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# Copper-catalyzed asymmetric allylic alkylation of racemic inert cyclic allylic ethers under batch and flow conditions†

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Highly enantioselective Cu-catalyzed asymmetric allylic alkylation of racemic inert cyclic allylic ethers is accomplished in this work. The use of Grignard reagents in combination with $BF_3 \cdot OEt_2$ and $CuBr \cdot SMe_2$/L2 is the key to enable employment of long-challenging low reactive allylic substrates in this AAA reaction. In addition, the approach exhibited a remarkable superiority in the construction of a stereogenic center involving challenging sterically hindered nucleophiles for both primary and secondary alkyl groups. Extension of this method under continuous flow conditions was also performed with excellent enantioselectivity in a short residence time. Mechanistic experiments indicated that the reaction proceeded through an *in situ* generated allylic bromide intermediate. All these advantages demonstrated that this chiral catalytic system is a valuable complement for existing asymmetric catalytic methods.

## Introduction

Asymmetric allylic alkylation (AAA) reactions are powerful synthetic tools to strategically install C–C bonds.[1–4] Generally, there are two main strategies for generating asymmetric C–C bonds in AAA reactions: (1) introduction of a chiral center from a prochiral substrate through the $S_N2'$ pathway[5–15] (Scheme 1a); (2) resolution,[16,17] dynamic kinetic processes[18–22] (DyKAT), or direct enantioconvergent transformation[23–27] (DECT) from racemic chiral starting materials. Compared to prochiral substrates, AAA reactions from racemic substrates were far less studied. There are two equal amounts of enantiomers in the starting materials which complicated the catalytic processes and made the reaction more challenging.[21] Even though the use of stabilized nucleophiles ($pK_a < 25$) in Pd-catalyzed AAA of racemic starting materials has been particularly successful since 1994,[22,28] the use of non-stabilized nucleophiles ($pK_a > 50$) in Cu-catalyzed AAA of racemic starting materials with high yields and enantioselectivities was not reported until 2009.[24] Many pioneers have made significant contributions to the development of this chemistry since then. For example, different copper–ligand complexes were synthesized,[20,23] and various non-stabilized nucleophiles such as Grignard reagents,[24,29] organolithium reagents,[26] and organozirconium reagents[17,30] were developed; versatile allylic substrates, such as bromides,[20,23,24] chlorides,[17,18,29] acetates[25] and phosphates[19] were employed (Scheme 1b). However, there still remain long-challenging issues in this field. First, Cu-catalyzed AAA reactions normally use allylic substrates with good leaving groups (such as Br, Cl, OCOR *etc.*) to enhance the reactivity and enantioselectivity.[24] However, these substrates are mostly sensitive, prone to deterioration, and hard to purify and store, which limits their applications in multistep reactions and synthesis.[8,31] Meanwhile, racemic inert substrates such as allylic ethers[31–34] have shown unsatisfactory performance in AAA reactions. The pioneering research reported by Consiglio and co-workers revealed moderate enantioselectivities in Ni-catalyzed AAA using phenyl-ethers.[35] Later on, Okamoto and co-workers achieved moderate results by employing pyridyl-ethers in Cu-catalyzed AAA with Grignard reagents.[36] In 2012, Feringa and co-workers developed a highly enantioselective Cu-catalyzed AAA reaction with prochiral linear allylic ethers using organolithium reagents.[8] However, the nucleophile scope was limited to *n*BuLi and *n*HexLi in this beautiful chemistry. To the best of our knowledge, despite extensive endeavours, highly efficient Cu-catalyzed AAA reactions with racemic inert substrates have not yet emerged.

