



# Dirhodium(II)-catalyzed [3 + 2] cycloaddition of *N*-arylamino-cyclopropane with alkyne derivatives

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## Full Research Paper

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### Keywords:

[3 + 2]; alkyne; cycloaddition; cyclopropanes; dirhodium catalysis; *N*-arylamino-cyclopropanes

*Beilstein J. Org. Chem.* **2019**, *15*, 542–550.

doi:10.3762/bjoc.15.48

Received: 13 October 2018

Accepted: 13 February 2019

Published: 25 February 2019

This article is part of the thematic issue "Cyclopropanes and cyclopropenes: synthesis and applications".

Guest Editor: M. Tortosa

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## Abstract

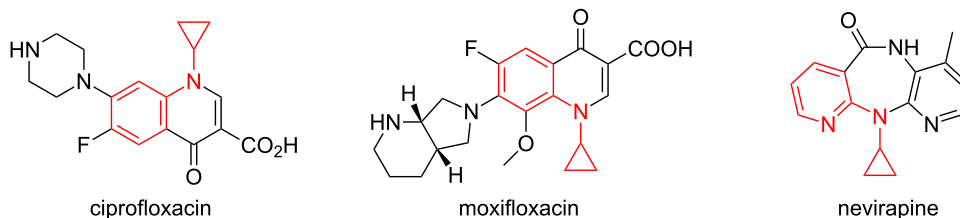
Dirhodium(II) complex-catalyzed [3 + 2] reactions between *N*-arylamino-cyclopropanes and alkyne derivatives are described. The cycloaddition products proved to be versatile synthetic intermediates. *trans*-Cyclic  $\beta$ -amino acids and derivatives thereof can be conveniently synthesized using this cycloaddition protocol.

## Introduction

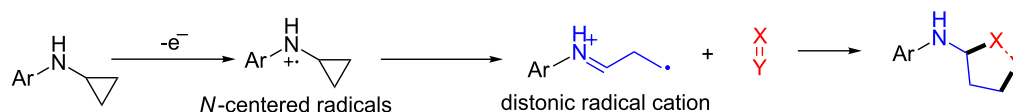
*N*-Arylamino-cyclopropanes **1** are important structural motifs for pharmaceuticals and are found especially in marketed fluoro-quinolone antibiotics [1], such as ciprofloxacin and moxifloxacin (Scheme 1), and reverse transcriptase inhibitors [2], such as nevirapine. Meanwhile, since **1** contains a three-membered ring with high tension [3–6] and a nitrogen prone to single-electron oxidation, ring opening readily occurs followed by *N*-centered radical formation. The generated distonic radical cation can be further trapped by an alkene, alkyne, or triplet oxygen to initiate radical cyclization (Scheme 1) [7–15]. Thus, as key synthons, this class of molecules may play an important role in organic synthesis during construction of a series of aminocyclic compounds. In fact, the synthesis of **1** has always

been a challenge [16,17]. Only recently an efficient synthesis method by arylation of cyclopropylamine has been developed and documented by Colacot et al. [16] and Stradiotto et al. [17], which has provided opportunities for further development of cycloaddition chemistry based on compound **1**. Zheng et al. [7] first reported on the [3 + 2] cycloaddition reaction of **1** with an alkene or alkyne mediated by visible light by the aid of the photocatalyst [Ru(bpz)<sub>3</sub>](PF<sub>6</sub>)<sub>2</sub>. Our group reported the metal catalyst itself, particularly the dinuclear rhodium complex (Rh<sub>2</sub>(II,II)), that efficiently catalyzes the ring opening of **1** to achieve cycloaddition with alkene substrates under an argon atmosphere [18]. During the reaction, no metal valence changes were observed. We proposed that Rh<sub>2</sub>(II,II) may coordinate

As structural motifs in marketed pharmaceuticals:



As key synthesis intermediates:



