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Microwave-accelerated cross-metathesis reactions of *N*-allyl amino acid substrates

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Abstract—Microwave heating has been utilised for the cross-metathesis reaction of *N*-allyl amino acid substrates to generate olefin homodimers. Remarkable acceleration of the cross-metathesis reaction (minutes compared to hours) over conventional reflux heating was observed. In addition, improved reaction yields and similar *E*/*Z* ratios for the cross-metathesis products were achieved.

Olefin metathesis using the carbene ruthenium catalysts developed by Grubbs is well studied in conventional organic chemistry, where reactions are most likely directed towards high yields and selective products (Fig. 1).[1] The cross-metathesis (CM) variant of the olefin metathesis reaction in general exhibits unpredictability in both these respects and consequently has much less representation in the organic synthesis literature when compared to the ring-opening metathesis polymerisation (ROMP) and ring-closing metathesis (RCM) variants. A general model of the selectivity of the CM reaction has recently been described by Grubbs and co-workers.[2] The model was derived from the propensity of olefin homodimers, rather than the terminal olefins themselves, to undergo CM, with the underlying premise to circumvent many of the complexities of a system in which both primary (from the terminal olefin counterpart) and secondary (from the olefin dimer) metathesis pathways participate and compete.

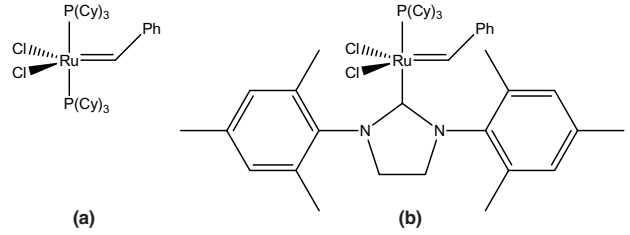
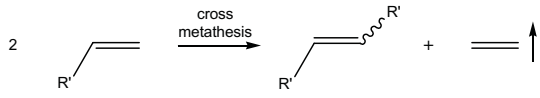


Figure 1. Grubbs first-generation catalyst (a) and Grubbs second-generation catalyst (b).

As part of our ongoing investigation into the development of newly modified amino acid building blocks for application of the metathesis reaction to dynamic combinatorial chemistry (DCC), we needed to synthesise amino acid building blocks containing a terminal olefin. *N*-Allyl amino acid precursors were chosen and synthesised; however, to simplify the complexity of the DCC system, it was decided to prepare the corresponding olefin homodimers for building blocks by CM, Scheme 1. We investigated both the Grubbs first- and second-generation catalysts. This manuscript reports the results with a number of our building blocks.

The synthesis of the *N*-allyl substituted amino acid precursors **2a**–**c** from commercially available amino acid methyl esters is outlined in Scheme 2.[3] The synthesis utilises the 2-nitrobenzene sulfonamide (*o*NBS) group for the concomitant protection and activation of the amino acid nitrogen. The electron withdrawing nature of the *o*NBS group increases the acidity of the amino acid N*H* proton improving the susceptibility for substitution



Scheme 1. CM reaction for the preparation of olefin homodimers.

Keywords: Olefin; Cross-metathesis; Microwave; Amino acids; *N*-Allylation.
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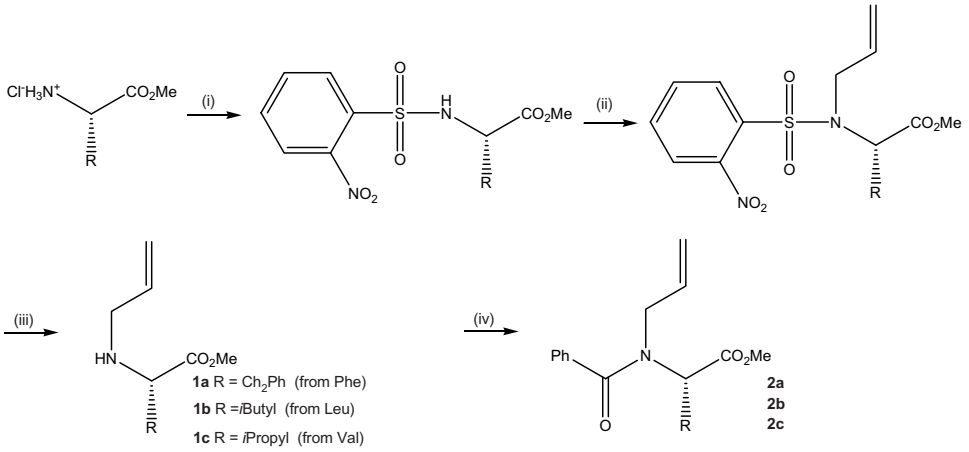


