Carbene Insertion

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Enantioselective Insertion of Metal Carbenes into N–H Bonds: A Potentially Versatile Route to Chiral Amine Derivatives

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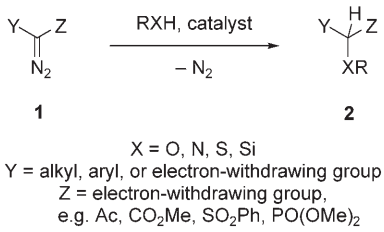
The formation of carbon–heteroatom bonds is one of the fundamental transformations of organic chemistry. One potentially powerful method is the insertion of metal carbenes, readily derived by transition-metal-catalyzed reactions of diazo compounds **1**, into X–H bonds (Scheme 1).[1] The reaction is a versatile route to a wide range of



Scheme 1. The X–H insertion reaction of carbenes and metal carbenes.

functionalized compounds **2** such as α-alkoxyesters, α-aminophosphonates, α-silylketones, and assumes even greater significance if it can be carried out in an asymmetric manner. Unfortunately, whilst asymmetric metal carbene C–H insertion reactions have become a well-established part of synthetic methodology,[2] much less progress has been made with the X–H counterparts, although some success has been enjoyed in the arena of Si–H insertion using chiral dirhodium carboxylates or carboxamides, or copper-based catalyst systems.[3] The attainment of excellent enantioselectivities in metal carbene C–H and Si–H insertion reactions using chiral dirhodium or copper catalysts presumably reflects the reaction mechanism—a concerted insertion into the X–H bond. With more polar X–H bonds, other mechanisms such as formation of ylide intermediates by attack of the heteroatom lone pair on the electrophilic metal carbene may operate,[4] and hence the situation is more complex. Thus little progress has been made with stereoselective S–H insertions,[5] and although the synthetically useful O–H insertion reaction has been widely studied,[6] it is only recently that an enantioselective variant has been reported. In this study, Maier and Fu describe the use of a copper/bisazaferrocene catalyst to effect O–H insertion (up to 98% *ee*) of metal carbenes derived from aryl diazoacetates **1** (Y = Ar, Z = CO_2Me).[7] However, given the wide occurrence of stereocenters bearing nitrogen in bioactive molecules, it is enantioselective N–H insertion reactions that would potentially have the most impact.

The reaction of diazo compounds with amines and their derivatives, resulting in loss of nitrogen and formation of the N–H insertion product, has a venerable history. Curtius reported in 1888 that decomposition of ethyl diazoacetate in the presence of aniline gave *N*-phenylglycine ethyl ester,[8] although it was not formulated as a carbene N–H insertion reaction. The first catalyzed N–H insertion reaction using copper bronze was reported by Yates[9a] over 50 years ago, and the reaction was further developed by Saegusa et al.[9b] Later Nicaud and Kagan employed chiral diazoesters and chiral amines to obtain roughly 25% *de* in N–H insertion reactions.[10] The introduction of dirhodium(II) tetracarboxylates as efficient catalysts for N–H insertion in 1974[11] led to an increase in the application of such reactions in synthesis; a notable early example was an intramolecular insertion into a β-lactam N–H bond, a key step in the Merck synthesis of thienamycin (Scheme 2).[12] In the last 25 years, carbene N–H insertion reactions have found increasing use, particularly in the synthesis of N-containing heterocycles, developed in our laboratory and elsewhere. Two examples are shown in Scheme 2.[13]

Throughout the 1990s, our own laboratory also sought to develop stereoselective intermolecular N–H insertion reactions using either chiral diazo compounds, chiral N–H components, or chiral dirhodium(II) catalysts, but to little avail since stereoselectivities were poor to modest (up to 37% *de* or 8% *ee*).[14] More recently others have been more successful in achieving highly diastereoselective intramolecular N–H insertion reactions using chiral amine derivatives.[15] The first significant progress with chiral catalysis came with the 1996 report by Garcia, McKervey, and Ye that an intramolecular N–H insertion reaction, catalyzed by dirho-

