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Catalytic Asymmetric Inverse-Electron-Demand 1,3-Dipolar Cycloaddition of C,N-Cyclic Azomethine Imines with Azlactones: Access to Chiral Tricyclic Tetrahydroisoquinolines

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Abstract: *Reported herein is a bifunctional-organocatalyst-mediated enantioselective inverse-electron-demand 1,3-dipolar cycloaddition of C,N-cyclic azomethine imines with azlactones. The strategy provides concise access to enantioenriched C1-substituted tetrahydroisoquinolines featuring a pyrazolidinone scaffold. Moreover, the scalability and practical utility of this protocol was well demonstrated by employing a gram-scale reaction and some representative transformations.*

Tetrahydroisoquinolines (THIQs), especially the chiral C1-substituted THIQs, have drawn tremendous attention from synthetic and medicinal chemists because of their prevalence in naturally occurring and bioactive molecules (Figure 1).[1] Consequently, extensive efforts have been made and corresponding methods,[2–5] such as Pictet–Spengler cyclization,[3] hydrogenation,[4] and nucleophilic addition to either dihydroisoquinolines or isoquinolines,[5] have been developed to provide access to such structural motifs. Nevertheless, some limitations still exist with respect to the limited substrate scope and the need of stoichiometric amounts of chiral sources. In this regard, the development of more general and efficient synthetic protocols toward structurally diverse C1-substituted THIQs in a catalytic asymmetric manner is still in great demand.

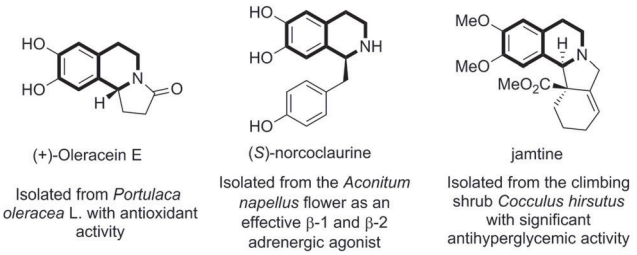

Figure 1. Examples of bioactive natural products containing chiral C1-substituted tetrahydroisoquinolines.

Recently, cycloadditions of C,N-cyclic azomethine imines have emerged as one of the most prevailing protocols for the construction of polycyclic THIQs, because such substrates can lead to normal-electron-demand 1,3-dipolar cycloadditions (NED 1,3-DCs) with electron-poor alkenes, as well as inverse-electron-demand 1,3-dipolar cycloadditions (IED 1,3-DCs) with electron-rich alkenes.[6–10] In 2010, the group of Maruoka disclosed a seminal asymmetric NED 1,3-DC of C,N-cyclic azomethine imines with α,β-unsaturated aldehydes by involving a titanium/BINOLate complex.[6a] Shortly after, a chiral dicarboxylic acid catalyzed asymmetric IED 1,3-DC of azomethine imines with vinyl ethers and vinylogous azaenamines was reported by the same group.[6b] Then, Wang et al. developed an amine-catalyzed asymmetric 1,3-DC of azomethine imines with aldehydes.[7] Meanwhile, chiral isothioureas and N-heterocyclic carbenes were also utilized to catalyze such transformations.[8] Very recently, groups of Shi and Guo independently published the phosphine-catalyzed enantioselective [3+2] and [3+3] cycloadditions, respectively, of azomethine imines with δ-substituted allenoates and MBH carbonates.[9] However, despite these advances, the available catalytic systems are extremely limited, and in most cases covalent catalysis was employed to realize stereochemical control, thus seriously narrowing the scope of the reaction partners.

Considering the significant advantages of bifunctional organocatalysis in the realm of asymmetric synthesis,[11] we assume that a double-activation mode by hydrogen bonding could be applied to promote the asymmetric cycloadditions of azomethine imines. Towards this goal, azlactones,[12–15] which contain multiple reactive sites enabling either [3+3][16] or [3+2] cycloadditions, were selected to react with azomethine imines to validate our hypothesis (Scheme 1 b). To the best of our knowledge, while the asymmetric 1,3-DCs of azlactones with electron-poor alkenes have been disclosed by Toste et al. and us (Scheme 1 a),[14] the asymmetric cycloadditions of azlactones with a 1,3-dipole have not yet been realized.

Our initial investigations commenced with a model reaction of the azomethine imine **2a** and azlactone **1a** in the presence of a typical Takemoto thiourea (**C1**; Table 1). As expected, the HOMO of **1a** and the LUMO of **2a** were simultaneously activated in this bifunctional activation system, and only the [3+2] cycloadduct **3aa** was generated in moderate yield and with a moderate *ee* value (entry 1).

