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Catalytic asymmetric intramolecular propargylation of cyclopropanols to access the cuparane core†

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The catalytic asymmetric propargylation of enol(ate) intermediates is a well-established method for the synthesis of α-propargyl-substituted carbonyl compounds. However, the propargylation of homo-enol(ate) or its equivalents for the synthesis of β-propargyl-substituted carbonyl compounds remains underdeveloped. A catalytic enantioselective decarboxylative intramolecular propargylation of cyclopropanols has been developed using a PyBox-complexed copper catalyst. This reaction offers an effective approach to assemble a cyclopentanone skeleton bearing an all-carbon quaternary stereogenic center and an adjacent quaternary *gem*-dimethyl carbon center, which is the core scaffold of the naturally occurring cuparenoids. Key to the success of this protocol is the use of a new structurally optimized PyBox ligand. This study represents the first example of catalytic asymmetric intramolecular propargylation of cyclopropanols.

Introduction

The catalytic asymmetric allylation and propargylation of enol(ate) intermediates are well-established methods to synthesize α-allyl- or α-propargyl-substituted carbonyl compounds.[1–8] In contrast, the analogous reactions of homo-enol(ate) or its equivalents for the synthesis of β-allyl- or β-propargyl-substituted carbonyl compounds have been lagging far behind (Fig. 1A).[9–14] As one of the most prominent homo-enol equivalents, cyclopropanol has been demonstrated to undergo facile ring-opening coupling reactions with various electrophiles.[9–14] Its catalytic asymmetric reaction with allyl electrophiles, however, remains underexplored until recently. Yin[15] and Trost[16] reported the catalytic asymmetric allylation of cyclopropanols with allyl phosphates.[15–22] Despite that, the catalytic asymmetric ring-opening propargylation of cyclopropanols, to the best of our knowledge, has not been reported yet (Fig. 1A).[23] In this context, establishment of a catalytic system ensuring an enantioselective propargylic substitution with cyclopropanols is highly desirable, not only because it expands the scope of the applicable electrophiles for the cyclopropanol, but also because it generates synthetically valuable β-propargyl ketones.

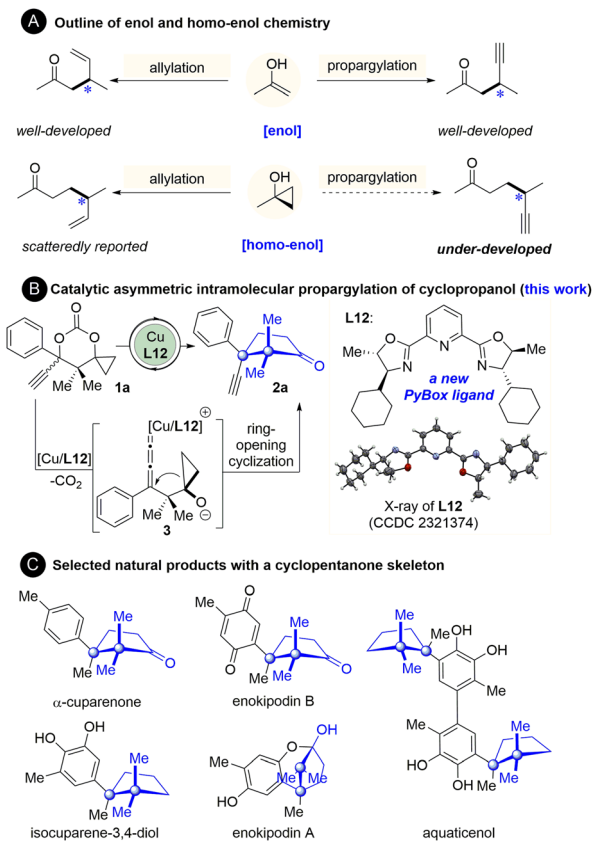

Fig. 1 Background and study synopsis. (A) Outline of the enol and homo-enol chemistry. (B) Catalytic asymmetric intramolecular propargylation of cyclopropanol (this work). (C) Selected natural products with a cyclopentanone skeleton.

