CATALYTIC ENANTIOSELECTIVE INSERTION OF RHODIUM-CARBENOIDS INTO ALIPHATIC C-H BONDS

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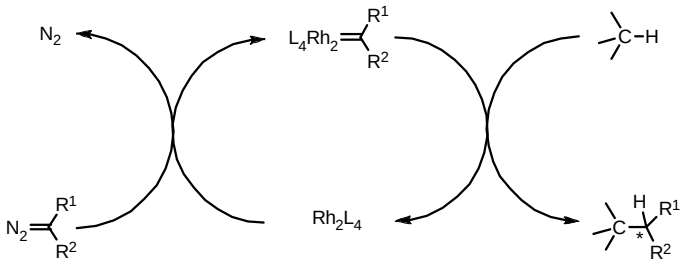
INTRODUCTION

The selective functionalization of unactivated C-H bonds represents one of the most direct and atom-efficient bond-forming reactions available to synthetic chemists.[1] Accordingly, research efforts toward direct functionalization of unreactive C-H bonds by transition-metal complexes have increased in recent decades providing many promising advances.[2] To accomplish this transformation, transition-metal complexes must be highly reactive to insert into the strong C-H bond. Moreover, *in situ* regeneration of such reactive species has been a daunting challenge. Not surprisingly, the evolution of C-H functionalizations into catalytic methods has not kept pace with stoichiometric methods, thus limiting their practicality. Insertion induced by dirhodium stabilized carbenoids (Scheme 1) represents a very attractive alternative.[1]

Scheme 1: Catalytic Cycle of Rhodium(II)-carbenoid C-H Insertion

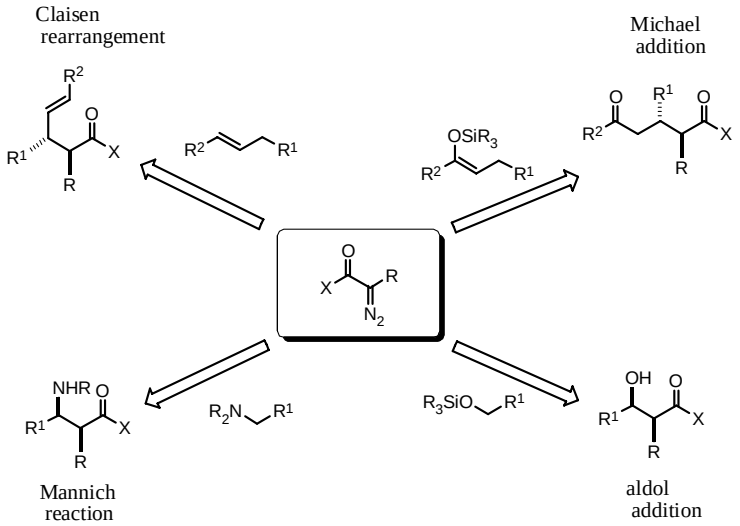


Free carbenes and metal-carbenoids have been extensively investigated for many years, but synthetically practical applications to C-H insertion have only been reported in the last three decades.[1,3] Formation of metal-carbenoids by transition-metal catalyzed decomposition of diazo compounds is well documented and represents a simple and reliable approach to generate species capable of C-H functionalization.[4] Furthermore, the metal modulates the highly reactive and normally unselective carbene and judicious selection of the metal ligands and carbene substituents can effect C-H insertion exclusively.[1] Although many reports of metal-carbenoid induced C-H insertion have been reported, dirhodium(II)-catalyzed decomposition of diazo compounds has emerged as the most effective and widely utilized approach.[1] Rhodium-carbenoids, derived by dirhodium-catalyzed decomposition of

diazo compounds, differ from most other organometallic complexes capable of C-H insertion in that the metal does not interact directly with the C-H bond. However, coordination of chiral ligands to the dirhodium complex can still induce highly enantioselective insertions under catalytic conditions. The first examples of highly selective metallocarbenoid-induced C-H insertions were intramolecular, yet the introduction of donor-acceptor carbenoids has allowed the transition to intermolecular methods without sacrifice of site- or enantioselectivity.[3]

Maturation of intermolecular rhodium(II) donor-acceptor-substituted carbenoids has led to asymmetric equivalents of several classic organic transformations including the aldol reaction, Michael reaction, Mannich reaction, and Claisen rearrangement (Scheme 2). The success of this chemistry offers unique, strategic C-C bond-forming reactions to the synthetic architect and has already been illustrated in several total syntheses.

