ORGANIC LETTERS

2011
Vol. 13, No. 16
4284–4287

Thermally Induced Cycloadditions of Donor/Acceptor Carbenes

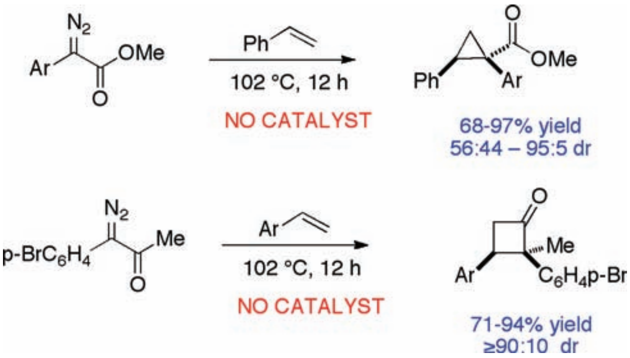
Stephanie R. Ovalles, Jørn H. Hansen, and Huw M. L. Davies*

Emory University, Department of Chemistry, 1515 Dickey Drive, Atlanta, Georgia 30322, United States

hmdavie@emory.edu

Received June 16, 2011

ABSTRACT



The thermal decomposition of aryldiazoacetates and aryldiazoketones in the absence of a catalyst leads to synthetically useful transformations. The thermal reaction of aryldiazoacetates with alkenes generates cyclopropanes in 68–97% yield and with good diastereoselectivity (up to 19:1 dr) when the aryl substituent is electron-rich. The thermal reaction of aryldiazoketones with alkenes generated cyclobutanones in 71–94% yield and with good diastereocontrol (≥9:1 dr).

Diazo compounds are widely used precursors for the generation of carbene intermediates under metal catalysis.[1] They can undergo a variety of useful synthetic transformations such as cyclopropanation,[2] C–H insertion,[3] and ylide formation.[4] A concern, however, with the use of diazo compounds is their thermal instability, although large-scale reactions have been reported.[5] We and others have conducted extensive studies on the metal-catalyzed reactions of aryldiazoacetates.[6] These reactions generate a class of intermediates, called donor/acceptor carbenoids, that are more selective than the traditional carbenoids lacking the donor group.[6b] This paper describes that, opposite to conventional wisdom, metal-free, thermal reactions of aryldiazo esters and aryldiazo ketones are also capable of highly selective transformations.

The most widely used catalysts for the reactions of donor/acceptor carbenoids have been dirhodium complexes.[7] Although these catalysts are extremely active,[5a,8] several other metals have been developed as catalysts for

---

[1] Doyle, M. P.; McKervey, M. A.; Ye, T. *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds: From Cyclopropanes to Ylides*; John Wiley & Sons, Inc.: New York, 1998.

[2] (a) Davies, H. M. L.; Antoulinakis, E. G. *Org. Reacts.* **2001**, *57*, 1–326. (b) Maas, G. *Chem. Soc. Rev.* **2004**, *33*, 183.

[3] (a) Davies, H. M. L.; Beckwith, R. E. J. *Chem. Rev.* **2003**, *103*, 2861. (b) Doyle, M. P.; Duffy, R.; Ratnikov, M.; Zhou, L. *Chem. Rev.* **2010**, *110*, 704.

[4] (a) Padwa, A.; Weingarten, M. D. *Chem. Rev.* **1996**, *96*, 223. (b) Padwa, A.; Hornbuckle, S. F. *Chem. Rev.* **1991**, *91*, 263.

[5] (a) Huang, Y.; Zhang, W.; Zhang, P.; Liu, X. *Ind. Eng. Chem. Res.* **2010**, *49*, 12164. (b) Simpson, J. H.; Godfrey, J.; Fox, R.; Kotnis, A.; Kacsur, D.; Hamm, J.; Totelben, M.; Rosso, V.; Mueller, R.; Delaney, E.; Deshpande, R. P. *Tetrahedron: Asymmetry* **2003**, *14*, 3569. (c) Saltzmann, T. N.; Ratcliffe, R. W.; Christensen, B. G.; Bouffard, F. A. *J. Am. Chem. Soc.* **1980**, *102*, 6161.

[6] (a) Zhang, Z.; Wang, J. *Tetrahedron* **2008**, *64*, 6577. (b) Hansen, J.; Autschbach, J.; Davies, H. M. L. *J. Org. Chem.* **2009**, *74*, 6555.

