ORGANIC LETTERS

2013
Vol. 15, No. 16
4114–4117

Rh(II)-Catalyzed Reactions of Differentially Substituted *Bis*(diazo) Functionalities

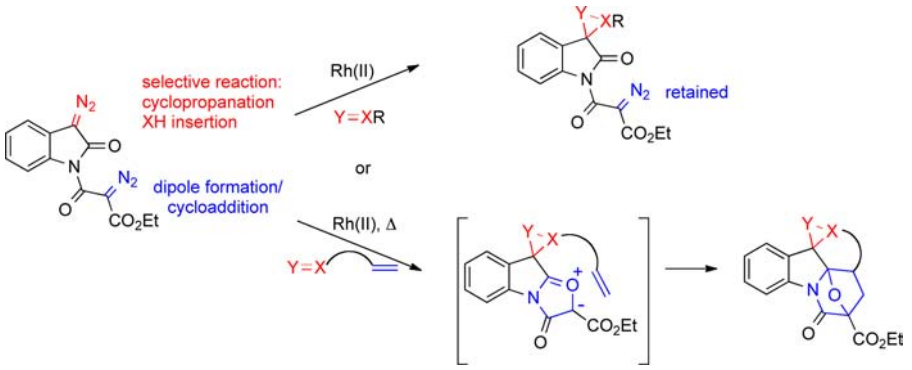
Sara A. Bonderoff and Albert Padwa*

Department of Chemistry, Emory University, Atlanta, Georgia 30322, United States

chemap@emory.edu

Received June 21, 2013

ABSTRACT



The chemoselective reaction of donor/acceptor (D/A) and acceptor/acceptor (A/A) diazo moieties in the same molecule was examined using 3-diazo-1-(ethyl 2-diazomalonyl)indolin-2-one under rhodium(II) catalysis. The D/A diazo group undergoes selective cyclopropanation as well as XH-insertion, leaving behind the second diazo group for a further intramolecular dipolar cycloaddition reaction.

The metal catalyzed decomposition of α-diazo carbonyl compounds represents a common method for generating metallocarbenoids, which exhibit versatile chemical behavior such as cyclopropanation, XH-insertion, and ylide formation.[1] These metallocarbenoids are generally classified into various reaction types based on the nature of the substituents flanking the carbenoid center. Most typically, electron donor or acceptor groups are employed, with donor/acceptor (D/A) and acceptor/acceptor (A/A) combinations being most frequently used. This classification is valuable, as there are substantial differences in reactivity between groups, manifesting in differing relative rates of metallocarbenoid generation and selectivity in the ensuing chemistry. For example, D/A-carbenoids are more easily formed under rhodium(II) catalysis than A-carbenoids[2] and D/A-carbenoids prefer to undergo CH insertion with 1,4-cyclohexadiene.[3] In contrast, ethyl diazoacetate, a well recognized precursor to an A-carbenoid intermediate, shows a distinct preference for cyclopropanation under identical reaction conditions.

There are a number of examples of *bis*(diazo) containing compounds reported in the literature; however, these structures are for the most part symmetrically substituted, and thus metallocarbenoid formation is unselective.[4] In 1998, Moody and Miller explored the selective behavior of a *bis*(diazo) system in the context of OH insertion chemistry.[5] More recently Muthusamy and Srinivasan reported an example of a formal CH insertion of a *bis*-(diazo) compound followed by 1,3-dipolar cycloaddition of the resulting carbonyl ylide.[6]

In light of the limited study of these interesting *bis*(diazo) systems, we were prompted to investigate the chemical

(1) (a) Doyle, M. P.; McKervey, M. A.; Ye, T. *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds*; Wiley: New York, NY, 1998. (b) Ye, T.; McKervey, M., A. *Chem. Rev.* **1994**, *94*, 1091. (c) Zhang, Z.; Wang, J. *Tetrahedron* **2008**, *64*, 6577.

(2) (a) Hansen, J., H.; Parr, B., T.; Pelphrey, P.; Jin, Q.; Autschbach, J.; Davies, H., M., L. *Angew. Chem., Int. Ed.* **2011**, *50*, 2544. (b) Pelphrey, P.; Hansen, J.; Davies, H. M. L. *Chem. Sci.* **2010**, *1*, 254.

(3) Müller, P.; Tohill, S. *Tetrahedron* **2000**, *56*, 1725.

