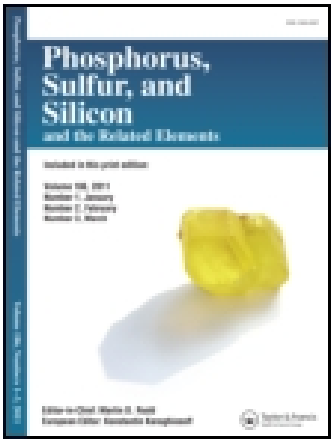

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ISOLATION AND CHARACTERISATION OF ALL FOUR DIASTEREOMERIC INTERMEDIATES FROM A HORNER-WITTIG REACTION

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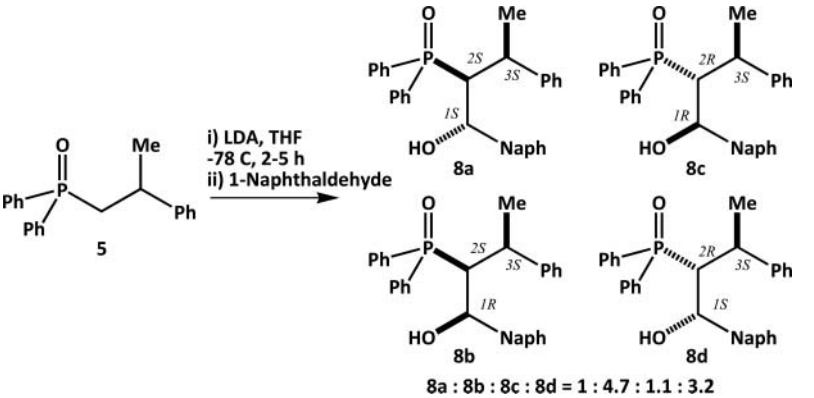
GRAPHICAL ABSTRACT



Abstract *The Horner-Wittig reaction between diphenyl(2-phenylpropyl)phosphine oxide and 1-naphtaldehyde affords an equal mixture of the cis and trans isomers even though the formation of the initial adduct is selective.*

Keywords Horner-Wittig; alkene; mechanism

The Horner-Wittig (HW) reaction between phosphorus stabilized carbanions, e.g. one derived from **1**, and carbonyl compounds, e.g., **2**, is widely used for the synthesis of alkenes. The reaction proceeds *via* the formation of a β-hydroxy phosphine oxide adduct, e.g., **3a** (1,2-*anti*) and **3b** (1,2-*syn*), which then eliminates the corresponding phosphinic acid to afford the alkenes, e.g., **4a** and **4b** respectively (Scheme 1).[1] The elimination of

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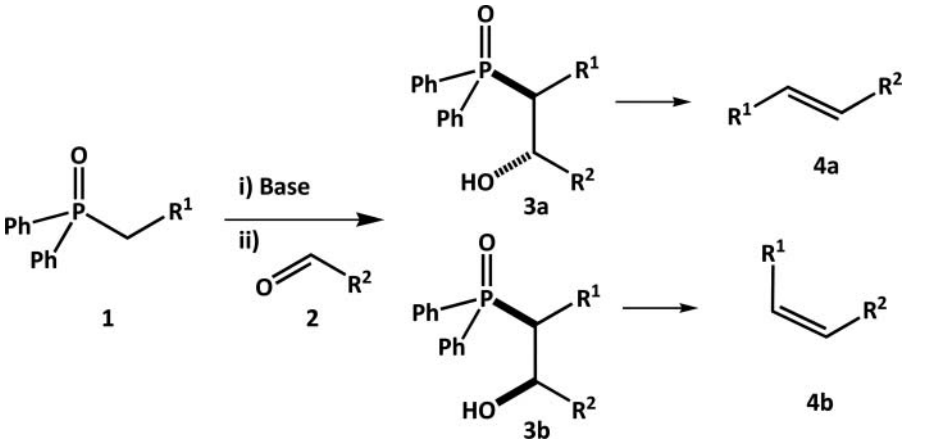


