Olefination

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Catalytic Wittig Reactions of Semi- and Nonstabilized Ylides Enabled by Ylide Tuning**

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In memory of Leonard Mostyn O'Brien and Clifford Henry Spence

Abstract: *The first examples of catalytic Wittig reactions with semistabilized and nonstabilized ylides are reported. These reactions were enabled by utilization of a masked base, sodium tert-butyl carbonate, and/or ylide tuning. The acidity of the ylide-forming proton was tuned by varying the electron density at the phosphorus center in the precatalyst, thus facilitating the use of relatively mild bases. Steric modification of the precatalyst structure resulted in significant enhancement of E selectivity up to >95:5, E/Z.*

The Wittig reaction is one of the most powerful methods for the construction of a carbon–carbon double bond.[1] In the 60 years since its discovery, this reaction has been extensively investigated, both in practical application[2] and mechanism.[3] However, the traditional Wittig reaction suffers from several limitations; in particular the removal of the phosphine oxide by-product can be challenging. In an effort to address this concern, in 2009 we developed the first catalytic Wittig reaction (CWR, catalytic in phosphine), which relied on an organosilane to chemoselectively reduce a cyclic phosphine oxide of type **1** (Figure 1).[4a] Subsequently, we have developed modified protocols to allow for use of a soluble base, acyclic phosphine oxides and lowering of the reaction temperature.[4] Although these protocols were confined to stabilized ylides,[4d] they represented the start of a process to develop a sustainable, robust, selective, user-friendly olefination methodology. Indeed, a recent life cycle analysis by Huijbregts and co-workers has shown that the CWR offers a clear reduction in both cumulative energy demand and greenhouse gas emissions compared to the stoichiometric Wittig reaction.[5] In addition, other research groups have applied our reduction strategy to the Appel, aza-Wittig, and Staudinger reactions.[6c,e,g,h] Moreover, related organophosphorus catalysis has also seen significant advancement.[6] The next major challenge was the design of a catalytic protocol that would enable CWRs with semistabilized and nonstabilized ylides. Herein, we demonstrate that this is now possible. The key design features include utilization of a masked base and ylide tuning.

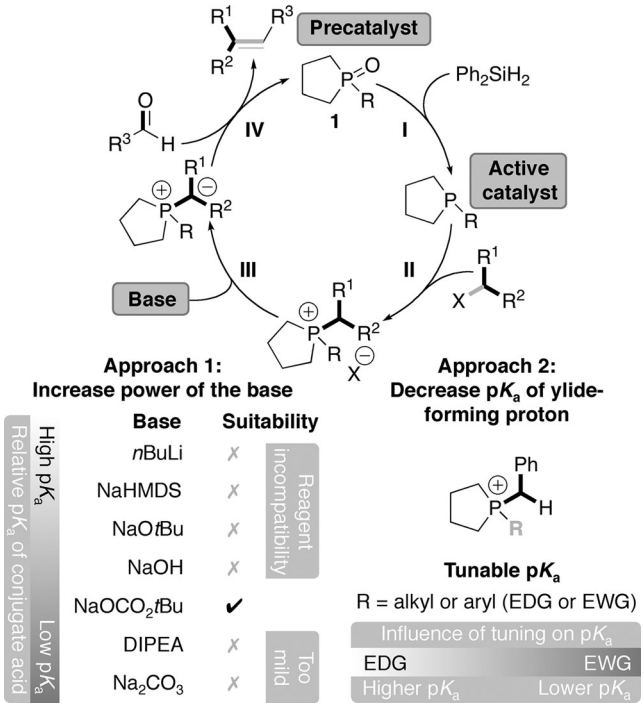

Figure 1. Key concepts in the proposed CWR. EDG = electron-donating group, EWG = electron-withdrawing group, HMDS = 1,1,1,3,3,3-hexamethyldisilazane, DIPEA = *N*,*N*-diisopropylethylamine.

