Asymmetric organocopper chemistry : Cu-catalyzed conjugate addition and allylic substitution

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Asymmetric Organocopper Chemistry

Cu-Catalyzed Conjugate Addition and Allylic Substitution

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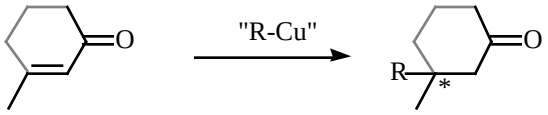
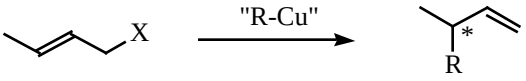
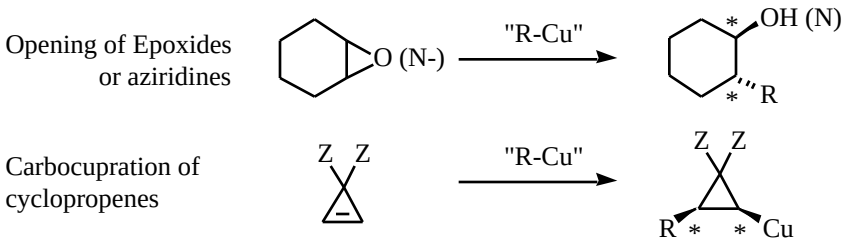
This review deals with the most recent developments in the asymmetric conjugate addition and allylic substitution. For the conjugate addition, the best enantioselectivities (>99%) have been attained with dialkylzinc reagents and 0.5-2% CuX and 1-4% of a chiral trivalent phosphorus ligand. The γ-allylic substitution can be achieved equally well with, either dialkylzinc or Grignard reagents, and the same catalysts.

Oragnocopper chemistry is a standard synthetic tool nowadays.[1] There are thousands of natural products, which have been synthesized using this chemistry, at least in one step. The most popular reactions are 1) the conjugate addition, 2) the substitution, and particularly the allylic substitution, 3) the cleavage of epoxides, and 4) the carbocupration.

Conjugate Addition 

Allylic Substitution 



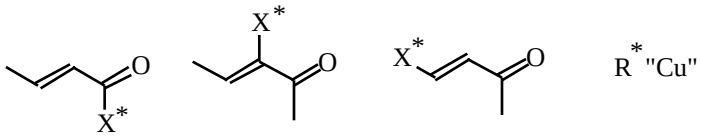
Scheme 1

Since all these topics generate new stereogenic centers, several solutions have been explored to control the enantioselectivity. It is, however, only recently that the copper-catalyzed reactions met a breakthrough, particularly for the first three reactions.

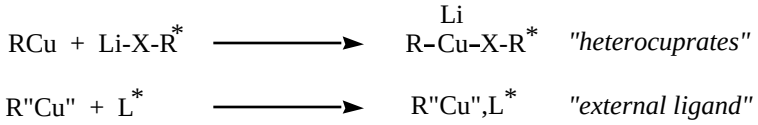
The conjugate addition

There are many ways to bring the asymmetric information. However, only the last approach allow for a catalytic use of chiral source.

1° Covalent chiral auxiliaries



2° Chiral ligands

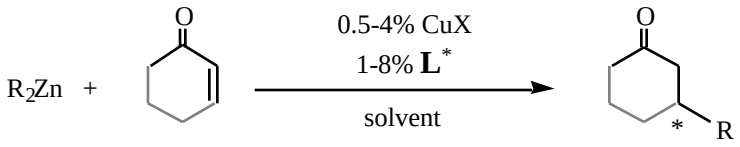


Scheme 2

For years, the covalent chiral auxiliary approach was the preferred one, and only few articles dealt with chiral ligands.[2] Although the heterocuprate way was considered as the most practical one, it is the external ligand that brought the solution to the problem.[3] A first notable success was reported in 1985 by Leyendecker who obtained 92% ee on conjugate addition to chalcone, with a stoichiometric proline-derived ligand.[4] Later on, Alexakis introduced, in 1991,

the use of chiral trivalent phosphorus ligands and demonstrated their efficiency.[5] For catalytic amount of copper salt, and therefore chiral ligand, the same authors showed that dialkylzinc reagents were more appropriate than the classical use of Grignard reagents.[6] It followed that in the last 6-7 years, a tremendous effort has been put, by more and more authors, in disclosing more and more efficient chiral ligands (>350 !), most of them bearing a phosphorus atom.

