Synthesis of substituted cycloalkene-1,1-dicarboxylates *via* olefin metathesis in water

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Dedicated to Professor Dr. Jürgen Martens on the occasion of his 67th birthday

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Abstract

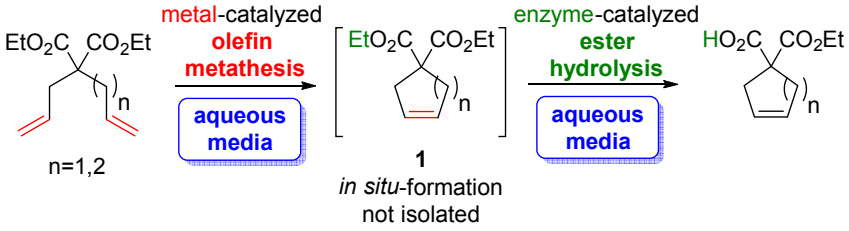
A range of substituted cycloalkene-1,1-dicarboxylates was synthesized through olefin metathesis starting from readily available acylic malonate precursors in an efficient fashion. As a metathesis catalyst, a Grubbs II-type catalyst was used in these experiments, which were run in water and gave the cyclic malonate products with high conversions of 94-100%. The catalytic amount was in the range of 0.5-5 mol% dependent on the structure of the starting material. The generality of this metathesis reaction in water was demonstrated as well as its suitability for the preparation of five and six-membered and alkyl as well as aryl-substituted prochiral cycloalkene-1,1-dicarboxylates.

Keywords: Cycloalkenes; cyclization, malonates; metathesis; reactions in water

Introduction

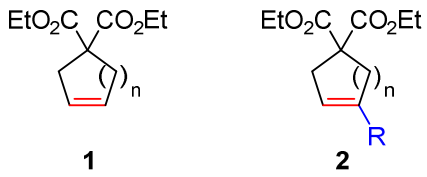
Metathesis reactions in water have gained increasing interest in the last years,[1-15] and provide a range of advantages such as a high potential for the development of sustainable syntheses. Our interest in this field also resulted from the goal to combine metathesis as a metal-catalyzed reaction with enzymatic reactions, which typically require water as *the* solvent of choice, towards one-pot processes running in the same (aqueous) solvent. Initial examples in this field have been recently reported by other and our groups.[14,15] In general, several successful examples of one-pot processes through combination of chemo- and bio-catalytic transformations have been established recently.[14-21] A prerequisite and challenge in this field of chemoenzymatic one-pot processes is to find conditions, which make the chemocatalytic step compatible with the

enzymatic one. Recently, we reported the proof of concept for such an one-pot process combining metathesis and enzymatic hydrolysis reactions exemplified for the synthesis of cycloalkene-1,1-dicarboxylate monoesters starting from readily available bis-substituted malonates (Scheme 1).[14] Notably, water turned out to represent an excellent solvent for the metathesis transformation even though the substrate is poorly soluble in water. The resulting cyclic malonate diesters have then be transformed via a selective hydrolysis by means of a biocatalyst (esterase) into their monoesters.[14] These monoesters are an interesting product class due to their application potential in organic synthesis, for example, in terms of conversion into the corresponding cyclic non-natural α-amino acids bearing a quaternary stereogenic center through amide formation and subsequent Hofmann degradation.[22,23] Thus, cycloalkene-1,1,-dicarboxylates as the intermediates formed in the metathesis step represent versatile organic molecules.



Scheme 1. Chemoenzymatic one-pot synthesis of cyclic malonates with a metathesis reaction as a key step.

However, since our earlier study (reported in a short communication)[14] only covered unsubstituted examples of type **1**, there remained an open question, with respect to the synthesis of cyclic malonates via metathesis in water, whether this method is general in terms of substrate scope, and if so, whether other sterically more complex prochiral substituted cycloalkene-1,1-dicarboxylates of type **2** could be prepared efficiently in a similar fashion.



