FEATURE ARTICLE

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Small peptides as ligands for catalytic asymmetric alkylations of olefins. Rational design of catalysts or of searches that lead to them?

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Amino acid-based chiral ligands have been developed for use in Cu-catalyzed enantioselective allylic alkylations and conjugate additions that allow access to optically enriched compounds that are otherwise difficult to prepare. These chiral ligands are easily modified and have been identified through mechanism-based library screening. The data presented point to the significance of the availability of a collection of catalysts, since subtle variations in substrate or nucleophile structure often call for a different optimal chiral ligand. Can a catalyst be truly "rationally designed" or do we design our search pathway that eventually leads us to such a catalyst? What is meant by a "general catalyst"? Do we need a class of effective catalysts instead? These and related questions are addressed in the context of the above studies.

…[A]s one superimposes a religion on blind laws of nature,…it was in vain.

…[W]henever we become conscious anew of beauty and happiness…, we invariably forget that these are individual qualities…. For we believed that we are taking happiness and beauty into account, whereas in fact we left them out and replaced them by syntheses in which there is not a single atom of either.

Marcel Proust, *Within a Budding Grove* (Moncrieff and Kilmartin translation)

Introduction

Discovery of effective chiral catalysts has occupied the time and minds of many investigators during the last two to three decades. One important question, likely often ruminated but rarely raised in public, is "How does one go about discovering an optimal catalyst?" The phrase "rational design" is used by researchers who believe that one can generally design effective catalysts based on mechanistic principles. More recently, screening strategies have been put forth to accelerate and increase the efficiency of the search process by those who suggest that—in the true definition of the word[1]—designing a catalyst might well be impossible. No doubt, one may utilize mechanism to identify and search paths that lead to a desirable catalyst. To identify a catalyst after months or years of preparing numerous candidates, however, should perhaps not be described as a victory for "rational design", but a pleasant conclusion to a rewarding search for a valuable synthetic method that may indeed have been influenced by logical thought. It has been argued that a mechanistic appreciation of activity and selectivity levels *subsequent* to a catalyst's identification does not justify the characterization of the original discovery as "rationally designed".

There is also the debate on catalyst generality. Can we have a chiral catalyst that is truly general or is it best that we identify and have access to a *selection* of them? And, much like the question of design, whether one believes that a catalyst is "general" or not depends on what one means by such an entity. As an example, is our definition of a general chiral hydrogenation catalyst one that allows us to reduce *all* olefins (cyclic, acyclic and of all substitution patterns) efficiently and with high selectivity (*e.g.*, > 90% ee)? Or should a catalyst be labeled as general when it is effective for a subclass of substrates (*e.g.*, sterically unencumbered *cis* cyclic disubstituted alkenes)?

During the past decade, we have faced and struggled with such questions in the course of our studies on the development of a variety of catalytic asymmetric reactions. In this account, in the context of one of our programs in asymmetric catalysis, we describe how we have attempted to appreciate, address and come to terms with the above fundamental issues.

Initial efforts: Zr- and Ni-catalyzed alkylations

Asymmetric alkylation of alkenes, promoted by chiral metal complexes, has been a topic of long-standing interest in these laboratories.[2] During the early to mid-nineties, we explored the

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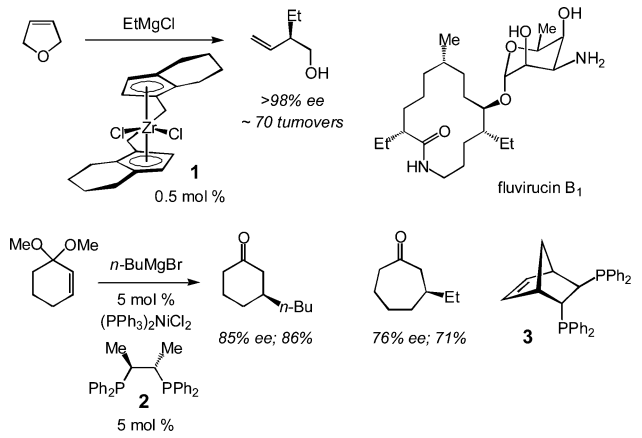
mechanism[3] and utility of Zr-catalyzed asymmetric additions of alkylmagnesium halides to cyclic allylic ethers (Scheme 1); these



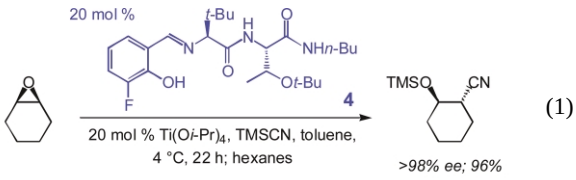
Scheme 1 Early examples of catalytic asymmetric olefin alkylation.

