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Microwave-assisted regioselective olefinations of cyclic mono- and di-ketones with a stabilized phosphorus ylide

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Abstract—A number of cyclic mono- and di-ketones underwent regioselective olefination with (carbethoxyethylidene)triphenylphospharane under controlled microwave heating. The Wittig reaction of 4-substituted cyclohexanones or 1,2- and 1,4-cyclohexanediones with the ylide at 190 °C for 20 min in MeCN afforded the exocyclic olefins in >94:6 isomer ratios. On the other hand, the same reactions carried out at 230 °C for 20 min in the presence of 20 mol % DBU furnished the endocyclic olefins in >83:17 isomer ratios. The base-mediated isomerization of the exocyclic olefins into the endocyclic isomers was primarily driven by thermodynamic stability of the products and the effect of ring structures on deconjugation was examined.

1. Introduction

Cycloalkylideneacetic acids have been reported to exhibit anticonvulsant activity[1] and to act as novel effectors of Ras/Raf interaction.[2] In the area of chemical synthesis cycloalkylideneacetic acids and their endocyclic deconjugative analogs have been used as the precursors of bromomethylenecycloalkanes[3] and the substrates for vinylogous Wolff rearrangment.[4] Various cycloalkylideneacetates and (4-oxocyclohexylidene)acetate were used for total synthesis of several natural products.[5] The unsaturated esters of 4-*tert*-amylcyclohexanone were used for the synthesis of [4-*tert*-pentylcyclohexyl]acetaldehyde, which was described as strong lilial-like and bourgeonal-like for use in perfumery.[6] Similarly, the *exo*- and *endo*-unsaturated esters of bicyclo-[3.3.0]octane-3,7-diones have been used as the key intermediates in synthesis of prostacyclin analogs[7] and as the chiroptical trigger for a liquid-crystal-based optical switch.[8] The Wittig reaction[9] and the Horner–Wadsworth–Emmons (HWE) olefination are the most popular methods of choice for preparation of cycloalkylideneacetates from cyclic mono- and di-ketones. For the reactions of the stabilized phosphorus ylides such as (carbethoxyethylidene)triphenylphospharane (**2**), high temperatures are required. Microwave irradiation[10] has been introduced to improve the efficiency of olefination using stabilized phosphorus ylides and the substrates have been extended to aldehydes,[11] ketones,[12] lactones,[13] and amides.[13a] Formation of phosphonium salts under microwave heating was also reported.[14] However, all these early studies except for the work of Westman[11h] were carried out on domestic microwave ovens, which are lacking temperature controlling capability. In some cases, isomerization of olefin products was observed under solvent-free conditions or in dry media presumably due to uncontrolled high reaction temperature.[12a,d] In connection with our interest in performing the Wittig reaction in aqueous media[15] and the asymmetric versions based on chiral stabilized arsonium ylides,[16] we have established a set of reaction conditions for achieving regioselective Wittig reaction of 4-substituted cyclohexanones under controlled microwave heating.[17–19] We report here the full details of an expanded study covering a number of cyclic mono- and di-ketones and provide an example that illustrates efficient control over regiochemistry at high temperatures under microwave dielectric heating.

2. Results and discussion

Ethyl cycloalkylideneacetates have been prepared via HWE reaction using triethyl phosphonoacetate in excellent yields.[3–5b,6,20] An alternative route is based on the Wittig reaction of cycloalkanones with (carbethoxyethylidene)triphenylphospharane (**2**) (Scheme 1) at high temperatures[21] including use of microwave irradiation.[12d,17] Recently, olefination of cycloalkanones with ethyl diazoacetate was reported to proceed at 80 °C in the presence of benzoic acid and a catalytic iron(III) porphyrin complex Fe(TPP)Cl.[22] Stepwise approaches to ethyl cycloalkylideneacetates were

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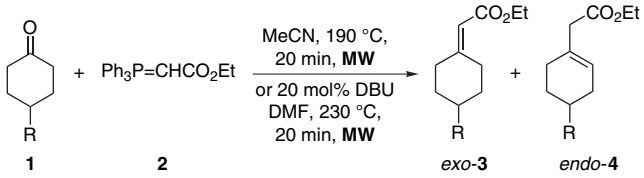
known and consist of formation of 1-[(ethoxycarbonyl)-methyl]cycloalkanols by addition of lithio ethyl acetate[23] or by the Reformatsky reaction[24] followed by acidic dehydration. However, mixtures of exocyclic (conjugated) and endocyclic (deconjugated) isomers were obtained in the stepwise synthesis and the isomer ratios were found to be ring size-dependent. The endocyclic isomers became much more favorable for the rings larger than seven primarily due to increased thermodynamic stability of the products.[24b] Deconjugation of ethyl cycloalkylideneacetates could be achieved by deprotonation and protonation operations[4,24c,25] or via photochemical process[26] to form ethyl cycloalken-1-ylacetates. The latter endocyclic olefines were also prepared selectively from the carbonation reactions of the allylic lithium reagents possessing two sp^2 carbons within the ring system.[27] In our preliminary studies,[12d,17] we found that the Wittig reactions of 4-substituted cyclohexanones **1** with the ylide **2** gave a mixture of the olefins *exo*-**3** and *endo*-**4** under microwave heating (Scheme 1). Isomerization of *exo*-**3** into *endo*-**4** was accelerated by high temperature, polar solvents, and base.[17] We established reaction conditions for regioselective formation of ethyl cyclohexylideneacetates *exo*-**3** and ethyl cyclohexen-1-ylacetates *endo*-**4**. The results are summarized in Table 1. Under controlled microwave heating at 190 °C for 20 min in MeCN, the conjugated olefins *exo*-**3a**–**h** were obtained in 33–66% yields and in 99:1 isomer ratios. Due to volatile nature of the products, the yields were not optimized. At reaction temperatures higher than 190 °C or using DMF and NMP as the solvent, deconjugation of *exo*-**3** was observed.[17] In order to promote in situ deconjugation, we carried out the Wittig reactions at 230 °C for 20 min in DMF in the presence of 20 mol % DBU, resulting in isolation of *endo*-**4a**–**h** as the major isomers in >84:16 ratios and in 52–82% combined yields (Table 1). Use of less amount of DBU or other bases such as 4-dimethylaminopyridine (DMAP) and 1,1,3,3-tetramethylguanidine (TMG) gave partial deconjugation. The esters *exo*-**3** and *endo*-**4** are not separable by column chromatography over silica gel and their ratios were estimated by ^{1}H NMR analyses.



