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# Enantioselective Double C–H Activation of Dihydronaphthalenes

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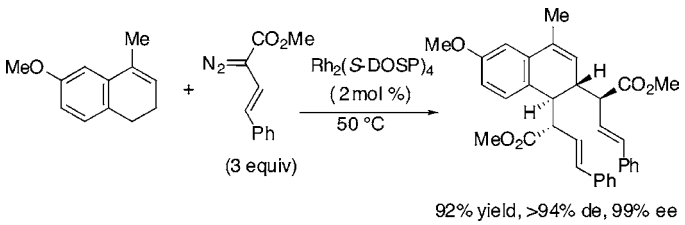
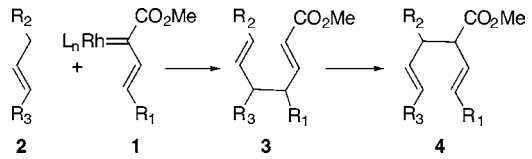
## ABSTRACT




**Dirhodium tetrakis((*S*)-*N*-dodecylbenzenesulfonyl)prolinate) ($Rh_2$(*S*-DOSP)$_4$) catalyzed reaction of 1,2-dihydronaphthalenes with an excess of methyl vinyldiazoacetates results in a formal double C–H activation, generating four new stereogenic centers with very high stereoselectivity. The mechanism of the C–H activation is complex, involving a combined C–H activation/Cope rearrangement followed by a retro-Cope rearrangement.**

The development of general methods for the selective transformation of C−H bonds is an area of intense current research.[1] One very practical method to achieve such transformations is the enantioselective C−H activation by means of rhodium carbenoid induced C−H insertion.[2] Over the past few years we have demonstrated that donor/acceptor substituted rhodium carbenoids are exceptional at intermolecular C−H insertions.[3,4] During the course of these studies, we discovered that the reaction of vinylcarbenoids (**1**) with allylic C−H bonds (**2**) can result in a highly stereoselective transformation, a combined C−H activation/Cope rearrangement to form **3**.[5] Furthermore, the products can undergo a retro-Cope rearrangement to generate the formal C−H activation products **4**. Dihydronaphthalenes are very effective substrates for this type of chemistry.[5d,e] In this paper we disclose that dihydronaphthalenes are capable of undergoing double C−H activation to generate products with four new stereocenters in >94% de and >98% ee. The scope of this remarkable reaction and related mechanistic studies will be described.

**Scheme 1**




During our studies to optimize the mono C−H activation of 4-methyl-1,2-dihydronaphthalene (**5**) we explored the use

(1) For selected reviews on other methods for C−H activation, see: (a) Shilov, A. E.; Shul'pin, G. B. *Chem. Rev.* **1997**, *97*, 2879. (b) Dyker, G. *Angew. Chem., Int. Ed.* **1999**, *38*, 1698. (c) Arndsten, B. A.; Bergman, R. G. *Science* **1995**, *270*, 1970. (d) Jia, C.; Kitamura, T.; Fujiwara, Y. *Acc. Chem. Res.* **2001**, *34*, 633. (e) Ritleng, V.; Sirlin, C.; Pfeffer, M. *Chem. Rev.* **2002**; *102*, 1731. (f) Kakiuchi, F.; Chatani, N. *Adv. Synth. Catal.* **2003**, *345*, 1077.

(2) Davies, H. M. L.; Beckwith, R. E. J. *Chem. Rev.* **2003**, *103*, 2861.

(3) For reviews, see: (a) Davies, H. M. L. *J. Mol. Catal. A* **2002**, *189*, 125. (b) Davies, H. M. L.; Antoulinakis, E. G. *J. Organomet. Chem.* **2001**, *617*−*618*, 47.

(4) For recent examples, see: (a) Davies, H. M. L.; Venkataramani, C.; Hansen, T.; Hopper, D. W. *J. Am. Chem. Soc.* **2003**, *125*, 6462. (b) Davies, H. M. L.; Beckwith, R. E. J.; Antoulinakis, E. G.; Jin, Q. *J. Org. Chem.* **2003**, *68*, 6126. (c) Davies, H. M. L.; Jin, Q. *Org. Lett.* **2004**, *6*, 1769.

(5) (a) Davies, H. M. L.; Stafford, D. G.;Hansen, T. *Org. Lett.* **1999**, *1*, 233. (b) Davies, H. M. L.; Stafford, D. G.; Hansen, T.; Churchill, M. R.; Keil, K. M. *Tetrahedron Lett.* **2000**, *41*, 2035. (c) Davies, H. M. L., Jin, Q. *Proc. Natl. Acad. Sci. U.S.A.*. **2004**, *101*, 5472. (d) Davies, H. M. L.; Jin, Q. *J. Am. Chem. Soc.* **2004**, *126*, 10862. (e) Davies, H. M. L.; Walji, A. M. *Angew. Chem., Int. Ed.* **2005**, *44*, 1733.

