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A facile method for the synthesis of dihydroquinoline-azide from the Lewis acid-catalyzed reaction of alkylidenecyclopropanes with $TMSN_3$†

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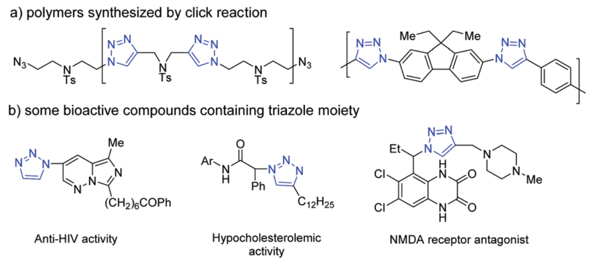
A facile synthetic method for the formation of dihydroquinoline-azide from alkylidenecyclopropanes and $TMSN_3$ under the catalysis of a Lewis acid has been developed, and a number of azide-containing compounds can be instantly accessed in moderate to good yields. A click reaction with these azido compounds was also realized along with a mechanistic investigation.

Click reactions are well known for their high efficiency in the synthesis of a vast variety of compounds.[1] Copper(I)-catalyzed azide–alkyne cycloaddition (CuAAC) for triazole synthesis is one of click reactions and has been widely applied in material synthesis,[2] drug development[3] and biochemistry[4] (Scheme 1). Currently, the development of a more feasible and efficient method to prepare various azide compounds has been an urgent task for chemists.[5]

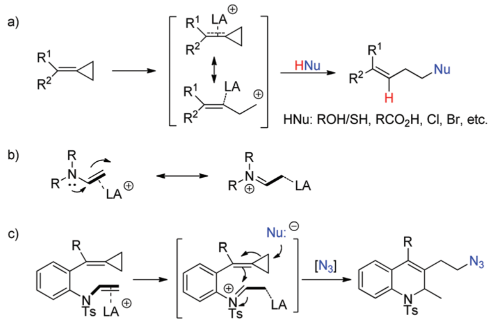
Alkylidenecyclopropanes (ACPs) are important building blocks in organic synthesis due to their diverse reactivities.[6] Our group and others have continuously made efforts to study the applications of ACPs in organic transformations.[7] Considering the importance of azide compounds in click reactions, we decided to explore the possibility of synthesizing valuable azide compounds from ACPs. It is well known that in the presence of a Lewis acid, ACPs together with nucleophiles could efficiently produce a variety of homoallylic compounds in good yields under mild conditions (Scheme 2a).[8] Moreover, an iminium species could be *in situ* generated from nucleophilic enamines upon treatment with Lewis acid (Scheme 2b).[9] Thus, we envisaged that it might be possible to afford azide products through a Lewis acid catalyzed cascade reaction of enamine-ACPs with stable and safe azide reagents such as $TMSN_3$ under simple operation (Scheme 2c).

We first investigated the reaction of ACP **1a** and $TMSN_3$ under the catalysis of $Fe(OTf)_3$ (20 mol%) in 1,2-dichloroethane (DCE) at 80 °C for about 7 h, and found that the desired azide product **2a** was successfully obtained in a yield of 51% (Scheme 3). The structure of **2a** was confirmed by X-ray crystal diffraction. Its ORTEP drawing is shown in Fig. 1 and the CIF data are presented in the ESI.†

Encouraged by this finding, we attempted to investigate the relevant factors involved which would affect the reaction outcomes of **1a** and $TMSN_3$. To establish the optimal conditions



Scheme 1 Applications of the CuAAC reaction in materials science and drug chemistry.



Scheme 2 Our proposal for the Lewis acid catalyzed synthesis of azide compounds through a cascade reaction of ACPs.

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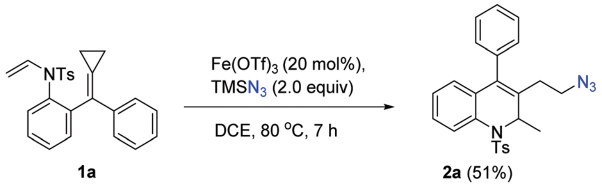


Scheme 3 A first examination on the reaction of **1a** with $TMSN_3$.

