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Asymmetric Synthesis of Novel Axially Chiral 2,2'-Bipyridine *N*,*N*′-Dioxides Bearing *α*-Amino Acid Residues and Their Applications in Enantioselective Allylation of Aromatic Aldehydes with Allyltrichlorosilane

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A series of novel axially chiral 2,2'-bipyridine *N*,*N*′-dioxides bearing C_1 or C_2-symmetry have been synthesized by the use of enantiopure *α*-amino acids as chiral sources. The absolute stereochemistry of the axial chirality of these organocatalysts has been clearly assigned by means of CD measurements together with literature protocols. The reactivities and enantioselectivities of these organocatalysts have been examined in the reactions of aromatic aldehydes with allyltrichlorosilane, thus providing the desired products with moderate yields and enantioselectivies.

Keywords 2,2'-bipyridine *N*,*N*′-dioxide, organocatalyst, asymmetric catalysis, enantioselective allylation, allyltrichlorosilane

Introduction

Axially chiral 2,2'-bipyridine *N*,*N*′-dioxides as shown in Figure 1 represent a class of Lewis-basic organocatalysts, and have received considerable attention due to their high reactivity and stereoselectivity in a wide range of asymmetric catalytic transformations, where silicon reagents are involved.[1] As asymmetric catalytic inducers, the chiral 2,2'-bipyridine *N*,*N*′-dioxides have found many applications in the fields of allylation of aldehydes,[2] Aldol reactions,[3] Strecker reactions,[4] ring opening of meso-epoxides[5] and Michael additions[6] and so on. It has been disclosed that the axial chirality of the 2,2'-chiral bipyridine *N*,*N*′-dioxides plays an important role in controlling stereoselectivity of the asymmetric organocatalytic reactions, and the stereocontrol efficiencies of the chiral 2,2'-bipyridine *N*,*N*′-dioxides are highly governed by the conformational changes caused by their complexation with silicon-containing reagents as strong oxygen donors. By now, it is well known that a wide array of axially chiral 2,2'-bipyridine *N*,*N*′-dioxides bearing diverse structural features have been developed as organocatalysts for the allylation of aromatic aldehydes with allyltrichlorosilane, and among the reported 2,2'-bipyridine *N*,*N*′-dioxides as organocatalysts, some of them exhibited excellent organocatalytic performances in the allylation of aromatic aldehydes with allyltrichlorosilane.[2a,2c,2e,2k,2n-2p] In addition, it should be mentioned that some of the other known 2,2'-bipyridine *N*,*N*′-dioxide organocatalysts are seriously limited because of their low reactivities and stereoselectivities as well as narrow substrate scopes.[2b,2f-2j,2l] Therefore, it is highly desired to design

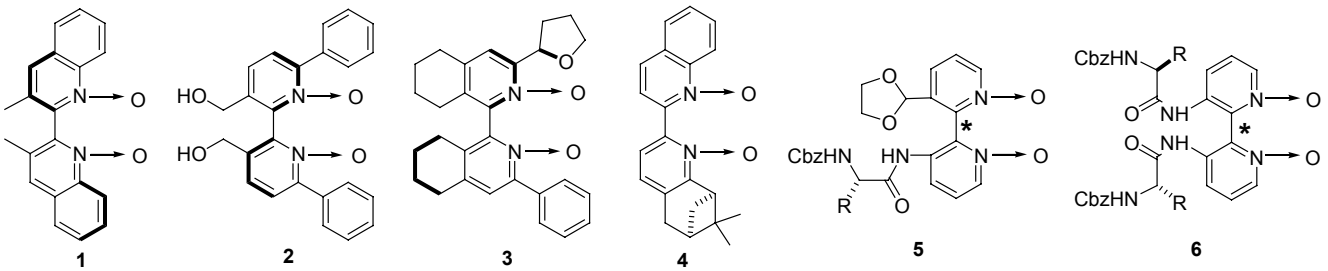

Figure 1 The reported 2,2'-bipyridine *N*,*N*′-dioxide organocatalysts **1**—**4** in the literature and the examined organocatalysts **5**—**6** in this work.

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and synthesize novel 2,2'-bipyridine *N*,*N*′-dioxides for the stereoselective allylation of aromatic aldehydes with a goal to achieve optimal organocatalytic efficiencies and broad substrate scopes in the allylation of aromatic aldehydes.

