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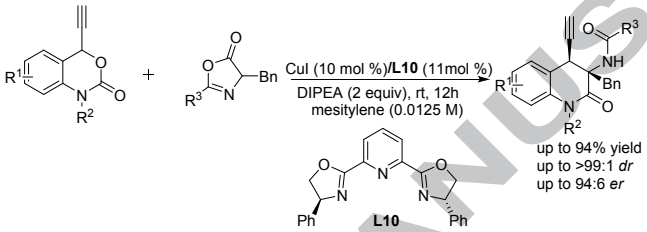

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Asymmetric [4 + 2] Cycloaddition of Azlactones with Dipolar Copper-Allenylidene intermediates for Chiral 3,4-Dhydroquinolin-2-one Derivatives

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ABSTRACT

In this paper, a pybox-copper catalyzed enantioselective decarboxylative [4 + 2] cycloaddition reaction of ethynyl benzoxazinanones with azlactones has been developed, which provides optically active 3,4-dihydroquinolin-2-ones in high yields with good enantioselectivities and diastereoselectivities. In this transformation, the chiral dipolar copper−allenylidene intermediates are kinetically generated via decarboxylative ethynyl benzoxazinanones, followed by the acttack of the enolate azlactones to form enantiomerically enriched 3,4-dihydroquinolin-2-one structures.

Introduction

Over the past decades, nitrogen-containing heterocyclic compounds have attracted extensive attention due to their important biological activities.[1] Specifically, 3,4-dihydroquinolin-2-one structures have proven to be quite important core backbones of many natural products and synthetic medicines, which commonly displays wide range of biological activities.[2] For example, compound A is used as a nonnucleoside reverse transcriptase inhibitors and plays a vital role in combination therapy for the treatment of AIDS[2a, 2c]. Compound B was isolated by the extraction of dried roots of Boronia pinnata Sma and found to have an inhibitory activity for tumor-promotion[2b]. Among a series of 1-aryl-3,4-dihydro-1*H*-quinolin-2-ones, compound C has been discovered as a potent and selective norepinephrine reuptake inhibitors[2d]. Additionally, compound D, which bears a *p*-methoxyphenylquinolinone skeleton fused with an isoprenyl pyran ring, is used as an antibiotic insecticide[2e] (Figure 1). In view of the interesting 3,4-dihydroquinolin-2-one structures and excellent biological properties, the development of new methods for the synthesis of 3,4-dihydroquinolin-2-one derivatives is highly desirable and interesting.

Asymmetric transition-metal catalysis involving a chiral organic ligand has been a powerful strategy for the construction of chiral core structures of many important medicinal compounds and agricultural candidates.[3] In fact, many organic reactions proceed via metal-associated dipolar intermediates, which contain two independent reaction centers.[4-5] The formation of dipolar metal intermediates in an organic reaction can be

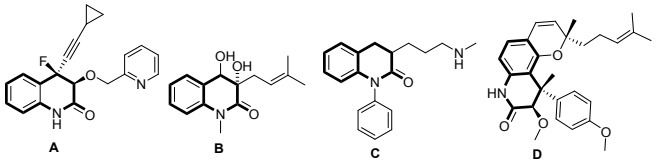
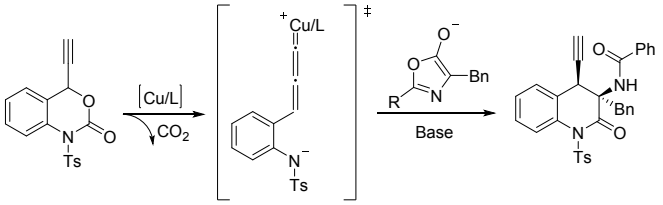


