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Well-defined chiral dinuclear copper-catalyzed tandem asymmetric propargylic amination–carboxylative cyclization sequence toward chiral 2-oxazolidinone derivatives†

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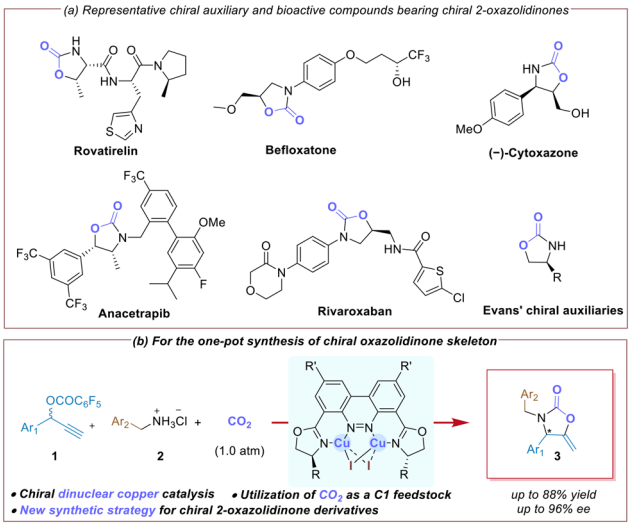
We report a novel strategy for the synthesis of chiral 2-oxazolidinones *via* a dinuclear copper-catalyzed asymmetric propargylic amination–carboxylative cyclization sequence of propargylic esters with nucleophilic alkyl amines under ambient pressure of carbon dioxide. A variety of chiral 2-oxazolidinones featuring an exocyclic methylene moiety was obtained in good yields with high enantioselectivities *via* a one-pot operation.

Introduction

Five-membered heterocyclic compounds like 2-oxazolidinones have found wide ranging applications in medicinal chemistry, organic synthesis and agrochemistry (Scheme 1a).[1] Moreover, chiral 2-oxazolidinones have been shown to be of great significance in the realm of asymmetric synthesis, serving as a versatile class of chiral auxiliaries or ligands in the stereoselective synthesis of enantioenriched compounds.[2] Therefore, the efficient synthesis of chiral 2-oxazolidinones and their derivatives is of great interest in organic chemistry and medicinal sciences.[3]

Utilization of carbon dioxide (CO_2) as an inexpensive, nontoxic, and renewable C1 feedstock has attracted attention in the past decades.[4] A variety of methods has been developed for the synthesis of achiral 2-oxazolidinones through the cyclization of propargylamines and carbon dioxide.[5] However, the use of CO_2 in catalytic asymmetric tandem reactions for the synthesis of chiral 2-oxazolidinones in one pot is largely underdeveloped.[6,7] In this context, two elegant methods have been developed for the synthesis of chiral *N*-aryl 2-oxazolidinones based on a tandem process, including the synthesis of chiral propargylamines from an asymmetric aldehyde–alkyne–amine (A^3) coupling reaction[6] or an asymmetric transfer hydrogenation of alkynyl ketimines,[7] followed by a carboxylative cyclization with CO_2. However, the synthesis of chiral 2-oxazolidinones bearing an exocyclic methylene motif has been less explored. Therefore, the development of a novel catalytic strat-



Scheme 1 Asymmetric propargylic amination–carboxylative cyclization sequence toward chiral 2-oxazolidinone derivatives.

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egy for the asymmetric synthesis of chiral 2-oxazolidinones derivatives is still highly desirable.[3]

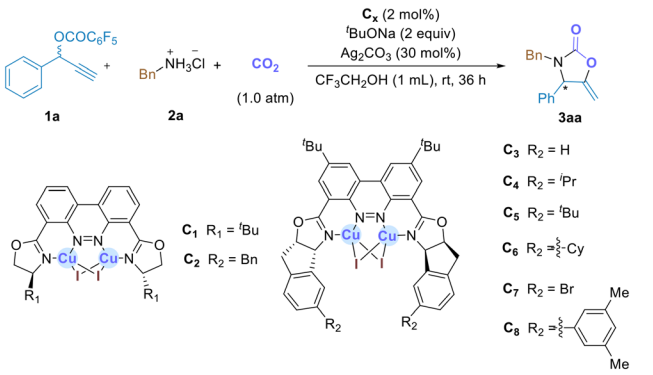
Although various bi/multi-nuclear copper complexes have been reported,[8] their applications in asymmetric catalysis are still much less developed.[9] Recently, we disclosed the successful development of a series of binuclear copper catalysts[10] based on chiral benzo[*c*]cinnoline dioxazoline frameworks,[11] and their applications in catalytic asymmetric propargylic substitution reactions. Since van Maarseveen and Nishibayashi's pioneering work in 2008,[12] copper-catalyzed asymmetric propargylic amination of propargylic esters has been an efficient method for the synthesis of chiral propargyl amines.[13] Herein, we report a novel strategy for the synthesis of chiral 2-oxazolidinones *via* a dinuclear copper-catalyzed asymmetric propargylic amination–carboxylative cyclization sequence of propargylic esters with alkyl amine hydrochlorides under an ambient pressure of carbon dioxide (Scheme 1b).[14] A variety of chiral 2-oxazolidinones featuring an exocyclic methylene motif and a *N*-alkyl group was obtained in good yields with excellent enantioselectivities.

