Tetrahedron Letters 51 (2010) 5068–5070

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Ag/ThioClickFerrophos catalyzed highly enantioselective 1,3-dipolar cycloaddition of azomethine ylides with alkenes

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ARTICLE INFO

Article history:
Received 11 June 2010
Revised 9 July 2010
Accepted 16 July 2010
Available online 6 August 2010

ABSTRACT

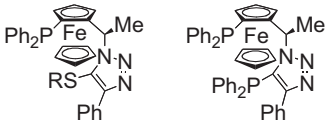
A silver(I)/ThioClickFerrophos complex catalyzed the *endo* selective asymmetric 1,3-dipolar cycloaddition reaction of methyl *N*-benzylideneglycinate (the source of azomethine ylides) with α,β-unsaturated esters and maleimides to give the *endo*-2,4,5- and 2,3,4,5-substituted pyrrolidines in good yields with high enantioselectivities (up to 99% ee). The complex also effectively catalyzed the *endo* selective reactions with β-nitrostyrene to give the 4-nitropyrrolidine in a high enantioselectivity.

1,3-Dipolar cycloaddition of azomethine ylide to electron-deficient olefins yields chiral pyrrolidines, an important class of heterocyclic compounds with widespread applications to the synthesis of biologically active compounds and natural products.[1] These cycloaddition reactions represent an important class of synthetic methods and have inspired much research interest in the development of asymmetric catalytic variants. Elegant studies in this field have often centered on chiral metal complex-catalyzed asymmetric 1,3-dipolar additions with azomethine ylides, and Cu^I and Ag^I/phosphine complexes often give moderate to excellent levels of stereoselectivity with methyl *N*-benzylideneglycinate (the source of azomethine ylides). Wang's Cu^I or Ag^I/TF-BiphamPhos,[2] Carretero's Cu^I/Fesulphos,[3] Zhang's Ag^I/xylyl-FAP,[4] Schreber's Ag^I/QUINAP,[5] Zhou's Ag^I/FPOX,[6] and Sansano's Ag^I/BINAP[7] are the representative effective chiral metal catalysts for the reaction. They give either *endo*- or *exo*-diastereomer of proline derivatives with good enantioselections (Fig. 1).

Recently, we reported a novel ClickFerrophos ligands (**L4**), whose Cu^I complexes exhibited highly *exo* stereoselectivity and excellent enantioselectivity in the asymmetric 1,3-dipolar cycloaddition of azomethine ylides with a vinyl sulfone.[8] We also succeeded in highly *endo* and enantioselective reaction with (*E*)-acyclic and cyclic α-enones by using Ag^I/ThioClickFerrophos complexes (**L1**–**L3**).[9] Extending the interest in the Ag^I/**L1**–**L3**-catalyzed cycloaddition reaction with other dipolarophiles (alkenes), we have found that it also worked effectively for α,β-unsaturated esters, amides, and β-nitrostyrene in high enantioselections.[10]

We initially focused on optimization of the enantioselective 1,3-dipolar cycloaddition. Methyl *N*-(4-chlorobenzylidene)glycinate **1b** and methyl acrylate **2a** were chosen as a dipolar (azomethine ylide) and a dipolarophile, respectively. The model reaction was carried out in toluene at room temperature for 12 h by using various Ag^I salts (5 mol %), ligands (**L1**–**L3**) (5 mol %), and Et_3N (18 mol %).[11] The *endo* to *exo* isomer ratio and enantiomeric excess (ee) of the product were determined by ^1H NMR and HPLC (Chiralpak AS-H), respectively. The reaction proceeded smoothly to give a mixture of *endo*/*exo* cycloadducts. The results are summarized in Table 1. Notably, the *endo* product was produced preferentially in contrast to the previous Cu^I/**L4** complex (entry 9).[8] From the optimization experiments, the combination of AgOAc and **L3** (R = *t*-Bu) was revealed to be the most effective catalyst for the reaction. Further, the ee could be improved up to 98% ee by carrying out the reaction in CH_2Cl_2 at 0 °C although the yield was decreased to some extent. Then, we concluded the optimal catalyst, solvents, and the reaction conditions are AgOAc/**L3** and CH_2Cl_2, 0 °C for 24 h, respectively to obtain the *endo*-adduct in good diastereo- and enantioselectivities. The combination of Cu^I salts with **L3** resulted in a lower enantioselectivity of *endo*-adduct (entry 10).

Next we examined the scope of the reaction with respect to azomethine ylide precursors (dipolars) **1** using **2a** as an alkene (dipolarophile) under the optimized conditions. The results are summarized in Table 2. High *endo*-selectivity (*endo*/*exo* = 98/2–99/1) and high ee of *endo*-adducts (**3a**–**h**) were obtained virtually independent of stereo and electronic properties of substituents; electron-withdrawing (Cl, Br, CN), -donating (Me, OMe), and a position of methyl group (entries 4–6) almost did not affect on the



L-1: R = Et
L-2: R = Cy
L-3: R = *t*-Bu

L-4

Figure 1. ClickFerrophos and ThioClickFerrophos.

