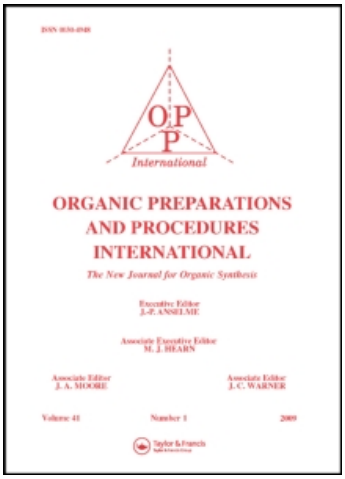

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ASYMMETRIC CATALYSIS OF ACYL TRANSFER BY LEWIS ACIDS AND NUCLEOPHILES. A REVIEW

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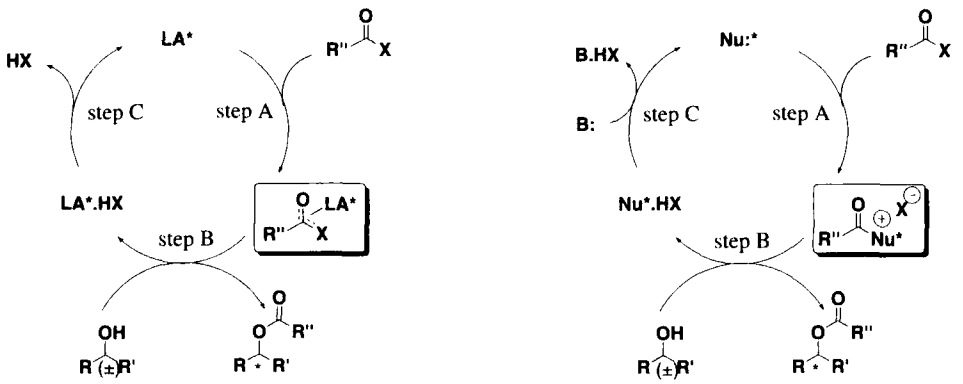
INTRODUCTION

Acyl transfer reactions (*e. g.* esterification of alcohols by acyl donors) are catalysed by Brønsted acids, Lewis acids, bases, and nucleophiles *via* mechanisms that have been extensively studied.[1-3] These modes of catalysis, and synergistic combinations thereof, also account for the highly efficient and selective catalysis of acyl transfer by hydrolase enzymes.[4-6] Despite this wealth of knowledge about acyl transfer catalysis, synthetic chemists have until recently relied almost exclusively on hydrolase enzymes (*e. g.* amidases, proteases, lipases, and esterases) as catalysts for asymmetric acyl transfer processes.[7] Such processes include kinetic resolution (KR)[8] of secondary alcohols,[9] and asymmetric desymmetrisation (AD)[10] of *meso*-diols and *meso*-anhydrides.[11] However, the development of non-enzymatic catalysts for asymmetric acyl transfer has seen growing attention in the last few years and some promising families of chiral catalysts have been developed.[12,13] Work has concentrated in two areas: the development of chiral Lewis acid and chiral nucleophilic catalysts (*Scheme 1*).



(a) *Lewis acid catalysed* (b) *nucleophile catalysed*

Scheme 1

Although the catalytic cycles depicted in Scheme 1 refer to KR of a secondary alcohol, analogous cycles can be constructed for other KR and AD processes. However, it is important to recognise that the stereo-differentiating step (SDS) for these processes may differ. For example, in the case of

KR of a secondary alcohol using a chiral nucleophilic catalyst [*Scheme 1*, (b)] the SDS is the acylation of the enantiomeric alcohols by the acyliminium salt (step B). Similarly, in the case of AD of a *meso*-diol the SDS is the acylation of the enantiotopic hydroxyl groups by the acyliminium salt (*cf.* step B). However, in the case of AD of a *meso*-anhydride with an achiral alcohol, either the formation of diastereomeric acyliminium salts from the enantiotopic carbonyl groups (*cf.* step A), or the acylation of the alcohol by the diastereomeric acyliminium salts (*cf.* step B), may constitute the SDS. These differences are obviously important for the design of chiral catalysts and for the interpretation of selectivity data.

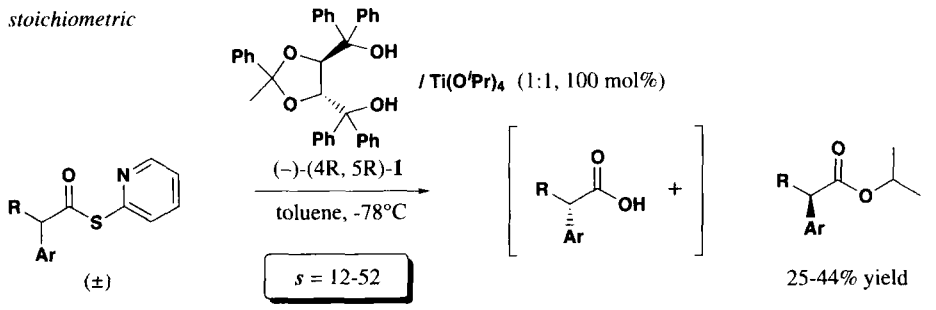
In this review, we endeavour to provide a comprehensive account of non-enzymatic asymmetric acyl transfer using chiral Lewis acids and chiral nucleophiles focusing particularly on catalytic processes, potentially catalytic processes, and recent developments.[14] The review concludes with a brief appraisal of the relative merits of the important methods developed to date and the prospects for the evolution of these into practical and versatile protocols for asymmetric synthesis.

I. CHIRAL LEWIS ACID CATALYSIS

The effectiveness of Lewis acids (*e. g.* $ZnCl_2$) as catalysts for the esterification of hindered alcohols with anhydrides and acid chlorides has been known since the 1930's.[15,16] Since then, a plethora of Lewis acids have been described as effective catalysts for the acylation of alcohols, not only with powerful acyl donors such as anhydrides and acid chlorides, but also with carboxylic acids and their esters (i.e. by transesterification).[17] These include: $BF_3{\cdot}Et_2O$,[18,19] $AlCl_3$,[20] $FeCl_3$,[21] $Ti(OR)_4$,[22] $TMSCl$,[23-25] $CoCl_2$,[26,27] R_2SnO,[28] R_2SnCl_2,[29] distannoxanes,[30,31] $TiCl_4/AgClO_4$,[32-36] $Sn(OTf)_2$,[34] $Sc(OTf)_3$,[37-39] $La(O^iPr)_3$,[40] $TiCl(OTf)_3$,[41] $Sc(NTf_2)_3$,[42] $Cp^*_2Sm(THF)_2$,[43] $Ln(OTf)_3$,[39,44] $TMSOTf$,[45,46] alkali-metal alkoxide clusters,[47,48] $TaCl_5$,[49] $In(OTf)_3$,[50] $Cu(OTf)_2$,[51] and $Y_5(O^iPr)_{13}O$.[52] Additionally, Lewis acid/amine combinations $MgBr_2/NR_3$[53] and $Sc(OTf)_3$/DMAP,[54,55] constitute powerful acylation systems. However, the use of chirally modified Lewis acids for asymmetric acyl transfer has, surprisingly, not been widely explored.

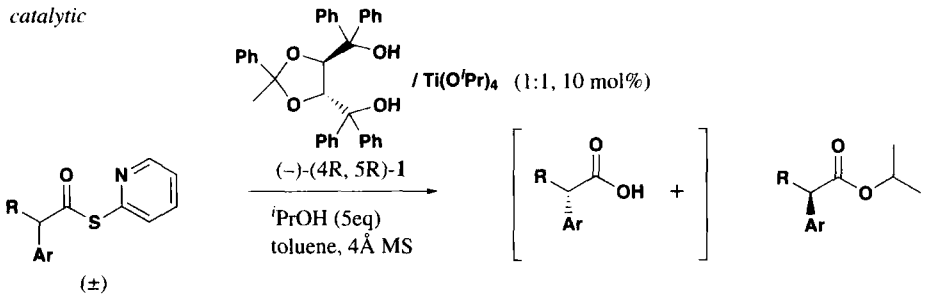
Narasaka reported the first example of a chiral Lewis acid-catalysed acylation in 1989.[56] He investigated the use of a chiral Lewis acid prepared from a 1:1 mixture of $Ti(O^iPr)_4$ with (–)-α,α,α',α'-tetraphenyl-2-methyl-2-phenyl-1,3-dioxolane-4,5-dimethanol (TADDOL-**1**) for the KR of α-aryl propionic(2-pyridinethiol) esters. Initial studies showed that the 2-pyridinethiol esters reacted with a stoichiometric quantity of the chiral Ti-TADDOLate to yield isopropyl esters with high selectivities[57] (*s* = 12-52) and in reasonable yields (25-44%) (*Scheme 2*). Modification of the conditions by the inclusion of ^iPrOH (5 eq) and 4Å molecular sieves (MS) enabled a catalytic reaction, requiring only 10 mol% of the Ti-TADDOLate. These optimised catalytic conditions gave selectivities (*s* = 26-42) and yields (19-41%) comparable to the stoichiometric system (*Table 1*).

In 1993, Fujisawa used a chiral Lewis acid prepared from a 1:1 mixture of Et_2Zn with (–)-cinchonidine (**2**) for the AD of a series of *meso*-cyclic anhydrides with MeOH.[58] The procedure involved the use of 140 mol% of this Lewis acid complex and MeOH (1.4 eq) at 0° in THF and



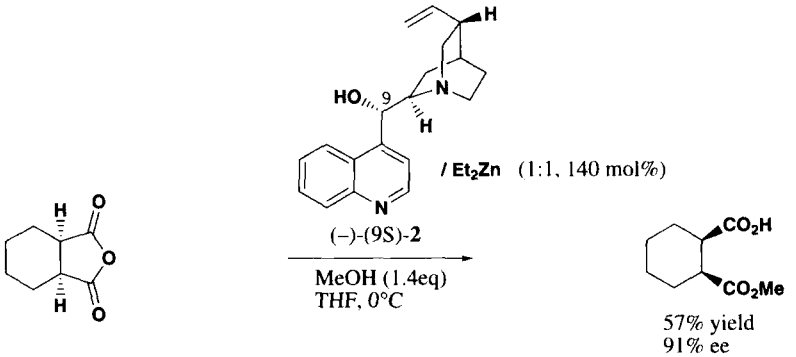
Scheme 2

Table 1 Narasaka's KR of α-Aryl Propionic Esters with a Catalytic Ti-TADDOLate.



