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Application of Donor/Acceptor-Carbenoids to the Synthesis of Natural Products[#]

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Abstract

The metal catalyzed reactions of diazo compounds have been broadly used in organic synthesis. The resulting metal-carbenoid intermediates are capable of undergoing a range of unconventional reactions, and due to their high energy, they are ideal for initiating a cascade sequence leading to rapid the rapid generation of structural complexity. This tutorial review will be give an overview of the most versatile reactions of donor/acceptor carbenoids, an exciting class of intermediates capable of highly selective reactions. This will include cyclopropanation, [4 + 3] cycloaddition, and C–H functionalization methodologies. The application of this chemistry to the synthesis of a range of natural products will be described.

Metal carbenoid intermediates are capable of a range of unusual reactions that can lead to novel strategies for synthesis.^{1–5} They are conveniently prepared by metal-catalyzed extrusion of nitrogen from diazo compounds. Their reactivity is highly dependent on the carbenoid structure, and consequently, they have been classified into three major groups, acceptor, acceptor/acceptor and donor/acceptor (Figure 1).^{6,7} Typical acceptor groups are keto, nitro, cyano, phosphonyl and sulfonyl, while typical donor groups are vinyl, aryl and heteroaryl. The metal carbenoids generally display electrophilic character; thus, acceptor groups will tend to make the carbenoids more reactive and less selective, and the reverse would be the case for donor groups. Consequently, the applications of carbenoids lacking a donor group in total synthesis mostly involve intramolecular reactions. A beautiful example of the synthetic potential of this type of application is the intramolecular cyclization/cycloaddition cascade reactions reviewed by Padwa in this thematic issue.⁸ An emerging area in total synthesis is the use of donor/acceptor-carbenoids because they display much greater selectivity than the conventional carbenoids. The applications of this versatile class of carbenoids will be highlighted in this review.

The chemistry of the donor/acceptor carbenoids has expanded greatly in recent years, and a number of impressive examples have emerged of the applications of these intermediates to the synthesis of complex targets. Representative targets are shown in Scheme 1.^{9–15} In all of these syntheses the carbenoid transformation is involved in a crucial disconnection and installs key stereocenters in the natural product targets. This tutorial will describe the reactivity of donor/acceptor carbenoids, in the context of their application to total synthesis, and will illustrate the controlling elements behind the stereoselective transformations. The

Part of the rapid generation of molecular complexity in organic synthesis themed issue.

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ground rules for this chemistry described herein will hopefully spur others to consider the use of carbenoid reactions as powerful disconnections for the synthesis of complex targets.

Metal-stabilized carbenoids are readily generated by metal-catalyzed decomposition of diazo compounds as illustrated in Scheme 2. Due to the enhanced stability of donor/acceptor carbenoids, they are capable of a variety of regio- and stereoselective reactions. When chiral catalysts are used, especially those derived from dirhodium tetracarboxylates, a variety of complex chiral building blocks can be rapidly assembled. The two most widely used reactions of donor/acceptor carbenoids in total synthesis have been cyclopropanation^{4,6} and C—H functionalization.⁷ The cyclopropanes can be readily rearranged or ring-opened in a stereocontrolled manner, leading to the synthesis of a wide variety of potential targets.⁴ C—H Functionalization is orthogonal to the normal strategies of synthesis relying on functional group interconversions, and consequently, have led naturally to unconventional retrosynthetic disconnections.³

Intermolecular Cyclopropanation of Alkenes

The intermolecular cyclopropanation chemistry of donor/acceptor carbenoids is routinely highly diastereoselective (>20: 1 dr). A representative example is the Rh₂(*S*-DOSP)₄-catalyzed reaction of styryldiazoacetate **1** with styrene, which generates the vinylcyclopropane **2** in 98% ee and >20 : 1 dr (Scheme 3).¹⁶ The vinylcyclopropane is a valuable chiral building block, which has been converted to the cyclopropane amino acids **3a** and **3b**,¹⁶ the cyclopropanedicarboxylate **4**, which can then be stereoselectively ring-expanded under Lewis acid catalyzed conditions with aldehydes,¹⁷ or ring-opened by a cuprate reagent, ultimately leading to the synthesis of the antidepressant (+)-sertraline **5**.¹⁸

