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Catalytic Cyclopropanation of Alkenes Using Diazo Compounds Generated in Situ. A Novel Route to 2-Arylcyclopropylamines

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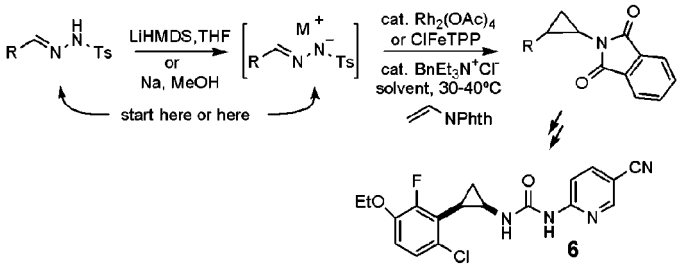
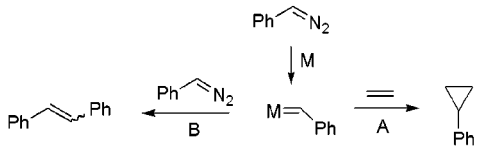
ABSTRACT



A user-friendly, one-pot process for catalytic cyclopropanation of alkenes from tosylhydrazones is described. The cyclopropanation of *N*-vinylphthalimide provides a new route to 2-arylcyclopropylamines, and this is exemplified in the efficient synthesis of the HIV-1 reverse transcriptase inhibitor 6.

Transition-metal-catalyzed cyclopropanation of alkenes using diazo compounds is not only highly efficient but also, through developments in chiral catalysts, control over relative and absolute stereochemistry can now be achieved in many cases.[1] However, to date developments in cyclopropanation have been restricted to diazo esters and α-substituted analogues for two reasons: (i) diazo esters are more stable (ethyl diazoacetate is commercially available) and therefore easier to handle than aryl-, alkenyl-, or alkynyldiazomethanes, which are unstable and potentially explosive,[2,3] and (ii) diazo esters are much less prone to metal-catalyzed diazo dimerization than the above diazo compounds. In fact, to achieve reasonable yields in cyclopropanation of alkenes with phenyldiazomethane, slow addition of this substrate is required (to minimize the concentration of $PhCHN_2$, thereby slowing the rate of path B, Scheme 1) together with a large excess of the alkene (to maximize the rate of cyclopropanation, path A); otherwise, stilbenes are the dominant product.[4]

Scheme 1



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(1) For recent reviews, see: Doyle, M. P.; McKervey, M. A.; Ye, T. *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds: From Cyclopropanes to Ylides*; Wiley-Interscience: New York, 1998. (b) Dörwald, F. Z. *Metal Carbenes in Organic Synthesis*; Wiley-VCH: New York, 1998. (c) Doyle, M. P. In *Comprehensive Organometallic Chemistry II*; Hedegeus, L. S., Ed.; Pergamon Press: New York, 1995; Vol. 12; Chapters 5.1 and 5.2. (d) Davies, H. M. L. *Eur. J. Org. Chem.* **1999**, 2459. (e) Doyle, M. P.; Forbes, D. C. *Chem. Rev.* **1998**, *98*, 911.

(2) Apart from diazomethane, diazoalkanes are not usually successful in cyclopropanation, as the metal carbene readily undergoes 1,2-hydrogen shifts to give alkenes: Doyle, M. P.; High, K. G.; Oon, H. S.-M.; Osborn, A. K. *Tetrahedron Lett.* **1989**, *30*, 3049. See also ref 1a.

(3) Regitz, M.; Maas, G. *Diazo Compounds: Properties and Synthesis*; Academic Press: London, 1996.

(4) Doyle, M. P.; Griffin, J. H.; Bagheri, V.; Dorow, R. L. *Organometallics* **1984**, *3*, 53.

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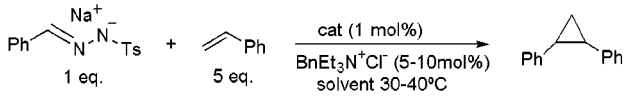
We recently reported a new method for generating aryl- and alkenyl diazomethanes from stable hydrazone derivatives and their use in catalytic epoxidation of carbonyl compounds.[5] As the diazo compounds were consumed as they were formed, their concentration in the reaction was always low and so there were no issues associated with handling or building up of these unstable intermediates.[3] Furthermore, as the diazo compounds were generated essentially one molecule at a time, their concentration in the reaction was always low. We were therefore keen to examine whether this new process could solve some of the traditional problems inherent in cyclopropanation of electron-rich alkenes. In this paper we report our success in achieving this goal and the development of a new user-friendly, one-pot cyclopropanation process in which the diazo compound is generated in situ.

