

## Highly regioselective Wittig reactions of cyclic ketones with a stabilized phosphorus ylide under controlled microwave heating

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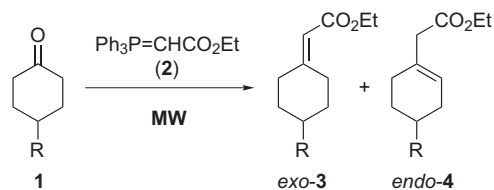
**Abstract**—Significant base and temperature effects on the Wittig reactions of cyclohexanones with (carbethoxymethylene)triphenylphosphorane under microwave irradiation were observed. For the Wittig reactions carried out in a domestic microwave oven under solvent-free conditions, the initially formed *exo*-olefin products isomerized into the thermodynamically more stable *endo*-olefins due to uncontrolled high reaction temperature. In sharp contrast, under controlled microwave heating, both *exo*- and *endo*-olefins have been selectively synthesized by accurately regulating the reaction temperature with or without a base.

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The Wittig reaction remains the most versatile synthetic method for preparation of olefins from carbonyl compounds.<sup>1</sup> However, the reactions of stabilized phosphorus ylides are often limited to aldehydes and ketones. For the latter forcing conditions are required, frequently giving low yields of the olefin products. One option is to use stabilized arsonium ylides for the olefination of ketones, which can be carried out at room temperature or below.<sup>2</sup> The greatly enhanced reactivity of arsonium ylides over the phosphorus analogs is particularly useful for carrying out asymmetric Wittig reactions at low temperature.<sup>3</sup> Since the first introduction of microwave heating into organic synthesis in 1986,<sup>4</sup> microwave-assisted organic synthesis becomes increasingly popular in conventional and combinatorial synthesis.<sup>5</sup> The Wittig reactions of stabilized phosphorus ylides with aldehydes,<sup>6</sup> ketones,<sup>7</sup> lactones,<sup>8</sup> and amides<sup>8a</sup> under microwave irradiation have been reported by using domestic microwave ovens except for the work of Westman.<sup>6h</sup> Formation of phosphonium salts under microwave heating was also disclosed.<sup>9</sup> Due to difficulty in controlling reaction temperature using domestic microwave ovens, solvent-free conditions (or in dry media) were commonly used. In one report, isomeriza-

tion was observed for the initially formed  $\alpha,\beta$ -unsaturated ester from the Wittig reaction of acetophenone with (carbethoxymethylene)triphenylphosphorane to give a  $\beta,\gamma$ -unsaturated by-product.<sup>7a</sup> It presumably arose from the uncontrolled high reaction temperature in the presence of basic residues in the reaction mixture. In connection with our recent work on microwave-assisted solid phase organic synthesis of an indole library,<sup>10</sup> we report here highly regioselective Wittig reactions of cyclohexanones with (carbethoxymethylene)triphenylphosphorane under controlled microwave dielectric heating and the effects of base and temperature on the regioselectivity of the olefination.

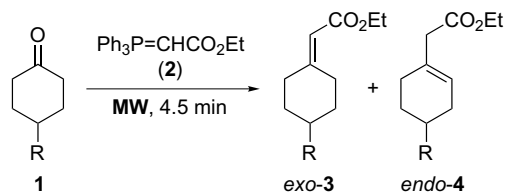
We initially carried out the Wittig reactions of cyclohexanones **1** with the stabilized ylide **2** by heating a mixture of both reagents in an open container in a domestic microwave oven at 300 W for 4.5 min (Scheme 1 and Table 1). We found that the reagent ratios had a



**Scheme 1.** Microwave-assisted Wittig reactions of cyclohexanones.

**Keywords:** Microwave; Wittig; Regioselectivity; Phosphorus ylide.

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**Table 1.** Wittig reaction of various cyclohexanones **1** with **2** in a domestic microwave oven under solvent-free conditions<sup>a</sup>

Entry	1: R	Ratio (1:2)	Yield (%) <sup>b</sup>	<i>exo-3:endo-4</i> <sup>c</sup>	<i>exo-3:endo-4</i> <sup>d</sup>
1	a: H	1:1	18	ND	
2	a: H	2:1	71	91:9	19:81
3	a: H	3:1	70	ND	
4	a: H	5:1	69	ND	
5	a: H	10:1	58	ND	
6	b: Me	2:1	59	86:14	17:83
7	c: <i>t</i> -Bu	2:1	63	95:5	14:86
8	d: Ph	2:1	65	72:28	

<sup>a</sup> Carried out in a domestic microwave oven at 300 W for 4.5 min.