Intramolecular Cyclopropanation of an Indole

An elegant application of an intramolecular cyclopropanation was recently described by Qin in the total synthesis of (±)-communesin F (**9**).¹⁵ The key step is the copper(I) triflate-catalyzed reaction of α-aryl-α-diazo ester **6**, which led to the formation of the cyclopropane **7** in 88% yield as a 1.6 : 1 mixture of diastereomers (Scheme 4). The formation of a diastereomeric mixture was inconsequential because this mixture converged to a single diastereomer **8** upon reduction of the azide and amino opening of the cyclopropane. With the central pentacyclic core installed in **8**, the synthesis of (±)-communesin F (**9**) was completed.

Intermolecular [4 + 3] Cycloaddition with Pyrroles

The intermolecular cyclopropanation between vinylcarbenoids and dienes is a broadly useful transformation, because the resulting *cis*-divinylcyclopropanes undergo a Cope rearrangement to generate cycloheptadienes in a stereodefined manner.¹⁹ Thus the synthetic sequence is a formal [4 + 3] cycloaddition between the vinylcarbenoids and dienes. An early example of the utilization of this chemistry is the total synthesis of (±)-ferruginine (**13**) (Scheme 5).²⁰ The key step is the dirhodium tetraoctanoate-catalyzed [4 + 3] cycloaddition between the vinyldiazoketone **10** and the pyrrole **11** to generate the tropane system **12** in 73% yield, which is readily converted to (±)-ferruginine.

The [4 + 3] cycloaddition approach to tropanes has been extended to enantioselective systems. The first approach used α-hydroxy esters as chiral auxiliaries as illustrated in Scheme 6.²¹ When *S*-lactate was used as the chiral auxiliary (**14**), the tropane **15** was formed in 64% yield and 66% de. More recently, the chiral dirhodium catalyst, Rh₂(*R*-PTAD)₄ was shown to be very effective in the reaction of the siloxyvinyldiazoacetate **16**

with *N*-Boc-pyrrole to generate the tropane **17** in 84% ee.²² Both **15** and **17** can be readily converted to intermediates that were used for the synthesis of ferruginine.

More elaborate systems can be used in the [4 + 3] cycloaddition with pyrroles as illustrated in the dirhodium tetraoctanoate-catalyzed reaction with the pyrrole **18** to generate the tropane **19** in 90% yield (Scheme 7).¹² This was a key step in Kende's elegant total synthesis of (±)-isostemofoline, as the tropane **19** is well functionalized to complete the total synthesis. In principle, this strategy could also be applied to the enantioselective synthesis of isostemofoline because the Rh₂(*R*-PTAD)₄-catalyzed reaction of **16** with **18** generated the tropane **19** in 84% ee.²²

Intermolecular [4 + 3] Cycloaddition with Dienes

The [4 + 3] cycloaddition between vinylcarbenoids and dienes can be highly regioselective. An impressive example of this feature is the key transformation used in the total synthesis of (±)-tremulenolide and (±)-tremulenediol (Scheme 8).¹¹ The rhodium catalyzed reaction of vinyl diazoacetate **22** in the presence of (*E*, *Z*)-diene **21** generated the cycloheptadiene **24** as a single regioisomer and diastereomer in 49% yield. Donor/acceptor carbenoids are very sensitive to steric influences during cyclopropanation. In this case, selective cyclopropanation of the (*Z*) double bond occurs to generate the divinylcyclopropane **23**. The Cope rearrangement of **23** proceeds through a boat transition state to generate **24** as a single diastereomer. The *cis*-olefin in cycloheptadiene **24** was selectively hydrogenated by Wilkinson's catalyst to form cycloheptene **25** in 90% yield. The acetyl group was hydrolyzed with aqueous potassium carbonate followed by *in situ* lactonization to complete the synthesis of (±)-tremulenolide A (**26**). Alternatively, DIBAL reduction of the two ester groups in cycloheptene **25** resulted in the synthesis of (±)-tremulenediol A (**27**).

