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Halodiazophosphonates, a New Class of Diazo Compounds for the Diastereoselective Intermolecular Rh(II) Catalyzed Cyclopropanation

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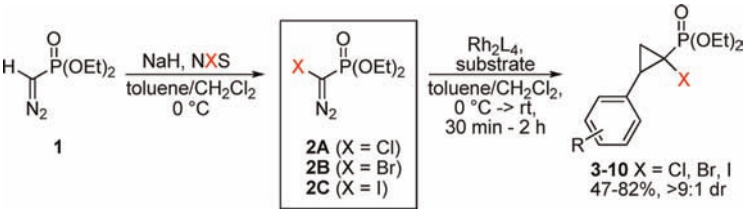
ABSTRACT



(Halodiazomethyl)phosphonates 2A–C have been generated by a one-pot procedure via a clean, efficient, and rapid deprotonation/electrophilic halogenation sequence from diethyl diazomethylphosphonate 1 (EDP). Subsequent intermolecular Rh(II)-catalyzed cyclopropanation afforded the corresponding halocyclopropylphosphonates 3–10 in moderate to high yields and high diastereomeric ratios. Catalyst loadings down to 0.1 mol % as well as clean and selective product formation were achieved.

Carbenoid chemistry has become a powerful tool in organic synthesis.[1] Numerous efficient transformations such as cyclopropanations,[2] C–H insertions,[3] cycloadditions[4] and ylide transformations[5] have been developed, as well as studies on reactivities and mechanisms of the involved transition-metal carbenoids.[6] The precursors for the carbenoids are in most cases diazo compounds, and several methods for their generation have been developed.[7] Among the frequently used and well-employed donor–acceptor[1b,d,6b,8] and acceptor–acceptor diazo compounds,[2c,9] our group recently reported halodiazoacetates[10] as a new class

(1) For recent reviews, see: (a) Padwa, A. *Chem. Soc. Rev.* **2009**, *38*, 3072. (b) Davies, H. M. L.; Denton, J. R. *Chem. Soc. Rev.* **2009**, *38*, 3061. (c) Zhang, Z.; Wang, J. *Tetrahedron* **2008**, *64*, 6577. (d) Davies, H. M. L.; Walji, A. M. Rhodium (II)-Stabilized Carbenoids Containing Both Donor and Acceptor Substituents. *Modern Rhodium-Catalyzed Organic Reactions*; Evans, P. A., Ed.; Wiley-VCH: Weinheim, 2005; pp 301–340. (e) Lydon, K. M.; McKervey, M. A. Cyclopropanation and C–H insertion with Rh. *Comprehensive Asymmetric Catalysis I-III*; Springer-Verlag: 1999; Vol. 2, pp 539–580. (f) Ye, T.; McKervey, M. A. *Chem. Rev.* **1994**, *94*, 1091.

(2) For reviews on cyclopropanations, see: (a) Pellissier, H. *Tetrahedron* **2008**, *64*, 7041. (b) Maas, G. *Chem. Soc. Rev.* **2004**, *33*, 183. For selected recent examples, see: (c) Lindsay, V. N. G.; Nicolas, C.; Charette, A. B. *J. Am. Chem. Soc.* **2011**, *133*, 8972. (d) Goto, T.; Takeda, K.; Anada, M.; Ando, K.; Hashimoto, S. *Tetrahedron Lett.* **2011**, *52*, 4200. (e) Doyle, M. P. *Angew. Chem., Int. Ed.* **2009**, *48*, 850. (f) Ghanem, A.; Gardiner, M. G.; Williamson, R. M.; Müller, P. *Chem.—Eur. J.* **2010**, *16*, 3291.

