Exploring Chiral Space *en route* to DPC 963: A Personal Account

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Abstract: DPC 961 and DPC 963 are non-nucleoside reverse transcriptase inhibitors (NNRTIs) for the treatment of HIV. These drug candidates contain a chiral quaternary center, which can be installed *via* addition of lithium cyclopropylacetylide to an *N*-acylketimine in the presence of a chiral moderator. This account describes our efforts to identify a cost-effective moderator by rapidly preparing, screening, and optimizing libraries of enantiopure β-amino alcohols. The result is a highly enantioselective process that has been used to produce these NNRTIs on a metric ton scale.

Keywords: β-amino alcohols; dihydroquinazolin-2-ones; enantioselective addition; epoxide ring-opening; HIV drugs; ligand design; N,O ligand

1 Introduction

This special issue of *Advanced Synthesis and Catalysis* underscores the growing importance of organometallic chemistry in general, and homogeneous catalysis in particular, in today's pharmaceutical industry. The reality is that, despite the early success of Bill Knowles and the Monsanto L-DOPA process,[1] pharmaceutical companies were not quick to embrace homogeneous catalysis as a key technology for drug manufacture. In my view, the Merck process group deserves much credit as pioneers in this area. Efficient routes to such drugs as cilastatin,[2] imipenem,[3] and ivermectin,[4] all developed during the early 1980's using homogeneous transition metal catalysis, attest to the correctness of their vision.

My experience in this field began in DuPont's Central Research and Development Department (CR&D). During the 1990's the application of asymmetric catalysis to fine chemical synthesis was a significant area of research in CR&D. For those of us who took part in this endeavor, the eventual fate of the program remains somewhat ironic. Following a series of licensing agreements and unanticipated corporate acquisitions, our portfolio of chiral technologies was acquired by DuPont's chief U.S. competitor, the Dow Chemical Company. We take some consolation in reports that the business is doing quite well.

Nevertheless, CR&D in the 1990's provided an extraordinary environment for research in exploratory chemistry. Dr. George Parshall, an outstanding scientist, served as Director of Chemical Sciences. Chemists were encouraged to consider the broader implications of their research problems and felt empowered – even obligated – to explore the interesting observations and serendipitous discoveries that invariably develop during the course of a research project. I was fortunate to lead a small research group[5] that included T.-V. RajanBabu (now Professor of Chemistry at the Ohio State University) and Mark Burk (currently Vice President of Chemical Product R&D at Diversa).

Most process chemists with an interest in homogeneous catalysis would probably agree that our field has an Achilles heel. The problem is that relatively few chiral ligands are commercially available "at scale". It is no accident that the successful exceptions, for example, BINAP or the Jacobsen salen ligand, tend to be molecules that are simple to synthesize. Replacing a classical resolution in a synthetic scheme with an asymmetric catalytic process may not be a bargain if the necessary ligand requires many difficult steps for its manufacture. To quote Neal Anderson's very useful textbook[6] on process chemistry, "From an industrial perspective the most elegant chemistry is the most economical chemistry."

This account concerns our efforts to identify an economical ligand to address a "real world" synthetic challenge. (Purists will note that the DPC 963 process is

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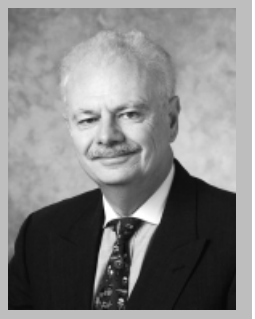
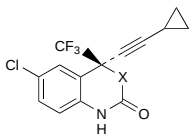


William Nugent was born in 1947 in Weymouth, Massachusetts, U. S. A. He obtained his B. S. in Chemistry from Purdue University in 1969. After several years as a high school chemistry teacher, he earned his Ph. D. in Organic Chemistry from Indiana University under the research direction of Professor J. K. Kochi. He joined DuPont Central Research in 1976. In 2001, DuPont's pharmaceutical business was acquired by Bristol-Myers Squibb so that he currently is a Research Fellow in the Process Research and Development Department of the latter company. Bill is co-author of the inorganic chemistry textbook "Metal-Ligand Multiple Bonds" and during 2002 he served as chair of the Division of Organic Chemistry of the American Chemical Society. His research interests focus on the application of homogeneous catalysis to pharmaceutical process chemistry.

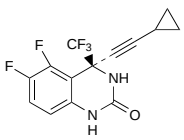
not formally "catalytic" although the ligand is recovered and recycled.) I will try to be even-handed in describing both the successes and the difficulties in our experimental approach.

2 The Targets

In the spring of 1997, Bobbie Dorow and Goss Kauffman, two of my colleagues from the then DuPont-Merck Pharmaceuticals Company, approached me with yet another interesting problem. There was a need for a more efficient synthesis of two HIV drug candidates, DPC 961 and DPC 963. These compounds are closely related to efavirenz[7] (Sustiva®), DuPont-Merck's successful non-nucleoside reverse transcriptase inhibitor. DPC 961 and DPC 963 are second generation NNRTIs that exhibit increased effectiveness against K103N-containing HIV as well as other NNRTI-resistant mutant viruses.[8] The key structural difference between efavirenz and the new analogues was the replacement of the oxygen atom in the heterocyclic ring with an NH group.

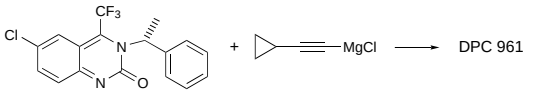


efavirenz, X = O
DPC 961, X = NH



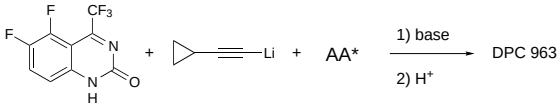
DPC 963

A viable route to DPC 961 had been developed[9] and involves the diastereoselective addition of a magnesium cyclopropylacetylide to an *in situ* generated azatetraene as shown in Equation 1. Remarkably this chemistry fails totally when applied to DPC 963.



