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Synthesis of C_3-Symmetric Tris(β-hydroxy amide) Ligands and Their Ti(IV) Complex-Catalyzed Enantioselective Alkynylation of Aldehydes

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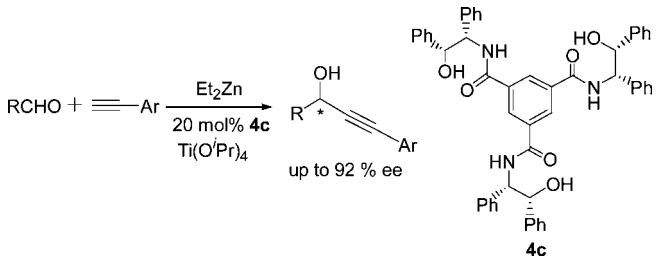
ABSTRACT



4c

A series of new chiral C_3-symmetric tris(β-hydroxy amide) ligands have been synthesized via the reaction of 1,3,5-benzenetricarboxylic chloride and optically pure amino alcohols (up to 96% yield). The asymmetric catalytic alkynylation of aldehydes with these new C_3-symmetric chiral tris(β-hydroxy amide) ligands and Ti (O^iPr)$_4$ was investigated. Ligand 4c synthesized from (1*R*,2*S*)-(−)-2-amino-1,2-diphenylethanol is effective for the enantioselective alkynylation of various aldehydes, and high enantioselectivity was obtained with aromatic aldehydes and α,β-unsaturated aldehyde (up to 92% ee).

C_3 symmetry is intriguing in chemistry, and many C_3-symmetric compounds and their applications in chiral molecular recognition and asymmetric catalysis have appeared in the literature.[1] For example, the rhodium(I) complexes of enantiomerically pure tripodal phosphanes with C_3 symmetry have been reported in the hydrogenation of dimethyl itachonate giving high ee (95%).[2] The C_3-symmetric diborate catalyzed the Diels−Alder reaction of cyclopentadiene and methacrolein in a highly enantioselective manner.[3] C_3-symmetric tris(2-hydroxypropyl)−amine Zr(IV) complex has been employed in the asymmetric ring-opening of *meso*-epoxides with high selectivity.[4] Katsuki and co-workers have developed tridentate tris(oxazoline) ligands as chiral auxiliaries in the asymmetric allylic oxidation of cycloalkenes, and moderate to excellent enantioselectivities (up to 93% ee) were obtained.[5] Chan and co-workers have also reported that the C_3-symmetric oxazolinyl ligands catalyzed the addition of diethylzinc to aromatic aldehydes to give secondary alcohols with high enantiomeric excesses (up to 90%).[6]

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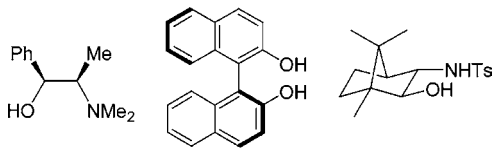
Development of new types of C_3-symmetric ligands for asymmetric reaction is an intriguing research area.[7]



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The catalytic asymmetric alkynylation of carbonyl compounds has attracted intense attention in recent years, and many significant chiral ligands in this area have been disclosed.[8−15] This process provides a very convenient route to afford chiral propargylic alcohols that have been applied widely in chemistry.[16] Among the catalytic methods developed for the asymmetric alkyne addition to aldehydes, several methods are currently considered to be practical. For example, Carreira and co-workers[9] developed a highly enantioselective catalyst based on *N*-methylephedrine **1** for the alkynylation of aliphatic aldehydes. Chan and co-workers[10b] and Pu's group,[11] respectively, reported that BINOL **2**−Ti(IV) complex can catalyze alkynylzinc addition to both aromatic and aliphatic aldehydes with high ee values and good yields. Recently, Wang and co-workers reported that sulfoamido alcohol **3** and other amino alcohols can catalyze alkynylzinc addition to aromatic aldehydes with very good efficiency.[12]

Although many significant results have been achieved in this area, much effort to develop new types of efficient chiral catalysts for this important asymmetric reaction is still in great need to probe the relation between the ligand structure and catalytic activity. To the best of our knowledge, no C_3-symmetric chiral ligand or catalyst has been successfully employed to the reaction of alkynylzinc addition to aldehydes. Herein, we report a new approach in which C_3-symmetric chiral tris(β-hydroxy amide) ligands combined with $Ti(O^iPr)_4$ are used to catalyze the enantioselective alkynylation of aldehydes.