[7] (a) Hansen, J.; Davies, H. M. L. *Coord. Chem. Rev.* **2008**, *252*, 545. (b) Doyle, M. P. *J. Org. Chem.* **2006**, *71*, 9253.

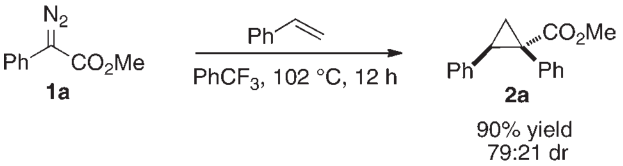
[8] Davies, H. M. L.; Bruzinski, P. R.; Lake, D. H.; Kong, N.; Fall, M. J. *J. Am. Chem. Soc.* **1996**, *118*, 6897.

[9] (a) Morilla, M. E.; Diaz-Requejo, M. M.; Belderrain, T. R.; Nicasio, M. C.; Trofimenko, S.; Perez, P. J. *Chem. Commun.* **2002**, 2998. (b) Yang, M. M.; Wang, X.; Livant, P. *J. Org. Chem.* **2001**, *66*, 6729. (c) Mbuvi, H. M.; Klobukowski, E. R.; Roberts, G. M.; Woo, L. K. *J. Porphyr. Phthalocyanines* **2010**, *14*, 284. (d) Del Zotto, A.; Baratta, W.; Rigo, P. *J. Chem. Soc., Perkin Trans. 1* **1999**, 3079. (e) Galardon, E.; LeMaux, P.; Simonneaux, G. *J. Chem. Soc., Perkin Trans. 1* **1997**, 2455. (f) Baumann, L. K.; Mbuvi, H. M.; Du, G.; Woo, L. K. *Organometallics* **2007**, *26*, 3995. (g) Mbuvi, H. M.; Woo, L. K. *Organometallics* **2008**, *27*, 637.

10.1021/ol201628d

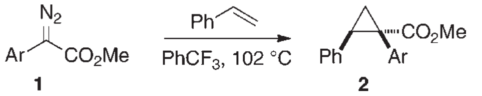
this chemistry but they often require reaction conditions above ambient temperature.[9] During exploratory studies on iron catalysis, we conducted a control experiment in which methyl phenyldiazoacetate (**1a**) was heated to reflux with styrene in trifluorotoluene over 12 h in the absence of catalyst (Scheme 1). Remarkably, under these conditions, a clean transformation was observed, generating the cyclopropane **2a** in 90% yield as a 4:1 E/Z mixture of diastereomers. Although photochemically induced reactions of aryldiazoacetates have been described in the literature,[10] reports of the thermally induced reactions of such diazo compounds is sparse.[11,12] Herein, we describe a study of how the nature of the substrate and diazo compound influences the course of thermally induced reactions of donor/acceptor carbenes.

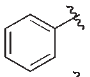
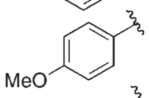
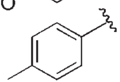
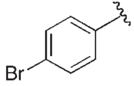
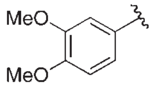
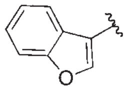
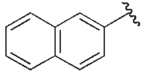
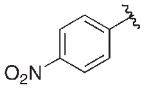
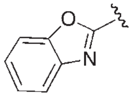
Scheme 1. Thermal Cyclopropanation of Styrene with **1a**



Theoretical studies have shown that the favored electronic structure of carbenes derived from aryldiazoacetates is dependent on the aryl substituent.[10a] The singlet ground state is favored when there is a donor substituent, such as a *p*-methoxy group, while the ground state is triplet when there is an acceptor substituent such as a *p*-nitro group.[10a] The thermal cyclopropanation reaction of a series of aryldiazoacetates was examined to see what impact the nature of the substituents would have on the reactivity (Table 1). The reaction of the aryldiazoacetate in the presence of 5 equiv of styrene in trifluorotoluene under reflux for 12 h was used as the standard reaction conditions. The cyclopropanes **2b**–**c**, **2f**–**g** derived from aryldiazoacetates **1b**–**g** were obtained in yields ranging from 90 to 97% whereas lower yields (57–68%) were obtained with the electron-deficient systems **1h,i**. The cyclopropanation reactions were highly diastereoselective (≥93:7 dr) with the most electron-rich substrates **1b**–**c**, **1e**–**f**, but the diastereoselectivity was only 56:44 dr for the *p*-nitro derivative **1h**. Many of the reactions proceeded in higher yields than the corresponding rhodium-catalyzed reactions,[2a] although the diastereoselectivity was inferior and no opportunity exists for asymmetric induction.[13] The reason for the marked difference in diastereoselectvity may be due to a change in the reactive electronic state of the carbene or an inherently more selective reaction by carbenes with a stronger donor substituent. Thermal reactions of styryldiazoacetates were not examined because these carbenoid precursors undergo thermal electrocyclization to pyrazoles rather than nitrogen extrusion.[14]