The [4 + 3] cycloaddition strategy can be conducted with heteroaryldiazoacetates as illustrated in the formal synthesis of (+)-frondosin B (**34**) (Scheme 9).²³ Reaction of heteroaryldiazoacetate **28** with *trans*-piperylene **29** in the presence of Rh₂(*R*-DOSP)₄ followed by immediate hydrogenation of the product using Pd/C produced the reduced [4 + 3] cycloadduct **33** in 57% yield over the two steps, with excellent diastereoselectivity (>30:1 dr), and enantioselectivity (97% ee). In this case the *cis*-divinylcyclopropane **30** undergoes a Cope rearrangement to form **31**, which then undergoes a stereoselective tautomerization to regenerate the aromatic benzofuran ring in **32**. Tricycle **33** was then further advanced to an intermediate used in the Danishefsky's synthesis of (+)-frondosin B.²⁴

An enantioselective [4 + 3] cycloaddition was a crucial step for the synthesis of (+)-5-*epi*-vibsanin E (**38**) (Scheme 10).¹⁰ Reaction of vinyl diazoacetate **16** with triene **35** in the presence of 0.5 mol % of Rh₂(*R*-PTAD)₄ produced the cycloheptadiene **36** in 65% yield, resulting in the formation of a quaternary stereocenter with good enantiocontrol (90% ee). The cycloheptadiene **36** was then converted to the tricyclic core **37** of the vibsanin natural products, which could then be elaborated to (+)-5-*epi*-vibsanin E (**38**). This strategy has also been applied to the synthesis of (±)-vibsanin E.²⁵

The use of chiral catalysis in the [4 + 3] cycloaddition can overcome the inherent directing nature of a chiral substrate. An intriguing example of this has been reported by Sarpong in a parallel kinetic resolution approach to the cyathane and cyanthiwigin diterpenes. (Scheme 11)²⁶ The Rh₂(*R*-DOSP)₄-catalyzed reaction of the (+)-enantiomer **39** preferentially forms the tricycle **41** while the reaction with the (–)-enantiomer **43** generated preferentially **44**, a different diastereomer of the tricycle. **41** is a potential precursor to (–)-cyanthiwigin G (**42**) while **44** is a potential precursor to (+)-cyanthi A₃ (**45**).

Intramolecular C—H Insertion

Catalytic intramolecular C—H insertion reaction of metal-carbenoids is a powerful tool for the formation of five-membered rings and occasionally other ring sizes.^{2,7} The reaction with acceptor-substituted carbenoids has been widely employed in numerous syntheses of natural products.^{2,7} The donor/acceptor variant, illustrated in generic form in the conversion of **46** to **47** (Scheme 12), has been integral to several recent total syntheses of natural products, which will be highlighted here.

C—H Insertion proceeds with retention of configuration at the C—H bonds. This phenomenon was exploited by Taber in his synthesis of (–)-hamigeran B (Scheme 13).²⁷ Reaction of α -aryl- α -diazoacetone **48** in the presence of $\text{Rh}_2(\text{S-PTTL})_4$ led to the C—H insertion product **49** in 83% yield, with full stereocontrol of the quaternary center. The reaction, however, produced a mixture of diastereomers *alpha* to the cabonyl. This stereocenter was readily equilibrated to the desired configuration during the subsequent steps in the synthesis of (–)-hamigeran B (**50**).

