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Stereoselective construction of fused cyclopropane from ynamide and its application to synthesis of small drug candidate molecules

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ABSTRACT

Herein, we report the development of an asymmetric intramolecular cyclopropanation reaction under silver catalysis. The strategy is based on diazo-free silver–carbene generation, providing γ-lactam fused cyclopropane in an enantioenriched form. The ring system of the product is frequently encountered in bioactive molecules and pharmaceuticals. To highlight the utility of this method, the fused cyclopropane was converted into drug candidate molecules in short steps. In addition, computational investigations were performed to elucidate the reaction pathway. The computation based on density functional theory rationalized the experimentally observed chemoselectivity between the desired cyclopropanation and overoxidation process.

Introduction

Azabicyclo[3.1.0]hexane variants with an aryl group at the 1-position exhibit diverse biological activities, and thus have an immense potential for pharmaceutical applications (Fig. 1). For instance, cycloclavine [1] acts as a 5-HT2C receptor antagonist and cyproximide exhibits activity as a central nervous system depressant, and is used as a tranquilizing agent, hypnotic agent, or muscle relaxant. Therefore, continuous endeavor has been directed toward constructing nitrogen-containing bicycles. Recently, Cramer et al. reported an asymmetric synthesis protocol for the pivotal scaffold via palladium(0)-catalyzed intramolecular C—H functionalization of cyclopropane [2,3].

Metal–carbenes are reactive species that can cause unique reaction manifolds, such as C—H insertion [4], cyclopropanation [6] of olefins and arenes, or ylide formation. Thus far, ruthenium [7], copper [8], and rhodium [9] catalysts have been used to construct heterocyclic systems through intramolecular cyclopropanation reactions using a diazo substrate as the carbene precursor (eq 1, Scheme 1). These methods have also been applied to asymmetric reactions using chiral complexes [10]. While these metal–carbene reactions have proven to be a powerful strategy for efficient molecular synthesis, some diazo compounds are potentially explosive; therefore, advantageous alternative methods are in demand. Indeed, considerable attention has been paid to metal–carbene generation under diazo-free conditions [11]. Among the possible methods, a combination of ynamide compounds with mild oxidants is easy to apply to generate metal–carbene species because of the stability and accessibility of ynamides [12].

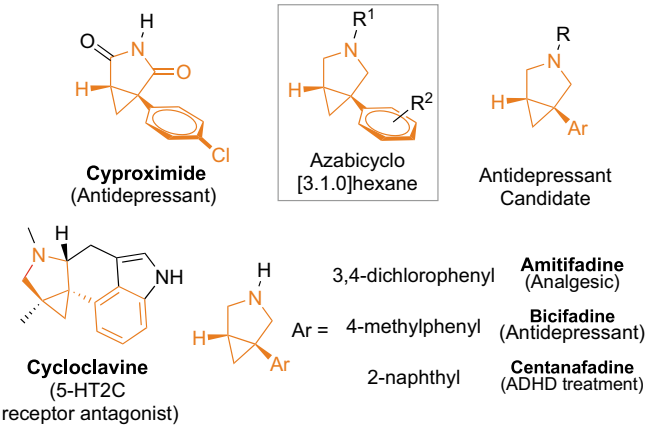

Fig. 1. Biologically active molecules with the 3- azabicyclo[3.1.0]hexane scaffold.

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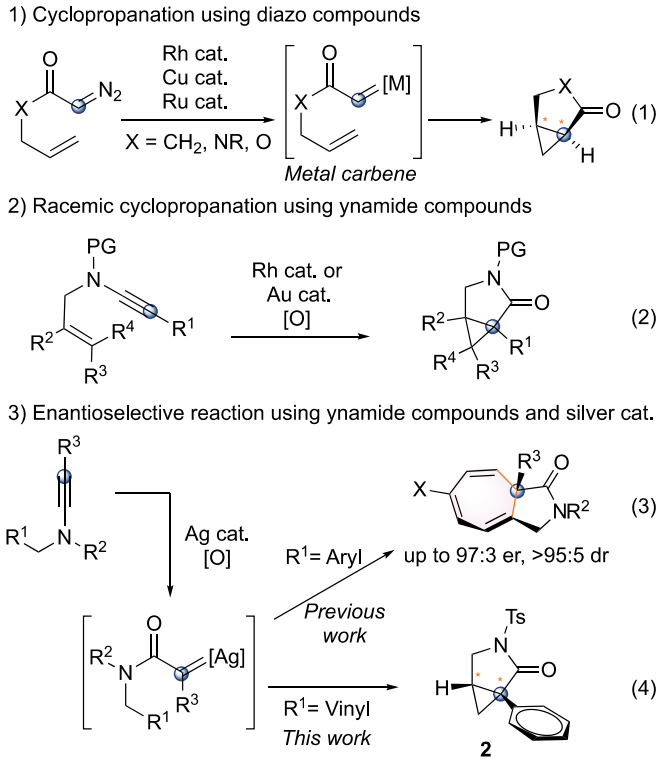


