ORGANIC
LETTERS

2003
Vol. 5, No. 14
2493−2496

Acid-Promoted Olefination of Ketones by an Iron(III) Porphyrin Complex

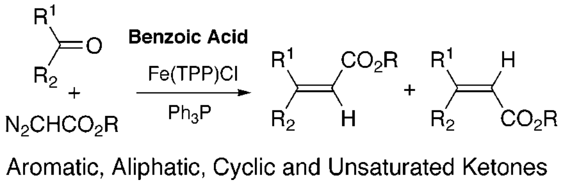
Ying Chen, Lingyu Huang, and X. Peter Zhang*

Department of Chemistry, University of Tennessee, Knoxville, Tennessee 37996-1600

pzhang@utk.edu

Received May 4, 2003

ABSTRACT



The acid-promoted olefination of unactivated ketones with diazo reagents in the presence of triphenylphosphine can be catalyzed by the commercially available iron(III) porphyrin complex Fe(TPP)Cl. The reactions were effectively carried out under mild conditions in a one-pot fashion with the use of a stoichiometric diazo reagents and substoichiometric benzoic acid. Examples include aromatic, aliphatic, cyclic, and unsaturated ketones with ethyl diazoacetate or *tert*-butyl diazoacetate.

Transition metal complex-mediated olefination of carbonyl compounds with diazo reagents in the presence of tertiary phosphines has received increased attention in recent years.[1] The new catalytic olefination approach promises to be advantageous over the classic Wittig reaction, which currently remains the method of choice for constructing carbon−carbon double bonds in organic synthesis for a variety of applications.[2] Specifically, the catalytic method can directly use easily accessible diazo compounds[3] for this important and fundamental organic transformation under neutral conditions, without the need for stepwise generation of phosphorane precursors under basic conditions. Furthermore, the involvement of transition metal complexes in this process could potentially allow the development of efficient asymmetric olefination under catalytic conditions.[4]

Recently, we have developed general and efficient catalytic systems, based on the commercially available Fe(TPP)Cl and Ru(TPP)(CO) (Figure 1), for highly selective olefination of a wide variety of aldehydes with ethyl diazoacetate (EDA) in the presence of triphenylphosphine under mild conditions.[5] Applying this methodology, we demonstrated that a series of *β*-trifluormethyl-α,*β*-unsaturated esters can be efficiently and stereoselectively synthesized form the corresponding trifluormethyl ketones with EDA or *tert*-butyl diazoacetate (*t*-BDA).[6] When the method was applied to unactivated ketones, however, no yields or very low yields of the desired olefins were observed. After many failed attempts, we have discovered that the addition of certain acids can dramatically improve the olefination of unactivated ketones under conditions similar to those for aldehydes. Herein, we report the first examples of acid-promoted olefination of unactivated

---

(1) (a) Santos, A. M.; Romão, C. C.; Kühn, F. E. *J. Am. Chem. Soc.* **2003**, *125*, 2414. (b) Zhang, X.; Chen, P. *Chem. Eur. J.* **2003**, *9*, 1852. (c) Cheng, G.; Mirafzal, G. A.; Woo, L. K. *Organometallics* **2003**, *22*, 1468. (d) Mirafzal, G. A.; Cheng, G.; Woo, L. K. *J. Am. Chem. Soc.* **2002**, *124*, 176. (e) Grasa, G. A.; Moore, Z.; Martin, K. L.; Stevens, E. D.; Nolan, S. P.; Paquet, V.; Lebel, H. *J. Organomet. Chem.* **2002**, *658*, 126. (f) Lebel, H.; Paquet, V. *Org. Lett.* **2002**, *4*, 1671. (g) Lebel, H.; Paquet, V.; Proulx, C. *Angew. Chem., Int. Ed.* **2001**, *40*, 2887. (h) Fujimura, O.; Honma, T. *Tetrahedron Lett.* **1998**, *39*, 625. (i) Ledford, B. E.; Carreira, E. M. *Tetrahedron Lett.* **1997**, *38*, 8125. (j) Herrmann, W. A.; Roesky, P. W.; Wang, M.; Scherer, W. *Organometallics* **1994**, *13*, 4531. (k) Herrman, W. A.; Wang, M. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1641. (l) Lu, X.; Fang, H.; Ni, Z. *J. Organomet. Chem.* **1989**, *373*, 77.

