Alkylidene Meldrum's Acids as Platforms for the Vinylogous Synthesis of Dihydropyranones

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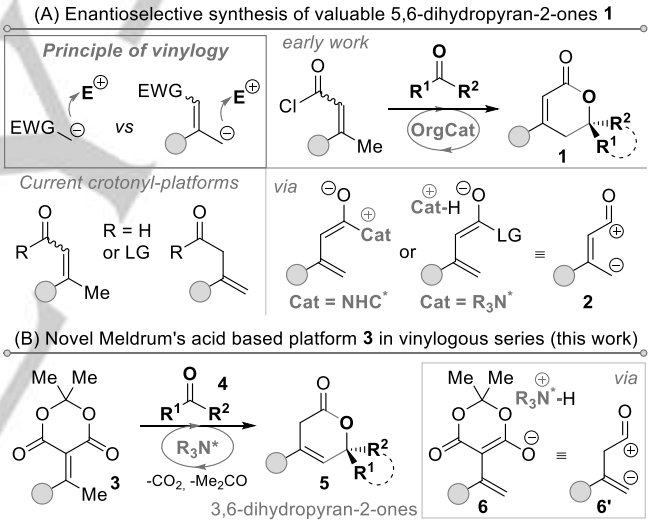
Alkylidene Meldrum's Acids as Novel Platforms for the Vinylogous Synthesis of Dihydropyranones

Stéphane Wittmann,[+a] Thomas Martzel,[+b] Cong Thanh Pham Truong,[a] Martial Toffano,[a] Sylvain Oudeyer,[b] Régis Guillot,[a] Chloée Bournaud,[a] Vincent Gandon,[a,c] Jean-François Brière,*[b] and Giang Vo-Thanh*[a]

Dedication ((optional))

Abstract: Upon Brønsted base organocatalysis, ketone derived alkylidene Meldrum's acids proved to be competent vinylogous platforms able to undergo a formal (4+2) cycloaddition reaction with dihydro-2,3-furandione to furnish an unprecedented route to 3,6-dihydropyran-2-ones **5** as spiro[4,5]decane derivatives with up to 98% ee thanks to the commercially available Takemoto catalyst. Preliminary investigation showed that this reaction could be extended to other activated ketones establishing these alkylidene Meldrum's acids as a novel C4-synthon in the vinylogous series.

The principle of vinylogy, as remarkably illuminated by Fuson in 1935,[1] allows the remote functionalization of a given functional group thanks to the propagation of electronic effects through a conjugated unsaturated backbone (Scheme 1A). More recently, synthetic chemists have tackled the more challenging regio- and enantioselective bond-forming events at remote positions of various electron-withdrawing groups by means of metal or organic catalysts.[2],[3] This methodology was especially illustrated by the groups of Jørgensen, Deng and Chen during the pioneering organocatalytic direct δ-functionalization of α,α-dicyanoolefins platforms.[4] The marked versatility of this vinylogous strategy has witnessed several achievements encompassing the use of various substrates suited for direct organocatalytic activation sequences.[2],[3] Upon the initiatives of Peters and Ye,[5],[6] the catalytic vinylogous transformation of crotonyl-based platforms, such as α,β-unsaturated acid chlorides, opened an avenue to the elaboration of 5,6-dihydropyran-2-ones **1** (Scheme 1A), a heterocyclic core-structure found in numerous bioactive compounds.[2],[3] By means of chiral *N*-Heterocyclic Carbenes (NHC) or amines (R_3N, Scheme 1A),[7],[8] efficient (4+2) annulation reactions were subsequently carried out with ketone derivatives and provided thereby the corresponding oxa-heterocycles **1** with the control of a congested tetrasubstituted stereocenter, even embedded into highly valuable spiro architectures.[9] Nevertheless, to the best of our knowledge, this strategy has exclusively led to 5,6-dihydropyran-2-ones **1**, with a conjugated carbon-carbon double bond to the C=O group (*via* C4 synthon **2**). In consequence, the development of novel platforms expanding the scope of this valuable vinylogous methodology is still of high interest.



