Nitrile assisted, Brønsted acid catalyzed regio and stereoselective diarylphosphonylation of allyl silyl ethers†

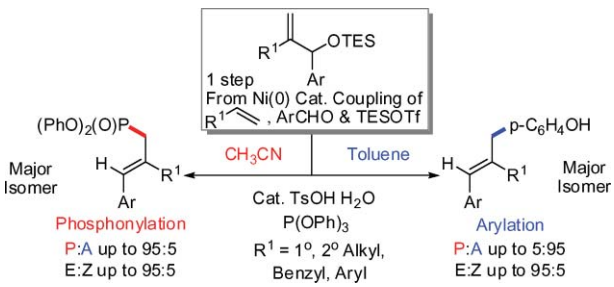
Chun-Yu Ho,*[a] Chun-Wa Chan,[a] Siu-Kwan Wo,[b] Zhong Zuo*[b] and Lai-Ying Chan[a]

Received 26th January 2010, Accepted 19th May 2010
First published as an Advance Article on the web 8th June 2010
DOI: 10.1039/c001660h

We have discovered a mild, catalytic protocol for the regio- and stereoselective synthesis of trisubstituted allyl diarylphosphonates from the corresponding disubstituted allyl silyl ethers, circumventing the challenges related to the preparation and availability of stereodefined trisubstituted olefins. A closely related arylation reaction was also discovered during the methodology development. By simply switching the reaction medium, high phosphonylation/arylation ratios and *vice versa* can be achieved. This may not be a direct result of changing solvent polarity. The allyl diarylphosphonates were evaluated as carboxylesterase inhibitors, and the screening results revealed that the inhibitory efficiency is highly related to the choice of alkenes and aryl substituents.

Introduction

Tetracoordinate phosphoryl groups are recognized as excellent mimics of the tetrahedral transition state of ester and amide hydrolysis.[1,2] Recently, strategies for preparing related stereodefined allyl phosphonates have received increasing attention,[3–7] providing a good platform from which to introduce chiral elements close to the phosphonate functionality through a wide range of enantioselective olefin transformations[8–12] and to synthesize dienes through the HWE reaction.[13–15] Although many diarylphosphonates have been identified as potent enzyme inhibitors, the synthesis of allyl diarylphosphonates is much less studied than that of their dialkyl relatives. Current methods for stereodefined allyl phosphonate synthesis with concomitant formation of a new C–P bond and an olefin generally focus on the addition of dialkyl phosphites $(RO)_2P(O)H$ to acrylate derived Baylis–Hillman adducts or rearrangement of dialkyl phosphonyl protected adducts.[16–18] However, we are aware of no related examples for allyl *diaryl*phosphonates, probably because of the lower nucleophilicity of aryl phosphites, and the synthesis involves a very different hydrolysis mechanism.[3c] Also, one of the inherent problems of the above approaches is that they have limited choices of β-substituents, generally bearing an electron-deficient group and yielding acrylic esters. Olefin cross-metathesis provides a powerful method of making allyl phosphonates, but the stereoselectivity of the allyl phosphonate group has been reported to be problematic when unsymmetrical higher substituted olefins were used.[19] As part of a programme evaluating phosphonates for chemical and biological applications (carboxylesterase inhibitors), we decided to develop a new method for allyl *diaryl*phosphonate preparations with high olefin stereoselectivity and β-substituent flexibility, with a view to obtaining a good platform for subsequent β-γ-position asymmetric functionalization. Herein we describe a novel synthetic strategy for that preparation by using triarylphosphites and allyl silyl ethers directly obtained from the corresponding Ni-catalyzed coupling.[20,21] Interestingly, by simply switching the solvent system employed, various stereodefined trisubstituted allyl arylation products can also be obtained (a Friedel–Crafts like reaction), which provides mechanistic insights for both reactions and should simulate further developments in this area (Scheme 1).



Scheme 1 Allyl phosphonylation *versus* arylation. P : A refers to the ratio of total phosphonylation isomers to total arylation isomers.

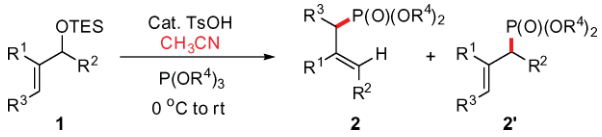
Result and discussion

Using the Ni-catalyzed alkene-aldehyde-silyl triflate coupling product **1a** (Table 1) reported previously by one of the authors here and Jamison[20a] with $P(OPh)_3$ as reaction partners, a systematic investigation led to the identification of the reaction conditions (Scheme 2). Our first attempts to synthesize the phosphonates involved heating the two reaction components together, which is analogous to other procedures commonly used for allyl *dialkyl*phosphonate synthesis, summarily failed.[16a–16e] Inspired by Spilling's pioneering work that used a stoichiometric amount of mild Lewis acidic silylating reagent (BSA) to facilitate the phosphonylation of acrylate derived Baylis–Hillman adducts with dialkyl phosphite,[16f] and the protic acid to accelerate dialkyl phosphonylation of conjugated imines reported by Stevens,[16g]

[a]*Center of Novel Functional Molecules, The Chinese University of Hong Kong, Shatin, New Territories, Hong Kong SAR. E-mail: jasonhcy@cuhk.edu.hk; Tel: +852-26096342*
[b]*School of Pharmacy, Faculty of Medicine, The Chinese University of Hong Kong, Shatin, New Territories, Hong Kong SAR. E-mail: joanzuo@cuhk.edu.hk; Tel: +852-26096832*

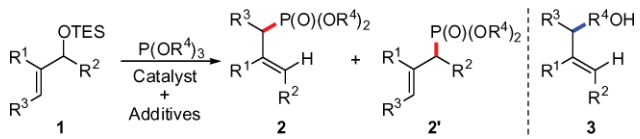
† Electronic supplementary information (ESI) available: Experimental details including screening of the reaction conditions, preparation of substrates, characterization of products and phosphonylation inhibitor screening results. See DOI: 10.1039/c001660h

Table 1 Catalytic stereoselective and regioselective synthesis of allyl diarylphosphonates.[a]



