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Copper(I)-Catalyzed Asymmetric Desymmetrization: Synthesis of Five-Membered-Ring Compounds Containing All-Carbon Quaternary Stereocenters

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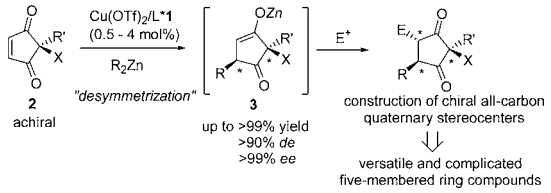
Supporting Information

ABSTRACT: A highly stereoselective catalytic alkylation sequence for the synthesis of highly functionalized and versatile five-membered-ring compounds bearing all-carbon quaternary stereocenters was developed. Enantioselective desymmetrization of achiral cyclopentene-1,3-diones was thus executed by chiral Cu–phosphoramidite catalysts. A variety of complicated cyclopentane derivatives can be synthesized with excellent stereoselectivities using a low catalyst loading in a one-pot operation.

For fine-chemicals and materials science, efficient synthetic methods for versatile building blocks in enantiopure forms have attracted much attention.[1] In comparison with the formation of quaternary stereocenters bonded to a heteroatom (e.g., tertiary alcohols or amines), the formation of all-carbon quaternary stereocenters poses a particular challenge due to the inherent steric congestion.[2] Thus, reliable and divergent methods for the catalytic formation of all-carbon quaternary stereocenters with excellent enantioselectivities are quite limited even in modern synthetic organic chemistry.[2] On the other hand, asymmetric desymmetrization,[3] especially using chiral transition-metal catalysts, is an efficient and powerful method for synthesizing optically active substances with complex structures. Through differentiation of two enantiotopic groups on readily prepared meso or achiral substrates, this process can afford chiral/nonracemic compounds bearing multiple chiral centers in a controlled fashion.[4,5]

Enantiomerically enriched five-membered-ring compounds such as cyclopentane and cyclopentene derivatives are highly important building blocks for the basic structural motifs of many natural products and bioactive compounds.[6] The development of synthetic methods for the preparation of these compounds has been strongly desired.[7] For this objective, we envisioned using enantioselective Cu-catalyzed conjugate additions because of the reliable and practical catalytic systems.[2c,8] Herein we report that asymmetric syntheses of complicated but versatile five-membered-ring compounds bearing all-carbon quaternary stereocenters can be achieved through desymmetrization of achiral cyclopentene-1,3-diones using Cu catalysts with chiral phosphoramidite ligands[9] (Scheme 1).[10] The advantage of this method is that various five-membered-ring compounds can be readily prepared with excellent stereoselectivity using not only a low catalyst loading (up to 0.5 mol %) but also a simple one-pot operation. The process can also be applied as a powerful tool for the concise synthesis of a precursor of madindolines A and B[11,12] containing their chiral cyclopentene-1,3-dione motif.

Scheme 1. Asymmetric Desymmetrization of Various Cyclopentene-1,3-diones Based on Chiral Cu Catalysts



Initially, we designed symmetrical cyclopentene-1,3-dione **2a** containing methyl and benzyloxymethyl groups as an achiral substrate for enantioselective desymmetrization. In the presence of a Cu salt (4 mol %) and phosphoramidite ligand **1b** (8 mol %) at −40 °C with Et_2Zn as an alkylation reagent, the reaction proceeded smoothly and afforded the alkylated product **3a** and its diastereomer **4a** in good to high yields (Table 1). In toluene and CH_2Cl_2 as noncoordinating solvents, the reaction gave high yields with low enantioselectivities and diastereomeric ratios similar to that obtained under the reaction conditions without **1b** (entries 2 and 3 vs 1). In this catalytic system, the solvent has a significant effect on not only the catalytic activity of the Cu complex but also the stereocontrol of the 1,4-addition (entries 2–8). Indeed, ether-type solvents increased the diastereo- and enantioselectivity (entries 5–8). Particularly, diethyl ether led to the best results, giving **3a** (dr > 95:5) in 91% yield and 60% ee within 30 min (entry 8). The effect of the Cu salt was also surveyed. $Cu(OAc)_2$ and $(CuOTf)\cdot C_6H_6$ showed slightly decreased enantioselectivities but gave almost the same results as $Cu(OTf)_2$ (entries 9 and 10). The use of cationic $Cu(CH_3CN)_4(BF_4)$ led to lower stereocontrol (entry 11). $CuBr\cdot SMe_2$ provided excellent diastereoselectivity but racemic product (entry 12). These data suggest that OTf^- and OAc^-, which can form chelates with Cu and Zn, play a key role in the enantio- and diastereoselection by the catalytic active species.[8a,13]