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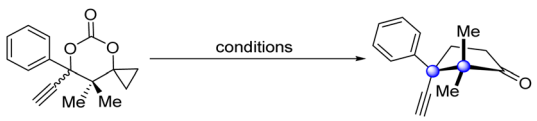
At the outset of the present study, the feasibility and challenges of propargylation of cyclopropanol were first considered. The great advances made in the area of catalytic asymmetric propargylic substitutions of propargylic electrophiles with an array of nucleophiles in the past few years indicate the feasibility of this reaction.[2–8,24] Despite that, there are inherent issues that need to be addressed. In Cha,[18] Yoshikai,[19] Yin,[15] and Trost's[16] ring-opening allylation of cyclopropanol, preactivation of the cyclopropanol unit as a zinc or potassium alkoxide salt is essential prior to the transmetallation with copper or nickel for the subsequent allylic substitution.[15–22] These studies together with our experience[25–30] and others' reports[31–36] on ring-opening reactions of cyclopropanols indicate that how to activate the cyclopropanol unit is key to the success of the ring-opening reactions of cyclopropanols and thus should be identified primarily. Furthermore, an asymmetric catalytic system applicable to the reaction of cyclopropanol remains underdeveloped,[9–14,37–43] which highlights the need to establish an effective asymmetric catalytic system for this new reaction.

To address the aforementioned issues, we have developed the first and highly enantioselective intramolecular propargylation of cyclopropanol, which was enabled by a new structurally optimized pybox ligand-complexed copper catalyst.[44] The cyclopropanol and propargyl units were simultaneously activated as cyclopropoxide and copper allenylidene respectively by decarboxylation. This protocol furnishes a series of cyclopentanones bearing an all-carbon quaternary stereogenic center adjacent to a quaternary *gem*-dimethyl carbon center (Fig. 1B). This sterically congested motif is the cuparane core shared by a number of naturally occurring cuparenoids, an eminent family of sesquiterpenes which were isolated from a culture broth of a mushroom (*Flammulina velutipes*) and other natural sources and exhibited a series of antimicrobial activities (Fig. 1C).[45–52]

Results and discussion

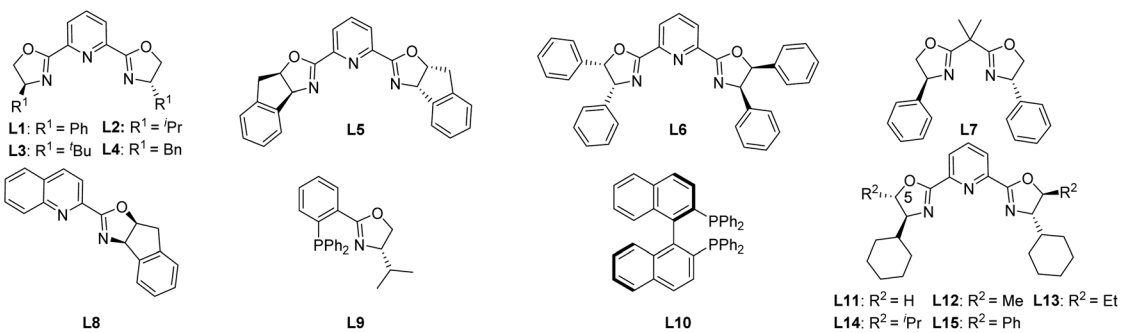
We commenced the study by using carbonate **1a** as the model substrate and by screening an array of chiral ligands (Table 1)

Table 1 Optimization of the reaction conditions[a]



1a **2a**

Entry	Metal salt	Ligand	Base	Yield[b] (%)	*ee*[c] (%)
1	$Cu(OTf)_2$	**L1**	DIPEA	35	20
2	$Cu(MeCN)_4PF_6$	**L1**	DIPEA	75	66
3	$Cu(MeCN)_4PF_6$	**L1**	$NaHCO_3$	86	68
4	$Cu(MeCN)_4PF_6$	**L2**	$NaHCO_3$	86	64
5	$Cu(MeCN)_4PF_6$	**L3**	$NaHCO_3$	19	40
6	$Cu(MeCN)_4PF_6$	**L4**	$NaHCO_3$	67	15
7	$Cu(MeCN)_4PF_6$	**L5**	$NaHCO_3$	57	−22
8	$Cu(MeCN)_4PF_6$	**L6**	$NaHCO_3$	48	6
9	$Cu(MeCN)_4PF_6$	**L7–L10**	$NaHCO_3$	0	—
10	$Cu(MeCN)_4PF_6$	**L11**	$NaHCO_3$	85	90
11	$Cu(MeCN)_4PF_6$	**L12**	$NaHCO_3$	90	94
12[d]	**$Cu(MeCN)_4PF_6$**	**L12**	**$NaHCO_3$**	**95**	**95**
13[d]	$Cu(MeCN)_4PF_6$	**L13**	$NaHCO_3$	85	95
14[d]	$Cu(MeCN)_4PF_6$	**L14**	$NaHCO_3$	85	86
15[d]	$Cu(MeCN)_4PF_6$	**L15**	$NaHCO_3$	20	70

