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Copper catalyzed tandem asymmetric conjugate addition–cyclization reaction in the presence of chiral phosphoramidite ligands

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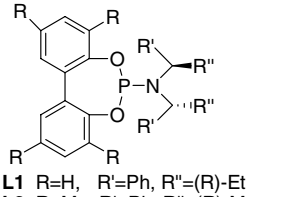
Abstract—Copper-catalyzed intramolecular conjugate addition–cyclization in the presence of chiral phosphoramidite ligands was described. Cyclic products with multiple chiral centers were obtained with up to 93:7 diastereomeric ratio and 94% ee.

Conjugate addition–cyclization is recognized as one of the most attractive strategies for carbon–carbon bond formation and the construction of cyclic compounds.[1] Few examples have shown that a catalytic conjugate addition–cyclization can be achieved by organocatalytic Michael cyclization[1a,b] or by using transition metal catalysts.[1c,d] In the latter, the transition metal catalysts are mainly limited to rhodium or palladium complexes. Less efforts were made toward the use of other cheaper metal catalysts. As part of research projects in our lab, copper chemistry was extensively investigated particularly for the copper-catalyzed 1,4-additon of dialkyl zinc or trialkyl aluminum reagents to α,β-unsaturated carbonyl compounds in the presence of phosphoramidite ligands.[2] Furthermore, several research groups disclosed that the intermediate zinc enolate can easily be trapped by electrophilic reagents such as aldehydes,[3] Pd-π-allyl,[3a,4] halides and tosylates,[5] and oxocarbenium ions.[6] Based on this concept, Krische[7] recently found that the conjugate addition of enones, possessing appendant ketone, ester and nitrile moieties to organozinc reagents in the presence of catalytic $Cu(OTf)_2/P(OEt)_3$ successfully provided the racemic cyclic products in good to excellent yields and diastereoselectivities. We herein present our results of the copper-catalyzed intramolecular conjugate addition–cyclization in the presence of chiral phosphoramidite ligands, which provides a novel and promising pathway to construct cyclic compounds with multiple chiral centers.

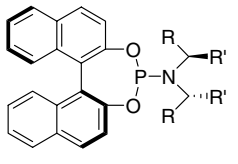
The chiral phosphoramidite ligands **L1**–**L7** were easily prepared from biphenol or binaphthol and the corresponding chiral amines according to the procedures we reported before (Fig. 1).[2a,b]

The initial screening of the chiral phosphoramidite ligands on substrate **S1** was performed under the standard conditions developed in our lab[2] (typical procedure see Ref. 8). The results are revealed in Table 1 (Scheme 1).

All the reactions proceeded with full conversion and the cyclic products were formed as a mixture of two diastereomers with various ratios that depended on the ligand used. The biphenol-derived ligands **L1**–**L4** gave the moderate diastereomeric ratios which varied from 63:37 to 86:14. For ligand **L2**, $Cu(OTf)_2$ (entry 2) was



L1 R=H, R'=Ph, R''=(R)-Et
L2 R=Me, R'=Ph, R''=(R)-Me
L3 R=Me, R'=Ph, R''=(R)-Et
L4 R=Me, R'=2-Napth, R''=(R)-Me



L5 R=Ph, R'=(R)-Me
L6 R=Ph, R'=(R)-Et
L7 R=2-Napth, R'=(R)-Me

Figure 1.

Keywords: Copper; Tandem; Conjugate addition; Cyclization; Chiral; Phosphoramidite ligands.
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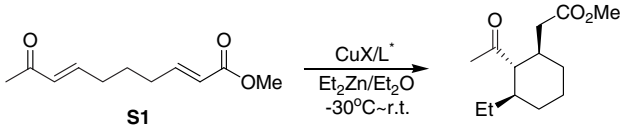
Table 1. Results of conjugated addition–cyclization on substrate **S1**