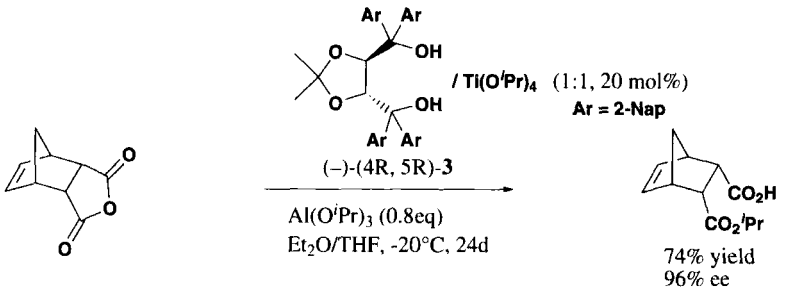
Entry	R	Ar	T (°C)	Yield$_E$ (%)	*s*
1	Et	Ph	-78	35	39
2	Me	Ph	-78	41	29
3	^{i}Pr	Ph	-45	22	42
4	^{i}Pr	4-ClC$_6$H$_4$	-45	19	26
5	^{t}Bu	Ph	-78	39	38

afforded the methyl hemi-ester of *e. g. cis*-1,2-cyclohexanedicarboxylic anhydride in 91% enantiomeric excess (ee) and 57% yield (*Scheme 3*). However, the enantioselectivities for other anhydrides were less impressive (33-52% ee).



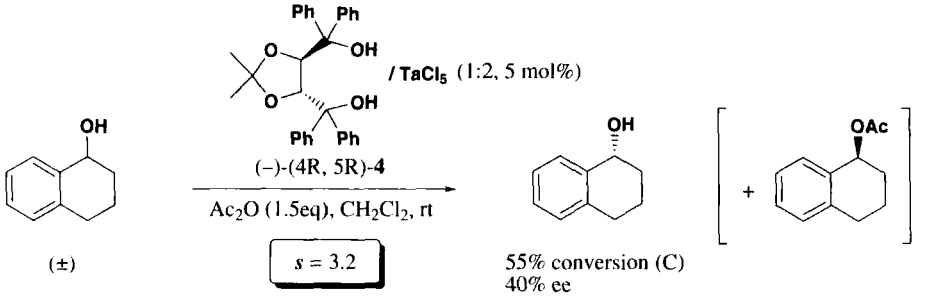
Scheme 3

In 1995, Seebach used chiral Lewis acids prepared from 1:1 mixtures of $Ti(O^iPr)_4$ with various TADDOLs for the AD of an analogous series of *meso*-cyclic anhydrides in Et_2O/THF at –30°.[59] Although greater than stoichiometric quantities of the Ti-TADDOLates (120 mol%) were employed, the isopropyl hemi-esters were formed with excellent enantioselectivities (90-98% ee) and yields (63-92%) for all anhydrides reported. However, the reactions were very slow, requiring 7 days for completion. Subsequently, Seebach reported that a polymer-bound Ti-TADDOLate Lewis acid gave comparable yields and selectivities in a heterogeneous reaction but required even longer reaction times.[60] The homogeneous process has recently also been rendered catalytic.[61] Thus, by employing just 10-20 mol% of the Ti-TADDOLate derived from (–)-α,α,α',α'-tetra(2-naphthyl)-2,2-dimethyl-1,3-dioxolane-4,5-dimethanol (TADDOL-**3**) in conjunction with $Al(O^iPr)_3$ (0.8-0.9 eq) at –20° over ~24 days, excellent enantioselectivities (52-96% ee) and high yields (74-88%) were obtained using four representative *meso*-anhydrides (*e. g. Scheme 4*).



Scheme 4

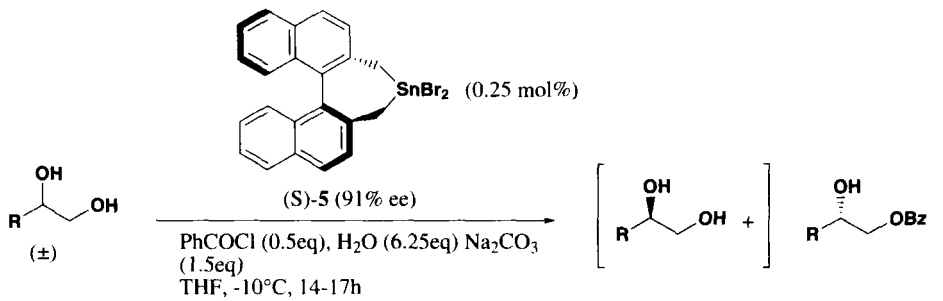
In 1998, Chandrasekhar investigated the use of chiral Lewis acids prepared from 1:1 or 2:1 mixtures of $TaCl_5$ with (–)-α,α,α',α'-tetraphenyl-2,2-dimethyl-1,3-dioxolane-4,5-dimethanol (TADDOL-**4**) or α,α-diphenyl-(R)-prolinol for the KR of a series of secondary alcohols.[49] The study arose following his finding that secondary alcohols could be acylated in high yield using $TaCl_5$ (10 mol%) and Ac_2O (1.5 eq) in CH_2Cl_2 at room temperature (rt). However, efficient KR was not achieved. The three alcohols reported gave low selectivities (s = 1-3.2) with both ligand systems, the best result being obtained with the Ta-TADDOLate (1:2, 5 mol%) and 1,2,3,4-tetrahydronaphthalen-1-ol (*Scheme 5*).



Scheme 5

Most recently, Matsumura has described a catalytic KR of 1,2-diols using an (S)-1,1'-binaphthalene (BINAP)-based organotindibromide (**5**, 0.25 mol%) in conjunction with BzCl (0.5 eq).[62,63] However, in this reaction the tin complex does not act as a Lewis acid but rather allows diastereoselective stannylene acetal formation and subsequent selective benzoylation. Five 1,2-diols were investigated giving moderate to good selectivities (s = 3.2-22.4), although it should be noted that the selectivities were corrected to allow for the fact that the catalyst was of just 91% ee (*Table 2*). This approach to diol KR was pioneered by Mukaiyama, who in 1984 performed efficient AD of *meso*-1,3-diols by acylation with BzCl following diastereoselective formation of a chiral stannylene acetal [obtained using (methylcyclopentadienyl)tin(II)chloride and an (S)-proline-derived diamine].[64] Catalytic stannylene acetal formation, which is key to the new procedure, was developed by Matsumura in 1998.[65]

Table 2 Matsumura's KR of 1,2 Diols with a Catalytic BINAP-Sn Complex.



Entry	R	$Yield_E$ (%)	$\%ee_E$	s
1	1-Nap	41	72	10.0
2	2-Nap	25	64	5.6
3	Ph	38	86	22.4
4	$Me(CH_2)_9$	5.2	59	5.2
5	Et	3.2	44	3.2

From the foregoing it is clear that important progress has been made towards the development of chiral Lewis acid catalysis for asymmetric acylation. However, although the Ti-TADDOLate complexes that have proved most successful so far are readily prepared from optically pure and inexpensive tartaric acids, it is probably true to say that none of the above procedures currently offers sufficient versatility and selectivity to encourage their widespread use by synthetic chemists. A major challenge in this area is achieving turnover in the face of product inhibition because the Lewis basicity of the product ester generally exceeds that of the acyl donor. It seems likely that the next few years will see further endeavours in this area, with expansion of the repertoire of metals employed, hopefully with attendant increases in selectivity and efficiency.

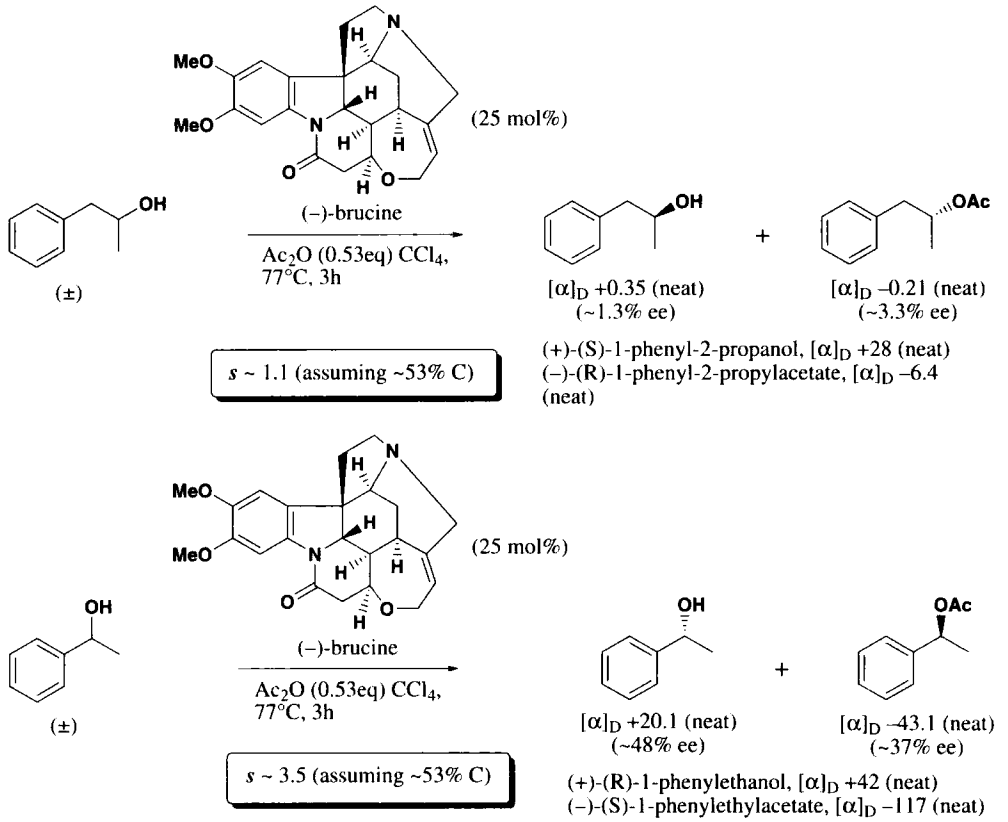
II. CHIRAL NUCLEOPHILE CATALYSIS

The accelerating influence of tertiary amines on acyl transfer reactions has been known since the late 1800's (*e. g.* Einhorn acylation using pyridine/Ac_2O)[66] but the first discussions of the phenomenon in terms of contributions from nucleophilic [*Scheme 1*, (b)] and general base catalysis appeared in the 1950's.[2,67,68] The definitive evidence for the involvement of nucleophilic catalysis in the acylation of alcohols with Ac_2O/pyridine came in 1970 with Fersht and Jencks' use of stopped-flow techniques to record the UV spectrum of the intermediate acetylpyridinium salt in water.[69-71] Subsequently, a number of highly nucleophilic tertiary amines [*e. g.* 4-(dimethylamino)pyridine (DMAP),[72,73] its congeners,[74] including polymer-bound variants,[75-77] and 1,4-diazabicyclo[2.2.2]octane (DABCO)[78-80]] have found prominence for the acylation of sterically hindered alcohols using acid chlorides and anhydrides (and for many related transformations).[74,81-84] Other tertiary amines [*e. g.* 1,2,2,6,6-pentamethylpiperidine (PMP)] have been employed for the selective acylation of primary alcohols in the presence of secondary/tertiary alcohols using acid chlorides and ketenes.[85,86] Additionally, phosphines (*e. g.* Bu_3P)[87,88] and iminophosphoranes [*e. g.* $P(MeNCH_2CH_2)_3N$][89,90] are potent and/or selective promotors of acyl transfer by nucleophilic catalysis.