Scheme 2: Asymmetric C-H Insertions Parallel to Classic Organic Transformations



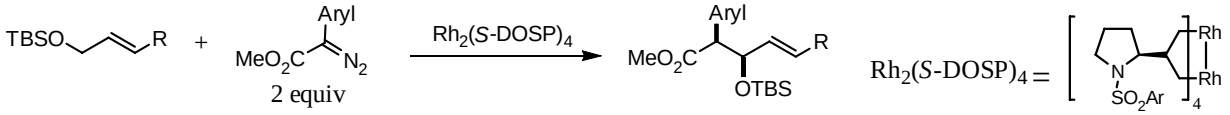
DEVELOPMENT OF SELECTIVE INTERMOLECULAR INSERTIONS

Pioneering work by Teyssié *et al.* proved that rhodium complexes were superior to those of copper as catalysts for carbenoid C-H insertion.[5] The site-selectivity of alkane C-H insertion by carbenoids formed from dirhodium(II) tetracarboxylates was modest, but more importantly, these early studies showed that the constitution of the catalyst influenced the selectivity.[5-6] The electrophilicity of the carbene largely dictates the chemoselectivity of metal-carbenoids. Highly electrophilic diazoacetate-derived carbenoids often lead to non-selective product formation during C-H insertions; side reactions such as cyclopropanation and carbene dimerization/oligomerization are observed.[6-8] These processes can be suppressed when diazoacetates are substituted with an electron-donating group on the carbene carbon. Practical intermolecular C-H insertions were not previously possible prior to Davies'

demonstration of the high chemoselectivity of donor-acceptor substituted carbenoids.[9] Aryl and vinyl substituted diazoacetates are typical substituents for this class of metallocarbenoids.[1] To date, the donor-acceptor substituted carbenoids offer the optimum balance between acceptable reactivity while retaining satisfactory selectivity for intermolecular C-H insertions.

Following the early reports of intermolecular rhodium-carbenoid insertions into alkanes, several useful classes of substrates emerged whose transformation correspond to surrogates for well-known organic transformations. The most prominent substrates are those containing benzylic[10], allylic[11], α-oxygen bearing[12-13], and α–nitrogen bearing C-H bonds.[14-15] Insertion into methylene C-H bonds α to oxygen in silyl ethers by diazoacetate-derived carbenoids yields protected β-hydroxy esters.[12] The use of C_2 symmetric dirhodium catalyst Rh_2(*S*-DOSP)$_4$ induces formation of the aldol products in Table 1 with good site-, diastereo-, and enantioselectivity. Reaction of both alkyl and allyl silyl ethers afforded one diastereomer almost exclusively; the particular enantiomer obtained from the catalyst is easily predicted from existing stereomodels.[12] A limitation of this process for construction of protected aldol products is the requirement of the donor-acceptor substituted diazoacetates. To date only aryldiazoacetates have been reported for insertion into silyl ethers, but as the technology matures new donor-acceptor carbenoids should be discovered to broaden the generality of this and other C-H insertion reactions.

