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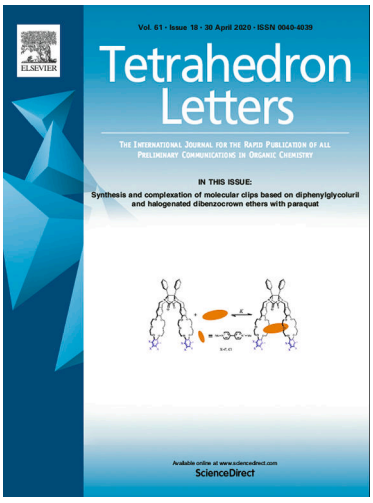

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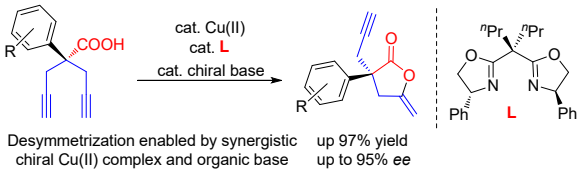

Desymmetrization enabled by synergistic chiral Cu(II) complex and organic base

up 97% yield
up to 95% *ee*

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Desymmetrization construction of chiral lactones by synergistic Cu(II) complex and organic base

Murad Ali[a], Changkun Li[a] *

[a] *Shanghai Key Laboratory for Molecular Engineering of Chiral Drugs, School of Chemistry and Chemical Engineering, Frontiers Science Center for Transformative Molecules, Shanghai Jiao Tong University, 800 Dongchuan Road, Shanghai 200240, China.*

* Corresponding author. e-mail: chkli@sjtu.edu.cn

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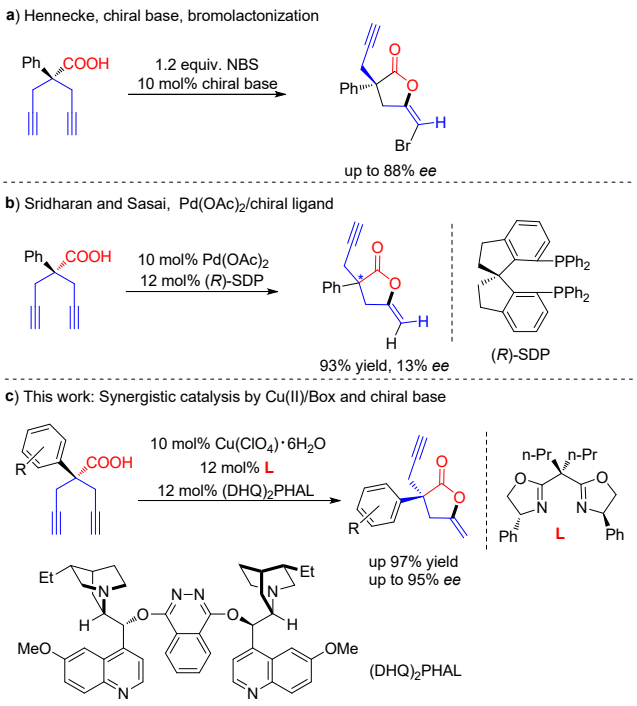
ABSTRACT

A highly enantioselective construction of quaternary carbon center has been realized by the desymmetrization strategy. Chiral enol lactones with up to 95% *ee* could be synthesized from prochiral dialkynoic acid under the catalysis of synergistic chiral Cu(II) complex and chiral $(DHQ)_2$-PHAL base.

Asymmetric construction of all-carbon quaternary carbon stereocenters is a challenging task in organic synthesis [1]. Desymmetrization conversion of only one between the two possible reaction sites in the prochiral substrates provides a successful strategy to build quaternary-carbon-containing chiral molecules [2]. Prochiral bisalkynes were frequently utilized for the versatile transformation of the triple bonds. Different types of reactions, such as hydroacylation [3], azide-alkyne cycloaddition [4], hydro-functionalization [5], were realized desymmetrically. In 2013, Hennecke reported the asymmetric bromolactonization of diynoic acid with chiral base $(DHQD)_2$-PHAL to prepare lactones with alkenyl bromide (Scheme 1) [6]. The enantioselectivity of lactone from terminal diynoic acid could be further improved to 88% with monomeric Cinchona alkaloid based catalyst [7]. The atom-economic direct lactonization could be catalyzed by many transition metals, such as Au, Pd, Ru, Rh, Ir, Cu, Co and others [8]. However, the asymmetric version is still far from optimal, due to the long distance between the reaction site and the prochiral stereocenter. Sridharan and Sasai developed a $Pd(OAc)_2$/(R)-SDP-catalyzed lactonization and low enantiomeric excess could be obtained for terminal diynoic acid [9]. Herein, we present the high enantioselective desymmetrization construction of chiral enol lactones by synergistic transition-metal catalysis and organocatalysis [10]. Up to 95% *ee* was obtained when catalytic amount of chiral Cu(II)/Box complex and chiral $(DHQ)_2$-PHAL were applied.

