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Catalytic Enantioselective Desymmetrization of 1,3-Diazido-2-propanol via Intramolecular Interception of Alkyl Azides with Diazo(aryl)acetates

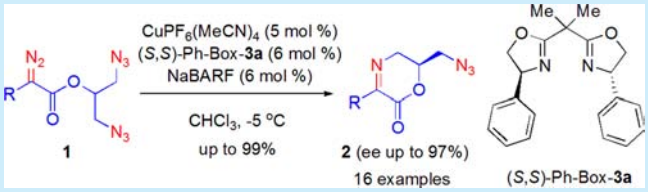
Xiu-Ping Wu,[†] Yan Su,[‡] and Peiming Gu*[,†]

[†]Key Laboratory of Energy Sources & Engineering, State Key Laboratory Cultivation Base of Natural Gas Conversion and Department of Chemistry, Ningxia University, Yinchuan 750021, China

[‡]State Key Laboratory of Applied Organic Chemistry, Department of Chemistry, Lanzhou University, Lanzhou 730000, China

Supporting Information

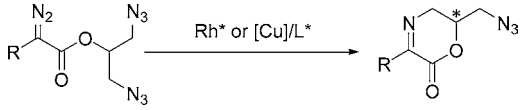
ABSTRACT: The first catalytic enantioselective desymmetrization of 1,3-diazido-2-propanol via an intramolecular interception of alkyl azides by Cu−carbenoids has been realized. A wide range of 1,3-diazidoisopropyl diazo(aryl)-acetates were converted to cyclic α-imino esters in the presence of bisoxazoline ligand (*S*,*S*)-Ph-Box with good to excellent yields, and the enantiomeric excess was up to 97%.



The highly functionalized C_3-fragment represents a very important type of building block in synthetic chemistry,[1] and the most well-known compounds include glycerol and serine. Inspired by the excellent enzymatic and nonenzymatic methods for the desymmetrization of diols,[2] the enantioselective desymmetrization of glycerol and its derivatives has been developed to satisfy the high demand for pure enantiomers of the fragment.[3] However, the fragments prepared in this way are generally functionalized with hydroxy substituents, and amino substituents are rarely observed.[4] Following our research on the reaction of alkyl azides with diazo compounds,[5] herein we describe the first catalytic enantioselective desymmetrization of the prochiral 1,3-diazido-2-propanol via an intramolecular interception of alkyl azides by Cu−carbenoids with high enantioselectivity.

The condensation of dichlorocarbene with alkyl azides to imines was first reported in 1968.[6] Accompanied by the great achievements in metal−carbenoid chemistry, the transition metal-catalyzed intramolecular reaction of diazo compounds with alkyl azides was reported, though it attracted much less attention.[7] Very recently the intermolecular interception of carbenoids with alkyl azides, producing α-keto esters from the unstable α-imino ester intermediates in good to excellent yields, had been explored with our effort.[5] The neglect of this conversion might be due mainly to the lack of chirality, as no stereo centers would be generated at the reaction sites. Although many chiral metal complexes had been successfully used in the decomposition of diazo compounds, the enantioselective desymmetrization with carbenoids has been much less studied,[8] mainly within the C−H insertion.[8b] The intramolecular desymmetrization of prochiral 1,3-diazido-2-propanol with chiral metal-carbenoids was envisioned to produce the enantio-enriched C_3-fragment with three different functional groups at each of its three carbons (Scheme 1). Furthermore, the promised product could be converted to chiral 1,3-diamino-2-propanol, which has been demonstrated to be a potent inhibitor of HIV-l.[9]

Scheme 1. Designed Intramolecular Enantioselective Desymmetrization of 1,3-Diazido-2-propanol



The first substrate **1a** was prepared[10] to test our proposal. Initially, the interception was examined with several commercially available chiral dirhodium(II) catalysts. Many efforts had been made, but the stereocontrol was unsatisfactory. The desired product, 6-(azidomethyl)-5,6-dihydro-3-phenyl-1,4-oxazin-2-one **2a**, was obtained with very poor enantioselectivity (ee = 44% with Rh_2(*S*-TCPTTL)$_4$(EtOAc)$_2$ and ee = 14% with Rh_2(*S*-DOSP)$_4$).

