Tetrahedron Letters 50 (2009) 5149–5151

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Asymmetric intermolecular cyclopropanation of alkenes by diazoketones catalyzed by Halterman iron porphyrins

Irène Nicolas [a], Thierry Roisnel [b], Paul Le Maux [a], Gérard Simonneaux [a,*]

[a] Ingénierie Chimique et Molécules pour le Vivant, Université de Rennes 1, Campus de Beaulieu, 35042 Rennes Cedex, France
[b] Centre de Diffractométrie X, UMR 6226, Université de Rennes 1, Campus de Beaulieu, 35042 Rennes Cedex, France

ARTICLE INFO

Article history:
Received 7 May 2009
Revised 19 June 2009
Accepted 29 June 2009
Available online 4 July 2009

Keywords:
Iron
Diazoketone
Halterman porphyrin
Asymmetric cyclopropanation
Cyclopropyl ketones

ABSTRACT

The asymmetric addition of diazoacetophenone to styrene derivatives to give optically active cyclopropyl ketones (ee up to 80%) was carried out using chiral iron porphyrins as homogeneous catalysts. Intermolecular N–H functionalization of anilines by means of carbenoid-induced N–H insertion was also possible but without enantioselectivity.

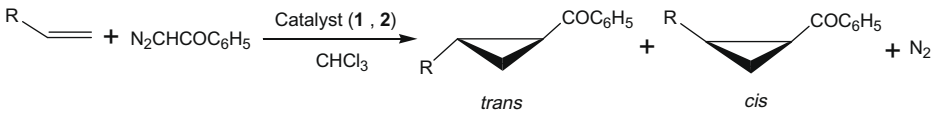
Most of the early studies on asymmetric carbenoid reactions were focused on intermolecular cyclopropanation using diazoacetate derivatives.[1] It is now widely recognized that a much wider field of nice carbenoid reactions is available and that the enantioselectivity and chemoselectivity are very dependant on the carbenoid structure. α-Diazoketones undergo a variety of transformations such as cyclopropanation, aziridine formation, ylide formation, C–H, S–H, N–H insertion reactions, and cyclization reactions.[2] Although asymmetric intramolecular carbene transfer has been quite developed,[3–5] there are very few reports on asymmetric intermolecular cyclopropanation using diazoketones, in particular using diazoacetophenone.[6,7] This is not too surprising since the absence of high enantioselectivity in transition metal-catalyzed decompositions of diazoketones is a well-known phenomenon.[8,9] To overcome this deficiency, we recently reported asymmetric cyclopropanation using diazoacetophenone with ruthenium porphyrins (Scheme 1).[7] We now want to report that chiral iron porphyrins can also be use to catalyze such asymmetric reaction with aryl diazoketones. It should also be noted that there are only few examples of asymmetric version of iron-catalyzed alkene cyclopropanation[10–13] despite the periodic relationship between iron and ruthenium and mainly with ethyl diazoacetate.

To evaluate the reactivity of diazoacetophenone compound, its iron-catalyzed decomposition was first examined in the presence of styrene in dichloromethane at room temperature by using tetraphenylporphyrin iron chloride **1** (Fig. 1) as catalyst (Table 1, entry 1). The cyclopropane was formed in 32% yield and with high diastereoselectivity (trans/cis = 91/9). As previously reported by Che and co-workers[13] with ethyl diazoacetate, we took benefit of the addition of pyridine to increase the reactivity and the trans/cis ratio. Actually, the absence of pyridine did not give any cyclopropanation reaction, probably due to the difficulty of reducing the ferric state to the ferrous state. We also investigated the cyclopropanation of *para*-substituted styrenes. As shown in the Table 1, *para*-substitution (*p*-X-styrene, X = MeO, CF_3, Cl, Br...) does not have a beneficial effect upon the chemical yield. Altogether using different styrene derivatives, the yield was quite low (20–33%) with a concomitant formation of the dimer (40–48%), resulting from coupling of two carbene precursors. Moreover, the reaction was not really sensitive to the electronic effect of the styrene substituent, suggesting a probable steric effect yielding a significant dimer formation. Whereas the reaction with *meta*-substituted styrenes (entries 8 and 10) and *ortho*-substituted styrene (entry 9) was also possible, the yields were also quite low and only traces of cyclopropanation were observed with *ortho*-CF_3 styrene.