Another key challenge in Cu-catalyzed AAA reactions is the generality of the non-stabilized nucleophile scope used in the catalytic systems. Employment of functionalized and sterically hindered nucleophiles was found to be extremely difficult

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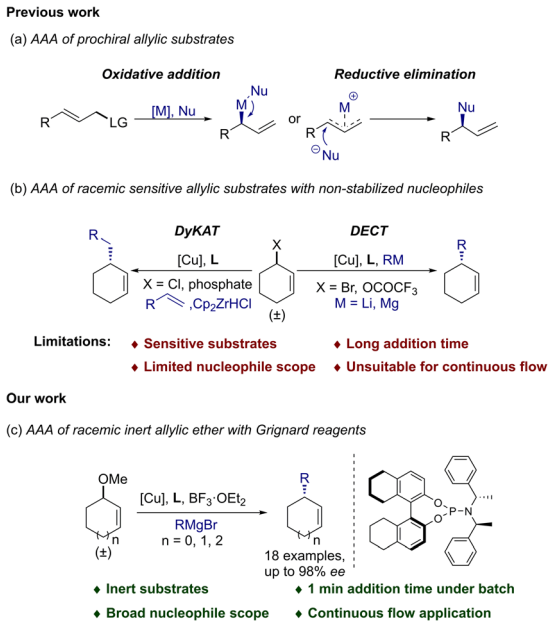


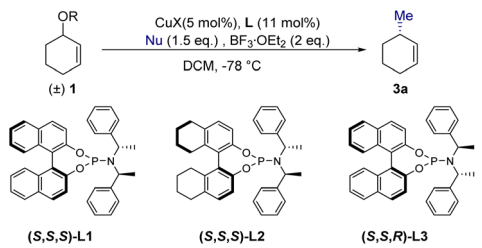

Scheme 1 Asymmetric allylic alkylation (AAA) procedures.

during the process.[24] Crucial pioneering work was first conducted by Alexakis and co-workers where sterically hindered secondary alkyl groups were accomplished in moderate enantioselectivities with racemic allylic bromides.[23] Later on, the improvement of the performance of secondary alkyl metal reagents was achieved with the same group by a well-designed catalytic system using racemic allylic trifluoroacetates, though it was not compatible with low reactive simple primary alkyl groups (such as MeMgBr).[25] At the same time, Fletcher and co-workers described the breakthrough of a Cu-catalyzed AAA of racemic allylic chlorides with organozirconium reagents. The reaction was able to tolerate a variety of functionalized primary alkyl groups under convenient mild conditions.[18,19] To the best of our knowledge, despite all these excellent advances, a general universal catalytic system which could enable efficient Cu-catalyzed AAA with challenging sterically hindered secondary and simple primary alkyl nucleophiles has not emerged. Herein, we reported a highly efficient Cu-catalyzed AAA reaction using racemic inert cyclic allylic ethers in combination with $BF_3\cdot OEt_2$ and $CuBr\cdot SMe_2$/**L2**. Noteworthily, this catalytic system delivered general efficiency for challenging sterically hindered Grignard reagents with both primary and secondary alkyl groups.

