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Catalytic Enantioselective 1,3-Dipolar Cycloaddition of C,N-Cyclic Azomethine Imines with α,β-Unsaturated Aldehydes

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Catalytic enantioselective 1,3-dipolar cycloaddition (1,3-DC) has arguably been one of the most ideal synthetic methods for the stereoselective construction of heterocycles with congested stereogenic centers and heterofunctionalized acyclic molecules produced by the subsequent reductive ring opening of the resulting cycloadducts.[1] Among the developments in this area, asymmetric 1,3-DC of azomethine imines has recently emerged as a relatively new field,[2] with which chiral pyrazolidines could be synthesized. Catalytic systems employing metallo- and organocatalysts have been successfully developed, facilitating asymmetric 1,3-DC with a variety of dipolarophiles. However, for the 1,3-dipole, use of bench stable N,N′-cyclized azomethine imines **i** has been the only option available,[3] thus severely narrowing its synthetic utility (Figure 1).

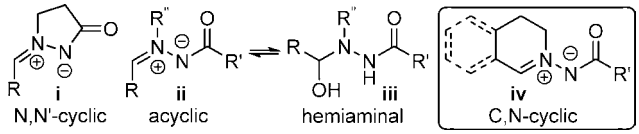


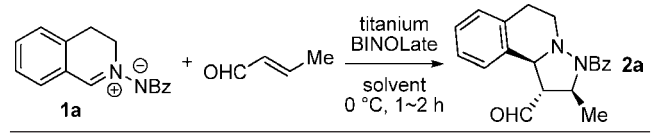
Figure 1. Classification of Azomethine Imines.

With regard to other azomethine imines, acyclic ones **ii** are known to exist as a hemiaminal form **iii** preferentially and have to be generated under harsh azeotropic conditions intolerant to asymmetric catalysis.[4,5] In line with these two, C,N-cyclic azomethine imines **iv** can be considered a third class of azomethine imines, though their property and synthetic utility have rarely been studied in the past and remain elusive.

We report herein the exploitation of yet-unexplored C,N-cyclic azomethine imines in highly enantioselective asymmetric 1,3-DC catalyzed by a titanium−BINOLate complex, which offers access to pharmaceutically attractive chiral tetrahydroisoquinolines and piperidines with a 1,3-diamine unit.[6,7] During the course of this study, we also uncovered a new protocol for using azomethine imines which preferably exist as the hemiaminal form in the identical catalysis.

At the beginning of this research, we were particularly intrigued by the early report of Tamura et al. in 1973 wherein the benzene-fused C,N-cyclic azomethine imine **1a** was synthesized as a metastable compound.[8,9] Accordingly, we set out to evaluate the viability of asymmetric 1,3-DC of C,N-cyclic azomethine imine **1a** and crotonaldehyde by using titanium−BINOLate complexes (Table 1) based on our related studies.[10] Gratifyingly, 1,3-DC proceeded smoothly in the presence of the 1:1 complex of $Ti(O^iPr)_4$ and (*S*)-BINOL as catalyst, giving the cycloadduct **2a** in high yield with moderate stereoselectivities. Examination of other titanium−BINOLates and reaction conditions revealed the high efficiency of the 2:1 (*S*)-BINOL/$Ti(O^iPr)_4$ complex using toluene as solvent at 0 °C, giving the cycloadduct in 94% yield with excellent enantio- and diastereoselectivity (entries 2−5). Notably, the high catalytic performance of this reaction system allowed us to decrease the catalyst loading to 3 mol % without affecting the yield or selectivity (entry 6).

