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A metal-catalyzed new approach for α-alkynylation of cyclic amines†

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The first catalytic α-alkynylation of cyclic amines with the help of the *N*-propargylic group to afford 2-(1-alkynyl) *N*-allylic cyclic amines with an exclusive *E*-stereoselectivity for the *in situ* formed C=C bond has been realized. Based on mechanistic studies, it is proven that the reaction proceeds through metal-mediated *anti*-1,5-hydride transfer forming an iminonium intermediate, which accepts the addition of the *in situ* generated 1-alkynyl metal species. The synthetic application has also been demonstrated.

Introduction

Due to the synthetic[1] and bio-importance[2–7] of cyclic amines much attention has been focused on the development of the related methodologies. One straightforward approach is α-functionalization of readily available cyclic amines.[8] Oxidative coupling of *N*-protected cyclic amines with terminal alkynes or 1-alkynyl trifluoroborate in the presence of a stoichiometric amount of an oxidant (eqn (1)) and the three-component reaction of *N*-non-protected cyclic amines with terminal alkynes and aldehydes have been well established (eqn (2)).[9,10] Starting from 2010, we have reported the ZnX_2,[11,12] CuI,[13] or $CuBr_2$[14]-mediated allenylation of terminal alkynes (ATA) reaction with aldehydes in the presence of different amines forming allenes. In this reaction, the second step is the metal-mediated 1,5-H transfer reaction of propargylic amines *in situ* formed in the first step, which was proven to be non-stereoselective by Nakamura *et al.* affording allylic propargylic amines with an *E*/*Z* ratio of 58/42–63/37 with acyclic amine.[15] Herein, we wish to report a highly stereoselective *N*-propargylic cyclic amine-based α-alkynylation providing stereodefined *N*-(*E*)-allylic 2-alkynyl cyclic amines by using $CdBr_2$ (or ZnI_2) as the catalyst (Scheme 1).

Results and discussion

Optimization of the reaction

When we studied the mechanism of the Cu-catalyzed allenylation of terminal alkynes in the presence of an amine,[13] it was observed that the reaction between *N*-alkynylic amine **1a** and phenylacetylene **2a** under CuBr catalysis provided a new product **3aa** in a low yield of 13% with 64% of starting material **1a** being recovered as judged by ^{1}H NMR analysis. This new product was identified as α-alkynylated cyclic amine with an *N*-allylic group bearing an exclusive *E* C=C bond (Table 1, entry 1). Due to the importance of cyclic amines, we further optimized the reaction conditions by screening a variety of metal salts such as CuX_2, ZnX_2, AgOTf and CdX_2, and $CdBr_2$[16] turned out to be the best providing the product **3aa** in 42% yield and 52% recovery of **1a** (Table 1, entries 2–7). On increasing the temperature to 120 °C, the yield was improved to 56% with 20% recovery (Table 1, entry 8).

Effect of solvents

Then solvents were screened: when ^{t}BuOMe was used as the solvent, the desired product **3aa** could be obtained in 63% yield with complete consumption of **1a** (Table 2, entries 1–7). In addition, reducing the catalyst loading to 10 mol% improved the yield slightly to 66% (Table 2, entries 8–9). Further reducing the catalyst loading resulted in the recovery of **1a** (Table 2, entry 10). Thus, **1a** (1 equiv.), **2a** (2 equiv.), and $CdBr_2$ (10 mol%) in ^{t}BuOMe at 120 °C were defined as the optimized reaction conditions for further study of this reaction.

Substrate scope

With the optimal reaction conditions in hand, diversified terminal alkynes were investigated to examine the scope of this α-alkynylation reaction with amine **1a.** Terminal aryl acetylenes bearing electron-donating *p*-Me and *p*-MeO, and electron-withdrawing and synthetically attractive *p*-F, *p*-Cl, *m*-Cl, *p*-NO_2, *p*-EtOOC, *p*-CN and *p*-Ac groups on the aryl ring could all afford the corresponding product **3** in moderate yields (Table 3, entries 1–10). In addition, alkyl-substituted terminal alkynes, such as 1-decyne (**2k**) and cyclohexylacetylene (**2l**), were found to be sluggish affording the corresponding products in 31% and 40%

