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Organocatalytic enantioselective conjugate addition of 2-nitrocyclohexanone to acrylaldehyde: a concise two-step synthesis of chiral building block 1-azaspiro[4.5]decan-6-one

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ABSTRACT

A gram-scale organocatalytic enantioselective Michael addition of α-nitrocyclohexanone to acrolein has been developed, and it was successfully applied to a concise two-step synthesis of (1*S*)-azaspiro[4.5]decan-6-one, a useful chiral building block for the synthesis of a variety of natural alkaloids.

1-Azaspiro ring systems uniquely incorporate a carbo- and a heterocycle by an aza-quaternary center, whose nitrogen atom is adjacent to the junction. Among them, the 1-azasipro[4.5]decane motif can be frequently observed in many natural alkaloids including cylindricine A,[1] lepadiformine A,[2] TAN1251A,[3] and FR901483[4] (Fig. 1). A considerable number of synthetic efforts have been reported to establish the peculiar structure, including closing the two rings in separate steps or achieving the spirocycle in a single step.[5] Furthermore, in the aforementioned natural products, the quaternary carbon bearing nitrogen atom is usually stereogenic, and necessary stereochemical control is thus required in its formation. Development of efficient enantioselective construction of the aza-quaternary carbon is always the crucial task in the synthesis. For example, stereoselective 1,3-dipolar cycloaddition,[6a] catalytic asymmetric Michael reaction, and tandem cyclization[6b] were applied in the synthesis of cylindricines[6] by Bochet and Shibasaki and co-workers. Since Kibayashi's revision of originally assigned configuration of lepadiformine[7a] utilizing *N*-acyliminium-initiated olefin azacyclization (to elaborate the azaspirocyclic core), several other elegant syntheses have also been reported.[7] Rychnovsky's group recently reported a new construction of the spirocyclic ring of (−)-lepadiformine using a trianion synthon derived from *N*-Boc α-amino nitrile.[7g,h] Most synthetic approaches to TAN1251A[8] and FR901483[9] involved initial formation of 1-azaspiro[4.5]decane followed by ring-closure to establish the tricyclic system. Undoubtedly, more efficient and direct approaches to elaborate the chiral 1-azaspiro[4.5]decane ring system are of extreme value in the synthesis of these biologically interesting alkaloids. Herein, we wish to report a catalytic enantioselective synthesis of the chiral 1-azaspiro[4.5]decane motif, using a newly developed organocatalyzed

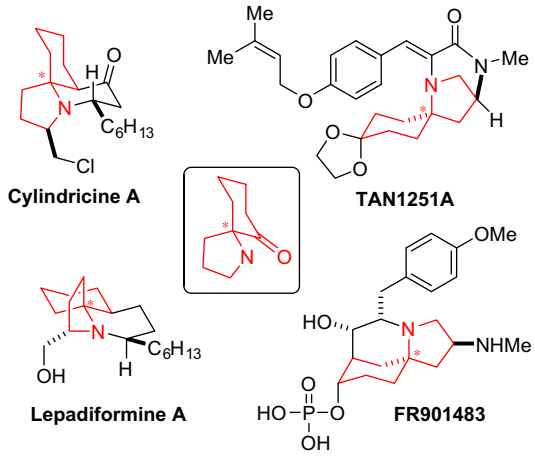

Figure 1. Several alkaloids containing 1-azaspiro[4.5]decane motif.

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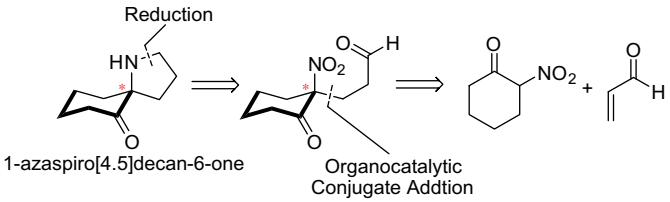


