Tetrahedron Letters 49 (2008) 7054–7057

Contents lists available at ScienceDirect

Tetrahedron Letters

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

Stereoselective Wittig olefination reactions employing a novel *ortho*-*P*-aryl alkoxide effect

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ARTICLE INFO

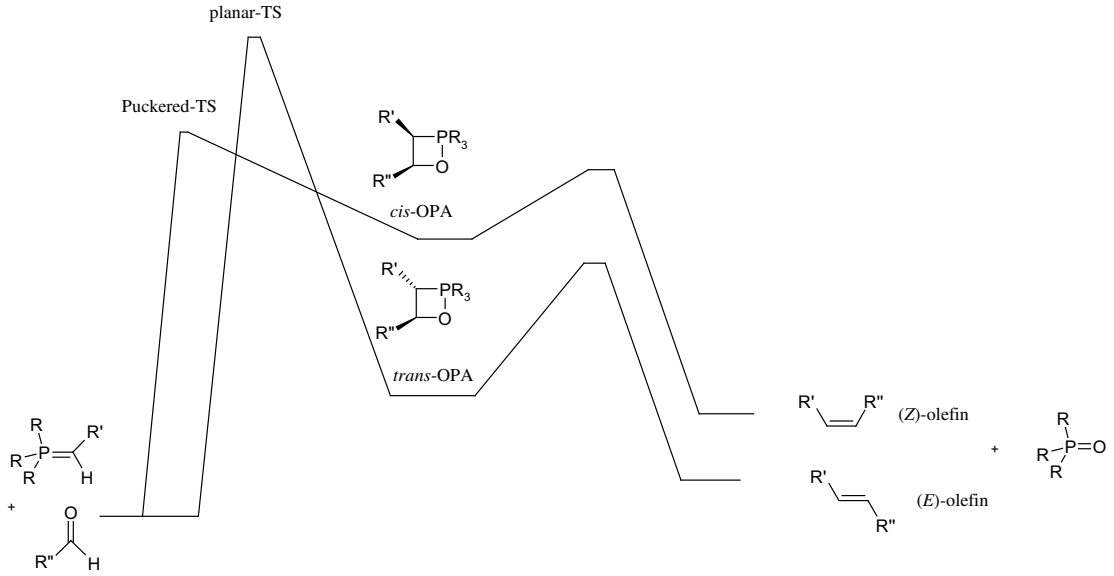
Article history:
Received 18 September 2008
Accepted 25 September 2008
Available online 1 October 2008

ABSTRACT

Non-stabilized *ortho*-*P*-alkoxy-substituted ylides react with aromatic and aliphatic aldehydes providing (*E*)-olefins with high stereocontrol, also allowing easy phosphine oxide removal in certain cases.

1. Introduction

Since its discovery in 1953, the Wittig reaction[1] has emerged as a powerful strategic carbon–carbon alkene bond forming process of wide applicability, Scheme 1. This highly reliable reaction allows for olefination with complete positional selectivity, relatively high chemoselectivity, and may be conducted in many cases with reliable and high stereocontrol.[2] The reaction has been the subject of extensive experimental[2] and theoretical[3a] investigations, and has been comprehensively reviewed.[2,3b] The reaction mechanism, qualitatively outlined in Scheme 1, is now believed to involve essentially irreversible, rate-determining addition of the ylide to the carbonyl component yielding either a cis- or a trans-substituted oxaphosphetane (OPA) intermediate. An interplay of 1,2- and 1,3-steric and electronic effects governs the relative transition states leading to either, or both of these intermediates. In general, it is believed that *cis*- to *trans*-OPA equilibration or Wittig reversal does not occur. Stereospecific *syn*-elimination of the phosphine oxide then leads to the (*Z*)- or (*E*)-olefins, respectively. Despite its advantages, the Wittig reaction still suffers from some



Scheme 1. General mechanism of the Wittig olefination reaction.

