J|A|C|S COMMUNICATIONS

Published on Web 12/21/2009

Rhodium-Catalyzed [3 + 2] Annulation of Indoles

Yajing Lian and Huw M. L. Davies*

Department of Chemistry, Emory University, 1515 Dickey Drive, Atlanta, Georgia 30322

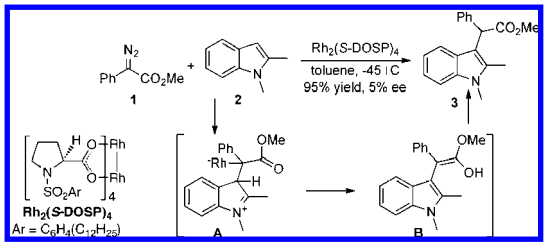
Received September 21, 2009; E-mail: hmdavie@emory.edu

Fused indolines are common subunits in a wide range of alkaloid natural products.[1] Many methodologies have been developed for the synthesis of this skeleton.[2] Strategies based on the annulation of indoles are particularly useful because indoles are readily available.[3,4] Methods for conversion of indoles into fused indolines have been reported,[3] but enantioselective variants are limited.[4] Recently, Barluenga et al.[5] developed an asymmetric C2−C3 cyclopentannulation of 2-substituted indoles with Fisher carbenes containing (*S*)-menthol as a chiral auxiliary. Herein, we describe a catalytic enantioselective [3 + 2] annulation of indoles using Rh-stabilized vinylcarbenoids.

For some time we have studied the enantioselective reactions of donor/acceptor-substituted carbenoids. Several highly enantioselective C−C bond-forming reactions have been developed, including cyclopropanation,[6] [3 + 2] cycloaddition,[7] [4 + 3] cycloaddition,[8] and C−H functionalization.[9] A series of chiral dirhodium tetracarboxylate catalysts have been used, of which the most notable is the prolinate catalyst Rh_2(*S*-DOSP)$_4$.[6] This study was part of our program directed toward generating new types of enantioselective transformations of donor/acceptor carbenoids that proceed via zwitterionic intermediates.[10,11]

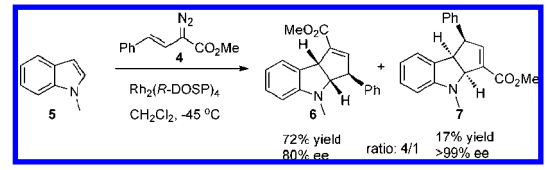
It is well-established that the reaction of carbenoids with *N*-alkylindoles generates zwitterionic intermediates.[12] This pathway is favored because the positive charge of the intermediate is stabilized by the electron-rich indole while the negative charge is stabilized by the carbenoid component. We began our studies with methyl phenyldiazoacetate (**1**) as the precursor to the donor/acceptor carbenoid. Even though the Rh_2(*S*-DOSP)$_4$-catalyzed reaction of **1** with 1,2-dimethylindole (**2**) is very efficient, generating the alkylation product **3** in 95% yield, negligible asymmetric induction (<5% ee) was observed (Scheme 1). The lack of asymmetric induction in the formation of **3** presumably occurs because the zwitterionic intermediate **A** could undergo a rapid proton transfer to generate the achiral enol **B**, which then would tautomerize to the observed product **3**. We reasoned that if the indoles were to react with a vinylcarbenoid intermediate, alternative pathways avoiding achiral intermediates would be possible. Our exploration of this chemistry, which led to a highly enantioselective entry to cyclopenta[*b*]indoles, is described in this paper.

Scheme 1



The Rh_2(R-DOSP)$_4$-catalyzed reaction of methyl (*E*)-phenylvinyldiazoacetate (**4**) with *N*-methylindole (**5**) in CH_2Cl_2 resulted in a very efficient transformation, but in this case the products were the two regioisomeric fused indoline derivatives **6** and **7** (Scheme 2). Unlike the reaction with **1**, these products were formed with high asymmetric induction (80% ee for the major isomer **6** and >99% ee for the minor isomer **7**). The relative configurations of **6** and **7** were determined by NOE analysis, and **6** had an exo configuration and **7** an endo configuration. Vinylcarbenoids are known to be reactive at either the carbenoid or the vinylogous site,[13] and at this stage it was uncertain whether the two products were derived from competition between reaction at these two sites or between initial attack of the carbenoid at the C2 or C3 position of the indole.