Figure 1 Selected natural products containing 3,4-dihydroquinolin-2-one skeletons

evidenced by chemical trapping of them. If dipolar metal intermediates are kinetically formed, successful trapping of dipolar intermediates is generally possible. For example, the group of Xiao reported an unprecedented decarboxylation-cycloaddition sequence of cyclic allylic esters with sulphur ylides through the enantioselective trapping of Pd-stabilized zwitterionic intermediates by the ylides in 2014.[4b] Chemists have noticed that this type of intermediates can serve as 1,4-carbon–nitrogen dipoles to perform formal [4 + n] cycloaddition. Subsequently, a series of Pd-catalyzed formal [4 + n] cycloadditions of vinyl benzoxazinanones were reported.[5] In particularly, when the intermediates are performed for a formal [4 + 2] cycloaddition, it is a shortcut to construct 3,4-dihydroquinolin-2-one backbones.[5b] Recently, the group of Shi has reported the iridium/B-H co-catalyzed reactions of vinyl benzoxazinanones with azlactones, giving the 3,4-dihydroquinolin-2-one derivatives in excellent yields with high to excellent diastereoselectivities, albeit with moderate enantioselectivity for the asymmetric version.[5f]

In 2016, Xiao and co-workers reported the first asymmetric formal [4 + 1] cycloaddition of sulfur ylides with copper−allenylidenes.[6] Later, various asymmetric reactions with copper−allenylidenes were developed to construct five,[7] six[8] and seven[9]-membered cyclic compounds. Over the past few years, azlactones were employed as the substrates in many enantioselective reactions.[10-11] Azlactones reacted with electrophiles at the C2 or C4 site to accomplish a series of [3 + 2] or [n + 2] cycloaddition reactions.[11] In this case, we envisioned that azlactones could serve as enolate nucleophiles to react with the decarboxylated copper−allenylidenes resulted from benzoxazinanones, which then underwent an intramolecular aminolysis to fullfill the formal [4 + 2] cycloaddition. Finally, the synthetic concept was successfully carried out, and a series of 3,4-dihydroquinolin-2-one derivatives were obtained in high yields with moderate enantioselectivities and excellent diastereoselectivities (Scheme 1). During the preparation of our manuscript, the enantioselective decarboxylative [4 + 2]-annulation of ethynyl benzoxazinanones with azlactones via cooperative copper and bifunctional tertiary aminourea catalysis has been reported by Mukherjee and co-workers.[12]



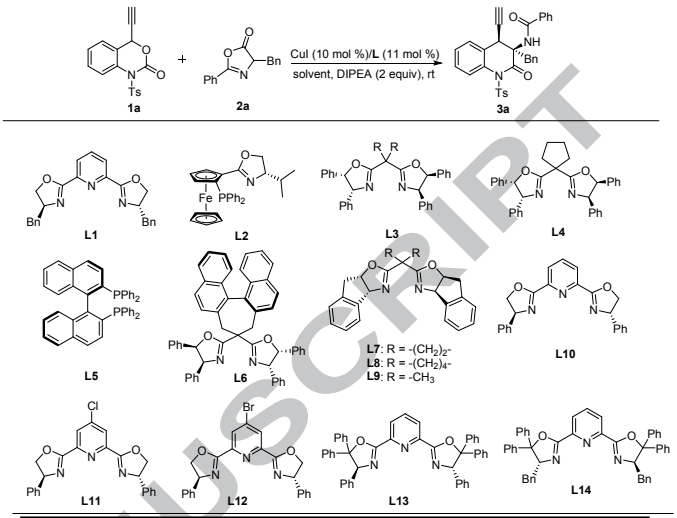
Scheme 1 Construction of the chiral 3,4-dihydroquinolin-2-ones via an amphiphilic Cu-allenylidene intermediate

