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A Three-Component Reaction Based on a Remote-Group-Directed Dynamic Kinetic Aza-Michael Addition: Stereoselective Synthesis of Imidazolidin-4-ones

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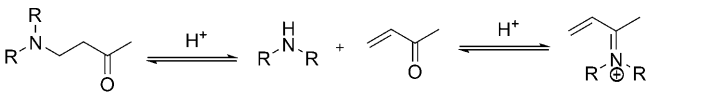
Imidazolidin-4-ones, and compounds of similar structure, constitute a widespread structural motif in natural products and pharmaceuticals.[1] Imidazolidin-4-one derivatives have shown a range of biological activities,[2] such as antimalarial activity,[3] antiproliferative activity for melanoma,[4] and so forth. Imidazolidin-4-ones have also been widely used in peptidomimetics,[5] as chiral auxiliaries for the synthesis of amino acids and other important compounds,[6] as an important chiral building block in the total synthesis of natural products,[7] and, most recently, as organocatalysts for iminium-based reactions.[8] Even though other methods are available,[9] the general synthetic approach to imidazolidin-4-ones is through condensation of protected amino acids or peptides with carbonyl compounds followed by intramolecular cyclization.[3,8–10] This reaction can be catalyzed by an acid[11] or a base.[5,12] Despite the presence of chiral center(s) in the amino acids/peptides, the diastereoselectivity of the formation of imidazolidin-4-ones is low. Furthermore, N1-unsubstituted imidazolidin-4-ones are unstable and readily undergo hydrolysis under acidic and neutral conditions.[10b] Given the importance of this class of compounds, a stereoselective synthesis of stabilized imidazolidin-4-ones is desirable.

Aza-Michael additions have grown into an important strategy for constructing C–N bonds.[13] These additions typically occur under basic conditions,[14] but Lewis acids[15] and organocatalysts[16] have also been shown to catalyze aza-Michael additions. In contrast, Brønsted acid catalyzed aza-Michael additions,[17] in particular intermolecular addition of simple amines, are very rare.[18] Herein, we report the highly diastereoselective formation of stable imidazolidin-4-one derivatives through a three-component reaction based on a Brønsted acid catalyzed, remote-group-directed dynamic kinetic aza-Michael addition.

N1-unsubstituted imidazolidin-4-ones can be stabilized by non-stereoselective formation of a salt[8] or by acylation.[3a,6b,19] We are interested in N1 alkylation through aza-Michael addition, which can provide a stable tertiary amine and, at the same time, introduce a new functional group (a carbonyl group) to the structural motif that could open up the compound to wider reaction possibilities. For simple secondary amines there will be competition between iminium activation and aza-Michael addition under acidic conditions (Scheme 1), and iminium formation is generally favored. We



Scheme 1. Iminium activation and aza-Michael addition of a secondary amine under acidic conditions.

intend to invert this by introducing a remote directing group,[20] so that the carbonyl of the unsaturated ketone is activated and the unstable secondary amine is oriented in a favorable position for the aza-Michael addition.

To test this idea, we synthesized N1-unsubstituted imidazolidin-4-ones **3a** and **4a** (Scheme 2). Under acidic conditions, pyridin-2-yl incorporated amino amide **1a** reacted with aldehyde **2a** to give a mixture of two diastereomers (**3a**/**4a**, 1:1.6). Compounds **3a** and **4a** were separated by column chromatography (silica). Even though **3a** and **4a** were stable enough to undergo column chromatography, isomerization was observed in solution under neutral conditions within two days (see Supporting Information).[21] It is expected that, under acidic conditions, the pyridyl moiety

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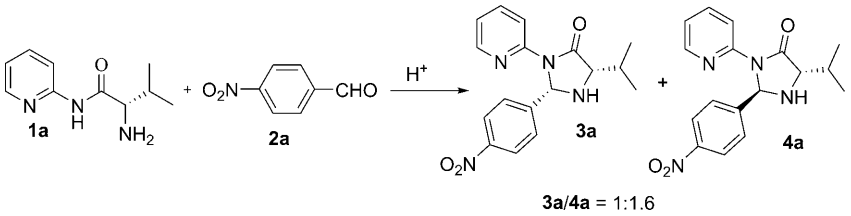


Scheme 2. Formation of N1-unsubstituted imidazolidin-4-ones under acidic conditions.

will be protonated, which will activate the Michael acceptor (methyl vinyl ketone, MVK) and, more importantly, the protonated pyridyl group will act as a remote directing group to position the Michael acceptor and the secondary amine in a favorable orientation for aza-Michael addition (Figure 1).