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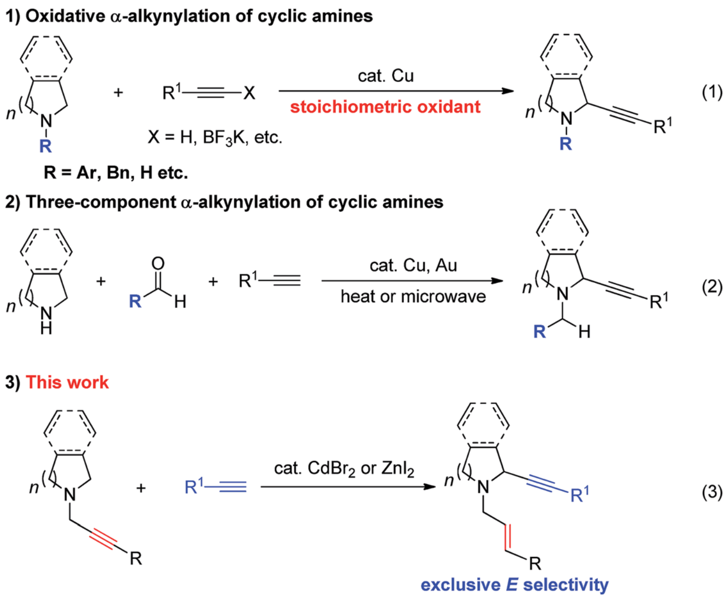
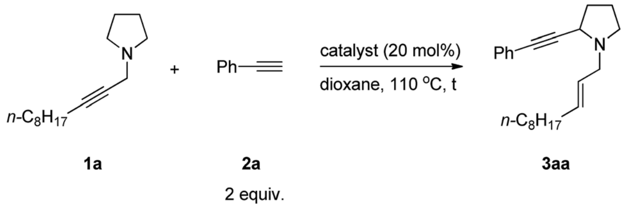


Scheme 1 Different approaches for α-alkynylation of cyclic amines.

yields, respectively (Table 3, entries 11 and 12). Interestingly, trimethylsilylacetylene could react with **1a** to furnish **3am** in 76% yield (Table 3, entry 13). Other substituted propargylic amines, such as **1b**, **1c**, **1d** and **1g** could also react smoothly to afford the desired products **3ba**, **3ca**, **3da** and **3ga** in 40–65% yields (Table 3, entries 14–16, 21). *N*-Terminal propargylic amine **1e** was next exposed to the optimized conditions with arylacetylenes substituted with different functional groups, such as electron-donating *p*-MeO and electron-withdrawing *p*-F and *p*-Cl, affording the corresponding products **3ea–3ee** in moderate yields with 30 mol% of ZnI_2 (Table 3, entries 17–20).

Tetrahydroisoquinoline is the core skeleton of a variety of natural bio-active compounds and drugs.[17] We first applied $CdBr_2$ in ^{t}BuOMe to *N*-propargylic tetrahydroisoquinoline derivative **1f** and phenylacetylene **2a.** The 1-alkynated product was obtained exclusively in 57% isolated yield with 24% **1f** recovery. Interestingly, using 10 mol% ZnI_2 as the catalyst and

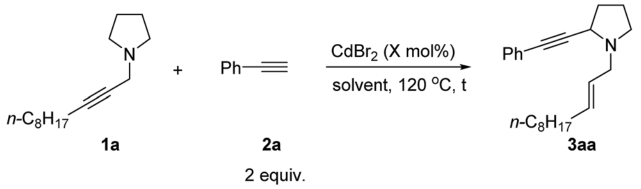
Table 1 Optimization of catalytic α-alkynylation of 1-(2-alkynyl) cyclic amine **1a** with **2a**[a]



Entry	Catalyst	Time (h)	Yield of **3aa**[b] (%)	Recovery of **1a**[b] (%)
1	CuBr	12	13	64
2	$CuBr_2$	10	13	—
3	$ZnCl_2$	10	24	—
4	$ZnBr_2$	10	39	—
5	AgOTf	12	5	95
6	CdI_2	10	40	—
7	$CdBr_2$	24	42	53
8[c]	$CdBr_2$	36	56	20
9[d]	$CdBr_2$	12	47	26

[a] The reaction was conducted using **1a** (1.0 mmol) and alkyne **2a** (2.0 mmol) in 6 mL of dioxane at 110 °C. [b] Determined by ^1H NMR analysis with CH_2Br_2 as the internal standard. [c] The reaction was conducted at 120 °C. [d] The reaction was conducted at 130 °C.