We commenced the study with phenyl substituted terminal diynoic acid **1a** as the model substrate (Table 1). When $Cu(OTf)_2$ and Box ligand **L1** were used, lactone **2a** was isolated with 92%yield and 42% *ee* (entry 1). Ligands with t-butyl and benzyl groups on the oxazoline rings were less selective than **L1** (entries 2 and 3). Keeping the phenyl on the oxazoline rings, the size effect of the ligand backbone was further examined. Lower



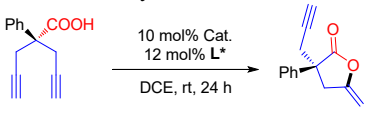
Scheme 1. Quaternary Carbon Centers Construction from Prochiral Dialkynes by Desymmetrical Lactonization.

en ther

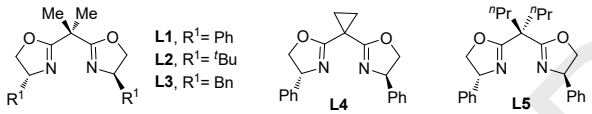
cyclopropane group was used (entry 4). While the reaction applying **L5** with bulkier two n-propyl groups lead to 62% *ee* (entry 5). $Cu(ClO_4)_2·6H_2O$ was proven to be a better catalyst precursor than $Cu(acac)_2$ and $Cu(MeCN)_4PF_6$ (entries 6-8), although the solubility of $Cu(ClO_4)_2·6H_2O$ is not good in DCE and a mixture of DCE and CH_3CN in 2 : 1 ratio has to be used as solvent. Lewis acidic Zn and Y metal salts other than Cu can also catalyze the reaction, albeit in lower enantioselectivities (entries 9-11). Inspired by the effect of chiral base in the bromolactonization reaction [6,7], several bases were added as additive. As we expected, the enantioselectivity increased to 89% *ee* when 12 mol% $(DHQ)_2$-PHAL was used (entry 12). The enantiomeric excess was further improved to 94% when the reaction was run at 0 °C (entry 13). Control experiments were conducted to examine the effect of the chiral base $(DHQ)_2$-PHAL. 90% of racemic **2a** was isolated when $(DHQ)_2$-PHAL was used without the help of any chiral Box ligand (entry 14). The other enantiomer of the product was obtained predominantly (-54% ee) when ent-**L5** (the other enantiomer of L5) and $(DHQ)_2$-PHAL were used (entry 15).

Table 1

Optimization of the Cu(II)/Box and $(DHQ)_2$-PHAL Co-catalyzed Lactonization of Terminal Diynoic Acid[a]