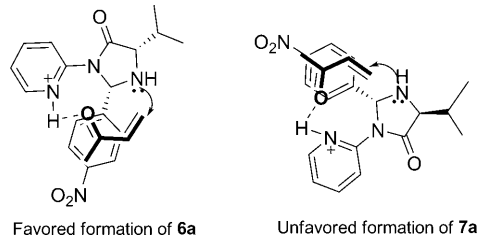
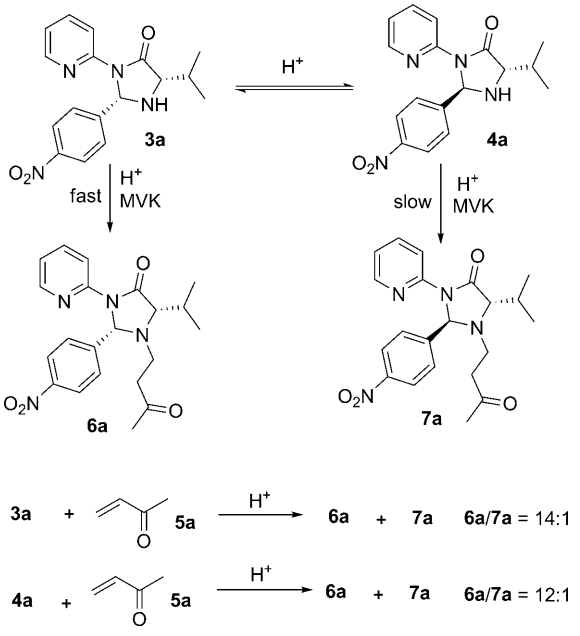


Figure 1. Proposed transition states of the aza-Michael addition.

N1-unsubstituted imidazolidin-4-ones **3a** and **4a** were then treated with MVK (**5a**) under acidic conditions (Scheme 3). We were excited to observe that both **3a** and **4a** reacted with MVK to afford the desired N1-substituted imidazolidin-4-ones **6a** and **7a**, respectively, in high yields (90 and 91%, respectively). To our surprise, both the *cis*-(**3a**) and *trans*-isomers (**4a**) gave the *cis*-product (**6a**) as the major product with a d.r. of 14:1 and 12:1, respectively.

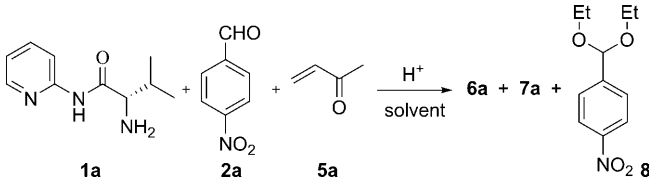


Scheme 3. Dynamic kinetic aza-Michael addition.

The preferred formation of the *cis*-product is likely to follow a dynamic kinetic pathway (Scheme 3).[22] Our ^{1}H NMR data have shown that an equilibrium exists between **3a** and **4a** (see Supporting Information). Therefore, we speculate that the reaction of **3a** with MVK is faster than that of **4a** due to its reduced steric hindrance (the isopropyl group assumes a pseudo axial orientation in the *trans*-isomer (**4a**), Figure 1),[23] and this rate difference enforces the highly diastereoselective formation of the *cis*-product **6a**.