(1)

An attractive alternative route to DPC 963 would be the enantioselective addition of lithium cyclopropylacetylide to the corresponding ketimine as shown in Equation 2. In the equation, AA* represents a chiral moderator (amino alcohol) which we hoped to recover and recycle. Previous studies[10] on related additions to cyclic *N*-acylketimines using norephedrine-based ligands (another discovery of the Merck Process Research group!) suggested the possibility of utilizing a chiral β-amino alcohol as a chiral moderator. However, for a cost-effective process, we needed to avoid the *N*-protection/deprotection protocol required in these earlier studies.



(2)

It was hard to envision the detailed mechanism for such a transformation. It seemed likely that the acidic NH hydrogen would be deprotonated under the requisite reaction conditions. David Collum's NMR studies[11] on the synthesis of efavirenz, which similarly involves the addition of lithium cyclopropylacetylide in the presence of an amino alcohol promoter, made it clear that the lithium alkoxides in such a system would exist in a variety of complex interconverting aggregates. Would the lithiated heterocycles be incorporated into these clusters, further complicating the scenario?

Under these circumstances "rational design" of an effective ligand seemed pretty unlikely. We decided to screen a wide range of amino alcohols under a variety of reaction conditions. How then to assemble a library of enantiopure β-amino alcohols?

3 Building the First Library

As a result of earlier research on homochiral trialkanolamines,[12] I was aware of how cleanly and easily amines add to epoxides.[13] A simple extension of this chemistry would provide the type of amino alcohols that we needed.[14] We hoped to synthesize our library without the use of added reagents, solvents, or subsequent purification of the ligands. The simple synthesis of these amino alcohols also meant, should any of them prove

effective, that they should be inexpensive to manufacture at a commercial scale.

However, we would need to be circumspect in our choice of epoxides. It was essential to avoid issues of regioselectivity, which would lead to mixtures of amino alcohols rather than the single compounds we sought. As shown in Figure 1 we initially identified four such epoxides on our laboratory shelves. These included the terminal epoxides **1**–**3** where a secondary amine was expected to add exclusively to the terminal position, and *trans*-stilbene oxide **4**, which (for reasons of symmetry) would produce the same product regardless of which C-O bond was cleaved.

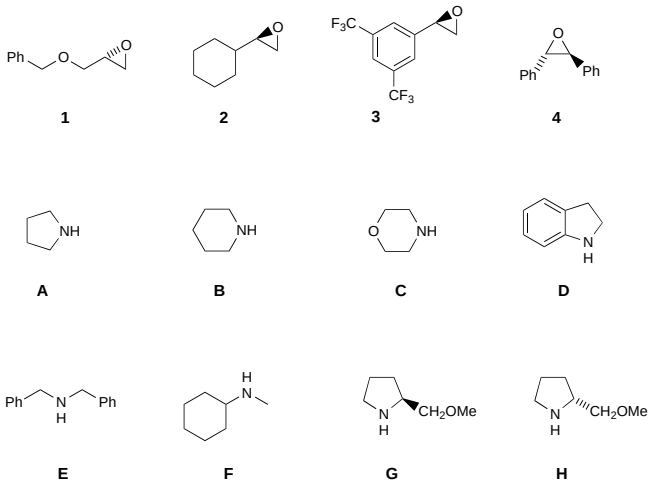
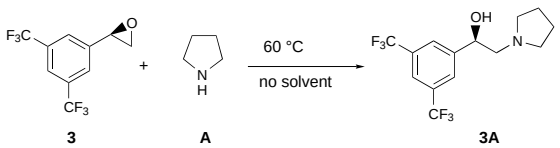


Figure 1. Enantiopure epoxides and secondary amines used in the preparing Library 1.

Also shown in Figure 1, the secondary amine building blocks (**A**–**H**) were commercially available substances. These included both cyclic and acyclic derivatives and even a pair of enantiomeric amines (**G** and **H**) to explore the effect of a second chiral center.

We charged a set of 32 vials with all combinations of these eight amines and four enantiopure epoxides. A slight excess (5%) of epoxides was used because control experiments had shown that unreacted amine could have a deleterious effect on reactions of interest. We heated the vials overnight at 60 °C. In some cases the results were spectacular. One example was the vial that had been charged with epoxide **3** and amine **A**, two liquid reactants. This vial (and a number of others) now contained a mass of snow-white crystals (Equation 3); the resultant ligand will be called **3A** reflecting its two components. By NMR the product was pristine except for the expected trace of unreacted excess epoxide.

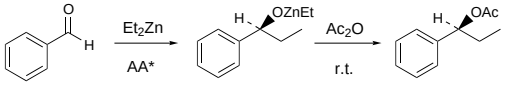


(3)

In other cases, especially reactions involving *trans*-stilbene oxide **4**, the reactions were incomplete. Therefore we gradually ramped the temperature up to 90 or 110 °C. After several days at this temperature, the remaining reactions appeared at least 90% complete by NMR. Our amino alcohol Library 1 was complete – but could we trust the results of screening using these compounds in unpurified form?

4 Validating Library 1

By this time, screening of the acetylide addition in Equation 2 was already under way. However, studies on this reaction were inherently slow. To gain confidence in the use of the crude ligands contained in Library 1, we desired an independent test using chemistry that is well-understood and amenable to rapid screening. The addition of diethylzinc to aldehydes[15] appeared ideal on both scores. There is, of course, a large body of work on these reactions that is described in several review articles.[16] Benzaldehyde has been a favorite substrate (Equation 4), presumably because additions tend to proceed in high enantiomeric excess. (One wonders about the wisdom of focusing on such a well-behaved aldehyde rather than one of the problem cases in the field, but benzaldehyde was ideal for our initial probe.)



