Silver-Mediated Organic Transformations of Propargylamines to Enones, α-Thioketones, and Isochromans

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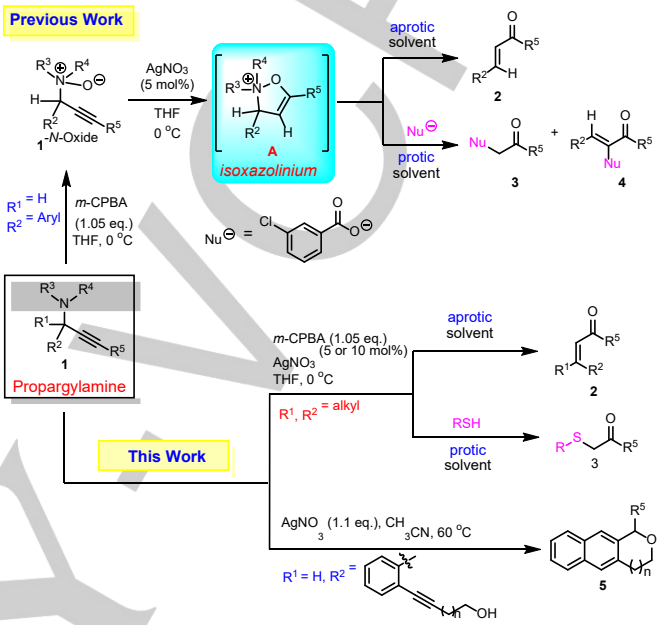
Abstract: This work describes a series of silver-mediated transformations of propargylamines to provide diverse patterns of products, including enones, *α*-thioketones, and isochromans. A variety of enone derivatives were obtained by silver-catalyzed transformation of propargylamines with 3-chloroperoxybenzoic acid (*m*-CPBA) in aprotic solvent. In contrast, when the reactions were carried out in protic solvent with *N*-Boc-L-cysteine methyl ester (Boc = tert-butoxycarbonyl) as nucleophile, *α*-thioketones were obtained. Moreover, the first silver-mediated cascade cyclization of alkynyl alcohol-linked propargylamines giving isochroman scaffolds was also described in this paper.

Introduction

Silver-mediated transformation has emerged as an important approach for organic synthesis, owing to its high selectivity, compatibility, mild reaction conditions and cost-effectiveness compared to other expensive transition metals.[1-3] Silver is effective to activate multiple bonds, such as alkenes, alkynes, and allenes by coordination. However, silver has only been used as either Lewis acids or co-catalysts for a long time. Recently, organic chemists have started to investigate the use of silver for promoting many types of organic transformations, which can be performed under mild reaction conditions.[3]

Propargylamines are versatile building blocks in organic synthesis and ubiquitous in a variety of natural products and pharmaceutical molecules.[4] For instance, propargylamines have been widely used as substrates in the synthesis of heterocyclic compounds bearing nitrogen atoms, such as pyrroles,[4c] pyrrolidine,[4b] pyrrolophane,[4d] aminoindolizine,[4g] 2-aminoimidaozels,[4j] oxazolidinones.[4g] During the past decade, our group has been keen on the synthesis and reactivity discovery of propargylamines.[5, 6] As part of our continuous interests in this area, we aim to explore the synthetic utility and to access molecular diversity from easily accessible propargylamines via silver catalysis.

Recently, we have disclosed a novel silver-catalyzed transformation of propargylamines to provide enones and acyloxy ketones *via* propargylic amine *N*-oxide in one pot process under mild reaction conditions.[6c] Mechanistic studies



Scheme 1. Silver-mediated transformations of propargylamines to provide diverse products.

indicated that *in situ* generated isoxazolinium ion **A** is the key intermediate which could convert to enone **2** in an aprotic solvent and to ketone **3** and enone **4** in a protic solvent (Scheme 1). This reaction scope has been explored by using propargylamines with different combinations of aldehydes (R^1 was H), amines and alkynes. To further demonstrate the substrate scope for the reaction, we designed and synthesized a series of sterically hindered propargylamines with adjacent quaternary carbon center ($R^1 \neq H$), which might be obtained through gold-catalyzed three-component coupling reaction by using ketones couple with amines and alkynes. Furthermore, to build up the molecular complexity, a class of alkynyl alcohol-linked propargylamines was also designed and synthesized to explore the silver-mediated transformation. Herein, we report a series of silver-mediated synthetic strategies from propargylamines to build molecular complexity and to provide a variety of structural scaffolds: enones, α-thioketones and isochromans (Scheme 1).