Fundamentally, the key barrier to the utilization of semistabilized and nonstabilized ylide classes in the CWR is the selective deprotonation of the phosphonium salt requisite for ylide generation (Figure 1, **III**). The success of this critical deprotonation hinges on the choice of base, which must be of sufficient power to remove the ylide-forming proton of the

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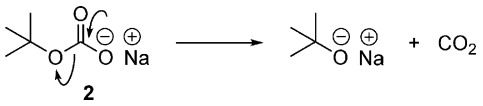
phosphonium salt (pK_a (in DMSO = dimethylsulfoxide, DMSO) 17–18 for semistabilized, 22–25 for nonstabilized),[7] but mild enough to be compatible with the wider CWR. A further challenge for nonstabilized ylides will be to ensure a viable rate of phosphonium salt formation (Figure 1, **II**).[3b]

We envisaged two possible approaches to achieving efficient deprotonation. The first was identification of a suitable base. A literature search showed that NaHMDS, *n*BuLi, NaOH, and NaO*t*Bu are typically used.[3g] However, these bases would be incompatible with the overall CWR, because of their likely reaction with the silane and possibly organohalide. Furthermore, the bases used in our previous investigations, Na_2CO_3 and DIPEA, would be insufficient to completely effect the desired deprotonation (pK_a of the conjugate acid in H_2O is less than 12). To balance the need for a stronger base while avoiding unwanted side reactions, we hypothesized that a masked base, such as carbonate **2**, could be used to slowly release NaO*t*Bu into the solution in situ (Scheme 1).[8]



Scheme 1. Proposed in situ generation of NaO*t*Bu.

As the pK_a of the ylide-forming proton for nonstabilized ylides is higher than 20, it is unlikely that **2** alone would achieve a viable rate of deprotonation necessary to employ this ylide class in the CWR. Therefore we would incorporate a second approach to lower the pK_a of the ylide-forming proton sufficiently in order to facilitate the use of **2**. Central to this strategy is the concept that the introduction of electron-withdrawing groups on the phenyl ring of the precatalyst would lead to a withdrawal of electron density from the phosphorus center, hence lowering the pK_a of the ylide-forming proton (Figure 1, approach 2).

The removal of electron density from the phosphorus center may come at a cost: lower nucleophilicity of the phosphine will have an impact upon 1) the rate of phosphonium salt formation (Figure 1, **II**), and 2) the rate of phosphine oxide reduction (Figure 1, **I**).[9] Consequently, to compensate for the retarded nucleophilicity of the phosphine and lower reduction rate, we envisioned that the reaction temperature would need to be increased to rebalance the catalytic cycle. Thus, the success of ylide tuning relies on the identification of a precatalyst structure that achieves the desired electron-withdrawing effect, while maintaining ease of reduction and a viable rate of phosphonium salt formation. To this end, an initial series of phosphine oxides **1a–d** (Figure 2) were prepared, where the electron density at the phosphorus center was varied by the introduction of electron-withdrawing or electron-donating substituents. Notably, theoretical calculations supported the idea that the pK_a of the ylide-forming proton may be tuned by modifying the substituent at the phosphorus center. Density functional theory (DFT) calculations (M06-2X/6-311 + G(d,p)//M06-2X/6-31G(d)) gave predictions of the pK_as of the *P*-benzyl-substituted phosphonium cations derived from **1a–d** (**1aa–1da**) and values of ΔG for deprotonation by DIPEA (Figure 2).[11] The decrease in electron density at the phosphorus center across the series **1aa–da** results in an 8 kcal mol^{-1} decrease in the value of ΔG for proton transfer in toluene, a 10^4-fold increase in the deprotonation equilibrium constant (Figure 1, **III**) at 110 °C.[12]

