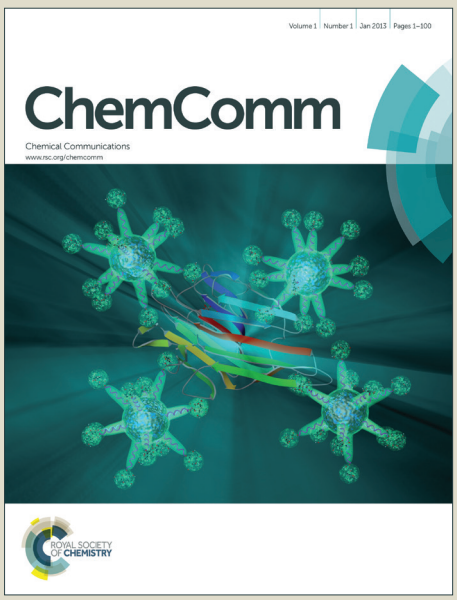
ChemComm

Accepted Manuscript



ROYAL SOCIETY OF CHEMISTRY

www.rsc.org/chemcomm

Journal Name

COMMUNICATION

Dinitrogen Extrusion from Enoldiazo Compounds under Thermal Conditions: Synthesis of Donor-Acceptor Cyclopropenes

Received 00th January 20xx,
Accepted 00th January 20xx

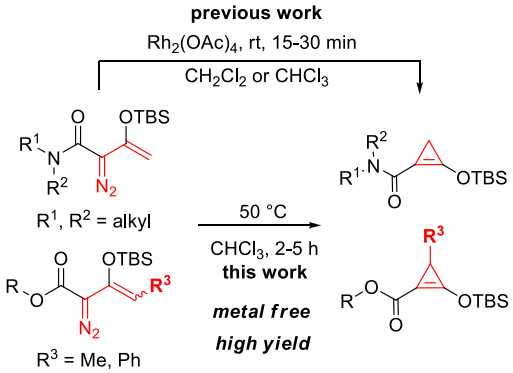
DOI: 10.1039/x0xx00000x

www.rsc.org/

Yongming Deng,[a] Changcheng Jing,[a,b] and Michael P. Doyle[a,]*

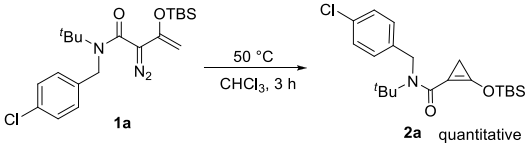
Donor–acceptor cyclopropenes are formed quantitatively or in high yield from enoldiazoacetates and enoldiazoacetamides under moderate thermal conditions. They are more versatile than their corresponding enoldiazocarbonyl compounds as carbene precursors.

The capability of cyclopropenes to form vinylcabene intermediates upon ring opening under thermal or photochemical conditions has been documented.[1] Recent reviews focused on the chemistry of cyclopropenes[2] summarized extensive investigations of 3-acyl- and 3-alkoxycarbonylcyclopropenes as precursors to metallocarbene intermediates in intramolecular reactions, mainly for the formation of furans. However, understanding that catalytic reactions of cyclopropenes could undergo a broader scope of metal carbene transformations has occurred only recently.[3] Over the last three years we discovered and have reported that donor-acceptor cyclopropenes generated from select enoldiazoacetates or enoldiazoacetamides through catalysis by rhodium acetate could be effectively employed for highly enantioselective dirhodium(II)-catalyzed [3+3]-cycloaddition and C-H-insertion reactions.[3d-3f] The formation of these isolable cyclopropenes with the use of catalytic amounts of rhodium acetate, first reported for β-substituted vinyldiazoacetates,[4] is a rapid process that requires careful monitoring so as not to catalyze subsequent reactions. To avoid this complication and to further develop donor–acceptor cyclopropenes in metal carbene chemistry,[5] we have searched for alternative conditions for their synthesis. In view of the well-established propensity of vinyldiazoacetates to form pyrazoles upon heating,[7] we were surprised to discover that thermal generation of donor-acceptor cyclopropenes from enoldiazoacetates and enoldiazoacetamides occurred in high yield under moderate conditions (Scheme 1) with the exclusion or near exclusion of pyrazoles. Additionally, we have discovered that donor–acceptor cyclopropenes are rapidly generated using a broad selection of late transition metal catalysts, and that they are more reactive towards metal carbene formation than the corresponding enoldiazocarbonyl compounds with dirhodium catalysts.