Results and discussion

Reaction development and scope

The studies were initiated by taking the reaction of propargyl carbonate (**1a**) with benzylamine hydrochloride (**2a**) under an atm of CO_2 as the model reaction and the feasibility of the proposed asymmetric propargylic amination–carboxylative cyclization sequence using the binuclear Cu complexes $\mathbf{C_1}$–$\mathbf{C_8}$ as catalysts was investigated. A careful survey of the reaction parameters using catalyst $\mathbf{C_1}$ revealed that the reaction proceeded well in CF_3CH_2OH at room temperature for 36 h in the presence of ^{t}BuONa (2.0 equiv.) and Ag_2CO_3 (30 mol%) as additives, affording the desired product **3aa** in 51% yield with 73% ee (Table 1, entry 1). Under otherwise identical conditions, other bicopper catalysts, $\mathbf{C_2}$–$\mathbf{C_8}$, with different substituents on the oxazoline units or the cinnoline backbone of the ligands were subsequently evaluated in the reaction (Table 1, entries 2–8). The reaction catalyzed by $\mathbf{C_2}$, with a benzyl group on the oxazoline unit, gave product **3aa** in 54% yield with 70% ee (entry 2). To our delight, upon using catalyst $\mathbf{C_3}$ with the ligand derived from 2-aminoindanol, the desired product **3aa** was obtained with an improved ee value of 79% (entry 3). The reaction using catalyst $\mathbf{C_4}$, with increased steric hinderance of the oxazoline units, led to a significant improvement in the ee to 85% (entry 4). Using catalyst $\mathbf{C_5}$ featuring further enhanced steric hindrance of the oxazolyl moiety, the ee value of **3aa** was increased to 87% (entry 5). Proceeding further by using $\mathbf{C_6}$ bearing cyclohexyl groups on the indanyl scaffold as the catalyst, the reaction afforded **3aa** in good isolated yield (64%) with excellent enantioselectivity (91% ee, entry 6). However, the introduction of an electron-withdrawing (–Br) group on the indanyl scaffold of catalyst $\mathbf{C_7}$ significantly decreased the enantioselectivity of the reaction (entry 7). In addition, catalyst $\mathbf{C_8}$, with large steric hinderance on the indenyl scaffold, was also tested, resulting in poor catalytic performance (47% yield, 70% ee) (entry 8). Furthermore, various silver salts had similar impact on the reaction and Ag_2CO_3 was found to be optimal for the reaction (see the ESI† for reaction details). In addition, free benzylamine was also tested under the optimized conditions (as shown in entry 6), and the desired product was obtained in 74% yield with slightly lower ee (88%). In comparison to free amines, amine hydrochloride salts present a more appealing option due to their widespread commercial availability, cost-effectiveness, and relative stability under atmospheric conditions.[15]

Table 1 Investigation of the dinuclear copper-catalyzed asymmetric propargylic amination–carboxylative cyclization sequence[a]