Scheme 1. Microwave-assisted olefinations of 4-substituted cyclohexanones **1** with the stabilized phosphorus ylide **2**.

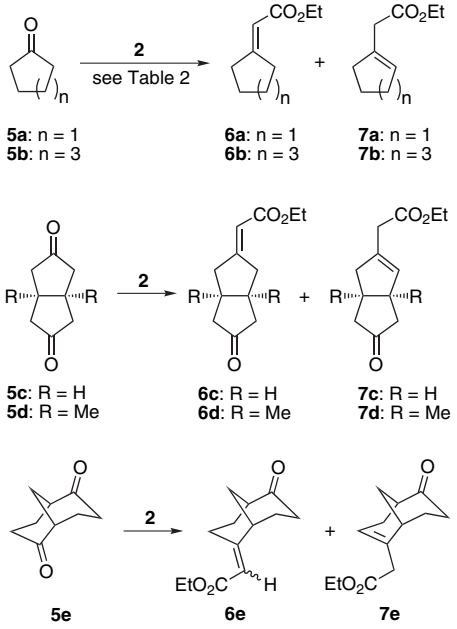
We then applied the reaction conditions for the olefinations of other cyclic mono- and di-ketones **5a**–**e** (Scheme 2 and Table 2). The reaction of cyclopentanone (**5a**) with **2** at 190 °C for 20 min gave similar result as that of cyclohexanone (**1a**), the exocyclic product **6a** was obtained in 60% yield and in 99:1 isomer ratio. But the endocyclic product **7a** was formed only in a very small amount at 230 °C for 20 min in the presence of DBU (Table 2, entry 1). On the other hand, the olefination of cycloheptanone (**5b**) afforded the products in significantly reduced yields under both reaction conditions. Although an excellent ratio of 99:1 was achieved for the reaction at 190 °C, a 57:43 mixture of **6b**:**7b** was formed for the reaction at 230 °C (Table 2, entry 2).

Table 1. Olefination of cyclohexanones **1** with **2** under controlled microwave heating[a]

Entry	**1**: R	190 °C, 20 min	230 °C, 20 min, 20 mol % DBU
		Yield (%);[b] **3**:**4**[c]	Yield (%);[b] **3**:**4**[c]
1	**a**: H	62; 99:1	78; 16:84
2	**b**: Me	60; 99:1	70; 14:86
3	**c**: *t*-Bu	61; 99:1	76; 13:87
4	**d**: Ph	66; 99:1	82; 13:87
5	**e**: Et	33; 99:1	59; 13:87
6	**f**: *n*-Pr	45; 99:1	63; 13:87
7	**g**: *i*-Pr	40; 99:1	52; 15:85
8	**h**: *t*-Amy	52; 99:1	74; 13:87

[a] Carried out with 3:1 ratio of **1** and **2** on a commercial technical microwave reactor. MeCN and DMF were used for reactions at 190 °C and 230 °C, respectively.
[b] Combined isolated yields of *exo*-**3** and *endo*-**4**.
[c] Determined by ^{1}H NMR.

This observation is quite different from the dehydration of 1-[(ethoxycarbonyl)methyl]cycloheptanol, which gave a 22.6:77.4 mixture of **6b**:**7b**.[24b] The diminished reactivity of the stabilized ylide **2** toward **5b** may be attributed to the cyclic transition state of the Wittig reaction.[9] The effect of ketone ring structures on the olefin product distribution was also observed in the reactions of bicyclic ketones **5c**–**e** (Scheme 2). The olefinations of *cis*-bicyclo[3.3.0]octane-3,7-dione (**5c**) and *cis*-1,5-dimethylbicyclo[3.3.0]octane-3,7-dione (**5d**) at both 190 °C and 230 °C provided good yields (Table 2, entries 3 and 4) but in a less regioselective manner. The isomer ratio of **6d**:**7d** could be improved to 94:6 by carrying out the reaction at 170 °C for 40 min at the expense of a reduced yield (Table 2, entry 5). The reaction of (±)-bicyclo[3.3.1]nonane-2,6-dione (**5e**), being a much more flexible bicyclic di-ketone, furnished the deconjugative olefin **7e** as the sole isomer at 230 °C in 77% yield (Table 2, entry 6). The olefination of **5e** with **2** at 190 °C for 20 min produced the exocyclic product **6e** as an inseparable 71:29 mixture of *E*- and *Z*-isomers, contaminating by ca. 5% of **7e**. The major isomer of **6e** was tentatively assigned as the *E* configuration.



Scheme 2. Microwave-assisted olefinations of ketones **5a**–**e**.