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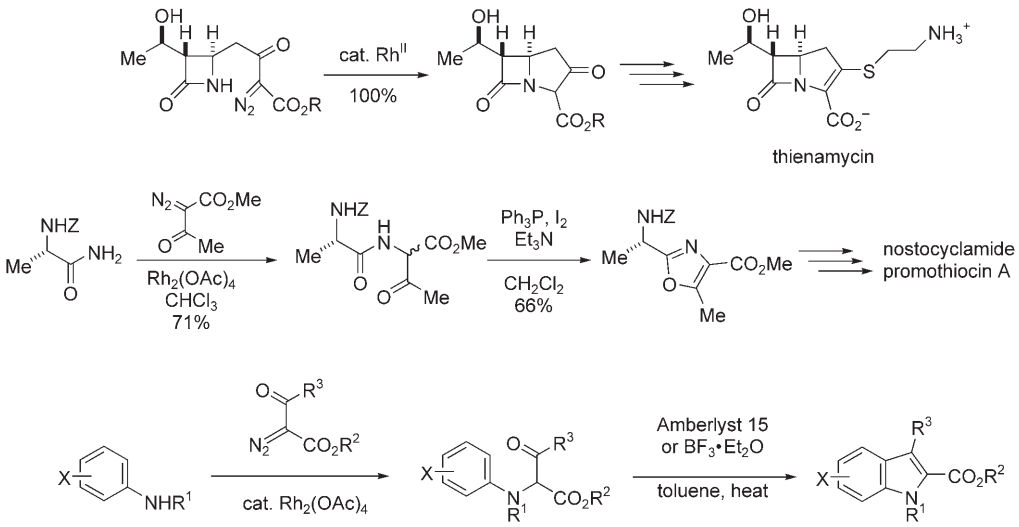
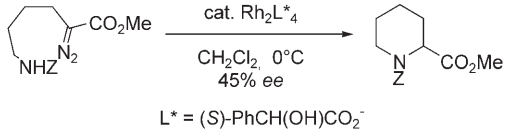


Scheme 2. Dirhodium(II) carbene N–H insertion reactions in synthesis.

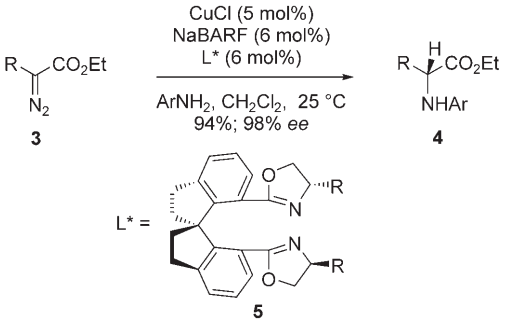
dium tetra-(*S*)-mandelate, gave *N*-Z-pipecolic acid methyl ester (Z = benzyloxycarbonyl) in 45% *ee* (Scheme 3).[16] Eight years later Jørgensen and co-workers reported enan-



Scheme 3. Intramolecular asymmetric N–H insertion reaction using a chiral dirhodium(II) tetracarboxylate catalyst.

tioselectivities of up to 28% *ee* in intermolecular N–H insertions of metal carbenes derived from alkyl and aryl diazoacetates using chiral copper(I) bisoxazoline complexes.[17] The analogous silver(I) complexes gave higher enantioselectivities (up to 48% *ee*) although chemical yields were low.

