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Enantioselective Intramolecular C–H Insertion Reactions of Donor–Donor Metal Carbenoids

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Ⓢ *Supporting Information*

ABSTRACT: The first asymmetric insertion reactions of donor–donor carbenoids, i.e., those with no pendant electron-withdrawing groups, are reported. This process enables the synthesis of densely substituted benzodihydrofurans with high levels of enantio- and diastereoselectivity. Preliminary results show similar efficiency in the preparation of indanes. This new method is used in the first enantioselective synthesis of an oligoresveratrol natural product (*E*-δ-viniferin).

Metal carbenoids, usually derived from diazo compounds, are important intermediates in organic synthesis.[1] The dual electrophilic and nucleophilic character has enabled these intermediates to participate in a wide array of useful transformations. In particular, asymmetric reactions involving chiral metal complexes have resulted in highly enantioseletive cyclopropanations as well as C–H,[2] N–H,[3] and O–H[4] insertion reactions. Early work in this area focused on the reactivity of diazo-dicarbonyl compounds and unsubstituted α-diazo esters, which form acceptor–acceptor and acceptor-substituted carbenoids (Figure 1). Subsequent pioneering studies by Davies explored the reactivity of donor–acceptor carbenes,[5] which engaged in selective intermolecular reactions. Although donor–donor-substituted diazo compounds have been known for many years,[6,7] metal-catalyzed insertion reactions with these substrates are rare,[8,9] and no enantioselective reactions have been reported to date.

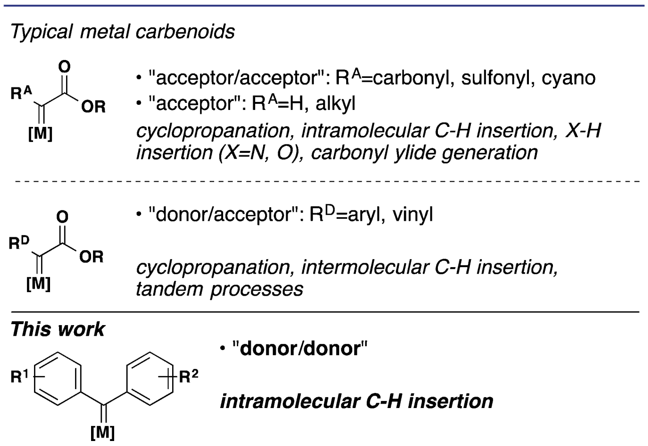

Figure 1. Structures of metal carbenoids.

We have explored C–H insertion reactions of donor–donor carbenoids for the rapid synthesis of complex natural products and other molecules with interesting biological properties. The highly substituted benzodihydrofurans and indanes embedded in **1**–**3** could each be accessed from strategic C–H insertion reactions of diarylcarbenoids (Figure 2). The requisite starting materials, i.e., diaryldiazomethane analogues, are easily prepared from hydrazones or toluenesulfonyl hydrazones. Herein we report our initial findings in the enantioselective intramolecular C–H insertion reactions of donor–donor rhodium carbenoids, culminating in the first enantioselective synthesis of *E*-δ-viniferin (**3**).

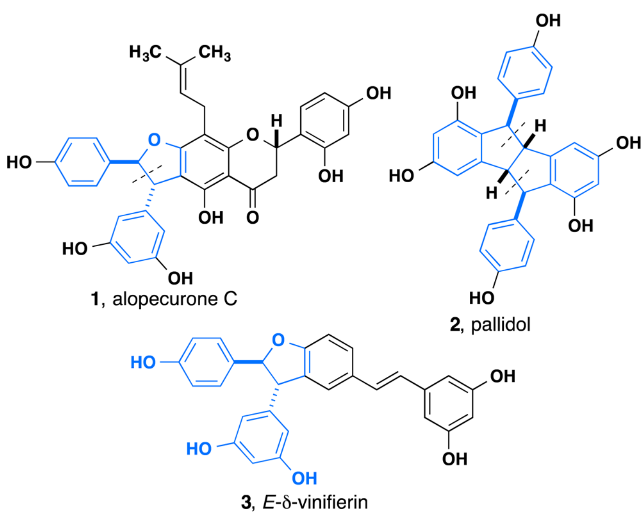

Figure 2. Target molecules featuring benzodihydrofuran and indane core structures.