Table 1: Rh_2(*S*-DOSP)$_4$-Catalyzed C-H Activation of Allyl *tert*-Butyldimethylsilyl Ethers



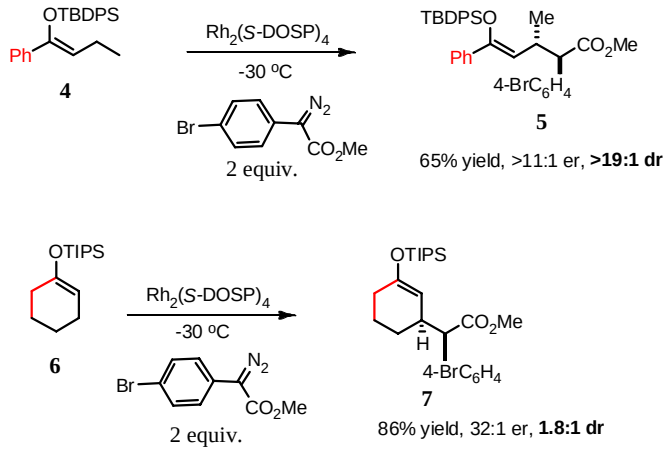
Ar = $C_{12}H_{25}C_6H_4$

R	aryl	temp, °C	yield, %	dr	er
CH_2CH_3	4-BrC_6H_4	23	40	>32:1	8:1
$CH{=}CHCH_3$	4-BrC_6H_4	23	70	24:1	14:1
CH_2OAc	4-BrC_6H_4	50	93	>32:1	4.3:1
H	4-BrC_6H_4	50	33	>32:1	12:1
C_6H_5	C_6H_5	-25	94	>32:1	16:1
CO_2CH_3	4-ClC_6H_4	23	93	>32:1	2.8:1

Insertion at an allylic methylene C-H bond of silyl enol ethers produces 1,5-dicarbonyl compounds as a parallel to Michael additions.[13] Site-selectivity is high corresponding to insertion at the methylene best able to stabilize accumulation of positive charge consistent with electrophilic attack by the carbene. The use of Rh_2(*S*-DOSP)$_4$ again produces the dicarbonyl products with high enantioselectivity. The substrate scope has not yet been fully described; nevertheless Davies has shown that the silyl enol ether structure has a significant impact on diastereoselectivity. Increasing the size of

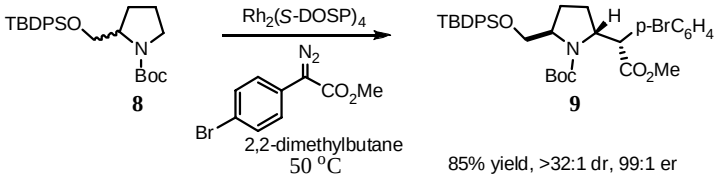
the methylene substituents (e.g. from CH_2 to C_6H_5, Scheme 3, **7** and **5**) increases the diastereomeric ratio from <2:1 to >19:1.

Scheme 3: Substituent Effects on Diastereoselectivity in Silyl Enol Ether C-H Insertions



Functionalization α to a nitrogen substituent with aryldiazoacetates produces β-amino carbonyl compounds, analogous to a Mannich reaction.[15] Insertion at HC(2) of *N*-Boc-pyrrolidine proceeds with excellent diastereo- and enantioselectivity. Interestingly, Davies noticed that double C-H activation of the protected pyrrolidine at each active methylene group in the presence of excess aryldiazoacetate results in a double-diastereoselection during the second insertion affording a single diastereomer containing four stereocenters in good yield.[14] Davies next exploited the inherent diastereoselection observed in the double C-H activation of *N*-Boc-pyrrolidine in the kinetic resolution of racemic 2-substituted pyrrolidine **8** (Scheme 4).[14] Excellent diastereo- and enantioselectivity are obtained again using Rh_2(*S*-DOSP)$_4$ as the catalyst. Unfortunately, the selectivity with piperidines fails to match that seen for pyrrolidines. Although the scope of insertion in cyclic amines is currently limited, insertion to acyclic amines has been successful yielding β-amino acid derivatives.[16]