During our studies, a series of C_3-symmetric ligands were easily prepared from commercially available amino alcohols in excellent yields. 1,3,5-Benzenetricarboxylic acid, $SOCl_2$, and several drops of DMF were refluxed to afford the 1,3,5-benzenetricarboxylic chloride. Without further purification, the trichloride reacted with chiral amino alcohols in the presence of excess triethylamine in CH_2Cl_2 at room temperature to afford tris(β-hydroxy amide)s **4a**−**d** in 88−96% yields (Figure 1).

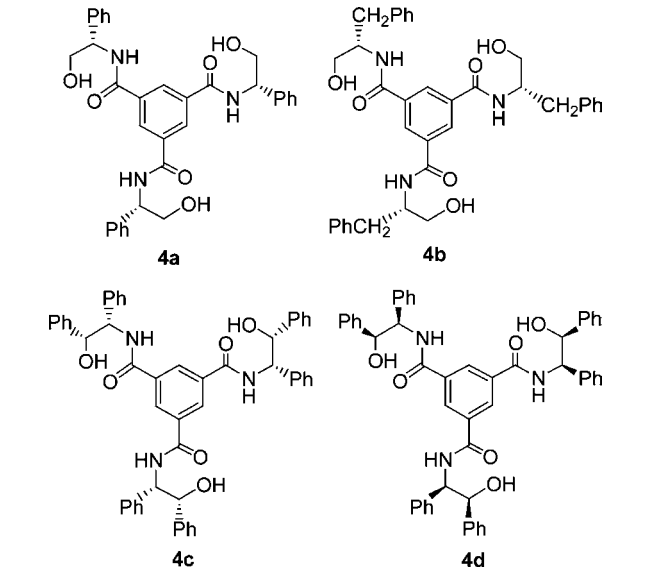

Figure 1. New C_3-symmetric ligands.

First, the C_3-symmetric ligands were examined in the asymmetric addition of phenylacetylene to benzaldehyde in the presence of Et_2Zn and $Ti(O^iPr)_4$. The zinc phenylacetylide was obtained using the method developed by Pu and co-workers,[11c] producing a white precipitate. The titanium complex was prepared by mixing the ligand with $Ti(O^iPr)_4$. The ligand itself was not very soluble in the reaction solvent, while a clear solution was formed after $Ti(O^iPr)_4$ was added.

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The addition reactions were carried out at room temperature for 6 h, and the results are summarized in Table 1. Ligands

Table 1. Enantioselective Addition of Phenylacetylene to Benzaldehyde[a]

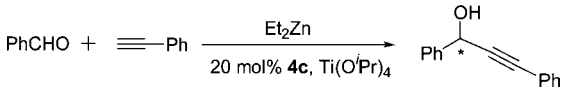
entry	ligand	ligand (mol %)	yield (%)[b]	ee (%)[c]	configuration[d]
1	**4a**	20	88	19	*R*
2	**4b**	20	76	6	*R*
3	**4c**	20	84	78	*S*
4	**4d**	20	80	11	*R*
5	**4c**	10	80	60	*S*
6	**4c**	5	74	33	*S*

[a] Mole ratio of PhCHO:phenylacetylene:Et_2Zn:$Ti(O^iPr)_4$ = 1:4:4:1.2, hexane/CH_2Cl_2 = 1:4, rt. [b] Isolated yield by column chromatography. [c] Ee was determined by HPLC analysis using Daicel Chiralcel OD column. [d] Absolute configurations were assigned by comparison with the literature.[17]

4a, **4b**, and **4d** gave low enantioselectivity (less than 20% ee), and the corresponding propargyl alcohol has *R* configuration (Table 1, entries 1, 2, and 4). A promising result was obtained with ligand **4c**, and the corresponding optically active propargyl alcohol was obtained in 85% yield and 78% ee with *S* configuration (Table 1, entry 3). Interestingly, the starting amino alcohols of ligands **4c** and **4d** are enantiomeric, but the results obtained in the enantioselective reactions carried out with the ligands **4c** and **4d** are quite different. A cooperative effect of the ligand and Lewis acid probably plays a decisive role. It was observed that a decrease in the catalyst loading from 20 to 10 or 5 mol % resulted in only a small loss of yield but a dramatic decrease in the enantioselectivity (Table 1, entries 3, 5, and 6).