<sup>b</sup> Combined isolated yield of *exo-3* and *endo-4*.

<sup>c</sup> Determined by <sup>1</sup>H NMR of the product mixture; ND = not determined.

<sup>d</sup> Obtained after treating the isolated product mixture with catalytic DBU at 300 W for 4.5 min in the same domestic microwave oven.

significant influence on the yield of the olefination and the products could be obtained in 60–70% yields when more than 2 equiv of the ylide were used (Table 1, entries 1–5). However, it was to our surprise that a by-product, *endo-4a*, was formed along with the normal olefination product, *exo-3a*, in a ratio of 91:9 (Table 1, entry 2). This observation was confirmed to be general and isomerization of olefins *exo-3* occurred for all reactions carried out in a domestic microwave oven. For 4-substituted cyclohexanones **1b–d**, the isomer ratios of *exo-3:endo-4* range from 95:5 to 72:28 (Table 1, entries 6–8). Since olefins *endo-4* are thermodynamically more stable than olefins *exo-3*, we assume that the isomerization should be promoted by uncontrolled high reaction temperature, that is a limiting factor generally accepted for use of domestic microwave ovens in microwave-assisted organic synthesis. We thought that isomerization of olefins *exo-3* into *endo-4* could be also facilitated by a base via a deprotonation/protonation process. It was confirmed that heating the initial product mixtures in the presence of catalytic DBU afforded olefins *endo-4* as the major isomers (Table 1, entries 2, 6, and 7).

We then turned our attention to running the Wittig olefination on an Emrys Creator in sealed reaction vials. Under this setting, the reactions can be carried out at accurately regulated temperature and under controlled pressure. It also provides superheating capability so that reactions can be done at temperatures well above the boiling point of the solvent. Table 2 summarizes some optimization data on the Wittig reaction of 4-phenylcyclohexanone **1d** with **2** in different solvents. It was found that the combined yield of the olefin products *exo-3d* and *endo-4d* formed in DMF increased from 37% to 75% when the reaction temperature increased from 180 to 230 °C (Table 2, entries 1–3 and Fig. 1). On the other hand, the isomer ratio of *exo-3d:endo-4d* decreased from 97:3 to 78:22 with increased reaction temperature. A similar trend was observed for the reactions in NMP

**Table 2.** Wittig reaction of 4-phenylcyclohexanone **1d** with **2** under accurately regulated microwave heating<sup>a</sup>

Entry	Solvent	<i>T</i> (°C); <i>t</i> (min)	Yield (%) <sup>b</sup>	<i>exo-3d:endo-4d</i> <sup>c</sup>
1	DMF	180; 10	37	97:3
2	DMF	200; 10	52	93:7
3	DMF	230; 10	75	78:22
4	NMP	200; 20	63	89:11
5	NMP	230; 20	69	75:25
6	MeCN	190; 20	66	99:1

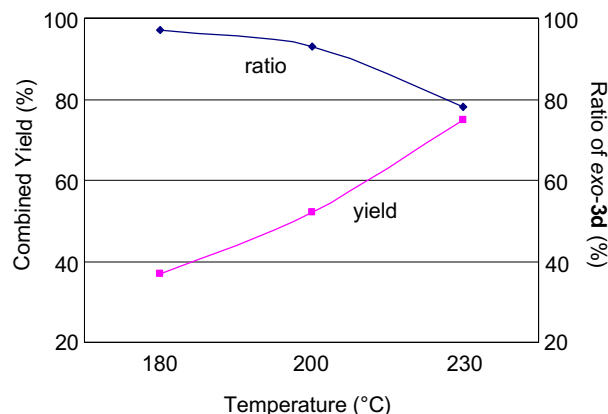
<sup>a</sup> Carried out on an Emrys Creator with 3:1 ratio of **1d** and **2**.