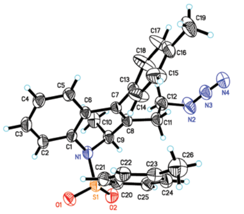


Fig. 1 The X-ray crystal structure of **2a**.

Table 1 Optimization of the reaction conditions

$$\mathbf{1a}\xrightarrow[\text{Solvent},T,\text{time}]{\text{catalyst (20 mol\%)},\text{TMSN}_3\text{ (2.0 equiv.)}}\mathbf{2a}$$

Entry[a]	Catalyst	Solvent	T (°C)	Time (h)	Yield[b]/%
1	$Eu(OTf)_3$	DCE	80	5	NR
2	$La(OTf)_3$	DCE	80	5	NR
3	$Ce(OTf)_3$	DCE	80	5	NR
4	$In(OTf)_3$	DCE	80	1	76 (68)[c]
5	$Sc(OTf)_3$	DCE	80	5	50
6	$AgSbF_6$	DCE	80	7	60
7	$Yb(OTf)_3$	DCE	80	5	23
8	$In(OTf)_3$	$CHCl_3$	80	7	39
9	$In(OTf)_3$	THF	80	7	ND
10	$In(OTf)_3$	Toluene	80	7	50
11	$In(OTf)_3$	CH_3CN	80	7	43
12	$\mathbf{In(OTf)_3}$	**DCE**	**60**	**2**	**89 (79)**[c]
13	$In(OTf)_3$	DCE	40	7	45
14	$In(OTf)_3$	DCE	20	24	30

[a] Reaction conditions: **1a** (0.2 mmol), $TMSN_3$ (0.4 mmol), and catalyst (20 mol%) were placed in a flask and 2 mL solvent was added. Then the mixture was stirred at different temperatures. [b] Determined by ^1H NMR spectroscopy, with 1,3,5-trimethoxybenzene as an internal standard. [c] Isolated yields.

Table 2 Optimization of the reaction conditions

$$\mathbf{1a}\xrightarrow[\text{DCE},60\,^\circ\text{C}]{\text{In(OTf)}_3\ (x\text{ mol\%}),\text{TMSN}_3\ (y\text{ equiv.})}\mathbf{2a}$$

Entry[a]	$In(OTf)_3$ (x/mol%)	$TMSN_3$ (y/equiv.)	Solvent	T (°C)	Time (h)	Yield[b]/%
1	10	2.0	DCE	60	7	40
2	30	2.0	DCE	60	2	65
3	20	1.0	DCE	60	2	55
4	20	2.0	DCE	60	2	79
5	**20**	**3.0**	**DCE**	**60**	**0.5**	**85**
6	20	4.0	DCE	60	0.25	84

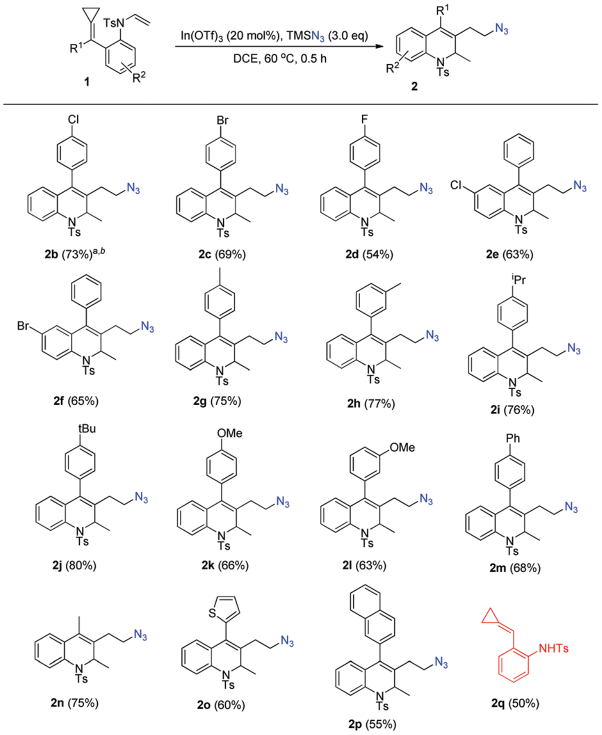
[a] Reaction conditions: **1a** (0.2 mmol), $TMSN_3$ (y mmol), and $In(OTf)_3$ (x mol%) were placed in a flask and 2 mL DCE was added. Then the mixture was stirred at 60 °C. [b] Isolated yields.