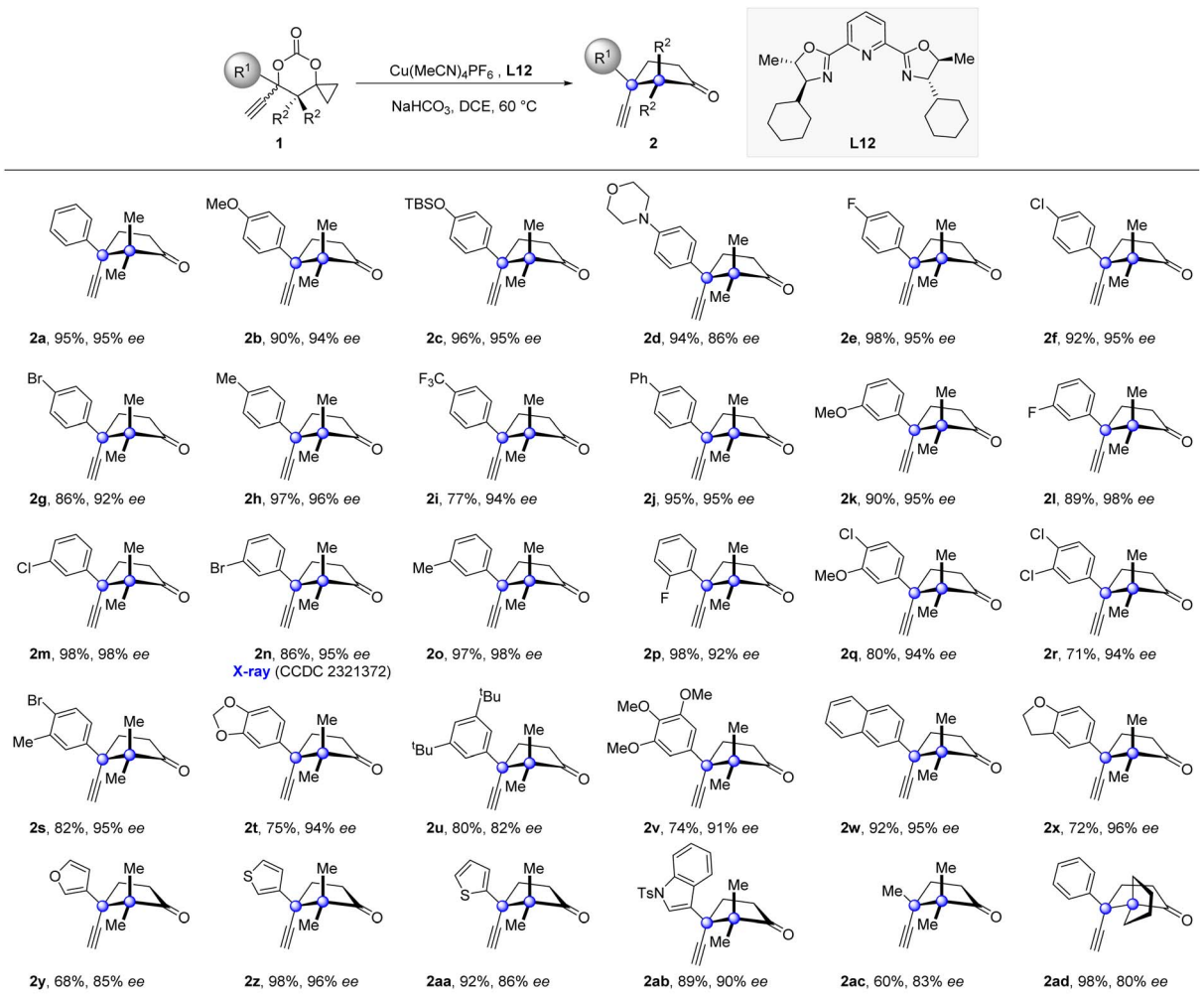


[a] Typical reaction conditions unless otherwise noted: **1a** (0.1 mmol), metal salt (10 mol%), ligand (12 mol%), base (1 equiv.), DCE (4 mL), 80 °C, 48 h. [b] Isolated yield of **2a**. [c] Determined by chiral HPLC analysis. [d] Reaction was conducted at 60 °C.

