ASYMMETRIC TRANSFER HYDROGENATION OF ENONES VIA COUNTERANION ENHANCED CATALYSIS

Fabian Scharinger, Ádám Márk Pálvölgyi and Katharina Schröder

Institute of Applied Synthetic Chemistry, TU Wien
Getreidemarkt 9/163, 1060 Vienna, Austria
fabian.scharinger@tuwien.ac.at

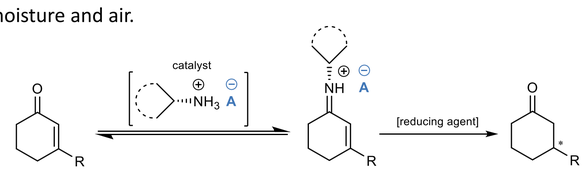
INTRODUCTION

Asymmetric counteranion directed catalysis (ACDC) has emerged as an attractive and useful tool for asymmetric transfer hydrogenations (ATH). In 2006, List and coworkers demonstrated that high levels of asymmetric induction and excellent yields can be obtained in the ATH of ketones using an ion paired salt composed of a chiral amino acid-based cation and a chiral phosphate anion [1]. However, while this concept of double stereoinduction provides a powerful method, it is also associated with high costs and tedious catalyst synthesis. Our research focuses on a novel ion paired catalyst based on natural L-amino acids as main source of chirality in combination with racemic, atropisomeric phosphate as counteranion. This catalytic system, in combination with a Hantzsch ester as hydrogen source for biomimetic transfer hydrogenation, enabled high enantioselectivities and excellent yields for a series of α,β-unsaturated cyclohexenones under mild conditions. Moreover, it is entirely derived from the chiral pool of natural products and could be prepared in a much more straightforward and significantly cheaper way compared to the classical ACDC system.

Organocatalytic ATH

Asymmetric transfer hydrogenation (ATH) is a powerful tool for the reduction of α,β-unsaturated aldehydes or ketones and provides products with high enantioselectivity. Unlike conventional hydrogenation with the use of hydrogen gas, ATH uses small molecules as hydrogen donors. The biomimetic Hantzsch ester (Figure 2) is an excellent reducing agent which is cheap, easy to synthesize and has a direct influence on the enantiodiscrimination [1]. This results in a mild reduction method that can be performed under laboratory conditions.

In general, asymmetric transfer hydrogenations can be carried out via conventional transition metal catalysis or with the emerging concept of organocatalysis. The organocatalytic pathway relies on reactions catalyzed by small organic molecules and provides a unique and booming strategy due to the mild conditions, the absence of expensive and toxic metals and the stability towards moisture and air.



A = achiral acid (example: TFA) → Iminium Catalysis
A = chiral acid (example: (R)-phosphoric acid) → ACDC

Figure 1. LUMO activation of cyclohexenones via iminium catalysis

Over the past years two catalyst types emerged and gave outstanding results in terms of yield and enantiodiscrimination. MacMillan's iminium catalytic approach relies on chiral imidazolidinones for asymmetric induction, in combination with a strong acid in order to generate the chiral ion paired salt (Figure 1) [1]. List and coworkers combined iminium catalysis with a chiral phosphoric acid counteranion (ACDC) to achieve even higher enantioselectivities (ee) via double asymmetric induction [2].

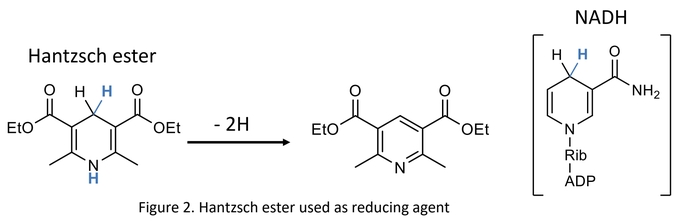


Figure 2. Hantzsch ester used as reducing agent

New concept: Counterion enhanced catalysis

Our new strategy involves natural L-amino acids as main chiral source in combination with atropisomeric, racemic phosphoric acids in order to generate the chiral ion-paired catalyst salt. Additionally a Hantzsch ester is used for transfer hydrogenation. The idea behind this concept is based on chirality transfer from the modified chiral amino acid to the atropisomeric phosphoric acid (Figure 3).