Scheme 1. Intramolecular olefin cyclopropanation for constructing a bicyclic system.

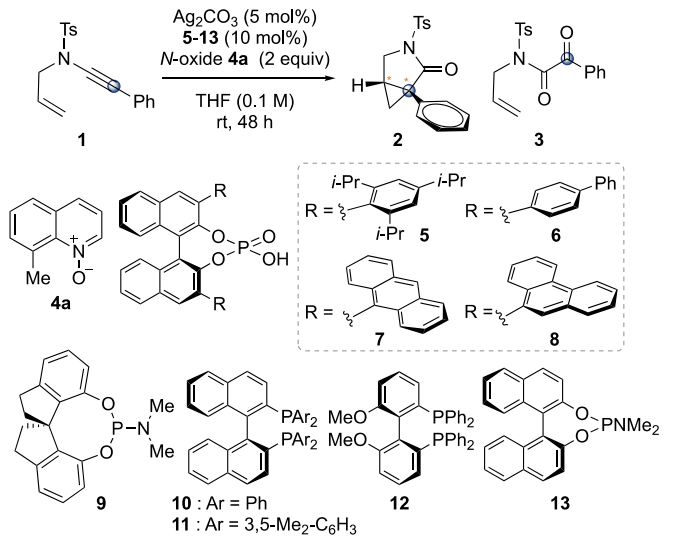
As part of our ongoing investigation to develop metal–carbene chemistry [12,14], we previously reported asymmetric intramolecular dearomatization [15] of nonactivated arenes with ynamides (eq 3) [16]. The silver-catalyzed reaction proceeds via enantioselective arene cyclopropanation [17] followed by electrocyclization. Based on the precedents and our previous studies, we anticipated that the synthesis of an azabicyclo[3.1.0]hexane derivative in an asymmetric format would be feasible based on the silver–carbene reaction. In fact, associated methods for synthesizing azabicyclo [3.1.0]hexane variants have been reported using an ynamide. In 2013, Xu and Tang used a rhodium(I) complex and 3,5-dichloropyridine *N*-oxide to generate Rh–carbene species (eq 2) [18]. A reaction pathway through carbene-mediated concerted cyclopropanation was proposed. Li et al. also reported a related transformation using ynamide with a gold catalyst in the same year [19]. Interestingly, a mechanism that does not involve carbene species was proposed. The two similar but distinct approaches afforded the azabicyclo[3.1.0]hexane ring system in a racemic format; since then, asymmetric synthesis from an ynamide has not been established.

In this context, we describe the development of a cyclopropanation reaction using an ynamide and a chiral silver catalyst to assemble azabicyclo[3.1.0]hexane derivatives in an enantioenriched form. The product was converted into bioactive products in short steps. Quantum computations for mechanistic studies were also conducted to shed light on the reaction pathway.

Results and discussion

First, we prepared an ynamide (**1**) with an allyl group as a substrate to develop asymmetric cyclopropanation (Table 1). The chiral catalyst system was examined by in-situ generation of a chiral catalyst using silver carbonate and phosphoric acids

Table 1
Survey of chiral catalysts.[a)]