The general reaction scheme is the following:



Scheme 3

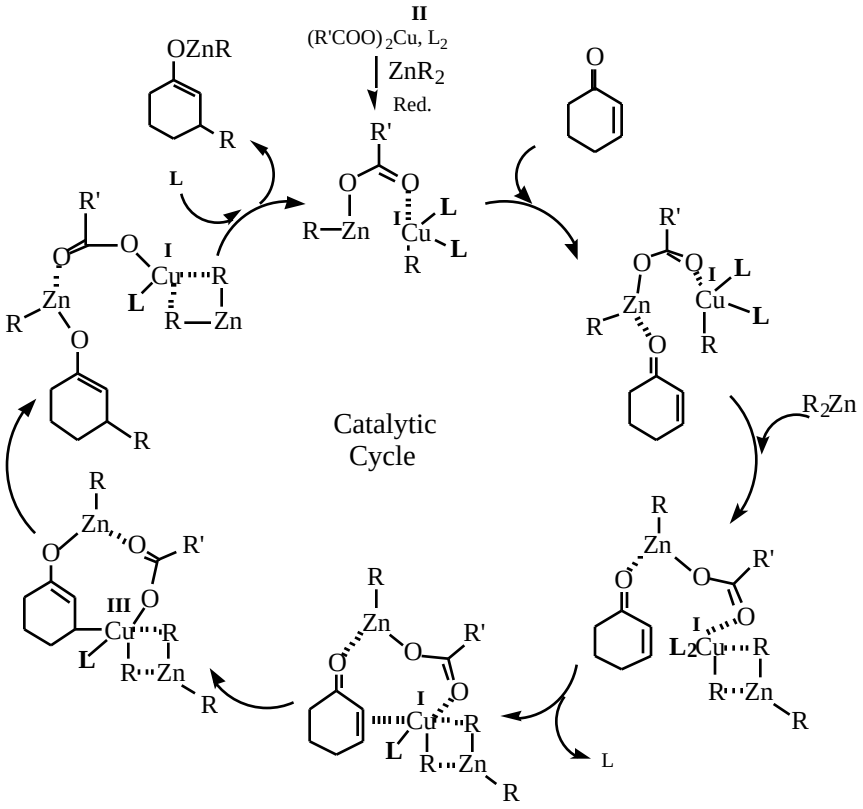
Dialkylzinc reagents react very sluggishly with enones, even in the presence of small amount of copper salt. A dramatic increase of reactivity is observed upon addition of the chiral ligand. This ligand *accelerated catalysis* is the cornerstone of this reaction, and is operative in non-coordinating (toluene, dichloromethane) or slightly coordinating solvents (Ether, THF, EtOAc).[7]

In addition to the solvent, all the other parameters of the reaction have been studied more or less. Copper (I) as well as copper (II) salts have been used. The true catalytic species is Cu(I), and therefore the reduction of Cu(II) is the first step in the process (see scheme 4). For practical reasons it is often more convenient to work with Cu(II) salts ($CuOTf_2$ or $CuOAc_2$ for example). Copper (II) triflate is most often the salt of choice, although copper acetate (as hydrate) and copper thiophenecarboxylate (CuTC) show superior enantioselectivity in many cases.[8]

A tentative catalytic cycle is shown in scheme 4, with a copper carboxylate. After, reduction to the Cu(I) species, a first transmetallation with dialkylzinc forms a zinc carboxylate associated with an alkyl copper. This stoichiometric species does not react easily with an enone, showing that a "higher order" cuprate species must be formed with one or more additional dialkylzincs. Such a dinuclear species should coordinate to the carbonyl of the enone by the most Lewis acidic metal, zinc. At the same time, a π complexation must occur between the enone and Cu. At that point, only one ligand should be present in this transition state, as most studies have shown little or negligible non-linear effects.[9] According to the usually accepted mechanism, an oxidative addition should give rise to the formation of a putative Cu(III) intermediate, which immediately collapses, by reductive elimination, to the conjugate adduct.[10] This zinc enolate may be trapped by other electrophiles than water (see below).