Scheme 1. Novel organocatalytic vinylogous synthesis of dihydropyran-2-ones.

In that vein, we started to investigate the alkylidene Meldrum's acid derivatives **3**, as an original platform in vinylogous series (Scheme 1B). These compounds are stable and readily available in one-step by the condensation reaction between Meldrum's acid and ketones.[10] With regard to the remarkable high acidity of the 2,2-dimethyl-1,3-dioxan-4,6-dione, namely Meldrum's acid (pK_a = 4.8 in water),[11] we anticipated a facile deprotonation of the distant methyl group of **3**, so that the formation of the enolate **6** with a γ-nucleophilic site would occur,[12] following the principle of vinylogy. Then, taking advantage of the marked electrophilic properties of carbonyl moieties of the 1,3-dioxan-4,6-dione backbone, the platform **3** was expected to be capable of undergoing a formal (4+2) cycloaddition with ketones through a domino aldol/cyclocondensation reaction towards the construction of dihydropyran-2-one. We are pleased to report on the alkylidene Meldrum's acid derivatives **3** as a novel precursor

[a] Dr. S. Wittmann, C. T. Pham Truong, Dr. M. Toffano, Dr. R. Guillot, Dr. C. Bournaud, Prof. V. Gandon and Prof. G. Vo-Thanh
Institut de Chimie Moléculaire et des Matériaux d'Orsay. CNRS UMR 8182, Université Paris Saclay
91405 Orsay Cedex, France.
E-mail: giang.vo-thanh@universite-paris-saclay.fr
[b] Dr. T. Martzel, Dr. S. Oudeyer and Dr. J.-F. Brière
Normandie Univ, UNIROUEN, INSA Rouen, CNRS, COBRA, 76000 Rouen, France.
E-mail: jean-francois.briere@insa-rouen.fr
[c] Prof. V. Gandon
Laboratoire de Chimie Moléculaire (LCM), CNRS UMR 9168, Ecole Polytechnique, Institut Polytechnique de Paris, route de Saclay, 91128 Palaiseau cedex, France
[+] These authors contributed equally to this work

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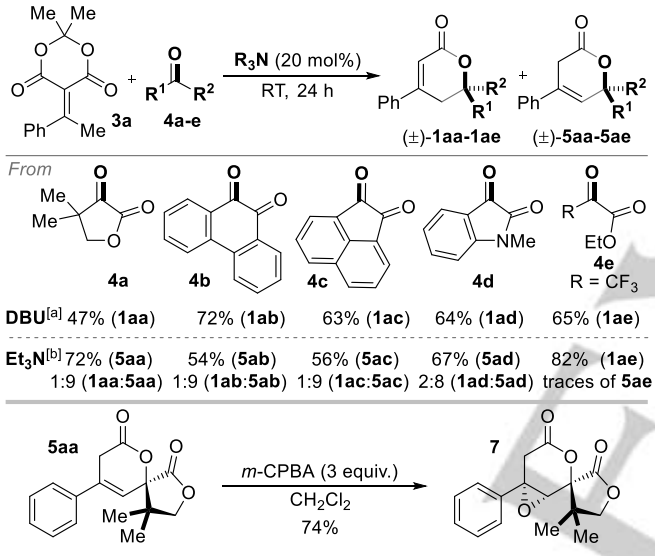
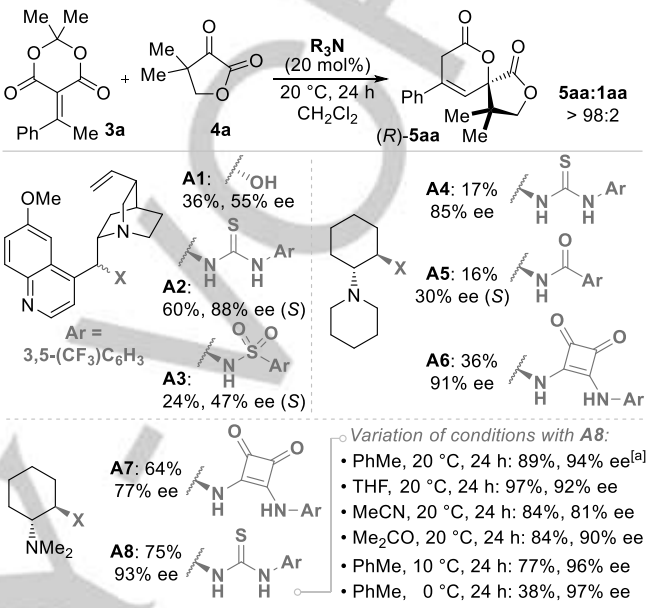
in enantioselective vinylogous transformations upon Brønsted base organocatalysis. The exquisite reactivity of platform **3** allows an unprecedented entry to non-racemic 3,6-dihydropyran-2-ones **5**, having a non-conjugated carbon-carbon double bond (*via* synthon **6'** instead of **2**) which, accordingly, extends the chemical space in the dihydropyran-2-one heterocyclic series.

