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ASYMMETRIC INTRAMOLECULAR AZA-MICHAEL REACTION USING ENVIRONMENTALLY FRIENDLY ORGANOCATALYSIS†

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Abstract – This communication describes enantioselective intramolecular aza-Michael reaction to prepare 1,2,3,4-tetrahydroisoquinolines by using organocatalysts. The organocatalytic reaction offers new green chemical process in heterocyclic chemistry. Additional noting, both enantiomers of the product were easily synthesized by using two types of organocatalysts prepared from the same amino acid.

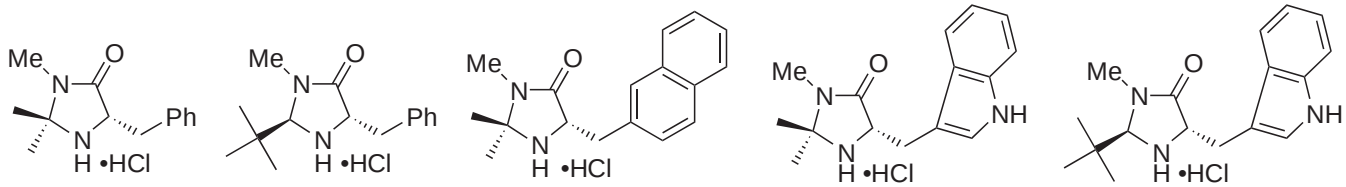
Aza-Michael reaction has been intensely investigated as an important C–N bond formation reaction in the synthesis of heterocyclic compounds.[1] Most of the cases a nitrogen nucleophile reacts with α,β-unsaturated carbonyl function as either a neutral nitrogen or an anionic nitrogen such as metal amide base. However, due to the strong Lewis basicity of the neutral or anionic nitrogen, catalytic aza-Michael reaction utilizing Lewis acid catalysis must be a difficult task. We have supposed that utilization of organocatalysts can solve the inherent problems. During the past few years, asymmetric organocatalysis[2] (only small organic molecule used as a reaction catalyst) has received intensive interests from the viewpoint of green chemistry as well as bioorganic chemistry. Recently, MacMillan and co-workers have revealed that organocatalysts (**1a**) and/or (**1b**) are significantly effective in enantioselective reactions with α,β-unsaturated carbonyl compounds, such as Diels-Alder reaction,[3] 1,3-dipolar addition[4] and Friedel-Crafts alkylation[5] (Figure 1). Through the asymmetric reactions the organocatalysts serves to activate the achiral Michael acceptor *via* formation of a chiral iminium species. It is noteworthy that MacMillan's process is very ecological; the reaction proceeds without metallic reagents/catalysts in

† Dedicated to Prof. Y. Kanaoka on the occasion of his 75th birthday.

alcohol and/or aqueous solution. In this communication, we report the first enantioselective organocatalytic intramolecular aza-Michael reaction to prepare nonracemic 1,2,3,4-tetrahydroisoquinolines under environmentally friendly conditions.[6,7]

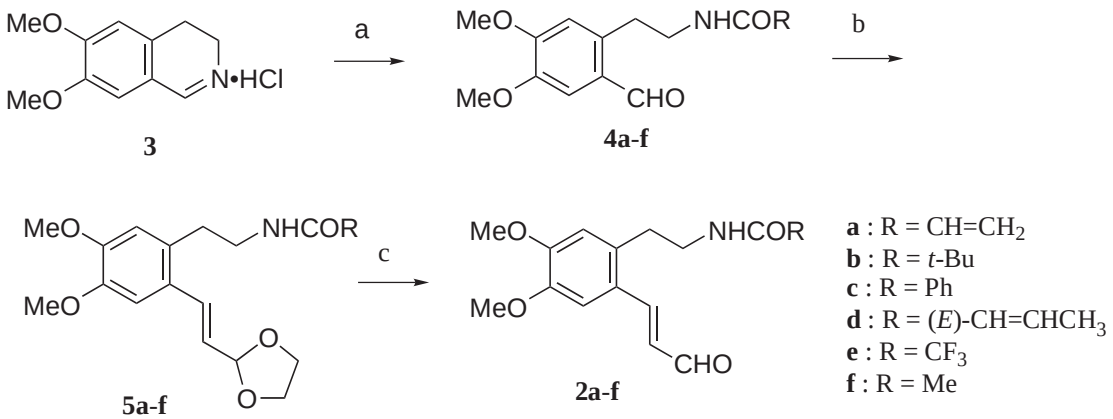
We have designed dopamine derivatives (**2**) as reaction substrates, which possess α,β-unsaturated aldehyde and amide functions at each ends. Compounds (**2a-f**) were synthesized from 3,4-dihydro-6,7-