(4) (a) Ihara, E.; Hara, Y.; Itoh, T.; Inoue, K. *Macromolecules* **2011**, *44*, 5955. (b) Li, G.-Y.; Che, C.-M. *Org. Lett.* **2004**, *6*, 1621. (c) Muthusamy, S.; Gunanathan, C.; Nethaji, M. *J. Org. Chem.* **2004**, *69*, 5631. (d) Aburel, P., S.; Undheim, K. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1891. (e) Del Zotto, A.; Baratta, W.; Verardo, G.; Rigo, P. *Eur. J. Org. Chem.* **2000**, 2795. (f) Doyle, M. P.; Hu, W.; Phillips, I. M. *Org. Lett.* **2000**, *2*, 1777. (g) Kulkowit, S.; McKervey, M. A. *J. Chem. Soc., Chem. Commun.* **1981**, 616. (h) Font, J.; Serratosa, F.; Valls, J. *Tetrahedron* **1973**, *30*, 455. (i) Bien, S.; Ovadia, D. *J. Org. Chem.* **1970**, *35*, 1028. (j) Font, J.; Serratosa, F.; Valls *J. Chem. Commun.* **1970**, 721.

(5) Moody, C., J.; Miller, D., J. *Tetrahedron* **1998**, *54*, 2257.

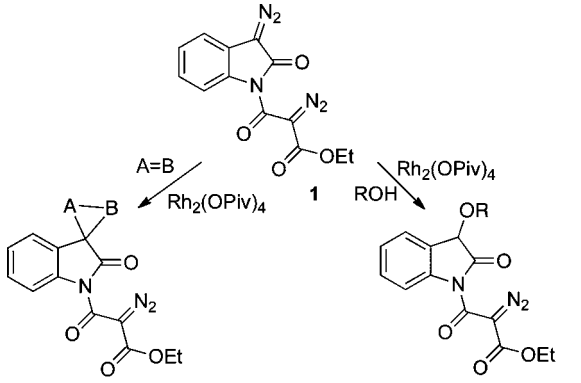
(6) Muthusamy, S.; Srinivasan, P. *Tetrahedron* **2009**, *65*, 1567.

10.1021/ol4017468
Published on Web 07/26/2013

behavior of differentially substituted *bis*(diazo) compounds using compound **1** as a test substrate (Scheme 1). We reasoned that an examination of the chemical reactivity of *bis*(diazo) **1** might prove to be fruitful since the cyclic D/A-carbenoid should be formed at a faster rate than the acyclic A/A-carbenoid. Compound **1** is easily available by the acylation of the known 3-diazoindolin-2-one[7] with ethyl 2-diazomalonyl chloride.[8] In order to ascertain whether it was possible to effect the selective reaction of only one of the diazo groups, **1** was subjected to catalytic $Rh_2(OPiv)_4$ in the presence of styrene at 0 °C (Scheme 1). The formation of cyclopropane **2a** with the second diazo group remaining intact encouraged us to examine the reaction of **1** with a variety of different reaction partners to ensure that other typical transformations of rhodium carbenoids could also be carried out selectively.

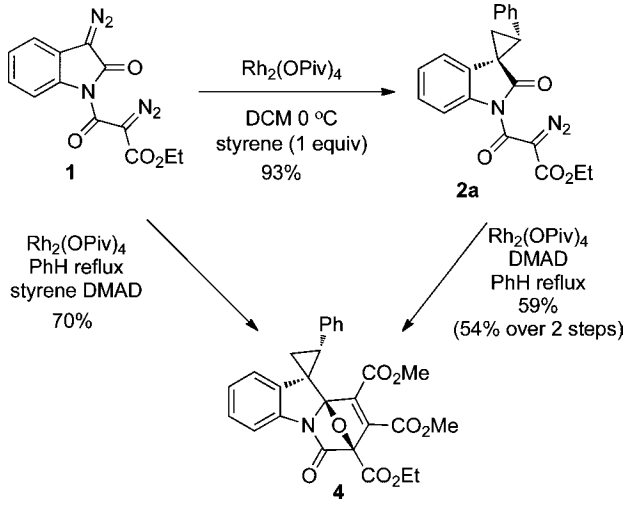
Cyclopropanation of **1** with vinyl acetate gave the acetoxy cyclopropane **2b** in 90% yield. The reaction of **1** with *cis*-disubstituted cyclopentene furnished **2c** in moderate yield (68%). The relative stereochemistry of cyclopropanes **2a**–**c** is assumed to be *trans* based on extensive literature precedent,[9] as well as spectroscopic evidence.[10] Homoallyl alcohol and *bis*(diazo) **1** react in the presence of a Rh(II)-catalyst to furnish the OH insertion product **3** in 54% isolated yield (vs cyclopropanation of the π-bond). Our ultimate intention (*vide infra*) was to carry out a tandem cascade reaction,[11] and thus avoid isolation of any labile intermediates.