(2) (a) Maryanoff, B. E.; Reitz, A. B. *Chem. Rev.* **1989**, *89*, 863. (b) Padwa, A.; Hornbuckle, S. F. *Chem. Rev.* **1991**, *91*, 263. (c) Cristau, H.-J. *Chem. Rev.* **1994**, *94*, 1299.

(3) (a) Ye, T.; McKervey, M. A. *Chem. Rev.* **1994**, *94*, 1091. (b) Doyle, M. P.; McKervey, M. A.; Ye, T. *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds: From Cyclopropanes to Ylides*; John Wiley & Sons: New York, 1998. (c) Doyle, M. P.; Forbes, D. C. *Chem. Rev.* **1998**, *98*, 911.

(4) (a) Rein, T.; Reiser, O. *Acta Chem. Scand.* **1996**, *50*, 369. (b) Li, A.-H.; Dai, L.-X.; Aggarwal, V. K. *Chem. Rev.* **1997**, *97*, 2341. (c) Rein, T.; Pederson, T. M. *Synthesis* **2002**, *5*, 579.

(5) Chen, Y.; Huang, L.; Ranade, M. A.; Zhang, X. P. *J. Org. Chem.* **2003**, *68*, 3714.

(6) Chen, Y.; Huang, L.; Zhang, X. P. *J. Org. Chem.* In press.

10.1021/ol0347444 CCC: $25.00

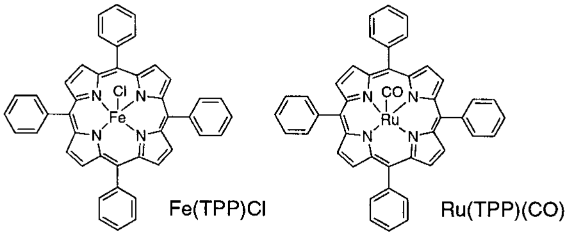
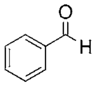
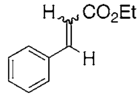
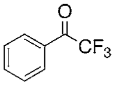
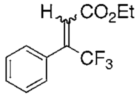
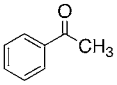
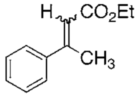
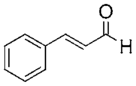
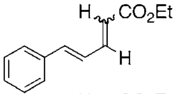
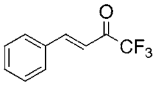
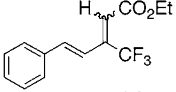
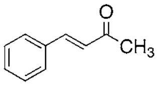
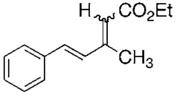
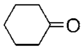
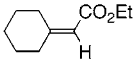
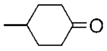
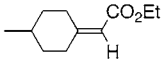
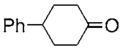
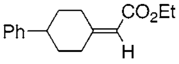


Figure 1. Structures of Fe(TPP)Cl and Ru(TPP)(CO).

ketones with diazo reagents in the presence of triphenyl phosphine catalyzed by the iron(III) porphyrin complex Fe(TPP)Cl.[7,8] The catalytic reactions can be performed in a one-pot fashion under mild conditions using substoichiometric amounts of acid and can be applied to a variety of simple ketones.

