Study on Synthesis, Characteristics and Catalysis Properties of Novel Chiral Metal Complexes Catalysts for 1,3-Dipolar Cycloaddition Reactions of Nitrone with Electron-rich Alkene

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As a new class of potential catalysts for 1,3-dipolar cycloaddition reactions, fourteen L-amino acid Schiff base Cu(II) and Ti(IV) complexes were synthesized, characterized, and evaluated for their catalytic activities in the reaction between C,N-diphenylnitrone and electron-rich ethyl vinyl ether under both homogeneous and *in situ* conditions. The methods for preparation and utilization of the catalysts were elucidated in detail, and the results of the catalytic reactions were described and discussed as well. Excellent reaction results were found in the presence of some catalysts (20 mol%) with > 90% endo-isoazolidines produced, compared with predominantly exo-isoazolidine produced without a catalyst. In addition, the reaction rate is found to be enhanced remarkably by a Cu(II) complex Schiff base catalyst at room temperature.

Keywords: Amino acid Schiff bases; Amino acid benzyl ester Schiff bases; 1,3-Dipolar cycloaddition; Diastereoselectivity.

INTRODUCTION

Schiff bases are widely used as ligands containing >C=O and >C=N groups in combination with transition metals, due to their attractive and important catalytic properties in asymmetric induction reactions, such as catalytic oxidation,[1,2] asymmetric synthesis of cyanohydrins,[3] hetero-ene reactions,[4] asymmetric cyclopropanation,[5] aldol reactions,[6] Michael addition reactions,[7] hetero-Diels-Alder cycloaddition reactions,[8] and so on. However, the use of amino acid Schiff base metal complexes in asymmetric 1,3-dipolar cycloadditions remains unexplored.

The 1,3-dipolar cycloaddition reaction is one of the most important reactions for the construction of five-membered heterocycles.[9-11] The diastereo-selectivity of the 1,3-dipolar cycloaddition reaction between electron-deficient alkenes and nitrones catalyzed by various metal complexes or Lewis acids has been described in numerous reports.[12-18] On the contrary, cycloaddition reactions between electron-rich alkenes and nitrones seem much less popular. Jørgensen[19] and co-workers reported a $Cu(OTf)_2$/t-Bu-BOX catalyzed cycloaddition reaction between t-butyl glyoxylate derived nitrone and vinyl ether, giving a ratio of 77:23 of the exo to endo cycloadduct. Jørgensen et al. also utilized one of the Binol derivatives, i.e., AlMe complex to catalyze the cycloaddition reaction of C,N-diphenylnitron with eletron-rich butyl vinyl ether and obtained an excellent result with the ratio of exo to endo product being about 95:5.[20] Regardless of the above reported catalysts giving exo-isoazolidines in good yields and high stereoselectivities, there have seldom been reports about endo-selective catalytic asymmetric reactions between electron-rich alkenes and nitrones,[21-24] and the development of the catalysts remains a significant challenge.

In this paper, we report two families of Schiff base metal complexes: one is Cu(II) complexes derived from L-amino acids, the other is $Cu(TOf)_2$ and $Ti(O^iPr)_4$ of L-amino acid benzyl ester Schiff bases. Fourteen catalysts have been synthesized and evaluated for their catalytic activities in 1,3-dipolar cycloaddition reactions between C,N-diphenylnitrone **1** and ethyl vinyl ether **2**, which are reported to produce exclusively the 5-substituted isoxazolines exo-**3** and endo-**3**, regardless of the existence of a catalyst (Scheme I).[19] To our surprise, a dominant endo product is achieved in the presence of 20 mol% catalyst.

RESULTS AND DISCUSSION

The catalysts **4a-d** were prepared according to the literature[26] (Scheme II).

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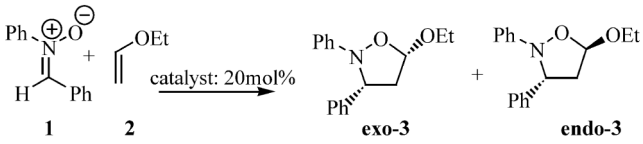
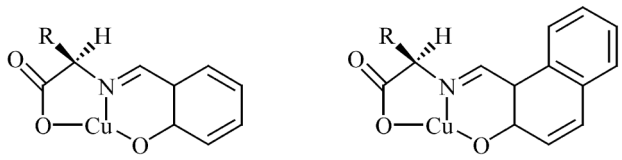
Scheme I



1 **2** **exo-3** **endo-3**

Scheme II



4a: R=Ph **4d:** R=CH_3

4b: R=^{i}Bu

4c: R=CH_3

The structure data of compounds **4a-c** have been reported previously.[26] The new complex **4d** single crystals for the X-ray crystal structure analysis were obtained by crystallization from DMF and methanol (10/1, V/V). The single-crystal X-ray diffraction study reveals that **4d** adopts a one-dimensional fishbone structure. As shown in Fig. 1, the Cu(II) ion shows five-coordinated square prism coordination geometry, coordinated equatorially by three oxygen atoms and one nitrogen atom from two deprotonated Schiff base ligands [Cu(1)–O(1) 1.886(3) Å, Cu(1)–O(2) 1.996(2), Cu(1)–O(2)I 1.981(2), Cu(1)–N(1) 1.904(3), I = -x, y-0.5, 1-z] and axially by one weakly coordinated carboxylic oxygen atom from another deprotonated Schiff base ligand [Cu(1)–O(3)II 2.633(3), II: x, y-1, z]. The selected bond lengths and angles of complex **4d** are shown in Table 1. CCDC 711289 contains the supplementary crystallographic data for **4d**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data.request/cif.