In the light of the foregoing, it is perhaps not surprising that attempts to effect asymmetric acyl transfer by employing optically active tertiary amines can be traced back to the 1930's. In a pioneering series of papers Wegler reported the partial KR of a series of alkyl aryl carbinols with either Ac_2O or BzCl in the presence of stoichiometric/catalytic amounts of brucine, strychnine, and other chiral tertiary amines.[91-94] In all reactions reported, which were performed in refluxing CCl_4, the product esters and the recovered alcohols were shown to rotate the plane of polarised light. Unfortunately, optical purities of the products were not determined.

Almost thirty years later, Bird reinvestigated these results and verified that reactions of both Ac_2O and BzCl with various secondary alcohols in the presence of brucine, strychnine, *O*-Ac-cinchonine, *O*-Ac-cinchonidine, and *O*-Ac-quinine led to optically active products.[95] Bird also failed to quantify the optical purities of the products. However, on the basis of both his own and Wegler's results, Bird did rationalise the *sense* of asymmetric induction as a function of the configuration and structure of the alkaloid employed. To do this, he postulated that an acyliminium salt was the active chiral acylating agent in these reactions and that steric factors dictated its conformation and subsequent diastereomeric interaction with the enantiomers of the relevant secondary alcohol. Although it is difficult to follow the details of Bird's reasoning, his approach was undoubtedly perceptive and constituted a valiant effort to understand the origin of asymmetric induction in these reactions.

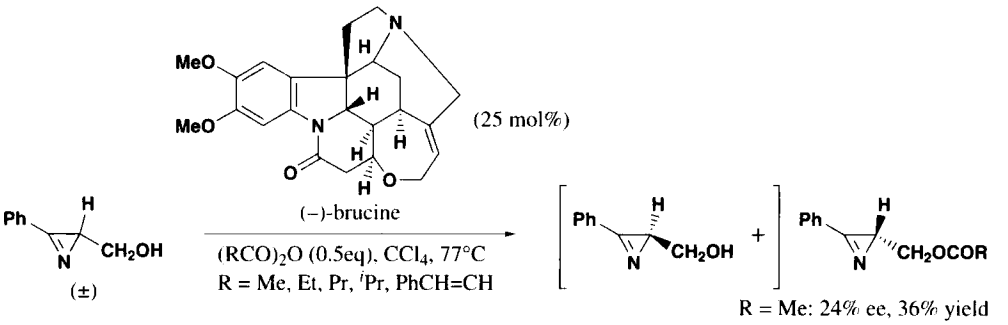
Re-examination of some of the optical rotation data provided by Wegler and Bird (with the aid of recent values for the specific rotations of enantiomerically pure materials)[96] suggests that although asymmetric induction in most of their reactions was almost negligible, [*e. g.* Bird's KR of 1-phenyl-2-propanol with Ac_2O/(–)-brucine, *Scheme 6*][95] one of Wegler's KR's of 1-phenylethanol with Ac_2O/(–)-brucine gave significant levels of induction (s = 3.2-3.9) (*Scheme 6*).[92,97]



Scheme 6

Subsequent to these pioneering studies, brucine, various cinchona alkaloids,[98] and other readily available homochiral tertiary amines have been assayed as nucleophilic catalysts for acylative KR and AD with varying degrees of success.

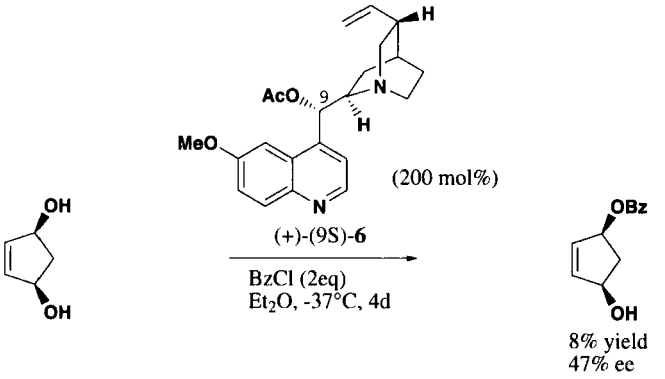
In 1978, Heimgartner used (–)-brucine (25 mol%) in conjunction with various achiral anhydrides (0.5 eq) in CCl_4 at rt to effect acylative KR of 3-phenyl-2H-azirine.[99] The only product ester for which the optical purity was determined was the acetate (24% ee, 36% yield) (*Scheme 7*).



Scheme 7

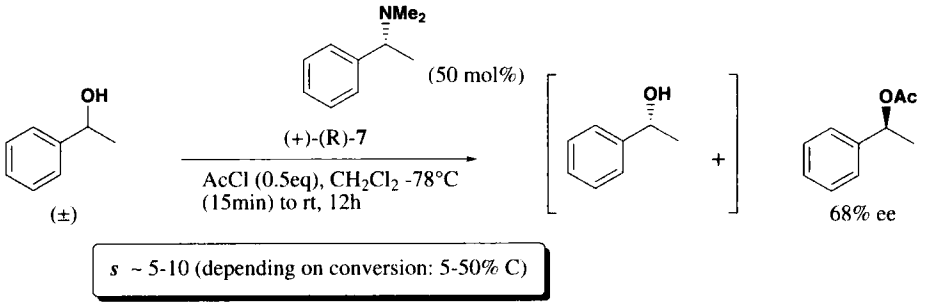
In the same year, Nakamura reported a pioneering study of the KR of 1-phenylethanol with Ac_2O using polymer-bound cinchona alkaloids as catalysts.[100] However, under essentially the same conditions as employed by Wegler, the maximum optical purity of the acetate obtained was just 1.13% ee.

In 1985, Duhamel found that (+)-*O*-Ac-quinidine (**6**, 200 mol%) was the best of a series of chiral tertiary amines screened to effect AD of *cis*-2-cyclopenten-1,4-diol (a *meso*-diol) with BzCl (2 eq) in Et_2O at –37°.[101] However, the product mono-acetate was obtained in a moderate 47% ee and just 8% yield after 4 days (*Scheme 8*).



Scheme 8

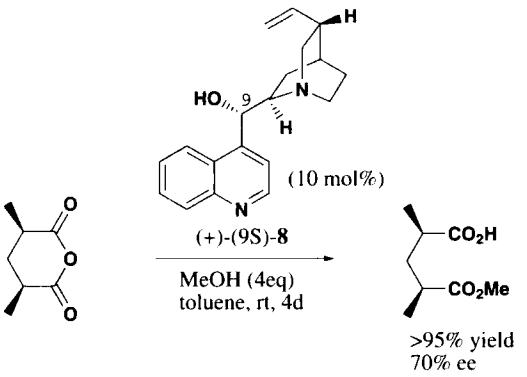
In 1989, Horner reported an extensive study on the ability of various chiral tertiary amines to effect KR of a series of secondary alcohols under a wide variety of conditions (different solvents, temperatures and stoichiometries).[102] The study essentially extended the work of Wegler and Bird to non-alkaloid 'catalysts'. However, although the optical purity of the products was determined on this occasion, no attempt was apparently made to correlate the new results with the original ones. The best result involved the KR of 1-phenylethanol using (+)-(R)-*N,N*-dimethyl-1-phenylethylamine (**7**, 50 mol%) with AcCl (0.5 eq) in CH_2Cl_2 from –78° (15 min) to rt over 12h to give (S)-1-phenylethylacetate in 68% ee and unspecified yield (*Scheme 9*). Vedejs, however, has recently reported that he was unable to reproduce this result, obtaining 1-phenylethylacetate in just 6% ee and 9% yield under the published conditions.[103] Additionally, Potapov has made an extensive study of the use of (–)-(S)-*N,N*-dimethyl-1-phenylethylamine (ent-**7**) for KR of 1-phenylethanol[104] and related alkyl aryl carbinols with Ac_2O (0.5 eq) in benzene and reported that the optical purities of the acetate products never exceeded 2.7% ee.[105] Even by employing alternative achiral anhydrides [$(CF_3CO)_2O$, $(EtCO)_2O$, Bz_2O, succinic anhydride, and phthalic anhydride], optical purities did not exceed 12% ee.[106,107] Poor KR was also achieved using ent-**7** for the acetalization-acetylation of CCl_3CHO with ROH-Ac_2O (R = Me, Et, Pr, ^{i}Pr, Bu, ^{t}Bu; 10.0-19.8% ee).[108] Potapov also reported that (–)-nicotine could effect KR of α-phenyl propanoic acid with MeOH, EtOH, and NH_2OH in the presence of *N,N'*-dicyclohexylcarbodiimide (DCC), but the levels of induction were disappointing (0.5-1.5% ee).[109]



Scheme 9

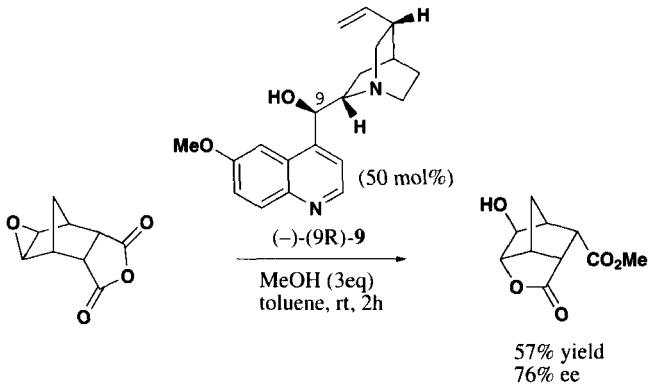
There have also been a number of studies pertaining to the AD by methanolysis of cyclic *meso*-anhydrides in the presence of cinchona alkaloids.