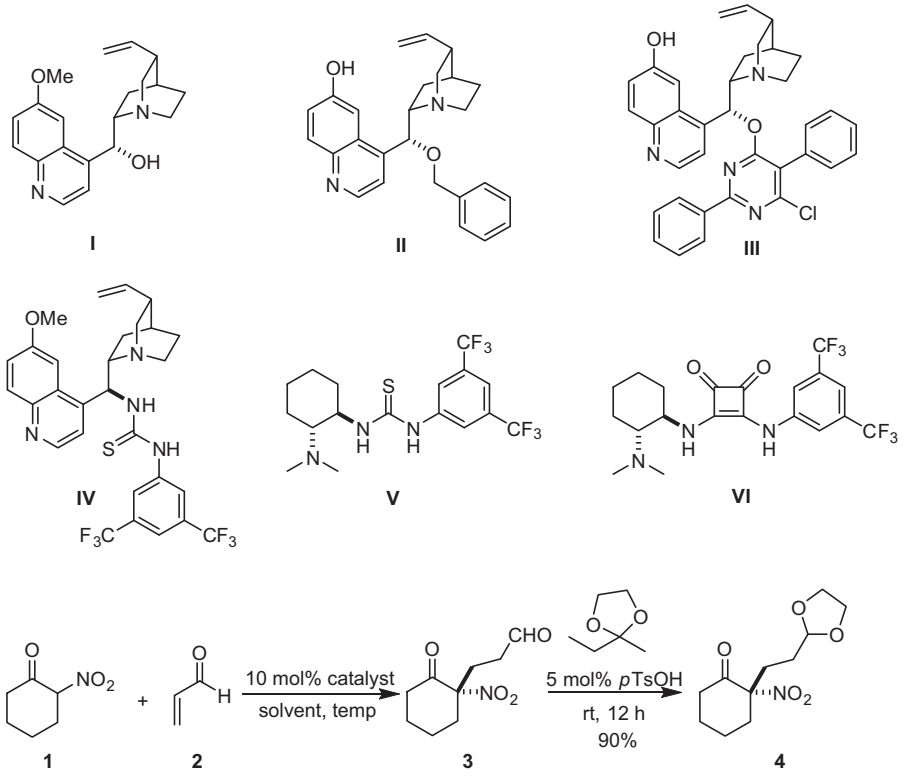
Figure 2. Asymmetric formation of 1-azaspiro[4.5]decane ring system.

Michael addition of α-nitrocycloketone to acrolein followed by C–N cyclization with reductive amination (Fig. 2).

Though organocatalytic conjugate additions[10] have been intensely explored and nitroalkanes and nitroalkenes have been widely used as Michael donor/acceptor in asymmetric synthesis in the last two decades,[11] few applications of α-nitroketones and α-nitrocycloketones[12–14] have been explored in organocatalytic reactions for their higher acidity ($pK_a \approx 4.0$) and considerable difficulty to be handled in such reactions. Therefore, exploration of the above mentioned transformation not only will help to establish a new concise synthesis of the required chiral building block, but also will provide new addition to current literatures on organocatalytic conjugate additions.

As mentioned, an organocatalytic Michael addition of α-nitrocyclohexanone to acrolein was considered as the crucial step to establish the aza-quaternary carbon (Fig. 2). Our study began with the screening for a proper organocatalyst. Usually, Michael

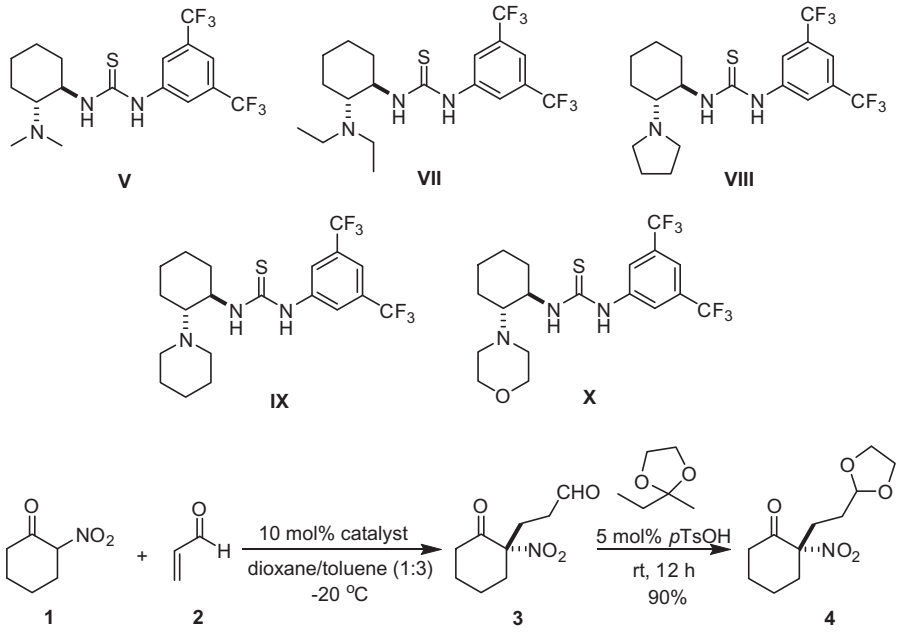
Table 1
Screening of conditions for the conjugate addition reaction



