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Organocatalytic Activity of N-Heterocyclic Carbenes in the Michael Addition of 1,3-Dicarbonyl Compounds: Application to a Stereoselective Spirocyclization Sequence

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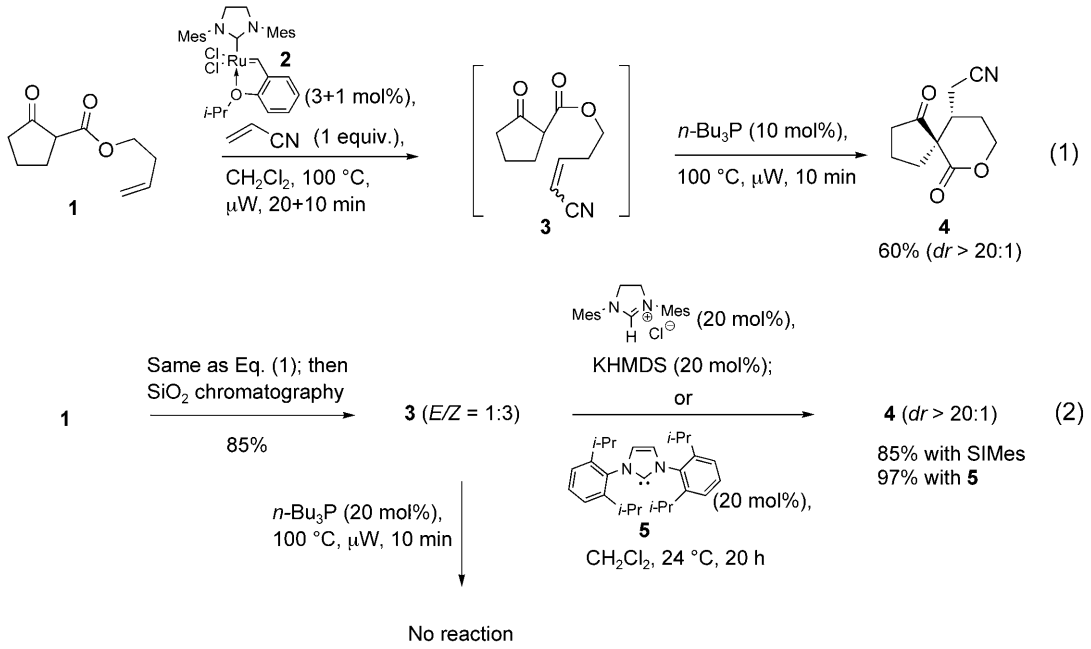
Abstract: An eco-compatible diversity-oriented synthesis of α-spirolactones and α-spirolactams is described. The overall transformation involves an olefin cross-metathesis followed by an intramolecular organocatalytic Michael-induced spirocyclization. Under microwave irradiation, the Hoveyda–Grubbs precatalyst can be iteratively used as the source of both the metathesis ruthenium-based catalyst, and the spirocyclization N-heterocyclic carbene catalyst.

Keywords: cross metathesis; Michael addition; N-heterocyclic carbenes; organocatalysis; spiro compounds

Organic molecules containing a spirobicyclic moiety are of broad scientific interest due to their unique chemical and conformational features as well as the biological properties often associated with the asymmetric spiro carbon atom. They have attracted considerable attention from the synthetic community.[1] In the case of complex bioactive molecules containing a spiranic subunit, it often occurs that simplified analogues retaining essentially the spiro structural domain exhibit a comparable biological profile with the parent compounds.[2] With this in mind for some applications to the synthesis of natural products and analogues, our recent objective has been the development of an efficient and diastereoselective diversity-oriented synthesis of α-spirolactones and α-spirolactams.[3] However, in the current molecular sciences era, the efficiency of a synthetic sequence is more than ever corroborated with its conciseness and sustainability issues, as witnessed by the tremendous research efforts currently directed at the development of multiple bond-forming and catalytic chemical processes. We disclose herein an eco-compatible[4] spirocyclization sequence through a consecutive transformation involving iterative metallo- and organocatalysis under microwave irradiation.

We recently reported that microwave irradiation has a pronounced beneficial effect on the cross-metathesis (CM) of various olefins.[5] Indeed, the β-oxo ester **3** could be obtained efficiently by microwave-assisted olefin cross-metathesis from the corresponding homo-allyl ester **1**[6] and only one equivalent of acrylonitrile in the presence of 4 mol% of the Hoveyda–Grubbs precatalyst **2**.[7] The final CM reaction mixture was essentially a dichloromethane solution of **3**, which should be a suitable medium for a Michael-induced spirocyclization.[8] Thus, we looked for relevant eco-compatible Michael addition promoters and surmised that phosphines could be suitable organocatalysts in this case.[9] Indeed, the addition of 10 mol% of tributylphosphine to the CM reaction mixture and an additional 10 min of dielectric heating at 100 °C yielded 60% of the expected spirolactone **4** as the only detectable diastereomer in a consecutive reaction [Scheme 1, Eq. (1)].[10] However, in a separate experiment, the treatment of pure **3** with up to 20 mol% of tributylphosphine left the starting material totally unchanged [Scheme 1, Eq. (2)]. These apparently contradictory results drove to the conclusion that the addition of phosphine to the CM product mixture generated *in situ* the active promoter of the Michael-induced spirocyclization. This in turn raised the hypothesis that tributylphosphine is acting as a competing ligand of the ruthenium CM catalyst and thus, the actual catalyst may be a ruthenium-phosphine complex or the metal-free SIMes N-heterocyclic carbene (NHC) originally present as an ancillary ligand in pre-