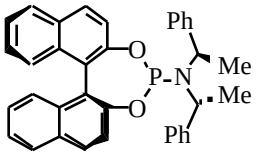
From this catalytic cycle it appears that only one equivalent of copper salt is needed. However, the early studies revealed that higher enantioselectivities were obtained with a 2:1 ratio of ligand to copper,[5, 6] and most authors systematically

used these conditions. In fact, we observed that the enantioselectivity remains roughly the same with as little as a 1.2:1 ratio. In the allylic substitution, this ratio may even go to a true 1:1 ratio.

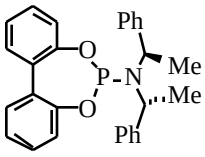


Scheme 4

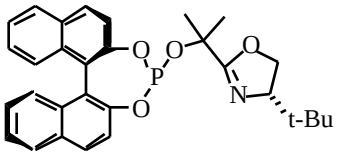
The initially explored chiral ligands were trivalent phosphorus ligands.[5, 6] Although other ligand types have been disclosed, the ones based on phosphorus are the most effective. Most ligands are monodentate, but some are bidentate, either P,P or P,N. An exhaustive review shows all the ligands known until April 2002 (329 at that date),[3e] and more have been disclosed since then. It is striking to see that most phosphorus ligands are of the phosphite and phosphoramidite type. Aryl phosphines are scarce, and successful only when associated with another coordination site.[11] The usual chiral diphosphines, such as BINAP, are ineffective in this reaction.[12] It should be pointed out that there is not yet a general ligand for all kind of Michael acceptors. Some of the most representative phosphorus ligands are shown in scheme 5.



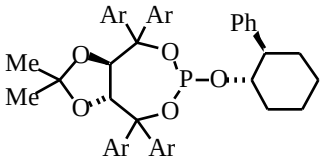
Feringa ref 13



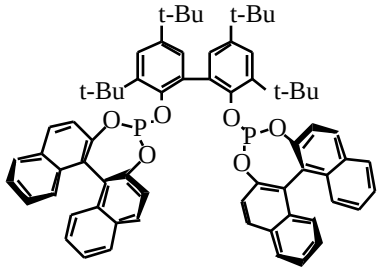
Alexakis ref 14



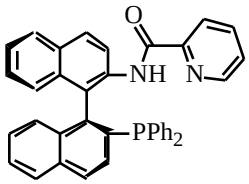
Pfaltz ref 15



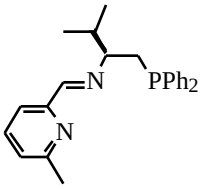
Alexakis ref 16

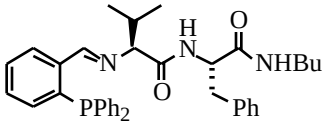


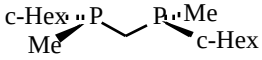
Chan ref 17



Zhang ref 18







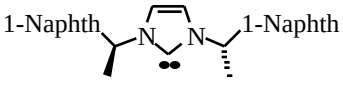
Imamoto ref 19

Morimoto ref 20

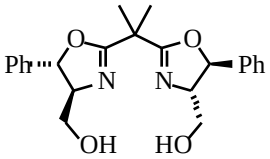
Hoveyda ref 21

Scheme 5

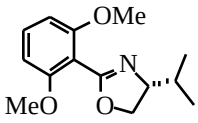
Other classes of ligands, without phosphorus atom, have also been studied. They are not yet as efficient, although ee's as high as 93%[22] have been achieved.