(3) For recent reviews on carbenoid C–H insertions, see: (a) Davies, H.; Dick, A. *Top. Curr. Chem.* **2010**, *292*, 303. (b) Doyle, M. P.; Duffy, R.; Ratnikov, M.; Zhou, L. *Chem. Rev.* **2010**, *110*, 704. (c) Davies, H. M. L.; Manning, J. R. *Nature* **2008**, *451*, 417. For selected recent examples, see: (d) Doyle, M. P.; Ratnikov, M.; Liu, Y. *Org. Biomol. Chem.* **2011**, *9*, 4007. (e) DeAngelis, A.; Shurtleff, V. W.; Dmitrenko, O.; Fox, J. M. *J. Am. Chem. Soc.* **2011**, *133*, 1650. (f) Gauthier, D.; Dodd, R. H.; Dauban, P. *Tetrahedron* **2009**, *65*, 8542. (g) Gomes, L. F. R.; Trindade, A. F.; Candeias, N. R.; Gois, P. M. P.; Afonso, C. A. M. *Tetrahedron Lett.* **2008**, *49*, 7372. (h) Wolckenhauer, S. A.; Devlin, A. S.; Du Bois, J. *Org. Lett.* **2007**, *9*, 4363. (i) Davies, H. M. L. *Angew. Chem., Int. Ed.* **2006**, *45*, 6422.

(4) For selected recent examples, see: (a) Wang, X.; Xu, X.; Zavalij, P. Y.; Doyle, M. P. *J. Am. Chem. Soc.* **2011**, *133*, 16402. (b) Lian, Y.; Davies, H. M. L. *J. Am. Chem. Soc.* **2010**, *132*, 440. (c) Lian, Y.; Miller, L. C.; Born, S.; Sarpong, R.; Davies, H. M. L. *J. Am. Chem. Soc.* **2010**, *132*, 12422. (d) Kano, T.; Hashimoto, T.; Maruoka, K. *J. Am. Chem. Soc.* **2006**, *128*, 2174.

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(6) (a) Herrmann, P.; Bach, T. *Chem. Soc. Rev.* **2011**, *40*, 2022. (b) Davies, H. M. L.; Morton, D. *Chem. Soc. Rev.* **2011**, *40*, 1857. (c) Bonge, H. T.; Hansen, T. *Tetrahedron Lett.* **2010**, *51*, 5378. (d) Hansen, J.; Autschbach, J.; Davies, H. M. L. *J. Org. Chem.* **2009**, *74*, 6555. (e) Davies, H. M. L.; Coleman, M. G.; Ventura, D. L. *Org. Lett.* **2007**, *9*, 4971. (f) Clark, J. S.; Dossetter, A. G.; Wong, Y.-S.; Townsend, R. J.; Whittingham, W. G.; Russell, C. A. *J. Org. Chem.* **2004**, *69*, 3886.

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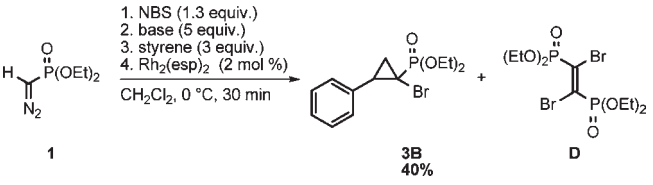
of diazo compounds. The analogous halodiazophosphonates **2B** and **2C** have once been synthesized and reported in 1979 by Regitz et al. via the corresponding silver salts.[11] However, because of their instability they could only be trapped with PPh_3 or methyl vinyl ketone but have never been used in synthesis to the best of our knowledge.

Phosphonates and the corresponding phosphonic acids and cyclopropyl groups are common structural units in biologically active molecules,[12] making halodiazophosphonates interesting targets in addition to the field of diazo chemistry. Thus, we aimed to extend our knowledge from our previously reported formation of halodiazoacetates from ethyl diazoacetate (EDA) via a deprotonation/electrophilic halogenation procedure toward the diazophosphonates.[13]

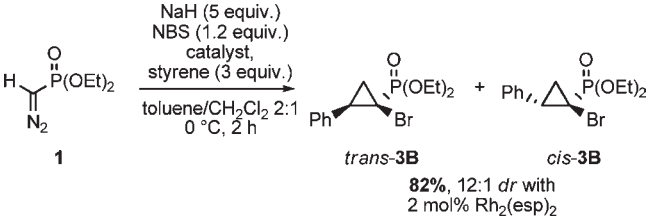
The original procedure involving a silica plug filtration[10a,b] proved to be incompatible with the halodiazophosphonates due to tailing and decomposition on silica and alumina. This focused our attention toward an efficient one-pot procedure which minimizes decomposition and side reactions. Careful choice of compatible reaction conditions with main focus on noncoordinating, clean, and easy to remove bases was necessary. Therefore, we focused on inorganic bases.