Scheme 1. Formation of donor–acceptor cyclopropenes from enoldiazoacetates and enoldiazoacetamides.

In our previous study with enoldiazoacetamides,[3f] donor-acceptor cyclopropenes were obtained by treatment with $Rh_2(OAc)_4$ followed by filtration to remove the metal catalyst. However, due to their high reactivity with dirhodium catalysts, around 8% of metal carbene reaction products from intramolecular C-H insertion coexisted with the donor–acceptor cyclopropenes even with short reaction times and rapid filtration. Upon further investigation we discovered that enoldiazoacetamide **1a** undergoes dinitrogen extrusion upon warming in a solution of $CHCl_3$ at 50 °C to generate donor–acceptor cyclopropene **2a** quantitatively within 3 hours (Eq 1). In different solvents, including hexanes, toluene, CH_3CN, and 1,2-dichloroethene (DCE), enoldiazoacetamide **1a** was also converted to donor–acceptor cyclopropene **2a** in high yield (see supporting information for the screening of reaction conditions). After removing the solvent, **2a** was fully characterized and could be used without further purification.

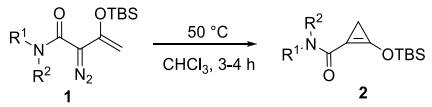


(1)

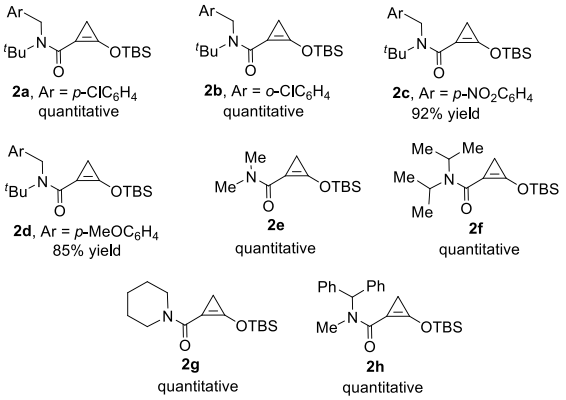
[a] Department of Chemistry, The University of Texas at San Antonio, San Antonio, Texas 78249, United States. [b] Institute for Interdisciplinary Research, East China Normal University, Shanghai, P.R. China.

† Electronic supplementary information (ESI) available: Experimental procedures, and spectral data for all new compounds. See DOI: 10.1039/x0xx00000x

Table 1. Scope of donor–acceptor cyclopropenes from enoldiazoacetamides.[a,b]



1 2

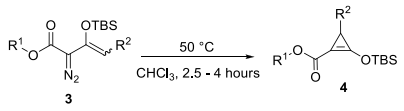


[a] Reactions were performed on a 0.4 mmol scale: 0.4 mmol **1** in 4 mL $CHCl_3$ at 50 °C. [b] The yield of cyclopropenes was determined by ^{1}H NMR analysis using an internal standard.