This project began by the exploration of alkylidene Meldrum's acid **3** reactivity as a potentially vinylogous platform (Scheme 2). To our delight, the model benzylidene Meldrum's acid **3a** and dihydro-4,4-dimethyl-2,3-furandione **4a** as electrophile led straightforwardly to the formation of virtually novel spiranic 5,6-dihydropyran-2-ones **1aa** in the presence of 20 mol% of DBU as a base (unoptimized conditions).[13] This smooth domino sequence could be applied to an array of diketones **4b-e** to afford the corresponding 5,6-dihydropyran-2-ones **1ab-1ae** derivatives as major products in yields ranging from 47% to 72%.



Scheme 2. Alkylidene Meldrum's acid **3a** as an original vinylogous platform. Percentage correspond to the isolated yield after column chromatography, and the ratio of isomers (**1**:**5**) was determined by ^{1}H NMR on the crude product. [a] In THF (0.2 M); only traces of **5a-** was observed. [b] In CH_2Cl_2 (0.4 M).

Surprisingly, in the course of these processes, we also detected minor amounts of the non-conjugated 3,6-dihydropyran-2-ones **5**. By means of triethylamine as a softer organocatalyst in dichloromethane, the outcome of the reaction was essentially balanced towards the construction of 3,6-dihydropyran-2-one isomers **5aa-ad** with yields ranging from 54-72%, except for the more reactive keto-ester **4e** giving the known 5,6-dihydropyran-2-ones **1ae** in good 82% yield.[7a] The structure of the novel compound **5aa** was fully proven especially by X-Ray single crystal diffraction.[14] Interestingly, the 3,6-dihydropyran-2-one product **5aa** isomerized into the conjugated isomer **1aa** in the presence of Et_3N for 24 hours. Then, we assume that **1aa** (thermodynamic product) is mainly originated from the kinetic product **5aa** during this domino sequence, whose outcome depends on both the strength of the base and the stability and/or acidity of the intermediates. Accordingly, alkylidene Meldrum's acid derivative **3a** proved to be an original and versatile vinylogous platform, while affording an unprecedented pathway to original 3,6-dihydropyran-2-ones **5**. Furthermore, the usefulness of these products was demonstrated through the stereoselective epoxidation reaction which took place regioselectively without C-C double bond migration (**7**, 74%). Then, we embarked towards the development of an organocatalytic enantioselective version.