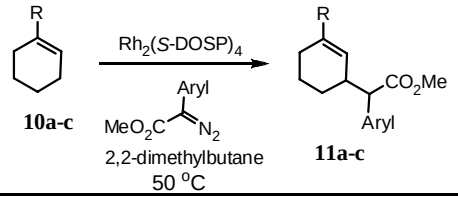
Scheme 4: Kinetic Resolution of 2-substituted N-Boc-Pyrrolidines



Insertion reactions with the most common substrate class, those with allylic C-H bonds, by aryl- or vinyldiazoacetates results in γ,δ-unsaturated esters, a class of products corresponding to a Claisen rearrangement. An early report by Müller (Table 2, entry **a**) using Rh_2(*S*-DOSP)$_4$ as the catalyst showed

that cyclopropanes are the major product.[8] Stereo-defined C-H insertion products are formed with good enantioselectively, but in low yield and poor diastereoselectivity. Davies argued that the *cis*-alkene **10a** in Müller's report was a poor substrate on which to demonstrate the utility of C-H insertion to form γ,δ-unsaturated esters due to their well established affinity to undergo cyclopropanation.[11] Davies' reexamination of Müller's results found that silyl derivatives **10b** and **10c** suppressed cyclopropanation and markedly improved diastereoselectivity up to 94:6.[11] The optimization of Muller's work highlights how significantly steric effects can alter the observed selectivity.

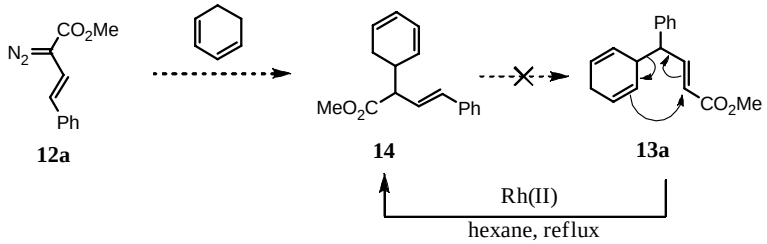
Table 2: Optimization of allylic C-H activation for cyclohexenes



substrate	R	aryl	yield, %	dr	er
a	H	Ph	33	1.1:1	7:1
b	TMS	4-BrC_6H_4	48	2.3:1	16:1
c	TBDPS	4-BrC_6H_4	64	16:1	39:1

In 1999 Davies reported an unusual bond migration that occurs during insertion of phenylvinyldiazoacetates into 1,3-cyclohexadiene (Table 3) toward the total synthesis of (+)-sertraline.[17] The product appears to be a tandem C-H insertion at the C(5) allylic methylene of 1,3-cyclohexadiene, followed by a Cope rearrangement. The unusual C-H insertion product was formed with extremely high enantioselectivity and prompted Davies to investigate the reaction in more detail.[17-19]

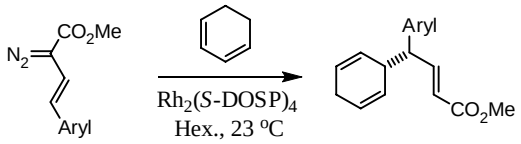
Scheme 5: [3,3] Sigmatropic rearrangment of 13a



Heating **13a** in the presence of Rh(II) induces a Cope rearrangement, thus proving the absence of thermodynamic basis for conversion of **14** to **13a** as originally proposed (Scheme 5).[19] Although the mechanism of the reaction is more complex than a tandem C-H insertion/Cope rearrangement, the

excellent selectivities observed suggest a strictly-defined approach of the C-H bond to the catalyst potentially through a chair transition structure.[14]

Table 3: C-H insertion/rearrangement for 1,3-cyclohexadiene



12a-f **13a-f**

Entry	Aryl	yield, %	er
a	Ph	63	99:1
b	4-$MeOC_6H_4$	58	200:1
c	3,4-$Cl_2C_6H_3$	59	200:1
d	2-naphthyl	50	200:1
e	2-$MeOC_6H_4$	17	>13:1
f	1-naphthyl	22	>11:1