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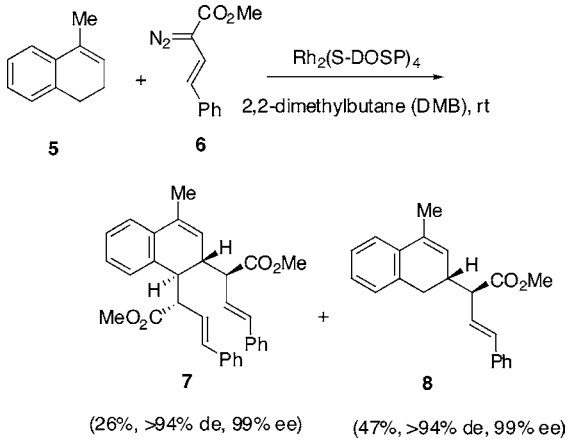
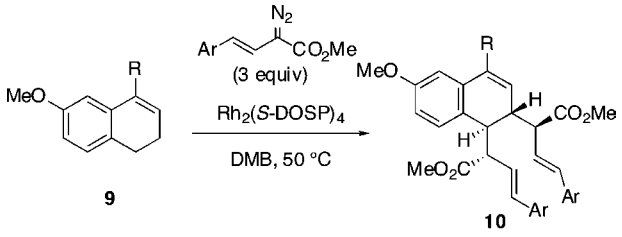
**Scheme 2**




of an excess of the vinyldiazoacetate **6** (Scheme 2). Surprisingly, under these conditions a significant amount of the double C−H activation product **7** was formed in addition to the expected mono C−H activation product **8**. Remarkably, **7** was formed with four new stereocenters in >94% de and 99% ee. Even though a few examples are known of double C−H activation reactions using donor/acceptor substituted carbenoids,[4a,c] this is the first example of functionalization of two adjacent C−H bonds.

The complete conversion of **5** to **7** was not possible even when a considerable excess of the vinyldiazoacetate **6** was used. The best result was obtained on conducting the reaction at 50 °C, yet this still only resulted in a 1.3:1 mixture of **7** and **8**. Consequently, more favorable substrates for the double C−H activation were examined. Both 6-methoxy derivatives **9a** and **9b** were found to be excellent substrates for this chemistry, capable of a very effective double C−H activation to form **10a** and **10b** in >85% yield, >94% de, and 99% ee (Scheme 3).

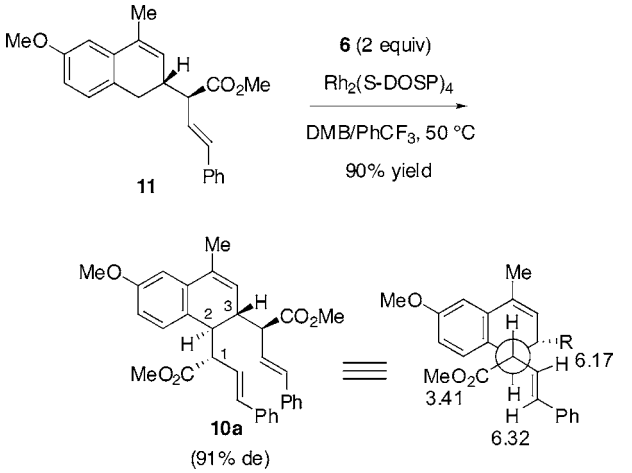
**Scheme 3**




| compound | R | Ar | yield, % | de, % | ee, % |
|---|---|---|---|---|---|
| **a** | Me | Ph | 92 | >94 | 99 |
| **b** | OTBS | *p*-BrPh | 86 | >94 | 99 |

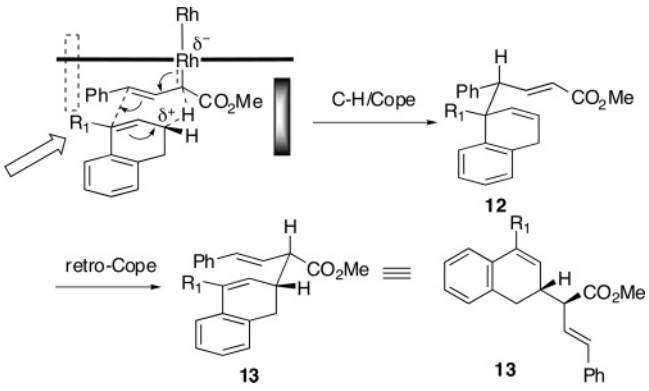
One of the most spectacular features of the double C−H activation is the formation of four stereocenters in a highly stereoselective manner. To determine the stereochemistry of this reaction, the mono insertion material **11** of known configuration[5d] was subjected to the C−H activation conditions (Scheme 4). This reaction also resulted in the formation of **10a** (84% yield, 91% de), which assigns the configuration of two of the stereocenters of **10a**. The coupling constant $J_{H2-H3} \approx 0$ Hz combined with the observed NOE enhancements confirmed the trans assignment between H2 and H3 for **10a**. The coupling constant $J_{H1-H2} = 9.8$ Hz indicates that H1 and H2 are in an antiperiplanar position, and the $\delta$ 3.41 chemical shift of the methyl ester indicates that it is in the shielding cone of the benzene ring.[6]

