CHEMISTRY
A EUROPEAN JOURNAL

FULL PAPER

DOI: 10.1002/chem.201301444

Part I: The Development of the Catalytic Wittig Reaction

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Dedicated to Georg Wittig (1897–1987) Nobel Prize 1979

Abstract: We have developed the first catalytic (in phosphane) Wittig reaction (CWR). The utilization of an organosilane was pivotal for success as it allowed for the chemoselective reduction of a phosphane oxide. Protocol optimization evaluated the phosphane oxide precatalyst structure, loading, organosilane, temperature, solvent, and base. These studies demonstrated that to maintain viable catalytic performance it was necessary to employ cyclic phosphane oxide precatalysts of type **1**. Initial substrate studies utilized sodium carbonate as a base, and further experimentation identified *N*,*N*-diisopropylethylamine (DIPEA) as a soluble alternative. The use of DIPEA improved the ease of use, broadened the substrate scope, and decreased the precatalyst loading. The optimized protocols were compatible with alkyl, aryl, and heterocyclic (furyl, indolyl, pyridyl, pyrrolyl, and thienyl) aldehydes to produce both di- and trisubstituted olefins in moderate-to-high yields (60–96%) by using a precatalyst loading of 4–10 mol%. Kinetic *E*/*Z* selectivity was generally 66:34; complete *E* selectivity for disubstituted α,β-unsaturated products was achieved through a phosphane-mediated isomerization event. The CWR was applied to the synthesis of **54**, a known precursor to the anti-Alzheimer drug donepezil hydrochloride, on a multigram scale (12.2 g, 74% yield). In addition, to our knowledge, the described CWR is the only transition-/heavy-metal-free catalytic olefination process, excluding proton-catalyzed elimination reactions.

Keywords: alkenes · homogeneous catalysis · olefination · organocatalysis · Wittig reaction

Introduction

The carbon–carbon double bond presents a myriad of opportunities for the synthetic chemist.[1] Olefins, other than offering a degree of structural rigidity, are the basis for many robust synthetic methodologies.[1] Therefore, an alkene precursor in a synthetic route may act as a pivot to many distinct structural classes or offer an alternative when problems present. Unsurprisingly, due to the synthetic versatility of olefins, a vast amount of effort has been directed at their construction. Arguably, other than direct elimination,[2] there are currently four general methodologies for the routine and reliable formation of alkenes:[3] 1) Wittig,[4] 2) Peterson,[5] 3) Julia–Lythgoe[6]/Julia–Kocienski[7] olefination reactions, and 4) metathesis.[8] In addition to these reactions, the Heck reaction may be utilized to produce certain alkene structures.[9] Of the olefinations listed, only metathesis and the Heck reaction are catalytic, both require alkene starting materials and use a transition-metal catalyst. Strictly, metathesis and the Heck reaction can be considered as alkene augmentation processes rather than olefinations. One stoichiometric protocol that offers the opportunity to evolve into a catalytic process is the Wittig reaction.[4] First disclosed in a 1953 report by Wittig and Geissler,[4a] this reaction involves the treatment of an aldehyde or ketone with a phosphonium ylide, thus resulting in an alkene concurrent with a phosphane oxide byproduct.[4] Since Wittig's discovery the reliability of his reaction has resulted in its extensive use in organic chemistry.[10] Nonetheless, the Wittig reaction suffers from several impediments, namely that the process is stoichiometric, which often results in difficulty in the removal of the phosphane oxide byproduct. Moreover, lack of a catalytic Wittig protocol, due to cost/benefit, removes the possibility to control the olefination event by alteration of phosphane structure. This deficiency is unfortunate because

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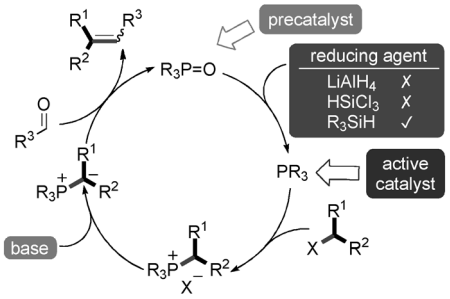
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201301444.

the phosphane structure has been demonstrated to have a substantial impact on the stereochemical outcome of the reaction.[11] Thus, carefully designed phosphanes may yield selective processes, and these endeavors would be enhanced if the phosphane was employed catalytically.[11e]

The obstacles to the development of a catalytic Wittig reaction are formidable, and the construction of a catalytic cycle relies on the completion of four discrete steps (Scheme 1): 1) formation of the phosphonium ylide precursor, typically a phosphonium salt;[10,11] 2) generation of the phosphonium ylide, normally by deprotonation;[10–12] 3) olefination with the concomitant generation of a phosphane oxide;[10–12] and 4) reduction of the phosphane oxide byproduct to produce a phosphane to re-enter the cycle. Most challenging of the above processes is the essential chemoselective reduction of the phosphane oxide, which must be accomplished in the presence of either aldehyde or ketone starting materials and an alkene product. Amelioration of this chemoselective reduction problem could be achieved by the exchange of the phosphorus atom with arsenic,[13] tellurium,[14] or antimony[15] because their oxides, due to bond strength, are appreciably easier to reduce.[16] Indeed, this strategy led to catalytic Wittig-type processes that employ arsines and tellurides.[17] A significant drawback to the broad adoption of the aforementioned methodologies are the high toxicity and carcinogenicity of arsenic,[18] tellurium,[19] and antimony compounds.[20] Environmental anthropogenic contamination, particularly of groundwater, is a major concern if these reactions were performed on a large scale.[21] The catalytic use of a phosphane would not suffer from these limitations; hence, a Wittig reaction catalytic in phosphane would find wider employment. Furthermore, such a process would marry the power of the Wittig olefination reaction to the synthetic benefits of a catalytic protocol without the poisoning issues that can plague transition-metal-catalyzed processes.[22] Recently, our laboratory disclosed the first catalytic Wittig reaction (CWR),[23] and herein we present in full our studies that led to the development of this protocol.