In 1985, Oda reported that (+)-cinchonine (**8**, 10 mol%) was the best of several cinchona alkaloids screened for AD of a series of *meso*-cyclic anhydrides with MeOH (4 eq) in toluene at rt.[110,111] The best result was obtained using *cis*-2,4-dimethylglutaric anhydride, which afforded the methyl hemi-ester in 70% ee and ≥95% yield after 4 days (*Scheme 10*). On the basis of an observed deuterium isotope effect (k_H/k_D) of ~2.3 (MeOH vs MeOD), Oda argued that the mechanism of this reaction involved general base and not nucleophilic catalysis.



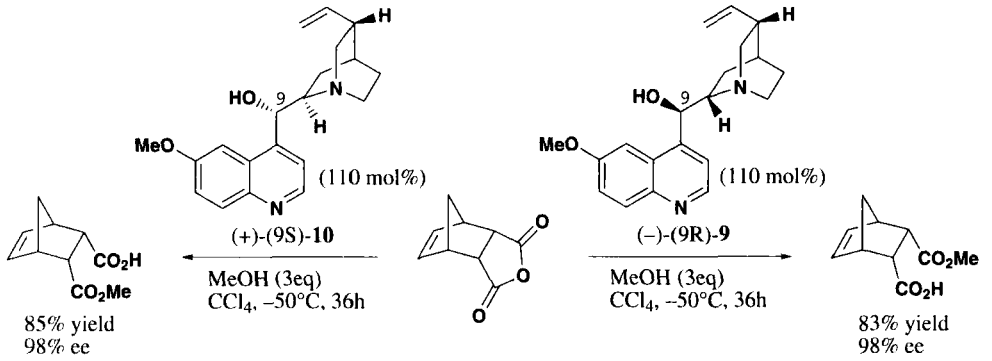
Scheme 10

In 1988, Aitken reported that (–)-quinine (**9**, 50 mol%) was the best of a series of cinchona alkaloids screened for AD of various bridged *meso*-tricyclic anhydrides with MeOH (3 eq) in toluene at rt.[112,113] The best results were obtained using the *exo*-epoxide of the *endo*-Diels-Alder adduct of cyclopentadiene and maleic anhydride. This gave the desymmetrised product in 76% ee and 57% yield after 2h (*Scheme 11*). A single recrystallisation with (–)-quinine was reported to furnish the product in ≥99% ee.



Scheme 11

In 1999, Bolm built upon the findings of Oda and Aitken to develop a highly enantioselective methanolysis of a series of cyclic *meso*-anhydrides.[114] Using the quasi-enantiomeric cinchona alkaloids (–)-quinine (**9**, 110 mol%) or (+)-quinidine (**10**, 110 mol%) with MeOH (3 eq) in CCl_4 at –50° for 36h, enantiomeric desymmetrised methyl hemi-esters could be obtained in 93-98% ee and 69-99% yields (*e. g. Scheme 12*).

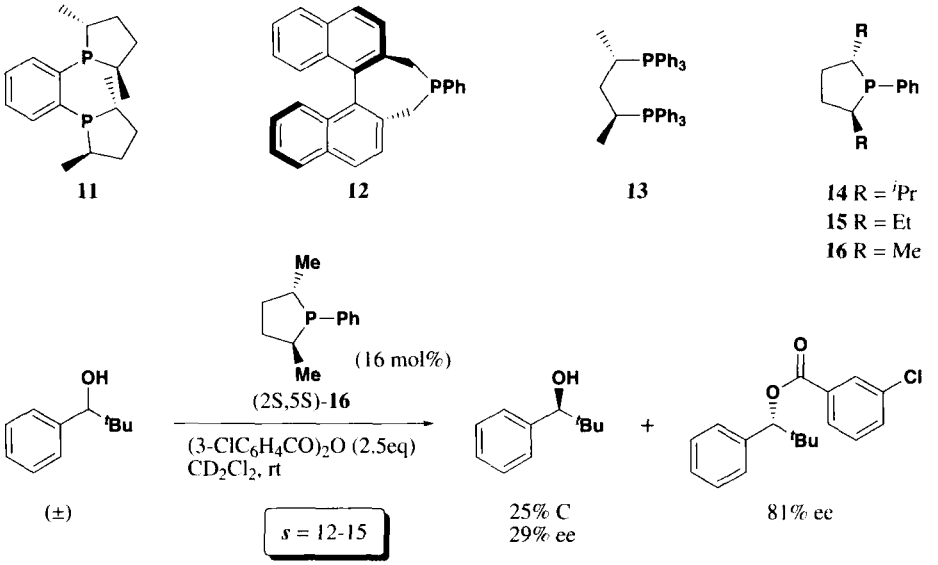


Scheme 12

Up until 1996, the aforementioned studies using 'off-the-shelf' chiral tertiary amines represented the state-of-the-art for non-enzymatic KR and AD processes. However, as the result of systematic studies by a number of groups on *designed* nucleophilic catalysts, dramatic advances have been made in this area over the last four years. The remainder of this review will survey the work of each of these groups, ordered chronologically according to date of their first relevant publication.

In 1996, Vedejs reported an investigation into the use of six C_2-symmetric chiral phosphines: **11-16** (16 mol%) for the AD of three *meso*-diols [*cis*-cyclopentane-1,2-diol, *cis*-cyclohexane-1,2-diol, and *meso*-hydrobenzoin] using Ac_2O or Bz_2O (1.5 eq) in CH_2Cl_2 at rt.[103] Phosphine **16** was

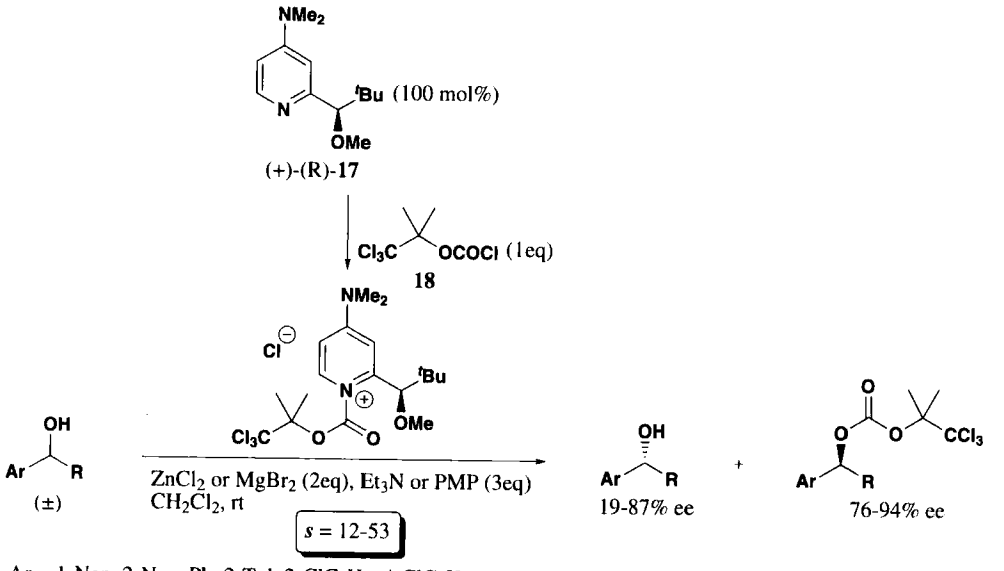
found to be the most selective catalyst for all three diols [s = 3.2 (Ac_2O), 4.3-5.1 (Ac_2O), and 5.5 (Bz_2O), respectively]. Switching to alkyl aryl carbinols as substrates and employing (3-$ClC_6H_4CO)_2O$ (2.5 eq) as acylating agent to enhance rates, phosphine **16** (16 mol%) gave selectivities as high as s = 12-15 (*e. g. Scheme 13*).



Scheme 13

Later in 1996, Vedejs reported on the first chiral DMAP derivative **17** (*Scheme 14*).[115] Unfortunately, this chiral DMAP derivative needed to be employed stoichiometrically in the presence of a Lewis acid and a base to effect acylation. Thus, DMAP **17** (100 mol%) was first pre-mixed with commercially available chloroformate **18** (1 eq), then on addition of the base (Et_3N or PMP, 3 eq) and Lewis acid ($MgBr_2$ or $ZnCl_2$, 2 eq) acyl transfer occurred. Alkyl aryl carbinols were used as substrates and selectivities in the range s = 12-53 were attained (*Scheme 14*). The highest selectivity, s = 53, corresponded to the KR of 1-(2-tolyl)ethanol using $ZnCl_2$ and PMP. Attempts to obtain catalytic turnover have so far apparently been unsuccessful.

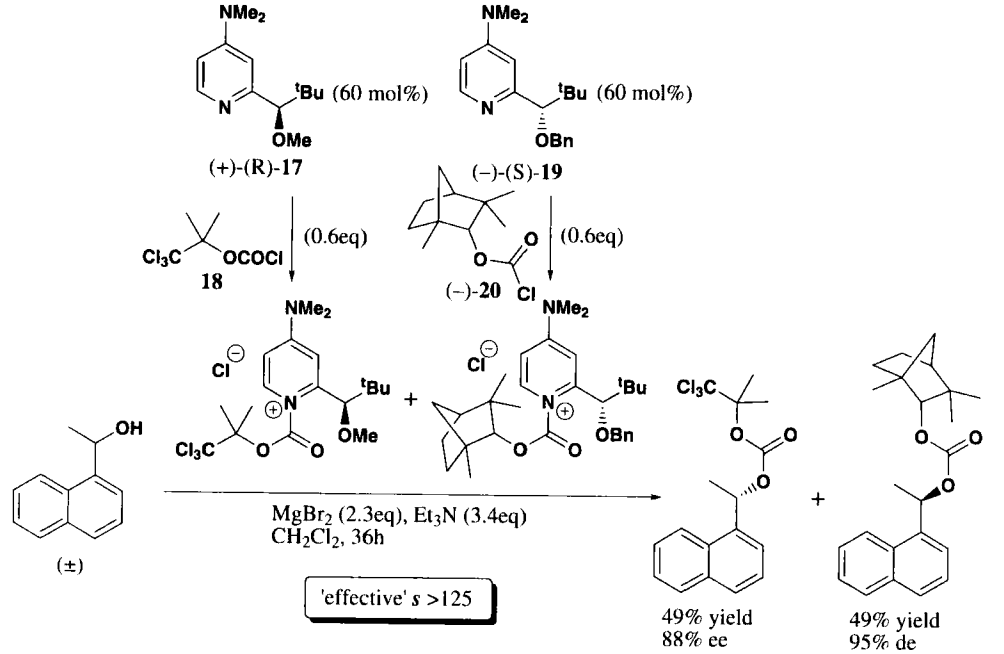
Subsequently, Vedejs used parallel KR (PKR)[116] to dramatically improve the enantiomeric purity of products formed in resolutions using chiral DMAP **17** and its pseudo-enantiomer **19** (*Scheme 15*).[117,118] The PKR experiment involves running two concomitant KR's in one-pot. While one reaction converts one enantiomer of the substrate to one type of product, the second reaction converts the other enantiomer to a different product. This technique relies on ensuring that the two reactions have essentially the same rate, so as to maintain the relative concentrations of the two enantiomers of the substrate approximately equal. Clearly, the two reactions must have opposite stereoselectivities. The reaction studied by Vedejs used pre-formed 'quasi'-enantiomeric acyl pyridinium salts obtained from DMAPs (R)-**17** and (S)-**19** with chloroformate **18** and fenchyl chloroformate [(–)-**20**], respectively.



