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Asymmetric Synthesis of Tetrahydropyridines via an Organocatalytic One-Pot Multicomponent Michael/Aza-Henry/Cyclization Triple Domino Reaction

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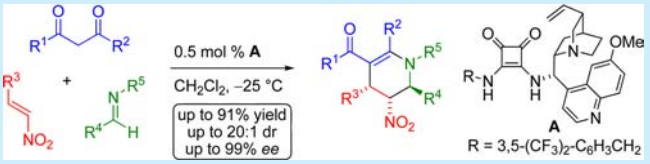
Supporting Information

ABSTRACT: A low loading of a quinine-derived squaramide efficiently catalyzes the triple-domino Michael/aza-Henry/cyclization reaction between 1,3-dicarbonyl compounds, β-nitroolefins, and aldimines to provide tetrahydropyridines bearing three contiguous stereogenic centers in good yields, excellent enantiomeric excesses, and up to high diastereomeric ratios.



The tetrahydropyridine ring belongs to a widespread substructure in naturally occurring compounds and some synthetic bioactive molecules.[1] The tetrahydropyridine **I** is an aroma compound generated from the Maillard reaction (Figure 1).[2] Arecoline **II** is a nicotinic acid based alkaloid possessing a stimulating effect due its agonistic influence on the muscarinic acetylcholine receptors.[3] Betanin **III**, a plant pigment, is another natural product containing a tetrahydropyridine unit used as a food additive.[4] The synthetic tetrahydropyridine derivative **IV** has shown proinflammatory protein inhibition activity.[5] In addition, these heterocycles also serve as precursor for the synthesis of valuable piperidine derivatives.[6]

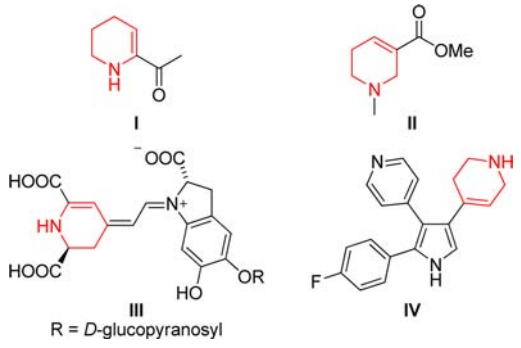
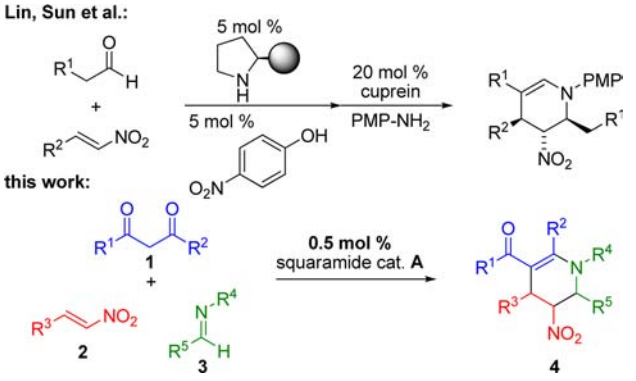


Figure 1. Selected bioactive tetrahydropyridine derivatives.

In the last 10 years, many interesting organocatalytic cascade sequences have emerged as powerful tools for the synthesis of valuable carbo- and heterocycles bearing multiple stereogenic centers in an highly stereoselective fashion.[7] Due to the broad range of bioactivity, the synthesis of tetrahydropyridine derivatives in a stereoselective manner is extremly useful. Hence, the application of organocascade sequences has been successfully extended for those compounds bearing two stereogenic centers.[8] Recently, Sun, Lin, and co-workers were able generate three stereogenic centers on a tetrahydropyridine ring by sequentially employing two different chiral organocatalysts (Scheme 1).[9] We envisaged that a tetrahydropyridine ring could be synthesized via a Michael/aza-Henry/cyclization domino sequence using merely one organocatalyst at lower catalyst loading without any other additives.

Scheme 1. Organocascade Strategies for the Synthesis of Tetrahydropyridine Derivatives



By following Rawal's[10] and others[11] as well as our own findings[12] on the squaramide-catalyzed Michael addition of dicarbonyl compounds on nitroalkenes, we synthesized the Michael adduct **5a** and carried out domino aza-Henry/half-aminalization reactions between **5a** and various imines in the presence of squaramide **A** at the onset. The *N*-tosylimine, however, did not provide any products, even in the presence of an additional base catalyst (Table 1, entry 1−5). The desired product was obtained in the case of *N*-(*p*-methoxybenzyl) (PMB) and *N*-(*p*-methoxypenyl) (PMP) imines, although the yield was not satisfactory (Table 1, entries 6−13). By switching

