Enantioselective Organocatalysis

Reactions and Experimental Procedures

Edited by
Peter I. Dalko

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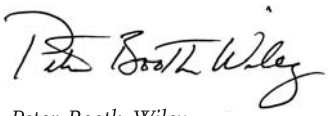

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Preface

Asymmetric synthesis, the ability of controlling the three dimensional structure of the molecular architecture has revolutionized chemistry in the second half of the XXth century. This concept continues to influence the development of basically all fields of science. Amongst the various ways of creating enantiomerically enriched products, catalytic methods (i.e. when chemical transformations are controlled by a small amount of chiral compounds) are considered as the most appealing. It is difficult to conceive that the impressive knowledge accumulated in this field was gained in a relatively short period of time. New concepts and methods are emerging continuously, allowing more selective, economically more appealing and environmentally friendlier transformations. In this context, asymmetric organocatalysis is a «fast lane» of the chemical highway: the progress in the last decade has been simply spectacular.

Performing chemical transformations with a small amount of organic molecules is not a novel concept: enantioselective organocatalytic transformations were developed prior to organometallic ones. The relatively narrow scope of these transformations, however, did not stir particular interest in the past. Nowadays the situation is changing. The renewed interest is due to the serendipitous discovery of a number of selective transformations and also to the realization of the tremendous potential which is inherent to these novel forms of activations, which are also complementary to the existing ones. After the milestone book of Berkessel and Gröger (*Asymmetric Organocatalysis, From Biomimetic Concepts to Applications in Asymmetric Synthesis* VCH, Weinheim, 2005), this multiauthor book is the state of the art of this rapidly evolving field. The chapters are written by organic chemists, leaders at the forefront of research and able to provide an insider's view. I am grateful to all colleagues who agreed to contribute to this project, despite their many other obligations and busy schedules: the result is more than impressive.

It is the aim of this book to provide a concise and comprehensive treatment of this rapidly evolving field, focusing on the preparative aspect of this chemistry. In fact, the use of organocatalytic transformations in a multistep synthesis remains scare. This book wishes to promote the application of these reactions, giving solid synthetic evidence. Additionally, a collection of sample procedures of typical

organocatalytic transformations is given in Appendix I. Despite the spectacular advancement, there is room for further development, and it is the wish of the Editor that this manual should be rapidly updated.

This book is suggested for graduate students as well as all organic chemists.

Paris, January 2007 *Peter I. Dalko*

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List of Abbreviations

Ac	acetyl
AIBN	2,2-azobis(isobutyronitrile)
Alloc	allyloxycarbonyl
ASD	asymmetric desymmetrization
BAMOL	1,1′-biaryl-2,2′-dimethanol
BEMP	2-*tert*-butylimino-2-diethylamino-1,3-dimethyl-perhydro-1,3,2-diazaphosphorine
[bmim]BF_4	1-butyl-3-methylimidazonium tetrafluoroborate
BINOL	1,1-bi(2-naphthol)
Bn	benzyl (CH_2Ph)
Boc	*tert*-butoxycarbonyl
C	conversion
CAN	ceric ammonium nitrate
cat	catalyst
Cbz	benzyloxycarbonyl
CD	cyclodextrin
CPME	cyclopentyl methyl ether
CVAM	catalytic asymmetric vinylogous Mukaiyama (reaction)
CX_n	calix [n]arene
Cy	cyclohexyl
d	day
DA	Diels-Alder (reaction)
DABCO	diazabicyclo[2.2.2]octane
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DEA	direct electrostatic activation
DETA	diethylenetriamide
$(DHQ)_2AQN$	hydroquinine anthraquinone-1,4-diyl diether
$(DHQD)_2AQN$	hydroquinidine anthraquinone-1,4-diyl diether
DIPEA	diisopropylethylamine
DKR	dynamic kinetic resolution
DMAP	4-(dimethylamino)pyridine
DMM	dimethoxymethane
E	electrophile