**Scheme 1:** Applications of *N*-arylamino cyclopropanes.

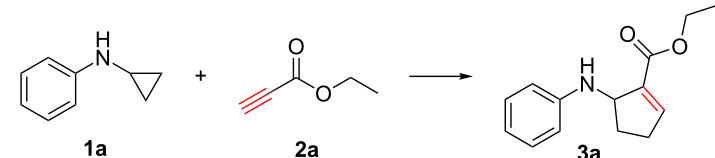
with the nitrogen in **1** to decrease the bond dissociation energy of N–H bonds, which may be beneficial to N-centered radical formation. However, due to the characteristics of the radical reaction, the resulting cycloaddition product mixtures have a low diastereoisomeric ratio, which increases the difficulty of separation and limits applications. In view of this, we applied alkyne derivatives as cycloaddition partners to make the developed methodology more applicable, as well as to investigate the possibility of chiral ring construction.

## Results and Discussion

Initially, phenylcyclopropylamine (**1a**) and ethyl propiolate (**2a**) were selected as substrates to study the cycloaddition in dichloromethane (DCM) with 1 mol % starting catalyst loading under the previously reported conditions [18]. In the absence of a catalyst, no cycloaddition product **3a** formed (Table 1, entry 1). We then studied the effect of common rhodium catalysts on the reactions. When 1 mol % Rh(I) catalyst  $[\text{Rh}(\text{CH}_2\text{CH}_2)_2\text{Cl}]_2$  was used (Table 1, entry 2), product **3a** was not detected. The commonly used Rh(III) catalyst  $[\text{Rh}(\text{Cp}^*)\text{Cl}_2]_2$  lead to a 72% yield of product **3a** (Table 1, entry 3). Next, the representative dirhodium(II) carboxylate such as  $\text{Rh}_2(\text{OAc})_4$ ,  $\text{Rh}_2(\text{TFA})_4$ ,  $\text{Rh}_2(\text{esp})_2$  and dirhodium(II) carboxamidate catalysts such as  $\text{Rh}_2(\text{cap})_4$ ,  $\text{Rh}_2(5S, R\text{-MenPY})_4$  were evaluated in the reaction.  $\text{Rh}_2(\text{OAc})_4$  created **3a** with a yield of 45% (Table 1, entry 4) and  $\text{Rh}_2(\text{TFA})_4$  improved the yield of **3a** to 52% (Table 1, entry 5). With the chelating catalyst  $\text{Rh}_2(\text{esp})_2$ , the yield further increased to 68% (Table 1, entry 6). Although the carboxamidate type  $\text{Rh}_2(\text{cap})_4$  resulted in a lower yield (Table 1, entry 7), the yield raised to 61% when  $\text{Rh}_2(5S, R\text{-MenPY})_4$  [19,20] was applied as the catalyst (Table 1, entry 8). Next, 0.1 mol % catalytic loading was tested in the reactions to investigate the effi-

ciency of the catalysts. Compared to the 1 mol % catalyst loading, the yield of **3a** dropped to 39 and 44% when  $\text{Rh}_2(\text{esp})_2$  and  $[\text{Rh}(\text{Cp}^*)\text{Cl}_2]_2$ , respectively, were used (Table 1, entries 9, 10), and kept practically consistent with  $\text{Rh}_2(5S, R\text{-MenPY})_4$  (Table 1, entry 11). These results indicate that the catalytic efficiency of  $\text{Rh}_2(5S, R\text{-MenPY})_4$  was the best of all the screened catalysts. Further solvent screening studies found the yields of **3a** obtained in non-coordinating solvents, such as DCM, hexane, toluene, and 1,2-dichloroethane (DCE), and weak coordinating solvents, such as 1,2-dimethoxyethane (DME), were similar (Table 1, entries 11–15). DCE was the best solvent, leading to a 67% yield of **3a**. Due to axial coordination of dirhodium(II) for a strong coordination solvent, the yield of the resulting cycloaddition product in *N,N*-dimethylformamide decreased to only 33% (Table 1, entry 16). Regrettably, though  $\text{Rh}_2(5S, R\text{-MenPY})_4$  is a chiral catalyst, the obtained cycloaddition products are racemic.

