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Recent advances in stereoselective synthesis involving diazocarbonyl intermediates

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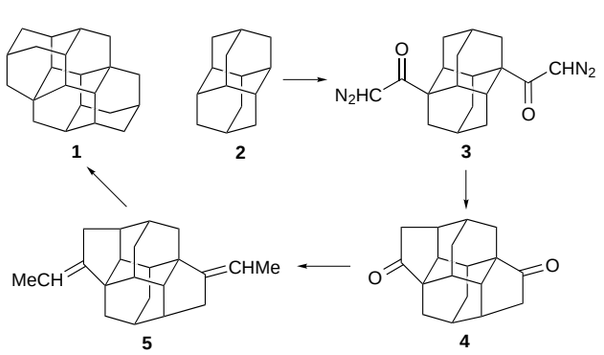
Two aspects of recent developments in enantioselective organic synthesis involving diazocarbonyl intermediates are highlighted: the introduction of chiral catalysts for asymmetric transformations and the use of enantiopure diazoketones derived from amino acids and peptides as chiral educts.

Introduction

Although much of our recent research in diazocarbonyl chemistry has been directed towards catalysed asymmetric synthesis and the use in synthesis of enantiopure diazoketones derived from natural amino acids and peptides, for one of us the first encounter with diazocarbonyl chemistry in the laboratory occurred in 1976 during the synthesis of the polycyclic hydrocarbon, *anti*-tetramantane **1**, a C_{22} fragment of the diamond lattice.[1] The plan was to transform diamantane **2** into *anti*-tetramantane by establishing new bridgehead positions *via* C–H insertion reactions of α-ketocarbenoid intermediates (Scheme 1). This could be realised by treatment of the diamantane bisdiazoketone **3** with copper sulfate in benzene, whereupon the heptacyclic diketone **4** was produced, albeit in low yield. The carbonyl groups of **4** were then used to add four more carbon atoms to produce diene **5**, an isomer of *anti*-tetramantane; and to complete the synthesis, the rearrangement of one to the other was brought about in the gas phase in hydrogen at 300 °C on a platinum–silica catalyst. Twenty years on there are still few chemical ways of functionalising unactivated C–H bonds as useful and versatile as metal-catalysed decomposition of diazoketones or diazoesters. In fact, C–H insertion is but one of an entire cornucopia of diazocarbonyl reactions with numerous useful applications in organic synthesis. These reactions include cyclopropanation, X–H insertion (X = C, N, O, S, Si, Se, P), aromatic cycloaddition, ylide formation, dipolar cycloaddition, Wolff rearrangement, acid-catalysed cyclisation, α,α-substitution, addition to aldehydes and ketones, β-elimination and oxidation.[2]

Diazocarbonyl chemistry often gets a bad press. While it is unquestionably true that substances such as diazomethane and sulfonyl azides such as tosyl azide and mesyl azide, important reagents in diazocarbonyl synthesis, are hazardous,[3] when due care is taken they can be handled confidently even on a large scale. The Merck thienamycin synthesis,[4] for example, involving a rhodium-catalysed N–H insertion of a diazomalonate whose synthesis requires the use of an arylsulfonyl azide, is routinely conducted on a multikilogram scale.

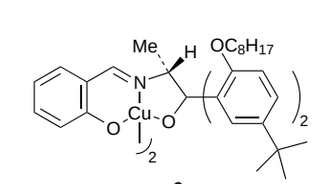


Scheme 1

Asymmetric synthesis of diazocarbonyl reactions: development of chiral catalysts

There are numerous opportunities for asymmetric synthesis employing diazocarbonyl substrates with the option of either covalently attaching a chiral auxiliary to one of the reactants or of using a chiral catalyst (or both). However, when one considers that the most synthetically useful diazocarbonyl reactions are in fact metal catalysed, the attractions of the latter option become very compelling.

Up to the late 1970s,[5] the single most important metal in catalysed diazocarbonyl decomposition was copper and the most frequently used reaction was cyclopropanation. The first successful asymmetric combination was that devised by Aratani[6] who prepared a series of chiral copper(II) chelates **6** from salicylaldehyde and optically active amino alcohols with which to catalyse intermolecular cyclopropanation of alkenes and dienes with ethyl diazoacetate. Enantioselectivities exceeding 90% could be achieved in selected cases as, for example, in the synthesis of ethyl 2,2-dimethylcyclopropane carboxylate [eqn. (1)]. There are now several copper-based catalysts capable of producing ee values up to 99% over a range of alkenes. These include the catalysts of Pfaltz **7**,[7] Masamune **8**,[8] Evans **9**[9] and Ito and Katsuki **10**,[10] all containing heterocyclic C_2-symmetric auxiliaries. Eqns. (2–4) illustrate some representative examples of their successes in enantioselective cyclopropanation.



