JOC The Journal of Organic Chemistry

Article

pubs.acs.org/joc

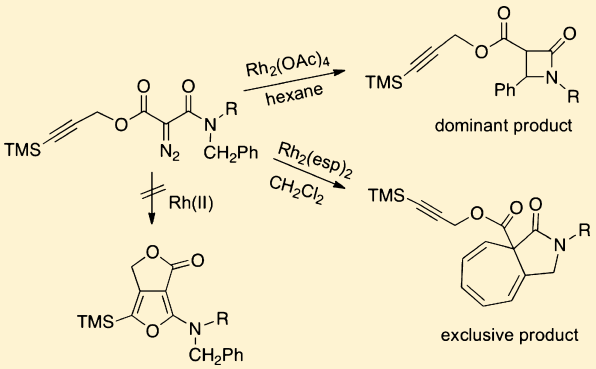
Solvent and Ligand Effects Associated with the Rh(II)-Catalyzed Reactions of α-Diazo-Substituted Amido Esters

Albert Padwa* and Yan Zou

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

Supporting Information

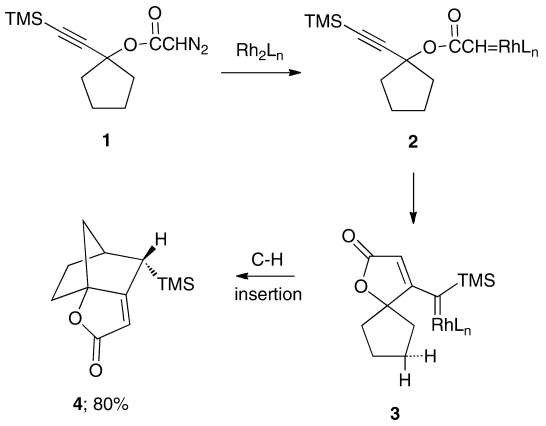
ABSTRACT: We report a detailed investigation into the Rh(II)-catalyzed reactions of 2-alkynyl 2-diazo amido-substituted esters. The distribution of products was found to be dependent on the substituent group on the nitrogen atom, the ligand on the Rh(II) center, and the solvent used. The dominant product obtained from the reaction of 3-(trimethylsilyl)prop-2-ynyl-2-(dibenzylcarbamoyl)-2-diazoacetate (**34**) with $Rh_2(OAc)_4$ in hexane corresponds to an azetidinone derived by CH-insertion of the carbenoid into the neighboring benzyl group. In contrast, the $Rh_2(esp)_2$-catalyzed reaction of **34** in CH_2Cl_2 afforded a 3-oxocyclohepta[*c*]pyrrole formed by cyclopropanation of the rhodium carbenoid across the aromatic π-bond. Related systems were studied, and CH-insertion into an adjacent alkyl group was found to be the dominant or exclusive pathway. In none of the cases studied was it possible to detect products derived from a carbenoid/alkyne cascade sequence as had previously been found with a series of 2-alkynyl-2-diazo-3-oxobutanoates.



INTRODUCTION

The intramolecular reactions of metal−carbene complexes derived from α-diazo carbonyl compounds have been extensively studied from both a mechanistic and synthetic viewpoint.[1−3] Rhodium carboxylates are particularly effective catalysts for the decomposition of diazo compounds, and many chemical syntheses are based on this methodology.[4] Among the more synthetically useful processes of the resulting carbenoid intermediates are intramolecular CH-insertion,[5] cyclopropanation,[6] and ylide generation.[7] In recent years, some attention has also been focused on the intramolecular cyclization of α-diazo carbonyl compounds containing tethered alkynes using transition-metal catalysts.[8,9] An interesting example of this type of reaction has recently been reported by May and involves a carbenoid cascade that constructs bridged bicyclic systems from alkynyl diazoesters (Scheme 1).[10]

Scheme 1



The mechanistic details of the diazocarbonyl/alkyne cyclization has been the subject of some study. In an early report, Hoye and Dinsmore demonstrated that the distribution of products was markedly dependent on the nature of the metal catalyst used.[8b] Thus, treatment of α-diazo ketoester **5** with catalytic palladium(II) acetoacetonate produced cyclopropane **6** in 78% yield, while the reaction with rhodium(II) acetate provided furan **7** in 56% yield (Scheme 2). Furan **7** arises from a 1,5-electrocyclization of the initially produced vinyl carbenoid intermediate onto the adjacent carbonyl group. The fact that the chemistry of **5** is catalyst dependent suggests that a metalated species is involved in the product-determining step.

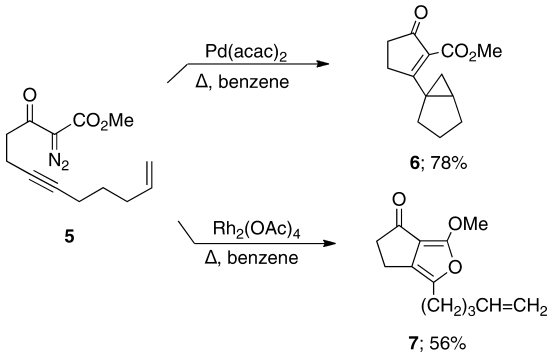
A series of investigations by our own research group showed that the exact pathway followed is often dependent on the specific metal/ligand employed and is also influenced by the nature of the solvent.[8] The resulting cyclized carbenoid intermediate **10** was found to undergo a wide assortment of reactions including cyclopropanation, 1,2-hydrogen migration, CH-insertion, addition to a tethered alkene, and ylide formation (Scheme 3).

Introduction of a heteroatom (i.e., X = oxygen or nitrogen) α to the diazo carbonyl group followed by reaction with a rhodium(II) catalyst led to fused furanyl systems which could be further induced to undergo an intramolecular [4 + 2]-

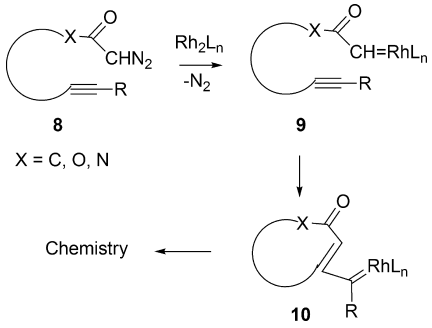
Received: December 2, 2014
Published: January 5, 2015

