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Organocatalyzed Multicomponent Synthesis of Isoxazolidin-5-ones

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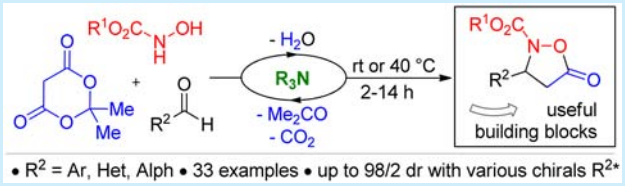
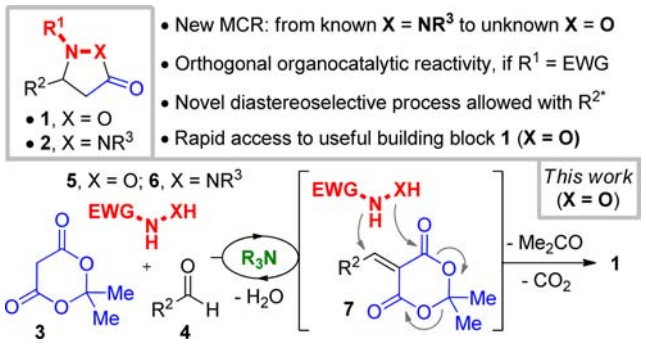
Supporting Information

ABSTRACT: An unprecedented multicomponent organocatalyzed Knoevenagel−aza-Michael−cyclocondensation reaction between Meldrum's acid, hydroxylamines, and aldehydes afforded a straightforward entry to a large array of racemic and *syn*-diastereoenriched isoxazolidinones as synthetically useful scaffolds. This process revealed a markedly facile aza-Michael−cyclocondensation sequence as a key domino reaction between RCO_2NHOH and transient alkylidene Meldrum's acid upon Brønsted base catalysis.



The construction of chiral heterocyclic architectures making use of organocatalytic multicomponent reactions (MCRs) not only shortened the synthetic efforts toward chemical diversity but paved the way for sustainable chemistry.[1] Nonetheless, the achievement of these modern domino processes ought to challenge (1) an orchestration of orthogonal organocatalytic modes of activation, (2) functional-group compatibility, and (3) a successful stereoselective outcome.[2] Isoxazolidin-5-ones **1** (Scheme 1, X = O) are valuable motifs

Scheme 1. Context of the Methodology



encountered in bioactive compounds,[3] and they have emerged as useful building blocks for the elaboration of β-amino acids,[3c,f] nucleoside mimics,[3e] and amino sugar derivatives,[3a] to name a few.[3b] The construction of chiral scaffolds **1** elicited recent developments of catalytic syntheses both racemic[4] and asymmetric.[4d−f,5,6] In particular, Sibi achieved the enantioselective 1,4-addition of BnNHOH to activated acrylamides upon the catalytic influence of magnesium complexes.[5] Córdova performed a chiral iminium promoted conjugated addition of BocNHOH to enals giving 5-hydroxyisoxazolidines, some of them being subsequently oxidized into isoxazolidin-5-ones **1**.[6] Nevertheless, the direct catalytic construction of isoxazolidinone derivatives **1** using a MCR process remains elusive. Relevant to this context, the multicomponent synthesis of isoxazolidine compounds developed by Bode allowed,[7] in few subsequent steps, the formation of enantiopure *N*-Boc isoxazolidin-5-one derivatives **1**.

We recently discovered an enantioselective formation of bicyclic pyrazolidinone derivatives **2** (X = NR^3) based on a multicomponent Knoevenagel−aza-Michael−cyclocondensation (KaMC) reaction making use of the reactivity of Meldrum's acid **3** (Scheme 1).[8] This process highlighted an unprecedented asymmetric and chemoselective aza-Michael reaction to NHR^1 of pyrazolidinones **6** (R^1 = EWG) to highly reactive transient alkylidene Meldrum's acids **7**,[9,10] unusually catalyzed at room temperature by a dedicated tertiary Brønsted base, namely $(DHQ)_2PHAL$.[8] This MCR complements racemic domino hetero-Michael−cyclocondensation reactions involving alkylidene Meldrum's acid **7**, which usually leads to six-membered rings and, in many cases, requires harsh conditions.[11−13] Nonetheless, we were not able to extrapolate this sequence to noncyclic hydrazine showing a specific reactivity in action. We are pleased to report herein a novel development of the organocatalytic multicomponent KaMC reaction between hydroxylamines **5** and Meldrum's acid **3**, achieving a straightforward construction of isoxazolidin-5-one derivatives **1**. Furthermore, this MCR process is performed under mild conditions and tolerates various chiral aldehydes **4**, allowing a new entry to diastereo- and enantioenriched scaffolds **1** as useful building blocks.