processes were subsequently employed in the total synthesis of biologically active molecules such as fluvirucin B_1.[4] However, the Zr-catalyzed transformations possess several limitations. One shortcoming is that Grignard reagents other than ethylmagnesium halides give rise to inefficient transformations.[3] Another problem is that alkylmagnesiums lacking an active β-hydrogen cannot participate in the alkylation process (*e.g.*, aryl- or vinylmagnesium halides). We therefore initiated studies to identify catalytic alkylations that do not suffer from such drawbacks. Two principles guided the latter investigations. We judged that exploration of transformations promoted by late transition metals might prove to be more fruitful; with this class of metal complexes, β-hydride abstraction or elimination is typically less facile, allowing us to use alkylmetals bearing aryl-, vinyl- and methyl groups. Furthermore, we appreciated that the difficulties we faced with the Zr-catalyzed alkylations, namely the inability to enhance enantioselectivity or yield, stemmed from the architectural inflexibility of chiral metallocenes (*e.g.*, **1** in Scheme 1). Steric and electronic modification of zirconocenes (particularly of the bridged variety) proved laborious and could only be effected with limited range. It should be noted that later methods developed by Negishi,[5] regarding Zr-catalyzed alkylations of unactivated olefins with trialkylaluminum reagents, addressed the issue regarding the requirement of a β-hydride. Nonethless, such protocols cannot be extended to allylic allylations and also require the limiting chiral zirconocene catalysts.

Our exploration of late transition metal-catalyzed processes resulted in the development of Ni-catalyzed asymmetric alkylation of cyclic unsaturated acetals (Scheme 1).[6] We discovered that enantioselective addition of aryl- and methylmagnesium halides, as well as EtMgBr and Grignard reagents bearing longer alkyl chains, can be carried out in the presence of a Ni salt and a chiral bis(phosphine). Because of the availability of a larger (relative to zirconocenes) selection of chiral catalyst candidates, efforts to enhance enantioselectivity proved to be more rewarding. We discovered that alkylations of six-membered ring allylic acetals proceed with improved selectivity (up to 90% ee) when carried out in the presence of chiraphos **2** (*vs.* ten or so other bis(phosphine)s). In contrast, with the cycloheptenyl substrates, it is norphos (**3**) that delivers the best enantioselectivity (~ 75% ee). We found it striking that use of chirophos to effect additions to the medium ring substrate, or of norphos to promote asymmetric alkylations of the cyclohexenyl acetal, leads to the formation of racemic products. It appeared that we were on the right path: since we had more ligands at our disposal, we could extend the Ni-catalyzed method to include reactions of medium ring electrophiles. However, enantioselectivities needed improvement. This led us to realize that, although chiral bisphosphines can be modified (such as changing the methyls of **2** to *i*-Pr or phenyl groups), such alterations again require lengthy procedures, are inefficient and can, at most, provide only a handful of ligand candidates within a reasonable amount of time (~ one week). Ease of ligand modification loomed large as we had observed on numerous occasions that mechanistic subtleties, which may unpredictably vary from substrate to substrate and can be influenced by changes in condition that would initially appear inconsequential, can alter efficiency and selectivity of a catalytic reaction (see below for additional discussion). As an example, we had just discovered that the Ni-catalyzed alkylation of acetals (Scheme 1) is significantly less enantioselective in the absence of the *achiral* PPh_3.[7] It was clear that our search for a more practical and generally useful class of chiral ligands for olefin alkylations was far from over.

Readily modifiable ligands for Cu-catalyzed asymmetric allylic alkylations

We did not have to look far for a more effective and general solution. While the above studies were in progress, another program in our laboratories involved the development of catalytic asymmetric methods for cyanide additions to epoxides and imines (eqns. (1–2)).[8] In these efforts, amino acid-based Schiff bases, such as **4** and **5**, were synthesized in significant numbers (40–50 in only a few days) on solid support in high yield and screened, leading to identification of the more desirable ligand/metal combinations. These ligands were especially attractive to us because of the ease with which they could be prepared and modified.[9] Moreover, we were intrigued that the decision to use these amino acid-derived ligands defied two of the more popular principles in asymmetric catalyst development: the peptidic chiral ligands are not C2-symmetric and carry not one but multiple sites for metal binding. In the course of our efforts involving peptide/metal complexes, we came to appreciate that these non-symmetric catalysts can impart significant asymmetric induction in a number of C–C bond forming processes. Ironically, the lack of ligand symmetry proved specially conducive to efficient synthesis of ligand libraries and their subsequent screening. Detailed mechanistic studies later indicated that, in the case of Ti-catalyzed asymmetric amino nitrile synthesis (eqn. (2)),[10] the presence of multiple Lewis basic sites, as long as they differ in their binding preferences, is advantageous and can lead to effective polyfunctional catalysis.