Table 2. Effect of ring structures on olefination[a]

Entry	Ketone	190 °C, 20 min	230 °C, 20 min, 20 mol % DBU
		Yield (%);[b] **6**:**7**[c]	Yield (%);[b] **6**:**7**[c]
1	**5a**: n=1	60; 99:1	72; 90:10
2	**5b**: n=3	27; 99:1	38; 57:43
3	**5c**: R=H	61; 88:12	78; 32:68
4	**5d**: R=Me	63; 88:12	78; 45:55
5	**5d**: R=Me	47; 94:6[d]	—
6	**5e**	64; 95:5[e]	70; 0:100

[a] Carried out with 3:1 ratio of the ketone and **2** on a commercial technical microwave reactor. MeCN and DMF were used for reactions at 190 °C and 230 °C, respectively.
[b] Combined isolated yields of *exo*- and *endo*-olefins.
[c] Determined by ^{1}H NMR.
[d] Carried out at 170 °C for 40 min.
[e] The *E*:*Z* ratio of **6e** is 71:29.

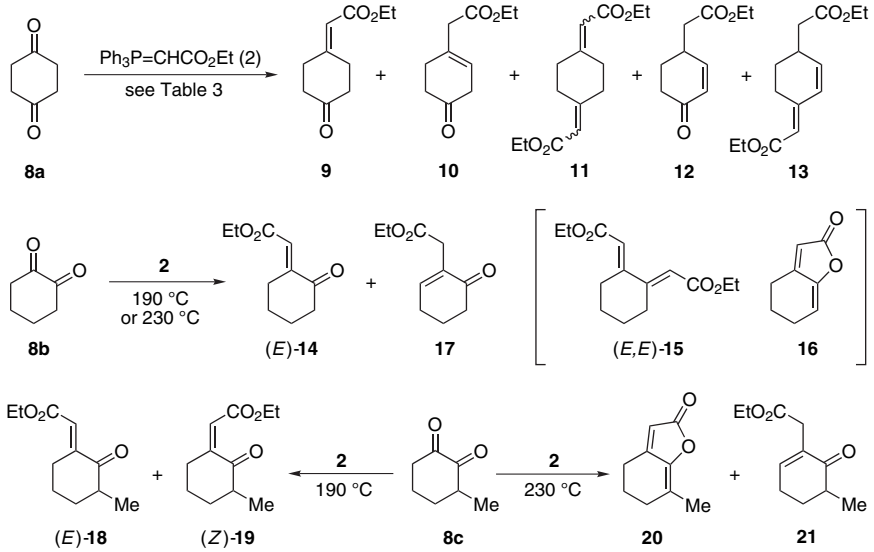
Table 3. Olefinations of 1,4- and 1,2-cyclohexanediones **8a–c**[a]

Entry	Ketone	190 °C, 20 min	230 °C, 20 min, 20 mol % DBU
		Yield (%);[b] ratio[c]	Yield (%);[b] ratio[c]
1	**8a**	**9**+**10**: 89; 94:6; **11**: 8 (*E*:*Z*=60:40)	**10**+**12**+**13**: 77; 9:83:8
2	**8b**	**14**: 44; uncharacterized byproducts[d]	**17**: 78; uncharacterized byproducts[d]
3	**8c**	(*E*)-**18**+(*Z*)-**19**: 63; 87:13	**20**+**21**: 73; 45:55

[a] Carried out with 3:1 ratio of the ketone and **2** on a commercial technical microwave reactor. MeCN and DMF were used for reactions at 190 °C and 230 °C, respectively.
[b] Combined isolated yields of *exo*- and *endo*-olefins.
[c] Determined by ^{1}H NMR.
[d] See text for details. Much more mass of the uncharacterized byproducts was formed at 190 °C than at 230 °C.

The Wittig reactions of 1,4-cyclohexanedione (**8a**) and 1,2-cyclohexanedione (**8b**) with the ylide **2** have been investigated by others[28a] with conventional thermal heating and a solvent effect on product distribution was observed. For the reaction of **8a** in DMF at refluxing for 7 h followed by stirring at room temperature for 1 day, the mono-olefination product **9**, and the bis-olefination products **11** were obtained in 83% yield and in a ratio of 91:5:4 for **9**:(*E*)-**11**:(*Z*)-**11** (see Scheme 3 for the structures).[28a] For the reaction of **8b** with **2** in DMF at refluxing for 6 h followed by stirring at room temperature for another 2 days, the exocyclic olefins (*E*)-**14** and (*Z*)-**14** and the rearranged enone **17** were isolated in 83% yield and in a 59:7:34 ratio for (*E*)-**14**:(*Z*)-**14**:**17**.[28a] Formation of **17** in EtOH was observed but to a very lower level of 4% of the total product mass.[28a] When the reaction of **8b** with **2** was carried out in refluxing PhH for 7 h, (*E*)-**14** was obtained in 76% yield as the sole product.[28b] Treatment of (*E*)-**14** with the sodium salt of triethyl phosphonoacetate in PhH at room temperature for 30 min afforded the bis-olefination product (*E*,*E*)-**15** and the (*E*,*Z*)-**15** in 41% and 11% yields, respectively (see Scheme 3 for the structures).[28b] The compounds **10**, **12**, (*E*)-**14**, and **17** have been prepared by non-Wittig type olefination procedures as well.[29] We investigated the microwave-assisted olefination of 1,4-cyclohexanedione (**8a**), 1,2-cyclohexanedione (**8b**), and 3-methyl-1,2-cyclohexanedione (**8c**) with the ylide **2** as shown in Scheme 3 and Table 3. The reaction of **8a** with **2** at 190 °C afforded the mono-olefination product **9**[5c–f] in 89% yield as a 94:6 inseparable mixture with **10**[29b] together with about 8% of the bis-olefination product **11**[30] in a ca. 60:40 ratio of *E*- and *Z*-isomers.[28a,30] The conjugated enone **12**[29a,b] was not detected in the reaction at 190 °C but it could be obtained as the major component by heating **8a** with **2** at 230 °C for 20 min in DMF in the presence of 20 mol % DBU (Table 3, entry 1). The enone **12** was isolated in 77% yield as an inseparable mixture[29b] with **10** and **13** and the ratio of **10**:**12**:**13** was estimated to be 9:83:8 by ^{1}H NMR analysis. The byproduct **13** seems not being reported in literature and the exocyclic double bond configuration is tentatively assigned. It could be formed by either isomerization of **11** or via a second Wittig reaction of **12**. On one occasion, we obtained pure **12** in 56% yield. It seems that a slight variation in reaction conditions resulted in different product distribution.