A model reaction was carried out with a stoichiometric mixture of Meldrum's acid **3**, dihydrocinnamaldehyde **4a**, and *N*-benzylhydroxylamine **5a** in the presence of Hünig base (20

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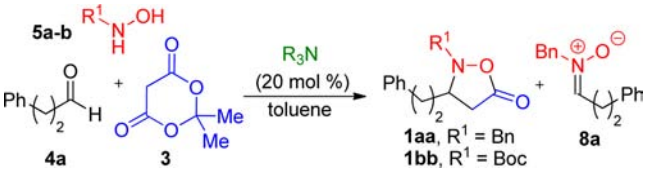
mol %) in toluene (Table 1, entries 1 and 2). A sluggish process was observed, and the corresponding *N*-Bn isoxazolidinone

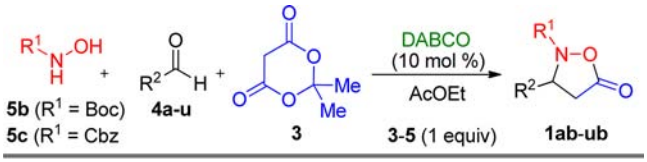
Table 1. Proof and Optimization[a]



entry	R^1	R_3N	temp (°C)	time (h)	yield[b] (%)
1	Bn (**5a**)	*i*-Pr_2EtN	20	14	11 (**1aa**)[c]
2	Bn (**5a**)	*i*-Pr_2EtN	40	14	50 (**1aa**)
3	Boc (**5b**)	*i*-Pr_2EtN	20	1	75 (**1ab**)
4	Boc (**5b**)		20	1	0 (**1ab**)
5	Boc (**5b**)	DMAP	20	1	61 (**1ab**)
6	Boc (**5b**)	DBU	20	1	82 (**1ab**)
7	Boc (**5b**)	piperidine	20	1	79 (**1ab**)
8	Boc (**5b**)	pyrrolidine	20	1	82 (**1ab**)
9	Boc (**5b**)	proline	20	1	28 (**1ab**)
10	Boc (**5b**)	DABCO	20	1	96 (**1ab**)

[a]Reaction performed at 0.1 M on 0.25 mmol scale with 1 equiv of each components. [b]NMR yield determined by an internal standard. [c]Formation of 3% of nitrone **8a**.

Scheme 2. Scope and Limitation



- R^1 = Boc, R^2 = Alph (2 h, rt)

1ab, R^2 = $Ph(CH_2)_2$, 75%
1bb, R^2 = $Me(CH_2)_4$ 66%
1cb, R^2 = *i*$Pr(CH_2)$, 84%
1db, R^2 = *i*Pr, 77%
1eb, R^2 = Cy, 84%
1fb, R^2 = Cyclopropyl, 77%
1gb, R^2 = CH_2=$CH(CH_2)_2$, 63%
1hb, R^2 = $BocNH(CH_2)_2$, 73%
1ib, R^2 = $BnO(CH_2)$, 59%
1jb, R^2 = $MeS(CH_2)_2$, 82%
1kb, R^2 = EtO_2C, 55%

- R^1 = Cbz, R^2 = Alph (2 h, rt)

1ac, R^2 = $Ph(CH_2)_2$, 70%
1hc, R^2 = $BocNH(CH_2)_2$, 68%

- R^1 = Boc, R^2 = Ar (2 h, rt
- (2-14 h, 40 °C)