We then investigated the cyclopropanation with chiral Halterman iron porphyrin **2**[14] (Table 2). With styrene, the cyclopropane was formed in 67% yield, 93/7 trans/cis ratio and with 76% enantioselectivity for the trans isomer (entry 1). We also investigated the asymmetric cyclopropanation of substituted styrene (Table 2). As shown in Table 2, the chemical yields are higher (~60%) than those obtained with unencumbered tetraphenylporphyrin iron chloride **1** (30%) and the enantioselectivity varies between

* Corresponding author.
E-mail address: gerard.simonneaux@univ-rennes1.fr (G. Simonneaux).

0040-4039/$ - see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2009.06.131



Scheme 1. Alkene cyclopropanation by diazoacetophenone.

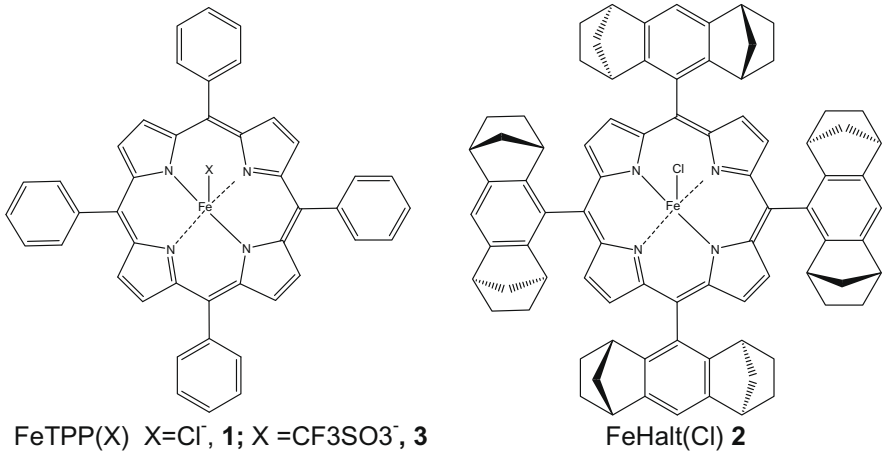


Figure 1. Iron porphyrin catalysts.

Table 1
Cyclopropanation with $N_2CHCOC_6H_5$ catalyzed by FeTPP(Cl)(**1**)[a]

Entry	Alkene R	Time (h)	Trans + cis[b]		Dimer (%)
			Yield (%)	Ratio	
1	C_6H_5	7	32	91:9	42
2	C_6H_5	15	<5	—	—
3	*p*-$CH_3C_6H_4$	7	32	96:4	43
4	*p*-$CH_3OC_6H_4$	7	31	93:7	45
5	*p*-$CF_3C_6H_4$	7	33	91:9	40
6	*p*-ClC_6H_4	7	20	93:7	48
7	*p*-BrC_6H_4	7	23	94:6	46
8	*m*-$CH_3C_6H_4$	7	30	91:9	58
9	*o*-$CH_3C_6H_4$	7	17	94/6	66
10	*m*-$CF_3C_6H_4$	7	10	90:10	75
11	*o*-$CF_3C_6H_4$	7	<5	94:6	83

[a] A molar ratio of 1:2:200:1000 for catalyst:pyridine:diazoacetophenone: alkene was employed at ambient temperature.
[b] Yields were determined by isolation of cyclopropanes by column chromatography on silica gel and the trans/cis ratio was calculated by gas chromatography with dodecane as an internal standard.