Figure 1. Asymmetric aminocatalysts



1a **1b** **1c** **1d** **1e**

dimethoxyisoquinoline hydrochloride (**3**) in a short sequence (Scheme 1). Namely, the reaction of **3** with acid chlorides in a mixture of dichloromethane and saturated aqueous sodium bicarbonate at room temperature afforded aldehydes (**4a-f**).[8] Wittig olefination of **4a-f** with 1,3-dioxolan-2-ylmethyltributyl-phosphonium bromide in the presence of potassium *t*-butoxide and catalytic amount of 18-crown-6 produced (*E*)-alkenyldioxolanes (**5a-f**) in good yields. Deacetalization of **5a-f** was achieved under neutral condition to furnish (*E*)-α,β-unsaturated aldehydes (**2a-f**) as key substrates. Novel MacMillan-type of asymmetric catalysts (**1c-e**)[9] were also prepared from the corresponding L-amino acid methyl esters by the same strategies as the syntheses of **1a** and **1b**.[3,5]



3 **4a-f** **5a-f** **2a-f**

Scheme 1. conditions; (a) RCOCl, $NaHCO_3$, CH_2Cl_2, rt; (b) 1,3-dioxolan-2-ylmethyltributylphosphonium bromide, *t*-BuOK, 18-crown-6, CH_2Cl_2, rt; (c) SiO_2, CH_2Cl_2–EtOH–H_2O, rt.

First, we evaluated the chiral organocatalysts (**1a-e**) for the intramolecular aza-Michael reaction of **2a** (Scheme 2, Table 1). The catalytic reaction was typically performed as follows. To a solution of the catalyst (**1**) (20 mol%) in MeOH/H_2O (95:5 v/v)[10] was added the substrate (**2**), and the reaction mixture

was stirred for 10 days at ambient temperature. After usual work up, the intramolecular aza-Michael product (**6**) was purified by column chromatography (silica gel). The enantiomeric excess (ee) of **6** was determined by HPLC analysis using a chiral column. Although no cyclized product was observed without catalyst but with HCl (run 1), the reaction in the presence of organocatalyst (**1a**) provided tetrahydroisoquinoline (+)-(**6a**) with 34% ee in 87% yield (run 2). Whereas alkenylacetal (**5a**) also furnished (+)-**6a** in good yield, its stereoselectivity decreased to 30% ee (run 3). Among various catalysts tested, catalyst (**1d**) derived from L-tryptophan was found to be the most effective in the asymmetric reaction of **2a** (run 6). Interestingly, we found that catalysts (**1a**) and (**1b**), which were both prepared from L-phenylalanine, gave raise to different enantiomers (+)-(**6a**) and (–)-(**6a**), respectively (runs 2 and 4). The similar phenomenon was observed in the reaction with **1d** and **1e** (runs 6 and 7). This result indicates that both enantiomers can be easily prepared using secondary amine catalysts derived from natural amino acids. The absolute configuration of (+)-**6a** was determined by comparison with the authentic sample after transformation into (+)-(*R*)-**7**.[11]

Results of asymmetric aza-Michael reaction of other substrates having various *N*-acyl function are

