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# A metal-catalyzed new approach for $\alpha$ -alkynylation of cyclic amines†

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The first catalytic  $\alpha$ -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 iminium 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<sup>1</sup> and bio-importance<sup>2–7</sup> of cyclic amines much attention has been focused on the development of the related methodologies. One straightforward approach is  $\alpha$ -functionalization of readily available cyclic amines.<sup>8</sup> 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)).<sup>9,10</sup> Starting from 2010, we have reported the ZnX<sub>2</sub>,<sup>11,12</sup> CuI,<sup>13</sup> or CuBr<sub>2</sub><sup>14</sup>-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.<sup>15</sup> Herein, we wish to report a highly stereoselective *N*-propargylic cyclic amine-based  $\alpha$ -alkynylation providing stereodefined *N*-(*E*)-allylic 2-alkynyl cyclic amines by using CdBr<sub>2</sub> (or ZnI<sub>2</sub>) 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,<sup>13</sup> 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 <sup>1</sup>H NMR analysis. This new product was identified as  $\alpha$ -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<sub>2</sub>, ZnX<sub>2</sub>, AgOTf and CdX<sub>2</sub>, and CdBr<sub>2</sub><sup>16</sup> 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<sub>2</sub> (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  $\alpha$ -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<sub>2</sub>, *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%

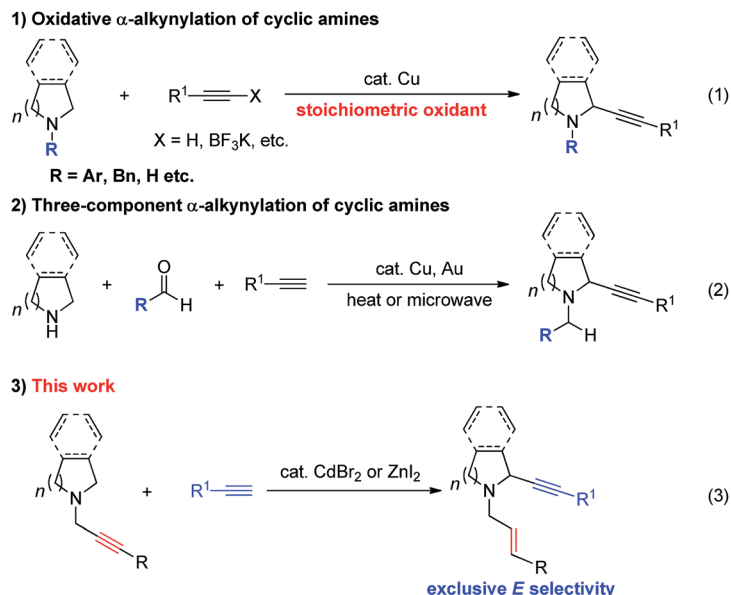
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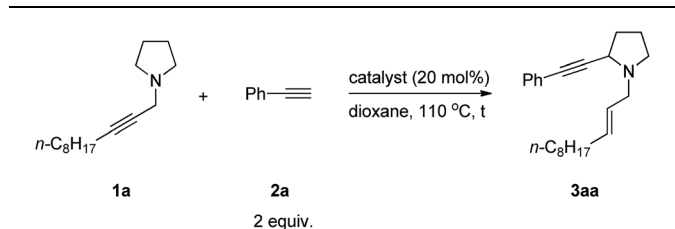
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Scheme 1 Different approaches for  $\alpha$ -alkynylation of cyclic amines.

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

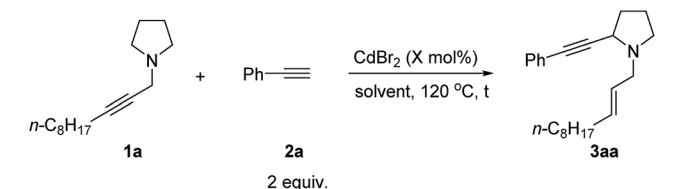
and *p*-Cl, affording the corresponding products **3ea–3ee** in moderate yields with 30 mol% of  $\text{ZnI}_2$  (Table 3, entries 17–20).