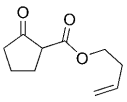
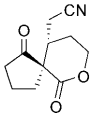
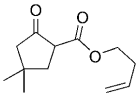
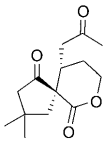
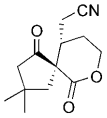
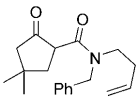
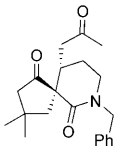
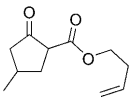
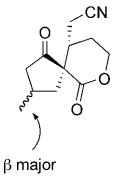
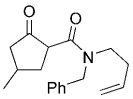
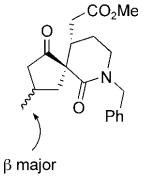
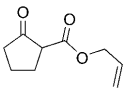
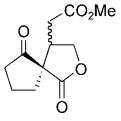
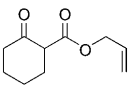
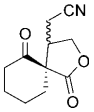
Scheme 1. Sequential cross-metathesis/Michael spirocyclization. Mes = mesityl = 2,4,6-trimethylphenyl; KHMDS = potassium bis(trimethylsilyl)amide.

catalyst **2**.[11] Ruthenium-catalyzed Michael additions have been described,[12] but NHC-catalyzed Michael additions are as yet limited to the specific case of aldehyde enols.[13] The determination of the active catalyst of the spirocyclization in Eq. (1) came out from the following control experiments: the treatment of pure **3** at 100 °C under microwave irradiation with 20 mol% of tributylphosphine in the presence of 4 mol% of the first generation Grubbs precatalyst $Cl_2(PCy_3)_2Ru(CHPh)$ containing no NHC ligand left the starting material unchanged (under both argon and ethylene atmosphere). On the other hand, and to our great satisfaction, the treatment of a dichloromethane solution of pure **3** at room temperature with 20 mol% of SIMes afforded the expected spirolactone **4** in good yield under organocatalytic conditions [Scheme 1, Eq. (2)],[14] demonstrating for the first time that NHCs can be efficient organocatalysts for the Michael addition of 1,3-dicarbonyl compounds. The commercially available NHC IPr (**5**) was found to be more efficient for this transformation affording **4** in 97% yield from **3**. The reaction presented in Eq. (1) is a nice example of a particularly attractive concept of a consecutive reaction where the precatalyst ruthenium complex **2** is successively the source of both metallic and organic catalysts.

The scope of this consecutive metallo- then organocatalyzed CM-Michael sequence was explored for the synthesis of α-spirolactones and α-spirolactams.[15] The results are summarized in Table 1. After the microwave-assisted CM reaction, the product mixture was directly treated with a catalytic amount of IPr (**5**) NHC, or alternatively with a catalytic amount of tributylphosphine to release *in situ* the SIMes NHC from the ruthenium. The Michael-induced spirocyclization was found to be highly diastereoselective for the formation of α-spiro-δ-lactones and α-spiro-δ-lactams (entries 1–8), probably due to the existence of a well-defined six-membered chair-like transition state with both *E* and *Z* CM products. Modest but effective chiral induction was observed with non-symmetrical substrates **8** and **9**, the Michael-induced spirocyclization occurring preferentially *anti* to the methyl group on the cyclopentanone (entries 7 and 8). The structures of compounds **13** and **15** (entries 4 and 7) have been secured by X-ray diffraction analysis.[16] In contrast, in the cases of α-spiro-γ-lactones where no significant stabilization of the transition state can be invoked, lower diastereoselectivities were observed in the spirocyclization step (entries 9–11). It should be noted that overall yields were generally higher when the CM-Michael sequence was performed in a stepwise manner (e.g., for **4**: 72% stepwise, 60% consecutive), but in the context of eco-compatibility, the consecutive reaction protocol which can be completed within 90 min including the single final purification was preferred.