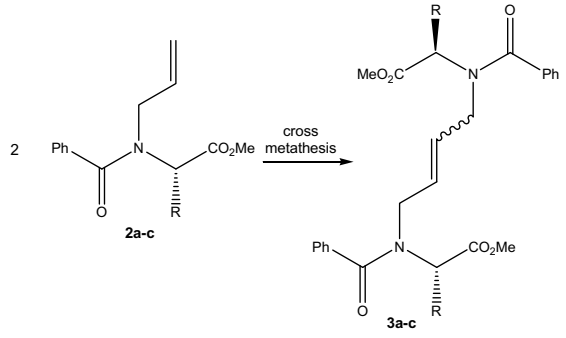
Scheme 2. General synthesis of *N*-allyl substituted amino acid precursors **2a**–**c**: (i) *o*NBSCl, Et_3N, CH_2Cl_2, rt, 16 h, 80–97%; (ii) K_2CO_3, DMF, allyl bromide, rt, 16 h, 83–85%; (iii) PhS^-Na^+, K_2CO_3 or LiOH, mercaptoacetic acid; DMF, rt, 2–3 h, 57–94%; (iv) BzCl, Et_3N, CH_2Cl_2, rt, 2 h, 65–72%.

with allyl bromide. Following allylation, the *o*NBS group is removed by either phenyl thiolate or mercaptoacetic acid. Finally, amide formation with benzoyl chloride generates the olefin precursors **2a**–**c**.[4]

With the three precursors **2a**–**c** in hand, the CM reaction for the preparation of the corresponding olefin homodimer building blocks **3a**–**c** was investigated, Scheme 3.[5] Initial studies with Grubbs first-generation catalyst failed to generate any CM product, even with varying reaction times either at room temperature or at elevated temperatures: refluxing CH_2Cl_2 (40 °C) or refluxing 1,2-dichloroethane (1,2-DCE) (80 °C). Analogues of α-allyl amino acid methyl esters (allylglycines) have undergone CM at room temperature with Grubbs first-generation catalyst,[6] so our results demonstrate the severely reduced efficiency of participation of *N*-allyl amino acid substrates in the CM reaction.

Grubbs second-generation catalyst is reported to have higher activity in the CM reaction[7] and an investigation with substrates **2a**–**c** was undertaken (Table 1). The second-generation catalyst was also not sufficient for CM of our substrates at room temperature (Table 1 entries 1, 2, 6 and 9). The use of refluxing 1,2-DCE for an extended period (18–72 h) was required to facilitate the thermal reaction, albeit with moderate yields (Table 1, entries 3, 4, 7 and 10).

In an attempt to increase the CM yield and shorten the reaction time, microwave (MW) irradiation, in place of conventional heating, was investigated. Thermally driven organic transformations can take place by conventional heating or MW-accelerated heating. MW irradiation, using either a domestic microwave oven or mono-mode reactors, has become a powerful tool for the preparation of organic compounds.[8] The premise for this investigation was the reported success of MW irradiation in the promotion of the RCM variant of the olefin metathesis reaction.[9] In RCM applications, MW irradiation has demonstrated improved yields, substantially reduced reaction times, and reduced thermal degradation of the ruthenium catalyst. It is believed that these improvements arise from the more effective and efficient heating compared to conventional thermal reactions. We could find only one reported example where MW irradiation has been applied to promote the CM variant of the metathesis reaction (in a RCM–CM domino reaction).[10] CM is, therefore, unexplored with respect to the application of MW irradiation and so presented itself as an ideal candidate reaction for the investigation of the effects of MW irradiation on reaction time and product yield. Herein, we report a systematic analysis of the effect of MW heating on the CM reaction on olefin substrates **2a**–**c**.[†]



Scheme 3. Synthesis of olefin homodimers **3a**–**c** from precursors **2a**–**c** by CM.