Results and Discussion

In contrast to the well-established three-component coupling reaction of aldehydes, amines, and alkynes to give secondary propargylamines, the present three-component coupling reaction of ketones that would lead to the formation of congested tertiary propargylamines. The steric-demanding propargylamines have been less investigated because ketones are less electrophilic than aldehydes and more steric hindered.[7] To date, only a few

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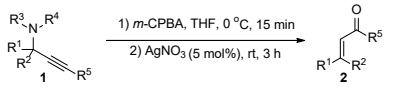
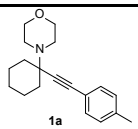
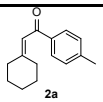
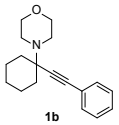
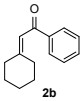
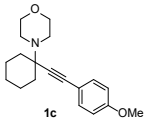
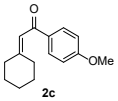
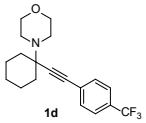
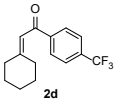
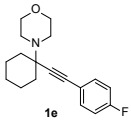
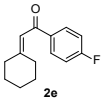
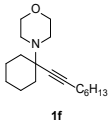
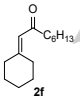
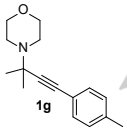
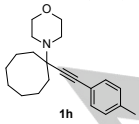
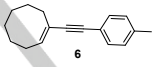
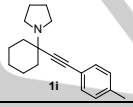
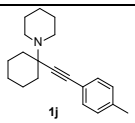
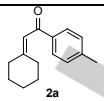
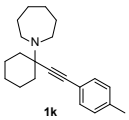
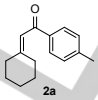
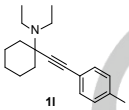
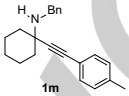
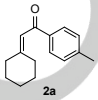
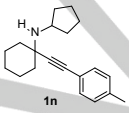
methods have been developed for the direct three-component coupling reaction of ketones, amines, and alkynes.[8] The existing protocols suffer from limitations, such as high temperature or the requirement of microwave irradiation. In an effort to find a suitable method to generate fully substituted propargylamines, we employed a novel C,O-chelated BINOL–gold(III) complex developed in our group[9] to explore the gold-catalyzed three-component coupling reaction of ketones, amines, and alkynes. To our pleasure, both cyclic and acyclic ketones can be used to obtain the corresponding propargylamines in good yields (For details, see the supporting information, Table S1).

Table 1. Scope of silver-catalyzed transformation of propargylamines **1** to enone **2**. [a]



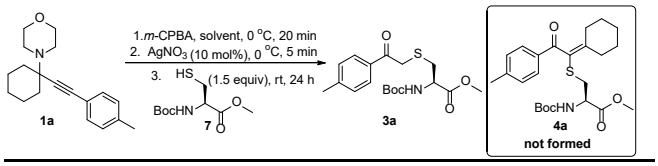
Entry	Substrate	Product	Yield of **2** (%)[b]
1			83
2			88
3			80
4			73
5			83
6			83
7			72
8			46
9			79
10			91
11			61
12			24
13			65
14			29

[a] Reactions were performed with **1** (0.5 mmol), *m*-CPBA (0.55 mmol), and $AgNO_3$ (0.025 mmol, 5 mol%) in THF (5 mL). [b] Isolated yield.

Next, we examined the reaction scope using the optimized conditions in THF. To our delight, the sterically hindered propargylamines (**1a-1n**) gave the enone products **2** smoothly. The results were summarized in Table 1. This reaction provides a straightforward entry to a variety of enone derivatives in moderate to good yields. When R^1, R^2 were cyclohexyl, R^3, R^4 were morpholine, and R^5 could vary from aryl with electron-withdrawing or electron-donating groups to alkyl group, the desired products **2a-2f** were obtained in high yields (entries 1-6, Table 1). Notably, when acyclic methyl was employed as R^1 and R^2, enone **2g** was also smoothly obtained in 72% isolated yield (entry 7, Table 1). However, cyclooctyl substrate **1h** did not provide the desired enone product**,** and it gave enyne product **6** in 46% yield (entry 8, Table 1). Furthermore, we studied the reaction scope by using propargylamines containing different amine components. Other cyclic secondary amines (pyrrolidine, piperidine and azepane) were shown to be compatible under the reaction conditions to afford enone product **2a** in synthetically useful yields (entries 9-11, Table 1). Interestingly, propargylamines with primary amines (benzylamine and cyclopentylamine) were also converted to give **2a** under the optimized conditions (entries 13-14, Table 1).