Results and Discussion

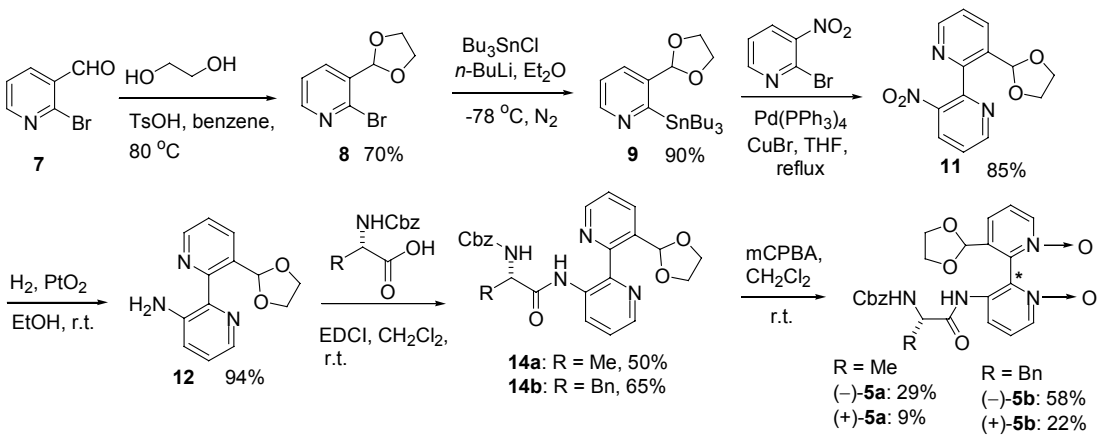
Herein, in this work our attention was focused on the asymmetric synthesis of novel axially chiral 2,2'-bipyridine *N*,*N*′-dioxide organocatalysts **5**—**6** as shown in Figure 1 and investigations on their enantioselective catalytic efficiencies in allylation of a variety of aromatic aldehydes with allyltrichlorosilane. In our organocatalysts **5** (C_1-symmetry) and **6** (C_2-symmetry), enantiopure *α*-amino acids were utilized as chiral sources to set up the axial configuration of 2,2'-bipyridine *N*,*N*′-dioxide subunits. The introduction of two highly functionalized pendants at 3,3'-positions of 2,2'-bipyidine *N*,*N*′-dioxide motifs is able to efficiently restrict the free rotation of chiral axes of 2,2'-bipyridine *N*,*N*′-dioxides as organocatalysts, and serves as additional binding sites for these organocatalysts to interact with substrates via nonbonding interactions. To the best of our knowledge, this is the first example on the asymmetric synthesis of 3,3'-disubstituted-2,2'-bipyridine *N*,*N*′-dioxides bearing *α*-amino acid residues as organocatalysts in the asymmetric organocatalytic allylation of aromatic aldehydes with allyltrichlorosilian.

The synthesis of chiral bipyridine *N*,*N*′-dioxide **5** was accomplished according to Scheme 1. Starting from compound **7**, compound **8** was achieved in 70% yield on treatment with ethyl glycol in the presence of TsOH in acetone at 80 ℃.[7] When compound **8** was lithiated with *n*-BuLi and subsequently quenched with Bu_3SnCl in anhydrous Et_2O at −78 ℃, compound **9** was obtained in 90% yield.[8] It was important to note that compound **9** is very sensitive to silica gel. When compound **9** was purified by flash column chromatography on silica gel, a serious decomposition of compound **9** took place, giving rise to the formation of a complicated and inseparable mixture. The successful purification of compound **9** was carried out using neutral Al_2O_3 as stationary phase. The Stille cross-coupling of compound **9** with compound **10** proceeded smoothly catalyzed by $Pd(PPh_3)_4$ and CuBr in anhydrous THF at reflux, thus furnishing desired compound **11** in 85% yield.[9] In the presence of PtO_2, compound **11** was readily hydrogenated to give compound **12** in 94% yield.[10] Initially, the catalytic hydrogenation of compound **11** was attempted using 10% Pd-C as a catalyst. However, the significant amount of the starting material was recovered after compound **11** was treated with H_2 (1 atm) overnight in EtOH at room temperature. With the required compound **12** in hand, in the presence of EDCI the condensation reactions with enantiopure *α*-amino acids **13a**—**13b** were affected to provide compounds **14a**—**14b** in 50% and 65% yields, respectively.[11] The oxidation of **14a** with 10.0 equiv. of *m*-CPBA in anhydrous CH_2Cl_2 at room temperature gave rise to a diastereoisomeric mixture of (−)-**5a** and (+)-**5a** in a ratio of 3∶1, and the isolation of diastereoisomers (−)-**5a** and (+)-**5a** was easily finished by flash column chromatography on silica gel.[2b] In a similar way, the oxidation of compound **14b** was carried out, providing diastereoisomers (−)-**5b** and (+)-**5b** in 58% and 22% yields, respectively.

