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Asymmetric Intramolecular Desymmetrization of *meso*-α,α′-Diazido Alcohols with Aryldiazoacetates: Assembly of Chiral C_3 Fragments with Three Continuous Stereocenters

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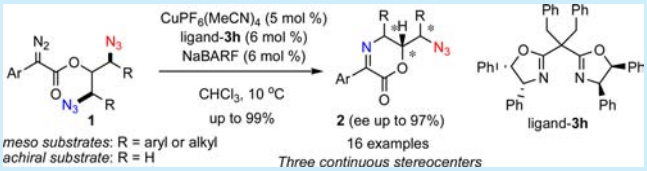
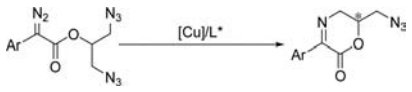
Supporting Information

ABSTRACT: The chiral Cu-complex-catalyzed intramolecular interception of *meso*-α,α′-diazido alcohols with aryldiazoacetates is explored. Most of the enantioenriched α-imino esters with three continuous stereocenters are produced with good to excellent yield and enantioselectivity, and a chiral pocket model is proposed for rationalization of the asymmetric desymmetrization.



Highly functionalized 2-propanols, such as glycerol, α,α′-diamino alcohols, and their derivatives, are very important building blocks[1] and conventional subunits of natural products, lead compounds, and drugs in pharmaceutical research.[2] Asymmetric desymmetrization of glycerol offers practical strategies for access to enantioenriched C_3 fragments, but the products are limited to the polyoxygenated propanes.[3] The optically active C_3 scaffolds substituted with different functional groups have been seldom addressed by the above method.[4] Recently, our group reported an intramolecular interception of achiral 1,3-diazido-2-propanols with chiral Cu-carbenoids for producing the C_3 fragments with three different functional groups (amino group, hydroxyl group, and azido group) at each of the three carbons,[5] which could be regarded as the potential precursors of chiral α,α′-diamino alcohols (Scheme 1). Further, this was the first report in which the interception reaction[6,7] of alkyl azides with carbenoids was directly applied in the asymmetric synthesis.

Scheme 1. Asymmetric Intramolecular Desymmetrization of Achiral 1,3-Diazido-2-propanol



The previous asymmetric desymmetrization affords α-imino esters with good to excellent yield and enantioselectivity, but the products possess only one stereocenter.[5] The α,α′-diamino alcohol units present in the active molecules generally have several continuous asymmetric carbons. For example, α,α′-diamino alcohol **I** is used as the HIV-1 protease inhibitor,[2a,b] and streptomycin **II** is applied clinically for treatment of tuberculosis[8] (Figure 1). Both of these important compounds contain the C_3 fragments with continuous stereocenters. Generally, construction of the carbon frameworks with continuous stereocenters is very challenging. The above facts stimulated us to initiate new research on the asymmetric desymmetrization of *meso*-alkyl bisazides. In this paper, we report the chiral Cu-complex-catalyzed intramolecular reaction of *meso*-α,α′-diazido alcohols with aryldiazoacetates to produce chiral C_3 fragments with three continuous stereocenters.

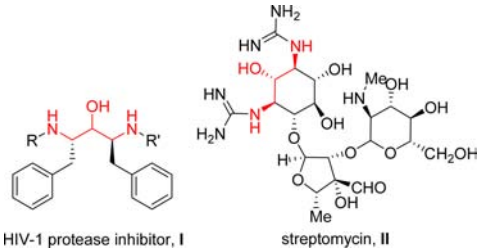


Figure 1. Representative pharmaceutical molecules with α,α′-diamino alcohol units.

The *meso* substrates for asymmetric desymmetrization were prepared[9] from α,α′-dibromo ketones (see Supporting Information for details). A representative four-step route for the synthesis of **1a** is outlined in Scheme 2. The preparation started from the reduction of a known mixture[10] of **5a** and **6a**, affording epoxide **7a**, epoxide **8a**, and alcohol **9a**. Structures of **7a**, **8a**, and **9a** were assigned by the products from the next step S_N2 azidation. Treatment of epoxide **7a** with NaN_3 afforded an unsymmetric diazido alcohol, which could not be used for further transformation. Azidation of **8a** and **9a** gave the same *meso*-diazido alcohol **11a**. The two different diazido alcohols could be easily recognized by NMR analysis. Only one structure could be