The ^{1}H NMR spectrum of **9** recorded on a 500 MHz instrument in $CDCl_3$ features a singlet peak at 5.85 ppm for the



Scheme 3. Microwave-assisted olefinations of di-ketones **8a–c** with the ylide **2**.

vinyl proton, which is consistent with the reported value of 5.82 ppm (t, J=1.4 Hz measured on a 200 MHz instrument in $CDCl_3$).[5d] The minor product **10** gives characteristic signals at 3.10 (s, 2H) and 5.64 (br s, 1H) ppm, the latter is consistent with the known value of 5.60 (m)[29b] for the vinyl proton. The *E*- and *Z*-isomers of **11** show the vinyl protons at 5.70 (s, major) and 5.78 (s, minor) ppm, which are in accord with the reported chemical shifts of 5.64 (s, *E*-) and 5.80 (s, *Z*-) ppm.[30a] The vinyl protons of the conjugated enone **12** are found at 6.84 (d, J=10.4 Hz) and 5.99 (dd, J=10.4, 2.0 Hz) ppm and agree well with the reported values of 6.82 (ddd, J=10, 3, 1 Hz) and 5.95 (dd, J=10, 2 Hz) ppm.[29b] The structure of **13** was tentatively assigned on the basis of the characteristic signals at 7.11 (d, J=8.4 Hz, 1H), 6.78 (d, J=8.4 Hz, 1H), 6.25 (br s, 1H), and 3.50 (s, 2H) ppm. The significant downfield shifts of these signals are indicative of the extended conjugation system.

The Wittig reactions of 1,2-cyclohexanedione (**8b**) with the ylide **2** were complicated by the formation of byproducts (Scheme 3). The reaction carried out at 190 °C gave the exocyclic olefin (*E*)-**14**[28] isomer in a pure form in 44% isolated yield. The majority of the remaining mass was an inseparable mixture of more than two components and the structures could not be fully characterized (Table 3, entry 2). The compounds (*E*,*E*)-**15**,[28b] (*E*,*Z*)-**15**[28b] and **16**[31] are known in literature. Chemical shifts of 5.87 (s) and 5.67 (m) ppm recorded on a 60 MHz instrument were reported for the vinyl protons of (*E*,*E*)-**15**[28b] and (*E*,*Z*)-**15**,[28b] respectively. For our mixture mentioned above, a vinyl proton appears at 6.16 (t, J=4.8 Hz on a 400 MHz instrument) ppm and its splitting pattern is similar to that of the vinyl proton of (*E*)-**14**, being a triplet (J=2 or 2.3 Hz) at 6.42 or 6.43 ppm in two independent reports[28a,b,32] and at 6.47 (t, J=2.2 Hz) ppm obtained in our study. Therefore, we are not sure whether (*E*,*E*)-**15** was formed in the reaction of **8b** with **2**. Also, the butenolide **16**, having chemical shifts of 1.57–2.92 (m, 6H) and 5.66–6.01 (m, 2H) ppm, was prepared from an intramolecular Wittig reaction of an adduct formed from **8b** and $Ph_3P{=}C{=}C(OEt)_2$ followed by acidic hydrolysis.[31] We only observed a singlet peak at 5.69 ppm (possibly for the vinyl proton of the butenolide ring) in the above mixture but the other enolic vinyl proton was not found. At this stage, no conclusion can be made about the formation of **16** although a similar analog **20** was formed in the reaction of **8c** with **2** (vide infra).

When the reaction of **8b** with **2** was carried out at 230 °C, the amount of the byproducts was significantly reduced to afford the endocyclic enone **17**[29b,c] in 78% isolated yield. The typical proton signals for **17** are found at 6.85 (t, J=4.0 Hz, 1H) and 3.17 (s, 2H) ppm, being consistent with the reported values of 6.83 (t, J=4.0) and 3.16 (d, J=0.5 Hz, 2H),[28a] 6.85 (t, J=4.0) and 3.28 (br s, 2H),[29b] or 6.86 (t, J=3.8 Hz) and 3.20 (s, 2H)[29c] ppm in three independent reports. Therefore, our microwave-assisted Wittig reactions of **8b** with **2** furnished only the exocyclic (at 190 °C in MeCN) and endocyclic (at 230 °C in DMF with DBU) olefins, respectively, being different from the reaction carried out in refluxing DMF with conventional thermal heating.[28a] Our reactions completed within 20 min but were accompanied by the formation of byproducts due to high reaction temperatures.