Tetrahydroisoquinoline is the core skeleton of a variety of natural bio-active compounds and drugs.<sup>17</sup> We first applied  $\text{CdBr}_2$  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%  $\text{ZnI}_2$  as the catalyst and

Table 1 Optimization of catalytic  $\alpha$ -alkynylation of 1-(2-alkynyl) cyclic amine **1a** with **2a**<sup>a</sup>

Entry	Catalyst	Time (h)	Yield of <b>3aa</b> <sup>b</sup> (%)	Recovery of <b>1a</b> <sup>b</sup> (%)
1	CuBr	12	13	64
2	CuBr <sub>2</sub>	10	13	—
3	ZnCl <sub>2</sub>	10	24	—
4	ZnBr <sub>2</sub>	10	39	—
5	AgOTf	12	5	95
6	CdI <sub>2</sub>	10	40	—
7	CdBr <sub>2</sub>	24	42	53
8 <sup>c</sup>	CdBr <sub>2</sub>	36	56	20
9 <sup>d</sup>	CdBr <sub>2</sub>	12	47	26

<sup>a</sup> The reaction was conducted using **1a** (1.0 mmol) and alkyne **2a** (2.0 mmol) in 6 mL of dioxane at 110 °C. <sup>b</sup> Determined by <sup>1</sup>H NMR analysis with  $\text{CH}_2\text{Br}_2$  as the internal standard. <sup>c</sup> The reaction was conducted at 120 °C. <sup>d</sup> The reaction was conducted at 130 °C.

Table 2 Optimization of reaction conditions for catalytic  $\alpha$ -alkynylation of *N*-internal 2-alkynyl cyclic amine **1a** with **2a**<sup>a</sup>

Entry	X	Solvent	t (h)	Yield of <b>3aa</b> <sup>b</sup> (%)	Recovery of <b>1b</b> <sup>b</sup> (%)
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	$\text{CH}_3\text{CN}$	23	39	—
7	20	<i>t</i> -BuOMe	36	63	—
8	15	<i>t</i> -BuOMe	36	64	—
9 <sup>c</sup>	10	<i>t</i> -BuOMe	36	66	—
10	5	<i>t</i> -BuOMe	36	69	10

<sup>a</sup> The reaction was conducted using **1a** (0.5 mmol) and alkyne **2a** (1.0 mmol) in 3 mL of solvent. <sup>b</sup> Determined by <sup>1</sup>H NMR analysis with  $\text{CH}_2\text{Br}_2$  as the internal standard. <sup>c</sup> The reaction was conducted using **1a** (1.0 mmol) and alkyne **2a** (2.0 mmol) in 6 mL of *t*-BuOMe at 120 °C.



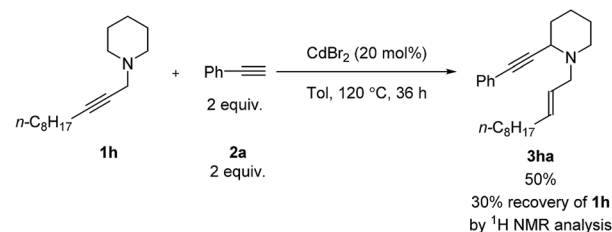
**Table 3** The scope of catalytic  $\alpha$ -alkynylation of *N*-internal 2-alkynylcyclic amines<sup>a</sup>