Further evaluation of the reaction with chiral copper catalysts generated in situ from $CuPF_6(MeCN)_4$ (5 mol %) and bisoxazoline ligands (6 mol %), such as (*S*,*S*)-Ph-Box-**3** (**3a**-**3c**), (*R*,*R*)-^{i}Pr-PyBox-**4**, and Spirobox (S_a,*S*,*S*)-**5**,[11] resulted in only moderate enantioselectivity at room temperature in dichloromethane. Fortunately, when NaBARF[12] (6 mol %) was added, better enantioselectivity was observed, especially with the ligand (*S*,*S*)-Ph-Box-**3a** (Table 1, entries 1 and 4). The larger and noncoordinating ion $BARF^-$ had been used to modify the enantioselectivity in a range of asymmetric transformation.[13−17] With NaBARF, Zhou's ligand Spirobox (S_a,*S*,*S*)-**5** also showed good enantioselectivity (ee = 73%); however, a better result could not be obtained after considerable effort (not shown in

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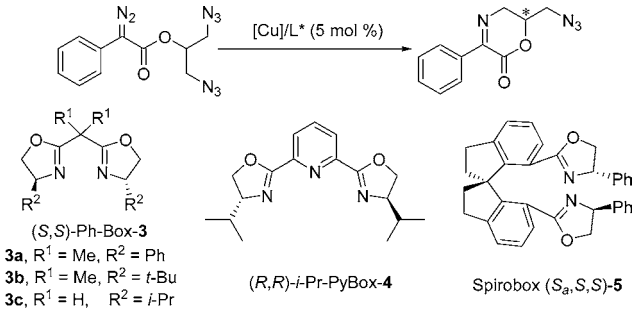
Table 1. Optimization of the Reaction Conditions for the Enantioselective Desymmetrization of 1,3-Diazoisopropyl Diazo(aryl)acetate[a]



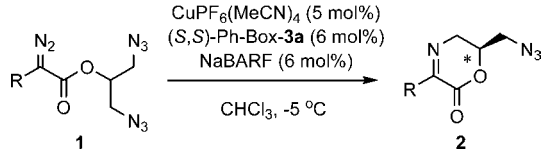
entry	L*	solvent	temp (°C)	time (h)	yield[b] (%)	ee[c] (%)
1[d]	**3a**	CH_2Cl_2	20	23	98	39
2[d]	**4**	CH_2Cl_2	20	48	trace	
3[d]	**5**	CH_2Cl_2	20	48	96	59
4	**3a**	CH_2Cl_2	20	38	89	81
5	**4**	CH_2Cl_2	20	69	17	−14
6	**5**	CH_2Cl_2	20	48	89	73
7	**3b**	CH_2Cl_2	20	42	89	49
8	**3c**	CH_2Cl_2	20	72	32	0
9	**3a**	EtOAc	20	68	63	40
10	**3a**	$CHCl_3$	20	3	93	85
11	**3a**	DCE	20	20	91	74
12	**3a**	hexane	20	68	35	72
13	**3a**	**$CHCl_3$**	**-5**	**41**	**96**	**89**
14	**3a**	$CHCl_3$	−20	122	91	90
15	**3a**	$CHCl_3$	−30	164	89	89
16[e]	**3a**	$CHCl_3$	−5	86	97	88
17[f]	**3a**	$CHCl_3$	−5	39	99	88

[a]Reaction conditions: $CuPF_6(MeCN)_4$ (0.010 mmol), ligand (0.012 mmol), and NaBARF (0.012 mmol) were mixed in solvent (2.0 mL) for 2 h at 25 °C, diazo phenylacetate **1a** (0.20 mmol) in solvent (1.0 mL) was added, and the reaction mixture was stirred under the conditions mentioned above. [b]Isolated yield after purification. [c]Determined by chiral HPLC. [d]Without NaBARF. [e]With 2 mol % of catalyst. [f]With 10 mol % of catalyst.

Table 1). Two additional ligands **3b** and **3c**, resembling bisoxazoline **3a** in general structure, were explored but also failed to afford better enantioselectivity (Table 1, entries 7 and 8). To our delight, interception of the diazo(aryl)acetate **1a** in $CHCl_3$ at room temperature with (*S*,*S*)-Ph-Box-**3a** furnished *α*-imino ester **2a** in 93% yield with 85% ee (Table 1, entry 10). If the temperature was lowered to −5 °C, the enantioselectivity was improved (ee = 89%) but with longer reaction time (Table 1, entry 13). No obviously enhanced enantioselectivity could be observed by carrying out the reaction at even lower temperature (Table 1, entries 14 and 15). Further experiments revealed that the amount of catalyst could not change the enantioselectivity but affected the reaction rate (Table 1, entries 16 and 17).