Fukuyama and coworkers utilized an intramolecular C—H functionalization of an α -aryl- α -diazoacetate to generate benzofurans as a key step in the synthesis of (–)-ephedradine A (**53**) (Scheme 14).^{9,13} The enantioselective catalysis of the basic transformation was established in model studies.^{28,29} The optimized conditions used in the synthesis were a combination of a chiral catalyst and a chiral auxiliary. Reaction of diazoacetate **51**, bearing a chiral auxiliary, with $\text{Rh}_2(\text{S-DOSP})_4$ yielded the dihydrobenzofuran **52** with a diastereomer ratio of 13:1. The dihydrofuran **52** was then converted in a series of steps to (–)-ephedradine A. (**53**)

A modified method for the synthesis of a chiral precursors of (–)-ephedradine A has been reported using $\text{Rh}_2(\text{S-PTAD})_4$ as catalyst. $\text{Rh}_2(\text{S-PTAD})_4$ gives much higher asymmetric induction in this type of reaction compared to $\text{Rh}_2(\text{S-DOSP})_4$, leading to reasonable asymmetric induction without the aid of a chiral auxiliary.³⁰ Reaction of aryldiazoacetate **54** in the presence of $\text{Rh}_2(\text{S-PTAD})_4$ generated the cis benzofuran **55** in 72% yield, with high diastereoselectivity (dr ~14:1), and good enantioselectivity (79% ee) (Scheme 15). Epimerization with sodium hydroxide lead to the trans benzofuran **56**, which is the diastereomer required for the total synthesis of **53**.

Fukuyama and coworkers have extended the intramolecular C—H insertion to even more elaborate systems.³¹ The key step in the synthesis of (–)-serotobenine (**59**) uses an indolyldiazoacetate as substrate (Scheme 16). Once again, a combination of a chiral catalyst and a chiral auxiliary was used to induce asymmetric induction whereby the $\text{Rh}_2(\text{S-DOSP})_4$ -catalyzed reaction of the indolyldiazoacetate **57** generated the fused dihydrobenzofuran **58** in 92% yield, with high asymmetric induction (dr~96:4). Conversion of **58** to (–)-serotobenine (**59**) was achieved in a series of steps.

Intermolecular C—H Insertion

Donor/acceptor carbenoids undergo highly regioselective and stereoselective C—H insertions.⁷ Although acceptor-substituted carbenoids will undergo intermolecular C—H insertions into substrates such as cyclohexane and tetrahydrofuran, overall, the range of substrates capable of selective functionalization with this type of carbenoid is limited.³² In contrast, donor/acceptor carbenoids display great regioselectivity, controlled by a delicate balance of steric and electronic influences. Furthermore, in the presence of chiral catalysts, highly enantioselective reactions can be achieved.

The intermolecular C—H insertion can be considered as a C—H functionalization strategy, complimenting many of the classic reactions of organic synthesis, as illustrated in Scheme 17. For example, C—H insertion α to oxygen, generates β -hydroxy esters,³³ products that are typically derived from an aldol reaction. The analogous C—H insertion α to nitrogen, generates β -amino esters,³⁴ the typical products of a Mannich reaction.

A wide variety of pharmaceutical agents have been synthesized using an enantioselective intermolecular C—H functionalization as the key step. Two examples are illustrated in Scheme 18. $\text{Rh}_2(\text{R-DOSP})_4$ -catalyzed allylic C—H insertion into cyclohexadiene by the thiophenyldiazoacetate **60** generated **61**, which was converted in two steps to the cholinesterase inhibitor, (+)-ceitidil (**62**).³⁵ *N*-methyldisilazane **63** is an effective substrate for C—H functionalization because the *N*-methyl group is electronically activated while the nitrogen is sterically protected. $\text{Rh}_2(\text{R-DOSP})_4$ -catalyzed reaction of the aryldiazoacetate **64** with **63** generated the β -amino ester **65** in 93% yield, which was converted in two steps to (*S*)-venlafaxine (**66**), an enantiomer of the antidepressant ($\pm$)-venlafaxine.³⁶ Other pharmaceutical targets that have been made using C—H functionalization strategies include (+)-methylphenidate^{34,37,38} and (+)-indatraline.³⁹

Selective intermolecular C—H insertion can occur at primary, secondary or tertiary C—H bonds by careful manipulation of steric and electronic influences. A C—H insertion at a primary benzylic position was used in the synthesis of (+)-imperanene and (–)- α -conidendrin (Scheme 19).⁴⁰ Both natural products could be derived from the reaction of the stryryldiazoacetate **67** with the catechol derivative **68** by using the appropriate enantiomer of the catalysts. The C—H insertion product **69** was formed in 91% ee in the $\text{Rh}_2(\text{R-DOSP})_4$ -catalyzed reaction and was readily converted to (+)-imperanene (**70**). The enantiomeric product *ent*-**69** was converted to (–)- α -conidendrin (**71**), in which the original stereocenter of the C—H insertion product controls the stereochemistry of the other two stereocenters in the natural product.