Ar = 1-Nap, 2-Nap, Ph, 2-Tol, 2-ClC_6H_4, 4-ClC_6H_4
R = Me, Et

Scheme 14

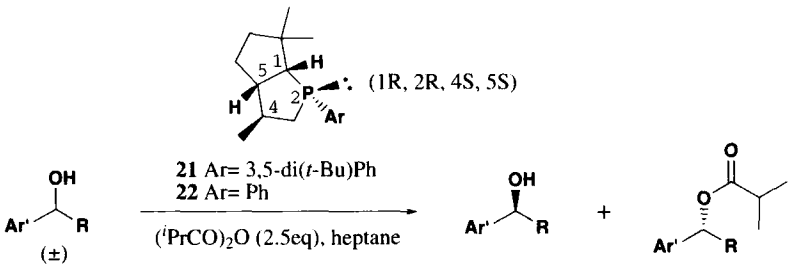
(*Scheme 15*). For the example shown below standard KR using either 'catalyst' gave s = 41-42. A standard KR would need to have operated at $s \geq 125$ to allow 49% recovery of one enantiomer with 95% ee as achieved in this PKR experiment (*Scheme 15*).



Scheme 15

In a continuation of his chiral phosphine studies, Vedejs has recently disclosed that bicyclic chiral phosphines **21** and **22** are extremely effective for the catalytic KR of alkyl aryl carbinols with achiral anhydrides in heptane (*Table 3*).[119,120] Phosphine **21** (2.5-12.1 mol%) with $(^{i}PrCO)_2O$, (2.5 eq) in heptane between –40° and rt proved to be the most selective catalyst (s = 15-369) for a range of alcohols. The highest selectivity factor originating from this study, s = 369, for the KR of 1-mesitylethanol is the highest reported so far for a non-enzymatic KR (catalytic or otherwise).

Table 3 Vedejs' KR of Alkyl Aryl Carbinols with Catalytic Bicyclic Chiral phosphines.

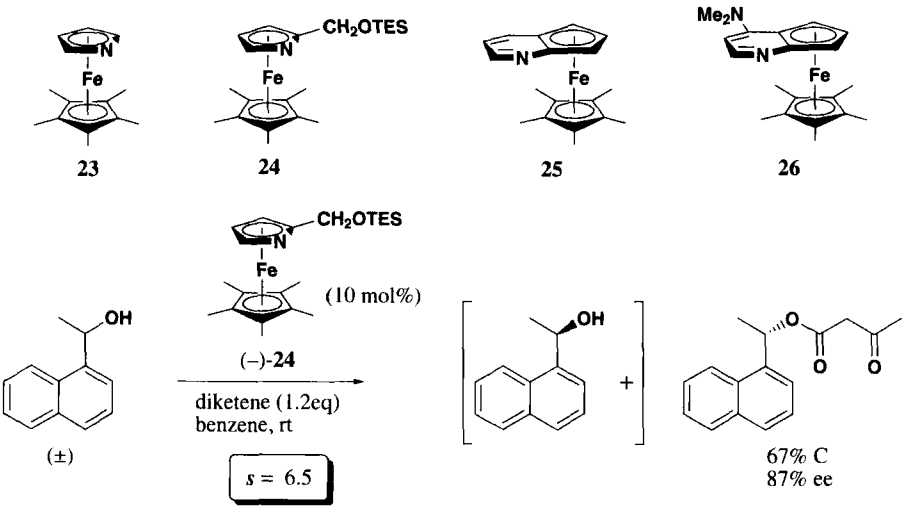


Ar'	R	T (°C)	mol% **21** (99.7% ee)	C	%ee$_A$	%ee$_E$	s
Ph	Me	rt	4	42.4	61.9	84.0	22
Ph	Me	-20	2.5	29.2	38.4	93.3	42
Ph	Bu	rt	3.7	39.3	53.6	83.0	18
Ph	Bu	-40	3.9	51.3	93.3	88.6	57
Ph	^{t}Bu[a,b]	rt	4.0	53.1	88.7	78.5	24
Ph	^{t}Bu[a,b]	-40	4.9	45.8	78.7	93.1	67
2-Tol	Me	rt	3.2	44.4	71.6	89.6	39
2-Tol	Me	-40	3.5	50.1	95.3	94.9	145
mesityl	Me[b,c]	rt	3.8	40.2	53.4	79.2	15
mesityl	Me[b,c]	-40	12.1	44.4	78.8	98.7	369
1-Nap	Me	rt	2.7	42.0	65.8	90.0	41
1-Nap	Me	-40	3.9	29.8	41.2	97.0	99

[a]catalyst **22** used with Bz_2O. [b]toluene used as solvent. [c]catalyst **21** with >99.9% ee used.

A key factor in achieving the outstanding selectivity displayed in reactions catalysed by chiral phosphine **21** is its high reactivity (>100 fold relative to phosphines **11-16**) which allows the reactions to be conducted at low temperatures. Vedejs has suggested that reactivity and selectivity may be correlated with the dihedral angle (θ) between the tetrahydrophosphole and aromatic rings, both being highest for intermediate values of θ between co-planar, (θ = 0°) and perpendicular, (θ = 90°).[120]

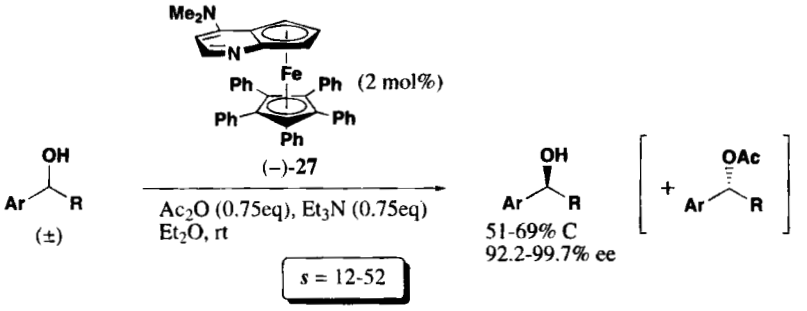
In 1996, soon after Vedejs published his chiral DMAP, Fu also published the results of his exploratory studies on using (π-heterocyclic)FeCp* complexes **23-26** as nucleophilic catalysts for acylative KR of alkyl aryl carbinols with diketene (*Scheme 16*, TES = triethylsilyl).[121] Although chiral DMAP (–)-**26** was found to be the most active catalyst in this series, pyrrole-based catalyst (–)-**24** turned out to be the most selective. Thus, employing just 10 mol% of catalyst (–)-**24,** selectivities as high as s = 6.5 could be obtained for acylation of 1-naphthylethanol with diketene (1.2 eq) (*Scheme 16*).



Scheme 16

Fu also found that the *t*-butyldimethylsilyl (TBS) analogue of pyrrole-based metallocene (+)-**24** (10 mol%) catalyses the enantioselective addition of MeOH to alkyl aryl ketenes to produce chiral α-aryl propionic acids in toluene at –78° with 2,6-di-*t*-butylpyridinium triflate (12 mol%) as proton transfer additive.[122] These studies built upon analogous reactions carried out using cinchona alkaloids and polymer-bound cinchona alkaloids by Pracejus in the 1960's[123-128] and Nakamura in the 1970's,[129-131] respectively. Fu found that his catalysts gave superior results to those obtained using the alkaloids, affording the products in 68-80% ee and 80-97% yields for an array of ketenes. The SDS in this process is believed to be the protonation of an enolate-type intermediate.

Fu subsequently published a much-improved system for the KR of secondary alcohols.[132] By replacing the pentamethylcyclopentadienyl group in catalyst (–)-**26** with a pentaphenylcyclopentadienyl group, a new catalyst (–)-**27** was produced that exhibited improved selectivities (s = 12-52) in the KR of alkyl aryl carbinols with Ac_2O (0.75 eq). Just 2 mol% of chiral DMAP (–)-**27** was required when Et_3N (0.75 eq) was employed as an auxilliary achiral base. The highest selectivity (s = 52) was obtained for the KR of 1-phenyl-2,2-dimethylpropanol (*Scheme 17*).

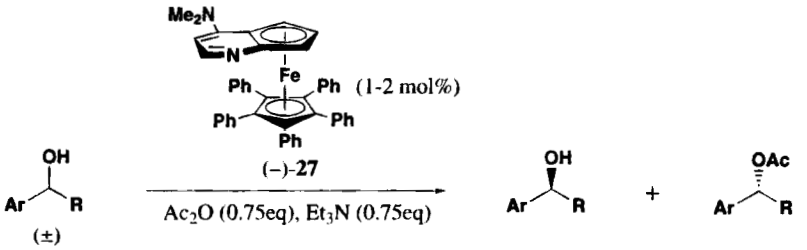


Ar = Ph, 4-FC_6H_4, 4-$OMeC_6H_4$, 1-Nap
R = Me, Et, ^{i}Pr, ^{t}Bu, CH_2Cl

Scheme 17

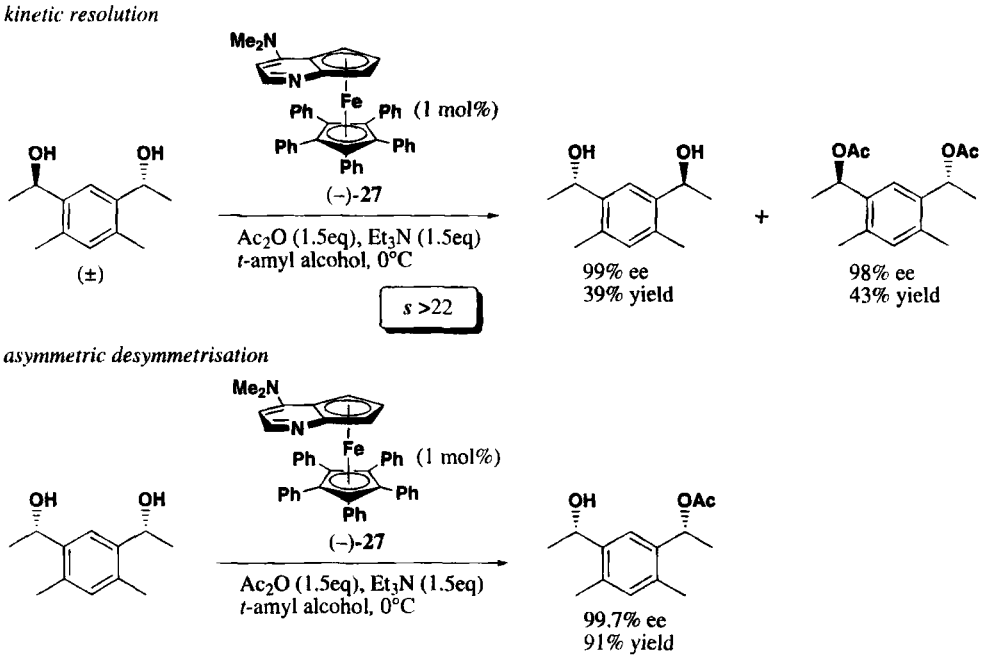
Fu then published an improvement to this system.[133] A solvent-effect study revealed that on changing the solvent from Et_2O to *t*-amyl alcohol, an increase in both rate and selectivity was observed. As a consequence of this increased rate of reaction, the temperature of the reaction could be reduced from rt to 0°, leading to a further increase in selectivity. By applying these improved conditions to alkyl aryl carbinols, selectivities (s = 32-95) could be obtained (*Table 4*).