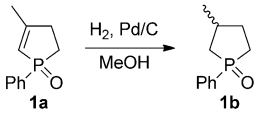


Scheme 1. Proposed catalytic Wittig reaction.

Results and Discussion

Fundamentally, the challenge in developing a CWR is the chemoselective reduction of the P=O bond in the presence of other reactive functionalities, in this case an aldehyde or ketone and an alkene. At the time, a literature review revealed there were few protocols for phosphane oxide reduction.[24–26] Of these methods, most would be unsuitable as a reductant in a proposed CWR: lithium aluminum hydride[25] is a harsh relatively unselective reducing agent and trichlorosilane (with or without an amine base)[24] has selectivity concerns that stem from the lability of the Si–Cl bond and control of the phosphorus center during the reduction. Yet the solution may be found in a structural relative of trichlorosilane; that is, both phenylsilane and diphenylsilane are known to reduce phosphane oxides and are likely to be compatible with a catalytic Wittig process (Scheme 1). Furthermore, these organosilanes have been shown to reduce phosphane oxides with retention of configuration at the phosphorus center.[27] The preservation of the stereochemical integrity at the phosphorus center during reduction is important if the structure of the phosphane is to be used later to impart diastereoselectivity on the Wittig reaction. Additionally, aryl silanes are unlikely to reduce any aldehyde or ketone because hydrosilylation normally requires a transition metal.[28]

Following the identification of a suitable class of reducing agent, the next consideration was the nature of the phosphane oxide precatalyst. One may consider triphenylphosphane oxide, itself a byproduct of many stoichiometric Wittig reactions, to be ideal. However, the ease of the reduction of the phosphane oxide was a crucial factor. From the outset, a key design criterion for the CWR was that it would be complete in 24 hours. To fulfill this condition, if a precatalyst loading of 10 mol% was employed then the catalyst must cycle once every 2.4 hours. We felt that use of triphenylphosphane oxide would not satisfy this requirement. The employment of cyclic phosphane oxides was more promising as ring strain is known to significantly aid the ease of reduction.[29] Following this rationale, commercially available 3-methyl-1-phenylphospholene-1-oxide (**1a**) was considered, but the presence of the double bond could prove troublesome; therefore, this double bond was removed by hydrogenation, thus yielding 3-methyl-1-phenylphospholane-1-oxide (**1b**) as a mixture of diastereomers (Scheme 2).



H-Cube Midi yield: 99%; ratio: 2:1
H_2 balloon yield: 99%; ratio 9:1

Scheme 2. Preparation of **1b** through hydrogenation (see the Supporting Information for full details).

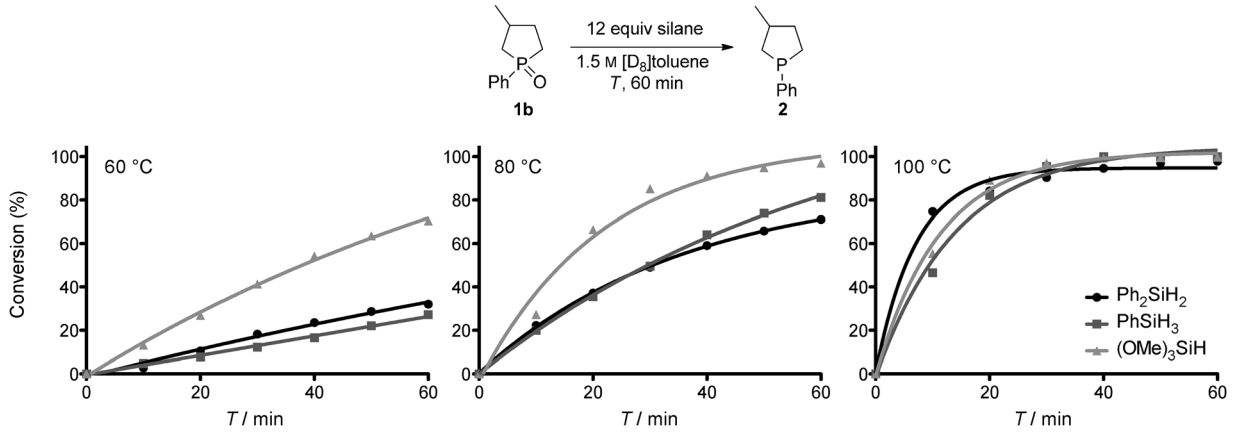


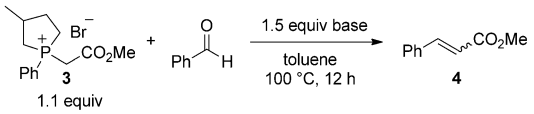
Figure 1. Optimization of organosilane reduction of phosphane oxide **1b**.

Subsequently, the reduction of **1b** was evaluated by using diphenylsilane, phenylsilane, and trimethoxysilane in [D_8]toluene at 60, 80, and 100 °C (Figure 1). From these experiments, it was clear that all three silane compounds were viable reducing agents at 100 °C because the conversion into a phosphane compound was nearly complete in just 20 minutes. At lower temperatures (i.e., 60 and 80 °C), the reduction was noticeably slower, with trimethoxysilane yielding the highest conversions. These results demonstrated that a reaction temperature of 100 °C was necessary for a viable CWR. In addition, it was confirmed that reduction proceeded with no inversion at the phosphorus center (see the Supporting Information).