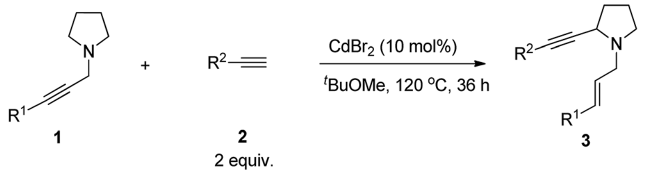
Table 2 Optimization of reaction conditions for catalytic α-alkynylation of *N*-internal 2-alkynylic cyclic amine **1a** with **2a**[a]



Entry	*X*	Solvent	*t* (h)	Yield of **3aa**[b] (%)	Recovery of **1b**[b] (%)
1	20	DMF	23	43	25
2	20	DMSO	23	20	35
3	20	Toluene	23	40	—
4	20	THF	23	48	—
5	20	DCE	23	3	—
6	20	CH_3CN	23	39	—
7	20	^{t}BuOMe	36	63	—
8	15	^{t}BuOMe	36	64	—
9[c]	**10**	**^{t}BuOMe**	**36**	**66**	**—**
10	5	^{t}BuOMe	36	69	10

[a] The reaction was conducted using **1a** (0.5 mmol) and alkyne **2a** (1.0 mmol) in 3 mL of solvent. [b] Determined by ^1H NMR analysis with CH_2Br_2 as the internal standard. [c] The reaction was conducted using **1a** (1.0 mmol) and alkyne **2a** (2.0 mmol) in 6 mL of ^{t}BuOMe at 120 °C.

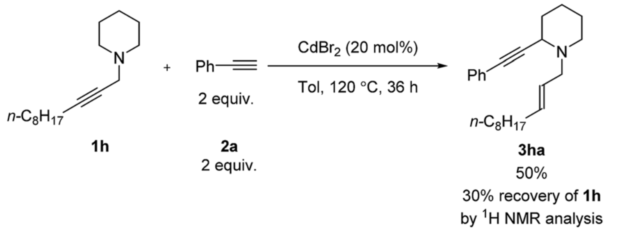
Table 3 The scope of catalytic α-alkynylation of *N*-internal 2-alkynylic cyclic amines[a]



Entry	**1** (R^1)	**2** (R^2)	Isolated yield of **3**[b] (%)
1	*n*-C_8H_{17} (**1a**)	C_6H_5 (**2a**)	63 (**3aa**)
2	*n*-C_8H_{17} (**1a**)	*p*-MeC_6H_4 (**2b**)	51 (**3ab**)
3[c]	*n*-C_8H_{17} (**1a**)	*p*-$MeOC_6H_4$ (**2c**)	45 (**3ac**)
4	*n*-C_8H_{17} (**1a**)	*p*-FC_6H_4 (**2d**)	55 (**3ad**)
5	*n*-C_8H_{17} (**1a**)	*p*-ClC_6H_4 (**2e**)	67 (**3ae**)
6	*n*-C_8H_{17} (**1a**)	*m*-ClC_6H_4 (**2f**)	66 (**3af**)
7	*n*-C_8H_{17} (**1a**)	*p*-$O_2NC_6H_4$ (**2g**)	60 (**3ag**)
8	*n*-C_8H_{17} (**1a**)	*p*-$EtOOCC_6H_4$ (**2h**)	60 (**3ah**)
9	*n*-C_8H_{17} (**1a**)	*p*-NCC_6H_4 (**2i**)	61 (**3ai**)
10	*n*-C_8H_{17} (**1a**)	*p*-AcC_6H_4 (**2j**)	59 (**3aj**)
11[d]	*n*-C_8H_{17} (**1a**)	*n*-C_8H_{17} (**2k**)	31 (**3ak**)
12[e]	*n*-C_8H_{17} (**1a**)	Cy (**2l**)	40 (**3al**)
13[f]	*n*-C_8H_{17} (**1a**)	TMS (**2m**)	76 (**3am**)
14	Cy (**1b**)	C_6H_5 (**2a**)	65 (**3ba**)
15[g]	*n*-C_4H_9 (**1c**)	C_6H_5 (**2a**)	57 (**3ca**)
16[h]	$(CH_3)_2(OH)C$ (**1d**)	C_6H_5 (**2a**)	62 (**3da**)
17[i]	H (**1e**)	C_6H_5 (**2a**)	47 (**3ea**)
18[i]	H (**1e**)	*p*-$MeOC_6H_4$ (**2c**)	45 (**3ec**)
19[i]	H (**1e**)	*p*-FC_6H_4 (**2d**)	48 (**3ed**)
20[i]	H (**1e**)	*p*-ClC_6H_4 (**2e**)	46 (**3ee**)
21[j]	Ph (**1g**)	C_6H_5 (**2a**)	40 (**3ga**)