Meanwhile, chiral 2,2'-bipyridine dioxides (−)-**6a** and (+)-**6a** bearing a C_2-symmetry were readily prepared according to the strategy as shown in Scheme 2. Starting from compound **15**, the coupling product **16** was obtained in 65% yield via Ullmann reation.[12] The catalytic hydrogenation of compound **16** provided the desired product **17** in 95% yield (H_2, 10% Pd-C, EtOH, r.t.).[14] The reaction of 2,2'-bipyridine diamine **17** with (*S*)-*N*-Cbz-Ala gave product **18** in 80% yield in the presence of EDCI in anhydrous CH_2Cl_2 at room temperature.[11] Upon treatment with 30% $H_2O_{2(aq)}$ in HOAc at 75 ℃, compound **18** was oxidized into chiral 2,2'-bipyridine dioxides (−)-**6a** and (+)-**6a** in 26% and 28% yield, respectively.[14]

Moreover, it turned out that the axial chirality of **5a**, **5b** and **6a** is thermodynamically stable at room tem-

Scheme 1 Synthesis of chiral 2,2'-bipyridine *N*,*N*′-dioxides **5**



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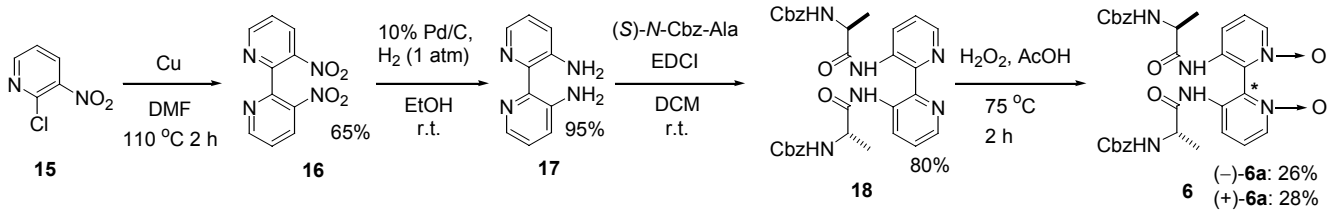
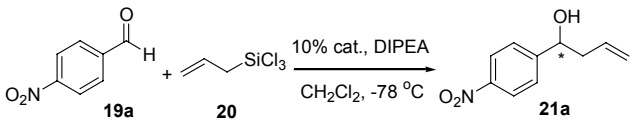
Scheme 2 Syntheis of chiral 2,2'-bipyridine *N*,*N*'-dioxides **6**



perature. When single diastereoisomers **5a**, **5b** and **6a** were stirred in CH_2Cl_2 at room temperature for 3 d, the atropisomerization did not take place at all. Even when sample (−)-**5a** was heated in toluene at 40 ℃ for 24 h, no atropisomerization was observed. At the same time, for the sake of the identification of absolute configuration of stereogenic axis in the 2,2'-bipyridine dioxides (−)-**6a** and (＋)-**6a**, the CD spectra of (−)-**6a** and (＋)-**6a** were recorded in MeOH solution, and the experimental details were presented in the Supporting Information. The CD spectra of (−)-**6a** displayed a strong negative Cotton effect at 266 nm and a weak strong Cotton effect at 314 nm; in contrast, the CD spectrum of (＋)-**6a** featured a strong positive Cotton effect at 266 nm and a weak negative Cotton effect at 315 nm. Obviously, the strong Cotton effects at 266 nm of both (−)-**6a** and (＋)-**6a** were originated from the twisted 2,2'-bipyridine dioxide motifs in these compounds, and they can be used as explorers in the determination of absolute configurations of helical chirality of compounds (−)-**6a** and (＋)-**6a**. In conjunction with the reported strategies in the literature,[11,15] the axial chirality of compound (−)-**6a** was determined as (*S*)-configuration, and compound (＋)-**6a** was assigned as (*R*)-configuration on the basis of their individual CD spectra. Furthermore, based on the comparison of the sign of specific optical rotations with compounds (−)-**6a** and (＋)-**6a** respectively, it was reasoned that compounds (−)-**5a** and (−)-**5b** have (*S*)-configured axial chirality, and (＋)-**5a** and (＋)-**5b** contained (*R*)-configured axial chirality, respectively.

