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Chiral Biscarboline *N,N′*-Dioxide Derivatives: Highly Enantioselective Addition of Allyltrichlorosilane to Aldehydes

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Abstract: The allylation of aromatic and aliphatic aldehydes with allyltrichlorosilanes has been catalyzed with a new Lewis base organocatalyst, 1,1′-biscarboline *N,N′*-dioxide with high enantioselectivities of up to 99% for 4-methoxybenzaldehyde and 97% *ee* for cycloformaldehyde, respectively. In total, 13 heteroaryl and aliphatic aldehydes were tested.

Keywords: allylation; asymmetric catalysis; 1,1′-biscarboline *N,N′*-dioxides; organocatalysts

Asymmetric additions of aldehydes with allyltrialkylsilanes[1] has been one of the most efficient methods to form homoallylic alcohols catalyzed by chiral Lewis or Brønsted acids,[2] especially using some binaphthyl derivatives.[3] Chiral phosphoramides, formamides or *N*-oxide derivatives possessing strong electron-donating properties also play important roles in the additions.[4–5] Since Nakajima's reports that axially chiral 2,2′-bipyridine *N,N′*-dioxides were effective as catalysts for the asymmetric allylation,[6] the class of 2,2′-bipyridine *N,N′*-dioxide derivatives has attracted considerable attention in the groups of Hayashi,[7] Malkov,[8] Dennmark,[9] Kotora,[10] and others.[11] Most of the axially chiral *N,N′*-dioxide derivatives reported were analogues of biquinolines and/or bipyridines.

It is found that only the catalysts that chelated with a metallic ion, for example, Ti complexes, **1**,[12] and **2**,[13] gave high enantioselectivities in the additions of both aromatic and aliphatic aldehydes with strongly toxic allyltributyltin (Figure 1). Catalysts **3**[14] and **4**[15] exhibited high enantioselectivities in additions of aliphatic aldehydes. However, **4** did not show high enantioselectivity in the addition of aromatic aldehydes with allylboronic acid pinacol ester. The N→O-containing catalysts, **5**[7a] and **6**,[6a] had high enantioselectivities in the additions of aromatic aldehydes with allyltrichlorosilanes but poor selectivities in the addition of aliphatic aldehydes. Herein, we report a series of axially chiral 1,1′-biscarboline *N,N′*-dioxide derivatives as the catalysts used in allylation. High enantioselectivity (up to 99% *ee* for benzaldehyde addition and up to 97% *ee* for cycloformaldehyde) were recorded, respectively, when 1 mol% of catalyst was used.