A broad range of substrates was investigated under the optimal reaction conditions established above (in bold, Table 1), and the results are presented in Table 2. The examined *α*-diazo(aryl)acetates were successfully converted to the imino esters in good to excellent yields, and generally high enantioselectivity was observed. The substituents on the aromatic ring slightly affected the enantioselectivity, and the electron-withdrawing group would improve the conversion. On the contrary, the electron-donating group would slightly

Table 2. Substrate Scope for the Enantioselective Desymmetrization[a]



entry	R	2	time (h)	yield[b] (%)	ee[c] (%)
1	C_6H_5	**2a**	41	96	89
2	4-FC_6H_4	**2b**	18	98	90
3	4-ClC_6H_4	**2c**	48	96	91
4	3-ClC_6H_4	**2d**	72	91	90
5	2-ClC_6H_4	**2e**	22	98	97
6	3,4-ClC_6H_3	**2f**	72	97	93
7	4-BrC_6H_4	**2g**	31	89	90
8	3-BrC_6H_4	**2h**	53	99	91
9	4-MeC_6H_4	**2i**	43	96	87
10	4-$MeOC_6H_4$	**2j**	22	90	84
11	3-$MeOC_6H_4$	**2k**	43	94	88
12	2-$MeOC_6H_4$	**2l**	43	99	58
13	3,4-$MeOC_6H_3$	**2m**	43	99	89
14	3-Br-4-$MeOC_6H_3$	**2n**	43	99	87
15	2-Naphth	**2o**	25	98	91
16	1-Naphth	**2p**	72	70	89

[a]Reaction conditions: $CuPF_6(MeCN)_4$ (3.7 mg, 0.010 mmol), (S,S)-Ph-Box-**3a** (4.0 mg, 0.012 mmol), and NaBARF (10.6 mg, 0.012 mmol) were mixed in chloroform (2.0 mL) for 2 h at 25 °C, then a solution of diazo arylacetate **1** (0.20 mmol) in chloroform (1.0 mL) was added at −5 °C and the mixture was kept at the conditions mentioned above. [b]Isolated yield after purification. [c]Determined by chiral HPLC.

decrease the enantioselectivity. It seemed that the ortho substituents had obvious impact on the enantioselectivity. For example, diazo ester **1e** with chloro attachment at the ortho position of the aromatic ring resulted in the imino ester **2e** with 97% ee; meanwhile, azide **1l** with a methoxyl group at the ortho position afforded the imino ester **2l** with only 58% ee. The naphthalene analogues **1o** and **1p** were also examined, and the stereochemistry was well controlled. Desymmetrization of diazo ester **1p** at −5 °C for 72 h afforded the imino ester **2p** in only 70% yield, as the substrate could not be completely consumed. The slow reaction rate might be due to the bulky steric hindrance.

Finally, the enantiopure isomers (>99% ee) of **2b** and **2c** could be obtained from recrystallization. The configuration of the stereocenter was assigned as *S* by single-crystal X-ray crystallography (Figure 1).[18]

The cyclic *α*-imino esters have been used as a good chiral template in some asymmetric synthesis[19] and are also known as reactants for the asymmetric Ugi three-component reaction.[20] We are more interested in the preparation of enantioenriched azido propylamines from the cyclic *α*-imino esters in the near future, which will be used to understand the extraordinary Schmidt reaction of aldehydes developed in our group recently.[21]

In conclusion, the first highly enantioselective desymmetrization of 1,3-diazido-2-propanol has been realized through Cu-complex-catalyzed intramolecular interception of alkyl azides by diazo(aryl)acetates. This conversion provides a reliable method for preparation of enantioenriched 6-substituted 5,6-dihydro-

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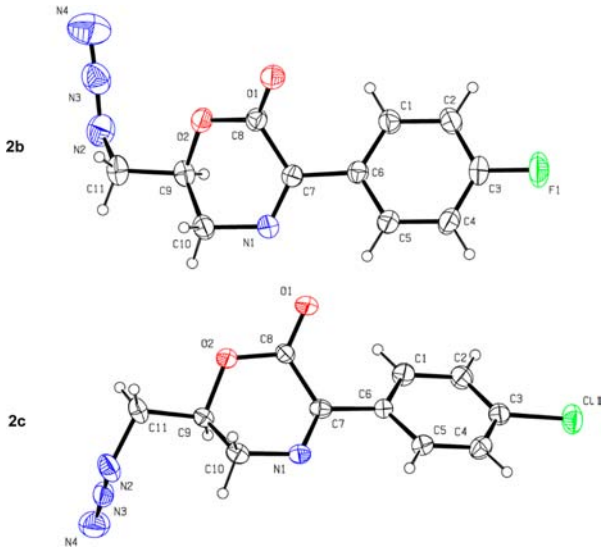

Figure 1. X-ray structure of imino esters **2b** and **2c**.

1,4-oxazin-2-ones under very mild reaction conditions. Further application of the conversion is underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and spectroscopic data and copies of NMR spectra for all new compounds and X-ray crystallographic data for compound **2b** and **2c**. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: gupm@nxu.edu.cn.

Notes

The authors declare no competing financial interest.

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