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Organocatalytic Asymmetric Synthesis of *trans*-1,3-Disubstituted Tetrahydroisoquinolines via a Reductive Amination/Aza-Michael Sequence

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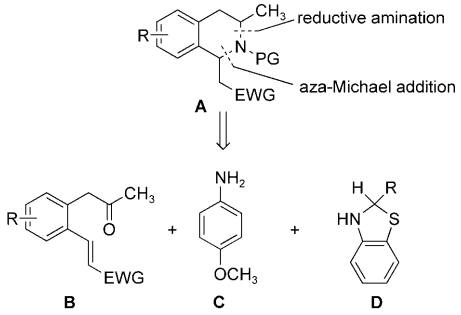
Dedicated to Professor José Barluenga on the occasion of his 70th birthday

In the rapidly evolving field of organocatalysis[1] chiral Brønsted acids have become one of the most powerful and versatile catalysts for a wide range of transformations.[2] One of the most important reactions catalyzed by this class of catalysts is the enantioselective reductive amination,[3] which leads to a broad range of chiral amines that are frequently found in natural products or pharmaceutically interesting compounds. While several organocatalytic reductions of imines using chiral Brønsted acids have been reported in the literature,[4] so far only very few organocatalytic protocols for the enantioselective direct reductive amination employing chiral Brønsted acid catalysis have been developed.[5] Recently, Akiyama et al. applied benzothiazolines as novel reducing agents for the stereoselective reduction of imines,[6] but to the best of our knowledge no direct reductive amination of ketones with this hydride source has been reported so far.

The tetrahydroisoquinoline motif is frequently found in biologically active substances,[7] such as antibiotics and antitumor agents and therefore the development of new diastereo- and enantioselective routes to this important substance class is desirable.[8,9] The most recent approaches to these compounds are metal-catalyzed reactions such as the asymmetric reduction of cyclic imines,[10] ring-contraction reactions[11] or C–H activation.[12]

We now wish to report that a three-component reductive amination using a novel 2-biphenyl-substituted benzothiazoline derivative as reducing agent leads to high yields and stereoselectivities in the asymmetric synthesis of 1,3-disubstituted tetrahydroisoquinolines. We envisioned that a Brønsted acid catalyzed reductive amination/aza-Michael sequence could lead to the title heterocycles **A**, starting under multicomponent conditions from keto enones **B**, *p*-anisidine (**C**), and benzothiazolines **D**, thereby allowing a great substitution pattern flexibility (Scheme 1).



Scheme 1. Retrosynthetic analysis of the tetrahydroisoquinoline synthesis.

To test this approach we synthesized the methylketone enoate **1** and submitted it to reductive amination conditions using MacMillans' Ph_3Si-substituted phosphoric acid catalyst and commercially available Hantzsch ester (**2**) as hydride source (Table 1, entry 1). The desired product **3** was obtained even though in only poor yield and enantioselectivity. List's TRIP (3,3′-bis(2,4,6-triisopropylphenyl)-1,1′-binaphthyl-2,2′-diyl hydrogenphosphate) catalyst[13] in turn showed very good conversions with high enantioselectivities (Table 1, entry 2).

N-Triflylamide catalysts gave very good yields and reactions rates, but unfortunately the asymmetric induction was low in each case. A catalyst loading of 10 mol% was necessary in order to obtain high yields, even though the stereoselectivity is only little affected when lower loadings are used (Table 1, entry 5 and 6). Next, the effect of the solvent and the type of hydride source was examined (Table 2). In

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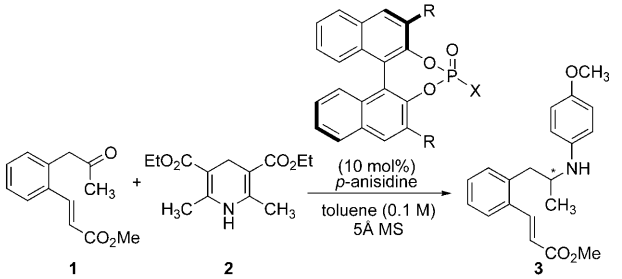
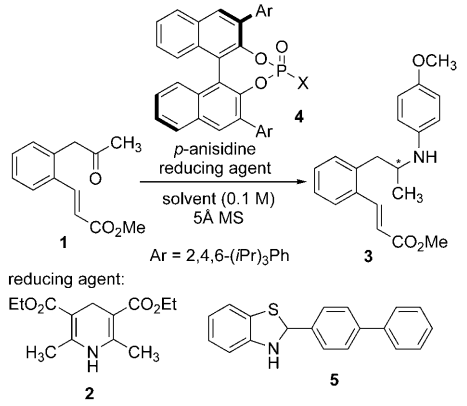
Table 1. Evaluation of the chiral Brønsted acid catalysts in the three-component. reductive amination reaction of ketone **1**.[a]



