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Donor-Substituted Nitrocyclopropanes: Immediate Ring-Enlargement to Cyclic Nitronates

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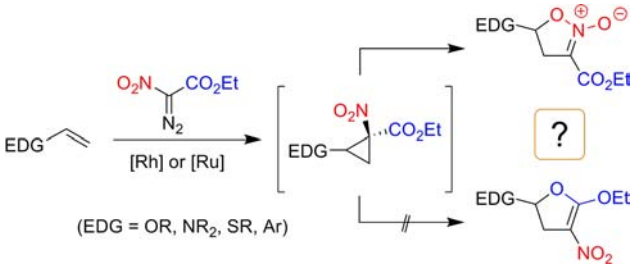
ABSTRACT



The reaction of donor-substituted alkenes with α-diazo-α-nitro ethyl acetate under Rh catalysis was investigated; respective nitrocyclopropanes with a geminal ester functionality were generated in situ. Strong electron donors immediately led to ring-enlargement. In all cases, the nitro group was inserted forming cyclic nitronates whereas the ester moiety was not incorporated into the ring system. DFT studies revealed that the formation of cyclic nitronates is kinetically as well as thermodynamically favored over the formation of cyclic ketene acetals.

Donor–acceptor (D–A) cyclopropanes **1** have enjoyed a renaissance in recent years. Although investigations first began in the 1970s,[1] they have recently become increasingly popular for the synthesis of a variety of carbo- and heterocyclic compounds.[2] Key to their special reactivity is the weak bond between the adjacent donor- and acceptor-substituted carbons of the three-membered ring.[2] Favored by the inherent ring strain of cyclopropane, 1,3-zwitterionic intermediates **2** stabilized by respective substituents are easily formed (Scheme 1). The tendency for a ring-opening is further increased by activation, either with Brønsted or Lewis acids. A variety of different pathways can be followed ranging from attack of nucleophiles or electrophiles to cycloadditions and rearrangement reactions.[2] During recent years, novel donor-acceptor systems were investigated,[3] stereoselective routes to chiral heterocycles[4] were developed, and natural product syntheses based on the special reactivity of D–A cyclopropanes were designed.[5] Our group has been especially interested in intramolecular ring-enlargement reactions of D–A cyclopropanes. In 2011, we studied 72 different cyclopropane

[†] Institut für Anorganische Chemie der Georg-August-Universität Göttingen (X-ray crystallography).

(1) Wenkert, E. *Acc. Chem. Res.* **1980**, *13*, 27–31.

(2) For reviews on donor–acceptor-substituted cyclopropanes, see: (a) Reissig, H.-U.; Zimmer, R. *Chem. Rev.* **2003**, *103*, 1151–1196. (b) Yu, M.; Pagenkopf, B. L. *Tetrahedron* **2005**, *61*, 321–347. (c) Agrawal, D.; Yadav, V. K. *Chem. Commun.* **2008**, 6471–6488. (d) Carson, C. A.; Kerr, M. A. *Chem. Soc. Rev.* **2009**, *38*, 3051–3060. (e) De Simone, F.; Waser, J. *Synthesis* **2009**, 3353–3374.

(3) (a) de Nanteuil, F.; Waser, J. *Angew. Chem., Int. Ed.* **2011**, *50*, 12075–12079. (b) Benfatti, F.; de Nanteuil, F.; Waser, J. *Chem.—Eur. J.* **2012**, *18*, 4844–4849. (c) Emmett, M. R.; Grover, H. K.; Kerr, M. A. *J. Org. Chem.* **2012**, *77*, 6634–6637. (d) Haubenreisser, S.; Hensenne, P.; Schröder, S.; Niggemann, M. *Org. Lett.* **2013**, *15*, 2262–2265. (e) Kaschel, J.; Schneider, T. F.; Schirmer, P.; Maaß, C.; Stalke, D.; Werz, D. B. *Eur. J. Org. Chem.* **2013**, 4539–4551. (f) Miyake, Y.; Endo, S.; Moriyama, T.; Sakata, K.; Nishibayashi, Y. *Angew. Chem., Int. Ed.* **2013**, *52*, 1758–1762.