Entry	1 ( <i>R</i> <sup>1</sup> )	2 ( <i>R</i> <sup>2</sup> )	Isolated yield of 3 <sup>b</sup> (%)
1	<i>n</i> -C <sub>8</sub> H <sub>17</sub> ( <b>1a</b> )	C <sub>6</sub> H <sub>5</sub> ( <b>2a</b> )	63 ( <b>3aa</b> )
2	<i>n</i> -C <sub>8</sub> H <sub>17</sub> ( <b>1a</b> )	<i>p</i> -MeC <sub>6</sub> H <sub>4</sub> ( <b>2b</b> )	51 ( <b>3ab</b> )
3 <sup>c</sup>	<i>n</i> -C <sub>8</sub> H <sub>17</sub> ( <b>1a</b> )	<i>p</i> -MeOC <sub>6</sub> H <sub>4</sub> ( <b>2c</b> )	45 ( <b>3ac</b> )
4	<i>n</i> -C <sub>8</sub> H <sub>17</sub> ( <b>1a</b> )	<i>p</i> -FC <sub>6</sub> H <sub>4</sub> ( <b>2d</b> )	55 ( <b>3ad</b> )
5	<i>n</i> -C <sub>8</sub> H <sub>17</sub> ( <b>1a</b> )	<i>p</i> -ClC <sub>6</sub> H <sub>4</sub> ( <b>2e</b> )	67 ( <b>3ae</b> )
6	<i>n</i> -C <sub>8</sub> H <sub>17</sub> ( <b>1a</b> )	<i>m</i> -ClC <sub>6</sub> H <sub>4</sub> ( <b>2f</b> )	66 ( <b>3af</b> )
7	<i>n</i> -C <sub>8</sub> H <sub>17</sub> ( <b>1a</b> )	<i>p</i> -O <sub>2</sub> NC <sub>6</sub> H <sub>4</sub> ( <b>2g</b> )	60 ( <b>3ag</b> )
8	<i>n</i> -C <sub>8</sub> H <sub>17</sub> ( <b>1a</b> )	<i>p</i> -EtOOC <sub>6</sub> H <sub>4</sub> ( <b>2h</b> )	60 ( <b>3ah</b> )
9	<i>n</i> -C <sub>8</sub> H <sub>17</sub> ( <b>1a</b> )	<i>p</i> -NCC <sub>6</sub> H <sub>4</sub> ( <b>2i</b> )	61 ( <b>3ai</b> )
10	<i>n</i> -C <sub>8</sub> H <sub>17</sub> ( <b>1a</b> )	<i>p</i> -AcC <sub>6</sub> H <sub>4</sub> ( <b>2j</b> )	59 ( <b>3aj</b> )
11 <sup>d</sup>	<i>n</i> -C <sub>8</sub> H <sub>17</sub> ( <b>1a</b> )	<i>n</i> -C <sub>8</sub> H <sub>17</sub> ( <b>2k</b> )	31 ( <b>3ak</b> )
12 <sup>e</sup>	<i>n</i> -C <sub>8</sub> H <sub>17</sub> ( <b>1a</b> )	Cy ( <b>2l</b> )	40 ( <b>3al</b> )
13 <sup>f</sup>	<i>n</i> -C <sub>8</sub> H <sub>17</sub> ( <b>1a</b> )	TMS ( <b>2m</b> )	76 ( <b>3am</b> )
14	Cy ( <b>1b</b> )	C <sub>6</sub> H <sub>5</sub> ( <b>2a</b> )	65 ( <b>3ba</b> )
15 <sup>g</sup>	<i>n</i> -C <sub>4</sub> H <sub>9</sub> ( <b>1c</b> )	C <sub>6</sub> H <sub>5</sub> ( <b>2a</b> )	57 ( <b>3ca</b> )
16 <sup>h</sup>	(CH <sub>3</sub> ) <sub>2</sub> (OH)C ( <b>1d</b> )	C <sub>6</sub> H <sub>5</sub> ( <b>2a</b> )	62 ( <b>3da</b> )
17 <sup>i</sup>	H ( <b>1e</b> )	C <sub>6</sub> H <sub>5</sub> ( <b>2a</b> )	47 ( <b>3ea</b> )
18 <sup>i</sup>	H ( <b>1e</b> )	<i>p</i> -MeOC <sub>6</sub> H <sub>4</sub> ( <b>2c</b> )	45 ( <b>3ec</b> )
19 <sup>i</sup>	H ( <b>1e</b> )	<i>p</i> -FC <sub>6</sub> H <sub>4</sub> ( <b>2d</b> )	48 ( <b>3ed</b> )
20 <sup>i</sup>	H ( <b>1e</b> )	<i>p</i> -ClC <sub>6</sub> H <sub>4</sub> ( <b>2e</b> )	46 ( <b>3ee</b> )
21 <sup>j</sup>	Ph ( <b>1g</b> )	C <sub>6</sub> H <sub>5</sub> ( <b>2a</b> )	40 ( <b>3ga</b> )

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

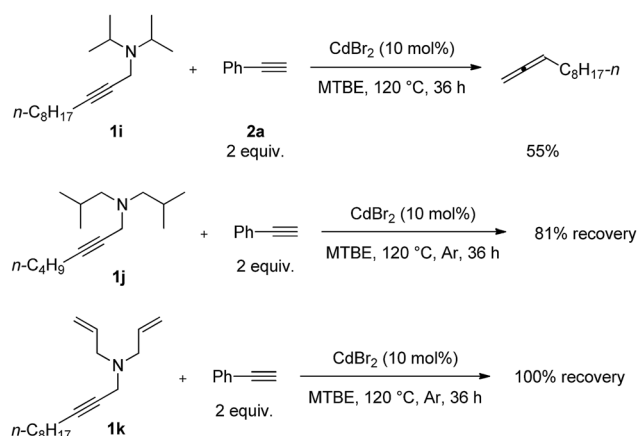
dioxane as the solvent, the reaction afforded **3fa** in a yield of 78%. Trimethylsilylacetylene (**2m**) and 1-hexyne (**2n**) are also compatible (Scheme 2).