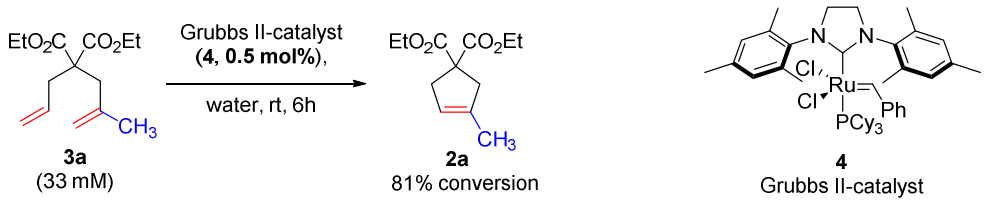
Scheme 2. Unsubstituted and substituted cycloalkene dicarboxylates **1** (previous study, see ref. 14) and **2** (this study), respectively.

In this paper we report our results addressing these issues, demonstrating the generality of this metathesis reaction in water as a suitable solvent by the preparation of a variety of such

sterically more complex prochiral cyclic malonates of type **2**, bearing a substituent at the cycloalkene ring.

Results and Discussion

As a first target molecule we focused on the synthesis of cycloalkene 1,1-dicarboxylate **2a**, with a five-membered ring bearing a methyl substituent as a representative of a small alkyl substituent (Scheme 3). As a substrate we chose the acyclic malonate derivative **3a**,[24] and as a catalyst we used the Grubbs II-catalyst **4** (which has been known to accept this substrate **3a** in non-aqueous medium).[25] Initial reaction conditions were based on the use of water and the choice of a reaction time of 6h (analogously to those reaction conditions when using the non-substituted cyclic malonate of type **1** with n = 1 as reported in our earlier work, see reference 14). We were pleased to find that also with this sterically more hindered substrate **3a** (bearing a bis-substituted carbon atom at the alkene moiety) in the presence of a low catalyst loading of 0.5 mol% of ruthenium complex **4**[25] as a catalyst the metathesis reaction gave a conversion of 81% after a reaction time of 6h when using water as solvent (Scheme 3).



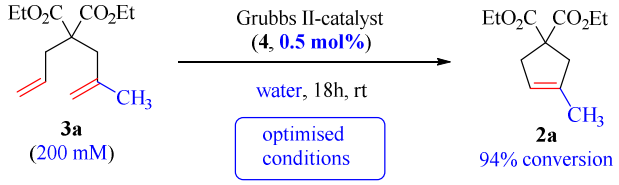
Scheme 3. The initial metathesis reaction of **3a** in water.

Mechanistically, to the best of our knowledge the reason for the beneficial role of water in this type of metathesis reaction is still not clear. As the metathesis catalyst **4** is not water-soluble, currently it appears that the metathesis reaction proceeds in particular "on" water and not "in" water. The high reaction rate of this metathesis "on" water might be due to a solubilization of the catalyst in the organic droplets of poorly water-miscible substrate **3a**, which then leads to a high concentration of the substrate in the phase with the catalyst and a resulting high reaction rate due to kinetic reasons.

However, when comparing this reaction shown in Scheme 3 with the analogous one using the less sterically hindered, non-substituted substrate of type **1** with n = 1 (98% and 100% conversion, see reference 14), it also has to be stated that **3a** is less reactive, which can be attributed to the presence of an additional substituent at the alkene moiety and the resulting steric hindrance in the metathesis step.

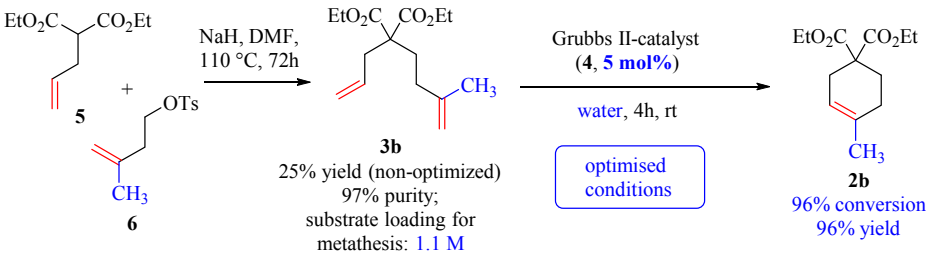
As a next step we focused on the optimization of this metathesis process in water for the synthesis of methyl-substituted cyclic malonate **2a** (Scheme 4). We were pleased to find that the

reaction also proceeds well at an increased substrate input (200 mM instead of 33 mM), thus entering the range of in general technically interesting substrate concentrations. Notably, even when using a low catalyst loading of 0.5 mol% at a reaction time of 18h, the cyclic malonate **2a** was formed with a high conversion of 94% (Scheme 4).