A number of phosphoramidite ligands[9] were next assayed with the aim of increasing the enantioselectivity (Table 2). Indeed, the investigation of the effect of a variety of substituents at the 3- and 3′-positions of the binaphthol backbone led to a remarkable improvement in the enantioselectivity. Ligand **1a**

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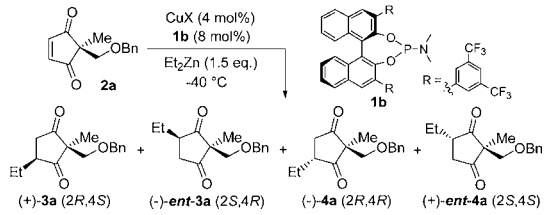
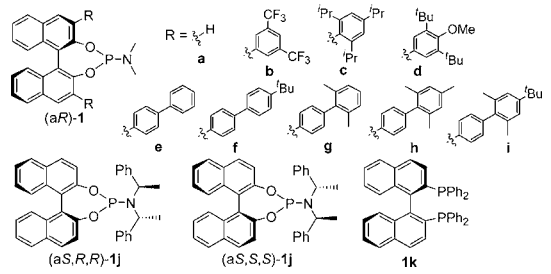
Table 1. Cu-Catalyzed Enantioselective Desymmetrization[a]



entry	CuX	solvent	*t* (h)	yield (%)[c]	*dr*[d] (**3a** : **4a**)	*ee* (%)[e] (**3a**)
1[b]	$Cu(OTf)_2$	toluene	1	79	66 : 34	-
2	$Cu(OTf)_2$	toluene	1	92	75 : 25	29 (+)
3	$Cu(OTf)_2$	CH_2Cl_2	0.5	97	73 : 27	29 (+)
4	$Cu(OTf)_2$	CH_3CN	4	87	53 : 47	2 (+)
5	$Cu(OTf)_2$	DME	24	87	80 : 20	68 (-)
6	$Cu(OTf)_2$	THF	24	83	81 : 19	51 (-)
7	$Cu(OTf)_2$	TBME	2	98	92 : 8	38 (-)
8	$Cu(OTf)_2$	Et_2O	0.5	91	>95 : 5	60 (-)
9	$Cu(OAc)_2$	Et_2O	0.5	90	>95 : 5	51 (-)
10	$(CuOTf)_2 \cdot C_6H_6$	Et_2O	0.5	94	>95 : 5	52 (-)
11	$Cu(CH_3CN)_4(BF_4)$	Et_2O	0.5	69	76 : 24	18 (-)
12	$CuBr \cdot SMe_2$	Et_2O	0.5	86	>95 : 5	0

[a]Conditions: **2a** (0.1 mmol), Et_2Zn (0.15 mmol), Cu salt (0.004 mmol), and chiral ligand **1b** (0.008 mmol) in solvent (1 mL) at −40 °C. [b]Chiral ligand **1b** was not used. [c]Isolated yields. [d]Determined by ^1H NMR analysis. [e]Determined by chiral HPLC analysis.

Table 2. Effects of Chiral Ligands 1a−k[a]



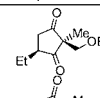
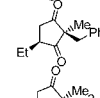
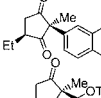
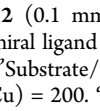
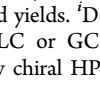
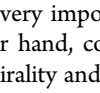
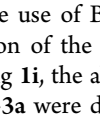
entry	L*	yield (%)[b]	*dr*[c] (**3a** : **4a**)	*ee* (%) of **3a**[d]
1	**1a**	86	71 : 29	2 (-)
2	**1b**	91	>95 : 5	60 (-)
3	**1c**	87	>95 : 5	32 (-)
4	**1d**	91	>95 : 5	37 (-)
5	**1e**	91	96 : 4	73 (+)
6	**1f**	90	>95 : 5	82 (+)
7	**1g**	96	>95 : 5	95 (+)
8	**1h**	99	>95 : 5	96 (+)
9	**1i**	98	>95 : 5	97 (+)
10	(aS,*R*,*R*)-**1j**	87	94 : 6	56 (+)
11	(aS,*S*,*S*)-**1j**	78	80 : 20	17 (-)
12[e]	**1k**	0[f]	-	-

[a]Conditions: **2a** (0.1 mmol), Et_2Zn (0.15 mmol), $Cu(OTf)_2$ (0.004 mmol), and chiral ligand **1** (0.008 mmol) in Et_2O (1 mL) at −40 °C for 30 min. [b]Isolated yields. [c]Determined by ^1H NMR analysis. [d]Determined by chiral HPLC analysis. [e]Me_2Zn instead was used of Et_2Zn. [f]Decomposition of substrate **2a**.