(4)

While developing our screening protocol, we made a useful discovery.[14] As also shown in Equation 4, if the initially formed zinc alkoxide is quenched with acetic anhydride (rather than water as is generally used in such studies) it is cleanly and quantitatively converted to the corresponding acetate ester. This allowed us to harness chiral capillary gas chromatography to simultaneously evaluate the yield and enantioselectivity of large sets of reactions. Typically we would charge the autosampler of the gas chromatograph with a set of 32 vials at the end of the day. The robot would analyze the samples overnight and by morning an Excel spreadsheet containing the results had been generated. Analysis time for each sample was 12 minutes or less depending on the aldehyde.

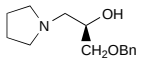
The ee's from one such data set are shown in Table 1. These results were obtained using 1 equivalent of diethylzinc relative to aldehyde rather than the 2 equivalents commonly employed. Nevertheless, ee's as high as 88% were observed in this screen. Also shown in parentheses in Table 1 are the corresponding enantiomeric excesses after purification of the ligands by flash chromatography.[17] In the majority of cases, the use of the analytically pure, chromatographed ligand had little

Table 1. Enantiomeric excess for Equation 4 using amino alcohol library 1 (5% catalyst, 25 °C).

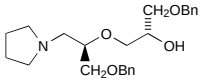
Amine/ Epoxide	**1**	**2**	**3**	**4**
A	+74 (+32)	−45	−63 (−47)	−84 (−85)
B	+31 (+27)	−68	−67 (−65)	−88 (−89)
C	+27 (+27)	−65	−70 (−61)	−78 (−89)
D	+11 (+11)	−16	−62 (−62)	+15 (+3)
E	−12 (−12)	+11	−23 (−21)	+1 (+4)
F	+13 (+12)	−13	−43 (−14)	−28 (−81)
G	+61 (+64)	+42	+19 (+19)	−57 (−80)
H	−65 (−66)	−55	−79 (−83)	−45 (−68)

effect on the enantioselectivity of the reaction. Most of the exceptions were cases where *trans*-stilbene oxide **4** was the epoxide precursor for the ligand. This was easy to understand. Addition of amines to the internal carbon atoms of **4** proceeded sluggishly and control experiments showed that unreacted amine could serve as an unselective catalyst for addition of diethylzinc to aldehydes.

But how does one explain a case like ligand **1A** where the enantiomeric excess *drops* 42% after chromatography? Examination of the impurities formed during the preparation of **1A** indicates that the crude ligand contains about 5% of the 2:1 adduct **9**. Formation of the 2:1 adduct is no doubt favored by the high reactivity of the epoxide, the substantial basicity of the 1:1 adduct, and the volatility of pyrrolidine. Adduct **9** was independently synthesized and was shown to be an efficient catalyst for Equation 4, promoting the addition in 93% yield and 91% enantiomeric excess. The higher enantiomeric excess obtained using this "chain extended" derivative is not without precedent. Both Hoshino[18] and Fu[19] have shown that chain extension of moderately selective amino alcohols with 1,1-diphenylethylene oxide can significantly enhance their selectivity for diethylzinc addition to aldehydes.



1A



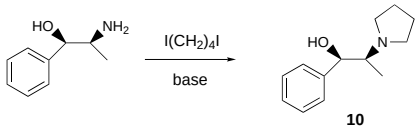
9

In order for the "structure-activity relationship" in these data to be useful, we hoped that the contributions of the ligand substructures would be independent and additive.[20] The last two lines of Table 1 raised some concerns on this point. Both the amine components **G** and **H** and epoxide building blocks are chiral in these diastereomeric pairs of ligands. Even within this small set of ligands, three distinct reactivity patterns are observed. For ligands derived from epoxides **1** and **2** the enantioselectivity seems to track only the chirality of the amine component, while in the ligands derived from epoxide **4**, it is the chirality of the epoxide that dominates. Only in the pair of ligands derived from epoxide **3** is there evidence of additive contributions from both components.

5 Library 2: The "Wrap-Around" Strategy

From the results of the organozinc reactions using Library 1, two facts seemed evident. First, amino alcohols in which the amine nitrogen was incorporated in a ring (piperidine, morpholine, and pyrrolidine derivatives) were consistently the most effective ligands for organozinc additions. (Moreover, the same pattern was observed in preliminary screening for acetylide additions for DPC 963 synthesis.) Secondly, it was becoming clear that our library was not sufficiently diverse. It was top-heavy with amino alcohols derived from terminal epoxides, which necessarily meant there was no substituent on the *N*-terminal end of the amino alcohol. Yet our results in the stilbene oxide series – and a great deal of literature precedent[16] – underscored the potential value of substitution at this position.

In order to generate a second, more focused library containing only cyclic amine derivatives, we took advantage of the entropic boost that is gained when nitrogen is dialkylated with an α,ω-dihalide. (In contrast, monoalkylating agents like methyl iodide give rise to a mixture of products including quaternary ammonium derivatives.) A variety of optically active primary amino alcohols are commercially available. Treatment of these with 1,5-dibromopentane, 1,6-dibromohexane, or 2-bromoethyl ether would afford the desired products. This "wrap-around" strategy was not new. For example, in 1991 Soai had reported[21] the use of this approach (Equation 5) for the preparation of pyrrolidinylnorephedrine **10**:

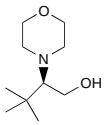
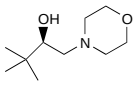
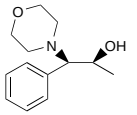
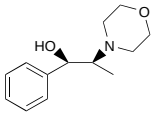
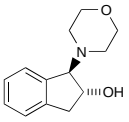
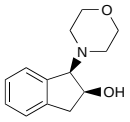
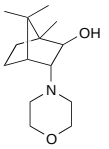
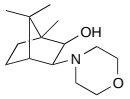
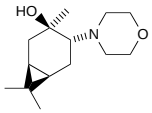
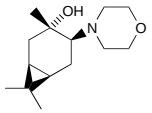


10 (5)

In general, the crude products obtained after extractive work-up were remarkably clean. However, duly chastened by our experience with Library 1, we elected to crystallize or chromatograph the product amino alcohols individually.