DOI: 10.1021/jo502725d
J. Org. Chem. 2015, 80, 1802−1808

Scheme 2

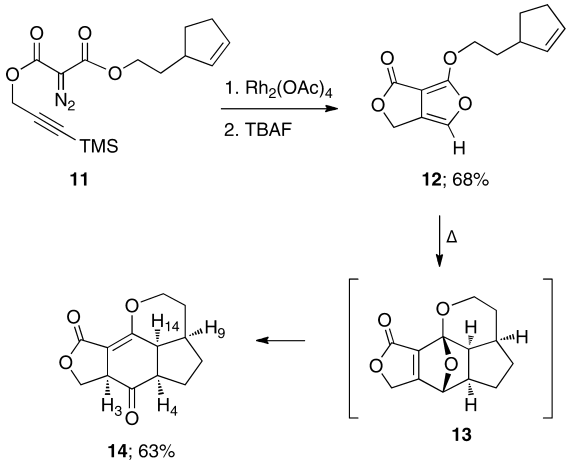


Scheme 3



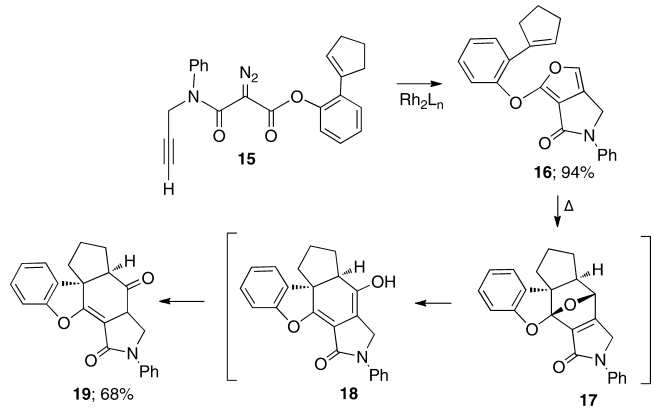
cycloaddition across a tethered π-bond.[9] For example, treatment of cyclopentenyl diazo ester **11** with rhodium(II) acetate at 80 °C in benzene followed by desilylation of the TMS group with TBAF gave furan **12** in 68% yield. Heating a sample of **12** at 145 °C in xylene afforded the tetracyclic product **14** in 63% yield. The initially formed Diels–Alder product **13** underwent ready oxabicyclic cleavage to produce the observed product (Scheme 4).

Scheme 4



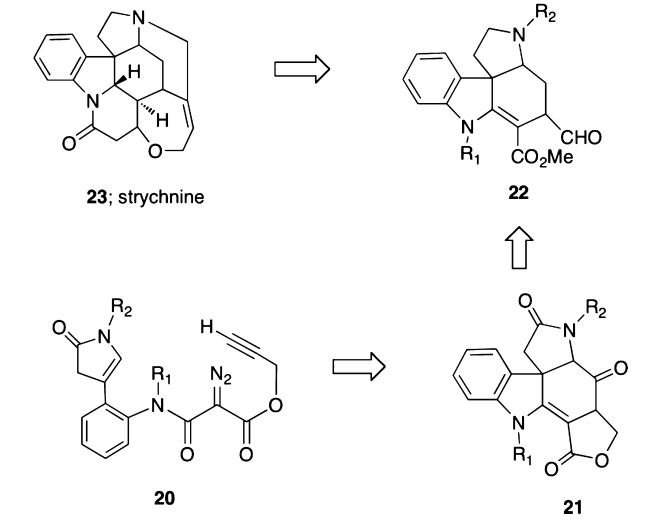
A related series of reactions was also observed when the diazo β-amino ester **15** was treated with a catalytic quantity of rhodium(II) perfluorobutyrate which afforded furan **16** in 94% isolated yield. Further heating of this furan at 145 °C furnished the novel pentacyclic product **19** as a single stereoisomer in 68% yield. Each of the bond-forming events is assumed to occur by the pathway outlined in Scheme 5.[9]

Scheme 5



To demonstrate the viability of this sequential cascade process as a practical strategy for the synthesis of complex heterocycles, we became interested in exploring the feasibility of this approach in the context of a total synthesis of strychnine (**23**).[11] The key step in our proposed synthesis would involve a sequential cyclization/IMDAF reaction[12] of a diazo-substituted amide (i.e., **20**) to furnish the rearranged cycloadduct **21** by a process similar to those outlined in Schemes 4 and 5. Lactone **21** would eventually be transformed into compound **22**, which had previously been converted into strychnine by Kuehne and Xu.[13] Thus, the formation of **22** from diazo amide **20** would constitute a formal synthesis of this challenging alkaloid (Scheme 6). With this in mind, we set out to examine a

Scheme 6



number of model systems to probe whether this sequence of cascade reactions[14] could be employed for an eventual synthesis of strychnine.

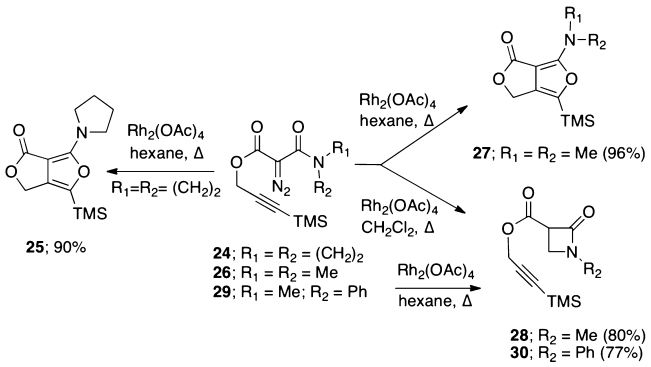
RESULTS AND DISCUSSION

To investigate the aforementioned strategy for an eventual synthesis of strychnine, we decided to more thoroughly study the Rh(II)-catalyzed behavior of several α-diazo amido esters containing alkynyl tethers. Our intention was to evaluate the efficiency of the initial cascade–cyclization reaction using various alkyl groups attached to the nitrogen atom. As was previously mentioned, we had observed that the related 2-

DOI: 10.1021/jo502725d
J. Org. Chem. 2015, 80, 1802–1808

alkynyl-2-diazo-3-oxobutanoate system proceeds by a reaction where the initially formed rhodium carbenoid undergoes addition to the acetylenic π-bond.[15] This results in the formation of an electrophilic vinyl carbenoid intermediate which subsequently reacts with the adjacent carbonyl oxygen bond. The resulting dipole undergoes a subsequent collapse to produce the substituted furan. Thus, exposure of diazoamides **24** and **26** to $Rh_2(OAc)_4$ in refluxing hexane produced furo[3,4-*c*]furans **25** and **27** in excellent yield.[9] In stark contrast to this result, the closely related *N*-phenyl-*N*-methyldiazoamide **29** afforded only azetidinone **30** (77%) when the reaction was performed employing similar catalytic conditions (Scheme 7).

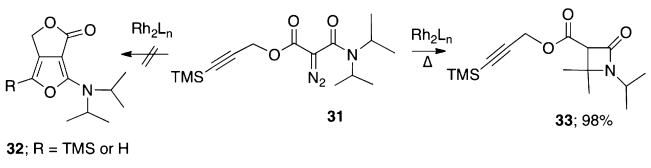
Scheme 7



The outcome of the Rh(II)-catalyzed reaction of the dimethylamido system **26** had been found to depend on the nature of the ligand group[16] attached to the metal as well as the solvent employed (i.e., **26** → **28** in CH_2Cl_2). We had previously suggested that the presence of an electron-withdrawing ligand (i.e., perfluorobutyrate) on the rhodium destabilizes the already electron-deficient carbenoid intermediate, thereby enhancing its overall reactivity with the electron-rich acetylenic π-bond. When a highly nonpolar solvent such as hexane is used, this also facilitates the electrocyclization pathway over the entropically more demanding 1,4-insertion route.

