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One-Step Synthesis of Nitrogen-Containing Medium-Sized Rings via α-Imino Diazo Intermediates

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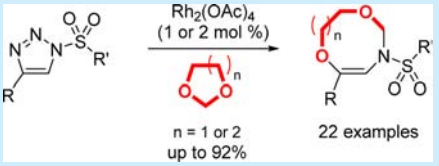
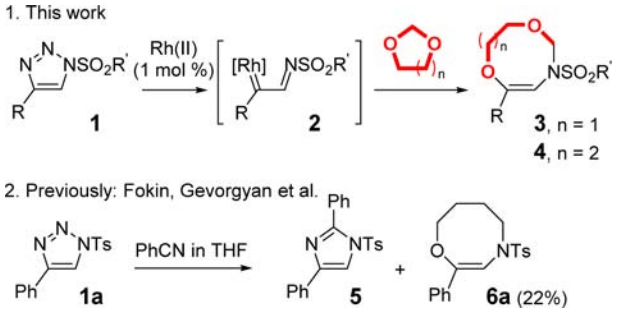
Supporting Information

ABSTRACT: Eight- and 9-membered dioxazocines and dioxazonines are readily synthesized starting from *N*-sulfonyl-1,2,3-triazoles in a single-step procedure. A perfect regioselectivity and generally good yields (up to 92%) are obtained under dirhodium catalysis using 1,3-dioxolane and 1,3-dioxane as solvents and reagents.



1,2,3-Triazoles are important building blocks used routinely in synthetic, biological, and medicinal chemistry.[1] These compounds are readily accessible through Huisgen 1,3-dipolar cycloaddition reactions.[2] Previously, it was shown that *N*-sulfonyl derivatives of type **1**, prepared from sulfonyl azides and terminal alkynes, decompose under thermal and/or metal-catalyzed conditions to afford electrophilic α-imino carbenes (e.g., **2**, Scheme 1, eq 1).[3,4] These intermediates undergo many interesting and original processes, from cyclopropanations to ylide forming reactions and subsequent transformations.[5,6] Herein, in a new development in this field, reactions of sulfonyl triazoles **1** with 1,3-dioxolane and 1,3-dioxane in the presence of $Rh_2(OAc)_4$ (1 or 2 mol %), are shown to generate unprecedented 8- and 9-membered dioxazocine and dioxazonine adducts. These medium-sized rings **3** and **4** are formed in generally good yields (up to 92%) and with a perfect regioselectivity.

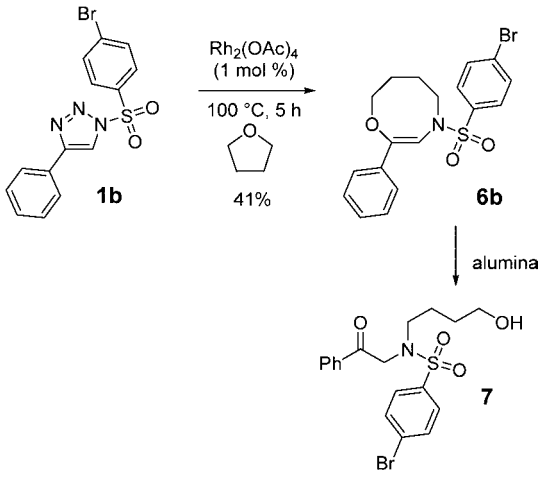
Scheme 1. Medium-Sized Ring Formation



As just mentioned, it is known that α-imino carbenes **2** react with Lewis bases to form reactive ylide intermediates that undergo further reactions including intermolecular condensations.[6i,7] For instance, when treated with nitriles, intermediates **2** react and form 1,3-imidazoles **5** in good yields and excellent selectivity (Scheme 1, eq 2).[7b] Interestingly, when the reaction was carried with triazole **1a** and PhC≡N in THF as solvent, 8-membered oxazocine **6a** derived from THF insertion was isolated (22%). This result raised our interest as the direct formation of medium-sized rings is not a trivial matter.[8,9] In addition, it has been shown that α-carbonyl analogues of intermediates **2** react with THF to form macrocycles rather than 8-membered rings.[10,11] It was then debatable whether a general medium-size ring synthesis could be achieved using *N*-sulfonyl-1,2,3-triazoles **1** and cyclic ethers; other reactants such as acetals being possibly better reactive partners for the formation of the 8- and 9-membered rings.[12]