We began our studies with styrene, $Rh_2(OAc)_4$, and the sodium salt of benzaldehyde tosylhydrazone and varied the solvent, the amount of PTC, and the temperature. From these studies we found that using either 1,4-dioxane and 10% PTC at 30 °C (conditions A) or toluene and 5% PTC at 40 °C (conditions B) gave the best results. We then screened a series of metal catalysts under both sets of conditions (Table 1). Contrary to expectation, copper catalysts, which are commonly employed in cyclopropation,[1] gave much poorer results (entries 1 and 2) than palladium catalysts[6] (entries 3−5). Rhodium acetate was superior to other rhodium salts (entries 6−8), and the iron porphyrin gave the highest yield (entry 9). Interestingly, rhodium acetate gave predominantly cis selectivity, while the iron porphyrin gave largely trans selectivity.

As rhodium acetate and the iron porphyrin gave the two highest yields and complementary selectivity (vide infra), these two catalysts were tested with a range of alkenes (Table 2). Moderate to good yields were achieved with most of the alkenes tested,[7] although, as expected, electron-rich alkenes performed better than less electron rich substrates (compare entries 3 and 4 with 9 and 10).[8] Dienes were also suitable substrates, and complete regioselectivity in favor of attack at the terminal alkene was observed with 1-methoxybutadiene (entries 13 and 14). Although *N*-vinylformamide gave poor yields in cyclopropanation, *N*-vinylphthalimide performed well and gave high cis selectivity with rhodium acetate (entry 15). This is the first example of the use of enamides in

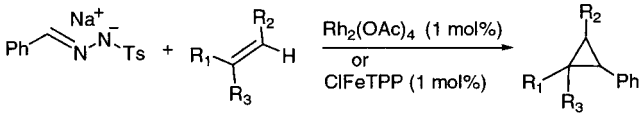
Table 1. Catalyst Influence in the in Situ Cyclopropanation

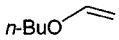
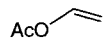
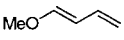
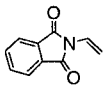


entry	catalyst[a]	conditions[b]	yield (%)[c]	trans:cis[d]
1	$Cu(MeCN)_4PF_6$	A	traces	
2	$Cu(OTf)_2$	A	13	87:13
3	$PdCl_2(PhCN)_2$	B	13	67:33
4	$Pd_2(dba)_3{\cdot}CHCl_3$	B	35	63:37
5	$Pd(PPh_3)_4$	A	20	71:29
6	$Rh_2(cap)_4$	A	traces	
7	$Rh_2(OAc)_4$	A	48	23:77
8	$Rh_2(pfb)_4$	B	traces	
9	ClFeTPP	B	73	91:9

[a] Abbreviations: cap = caprolactam, pfb = perfluorobutyrate, TPP = tetraphenylporphyrin. [b] All the catalysts were tested using conditions A (1,4-dioxane, 10 mol % PTC, 30 °C) and B (toluene, 5 mol % PTC, 40 °C), but only the best results are given in the table. [c] Isolated yields. [d] Determined by GC.

Table 2. Yields and Ratios of Cyclopropanes Formed from Alkenes and Benzaldehyde Tosylhydrazone Sodium Salt Using $Rh_2(OAc)_4$ and ClFeTPP



entry	alkene[a]	catalyst[b]	yield (%)[c]	*trans:cis*[d]
1		$Rh_2(OAc)_4$	65	5:95
2		ClFeTPP	-	-
3		$Rh_2(OAc)_4$	49	23:77
4		ClFeTPP	43	68:32
5		$Rh_2(OAc)_4$	48	23:77
6		ClFeTPP	73	91:9
7		$Rh_2(OAc)_4$	44	50:50
8		ClFeTPP	73	90:10
9		$Rh_2(OAc)_4$	19	2:98
10		ClFeTPP	10	2:98
11		$Rh_2(OAc)_4$	24	79:21
12		ClFeTPP	39	88:12
13		$Rh_2(OAc)_4$	46	9:91
14		ClFeTPP	86	59:41
15		$Rh_2(OAc)_4$	45	4:96
16		ClFeTPP	32	35:65

[a] A 5-fold excess of alkenes was employed, except in entries 9−12, where 10 equiv was used. [b] Reactions with different catalysts were performed according to the optimal conditions described in Table 1. [c] Isolated yields. [d] Determined by GC.