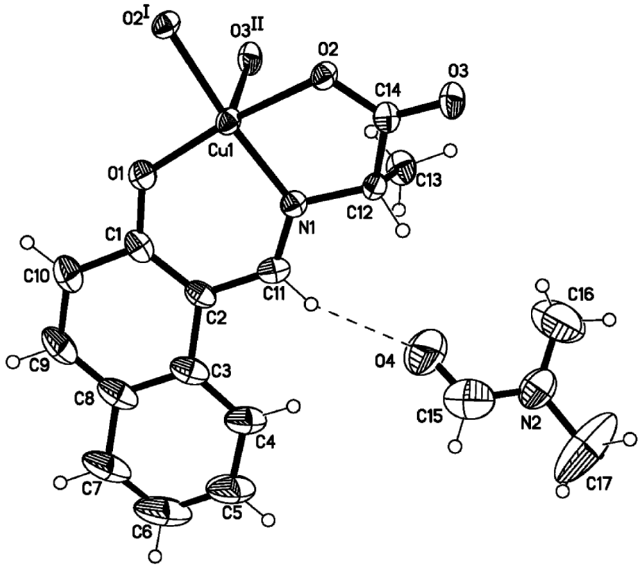


Fig. 1. The X-ray crystal structure of catalyst **4d**.

The catalytic properties of various Cu(II)-L-amino acid Schiff bases in a typical 1,3-dipolar cycloaddition reaction were studied. As shown in Table 2, both the catalytic activities and the influences of different Cu(II)-complexes on the diastereoselectivity are presented. It can be found that in the absence of a catalyst, exo-3 is predominantly formed in CH_2Cl_2 (Table 2, Entry 1). By using Cu-complexes **4a-d** as catalysts, exo-**3** is still the main product when CH_2Cl_2 is used as solvent (Table 2, Entries 2-5). In a word, Cu-complexes exhibit even no catalytic activity in the present reaction. Since catalysts **4a-d** are insoluble in CH_2Cl_2, it is presumed that the major reason for the inertness of the catalysts is that the reaction may proceed under heterogeneous conditions. In order to prove this idea, a new

Table 1. Selected bond lengths (Å) and angles (°) of complex **4d**

Cu(1)–O(1)	1.886(3)	Cu(1)–O(2)	1.996(2)
Cu(1)–N(1)	1.904(3)	Cu(1)–O(3)^{II}	2.633(3)
Cu(1)–O(2)^{I}	1.981(2)	C(11)–N(1)	1.297(4)
O(1)–Cu(1)–N(1)	92.7(1)	O(1)–Cu(1)–O(2)	169.5(1)
O(1)–Cu(1)–O(2)^{I}	90.6(1)	O(1)–Cu(1)–O(3)^{II}	94.7(1)
O(2)–Cu(1)–O(2)^{I}	94.7(1)	O(2)–Cu(1)–O(3)^{II}	95.5(1)
O(2)^{I}–Cu(1)–O(3)^{II}	77.6(1)	N(1)–Cu(1)–O(2)	83.1(1)
N(1)–Cu(1)–O(2)^{I}	171.9(1)	N(1)–Cu(1)–O(3)^{II}	94.4(1)

Symmetry code: I: -x, y-0.5, 1-z; II: x, y-1, z

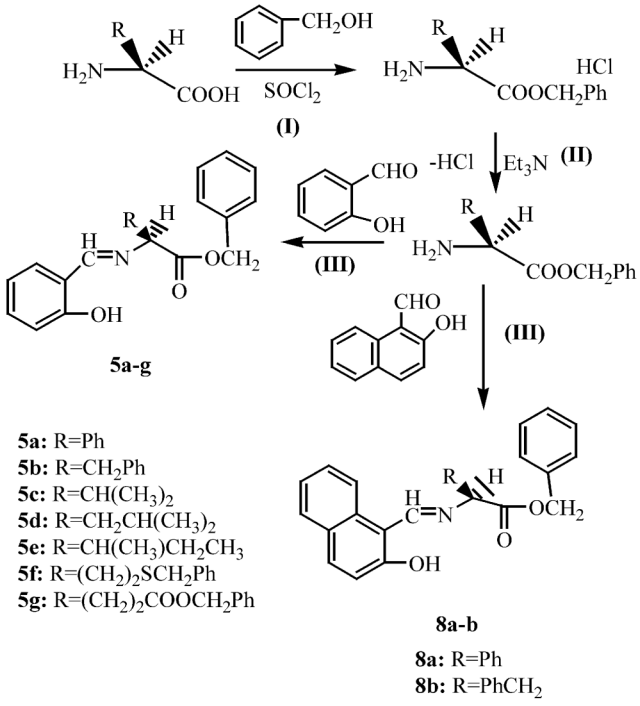
Table 2. Influence of Cu-amino acid complexes on the diastereoselectivity of the reaction between **1** and **2** under both heterogeneous and homogeneous conditions

