Organocatalysis

DOI: 10.1002/anie.201001715

Catalytic Asymmetric Reductive Amination of α-Branched Ketones**

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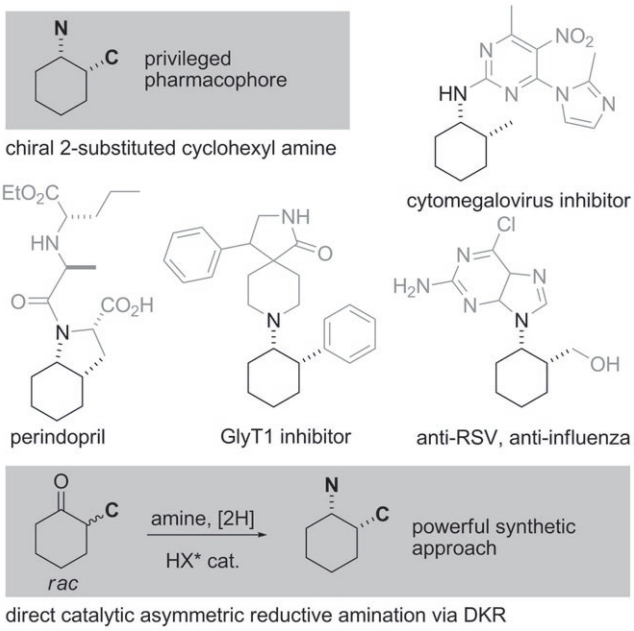
The reductive amination of carbonyl compounds is a powerful and versatile method for the creation of carbon–nitrogen bonds. However, despite its importance in both, medicinal chemistry and process chemistry, only a few asymmetric versions exist.[1] Recently, we have developed a chiral acid-catalyzed reductive amination of ketones using Hantzsch esters as a hydride source and 3,3′-bis(2,4,6-triisopropylphenyl)-1,1′-binaphthyl-2,2′-diyl hydrogen phosphate (TRIP) as a Brønsted acid organocatalyst.[2–4] The groups of Rueping[3a] and MacMillan[3b] have both independently developed alternative variants and additional applications of this methodology appeared subsequently.[3,5] However, asymmetric reductive amination reactions of racemic ketones by dynamic kinetic resolution (DKR) have not yet been reported.

The 2-substituted cyclohexylamine pharmacophore is a privileged and frequently occurring motif in drug design and, in addition to the ACE-inhibitor perindorpil, there are hundreds of reported pharmacologically active compounds that incorporate this subunit (Scheme 1).[6,7] We hypothesized that reductive amination of the corresponding α-branched cyclohexanones should provide a powerful approach towards such enantiopure cyclohexylamines using dynamic kinetic resolution. Herein, we show that this concept is indeed possible and report, to the best of our knowledge, the first example of the catalytic asymmetric reductive amination of racemic ketones using DKR.

Despite the enormous advances in the asymmetric reduction of configurationally labile carbonyl compounds by DKR,[8] the analogous reductive amination reactions are underexplored. In 2005, Lassaletta and co-workers reported the first example of a transition-metal-catalyzed asymmetric transfer-hydrogenation of α-branched ketimines.[9] Most recently, Kočovský and co-workers reported the synthesis of β-amino acids using a catalytic trichlorosilane reduction of enamines, suggesting a DKR mechanism.[10] However, the direct reductive amination of racemic α-branched ketones have remained unknown; we have now systematically developed a powerful and general procedure for this transformation (Table 1).



Scheme 1. The direct reductive amination of racemic ketones by dynamic kinetic resolution leads to biologically active amines.

Accordingly, treating cyclohexanones **1** with *para*-anisidine (**2**, PMP-NH_2, 1.1 equiv), Hantzsch ester **3** (1.4 equiv), and only 1 mol% of TRIP readily provided the desired products **4**. Remarkably, with this combination of commercially available reagents and catalyst, a broad array of ketones **1** could be converted into their corresponding cyclohexylamines (**4**) in good yields and diastereoselectivities, and high enantioselectivities.

Although the previously developed unsymmetrical Hantzsch ester **5** afforded slightly higher enantioselectivity for the reaction of 2-methylcyclohexanone (*rac*-**1a**; Table 1, entry 1 vs 2), for practical reasons we used its inexpensive analogue **3** throughout our studies. The substrate scope of the reaction is summarized in Table 1. An important feature of our process is its tolerance of a variety of different substituents whilst maintaining excellent enantioselectivity. Simple alkyl-substituted substrates are particularly reactive, requiring only a very low amount of catalyst (1 mol%; Table 1, entries 1–5). With sterically more-demanding substrates (Table 1, entries 6 and 7), as well as with aromatic substrates (Table 1, entries 8–10), slightly higher catalyst loadings were used. Whilst diastereoselectivities varied from reasonably good to excellent, the enantioselectivities were generally very high. The relative and absolute configuration of product **4a** was determined to be 1*R*,2*S* by deprotection using H_5IO_6 to give known *cis*-2-methyl cyclohexyl amine (see the Supporting Information).[11]

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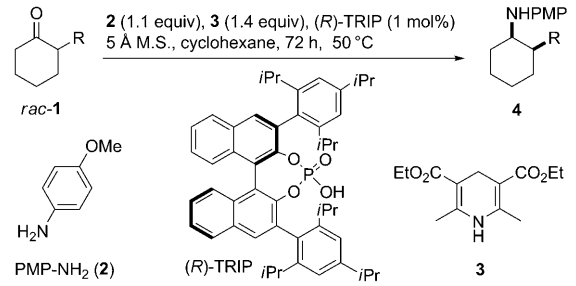
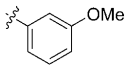
[**] Generous support by the Max Planck Society, the DFG (SPP 1179, *Organocatalysis*), and the Fonds der Chemischen Industrie, is gratefully acknowledged. We also thank Wacker and Sanofi-Aventis for support.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201001715.