without substituents at the 3- and 3′-positions gave almost racemic product (entry 1). In addition, **1c** and **1d** with ortho- and meta-substituted phenyl rings, respectively, afforded lower enantioselectivities, probably because of increased steric repulsion (entries 3 and 4). In sharp contrast, the use of **1f** with para-substituted aryl rings increased the enantioselectivity (82% ee), and interestingly, the absolute configuration of the obtained product, (2*R*,4*R*)-(+)-**3a**, was opposite to that of (2*S*,4*S*)-(−)-**3a** obtained by the reactions using **1a−d** (entry 6). Moreover, the use of **1g−i** dramatically increased the enantioselectivity, with **1i** giving the highest enantiomeric excess (97% ee) and an excellent yield (entry 9). These results definitely indicate that appropriate steric hindrance by the substituents at the 3- and 3′-positions of the binaphthol backbone is very important for control of the stereochemistry. On the other hand, commercially available ligand **1j** with two centers of chirality and one center of *S*-axial chirality performed poorly concerning both yield and stereoselectivity (entries 10 and 11). The use of BINAP (**1k**) as a bidentate ligand led to decomposition of the substrate (entry 12). In the case of the reaction using **1i**, the absolute and relative configurations of the product (+)-**3a** were determined to be 2*R*,4*S* by X-ray analysis of a single crystal of **6a** (see below).

With the effective catalyst system identified via screening of phosphoramidite ligands in hand, the substrate scope with respect to the substituents of the quaternary carbon center was explored (Table 3). Reactions with Me_2Zn and $^nBu_2Zn$ instead of Et_2Zn provided the corresponding products **3a-Me** and **3a-Bu** in excellent yields and stereoselectivities (entries 2 and 6). For Me_2Zn in particular, even with a lower catalyst loading (0.5 mol %), the excellent yield and stereoselectivity were maintained (entry 3). High enantioselectivity was also achieved in the presence of a 1:1 ratio of $Cu(OTf)_2$ and ligand **1i** (entry

Table 3. Use of a Variety of Cyclopentene-1,3-diones 2a−k[a]

entry	product		yield (%)[h]	*dr*[i] (**3** : **4**)	*ee* (%)[j] of **3**
1[b]		**3a**	98	>95 : 5	97 (+) (2*R*,4*S*)
2		**3a-Me**	96	>95 : 5	>99 (+) (2*R*,4*S*)
3[c]		**3a-Me**	94	>95 : 5	99 (+) (2*R*,4*S*)
4[d]		**3a-Me**	96	>95 : 5	>99 (+) (2*R*,4*S*)
5[e]		**3a-Me**	97	>95 : 5	>99 (+) (2*R*,4*S*)
6		**3a-Bu**	98	>95 : 5	98 (+)
7[b]		**3b-Me**	93	>95 : 5	>99 (+)
8		**3c**	99	>95 : 5	95 (+)
9		**3d**	>99	>95 : 5	98 (+)
10		**3e**	97	>95 : 5	97 (+)
11		**3f**	>99	90 : 10	91 (+)
12		**3g**	95	>95 : 5	88 (+)
13		**3h**	96	80 : 20	70 (+)
14		**3i**	85	91 : 9	88 (+)
15[f]		**3j**	92	93 : 7	75 (-)
16		**3k**	96	90 : 10	81 (+)
17		**3l**	41	5 : >95	36 (+)[k]
18[g]		**3l**	88	5 : >95	50 (-)[k]

[a]Conditions: **2** (0.1 mmol), R_2Zn (0.15 mmol), $Cu(OTf)_2$ (0.004 mmol), and chiral ligand **1i** (0.008 mmol) in Et_2O (1 mL) at −40 °C for 30 min. [b]Substrate/catalyst (**2a** or **2b**/Cu) = 100. [c]Substrate/catalyst (**2a**/Cu) = 200. [d]6 mol % **1i** was used. [e]4 mol % **1i** was used. [f]Ligand (aS,*S*,*S*)-**1j** was used instead of **1i**. [g]Ligand **1d** was used instead of **1i**. [h]Isolated yields. [i]Determined by ^1H NMR analysis. [j]Determined by chiral HPLC or GC analysis. [k]Enantiopurity of diastereomer **4** determined by chiral HPLC analysis.

