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Rhodium Carbenoid Approach for Introduction of 4-Substituted (*Z*)-Pent-2-enoates into Sterically Encumbered Pyrroles and Indoles

Yajing Lian and Huw M. L. Davies*

Department of Chemistry, Emory University, 1515 Dickey Drive, Atlanta, Georgia

hmdavie@emory.edu

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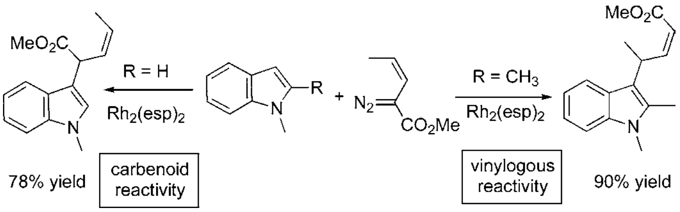
ABSTRACT



An unusual rhodium carbenoid approach for introduction of 4-substituted (*Z*)-pent-2-enoates into sterically encumbered pyrroles and indoles is described. These studies show that (*Z*)-vinylcarbenoids have a greater tendency than (*E*)-vinylcarbenoids to react at the vinylogous position of the carbenoid rather than at the carbenoid center.

Highly functionalized indoles and pyrroles are constituents of a variety of natural products and pharmaceutical targets.[1] The development of novel strategies to these targets is still an active field of organic synthesis.[2] In particular, the selective introduction of functionalized alkyl groups into the heterocycles has drawn considerable attention.[3] In this paper we describe a rhodium carbenoid approach for introduction of 4-substituted (*Z*)-pent-2-enoates into sterically encumbered pyrroles and indoles.

For some time, we have explored the reactions of rhodium-stabilized donor/acceptor carbenoids with pyrroles and indoles.[4] The rhodium-catalyzed reaction of vinyldiazoacetates with *N*-Boc-pyrroles offers a direct entry into tropanes by means of a tandem cyclopropanation/Cope rearrangement.[5] When *N*-methylpyrroles are used as substrates, alkylation occurs rather than cyclopropanation.[5a] The reaction of aryldiazoacetates with *N*-Boc-pyrrole results in double cyclopropanation of the pyrrole rings.[6] Similarly, reaction of *N*-Boc-indoles with aryldiazoacetates causes double cyclopropanation of the benzene ring to occur.[6] However, if the indole is 6-substituted, C−H functionalization of a side-chain becomes the preferred reaction.[6] Francis has shown that vinyldiazoacetates will alkylate 3-alkylindoles and that this can be used to selectively derivatize proteins.[7] Rainier has reported an unusual reaction between vinylcarbenoids and

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(1) (a) Dewick, P. M. *Medicinal Natural Products: A Biosynthetic Approach*; John Wiley& Sons Inc.: Chichester, 2009. (b) Barton, D. H. R.; Nakanishi, K.; MethCohn, O.; Kelly, J. W. *Comprehensive Natural Products Chemistry*; Pergamon Press: Oxford, 1999.

(2) For representative reviews, see: (a) Cacchi, S.; Fabrizi, G. *Chem. Rev.* **2005**, *105*, 2873. (b) Maryanoff, B. E.; Zhang, H.; Cohen, J. H.; Turchi, I. J.; Maryanoff, C. A. *Chem. Rev.* **2004**, *104*, 1431. (c) Saracoglu, N. *Top. Heterocycl. Chem.* **2007**, *11*, 1.

(3) For recent achievements, see: (a) Arai, T.; Yokoyama, N. *Angew. Chem., Int. Ed.* **2008**, *47*, 4989. (b) Poulsen, T. B.; Jørgensen, K. A. *Chem. Rev.* **2008**, *108*, 2903. (c) Trost, B. M.; Müller, C. *J. Am. Chem. Soc.* **2008**, *130*, 2438. (d) Evans, D. A.; Fandrick, K. R.; Song, H.; Scheidt, K. A.; Xu, R. *J. Am. Chem. Soc.* **2007**, *129*, 10029. (e) Austin, J. F.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 1172. (f) Sun, Y.; Li, N.; Zheng, Z.; Liu, L.; Yu, Y.; Qin, Z.; Fu, B. *Adv. Synth. Catal.* **2009**, *351*, 3113.