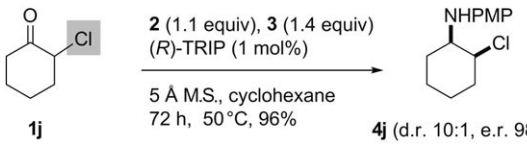
Table 1: Reductive amination of α-substituted ketones.[a]



Entry	R	Product	Yield [%]	d.r.[b]	e.r.[c]
1	Me	**4a**	82	5:1	93:7
2[d]	Me	**4a**	76	5:1	95:5
3	Et	**4b**	87	6:1	94:6
4	*n*Pr	**4c**	91	5:1	95:5
5		**4d**	80	8:1	95:5
6[e]		**4e**	63	>99:1	98:2
7[e]	Bn	**4f**	92	6:1	96:4
8[f]	Ph	**4g**	63	16:1	94:6
9[e]		**4h**	73	6:1	94:6
10[e,g]		**4i**	81	17:1	96:4

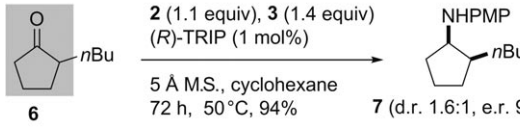
[a] 0.5 mmol scale. [b] Determined by GC or NMR analysis. [c] The e.r. of the *cis* product determined by HPLC analysis on a chiral stationary phase. [d] Dimethyl 2-isopropyl-6-methyl-1,4-dihydropyridine-3,5-dicarboxylate (**5**) was used. [e] 5 mol% catalyst. [f] 10 mol% catalyst. [g] **3** (3 equivalents) was used.

Our reaction is not limited to alkyl- or aryl-substituted cyclohexanones, even chlorine is tolerated in the α position. Upon subjecting 2-chlorocyclohexanone (**1j**) to our standard reaction conditions, 2-chlorocyclohexyl amine **4j** was obtained in excellent yields and stereoselectivities [Eq. (1)].

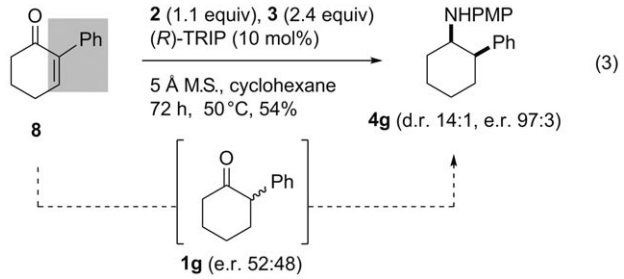


(1)

We also studied other ring sizes and found that racemic 2-butylcyclopentanone (**6**) furnished the corresponding amine **7** in good yield, but somewhat lower stereoselectivities [Eq. (2)]. Surprisingly, the corresponding cycloheptanone did not undergo reductive amination under these conditions. Remarkably though, by employing 2.4 equivalents of the Hantzsch ester, even α,β-unsaturated, α-branched ketone **8** could be converted into product **4g** in reasonable yields and excellent selectivity [Eq. (3)]. As expected, when only 1 equivalent of Hantzsch ester was used, 2-phenylcyclohexanone **1g** was obtained with complete conversion and poor enantioselectivity.

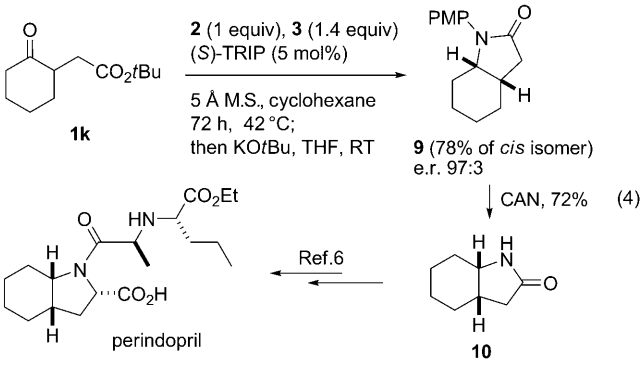


(2)



(3)

As a further illustration of the synthetic utility of this transformation, a short synthesis of lactam **10** was developed [Eq. (4)]. This compound is the key intermediate in the synthesis of Coversyl (perindopril), a long-acting ACE inhibitor.[6] Reductive amination of ketone **1k**, followed by an in situ base-mediated cyclization, afforded lactam **9** in 92% yield and a 5:1 *cis*/*trans* ratio. The desired isomer *cis*-**9** was isolated in 78% yield with a 97:3 e.r. Oxidative removal of the PMP group then provided known lactam **10** in 72% yield. The conversion of lactam **10** into perindopril has already been established in the patent literature.[6]



(4)

In conclusion, we have developed a catalytic asymmetric reductive amination of α-branched ketones using dynamic kinetic resolution. Our new reaction provides an efficient diastereoselective and enantioselective synthesis of valuable *cis*-2-substituted cyclohexylamines, as illustrated with a synthesis of a key pharmaceutical intermediate.

Currently, substituted cyclohexanones are ideal substrates for our reaction, and both aromatic and aliphatic substituents give products with highly stereoselectivity. We expect to further expand the substrate scope in ongoing studies in our laboratory.

Received: March 22, 2010
Published online: May 20, 2010

Keywords: asymmetric catalysis · chiral amines · ketones · organocatalysis · reductive amination

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