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Asymmetric copper-catalyzed alkynylallylic dimethylamination†

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A feasible protocol for Cu-catalyzed asymmetric alkynylallylic dimethylamination is developed with the discovery of tetramethyldiaminomethane 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 η^3-substitution reactions have been widely used for the construction of different stereogenic centers.[1–6] In particular, since the pioneering work of van Maarseveen[7] and Nishibayashi[8] groups, Cu-catalyzed propargylic substitution has emerged as a reliable strategy to introduce C–N,[9–16] C–O,[17–20] C–C[21–29] and C–S[30,31] bonds vicinal to an alkyne unit stereoselectively. In this case, a propargylic leaving group is required to be preprepared 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 propargylic substitution. Recently, Fang,[32] Xu[33] and our group[34,35] independently demonstrated the concept of Cu-catalyzed remote propargylic substitution reactions. In these studies, an olefin[32–34] or aryl unit[35] 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 group[34] and Xu[33] sequentially described the first asymmetric alkynylallylic substitution processes, in which both S_N2' 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 antibiotics[37] (Scheme 1a). Based on our previous work,[34] 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 dimethylamino stereocenter. 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 dimethylamination reaction. Here, we discovered that tetramethyldiaminomethane[38] worked as a novel and reliable precursor of dimethylamine and enabled enantioselective Cu-catalyzed alkynylallylic dimethylaminations to construct valuable chiral 1,4-enynes[39] (Scheme 1b). A variety of 1,4-enynes bearing a dimethylamino stereocenter 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 tetramethyldiaminomethane first participated in the reaction as a neutral

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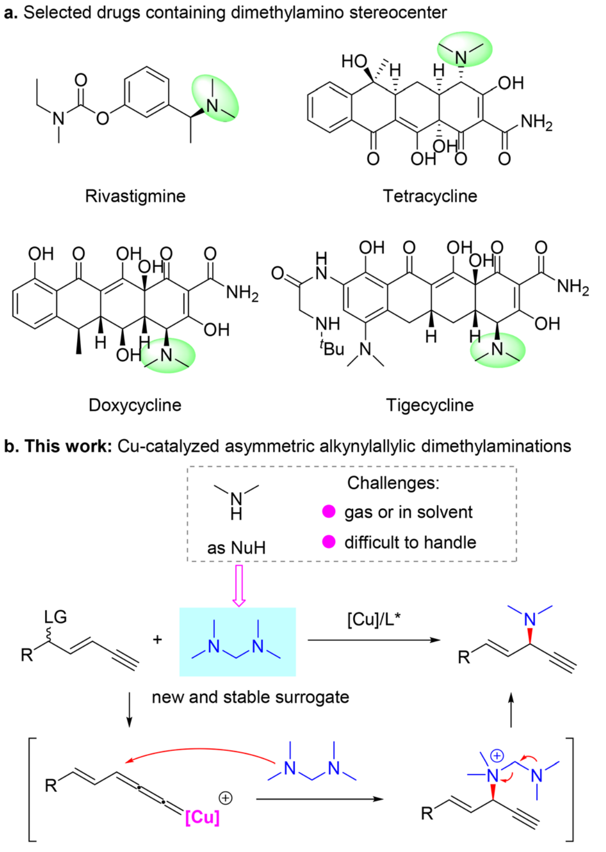


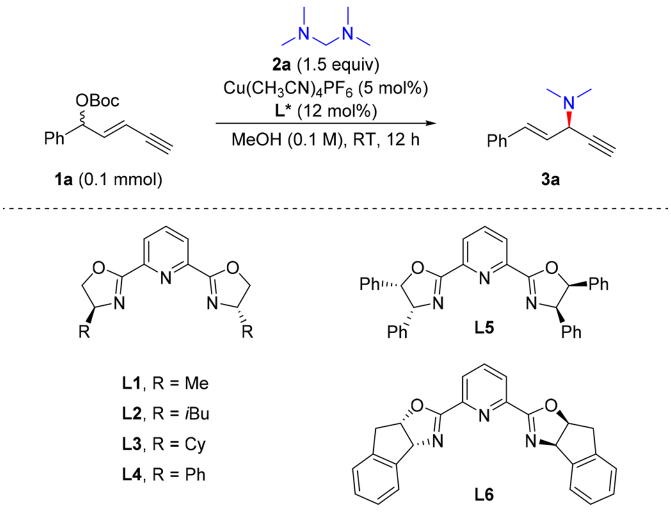
Scheme 1 Representative drugs with dimethylamino stereocenters and our design.

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 substitutions[32–34] 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.), nucleophile **2a** (1.5 equiv.), Cu(MeCN)$_4$PF$_6$ (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).