We first evaluated Fe(TPP)Cl-mediated olefination reactions of different ketones under conditions that are similar to those used for olefination of aldehydes[5] and activated trifluoromethyl ketones:[6] the reactions were carried out in toluene at 80 °C with 1.2 equiv of EDA using 1.5 mol % Fe(TPP)Cl in the presence of 1.2 equiv of Ph_3P per ketone at a concentration of 0.25 M (0.50 mmol of ketone/2 mL of toluene).[9] Selected results are summarized in Table 1, along with previous results for corresponding aldehydes[5] and trifluoromethyl ketones.[6] As clearly shown in Table 1, it is the electronic effect, not the steric effect, that is responsible for the poor reactivities of simple ketones. For example, only 2% yield of desired olefin was observed for the reaction of acetophenone under the aforementioned conditions after 51 h (Table 1, entry 3). As reported previously,[5,6] the reactions of benzaldehyde and trifluoroacetophenone under the same conditions gave the corresponding olefins in 96 and 93% yields, respectively, in much shorter reaction time (Table 1, entries 1 and 2). Similar differences in reactivity were also observed among α,β-unsaturated ketone *trans*-4-phenyl-3-buten-2-one (18% yield in 50 h, Table 1, entry 6), *trans*-cinnamaldehyde (99% yield in 1 h, Table 1, entry 4), and *trans*-1,1,1-trifluoro-4-phenyl-3-buten-2-one (77% yield in 16 h, Table 1, entry 5). Low yields were also found for the reactions of other ketones such as cyclic ketones (Table 1, entries 7−9). Considering that the steric bulkiness of the $-CF_3$ group is at least the same as that for the $-CH_3$ group, the electron-withdrawing ability of the $-CF_3$ group, which enhances the electrophilicity of the carbonyl unit, is thus probably related to the much higher olefination reactivity of trifluoromethyl ketones than simple ketones.

Table 1. Olefination of Aldehydes and Activated and Unactivated Ketones with EDA Catalyzed by Fe(TPP)Cl[a]

entry	substrate	product	time (h)[b]	yield (%)[c]
1			1	96[d]
2			17	93[e]
3			51	2
4			1	99[d]
5			16	77[e]
6			50	18
7			24	8
8			24	10
9			24	30

[a] Reactions were carried out at 80 °C in toluene under N_2 with 1.0 equiv of ketone, 1.2 equiv of EDA, 1.2 equiv of Ph_3P, and 1.5 mol % Fe(TPP)Cl. Concentration: 0.5 mmol of ketone/2 mL of toluene. [b] Reaction times have not been optimized. [c] Yields were determined by GC. [d] Results from ref 5. [e] Results from ref 6.

Realization of the importance of carbonyl unit's electrophilicity in olefination reactions led us to search for potential additives that could reduce the electron density of carbonyls in simple ketones. Encouraged by previous reports on hydrogen bonding- and Lewis acid-promoted reactivities of unactivated ketones in different reactions,[10] olefination reactions of acetophenone in the presence of various additives were systematically carried out. The results are summarized in Table 2. Lewis acids had no effect on the reaction, suggesting insufficient interaction between Lewis acid and the carbonyl unit of acetophenone. For example, no formation of desired olefin was observed when the reaction was conducted in the presence of 0.3 equiv of BF_3 for 19 h (Table 2, entry 1). Additives that could potentially form hydrogen bonding with the carbonyl group were then examined. While simple alcohols, even used as solvents, showed no activation of the carbonyl group (Table 2, entry 2), addition of 1.0 equiv of phenol resulted in formation of the desired olefin in 59% isolated yield (Table 2, entry 4). No further improvement was obtained with an increased amount of phenols (Table

---

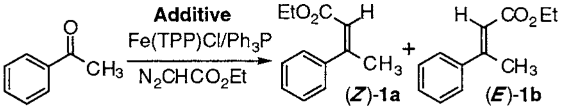
[7] For catalytic olefination of fluorine-containing activated ketones, see refs 6 and 1f.

[8] For a recent report on unsuccessful attempts to carry out catalytic olefination of ketones under conditions similar to those used for aldehydes, see ref 1c. With the use of large excesses of ketone and 2−4 days of reaction time, the authors reported that acceptable yields of olefination products (based on diazo reagent EDA) were obtained for a limited number of ketones.

[9] Caution: diazo compounds in general should always be presumed to be potentially explosive, especially in large scale at high temperatures.