(4) Davies, H. M. L.; Hedley, S. J. *Chem. Soc. Rev.* **2007**, *36*, 1109.

(5) (a) Davies, H. M. L.; Saikali, E.; Young, W. B. *J. Org. Chem.* **1991**, *56*, 5696. (b) Davies, H. M. L.; Matasi, J. J.; Hodges, L. M.; Huby, N. J. S.; Thornley, C.; Kong, N.; Houser, J. H. *J. Org. Chem.* **1997**, *62*, 1095. (c) Reddy, R. P.; Davies, H. M. L. *J. Am. Chem. Soc.* **2007**, *129*, 10312.

(6) Hedley, S. J.; Ventura, D. L.; Dominiak, P. M.; Nygren, C. L.; Davies, H. M. L. *J. Org. Chem.* **2006**, *71*, 5349.

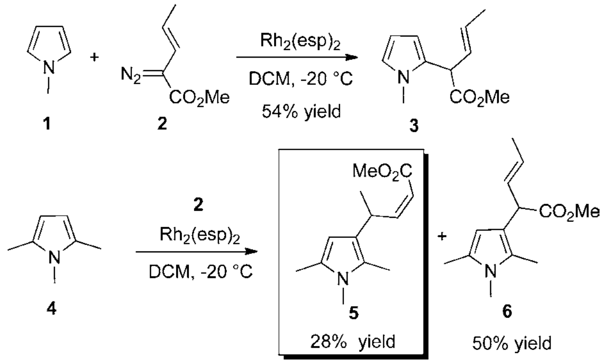
10.1021/ol9028385

thioindoles, which generates indolinethiones by means of ylide formation, followed by proton transfer and a [3,3]-sigmatropic rearrangement.[8]

One of the more unusual features of the chemistry of vinylcarbenoids is the occurrence of vinylogous reactivity when the vinyl group is unsubstituted.[5a,9] The reaction with pyrroles leads to 4-pyrrolylbutenoates,[5a] and this reactivity can be enhanced by using either polar solvents,[5a] bulky esters on the carbenoid,[9] or diruthenium catalysts.[10] In this paper we describe a new approach to enhance vinylogous reactivity, which led to a practical method to functionalize indoles and pyrroles.

The impetus for this investigation was an unexpected result observed during studies on the reaction of *N*-methylpyrroles with vinyldiazoacetates (Scheme 1). The $Rh_2(esp)_2$-catalyzed[11] decomposition of (*E*)-vinyldiazoacetate **2** with *N*-methylpyrrole **1** (6 equiv) afforded the expected aromatic substitution product **3**. This is a well-precedented type of product from the reaction of carbenoids with electron-rich heterocycles.[12]

Scheme 1



When the reaction was repeated with the more bulky substrate 1,2,5-trimethylpyrrole **4**, an unexpected product **5** was formed (28% yield) in addition to the expected aromatic substitution product **6**. Two features of this reaction were intriguing. First, **5** was formed exclusively as the *Z* isomer. Second, **5** is the type of product that would be generated from attack at the vinylogous position of the vinylcarbenoid.[9] This type of reactivity profile had not been seen previously in rhodium-catalyzed reactions of vinylcarbenoids with a substituent at the vinyl terminus.[13] Therefore, we decided to explore further this unusual reactivity.

Rhodium-stabilized vinylcarbenoids could in principle exist in two possible conformations, *s-cis* (conformer **A**) and *s-trans* (conformer **B**) (Figure 1). The catalyst face is considered to be a steric wall, but neither conformer **A** nor conformer **B** would be expected to have significant interference with this wall. Few studies have been carried out to determine which of the two conformers is likely to be the most reactive form in rhodium vinylcarbenoid chemistry.[14] The formation of **5** as the (*Z*)-isomer is indicative that the vinylogous reactivity occurs through conformer **B**. This leads us to propose that the highly substituted pyrrole **4** is sterically too crowded for an effective reaction at the carbenoid center and leads to competing vinylogous reactivity, occurring through conformer **B**. We then became intrigued with the concept that the vinylogous reactivity could be enhanced if the (*Z*)-vinylcarbenoid was used as substrate. In this case, the *s-cis* conformation of the carbenoid (conformer **C**) would be expected to interfere with the catalyst wall, and so the (*Z*)-vinylcarbenoid would be expected to preferentially exist in the *s-trans* conformation (conformer **D**).