Then, we examined the silver-catalyzed transformation of propargylic amine *N*-oxides in protic solvents. Based on the previous study, the key intermediate **A** could transform to ketone **3** and enone **4** by being attacked by the nucleophilic 3-chlorobenzoxy anion which was formed *in situ* from *m*-CPBA in a protic solvent (see Scheme 1). Over the years, we have been devoting ourselves to develop approaches for selective modification of cysteine-containing peptides and proteins.[5e, 10] Along with our ongoing interest, we have been studying the silver-catalyzed transformation of propargylic amine *N*-oxides on bioconjugation of cysteine-containing peptides. To explore this bioconjugation, we chose *N*-(*tert*-butoxycarbonyl)-L-cysteine methyl ester **7** as the model nucleophile to investigate the reaction of it and fully substituted propargylamines.

Table 2. Solvent effect of silver-catalyzed transformation of propargylamines **1a** to α-thioketone **3a**.[a]

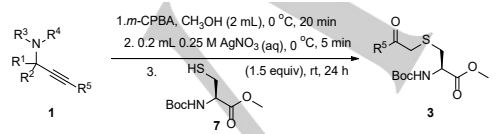


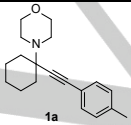
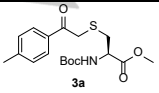
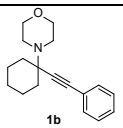
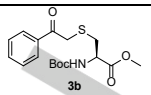
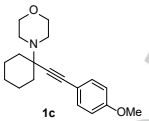
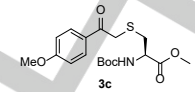
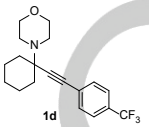
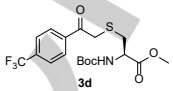
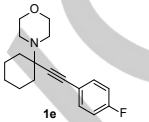
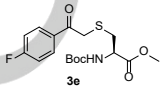
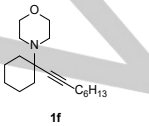
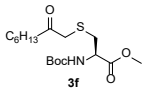
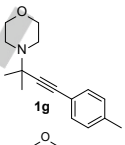
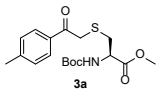
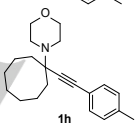
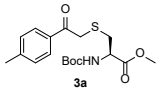
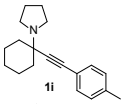
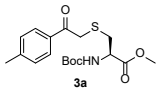
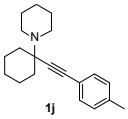
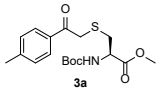
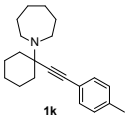
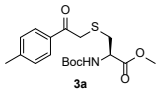
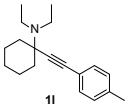
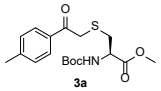
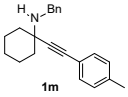
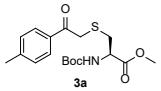
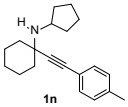
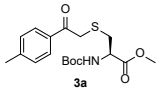
Entry	Solvent	Yield of **3a** (%)[b]
1	THF	11
2	DCM	14
3	MeOH	50
4	*i*-PrOH	42
5	*n*-BuOH	35
6	*t*-BuOH	20
7	EtOH	36
8	MeOH:H_2O (10:1)	73

[a] Reactions were performed with **1a** (0.5 mmol), *m*-CPBA (0.55 mmol), **7** (0.75 mmol) and $AgNO_3$ (0.05 mmol) in solvent (2 mL). [b] Isolated yield.

As discussed, different products from propargylic amine *N*-oxide were obtained depending on the employed solvent systems. To this end, various solvents were examined in this reaction. In aprotic solvents, such as THF and DCM, only 11% and 14% yields of product **3a** were generated (entries 1-2, Table 2). In contrast, the products **3a** were obtained in moderate yields in the alcoholic solvents except *t*-BuOH (entries 3-7, Table 2). It is observed that optimal result was achieved by using a mixed solvent of MeOH/H_2O (10:1), giving **3a** in 73% yield (entry 8, Table 2). The formation of α, β-unsaturated ketone **4a** was not observed in all the solvents tested.