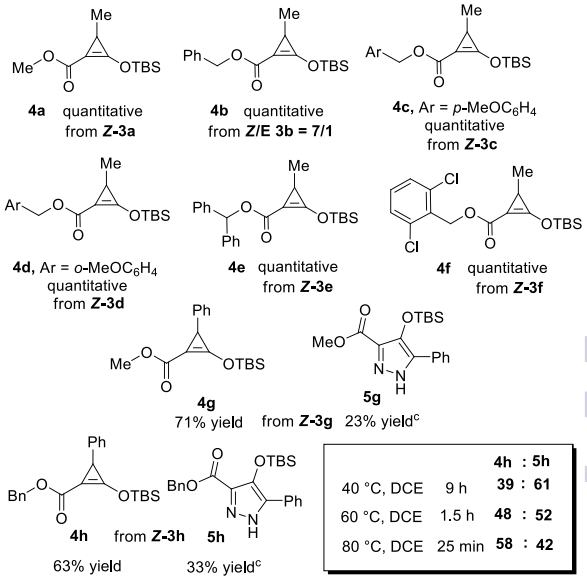
Having in hand a convenient and clean protocol (in $CHCl_3$ at 50 °C) for the formation of a donor–acceptor cyclopropene, this study was extended to other enoldiazoacetamides (Table 1). Enoldiazoacetamides, constructed from aliphatic secondary amines successfully underwent N_2 extrusion to give corresponding donor–acceptor cyclopropenes in quantitative or high yields. However, when a *N*-aryl substituent was used instead of the aliphatic group, the formation of cyclopropene was not detected under thermal conditions; only slow decomposition of the enoldiazoacetamide was observed in a broad survey of conditions that examined a range of temperatures (30–80 °C). Only the *N*-aryl group of the enoldiazoacetamide with R_1 = *p*-$MeOC_6H_4$ and R_2 = *p*-$ClC_6H_4CH_2$ could the corresponding cyclopropene **2i** be observed, albeit in only 22% yield after 3 h, with starting material remaining along with products from decomposition; but further heating did not increase the yield of **2i** although no reactant remained. The lack of formation of cyclopropene from *N*-arylenoldiazoacetamides was unexpected but could be due to conformational and/or electronic constraints from the aromatic ring adjacent to the nitrogen atom.

Enoldiazoacetates were also investigated to probe the generality of donor–acceptor cyclpropenes generation from enoldiazocarbonyl compounds under thermal conditions. Reactions of γ-methyl-enoldiazoacetates **3a** - **3f** (R^2 = Me) proceeded smoothly to generate donor–acceptor 3-methylcyclpropenes quantitatively under the optimized conditions (Table 2). However, when the thermal reactions of γ-phenyl-enoldiazoacetates **3g** and **3h** (R^1 = Ph) were explored, 1*H*-pyrazoles (**5g** and **5h**) were cogenerated with the donor-acceptor 3-phenylcyclopropenes (**4g** and **4h**). The effect of temperature on the distribution of pyrazole and cyclopropene products from reactions of **3h** in DCE shows that cyclopropene formation increases moderately with increasing reaction temperature, but temperatures at or above 80 °C led to a loss of

Table 2. Scope of donor–acceptor cyclopropenes from enoldiazoacetate.[a,b]



3 4

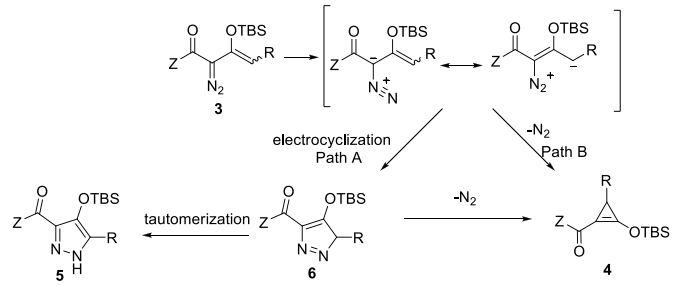


		4h : 5h
40 °C, DCE	9 h	39 : 61
60 °C, DCE	1.5 h	48 : 52
80 °C, DCE	25 min	58 : 42