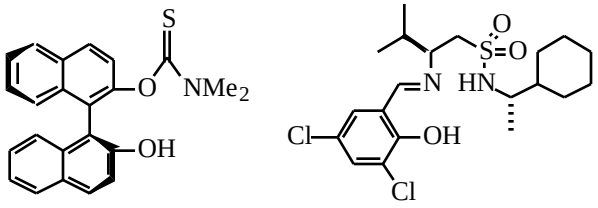
Alexakis ref 22



Reiser ref 23



Iwata ref 24

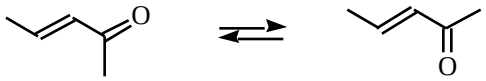


Woodward ref 25 Gennari ref 26

Scheme 6

In all the above-discussed reactions, dialkylzinc reagents have been used. Only in few cases, trialkylaluminum (R_3Al) were tested, but they represent an interesting alternative.[24, 25, 27] Among R_2Zn reagents, Et_2Zn is by far the most used. Me_2Zn is about 30 times less reactive,[28] and gives lower ee's,[29] although quite high in some cases (>95%).[30] Functionalized dialkylzincs afford comparable enantioselectivities as Et_2Zn.[13, 15, 21] The compatibility of R_2Zn with many functional groups is clearly an advantage of the methodology.[31] However, it should be pointed out that diaryl or divinyl zinc reagents are scarce. There is only one report on Ph_2Zn, with low ee.[23] Clearly, for the transfer of an aryl or vinyl group, the Miyaura-Hayashi methodology ($ArB(OH)_2$ and Rh catalysis) is superior, and complementary to the present one.[32]

The range of Michael acceptors is quite large. Traditionally, cyclohexenone has been the substrate of choice for testing a new ligand. This cyclic enone avoids the *s-cis/s-trans* interconversion of acyclic substrates.

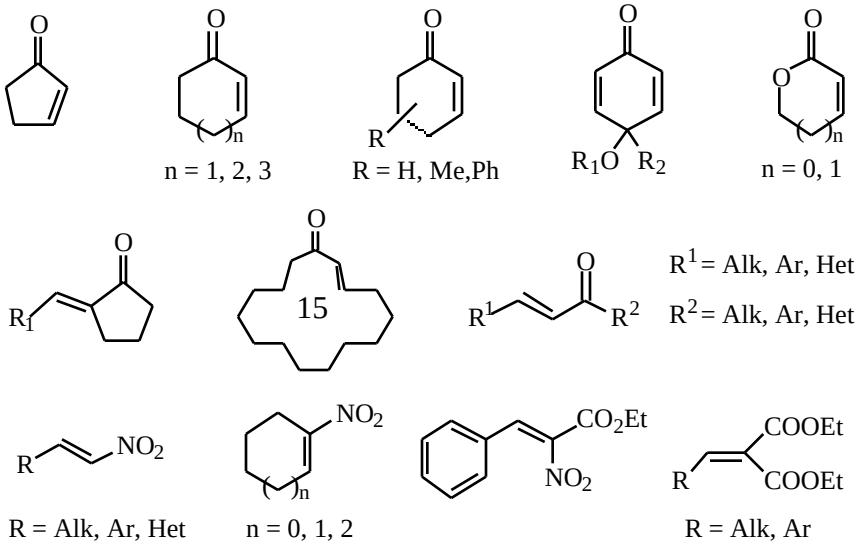


s-trans s-cis

Scheme 7

Most of the Michael acceptors are shown in scheme 8. Cycloheptenone and cyclooctenone behave exactly as cyclohexenone and give high ee's with the same ligands. Cyclopentenone however, is rather a flat molecule. Specific ligands have been developed especially for this substrate.[21, 33] Other cyclic enones include substituted cyclohexenone and cyclohexadienones.[34] They give rise to efficient kinetic resolution, depending on the position of the substituent in the ring.

