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Breaking the Ring through a Room Temperature Catalytic Wittig Reaction

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Discovery of new and refinement of existing synthetic methodologies are essential if chemistry is to adapt to the changes and consequent challenges in its application landscape.[1] These impediments can be represented in terms of substrate diversity, energy cost, ease-of-use or deployment.[2] In regard to organic synthesis this generally relies on the interplay and reactivity of functional groups. Carbon–carbon double bonds present a multitude of synthetic opportunities.[2,3] Arguably, the most utilized methodology for the construction of this important functional group is the Wittig reaction.[4] Consequently, the Wittig reaction has received considerable attention by numerous groups both in application[5] and mechanistic understanding.[6] Recently, our laboratory was successful in developing the first catalytic Wittig reaction (CWR, in phosphine).[7] Though these results were an advance[7b–c] they represented the start of the process to develop a robust user-friendly olefination methodology. Indeed, the reactions were performed at high temperature (100 °C) and were not kinetically highly diastereoselective. The observed high *E* selectivity relied on a phosphine-mediated post-olefination isomerization event.[7a] The actual kinetic selectivity ranged from *E*/*Z*: 2:1 to 3:1. Furthermore, the protocol was reliant on the use of a cyclic phosphine oxide. Ideally a catalytic Wittig process performed at room temperature and/or utilizing readily available acyclic trialkyl or triaryl phosphine oxides would offer greater synthetic flexibility and aid wider adoption of the methodology.

Yet, both of these enhancements hinge on the key problem of selective reduction of the phosphine oxide in the presence of other reactive functionalities. The employment of silane yielded the answer in our previous work.[7] Subsequently others applied this reduction strategy to the Appel and Staudinger reactions.[8] In regard to the Wittig reaction, we found that a temperature of 100 °C was required to achieve a viable turnover rate of the phosphine oxide/phosphine required for adoption in a catalytic process.[9] Consequently, to decrease the reaction temperature an increase in the reactivity of either the phosphine oxide (toward reduction) or silane must be achieved.

To achieve this, two possible strategies can be employed in isolation or in combination: 1) modify the phosphine oxide or silane structure or 2) the inclusion of an additive, for example, a Lewis acid,[10] to increase the rate of reduction. We were concerned that the use of an organometallic or boron-based Lewis acid would yield significant chemoselectivity issues. The most rudimentary of Lewis acids is a proton; therefore, could the addition of a protic acid yield an enhancement in rate of phosphine oxide reduction? This was postulated based on mechanistic studies of phosphine oxide reduction by silanes,[11] and supported by re-examination of results in which aged benzaldehyde was used.[11c] Consequently we probed the use of aryl carboxylic acids as reduction aids. To ease integration in the final CWR, reductions were performed in the presence of base (iPr$_2$NEt) and mimicked a theoretical 10 mol% catalyst loading based on the future aldehyde. Employing the same reasoning the silane would represent 1.4 equivalents. This rationale led to the final conditions as depicted in Table 1 and the results were striking. Addition of an equimolar amount of an aryl carboxylic acid notably enhanced phosphine oxide reduction.[12] Indeed, the reduction of **1** was almost complete in just 60 min at room temperature (Table 1, entry 1).

To probe this reduction a series of aryl carboxylic acids varying in pK_a were screened. Diphenylsilane replaced phenylsilane as the lower reactivity of this silane would offer greater resolution in terms of reactivity differences between acids. The effect of the pK_a of the acid was significant, 4-nitrobenzoic acid, which has the lowest pK_a (~3.4 in water, ~9.1 in DMSO), yielded the greatest enhancement in reduction (Table 1, entries 3–7). A control reaction performed with no carboxylic acid additive yielded just 6% (entry 2). Moreover, reduction employing phenylsilane and 4-nitrobenzoic acid achieved a high conversion at room temperature in just 2 min (entries 8–10)! Though the rates observed for reduction of cyclic phosphine oxides **1** and **2** were impressive, a barrier remained, reduction of acyclic phosphine oxides. Pleasingly, we observed that **3** and **4** were reduced with reasonable yield in just 10 min at 100 °C (entries 11 and 12). Further enhancement in reduction of triphenylphosphine oxide was accomplished by substitution of phenylsilane with 4-(trifluoromethyl)phenylsilane, which yielded an increase from 50 to 81% yield (footnote [c]).