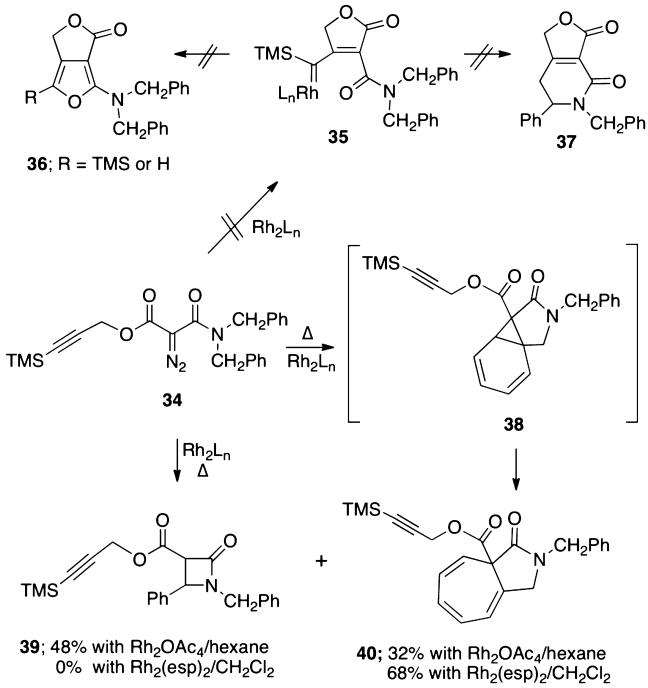
These earlier observations led us to examine a number of related diazoamido systems to help clarify the preferred reaction pathways. Reaction of the known 2-((3-trimethylsilyl)-prop-2-ynyloxy)carbonyl)acetic acid[9] with diisopropylamine followed by diazo transfer using *p*-nitrobenzensulfonyl azide[18] and triethylamine delivered diazoamide **31** in good yield. Exposure of **31** to $Rh_2(OAc)_4$ in refluxing benzene produced azetidinone **33** in 98% yield as the exclusive product (Scheme 8). No signs of furo[3,4-*c*]furan **32** could be detected in the crude reaction mixture. Changing the solvent to CH_2Cl_2 or using other ligand groups on the rhodium metal such as $Rh_2(esp)_2$ afforded the same product (i.e., **33**) in essentially the same yield.

Scheme 8



The CH-insertion reaction encountered with the Rh(II)-catalyzed reaction of **31** → **33** was extended to the related dibenzylamido system **34**. Decomposition under the standard conditions using $Rh_2(OAc)_4$ in hexane afforded none of the cyclized furan **36** nor the product derived from insertion of a cyclized carbenoid **35** into the benzylic position (i.e., **37**). Instead, two products were formed in a 5:3 ratio. The major product isolated in 48% yield was azetidinone **39**, derived by CH-insertion into one of the amido benzyl groups. The minor product corresponded to 3-oxocyclohepta[*c*]pyrrole **40** formed by an initial cyclopropanation of the transient carbenoid onto one of the aromatic rings to give **38** as a transient species (Scheme 9). A subsequent electrocyclization ring opening of **38**

Scheme 9



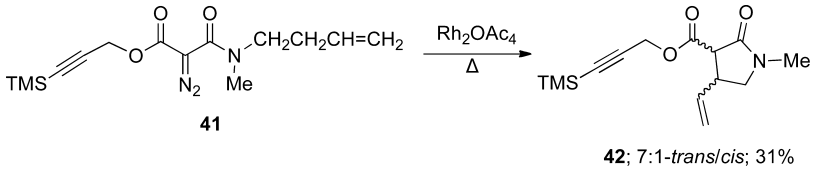
produced **40**. Interestingly, the product distribution was found to be markedly dependent on the ligand group attached to the rhodium metal and the solvent employed. Thus, when $Rh_2(esp)_2$[19] in CH_2Cl_2 was used, a clean transformation was observed and cycloheptatriene **40** was isolated in 68% yield, with no detectable quantities of azetidinone **37** being formed.

We next focused our attention on the $Rh_2(OAc)_4$-catalyzed reaction of the *N*-methyl-*N*-(but-3-enyl)-substituted diazoamide **41** in order to evaluate the chemoselectivity of the CH-insertion. In this case, insertion into the methyl group would produce an azetidinone as was encountered with diazoamides **31** and **34**. The alternate possibility would involve insertion into the allylic position of the but-3-enyl group giving rise to a 4-vinyl pyrrolidinone product. In fact, heating a sample of **41** with $Rh_2(OAc)_4$ as the catalyst in benzene afforded a 7:1 *trans*/*cis* mixture of **42** in only 31% yield together with several unidentifiable products. Careful examination of the crude reaction mixture revealed no detectable quantities of a β-lactam product. Thus, insertion into the more activated allylic position is the preferred pathway over what is generally the entropically more favorable 1,4-insertion pathway.

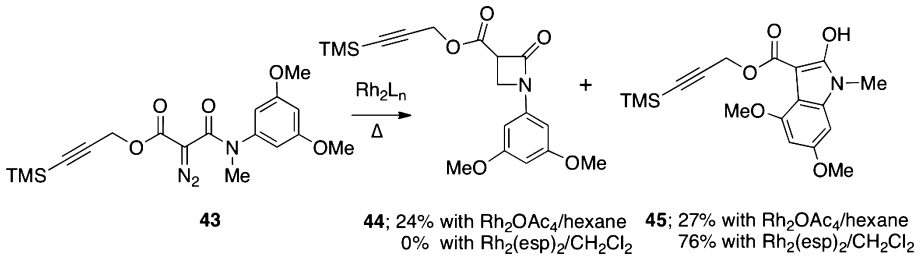
We subsequently studied the Rh(II)-catalyzed behavior of diazoamide **43** where both a methyl and an electron-rich aryl

