Asymmetric copper-catalyzed alkynylallylic dimethylation†

Si-Yuan Luo,a,b,c Guo-Qiang Linb,b and Zhi-Tao Hea,c,d

A feasible protocol for Cu-catalyzed asymmetric alkynylallylic dimethylation is developed with the discovery of tetramethylaminomethane as a new, stable and convenient surrogate of dimethylamine. A series of enantioenriched 1,4-enynes are constructed in reasonable yields, high regioselectivities and moderate to good enantioselectivities. Mechanistic experiments show that the tertiary amine works as a nucleophile directly followed by the release of the expected dialkylamine unit, different from the conventional primary and secondary amines with the cleavage of a proton as the nucleophile. DFT calculations elucidate the origin of regio- and enantioselectivity for the present transformation.

Introduction

Transition metal-catalyzed η3-substitution reactions have been widely used for the construction of different stereogenic centers.1–6 In particular, since the pioneering work of van Maarseveen7 and Nishibayashi8 groups, Cu-catalyzed propargylic substitution has emerged as a reliable strategy to introduce C–N,9–16 C–O,17–20 C–C21–29 and C–S30,31 bonds vicinal to an alkyne unit stereoselectively. In this case, a propargylic leaving group is required to be prepared for the following generation of a critical Cu-allenylidene intermediate. However, when a leaving group is located at a remote position to the alkyne unit, such a motif is generally not considered a potential substrate for propargyl substitution. Recently, Fang,32 Xu33 and our group34,35 independently demonstrated the concept of Cu-catalyzed remote propargyl substitution reactions. In these studies, an olefin32–34 or aryl unit35 was used to link the alkyne unit and the γ-leaving group, and the reactive alkene-tethered or dearomatization-induced Cu-allenylidene intermediate was smoothly formed to induce the expected substitution. In particular, our group34 and Xu33 sequentially described the first asymmetric alkyneallylic substitution processes, in which both Sn2 and in situ substitution models were shown to be feasible to form chiral 1,4-enyne products and spirocycles, respectively. However, the substrate scope and reaction models are heavily limited to the use of common nucleophiles. Thus, the discovery of new applications and the establishment of efficient catalytic systems suitable for the less developed remote propargylic substitution reactions are highly desired.

The chiral dimethylamino unit exists widely in bioactive molecules, such as rivastigmine,36 which is used to treat Alzheimer’s disease, and the tetracycline family including tetracycline, doxycycline and tigecycline, a series of broad-spectrum antibiotics37 (Scheme 1a). Based on our previous work34 we envisioned that with dimethylamine as the nucleophile, Cu-catalyzed asymmetric alkynylallylic substitution might provide a novel and valuable route to construct chiral 1,4-enynes bearing a dimethylaminostereocenter. The vicinal olefin and alkyne units could further be transformed into a series of functional groups, thus largely broadening the application potential of this methodology. However, dimethylamine is gaseous at room temperature and usually stored in special solvents, which limits the convenient use of this reagent and also influences the efficiency of the corresponding transformation (Scheme 1b). Therefore, the identification of different and efficient surrogates of the dimethylamine nucleophile is critical to realize the expected alkynylallylic dimethylation reaction. Here, we discovered that tetramethylaminomethane18 worked as a novel and reliable precursor of dimethylamine and enabled enantioselective Cu-catalyzed alkynylallylic dimethylation to construct valuable chiral 1,4-enynes39 (Scheme 1b). A variety of 1,4-enynes bearing a dimethylaminostereocenter were constructed in good yields and moderate to good enantioselectivities. Mechanistic experiments and DFT calculations elucidated the origin of regio- and enantioselectivity and revealed that tetramethylaminomethane first participated in the reaction as a neutral
tertiary amine nucleophile and then released the dimethylamino unit from the ammonium intermediate.

Results and discussion

We initiated the reaction with racemic 1,3-enyne 1a as the electrophile and tetramethyldiaminomethane (2a) as a new dimethylamine source under copper(I) catalysis (Table 1). A set of PyBox ligands which were proven to be efficient for stereocontrol in the previous alkynylallylic substitutions32–34 were evaluated first. When L1 was used, the reaction proceeded smoothly, providing 3a in a total 42% yield, 75 : 25 er and 2.5 : 1 rr (entry 1). Other PyBox ligands showed similar reactivity and stereocontrol effects to L1 as the ligand (entries 2–5). However, when L6 was used as the ligand, 3a was obtained in a high yield and good stereoselectivity, i.e., 94% yield, 19 : 1 rr and 91 : 9 er (entry 6). When the solvent was changed to EtOH or DCM, obvious erosion of the yield and enantioselectivity of 3a was observed (entries 7 and 8). Reducing the loading of the ligand led to a slight increase in the enantioselectivity, reaching 93 : 7 er (entry 9). The evaluations of reaction temperature were unfavourable to the regio- and enantioselectivity of 3a (entries 10–12). In addition, when OBoc as the leaving group in 1a was changed to OAc, the alkynylallylic amination proceeded with lowered efficiency and stereocontrol (entry 13).