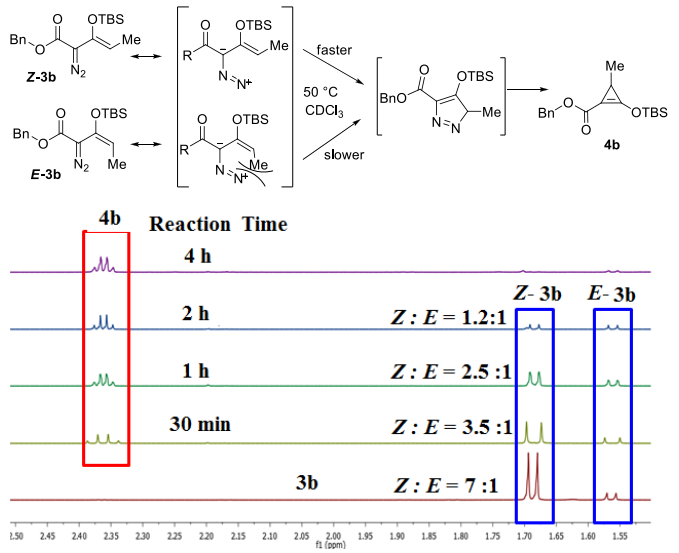
[a] Reactions were performed on a 0.4 mmol scale: 0.4 mmol **1** (either as the pure *Z*-isomer with both R^2 = Me and Ph, or as a 7/1 mixture of *Z*/*E*-isomers with R^2 = Me without difference in product yield) in 4 mL $CHCl_3$ at 50 °C. [b] Yield of cyclopropenes was determined by ^{1}H NMR analysis using an internal standard. [c] Isolated yield.

cyclopropene. The cyclopropene from the parent enoldiazoacetate **3** (R^2 = H, R^1 = Me) was not formed under these thermal conditions (30-80 °C, up to 12 h), and unreacted enoldiazoacetate was recovered; however, this cyclopropene was readily formed at room temperature with catalysis by rhodium acetate.[3d,4]

The formation of 1*H*-pyrazoles from vinyldiazo compounds through electrocyclic ring closure under thermal or photochemical conditions has been well documented.[6,7] These reactions occur by initial 6π-electrocyclization followed by 1,5-hydrogen shift of the initially formed 3*H*-pyrazole.[8] Indeed, Padwa and coworkers found that thermal reactions of a variety of vinyldiazoesters generated 1*H*-pyrazoles, and cyclopropenes were not observed.[7] With the observation of 1*H*-pyrazoles **5** from **3g** and **3f**, two pathways are proposed for the formation of donor-acceptor cyclopropenes **4** (Scheme 2). In path A, the 3*H*-pyrazole **6** formed by 6π-electrocyclization accounts for the formation of 1*H*-pyrazole **5** (1,5-hydrogen shift) and cyclopropene **4** (dinitrogen extrusion),[9] and this pathway is suggested by the thermal dependence of product formation observed with **3h** (Table 2). However, the generation of cyclopropene **4** directly from enoldiazo compound with N_2 extrusion could not be excluded (Path B in Scheme 2). That γ-phenyl-enoldiazoacetates **3g** and **3h** form the corresponding pyrazoles, but the γ-methyl-enoldiazoacetates **3a** - **3f** do not is consistent with the increased polarization of the enoldiazoacetate



Scheme 2. Formation of donor–acceptor cyclopropenes and 1*H*-pyrazoles from enoldiazo compounds.



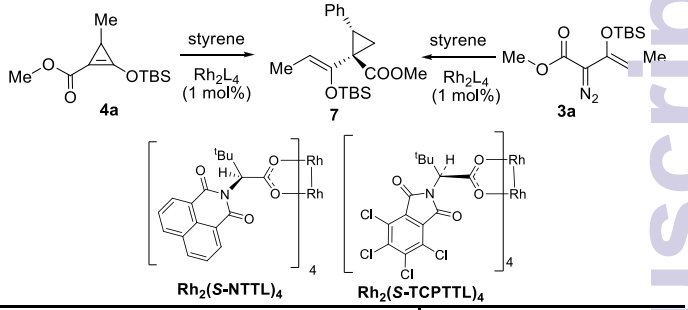
Scheme 3. NMR spectroscopy monitoring of cyclopropene **4b** formation from mixture of *Z*-**3b** and *E*-**3b**.

provided by the phenyl group at the gamma position. Donor-acceptor diazoacetates that are vinyldiazoacetates are stabilized by electron donating atoms or groups at the beta position and destabilized by net electron withdrawing groups in the gamma position.

