ORGANIC LETTERS

2006
Vol. 8, No. 10
2195−2198

Regioselective Carbene Insertion on Polysubstituted Dihydroaromatic Compounds

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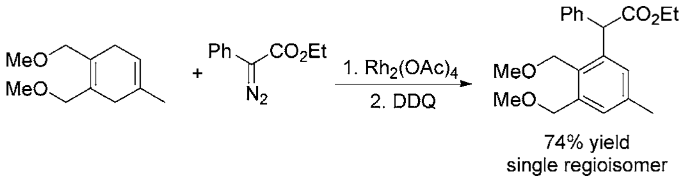
Received March 27, 2006

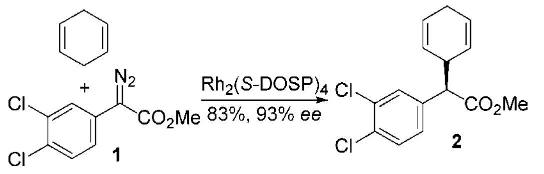
ABSTRACT



The rhodium-catalyzed CH-insertion reaction of diazo ester derivatives into dihydroaromatic compounds was expanded to the application of various polysubstituted and functionalized 1,4-dienes generated from a cobalt-catalyzed Diels–Alder reaction. The highly regioselective CH-insertion process produces after DDQ oxidation polysubstituted, polyfunctionalized aromatic compounds in good overall yields.

The research of efficient ways to construct complex chemical structures from readily available starting materials continues unabated. C−H activation by means of rhodium-carbenoid-induced C−H insertion represents one of the major progresses in synthetic organic chemistry of the past decade.[1] Müller and Davies reported that $Rh_2(OAc)_4$ catalyzes the decomposition of ethyl 2-diazopropionate in the presence of 1,4-cyclohexadiene affording the CH-insertion product, whereas the formation of a cyclopropanation product could not be detected.[2] This reaction can be used for the synthesis of natural products and biologically active compounds such as **2** (Scheme 1).[1h,i,3] However, in these transformations, the commercially available 1,4-cyclohexadiene is used in large excess to the diazo ester **1**.

Scheme 1. Stereoselective-Catalyzed CH-Insertion into Dihydroaromatic Compounds



We are not aware of any rhodium-catalyzed CH-insertion reactions where other more complicated monocyclic, multiply substituted, or highly functionalized dihydroaromatic compounds have been used thus far, besides the polycyclic dihydronaphthalene derivatives.[1g−j]

Because the cobalt(I)-catalyzed Diels−Alder reaction of alkynes and acyclic 1,3-dienes is a powerful tool for the

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(1) For reviews see: (a) Davies, H. M. L.; Loe, O. *Synthesis* **2004**, 2595. (b) Merlic, C. A.; Zechman, A. L. *Synthesis* **2003**, 1137. (c) Davies, H. M. L.; Beckwith, R. E. J. *Chem. Rev.* **2003**, *103*, 2861. (d) Lydon, K. M.; McKervey, M. A. in *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: New York, 1999, Chapter 16.2, 539. (e) Dorwald, F. Z. *Metal Carbenes in Organic Synthesis*; Wiley-VCH: Weinheim, Germany, 1999. (f) Arndtsen, B. A.; Bergman, R. G.; Mobley, T. A.; Peterson, T. H. *Acc. Chem. Res.* **1995**, *28*, 154. For recent selected examples see: (g) Davies, H. M. L.; Jin, Q. *J. Am. Chem. Soc.* **2004**, *126*, 10862. (h) Davies, H. M. L.; Dal, X.; Long, M. S. *J. Am. Chem. Soc.* **2006**, *128*, 2485. (i) Davies, H. M. L.; Manning, J. R. *J. Am. Chem. Soc.* **2006**, *128*, 1060. (j) Davies, H. M. L.; Jin, Q. H. *Org. Lett.* **2005**, *7*, 2293.

(2) Müller, P.; Tohill, S. *Tetrahedron* **2000**, *56*, 1725. Davies, H. M. L.; Stafford, D. G.; Hansen, T. *Org. Lett.* **1999**, *1*, 233.