Scheme 4. Optimized metathesis reaction for the synthesis of **2a.**

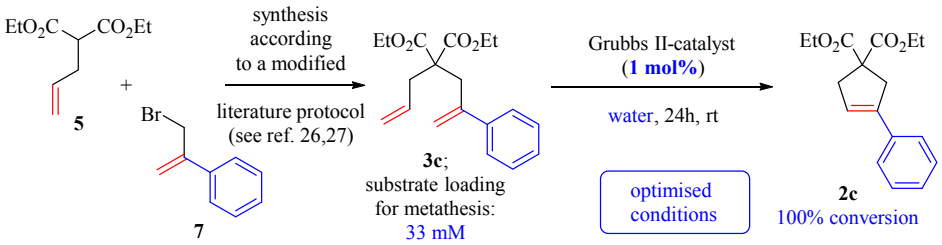
A further interesting prochiral cyclic cycloalkene-1,1-dicarboxylate, challenging for later desymmetrization, is the analogous methyl-substituted six-membered cyclic malonate **2b** (which only is prochiral due to the presence of a double bond in the cyclic system). First, the bis-substituted malonate **3b** as required substrate for the metathesis reaction was synthesized starting from diethyl 2-allylmalonate (**5**) and 3-methylbut-3-en-1-yl tosylate (**6**) in a substitution reaction according to a modified literature[26] protocol (Scheme 5). Subsequent metathesis reaction of **3b** with initially 5 mol% of Grubbs II-catalyst **4** at a substrate concentration of 0.25 M gave the desired metathesis product **2b** with 96% conversion. It was possible to increase the substrate loading even to a high substrate concentration of 1.1 M with unchanged high efficiency, leading to the cyclic malonate with 96% conversion (after 4h) and in 96% yield (Scheme 5). However, at a lower catalytic amount of 0.5 mol%, the conversion decreased significantly with only 48% even after a prolonged reaction time of 6h. This lower conversion indicates that this catalytic metathesis process takes somewhat longer compared with the one for the analogous synthesis of the five-membered ring **2a** (81% under same conditions; see Scheme 4).



Scheme 5. Optimized metathesis reaction for the synthesis of **2b.**

In addition to aliphatic substituents (as in case of **2a** and **2b**), aryl-substituted cyclic malonates of type **2c** are of synthetic interest as well. Accordingly, we focused on the synthesis of the phenyl-substituted cycloalkene-1,1-dicarboxylate **2c** as a representative example of this

class of compound. The preparation of the required substrate for this metathesis reaction was carried out starting from readily available 2-allyl malonate **5** through an alkylation with the electrophile **7** according to a modified literature protocol.[27] We were pleased to find that in spite of the more bulky phenyl-substituent at the terminal olefin position, the metathesis reaction proceeds well in water when using the Grubbs II-catalyst **4** even with a low catalyst loading. In the presence of only 0.5 mol% and at a reaction time of 6 h, already a high conversion of 96% was found. After subsequent process optimization, the desired cyclic malonate **2c** was even obtained with quantitative conversion (100%) when operating at a catalytic amount of 1 mol% of metathesis catalyst **4** and at a reaction time of 24 h (Scheme 6).

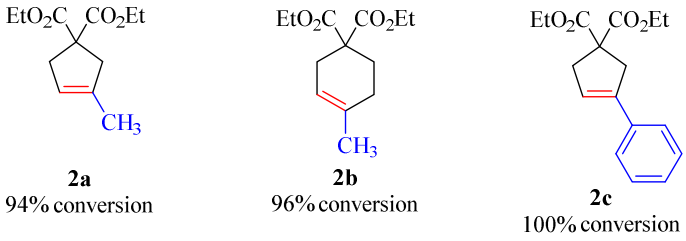


Scheme 6. Optimized metathesis reaction for the synthesis of **2c.**

Notably, the choice of the metathesis catalyst plays an important role as has been demonstrated when using alternatively an analogous modified Grubbs-type catalyst, in which the 2,4,6-trimethylphenyl moieties have been replaced by 2,6-diisopropylphenyl groups: here instead of a quantitative conversion (as in case of catalyst **4**) only a low conversion of 7% was found after the same reaction time of 24h (substrate concentration: 33 mM; detailed data not shown).