Scheme 2

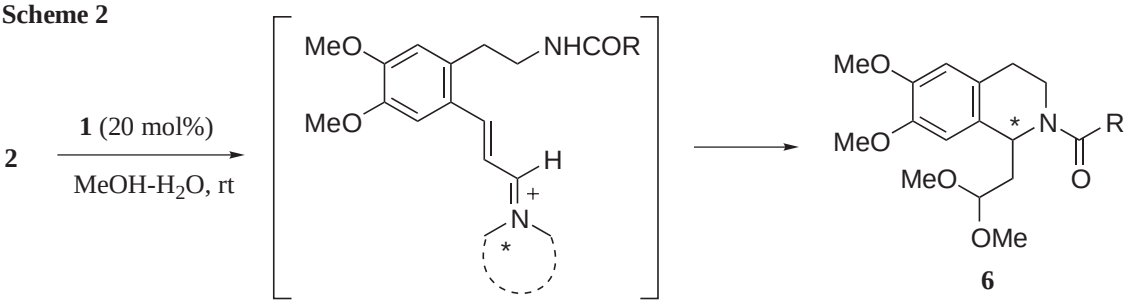
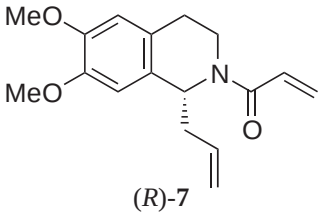


Table 1. Catalytic asymmeytic intramolecular aza-Michael reactions of **2a**.[a]

run	catalyst	substrate	product	% yield	% ee (*config*)
1	HCl	**2a**	**6a**	0	—
2	**1a**	**2a**	(+)-**6a**	87	34 (*R*)
3	**1a**	**5a**	(+)-**6a**	89	30 (*R*)
4	**1b**	**2a**	(–)-**6a**	85	18 (*S*)
5	**1c**	**2a**	(+)-**6a**	88	30 (*R*)
6	**1d**	**2a**	(+)-**6a**	90	46 (*R*)
7	**1e**	**2a**	(–)-**6a**	85	25 (*S*)

[a] All reactions were performed by treatment of substrate with 20 mol% of catalyst in MeOH/H_2O (19 : 1) at room temperature for 10 days.



(*R*)-**7**

summarized in Table 2. From this study, it is found that reaction of **2** possessing less bulky *N*-acyl moiety tends to achieve **6** with higher enantioselectivity (runs 2, 3 and 5 in Table 2, and run 6 in Table 1).

Although the enantioselectivity was not satisfactory, highest asymmetric induction (53 %ee) was achieved in the reaction of acetamide (**2f**) (run 5 in Table 2). On the contrary, no cyclization was observed in the reaction of **2b** and **2e** (runs 1 and 4).

Table 2. Catalytic asymmeytic aza-Michael reactions with (*S*)-**1d**.

run	substrate	product	% yield	% ee
1	**2b** (R = ^{t}Bu)	**6b**	0	—
2	**2c** (R = Ph)	(+)-**6c**	70	34
3	**2d** (R = (*E*)-CH=CHCH$_3$)	(+)-**6d**	88	43
4	**2e** (R = CF$_3$)	**6e**	0	—
5	**2f** (R = Me)	(+)-**6f**	85	53

[a] All reactions were performed by treatment of **2** with 20 mol% of (*S*)-**1d** in MeOH/H$_2$O (19 : 1) at room temperature until **2** was fully comsumed.

In conclusion, we demonstrated a new strategy for enantioselective intramolecular aza-Michael reaction by using MacMillan-type organocatalysts, although there still stands improvement in enantioselectivity and reaction rate. Both enantiomers of 1-substituted 1,2,3,4-tetrahydroisoquinolines can be easily synthesized by using two types of organocatalysts prepared from the same amino acid. We believe the further studies will pave way for a new synthetic method towards various chiral heterocycles.

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9. Selected spectral data; (*S*)-**1d** (as HCl salt): colorless solids, mp 237-238 °C (decomp); $[\alpha]_D^{23}$ –101.1° (c 1.43, MeOH); IR (KBr): ν 3370, 1725, 1647 cm^{-1}; ^1H NMR (400 MHz, CD_3OD): δ 7.62-7.64 (m, 1H), 7.35-7.40 (m, 2H), 7.05-7.17 (m, 2H), 4.65 (dd, *J* = 10.5, 3.4 Hz, 1H), 3.62-3.67 (m, 1H), 3.22-3.31 (m, 2H), 2.90 (s, 3H), 1.67 (s, 3H), 1.55 (s, 3H); ^{13}C NMR (100 MHz, CD_3OD): δ 168.0, 138.2, 127.7, 125.5, 122.9, 120.2, 119.0, 112.6, 108.3, 79.0, 58.7, 25.7, 25.6, 24.4, 22.4; HRMS (as free amine) *m/z* calcd for $C_{15}H_{19}N_3O$ (M^+) 257.1528, found 257.1512.
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