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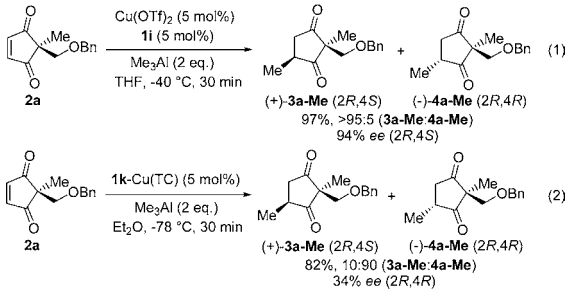
5). Almost complete stereoselectivity through the methylation was obtained with a *p*-methoxybenzyl (PMB)-substituted substrate (entry 7). The catalyst system could tolerate the presence of an ester group, providing highly enantioenriched product **3c** (entry 8). The catalyst system could also permit more sterically demanding groups on the all-carbon quaternary stereocenter: reactions with **2d**–**f** bearing Et, ^{i}Pr, and Ph groups instead of the Me group maintained the high catalytic activity and stereoselectivity (entries 9–11). While substrate **2g** with benzyl and methyl groups produced the product with high stereoselectivity, substrates **2h** and **2i** with 2-naphthyl and spiro groups gave decreased diastereoselectivities (entries 12–14). The reactions using **2j** and **2k** with phenyl and 2-naphthyl groups, respectively, on the quaternary carbon center also afforded the corresponding products in high yields with good diastereo- and enantioselectivities (entries 15 and 16). Interestingly, the products **3a**–**k** were obtained with high to good diastereoselectivities via the syn addition to the more hindered $BnOCH_2$, $ArCH_2$, and Ar groups, probably because of BnO- and π-directing effects. Thus, the reaction using **2l** bearing a $TBDPSOCH_2$ group, which is less capable of chelation, provided the diastereomer **4l** through opposite diastereofacial selection (i.e., anti addition by the steric effect), albeit in lower yield and enantioselectivity (entry 17). The use of **1d** instead of **1i** increased the yield of the product with the opposite absolute configuration (entry 18). The absolute configuration of (+)-**3a-Me** was determined to be 2*R*,4*S* by comparison of the optical rotation to **15** in the literature value (see below).[12c] The relative configurations of **3a-Me**, **3g**, and **3l** were determined by nuclear Overhauser effect experiments of their derivatives.[14] The relative configuration of **3j** was determined by X-ray analysis of a single crystal of **6d**, but the absolute configuration could not be determined (see below).

Enticed by these results, we investigated the effect of using different alkylation reagents.[15] For the reaction using Me_3Al, higher enantioselectivity was obtained in THF (dr > 95:5, 94% ee; eq 1 in Scheme 2) than in Et_2O (−78 °C for 30 min; >99%

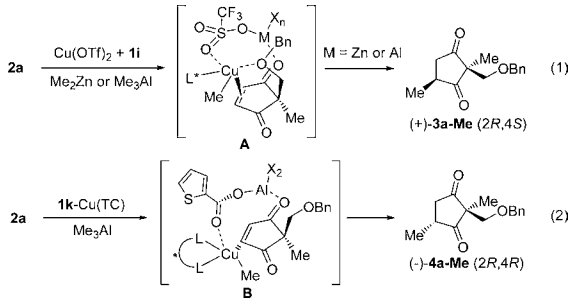
Scheme 2. Enantioselective Desymmetrization Using Me_3Al



yield, dr > 95:5, 75% ee). Significantly, the use of **1k**-Cu(TC) (TC = thiophene-2-carboxylate) provided (2*R*,4*R*)-(−)-**4a-Me** as the major product with 10:90 dr, albeit with low enantioselectivity (eq 2 in Scheme 2). In contrast, the substrate decomposed in the reaction using Me_2Zn under the same conditions.

Although the reason for the observed diastereoselectivity has not yet been clarified, we propose that the alkylated Cu(I)/Zn and Cu(I)/Al species **A** bearing monodentate ligand **1i** before oxidative addition interacts with the double bond via coordination of the benzyloxy group to the Cu center (eq 1 in Scheme 3).[8,13] The alkylated Cu(I)/Al species **B** bearing the