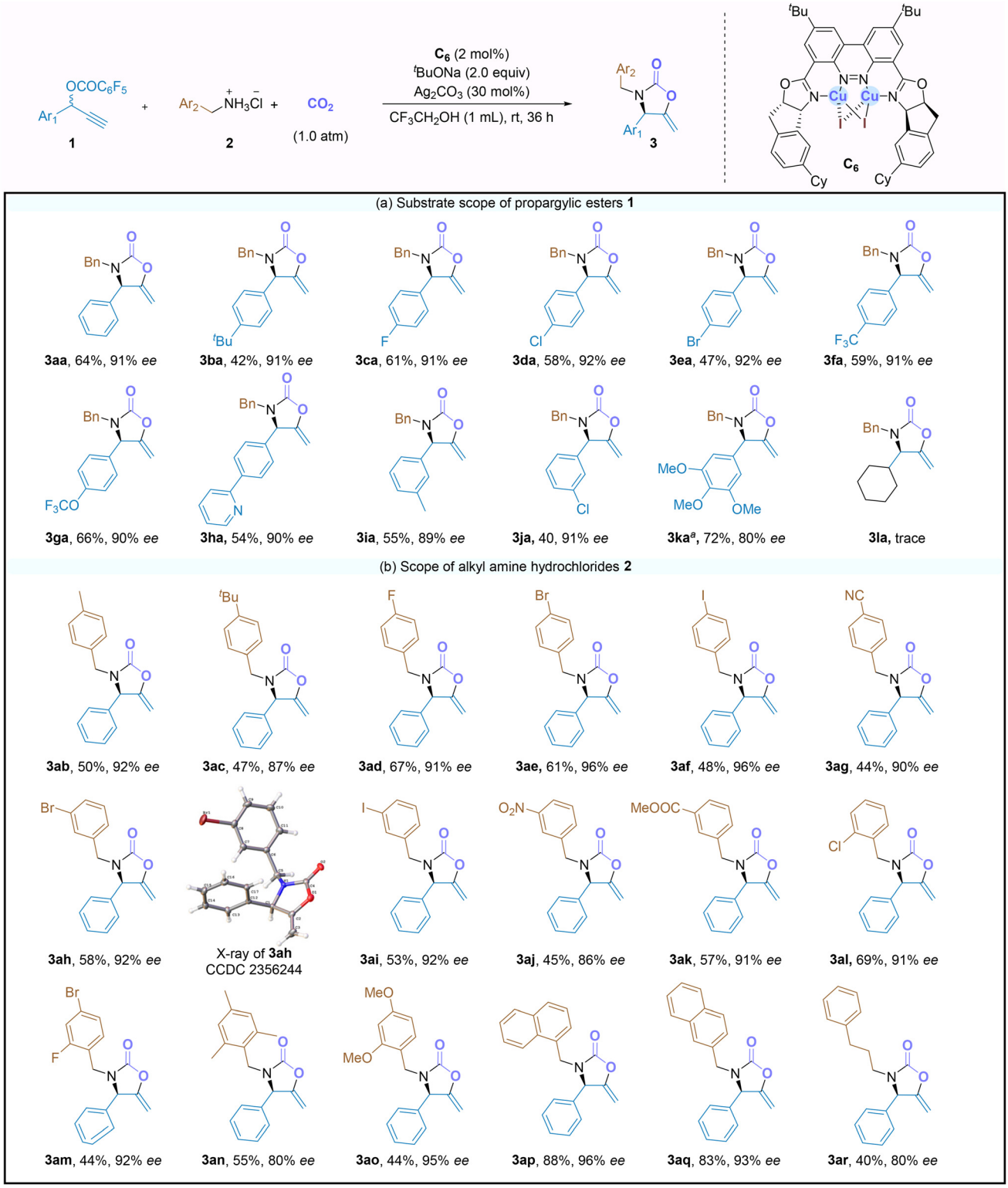


Entry	Cat.	Yield[b] (%)	ee[c] (%)
1	$\mathbf{C_1}$	51	73 (*S*)
2	$\mathbf{C_2}$	54	70 (*S*)
3	$\mathbf{C_3}$	49	79 (*R*)
4	$\mathbf{C_4}$	64	85 (*R*)
5	$\mathbf{C_5}$	59	87 (*R*)
6	$\mathbf{C_6}$	**70 (64)[d]**	**91 (*R*)**
7	$\mathbf{C_7}$	54	65 (*R*)
8	$\mathbf{C_8}$	47	70 (*R*)

[a] Unless otherwise noted, reaction conditions are as follows: **1a** (0.1 mmol), **2a** (0.15 mmol), ^{t}BuONa (2.0 equiv.), Ag_2CO_3 (30 mol%), $\mathbf{C_x}$ (2 mol%), CF_3CH_2OH (1 mL), rt, 36 h. [b] ^{1}H NMR yield using mesitylene as the internal standard. [c] The ee value of **3aa** was determined by HPLC on a chiral column IA. [d] Isolated yield.