Our initial studies explored the reactions of diaryl-diazomethanes. Commercially available 2-hydroxybenzophenone, alkylated with a PMB group, was converted to a diazo compound in two steps and then added by syringe pump to a solution of various catalysts (1 mol %; Table 1). Dirhodium tetraacetate was a highly effective catalyst, producing predominantly the syn diastereomer of dihydrobenzofuran **5** in high yield. Variation of solvent, temperature, and catalyst (to $Rh_2(TFA)_4$) maintained the high yield of product and had little impact on the diastereoselectivity. Initial exploration of chiral catalysts was

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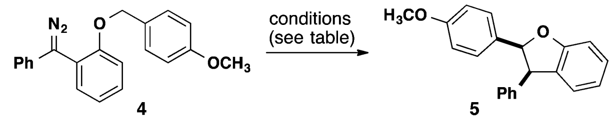
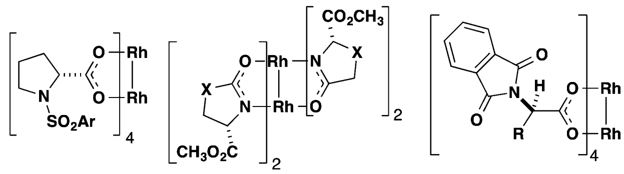
Table 1. Catalyst Optimization



entry	catalyst (1 mol%)	solvent (temp.)	dr	er	yield
1	$Rh_2(OAc)_4$	CH_2Cl_2 (0–23 °C)	76:24	–	78%
2	$Rh_2(OAc)_4$	CH_2Cl_2 (−42–23 °C)	80:20	–	89%
3	$Rh_2(TFA)_4$	CH_2Cl_2 (0–23 °C)	50:50	–	89%
4	$Rh_2(OAc)_4$	benzene (10–23 °C)	80:20	–	94%
5	$Rh_2(OAc)_4$	toluene (0–23 °C)	80:20	–	85%
6	$Rh_2(OAc)_4$	pentane (0–23 °C)	80:20	–	85%
8	Rh_2(R-DOSP)$_4$	CH_2Cl_2 (0–23 °C)	94:6	36:64	95%
9	Rh_2(4S-MPPIM)$_4$	CH_2Cl_2 (0–23 °C)	–	–	0%
10	***Rh_2(R-PTAD)$_4$***	***CH_2Cl_2 (0–23 °C)***	***99:1***	***99:1***	***90%***



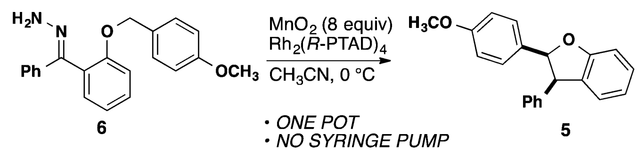
Rh_2(*R*-DOSP)$_4$ [Ar=*p*-$C_{12}H_{25}C_6H_4$] Rh_2(4*S*-MPPIM)$_4$ X=$NCOCH_2CH_2Ph$ Rh_2(*R*-PTAD)$_4$ R=1-adamantyl

immediately fruitful. Davies's catalyst (Rh_2(*R*-DOSP)$_4$) resulted in high diastereoselectivity, albeit with little control of enantioselectivity.[10] Doyle's imidazolone catalyst ((Rh_2(4*S*-MPPIM)$_4$) gave no conversion.[11] Finally, the phthalimide-based catalyst Rh_2(*R*-PTAD)$_4$[12] *produced* **5** *in high yield (90%) and with exquisite diastereo- and enantioselectivities, both of 99:1.*

We explored several avenues for enhancing the efficiency of this new method. A brief solvent screen (not shown) revealed that acetonitrile often improves both yield and diastereoselectivity while maintaining high enantioselectivity. Unlike acceptor-substituted diazo compounds, which are typically made from diazo-transfer reagents, diphenyldiazo methane is typically made by oxidation of the corresponding hydrazine. After examining several methods, including the recently reported Swern conditions,[13] we found that MnO_2[14] oxidized **6** to **4** in quantitative yield after simple filtration. Moreover, generation of **4** and the subsequent C−H insertion reaction could be carried out in one pot by simply mixing MnO_2 and the rhodium catalyst with the hydrazone, without the need for slow addition. Finally, the limits of the catalyst loading were also explored (Table 2). We were pleased to see that despite the longer required reaction times, high yield and selectivity were maintained down to 0.001 mol % of the rhodium catalyst. The reaction was also amenable to scale-up, and a gram-scale insertion was accomplished with only 0.1 mol % in 95% yield (Table 2, entry 7). The low catalyst loading and avoidance of diazo transfer reagents and diazoalkane intermediates all contribute to the high efficiency of this transformation.

