ChemPubSoc Europe

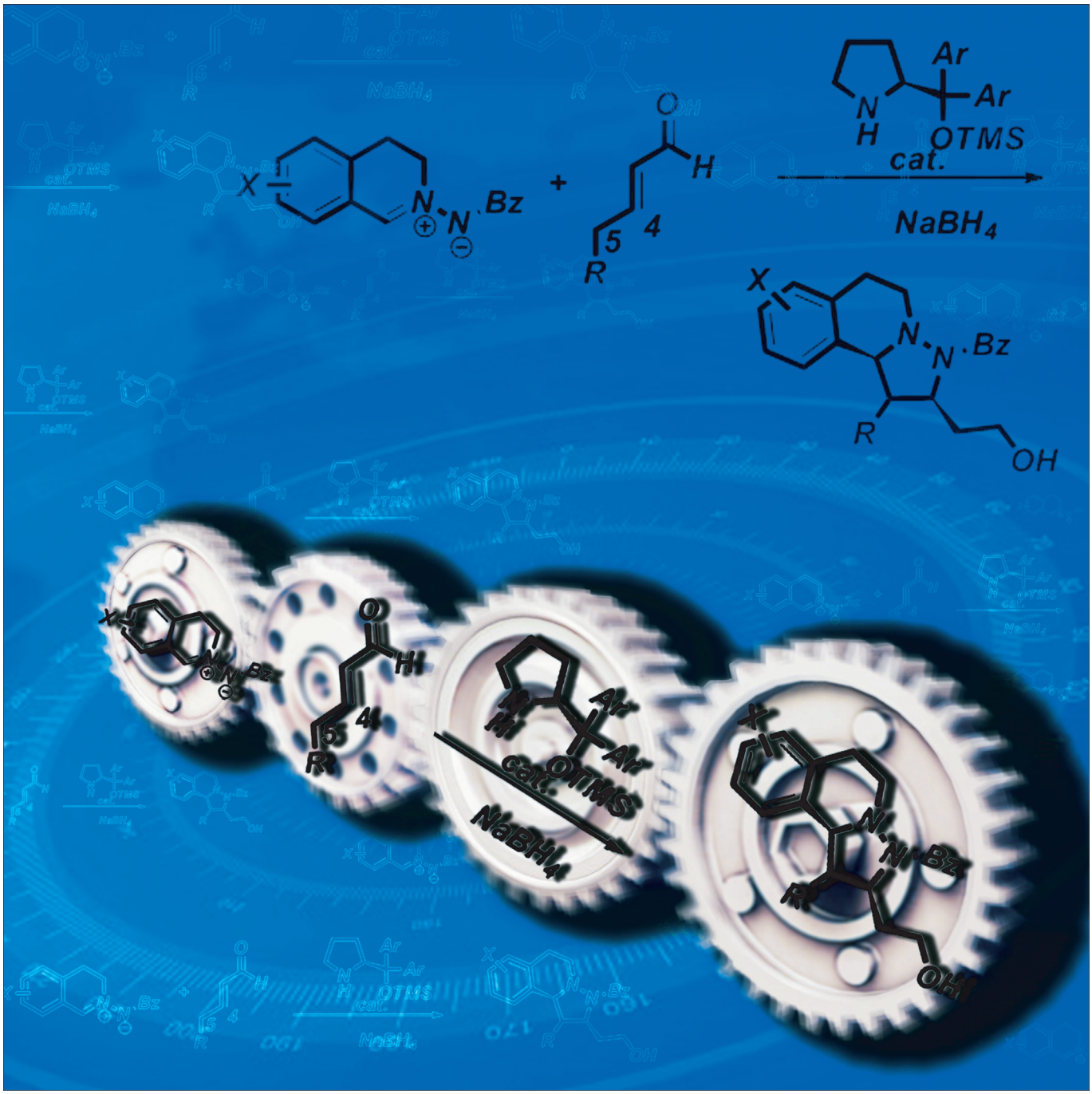
DOI: 10.1002/chem.201402089

CHEMISTRY
A European Journal
Communication

Organocatalysis

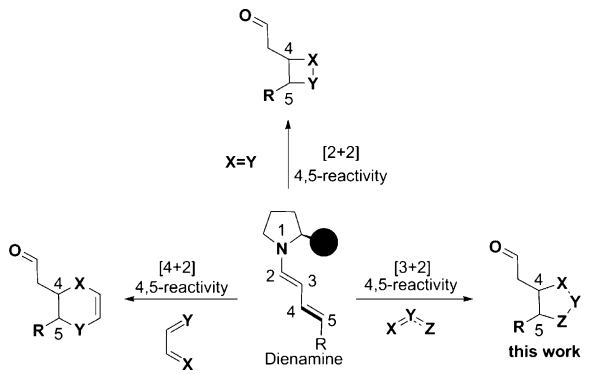
Asymmetric Synthesis of Tetrahydroquinolines through a [3+2] Cycloaddition Controlled by Dienamine Catalysis

Wenjun Li,[a, b] Jia Wei,[a] Qianfa Jia,[a] Zhiyun Du,*[a] Kun Zhang,[a] and Jian Wang*[a, b]



Abstract: A dienamine-mediated enantioselective 1,3-dipolar cycloaddition catalyzed by a chiral prolinol silyl ether catalyst has been developed. Removal of the benzamide group of the intermediates could furnish chiral C-1 substituted tetrahydroisoquinolines (see scheme) in high yields and excellent stereoselectivities.

The field of asymmetric organocatalysis has become extremely attractive over the last decade.[1] The activation of carbonyl compounds by enamines, iminium ions, or the SOMO-activation strategy has become a fundamental approach in asymmetric synthesis.[2] Moreover, the catalytic modes of amines are still under further investigation.[3] In 2006, Jørgensen and coworkers first developed dienamine catalysis by inverting the inherent reactivity of α,β-unsaturated aldehydes, which acted as nucleophiles for the direct enantioselective γ-amination with diethyl azodicarboxylates.[4] Although several elegant examples have been made, the synthetic potential of dienamine catalysis seems to be underestimated and only limited progress has been made to date.