After the identification of a suitable reduction strategy, the next consideration was the actual Wittig reaction, reliant on ylide formation through deprotonation of the phosphonium salt. For this step, the choice of base is critical. The base must have a pK_a value (of the conjugate acid) that is sufficient to deprotonate the ylide-forming proton of the phosphonium salt, yet not lead to incompatibilities with other reagents (such as the silane, organohalide, or olefin). Phosphonium salt **3**, formed from the reaction of phosphane **2** with methyl bromoacetate, was prepared and evaluated with a series of bases. It was anticipated that the ylide-forming proton of this salt would have a pK_a value of approximately 9, therefore the use of common bases of pK_a 9–12 (for conjugate acid) were investigated (Table 1). These studies identified sodium carbonate as the base of choice by combining high yield and ease of handling.[30]

Next, the full CWR was assembled by combining the optimized conditions for catalyst, temperature, reductant, and base (Table 2). Interestingly, although trimethoxysilane gave the best results in the reduction studies, this result did not translate into the full reaction system, and diphenylsilane give the optimal yield and selectivity. After having demonstrated the first catalytic in phosphane Wittig reaction, we sought to optimize the reaction further by alteration of the solvent (Table 3) and reaction temperature (Table 4). Acetonitrile and toluene were shown to give the greatest yields after both 5 and 24 hours, respectively. However, the use of

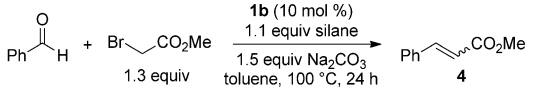
Table 1. Base study using phosphonium salt.[a]



Entry	Base	Conversion [%][b]	E/Z[c]
1	K_3PO_4	100	75:25
2	K_2CO_3	95 (90)	75:25
3	Na_2CO_3	98 (90)	75:25
4	Na_2SO_3	54	62:38

[a] Benzaldehyde (1.0 mmol), **3** (1.1 mmol), base (1.5 mmol), and toluene (3.0 M). [b] Conversions were determined by using ^{1}H NMR spectroscopy; selected examples were purified to determine the yield of the isolated product (shown in parentheses). [c] E/Z ratio was determined by ^{1}H NMR spectroscopic analysis of the unpurified reaction mixture.

Table 2. Optimization of organosilane for CWR.[a]

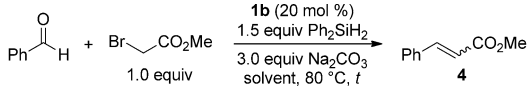


Entry	Silane	Yield [%][b]	E/Z[c]
1	Ph_3SiH	trace	n.d.
2	Ph_2SiH_2	75	>95:5
3	$PhSiH_3$	46	>95:5
4	$(MeO)_3SiH$	61	70:30

[a] Benzaldehyde (1.0 mmol), methyl bromoacetate (1.3 mmol), **1b** (0.1 mmol), sodium carbonate (1.5 mmol), silane (1.1 mmol), and toluene (3.0 M). [b] Yields were determined by GCMS/MS against a calibrated internal standard (undecane) and were performed in duplicate. [c] E/Z ratio was determined by GCMS/MS. n.d. = not determined.

acetonitrile at a temperature greater than 80 °C necessitated the use of a sealed vessel, thus toluene offered greater ease of use. Increasing the reaction temperature from 80 to 100 °C did not lead to a significant variation in yield, but gave enhanced diastereoselectivity (Table 4, entries 3 and 4). It was observed that the E/Z selectivity of the reaction after just 5 hours was generally 66:34, whereas the reaction was E-selective after 24 hours (cf. Table 3). This finding suggests

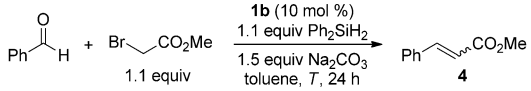
Table 3. Optimization of solvent.[a]



Entry	Solvent	t [h]	Yield [%][b]	E/Z[c]
1	toluene	5	35	66:34
2	toluene	24	73	95:5
3	acetonitrile	5	42	67:33
4	acetonitrile	24	85	>95:5
5	dimethoxyethane	5	42	67:33
6	dimethoxyethane	24	56	>95:5
7	1,4-dioxane	5	35	66:34
8	1,4-dioxane	24	55	>95:5
9	DMF	5	34	75:25
10	*tert*-butanol	5	10	60:40

[a] Benzaldehyde (1.0 mmol), methyl bromoacetate (1.0 mmol), **1b** (0.2 mmol), sodium carbonate (3.0 mmol), diphenylsilane (1.5 mmol), and requisite solvent (3.0 M). [b] Yields were determined by GCMS/MS against a calibrated internal standard (undecane) and were performed in duplicate. [c] E/Z ratio was determined by GCMS/MS.

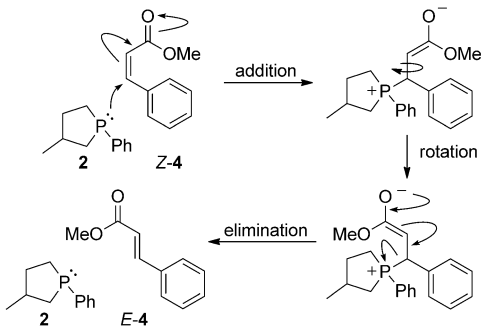
Table 4. Temperature study.[a]



Entry	T [°C]	Yield [%][b]	E/Z[c]
1	60	33	66:34
2	70	49	66:34
3	80	62	66:34
4	100	60	>95:5

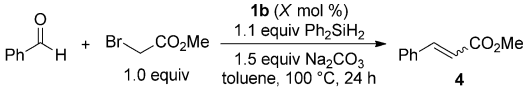
[a] Benzaldehyde (1.0 mmol), methyl bromoacetate (1.1 mmol), **1b** (0.1 mmol), sodium carbonate (1.5 mmol), diphenylsilane (1.5 mmol), and toluene (3.0 M). [b] Yields were determined by GCMS/MS against a calibrated internal standard (undecane) and were performed in duplicate. [c] E/Z ratio was determined by GCMS/MS.

that the kinetic selectivity of the reaction is 66:34 and a post-olefination isomerization occurs, thus converting the Z olefin into an E olefin over time. We postulate that this isomerization is phosphane mediated (Scheme 3). The lack of a diastereoselective process when either trimethoxysilane or temperatures lower than 100 °C are employed (compare Table 2, entry 4 and Table 4, entries 1–3) may result from an



Scheme 3. Proposed phosphane-mediated isomerization of (*Z*)-**4**.