γ-Methyl-enoldiazoacetate **3b** was formed from the corresponding β-keto-α-diazoester as a diastereomeric mixture of *E* and *Z* isomers (*Z*/*E* = 7:1). We hypothesized that if Path A of Scheme 2 was operative, *E*-3b would undergo slower formation of cyclopropene than *Z*-**3b** in the electrocyclization step due to steric interference from the γ-methyl group *cis* to the diazo group. Consistent with this prediction, slower conversion of *E*-**3b** to cyclopropene **4b** was detected by ^{1}H NMR monitoring of the reaction mixture (Scheme 3).

Although the viability of donor-acceptor cyclopropenes has been demonstrated for C-H insertion reactions of the carboxamidates, there has not been a report of their utilization for catalytic cyclopropanation. Enoldiazoacetate **3** (R^2 = H, R^1 = Me) has been reported to undergo highly diastereo- and enantioselective cyclopropanation of styrene,[10] but its cyclopropene analog was not investigated for the same transformation and under the same conditions. To compare enoldiazoacetate and donor-acceptor cyclopropenes as metal carbene precursors we applied the

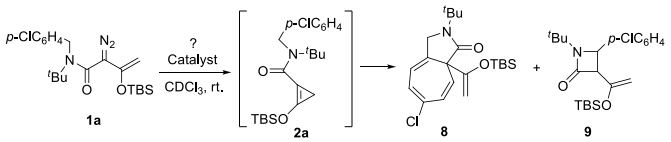
Table 3. Asymmetric cyclopropanation of donor–acceptor cyclopropene with styrene



entry	T (°C)	From cyclopropene 4a t (h)	yield[b] (%)	dr[c]	ee[d] (%)	From enoldiazoacetate 3a t (h)	yield[b] (%)	dr[c]	e (%)
1[e]	0	3	87	>95:5	70	3	85	>95:5	7
2[f]	-20	6	90	>95:5	91	20	65	>95:5	9
3[f]	-40	9	83	>95:5	91	9	<5	-	

[a] Reactions were performed on a 0.3 mmol scale: addition of a 1.0 mL Et_2O solution of **3a** or **4a** (0.3 mmol), to 0.003 mmol of catalyst (1.0 mol%), an mmol of styrene in 1.0 mL of Et_2O. [b] Isolated yield of **7** based on limiting reagent **3a** or **4a**. [c] Diastereoselectivities were determined by ^{1}H NMR spectral analysis of the reaction mixture. [d] Determined by HPLC analysis with chiral columns. [e] Rh_2(*S*-NTTL)$_4$ was the catalyst, toluene was used as solvent. [f] Rh_2(*S*-TCPTTL)$_4$ was t catalyst.

reported conditions (toluene, 0 °C) used by Müller[10] for cyclopropanation reactions of 3-methylcyclopropene **4a** and γ-methyl-enoldiazoacetates **3a** with styrene catalyzed by Hashimoto's Rh_2(*S*-NTTL)$_4$.[11] Both metal carbene precursors gave cyclopropane **7** in the same yield with the same diastereoselectivity and enantiocontrol over the same reaction time (Table 3, entry 1). During the reaction of enoldiazoacetate **3a**, the formation of cyclopropene **4a** was observed by ^{1}H NMR monitoring of the reaction mixture, and this process preceeded cyclopropanation. That the donor/acceptor cyclopropene intermediate serves as a resting state for the reactive metal carbene intermediate is consistent with our previous reports in which we documented observation of the parent enoldiazoacetate **3** (R^2 = H, R^1 = Me) during the course of dirhodium(II) catalysed cycloaddition reactions.[3d,e] In a separate study designed to evaluate the relative reactivity of these two metal carbene precursors, cyclopropanation product **7** was obtained from cyclopropene **4a** in 90% yield with 91% ee at -20 °C in 6 h by using the more reactive and enantioselective Rh_2(*S*-TCPTTL)$_4$ catalyst.[12] However, a reaction time of 20 h for enoldiazoacetate **3a** with styrene was needed to achieve total conversion, producing **7** in 65% yield (Table 3, entry 2). 3-Methylstyrene also reacted smoothly with donor-acceptor 3-methylcyclopropene **4a** at -20 °C forming the corresponding cyclopropane compound with 92% ee in 86% yield after 9 h. Notably, when the temperature was lowered to -40 °C, reaction with donor-acceptor 3-methylcyclopropene **4a** formed **7** with high enantioselectivity and yield (Table 3, entry 3) over 9 h, whereas no reaction occurred with the corresponding enoldiazoacetate at -40 °C. This result revealed the higher reactivities of donor–acceptor cyclopropenes towards metal carbene formation compared to the corresponding enoldiazo compounds.