## Results and discussion

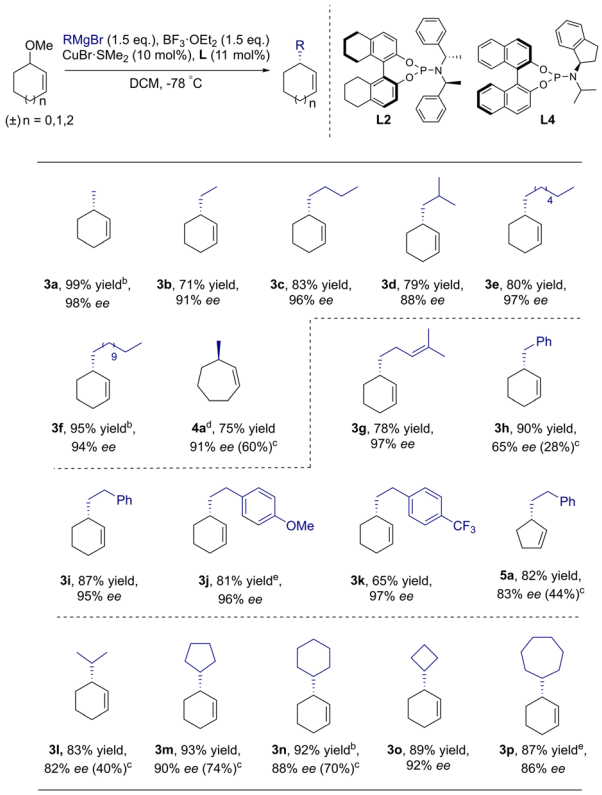
We started our investigation by examining the AAA reactions of 3-benzyloxycyclohexene (**1a**) with 1.5 equivalents of MeLi as a nucleophile in the presence of $BF_3\cdot OEt_2$ (2 eq.), catalyzed by $CuBr\cdot SMe_2$ (5 mol%) and phosphoramidites (*S*,*S*,*S*)-**L2** (11 mol%) in DCM. The reaction gave 3-methylcyclohexene (**3a**) in 70% yield with 48% ee (Table 1, entry 1). To enhance the enantioselectivity of **3a**, we screened different copper sources, ligands and Lewis acids. However, employment of copper sources (such as CuCl, CuTc and $Cu(OTf)_2$), ligands (such as (*S*,*S*,*S*)-**L1** and (*S*,*S*,*R*)-**L3**), and Lewis acids ($BF_2OTf$ generated *in situ* from $BF_3\cdot OEt_2$ and TMSOTf) gave poor results (Table 1, entries 1–7). Encouragingly, the enantioselectivity of **3a** improved to 87% ee by using less reactive MeMgBr (Table 1, entry 8). Meanwhile, the copper/ligand ratio was found to have little effect on this catalytic system (Table 1, entries 8 *vs.* 9). When diluted MeMgBr (0.5 M in $Et_2O$) was used, the enantioselectivity increased further to 96% ee in 46% yield (Table 1, entry 10). Delightfully, the yield of **3a** was also optimized to 85% maintaining the high enantioselectivity by adjusting –OBn to the less hindered –OMe group (Table 1, entry 11). Benefiting from this low activity of the ether substrate, MeMgBr could be added dropwise for only 1 min instead of the 0.5 h or 2 h reported in previous work[8,25] (Table 1, entries 11 *vs.* 12). Finally, single isomer **3a** was produced in excellent yield and enantioselectivity with 10 mol% catalyst loading (99% yield, 98% ee, Table 1, entry 13). It was worth noting that the enantioselectivity of the product (Table S2,† entry 3, 94% ee) remained excellent even at a low catalyst loading (1 mol%), but the conversion rate of 3-methoxycyclohex-1-ene (**1b**) showed a significant decline at 1 mol% catalyst loading (Table S2,† entry 3, 78% conversion rate), despite extending the reaction time to 4 hours.

Table 1 Selected optimization experiments[a]




| Entry | Nu | R | CuX | L | Yield[d] | ee[i] |
|---|---|---|---|---|---|---|
| 1 | MeLi | Bn | $CuBr\cdot SMe_2$ | **L2** | 70% | 48% |
| 2 | MeLi | Bn | CuCl | **L2** | 57% | 24% |
| 3 | MeLi | Bn | CuTc | **L2** | 61% | 37% |
| 4 | MeLi | Bn | $CuBr\cdot SMe_2$ | **L1** | 74% | <10% |
| 5 | MeLi | Bn | $CuBr\cdot SMe_2$ | **L3** | 54% | 15% |
| 6 | MeLi | Bn | $Cu(OTf)_2$ | **L3** | N.D. | — |
| 7[c] | MeLi | Bn | $CuBr\cdot SMe_2$ | **L2** | N.D. | — |
| 8[b,f] | MeMgBr | Bn | $CuBr\cdot SMe_2$ | **L2** | 48% | 87% |
| 9[b] | MeMgBr | Bn | $CuBr\cdot SMe_2$ | **L2** | 45% | 87% |
| 10[b] | MeMgBr[e,h] | Bn | $CuBr\cdot SMe_2$ | **L2** | 46% | 96% |
| 11[b] | MeMgBr[e,h] | Me | $CuBr\cdot SMe_2$ | **L2** | 85% | 96% |
| 12[b] | MeMgBr[h] | Me | $CuBr\cdot SMe_2$ | **L2** | 88% | 96% |
| 13[b,g] | MeMgBr[h] | Me | $CuBr\cdot SMe_2$ | **L2** | 99% | 98% |