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doi:10.1016/j.tetlet.2008.09.150

stereochemical limitations, for example, the stereoselective formation of aliphatic (*E*)-olefins from non-stabilized ylides and aromatic or aliphatic aldehydes,[2,4] as well as from the very practical issue of phosphine oxide side-product removal.[5] The selective formation of (*E*)-olefins from non-stabilized ylides has only been achieved in limited cases, for example, using the Schlosser modification,[4a,b] which employs excess of an alkyl lithium base, or through the use of ylides containing bulky alkyl groups attached to phosphorus.[4c]

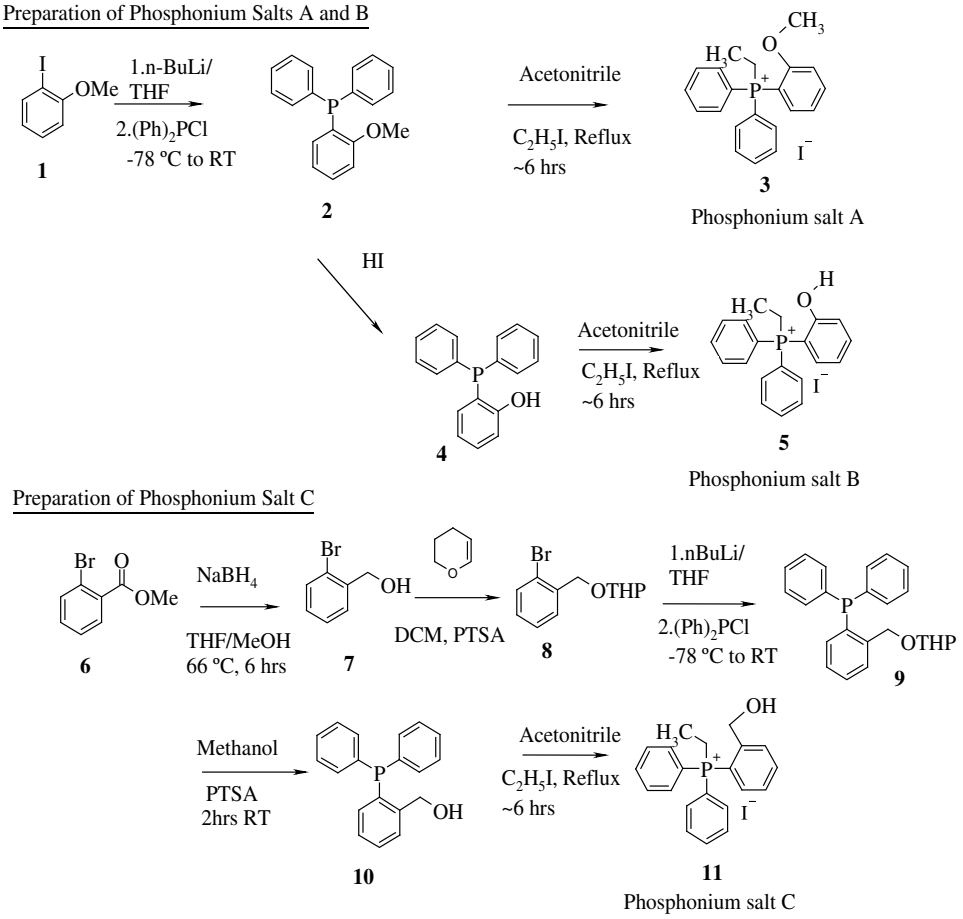
In this regard, the use of *ortho*-substituted aryl groups on phosphorus has been shown to modulate (*E*)/(*Z*)-selectivity also, increasing the level of (*E*)-selectivity slightly with *ortho*-methoxy groups,[6a] but increasing (*Z*)-selectivity in the case of *ortho*-methoxymethyl-substituted aryl groups.[6b] The precise role of the *ortho*-alkoxy groups in these cases is ambiguous at present. *ortho*-Halo substituents have also been shown to provide higher levels of (*E*)-stereoselectivity in limited cases.[6c] We were attracted to a recent paper that disclosed a fascinating solvent-quench effect on the stereoselectivity of the Wittig reaction, in which protic solvents were shown to increase levels of (*E*)-stereoselection significantly in the reaction with Garner's aldehyde.[7] While an intramolecular stereochemical effect of alkoxy and other nucleophilic groups on the alkylidene portion on ylides has been investigated, also resulting in higher levels of (*E*)-olefin,[8] to our knowledge, the role of related substituents on the aryl portion of the ylide has not been investigated. Although the effect was limited in scope, mechanistically it was attributed to *cis*-OPA protonation and alkoxide-mediated isomerization to the *trans*-OPA. Overall, the combination of the *ortho*-substituent effects[6] and this intriguing intermolecular alkoxide effect[7] prompted us to consider intramolecular *ortho*-aryl alkoxy effects as a possible means of modulating (*E*)-stereocontrol, and that might also allow easy phosphine oxide removal. Herein, we report our preliminary findings that support both of these hypotheses.

