ORGANIC LETTERS

2005
Vol. 7, No. 21
4569−4572

A Convenient Procedure for the Catalytic Asymmetric 1,3-Dipolar Cycloaddition of Azomethine Ylides and Alkenes

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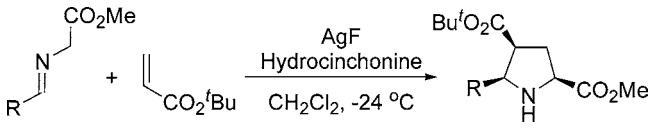
Received June 23, 2005

ABSTRACT



Silver fluoride and cinchona alkaloids catalyze the diastereo- and enantioselective 1,3-dipolar cycloaddition between azomethine ylides, generated from *N*-alkylideneglycine esters, and acrylates to give the corresponding *endo*-adducts. Azomethine ylides derived from aromatic and aliphatic aldehydes react in a highly diastereoselective reaction with good yields and enantioselectivities of the substituted pyrrolidines.

The pyrrolidine ring is present in many biologically active natural compounds and pharmaceuticals.[1] Furthermore, pyrrolidines are important building blocks in organic synthesis, and in the past years have emerged as privileged organocatalysts.[2] The [3 + 2] cycloaddition reaction of azomethine ylide 1,3-dipoles with olefinic dipolarophiles constitutes a straightforward approach to the synthesis of highly substituted pyrrolidine derivatives.[3]

Azomethine ylides are unstable and have to be prepared in situ. Several methods have been developed for the synthesis of azomethine ylides: ring opening of aziridines,[4] 1,2-proton shift of *N*-arylidene-benzylamines,[5] and deprotonation of iminium salts[6] or metalated imino esters (metalloazomethine ylides),[7] the last one being the most used in organic chemistry. The stereoselective version of the [3 +

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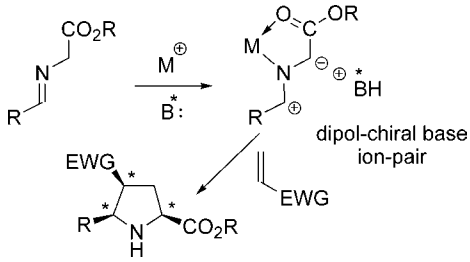
10.1021/ol0514653 CCC: $30.25
Published on Web 09/13/2005

2] cycloaddition reaction of azomethine ylides with alkenes has been developed in the past years mainly using optically pure dipolarophiles[8] and more recently by using metal complexes. After the pioneering work by Grigg et al. on the use of chiral transition metal complexes, which required a stoichiometric amount of the metal complex,[9] a relatively limited number of procedures that employ substoichiometric amounts of a chiral metal complex have been reported. Zhang et al. reported the cycloaddition of methylglycine imines with different dipolarophiles catalyzed by Ag(I) complexes with chiral diphosphines,[10] obtaining good enantioselectivities with doubly deactivated alkenes but modest selectivity with methyl acrylate. We described at the same time the use of chiral Zn(II)-bisoxazoline complexes as catalysts for the enantioselective cycloaddition of methylglycine esters to acrylates as a simple approach to optically active proline derivatives.[11] Schreiber et al. used the combination of silver acetate and P,N ligands[12] to give good yields and stereoselectivities of the expected *endo*-adducts. On the other hand, Komatsu et al.[13] have reported the use of chiral phosphine-copper triflate complexes yielding the *exo*-adducts as the predominant products in the cycloaddition of azomethine ylides and *N*-phenylmaleimide; however, moderate enantioselectivity was obtained. Although some of these procedures afford the corresponding cycloadducts in good yields and high enantioselectivities, they normally require preformation of the catalysts, dry and deoxygenated solvents, and glovebox techniques. Also, the reactions must be carried out under an inert atmosphere, which may limit their application from a practical point of view. Therefore, the development of new procedures that effect this 1,3-dipolar cycloaddition with high yields and diastereo- and enantioselectivities under more convenient reaction conditions is an important challenge.