Having observed the highly diastereoselective alkylation of unstable secondary amines, we decided to attempt a three-component reaction to take advantage of the dynamic kinetic aza-Michael addition. Multicomponent reactions (MCRs) have become an important synthetic strategy in organic synthesis to build up structural and functional complexity owing to their reaction efficiency, low cost, and atom economy.[24] However, due to the coexistence of multiple substrates and functional groups, the chemo- and stereoselectivity of MCRs remains a challenge. The three-component reaction was carried out by mixing **1a**, **2a**, and **5a** directly in ethanol in the presence of trifluoroacetic acid (TFA; Table 1, entry 2). Two equivalents of TFA were

Table 1. Optimization of reaction conditions.[a]



Entry	Acid	Solvent	T [°C]	t [h]	d.r.[c]	Yield [%][d]
1	–	EtOH	25	24		0
2	TFA (2 equiv)	EtOH	25	12	>50:1	37(51)[e]
3	TsOH (20%)	EtOH	25	12	23:1	40 (40)[e]
4	$Cu(OTf)_2$(10%)	EtOH	25	24	7:1	54
5	$Yb(OTf)_3$(10%)	EtOH	70	12	9:1	61
6	TFA (20%)	EtOH	25	24	3:1	50
7	TFA (2 equiv)	THF	66	24	9:1	40
8	TFA (1 equiv)	THF	25	36	3:1	50
9	TFA (20%)	THF	66	24	1.4:1	30
10	TFA (2 equiv)	DMF	25	48	>50:1	63
11	TFA (2 equiv)	CH_3CN	25	48	14:1	50
12	TFA (2 equiv)	CH_2Cl_2	44	15	>50:1	67
13	TFA (2 equiv)	isopropanol	25	48	>50:1	85
14[b]	TFA (2 equiv)	isopropanol	25	48	5:1	35
15[b]	TsOH (20%)	isopropanol	25	48	9:1	67

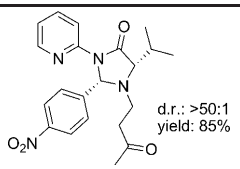
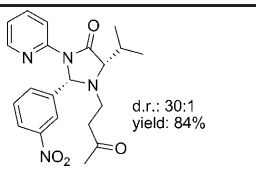
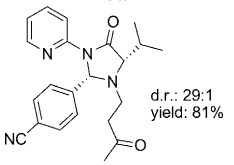
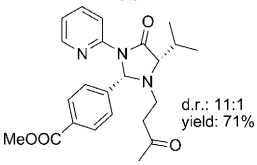
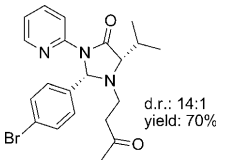
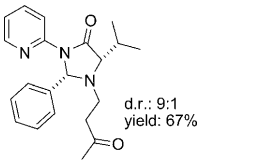
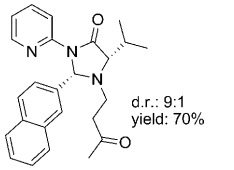
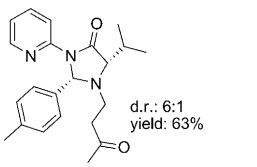
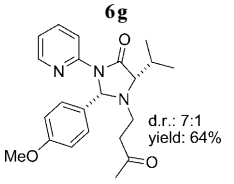
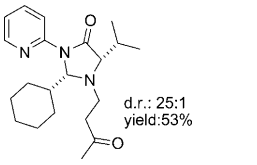
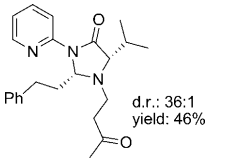
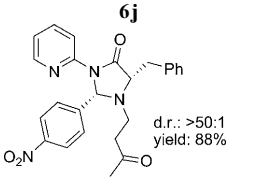
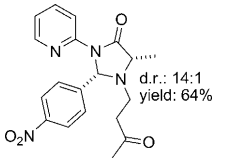
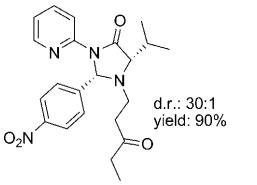
[a] The reactions were carried out with **1a** (0.2 mmol), aldehyde (0.22 mmol), and MVK (0.1 mL) in 1.5 mL solvent. [b] Benzaldehyde was used. [c] Determined by ^{1}H NMR spectroscopy of the crude product, *cis*-products are the major isomer. [d] Isolated yield of the major product. [e] Yield of the byproduct is given in brackets.