[5] Most examples of HOMO-raising dienamines promote 1,3-, 1,5-, or 2,5-reactivity,[5] and only a few catalytic approaches are available for the direct 4,5-reactivity of dienamines. In 2012, the Jørgensen group reported the first H-bond-directed inverse-electron-demand hetero-Diels–Alder reaction ([4+2] cycloaddition) proceeding via a dienamine intermediate (Scheme 1).[6] More recently, the Jørgensen[7] and Vicario[8] groups independently reported a [2+2] cycloaddition reaction of α,β-unsaturated aldehydes and nitroalkenes through dienamine catalysis (Scheme 1). To the best of our knowledge, an example of asymmetric catalytic [3+2] cycloaddition reactions through 4,5-reactivity of dienamines has not been reported.



Scheme 1. Asymmetric [*n*+2] cycloadditions of dienamines based on 4,5-reactivity.

As a model system, the reaction between C,N-cyclic azomethine imine **1a** and α,β-unsaturated aldehyde **2a** was chosen. The high reactivity of C,N-cyclic azomethine imines **1** has previously been shown to enable successful organocatalytic cycloadditions of a variety of different carbonyl compounds.[9] The reaction was tested in the presence of a number of chiral prolinol silyl ethers **I**–**IV** (Figure 1) as catalysts and in the presence of different additives in various solvents. Selected results are presented in Table 1.