Combined C—H Activation/Cope Rearrangement

The most unusual reaction of donor/acceptor carbenoids is the combined C—H activation/Cope rearrangement.⁴¹ The reaction generates products that are formally derived from a C—H functionalization, followed by a Cope rearrangement. Interestingly, the C—H functionalization product was found not an intermediate in this reaction as it is thermodynamically the most stable product. It has been proposed that the reaction is as illustrated in Scheme 20, initially following the C—H functionalization pathway to **72**, but is then interrupted by the Cope rearrangement, forming the observed product **73**.⁴¹

The concerted nature of the combined C—H activation/Cope rearrangement causes the reaction to be highly diastereoselective. This is clearly seen in the reaction of two model substrates **74** and **76** (Scheme 21).⁴² In both cases, the C—H functionalization products, **75** and **77**, are produced with very high diastereoselectivity and enantioselectivity. The predominant diastereomer is consistent with the Cope rearrangement occurring through a chair transition state as illustrated in Scheme 20.

The combined C—H activation/Cope rearrangement has been applied to the synthesis of the antidepressant (+)-sertraline as illustrated in Scheme 22.⁴³ The $\text{Rh}_2(\text{S-DOSP})_4$ -catalyzed reaction of the vinyl diazoacetate **78** with 1,3-cyclohexadiene generated the 1,4-cyclohexadiene **79** in 99% ee. A four-step sequence converted **79** to the 4-aryltetralone **80**, and this represents a formal synthesis of (+)-sertraline (**5**).

Due to the high asymmetric induction possible in the reactions of donor/acceptor carbenoids, these intermediates are capable of reacting differentially with the two enantiomers of a chiral substrate. An impressive example of this phenomenon is seen in the kinetic resolution of racemic dihydronaphthalenes.⁴⁴ As illustrated in the model study shown in Scheme 23, one enantiomer of **81** undergoes a combined C—H activation/Cope rearrangement to form **82**, while the other enantiomer of **81** is cyclopropanated to form **83**. Both **82** and **83** are formed with very high diastereo- and enantiocontrol.

The enantiodivergent reactions of dihydronaphthalenes has been applied to the synthesis of various natural products. The first example shown in Scheme 24 describes a concise synthesis of (+)-erogorgiaene (**87**).⁴⁴ Reaction of the vinyl diazoacetate **84** with the racemic dihydronaphthalene **85** generates all three stereogenic centers present in (+)-erogorgiaene. Hydrogenation followed by lithium aluminum reduction of the initially formed product generated the alcohol **86** in 90% ee, in 62% yield (considering that only one of the enantiomers of **85** is forming **86**). The completion of the synthesis of (+)-erogorgiaene (**87**) is readily achieved by oxidation of the alcohol in **86** followed by a Wittig reaction.

The enantiodivergent reactions have been extended to more elaborate systems as illustrated in Scheme 25 with the total synthesis of (–)-colombiasin A (**90**) and (–)-elisapterosin B (**91**).¹⁴ The reaction of the racemic dihydronaphthalene **88** and the vinyl diazoacetates **84** generated a 1:1 mixture of cyclopropanation and C—H functionalization products. Direct hydrogenation and reduction of the crude product generated the alcohol **89** with excellent diastereocontrol and enantiocontrol. The completion of the synthesis of total synthesis of (–)-colombiasin A (**90**) and (–)-elisapterosin B (**91**) was achieved using standard chemistry. A variety of related natural products have also been prepared.^{45,46}