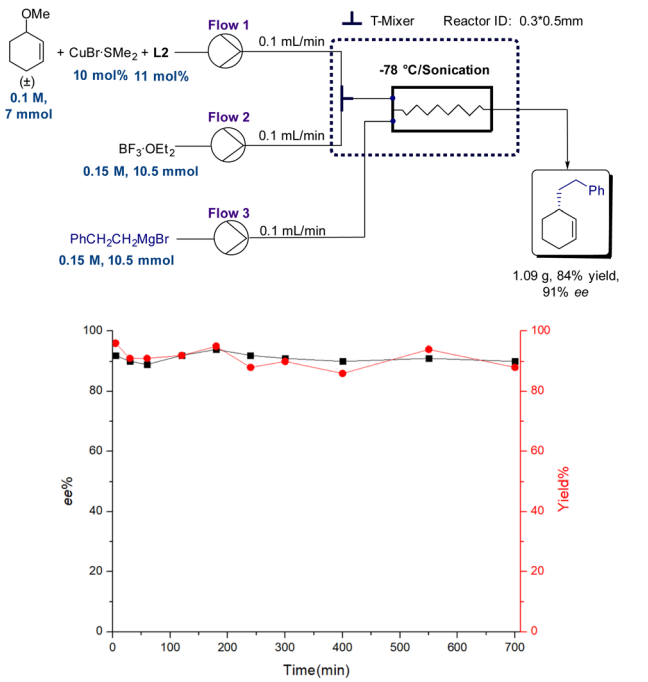
[a] Conditions: racemic **1** (0.4 mmol), CuX (5% mol), **L** (11% mol), $BF_3\cdot OEt_2$ (2 eq.), $CH_2Cl_2$ (4 mL), −78 °C, MeLi (1.5 eq.), 2 h addition time. [b] Conditions: racemic **1** (0.4 mmol), CuX (5% mol), **L** (6% mol), $BF_3\cdot OEt_2$ (1.5 eq.), $CH_2Cl_2$ (4 mL), −78 °C, MeMgBr (3 M in $Et_2O$, 1.5 eq.), 1 min addition time. [c] 2 eq. $BF_3\cdot OEt_2$ and 6 eq. TMSOTf were used. [d] Yield was determined by GC. [e] 2 h addition time. [f] CuX (5% mol) and **L** (11% mol) were used. [g] CuX (10% mol) and **L** (11% mol) were used. [h] MeMgBr (0.5 M in $Et_2O$) was used. [i] ee was determined by chiral GC.