Scheme 1. Initial Experiment



Initial experiments were performed by adding the base (5 equiv) to a mixture of the Seyferth–Gilbert[14] analogue diethyl diazomethylphosphonate (EDP) **1** and *N*-bromosuccinimide (NBS, 1.3 equiv) in dry dichloromethane at 0 °C and following consumption of **1** by TLC analysis. Full consumption of EDP **1** within 5 min with NaH as base was achieved.[15] Addition of styrene (3 equiv) and 2 mol % of $Rh_2(esp)_2$,[16] which proved to be a reliable and robust catalyst for the cyclopropanations with halodiazoacetates,[10b] resulted in instant gas evolution and decolorization of the deep orange mixture and afforded the corresponding bromo cyclopropylphosphonate **3B** in 40% isolated yield along with products from dimerizations **D** and overbromination to diethyl dibromomethylphosphonate (Scheme 1).[17]

Scheme 2. One-Pot in situ Synthesis of **3B** via General Procedure A



To minimize dimerizations and increase selectivity, we considered an in situ generation of the halodiazophosphonates via dropwise addition of EDP **1**. The presence of base, *N*-halosuccinimide and substrate in excess as well as a low concentration of the diazo compound at any time during the reaction should provide rapid formation of the halodiazophosphonates and favor catalytic cyclopropanation.

Thus, dropwise addition of a solution of EDP **1** (0.7 mmol) in dry dichloromethane (5 mL) over 2 h to a mixture of $Rh_2(esp)_2$ (2 mol %), NBS (1.2 equiv), NaH (5 equiv), and styrene (3 equiv) in dry toluene/CH_2Cl_2 (10 mL/5 mL) at 0 °C was performed and afforded the cyclopropane **3B** as a 12:1 *trans*/*cis* mixture in 82% isolated yield with only traces of dimerization (Scheme 2, Table 1, entry 2, general procedure A in the Supporting Information). Thus, a clean and selective reaction to the halo cyclopropylphosphonate **3B** is achieved.

The same procedure could be applied to the iodination with *N*-iodosuccinimide (NIS), affording the corresponding iodocyclopropylphosphonate **3C** in 77% isolated yield

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(9) (a) Zhu, S.; Perman, J. A.; Zhang, X. P. *Angew. Chem., Int. Ed.* **2008**, *47*, 8460. (b) John, J. P.; Novikov, A. V. *Org. Lett.* **2007**, *9*, 61.

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(12) (a) Engel, R. *Chem. Rev.* **1977**, *77*, 349. (b) Christensen, B. G.; Leanza, W. J.; Beattie, T. R.; Patchett, A. A.; Arison, B. H.; Ormond, R. E.; Kuehl, F. A.; Albers-Schonberg, G.; Jardetzky, O. *Science* **1969**, *166*, 123. (c) Hercouet, A.; Le Corre, M.; Carboni, B. *Tetrahedron Lett.* **2000**, *41*, 197. (d) Erion, M. D.; Walsh, C. T. *Biochemistry* **1987**, *26*, 3417. (e) Reid, J. R.; Marmor, R. S. *J. Org. Chem.* **1978**, *43*, 999. (f) Hanessian, S.; Cantin, L.-D.; Roy, S.; Andreotti, D.; Gomtsyan, A. *Tetrahedron Lett.* **1997**, *38*, 1103. (g) El-Gokha, A.; Maas, G. *Tetrahedron* **2011**, *67*, 2849.