2. Results and discussion

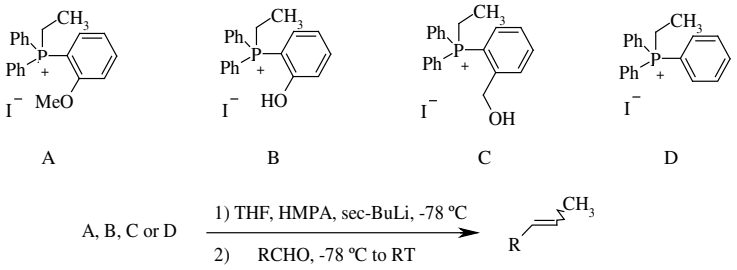
The ethyl phosphonium salts of the three *ortho*-substituted phosphines A–C were prepared employing standard techniques outlined in Scheme 2, as well as of the unsubstituted control derivative D.

The ylides were generated from phosphonium salts A–D employing 1.1 or 2.1 equiv of *sec*-BuLi under kinetically controlled conditions at −78 °C in the presence of HMPA, followed by the addition of a range of aldehydes as shown in Scheme 3.[10] The overall results of this study are reported in Table 1.

To begin with, the control ylide derived from phosphonium salt D reacted with aromatic aldehydes giving alkenes with good (*Z*)-selectivity as expected and with high selectivity in the case of the aliphatic aldehyde undecanal. The ylide derived from the *ortho*-methoxy derivative A was less selective, but delivered more (*E*)-olefin, similar to the literature data,[6a] with the exception of the reaction with the undecanal which provided very high (*Z*)-selectivity. This result appears to indicate an overriding steric effect of the long alkyl chain, possibly due to 1,2-interactions with the ylide substituent, favoring the early cis-puckered transition state. More revealing however are the results with the ylides derived from the *ortho*-hydroxyl and benzyl alcohol-substituted derivatives B and C. In both these cases, the ylides were generated under kinetically controlled conditions using 2.1 equiv of *sec*-BuLi in

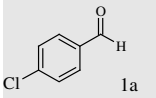
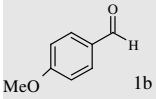
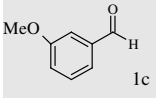
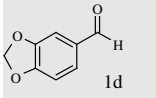
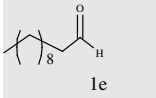


Scheme 2. Synthesis of phosphonium salts A–C.



Scheme 3. *ortho-P*-Substituted phosphonium salts employed in this study.

Table 1
Wittig reactions of aromatic and aliphatic aldehydes (*Z*):(*E*)[a,b]

Aldehyde	Ylide derivative			
	A	B	C	D
 1a	39:61	ND	12:88	71:29
 1b	23:77	8:92	8:92	63:37
 1c	54:46	10:90	17:83	80:20
 1d	31:69	8:92	12:88	67:33
 1e	95:5	38:62	38:62	90:10

[a] (Z):(*E*) ratios were determined by ^{1}H NMR.
[b] Reported ratios are the averaged values of (*Z*):(*E*) after carrying out individual reaction for at least 3 or 4 times. NMR data for all the olefins are in accordance with the literature data.[12] There was no significant change in the (Z):(E) ratios of the crude and purified material.

order to assure the formation of the phenoxide and alkoxide intermediates. A pronounced effect was observed with both of these ylides in their reactions with aromatic aldehydes, yielding olefins with high (*E*)-selectivity, while a moderate increase in (*E*)-selectivity was observed with the aliphatic undecanal.

In comparing the results of the methoxy derivative A to the alkoxide containing derivatives B and C, the stereochemical results are not simply due to lone pair interactions or steric factors alone,[6a,b] the involvement of an alkoxide effect is evident. The present intramolecular alkoxide effect does not require initial protonation of the OPA intermediate, and therefore does not appear to involve a β-hydroxy phosphonium intermediate.[2c,7] Furthermore, the similarity of the stereochemical effect in comparing the ylides derived from B and C strongly suggests that the result is not manifested via conjugative or inductive dipolar effects,[9] but it involves a direct through space interaction of the alkoxy oxygen.

