ORGANIC LETTERS

2009
Vol. 11, No. 4
787−790

Enantioselective Reactions of Donor/Acceptor Carbenoids Derived from α-Aryl-α-Diazoketones

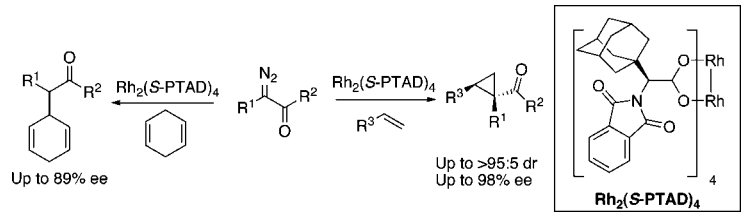
Justin R. Denton[†] and Huw M. L. Davies*[,‡]

Department of Chemistry, University at Buffalo, The State University of New York, Buffalo, New York 14260-3000, and Department of Chemistry, Emory University, 1515 Dickey Drive, Atlanta, Georgia 30322

hdavies@acsu.buffalo.edu

Received November 12, 2008

ABSTRACT



The reaction of a variety of α-aryl-α-diazo ketones with activated olefins, catalyzed by the adamantyl glycine-derived dirhodium complex Rh_2(*S*-PTAD)$_4$, generates cyclopropyl ketones with high diastereoselectivity (up to >95:5 dr) and enantioselectivity (up to 98% ee). Intermolecular C−H functionalization of 1,4-cyclohexadiene by means of carbenoid-induced C−H insertion was also possible with this type of carbenoid.

The metal-catalyzed reactions of diazo compounds, proceeding *via* metal carbenoid intermediates, have broad utility in organic synthesis.[1] Recent studies have shown that donor/acceptor carbenoids offer many synthetic advantages over the conventional carbenoids, which lack the combination of a donor and an acceptor group.[2] The acceptor group makes this class of carbenoids electrophilic, while the donor group modulates the reactivity sufficiently to allow highly regio- and stereoselective reactions to occur.[3] Major breakthroughs within this class of carbenoids include diastereoselective intermolecular cyclopropanations,[4] [4 + 3] cycloadditions between vinylcarbenoids and dienes,[5] intermolecular C−H,[2,6] Si−H,[7] N−H,[8] and O−H[9] insertions, and a range of novel

[†] University at Buffalo, The State University of New York.
[‡] Emory University.

(1) Doyle, M.; Mckervey, M.; Ye, T. *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds: From Cyclopropanes to Ylides*; John Wiley & Sons Inc.: New York, 1998.

(2) For reviews, see: (a) Davies, H. M. L.; Antoulnakis, E. G. *Org. React.* **2001**, *57*, 1. (b) Davies, H. M. L.; Beckwith, R. E. J. *Chem. Rev.* **2003**, *103*, 2861. (c) Davies, H. M. L.; Loe, Ø., *Synthesis* **2004**, *16*, 2595. (d) Davies, H. M. L.; Manning, J. R. *Nature* **2008**, *451*, 417.

(3) Davies, H. M. L.; Panaro, S. A. *Tetrahedron* **2000**, *56*, 4871.

(4) (a) Davies, H. M. L.; Bruzinski, P. R.; Fall, M. J. *Tetrahedron Lett.* **1996**, *37*, 4133. (b) Davies, H. M. L.; Bruzinski, P.; Lake, D.; Kong, N.; Fall, M. *J. Am. Chem. Soc.* **1996**, *118*, 6897. (c) Davies, H. M. L.; Nagashima, T.; Klino, J. L., III. *Org. Lett.* **2000**, *2*, 823. (d) Xu, Z.-H.; Zhu, S.-N.; Sun, X.-L.; Tang, Y.; Dai, L.-X. *Chem. Commun.* **2007**, *19*, 1960. (e) Thompson, J. L.; Davies, H. M. L. *J. Am. Chem. Soc.* **2007**, *129*, 6090. (f) Bykowski, D.; Wu, K.-H.; Doyle, M. P. *J. Am. Chem. Soc.* **2006**, *128*, 16038.