(13) For selected examples of applications of diazophosphonates, see: (a) Charette, A. B.; Bouchard, J.-E. *Can. J. Chem.* **2005**, *83*, 533. (b) Ferrand, Y.; Le Maux, P.; Simonneaux, G. *Org. Lett.* **2004**, *6*, 3211. (c) Gois, P. M. P.; Afonso, C. A. M. *Eur. J. Org. Chem.* **2003**, *2003*, 3798. (d) Paul-Roth, C.; De Montigny, F.; Rethoré, G.; Simonneaux, G.; Gulea, M.; Masson, S. *J. Mol. Catal A: Chem.* **2003**, *201*, 79. (e) Davies, H. M. L.; Lee, G. H. *Org. Lett.* **2004**, *6*, 2117. For examples of electrophilic functionalization of diazo compounds, see: (f) Hashimoto, T.; Kimura, H.; Nakatsu, H.; Maruoka, K. *J. Org. Chem.* **2011**, *76*, 6030. (g) Zhang, Y.; Wang, J. *Chem. Commun.* **2009**, 5350. (h) Zhao, Y.; Wang, J. *Synlett* **2005**, *2005*, 2886. (i) Fink, J.; Regitz, M. *Synthesis* **1985**, 569. (j) Regitz, M. *Angew. Chem., Int. Ed.* **1975**, *14*, 222.

(14) (a) Seyferth, D.; Marmor, R. S. *Tetrahedron Lett.* **1970**, *11*, 2493. (b) Seyferth, D.; Marmor, R. S.; Hilbert, P. *J. Org. Chem.* **1971**, *36*, 1379. (c) Gilbert, J. C.; Weerasooriya, U. *J. Org. Chem.* **1979**, *44*, 4997.

(15) Other bases such as Na_2CO_3, K_2CO_3, and Cs_2CO_3 were less active and gave lower yields of the isolated bromo cyclopropylphosphonate **3B**, though further studies on carbonate bases and crown ethers are in progress.

(16) Espino, C. G.; Fiori, K. W.; Kim, M.; Du Bois, J. *J. Am. Chem. Soc.* **2004**, *126*, 15378.

(17) Isolation of the halo-EDP **2B** was attempted but unsuccessful.

(18) Selectfluor and *N*-fluoro-*o*-benzenedisulfonimide (NFSI) as F sources with different solvents.

(19) Davis, F. A.; Han, W.; Murphy, C. K. *J. Org. Chem.* **1995**, *60*, 4730.

Scheme 3. Overall Reaction Scheme for Chlorination via Bulk Addition (Procedure B) and Iodination and Bromination via in situ Generation of Halodiazophosphonates **2B** and **2C** (General Procedure A)

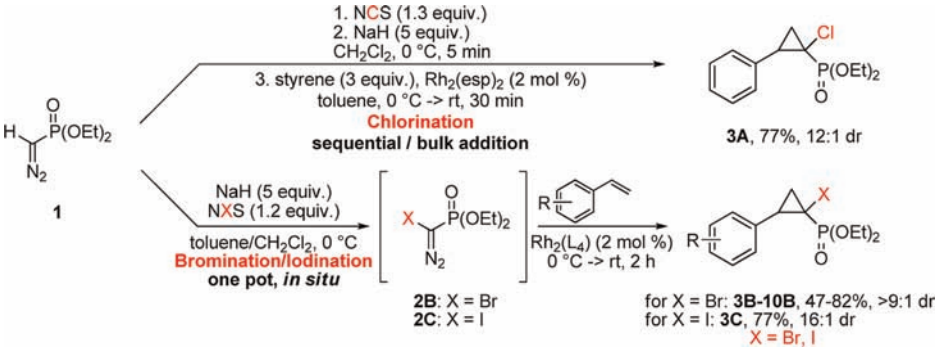
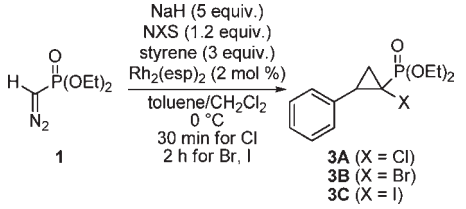


Table 1. Variation of Halogens To Afford Halocyclopropylphosphonates **3A**–**C**



entry	X	product	yield[a] (%)	dr (*trans*/*cis*)[b]
1	Cl[c]	**3A**	77	12:1
2	Br	**3B**	82	12:1
3	I	**3C**	77	16:1
4	F[d]		0	

[a] Isolated yields of both diastereomers. [b] Estimated by ^{1}H NMR spectra of the crude product mixture. [c] Bulk addition of NaH (5 equiv) to a mixture of EDP (1 equiv) and NCS (1.3 equiv) in dry CH_2Cl_2 at 0 °C, exchange of CH_2Cl_2 with toluene (see procedure B in the Supporting Information). [d] Selectfluor and NFSI[19] as F sources.

