

Communication

Synthesis of Dendritic Schiff Base Ligands for Titanium Catalyzed Enantioselective HDA Reaction of Danishelfsky's Diene with Aldehydes[†]

JI, Bao-Ming^{a,b} (吉保明) DING, Kui-Ling^{* ,b} (丁奎岭) MENG, Ji-Ben^{* ,a} (孟继本)^a Department of Chemistry, Nankai University, Tianjin 300071, China^b State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, Shanghai 200032, China

A new type of dendritic NOBIN derived Schiff base ligands has been synthesized and applied to titanium catalyzed hetero-Diels-Alder reaction of Danishelfsky's diene and aldehydes, affording the corresponding 2-substituted 2,3-dihydro-4*H*-pyran-4-one in good yields and moderate enantioselectivities (up to 59.2% *ee*). It was found that the size of dendron attached to the tridentate ligands has slight impact on the enantioselectivity of the reaction and the second generation of dendritic ligand exhibited the best enantioselectivity.

Keywords asymmetric catalysis, dendrimer, hetero Diels-Alder, Schiff base, titanium

Since the pioneering work of van Koten,¹ the use of dendrimer-based catalysts, particularly of chiral dendrimer catalysts,² has been an interesting topic in catalyst chemistry. Various dendritic catalysts containing TADDOL, BINOL, BINAP and Salen cores have been developed and utilized in asymmetric catalysis.² Optically active 2-amino-2'-hydroxy-1,1'-binaphthyl (NOBIN), a non-*C*₂-symmetric chiral scaffold and derivatives have received extensive interests in asymmetric catalysis.³ Particularly, chiral Ti(IV) Lewis acid modified by NOBIN-derived tridentate Schiff base ligand and 3,5-di-*tert*-butylsalicylic acid showed excellent asymmetric induction in Mukaiyama aldol-type reactions. However, titanium (IV) complex of polymer-supported salicylaldehyde ligand showed rather poor reactivity and enantioselectivity (32% conversion and 26% *ee*) for the same reaction.⁴ In our previous work, we disclosed that titanium (IV) complexes of NOBIN Schiff base derivatives could be dramatically activated by carboxylic acids to promote hetero Diels-Alder (HAD) reaction of Danishelfsky's diene and aldehyde with high efficiency and enantioselectivity.⁵ In the present communication, we report the development of NOBIN-derived dendritic Schiff base ligands for titanium catalyzed hetero-

Diels-Alder (HDA) reaction.

As shown in Scheme 2, dendritic salicylaldehyde derivatives (12—14) are key intermediates for the synthesis of NOBIN derived dendrimer Schiff base ligands (16—18). Therefore, we firstly synthesized 2-benzyl protected salicylaldehyde derivative 4 by the reaction of 2,5-dihydroxy-3-bromobenzaldehyde (1) with benzylbromide (2) in the presence of 1.25 equiv. of K₂CO₃ and catalytic amount of KI (Scheme 1). The reaction proceeded smoothly to give two major products 4 (yield 52.0%) and 5 (yield 43.7%), as well as a minor side product 3 with 4% yield. Dibenzyl protected product 5 could be efficiently transformed to compound 3, which is a useful intermediate for the preparation of nondendritic ligand 15 as shown in Scheme 2, in 95% yield by reaction with freshly prepared MgBr₂ followed by treatment with 2 N HCl. With compound 4 in hand, the preparation of dendritic salicylaldehyde derivatives (12—14) was carried out by coupling with Frechet's dendron bromide in the presence of 1.25 equiv. of K₂CO₃ to give benzyl protected dendritic salicylaldehyde derivatives (9—11) in 89%—95% yields, followed by deprotection of benzyl group with MgBr₂. The yields ranged from 64% to 99% with the change of dendron size attached to the molecules.

As shown in Scheme 2, the synthesis of dendrimer-based NOBIN derived Schiff base ligands ((*S*)-16—18) was achieved in a straightforward manner by simple condensation of (*S*)-NOBIN with the corresponding dendritic salicylaldehyde derivatives (12—14) in the presence of dried MgSO₄ and catalytic amount of TsOH in 88%—92% yields. The non-dendritic ligand (*S*)-15 was prepared by similar condensation of (*S*)-NOBIN with salicylaldehyde derivative 3 in 89% yield. All four kinds of dendritic and non-dendritic Schiff base ligands (*S*)-15—18 gave very

* E-mail: kding@mail.sioc.ac.cn

Received May 15, 2003; revised June 4, 2003; accepted June 6, 2003.

Project supported by the National Natural Science Foundation of China, Chinese Academy of Sciences and the Major State Basic Research Development Program of China (No. G2000077506).