[a] The reaction was conducted using **1** (1.0 mmol) and 1-alkyne **2** (2.0 mmol) in 6 mL of MTBE at 120 °C for 36 h. [b] *E*/*Z* > 20 : 1, if any. [c] 22% of **1a** was recovered. [d] 20% of $CdBr_2$ was used and 27% of **1a** was recovered. [e] 50% of **1a** was recovered. [f] The reaction was conducted at 130 °C and 3% of **1a** was recovered. [g] 15% of $CdBr_2$ was used. [h] The reaction was conducted at 130 °C and 4% of **1d** was recovered. [i] The reaction was conducted using **1e** (1.0 mmol), alkyne **2** (2.0 mmol) and ZnI_2 (0.3 mmol) in 6 mL of dioxane at 110 °C for 10 h. [j] The reaction was conducted in 6 mL of toluene and 25% of **1g** was recovered.

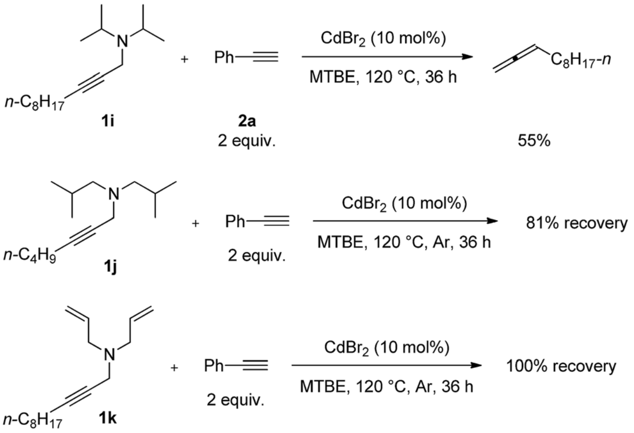
dioxane as the solvent, the reaction afforded **3fa** in a yield of 78%. Trimethylsilylacetylene (**2m**) and 1-hexyne (**2n**) are also compatible (Scheme 2).



Scheme 3 Catalytic α-alkynylation of piperidine **1h**. The reaction was conducted using **1h** (1.0 mmol) and phenylacetylene **2a** (2.0 mmol) in 6 mL of toluene at 120 °C.

For piperidine derivative **1h**, a larger catalyst-loading is required and toluene was also necessary since the reaction in MTBE resulted in 13% yield of the target product with 89% recovery of **1h**. Unfortunately, morpholine did not work (Scheme 3).

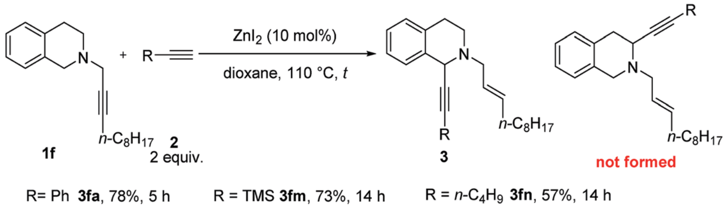
Furthermore, several non-cyclic amines were investigated. The reaction of diisopropylamine **1i** with phenylacetylene **2a** generated 55% yield of 1,2-undecadiene[11–14] (Scheme 4). When we applied diisobutylamine **1j** and diallylamine **1k** under the standard reaction conditions, such reactions were not observed.



