JOC*Note*

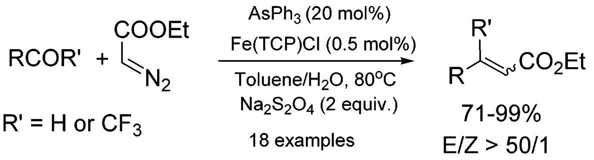
Ph_3As-Catalyzed Wittig-Type Olefination of Aldehydes with Diazoacetate in the Presence of $Na_2S_2O_4$

Peng Cao,[†] Chuan-Ying Li,[†] Yan-Biao Kang,[†] Zuowei Xie,[‡]
Xiu-Li Sun,[†] and Yong Tang*,[†]

State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 354 Fenglin Lu, Shanghai 200032, China, and Department of Chemistry, The Chinese University of Hong Kong, Shatin, New Territories, Hong Kong, China

tangy@mail.sioc.ac.cn

Received May 18, 2007



In the presence of sodium hydrosulfite and a catalytic amount of $AsPh_3$ and Fe(TCP)Cl, aldehydes react with ethyl diazoacetate to give the corresponding α,β-unsaturated esters in high yields with excellent stereoselectivities ($E/Z > 50/1$).

The Wittig reaction[1] and its variants[2] are some of the most powerful synthetic tools for constructing carbon−carbon double bonds in organic synthesis. Very recently, much attention has been paid to ylide olefination of aldehydes[3,4] and ketones[5] with readily accessible diazo compounds in the presence of a catalytic amount of a transition metal complex, providing an elegant protocol for the Wittig reaction under neutral conditions. For all these reactions, however, a stoichiometric amount of tertiary phosphines or arsines[4] is required, and the reactions are not atom-economical because of the formation of phosphine oxide or arsine oxide. As our ongoing research project on ylide chemistry,[6] we are particularly interested in developing a new process for this olefination using a catalytic amount of PPh_3 or $AsPh_3$. Since triphenylphosphine oxide is very hard to be reduced under mild conditions,[7] PPh_3 was not investigated further. During the course of our study, we fortunately found that $AsPh_3$ can catalyze the Wittig-type reaction of aldehydes with diazoacetate to give the corresponding olefins with high yields and excellent stereoselectivities in the presence of a reducing agent. Our preliminary results are reported in this paper.

Both $AsBu_3$[8] and tellurides[9] proved to be good catalysts for the reaction of aldehydes with bromoacetates under basic conditions. Considering that the tellurides were found to be partially decomposed to toxic tellurate,[9c] we chose stable triphenylarsine to initiate the study. An attempted olefination of *p*-chlorobenzaldehyde with ethyl diazoacetate (EDA) gave the desired product stereoselectively ($E/Z > 99/1$) in 89% yield in the presence of 1.2 equiv of $AsPh_3$ and 1.0 mol % of Fe(TCP)Cl (TCP = tetra(*p*-chlorophenyl)porphyrinate).[10] This result encouraged us to develop a catalytic version by in situ reduction of Ph_3AsO to regenerate $AsPh_3$. Although $P(OPh)_3$ could reduce Ph_3AsO to $AsPh_3$ under mild conditions,[8,11] in order to make this olefination practical and environmentally friendly, we evaluated inorganic salts as reducing reagents. After many attempts, we found that sodium hydrosulfite ($Na_2S_2O_4$) could be used as a reducing reagent for this reaction.[11] As shown in Table 1, the solvent, the reaction temperature, and the loading of Fe(TCP)Cl strongly influenced the yield of product **3a**. Under optimal conditions, *p*-chlorobenzaldehyde can react with EDA to give the olefin product in 83% yield with excellent stereoselectivity in the presence of 10 mol % of $AsPh_3$ and 0.5 mol % of Fe(TCP)Cl in toluene/water biphasic system (entry 11, Table 1). When 20 mol % of $AsPh_3$ was used, 97% yield was achieved (entry 10, Table 1).

To explore the generality of this reaction, a variety of aldehydes and ketones were investigated under the optimal conditions. As shown in Table 2, both aromatic and aliphatic

---

[†] Chinese Academy of Sciences.

[‡] The Chinese University of Hong Kong.

(1) Wittig, G.; Geissler, G. *Liebigs Ann. Chem.* **1953**, *580*, 44.