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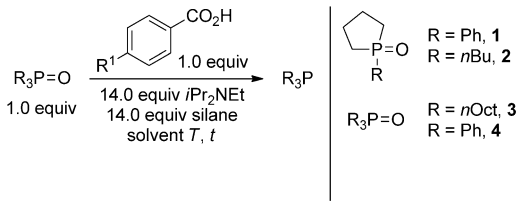
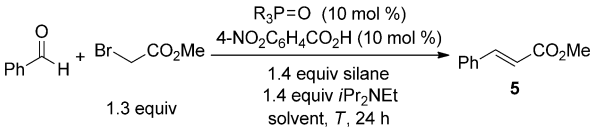
Table 1. Carboxylic acid enhanced phosphine oxide reduction.[a]



Entry	R_3PO	Silane	R^1	T [°C]	t [min]	Conv. [%][b]
1	**1**	$PhSiH_3$	H	RT	60	94
2	**1**	Ph_2SiH_2	–	RT	60	6
3	**1**	Ph_2SiH_2	OMe	RT	60	20
4	**1**	Ph_2SiH_2	CH_3	RT	60	25
5	**1**	Ph_2SiH_2	H	RT	60	34
6	**1**	Ph_2SiH_2	CF_3	RT	60	57
7	**1**	Ph_2SiH_2	NO_2	RT	60	61
8	**1**	$PhSiH_3$	NO_2	RT	2	74
9	**2**	$PhSiH_3$	NO_2	RT	2	82
10	**2**	$PhSiH_3$	NO_2	RT	2	85
11	**3**	$PhSiH_3$	NO_2	100	10	73
12	**4**	$PhSiH_3$	NO_2	100	10	50[c]

[a] Phosphine oxide (0.1 mmol), 4-substituted benzoic acid (0.1 mmol), iPr_2NEt (1.4 mmol), silane (1.4 mmol), 0.3 M in requisite solvent (entries 1–9, THF; entry 10, EtOAc; entries 11 and 12, toluene). For full details of carboxylic acid enhanced phosphine oxide reduction see the Supporting Information. [b] Conversion determined by ^{31}P NMR spectral analysis, triphenylphosphine oxide as a calibrant (not used for entry 12). [c] Conversion employing 4-(trifluoromethyl)phenylsilane was 81%.

Table 2. Optimization of the CWR with primary bromides.[a]

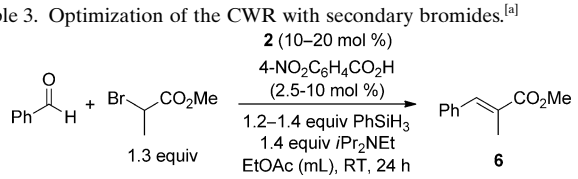


Entry	R_3PO	Solvent	T [°C]	Conv. [%][b,c]	E/Z[d,e]
1	**1**	THF	RT	100 (91)	75:25
2	**2**	THF	RT	100	86:14
3	**2**	CPME	RT	100	86:14
4	**2**	EtOAc	RT	100 (85)	86:14
5	**3**	CPME	100	100 (81)	89:11
6	**3**	toluene	100	96 (85)	91:9
7	**4**	toluene	100	89	90:10

[a] For full details of the optimization see the Supporting Information. Benzaldehyde (1.0 mmol), organohalide (1.3 mmol), phosphine oxide (0.1 mmol), 4-nitrobenzoic acid (0.1 mmol), iPr_2NEt (1.4 mmol), silane (1.4 mmol; entries 1–6, phenylsilane; entry 7, 4-(trifluoromethyl)phenylsilane) 3.0 M in requisite solvent. [b] Conversion determined by ^1H NMR spectroscopy. [c] Isolated yields shown in parentheses. [d] E/Z ratio determined by ^1H NMR spectroscopy of the unpurified reaction mixture. [e] A repeat of entry 4 without acid additive gave a selectivity of E/Z 86:14.