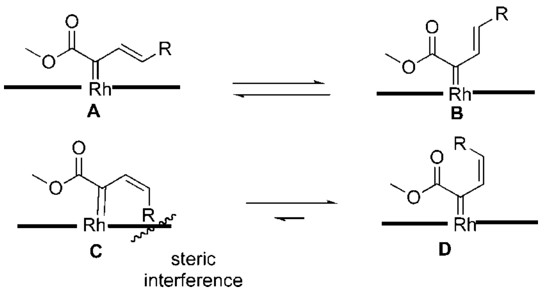
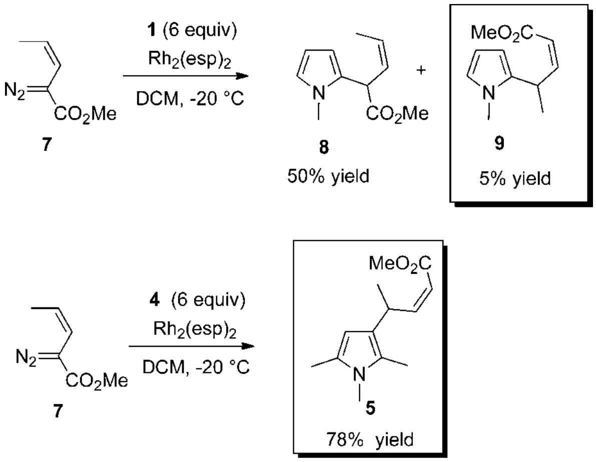


Figure 1. Conformations of vinylcarbenoids.

To probe the role of the vinylcarbenoid geometry, the reactions of *N*-methylpyrrole (**1**) and 1,2,5-trimethylpyrrole (**4**) were repeated using the (*Z*)-vinyldiazoacetate **7** as the carbenoid source (Scheme 2). The reaction with *N*-methylpyrrole still

Scheme 2



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[7] (a) Antos, J. M.; Francis, M. B. *J. Am. Chem. Soc.* **2004**, *126*, 10256. (b) Antos, J. M.; McFarland, J. M.; Iavarone, A. T.; Francis, M. B. *J. Am. Chem. Soc.* **2009**, *131*, 7558.

[8] (a) Boyarskikh, V.; Nyong, A.; Rainier, J. D. *Angew. Chem., Int. Ed.* **2008**, *47*, 5374. (b) Nyong, A. M.; Rainier, J. D. *J. Org. Chem.* **2005**, *70*, 746. (c) Novikov, A. V.; Kennedy, A. R.; Rainier, J. D. *J. Org. Chem.* **2003**, *68*, 993.

[9] Davies, H. M. L.; Hu, B.; Saikali, E.; Bruzinski, P. R. *J. Org. Chem.* **1994**, *59*, 4535.

[10] Sevryugina, Y.; Weaver, B.; Hansen, J.; Thompson, J.; Davies, H. M. L.; Petrukhina, M. A. *Organometallics* **2008**, *27*, 1750.

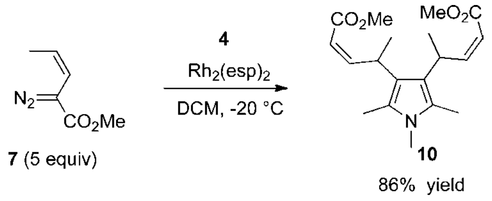
[11] $Rh_2(esp)_2$: Bis[rhodium(αα, α′,α′-tetramethyl-1,3-benzenedipropionic acid)]. For a leading reference, see: Zalatan, D. N.; Bois, J. D. *J. Am. Chem. Soc.* **2009**, *131*, 7558.