Table 5. Catalyst loading study.[a]



Entry	Loading **1b** [mol %]	Yield [%][b]	E/Z[c]
1	4	70	>95:5
2	10	68	>95:5
3	20	80	>95.5

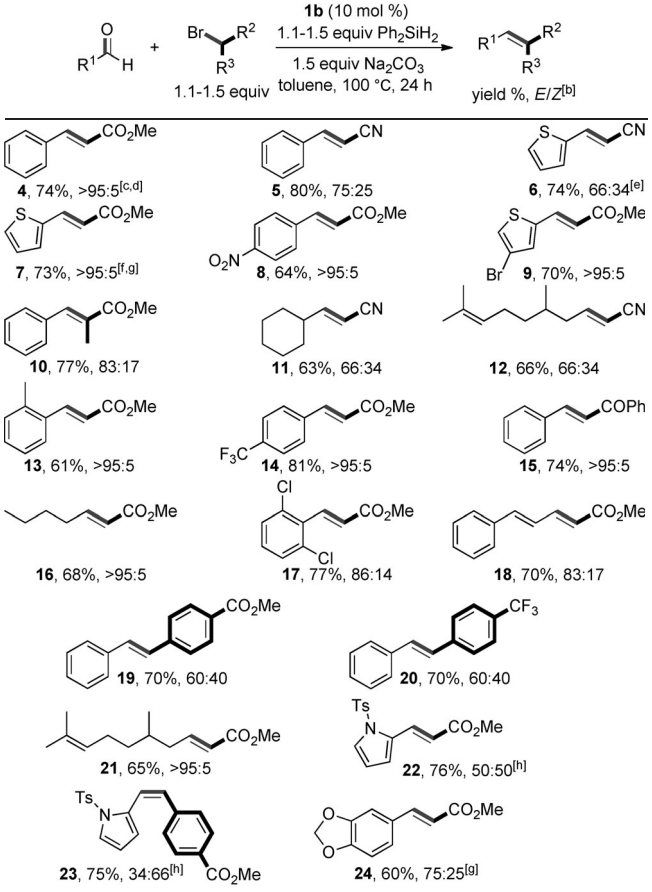
[a] Benzaldehyde (1.0 mmol), methyl bromoacetate (1.0 mmol), **1b** (0.04-0.2 mmol), sodium carbonate (1.5 mmol), diphenylsilane (1.1 mmol), and toluene (3.0 M). [b] Yields were determined by GCMS/MS against a calibrated internal standard (undecane) and were performed in duplicate. [c] E/Z ratio was determined by GCMS/MS.

insufficient rate of phosphane formation to effect the isomerization of the product after consumption of the aldehyde (see further).

Following optimization of the base, an assessment of the precatalyst loading was performed (Table 5). Pleasingly, the results demonstrated that a loading of just 4 mol % was necessary to achieve an acceptable yield (Table 5, entry 1). Importantly, a loading of 4 mol % is often used in palladium cross-coupling reactions and a comparable loading of an organocatalyst is impressive.[31] Indeed, there was no difference between loadings of 4 and 10 mol % (Table 5, entries 1 and 2, respectively).

Subsequent to protocol optimization, a substrate evaluation was undertaken (Table 6) by utilizing aliphatic, aryl, and heterocyclic aldehydes in combination with organohalides containing ylide-stabilizing ester, nitrile, ketyl, and electron-deficient benzyl moieties. Of particular note is the use of heterocyclic aldehydes in the synthesis of **6**, **7**, **9**, and **22**–**24**. The synthesis of **23** is of specific significance because this reaction was the first Z-selective catalytic Wittig reaction. This Z selectivity may be because the N–Ts group stabilizes the formation of *cis*-oxaphosphetane, as observed by Byrne and Gilheany.[12] Alternatively, steric influences could explain the selectivity; nevertheless, this result offers key insight toward the development of a Z-selective methodology. In addition, the use of aliphatic aldehydes, in particular citronellal, gave olefins **12**, **16**, and **21** in good yields. The use of electron-deficient benzyl bromides produce stilbene derivatives **19** and **20** in good yields, but with moderate selectivity (E/Z = 60:40). To demonstrate the application of the catalytic Wittig methodology further, **7** was produced on a scale of 30 mmol (67 % yield, E/Z > 95:5, 48 h, 90 °C) using just 4 mol % of **1b**. Although diphenylsilane was the reducing agent of choice for the majority of substrates, trimethoxysilane was employed in situations in which the removal of a siloxane byproduct was an issue, for example in the synthesis of **22**–**24**. These results neatly highlighted the benefit in decoupling the terminal reducing agent from the olefinating agent because simply switching the silane compound solves purification issues.