Subsequently, integration into the CWR was undertaken (Tables 2 and 3). Satisfyingly, the acid-enhanced reduction strategy was effectively adopted into the CWR resulting in a room temperature CWR (RT-CWR) with complete conversion of the aldehyde (Table 2, entries 1 and 2). To the best of our knowledge this is the first time a CWR has been achieved at room temperature. Alkyl cyclic phosphine oxide **2** as predicted by the literature led to higher E selectivity and

Table 3. Optimization of the CWR with secondary bromides.[a]



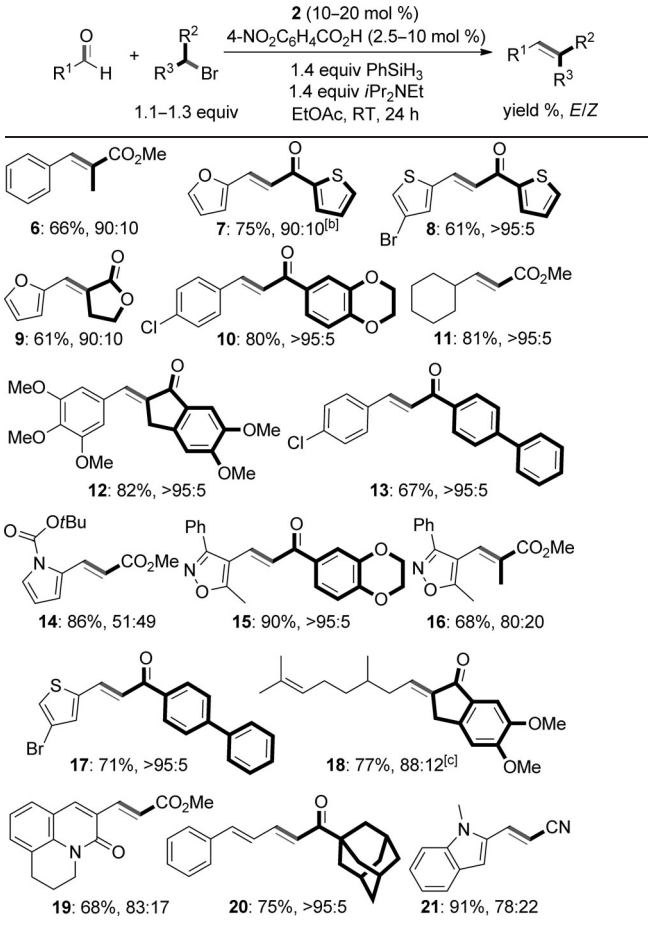
Entry	**2** [mol%]	Acid [mol%]	V EtOAc [mL]	Yield [%][b]	E/Z[c]
1	10	10	0.33	28	87:13
2[d]	20	5	1.0	75	90:10
3[e]	20	2.5	2.0	52	90:10
4[f]	10	2.5	0.5	66	90:10

[a] For full details of the optimization study see the Supporting Information. Benzaldehyde (1.0 mmol), organohalide (1.3 mmol), phosphine oxide (0.1–0.2 mmol), 4-nitrobenzoic acid (0.025-0.1 mmol), iPr_2NEt (1.4 mmol), phenylsilane (1.2–1.4 mmol), EtOAc (X mL). [b] Isolated yield. [c] E/Z ratio determined by ^1H NMR spectroscopy of the unpurified reaction mixture. [d] Aldehyde added in four portions every 3 h. [e] 17.5 mol% tetrabutylammonium tetrafluoroborate was added. [f] Aldehyde added in 10 portions every 1.5 h.