The limiting reagent **1a** was found to be consumed within 4 h, as observed by 1H NMR spectroscopy. The reaction proceeded with good enantioselectivity and excellent diastereoselectivity in CH_2Cl_2 at room temperature (Table 1, entry 1, 84% *ee*, d.r. = 20:1). This initial result provided an excellent platform for further experiments and improvement of the diastereoselectivity. A screening of the temperature showed that performing the reaction at −20 °C improved the *ee* and the d.r. (Table 1, entry 3, 92%, >25:1). It was also found that the use of other solvents lowered the *ee* values considerably (en-

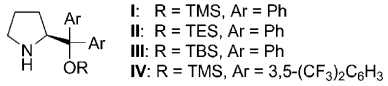
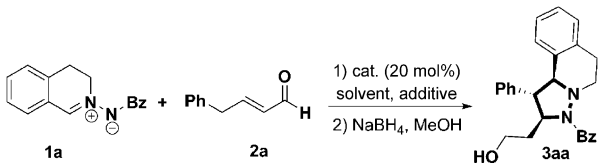


Figure 1. Screened catalysts.

Table 1. Optimization of reaction conditions.[a]



Entry	Cat.	Solvent	Additive	*T* [°C]	Yield [%][b]	*ee* [%][c]	d.r.[d]
1	**I**	CH_2Cl_2	AcOH	RT	83	84	20:1
2[e]	**I**	CH_2Cl_2	AcOH	0	86	90	>25:1
3[f]	**I**	CH_2Cl_2	AcOH	−20	86	92	>25:1
4[g]	**I**	CH_2Cl_2	AcOH	−40	85	92	>25:1
5[f]	**I**	$CHCl_3$	AcOH	−20	85	92	>25:1
6[f]	**I**	toluene	AcOH	−20	87	80	>25:1
7[f]	**I**	THF	AcOH	−20	55	85	>25:1
8[f]	**I**	anisole	AcOH	−20	85	80	>25:1
9[f]	**I**	Et_2O	AcOH	−20	72	85	>25:1
10[f]	**II**	CH_2Cl_2	AcOH	−20	63	87	>25:1
11[f]	**III**	CH_2Cl_2	AcOH	−20	81	87	>25:1
12[f]	**IV**	CH_2Cl_2	AcOH	−20	82	94	>25:1
13[f]	**IV**	CH_2Cl_2	CF_3CO_2H	−20	81	94	>25:1
14[f]	**IV**	CH_2Cl_2	$PhCO_2H$	−20	85	94	>25:1
15[f,h]	**IV**	CH_2Cl_2	2,4-DNBA	−20	87	97	>25:1

[a] Reaction conditions: a mixture of **1a** (0.10 mmol), **2a** (0.15 mmol), additive (20 mol%), and catalyst (20 mol%) in the solvent (0.3 mL) was stirred at room temperature for 4 h. [b] Isolated yield. [c] Determined by HPLC. [d] Determined by crude NMR analysis. [e] The reaction was conducted at 0 °C for 6 h. [f] The reaction was conducted at −20 °C for 12 h. [g] The reaction was conducted at −40 °C for 24 h. [h] 2,4-DNBA = 2,4-dinitrobenzoic acid.

[a] *W. Li, J. Wei, Q. Jia, Prof. Z. Du, Prof. K. Zhang, Prof. Dr. J. Wang*
Allan H. Conney Laboratory for Anticancer Research
Guangdong University of Technology
Guang Dong, 510006 (China)
E-mail: zhiyundu@foxmail.com

[b] *W. Li, Prof. Dr. J. Wang*
Department of Chemistry, National University of Singapore
3 Science Drive 3, Singapore 117543 (Singapore)
Fax: (+65) 6516-1691
E-mail: chmwangj@nus.edu.sg