**Scheme 4**



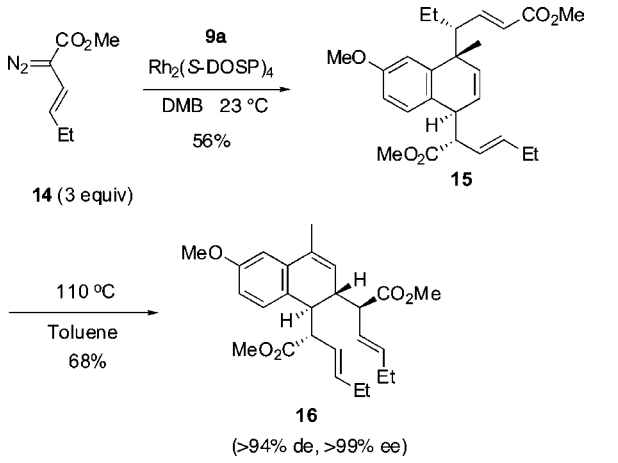

The high stereoselectivity of the initial C−H activation has been shown to be due to a complex mechanism involving a combined C−H activation/Cope rearrangement to form **12** followed by a retro-Cope rearrangement to form **13** (Scheme 5).[5d] The second C−H activation could either occur on **12** or **13**. In principle, **12** would be capable of undergoing a combined C−H activation/Cope rearrangement followed by two retro-Cope rearrangements to form the double C−H activation products, but such a mechanism would predict the formation of a different diastereomer of **7** and **11**. Alternatively, the products could be formed by a direct C−H activation on **13**, although a direct C−H activation is only occasionally highly diastereoselective.[3,4a,b]

**Scheme 5**



The conversion of **11** to **10a** (Scheme 4), demonstrates that **13** would be a viable precursor for the C−H activation. To determine if **12** is also a viable precursor for the second C−H activation step, the reaction between the dihydronaphthalene **9a** and 3-pentenyldiazoacetate (**14**) was examined (Scheme 6). The retro-Cope rearrangement is known to be

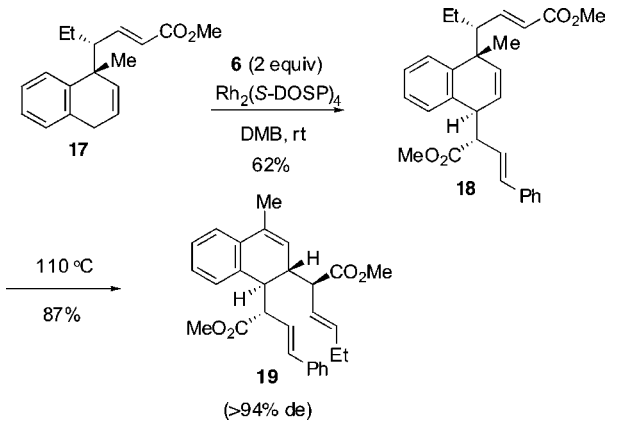
**Scheme 6**




slower with these substrates[5d] and when the reaction was conducted with an excess of **14**, the product was the 1,4-disubstituted product **15**. On heating in refluxing toluene, **15** rearranged to the formal double C−H activation product **16**. On the basis of these results, both **12** and **13** are feasible precursors for the second C−H activation products.

As the initial combined C−H activation/Cope rearrangement product appears to be a viable partner in the second C−H activation step, an opportunity exists for functionalization with two different carbenoid systems. To test this hypothesis, the reaction of **17** with the vinyldiazoacetate **6** was examined under $Rh_2(S\text{-DOSP})_4$ catalysis. This gave rise to the 1,4-functionalized product **18**, which on heating, underwent rearrangement to the double C−H activation product **19**.