Table 3. The reaction scope of silver-catalyzed transformation of propargylamines **1** to α-thioketones **3**. [a]



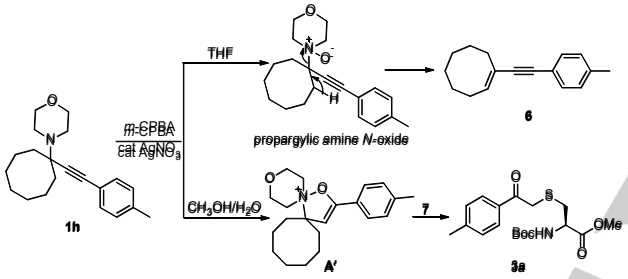
Entry	Substrate	Product	Yield of **3** (%)[b]
1			73
2			65
3			71
4			43
5			92
6			91
7			96
8			39
9			20
10			81
11			36
12			38
13			0
14			0

[a] Reactions were performed with **1** (0.5 mmol), *m*-CPBA (0.55 mmol), **7** (0.75 mmol) and $AgNO_3$ (0.25 M, 0.2 mL H_2O) in CH_3OH (2 mL). [b] Isolated yield.

After identifying the optimized reaction conditions, we set to explore the reaction scope by using various propargylamines **1a-1n**. Propargylamines **1a-1l** with different combinations of R^1, R^2

(cyclic or acyclic alkyl), R^5 (aryl/alkyl) and amine components (morpholine, piperidine, pyrrolidine, azepane and diethylamine) showed good tolerance for this reaction (entries 1-12, Table 3). A variety of α-thioketones **3a-3f** were synthesized in moderate to excellent yields (up to 96%). However, the propargylamine substrates **1m** and **1n** bearing primary amine moieties (benzylamine and cyclopentylamine) are not compatible with this reaction (entries 13-14, Table 3).

Interestingly, the desired product **3a** was obtained in 36% yield when eight-membered ring substrate **1h** was conducted under the optimal reaction conditions (Scheme 2). The outcome was different from the result obtained in aprotic solvent THF. These findings further supported the mechanism proposed, the isoxazolinium intermediate **A'** was more stable in a protic solvent which could be attacked by nucleophile **7** to give the α-thioketone **3a**. In contrast, the isoxazolinium intermediate **A'** could not formed in aprotic solvent THF due to its steric hindrance between six-membered ring and eight-memberedring, which lead to the propargylic amine *N*-oxide was favorable to undergo elimination to generate the enyne product **6**.



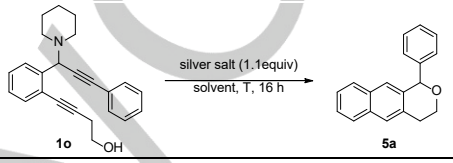
Scheme 2. The reactivities of propargylamine **1h** in different solvents.

Cascade cyclization has been a long-standing interest for synthetic chemists as molecular complexity can be built up from simple starting materials via tandem reaction sequences in a one-pot reaction. In particular, transition metal-mediated cycloisomerizations of allenynes have provided novel synthetic routes to diverse product formation with high atom economy.[11]

As we have disclosed enantioselective syntheses of allenes from chiral propargylamines with gold and silver catalysts.[6a, 6b] We hypothesized that the allene moieties generated from propargylamines would be amenable for further synthetic elaboration via cycloisomerization with alkynes. To the best of our knowledge, the cycloisomerization chemistry of alkynyl alcohol-linked propargylamines **1** has not been reported. Herein, we attached propargylamines with alkynyl alcohols by Sonogashira reaction in order to explore the chemistry of this new type of propargylamines **1o-1x** (See the Supporting Information Table S3).

At the outset, we commenced our study with propargylamine **1o** as the substrate. The reaction was conducted using $AgNO_3$ (1.1 equiv) in CH_3CN at 80 °C for 16 h in the absence of light, full conversion of propargylamine **1o** was observed and isochroman **5a** was isolated in 5% yield (entry 1, Table 4). Then, attention was paid to the optimization of the reaction solvents for this transformation. It was found that most of the tested solvents were not suitable for the reaction to afford the desired product **5a**, such as toluene, THF, DCE, 1,4-dioxane, Et_2O and DMF (entries 2-8, Table 4). The use of different silver salts, such as $AgOCOCF_3$, $AgBF_4$, AgOTf, $AgPF_6$ and $AgNO_3$ or the employment of 5% PPh_3AuCl as co-catalyst, proved to be unsuccessful (entries 9-13, Table 4). To our delight, lowering the reaction temperature from 80 °C to 60 °C the yield of **5a** was improved from 5% to 19% (entry 14, Table 4). No improvement was obtained by further decreasing the temperature to 45 °C or room temperature (entries 15-16, Table 4).