(Table 1, entry 3, Scheme 3). However, the analogous chlorination with *N*-chlorosuccinimide (NCS) did not give the desired product **3A**, instead the cyclopropanation with the nonhalogenated EDP **1** occurred. This issue could be solved via bulk addition of base NaH to a mixture of EDP **1** and NCS in dichloromethane at 0 °C followed by exchange of solvent with toluene and addition of $Rh_2(esp)_2$ and the substrate (Scheme 3). The product **3A** was obtained in a good isolated yield of 77% with only traces of overchlorinated product compared to the initial experiment with NBS (Table 1, entry 1).

Fluorination was attempted but unsuccessful.[18]

The halogen transfer from NCS to EDP **1** is slower compared to NIS and NBS; thus, cyclopropanation of EDP **1** precedes formation of the chlorinated diazo compound. This means that the halogen transfer can be considered as the rate determining step in the case of the chlorination, whereas the catalytic cyclopropanation is the rate-determining step for the iodination and bromination.

Table 2. Screening of Catalysts for the Cyclopropanation to **3B**[a]

entry	catalyst	loading (mol %)	yield of **3B**[b] (%)	dr (*trans*/*cis*)[c]
1a	$Rh_2(esp)_2$	2	82, 78,[d] 0[e]	12:1
1b		1	88[f,g]	
1c		0.5	78[f,h]	
1d		0.1	74[f,i]	
1e		0	0[f,j]	
2	$Rh_2(piv)_4$	2	78	12:1
3	$Rh_2(oct)_4$	2	73	14:1
4	$Rh_2(OAc)_4$	2	54	14:1
5	$Rh_2(TPA)_4$	2	43	9:1
6	$Rh_2(TFA)_4$	2	40	10:1
7	Rh_2(*S*-PPTL)$_4$	2	66	14:1
8	Rh_2(*S*-TBSP)$_4$	2	47	13:1
9	CuCl	2	0	
10	$Cu(OTf)_2$	5	0	
11	$Cu(acac)_2$	10	0	
12	$RuCl_3$	10	0	
13	Ag(OAc)	2	0	

[a] Conditions: EDP **1** (0.7 mmol, 1 equiv) in 5 mL of dry CH_2Cl_2 was added dropwise to NaH (5 equiv), NBS (1.2 equiv), styrene (3 equiv), and catalyst in toluene/CH_2Cl_2 (10 mL/5 mL), general procedure A, Scheme 2. [b] Isolated yield of both diastereomers after column chromatography. [c] Measured by ^{1}H NMR spectra of the crude product mixture. [d] 1.2 equiv of NaH. [e] Reaction at room temperature. [f] Measured by internal standard from ^{1}H NMR of crude reaction mixture for both diastereomers. [g] 3 h addition time. [h] 4 h addition time. [i] 5 h addition time. [j] Only dimer **D** could be detected.

Dichloromethane was required to provide solubility of the *N*-halosuccinimide and was removed in vacuo at 0 °C after complete addition of EDP **1** to leave the toluene reaction mixture at room temperature for 30 min. Toluene provides precipitation of the sodium succinimide to make a convenient workup by filtration through Celite possible.[20]

(20) A reaction in pure DCM gave slightly lower yields with an ^{1}H NMR spectrum of the crude product mixture containing more succinimide than with toluene.

After having shown the efficiency of $Rh_2(esp)_2$ for the studied system, several Rh(II) as well as other metal based catalysts were tested (Table 2).

Besides $Rh_2(esp)_2$ with bischelating carboxylates, different Rh(II) catalysts with monochelating carboxylates gave moderate to high yields of **3B** with the pivalate and octanoate catalysts as the most active ones affording 78% and 73% yield (Table 2, entries 2 and 3). This trend is in accordance with the literature for intermolecular cyclopropanations with the nonhalogenated diethyl diazomethylphosphonate **1**.[13a] High diastereomeric ratios of > 9:1 *trans:cis* with all catalysts could be obtained in the studied system. Two chiral Rh(II) catalysts gave medium yields of **3B**; however, enantiomeric excess was below 15% ee in both cases (Table 2, entries 7 and 8).[21] Other transition-metal-based catalysts did not show any product formation at all. $Cu(acac)_2$ has been used before for cyclopropanation with trifluoromethylated diazophosphonates[22] but was inactive in our system (Table 2, entry 11).