EDTA	ethylenediaminetetraacetic acid
ee	enantiomeric excess
ent	enantiomeric
er	enantiomeric ratio
EWG	electron withdrawing group
FADH	dihydroflavin adenin dinucleotide
Fmoc	9-fluorenylmethyloxylacrbonyl
GABA	γ-aminobutyric acid
GC	gas chromatography
GLC	gas-liquid chromatography
GTLC	gradient thin layer chromatography
HDA	hetero-Diels-Alder (reaction)
3-HDQ	3-hydroxy quinuclidine
HEPES	4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid (widely used buffering agent to maintain physiological pH)
HFIPA	1,1,1,3,3,3-hexafluoroisopropyl acryl ester
HMPA	hexamethylphosphoramide
HOMO	highest occupied molecular orbital
HPLC	high pressure liquid chromatography
i	iso
ICD	isocupreidine
KR	kinetic resolution
LDA	lithium diisopropylamide
LUMO	lowest unoccupied molecular orbital
MBH	Morita-Baylis-Hillman (reaction)
MIP	molecular imprinted polymer
MS	molecular sieve
MVK	methyl vinyl ketone
n	normal
N/A	not available
NADH	dihydronicotinamide adenine dinucleotide
Nap	naphthyl
NCS	*N*-chlorosuccinimide
NFSI	*N*-fluorobenzenesulfonimide
NHC	*N*-heterocyclic carbenes
NMP	*N*-methylpyrrolidine
NMR	nuclear magnetic resonance
NOBIN	2-amino-2′-hydroxy-1,1′-binaphthyl
Nu	nucleophile
Oxone	$2KHSO_5 \cdot KHSO_4 \cdot K_2 \cdot SO_4$
PBO	*P*-aryl-2-phosphabicyclo[3.3.0]octane
Phe	(*S*)-phenylalanyl
PIP	2-phenyl-2,3-dihydroimidazo[1,2a]pyridine
PIQ	2-phenyl-1,2-dihydroimidazo[1,2a]quinoline
PKR	parallel kinetic resolution

PMHS	polymethylhydrosiloxane
PMP	*p*-methoxyphenyl
PNA	peptide nucleic acid
PNP	*p*-nitrophenyl
PPY	4-(pyrrolidino)pyridine
Pyr	pyridine
RDS	rate-determining step
rec SM	recovered starting material
ROMP	ring opening metathesis polymerisation
rt	room temperature
s	(enantio)selectivity value
sec	secondary
SES	(trimethylsilyl)ethansulfonyl
TADDOL	*trans*-4,5-bis-(diphenyl-hydroxymethyl)-2,2-dimethyl-1,3-dioxolane
TADMAP	3-(2,2-triphenyl-1-acetoxyethyl)-4-dimethylamino)pyridine
TBAF	tetra-*n*-butylammonium fluoride
TBDPS	*tert*-butyldiphenylsilyl
TBS	*tert*-butyldimethylsilyl
TCA	trichloroacetic acid
tert	tertiary
TES	triethylsilyl
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
TIPS	triisopropylsilyl
TLC	tin layer chromatography
TMG	1,1,3,3-tetramethylguanidine
TMP	thymidine monophosphate
TMSCN	trimethylsilyl cyanide
TOF	turnover frequency
TON	turnover number
Troc	2,2,2-trichloroethyl
Trt	trityl (triphenylmethyl)
Ts	tosyl, *p*-toluenesulfonyl
TS	transition state
UNCA	urethane-protected α-amino acid *N*-carboxy anhydride
VAPOL	vaulted biphenantrol
VMA	vinilogous Mukaiyama aldol (reaction)

1
Asymmetric Organocatalysis: A New Stream in Organic Synthesis

Peter I. Dalko

1.1 Introduction

In common with metal complexes and enzymes, small organic molecules may promote chemical transformations. Organocatalysis provides a means of accelerating chemical reactions with a substoichiometric amount of organic molecules, which do not contain a metal element [1, 2].

Despite this rich historical past, the use of small organic molecules as chiral catalysts has only recently been recognized as a valuable addition and/or alternative to existing, well-established, often metal-based methodologies in asymmetric synthesis. Driven both by distinguished scientific interest, which usually accompanies emerging fields, and the recognition of the huge potential of this new area, organocatalysis has finally developed into a practical synthetic paradigm [3–15]. The question must be asked, however, as to why it has taken so long for chemists to appreciate and exploit the potential of small organic molecules as chiral catalysts. Why was not the imagination of the vast majority of the chemical community captured by the perspectives of asymmetric organocatalysis, when metal complex-derived catalysis underwent steady development for enantioselective reactions?