Table 6. Substrate study using sodium carbonate for the CWR.[a]

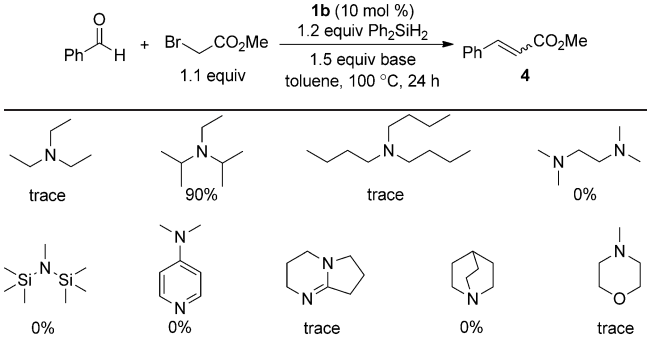


[a] The compound number, yield, and *E*/*Z* ratio are given for each product; the reactions were performed in duplicate (see the Supporting Information for detail). [b] *E*/*Z* ratio was determined by ^{1}H NMR spectroscopic analysis of the unpurified reaction mixture. [c] This reaction performed with 4 mol% of **1b** resulted in 73% yield. [d] This reaction performed with methyl chloroacetate resulted in 68% yield. [e] A single reaction with $(MeO)_3SiH$ (2.0 mmol) resulted in 85% yield. [f] This reaction performed on a scale of 10.7 mmol with 10 mol% **1b** resulted in 63% yield. [g] This reaction performed on a scale of 30 mmol with 4 mol% of **1b** at 90 °C over 48 h resulted in 67% yield. [h] Performed with $(MeO)_3SiH$ (2.0 mmol).

Further examination of our substrate study revealed a trend in diastereoselectivity, α,β-unsaturated products demonstrated considerably higher *E* selectivity relative to propenenitrile products (i.e., **5**, **6**, **11**, and **12**). To probe this difference in diastereoselectivity, we revisited the proposed phosphane-mediated isomerization event (Scheme 3) and carried out an isomerization study with both (*Z*)-**4** and (*Z*)-**5** (Figure 2). The results were striking, after 10.5 hours full isomerization was observed for **4**, whereas **5** showed only a trace of isomerization (below the limit of quantitation). Indeed, after 50 hours the conversion of (*Z*)-**5** into (*E*)-**5** had proceeded in just 6% conversion (see the Supporting Information). In the absence of a phosphane, no isomerization to (*E*)-**4** occurred (see the Supporting Information). These results point to the production of propenenitriles (through bromoacetonitrile as the organohalide) as a better probe for the selectivity of the catalytic Wittig system rather than α,β-unsaturated products because propenenitrile olefins do not undergo phosphane-mediated isomerization. These findings may also have implications for the assessment of diastereoselectivity in stoichiometric Wittig reactions.

Although the results illustrate the considerable scope of the catalytic Wittig reaction (Table 6), some difficulties were noted during the application of the reaction. It was necessary to use finely ground sodium carbonate to achieve high yields and to ensure rapid stirring throughout the reaction. The use of a soluble base would alleviate this concern; therefore, a series of soluble bases with a range of pK_a values (in water) for the conjugate acid between pK_a 7 and 14 were screened for the CWR (Table 7). Of the soluble

Table 7. Soluble base study.[a]



[a] Benzaldehyde (1.0 mmol), methyl bromoacetate (1.1 mmol), **1b** (0.1 mmol), base (1.5 mmol), diphenylsilane (1.2 mmol), and toluene (3.0 M); the yields were determined by GCMS/MS against a calibrated internal standard (undecane) and were performed in duplicate.

bases examined, only *N*,*N*-diisopropylethylamine (DIPEA; Hünig's base) was shown to be suitable for use in the CWR. The success of DIPEA hinged on two points: 1) the pK_a value of DIPEA-H$^+$ is 11.4 (in water; 9.1 in DMSO), which is ideal for the deprotonation of the phosphonium salt; 2) the steric bulk and lack of nucleophilicity of DIPEA ensured that unwanted side reactions did not occur.

After the identification of a soluble base, an assessment of the phosphane oxide/phosphane structure was undertaken (Table 8). Unsurprisingly, **1b** and **1c** were equally effective in the CWR and could be used interchangeably, thus demonstrating that the methyl group in **1b** was a mere spectator in the CWR. Additionally, the unreduced analogue of **1b**, that is, **1a**, was also effective in the CWR, thus indicating that reductive removal of the carbon–carbon double bond in **1a** may have been unnecessary. Acyclic phosphanes, including triphenylphosphane (TPP), were essentially ineffective and resulted in <5% yield. The failure of acyclic phosphanes in the CWR stems from an insufficient rate of oxide reduction and vindicates the initial decision to employ cyclic phosphane oxides in the preliminary studies. Of the other phosphane structures screened, only 5-phenyldibenzophosphole (**27**) gave a quantifiable yield (30%, *E*/*Z* = 80:20). This phosphane is analogous to triphenylphosphane, with