[10] (a) Huang, Y.; Rawal, V. H. *J. Am. Chem. Soc.* **2002**, *124*, 9662. (b) Jiang, S.; Turos, E. *Tetrahedron Lett.* **1991**, *32*, 4639. (c) Yasuda, M.; Kitahara, N.; Fujibayashi, T.; Baba, A. *Chem. Lett.* **1998**, 743.

Table 2. Additive Effect on Olefination of Acetophenone with Ethyl Diazoacetate (EDA) Catalyzed by Fe(TPP)Cl[a]



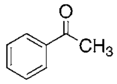
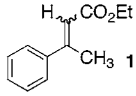
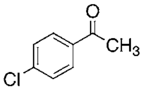
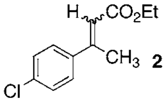
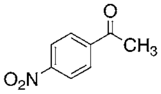
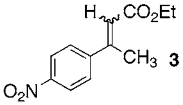
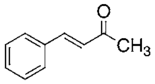
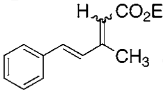
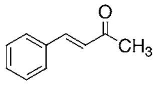
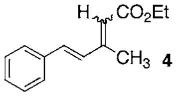
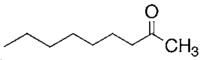
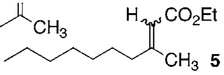
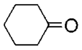
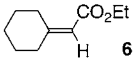
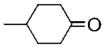
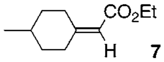
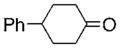
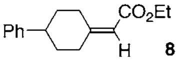
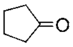
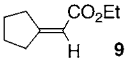
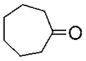
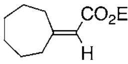
(*Z*)-**1a** (*E*)-**1b**

entry	additive	equiv	temp (°C)	time (h)[b]	yield (%)[c]	*Z*/*E*[d]
1	BF_3	0.3	80	19	0	—
2	C_2H_5OH	solv	80	50	0	—
3	C_6H_5OH	0.5	80	50	4	—
4	C_6H_5OH	1.0	80	50	59[e]	59/41
5	C_6H_5OH	2.0	80	50	55	54/46
6	$C_6H_5CO_2H$	0.015	80	50	24	64/36
7	$C_6H_5CO_2H$	0.1	80	50	73	60/40
8	$\mathbf{C_6H_5CO_2H}$	**0.5**	**80**	**50**	**84**	**59/41**
9	$C_6H_5CO_2H$	2.5	80	50	65	62/38
10	$C_6H_5CO_2H$	0.5	80	12	52	58/42
11	$C_6H_5CO_2H$	0.5	80	23	73	59/41
12	$C_6H_5CO_2H$	0.5	23	50	3	—
13	$C_6H_5CO_2H$	0.5	50	50	41	66/34
14	$C_6H_5CO_2H$	0.5	110	50	71	59/41
15	$C_6H_5CO_2H$	0.5	80	47	77	63/37
16	*p*-$ClC_6H_4CO_2H$	0.5	80	47	72	60/40
17	*p*-$MeOC_6H_4CO_2H$	0.5	80	47	68	60/40
18	*o*-$MeC_6H_4CO_2H$	0.5	80	47	68	61/39

[a] Reactions were carried out in toluene under N_2 with 1.0 equiv of ketone, 1.2 equiv of EDA, 1.2 equiv of Ph_3P, and 1.5 mol % Fe(TPP)Cl in the presence of acid. Concentration: 0.5 mmol of ketone/2 mL of toluene. [b] Reaction times have not been optimized. [c] Yields were determined by GC. [d] Ratio of *E*:*Z* isomers was determined by GC. [e] Yields represent isolated yields of >95% purity as determined by GC and ^{1}H NMR.

