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Highly Diastereoselective and Enantioselective C−H Functionalization of 1,2-Dihydronaphthalenes: A Combined C−H Activation/Cope Rearrangement Followed by a Retro-Cope Rearrangement

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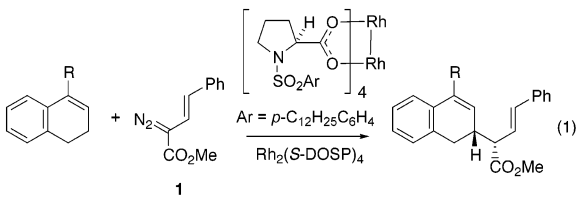
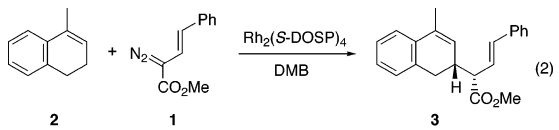
Over the past few years, the intermolecular C−H insertion chemistry of donor/acceptor-substituted rhodium carbenoid intermediates has become a very effective method for catalytic enantioselective C−H activation.[1] Two stereocenters are generated when the C−H activation occurs at methylene sites,[2] and in systems with good size differentiation between the methylene substituents, highly diastereoselective and enantioselective reactions can be achieved. In this paper we describe the reaction between vinylcarbenoids and 1,2-dihydronaphthalenes and related systems (eq 1), which results in the formation of formal C−H activation products with very high diastereoselectivity (>98% de) and enantioselectivity (91−99.6% ee).

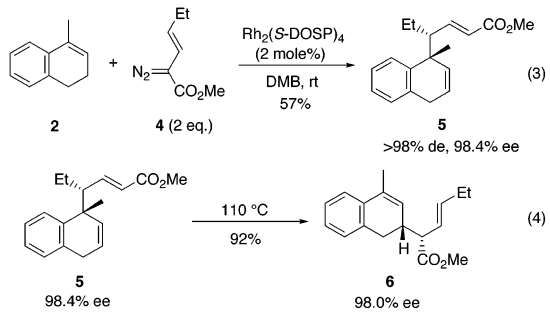


The exceptional reactivity between vinylcarbenoids and 1,2-dihydronaphthalene was discovered while studying the Rh_2(*S*-DOSP)$_4$-catalyzed decomposition of the vinyldiazoacetate **1** in the presence of 4-methyl-1,2-dihydronaphthalene (**2**). Under the standard reaction conditions of 1 mol % of catalyst and 2 equiv of **2** at 23 °C with 2,2-dimethylbutane (DMB) as solvent, a very clean transformation was observed (eq 2). The formal C−H activation product **3** was formed in 92% yield, >98% de, and 98.9% ee. When only 1.2 equiv of **2** and 0.1 mol % of catalyst were used, the yield of **3** was still 82% and virtually no loss in stereoselectivity was observed. The optimum conditions were using 1.1 equiv of diazo compound **1** at 0 °C.

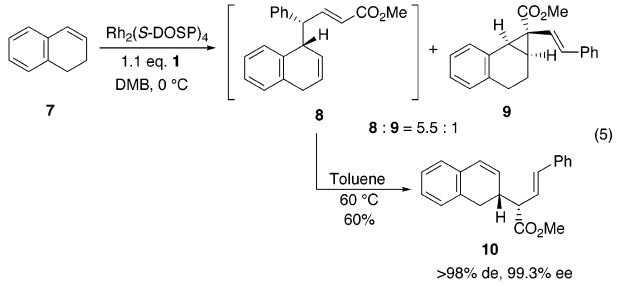


1 : 2	Rh_2(*S*-DOSP)$_4$	temp, °C	yield, %	de, %	ee, %
1 : 2	1 mole%	23	92	> 98	98.9
1 : 1.2	0.1 mole%	23	82	> 98	98.3
1.1 : 1	0.5 mole%	0	95	> 98	99.5

The highly stereoselective nature of the reaction to form **3** was unexpected because earlier studies on the reaction of aryldiazoacetates with cycloalkenes displayed only moderate diastereoselectivity.[2d,f] A possible explanation for the high diastereoselectivity is the involvement of a more elaborate reaction mechanism than a direct C−H activation. It is conceivable that the reaction could occur by a combined C−H activation/Cope rearrangement[3] followed by a retro-Cope rearrangement. To explore the mechanism of the C−H activation, the reaction of **2** with the ethyl-substituted vinyldiazoacetate **4** was examined (eq 3). This resulted in the formation of the combined C−H activation/Cope rearrangement product **5** in 57% yield and very high diastereoselectivity (>98% de) and enantioselectivity (98.4% ee). In this case, the reverse Cope rearrangement is not as favored because the product **6** is not as fully conjugated as **3**. However, on heating in toluene for 6 h, **5** does rearrange to **6** in 92% yield (eq 4).