Finally, we carried out the Wittig reactions of 3-methyl-1,2-cyclohexanedione (**8c**) with the ylide **2** in order to examine the influence of the methyl group on reactivity and regiochemistry. Under controlled microwave heating at 190 °C for 20 min, the reaction gave only the exocyclic olefins (*E*)-**18** and (*Z*)-**19** in 63% isolated yield as an 87:13 ratio of inseparable mixture. The vinyl protons having chemical shift at 6.33 (t, J=1.2 Hz) and 6.26 (s) ppm are assigned for (*E*)-**18** and (*Z*)-**19**, respectively. This is in accord with the upfield chemical shift of 5.63 ppm reported for (*Z*)-**14**.[28a,32] When the olefination of **8c** was performed at 230 °C, the butenolide **20** was formed together with the expected endocyclic enone **21** (Table 3, entry 3). Compounds **20** and **21** were isolated in 73% yield as an inseparable mixture of 45:55 ratio. Compound **20** features a vinyl proton at 5.65 (s) ppm while the enone **21** has the vinyl proton appearing at 6.77 (t, J=4.4 Hz) and the CH_2CO_2 protons at 3.15 (ABq, J=15.4 Hz, 2H) ppm.

3. Conclusion

In summary, we have investigated the Wittig reactions of a number of cyclic mono- and di-ketones under controlled microwave heating. By selecting suitable reaction temperature, solvent, and base, we are able to demonstrate high regioselective olefinations of 4-substituted cyclohexanones (**1a–h**) and the bicyclic di-ketone **5e** to selectively form either the exocyclic olefins (MeCN, 190 °C, 20 min) or the deconjugated olefins (DMF, DBU, 230 °C, 20 min). We found that the ring structures have a major effect on isomerization of the initially formed olefins and poor results in deconjugation were observed for the substrates **5a–d**. Reactions of the cyclohexanediones **8a–c** were somewhat complicated due to the formation of inseparable byproducts, but good regioselectivity was obtained for the products **9**, **12**, (*E*)-**14**, **17**, (*E*)-**18**, and (*Z*)-**19**. These results clearly demonstrate the importance of temperature regulation in microwave-assisted organic synthesis. Therefore, use of controlled microwave heating is the direction of future advancement in this rapidly growing area of chemical synthesis.

4. Experimental

^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ (500, 400, or 300 MHz for ^1H and 75 MHz for ^{13}C) with $CHCl_3$ as the internal reference. IR spectra were taken on an FTIR spectrophotometer. Mass spectra (MS) were measured by the +CI or ESI method. All reactions were carried out on an Emrys creator from Personal Chemistry AB (now under Biotage AB, Uppsala, Sweden) with temperature measured by an IR sensor. The microwave-assisted reaction time is the hold time at the final temperature. The reaction mixture was checked by thin-layer chromatography on silica gel plates (60 F-254) using UV light, or 7% ethanolic phosphomolybdic acid and heating as the visualizing methods. Flash column chromatography over silica gel was used for purification. Yields refer to chromatographically and

spectroscopically (^{1}H NMR) homogeneous materials. Reagents were obtained commercially and used as received.

4.1. Representative procedure for Wittig reactions of 2 with cyclic mono- and di-ketones under controlled microwave heating at 190 °C in MeCN

4.1.1. Ethyl (4-phenylcyclohexylidene)acetate [(*exo*)-3d].[22] A 10 mL pressurized process vial containing a magnetic stirring bar was charged with 4-phenylcyclohexanone (214.5 mg, 1.23 mmol), (carbethoxymethylene)triphenylphosphorane (**2**, 142.6 mg, 0.41 mmol) and MeCN (3 mL) and then the vial was sealed with a cap containing a silicon septum. The loaded vial was placed into the cavity of the microwave reactor and heated at 190 °C for 20 min. The reaction mixture was diluted with diethyl ether and washed with aqueous NH_4Cl. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. (Caution: it is essential to control the pressure carefully to avoid removal of the volatile products.) The residue was purified by flash column chromatography (5% EtOAc–hexane) to give *exo*-**3d** (66 mg, 66%) as a 99:1 inseparable mixture with *endo*-**4d** (Table 1, entry 4). The ratio of regioisomers was determined by ^{1}H NMR. Other results are listed in Tables 1–3. *Compound exo*-**3d**: IR (film) 2931, 1713, 1651, 1144, 1178 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.24–7.18 (m, 5H), 5.71 (s, 1H), 4.18 (q, J=7.1 Hz, 2H), 4.02–3.97 (m, 1H), 2.81–2.78 (m, 1H), 2.41–2.35 (m, 2H), 2.11–2.06 (m, 3H), 1.69–1.62 (m, 2H), 1.31 (t, J=7.1 Hz, 3H); MS (ESI) m/z 245 (M+H$^+$).

4.1.2. Ethyl cyclohexylideneacetate [(*exo*)-3a].[3,22,24b] *Compound exo*-**3a**: IR (film) 2928, 1722, 1648, 1266 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.71 (s, 1H), 4.15 (q, J=7.1 Hz, 2H), 2.85–2.81 (m, 2H), 2.35–2.17 (m, 8H), 1.28 (t, J=7.1 Hz, 3H); MS (+CI) m/z 167 (M−H$^+$).

4.1.3. Ethyl (4-methylcyclohexylidene)acetate [(*exo*)-3b].[21b,22] *Compound exo*-**3b**: IR (film) 2926, 1714, 1651, 1191, 1153 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.60 (s, 1H), 4.14 (q, J=7.1 Hz, 2H), 3.75–3.70 (m, 1H), 2.24–2.16 (m, 2H), 1.94–1.81 (m, 3H), 1.75–1.53 (m, 1H), 1.27 (t, J=7.1 Hz, 3H), 1.14–1.05 (m, 2H), 0.91 (d, J=6.5 Hz, 3H); MS (+CI) m/z 167 (M−Me$^+$).