Entry[a]	Cat.	Solvent	T (°C)	Time (h)	Yield (%)	ee[b] (%)
1	**I**	DCM	rt	0.1	81	17
2	**II**	DCM	rt	0.3	79	27
3	**III**	DCM	rt	0.3	85	21
4	**IV**	DCM	rt	0.2	83	43
5	**V**	DCM	rt	0.5	89	64
6	**VI**	DCM	rt	0.3	75	4
7	**V**	Toluene	rt	1	87	68
8	**V**	Dioxane	rt	5	73	73
9	**V**	2-MeTHF	rt	3	76	68
10	**V**	Et_2O	rt	7	86	53
11	**V**	$CHCl_3$	rt	1	83	44
12	**V**	1,2-DCE	rt	1	72	37
13	**V**	Acetone	rt	4.5	92	37
14	**V**	DMF	rt	5	79	20
15	**V**	MeOH	rt	5	76	31
16	**V**	Dioxane/toluene (1:2)	0	6	90	68
17	**V**	Dioxane/toluene (1:2)	−10	6.5	90	80
18	**V**	Dioxane/toluene (1:2)	−20	9	89	82
19	**V**	Dioxane/toluene (1:2)	−30	12	76	82
20	**V**	Dioxane/toluene (1:3)	−20	9	91	87
21	**V**	Dioxane/toluene (1:4)	−20	9	93	80

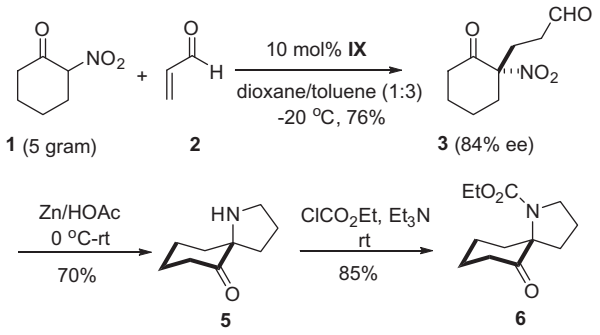
[a] Unless otherwise noted, the reaction was carried out with **1** (0.125 mmol), **2** (0.15 mmol), and catalyst (0.0125 mmol) in solvent (1.25 mL).
[b] ee value of **4** was determined by chiral HPLC.

Table 2
Application of derivatives of Takemoto's catalyst in the conjugate addition

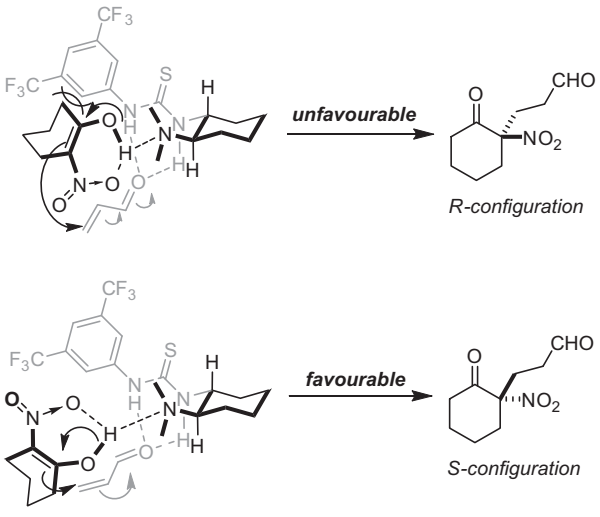


Entry[a]	Cat.	Time (h)	Yield (%)	ee[b] (%)
1	**V**	9	81	87
2	**VII**	10	80	73
3	**VIII**	10	84	88
4	**IX**	10	86	89
5	**X**	10	82	83

[a] Unless otherwise noted, the reaction was carried out with **1** (0.125 mmol), **2** (0.15 mmol), and catalyst (0.0125 mmol) in solvent (1.25 mL).
[b] ee value of **4** was determined by chiral HPLC.



Scheme 1. Scale-up of the reaction and determination of the absolute configuration.