Table 4 Fu's KR of Alkyl Aryl Carbinols with Catalytic Chiral DMAP (–)-**27**.



			s	
			Et_2O, rt	*t*-amyl alcohol, 0°C
Entry	Ar	R	(2 mol% cat)	(1 mol% cat)
1	Ph	Me	14	43
2	Ph	^{t}Bu	52	95
3	4-FPh	Me	18	68
4	Ph	CH_2Cl	12	32
5	2-Tol	Me	22	71
6	1-Nap	Me	22	65

The utility of this new system for AD and KR of C_2-symmetric- and *meso*-diols, respectively, can be seen from the following examples (*Scheme 18*).

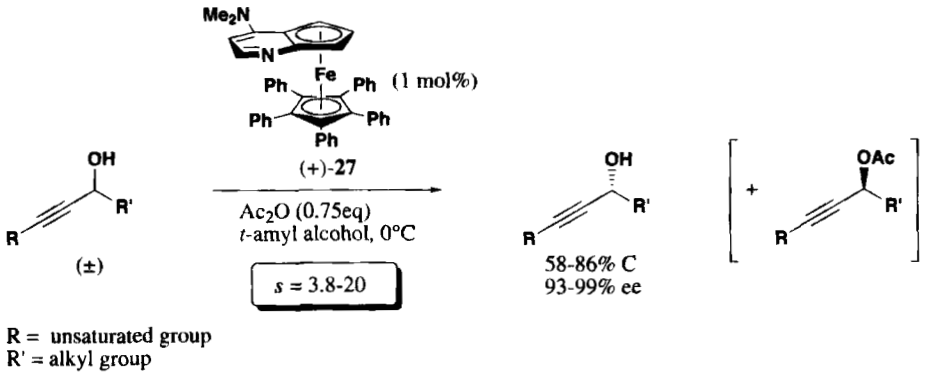


Scheme 18

A study was also carried out to determine the effect of changing the metal from Fe to Ru metallocenes.[134] It was envisaged that replacing Fe with Ru would enhance the nucleophilicity of the attached heterocycle, and that this might be beneficial for enantioselectivity. In the event, although the Ru analogue of chiral DMAP (–)-**27** did display higher reactivity and turnover, it mediated KR of alkyl aryl carbinols with significantly lower enantioselectivities [*e. g.* KR of 1-phenylethanol with Ac_2O, Et_3N, *t*-amyl alcohol, 0°; 1 mol% chiral DMAP (–)-**27**, $s = 43$; *cf.* Ru analogue of chiral DMAP (–)-**27** (1 mol%), $s = 10$]. Interestingly, for deracemising/ring-opening of azlactones, a dynamic KR (DKR) process which is catalysed by chiral DMAP (–)-**27**, and which has also been investigated by Fu, the Ru catalyst is superior in terms of selectivity.[134-136]

More recently, Fu has described the KR of propargylic alcohols using chiral DMAP (+)-**27**.[137] Screening of reactions conditions showed that using Ac_2O (0.75 eq) in *t*-amyl alcohol at 0° and employing no base, moderate selectivities ($s = 3.8$-20) could be obtained (*Scheme 19*). The best results were obtained where R = phenyl and R' = methyl ($s = 20$). Although these results are not as good as those for the KR of alkyl aryl carbinols, they still constitute a useful alternative to asymmetric propargyl ketone reduction as a means to access this synthetically important class of chiral alcohol.

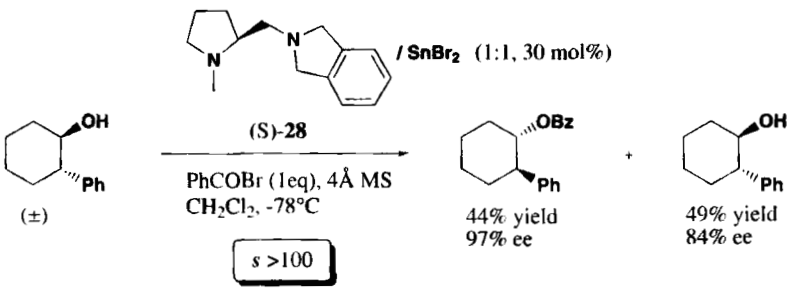
In his most recent work, Fu has shown that KR of primary amines can be achieved using the pyrrolidinopyridine (PPY) analogue of chiral DMAP **27**. However, the procedure involves pre-forming its acetyl pyridinium salt with AcCl and using this 'stoichiometrically' (50 mol%) in CH_2Cl_2 at –78°.[138] In this manner enantiomerically enriched acetamides (66-91% ee) could be obtained from a range of alkyl aryl amines (Ar = Ph, 4-$MeOC_6H_4$, 4-$CF_3C_6H_4$, 1-Nap, 2-Tol; R = Me, Et).



Scheme 19

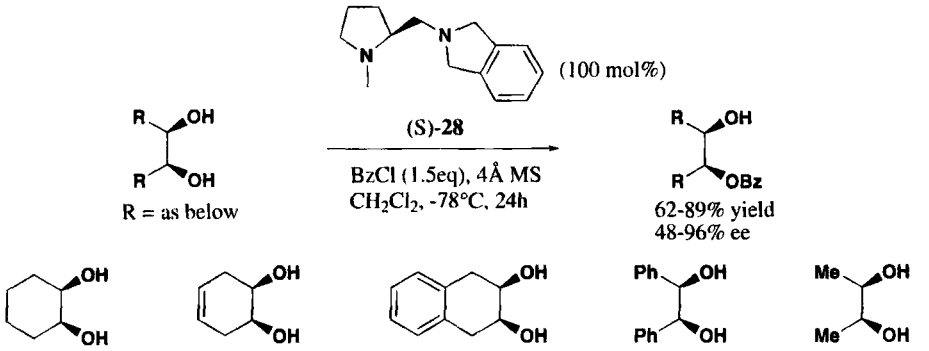
Although Fu is still investigating the origin of enantioselection in acylation processes catalysed by his ferrocenyl chiral DMAPs, he has published an X-ray structure[137] of an *N*-acetylated salt of (–)-**27** which reveals a conformation in which the acetyl carbonyl is co-planar with the pyridine ring and orientated towards the ring-fusion. A nuclear Overhauser effect (n*O*e) between the acetyl methyl group and the pyridyl H(2) suggests that this is also the major conformation in solution and Fu has asserted that effective blocking of one face of this carbonyl by the pentaphenylcyclopentadienyl group is probably critical for chirality transfer *via* axially-planar acyl pyridinium salts derived from chiral DMAP (–)-**27**.

In 1996, Oriyama published a study on the use of an (S)-proline-derived chiral diamine for KR of secondary alcohols. Preliminary investigations revealed highly enantioselective acylations could be achieved with BzBr or BzCl (1-1.5 eq) in the presence of 4Å MS and sub-stoichiometric quantities (10-40 mol%) of a 1:1 complex of chiral diamine (S)-**28** and $SnBr_2$ at remarkably low temperature (-78°).[139] After optimisation of the conditions, eight secondary alcohols were examined as substrates for KR, giving selectivity factors, s = 4.5-100 (*e. g. Scheme 20*).



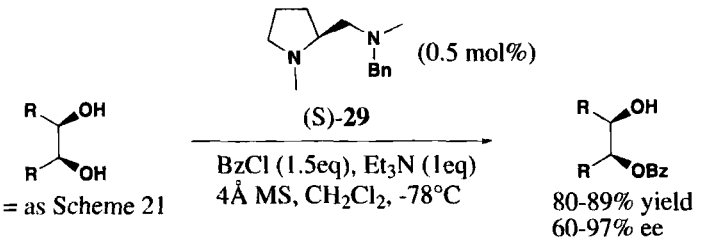
Scheme 20

Under these conditions, five *meso*-diols were shown to be poor substrates for AD (*e. g. cis*-cyclohexane-1,2-diol to *cis*-1-benzoyloxycyclohexan-2-ol: 81% ee, 6% yield). However, omission of the $SnBr_2$ and employing chiral diamine (S)-**28** in stoichiometric quantities led to good enantioselectivities (48-96% ee) and yields (62-89%) of acylated products (*Scheme 21*).[140] This result demonstrated that the diamine was acting as a nucleophilic catalyst and not as a ligand on the Sn to give a chiral Lewis acid complex.



Scheme 21

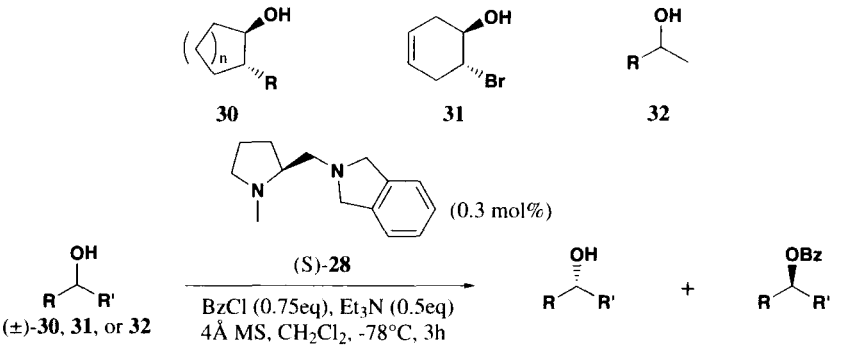
Further studies showed that by employing an auxiliary stoichiometric achiral base (Et_3N, 1 eq), as little as 0.5 mol% of chiral diamine (S)-**29**, (which is closely related to diamine (S)-**28** but has a benzylmethylamino unit in place of the dihydroisoindoline) was sufficient for efficient catalysis.[141] Employing the same five *meso*-diols as before, the reaction times could be decreased from 24 to just 3h with no loss in optical purity (60-97% ee) or yield (80-89%) of the products (*Scheme 22*).