Scheme 1. Cyclopropanation and Insertion Chemistry



With cyclopropane **2a** in hand, we next investigated the chemical behavior of the remaining diazo moiety. Related 1-(ethyl 2-diazomalonyl)indolin-2-ones have been shown to undergo dipole formation and subsequent intermolecular cycloaddition with added dipolarophiles.[12] To effect the reaction of the A/A diazo group of **2a**, the solvent was changed to benzene and the Rh(II)-catalyzed reaction was carried out at reflux (Scheme 2). Cycloadduct **4** was formed in 54% yield over the two-step sequence. We then tested the feasibility of a one-pot process. Starting from *bis*(diazo) **1**, cycloadduct **4** was now formed in 70% yield in contrast to the two-step procedure. We assume that at the elevated temperatures the lactam diazo moiety still undergoes preferential reaction. It should be noted, however, that both cyclopropanation/dipole formation and dipole formation/cyclopropanation would lead to the same product **4**.

Scheme 2. Stepwise and One-Pot Cyclopropanation/Cycloaddition Sequence



In order to determine the exact sequence of events and validate our assumption that a selective reaction also occurs at the higher temperature, we examined the behavior of **1** with the difunctionalized reaction partner, 2-phenyl-1,5-hexadiene (Scheme 3). This diene was chosen to satisfy the following requirements: (1) cyclopropanation should take place preferentially with the phenyl-substituted alkene rather than the monosubstituted π-bond, and (2) the size difference between the phenyl and butenyl groups should lead to preferential formation of the cyclopropane where the alkene is oriented *cis* to the incipient dipole, thereby making the intramolecular cycloaddition reaction geometrically feasible.[9] Since monoalkyl-substituted alkenes do not undergo intermolecular cycloadditions with isomünchnones, the formation of product **5** provides

(7) Song, H.; Yang, J.; Chen, W.; Qin, Y. *Org. Lett.* **2006**, *8*, 6011.

(8) Marino, J. P., Jr.; Osterhout, M., H.; Price, A., T.; Sheehan, S. M.; Padwa, A. *Tetrahedron Lett.* **1994**, *35*, 849.

(9) (a) Reddy, B. V. S.; Rajasedaran, T.; Karthik, G.; Rao, T. P. *Tetrahedron Lett.* **2012**, *53*, 3416. (b) Muthusamy, S.; Azhagan, D.; Gnanaprakasam, B.; Suresh, E. *Tetrahedron Lett.* **2010**, *51*, 5662. (c) Cao, Z.-Y.; Wang, X.; Tan, C.; Zhao, X.-L.; Zhou, J.; Ding, K. *J. Am. Chem. Soc.* **2013**, *135*, 8197. (d) Awata, A.; Arai, T. *Synlett* **2013**, *24*, 29. (e) Cao, Z.-Y.; Zhou, F.; Yu, Y.-H.; Zhou, J. *Org. Lett.* **2013**, *15*, 42.

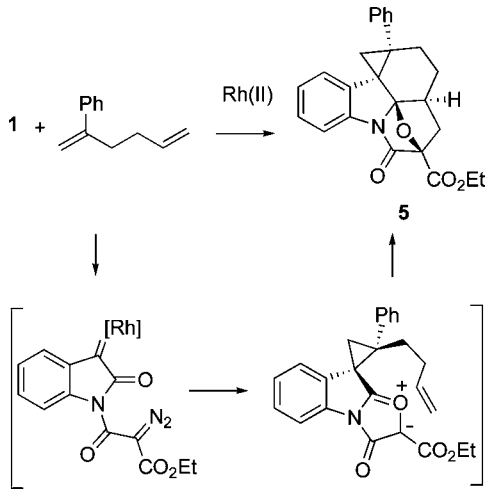
(10) Assignment of the phenyl group as having a *trans* relationship with the imide carbonyl in **2a** was made based on the anisotropic shielding of the proton at the 4-position of the indolinone (δ5.92) by the proximal phenyl group.

(11) (a) Padwa, A. *Chem. Soc. Rev.* **2009**, *38*, 3072. (b) Padwa, A. *Tetrahedron* **2011**, *67*, 8057.

(12) (a) England, D. B.; Eagan, J. M.; Merey, G.; Anac, O.; Padwa, A. *Tetrahedron* **2008**, *64*, 988. (b) Li, H.; Cheng, B.; Boonnak, N.; Padwa, A. *Tetrahedron* **2011**, *67*, 9829.

