

Highly Enantioselective Transfer Hydrogenation of α,β -Unsaturated Ketones

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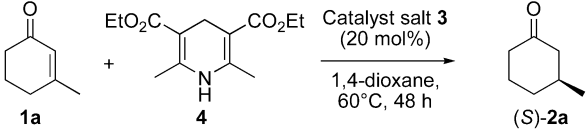
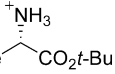
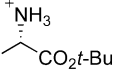
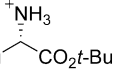
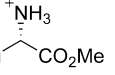
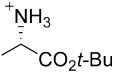
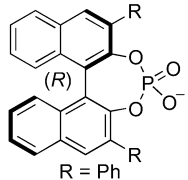
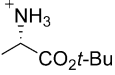
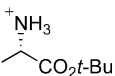
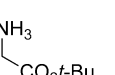
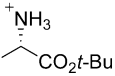
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Recently, asymmetric counteranion directed catalysis (ACDC) has been introduced as a useful strategy for organic synthesis.¹ According to this concept, catalytic reactions that proceed via cationic intermediates can be conducted asymmetrically via the use of a chiral enantiomerically enriched anion incorporated into the catalyst. As an illustration of the concept and proof of principle, we have shown that salts made from an achiral secondary amine and a chiral phosphoric acid can function as highly enantioselective iminium catalysts in the conjugate reduction of α,β -unsaturated aldehydes with Hantzsch esters.² Our new catalysts significantly widened the substrate scope of this reaction by allowing us to reduce simple aliphatic substrates, such as citral, with high enantioselectivity. However, neither these ACDC catalysts nor the previously developed chiral imidazolidinone catalysts gave satisfying yields or enantioselectivities in the conjugate reduction of α,β -unsaturated ketones.³ We have now developed a new class of catalytic salts, in which both the cation and the anion are chiral. In particular, valine ester phosphate salt **3f** proved to be an active catalyst for the transfer hydrogenation of a variety of α,β -unsaturated ketones **1** with commercially available Hantzsch ester **4** to give saturated ketones **2** in excellent enantioselectivities.

As expected, MacMillan imidazolidinium catalysts,⁴ which are highly effective for the iminium catalytic transfer hydrogenation of α,β -unsaturated aldehydes with Hantzsch esters, proved to be much less efficient with ketone substrates.^{5,6} Hypothesizing that primary amine catalysts, due to their reduced steric requirements, might be suitable for the activation of ketones, we studied various salts of α -amino acid esters (**3**, Table 1).⁷ Initially we investigated salts with achiral counteranions, and of those, the trifluoroacetates generally gave the highest conversion in the reduction of 3-methylcyclohex-2-enone (**1a**) to (*S*)-3-methylcyclohexanone (**2a**). While the effect of the amino acid ester α -substituent on the enantioselectivity was not very pronounced, the highest enantiomeric ratio was obtained with the valine derivative (entry 2). In addition, catalysts incorporating the *tert*-butyl ester group gave the best yields and enantiomeric ratios (i.e., compare entries 3 and 4). Encouraged by our previous studies on asymmetric, counteranion directed catalysis, we also investigated chiral binaphthol derived phosphate counteranions.⁸ With phenyl-substituted derivative **3e**, the enantiomeric ratio improved from 77:23 to 87:13. Remarkably, of the many phosphate salts we have studied, the TRIP⁹ counteranion once again gave the highest enantioselectivity (entry 6).^{1,8e,g,h} Moreover, the yield could be significantly increased by running the reaction in ether (entry 7). The chirality present in the amino acid seems to be required as glycine derived catalyst **3g** gave significantly reduced enantioselectivity (entry 8). The phosphoric acid derivative alone (**3h**, (*R*)-TRIP) was much less active than the amino acid ester salts and gave the product in only 40:60 *er* (entry 9). Interestingly, when we used the opposite enantiomeric counteranion in catalyst **3i**, the same enantiomeric product was formed but with much lower enantioselectivity, illustrating a dramatic case of a matched/mismatched catalyst-ion pair combination (entry 10). Valine derivative **3f** was chosen for further studies as it proved superior