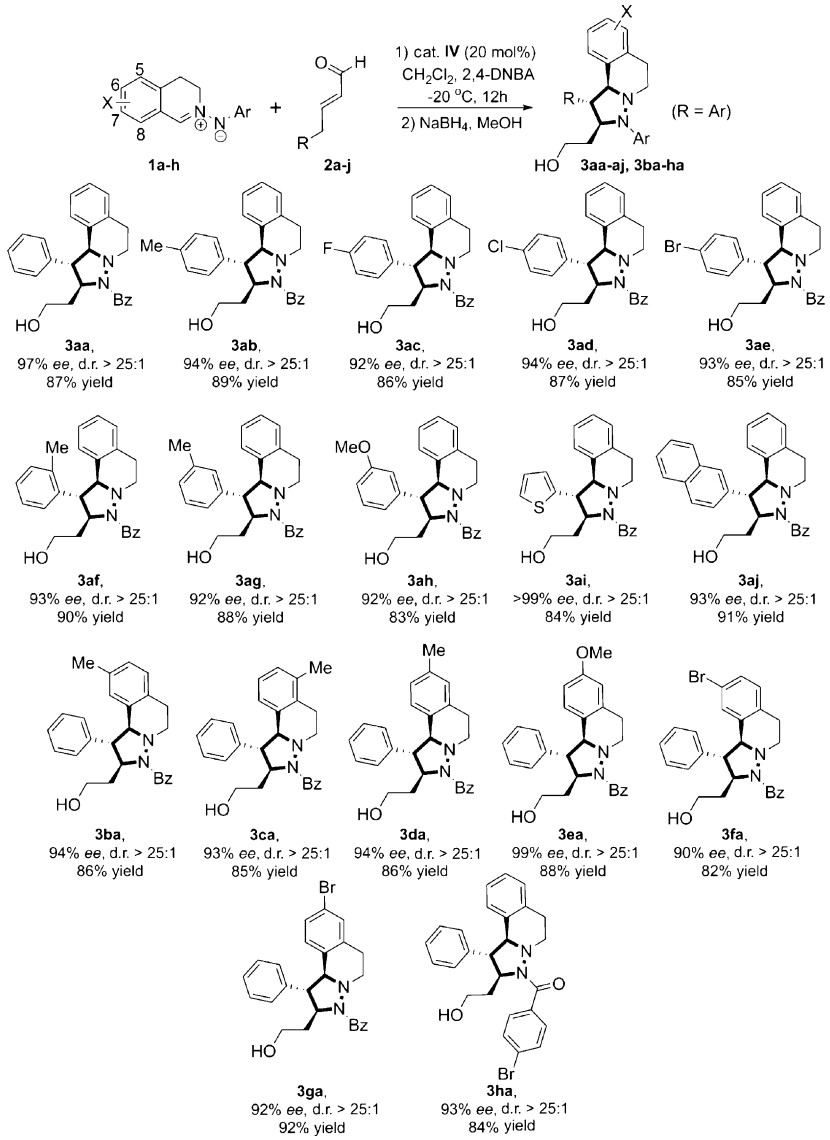
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201402089.

tries 6–9). A survey of chiral prolinol silyl ethers **I**–**IV** showed that employing catalyst **IV** slightly increased the *ee* to 94% (entry 12). The effect of acid additives was also studied. The presence of 20 mol% 2,4-dinitrobenzoic acid (2,4-DNBA) enhanced the *ee* value to 97% (entry 15).

With the optimized conditions in hand, the generality of the reaction was evaluated. A range of substrates was shown to be compatible with the developed protocol for the [3+2] cycloaddition of C,N-cyclic azomethine imines to α,β-unsaturated aldehydes by using 2-[bis(3,5-bistrifluoromethylphenyl)-trimethylsilanyloxymethyl] pyrrolidine **IV** as the catalyst (Table 2). The reaction proceeds well with α,β-unsaturated aldehydes in which R is an aromatic ring. Aromatic substituents on the side chain, albeit heterocycles, all gave good results (**3aa**–**3aj**, 92–99% *ee*, d.r. > 25:1, 83–91% yield). With this promising result in hand, we then investigated the generality of the C,N-cyclic azomethine imines. An increase in the steric bulk of the side chain, as in **1g**, led to a significantly higher reaction time, but with a comparable enantioselectivity and slightly lower yield. The presence of heteroatoms, such as the sulfur atom in the side chain of compound **1h**, is also tolerated, and the enantiomeric excess was retained. As for the substitution pattern of the C,N-cyclic azomethine imines, 5-, 6-, and 7-Me/MeO/or Br substituents were all tolerated, giving the desired products in high yields and steroselectivities (**3ba**–**3ha**). The absolute configuration of the products was assigned based on single-crystal X-ray analysis of Ts-protected **3aa**.[10]