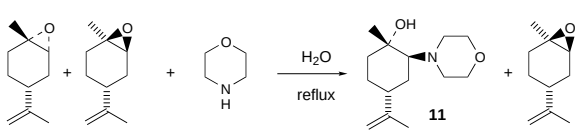
One attractive feature of this approach is that "matched pairs" of amino alcohols can be prepared to test individual stereoelectronic issues: For a given transformation, is steric bulk more important at the N-terminal or O-terminal end of the amino alcohol? In cyclic derivatives, is a *cis* or *trans* relationship between the amine and alcohol functionality more effective? Yield and ee data for the addition of diethylzinc to trimethylacetaldehyde (a challenging substrate due to

Table 2. Comparison of "matched pairs" of amino alcohols for the addition of diethylzinc to pivalaldehyde (5% catalyst, 24 h, 25 °C).

	11% ee 11% yield	91% ee 64% yield	
	88% ee 44% yield	86% ee 54% yield	
	17% ee 5% yield	33% ee 13% yield	
	11% ee 6% yield	97% ee 62% yield	
	76% ee 13% yield	82% ee 17% yield	

competing reduction to neopentyl alcohol) using several such matched pairs are shown in Table 2.

One compound in Library 2, which was to play an important role in the DPC 963 story, came from an outside source. During a seminar visit to the University of California at Santa Cruz, Professor Bakthan Singaram told me of an interesting breakthrough that had been achieved in his laboratory. Commercial limonene oxide is sold as a 1:1 mixture of diastereomers so that, at first blush, it would seem a poor candidate for conversion to an amino alcohol ligand. However, Prof. Singaram and undergraduate Will Chrisman had discovered conditions where one diastereomer would react with a cyclic amine to afford a single amino alcohol product, leaving the diastereomeric epoxide untouched (Equation 6).[22] Bakthan kindly provided a sample of amino alcohol **11** which we gladly incorporated into Library 2.



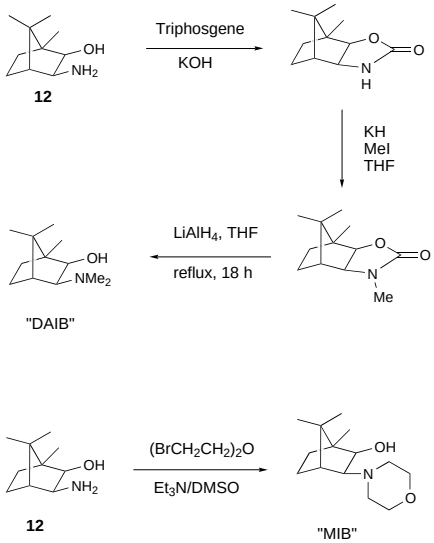
(6)

6 MIB: Improving a Classic Ligand

Arguably the most venerable amino alcohol ligand in the field of asymmetric catalysis is 3-*exo*-(dimethylamino)isoborneol or DAIB, which was first prepared by the Noyori group. DAIB was the first ligand to provide very high enantioselectivities in the addition of organozinc reagents to aldehydes.[23] It served as the basis for many of the early mechanistic studies on organozinc additions[24] and new applications for this remarkable ligand continue to appear.[25] Recently detailed procedures for its synthesis[26] and use[27] have been published in *Organic Syntheses.*

From an industrial chemist's viewpoint, three problems limit the potential of DAIB for use in commercial production of fine chemicals. (1) The most efficient synthesis shown in Scheme 1 still requires three steps for the conversion of the amino alcohol **12** to DAIB (six steps overall from camphor). (2) DAIB is an air-sensitive liquid, which decomposes upon storage. (3) While DAIB-promoted addition of organozinc reagents to aromatic aldehydes proceeds in excellent enantiomeric excess, it has not yet proven possible to obtain similar ee's in the case of α-branched aliphatic aldehydes. (Such additions would be especially valuable in the field of pharmaceutical synthesis, for example, in the manufacture of matrix metalloproteinase inhibitors.)

Our experience with Libraries 1 and 2 led us to question whether the dimethylamino functionality in DAIB is in fact optimal. We prepared *N*-cyclic analogues of DAIB each in a single step from amino alcohol **12** using the wrap-around technique.[28] For the case of the morpholine analogue[29] [3-*exo*-(*N*-morpholino)isoborneol or "MIB"] this straightforward procedure is also shown in Scheme 1.

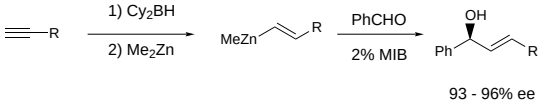


Scheme 1.

In addition to its greatly simplified synthesis, MIB offers other advantages over DAIB. MIB is a crystalline solid, mp 65 – 67 °C and remains stable after months of storage. Like DAIB, it promotes the addition of diethylzinc to aromatic aldehydes cleanly and in high enantiomeric excess as shown in Table 3. However, also shown in Table 3, the addition of Et_2Zn to several α-branched aliphatic aldehydes also proceeded in 97 – 99% enantiomeric excess. Only in the case of methacrolein and the straight-chain aliphatic aldehyde hexanal did the ee begin to erode. (Data for HHL are discussed later.)