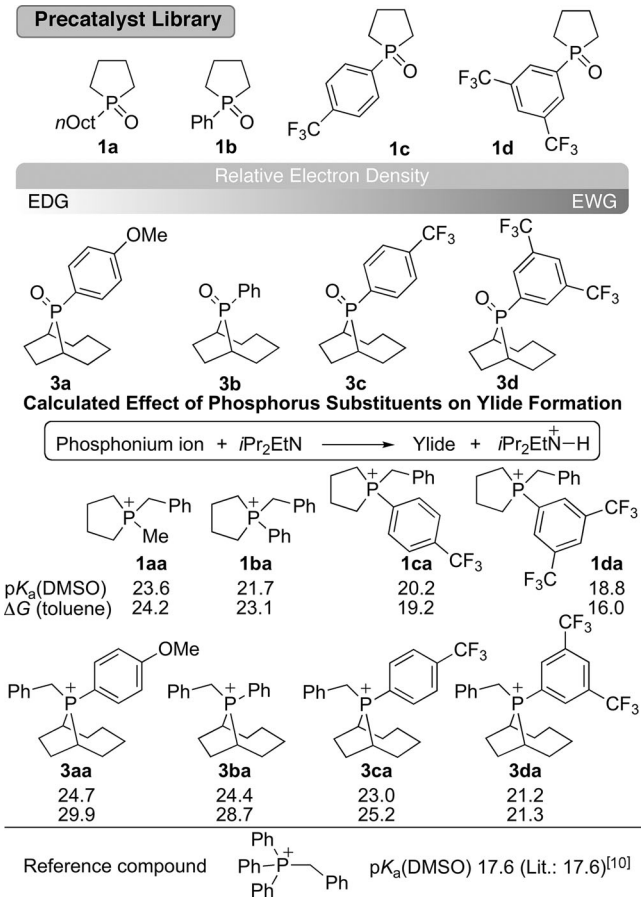
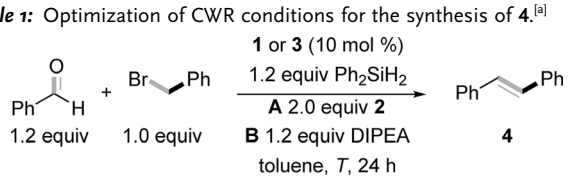


Figure 2. Precatalyst library, computed pK_as (DMSO), and values of ΔG for proton transfer from phosphonium ions to DIPEA (toluene).

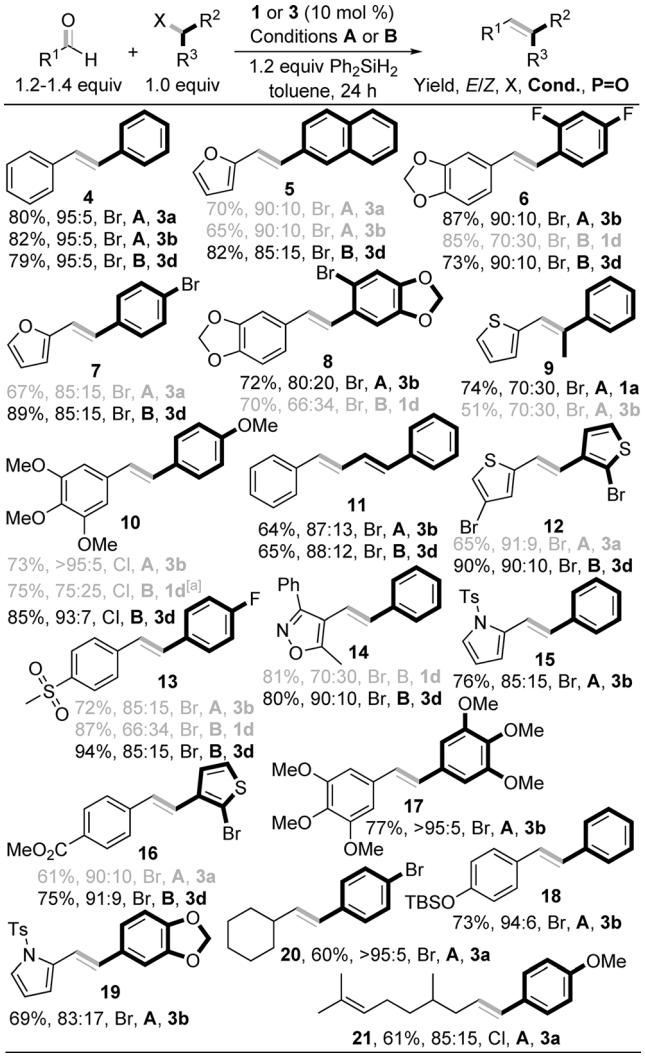
With the strategy set, we began our CWR studies by examining the synthesis of stilbene (**4**) employing precatalysts **1a–d** (Table 1). Base **2** in combination with **1b** resulted in the desired CWR, producing **4** in a yield of 81% and *E*/*Z* selectivity of 66:34 (Table 1, entry 1). Importantly, the synthesis of **4** could not be achieved in high yield with any of our previous CWR conditions or by utilizing NaO*t*Bu as the base (Table 1, footnote [c].) Following the successful adoption of masked base **2** into the CWR, we probed the effect of varying the electron density at the phosphorus center by employing the less basic DIPEA. Gratifying, ylide tuning was clearly demonstrated by the increase in yield observed when progressing from electron-rich **1a** to electron-deficient **1d** (entries 6–9, Table 1), albeit at the anticipated elevated temperature. To the best of our knowledge, this is the mildest base used for Wittig reactions employing semistabilized ylides.[13]