was adopted from this point.[6] Following these results, a brief solvent study was performed that focused on green solvents that would offer the possibility of implementation in process scale applications.[13] In this regard, cyclopentyl methyl ether (CPME) and EtOAc were effective solvents and worked equally well without distillation (entries 3 and 4). Olefinations involving acyclic phosphine oxides also proceeded smoothly at 100 °C and in high conversions and yield (entries 6 and 7). This is the first time an acyclic phosphine oxide has been utilized as a catalyst in the CWR and the use of phosphine oxides **3** and **4** resulted in high kinetic diastereocontrol. Next the RT-CWR was successfully applied to the production of trisubstituted olefins, as **6** was synthesized in good yield at room temperature with slow addition of aldehyde (Table 3, entry 4).

Following optimization of the cyclic phosphine oxide catalysed room temperature (RT-CWR), and acyclic phosphine oxide catalysed (AC-CWR) high temperature catalytic Wittig reactions, substrate studies were performed (Tables 4–6). Notable results employing the RT-CWR protocol (Table 4) were the syntheses of **7**–**9**, **14**–**16**, **19** and **21** that demonstrated the employment of heterocyclic aldehydes and/or organobromides. Compound **12** also has structural similarities to resveratrol and derivatives, which have anticancer properties, illustrating the medicinal chemistry applications of this methodology.[14] In all cases, except **14**, good E diastereoselectivity was achieved. The use of a 1,2-oxazole carboxaldehyde, producing **15** and **16** was noteworthy as these heterocycles are often employed in medicinal chemistry.[15] The mild nature of the protocol was demonstrated by the toleration of the *tert*-butoxycarbonyl (BOC) protecting group yielding compound **14**. Erosion of diastereoselectivity in this case most likely results from the BOC group stabilizing the formation of the *cis*-oxaphosphetane as outlined by Byrne and Gilheany.[6a] The reasonable E selectivity in the synthesis of **21** is interesting as the use of bromoacetonitrile led to poor selectivity (E/Z: 66:34) in our previous protocol.[7a]

Table 4. Room temperature substrate study employing **2** as the catalyst.[a]

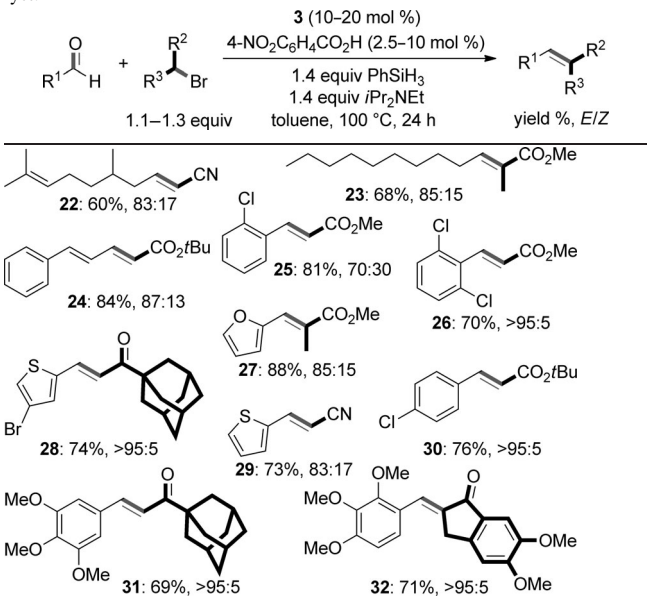


[a] For each product the compound number, isolated yield and *E*/*Z* ratio, determined by ^{1}H NMR spectroscopy of the unpurified reaction mixture, are given. The reactions were performed in duplicate; see the Supporting Information for details. [b] Only the *E* diastereomer was isolated. [c] When performed on a 19.1 mmol scale, the yield was 72% (4.46 g, *E*/*Z*: 88:12).