With these 2,2'-bipyridine *N*,*N*'-dioxide organocatalysts in hand, their reactivities and enantioselectivities were examined in the allylation of *p*-nitrobenzaldehyde with allyltrichlorosilane as shown in Table 1. In the case of chiral 2,2'-bipyridine *N*,*N*'-dioxides (−)-**5a** and (＋)-**5a** with a C_1-symmetry, they gave the opposite enantiomers of product **21a** in different yields and enantioselectivities (Table 1, entries 1, 2). The same case was observed with organocatalysts (−)-**6a** and (＋)-**6a** bearing C_2-symmetry (Table 1, entries 5, 6). Catalyzed by (−)-**5b** and (＋)-**5b**, the reactions provided the desired products with the opposite enantiomers in comparable yields and *ee* values (Table 1, entries 3, 4). Moreover, in most cases, it was noted that organocatalysts with C_1-symmetry did not show much differences in enantioselectivities by comparison with organocatalysts with C_2-symmetry (Table 1, entries 2−4 vs. 5, 6). On the basis of these results, it was reasoned that the observed asymmetric inductions with **5a**, **5b** and **6a** in the allylation of *p*-nitrobenzaldehyde with trichloroallylsilane were mainly controlled by the axial chirality present in chiral 2,2'-bipyridine *N*,*N*′-dioxide organocatalysts. At this moment, the stereochemical correlation between the axial chirality of these organocatalysts and the induced chiral sense of the desired products in the allylation of *p*-nitrobenzaldehyde with allyltrichlorosilanem was clarified as follows: (*S*)-configured stereogenic axial chirality of the organocatalysts induces (*R*)-configured central chirality of the allylation products; (*R*)-configured axially chiral sense of the organocatalysts results in (*S*)-configuration of the allylation products. Obviously, in our cases, the asymmetric inductions were in full agreement with Kotora's observations.[2h,2m, 2n]

Table 1 Asymmetric catalytic allylation of *p*-nitrobenzaldehyde with allyl(trichloro)silane catalyzed by organocatalysts[a]

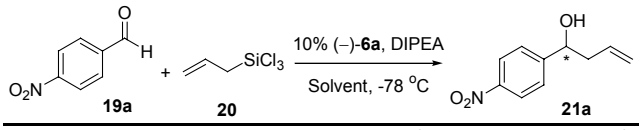


Entry	Catalyst	Time/h	Yield[b]/%	*ee*[c]/%	Config.[d]
1	(−)-**5a**	8	54	40	*R*
2	(＋)-**5a**	12	61	27	*S*
3	(−)-**5b**	9	66	35	*R*
4	(＋)-**5b**	10	65	31	*S*
5	(−)-**6a**	4	48	33	*R*
6	(＋)-**6a**	5	41	27	*S*

[a] The reaction was carried out with 10 mol% of catalyst, 1.5 equiv. of allyltrichlorosilane and 1.5 equiv. of DIPEA in anhydrous CH_2Cl_2 at −78 ℃. [b] Isolated yields. [c] Determined by HPLC or SFC on a Chiralpak column. [d] Assigned by comparison of chiral HPLC retention times with literature data.

Meanwhile, with the use of (−)-**6a** as organocatalyst, the solvent effects on the organocatalytic allylation reactions were investigated as shown in Table 2. Noticeably, the chemical yields and enantioselectivities of the allylation reactions were significantly changed with the used solvents. For instances, the choice of DMF as the reaction solvent furnished the desired product in 50% yield as a racemate (Table 2, entry 9). In toluene, the allyation reaction occurred in very low yield and enantioselectivity (Table 2, entry 1). Using other solvents as reaction mediums, the allylation reactions afforded

Table 2 Screening of solvent effects on the allylation reaction[a]