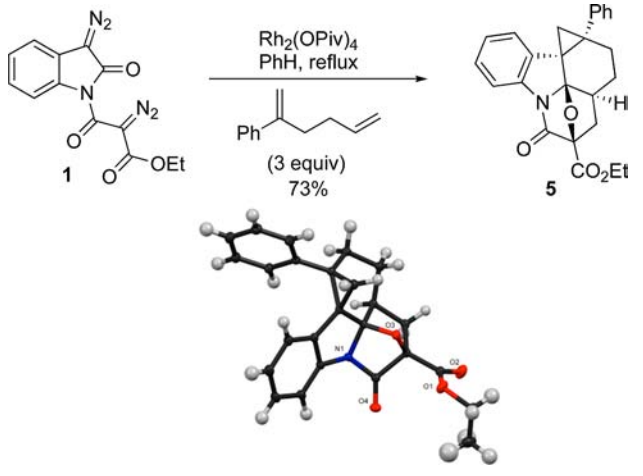
support that the dipolar cycloaddition reaction occurs after the cyclopropanation.

Scheme 3. Proposed Cyclopropanation/Intramolecular Cycloaddition Sequence



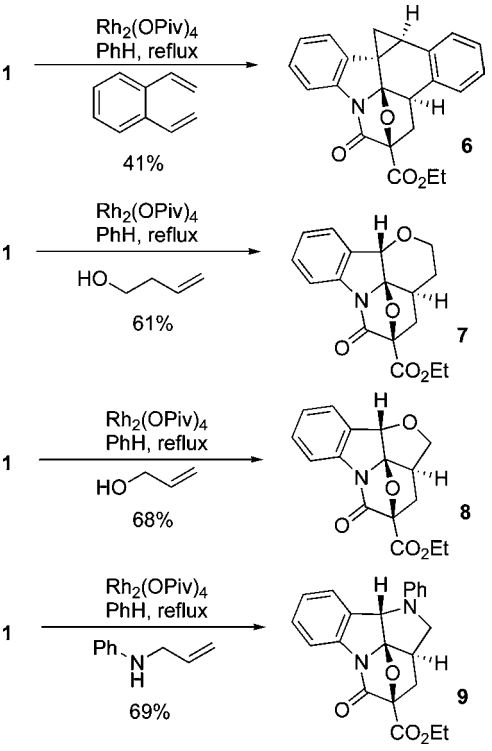
Indeed, the reaction of **1** with the bifunctionalized diene resulted in the formation of adduct **5** as a single diastereomer in 73% yield (Scheme 4). The relative stereochemistry of **5** was determined by X-ray crystallographic analysis. Not only does this result demonstrate that selective diazo decomposition can be achieved at elevated temperatures, but the overall reaction also demonstrates that a complex azapolyclic structure containing four new rings and five stereogenic centers occurs with complete diastereoselectivity from an easily accessible precursor in a single operation.

Scheme 4. Tandem Cyclopropanation/Intramolecular Cycloaddition of **1**



With this encouraging result in hand, we next surveyed a selection of additional reaction partners using *bis*(diazo) **1** (Scheme 5). The smooth reaction of **1** with *o*-divinylbenzene indicates that an aryl group can also function as the tethering group, giving **6** in 41% yield. Insertion of the diazo group into an XH group (X = O or N) was also compatible with the tandem process. Insertion/cycloaddition of **1** with homoallyl alcohol and allyl alcohol afforded the six- and five-membered ring ethers **7** and **8** in 61% and 68% yield, respectively. NH insertion of **1** with *N*-allylaniline furnished **9** in 69% yield. In the XH insertion reactions, it was best to use only 1 equiv of the alcohol or amine, and the catalyst loading was doubled to 1 mol % in the case of *N*-allylaniline so as to ensure complete consumption of the intermediate NH insertion product. Each of the resulting adducts was isolated as a single diastereomer.

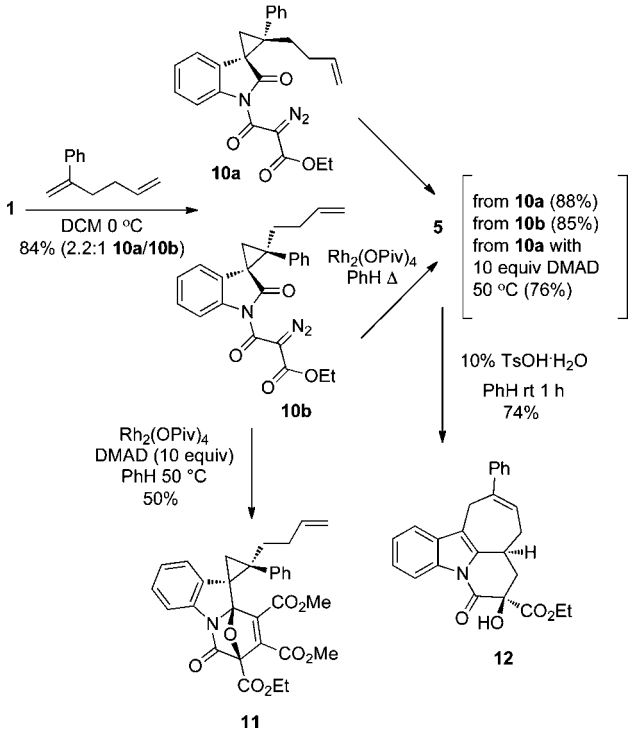
Scheme 5. Survey of Bifunctional Reaction Partners