In this communication we present a new catalytic asymmetric strategy for the 1,3-dipolar cycloaddition of azomethine ylides with alkyl acrylates, which does not require special precautions with regard to drying, degasifying solvents, or using an inert atmosphere and which therefore presents several advantages from a practical point of view with regards to the previously described metal-complex-catalyzed procedures.

Our strategy is based on the use of a metal salt and a chiral base, both in catalytic amount. We envisioned that chelation of the metal to the iminoester followed by deprotonation by a cinchona alkaloid, acting as the chiral base, would form a metallo-azomethine ylide-chiral base ion pair. This species would then react with the dipolarophile in a chiral environment to afford the expected cycloadduct stereoselectively (Scheme 1).

Scheme 1. 1,3-Dipolar Cycloaddition of Azomethine Ylides, Activated by a Metal Salt and a Chiral Base, and Alkenes



The 1,3-dipolar cycloaddition reaction of methyl *N*-(4-methylbenzylidene) glycinate **1a** and methyl acrylate **2a** in the presence of a cinchona alkaloid[14] as the chiral base (Figure 1) and a metal salt was used for the screening process (Scheme 2). Some representative results are summarized in Table 1.

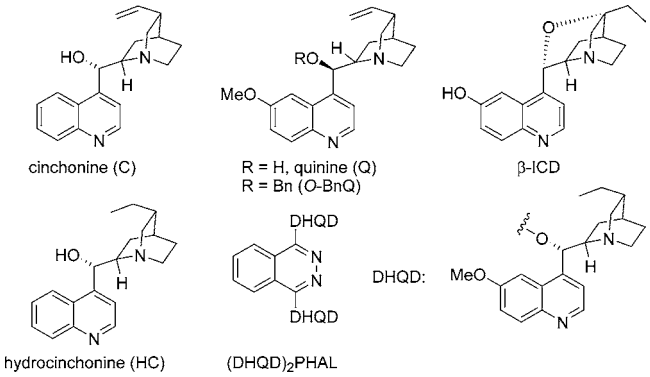


Figure 1. Cinchona alkaloids screened in this work.

For the screening of metal salts, lithium, zinc, and silver salts were explored. The reaction yielded almost exclusively the *endo*-adduct **3a** in all cases. With the exception of AgCl, silver salts were superior to lithium[15] and zinc salts (Table 1, entries 1−4 and 14). We believe the low solubility of AgCl in the reaction solvent reduces its efficacy. $AgNO_3$ and AgF gave similar results with cinchonine in toluene (Table 1, entries 3 and 4), but AgF gave better conversions and more reproducible results. We therefore chose AgF for the rest of the screening. Cinchonine and quinine (entries 4 and 5) gave similar results when used as chiral bases, but they lead to different enantiomers, as usually happens when comparing reactions catalyzed by this pair of cinchona alkaloids. They gave also better conversions and enantioselectivites than other cinchona alkaloid derivatives (entries 6, 7, and 13). Several solvents were tested using the combination AgF-cinchonine;

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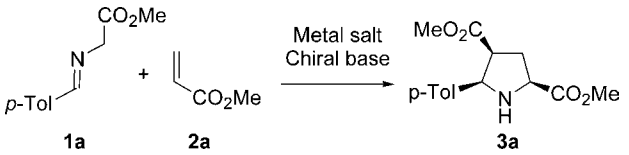
Scheme 2. 1,3-Dipolar Cycloaddition of *N*-(4-Methylbenzylidene) Glycinate **1a** with Methyl Acrylate **2a**[a]



[a] Room temperature, overnight, 20 mol% base, 20 mol% metal salt.

the best and most reproducible results (full conversion, 41% ee at room temperature) were obtained in CH_2Cl_2. Finally, hydrocinchonine was the best of the chiral bases tested, providing full conversion and 57% ee at room temperature (entry 12), higher than those obtained with cinchonine at −24 °C (entry 11).