(5) For recent examples, see: (a) Olson, J. P.; Davies, H. M. L. *Org. Lett.* **2008**, *10*, 573. (b) Reddy, R. P.; Davies, H. M. L. *J. Am. Chem. Soc.* **2007**, *129*, 10312. (c) Davies, H. M. L.; Loe, Ø.; Stafford, D. G. *Org. Lett.* **2005**, *7*, 5561.

(6) For recent examples, see: (a) Davies, H. M. L.; Coleman, M. G.; Ventura, D. L. *Org. Lett.* **2007**, *9*, 4971. (b) Dai, X.; Wan, Z.; Kerr, R. G.; Davies, H. M. L. *J. Org. Chem.* **2007**, *72*, 1895. (c) Davies, H. M. L.; Ni, A. *Chem. Commun.* **2006**, 3110.

(7) (a) Davies, H. M. L.; Hansen, T.; Rutberg, J.; Bruzinski, P. *Tetrahedron Lett.* **1997**, *38*, 1741. (b) Bulugahapitiya, P.; Landais, Y.; Parra-Rapado, L.; Planchenault, D.; Weber, V. *J. Org. Chem.* **1997**, *62*, 1630.

(8) (a) Liu, B.; Zhu, S.-F.; Zhang, W.; Chen, C.; Zhou, Q. L. *J. Am. Chem. Soc.* **2007**, *129*, 5834. (b) Lee, E. C.; Fu, G. C. *J. Am. Chem. Soc.* **2007**, *129*, 12066. (c) Moody, C. J. *Angew. Chem., Int. Ed.* **2007**, *46*, 9148. (d) Deng, Q.; Xu, H.; Yuen, A. W.; Xu, Z.; Che, C. *Org. Lett.* **2008**, *10*, 1529.

(9) (a) Maier, T. C.; Fu, G. C. *J. Am. Chem. Soc.* **2006**, *128*, 4594. (b) Chen, C.; Zhu, S.; Liu, B.; Wang, L.; Zhou, Q. *J. Am. Chem. Soc.* **2007**, *129*, 12616. (c) Zhu, S.; Chen, C.; Cai, Y.; Zhou, Q. *Angew. Chem., Int. Ed.* **2008**, *47*, 932.

10.1021/ol802614j CCC: $40.75
Published on Web 01/15/2009

reactions involving ylide intermediates.[10] The most widely used acceptor group has been a methyl ester (Figure 1).[4]

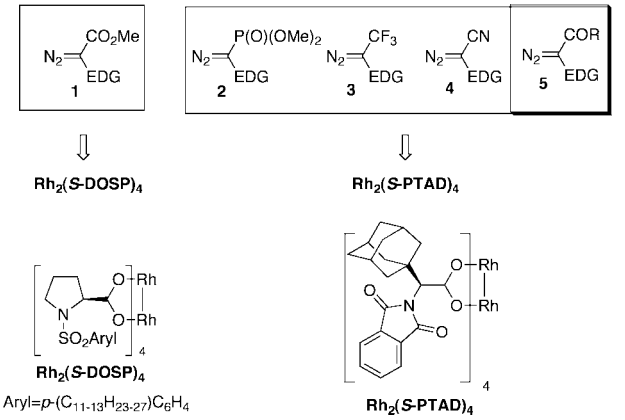


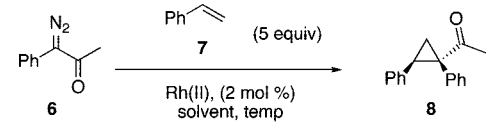
Figure 1. Optimal chiral catalysts for the different classes of donor/acceptor-substituted diazo compounds.

The dirhodium tetaprolinate Rh_2(*S*-DOSP)$_4$ is an exceptional chiral catalyst with the donor-substituted methyl diazoacetates (**1**) in cyclopropanations,[4b] C−H insertions,[6] and Si−H insertions.[7a] Various chiral copper catalysts have performed well in enantioselective N−H[8] and O−H[9] insertions. Rh_2(*S*-DOSP)$_4$ is not an effective chiral catalyst if the methyl ester on the carbenoid is replaced by another acceptor group, and Rh_2(*S*-PTAD)$_4$[11] has been found to be the catalyst of choice in these cases.[12] Excellent results have been obtained in enantioselective cyclopropanation with the diazo-phosphonate (**2**),[12a] diazo-trifluoromethyl (**3**),[12b] and the diazo-nitrile (**4**)[12c] systems. In this paper we expand the range of Rh_2(*S*-PTAD)$_4$ catalysis and describe that α-aryl-α-diazo ketones (**5**) can undergo highly enantioselective intermolecular reactions.