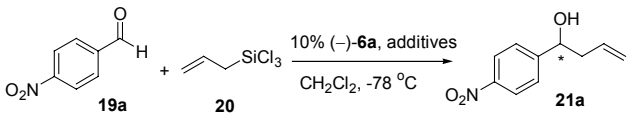
Entry	Solvent	Time/h	Yield[b]/%	*ee*[c]/%	Config.[d]
1	PhMe	12	5	5	*R*
2	*n*-Hexane	12	2	27	*R*
3	THF	12	27	21	*R*
4	EtOAc	11	17	17	*R*
5	Et_2O	11	8	15	*R*
6	MeCN	11	35	41	*R*
7	$CHCl_3$	11	35	31	*R*
8	PhCl	11	22	13	*R*
9	DMF	11	50	0	—

[a] The reaction was carried out with 10 mol% of (–)-**6a,** 1.5 equiv. of allyltrichlorosilane and 1.5 equiv. of DIPEA in anhydrous indicated solvents at −78 ℃ for 11－12 h. [b] Isolated yields. [c] Determined by HPLC on a Chiralpak column. [d] Assigned by comparison of chiral HPLC retention times with literature data.

the desired products in 2%－35% yields with 13%－41% *ee*s (Table 2, entries 2－8). Conclusively, among all the solvents tested, CH_2Cl_2 and MeCN seemed to be better solvents for the allylation reactions.

In addition, in the presence of (–)-**6a** as an organocatalyst, a series of basic additives were attempted in the allylation reactions as summarized in Table 3. It was found that the comparable yields and enantioselectivities were achieved with Et_3N, piperazine and 2,6-Lutidine as basic additives (Table 3, entries 1－3), and the same case was observed with the use of pyridine and DABCO as additives (Table 3, entries 5, 6). The lowest enantioselectivity was generated when DMAP was applied as an additive in the allylation reaction (Table 3, entry 4).

Table 3 Screening of additive effects on the allylation reactions[a]

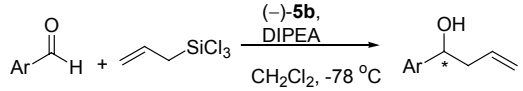


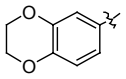
Entry	Additive	Time/h	Yield[b]/%	*ee*[c]/%	Config.[d]
1	Et_3N	11	26	41	*R*
2	piperazine	11	23	36	*R*
3	2,6-Lutidine	11	28	47	*R*
4	DMAP	10	32	–3	*S*
5	pyridine	10	11	17	*R*
6	DABCO[e]	10	15	25	*R*

[a] The reaction was carried out with 10 mol% of (–)-**6a**, 1.5 equiv. of allyltrichlorosilane and 1.5 equiv. of indicated additives in anhydrous CH_2Cl_2 at −78 ℃ for 10－11 h. [b] Isolated yields. [c] Determined by HPLC on a Chiralpak column. [d] Assigned by comparison of chiral HPLC retention times with literature data. [e] 1,4-Diaza[2.2.2]bicyclooctane.

Subsequently, (–)-**5b** was used as organocatalyst to extend the substrate scope as shown in Table 4. In all cases, the reactions proceeded smoothly, thus delivering the desired products in 54%－67% yields. Substrates **19b**－**19d** afforded the desired products in comparable yields and *ee* values (Table 4, entries 2－4). When **19e** was chosen as a substrate, the *ee* value of the reaction dropped significantly, and only 3% *ee* value was obtained with the desired product **21e**. As substrates **19f** and **19g** were concerned, the desired prodcuts **21f** and **21g** were obtained in 63% and 65% *ee* values, respectively (Table 4, entry 6 vs. 7). In general, it can be seen in the Table 2 that, except for substrate **19e**, the allylation of benzaldehydes with an electron-donating group tended to give the desired products in higher *ee* values than those obtained with the benzaldehydes bearing an electron-withdrawing group (Table 4, entries 2－4 vs. 6, 7).

Table 4 The reaction scope in the presence of (–)-**5b**[a]



Entry	Ar	Product	Yield[b]/%	*ee*[c]/%	Config.[d]
1	4-$NO_2C_6H_5$	**21a**	66	35	*R*
2	4-BrC_6H_5	**21b**	67	42	*R*
3	3-ClC_6H_5	**21c**	58	45	*S*
4	4-ClC_6H_4	**21d**	54	49	*R*
5	4-$MeOC_6H_4$	**21e**	58	3	*R*
6	4-MeC_6H_4	**21f**	65	65	*S*
7		**21g**	61	63	ND[e]

[a] The reaction was carried out with 10 mol% of (–)-**5b**, 1.5 equiv. of allyltrichlorosilane and 1.5 equiv. of DIPEA in anhydrous CH_2Cl_2 at −78 ℃ for 8－12 h. [b] Isolated yields. [c] Determined by HPLC or SFC on a Chiralpak column. [d] Assigned by comparison of chiral HPLC retention times with literature data. [e] Not determined.

