Multicomponent Catalytic Enantioselective Synthesis of Isoxazolidin-5-Ones

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Julien Annibaletto, Thomas Martzel, Vincent Levacher, Sylvain Oudeyer and Jean-François Brière*

[a] Normandie Univ, UNIROUEN, INSA Rouen, CNRS, COBRA, 76000 Rouen, France.
E-mail: jean-francois.briere@insa-rouen.fr

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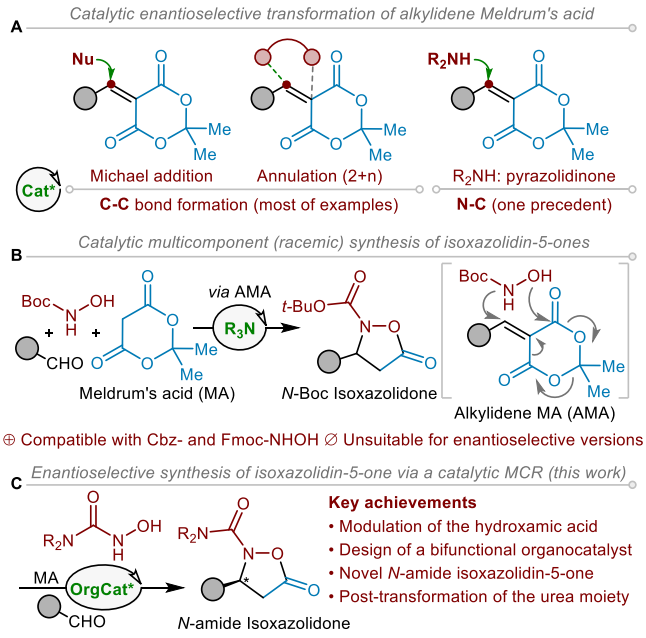
Abstract. We report herein a strategy to afford a multicomponent catalytic enantioselective synthesis of β-substituted isoxazolidin-5-ones *via* a KMC process promoted by a suited cupreine used as bifunctional organocatalyst. The hydroxamic acid component, with a sterically hindered amide moiety, proved to be key for the successful formation and transformation of the obtained original *N*-amide isoxazolidin-5-ones.

Keywords: Meldrum's acid; Multicomponent reaction; Organocatalysis; Cupreine; Isoxazolidinone

The synthetic strategy of multicomponent reaction (MCR) paves the way to versatile, straightforward and atom-economic construction of heterocyclic architectures.[1] Nevertheless, the development of catalytic enantioselective MCR, in order to tackle the synthesis of valuable chiral heterocycles while affording the opportunity of exploring the 3D-chemical space, remains a challenging endeavor in research.[2] The design of a catalyst and a catalytic manifold capable of orchestrating the selectivity issues within the complex reaction pathways of MCR is not a trivial task.[3] In that field, the Meldrum's acid (MA) based MCRs, in particular generating *in situ* the highly electrophilic alkylidene MA species (AMA),[4] have encountered a myriad of applications for heterocycles elaboration (Scheme 1).[5] Nevertheless, the catalytic enantioselective MC-transformations of alkylidene MA have essentially focused on the formation of C-C bond in processes such as Michael reactions and (2+n) annulation (n = 1, 3-4) sequences (Scheme 1A).[4],[6],[7] Recently, we successfully devised an unprecedented enantioselective catalytic aza-Michael reaction of pyrazolidinones to alkylidenes MA.[8] To the best of our knowledge, this is the single catalyst-controlled asymmetric C-N bond formation on such markedly electrophilic and thereby challenging Michael acceptors.[9]