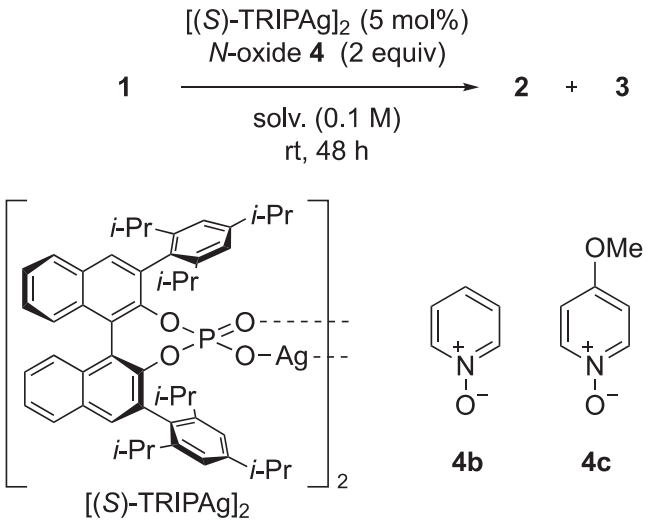
Entry	**5**–**13** (mol%)	Yield (%) **2**	**3**	er of **2**
1	**5** (10)	50	5	76:24
2	**6** (10)	58	32	46:54
3	**7** (10)	4	8	31:59
4	**8** (10)	4	2	61:39
5[b)]	**9** (20)	27	41	46:54
6[b)]	**10** (20)	20	28	50:50
7[b)]	**10** (10)	36	28	50:50
8[b)]	**11** (20)	14	10	48:52
9[b)]	**11** (10)	34	33	50:50
10[b)]	**12** (20)	23	13	53:47
11[b)]	**12** (10)	48	40	51:49
12[b)]	**13** (20)	28	16	54:46

a) Reactions were performed at 0.1 mmol scale.
b) $AgNTf_2$ (20 mol%) was used instead of Ag_2CO_3.

[20]. The reaction of **1** with **5** and *N*-oxide **4a** in THF solvent at room temperature provided the desired azabicyclo[3.1.0]hexane **2** in 50% yield with an enantiomeric ratio (er) of 76:24, as well as α-keto amide **3** through an overoxidation process (entry 1). A survey of several chiral phosphoric acids did not improve the enantioselectivity of **2** (entries 2–4). With reference to the previous literature regarding asymmetric reactions of silver–carbenes [21], a catalyst system consisting of chiral phosphine/$AgNTf_2$ was also investigated. Unfortunately, reactions using phosphine or phosphoramidite ligands gave unsatisfactory results (entries 5–12).

The reaction conditions were further optimized using a preformed [(*S*)-TRIPAg]$_2$ catalyst (Table 2) [16]. The reaction using [(*S*)-TRIPAg]$_2$ produced **2** in an enhanced yield with a comparable level of enantioselectivity (entry 1 in Table 2 vs. entry 1 in Table 1). Less sterically hindered oxidants **4b** and **4c** decreased the yield of **2** (32% and 36% yield, entries 2 and 3, respectively). In light of the outcome in entries 4 and 5, two equivalents of **4a** were deemed sufficient for this transformation. Subsequent solvent screening revealed that chlorobenzene was the best reaction medium (entries 6–9). The use of MS3A showed a slight positive impact on the enantioinduction, providing **2** in 85% yield with 83:17 er (entry 10).

Table 2
Optimization of reaction conditions.[a)]



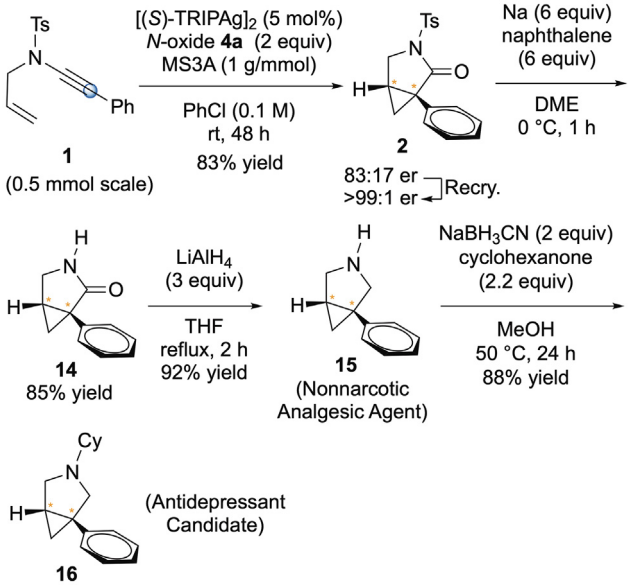
Entry	*N*-oxide	solv.	Yield (%) **2**	**3**	er of **2**
1	**4**	THF	80	14	79:21
2	**4b**	THF	32	7	77:23
3	**4c**	THF	36	11	75:25
4[b)]	**4a**	THF	34	6	77:23
5[c)]	**4a**	THF	80	20	75:25
6	**4a**	DCE	66	25	75:25
7	**4a**	Et_2O	66	34	83:17
8	**4a**	Toluene	54	34	80:20
9	**4a**	PhCl	82	18	78:22
10[d)]	**4a**	PhCl	85	15	83:17