[12] Muthusamy, S.; Gnanaprakasam, B. *Tetrahedron Lett.* **2008**, *49*, 475.

preferentially formed the normal alkylation product **8**, but a trace of the vinylogous substitution product **9** was also formed. In contrast, the reaction with 1,2,5-trimethylpyrrole **4** led to the formation of the vinylogous substitution product **5** in 78% yield, exclusively as the *Z* isomer without any detectable amount of the product derived from reaction at the carbenoid center. The reaction could also be conducted with some of the more standard catalysts such as rhodium acetate and rhodium trifluoroacetate, but the highest yield of **5** was obtained using Du Bois' $Rh_2(esp)_2$.[11]

Normally, the reaction of vinylcarbenoids at the carbenoid site is very sensitive to steric crowding,[15] and this may explain why vinylogous reactivity is more favored in a crowded substrate. Consequently, we explored if a double alkylation process was feasible. The $Rh_2(esp)_2$-catalyzed reaction using 5 equiv of the (*Z*)-vinyldiazoacetate **7** with 1,2,5-trimethylpyrrole (**4**) generated the bis-alkylated product **10** in 86% yield (Scheme 3). **10** was formed as a mixture of diastereomers, as would be expected for this type of reaction conducted with an achiral catalyst.

Scheme 3



The vinylogous reactions of diazoacetate **7** are applicable to other sterically crowded pyrroles, forming the alkylated pyrroles **11**−**13** in 59−87% yield (Figure 2). Not only N-protected pyrroles undergo the alkylation with vinyldiazoacetate **7**, but also an N-unprotected pyrrole was able to furnish the vinylogous product **11**. The regiochemistry in the formation of **12** and **13** reveals that *N*-TIPS is acting as a bulky protecting group,[16] blocking the reactivity at the 2-position and forcing the reaction to occur at the 3-position to form **13**.

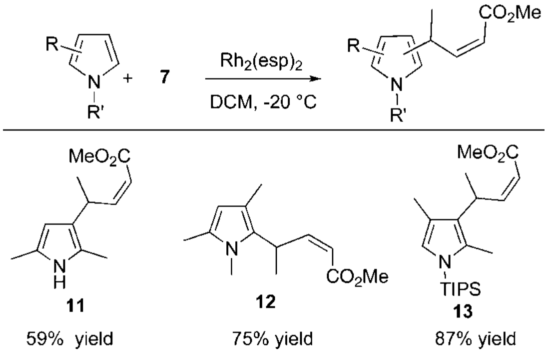
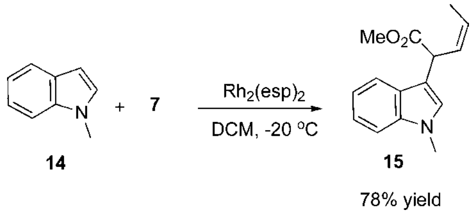


Figure 2. Vinylogous reaction of **7** with pyrroles.

When this reaction was extended to *N*-methylindole **14**, the standard substitution product **15** was isolated in 78% yield (Scheme 4). This result is consistent with the data obtained from the pyrrole derivatives that a sterically crowded aromatic systems is essential to achieve highly selective vinylogous reactivity.

Scheme 4



The vinylogous reaction can be applied to indoles as long as they are sufficiently crowded. Representative examples are shown in Figure 3. The reactions could be conducted at temperatures as low as −45 °C, presumably because of the greater nucleophilicity of indoles over pyrroles.[17] Both unprotected and protected (methyl or benzyl) 2-methylindoles afforded the vinylogous products in good yields. Typically, substitution at the 2-position of the indole is necessary for the vinylogous reactivity to occur. However, a similar effect can be achieved when a bulky substituent is introduced at the 4-position of the indole, as illustrated in the formation of **18**.