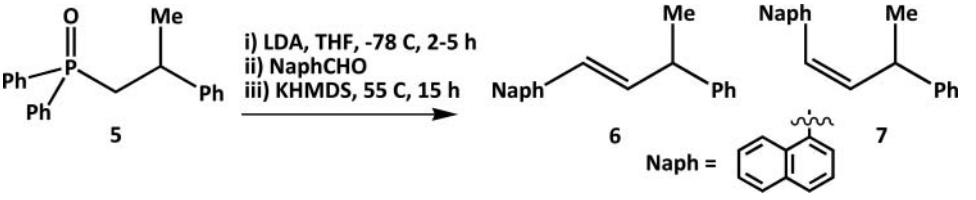
Scheme 1

diphenylphosphinic acid from the adducts **3a** and **3b** is *syn*, meaning that *trans* alkene **4a** is obtained from adduct **3a**, and *cis* alkene **4b** is obtained from adduct **3b**. In other words, the configuration of the alkenes is determined by the relative configurations of the R^1 and R^2 groups in the adducts. Therefore, it is generally believed that the ratio of **3a/3b** is expected to determine the ratio of **4a/4b**.

The HW reaction has been studied in detail over the years, and it has been shown that if R^1 is an anion stabilizing group, the first step becomes reversible resulting in accumulation of **3a** and favoring the formation of the *trans* isomer, **4a**. However, if R^1 is not an anion stabilizing group, the reaction affords a mixture of adducts **3a** and **3b** and hence a mixture of *cis* and *trans* isomers, **4a** and **4b**.

Our group is currently investigating if the 1,2-*syn*/1,2-*anti* ratio, i.e. the ratio of **3a/3b**, and hence the *cis*/*trans* ratio of the alkene product, i.e. the ratio of **4a/4b**, can be controlled through existing stereocenters in the R^1 and R^2 groups and here we report some aspects of our early results.

For a model study, we chose diphenyl(2-phenylpropyl)phosphine oxide **5**[2] which contains a symmetric center at the position β to the phosphorus atom. Treatment of **5** with lithium diisopropylamide (LDA) in tetrahydrofuran (THF) followed by 1-naphthaldehyde at −78°C, then warming to room temperature and heating at 55°C afford a 1:1 mixture of *cis* and *trans* alkenes **6** and **7** in a relatively modest yield of 15%. The use of non-coordinating cations improves the efficiency of the elimination step. Indeed using potassium hexamethyldisialzide (KHMDS) for the elimination step resulted in improvement of the yield to 72% but affected no change in *cis*/*trans* ratio (Scheme 2).