Enantioselective intermolecular cyclopropanations with α-diazo ketones have not been extensively explored.[13,14] The best results to date have been asymmetric cyclopropanation with diazoacetophenone using a chiral ruthenium porphyrin catalyst.[13a] As far as we are aware, no examples of intermolecular reactions by α-aryl-α-diazo ketones (**5**)[15] have been reported prior to this study.

1-Phenyl-1-diazoacetone (**6**) was used as a prototypical substrate to inititate this study on the reactions of donor-substituted ketocarbenoids (Table 1). The Rh_2(*S*-DOSP)$_4$-catalyzed (2 mol %) reaction of **6** in the presence of styrene (**7**, 5 equiv) with hexane as solvent at room temperature resulted in the formation of the cyclopropane **8** in 70% yield. The diastereoselectivity is high (dr >95:5, entry 1), which is a typical feature of cyclopropanation reactions with donor/acceptor carbenoids. The enantioselectivity for the formation of **8** was negligible (<5%), illustrating once again that Rh_2(*S*-DOSP)$_4$ is ideally suited only for reactions of donor-substituted methyl diazoacetates. In contrast, the Rh_2(*S*-PTAD)$_4$-catalyzed reaction at room temperature gave much higher asymmetric induction (88% ee); however, the reaction was inefficient, resulting in only 18% yield of **8** (entry 2). When the reaction was conducted in refluxing hexane, however, **8** was formed in 80% yield with only a slight drop in enantioselectivity (81% ee, entry 3). The reactions conducted in refluxing 2,2-dimethylbutane gave similar trends (entries 4 and 5). Hashimoto's *tert*-butyl leucinate catalyst, Rh_2(*S*-PTTL)$_4$,[11] was also effective in this chemistry but gave enantioselectivity (77% ee, entry 6) slightly lower than that using Rh_2(*S*-PTAD)$_4$. Conducting the reaction with only 2 equiv of styrene (entry 7) or with 1 mol % of catalyst (entry 8) gave results comparable to those of the standard reaction with 5 equiv of styrene and 2 mol % of catalyst.

Table 1. Optimization of the Intermolecular Cyclopropanation of Styrene



entry	Rh(II)	solvent	temp	yield[a] (%)	dr[b] (*E*:*Z*)	ee[c] (%)
1	Rh_2(*S*-DOSP)$_4$	hexanes	rt	70	>95:5	<5
2	Rh_2(*S*-PTAD)$_4$	hexanes	rt	18	>95:5	88
3	Rh_2(*S*-PTAD)$_4$	hexanes	reflux	80	>95:5	81
4	Rh_2(*S*-DOSP)$_4$	DMB[d]	reflux	93	>95:5	<5
5	Rh_2(*S*-PTAD)$_4$	DMB[d]	reflux	92	>95:5	85
6	Rh_2(*S*-PTTL)$_4$	DMB[d]	reflux	72	>95:5	77
7	Rh_2(*S*-PTAD)$_4$	DMB[d,e]	reflux	80	>95:5	85
8	Rh_2(*S*-PTAD)$_4$	DMB[d,f]	reflux	90	>95:5	85

[a] Isolated yield after purification. [b] Determined from crude material by ^{1}H NMR. [c] Determined by chiral HPLC. [d] 2,2-Dimethylbutane. [e] 2 equiv of styrene. [f] 1 mol % of Rh_2(*S*-PTAD)$_4$.

(10) (a) Hodgson, D. M.; Pierard, F. Y. T. M.; Stupple, P. A. *Chem. Soc. Rev.* **2001**, *30*, 50. (b) Doyle, M. P.; Hu, W.; Timmons, D. J. *Org. Lett.* **2001**, *3*, 933. (c) Lu, C.-H.; Liu, H.; Chen, Z.-Y.; Hu, W.-H.; Mi, A.-Q. *Org. Lett.* **2005**, *7*, 83. (d) Guo, Z.; Huang, H.; Fu, Q.; Hu, W. *Synlett* **2006**, *15*, 2486.