(4) (a) Pohlhaus, P. D.; Sanders, S. D.; Parsons, A. T.; Li, W.; Johnson, J. S. *J. Am. Chem. Soc.* **2008**, *130*, 8642–8650. (b) Pohlhaus, P. D.; Johnson, J. S. *J. Am. Chem. Soc.* **2005**, *127*, 16014–16015. (c) Parsons, A. T.; Johnson, J. S. *J. Am. Chem. Soc.* **2009**, *131*, 3122–3123. (d) Yu, M.; Pagenkopf, B. L. *Org. Lett.* **2003**, *5*, 5099–5101. (e) Yu, M.; Pantos, G. D.; Sessler, J. L.; Pagenkopf, B. L. *Org. Lett.* **2004**, *6*, 1057–1059. (f) Ma, X.; Tang, Q.; Ke, J.; Yang, X.; Zhang, J.; Shao, H. *Org. Lett.* **2013**, *15*, 5170–5173.

(5) (a) De Simone, F.; Gertsch, J.; Waser, J. *Angew. Chem., Int. Ed.* **2010**, *49*, 5767–5770. (b) Weisser, R.; Yue, W.; Reiser, O. *Org. Lett.* **2005**, *7*, 5353–5356.

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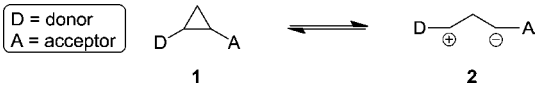
systems by quantum chemical calculations with respect to their rearrangement to five-membered rings.[6] We have already experimentally investigated several of these reactions to generate spiroketals,[7] oligoacetals,[8] bisthiophenes,[9] and oligopyrroles.[10]

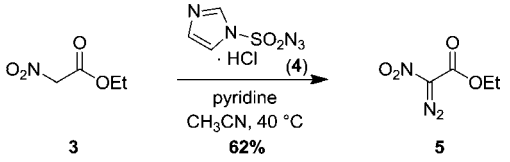
Scheme 1. 1,3-Zwitterionic Relationship in D−A Cyclopropanes



In this paper, we report on our investigations to react electron-rich alkenes and α-nitro-substituted ethyl diazo acetate to afford cyclopropanes bearing geminal nitro and ester moieties. Their tendency for ring-enlargement was investigated by experimental and theoretical means. Several different types of donor substituents attached to the alkene were studied such as oxygen, nitrogen, and sulfur, but also aryl residues.

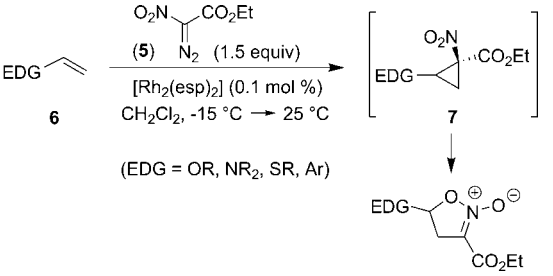
We started our investigations by establishing a new route to α-diazo-α-nitro ethyl acetate (**5**). For decades, this reagent has been prepared by a method developed by Schöllkopf starting from ethyl diazo acetate which has been treated with N_2O_5.[11a] Alternatively, **5** was prepared by using trifluoromethanesulfonyl azide, which is quite difficult to handle because of its high reactivity.[11b] We adjusted a recently described protocol[12] for diazotization to the preparation of **5** involving the relatively stable imidazole-1-sulfonyl azide hydrochloride (**4**). α-Nitro-substituted ethyl acetate **3** was treated with **4** at 40 °C in acetonitrile in the presence of an excess of pyridine as base (Scheme 2). The desired cyclopropanation agent **5** could be isolated in 62% yield by column chromatography.

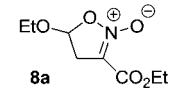
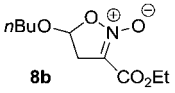
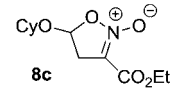
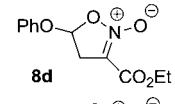
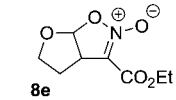
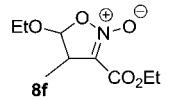
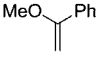
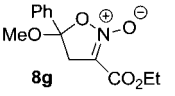
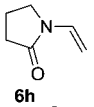
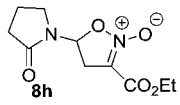
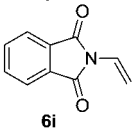
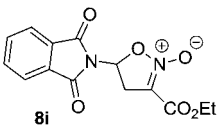
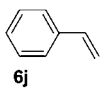
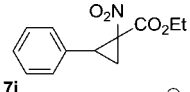
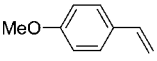
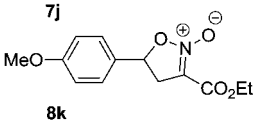
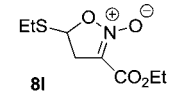
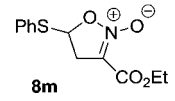
Scheme 2. Synthesis of Nitro Diazo Ethyl Acetate **5**