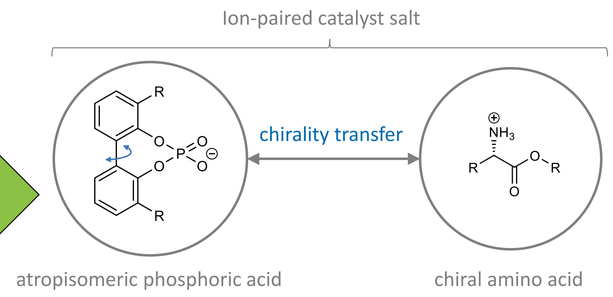


Figure 3. Concept of chirality transfer

This unique approach results in a cheap catalyst system due to the use of a natural derived amino acid and a simple racemic phosphoric acid that can be easily synthesized.
We initially proved our concept by using different acids as counteranions in the ATH reaction (Table 1). Successively, we performed extensive screening of solvents, amino acids, phosphoric acids and Hantzsch esters to established the optimal catalyst components and conditions.

Table 1. Proof of concept, (dioxane, 60 °C, 48 h, 20 mol% cat.)

cation	anion	yield [%]	ee [%]	Δee [%]
		49	54	-
		27	64	10
		13	54	0
	(R)	13	54	0
	(S)	15	54	0

Higher reactivity and ee of flexible diphenyl phosphoric acid was observed compared to achiral trifluoro acetic acid and enantiopure or racemic binaphtyl phosphoric acid.

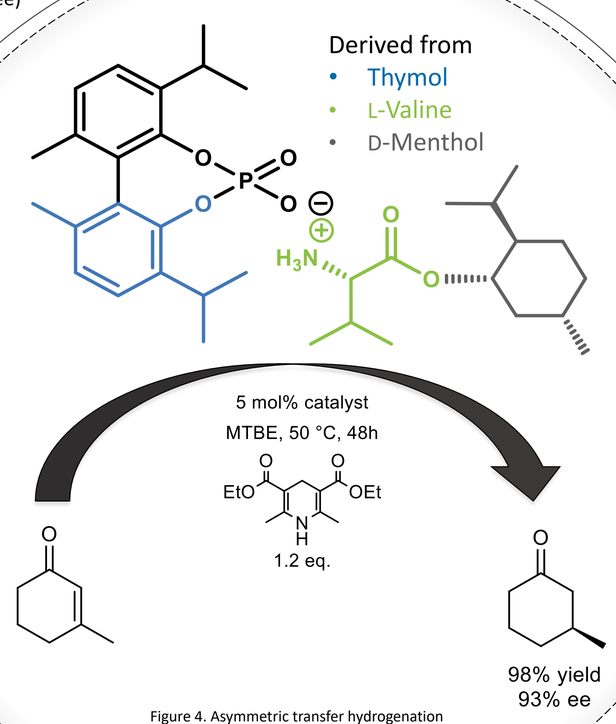


Figure 4. Asymmetric transfer hydrogenation of 3-methylcyclohexenone via counteranion enhanced catalysis

A Solvent screening

Table 2. (60 °C, 48 h, 20 mol% cat.)

solvent	yield [%]	ee [%]
EtOAc	48	67
2-MTHF	60	68
Dioxane	27	64
MTBE	72	74
$CHCl_3$	23	53
Toluene	17	75
BuOAc	41	62
Bu_2O	16	62
H_2O	9	42

B Phosphoric acid screening

Table 3. (MTBE, 60 °C, 48 h, 20 mol% cat.)

cation	anion	yield [%]	ee [%]
L-Valine-tbu	DIPOLP	72	75
	DIPOLP-tbu-p	70	77
	DIPOLP-iPr-m	94	80
	DIPOLP-tbu-m	43	76

C Amino acid screening

Table 4. (MTBE, 60 °C, 48 h, 20 mol% cat.)

cation	anion	yield [%]	ee [%]
L-Valine-tbu	DIPOLP-iPr-m	94	80
L-Leucine-tbu		52	77
L-Isoleucine-tbu		73	72
L-Phenylalanine-tbu		83	60
L-Tertleucine-tbu		91	76
L-Phenylleucine-tbu		55	9

D Amino acid ester screening

Table 5. (MTBE, 60 °C, 48 h, 20 mol% cat.)