Like DAIB before it, MIB has been used to provide new mechanistic insight into organozinc additions. Donna Blackmond and her coworkers used state-of-the art microcalorimetric techniques to demonstrate that MIB-mediated organozinc additions (and by extension those promoted by other amino alcohols) are subject to product inhibition.[30] Patrick Walsh and his coworkers investigated the extraordinary chiral amplification that characterizes organozinc additions using MIB.[31] They were able to demonstrate for the first time that such non-linear effects are *substrate dependent*, an observation with significant mechanistic implications for this class of reactions.

When we introduced MIB to the literature, we had little doubt that other research groups would develop exciting applications for this ligand. It did not take long for this expectation to be fulfilled. Walsh and coworkers recently reported an excellent protocol for the enantioselective (93 – 96% ee) addition of vinyl groups to aldehydes (Equation 7).[32] They have further shown that Equation 7 opens up an important new route to enantiopure allylic amines and α-amino acids.



(7)

7 HHL: Group Additivity in Ligand Design

Our experience with MIB further reinforced our belief that amino alcohols where the amine was part of a 6-membered ring (piperidinyl or morpholinyl) would often be optimal for promoting organozinc additions. What else could the structure-activity relationship of our libraries teach us about ligand design? An intriguing feature for the acyclic derivatives was that both the N-terminal and O-terminal substituents play a significant role in controlling the enantioselectivity of organozinc additions. An interesting way to visualize this is shown in Figure 2.

The prototypical "stripped down" ligand **13** provided virtually no enantioselectivity for addition of diethylzinc to benzaldehyde (Equation 4). Introduction of a phenyl group at the N-terminal position (ligand **14**) sharply increases enantioselectivity to 83%, while sterically "inflating" the methyl group of **13** to the level of a cyclohexyl substituent (ligand **15**) increases enantioselectivity to 67%. This led to the proposal[14] that ligand **16**, which incorporates both of these structural features, might provide even higher ee values for Equation 4.

Amino alcohol **16** appeared difficult to prepare. This would limit its value from an industrial perspective, and we did not initially pursue its synthesis. However, we subsequently prepared **16** as the result of a "happy accident".[33]

Table 3. Yield and enantiomeric excess for addition of diethylzinc to various aldehydes in the presence of 5% of β-amino alcohols MIB or HHL.

Aldehyde	% Yield (MIB)	% ee (MIB)	% Yield (HHL)	% ee (HHL)
benzaldehyde	98	98	98	**99**
m-tolualdehyde	97	98	97	**99**
p-tolualdehyde	98	**99**	96	98
m-anisaldehyde	n.d.	n.d.	97	**98**
p-fluorobenzaldehyde	98	98	98	**99**
p-chlorobenzaldehyde	95	97	97	**98**
isobutyraldehyde	94	**99**	93	98
2-ethylbutyraldehyde	92	**99**	91	**99**
cyclohexanecarboxaldehyde	94	**99**	93	98
cyclopropanecarboxaldehyde	91	**98**	87	96
trimethylacetaldehyde	62	97	73	**99**
2,2-dimethyl-4-pentenal	57	98	78	**99**
3-thiophenecarboxaldehyde	n.d.	n.d.	94	**96**
3-furaldehyde	91	**97**	n.d.	n.d.
methacrolein	94	89	95	**94**
hexanal	96	**91**	96	87

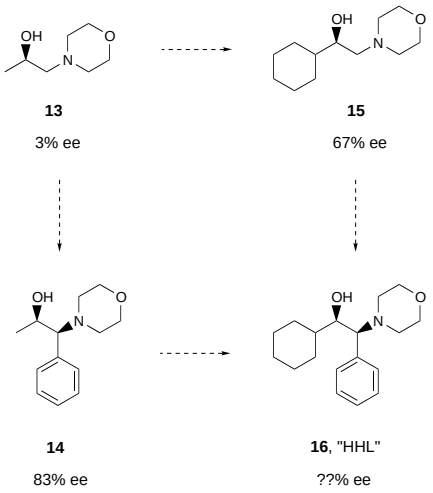
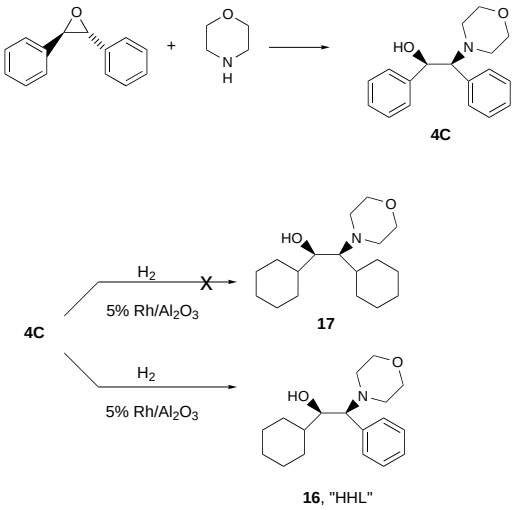


Figure 2. Observed enantioselectivity for addition of diethylzinc to benzaldehyde using selected β-amino alcohol from Libraries 1 and 2.

We were attempting to expand our amino alcohol library by hydrogenating the two benzene rings of the *trans*-stilbene oxide derivative **4C** using 5% rhodium on alumina as a heterogeneous catalyst. Crude amino alcohol, which still contained some unreacted morpholine, was used, and this turned out to be crucial for the observed chemistry. As shown in Scheme 2, morpholine acts as a selective catalyst poison such that the product was not the intended dicyclohexyl compound **17** but rather the monocyclohexyl analogue **16**. An X-ray crystal structure confirmed that the cyclohexyl substituent was at the O-terminal end of the molecule.