1lb, R^2 = Ph, 73%
1mb, R^2 = 4-$MeOC_6H_4$, 66%
1nb, R^2 = 4-ClC_6H_4, 67%
1ob, R^2 = 4-$NO_2C_6H_4$, 71%
1pb, R^2 = 2-benzothiophene, 65%
1qb, R^2 = 6-Br-2,3-$MeOC_6H_2$, 13%
1qb, R^2 = 6-Br-2,3-$MeOC_6H_2$, 86%
1rb, R^2 = 4-HO-3-$MeOC_6H_3$, 59%
1sb, R^2 = 3-pyridyl, 81%
1tb, R^2 = 3-*N*Boc-indol, 81%
1ub, R^2 = *trans*-PhCHCH, 42%
1ub, from alkylidene MA **7u**, 76%

product **1aa** was obtained up to 50% NMR yield even at 40 °C (entries 1 and 2). In line with our previous observations, the presence of nitrone **8a** at rt showed that a slow and concurrent (3 + 2)-cycloaddition between **8a** and Meldrum's acid **3** might occur (entry 1).[4d] We turned our attention to the electron-poor *N*-Boc hydroxylamine **5b** in order to prevent the in situ formation of dipole species.[14] Furthermore, this approach is meant to furnish directly *N*-carbamate isoxazolidin-5-ones **1ab**, useful precursors for *β*-peptides elaboration or total synthesis.[6a,7,3b] To our delight, the rapid formation of the *N*-Boc isoxazolidinone **1ab** took place at 20 °C in 75% NMR yield upon Hünig base catalysis (entries 3 and 4). This MCR process was promoted by various tertiary (entries 5 and 6) and secondary amines (entries 7 and 8) to give **1ab** with yields ranging from 28 to 82%. Among them, DABCO achieved the highest 96% yield within only 1 h (entry 9; see the SI for further details). This unprecedented multicomponent construction of isoxazolidinones **1** not only opens a straightforward access to these useful architectures but also highlights an extremely facile domino KaMC process involving the unique Meldrum's acid reactivity.[9]

A survey of conditions revealed the acceleration of the multicomponent KaMC reaction in more polar and greener AcOEt solvent (see the SI), which allowed us to probe a large array of aldehydes **4** in the presence of 10 mol % of DABCO catalyst (Scheme 2). After 2 h at room temperature, the MCR occurred with linear **4a**–**c**, *α*-branched **4d**–**f**, and an alkene-derived aliphatic aldehyde **4g** to give the corresponding *N*-Boc-isoxazolidinones **1ab**–**gb** with isolated yields ranging from 63 to 84%. This reaction also tolerated aliphatic aldehydes flanked by NHBoc (**4h**), ether (**4i**), thioether (**4j**), and ester (**4k**) functional groups furnishing products **1hb**–**kb** with 55–82% yields. This approach was also carried out from CbzNHOH **5c** to afford *N*-Cbz isoxazolidinones **1ac** and **1hc** in 68–70% yields displaying orthogonal protective groups. Moreover, aromatic- and benzothiophenone-derived aldehydes **4l**–**p** were easily transformed into *N*-Boc-5-arylisoxazolidinones **1lb**–**pb** in 65–73% yield. Aldehyde **4q** having an aryl pendant with two electron-donating methoxy functional groups was reluctant to react under these conditions (13% after 2 h at rt). However, heating at 40 °C during 14 h restored the efficiency of the MCR process to give products **1qb**–**rb** with electron-rich aryl moieties in 86 and 59% yield, respectively. In these conditions, isoxazolidinones flanked by a heterocyclic ring such as 3-pyridyl **1sb** and *N*-Boc-indole **1tb** were easily obtained with 81% yield. We found that cinnamaldehyde **4u** underwent a slow transformation into the novel allylic isoxazolidinone **1ub** (42% yield). Nevertheless, improved 76% isolated yield was obtained by starting from the Meldrum's acid (MA) aza-Michael acceptor **7u**.[9]

Despite previous occurrences of diastereoselective Michael reaction onto *γ*-chiral alkylidene Meldrum's,[15] even upon organocatalytic MCR conditions,[16] the stereoselective N–C bond formation has yet to be developed.[17] To our delight, the stereoselective multicomponent KaMC reaction took place smoothly upon DABCO catalysis. Glyceraldehyde **4v** and Ley's aldehyde **4w**[18] led to *γ*-chiral *N*-Boc and *N*Cbz isoxazolidinones **1vb**–**wc** with high dr >96:4 as testified by ^{1}H NMR of the crude mixture (Scheme 3). An erosion of the enantiopurity of products **1vb**–**vc** was observed (88–91% ee) due to the configurational fragility of glyceraldehyde **4v**. However, the use of pyrrolidine instead of DABCO minimized the racemization, likely via an iminium-catalyzed Knoevenagel condensation,[15b,16b,19] and furnished products **1vb** and **1vc** with ee of 99% and 96%, respectively, and a slight erosion of dr (80/20 and 90/10). The major *syn*-isomers **1vb**–**wc** were easily obtained with 65–88% isolated yields and at least 98/2 dr after flash column chromatography. Importantly, the use of electron-rich BnNHOH **5a** led to low dr and sluggish reaction rates and demonstrated the uniqueness of our conditions (see the SI for more details).[17] Along this line, 10 mol % of pyrrolidine allowed the transformation of Garner's aldehyde **4x** (85% and 59% for **1xb**–**xc**), 2-pyrrolidine carboxaldehyde **4y** (72% and 70% for **1yb**–**yc**), and thiazolidine carboxaldehyde **4z** (78% and 73% for **1zb**–**zc**) into the corresponding *syn*-isoxazolidinones (dr >95/5–98/2 after purification) with ee's ranging from 95 to 99%.

