Reluctant Cross-Metathesis Reactions: The Highly Beneficial Effect of Microwave Irradiation

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Abstract: The beneficial effect of microwave irradiation versus classical thermal conditions is demonstrated through a series of comparative cross-metathesis reactions.

Key words: carbene complexes, catalysis, cross coupling, metathesis, olefination

The establishment of olefin metathesis as a powerful synthetic tool for C=C bond formation is essentially due to the initial discovery of the Schrock molybdenum-based catalyst, followed by the extensive development of ruthenium-based catalysts such as 1a,b and their derivatives introduced by Grubbs and co-workers. More specifically, cross metathesis (CM) of simple alkenes has now become one of the methods of choice to access substituted alkenes, although its development has been somewhat delayed compared to Ring-Closing Metathesis (RCM) and Ring-Opening Metathesis Polymerization (ROMP) due to initial functional group compatibility problems.1 In some cases, and in particular with electron-deficient alkenes, the CM reaction is less effective and requires specific conditions to prevent catalyst deactivation. Among them, the addition of chlorodicyclohexylborane or titanium(IV) propoxide have proven useful with substrates bearing a Lewis base functional group.2,3b CM reactions with reluctant partners such as acrylonitrile derivatives have been the topic of several studies, and specific conditions, as well as more reactive phosphine-free catalysts, have been developed.3 Recently, some reports have appeared on the dramatic improvement in reaction rates and yields in microwave-assisted olefin metathesis reactions.5

In connection with our studies on 1,3-dicarbonyl derivatives, we recently prepared a number of allylic derivatives by CM reactions with various functionalized alkenes using catalysts 1a,b (Figure 1). If the desired products could, indeed, be obtained under classical thermal conditions, reaction times were rather long, and in some cases the yields were modest to very low, probably due to the polar functionalities present on the substrate. Considering the precedents of microwave (μW) irradiation during metathesis reactions,5 we tested this method of activation in the cases of our reluctant substrates. We observed a highly beneficial effect on the rate of CM reactions under microwave irradiation, and our results are reported herein (Table 1). It should be noted that microwave-assisted CM reactions have been little reported, and only with ethyl acrylate,3i for the homodimerization of N-allylamino acids,5p and, recently, with peptides.5q We initiated our study with the cross metathesis of allylic derivatives and allyl(trimethyl)silane (3a). The β-oxoamide 2a is reluctant to undergo CM with allyl(trimethyl)silane (3a) under classical thermal conditions, resulting in poor conversion leading to a low yield of the desired cross-coupled product 4a, which is always accompanied by substantial amounts of products resulting from homocoupling of the substrate and partial isomerization of the allyl(trimethyl)silane 4a to the vinylsilane (Table 1, entry 1). The same reaction performed under microwave irradiation resulted in a dramatic increase in the rate of CM to give 60% of the expected cross-coupling product 4a (87% conversion) after only 30 seconds at 60 °C (entry 1). The isomerization of allyl(trimethyl)silane 4a could be completely suppressed by the addition of 10% of 1,4-benzoquinone.5 When the amount of catalyst is reduced to 0.6 mol%, this reaction is still productive yielding 4a in 38% yield after 30 minutes of irradiation (entry 2). A similar accelerating effect was observed for the cross-coupling reactions of β-oxo sulfone 2b with allyl(trimethyl)silane (3a), which gave the expected alkene 4b in 68% yield after 35 minutes of irradiation compared to 51% yield after 24 hours under thermal conditions (entry 3). The beneficial effect of microwave irradiation is even more striking with the diketone 2c, as the CM product 4c is obtained in 75% yield after 10 minutes, while 10% yield is obtained after 16 hours at 100 °C without irradiation (entry 4). The CM of the more sensitive and probably more chelating nitro ketone 2d required the addition of titanium(IV) isopropoxide and microwave irradiation to proceed smoothly (entry 5). The cross cou-

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pling of the homoallylic bromide 2e and allyl(trimethyl)silane (3a) under thermal conditions gave a very sluggish reaction while microwave irradiation allowed the isolation of the alkene 4e in 77% yield after only 40 seconds (entry 6). Interestingly, scaling up the reaction to 15 mmol allowed the amount of catalyst to be reduced to 0.15% to produce 4e in 69% yield after 3 minutes of irradiation (entry 7). This corresponds to an exceptionally high TON of 460 for catalyst 1a.