According to previous reports [16], after a series of arylcyclopropylamines **1** with different substituents were synthesized, the scope of **1** was then explored and the results are shown in Table 2. The data suggest that the electronic effect on the aromatic ring of **1** influences the results of the reactions. Compound **1** with electron-donating groups, such as methoxy, *tert*-butyl, and methyl groups, all reacted smoothly to produce products with good yields (Table 2, entries 1–3). The cyclization of substrate **1** containing electron-withdrawing groups at the aromatic substituent proceeded slowly, producing considerably lower yields of the corresponding products. For instance, multiple-substituted compound **1** (with a 3,5-disubstituted trifluoromethyl **1f**) generated product **3f** with a yield of 36% (88% brsm) after 24 h (Table 2, entry 5), but 3,5-dimethyl compound

**Table 1:** Catalyst screening and optimization of reaction conditions<sup>a</sup>.


Reaction scheme showing the cycloaddition of **1a** (N-cyclopropylbenzylamine) and **2a** (ethyl propargylcarbamate) to form **3a** (ethyl 2-(cyclopropylamino)cyclopent-1-enecarboxylate).

Chemical structures of catalysts shown:

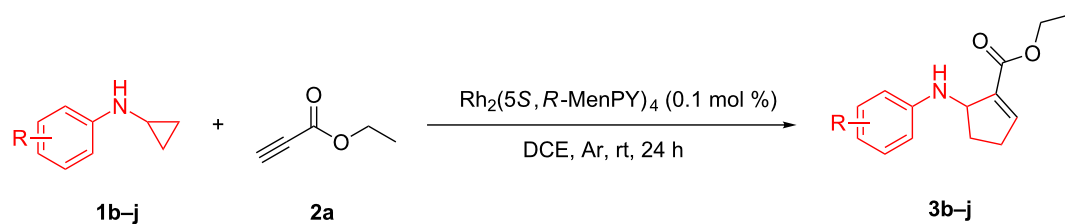
- $\text{Rh}_2(\text{esp})_2$
- $\text{Rh}_2(\text{OAc})_4$
- $[\text{Rh}(\text{Cp}^*)\text{Cl}_2]_2$
- $[\text{Rh}(\text{CH}_2\text{CH}_2)_2\text{Cl}]_2$
- $\text{Rh}_2(\text{TFA})_4$
- $\text{Rh}_2(\text{cap})_4$
- $\text{Rh}_2(5S, R\text{-MenPY})_4$

Entry	Conditions	Solvent	Yield <sup>b</sup> (%)
1	no catalyst	DCM	NR
2	$[\text{Rh}(\text{CH}_2\text{CH}_2)_2\text{Cl}]_2$	DCM	ND
3	$[\text{Rh}(\text{Cp}^*)\text{Cl}_2]_2$	DCM	72
4	$\text{Rh}_2(\text{OAc})_4$	DCM	45
5	$\text{Rh}_2(\text{TFA})_4$	DCM	52
6	$\text{Rh}_2(\text{esp})_2$	DCM	68
7	$\text{Rh}_2(\text{cap})_4$	DCM	40
8	$\text{Rh}_2(5S, R\text{-MenPY})_4$	DCM	61
9 <sup>c</sup>	$\text{Rh}_2(\text{esp})_2$	DCM	39
10 <sup>c</sup>	$[\text{Rh}(\text{Cp}^*)\text{Cl}_2]_2$	DCM	44
11 <sup>c</sup>	$\text{Rh}_2(5S, R\text{-MenPY})_4$	DCM	58
12 <sup>c</sup>	$\text{Rh}_2(5S, R\text{-MenPY})_4$	DCE	67
13 <sup>c</sup>	$\text{Rh}_2(5S, R\text{-MenPY})_4$	hexane	59
14 <sup>c</sup>	$\text{Rh}_2(5S, R\text{-MenPY})_4$	toluene	59
15 <sup>c</sup>	$\text{Rh}_2(5S, R\text{-MenPY})_4$	DME	60
16 <sup>c</sup>	$\text{Rh}_2(5S, R\text{-MenPY})_4$	DMF	33