For the NHC-catalyzed Michael addition, it is tempting to postulate that the reaction involves the basic properties of the NHC to generate the enolate of the 1,3-dicarbonyl compound.[17] However, the reaction of **3** with a catalytic amount of DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) as the promoter afforded a complex mixture containing the expected

Table 1. Table 1Synthesis of α-spirolactones and α-spirolactams.[a]

Entry	Substrate[b]	Olefin	Conditons[c]	Product	Yield[d] [%]
1	**1** 		P(*n*-Bu)$_3$	**4** 	60 (>20:1)
2	**1**		IPr	**4**	54 (>20:1)
3	**6** 		IPr	**12** 	44 (>20:1)
4	**6**		P(*n*-Bu)$_3$	**13** 	41 (>20:1)
5	**6**		IPr	**13**	40 (>20:1)
6	**7** 		IPr	**14** 	79 (>20:1)
7	**8** 		IPr	**15** 	44 (4:1)
8	**9** 		IPr	**16** 	54 (2.8:1)
9	**10** 		P(*n*-Bu)$_3$	**17** 	53 (1.6:1)
10	**11** 		P(*n*-Bu)$_3$	**18** 	52 (1.8:1)
11	**11**		IPr	**18**	50 (2.7:1)

[a] All reactions were conducted in CH_2Cl_2 with 1 equiv. of olefin. CM reactions were performed in a sealed tube under microwave irradiation at 100 °C for 20+10 min using 3+1 mol% of precatalyst **2**, and the reaction mixture was directly treated with the spirocyclization promoter according to the conditions described.

[b] See ref.[6]

[c] *Conditions with P(n-Bu$_3$):* P(*n*-Bu)$_3$ (10 mol%), μW, 100 °C, 10 min for entry 1; otherwise: P(*n*-Bu)$_3$ (20 mol%), μW, 100 °C, 20 min. *Conditions with IPr:* IPr (**5**, 20 mol%), 24 °C, 20 h.

[d] Yields for isolated products (SiO_2 flash chromatography); diastereomeric ratios are in brackets (determined by NMR); see Supporting Information for characterization data.

spiro compound **4** as a very minor component, while very low conversions (*ca.* <5%) were observed with a stoichiometric (1 equiv.) amount of other bases {e.g., K_2CO_3 in acetone, *i*-Pr_2EtN in CH_3CN, *t*-BuOK in THF, KHMDS [potassium bis(trimethylsilyl)amide] in THF}. Alternative mechanisms involving the nucleophilic properties of the NHC can also be envisioned. For example, the conjugate addition of the carbene to the activated olefin would generate a basic imidazolium enolate (or homo-enolate[18]), but this appears un-

likely when considering the chemical inertness of **3** in the presence of tributylphosphine, tricyclohexylphosphine or DABCO (1,4-diazabicyclo[2.2.2]octane). At this early stage, more experimental data are required to clearly understand the mechanism of this new promising organocatalytic reaction.

In summary, an eco-compatible stereoselective synthesis of α-spirolactones and α-spirolactams was developed from simple precursors involving a microwave-assisted iterative metallo- and organocatalytic consecutive CM-Michael sequence. Of importance, an unprecedented organocatalytic activity of NHCs as excellent promoters of the Michael addition with 1,3-dicarbonyl compounds has been demonstrated. Current work concentrates on the development of this reaction.

Experimental Section

Preparation of 4; Representative Procedure

In a 10-mL sealable Pyrex tube equipped with a Teflon-coated magnetic stirring bar containing a solution of **1** (91 mg, 0.50 mmol) in anhydrous CH_2Cl_2 (5 mL) was added acrylonitrile (33 μL, 0.50 mmol) and precatalyst **2** in two portions (10 mg at the start, then 3 mg after 20 min; 0.02 mmol overall). The sealed reaction vessel was irradiated with microwaves (μW) at 100 °C for 30 min overall. To the cooled reaction mixture, was added tributylphosphine (13 μL, 0.05 mmol) and the mixture was irradiated with microwaves at 100 °C for 10 min. The solvent and volatiles were evaporated under vacuum and the resulting crude product was purified by flash chromatography on silica gel eluted with ethyl acetate/petrol ether (2:3) to afford **4** as the only detectable isomer; yield: 62 mg (60%).

Alternatively, after the CM step, the cooled reaction mixture was treated with IPr (**5**) (39 mg, 0.10 mmol) and the mixture was stirred under an argon atmosphere at 24 °C for 20 h. The solvent and volatiles were evaporated under vacuum and the resulting crude product was purified as above to afford **4** as the only detectable isomer; yield: 56 mg (54%); $R_f = 0.31$ (EtOAc/petrol ether, 1:1); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 213.4$ (C), 169.2 (C), 117.0 (C), 68.1 (CH_2), 59.1 (C), 38.2 (CH_2), 33.4 (CH), 30.1 (CH_2), 25.2 (CH_2), 19.2 (CH_2), 19.1 (CH_2); ^1H NMR (300 MHz, $CDCl_3$): $\delta = 4.57–4.37$ (m, 2H), 2.83–2.61 (m, 2H), 2.42–2.18 (m, 6H), 2.11–1.82 (m, 3H); HR-MS (ESI+): $m/z = 208.0967$ $[M+H]^+$, calcd.: 208.0968.

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