Lewis Acid-Catalyzed Enantioselective 1,3-Dipolar Cycloadditions of Diazoalkane: Chiral Ligand/ Achiral Auxiliary Cooperative Chirality Control

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No single examples have been reported so far for the Lewis acid-catalyzed enantioselective 1,3-dipolar cycloaddition reactions of diazoalkanes.[1,2] On the basis of the kinetic data on the relative reaction rates observed by Huisgen in the competitive cycloadditions of diazomethane between 1-alkene and acrylic ester, it is clear that diazomethane is one of the most nucleophilic 1,3-dipoles ever examined ($k_{acrylate}/k_{1-alkene} = 250\,000$).[3] Accordingly, diazoalkanes can be a strong candidate which should be most successfully applied to Lewis acid-catalyzed reactions if this 1,3-dipole is not strongly coordinating to Lewis acid catalysts causing fatal deactivation of the catalyst. The author's group was aware of this possibility and started to study the catalyzed enantioselective diazoalkane cycloadditions to 3-(2-alkenoyl)-2-oxazolidinones.

Diazoalkane cycloadditions to alkenes produce 1-pyrazolines as the initial cycloadducts which are usually not so stable that these undergo spontaneous 1,3-proton migration leading to thermodynamically more stable 2-pyrazoline derivatives.[4] Usually more acidic hydrogen migrates, and consequently the chirality at this position disappears. Carreira and co-workers have recently reported the diastereoselective diazoalkane cycloadditions of trimethylsilyldiazomethane to chiral alkenes.[5] Upon treatment with protonic acid or acid chloride/silver triflate after the completion of reaction, regioselective protodesilylation or acyldesilylation is found to occur at the 2,3-diazaallylsilane moiety masked in the 1-pyrazoline rings to produce 2-pyrazolines.

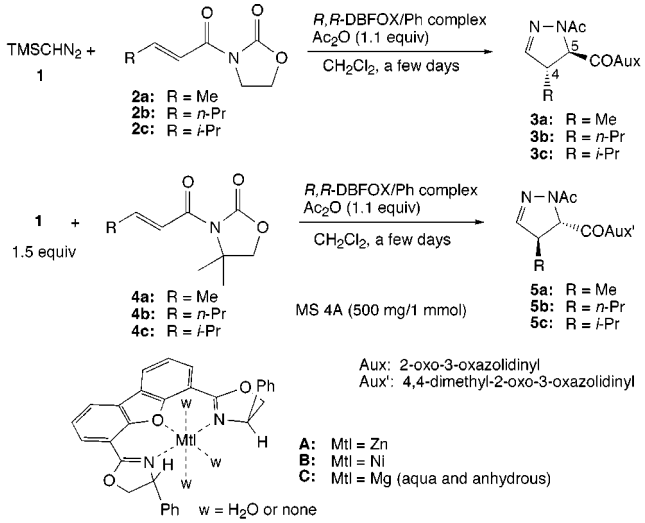
The transition metal aqua complexes of *R,R*-DBFOX/Ph ligand[6] are known to show high stability in air and high tolerance to coordinating reagents, and therefore they have been successfully utilized in Diels−Alder reactions of cyclopentadiene,[7] nitrone cycloadditions,[8] and thiol conjugate additions.[9] The authors expected that the *R,R*-DBFOX/Ph−transition metal aqua complexes would be a powerful catalyst in ever unprecedented enantioselective diazoalkane cycloadditions. This work presents the first successful examples of Lewis acid-catalyzed enantioselective cycloaddition reactions of trimethylsilyldiazomethane.

Table 1. Reactions of Trimethylsilyldiazomethane (**1**) with Dipolarophiles **2** and **4**[a] Leading to **3** or **5**