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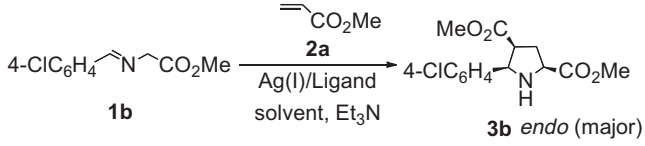
doi:10.1016/j.tetlet.2010.07.085

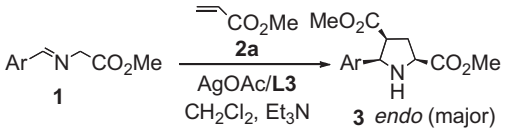
Table 1
Optimization experiments of 1,3-dipolar reaction of azomethine ylide with methyl acrylate **2a**[a]



Entry	Ag(I) salt	Ligand	Yield[b] (%) *endo*/*exo*[c]	ee[c] (%) (*endo*)
1	AgOAc	**L1**	93, 98/2	63
2	AgOTf	**L1**	87, 98/2	45
3	$AgPF_6$	**L1**	90, 98/2	49
4	$AgSbF_6$	**L1**	91, 98/2	45
5	$AgOCOCF_3$	**L1**	88, 98/2	37
6	AgOAc	**L2**	74, 98/2	88
7	AgOAc	**L3**	86, 98/2	96
8[d]	AgOAc	**L3**	78, 98/2	98
9[e]	AgOAc	**L4**	89, 30/70	96
10	CuOAc	**L1**	71, 91/9	35

[a] Methyl *N*-(*p*-chlorobenzylidene)glycinate (0.2 mmol), methyl acrylate (0.3 mmol), Ag(I) salts (0.01 mmol), Et_3N (0.036 mmol), ligand (0.011 mmol), toluene (2.0 mL); rt, 12 h.
[b] Isolated yield (*endo*).
[c] Determined by HPLC (Chiralpak AS-H).
[d] The reaction was carried out at 0 °C in CH_2Cl_2.
[e] Ref. 8, ee % is for *exo* adduct.

Table 2
The scope of the reactions with respect to dipoles[a]



Entry	Dipole	Ar	Product and yield[b] (%)	ee[c] (%)
1	**1a**	Ph	**3a**, 71	97
2	**1b**	4-ClC_6H_4	**3b**, 78	98
3	**1c**	4-BrC_6H_4	**3c**, 91	98
4	**1d**	2-MeC_6H_4	**3d**, 81	95
5	**1e**	3-MeC_6H_4	**3e**, 84	98
6	**1f**	4-MeC_6H_4	**3f**, 78	98
7	**1g**	4-$MeOC_6H_4$	**3g**, 91	98
8	**1h**	4-CNC_6H_4	**3h**, 57[d]	97
9	**1i**	2-C_8H_9	**3i**, 74	98

[a] Dipole (0.2 mmol), methyl acrylate (0.3 mmol), AgOAc (0.01 mmol), **L3** (0.011 mmol), CH_2Cl_2 (2.0 mL): 0 °C, 15–24 h.
[b] Isolated yield of *endo* product.
[c] ee of *endo* isomer (*endo*/*exo* = 98/2–99/1) was determined by HPLC.
[d] *endo*/*exo* = 95/5.

enantioselectivity, although yield was low in the reaction with **1h** (Ar = 4-CNC_6H_4). The reaction with 2-naphthyl derivative **1i** also gave the high ee values as phenyl derivatives (entry 9).

Finally, we examined the scope of the reaction with respect to alkenes (dipolarophiles) using **1b** as an azomethine source. The results are outlined in Table 3. In the reaction with *tert*-butyl acrylate **2b**, *endo* and enantioselectivities were almost the same as the reaction with methyl acrylate (entry 1). In the reaction with methyl methacrylate **4**, *endo*-adduct **10** was produced regioselectively with 94% ee (entry 2). It must be noteworthy that high enantioselectivity was achieved by using Ag^I/**L3** complex, while Oh and coworkers reported that Ag^I/brucine-derivative complex affords the adduct in 60% ee.[12] In the reactions with dimethyl maleate **5** and fumarate **6** the corresponding *endo* isomers **11** and **12** were obtained, respectively (*endo*:*exo* = 98:2) with a high enantioselectivity (95% ee, entries 3–4). The reaction with *N*-methyl-maleimide **7a** gave the *endo*-adduct **13a** with high diastereoselectivity

Table 3
The scope of the reaction with respect to dipolarophiles[a]