To improve the enantioselectivity, the reaction conditions, including solvent, temperature, and amount of $Ti(O^iPr)_4$, were optimized with **4c**. The results were summarized in Table 2. We found that this reaction was strongly influenced by solvents and the amount of $Ti(O^iPr)_4$. When the reaction was carried out in toluene, no enantioselectivity was afforded (Table 2, entry 1). In dichloromethane, hexane, and hexane/toluene (v/v 1:4), low ee values (no more than 30%) were observed (Table 2, entries 2−4). The best solvent was hexane/dichloromethane (v/v 1:4). Gradually decreasing the amount of $Ti(O^iPr)_4$ from 1:6 to 1:1 dramatically decreased the enantioselectivity (Table 2, entries 7−10). Fine-tuning the ratio of **4c**/$Ti(O^iPr)_4$ from 1:6 to 1:7 produced the best result. The corresponding optically active propargyl alcohol was obtained in 84% yield and 86% ee (Table 2, entry 6). When the ratio of **4c**/$Ti(O^iPr)_4$ exceeded 1:7, the enantioselectivity also decreased dramatically (Table 2, entry 5). When the temperature of this reaction was decreased from room temperature to 0 or −15 °C, no significant change in enantioselectivity occurred but a long reaction time was needed (Table 2, entries 11 and 12). The concentration of the reaction is also important, as the enantiomeric excess decreased in diluted conditions (Table 2, entries 13 and 14). Other conditions were also tested. When Chan's method[10a]

Table 2. Asymmetric Addition of Phenylacetylene to Benzaldehyde under Different Conditions[a]



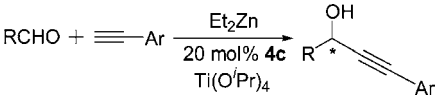
entry	solvent	L*/$Ti(O^iPr)_4$	*T* (°C)	*t* (h)	yield (%)[b]	ee (%)[c,d]
1	toluene 4 mL	1:7	rt	6	76	0
2	CH_2Cl_2 4 mL	1:7	rt	6	80	10
3	hexane 4 mL	1:7	rt	6	84	29
4	hexane 1 mL, toluene 4 mL	1:7	rt	6	82	7
5	hexane 1 mL, CH_2Cl_2 4 mL	1:8	rt	6	80	49
6	hexane 1 mL, CH_2Cl_2 4 mL	1:7	rt	6	84	86
7	hexane 1 mL, CH_2Cl_2 4 mL	1:6	rt	6	85	78
8	hexane 1 mL, CH_2Cl_2 4 mL	1:5	rt	6	84	64
9	hexane 1 mL, CH_2Cl_2 4 mL	1:3	rt	6	78	33
10	hexane 1 mL, CH_2Cl_2 4 mL	1:1	rt	6	72	13
11	hexane 1 mL, CH_2Cl_2 4 mL	1:6	0	12	83	77
12	hexane 1 mL, CH_2Cl_2 4 mL	1:6	−15	24	80	78
13	hexane 2 mL, CH_2Cl_2 8 mL	1:7	rt	8	78	55
14	hexane 3 mL, CH_2Cl_2 12 mL	1:7	rt	8	70	37

[a] Reaction was performed with mole ratio of PhCHO:phenylacetylene:Et_2Zn = 1:4:4. [b] Isolated yield by column chromatography. [c] Ees were determined by HPLC analysis on a Chiracel OD column. [d] Absolute configurations were assigned as *S* by comparison with the literature.[17]

was applied, the corresponding product was obtained in 60% yield and 3% ee, and 86% yield and 25% ee was obtained using Wang's method.[12a]

Under the optimal reaction conditions, ligand **4c** was applied to the reaction of phenylacetylene with a variety of aromatic and aliphatic aldehydes. As the results summarized in Table 3 show, highly enantioselective additions of phenylacetylene to substituted benzaldehydes containing