Entry	R	X	T [°C]	Yield [%][b]	*ee* [%][c]
1	Ph_3Si	OH	45	28	30
2	(2,4,6-*i*Pr)Ph	OH	45	92	89
3	(2,4,6-*i*Pr)Ph	NHTf	45	89	30
4	(2,4,6-*i*Pr)Ph	NHTf	30	99	26
5	(2,4,6-*i*Pr)Ph	OH	30	64	91
6[d]	(2,4,6-*i*Pr)Ph	OH	30	56	84
7	3,5-CF_3Ph	NHTf	30	72	7

[a] Unless otherwise specified, the reactions were performed on a 0.16 mmol scale of *p*-anisidine using 2 equiv of ketone **1**, 1.4 equiv of Hantzsch ester **2** and 10 mol% catalyst. [b] Yield of isolated amine **3**. [c] Determined by chiral stationary phase HPLC analysis. [d] 5 Mol% of catalyst was used.

Table 2. Effects of solvent and reducing agent in the reductive amination reaction of ketone **1**.[a]



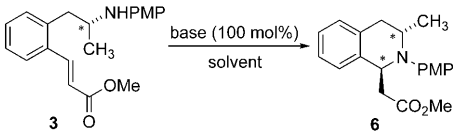
Entry	Solvent	T [°C]	Reducing agent	Yield [%][b]	*ee* [%][c]
1	benzene	30	**2**	79	88
2	toluene	30	**2**	64	91
3	xylenes	30	**2**	38	89
4	mesitylene	30	**2**	74	93
5	mesitylene	50	**5**	98	88

[a] Unless otherwise specified, the reactions were performed on a 0.16 mmol scale of *p*-anisidine using 2 equiv of ketone, 1.4 equiv of reducing agent and 10 mol% catalyst **4**. [b] Yield of isolated amine **3**. [c] Determined by chiral stationary phase HPLC analysis.

agreement with the previously reported results,[5,6] aromatic and highly non-polar solvents gave the best results. Interestingly, the substituted 2-biphenyl-substituted benzothiazole derivate **5** proved to be more reactive as well as more selective as compared to the Hantzsch ester **2** thereby increasing the yield and enantioselectivity of the reaction.

The enantioselectivity of the reductive amination turned out to be very temperature dependent. Therefore careful monitoring of the reaction temperature was required. To find out the optimal conditions for the cyclisation of the amines obtained, several bases were screened, however, only strong bases such as 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) or potassium *tert*-butoxide were able to induce cyclization (Table 3). When *t*BuOK was used the cyclization occurred within seconds and gave exclusively the *trans*-diastereomer of the desired tetrahydroisoquinoline product in good yields. As a side product the corresponding *tert*-butylester was also observed, obviously formed via transesterification. Therefore in subsequent reactions the *tert*-butylacrylate substituted ketone was used. We noticed that no cyclization occurred when older batches of *t*BuOK were employed and only freshly sublimed reagent gave optimal results.

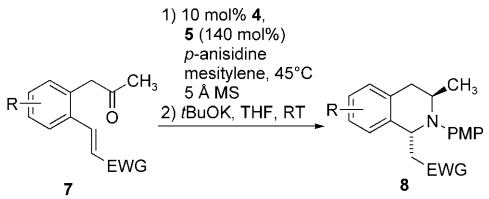
Table 3. Screening of bases for the aza-Michael cyclisation.



Entry	Base	Solvent	Yield [%][a]	d.r.[b]
1	K_2CO_3	H_2O/Et_2O	no reaction	–
2	Et_3N	THF	no reaction	–
3	DBN	toluene	n.d.	2:1.1
4	*t*BuOK	Et_2O	no reaction	–
5	*t*BuOK	THF	60	6:1

[a] Yield of isolated **6**. [b] Determined by NMR.

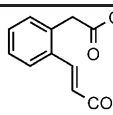
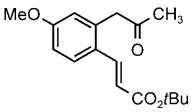
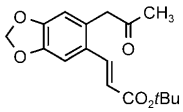
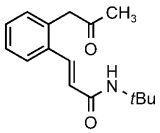
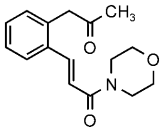
In order to test the substrate scope of the reaction several methyl ketones bearing different α,β-unsaturated Michael acceptors in *ortho* position were synthesized and used in the reductive amination/aza-Michael sequence (Scheme 2, Table 4). In general, substitution on the aromatic ring had no negative effects on the reaction even when doubly *ortho*-substituted substrates were used. Also primary and secondary acrylamides are possible substrates and can be converted to the corresponding tetrahydroisoquinolines (entry 4 and 5). In all cases complete *trans*-diastereoselectivity was observed. Reactions on a larger scale (1.6 mmol) did not influence the selectivity or yield and for instance tetrahydroisoquinoline **8e** could be synthesized in 81% yield (480 mg, Table 4, entry 4). So far, the reaction is limited to methyl ke-



Scheme 2. Three-component reductive amination/aza-Michael sequence.

tones, since all other synthesized derivatives show only low conversion, most probably due to the slower imine formation.[14]

