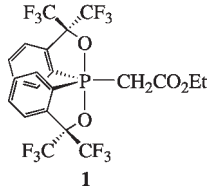
Highly *Z*-Selective Synthesis of Disubstituted α, β-Unsaturated Cyanides and Amides Using 10-P-5 Wittig Type Reagents

Satoshi Kojima, Kazuhiro Kawaguchi, Shiro Matsukawa, Keiichiro Uchida, and Kin-ya Akiba*
Department of Chemistry, Graduate School of Science, Hiroshima University, Kagamiyama, Higashi-Hiroshima 739-8526

(Received November 19, 2001; CL-011166)

Phosphoranes (10-P-5) bearing cyanomethyl, acetamide, and *N*,*N*-dimethylacetamide groups were examined for Wittig type reactions. All three reacted to give the corresponding olefins. The reaction of the cyanomethyl reagent with aldehydes gave α, β-unsaturated cyanides with high *Z*-selectivity in the case of aliphatic aldehydes ($Z : E = 94 : 6$ to $99 : 1$). On the other hand, the reactions of the two amide reagents with aldehydes yielded α, β-unsaturated amides with high *Z*-selectivity for both aromatic and aliphatic aldehydes ($Z : E = 99 : 1$ to $>99 : <1$).

The Wittig and Horner-Wadsworth-Emmons (HWE) reactions represent extremely useful methods for the regioselective and stereoselective formation carbon-carbon double bonds.[1] It has been established that these reactions proceed via 10-P-5 intermediates. However, until quite recently, it was not known that phosphorus already in the state of 10-P-5 could also function as Wittig-type reagents.[2–6] The recent success has added but a new group of reagents to the list of variants of the Wittig reaction, and has demonstrated yet another useful aspect of a somewhat exotic group of compounds, hypervalent compounds.[7] We have found that by the use of spirophosphorane **1** bearing Martin ligands[8] with an ester group as the electron-withdrawing group, extremely high *Z*-selectivities, typically $Z : E = 95 : 5$ or better could be achieved.[3b] As for other methods that are efficient for the selective preparation of the thermodynamically less stable *Z* olefin bearing carbon based electron-withdrawing groups, the number is limited and new variants are desirable.[9–17] These circumstances have inspired us to look into phosphoranes analogous to **1** bearing other electron-withdrawing groups, namely, the cyano group (**3**), and the amide group (**4**, **5**). Although there exist efficient methods for the former based on Si,[9] methods for the latter[15–17] are not as satisfactory as those for ester based olefins.[3b,11–13] We have found that these reagents react and give olefins with high *Z*-selectivity as described herein.

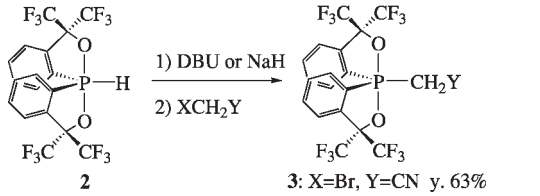


1

Phosphoranes **3**-**5** were easily prepared similarly to **1**[3b] from spirophosphorane **2** as outlined in Scheme 1.[18–20]

Since phosphorane **1** had been found to give good results at 0 °C, an examination of base was carried out at 0 °C in THF for **3** with benzaldehyde as the substrate. Upon the use of *n*-BuLi, *n*-BuLi-TMEDA, NaH, *t*-BuOK, and *t*-BuOK-18-c-6, only *t*-BuOK lead to *Z*-selectivity, though modest (Table 1, Entry 1).

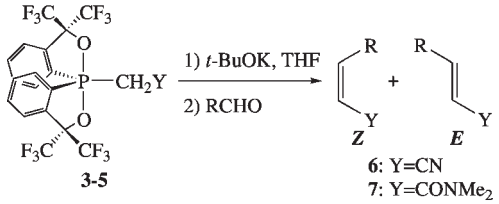
Thus, with *t*-BuOK as the optimum base, other aldehydes were



2

3: X=Br, Y=CN y. 63%
4: X=Cl, Y=CONMe$_2$ y. 89%
5: X=I, Y=CONH$_2$ y. 60%

Scheme 1.