Scheme 2

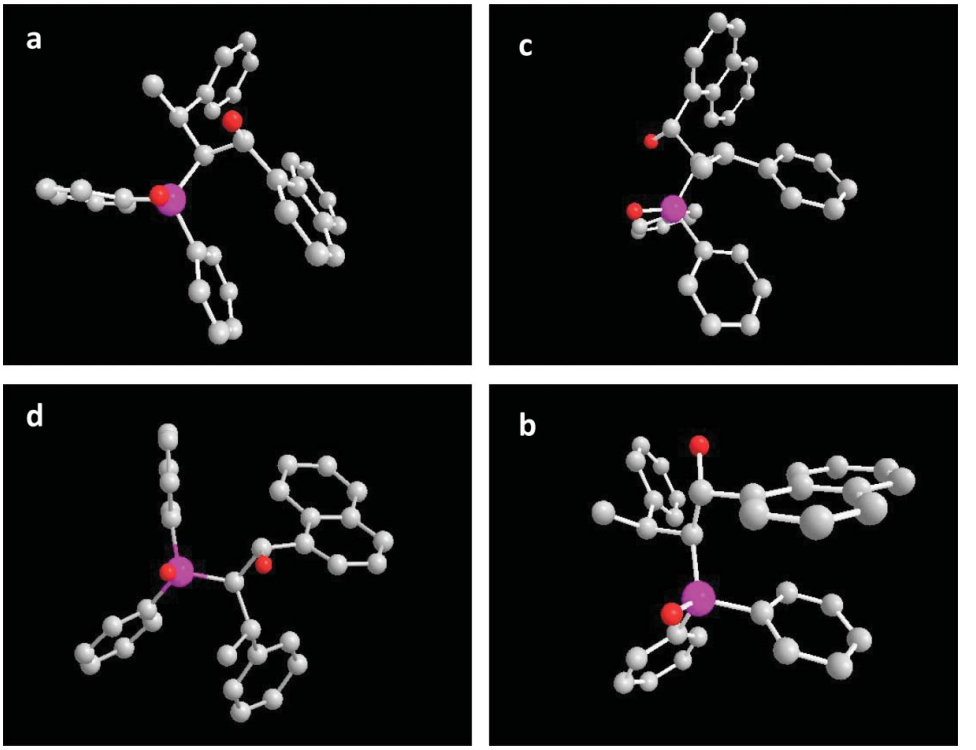


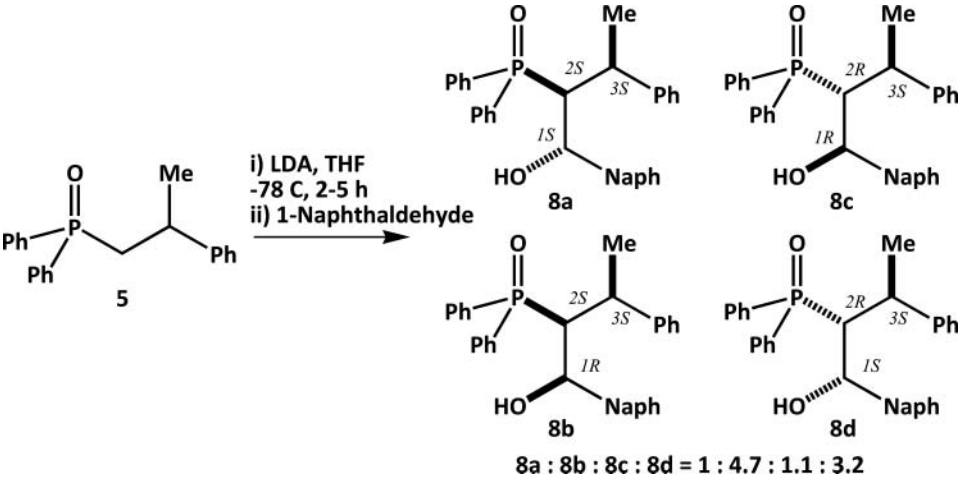
Figure 1 X-ray crystal structure of all four diastereomers of compound **8 (a-d)**. (Color figure available online).

This observation led to a question: Is the lack of selectivity in the formation of **6** and **7** because of a lack of selectivity in the formation of the intermediate β-hydroxy phosphine oxide adducts? To answer this question, we decided to isolate all four diastereomeric β-hydroxy phosphine oxide adducts from the first step and investigate their elimination individually.

Diphenyl(2-phenylpropyl)phosphine oxide **5** was treated with lithium diisopropylamide (LDA) in tetrahydrofuran (THF) at -78°C followed by naphthaldehyde to afford only β-hydroxy phosphine oxide adducts **8a-d** (Scheme 2). Under these reaction conditions, no elimination to afford alkenes occurred. The ratio of **a**:**b**:**c**:**d** diastereomers was found to be 0.10:0.47:0.11:0.32.

All four diastereomers resulting from the addition of **5** to 1-naphtaldehyde, compounds **8a**-**d**, were separated in pure form using a combination of chromatography and fractional crystallization, and their relative configurations were assigned by X-ray crystallography (Figure 1).

We note that the induction of chirality is modest. Comparing the two 2,3-*syn* diastereomers **a** and **b** combined with the two 2,3-*anti* diastereomers **c** and **d**, we get a ratio of 1.25. Considering that the methyl group is fairly small, that is perhaps not surprising. In contrast, comparing the two 1,2-*syn* diastereomers **a** and **c** with the two 1,2-*anti* diastereomers **b** and **d**, the ratio is 3.75. Interestingly, the 1,2-*syn* to 1,2-*anti* ratio observed here is significantly different to that reported by Warren in the reaction between **5** and benzaldehyde (Scheme 4).[2]