Scheme 4. Are donor-acceptor cyclopropenes intermediates in catalytic metal carbene reactions of enoldiazocarbonyl compounds?

Finally, with our current understanding that dirhodium compounds can form donor-acceptor cyclopropene compounds from enoldiazoacetates or enoldiazoacetamides as reaction intermediates or products,[3d-3f] we sought to evaluate if they could be formed from catalysts other than those of dirhodium(II). The compound selected for this evaluation was enoldiazoacetamide **1a** which is known to produce products from aromatic cycloaddition (**8**) and C-H insertion (**9**) in high yield (Scheme 4).[3f] Reactions were followed by ^{1}H NMR spectroscopy to observe the distinctive absorption for donor-acceptor cyclopropene **2a** at δ 1.8. Accordingly, **2a** was easily observed within 5 min to 30 min from reactions performed in the presence of $Cu(MeCN)_4PF_6$, $AgSbF_6$ and AgOTf, $Pd(OAc)_2$, and $ZnCl_2$, but not at all with Lewis acids such as BF_3OEt_2 or $Sc(OTf)_3$, or with $Zn(OTf)_2$ or $Fe(OAc)_3$ over much longer times. Once formed, **2a** continued catalytic reaction to **8** and **9**. Thus, donor-acceptor cyclopropenes are reaction intermediates in reactions catalysed by a broader set of catalysts than those of dirhodium (II), and efforts are underway to evaluate catalyst applicability in the formation and reactions of donor-acceptor cyclopropenes.

Conclusions

Under moderate thermal conditions the donor–acceptor cyclopropenes substituents are formed exclusively or nearly so from various enoldiazoacetates and enoldiazoacetamides. In most cases, solvent evaporation forms the pure cyclopropene product, and these compounds are stable for at least three days at room temperature. This convenient and metal-free protocol provides a new synthetic approach to donor–acceptor cyclopropenes. 1*H*-Pyrazoles that are commonly formed from vinyldiazoacetates are not produced except from *γ*-phenyl-enoldiazoacetates where they were by-products of donor-acceptor 3-phenylcyclopropene productions. The capability of donor–acceptor cyclopropenes as effective carbene precursors was demonstrated by asymmetric cyclopropanation with styrene. Higher reactivities for metal carbene formation were found with donor–acceptor cyclopropenes than with the corresponding enoldiazo compounds. Initial results demonstrate that donor-acceptor cyclopropenes are metal carbene precursors in reactions with diverse catalysts. The development of new methodologies for metal carbene formation from donor–acceptor cyclopropenes are being undertaken in our laboratory.

Notes and references

1 *(a)* M. Baird, in *Small ring compounds in organic synthesis II*, Springer Berlin Heidelberg, 1988, vol. 144, pp. 137-209; *(b)* H.Hopf, in *Carbocyclic Three- and Four-Membered Ring Compounds*, ed. A. de Meijere, Thieme, Stuttgart, 1997, vol. E17d, pp. 2745–2746; *(c)* M. S. Baird, *Chem. Rev.* 2003, **103**, 1271.

2 *(a)* M. Rubin, M. Rubina, V. Gevorgyan, *Chem. Rev.* 2007, **107**, 3117; *(b)* Z. B. Zhu, Y. Wei, M. Shi, *Chem. Soc. Rev.* 2011, **40**, 5534; *(c)* M. Rubin, M. Rubina, V. Gevorgyan, *Synthesis* 2006, **8**, 1221; *(d)* I. Marek, S. Simaan, A. Masarwa, *Angew. Chem. Int. Ed. Engl.* 2007, **46**, 7364.