[a)] Reactions were performed at 0.1 mmol scale.
[b)] *N*-oxide (1.0 equiv).
[c)] *N*-oxide (4.0 equiv).
[d)] MS3A (1 g/mmol) was used.

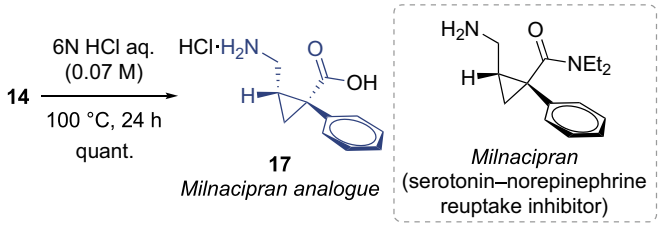
The practicality of the developed strategy was demonstrated through the following synthetic applications. Reaction under the optimum conditions at 0.5 mmol scale showed the same results as in entry 10 in Table 2 (Scheme 2). After recrystallization of **2** from MeOH to enhance the optical purity (>99:1 er, 32% yield), the reductive cleavage of the Ts group using Na/-naphthalene yielded the corresponding secondary amide **14**. The transformation of **14** into the pyrrolidine variant and *N*-alkylation produced bioactive molecules **15** and **16** in good yields [22]. The absolute configuration of **16** was confirmed by comparing the value of optical rotation with that of the reported compound [21c].

The ring opening reaction of **14** by acid treatment provided conformationally restricted γ-amino butyric acid (GABA) derivative **17** in a quantitative yield (Scheme 3).

The developed reaction process was analyzed on the basis of computational quantum mechanical modeling (Fig. 2). In previous studies using ynamides and gold catalysts reported by Li et al., interesting pathways were proposed; the 6-*endo*-dig cyclization mode from ynamide or 6-*endo*-trig cyclization mode from the vinyl metal intermediate (**SM** → **CPA**, **CP2** → **CP3′**, respectively, in this case). However, these elemental reaction pathways were not observed on the computed potential energy surface when using a silver catalyst. Instead, the silver–carbene species, **CP3** (C = Ag, 2.09 Å), was generated through the nucleophilic addition of 8-methylquinoline oxide followed by the elimination of 8-methylquinoline with reasonable activation barriers (+10.41, 8.65 kcal/mol, **TS1**, **TS2**, respectively). A concerted intermolecular cyclopropanation (**TS3**) from **CP3** occurred, producing the desired bicyclic molecule **PRO2** concomitant with catalyst regeneration. The overoxidation process was also computed to gain mechanistic insight into the chemoselectivity. The second addition of 8-methylquinoline oxide into **CP3** provided $\mathbf{CP_{EO}}$, which evolved into **PRO3** via $\mathbf{TS_{EO2}}$. The slightly favorable energy gap ($\Delta\Delta G^{\ddagger}$ = 0.87 kcal/mol) between **TS4** and $\mathbf{TS_{EO1}}$ could explain the experimentally observed product selectivity.



Scheme 2. Synthesis of drug candidates.



Scheme 3. Synthesis of a pharmaceutically relevant molecule.