Many authors have equally well tested acyclic enones.[25, 29, 35] The specific class of chalcone-type enones ($R^1 = R^2 =$ Aryl) usually needs different ligands than the other ones.[18, 34] Many ligands are able to bring high enantioselectivity (>95%). Of particular interest is the 15-membered macrocyclic enone, which allow the formation of (R)-Muscone, a valuable natural fragrance.[25, 29]

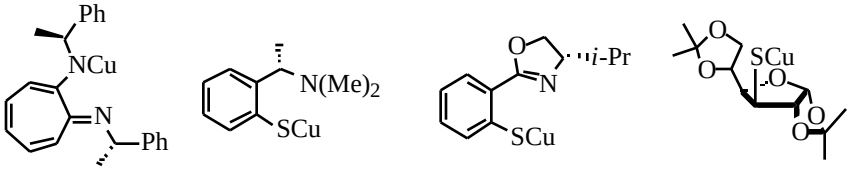


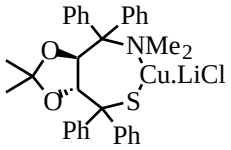
Scheme 8

Nitro-olefins are another class of excellent Michael acceptors for this reaction.[12] Again, the efficient ligands are different from the previous ones.[30, 36] The chiral adducts are valuable synthons, since the nitro group has successfully been transformed into amino group (by reduction) or to carbonyl groups (by a Nef reaction).

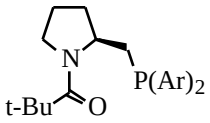
Simple α,β-ethylenic esters are not reactive enough. A good alternative is a double activation with alkylidene malonates.[37] Recently, N-acyloxazolidinones have been shown to also be good ester equivalents.[38]

Compared to the amount of work done recently with dialkylzincs, Grignard reagents seem to have been neglected. Historically, the first interesting levels of enantioselectivities (74%) were obtained by Lippard, in 1988, with 3% of an amidocopper catalyst.[39] Later on, various copper thiolates gave moderate to good results on cyclic and acyclic enones.[40-43] The best results were however obtained with external ligands, by Tomioka[44] and Sammakia.[45] Since the late 90's all authors focused on the dialkylzinc procedure.

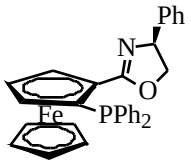




Seebach ref 43



Tomioka ref 44

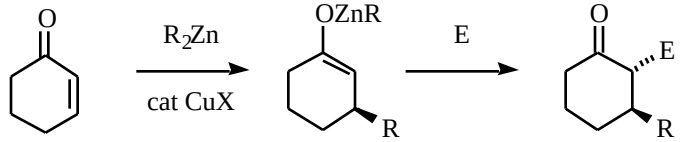


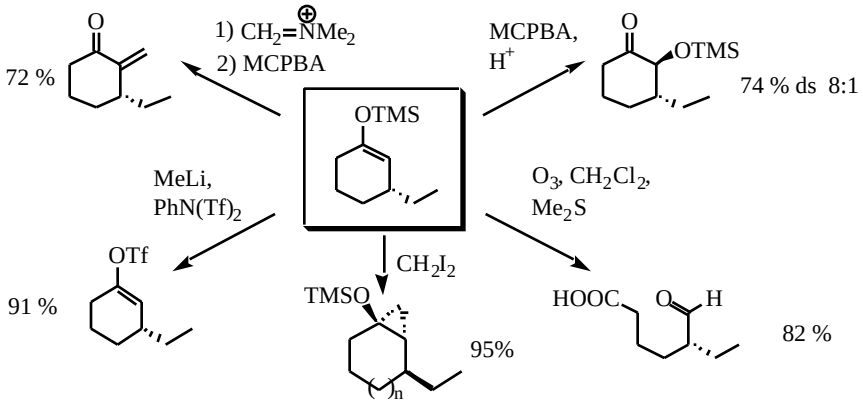
Sammakia ref 45

Scheme 9

The range of substrates tested with Grignard reagents is rather limited to cyclohexenone and cycloheptenone, for cyclic substrates, and chalcone and benzalacetone for acyclic ones. However, the variety of Grignard reagents is larger, with alkyl, aryl and vinyl Grignards. The enantioselectivities are in the 80-90% at best, and the catalyst loading rather high (5-15% CuX, 10-30% L*) as compared to the dialkylzinc procedure.