Figure 1 depicts the expected kinetically produced *cis*-OPA intermediates derived from salts B and C. These species are now set up to participate in an intramolecular variation of the alkoxy effect demonstrated by Kim and co-workers[7] through rapid isomerization of the *cis*-OPA intermediate, isomerizing to the *trans*-

Figure 1. Oxaphosphetane intermediates.

OPA through a 6- or 7-member transition state, and leading to the (*E*)-olefins with high selectivity. It is not clear if the isomerization involves initial ionization of the OPA to a betaine, but we do not believe that such ionization is a requirement for the cis to trans isomerization. Given the dipole moment and polarizability of the O–P bond in the OPA, we believe that the acidity of the alkyl proton α to phosphorus in conjunction with the intramolecular alkoxide is sufficient to allow epimerization. Our present view is therefore the direct epimerization of the OPA intermediates as depicted in Figure 1. These results support the alkoxide-mediated isomerization pathway postulated by Kim and co-workers,[7] which were limited to the Garner aldehyde. The intramolecular variant described here expands the scope to aromatic aldehydes, allowing for a significant increase in (*E*)-stereoselectivity in their Wittig reaction with unstabilized ylides.

Finally, in the case of the reactions with the phenoxide reagent B, in addition to the high (*E*)-olefination observed, we were able to remove the *ortho*-hydroxyl-triphenylphosphine oxide side product employing a simple base extraction protocol.[11] The reaction mixture was quenched with saturated NH_4Cl, and the olefin partitioned into dichloromethane. The combined organic fractions in dichloromethane were simply shaken with 10% NaOH (aq) which completely removed the phosphine oxide, followed by normal work-up procedures.

3. Conclusion

In conclusion, we have demonstrated an intramolecular alkoxide effect in stereocontrolled Wittig olefination reactions that is consistent with ready cis to trans isomerization of OPA intermediates. This intramolecular probe extends the known intermolecular effect[7] to a wider range of aldehydes. In particular, aromatic aldehydes are shown to react with alkoxy-ylides leading to (*E*)-olefins with high selectivity. Phosphine oxide removal is readily accomplished in the case of phenolic derivative B. Further extension and application of the method are currently under investigation.

Acknowledgments

We thank NSERC, Cytec Canada Inc. and McMaster University for financial support of this work.