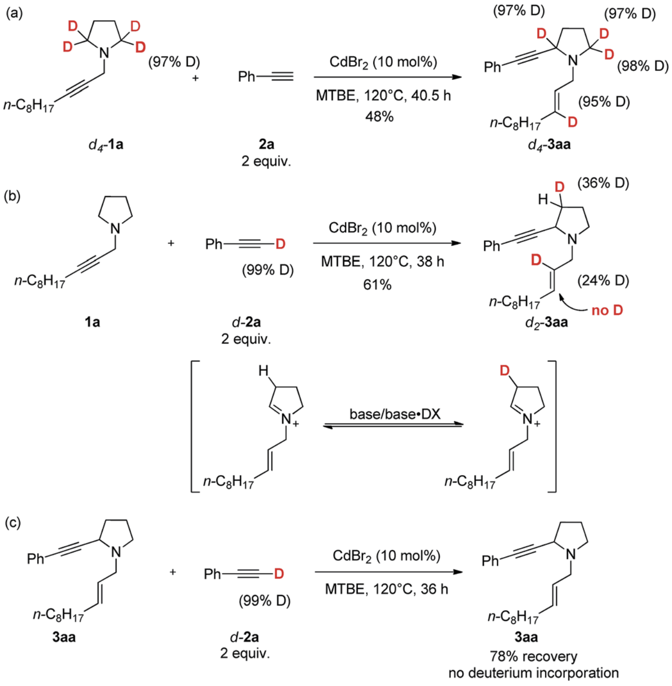
Scheme 4 The reaction of non-cyclic amine **1i–1k**. The reaction was conducted using **1i–1k** (1.0 mmol) and phenylacetylene **2a** (2.0 mmol) in 6 mL of MTBE at 120 °C.

Deuterium experiments

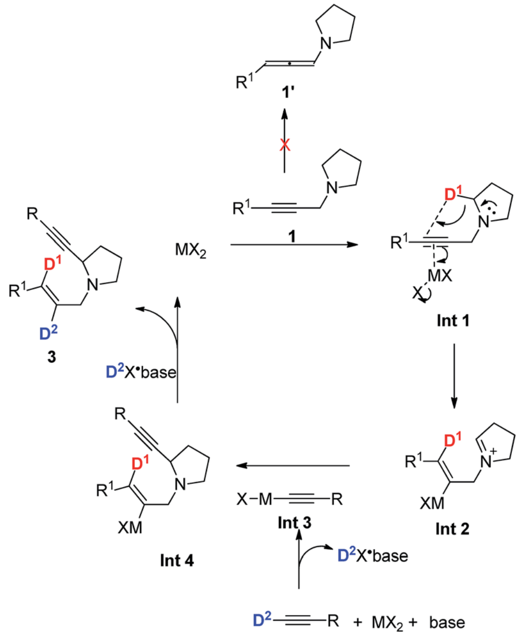
To gain insight into the mechanism of this reaction, deuterium-labeled *d*₄-**1a** was treated with **2a** under standard conditions to



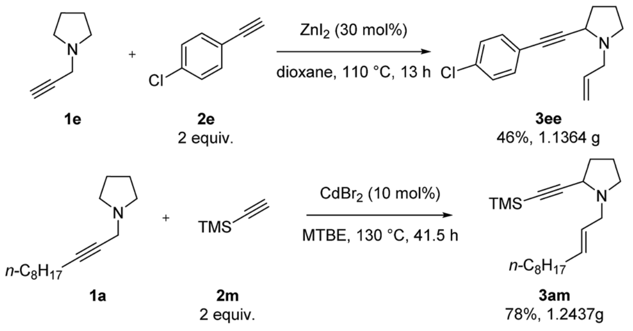
Scheme 2 The scope of catalytic α-alkynylation of tetrahydroisoquinoline **1f**. The reaction was conducted using **1f** (1.0 mmol) and alkyne **2** (2.0 mmol) in 6 mL of dioxane at 110 °C.



Scheme 5 Deuterium labeling experiments.



Scheme 6 A plausible mechanism for the formation of 3.