DOI: 10.1021/jo502725d
J. Org. Chem. 2015, 80, 1802−1808

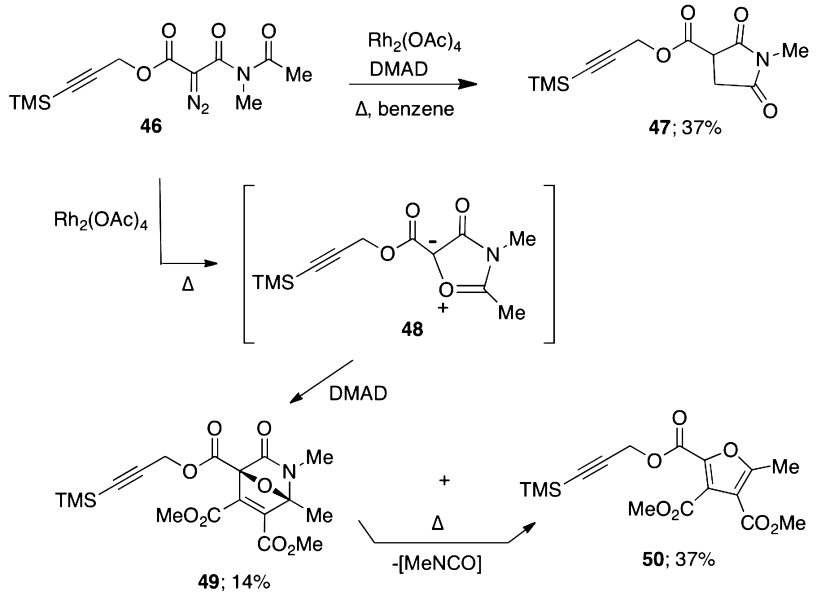
Scheme 10



Scheme 11



Scheme 12



group are attached to the nitrogen atom of the amide. Heating a sample of **43** in hexane at 80 °C with $Rh_2(OAc)_4$ as the catalyst afforded a 1:1-mixture of compounds **44** and **45** in 51% overall yield (Scheme 11). Structure **45** is derived by insertion of the rhodium carbenoid intermediate into the aryl C−H bond. Interestingly, when $Rh_2(esp)_2$ was employed as the catalyst with CH_2Cl_2 as the solvent, only compound **45** was formed and now in 76% yield. No trace of azetidinone **44** could be detected in the crude reaction mixture. The exact rationale to account for this ligand/solvent effect is not totally clear but may be related to a more favorable interaction of the rhodium carbenoid with the electron-rich aryl ring, thereby favoring CH-insertion into the aromatic ring.

Next, the chemoselectivity of the rhodium−carbenoid intermediate derived from 2-diazoacetate **46** was examined. Several possible modes of reaction are possible including (1) CH-insertion into the methyl group, (2) a metathesis type of reaction with the alkynyl group, and (3) cyclization onto the neighboring imido carbonyl group to provide an isomünchnone dipole.[20] We found that when **46** was heated at 80 °C in benzene in the presence of catalytic amounts of $Rh_2(OAc)_4$ and DMAD, three products were formed. In addition to 2,5-dioxopyrrolidine **47** (37%) originating from CH-insertion into the methyl group, two additional compounds were isolated (Scheme 12). The minor component **49** (14%) was assigned as the 1,3-dipolar cycloadduct derived by trapping of the expected isomünchnone **48** with DMAD. The other product corresponded to furan **50** (37%), which we assumed was formed by thermal loss of methyl isocyanate from **49**. Indeed, heating a pure sample of **49** in benzene at 80 °C for an additional 30 min gave **50** in essentially quantitative yield. No signs of any products emanating from an interaction of the carbenoid intermediate with the alkynyl group could be detected in the crude reaction mixture. Moreover, the distribution of products obtained from the Rh(II)-catalyzed reaction of **46** was not impacted by changing the ligand groups on the rhodium metal.

In conclusion, the Rh(II)-catalyzed reaction of several 2-alkynyl 2-diazo amido-substituted esters was investigated. The dominant products isolated from most of the systems studied corresponded to CH-insertion of the rhodium carbenoid into

DOI: 10.1021/jo502725d
J. Org. Chem. 2015, 80, 1802−1808

an adjacent alkyl group. In some cases, the product distribution was found to be sensitive to the ligand group on the rhodium metal or to the solvent employed. In none of the cases examined was it possible to detect products derived from a carbenoid/alkyne cascade sequence as had previously been found with a series of 2-alkynyl-2-diazo-3-oxobutanoates. It would seem as though subtle electronic and/or conformational effects play an important role in the ensuing chemistry.

EXPERIMENTAL SECTION

General Procedures. Melting points are uncorrected. Mass spectra were determined at an ionizing voltage of 70 eV. The mass analyzer type used for the HRMS measurenments was TOF with electrospray as the ionization method. Unless otherwise noted, all reactions were performed in flame-dried glassware under an atmosphere of either dry nitrogen or argon. All solvents were distilled prior to use. Solutions were evaporated under reduced pressure with a rotary evaporator, and the residue was chromatographed on a silica gel column (0.04−0.062 mm) using an ethyl acetate/hexane mixture as the eluent unless specified otherwise. All solids were recrystallized from ethyl acetate/hexane for analytical data. Yields refer to isolated, spectroscopically pure compounds. $Rh_2(OAc)_4$ and $Rh_2(esp)_2$ were acquired from commercial vendors.

3-(Trimethylsilyl)prop-2-ynyl-2-(diisopropylcarbamoyl)-2-diazoacetate (31). To a solution containing the known 2-((3-(trimethylsilyl)prop-2-ynyloxy)carbonyl)acetic acid[9] and diisopropylamine in DCM (4 mL) under argon was added DMAP (36 mg, 0.17 mmol) and DCC (386 mg, 1.87 mmol). The reaction mixture was stirred at rt for 20 h. The resulting suspension was filtered and washed with small amount of DCM. The filtrate was concentrated under reduced pressure, and the crude residue was subjected to silica gel chromatography to give 3-(trimethylsilyl)prop-2-ynyl 2-(diisopropylcarbamoyl)acetate as a white solid in 69% yield: mp 37−38 °C; IR (film) 2966, 2186, 1746, 1645, 1445, 1370, 1340, and 1250 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.14 (s, 9H), 1.18 (d, 6H, J = 6.8 Hz), 1.37 (d, 6H, J = 6.8 Hz), 3.44 (brs, 3H), 3.77 (sept, 1H, J = 6.8 Hz), and 4.71 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −0.2, 20.5, 20.9, 43.4, 46.3, 50.1, 53.6, 92.6, 98.7, 164.3 and 167.4.

To the above amido ester were added 4-nitrobenzenesulfonyl azide[18] (329 mg, 1.28 mmol) and TEA (0.36 mL, 2.57 mmol) under an argon atmosphere. The reaction mixture was stirred at rt for 24 h and was then added dropwise to 50 mL of hexane with stirring. The resulting precipitate that formed was filtered, and the filtrate was concentrated under reduced pressure. The crude residue was subjected to silica gel chromatography to give the titled compound **31** as a pale yellow liquid in 56% yield: IR (film) 2964, 2122, 1714, 1626, 1434, 1368, 1329, 1277, 1251, 1207, 1130, 1077 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.15 (s, 9H), 1.31 (d, 12H, J = 6.8 Hz), 3.85 (sept, 2H, J = 6.8 Hz), 4.75 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −0.3, 20.9, 49.4, 53.2, 66.6, 92.7, 98.6, 159.1, 162.3.