entry	metal salt/mol %	**1**/equiv	**2**	temp/°C	**3**	yield/%	% ee
1	$Zn(ClO_4)_2{\cdot}6H_2O$/10	2	**2a**	rt	**3a**	49	40
2	$Zn(ClO_4)_2{\cdot}6H_2O$/10	2	**2a**	−20	**3a**	85	92
3	$Zn(ClO_4)_2{\cdot}6H_2O$/10	2	**2a**	−40	**3a**	85	96
4	$Zn(ClO_4)_2$/10	2	**2a**	−40	**3a**	81	97
5	$Zn(ClO_4)_2{\cdot}6H_2O$/10	1.2	**2a**	−40	**3a**	87	99
6	$Zn(ClO_4)_2{\cdot}6H_2O$/10	1.2	**2a**	−40	**3a**	79	96
7	$Ni(ClO_4)_2{\cdot}6H_2O$/10	1.2	**2a**	−40	**3a**	79	93
8	$Mg(ClO_4)_2$/10	1.2	**2a**	rt	**3a**	61	64
9	$Mg(ClO_4)_2$/10	1.2	**2a**	−20	**3a**	64	82
10	$Mg(ClO_4)_2{\cdot}6H_2O$/10	1.2	**2a**	−40	**3a**	75	37
11	$Zn(ClO_4)_2{\cdot}6H_2O$/10	2	**2b**	−55	**3b**	81	47
12	$Zn(ClO_4)_2{\cdot}6H_2O$/10	2	**2c**	−40	**3c**	89	71
13	$Mg(ClO_4)_2$/10	1.5	**4a**	−40	**5a**	71	89
14	$Mg(ClO_4)_2$/10[b]	1.5	**4a**	−40	**5a**	63	82
15	$Mg(ClO_4)_2$/10	1.5	**4a**	−78	**5a**	75	97
16	$Mg(ClO_4)_2$/10	1.5	**4b**	−60	**5b**	62	98
17	$Mg(ClO_4)_2$/10	1.5	**4c**	−60	**5c**	93	98

[a] All of the reactions were performed in dichloromethane in the presence of acetic anhydride (1.1 equiv), MS 4A (500 mg/1 mmol scale), and the catalysts derived from *R,R*-DBFOX/Ph and metal salts. [b] In the absence of MS 4A.

Scheme 1



After several chiral catalysts were screened, the nickel(II) and zinc(II) aqua complexes (**A** and **B**) of *R,R*-DBFOX/Ph ligand were found to be effective in catalytic amounts (10 mol %), especially the zinc(II) complex being the best catalyst of all examined. When trimethylsilyldiazomethane (**1**, 1.1 equiv) was treated with 3-crotonoyl-2-oxazolidinone (**2a**), acetic anhydride (1.1 equiv), and MS 4A in dichloromethane in the presence of the *R,R*-DBFOX/Ph·$Zn(ClO_4)_2{\cdot}3H_2O$[10] (10 mol %) at −40 °C for 72 h, the desilylacetylated 2-pyrazoline cycloadduct **3a** was produced in 87% yield in 99% ee (Scheme 1, Table 1). The role of MS 4A is simply a dehydrating agent in this case since the comparable results were obtained in the reaction catalyzed by the anhydrous complex catalyst **A** (w = none) prepared from *R,R*-DBFOX/Ph, ZnI_2, and $2AgClO_4$ (81%, 97% ee). However, use of the aqua complex is more preferable because its simple preparation procedure is an advantage.[10] The nickel(II) aqua complex **B** was a little less effective in enantioselectivity than the zinc(II) aqua complex **A**. The reactions catalyzed by the magnesium complex

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(1) Gothelf, K. V.; Jørgensen, K. A. *Chem. Rev.* **1998**, *98*, 863−909.

(2) Jørgensen cited his unpublished results in a review (see ref 1), describing that the Ti-taddolate-catalyzed reactions have provided moderate enantioselectivities in the reaction of ethyl diazoacetate with 3-acryloyl-2-oxazolidinone.

(3) Huisgen, R. 1,3-Dipolar Cycloadditions - Introduction, Survey, Mechanism. In *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; Wiley: New York, 1984; Vol. 1, pp 1−176.

(4) Regitz, M.; Heydt, H. Diazoalkane. In *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; Wiley: New York, 1984; Vol. 1, pp 393−558.

(5) (a) Mish, M. R.; Guerra, F. M.; Carreira, E. M. *J. Am. Chem. Soc.* **1997**, *119*, 8379−8380. (b) Whitlock, G. A.; Carreira, E. M. *J. Org. Chem.* **1997**, *62*, 7916−7917.

(6) (a) Kanemasa, S.; Oderaotoshi, Y.; Yamamoto, H.; Tanaka, J.; Wada, E.; Curran, D. P. *J. Org. Chem.* **1997**, *62*, 6454−6455. (b) Iserloh, U.; Curran, D. P.; Kanemasa, S. *Tetrahedron Asymmetry* **1999**, *10*, 2417−2428.