The nitroalkene 2f also underwent CM with allyl(trimethyl)silane (3a) in decent yield after 30 seconds of irradiation (entry 8). Hex-1-ene (3b) and allyl acetate (3c) were also used successfully as CM partners under microwave irradiation with the β-oxo ester 2g, giving the product with good Z selectivity in the latter case (entries 9 and 10). When acrylonitrile (3d) is used as the CM partner with the β-oxo ester 2h, catalyst 1b was by far superior to 1a, as illustrated in entries 11–15. For both thermal and microwave conditions, the reactions were performed at 100 °C with the same catalyst loading and times. Comparable results were obtained in 1,2-dichloroethane or dichloromethane (compare entries 11 with 12, and 13 with 14). However, with catalyst 1a (entries 11 and 12) slightly lower yields were obtained under microwave irradiation, probably due to faster decomposition of the catalyst. The decomposition of catalyst 1b under the reaction conditions is also evidenced in entries 14 and 15, as for the same total amount of catalyst, better results are obtained by introduction of the catalyst in two portions. As previously reported, CM reactions with acrylonitrile (3d) exhibit pronounced Z selectivity in the product.

Table 1 Comparative Cross-Metathesis Reactions under Thermal and Microwave Conditions

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Alkene</th>
<th>Catalyst</th>
<th>Product</th>
<th>Thermal conditions</th>
<th>Microwave irradiation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Conditions</td>
<td>Yield (%)</td>
</tr>
<tr>
<td>1</td>
<td>2a</td>
<td>3a</td>
<td>1a (2)</td>
<td>4a</td>
<td>neat, 90 °C, 16 h</td>
<td>14; 3:1</td>
</tr>
<tr>
<td>2</td>
<td>2a</td>
<td>3a</td>
<td>1a (0.6)</td>
<td>4a</td>
<td>not tested</td>
<td>–</td>
</tr>
<tr>
<td>3</td>
<td>2b</td>
<td>3a</td>
<td>1a (3)</td>
<td>4b</td>
<td>neat, 90 °C, 24 h</td>
<td>51; 1:1</td>
</tr>
<tr>
<td>4</td>
<td>2c</td>
<td>3a</td>
<td>1a (2)</td>
<td>4c</td>
<td>neat, 100 °C, 16 h</td>
<td>10; 1.8:1</td>
</tr>
<tr>
<td>5</td>
<td>2d</td>
<td>3a</td>
<td>1a (4)</td>
<td>4d</td>
<td>CH2Cl2, 40 °C, 16 h</td>
<td>40; 1.8:1</td>
</tr>
<tr>
<td>6</td>
<td>2e</td>
<td>3a</td>
<td>1a (0.8)</td>
<td>4e</td>
<td>neat, 90 °C, 8 h</td>
<td>6; nd</td>
</tr>
<tr>
<td>7</td>
<td>2e</td>
<td>3a</td>
<td>1a (0.15)</td>
<td>4e</td>
<td>not tested</td>
<td>–</td>
</tr>
<tr>
<td>8</td>
<td>2f</td>
<td>3a</td>
<td>1a (1.5)</td>
<td>4f</td>
<td>not tested</td>
<td>–</td>
</tr>
<tr>
<td>9</td>
<td>2g</td>
<td>3b</td>
<td>1a (2)</td>
<td>4g</td>
<td>neat, 90 °C, 16 h</td>
<td>50; 4:1</td>
</tr>
</tbody>
</table>
Table 1  Comparative Cross-Metathesis Reactions under Thermal and Microwave Conditions (continued)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Alkene</th>
<th>Catalyst (%)</th>
<th>Product</th>
<th>Thermal conditions</th>
<th>Microwave irradiation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Conditions</td>
<td>Yield (%)</td>
</tr>
<tr>
<td>10</td>
<td>2g</td>
<td>3c</td>
<td>1a (3)</td>
<td>4h</td>
<td>CH₂Cl₂, 40 °C, 12 h</td>
<td>41; 1:5.7</td>
</tr>
<tr>
<td>11</td>
<td>2h</td>
<td>3d</td>
<td>1a (3 + 1)</td>
<td>4i</td>
<td>CH₂Cl₂, 100 °C, 20 + 10 min</td>
<td>35; 1:3.8</td>
</tr>
<tr>
<td>12</td>
<td>2h</td>
<td>3d</td>
<td>1a (3 + 1)</td>
<td>4i</td>
<td>DCE, 100 °C, 20 + 10 min</td>
<td>24; 1:3.4</td>
</tr>
<tr>
<td>13</td>
<td>2h</td>
<td>3d</td>
<td>1b (3 + 1)</td>
<td>4i</td>
<td>CH₂Cl₂, 100 °C, 20 + 10 min</td>
<td>79; 1:3.1</td>
</tr>
<tr>
<td>14</td>
<td>2h</td>
<td>3d</td>
<td>1b (3 + 1)</td>
<td>4i</td>
<td>DCE, 100 °C, 20 + 10 min</td>
<td>70; 1:3.6</td>
</tr>
<tr>
<td>15</td>
<td>2h</td>
<td>3d</td>
<td>1b (4)</td>
<td>4i</td>
<td>not tested</td>
<td>–</td>
</tr>
</tbody>
</table>