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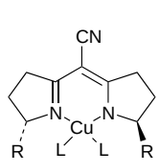
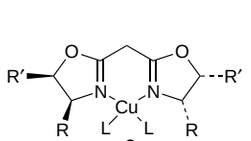
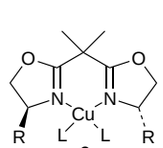


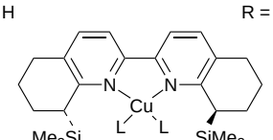
7
R = CMe_2OH



8
R = Me, R′ = Ph
R = CH_2OH, R′ = H
R = Et, R′ = H



9
R = $CHMe_2$
R = Bu^t



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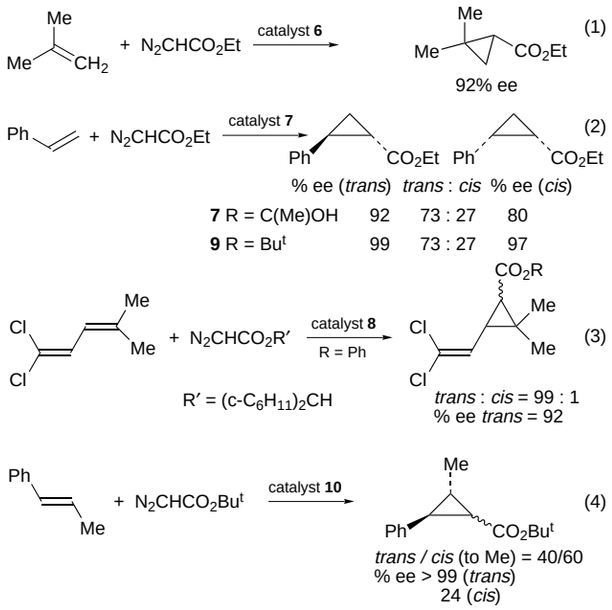
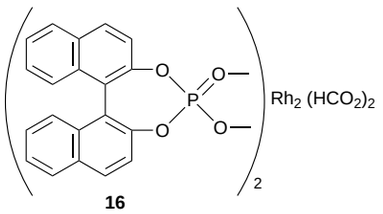


The introduction of rhodium(II) carboxylates for diazocarbonyl decomposition by Teyssie, Hubert and Noels[11] in 1973 opened the way to new initiatives in catalysed asymmetric synthesis. Unlike many of the copper catalysts whose catalytic activity was restricted largely to cyclopropanation, rhodium(II) carboxylates were to display a reactivity that, in addition to cyclopropanation, encompassed C–H, N–H, O–H, S–H, Si–H and Se–H insertion, aromatic and 1,3-dipolar cycloaddition, electrophilic substitution, and ylide formation with sigmatropic rearrangement. It was not surprising therefore that interest turned towards chiral rhodium(II) catalysts. Three groups, those of Brunner,[12] Ikegami[13] and McKervey,[14] independently introduced rhodium(II) salts with chiral carboxylates attached to the metal core. Enantiopure carboxylates of the type $R^1R^2R^3CCO_2$ **11**, whose substituents varied from H, Me and Ph to OH, NHAc and CF_3, were assessed by Brunner for enantioselective cyclopropanation of styrene with ethyl diazoacetate with disappointing results (< 12% ee).

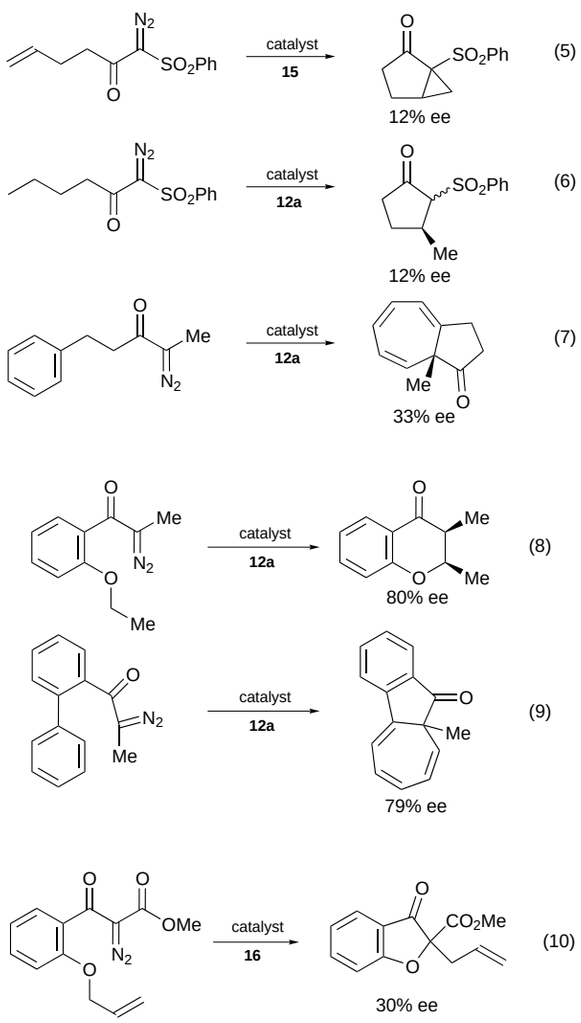
In our own work the availability of a range of enantiopure α-amino acids prompted a survey of their efficacy as rhodium(II) carboxylate catalysts **12**–**14**. Rhodium(II) (*S*)-mandelate **15**,[15] a known compound, was also included in the survey. While these catalysts proved to be very efficient chemically, in some cases at temperatures as low as −80 °C, early results suggested that the extent to which they are capable of exerting enantiocontrol in selected intramolecular reactions, *viz* cyclopropanation, 12% ee [eqn. (5)]; C–H insertion, 12% ee [eqn. (6)] and aromatic cycloaddition, 33% ee [eqn. (7)], was limited.[14] However, recent work with more rigid substrates has shown that significantly higher levels of enantiocontrol can be achieved in C–H insertion where ee values of up to 80% have been realised with the *N*-benzenesulfonyl (*L*)-prolinate catalyst **12a** [eqn. (8)]. Similarly, in the aromatic cycloaddition reaction shown in eqn. (9), use of the prolinate catalyst[16] produced an ee of 79%.[17]

