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Catalytic enantioselective synthesis of azacycloalkenes via intermolecular rhodium carbenoid C–H insertion/ring-closing metathesis sequence

Mark C. McMills, Ross J. Humes, Oksana M. Pavlyuk *

Department of Chemistry and Biochemistry, 377 Clippinger Laboratories, Ohio University, Athens, OH 45701, USA

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ABSTRACT

Enantiomerically enriched cyclopropanes and products of C–H insertion reactions were obtained in excellent combined yields and enantioselectivities as a consequence of rhodium-catalyzed decomposition of vinyl diazoacetate in the presence of *tert*-butoxycarbonyl-(Boc)-protected amines as trapping agents. A series of enantiomerically enriched six- to eight-membered nitrogen-containing heterocycles were subsequently prepared via ring-closing metathesis of the dienes catalyzed by ruthenium benzylidene complex.

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Development of new methods for the synthesis of structurally advanced intermediates of the general type **A** and **B** (Fig. 1) is significant to synthetic organic chemists since such heterocyclic scaffolds are present in a variety of alkaloids and biologically active molecules.[1] Ring-closing metathesis (RCM) is considered one of the key reactions for the construction of carbo- and heterocyclic compounds of various ring sizes.[2] In combination with other reaction processes, such as C–H[3] or X–H (X = N, O)[4] insertion, RCM has become one the most powerful techniques available for the construction of highly functionalized heterocyclic rings.

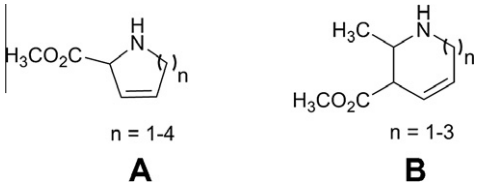

Figure 1. Nitrogen-containing heterocyclic scaffolds.

In our previous Letter we reported racemic synthesis of a series of five- to eight-membered heterocycles of type **A** via a tandem N–H insertion/RCM sequence.[5] Based on those preliminary results, we have expanded this methodology to include a similar carbenoid insertion into the C–H bond of a methylene carbon α to the nitrogen followed by RCM to afford azacycloalkenes of the type **B** in good overall yields and excellent enantioselectivities. Regioselective C–H activation next to the nitrogen atom was first reported by Davies and Venkataramani,[6] where the authors described an unprecedented, selective carbenoid insertion into a methyl C–H bond in deference to the electronically favorable allylic C–H bond. Based on this seminal study, we decided to test the chemo- and regioselectivity of the acceptor/donor carbenoid derived from vinyldiazoacetate with a series of simple *N*-Boc-protected ethyl amines. Specifically, we wanted to determine which of the two methylenes α to the nitrogen would be prone to C–H activation. For this purpose, we prepared a series of alkenyl amines **1a–d** (Scheme 1) using a straightforward two-step synthetic sequence involving Boc-protection of the commercially available allyl- and butenylamines followed by alkylation with iodoethane in the presence of NaH.[7] Pentenyl- and hexenylamines were prepared from the corresponding nitriles by reduction with LAH.[8] The choice of nitrogen protecting group was influenced by the findings of Davies and Venkataramani,[6] where it has been determined that changing the nitrogen protecting group from Boc to Cbz does not alter the yields or the regioselectivity of the C–H insertion. However, in the same study it has been demonstrated that changing the nitrogen protecting group from Boc to Fmoc or Teoc results in the significantly lower reaction yields. For these reasons, we have decided to protect the nitrogen as a *tert*-butyl carbamate in our study.

The electron acceptor/electron donor α-diazocarbonyl **2** developed by Davies et al. was prepared in two steps from the commercially available *trans*-styryl acetic acid through Fischer esterification followed by diazo transfer with *p*-acetamidobenzenes ulfonyl azide (*p*-ABSA), and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU).[9] Excellent yields of the methyl styryldiazoacetate were obtained provided the crude reaction

* Corresponding author.
E-mail address: op387905@ohio.edu (O.M. Pavlyuk).