4.1.4. Ethyl (4-*tert*-butylcyclohexylidene)acetate [(*exo*)-3c].[20e,22,24b] *Compound exo*-**3c**: IR (film) 2959, 1716, 1652, 1185 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.71 (s, 1H), 4.17 (q, J=7.1 Hz, 2H), 3.95–3.82 (m, 1H), 2.28–1.98 (m, 8H), 1.27 (t, J=7.1 Hz, 3H), 0.87 (s, 9H); MS (+CI) m/z 225 (M+H$^+$).

4.1.5. Ethyl (4-ethylcyclohexylidene)acetate [(*exo*)-3e].[21b] *Compound exo*-**3e**: IR (film) 2931, 1719, 1654, 1186 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.60 (s, 1H), 4.13 (q, J=7.1 Hz, 2H), 3.77–3.71 (m, 1H), 2.30–2.10 (m, 2H), 2.03–1.84 (m, 3H), 1.50–1.35 (m, 1H), 1.30–1.20 (m, 5H), 1.17–0.95 (m, 2H), 0.88 (d, J=7.4 Hz, 3H); MS (+CI) m/z 197 (M+H$^+$).

4.1.6. Ethyl (4-propylcyclohexylidene)acetate [(*exo*)-3f]. *Compound exo*-**3f**: IR (film) 2928, 1713, 1649, 1185, 1151 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.60 (s, 1H), 4.13 (q, J=7.1 Hz, 2H), 3.80–3.68 (m, 1H), 2.32–2.10 (m, 2H), 2.00–1.82 (m, 3H), 1.58–1.42 (m, 1H), 1.38–0.95 (m, 9H), 0.88 (d, J=7.1 Hz, 3H); MS (+CI) m/z 211 (M+H$^+$).

4.1.7. Ethyl (4-*iso*-propylcyclohexylidene)acetate [(*exo*)-3g]. *Compound exo*-**3g**: IR (film) 2958, 1717, 1649, 1189, 1152 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.59 (s, 1H), 4.13 (q, J=7.1 Hz, 2H), 3.86–3.75 (m, 1H), 2.37–2.10 (m, 2H), 1.96–1.82 (m, 3H), 1.55–1.42 (m, 1H), 1.38–1.05 (m, 6H), 0.86 (d, J=6.8 Hz, 6H); MS (+CI) m/z 209 (M−H$^+$).

4.1.8. Ethyl (4-*tert*-amylcyclohexylidene)acetate [(*exo*)-3h].[6] *Compound exo*-**3h**: IR (film) 2963, 1716, 1651, 1181, 1144 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.71 (s, 1H), 4.16 (q, J=7.1 Hz, 2H), 3.95–3.86 (m, 1H), 2.38–1.80 (m, 8H), 1.38–1.10 (m, 5H), 0.83 (t, J=7.5 Hz, 3H), 0.81 (s, 6H); MS (+CI) m/z 239 (M+H$^+$).

4.1.9. Ethyl cyclopentylideneacetate (6a).[3,22,24b] *Compound* **6a**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.79 (br s, 1H), 4.14 (q, J=7.2 Hz, 2H), 2.76 (t, J=7.0 Hz, 2H), 2.43 (t, J=7.0 Hz, 2H), 1.77–1.62 (m, 4H), 1.27 (t, J=7.2 Hz, 3H).

4.1.10. Ethyl cycloheptylideneacetate (6b).[3,22,24b] *Compound* **6b**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.65 (t, J=1.2 Hz, 1H), 4.14 (q, J=7.2 Hz, 2H), 2.86 (td, J=6.2, 1.4 Hz, 2H), 2.39 (t, J=6.0 Hz, 2H), 1.73–1.47 (m, 8H), 1.27 (t, J=7.2 Hz, 3H).

4.1.11. 7-[(Ethoxycarbonyl)methylene]-*cis*-bicyclo-[3.3.0]octan-3-one (6c).[8] *Compound* **6c**: IR (film) 2939, 1741, 1709, 1654, 1207, 1124 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.78–5.76 (m, 1H), 4.08 (q, J=7.2 Hz, 2H), 3.20–3.05 (m, 1H), 2.80–2.60 (m, 4H), 2.45–2.30 (m, 3H), 2.08–1.90 (m, 2H), 1.21 (t, J=7.2 Hz, 3H); MS (+CI) m/z 209 (M+H$^+$).

4.1.12. 7-[(Ethoxycarbonyl)methylene]-*cis*-1,5-dimethylbicyclo[3.3.0]octan-3-one (6d).[8] *Compound* **6d**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.81–5.78 (m, 1H), 4.13 (q, J=7.2 Hz, 2H), 2.97 and 2.90 (ABq, J=21.4 Hz, 2H), 2.57 (s, 2H), 2.35–2.15 (m, 4H), 1.26 (t, J=7.2 Hz, 3H), 1.09 (s, 3H), 1.07 (s, 3H); MS (ESI) m/z 259 (M+Na$^+$).

4.1.13. (±)-6-[(Ethoxycarbonyl)methylene]bicyclo-[3.3.1]nonan-2-one (6e). *Compound* **6e**: For (*E*)-isomer (major): IR (film) 2933, 1710 (br), 1641, 1164 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.75 (d, J=1.6 Hz, 1H), 4.15 (q, J=7.2 Hz, 2H), 3.81 (dd, J=16.6, 5.8 Hz, 1H), 2.75–1.60 (m, 11H), 1.26 (t, J=7.2 Hz, 3H); MS (+CI) m/z 223 (M+H$^+$). For (*Z*)-isomer (minor): ^{1}H NMR (400 MHz, $CDCl_3$) δ 568 (br s, 1H), 4.30 (br s, 1H).