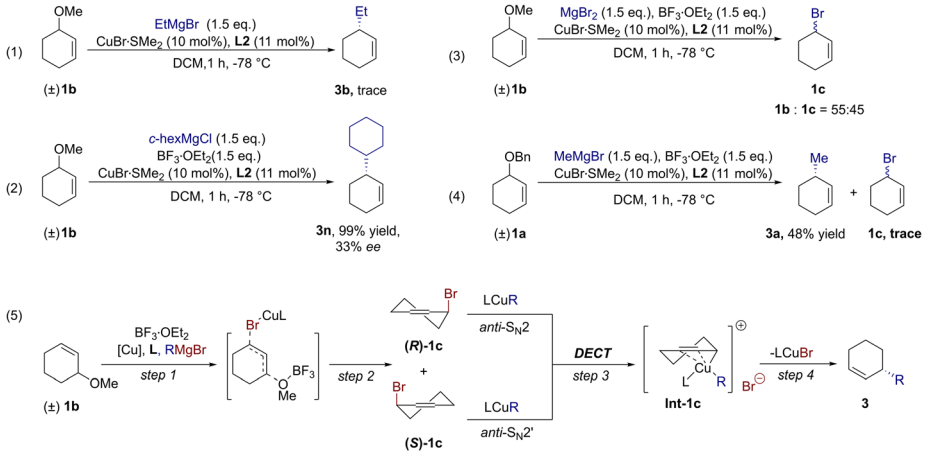

Scheme 2 Substrate scope. [a]Conditions: racemic **1** (0.4 mmol), $CuBr{\cdot}SMe_2$ (10% mol), **L2** (11% mol), $BF_3{\cdot}OEt_2$ (1.5 eq.), $CH_2Cl_2$ (4 mL), −78 °C, MeMgBr (1.5 eq.). ee was determined by chiral GC. [b]Yield was determined by GC or NMR. [c]The highest ee reported for the alkylation of analogous allylic bromides is given in parenthesis. [d]**L4** was used. [e]Isolated yield of the corresponding diastereoisomeric epoxides.

With the optimal conditions in hand, the nucleophile scope of this novel protocol was then evaluated. Several enantiomerically enriched cycloalkenes were obtained with excellent enantioselectivities by using simple unfunctionalized primary alkyl (**3a–3f**, **4a**), alkenyl (**3g**) and aromatic Grignard reagents (**3i–3k**, **5a**). Surprisingly, bulky alkyl groups such as secondary alkyl Grignard reagents also reacted smoothly to give the corresponding products **3l–3p** in 83–93% yields with excellent enantioselectivities. In particular, decent improvements were achieved for previously challenging sterically hindered nucleophiles in AAA of the reported allylic bromide approaches,[23] such as **3h** (65% ee *vs.* 28% ee), **3l** (82% ee *vs.* 40% ee), **3m** (90% ee *vs.* 74% ee), and **3n** (88% ee *vs.* 70% ee) and for different ring sizes **4a** (91% ee *vs.* 60% ee) and **5a** (83% ee *vs.* 44% ee). To further extend the generality of this catalytic system, the reaction conditions were applied to challenging acyclic ether. However, only 15% ee was obtained in the reaction (Scheme S1†), which was similar to the previous result with acyclic bromide (8% ee).[23] Preliminary experiments of AAA reactions using challenging 3-methoxy-1-methylcyclohex-1-ene to form a more complex quaternary cycloalkene were also performed. A mixture of 1,1- and 1,3-disubstituted alkylation products was obtained with moderate enantioselectivities (Scheme S2,† 35% yield, 83% ee for 1,1-disubstituted quaternary cycloalkene and 12% yield, 53% ee for 1,3-disubstituted cycloalkene). Further research focused on the construction of a stereogenic quaternary center is currently under study and will be reported in due course.

Although satisfactory results were achieved under batch conditions, an intractable question worth thinking about is whether Grignard reagents are too reactive to scale up.[37–39] The recent emerging continuous flow technology demonstrated many advantages, including higher safety and efficiency, accurate control, better heat and mass transfer, easier amplification and better sustainability.[40–43] Thus, we also explored the application of this protocol under continuous flow conditions. However, the enantioselectivities of the products dropped significantly under continuous flow conditions when using allylic bromide as the substrate in previous reports (up to 33% ee).[26] Generally, the organometallic reagents were added dropwise over 2 h (ref. 26) or 0.5 h (ref. 25) to a solution of substrates to avoid side-reactions under batch conditions. In contrast, substrates and organometallic reagents are mixed simultaneously under flow conditions; the highly active allylic bromides may undergo uncatalyzed reactions[6] or react with "ate" and "aggregated" copper species[25] generated by a chiral catalyst exposed to an excess of organometallic reagents during the process. We suspected that the difference in contact mode between batch and flow mainly resulted in a decrease in enantioselectivities. Thus, we started our investigation by employing inert allylic ethers instead of high reactive allylic substrates here. The flow system was set up as shown in Scheme 3. Solutions of $CuBr{\cdot}SMe_2$, ligand **L2** and cyclic racemic substrate **1b** were first mixed with a $BF_3{\cdot}OEt_2$ stream, and then, another stream of phenylethyl Grignard reagent was pumped into a microchip reactor. A




Scheme 3 Cu-catalyzed AAA reaction of **1b** under continuous flow conditions.