Table 2
Cyclopropanation with $N_2CHCOC_6H_5$ catalyzed by FeHalt(Cl)(**2**)[a]

Entry	Alkene R	Trans + cis[b]		% ee[c] trans	Dimer (%)
		Yield (%)	Ratio		
1	C_6H_5	67	93:7	76	16
2	*p*-$CH_3C_6H_4$	53	96:4	76	26
3	*p*-$CH_3OC_6H_4$	58	93:7	76	22
4	*p*-$CF_3C_6H_4$	54	93:7	62	25
5	*p*-ClC_6H_4	58	94:6	76	20
6	*p*-BrC_6H_4	58	92:8	69	20
7	*m*-$CH_3C_6H_4$	64	92:8	68	18
8	*o*-$CH_3C_6H_4$	58	92:8	80	23
9	*m*-$CF_3C_6H_4$	25	90/10	74	45
10	*o*-$CF_3C_6H_4$	24	90:10	78	48

[a] A molar ratio of 1:2:200:1000 for catalyst:pyridine:diazoacetophenone: alkene was employed at 40 °C.
[b] Yields were determined by isolation of cyclopropanes by column chromatography on silica gel and the trans/cis ratio was calculated by gas chromatography with dodecane as an internal standard.
[c] ees were determined by chiral HPLC using a Chiralcel OJ column.

62% and 80% ee depending upon the nature and the position of the substituent on the phenyl ring. By comparison with Halterman ruthenium porphyrin (ee: 83–86%),[7] the enantiomeric excesses are slightly lower with iron porphyrins but much higher than those obtained in asymmetric cyclopropanation with chiral cobalt complexes.[6] It should be emphasized that resonance interactions between the phenyl ring and the carbonyl group in the carbene complex will result in a decrease in positive charge at the carbonyl group and consequently, render the carbene less electron deficient. As previously suggested,[9] this situation will lead to higher selectivity due to a possible later transition state.

The previous assignment of the absolute configuration of cyclopropyl ketones[6] was based solely on analogy to the established configurations of related products produced by reaction of optically active ylides with *trans*-chalcone.[15] To assure the absolute configuration, an X-ray structure determination of cyclopropyl ketone obtained from the *p*-Br-styrene adduct was undertaken. Although at the end of the cyclopropanation, the ee was of only 69%, simple recrystallization of the product from isopropanol easily raises the optical purity to nearly 100%. The X-ray structure of monocrystals obtained from the bromo derivatives confirms the 1*R*,2*R* configuration for the trans isomer ($[\alpha]_D$ −394, CH_2Cl_2) (see Fig. 2).

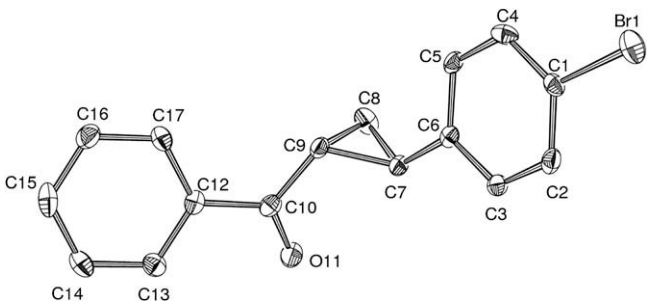
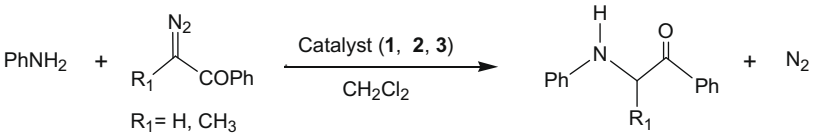


Figure 2. ORTEP structure of compound (1R)(C9), (2R)(C7)-*trans*-2-*p*-Br-phenyl-1-benzoylcyclopropane.



Scheme 2. N–H insertion into aniline by diazoketones.