As seen above, all the conjugate addition reactions end up with a zinc enolate. Its reaction with an electrophile, other than simple water, could be an excellent way to quickly build more complex molecules. Despite their low reactivity, zinc enolates have been reported to react with aldehydes,[7a, 28, 46] with acetals (with $BF_3.Et_2O$ as additive),[47] with allylic acetates (with Pd catalysis)[7a, 28, 48] and with homopropargylic iodide,[21] methyl iodide[49] or benzyl iodide[11d] (tenfold excess and 10 equiv. HMPA as additive).



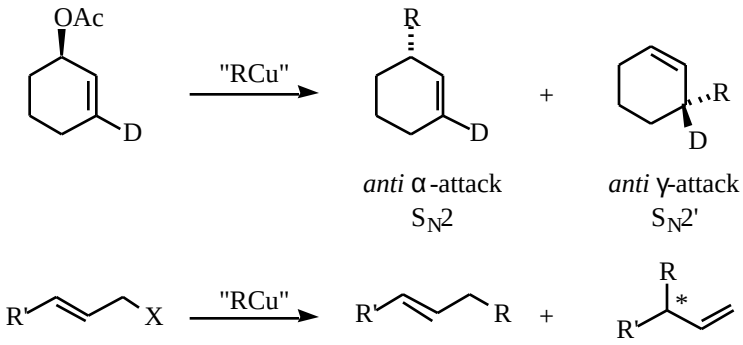


Scheme 10

Another possibility is to trap the enantiopure zinc enolate with a silylating agent.[50] The resulting silyl enol ether becomes a versatile building block, able to provide many new synthons (scheme 11).[51]

The allylic substitution

This topic adds on the difficulties, as it needs the additional control of the regioselectivity. The stereochemical outcome of the allylic substitution with organocopper reagents is well established.[10, 52] The reaction proceed through an S_N2 or S_N2' path with a clean *anti* selectivity. The control of the regioselectivity is usually done by the proper choice of the Cu salt, of the solvent and the additive (such as $BF_3.Et_2O$).[53] There are only two exceptions affording a clean *syn* S_N2': when the leaving group X is a secondary carbamate[54] or an o-diphenylphosphino benzoate.[55]

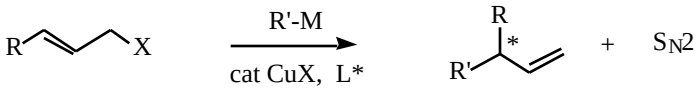


Scheme 11

The enantioselective allylic substitution, when no stereogenic centers are on the substrate, has not been studied extensively. There are four authors who described such a reaction with a stoichiometric auxiliary, placed on the leaving group. These are chiral C2 symmetrical acetals,[56] carbamates,[57] oxazolinyl thioethers[58] and sulfoximines.[59]

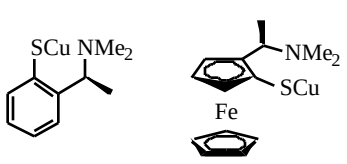
The first report on the catalytic version is due to Backvall and van Koten, in 1995.[60] They used a Grignard reagent as primary organometallics, and a copper thiolate as chiral catalyst (15%). With Alexakis, they are the only authors to report on Grignard reagents;[61] all other authors have used dialkylzinc instead. Following Knochel's work, in 1999,[62] Feringa,[63] Hoveyda,[64] Woodward[65] and Gennari[66] have reported their results with dialkylzincs. The general equation, and the various ligands used are shown in scheme 12. The scope of the reaction is not yet very large as the substrate is concerned. Knochel's procedure is better for hindered dialkylzincs (ee's up to >95%), whereas Hoveyda's one allow for

the efficient reaction with trisubstituted allylic phosphates. Alexakis has shown that ω-ethylenic Grignard reagents can be used, and treated *in situ* with Grubbs' metathesis catalyst to afford directly new chiral synthons.[61b]