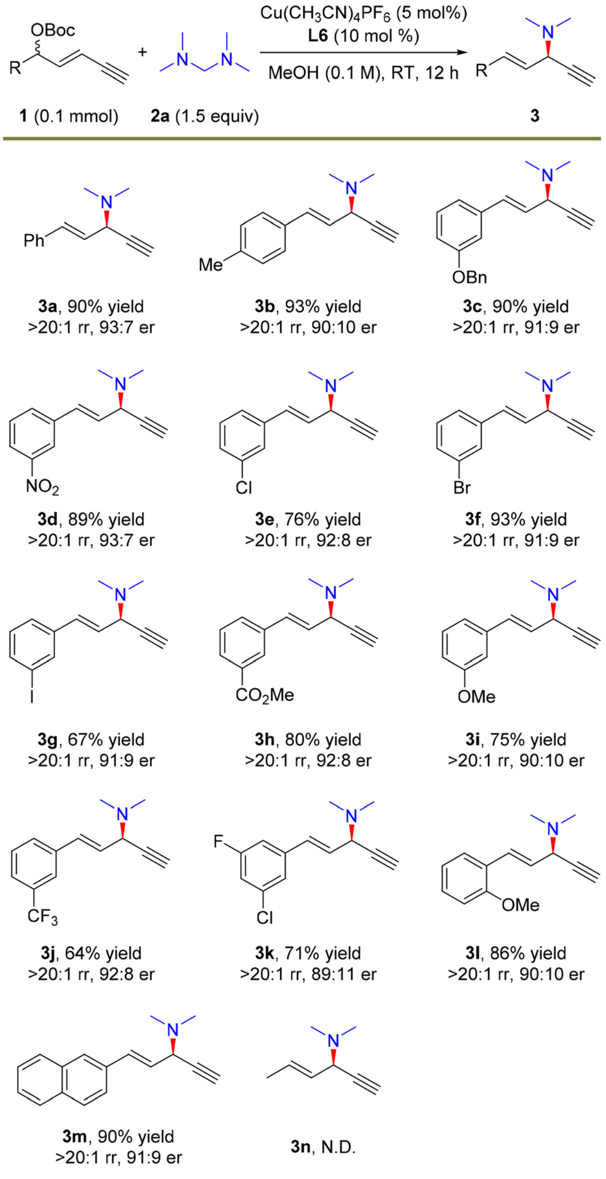
Table 1 Optimization of the reaction conditions[a]



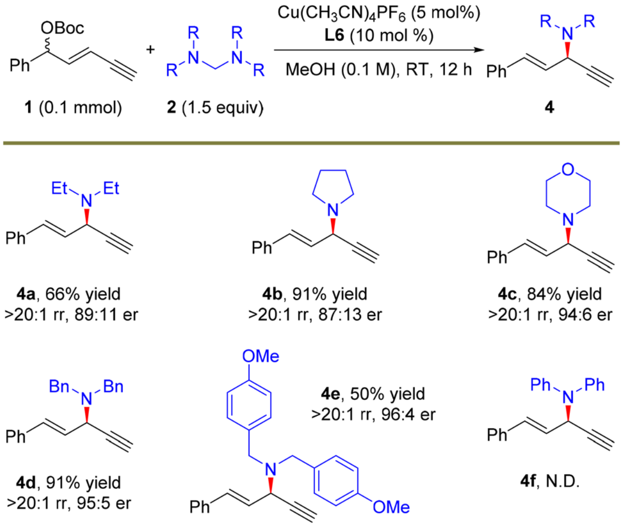
Entry	L*	Yield (%)	rr	er
1	**L1**	42	2.5 : 1	75 : 25
2	**L2**	39	1 : 1	77 : 23
3	**L3**	34	1.2 : 1	81 : 19
4	**L4**	58	15 : 1	73 : 27
5	**L5**	45	1.9 : 1	54 : 46
6	**L6**	94	19 : 1	91 : 9
7[b]	**L6**	66	13 : 1	86 : 14
8[c]	**L6**	21	>20 : 1	56 : 44
9[d]	**L6**	90	>20 : 1	93 : 7
10[d,e]	**L6**	72	10 :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

[a] The reactions were carried out on a 0.1 mmol scale. The yields and rr values were determined by crude ^{1}H 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.

With the optimal conditions in hand, we investigated the scope of 1,3-enyne electrophiles for this remote propargylic dimethylamination 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 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.