*Yields of isolated homogeneous product. The E/Z ratio was determined by NMR analysis of the crude mixture.
*b The times indicated does not include ramp-up time (which is 20–80 s depending on conditions).
*c 10% 1,4-benzoquinone was added.
*d 15% Ti(Or-Pr)₃ was added.
*nd = not determined.

Paralleling the remarks of Hoveyda,⁴⁶ acrylonitrile might be categorized as a type III alkene with catalyst 1b and type IV with 1a (although it is not truly spectator to CM) in the Grubbs’ categorization of alkenes.¹² Trace amounts (<0.1%) of the Z-homodimer of acrylonitrile (3d) are detected with both catalyst 1a,b, and a minor amount (<5%) of the E-homodimer of the substrate are also observed.

Through this series of comparative CM reactions performed under classical thermal conditions and under microwave irradiation, the beneficial effects of microwave activation are clear, particularly in reluctant cases. However, a specific non-thermal microwave effect could not be evidenced.⁴⁴–⁴⁶ The better yields and conversions observed under microwave irradiation appear to result from the rapid heating allowed in the microwave oven (purely thermal/kinetic effect), and a faster cross-metathesis reaction relative to catalyst decomposition by suppression of wall effects. In some cases, the latter effect allowed a substantial decrease in the amount of catalyst.

In conclusion, we have demonstrated that microwave irradiation does not only dramatically reduce the reaction times of cross metathesis, but also allows a higher TON for the catalysts and ultimately renders efficient otherwise unproductive reactions.

CH₂Cl₂ and DCE were dried by refluxing with CaH₂ and then distilled under an argon atmosphere. The reactions were monitored by TLC, which were performed on Merck 60F254 plates and visualized with p-anisaldehyde and H₂SO₄ in EtOH or molybdophosphoric acid in EtOH. Flash chromatography was performed with Merck 40–63 μm silica gel eluted with Et₂O or EtOAc in petroleum ether (bp 40–60 °C). NMR data were recorded on a Bruker Avance 300 spectrometer in CDCl₃ using as internal standards the residual chloroform signal for ¹H NMR (δ = 7.26) and the deuterated solvent signal for ¹³C NMR (δ = 77.0). Mass spectra were recorded on an API III Plus Sciex spectrometer, or an Applied Biosystems 3200 Qtrap both equipped with an ESI source. Allyl(trimethyl)silane, allyl acetate, hex-1-ene, 4-bromobut-1-ene, 5-nitropent-1-ene and catalysts 1a.b were used as received (Aldrich). Acrylonitrile was distilled prior use. 2a–d and 2g were obtained by standard allylation methodology from the corresponding activated ketones and allyl bromide (2h.e–g: K₂CO₃, acetone; 2a: LiOH, THF; 2d: NaH, DMF), and 2h was obtained by transesterification of the corresponding ethyl ester (Aldrich) with but-3-en-1-ol (DMAP, toluene).

**Thermal Solvent-Free CM Reactions to Give 4a–c,e,g; General Procedure**

Neat 2a–c.e.g (1.0 mmol), the appropriate alkene 3a,b (3.0 mmol) and the required amount of catalyst 1a (see Table 1) were placed in a small sealed tubular reaction vessel (7 mL) equipped with a Teflon coated stirrer bar under an argon atmosphere. The reaction vessel was placed in a preheated oil bath at the required temperature for the desired time (see Table 1). The excess of alkene 3a,b was evaporated under reduced pressure and the residue was purified by flash chromatography to afford pure 4a–c.e.g.
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Thermal CM Reactions with Solvent to Give 4d,h,i; General Procedure
A 0.1 M soln of 2d or 2g,h (0.15 mmol), the appropriate alkene 3a (0.45 mmol) or 3c,d (0.30 mmol), Ti(OiPr)$_4$ (0.023 mmol) in the case of entry 5, and the required amount of catalyst 1a,b (see Table 1; for entries 11–14, the catalyst was added in two portions: 3 mol% at the start, and 1 mol% after 20 min) were placed in a small sealed tubular reaction vessel (7 mL) equipped with a Teflon coated stirrer bar under an argon atmosphere. The reaction vessel was placed in a preheated oil bath at the required temperature for the desired time (see Table 1). The solvent and the excess of alkene 3a or 3c,d were evaporated under reduced pressure and the residue was purified by flash chromatography to afford pure 4d,h,i.