Entry	Catalyst	Solvent	Conversion (%)	Endo-**3**:exo-**3**
1	none	CH_2Cl_2	83	7:93
2	**4a**	CH_2Cl_2	81	6:94
3	**4b**	CH_2Cl_2	85	6:94
4	**4c**	CH_2Cl_2	83	10:90
5	**4d**	CH_2Cl_2	90	13:87
6	none	DMF	85	9:91
7	**4a**	DMF	84	85:15
8	**4b**	DMF	87	91:9
9	**4c**	DMF	90	> 95:< 5
10	**4d**	DMF	90	100:0

series of reactions was conducted employing DMF as solvent in which Cu-complexes are soluble. As expected, the diastereoselectivity of the reaction between **1** and **2** changes dramatically in the presence of the same catalysts **4a-d** (Table 2, Entries 8-10), despite the fact that no appreciable difference exists in the results of the control experiments without catalyst (Table 2, Entry 1 and Entry 6). Particularly when **4c** is applied as the catalyst an astonishingly high endo-selectivity is achieved, as indicated from an endo-**3**: exo-**3** ratio of >95: <5 (Table 2, Entry 9). The most exciting results can be obtained when complex **4d** is employed as the catalyst; the product is analyzed to contain endo-**3** as the only observable diastereomer (Table 2, Entry 10). It is worth noting that by concentration and extraction, the catalysts **4a-d** can be recovered and reused without any decrease in reactivity and diastereoselectivity, which makes the current catalytic method very attractive.

To further evaluate the catalytic performances of the amino acid Schiff base-metal complexes, we turned our attention to the *in situ* reaction since most of the metal catalysts for 1,3-dipolar cycloaddition reactions are prepared *in situ* in non-polar solvents such as CH_2Cl_2.[9-24] However, the applicability of amino acid Schiff bases as ligands is seriously limited because of their insolubility in non-polar solvents. So we converted amino acid Schiff bases into amino acid ester Schiff bases to improve the solubility of the ligands in non-polar solvents. Initially, we tried to synthesize Schiff bases of amino acid methylesters or ethylesters, but found all these Schiff bases are difficult to be purified because they exist as orange oil at room temperature. Thus, subsequent efforts focused on synthesizing crystalline Schiff bases which are easy to handle at room temperature by introducing more bulky ester groups into the molecules. In this paper, all the synthesized Schiff bases were prepared according to this synthetic method (Scheme III). Ligands **5a-g** and **8a-b**, comprising two series of Schiff bases were derived from salicylaldehyde and 2-hydroxy-1-naphthaldehyde, respectively. The group R can be $-C_6H_5$, $-CH_2C_6H_5$, $-CH(CH_3)_2$, $-CH_2CH(CH_3)_2$, $-CH(CH_3)CH_2CH_3$, $-(CH_2)_2SCH_2C_6H_5$ or $-(CH_2)_2COOCH_2C_6H_5$, corresponding to a Schiff base derived from the amino acid of L-phenylglycine, L-phenylalanine, L-valine, L-leucine, L-isoleucine, L-methionine or L-glutamic acid, respectively. The Schiff base was prepared by esterification of the corresponding amino acid (Scheme III, **I**), neutralization of the produced amino acid benzylester hydrochloride (Scheme III, **II**) followed by condensation of the benzylester with salicylaldehyde or 2-hydroxy-1-naphthaldehyde (Scheme III, **III**). Without exception, nine amino acid benzylester Schiff bases were easily recrystallized from methanol as beautiful light yellow needles. It was found that the Schiff bases formed by amino acid benzyl esters and salicylaldehyde or 2-hydroxy-1-naphthaldehyde were more stable than those formed by amino acids and the corresponding o-hydroxyl aldehydes.[27] Moreover, the results show the amino acid benzyl ester Schiff bases exhibit excellent solubility both in polar solvents and non-polar solvents such as alcohols, dichloromethane, tetrahydrofuran, acetic ether, ethyl ether, and so on.