Table 1. Influence of Diazo Compound Structure[a]



compd	Ar	yield (%)	E/Z ratio[b]
a		90	79:21
b		92	95:5
c		93	95:5
d		76	81:19
e		68	95:5
f		95	93:7
g		97	82:18
h		57	56:44
i		68	77:23

[a] A dry round-bottom flask was charged with styrene (5.0 equiv) and dry trifluorotoluene. The reaction mixture was heated to reflux, and then the diazo compound (1.0 equiv) was added by syringe pump over a period 3 h. [b] From ^{1}H NMR of crude reaction mixture.

Studies have shown that the reactivity of metal carbenoids is highly dependent on the substituents.[15] Therefore, the thermal reactions of the aryldiazoacetates were compared with those of the other major classes of carbenes, the

---

(10) (a) Geise, C. M.; Wang, Y. H.; Mykhaylova, O.; Frink, B. T.; Toscano, J. P.; Hadad, C. M. *J. Org. Chem.* **2002**, *67*, 3079. (b) Tomioka, H.; Okuno, H.; Izawa, Y. *Tetrahedron Lett.* **1982**, *23*, 1917. (c) Tomioka, H.; Ozaki, Y.; Izawa, Y. *Tetrahedron* **1985**, *41*, 4987. (d) Mizushima, T.; Ikeda, S.; Murata, S.; Ishii, K.; Hamaguchi, H. *Chem. Lett.* **2000**, 1282.

(11) For examples that are likely to include thermally induced reactions, see: (a) Sharma, A.; Guenee, L.; Naubron, J.-V.; Lacour, J. *Angew. Chem., Int. Ed.* **2011**, *50*, 1. (b) Petrukhina, M. A.; Andreini, K. W.; Walji, A. M.; Davies, H. M. L. *Dalton Trans.* **2003**, *22*, 4221.

(12) Huisgen has conducted extensive studies on the 1,3-dipolar cycloaddition of diazo compounds with alkenes, and some of the resulting cycloadducts under forcing conditions extrude nitrogen to generate cyclopropanes. Typically, the dipolarophiles are electron deficient or strained and the 1,3-dipolar cycloaddition is conducted at temperatures below the decomposition temperatures of the diazo compounds. For a leading review, see: Huisgen, R. *Angew. Chem.* **1963**, *75*, 604.

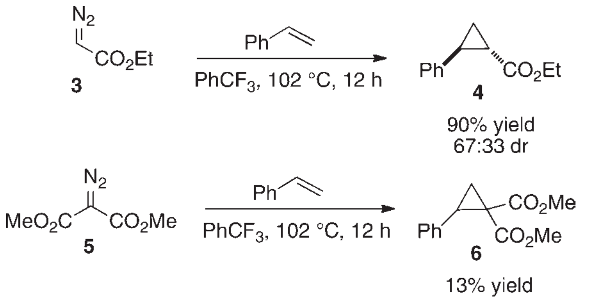
(13) See details in the Supporting Information for the results of the corresponding rhodium-catalyzed reactions.

(14) Davies, H. M. L.; Huby, N. J. S.; Cantrell, W. R., Jr.; Olive, J. L. *J. Am. Chem. Soc.* **1993**, *115*, 9468.

(15) Davies, H. M. L.; Hedges, L. M.; Matasi, J. J.; Hansen, T.; Stafford, D. G. *Tetrahedron Lett.* **1998**, *39*, 4417.

acceptor carbenes, and the acceptor/acceptor carbenes (Scheme 2). The more traditional carbene precursor, ethyl diazoacetate **3**, afforded the cyclopropane **4** in 90% yield and 67:33 dr. Methyl diazomalonate (**5**) generated the cyclopropane **6** in only 13% yield after 12 h because the conversion of **5** was very slow under these conditions.