Reaction scope

Under the optimized reaction conditions, the scope of propargyl carbonates **1** was first explored in the reaction with benzylamine hydrochloride **2a**, and the results are shown in Scheme 2a. The propargyl carbonates bearing either electron-donating (–^{t}Bu) or electron-withdrawing (–F, Cl, Br, CF_3, $-OCF_3$ and pyridine-containing carbonate) substituents at the *para*-position of the aryl group reacted smoothly with **2a**, affording the corresponding 2-oxazolidinones **3ba–3ha** in 42–66% yields with 90–92% ee. Substrates bearing *meta*-methyl, *meta*-chloro, and 3,4,5-trimethoxy substituted arenes were also amenable to the procedure, and the reactions provided **3ia–3ka** in good yields (40–72%) with 80–91% ee. However, the reactions using the cycloalkyl substituted propargylic carbonate **1l** only provided a trace amount of the corresponding product **3la**.



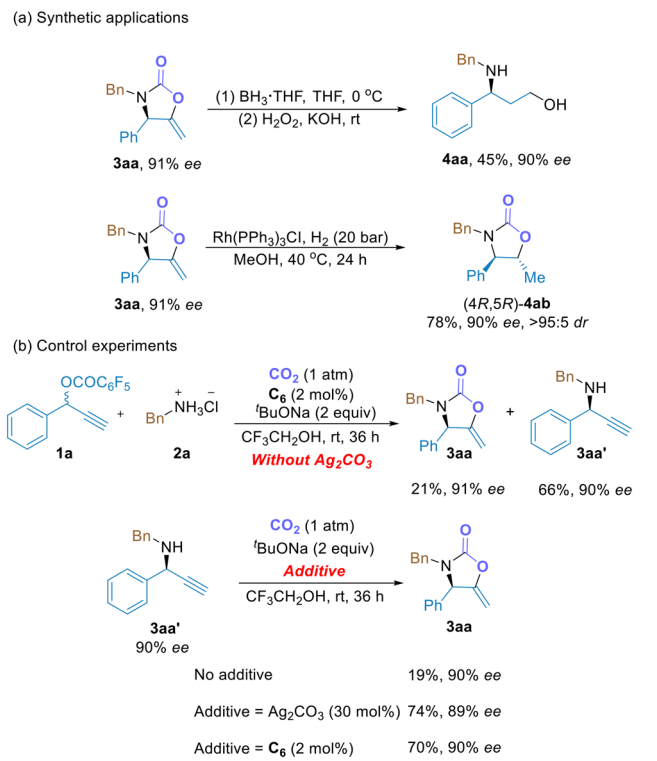
Scheme 2 Substrate scope. Reaction conditions: unless otherwise noted, all reactions were carried out using **1** (0.1 mmol), **2** (0.15 mmol), ^{t}BuONa (2.0 equiv.), Ag_2CO_3 (30 mol%), **C$_6$** (2.0 mol%), CF_3CH_2OH (1.0 mL), rt, 36 h. [a] Leaving group of the propargyl substrate = OBoc.

Subsequently, the scope of alkyl amines hydrochloride **2** was further evaluated in the reactions with propargyl carbonate **1a** (Scheme 2b). To our delight, this catalytic system exhibited good tolerance toward various hydrochloride salts of alkyl amines. For instance, the reactions of benzylamines bearing either electronic donating (–Me, and –^{t}Bu) or withdrawing (–F,

–Br, –I and –CN) groups on the phenyl ring afforded the corresponding products **3ab–3ag** in 44–67% yields with good enantioselectivities (87–96% ee). Changing the substituents of the benzylamines from the *para*- to *meta*- or *ortho*-position had no negative effect on the catalysis, smoothly leading to products **3ah–3al** in 45–69% yields with 86–92% ee. The absolute configuration of **3ah** was established as (*R*) by X-ray crystallography (CCDC 2356244†), while those of other chiral 2-oxazolidinone products were assigned by analogy. The catalytic system also turned out to be effective for the reactions of polysubstituted benzylamines **2m–2o**, giving the corresponding products **3am–3ao** in 44–55% yields with 80–95% ee. Furthermore, amine substrates containing an α- or a β-naphthyl group (**2p** and **2q**) were compatible with the protocol, and the reactions gave the corresponding products **3ap** and **3aq** in 83–88% yields with 93–96% ee. In addition, a primary amine hydrochloride bearing a long alkyl chain, such as **2r**, was also a suitable substrate, leading to the formation of the desired 2-oxazolidinone **3ar** in 40% yield with 80% ee. Notably, a variety of important functional groups, including –OMe, –F, –Br, –Cl, –I, $–CF_3$, $–OCF_3$, $–CO_2Me$, –CN, and $–NO_2$, was tolerated in the reaction, and the corresponding products showed good compatibility for downstream transformations.