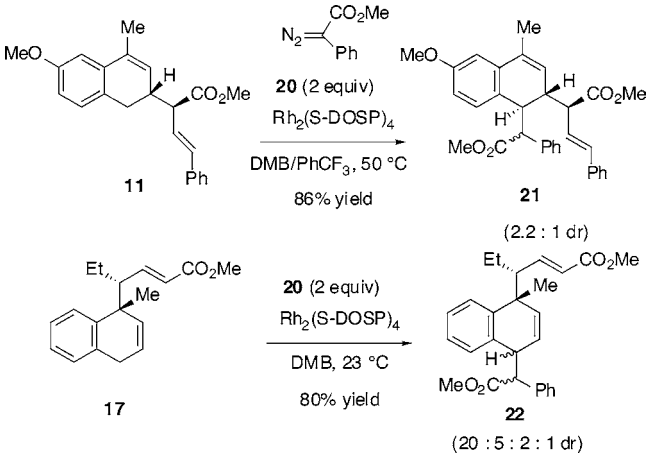
**Scheme 7**




If the second C−H activation step is a direct C−H insertion, then the highly diastereoselective nature of this second step is unprecedented. Although highly diastereoselective intermolecular C−H insertions are known for the donor/acceptor substituted carbenoids, [3a,4a,b] these have not been seen for benzylic C−H insertions.[7] In contrast, the combined C−H activation/Cope rearrangement is always highly diastereoselective, but in this case, it would not predict the observed stereochemistry.

To test this issue further, the direct C−H activation of **11** and **17** with methyl phenyldiazoacetate (**20**) was examined. In general, aryldiazoacetates give higher yield in the direct C−H activation than vinyldiazoacetates, but they would not be expected to undergo a combined C−H activation/Cope rearrangement. $Rh_2(S\text{-DOSP})_4$-catalyzed reaction of **11** with phenyldiazoacetate **20** gave 86% yield of the C−H insertion product **21** as a 2.2:1 mixture of diastereomers, whereas the $Rh_2(S\text{-DOSP})_4$-catalyzed reaction of **17** with **20** gave rise to the C−H insertion product **22** in 80% yield but as a mixture of four diastereomers. Therefore the second C−H activation by aryldiazoacetates is much less diastereoselective than the corresponding reaction with vinyldiazoacetates.

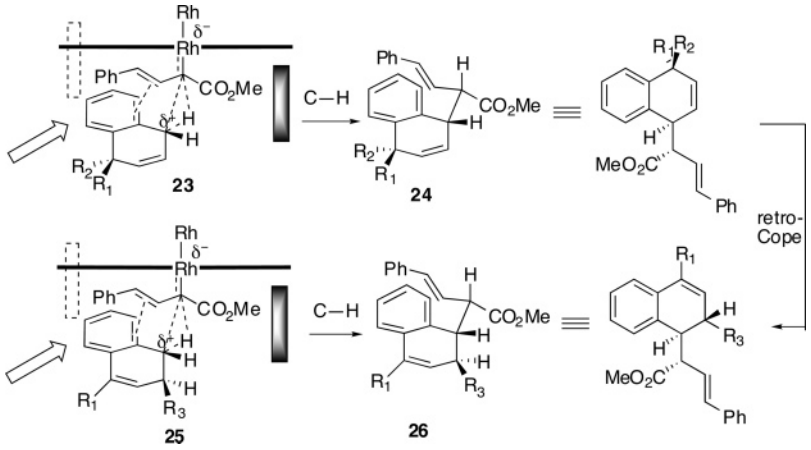
**Scheme 8**




On the basis of the high efficiency and stereoselectivity of the second C−H activation step of vinyldiazoacetates, we propose that this reaction is more than just a direct C−H insertion. A reasonable mechanism that would predict the observed diastereoselectivity and explain the vital role of the vinylcarbenoid structure is illustrated in Scheme 9. The vinyl group is proposed to be interacting with the aromatic ring of the dihydronaphthalene (**23** or **25**) in a manner somewhat analogous to the combined C−H activation/Cope rearrangement shown in Scheme 5. In this case, however, the C−H activation product is observed rather than the combined C−H activation/Cope rearrangement product as this would avoid loss of aromatic stabilization. At this stage,

(6) Davies, H. M. L.; Ren, P. *Tetrahedron Lett.* **2001**, *42*, 3149.
(7) Davies, H. M. L.; Jin, Q.; Ren, P.; Kovalevsky, A. *J. Org. Chem.* **2002**, *67*, 4165.

**Scheme 9**




it is not possible to distinguish whether the second C−H activation occurs on the 1,4-dihydronaphthalene (**23** to **24** to **26**) or the 1,2-dihydronaphthalene (**25** to **26**), but as shown in Scheme 9, both predict the generation of **26** with the same stereochemistry.

In summary, we have discovered an unusual C−H transformation involving two C−H activation steps, which generates four new stereocenters with excellent diastereo- and enantiocontrol. The mechanistic studies indicate that the reaction proceeds by a complex mechanism involving the combined C−H activation/Cope rearrangement as the key stereodefining step. Furthermore, these studies describe the first examples of highly diastereoselective benzylic C−H functionalization by rhodium carbenoid intermediates.

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**Supporting Information Available:** Experimental data for the reported reactions. This material is available free of charge via the Internet at http://pubs.acs.org.

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