(2) For selected reviews, see: (a) Maryanoff, B. E.; Reitz, A. B. *Chem. Rev.* **1989**, *89*, 863. (b) Cristau, H.-J. *Chem. Rev.* **1994**, *94*, 1299. (c) Rein, T.; Pederson, T. M. *Synthesis* **2002**, *5*, 579.

(3) For selected examples, see: (a) Lu, X.; Fang, H.; Ni, Z. *J. Organomet. Chem.* **1989**, *373*, 77. (b) Huang, Y.-Z.; Liao, Y. *Tetrahedron Lett.* **1990**, *31*, 5897. (c) Herrmann, W. A.; Wang, M. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1641. (d) Ledford, B. E.; Carreira, E. M. *Tetrahedron Lett.* **1997**, *38*, 8125. (e) Fujimura, O.; Honma, T. *Tetrahedron Lett.* **1998**, *39*, 625. (f) Lebel, H.; Paquet, V.; Proulx, C. *Angew. Chem., Int. Ed.* **2001**, *40*, 2887. (g) Mirafzal, G. A.; Cheng, G.; Woo, L. K. *J. Am. Chem. Soc.* **2002**, *124*, 176. (h) Chen, Y.; Huang, L.; Ranade, M. A.; Zhang, X. P. *J. Org. Chem.* **2003**, *68*, 3714. (i) Santos, A. M.; Romao, C. C.; Kuhn, F. E. *J. Am. Chem. Soc.* **2003**, *125*, 2414. (j) Aggarwal, V. K.; Fulton, J. R.; Sheldon, C. G.; de Vincente, J. *J. Am. Chem. Soc.* **2003**, *125*, 6034. (k) Santos, A. M.; Pedro, F. M.; Yogalekar, A. A.; Lucas, I. S.; Romao, C. C.; Kuhn, F. E. *Chem.−Eur. J.* **2004**, *10*, 6313.

(4) Zhu, S.; Liao, Y.; Zhu, S. *Org. Lett.* **2004**, *6*, 377.

(5) (a) Cheng, G.; Mirafzal, G. A.; Woo, L. K. *Organometallics* **2003**, *22*, 1468. (b) Lee, M.-Y.; Chen, Y.; Zhang, X. P. *Organometallics* **2003**, *22*, 4905. (c) Chen, Y.; Huang, L.; Zhang, X. P. *J. Org. Chem.* **2003**, *68*, 5925. (d) Chen, Y.; Huang, L.; Zhang, X. P. *Org. Lett.* **2003**, *5*, 2493. (e) Pedro, F. M.; Santos, A. M.; Baratta, W.; Kuhn, F. E. *Organometallics* **2007**, *26*, 302.

(6) (a) Ye, S.; Huang, Z.-Z.; Xia, C.-A.; Tang, Y.; Dai, L. X. *J. Am. Chem. Soc.* **2002**, *124*, 2432. (b) Liao, W.-W.; Li, K.; Tang, Y. *J. Am. Chem. Soc.* **2003**, *125*, 13030. (c) Zheng, J.-C.; Liao, W.-W.; Tang, Y.; Sun, X.-L.; Dai, L.-X. *J. Am. Chem. Soc.* **2005**, *127*, 12222. (d) Deng, X.-M.; Cai, P.; Ye, S.; Sun, X.-L.; Liao, W.-W.; Li, K.; Tang, Y.; Wu, Y.-D.; Dai, L.-X. *J. Am. Chem. Soc.* **2006**, *128*, 9730. (e) Li, C.-Y.; Sun, X.-L.; Jing, Q.; Tang, Y. *Chem. Commun.* **2006**, 2980. (f) Li, C.-Y.; Wang, X.-B.; Sun, X.-L.; Tang, Y.; Zheng, J.-C.; Xu, Z.-H.; Zhou, Y.-G.; Dai, L.-X. *J. Am. Chem. Soc.* **2007**, *129*, 1494.

(7) Imamoto, T.; Kikuchi, S.; Miura, T.; Wada, Y. *Org. Lett.* **2001**, *3*, 87.

(8) Shi, L.-L.; Wang, W.-B.; Wang, Y.-C.; Huang, Y.-Z. *J. Org. Chem.* **1989**, *54*, 2027.