When we tested the new ligand **16**, which became known locally as the "hexahydro ligand" or just "HHL", we were delighted to find that it promoted the addition



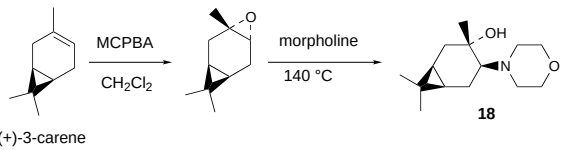
Scheme 2. Serendipitous synthesis of the "hexahydro ligand" **16**.

of diethylzinc to benzaldehyde in 98% yield and 99% enantiomeric excess. In contrast, the diphenyl compound **4C** gave only 89% ee while the dicyclohexyl compound **17** (prepared by a different route) gave 92% ee. HHL was then tested against a full battery of aldehydes with the results shown in Table 3. In general, these additions proceeded in excellent enantiomeric excesses, although the primary aliphatic aldehyde hexanal remains a problem substrate.[34]

8 The Assault on DPC 963

By this point, the lab was littered with vials containing over a hundred enantiopure amino alcohols and we began devoting all of our efforts to screening the acetylide addition (Equation 2). The results were generally disappointing. With most of the amino alcohols the addition proceeded in low enantioselectivity ($<$ 20%) and limited conversion ($<$30%). A notable exception was Singaram's limonene oxide-derived amino alcohol **11**, which promoted the desired addition in up to 74% enantiomeric excess at 84% conversion.

What was special about this particular ligand? One obvious structural feature that distinguished **11** from most of our other amino alcohols was the presence of a tertiary alcohol substructure. To improve selectivity, we felt that we needed to retain this feature but hoped to prepare a more rigid – what pharmaceutical scientists would call "locked" – version of **11**. Here nature in her abundance was very kind in providing (+)-3-carene. This enantiopure olefin is abundantly and inexpensively available. Unlike limonene, epoxidation of 3-carene produces a single diastereomer (Equation 8). Interestingly, the addition of morpholine to 3-carene oxide to give amino alcohol **18** had been reported several years ago.[35] Although this direct uncatalyzed addition afforded **18** in limited yield, we could obtain enough material for our screening studies.



(8)

We were pleased to discover that under the conditions of our screen, **18** promoted the desired addition of lithium cyclopropylacetylide (Equation 2) in 80% enantiomeric excess. A curious feature, which was also observed in the case of Singaram's ligand, was that the highest ee's were obtained at ligand-to-acetylide ratios substantially higher than 1:1. This seemed to be at odds with David Collum's studies[11] on related additions using pyrollidinylnorephedrine **10** in which the importance of 2:2 tetrameric aggregates had been demonstrated using multi-nuclear NMR.

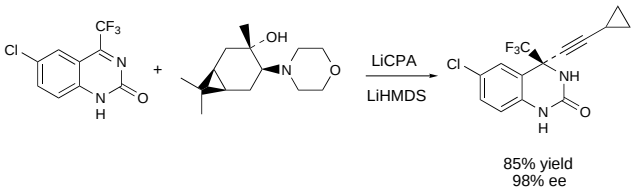
With this lead in hand, development was transferred to Pat Confalone's stellar process research group at DuPont-Merck and things began to move ahead very quickly.[36] Working with a talented team of process chemists under the project leadership of Rod Parsons proved to be one of the more exhilarating experiences of my professional life (so exciting in fact that I subsequently transferred from CR&D into the pharmaceutical process research organization).

Synthesis of **18** using Equation 8 was too slow and inefficient for use as a manufacturing process. Goss Kaufmann reasoned that sterically smaller ammonia would add more rapidly to 3-carene oxide than did morpholine; applying the wrap-around chemistry to the resulting primary amino alcohol would give **18**. This worked well but, still not satisfied, Goss successfully demonstrated the use of lithium perchlorate to promote the addition of morpholine itself to 3-carene oxide. Concerns over safety led Ben Stone and Greg Harris to look for alternative Lewis acids. Magnesium chloride promoted the addition but at high concentrations the reaction mass tended to "set up" and solidify. The use of magnesium bromide circumvented this problem. Ben Stone made the important discovery that **18** formed a salt with 2,4-dihydroxybenzoic acid that was uniquely effective in shedding isomeric impurities.

Lilian Radesca, Akin Davulcu and Bobbie Dorow made significant breakthroughs while optimizing reaction conditions for Equation 2. Lithium bis(trimethylsilyl)amide was superior to other bases. Remarkably, our observation that the highest ee's were obtained at ligand to acetylide ratios greater than 1:1 was confirmed; a 3:1 ratio was optimal in the case of **18**. Subsequent NMR studies[37] by David Collum at Cornell would provide a rational basis for both the superiority of Li-HMDS and the 3:1 stoichiometry. An intriguing observation by Akin Davulcu was that the highest ee's were obtained when the ketimine substrate contained traces of benzenesulfonic acid left over from the dehydration process used in its manufacture.

With all of the pieces in place, the team's vision could be realized. Amino alcohol **18** was manufactured in up to 400 kg quantities using the improved procedure. The scale-up of the process as applied to DPC 963 proceeded flawlessly and has been described elsewhere.[36] However, there was to be one additional twist in the NNRTI story: the decision was made to proceed with development of DPC 961 rather than DPC 963.

Although DPC 961 can be manufactured using Equation 1, it seemed likely that our DPC 963 process could be modified to provide DPC 961 more cheaply and efficiently. The conditions were re-optimized for this target. As illustrated in Equation 9, the chemistry worked very well indeed and provided the crude product in $>98\%$ enantiomeric excess; crystallization then raised the ee to 99.8%. DPC 961 was prepared in metric ton quantities using this approach. Very importantly, the chiral moderator **18** is recovered and recycled without loss in activity or selectivity.