Scheme III

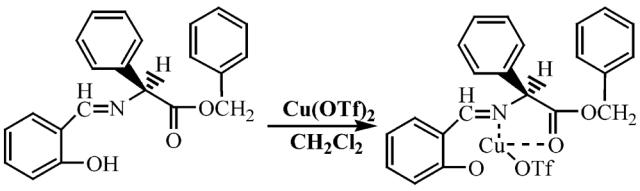


5a: R=Ph
5b: R=CH_2Ph
5c: R=$CH(CH_3)_2$
5d: R=$CH_2CH(CH_3)_2$
5e: R=$CH(CH_3)CH_2CH_3$
5f: R=$(CH_2)_2SCH_2Ph$
5g: R=$(CH_2)_2COOCH_2Ph$

8a: R=Ph
8b: R=$PhCH_2$

After synthesizing *in situ* successfully, the catalytic activity of the $Cu(OTf)_2$ Schiff base of L-phenylglycine benzyl ester salicylaldehyde (**6a**) (Scheme IV) was firstly

Scheme IV



5a **6a**

Table 3. Influence of the catalyst **6a** on the diastereoselectivity of the reaction between **1** and **2** under various reaction conditions

Entry	Catalyst	Temp (°C)	Time	Conversion (%)	Endo-**3**:exo-**3**
1	none	rt	72 h	83	7:93
2	**5a**	rt	72 h	82	6:94
3	$Cu(OTf)_2$	rt	10 min	-	-
4	**6a**	rt	10 min	100	13:87
5	**6a**	-40	2 h	100	53:47
6	**6a**	-78	10 h	100	72:28

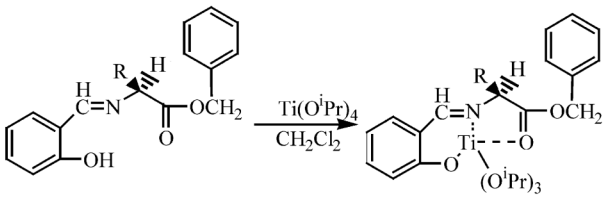
evaluated in the reaction between **1** and **2** under various conditions, and the results are presented in Table 3.

It seems that *exo*-**3** is still predominantly formed by using ligand **5a** as the catalyst and little diastereoselectivity change takes place after 72 h of reaction (Table 3, Entries 1-2). In the presence of $Cu(OTf)_2$ catalyst, no product was obtained because the nitrone **1** was completely destroyed (Table 3, Entry 3). Surprisingly, in the presence of 20 mol% **6a** catalyst, the reaction was completed within 10 min at ambient temperature, although with a similar diastereoselectivity (Table 3, Entry 4). When the reaction was carried out at a low temperature (-40 °C), a conversion of 100% was accomplished after 2 h with an endo-**3**:exo-**3** ratio of 53:47 (Table 3, Entry 5). By optimizing the reaction conditions (lowering the temperature to -78 °C, and lengthening the reaction time to 10 h), the diastereoselectivity could be improved to endo:exo = 72:28 (Table 3, Entry 6). Although the rate as well as diastereoselectivity of the cycloaddition reaction can be enhanced prominently in the presence of catalyst **6a**, the unsatisfying diastereoselectivity catalyzed by the $Cu(OTf)_2$ complex prompted us to select Ti-catalysts for further exploration.

Ti-complexes were prepared according to Scheme V and Scheme VI; for details see Experimental Section. The results of the 1,3-dipolar cycloaddition reaction between **1** and **2** (Scheme I) in the presence of various Ti-complexes (**7a-g** and **9a-b**) are presented in Table 4.

It can be seen that in the presence of $Ti(O^iPr)_4$ catalyst, the reaction does not proceed since the nitrone **1** is completely decomposed (Table 4, Entry 1). Application of catalyst **9b** leads to a somewhat reversal of the product configuration from the exo-**3** to endo-**3**, resulting in a lack of diastereoselectivity (endo:exo = 49:51) (Table 4 , Entry 2). Lowering the reaction temperature to 10 °C resulted in a very high endo-selectivity but an obvious lower reaction

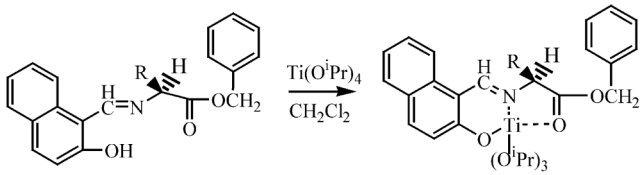
Scheme V



5a: R=Ph
5b: R=CH_2Ph
5c: R=$CH(CH_3)_2$
5d: R=$CH_2CH(CH_3)_2$
5e: R=$CH(CH_3)CH_2CH_3$
5f: R=$(CH_2)_2SCH_2$Ph
5g: R=$(CH_2)_2COOCH_2$Ph

7a: R=Ph
7b: R=CH_2Ph
7c: R=$CH(CH_3)_2$
7d: R=$CH_2CH(CH_3)_2$
7e: R=$CH(CH_3)CH_2CH_3$
7f: R=$(CH_2)_2SCH_2$Ph
7g: R=$(CH_2)_2COOCH_2$Ph

Scheme VI



8a: R=Ph
8b: R=CH_2Ph

9a: R=Ph
9b: R=CH_2Ph

rate, which is indicated by a slight decrease in the conversion after a prolonged time of reaction (Table 4, Entry 11). It is interesting to note that in all cases with the Ti-complexes as catalysts the diastereoselectivity of the reaction was dramatically reversed by lowering the reaction temperature (Table 4, Entries 3-11), which is similar to the results of catalyst **6a** (Table 3, Entries 4-6). The reason for this re-