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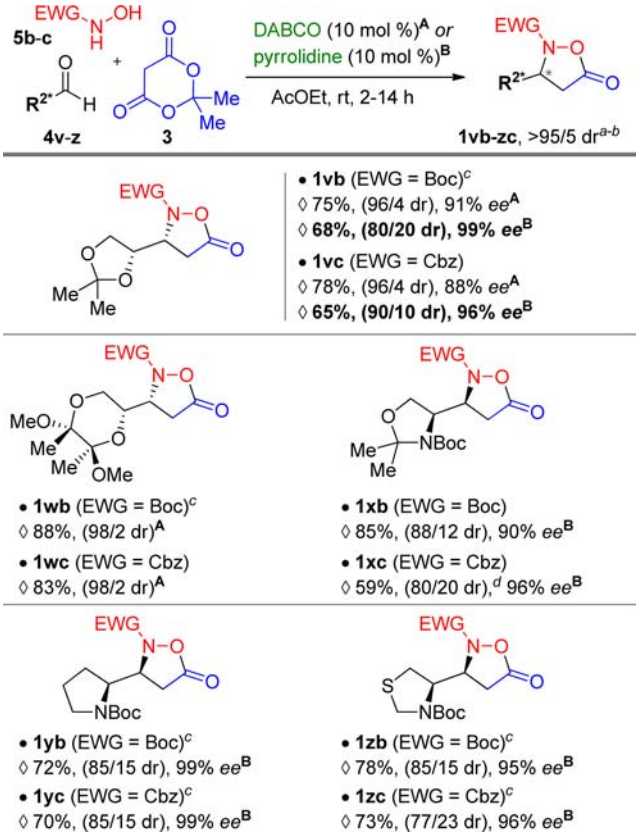
Scheme 3. Diastereoselective Approach

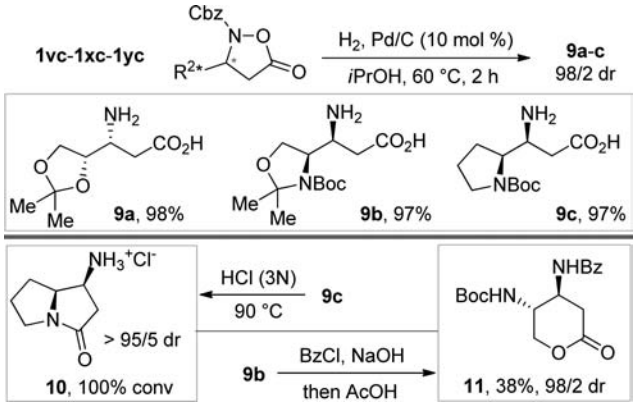


[a]Yields of the major *syn*-diastereomer (>98/2 dr except for **1xb**, **1zb**, and **1zc** > 95/5 dr) isolated after flash column chromatography. [b]dr (in parentheses) determined by ^{1}H NMR on the crude product. [c]Determined by single-crystal X-ray diffraction. [d]At 0 °C.

The labile Garner's aldehyde **4x** provided the corresponding *N*-Boc products **1xb** with somewhat lower 90% ee. Most notably, the determination of dr ratios of compounds **1xb−zc** was not trivial as these carbamate derivatives displayed rather stable rotamers. Nonetheless, a complete characterization by NMR, including variable-temperature NMR and chemical-exchange NMR experiments (EXSY), allowed the discrimination of rotamer/diastereoisomer NMR signals (see the SI). Accordingly, an estimation of the stereoselectivity on the crude mixtures revealed dr ranging from 77/23 to 88/12 for **1xb−zc** in favor of the *syn* stereoisomer in all cases. The remarkable general *syn* induction was unequivocally proven by a series of six single-crystal X-ray diffractions (Scheme 3) and chemical transformations (vide infra).