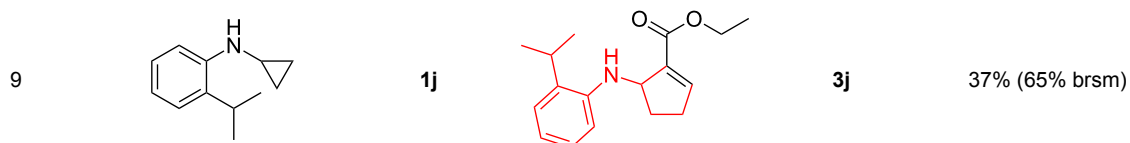
<sup>a</sup>Reaction conditions: **1a** (0.5 mmol, 0.2 M in degassed solvent), **2a** (2.5 mmol), catalyst (1 mol %) under argon at room temperature for 24 h unless otherwise noted. <sup>b</sup>Isolated yield. <sup>c</sup>0.1 mol % of catalyst. esp =  $\alpha, \alpha, \alpha', \alpha'$ -tetramethyl-1,3-benzenedipropionate, cap = caprolactamate, 5S, R-MenPY = (S)-(1R,2S,5R)-2-isopropyl-5-methylcyclohexyl 2-oxopyrrolidine-5-carboxylate, NR = no reaction, ND = not detected.

**1d** afforded the desired product **3d** with an excellent yield of 91% (Table 2, entry 3). We reasoned the electron-withdrawing groups on the arene increased the nitrogen–hydrogen bond dissociation energy ( $\text{BDE}_{\text{N-H}}$ ) of compound **1** [21], decreasing the rate of ring opening. Substrates **1i,j** containing hindered substituents lead to low conversion of the substrates, producing only poor yields of products **3i,j** (Table 2, entries 8 and 9), which implied that steric hindrance greatly influenced the reactions.

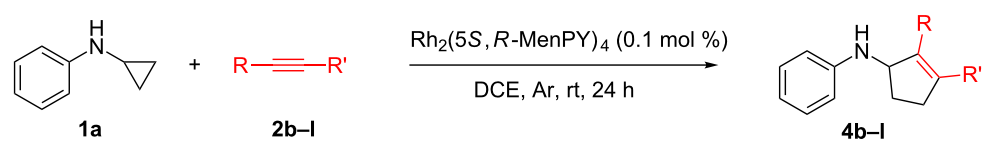
Next, we surveyed the different alkyne substrates **2** for cycloaddition under optimized reaction conditions. The terminal alkynes with electron-withdrawing groups reacted smoothly to produce the desired products, while alkyl-substituted terminal aldehydes, such as pent-1-yne (**2b**, Table 3, entry 1), did not produce the cycloaddition product [22–24]. *tert*-Butyldimethylsilyl-protected propargyl alcohol **2c** had a greatly reduced reactivity (Table 3, entry 2) and the obtained yield was less than 10%. For aromatic terminal alkynes, moderate yields

**Table 2:** Substrate scope of *N*-arylamincyclopropanes<sup>a</sup>.

Entry	Substrate	Product	Yield <sup>b</sup>
1			59%
2			78%
3			91%
4			85%
5			36% (88% brsm)
6			67%
7			24% (52% brsm)
8			20% (67% brsm)

**Table 2:** Substrate scope of *N*-arylamincyclopropanes<sup>a</sup>. (continued)

<sup>a</sup>Reaction conditions: **1b–j** (1 mmol, 0.2 M in degassed solvent), **2a** (5 mmol), catalyst (0.1 mol %) at room temperature for 24 h unless otherwise noted. <sup>b</sup>Isolated yield; brsm = based on recovered starting material.