Table 4. Effect of solvent, silver salts, and temperature. [a]



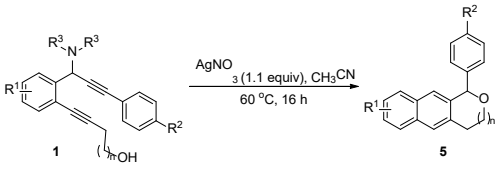
Entry	T(°C)	Solvent	Silver salt	Conversion (%)	Yield of **5a** (%)[b]
1	80	CH_3CN	$AgNO_3$	100	5
2	80	toluene	$AgNO_3$	46	trace
3	80	THF	$AgNO_3$	55	trace
4	80	DCE	$AgNO_3$	90	0
5	80	DCE	$AgNO_3$[c]	100	0
6	80	1,4-dioxane	$AgNO_3$	100	trace
7	80	Et_2O	$AgNO_3$	0	0
8	80	DMF	$AgNO_3$	0	0
9	80	CH_3CN	$AgOCOCF_3$	20	trace
10	80	CH_3CN	$AgBF_4$	36	trace
11	80	CH_3CN	AgOTf	27	trace
12	80	CH_3CN	$AgPF_6$	35	trace
13	80	CH_3CN	$AgNO_3$[d]	100	0
14	60	CH_3CN	$AgNO_3$	100	19
15	45	CH_3CN	$AgNO_3$	80	12
16	rt	CH_3CN	$AgNO_3$	20	0

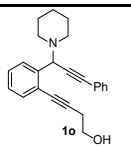
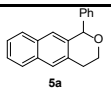
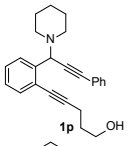
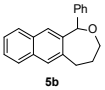
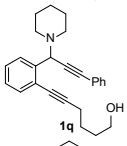
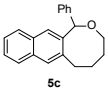
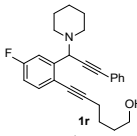
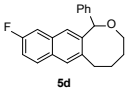
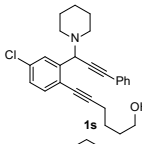
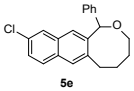
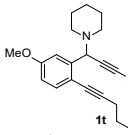
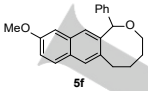
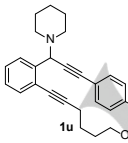
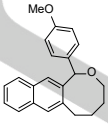
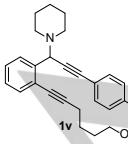
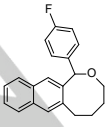
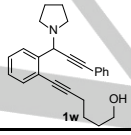
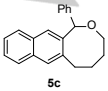
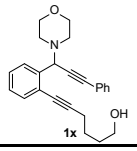
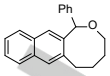
[a] Reactions were performed with **1o** (0.5 mmol) and silver salts (0.55 mmol) in solvents (5 mL). [b] Isolated yield. [c] 3 equivalents of AcOH was added. [d] 5 mol% PPh_3AuCl was added.

With the optimized protocol in hand, we turned to demonstrate the generality of this reaction. The results were summarized in Table 5. To our delight, the yields of isochroman derivatives **5** were improved by increasing the length of the alkyl chain of propargyl alcohols (entries 1-3, Table 5). Notably, the eight-membered ring product **5c**, which is difficult to access

otherwise due to their unfavorable transannular interactions and entropic factors,[12] was obtained in synthetically useful yield (entry 3, Table 5). Both R^1 and R^2 could be hydrogen or electron-donating groups or electron-withdrawing groups, to give the desired eight-membered ring products **5** in moderate yields (entries 3-8, Table 5).

Table 5. Reaction scope of transformation from **1** to **5**. [a]



Entry	Substrate	Product	Yield of **5** (%)[b]
1			19
2			30
3			42
4			31
5			26
6			26
7			28
8			31
9			19
10			7

[a] Reactions were performed with **1** (0.5 mmol) and $AgNO_3$ (0.55 mmol) in CH_3CN (5 mL). [b] Isolated yield.