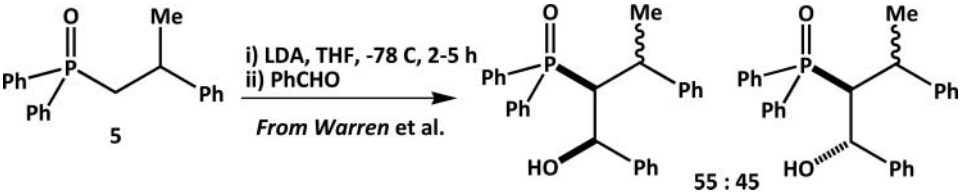


Scheme 3

As previously indicated, the ratio of 1,2-*syn* to 1,2-*anti* is relevant to the elimination. Since the 1,2-*syn* affords the *cis* alkene on elimination and the 1,2-*anti* affords the *trans* alkene, we should expect a roughly similar ratio of 3.75 between the *cis* and *trans* isomers in favour of the former. Since direct conversion of **5** to **6** and **7** only affords them in an equal ration, there must be kinetic factors, which influence the elimination step in the individual diastereomers.

We subjected each of diastereomers **8a**-**d** to the same conditions used for the transformation of **5** to **6** and **7** (KHMDS at 55°C for 15 h). The results are shown below (Table 1).

From the results in Table 1 we can deduce that whilst the minor 1,2-*anti* diasteromers **8a** and **8c** efficiently afford the *trans* alkene, the major 1,2-*syn* diastereomers **8b** and **8d** afford the *cis* alkene very inefficiently. The reactions of 1,2-*syn* diastereomers are accompanied by significant retro-addition leading to the reformation of **5** and naphthaldehyde. The sluggishness in the elimination of 1,2-*syn* diastereomers of course can be easily rationalized in terms of the significant steric repulsion between the naphthyl and α-phenylethyl substituents in the transition state leading to the elimination of phenylphosphinic acid (Figure 2). This steric repulsion means that the molecule cannot easily adopt the required conformation for the elimination to the *cis* isomer and instead fragments to naphthaldehyde and starting material, **5**.



Scheme 4

Table 1 Results for the transformation of compound **5** to compounds **6** and **7**

	Isolated Yield (%)*	**5** (recovered%)	**6** : **7****
8a	54	0	> 95 : 5
8b	56	22	> 5 : 95
8c	96	0	> 95 : 5
8d	50	14	> 5 : 95

*Unreacted starting material accounts for mass balance.
**Single isomer within the limits of detection by NMR.

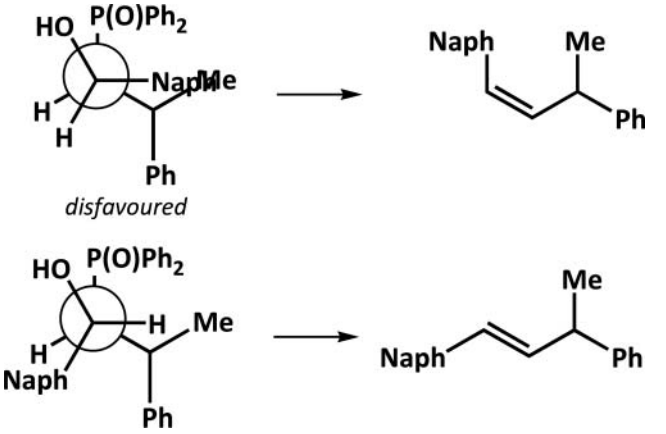


Figure 2 Proposed conformations of intermediates leading to both the *cis* and *trans* alkene products.

The observations we have described here, provide the evidence that during the HW reaction of **5** with naphthaldehyde, the formation of the initial adduct is selective and favours the formation of the 1,2-*syn* β-hydroxy phosphine oxide. However, the elimination of this 1,2-*syn* β-hydroxy phosphine oxide to the *cis* alkene is inefficient. In contrast, the minor 1,2-*anti* β-hydroxy phosphine oxide efficiently affords the *trans* isomer. Therefore, in this example at least, the overall parity between the *cis* and *trans* isomers is not because of a lack of selectivity in the formation of the β-hydroxy phosphine oxide adducts.

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