Principally, asymmetric organocatalytic reactions were, for a long time, considered to be inefficient and limited in scope. In parallel, organometallic catalysts provided a flexible ground for all types of reaction, and thus received disproportionate emphasis. Although today the vast majority of reactions in asymmetric catalysis continue to rely on organometallic complexes, this picture is changing, and organic catalysis is becoming an increasingly important segment of organic chemistry, offering a number of advantages over metal-based and bioorganic methods.

Today, reactions can be performed under an aerobic atmosphere, with wet solvents; indeed, the presence of water is often beneficial to the rate and selectivity of the reaction. The operational simplicity and ready availability of these mostly inexpensive bench-stable catalysts – which are incomparably more robust than

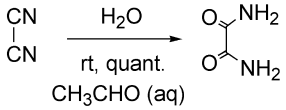
enzymes or other bioorganic catalysts – makes organocatalysis an attractive method for the synthesis of complex structures. Unlike any earlier developed system, organocatalytic reactions provide a rich platform for multicomponent, tandem, or domino-type multistep reactions [16], allowing increases in the structural complexity of products in a highly stereocontrolled manner. In addition, fewer toxicity issues are often associated with organocatalysis, although this applies only when utilizing the more notorious metals. It should also be pointed out that little is currently known regarding the toxicity of many organic catalysts; moreover, there is no risk of metal leakage, and no expensive recovery process is required for waste treatment. Nowadays, increasing numbers of industrial applications are based on asymmetric organocatalytic reactions, and the environmentally friendly, ''green'' aspect of this chemistry – coupled with the sustainability of the catalysts – is considered widely for replacing standard, metal-based reactions [17, 18].

1.2 Historical Background

The history of organocatalytic reactions has a rich past, there being evidence that such catalysis has in the past played a determinant role in the formation of prebiotic key building blocks such as sugars. In this way, the reactions have led to the introduction and widespread use of homochirality in the living word [19]. Enantiomerically enriched amino acids such as L-alanine and L-isovaline, which may be present in up to 15% enantiomeric excess (*ee*) in carbonaceous meteorites, were able to catalyze the aldol-type dimerization of glycolaldehyde, as well as the reaction between glycolaldehyde and formaldehyde producing sugar derivatives. For example, Pizzarello and Weber were able to demonstrate that L-isovaline, which was found in the Murchison meteorite, promotes the self-aldol reaction of glycolaldehyde in water, generating aldol products such as L-threose and D-erythrose with up to $10.7 \pm 1.2\%$ and 4.8 ± 0.9 *ee*, respectively [19]. Proline, the most efficient natural amino acid catalyst in aldol-type condensations is scarcely present in meteorites. Asymmetric photolysis in interstellar clouds may produce optically active proline, however, indicating that proline may also have been transported to Earth [20]. The formation of sugars under prebiotic conditions was amplified in a number of elegant *de-novo* constructions of complex, differentiated carbohydrates by chemical synthesis [21]. It is likely, therefore, that these aldol products were the precursor of complex molecules such as RNA and DNA. Prebiotic RNA most likely played a central role in orchestrating a number of key biochemical transformations necessary for life, in which sugars served as chiral templates [22]. For example, it is considered, that amino acid homochirality in proteins was determined during asymmetric aminoacylation, which is the first step in protein synthesis and thus was critical for the transition from the putative RNA world to the theater of proteins [23]. According to this concept, the se-

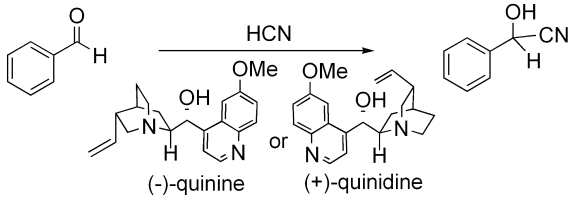
lectivity (L or D) of amino acids was determined in large part by the preestablished homochirality of RNA.

Organic molecules have been used as catalysts from the early age of synthetic chemistry. Indeed, the discovery of the first organocatalytic reaction is attributed to J. von Liebig, who found – accidentally – that dicyan is transformed into oxamide in the presence of an aqueous solution of acetaldehyde (Scheme 1.1). Subsequently, this efficient reaction found industrial application by forming the basis of the Degussa oxamide synthesis.



Scheme 1.1 von Liebig's oxamide synthesis.