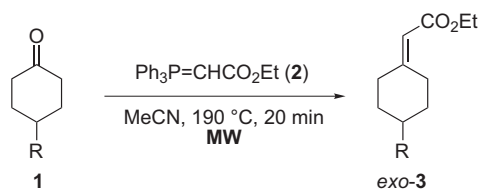
<sup>b</sup> Combined isolated yield of *exo-3d* and *endo-4d*.

<sup>c</sup> Determined by <sup>1</sup>H NMR of the product mixture.

(Table 2, entries 4 and 5). We found that isomerization of *exo-3d* could be suppressed under controlled microwave heating at 190 °C in MeCN for 20 min to furnish *exo-3d*<sup>11</sup> in 66% yield and in 99:1 ratio (Table 2, entry 6).

Table 3 lists the results of the microwave-assisted Wittig reactions of a series of cyclohexanones with the stabilized phosphorus ylide **2** in MeCN at 190 °C for 20 min.

**Figure 1.** Temperature dependence of yield and isomer ratio of the Wittig olefination of **1d** with **2**.

**Table 3.** Wittig reactions of various cyclohexanones **1** with **2** under accurately regulated microwave heating<sup>a</sup>

Entry	<b>1</b> : R	Yield (%) <sup>b</sup>	<i>exo</i> - <b>3</b> : <i>endo</i> - <b>4</b> <sup>c</sup>
1	<b>a</b> : H	62	99:1
2	<b>b</b> : Me	60	99:1
3	<b>c</b> : <i>t</i> -Bu	61	99:1
4	<b>d</b> : Ph	66	99:1
5	<b>e</b> : Et	33	99:1
6	<b>f</b> : <i>n</i> -Pr	45	99:1
7	<b>g</b> : <i>i</i> -Pr	40	99:1
8	<b>h</b> : <i>t</i> -Amy	52	99:1

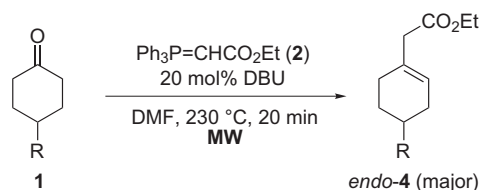
<sup>a</sup> Carried out on an Emrys Creator with 3:1 ratio of **1** and **2**.<sup>b</sup> Isolated yield of *exo*-**3**.<sup>c</sup> Determined by <sup>1</sup>H NMR of the product.

An excellent regioselectivity of 99:1 was achieved in all cases for formation of the olefin products *exo*-**3**. The chemical yields of **3a–d** are good (60–66%) compared with those of **3e–h** (33–52%), which could be improved by running the reactions at higher temperature at the expense of decreased regioselectivity (vide infra).

As shown in Table 1, base promotes isomerization of olefins *exo*-**3** into *endo*-**4**. In order to optimize the conditions for selective formation of olefins *endo*-**4**, we examined the base and temperature effects on regioselectivity of the Wittig olefination of **1d** with **2** (Table 4). Among the three bases we tried, DBU was the most effective compared with DMAP and TMG (Table 4, entries 1–3). Reaction temperature also significantly affects both chemical yield and isomer ratio of the reaction (Table 4, entries 5–7). Regardless the amount of DBU ranging from 10 to 100 mol%, the reactions at 230 °C gave almost the same ratio of the olefin isomers, presumably reaching the equilibrium composition (Table 4, entries 4, 7, and 8). With 20 mol% DBU, *endo*-

**Table 4.** Effects of base and temperature on Wittig reactions of 4-phenylcyclohexanone **1d** with **2**<sup>a</sup>

Entry	Base, <sup>b</sup> <i>T</i> (°C), <i>t</i> (min)	Yield (%) <sup>c</sup>	<i>exo</i> - <b>3d</b> : <i>endo</i> - <b>4d</b> <sup>d</sup>
1	DMAP, 200, 10	48	83:17
2	TMG, 200, 10	54	32:68
3	DBU, 200, 10	55	14:86
4	DBU, 230, 10	67	13:87
5	DBU, <sup>e</sup> 180, 10	34	49:51
6	DBU, <sup>e</sup> 200, 10	56	28:72
7	DBU, <sup>e</sup> 230, 10	77	15:85
8	DBU, <sup>f</sup> 230, 20	82	13:87