for the reaction, different Lewis acids, solvents, temperatures and reaction times were tested, and the results are shown in Table 1.

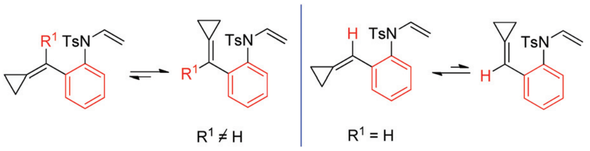
Firstly, we screened several Lewis acids in this reaction and revealed that $Eu(OTf)_3$, $La(OTf)_3$ and $Ce(OTf)_3$ (20 mol%) could not catalyze the reaction under identical conditions (Table 1, entries 1–3), but $In(OTf)_3$ enhanced the yield of **2a** to 76% within 1 h (Table 1, entry 4). Furthermore, $Sc(OTf)_3$, $AgSbF_6$ and $Yb(OTf)_3$ could also catalyze the reaction, giving **2a** in moderate yields ranging from 20%–60% (Table 1, entries 5–7). Therefore, $In(OTf)_3$ was identified as the most efficient Lewis acid in this transformation. Then, we examined different solvents other than DCE and found that $CHCl_3$, toluene and acetonitrile could all afford **2a** in moderate yields (Table 1, entries 8, 10 and 11), while THF would suppress the reaction completely without the formation of product **2a** (Table 1, entry 9). On the basis of these examinations, DCE was the most suitable solvent in this reaction. We also adjusted the reaction temperature using $In(OTf)_3$ as the catalyst in DCE and determined that carrying out the reaction at 60 °C afforded **2a** in an isolated yield of 79% within 2 h (Table 1, entries 12–14).

To further optimize the reaction conditions, we screened the loading amounts of $In(OTf)_3$ and $TMSN_3$ in this reaction (Table 2). On using 10 mol% of Lewis acid the yield of **2a** decreased to 40% (Table 2, entry 1), but on increasing the concentration of Lewis acid to 30 mol% the yield of **2a** also decreased presumably due to the decomposition of **1a** in the presence of excess amounts of Lewis acid (Table 2, entry 2). We also screened the amount of $TMSN_3$ in this reaction, and it was revealed that when the dosage of $TMSN_3$ was reduced to 1.0 equiv., the yield of **2a** decreased to 55% (Table 2, entry 3) and when the dosage was increased to 3.0 equiv., the yield of **2a** could be increased to 85% along with the reaction time being reduced to 0.5 h (Table 2, entry 5). Further increasing the dosage of $TMSN_3$ to 4.0 equiv. did not improve the yield of **2a** after the reaction was performed for 0.25 h (Table 2, entry 6). Thus, we have found the optimal conditions under which the corresponding azide compound **2a** could be obtained in the highest yield (Table 2, entry 5).

With the optimal conditions in hand, we next examined the substrate scope and the results are shown in Scheme 4. For halogen atom substituted substrates **1b–1f**, the reactions were compatible, affording the desired products **2b–2f** in moderate to good yields ranging from 54%–70%. In the case of fluorine atom including substrate **1d**, the corresponding product **2d** was formed in a moderate yield (54%). Introduction of an alkyl group such as the methyl, isopropyl or *tert*-butyl group into the benzene ring of substrates **1** could afford the desired products **2g–2j** in good yields ranging from 70%–80%. In addition, methoxyl group and phenyl group substituted substrates **1k**, **1l** and **1m** were also tolerated, giving the azide products **2k–2m** in 63%–68% yields. All these results suggested that the substituent on the benzene ring of **1** did not have a significant influence on the transformation. Furthermore, when R^1 was a methyl, a thienyl or a naphthyl group, the corresponding pro-



Scheme 4 Screening of the substrate scope. ^{a} Reaction conditions: **1a** (0.2 mmol), TMSN$_3$ (0.6 mmol), and In(OTf)$_3$ (20 mmol%) were placed in a flask and 2 mL DCE was added. Then the mixture was stirred at 60 °C within 30 min. ^{b} Isolated yields.