3-(Trimethylsilyl)prop-2-ynyl 1-Isopropyl-2,2-dimethyl-4-oxoazetidine-3-carboxylate (33). The above diazo amido ester **31** (29 mg, 0.084 mmol) was dissolved in 1.7 mL of benzene, and $Rh_2(OAc)_4$ (0.6 mg, 0.0014 mmol) was added under an argon atmosphere. The reaction mixture was heated at 80 °C for 30 min. After being cooled to rt, the mixture was filtered through a pad of silica gel and rinsed with a 2:1 mixture of hexane/EtOAc. The filtrate was concentrated under reduced pressure to give the titled compound **33** (26 mg, 98%) as a colorless liquid: IR (film) 2970, 2184, 1762, 1739, 1410, 1373, 1347, 1320, 1250, 1144 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.10 (d, 9H, J = 0.9 Hz), 1.28 (ddd, 6H, J = 6.9, 1.6, and 0.8 Hz), 1.37 (d, 3H, J = 0.9 Hz), 1.48 (d, 3H, J = 0.9 Hz), 3.54 (pd, 1H, J = 6.8 and 0.9 Hz), 3.65 (d, 1H, J = 0.9 Hz), 4.68 (dd, 2H, J = 9.9 and 0.9 Hz), ^{13}C NMR (100 MHz, $CDCl_3$) δ −0.3, 21.77, 21.83, 22.2, 27.5, 44.8, 53.2, 59.7, 63.3, 92.5, 98.7, 160.6, 166.7; HRMS calcd for $[C_{15}H_{26}O_3NSi + H^+]$ 296.1677, found 296.1675.

3-(Trimethylsilyl)prop-2-ynyl-2-(dibenzylcarbamoyl)-2-diazoacetate (34). A sample of 3-(trimethylsilyl)prop-2-ynyl-2-(dibenzylcarbamoyl)acetate was prepared from 2-((3-(trimethylsilyl)-prop-2-ynyloxy)carbonyl)acetic acid and dibenzylamine and was obtained as a colorless liquid in 86% yield: IR (film) 2955, 2925, 2186, 1746, 1652, 1495, 1444, 1363, 1319, 1249, 1148 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.18 (s, 9H), 3.60 (s, 2H), 4.44 (s, 2H), 4.65 (s, 2H), 4.77 (s, 2H), 7.16 (d, 2H, J = 7.6 Hz), 7.40−7.26 (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −0.2, 41.3, 48.6, 50.7, 53.9, 92.9, 98.5, 126.6, 127.7, 128.1, 128.3, 128.9, 129.3, 135.8, 136.7, 166.6, 167.0.

Diazo transfer of the above amido ester using standard diazo transfer methodology as described above afforded 3-(trimethylsilyl)-prop-2-ynyl-2-(dibenzyl-carbamoyl)-2-diazoacetate (**34**) as a yellow liquid in 75% yield: IR (film) 3031, 2958, 2926, 2361, 2304, 2181, 2132, 1713, 1629, 1496, 1454, 1419, 1387, 1290, 1251, 1204, 1094, 1076, 1030 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.18 (s, 9H), 4.02 (s, 4H), 4.81 (s, 2H), 7.18 (d, 4H, J = 6.8 Hz), 7.37−7.27 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −0.2, 50.6, 53.6, 67.2, 93.1, 98.5, 127.8, 128.0, 128.9, 136.3, 161.8, 162.2.

Rhodium(II) Catalyzed Reaction of 3-(Trimethylsilyl)prop-2-ynyl-2-(dibenzyl-carbamoyl)-2-diazoacetate (34). A mixture containing $Rh_2(OAc)_4$ (1.2 mg, 0.0028 mmol) was suspended in 1.5 mL of degassed hexane and was heated at 80 °C for 10 min. To this mixture was added dropwise a solution of diazo amido ester **34** (60 mg, 0.14 mmol) in 1.5 mL of benzene. The reaction mixture was heated at 80 °C for 30 min. After cooling to rt, the mixture was concentrated under reduced pressure and the crude residue was subjected to silica gel chromatography to give 27 mg (48%) of 3-(trimethylsilyl)-prop-2-ynyl 1-benzyl-2-oxo-4-phenylazetidine-3-carboxylate (**39**) as a colorless liquid; IR (film) 2959, 2361, 2186, 1770, 1735, 1497, 1455, 1370, 1249, 1186, 1153, 1057, 1029 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.15 (s, 9H); 3.80 (dd, 1H, J = 15.3 and 1.0 Hz), 3.96 (dd, 1H, J = 2.4 and 0.9 Hz), 4.74−4.65 (m, 2H), 4.91−4.78 (m, 2H), 7.18−7.12 (m, 2H), 7.25−7.20 (m, 5H), 7.35−7.25 (m, 3H), ^{13}C NMR (100 MHz, $CDCl_3$) δ −0.2, 44.9, 54.1, 57.1, 63.1, 77.6, 93.0, 98.2, 126.9, 127.9, 128.3, 128.9, 129.3, 134.6, 135.8, 162.0, 166.2; HRMS calcd for $[C_{23}H_{26}O_3NSi + H^+]$ 392.1676, found 392.1674.

In addition to azetidinone **39**, 18 mg (32%) of (4*Z*,6*Z*,8*E*)-3-(trimethylsilyl)prop-2-ynyl 2-benzyl-1,2,3,3*a*-tetrahydro-3-oxocyclohepta[*c*]pyrrole-3*a*-carboxylate (**40**) was obtained as a white solid: mp 100−101 °C; IR (film) 2957, 2185, 1752, 1700, 1652, 1496, 1477, 1428, 1361, 1250, 1183, 1109, 1053, 1028 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.13 (s, 9H), 3.98 (dd, 1H, J = 15.1 and 1.7 Hz), 4.27 (dd, 1H, J = 15.1 and 1.7 Hz), 4.44 (d, 1H, J = 14.9 Hz), 4.55 (d, 1H, J = 15.7 Hz), 4.60 (d, 1H, J = 15.7 Hz), 4.76 (d, 1H, J = 14.9 Hz), 5.71−5.58 (m, 1H), 6.30−6.19 (m, 1H), 6.57−6.37 (m, 3H), 7.42−7.18 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −0.1, 47.0, 50.3, 54.0, 60.0, 92.4, 98.7, 99.5, 121.0, 122.1, 128.1, 128.6, 128.8, 129.1, 130.0, 130.3, 135.6, 167.3, 170.8; HRMS calcd for $[C_{23}H_{26}O_3NSi + H^+]$ 392.1676, found 392.1674.

When the reaction of **34** was carried out under identical experimental conditions as described above, but in CH_2Cl_2 and using $Rh_2(esp)_2$ as the catalyst, only cycloheptatriene **40** was obtained in 68% yield.