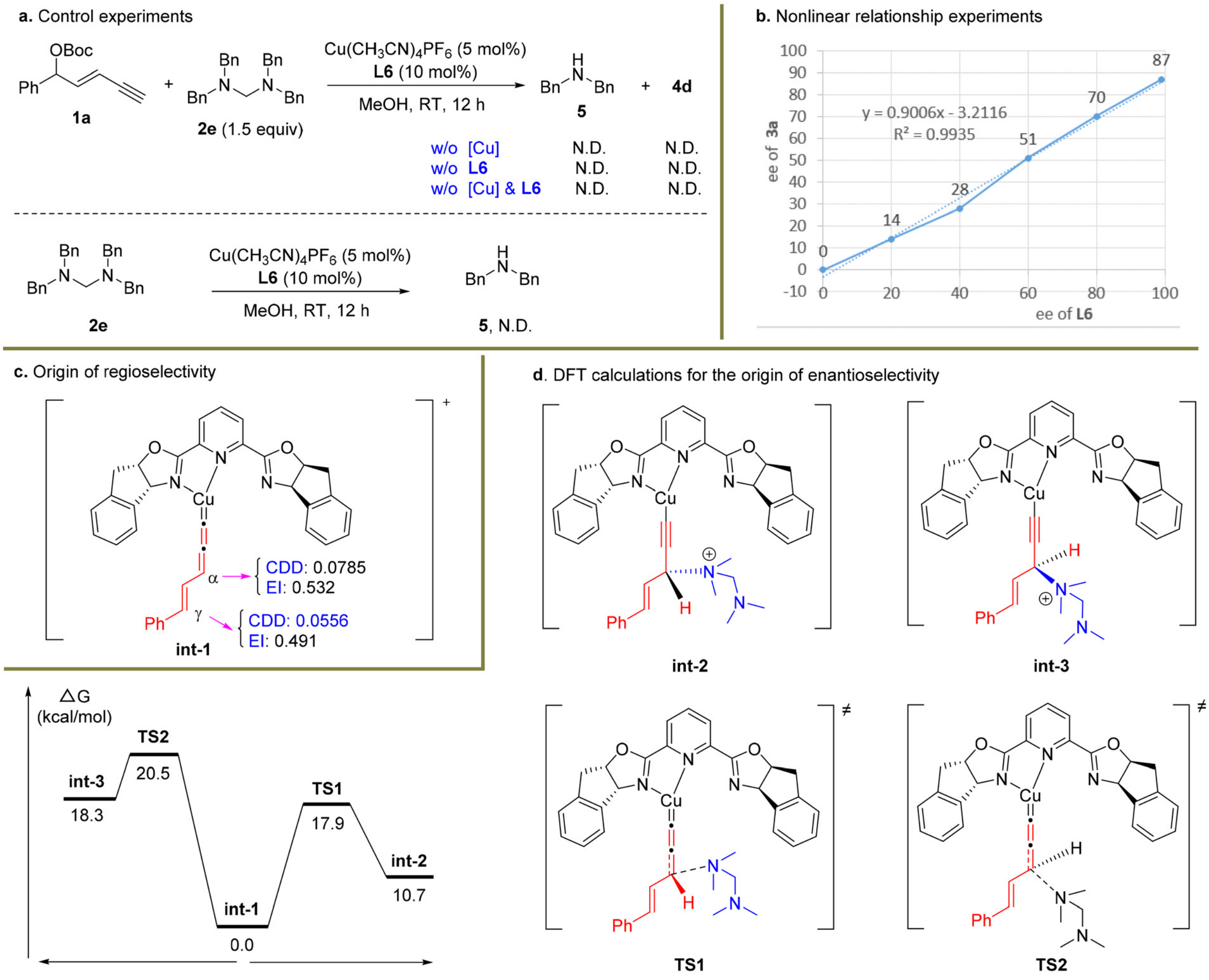
Scheme 3 The scope of amine precursors. The reactions were carried out on a 0.1 mmol scale. Isolated yields. The rr values were determined by ^1H NMR. The er values were determined by HPLC analysis.

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.[34a] 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]

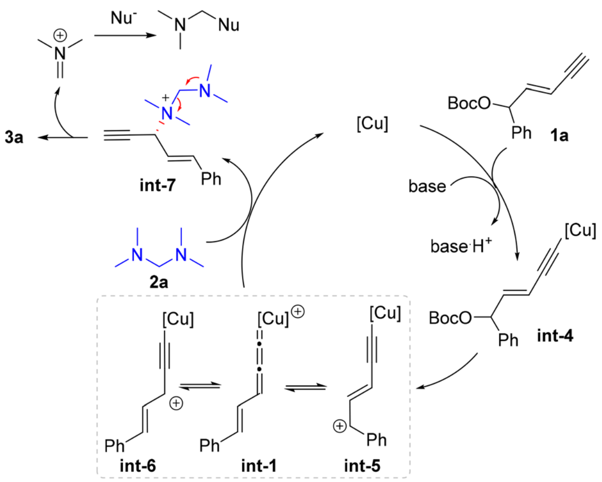
Next, a nonlinear relationship experiment showed a linear curve between the enantiopurity of chiral ligand **L6** and that of the product **3a** (Scheme 4b). This result suggested that monocopper/**L6** as the catalyst might be involved in the enantio-determining step. Based on this fact, DFT calculations were conducted to uncover the origin of regio- and enantioselectivity 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 4 Preliminary mechanistic studies. BP86/def2tzvp/SMD(methanol)//B3LYP-D3(BJ)/6-31g*/SDD was used for DFT calculations.

(Scheme 4c).[40,41] 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]



Scheme 5 Proposed mechanism.

Conclusions

In summary, we have established a feasible protocol for an asymmetric alkynylallylic 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 alkynylallylic 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.

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