[†] In the CEM Discover microwave system used in this study, a circular single-mode cavity directs the microwave energy into a defined area, resulting in a homogenous field pattern surrounding the sample and an instantaneous coupling to all polar and ionic components in the sample, leading to a rapid rise in temperature. This microwave can accommodate a single 10 mL 25 bar pressure rated sealed reaction vial. The system incorporates both temperature and pressure feedback systems for control of the reaction conditions. The temperature feedback system uses an infrared temperature sensor positioned below the reaction vessel to permit reproducible temperature control. The reactions were quenched following heating by forced gas cooling with nitrogen gas.

Table 1. CM of *N*-allyl amino acids **2a–c** with Grubbs second-generation catalyst

Entry	CM Substrate	Heating conditions	Temperature (°C)	Catalyst (mol %)	Time	Yield[a] (%)	*E*/*Z* Ratio[b]
1	**2a**	None	24	7.5	18 h	0	
2		None	24	7.5	72 h	0	
3		Reflux	80	7.5	18 h	29	2.3/1
4		Reflux	80	7.5	72 h	34	2.3/1
5		MW	100	5	10 min	48	2.7/1
6	**2b**	None	24	15	18 h	0	
7		Reflux	80	15	72 h	32	3.0/1
8		MW	100	20	10 min	54	2.1/1
9	**2c**	None	24	15	18 h	0	
10		Reflux	80	15	72 h	27	4.3/1
11		MW	100	20	10 min	40	4.8/1

[a] Yield calculated following reaction workup and purification by chromatography.
[b] ^{1}H NMR spectroscopy was used to determine *E*/*Z* ratio.

We first investigated the effect of MW heating in the application of CM to the synthesis of the olefin homodimer building block **3a** in the presence of Grubbs first-generation catalyst. Our procedure used 1,2-DCE as solvent with MW irradiation at 100 °C for 10 min.[11] No CM product was produced. We then turned our attention to Grubbs second-generation catalyst. The yields obtained with 10 min of MW irradiation at 100 °C are given in Table 1, entries 5, 8 and 11. An improvement in yield of the CM homodimer products compared to conventional reflux (Table 1, entries 3, 4, 7 and 10) was observed for each substrate, this improvement was in the order of 40–60%. Higher MW reaction temperatures (120 and 150 °C) were also studied, but gave no further improvement in yield.

This is the first report of MW irradiation applied solely to the CM variant of the metathesis reaction. Specifically, we have demonstrated the application of MW irradiation to CM of *N*-allyl amino acid substrates to generate olefin homodimers. The CM reaction with these allylic amine substrates was not viable with either the Grubbs first- or second-generation catalysts at room temperature and only moderately viable with Grubbs second-generation catalyst after lengthy reaction times at elevated temperatures. With MW irradiation, an impressive acceleration of reaction time (10 min compared to 72 h) and increase in overall yield were observed when compared to conventional reflux. The synthesis is both practical and efficient for each substrate. This preliminary study demonstrates that MW irradiation has potential as one of the easiest and most efficient routes for the preparation of olefin homodimers using CM. A larger investigation of the CM reactions using microwave irradiation is underway.