Care was first taken to reproduce the THF insertion reaction in the absence of benzonitrile.[7b] A series of *N*-sulfonyltriazoles was prepared following a copper-catalyzed procedure.[13] It was found that compounds **1** are quite sensitive to light and/or acidic conditions.[14] Compound **1b** (R = Ph, R′ = *p*-BrC_6H_4) was more stable than others, and it was thus chosen for the initial trials using a catalytic amount of $Rh_2(OAc)_4$ (1 mol %, Scheme 2). High temperature (100 °C) was necessary to

Scheme 2. Reactivity of Triazole 1b in the Presence of THF



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achieve full conversion within 5 h. A single product **6b** was identified and isolated (41% yield). While satisfactory, this result led us to notice a sensitivity of compounds **6** to purification conditions; extended contact time on chromatographic phases leading to a rearrangement of products **6** into derivatives of type **7** (Scheme 2). In view of this intrinsic liability, it was decided to find an alternative reactivity that would still afford 8- and 9-membered heterocycles but with better yields and overall stability. Recently, it was shown that α-diazo-β-ketoesters react in the presence of catalytic amounts of $Rh_2(OAc)_4$ with cyclic acetals to form trioxocines and trioxonines.[12] These medium-sized rings were obtained in generally good yields (up to 90%) and displayed a surprisingly high stability. In view of this precedent, the reactivity of *N*-sulfonyl triazoles **1** with 1,3-dioxolane and 1,3-dioxane was considered.

In practice, after a few experiments made to determine the optimal conditions (see the Supporting Information), reactions were performed in dry 1,3-dioxolane as solvent by treatment of solutions of triazoles **1** (1.0 equiv) with $Rh_2(OAc)_4$ (1 mol %) (Scheme 3).[15,16] Complete consumption of **1b** was again achieved in 5 h at 100 °C. Analysis of the reaction mixture indicated the formation of one major product (**3b**, 92%). Based on detailed ^{1}H, ^{13}C, and IR analyses, only an original cyclic dioxazocine structure was consistent with the data, the motif being confirmed by X-ray diffraction studies (Figure 1). With this result in hand, the influence of the sulfonyl group on the reactivity was investigated. Triazole **1c** carrying also an electron-withdrawing group (R′ = *p*-$NO_2C_6H_4$, Scheme 3) was found to react under the same conditions and afforded desired product **3c**; the moderate solubility of **1c** in 1,3-dioxolane being probably the reason for the moderate yield (64%). Triazoles with donating groups on the sulfonyl moiety were also tested. Substrates **1a**, **1d**, **1e**, **1f**, and **1g** were all reactive, and reactions proceeded generally well (76−85% yields). Clearly, steric hindrance does not perturb the reactivity as products **3e** and **3f** were obtained in 77 and 85% yields, respectively (R′ = mesityl, 1-naphthyl). The phenyl group at carbon-4 of triazoles **1** was also modified. Substrates **1h**, **1i**, and **1j** afforded the corresponding products in good to excellent yields (78−91%); the nature of the substituent (Me, CF_3) on the aromatic moiety or the presence of a vinylic group have little influence on the outcome.