		R^1	R^2	R^3	R^4	Yield (%)[b]	**2**:**2′**[c] **2** *E*:*Z*[c]
1	**1a**	*n*-Hex	*p*-C_6H_4OMe	H	Ph	88	3.0:1 *E only*
2[d]		*n*-Bu				80	3.0:1 *E only*
3[e]						79	3.5:1 *E only*
4[f]						77	4.3:1 *E only*
5	**1b**	CH_2*i*-Pr				90	4.0:1 *E only*
6	**1c**	*c*-Hex				99	1:1.2 *13.0:1*
7	**1d**	Ph				86	3.0:1 *E only*
8	**1e**	$PhCH_2$				78	3.3:1 *E only*
9	**1f**	$BnCH_2$				86	4.0:1 *E only*
10[g]	**1g**	*n*-Hex	*o*-C_6H_4OMe			61	1:1.7 *E only*
11	**1h**		*o*,*p*-$C_6H_3(OMe)_2$			85	1:2.7 *E only*
12[g]	**1i**		*p*-C_6H_4Me			52	2.0:1 *E only*
13[g]	**1j**		Ph			52	2.0:1 *E only*
14[g]	**1k**		*p*-C_6H_4Cl			18	1.5:1 *1.3:1*
15[g]	**1l**		*m*-C_6H_4OMe			35	1.5:1 *3.0:1*
16[h]	**1m**		*p*-$C_6H_4NMe_2$			92	1:1 *E only*
17	**1n**	Me	*p*-C_6H_4OMe	Ph		90	1:5.7 *E only*
18	**1a**	*n*-Bu	*p*-C_6H_4OMe	H	*p*-C_6H_4Me	90	3.3:1 *E only*
19					*p*-C_6H_4Cl	99	4.0:1 *E only*

See Scheme 2 for structures and Experimental section for details.[a] Typical conditions: 0.1 mmol substrate, 500 mol% $P(OPh)_3$, 5 mol% *p*-TsOH·H_2O, 2 mL CH_3CN. [b] Isolated yield of phosphonylation (**2**+**2′**, average of at least two runs, separable by column chromatography). [c] Determined by ^1H NMR, olefin stereochemistry was determined by NOESY. [d] 3 times the scale. [e] Using 2 mL PhCN. [f] Using 2 mL *i*-PrCN. [g] Using 100 mol% *p*-TsOH·H_2O, run at 35 °C for 18 h. [h] Using 105 mol% of *p*-TsOH·H_2O.



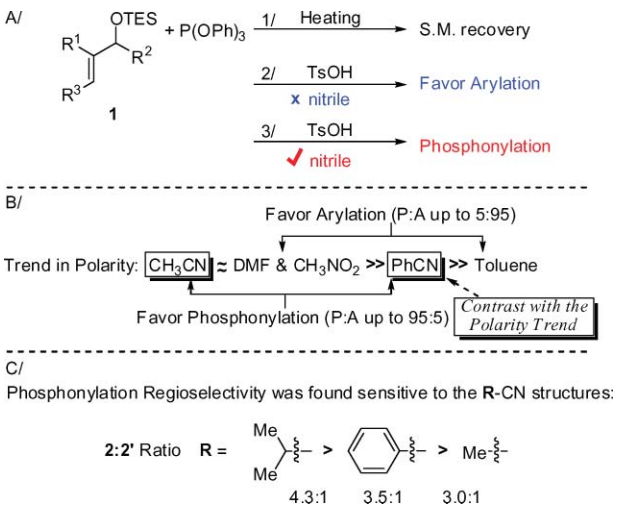
Scheme 2 Catalytic stereoselective trisubstituted olefin synthesis.

p-toluenesulfonic acid was selected as a promoter for our *di-aryl*phosphonylation. The hope was to enhance the electrophilicity of our silyl allylic components toward weakly nucleophilic triarylphosphites. To our delight, by using only a catalytic amount of TsOH in neat conditions and simply at room temperature in open air, the desired allyl diarylphosphonates were obtained. This consisted of 2 different regio-isomers (**2a**, **2′a**), favoring the one forming an *E*-trisubstituted olefin (Table 1, see ESI for details). They can be separated by typical silica gel column chromatography without any decomposition. This procedure allowed *in situ* hydrolysis of the phosphonium salts and the typical strictly anhydrous condition employed for the phosphonylation step can be avoided. However, this modification *alone* is not a practical method for allyl diaryl phosphonates synthesis. An unexpected allyl arylation pathway (or aromatic allylation, giving **3a**) is operating as a major side reaction with phosphonylation : arylation (P : A) equal to 38 : 62 (Scheme 2).[22–25]

We suspected that the formation of the arylation product could be attributable to the phenol generated after the phosphonylation step and the acid catalyzed phosphite hydrolysis.[26] Extensive variation of physical parameters including acidic additives stoichiometry, rate/order of addition and reaction temperature failed to favor the phosphonylation pathway. We thus required an

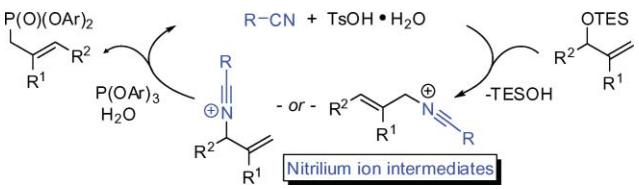
alternative means of overcoming this problem and acquiring phosphonylation more easily.

As the phosphite hydrolysis in aqueous organic solution may increase on account of the interaction of water molecules with the organic medium,[27] we tried to use toluene as the reaction medium on the presumption that it might help to slow down phosphite hydrolysis. Unfortunately, this strategy failed to favor the phosphonylation pathway, and strongly favored the arylation pathway. Next, we shifted our attention to look for additives that might facilitate the nucleophilic phosphonylation but that would also be compatible with the phosphonium ion hydrolysis step. Noting that CH_3CN was frequently employed to modulate nucleophilic displacement reaction pathways, such as in the preparation of various glycoside linkages by forming nitrilium conjugates and the Ritter reaction, we tested CH_3CN as an additive for our phosphonylation.[28] We were mindful of the fact that this approach could result in faster phosphite hydrolysis and provide a higher phenol availability for the arylation, and could also incorporate CH_3CN into the substrate in a manner similar to the N-glycosyl amine formation. Nevertheless, the CH_3CN was found to be a superior additive for the phosphonylation. This additional modification *reversed the selectivity* observed when toluene or $P(OPh)_3$ was used as reaction medium and provided a new system for allyl diarylphosphonate preparation with good yield (P : A = 87 : 13). This remarkable result prompted us to screen other solvents as reaction medium further for completeness, but none promoted the phosphonylation pathway to the extent that CH_3CN did (Scheme 3, see ESI for details). Other solvents examined included $CHCl_3$, Acetone, THF, CH_3NO_2, DMF and NEt_3. In fact, we also could not find any direct correlation between the product selectivity with the solvent polarity or dielectric constant. In particular, CH_3NO_2 and DMF are solvents having similar polarity or dielectric constant with CH_3CN (with ε_r ~ 35–37),[29] however, experimental results showed that they strongly favored the undesired arylation pathway, and the phosphonylation was observed only in minor amounts (P : A = 24 : 76; 14 : 86). In addition, when PhCN was employed as the medium, which has a much lower dielectric constant (with ε_r ~ 26), the reaction outcome (P : A = 81 : 19) sharply contrasted with those obtained with CH_3NO_2 and DMF. Together with the change in phosphonylation regioselectivity observed when a more bulky nitrile source was employed as reaction medium (see later section), all of the above indicated that the superiority of using CH_3CN *may not entirely be* the result of a higher $P(OPh)_3$ nucleophilicity in a more polar solvent, suggesting the nitrile functionality may play a substantial role.