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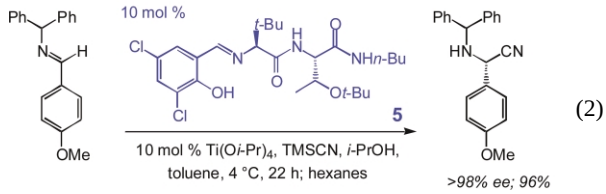
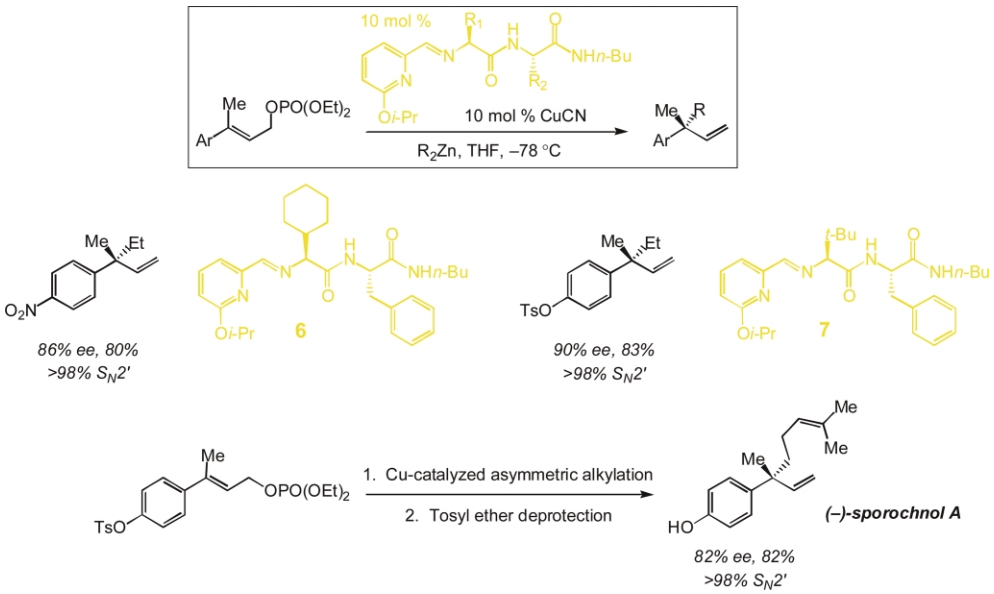


(2)

Adapting amino acid-based ligands to catalytic asymmetric alkylations of olefins required certain adjustments however. First, as we continued to suspect that late transition metal catalysis would be required, we surmised that chiral salicyl-based ligands (*e.g.*, **4** and **5**) would have to be modified to accommodate proper coordination to the metal. Furthermore, use of less nucleophilic alkylating agents would, at least initially, be preferred, since the electrophilicity and acidity (NH) of secondary amides might prove to be incompatible with Grignard reagents. It was based on such logic that we set out to develop enantioselective olefin alkylations



Scheme 2 First generation Cu-catalyzed asymmetric allylic alkylations.

in the presence of late transition metal salts and modified peptidic ligands.

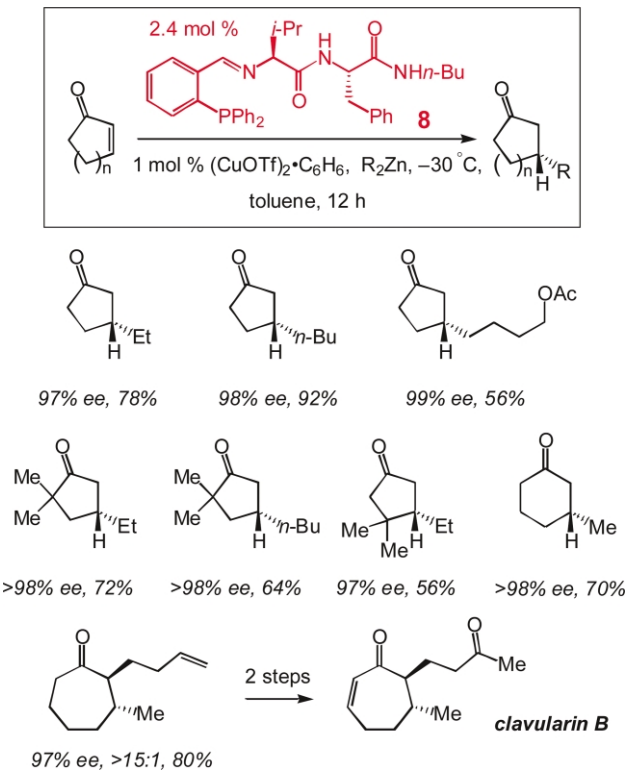
Our initial testing ground was in connection with the development of catalytic alkylations with hard alkylmetals, which, in spite of several critical studies reported by van Koten, Backvall, Feringa and Knochel, represented a largely unsolved and important problem is synthetic methodology.[11] The results of our efforts regarding reactions of allylic phosphates are summarized in Scheme 2.[12] Screening studies indicated that the combination of CuCN and pyridyl dipeptide ligands (*cf.* **6** and **7**, Scheme 2) promote regioselective (> 98% S_N2') alkylations of trisubstituted unsaturated phosphates with various alkylzinc reagents (not only with the ever-popular Et_2Zn). Further ligand optimization, through the use of positional scanning strategy,[8a] indicated that dipeptides **6** and **7** deliver non-racemic products bearing quaternary carbon stereogenic centers in 78–90% ee. A concise enantioselective total synthesis of (−)-sporochnol A highlighted the utility of the catalytic protocol. It is important to note that the salicyl aldehyde-derived Schiff base ligands (*cf.* **4** and **5** in eqn (1–2)), used in conjunction with CuCN, give rise to significantly lower enantioselectivity.

