Organocatalysis

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Asymmetric Inverse-Electron-Demand 1,3-Dipolar Cycloaddition of C,N-Cyclic Azomethine Imines: An Umpolung Strategy**

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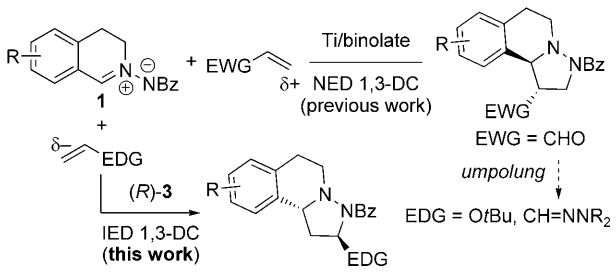
The catalytic asymmetric 1,3-dipolar cycloaddition (1,3-DC) has now become one of the most established methods for the stereoselective synthesis of five-membered heterocycles having contiguous stereogenic centers, concurrent with the development of chiral Lewis acids and organocatalysts.[1] As a reaction mode for 1,3-DCs, normal-electron-demand (NED) 1,3-DCs proceed by the interaction of a catalytically activated LUMO of electron-deficient alkenes with the HOMO of the 1,3-dipoles; alternatively, the inverse-electron-demand (IED) 1,3-DCs are facilitated by the interaction of the LUMO of an acid-activated 1,3-dipole and the HOMO of electron-rich alkenes. Although synchronous development of both features in the realm of asymmetric catalysis would be highly desirable to produce a diverse array of cycloadducts, IED 1,3-DCs are far less developed to date and remain a challenge in contrast to the sophistication and diversification of their NED counterparts.[2,3,5h–j,11a]

We recently succeeded in shedding light on the as of yet unexplored utility of C,N-cyclic azomethine imines **1** in the titanium/binolate catalyzed NED 1,3-DC using enals as dipolarophiles (Scheme 1).[4,5] As the next step of the study, we set out to investigate the asymmetric IED 1,3-DC of these 1,3-dipoles,[6] coupled with the fact that the related methods for catalytic asymmetric di- and tetrahydroisoquinoline syntheses by the nucleophilic addition to (dihydro)isoquinoline derivatives are still far from established in terms of the generality and selectivity.[7]



Scheme 1. Normal- and inverse-electron-demand 1,3-dipolar cycloadditions of C,N-cyclic azomethine imines. binol = 2,2′-dihydroxy-1,1′-binaphthyl, Bz = benzoyl.

We report herein the investigation toward this end using vinyl ether as a conventional electron-rich dipolarophile and the axially chiral dicarboxylic acid originally developed in our group as a chiral Brønsted acid catalyst,[8] which succeeded in attaining a remarkably broad substrate scope to give a variety of C1-chiral tetrahydroisoquinolines with excellent enantioselectivity irrespective of the position and electronic nature of the substituents. In addition, unique Lewis acid catalyzed functionalizations of the cycloadducts were disclosed in which tetrahydroisoquinolines with additional chiral stereocenter at the C1 side chain could be generated stereoselectively. This accomplishment prompted us to introduce a new concept called the IED umpolung 1,3-DC, which gives cycloadducts regioisomeric to the products of the previously reported titanium/binolate-catalyzed NED 1,3-DC starting from the same enals. This tactic could be realized by the umpolung nature of enals imposed by the formation of the corresponding *N*,*N*-dialkylhydrazones,[9] also known as vinylogous azaenamines (Scheme 1).