Results and discussion

Initially, a model reaction between ethynyl benzoxazinanone **1a** and azlactone **2a** were chosen to examine the feasibility of Cu-catalyzed [4 + 2] cycloaddition reactions. The screening results are given in Table 1 (see the ESI† for more details). It was found that this reaction was carried out well in the presence of 10 mol % of CuI and ligand **L1** and with two equiv of $^{i}Pr_2NEt$ in toluene at room temperature, the desired product **3a** was obtained in 84% yield with 87 : 13 *dr* and 75 : 25 *er* (Table 1, entry 1). Then, a series of chiral ligands **L2**–**L10** were examined (Table 1, entries 2–10). According to the catalytic results, chiral ligands had a profound influence on the catalytic outcomes, and the ph-pybox **L10** was proven to be the optimal ligand. The corresponding reaction proceeded smoothly to give the desired product **3a** in 88% yield with 90 : 10 *er* and 92 : 8 *dr* (Table 1, entry 10). In addition, other types of chiral pyboxs were also investigated (Table 1, entries 11–14), but no improvements was observed. To further optimize the reaction conditions, several solvents, such as mesitylene, dichloroethane, tetrahydrofuran and acetonitrile, were investigated (Table 1, entries 15−19). Finally, the use of mesitylene as the reaction medium resulted in a considerable improvement on reactivity (Table 1, entry 15).

Subsequently, some azlactones **A**–**E** were synthesized from some aromatic or aliphatic *α*-amino acids, including phenylglycine-derived azlactone (**2aa**), *tert*-leucine-derived azlactone (**2ab**), alanine-derived azlactone (**2ac**), aminobutyric acid-derived azlactone (**2ad**) as well as valine-derived azlactone (**2ae**). The catalytic results are shown in Table 2. It was disclosed that the alkyl and aryl substituents on azlactones had significantly effect on the catalytic results. The phenylglycine-derived azlactone (**2aa**) displayed very poor diastereo- and enantio-selectivity, albeit with high reactivity (Table 2, entry 2). The *tert*-leucine-derived azlactone (**2ab**) only gave trance amount of the desire product (Table 2, entry 3). The azlactones **2ac**–**2ae** provided the corresponding products in good yields with good diastereoselectivity, but with decreased enantioselectivity

Table 1 Optimization of the reaction conditions [a]



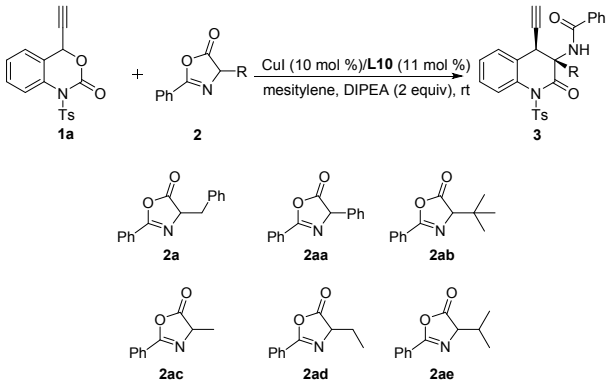
entry	L	solvent	yield (%) [b]	*dr* [c]	*er* (%) [d]
1	**L1**	toluene	84	87:13	75:25
2	**L2**	toluene	93	50/50	54:45
3	**L3**	toluene	trace	--	--
4	**L4**	toluene	93	90/10	12:88
5	**L5**	toluene	92	90/10	87:13
6	**L6**	toluene	92	94/6	40:70
7	**L7**	toluene	78	43/57	59:41
8	**L8**	toluene	68	40/60	60:40
9	**L9**	toluene	66	38/62	64:36
10	**L10**	toluene	88	92/8	90:10
11	**L11**	toluene	90	88/12	91:9
12	**L12**	toluene	75	84/16	78:22
13	**L13**	toluene	88	82/18	83:17
14	**L14**	toluene	80	83/17	16:84
15	**L10**	mesitylene	92	94/6	91:9
16	**L10**	DCE	92	65/35	82:18
17	**L10**	THF	85	83/17	81:19
18	**L10**	dioxane	78	88/12	91:9
19	**L10**	CH_3CN	78	75/25	53:47

[a] Reaction conditions: **1a** (0.05 mmol), **2a** (0.06 mmol), CuI (10 mol %), **L** (11 mol %), DIPEA (0.1 mmol), solvents (0.5 mL), 2 hours. [b] Isolated yield. [c] Determined by HPLC analysis and the *er* values refer to the major diastereoisomer. [d] Determined by HPLC analysis.