Undoubtedly, the discovery of enzymes and enzyme functions had an important impact on the development of asymmetric catalytic reactions. The first asymmetric reaction – a decarboxylative kinetic resolution – was discovered by Pasteur [24], who observed that the organism *Penicillium glauca* destroyed more rapidly one of the enantiomers (*d*) from a racemic solution of ammonium tartrate. Asymmetric decarboxylation reactions were re-examined under non-enzymatic conditions by Georg Breding during the early 1900s. Breding, who had a remarkably wide interdisciplinary interest, was motivated to find the chemical origin of enzyme activity observed in living organisms. In his early experiments he showed enantiomerical enrichment in the thermal decarboxylation of optically active camphorcarboxylic acid in *d* and *l* limonenes, respectively [25]. As an extension of this work he studied this decarboxylation reaction in the presence of chiral alkaloids, such as nicotine or quinidine, and established the basic kinetic equations of this kinetic resolution [26]. The first asymmetric C–C bond forming reaction is attributed also to his name. This milestone achievement is related to Rosenthaler's work, who was able to prepare mandelonitrile by the addition of HCN to benzaldehyde in the presence of an isolated enzyme, emulsin [27]. Breding was also able to perform this reaction in the presence of alkaloids as catalysts, such as the pseudoenantiomeric quinine and quinidine (Scheme 1.2) [28]. It should be noted



Scheme 1.2

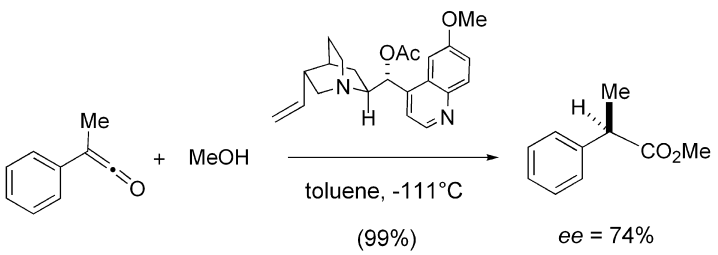
that, although these studies were considered as conceptually groundbreaking, the enantioselectivity of the reaction was less than 10%.

Although catalytic transformations gained increasing importance after the First World War, asymmetric reactions were considered at the time to be an academic curiosity. Of note, the determination of enantioselectivity was hampered by a lack of methods to achieve not only efficient purification but also reliable analyses. Hence, the presence of a chiral impurity – which often arose from the catalyst – spoiled the determination of the correct, optical rotation-based *ee*-values.

Nitrogen-containing natural products such as alkaloids (in particular strychnine, brucine and cinchona alkaloids) and amino acids (including short oligopeptides) were among the first organic catalysts to be tested. The acylative kinetic resolution of racemic secondary alcohols was initiated during the late 1920s by Vavon and Peignier in France [29], and, independently, also by Wegler in Germany [30]. These authors showed that brucine and strychnine were able to induce enantiomeric enrichment either in the esterification of *meso* dicarboxylic acids or in the kinetic resolution of secondary alcohols, albeit with low *ee*-values.

Also, Wolfgang Langenbeck's contribution should be remembered, who developed reactions, which were promoted by simple amino acids, or, by small oligopeptides [31]. A major part of these studies were dedicated to reactions which emulated enzyme functions by using simple amino acids or small peptides. Not surprisingly, enamine-type reactions were among the first to be discovered. This finding was initiated by the studies of Dakin who, in 1909, noted that in a Knoevenagel-type condensation between aldehydes and carboxylic acids or esters with active methylene groups, the amine catalysts could be mediated by amino acids [32]. The reaction was extended to aldol and related transformations, and studied systematically from the early 1930s onwards with notable success, essentially with non-asymmetric systems.

The reinvestigation of Breding's asymmetric cyanohydrin synthesis by Prelog during the mid-1950s [33] undoubtedly promoted the concept of asymmetric synthesis, and led the way to more efficient reactions. The advent of synthetically useful levels of enantioselectivity can be dated to the late 1950s, when Pracejus reported that methyl phenyl ketene could be converted to (−)-α-phenyl methylpropionate in 74% *ee* by using *O*-acetylquinine as catalyst [34].



Scheme 1.3 Pracejus' enantioselective ester synthesis from phenyl methyl ketene.