Conclusions

In conclusion, we showed that using the Grubbs II catalyst **4** at a catalytic amount of 0.5 to 5 mol% for metathesis reactions of substrates of type **3** in water leads to high conversions of 94-100% for the resulting cyclized malonates **2** (Scheme 7), thus indicating the generality of this metathesis reaction in terms of its suitability for the preparation of a variety of substituted prochiral cyclic malonates, comprising five and six-membered and alkyl as well as aryl-substituted derivatives.



Scheme 7. Overview of the synthesized substituted cyclic 5- and 6-membered malonates **2.**

Future work will address a further expansion of the substrate spectrum (with a specific focus also on the synthesis of cyclic malonates with enlarged ring-size) as well as the application of the resulting cyclic malonates **2** as substrates for enzymatic desymmetrization in water. Furthermore, such a chemoenzymatic one-pot synthesis offers interesting re-use opportunities of the metathesis catalyst **4** after simple product separation: due to the low solubility of the Grubbs II catalyst **4** in aqueous medium, its "immobilization" in an organic phase and separation from the aqueous phase after metathesis and biotransformation (which then contains the water-miscible final product after enzymatic hydrolysis in the aqueous phase), followed by a recycling of the organic phase bearing the metathesis catalyst **4** will be evaluated.

Experimental Section

General. The reagents were purchased from commercial sources and used without further purification. ^{1}H NMR spectra were recorded on a Bruker DRX 500 FT-NMR spectrometer. All chemical shift values refer to $CDCl_3$ ($\delta(^1H)$, 7.26 ppm).

General procedure for the synthesis of substituted cyclopent-3-ene-1,1-dicarboxylates 2
The 2,2-bis-substituted diethyl malonate of type **3** (0.25 - 1.0 mmol) was suspended in water (5 - 7.5 mL) and then the Grubbs II catalyst (**4**, 0.5 - 5 mol%) was added. The reaction mixture was stirred at room temperature for 3 - 24 hours. Subsequently, the reaction mixture was extracted three times with methylene chloride or methyl *tert*-butyl ether (MTBE, 10 - 20 mL) and the combined organic phases were dried over magnesium sulfate. The resulting solution was filtered over celite, and the volatile components were removed in vacuo. The conversion was determined by ^{1}H-NMR spectroscopy of the resulting crude product.
Synthesis of diethyl 3-methylcyclopent-3-ene-1,1-dicarboxylate (**2a**). The synthesis was conducted according to the general procedure starting from diethyl 2-allyl-2-(2-methylallyl)malonate[25] (**3a**, 254.3 mg, 1.0 mmol) in water (5 mL) and using the Grubbs II catalyst (**4**, 4.24 mg, 5.00 µmol, 0.5 mol%). The reaction time was 18 hours, and methylene chloride (3 × 20 mL) was used for extraction. The separation of the catalyst was done through

filtration over celite, and the conversion was determined by means of ^{1}H-NMR spectroscopy. The conversion was 94%. The ^{1}H-NMR spectroscopic data are in good agreement with those reported in literature (reference 28).

Synthesis of diethyl 4-methylcyclohex-3-ene-1,1-dicarboxylate (**2b**). The synthesis was conducted according to the general procedure starting from diethyl 2-allyl-2-(3-methylbut-3-en-1-yl)malonate (**3b**, 98% purity, 68.36 mg, 0.25 mmol) in water (7.5 mL) and using the Grubbs II catalyst (**4**, 10.82 mg, 12.74 μmol, 5 mol%). The reaction time was 3 hours (with a rapid stirring rate of 1200 rpm at the beginning for ca. 1 min, and a medium stirring rate of 500 rpm for the rest of the reaction time), and methylene chloride (3 × 10 mL) was used for extraction. The resulting solution obtained after drying over magnesium sulfate was filtered over celite and silica gel. The conversion was 96%. The ^{1}H-NMR spectroscopical data are in good agreement with those reported in literature (reference 28).