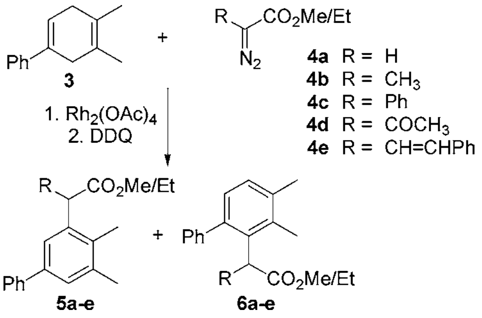
(3) (a) Davies, H. M. L.; Gregg, T. M. *Tetrahedron Lett.* **2002**, *43*, 4951. (b) Davies, H. M. L.; Walji, A. M.; Townsend, R. J. *Tetrahedron Lett.* **2002**, *43*, 4981.

10.1021/ol060739z CCC: $33.50

generation of dihydroaromatic compounds in excellent yields,[4] a possible approach to highly substituted benzene derivatives was envisioned.

Because the experimental procedure described by Müller[2] was believed to not be suitable, especially regarding the considerable excess of the reacting 1,4-cyclohexadiene (10 equiv), a large excess of dihydroaromatic compound should be avoided because the diazo ester as well as the dihydroaromatic compounds are equally valuable. More economic reaction conditions were reported by Davies avoiding a large excess of reagents in the reaction of valuable dihydronaphthalene derivatives.[1g−j] Therefore, an optimization process was started first. Preliminary tests with the 1,4-diene **3** and ethyl diazoacetate (**4a**, R = H) showed that mixtures of insertion and cyclopropanation products were formed. In a further set of experiments, ethyl 2-diazopropionate (**4b**, R = CH_3) and methyl 2-diazophenylacetate (**4c**, R = Ph) were tested (Scheme 2).

Scheme 2. Regioselective Formation of Polysubstituted Benzene Derivatives



With these alkyl/acceptor (**4a**) and acceptor/donor (**4b**) substituted carbene precursors, respectively, the CH-insertion product was generated exclusively.[5] The lower yield of the diazo ester **4a** could be rationalized by the altered reactivity profile of such carbenoids compared to acceptor/donor carbenoids such as **4b**.[6]

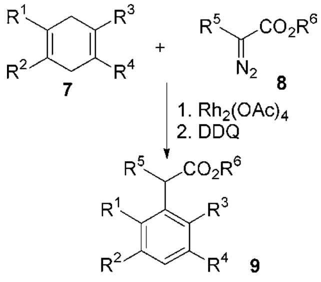
On the other hand, acceptor/acceptor substituted carbene precursors such as ethyl diazoacetoacetate (**4d**, R = $COCH_3$) gave very low or no conversion of the 1,4-diene **3**. In the reactions with ethyl 2-diazopropionate (**4b**) and methyl 2-diazophenylacetate (**4c**), the regioselectivity for the CH-insertion process could already be evaluated. It was found that the rhodium-catalyzed carbon−carbon bond formation exclusively takes place at the less-hindered CH_2 group of the dihydroaromatic compound forming the products of type **5** exclusively.

The effect of the temperature was examined next. No substantial improvement in the yield was obtained lowering the temperature to −18 °C, and at −78 °C, no reaction occurred (Table 1, entries 1−3). A fast addition of the diazo ester **4b** favored the carbene dimerization with consequently low yield of the desired C−H insertion product (entry 4). When the diene/diazo ester ratio was reduced to 1:2 and 0.5 mol % of the catalyst was used, the isolated yield could be raised to 52% (entry 5). A similar trend was also observed with the diazo ester **4c** (entries 7 and 8), and the corresponding insertion product **5c** was isolated in excellent 89% yield after DDQ oxidation. Consequently, the best results for the CH-insertion process were obtained when the diazo esters were added at 0 °C over a period of 1 h by syringe pump. The amount of excess diazo ester could then be reduced to 2 equiv to produce the desired product **5** in acceptable to good yields. Improved yields were also obtained when the rhodium catalyst loading was reduced, indicating that the rate of decomposition of the intermediately formed rhodium carbene species is enhanced when higher catalyst concentrations are used. Although the yields are slightly higher in the case of a larger excess of diazo ester **4b** (entries 1 and 2), under an economical point of view, the conditions in entry 5 are preferable on the basis of the lower amount of expensive rhodium catalyst and the lower excess of diazo ester needed.