Scheme 3 Remarkable observations by using nitriles as medium. P : A refers to the ratio of total phosphonylation isomers to those in arylation.

We propose a possible scenario here which may account for these unusual observations and this is shown in Scheme 4. The nitrile employed may first provide a nitrilium ion intermediate with the allyl silyl ether under a tosyl acid accelerated addition, which is analogous to the Ritter reaction. The weakly nucleophilic triarylphosphite may regenerate the nitrile at this point, and provide the phosphonium ion intermediate. Followed by an *in situ* hydrolysis step in open air atmosphere, the desired allyl diarylphosphonate was obtained. Slightly higher **2** : **2′** ratios were observed in reactions using a more bulky nitrile source and may be a result of a more selective formation of nitrilium ion owing to steric considerations. This change in phosphonylation regioselectivity also supports the theory that this is not a direct S_N1 or S_N1' reaction. It should be noted that we could not observe any nitrilium ion formation directly by spectroscopic techniques and could not isolate any Ritter products, thus the reason(s) for the selectivity improvement (P : A and regioselectivity) remains elusive. Further studies revealed that $P(OPh)_3$ is the nucleophile responsible for the phosphonylation. Control experiments showed that the $HP(O)(OPh)_2$ which resulted from $P(OPh)_3$ hydrolysis did not produce any desired phosphonylation product under the standard $TsOH/CH_3CN$ conditions, but the arylation product was obtained in good yield (a result of further hydrolysis of $HP(O)(OPh)_2$).



Scheme 4 A possible rationale for the unusual observation: nitrile assisted catalytic allyl diarylphosphonylation.

Scope of allyl diarylphosphonylation

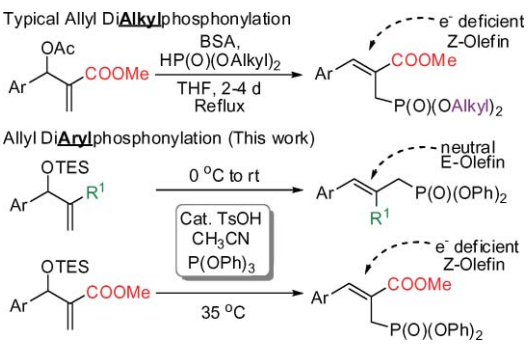
After further optimization, we found that only 5 mol% of $TsOH{\cdot}H_2O$ was necessary, with a ratio of P : A further improved to 93 : 7. With this new protocol in hand, the scope and generality of the system was explored, with the results summarized in Table 1. This new system generally allowed a highly selective allyl diaryl phosphonylation over arylation, provided excellent olefin stereoselectivity and expanded the scope particularly at the β-position (R^1).

Scaling up the reaction or employing more sterically encumbered substrates, such as R^1 = α-branch, β-branch, benzyl and aryl, did not compromise the high phosphonylation to arylation ratio, high olefin stereoselectivity and yield of phosphonylation (P : A = 7.3–19; $E : Z \geq 93 : 7$; 78–99% yield; entries 2–9). Also, the trisubstituted olefin **2** is generally favored over the terminal olefin **2′** by a factor of 3–4 in this series except in case of

1c. Moderate improvement in **2**:**2′** can be obtained when *i*-PrCN was employed as reaction medium, but the yield was diminished considerably (entries 1 and 4, from 3.0:1 to 4.3:1). Although an *o*-anisyl group is required as directing group, the phosphonylation regioselectivity can be swapped to favor **2′** without sacrificing the high P:A ratio (entries 1 *vs.* 10, 11). The possibility of forming a benzopyran-like intermediate may account for this interesting observation. We found that the yields of the desired phosphonylation were decreased considerably when less electron-rich substrates were employed (entries 12–15), but the substrate with R^2 bearing basic aryl/alkyl amine substituent can still undergo the phosphonylation reaction with high yield and required no specialized protecting group (entry 16).

While the effect of additional alkene substituents ($R^3 \neq H$) in approaches using Baylis–Hillman adducts on yield and selectivity was not examined,[16] it should be noted that a higher substituted allyl silyl ether (R^3 = Ph) synthesized by Ni-catalyzed *alkyne*-aldehyde coupling[21] was found also a compatible substrate for this new method, providing α-branched allyl diarylphosphonate in good yield and selectivity (entry 17). Furthermore, substituents on the triarylphosphite are well-tolerated (R^4), providing additional flexibility in synthesis when necessary (entries 18, 19).

Several notable features of this new methodology deserve further comment. Strictly anhydrous conditions, high reaction temperature, a stoichiometric amount of additive, or strongly acidic medium are required most of the time in the allyl phosphonylation, particularly for those with concomitant formation of a new C–P bond and an olefin.[1f,16b–16f] Our catalytic system did not require a strictly anhydrous medium to proceed, allowed *in situ* hydrolysis of the highly unstable allyl diarylphosphonium intermediate without isolation or delicate hydrolysis steps, and can be conducted at r.t. using only a catalytic amount of additive, overall highlighting their technical advantages and providing good functional group tolerance. Existing methods of stereoselective allyl phosphonate synthesis generally focused on acrylate derived Baylis–Hillman adducts and alkyl phosphites, which results in the dialkyl phosphonates having an electronically activated *Z*-trisubstituted olefin (Scheme 5). The new approach and findings here complement the existing methods in several respects, allowing diaryl derivatives to be synthesized with an electronically neutral *E*-trisubstituted olefin, and expanding the scope particularly at the β-position. In addition, subsequent trials showed that the Baylis–Hillman adduct diarylphosphonylation can also be done with 81% yield by using our tosyl acid–CH_3CN combination at 35 °C



Scheme 5 Complementarity of allyl phosphonylation of acrylates and allyl silyl ethers. Remarkable substituent effect on olefin selectivity.