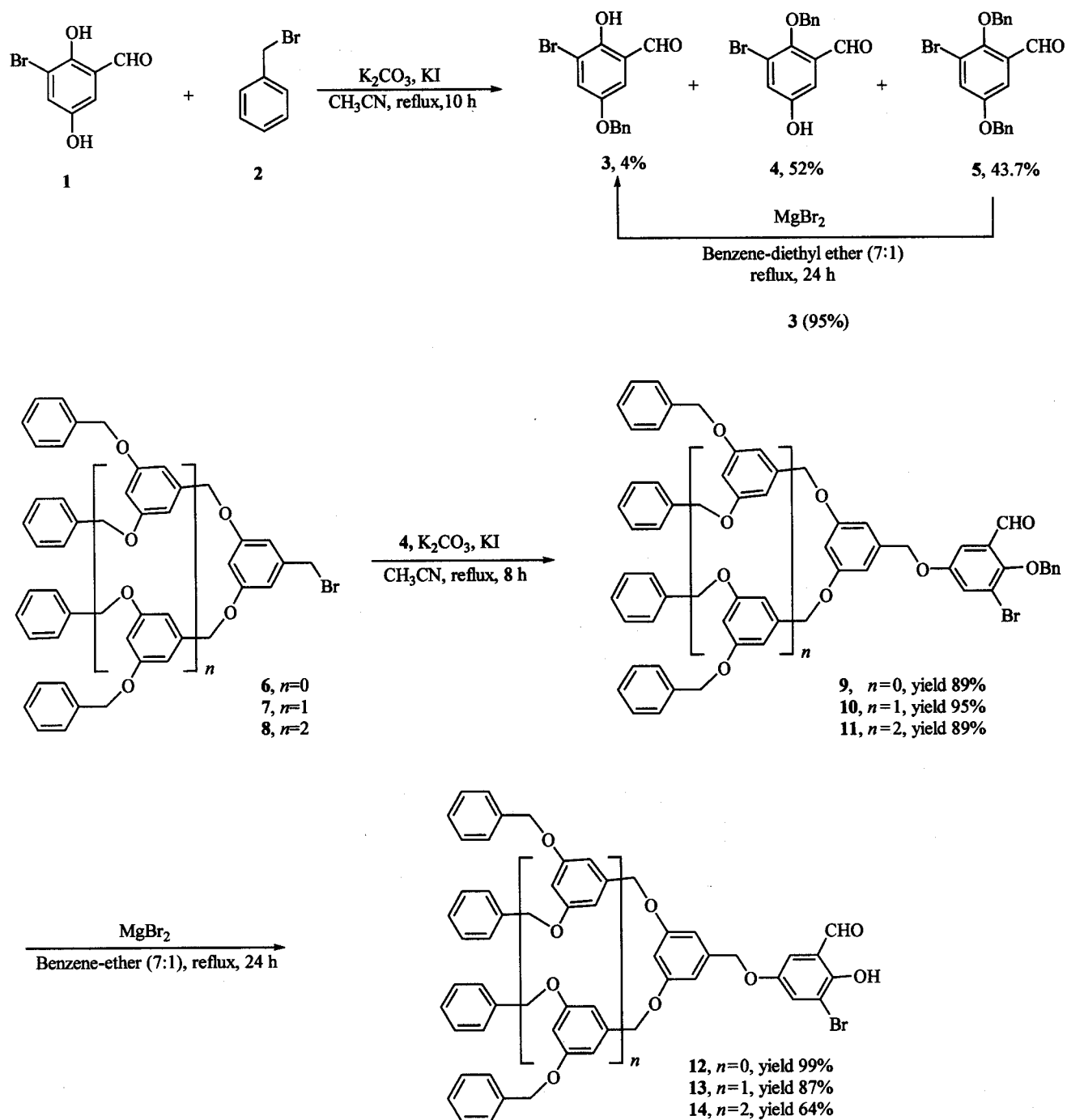
[†]Dedicated to Professor ZHOU Wei-Shan on the occasion of his 80th birthday.

well-resolved ^1H and ^{13}C NMR spectra consistent with their structures. Other spectral characterizations, including ^{13}C NMR, IR, MS, HRMS, were also identical to the composition and the structure of ligands prepared.