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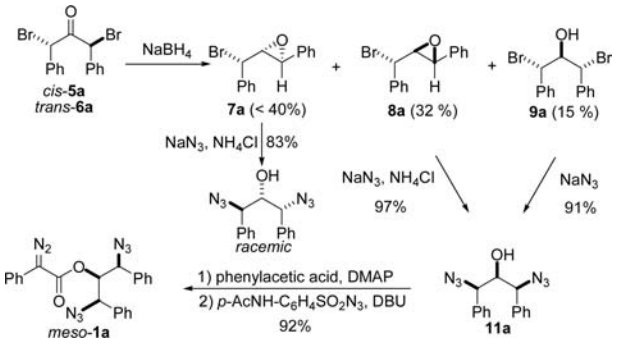
Scheme 2. Preparation of *meso* Substrate 1a



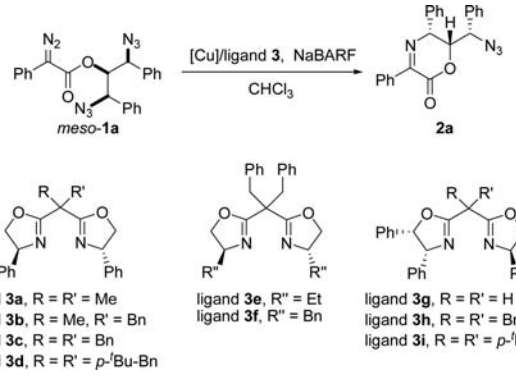
assigned for the unsymmetric diazido alcohol, then the configuration of epoxide **7a** was ascertained. The setting structure for **11a** was supported by X-ray analysis of the ultimate desymmetrization product. Thereafter, the precursors of **11a**, epoxide **8a**, and alcohol **9a** were firmly identified. Esterification of **11a** with phenylacetic acid followed by diazo transfer reaction successfully gave the desired *meso* substrate **1a** with 92% yield in two steps.

With **1a** in hand, screening experiments of chiral catalysts for the asymmetric desymmetrization reaction were undertaken (Table 1). Initially, the previous chiral Cu complex for desymmetrization of the achiral 1,3-diazido-2-propanol, prepared in situ from $CuPF_6(MeCN)_4$, ligand **3a**, and sodium tetrakis[3,5-bis(trifluoromethyl)phenyl]borate (NaBARF), was used for the *meso* substrate. The larger and noncoordinating ion $BARF^-$ was found to be good for the enantioselectivity of the desymmetrization reaction in our previous paper. The α-imino ester **2a** was obtained in nearly quantitative yield, but the enantioselectivity (70% ee) was unsatisfactory (Table 1, entry 1). Replacement of Cu with other metals also encountered failures (Table 1, entries 2−4), resulting in trace **2a** with lower enantioselectivity at room temperature.

We then switched our attention to the extensive modification of bisoxazoline ligand **3a** to obtain better enantioselectivity and yield. Good results were observed when the size of two substituents that were attached to the carbon linker of the bisoxazoline ligand was enlarged (Table 1, entries 5−7). The α-imino ester **2a** was obtained with 90% ee and 99% yield in the presence of ligand **3c**/Cu complex. Ligands **3e** and **3f** were prepared by modification of the substituent at bisoxazoline units of ligand **3c**, but after evaluation, both failed to give better enantioselectivity. The more exciting results were achieved with the ligands **3h** and **3i** possessing two phenyl groups at each of the oxazoline rings, which were prepared through alkylation of the commercially available bisoxazoline **3g**.[11] After careful optimization, the best enantioselectivity (97% ee) was observed with bisoxazoline **3h** at 10 °C in $CHCl_3$, and it should be noted that the product showed absolute configuration opposite of that from the reaction catalyzed by ligands **3a**−**3f**.

With the optimal ligand **3h**, we next examined the scope of substrates, and the results are presented in Scheme 3. The conversion of phenyldiazoacetate **1a** to enantioenriched **2a** was re-examined at 0.25 mmol scale, and the product was obtained with 99% yield, though the enantioselectivity (96% ee) dropped slightly. The *meso* substrates **1b**−**1m** were successfully converted to the cyclic α-imino esters **2b**−**2m** with excellent yields. It seemed that electron-withdrawing groups on the aromatic ring would slightly affect the enantioselectivity (**2a**−**2d**), while the electron-donating group would have a negative impact on the

Table 1. Optimization of Reaction Conditions for the Asymmetric Desymmetrization of 1a[a]