4.1.14. Ethyl (4-oxocyclohexylidene)acetate (9).[5c–f,28a] *Compound* **9**: IR (KBr) 2963, 1709 (br), 1646, 1167 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.85 (s, 1H), 4.17 (q, J=7.0 Hz, 2H), 3.21 (t, J=6.5 Hz, 2H), 2.67 (t, J=6.5 Hz, 2H), 2.52–2.40 (m, 4H), 1.29 (t, J=7.0 Hz, 3H); MS (+CI) m/z 183 (M+H$^+$).

4.1.15. Ethyl (2-oxocyclohexylidene)acetate [(*E*)-14].[28a,b,29c,32] *Compound* **14**: IR (film) 2940, 1719 (br), 1697, 1187 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.47 (s, 1H), 4.21 (q, J=7.0 Hz, 2H), 3.11–3.07 (m, 2H), 2.53

(t, J=6.6 Hz, 2H), 1.94–1.90 (m, 2H), 1.83–1.78 (m, 2H), 1.30 (t, J=7.0 Hz, 3H); MS (+CI) m/z 183 ($M+H^+$).

4.1.16. Ethyl (3-methyl-2-oxocyclohexylidene)acetate [(*E*)-18]. *Compound* (*E*)-**18**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.34–6.32 (m, 1H), 4.17 (q, J=7.2 Hz, 2H), 3.70–3.57 (m, 1H), 2.70–2.32 (m, 2H), 2.20–2.02 (m, 1H), 2.00–1.80 (m, 1H), 1.77–1.50 (m, 2H), 1.27 (t, J=7.2 Hz, 3H), 1.13 (d, J=6.4 Hz, 3H); MS (ESI) m/z 219 ($M+Na^+$).

4.2. Representative procedure for Wittig reactions of 2 with cyclic mono- and di-ketones under controlled microwave heating at 230 °C in DMF in the presence of 20 mol % DBU

4.2.1. Ethyl (4-phenylcyclohexen-1-yl)acetate [(*endo*)-4d]. A 10 mL pressurized process vial containing a magnetic stirring bar was charged with 4-phenylcyclohexanone (214.5 mg, 1.23 mmol), (carbethoxymethylene)triphenylphosphorane (**2**, 142.6 mg, 0.41 mmol), DBU (13 μL), and DMF (3 mL) and then the vial was sealed with a cap containing a silicon septum. The loaded vial was placed into the cavity of the microwave reactor and heated at 230 °C for 20 min. The reaction mixture was diluted with diethyl ether and washed with aqueous NH_4Cl. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. (Caution: control the pressure carefully to avoid removal of the volatile products.) The residue was purified by flash column chromatography (5% EtOAc–hexane) to give *endo*-**4d** (82 mg, 82%) as an 87:13 inseparable mixture with *exo*-**3d** (Table 1, entry 4). The ratio of regioisomers was determined by ^{1}H NMR. Other results are listed in Tables 1–3. *Compound endo*-**4d**: IR (film) 2918, 1738, 1163 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35–7.19 (m, 5H), 5.72–5.67 (m, 1H), 4.19 (q, J=7.1 Hz, 2H), 3.04 (s, 2H), 2.89–2.74 (m, 1H), 2.45–1.80 (m, 6H), 1.32 (t, J=7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.4, 147.4, 131.7, 129.0 (×2), 127.5 (×2), 126.6, 125.9, 61.3, 44.0, 40.4, 34.3, 30.6, 29.8, 15.1; MS (+CI) m/z 245 ($M+H^+$).

4.2.2. Ethyl cyclohexen-1-ylacetate [(*endo*)-4a].[4,24c,27] *Compound endo*-**4a**: IR (film) 2933, 1728, 1275, 1121 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.57 (br s, 1H), 4.14 (q, J=7.1 Hz, 2H), 2.94 (s, 2H), 2.11–1.95 (m, 4H), 1.75–1.53 (m, 4H), 1.27 (t, J=7.1 Hz, 3H); MS (+CI) m/z 167 ($M-H^+$).

4.2.3. Ethyl (4-methylcyclohexen-1-yl)acetate [(*endo*)-4b]. *Compound endo*-**4b**: IR (film) 2928, 1728, 1274, 1121 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.53 (br s, 1H), 4.13 (q, J=7.1 Hz, 2H), 2.95 (s, 2H), 2.38–1.56 (m, 7H), 1.26 (t, J=7.1 Hz, 3H), 0.95 (d, J=5.9 Hz, 3H); MS (+CI) m/z 183 ($M+H^+$).

4.2.4. Ethyl (4-*tert*-butylcyclohexen-1-yl)acetate [(*endo*)-4c].[4,27] *Compound endo*-**4c**: IR (film) 2961, 1736, 1167 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.56 (br s, 1H), 4.14 (q, J=7.1 Hz, 2H), 2.95 (s, 2H), 2.32–1.75 (m, 7H), 1.27 (t, J=7.1 Hz, 3H), 0.86 (s, 9H); MS (+CI) m/z 225 ($M+H^+$).

4.2.5. Ethyl (4-ethylcyclohexen-1-yl)acetate [(*endo*)-4e]. *Compound endo*-**4e**: IR (film) 2962, 2932, 1732, 1187 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.58 (br s, 1H), 4.12 (q, J=7.1 Hz, 2H), 2.93 (s, 2H), 2.22–1.25 (m, 11H), 0.88 (t, J=7.3 Hz, 3H); MS (+CI) m/z 195 ($M-H^+$).

4.2.6. Ethyl (4-propylcyclohexen-1-yl)acetate [(*endo*)-4f]. *Compound endo*-**4f**: IR (film) 2925, 1738, 1181, 1151 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.52 (br s, 1H), 4.12 (q, J=7.1 Hz, 2H), 2.93 (s, 2H), 2.20–1.14 (m, 13H), 0.88 (t, J=6.9 Hz, 3H); MS (+CI) m/z 211 ($M+H^+$).