(9)

9 Conclusion: What Did We Learn?

From an industrial perspective, the most significant outcome of this research was the development of an efficient and robust manufacturing process for DPC 963 and related NNRTI's. Along the way we discovered two highly selective catalysts for organozinc additions, MIB and HHL, which likewise appear destined to see use in the manufacture of fine chemicals.

The reaction of enantiopure epoxides with secondary amines was indeed a rapid way to generate a library of chiral amino alcohol ligands. However, efficiency came at a price. The need to control the regiochemistry of epoxide opening limited the choice of epoxides and this in turn restricted the portion of chiral space that was being probed. In this regard it is ironic to note that the successful ligand **18** was ultimately prepared using such an addition. However, 3-carene oxide was rejected as a building block in the original library design because of concerns that the addition would be inefficient coupled with the preconceived notion that the amino alcohols should be generated without the need for purification.

A couple of other lessons can be gleaned from our experience. It is evident that, especially in catalytic applications, the generation and screening of crude, unpurified ligands can be treacherous. As an alternative, generation of such ligand libraries on a solid support and their subsequent cleavage from the resin may combine the advantages of rapid synthesis and ready purification.[38] It can also be critically important to carry out screening under a variety of reaction conditions rather than under a single protocol. Because the optimal 3:1 stoichiometry for additions using Singaram's ligand **11** differed so greatly from our original 2:2 model based on pyrollidinylnorephedrine, we were frankly fortunate to have recognized the effectiveness of **11** during our initial screen.

Finally I would like to note the value of having a library of amino alcohols available "on the shelf". Process research in the pharmaceutical industry is often carried out under extreme time pressure. Amino alcohols are broadly useful ligands for a number of asymmetric transformations.[39] Once a collection of amino alcohols like the one described here has been

generated, it becomes a useful resource, instantly available for screening whenever the need arises.

Acknowledgements

Thanks are due to all of my co-authors on the publications cited in this review. Obviously I (and Bristol-Myers Squibb) owe a large debt of gratitude to Professor Bakthan Singaram and Dr. Will Chrisman for providing the initial sample of amino alcohol ***11*** *which plays a pivotal role in this story.*