(11) Rh_2(*S*-PTAD)$_4$ is related to a series of rhodium phthalimidocarboxylate catalysts pioneered by Hashimoto. See: (a) Takahashi, T.; Tsutsui, H.; Tamura, M.; Kitagaki, S.; Nakajima, M.; Hashimoto, S. *Chem. Commun.* **2001**, 1604. (b) Minami, K.; Saito, H.; Tsutsui, H.; Nambu, H.; Anada, M.; Hashimoto, S. *Adv. Synth. Catal.* **2005**, *347*, 1483.

(12) (a) Reddy, R. P.; Lee, G. H.; Davies, H. M. L. *Org. Lett.* **2006**, *8*, 3437. (b) Denton, J. R.; Sukumaran, D.; Davies, H. M. L. *Org. Lett.* **2007**, *9*, 2625. (c) Denton, J. R.; Cheng, K.; Davies, H. M. L. *Chem. Commun.* **2008**, 1238.

(13) (a) Nicolas, I.; Maux, P. L.; Simmoneaux, G. *Tetrahedron Lett.* **2008**, *49*, 2111. (b) Nakamura, A.; Konishi, A.; Tatsuno, Y.; Otsuka, S. *J. Am. Chem. Soc.* **1978**, *100*, 3443.

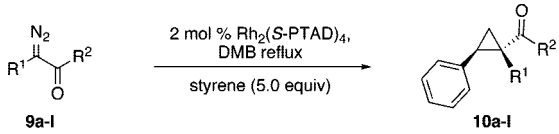
(14) For examples of alternative strategies for the stereoselective synthesis of highly functionalized cyclopropyl ketones, see: (a) Concellón, J. M.; Rodríguez-Solla, H.; Méjica, C.; Blanco, E. G.; García-Granda, S.; Díaz, M. R. *J. Org. Chem.* **2008**, *73*, 3828. (b) Yadav, A. K.; Peruncheralathan, S.; Ila, H.; Junjappa, H. *J. Org. Chem.* **2007**, *72*, 138. (c) Chen, H.; Deng, M.-Z. *Org. Lett.* **2000**, *2*, 1649.

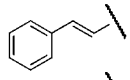
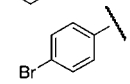
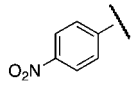
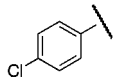
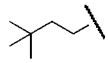
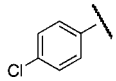
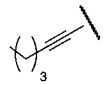
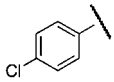
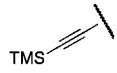
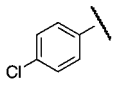
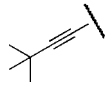
(15) For examples of enantioselective intramolecular reactions of α-aryl-α-diazo ketones, see: (a) Taber, D. F.; Tain, W. *J. Org. Chem.* **2008**, *73*, 7560. (b) Taber, D. F.; Tain, W. *J. Org. Chem.* **2007**, *72*, 3207.

(16) The X-ray crystallographic data has been submitted by Pitak, M. and Coppens, P. 2008, CCDC 699498.

The next series of experiments evaluated the effect of the carbenoid substituents on the cyclopropanation selectivity (Table 2). These reactions were conducted using the optimum

Table 2. Intermolecular Cyclopropanation of Diazo Ketones



entry	compd	R^1	R^2	yield[a] (%)	dr[b] (*E*:*Z*)	ee[c] (%)
1	**a**		CH_3	85	>95:5	54
2	**b**		CH_3	93	>95:5	89
3	**c**		CH_3	82	>95:5	88
4	**d**	Ph		95	>95:5	85
5	**e**	Ph		91	>95:5	91
6	**f**	Ph		82	>95:5	94
7	**g**	Ph		91	>95:5	51
8	**h**	Ph		traces	ND	ND
9	**i**			81	>95:5	93
10	**j**			93	>95:5	95
11	**k**			90	>95:5	98[d]
12	**l**			93	>95:5	95
13				86[e]	>95:5[e]	95[e]
14				92[f]	>95:5[f]	56[f]