Table 4. Influence of the catalysts **7a-g** and **9a-b** on the diastereoselectivity of the reaction between 1 and 2 under various reaction conditions

Entry	Catalyst	Temp (°C)	Time	Conversion (%)	Endo-**3**:exo-**3**
1	$Ti(O^iPr)_4$	30	2 days	-	-
2	**9b**	30	2 days	90	49:51
3	**7a**	10	4 days	83	92:8
4	**7b**	10	4 days	80	94:6
5	**7c**	10	4 days	82	94:6
6	**7d**	10	4 days	84	96:4
7	**7e**	10	4 days	83	90:10
8	**7f**	10	4 days	80	93.5:6.5
9	**7g**	10	4 days	83	95:5
10	**9a**	10	4 days	81	93:7
11	**9b**	10	4 days	84	>98:<2

versal from exo- to endo-selectivity is not clear currently and further investigations in order to explain the role of the amino acid Schiff bases and the amino acid benzylester Schiff base metal complexes from a mechanistic point of view are in progress.

CONCLUSION

A remarkable reverse of the selectivity from exo- to endo-product can be achieved in 1,3-dipolar cycloadditon reaction between C,N-diphenylnitrone **1** and eletron-rich ethyl vinyl ether **2** catalyzed by an amino acid Schiff base copper complex under homogeneous conditions or catalyzed by an amino acid benzylester Schiff base copper or titanium complex under *in situ* conditions. Particularly, when Cu complex **7d** is used as the catalyst, 100% endo-**3** can be obtained in DMF and Ti complex **9b** as the catalyst, the reaction in CH_2Cl_2 could produce >98% endo-**3**. In addition, the reaction rate can be markedly enhanced when 20 mol% L-phenylglycine benzyl ester salicylaldehyde Schiff base-$Cu(OTf)_2$ (**6a**) is used as the catalyst.

EXPERIMENTAL

General

The X-ray crystal structure analysis was carried out on a Rigaku R-axis rapid diffractometer. The ^{1}H-NMR and ^{13}C-NMR spectra were acquired from a Bruker Avance 300 MHz Digital FT-NMR Spectrometer in $CDCl_3$ with TMS as internal standard. Infrared spectra in the region of 4000-400 cm^{-1} were obtained from KBr-pellets on a Nicolet Avatar 370 FT-IR spectrophotometer. MS spectra were recorded from an Agilent 1100 Series LC/MSD Trap. Elemental analysis was finished on a Thermo Flash EA1112 instrument. Melting points (mp) were uncorrected.

The amino acids (L-alanine L-valine, L-leucine, L-isoleucine, L-phenylglycine, L-phenylalanine, L-methionine, L-glutamic acid), 2-hydroxy-1-naphthaldehyde, ethyl vinyl ether, $Cu(OTf)_2$ and $Ti(O^iPr)_4$ were purchased from Alfa Aesar and used directly. Both CH_2Cl_2 and DMF were dried by standard methods. Other reagents were also obtained commercially and used without further purification. C,N-diphenylnitrone **1** was synthesized according to the literature.[25] The structure data of compounds exo- and endo-3 have been reported previously,[20a] but endo-3 is white needle crystals after recrystallization from methanol, not clear oil.[20a] Mp: 81.9 °C. Formula: $C_{17}H_{19}O_2N$ (269.1): Calcd. C 75.82, H 7.11, N 5.20; Found. C 75.59, H 7.03, N 4.89. MS: 292.3 ($^+$M+Na). Endo-**3**:exo-**3** ratio was determined by ^{1}H MNR spectroscopy using the following integral ratio: endo-3 gives δ 4.77 (dd, J = 7.10, 10.23 Hz, 1H), correspondingly exo-3 gives δ 4.30 (dd, J = 6.70, 9.50 Hz, 1H).

Preparation of Cu-Amino Acid Schiff Base Catalyst (4a-d)

The catalysts **4a-d** were prepared according to the literature.[26]

General Procedure for the Reaction Using 20 mol% Cu-Amino Acid Schiff Base (4a-d) Catalyst (Table 2)

To a 20 mL reaction flask containing a magnetic stirring bar and 10 mL DMF (or CH_2Cl_2) were added C,N-diphenylnitrone **1** (0.5 mmol) and ethyl vinyl ether **2** (2.5 mmol), followed by the 20 mol% catalyst **4a** (or **4b**, **4c**, **4d**). The resultant mixture was stirred at room temperature for 72 h. When the reaction was completed as monitored by TLC plates, the solvent was removed in a high vacuum (2-5 Pa) at not exceeding 30 °C. After most of the solvent was removed, 5 mL ethyl acetate was added and then the precipitate of copper complex appeared. The blue mixture was cooled for 3 h and collected after filtration, then washed with ethyl acetate (2 × 10 mL) to give the catalyst in 95% recycled yield. Endo- and exo-products were left in the filtrate and washing liquor. The solvent in the combined fractions was evaporated off and then the crude product was purified by column chromatography (silica gel, petroleum ether/ethyl acetate = 20:1, volume ratio) to give the mixture of endo-**3** and exo-**3**. The diastereomers of **3** can be separated by preparative TLC method, in which exo-3 possesses a lower R_f value than endo-3 ($\Delta R_f = 0.1$).