(7) Kanemasa, S.; Oderaotoshi, Sakaguchi, S.; Y.; Yamamoto, H.; Tanaka, J.; Wada, E.; Curran, D. P. *J. Am. Chem. Soc.* **1998**, *120*, 3074−3088.

(8) Kanemasa, S.; Oderaotoshi, Y.; Tanaka, J.; Wada, E. *J. Am. Chem. Soc.* **1998**, *120*, 12355−12356.

(9) Kanemasa, S.; Oderaotoshi, E.; Wada, E. *J. Am. Chem. Soc.* **1999**, *121*, 8675−8676.

(10) This zinc(II) complex was in situ prepared in dichloromethane by stirring equimolar amounts of the *R,R*-DBFOX/Ph ligand and $Zn(ClO_4)_2{\cdot}6H_2O$ at room temperature for a few hours.

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C showed the maximum enantioselectivity of 82% ee at −20 °C, while the selectivity was lowered at a lower reaction temperature (37% ee at −40 °C).

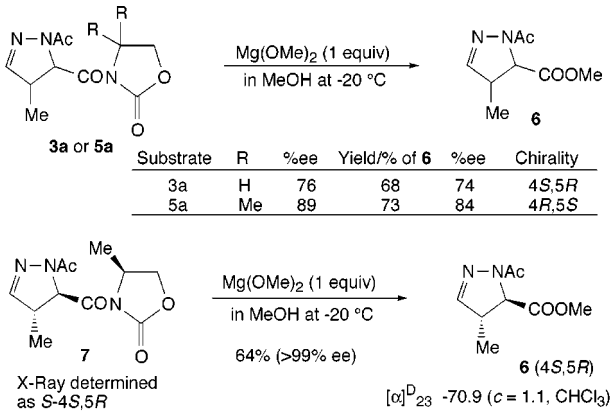
Unfortunately the reaction of **1** with 3-acryloyl-2-oxazolidinone catalyzed by the zinc aqua complex **A** (10 mol %) led to a racemic result.[11,12] It was surprising that both 3-(2-hexenoyl)-2-oxazolidinone (**2b**) and 3-(4-methyl-2-pentenoyl)-2-oxazolidinone (**2c**) were much less enantioselective than the methyl-substituted dipolarophile **1a**. Especially, the reaction of **2b** as the primary alkyl-substituted dipolarophile never exceeded an enantioselectivity of 50% ee. These β-substituents, isopropyl and propyl moieties, have higher mobility than the methyl substituent, and therefore, some steric hindrance should exist against one of the shielding phenyl groups so that the reaction site departs from the shielding zone of the 4-phenyl group. As a result, efficiency of chiral shielding became rather ineffective.

On the other hand, use of 4,4-dimethyl-2-oxazolidinone as chiral auxiliary was very effective. It was found that the *R*,*R*-DBFOX/Ph·Mg$(ClO_4)_2$ complex **C** was the catalyst of choice to mediate the reactions of 3-crotonoyl-4,4-dimethyl-2-oxazolidinone (**4a**), while both the *R*,*R*-DBFOX/Ph−zinc(II) and −nickel(II) complexes, **A** and **B**, were totally inactive.[13] Thus, the *R*,*R*-DBFOX/Ph·Mg$(ClO_4)_2$-catalyzed reaction of **1** with **4a** in the presence of MS 4A proceeded smoothly even at −78 °C to give the corresponding cycloadduct **5a** in 75% yield with the enantioselectivity of 97% ee. Other dipolarophiles **4b,c** having 2-hexenoyl and 4-methyl-2-pentenoyl substituents at the nitrogen atom of the oxazolidinone chelating auxiliary, showed similarly high enantioselectivities of 98% ees regardless of the β-substituents of dipolarophiles.

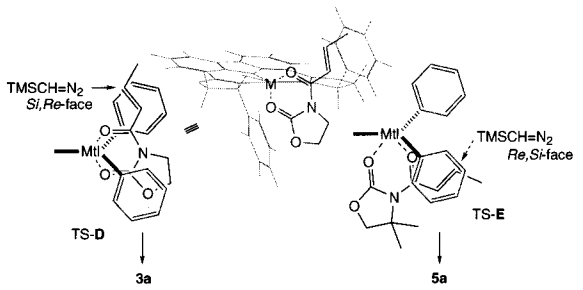
The desilylacetylated cycloadducts **3a** and **5a**, which were derived from **2a** and **4a**, respectively, were transformed to the methyl esters, methyl *trans*-1-acetyl-4-methyl-1-pyrazoline-5-carboxylates **6**, through the reactions with dimethoxymagnesium at −20 °C (Scheme 2). When optical rotations and chiral HPLC data of these two esters were compared, these two products **3a** and **5a** were found to have the opposite absolute stereochemistry. The absolute configuration of **3a** was determined on the basis of the X-ray-determined structure of the major diastereomer of cycloadduct **7** which was derived from the reaction of **1** to (*S*)-3-crotonoyl-4-methyl-2-oxazolidinone.[14]