(6) Schneider, T. F.; Werz, D. B. *Org. Lett.* **2011**, *13*, 1848–1851.
(7) Brand, C.; Rauch, G.; Zanoni, M.; Dittrich, B.; Werz, D. B. *J. Org. Chem.* **2009**, *74*, 8779–8786.
(8) (a) Schneider, T. F.; Kaschel, J.; Dittrich, B.; Werz, D. B. *Org. Lett.* **2009**, *11*, 2317–2320. (b) Schneider, T. F.; Kaschel, J.; Awan, S. I.; Dittrich, B.; Werz, D. B. *Chem.—Eur. J.* **2010**, *16*, 11276–11288.
(9) Kaschel, J.; Schmidt, C. D.; Mumby, M.; Kratzert, D.; Stalke, D.; Werz, D. B. *Chem. Commun.* **2013**, *49*, 4403–4405.
(10) (a) Kaschel, J.; Schneider, T. F.; Kratzert, D.; Stalke, D.; Werz, D. B. *Angew. Chem., Int. Ed.* **2012**, *51*, 11153–11156. (b) Kaschel, J.; Schneider, T. F.; Kratzert, D.; Stalke, D.; Werz, D. B. *Org. Biomol. Chem.* **2013**, *11*, 3494–3509.
(11) (a) Schöllkopf, U.; Tonne, P.; Schäfer, H.; Markusch, P. *Liebigs Ann. Chem.* **1969**, *722*, 45–51. (b) Charette, A. B.; Wurz, R. P.; Ollevier, T. *J. Org. Chem.* **2000**, *65*, 9252–9254.

Table 1. Cyclopropanation and Subsequent Ring-Enlargement Reaction To Afford Cyclic Nitronates and its Substrate Scope



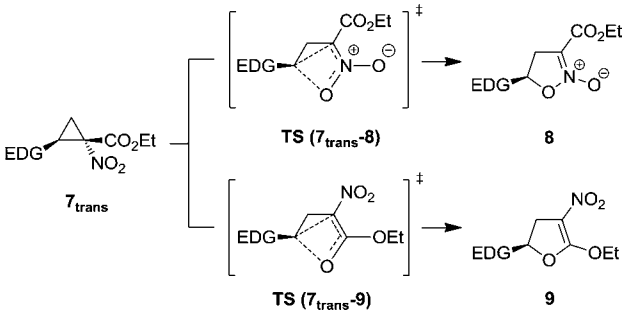
entry	substrate	product	yield (%)
1	 **6a**	 **8a**	73
2	 **6b**	 **8b**	72
3	 **6c**	 **8c**	51
4	 **6d**	 **8d**	56
5	 **6e**	 **8e**	62
6	 **6f**	 **8f**	*cis*: 10 *trans*: 27
7	 **6g**	 **8g**	96
8	 **6h**	 **8h**	87
9	 **6i**	 **8i**	51
10	 **6j**	 **7j**	85[14]
11	 **6k**	 **8k**	77
12[15]	 **6l**	 **8l**	25
13[15]	 **6m**	 **8m**	traces

With this compound in hand, we tested a series of different alkenes **6a**−**m** in the Rh-catalyzed cyclopropanation reaction (Table 1). Optimization studies with different Rh catalysts revealed that the use of bis[rhodium (α,α,α′,α′-tetramethyl-1,3-benzenedipropionate)] [$Rh_2(esp)_2$] was superior to [$Rh_2(OAc)_4$].[13] Best results were obtained when 0.1 mol % of rhodium catalyst and 1.5 equiv of diazo reagent were used and the reaction was conducted in dichloromethane at temperatures between −15 and 0 °C. Enol ethers **6a**−**g** as substrates were the focus of our study (Table 1); we used terminal and internal substrates as well as a 1,1-disubstituted example (**6g**). In addition, enamides (**6h** and **6i**) and thioenol ethers (**6l** and **6m**)[15] were studied. Furthermore, two simple aryl-substituted alkenes (**6j** and **6k**) were examined.