Propargylamines with pyrrolidine moiety could also smoothly give the corresponding product **5c** in 19% yield (entry 9, Table 5). In contrast, only 7% product yield was observed for the cascade cyclization of the morpholine substrate **1x** under the identical reaction conditions (entry 10, Table 5). The structure of the product was further confirmed by X-ray diffraction studies of **5b** (Figure 1).

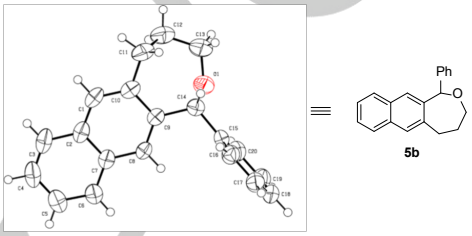
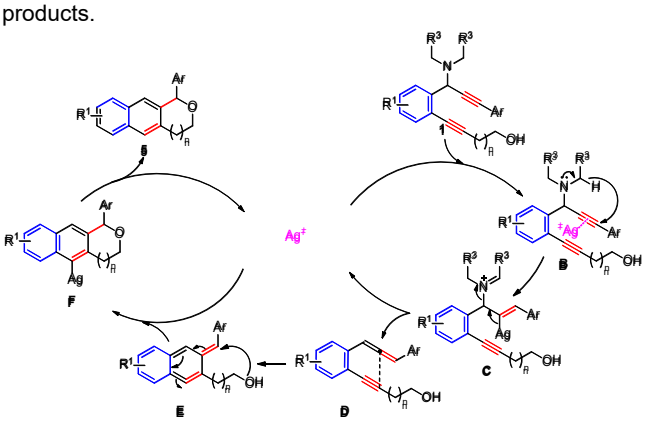


Figure 1. X-Ray crystallographic structure of compound **5b**.[13]

Based on the results and previous work,[6b, 14-16] the reaction is postulated to proceed via sequential rearrangements (Scheme 3). First, coordination of silver to the alkyne moiety of the propargylamine **1** generated intermediate **B**, which underwent an intramolecular 1,5-hydride transfer[6b, 15] to obtain intermediate **C**. Then, elimination occurred to afford alkynylallene intermediate **D**, which generated the strained cyclic allene **E**[16] through an intramolecular Diels-Alder reaction. Second, nucleophilic attack of alcohol to the alkene moiety to form the intermediate **F**. This intermediate was further protonated to deliver the desired isochroman **5**. Further investigations on this reaction, specifically on improving the yield of the isochroman products.



Scheme 3. A proposed reaction mechanism.

Conclusions

In conclusion, we have developed a series of efficient silver-mediated transformations of propargylamines to provide diverse product patterns including enones, α-thioketones, and isochromans.

Supporting Information Summary

Electronic Supplementary Information is available including experimental details and characterizing data (^{1}H NMR, ^{13}C NMR, and MS) for all materials and products.

Acknowledgments

We are grateful for the financial support of Hong Kong Research Grants Council (PolyU 153031/14P and X-ray diffractometer-PolyU11/CRF/13E), the Shenzhen Basic Research Program (JCYJ20170818104257975), State Key Laboratory of Chemical Biology and Drug Discovery and Department of Applied Biology and Chemical Technology, and Southern University of Science and Technology (Y01216234).

Conflict of Interest

The authors declare no conflict of interest

Keywords: Enones • Isochromans • Propargylamines • Silver • Thioketones

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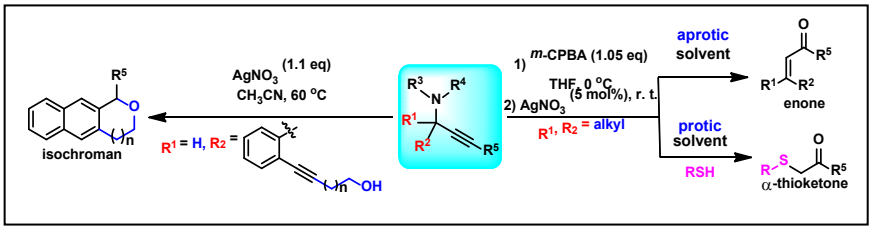

A series of silver-mediated synthetic strategies for propargylamines to build molecular complexity which provided a variety of structural scaffolds including enones, *α*-thioketones, and isochromans have been developed. Propargylic amine *N*-oxides generated *in situ* from the corresponding propargylamines through oxidation were converted to enones in aprotic solvent by silver catalysis, and α-thioketones were obtained by using protic solvent. Silver-mediated transformation of alkynyl alcohol-linked propargylamines provided isochromans.