(Table 2, entries 4−6). In contrast, the phenylalanine-derived azlactone **2a** was finally proven to be the optimal substrate (Table 2, entry 1). Next, the substrate concentration was further examined for the reaction (Table 2, entries 7−9). When the substrate concentration was adjusted from 0.1 M to 0.0125 M, the reaction furnished the desired product **3a** in 90% yield with 96 : 4 *dr* and 93 : 7 *er*, albeit with prolonged reaction time of 12 hours (Table 2, entry 7, see ESI for details).

With the optimized conditions in hand, we proceeded to investigate the utility of the process for the synthesis of optically active 3,4-dihydroquinolin-2-one derivatives. As summarized in Scheme 2, the variation of ethynyl benzoxazinanones **1** was first studied. Substrates **1b**−**1f** with -methyl, -methoxyl, -chloro, and -

Table 2 Azlactone effects for copper-catalyzed formal [4+2] cycloaddition [a]

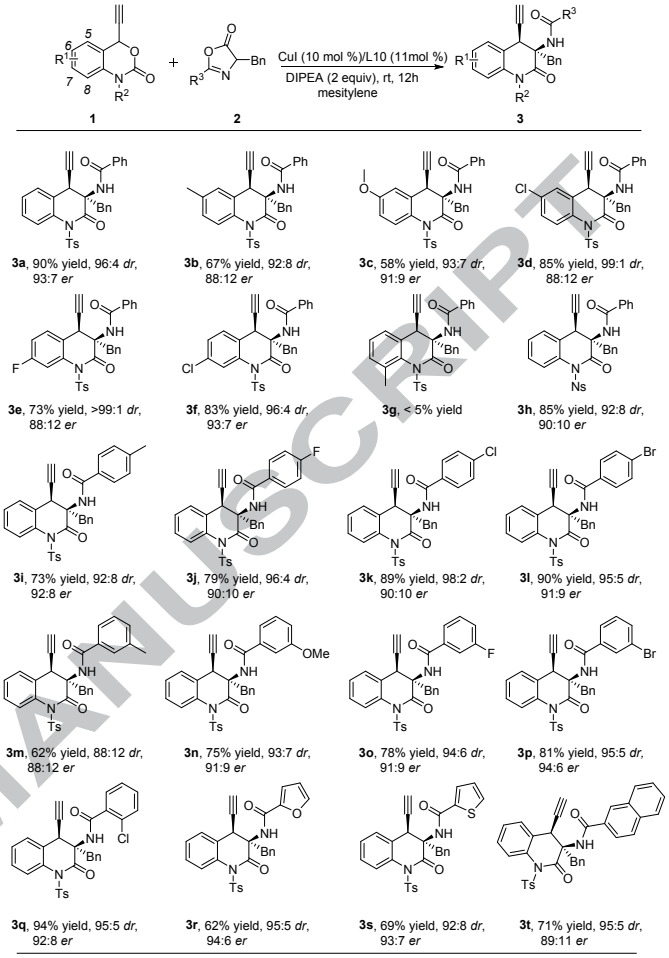


entry	azlactone	yield(%) [b]	dr [c]	*er* (%) [d]
1	**2a**	92	94/6	91:9
2	**2aa**	93	50/50	54:46
3	**2ab**	trace	--	--
4	**2ac**	93	90/10	88:12
5	**2ad**	92	90/10	86:14
6	**2ae**	92	94/6	70:30
7 [e]	**2a**	90	96/4	92:8
8 [f]	**2a**	90	96/4	93:7
9 [g]	**2a**	83	96/4	93:7

[a] Unless otherwise noted, reactions were carried out with **1a** (0.05 mmol), **2a** (0.06 mmol, 1.2 equiv), CuI (10 mol %) and **L10** (11 mol %), 0.1 M based on **1a**, 2 hours. [b] Isolated yield. [c] Determined by HPLC analysis and the *er* values refer to the major diastereoisomer. [d] Determined by HPLC analysis. [e] 0.025 M based on **1a**, 4 hours. [f] 0.0125 M based on **1a**, 12 hours. [g] 0.01 M based on **1a**, 12 hours.

