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Addition of aldehydes with allyltrichlorosilane catalyzed by chiral bis-N–O secondary amides

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ABSTRACT

New axially *N*-oxide amides derived from L-tryptophan were prepared and used as organocatalysts in enantioselective allylation of aromatic aldehydes with allyltrichlorosilanes. The corresponding addition adducts homoallylic chiral alcohols obtained high enantioselectivities (up to 96% ee) when 1 mol % of catalyst was used. The unexpected result is the addition product's absolute configuration is *R* when (*R*)-chiral amides was used, in contrast, it was (*S*) when (*R*)-chiral methyl ester were used in allylation. It exhibited that the N atoms of amides take part in the transition state procedure.

1. Introduction

Asymmetric additions of aldehydes with allylic reagents represent an important method to prepare highly useful chiral building blocks in organic synthesis due to synthetic versatility of propylene unit.[1] In 1994, Denmark reported the first example of asymmetric allylation utilizing chiral phosphoramides as chiral Lewis basic ligands.[2] Following this report, a series of chiral Lewis bases have been designed and investigated in the asymmetric allylation with allytrichlorosilanes.[3–6] Among these Lewis bases, *N*-oxide compounds, for their strong dipole and high nucleophilicity, serving as organocatalysts to catalyze asymmetric allylations have attracted considerable attention in the past two decades.[7] Since Nakajima first reported the axially chiral biquinoline *N*,*N*′-dioxide was an excellent catalyst for Sakurai–Hosomi reaction in 1998,[5a] several kinds of *N*-oxides derivatives from pyridines and tertiary amines have been synthesized and used for the asymmetric allylation by Malkov and Kocovsky,[8] Hayashi,[9] Kotora,[10] Zhu,[11] and others.[12] Some axially chiral *N*,*N*′-dioxide have shown modest to good enantioselectivities, and these catalysts were effective for aromatic aldehydes but stranded in aliphatic aldehydes.[7] On basis of aforementioned results and intrigued by the unique properties of *N*-oxides, a type of new axial Lewis bases embracing biscarboline moiety were developed for enantioselective allylation in our study recently.[11] We have found that 1,1′-biscarboline-*N*,*N*′-dioxide was useful for allylation of aldehydes. Inexpensive material, low catalytic amount (1 mol %) and convenient to manipulate of this catalysts promote us to study it profoundly and we continued to synthesize axial amides using the similar methods.

The unexpected result reported in this study is the addition products had (*R*) configuration using (*R*)-axially chiral 1,1′-biscarboline *N*,*N*′-dioxide amides (e.g., (*R*)-(+)-**5a**). In contrast, the absolute configuration of addition product was all (*S*) configuration when (*R*)-axially chiral 1,1′-biscarboline *N*,*N*′-dioxide methyl ester (like (*R*)-(+)-**9**) was used.

2. Results and discussion

Tryptophan **1** was converted to the corresponding methyl ester using $SOCl_2$ in methanol. After Pictet–Spengler reactions and hydrolysis, **1** was transferred to **2** based on our recent report. Seven secondary amines (**3a**–**g**) and carboxylic acid **2** were condensed to form the corresponding amides, which were further oxidized by MCPBA or UHP. The specific route to amides **5a**–**g** is illustrated in Scheme 1.

The chiral separation of (+)-**5** from (−)-**5** was performed via chiral column with the eluent DCM/MeOH (v/v=90/10 to 95/5) at a rate of 2 or 2.5 mL/min. Optical rotation of (*R*)-**5g** was computed using density functional theory (DFT) at the B3LYP/6-311+G(d)

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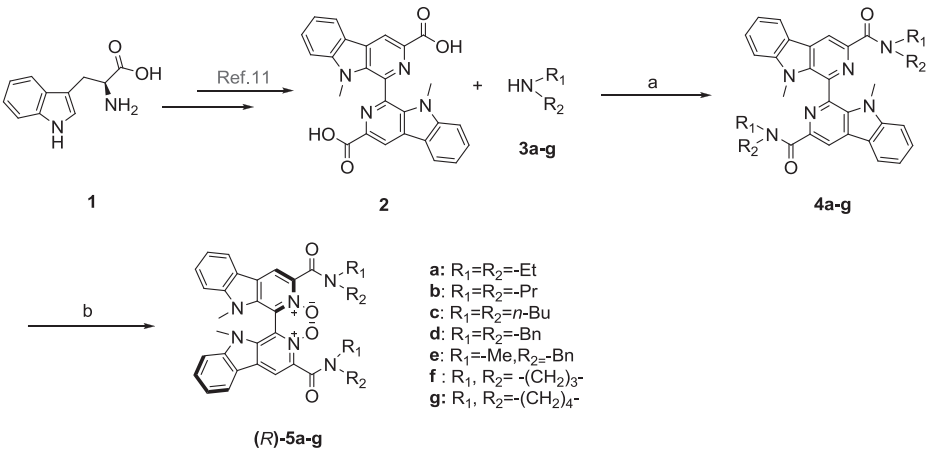
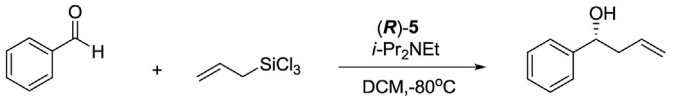


Scheme 1. Preparation of axially chiral catalysts (*R*)-**5a**–**g**. Reaction conditions: (a) (i) **2**, isobutyl-chloroformate (2.2 equiv), Et_3N (4 equiv), DCM, 0 °C, 15–20 min; (ii) amine (2.2 equiv), rt, 10 h. (**b**) (i) Unless otherwise noted, the reaction was carried out in DCM and MCPBA (6 equiv) at rt for 12 h; (ii) **5f** was oxidized by UHP (6 equiv) and TFA (6 equiv) in DCM at rt for 12 h. (iii) The racemic products were resolutioned by chiral HPLC on a CHIRALPAK ID column.

level in the gas phase.[13] The predicted optical rotation for (*R*)-**5g** should have positive optical rotations. The experimental data was +697.0 in $CHCl_3$. Obviously, (+)-**5g** owns (*R*) configuration.