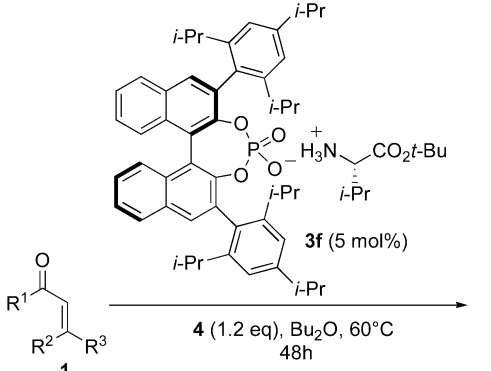
Table 1. Selected Catalyst Screening Results^a

					
entry	catalyst-cation	-anion	cat.	conv. [%] ^b	<i>er</i> ^b
1		CF ₃ COO ⁻	3a	23	75:25
2		CF ₃ COO ⁻	3b	66	77:23
3		CF ₃ COO ⁻	3c	72	76:24
4		CF ₃ COO ⁻	3d	42	64:36
5 ^c			3e	25	87:13
6		R = 2,4,6-(<i>i</i> -Pr) ₃ C ₆ H ₂	3f	14	95:5
7 ^c		R = 2,4,6-(<i>i</i> -Pr) ₃ C ₆ H ₂	3f	81	97:3
8		R = 2,4,6-(<i>i</i> -Pr) ₃ C ₆ H ₂	3g	66	74:26
9 ^c	H ⁺	R = 2,4,6-(<i>i</i> -Pr) ₃ C ₆ H ₂	3h	5	40:60
10 ^c		R = 2,4,6-(<i>i</i> -Pr) ₃ C ₆ H ₂ (<i>S</i>)-Enantiomer	3i	45	58:42

^a For additional studied catalysts, see the Supporting Information.
^b Determined by GC. ^c Reaction in Bu₂O.

in comparison with other amino acid esters, such as *tert*-leucine, with regard to catalytic efficiency, enantioselectivity, and cost. After further optimization of solvent, temperature, substrate concentration, Hantzsch ester structure, and catalyst loading, we identified the following protocol as optimal: Treating the enone (0.33 M) with commercially available Hantzsch ester **4** (1.2 equiv) in the presence of catalytic salt **3f** (5 mol%) at 60 °C in dibutyl ether for 48 h gave the saturated ketones in high yields and enantioselectivities (Table 2).

Because most products are volatile, yields have been determined by using GC or HPLC. However, if the product was isolated (entry

Table 2. Preliminary Scope of the Transfer Hydrogenation


entry	enone	product	yield [%] ^a	er ^{a,b}
1			99	97:3
2	R = Me	2a	99	97:3
3	R = Et	2b	98	98:2
4	R = <i>i</i> -Bu	2c	89	98:2
5	R = <i>i</i> -Pr	2d	94	99:1
6	R = CH ₂ CH ₂ Ph	2e	99 ^c	98:2 ^d
7	R = Ph	2f	99	92:8
8			78 ^e	99:1
9	R = Me	2g	78 ^e	99:1
10	R = Et	2h	71 ^e	98:2
11	R = CH ₂ CH ₂ Ph	2i	68 ^{d,e}	98:2 ^d
12			>99	98:2
13			>99	98:2
14			>99	92:8
15	R = CO ₂ Et	2k	>99	92:8
16	R = Ph	2l	81	85:15

^a Determined by GC. ^b Absolute configuration of **2g** was determined by comparison with a commercial sample, all others were assigned by analogy. ^c Isolated yield. ^d Determined by HPLC. ^e With 10 mol% of catalyst **3f**.

5), chromatographically determined and isolated yields were identical. The method is particularly well suited for cyclohexenones (entries 1–6), in which case the products are generally formed in very high yields and good to excellent enantioselectivities. Cyclopentenones are slightly less reactive but provide the products in equally high enantioselectivities (entries 7–9). Cycloheptenones are also suitable substrates, and 3-methylcyclohept-2-enone (**1j**) gave the desired product **2j** with excellent yield and enantioselectivity (entry 10). Acyclic ketones may be used but gave the products in slightly lower enantioselectivities (entries 11 and 12). Mechanistically, we assume the reaction proceeds via an iminium-phosphate ion pair that may be stabilized by hydrogen bonding interactions. In addition to binding the iminium ion, the phosphate counteranion may also interact with the Hantzsch ester via an additional hydrogen bond. The detailed mechanism and transition

state structure of this new reaction will be investigated in future studies.

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

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