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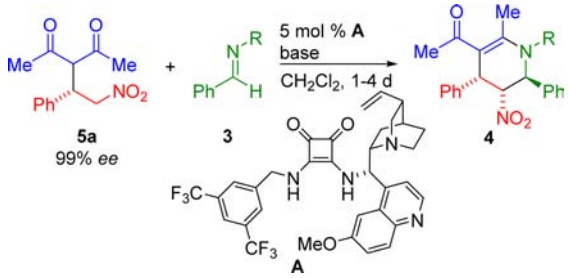
Table 1. Screening of Various Imines and Conditions for the Optimization of the Aza-Henry/Condensation Reaction Sequence[a]



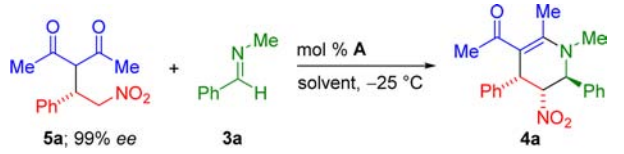
entry	R	base[b]	temp (°C)	yield[c] (%)	dr[d]	ee[e] (%)
1	Ts		−25	0		
2	Ts	DBU (20)	−25	0		
3	Ts	DBU (20)	25	0		
4	Ts	K_2CO_3 (50)	−25	0		
5	Ts	morpholine (20)	−25	0		
6	PMP		−25	14	n.d.	n.d.
7	PMP	DBU (20)	−25	18	n.d.	n.d.
8	PMP	DBU (20)	25	0		
9	PMP	K_2CO_3 (50)	−25	0		
10	PMB		−25	13	n.d.	n.d.
11	PMB		25	11	n.d.	n.d.
12	PMB	DBU (20)	−25	41	1.4:1	n.d.
13	PMB	DBU (25)	25	5	n.d.	n.d.
14	Me		−25	79	1.9:1	98
15	Me		25	67	1:1.1	n.d.
16	Me	DBU (30)	25	21	1:1.3	n.d.
17	*t*-Bu		−25	0		

[a]Reactions were carried out on a 0.25 mmol scale with 0.5 mmol (2.0 equiv) of imine and 5 mol % of squaramide catalyst **A** in 0.2 mL of CH_2Cl_2 (c = 1.25 M) for 1.5−4 days. [b]Amount of additive given in mol % in parentheses. [c]Yield of the isolated product after flash chromatography. [d]Diastereomeric ratio of (4*R*,5*R*,6*S*) to (4*R*,5*R*,6*R*). [e]Determined by HPLC with a chiral stationary phase.

to an *N*-methylimine, the desired tetrahydropyridine was obtained in 79% yield, 1.9:1 dr, and 98% ee (Table 1, entry 14). In order to distinguish between beneficial steric or electronic effects, we also tried the *tert*-butylimine as substrate (Table 1, entry 17). The fact that no reaction was observed in this case suggests that the steric hindrance is the limiting factor for this reaction step.

With the best imine found, we went on to optimize the general reaction conditions by first screening different solvents. In contrast to the enantiomeric excess, which remained constant, the yield turned out to be strongly dependent on the nature of the solvent. Among the tested mediums, toluene, diethyl ether, acetonitrile, and CH_2Cl_2, the latter turned out to be the best one (Table 1, entry 14, and Table 2, entries 1−3). Second, we varied the catalyst loading. Interestingly, the catalyst promotes the reaction more efficiently at lower loadings. Thus, merely 0.5 mol % of catalyst **A** was found to be sufficient to obtain **4a** in high yield of 87% in a slightly prolonged reaction time without any loss of enantioselectivity (Table 2, entry 6). Lastly, we expanded the optimization on the amount of imine to determine its impact on the yield and the selectivity. We found that the diastereomeric ratio slightly increased by varying the amount, whereas the overall yield decreased (Table 2, entries 7−10). Consequently,

Table 2. Optimization of the Aza-Henry/Cyclization Reaction Sequence[a]



entry	solvent	catalyst loading (mol %)	**3a** (equiv)	time (d)	yield[b] (%)	dr[c]	ee[d] (%)
1	toluene	5	2	2.5	33	1.2:1	94
2	Et_2O	5	2	5	58	2.1:1	97
3	MeCN	5	2	4	83	1.9:1	97
4	CH_2Cl_2	10	2	0.5	69	1.7:1	98
5	CH_2Cl_2	1	2	1.5	82	1.7:1	97
6	CH_2Cl_2	0.5	2	1.5	87	1.8:1	98
7	CH_2Cl_2	0.5	1.1	1.5	54	2.4:1	98
8	CH_2Cl_2	0.5	1.5	1.5	78	1.7:1	98
9	CH_2Cl_2	0.5	4	1.5	79	2.1:1	98
10	CH_2Cl_2	0.5	10	1.5	60	6.4:1	99