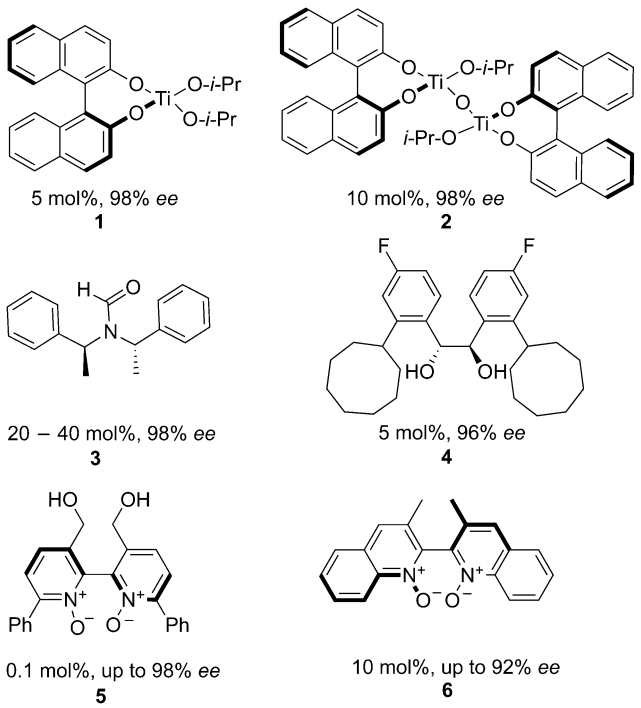
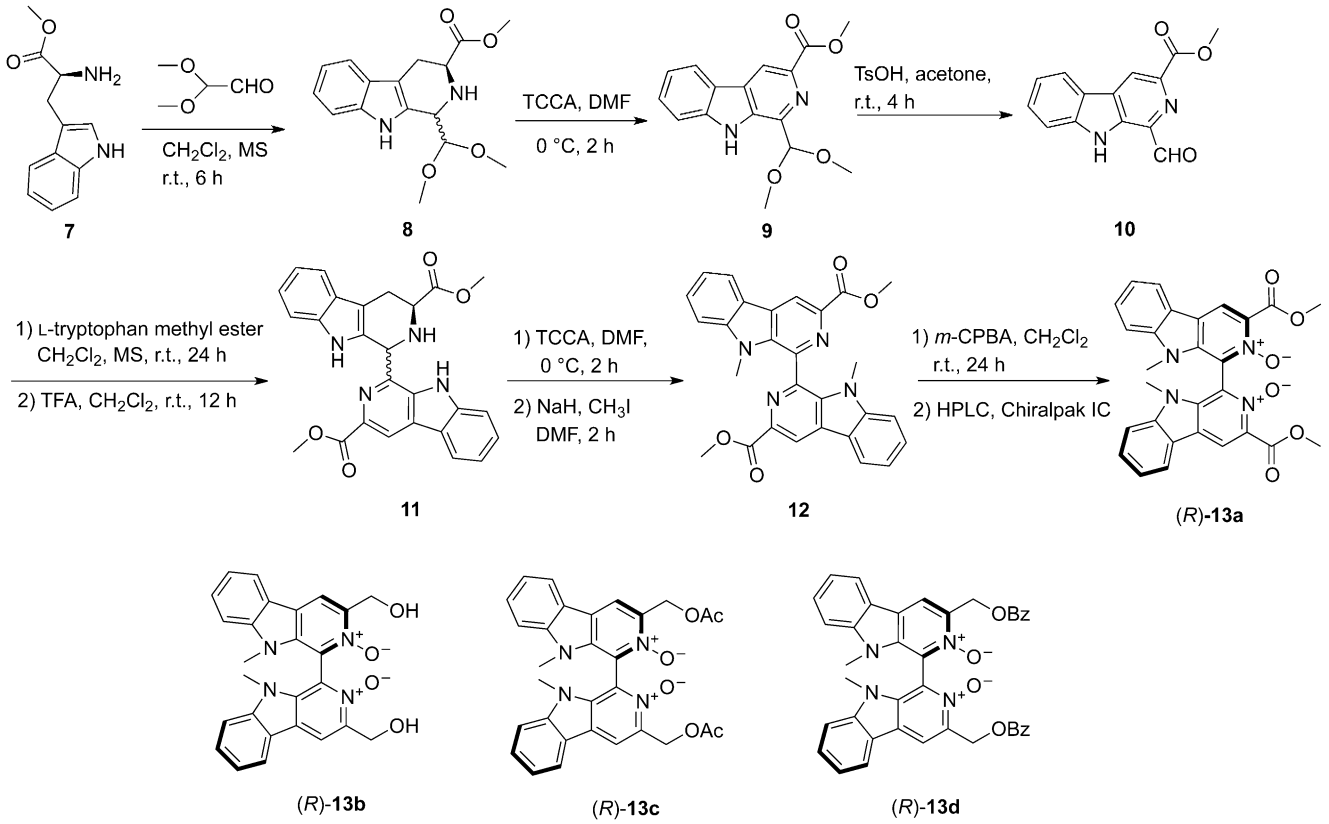


Figure 1. Previously reported, effective catalysts.



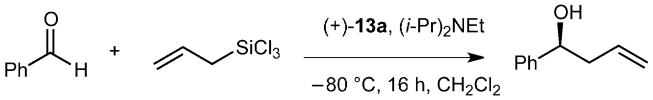
Scheme 1. Synthesis of axially chiral catalysts **13**.

The synthetic route to biscarboline *N,N′*-dioxide derivatives is illustrated in Scheme 1. The Pictet–Spengler reaction was employed firstly to form tetrahydrocarboline **8**. L-Tryptophan methyl ester and glyoxal were not used as starting materials since the product 1,1′-bistetrahydrocarboline cannot be obtained in any conditions. Carboline **9** which is derived from the arylation of **8** using trichloroisocyanuric acid was hydrolyzed in the presence of *p*-toluenesulfonic acid to give aldehyde **10**, the latter underwent another Pictet–Spengler condensation to form epimer **11**. 1,1′-Biscarboline **12** was obtained through indole *N*-methylation of the arylated **11** in the presence of sodium hydride as a base. Oxidation of the 1,1′-bicarboline **12** afforded dioxide **13** (48%) and monoxide (37%) along with traces of the unreacted **12** (<5%). The racemates **13** were resolved into enantiomers by using HPLC with a Chiralpak IC column. The reduction of **13a** using lithium aluminum hydride afforded **13b**, and acetylation and benzoylation of **13b** produced the corresponding **13c** and **13d**, respectively.