A clue to the development of asymmetric IED 1,3-DCs of C,N-cyclic azomethine imines with vinyl ether was provided from our early observation that these 1,3-dipoles easily form stable protonated salts in the presence of a hydrobromic acid.[4] This fact naturally led us to the use of a chiral Brønsted acid, which has recently emerged as a powerful tool for numerous stereoselective organic transformations.[10,11] As we have been intensively working on the development of axially chiral dicarboxylic acids as a class of chiral Brønsted acid catalysts, we commenced the study of the asymmetric IED 1,3-DC between C,N-cyclic azomethine imine **1a** and *tert*-butyl vinyl ether using the most general axially chiral dicarboxylic acid (*R*)-**3a** that bears 2,6-Me_2-4-*t*Bu-C_6H_2 groups as key 3,3′ substituents. As anticipated, (*R*)-**3a** facilitated the reaction in CH_2Cl_2 at 0 °C to give the *exo* and *endo* adducts in 78% and 18% yields, respectively, but the enantioselectivities were disappointingly low (Table 1, entry 1). Screening of a series of catalysts bearing different aryl substituents resulted in unsatisfactory selectivities (entries 2–4). A breakthrough came when we developed the new catalyst (*R*)-**3e** having diphenylmethyl groups at the 3,3′-positions, with which the cycloadduct was furnished with a drastically improved enantioselectivity and exo/endo ratio (entry 5). Replacement of the phenyl group by a 2-naphthyl group further enhanced the enantioselectivity to 82% (entry 6). Finally, by changing the solvent to $CHCl_3$ and lowering the reaction temperature to −30 °C, the *exo*-adduct **2a** could be obtained exclusively in 98% yield and 95% *ee*

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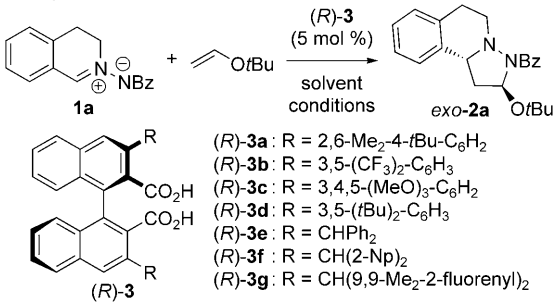
Table 1: Optimization of the reaction conditions.[a]



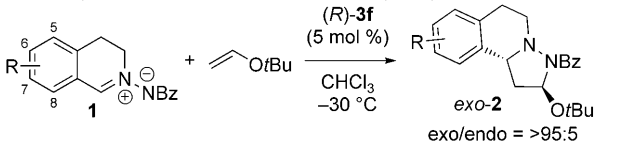
Entry	Catalyst	Solvent	T [°C]	t [h]	Yield [%][b]		*ee* [%][c]	
					exo	*endo*	*exo*	*endo*
1	(*R*)-**3a**	CH_2Cl_2	0	8	78	18	1	14
2	(*R*)-**3b**	CH_2Cl_2	−20	4	67	23	44	32
3	(*R*)-**3c**	CH_2Cl_2	0	4	63	13	18	49
4	(*R*)-**3d**	CH_2Cl_2	−20	24	47	18	32	5
5	(*R*)-**3e**	CH_2Cl_2	−20	24	73	<5	67	n.d.[d]
6	(*R*)-**3f**	CH_2Cl_2	−20	12	85	11	82	31
7	(*R*)-**3f**	$CHCl_3$	−20	5	95	<5	92	n.d.[d]
8	(*R*)-**3f**	$CHCl_3$	−30	10	98	<2	95	23

[a] Reaction conditions: **1a** (0.10 mmol) and *tert*-butyl vinyl ether (0.30 mmol) in the presence of 5 mol% (*R*)-**3** (0.005 mmol). [b] Yield of isolated product. [c] Determined by HPLC on a chiral stationary phase. [d] Not determined. Np = napthyl.

(entries 7 and 8).[12] It is also worth noting that these reactions could be carried out without the exclusion of moisture and air.