Table 3
NH Insertion of aniline with $N_2CHCOC_6H_5$ and $N_2C(CH_3)COC_6H_5$ catalyzed by Fe TPP (Cl) (**1**), Fe Halt (Cl)(**2**), and Fe TPP triflate (**3**)[a]

Entry	Catalyst	Diazo	*T* (°C)	Time (h)	Yield[b] (%)
1	**1**	$N_2CHCOC_6H_5$	20	0.25	90
2	**1**	$N_2C(CH_3)COC_6H_5$	40	2	66
3	**2**	$N_2C(CH_3)COC_6H_5$	40	2	51[c]
4	**3**	$N_2CHCOC_6H_5$	20	0.25	92
5	**3**	$N_2C(CH_3)COC_6H_5$	20	2	20

[a] A molar ratio of 1:200:200 for catalyst: diazo: aniline was employed.
[b] Yields were determined by isolation of product by column chromatography on silica gel.
[c] ee of the insertion product was controlled by chiral HPLC using a Chiralcel OJ column, ee = 0.

Finally, we investigated possible asymmetric N–H insertion into aniline (Scheme 2) catalyzed by chiral iron porphyrin since a successful example was reported by Zhou with copper complexes of chiral spiro ligands, very recently.[16] The results are summarized in Table 3. With diazoacetophenone, the catalytic reaction was very effective at room temperature, (90–92% yield) to give N–H insertion, both with complex **1** or complex **3** (entry 1 or 4, Table 3). Using α-methyl acetophenone, chosen to get a possible asymmetric induction, N–H insertion was also possible but with lower yield (51%). Unfortunately, no chiral induction was detected using iron chiral porphyrin as the catalyst (entry 3). A similar situation was previously observed with ethyl diazoacetate insertion into N–H bond catalyzed by heme derivatives.[17]

In conclusion, chiral iron porphyrins are good catalysts for asymmetric cyclopropanation of styrene[18] yielding optically active cyclopropyl ketones[19] and for N–H insertion of aniline[20] but without any asymmetric induction in the latter case.