3-5

6: Y=CN
7: Y=CONMe$_2$
8: Y=CONH$_2$

Scheme 2.

examined with THF as the solvent, as shown in Table 1. The reactions of the electron-deficient 4-nitro- and 4-chloro-benzaldehyde at 0 °C lead to results similar to that of benzaldehyde. Initiating the reaction at −78 °C and allowing the reaction temperature to rise lead to only small improvements. The reactions of less reactive 4-anisaldehyde and 4-(dimethylamino)benzaldehyde were sluggish and less than 10% of product was obtained. 2-Substituted aromatic aldehydes, are generally known to give higher *Z*-product than the corresponding 4-substituted isomer in HWE reactions.[1] The situation turned out to be the same here as $Z : E = 98 : 2$ selectivity was attained with 2-chlorobenzaldehyde at −78 °C. For the more hindered 2,6-dichlorobenzaldehyde, a turnaround in selectivity favoring the *E*-isomer was observed.

In *Z*-selective HWE reactions of aliphatic aldehydes with corresponding ester based reagents, selectivity has been known to decrease as the degree of branching at the carbon α to the formyl group decreases.[15,16] In the case of 3-phenylpropionaldehyde, an unbranched aldehyde, the selectivity with spirophosphorane **3** was found to be only moderate at 0 °C. However, selectivities rose up to 94 : 6 upon lowering the reaction temperature. The result from conditions B to D indicate that the actual reaction temperature is in between −78 and 0 °C. Since the actual optimum reaction temperature appeared to vary according to substrate, a detailed investigation was not carried out. The reaction of 2-phenylpropionaldehyde, an α branched aldehyde, lead to high selectivity even at 0 °C with a ratio of 93 : 7, and was found to summit at 99 : 1 under condition B. The reaction of 2-methyl-2-phenylpropionaldehyde was found to be sluggish at 0 °C but went on to completion at rt. Nonetheless, the selectivity towards the *Z*-product was maintained at a high level of 95 : 5. Thus, in the case of aliphatic aldehydes, regardless of the branching pattern of the saturated carbon α to the

Table 1. Reactions of **3** (Y=CN) with various aldehydes

Entry	R	Conditions[a]	$Z:E$	Yield/%
1	C_6H_5	A	66 : 34	96
2		B	77 : 23	47[b]
3	4-$(NO_2)C_6H_4$	A	69 : 31	81
4		B	82 : 18	46[b]
5	4-ClC_6H_4	A	67 : 33	85
6		B	72 : 28	37[b]
7	2-ClC_6H_4	A	90 : 10	85
8		B	98 : 2	93
9	2,6-$Cl_2C_6H_3$	A	18 : 82	93
10	$PhCH_2CH_2$	A	76 : 24	94
11		B	87 : 13	84
12		C	91 : 9	85
13		D	94 : 6	87
14	PhMeCH	A	93 : 7	98
15		B	99 : 1	100
16	$PhMe_2C$	E	95 : 5	97
17	(*E*)-PhCH=CH	A	43 : 57	97

[a]Condition A: 0 °C, 1 h. Condition B: −78 °C, 30 min, then rt, 30 min (the cooling bath was removed). Condition C: −78 °C, 36 h, then rt, 30 min (the cooling bath was removed). Condition D: −78 °C, then rt, 9 h (without removal of the cooling bath). Condition E: 0 °C, then rt, overnight (without removal of the cooling bath). [b]The yield was not optimized.

formyl group, the selectivity was uniformly high. The reaction of the unsaturated cinnamaldehyde was unfortunately unselective.

Table 2. Reactions of amides **4** and **5** with various aldehydes[a]

Entry	Y	R	$Z:E$	Yield/%
1	$CONMe_2$	C_6H_5	<99 : <1	84
2		$PhCH_2CH_2$	99 : 1	67
3		PhMeCH	99 : 1	66
4	$CONH_2$	C_6H_5	99 : 1	71
5		$PhCH_2CH_2$	99 : 1	70
6		PhMeCH	>99 : <1	92

[a]All reactions were carried out at rt.

Next examined were amide based reagents **4** (Y = $CONMe_2$) and **5** (Y = $CONH_2$). Of high expectations was the latter reagent, since the presence of hydrogen atoms would in principle allow further functionalization and no attempts on unsubstituted amides had previously been reported. Since amides are generally more bulky than esters, predictions were that the reaction would become sluggish and that the selectivity would diminish somewhat as seen with HWE type reagents.[16,17] Fortunately for us, however, the reaction carried out at rt with aldehydes furnished the corresponding disubstituted α,β-unsaturated amides without event and the *Z*-selectivity was exceptionally high for both aromatic and aliphatic aldehydes, as tabulated in Table 2. For **5**, although both the reagent and olefinic products bear active hydrogens on nitrogen, excess amounts of base were not required.