[a]Reactions were carried out on a 0.25 mmol scale with the indicated amount of imine and squaramide catalyst **A** in 0.2 mL of solvent (c = 1.25 M) for the stated time at −25 °C. [b]Yield of the isolated product after flash chromatography. [c]Diastereomeric ratio of (4*R*,5*R*,6*S*) to (4*R*,5*R*,6*R*). [d]Determined by HPLC with a chiral stationary phase.

the best conditions were found with 0.5 mol % of **A** and 2 equiv of an *N*-methylimine in CH_2Cl_2 at −25 °C.

With the optimized reaction conditions in hand, we started to examine the scope of this organocatalytic asymmetric Michael/aza-Henry/cyclization cascade starting from the Michael addition of the dicarbonyl compound to the nitroalkene. *β*-Nitroolefins bearing various substituents on the aryl ring provided the corresponding tetrahydropyridines **4a−d** in 69−88% yield and high enantioselectivities. Furthermore, the nitroalkene substituted with a heteroaromatic ring was also tolerated under the standard reaction conditions, hence yielding **4e** in an excellent yield of 91% with high enantiomeric excess. To our delight, even an aliphatic nitroalkene provided **4f** in 32% yield with excellent dr of >20:1 and 93% ee. Interestingly, the thienyl- as well as the cyclohexyl-substituted nitroolefins gave a higher dr. For the next set of reactions, we varied the substituents of the 1,3-dicarbonyl compound. Both *β*-ketoesters tested gave high yields and enantiomeric excesses of the corresponding products **4g** and **4h**. Moreover, **4i** was obtained in 89% yield and high enantiomeric excess by using a phenyl-substituted diketone. Although *β*-ketoamides and various cyclic dicarbonyl compounds could be transformed to the corresponding Michael adducts, they did not react in the second step. Finally, we employed aldimines with different substituents. As expected, the nature with regard to steric hindrance of the imine carbon and the bulkiness of the R^4 moiety is crucial for the outcome of the reaction. Whereas several *ortho*- and *meta*-substituted imines did not react, the *para*-substituted imines led to the desired tetrahydropyridines **4j** and **4k**. Furthermore, different heterocyclic substituted imines, e.g., 2-furanyl and 3-Boc-indolyl, have proven to be suitable substrates for this transformation (Table 3, **4l,m**). Imines bearing an alkyne group also worked well to provide synthetically interesting 6-ethynyl-substituted *N*-heterocycle **4n** in 62% yield, 1.5:1 dr and 99% ee. The alkyne-substituted *N*-(*p*-methoxybenzyl)imine gave 22% yield of **4o** in excellent dr and enantiomeric excess.

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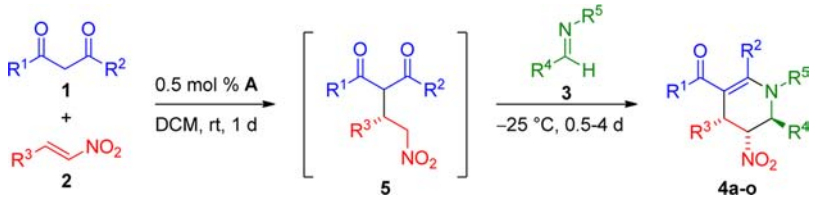
Table 3. Scope of the One-Pot Reaction to Tetrahydropyridines[a]