(5) Aggarwal, V. K.; Alonso, E.; Hynd, G.; Lydon, K. M.; Palmer, M. J.; Porcelloni, M.; Studley, J. R. *Angew. Chem., Int. Ed.* **2001**, *40*, 1430. We have also used this procedure for aziridination of imines and cyclopropanation of electron-deficient alkenes: Aggarwal, V. K.; Alonso, E.; Fang, G.; Ferrara, M.; Hynd, G.; Porcelloni, M. *Angew. Chem., Int. Ed.* **2001**, *40*, 1433. In addition, this procedure has been utilized for homologation of aldehydes: Aggarwal, V. K.; de Vicente, J.; Pelotier, B.; Holmes, I. H.; Bonnert, R. V. *Tetrahedron Lett.* **2000**, *41*, 10327.

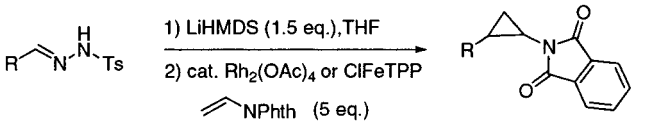
cyclopropanation, and we were surprised to find that they had not previously been employed, especially as there are a number of biologically important cyclopropylamines (vide infra).

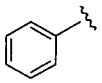
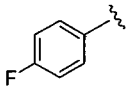
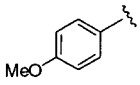
Using the Rh- and Fe-based catalyst, complementary diastereoselectivity was observed in most cases.[9] Only alkenes bearing β-carbonyl groups showed cis selectivity with both metals (entries 9, 10, 15, and 16). The observed diastereoselectivity with rhodium[1a,4,10] and iron[11] is largely in keeping with the literature. The iron porphyrin gives trans selectivity because it is a less electrophilic carbene and so has a later (more product-like) transition state.[11,12] The rhodium carbene, being more electrophilic, has an earlier transition state and cyclopropanation is less synchronous.[4,13]

We have also found that the tosylhydrazone salt can be generated in situ from the corresponding tosylhydrazone and base, and in fact, improved yields were obtained (Table 3). Several other diazo precursors were employed with *N*-vinylphthalimide, showing the generality of the new procedure.[14]

2-Arylcyclopropylamines and derivatives have received considerable attention following the introduction of *trans*-2-phenylcyclopropylamine for the treatment of depression in 1961.[15] They have also been found to be potent agonists for the 5-hydroxytryptamine (5-HT) receptor,[16] and more recently urea derivatives of arylcyclopropylamines have emerged as a new class of highly effective HIV-1 reverse transcriptase inhibitors.[17] Arylcyclopropylamines are generally prepared from the corresponding ester using a three-step sequence (Scheme 2):[18] basic hydrolysis of the ester, Curtius rearrangement, and finally hydrolysis of the isocyanate. The cyclopropyl ester is prepared by either metal-catalyzed cyclopropanation of ethyl diazoacetate with styrene or that of diazomethane with ethyl cinnamate (4 steps in total). The former, more commonly used process is usually moderately trans selective ((50:50)−(75:25)).[1,19] Our pro-

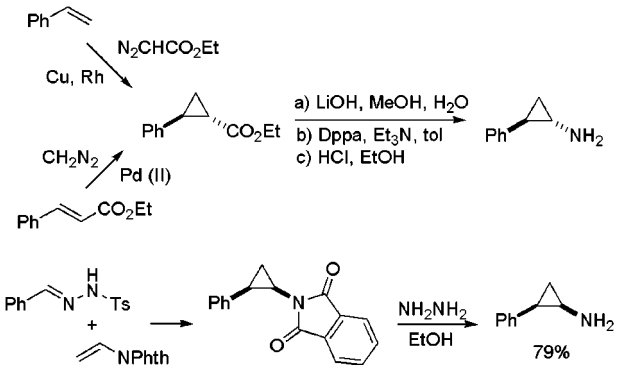
Table 3. Yields and Ratios of Cyclopropanes Formed from Different Hydrazones and *N*-Vinylphthalimide Using $Rh_2(OAc)_4$ and ClFeTPP



entry	R	catalyst[a]	yield (%)[b]	*trans:cis*[c]
1		$Rh_2(OAc)_4$	52	4:96
2		ClFeTPP	71	33:67
3		$Rh_2(OAc)_4$	49	3:97
4		ClFeTPP	53	32:68
5		$Rh_2(OAc)_4$	14	3:97
6		ClFeTPP	51	25:75

[a] Reactions with different catalysts were performed according to the optimal conditions described in Table 1. [b] Isolated yields. [c] Determined by GC.