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10. (a) Typical procedure for the Wittig reaction with phosphonium salts A and D: Phosphonium salt A or D (0.50 mmol), in a 25 mL flame-dried flask equipped with magnetic stir bar, rubber septum and an argon inlet, was suspended in anhydrous THF (2.0 mL), and the suspension was cooled to −78 °C. *sec*-BuLi (0.55 mmol, 1.4 M in pentane) was added to the reaction mixture to yield a red solution. After 15 min, HMPA (0.55 mmol) was added to the reaction mixture at −78 °C. After 2 h, the corresponding aldehyde (0.50 mmol) was slowly added to the flask at −78 °C. The reaction mixture was stirred for 2 h at −78 °C, and then gradually warmed to room temperature and stirred for an additional 3 h. TLC analysis of the reaction mixture showed complete consumption of the aldehyde. The reaction mixture was quenched with saturated NH_4Cl solution. The clear solution was extracted with (2×20 mL) dichloromethane. The combined organic fractions were washed with brine and dried over Na_2SO_4. Dichloromethane was removed on a rotary evaporator leaving an oily residue which was purified by column chromatography (10:90 ethyl acetate/hexane) to give the alkene as an oil.
    (b) Typical procedure for the Wittig reaction with phosphonium salts B and C: Phosphonium salt B or C (0.50 mmol) was suspended in anhydrous THF (2.00 mL) in a 25 mL flame-dried flask equipped with magnetic stir bar, rubber septum, and an argon inlet, and the suspension was cooled to −78 °C. *sec*-BuLi (1.05 mmol, 1.4 M in pentane) was added to the reaction mixture to yield a red solution. After 15 min, HMPA (1.05 mmol) was added to the reaction mixture at −78 °C. After 2 h, the corresponding aldehyde (0.50 mmol) was slowly added to the flask at −78 °C and the reaction mixture was stirred for 2 h at −78 °C, and then gradually warmed to room temperature and stirred for an additional 3 h. TLC analysis of the reaction mixture showed complete consumption of the aldehyde. The reaction mixture was quenched with saturated NH_4Cl solution. The clear solution was extracted with (2×20 mL) dichloromethane. The combined organic fractions were washed with brine and dried over Na_2SO_4. Dichloromethane was removed on a rotary evaporator leaving an oily residue which was purified by column chromatography (10:90 ethyl acetate/hexane) to give the alkene as an oil.
11. General protocol for removal of phosphine oxide: After complete consumption of the corresponding aldehyde in the Wittig reactions employing phosphonium salt 'B', the reaction mixture was quenched with saturated NH_4Cl. The reaction mixture containing the required olefin and the phosphine oxide by product was partitioned between dichloromethane, and washed successively with (2×10 mL) 10% NaOH solution to remove the phosphine oxide from the reaction mixture.
12. NMR data for olefins (derived from (**1a–e**): ^{1}H NMR (200 MHz, $CDCl_3$); δ (ppm): as a mixture of (*Z*)- and (*E*)-isomers,
    1-(4′-Chlorophenyl)prop-1-ene (from **1a**):[13] δ 7.29 (2H, d, J = 8.74 Hz, ArH), 7.21 (2H, d, J = 8.52 Hz, ArH), 6.30–6.43 (1H$_a$, m, J = 16.37 Hz, CH_a=CH_bMe), 6.19 (1H$_b$, dq, J = 6.12 Hz, J = 15.76 Hz, *E*-isomer), 5.80 (1H$_b$, dq, J = 7.18 Hz, J = 11.53 Hz, *Z*-isomer), 1.87 (3H, d, J = 7.2 Hz, *Z*-isomer and J = 6.12 Hz, *E*-isomer).
    1-(4′-Methoxyphenyl)prop-1-ene (from **1b**):[14–18] δ 7.26 (2H, d, J = 8.7 Hz, ArH), 6.83 (2H, d, J = 8.7 Hz, ArH), 6.34 (1H$_a$, m, J = 15.86 Hz, CH_a=CH_bMe), 6.08 (1H$_b$, dq, J = 6.44 Hz, J = 15.66 Hz, *E*-isomer), 5.70 (1H$_b$, dq, J = 7.04 Hz, J = 11.37 Hz, *Z*-isomer), 3.81 (3H, s, OMe, *Z*-isomer), 3.79 (3H, s, OMe, *E*-isomer), 1.89 (3H, d, J = 7.04 Hz, *Z*-isomer), 1.85 (3H, d, J = 6.46 Hz, *E*-isomer).
    1-(3′-Methoxyphenyl)prop-1-ene (from **1c**):[14–17] δ 7.16–7.29 (1H, m, ArH), 6.83–6.96 (2H, m, ArH), 6.71–6.80 (1H, m, ArH), 6.33–6.45 (1H$_a$, m, J = 16.73 Hz, CH_a=CH_bMe), 6.22 (1H$_b$, dq, J = 6.1 Hz, J = 15.82 Hz, *E*-isomer), 5.79 (1H$_a$, dq, J = 7.21 Hz, J = 11.60 Hz, *Z*-isomer), 3.81 (3H, s, OMe, *Z*-isomer), 3.80 (3H, s, OMe, *E*-isomer), 1.90 (3H, d, J = 7.21 Hz, *Z*-isomer), 1.87 (3H, d, J = 6.1 Hz, *E*-isomer).
    1-(3′,4′-Dioxymethylenephenyl)prop-1-ene (from **1d**):[15,17,19] δ 6.69–6.90 (3H, m, ArH), 6.31 (1Ha, m, J = 15.75 Hz, CH_a=CH_bMe), 6.05 (1H$_b$, dq, J = 6.47 Hz, J = 15.65 Hz, *E*-isomer), 5.69 (1H$_b$, dq, J = 7.12 Hz, J = 11.54 Hz, *Z*-isomer), 5.94 (2H, s, –OCH_2O–, *Z*-isomer), 5.92 (2H, s, –OCH_2O–, *E*-isomer), 1.87 (3H, d, J = 7.12 Hz, *Z*-isomer), 1.84 (3H, d, J = 6.47 Hz, *E*-isomer).
    Tridec-2-ene (from **1e**):[20] ^{1}H NMR (600 MHz, $CDCl_3$); δ 5.37–5.45 (2H, m), 1.94–1.97 (2H, m, *E*-isomer), 2.00–2.05 (2H, m, *Z*-isomer), 1.63–1.64 (3H, d, J = 4.2 Hz, *E*-isomer), 1.59–1.60 (3H, d, J = 6.6 Hz, *Z*-isomer), 1.24–1.33 (16H, m), 0.86 (3H, t, J = 7.2 Hz).
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