For piperidine derivative **1h**, a larger catalyst-loading is required and toluene was also necessary since the reaction in

**Scheme 3** Catalytic  $\alpha$ -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.

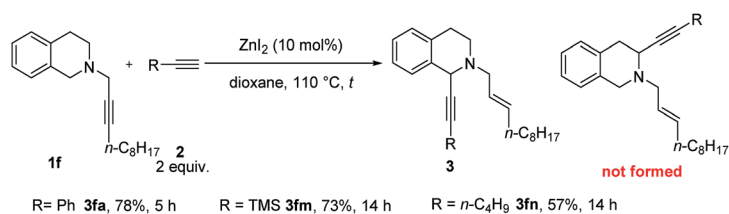
MTBE resulted in 13% yield of the target product with 89% recovery of **1h**. Unfortunately, morpholine did not work (Scheme 3).

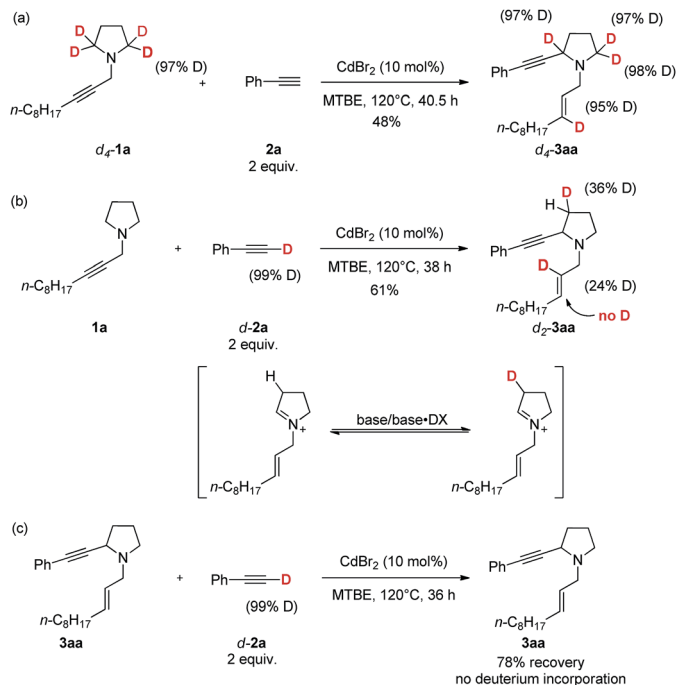
Furthermore, several non-cyclic amines were investigated. The reaction of diisopropylamine **1i** with phenylacetylene **2a** generated 55% yield of 1,2-undecadiene<sup>11–14</sup> (Scheme 4). When we applied diisobutylamine **1j** and diallylamine **1k** under the standard reaction conditions, such 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*<sub>4</sub>-**1a** was treated with **2a** under standard conditions to