Scheme 2



(6) Palladium(II) salts have been used extensively in the cyclopropanation of electron-deficient alkenes with diazomethane: Denmark, S. E.; Stavenger, R. A.; Faucher, A. M.; Edwards, J. P. *J. Org. Chem.* **1997**, *62*, 3375 and references therein. They have also occasionally been employed in cyclopropanation of electron-rich alkenes with ethyl diazoacetate: Miller, K. J.; Baag, J. H.; Abu-Omar, M. M. *Inorg. Chem.* **1999**, *38*, 4510 and references therein. However, there are only sporadic examples of the use of Pd(0) in cyclopropanation: Nakamura, A.; Koyama, T.; Otsuka, S. *Bull. Chem. Soc. Jpn.* **1978**, *51*, 593. Anciaux, A. J.; Hubert, A. J.; Noels, A. F.; Petiniot, N.; Teyssié, P. *J. Org. Chem.* **1980**, *45*, 695.

(7) It has been reported that 1,2-disubstituted alkenes are poor substrates with iron porphyrin catalysts,[10] hence the low yield with dihydropyran (entry 2).

(8) 1-Octene, cyclohexene, and 1-methyl-1-cyclohexene were poor substrates. This is keeping with Doyle's observations.[4]

(9) The assignment of the cis and trans isomers of the unknown cyclopropanes synthesized was determined by ^{1}H NMR on the basis of the diamagnetic anisotropy effect in the chemical shift caused by the aryl group ($\delta_{cis} > \delta_{trans}$) and confirmed by the coupling constans ($J_{cis} > J_{trans}$). The relative stereochemistry of *cis*- and *trans*-2-isopropenyl-2-methyl-1-phenylcyclopropane (entries 11 and 12, Table 2) was also confirmed by NOE experiments.

(10) de Meijere, A.; Schulz, T.-J.; Kostikov, R. R.; Graupner, F.; Murr, T.; Bielfeldt, T. *Synthesis* **1991**, 547.

(11) Wolf, J. R.; Hamaker, C. G.; Djukic, J.-P.; Kodadek, T.; Woo, L. K. *J. Am. Chem. Soc.* **1995**, *117*, 9194.

(12) In contrast to iron porphyrins, Hossain's iron Lewis acid [(η^5-C_5H_5)Fe(CO)$_2$THF] give largely cis cyclopropanes with $PhCHN_2$: Seitz, W. J.; Hossain, M. M. *Tetrahedron Lett.* **1994**, *35*, 7561. For a discussion on the mechanism, see ref 1a.

(13) Similar diastereoselectivity was originally found by Casey using an electrophilic tungsten phenylcarbene: Casey, C. P.; Polichnowski, S. W.; Shusterman, A. J.; Jones, C. R. *J. Am. Chem. Soc.* **1979**, *101*, 7282.

(14) None of the reactions presented in Table 3 have been optimized.

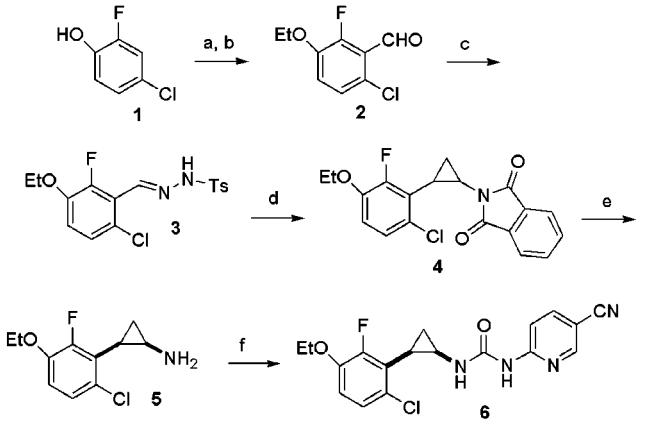
(15) (a) Zirkle, C. L.; Kaiser, C.; Tedeschi, D. H.; Tedeschi, R. E.; Burger, A. *J. Med. Chem.* **1962**, *5*, 1265. (b) Baldessarini, R. J. In *The Pharmacological Basis of Therapeutics*, 7th ed.; Gilman, A. G., Goodman, L. S., Rall, T. W., Murad, F., Eds.; Macmillan: New York, 1985; Chapter 19.

