A.; Studer, A.; Fuchs, H. *J. Phys. Chem. C* **2013**, *117*, 18595. (c) Gao, H.-Y.; Wagner, H.; Zhong, D.-Y.; Franke, J.-H.; Studer, A.; Fuchs, H. *Angew. Chem., Int. Ed.* **2013**, *52*, 4024.
(24) (a) Kamal, A.; Howard, P. W.; Reddy, B.S. N.; Reddy, B.S. P.; Thurston, D. E. *Tetrahedron* **1997**, *53*, 3223. (b) Kamal, A.; Devaiah, V.; Reddy, K. L.; Shankaraiah, N. *Adv. Synth. Catal.* **2006**, *348*, 249.
(25) (a) Grunewald, G. L.; Sall, D. J.; Monn, J. A. *J. Med. Chem.* **1988**, *31*, 824. (b) Chakka, S. K.; Andersson, P. G.; Maguire, G. E. M.; Kruger, H. G.; Govender, T. *Eur. J. Org. Chem.* **2010**, 972.
(26) Molander, G. A.; Sommers, E. M.; Baker, S. R. *J. Org. Chem.* **2006**, *71*, 1563.
(27) Ohmiya, H.; Yang, M.; Yamauchi, Y.; Ohtsuka, Y.; Sawamura, M. *Org. Lett.* **2010**, *12*, 1796.
(28) Myers, A. G.; Zheng, B. *J. Am. Chem. Soc.* **1996**, *118*, 4492.