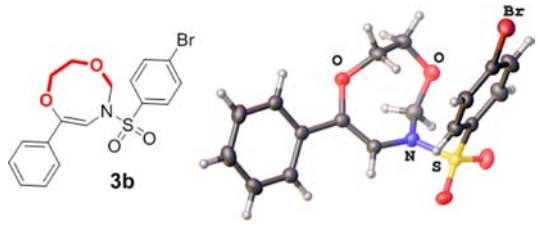


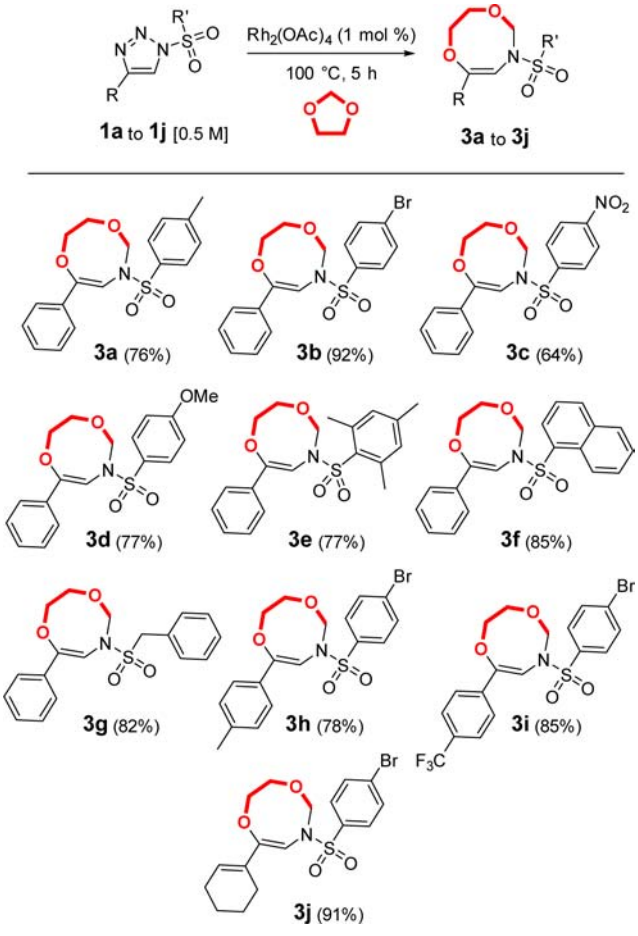
Figure 1. Anisotropic displacement ellipsoids plot of the crystal structure of **3b**. Thermal ellipsoids are drawn at 50% probability.

Then, reactions with **1a−j** were repeated in dry 1,3-dioxane as solvent to afford products of type **4** (Scheme 4). It was, however, necessary to modify the protocol in some cases. In fact, some of the 9-membered dioxazonine adducts seemed unstable under the reaction conditions, decomposing to some extent before full conversion of the triazole substrates. In these instances noted in Scheme 4, care was taken to shorten the reaction time by increasing the catalyst loading to 2 mol %. Then, products **4** were generally obtained in good yields (81−86%). A poorer reactivity was however noticed in the case of **4b** and **4c** carrying electron-withdrawing groups (73 and 59%, respectively). Also, even after adjusting the reaction conditions, it was not possible to isolate product **4j** (Scheme 4).

A mechanistic rationale coherent with the above-detailed experimental results is proposed in Scheme 5.[12] Most likely, as detailed in the introduction, the reaction pathway involves the generation of electrophilic α-imino carbenes of type **2** (Scheme 5). Nucleophilic attack of an oxygen atom from the cyclic acetals generates the corresponding oxonium ylide of type **8**. Then, the lone-pair of the unbound oxygen atom provokes an opening of the acetal ring leading to the formation of unsaturated oxocarbenium ions of type **9**. This intermediate **9** is then ideally suited to undergo favored 8- or 9-*endo-trig* cyclization reactions responsible for the formation of the medium-sized products.[17,18] In addition, this rationale explains the regiochemistry and the perfect selectivity; ring-opening and -closing reactions always occur after the ylide formation at the acetal carbon preferentially.

With this rationale in mind, reactions were performed with unsymmetrical 4-methyl-1,3-dioxane **10** and 4-methyl-1,3-dioxolane **11**; the extra methyl group leading possibly to regioisomers (Scheme 6). Interestingly, with **10** as solvent, ^{1}H NMR analysis of the crude reaction mixture indicated the exclusive formation of a single regioisomer **12b$_1$**, which was isolated in good yield (79%). Its structure was assigned by

Scheme 3. Eight-Membered Dioxazocine Synthesis[a]



[a]All yields correspond to isolated yields.