Table 1. Optimization of Reaction Conditions[a]



entry	catalyst (mol %)	solvent	yield (%)[b]	exo/endo[c]	ee(%)[d]
1	(*S*)-BINOL (10) $Ti(O^iPr)_4$ (10)	CH_2Cl_2	92	89:11	60/−
2	(*S*)-BINOL (20) $Ti(O^iPr)_4$ (10)	CH_2Cl_2	94	>95:5	85
3	(*S*)-BINOL (20) $O[Ti(O^iPr)_3]_2$ (10)	CH_2Cl_2	83	>95:5	80
4	(*S*)-BINOL (20) $Ti(O^iPr)_4$ (10)	toluene	94	>95:5	92
5[e]	(*S*)-BINOL (20) $Ti(O^iPr)_4$ (10)	toluene	95	>95:5	86
6	(*S*)-BINOL (6) $Ti(O^iPr)_4$ (3)	toluene	95	>95:5	90

[a] Performed with **1a** (0.50 mmol) and crotonaldehyde (1.0 mmol). [b] Isolated yield. [c] Determined by the ^1H NMR of the crude mixture. [d] Determined by chiral HPLC after reduction of **2a**. [e] Performed at −20 °C.

With this promising result in hand, we investigated the generality of this unprecedented asymmetric 1,3-DC (Table 2). As for the substitution pattern of the C,N-cyclic azomethine imines, 5-, 6-, and 7-methyl substituents were all tolerated, furnishing the cycloadducts in high yields and selectivities (entries 1−3). The only exception was the incorporation of the 8-methyl substituent wherein the reaction resulted in moderate enantio- and diastereoselectivity (entry 4). C,N-Cyclic azomethine imines having an electron-donating or -withdrawing group could be utilized as well (entries 5−7). The absolute stereochemistry was determined by X-ray crystallographic analysis of **2h**, by which the exoselective fashion of this 1,3-DC was confirmed.[11] The focus was then moved to the examination of applicable α,β-unsaturated aldehydes. With regard to the β-substituents, both a longer alkyl chain and an aromatic group were tolerated (entries 8 and 9). Additionally, rather unreactive α,β-disubstituted enals could also be utilized (entries 10 and 11). In the case of α,β-unsaturated aldehydes lacking a β-substituent, almost equal amounts of two diastereomers were obtained (entries 12 and 13), suggesting the importance of the steric factor for the exoselectivity.

This study prompted us to develop structurally distinct C,N-cyclic azomethine imines which are not fused to the aromatic ring (Table 3).[12] In this regard, the hydrobromic acid salt of such azomethine imines could be prepared as a bench stable precursor **3**. However, attempted isolation of the free azomethine imine **4** after the treatment with a base failed due to the preferential formation of the corresponding hemiaminal **5**. To address this issue, we implemented the *in situ* generation of **4** under the anhydrous reaction condition,[13] using 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP) as

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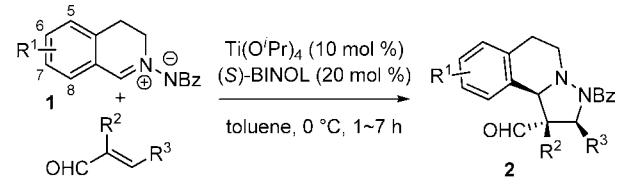
a base compatible with a Lewis acid catalyst. As summarized in Table 3, the reaction could be conducted under otherwise identical conditions to give a couple of cycloadducts **6** (entries 1−4),[14] although the use of α,β-disubstituted enals led to low conversion (data not shown). In the case of β-unsubstituted enals, the reaction predominantly gave the endo isomer with uniformly high enantioselectivities (entries 5−9).

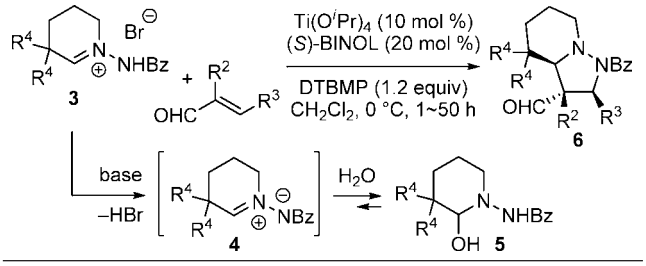
Table 2. Asymmetric 1,3-DC of C,N-Cyclic Azomethine Imines[a]