Meanwhile, as shown in Table 5, the reactivities and stereoselectivities of organocatalysts (–)-**6a** and (＋)-**6a** bearing a C_2-symmetry were examined in the allylations of allyltrichlorosilane with a variety of aromatic aldehydes. As for the same substrate examined in the reaction, organocatalysts (–)-**6a** and (＋)-**6a** afforded comparable yields and enantioselectivities with opposite chiral inductions. In contrast, catalyzed by organocatlysts (–)-**6a** or (＋)-**6a**, electron-enriched aromatic aldehydes tended to give better *ee* values in comparison with those of electron-poor aromatic aldehydes (Table 3, entries 1－3 vs. 4－7; entries 8－10 vs. 11－14). Among all the examined substrates, substrate **19d** with a nitro group furnished the desired product in the lowest *ee* values no matter (–)-**6a** or (＋)-**6a** was uesd as an organocatalyst (Table 3, entries 3, 10). On the contrary, in the presence of (–)-**6a** or (＋)-**6a**, substrate **19e** with a methyl group afforded the best enantioselectivities in the reactions (Table 3, entries 4, 11). In addition, it was noted that increasing catalyst loading from 10% to 20%

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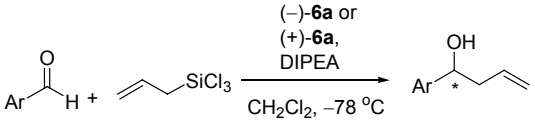
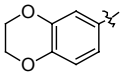
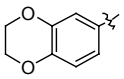
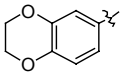
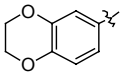
indeed led to the significant increases in chemical yields, however, no much differences in enantioselectivities were observed in the reactions (Table 3, entries 4 vs. 5; 6 vs. 7; 11 vs. 12; 13 vs. 14). Finally, organocatalytic allylation of benzaldehyde was carried out in THF or CH_2Cl_2 in the presence of (−)-**6a** as organocatalyst respectively. In CH_2Cl_2, the best enantioselectivity of the allylation reaction was accessed with the use of (−)-**6a** as organocatalyst (Table 5, entry 15).

Table 5 The reaction scope in the presence of (−)-**6a** and (+)-**6a**[a]



19b–19g **20** **21b–21g**

Entry	Ar	Prodcut	Yield[f]/%	*ee*[g]/%	config.[h]
1[b]	3-ClC_6H_5	**21c**	46	43	*S*
2[b]	4-ClC_6H_4	**21d**	31	49	*R*
3[b]	4-$NO_2C_6H_4$	**21a**	48	33	*R*
4[b]	4-MeC_6H_4	**21f**	23	61	*S*
5[d]	4-MeC_6H_4	**21f**	46	53	*S*
6[b]		**21g**	14	53	ND[i]
7[d]		**21g**	40	51	ND[i]
8[c]	3-ClC_6H_5	**21c**	32	39	*R*
9[c]	4-ClC_6H_4	**21d**	67	51	*S*
10[c]	4-$NO_2C_6H_4$	**21a**	41	27	*S*
11[c]	4-MeC_6H_4	**21f**	30	65	*R*
12[e]	4-MeC_6H_4	**21f**	36	53	*R*
13[c]		**21g**	44	59	ND[i]
14[e]		**21g**	59	61	ND[i]
15[b]	C_6H_5	**21h**	13	55	*R*
16[b,j]	C_6H_5	**21h**	11	15	*R*

[a] The reaction was carried out with 1.5 equiv. of allyltrichlorosilane and 1.5 equiv. of DIPEA in the presence of catalysts in anhydrous CH_2Cl_2 at −78 ℃ for 5−10 h. [b] (−)-**6a**, 10 mol%. [c] (+)-**6a**, 10 mol%. [d] (−)-**6a**, 20 mol%. [e] (+)-**6a**, 20 mol%. [f] Isolated yields. [g] Determined by HPLC on a Chiralpak column. [h] Assigned by comparison of chiral HPLC retention times with literature data. [i] Not determined. [j] THF is used as solvent.