References and notes

1. (a) Doyle, M. P. *Angew. Chem., Int. Ed.* **2009**, *48*, 850–852; (b) Lebel, H.; Marcoux, J. F.; Molinaro, C.; Charette, A. B. *Chem. Rev.* **2003**, *103*, 977–1050.
2. Ye, T.; McKervey, M. A. *Chem. Rev.* **1994**, *94*, 1091–1160.
3. Pfaltz, A. *Acc. Chem. Res.* **1993**, *26*, 339–345.
4. Piqué, C.; Fähndrich, B.; Pfaltz, A. *Synlett* **1995**, 491–492.
5. Saha, B.; Uchida, T.; Katsuki, T. *Chem. Lett.* **2002**, 846–847.
6. Nakamura, A.; Konishi, A.; Tatsuno, Y.; Otsuka, S. *J. Am. Chem. Soc.* **1978**, *100*, 3443–3448.
7. Nicolas, I.; Le Maux, P.; Simonneaux, G. *Tetrahedron Lett.* **2008**, *49*, 2111–2113.
8. Doyle, M. P.; Eismont, M. Y.; Zhou, Q. L. *Russ. Chem. Bull.* **1997**, *46*, 955–958.
9. Müller, P.; Maîtrejean, E. *Collect. Czech. Chem. Commun.* **1999**, *64*, 1807–1826.
10. Gross, Z.; Galili, N.; Simkhovich, L. *Tetrahedron Lett.* **1999**, *40*, 1571–1574.
11. Hamaker, C. G.; Mirafzal, G. A.; Woo, L. K. *Organometallics* **2001**, *20*, 5171–5176.
12. Le Maux, P.; Juillard, S.; Simonneaux, G. *Synthesis* **2006**, *10*, 1701–1704.
13. Lai, T. S.; Chan, F. Y.; So, P. K.; Ma, D. L.; Wong, K. Y.; Che, C. M. *Dalton Trans.* **2006**, 4845–4851.
14. Halterman, R. L.; Jan, S. T. *J. Org. Chem.* **1991**, *56*, 5253–5254.
15. Johnson, C. R.; Schroeck, C. W. *J. Am. Chem. Soc.* **1968**, *90*, 6852–6854.
16. Liu, B.; Zhu, S. F.; Zhang, W.; Chen, C.; Zhou, Q. L. *J. Am. Chem. Soc.* **2007**, *129*, 5834–5835.
17. Aviv, I.; Gross, Z. *Chem. Eur. J.* **2008**, *14*, 3995–4005.
18. A solution of diazoacetophenone (29.2 mg, 0.2 mmol) in 0.2 ml chloroform was added dropwise to a 0.8 ml chloroform solution of Fe TPP (Cl) **1** (0.7 mg, 1 μmol), pyridine (0.16 mg, 2 μmol), and styrene (104 mg, 1 mmol) under a nitrogen atmosphere. The reaction mixture was stirred until complete transformation of the diazo compound (the reaction was monitored by TLC). The solvent was then removed under reduced pressure and the residue was purified by column chromatography on silica gel (pentane:CH_2Cl_2 = 1:1) to give a mixture of *cis* and *trans*-2-phenyl-1-benzoyl cyclopropane (14 mg, 32% yield). The diastereoselectivity was determined by GC analysis, 91:9, using a CP-Chirasil-Dex column. The dimer product was then recovered after elution with a pentane: CH_2Cl_2 mixture (1:2) (10 mg, 42% yield).
19. X-ray crystallographic study: ($C_{16}H_{13}Br_1O_1$); M = 301.17. APEXII, Bruker-AXS diffractometer, Mo-Kα radiation (λ = 0.71073 Å), T = 100(2) K; orthorhombic P 21 21 21, a = 5.1692(9), b = 7.9218(12), c = 32.549(5) Å, V = 1332.9(4) Å^3, Z = 4, d = 1.501 g cm^{-3}, μ = 3.068 mm^{-1}. The structure was solved by direct methods using the SIR97 program [a], and then refined with full-matrix least-square methods based on F^2 (SHELX-97) [b] with the aid of the WINGX [c] program. All non-hydrogen atoms were refined with anisotropic thermal parameters. H atoms were finally included in their calculated positions. A final refinement on F^2 with 3024 unique intensities and 163 parameters converged at $\omega R(F^2)$ = 0.0479 ($R(F)$ = 0.0292) for 2611 observed reflections with $I > 2\sigma(I)$. (a) Altomare, A., Burla, M. C.; Camalli, M.; Cascarano, G.; Giacovazzo, C.; Guagliardi, A.; Moliterni, A. G. G.; Polidori, G.; Spagna, R. *J. Appl. Crystallogr.* **1999**, *32*, 115–119. (b) SHELX97—Programs for Crystal Structure Analysis (Release 97-2). G. M. Sheldrick, Institüt für Anorganische Chemie der Universität, Tammanstrasse 4, D-3400 Göttingen, Germany, 1998. (c) Farrugia, L. J. J. *Appl. Cryst.* **1999**, *32*, 837–838.
20. Fe TTP (Cl) **1** (0.7 mg, 1 μmol), diazoacetophenone (29.2 mg, 0.2 mmol), and aniline (18.6 mg, 0.2 mmol) were stirred in a solution of CH_2Cl_2 (1 ml) at room temperature under a nitrogen atmosphere until complete consumption of diazo was evident by TLC (10 min). The solvent was then removed under reduced pressure and the residue was purified by column chromatography on silica gel (pentane: ether = 19:1) to give the insertion product (38 mg, 90% yield). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.53 (d, J = 6.8 Hz,3H), 4.76 (s, 1H), 5.18 (q, J = 6.6 Hz, 1H), 6.72 (d, J = 8.2 Hz, 2H), 6.76 (t, J = 8.0 Hz, 1H), 7.23 (t, J = 7.8 Hz, 2H), 7.52–7.66 (m, 3H), 8.06 (d, J = 8.0 Hz, 2H).