The cycloaddition product **3a** derived from 3-crotonoyl-2-oxazolidinone (**2a**) was identified to be the 4*S*,5*R*-enantiomer of 2-pyrazoline cycloadduct, indicating that the *Re*,*Si*-enantioface of the unsaturated bond of dipolarophile **2a** was attacked by **1** as a result of the chiral shielding by the top 4-phenyl substituent, as

Scheme 2



Scheme 3



shown in the trigonal bipyramid transition structure TS-**D** (Scheme 3). The selected enantioface of 3-crotonoyl-2-oxazolidinone (**2a**) was the same to that involved in the transition structure of the *R*,*R*-DBFOX/Ph·Ni$(ClO_4)_2$·3H_2O-catalyzed Diels−Alder reaction of cyclopentadiene with the same dienophile.[7] Consequently, the absolute configuration of the cycloaddition product **5a** produced in the diazo cycloaddition reaction of 3-crotonoyl-4,4-dimethyl-2-oxazolidinone (**4a**) was the 4*R*,5*S*-enantiomer, which resulted from the selection of *Si*,*Re*-enantioface of the reacting site of oxazolidinone dipolarophile **4a**. Steric effects of the two methyl groups at the oxazolidinone ring probably force the substrate into a different coordination geometry as shown in Scheme 3, but the reason only the Mg complex is active is unclear.

In conclusion, the first effective enantioselective 1,3-dipolar cycloaddition reactions of trimethylsilyldiazomethane have been attained in the presence of the *R*,*R*-DBFOX/Ph−metal perchlorate complexes. The reaction of 3-crotonoyl-2-oxazolidinone catalyzed by the *R*,*R*-DBFOX/Ph·Zn$(ClO_4)_2$·3H_2O at −40 °C produces (4*S*,5*R*)-1-acetyl-5-(2-oxo-3-oxazolidinylcarbonyl)-2-pyrazoline in 99% ee, while the reaction of 3-crotonoyl-4,4-dimethyl-2-oxazolidinone catalyzed by the *R*,*R*-DBFOX/Ph·Mg$(ClO_4)_2$ at −78 °C gives (4*R*,5*S*)-1-acetyl-5-(4,4-dimethyl-2-oxo-3-oxazolidinylcarbonyl)-2-pyrazoline in 97% ee. Thus, almost complete switch of enantioselectivity has been performed simply by adding substituents to the same achiral chelating auxiliary.

Supporting Information Available: Details of experimental procedures, analytical data, and X-ray structure are included (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) Since 3-acryloyl-2-oxazolidinone is terminally unsubstituted, its reaction presumably proceeded through a different reaction mechanism, either the *exo* approach of trimethylsilyldiazomethane[12] or the stepwise linear approach. This may be a reason for the racemic results observed.

(12) The cycloaddition reaction of **1** to β-substituted dipolarophiles **2a**−**c** is anticipated to proceed through the *endo*-approach since the *exo*-transition structure is expected to be less stable dut to the steric repulsion working between the bulky trimethylsilyl substituent and the β-substituent of **2**.

(13) No corresponding cycloadducts were produced. The remainder of the starting diazo compound **1** was confirmed by nitrogen evolution on aqueous workup, and the acceptors **2** were recovered intact.

(14) The reaction of **1** (1.2 equiv) with (*S*)-3-crotonoyl-4-methyl-2-oxazolidinone, in the presence of the *R*,*R*-DBFOX/Ph·Mg$(ClO_4)_2$ (10 mol %), acetic anhydride (1.1 equiv), and MS 4A (500 mg/mmol) in dichloromethane at −78 °C for 96 h, provided an 83:17 mixture of diastereomeric cycloadducts in 56% yield. The major diastereomer was purified by crystallization to give the pure (4*S*,5*R*)-enantiomer of **6** (Scheme 2).