More recent efforts indicate that a different Cu salt/amino acid-derived chiral ligand mixture offers a more effective combination for catalyzing the above asymmetric allylic alkylations. We shall return to this topic after discussing findings regarding catalytic asymmetric conjugate additions (ACA). The results of the latter studies will allow for a more lucid appreciation of the significance of ligand diversity and the unpredictability that shadows the process of determining the identity of an optimal catalyst.

Chiral amino acid-derived phosphines for efficient catalytic asymmetric conjugate additions

As noted above, another class of late transition metal-catalyzed alkylations that we have focused on are conjugate additions of alkylmetals to unsaturated carbonyls. At the time we initiated our studies, there were a number of disclosures, notably by Feringa, Pfaltz and Alexakis, centered on development of Cu-catalyzed ACA of alkylzincs to enones.[13] Accordingly, we set out to design and develop catalytic ACA reactions that remained problematic in spite of the extant reports. Effective and highly enantioselective catalytic ACA of alkylmetals to cyclopentenones, acyclic unsaturated carbonyls and unsaturated carbonyls with olefins of higher substitution thus stood as our initial goals.

Our first breakthrough was the discovery that dipeptide phosphine **8** (Scheme 3) in the presence of $(CuOTf)_2{\cdot}C_6H_6$ effectively and enantioselectively promotes ACA of different alkylzincs to six-

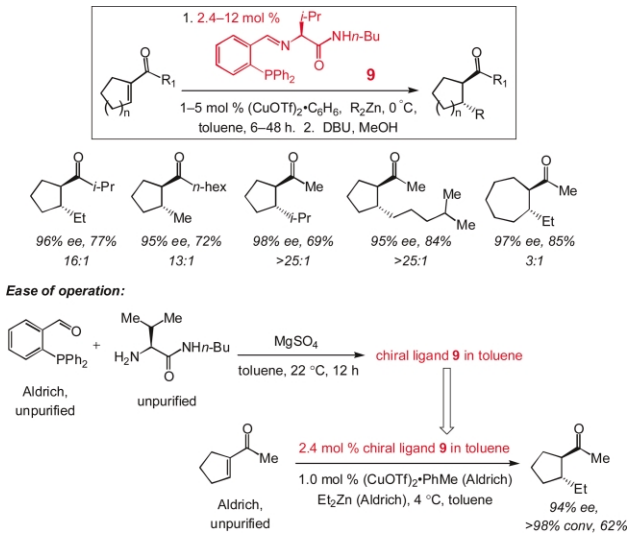


Scheme 3 Cu-catalyzed ACA of alkylzincs to disubstituted cyclic enones.

and seven-membered ring enones.[14] In contrast, the derived salicyl and pyridyl ligands afford racemic products. Importantly, reactions involving cyclopentenones—including those bearing sterically congested olefins—can be induced to undergo additions with high enantioselectivity (Scheme 3). In most cases, 2–3 mol% catalyst loading is sufficient for clean and complete conversion within a few hours. Synthetic utility was demonstrated through a brief enantioselective synthesis of anticancer agent clavularin B, wherein the purported Zn-enolate intermediate was alkylated *in situ* to afford

the desired functionalized cycloheptanone in excellent yield and with high diastereo- and enantioselectivity. It is noteworthy that the same chiral ligand, phosphine **8**, may be used to promote ACA to various cyclic enones. That is, although the modularity of the amino acid-based ligands was used to identify the optimal chiral catalyst, we did not need to exploit this attribute to enhance reactivity and/or enantioselectivity when performing additions to cyclic enones of different sizes. The latter approach has proved crucial on several occasions (*e.g.*, studies summarized in Scheme 2), a strategic advantage that will be treated in more detail after certain other aspects of our studies have been presented.

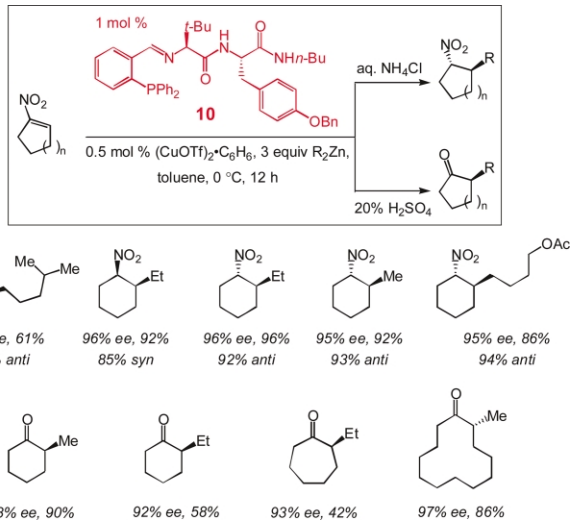
In contrast to catalytic ACA of cyclic enones bearing disubstituted olefins, screening studies indicated that reactions of the more substituted cyclic alkenes, shown in Scheme 4, can be