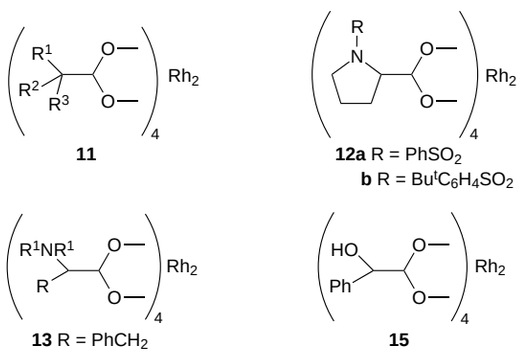
The rhodium(II)-(*S*)-(+)-1,1′-binaphthyl phosphate catalyst **16**[18] introduced in 1992 also shows promise in other diazocarbonyl reactions. For example, the tandem ylide formation–[2,3]sigmatropic rearrangement process in eqn. (10) can be catalysed by **16** to give the furanone product with an ee of 30%.



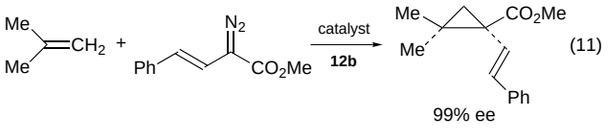
16

One feature of the performance of the amino acid based catalysts[19] which offered scope for optimisation was the dependence of the enantioselectivity on the nature of the protecting group on the nitrogen atom. This is nicely illustrated in the use of rhodium(II) prolinates as catalysts for intermolecular cyclopropanation, where enantioselectivities up to 97% have now been achieved. Whereas the benzenesulfonyl derivative **12a** exhibits limited enantiocontrol in cyclopropanation with ethyl diazoacetate, Davies has reported that



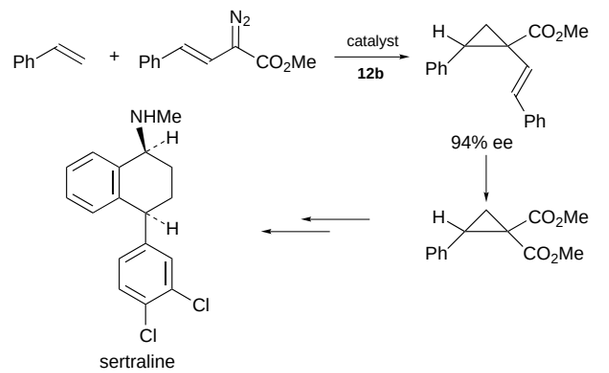


the *p-tert*-butylbenzenesulfonyl counterpart **12b** is especially active for highly enantioselective cyclopropanations with vinyl diazoesters, an illustration being that in eqn. (11). Enantiomeric excesses of 59% ($EtOCH{=}CH_2$) and higher, but generally at or greater than 90% were observed for monosubstituted alkenes.[20]



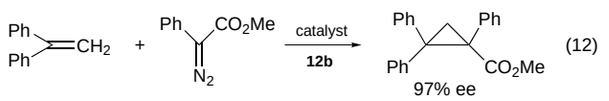
(11)

Higher ee values were reported for reactions in pentane as compared with benzene or dichloromethane. Corey and Grant[21] have used this methodology for cyclopropanation of styrene (94% ee) in an asymmetric synthesis of sertraline (Scheme 2). In a detailed study of the asymmetric synthesis of 2-phenylcyclopropane-1-amino acid, Davies *et al.*[22] concluded that the optimised catalyst for addition of vinyldiazoesters was rhodium *p*-dodecylbenzenesulfonyl prolinate.