Preparation of the Ligands: L-Amino Acid Benzyl ester Schiff Bases 5a-g, 8a-b (Scheme I); Preparation of the amino acid benzyl esters hydrochlorides

Benzyl ester hydrochlorides of L-phenylglycine, L-phenylalanine, L-valine, L-leucine, L-isoleucine, L-methionine, and L-glutamic acid were prepared according to the same method: 20 mmol amino acid to be esterified was suspended in 120 mL benzyl alcohol, and cooled to 5 °C. 20 mL thionyl chloride was added slowly to the suspension over a period of 20 min, and the reaction mixture was then heated on a steam bath for 5 hours. Benzyl alcohol was removed by gentle heating *in vacuo* at a bath temperature not exceeding 80 °C. After most of the benzyl alcohol was removed, 100 mL ether was added when the reaction system had been cooled sufficiently to prevent the ether from boiling too vigorously and turbidity appeared. The mixture was then refrigerated (to about -15 °C) for a few hours; mean-

while the benzyl ester hydrochloride crystallized. The product was collected after filtration and recrystallized from an absolute ethanol-ether mixture. Yields of benzyl ester hydrochlorides of L-phenylglycine, L-phenylalanine: >95%. Yields of benzyl ester hydrochlorides of L-valine, L-isoleucine: approx. 70%. Yields of benzyl ester hydrochlorides L-leucine, L-methionine, and L-glutamic acid: approx. 85%.

Preparation of the free amino acid benzyl esters

To a suspension of 20 mmol of the amino acid benzyl ester hydrochlorides in 50 mL of chloroform, 4 g (40 mmol) of triethylamine was added over a period of ten minutes at 0-5 °C. Subsequently, 100 mL of absolute ether was added and then the mixture was allowed to stand for ten minutes. Afterwards the precipitated triethylammonium hydrochloride was filtered off and the ethereal solution was concentrated *in vacuo* with rigid exclusion of moisture. The remaining pale yellow oil was the amino acid benzyl ester. Yield: >90%.

General procedure for the preparation of amino acid benzyl ester Schiff bases (5a-g and 8a-b)

All Schiff bases were prepared in a way described below: 10 mmol free amino acid benzyl esters was dissolved in 10 mL methanol, and 10 mmol salicylaldehyde or 2-hydroxy-1-naphthaldehyde was added therein rapidly. Immediately, the color of the solution changed from colorless to bright lemon-yellow with a small quantity of heat released. The reaction was allowed to come to completion by stirring for not less than 5 minutes at room temperature and then the products precipitated directly from methanol. The obtained yellow solid was further purified by recrystallization from methanol.

SalPhgOCH$_2$Ph (5a)

Yield: 96%. Mp: 90-91.3 °C. IR (KBr): 3449, 1732, 1625, 1280, 1257, 1150 cm^{-1}. ^{1}H NMR: δ 5.21 (m, 3H, -OCH$_2$, -CH), 6.87~7.46 (m, 14H, Ar-H), 8.37 (s, 1H, -CH=N), 13.12 (s, 1H, -OH). ^{13}C NMR: δ 67.23, 74.85, 117.26, 118.67, 118.83, 127.78, 128.01, 128.33, 131.96, 133.06, 135.45, 137.02, 161.12, 166.99, 170.10. MS: *m/z* = 346.2, 368.0, 383.9 (MS+). Anal. Calcd. for $C_{22}H_{19}O_3N$: C 75.53, H 5.56, N 4.06. Found: C 75.38, H 5.76, N 3.90.

SalPheOCH$_2$Ph (5b)

Yield: 97%. Mp: 90.7-91.5 °C. IR (KBr): 3440, 1736, 1636, 1281, 1261, 1151 cm^{-1}. ^{1}H NMR: δ 3.14 (dd, J = 8.75 H$_Z$, J = 13.6 H$_Z$, 1H, -CH$_2$), 3.37 (dd, J = 13.6 H$_Z$, J = 5.0 H$_Z$, 1H, -CH$_2$), 4.21 (dd, J = 5.0 H$_Z$, J = 8.75 H$_Z$, 1H, -CH), 5.19 (s, 2H, -OCH$_2$), 6,83~7.34 (m, 14H, Ar-H), 7.98 (s, 1H, -CH=N), 12.71 (S, 1H, -OH). ^{13}C NMR: δ 40.02, 67.11, 73.10, 117.15, 118.46, 118.72, 126.91, 128.25, 128.42, 128.57, 128.64, 129.62, 131.80, 132.86, 135.43, 136.64, 161.03, 167.01, 170.65. MS: *m/z* = 360.4, 382.0, 336.2, 397.9 (MS+). Anal. Calcd. for $C_{23}H_{21}O_3N$: C 76.86, H 5.89, N 3.89; Found: C 76.68, H 6.00, N 3.61.