Thus, the optimal conditions for alkynylallylic substitution were identified as the combination of 1,3-enyne 1a (1 equiv.), copper(1) complex (5 mol%), and L6 (10 mol%) in MeOH (0.1 M) at room temperature for 12 h. In this context, when dimethylamine in methanol solution was used directly as the nucleophile, a heavily decreased yield, regioselectivity and enantioselectivity of 3a were observed (entry 14).

With the optimal conditions in hand, we investigated the scope of 1,3-enyne electrophiles for this remote propargylic dimethylation reaction and the results are summarized in Scheme 2. Various electron-rich and electron-deficient functional groups at the para- or meta-positions of aryl-substituted 1,3-enynes 1 showed high compatibility with the substitution. For example, alkoxyl, nitryl, halide, and ester moieties were well tolerated in the reaction, providing the corresponding di-

![Scheme 1](image1)

**Table 1** Optimization of the reaction conditions. 

<table>
<thead>
<tr>
<th>Entry</th>
<th>L*</th>
<th>Yield (%)</th>
<th>rr</th>
<th>er</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>L1</td>
<td>42</td>
<td>2.5 : 1</td>
<td>75 : 25</td>
</tr>
<tr>
<td>2</td>
<td>L2</td>
<td>39</td>
<td>1 : 1</td>
<td>77 : 23</td>
</tr>
<tr>
<td>3</td>
<td>L3</td>
<td>34</td>
<td>1.2 : 1</td>
<td>81 : 19</td>
</tr>
<tr>
<td>4</td>
<td>L4</td>
<td>58</td>
<td>15 : 1</td>
<td>73 : 27</td>
</tr>
<tr>
<td>5</td>
<td>L5</td>
<td>45</td>
<td>1.9 : 1</td>
<td>54 : 46</td>
</tr>
<tr>
<td>6</td>
<td>L6</td>
<td>94</td>
<td>19 : 1</td>
<td>91 : 9</td>
</tr>
<tr>
<td>7b</td>
<td>L6</td>
<td>66</td>
<td>13 : 1</td>
<td>86 : 14</td>
</tr>
<tr>
<td>8c</td>
<td>L6</td>
<td>21</td>
<td>&gt;20 : 1</td>
<td>56 : 44</td>
</tr>
<tr>
<td>9d</td>
<td>L6</td>
<td>90</td>
<td>&gt;20 : 1</td>
<td>93 : 7</td>
</tr>
<tr>
<td>10e</td>
<td>L6</td>
<td>72</td>
<td>10 : 1</td>
<td>91 : 9</td>
</tr>
<tr>
<td>11f</td>
<td>L6</td>
<td>79</td>
<td>&gt;20 : 1</td>
<td>90 : 10</td>
</tr>
<tr>
<td>12g</td>
<td>L6</td>
<td>55</td>
<td>11 : 1</td>
<td>87 : 13</td>
</tr>
<tr>
<td>13h</td>
<td>L6</td>
<td>55</td>
<td>&gt;20 : 1</td>
<td>90 : 10</td>
</tr>
<tr>
<td>14i</td>
<td>L6</td>
<td>68</td>
<td>3.8 : 1</td>
<td>79 : 21</td>
</tr>
</tbody>
</table>

a The reactions were carried out on a 0.1 mmol scale. The yields and rr values were determined by crude 1H NMR. The er values were determined by HPLC analysis. b EtOH as the solvent. c DCM as the solvent. d L6 (10 mol%) was added. Isolated yield. e The reaction temperature was −20 °C. f The reaction temperature was −10 °C. g The reaction temperature was 60 °C. h OAc was used instead of OBoc as the leaving group. i Dimethylamine was used as the nucleophile.
methylamination products in 64–93% yields with generally >20:1 rr and >90:10 er (3b–3j and 3m). Notably, substrates that are prone to cross-coupling reactions also yielded amination products smoothly (3f and 3g). Multi-substituted aryl enyne was also a suitable electrophile for the transformation (3k). In addition, 1,3-enyne bearing an ortho-methoxy unit afforded 3l in 86% yield, >20:1 rr and 90:10 er. However, alkyl-derived enyne as the electrophile failed to undergo the alkynylallylic dimethylamination reaction (3n).