Scheme 2

We have established that the *p-tert*-butylbenzenesulfonylprolinate catalyst **12b** gives the highest levels of enantiocontrol relative to either chiral rhodium(II) carboxamidates or bisoxazoline ligated copper(I) **9** for intermolecular cyclopropanation reactions of methyl phenyldiazoacetate, where 97% ee has been realized with 1,1-diphenylethene [eqn. (12)], and we have proposed that solvent enhancement of enantiocontrol is due to solvent-induced favourable orientation of the prolinate ligands.[23]



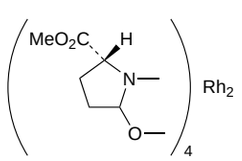
(12)

Efficient syntheses of carboxamidate-ligated dirhodium(II)[24] have made possible the construction of a set of chiral catalysts whose applications have already demonstrated exceptional enantiocontrol for intramolecular and certain intermolecular reactions of diazoacetates and diazoacetamides. Exemplified by Rh_2(5*S*-MEPY)$_4$ and its enantiomer Rh_2(5*R*-MEPY)$_4$ **17**, where MEPY = methyl 2-oxopyrrolidine-5-carboxylate, the dirhodium(II) core is surrounded by four bridging amide ligands with two oxygen and two nitrogen donor atoms bound to each rhodium in a *cis* configuration. Analogous chiral dirhodium(II) carboxamidates derived from oxazolidinones **18**[25] and imidazolidinones **19** and **20**[26] provide a set of catalysts that effectively control regioselectivity and diastereoselectivity, as well as enantioselectivity in reactions that involve metal carbene intermediates. In each of these catalysts the chiral centre of the ligand is the carbon atom directly bonded to nitrogen, so that the CO_2Me functional attachment lies in a spatial region that influences both the orientation of the bound carbene and the approach of the substrate to the carbene centre.

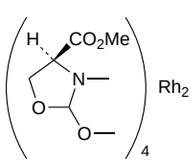
The exceptional ability of chiral dirhodium(II) carboxamidates to direct highly enantioselective intramolecular cyclopropanation reactions has been demonstrated with allylic and homoallylic diazoacetates and diazoacetamides [eqns. (13) and (14)], where with allylic substrates % ee values > 92% are, with few exceptions, obtained.[27,28] Applications of this catalytic methodology include Martin's synthesis of 1,2,3-trisubstituted cyclopropanes as conformationally restricted peptide isosteres for renin **21**[29] and collagenese[30] inhibitors and Poulter's synthesis of presqualene diphosphate **22** by intramolecular cyclopropanation of farnesyl diazoacetate [eqn. (15)].[31] With homoallylic systems there is a moderate reduction in enantiocontrol with the use of these catalysts (71–90% ee).[27] Other chiral catalysts have not proven to be similarly effective for intramolecular cyclopropanation reactions of this wide range of diazocarbonyl compounds.[32]

Dirhodium(II) catalysts are uniquely effective for intramolecular carbon–hydrogen insertion reactions and, as exemplified in eqn. (16),[25] chiral carboxamidate ligands provide high enantiocontrol for the synthesis of lactones and lactams. The exceptional regiocontrol of these reactions has been demonstrated in the construction of chiral lignan lactones such as (−)-hinokinin **23** in a synthetic process that begins with a cinnamic acid (Scheme 3).[33] The high level of diastereocontrol that can be achieved in these reactions is exemplified in the short synthesis of deoxyxylolactone **24** from 1,3-dichloropropan-2-ol (Scheme 4).[34] Even higher diastereoselectivities have been reported for the syntheses of **25** [eqn. (17)][35] and its fused carbocyclic analogues from cycloalkyl diazoacetates.[26,36] The construction of pyrrolizidine bases such as heliotridane **26**, whose pendant methyl group is *syn* is dependent on the use of chiral carboxamidate ligated dirhodium(II) (Scheme 5).[37] Individual enantiomers of substituted cyclohexyl diazoacetates or 2-octyl diazoacetates matched with a configurationally suitable chiral dirhodium(II) carboxamidate catalyst provide an effective methodology for the synthesis of lactones with exceptional diastereo- and regio-control,[38] forming only one isomer out of at least four that are possible.

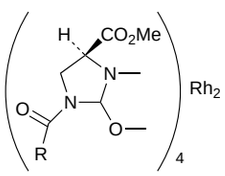
Applications to intermolecular cyclopropenation (carbene addition to alk-1-ynes[39] and β-lactam formation by intramolecular C–H insertion[40]) have also been reported. In general, Doyle's chiral carboxamide dirhodium(II) catalysts are recognized as providing the highest levels of stereocontrol in cyclopropanation and C–H insertion reactions of diazoacetates and diazoacetamides. There are other X–H insertion reactions of ketocarbenoids which have not yet reached stages of development comparable to these highly efficient asymmetric C–H insertions. Although several examples of inter- and intramolecular O–H insertions of water and alcohols are known,[2]