SalValOCH$_2$Ph (5c)

Yield: 91%. Mp: 53.4-54.5 °C. IR (KBr): 3448, 1731, 1629, 1279, 1152 cm^{-1}. ^{1}H NMR: δ 0.97 (d, J = 6.7 H$_Z$, 6H, CH$_3$), 2.41 (m, J = 6.7 H$_Z$, J = 6.1 H$_Z$, 1H, CH), 3,79 (d, J = 6.1 H$_Z$, 1H, N-CH), 5.22 (s, 2H, -OCH$_2$), 6.88~7.38 (m, 10H, Ar-H), 8.33 (s, 1H, -CH=N), 13.15 (s, 1H, -OH). ^{13}C NMR: δ 18.19, 19.43, 31.92, 66.82, 77.91, 117.22, 118.58, 118.73, 128.26, 128.37, 128.63, 131.79, 132.86, 135.62, 161.23, 166.72, 170.90. MS: *m/z* = 312.4, 334.1, 350.1 (MS+). Anal. Calcd. for $C_{19}H_{21}O_3N$: C 73.29, H 6.80, N 4.50; Found: C 73.51, H 6.91, N 4.58.

SalLeuOCH$_2$Ph (5d)

Yield: 93%. Mp: 63-64.5 °C. IR (KBr): 3465, 1740, 1631, 1278, 1142 cm^{-1}. ^{1}H NMR: δ 0.84 (m, 6H, CH$_3$), 1.53 (m, 1H, -CH), 1.79 (m, 2H, -CH$_2$), 4.04 (m, 1H, -CH), 5.11 (s, 2H, -OCH$_2$), 6.79~7.29 (m, 9H, Ar-H), 8.29 (s, 1H, -CH=N), 12.96 (s, 1H, -OH). ^{13}C-NMR: δ 21.55, 23.06, 24.52, 42.34, 66.92, 69.79, 117.20, 118.62, 118.76, 128.17, 128.64, 131.77, 132.83, 135.61, 161.12, 166.52, 171.46. MS: *m/z* = 326.2, 348.1, 363.9 (MS+). Anal. Calcd. for $C_{20}H_{23}O_3N$: C 73.82, H 7.10, N 4.30; Found. C 73.88, H 6.95, N 4.38.

SalILeuOCH$_2$Ph (5e)

Yield: 82%. Mp: 36-37 °C. IR (KBr): 3436, 1746, 1630, 1281 cm^{-1}. ^{1}H NMR: δ 0.92 (m, 6H, CH$_3$), 3.88 (d, 1H, -CH), 5.22 (s, 2H, -OCH$_2$), 6.91~7.39 (m, 9H, Ar-H), 8.34 (s, 1H, -CH=N), 13.14 (s, 1H, -OH). ^{13}C NMR: δ 11.27, 15.88, 25.04, 38.41, 66.82, 77.23, 117.23, 118.50, 118.74, 128.26, 128.36, 128.61, 131.80, 132.94, 135.58, 161.26, 166.67, 170.88. MS: *m/z* = 326.0, 348.4, 363.9 (MS+). Anal. Calcd. for $C_{20}H_{23}O_3N$: C 73.82, H 7.10, N 4.30; Found. C 73.44, H 7.13, N 4.27.

SalMetOCH$_2$Ph (5f)

Yield: 90%. Mp: 58.4-59.7 °C. IR (KBr): 3437, 1735, 1727, 1632, 1296, 1282, 1160, 1150 cm^{-1}. ^{1}H NMR: δ 2.22 (m, 2H, -CH$_2$), 2.35 (m, 1H, -CH$_2$), 2.50 (m, 1H, -CH$_2$), 3.68 (s, 2H, -SCH$_2$), 4.21 (m, 1H, -CH), 5.19 (s, 2H, -OCH$_2$), 6.89~7.39 (m, 14H, Ar-H), 8.33 (s, 1H -CH=N), 12.85 (s, 1H, -OH). ^{13}C MNR: δ 27.25, 32.26, 36.02, 67.09, 69.58, 117.20, 118.45, 118.83, 127.08, 128.18, 128.43, 128.54, 128.66, 128.82, 132.02, 133.08, 135.46, 138.06,

161.11, 167.72, 170.73. MS: *m/z* = 420.0, 442.0, 457.8 (MS+). Anal. Calcd. for $C_{25}H_{25}SO_3N$: C 71.57, H 6.01, N 3.34, S 7.64; Found. C 71.87, H 6.02, N 3.34, S 7.73.