Scheme 2. Thermal Cyclopropanation of Styrene with **3** and **5**



Having established the thermal cyclopropanation of the aryldiazoacetates, the reactions of electron-rich aryldiazoacetates **1b** and **1e** were examined with other olefinic substrates (Figure 1). Highly diastereoselective reactions were observed with substituted styrenes (**7a**–**b** dr > 91:9). Butyl vinyl ether afforded **7c** in moderate 86:14 dr, but in good combined yield of 85%. A cyclic vinyl ether, 1,2-dihydrofuran, afforded the corresponding cyclopropane **7d** in > 95:5 dr and 71% yield. The reaction between **1e** and *cis*-*β*-methylstyrene afforded cyclopropane **7e** in 72% yield and diastereoselectivity (dr = 92:8). The high stereoselectivity in this reaction lends support to a mechanism involving predominantly singlet carbene for the cyclopropanation.[16]

Even *trans*-*β*-methylstyrene readily underwent cyclopropanation under these conditions to afford **7f** in 62% yield and > 95:5 dr. Cyclopropanation of *trans*-alkenes cannot be achieved under rhodium-catalyzed conditions unless the alkene is very electron-rich.[17] Using 1,2-dihydronaphthalene as a substrate afforded **7g** in 50% yield and > 95:5 dr. Even cyclopropenation was feasible as the use of phenylacetylene as a trap afforded cyclopropene **7h** in 44% yield.

Attempts at extending the thermal cyclopropanation to aryldiazoketones resulted in a totally different reaction. The resulting carbene preferably underwent a Wolff rearrangement to a ketene, whose presence could be identified by React IR, followed by a much slower thermal [2 + 2]-cycloaddition with the styrene (Table 2).[18] The reaction of **8** with a series of styrenes proceeded in high yield and diastereoselectivity. As reported for other ketene cycloadditions, the *syn*-diastereomer was formed preferentially, consistent with the [$_{\pi}2_s + _{\pi}2_a$]-mechanism.[18b] The structure of the major product (entry 1) was confirmed unambiguously by X-ray crystallography (see Supporting Information).

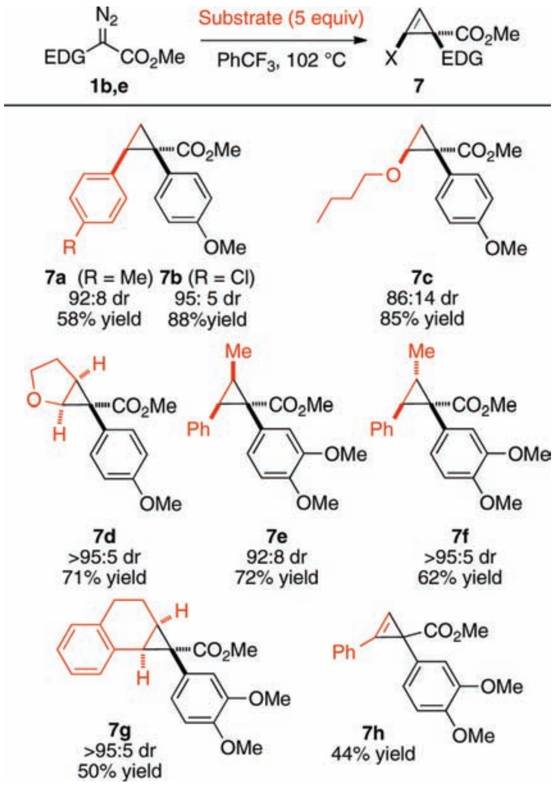
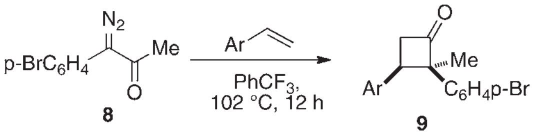


Figure 1. Thermal cycloaddition with various substrates.

The synthetic studies conducted above indicated that the thermal stability of the diazo compounds was structurally dependent. This was examined in more detail by conducting ReactIR studies on the electronically differentiated aryldiazoacetates **1a**–**b**, **1h** and ethyl diazoacetate **3**. The disappearance of the diazo compounds was monitored by

Table 2. Thermal [2 + 2]-Cycloadditions of Diazoketone **8**



compd	Ar	yield (%)[a]	dr[b]
a	-C_6H_5	69	91:9
b	-(*p*-Me)C_6H_4	91	90:10
c	-(*p*-CI)C_6H_4	94	90:10
d	-(*p*-MeO)C_6H_4	71	>95:5

