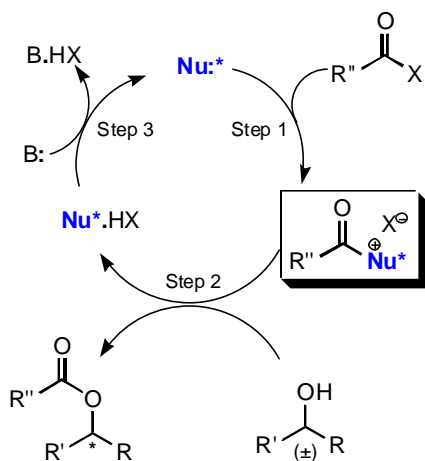


Asymmetric Nucleophilic Acyl Transfer Catalysts

Introduction

Acyl transfer by chiral nucleophiles has received significant attention in recent years.¹

Among the synthetically useful acyl transfer reactions, the one of greatest general utility is the



Scheme 1. Catalytic cycle of Nucleophilic Acyl Transfer Catalyst

kinetic resolution of secondary alcohols. Enantiopure alcohols are an important class of readily derivatized organic compounds that can be incorporated into a variety of synthetic strategies. The cycle by which asymmetric nucleophiles catalyze acyl transfer in the kinetic resolution of secondary alcohols can be seen as a three step process (**Scheme 1**). Step one involves attack of the chiral nucleophile on an achiral acylating agent.

The new chiral acylating agent will then undergo attack by a racemic mixture of alcohols (step 2). When one of the two enantiomeric secondary alcohols reacts faster with the asymmetric acyl transfer agent, resolution occurs. The chiral nucleophile can then be regenerated by a stoichiometric amount of achiral base (step 3). The selectivity (*s*) of asymmetric acyl transfer is the ratio of the rate of the faster reacting enantiomer vs. the rate of the slower reacting enantiomer (**Figure 1**).²

The accelerating influence of selected nucleophiles in acyl transfer was reported first in the late 1800's. Pyridine was recognized

$$s = \frac{k_R}{k_S}$$

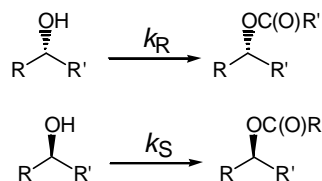


Figure 1. Selectivity factor (*s*) is determined by the reaction rates of the two competing enantiomers in a given reaction

for its ability to accelerate the acylation of secondary alcohols by acetyl chloride.³ Subsequently a number of highly active nucleophiles involved in acyl transfer catalysis have been reported, including: 4-(dimethylamino)pyridine⁴ (probably the most widely used), imidazoles, and phosphines.⁵

Early discovery of nucleophilic acyl transfer catalysts was soon followed by asymmetric versions. In 1932 Wegler reported the use of (-)-brucine in the kinetic resolution of 1-phenyl ethanol.⁶ Since, there have been numerous reports using brucine and various cinchona alkaloids as chiral nucleophiles in acyl transfer catalysis.⁷ Unfortunately, synthetically useful selectivity (s) has not been reported in the kinetic resolution of racemic secondary alcohol mixtures.

In 1996 the groups of Vedejs and Fu independently reported synthetic nucleophilic catalysts that could carry out asymmetric acyl transfer.^{8,9} These two very different classes of nucleophiles have developed into the state of the art in asymmetric acylating agents. Kinetic resolutions with a number of useful secondary alcohols have been demonstrated with selectivity factors (s) approaching those of natural enzymes. Other groups have also placed interest in the topic and the significant advancements in the field will be covered in this report.¹⁰⁻¹³

PBO (phosphabicyclo[3.3.0]octane) catalysts

The Vedejs group demonstrated in 1993 that tribulylphosphine can serve as an effective catalyst for acylation of hindered alcohols.¹⁴ They soon became interested in using chiral phosphines as catalysts. The intuitive direction of looking at C₂ symmetric phosphines was first explored, due to the vast utility of C₂ symmetric catalysts in asymmetric transformations and also the