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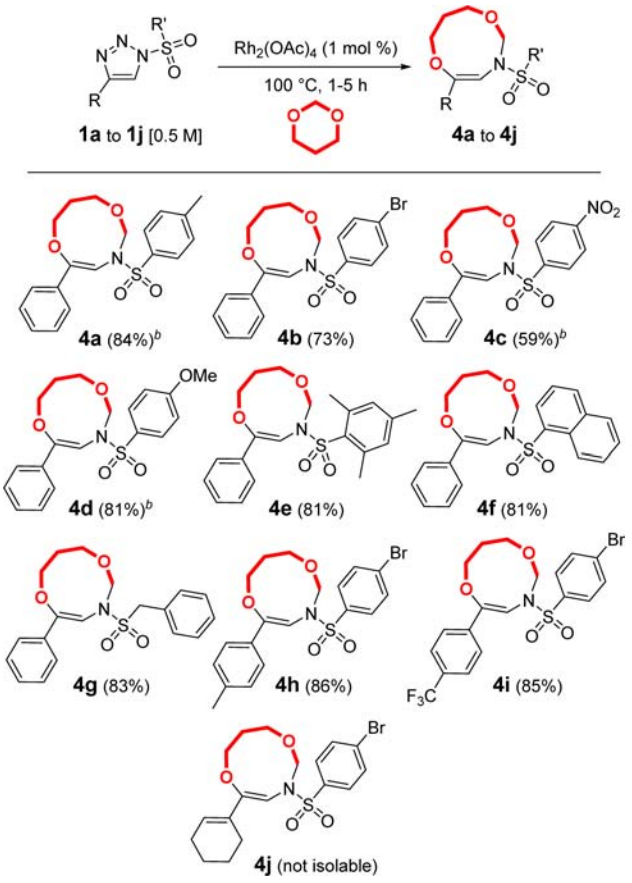
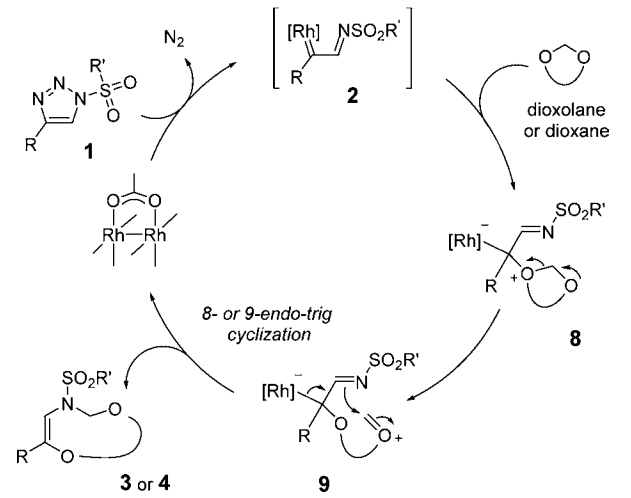
Scheme 4. Nine-Membered Dioxazonine Synthesis[a]



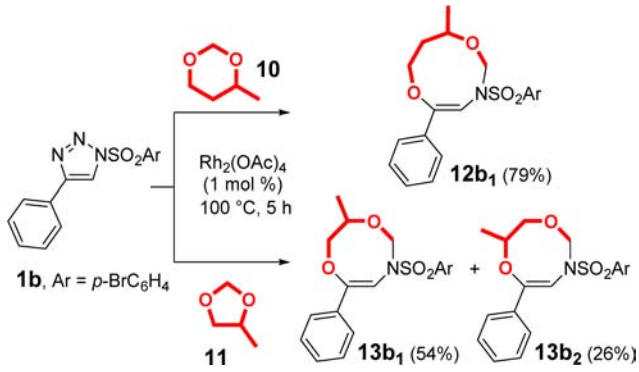
[a]All yields correspond to isolated yields. [b]Reaction performed with 2 mol % of $Rh_2(OAc)_4$ instead.