(see the ESI† for details). Encouragingly, an initial attempt with $Cu(OTf)_2$ and Ph-PyBox ligand **L1** produced the desired propargylation product **2a** albeit in 35% yield and with 20% *ee* value (Table 1, entry 1). With this promising result, other copper salts were then screened. After evaluation of several copper(I) and (II) salts (see the ESI† for details), $Cu(MeCN)_4PF_6$ was identified as the best one, which improved both the yield and *ee* value significantly (Table 1, entry 2). After evaluation of other bases (see the ESI† for details), $NaHCO_3$ proved to be the best choice, improving the yield to 86% and *ee* value to 68% (Table 1, entry 3). Since the subtle structural changes of the ligands would have a significant impact on the reaction outcome, an array of known bidentate and tridentate ligands including the PyBox ligands (**L2**–**L6**, **L11**), Box ligand **L7**, QuinOx ligand **L8**, PhOx ligand **L9**, and Binap **L10** were then evaluated to improve the enantioselectivity (Table 1, entries 4–9). All these ligands resulted in a substantial decrease of not only the yield but also the enantioselectivity except the Cy-PyBox ligand **L11** which provided an improved level of enantiocontrol (90% *ee*, Table 1, entry 10). On the basis of these results, we resorted to the design and synthesis of new PyBox ligands to further improve the reaction efficiency. Gratifyingly, introducing a methyl group at C5 of each oxazoline motif of the Cy-PyBox ligand **L11** delivered an excellent yield and enantioselectivity (90% yield, 94% *ee*, Table 1, entry 11), which was slightly improved by reducing the reaction temperature from 80 to 60 °C (Table 1, entry 12), while introducing more hindered groups such as Et-, ^{i}Pr-, and Ph- at C5 was fruitless (**L13**–**L15**, Table 1, entries 13–15).

Having established the optimized catalytic system, we then explored the generality of this enantioselective propargylation of cyclopropanols (Table 2). A broad range of substrates, possessing both electro-donating and -withdrawing groups at the *para*-position of the phenyl ring, were well tolerated to furnish the desired products in high yields with excellent enantioselectivies (**2b**–**2j**). The variation of the substituent pattern has a subtle impact on the reaction outcome. For instance, the substrates **1k**, **1l**, **1m**, **1n**, **1o**, and **1p**, which possess MeO-, F-, Cl-, Br-, and Me- substituents at the *meta*- or *ortho*-position of the

Table 2 Substrate scope[a]



[a] Reaction conditions: **1** (0.1 mmol), $Cu(MeCN)_4PF_6$ (10 mol%), **L12** (12 mol%), $NaHCO_3$ (1 equiv.), DCE (4 mL), 60 °C, 24–48 h; isolated yields were reported and *ee* values were determined by chiral HPLC analysis.

phenyl ring, all participated in the transformations and thus provided cyclopentanones (**2k**–**2p**) in high enantioselectivities with handles for further derivations. Furthermore, substrates with two or three substituents of different nature at the phenyl ring were tolerated as well (**2q**–**2v**). **1w** and **1x** bearing a bicyclic aromatic substituent also proved to be viable substrates. The substrate scope was further expanded to include substrates substituted with heteroaryl groups, including furyl, thienyl, and indolyl groups (**2y**–**2ab**). Notably, replacing the phenyl group with a methyl group also produced product **2ac** with good enantioselectivity in synthetically useful yield. Moreover, **1ad** with a spiropentyl group was also a suitable substrate. The relative and absolute configurations of **2n** were determined by single-crystal X-ray crystallographic analysis (see the ESI† for details), and the same configurations were analogously assigned to the other products.

Since the products generated by this new protocol bear a naturally occurring cuparane core, introduction of such a fragment into therapeutic molecules would be of pharmaceutical significance.[53] To demonstrate the potential synthetic utility of this protocol in drug development, derivations of drugs were carried out (Fig. 2). The fructose with two acetal groups, core scaffold of the anticonvulsant drug topiramate, was introduced with cuparane cores having different absolute configurations in high diastereoselectivities under the typical reaction conditions with **L12** or *ent*-**L12** (**2ae** and **2ae′**) as the ligand. The same manipulation was also applied to the anti-inflammatory drugs naproxen and indomethacin (**2af**, **2af′**, and **2ag**).