With the optimized conditions in hand, the scope of this asymmetric IED 1,3-DC was investigated as summarized in Table 2. The substitution patterns of azomethine imines had little impact on the yields or enantioselectivities, thereby providing the *exo* adduct exclusively with *ee* values ranging from 92 to 97% (entries 1–4). C,N-cyclic azomethine imines bearing electron-withdrawing groups could be utilized as well in good yields with rigorous stereoselectivities (entries 5–7). As the azomethine imine with an electron-donating methoxy group displayed lower reactivity, the reaction was conducted

Table 2: Asymmetric IED 1,3-DC with *tert*-butyl vinyl ether.[a]



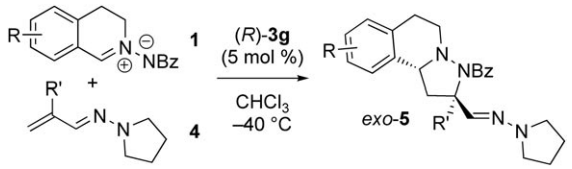
Entry	R	Yield [%][b]	*ee* [%][c]
1	5-Me (**1b**)	>99 (**2b**)	97
2	6-Me (**1c**)	90 (**2c**)	95
3	7-Me (**1d**)	98 (**2d**)	94
4	8-Me (**1e**)	>99 (**2e**)	92
5	6-Br (**1f**)	>99 (**2f**)	95
6	7-Br (**1g**)	94 (**2g**)	92
7	7-CO_2Me (**1h**)	>99 (**2h**)	93
8[d]	6-OMe (**1i**)	95 (**2i**)	94

[a] Reaction conditions: **1** (0.10 mmol) and *tert*-butyl vinyl ether (0.30 mmol) in the presence of 5 mol% (*R*)-**3f** (0.005 mmol) for 7–20 h. [b] Yield of the isolated *exo* isomer. [c] The *ee* value of the *exo* isomer was determined by HPLC on a chiral stationary phase. [d] Performed at −20°C for 12 h.

at −20°C to afford *exo*-**2i** in 95% yield with 94% *ee* (entry 8).[13]

With the successful implementation of highly enantioselective IED 1,3-DCs of C,N-cyclic azomethine imines and vinyl ether, we moved our focus to the use of a different type of dipolarophile. Vinylogous aza-enamines **4** (Table 3) are a

Table 3: Asymmetric IED umpolung 1,3-DC with vinylogous aza-enamines.[a]



Entry	R	R′	Yield [%][b]	*exo*/*endo*[c]	*ee* [%][d]
1	H	H (**4a**)	97 (**5a**)	4.4:1	90
2	5-Me	H (**4a**)	94 (**5b**)	3.9:1	83
3	6-Me	H (**4a**)	>99 (**5c**)	6.7:1	95
4	7-Me	H (**4a**)	>99 (**5d**)	4.0:1	90
5[e]	8-Me	H (**4a**)	>99 (**5e**)	3.2:1	65
6	6-Br	H (**4a**)	>99 (**5f**)	3.8:1	91
7[f]	6-MeO	H (**4a**)	96 (**5g**)	2.8:1	84
8	7-MeO_2C	H (**4a**)	>99 (**5h**)	3.0:1	92
9	H	Me (**4b**)	>99 (**5i**)	1.0:2.4	68

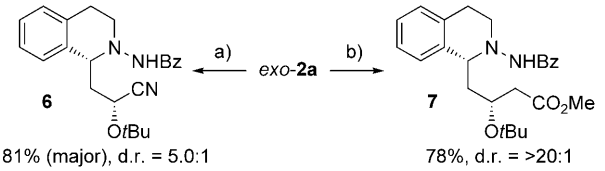
[a] Reaction conditions: **1** (0.10 mmol) and **4** (0.30 mmol) in the presence of 5 mol% (*R*)-**3g** (0.005 mmol) for 24–72 h. [b] Combined yield of isomers. [c] Determined by ^{1}H NMR analysis of the crude reaction mixture. [d] The *ee* values of the *exo* isomer determined by HPLC on a chiral stationary phase. [e] Performed at −30°C for 48 h. [f] Performed at −20°C for 48 h.

class of umpolung substrates prepared from the simple condensation of *N*,*N*-dialkylhydrazine and enals. As a result of the electron donation from the *N*,*N*-dialkylamino moiety, they are known to exhibit a nucleophilic character at their β position, and this property was recently exploited for the first time in asymmetric catalysis by our group.[8f] Taking into account their reversed polarity relative to the parent enals and the electron richness of the alkene moiety, we envisaged that their use as a dipolarophile in the IED 1,3-DC developed herein would provide a logical and distinguished way to give the regioisomeric cycloadduct relative to that obtained by the titanium/binolate-catalyzed NED 1,3-DC of C,N-cyclic azomethine imines with enals (Scheme 1).[4,14]