Chiral *N*-Bn isoxazolidinone derivatives flanked by a δ-C*−X bond (X = O, N) are known to be high value building blocks for the elaboration of bioactive compounds.[3c,e,20] In order to highlight the usefulness of our readily available and orthogonal *N*-carbamate homologues, it was shown that *N*-Cbz isoxazolidinones **1vc,xc,yc** underwent clean hydrogenolysis reactions to give various β-amino acids **9a−c** (Scheme 4). The cyclization of **9c** upon acidic conditions allowed a concise access to aminopyrrolizidine **10** and complemented literature procedures.[21] Eventually, inspired by Merino's work,[20b] we showed that β-amino acid **9b** is a useful precursor to functionalized lactone **11** obtained in 38% yield over two steps but along a one-pot sequence providing a single *anti*-diastereoisomer. During

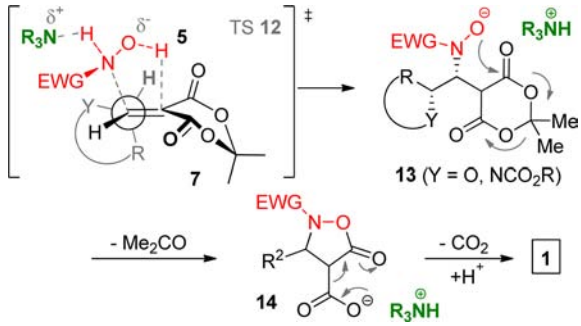
Scheme 4. Useful Chemical Transformations



these sequences, the initial diastereoselective ratio were virtually preserved.

Since the early observations,[22] recent mechanistic investigations[17] have explained the facility with which electron-rich *N*-alkyl hydroxylamines add to acrylates due to a noncatalyzed concerted (3 + 2) cycloaddition-like process. Furthermore, the high electrophilic character of alkylidene Meldrum's acid derivatives **7** (>10[11] than the corresponding benzylidene malonate)[9] has been highlighted during model aza-Michael reactions, which were assumed to be accelerated by an intramolecular hydrogen bond between the R_2N-H nucleophile and the forming enolate moiety in the transition state (TS).[23] Based on this background knowledge, we propose that the N−C bond formation to alkylidene Meldrum's acid **7** occurs with the concomitant hydrogen transfer from OH of **5** to give **13** following a (3 + 2) cycloaddition process (TS **12**, Scheme 5).[24]

Scheme 5. Mechanistic Proposal



The Brønsted base catalyst may promote the addition reaction of the *N*-EWG hydroxylamine **5** leading to the rapid transformation of the transient Knoevenagel product **7**.[19] It is also assumed that the *N*-EWG facilitates the base catalyzed decarboxylation event of **14** by stabilizing the corresponding enolate of isoxazolidinones **1** and the TS derived thereof.[4e]

As a preliminary proposal, the general *syn*-selectivity could be rationalized in line with Yamamoto's model (TS **12**),[15b,16b,25] in which the allylic 1,3-strain is minimized when C-*H* and Meldrum's acid moiety faced to each other. Then, the incoming nucleophile would approach from the same face of the "outside" positioned γ-heteroatom (Y) of the more reactive conformation.

In summary, we discovered an extremely facile organocatalyzed multicomponent KaMC reaction between aldehydes, Meldrum's acid **3**, and *N*-carbamate-NHOH **5**. This MCR allows not only a straightforward elaboration of a large array of racemic

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isoxazoldin-5-ones **1** but affords a new entry to diastereo- and enantioenriched scaffolds **1** as useful building blocks in organic synthesis. The development of an enantioselective MCR is currently under investigation.[26]

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02755.

Experimental procedures and characterization for new compounds (PDF)
X-ray data for **1vb** (CIF)
X-ray data for **1wb** (CIF)
X-ray data for **1yb** (CIF)
X-ray data for **yc** (CIF)
X-ray data for **1zb** (CIF)
X-ray data for **zc** (CIF)

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Notes

The authors declare no competing financial interest.

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