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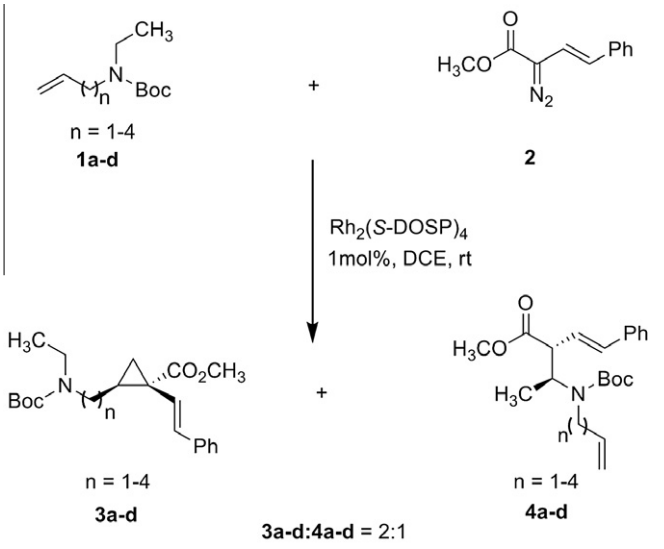


Scheme 1. Rh_2(*S*-DOSP)$_4$-catalyzed decomposition of vinyldiazoacetate **2**.

mixture was quickly filtered through a short plug of silica and avoiding heating by removing the solvent under reduced pressure at ⩽20 °C. Moreover, a freshly prepared solution (0.1 M in dichloroethane) of the α-diazocarbonyl substrate was immediately added via cannula to a solution of *N*-Boc ethyl alkenylamine and Rh_2(*S*- or *R*-DOSP)$_4$ in order to avoid the undesired electrocyclization of the vinyldiazoacetate **2** to the 3*H*-pyrazole.[10] Interestingly, the insertion reaction provided mixtures of cyclopropanes **3a–d** in addition to the C–H insertion products **4a–d** in a 2:1 ratio. This product distribution was unaffected by the choice of the rhodium catalyst ($Rh_2(OAc)_4$, $Rh_2(pfb)_4$, $Rh_2(TFA)_4$, $Rh_2(TPA)_4$) or solvent variation (hexanes, benzene). Observed chemoselectivity is in stark contrast to our previous findings, where no stereoselective cyclopropanation or C–H insertion took place with the same vinyldiazoacetate/chiral catalyst system and using *N*-Boc alkenyl amines as trapping agents.[5] Instead, only racemic N–H insertion products were isolated, leading to a conclusion that N–H insertions are mechanistically different processes from C–H insertions and cyclopropanations. N–H insertions can be thought to proceed via ylide-like intermediates, where decomplexation of the chiral catalyst from the active intermediates is likely. Alternatively, this transformation may proceed through an early transition state, where bond formation between the reacting species may occur at greater distances from each other, and little or no influence of the chiral catalyst is observed. This early transition state may be a result of greater polarization of the N–H bond in comparison to the C–H bond. Therefore, nitrogen is a better nucleophile and competing processes such as cyclopropanation are suppressed resulting in a highly chemoselective transformation. In contrast, C–H insertion and cyclopropanation reactions can be viewed as concerted 3-bond processes. As a result of lower bond polarity, C–H bonds and olefins are weaker nucleophiles, and the presence of the neighboring electron-donating groups such as nitrogen is necessary to stabilize the positive charge buildup at the site undergoing insertion. However, this low bond polarity may result in a later transition state allowing the chirality transfer from the catalyst to the newly forming bond of the reacting species. This transfer of chiral information is possible if the bond breaking and new bond formation with the carbene carbon proceeds at the same time as the ligated rhodium catalyst dissociates.[11]

Complete consumption of vinyldiazoacetate **2** resulted in the combined product yields of 82–96% and both the cyclopropanes **3a**–**d** and the C–H insertion products **4a**–**d** were formed essentially as single diastereomers with high enantioselectivity as determined by chiral HPLC analysis (Table 1). The relative stereochemistry of the isolated products was determined by ^{1}H–^{1}H NOESY. Since no H–C–C–H correlation was observed for the methyl hydrogens α to the nitrogen and the styryl hydrogens in **4a**, these substituents were assigned to be *trans* to one another. Moreover, the crosspeak between the methines α to the nitrogen and α to the ester in **4a** indicated the *cis* relationship for these hydrogens. NOESY analysis showed a direct correlation of the styryl hydrogens and the hydrogens of the methylene α to the nitrogen in **3a**, indicating a *cis* relationship between these two substituents. Most interesting, however, was that no C–H insertion occurred at the methylene of the alkenyl chain, resulting in highly regioselective C–H activation of the ethyl methylene. Since the two methylenes α to the nitrogen are both electronically activated, the regioselective reactivity of the ethyl methylene may be a result of the acceptor/donor rhodium carbenoid's steric demand as described by Davies and Venkataramani.[6] That is, vinylcarbenoid–rhodium tetraprolinate complex adopts a very specific conformation, resulting in a restricted approach of the corresponding trapping agent and a highly specific transition state characteristic of stereoselective transformations. No C–H insertion was observed at the methyl position of the ethyl substituent, likely a result of C–H bond β to the nitrogen not being electronically activated.