Scheme 2



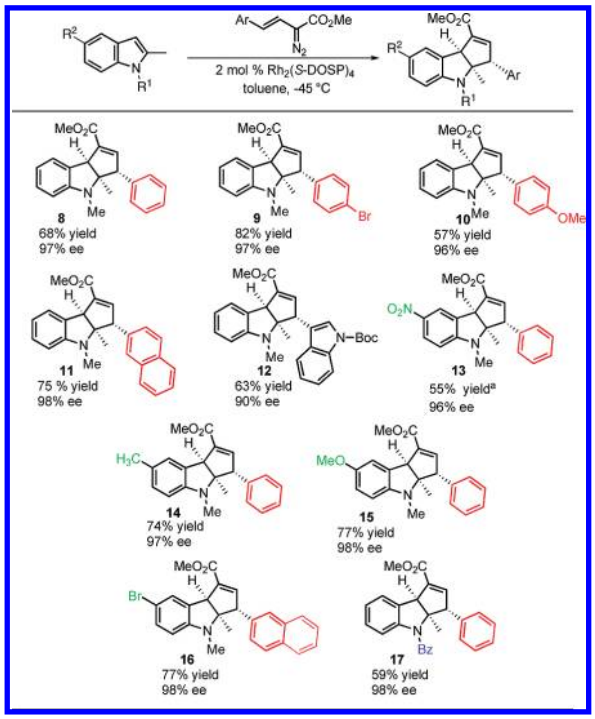
In order to determine the cause of the formation of the two regioisomers, the reaction was extended to 1,2-disubstituted indoles, as these would be expected to undergo initial electrophilic attack only at C3. With these substrates, only a single regioisomer of each fused indoline was formed. The Rh_2(*S*-DOSP)$_4$-catalyzed [3 + 2] annulation is applicable to a range of (*E*)-arylvinyldiazoacetates and 1,2-disubstituted indoles (Table 1), producing the fused indolines **8**−**17** with very high asymmetric induction (90−98% ee) exclusively as the exo diastereomers. The absolute configurations of **10** and **16** were unambiguously assigned by X-ray crystallography.[14] The relative configurations of **6**, **8**, **9**, **11**−**15**, and **17** were assigned by NOE, while their absolute configurations were tentatively assigned by assuming a similar mode of asymmetric induction for all of the substrates.

When the reaction was extended to 1,3-disubstituted indolyl derivatives, the opposite regioisomeric series of fused indolines was formed (Table 2). As was observed in the reaction with **5**, the asymmetric induction for this series of compounds was exceptionally high (99% ee) and only the endo diastereomer was observed. The absolute configuration of **20** was unambiguously assigned by X-ray crystallography,[14] while the relative configurations of **7**, **18**, and **19** were assigned by NOE and the absolute configurations tentatively assigned by analogy.

A remarkable feature of the [3 + 2] cycloaddition is that exo isomers are produced from 1,2-disubstituted indoles while endo isomers are produced from 1,3-disubstituted indoles. Furthermore, the two types of indoles give opposite absolute configurations at the ring-fusion stereocenters. Although the detailed mechanism of the transformation is not well understood, a plausible mechanism that rationalizes the observed relative and absolute stereochemistries is shown in Figure 1. A model for the high asymmetric induction generated by Rh_2(*S*-DOSP)$_4$ has the catalyst adopting a D_2-symmetric conformation in which a blocking group is in front of the ester and behind the vinyl group.[6,9b] In cyclopropanation reactions, the alkene approaches over the vinyl group, and it would be reasonable to assume that a similar arrangement occurs here, even though the reaction proceeds via a zwitterionic intermediate and never reaches the cyclopropane stage. The difference in the ring-fusion stereochemistry can be rationalized in terms of whether the initial attack occurs at C2 or C3 of the indole.[12b,c] Similar changes in the absolute configurations of the