**Scheme 2** The scope of catalytic  $\alpha$ -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.

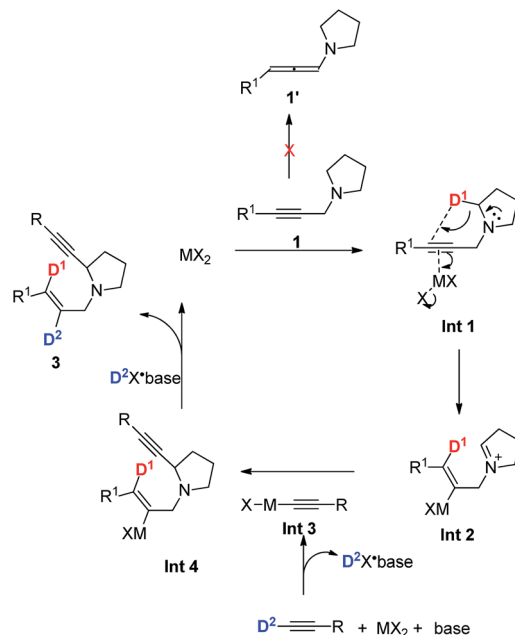
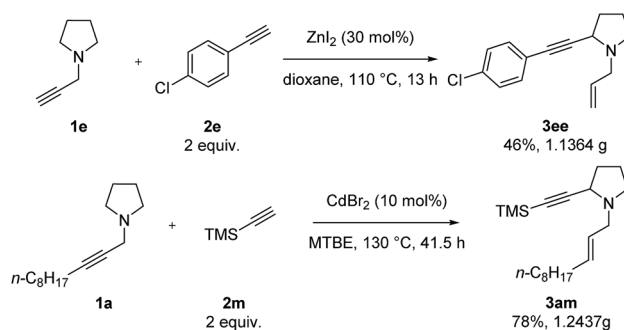
give  $d_4\text{-3aa}$  with 95% D incorporation, which reveals that the hydrogen at the  $\gamma$ -position of the allylic group comes from the  $\alpha$ -position of the amine unit (Scheme 5a). In addition, 24% of deuterium incorporation was observed in the 2-position of the  $N$ -allylic group in product  $d_2\text{-3aa}$  of the reaction between deuterium-labeled  $d_2\text{-2a}$  and  $\text{1a}$  (Scheme 5b). The control experiment of treating  $\text{3aa}$  with  $d_2\text{-2a}$  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  $\text{MX}_2$  to form **Int 1**, which would undergo *anti*-1,5-hydride transfer to form cationic **Int 2** in the  $E$  configuration.<sup>15</sup> Subsequently, 1-alkynyl cadmium species **Int 3**, *in situ* generated from terminal alkyne,  $\text{CdBr}_2$ , and amine, would react with the iminium ion **Int 2** to afford the corresponding  $\alpha$ -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  $\text{CdBr}_2$  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

Scheme 6 A plausible mechanism for the formation of **3**.

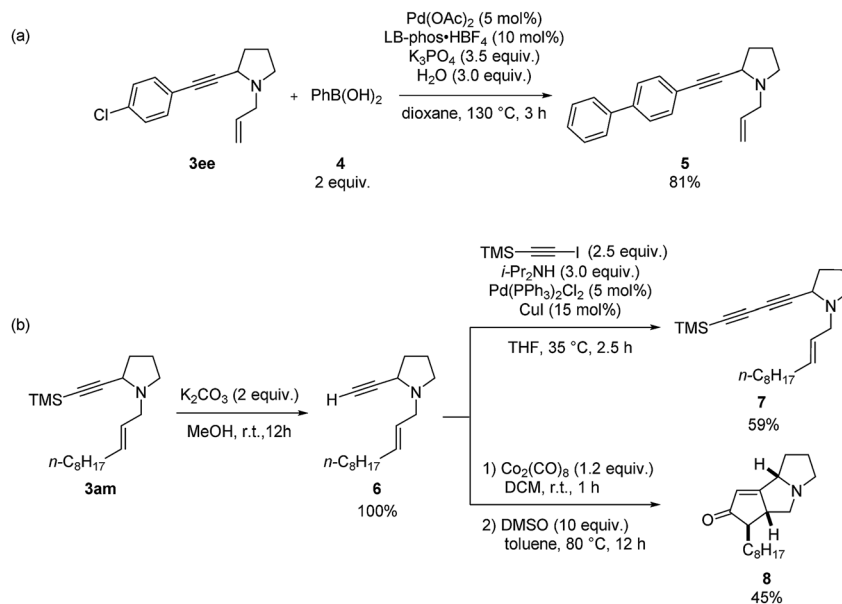
Scheme 7 Gram-scale synthesis.

phenyl boronic acid using  $\text{LB-Phos}\cdot\text{HBF}_4$ <sup>18</sup> affords **5** in 81% yield (Scheme 8a). Deprotection of the TMS group in **3am** with  $\text{K}_2\text{CO}_3$  in MeOH afforded enyne **6**, which may react with 1-trimethylsilyl ethynyl iodide to afford conjugated diyne **7** (Scheme 8b). Sequential treatment of **6** with 1.2 equiv. of  $\text{Co}_2(\text{CO})_8$  and 10 equiv. of DMSO afforded the Pauson–Khand reaction product **8** in 45% yield.<sup>19</sup>

## Conclusions

In conclusion, we have succeeded in developing a catalytic  $\alpha$ -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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