The absolute configuration of ligand **13a** was identified based on the experimental optical rotation (OR) values relative to the one that was calculated using density functional theory (DFT). The DFT method has been widely used for OR computations, by which the OR values were calculated to determine absolute configuration for chiral compounds, especially for rigid chiral compounds.[16] Conformational searches for **13a** were performed using MMFF94S force field, the stable conformations were then optimized at the B3LYP/6-31G(d) level. Only the lower energy conformations with the relative energy from 0–2.5 kcal mol^{-1} were used in OR computations at the B3LYP/6-311++G(2d,p) level. Boltzmann statistics were then used for whole conformational OR computations. (*S*)-**13a** had the OR magnitudes of −941.5. It was found that one enantiomer of **13a** had the OR values of +750.0 (*c* 0.27, $CHCl_3$). Thus, (+)-**13a** was assigned as the (*R*) configuration. Similarly, (+)-**13b** to (+)-**13d** were assigned as (*R*) too based on the positive OR magnitudes.[17]

The addition of allyltrichlorosilane **15** to benzaldehyde (**14**) was carried out in the presence of (+)-**13** near −80 °C for 16 h.The effect of solvents, such as toluene, THF, EtOAc, acetonitrile and dichloromethane on the addition reactions was investigated. The former three solvents led to enantioselectivities from 85–90% but poor conversion (about 10%). Only CH_2Cl_2 exhibited good conversion (100%) and high enantioselectivity. Thus, CH_2Cl_2 was used in the addition reactions. Enantioselectivity as high as 95% *ee* was recorded when 5% of catalyst was used. The high enantioselectivity (up to 95% *ee*) was retained when

Table 1. Enantioselectivities in the addition of allyltrichlorosilane to benzaldehyde.[a]



14 15 16

Entry	Cat.* (mol%)	Conversion [%][b]	*ee* [%][c]
1	(+)-**13a** (10)	100	95 (*S*)
2	(+)-**13a** (1)	100	95 (*S*)
3	(+)-**13a** (0.1)	26	95 (*S*)
4	(+)-**13b** (5)	100	60 (*S*)
5	(+)-**13c** (5)	100	77 (*S*)
6	(+)-**13d** (5)	100	79 (*S*)

[a] *Reaction conditions:* **14** (0.5 mmol), **15** (0.6 mmol), (+)-**13** (0.1–10 mol%).
[b] Estimated by recovering unreacted PhCHO.
[c] By HPLC using chiral column.

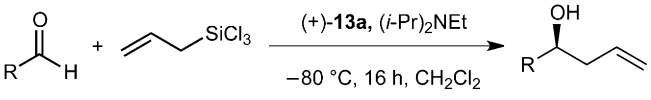
the quantity of (+)-**13a** was reduced to 1 mol%. It was fascinating that (+)-**13a** gave 95% enantioselectivity when 0.1 mol% of (+)-**13a** was used although a lower conversion (26%) was recorded when the addition was carried out for 16 h. Ligands (+)-**13b**, (+)-**13c** and (+)-**13d** had low enantioselectivities (Table 1, entries 4, 5, 6).

(*R*)-(+)-**13a** (1 mol%) was used in addition of other aldehydes (Table 2). The observed % *ee* values for most aldehydes additions were over 96%. Especially, this catalyst had both strong enantioselectivity in addition to aliphatic aldehydes, for example, cycloformaldehyde (97% *ee*) and high conversion (up to 100%). In contrast, most reported metallic ion-free catalysts exhibited low to moderate enantioselectivities in the additions of allyltrichlorosilane to aliphatic aldehydes.[1c,7a,8a] Enantiomer (−)-**13a** had the same catalytic ability as (+)-**13a** as expected, including the conversion (100%) and % *ee* values (up to 96% *ee*) in the addition of benzaldehyde with allyltrichlorosilane, its addition product had the opposite OR sign. The strong enantioselective ability that **13a** exhibited is one of the best known for current catalysts.