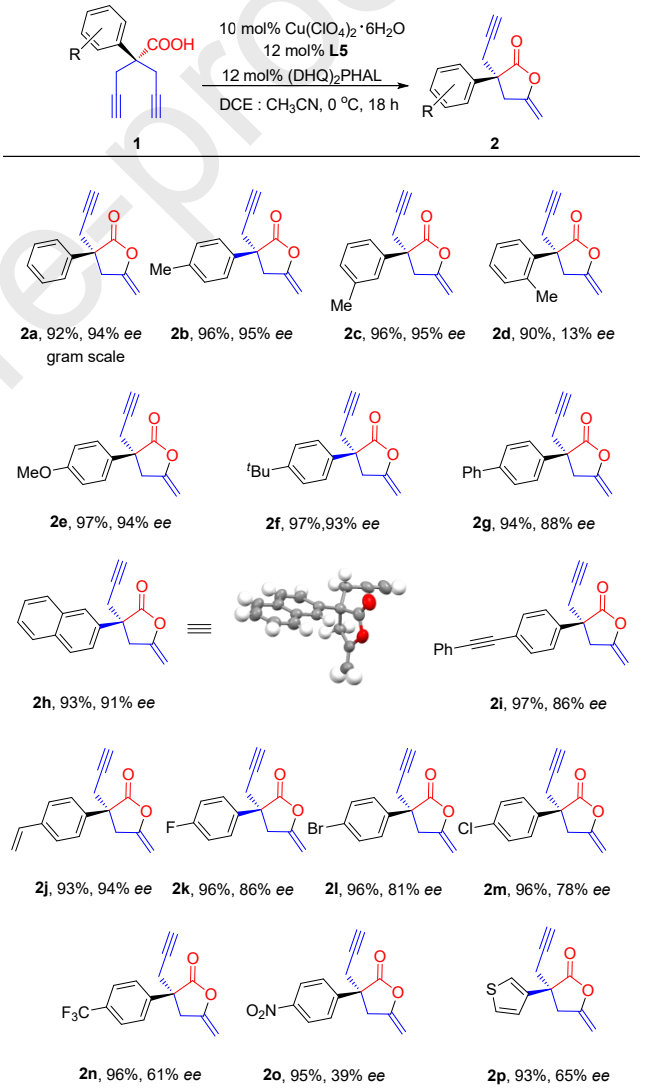
1a, 0.2 mmol **2a**



entry	catalyst	ligand	yield (%)[b]	*ee* (%)[c]
1	$Cu(OTf)_2$	**L1**	92	42
2	$Cu(OTf)_2$	**L2**	94	26
3	$Cu(OTf)_2$	**L3**	90	2
4	$Cu(OTf)_2$	**L4**	59	30
5	$Cu(OTf)_2$	**L5**	93	62
6[d]	$Cu(ClO_4)_2·6H_2O$	**L5**	97	66
7	$Cu(acac)_2$	**L5**	91	47
8	$Cu(CH_3CN)_4PF_6$	**L5**	90	61
9	$Zn(OTf)_2$	**L5**	94	30
10	$Zn(BF_4)_2$	**L5**	87	35
11	$Y(OTf)_3$	**L5**	85	13
12[d,e]	$Cu(ClO_4)_2·6H_2O$	**L5**	93	89
13[d,e,f]	$Cu(ClO_4)_2·6H_2O$	**L5**	93	94
14[d,e]	$Cu(ClO_4)_2·6H_2O$	-	90	0
15[d,e,f]	$Cu(ClO_4)_2·6H_2O$	***ent*-L5**	95	-54

[a] Conditions: 0.2 mmol of **1a** in DCE (2.0 mL).
[b] Isolated yield.
[c] The enantiomeric excess of **2a** was determined by HPLC with a chiral column.
[d] A mixture of DCE and CH_3CN in 2 : 1 ratio was used as solvent.
[e] 12 mol% of $(DHQ)_2$-PHAL was added, 12 h.
[f] Reaction was run at 0 °C, 18 h.

With the optimized condition in hand, we examined the scope of the Cu(II)/Box and $(DHQ)_2$-PHAL co-catalyzed lactonization (Scheme 2). Firstly, the synthesis of **2a** could be conducted in 1 gram scale without erosion of the enantioselectivity. Methyl groups at para- or meta-position of the phenyl ring have neglectable effect to the enantioselectivities of the lactones (**2b** and **2c**). On the contrast, only 13% ee was obtained in **2d** with an ortho-methyl substituted phenyl group. The electronic effect of



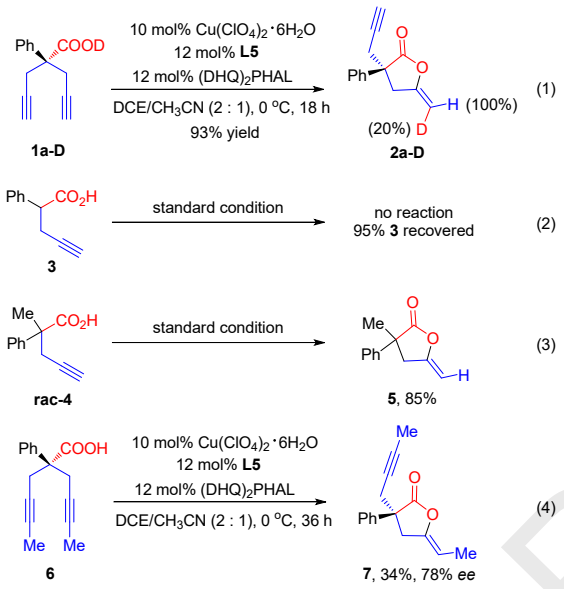
2a, 92%, 94% *ee* gram scale; 2b, 96%, 95% *ee*; 2c, 96%, 95% *ee*; 2d, 90%, 13% *ee*; 2e, 97%, 94% *ee*; 2f, 97%,93% *ee*; 2g, 94%, 88% *ee*; 2h, 93%, 91% *ee*; 2i, 97%, 86% *ee*; 2j, 93%, 94% *ee*; 2k, 96%, 86% *ee*; 2l, 96%, 81% *ee*; 2m, 96%, 78% *ee*; 2n, 96%, 61% *ee*; 2o, 95%, 39% *ee*; 2p, 93%, 65% *ee*

Scheme 2. Scope for Cu(II)/Box and $(DHQ)_2$-PHAL Co-catalyzed Lactonization.

product **2p** in high yield with modest enantioselectivity (65% *ee*).