Besides the high yields and enantioselectivity, this key cyclization reaction boasts good scalability. Grams of **2h** were conveniently accumulated by the reaction conducted at the gram scale without affecting the reaction efficiency and enantioselectivity (Fig. 3). Further elaborations at the alkynyl-substituted cuparane core of **2h** were carried out. Saturation of the alkynyl group of **2h** delivered the natural product analogue 6-methyl-α-cuparenone (**4**) in 95% yield. The click reaction of **2h** and azide **5** possessing a biotin segment provided **6**, which could serve as a chemical probe to investigate the biological properties of the cuparenoids. Taking advantage of the alkynyl group, a reaction of Larock indole synthesis delivered indolyl-substituted product **7**. Furthermore, a sequence of partial saturation of the alkyne, allyl addition to the ketone group, and ring closing metathesis with the Grubbs II catalyst furnished the bridged product **8** in a synthetically useful yield.

To gain more mechanistic insights into the current reaction, several experiments were conducted (Fig. 4). Substrate **1ah** with an additional PMB group at the cyclopropane moiety generated product **2ah** with the cleavage of the less substituted bond (Fig. 4A). This result indicates that an ionic cyclopropanol ring-opening mechanism might operate since it is generally accepted that the radical cyclopropanol ring-opening process favors breaking the more substituted to produce a more stable radical intermediate, while the ionic ring-opening process tends to break the less substituted one.[9–14] The reaction of **1a** proceeded well in the presence of the radical scavenger TEMPO or BHT, further confirming that this is a non-radical process (Fig. 4B). Non-linear effect experiments were carried out with *ee*-varied chiral **L12** (Fig. 4C). The results clearly showed the linear relationship between the *ee* value of **L12** and the *ee* value of product **2a**, indicating that a monomeric complex may work as a catalyst in the reaction.[8] On the basis of our mechanistic experiments and the literature precedents,[2–8,24] a plausible catalytic cycle and stereoinduction model were proposed (Fig. 4D). First, deprotonation of **1a** generated the copper acetylide intermediate **9**. The monocopper allenylidene complex **3**

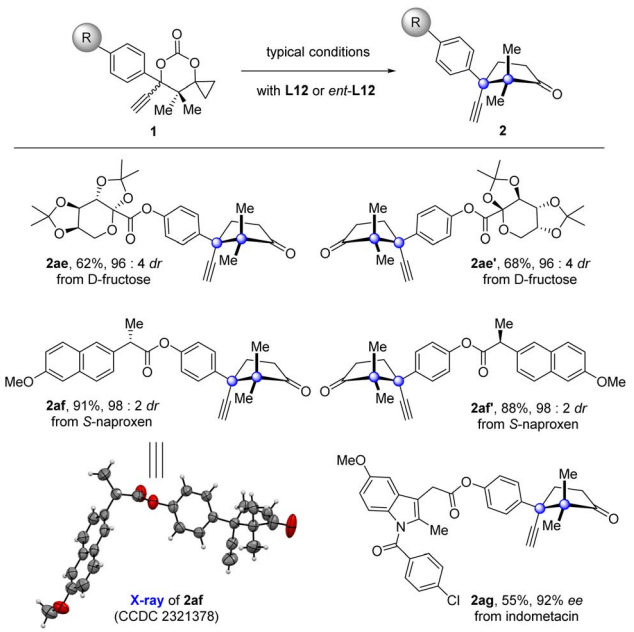


Fig. 2 Drug derivations. **L12** was used for **2ae**, **2af**, and **2ag**; *ent*-**L12** was used for **2ae′** and **2af′**.

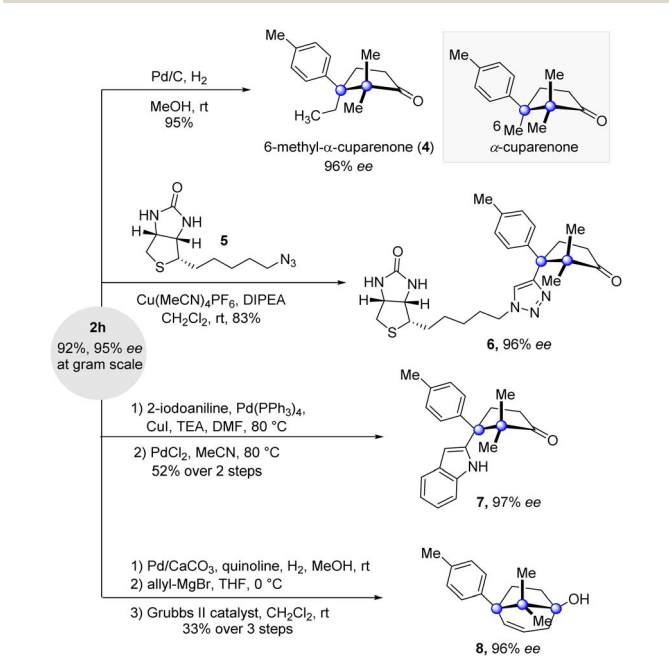


Fig. 3 Product derivations.