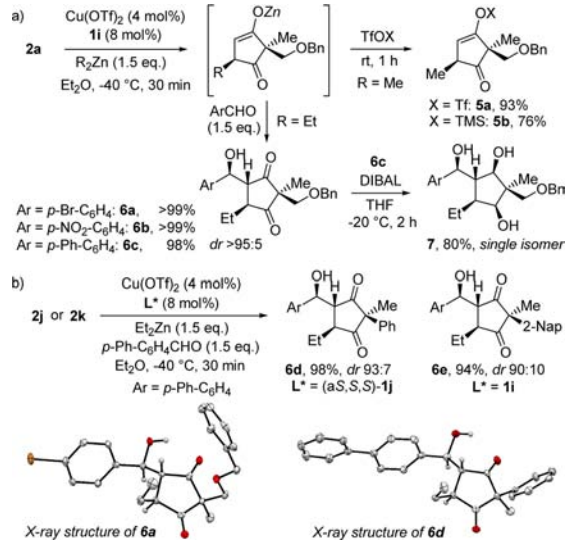
Scheme 3. Proposal for the Sense of the Diastereoselectivity



bidentate TC ligand would interact with the double bond without the chelate control (eq 2 in Scheme 3). Indeed, a nonlinear effect (NLE)[16] was not observed using either Me_2Zn or Me_3Al with a 1:1 $Cu(OTf)_2$/**1i** ratio (see Table 3, entry 5).[14,17] Thus, a rational choice of ligand can lead to selective production of either **3a-Me** or **4a-Me**.

As a great advantage of the Cu-catalyzed alkylation of α,β-unsaturated ketones, the zinc enolate intermediate can be employed for tandem reactions. The reactions with various electrophiles (e.g., aldehydes) can furnish short syntheses of complicated chiral cyclopentane derivatives. Additions of the zinc enolate to benzaldehyde derivatives were smoothly promoted, providing the corresponding adducts **6a**–**c** with excellent diastereoselectivities and yields. Thus, four new chiral centers were created in a one-pot operation (Scheme 4a).

Scheme 4. Asymmetric Syntheses of Complicated Cyclopentane Derivatives via One-Pot Operation



Further treatment of **6c** with DIBAL led to highly oxygenated cyclopentane **7** containing six continuous chiral centers and an all-carbon quaternary stereocenter in only two steps. Also, one-pot enol triflate and enol silyl ether formation gave synthetically useful building blocks **5a** and **5b**, respectively (Scheme 4a). Moreover, we succeeded in converting enol triflate **5a** into various five-membered-ring compounds **8**–**13** containing all-carbon quaternary setereocenters (see pp S31–S36 in the Supporting Information). In addition, the use of **2j** and **2k** with phenyl and 2-naphthyl groups produced the corresponding aldol products with high diastereoselectivities (Scheme 4b).

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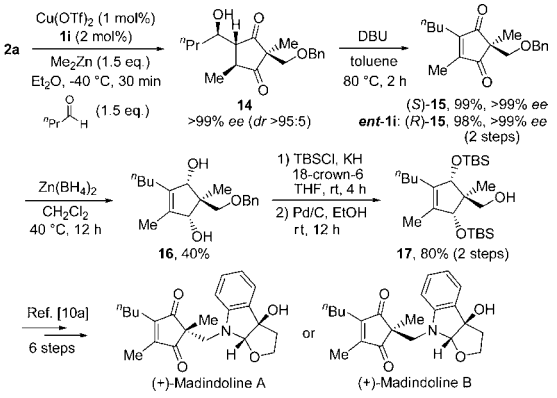
Finally, the Cu-catalyzed enantioselective alkylation was applied to the concise synthesis of a precursor of madindolines A and B (Scheme 5).[11,12] The reaction of butyraldehyde with

Scheme 5. Concise Synthesis of a Precursor of Madindolines



the zinc enolate gave **14** with excellent diastereo- and enantioselectivity. Treatment of **14** with DBU in toluene afforded cyclopentene-1,3-dione (*S*)-**15** bearing an all-carbon quaternary stereocenter in 99% yield with >99% ee in two steps. The Cu catalyst with *ent*-**1i** bearing the opposite *S*-axial chirality produced the other enantiomer, (*R*)-**15**. Reduction of **15** using $Zn(BH_4)_2$ stereoselectively provided diol **16**, which was converted into **17**, the important intermediate[11a,12b] for madindolines A and B, via TBS protection of the diol moiety followed by deprotection of the benzyl group.

In summary, we have succeeded in the asymmetric synthesis of versatile five-membered-ring compounds bearing all-carbon quaternary stereocenters through desymmetrization of achiral cyclopentene-1,3-diones in the presence of chiral Cu catalysts with phosphoramidite ligands. This straightforward process can offer excellent stereoinduction not only with low catalyst loading (up to 0.5 mol %) but also in a one-pot operation. In addition, the catalytic process can be also applied to the concise synthesis of a precursor of madindolines A and B. Further synthetic studies of complicated compounds via the catalytic asymmetric desymmetrization are underway.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, compound characterization data, and a CIF file. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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