**Table 3:** Substrate scope of alkyne derivatives<sup>a</sup>.

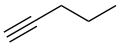
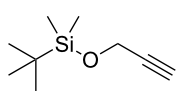
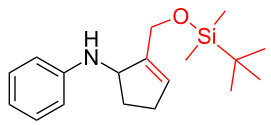
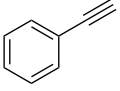
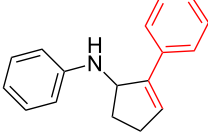
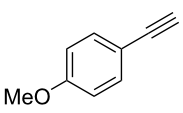
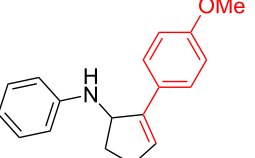
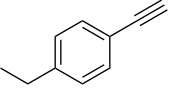
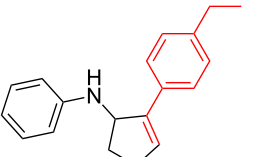
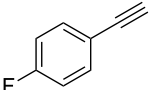
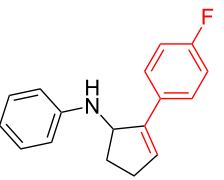
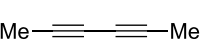
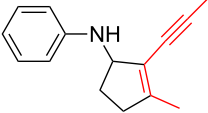
Entry	Substrate	Product	Yield <sup>b</sup> (%)
1	 <b>2b</b>	N.D.	<b>4b</b> N.R.
2	 <b>2c</b>	 <b>4c</b>	<10
3	 <b>2d</b>	 <b>4d</b>	65
4	 <b>2e</b>	 <b>4e</b>	64
5	 <b>2f</b>	 <b>4f</b>	65
6	 <b>2g</b>	 <b>4g</b>	64
7	 <b>2h</b>	 <b>4h</b>	31

Table 3: Substrate scope of alkyne derivatives<sup>a</sup>. (continued)

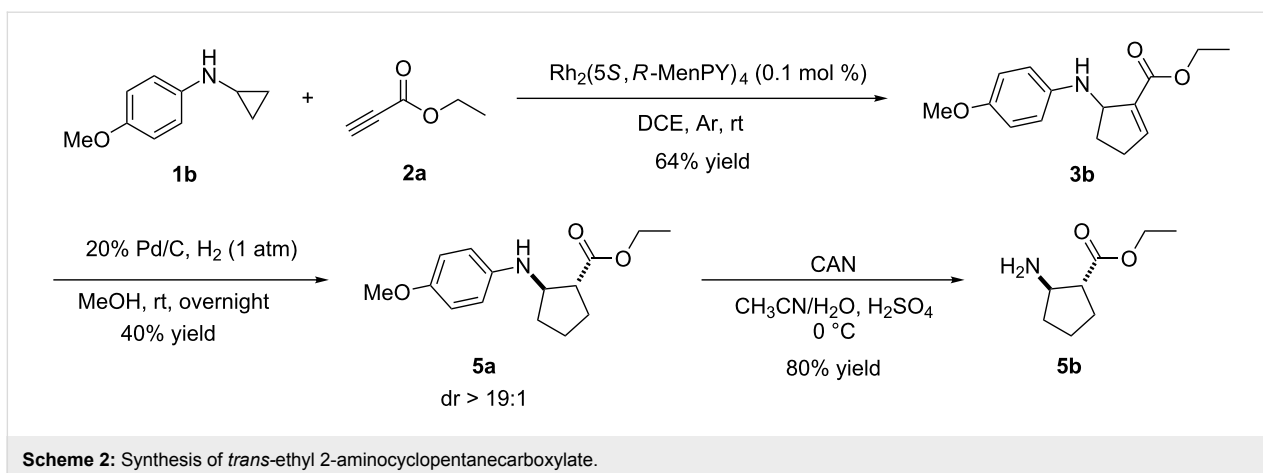
8 <sup>c</sup>		2i		4i <sup>d,e</sup>	45 (17:83) <sup>f</sup>
9		2j		4j	41 (30:70) <sup>f</sup>
10		2k		4k	44
11 <sup>c</sup>		2l		4l <sup>d</sup>	40

<sup>a</sup>Reaction conditions: **1a** (1 mmol, 0.2 M in degassed solvent), **2b–l** (5 mmol), catalyst (0.1 mol %) at room temperature for 24 h unless otherwise noted. <sup>b</sup>Isolated yield. <sup>c</sup>*N*-Arylamino-cyclopropane **1d** was used instead of **1a**. <sup>d</sup>Major isomer shown. <sup>e</sup>Isomer ratio 89:11. <sup>f</sup>Diastereoisomeric ratios (*cis/trans*) were determined by <sup>1</sup>H NMR spectroscopy of the crude products.