Rh_2 (5*R*-MEPY)$_4$
17

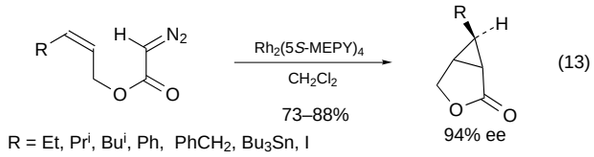


Rh_2 (4*S*-MEOX)$_4$
18



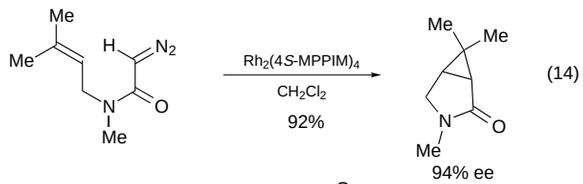
Rh_2 (4*S*-MACIM)$_4$
R = Me
19

Rh_2 (4*S*-MPPIM)$_4$
R = $PhCH_2CH_2$
20



R = Et, Pr^{i}, Bu^{i}, Ph, $PhCH_2$, Bu_3Sn, I

(13)



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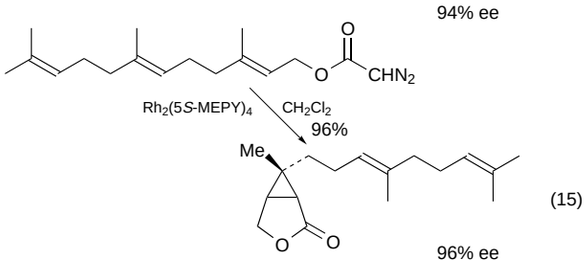

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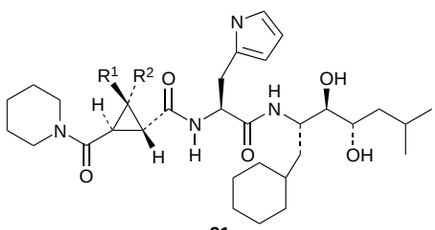
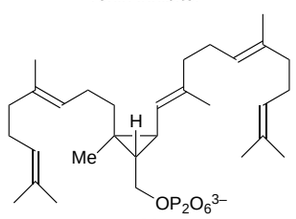
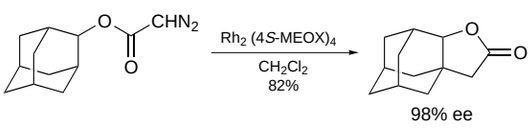


21
renin inhibitor



22
presqualene diphosphate



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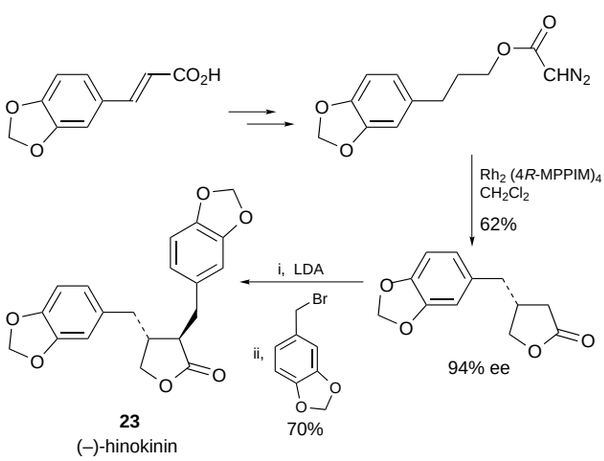
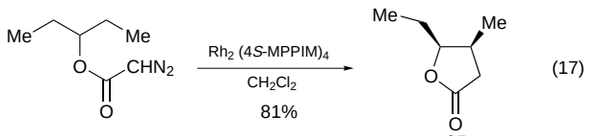


23
(–)-hinokinin

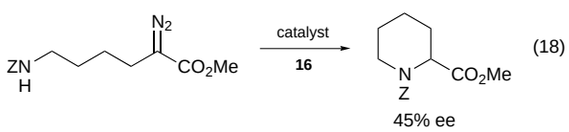
Scheme 3

high enantioselectivities through the use of chiral catalysts have yet to be realised.[41] There is now one example of the use of chiral catalysts in asymmetric N–H insertion where rhodium(II) (*S*)-mandelate was used to produce the pipecolic acid derivative in eqn. (18) with an ee of 45%.[42] Asymmetric Si–H insertion into $PhMe_2SiH$ with methyl phenydiazoacetate has been reported to occur in 46% ee with the use of $Rh_2(MEPY)_4$ catalysts.[43]



25
99% ee
94% de

(17)



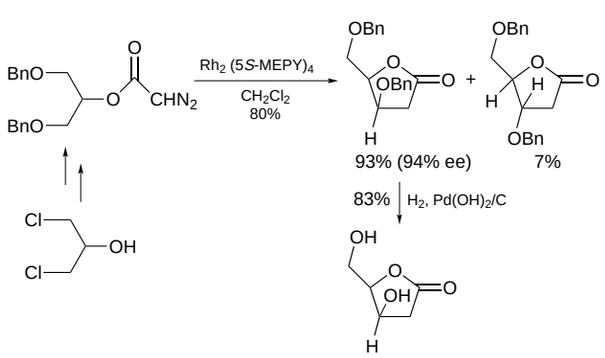
45% ee

(18)