Scheme 7 Gram-scale synthesis.

give d_4-**3aa** with 95% D incorporation, which reveals that the hydrogen at the γ-position of the allylic group comes from the α-position of the amine unit (Scheme 5a). In addition, 24% of deuterium incorporation was observed in the 2-position of the *N*-allylic group in product d_2-**3aa** of the reaction between deuterium-labeled *d*-**2a** and **1a** (Scheme 5b). The control experiment of treating **3aa** with *d*-**2a** led to no deuterium incorporation (Scheme 5c).

Based on the above deuterium labeling experiments and the products in the *E* configuration, a plausible mechanism proposed is shown in Scheme 6. The propargylic amine **1** coordinates to MX_2 to form **Int 1**, which would undergo *anti*-1,5-hydride transfer to form cationic **Int 2** in the *E* configuration.[15] Subsequently, 1-alkynyl cadmium species **Int 3**, *in situ* generated from terminal alkyne, $CdBr_2$, and amine, would react with the iminium ion **Int 2** to afford the corresponding α-substituted cyclic amine **3** (Scheme 6). In addition, the possibility of forming the product from allenyl amine **1′** is excluded since there is no D-incorporation at the 3-position of the *E*-allylic unit in the product of eqn (b) of Scheme 5. It is believed that $CdBr_2$ may coordinate better with the C–C triple bond to trigger the 1,5-H transfer reaction.

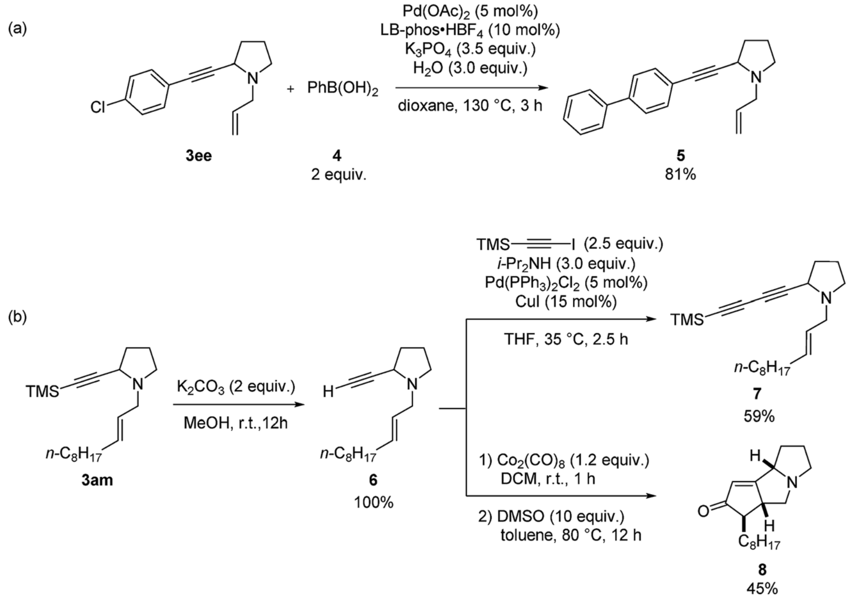
Finally, we conducted a gram-scale synthesis of both **3ee** and **3am** (Scheme 7).

Synthetic applications

Furthermore, diversified synthetic utilities of these two products were demonstrated. Suzuki coupling between **3ee** and phenyl boronic acid using LB-Phos·HBF_4[18] affords **5** in 81% yield (Scheme 8a). Deprotection of the TMS group in **3am** with K_2CO_3 in MeOH afforded enyne **6**, which may react with 1-trimethylsilylethynyl iodide to afford conjugated diyne **7** (Scheme 8b). Sequential treatment of **6** with 1.2 equiv. of $Co_2(CO)_8$ and 10 equiv. of DMSO afforded the Pauson–Khand reaction product **8** in 45% yield.[19]

Conclusions

In conclusion, we have succeeded in developing a catalytic α-alkynylation of *N*-propargylic cyclic amines, providing 1-(2(*E*)-alkenyl) 2-(1-alkynyl) cyclic amines highly stereoselectively. Further studies on identifying the chiral catalyst, the scope of nucleophiles, and their applications to natural products are being actively pursued in the laboratory.



Scheme 8 Synthetic applications.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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