During the course of the room temperature substrate study various factors became apparent that would ensure acceptable yields. 1) The reduction of the phosphine oxide to phosphine even at room temperature may not always be rate-limiting. Indeed, for secondary organohalides the resting state of the catalyst was often found to be predominantly phosphine and not oxide.[16] This points, in these cases, to the formation of the phosphonium salt or the actual Wittig reaction being rate-limiting. 2) At room temperature, the solubility of the phosphonium salt often became a factor. For example, in the syntheses of **12** and **18**, both a phase-transfer catalyst (tetrabutylammonium tetrafluoroborate) and additional solvent were required to achieve optimal yields.[16] During the standard RT-CWR the generation of diisopropylethylammonium 4-nitrobenzoate is possible and may aid in solubilization of the phosphonium salt.[17] Hence, the addition of 4-nitrobenzoic acid may produce a dual effect enhancing reduction of the phosphine oxide and aiding in the solubility of the produced phosphonium salt.[17b] 3) In the case of CWRs in which the reduction of the phosphine oxide was not rate-limiting, the amount of carboxylic acid additive should be decreased or reduction of the aldehyde can occur.

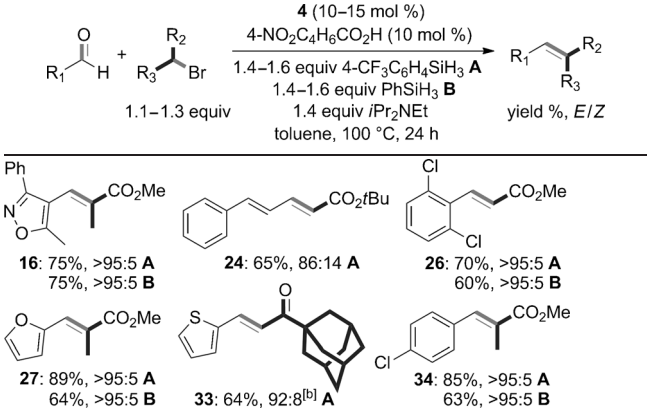
Similarly the utilization of trioctylphosphine oxide **3** and triphenylphosphine oxide **4** was equally effective (Table 5 and 6). Again heterocyclic aldehydes were well tolerated. Noteworthy results involving catalysis by **3** include the syntheses of **22**, **27**, **29** and **32**. Again the use of bromoacetonitrile resulted in good selectivity as **22** and **29** were produced

Table 5. Substrate study employing trioctylphosphine oxide **3** as the catalyst.[a]



[a] For each product the compound number, isolated yield and *E*/*Z* ratio, determined by ^{1}H NMR spectroscopy of the unpurified reaction mixture, are given. The reactions were performed in duplicate; see the Supporting Information for details.

Table 6. Substrate study employing triphenylphosphine oxide **4** as the catalyst.[a]



[a] For each product the compound number, isolated yield and *E*/*Z* ratio, determined by ^{1}H NMR spectroscopy of the unpurified reaction mixture, are given. The reactions were performed in duplicate; see the Supporting Information for details. [b] Only the *E* diastereomer was isolated.

with a ratio of *E*/*Z*: 83:17 (Table 5). Significantly the synthesis of **22** in our previous protocol proceeded with a selectivity of *E*/*Z*: 66:34.[7a] When triphenylphosphine oxide **4** was employed as a catalyst with 4-(trifluoromethyl)phenylsilane the same generality was maintained in terms of aldehydes and organobromides (Table 6). Of note is that compound **27** was produced with total *E* diastereoselectivity employing **4**, whereas the use of **3** produced small amounts of the *Z* product (compare **27** in Tables 5 and 6). Tables 4–6 taken as a whole bring a significant degree of synthetic flexibility to the CWR; reactions can be performed at room temperature with cyclic phosphine oxides or at higher temperatures with acyclic phosphine oxides.