As proof of this concept, we set out to examine this IED umpolung 1,3-DC between azomethine imine **1a** and the acrolein-derived vinylogous aza-enamine **4a** under identical reaction conditions using (*R*)-**3f** as the catalyst. The reaction proceeded smoothly, giving the expected regioisomer **5a** with a 2.0:1 *exo*/*endo* ratio and moderate enantioselectivities (78% *ee* and 23% *ee*, respectively). The stereoselectivity could be improved using the additionally modified catalyst (*R*)-**3g** having bis(9,9-dimethyl-2-fluorenyl)methyl groups (see Table 1) at a lower temperature (Table 3, entry 1). C,N-cyclic azomethine imines bearing a variety of substituent patterns and electron-withdrawing and electron-donating groups were all tolerated, giving the corresponding cycloadducts in almost quantitative yields with modest *exo* selec-

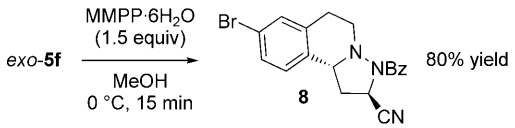
tivities and high enantioselectivities for these *exo* isomers (entries 2–8).[15] The reaction also proceeded with a methacrolein-derived α-substituted vinylogous aza-enamine, but the *endo* isomer was generated preferentially with low enantioselectivity (entry 9). At present, β-substituted vinylogous aza-enamines, such as the one derived from crotonaldehyde could not be applied because of the generation of some isomers arising from the nucleophilic attack of the vinylogous aza-enamine at the β position.

In an attempt to demonstrate the synthetic utility of so-obtained cycloadducts, we carried out Lewis acid catalyzed cyanation and Mukaiyama-type addition of a ketene silyl acetal to *exo*-**2a** in anticipation of the replacement of the *tert*-butoxy group by these nucleophiles (Scheme 2). To our surprise, the reactions proceeded such that the *tert*-butoxy groups were retained in the products, thereby giving **6** and **7** with high diastereoselectivities. These results are in keeping with proceeding via the oxocarbenium ion as a key intermediate.[16]



Scheme 2. Synthetic application of the cycloadduct: a) $BF_3{\cdot}Et_2O$ (1.5 equiv), TMSCN (2.0 equiv), CH_2Cl_2, −78 to 0 °C, 3 h; b) $BF_3{\cdot}Et_2O$ (1.5 equiv), $H_2C{=}C(OMe)OTBS$ (2.0 equiv), CH_2Cl_2, −78 to 0 °C, 3 h. TBS = *tert*-butyldimethylsilyl, TMS = trimethylsilyl.

As one typical application of the cycloadduct derived from the IED umpolung 1,3-DC, the aza-enamine part of *exo*-**5f** was converted into nitrile **8** by magnesium monoperoxyphthalate (MMPP) without deterioration of the stereochemical integrity as shown in Scheme 3.[17]



Scheme 3. Conversion of the aza-enamine moiety into the nitrile.

In summary, we have developed an asymmetric IED 1,3-DC of C,N-cyclic azomethine imines and vinyl ether catalyzed by a newly developed axially chiral dicarboxylic acid having diarylmethyl groups at the 3,3′-positions. Based on this finding, the concept of IED umpolung 1,3-DC was introduced as a strategy for switching the regioselectivity of the cycloaddition from that of the titanium/binolate-catalyzed NED 1,3-DC with enals by using vinylogous aza-enamines as umpolung substrates.

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[12] No isomerization of the *exo* and *endo* isomers was detected under the reaction conditions. Treatment of the isolated *exo* isomer with $BF_3{\cdot}Et_2O$ at room temperature led to immediate isomerization into the *endo* isomer.
[13] The absolute stereochemistry was determined by X-ray crystallographic analysis of **2f**. See the Supporting Information for details.
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