3 *(a)* A. Archambeau, F. Miege, C. Meyer, J. Cossy, *Acc. Chem. Res.* 2015, **48**, 1021; *(b)* P. Müller, N. Pautex, M. P. Doyle, A. Bagheri, *Helve. Chim. Acta.* 1990, **73**, 1233; *(c)* G. Seidel, R. Mynott, A. Furstner, *Angew. Chem. Int. Ed. Engl.* 2009, **48**, 2510. *(d)* X. Xu, P. Y. Zavalij, M. P. Doyle, *J. Am. Chem. Soc.* 2013, **135**, 12439; *(e)* X. Xu, P. J. Zavalij, M. P. Doyle, *Chem. Comm.* 2013, **49**, 10287. *(f)* X. Xu, Y. Deng, D. N. Yim, P. Y. Zavalij, M. P. Doyle, *Chem. Sci.* 2015, **6**, 2196.

4 *(a)* H. M. L. Davies, B. H. Hu, E. Saikali, P. R. Bruzinski, *J. Org. Chem.* 1994, **59**, 4535; *(b)* H. M. L. Davies, J. H. Houser, G. Thornley, *J. Org. Chem.* 1995, **60**, 7529.

5 *(a)* P. M. Truong, M. D. Mandler, P. Y. Zavalij, M. P. Doyle, *Org. Lett.* 2013, **15**, 3278; *(b)* X. Xu, D. Shabashov, P. Y. Zavalij, M. P. Doyle, *Org. Lett.* 2012, **14**, 800; *(c)* X. Wang, C. M. Abrahams, P. Y. Zavalij, M. P. Doyle, *Angew. Chem. Int. Ed. Engl.* 2012, **51**, 5907; *(d)* X. Xu, D. Shabashov, P. Y. Zavalij, M. P. Doyle, *J. Org. Chem.* 2012, **77**, 5313.

6 *(a)* A. Padwa and W. Pearson, *Synthetic applications of 1,3-dipolar cycloaddition chemistry toward heterocycles and natural products*, Wiley, New York Chichester, 2002; *(b)* J. L. Brewbake, H. Hart, *J. Am. Chem. Soc.* 1969, **91**, 711; *(c)* D. Babinski, H. R. Aguilar, R. Still, D. E. Frantz, *J. Org. Chem.* 2011, **76**, 5915. Pyrazoles have been isolated as byproduct in Rh(II)-catalyzed reactions of vinyldiazo compounds. See: *(d)* H. M. L. Davies, N. J. S. Huby, W. R. Cantrell, J. L. Olive, *J. Am. Chem. Soc.* 1993, **115**, 9468; *(e)* M. P. Doyle, M. Yan, *J. Org. Chem.* 2002, **67**, 602.

7 Padwa, A. Kulkarni, Y. S. Zhang, Z. *J. Org. Chem.* 1990, **55**, 4144.

8 *(a)* R. Huisgen, *Angew. Chem. Int. Ed. Engl.* 1980, **19**, 947; *(b)* E. C. Taylor, I. J. Turchi, *Chem. Rev.* 1979, **79**, 181.

9 *(a)* P. S. Engel, *Chem. Rev.* 1980, **80**, 99; (b) A. Desjardins, J. Flemming, E. D. Sternberg, D. Dolphin, *Chem. Commun.* 2002, **22** 2622.

10 P. Müller, G. Bernardinelli, Y. F. Allenbach, M. Ferri, H. D. Flack, *Org. Lett.* 2004, **6**, 1725.

11 *(a)* P. Müller, Y. Allenbach, E. Robert, *Tetrahedron Asymmetry* 2003, **14**, 779; *(b)* A. Ghanem, M. G. Gardiner, R. M. Williamson, P. Müller, *Chem. Eur. J.* 2010, **16**, 3291.

12 *(a)* N. Shimada, M. Anada, S. Nakamura, H. Nambu, T. Tsutsui, S. Hashimoto, *Org. Lett.* 2008, **10**, 3603; *(b)* N. Shimada, T. Oohara, J. Krishnamurthi, H. Nambu, S. Hashimoto, *Org. Lett.* 2011, **13**, 6284.