Conclusions

In conclusion, a series of axially chiral 2,2'-bipyridine *N*,*N*'-dioxides were synthesized as organocatalysts starting from enantiopure *α*-amino acids. The absolute configuration of these organocatalysts was clearly determined based on the CD measurements in combination with literature protocols. It was disclosed that the obtained organocatalysts have shown moderate enantioselectivities and reactivities in the allylation of aromatic aldehydes with trichloroallylsilane. Currently, our intensive efforts are focused on the optimization of the reaction conditions and organocatalysts, and the results will be reported in short course.

Experimental

General

Unless noted otherwise, all reagents were commercially available and used without further purification. All solvents were distilled from the appropriate drying agents immediately before use. All air and moisture sensitive reactions were carried out under an inert atmosphere of dry nitrogen. Purification of the crude products was performed using flash column chromatography on silica gel (0.035−0.070 mm). Reactions were monitored by TLC carried out on 0.25 mm SDS silica gel coated glass plates (60F254) and compounds were detected with UV light and/or with iodide. Optical rotations were measured with a Perkin-Elmer 241 polarimeter. NMR spectra were recorded on Bruker DRX 400 instrument and calibrated using tetramethylsilane as internal reference. The following abbreviations were used to designate the multiplicities: s＝singlet, d＝doublet, t＝triplet, q＝quartet, quint＝quintuplet, m＝multiplet, br＝broad. High resolution mass spectra (HRMS) were recorded under electrospray ionization (ESI) conditions. Enantiomeric excesses were determined by HPLC analysis on Shimadzu LC 20 with UV detector SPD-20A or SFC analysis on JASCO SF-2000 analytical system using CHIRALPAK OD-H column (25 cm×0.46 cm), CHIRALPAK AY-H (25 cm×0.46 cm), CHIRALPAK AD-H (25 cm × 0.46 cm) and CHIRALPAK OJ-H (25 cm × 0.46 cm) by Daicel Chemical Ind., Ltd.

2-Bromo-3-(1,3-dioxolan-2-yl)pyridine (8)[7] Under nitrogen *p*-toluenesulfonic acid monohydrate (41.9 mg, 0.22 mmol, 0.1 equiv.) was added to a well stirred solution of 2-bromonicotinaldehyde **7** (407.0 mg, 2.2 mmol, 1.0 equiv.), glycol (0.5 mL, 8.8 mmol, 4.0 equiv.) and catalytic amount of molecular sieves (40.0 mg) in dried benzene (20.0 mL) at room temperature. The mixture was stirred at reflux for 2.5 h. The reaction mixture was diluted with EtOAc (50.0 mL) and washed with sat. $NaHCO_3$ (aq) (10 mL×3). The organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified with flash column chromatography on silica gel (eluent: EtOAc/petroleum ether＝1∶4) to afford **8** (352.7 mg, 70% yield) as yellow semi-solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.38 (dd, J＝4.8, 2.0 Hz, 1H), 7.89 (dd, J＝8.0, 2.0 Hz, 1H), 7.30 (dd, J＝7.8, 4.0 Hz, 1H), 6.02 (s, 1H), 4.00−4.20 (m, 4H).

2-(Tributylstannyl)-3-(1,3-dioxolan-2-yl)pyridine (9)[8] Under N_2 to a well stirred solution of *n*-BuLi in hexanes (0.96 mL, 1.6 mol/L in hexanes) was added a solution of 2-(2-bromo-3-pyridyl)-1,3-dioxolane **8** (1.56 g, 0.68 mmol) in anhydrous diethyl ether (3.0 mL)

dropwisely via a syringe at −78 ℃. After stirred at −78 ℃ for 30 min, the resulting reaction solution was transferred via a cannula into a well stirred suspension of tributyltin chloride (0.66 mg, 2.04 mmol) in anhydrous diethyl ether (1.0 mL) at −78 ℃. After the reaction mixture was stirred at −78 ℃ for 3 h, the reaction was quenched with 2.0 mL of water and extracted with CH_2Cl_2 (10 mL×3). The organic extracts were washed with saturated brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude product was purified with flash column chomatography on neutral aluminum oxide (eluent: EtOAc/petroleum ether=1∶40) to afford compound **9** (269.4 mg, 90% yield) as colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.71 (dd, J=4.8, 2.0 Hz, 1H), 7.73 (dd, J=8.0, 1.4 Hz, 1H), 7.10−7.20 (m, 1H), 5.77 (s, 1H), 3.90−4.20 (m, 4H), 1.50−1.70 (m, 6H), 1.25−1.40 (m, 6H), 1.15−1.25 (m, 6H), 0.80−0.95 (m, 9H).