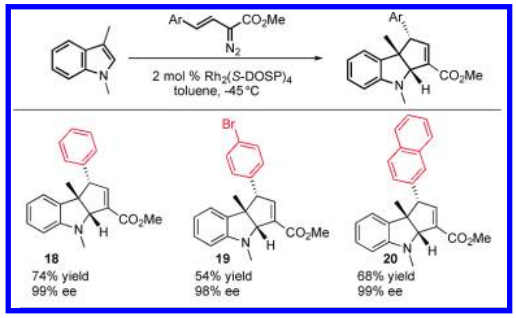
10.1021/ja9078094

Table 1. Annulation of 1,2-Disubstituted Indoles



[a] The reaction was conducted at −20 °C.

Table 2. Annulation of 1,3-Disubstituted Indoles



products when using the same chiral catalyst have been observed in the cyclopropanation chemistry of furans, benzofurans, and *N*-Boc-pyrroles.[12b,c] The formation of exo or endo products would then be governed by whether the closure occurs from an intermediate derived from a carbenoid in an s-cis or s-trans configuration. In Figure 1, the mechanism has been drawn as if the 1,2-disubstituted indoles react with the *s-trans*-vinylcarbenoids and the 1,3-disubstituted indoles react with the *s-cis*-vinylcarbenoids, but it is also possible that the differentiation occurs by vinyl group orientation of the zwitterionic intermediates **T-1** and **T-2** prior to cyclization. Further studies will be needed to confirm this mechanistic hypothesis.

In conclusion, an effective Rh_2(*S*-DOSP)$_4$-catalyzed asymmetric cyclopentannulation of indolyl rings has been developed. Depending on the substitution pattern of the indole, two distinct regioisomeric products can be generated. These studies demonstrate that Rh-catalyzed reactions of donor/acceptor carbenoids proceeding by means of zwitterionic intermediates can be carried out with very high asymmetric induction.

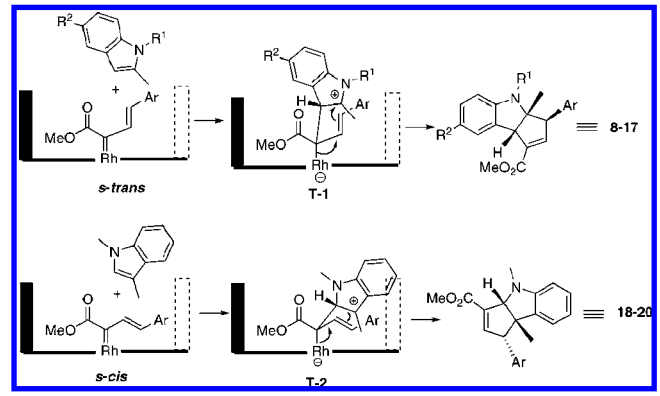


Figure 1. Proposed reaction mechanism.

Acknowledgment. This research was supported by the National Science Foundation (CHE-0907936). We thank Dr. Ken Hardcastle for the X-ray crystallographic structure determination.