3-(Trimethylsilyl)prop-2-ynyl-2-(*N*-(but-3-enyl)-*N*-methylcarbamoyl)-2-diazoacetate (41). A sample of 3-(trimethylsilyl)prop-2-ynyl-2-(*N*-(but-3-enyl)-*N*-methylcarbamoyl)acetate was prepared from 2-((3-(trimethylsilyl)prop-2-ynyloxy)carbonyl)acetic acid and *N*-methylbut-3-en-1-amine and was isolated as a colorless liquid in 71% yield: IR (film) 2926, 2335, 2186, 1747, 1651, 1452, 1403, 1366, 1319, 1250, 1154, 1052 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.17 (s, 9H), 2.36−2.29 (m, 2H), 2.96 (s, 1H), 2.99 (s, 2H), 3.33 (t, 1H, J = 7.6 Hz), 3.45 (t, 1H, J = 7.6 Hz), 3.50 (d, 2H, J = 6.4 Hz), 4.74 (s, 2H), 5.15−5.02 (m, 2H), 5. 80−5.68 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −0.2, 31.8, 32.8, 33.7, 36.4, 41.1, 41.7, 47.8, 50.3, 53.8, 53.9, 92.8, 98.6, 117.2, 118.4, 134.0, 135.3, 165.6, 165.7, 167.0, 167.1.

Diazo transfer of the above amido ester using standard diazo transfer methodology afforded the titled compound **41** as a yellow liquid in 73% yield which was used in the next step without further purification: IR (film) 2959, 2361, 2126, 1715, 1630, 1483, 1432, 1400, 1369, 1287, 1250, 1144, 1064 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.18 (s, 9H), 2.35 (q, 2H, J = 7.2 Hz), 2.98 (s, 3H), 3.44 (t, 2H, J = 7.2 Hz), 4.78 (s, 2 H), 5.05 (dd, 1H, J = 10.0 and 1.2 Hz), 5.10 (dd, 1H, J

DOI: 10.1021/jo502725d
J. Org. Chem. 2015, 80, 1802−1808

= 17.2 and 1.6 Hz), 5.83−5.71 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −0.2, 31.9, 36.4, 49.3, 53.4, 66.6, 92.9, 98.6, 117.4,134.8, 161.3, 161.6.

3-(Trimethylsilyl)prop-2-ynyl 1-Methyl-2-oxo-4-vinylpyrrolidine-3-carboxylate (42). The above diazo amido ester **41** (81 mg, 0.26 mmol) was dissolved in 2 mL of benzene and was heated to 80 °C while $Rh_2(OAc)_4$ (2.3 mg, 0.0052 mmol) was added under an argon atmosphere. The reaction mixture was stirred at 80 °C for 1 h. After being cooled to rt, the reaction mixture was concentrated under reduced pressure and the crude residue was subjected to silica gel chromatography to give **42** (23 mg, 31%) as a 7:1 *trans*/*cis* mixture of diastereomers that was isolated as a pale yellow liquid. The major isomer showed the following spectral properties: IR (film) 2957, 2360, 2185, 1744, 1698, 1497, 1432, 1403, 1374, 1324, 1250, 1164, 1116, 1053 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.17 (s, 9H), 2.88 (s, 3H), 3.18 (dd, 1H, J = 9.0 and 7.6 Hz), 3.35 (t, 1H, J = 9.0 Hz), 3.43 (qd, 1H, J = 7.6 and 1.2 Hz), 3.56 (dd, 1H, J = 11.2 and 8.0 Hz), 4.73 (d, 1H, J = 15.6 Hz), 4.82 (d, 1H, J = 15.6 Hz), 5.15 (d, 1H, J = 10.0 Hz), 5.20 (dt, 1H, J = 16.8 and 1.0 Hz), 5.80 (ddd, 1H, J = 20.0, 14.9, and 8.0 Hz), ^{13}C NMR (100 MHz, $CDCl_3$) δ −0.2, 30.1, 40.4, 40.8, 52.9, 53.3, 53.4, 54.0, 54.2, 92.7, 98.7, 117.8, 119.4, 133.6, 136.3, 168.8, 169.0; HRMS calcd for $[C_{14}H_{22}NO_3Si + H^+]$ 280.1364, found 280.1360.

3-(Trimethylsilyl)prop-2-ynyl-2-(*N*-(3,5-dimethoxyphenyl)-*N*-methylcarbam-oyl)-2-diazoacetate (43). A sample of 3-(trimethylsilyl)prop-2-ynyl-2-(*N*-(3,5-dimethoxy-phenyl)-*N*-methyl-carbamoyl)acetate was prepared from 2-((3-(trimethylsilyl)prop-2-ynyloxy)carbonyl)acetic acid and 3,5-dimethoxy-*N*-methylbenzen-amine and was obtained as a colorless liquid in 78% yield: IR (film) 2925, 2185, 1747, 1663, 1592, 1451, 1427, 1384, 1350, 1318, 1249, 1205, 1155, 1114, 1043 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.16 (s, 9H), 3.28 (s, 3H), 3.32 (s, 2H), 3.79 (s, 6H), 4.69 (s, 2H), 6.38−6.37 (m, 2H), 6.44 (t, 1H, J = 2.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ −0.2, 37.5, 41.3, 53.7, 55.7, 92.7, 98.6, 100.4, 105.5, 145.1, 161.7, 165.6, 167.3.

Diazo transfer of the above amido ester using standard diazo transfer methodology afforded the titled compound **43** as a yellow liquid in 90% yield which was used in the next step without further purification: IR (film) 2957, 2117, 1728, 1639, 1592, 1459, 1428, 1373, 1338, 1285, 1250, 1205, 1155, 1093, 1052 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.15 (s, 9H), 3.33 (s, 3H), 3.76 (s, 6H), 4.61 (s, 2H), 6.34 (brs, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −0.2, 38.9, 53.5, 55.7, 66.4, 66.6, 92.8, 98.6, 99.1, 104.5, 145.4, 161.4, 161.5.

Rhodium(II)-Catalyzed Reaction of 3-(Trimethylsilyl)prop-2-ynyl-2-(*N*-(3,5-dimethoxyphenyl)-*N*-methylcarbamoyl)-2-diazoacetate (43). A sample of $Rh_2(OAc)_4$ (0.8 mg, 0.00183 mmol) was suspended in 1 mL of degassed hexane and was heated at 80 °C for 10 min. A solution of the above diazo amido ester **43** (36 mg, 0.092 mmol) in 1 mL of hexane was added dropwise. The reaction mixture was heated at 80 °C for 30 min. After being cooled to rt, the reaction mixture was concentrated under reduced pressure and the crude residue was subjected to silica gel chromatography to give 9 mg (24%) of 3-(trimethylsilyl)prop-2-ynyl 1-(3,5-dimethoxyphenyl)-2-oxoazetidine-3-carboxylate (**44**) as a yellow oil: IR (film) 2959, 2358, 2185, 1766, 1738, 1597, 1481, 1461, 1431, 1369, 1324, 1235, 1206, 1155, 1022 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.19 (s, 9H); 3.84−3.74 (m, 7H), 3.95 (ddd, 1H, J = 6.0, 2.9, and 0.7 Hz), 4.24 (ddd, 1H, J = 5.7, 2.9, and 0.7 Hz), 4.76 (dd, 1H, J = 15.7 and 7.0 Hz), 4.87 (dd, 1H, J = 15.7 and 7.0 Hz), 6.25 (td, 1H, J = 2.2 and 0.6 Hz), 6.54 (dd, 2H, J = 2.2 and 0.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ −0.1, 41.9, 52.9, 54.3, 55.7, 93.3, 95.2, 96.9, 98.2, 139.5, 158.6, 161.5, 166.3, HRMS calcd for $[C_{18}H_{24}O_5NSi + H^+]$ 362.1424, found 362.1417.