Acknowledgements

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4. *General synthesis of N-allyl substituted amino acid precursors* ***2a–c***: Typical procedures for the synthesis of *N*-allylamino acid methyl esters to generate H–(*N*all)aa–OMe **1a–c** can be found in Ref. 3. Compound **1a** (250 mg, 1.1 mmol), benzoyl chloride (0.26 mL, 2.2 mmol) and triethylamine (0.32 mL, 2.2 mmol) were stirred in anhydrous CH_2Cl_2 (5 mL) at room temperature for 2 h. The reaction mixture was diluted with CH_2Cl_2 (5 mL) and washed with citric acid (50% solution in water, 10 mL) and brine (10 mL). The organic fraction was dried over anhydrous $MgSO_4$, filtered and the volatiles were removed. The remaining residue was purified by solid phase extraction on normal phase silica sorbent, eluted with hexane/EtOAc (3:1, v/v) to generate **2a** in 71% yield. ^{1}H NMR (400 MHz, toluene-d_8, 90 °C, ppm): δ 2.86 (d, 2H, $J = 6.6$ Hz, βCH_2), 3.38 (s, 3H, OCH_3), 3.89–4.06 (m, 2H, AllCH_2), 4.45–4.48 (t, 1H, $J = 6.4$ Hz, αCH), 4.91–5.06 (m, 2H, $=CH_2$), 5.79–5.88 (m, 1H, =CH), 6.97–6.99 (m, 4H, ArH), 7.04–7.07 (m, 5H, ArH), 7.34–7.37 (m, 1H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 37.2 (βCH_2), 48.4 (AllCH_2), 51.6 (αCH), 59.8 (OCH_3), 118.6 ($=CH_2$), 123.9, 128.6, 129.8, 132.4, 134.2 and 136.4 (ArCH, =CH), 172.3 (CO); ESI MS: *m*/*z* 324.5 $[M+H]^+$, 346.6 $[M+Na]^+$; HRMS (ESI) 324.1595. Calcd for $C_{20}H_{21}N_1O_3{\cdot}H^+$: 324.1594. Synthesis of **2b** and **2c** proceeded similarly. Compound **2b**: Yield 65%; ^{1}H NMR (400 MHz, toluene-d_8, 90 °C, ppm): δ 0.89 (d, 6H, $J = 6.1$ Hz, δCH_3, $\delta' CH_3$), 1.60–1.74 (m, 2H, βCH_2), 1.89–1.96 (m, 1H, γCH), 3.39 (s, 3H, OCH_3), 3.81–3.97 (m, 2H, AllCH_2), 4.63 (t, 1H, $J = 7.0$ Hz, αCH), 4.89–4.92 (dd, 1H, $=CH_2$), 4.93–4.98 (d, 1H, $=CH_2$), 5.80–5.87 (d, 1H, =CH), 6.67–6.99 (m, 2H, ArH), 7.04–7.07 (m, 2H, ArH), 7.35–7.37 (m, 1H, ArH); ^{13}C NMR (50 MHz, $CDCl_3$, ppm): δ 20.2 and 21.9 (δCH_3, $\delta' CH_3$), 24.7 (γCH), 40.6 (βCH_2), 49.0 (AllCH_2), 52.6 (αCH), 57.4 (OCH_3), 115.8 ($=CH_2$), 126.9, 128.6, 129.3, 129.7 and 134.5 (ArCH, =CH), 172.6 (CO); ESI

MS: m/z 290.3 $[M+H]^+$, 312.5 $[M+Na]^+$; HRMS (ESI) 290.1779. Calcd for $C_{17}H_{23}N_1O_3{\cdot}H^+$: 290.1750. Compound **2c**: Yield 72%; ^{1}H NMR (400 MHz, toluene-d_8, 90 °C, ppm): δ 0.86 (d, 3H, $J = 6.6$ Hz, γCH_3), 0.88 (d, 3H, $J = 6.8$ Hz, $\gamma' CH_3$), 2.32–2.42 (m, 1H, βCH), 3.41 (s, 3H, OCH_3), 3.81–3.88 (m, 1H, $AllCH_2$), 4.08–4.16 (m, 1H, $AllCH_2$), 4.30–4.34 (d, 1H, $J = 7.0$ Hz, αCH), 4.94–5.02 (m, 2H, $=CH_2$), 5.81–5.92 (m, 1H, =CH), 7.08–7.12 (m, 3H, ArH), 7.38–7.42 (m, 2H, ArH); ^{13}C NMR (50 MHz, $CDCl_3$, ppm): δ 19.3, 20.2 (γCH_3, $\gamma' CH_3$), 28.2 (βCH), 51.7 ($AllCH_2$), 52.6 (αCH), 57.4 (OCH_3), 115.9 ($=CH_2$), 127.3, 128.6, 129.1, 129.8, 130.8 and 136.5 (ArCH and =CH), 172.6 (CO); ESI MS: m/z 276.3 $[M+H]^+$, 298.5 $[M+Na]^+$; HRMS (ESI) 276.1602. Calcd for $C_{16}H_{21}N_1O_3{\cdot}H^+$: 276.1594.