entry	L*	[M]	temp (°C)	time (h)	yield (%)[b]	ee (%)[c]
1	**3a**	$CuPF_6(MeCN)_4$	25	31	99	−70[d]
2	**3a**	$FeCl_2$	25			
3	**3a**	$NiCl_2$	25	80	trace	−60[d]
4	**3a**	$PdCl_2$	25	80	trace	−70[d]
5	**3b**	$CuPF_6(MeCN)_4$	25	27	98	−78[d]
6	**3c**	$CuPF_6(MeCN)_4$	25	20	99	−90[d]
7	**3d**	$CuPF_6(MeCN)_4$	25	36	99	−86[d]
8	**3e**	$CuPF_6(MeCN)_4$	25	14	99	26
9	**3f**	$CuPF_6(MeCN)_4$	25	14	99	0
10	**3g**	$CuPF_6(MeCN)_4$	25	92	86	84
11	**3h**	$CuPF_6(MeCN)_4$	25	4	93	93
12	**3i**	$CuPF_6(MeCN)_4$	25	5	98	91
13	**3h**	**$CuPF_6(MeCN)_4$**	**10**	**15**	**92**	**97**
14	**3i**	$CuPF_6(MeCN)_4$	10	21	94	93
15	**3h**	$CuPF_6(MeCN)_4$	5	64	90	96
16	**3i**	$CuPF_6(MeCN)_4$	5	72	77	92

[a]Reaction conditions: $CuPF_6(MeCN)_4$ (0.0025 mmol), ligand (0.0030 mmol), and NaBARF (0.0030 mmol) were mixed in solvent (0.4 mL) for 2 h at 25 °C; then diazo phenylacetate **1a** (0.05 mmol) in solvent (0.4 mL) was added, and the reaction mixture was stirred at the conditions mentioned above. [b]Isolated yield after purification. [c]Determined by chiral HPLC. [d]Opposite enantioselectivity.

stereocontrol (**2f**). Naphthalene analogue **2g** was also produced with good control of stereochemistry. Further evaluation of the two R groups of the α,α'-diazido alcohol unit revealed that excellent enantioselectivity could be observed when they were aryl groups with electron-withdrawing substituents (**2h**−**2j**). The effect of electron-donating groups on this aryl ring was not investigated due to the failure of substrate preparation. If the two R groups of α,α'-diazido alcohol were alkyl groups, such as methyl or benzyl, the enantioselectivity was decreased (**2k**−**2l**). It was very interesting that when the two alkyl groups were locked as a cyclopentane ring, the enantioselectivity was excellent (**2m**). Here, we would like to emphasize the fact that α-imino ester **2l** could be regarded as a precursor of the analogue of HIV-1 protease inhibitor[12] mentioned above (Figure 1). The previous substrate, achiral **1n**, was reinvestigated with the new Cu complex, affording **2n** with a disappointing enantioselectivity (82% ee).

Furthermore, a 2 g scale reaction of **1i** was carried out, producing the imino ester **2i** with 97% ee in 87% yield. The yield of the gram-scale reaction decreased a bit, while the enantioselectivity was more excellent. The absolute configuration of the newly generated stereocenter substituted by the ester group was assigned as *R*, and the structure of α-imino ester

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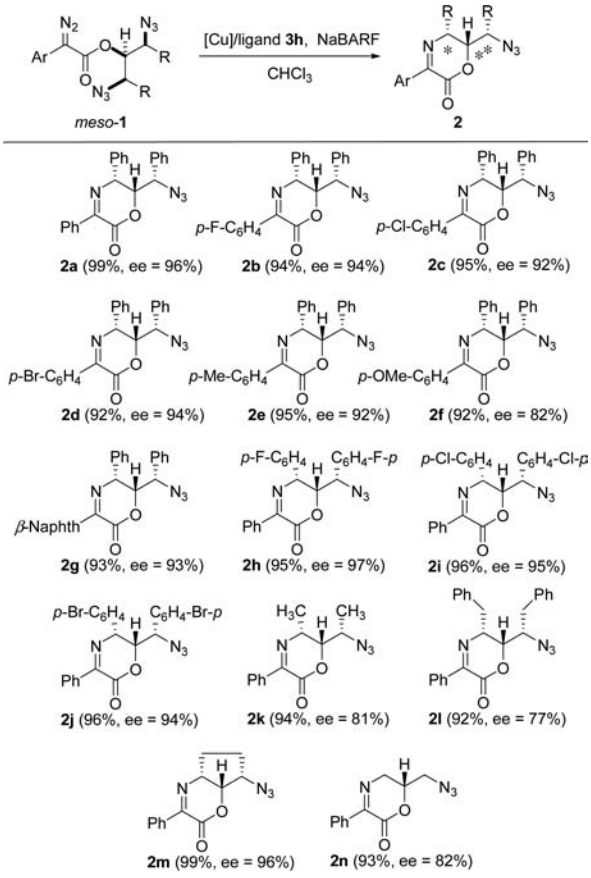
Scheme 3. Scope of the Aryldiazoacetates[a]



[a]Conditions: $CuPF_6(MeCN)_4$ (0.0125 mmol), ligand (0.015 mmol), and NaBARF (0.015 mmol) were mixed in $CHCl_3$ (1.0 mL) for 2 h at 25 °C; then diazo phenylacetate **1** (0.25 mmol) in solvent (1.0 mL) was added, and the reaction mixture was stirred at 10 °C for 9 h.