Transformations of enantiopure α-diazoketones derived from α-amino acids and peptides

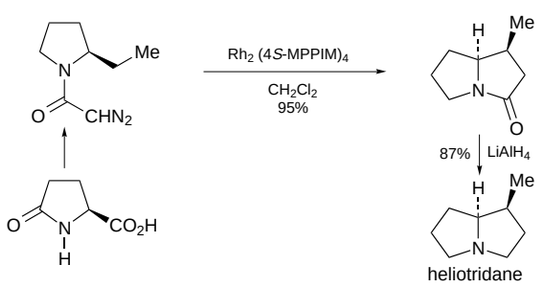
Whereas the primary objective of using chiral catalysts in diazocarbonyl reactions was to achieve high levels of enantiocontrol in selected reactions, that of using α-diazoketones derived from α-amino acids and peptides was to have enantiopure educts for chiral group transfer reactions. With appropriate *N*-protection α-amino acids and peptides can be easily transformed into diazoketones without racemization [eqn. (19)].[44]

A selection of the many racemization-free reactions which these diazoketones undergo are summarised in eqns. (20–25), the feature common to all being the transfer of an enantiopure α-amino ketone moiety to a new structural or functional group environment. It is possible, for example, to titrate *N*-protected



24 (3*R*, 4*R*)-2-deoxyxylolactone

Scheme 4

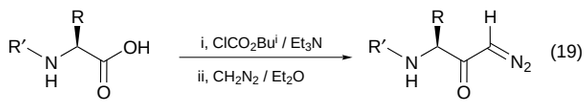


heliotridane
26

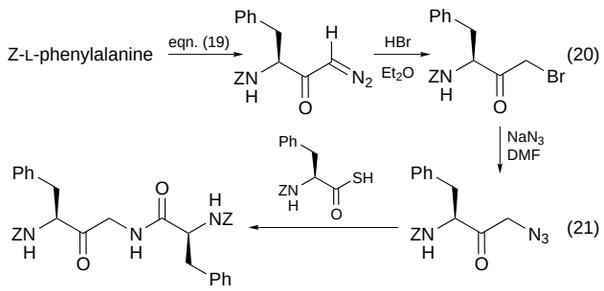
Scheme 5

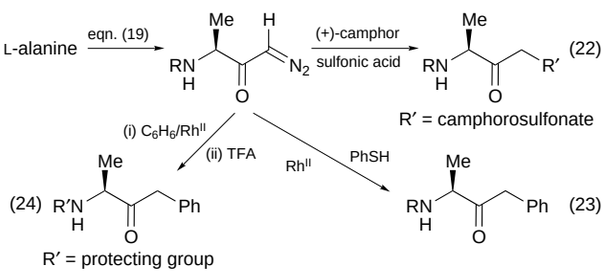
α-amino diazoketones with ethereal hydrogen chloride or bromide to form enantiopure α-halogenoketones[45] [eqn. (20)] which in turn provide access to α-keto azides of the type shown in eqn. (21). Reductive acylation of these α-keto azides using *N*-protected aminothiocarboxylic *S*-acids derived from *N*-protected amino acids produces homopeptides.[46] A typical example of this type of peptide modification is shown in eqn. (21). α-Keto sulfonates can be similarly prepared using sulfonic acids [eqn. (22)].[47] Insertion into S–H bonds under rhodium(II) catalysis provides access to α-sulfenyl ketones [eqn. (23)].[47] Aromatic cycloaddition, again with rhodium(II) assistance, can be used to prepare cycloheptatrienes which rearomatise in the presence of trifluoroacetic acid to yield enantiopure α-amino benzyl ketones [eqn. (24)] from benzene.[48] Rhodium catalysed ring unravelling reactions of furan yield polyfunctional aldehydes (eqn. (25)].[49] Yet another intermolecular process which provides access to enantiopure polyfunctional molecules is that involving the formation of lithium enolates from diazoketones without disturbing the diazofunction using suitable bases, *e.g.* LDA. These enolates can add to aldehydes or ketones to form diazoketols which on brief exposure to catalytic rhodium(II) acetate are smoothly transformed into β-diketones (Scheme 6).[44]

The Arndt–Eistert homologation of diazoketones has long been a popular way of converting α-amino acids into β-amino acids, although with early examples it is not always clear that retention of configuration has been adequately established. However, modern techniques do indicate that in the majority of cases retention is observed. In our own work, we have used the Arndt–Eistert reaction as one step in a process, the overall objective of which was to devise a synthesis of enantiopure α-keto-β-amino carboxylic acids and esters,[50] molecules already known in racemic form to possess significant inhibitory