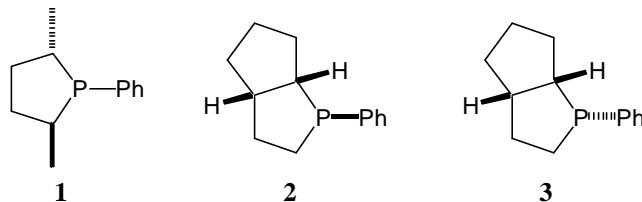
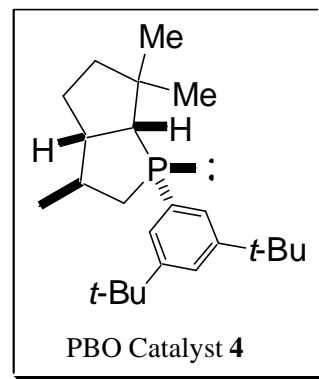


Figure 2. Phosphines developed by Vedejs *et al* for asymmetric acyl transfer.

availability of some C_2 symmetric phosphine ligands that could serve as catalysts in the initial screening.

Phosphine **1** was first looked at with a number of other C_2 symmetric phosphines.⁸ **1** showed some selectivity in the kinetic resolution of secondary alcohols ($s=3-15$). The reactions were sluggish and further exploration led to the discovery of much more reactive bicyclic phosphines, **2** and **3**. Enantiopure bicyclic catalyst **4** was synthesized and found to be very selective in the kinetic resolution of secondary alcohols.¹⁵ Further optimization of conditions led to catalysts showing $s = 30-369$ in the kinetic



resolution of arylalkylcarbinols. The Vedejs group has also demonstrated that some synthetically useful allylic alcohols can be efficiently resolved using this new PBO catalyst.¹⁶

DMAP-based catalysts

Fu and coworkers have also developed new nucleophilic catalysts, based on a “planar-chiral” DMAP.¹⁷ In order to use DMAP as a chiral acylation agent, one must differentiate the two mirror planes. Fu came up with an ingenious way of differentiation based on use of a metal complex to block

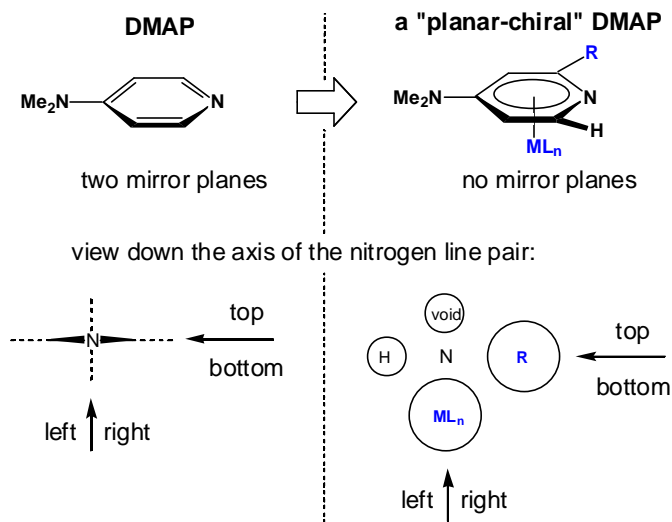


Figure 3. Development of planar-chiral DMAP

top/bottom plane of the DMAP and a fused ring alkyl group to differentiate the left from right.

Catalyst **5** (**Figure 4**) based on this model were found to be active in the resolution of secondary

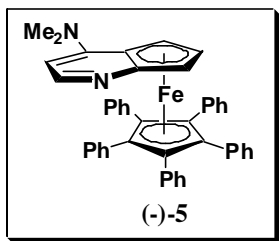
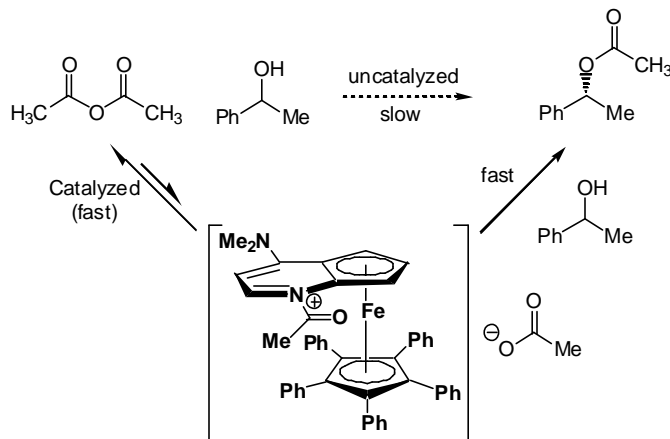


