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Rapid synthesis of cyclobutene diesters using a microwave-accelerated ruthenium-catalysed [2+2] cycloaddition

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ABSTRACT

A range of cyclobutene diesters was synthesised using a ruthenium-catalysed, microwave-assisted, [2+2] cycloaddition. Excellent yields of the desired products were realised using reaction times of only 2 min.

The photochemical [2+2] cycloaddition of two alkenes to form cyclobutanes is well known,[1] however, the corresponding reaction of alkynes with alkenes to form cyclobutenes is less common.[2] Nevertheless, a number of approaches for the construction of cyclobutenes have been developed including thermal processes[3] (requiring a reactive alkene), Lewis acid-activated methods,[4] Wittig reactions[5] and metal-catalysed transformations.[6,7] In the context of transition metal-catalysed reactions, Mitsudo et al. identified ruthenium complexes such as $[RuH_2(PPh_3)_4]$, $[RuH_2(CO)(PPh_3)_3]$, [Ru(cod)(cot)] and $[RuCp^*Cl(cod)]$ as efficient catalysts for the [2+2] cycloaddition of norbornenes with acetylenes.[8] The scope of these reactions has been further investigated by Tam.[9]

The $[RuH_2(CO)(PPh_3)_3]$-catalysed [2+2] reaction of functionalised norbornenes with acetylenes (in particular dimethyl acetylenedicarboxylate, DMAD (**1**), Scheme 1) has been widely used in the synthesis of fused [*n*]polynorbornanes[10] (e.g., **5**, Scheme 1), in which a two-step process involving cyclobutene diester formation then epoxidation is employed to generate cyclobutane epoxides (e.g., **4**, Scheme 1) to use in ACE (alkene + cyclobutane epoxide) 1,3-dipolar cycloaddition.[11] The resulting functionalised [*n*]polynorbornanes have been used in the study of electron transfer processes,[12] as DNA intercalators,[13] and as supramolecular hosts for anions.[14,15]

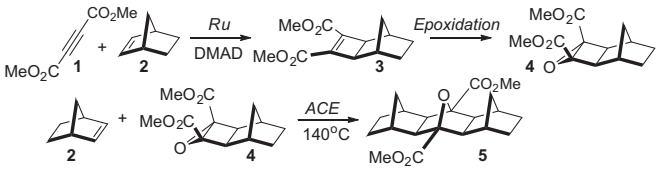
Due to our interest in conformationally preorganised frameworks, norbornanes and [*n*]polynorbornanes have been extensively used.[16] As such, the $[RuH_2(CO)(PPh_3)_3]$-catalysed reaction is routinely employed, and in our hands, when carried out using conventional heating, reaction times from 6 to 72 h are required to obtain good yields (50–83%) of the desired functionalised cyclobutene diesters.[13–15]

Microwave irradiation has been used as a means of accelerating many reactions[17] including cycloadditions[18] and those involving metal catalysts.[19] Whilst examples of microwave-accelerated reactions involving Ru catalysts to form [2+2] adducts exist, they are rare and typically involve intramolecular reaction of highly reactive alkenes such as allenes.[20] Indeed, the microwave-mediated Ru-catalysed intermolecular [2+2] reaction of norbornenes with acetylenes has hitherto not been explored. Herein we report that microwave irradiation markedly accelerates the reaction and the desired cyclobutenes are produced in high isolated yields.

The reaction chosen for initial investigation was taken directly from previous work where preorganised frameworks were synthesised as hosts for anions.[14] The research required the $[RuH_2(CO)(PPh_3)_3]$-catalysed reaction of *endo* norborneneimide **6** with DMAD (Scheme 2).[14]

To provide a benchmark for comparison the reaction was carried out under conventional thermal conditions (60 °C) using THF as solvent and a catalyst loading of 10 mol % (Table 1, entry 1). Using these conditions the desired cycloadduct **7** was produced in moderate isolated yield (53%) after an extended reaction time of 72 h. This reaction was repeated in DMF for 16 h at 100 °C and excellent conversion (89%) and a high isolated yield (87%) of the desired product were realised (Table 1, entry 2). As such, the reaction was repeated for one hour in DMF (Table 1, entry 3) and again a high conversion rate and isolated yield were noted (88% and 84%, respectively).

In light of these improved results with a simple solvent change, our attention turned to further accelerating this reaction in a microwave reactor. Initially, 20 min reaction times were employed and a range of common solvents investigated for their effect on



Scheme 1. Sequence of Ru-catalysed [2+2] cycloaddition, epoxidation and ACE cycloaddition to form a fused [*n*]polynorbornane.

