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Catalytic Asymmetric Reductive Amination of Aldehydes via Dynamic Kinetic Resolution

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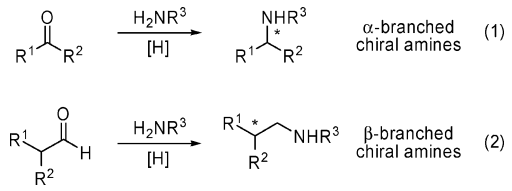
Catalytic asymmetric reductive aminations of carbonyl compounds are useful for the synthesis of chiral amines and also powerful C−N bond forming fragment coupling reactions.[1] Although selected asymmetric reductive aminations of ketones to give chiral, α-branched amines in an enantioface-differentiating process have been reported (eq 1),[2,3] the corresponding reactions of aldehydes are unknown. We reasoned that such a process might be realized if enolizable, α-branched aldehydes are employed. Their asymmetric reductive amination should give *β*-branched amines via an enantiomer-differentiating kinetic resolution (eq 2).

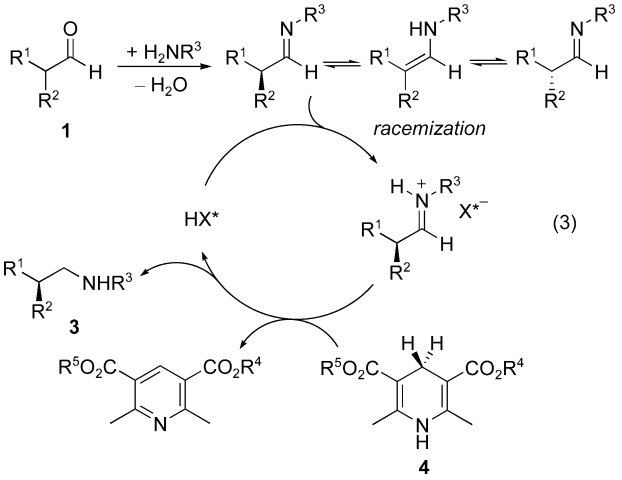


We have recently reported an organocatalytic ketimine reduction as well as a reductive amination of ketones using Hantzsch esters as hydride source and chiral Brønsted acids as catalysts.[3,4] One of the most efficient and enantioselective catalysts identified to date is 3,3′-bis(2,4,6-triisopropylphenyl)-1,1′-binaphthyl-2,2′-diyl hydrogen phosphate (TRIP, **5f**),[5] which at only 1 mol % catalyst loading provides products of aromatic and aliphatic ketimine intermediates in high enantioselectivities.[3] We now report an extension of this methodology to aldehyde substrates. We found that TRIP also catalyzes the direct reductive amination of α-branched aldehydes in an efficient dynamic kinetic resolution.

At the onset of this study, we hypothesized that under our reductive amination conditions an α-branched aldehyde substrate would undergo a fast racemization in the presence of the amine and acid catalyst via an imine/enamine tautomerization. The reductive amination of one of the two imine enantiomers would then have to be faster than that of the other, resulting in an enantiomerically enriched product via a dynamic kinetic resolution (eq 3).[6] Despite their general tendency toward facile racemization, α-branched aldehydes have rarely been used in dynamic kinetic resolutions before.[7,8]

Indeed, when we studied various phosphoric acid catalysts for the reductive amination of hydratopicaldehyde (**1a**) with *p*-anisidine ($PMPNH_2$, **2**) in the presence of Hantzsch ester **4** to give amine **3a**, the observed enantioselectivities and conversions are consistent with a facile in situ racemization of the substrate and a resulting dynamic kinetic resolution (eq 4, Table 1). TRIP (**5f**) once again turned out to be the most effective and enantioselective catalyst for this transformation and provided the chiral amine product under unoptimized conditions in 50% yield and an enantiomeric ratio of 84:16.

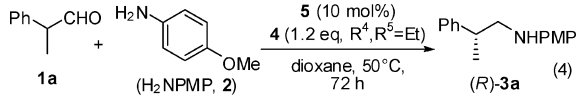
Other catalysts, such as **5e**, which has previously been used in the reductive amination of ketones, gave significantly inferior results under identical conditions.[3] After further optimization, which

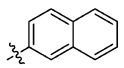
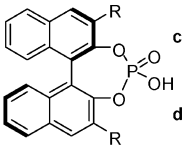
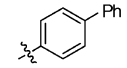
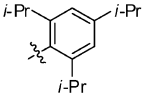


included changing the dihydropyridine,[9] lowering the catalyst loading, reducing the temperature, changing the solvent, and adding molecular sieves, the enantioselectivity could be improved significantly (98:2 er) and the optimized protocol was used for the direct reductive amination of a variety of different aldehydes (Table 2).