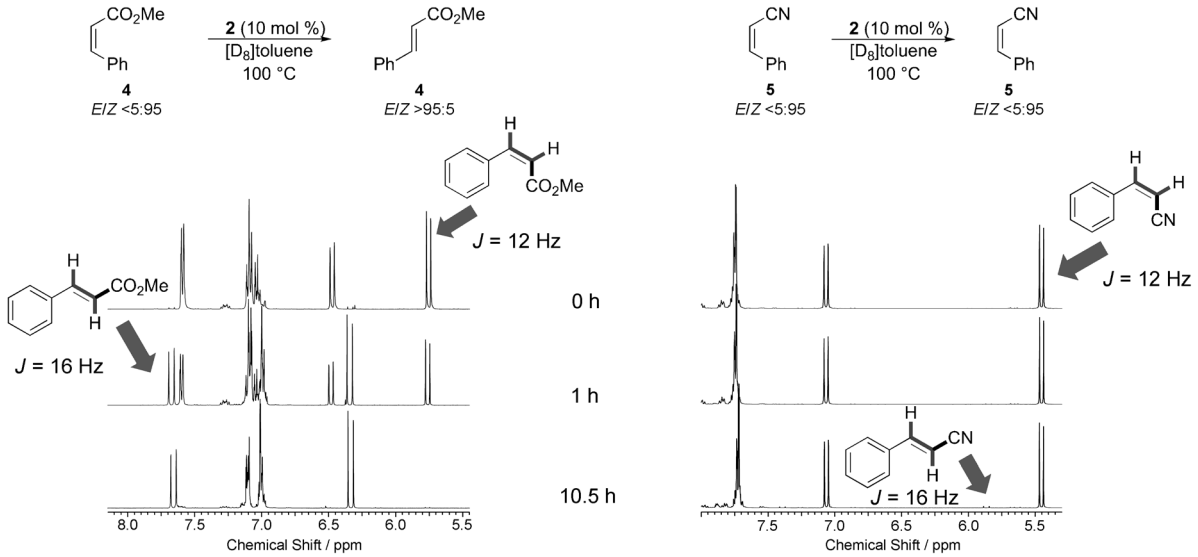
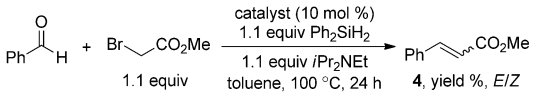
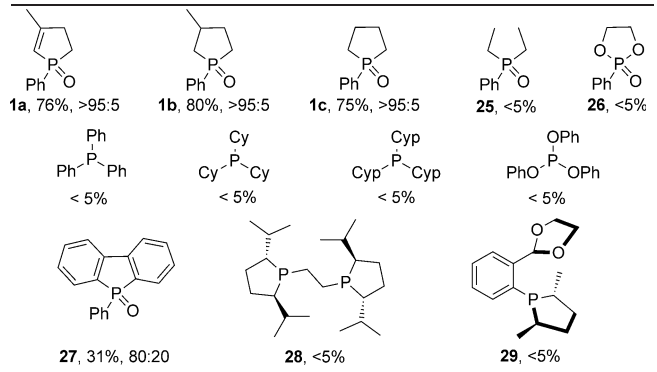


Figure 2. Isomerization of (*Z*)-**4** and (*Z*)-**5**.

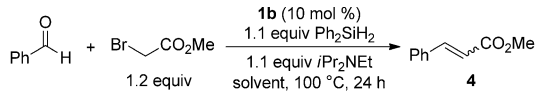
Table 8. Screening of phosphane catalysts.[a]





[a] Benzaldehyde (1.0 mmol), methyl bromoacetate (1.1 mmol), catalyst (0.1 mmol), DIPEA (1.1 mmol), diphenylsilane (1.1 mmol), and toluene (3.0 M); the yields were determined by GCMS/MS against a calibrated internal standard (undecane) and were performed in duplicate. *E*/*Z* ratio was determined by GCMS/MS. Cy = cyclohexyl. Cyp = cyclopentyl.

Table 9. Process-friendly solvents study.[a]



Entry	Solvent	Conversion [%][b]	*E*/*Z*[c,d]
1	toluene	96 (85)	72:28
2	cyclopentyl methyl ether	96 (85)	69:31
3	*tert*-butyl acetate	94	69:31
4	2-methyltetrahydrofuran	93	69:31
5	dimethyl carbonate	92	70:30
6	3-methyl-2-butanone	82	70:30
7	α,α,α-trifluorotoluene	80	69:31

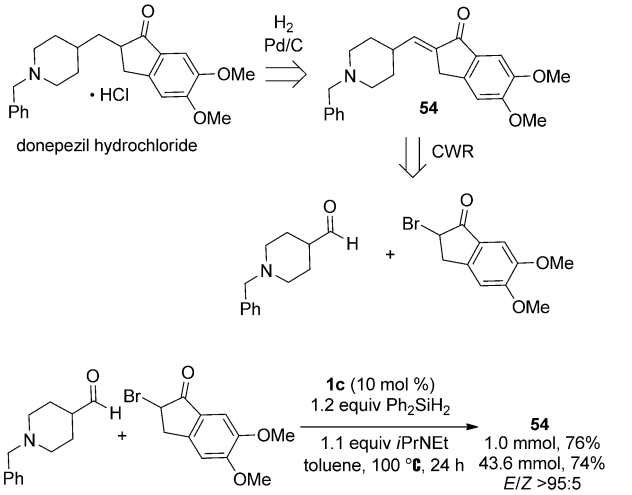
[a] Benzaldehyde (1.0 mmol), methyl bromoacetate (1.2 mmol) **1b** (0.1 mmol), DIPEA (1.1 mmol), diphenylsilane (1.1 mmol), and the requisite solvent (3.0 M). [b] Conversions were determined by using ^{1}H NMR spectroscopy, and selected examples were purified to determine the yield of the isolated product (shown in parentheses). [c] *E*/*Z* ratio was determined by ^{1}H NMR spectroscopic analysis of the unpurified reaction mixture. [d] When the reactions were performed with 1.2 equivalents of diphenylsilane, which ensured phosphane predominated at the end of the reaction, the *E*/*Z* selectivity was >95:5 as expected.

additional ring strain caused by fusing two of the aromatic rings and, consequently, it proves to be more susceptible to reduction than TPP oxide. The inferior yield and diastereoselectivity obtained by utilizing **27** relative to type **1** catalysts probably results from the lower nucleophilicity of the lone pair of electrons on the phosphorus atom to that of **1a**–**c**. This effect stems from delocalization of the lone pair of electrons in the corresponding phosphane of **27** within its wider π system. Such a delocalization of the lone pair of electrons on the phosphorus atom would impact the rate of formation of the phosphonium salt and consequently effect the yield of the olefin. Retardation in the nucleophilicity of the lone pair of electrons on the phosphorus atom would also influence the effectiveness of the phosphane-led alkene-isomerization process, which would result in erosion of the diastereoselectivity.

