Communication

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

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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 tridentated 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, 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, BI-NOL, 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-C2-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 salicylaldimine ligand showed rather poor reactivity and enantioselectivity (32% conversion and 26% ee) for the same reaction. 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 heteroDiels-Alder (HDA) reaction.

As shown in Scheme 2, dendritic salicylicaldehyde 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 salicyaldehyde 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 intermidiate 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 salicylicaldehyde 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 salicylicaldehyde derivatives (9-11) in 89%-95% yields, followed by deprotection of benzyl group with Mg-Br₂. 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 salicylicaldehyde 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 salicylicaldehyde derivative 3 in 89% yield. All four kinds of dendritic and non-dendritic Schiff base ligands (S)-15-18 gave very

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well-resolved ¹H and ¹³C NMR spectra consistent with their structures. Other spectral characterizations, including ¹³C 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 Danishelfsky'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, (S)-

naproxen was taken as an additive to activate the titanium catalyst formed in situ by reaction of (S)-15 (20%) with $Ti(O^iPr)_4(10\%)$. 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 salicylical dehyde 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 $Ti(O^iPr)_4$ 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-4H-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 Danishelfsky's diene and aldehydes, affording the corresponding 2-substituted 2,3-dihydro-4H-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 tridentated ligands has slight impact on the enantioselectivity of the reaction and the second generation of dendritic ligand

Table 1 Dendritic or non-dendritic chiral Schiff base-Ti(IV) catalyzed asymmetric HDA reaction of Danishelfsky's diene 19 with aldehydes 20°

19 20a - 20f

21a - 21f

Entry	R	Ligand	$\mathrm{Yield}^b(\%)$	ee ^c (%)
1	Phenyl (20a)	(S)-15	27	22.0^{d}
2	Phenyl (20a)	(S)-15	84	46.5
3	Phenyl (20a)	(S)-16	72	48.2
4	Phenyl (20a)	(S)-17	87	55.2
5	Phenyl (20a)	(S)-18	75	54.6
6	3-Methylphenyl (20b)	(S)-17	89	56.0
7	4-Methylphenyl (20c)	(S)-17	93	58.5
8	3-Chlorophenyl (20d)	(S)-17	90	59.2
9	3-Bromophenyl (20e)	(S)-17	95	53.1
10	4-Methoxyphenyl (20f)	(S)-17	73	58.2

^a All reactions were carried out with ligand/ $Ti(O^iPr)_4$ /additive/substrate = 0.2:0.1:0.05:1 at room temperature in toluene for 48 h. ^b Isolated yields for two steps. ^c The enantiomeric excesses were determined by HPLC on Chiralcel OD column. ^d In the absence of (S)-naproxen.

exhibited the best enantioselectivity. The further study on the improvement of enantioselectivity of the reaction by tuning the electronic and steric nature of substituent in the core moiety of the dendrimer ligand is undergoing in this laboratory.

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- 6 A typical procedure for HDA reaction: To a 10-mL flame dried Schlenck tube was added activated powdered 4 Å (50 mg), (S)-dendritic Schiff Base (0.05 mmol) ligand and naproxen (0.0125 mmol) under argon atmosphere. Dried toluene (1 mL) and Ti(0'Pr)₄ in dichloromethane (0.5 mol/L, 50 μ L, 0.025 mmol) were subsequently injected, respectively. The resulting red solution was heated to 50 °C for 2 h and then cooled to room temperature. Aldehyde (0.25 mmol) and Danishelfsky's diene (80 μ L, 0.4 mmol) were added sequentially. The mixture was stirred at room temperature for 48 h before quenched with 10 drops of TFA. After stirring for additional 5 min, the mixture was neutralized with saturated NaHCO3 (about 3 mL) and extracted with ethyl ether (3 × 6 mL). The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated to dryness. The residue was purified by flash chromatography to give the cycloadduct.

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