[a] Isolated yield after purification. [b] Determined from crude material by ^{1}H NMR. [c] Determined by chiral HPLC. [d] The reaction was run with 1.0 mol % of Rh_2(*S*-PTAD)$_4$. [e] The reaction was run with 0.5 mol % of Rh_2(*S*-PTAD)$_4$. [f] The reaction was run with 1.0 mol % of Rh_2(*S*-DOSP)$_4$.

catalyst, Rh_2(*S*-PTAD)$_4$, and styrene as the trapping agent. In all cases, the diastereoselectivity was uniformly high (>95:5 dr). Three different donor groups (R^1) were first examined (entries 1−3). Substituting the aryl group with a styryl group caused a drop in enantioselectivity (54% ee, entry 1). Introduction of *para*-substituents on the phenyl ring effected little change in enantioselectivity (entries 2 and 3).

Altering the structure of the ketone functionality (R^2) had an unexpected influence on the enantioselectvity of the cyclopropanation. Increasing the size of the ketone group from methyl to ethyl, propyl, and isobutyl resulted in enhanced enantioselectivity (entries 4−6). Increasing the length of the alkyl chain beyond propyl was unproductive as intramolecular C−H insertion became a competing reaction. Bulky groups close to the carbonyl such as phenyl or isopropyl were unfavorable. In the case of the phenyl ketone **10g**, the enantioselectivity dropped to 51% ee (entry 7), while only traces of cyclopropane were obtained with isopropyl ketone **10h** (entry 8).

Further optimization studies were directed toward ketone groups lacking bulk immediately adjacent to the carbonyl. The chosen groups were also unlikely to undergo intramolecular C−H insertion. The 3,3-dimethylbutyl derivative **10i** was very effective (entry 9), but the most impressive results were obtained when alkynyl dervatives **10j**−**l** were used. In each case the cyclopropanes were produced in >90% yield, >95:5 dr, and 95−98% ee (entries 10−13). Similar results were obtained when the amount of Rh_2(*S*-PTAD)$_4$ was reduced to 0.5 mol % (entry 13), while the Rh_2(*S*-DOSP)$_4$-catalyzed reaction still gave much lower and opposite enantioselectivity (56% ee, entry 14).

On the basis of the established model for asymmetric cyclopropanation by donor/acceptor carbenoids, the major cyclopropane formed in a Rh_2(*S*-DOSP)$_4$-catalyzed reaction is predicted to be (1*R*,2*S*),[4b] whereas Rh_2(*S*-PTAD)$_4$ tends to form the opposite enantiomer.[12] The relative and absolute configuration of **10l** was determined to be (1*S*,2*R*) by X-ray crystallographic analysis (Figure 2), in agreement with the

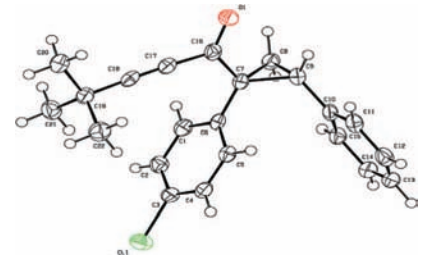


Figure 2. X-ray crystal structure of **10l**.

predicted assignment.[16] All other ketone-substituted cyclopropanes are assigned the same relative and absolute configuration by analogy.

The scope of the intermolecular cyclopropanation was then explored using the diazo ketone **9l** (Table 3). In all cases in

Scheme 1. Cyclopropanation of *n*-Butyl Vinyl Ether

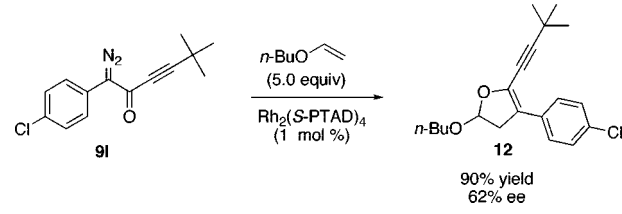
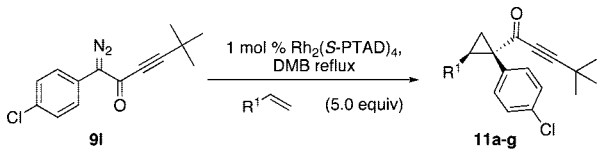
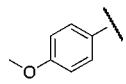
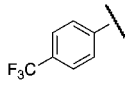
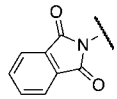
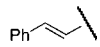
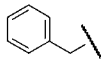