References and Notes

[1] W. S. Knowles, *Acc. Chem. Res.* **1983**, *16*, 106.
[2] T. Aratani, *Pure Appl. Chem*. **1985**, *57*, 1839. The key enanantiopure cyclopropane intermediate for cilastatin was manufactured for Merck by Sumitomo.
[3] D. G. Melillo, I. Shinkai, T. Liu, K. Ryan, M. Sletzinger, *Tetrahedron Lett.* **1980**, *21*, 2783.
[4] J. C. Chabala, M. Mrozik, R. L. Tolman, P. Eskola, A. Lusi, L. H. Peterson, M. F. Woods, M. H. Fisher, W. C. Campbell, J. R. Egerton, D. A. Ostlind, *J. Med. Chem*. **1980**, *23*, 1134.
[5] For the group's research manifesto, see: W. A. Nugent, T.-V. RajanBabu, M. J. Burk, *Science* **1993**, *259,* 479.
[6] N. G. Anderson, *Practical Process Research & Development*, Academic Press, San Diego, **2000**, p. 341.
[7] S. D. Young, S. F. Britcher, L. O. Tran, L. S. Payne, W. C. Lumma, T. A. Lyle, J. R. Huff, P. S. Anderson, D. B. Olsen, S. S. Carroll, D. J. Pettibone, J. A. O'Brien, R. G. Ball, S. K. Balani, J. H. Lin, I.-W. Chen, W. A. Schleif, V. V. Sardana, W. J. Long, V. W. Byrnes, E. A. Emini, *Antimicrobr. Agents Chemother.* **1995**, *39*, 2602.
[8] J. W. Corbett, S. S. Ko, J. D. Rodgers, S. Jeffrey, L. T. Bacheler, R. M. Klabe, S. Diamond, C.-M. Lai, S. R. Rabel, J. A. Saye, S. P. Adams, G. L. Trainor, P. S. Anderson, S. K. Erickson-Viitanen, *Antimicrobr. Agents Chemother.* **1999**, *43*, 2893.
[9] N. A. Magnus, P. N. Confalone, L. Storace, *Tetrahedron Lett*. **2000**, *41*, 3015.
[10] M. A. Huffman, N. Yasuda, A. E. DeCamp, E. J. J. Grabowski, *J. Org. Chem*. **1995**, *60*, 1590.
[11] A. Thompson, E. G. Corley, M. F. Huntington, E. J. J. Grabowksi, J. F. Remenar, D. B. Collum, *J. Am. Chem. Soc*. **1998**, *120*, 2028.
[12] a) W. A. Nugent, *J. Am. Chem. Soc*. **1992**, *114*, 2768; b) W. A. Nugent, R. L. Harlow, *J. Am. Chem. Soc*. **1994**, *116*, 6142; c) W. A. Nugent, *J. Am. Chem. Soc*. **1998**, *120*, 7139; d) M. Bonchio, G. Licini, F. DiFuria, S. Mantovani, G. Modena, W. A. Nugent, *J. Am. Chem. Soc*. **1999**, *121*, 6258.
[13] Sharpless has incorporated the addition of amines to (racemic) epoxides as part of his "click chemistry" protocol; see also: B. L. Chang, A. Ganesan, *Bioorg. Med. Chem. Lett*. **1997**, *7*, 1511.
[14] W. A. Nugent, G. Licini, M. Bonchio, O. Bortolini, M. G. Finn, B. W. McCleland, *Pure Appl. Chem.* **1998**, *70*, 1041.
[15] N. Oguni, T. Omi, *Tetrahedron Lett.* **1984**, *25*, 2823.
[16] a) L. Pu, H.-B. Yu, *Chem. Rev.* **2001**, *101*, 757; b) K. Soai, S. Niwa, *Chem. Rev.* **1992**, *92*, 833; c) R. Noyori, *Assymetric Catalysis in Organic Synthesis*, Wiley, New York, **1994**, Chapter 5.
[17] This feat was accomplished in less than one week by my intrepid CR&D technician, David M. Lattomus. Thanks again, Dave, for 18 years of energetic teamwork.
[18] M. Ishizaki, K.-i. Fujita, M. Shimamoto, O. Hoshino, *Tetrahedron: Asymmetry* **1994**, *5*, 511.
[19] P. I. Dosa, J. C. Ruble, G. C. Fu, *J. Org. Chem.* **1997**, *62*, 444.
[20] This notion was first applied to modular ligand design by Snapper and Hoveyda who noted "The described strategy assumes that the influence of each ligand subunit is independent and additive: it is impossible to rule out cooperative effects without individually testing each combination". B. M. Cole, K. D. Shimizu, C. A. Krueger, J. P. A. Harrity, M. L. Snapper, A. H. Hoveyda, *Angew. Chem. Int. Ed. Engl*. **1996**, *35*, 1668.
[21] K. Soai, S. Yokoyama, T. Hayasaka, *J. Org. Chem*. **1991**, *56*, 4264. For a similar preparation of the morpholinyl analogue of **10** see: T. Fujisawa, S. Itoh, M. Shimizu, *Chem. Lett*. **1994**, *10*, 1777.
[22] W. Chrisman, J. N. Camara, K. Marcellini, B. Singaram, C. T. Goralski, D. L. Hasha, P. R. Rudolf, L. W. Nicholson, K. K. Borodychuk, *Tetrahedron Lett.* **2001**, *42*, 5805.
[23] M. Kitamura, S. Suga, K. Kawai, R. Noyori, *J. Am. Chem. Soc*. **1986**, *108*, 6071.
[24] a) M. Kitamura, S. Suga, H. Oka, R. Noyori, *J. Am. Chem. Soc*. **1998**, *120*, 9800; b) M. Yamakawa, R. Noyori, *Organometallics* **1999**, *18*, 128.
[25] a) P. I. Dosa, G. C. Fu, *J. Am. Chem. Soc*. **1998**, *120*, 445; b) A. H. M. deVries, J. F. G. A. Jansen, B. L. Feringa, *Tetrahedron* **1994**, *50*, 4479; c) W. Oppolzer, R. N. Radinov, *J. Am. Chem. Soc*. **1993**, *115*, 1593; d) W. Oppolzer, R. N. Radinov, J. De Brabander, *Tetrahedron Lett.* **1995**, *36*, 2607.
[26] J. D. White, D. J. Wardrop, K. F. Sundermann, *Org. Synth*. **2002**, *79*, 130.
[27] M. Kitamura, H. Oka, S. Suga, R. Noyori, *Org. Synth*. **2002**, *79*, 139.
[28] In fact, conversion of amino alcohol **12** to its pyrrolidinyl analogue using this approach had been reported by two research groups. See Ref.[25b] and M. Shimizu, Y. Teramoto, T. Fujisawa, *Tetrahedron Lett*. **1995**, *36*, 729.
[29] W. A. Nugent, *Chem. Commun.* **1999**, 1369.
[30] T. Rosner, P. J. Sears, W. A. Nugent, D. G. Blackmond, *Org. Lett.* **2000**, *2*, 2511.
[31] Y. K. Chen, A. M. Costa, P. J. Walsh, *J. Am. Chem. Soc.* **2001**, *123*, 5378.
[32] Y. K. Chen, A. E. Lurain, P. J. Walsh, *J. Am. Chem. Soc.* **2002**, *124*, 12225.
[33] W. A. Nugent, *Org. Lett*. **2002**, *4*, 2133.
[34] Lest we become too enamored with the apparent success of Figure 2, we note the following: replacement of the cyclohexyl group of **15** with a *t*-butyl group gives a known amino alcohol (M. Hayashi, T. Kaneko, N. Oguni,

J. Chem. Soc. Perkin Trans. 1, **1991**, 25) which promotes the addition of diethylzinc to benzaldehyde in 98% ee. Yet replacement of the cyclohexyl group in HHL with a *t*-butyl group did not further increase enantioselectivity.

[35] I. V. Fedyunina, V. V. Plemenkov, G. Sh. Bikbulatova, L. E. Nikitina, I. A. Litvinov, O. N. Kataeva, *Chem. Nat. Compd. (Engl. Transl.)* **1992**, *28*, 173.

[36] G. S. Kauffman, G. D. Harris, R. L. Dorow, B. R. P. Stone, R. L. Parsons, Jr., J. A. Pesti, N. A. Magnus, J. M. Fortunak, P. N. Confalone, W. A. Nugent, *Org. Lett*. **2000**, *2*, 3119.

[37] R. L. Parsons, Jr., J. M. Fortunak, R. L. Dorow, G. D. Harris, G. S. Kauffman, W. A. Nugent, M. D. Winemiller, T. F. Briggs, B. Xiang, D. B. Collum, *J. Am. Chem. Soc*. **2001**, *123*, 9135.

[38] For examples of amino alcohol libraries generated using this approach, see: a) M. R. Tremblay, P. Wentworth, Jr., G. E. Lee, K. D. Janda, *J. Combinatorial Chem.* **2000**, *2*, 698; b) S. Kobayashi, M. Moriwaki, R. Akiyama, S. Suzuki, I. Hachiya, *Tetrahedron Lett*. **1996**, *37*, 7783; c) B. Altava, M. I. Burguete, E. Garcia-Verdugo, S. V. Luis, O. Pozo, R. V. Salvador, *Eur. J. Org. Chem*. **1999**, 2263.

[39] D. J. Ager, I. Prakash, D. R. Schaad, *Chem. Rev*. **1996**, *96*, 835.