In summary, we have found that spirophosphoranes **3**-**5** undergo Wittig type reactions with aldehydes to give the corresponding α,β-unsaturated cyanides and amides with practical levels of *Z*-selectivity in the case of **3** with aliphatic aldehydes ($Z:E = 94:6$ to $99:1$), and **4** or **5** with both aromatic and aliphatic aldehydes ($Z:E = 99:1$ to $>99:<1$).

The authors are grateful to Central Glass Co. Ltd. for supplying us with hexafluorocumyl alcohol.

Dedicated to Prof. Teruaki Mukaiyama on the occasion of his 75th birthday.

References and Notes

Present address: Advanced Research Center for Science and Engineering, Waseda University, 3-4-1 Ohkubo, Shinjuku-ku, Tokyo 169-8555, Japan. Tel & Fax +81-3-5286-3165. E-mail: akibaky@mn.waseda.ac.jp

1 For leading references see: a) W. S. Wadsworth Jr., *Org. React.*, **25**, 73 (1977). b) J. I. G. Cadogan, "Organophosphorus Reagents in Organic Synthesis," Academic Press, New York (1979). c) B. E. Maryanoff and A. B. Reitz, *Chem. Rev.*, **89**, 863 (1989). d) S. E. Kelly, "Comprehensive Organic Synthesis," ed. by B. M. Trost, I. Fleming, Pergamon Press, Oxford (1991) Vol. 1, p 730. e) A. W. Johnson, "Ylides and Imines of Phosphorus," Wiley-Interscience, New York (1993). f) O. I. Kolodiazhnyi, "Phosphorus Ylides," Wiley-VCH, Weinheim (1999). g) K. Ando, *J. Synth. Org. Chem., Jpn.*, **58**, 869 (2000).
2 M. L. Bojin, S. Barkallah, and S. A. Evans, Jr., *J. Am. Chem. Soc.*, **118**, 1549 (1996).
3 a) S. Kojima and K.-y. Akiba, *Tetrahedron Lett.*, **38**, 547 (1997). b) S. Kojima, R. Takagi, and K.-y. Akiba, *J. Am. Chem. Soc.*, **119**, 5970 (1997). c) S. Kojima, K. Kawaguchi, and K.-y. Akiba, *Tetrahedron Lett.*, **38**, 7753 (1997).
4 T. Kawashima, K. Watanabe, and R. Okazaki, *Tetrahedron Lett.*, **38**, 551 (1997).
5 F. Carré, M. Chauhan, C. Chuit, R. J. P. Corriu, and C. Reyé, *Phosphorus Sulfur Silicon*, **123**, 181 (1997).
6 Z. Wang and J. G. Verkade, *Tetrahedron Lett.*, **39**, 9331 (1998).
7 "Chemistry of Hypervalent Compounds," ed. by K.-y. Akiba, Wiley-VCH, New York (1999).
8 J. C. Martin, *Science*, **221**, 509 (1983) and references therein.
9 a) Y. Yamakado, M. Ishiguro, N. Ikeda, and H. Yamamoto, *J. Am. Chem. Soc.*, **103**, 5568 (1981). b) R. Haruta, M. Ishiguro, K. Furuta, A. Mori, N. Ikeda, and H. Yamamoto, *Chem. Lett.*, **1982**, 1093. c) K. Furuta, M. Ishiguro, R. Haruta, A. Mori, N. Ikeda, and H. Yamamoto, *Bull. Chem. Soc. Jpn.*, **57**, 2768 (1984).
10 T. Y. Zhang, J. C. O'Toole, and J. M. Dunigan, *Tetrahedron Lett.*, **39**, 1461 (1998).