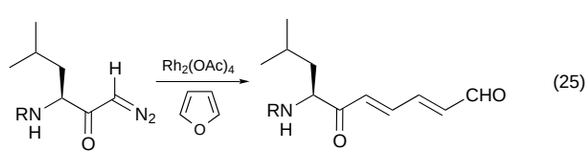


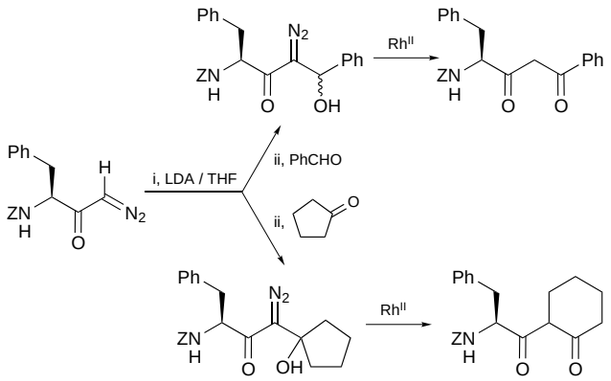
R′ = protecting group or amino acid residue (peptide)





R′ = protecting group

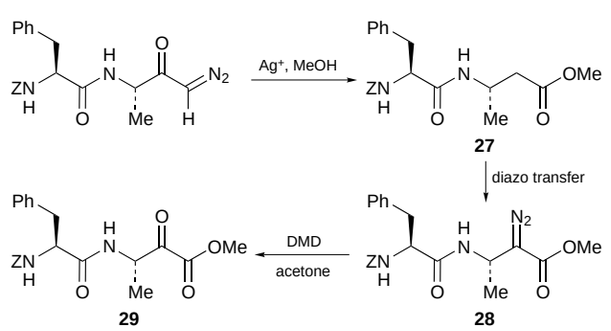




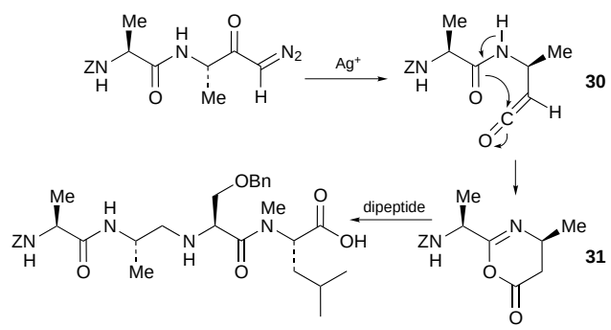
Scheme 6

activity towards members of the protease family of enzymes. The process, illustrated in Scheme 7, for the Phe-Ala derivative, commenced with Arndt–Eistert homologation using silver benzoate in methanol. Next, a diazo group was reintroduced alpha to the ester function of **27** to form **28** and in the final stage the diazo group was replaced by a carbonyl group as in **29** *via* oxidation with dimethyldioxirane in acetone. Retention of configuration was maintained throughout the sequence. Seebach and Podlech[51] have recently described a particularly useful application of the Arndt–Eistert process to the formation of homopeptides from diazoketones. The objective was to generate a peptidic ketene **30** from a diazoketone in an non-nucleophilic solvent and trap it intermolecularly with the free amino function of a second amino acid or peptide. An example of the process is shown in Scheme 8 where the ketene is derived from L-alanine and the amino function is that of a dipeptide. Although ketene **30** is undoubtedly an intermediate in the process, closer inspection revealed that it is not the immediate precursor of the homopeptide product. Rather, it was transformed, through involvement of the neighbouring amide bond, into dihydrooxazinone **31**, a reactive cyclic iminoanhydride which is readily attacked to form homopeptides.

Intramolecular insertion reactions of amino acid-derived diazoketones are also possible. We and others have found that



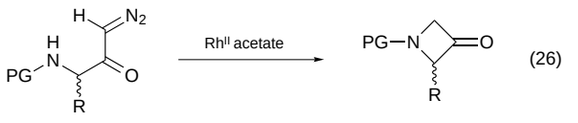
Scheme 7



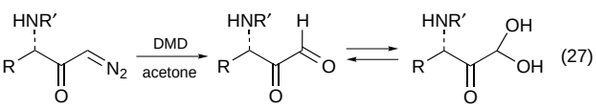
Scheme 8

rhodium(II) acetate-catalysed decomposition of the diazoketones in eqn. (26) furnish enantiopure 2-substituted azetidin-3-ones *via* N–H insertion.[52] The product from L-serine was subsequently tranformed by Hanessian[52b] *et al.* into *cis*- and *trans*-polyoximic acid.