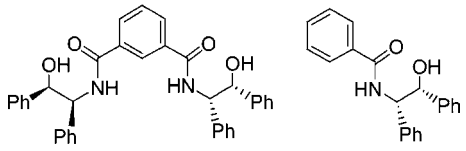
Table 3. Catalytic Asymmetric Alkynylation of Aldehydes[a]



entry	R	Ar	yield (%)[b]	ee (%)[c,d]
1	C_6H_5	Ph	84	87
2	2-$CH_3OC_6H_4$	Ph	86	92
3	4-$CH_3OC_6H_4$	Ph	84	82
4	2-$CH_3C_6H_4$	Ph	81	92
5	4-$CH_3C_6H_4$	Ph	78	90
6	2-FC_6H_4	Ph	83	87
7	2-ClC_6H_4	Ph	79	87
8	4-ClC_6H_4	Ph	83	84
9	1-naphthyl	Ph	72	90
10	PhCH=CH	Ph	81	91
11	$PhCH_2CH_2$	Ph	81	72
12	$(CH_3)_2CH$	Ph	64	47
13	C_6H_5	4-$CH_3C_6H_4$	79	82
14	C_6H_5	4-BuC_6H_4	77	85

[a] Reaction conditions: mole ratio of aldehyde:phenylacetylene:Et_2Zn:$Ti(O^iPr)_4$ = 1:4:4:1.4, hexane/CH_2Cl_2 = 1:4 as a solvent. [b] Isolated yield by column chromatography. [c] Ees were determined by HPLC analysis on Chiracel OD column (hexane/2-propanol 90:10, 1.0 mL/min). [d] Absolute configurations were assigned as *S* according to the literature.[17]

electron-withdrawing or electron-donating groups have been achieved by using the **4c**−Ti(O^{i}Pr)$_4$ catalyst (Table 3, entries 1−9). α,β-Unsaturated *trans*-cinnamaldehyde also afforded high enantioselectivity (Table 3, entry 10). Aliphatic aldehydes such as 3-phenylpropionaldehyde and *iso*-butyraldehyde also gave moderate to good enantioselectivity (Table 3, entries 11 and 12). Other aryl-substituted alkynes also worked in this reaction; 4-methyl or 4-butylphenyl acetylene also gave high ees in the enantioselective addition to benzaldehyde. However, alkyl-substituted acetylenes such as (trimethylsilyl)acetylene and (triisopropylsilyl)acetylene did not work in our conditions.



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To verify the structure of the titanium complex, we carried out ^{1}H NMR measurement. However, from the NMR data, we cannot confirm the formation of C_3 titanium complexes. To confirm the catalytic activity of tris(β-hydroxy amide) ligands, C_2- and C_1-symmetric ligands **5** and **6** were synthesized. When 20 mol % ligand **5**−Ti(IV) complex was used to catalyze the addition of phenylacetylene to benzaldehyde, the corresponding alcohol was obtained in 51% ee and 86% yield. The 20 mol % ligand **6**−Ti(IV) complex furnished 62% ee and 82% yield. When 30 mol % ligand **5** was used, the enantioselectivity was enhanced only slightly (60% ee and 85% yield). Use 60 mol % ligand **6** gave the corresponding alcohol in 40% ee and 88% yield. This result demonstrates the efficiency of C_3-symmetric ligands.

In summary, a series of new C_3-symmetric tris(β-hydroxy amide) ligands have been conveniently synthesized from commercially available chiral amino alcohols in two steps with excellent yields. In combination with Ti(O^{i}Pr)$_4$, they have been successfully applied in the asymmetric addition of aryl alkynes to various types of aldehydes. **4c**−Ti(O^{i}Pr)$_4$ complex is a highly enantioselective catalyst for the alkynylzinc addition to aromatic and α,β-unsaturated aldehydes. This simple catalyst system is practical for the asymmetric synthesis of chiral propargylic alcohols containing aromatic rings. The development of a library of C_3-symmetric ligands and new reactions is ongoing in our group.

Acknowledgment. This project was supported by National Natural Science Foundation of China (Grants 20372001 and 20172001) and Peking University.

Supporting Information Available: Experimental procedure for synthesis of **4**−**6**, copies of ^{1}H and ^{13}C NMR spectra of **4a**−**d**, and the general procedure for asymmetric addition. This material is available free of charge via the Internet at http://pubs.acs.org.

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