<sup>a</sup> Carried out on an Emrys Creator with 2:1 ratio of **1d** and **2** in DMF.<sup>b</sup> Using 1 equiv of base. TMG = 1,1,3,3-tetramethylguanidine.<sup>c</sup> Combined isolated yield of *exo*-**3d** and *endo*-**4d**.<sup>d</sup> Determined by <sup>1</sup>H NMR of the product.<sup>e</sup> Using 10 mol% DBU.<sup>f</sup> Using 20 mol% DBU.**Table 5.** Wittig reactions of various cyclohexanones **1** with **2** in the presence of DBU<sup>a</sup>

Entry	<b>1</b> : R	Yield (%) <sup>b</sup>	<i>exo</i> - <b>3</b> : <i>endo</i> - <b>4</b> <sup>c</sup>
1	<b>a</b> : H	78	16:84
2	<b>b</b> : Me	70	14:86
3	<b>c</b> : <i>t</i> -Bu	76	13:87
4	<b>d</b> : Ph	82	13:87
5	<b>e</b> : Et	59	13:87
6	<b>f</b> : <i>n</i> -Pr	63	13:87
7	<b>g</b> : <i>i</i> -Pr	52	15:85
8	<b>h</b> : <i>t</i> -Amy	74	13:87

<sup>a</sup> Carried out on an Emrys Creator with 3:1 ratio of **1** and **2**.<sup>b</sup> Combined isolated yield of *exo*-**3** and *endo*-**4**.<sup>c</sup> Determined by <sup>1</sup>H NMR of the product.

**4d**<sup>11</sup> was isolated in 82% yield and in 13:87 isomer ratio (Table 4, entry 8).

We then explored the Wittig reactions under microwave heating at 230 °C for 20 min in the presence of 20 mol% DBU on an Emrys Creator and the results are summarized in Table 5. In all cases, olefins *endo*-**4** were obtained in 52–82% yields and in 84:16–87:13 isomer ratios. As the result of higher reaction temperature, the yields of the olefins given in Table 5 are much more improved than those listed in Table 3.

In summary, we have established highly regioselective Wittig reactions of 4-substituted cyclohexanones with a stabilized phosphorus ylide under controlled microwave heating. By accurately regulating the reaction temperature at 190 °C in MeCN, the olefin products *exo*-**3** could be prepared in 99:1 isomer ratio. On the other hand, the same olefination carried out at 230 °C in DMF in the presence of 20 mol% DBU afforded the thermodynamically more stable olefins *endo*-**4** in >84:16 isomer ratios. Our study represents the first regioselective microwave-assisted Wittig reactions of ketones with a stabilized phosphorus ylide. It also demonstrates the benefit of controlled microwave heating in stereoselective reactions over the organic synthesis performed in domestic microwave ovens. Finally, the temperature-dependent nature of isomerization of *exo*-**3** into *endo*-**4** may provide a working curve for temperature calibration of reaction devices where direct temperature measurement is difficult.

### Acknowledgements

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11. NMR data for *exo-3d* and *endo-4d*. *exo-3d*:  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.54–7.38 (m, 5H), 5.91 (s, 1H), 4.38 (q,  $J = 7.11$  Hz, 2H), 4.22–4.17 (m, 1H), 3.08–2.99 (m, 1H), 2.70–2.45 (m, 2H), 2.38–2.15 (m, 3H), 1.98–1.72 (m, 2H), 1.51 (t,  $J = 7.11$  Hz, 3H). *endo-4d* as a 87:13 mixture with *exo-3d*:  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.55–7.38 (m, 5H), 5.88 (s, 1H), 4.39 (q,  $J = 7.14$  Hz, 2H), 3.23 (s, 2H), 3.10–2.92 (m, 1H), 2.70–1.85 (m, 6H), 1.51 (t,  $J = 7.11$  Hz, 3H).