2, entry 5); dramatic yield reduction was observed when a substoichiometric amount of phenol was used (Table 2, entry 3). A more remarkable effect, however, was noticed when certain organic acids were used as additives. For example, with addition of 0.5 equiv of benzoic acids, the olefination of acetophenone with EDA at 80 °C in toluene changed from a negative reaction (Table 1, entry 3) to a successful one that afforded the desired olefin in 84% yield (Table 2, entry 8). This acid effect was observed even in the presence of only 1.5−10 mol % benzoic acids (Table 2, entries 6 and 7), albeit to a lesser extent. It appeared that excess benzoic acids could inhibit the reaction as observed in the reaction with 2.5 equiv of the acids (Table 2, entry 9). Relatively longer reaction times (~50 h) and elevated temperatures (~80 °C) were needed for productive reactions, as lower yields were obtained in either shorter reaction times (Table 2, entries 10 and 11) or at reduced reaction temperatures (Table 2, entries 12 and 13). Higher reaction temperatures did not improve the reaction further (Table 2, entry 14). Several benzoic acid derivatives were also evaluated for possible differences in promoting the reaction, including those having an electron-withdrawing group (Table 2, entry 16), an electron-donating group (Table 2, entry 17), or an ortho-substituted group (Table 2, entry 18).[11] In all cases, however, no noticeable differences in yields and (*E*)-selectivity were found.

Table 3. Acid-Promoted Olefination of Unactivated Ketones with Ethyl Diazoacetate (EDA) Catalyzed by Fe(TPP)Cl[a]

entry	substrate	product	time (h)[b]	yield (%)[c]	*Z*/*E*[d]
1		 **1**	50	84[e]	59/41
2		 **2**	24	83	70/30
3		 **3**	24	93	69/31
4		 **4**	8	80[e]	73/27
5		 **4**	50	92	72/28
6		 **5**	50	54	58/42
7		 **6**	24	83	--
8		 **7**	24	84	--
9		 **8**	24	89	--
10		 **9**	48	51	--
11		 **10**	48	42	--

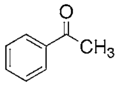
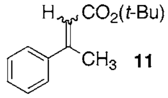
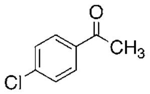
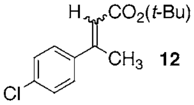
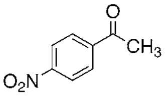
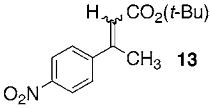
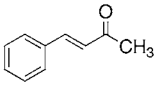
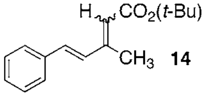
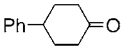
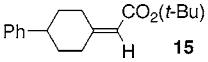
[a] Reactions were carried out at 80 °C in toluene under N_2 with 1.0 equiv of ketone, 1.2 equiv of EDA, 1.2 equiv of Ph_3P, and 1.5 mol % Fe(TPP)Cl in the presence of 0.5 equiv of benzoic acid. Concentration: 0.5 mmol of ketone/2 mL of toluene. [b] Reaction times have not been optimized. [c] Yields represent isolated yields of >95% purity as determined by GC and ^{1}H NMR. [d] Ratio of *E*:*Z* isomers was determined by GC or ^{1}H NMR. [e] Yields were determined by GC.

Using the above optimized reaction conditions (0.5 equiv of benzoic acids at 80 °C in toluene) allowed the substrate generality of the acid-promoted olefination to be investigated using a variety of unactivated ketones (Table 3). Acetophenone having a *para*-chloro group could be olefinated in the same yield as acetophenone, but in shorter reaction time and better (*E*)-selectivity (Table 3, entries 1 and 2). When 4-nitroacetophenone was used, the desired olefin was obtained in 93% yield and 69% (*E*)-selectivity (Table 3, entry 3). The 18% olefination yield of the α,*β*-unsaturated ketone *trans*-4-phenyl-3-buten-2-one (Table 1, entry 6) was improved to 92% with 72% (*E*)-selectivity by adding 0.5 equiv of benzoic acid (Table 3, entry 5). The same acid-promoted reaction could be performed in a much shorter time in a lower

---

(11) Use of strong organic acids such as trifluoroacetic acid and toluenesulfonic acid gave only trace amounts of the desired product.