Scheme 5. Mechanistic Rationale



NMR spectroscopy. This result indicates that the less hindered oxygen atom (without the adjacent methyl substituent) reacts first with the carbene **2**.[19] The second O atom, next to the methyl group, then helps generate the electrophilic oxocarbenium intermediate of type **9** that is trapped to form the product with the observed regioselectivity. With 4-methyl-1,3-dioxolane **11**, the situation was less favorable as a 2:1 mixture of regioisomers was obtained. Adducts $\mathbf{13b_1}$ and $\mathbf{13b_2}$ were isolated by flash chromatography in 54% and 26% yields,

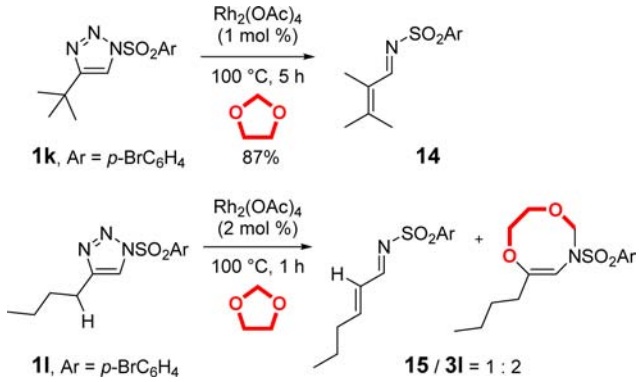
Scheme 6. Reactions with Unsymmetrical Acetals



respectively. The structures were assigned by NMR spectroscopy, and in the case of $\mathbf{13b_1}$, the attribution was confirmed by X-ray analysis (see Figure S1, Supporting Information).

Finally, to gather further information on the reactivity and develop an even better understanding, two 4-alkyl-*N*-sulfonyl-triazoles **1k** (R = *t*-butyl) and **1l** (R = *n*-butyl) were prepared and tested with 1,3-dioxolane as solvent (Scheme 7). In line

Scheme 7. Reactivity of the 4-Alkyl-*N*-sulfonyl-1,2,3-triazoles



with literature precedents,[20] substrate **1k** did not afford the 8-membered heterocycle but only product **14** of 1,2-methyl shift (87% yield, Scheme 7). Gratifyingly, crude NMR analysis of the reaction involving **1l** showed the presence of both the product of 1,2-hydride shift **15** but also this time of dioxazocine **3l** in a 1:2 ratio (Scheme 7). Purification of the crude afforded however only a small amount of **3l** (9%). These reactions thus confirm the existence of rapid alkyl and hydride shifts[21] when the *N*-sulfonyltriazoles are substituted with alkyl groups and treated with $Rh_2(OAc)_4$. Clearly, with the α-imino carbene derived from **1l**, the intramolecular shift (→**15**) is less favored than the intermolecular attack from dioxolane (→**3l**). With the carbene derived from **1k**, the steric hindrance of the *tert*-butyl group favors the intramolecular process as only product **14** can be detected.

In conclusion, the one-pot synthesis of nitrogen-containing 8- and 9-membered dioxazocines and dioxazonines has been achieved under dirhodium catalysis using *N*-sulfonyl-1,2,3-triazoles as substrates. Perfect regioselectivity was noticed for the medium-size ring formation that can be explained by a clear mechanistic rationale. It was, however, shown that only 4-aryl (and 4-vinyl) triazoles are directly amenable for this transformation.

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■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and full spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Kolb, H. C.; Finn, M. G.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2001**, *40*, 2004−2021. (b) Lewis, W. G.; Green, L. G.; Grynszpan, F.; Radic, Z.; Carlier, P. R.; Taylor, P.; Finn, M. G.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2002**, *41*, 1053−1057. (c) Amblard, F.; Cho, J. H.; Schinazi, R. F. *Chem. Rev.* **2009**, *109*, 4207−4220. (d) Le Droumaguet, C.; Wang, C.; Wang, Q. *Chem. Soc. Rev.* **2010**, *39*, 1233−1239. (e) Thirumurugan, P.; Matosiuk, D.; Jozwiak, K. *Chem. Rev.* **2013**, *113*, 4905−4979.

(2) (a) Meldal, M.; Tornoe, C. W. *Chem. Rev.* **2008**, *108*, 2952−3015. (b) Hein, J. E.; Fokin, V. V. *Chem. Soc. Rev.* **2010**, *39*, 1302−1315. (c) Schulze, B.; Schubert, U. S. *Chem. Soc. Rev.* **2014**, *43*, 2522−2571.

(3) (a) Harmon, R. E.; Stanley, F.; Gupta, S. K.; Johnson, J. *J. Org. Chem.* **1970**, *35*, 3444−3448. (b) Harmon, R. E.; Earl, R. A.; Gupta, S. K. *J. Chem. Soc. D* **1971**, 296−297.