However, aliphatic α,β-unsaturated aldehydes **2k**–**n** gave different [3+2] cycloadducts (Table 3, **3ak**–**3an**). We speculate that the reaction of aliphatic α,β-unsaturated aldehydes and secondary-amine catalyst **IV** preferably proceeds through the formation of an α,β-unsaturated iminium ion (3,4-reactivity of iminium ion vs. 4,5-reactivity of dienamine), which lowers the energy of the dienophile LUMO. The iminium ion plays a key role in triggering the 1,3-dipolar cycloaddition reaction, which upon reduction furnished the normal-electron-demand [3+2] cycloaddition products **3ak**–**3an**.[12]

Table 2. Substrate scope.[a]



[a] Reaction conditions: a mixture of **1** (0.10 mmol), **2** (0.15 mmol), 2,4-DNBA (20 mol%), and catalyst **IV** (20 mol%) in CH_2Cl_2 (0.3 mL) was stirred at −20 °C for 12 h.

The viability of trienamine activation was also investigated [Eq. (1)].[11] The desired cycloadduct **3ao** was obtained in 80% combined yield under standard conditions, but only with moderate diastereoselectivity (d.r. = 4:3, 92 and 72% *ee*, respectively). In this process, we envisioned that the condensation of catalyst **IV** with 2,4-dienal **2o** can lead to the transient formation of the extended conjugated trienamine intermediate, which subsequently reacts with C,N-cyclic azomethine imine **1a** to give the final cycloaddition product.

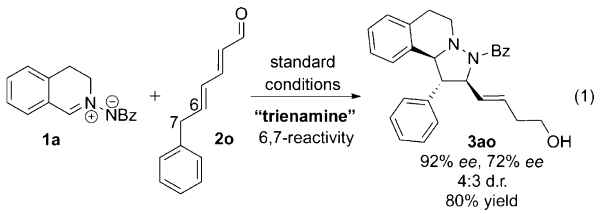
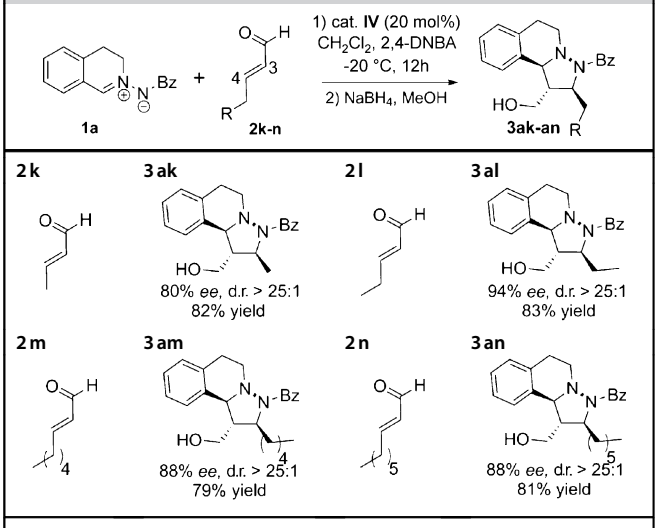


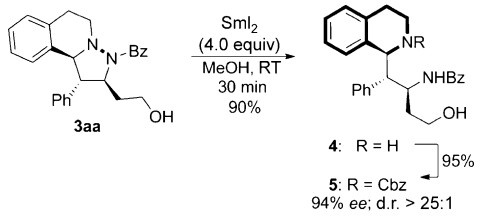
Table 3. Reactions of aliphatic α,β-unsaturated aldehydes with *C,N*-cyclic azomethine imines.[a]