Table 4. Acid-Promoted Olefination of Unactivated Ketones with *tert*-Butyl Diazoacetate (*t*-BDA) Catalyzed by Fe(TPP)Cl[a]

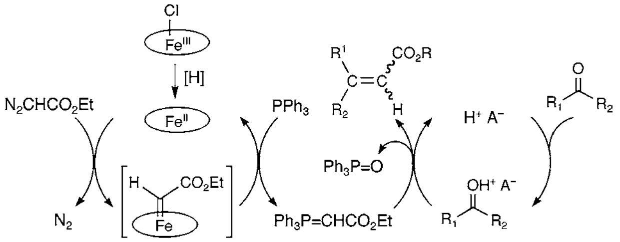
entry	substrate	product	yield (%)[b]	*Z*/*E*[c]
1		 **11**	38[d]	51/49
2		 **12**	48[d]	59/41
3		 **13**	68	69/31
4		 **14**	53	75/25
5		 **15**	65	--

[a] Reactions were carried out at 80 °C in toluene under N_2 with 1.0 equiv of ketone, 1.4 equiv of *t*-BDA, 1.2 equiv of Ph_3P, and 1.5 mol % Fe(TPP)Cl. Concentration: 0.5 mmol of ketone/2 mL of toluene. Reaction times were 24 h. [b] Yields represent isolated yields of >95% purity as determined by GC and ^1H NMR. [c] Ratio of *E:Z* isomers was determined by GC or ^1H NMR. [d] Yields were determined by GC.

but acceptable yield (Table 3, entry 4). Aliphatic ketones can also be olefinated as demonstrated with 2-nonanone (54% yield, Table 3, entry 6). The olefination yields of cyclohexanone and its derivatives increased from 8−30% in the absence of additives (Table 1, entries 7−9) to 83−89% in the presence of 0.5 equiv of benzoic acid. (Table 3, entries 7−9). The benzoic acid-promoted olefination is also suitable to five- and six-membered cyclic ketones such as cyclopentanone and cycloheptanone, giving the corresponding olefins in moderate yields (Table 3, entries 10 and 11).

In addition to the commonly used ethyl diazoacetate, the acid-promoted catalytic olefination of unactivated ketones can also be applied to the sterically hindered *tert*-butyl diazoacetate. As shown in Table 4 for several different ketones, the reaction yields with *t*-BDA are generally lower than those with EDA, but with similar (*E*)-selectivities.

Scheme 1. Possible Mechanism for Acid-Promoted Olefination of Ketones by Fe(TPP)Cl



These reactions are assumed to proceed via a metallocarbene-phosphorane mechanism that was proposed previously (Scheme 1).[1,5,6] The Fe(III) porphyrin was presumably reduced in situ by diazo reagents to the catalytically active Fe(II) porphyrin.[12] The activation of ketones by acids operates possibly through protonation of the carbonyl oxygen, which would render the carbonyl group a stronger electrophile toward reaction with phosphorane.

In summary, we have developed a general transition metal complex-based catalytic system for olefination of unactivated ketones with diazo reagents in the presence of tertiary phosphine. The results above demonstrate a remarkable acid enhancement effect on the catalytic reaction. We are currently working to improve the stereoselectivity of the reactions by using other possible acid additives under different reaction conditions.

Acknowledgment. We are grateful for financial support of this work from the Department of Chemistry of the University of Tennessee. We wish to acknowledge Dr. Al Tuinman of the University of Tennessee Mass Spectroscopy Center for assistance with high-resolution mass spectroscopy.

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

OL0347444

---

[12] (a) Wolf, J. R.; Hamaker, C. G.; Djukic, J.-P.; Kodadek, T.; Woo, L. K. *J. Am. Chem. Soc.* **1995**, *117*, 9194. (b) Salomon, R. G.; Kochi, J. K. *J. Am. Chem. Soc.* **1973**, *95*, 3300.