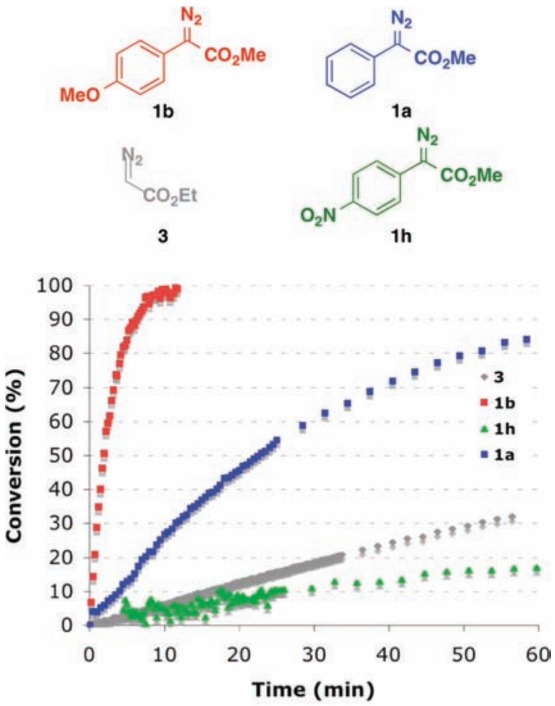
[a] Combined yield of both diastereomers. [b] From ^{1}H NMR of crude reaction mixture

---

(16) (a) Woodworth, R. C.; Skell, P. S. *J. Am. Chem. Soc.* **1959**, *81*, 3383. (b) Keating, A. E.; Merrigan, S. R.; Singleton, D. A.; Houk, K. N. *J. Am. Chem. Soc.* **1999**, *121*, 3933.

(17) Ventura, D. L.; Li, Z.; Coleman, M. G.; Davies, H. M. L. *Tetrahedron* **2009**, *65*, 3052.

(18) Kirmse, W. *Eur. J. Org. Chem.* **2002**, 2193. (b) Brady, W. T.; Roe, R. *J. Am. Chem. Soc.* **1971**, *93*, 1662.



Donor	Compd	k_1 (h^{-1})	$t_{1/2}$ (min)
(4-MeO)Ph	**1b**	22.87 ± 0.03	1.82
Ph	**1a**	1.92 ± 0.02	21.7
(4-NO_2)Ph	**1h**	0.147 ± 0.009	283
H	**3**	0.422 ± 0.008	98.6

Figure 2. Kinetic studies on the thermal decomposition of **1a**–**b**, **1h**, and **3** in the presence of styrene (5 equiv).

tracking the C=N_2 stretch frequency (~2100 cm^{-1}). Figure 2 shows a conversion plot of the reaction progress over 1 h for the thermal decomposition in refluxing trifluorotoluene in the presence of styrene. The diazo compounds decomposed with first-order kinetics, but the rates of decomposition were very different. The first-order rate constants were extracted from ln(ΔA) vs time plots and are reported with error bars from the linear regression analysis (see Supporting Information). The nature of the aromatic substituent was profound; the *p*-methoxy derivative **1b** had a half-life of 1.82 min, whereas the *p*-nitro derivative **1h** had a half-life of ~5.2 h. Ethyl diazoacetate (**3**) displayed a half-life of ~1.6 h, in between the half-lives of the unsubstituted aryl derivative **1a** (21.7 min) and the *p*-nitro derivative **1h**. These studies demonstrate that acceptor groups stabilize diazo compounds.[1] Even though these solution phase thermal reactions proceed very controllably with first-order kinetics, one should always be cautious when heating diazo compounds, especially on large scale.

These studies demonstrate that the thermal cyclopropanation chemistry of aryldiazoacetates in the absence of a transition metal catalyst can be a high-yielding process. Furthermore, when the aryl goup is electron-rich, the reaction is highly diastereoselective. Decomposition of aryldiazoketones under similar reaction conditions results in the formation of cyclobutanones in high yield and diastereocontrol, via the intermediacy of ketenes. Kinetic studies of the thermal reactions show that acceptor groups stabilize diazo compounds. These studies also suggest that reported catalytic reactions at high temperatures[9] may have significant thermal background reactions.

Acknowledgment. Financial support for this work by the National Science Foundation is gratefully acknowledged (CHE 0750273). We wish to acknowledge Mr. Evan L. T. Davies from the Gwinnet School of Math, Science & Technology for his initial studies on iron catalysis, which were an inspiration for this study.

Supporting Information Available. Experimental procedures, characterization and spectral data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.