In addition to azetidinone **44**, 10 mg (27%) of 3-(trimethylsilyl)-prop-2-ynyl 2-hydroxy-4,6-dimethoxy-1-methyl-1*H*-indole-3-carboxy-late (**45**) was obtained as a white solid: mp 141−143 °C; IR (film) 2857, 2357, 2184, 1748, 1703, 1646, 1629, 1592, 1535, 1508, 1453, 1437, 1346, 1309, 1248, 1209, 1179, 1153, 1130, 1108, 1039 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.20 (s, 6H), 3.81 (s, 3H), 3.88 (s, 3H), 3.95 (s, 3H), 4.97 (s, 2H), 6.08 (d, 1H, J = 1.8 Hz), 6.18 (d, 1H, J = 1.8 Hz), 8.90 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ −0.1, 32.2, 52.6, 55.7, 55.9, 84.1, 91.8, 92.8, 98.9, 102.3,107.2, 140.5, 150.3, 156.3, 162.2, 162.9; HRMS calcd $[C_{18}H_{24}O_5NSi + H^+]$ 362.1424, found 362.1416.

When the reaction of **43** was carried out under identical experimental conditions as that described above, but in CH_2Cl_2 and using $Rh_2(esp)_2$ as the catalyst, only indole **45** was obtained in 76% yield.

3-(Trimethylsilyl)prop-2-ynyl-2-(*N*-acetyl-*N*-methylcarbamo-yl)-2-diazoacetate (46). To a solution of 2-((3-(trimethylsilyl)prop-2-ynyloxy)carbonyl)acetic acid (364 mg, 1.7 mmol) in 12 mL of dry pentane were added oxalyl chloride (311 μL, 3.57 mmol) and DMF (13 μL, 0.17 mmol) under an argon atmosphere. The reaction mixture was stirred at rt for 20 h, and the pentane layer was decanted and concentrated under reduced pressure to afford a light yellow oil which was taken up in 6.5 mL of toluene. To this solution was added *N*-methylacetamide (91 μL, 1.18 mmol), and the solution was stirred at 80 °C for 4 h and then cooled to rt. The reaction mixture was diluted with 10 mL of ether and washed with a saturated $NaHCO_3$ solution followed by brine, dried over $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure, and the resulting oil was taken up in 6 mL of THF. To this solution were added MsN_3 (197 μL, 2.34 mmol) and TEA (652 μL, 4.68 mmol). The reaction mixture was stirred at rt for 16 h and concentrated under reduced pressure, and the crude residue was subjected to silica gel chromatography to give 310 mg (62%) of the titled diazo amido ester **46** as a pale yellow liquid which was used in the next step without further purification: IR (film) 2960, 2139, 1705, 1656, 1471, 1423, 1369, 1326, 1291, 1250, 1215, 1122, 1304 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.18 (s, 9H), 2.31 (s, 3H), 3.10 (s, 3H), 4.80 (s, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −0.2, 24.5, 33.9, 53.9, 93.5, 98.0, 159.9, 166.3, 172.7.

Rhodium(II)-Catalyzed Reaction of 3-(Trimethylsilyl)prop-2-ynyl-2-(*N*-acetyl-*N*-methylcarbamoyl)-2-diazoacetate (46). A sample of $Rh_2(OAc)_4$ (3 mg, 0.004 mmol) was suspended in 1 mL of degassed benzene together with DMAD (13 μL, 0.10 mmol), and the mixture was heated at 80 °C for 10 min. A solution of the above diazo amido ester **46** (30 mg, 0.10 mmol) in 1 mL of benzene was added dropwise, and the resulting mixture was heated at 80 °C for 50 min. After being cooled to rt, the reaction mixture was concentrated under reduced pressure and the crude residue was subjected to silica gel chromatography to give 10 mg (37%) of 3-(trimethylsilyl)prop-2-ynyl-1-methyl-2,5-dioxopyrrolidine (**47**) as a clear oil: IR (film) 2958, 2395, 2187, 1786, 1743, 1701, 1435, 1383, 1323, 1282, 1249, 1161, 1119, and 1031 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ and 0.19 (s, 9H); 2.95 (dd, 1H, J = 18.3 and 9.4 Hz), 3.04 (s, 3H), 3.12 (dd, 1H, J = 18.3 and 4.8 Hz), 3.85 (dd, 1H, J = 9.4 and 4.8 Hz), 4.76 (d, 1H, J = 15.7 Hz), 4.85 (d, 1H, J = 15.7 Hz), ^{13}C NMR (100 MHz, $CDCl_3$) δ −0.2, 25.7, 32.4, 46.4, 54.8, 93.7, 97.8, 167.1, 171.9 and 175.2; HRMS calcd for $[C_{12}H_{18}O_4NSi + H^+]$ 268.1000, found 268.0998.

In addition to dioxopyrrolidine **47**, 6 mg (14%) of (1*S*,4*R*)-2,3-dimethyl 4-(3-(trimethylsilyl)prop-2-ynyl) 1,6-dimethyl-5-oxo-7-oxa-6-azabicyclo[2.2.1]hept-2-ene-2,3,4-tricarboxylate (**49**) was isolated from the column as a clear oil: IR (film) 2957, 2359, 2185, 1727, 1608, 1564, 1442, 1407, 1373, 1327, 1294, 1250, 1222, 1151, 1099, 1085 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.15 (s, 9H), 1.96 (s, 3H), 2.80 (s, 3H), 3.81 (s, 3H), 3.85 (s, 3H), 4.89 (AB, 2H, J = 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ −0.2, 15.3, 28.1, 53.2, 53.4, 55.2, 90.2, 94.0, 97.4, 99.0, 145.4, 146.5, 162.0, 162.1, 162.4, 170.8; HRMS calcd for $[C_{18}H_{24}O_8NSi + H^+]$ 410.1266, found 410.1266.

The final fraction isolated from the chromatography column contained 14 mg (38%) of 3,4-dimethyl 2-(3-(trimethylsilyl)prop-2-ynyl) 5-methylfuran 2,3,4-tricarboxylate (**50**) and was obtained as a white solid: mp 62−63 °C; IR (film) 2955, 2187, 1723, 1607, 1563, 1443, 1409, 1374, 1326, 1293, 1249, 1219, 1186, 1152, 1097, 1057 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.19 (s, 4H), 2.67 (s, 1H), 3.85 (bs, 2H), 3.96 (bs, 2H), 4.88 (bs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −0.2, 14.5, 52.4, 53.3, 54.0, 93.4, 97.9, 114.3, 126.9, 138.6, 156.5, 162.2, 162.9, 163.6; HRMS calcd for $[C_{16}H_{21}O_7Si + H^+]$ 353.1051, found 353.1052.