Scheme 4 Cu-catalyzed ACA of alkylzincs to trisubstituted cyclic enones.

promoted with excellent enantioselectivity in the presence of $(CuOTf)_2{\cdot}C_6H_6$ and phosphine ligand **9** (Scheme 4).[15] That the presence of a second amino acid is not required may have significant mechanistic implications (under study). That the requisite amino acid is commercially available and inexpensive (both antipodes) renders this class of asymmetric transformations especially easy to utilize. The facility with which the present protocol can be used is demonstrated by an example depicted in Scheme 4: the chiral ligand can be prepared and utilized *in situ* with unpurified and commercially available enone, alkylzinc and Cu salt to deliver the desired ACA product in good yield and excellent enantioselectivity. Initial diastereoselectivity is low, but higher stereoisomeric purity can be achieved in many cases through treatment with DBU. Furthermore, whereas five- and seven-membered trisubstituted enones undergo addition, the corresponding cyclohexenyl substrate is recovered unchanged (more on this later).

A related class of catalytic ACA involves reactions of cyclic nitroalkenes (Scheme 5).[16] Transformations are promoted in the presence of 1–10 mol% chiral phosphine **10** (depending on the nature of the alkylzinc) and $(CuOTf)_2{\cdot}C_6H_6$ to afford, after mild acidic workup, functionalized nitroalkanes in high enantio- and diastereoselectivity. Unlike reactions of trisubstituted enones shown in Scheme 4, the six-membered ring nitroalkene readily undergoes Cu-catalyzed ACA. Another point regarding the reactions of cyclohexenyl substrates is that it is the *syn*—not the *anti* diastereomer—that is obtained kinetically; treatment of the initial product with DBU delivers the *anti* isomer. Perhaps the most synthetically useful aspect of the Cu-catalyzed asymmetric protocol is that workup under stronger acidic conditions (20% H_2SO_4) leads to the formation of the corresponding α-alkyl cyclic ketones

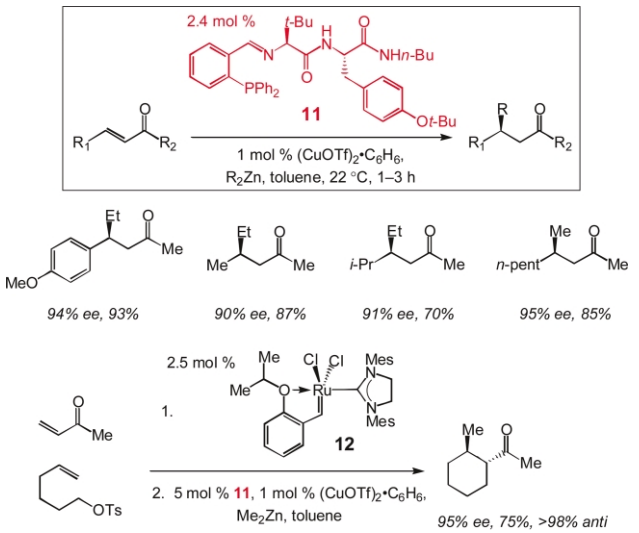


Scheme 5 Cu-catalyzed ACA of alkylzincs to trisubstituted cyclic nitroalkenes.

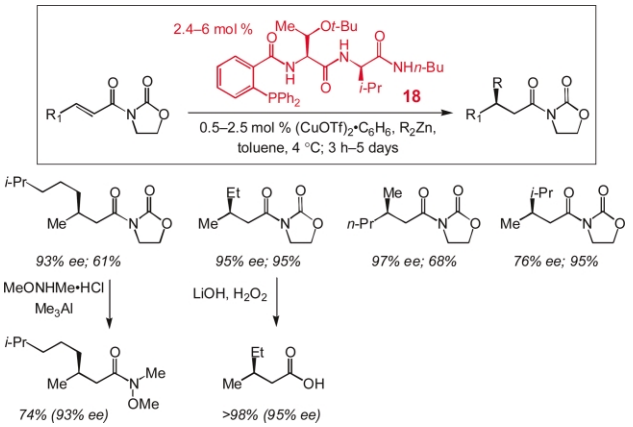
in high optical purity. Representative examples of small, medium and large ring ketone products are illustrated in Scheme 5. It should be mentioned that highly efficient and enantioselective Rh-catalyzed conjugate additions of boronic acids to various nitroalkenes have been reported by Hayashi,[17] but the present method represents the first general method for efficient, catalytic and highly enantioselective ACA of *alkyl*metals to cyclic nitroalkenes.[18]