(Table 3, entries 3–6) were obtained regardless of the electron-donating or electron-withdrawing groups, indicating the electronic effect on the aromatic ring of **2** had little effect on the results of the reactions. Due to the decrease in the activity of the alkyne, the conjugated 2,4-hexadiyne (**2h**) produced a poor yield of only 31% (Table 3, entry 7). To study the chemical selectivity of the reaction, we examined conjugated alkyne substrates. For 2-methylbut-1-en-3-yne (**2i**) containing both terminal alkenes and alkynes, the activity of the olefin was greater than that of the alkyne, which favors alkene cycloaddition products with a ratio of 89:11. The observed selectivity of product **4i** is similar to that previously reported [11] (Table 3, entry 8), indicating the results of this type of reaction are mainly determined by the stability of the free radical intermediate during the reaction. Further investigation revealed cycloaddition preferentially proceeded with the terminal alkene or alkyne. Product **4j** was obtained with a 41% yield due to cycloaddition with an olefin group in **2j** (Table 3, entry 9). When **2k** was applied in the reaction, the addition product was obtained with a yield of

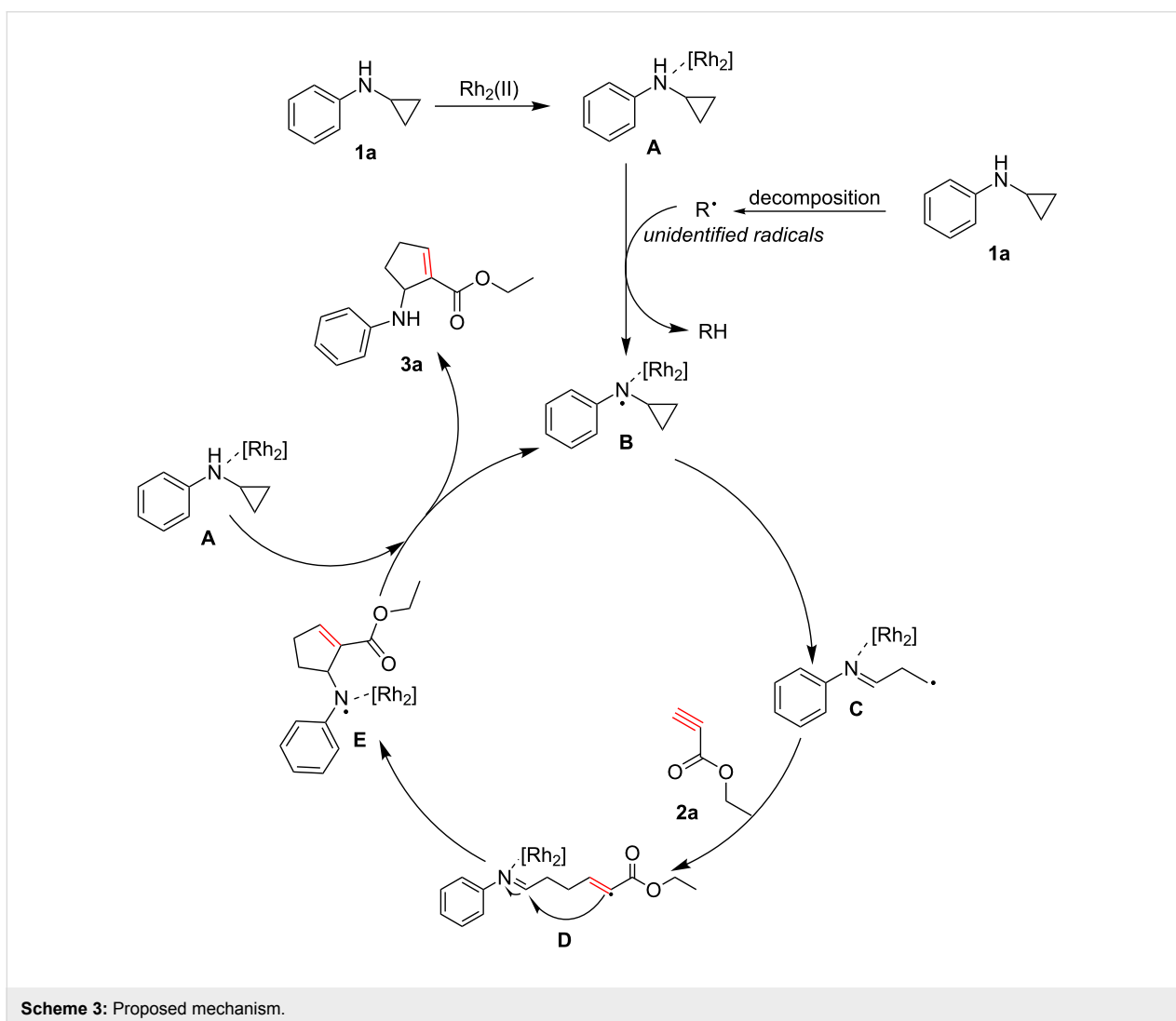
44% with the alkyne group being involved in the reaction (Table 3, entry 10). The reaction with **2l** mainly produced 1,3-diene product **4l** with a yield of 40% (Table 3, entry 11). In addition, we also examined some alkynes containing heterocycles, such as 3-ethynylpyridine and 2-ethynylthiophene. Because the heteroatoms were axially tightly coordinated to the dirhodium(II) catalyst, coordination of the cyclopropylamine with the dirhodium(II) catalyst was inhibited, resulting in no cycloaddition reaction occurring.