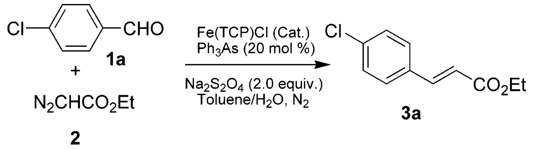
(9) (a) Huang, Y.-Z.; Shi, L.-L.; Li, S.-W.; Wen, X.-Q. *J. Chem. Soc., Perkin Trans. 1* **1989**, 2397. (b) Huang, Z.-Z.; Ye, S.; Xia, W.; Tang, Y. *Chem. Commun.* **2001**, 1384. (c) Huang, Z.-Z.; Ye, S.; Xia, W.; Yu, Y.-H.; Tang, Y. *J. Org. Chem.* **2002**, *67*, 3096. (d) Huang, Z.-Z.; Tang, Y. *J. Org. Chem.* **2002**, *67*, 5320. (e) Li, K.; Ran, L.; Yu, Y.-H.; Tang, Y. *J. Org. Chem.* **2004**, *69*, 3986.

(10) $AsPh_3$ is less nucleophilic than PPh_3. See: Methot, J. L.; Roush, W. R. *Adv. Synth. Catal.* **2004**, *346*, 1035.

(11) Ph_3AsO was reported to be reduced by $Na_2S_2O_4$ to triphenyl arsine in H_2O. See: Lu, X.; Wang, Q.-W.; Tao, X.-C.; Sun, J.-H.; Lei, G.-X. *Acta Chim. Sinica* **1985**, *43*, 450.

10.1021/jo0709899 CCC: \$37.00

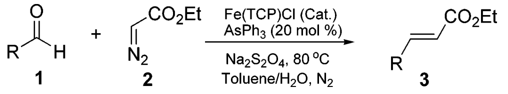
TABLE 1. Effects of Reaction Conditions on Olefination of *p*-Chlorobenzaldehyde[a]



entry	toluene/H_2O (v/v)	*T* (°C)	Fe(TCP)Cl (mol %)	yield[b] (%)
1	10.0	70	2.0	39
2	4.0	70	2.0	78
3	2.4	70	2.0	85
4	1.0	70	2.0	69
5	2.4	60	2.0	58
6	2.4	80	2.0	88
7	2.4	90	2.0	40
8	2.4	80	1.0	90
9	2.4	80	0.5	90
10	2.4	80	0.5	97[c]
11	2.4	80	0.5	83[c,d]

[a] Conditions: the reaction was carried out under N_2; 0.4 mmol (0.13 mol/L) of aldehyde, 20 mol % of $AsPh_3$, Fe(TCP)Cl (cat.), 0.8 mmol of $Na_2S_2O_4$ were mixed with toluene and H_2O, EDA (0.8 mmol) was slowly added within 8 h through a syringe pump or in portions. [b] Isolated yields. [c] Concentration of the aldehyde: 0.2 mol/L. [d] 10 mol % of $AsPh_3$ was used.

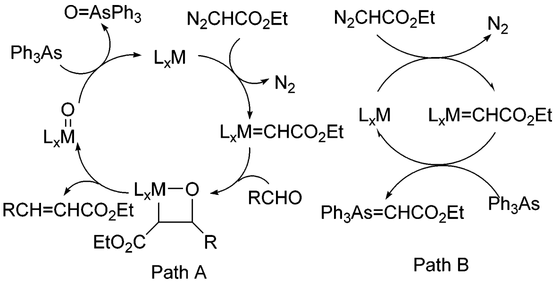
TABLE 2. Catalytic Ylide Olefination under Biphasic Conditions[a]