Entry	Ligand	CuX	Conv.%[a]	dr[a]	ee%[b]	Config.[e]
1	**L1**	$Cu(OTf)_2$	>99	74:26[c]	68(3)	(*R*,*S*,*R*)-
2	**L2**	$Cu(OTf)_2$	>99	73:27	72(9)	(*R*,*S*,*R*)-
3	**L2**	CuTC	>99	67:33	34(36)	(*R*,*S*,*R*)-
4	**L2**	$Cu(OAc)_2{\cdot}H_2O$	>99	63:37	25(37)	(*R*,*S*,*R*)-
5[d]	**L2**	$Cu(OTf)_2$	>99	86:14	81(18)	(*R*,*S*,*R*)-
6	**L3**	$Cu(OTf)_2$	>99	73:27	17(67)	(*R*,*S*,*R*)-
7	**L4**	$Cu(OTf)_2$	>99	75:25	70(9)	(*R*,*S*,*R*)-
8	**L5**	$Cu(OTf)_2$	>99	80:20	66(1)	(*S*,*R*,*S*)-
9	**L6**	$Cu(OTf)_2$	>99	80:20	47(30)	(*S*,*R*,*S*)-
10	**L7**	$Cu(OTf)_2$	>99	87:13	33(86)	(*S*,*R*,*S*)-

[a] Determined by GC–MS.
[b] Ee measured by Chiral GC on the major diastereomer in parenthesis, ee of the minor one. Separation condition: Hydrodex-B-3P, 40 cm/s, 60-0-1-170-10, $T1 = 85.43$ min, $T2 = 85.81$ min, $T3 = 89.95$ min, $T4 = 90.33$ min.
[c] 76:24 ratio after isomerization using DBU (1,8-diazabicyclo[5,4,0]undec-7-ene) in MeOH.
[d] Toluene used as solvent.
[e] Absolute configuration assigned by comparison with analogous adduct derived from *trans*-3-nonen-2-one and Et_2Zn.[2c,9]

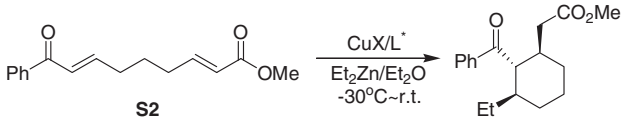


Scheme 1.

found to be more efficient than CuTC (copper thiophene-2-carboxylate) (entry 3) and $Cu(OAc)_2{\cdot}H_2O$ (entry 4) for the ratio improvement. The best ratio (86:14) was obtained using toluene as solvent (entry 5). Under the same condition, a better ratio (75:25) was obtained from ligand **L4** (entry 7) possessing a bulky group on the amino part. This effect was also observed in the binaphthol based ligand **L7** (entry 10). In this case, the ratio was increased to 87:13, which was better than ligand **L5** (entry 8) and the slightly modified one **L6** (entry 9). Concerning the enantioselectivities, it was found that the ligands **L2**–**L4** with a tetramethyl substituted biphenol backbone exhibited higher enantioselectivity (entry 2, 6, and 7) than ligand **L5** (entry 8) under the same conditions. For ligand **L2**, some variations of the ee were detected using various copper salts (entries 2–4). The non-coordinating solvent toluene was proved to be useful for the improvement of both the ratio and the ee (entry 5). The reaction with other ligands provided the expected cyclic product with moderate ratios and enantioselectivities. The ratio of isomers almost did not change after isomerization with DBU (entry 1).

To examine the effect of substrate structure on the ratio and enantioselectivity, we synthesized substrate **S2** containing an aromatic group on the enone moiety and carried out the conjugate addition–cyclization reaction in the presence of a variety of chiral ligands (Scheme 2). The results are summarized in Table 2.

In comparison with substrate **S1**, it was interesting to find that in most cases both the diastereomeric ratios



Scheme 2.