Figure 5. A "planar-chiral" DMAP catalyst

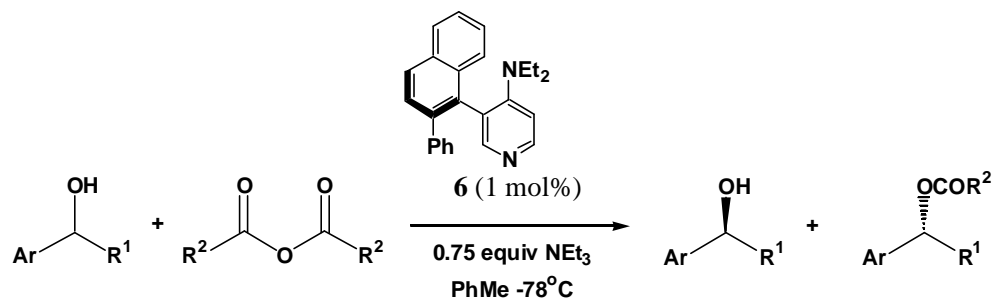
catalyst.²⁰⁻²²

The source of the exquisite selectivity is still under investigation, but from x-ray crystal data of the acylated catalyst the authors propose a mechanism as shown in **Scheme 2**.²¹ The exact placement of the acetate ion is not currently known.



Scheme 2. Fu catalyst in the asymmetric acetylation of 1-phenylethanol

Other advances in DAMP-based chiral catalysts have come from the lab of Spivey. His "axially chiral" analogs of DMAP (**6**, **Scheme 3**) use the high rotation of barrier about the aryl-aryl bond to produce atropisomers that are selective in the acylation of secondary alcohols.¹³ These novel DMAP catalysts show similar preferences to the Fu catalysts (as one might expect). They may still hold some promise due to their high activity (much greater than the analogous Fu catalysts), but current selectivity between enantiomers is 3-5 times lower than the Fu catalyst based on similar substrates.



Scheme 3. "Axially-chiral" analog of DMAP (**6**) used in kinetic resolution of secondary alcohols

Around the time that Vedejs and Fu began reporting new catalysts for asymmetric acyl transfer, Fuji and coworkers came up with an interesting design for mimicking induced-fit catalysis demonstrated by some enzymes.¹⁰ This design was again based on a DMAP-type reactive center (**A**, **Figure 6**). The novel design relies on very remote stereocenters for asymmetric induction. The catalyst when in the active acylated form (**B**) closes off one face of the reactive acyl group. This then allows for asymmetric acylations of secondary alcohols. Although the selectivity of the catalyst ($s = 2.4\text{--}10.1$) for selective cyclic secondary alcohols is not useful synthetically, the unique design deserves some merit. No further work has been published on this system.

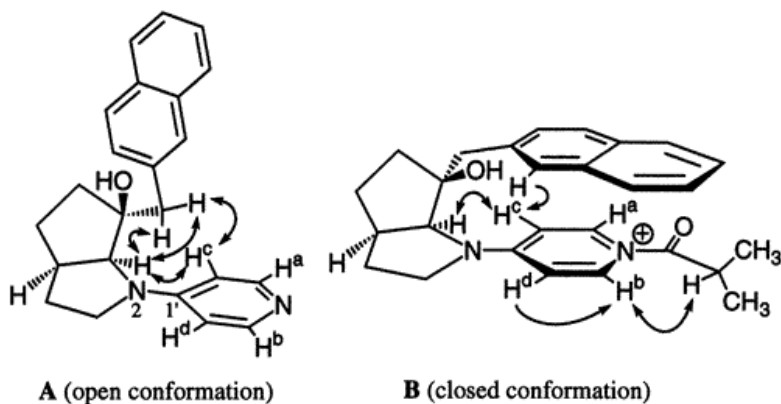
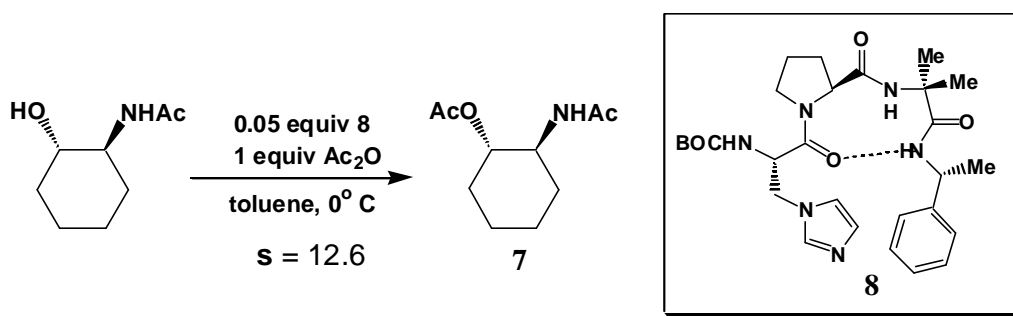