After demonstrating the feasibility of the remote propargylic dimethylamination with this novel dimethylamine source, we further explored the application potential of this protocol with other amine nucleophiles and the results are summarized in Scheme 3. A set of secondary amine sources as the surrogates of dimethylamine, pyrrolidine and morpholine were suitable for the alkynylallylic substitution, furnishing the corresponding products 4a–4c in high yields, >20:1 regioselectivity and up to 94:6 er. This strategy was also applicable to the introduction of different diarylmethyl amines, and the corresponding products 4d and 4e were obtained in 95:5 and 96:4 er, respectively. The absolute configuration of 4d was determined to be (R)-4d based on the same reported compound.34 However, the introduction of the diarylamine moiety via this route did not work (4f).

To figure out the potential reaction mechanism, a set of mechanistic studies were conducted (Scheme 4). As it was unclear whether the nucleophile 2a underwent the substitution via the in situ release of dimethylamine or serving as the tertiary amine nucleophile first and then releasing the dimethylamine unit, several control experiments were carried out with 2e as the substrate (Scheme 4a). When the reaction was conducted under standard conditions without a Cu catalyst or ligand or Cu/ligand, no product 4d was formed in these cases. In particular, dibenzylamine 5 was not detected. When electrophile 1a was not used under the standard conditions, no dibenzylamine 5 was observed similarly. These facts indicated that the in situ generation of 5 from 2e might be unfavourable under the present reaction system, and tertiary amine 2e might directly work as the nucleophile.38 Next, a nonlinear relationship experiment showed a linear curve between the enantiopurity of chiral ligand L6 and that of the product 3a (Scheme 4b). This result suggested that monocupper/L6 as the catalyst might be involved in the entantiodetermining step. Based on this fact, DFT calculations were conducted to uncover the origin of regio- and enantio-selectivity for the alkynylallylic amination reaction. Both the condensed dual descriptor (CDD) and electrophilicity index (EI) were determined for the optimized structure of int-1.

Scheme 2 The scope of electrophiles. The reactions were carried out on a 0.1 mmol scale. Isolated yields. The rr values were determined by 1H NMR. The er values were determined by HPLC analysis.

Scheme 3 The scope of amine precursors. The reactions were carried out on a 0.1 mmol scale. Isolated yields. The rr values were determined by 1H NMR. The er values were determined by HPLC analysis.
The relatively larger CDD and EI data for the α-carbon center than those for the γ-carbon center showed that the α-carbon center is more electrophilic than the γ-carbon center. This is consistent with the observed preferred nucleophilic attack at the α-carbon position. Finally, calculations were conducted to uncover the energy profile of enantioselective substitution processes (Scheme 4d). It was obvious that the Re-face nucleophilic attack occurred via TS1 with only 17.9 kcal mol\(^{-1}\) while the Si-face nucleophilic attack via TS2 was 20.5 kcal mol\(^{-1}\). Therefore, the (R)-configuration for the formed stereocenter was observed in the present transformation.

Based on the above experimental and computational results, the proposed catalytic cycle is described in Scheme 5. The enyne substrate 1a first reacted with the copper catalyst in the presence of a base to give alkynyl copper intermediate int-4, which sequentially generated the Cu-allenylidene intermediate int-1 and tautomers int-5 and int-6 via the cleavage of the leaving group. Then an outer-sphere nucleophilic attack by tertiary amine 2a occurred to provide ammonium salt int-7, which then released product 3a and regenerated the Cu catalyst. The released dimethylaminium might be further captured by potential nucleophiles in the reaction systems, such as methoxide.\(^{38,42}\)
Conclusions

In summary, we have established a feasible protocol for an asymmetric alkylnallylic dimethylamination reaction with the use of tetramethylmethanediamine as a new dimethylamine source. The novel protocol features reasonable functional group compatibility, high regioselectivity and moderate to good enantioselectivity. Different from the commonly used primary and secondary amines as nucleophiles with the cleavage of a proton, mechanistic experiments support the involvement of the tertiary amine as a neutral nucleophile directly followed by the release of dialkylamine. DFT calculations further elucidate the origin of regio- and enantioselectivity for the alkylnallylic substitution reaction.

Author contributions

Z.-T. H. conceived the project. S.-Y. L. conducted the experiments and calculations. Z.-T. H. and G.-Q. L. supervised the project. Z.-T. H. and S.-Y. L. co-wrote the manuscript with feedback from all authors. Yuan-Xiang Yang is acknowledged for checking some results.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

We acknowledge the National Natural Science Foundation of China (22371292 and 22071262), the Natural Science Foundation of Ningbo (2023J036), the Shanghai Municipal Committee of Science and Technology (22ZR1475200), and the Shanghai Institute of Organic Chemistry for financial support.

References

16 W. Guo, L. Zuo, M. Cui, B. Yan and S. Ni, Propargylic amination enabled the access to enantioenriched acyclic \( \alpha\)-quaternary \( \alpha\)-amino ketones, J. Am. Chem. Soc., 2021, 143, 7629–7634.
Organic Chemistry Frontiers

Research Article