5. *General experimental procedure for CM using conventional reflux heating*: To a stirred solution of **2c** (58 mg, 0.21 mmol) in 1,2-DCE (0.8 mL) was added Grubbs second-generation catalyst (26 mg, 15 mol %). The reaction mixture was refluxed at 80 °C for 72 h. Removal of the solvent afforded a black oil. This crude material was purified by solid phase extraction on normal phase silica sorbent, eluted with hexane/EtOAc (3:1, v/v) to generate **3c** as a yellow syrup in 27% yield. The E/Z ratio was determined by integration of ^{1}H NMR peaks at 5.46 and 5.59 ppm. ^{1}H NMR (400 MHz, toluene-d_8, 90 °C, ppm): δ 0.77 (d, 12H, $J = 6.8$ Hz, γCH_3, $\gamma' CH_3$), 2.22–2.27 (m, 2H, βCH), 3.45 (s, 6H, OCH_3), 3.73–3.78 (m, 2H, $AllCH_2$), 3.92–4.02 (m, 2H, $AllCH_2$), 4.16–4.18 (d, 2H, $J = 9.2$ Hz, αCH), 5.59 (br s, 2H, =CH), 6.90–6.92 (m, 4H, ArH), 6.99–7.03 (m, 4H, ArH), 7.35–7.37 (m, 2H, ArH); ^{13}C NMR (50 MHz, $CDCl_3$, ppm): δ 19.1, 19.9 (γCH_3, $\gamma' CH_3$), 27.8 (βCH), 52.6 ($AllCH_2$), 52.9 (αCH), 57.2 (OCH_3), 128.2, 129.0, 130.0, 130.7 and 135.5 (ArCH and =CH), 173.9 (CO); ESI MS: m/z 523.7 $[M+H]^+$, 545.6 $[M+Na]^+$; HRMS (ESI) 545.2623. Calcd for $C_{30}H_{38}N_2O_6Na^+$: 545.2622. Synthesis of **3a** and **3b** proceeded similarly. Compound **3a**: Yield 34%; the E/Z ratio was determined by integration of ^{1}H NMR peaks at 5.76 and 5.92 ppm; ^{1}H NMR (400 MHz, toluene-d_8, 90 °C, ppm): δ 2.93 (d, 4H, $J = 6.6$ Hz, βCH_2), 3.42 (s, 6H, OCH_3), 4.18–4.22 (m, 4H, $AllCH_2$), 4.29–4.33 (t, 2H, $J = 7.0$ Hz, αCH), 5.83–6.01 (m, 2H, =CH), 6.90–7.02 (m, 18H, ArH), 7.14–7.16 (m, 2H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 36.4 (βCH_2), 48.8 ($AllCH_2$), 52.3 (αCH), 59.9 (OCH_3), 124.2, 127.9, 128.3, 131.4, 133.7 and 135.9 (ArCH and =CH), 171.8 (CO); ESI MS: m/z 619.7 $[M+H]^+$, 641.5 $[M+Na]^+$; HRMS (ESI) 619.2802. Calcd for $C_{30}H_{38}N_2O_6{\cdot}H^+$: 619.2809. Compound **3b**: Yield 32%; the E/Z ratio was determined by integration of ^{1}H NMR peaks at 3.35 and 3.43 ppm; ^{1}H NMR (400 MHz, toluene-d_8, 90 °C, ppm): δ 0.93 (d, 12H, $J = 6.4$ Hz, δCH_3, $\delta' CH_3$), 1.58–1.76 (m, 4H, βCH_2), 1.92–1.97 (m, 2H, γCH), 3.43 (s, 6H, OCH_3), 3.82–3.99 (m, 4H, $AllCH_2$), 4.65 (t, 2H, $J = 7.2$ Hz, αCH), 5.69–5.72 (d, 2H, =CH), 6.85–6.90 (m, 4H, ArH), 7.01–7.06 (m, 4H, ArH), 7.38–7.41 (m, 2H, ArH); ^{13}C NMR (50 MHz, $CDCl_3$, ppm): δ 22.4, 22.9 (δCH_3, $\delta' CH_3$), 25.6 (γCH), 39.6 (βCH_2), 51.7 ($AllCH_2$), 51.9 (αCH), 58.1 (OCH_3), 127.1, 127.5, 127.7, 128.9 and 132.7 (ArCH and =CH), 171.9 (CO); ESI MS: m/z 551.5 $[M+H]^+$, 573.3 $[M+Na]^+$; HRMS (ESI) 551.3109. Calcd for $C_{32}H_{42}N_2O_6{\cdot}H^+$: 551.3115.
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11. *General experimental procedure for microwave accelerated CM*: All reactions were carried out in a pressure tube, sealed with a Teflon septum. Reactions contained the *N*-allyl amino acid substrate **2a–c** (0.1–0.2 mmol) and Grubbs second-generation catalyst (5–20%) in 1,2-DCE (0.8 mL). The pressure tube was introduced to the centre of a CEM Discover microwave oven and then heated to 100 °C for 10 min. On completion of the heating cycle, the reaction mixture was purified and characterised in a manner identical to that described in Ref. 5. Yields: **3a** 48%, **3b** 54%, **3c** 40%.