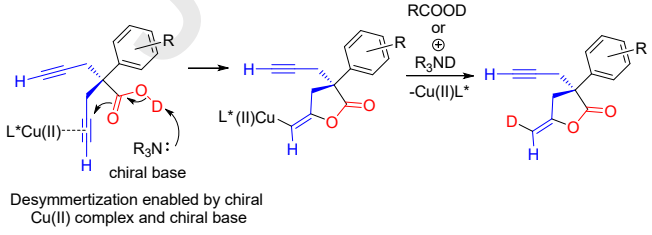
To gain more insight into reaction mechanism, some control experiments were conducted (scheme 3). Deuterium labelled diynoic acid **1a**-D was tested under standard reaction condition

(eq in transformed into D (20%), which was supported by the NOE analysis. This result may suggest that an intramolecular anti-addition of the carboxylic acid to a Cu-activated alkyne intermediate is involved. When 2-phenylpent-4-ynoic acid **3** was tested, no any cyclization product was observed and the substrate was recovered in 95% yield (eq 2). However, 2-methyl-2-phenylpent-4-ynoic acid **rac-4** with a quaternary carbon center was converted to the lactone **5** in 85% yield, probably due to the short distance between acid and alkyne group caused by Thorpe-Ingold effect (eq 3). Finally, **6** with two internal alkynes was converted to the enol lactone **7** in relatively lower yield and enantioselectivity, which indicates the terminal alkynes are not mandatory for the reactivities and the Cu-acetylide formation might be not involved (eq 4).



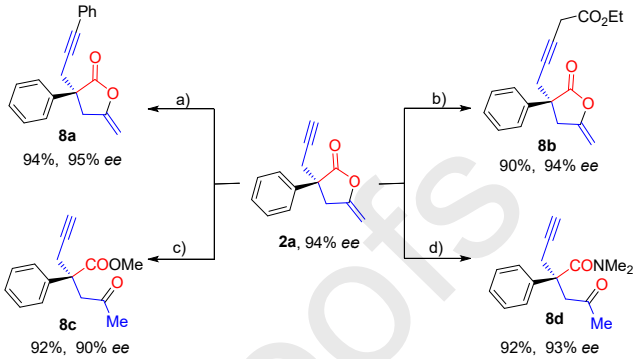
Scheme 3. Mechanism Studies.

Based on the experiments above and the literature reports, a tentative mechanism was proposed in Scheme 4. Chiral Cu(II) complex coordinates with one of the two alkyne groups selectively under the help of matched chiral organic base, which is the key step for the desymmetrization process. When R on the phenyl is a neutral or electron-donating group, a concerted deprotonation by the chiral base and anti-attack of the carbonyl oxygen to the Cu-activated alkyne affords the alkenyl Cu intermediate. Further protonation of the Csp^2-Cu bond by the ammonium salt or the free carboxylic acid delivers the enol lactone **2** and releases the Cu(II) catalyst. In case R is an electron-withdrawing group, the acidity of the carboxylic acid increases and the anti-addition to the alkyne is at least partially not controlled by the chiral amine, which leads to the low enantioselectivities observed.



Scheme 4. Mechanism Proposal.

To illustrate the potential synthetic application of newly developed method, further transformations of the chiral enol lactone **2a** were performed (Scheme 5). Sonogashira coupling of **2a** with phenyl bromide under Pd/Cu catalysis delivers **8a** in good yield and the enantioselectivity remains. Reaction of **2a** in good yield and *ee* [12]. Ring opening of the enol lactone by nucleophilic addition of methanol or dimethylamine to **2a** produces ester **8c** and amide **8d** respectively under mild reaction conditions in good yields with small erosion of *ee*. An all-carbon quaternary carbon center with three versatile functional groups (alkyne, ketone and ester or amide) could be constructed with high enantioselectivities.



Scheme 5. Synthetic Transformation of Enol lactone **2a**. [a]Conditions: a) PhBr (2.5 equiv), $Pd(PPh_3)_2Cl_2$ (2 mol%), CuI (4 mol%), Et_3N (2 equiv), DMF, 50 °C, 12 h. b) N_2CHCO_2Et (1.1 equiv), CuI (5 mol%), MeCN, rt, 5 h. c) CH_3OH (1 ml, excess), $NH(CH_3)_2$ (2 M in THF, 1.1 equiv), 50 °C, 3 h. d) $NH(CH_3)_2$ (1 ml, 2 M in THF), rt, 12 h..

In conclusion, we have developed a highly enantioselective synthesis of enol lactones with a quaternary carbon centre. Chiral enol lactones with up to 95% *ee* could be synthesized from prochiral dialkynoic acid under the catalysis of synergistic chiral Cu(II) complex and chiral $(DHQ)_2$-PHAL base. The reaction could be conducted in gram scale and the products were easily transformed to chiral molecules with different functional groups. The extension of this strategy to other types of reactions from prochiral bisalkynes is under investigation in our group.

Acknowledgments

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