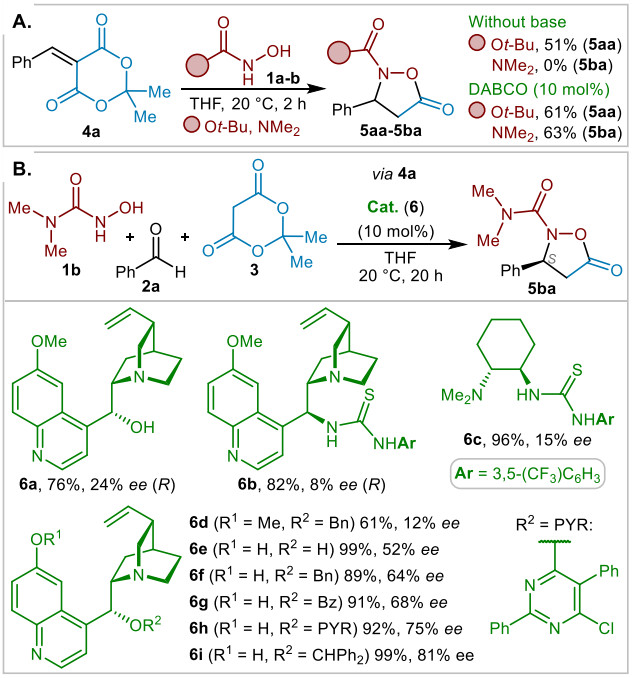


Scheme 1. Context of the investigation.

We recently disclosed an unprecedented multicomponent synthesis of β-substituted isoxazolidin-5-one derivatives (Scheme 1B),[10] which are useful precursors of valuable β^3-amino acid derivatives subsequent to the easy N-O bond cleavage.[11] However, the development of an enantioselective version of this unique multicomponent Knoevenagel-aza-Michael-Cyclocondensation (KMC) reaction, via the *N*-BocNHOH addition to alkylidene MA intermediates, proved to be very challenging thus far.[10a],[12] Indeed, few groups succeeded in the direct catalytic enantioselective construction of valuable β-substituted isoxazolidin-5-ones having a versatile *N*-EWG pendant such as a Boc group.[11],[13],[14],[15] Very recently, the group of Birman exploited the readily availability of racemic *N*-Boc isoxazolidin-5-ones by means of the multicomponent KMC reaction,[10a] to perform an elegant while efficient kinetic resolution

through an alcoholysis sequence.[16] This work prompts us to report our effort towards the development of an unprecedented catalytic enantioselective multicomponent synthesis of isoxazolidin-5-ones (Scheme 1C). This achievement sheds light on (1) the key reactivity modulation (through *N*-EWG) of hydroxamic acid component (2) and the use of a suitable bifunctional chiral organocatalyst, in order to successfully secure the asymmetric construction of original *N*-amide isoxazolidin-5-ones.

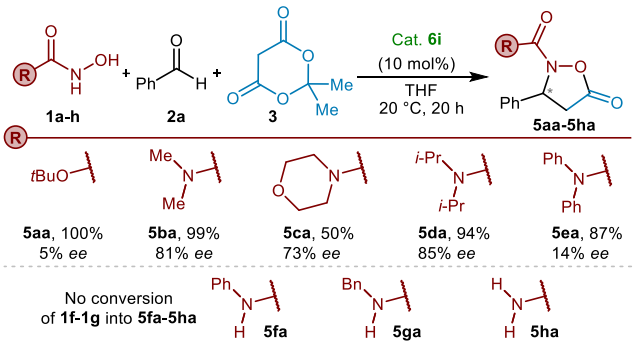
Our working hypothesis was based on the initial observation that *N*-Boc hydroxylamine **1a** leads to a rather facile domino addition-cyclocondensation sequence to alkylidene Meldrum's acid **4a** even in the absence of a Brønsted base (Scheme 2A). This marked background process might compete with an asymmetric sequence. Interestingly, the analogous *N*-amide hydroxylamine **1b** did not show any uncatalyzed reaction, although a smooth formation of isoxazolidinone **5ba** occurred in 63% yield (2 hours) in the presence of 10 mol% of DABCO. Importantly, these types of *N*-amide isoxazolidinone **5ba** are not well investigated in the literature and constitute a novel platform in this series on their own. Then, we embarked in the development of an enantioselective multicomponent KMC from *N*-amide hydroxylamine **1b** (Scheme 2B).