With the exception of styrene (**6j**), all substrates yielded directly the ring-enlarged five-membered products of type **8**. Typical NMR signals of a cyclopropane unit were only found in the case of the Ph residue, which was the worst electron donor within the series. Table 1 clearly indicates that the yield of the ring-enlarged product strongly depends on the type of donor adjacent to the cyclopropane. Excellent yields were obtained with the 1,1-disubstituted alkene **6g** and the amide-substituted olefin **6h**, whereas yields less than 40% were found for the internal alkene **6f** and the vinyl sulfides **6l** and **6m** (Table 1). Particularly in the latter case, we assume that the cyclopropanation in the presence of a thioether moiety is problematic, although a more tolerant Ru-based catalyst was employed.[15]

The intermediary cyclopropanes bear two acceptor units in the geminal position. From NMR data it is hard to distinguish whether the five-membered ring formation takes place via the insertion of the nitro group leading to **8** or via insertion of the ester moiety leading to **9** (Table 2). In the first case, a cyclic nitronate **8** would be formed, whereas in the second case the cyclic nitro-substituted ketene acetal **9** would be generated.[16] While NMR data provide only rather limited insights to the structural features, IR data should be of greater value. Thus, we performed quantum chemical calculations of the alternative products using density functional theory[17] by applying

Table 2. Transition-State Energies ($\Delta G^{\ddagger}$) and Gibbs Free Energies of Reaction ($\Delta_r G$) Leading from Nitrocycloyclopropanes **7**[a] to Cyclic Nitronates **8** or to Cyclic Ketene Acetals **9**, Respectively



entry	TS	EDG	$\Delta G^{\ddagger}$ (kcal/mol)	$\Delta_r G$ (kcal/mo)
1	$\mathbf{7_{trans}}$-**8**	MeO	26.7	−15.1
	$\mathbf{7_{trans}}$-**9**	MeO	28.1	+0.8
2	$\mathbf{7_{trans}}$-**8**	N(Me)COMe	18.5	−10.4
	$\mathbf{7_{trans}}$-**9**	N(Me)COMe	19.5	+3.9
3	$\mathbf{7_{trans}}$-**8**	*p*-MeO-Ph	29.1	−7.0
	$\mathbf{7_{trans}}$-**9**	*p*-MeO-Ph	30.1	+8.0
4	$\mathbf{7_{trans}}$-**8**	MeS	31.5	−8.8
	$\mathbf{7_{trans}}$-**9**	MeS	33.2	+7.0
5	$\mathbf{7_{trans}}$-**8**	Ph	33.6	−6.8
	$\mathbf{7_{trans}}$-**9**	Ph	34.5	+8.0

[a] For the calculations, we used the isomer in which EDG and NO_2 are *trans* to each other. For EDG = MeO the scenario using the *cis*-isomer was computed as well. The general outcome was very similar.

the three-parameter hybrid functional (B3)[18] and the correlation functional by Lee, Yang, and Parr (LYP).[19] As the basis set we used 6-311G(d,p) as suggested by Pople,[20] implemented in Gaussian 09.[21] A harmonic vibrational analysis provided insights into the type of five-membered ring that was obtained. A comparison with the experimentally recorded IR data demonstrated that only the nitro group was incorporated into the ring system since the typical N−O stretching frequency of a nitro group disappeared. This result contrasts a study by Charette in which 1-nitrocyclopropylketones were reacted with amines and the nitro group was not incorporated into the emerging five-membered ring system.[22]

Thus, we became interested in whether the cyclic nitronates are thermodynamically or kinetically favored products of this rearrangement. For our quantum chemical investigations we used five different types of donors as models (MeO, N(Me)COMe, *p*-MeO-Ph, MeS, and Ph).

(12) Goddard-Borger, E. D.; Stick, R. V. *Org. Lett.* **2007**, *9*, 3797–3800.

(13) González-Bobes, F.; Fenster, M. D. B.; Kiau, S.; Kolla, L.; Kolotuchin, S.; Soumeillant, M. *Adv. Synth. Catal.* **2008**, *350*, 813–816.