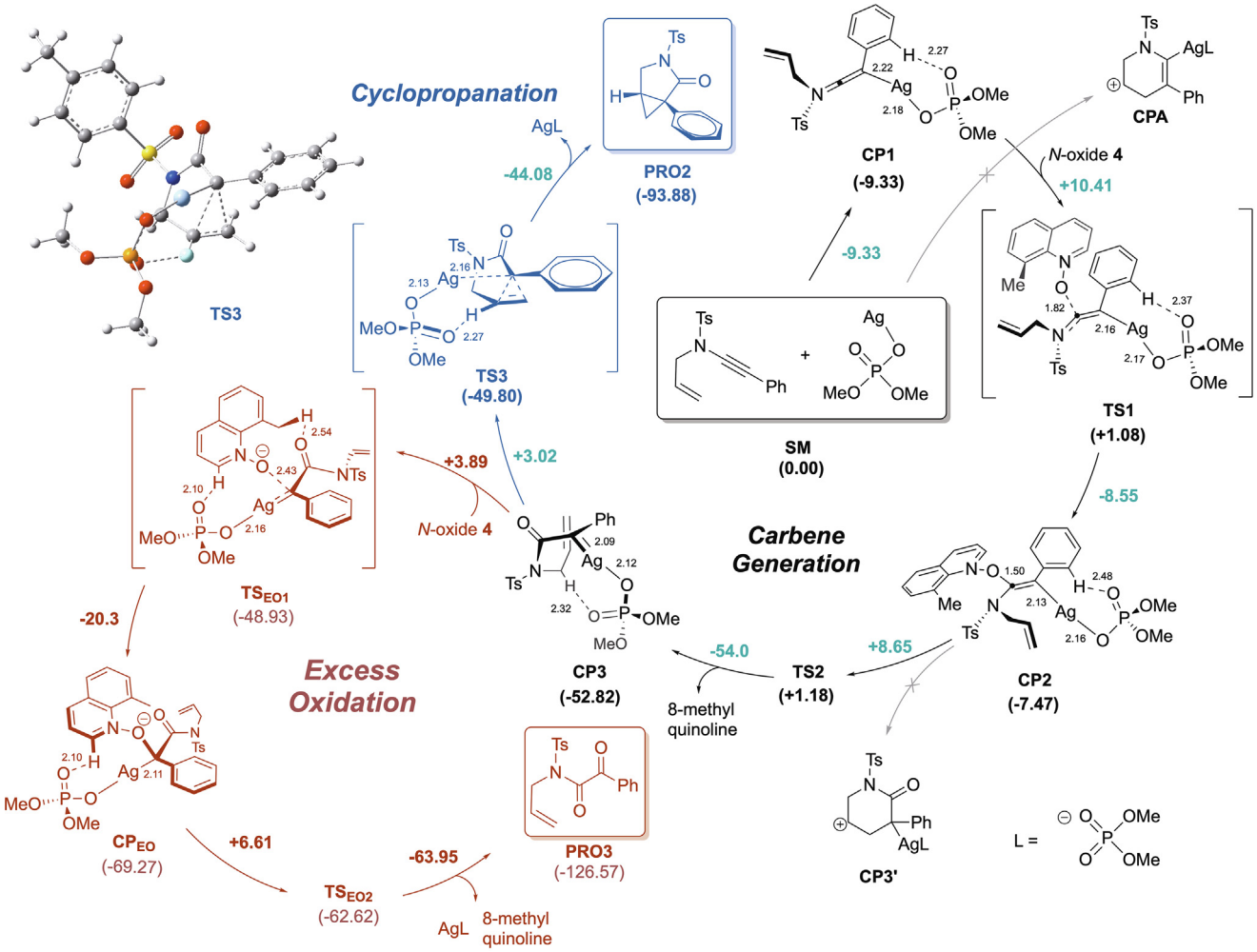


Fig. 2. Computed reaction route for the cyclopropanation and side reaction based on the RMN15/SDD (Ag)/6–311++G**//RB3LYP/LANL2DZ(Ag)/6–31G* levels of theory. Bond lengths are shown in Å. ΔG: kcal/mol.

Conclusions

A stereoselective olefin cyclopropanation reaction was developed without using a diazo compound as an advantageous alternative method. After recrystallization to increase the optical purity, the obtained bicyclic lactam was transformed into pharmaceutically relevant molecules in enantiopure forms via simple operations. Computational studies indicated that the reaction proceeds through silver–carbene generation followed by concerted cyclopropanation. This process is distinct from the previously proposed mechanism using a group 11 coinage metal complex [19]. Further methodology development based on the diazo-free strategy is underway by our group.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2021.152985.

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