The enantioselectivity of the catalysts is listed in Table 1. It was found that the higher ee% values were obtained by catalyst (*R*)-**5f**,**g** with cyclic amides (entries 10–15) at the C-3 and C-3′ positions. Among these ligands, (*R*)-**5g** with pyrrolidine moiety (entry 13) presented the best result (100% conv., 87%ee). *N*,*N*′-Dioxide catalysts with aliphatic amides (entries 1–9) at the C-3 and C-3′ positions (*R*)-**5a**–**e** were found to possess high conversion but low enantioselectivity. As illustrated in entries 1–9, a change in the amide substituent resulted in little or no difference in enantioselectivity. An interesting phenomenon was that the enantioselectivity was higher in the presence of 1 mol % of catalyst (*R*)-**5g** than using 10 mol % and 5 mol % in the catalytic reaction. However, the enantioselectivity was not improved with lower catalytic amount (0.5 mol % and 0.1 mol %) of (*R*)-**5g** and the conversion was poor in the reactions. The catalysts with aliphatic amides did exhibit low ee% values in the reaction.[14] The unexpected discovery is that the obtained addition products had (*R*) configuration using axially chiral 1,1′-biscarboline *N*,*N*′-dioxide amide, (*R*)-**5g**. This is different from what we obtained recently. In our recent report, it was found that the addition product had the (*S*)-configuration when using axially chiral (*R*)-1,1′-biscarboline *N*,*N*′-dioxide methyl ester. The problem of reverse configuration of product would be discussed later according to mechanism analysis.

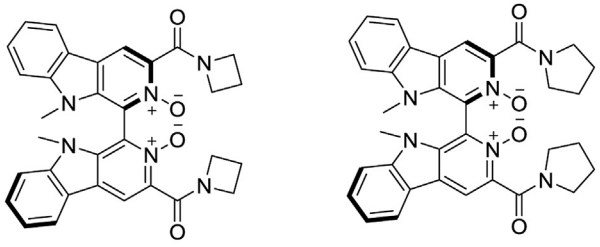
Table 1
Enantioselectivity of ligands (*R*)-**5a**–**g** in addition of aldehydes with allytrichlorosilane[a]



6a **7** **(*R*)-8a**

Entry	Cat.*	Amount (mol %)	ee[b,c] (%)
1	**5a**	1	17
2	**5a**	10	24
3	**5b**	1	22
4	**5b**	10	40
5	**5c**	1	11
6	**5c**	10	28
7	**5d**	10	31
8	**5e**	1	16
9	**5e**	10	19
10	**5f**	1	84
11	**5g**	0.1	78
12	**5g**	0.5	84
13	**5g**	1	87
14	**5g**	5	77
15	**5g**	10	69

[a] Reaction condition: **6a**, **7** (1.5 equiv), *i*-Pr_2NEt (3 equiv), 20 h.
[b] Determined by chiral HPLC on a CHIRAPAK IB column, see Experimental section for details.
[c] The absolute configuration of the major product was (*R*), which was determined by comparison with the reported value of optical rotation, see Ref. 11.



(*R*)-**5f** (*R*)-**5g**

Effects from solvent and temperature on the enantioselectivity were investigated. DCM, CH_3CN, toluene, THF, and other aprotic solvent were employed.[1,2] It was found that DCM was the suitable solvent. The results are summarized in Table 2. Temperature had great effect on ee% values, e.g., the 87% of ee% observed at −80 °C decreased to 56% while the temperature increased to −60 °C, and this magnitude decreased to 30% once the temperature raised to −40 °C (Table 2, entries 1–3).

It was found that (*R*)-**5g** could catalyze the reaction in a high enantioselectivity. Therefore, catalyst (*R*)-**5g** was used in the additions for other aldehydes (Table 3). Aldehydes with electron-donating groups, e.g., MeO at C-3 and C-4 catalyzed by (*R*)-**5g** exhibited good enantioselectivity (entries 3 and 4). Those aldehydes with strong electron-withdrawing group, e.g., 4-cyanobenzaldehyde, 3-nitrobenzaldehyde, and 4-nitrobenzaldehyde were catalyzed to give good enantioselectivities (entries 8, 11, and 12). Some aldehydes with electron-donating group, for example, 2-methoxyben zaldehyde present unsatisfied ee% value (67%ee, entry 2). The aliphatic aldehydes, e.g., cyclohexanecarboxaldehyde and phenylpropyl aldehyde were investigated to test the catalytic activity of (*R*)-**5g**. However, the resolution result showed that (*R*)-**5g** was not very effective for aliphatic aldehydes. The ee% value of the above two aliphatic aldehydes was 40% and 41%, respectively.