2h was confirmed by single-crystal X-ray crystallography (Figure 2).

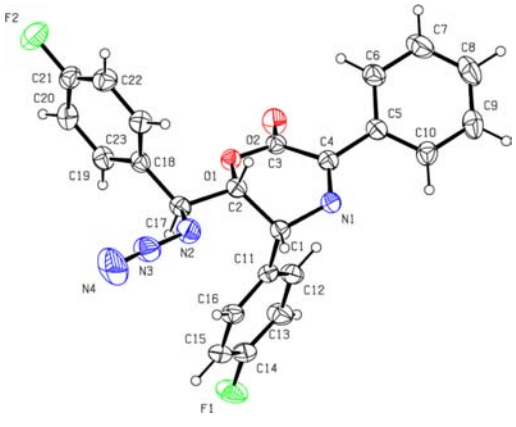
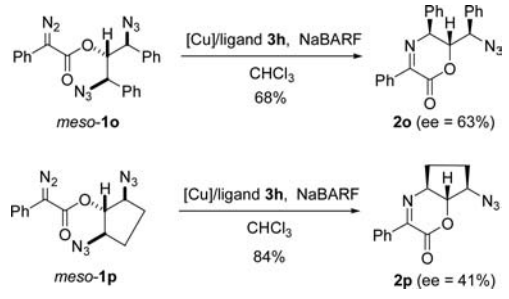


Figure 2. X-ray structure of imino ester **2h**.

Finally, two more substrates, phenyldiazoacetates **1o** and **1p**, were investigated to reveal the impact of relative configuration of the hydroxyl group with the two azido groups (Scheme 4). The comparability study revealed that these two substrates were not very suitable for the asymmetric desymmetrization process. The

Scheme 4. Desymmetrization of α-Diazo(aryl)acetates 1o and 1p



α-imino ester **2o** was obtained in 68% yield with 63% ee, and **2p** was produced in 84% yield with only 41% ee.

A very reasonable process for the interception of alkyl azides with carbenoids had been proposed by Lecourt and Micouin's group.[7b] A possible induction model for the asymmetric desymmetrization reaction is outlined in Figure 3, which was

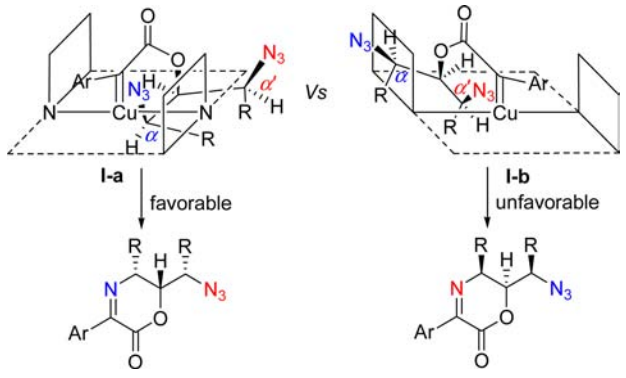


Figure 3. Possible induction model for the desymmetrization.

first reported in the Cu-complex-catalyzed N−H insertion reaction with diazoesters by Zhou and co-workers.[13] They had prepared several crystals of binuclear chiral spiro-bisoxazoline/copper complexes and observed that the reactive copper center was in a chiral pocket. In this paper, we employed the different chiral bisoxazoline ligands, though we could not get the crystal of the catalyst. The suggested chiral induction model could be accounted for by the observed results here. For substrates **1a**–**1m**, the bulky R group and α′-carbon substituent would point back to the blocking wall in the model **I-a** (Figure 3), affording the observed products. While the bulky groups faced the catalyst wall in model **I-b**, which would severely restrict the formation of α-imino esters with opposite enantioselectivity.

In summary, asymmetric intramolecular desymmetrization of the *meso*-1,3-diazido-2-propanol derivatives by chiral Cu-carbenoids has been addressed, producing enantioenriched α-amino-α′-azido alcohols with three continuous stereocenters. The chiral pocket model was applied for rationalization of the conversion. Further research on this topic in our laboratory will focus on the intermolecular enantioselective desymmetrization of the *meso*-alkyl bisazides.

■ ASSOCIATED CONTENT

Supporting Information

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Experimental procedures and spectroscopic data and copies of NMR spectra for all new compounds (PDF)
X-ray crystallographic data for **2h** (CIF)

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Notes

The authors declare no competing financial interest.

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(9) Caution: organic azides are potentially explosive compounds; careful precautions must be taken in its handling. Thermogravimetry analysis and differential scanning calorimetry experiment of **1a** revealed that the decomposition occurred at about 106 °C. In addition, we did not encounter any incidents during preparation of such materials.

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