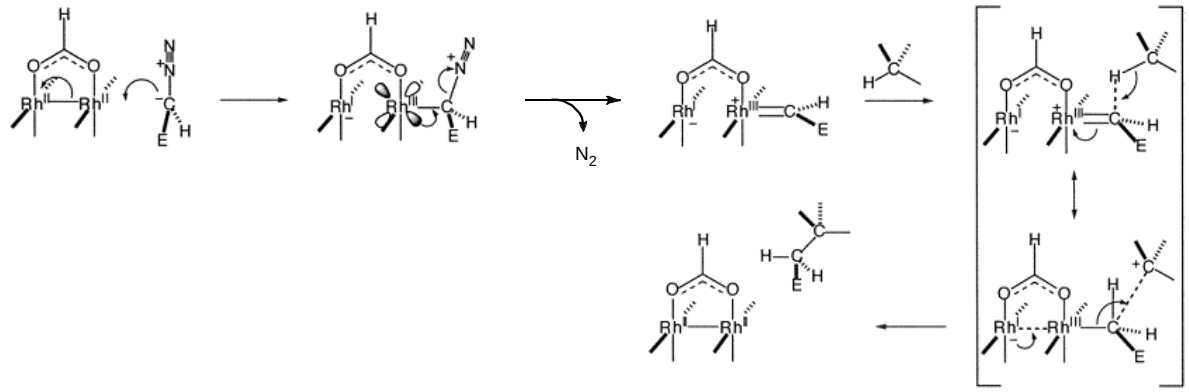
MECHANISTIC INVESTIGATIONS

Enantioselective intermolecular and intramolecular rhodium-carbenoid induced C-H insertions validate that C-H activation can be used as a practical synthetic tool however, a clear mechanistic basis for the origin of enantioselectivity, and to some extent site-selectivity, is still needed. The catalytic cycle empirically postulated for many years has been validated recently by Nakamura in a theoretical study (Scheme 6).[20] Back donation of electron density from the $4d_{xz}$ orbital extending from the Rh^{II}-Rh^{II} axis in the catalyst into the σ* orbital of the C-N bond in the diazo compound results in extrusion of nitrogen and formation of the carbenoid. Approach of a substrate results in overlap of the empty p orbital of the carbene and the σ orbital of the C-H bond. After hydride transfer, donation of electron density by Rh^{I} to Rh^{III} weakens the Rh^{II}-C bond and results in C-C bond formation and regeneration of the Rh^{II}-Rh^{II} complex completing the catalytic cycle.

Following substrate binding, transfer of a hydride to the carbene carbon precedes carbon-carbon bond formation in a concerted but non-synchronous process, leading to buildup of positive charge on the substrate carbon.[20] Thus, substrates that can stabilize buildup of positive charge are expected to react faster. Empirical evidence finds relative rates of reactivity for C-H bonds are methine ~ methylene >> methyl consistent with Nakamura's conclusion.[21] In the absence of steric effects, methine C-H bonds react faster than methylene C-H bonds, however most chiral dirhodium catalysts are bulky leading to the observed reactivity at the sterically conjested sites.[20]

The success of donor-acceptor substituted carbenoids for stereoselective insertion can be attributed to a relative decrease of the carbene electrophilicity; less positive character at the carbene