Table 1: Optimization of CWR conditions for the synthesis of **4**.[a]



Entry	P=O	Cond.	*T* [°C]	Conv. (Yield) [%]	*E*/*Z*[b]
1[c]	**1b**	**A**	110	100 (81)	66:34
2	**1a**	**A**	110	100 (80)	80:20
3	**3a**	**A**	110	100 (82)	95:5
4	**3b**	**A**	110	100 (80)	95:5
5	**3c**	**A**	110	100 (82)	95:5
6	**1a**	**B**	140	55 (37)	75:25
7	**1b**	**B**	140	65 (43)	80:20
8	**1c**	**B**	140	88 (61)	75:25
9	**1d**	**B**	140	91 (72)	82:18
10	**3a**	**B**	140	42	94:6
11	**3b**	**B**	140	46	95:5
12	**3c**	**B**	140	71	95:5
13	**3d**	**B**	140	84 (79)	94:6

[a] Benzaldehyde (1.2 mmol), benzyl bromide (1.0 mmol), phosphine oxide **1** or **3** (0.1 mmol), Ph_2SiH_2 (1.2 mmol), **A**) **2** (2.0 mmol), 1.0 M in toluene, or **B**) DIPEA (1.2 mmol), 3.0 M in toluene. [b] *E*/*Z* ratio determined by ^{1}H NMR spectroscopy of the unpurified reaction mixture. [c] Using Na_2CO_3 (1.5 mmol), the yield was 21%, and using NaO*t*Bu (1.5 mmol) or DIPEA (1.2 mmol), only a trace of product was observed.



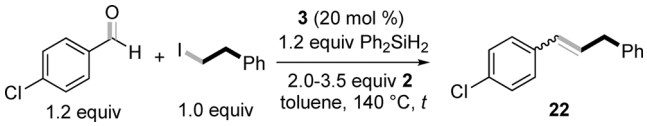
Scheme 2. Substrate study utilizing semistabilized ylides. For each product the compound number, yield of isolated product, *E*/*Z* ratio (determined by ^{1}H NMR spectroscopy of the unpurified reaction mixture), halide, and reaction conditions are given (**A: 2** (2.0 mmol), 110°C, 1.0 M in toluene; **B:** DIPEA (1.2 mmol), 140°C, 3.0 M in toluene). The reactions were performed in duplicate; see the Supporting Information for details. [a] On a 25 mmol scale, the yield was 77% (5.8 g). Ts = 4-toluenesulfonyl.