11 W. C. Still and C. Gennari, *Tetrahedron Lett.*, **24**, 4405 (1983).
12 a) K. Ando, *Tetrahedron Lett.*, **36**, 4105 (1995). b) K. Ando, *J. Org. Chem.*, **62**, 1934 (1997). c) K. Ando, *J. Org. Chem.*, **63**, 8411 (1998). d) K. Ando, *J. Org. Chem.*, **64**, 8406 (1999). e) K. Ando, *J. Org. Chem.*, **65**, 4745 (2000).
13 K. Kokin, J. Motoyoshiya, S. Hayashi, and H. Aoyama, *Synth. Commun.*, **27**, 2387 (1997).
14 W. Yu, M. Su, and Z. Jin, *Tetrahedron Lett.*, **40**, 6725 (1999).
15 S. Kojima, H. Inai, T. Hidaka, and K. Ohkata, *Chem. Commun.*, **2000**, 1795.
16 K. Ando, *Synlett*, **2001**, 1272.
17 S. Kojima, T. Hidaka, Y. Ohba, and K. Ohkata, *Phosphorus Sulfur Silicon*, **179**, 191 (2001).
18 a) I. Granoth and J. C. Martin, *J. Am. Chem. Soc.*, **101**, 4418 and 4623 (1979). b) E. F. Perozzi, R. S. Michalak, G. D. Figuly, W. H. Stevenson, III, D. B. Dess, M. R. Ross, and J. C. Martin, *J. Org. Chem.*, **46**, 1049 (1981).
19 a) S. Kojima, K. Kajiyama, and K.-y. Akiba, *Tetrahedron Lett.*, **35**, 7037 (1994). b) S. Kojima, K. Kajiyama, and K.-y. Akiba, *Bull. Chem. Soc. Jpn.*, **68**, 1785 (1995).
20 **3**: Mp 114–117 °C. ^{1}H NMR (400 MHz, $CDCl_3$, δ) 8.44 (dd, $J = 11.6$, 7.3 Hz, 2H), 7.84–7.75 (m, 6H), 3.47 (dd, $^2J_{PH} = 22.7$ Hz, $^2J_{HH} = 16.4$ Hz, 1H), 3.22 (dd, $^2J_{PH} = 15.2$ Hz, $^2J_{HH} = 16.4$ Hz, 1H); ^{19}F NMR (376 MHz, $CDCl_3$, δ) −75.0 (q, $^4J_{FF} = 8.5$ Hz, 6F), −75.1 (q, $^4J_{FF} = 8.5$ Hz, 6F); ^{31}P NMR (162 MHz, $CDCl_3$, δ) −30.6; Anal. Calcd for $C_{20}H_{10}F_{12}NO_2P$: C, 43.26, H, 1.82; N, 2.52%. Found: C, 42.96; H, 1.75; N, 2.30%. **4**: Mp 158–159 °C. ^{1}H NMR (400 MHz, $CDCl_3$, δ) 8.48–8.44 (m, 2H), 7.72–7.68 (m, 6H), 3.68 (dd, $^2J_{PH} = 18.5$ Hz, $^2J_{HH} = 15.1$ Hz, 1H), 3.52 (dd, $^2J_{PH} = 18.0$ Hz, $^2J_{HH} = 15.1$ Hz, 1H), 2.91 (s, 3H), 2.85 (s, 3H); ^{19}F NMR (376 MHz, $CDCl_3$, δ) −74.5 (q, $^4J_{FF} = 9.5$ Hz, 6F), −75.2 (q, $^4J_{FF} = 9.5$ Hz, 6F); ^{31}P NMR (162 MHz, $CDCl_3$, δ) −24.5; Anal. Calcd for $C_{22}H_{16}F_{12}NO_3P$: C, 43.94, H, 2.68; N, 2.33%. Found: C, 43.58; H, 2.49; N, 2.24%. **5**: Mp 198–199 °C. ^{1}H NMR (400 MHz, $CDCl_3$, δ) 8.43–8.38 (m, 2H), 7.76–7.70 (m, 6H), 6.02 (bs, 1H), 5.31 (bs, 1H), 3.45 (dd, $^2J_{PH} = 21.0$ Hz, $^2J_{HH} = 13.7$ Hz, 1H), 3.29 (dd, $^2J_{PH} = 14.2$ Hz, $^2J_{HH} = 13.7$ Hz, 1H); ^{19}F NMR (376 MHz, $CDCl_3$, δ) −74.8 (q, $^4J_{FF} = 9.2$ Hz, 6F), −75.0 (q, $^4J_{FF} = 9.2$ Hz, 6F); ^{31}P NMR (162 MHz, $CDCl_3$, δ) −27.1; Anal. Calcd for $C_{20}H_{12}F_{12}NO_3P$: C, 41.90, H, 2.11; N, 2.44%. Found: C, 41.92; H, 2.04; N, 2.36%.