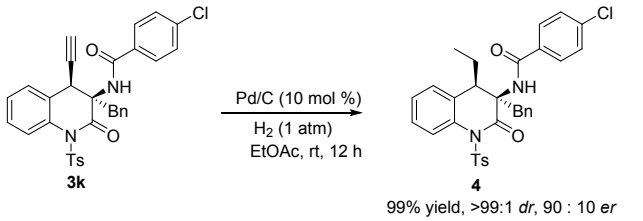
fluoro groups on the 6- or 7- positions of phenyl rings were tested in the reactions, which provided the annulation products in 58−85% yields with 92 : 8 to >99 :1 *dr*s and 88: 12 to 93 : 7 *er*s, respectively. However, 8-methyl-substituted substrate **1g** almost did not react with the substrate **2a** under the optimized conditions, affording the desired product **3g** in less than 5% yield. Then, the substrate **1h** with *N*-(4-nitrophenyl) sulfonyl group were also well-tolerated, which gave the desired product **3h** in 85% yield with 92 : 8 *dr* and 90 : 10 *er*. Then, the azlactones **2** were further investigated for this transformation. Those azlactones **2b–2i** bearing -methyl, -methoxyl, -fluoro, -chloro, and -bromo groups on the 3- or 4- positions of phenyl rings were all suitable partners for the reactions, which provided the desire products **3i–3p** with 62–90% yields, 88 : 12 to 98 : 2 *dr*, and 88 : 12 to 94 : 6 *er*, respectively. When the azlactone **2j** with a -chloro group on the 2- position of phenyl ring was employed in the reaction, and the desired product **3q** was obtained in 94% yield with 95 : 5 *dr* and 92 : 8 *er*. In addition, the substrates **2k** and **2l** containing heteroaromatic rings of 2-furyl or 2-thienyl were also suitable substrates, and the corresponding reactions resulted in the corresponding products **3r** and **3s** in 62% and 69% yields with 95 : 5 and 92 : 8 *dr* and 94 : 6 and 93 : 7 *er*, respectively. The substrate **2m** bearing a fused aromatic ring of 2-naphthyl was also well-tolerated for this reaction, which gave the desired products **3t** in 71% yield with 95 : 5 *dr* and 89 : 11 *er*.

The alkynyl group of the resulted products is a versatile and valuable functional group. To demonstrate the potential of this method for synthetic application, a hydrogenation reaction of **3k** was smoothly performed with the Pd/C catalyst under 1 atm



[a] Unless otherwise noted, reactions were carried out with **1a** (0.1 mmol), **2a** (0.12 mmol, 1.2 equiv), CuI (10 mol %) and **L10** (11 mol %), 0.0125 M based on **1a**.

Scheme 2 The substrate scope of the copper-catalyzed formal [4+2] cycloaddition [a]



Scheme 3 Hydrogenation reaction of **3k**

hydrogen pressure, which provided the desire product **4** in 99% yield with over 99 : 1 *dr* and 90 : 10 *er* (Scheme 3).

Conclusion

In summary, we have developed a formal [4 + 2] cycloaddition reaction between ethynyl benzoxazinanones and azlactones, which is catalyzed by a chiral copper−pybox mediated complex. A series of enantiomerically enriched 3,4-dihydroquinolin-2-one derivatives were obtained in high yields with good enantioselectivities and diastereoselectivities. Notably, 3,4-dihydroquinolin-2-one backbones are constructed by the reaction of the dipolar copper−allenylidene intermediates with the ready enolate azlactones. Generally, this transformation provides a

powerful synthetic route for the development of chiral 3,4-dihydroquinolin-2-one backbones.

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Supplementary Material

Highlights

1. Developing a high efficient enantioselective decarboxylative [4 + 2] cycloaddition

2. Providing a series of enantio-enriched 3,4-dihydroquinolin-2-one derivatives in high yields

3. Dipolar copper−allenylidenes as the key intermediates to react enolate azlactones

Graphical Abstract

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Asymmetric [4 + 2] Cycloaddition of Azlactones with Dipolar Copper-Allenylidene intermediates for Chiral 3,4-Dhydroquinolin-2-one Derivatives

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