Although the CWR had been extended fully to semistabilized ylides using two protocols, the diastereoselectivity effected by the **1** series of precatalysts was poor, typically around 66:34, *E*/*Z*. Moreover, varying the acyclic substituent on phosphorus provided only slight improvement in *E*/*Z* selectivity (Table 1, entries 1 and 2). Further improvement of diastereocontrol would require a new cyclic core structure of the precatalyst. An analysis of the reports on Wittig reactions showed that Vedejs and co-workers accomplished highly *E*-selective Wittig reactions by employing a bicyclic phosphine, reduced **3b**.[14] Crucially, use of **3b** would couple the required five-membered cyclic structure, which is vital to ensure a sufficient rate of phosphine oxide reduction, with a steric shield that should provide high *E* selectivity.[4a,14] DFT calculations also predicted that precatalysts of type **3** would afford a higher *E*/*Z* selectivity than series **1**. For example, the computed *E* selectivity for the formation of stilbene (**4**) from **3ba** is 3.0 kcal mol^{-1} ($\Delta\Delta G^{\ddagger}$), compared to 1.7 kcal mol^{-1} from **1ba** (see the Supporting Information).

With a new catalyst structure identified, another precatalyst library (Figure 2, **3a**–**d**) was prepared and tested (Table 1). All type-**3** precatalysts produced **4** with high *E* selectivity, while essentially mirroring the yields obtained with series **1**. Following optimization of both deprotonation and diastereoselectivity, we embarked on a substrate study employing both **2** and DIPEA as base (Scheme 2). The results demonstrated that the CWR utilizing semistabilized ylides could tolerate a variety of aryl, heteroaryl, and aliphatic aldehydes and organohalides. Notable results are the synthesis of resveratrol analogues **10** and **17**, which have been demonstrated to have more potent anticancer activity than resveratrol.[15] The protocol performed well on a multigram scale, as 5.8 g of **10** (77% yield) was prepared with 25 mmol of the organohalide using **1d** and DIPEA. However, no difference in diastereoselectivity was observed when switching from type-**1** to type-**3** precatalysts for secondary halides (Scheme 2, compound **9**).

To further extend the scope of the CWR, the use of nonstabilized ylides was investigated. Anticipating a slow rate of phosphonium salt formation, we used organoiodides rather than organobromides. Pleasingly, the combination of masked base **2** and ylide tuning, **3a**–**d**, allowed the CWR to be applied to this ylide class with moderate *E* selectivity (Table 2). As a result of the slow rate of phosphonium salt formation, the reaction time was extended to 48 h for maximum yield. Interestingly, **3c** and not **3d** turned out to be the optimum precatalyst (Table 2). This highlights the importance of

Table 2: Optimization of CWR conditions for the synthesis of **22**.[a]