(2:2′ = 3.2:1.). Notably, the olefin stereochemistry preference (*E*:*Z* = 18:82) were found opposite to what we observed in Table 1, and was found parallel to those observed in typical allyl dialkylphosphonylations, these experimental results highlighted the important role of R^1 substituents in these reactions (see ESI for details). The stereodefined olefins obtained may offer a correlated foundation for enantioselective olefin transformation or HWE reactions.

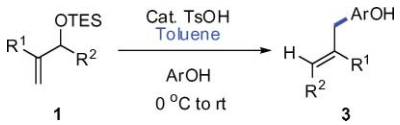
A variety of organophosphorus compounds were identified as potent human blood monocyte carboxylesterase (CBE) inhibitors, especially O=P(OPh)$_3$ and P(OPh)$_3$.[30] However, we are aware of no study using allyl phosphonates being reported. Therefore our newly synthesized allyl diarylphosphonates were evaluated as carboxylesterase inhibitors in rat plasma (see ESI for details).[31,32] The results showed that our newly synthesized allyl diarylphosphonates were potent carboxylesterase inhibitors with a broad range of inhibitory efficiency (IC_{50} = 4.99–0.52 μM), revealing that the alkene inclusion (or/and the substituents) may provide a positive effect on inhibition and providing room for fine tuning when necessary. Allyl diarylphosphonates with much stronger inhibitory effects than P(OPh)$_3$ were identified quickly through our small chemical library developed here and provided us with new directions for the development of a new generation of carboxylesterase inhibitors in our programme.

Scope of allyl arylation.

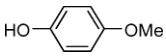
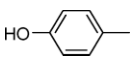
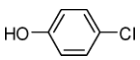
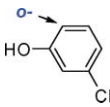
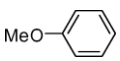
Next, we decided to study the closely related arylation using the same silyl allyl ether starting material based on the findings discovered in preliminary screening. This arylation method is attractive to us, not only because it may provide insight on how to improve the P:A selectivity, but also because it yields only one single regioisomer over all the other 5 possible isomers (terminal/carbinol position of allyl silyl ethers and *o*-/*m*-/*p*- of the aromatic nucleophile) in a single operation, together with excellent trisubstituted olefin stereoselectivity, C- to O-allylation ratio and no multiple allylations observed on phenol or on the allyl silyl ether (Table 2, entry 1).[22–24]

Although unable to exclude direct arylation between the allyl silyl ethers and the phosphite, we believe that the arylation product was formed mainly from the reaction between the substrates and phenol. The control experiments showed that using phenol in place of P(OPh)$_3$ with **1a** also provided the arylation product successfully with no oxy-allylation product observed under otherwise the same reaction conditions, suggesting that phenol is the actual substrate for the aromatic allylation and protecting the O with a P atom is not necessary. Also, in an experiment where P(OPh)$_3$, HP(O)(OPh)$_2$ and phenol were allowed to run in parallel, the reaction employing phenol provided the highest yield with a reduced reaction time, which also supports the hypothesis. In view of these control experiments and the observations of phosphonylation, we believe the change in the P:A ratio observed after switching the solvent employed is similar to that incurred by adding two different reagents to carry out the experiment, one providing phenol and one accelerated C–P bond formation, rather than a direct result of the difference in solvent physical properties. Therefore, the change is not an example of solvent-dependent chemoselectivity between an sp^2 carbon center and a phosphorus atom on the P(OPh)$_3$. With the genuine aryl nucleophile identified, various allyl silyl

Table 2 Stereoselective and regioselective arylation of allyl silyl ethers[a]



1 3

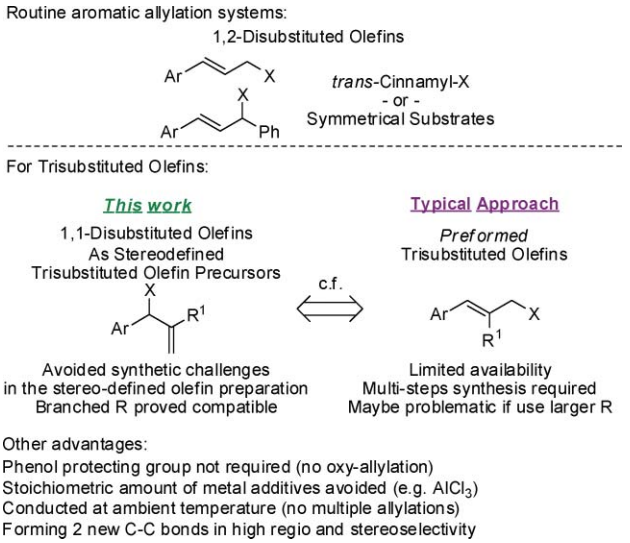
			Yield (%)[b]	Regioselectivity ratio[c,e]		
		ArOH	$E:Z$[c,d]	*p*	*o*	*m*
1	**1a**	$P(OPh)_3$ or (phenol)	85 or 92 *E only*	100	—	—
2	**1b**		93 *E only*	100	—	—
3	**1c**		98 *E only*	21	77	—
4	**1d**		40 *Z only*	100	—	—
5	**1e**		100 *E only*	100	—	—
6	**1f**		91 *E only*	100	—	—
7[f]	**1g**		73 *E only*	72	28	—
8[f]	**1i**		99 *E only*	61	39	—
9[f]	**1l**		54 *E only*	53	47	—
10[g]	**1a**		92 *E only*	—	92	8
11[g]			98 *E only*	—	100	—
12[g]			80 *E only*	—	100	—
13[g]			99 *E only*	65	35	—
14[h]			86 *E only*	100	—	—

No phosphonylation product was observed in all cases examined when using $P(OPh)_3$; see Scheme 2 for structures and Experimental section for details.[a] Typical conditions: 0.1 mmol substrate, 500 mol% $P(OPh)_3$, 20 mol% *p*-TsOH·H_2O, 2 mL toluene. [b] Combined yield of *p*-, *o*- and *m*-substituted products (average of at least two runs, isolated and separable by column chromatography). [c] Determined by ^1H NMR analysis. [d] Determined by NOESY, for all regioisomers. [e] Regioselectivity relative to the hydroxyl group. [f] Using 40 mol% of catalyst. [g] Using 1.5 equivalents of alcohols in place of phosphite. [h] Using 5 equivalent of anisole in place of phosphite.

ethers and several aromatic alcohols were subjected to the TsOH–toluene conditions (Table 2).