Table 3. Intermolecular Cyclopropanation of Various Alkenes



entry	compd	R^1	yield[a] (%)	dr[b] (*E*:*Z*)	ee[c] (%)
1	**11a**		91	>95:5	94
2	**11b**		90	>95:5	98
3	**11c**		95	>95:5	97
4	**11d**		87	>95:5	88
5	**11e**		90	>95:5	88
6	**11f**		91	>95:5	86
7	**11g**		37[d]	2:1	88[d]

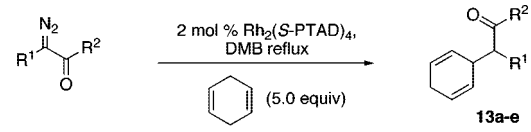
[a] Reported yields of isolated product. [b] Determined from crude material by ^{1}H NMR. [c] Determined by chiral HPLC. [d] Values are for the major diastereomer only.

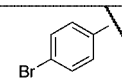
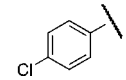
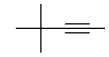
which the substrate alkene is electron-rich, the diastereoselectivity was very high. Styrene derivatives underwent the cyclopropanation with high enantioselectivities (entries 1 and 2). Similarly, *N*-vinyl phthalimide generated the cyclopropane with very high enantioselectivity (97% ee, entry 3). The reactions with vinyl acetate and dienes were not as enantioselective (86−88% ee, entries 4−6). The unactivated olefin allyl benzene was not an effective substrate. The cyclopropane **11g** was formed in only 37% yield and as a 2: 1 mixture of diastereomers, although the major diastereomer was still produced in 88% ee (entry 7).

The Rh_2(*S*-PTAD)$_4$-catalyzed reaction of **9l** with *n*-butyl vinyl ether did not result in the formation of a cyclopropyl ketone. Instead, the dihydrofuran **12** was formed in 90% yield and 62% ee. This type of [3 + 2] cycloadduct is typically considered to be formed by means of zwitterionic intermediates.[2a] The moderate level of enantioselectvity observed in the formation of **12** suggests that the chiral catalyst is still associated at the zwitterionic intermediate stage.

Another major reaction of donor/acceptor carbenoids is intermolecular C−H functionalization by means of carbenoid-induced C−H insertion.[2,6] In order to evaluate if these ketocarbenoids are capable of similar reactions, tests were conducted with 1,4-cyclohexadiene (Table 4). The Rh_2(*S*-PTAD)$_4$-catalyzed reactions gave excellent yields of the C−H insertion products **13a**−**e**. The enantioselectivities ranged from 71% to 89% ee.

Table 4. Intermolecular C−H Insertion of 1,4-Cyclohexadiene



entry	compd	R^1	R^2	yield[a] (%)	ee[b] (%)
1	**13a**		CH_3	88 traces[c]	89 N.D.
2	**13b**	Ph	CH_3	90	80
3	**13c**	Ph		84	71
4	**13d**	Ph		81	80
5	**13e**			75	81

[a] Reported yields of isolated products. [b] Determined by chiral HPLC. [c] The reaction was run at room temperature.

In summary, cyclopropylketones are readily synthesized by Rh(II)-catalyzed intermolecular cyclopropanation of olefins with α-aryl-α-diazo ketones. The reaction can proceed in a stereocontrolled fashion utilizing the chiral catalyst Rh_2(*S*-PTAD)$_4$. Intermolecular C−H insertions were also feasible with these carbenoid precursors. These studies further expand the range of donor/acceptor-substituted rhodium carbenoids that are capable of highly stereoselective transformations.

Acknowledgment. Financial Support of this work by the National Science Foundation (CHE-0750273) is gratefully acknowledged. We thank Dr. Mateusz Pitak, University at Buffalo, for the X-ray crystallographic analysis.

Supporting Information Available: Experimental data for the reported reactions and a CIF file for the X-ray crystallogrphic data for **10l**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL802614J