Table 1. Optimization for the Rhodium-Catalyzed CH-Insertion

entry	diazo ester	**3/4** ratio	$Rh_2(OAc)_4$ (mol %)	temp (°C)	addition time (min)	% yield (**5b/5c**)
1	**4b**	1:3	2.0	0	60	58
2	**4b**	1:3	2.0	−18	60	59
3	**4b**	1:3	2.0	−78	60	0
4	**4b**	1:2	2.0	0	5	30
5	**4b**	**1:2**	**0.5**	**0**	**60**	**52**
6	**4b**	1:2	0.5	0	60	30
7	**4c**	1:3	2.0	0	60	70
8	**4c**	**1:2**	**0.5**	**0**	**60**	**89**
9	**4c**	1:2	0.5	0	60	78

Scheme 3. Rhodium-Catalyzed CH-Insertion into Various Dihydroaromatic Compounds



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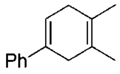
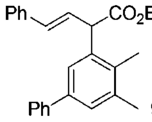
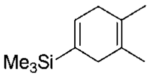
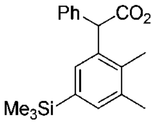
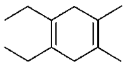
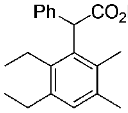
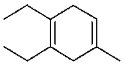
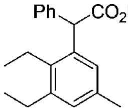
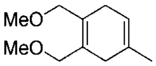
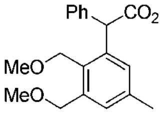
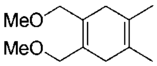
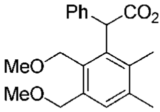
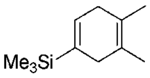
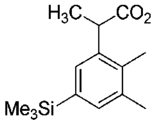
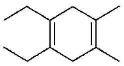
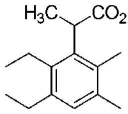
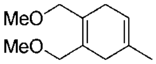
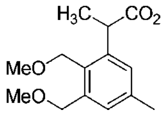
[4] For leading references, see: (a) Hilt, G.; Lüers, S.; Smolko, K. I. *Org. Lett.* **2005**, *7*, 251. (b) Hilt, G.; Lüers, S.; Harms, K. *J. Org. Chem.* **2004**, *69*, 624. (c) Hilt, G.; Smolko, K. I. *Angew. Chem.* **2003**, *115*, 2901; *Angew. Chem., Int. Ed.* **2003**, *42*, 2795.

[5] For the donor/acceptor carbenoid concept, see: (a) Davies, H. M. L.; Loe, Ø. *Synthesis* **2004**, 2595. (b) Davies, H. M. L. *Eur. J. Org. Chem.* **1999**, *9*, 2459. (c) Davies, H. M. L. *Curr. Org. Chem.* **1998**, *2*, 463. (d) Davies, H. M. L.; Rusiniak, L. *Tetrahedron Lett.* **1998**, *39*, 8811. (e) Davies, H. M. L. *Aldrichimica Acta* **1997**, *30*, 107. (f) Davies, H. M. L. *Tetrahedron* **1993**, *49*, 5203. (g) Davies, H. M. L.; Clark, T. J.; Church, L. A. *Tetrahedron Lett.* **1989**, *30*, 5057.

[6] Davies, H. M. L.; Bruzinski, P. R.; Fall, M. J. *Tetrahedron Lett.* **1996**, *37*, 4133.

Table 2. Results of the Rhodium-Catalyzed CH-Insertion into Dihydroaromatic Compounds

Entry	1,4-Diene (**7**)	Product (**9**)	Yield[a]
1		 **9a**	60%
2		 **9b**	77%
3		 **9c**	44%
4		 **9d**	60%
5		 **9e**	74%
6		 **9f**	62%
7		 **9g**	55%
8		 **9h**	9%
9		 **9i**	traces

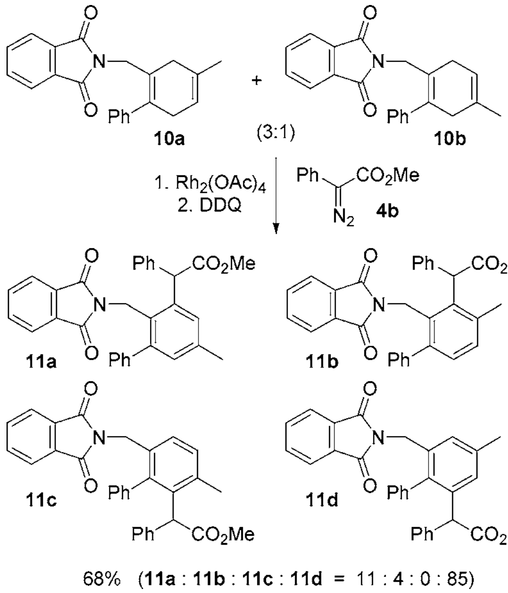
[a] Yields are based on the content of the dihydroaromatic compound determined prior to the reaction by NMR spectroscopy.