To our delight, the reactions generally proceeded with high yields by using a slight excess of aromatic alcohols, with good arylation regioselectivity and olefin stereoselectivity. Less electron-rich substrate **1i** can be used by increasing the catalyst loading (entry 8). When the *para*-position of the phenol was blocked by an additional substituent or difficult to access (OMe, Me, Cl), the allylation can still take place with high yield at the *ortho*-position, providing structures that were analogous to an allyl aryl ether thermo Claisen rearrangement without sacrificing the high olefin stereoselectivity and without increasing the reaction temperature or catalyst loading (entries 10–12). The allylation was found more favorable to take place at the *para*-position when the phenol was substituted with a *meta*-Cl group (entry 13). Typical aromatic allylation substrates such as aryl alkyl ether (entry 14, anisole), was found less reactive than phenol but was also allylated successfully in this system, providing an ethereal compound that should also be accessible from **3a**.

The success of stereodefined trisubstituted allyl phenol (or trisubstituted styrenes) synthesis found here is informative to the field of allylic alkylation of aromatic compounds. It should be noted that most of the aromatic allylation reports in the literature employed cinnamyl alcohol types of substrates (*trans*-disubstituted alkene) or symmetrical substrates for aromatic allylation, and leaving the effect of an additional alkene substituent on yield and selectivity not well-examined (Scheme 6). We surmised that this observation is probably due to the limited availability of



Scheme 6 Preparation of allyl phenolic compounds: 1,1-disubstituted olefins as aromatic allylation precursors.

stereodefined trisubstituted allylic alcohols or their synthetic challenge. It should be noted that our method avoided that synthetic challenge, simply forming the targets directly from Ni-catalyzed coupling products (terminal disubstituted alkenes) through a conjugated addition with concomitant formation of two new C–C bonds with excellent regioselectivity and olefin stereoselectivity outcome. The trisubstituted allyl arylation products may be also difficult to prepare with high olefin selectivity by dehydration of the corresponding alcohols or by olefin cross-metathesis (*e.g.* Table 2, entry 5, benzyl *vs p*-hydroxybenzyl).

Conclusions

In summary, we have discovered two novel *catalytic* synthetic strategies for the intermolecular stereo and regioselective allyl *diaryl*phosphonylation and allyl arylation that complements existing methods under mild conditions. The allyl silyl ethers obtained from Ni-catalyzed aldehyde-alkene/alkyne coupling were first identified as valuable precursors and seem generally useful for highly stereoselective synthesis of functionalized trisubstituted olefins by forming two new bonds, providing alternatives to those strategies involving prior preparations of stereodefined trisubstituted olefins bearing a good leaving group with a regioselective substitution. The stereodefined alkenes obtained here may be a useful platform for chiral center introduction at the phosphonate's and phenol's β,γ-positions by conventional catalytic asymmetric olefin functionalization technologies. The diaryl phosphonylation works best for electron-rich systems and provided olefin stereoselectivity outcome contrasted with previous work. The novel use of nitriles in terms of differentiating the reaction pathways and accelerating phosphonylation is one of the keys for the above accomplishments. The newly synthesized allyl diarylphosphonates from this work were first identified as potent carboxylesterase inhibitors and provided us with important clues for further development. The results obtained here should find applications in both chemical transformations and biological studies.

Experimental

p-Toluenesulfonic acid monohydrate and phosphorous trichloride were purchased from Acros Organics and used without further purification. Triphenyl phosphite was purchased from International Laboratory and used as received. Sodium hydride (60% in mineral oil) was purchased from Panreac Sintesis. Triethylamine and phosphorous trichloride were distilled over calcium hydride. All solvents were purchased from LAB-SCAN and used as received. Analytical thin layer chromatography (TLC) was performed using EM Science silica gel 60 F254 plates. The developed chromatogram was analyzed by UV lamp (254 nm), ethanolic phosphomolybdic acid (PMA) or potassium permanganate ($KMnO_4$). Liquid chromatography was performed using a forced flow (flash chromatography) of the indicated solvent system on Silicycle Silica Gel (230–400 mesh). ^1H, ^{13}C and ^{31}P NMR spectra were recorded on Bruker 300 or 400 MHz spectrometers in $CDCl_3$. High resolution mass spectra were obtained on a Finnigan MAT 95XL GC Mass Spectrometer by Miss H.-Y. Ng.

General procedure for allyl diarylphosphonylation and arylation

A mixture of 0.1 mmol substrate with 500 mol% of $P(OPh)_3$ and 5 mol% *p*-TsOH·H_2O in 2 mL of CH_3CN (for phosphonylation) or 20 mol% *p*-TsOH·H_2O in 2 mL of toluene (for arylation) was stirred at 0 °C for 2 h in open air and then stirred at r.t. for 9 h. Solvent was removed under reduced pressure. The yield and the selectivity were averages of at least two runs. Purification *via* flash chromatography on silica gel afforded the desired product. The stereochemistry of the olefin was determined by NOESY using isolated product.

Representative spectroscopic data for allyl diaryl phosphonylation and arylation (see ESI for details):

Allyl diarylphosphonylation:

2a: ^1H NMR (400 MHz, $CDCl_3$) δ: 7.33–7.29 (m, 5H), 7.19–7.10 (m, 7H), 6.86 (d, J = 8.7 Hz, 2H), 6.48 (d, J = 6.1 Hz, 1H), 3.82 (s, 3H), 3.05 (d, J = 22.3 Hz, 2H), 2.47–2.42 (m, 2H), 1.54–1.42 (m, 2H), 1.35–1.25 (m, 6H), 0.88–0.83 (m, 3H).

^{31}P NMR (121 MHz, $CDCl_3$) δ: 20.36.