Scheme 2. (A) Working hypothesis and (B) proof of principle.

At the onset, the regular Cinchona alkaloid derived organocatalysts such as quinine derivatives **6a** or **6b**, together with Takemoto bifunctional cyclohexanediamine **6c** led to isoxazolidinone **5ba** with enantiomeric excesses (*ee*) lower than 24% and good NMR yields ranging from 76% to 96% (see SI for the overall screening conditions). In spite of the fully *O*-substituted quinine **6d** furnished low 12% *ee* in moderate 61% yield, the counterpart **6e**, with the two free hydroxyl functional groups gave improved 52% *ee* and excellent 99% yield.[17] The use of cupreine *O*-protected at C9 (**6f-g**, R^2 = Bn, Bz and PYR) benefited to the selectivity of the MCR, and the most sterically hindered PYR-derivative **6h** developed by Deng provided product **5ba** with good 75% *ee*.[18] Eventually, the original and bulky benzhydryl-derived cupreine **6i**, that we have recently developed for an asymmetric decarboxylative protonation reaction,[19] turned out to be the best organocatalyst giving rise to the formation of **5ba** with 81% *ee* and excellent 99% yield.

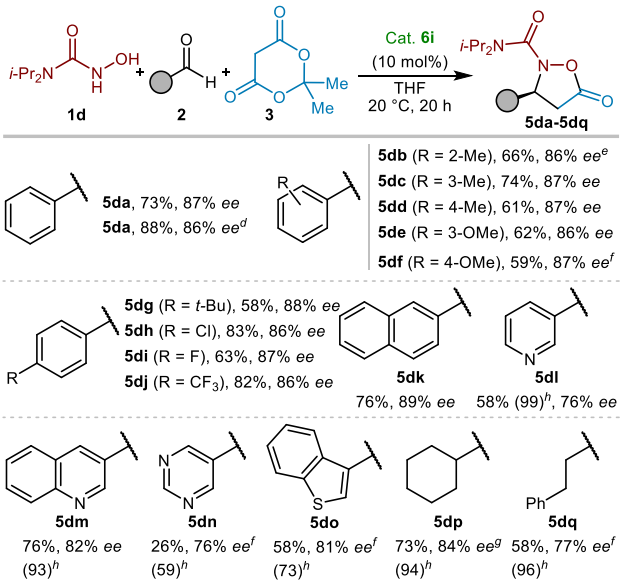
Having this competent catalyst **6i** in hands, we subsequently investigated the influence of the amide moiety of a series of hydroxamic acids (Scheme 3). At first, it was confirmed that *N*-Boc-NHOH **1a** was not a suited nucleophile even in the presence of the most efficient cupreine catalyst **6i** (5% *ee*). On the other hand, the morpholine precursor **5c** led to the corresponding isoxazolidinone **5ca** with a decreased *ee* of 73% and aniline type hydroxylamine **5e** gave a poor selectivity (14% *ee*), which tends to demonstrate that a pronounced electron-poor property of the amide function does not benefit to *ee*. Then, we moved to the bulkier *bis-iso*-propyl derivative **5d** which advantageously allowed an improved selectivity of 85% *ee* while securing a good 94% yield. Eventually, the reagents having a secondary amine moiety (**1f-h**) were unable to be engaged into the MCR, *showing the subtle topology prerequisite for achieving the successful enantioselective catalytic multicomponent KMC reaction.*



Scheme 3. Evaluation of various hydroxamic acids.