The structural similarity between trisubstituted enones in Scheme 4 and cyclic nitroalkenes in Scheme 5 leads one to wonder whether phosphine **10** is effective in promoting the Cu-catalyzed ACA of the ketones and if the Val-derived **9** can initiate additions to the nitroalkenes. The answer to this question underlines one of the more powerful attributes of this general class of amino acid-based chiral ligands and the screening strategies that are used to identify optimal ligands (*not* ligand). It is not unusual that a screening study leads to several ligand candidates that promote a particular process effectively. These structures are subsequently prioritized based on factors such as costliness and general effectiveness. Thus, it is possible that a ligand that is identified as most potent for one set of transformations can also promote some—but not all—reactions of another set with similar facility and selectivity. As might be expected, such overlap becomes more likely as the structure of the substrates resemble one another. Thus, ligand **10** can initiate many reactions of trisubstituted enones with high enantioselectivity, but cost considerations and ease of operation point to **9** as the ligand of choice. It is even possible that, *in a particular case*, a lower priority ligand (one that typically is less effective and/or gives lower selectivity) that has been identified through screening can prove to be more effective (see below for an example).

We next focused our attention on Cu-catalyzed ACA involving acyclic enones, a class of substrates that had proven particularly problematic in previous studies.[19] As summarized in Scheme 6, chiral phosphine **11** is effective in promoting Cu-catalyzed ACA of alkylzincs to acyclic α,β-unsaturated ketones.[20] Reactions proceed at ambient temperature with 2–3 mol% catalyst loading. Substrates are easily accessed through catalytic cross metathesis, most effectively promoted by Ru complex **12** (Aldrich), also developed in our laboratories.[21] As the representative example in Scheme 6 illustrates, the derived enolate can be alkylated intramolecularly to afford optically enriched cyclic ketones with high diastereoselectivity. This is the same product that would be obtained through reactions of trisubstituted cyclic enones; successful formation of the cyclohexenyl products thus offers a solution to the lack of reactivity of the trisubstituted six-membered ring enones (*cf.* Scheme 4 and the related discussion).



Scheme 6 Cu-catalyzed ACA of alkylzincs to acyclic enones.



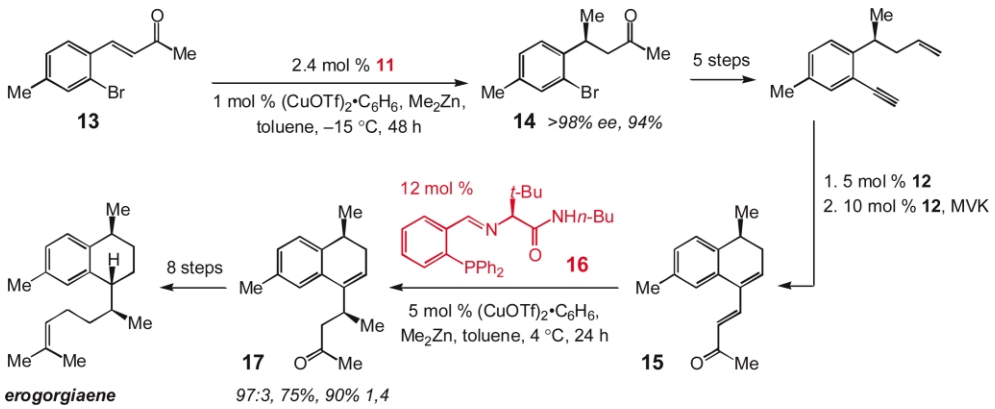
Scheme 8 Cu-catalyzed ACA of alkylzincs to acyclic unsaturated *N*-acyloxazolidinones.

The Cu-catalyzed ACA of acyclic enones was scrutinized by application to the enantioselective total synthesis of antimycobacterial agent erogorgiaene.[22] Several critical steps of the synthesis are illustrated in Scheme 7. One key transformation is the catalytic ACA of Me_2Zn to enone **13** to afford **14** in the presence of 2.4 mol% dipeptide phosphine **11**; the addition proceeds smoothly when carried out in multigram scale. Conversion to dienone **15** was effected in seven steps, including sequential enyne ring-closing metathesis/cross metathesis with methyl vinyl ketone promoted by Ru complex **12**. The difficult problem of remote stereocontrol was addressed through a site- and enantioselective Cu-catalyzed ACA of Me_2Zn to **15** in the presence of 12 mol% **16** to afford **17**. With Me_2CuLi, the undesired diastereomer was generated predominantly (3:1). Moreover, formation of ketone **17** in the presence of dipeptide **11** proceeds with high asymmetric induction (92% ee) but with minimal regioselectivity (1.5:1, 1,4:1,6 addition *vs.* 9:1 with **16**). The principle of ligand diversity, as well as the importance of chiral ligands that are readily modular, is underlined again.[9] Phosphine **16**, a less effective ligand for conjugate addition to **13**, happens to be a significantly more attractive choice for promoting the reaction of dienone **15**. This is an example where the availability of a selection of easily accessible ligands that are structurally different but related and can all promote a set of transformations leads to significant synthetic versatility.