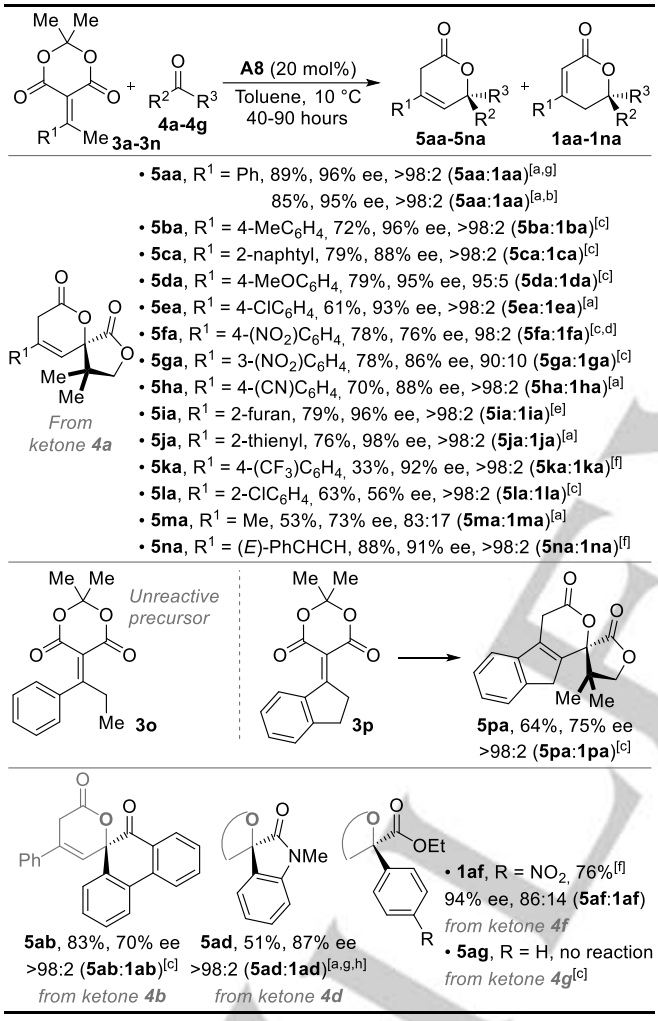


Scheme 3. Towards an enantioselective process. Reaction conditions: **3a** (0.15 mmol), ketone **4a** (1 equiv), **catalyst** (20 mol%) in the given solvent (0.5 M) at 20 °C for 24 hours. Percentage of isolated yield after column chromatography, enantiomeric excess (ee) determined by chiral HPLC and the ratio of isomers (**5aa**:**1aa**) was determined by ^{1}H NMR on the crude product. [a] 94:6 (**5aa**:**1aa**) was measured.

Various Cinchona-derived organocatalysts (see SI for full details) were first assessed for the transformation of the dihydro-4,4-dimethyl-2,3-furandione **4a** to 3,6-dihydropyran-2-ones **5aa** (Scheme 3). The bifunctional thiourea organocatalyst **A2** (60% yield, 88% ee) proved to be more effective than the native quinine **A1** (36% yield, 55% ee and reverse enantioselectivity) or the sulfonamide derivatives **A3** (24%, 47% ee) both in terms of yields and ee. This marked outcome with regard to bifunctional-topology was also observed with organocatalysts **A4-A6**, having a cyclohexanediamine backbone, albeit lower yields were measured probably due to the sterically hindered piperidine moiety. Nevertheless, the squaramide derived catalyst **A6** provided 91% ee in 36% yield. Importantly, in this series, the catalyst **A5** having an amide functional group led to inverse enantioselectivity (30% ee) in comparison to thiourea or squaramide analogues **A4** and **A6**, showing the key importance of the hydrogen bonding donor moiety. To our delight, the less encumber catalysts **A7-A8**, having a dimethylamine moiety, furnished the 3,6-dihydropyran-2-ones **5aa** with improved 64-75% yields and up to 93% ee for the original Takemoto catalyst **A8**. Interestingly, the catalysts **A7-A8** possessing a NMe_2 Brønsted base display a reverse influence of the NH-hydrogen bonding donor part onto ee as the thiourea derivative **A8** led to better ee