In summary, this tutorial describes the scope of novel synthetic disconnection that can be achieved using donor/acceptor-substituted carbenoids as key intermediates. Due to their greater selectivity, these intermediates are capable of highly selective intermolecular reactions not accessible by acceptor-substituted carbenoids. The selectivity is controlled by a delicate balance of steric and electronic effects. The cyclopropanation chemistry of these intermediates is now firmly established. In particular, the tandem cyclopropanation/Cope rearrangement has resulted in numerous examples in total synthesis. The C—H functionalization methodology is still emerging, but the impressive applications in total synthesis already achieved indicate the great potential for future growth in this area of chemistry.

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Biographies

Huw M. L. Davies was born in Aberystwyth, Wales, UK. He began his independent academic career at Wake Forest University. In 1995 he moved to the University at Buffalo, the State University of New York, where he held the positions of UB Distinguished Professor and Larkin Professor of Organic Chemistry. In 2008, he joined the faculty at Emory University as the Asa Griggs Candler Professor of Chemistry. His research program covers design of chiral catalysts, development of new synthetic methodology, total synthesis of biologically active natural products, and development of chiral therapeutic agents. A major current research theme in his group is catalytic asymmetric C–H functionalization.

Justin R. Denton was born in Cooperstown, New York in 1982. He received a B.S. degree in Chemistry from SUNY Environmental Science and Forestry & Syracuse University in 2004. He went on to earn a Ph.D. in Organic Chemistry from the State University of New York at Buffalo under the guidance of Prof. Huw M. L. Davies in 2008, where he focused on the development of new synthetic methodologies utilizing donor/acceptor-substituted rhodium carbenoids. He is currently a post-doctoral researcher at Obiter Research in Champaign, Illinois. Justin's current research interests are in the realm of green chemistry, specifically directed towards developing more economically efficient methodologies for synthesis.

Figure 1.

Classes of metal carbenoids

EAG = Electron Accepting Group (CO_2R , COR , CONR_2 , CN , PO(OR)_2 , SO_2R , NO_2 , CF_3)

EDG = Electron Donating Group (vinyl, aryl, heteroaryl)

Scheme 1.

Representative natural products synthesized using donor/acceptor carbenoids

Scheme 2.
Cyclopropanation and C—H functionalization

Scheme 3.

Intermolecular cyclopropanation applied to synthesis.

Scheme 4.
Total Synthesis of (±)-communesin F

Scheme 5.
Synthesis of (±)-ferruginine

Scheme 6.
Asymmetric [4 + 3] cycloadditions with pyrroles

Scheme 7.
Total synthesis of (±)-isostemofoline

Scheme 8.
Synthesis of (±)-tremulenolide and (±)-tremulenediol

Scheme 9.
Formal synthesis of (+)-frondosin B

Scheme 10.
Total synthesis of (+)-5-*epi*-vibsanin E

Scheme 11.

Diastereoselective entry to the cyathane and cyanthiwigin diterpenes

Scheme 12.
Intramolecular C—H functionalization

Scheme 13.
Synthesis of (-)-hamigeran B

Scheme 14.
Synthesis of (-)-ephedradine A.

Scheme 15.
Chiral catalyst approach to (-)-ephedradine A precursor.

Scheme 16.
Asymmetric synthesis of (-)-serotobenine

Scheme 17.
C—H functionalization as a strategic reaction

Scheme 18.

C—H functionalization applied to the synthesis of pharmaceutical targets

Scheme 19.

Total synthesis of (+)-imperanene and (-)-α-conidendrin.

Scheme 20.

Proposed pathway for the combined C—H activation/Cope rearrangement

Scheme 21.

Model substrates for the combined C—H activation/Cope rearrangement

Scheme 22.
Formal synthesis of (+)-sertraline

Scheme 23.
Kinetic resolution of racemic dihydronaphthalenes

Scheme 24.
Total synthesis of (+)-erogorgiaene

Scheme 25.

Total synthesis of (-)-colombiasin A and (-)-elisapterosin B