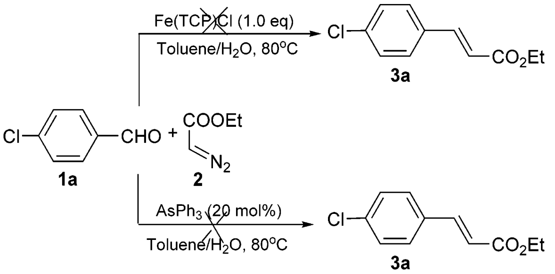
entry	R	time (h)	Fe(TCP)Cl (mol %)	*E*/*Z*[c]	yield[b] (%)
1	4-ClC_6H_4 (**1a**)	8	0.5	99/1	97
2	3-ClC_6H_4 (**1b**)	8	0.5	99/1	95
3	4-BrC_6H_4(**1c**)	8	0.5	99/1	95
4	2-BrC_6H_4(**1d**)	8	0.5	99/1	91
5	4-$MeOOCC_6H_4$ (**1e**)	8	0.5	99/1	99
6	4-$CF_3C_6H_4$ (**1f**)	8	0.5	99/1	89
7	4-FC_6H_4 (**1g**)	8	0.5	99/1	92
8	2,4-$Cl_2C_6H_3$ (**1h**)	8	0.5	99/1	96 (97[d])
9	2,6-$Cl_2C_6H_3$ (**1i**)	8	0.5	99/1	71
10	C_6H_5 (**1j**)	8	0.1	99/1	86
11	4-MeC_6H_4 (**1k**)	8	1.0	99/1	81
12	4-$MeOC_6H_4$(**1l**)	8	1.0	99/1	81
13	2-(but-3-enyl)C_6H_4 (**1m**)	12	1.0	99/1	78[e]
14	2-furyl (**1n**)	8	0.5	99/1	87
15	$CH_3(CH_2)_7$ (**1o**)	12	0.75	99/1	80[e]
16	cyclohexyl (**1p**)	8	1.0	50/1	78
17	4-$CH_3COC_6H_4$ (**1q**)	8	0.5	99/1	93
18	CF_3/4-ClC_6H_4 (**1r**)	8	1.0	99/1	85

[a] Conditions: carbonyl compounds (0.6 mmol), EDA (1.2 mmol), $Na_2S_2O_4$ (1.2 mmol), toluene/H_2O (3 mL/1.25 mL), 80 °C. EDA was slowly added within 8 h via a syringe pump or in portions. [b] Isolated yield. [c] Determined by 300 MHz ^1H NMR. [d] In 6 mmol scale. [e] Fe(TCP)Cl was added in portions and 3.0 equiv of EDA was added within 12 h via a syringe pump or in portions.

SCHEME 1. Two Mechanisms for the Olefination Catalyzed by Transition Metal Decomposition of Diazoacetate



SCHEME 2. Control Experiments



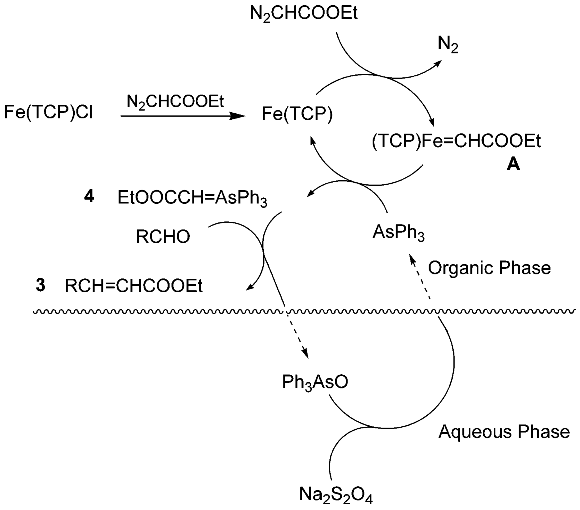
aldehydes worked well to give the desired products with excellent stereoselectivities in high yields. In most cases, only *E*-isomers were obtained. Aromatic aldehydes with electron-withdrawing groups afforded α,*β*-unsaturated esters stereoselectively in excellent yields (entries 1−8). The yield for 2,6-$Cl_2C_6H_3CHO$ **1i** decreased, probably due to steric effects (entry 9). Although aromatic aldehydes with electron-donating groups were always less reactive in ylide reactions,[3g,h] they were good substrates for this olefination when 1.0 mol % of Fe(TCP)Cl was employed (entries 11 and 12). 2-Furaldehyde also worked well to give the desired ester in 87% yield with excellent selectivity (entry 14). Both ester and alkenyl groups were well-tolerated in this reaction (entries 5 and 13). Aliphatic aldehydes could give the corresponding products in high yields with excellent selectivities (entries 15 and 16). When 4-acetylbenzaldehyde was employed, only the aldehyde was olefinated, suggesting that the chemoselectivity for ketone and aldehyde is quite good (entry 17). Noticeably, this olefination was practically useful since an excellent yield was still achieved when the reaction was carried out in gram scale (entry 8). In addition, trifluoromethyl ketone **1r** can be readily converted to the corresponding *β*-trifluoromethyl α,*β*-unsaturated esters with excellent stereoselectivity in 85% yield, offering an easy access to trifluoromethylvinyl compounds (entry 18).