The Rh-catalyzed C−H insertion reaction of donor−donor carbenoids is useful in the synthesis of a broad range of benzodihydrofurans. Benzyl ethers of 2-hydroxybenzophenones are consistently converted to dihydrobenzofurans in high yield, with high enantioselectivity and high disatereoselectivity for the formation of the syn isomer (Table 3). Although the reaction is most efficient when the substrate is appended with electron-donating groups, good reactivity is maintained when a cyano group is added to either the benzyl ether or the phenyl ring of the benzophenone (Table 3, entries 2 and 7). The absolute and

Table 2. Catalyst Loading and Scale-up



entry	mol %	time (h)	dr	er	yield
1	1.0	16	>99:1	99:1	90%
2[a]	0.1	4	>99:1	97:3	93%
3[a]	0.01	4	>99:1	96:4	63%
4[a]	0.01	24	>95:5	93:7	82%
5	0.001	24	>95:5	94:6	83%
6	0.0001	144	>99:1	94:6	51%
7[b]	0.1	4	>99:1	96:4	95%

[a]Catalyst was dissolved in CH_2Cl_2 [b]Reaction performed at −20 °C on gram scale.

relative configuration of **5** was determined by X-ray crystallography, and the remaining substrates are tentatively assigned based on chemical shift correlation. The coupling constants of the syn and anti isomers are too similar to provide any confidence in the assignment of the two diastereomers.

Allylic ethers also reacted smoothly in the C−H insertion process (Scheme 1). In all cases, only insertion was observed with no detectable products of cyclopropanation. Substituted allylic substrates with either *E*- or *Z*-configured alkenes provided dihydrobenzofuran products with no change in the alkene geometry (**10c** and **10d**).

The success of the insertion reaction with benzylic and allylic ethers prompted us to explore a wide variety of related substrates. Diastereoselectivities for alkyl ethers were generally lower than for the benzylic and allylic substrates. Alkyl methylene groups reacted with high yield and enantioselectivity (**19**−**21**) (Scheme 2), while the methine group of an isopropyl ether exhibited slightly eroded enantioselectivity or yield depending on the solvent used. Propargyl ether **24** reacted efficiently, albeit with low enantioselectivity. The reaction of substrate **23**, which is

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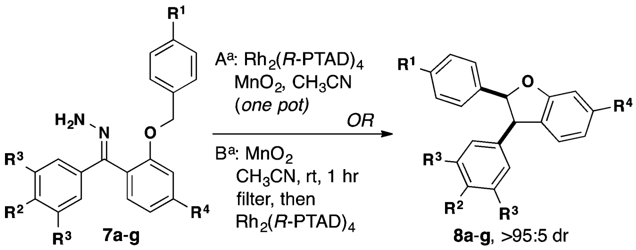
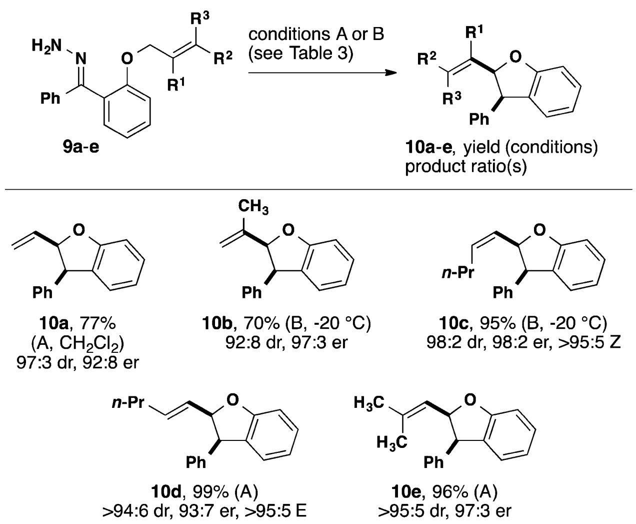
Table 3. Insertion into Benzylic C−H Bonds



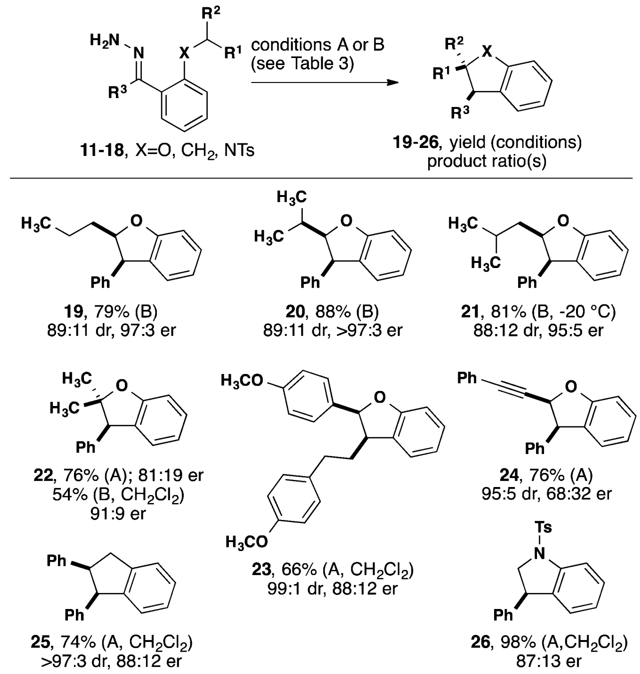
entry	product	R[1]	R[2]	R[3]	R[4]	yield, er (conditions)
1	**8a**	Br	H	H	H	90%, 95:5 (A)
2	**8b**	CN	H	H	H	77%, 97:3 (A)
3	**8c**	H	H	H	H	92%, 95:5 (A)
4	**8d**	CH_3O	H	CH_3O	H	68%, 92:8 (A)
5	**8e**	CH_3O	H	H	OPMB	70%, 98:2 (B)
6	**8f**	CH_3O	CH_3O	H	H	83%, 97:3 (B)
7	**8g**	CH_3O	CN	H	H	97%, 98:2 (B)