Heating a pure sample of cycloadduct **49** in benzene at 80 °C for 30 min afforded furan **50** in quantitative yield.

DOI: 10.1021/jo502725d
J. Org. Chem. 2015, 80, 1802−1808

■ ASSOCIATED CONTENT

Supporting Information

^{1}H and ^{13}C NMR data of various key compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: chemap@emory.edu.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We greatly appreciate financial support provided by the National Science Foundation (CHE-1057350).

■ REFERENCES

(1) (a) Doyle, M. P. In *Comprehensive Organometallic Chemistry II*; Hegedus, L. S., Ed.; Pergamon: New York, 1995; Vol. *12*, Chapter 5.2, pp 919−939. (b) Doyle, M. P. *Chem. Rev.* **1986**, *86*, 919.

(2) Ye, T.; McKervey, M. A. *Chem. Rev.* **1994**, *94*, 1091.

(3) Padwa, A.; Weingarten, M. D. *Chem. Rev.* **1996**, *96*, 223.

(4) (a) Padwa, A.; Curtis, E. A.; Sandanayaka, V. P. *J. Org. Chem.* **1997**, *62*, 1317. (b) Dauben, W. G.; Dinges, J.; Smith, T. C. *J. Org. Chem.* **1993**, *58*, 7635. (c) Koyama, H.; Ball, R. G.; Berger, G. D. *Tetrahedron Lett.* **1994**, *35*, 9185.

(5) For leading references on C−H insertion, see: (a) Davies, H. M. L.; Lian, Y. *Acc. Chem. Res.* **2012**, *45*, 923. (b) Davies, H. M. L.; Morton, D. *Chem. Soc. Rev.* **2011**, *40*, 1857. (c) Davies, H. M. L.; Manning, J. R. *Nature* **2008**, *451*, 417. (d) Doyle, M. P.; McKervey, M. A.; Ye, T. *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds*; Wiley: New York, 1998. (e) Doyle, M. P.; Forbes, D. C. *Chem. Rev.* **1998**, *98*, 911. (f) Doyle, M. P. *Modern Rhodium-Catalyzed Organic Reactions*; Evans, P. A., Ed.; Wiley-VCH: Weinheim, 2005; pp 341−355.

(6) For leading references on cyclopropanation, see: (a) Davies, H. M. L.; Antoulinakis, E. G. *Org. React.* **2001**, *57*, 1. (b) Lebel, H.; Marcoux, J.-F.; Molinaro, C.; Charette, A. B. *Chem. Rev.* **2003**, *103*, 977. (c) Brackmann, F.; de Meijere, A. *Chem. Rev.* **2007**, *107*, 4538.

(7) For carbene-initiated ylide reactions, see: (a) Bur, S.; Padwa, A. *Modern Tools for the Synthesis of Complex Bioactive Molecules*; Arseniyadis, S., Cossy, J., Eds.; John Wiley & Sons: New York, 2012; Chapter 13, pp 433−484. (b) DeAngelis, A.; Panne, P.; Yap, G. P. A.; Fox, J. M. *J. Org. Chem.* **2008**, *73*, 1435.

(8) (a) Hoye, T. R.; Dinsmore, C. J.; Johnson, D. S.; Korkowski, P. F. *J. Org. Chem.* **1990**, *55*, 4518. (b) Padwa, A.; Xu, S. L. *J. Am. Chem. Soc.* **1992**, *114*, 5881. (c) Padwa, A.; Kassir, J. M.; Xu, S. L. *J. Org. Chem.* **1991**, *56*, 6971.

(9) Padwa, A.; Straub, C. S. *J. Org. Chem.* **2003**, *68*, 227.

(10) Jansone-Popova, S.; May, J. A. *J. Am. Chem. Soc.* **2012**, *134*, 17877.

(11) Woodward, R. B.; Cava, M. P.; Ollis, W. D.; Hunger, A.; Daeniker, H. U.; Schennker, K. *J. Am. Chem. Soc.* **1954**, *76*, 4749.

(12) For a review on intramolecular Diels−Alder reactions of furans (IMDAF), see: Padwa, A.; Flick, A. C. *Advances in Heterocyclic Chemistry*; Elsevier: New York, 2013, *110*, pp 1−41.

(13) Kuehne, M. E.; Xu, F. *J. Org. Chem.* **1993**, *58*, 7490.

(14) For a review on tandem cascade chemistry, see: (a) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115. (b) Tietze, L. F.; Beifuss, U. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 131. (c) Ho, T. L. *Tandem Organic Reactions*; Wiley: New York, 1992. (d) Bunce, R. A. *Tetrahedron* **1995**, *51*, 13103. (e) Parsons, P. J.; Penkett, C. S.; Shell, A. J. *Chem. Rev.* **1995**, *95*, 195.

(15) Padwa, A.; Dean, D. C.; Fairfax, D. J.; Xu, S. L. *J. Org. Chem.* **1993**, *58*, 4646.

(16) (a) Davies, H. M. L.; Saikali, E.; Clark, T. J.; Chee, E. H. *Tetrahedron Lett.* **1990**, *31*, 6299. (b) Davies, H. M. L.; Saikali, E.; Young, W. B. *J. Org. Chem.* **1991**, *56*, 5696. (c) Davies, H. M. L.; Clark, T. J.; Kimmer, G. *J. Org. Chem.* **1991**, *56*, 6440 [17].

(17) For a review of ligand effects on the Rh(II)-catalyzed reaction of α-diazo carbonyls, see: Padwa, A.; Austin, D. J. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1797.

(18) Bollinger, F. W.; Tuma, L. D. *Synlett* **1996**, 407.

(19) For $Rh_2(esp)_2$ (i.e., bis[rhodium(α,α,α′,α′-tetramethyl-1,3-benzenedipropionic acid)), see: Espino, C. G.; Fiori, K. W.; Kim, M.; Du Bois, J. *J. Am. Chem. Soc.* **2004**, *126*, 15378.

(20) (a) Osterhout, M. H.; Nadler, W. R.; Padwa, A. *Synthesis* **1994**, 123. (b) Hamaguchi, M.; Ibata, T. *Tetrahedron Lett.* **1974**, *15*, 4475. (c) Gillon, A.; Ovadia, D.; Kapon, M.; Bien, S. *Tetrahedron* **1982**, *38*, 1477. (d) Maier, M. E.; Schöffling, B. *Chem. Ber.* **1989**, *122*, 1081.

DOI: 10.1021/jo502725d
J. Org. Chem. 2015, 80, 1802−1808