Microwave-Assisted CM Reactions to Give 4a–i; General Procedure
Microwave irradiations were performed in a CEM Discover 1-300W oven in sealed tubes (10 mL) equipped with a Teflon-coated stirrer bar under argon at the temperature and times shown in Table 1 (mode discover standard). The mixtures were prepared as described above, except in the cases of entries 1 and 2 where 1,4-dioxane (4b) or 1,4-benzoquinone (0.1 mmol, 10 mol%) was added. The products were purified as described above.

N,N-Diethyl-2-oxo-1-[4-(trimethylsilyl)but-2-yl]cyclopen
tanecarboxamide (4a)
Colorless oil; ratio E/Z 3:1.

1H NMR (mixture of isomers): $\delta = -0.03/-0.01$ (s/s, 9 H), 1.08 (t, $J = 7.1$ Hz, 6 H), 1.40 (d, $J = 8.0$ Hz, 1 H), 1.44 (d, $J = 9.2$ Hz, 1 H), 1.56–2.06 (m, 3 H), 2.06–2.70 (m, 5 H), 3.14–3.55 (m, 4 H), 5.05–5.25 (m, 1 H), 5.33–5.56 (m, 1 H).

13C NMR (mixture of isomers): 121.5 (CH), 128.4 (CH), 168.5 (C), 215.5 (C).

2-(Phenylsulfonyl)-2-[4-(trimethylsilyl)but-2-yl]cyclohexa
anone (4b)
Colorless oil; ratio E/Z 1:1.

1H NMR (mixture of isomers): $\delta = -0.07$ (s, 9 H), 1.20–1.45 (m, 2 H), 1.50–1.84 (m, 2 H), 1.85–2.84 (m, 7 H), 3.01 (ddm, $J = 6.2, 2.4$ Hz, 1 H), 4.76–5.00 (m, 1 H), 5.25–5.62 (m, 1 H), 7.42–7.75 (m, 5 H).

13C NMR (mixture of isomers): 123.1 (CH), 130.7 (CH), 168.6 (C), 215.8 (C).

Ethyl 1-(Hept-2-enyl)-2-oxocyclopentanecarboxylate (4c)
Light brown oil; ratio E/Z 1:1.

1H NMR (mixture of isomers): $\delta = 0.00/0.01$ (s/s, 9 H), 1.44 (d, $J = 8.2$ Hz, 1 H), 1.49 (q, $J = 7.7$ Hz, 0.7 H), 2.49–2.62 (m, 2 H), 3.35 (t, $J = 7.2$ Hz, 2 H), 5.16–5.32 (m, 1 H), 5.46–5.62 (m, 1 H).

13C NMR (E-isomer): $\delta = -1.9$ (CH$_3$), 23.0 (CH$_2$), 33.6 (CH$_2$), 74.9 (CH$_2$), 124.9 (CH), 130.3 (CH).

13C NMR (Z-isomer): $\delta = -1.7$ (CH$_3$), 19.0 (CH$_3$), 32.7 (CH$_3$), 123.6 (CH), 129.0 (CH).


(5-Bromopent-2-enyl)trimethylsilane (4e)
Colorless oil; ratio E/Z 1:1.

1H NMR (mixture of isomers): $\delta = 0.02/-0.01$ (s/s, 9 H), 1.40–1.47 (m, 2 H), 2.00–2.12 (m, 4 H), 4.32–4.42 (m, 2 H), 5.05–5.25 (m, 1 H), 5.36–5.54 (m, 1 H).

13C NMR (E-isomer): $\delta = -1.9$ (CH$_3$), 22.9 (CH$_2$), 27.6 (CH$_2$), 29.4 (CH$_3$), 74.9 (CH$_3$), 125.5 (CH), 129.3 (CH).

13C NMR (Z-isomer): $\delta = -1.7$ (CH$_3$), 18.7 (CH$_3$), 23.7 (CH$_3$), 27.4 (CH$_2$), 75.1 (CH$_2$), 124.2 (CH), 128.3 (CH).