Figure 6. Open and closed conformations of Fuji's "Induced-fit" catalyst

Other tertiary amine catalysts

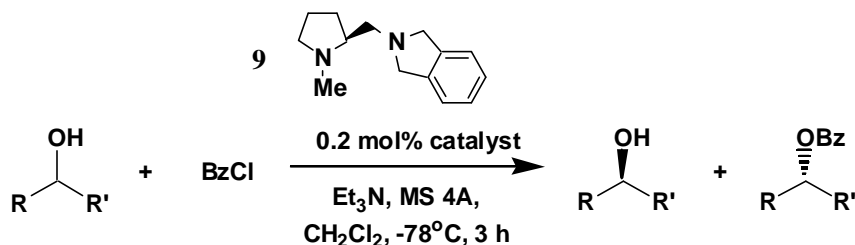
The group of Miller has taken a different approach to looking at asymmetric nucleophilic acylation. They have used a peptide based backbone along with an active acylating N-alkyl imidazole subunit to selectively acylate secondary alcohol enantiomers (**Scheme 4**).¹¹ The peptide backbone may serve in recognition and stabilization of the transition state leading to acylated product. Peptide structure has proven to be important in the selection of enantiomers and activity of the catalyst.²³ The peptide catalysts are also attractive for use in combinatorial library synthesis, providing a modular structure that can be easily modified. The Miller group has identified peptide octamers from combinatorial libraries that show synthetically useful kinetic resolutions of a number of secondary alcohols.²⁴ Another important and interesting note about the Miller peptide catalysts is that the reaction rates of the catalysts are faster than the unmodified reactive acylating group (N-methyl imidazole).²⁵ This accelerating affect of the catalyst has not been seen in the catalysts described previously, rather a decelerating of the less reactive enantiomer by steric hinderances.



Scheme 4. Kinetic resolution of amide containing secondary alcohol by Miller peptide **8**

Finally, the simplest catalyst has been developed by Oriyama and coworkers. Catalyst **9** (**Scheme 5**), which is a derivative of proline, can server in the kinetic resolution of a number of cyclic alcohols (5-8-membered rings) with selectivity factor (s) ranging from 37-190!¹² The authors propose the possibility of a cyclic intermediate in which both amines participate in

coordination to the carbonyl, based on their work with 1,2 diamine, TMEDA (*N,N,N',N'*-tetramethylethylenediamine).²⁶



Scheme 5. Oriyama's diamines used in kinetic resolution of secondary alcohols by BzCl

Conclusion

Chiral nucleophilic acylating agents can in some cases be compared favorably with enzymatic hydrolytic enzymes in the kinetic resolution of secondary alcohols. Although not completely general many synthetically useful intermediates can be generated by the blossoming group of catalysts. The catalysts developed by Vedejs (“PBO”) and Fu (“planar-chiral” DMAP) are by far the most selective, but don’t enjoy the relative ease of synthesis that Oriyama (proline-based diamine) and Miller (peptides) catalysts possess. Fuji’s induced-fit, enzyme-like catalyst is interesting from a mechanistic standpoint but offers little synthetic utility. Spivey’s “axially-chiral” DMAP, although analogous to the Fu catalyst, is less useful synthetically. Miller’s peptide based catalysts are amenable to combinatorial library searches, which have led to discovery of more general catalysts. These peptide catalysts are mechanistically interesting due to the accelerative process by which they react (mechanism still to be determined). The field of asymmetric nucleophilic acyl transfer remains a hot topic in organic chemistry and it will be interesting to see how the pool of catalysts continues to grow and develop.

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