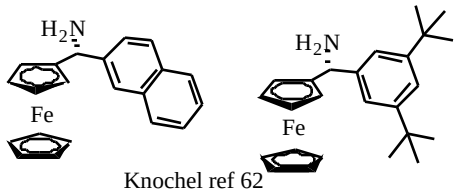


R = Alk, Ar
X = Cl, Br, OAc, $OP(O)(OEt)_2$

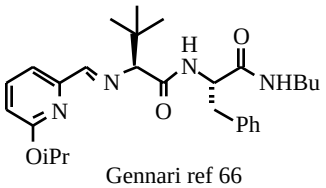
M = MgX, Zn
CuX = CuI, CuCN, CuOTf, $CuBr.Me_2S$, Cu-thiophene carboxylate (CuTC)



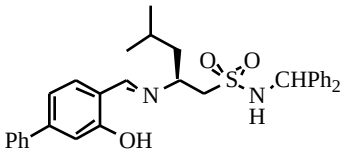
Backvall, van Koten ref 60



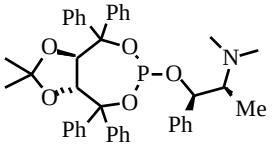
Knochel ref 62



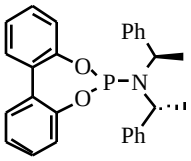
Gennari ref 66



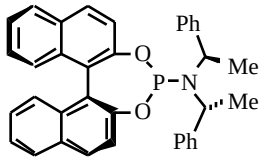
Hoveyda ref 64



Alexakis ref 61a



Alexakis ref 61b



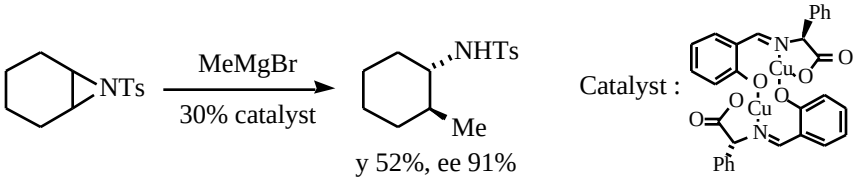
Feringa ref 63

Scheme 12

Reactions with epoxides and aziridines

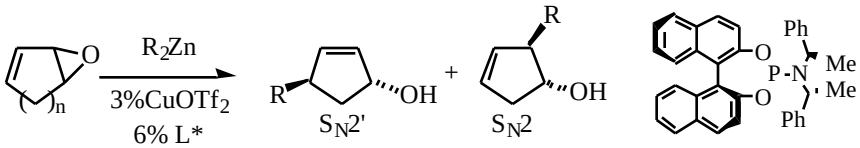
Organocopper chemistry is also useful for smooth ring opening of epoxides.[67] Meso-type epoxides, such as cyclohexene oxide, are the substrates of choice for studying enantioselective versions.[68] Until now, there is no report on such a copper-catalyzed reaction with ee's over 20-30%. Interestingly, the

asymmetric ring opening of meso aziridines is quite efficient (15-91% ee). Among the many catalysts tested, the following copper carboxylate gave the highest enantioselectivity with yields. It should be pointed out that the amount of catalyst is crucial: with 10%, the ee is only 55%, and with 20%, it jumps to 77%, the highest ee 91% being attained with 30% catalyst.[69] The same reaction on cyclohexene oxide afforded only 10% ee.[69]



Scheme13

Pineschi and Feringa have studied the kinetic resolution on a more reactive class of epoxides: the α,β-unsaturated ones. They found that dialkylzinc reagents undergo a copper-catalyzed S_N2' type reaction. At mid-conversion, the S_N2' products may reach high ee's: 50-96%.[34, 70] The reaction has been applied, with equal success, to structurally related epoxides.[71]



Scheme 14

This short review points to the booming recent interest for the asymmetric reactions of organocopper chemistry. The synthetic potentiality of the resulting synthons makes this methodology among the most versatile for the synthesis of useful natural products, such as pharmaceuticals, fragrances etc … Of course, further improvements are needed to enhance the enantioselectivities or the scope of these reactions, but, after 30 years of investigations, efficient solutions have finally came up.

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