4.2.7. Ethyl (4-*iso*-propylcyclohexen-1-yl)acetate [(*endo*)-4g]. *Compound endo*-**4g**: IR (film) 2926, 1729, 1265 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.54 (br s, 1H), 4.13 (q, J=7.1 Hz, 2H), 2.94 (s, 2H), 2.40–1.40 (m, 8H), 1.27 (t, J=7.1 Hz, 3H), 0.91 (d, J=7.4 Hz, 3H), 0.87 (d, J=7.3 Hz, 3H); MS (+CI) m/z 211 ($M+H^+$).

4.2.8. Ethyl (4-amylcyclohexen-1-yl)acetate [(*endo*)-4h]. *Compound endo*-**4h**: IR (film) 2964, 1736, 1162 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.60–5.56 (m, 1H), 4.14 (q, J=7.1 Hz, 2H), 2.96 (s, 2H), 2.47–1.70 (m, 7H), 1.45–1.14 (m, 5H), 0.87–0.75 (m, 9H); MS (+CI) m/z 239 ($M+H^+$).

4.2.9. Ethyl cyclohepten-1-ylacetate (7b).[24c,27] As a 57:43 inseparable mixture of **6b**:**7b**. *Compound* **7b**: Partial ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.68 (t, J=6.5 Hz, 1H), 2.97 (s, 2H).

4.2.10. 3-Ethoxycarbonylmethyl-*cis*-bicyclo[3.3.0]oct-2-en-7-one (7c). As a 32:68 inseparable mixture of **6c**:**7c**. *Compound* **7c**: IR 2933, 1739, 1206, 1172 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.42 (br s, 1H), 4.11 (q, J=7.2 Hz, 2H), 3.45–3.33 (m, 1H), 3.08 (s, 2H), 3.05–1.85 (m, 7H), 1.23 (t, J=7.2 Hz, 3H); MS (+CI) m/z 209 ($M+H^+$).

4.2.11. 3-Ethoxycarbonylmethyl-*cis*-1,5-dimethyl-bicyclo[3.3.0]oct-2-en-7-one (7d). As a 45:55 inseparable mixture of **6d**:**7d**. *Compound* **7d**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.42 (br s, 1H), 4.14 (q, J=7.2 Hz, 2H), 3.11 and 3.04 (ABq, J=16.2 Hz, 2H), 2.50–2.15 (m, 6H), 1.26 (t, J=7.2 Hz, 3H), 1.13 (s, 3H), 1.08 (s, 3H); MS (+CI) m/z 237 ($M+H^+$).

4.2.12. (±)-3-[(Ethoxycarbonyl)methyl]bicyclo[3.3.1]-nonan-2-en-6-one (7e). *Compound* **7e**: IR (film) 2931, 1731, 1709, 1158 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.71 (br s, 1H), 4.14 (q, J=7.0 Hz, 2H), 3.08 and 3.01 (ABq, J=15.0 Hz, 2H), 2.69 (br s, 1H), 2.49–2.34 (m, 3H), 2.27 (dd, J=15.5, 5.0 Hz, 1H), 2.03–1.81 (m, 5H), 1.26 (t, J=7.0 Hz, 3H); MS (+CI) m/z 223 ($M+H^+$).

4.2.13. Ethyl (4-oxo-cyclohexen-2-yl)acetate (12).[29a,b] *Compound* **12**: IR (film) 2981, 1732, 1680, 1182, 1163 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.84 (d, J=10.4 Hz, 1H), 5.99 (dd, J=10.4, 2.0 Hz, 1H), 4.16 (q, J=7.2 Hz, 2H), 3.00–2.80 (m, 1H), 2.55–2.32 (m, 4H), 2.24–2.15 (m, 1H), 1.80–1.67 (m, 1H), 1.27 (t, J=7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.7, 172.2, 153.5, 130.3, 61.5, 39.6, 37.4, 33.6, 29.4, 14.9; MS (+CI) m/z 183 ($M+H^+$).

4.2.14. Ethyl (6-oxo-cyclohexen-1-yl)acetate (17).[28a,29b,c] *Compound* **17**: IR (film) 2937, 1737, 1675, 1179 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.85 (t, J=4.0 Hz, 1H), 4.11 (q, J=7.2 Hz, 2H), 3.17 (s, 2H), 2.47–2.36 (m, 4H), 2.04–1.99 (m, 2H), 1.23 (t, J=7.2 Hz, 3H); MS (+CI) m/z 183 ($M+H^+$).

4.2.15. 5,6-Dihydro-7-methylbenzofuran-2(4*H*)-one (20). As a 45:55 inseparable mixture of **20**:**21**. *Compound* **20**: IR (film) 1770, 1189 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.65 (s, 1H), 2.62 (t, J=6.4 Hz, 2H), 2.44–1.60 (m, 4H), 1.93 (s, 3H); MS (+CI) m/z 151 ($M+H^+$).

4.2.16. Ethyl (5-methyl-6-oxo-cyclohexen-1-yl)acetate (21). As a 45:55 inseparable mixture of **20**:**21**. *Compound* **21**: IR (film) 2931, 1739, 1675, 1179 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.77 (t, J=4.4 Hz, 1H), 4.09 (q, J=7.6 Hz, 2H), 3.19 and 3.11 (ABq, J=15.4 Hz, 2H), 2.44–1.60 (m, 5H), 1.21 (t, J=7.6 Hz, 3H), 1.11 (d, J=6.8 Hz, 3H); MS (+CI) m/z 197 ($M+H^+$).

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