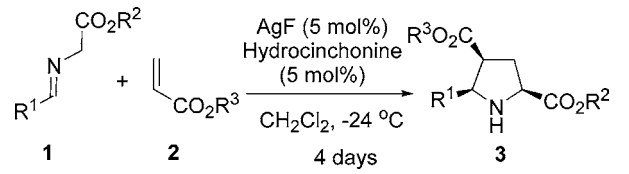
Table 1. Screening of Metal Salts and Chiral Bases

entry	metal salt	chiral base	solvent	conversion[a] (%)	ee[b] (%)
1	LiBr	C	toluene	43	0
2	$ZnCl_2$	C	toluene	<5	5
3	$AgNO_3$	C	toluene	72	22
4	AgF	C	toluene	>95	19
5	AgF	Q	toluene	>95	−20
6	AgF	$(DHQD)_2$ PHAL	toluene	>95	2
7	AgF	β-ICD	toluene	74	7
8	AgF	C	Et_2O	>95	10
9	AgF	C	MeCN	>95	13
10	AgF	C	CH_2Cl_2	>95	41
11[c]	AgF	C	CH_2Cl_2	>95 (3 days)	50
12	AgF	HC	CH_2Cl_2	>95	57
13	AgF	O−BnQ	DCE	>95	−13
14	AgCl	C	DCE	0	

[a] Conversions determined by ^{1}H NMR analysis. [b] Determined by HPLC analysis using Daicel Chiralpack AS. [c] Reaction carried out at −24 °C during 3 days.

We also investigated the effect exerted by the ester groups on the imine **1** and the acrylate **2** (Scheme 3). Increasing

Scheme 3. 1,3-Dipolar Cycloaddition of Azomethine Ylides with Acrylates



the bulkiness of the ester group in the imino ester (Table 2, entries 1 and 2) had a negative effect on the enantioselectivity of the reaction. On the other hand, increasing the bulkiness

Table 2. [1,3]-Dipolar Cycloaddition of Azomethine Ylides; Substrate Scope

entry	R^1, R^2	1	R^3	2	yield (%)[a]	3	ee (%)[b]
1[c]	*p*-Me-C_6H_4, Me	**1a**	Me	**2a**	>95[d]	**3a**	41
2[c]	*p*-Me-C_6H_4, *t*-Bu	**1b**	Me	**2a**	93[d]	**3b**	32
3[c]	*p*-Me-C_6H_4, Me	**1a**	*t*-Bu	**2b**	>95[d]	**3c**	50
4	*p*-Me-C_6H_4, Me	**1a**	*t*-Bu	**2b**	89	**3c**	70
5	*o*-Me-C_6H_4, Me	**1c**	*t*-Bu	**2b**	97	**3d**	64
6	C_6H_4, Me	**1d**	*t*-Bu	**2b**	88	**3e**	64
7	*o*-MeO-C_6H_4, Me	**1e**	*t*-Bu	**2b**	63	**3f**	56
8	*m*-MeO-C_6H_4, Me	**1f**	*t*-Bu	**2b**	93	**3g**	70
9	*p*- MeO-C_6H_4, Me	**1g**	*t*-Bu	**2b**	89	**3h**	56
10	*p*-Me_2N-C_6H_4, Me	**1h**	*t*-Bu	**2b**	86 (41)[e]	**3i**	67 (92)[e]
11	*p*-Br-C_6H_4, Me	**1i**	*t*-Bu	**2b**	88	**3j**	66
12	*p*-NC-C_6H_4, Me	**1j**	*t*-Bu	**2b**	86	**3k**	70
13	*p*-MeO_2C-C_6H_4, Me	**1k**	*t*-Bu	**2b**	82 (41)[e]	**3l**	61 (85)[e]
14	2-furyl, Me	**1l**	*t*-Bu	**2b**	86	**3m**	73
15	1-naphthyl, Me	**1m**	*t*-Bu	**2b**	88	**3n**	64
16	2-naphthyl, Me	**1n**	*t*-Bu	**2b**	86	**3o**	62
17	cyclohexyl, Me	**1o**	*t*-Bu	**2b**	65	**3p**	41
18	*t*-Bu-CH_2, Me	**1p**	*t*-Bu	**2b**	78	**3q**	41
19	*i*-Pr, Me	**1q**	*t*-Bu	**2b**	67	**3r**	52