2′a: ^1H NMR (400 MHz, $CDCl_3$) δ: 7.42 (d, J = 8.8 Hz, 2H), 7.31–7.02 (m, 8H), 6.86 (d, J = 8.8 Hz, 2H), 6.84 (d, J = 8.8 Hz, 2H), 5.69 (d, J = 2.8 Hz, 1H), 5.19 (d, J = 2.8 Hz, 1H), 4.06 (d, J = 24.8 Hz, 1H), 3.80 (s, 3H), 2.07–1.90 (m, 2H), 1.41–1.37 (m, 2H), 1.36–1.20 (m, 6H), 0.89–0.83 (m, 3H).

^{31}P NMR (121 MHz, $CDCl_3$) δ: 18.42.

Allyl arylation:

3a: ^1H NMR (400 MHz, $CDCl_3$) δ: 7.15 (d, J = 8.6 Hz, 2H), 7.10 (d, J = 8.4 Hz, 2H), 6.85 (d, J = 8.6 Hz, 2H), 6.76 (d, J = 8.4 Hz, 2H), 6.21 (s, 1H), 5.05 (brs, 1H), 3.80 (s, 3H), 3.39 (s, 2H), 2.13 (t, J = 8.2 Hz, 2H), 1.47–1.41 (m, 2H), 1.28–1.20 (m, 6H), 0.86 (t, J = 7.1 Hz, 3H).

Acknowledgements

We thank the Center of Novel Functional Molecule, The Chinese University of Hong Kong (2060366, 2060376) for financial support. C.-W. C. thanks The Chinese University of Hong Kong for post-graduate studentship (3250049). L.-Y. C. thanks Chung Chi College for an undergraduate Student Helper Award.

References

1 For general review on the organophosphorus oxide chemistry: (*a*) H. Hays and D. J. Peterson, *Organic Phosphorus Compounds*, 1972, **3**, 341; (*b*) A. K. Bhattacharya and G. Thyagarajan, *Chem. Rev.*, 1981, **81**, 415; (*c*) A. K. Bhattacharya and N. K. Roy, *The Chemistry of Organophosphorus Compounds*, 1992, **2**, 195; (*d*) T. Minami, *Comprehensive Organic Functional Group Transformation*, 1995, **2**, 819; (*e*) T. Minami, *Comprehensive Organic Functional Group Transformations II*, 2005, 853; (*f*) D. Enders, A. Saint-Dizier, M.-I. Lannou and A. Lenzen, *Eur. J. Org. Chem.*, 2005, 29; For arylphosphine oxides synthesis: (*g*) C. A. Ramsden, *Science of Synthesis*, 2007, **31**, 2035.

2 For recent reviews on phosphonic acids and their derivatives as inhibitors: (*a*) K. Moonen, I. Laureyn and C. V. Stevens, *Chem. Rev.*, 2004, **104**, 6177; (*b*) F. Palacios, C. Alonso and J. M. de los Santos, *Chem. Rev.*, 2005, **105**, 899; (*c*) N. J. Wardle, S. W. A. Bligh and H. R. Hudson, *Curr. Org. Chem.*, 2005, **9**, 1803; (*d*) L. Azema, R. Baron and S. Ladame, *Curr. Enzyme Inhib.*, 2006, **2**, 61; (*e*) V. D. Romanenko and V. P. Kukhar, *Chem. Rev.*, 2006, **106**, 3868.

3 (*a*) G. H. Birum, *J. Org. Chem.*, 1974, **39**, 209; (*b*) J. Oleksyszyn, L. Subotkowska and P. Mastalerz, *Synthesis*, 1979, 985; (*c*) Mechanism revised: M. Soroka, *Liebigs Ann. Chem.*, 1990, 331; (*d*) H. R. Hudson, F. Ismail, M. Pianka and C. W. Wan, *Phosphorus, Sulfur Silicon Relat. Elem.*, 2000, **164**, 245; (*e*) P. Merino, E. Marques-Lopez and R. P. Herrera, *Adv. Synth. Catal.*, 2008, **350**, 1195.

4 Pioneer example in the preparation of dialkyl allylphosphonate from allyl halides and dialkylphosphite at reflux: (*a*) G. M. Kosolapoff, *J. Am. Chem. Soc.*, 1951, **73**, 4040; Using $(PhO)_2P(OTMS)$: (*b*) R. Francke and G. V. Roeschenthaler, *Phosphorus Sulfur Relat. Elem.*, 1988, **36**, 125; Modification employing TBAI/$CsCO_3$ with monosubstituted allyl bromide: (*c*) R. J. Cohen, D. L. Fox, J. F. Eubank and R. N. Salvatore, *Tetrahedron Lett.*, 2003, **44**, 8617; Phenyl phosphorochloridite with allyl halide: (*d*) I. Pergament and M. Srebnik, *Org. Lett.*, 2001, **3**, 217; (*e*) H. Zhang, R. Tsukuhara, G. Tigyi and G. D. Prestwich, *J. Org. Chem.*, 2006, **71**, 6061; Direct addition of $P(OPh)_3$ to conjugated imine catalyzed by $SnCl_4$: (*f*) P. Van der Veken, I. El Sayed, J. Joossens, C. V. Stevens, K. Augustyns and A. Haemers, *Synthesis*, 2005, 634.

5 From vinylphosphonate *via* isomerization: base-catalyzed: (*a*) J. J. Kiddle and J. H. Babler, *J. Org. Chem.*, 1993, **58**, 3572; Prototropic equilibria of diethyl alkenylphosphonates: (*b*) J. P. Gerber, T. A. Modro, C. C. P. Wagener and A. Zwierzak, *Heteroat. Chem.*, 1991, **2**, 643.

6 Using sulfone elimination strategy: Y. Vo-Quang, D. Carniato, L. Vo-Quang, A. M. Lacoste, E. Neuzil and F. Le Goffic, *J. Med. Chem.*, 1986, **29**, 579.

7 Pd-catalyzed hydrophosphorylation of monoallenes and 1,1-disubstituted allenes: (*a*) C.-Q. Zhao, L.-B. Han and M. Tanaka, *Organometallics*, 2000, **19**, 4196; Highly substituted allenes do not undergo the addition. 1,3-Dienes gave products through least hindered reductive elimination: (*b*) F. Mirzaei, L.-B. Han and M. Tanaka, *Tetrahedron Lett.*, 2001, **42**, 297; Atom-economical preparation of related allyl phosphonic acids from concentrated hypophosphorous acid and stereodefined trisubstituted allyl alcohols (no β-substituted allyl alcohol example) using a Pd_2dba_3-xantphos catalyst at 85–110 °C, please see: (*c*) K. Bravo-Altamirano and J.-L. Montchamp, *Tetrahedron Lett.*, 2007, **48**, 5755.