than the squaramide **A7** in the contrary to piperidine derivatives **A4** and **A6**; then a subtle cooperation between the two functionalities of the catalyst is set for this new transformation (**3a** to **5aa**). An optimization of reaction conditions with catalyst **A8** showed that toluene furnished improved ee (94%) and yields (89%) albeit with the formation of a small amount of 5,6-dihydropyran-2-ones **1a**. Nonetheless, the selectivity between isomers **5aa**:**1aa** was in favor of the 3,6-dihydropyran-2-ones **5aa** (> 98/2 **5aa**:**1aa**) at 10°C, obtained in 77% isolated yield and excellent 96% ee, while lower temperature (0°C) led to a drop of yield (38%).

Table 1. Scope and limitations.[a]

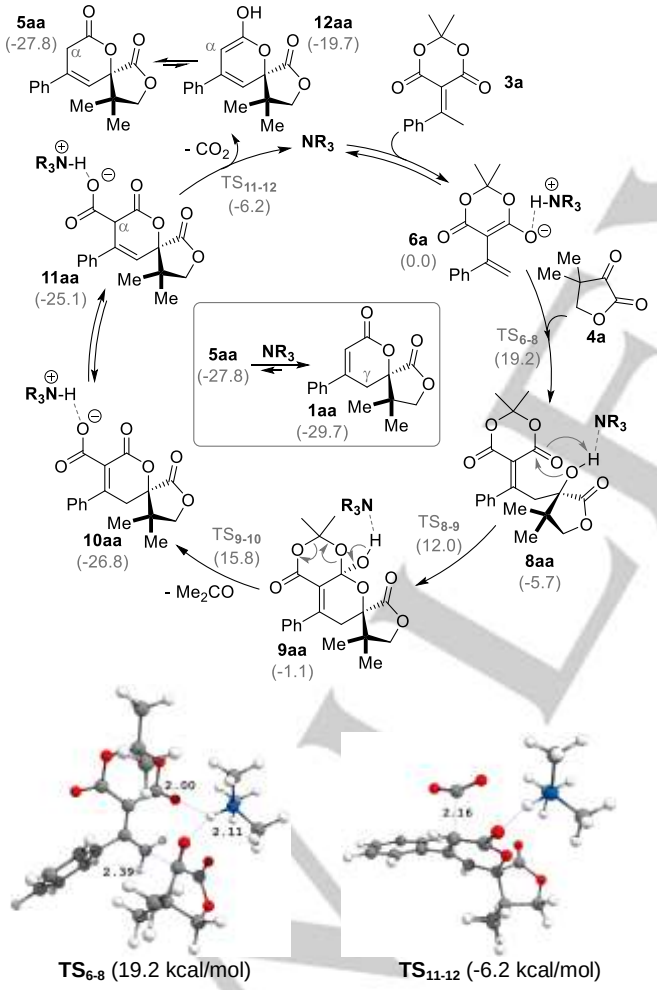


Reaction conditions: **3** (0.15 mmol), ketones **4** (1 equiv), catalyst **A8** (20 mol%) in PhMe (0.5 M) at 10 °C. Percentage of isolated yield of the pure major isomer **5** after column chromatography (unless otherwise noted), enantiomeric excess (ee) determined by chiral HPLC and the ratio of isomers (**5**:**1**) was determined by ^{1}H NMR on the crude product. [a] 40 hours of reaction. [b] On 1 mmol scale. [c] 90 hours of reaction. [d] in CH_2Cl_2 for solubility issue. [e] At 20 °C in CH_2Cl_2 for 72 hours. [f] 72 hours of reaction. [g] The absolute configurations were determined by X-Ray diffraction for (*R*)-**5aa** and from similar structure in the literature for (*R*)-**5ad**[6] (see SI); the absolute stereochemistry of the other products was drawn by analogy. [h] 1.3 equivalent of alkylidene Meldrum's acid **3a** and catalyst **A3** was used instead of **A8** which gave **5ab** in 74% yield and 55% ee (see SI).