Following the modification of the CWR to accommodate the use of a soluble base, the choice of the reaction solvent was revisited, focusing on process-friendly solvents (Table 9).[32] The solvent is well known to have an effect on the diastereoselectivity of the Wittig reaction,[11] therefore conditions were selected that prevented phosphane-mediated isomerization. Such conditions would allow our solvent study to identify a deviation in yield and diastereoselectivity. The results revealed that a high yield of the olefin was maintained across all the solvents tested (Table 9). Furthermore, identical diastereoselectivity was also observed, thus indicating that the geometry of the olefin is governed by the phos-

phane structure and not a solvent effect. These results demonstrate that optimization of the phosphane/phosphane oxide structure should produce a more selective process.

Employment of the DIPEA/CWR conditions broadened the reaction scope to include furyl, indolyl, and pyridyl aldehydes (Table 10, **34**, **39**–**41**, **47**, **49**, and **50**). In addition, the DIPEA conditions were used to prepare a further 21 examples of trisubstituted olefins. A comparison of **1b** and **1c** shows that the methyl group in **1b**, as expected, does not result in a significant difference in yield or selectivity (see **37**–**40**, **42**, and **47**) and that these phosphane oxides may be used interchangeably. Compounds **44**–**46** are of particular interest because these are structurally similar to resveratrol, and various methoxylated derivatives of resveratrol have been shown to have anticancer activity.[33] The preparation of **52**, which features a free N–H functional group, demonstrates the mild nature of these reaction conditions. To highlight the utility of the CWR further, its application in the synthesis of the real-world example donepezil hydrochloride was undertaken. Donepezil, under the trade name Aricept, is used in the palliative treatment of mild-Alzheimer disease.[34] Donepezil hydrochloride is readily available from precursor **54** through a hydrogenation reaction and HCl-salt formation (Scheme 4). Compound **54** in turn is accessible through a CWR. Pleasingly, **54** was easily prepared on a multigram scale (12.2 g, 74%, $E/Z > 95:5$) by utilizing a 10 mol% loading of **1c**. When prepared on a small scale



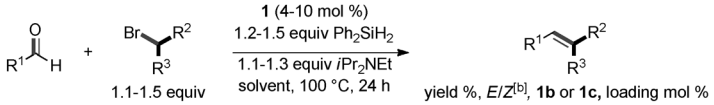
Scheme 4. Retrosynthesis of donepezil hydrochloride and preparation of **54** by using CWR.

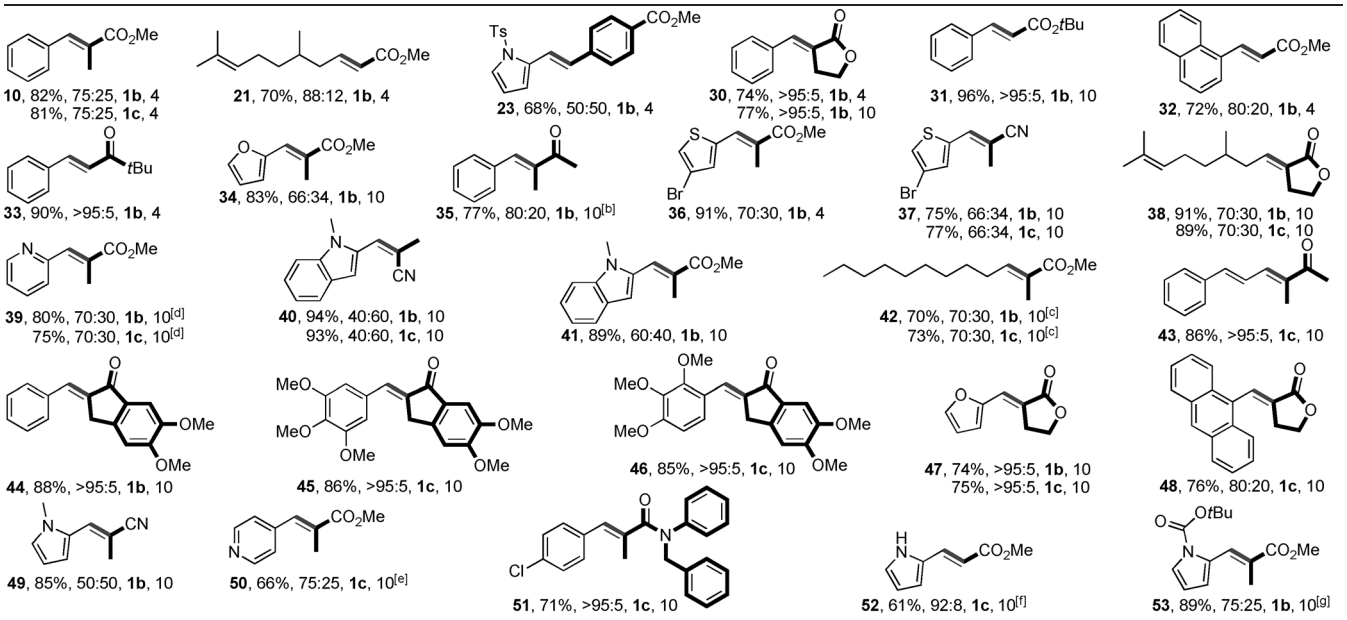
(1.0 mmol), this compound was obtained in 76% yield, thus demonstrating that the scale has little variation on the yield.