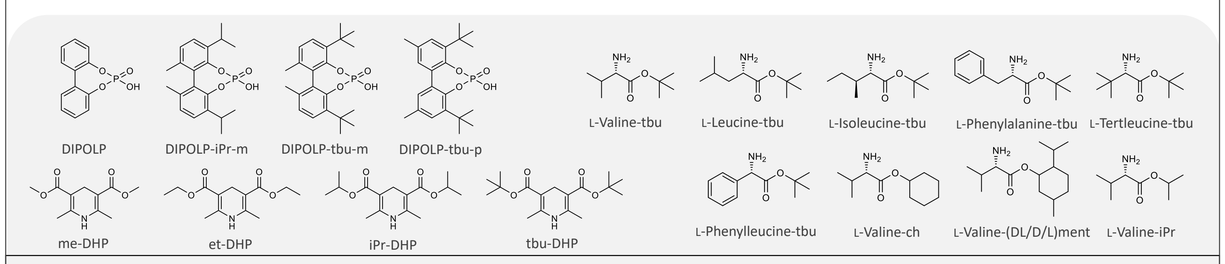
cation	anion	yield [%]	ee [%]
L-Valine-me	DIPOLP	7	32
L-Valine-iPr		56	68
L-Valine-tbu		72	75
L-Valine-Bz		90	36
L-Valine-ch		52	65
L-Valine-(DL)ment		73	81
L-Valine-4tbu-ch		47	67

E Hantzsch ester screening

Table 6. (MTBE, 25 °C, 48 h, 20 mol% cat.)

Hantzsch ester	catalyst	yield [%]	ee [%]
me-DHP		13	83
et-DHP		17	88
tbu-DHP		60	67

Initially, we evaluated different solvents and established solvents with low dielectric constant as best candidates (Table 2, **A**) [3]. Studies on the phosphoric acid gave the ideally substituted phosphoric acid which provided the highest ee and nearly quantitative yield (Table 3, **B**).
Further studies revealed that L-Valine tert-butyl or menthyl esters are most suited for this particular reaction (Table 4 & 5). Eventually, Hantzsch ethyl ester was identified as ideal reducing agent (Table 5).



Catalyst screening

Once the best catalytic system, L-Valine D-menthol ester combined with an isopropyl substituted diphenyl phosphoric acid was identified, the reaction conditions were further optimized. Highest enantioselectivities of up to 95% ee were obtained with the D-menthyl ester at 40 °C (Table 7). Moreover, the catalyst loading could be reduced from 20 mol% to 5 mol% while maintaining the excellent yield and selectivity (Table 8).

To further study scope and limitation of the newly established catalytic system, the substrate pool was widened to investigate the asymmetric transfer hydrogenation of different 3-substituted cyclohexenones in order to reduce them with our optimal catalyst and conditions. Enantioselectivities of more than 80% ee were obtained with all substrates. Given that reaction conditions, *i.e.* catalyst loading or reaction temperature, can still be optimized for these substrates to further improve yield and selectivity, this screening clearly showed the versatility and broad application range of the newly established system.

Table 9. (MTBE, 50 °C, 48 h, 5 mol% cat.)

entry	substrate	yield [%]	ee [%]
7	Me	98[a]	93 (*S*)
8	Et	90[a]	91 (*S*)
9	Pr	55	91 (*S*)
10	Bu	87	90 (*S*)
11	iPr	68	85 (*S*)
12	iBu	60	84 (*S*)
13	Ph	84	80 (*S*)
14		60[b]	90 (*S*)
15	COOEt	41	56 (*S*)

[a]yield determined by GC due to low volatility (rest isolated yields). [b]with 20 mol% cat.

Table 7. (MTBE, 40 °C, 48 h, 20 mol% cat.)

entry	cation	anion	yield [%]	ee [%]	Δee
1	L-Valine-tbu	DIPOLP-iPr-m	72	82	2
2	L-Valine-(DL)ment		97	89	9
3	L-Valine-(D)ment		98	95	15
4	L-Valine-(L)ment		98	86	6

Table 8. Catalyst loading, (MTBE, 48 h)

entry	cation	anion	mol%	conv. [%]	yield [%]	ee [%]
5			10	90[a] 98[b] 99[c]	90[a] 98[b] 99[c]	95[a] 95[b] 94[c]
6			5	79[a] 92[b] 98[c]	79[a] 92[b] 98[c]	95[a] 94[b] 93[c]

[a]at 40 °C. [b]at 45 °C. [c]at 50 °C

Optimization and substrate scope

[1] MacMillan, D. W. C.; Quellet, S. G.; Tuttle, J. B. Organocatalytic Transfer Hydrogenation of Cyclic Enones. *J. Am. Chem. Soc.* **2006**, *128 (39)*, 12662-12663.
[2] List, B.; Quellet, S. G.; Martin, N. J. A. Selective Transfer Hydrogenation of α,β-Unsaturated Ketones. *J. Am. Chem. Soc.* **2006**, *128 (39)*, 13368-13369.
[3] Jacobsen, E. N.; Brak, K. Asymmetric Ion Pair Catalysis. *Angew. Chem. Int. Ed.* **2013**, *52 (2)*, 535.

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