Having these conditions in hands, the substrate scope was addressed (Table 1). Increasing the reaction time to 40 hours allowed the formation of the expected product **5aa** in 89% yield while keeping an excellent enantiomeric excess of 96% ee, even on 1 mmol scale (85%, 95% ee). A series of alkylidene Meldrum's acid derivatives **3b-3j** were engaged into a vinylogous transformation of dihydro-4,4-dimethyl-2,3-furandione **4a** into 3,6-dihydropyran-2-ones **5ba-5ja** as major products with yields between 61-79% and ees ranging from 76% to 98%. The alkylidene Meldrum's acid flanked by a 4-$CF_3C_6H_4$ moiety led to the corresponding 3,6-dihydropyran-2-ones **5ka** with an excellent 92% ee but a moderate yield of 33% (42% of conversion). The conversion could be improved (> 90% of conversion) after 90h of reaction but a lower ratio of **5ka**:**1ka** (74:26) was measured. In this series, product **5la** obtained from the Meldrum's acid derivative **3l**, having a 2-chlorophenyl moiety, proved to be more challenging (Table 1). Then, only 77% of conversion after 90 hours at 10°C was measured giving product **5la** in moderate 63% isolated yield and 56% ee. In order to further probe the structure/activity relationship, one can consider that alkylidene Meldrum's acid flanked by two methyl group is still able to be involved into this aldol process, albeit lower reaction rate (67% of conversion) and selectivity (**5ma**:**1ma** 83:17) was observed giving **5ma** in 53% yield and 73% ee. On the other hand, the original product **5na**, having a versatile styrenyl group, was synthesized easily in 91% ee and 88% yield from the corresponding dienyl Meldrum's acid **4n**. Additionally, although more sterically hindered ethyl-derivative **3o** proved to be unreactive, the cyclic-analogue, namely the indenyl-derived Meldrum's acid **3p**, was transformed into the corresponding tetracyclic product **5pa** in 75% ee (64% yield). Subsequently, we wondered whether this Meldrum's acid-based platform **3a** could react with other ketones, known as good starting materials for the efficient enantioselective vinylogous synthesis of 5,6-dihydropyran-2-ones **1**.[7],[8a-e, 8g-i] However, in our case, we expected to extend the chemical diversity with the formation of isomeric and non-racemic 3,6-dihydropyran-2-one architectures **5**. Accordingly, the transformation of various ketones **4b**, **4d**, **4f-g** proceeded with moderate to good yields (50-83%) in favor of the major 3,6-dihydropyran-2-one products. However, the diketones **4b**[8e] and **4d**[6] were transformed into products **5ab** and **5ad** in only 70% and 55% ee respectively. To our delight, by means of *epi*-tosylamide quinine catalyst **A3** instead of **A8**, the *spiro*-oxindole **5ad** was obtained with improved 87% ee. In spite of the less activated phenyl α-keto esters **4g** did not react in these conditions,[8f] the more electrophilic *para*-NO_2-phenyl α-keto esters **4f** furnished the corresponding dihydropyranones **5af** and **1af** as a 86:14 mixture of isomers as determined on the crude product. However, a complete isomerization of this mixture into the 5,6-dihydropyran-2-one product occurred during purification by silica gel column chromatography to afford **1af** in good 76% yield and 94% ee.[15]