(14) This compound was synthesized before, with Lewis acid ring-enlargement taking place: (a) O'Bannon, P. E.; Dailey, W. P. *J. Org. Chem.* **1989**, *54*, 3096–3101. (b) O'Bannon, P. E.; Dailey, W. P. *Tetrahedron* **1990**, *46*, 7341–7358. (c) Charette, A. B.; Wurz, R. P.; Ollevier, T. *Helv. Chim. Acta* **2002**, *85*, 4468–4484.

(15) Sulfur-containing substrates often do not react in the presence of the respective Rh-based cyclopropanation catalysts; therefore, a porphyrin-based Ru catalyst (tpp)Ru(CO) was employed: Galardon, E.; Le Maux, P.; Simonneaux, G. *Tetrahedron* **2000**, *56*, 615–621.

(16) Formation of cyclic nitronates by a 1,3-dipolar cycloaddition and by radical reaction: (a) Kunetsky, R. A.; Dilman, A. D.; Ioffe, S. L.; Struchkova, M. I.; Strelenko, Y. A.; Tartakovsky, V. A. *Org. Lett.* **2003**, *5*, 4907–4909. (b) Sommermann, T.; Kim, B. G.; Peters, K.; Peters, E.-M.; Linker, T. *Chem. Commun.* **2004**, 2624–2625.

(17) (a) Kohn, W.; Sham, L. J. *Phys. Rev.* **1965**, *140*, 1133–1138. (b) Parr, R. G.; Yang, W. *Density Functional Theory of Atoms and Molecules*; Oxford University Press: Oxford, U.K., 1989. (c) Koch, W.; Holthausen, M. C. *A Chemist's Guide to Density Functional Theory*; Wiley-VCH: Weinheim, 2000.

(18) (a) Becke, A. D. *J. Chem. Phys.* **1992**, *96*, 2155–2160. (b) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648–5652. (c) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 1372–1377.

(19) (a) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785–789. (b) Stephens, P. J.; Devlin, F. J.; Chabalowski, C. F.; Frisch, M. J. *J. Phys. Chem.* **1994**, *98*, 11623–11627.

(20) Krishnan, R.; Binkley, J. S.; Seeger, R.; Pople, J. A. *J. Chem. Phys.* **1980**, *72*, 650–654.

(21) Gaussian 09, Revision A.02, Frisch, M. J. et al. Gaussian, Inc., Wallingford, CT, 2009 (see the Supporting Information for the complete citation).

(22) Wurz, R. P.; Charette, A. B. *Org. Lett.* **2005**, *7*, 2313–2316.

Table 3. Solvent-Corrected Transition-State Energies ($\Delta G^{\ddagger}_{solv}$) and Gibbs Free Energies of Reaction ($\Delta_r G_{solv}$) Calculated for the Cyclic Rearrangement of Nitrocyclopropanes **7** to Cyclic Nitronates **8** or to Cyclic Ketene Acetals **9** Using the Polarizable Continuum Model (PCM) and CH_2Cl_2 as Solvent Implemented in Gaussian 09

entry	TS	EDG	$\Delta G^{\ddagger}_{solv}$ (kcal/mol)	$\Delta_r G_{solv}$ (kcal/mol)
1	$\mathbf{7_{trans}}$-**8**	MeO	18.4	−15.4
	$\mathbf{7_{trans}}$-**9**	MeO	19.6	−2.4
2	$\mathbf{7_{trans}}$-**8**	N(Me)COMe	10.7	−13.5
	$\mathbf{7_{trans}}$-**9**	N(Me)COMe	11.3	−1.6
3	$\mathbf{7_{trans}}$-**8**	*p*-MeO-Ph	20.5	−7.7
	$\mathbf{7_{trans}}$-**9**	*p*-MeO-Ph	21.8	+3.3
4	$\mathbf{7_{trans}}$-**8**	MeS	24.0	−9.4
	$\mathbf{7_{trans}}$-**9**	MeS	25.1	+3.7
5	$\mathbf{7_{trans}}$-**8**	Ph	28.3	−8.0
	$\mathbf{7_{trans}}$-**9**	Ph	29.0	+5.9

Interestingly, most of the cyclic ketene acetals were not only higher in energy than the corresponding cyclic nitronates but also higher in energy than the corresponding three-membered ring starting materials (Table 2).[23]