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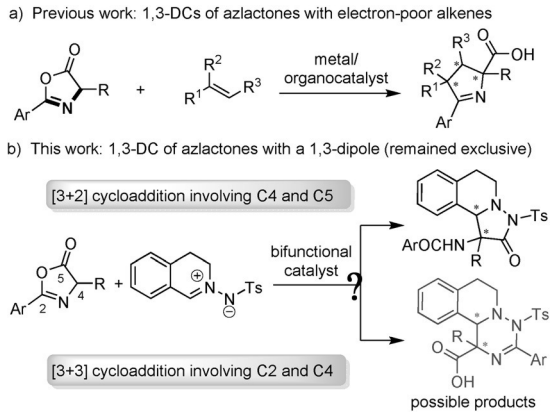
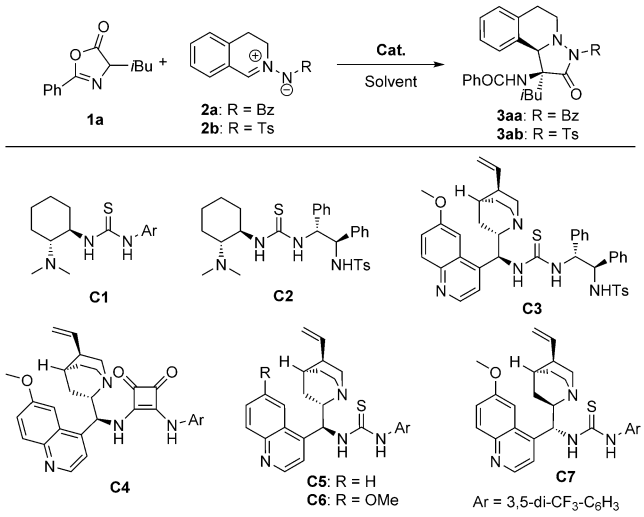


Scheme 1. Azlactones in catalytic asymmetric 1,3-DCs.

Table 1: Optimization of reaction conditions.[a]

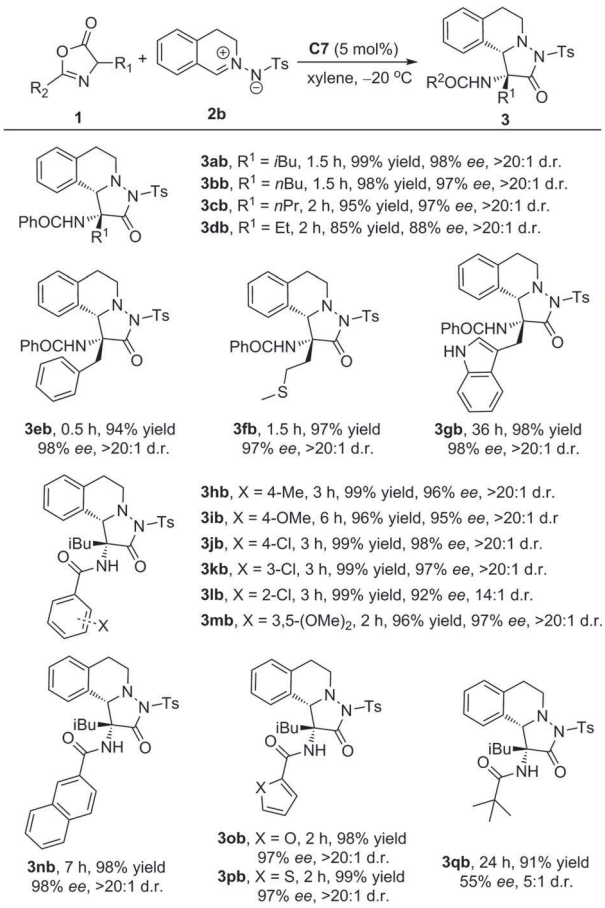


Entry	2	Cat.	Solvent	*t*	Yield [%][b]	*ee* [%][c]	d.r.[d]
1	**2a**	**C1**	$CHCl_3$	10 h	76	47	9:1
2	**2a**	**C2**	$CHCl_3$	10 h	62	6	1.5:1
3	**2a**	**C3**	$CHCl_3$	10 h	65	6	5.5:1
4	**2a**	**C4**	$CHCl_3$	10 h	72	33	>20:1
5	**2a**	**C5**	$CHCl_3$	10 h	81	60	>20:1
6	**2a**	**C6**	$CHCl_3$	10 h	79	62	>20:1
7	**2b**	**C6**	$CHCl_3$	5 min	99	78	17:1
8	**2b**	**C6**	CH_2Cl_2	5 min	99	82	16:1
9	**2b**	**C6**	THF	5 min	98	73	9:1
10	**2b**	**C6**	MTBE	10 min	96	86	13:1
11	**2b**	**C6**	toluene	5 min	99	92	>20:1
12	**2b**	**C6**	xylene	5 min	99	93	>20:1
13[e]	**2b**	**C6**	xylene	5 min	99	95	>20:1
14[e]	**2b**	**C7**	xylene	5 min	99	−97	>20:1
15[e,f]	**2b**	**C7**	xylene	1.5 h	99	−98	>20:1