(4) For examples with triazoles other than sulfonyl, see: (a) Regitz, M. *Tetrahedron Lett.* **1965**, *6*, 3287−3293. (b) Hermes, M. E.; Marsh, F. D. *J. Am. Chem. Soc.* **1967**, *89*, 4760−4764. (c) Huisgen, R.; Vonfraun, K.; Sturm, H. J. *Tetrahedron Lett.* **1969**, 2589−2594. (d) Zibinsky, M.; Fokin, V. V. *Org. Lett.* **2011**, *13*, 4870−4872. (e) Kwok, S. W.; Zhang, L.; Grimster, N. P.; Fokin, V. V. *Angew. Chem., Int. Ed.* **2014**, *53*, 3452−3456.

(5) (a) Chattopadhyay, B.; Gevorgyan, V. *Angew. Chem., Int. Ed.* **2012**, *51*, 862−872. (b) Davies, H. M. L.; Alford, J. S. *Chem. Soc. Rev.* **2014**, DOI: 10.1039/c4cs00072b.

(6) (a) Parr, B. T.; Davies, H. M. L. *Angew. Chem., Int. Ed.* **2013**, *52*, 10044−10047. (b) Parr, B. T.; Green, S. A.; Davies, H. M. *J. Am. Chem. Soc.* **2013**, *135*, 4716−4718. (c) Gulevich, A. V.; Gevorgyan, V. *Angew. Chem., Int. Ed.* **2013**, *52*, 1371−1373. (d) Schultz, E. E.; Sarpong, R. *J. Am. Chem. Soc.* **2013**, *135*, 4696−4699. (e) Chuprakov, S.; Worrell, B. T.; Selander, N.; Sit, R. K.; Fokin, V. V. *J. Am. Chem. Soc.* **2014**, *136*, 195−202. (f) Kwok, S. W.; Zhang, L.; Grimster, N. P.; Fokin, V. V. *Angew. Chem., Int. Ed.* **2014**, *53*, 3452−3456. (g) Miura, T.; Funakoshi, Y.; Murakami, M. *J. Am. Chem. Soc.* **2014**, *136*, 2272−2275. (h) Miura, T.; Funakoshi, Y.; Tanaka, T.; Murakami, M. *Org. Lett.* **2014**, *16*, 2760−2763. (i) Boyer, A. *Org. Lett.* **2014**, *16*, 1660−1663. (j) Yadagiri, D.; Anbarasan, P. *Org. Lett.* **2014**, *16*, 2510−2513. (k) Shang, H.; Wang, Y.; Tian, Y.; Feng, J.; Tang, Y. *Angew. Chem., Int. Ed.* **2014**, *53*, 5662−5666. (l) Xing, Y.; Sheng, G.; Wang, J.; Lu, P.; Wang, Y. *Org. Lett.* **2014**, *16*, 1244−1247. (m) Yang, J.-M.; Zhu, C.-Z.; Tang, X.-Y.; Shi, M. *Angew. Chem., Int. Ed.* **2014**, *53*, 5142−5146.

(7) (a) Chuprakov, S.; Hwang, F. W.; Gevorgyan, V. *Angew. Chem., Int. Ed.* **2007**, *46*, 4757−4759. (b) Horneff, T.; Chuprakov, S.; Chernyak, N.; Gevorgyan, V.; Fokin, V. V. *J. Am. Chem. Soc.* **2008**, *130*, 14972−14974. (c) Miura, T.; Tanaka, T.; Biyajima, T.; Yada, A.; Murakami, M. *Angew. Chem., Int. Ed.* **2013**, *52*, 3883−3886. (d) Yadagiri, D.; Anbarasan, P. *Chem.—Eur. J.* **2013**, *19*, 15115−15119. (e) Miura, T.; Tanaka, T.; Yada, A.; Murakami, M. *Chem. Lett.* **2013**, *42*, 1308−1310. (f) Jung, D. J.; Jeon, H. J.; Kim, J. H.; Kim, Y.; Lee, S.-g. *Org. Lett.* **2014**, *16*, 2208−2211.