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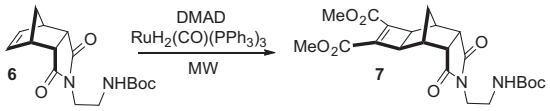


Scheme 2. [2+2] cycloaddition optimisation.

Table 1
Optimisation of temperature, time and solvent[21]

Entry	Time (min)	Temp (°C)	Solvent[a]	Conversion[b] (yield)
1[c]	72 h	60	THF	60% (53%)
2[c]	16 h	100	DMF	89% (87%)
3[c]	60	100	DMF	88% (84%)
4	20	90	THF	25%
5	20	90	Toluene	25%
6	20	90	1,4-Dioxane	22%
7	20	100	Acetone	86%
8	20	100	EtOH	54%
9	40	140	THF	78%
10	20	160	DMF	87% (84%)
11	20	150	MeCN	8%
12	20	150	1,4-Dioxane	32%

[a] Solvent and DMAD used in a 5:1 ratio (v/v).
[b] Isolated yield following column chromatography.
[c] Carried out using conventional thermal conditions.

Table 2
Optimisation of catalyst loading and reaction time

Entry	Catalyst loading (mol %)	Time[a] (min)	Temp (°C)	Conversion[b] (yield)
1	5	20	160	24%
2	5	40	160	26%
3	10	10	160	81% (70%)
4	10	5	160	84% (75%)
5	10	2	160	86% (73%)
6	10	1	160	87% (77%)
7	10	0[a]	160	87% (79%)
8	10	2	100	94% (93%)
9	10	2	70	45%
10[c]	10	2	100	18%

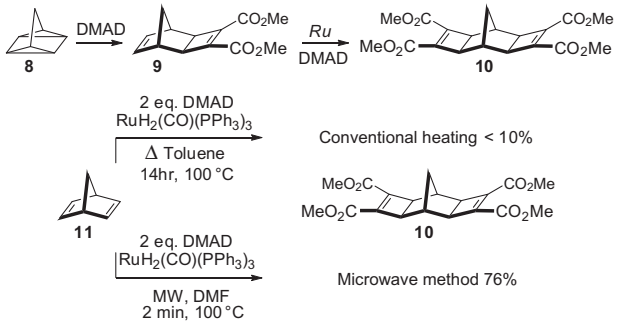
[a] This value refers to the duration of time that the reaction was held at the specified temperature; this does not include the time taken to heat the vessel (cf. 2 min).
[b] Isolated yield following column chromatography.
[c] Reaction carried out in acetone.

reaction outcome. Poor to moderate conversion into the desired product was observed when THF, toluene or 1,4-dioxane (Table 1, entries 4, 5 and 6) were used as the reaction solvent. Finally, acetone and ethanol (Table 1, entries 7 and 8) were trialled with good and moderate conversion was noted (86% and 54%, respectively).

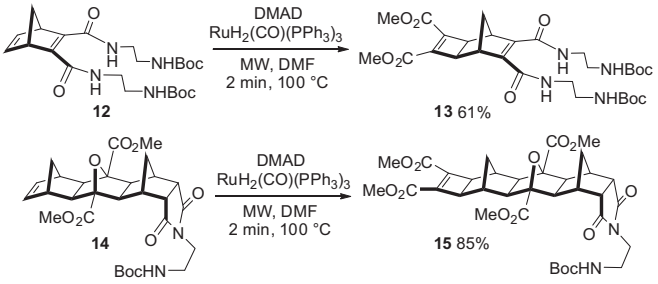
Higher reaction temperatures (140–160 °C) were next investigated and excellent conversion was observed when THF (Table 1, entry 9) was used as the solvent, however, an extended reaction time (40 min) in the microwave reactor was required in addition to the elevated reaction temperature. Dimethylformamide proved to be a superior solvent for a 20 min reaction duration giving excellent conversion (87%) and 84% isolated yield (Table 1, entry 10). The use of 1,4-dioxane or acetonitrile (Table 1, entries 11 and 12) gave poor conversions to the desired product. Therefore, it was apparent that DMF was the optimum solvent for this reaction.

Next, additional optimisation studies were undertaken using microwave irradiation. Variables of interest included: catalyst loading, reaction time and reaction temperature (Table 2).

Repeating the reaction with half the catalyst loading (5 mol %) under the optimised conditions gave only poor conversion to the cyclobutene diester **7** (24%, Table 2, entry 1). Even when the



Scheme 3. Synthesis of dicyclobutene tetraester **10**.