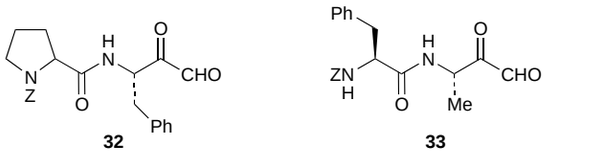
We have already touched briefly on the use of dimethyldioxirane in acetone as an oxidant in the synthesis of enantiopure β-amino-α-keto esters **26**. Distilled DMD in acetone offers particular advantages as an oxidant when one wishes to generate delicate intermediates in a clean environment free of extraneous nucleophiles or electrophiles. Terminal diazoketones derived from amino acids or peptides are also prone to DMD oxidation yielding glyoxals which have proved to be useful enantiopure educts.[53] Prior to this work, α-amino glyoxals were unknown; without *N*-protection they would be expected to undergo spontaneous polymerisation. We found that with suitable *N*-protection amino diazoketones can be oxidised to amino glyoxals in quantitative yield. Some representative examples are shown in eqn. (27). The glyoxals were obtained exclusively in the hydrated form. Interestingly, several of the dipeptide glyoxals were found to possess significant protease inhibitory properties.[54] For example, the sequences Z-Pro-Phe-CHO **32** and Z-Phe-Ala-CHO **33** inhibit chymotrypsin and cathepsin B, respectively, with K_i values some 10-fold lower than those for the corresponding peptide aldehydes. These glyoxals could also be used directly as reaction intermediates, there being no by-products of oxidation other than acetone and nitrogen. Among the reactions that we have used to demonstrate the versatility of *N*-protected amino glyoxals as enantiopure educts in amino acid and peptide modification are alkenation with Wittig reagents, *e.g.* eqns. (28), (29) and (30), condensation with amines to form imines, *e.g.* eqn. (31), and with 1,2-diaminobenzene to form quinoxalines,[53] *e.g.* eqn. (32). These compounds are in turn potentially useful enantiopure educts for further amino acid and peptide modification. Their biological properties, particularly their efficacy as protease inhibitors, are under investigation in collaboration with Dr B. Walker, School of Biology and Biochemistry, Queen's University.



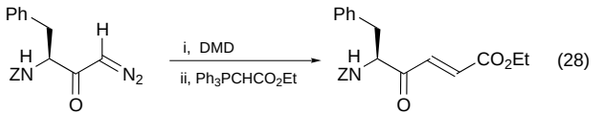
PG = Boc or Z; R = Me, Pr^i, $PhCH_2$, $PhCH_2OCOCH_2$

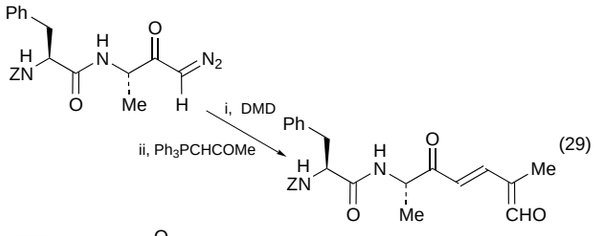


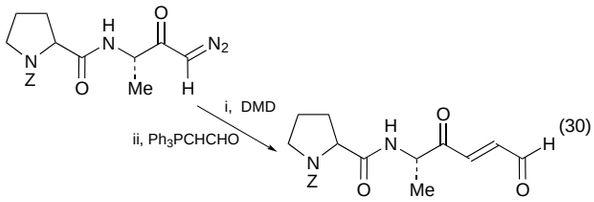
R = $PhCH_2$, Me, Me_2CH
R′ = protecting group or peptide residue

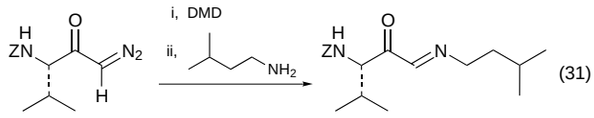


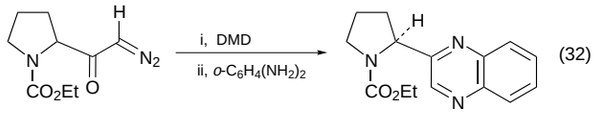
32 **33**











Conclusion

We hope that we have demonstrated that modern organic synthesis with ever increasing requirements for stereocontrol *via* catalysed or uncatalysed transformation continues to benefit from the outstanding versatility of diazocarbonyl compounds.

Acknowledgements

We are indebted to our co-workers whose names appear in the references with whom it has been a great pleasure to work.

Michael P. Doyle was raised in Minneapolis, Minnesota. He received his PhD degree with W. S. Trahanovsky from Iowa State University in 1968, where he was a U.S. Public Health Service Predoctoral Fellow. He was a postdoctoral associate with J. Rocek and Instructor at the University of Illinois at Chicago before he began his academic career at Hope College in 1968. In 1984 he moved to Trinity University as the first Dr D. R. Semmes Distinguished Professor of Chemistry. His research interests include the design of chiral catalysts for highly enantioselective chemical tranformations, the development of new synthetic methods involving metal carbenes, and macrocyclization reactions.

M. Anthony McKervey received his BSc, PhD and DSc degrees from Queen's University, Belfast and, following a period at M.I.T., joined the academic staff at Queen's in 1966. In 1976 he was appointed to the Chair of Organic Chemistry in University College Cork, Irish Republic. He returned to Belfast in 1990 as Professor of Organic Chemistry and Head of the Research Division of the School of Chemistry. Apart from diazocarbonyl chemistry, his research interests include calixarenes, the synthetic chemistry of furans, and clean synthesis for chemical development.

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