Scheme 4 Mechanistic analysis and a plausible reaction mechanism.

sonication device was employed to increase reaction mixing and prevent solid aggregation. Encouragingly, the desired products were obtained in high yield with excellent enantioselectivity within 3.6 s under optimized flow conditions (Table S1 and Scheme S3†). And the system could continue operating for over 700 min without any loss of activity or enantioselectivity to provide 1.09 g product (84% yield, 91% ee).

We then paid our attention to the mechanism of this new Cu-catalyzed AAA protocol. A Lewis acid was confirmed to be the key for the formation of desired products from racemic inert cyclic allylic ethers here.[44] We carried out the AAA reaction of **1b** without $BF_3 \cdot OEt_2$, and the starting material **1b** could be almost completely recovered (Scheme 4 – (1)). It suggested that ether groups could act as a robust protecting group for former stages of synthetic schemes in the absence of a Lewis acid. Conversely, the ether groups could become leaving groups to perform enantioselective C–C bond formation in the presence of a Lewis acid and copper catalyst. This provided new opportunities for the application of the Cu-catalyzed AAA protocol using racemic inert cyclic allylic ethers in multistep reactions and synthesis.[31] In addition, we examined the AAA reaction of **1b** using cyclohexylmagnesium chloride as a nucleophile instead of cyclohexylmagnesium bromide (88% ee, Scheme 2, **3n**). Surprisingly, the enantioselectivity of product **3n** using cyclohexylmagnesium chloride was very low (Scheme 4 – (2), 33% ee). This phenomenon indicated that halogen anions from Grignard reagents might be involved in the reaction and influence the enantioselectivity of the product. A similar phenomenon was also observed in Fletcher and co-workers's work.[18,19] They considered that allyl halide formed *in situ* from a halogen anion and phosphate in the reaction and reacted with nucleophiles to prove enantio-enriched alkylation products. We suspected that the allylic ethers might undergo analogical transformation here. To gain more insight into the reaction mechanism, $MgBr_2$, instead of Grignard reagents was added to the mixture of **1b** and $BF_3 \cdot OEt_2$. As we expected, 45% cyclic allylic bromide (**1c**) was observed in 1 h (Fig. S3†), indicating that **1c** could be generated *in situ* from **1b** in this catalytic system (Scheme 4 – (2) and (3)). Furthermore, since we were not able to observe the intermediate **1c** in the reaction of racemic allylic ethers, an even lower reactive **1a** substrate was employed in our experiments. Inspiringly, trace **1c** was observed during our standard AAA reaction (Scheme 4 – (4), Fig. S1 and S2†). In combination with the inspiration from Alexakis's and co-workers pioneering work for DECT progress,[25] we proposed a plausible mechanistic route for this new Cu-catalyzed AAA protocol using racemic inert cyclic allylic ethers. First, racemic **1c** is generated from **1b** in the presence $BF_3 \cdot OEt_2$ and $Br^-$. Then, (*R*)-**1c** and (*S*)-**1c** underwent a DECT process to form the same intermediate **Int-1**. Finally, **Int-1c** underwent reductive elimination to provide the desired single product **3** in high yield and enantioselectivity (Scheme 4 – (5)).

## Conclusions

In summary, a highly efficient Cu-catalyzed AAA reaction of racemic inert cyclic allylic ethers was developed here. The use of $BF_3 \cdot OEt_2$ with $CuBr \cdot SMe_2$/**L2** was confirmed to be crucial in this catalytic system through the proposed allylic bromide intermediate. Meanwhile, the new method showed significant advantages in nucleophile scope over existing protocols with racemic sensitive allylic substrates. In addition, application of the method under continuous flow conditions was also conducted successfully with excellent enantioselectivity and yield in a short residence time. We anticipate that this research will aid the development of a new AAA reaction with inert substrates and provide a valuable tool for existing asymmetric catalytic methods. Intensive efforts are now directed toward the extension of this process to other inert allylic substrates in our lab.

## Data availability

The ESI† is available and contains experimental and analytical data.

## Author contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

## Conflicts of interest

There are no conflicts to declare.

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