entry	R^1	R^2	R^3	yield (%)[b]	exo/endo[c]	ee(%)[d]
1	5-Me (**1b**)	H	Me	85 (**2b**)	>95:5	89
2	6-Me (**1c**)	H	Me	99 (**2c**)	>95:5	92
3	7-Me (**1d**)	H	Me	93 (**2d**)	>95:5	92
4	8-Me (**1e**)	H	Me	94 (**2e**)	84:16	62/22[e]
5	6-MeO (**1f**)	H	Me	96 (**2f**)	>95:5	82
6	6-Br (**1g**)	H	Me	93 (**2g**)	>95:5	95
7	7-Br (**1h**)	H	Me	92 (**2h**)	>95:5	93
8	H (**1a**)	H	Pr	86 (**2i**)	>95:5	85
9	H	H	Ph	94 (**2j**)	>95:5	99
10	H	Me	Me	85 (**2k**)	95:5	88
11	H	−(CH$_2$)$_3$−		93 (**2l**)	92:8	89/86[e]
12	H	Me	H	98 (**2m**)	50:50	96/98[e]
13[e]	H	H	H	97 (**2n**)	61:39	62/74[e]

[a] Performed with **1** (0.50 mmol) and aldehyde (1.0 mmol). [b] Combined yield of exo/endo isomers. [c] Determined by the ^{1}H NMR of the crude mixture. [d] Determined by chiral HPLC after reduction of **2**. [e] Ee value of the endo isomer.

Table 3. Asymmetric 1,3-DC of in Situ Generated C,N-Cyclic Azomethine Imines[a]

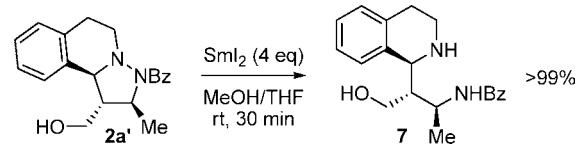


entry	R^4	R^2	R^3	yield (%)[b]	exo/endo[c]	ee (%)[d]
1	(CH$_2$)$_4$ (**3a**)	H	Me	74 (**6a**)	81:19	90
2	(CH$_2$)$_3$ (**3b**)	H	Me	64 (**6b**)	77:23	86
3	Me (**3c**)	H	Me	65 (**6c**)	88:12	76
4	(CH$_2$)$_4$ (**3a**)	H	Pr	36 (**6d**)	67:33	75
5	(CH$_2$)$_4$ (**3a**)	Me	H	98[e] (**6e**)	22:78	96/97[f]
6	Me (**3c**)	Me	H	99[e] (**6f**)	11:89	98/98[f]
7	(CH$_2$)$_4$ (**3a**)	H	H	98[e] (**6g**)	15:85	83/96[f]
8	(CH$_2$)$_3$ (**3b**)	H	H	97[e] (**6h**)	13:87	89/96[f]
9	Me (**3c**)	H	H	98[e] (**6i**)	7:93	75/97[f]

[a] Performed with **3** (0.25 mmol) and aldehyde (0.50 mmol). [b] Isolated yield of the exo isomer. [c] Determined by the ^{1}H NMR of the crude mixture. [d] Determined by chiral HPLC after reduction of **6**. [e] Combined yield of the isomers. [f] Ee value of the endo isomer.

Finally, SmI_2-mediated ring opening of the cycloadduct **2a′** was implemented to furnish the tetrahydroisoquinoline **7** having a side chain with three contiguous stereogenic centers (Scheme 1).

Scheme 1. Reductive Cleavage of the N−N Bond



In summary, we successfully demonstrated that C,N-cyclic azomethine imines can be utilized as a promising 1,3-dipole in asymmetric 1,3-DC. As the synthetic utility of azomethine imines has been moving beyond archetypal 1,3-DCs,[15] uncovering a new class of useful azomethine imines would also offer new opportunities in these growing fields.

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Supporting Information Available: Experimental details and characterization data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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