Conclusion

We have developed the first catalytic (in phosphane) Wittig reaction by utilizing an organosilane that chemoselectively

Table 10. Substrate study using DIPEA in the CWR.[a]





[a] The compound number, yield, E/Z ratio, phosphane oxide, and loading are given for each product. The reactions were performed in duplicate (see the Supporting Information for details). [b] E/Z ratio was determined by ^{1}H NMR spectroscopic analysis of the unpurified reaction mixture. [c] The reaction was performed with $(MeO)_3SiH$ (2.0 mmol). [d] Reaction time was 12 h. [e] The aldehyde and organohalide were added together in 12 portions over 6 h. [f] The reaction was performed with phenylsilane in cyclopentyl methyl ether at 60 °C; only the E diastereomer was isolated. [g] The reaction was performed with phenylsilane in ethyl acetate at 60 °C.

reduces a phosphane oxide precatalyst to a phosphane. Furthermore, to our knowledge, this is the only transition-/heavy-metal-free catalytic olefination process to date, excluding proton-catalyzed elimination reactions. The generality of this methodology is demonstrated in Tables 6 and 10, with 23 examples prepared by using sodium carbonate and a further 27 examples by using DIPEA. Both protocols can employ aliphatic, aryl, and heterocyclic aldehydes to produce both di- and trisubstituted olefins in moderate-to-high yields (60–96%). The CWR may be carried out on a large scale, as highlighted in the synthesis of **54** on a 44 mmol scale to yield 12.2 g (74%) of a precursor to the Alzheimer drug donepezil hydrochloride. Kinetic *E*/*Z* selectivity was generally 66:34; however, *E* selectivity could be achieved through a phosphane-mediated isomerization event for α,β-unsaturated products. Of note are the synthesis of **23** and **40**, which are the first examples of *Z*-selective CWRs. These results may offer valuable insight for further studies toward the development of a *Z*-selective CWR. Further investigations toward lowering the reaction temperature and extending the methodology to other ylide types and carbonyl substrates are on-going and will be reported in due course.

Experimental Section

See the Supporting Information for the general experimental and full details of the syntheses and characterizations. Representative procedures are given below.

General procedure for the CWR with sodium carbonate: A 1-dram vial equipped with a stirring bar was charged with phosphane oxide **1b** (19 mg, 0.10 mmol, 10 mol%) and sodium carbonate (1.5 mmol, 1.5 equiv) in air. Other solid reagents were added to the mixture at this point, such as the aldehyde (1.0 mmol, 1.0 equiv) and organohalide (1.3–1.5 mmol, 1.3–1.5 equiv). The vial was sealed with a septum and purged with argon. Toluene (0.33 mL) and liquid reagents were introduced into the mixture, such as the aldehyde (1.0 mmol, 1.0 equiv), organohalide (1.1–1.5 mmol, 1.1–1.5 equiv), and silane (1.1–2.0 mmol, 1.1–2.0 equiv). The septum was replaced with a PTFE-lined screw cap under an inert atmosphere, and the reaction was heated at 100°C for 24 h. The crude reaction mixture was filtered through a plug of Celite, concentrated in vacuo, and purified by means of flash-column chromatography. Note that it is important that the reactions are stirred vigorously to achieve the maximum yield.

General procedure for the CWR with DIPEA: A 1-dram vial equipped with a stirring bar was charged with phosphane oxide **1b** or **1c** (0.04–0.1 mmol, 4–10 mol%). Other solid reagents were added at this point, such as the aldehyde (1.0 mmol, 1.0 equiv) and organohalide (1.1 mmol, 1.1 equiv). The vial was sealed with a septum and purged with argon. The solvent (0.33–0.50 mL) and any liquid reagents were introduced to the mixture, such as the aldehyde (1.0 mmol, 1.0 equiv), organohalide (1.1–1.5 mmol, 1.1–1.5 equiv), DIPEA (1.1–1.3 mmol, 1.1–1.3 equiv), and silane (1.1–2.0 mmol, 1.1–2.0 equiv). The septum was replaced with a PTFE-lined screw cap under an inert atmosphere, and the reaction was heated at 100°C for 24 h. The crude reaction mixture was concentrated in vacuo and purified by means of flash-column chromatography.

Synthesis of 54 on a multigram scale: Compound **54** was prepared from 1-benzylpiperidine-4-carbaldehyde (8.9 g, 43.6 mmol, 1.0 equiv), 2-bromo-5,6-dimethoxy-1-indanone (13.0 g, 48.0 mmol, 1.1 equiv), DIPEA (8.4 mL, 48.0 mmol, 1.1 equiv), and diphenylsilane (9.7 mL, 52.3 mmol, 1.2 equiv) with **1c** (785 mg, 4.3 mmol, 10 mol%) in toluene (14.4 mL) in a pressure vessel (350 mL) at 100°C for 24 h. The crude product was purified by means of dry flash chromatography (hexane/ethyl acetate, 10:90→0:100) to afford **54** as a brown solid (12.2 g, 74%, *E*/*Z* > 95:5). ^{1}H NMR (400 MHz, $CDCl_3$, 20°C): δ = 7.13–7.30 (m, 6H), 6.82 (br s, 1H), 6.58 (br d, J = 9.6 Hz, 1H), 3.90 (s, 3H), 3.85 (s, 3H), 3.51 (d, J = 0.8 Hz, 2H), 3.46 (s, 2H), 2.86 (br d, J = 11.6 Hz, 2H), 2.21–2.31 (m, 1H), 1.99 (td, J = 11.2, 2.0 Hz, 2H), 1.50–1.65 ppm (m, 4H); ^{13}C NMR (100 MHz, CDCl3): δ = 192.7, 155.3, 149.5, 144.6, 139.9, 138.2, 135.7, 131.9, 129.3, 128.3, 127.1, 107.3, 105.1, 63.6, 56.3, 56.2, 53.1, 37.3, 31.3, 29.6 ppm; the spectral data was consistent with previous data.[34b]

Acknowledgements

We thank Peakdale Molecular Ltd for the gift of heterocyclic aldehydes, and Dr. M. Feeney (Trinity College Dublin) for high-resolution mass spectrometry. Financial support for this work was received from The University of Texas at Arlington, Dublin City University (DCU, Career Start), and Enterprise Ireland (EI, Grant No. CF/2011/1029).

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Received: April 16, 2013
Published online: September 25, 2013