8 Epoxidation of allylphosphonate: (*a*) T. R. Boehlow and C. D. Spilling, *Tetrahedron Lett.*, 1996, **37**, 2717; (*b*) M. Mitchell, L. Qaio and C.-H. Wong, *Adv. Synth. Catal.*, 2001, **343**, 596.

9 Dihydroxylation and regioselective amination: (*a*) T. Yamagishi, K. Fujii, S. Shibuya and T. Yokomatsu, *Synlett*, 2004, 2505; With AD-mix reagents: (*b*) T. Yokomatsu, T. Yamagishi, T. Sada, K. Suemune and S. Shibuya, *Tetrahedron*, 1998, **54**, 781; (*c*) T. Yamagishi, K. Fujii, S. Shibuya and T. Yokomatsu, *Tetrahedron*, 2006, **62**, 54.

10 Highly stereo- and regiocontrolled cyclopent-annulation: (*a*) G. Agnel and E. Negishi, *J. Am. Chem. Soc.*, 1991, **113**, 7424; Asymmetric Michael addition reaction: (*b*) S. E. Denmark and J.-H. Kim, *J. Org. Chem.*, 1995, **60**, 7535; Regioselective alkylation and olefination: (*c*) B. S. Lee, J. M. Gil and D. Y. Oh, *Tetrahedron Lett.*, 2001, **42**, 2345.

11 As key intermediates in drug synthesis: (*a*) D. A. Evans and B. T. Connell, *J. Am. Chem. Soc.*, 2003, **125**, 10899; (*b*) A. A. Fokin, A. G. Yurchenko, V. N. Rodionov, P. A. Gunchenko, R. I. Yurchenko, A. Reichenberg, J. Wiesner, M. Hintz, H. Jomaa and P. R. Schreiner, *Org. Lett.*, 2007, **9**, 4379.

12 Recent advance in catalytic asymmetric synthesis of *a*-hydroxy or amino allyl phosphonates: (*a*) G. D. Joly and E. N. Jacobsen, *J. Am. Chem. Soc.*, 2004, **126**, 4102; (*b*) X. Zhou, X. Liu, X. Yang, D. Shang, J. Xin and X. Feng, *Angew. Chem., Int. Ed.*, 2008, **47**, 392; (*c*) J. P. Abell and H. Yamamoto, *J. Am. Chem. Soc.*, 2008, **130**, 10521; (*d*) L. Albrecht, A. Albrecht, H. Krawczyk and K. A. Jørgensen, *Chem.–Eur. J.*, 2010, **16**, 28; (*e*) K. Suyama, Y. Sakai, K. Matsumoto, B. Saito and T. Katsuki, *Angew. Chem., Int. Ed.*, 2010, **49**, 797.

13 Allylphosphonates have been widely used in the preparation of dienes and polyenes, an advantage of allylphosphonates in the olefination over the corresponding phosphonium salts is exemplified by their stereoselectivity and stereospecificity observed in the reactions: (*a*) B. E. Maryanoff and A. B. Reitz, *Chem. Rev.*, 1989, **89**, 863; (*b*) R. S. Edmundson, *Chem. Funct. Groups*, 1996, **4**, 495; Condensation of an allylic phosphonium ylide: (*c*) E. J. Corey and B. W. Erickson, *J. Org. Chem.*, 1974, **39**, 821; Recent advance in the synthesis of densely substituted 1,3-butadienes: (*d*) S. M. Date and S. K. Ghosh, *Angew. Chem., Int. Ed.*, 2007, **46**, 386; Affording conjugated dienes with high *cis* selectivity: (*e*) Q. Wang, M. El Khoury and M. Schlosser, *Chem.–Eur. J.*, 2000, **6**, 420.

14 Wittig olefination reaction and modifications involvingphosphoryl-stabilized carbanions: B. E. Maryanoff and A. B. Reitz, *Chem. Rev.*, 1989, **89**, 863.

15 (*a*) For selected publications on the Horner–Wadsworth–Emmons reaction: W. S. Wadsworth, Jr, *Organic Reactions*, Wiley, New York, 1977, Vol. 25, pp 73; (*b*) E. L. Eliel, and S. H. Wilen, *Stereochemistry of Organic Compounds*, Wiley, New York, 1994, Chapter 14.

16 (*a*) Recent advance in stereoselective allylphosphonate (phosphono unsaturated esters) synthesis employing Baylis–Hillman adducts: W. R. Schoen and W. H. Parsons, *Tetrahedron Lett.*, 1988, **29**, 5201; (*b*) T. Janecki and R. Bodalski, *Synthesis*, 1990, 799; (*c*) D. Basavaiah and S. Pandiaraju, *Tetrahedron*, 1996, **52**, 2261; (*d*) M. Matziari, D. Georgiadis, V. Dive and A. Yiotakis, *Org. Lett.*, 2001, **3**, 659; (*e*) C. Muthiah, K. Senthil Kumar, J. J. Vittal and K. C. Kumara Swamy, *Synlett*, 2002, 1787; (*f*) P. A. Badkar, N. P. Rath and C. D. Spilling, *Org. Lett.*, 2007, **9**, 3619; (*g*) Typical condition: BSA, substrate, dialkylphosphite in 1 : 1 : 1 ratio, heated for reflux for 2–4 days in THF. The *in situ* formation of silyl phosphonates was often envisaged as a key to enhance the nucleophilicity of the dialkylphosphites, however, the Lewis acidic nature of silylating reagent may also enhance the electrophilicity of carbonyls towards nucleophilic addition, especially at higher temperature; (*h*) for the effect of protic acid on alkylphosphonylation with conjugated imine: K. Moonen, E. Van Meenen, A. Verwee and C. V. Stevens, *Angew. Chem., Int. Ed.*, 2005, **44**, 7407.

17 Stobbe-type condensations providing *Z*-allyl dialkylphosphonates analogous to phosphonylation of Baylis–Hillman adducts: (*a*) H. G. McFadden, R. L. N. Harris and C. L. D. Jenkins, *Aust. J. Chem.*, 1987, **40**, 1619; (*b*) D. J. Martin, M. Gordon and C. E. Griffin, *Tetrahedron*, 1967, **23**, 1831.

18 Although it received much less attention, we found that acrylonitrile derived Baylis–Hillman adducts also undergo phosphonylation, providing the corresponding *dialkyl* phosphonates with an electronically activated *E*-allyl dialkylphosphonates, see ref. 16*c*.