Scheme 2. Proposed reaction mechanism.

reaction of α-nitroketones and α,β-unsaturated aldehydes could be conventionally carried out in organic solvents using DBU, Ph_3P, and nBu$_4$N$^+$F$^-$ as catalysts,[15] or in water without adding catalysts.[16] To achieve a satisfactory control of stereochemistry, the bifunctional organocatalysts equipped with a tertiary-amine moiety and a hydrogen-bond donor were considered to bind both substrates with correct configurations in the transition state. Initial application of natural quinine (**I**) showed a very weak influence on the enantioselectivity (Table 1, entry 1). Modified catalysts **II** and **III**[17] by replacing the 6′-methoxyquinoline moiety of quinine with 6′-hydroxyquinoline and masking the C-9 alcohol slightly increased the enantiomeric excess of product **4** (Table 1, entries 2 and 3). To our delight, utilization of thiourea moiety as the hydrogen-bond donor in the catalysts **IV** and **V**,[18,19] instead of the hydroxyl group in quinine derivatives, remarkably improved the enantioselectivity (Table 1, entries 4 and 5). However, the catalyst **VI** with squaramide moiety[20] turned out to be invalid (Table 1, entry 6).

Based on the above observation, effects of solvent and temperature were then examined in the reactions with Takemoto's thiourea-tertiary amine **V** (Table 1, entries 7–19). Reaction in toluene gave a similar result as that in dichloromethane (Table 1, entries 5 and 7). The reactions afforded the Michael product with

moderate enantiomeric excesses in ether solvents 1,4-dioxane, 2-methyltetrahydrofuran, and diethyl ether (Table 1, entries 8–10). Chloroform and 1,2-dichloroethane and more polar solvents, such as acetone, DMF, and methanol were detrimental to the enantioselectivity (Table 1, entries 11–15). Occasionally, a mixed solvent of 1,4-dioxane and toluene (v/v = 1/2) was found to give 68% ee of the product at 0 °C (Table 1, entry 16). Thus, it was chosen as the media for further temperature screening (Table 1, entries 17–19). These experiments revealed that the best results with regard to chemical yield and enantioselectivity were obtained at −20 °C (Table 1, entry 18). Further decrease in temperature did not show any significant improvement on the selectivity (Table 1, entry 19). Finally, the volume ratio of the solvents (1,4-dioxane and toluene) was adjusted to 1:3, affording product **4** in 87% ee (Table 1, entry 20).

Under the above optimized conditions, we decided to further modify the tertiary amine functionality of the catalyst (Table 2). The diethylamine-substituted catalyst **VII** showed a negative influence on the selectivity (Table 2, entry 2), while pyrrolidine-thiourea catalyst **VIII** provided a slightly improved enantioselectivity (Table 2, entry 3). With piperidine-thiourea catalyst **IX**, the enantiomeric excess of the product **4** was proven to be the best, up to 89% (Table 2, entry 4). Whereas, a similar morpholine-thiourea catalyst **X** resulted in a slight decrease of the enantioselectivity.

For provision of adequate materials for the total synthesis of natural products, we then examined the scale-up capability of target transformation under the optimal reaction conditions. A five gram-scale reaction between **1** and **2** was attempted with 10 mol % loading of the catalyst **IX**. To our delight, the conjugated addition product was obtained in 76% yield and 84% ee (Scheme 1). Afterward, the nitro group of **3** was reduced to amine with zinc dust in HOAc,[21] which spontaneously underwent an intramolecular reductive amination with 2′-aldehyde to give the spiro-pyrrolidine ring. Therefore, we completed a concise catalytic asymmetric synthesis of 1-azaspiro[4.5]decan-6-one, a potential useful chiral building block in various total syntheses, in two steps from the simple starting materials. In order to determine the absolute configuration, product **5** was converted into the known derivative **6**,[22] whose *N*-acyl derivatives were reported as potent opioid receptor ligands.[23] Accordingly, the aza-quaternary center of the 1-azaspiro[4.5]decane ring system was determined to be of *S* configuration.

According to the absolute configuration of the product, mechanism of the bifunctional catalysis was proposed as Scheme 2. The enantioselectivity might be caused by the steric hindrance between the aryl moiety of the catalyst and the cyclohexanone.

In conclusion, we have developed a gram-scale enantioselective organocatalytic Michael addition of α-nitrocyclohexanone to acrolein, with 84% ee.[24] This protocol offers a concise two-step chiral synthesis of 1-azaspiro[4.5]decan-6-one, a potential useful chiral building block in the synthesis of a variety of natural alkaloids.

Acknowledgements

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.01.114.

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24. Generality of the reaction between α-nitrocyclohexanone and a variety of α,β-unsaturated aldehydes was also explored. Unfortunately, the yields of the Michael adducts dropped dramatically under the optimized conditions. It is speculated that additional substituents of acrylaldehyde might unfavorably interact with the catalyst and make the transition state unstable.