Ethyl 1-[(Hept-2-enyl)-2-oxy]cyclopentanecarboxylate (4g)
Colorless oil; ratio E/Z 1:1.

1H NMR (E-isomer): $\delta = 0.80–0.90$ (m, 2 H), 1.22 (t, $J = 7.2$ Hz, 3 H), 1.25–1.35 (m, 3 H), 1.78–2.09 (m, 6 H), 2.10–2.48 (m, 5 H), 2.56 (ddd, $J = 1.0, 7.2, 13.8$ Hz, 1 H), 4.12 (q, $J = 7.2$ Hz, 2 H), 5.24 (tt, $J = 1.0, 7.2, 15.4$ Hz, 1 H), 5.47 (ttd, $J = 1.0, 6.7, 15.4$ Hz, 1 H).

13C NMR (E-isomer): $\delta = 13.9$ (CH$_3$), 14.1 (CH$_2$), 19.5 (CH$_2$), 22.2 (CH$_2$), 31.5 (CH$_2$), 32.0 (CH$_2$), 32.3 (CH$_2$), 36.7 (CH$_2$), 38.2 (CH$_2$), 60.3 (CH), 61.4 (CH$_2$), 124.1 (CH$_2$), 135.1 (CH$_2$), 171.1 (CH), 214.8 (CH$_2$).


Ethyl 1-(4-Acetoxybut-2-enyl)-2-oxy]cyclopentanecarboxylate (4h)
Colorless oil; ratio E/Z 1:5.7.

1H NMR (Z-isomer): $\delta = 1.22$ (t, $J = 7.2$ Hz, 3 H), 1.82–1.98 (m, 3 H), 2.02 (s, 3 H), 2.20–2.32 (m, 1 H), 2.32–2.48 (m, 3 H), 2.59–2.69 (m, 1 H), 4.13 (q, $J = 7.2$ Hz, 2 H), 4.47 (d, $J = 4.6$ Hz, 2 H), 5.63 (m, 2 H).
13C NMR (Z-isomer): δ = 14.2 (CH3), 19.6 (CH3), 21.0 (CH3), 32.3 (CH3), 36.3 (CH3), 38.1 (CH3), 59.9 (C), 61.6 (CH3), 64.7 (CH3), 128.6 (CH), 130.0 (CH), 170.8 (C), 170.9 (C), 214.5 (C).


4-Cyanobut-3-enyl 2-Oxocyclopentanecarboxylate (4i)

Colorless oil; ratio E/Z = 1:2.4.

1H NMR (mixture of isomers): δ = 1.78–1.91 (m, 1 H), 2.04–2.18 (m, 1 H), 2.20–2.33 (m, 4 H), 2.55 (pseudo q, J = 6.4 Hz, 1.4 H), 2.74 (pseudo q, J = 6.4 Hz, 0.6 H), 3.12 (dd, J = 9.2, 0.9 Hz, 0.7 H), 3.13 (dd, J = 9.5, 9.0 Hz, 0.3 H), 4.08–4.30 (m, 2 H), 5.43 (dd, J = 10.8, 1.3 Hz, 0.7 H), 5.44 (dd, J = 16.4, 1.5 Hz, 0.3 H), 6.68 (dd, J = 16.4, 7.1, 6.9 Hz, 0.7 H), 6.52 (ddd, J = 14.2, 7.1, 6.9 Hz, 1.4 H), 6.11 (ddd, J = 10.8, 7.7, 7.4 Hz, 0.3 H).

13C NMR (Z-isomer): δ = 20.8 (CH2), 27.1 (CH3), 31.1 (CH3), 37.9 (CH3), 54.6 (CH2), 62.4 (CH2), 102.0 (CH), 115.4 (C), 149.9 (CH), 169.0 (C), 212.0 (C).

13C NMR (E-isomer): δ = 20.7 (CH2), 27.0 (CH3), 32.4 (CH3), 37.8 (CH3), 54.5 (CH2), 62.2 (CH2), 102.3 (CH2), 116.8 (C), 150.7 (CH), 169.0 (C), 211.8 (C).


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References


(6) As CM is a reversible process, the TON (turnover number) represents the average number of substrate molecules converted into the cross product per molecule of catalyst. A typical loading of 1.0 in CM reaction is 2–10%, which corresponds to a maximum TON of 10–50. For a recent TON study in ruthenium carbene catalyzed ring-closing metathesis, see: Maechling, S.; Zaja, M.; Blechert, S. Adv. Synth. Catal. 2005, 347, 1413.