Table 2. Conjugated addition–cyclization on **S2** with diethyl zinc

Entry	Ligand	CuX	Conv.[a]	dr[a]	ee%[b]	Config.[e]
1	**L1**	$Cu(OTf)_2$	>99	91:9	47(62)	(*R*,*S*,*R*)-
2	**L2**	$Cu(OTf)_2$	>99	78:22	54(48)	(*R*,*S*,*R*)-
3	*ent*-**L3**	$Cu(OTf)_2$	>99	81:19	88(90)	(*S*,*R*,*S*)-
4	*ent*-**L3**	CuTC	>99	92:8	91(90)	(*S*,*R*,*S*)-
5[c]	**L3**	CuTC	>99	93:7	92(86)	(*R*,*S*,*R*)-
6	*ent*-**L3**	$Cu(OAc)_2{\cdot}H_2O$	>99	90:10	92(87)	(*S*,*R*,*S*)-
7	**L4**	$Cu(OTf)_2$	>99	65:35	45(43)	(*R*,*S*,*R*)-
8	**L5**	$Cu(OTf)_2$	>99	76:24	7(49)	(*S*,*R*,*S*)-
9	**L6**	$Cu(OTf)_2$	>99	80:20	72(51)	(*S*,*R*,*S*)-
10	**L7**	$Cu(OTf)_2$	>99	69:31[d]	45(2)	(*S*,*R*,*S*)-

[a] Determined by GC–MS.
[b] Ee measured by SFC on the major diastereomer in parenthesis, ee of the minor one. Separation condition: Chiral OD-H, 200Bar, 2%-6-1-15%, 2 ml/min, 10 °C, $T1 = 3.93$ min, $T2 = 4.12$ min, $T3 = 4.49$ min, $T4 = 4.83$ min.
[c] Toluene used as solvent.
[d] 70:30 ratio after isomerization using DBU in MeOH.
[e] Absolute configuration assigned by comparison with analogous adduct derived from *trans*-3-nonen-2-one and Et_2Zn.[2c,9]

and the enantioselectivities of the two isomers were remarkably improved. For the simple ligand **L1** (entry 1), good ratio (91:9) was resulted but only moderate enantiomeric excess was obtained. Ligand **L2** derived from tetramethyl substituted biphenol led to a 78:22 ratio and moderate ee (entry 2). The structurally similar ligand **L3** improved both the ratio and the enantiomeric excess. Further investigation on the copper salt effect was performed. $Cu(OTf)_2$/*ent*-**L3** (entry 3) catalyzed conjugate addition–cyclization of **S2** providing the product with 81:19 ratio, 88% ee and 90% ee, respectively. The ratio was increased to 92:8 using CuTC (entry 4) instead of $Cu(OTf)_2$ and also a slight improvement of the ee was observed. Finally, the cheaper copper salt $Cu(OAc)_2{\cdot}H_2O$ also gave very good results (entry 6). The ratio increased to 93:7 but no significant change of the ee was observed when toluene was used as solvent (entry 5). In contrast to the results obtained with substrate **S1**, we found that the binaphthol based ligand **L5** and **L7** (entries 8 and 10) and the much more sterically hindered ligand **L4** (entry 7) showed lower diastereomeric ratios and lower enantioselectivities. Ligand **L6** (entry 9), possessing an ethyl group instead of methyl on the amine part, afforded higher ratio and ee compared with ligand **L5** and ligand **L7**. No change of the ratio was observed after isomerization using DBU (entry 10).

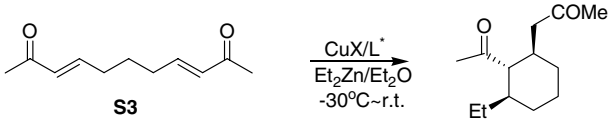
The dienone substrate **S3** was also subject to this reaction in the presence of the chiral ligands (Scheme 3). Diethyl zinc (1.2 equiv) was used to avoid the formation of by-products due to the existence of two reactive positions in this molecule.

The results presented in Table 3 showed that the ligand structure has no significant influence on the ratio, which slightly varied from 80:20 to 84:16. This effect was not found in the case of substrate **S1** and **S2**. Concerning the enantioselectivities in most of the cases, moderate to good enantiomeric excesses of the two isomers were obtained. The best result was obtained with the binaphthol based ligand **L7** which led to 79% ee and 88% for the two isomers, respectively.