It is interesting to note that divinyl benzene is an efficient reaction partner, since the aryl substituent present on the cyclopropane ring should be located in a *trans* relationship to the 1,3-dipole, in contrast to the stereochemistry necessary for the cycloaddition. Consequently, we further examined the cyclopropanation reaction of *bis*(diazo) **1** with 2-phenyl-1,5-hexadiene so as to gain some insight into this apparent anomaly (Scheme 6). When the cyclopropanation reaction was conducted at 0 °C, two diastereomeric cyclopropanes (i.e., **10a** and **10b**) were formed with a combined yield of 84% in a 2.2:1 ratio, in contrast to the apparent selectivity observed in the tandem reaction. The stereochemistry of the diastereomers was assigned based on the upfield shift of the proton at the 4-position of the indolinone ring for the *trans* isomer **10a** (δ 5.50) due to anisotropic shielding by the *cis* phenyl substituent.

Diastereomer **10a** gave the expected cycloadduct **5** in good yield on exposure to the rhodium(II) catalyst.

Scheme 6. Stereoconvergent Production of **5** and Isomerization to **12**



Interestingly, the *cis* diastereomer **10b** also produced **5** in comparable yield. This requires isomerization about the cyclopropane ring[13] prior to cycloaddition. Support for this isomerization was obtained by carrying out the reaction at 50 °C with added DMAD (10 equiv). Compound **10a** underwent intramolecular cycloaddition with the unactivated π-bond at a faster rate than the bimolecular reaction with DMAD, producing only adduct **5** with no evidence for trapping of the 1,3-dipole with DMAD. In contrast, compound **10b** gave only the bimolecular cycloadduct **11**, thereby indicating that cyclopropane isomerization is necessary for the subsequent intramolecular cycloaddition and that it occurs at a slower rate than the bimolecular cycloaddition with DMAD. We assume that a similar isomerization is responsible for the formation of cycloadduct **6**.

The bridging oxygen group in **5** was easily cleaved in the presence of catalytic acid to give alcohol **12** (Scheme 6). Although loss of the more acidic methylene proton could lead to a presumably more thermodynamically stable conjugated olefin, only structure **12** containing the nonconjugated π-bond was isolated from the reaction mixture. This is consistent with a concerted deprotonation/cyclopropane ring opening and can be attributed to the alignment of the CH bond with the breaking C−C bond in the cyclopropane ring, as can be seen by an examination of the X-ray crystal structure of **5** (Scheme 4).

In conclusion, we have demonstrated that the Rh(II)-catalyzed transformations of a D/A substituted diazo moiety occurs preferentially without affecting the second A/A substituted diazo group present in the same molecule. Furthermore, tandem cascade reactions of the two diazo functionalities can also be performed selectively even at elevated temperatures to give polycyclic structures with excellent control over both chemo- and diastereoselectivity. Further studies with related systems will be reported in due course.

Acknowledgment. We greatly appreciate the financial support provided by the National Science Foundation (CHE-1057350). We would like to thank Marika Wieliczko and the X-ray Crystallography Center at Emory University for X-ray crystallographic analysis of compound **5**.

Supporting Information Available. Experimental procedures for preparation and characterization data for all new compounds, including X-ray crystallographic data for **5**. This material is available free of charge via the Internet at http://pubs.acs.org.

(13) (a) Salomon, R. G.; Salomon, M. F.; Kachinski, J. L. C. *J. Am. Chem. Soc.* **1977**, *99*, 1043. (b) Williams, J. L.; Rettig, M. F. *Tetrahedron Lett.* **1981**, *22*, 385. (c) Doyle, M. P.; van Leusen, D. *J. Org. Chem.* **1982**, *47*, 5326. (d) von der Saal, W.; Quast, H. *J. Org. Chem.* **1995**, *60*, 4024.

The authors declare no competing financial interest.