[a] Unless otherwise specified, the reaction was conducted on a 0.1 mmol scale with **1a** (1.2 equiv), **2** (1.0 equiv), and catalyst (20 mol%) in 0.6 mL solvent. [b] Yield of isolated product as a mixture of diastereoisomers. [c] Determined by HPLC analysis on a chiral stationary phase. [d] Determined by ^{1}H NMR analysis of the crude reaction mixture. [e] Used 5 mol% catalyst. [f] Conducted at −20°C. Bz = benzoyl, MTBE = methyl *tert*-butyl ether, THF = tetrahydrofuran.

Subsequently, some other bifunctional catalysts were evaluated, and relatively higher enantioselectivity and excellent diastereoselectivity were observed by using the quinine-derived thiourea **C6** (entry 6). Pleasingly, under similar reaction conditions, the azomethine imine **2b** exhibited notably enhanced reactivity and afforded the product **3ab** in 99% yield with 78% *ee* and 17:1 d.r. within 5 minutes (entry 7). Screening of the solvents revealed a preference for xylene (entry 12). When the catalyst loading was lowered to 5 mol%, the same excellent outcome was obtained (entry 13). It should be noted that the enantiomer of the product could also be obtained with a slightly increased enantioselectivity when **C7** was used at −20°C (entry 15).

Having identified the optimal reaction conditions (Table 1, entry 15), the scope of the catalytic asymmetric IED 1,3-DC was investigated by using **2b** and a series of azlactones (Scheme 2). In general, all of the azlactones derived from different amino acids were well tolerated, and the corresponding cyclization products were obtained in high yields with excellent stereoselectivity (**3ab–gb**). Only in the case of the 2-aminobutyric-acid-derived azlactone **1d** was

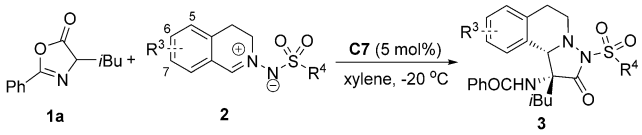


Scheme 2. The substrate scope with respect to azlactones. Reaction conditions: 0.12 mmol **1**, 0.10 mmol **2b** and 5 mol% **C7**, in xylene (0.6 mL) at −20°C. Yield is that of the isolated product as a mixture of diastereoisomers. The ee values were determined by HPLC analysis using a chiral stationary phase and the d.r. values were determined by ^{1}H NMR (300 MHz)spectroscopy of the crude mixture. Ts = 4-toluenesulfonyl.

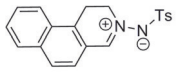
a relatively lower *ee* value afforded. Both electron-donating and electron-withdrawing substituents in the *ortho*-, *meta*-, and *para*-positions of the phenyl ring in substrate **1** were well tolerated (**3hb–lb**). It was worth noting that azlactones with either a disubstituted phenyl ring or heteroaryl groups at the C2-position also worked well (**3mb–pb**). Moreover, the azlactone **1q**, possessing an alkyl group ($R^2 = t$Bu) was further examined, and the product **3qb** was isolated in high yield, but with only moderate stereoselectivity (5:1 d.r. and 55% *ee*).

Next, we explored the generality of this protocol by involving various structurally diverse C,N-cyclic azomethine imines. Azomethine imines (**2**) having different substituents at the 4-position of the phenyl ring of the arylsulfonyl protecting group were compatible (Table 2, **3ac–af**). As for

Table 2: Substrate scope with respect to azomethine imines.[a]