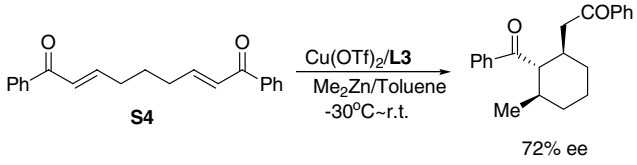
As shown above, no obvious change of the diastereomeric ratio was observed (Table 1, entry 1 and Table 2, entry 10) after isomerization using DBU. It indicates that the ratios reflected upon the *trans*-/*cis*- in the cyclization step. To further determine the stereochemistry of the cyclic products, we prepared the known compound from substrate **S4** and dimethyl zinc in the presence of ligand **L3** (Scheme 4). GC–MS and NMR analysis suggested that only one isomer was formed. And the NMR spectrum (^1H, ^{13}C) is absolutely identical as the structurally determined diastereomer described in the previously reported literature.[10] It means that the reaction proceeds as the *trans* conjugate addition followed by the *trans* trapping of the zinc enolate. By analogy with this result and Krische's[10] work, the stereochemistry of all the major cyclic products should be determined as *trans*,*trans*-conformation and *trans*,*cis*-conformation for the minors.

To illustrate the synthetic potential of this transformation, preliminarily, we carried out the further cyclization under basic conditions (Scheme 5). In both of the cases, the bicyclic compound[11] was formed and isolated as a single isomer with high enantiomeric excess. The assignment of stereochemistry of the bicyclic products is still in progress.

In summary, we disclosed an efficient pathway to build cyclic compounds with multi-chiral centers that allows



Scheme 3.



Scheme 4.

Table 3. Conjugated addition–cyclization on substrate **S3**

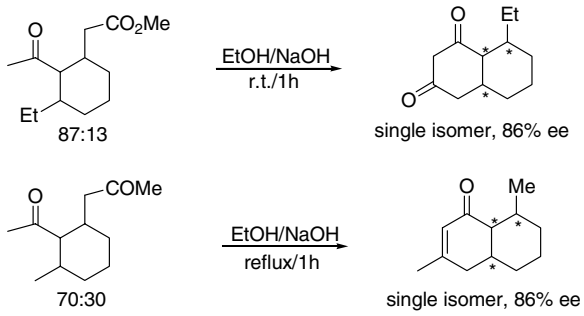
Entry	Ligand	CuX	Conv.%[a]	dr[a]	ee%[b]	Config.[d]
1	**L1**	$Cu(OTf)_2$	>99	80:20	53(75)	(*R*,*S*,*R*)-
2	*ent*-**L2**	$Cu(OTf)_2$	>99	82:18	60(79)	(*S*,*R*,*S*)-
3	**L3**	$Cu(OTf)_2$	>99	84:16	27(65)	(*R*,*S*,*R*)-
4	**L4**	$Cu(OTf)_2$	>99	80:20	62(83)	(*R*,*S*,*R*)-
6	*ent*-**L5**	$Cu(OTf)_2$	>99	79:21	67(82)	(*R*,*S*,*R*)-
7	**L6**	$Cu(OTf)_2$	>99	80:20	58(75)	(*S*,*R*,*S*)-
8	**L7**	$Cu(OTf)_2$	>99	80:20	79(88)	(*S*,*R*,*S*)-
9[c]	**L7**	$Cu(OTf)_2$	>99	70:30	88(94)	(*S*,*R*,*S*)-

[a] Determined by GC–MS.

[b] Ee measured by SFC on the major diastereomer in parenthesis, ee of the minor one. Separation condition: Hydrodex-B-3P, 30 cm/s, 60-0-1-170-10, $T1 = 78.33$ min, $T2 = 79.48$ min, $T3 = 85.48$ min, $T4 = 86.27$ min.

[c] Me_2Zn was used, toluene as solvent.

[d] Absolute configuration assigned by comparison with analogous adduct derived from *trans*-3-nonen-2-one and Et_2Zn.[2c,9]



Scheme 5.

the possibility to construct elaborated natural products. This work is still in progress in our laboratories.

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References and notes

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