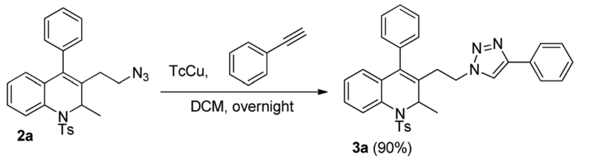


Scheme 5 Conformational analysis of substrate **1**.

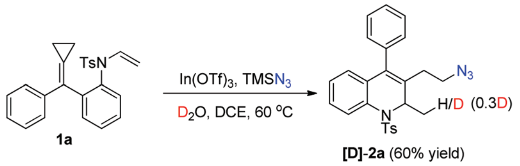
ducts **2n** (75%), **2o** (60%) and **2p** (55%) could also be obtained successfully, demonstrating a broad substrate scope for this reaction. However, for substrate **1q**, in which R^1 was a hydrogen atom, a decomposed product **2q** was formed in 50% yield. To explain this observation, the conformation of substrate **1** was analyzed. As shown in Scheme 5, when R^1 was not a hydrogen atom, the sterically large R^1 substituent forced the methylenecyclopropane moiety in substrate **1** to approach the *in situ* formed electrophilic center (Scheme 2c), triggering the cascade reaction. However, when R^1 was a hydrogen atom, the conformation did not facilitate electrophilic cyclization, leading to its decomposition.

The CuAAC reaction of **2a** with phenylacetylene under the catalysis of CuTc (copper(I)thiophene-2-carboxylate) was then performed, delivering the corresponding triazole compound **3a** in a yield of 90% (Scheme 6).

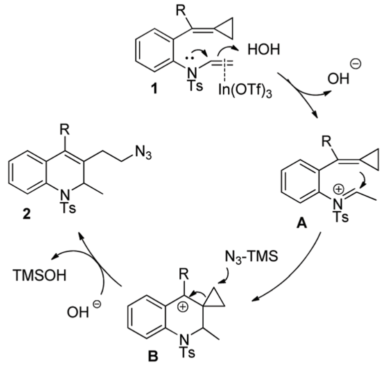
To gain more insights into this cascade azidation reaction mechanism, an isotopic labeling experiment by adding D$_2$O to the reaction system was conducted to identify the source of the hydrogen atom (Scheme 7). We found that **2a** was afforded in 60% yield along with 30% deuterium incorporation ([D]-**2a**), suggesting that the extra hydrogen atom was derived from the ambient proton source (see the ESI† for more details). On the basis of these experimental results and previous reports,[10] a plausible mechanism is outlined in Scheme 8. Firstly, In(OTf)$_3$ activated the enamine moiety of **1** to give a highly electrophilic iminium intermediate **A**, which gave intermediate **B** through aza-Prins cyclization. Then intermediate **B** underwent a cyclopropane ring-opening process *via* the nucleophilic attack of TMSN$_3$ to afford the desired product **2**.



Scheme 6 Application of **2a** in the CuAAC reaction.



Scheme 7 Deuteration labeling experiment.



Scheme 8 The plausible mechanism for the cascade azidation reaction.

In summary, we have developed a facile and highly efficient method for the rapid synthesis of azide products through a In(OTf)$_3$-catalyzed cascade reaction of ACPs with TMSN$_3$ under mild conditions. A preliminary investigation on the mechanism revealed a plausible reaction pathway for this cascade azidation process. Further application of this new azidation method is under investigation in our lab.

Conflicts of interest

There are no conflicts of interest to declare.

Acknowledgements

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