The efficient removal of water formed during the reaction seems to be important as the enantiomeric ratio improved considerably upon using 5 Å molecular sieves. This reagent has been used previously in the reductive amination of ketones, and other dehydrating reagents proved less useful. Furthermore, oxygen-free conditions are required as substantial acetophenone and *p*-formylanisidine formation was observed in the presence of oxygen,

Table 1. Catalyst Screening



Catalyst		R	Yield [%][a]	er[b]
	a	H	-	0
	b		48	57:43
	c		72	55:45
	d		55	60:40
	e	$SiPh_3$	7	61:39
	f		50	84:16

5

[a] Determined by GC with internal standard. [b] Determined by HPLC.

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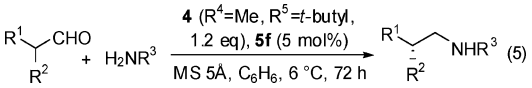
Table 2. Scope of the Catalytic Asymmetric Reductive Amination of Aldehydes



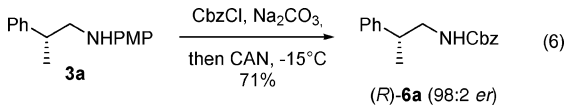
entry	R^1	R^2	R^3	yield (%)	er[a]
1	Ph (**3a**)	Me	PMP	87	98:2
2[b]	Ph (**3a**)	Me	PMP	80	99:1
3	4-MeC_6H_4 (**3b**)	Me	PMP	86	97:3
4	4-MeOC_6H_4 (**3c**)	Me	PMP	81	97:3
5	1-naph (**3d**)	Me	PMP	85	99:1
6	2-naph (**3e**)	Me	PMP	96	98:2
7	4-BrC_6H_4 (**3f**)	Me	PMP	92	97:3
8	2-F C_6H_4 (**3g**)	Me	PMP	89	97:3
9	3-F C_6H_4 (**3h**)	Me	PMP	84	97:3
10	thiophen-2-yl (**3i**)	Me	PMP	49	94:6
11	cyclohexyl (**3j**)	Me	PMP	81	89:11
12	*tert*-butyl (**3k**)	Me	PMP	77	90:10
13	CF_3 (**3l**)	Me	PMP	40	90:10
14	*n*-Pr (**3m**)	Me	PMP	39	70:30
15	Ph (**3n**)	Et	PMP	92	99:1
16	Ph (**3o**)	Me	Ph	78	97:3
17[c]	Ph (**3p**)	Me	4-$CF_3C_6H_4$	54	95:5

[a] Determined by HPLC. [b] Reaction was run for 96 h, using di-*tert*-butyl 2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate as the reductant. [c] After 168 h.

presumably via an oxidative cleavage of the hydratopicaldehyde enamine intermediate.[10]

The generality of the methodology is shown in Table 2, using a broad range of aldehydes and amines under optimized conditions. A variety of 2-arylpropionaldehydes can be successfully used with *p*-anisidine as the amine component (entries 1−10). Noteworthy, except in case of thiophene derivative **3e**, all of the products derived from both electron-deficient and electron-rich aromatic substrates were obtained in very good yields (80−96%) and enantiomeric ratios (97:3−99:1). Aliphatic aldehydes can also be employed in the dynamic kinetic resolution (entries 11−14), although with lower enantiomeric ratios. Interestingly, an ethyl—rather than a methyl—substituent in the α-position of the aldehyde is also well tolerated (entry 15). Electronically different anilines (entries 16 and 17) have also been studied. While the enantiomeric ratios remain high, the best yields were obtained using electron-rich *p*-anisidine.

The absolute configuration of amine **3a** was established via oxidative removal of the PMP group.[9] An example for the synthetic utility of amines **3** is shown in eq 6. Upon sequential protection with benzyl chloroformate (CbzCl) and treatment with cerium(IV) ammonium nitrate (CAN), carbamate **6a** was obtained in good yield and with no loss of enantiomeric purity (eq 6).[11]



In summary, we have developed an efficient enantioselective reductive amination of α-branched aldehydes via dynamic kinetic resolution. Our process is broad in scope, and both aromatic and aliphatic aldehydes can be used, although enantiomeric ratios are typically lower with simple aliphatic aldehydes. Currently, our reaction is limited to the use of aromatic amines, but we expect to overcome this limitation in ongoing studies in our laboratory.

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Supporting Information Available: Experimental procedures, compound characterization, NMR spectra, and HPLC traces (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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