[a]One mol % catalyst, 8 equiv of MnO_2. Catalyst added to reaction mixture at 0 °C before warming the reaction mixture to room temperature for 4−16 h.

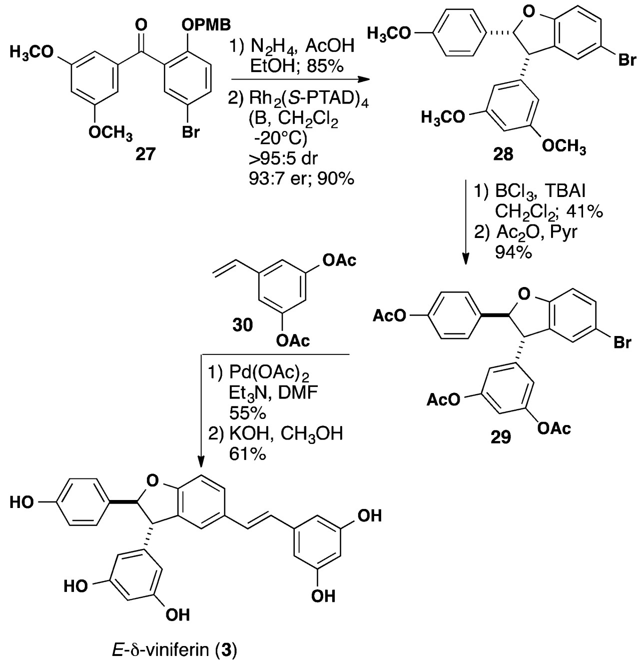
Scheme 1. Reactions of Allylic Substrates



Scheme 2. Insertion Reactions of Various Substrates



Scheme 3. Synthesis of *E*-δ-Viniferin



derived from an alkyl−aryl ketone, also provided insertion product efficiently, suggesting that the carbenoid's insertion is significantly faster than elimination. Finally, preliminary results into the synthesis of other five-membered rings are encouraging with the successful syntheses of indane **25** and indoline **26** from alkane and sulfonamide substrates, respectively.

The enantioselective insertion of donor−donor carbenoids is a useful method for the assembly of complex natural products. *E*-δ-Viniferin is a resveratrol dimer isolated from grapes in response to fungal infection.[15] This secondary metabolite is a member of a large family of oligoresveratrol natural products, which has received intense synthetic effort in recent years.[16] Although these molecules sometimes occur as racemates, presumably from nonenzymatic processes, many are isolated as single enantiomers and few methods for the enantioselective installation of the requisite dihydrobenzofuran rings have been reported. Benzophenone **27**, available in five steps from commercially available starting materials, was easily converted to the corresponding hydrazone (Scheme 3). The hydrazone underwent smooth C−H insertion with high selectivity and in high yield. Simultaneous demethylation and epimerization[17] was accomplished with BCl_3 and TBAI. Control experiments confirmed that epimerization occurred with no loss of enantiomeric purity.[18] The benzodihydrofuran core was acetylated and employed in Heck coupling with styrene **30**. Global deacetylation[19] provided *E*-δ-viniferin, which exhibited ^{1}H- and ^{13}CNMR spectra identical to those reported for the natural material. In addition, the optical rotation of the synthetic sample compared favorably to the reported value.[20] This route represents the first enantioselective synthesis of any member of the oligoresveratrol family of natural products.

The enantioselective intramolecular insertion of donor–donor carbenoids is a useful method for the assembly of complex molecules. Insertion into a variety of ethers proceeds with high efficiency and stereoselectivity, and preliminary results indicate that this strategy might be generalized to the construction of carbon- and nitrogen-based compounds.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures with characterization data and NMR spectra for all compounds, HPLC traces for all enantiomerically enriched insertion products, and X-ray crystallographic data (.cif) for compound **5**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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