A reaction at room temperature under otherwise identical conditions only gave the dimer **D** of bromo-EDP, showing the instability of the halodiazophosphonates. At lower temperatures, the solubility of NBS in dichloromethane dropped and the yield of product **3B** decreased.

The catalyst loading for the most active $Rh_2(esp)_2$ could be decreased to 0.1 mol % without significant decrease of yield. However, adjustment of addition time of EDP **1** was necessary (Table 2).

A substrate scope mainly focusing on styrene derivatives was performed. Electron-rich and sterically less hindered styrene derivatives gave highest yields (Table 3, entries 1−3). 1,1-Disubstituted and electron-deficient double bonds gave lower yields (entries 5−8), and all products showed high diastereomeric ratios in favor of the *trans* isomer.

Structure elucidation was performed. The 2D-NOESY NMR of the major isomer of **3B** showed NOE correlations between the cyclopropyl proton H_1 of the CH group with the $POCH_2CH_3$ groups which is only expected for the *trans* isomer. Additionally, no correlation between the phosphonate ester and the aryl protons was detected. Furthermore, the ^{31}P proton-decoupled NMR spectrum showed one ^{31}P signal at 20.03 ppm, indicating the presence of only one diastereomer.[23]

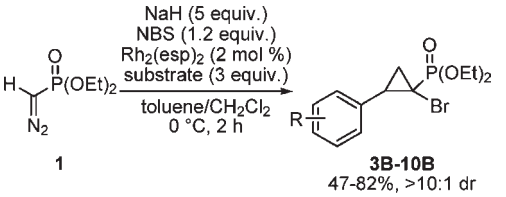
(21) Enantiomeric excess determined by HPLC: ChiralcelOD-H column, 1% iPrOH/isohexane. See the Supporting Information.

(22) Titanyuk, I. D.; Beletskaya, I. P.; Peregudov, A. S.; Osipov, S. N. *J. Fluorine Chem.* **2007**, *128*, 723.

(23) 2D-NOESY and ^{31}P NMR spectra for *trans*-**3B** are available in the Supporting Information.

(24) The crystal structure of *trans*-**9B** has been deposited at the Cambridge Crystallographic Data Centre. Deposition no.: CCDC 873532.

Table 3. Synthesis of Cyclopropylphosphonates **3B**−**10B**[a]



entry	substrate	product	yield[b] (%)	dr (*trans*/*cis*)[c]
1	styrene	**3B**	82	12:1
2	4-methylstyrene	**4B**	79	15:1
3	4-methoxystyrene	**5B**	81	17:1
4	4-chlorostyrene	**6B**	67	13:1
5	4-trifluoromethyl-styrene	**7B**	62	13:1
6	2-vinylnaphthalene	**8B**	64	9:1
7	*N*-vinylphthalimide	**9B**	64	10:1
8	1,1-diphenylethylene	**10B**	47	

[a] Conditions: EDP **1** (0.7−1.0 mmol, 1 equiv) in 5 mL of dry CH_2Cl_2 added dropwise to NaH (5 equiv), NBS (1.2 equiv), substrate (3 equiv), and $Rh_2(esp)_2$ (2 mol %) in toluene/CH_2Cl_2 (10 mL/5 mL), general procedure A. [b] Isolated yield of both diastereomers after column chromatography. [c] Measured by ^1H NMR spectra of the crude product mixture.

The X-ray crystal structure of the main isomer of product **9B** also clearly shows the *trans* configuration of the phosphonate group and the aryl substituent.[24]

In conclusion, we developed a convenient, one-pot procedure for the generation of halodiazophosphonates and their subsequent diastereoselective intermolecular cyclopropanation with styrene derivatives with various Rh(II) catalysts. Moderate to high yields as well as high diastereomeric ratios were obtained, and low catalyst loadings of 0.1 mol % could be achieved.

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Supporting Information Available. Experimental procedures and full characterization of all products **3**−**10** including ^1H and ^{13}C spectra and X-ray crystal structure data. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.