To explore the synthetic practicality of this transformation, racemic compound **3b** resulting from **1b** and **2a** was reduced using hydrogen and palladium on carbon (Scheme 2). It is interesting to note that only *trans*-**5a** was obtained and no *cis* product formed. After further removal of the *para*-methoxyphenyl (PMP) group using ammonium cerium nitrate (CAN), the cyclic  $\beta$ -amino acid ester **5b** was obtained with a yield of 80%. Cyclic  $\beta$ -amino acids and derivatives have good bioactivity and are widely used as key synthetic intermediates in biomedical



research [25–29]. Thus, based on this cycloaddition protocol, a convenient strategy can be established to synthesize *trans*-cyclic  $\beta$ -amino acids.

The mechanism of the [3 + 2] cycloaddition reaction of **1a** and **2a** is similar to that previously reported [18] (Scheme 3). The distonic radical cation **C** resulting from cyclopropane ring



opening reacts with alkyne substrate **2a** generating radical **D**. The intermediate radical **D** yielded **E** through intramolecular radical addition. After hydrogen atom transfer (HAT) from complex **A**, the desired product is obtained with regeneration of the N-centered radical **B**, which continues to catalyzing the reaction.

## Conclusion

In conclusion, we report on the [3 + 2] cycloaddition reaction catalyzed by dirhodium(II) based on arylcyclopropylamine, which broadens the scope of this method to the alkynyl group. This study demonstrated that this cycloaddition method has potential synthetic practicality by providing a convenient way to synthesize *trans*-cyclic  $\beta$ -amino acid derivatives. Further application of this method with other cycloaddition partners and asymmetric synthesis of the chiral ring with the help of chiral auxiliaries are currently underway.

## Experimental

**General procedure for the [3 + 2] annulation of cyclopropyl-anilines:** An oven-dried Schlenk tube equipped with a stirring bar was charged with  $\text{Rh}_2(5S,R\text{-MenPY})_4$  (0.1 mol %), alkyne (5.0 mmol), and dry DCE (5 mL). The tube was degassed through three freeze–pump–thaw cycles. After evacuating and backfilling the tube with argon three times, cyclopropylamine (1 mmol) was added. The reaction mixture was stirred at room temperature for 24 hours. After the reaction was complete, the mixture was concentrated and the residue was purified by flash chromatography to obtain the desired allylic amine.

## Supporting Information

### Supporting Information File 1

Experimental procedures, compound characterization, and NMR spectra.

[<https://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-15-48-S1.pdf>]

## Acknowledgements

We are grateful for financial support from National Science Foundation of China (Grant No. 21272162).

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