With dienes **4a**–**d** in hand, the C–H insertion products were then treated with second generation Hoveyda–Grubbs catalyst in refluxing DCE, resulting in the rapid cyclization of the dienes to produce the corresponding azacycloalkenes **5a–c** (Scheme 2) as a mixture of Boc-rotamers in 95–98% isolated yields and 92–95% ee (Table 2). No nine-membered ring was isolated when **4d** was subjected to the RCM conditions described above. Alternate reaction conditions (Grubbs I or Grubbs II catalysts, DCM, rt) did not change the reaction outcome, with polymerized dienes obtained in each case. Although five- to eight-membered rings can be easily obtained via RCM, 9- and 10-membered rings are notoriously more difficult to make.[2] A similar trend was observed in our case, where six- to eight-membered nitrogen heterocycles were formed with relative ease and in excellent yields and the nine-membered ring did not form at all. Highly functionalized compounds **5a**–**c** can lend themselves to further structural elaboration.

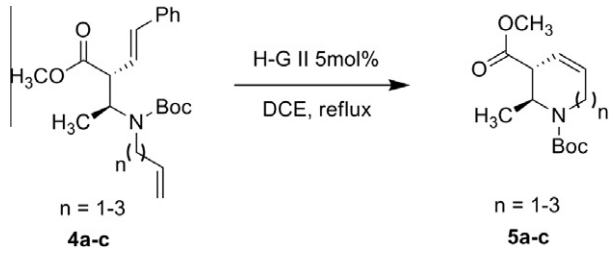
One-pot protocol for the synthesis of azacycles of the general type **B** described in our previous report[5] was attempted; however, only complex mixtures of products were obtained. This may be due to the competing cyclopropanation reaction, which complicates the subsequent metathesis step by allowing cross-metathesis to take place in addition to the desired intramolecular process.

We have addressed the stereoselective synthesis of various azacycloalkenes in a highly regio-, diastereo-, and enantioselective fashion by employing α-diazocarbonyl insertions into the activated C–H bonds followed by RCM. Additionally, interesting chemoselectivity trends of the acceptor/donor rhodium carbenoid were observed. In contrast to the N–H insertion, where no

Table 1
Rh_2(*S*-DOSP)$_4$-catalyzed decomposition of vinyl diazoacetate **2**

Product	Yield[a] (%)	de[b] (%)	ee[c] (%)
3a	64	95	96
3b	61	98	92
3c	59	98	95
3d	55	98	92
4a	32	90	92
4b	30	94	90
4c	28	98	85
4d	27	98	83

[a] Isolated yield after chromatography.
[b] Determined by ^{1}H NMR of crude material.
[c] Determined by chiral HPLC on a (*R*,*R*)-Whelk-O 1 column.



Scheme 2. Ruthenium-catalyzed ring-closing metathesis of C–H insertion products **4a–c**.

Table 2
RCM of the C–H insertion products **4a–d**

Product	Yield[a] (%)	de[b] (%)	ee[c] (%)
5a	98	>98	93
5b	96	>98	95
5c	95	>98	92
5d	[d]	—	—

[a] Isolated yields after chromatography.
[b] Determined by ^{1}H NMR of crude material.
[c] Determined by chiral HPLC on a (*R*,*R*)-Whelk-O 1 column.
[d] Not isolated.

cyclopropanation products were detected,[5] alkene addition predominates with respect to C–H insertion. Finally, while no enantioselectivity was observed for the N–H insertion, the identical conditions for the rhodium catalyst and acceptor/donor diazocarbonyl result in the isolation of cyclopropanes and C–H insertion products in high diastereo- and enantiomeric excess. Given these findings, synthetic task becomes finding a catalyst system that would combine chemoselectivity of the N–H insertions with stereoselectivity of the C–H insertions.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.12.019.

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