Next, we probed the scope and limitation of this unprecedented catalytic enantioselective multicomponent synthesis of β-substituted isoxazolidin-5-ones **5** with various aldehydes and hydroxamic acid **1d** (Scheme 4). The model reaction with benzaldehyde allowed to obtain the corresponding product **5da** with 86-87% *ee* and isolated yields of 73%, which was improved to 88% on 1 mmol scale. As a rule of thumb, a slight drop in isolated yields was observed due to the likely somewhat hydrolytic sensitivity of these products

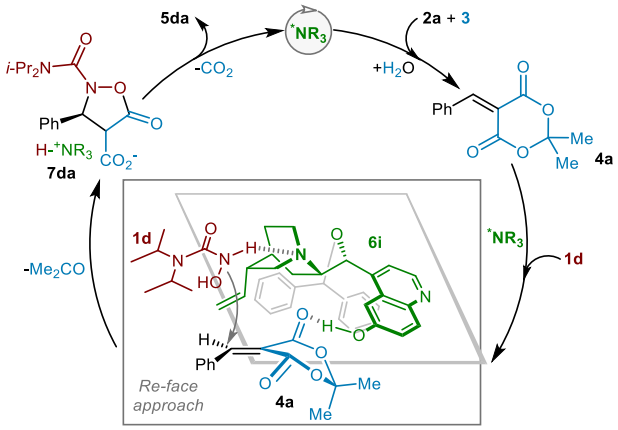
during silica gel column chromatography. A large series of *ortho*- (**5db**: 2-Me, 66%, 86% *ee*), *meta*- (**5dc**: 3-Me, 74%, 87% *ee* and **5de**: 3-OMe, 62%, 86% *ee*) and *para*-substituted (**5dd**, **5df** and **5dg**-**5dj**, 59-83%, 86-88% *ee*) isoxazolidinones **5db**-**5dj** were easily synthesized from aromatic aldehyde derivatives with homogenous *ee* of 86-88%, regardless to the nature of the R-group, and yields ranging from 59% to 89%. The product **5dk** was obtained in 76% yield and good 89% *ee* from 2-naphthaldehyde **2k**, and pyridine-2-carboxaldehyde **2l** allowed the construction of the corresponding product **5dl** in 58% yield (99% estimated by ^{1}H NMR with an internal standard) albeit in drop of *ee* to 76%. Accordingly, a slightly less homogenous series stemmed from the use of more challenging heteroaromatic aldehydes as seen with quinoline derived product **5dm** which was obtained in 82% *ee* (76% yield), while 5-pyrimidyl **5dn** and benzothiophene **5do** derivatives were isolated in 76% *ee* (26% yield) and 81% *ee* (58% yield). Interestingly, the more sensitive aliphatic aldehydes **2p**-**2q**, leading to rather unstable transient alkylidene MA,[4],[20] still allowed the construction of the corresponding isoxazolidinones **5dp** and **5dq** in 84% *ee* (73% yield) and 77% *ee* (58% yield) respectively, thanks to the MCR procedure.



Reaction condition: 0.2 mmol of each component in THF (1.3 mL) at 20 °C for 24 hours. [b] Isolated yield after column chromatography. [c] *ee* determined by chiral HPLC. [d] Carried out on 1.2 mmol scale. [e] Reaction performed at 25 °C for 48 hours. [f] Reaction performed at 30 °C for 48 hours. [g] Reaction performed at 40 °C for 48 hours. [h] Yield determined with an internal standard by ^{1}H NMR.

Scheme 4. Scope and limitations.

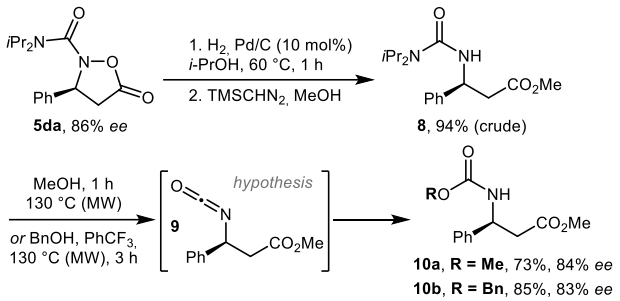
We propose a plausible mechanistic pathway as depicted in Scheme 5. At first, the organocatalyst **6i** catalyzes Knoevenagel condensation between benzaldehyde **2a** and Meldrum's acid **3** to afford the corresponding alkylidene MA **4a**.[4] Next, the hydroxylamine addition would take place on the *Re*-face of the alkylidene MA upon the guidance (through N-H activation or deprotonation events)[21] by the quinuclidine part of cupreine **6i**. Thereby, the Ph-moiety of the aza-Michael acceptor is lying away from the catalyst (preventing a steric clash), while the phenol moiety of **6i** would organized the transition state by H-bonding with one of the carbonyl of **4a**. In this scenario, we suppose that cupreine **6i** adopts a preferred *anti*-opened conformation as proposed by Cheng during insightful mechanistic investigations.[22] Then, a rapid cyclocondensation sequence would occur to give the carboxylate **7da**, in order to prevent any equilibrated aza-Michael step leading to racemization. Finally, a decarboxylative-protonation sequence furnishes the corresponding *S*-isoxazolidinone **5da** and releases the catalyst.