The general mechanism was proposed by Nakajima. During the allylation reaction, the *N*-oxide functional group possesses a notable electron-pair donor property, and exhibits a significant nucleophilicity towards the silicon atom.[6a] The allyl group was then transferred to the carbonyl group *via* a chair-like six-membered cyclic transition state.

In conclusion, a highly efficient, axially chiral 1,1′-biscarboline *N,N′*-dioxide, (*R*)-(+)-**13a**, has been developed and this catalyst exhibited excellent enantioselectivity in the asymmetric allylation of various aldehydes. Studies on expanding the scope and considering the mechanism of enantioselective reactions are in progress and will be reported in the future.

Table 2. Asymmetric allylation to aldehydes catalyzed by (*R*)-(+)-**13a**.[a]



Entry	R	Yield[b] [%]	*ee*[c] [%]	Configuration[d]
1	Ph	88	95	(*S*)
2	4-MeO-C_6H_4	75	99	(*S*)
3	3-Cl-C_6H_4	74	97	(*S*)
4	4-Cl-C_6H_4	77	97	(*S*)
5	3-F-C_6H_4	71	95	(*S*)
6	4-F-C_6H_4	76	97	(*S*)
7	4-Me-C_6H_4	74	95	(*S*)
8	2-thiophenyl	83	97	(*S*)
9	1-naphthyl	82	96	(*S*)
10	2,6-di-Cl-C_6H_s	87	97	(*R*)[e]
11	$PhCH{=}CH_2$	90	91	(*S*)
12	$PhCH_2CH_2$	73	92	(*R*)
13	*c*-C_6H_{11}	53	97	(*S*)[f]

[a] *Reaction conditions:* aldehyde (0.5 mmol), **15** (0.6 mmol), (+)-**13a** (1 mol%).
[b] Isolated yield. Some products are fairly volatile.
[c] Determined by HPLC using a chiral column.
[d] Determined by comparing OR data and retention times using HPLC.
[e] The absolute configuration was determined using two methods: one is to refer the report (Ref.[18]), the other one is to compute its det(D) values (Ref.[19]). The computed det(D) for the (*S*) enantiomer was −20.9. The recorded optical rotation was +10.0 with the corresponding k_0 of −0.48. Thus, only (*R*) enantiomer has negative OR values.
[f] Determined after conversion to the 3,5-dinitrobenzoate ester.

Experimental Section

1,1′-Biscarboline *N,N′*-Dioxide [(±)-13a]

m-Chloroperoxybenzoic acid (70%, 3 mmol) was added portion-wise to a stirred solution of **12** (1 mmol) in CH_2Cl_2 (50 mL) at 0 °C, and the stirring was continued at room temperature for further 24 h. Then the mixture was poured into saturated aqueous $NaHCO_3$ (50 mL) and extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4. The filtered solution was concentrated under vacuum. The residue was purified by chromatography (silica gel) eluting with CH_2Cl_2/CH_3OH (80/1) to give dioxide (±)-**13a** as a pale yellow solid; yield: 245 mg (48%). The racemic mixtures of (±)-**13a** were resolved by HPLC on a Chiralpak-IC column (250×10 mm, CH_2Cl_2/CH_3OH = 40/60) and both (+)-**13a** and (−)-**13a** were obtained in 48% and 47% yields, respectively.

(+)-**13a:** $[\alpha]_D$: +750 (*c* 0.27, $CHCl_3$); mp > 300 °C (decomp.); MS-ESI: *m/z* = 511 $[M+H]^+$; HR-MS: *m/z* = 511.1608, calcd. for $C_{28}H_{23}N_4O_6$ $[M+H]^+$: 511.1617; IR (KBr): ν = 3440, 1738, 1598, 1436, 1392, 1284, 1242,

751 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 3.44$ (s, 3H×2, NCH_3), 4.01 (s, 3H×2, $COOCH_3$), 7.36–7.39 (m, 2H×2), 7.57 (t, $J = 7.2$ Hz, 1H×2), 8.08 (d, $J = 7.7$ Hz, 1H×2), 8.55 (s, 1H×2); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 29.4$, 53.1, 109.8, 119.4, 120.1, 120.9, 121.1, 121.7, 126.2, 128.4, 133.1, 139.3, 143.5, 163.1.

Experimental procedures, spectral data and copies of the NMR spectra for the key compounds are available in the Supporting Information.

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