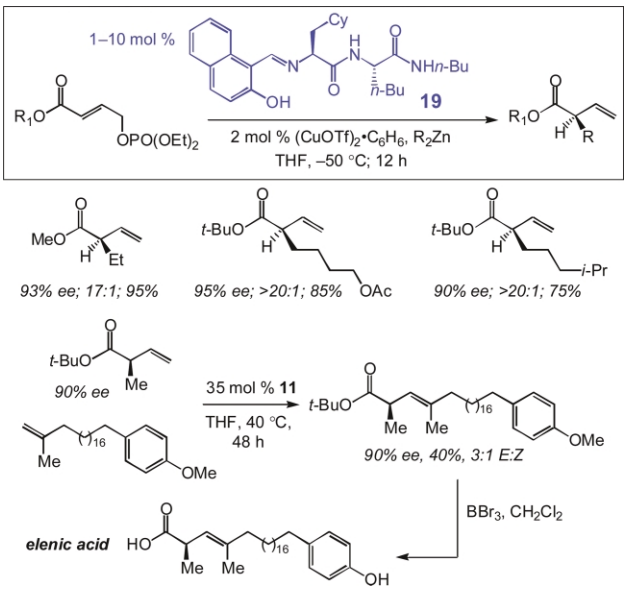
To expand the scope of Cu-catalyzed ACA of linear unsaturated carbonyls to include carboxylic acid derivatives, we later developed efficient enantioselective additions of alkylzincs to unsaturated *N*-acyloxazolidinones (Scheme 8).[23] The resulting ACA products are readily and efficiently converted to synthetically useful optically enriched carbonyl intermediates (such as Weinreb amide and carboxylic acid shown in Scheme 8). It is important to note that this class of catalytic ACA reactions proceed in < 40% ee in the presence of chiral phosphines **8–11** or mono-amino acid bearing ligands such as **16**. Extensive screening studies led us to identify phosphine **18** (Scheme 8) as the optimal ligand. Chiral dipeptide **18** differs in two critical aspects from the phosphines employed in the above studies: The peptide-phosphine linkage is an amide (*vs.* an imine), and the dipeptide bears an L and a D amino acid (*vs.* two D or L residues). Although detailed mechanistic studies have not yet been performed, significant alteration of the ligand structure is not surprising. The availability of the additional Lewis basic carbonyl of the carbamate group likely alters the substrate–catalyst complex (*vs.* reactions of ketones) and requires an alternative chiral catalyst for optimal results.

Cu-catalyzed asymmetric allylic alkylation revisited

In light of the advances made by the chiral phosphine ligands in promoting various ACA reactions in conjunction with $(CuOTf)_2{\cdot}C_6H_6$, we decided to examine whether the related allylic alkylations can be effected more selectively with this ligand/metal combination (*vs.* pyridyl peptide/CuCN mixture shown in Scheme 2). Such re-evaluation appeared particularly imperative since, for reasons of efficiency we typically do not examine every possible metal/ligand system in searching for the optimal conditions. To test the above hypothesis, we chose the allylic alkylation illustrated in Scheme 9, where the expected products are the synthetically versatile α-alkyl,β,γ-unsaturated esters. Extensive screening indicated that a combination of certain dipeptidic phosphines (*e.g.*, **10** or **11**) in the presence of CuOTf result in the formation of the desired products in high ee; however, little or no regioselectivity was observed (50% achiral S_N2 product formed).[24] These investigations led us to determine that salicyl-based dipeptide **19**



Scheme 7 Application of Cu-catalyzed ACA of alkylzincs to acyclic enones to the total synthesis of erogorgiaene.



Scheme 9 Cu-catalyzed asymmetric allylic alkylations giving β,γ-unsaturated esters.

(Scheme 9)—a member of a class of ligands thought to be more effective for early transition metal catalysis (eqns. (1–2))—in combination with $(CuOTf)_2{\cdot}C_6H_6$ delivers the desired products efficiently and in high enantio- and regioselectivity. An asymmetric total synthesis of elenic acid served to demonstrate the synthetic utility of the Cu-catalyzed alkylation (as well as underline that better cross metathesis catalysts are needed). Ongoing studies indicate that dipeptide **19** and $(CuOTf)_2{\cdot}C_6H_6$ afford significantly higher enantioselectivity in alkylations shown in Scheme 2 as well.[25]

Why not a "general catalyst" for all alkylations or conjugate additions?

That effective ACA (or any other reactions) of various unsaturated carbonyls may require different ligands is neither surprising nor should it be considered a weakness of the present methods. It is seldom that catalysis is predictable or general.[9] Subtle energetic changes in any of the steps within a catalytic cycle can lead to startling alterations in reactivity and selectivity caused by substrate or catalyst structure; it is unwise to generalize the origin of such changes. Our approach is therefore to exploit mechanistic principles to design—not a particular catalyst—but a collection of catalysts or strategies that allow us to search for optimal conditions to promote catalytic transformations.