Scheme 5. Proposed catalytic cycle and transition state.

The *N*-amide isoxazolidinones **5d** are original compounds on their own whose reactivity remains to be explored.[23] Thus, we triggered the investigation of their transformation into valuable β^3-amino acid derivatives (Scheme 6). We were especially interested in recent investigations related to the enhanced reactivity observed with sterically hindered tertiary-amides and ureas.[24] At the onset, we carried out regular hydrogenolysis conditions in the presence of palladium on charcoal of **5da**, followed by a $TMSCH_2N_2$ promoted esterification. This sequence afforded a straightforward elaboration of the phenyl β^3-amino acid **8** as crude product in 94% yield, pure enough for the subsequent step. Then, after the exploration of reaction conditions, it was found that substrate **8**, under microwave irradiation conditions at 130 °C in the presence of an alcohol (MeOH or BnOH), led to a smooth transformation of the urea moiety into the corresponding methylcarbamate **10a** (73% yield and 84% *ee*) and the versatile *N*-Cbz derivative **10b** (85% yield and 83% *ee*) with almost no loss of *ee*. This sequence also allowed us to confirm the absolute configuration of the isoxazolidinone **5da** by chemical analogy with known compound from the literature (see SI).[25] Based on the insightful investigations of Lloyd-Jones and Booker-Milburn,[24b] we propose the formation of an isocyanate intermediate **9** under neutral conditions, which would be rapidly trapped by the external alcohol as nucleophile to provide

carbamate **10**. Nevertheless, this achievement constitutes a novel application of the salient reactivity of bulky urea functional groups to the chemistry of amino acids.



Scheme 6. Functional group transformation.

In summary, we are pleased to report hereby an enantioselective and catalytic multicomponent KMC synthesis of isoxazolidin-5-one derivatives, thanks to reactivity modulation of *N*-amide hydroxylamide reagents in combination with an original benzhydryl-derived cupreine organocatalyst **6i**. This work also sheds light on the construction of original *N*-amide isoxazolidinone derivatives, and their unique reactivity derived thereof, which takes advantage of a versatile bulky urea functional group. Further application of these types of reactivity in organic synthesis and catalysis are under investigation.

Experimental Section

To a mixture of diisopropylhydroxyurea **1d** (32 mg, 0.2 mmol, 1 equiv), Meldrum's acid **3** (28.8 mg, 0.2 mmol, 1 equiv) and cupreine organocatalyst **6i** (9.5 mg, 0.02 mmol, 10 mol%) were introduced into a tube under nitrogen and anhydrous THF was added (1.3 mL, 0.15 M/Meldrum's acid) and the aldehyde **2a** (0.2 mmol, 1 equiv) at room temperature. The resulting solution was stirred at 20 °C for 20 hours. The crude mixture was then diluted with an aqueous Na_2CO_3 solution (10% w/w) and the aqueous layer was extracted three times with CH_2Cl_2. The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was quickly purified by flash column chromatography on silica gel to afford isoxazolidin-5-one **5da** (38 mg, 73%, 87% *ee*). The reaction was carried out on 1.2 mmol to give **5da** in 88% yield (307 mg, 86% *ee*).

Acknowledgements

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