[a] Yields after column chromatography. [b] Determined by HPLC analysis using Daicel Chiralpack AS. [c] Room temperature, overnight, 20 mol% base, 20% mol metal salt. [d] Conversions determined by ^{1}H NMR analysis. [e] Yield and ee after recrystallization.

of the ester group in the acrylate brought about an increase in the enantioselectivity (Table 2, entry 3). This result contrasts with that observed in the Zn-bisoxazoline catalyzed reaction.[10] Hence, we established that imines derived from methyl glycine as the best dipole precursors and *tert*-butyl acrylate **2b** are the best dipolarophiles for this reaction. A further improvement was achieved by carrying out the reaction at −24 °C. Under these conditions the *endo*-adduct was obtained in 89% isolated yield and 70% ee (Table 2, entry 4).

We also found that catalyst loading could be decreased to 5 mol %, both for AgF and hydrocinchone, without noticeable effect on yield and enantioselectivity.

To assess the scope of the process, we investigated the reaction between *tert*-butyl acrylate **2b** and a variety of α-imino esters **1** prepared from methyl glycinate and aromatic and aliphatic aldehydes (Table 2, entries 4−19). Utilizing the optimized conditions, the reaction showed excellent levels of diastereoselectiviy with the *endo*-adduct being obtained almost exclusively in all the cases. Aromatic imino esters yielded the expected pyrrolidine derivatives with

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high yields ranging from 80% to 97%, with the only exception of methyl *N*-(2-methoxybenzylidene) glycinate (**1e**). Remarkably, the efficiency of the reaction is nearly independent of the characteristics of the aromatic ring. Thus, a strong electron-donating substituent such as *p*-Me_2N (entry 10) and electron-withdrawing groups such as Br, CN, or CO_2Me (entries 11−13) afford the corresponding cycloadducts in high yields (82−88%) and good enantioselectivities (61−70%). In the same way, *ortho* (**1b**), *meta* (**1e**), or unsubstituted (**1c**) derivatives (entries 5, 8, and 6, respectively) as well as 1- (**1l**) and 2-naphthylmethylidene (**1m**) glycinates (entries 15 and 16) give similar results (86−97% yield, 62−70% ee). The highest ee was obtained with the heterocyclic imino ester **1l** (entry 14).

On the other hand, the less stable aliphatic imino esters (entries 17−19) gave somewhat lower yield (65−78%) and moderate enantioselectivities (41−52%).

It is worth mentioning that the use of *tert*-butyl acrylate not only gives higher enantioselectivity than methyl acrylate but also the resulting pyrrolidines having two ester groups orthogonally protected. This feature will allow independent manipulation of both ester groups in the case of further transformations on these products. Furthermore, most of the pyrrolidine derivatives obtained from *tert*-butyl acrylate are solids that may be enantiomerically enriched by crystallization. For instance, pyrrolidines **3i** and **3l** could be enriched up to 94% ee and 85% ee (entries 10 and 13), respectively, upon crystallization from hexane-CH_2Cl_2.

In summary, we present here the first example of enantioselective 1,3-dipolar cycloaddition of azomethine ylides and alkenes, which is carried out under conditions that do not require moisture or air exclusion. The reaction between *N*-alkylidene glycine esters and *tert*-butyl acrylate catalyzed by silver fluoride and a commercially available chiral base (hydrocinchonine) proceeds with high *endo* diastereoselectivity and fair enantioselectivity to give proline derivatives bearing two esters groups, orthogonally protected. Enantiomeric excesses can be increased upon recrystallization of the adducts.

Acknowledgment. This work was made possible by a grant from The Danish National Research Foundation. G.B. thanks UV and MEC (Spanish Government) for supporting his stay at Aarhus University.

Supporting Information Available: Experimental procedures and characterization of the products. ^1H NMR and ^{13}C NMR spectra of compounds **3c**−**r**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0514653