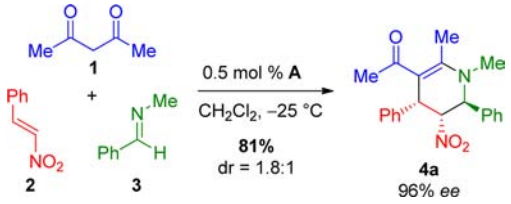


4	R^1	R^2	R^3	R^4	R^5	time[b] (d)	yield[c] (%)	dr[d]	ee[e] (%)
a	Me	Me	Ph	Ph	Me	1 + 2	81	1.7:1	98 (99)
b	Me	Me	*p*-MeC_6H_4	Ph	Me	1 + 2	80	2.1:1	97 (99)
c	Me	Me	*p*-FC_6H_4	Ph	Me	1 + 2	69	2.1:1	99
d	Me	Me	*o*-ClC_6H_4	Ph	Me	1 + 2	88	2.3:1	98
e	Me	Me	2-thienyl	Ph	Me	1 + 0.5	91	13.3:1	98 (96)
f	Me	Me	Cy	Ph	Me	1 + 3	32	>20:1	93
g	OMe	Me	Ph	Ph	Me	1 + 2	80	1.5:1	98
h	OEt	Me	Ph	Ph	Me	1 + 2	88	1.5:1	99
i[f]	Ph	Me	Ph	Ph	Me	1 + 2	89	1.1:1	99[g]
j	Me	Me	Ph	*p*-BrC_6H_4	Me	1 + 2	37	1.5:1	99
k	Me	Me	Ph	*p*-MeC_6H_4	Me	1 + 2	77	1.7:1	99
l	Me	Me	Ph	2-furanyl	Me	1 + 2	78	1.2:1	96[g]
m	Me	Me	Ph	2-(*N*-Boc-indolyl)	Me	1 + 2	45	1:1.4	99
n[h]	Me	Me	Ph	PhC≡C	Me	1 + 4	62	1.5:1	99
o[h]	Me	Me	Ph	PhC≡C	PMB	1 + 4	22	>20:1	95

[a]Reactions were carried out with 0.25 mmol of **1** and **2** combined with 0.5 mol % of **A** in 0.2 mL (c = 1.25 M) of CH_2Cl_2. After 1 day, 0.5 mmol (2.0 equiv) of **4** was added and the reaction was continued at −25 °C for the indicated time. [b]Reaction time of first + second step. [c]Yield of the isolated product after flash chromatography. [d]Diastereomeric ratio of (4*R*,5*R*,6*S*) to (4*R*,5*R*,6*R*). [e]Enantiomeric excess of the main diastereomer determined by HPLC with a chiral stationary phase. Values for the recrystallized samples are given in parentheses. [f]A small amount of the (4*R*,5*S*,6*S*) isomer was also obtained. [g]Enantiomeric excess of the (4*R*,5*R*,6*R*) diastereomer. [h]Reactions were carried out with 0.5 mmol of **1** and **2** combined with 0.5 mol % **A** in 0.4 mL of CH_2Cl_2 (c = 1.25 M) and 1.0 mmol of **3** after 1 day.

Finally, we demonstrated that a domino reaction proceeds smoothly without any loss of efficiency when all the substrates as well as the catalyst **A** were added together at the beginning (Scheme 2). Furthermore, a gram-scale reaction was successfully

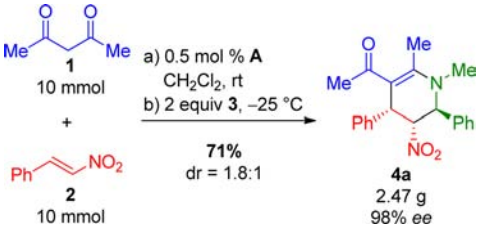
Scheme 2. Synthesis of Tetrahydropyridines under Domino Conditions



performed without much alternation of the product yield and stereoselectivity, which shows the practical and preparative utility of this domino process (Scheme 3).

The relative configuration was determined by NOE contacts between the concerning hydrogen atoms, whereas the absolute configuration was assigned by the X-ray crystal structure (Figure 2).[13,14]

Scheme 3. Gram-Scale Synthesis of Tetrahydropyridines



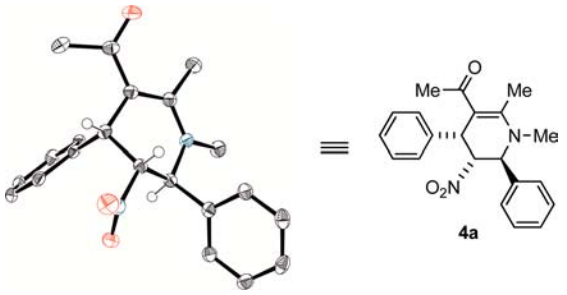


Figure 2. X-ray crystal structure of **4a**.[14]

In conclusion, we have developed a squaramide-catalyzed asymmetric multicomponent Michael/aza-Henry/cyclization triple domino reaction of 1,3-dicarbonyl compounds, β-nitroolefins, and imines to provide potentially bioactive 1,4,5,6-tetrahydropyridines in very good yields and up to high diastereo- and excellent enantioselectivities. Additionally, this protocol required only one catalyst at an extremely low catalyst loading of 0.5 mol %. The new procedure can be successfully scaled up to gram amounts without losing the reaction efficiency. Further applications of squaramide-catalyzed organocascade sequences for the synthesis of valuable chiral heterocycles are under investigation, and the results will be reported in due course.

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■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and characterization data including copies of the NMR and HPLC spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(13) The complete determination of the relative configuration can be found in the Supporting Information.

(14) CCDC 1021665. The crystallographic data of compound **4a** are available free of charge at http://www.ccdc.cam.ac.