In conclusion, the employment of 2.5–10 mol% of 4-nitrobenzoic acid with phenylsilane led to the development of a room temperature catalytic Wittig reaction. Furthermore, these enhanced reduction conditions also facilitated the use of acyclic phosphine oxides as catalysts. Indeed, triphenylphosphine oxide for the first time is a viable olefination catalyst. A series of di- and trisubstituted alkenes were produced in moderate to high yield with good to excellent *E* selectivity, by utilizing heteroaryl, aryl and alkyl aldehydes and organobromides. The RT-CWR protocol was also demonstrated on scale, 4.46 g of **18** was produced (72% yield) with 20 mol% loading of **2** (Table 4, footnote [b]). The utilization of process-friendly solvents coupled with both room temperature and high temperature conditions delivers the synthetic flexibility that should promote wider adoption of the methodology.

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Keywords: alkenes · homogeneous catalysis · olefination · room temperature · Wittig reaction

[1] a) EPSRC's Grand Challenges can be found under http://www.epsrc.ac.uk/ourportfolio/themes/physicalsciences/introduction/Pages/chemscieng.aspx; b) NSF priority areas in chemistry can be found under http://www.nsf.gov/div/index.jsp?div=CHE.

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[9] If a catalyst loading of 10 mol% is employed with a maximum reaction time of 24 h, 10 cycles will be required for the reaction to achieve 100% yield. Therefore, a synthetically viable catalytic system requires each cycle to be complete within 2.4 h.

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[12] Whilst this manuscript was in preparation a similar enhancement in silane reduction of acyclic phosphine oxides was reported by Y. Li, L.-Q. Lu, S. Das, S. Pisiewicz, K. Junge, M. Beller, *J. Am. Chem. Soc.* **2012**, *134*, 18325–18329. The results in this work were first presented at the Young Investigators' Workshop, Vienna, EuCheMs, on the 23rd August 2012. Details can be found at http://investigator.ias.tuwien.ac.at/index.shtml. Furthermore, in the synthesis of **11** (Table 4), 4-nitrobenzoic acid was found to be more effective than bis(4-nitrophenyl)phosphonate and isolated yields of **11** with each additive were 76 and 34%, respectively, after 12 h. This demonstrates the difficulty in adopting an acid-catalyzed reduction strategy into the CWR, thus achieving a high yield of alkene.

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[16] a) Reactions monitored by ^{31}P NMR spectroscopy revealed for primary halides that the main ^{31}P species were the phosphine oxide

and phosphonium salt, which indicates a rapid reaction between the phosphine and halide. For secondary halides, phosphine predominated, which indicates that formation of the phosphonium salt proceeds slowly. See the Supporting Information for details. b) Phosphonium bromides were poorly soluble in the reaction solvents. ^{31}P NMR spectroscopic experiments demonstrated that the utilization of a phase-transfer catalyst improved solubility significantly.

[17] a) The position of this equilibrium is unclear, the pK_a of *i*Pr$_2$NEt and 4-nitrobenzoic acid may be similar in EtOAc. The pK_a of *i*Pr$_2$NEt in DMSO is 8.5, for 4-nitrobenzoic acid in DMSO it is ~9, and in acetone it is ~16. See: J. Jover, R. Bosque, J. Sales, *QSAR Comb. Sci.* **2008**, *27*, 563–581 and S. D. Lepore, A. Khoram, D. C. Bromfield, P. Cohn, V. Jairaj, M. A. Silvestri, *J. Org. Chem.* **2005**, *70*, 7443–7446; b) diisopropylethylammonium 4-nitrobenzoate was as efficient as 4-nitrobenzoic acid, yet tetrabutylammonium benzoate was ineffective. This indicates that the presence of an acidic proton on *i*Pr$_2$NEt may be essential; studies are ongoing.

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