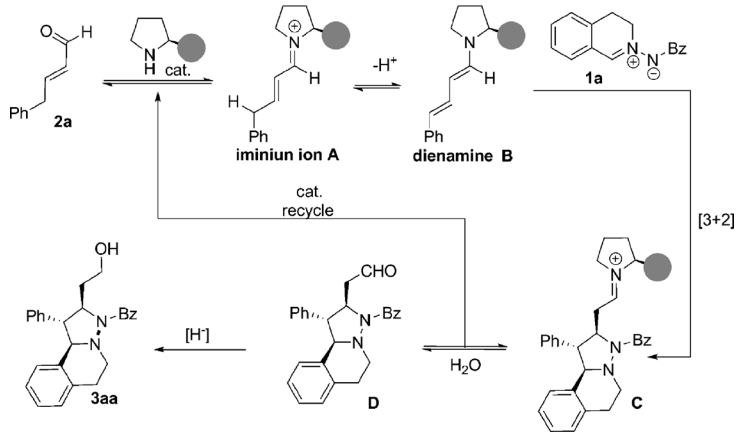
[a] Reaction conditions: a mixture of **1a** (0.10 mmol), **2k–n** (0.15 mmol), 2,4-DNBA (20 mol%), and catalyst **IV** (20 mol%) in DCM (0.3 mL) was stirred at −20 °C for 12 h.

Removal of the benzamide group of compound **3aa** was performed to access chiral tetrahydroisoquinoline **4**. As shown in Scheme 2, the N–N bond (**3aa**) could be easily cleaved by SmI_2 to give the tetrahydroisoquinoline **4** in 90% yield. The *ee* value of **4** was determined by HPLC analysis of the N-Cbz-protected compound **5** (Cbz = carbobenzyloxy).

A plausible mechanism is illustrated in Scheme 3. The reaction starts with the condensation of chiral prolinol silyl ether



Scheme 2. Synthetic transformations.



Scheme 3. Plausible mechanism.

catalyst **IV** and aldehyde **2a**, forming iminium-ion intermediate **A**. The iminium ion is then deprotonated to form the dienamine intermediate **B**, which reacts with the C,N-cyclic azomethine imine **1a** to generate the polycyclic intermediate **C**. Intermediate **C** is then hydrolyzed to give intermediate **D**, which undergoes a reduction step to form the final product **3aa**.

In summary, the first dienamine-mediated enantioselective 1,3-dipolar [3+2] cycloaddition was developed, demonstrating the viability of this activation strategy. The reaction between diversely substituted C,N-cyclic azomethine imines and α,β-unsaturated aldehydes proceeded smoothly to give the desired products in a highly stereoselective manner. Furthermore, it was demonstrated that the obtained cycloadducts can be transformed into useful tetrahydroisoquinoline frameworks. We also believe that the strategy could be applicable to other 1,3-dipolar cycloadditions. These studies are currently under way in our laboratory and the results will be reported in due course.

