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Conformational analysis and stereochemical assignments of products derived from C–H activation at secondary sites

Huw M. L. Davies* and Pingda Ren

Department of Chemistry, University at Buffalo, The State University of New York, Buffalo, NY 14260-3000, USA

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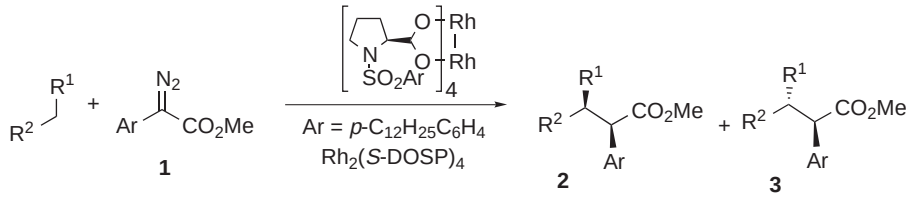
Abstract—The products derived from C–H activation of secondary sites by rhodium–carbenoids exist in a well-defined conformation. Consequently, their stereochemical assignment can be readily determined on the basis of chemical shift arguments.

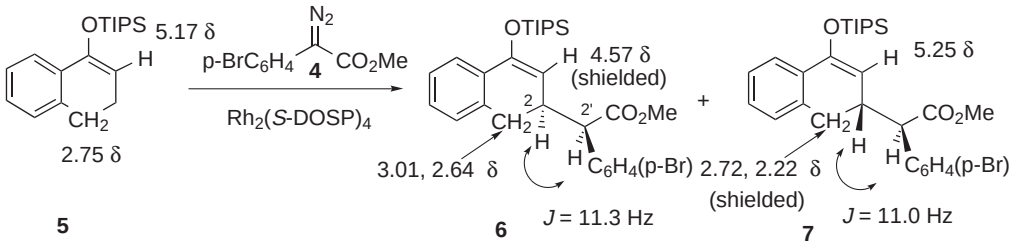
C–H activation by means of metal carbenoid induced C–H insertion has great synthetic potential.[1] It has recently been established that $Rh_2(S\text{-DOSP})_4$ catalysed decomposition of aryldiazoacetates **1** results in highly enantioselective intermolecular C–H activation on a range of substrates as illustrated in Eq. (1).[2,3] One of the major challenges associated with this work has been the assignment of relative stereochemistry of the C–H activation products, **2** and **3**. In this paper, we describe these C–H activation products preferentially exist in a well-defined conformation, and their relative configuration is readily determined from their distinctive proton NMR chemical shift data.

In our initial studies on the intermolecular C–H activation, the relative configuration of the products was determined by X-ray crystallography or by conversion to compounds of known relative configuration.[2a–h] Having now prepared a variety of different compounds, we find that all the compounds exist in a well-defined conformation, and that the stereochemistry can be assigned from the distinctive proton NMR chemical shift differences between the two diastereomers. Our recent study on the reaction of *p*-bromophenyldiazoacetate **4** with dihydronaphthalene **5** illustrates this point (Eq. (2)).[2h] Two diastereomers, **6** and **7**, were formed in this reaction and the configuration of the



(1)

R^1 = alkyl, alkenyl, Osilyl, NBOC
R^2 = alkyl, alkenyl



(2)

* Corresponding author. E-mail: hdavies@acsu.buffalo.edu

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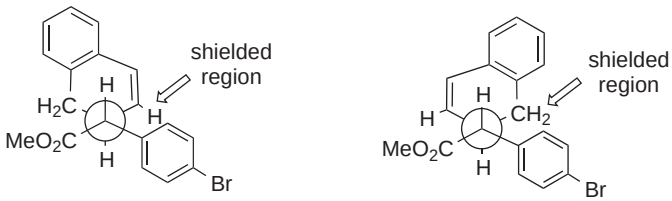
major diastereomer **6** was unambiguously determined by X-ray crystallography. Both diastereomers, however, have a large $J^{H2'-H2}$ ($\sim$11 Hz), which indicates that for both compounds the H2′–H2 protons preferentially exist in an antiperiplanar conformation. Furthermore, the proton NMR signals for the vinyl hydrogen in **6** and the methylene group in **7** are significantly shielded. This shielding effect can be rationalised as illustrated in Fig. 1. If the compounds preferentially exist in the antiperiplanar arrangement then the phenyl ring lies over the vinyl proton in **6** and the methylene site in **7**.