(8) (a) Illuminati, G.; Mandolini, L. *Acc. Chem. Res.* **1981**, *14*, 95−102. (b) Evans, P. A.; Holmes, A. B. *Tetrahedron* **1991**, *47*, 9131−9166. (c) Yet, L. *Chem. Rev.* **2000**, *100*, 2963−3008.

(9) According to Baldwin's rule, the formation of **6a** from the corresponding ylide intermediate should be disfavored as it involves in its most direct pathway an intramolecular 5-*endo-tet* cyclization. See the discussion in refs 11 and 12.

(10) (a) Cenini, S.; Cravotto, G.; Giovenzana, G. B.; Palmisano, G.; Tollari, S. *Tetrahedron* **1999**, *55*, 6577−6584. (b) Zeghida, W.; Besnard, C.; Lacour, J. *Angew. Chem., Int. Ed.* **2010**, *49*, 7253−7256. (c) Vishe, M.; Hrdina, R.; Guénée, L.; Besnard, C.; Lacour, J. *Adv. Synth. Catal.* **2013**, *355*, 3161−3169.

(11) Macrocyclization reactions are also observed using Pd(II) catalysts with diazocarbonyles in THF; see: Kitamura, M.; Kisanuki, M.; Kanemura, K.; Okauchi, T. *Org. Lett.* **2014**, *16*, 1554−1557.

(12) Ballesteros-Garrido, R.; Rix, D.; Besnard, C.; Lacour, J. *Chem.—Eur. J.* **2012**, *18*, 6626−6631.

(13) Raushel, J.; Fokin, V. V. *Org. Lett.* **2010**, *12*, 4952−4955.

(14) Adducts **1** are however stable for months when stored in the dark at 4 °C.

(15) Dry solvents need to be used in these reactions as presence of water lead to a denitrogenative hydratation pathway leading to the formation of α-amino ketone products, see: Miura, T.; Biyajima, T.; Fujii, T.; Murakami, M. *J. Am. Chem. Soc.* **2012**, *134*, 194−196.

(16) The reaction can be performed in toluene as solvent using an excess of acetal (5 equiv) leading, however, to a lower yield (52%, Supporting Information). However, $Rh_2(OAc)_4$ can be substituted by $Rh_2(Oct)_4$ with little change.

(17) (a) Baldwin, J. E. *J. Am. Chem. Soc.* **1976**, 734−736. (b) Buergi, H. B.; Dunitz, J. D. *Acc. Chem. Res.* **1983**, *16*, 153−161.

(18) *n-endo-trig* cyclizations are favored when $n \geq 6$.

(19) Acetals carrying substituents at the acetal carbon do not perform the titled chemistry. For instance, reactions with 2-methyl-1,3-dioxolane do not lead to products of cyclization, and this is probably for steric reasons.

(20) (a) Miura, T.; Funakoshi, Y.; Morimoto, M.; Biyajima, T.; Murakami, M. *J. Am. Chem. Soc.* **2012**, *134*, 17440−17443. (b) Selander, N.; Worrell, B. T.; Fokin, V. V. *Angew. Chem., Int. Ed.* **2012**, *51*, 13054−13057.

(21) (a) Aggarwal, V. K.; Sheldon, C. G.; Macdonald, G. J.; Martin, W. P. *J. Am. Chem. Soc.* **2002**, *124*, 10300−10301. (b) Jiang, N.; Qu, Z. H.; Wang, J. B. *Org. Lett.* **2001**, *3*, 2989−2992. (c) Jiang, N.; Ma, Z. H.; Qu, Z. H.; Xing, X. Y.; Xie, L. F.; Wang, J. B. *J. Org. Chem.* **2003**, *68*, 893−900. (d) Shi, W. F.; Xiao, F. P.; Wang, J. B. *J. Org. Chem.* **2005**, *70*, 4318−4322. (e) Vitale, M.; Lecourt, T.; Sheldon, C. G.; Aggarwal, V. K. *J. Am. Chem. Soc.* **2006**, *128*, 2524−2525. (f) Xiao, F. P.; Wang, J. B. *J. Org. Chem.* **2006**, *71*, 5789−5791.