Experimental Section

General procedure

Catalyst **IV** (0.02 mmol) and 2,4-dinitrobenzoic acid (0.02 mmol) were added to a solution of C,N-cyclic azomethine imine **1a** (0.10 mmol) and aldehyde **2a** (0.15 mmol) in CH_2Cl_2 (0.3 mL). The mixture was stirred at −20 °C for 12 h and then the solvent was removed under vacuum to give the crude product. $NaBH_4$ (0.20 mmol) was added to a solution of the crude product in methanol (2.0 mL), the reaction mixture was stirred at room temperature for 2 h, and then the solvent was removed under vacuum to give a residue, which was purified by silica gel chromatography to yield the desired product **3aa** as yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz): $\delta = 7.83$ (d, $J = 7.0$ MHz, 2H), 7.46–7.33 (m, 6H), 7.28–7.26 (m, 2H), 7.12–7.08 (m, 2H), 6.89–6.86 (m, 1H), 6.16 (d, $J = 8.0$ MHz, 1H), 4.82–4.77 (m, 1H), 4.37–4.35 (m, 1H), 4.31–4.28 (m, 1H), 3.78–3.69 (m, 2H), 3.49–3.42 (m, 1H), 3.40–3.38 (m, 1H), 3.35–3.32 (m, 1H), 3.06–2.99 (m, 1H), 2.79–2.75 (m, 1H), 2.29–2.23 (m, 1H), 1.84–1.79 ppm (m, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz): $\delta = 173.1$, 138.7, 135.1, 133.8, 132.6, 130.5, 129.1, 128.6, 128.3, 127.7, 127.1, 126.7, 125.8, 69.8, 66.1, 60.2, 59.5, 49.5, 40.8, 29.7 ppm; HRMS (ESI): *m/z* calcd for $C_{26}H_{27}N_2O_2$: 399.2067 $[M]^+$; found: 399.2064; HPLC (Chiralpak IA, isopropanol/hexane 10:90, flow rate: 1.0 mL min^{-1}, $\lambda = 254$ nm): t_R (major) = 33.0 min, t_R (minor) = 36.2 min, *ee* = 97%, d.r. > 25:1; $[\alpha]_D^{25} = +7.6$ ($c = 1.0$ in CH_2Cl_2).

Acknowledgements

The authors acknowledge the financial support from National University of Singapore (Academic Research Grant: R143000532112 and NRF-CRP7-2010-03) and Guangdong University of Technology (China). The authors also thank Prof. Keiji Maruoka for providing some important C,N-cyclic azomethine imines.

Keywords: asymmetric synthesis · azomethine imines · dienamines · cycloaddition · tetrahydroisoquinolines

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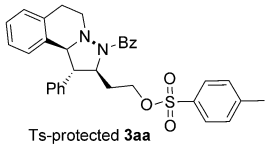
[10] CCDC 920367 (Ts-protected **3aa**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.



Ts-protected **3aa**

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Received: February 9, 2014
Published online on ■■ ■■, 0000

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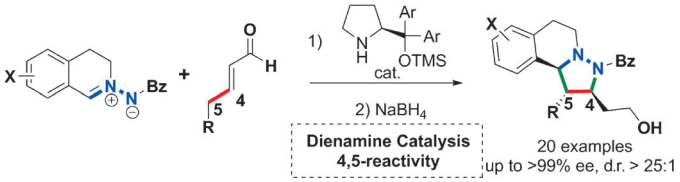
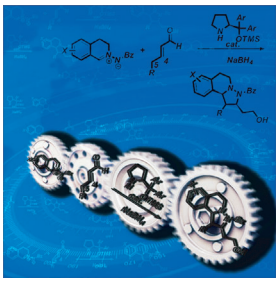
Asymmetric Synthesis of Tetrahydroquinolines through a [3+2] Cycloaddition Controlled by Dienamine Catalysis



A dienamine-mediated enantioselective 1,3-dipolar cycloaddition catalyzed by a chiral prolinol silyl ether has been developed. Removal of the benzamide group of the intermediates afforded chiral C1-substituted tetrahydroisoquinolines in high yields and excellent stereoselectivities (see scheme).



Dienamine Catalysis

Typically, HOMO-raising dienamine catalysts promote1,3-, 1,5-, or 2,5-reactivity. In contrast, asymmetric catalytic [3 + 2] cycloaddition reactions that promote 4,5-reactivity of dienamines have not been reported. A dienamine-mediated enantioselective 1,3-dipolar cycloaddition catalyzed by a chiral prolinol silyl ether has been developed. Removal of the benzamide group of the intermediates afforded chiral C1-substituted tetrahydroisoquinolines in high yields and excellent stereoselectivities. For more details see the Communication by Z. Du, J. Wang et al. on page ■■ ff.