On the basis of preliminary set of computations with trimethylamine as a model organocatalyst (see SI for full details), a proposed catalytic cycle is shown in Scheme 4. First, the deprotonation of alkylidene Meldrum's acid **3a** gives the enolate **6a** flanked by the H-bonded tertiary ammonium (R_3NH^+). Then, the addition to the ketone-electrophile **4a** gives the adduct **8aa** (enantioselective step), though a transition state ($TS_{6\text{-}8}$ = 19.2

kcal/mol) showing a comgoplete proton-transfer from the ammonium to the alcohol-product **8aa**. The subsequent cyclization leads to the *ortho*-ester **9aa** along with a base-promoted proton migration. Importantly, it was found that the alternative (4+2) cycloaddition reaction (**6a** + **4a** to **9aa**) was more energetically demanding than the nucleophilic addition of dienolate **6a** to **4a** (24.9 vs 19.2 kcal/mol). The subsequent fragmentation process liberates a molecule of acetone to furnish the carboxylate **10aa**.[16] Although the detail of the formal symmetry forbidden 1,3-H shift was not easy to address from the computational point of view, it is believed that a C-C double bond isomerization occurs to reveal the hemi-malonate backbone of **11aa**. This Csp^3-CO_2 framework is then able to undergo a stepwise decarboxylation/tautomerization sequence ($TS_{11\text{-}12}$ = -6.2 kcal/mol) to eventually deliver the kinetic product **5aa**. Importantly, by means of a stronger base or longer reaction time an equilibration event occurs leading to the C-C double bond migration of **5aa** to provide the more stable 5,6-dihydropyran-2-one **1aa** having a conjugated alkene to the carbonyl functional group (via a formal protonation to γ-position).



$TS_{6\text{-}8}$ (19.2 kcal/mol) **$TS_{11\text{-}12}$** (-6.2 kcal/mol)

Scheme 4. Proposed mechanism based on DFT calculations. [a] The computed free energies (ΔG_{298}) of intermediates and transition states (TS) are given in kcal/mol in brackets with Me_3N as catalyst (selected distances in Å).

In conclusion, we have shown that ketone derived alkylidene Meldrum's acids **3** are novel C4-synthon capable of being engage into a vinylogous formal (4+2) cycloaddition reaction with reactive ketones to furnish an unprecedented route to 3,6-dihydropyran-2-ones **5** upon Brønsted base catalytic conditions. By means of the commercially available bifunctional Takemoto organocatalyst up to 98% ee were obtained, especially for original spiro compound 3,6-dihydropyran-2-ones **5**. The exploitation of this novel and readily available vinylogous platform in enantioselective transformations and the use of original products obtained thereby is currently under investigation.

Acknowledgements

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Keywords: asymmetric synthesis • dihydropyranones • Meldrum's acid • organocatalysis • vinylogy

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[14] CCDC 1998088, 1998089 and 1992496 contain the supplementary crystallographic data for compound (+/-)-**1aa**, (+/-)-**5aa** and (*R*)-**5aa**.

[15] The vinylogous addition of **3a** successfully took place to acyclic trifluoroacetophenone (67% yield and 93% ee) and *para*-CN-phenyl α-keto ethylester (50% yield and 82% ee) but led to the corresponding 5,6-dihydropyran-2-ones **1** due to an isomerization event for a prolonged reaction time and purification on silica gel column chromatography.

[16] In the presence of tetramethylguanidine, an intermediate like **10aa**, as a guanidinium carboxylate salt, precipitated out of the solution to provide a crystal suited for X-Ray diffraction analysis (see SI).

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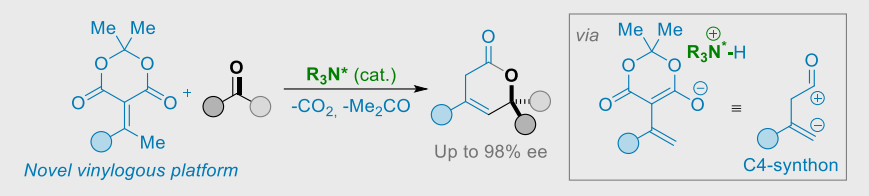

Disubstituted alkylidene Meldrum's acids proved to be novel C4-synthon capable of undergoing a vinylogous formal (4+2) cycloaddition reaction with reactive ketones to furnish an unprecedented route to chiral 3,6-dihydropyran-2-ones upon Brønsted base organocatalytic conditions.

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