(16) (a) Arvidson, L.-E.; Johanson, A. M.; Hacksell, U.; Nilsson, J. L.-G.; Svensson, K.; Hjorth, S.; Magnusson, T.; Carlsson, A.; Lindberg, P.; Andersson, B.; Sanchez, D.; Wikström, H.; Sundell, S. *J. Med. Chem.* **1988**, *31*, 92. (b) Vallgårda, J.; Appelberg, U.; Arvidsson, L.-E.; Hjorth, S.; Svensson, B. E.; Hacksell, U. *J. Med. Chem.* **1996**, *39*, 1485. (c) Appelberg, U.; Mohell, N.; Hacksell, U. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 415.

(17) (a) Sahlberg, C.; Noréen, R.; Engelhardt, P.; Högberg, M.; Kangasmetsä, J.; Vrang, L.; Zhang, H. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 1511. (b) Högberg, M.; Sahlberg, C.; Engelhardt, P.; Noréen, R.; Kangasmetsä, J.; Johansson, N. G.; Öberg, B.; Vrang, L.; Zhang, H.; Sahlberg, B.-L.; Unge, T.; Lövgren, S.; Fridborg, K.; Bäckbro, K. *J. Med. Chem.* **1999**, *42*, 4150.

(18) Kaiser, C.; Weinstock, J. *Org. Synth.* **1971**, *51*, 48.

Scheme 3[a]



[a] Reaction conditions: (a) ethyl iodide, acetone, K_2CO_3, 55 °C, 100%; (b) *n*-BuLi, THF, −65 °C, followed by DMF, THF −65 °C to room temperature, 87%; (c) $TsNHNH_2$, MeOH, room temperature, 72%; (d) LiHMDS, THF, −78 °C to room temperature, then *N*-vinylphthalimide, $Rh_2(OAc)_4$, 10% PTC, 1,4-dioxane, room temperature, trans:cis 15:85, 76%; (e) $H_2NNH_2 \cdot H_2O$, EtOH, 40 °C, then 1 M HCl, EtOH, 78%; (f) 2-amino-5-cyanopyridine, triphosgene, THF, −78 °C to room temperature, 56%.

posed route involves two simple steps: cyclopropanation using a diazo compound generated in situ followed by hydrazinolysis, and both steps have proved to be efficient (Scheme 2). Furthermore, this process provides a route to the less easily accessible cis isomer with high diastereoselectivity.

The process has been further exemplified in the efficient synthesis of **6**, which is one of the most active members of the class of HIV-1 reverse transcriptase inhibitors[17] (Scheme 3). Aldehyde **2** was prepared from the commercially available phenol **1** in two steps and converted into the tosylhydrazone **3**. Deprotonation with LiHMDS and treatment with *N*-vinylphthalimide, PTC, and rhodium acetate[20] gave the cyclopropane **4** in 76% yield and as an 85:15 mixture in favor of the required cis isomer. We were pleased to note that even though a hindered 2,3,6-trisubstituted arylhydrazone was employed, *high yield and high cis selectivity was still achieved*. Following hydrazinolysis, the amine was coupled with 2-amino-5-cyanopyridine in the presence of triphosgene to give the urea **6**. This compound was spectroscopically identical with that reported.[17b] Our overall yield (18%) is markedly higher than that reported (0.7%).

In summary, we have developed a highly practical one-pot process for catalytic cyclopropanation of alkenes by in situ generation of the diazo compound. Furthermore, we have designed the simplest route to access *cis*-arylcyclopropylamines by a unique cyclopropanation of an enamide. This strategy was successfully employed as the key step in the synthesis of HIV-1 reverse transcriptase inhibitor **6** in 18% overall yield.

Acknowledgment. We gratefully thank AstraZeneca for support of a studentship (J.d.V.).

Supporting Information Available: Experimental details and characterization data for the products. This material is available free of charge via the Internet at http://pubs.acs.org.

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(19) During the course of this work, Pérez described a cis selective cyclopropanation of styrene with ethyl diazoacetate using a copper(I) tris(pyrazoyl)borate species: Díaz-Requejo, M. M.; Belderaín, T. R.; Trofimenko, S.; Pérez, P. J. *J. Am. Chem. Soc.* **2001**, *123*, 3167.

(20) Commercially available chiral Rh_2(S-DOSP)$_4$ catalyst only gave low enantioselectivity.