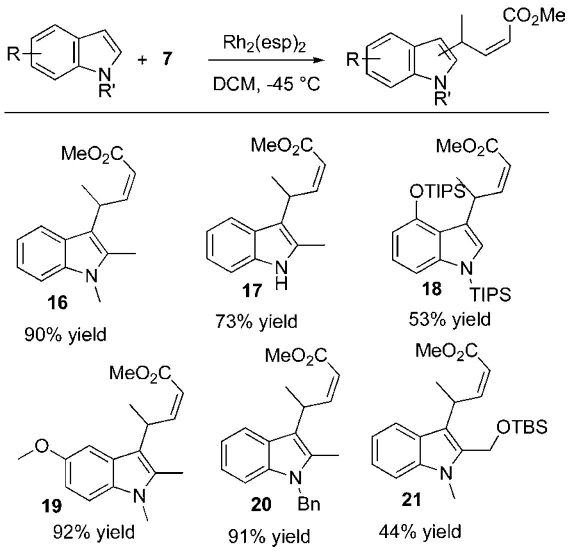
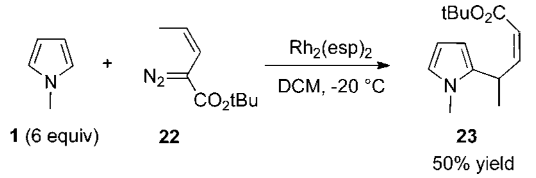


Figure 3. Vinylogous reaction of **7** with indoles.

To further extend this transformation to less crowded indoles, the use of a (*Z*)-vinyldiazoacetate approach combined with a complementary strategy for enhancing vinylogous reactivity was examined. Increasing the size of the ester group enhances vinylogous reactivity,[8] and so, *tert*-butyl (*Z*)-vinyldiazoacetate **22** was prepared and tested (Scheme 5). The $Rh_2(esp)_2$-catalyzed

Scheme 5



reaction of **22** with 6.0 equiv of *N*-methylpyrrole **1** caused a major change in the reaction outcome. No evidence of the regular alkylation product was observed, and the vinylogous product **23** could be isolated in 50% yield.

In summary, these studies demonstrate that (*Z*)-vinylcarbenoids have a greater tendency than (*E*)-vinylcarbenoids for reaction at the vinylogous position of the carbenoid rather than at the carbenoid center. This type of reactivity leads to an effective method for the functionalization of pyrroles and indoles.

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Supporting Information Available: Full experimental data for the compounds described in the paper. This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) Vinylogous reactivity of substituted vinylcarbenoids has been observed with silver catalysis and diruthenium catalysis. For examples, see: (a) Yue, Y.; Wang, Y.; Hu, W. *Tetrahedron Lett.* **2007**, *48*, 3975. (b) Ref 9.

(14) The models used to describe the reactions of vinylcarbenoids have assumed that the reaction occurs through a particular carbenoid conformation. For example, the combined C−H activation/Cope rearrangement and a [3 + 2] cycloaddition have been proposed to involve a reaction where the vinylcarbenoid is in the *s-cis* conformation. For details, see: (a) Davies, H. M. L.; Jin, Q. *J. Am. Chem. Soc.* **2004**, *126*, 10862. (b) Davies, H. M. L.; Xiang, B.; Kong, N.; Stafford, D. G. *J. Am. Chem. Soc.* **2001**, *123*, 746. Recently, we proposed that the [3 + 2] annulation of indoles by vinylcarbenoids may occur via the *s-trans* conformation of the vinylcarbenoid. For details, see: (c) Lian, Y.; Davies, H. M. L. *J. Am. Chem. Soc.* **2010**, *132*, ASAP.

(15) Davies, H. M. L.; Antoulinakis, E. G. *Org. React.* **2001**, *57*, 1. (b) Davies, H. M. L.; Beckwith, R. E. J. *Chem. Rev.* **2003**, *103*, 2861.

(16) For a leading review, see: Jolicoeur, B.; Chapman, E. E.; Thompson, A.; Lubell, W. D. *Tetrahedron* **2006**, *62*, 11531.

(17) Mayer, H.; Kempf, B.; Ofial, A. R. *Acc. Chem. Res.* **2003**, *36*, 66.