Entry	Alkene	Product	Yield[b] (%), *endo*/*exo*[c]	ee (%) (*endo*)[d]
1	**2b**	**9**	82, 98/2	96
2	**4**	**10**	79, 98/2	94
3	**5**	**11**	85, 94/6	91
4	**6**	**12**	86, 85/15	95
5	**7a**	**13a**	91, 98/2	99
6	**7b**	**13b**	93, 98/2	86
7	**8**	**14**	36, 65/35	91

[a] **1b** (0.2 mmol), dipolarophile (0.3 mmol), AgOAc (0.01 mmol), **L3** (0.011 mmol), CH_2Cl_2 (2.0 mL): 0 °C, 24 h.
[b] Total isolated yield of *endo*-adduct.
[c] Determined by ^1H NMR.
[d] Determined by HPLC.

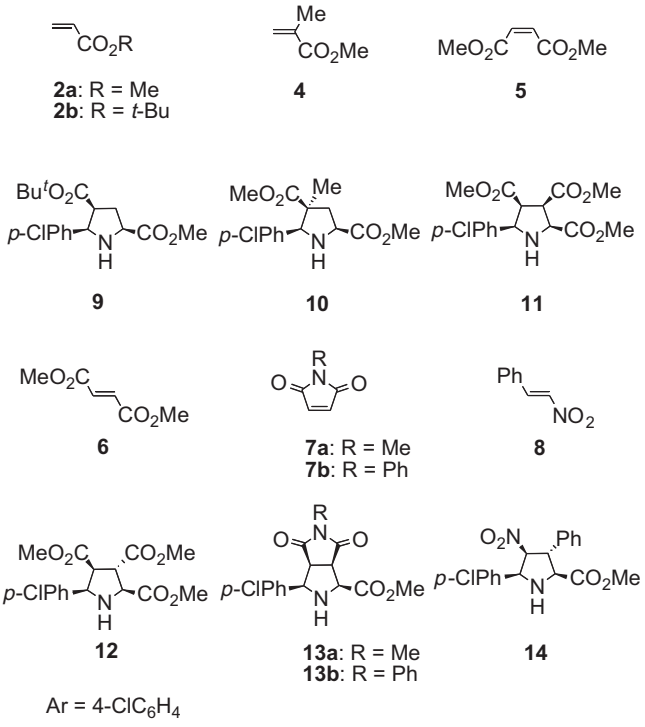


Figure 2. Dipolarophiles and products.

(*endo*:*exo* = 98:2) and 99% ee (entry 5). Enantioselectivity was decreased by displacing *N*-methyl group by *N*-phenyl group **7b**, ee value being 86% (entry 6). The reaction with β-nitrostyrene gave a low yield of the cycloadduct **14** as a mixture of diastereomers (*endo*/*exo* = 65/35), yield and ee of *endo* isomer being 36% and 91% ee, respectively (entry 7).

In conclusion Ag^I/**L3** complex-catalyzed asymmetric 1,3-dipolar cycloaddition of azomethine ylide could be extended to α,β-unsaturated esters, amides, and β-nitrostyrene in addition to previous α-enones. The reaction proceeded to give the *endo* cycloadduct predominantly with excellent enantioselectivities (Fig. 2).

Acknowledgments

This study was financially supported by a Grant-in-Aid, No. 22550044, for the Scientific Research from the Japan Society for the Promotion of Science (JSPS) and a Chuo University Grant for Special Research.

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11. The following provide a typical experimental procedure of asymmetric 1,3-dipolar cycloaddition of azomethine ylide with dipolarophiles. In a 20-mL Schlenk tube containing a stirring bar, AgOAc (1.7 mg, 0.01 mmol) and L3 (6.9 mg, 0.011 mmol) were dissolved in CH_2Cl_2 (1.0 mL) and stirred at room temperature for 30 min under nitrogen. The mixture was cooled to 0 °C, and then a CH_2Cl_2 (1.0 mL) solution of methyl *N*-(*p*-chlorobenzylidene)glycinate **1a** (42.4 mg, 0.2 mmol), methyl acrylate **2a** (26.0 mg, 0.3 mmol), and Et_3N (5 μL, 0.036 mmol) was added. The resulting solution was stirred at the same temperature for 24 h and then filtered through Celite and concentrated. The ^1H NMR measurement of the crude product showed the presence of a diastereomeric mixture of adducts (*endo*/*exo* = 98/2). The residue was purified by preparative PTLC (*n*-hexane/EtOAc = 2:1) to afford *endo*-**3b**, yield 46.5 mg (78%). Enantiomeric excess of *endo*-**3b** was determined by HPLC (Chiralpak As-H): *i*-PrOH/hexane 10:90, flow rate 1.0 mL/min, 210 nm): t_R = 15.8 min (2*S*,4*S*,5*R*)-isomer, 23.8 min (2*R*,4*R*,5*S*)-isomer.
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