Scheme 22

Oriyama has recently applied his (S)-prolinol-derived dihydroisoindoline catalyst (S)-**28**/Et_3N system to the KR of secondary alcohols.[142] Employing this chiral diamine in just 0.3 mol%, good to excellent selectivities (s = 4-170) and yields (39-49% of both recovered alcohols and product esters) were achieved for ten alcohols (*Table 5*). The benzylmethylamine catalyst (S)-**29** (5 mol%) was also screened against alcohol **30a** and gave s = 200. However, the dihydroisoindoline analogue (S)-**28** is a more reactive catalyst which allows the use of lower catalyst loadings whilst maintaining reasonable reaction times.

Table 5 Oriyama's KR of Secondary Alcohols with Catalytic Chiral Diamine (S)-**28**.



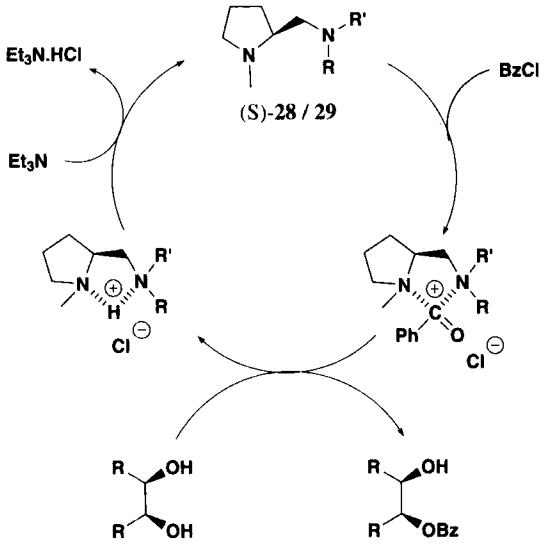
Entry	Alcohol	Alcohol YieldA (%)	Alcohol %ee$_A$	Ester Yield$_E$ (%)	Ester %ee$_E$	s
1	**30a** (n = 2, R = Ph)	49	96 (1S, 2R)	48	95 (1R, 2S)	160
2	**30b** (n = 1, R = Ph)	45	89 (1S, 2R)	42	88 (1R, 2S)	37
3[a]	**30c** (n = 4, R = Ph)	44	95	47	79	88
4	**30d** (n = 2, R = CO_2Et)	46	85	46	90	27
5	**30e** (n = 2, R = $CO_2{}^iPr$)	48	84	46	90	27
6[b]	**30f** (n = 2, R = Br)	47	96 (1S, 2S)	39	95 (1R, 2R)	130
7[b]	**31**	46	97 (1S, 2S)	43	91 (1R, 2R)	170
8	**32a** (R = Ph)	43	69 (S)	41	67 (R)	9
9	**32b** (R = 2-Tol)	45	82	49	78	20
10	**32c** (R = Bn)	49	46 (S)	39	51 (R)	4

[a]reaction performed for 24h. [b]$^iPr_2NEt$ used instead of Et_3N.

Although the reaction mechanism has not been definitively established, Oriyama proposed that an intermediate complex is formed in which both nitrogens of the chiral diamine chelate to the carbonyl carbon of the BzCl in a rigid bidentate manner (*Scheme 23*). That such a complex is involved is consistent with the finding that neither 1,1-, 1,3-, nor 1,4-diamines are effective catalysts[143] and might explain why acylations with AcCl, which can eliminate to form the less reactive ketene, are much slower under these conditions. Chelate formation is also supported by ^{1}H-NMR chemical shift and signal multiplicity data for a 1:1 complex between *N,N,N',N'*-tetramethylethylenediamine (TMEDA, which is a potent *achiral* catalyst for the benzoylation of secondary alcohols)[143] and BzCl.

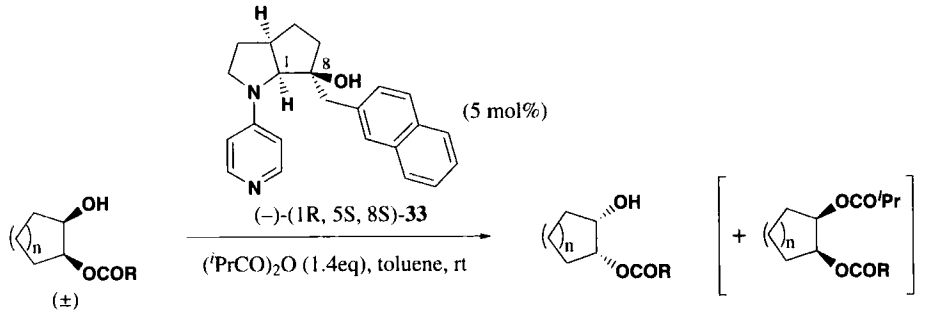
In 1997, Fuji published the results of his investigation into the KR of a series of cyclic mono-esterified *cis*-diols using a novel chiral PPY derivative (–)-**33** (*Table 6*).[144]

Fuji proposed that catalyst (–)-**33** was selective, despite the distance between the C(1)/C(8) chiral centres and the carbonyl 'active site', as the result of remote chirality transfer by face to face π–π stacking interactions between the naphthalene substituent and the pyridinium ring. Thus, analysis of



Scheme 23

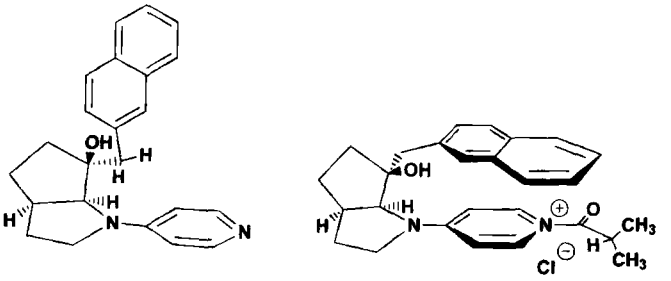
Table 6 Fuji's KR of Secondary Alcohols with Catalytic Chiral PPY (–)-**33**.



Entry	n	R	C (%)	%ee$_A$	*s*
1	2	^{i}Pr	69	76	4.3
2	2	^{t}Bu	68	94	8.3
3	2	4-$NO_2C_6H_4$	73	54	2.4
4	2	Ph	71	81	4.5
5	2	4-$MeOC_6H_4$	70	85	5.3
6	2	4-$Me_2NC_6H_4$	65	97	12.3
7	2	4-$Me_2NC_6H_4$[a]	68	93	7.7
8	1	4-$Me_2NC_6H_4$	71	97	8.3
9	3	4-$Me_2NC_6H_4$	70	92	6.5
10	4	4-$Me_2NC_6H_4$	73	92	5.8

[a]0.5 mol% of catalyst **33.**

^{1}H NMR chemical shifts and n*Oe* measurements revealed that catalyst (–)-**33** interconverted between two conformations (open and closed) depending on whether it was in the 'free' or acyl pyridinium state (*Scheme 24*).



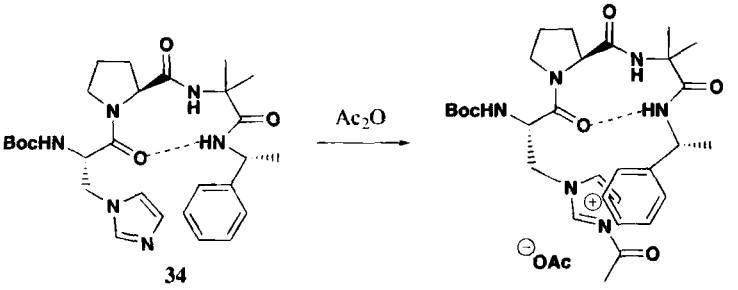
open conformation *closed conformation*

Scheme 24

In the closed conformation the carbonyl group is orientated towards the naphthalene system and consequently its *Si*-face is blocked such that only the *Re*-face is available to react with an incoming alcohol nucleophile. The relative orientation of this nucleophile is also presumably ordered by π-π stacking interactions given that secondary alcohol nucleophiles incorporating an electron rich aryl ester (*e. g.* R = *p*-$Me_2NC_6H_4$) lead to the highest selectivities.

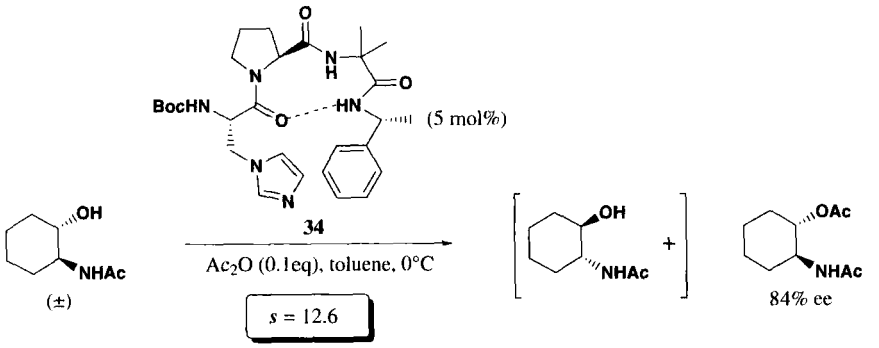
Indirect evidence that the rigid bicyclic nature of the Fuji's chiral PPY (–)-**33** may be an important factor in attaining high levels of asymmetric induction comes from recent work by Kotsuki who found that structurally related mono-cyclic prolinol-derived PPY catalysts (5 mol%) gave very low levels of selectivity (*s* = 1.5) in the KR of 1-phenylethanol with Ac_2O (0.5 eq) in CH_2Cl_2 at –78° in 3h.[145]

In 1998, Miller described the results of his studies on employing small peptides, such as tripeptide **34**, which contains 3-(1-imidazolyl)-(S)-alanine as the *N*-terminal amino acid, as 'biomimetic', enantioselective acyl transfer catalysts.[146] The aim was to allow the formation of an acyl imidazolium intermediate in a chiral environment formed by folding of the short peptide. Incorporation of a C-terminal (R)-α-methylbenzylamide was anticipated to encourage order-inducing π-π stacking interactions (*Scheme 25*).