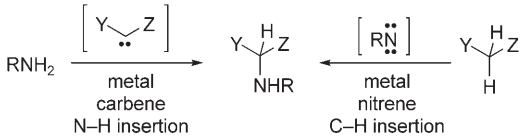
It is with this background that the recent report of highly enantioselective metal carbene N–H insertion reactions by Zhou and co-workers represents a significant development.[18] Initially the researchers used ethyl 2-diazopropanoate **3** (R = Me) as their test diazocarbonyl compound and aniline as the N–H component. Using a catalyst generated in situ from $[Cu(MeCN)_4]PF_6$ and the spirobisoxazoline ligand **5** (R = Ph), developed in the authors' laboratory for copper-catalyzed asymmetric cyclopropanation and allylic oxidation,[19] the N–H insertion product, ethyl 2-phenylaminopropanoate (*N*-phenylalanine ethyl ester) **4** (R = Me, Ar = Ph), was obtained in 78% yield with 43% *ee*. In order to improve the enantioselectivity, the larger noncoordinating counterion tetrakis[3,5-bis(trifluoromethyl)phenyl]borate ($BARF^-$) was employed. Thus a catalyst generated from ligand **5** (R = Ph), CuCl, and NaBARF resulted in formation of the N–H insertion product in 94% yield with 98% *ee* as the *R* enantiomer (Scheme 4). A wide range of anilines participated in the reaction to give the corresponding *N*-aryl-alanine ethyl



Scheme 4. Enantioselective N–H insertion reactions using copper complexes of spirobisoxazoline ligands.

esters **4** (R = Me) in 85–98% *ee*. Although the nature of the alkoxy group in the ester has negligible effect, the other substituent on the diazoester does influence the reaction markedly—the corresponding diazobutanoate derivative **3** (R = Et) reacts more slowly, and although the *ee* of the product remains good (94%) the yield is lower (51%). The diazophenylacetate **3** (R = Ph), on the other hand, gives a good yield of *N*-phenyl phenylglycine ethyl ester **4** (R = Ar = Ph) but with very poor selectivity (8% *ee*). Likewise, use of benzamide as the N–H component results in a racemic product, whilst alkylamines such as cyclohexylamine appear to be inert under the reaction conditions.

Clearly further experimentation is needed to expand the scope of the above enantioselective N–H insertion reactions and to understand the reaction mechanism. Interestingly, the same is true for a closely related route to chiral amines, namely the insertion of nitrenes (or metal nitrenes) into C–H bonds, a reaction reviewed in a recent Highlight.[20] As shown in Scheme 5, the routes are complementary and at present suffer from similar limitations. However, given the longer history of metal carbene insertion chemistry, the N–H insertion route may eventually prove to be more useful.



Scheme 5. Complementary routes to amines: carbene N–H insertion and nitrene C–H insertion.

In closing, it is fascinating to note that although many of the metal carbene N–H insertion reactions used in synthesis rely on dirhodium(II) catalyzed reactions of diazocarbonyl compounds (see Scheme 2), it is the return to copper catalysis, first reported by Yates over 50 years ago, that has led to this breakthrough in developing an asymmetric variant of the reaction. Hence the use of copper complexes of spirobisoxazoline ligands to achieve high enantioselectivity in metal carbene insertions into the N–H bond of aniline derivatives constitutes a major advance and provides a new route for the asymmetric synthesis of α-amino acid derivatives. However, if the methodology is to fulfill its true potential it needs to be more general with respect to the starting diazoesters. Likewise, for real generality, the N–H component needs to be an "ammonia equivalent," and it is somewhat unfortunate that, at present, use of RNH_2 compounds where R is a potentially removable group such as 4-methoxyphenyl or benzoyl leads to poorer results. It would be interesting to know how other potential ammonia equivalents such as alkyl carbamates behave under the reaction conditions. Also, how do these catalysts systems perform in O–H or S–H insertion reactions? Further developments are awaited with interest.[21]

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[21] Note added in proof: Very recently Lee and Fu have reported a further major advance in enantioselective carbene N–H insertion reactions (E. C. Lee, G. C. Fu, *J. Am. Chem. Soc.* **2007**, *129*, 12066): Using a copper/planar chiral ferrocene bipyridine catalyst, they achieved excellent enantioselectivities with *tert*-butyl aryldiazoacetates and benzyl or *tert*-butyl carbamates as the N–H components. This development immediately addresses one of the limitations of the aforementioned work by Zhou and co-workers in that the nitrogen substituent (Boc or Z) is now readily removable by standard deprotections methods. Hence a range of Boc- or Z-protected arylglycine *tert*-butyl esters can be prepared in 80–98% *ee* by catalytic asymmetric N–H insertion.