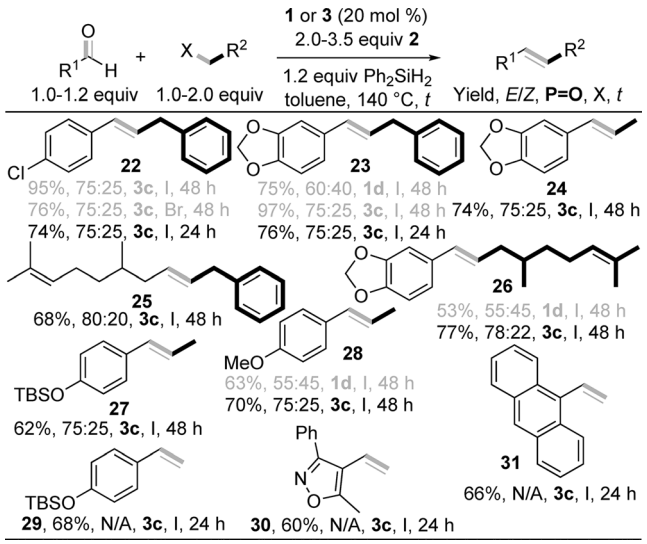


Entry	P=O	*t* [h]	Conv. (Yield) [%]	*E*/*Z*[b]
1	**3a**	48	100 (64)	75:25
2	**3b**	48	88 (70)	75:25
3[c]	**3c**	48	100 (95)	75:25
4	**3c**	24	88 (74)	75:25
5	**3d**	48	100 (83)	75:25

[a] 4-Chlorobenzaldehyde (1.2 mmol), (2-iodoethyl)benzene (1.0 mmol), phosphine oxide **1** or **3** (0.2 mmol), Ph_2SiH_2 (1.2 mmol), **2** (2.0 mmol added at 0 h, additional 1.5 mmol added at 24 h for 48 h reactions), 0.7 M in toluene, 140 °C. [b] *E*/*Z* ratio determined by ^{1}H NMR spectroscopy of the unpurified reaction mixture. [c] Using (2-bromoethyl)benzene, the yield was 76%.

finding a balance between lowering the pK_a of the phosphonium salt, while maintaining a sufficient rate of phosphonium salt formation. Though organoiodides proved optimal, bromides could be employed with a 20% drop in yield (Table 2, entry 3). A substrate study (Scheme 3) showed that aryl, heteroaryl, and aliphatic aldehydes could be employed with a variety of organohalides. Significant results were the synthesis of **25**, **26**, and **27** that highlight both the diversity of potential products and the relatively mild nature of the protocol as the TBS group was retained. Furthermore, terminal olefination was also viable, shown by the synthesis of **29**, **30**, and **31**.

In conclusion, the first catalytic Wittig reactions using a wide range of semistabilized and nonstabilized ylides have been shown. The use of **2**, a masked form of NaO*t*Bu, enabled the full employment of semistabilized ylides. Notably, catalytic use of phosphorus species offers a strategic advantage, the ability to tailor the electronic and steric structure of the catalyst. This was highlighted with the concept of ylide tuning; addition of EWGs to the precatalyst allowed semistabilized ylides to be formed using the mild base DIPEA. A combination of ylide tuning and **2** allowed nonstabilized ylides to be employed in the CWR for the first time. An increase in diastereoselectivity was achieved through modification of the precatalyst core structure, attaining an *E*/*Z* selectivity of up to >95:5 for semistabilized, and 75:25 for nonstabilized ylide types.



Scheme 3. Substrate study using nonstabilized ylides. For each product the compound number, yield of isolated product, *E*/*Z* ratio (determined by ^{1}H NMR spectroscopy of the unpurified reaction mixture), phosphine oxide, halide, and reaction time are given. The reactions were performed in duplicate; see the Supporting Information for details. N/A = not applicable, TBS = *tert*-butyldimethylsilyl.

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[12] Ion-pairing effects significantly promoted deprotonation. For example, the computed ΔG for deprotonation of **1ba** decreases by 11 kcal mol^{-1} when a Br^- counterion is included.

[13] To our knowledge, the mildest base used for traditional Wittig reactions of semistabilized and nonstabilized ylides is 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU; pK_a (in H_2O) ca. 12, (in acetonitrile) 24), see: K. Okuma, O. Sakai, K. Shioji, *Bull. Chem. Soc. Jpn.* **2003**, *76*, 1675 – 1676. However, DBU reacts with organohalides (methyl iodide and benzyl bromide) and is incompatible with the CWR. For use of guanidine bases (pK_a (acetonitrile) 22 – 26), see: D. Simoni, M. Rossi, R. Rondanin, A. Mazzali, R. Baruchello, M. Malagutti, F. P. Invidiata, *Org. Lett.* **2000**, *2*, 3765 – 3768.

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