Scheme 4. Synthesis of additional cyclobutene diesters.

reaction time was doubled to compensate for catalyst dilution, poor conversion was noted (26%, Table 2, entry 2). In light of these results a catalyst loading of 10 mol % was used in all further experiments. When the reaction time was halved from 20 min to 10 min (Table 2, entry 3), a conversion (81%) and yield (70%) similar to the reaction carried out for 20 min were obtained (Table 1, entry 10). Reducing the reaction duration even further to 5, 2 and 1 min(s) gave the desired cyclobutene **7** in good yields of 75%, 73% and 77%, respectively (Table 2, entries 4–6). Indeed, the reaction was so rapid that simply heating the reaction to 160 °C, followed by immediate cooling,[22] resulted in an 87% conversion and 79% isolated yield of cyclobutene **7** (Table 2, entry 7).

Given that the reaction reached completion so quickly at 160 °C the reaction temperature was lowered to see the effect on conversion and yield. The use of lower temperatures minimises the potential for thermal degradation during the reaction. As such, the reaction was repeated at 100 °C and again excellent conversion (94%) and yield (93%) were obtained (Table 2, entry 8). Nevertheless, only 45% conversion was realised when the reaction temperature was further reduced to 70 °C (Table 2, entry 9).

As DMF can be troublesome to remove, the reaction was repeated in acetone (Table 2, entry 10) using the milder conditions as this solvent gave encouraging results in the initial investigations (Table 1, entry 7). Unfortunately, very poor conversion was noted (18%) when the reaction duration was reduced to 2 min, thus reinforcing the key role of DMF as solvent for this reaction.

Given the positive results from the optimisation study, the DMAD cycloaddition conditions (DMF, 2 min, 100 °C) were applied to other norbornene substrates.

Dicyclobutene tetraester **10** (Scheme 3) is a necessary building block for the synthesis of larger [*n*]polynorbornanes. Current methodology for the synthesis of **10** involves a two-step approach; first quadricyclane **8** and DMAD are reacted to form the 1:1 cycloadduct **9** then single Ru-catalysed [2+2] reaction of diester **9** with a second equivalent of DMAD provides the desired 1:2 adduct **10**.[23] Whilst theoretically appealing, the twin cycloaddition from norbornadiene **11** has never provided useful yields of the desired bisadduct **10**, and as such, the two-step approach has been required.[24] However, using the microwave method developed herein norbornadi-

ene **11** was smoothly converted into the desired dicyclobutene **10** in 76% yield. The success of the single step process is a significant improvement over the existing methodology.

In additional reactions norbornadiene bis-carbamate **12**[15b] (Scheme 4) was subjected to the optimised reaction conditions to give cyclobutene **13**[15b] in a good isolated yield of 61%. Finally, the new methodology was applied to a pre-existing [3]polynorbornene scaffold[15b] (**14**, Scheme 4), and again the optimised protocol gave the desired cyclobutene product **15**[15b] in an excellent isolated yield (85%).

In conclusion the $[RuH_2(CO)(PPh_3)_3]$-catalysed [2+2] cycloaddition of norbornenes with DMAD[25] can be accelerated significantly when microwave irradiation is employed with DMF as the solvent. High yields can be obtained using only 2 min reaction times. The methodology was successfully applied to a range of norbornene scaffolds indicating that the procedure is tolerant to functional group diversity.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.08.119.

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21. Representative experimental procedure (see Supplementary data for detailed experimental information including ^1H NMR spectra): a solution of norbornene (100 mg, 0.33 mmol), dimethyl acetylenedicarboxylate (DMAD) (0.1 mL, 0.82 mmol, 2.5 equiv), $RuH_2(CO)(PPh_3)_3$ (30 mg, 10 mol %) and 0.5 mL of solvent were added to a 10 mL microwave vial. The vial was sealed and subjected to the conditions stated in Table 1 or 2. After cooling, the solvent was removed under reduced pressure and the conversion rate was determined by analysing a sample of the crude reaction mixture by ^1H NMR spectroscopy. The crude product was purified by column chromatography (1:1 EtOAc/petroleum spirits) to afford the pure product in the yield stated.
22. See Supplementary data for temperature, pressure, and power profiles for this reaction.
23. For the reaction of quadricyclane with DMAD, see: Smith, C. D. *J. Am. Chem. Soc.* **1966**, *88*, 4273–4274. . Yields of the second addition of DMAD to form **10** are typically modest: see Ref. 8d.
24. Mitsudo, in Ref. 8d, reported <10% yield of **10** using the twin addition approach from norbornadiene.
25. The reaction was trialled using diphenylacetylene as the alkyne partner, however, only a trace of the desired product was detected in the crude reaction mixture.