Synthetic applications and control experiments

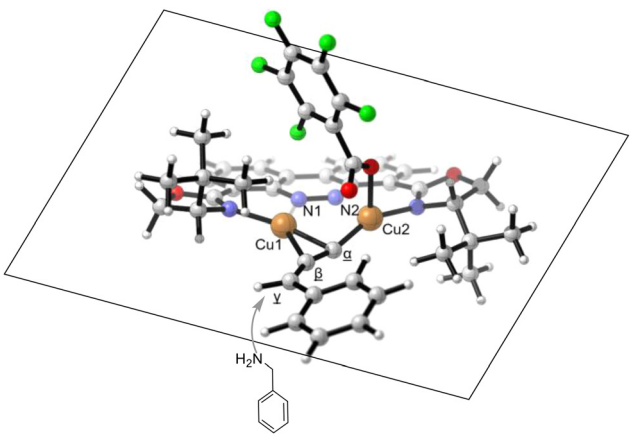
5-Methylene 2-oxazolidinones are useful chiral building blocks, as demonstrated by a two-step transformation of **3aa** to the synthetically useful chiral γ-amino alcohol **4aa** without any erosion of ee value (Scheme 3a). In addition, catalytic hydrogenation of the exocyclic C=C double bond of **3aa** using $Rh(PPh_3)_3Cl$ as the catalyst provided (4*R*,5*R*)-**4ab** in high yield (78%) with excellent diastereoselectivity (>95 : 5 dr). To gain an insight into the reaction mechanism, control experiments were carried out (Scheme 3b). Under otherwise standard conditions, the reaction of **1a** and **2a** in the absence of Ag_2CO_3 delivered the target product **3aa** in a low yield of only 21% with 91% ee, along with the generation of a substantial amount of **3aa′** with similar ee value (66%, 90% ee), suggesting that Ag_2CO_3 might promote the carboxylative cyclization of **3aa′** in the title reaction. This was confirmed by the reaction of the intermediate **3aa′** with CO_2 and without Ag_2CO_3 or the Cu catalyst; in this case, the cyclization product **3aa** was formed in only 19% yield. In contrast, the reaction of intermediate **3aa′** with CO_2 in the presence of Ag_2CO_3 or the binuclear Cu catalyst gave **3aa** in significantly improved yields of 74% and 70%, respectively. These results indicated that the title reaction is a tandem binuclear Cu-catalyzed asymmetric propargylic amination and Ag_2CO_3 promoted the carboxylative cyclization process. The copper catalyst in the first step may also have positive effect on the cyclization process. In addition, the enantioselectivity of **3aa** was determined in the propargylic amination step.



Scheme 3 Synthetic applications and control experiments.

Proposed transition state model

Based on the X-ray crystallographic structure of product **3ah** and previous computational studies by our group,[10] we proposed a stereochemical model to rationalize the observed chiral induction of the system using catalyst $\mathbf{C_1}$ (Scheme 4). Due to the large steric bulkiness of the $–^tBu$ and the $–OCOC_6F_5$ moieties located on the upper part of the ligand plane, the nucleophilic alkyl amines would preferentially attack the terminal carbon of the allene moiety from the bottom side. Subsequent carboxylative cyclization of the resulting chiral propargylamine with CO_2 would form the cycloadduct (*S*)-**3aa** with retention of the stereochemistry, which is consistent with the results obtained using $\mathbf{C_1}$ as the catalyst.



Scheme 4 Proposed chiral induction model based on the catalyst $\mathbf{C_1}$.

Conclusions

In summary, we have developed an efficient dinuclear copper-catalyzed asymmetric propargylic amination–carboxylative cyclization sequence of propargylic esters with alkyl amine hydrochlorides and CO_2, affording a variety of chiral 2-oxazolidinones bearing an exocyclic methylene moiety in good yields with high enantioselectivities.

Author contributions

Y. L., Q. C., and X. W. directed the project; Y. L., P. L., Z. F., L. S. and Q. C. performed all the experiments and analyzed all the data; Y. L., Q. C, and X. W. wrote the manuscript with contributions from all authors.

Data availability

The data supporting this article have been included as part of the ESI.†

Conflicts of interest

There are no conflicts to declare.

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