SalGluOCH$_2$Ph (5g)

Yield: 90%. Mp: 60.2-61.6 °C. IR (KBr): 3449, 1740, 1629, 1277, 1190, 1163 cm^{-1}. ^{1}H NMR: δ 2.29~2.43 (m, 4H, -CH$_2$), 4.13 (m, 1H, -CH), 5.11 (q, 2H, -OCH$_2$), 5.20 (q, 2H, -OCH$_2$), 6.88~7.37 (m, 14H, Ar-H), 8.32 (s, 1H, -CH=N), 12.75 (s, 1H, -OH). ^{13}C NMR: δ 28.45, 30.21, 66.52, 67.14, 117.21, 118.45, 118.87, 128.19, 128.36, 128.44, 128.62, 128.66, 131.99, 133.10, 135.41, 135.76, 161.05, 167.81, 170.49, 172.34. MS: *m/z* = 432.1, 454.0, 469.8 (MS+). Anal. Calcd. for $C_{26}H_{25}O_5N$: C 72.37, H 5.84, N 3.25; Found. C 72.42, H 5.94, N 3.18.

NapPhgOCH$_2$Ph (8a)

Yield: 90%. Mp: 104.5-105.2 °C. Anal. Calcd. for $C_{26}H_{21}O_3N$: C 78.97, H 5.35, N 3.54; Found. C 79.29, H 5.35, N 3.54. IR (KBr): 3461, 1738, 1625, 1262, 1140 cm^{-1}. ^{1}H NMR: δ 5.20 (s, 2H, -OCH$_2$), 5.36 (s, 1H, -CH), 7.10~9.04 (m, 16H, Ar-H), 9.06 (s, 1H, -CH=N), 14.82 (s, 1H, -OH). ^{13}C NMR: δ 67.48, 108.31, 118.75, 121.82, 123.31, 127.24, 127.68, 127.91, 128.09, 128.40, 128.60, 128.79, 129.13, 129.25, 133.06, 135.28, 136.08, 136.64, 160.76, 168.49, 169.79. MS: *m/z* = 396.1, 418.0, 433.8 (MS+).

NapPheOCH$_2$Ph (8b)

Yield: 90%. Mp: 105-106.4 °C. IR (KBr): 3453, 1734, 1629, 1219, 1176 cm^{-1}. ^{1}H MNR: δ 3.177 (dd, *J* = 8.9 HZ, *J* = 13.8 HZ, 1H, -CH$_2$), 3.420 (dd, *J* = 4.913.8, 1H, -CH$_2$), 4.36 (dd, *J* = 4.9 H$_Z$, *J* = 8.9 H$_Z$, 1H, -CH), 5.22 (s, 2H, -CH$_2$), 7.06~7.75 (m, 16H, Ar-H), 8.61 (s, 1H, -CH=N), 14.41 (s, 1H, -OH). ^{13}C MNR: δ 40.21, 67.36, 70.52, 107.95, 118.75, 121.84, 123.18, 127.16, 127.76, 128.37, 128.51, 128.69, 128.74, 129.14, 129.65, 133.05, 135.30, 135.86, 136.25, 160.88, 168.45, 170.40. MS: *m/z* = 410.1, 432.0, 447.9 (MS+). Anal. Calcd. for $C_{27}H_{23}O_3N$: C 79.20, H 5.66, N 3.42; Found. C 79.51, H 5.64, N 3.43.

Synthesis of catalyst 6a

To Schiff base **5a** (0.1 mmol) in a 5 mL flask under N_2 was added Cu(OTf)$_2$ (0.1 mmol) and CH_2Cl_2 to give a total volume of 1 mL. The color of the solution changed from yellow to blue rapidly. After stirring for 30 min the catalyst solution (0.1 M) of **6a** was ready for use (Scheme III).

Synthesis of catalysts 7a-g and 9a-b

The process is similar to that of catalyst **6a**. To Schiff base **5a** (or **5b-g**, **8a-b**) (0.1 mmol) in a 5 mL flask under N_2 was added of Ti(O^{i}Pr)$_4$ (0.1 mmol) and CH_2Cl_2 to give a total volume of 1 mL. The color of the solution turned from black red to pale yellow after stirring for 1 h (Scheme IV).

General Procedure for the 1,3-dipolar cycloaddition reaction catalyzed by 20 mol% Cu(OTf)$_2$ or Ti(O^{i}Pr)$_4$-L-Amino Acid Benzyl ester Schiff Base

To a 20 mL reaction flask containing a magnetic stirring bar and 10 mL CH_2Cl_2 were added C,N-diphenylnitrone **1** (0.5 mmol) and ethyl vinyl ether **2** (2.5 mmol). The resultant mixture was stirred at a definite temperature (see Table 3 and Table 4), at the same time one of the above mentioned catalyst solution of **6a** or **7a-g** or **9a-b** (1 mL, 20% mol) was added via syringe. When the reaction was completed as monitored by TLC plates, the mixture was filtered through a 30 mm layer of silica gel. The silica gel layer was washed with 5 mL diethyl ether and the solvent evaporated *in vacuo*. ^{1}H NMR spectroscopy revealed conversions in all entries as shown in Table 3 and Table 4. The diastereomers of **3** were separated by the preparative TLC method.

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