Under the now optimized reaction conditions, several dihydroaromatic compounds were converted by rhodium catalysis and DDQ oxidation to the corresponding adducts (Scheme 3). During the course of the investigation, we found that the dihydroaromatic compounds **7** should be better isolated by short column chromatography followed by Kugelrohr distillation. Thereby, an unknown impurity could be removed which diminishes the yields of the reaction by approximately 10−20%. The oxygen-sensitive dihydroaromatic compounds were freshly prepared, and the content was directly verified by NMR before use.

The results of the rhodium-catalyzed CH-insertion reactions on various dihydroaromatic compounds are summarized in Table 2. Although the yields for the trisubstituted dihydroaromatic compounds are good, lower yields were obtained when tetrasubstituted derivatives were used. As before, lower yields and increased decomposition were observed using **4b**. The combination of **4b** with a tetrasubstituted dihydroaromatic derivative (entry 8) gave only very low yields. Nevertheless, even when a higher excess of the diazo esters was used, only the mono CH-insertion products **9** were formed.

When isoprene was employed in the cobalt(I)-catalyzed Diels−Alder reaction, two regioisomers **10a** and **10b** were formed and the unsymmetrical nitrogen-functionalized diene was obtained as a nonseparable mixture in a 2.5:1 ratio (Scheme 4). Because of the asymmetry of the dienes **10a** and **10b**, a complex mixture of products (**11**) was expected from the reaction with ethyl phenyldiazoacetate (**4b**) under rhodium catalysis and subsequent DDQ oxidation.

Scheme 4. Rhodium-Catalyzed Carbene Insertion into the Unsymmetrical Dihydroaromatic Compound **10a**,**b**



Out of the four possible products, **11a**−**d**, a mixture of three isomers in an 85:11:4 ratio could be isolated in 68% yield. The major product was assigned by two-dimensional NMR techniques (Figure 1) to be the isomer **11d**, whereas the second most abundant isomer detected in 11% is **11a**.[7] The isomer **11c** is unlikely formed based on the greater sterical hindrance compared to the formation of the regioisomer **11b** which is proposed to be the third isomer detected.

Whereas the signals for **11d** in the HMBC experiment could be clearly assigned, the intensity of the other isomers was not strong enough for a distinct assignment.

In conclusion, we developed a rhodium-catalyzed carbene CH-insertion process into the bisallylic position of polysubstituted dihydroaromatic compounds. The reactions were

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(7) The ratios were determined by integration of the signals for the methyl groups in ^1H NMR.

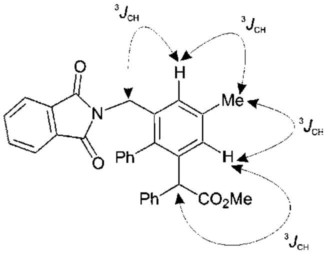

Figure 1. Significant HMBC signals for the elucidation of the regiochemistry of the main product **11d**.

performed using only a double excess of the diazo compound and a low catalyst loading of 0.5 mol %. The reactions are highly chemoselective by exclusively forming the insertion rather than the cyclopropanation products. The regioselectivity of the rhodium-catalyzed reactions for unsymmetrical products is also excellent so that after DDQ oxidation various tetra- and pentasubstituted benzene derivatives could be isolated in good yields of up to 85%.

Acknowledgment. This work was supported by the German Science Foundation (Deutsche Forschungs-gemeinschaft). We thank the Umicore AG for the generous donation of rhodium acetate. We thank Markus Pfitzenmaier and Prof. Armin Geyer for NMR measurements and helpful discussions.

Supporting Information Available: Experimental procedures and analytical data for all the new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL060739Z