Supporting Information Available: Full experimental data for the compounds described in the paper and X-ray crystallographic data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) (a) Dewick, P. M. *Medicinal Natural Products: A Biosynthetic Approach*, 2nd ed.; Wiley: New York, 2002. (b) Gataullin, R. R. *Russ. J. Org. Chem.* **2008**, *45*, 321.
(2) For some recent examples, see: (a) Li, J.; Mei, T.; Yu, J. *Angew. Chem., Int. Ed.* **2008**, *47*, 6452. (b) Wipf, P.; Maciejewski, J. P. *Org. Lett.* **2008**, *10*, 4383. (c) Minatti, A.; Buchwald, S. L. *Org. Lett.* **2008**, *10*, 2721. (d) Gilmore, C. D.; Allan, K. M.; Stoltz, B. M. *J. Am. Chem. Soc.* **2008**, *130*, 1558. (e) Garcá Ruano, J. L.; Alemán, J.; Catalán, S.; Marcos, V.; Monteagudo, S.; Parra, A.; Del Pozo, C.; Fustero, S. *Angew. Chem., Int. Ed.* **2008**, *47*, 7941. (f) Arp, F. O.; Fu, G. C. *J. Am. Chem. Soc.* **2006**, *128*, 14264.
(3) For some recent examples, see: (a) Bajtos, B.; Yu, M.; Zhao, H.; Pagenkopf, B. L. *J. Am. Chem. Soc.* **2007**, *129*, 9631. (b) Zhang, G.; Huang, X.; Li, G.; Zhang, L. *J. Am. Chem. Soc.* **2008**, *130*, 1814.
(4) For some representative examples, see: (a) Trost, B. M.; Quancard, J. *J. Am. Chem. Soc.* **2006**, *128*, 6314. (b) Kuwano, R.; Sato, K.; Kurokawa, T.; Karube, D.; Ito, Y. *J. Am. Chem. Soc.* **2000**, *122*, 7614.
(5) Barluenga, J.; Tudela, E.; Ballesteros, A.; Tomás, M. *J. Am. Chem. Soc.* **2009**, *131*, 2096.
(6) Davies, H. M. L.; Bruzinski, P. R.; Lake, D. H.; Kong, N.; Fall, M. J. *J. Am. Chem. Soc.* **1996**, *118*, 6897.
(7) (a) Davies, H. M. L.; Xiang, B.; Kong, N.; Stafford, D. G. *J. Am. Chem. Soc.* **2001**, *123*, 7461. (b) Davies, H. M. L.; Kong, N.; Churchill, M. R. *J. Org. Chem.* **1998**, *63*, 6586.
(8) (a) Davies, H. M. L.; Ahmed, G.; Churchill, M. R. *J. Am. Chem. Soc.* **1996**, *118*, 10774. (b) Davies, H. M. L.; Stafford, D. G.; Doan, B. D.; Houser, J. H. *J. Am. Chem. Soc.* **1998**, *120*, 3326.
(9) (a) Davies, H. M. L.; Beckwith, R. E. J. *Chem. Rev.* **2003**, *103*, 2861. (b) Hansen, J.; Davies, H. M. L. *Coord. Chem. Rev.* **2008**, *252*, 545.
(10) For examples of enantioselective reactions of donor/acceptor rhodium carbenoids involving zwitterionic intermediates, see: (a) Zhang, X.; Qu, Z.; Ma, Z.; Shi, W.; Jin, X.; Wang, J. *J. Org. Chem.* **2002**, *67*, 5621. (b) Liao, M.; Wang, J. *Green Chem.* **2007**, *9*, 184. (c) Zhang, X.; Ma, M.; Wang, J. *Tetrahedron: Asymmetry* **2003**, *14*, 891. (d) Hu, W.; Xu, X.; Zhou, J.; Liu, W.; Huang, H.; Hu, J.; Yang, L.; Gong, L. *J. Am. Chem. Soc.* **2008**, *130*, 7782. (e) Yan, M.; Jacobsen, N.; Hu, W.; Gronenberg, L. S.; Doyle, M. P.; Colyer, J. L.; Bykowski, D. *Angew. Chem., Int. Ed.* **2004**, *43*, 6713.
(11) Li, Z.; Davies, H. M. L. *J. Am. Chem. Soc.* **2010**, *132*, 396.
(12) (a) Davies, H. M. L. *Adv. Nitrogen Heterocycl.* **1995**, *1*, 1. (b) Davies, H. M. L.; Hedley, S. J. *Chem. Soc. Rev.* **2007**, *36*, 1109. (c) Hedley, S. J.; Ventura, D. L.; Dominiak, P. M.; Nygren, C. L.; Davies, H. M. L. *J. Org. Chem.* **2006**, *71*, 5349.
(13) (a) Davies, H. M. L.; Smith, H. D.; Hu, B.; Klenzak, S. M.; Hegner, F. J. *J. Org. Chem.* **1992**, *57*, 6900. (b) Muthusamy, S.; Gnanaprakasam, B. *Tetrahedron. Lett.* **2008**, *49*, 475.
(14) The crystal structures of **10**, **16**, and **20** have been deposited at the Cambridge Crystallographic Data Centre under deposition numbers CCDC 747614, 747615, and 747616, respectively.

JA9078094