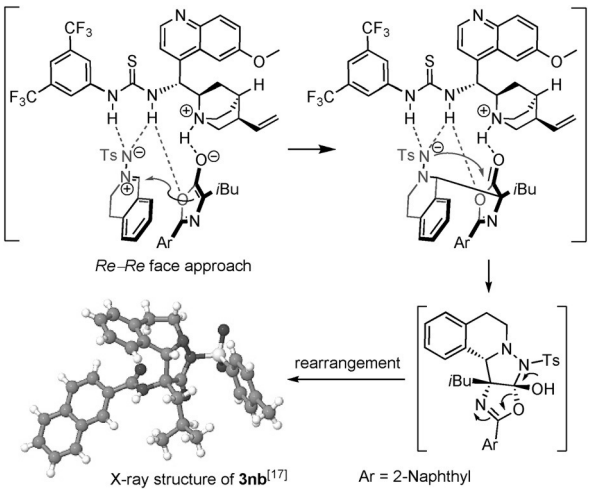
1a 2 3

Entry	R^3/R^4	*t* [h]	Yield [%]	*ee* [%]	d.r.
1[b]	H/C_6H_5	24	91 (**3ac**)	90	>20:1
2	H/4-$CF_3C_6H_4$	1	92 (**3ad**)	94	>20:1
3	H/4-*t*BuC_6H_4	3	91 (**3ae**)	97	>20:1
4	H/4-MeOC_6H_4	22	98 (**3af**)	94	>20:1
5	5-Me/4-MeC_6H_4	7	91 (**3ag**)	92	>20:1
6	7-Me/4-MeC_6H_4	7	95 (**3ah**)	92	>20:1
7	7-Cl/4-MeC_6H_4	9	93 (**3ai**)	94	18:1
8	6-Br/4-MeC_6H_4	9	87 (**3aj**)	88	15:1
9	7-Br/4-MeC_6H_4	9	90 (**3ak**)	94	>20:1
10		24	99 (**3al**)	98	>20:1

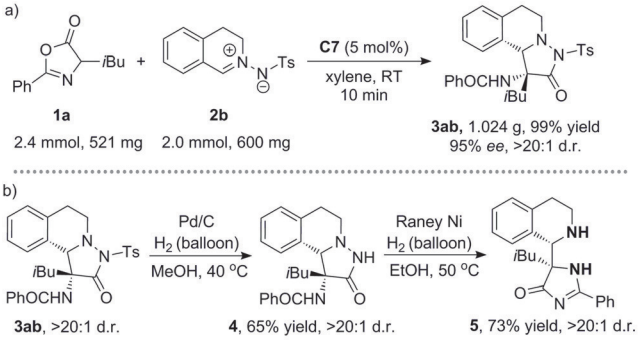
[a] Reaction conditions: 0.12 mmol **1a**, 0.10 mmol **2** and 5 mol% **C7**, in xylene (0.6 mL) at −20°C. [b] Conducted at room temperature.

the substitution on the aromatic ring of azomethine imines, irrespective of methyl and halogen substituents, all were well tolerated and afforded the corresponding products in high yields and stereoselectivities (**3ag–ak**). Furthermore, the condensed-ring azomethine imine **2l** underwent the current reaction. The absolute configuration of the products was determined by X-ray crystallographic analysis of **3nb**.[17] Accordingly, a model was speculated to explicate the observed stereochemical preference (Scheme 3).[18] Under the catalysis of **C7**, the *Re* face of the azomethine imine was attacked by the *Re* face of the enolate of the azlactone. And subsequent rearrangement of the unstable cyclized intermediate led to the desired product.

To demonstrate the scalability and the practicality of this protocol, we conducted a gram-scale reaction with **1a** and **2b** in the presence of 5 mol% **C7** at room temperature (Scheme 4a). Gratifyingly, the reaction proceeded smoothly and **3ab** was isolated with comparably high yield and stereoselectivity. Furthermore, some representative transformations of the cyclic product **3ab** were carried out. Subjecting **3ab** to



Scheme 3. Proposed transition states.



Scheme 4. Gram-scale preparation and representative transformations of product **3ab**.

a Pd/C-catalyzed hydrogenation reaction afforded **4** in 65% yield, which could be easily transformed into **5** when treated with Raney Ni under H_2 (Scheme 4b).[8d]

In conclusion, an organocatalyzed asymmetric IED 1,3-DC of C,N-cyclic azomethine imines with azlactones has been developed. This simple and efficient methodology offers a novel scheme for the stereocontrolled synthesis of various C1-substituted THIQs bearing vicinal tertiary and aza-quaternary stereocenters. Given the occurrence of both C1-substituted THIQ and pyrazolidinone scaffolds in bioactive molecules, the tricyclic THIQs incorporating the two useful motifs might dramatically expand the library of drug candidates. Further biological evaluation of the newly synthesized ring-fused THIQ derivatives is under way in our laboratory.

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Keywords: cycloaddition · hydrogen bonds · lactones · organocatalysis · synthetic methods

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