added to ensure the protonation of the pyridyl moiety. To our delight, this three-component reaction occurred at room temperature to give the desired product, **6a**, in 37% yield, but with excellent diastereoselectivity (**6a**/**7a** > 50:1). The excellent diastereoselectivity is attributed to the dynamic kinetic approach of the aza-Michael addition. The other major byproduct was identified as acetal **8** (51% yield, Table 1). Encouraged by these preliminary results, we decided to optimize the reaction conditions (Table 1). It was found that the strength and the amount of acid played pivotal roles in this reaction (entries 1–9). The reaction did not occur at all in the absence of an acid (entry 1). A stronger Brønsted acid (TsOH) gave the desired product in very good diastereoselectivity (d.r. = 23:1), but in low yield (40%) and quantitative formation of byproduct **8** (40% yield; entry 3). Metal Lewis acids also catalyzed the reaction, but with lower diastereoselectivity (entries 4 and 5). When less TFA was used, the diastereoselectivity decreased significantly both in ethanol (entries 2 and 6) and in THF (entries 7–9). Other solvents were also screened in order to suppress the formation of byproduct **8**. When isopropanol was used (entry 13), **6a** was obtained in 85% yield and excellent diastereoselectivity (d.r. > 50:1).

Having established optimum conditions for the three-component reaction, we investigated the substrate scope of aldehyde **2**. All of the electron-poor aromatic aldehydes gave the desired product in good yields and excellent diastereoselectivities when reacted in the presence of two equivalents of TFA in isopropanol (Table 2, entries 1–4, 12–14). However, when an electron-rich aromatic aldehyde, for example benzaldehyde, was used under similar conditions the reaction resulted in a low yield (35%) and low diastereoselectivity (d.r. 5:1; Table 1, entry 14). The reaction conditions were then optimized for electron-rich aromatic aldehydes (20 mol% of TsOH, isopropanol, Table 1, entry 15). Under these optimized conditions, all the electron-rich aromatic aldehydes produced the desired products in good yields and diastereoselectivities (entries 5–9). Electron-rich aliphatic aldehydes required higher temperatures, but also generated the desired product in reasonable yields and excellent diastereoselectivities (entries 10 and 11). Amino amides derived from L-alanine and L-phenylalanine were examined for this three-component reaction and lead to the desired product with excellent diastereoselectivities (entries 12 and 13). The reaction of ethyl vinyl ketone (EVK), another Michael acceptor, gave the expected product in 90% yield and d.r. > 50:1. However, chalcone and methyl acrylate are not reactive enough to furnish any product.

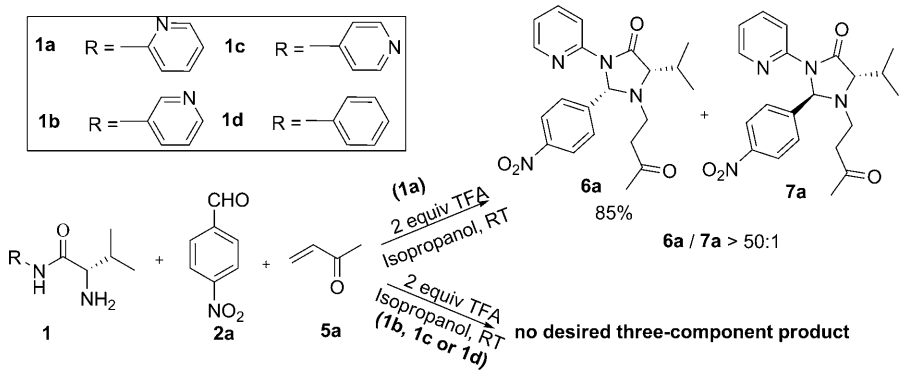
To illustrate the importance of the directing group, amides **1b**, **1c**, and **1d** were prepared (see Supporting Information for synthetic details). In sharp contrast to the reaction of **1a**, the reaction of **1b**–**1d** with **2a** and **5a** did not generate any desired three-component product (Scheme 4). These results strongly suggest that the presence of the directing group (the protonated pyridyl group) is crucial for the three-component reaction (compare **1a** and **1d**); these results also demonstrate that the directing group must be arranged in a favorable position in order to facilitate the reaction (compare **1a** with **1b** and **1c**).