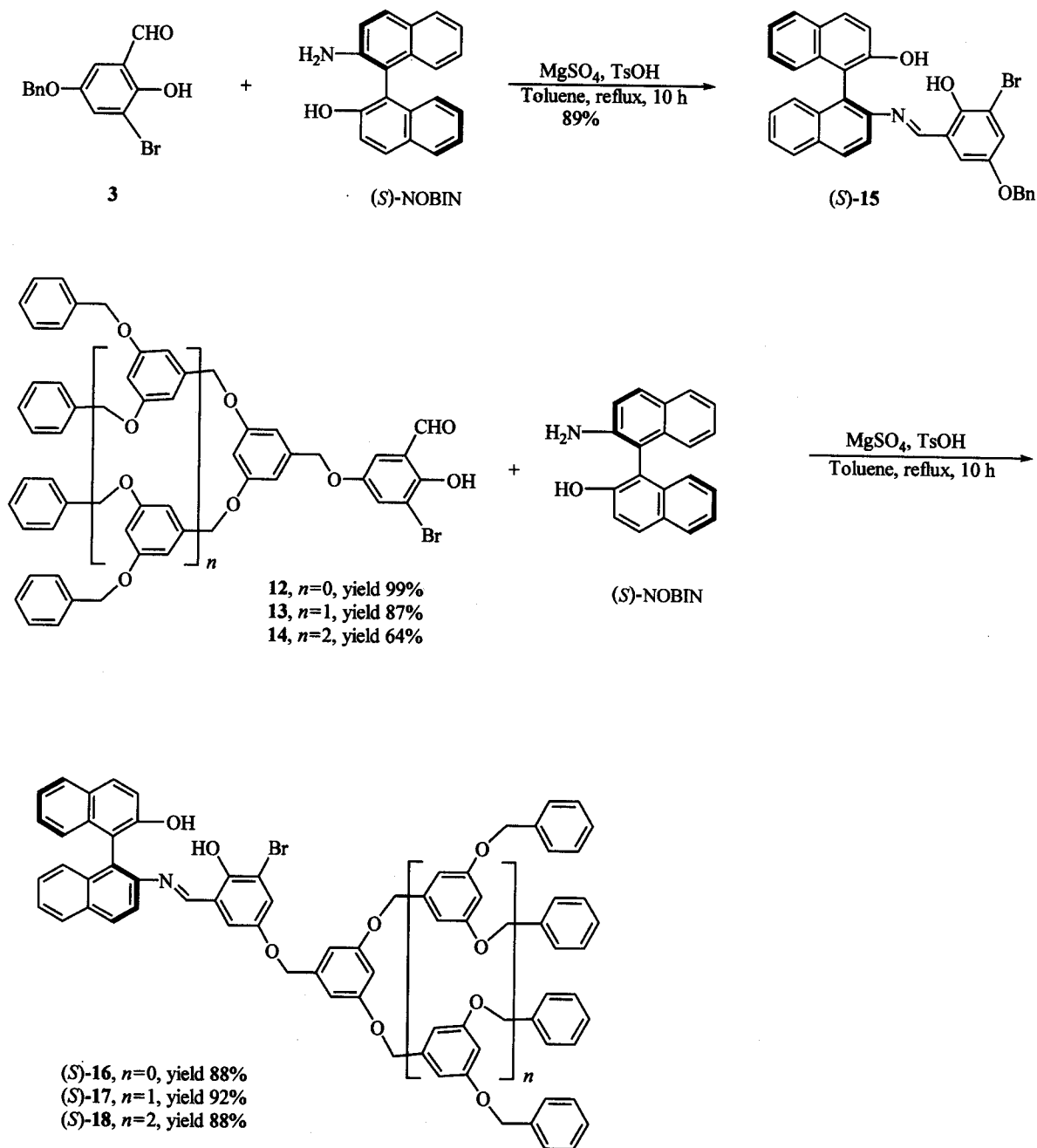
With the dendritic and nondendritic ligands (*S*)-**15**–**18** in hand, we then studied their application in titanium catalyzed hetero-Diels-Alder reaction of Danishefsky's diene with aldehydes. On the basis of our previous discovery of a synergetic effect of carboxylic acid on the reactivity and enantioselectivity of the reaction,⁵ (*S*)-

naproxen was taken as an additive to activate the titanium catalyst formed *in situ* by reaction of (*S*)-**15** (20%) with $\text{Ti}(\text{O}^i\text{Pr})_4$ (10%). As we expected, the addition of 5 mol% of (*S*)-naproxen could significantly enhance the enantioselectivity of the reaction from 22.0% *ee* to 46.5% *ee*. (Table 1, Entry 2 vs. Entry 1). The size of the dendron attached to the ligands has slight influence on the enantioselectivity of the reaction for **20a** (Entries 2–5)⁶. It was found that (*S*)-**17** showed the best catalytic activity

Scheme 1 Synthesis of dendritic salicylaldehyde derivatives



Scheme 2 Synthesis of non-dendritic and dendritic and Schiff base ligands



and enantioselectivity among the dendrimer ligands prepared. Therefore, we selected dendritic ligand (S)-17 to extend the scope of the substrates. As shown in Table 1, the catalyst prepared from (S)-17 and $\text{Ti}(\text{O}^i\text{Pr})_4$ in the presence of 5 mol% of (S)-naproxen was applicable for the promotion of HAD reaction of **19** with a variety of aromatic aldehydes **20b**—**20f** (Entries 4, 6—10) to give the corresponding 2-substituted-2,3-dihydro-4*H*-pyran-4-ones **21b**—**21f** in good yields and moderate enantioselectivities (up to 59.2% *ee*). Although the enantioselectivity of the reaction was not satisfactory at the moment, this research provided a possibility to improve the enantioselectivity by

changing the substituent equipped in the core ligand because the dendron moiety itself has no significant negative effect on the reactivity and selectivity of the reaction.

In conclusion, a new type of dendritic NOBIN derived Schiff base ligands have been synthesized and applied to titanium catalyzed hetero-Diels-Alder reaction of Danishefsky's diene and aldehydes, affording the corresponding 2-substituted 2,3-dihydro-4*H*-pyran-4-one in good yields and moderate enantioselectivities (up to 59.2% *ee*). It was found that the size of dendron attached to the tridentate ligands has slight impact on the enantioselectivity of the reaction and the second generation of dendritic ligand