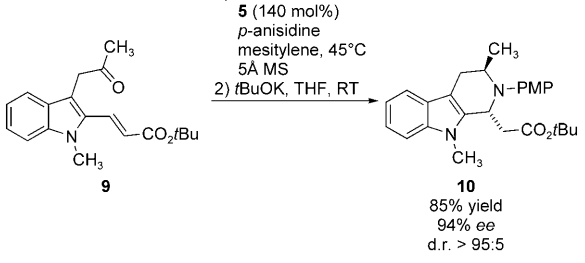
Table 4. Scope of the reductive amination/aza-Michael sequence.[a]

Entry	Ketone	Product	Yield [%][b]	*ee* [%][c]	d.r.[d]
1		**8a**	93	94	>95:5
2		**8b**	87	96	>95:5
3		**8c**	93	94	>95:5
4		**8d**	81	93	>95:5
5		**8e**	97	98	>95:5

[a] The reactions were performed on 0.25-1.6 mmol scale of *p*-anisidine using 2 equiv of ketone, 1.4 equiv of reducing agent and 10 mol% catalyst **4**. See Supporting Information for details. [b] Yield of isolated **8**. [c] Determined by chiral stationary phase HPLC analysis. [d] Determined by NMR spectroscopy.

Gratifyingly also indole-derived acrylates are possible substrates for the three-component reductive amination/aza-Michael sequence leading to the important class of β-carbolines. When indole enoate **9** was subjected to the reaction conditions, the corresponding *trans*-disubstituted β-carbonline **10** was obtained in 85% yield, >90% *de*, and 94% *ee* (Scheme 3).

The absolute configuration of the stereogenic centers created in the reductive amination step and the aza-Michael addition was determined to be *R* by X-ray analysis of a camphanoyl derivative,[15] which could be obtained by DIBAl-H reduction of the *tert*-butyl ester moiety of **8a** and subsequent reaction with camphanic chloride.[16] Additionally, the *trans*-configuration of the products was confirmed by NOESY NMR measurements in each case (Figure 1).



Scheme 3. Extension of the methodology for the diastereo- and enantioselective synthesis of β-carbolines.

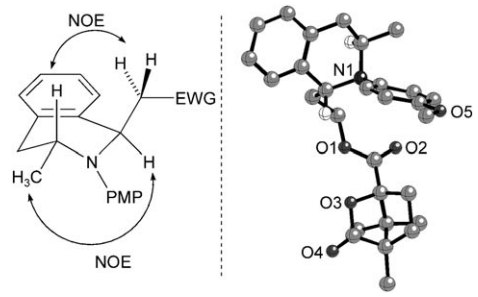
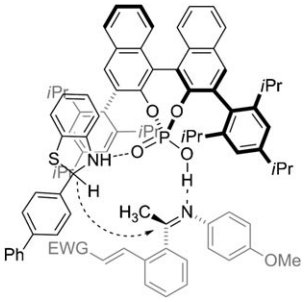


Figure 1. Determination of the relative (NOE) and absolute configuration (X-ray).

In analogy to the previously reported results by Goodman et al.[17] we propose a transition state in which the (*Z*)-imine is protonated by the acidic phosphoric acid group while the benzothiazoline coordinates with the Lewis basic oxygen atom. The hydride is then transferred to the *Si* face of the imine (see below).



In conclusion, we have developed an efficient organocatalytic reductive amination procedure using a biphenyl-substituted benzothiazoline as hydride source and employed it in a reductive amination/aza-Michael sequence for the highly diastereo- and enantioselective synthesis of *trans*-1,3-disubstituted tetrahydroisoquinolines. Starting from an indole-derived keto enoate the corresponding *trans*-disubstituted β-carboline is obtained as well in excellent yield and stereoselectivity.

Experimental Section

General procedure for the synthesis of *trans*-1,3-disubstituted tetrahydroisoquinolines: A flame-dried Schlenk tube was charged with *p*-anisidine (1 equiv), ketone **7** (2 equiv), thiazoline **5** (1.4 equiv), chiral Brønsted acid **4** (0.1 equiv) and activated 5 Å molecular sieves. Dry mesitylene (0.1 M) was added and the reaction mixture was stirred at 40 °C until TLC analysis indicated full conversion (usually 2–3 d). The crude product was directly purified by column chromatography and then dissolved in THF (0.1 M). Freshly sublimed *t*BuOK was added at room temperature and the

reaction was quenched with brine after 1 min. Extraction with diethyl ether and filtration through a plug of silica yielded the pure 1,3-disubstituted tetrahydroisoquinolines **8**.

Acknowledgements

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Keywords: asymmetric synthesis · Michael addition · organocatalysis · phosphoric acid · reductive amination

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[14] For example the corresponding ethyl ketone of **7e** could be reduced with 92% *ee* but only 23% yield was obtained.

[15] CCDC-773769 contains the supplementary crystallographic data for this paper (excluding structure factors). These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[16] See the Supporting Information for details.

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