Further evidence for the more elaborate reaction mechanism was observed in the reaction with 1,2-dihydronaphthalene (**7**). When the reaction was conducted at 0 °C, the crude NMR indicated the predominant formation of the combined C−H activation/Cope rearrangement product **8** and the cyclopropane **9**. Products **8** and **9** can be isolated as a mixture in 77% yield. On heating in toluene for 48 h at 60 °C, **8** underwent rearrangement to the formal C−H activation product **10**, which was isolated in 60% overall yield, >98% de, and 99.4% ee (eq 5). The selective introduction of the two stereocenters in **8** could be of general utility for the rapid construction of diterpene natural products such as erogorgianene.[4]



The intermediacy of the combined C−H activation/Cope rearrangement product can be used in a very advantageous manner as illustrated in the reaction of **1** with 4-acetoxy-1,2-dihydronaphthalene **11** (eq 6). A very clean transformation was observed, but the product is the naphthalene derivative **13** formed in 85% yield and 99.6% ee. In this case aromatization of the intermediate **12** by elimination of acetic acid occurs faster than the retro-Cope

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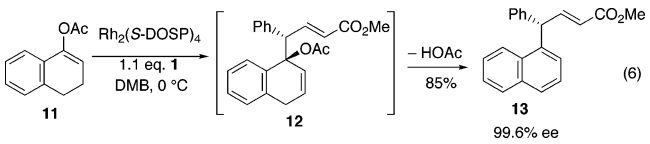
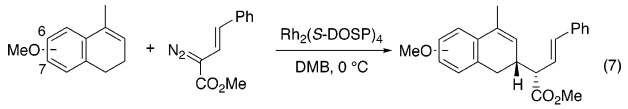
rearrangement. This scheme has the potential to be a very effective method for the enantioselective synthesis of 1,1-diarylalkyl derivatives, units which have been incorporated into various pharmaceutical agents.[5]

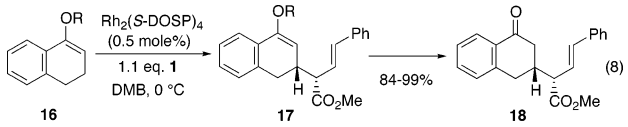


The formal C−H activation can be applied to a range of substrates. Both 7-methoxy- and 6-methoxy-4-methyl-1,2-dihydronaphthalene **14** are suitable substrates to form **15**, but the reaction is more efficient with **14a** because with **14b** competing benzylic C−H activation occurs to a minor extent (eq 7).



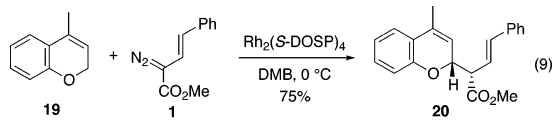
Entry (Comp.)	yield, %	de, %	ee, %
a (**14a**, 7-methoxy)	90	> 98	98.9
b (**14b**, 6-methoxy)	77	> 98	99.3

The reactions with 4-siloxy-1,2-dihydronaphthalenes **16** are very interesting transformations because the products **17** can be formally considered to be equivalent to the Michael addition products with the keto tautomer of 1-naphthol, clearly an impossible transformation (eq 8). Interestingly, the increase size of the silyl group does not affect the diastereoselectivity, but only slightly drops the ee. The silyl enol ethers can be easily deprotected by using HCl (for **17a**) or HF (for **17b** and **17c**) to form **18** in a range of 84−99% yield.



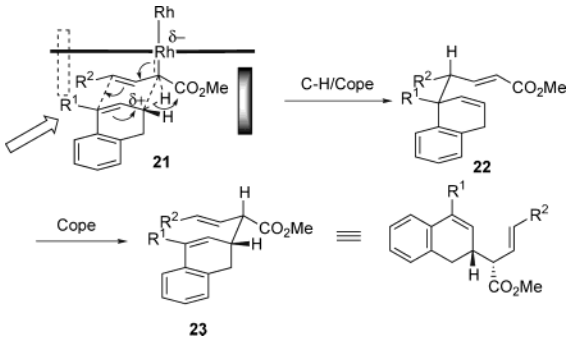
Entry	R	yield, %	de, %	ee, %
a	TMS	55	>98	97.5
b	TBS	78	>98	95.2
c	TIPS	53	>98	91.3

The reaction can also be extended to 2*H*-chromene derivative **19** (eq 9). Once again, a very selective reaction occurs to form the C−H activation product **20** in 75% yield, 95% ee, and >98% de (eq 9).



The relative and absolute configuration of the *p*-bromo derivative of **18** was determined by X-ray crystallography,[6] while the configuration of **10** was confirmed by its conversion to **18**. The observed configuration is consistent with the previously demonstrated stereochemistry of the combined C−H activation/Cope rearrangement,[3a,c] followed by the retro-Cope rearrangement occurring through the expected chair transition state (Scheme 1).[7] In this model, the catalyst is considered to exist in a D_2-symmetric arrangement and can be simply viewed as having two blocking groups as indicated in **21**.[8] The substrate is approaching from the front side and over the vinyl portion of the carbenoid,[3a] which is necessary for occurrence of the combined C−H activation/Cope rearrangement to form **22**. A retro-Cope rearrangement of **22** through a chair transition state would generate a formal C−H insertion product **23** of defined stereochemistry. The assigned stereochemistry for the other products is assumed on the basis of this predictive model. The high diastereoselectivity is an indication that very little direct C−H activation is occurring,[2d] in contrast to our previous diastereoselective examples of the combined C−H activation/Cope rearrangement.[3c]

Scheme 1. Predictive Model



In summary, we have described herein a highly diastereoselective and enantioselective method for the C−H functionalization of dihydronaphthalenes. The actual mechanism of the reaction is complicated and involves a combined C−H activation/Cope rearrangement followed by a retro-Cope rearrangement. Dihydronaphthalenes such as **8** and naphthylaryl derivatives such as **13** are very useful chirons, whose application in organic synthesis is currently under investigation. These studies further demonstrate the broad synthetic utility of donor/acceptor-substituted rhodium carbenoid intermediates.

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Supporting Information Available: Full experimental data for the compounds described in this paper, ^{1}H and ^{13}C spectra of selected compounds, and X-ray structure of *p*-bromophenyl derivative of **18** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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