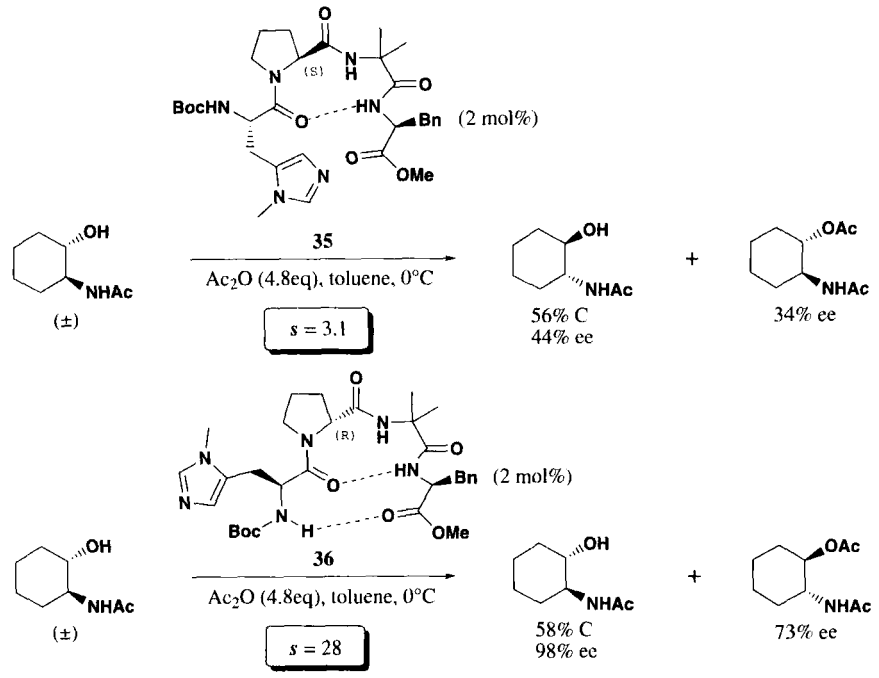
Scheme 25

Miller found that when using peptide **34** essentially no selectivity was achieved in attempted KR of alkyl aryl carbinols. The most selective substrate for this system was *trans*-2-(*N*-acetylamino)-cyclohexan-1-ol, possibly due to its ability to act as a hydrogen bond donor through the amide group. Non-polar, non-Lewis basic solvents, which favour hydrogen bonding, led to the greatest selectivities. (*Scheme 26*).



Scheme 26

Miller has also shown that changing the configuration of the proline from (R) to (S) in related peptides **35** and **36** effects a dramatic change in both the level and sense of enantioselectivity.[147] The (R)-proline containing tetrapeptide **36** gives selectivity s = ~28 in the KR of *trans*-2-(*N*-acetylamino)-cyclohexan-1-ol (*Scheme 27*). It was suggested that the enhanced rigidity of **36** relative to **35**, as the result of the presence of an extra hydrogen bond, might be the cause of the enhanced selectivity.



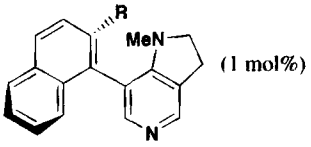
Scheme 27

To ascertain whether increasing the rigidity of the peptide through increased molecular complexity would lead to greater enantioselectivity, Miller prepared an octapeptide that contained the β-hairpin structure of tetrapeptide **36** and found that under otherwise identical conditions, *s* increased to 51 and good selectivities (*s* = 15 and 27) could also be achieved with the analogous 5- and 7-membered ring substrates.[148] Miller has examined the KR of a number of other secondary alcohols using this improved octapeptide, but to date their selectivities are lower than for *trans*-2-(*N*-acylamino)-cyclohexan-1-ol.

In connection with this work, Miller has also devised an elegant fluorescent chemosensor-based screening protocol to assay for acylation.[149] An alternative method based on IR thermal imaging has also been disclosed by Morken.[150] As Miller has correlated rate of reaction with degree of enantioselectivity for his catalysts, the combination of high-throughput screening (HTS) and rapid peptide-based catalyst synthesis by automated combinatorial techniques offers exciting prospects for the rapid discovery of new catalysts of this type.[151]

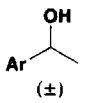
The most recent examples of enantioselective nucleophilic acyl transfer catalysts are our own atropisomeric DMAP derivatives **37-40** which contain a chiral axis *meta* to the pyridyl nitrogen.[152-154] By situating the chiral axis at this position the potent nucleophilicity of DMAP is maintained, thereby allowing KR studies to be performed at low temperature [*cf.* Vedejs' chiral DMAP (+)-**17** and Fu's chiral DMAP (–)-**27**, both of which have substituents *ortho* to the pyridyl nitrogen]. Our initial work focused on 5-azaindoline derived catalysts **37-39**, as we envisaged that this bicyclic core unit would impart higher rotational barriers to racemisation than the corresponding DMAP core.[152,153] Although these catalysts were highly active (allowing the use of just 1 mol% at –78° in toluene) the selectivities for KR of 1-phenylethanol and 1-naphthylethanol using Ac_2O (0.75 eq) [and $(^iPrCO)_2O$ (2 eq)] displayed by these catalysts were somewhat disappointing (*s* = 1.5-4.7) (*Table 7*).

Table 7 Spivey's KR of Alkyl Aryl Alcohols with Catalytic Atropisomeric DMAP.



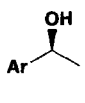
(1 mol%)

(+)-37 R=Me
(–)-38 R=Ph
(–)-39 R=3,5-*bis*(3,5-dimethylphenyl)phenyl

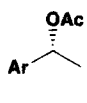


(±)

Ac_2O (0.75eq), Et_3N (0.75eq) toluene, –78°C



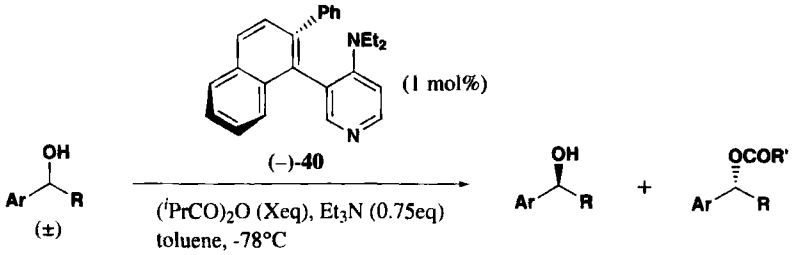
+



Entry	Cat	Ar	C (%)	%ee$_A$	%ee$_E$	*s*
1	(+)-**37**	Ph	35.0	9.1	16.9	1.5
2	(–)-**38**	Ph	26.0	11.6	33.0	2.2
3	(–)-**38**	1-Nap	18.3	9.0	40.1	2.5
4	(–)-**39**	1-Nap	17.6	13.1	61.2	4.7

Reasoning that these moderate selectivities might be a consequence of insufficient left-from-right differentiation on the more accessible face of these catalysts we next prepared resolvable atropisomeric catalyst **40**, based on the 4-(diethylamino)pyridine catalytic core.[154] This catalyst, which surprisingly has greater configurational stability than its 5-azaindoline counterpart **38**,[153] was indeed found to mediate far more selective KR of alkyl aryl carbinols than any of the 5-azaindoline based catalysts (*s* up to 29), particularly when employing $(^{i}PrCO)_2O$ as acylating agent (*Table 8*).[154]

Table 8 Spivey's KR of Alkyl Aryl Carbinols with Catalytic Atropisomeric DMAP (–)-**40**.



Entry	Ar	R	X	C (%)	%ee$_A$	%ee$_E$	*s*
1	1-Nap	Me	2.0	17.2	18.6	89.3	21
2	1-Nap	Me	1.0	22.3	26.3	91.4	29
3	Ph	Me	2.0	39.0	49.9	78.1	13
4	2-Tol	Me	2.0	41.4	60.7	86.0	25
5	Ph	^{t}Bu	2.0	17.5	18.8	88.8	20

We are currently evaluating related catalysts, alternative acylating agents, and various additives to try to identify more selective systems for KR and AD processes. We are also conducting experiments to elucidate the origins of the enantioselectivity displayed by our catalysts.

CONCLUSIONS

A number of the recently developed chiral nucleophilic acyl transfer catalysts can now be compared favourably with hydrolytic enzymes for use in synthetically important KR and AD processes. If we take the selectivity factor (*s*) in the KR of 1-(2-tolyl)ethanol as giving a very approximate indication of the extent of selectivity characteristic of the four best-described catalyst systems, we find Vedejs' bicyclic phosphine **21** (*s* = 145) and Fu's ferrocenyl DMAP **27** (*s* = 71) are by far the most selective, with our atropisomeric DMAP **40** (*s* = 25), and Oriyama's diamine **28** (*s* = 20) being significantly less so. Given that KR's giving *s* >7 can be regarded as practically useful (because they guarantee at least 20% recovery of the less reactive enantiomer with ≥99% ee)[8] all these systems constitute significant milestones in the search for low molecular weight alternatives to hydrolytic enzymes for KR. However, there is still room for improvement. Preparation of Vedejs' bicyclic phosphine **21** involves a demanding 5-step synthesis (~8% overall yield) from (S)-ethyl lactate (1L, 98%

ee, £16.20, Aldrich)[120] and currently works best with (^{i}PrCO)$_2$O in degassed heptane at -40° (*Table 3*). The catalyst is also susceptible to aerial oxidation to the catalytically inactive phosphine oxide. Preparation of Fu's ferrocenyl DMAP **27** involves a 13-step synthesis (~1% overall yield)[155,156] from adipic acid (1Kg, £6.50, Aldrich), followed by chiral HPLC resolution and currently works best with Ac_2O in *t*-amyl alcohol at 0° (*Table 4*). Preparation of our atropisomeric DMAP **40** involves a 6-step synthesis (~28% overall yield)[154] from 4-pyridone (100g, £47.90, Aldrich) followed by chiral HPLC resolution and currently works best with (^{i}PrCO)$_2$O in toluene at –78° (*Table 8*). Preparation of Oriyama's diamine **28** involves a 2-step synthesis (~53% overall yield)[157] from (S)-*N*-Boc-proline (25g, >99% ee, £43.30, Aldrich) and currently works best with BzCl in CH_2Cl_2 at –78° (*Table 5*). If additionally one starts to consider the prospects for rapid generation of analogues for structure-selectivity optimisation studies then the advantages of Miller's peptidic catalysts (*e. g.* tetrapeptide **36**) become apparent. It remains to be seen how this exciting field evolves but it seems inevitable that the coming years will see the emergence of yet more selective, general and easily accessible catalysts and their application in increasingly demanding synthetic environments.

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