19 Metathesis strategy: (*a*) A. K. Chatterjee, T.-L. Choi and R. H. Grubbs, *Synlett*, 2001, 1034; (*b*) A. K. Chatterjee, D. P. Sanders and R. H. Grubbs, *Org. Lett.*, 2002, **4**, 1939; (*c*) M. J. Comin, D. A. Parrish, J. R. Deschamps and V. E. Marquez, *Org. Lett.*, 2006, **8**, 705; (*d*) J. Moiese, S. Arseniyadis and J. Cossy, *Org. Lett.*, 2007, **9**, 1695.

20 (*a*) C.-Y. Ho and T. F. Jamison, *Angew. Chem., Int. Ed.*, 2007, **46**, 782; (*b*) S.-S. Ng, C.-Y. Ho and T. F. Jamison, *J. Am. Chem. Soc.*, 2006, **128**, 11513.

21 General reviews on Ni-catalyzed multicomponents coupling: (*a*) J. Montgomery, *Acc. Chem. Res.*, 2000, **33**, 467; (*b*) J. Montgomery, *Angew. Chem., Int. Ed.*, 2004, **43**, 3890; (*c*) R. M. Moslin, K. Miller-Moslin and T. F. Jamison, *Chem. Commun.*, 2007, 4441; (*d*) S.-S. Ng, C.-Y. Ho, K. D. Schleicher and T. F. Jamison, *Pure Appl. Chem.*, 2008, **80**, 929.

22 (*a*) G. A. Olah, *Aromatic allylation and Related Reactions*, Wiley-Interscience, New York, 1964, Vol. 2, Part 1; (*b*) R. M. Roberts, and A. A. Khalaf, *Friedel–Crafts Alkylation Chemistry. A Century of Discovery*, Marcel Dekker, New York, 1984; (*c*) G. A. Olah, R. Krishnamurti, G. K. S. Prakash, Friedel–Crafts Alkylations in *Comprehensive Organic Synthesis*, ed. B. M. Trost, I. Flemin, Pergamon

Press, Oxford, 1991; (*d*) G. A. Olah, *J. Org. Chem.*, 2001, **66**, 5943; (*e*) M. Bandini, A. Melloni and A. Umani-Ronchi, *Angew. Chem., Int. Ed.*, 2004, **43**, 550.

23 Recent advances on aromatic allylation of Baylis–Hillman adducts using: $AlCl_3$: (*a*) D. Basavaiah, S. Pandiaraju and K. Padmaja, *Synlett*, 1996, 393; Catalytic conc H_2SO_4 at reflux: (*b*) D. Basavaiah, M. Krishnamacharyulu, R. S. Hyma and S. Pandiaraju, *Tetrahedron Lett.*, 1997, **38**, 2141; Reflux with TMSOTf: (*c*) S. Ravichandran, *Synth. Commun.*, 2001, **31**, 2345; Montmorillonite clay catalyzed: (*d*) D. Saib and A. Foucaud, *J. Chem. Res., Synopses*, 1987, 372; (*e*) B. Das, A. Majhi, J. Banerjee, N. Chowdhury and K. Venkateswarlu, *Chem. Lett.*, 2005, **34**, 1492; Microwave conditions: (*f*) P. Shanmugam and P. Rajasingh, *Chem. Lett.*, 2005, **34**, 1494; For a recent example that may favor *O*-allylations over *C*-allylations, please see: (*g*) E. Ramesh and R. Raghunathan, *Tetrahedron Lett.*, 2008, **49**, 1125.

24 Pioneer work on highly regio- and stereoselective aromatic allylation of allylic alcohols mediated by iron carbonyl: (*a*) J. W. Dieter, Z. Li and K. M. Nicholas, *Tetrahedron Lett.*, 1987, **28**, 5415; Recent advances in arylation of benzylic alcohols using stoichiometric amount of Brønsted acid: (*b*) F. Mühlthau, O. Schuster and T. Bach, *J. Am. Chem. Soc.*, 2005, **127**, 9348; Using only catalytic amount of Brønsted acid at refluxing DCM or CH_3CN: (*c*) R. Sanz, A. Martinez, D. Miguel, J. M. Álvarez-Gutiérrez and F. Rodríguez, *Adv. Synth. Catal.*, 2006, **348**, 1841; $AuCl_3$ catalyzed: (*d*) W. Rao and P. W. H. Chan, *Org. Biomol. Chem.*, 2008, **6**, 2426.

25 Some potential applications for the aromatic allylation products: (*a*) B. Kramer and S. R. Waldvogel, *Angew. Chem., Int. Ed.*, 2004, **43**, 2446; Trimethylenemethane-based ligands: (*b*) G. Rodriguez and G. C. Bazan, *J. Am. Chem. Soc.*, 1997, **119**, 343.

26 E. N. Walsh, *J. Am. Chem. Soc.*, 1959, **81**, 3023.

27 Mechanism of the hydrolysis of condensed phosphates in aqueous organic solvents: M. Watanabe, S. Sato and H. Saito, *Bull. Chem. Soc. Jpn.*, 1976, **49**, 2474.

28 For reviews on glycoside synthesis: (*a*) X. Zhu and R. R. Schmidt, *Angew. Chem., Int. Ed.*, 2009, **48**, 1900; Nitrile effect on glycoside anomeric stereocontrol: (*b*) R. R. Schmidt, M. Behrendt and A. Toepfer, *Synlett*, 1990, 694; For a recent review on the Ritter reaction: (*c*) A. R. E. Brewer, in *Name Reactions for Functional Group Transformations*, ed. J. J. Li, E. J. Corey, John Wiley & Sons, 2007.

29 *Landolt-Börnstein: Numerical Data and Functional Relationships in Science and Technology - New Series*; ed. C. Wohlfarth, M. D. Lechner Group 4: Physical Chemistry; Springer Berlin Heidelberg, 2008, Vol.17.

30 A. M. Saboori, D. M. Lang and D. S. Newcombe, Structural requirements for the inhibition of human monocyte carboxylesterase by organophosphorus, *Chem.-Biol. Interact.*, 1991, **80**, 327.

31 G. He, J. Massarella and P. Ward, *Clin. Pharmacokinet.*, 1999, **37**, 471.

32 Q. Chang, M. S. S. Chow and Z. Zuo, *Biomed. Chromatogr.*, 2009, **23**, 852.