Table 2. Substrate scope of the three-component reaction.

Entry	Product	Entry	Product
1[a]	 d.r.: >50:1 yield: 85% **6a**	2[a]	 d.r.: 30:1 yield: 84% **6b**
3[a]	 d.r.: 29:1 yield: 81% **6c**	4[a]	 d.r.: 11:1 yield: 71% **6d**
5[b]	 d.r.: 14:1 yield: 70% **6e**	6[b]	 d.r.: 9:1 yield: 67% **6f**
7[b]	 d.r.: 9:1 yield: 70% **6g**	8[b]	 d.r.: 6:1 yield: 63% **6h**
9[b]	 d.r.: 7:1 yield: 64% **6i**	10[c]	 d.r.: 25:1 yield:53% **6j**
11[c]	 d.r.: 36:1 yield: 46% **6k**	12[a]	 d.r.: >50:1 yield: 88% **6l**
13[a]	 d.r.: 14:1 yield: 64% **6m**	14[a]	 d.r.: 30:1 yield: 90% **6n**

[a] TFA (2 equiv), RT. [b] TsOH (20 mol%), RT. [c] TsOH (20 mol%), 80°C.

The structures of the products from the three-component reactions were determined using ^{1}H NMR, ^{13}C NMR, ^{1}H-COSY, NOESY, ESI-MS and HR-MS (see Supporting Information). A crystal structure was also determined for compound **6c** (Figure 2), further confirming its absolute configuration.



Scheme 4. Three-component reaction and the effect of remote group control.

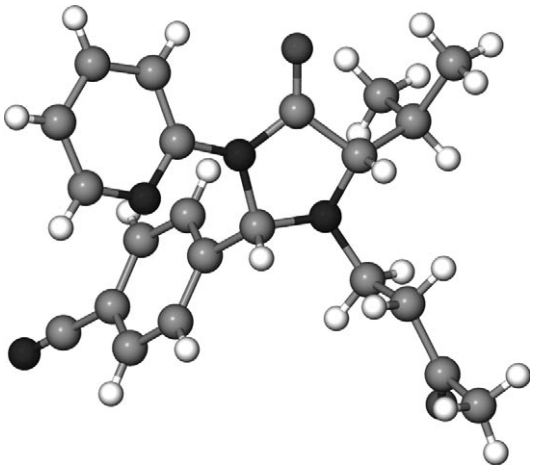


Figure 2. X-ray crystal structure of compound **6c** (see Supporting Information for experimental details).

In conclusion, we developed a highly stereoselective three-component reaction for the convenient synthesis of an important class of heterocyclic compounds. A remote group was introduced to invert the reaction process and to direct the reaction towards the desired aza-Michael addition. Dynamic kinetic transformation was applied to enforce the high diastereoselectivity. To our knowledge, this is the first example of dynamic kinetic aza-Michael addition. This design and strategy may be applied to other syntheses and multicomponent reactions.

Experimental Section

Three-component reaction: A mixture of **1a** (0.2 mmol), aldehyde (0.22 mmol), **5a**, (0.1 mL), and TFA (0.4 mmol, 30 μL) or TsOH (20 mol%, 8 mg) was stirred in isopropanol (1.5 mL) at room temperature (80 °C for aliphatic aldehydes). After the reaction was completed (monitored by TLC), the reaction mixture was treated with saturated sodium bicarbonate solution, and extracted with ethyl acetate. The solvent was removed, and a ^{1}H NMR spectrum of the mixture was taken to determine the diastereoselectivity. The mixture was then separated and purified by column chromatography (silica) to give the pure products (**6** and **7**).

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Keywords: Brønsted acid catalysis · diastereoselectivity · dynamic kinetic alkylation · Michael addition · multicomponent reactions

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