Furthermore, we extended our computations to the respective transition states (TS) leading from **7** either to **8** or **9**, respectively. It became evident that the activation barrier strongly depends on the type of donor used. A nitrogen donor favors the rearrangement much more than an oxygen donor, whereas an electron-rich aryl behaves similarly to an oxygen donor. A sulfur as electron-pushing substituent is less suited for the anticipated ring-enlargement. However, the highest activation barrier is observed for a phenyl residue. In this case no rearranged product was found. These observations are in line with our previous theoretical studies on D−A cyclopropanes.[6]

To get a more realistic view, we calculated the free energies (single point) of this process using the polarizable continuum model (PCM).[24] Based on our experimental outcome, we employed CH_2Cl_2 as solvent. In general, the transition-state energies and the free energies of reaction depicted in Table 3 benefited from the solvation; the activation barriers are up to 8.5 kcal/mol lower in energy than the corresponding ones in the gas phase.

(23) Recently, a ring-contraction of a five-membered ketene acetal to a cyclopropyl ester was observed: Kessler, S. N.; Neuburger, M.; Wegner, H. A. *J. Am. Chem. Soc.* **2012**, *134*, 17885–17888.

(24) For the evaluation of solvent effects the self-consistent reaction field (SCRF) theory using the PCM-united atom topological model (UAHF, radii of interlocking spheres) was employed as implemented in Gaussian 09: Tomasi, J.; Mennucci, B.; Cammi, R. *Chem. Rev.* **2005**, *105*, 2999–3093.

(25) (a) Kottke, T.; Stalke, D. *J. Appl. Crystallogr.* **1993**, *26*, 615. (b) Bruker, SAINT V7.68A, Bruker AXS Inc., Madison, WI, 2005. (c) Sheldrick, G. M. SADABS 2008/2, Göttingen, 2008. (d) Sheldrick, G. M. *Acta Crystallogr., Sect. A* **2008**, *64*, 112.

(26) CIF files have also been deposited with the Cambridge Crystallographic Data Centre as "supplementary publication nos. CCDC-945470 (**8e**), CCDC-945468 (**8h**), and CCDC-945469 (**8k**)". Copies can be obtained via email: data_request@ccdc.cam.ac.uk.

Finally, we were also able to unambiguously prove the structure of the cyclic nitronate by X-ray crystallographic analyses for compounds **8e**,**h**,**k**.[25,26] The first compound represents an example with an oxygen donor, the second one with a nitrogen donor, and the third one with an electron-rich arene. The molecular structure of nitrogen-substituted cyclic nitronate **8h** is depicted in Figure 1.

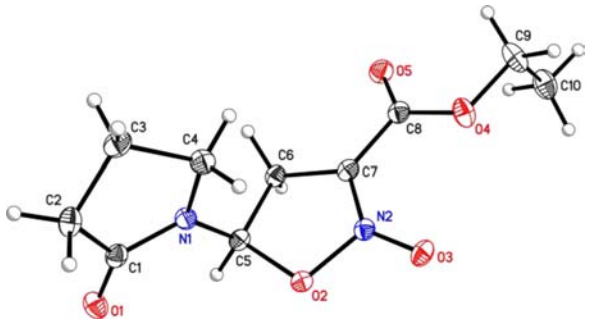


Figure 1. Molecular structure (50% ellipsoid probability) of **8h** in the solid state.[25,26] Oxygen atoms are shown in red, nitrogen atoms are shown in blue.

In conclusion, we were able to develop a cyclopropanation/ring-enlargement sequence to afford cyclic nitronates in one step from electron-rich alkenes and α-nitro α-diazo ethyl acetate. Enol ethers, enamides, thioethers, and electron-rich arenes served as starting materials. The ring-enlargement from the three- to the five-membered ring exclusively took place via insertion of the nitro group to generate cyclic nitronates of type **8**, which has also been proven by several X-ray structural analyses. The insertion of the ester group was not observed. Corresponding quantum chemical studies revealed that the transition state to the cyclic nitronate is slightly lower in energy than the alternative via insertion of the ester group.

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Supporting Information Available. Experimental procedures, spectroscopic data, and NMR spectra for all new compounds. X-ray data for **8e**,**h**,**k** (CIF).[25] Gaussian archive entries and thermochemistry values for all calculated structures. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.