Synthesis of diethyl 3-phenylcyclopent-3-ene-1,1-dicarboxylate (**2c**). The synthesis was conducted according to the general procedure starting from diethyl 2-allyl-2-(2-phenylallyl)malonate[27] (**3c**, 79.1 mg, 250 μmol) in water (7.5 mL) and using the Grubbs II catalyst (**4**, 2.12 mg, 2.50 μmol, 1 mol% or 1.06 mg, 1.25 μmol, 0.5 mol%). The reaction time was 6 or 24 hours, and methylene chloride or methyl *tert*-butyl ether (MTBE, 3 × 20 mL) was used for extraction. The separation of the catalyst was done through filtration over celite, and the conversion was determined by means of ^{1}H-NMR spectroscopy. The conversion was 96% (with 1 mol% of **4** and at 6h) or 100% (with 0.5 mol% of **4** and at 24h). The ^{1}H-NMR spectroscopical data are in good agreement with those reported in literature (reference 26).

Synthesis of diethyl 2-allyl-2-(3-methylbut-3-enyl)malonate (3b). The preparation of compound **3b** was carried out according to a modified protocol reported in reference 26. In detail, diethyl 2-allylmalonate (**5**, 98%, 986 μL, 5 mmol) was dissolved in DMF (30 mL). At 0 °C sodium hydride (60%, 218.40 mg, 5.46 mmol, 1.1 equiv.) was slowly added and the mixture was stirred until gas evolution stopped. After warming the solution to room temperature 3-methylbut-3-en-1-yl 4-methylbenzenesulfonate (**6**, 98%, 1.39 g, 6.20 mmol, 1.2 equiv.) dissolved in DMF (40 mL) was added. The reaction mixture was stirred for 72h at 110 °C, and after cooling ethyl acetate (40 mL) was added. Subsequent filtration of the solution, followed by extraction of the filtrate with saturated aqueous sodium bicarbonate (30 mL), distilled water (30 mL) and saturated aqueous sodium chloride (30 mL). The combined organic phases were dried over magnesium sulfate and after filtration the volatile components were removed in vacuo. The resulting crude product was purified through column chromatography and fractional vacuum distillation using cyclohexane / ethyl acetate (95:5) as an eluent. The compound **3b** was obtained in 25% yield (343.92 mg, 1.24 mmol). The ^{1}H-NMR spectroscopic data are in good agreement with those reported in literature (reference 29).

Synthesis of 3-methylbut-3-en-1-yl 4-methylbenzenesulfonate (6). The preparation of compound **6** was carried out according to a modified protocol reported in reference 30. In detail, at 0°C a solution of tosylchloride (18.47 g, 96.9 mmol) in dried pyridine (120 mL) was slowly added to solution of 3-methylbut-3-en-1-ol (97%, 10 mL, 96.9 mmol) in dried pyridine (50 mL)

and after warming up to room temperature the resulting solution was stirred for 18h. Subsequently, saturated aqueous sodium bicarbonate (40 mL) was added, and the mixture was stirred for 40 min. After removal of the solvent in vacuo, the residue was dissolved in chloroform and subsequently washed with diluted hydrochloric acid (2M, 20 mL), distilled water (40 mL) and saturated aqueous sodium bicarbonate (40 mL). The combined organic phases were dried over magnesium sulfate and after filtration the volatile components were removed in vacuo. The resulting crude product was purified through column chromatography. The compound **6** was obtained in 18% yield (3.90 g, 17.03 mmol, 98% purity). The ^{1}H-NMR spectroscopic data are in good agreement with those reported in literature (references 30 and 31).

Acknowledgements

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24. For a synthetic procedure of this compound **3a**, which is based on the use of methallyl chloride as a substrate and sodium ethoxide as a base, see reference 26; in our synthesis conducted in a slightly modified manner the analogous bromo compound methallyl bromide (as a substrate) and NaH (as a base) were used. After addition of the bromo compound reaction temperature was 100 °C for 18h. Extraction steps were based on the use of ethyl acetate as organic solvent and sodium thiosulfate solution (5%) for the washing step. Purification via column chromatography is based on cyclohexane / ethyl acetate (95:5) as an eluent.
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27. For a synthetic procedure of this compound **3b**, see ref. 26; in our synthesis conducted in a slightly modified manner NaH was used as a base and added at 0°C to a solution of **5** in DMF followed by warming up the resulting solution to room temperature prior to addition of α-(bromomethyl)styrene (**7**) dissolved in DMF. Extraction steps were based on the use of ethyl acetate as organic solvent and sodium thiosulfate solution (5%) for the washing step. Purification via column chromatography is based on cyclohexane / ethyl acetate (95:5) as an eluent.
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