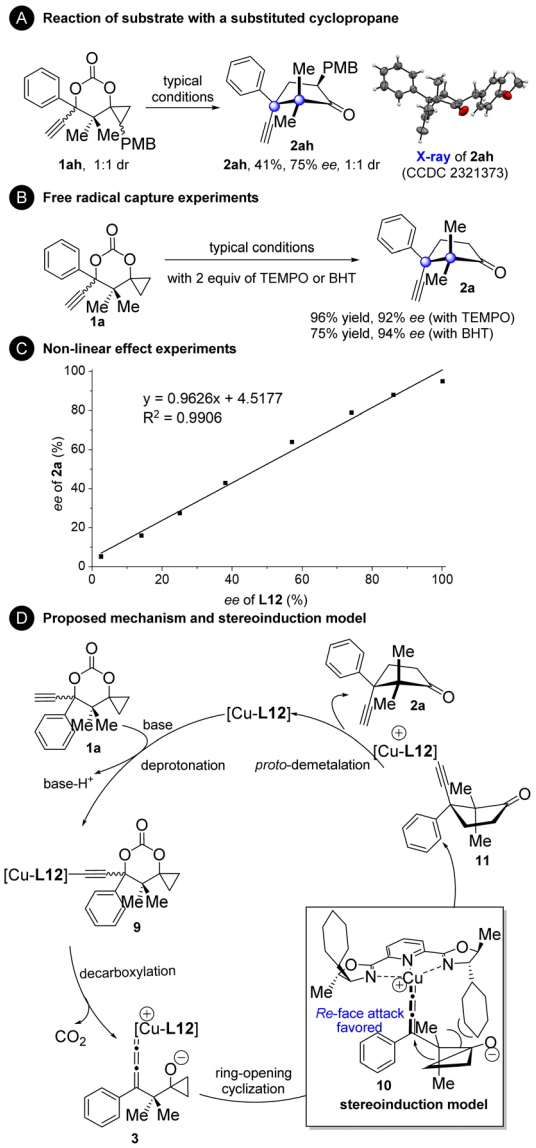


Fig. 4 Mechanism studies. (A) Reaction of substrate with a substituted cyclopropane. (B) Free radical capture experiments. (C) Non-linear effect experiments. (D) Proposed mechanism and stereoinduction model.

with the cyclopropanol segment activated as a cyclopropoxide is then formed by decarboxylation. Ring-opening cyclization of the cyclopropoxide unit to the copper allenylidene affords intermediate **11**. The asymmetric induction may be rationalized by a spatial repulsion exerted by the cyclohexyl group, in which re-face attack on the copper allenylidene occurs preferentially. Finally, protodemetalation occurs to furnish product **2a** and to release the **L12**-complexed copper species, which re-enters the catalytic cycle.

Conclusion

In summary, we have developed a highly enantioselective copper-catalyzed intramolecular propargylation of cyclopropanols. Key to the success of this method is the meticulous structural optimization of the PyBox ligand, which ensures good yields and excellent enantioselectivities for this reaction. This novel protocol presents a reasonably broad substrate scope and excellent functional group tolerance and provides straightforward access to a diverse range of difficult to access cyclopentanones bearing an all-carbon quaternary stereogenic center and an adjacent quaternary *gem*-dimethyl carbon center. This study represents the first catalytic asymmetric intramolecular propargylation of cyclopropanols and thus enriches the homoenol(ate) chemistry.

Data availability

All data associated with this article are available in the ESI.†

Author contributions

Conceptualization: M. Z.; investigation: Y. Z., H. Y., Y. Z., T. Z., M. T., C. Z. and S. Y.; formal analysis: Y. Z., H. Y., Y. Z., T. Z., M. T., C. Z. and S. Y. writing – original draft: M. Z., Y. Z. and H. Q.; writing – review and editing: Y. Z., H. Q. and L. H. All authors discussed the results and gave their approval of the final version.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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