A similar shielding effect is apparent in a wide variety of C–H activation products as illustrated in Table 1. In the case of **10**,[2f] **12**,[2d] **15**,[2d] and **18**,[2f] the relative configuration has been unambiguously assigned on the basis of X-ray crystallography or by correlation to compounds of known stereochemistry. The same shielding effect extends to saturated and unsaturated cyclic systems. Even acyclic systems, **18** and **19**, exhibit the same shielding behaviour. In all cases, the coupling constant between the two hydrogens at the newly formed stereogenic centres is large (8–11 Hz), indicative of a strong preference for these hydrogens to exist in an antiperiplanar arrangement. Early conformational analysis on tetrasubstituted ethanes has shown that steric effects cause the antiperiplanar arrangement to be the favoured conformation.[4] The conformational analysis

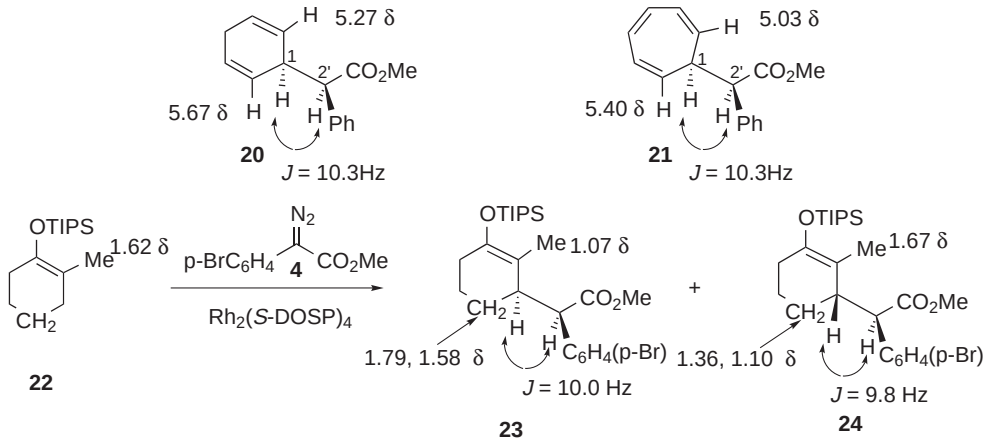


antiperiplanar conformation of **6** antiperiplanar conformation of **7**

Figure 1. Newman projections of **6** and **7**.

Table 1. Proton NMR data ($CDCl_3$, rt) of selected C–H activation substrates and products

Substrate	C-H Activation products		Δ δ
1.85 δ **8**	1.69, 1.47 δ CO2Me, 2-naphthyl **9** *J* = 10.1 Hz	2.14, 1.69 δ CO2Me, 2-naphthyl **10** *J* = 8.3 Hz	+0.45, +0.22
1.53 δ **11**	1.25, 0.96 δ CO2Me, Ph **12** *J* = 10.2 Hz	1.80, 1.24 δ CO2Me, Ph **13** *J* = 10.3 Hz	+0.55, +0.28
5.78 δ **14**	5.20 δ CO2Me, Ph **15** *J* = 10.5 Hz	5.70 δ CO2Me, Ph **16** *J* = 10.5 Hz	+0.50
1.15 δ 0.87 δ **17**	0.82 δ 0.96 δ CO2Me, C6H4(p-Br) **18** *J* = 10.7 Hz	1.11 δ 0.63 δ CO2Me, C6H4(p-Br) **19** *J* = 10.7 Hz	+0.29 -0.33



of certain compounds in this group such as ritalin (**12**) has been extensively studied, and this work has shown that **12** exists in an antiperiplanar conformation in solution.[5] The effect of this alignment, however, on the chemical shift has not been discussed previously.

The C–H activation products **20**[2b] and **21**[2e] derived from reaction with 1,4-cyclohexadiene and 1,3,5-cycloheptatriene, respectively, display a similar shielding effect. The proton NMR signals for the two adjacent vinyl protons have a considerable difference in chemical shift. The large $J^{H1-H2'}$ (10–12 Hz) is again indicative of the antiperiplanar conformation and this would cause the observed shielding.

An example of how this distinctive shielding effect can be used to determine the relative stereochemistry of new compounds from the C–H activation reaction is illustrated in Eq. (3).[2h] The C–H activation product **23** is formed with moderate diastereocontrol. The $J^{H1-H2'}$ ($\sim$10 Hz) is large for both diastereomers, and in the proton NMR of the major diastereomer **23**, the methyl group is shielded while the methylene group is not. The opposite is seen for the minor diastereomer **24**. On the basis of this information, the relative stereochemistry can be assigned as drawn for **23** and **24** with reasonable confidence.

In conclusion, the stereochemical assignment of the products derived from C–H activation at secondary sites can be readily determined on the basis of chemical shift arguments. All such compounds preferentially exist in an antiperiplanar conformation leading to predictable effects on proton NMR chemical shifts. The general trends in chemical shifts described herein will be extremely useful for the assignment of relative configuration for C–H activation products and related systems.

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