To design a catalyst may well be impossible (design in the true sense);[9] this may explain why the detailed and cohesive mechanisms by which the so-called "designed catalysts" operate are largely mysterious distant landscapes that remain subject to perennial restorations. The data shown in Fig. 1 help underline the significance of these points.[26] The same Cu-catalyzed ACA initiated by two structurally similar dipeptide phosphines exhibit entirely different temperature/selectivity profiles. Such observations, as well as those summarized in this article, bring home the point that ligand diversity and facile modularity are critical to catalyst identification and development. Vicissitudes in the energetics of catalyst cycles are too unpredictable and our knowledge of such intricacies remains too limited for us to boast of designing catalysts.[1]

We have seen in numerous cases that the availability of a group of catalysts can lead one to identify effective solutions to problems in reactivity and selectivity (*e.g.*, ACA in Scheme 7). Several additional cases are presented in Scheme 10. The enantioselectivity in Cu-catalyzed ACA of $(i\text{-Pr})_2Zn$ to cyclohexenone can be

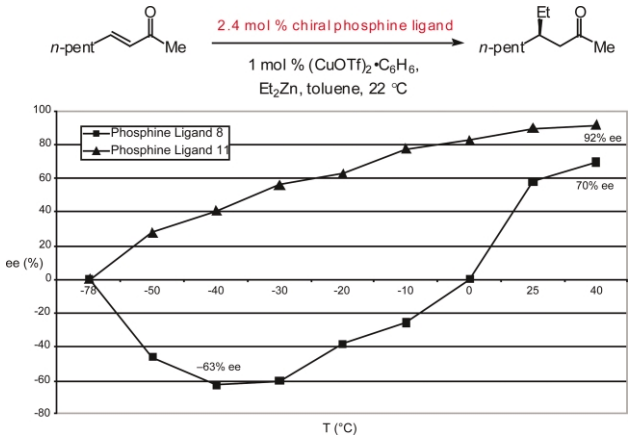
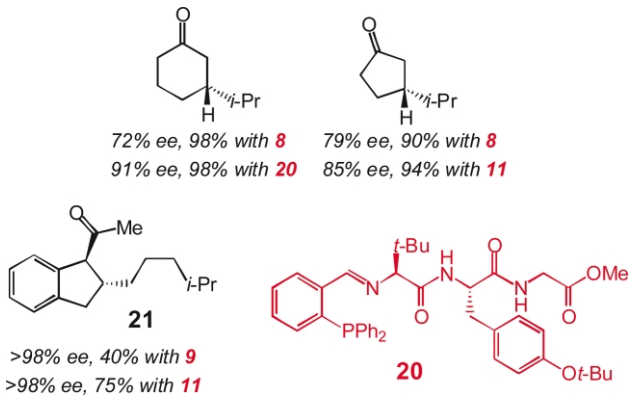


Fig. 1 Subtle changes in chiral ligand structure can lead to significant and unpredictable variations in enantioselectivity.



Scheme 10 Utility of modular chiral catalysts and unpredictable influence of ligand structure on enantioselectivity.

improved when **20** is used instead of **8** (*cf.* Scheme 3), but that of cyclopentenone is enhanced only when **11** is utilized; phosphine **20** gives lower ee than **8** in this case. Enantioselective synthesis of **21**, unlike most other cyclic trisubstituted enones, is hampered by significant byproduct formation in the presence of **9** (*cf.* Scheme 4); when **11** is used in this case, the desired product can be obtained in significantly better yield.

Conclusions

We have been able to identify a class of chiral ligands, composed of amino acid units, that can be used to promote Cu-catalyzed asymmetric allylic alkylations and conjugate additions. Importantly, what the present catalytic methods, many of which are unique, offer is a selection of chiral ligands (*e.g.*, phosphines **8–11**, **16** and **18** for Cu-catalyzed ACA) for use in specific types of transformations. If the primary ligand of choice (*e.g.*, **11** for acyclic enones) is judged to be less than optimal, then others on the short list are examined; the exact priority of ligands on the short list can depend on a particular application (see above for examples). It would be difficult to argue that such an approach is inferior to the more classical strategies, where the possibility of an effective solution largely rests on a single ligand, where the catalyst is often effective for a small selection of substrates and selectivities can vary widely. The present approach offers solutions for such several specific longstanding complications. The goal of the field of chemical synthesis, after all, is not to have the minimum number of ligands or catalysts; rather, its mission should be to offer the most effective ones for as many transformations as possible.

Future efforts will focus on the development of additional classes of allylic alkylations and ACA reactions, particularly those that give rise to the formation of quaternary carbon centers. Catalytic

asymmetric transformations that utilize other alkylmetals (*vs.* alkylzincs), particularly those that complement alkylzinc reagents will be a focus of upcoming investigations. Our search for entirely new chiral ligand scaffolds that still adapt to the powerful screening strategies will be another goal of our efforts. Such architectures should allow us to design and develop entirely different classes of catalytic enantioselective C–C bond forming reactions.

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Notes and references

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