Scheme 6: Catalytic cycle for dirhodium(II)-carbenoid C-H insertion

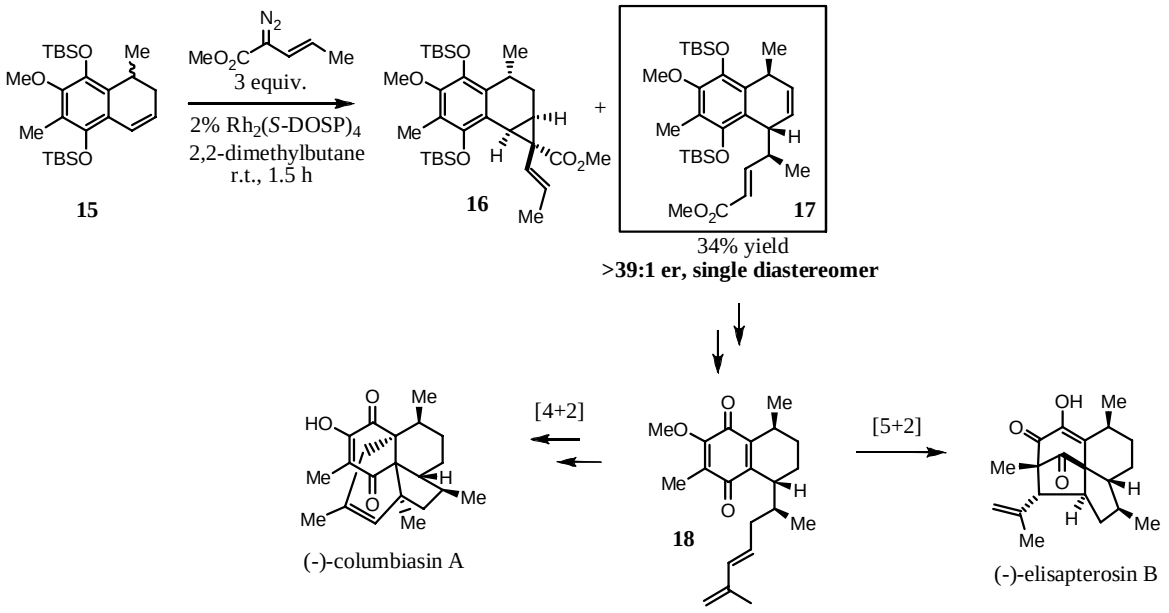


carbon results in a later transition state (more sp^3 character). By inducing a later transition state, the stereochemical influence of the catalyst during C-H cleavage/C-C bond formation is enhanced.

Catalyst selection for intermolecular insertion with donor-acceptor carbenoids relies primarily on the nature of the C-H bond in the substrate. The most general catalyst for the range of intermolecular insertions of donor-acceptor substituted carbenoids is the tetraprolinate Rh_2(*S*-DOSP)$_4$ developed by Davies.[1] However, the level of selectivity achieved for any catalyst/substrate pair is always affected by a subtle combination of electronic, steric, and conformational effects.

Despite the limited current mechanistic understanding of the reaction, many examples of practical application in total synthesis of enantioselective metallocarbenoid C-H insertions are known, especially in the case of intramolecular insertion. Examples of total syntheses illustrating intermolecular metallocarbenoid C-H insertion for key steps include (+)-indatraline, (+)-imperanene, (+)-sertraline, (+)-cetiedil, (-)-α-conidendrin, (-)-columbiasin, and (-)-elisapterosin.[10,17,22-24] The later two are particularly elegant examples where three stereocenters are set during an enantiodivergent C-H insertion step yielding a single diastereomer with excellent enantioselectivity (Scheme 7).[24]

Scheme 7: Selected Total Syntheses Utilizing Enantioselective Intermolecular Rh(II)-carbenoid C-H Insertion



CONCLUSION

Rhodium(II)-carbenoids are effective catalysts for C-H insertions with a wide substrate scope and with good to excellent site-, diastereo-, and enantioselectivity. A broad range of products is formed including those traditionally belonging to asymmetric aldol reactions, Michael reactions, Mannich reactions, and Claisen rearrangements. Additionally, activation of allylic sites with vinyldiazoacetates form products through a highly enantioselective concerted C-H activation/ rearrangement. Further mechanistic understanding of the catalytic cycle, particularly approach of the C-H bond to the carbenoid, must be established to facilitate better predictive power in catalyst design and subsequent enhancement of stereocontrol. Nonetheless, the power of this synthetic approach has already been showcased in a number of total syntheses with excellent success. Enantioselective metallocarbenoid-induced C-H insertion will no doubt be adapted in synthetic endeavors as this chemistry evolves.

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