For olefination of aldehydes with diazoacetate catalyzed by a transition metal complex, there are two possible mechanisms[3−5] as shown in Scheme 1. In the present reaction, it was found that the desired product was not detected in the reaction of *p*-chlorobenzaldehyde with EDA in the absence of Ph_3As even when a stoichiometric amount of Fe(TCP)Cl was used. This has ruled out the possibility of path A. In addition, the desired product **3a** was not observed in the absence of Fe(TCP)Cl (Scheme 2).

These results suggested that the aforementioned olefination proceeds via an ylide route, similar to the mechanism proposed in the phosphine-mediated olefination by Woo.[3g] Thus, the reaction path is proposed in Scheme 3. Fe(TCP)Cl is first reduced to Fe(TCP) by EDA in situ. Then it decomposes diazoacetate to form iron−carbene intermediate **A**, followed by converting $AsPh_3$ to arsonium ylide **4**. The ylide reacts with aldehyde to afford olefin **3** and the byproduct Ph_3AsO which is reduced by $Na_2S_2O_4$ in the aqueous phase to regenerate triphenylarsine to complete the catalytic cycle.

In summary, we have developed the first example of catalytic Wittig-type reaction of aldehyde with diazoacetate using 20 mol % of $AsPh_3$, based on porphyrin iron mediated carbene transfer under the toluene/water biphasic condition. The preliminary mechanistic studies have shown that the olefination proceeded

SCHEME 3. A Proposed Mechanism



via an ylide route, suggesting that ylide **4** and iron carbene **A** are water-tolerant under the reaction conditions. The high yield, excellent stereoselectivity, mild reaction conditions, and, in particular, use of a catalytic amount of $AsPh_3$ and cheap inorganic reducing reagent make the current method practically useful for the synthesis of α,*β*-unsaturated esters.

Experimental Section

Representative Procedure for Iron(III) Porphyrin and Triphenylarsine-Catalyzed Olefination Reaction (For *p*-Bromobenzaldehyde). Fe(TCP)Cl (2.5 mg, 0.003 mmol), Ph_3As (37 mg, 0.12 mmol), and $Na_2S_2O_4$ (210 mg, 1.2 mmol) were mixed in a Schlenk tube. The tube was evacuated and backfilled with nitrogen. *p*-Bromobenzaldehyde (111 mg, 0.6 mmol) was added, followed by toluene (3.0 mL) and water (1.25 mL). The reaction mixture was heated to 80 °C, and 2.0 equiv of EDA (126 μL, 1.2 mmol) was added within 8 h via a syringe pump or in portions. After the reaction was complete, the resulting mixture was cooled to room temperature, extracted with CH_2Cl_2, dried with Na_2SO_4, and concentrated. The residue was purified by flash chromatography (silica gel) to give the product **3c**: 145 mg (95%); ^{1}H NMR (300 MHz, $CDCl_3$/TMS) δ 7.62 (d, J = 16.2 Hz, 1H), 7.53 (d, J = 8.4 Hz, 2H), 7.40 (d, J = 8.4 Hz, 2H), 6.43 (d, J = 16.2 Hz, 1H), 4.27 (q, J = 7.2 Hz, 2H), 1.34 (t, J = 7.2 Hz, 3H).

Acknowledgment. We are grateful for the financial support from the National Natural Science Foundation of China (NSFC), the Major State Basic Research Development Program (Grant No. 2006CB806105), The Chinese Academy of Sciences, the Science and Technology Commission of Shanghai Municipality, and NSFC and the RGC of Hong Kong Joint Research Scheme (Grant No. 20710011 to Y.T. and N_CUHK446/06 to Z.X.).

Supporting Information Available: Detailed experimental procedures and characterization data for all new compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

JO0709899