2-(3-(1,3-Dioxolan-2-yl)pyridin-2-yl)-3-nitropyridine (11) Under N_2 to a well stirred solution of 2-(2-trimethylstannyl-3-pyridyl)-1,3-dioxolane **9** (105 mg, 0.238 mmol) in anhydrous THF (7.0 mL) was added 2-bromo-3-nitropyridine (72.1 mg, 0.357 mmol), $Pd(PPh_3)_4$ (27.5 mg, 0.024 mmol) and CuBr (2.7 mg, 0.019 mmol) successively at room temperature. After reaction mixture was stirred at 67 ℃ for 4.5 h, the excess reaction solvent was removed under reduced pressure. The crude product was purified with flash column chomatography on silica gel (eluent: EtOAc/petroleum ether=2∶1) to afford compound **11** (52.9 mg, 85% yield) as light yellow semi-solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.88 (dd, J=4.6, 1.4 Hz, 1H), 8.62 (dd, J=4.8, 1.6 Hz, 1H), 8.40 (dd, J=8.2, 1.4 Hz, 1H), 8.06 (dd, J=7.8, 1.4 Hz, 1H), 7.55 (dd, J=8.4, 4.8 Hz, 1H), 7.42 (dd, J=8.0, 4.8 Hz, 1H), 6.10 (s, 1H), 3.80−3.95 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 154.0, 153.1, 152.0, 149.4, 145.8, 135.6, 132.6, 132.4, 132.1, 132.0, 131.9, 128.6, 128.5, 123.6, 123.5, 100.5, 65.1 (2C); HRMS (ESI) calculated for $C_{13}H_{12}N_3O_4$ ($M+H^+$): 274.0822, found 274.0828.

2-(3-(1,3-Dioxolan-2-yl)pyridin-2-yl)pyridin-3-amine (12) A reaction mixture of compound **11** (52.9 mg, 0.194 mmol) and PtO_2•$3H_2O$ (5.45 mg, 0.019 mmol) in absolutely anhydrous EtOH (8.0 mL) was stirred under 1 atm of H_2 overnight. The reaction mixture was diluted with anhydrous EtOH (10 mL), and filtered through a celite bed to remove the catalyst under reduced pressure. The filtrate was concentrated under reduced pressure, and the resulted residue was purified with flash column chromatography on silica gel (eluent: petroleum ether/EtOAc=1∶4) to provide compound **12** (44.3 mg, 94% yield) as yellow semi-solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.60 (dd, J=4.8, 2.0 Hz, 1H), 8.13 (dd, J=8.0, 2.0 Hz, 1H), 8.07−8.10 (m, 1H), 7.60−7.70 (m, 1H), 7.40−7.50 (m, 1H), 7.34 (dd, J=8.0, 4.8 Hz, 1H), 6.26 (s, 1H), 4.60−4.80 (br, NH_2), 4.05−4.15 (m, 2H), 3.90−4.00 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 156.5, 148.5, 142.4, 141.2, 138.6, 133.6, 132.1, 132.0, 131.9, 128.6, 128.5, 124.0, 123.8, 122.9, 100.3, 65.5; HRMS (ESI) calculated for $C_{13}H_{14}N_3O_2$ ($M+H^+$): 244.1081, found 244.1089.

Benzy-(*S*)-1-(2-(3-(1,3-dioxolan-2-yl)pyridin-2-yl)-pyridin-3-ylcarbamoyl)ethylcarbamate (*S*)-14a Under nitrogen to a well stirred solution of **12** (100.0 mg, 0.4 mmol, 1.0 equiv.) and (*S*)-Cbz-Ala (135.0 mg, 0.60 mmol, 1.5 equiv.) in dried CH_2Cl_2 (10.0 mL) was added EDCI (191.7 mg, 0.6 mmol, 1.5 equiv.) in one portion. The resulting reaction solution was stirred at room temperature overnight. The reaction mixture was diluted with CH_2Cl_2 (5.0 mL), and then washed with water (5 mL×3). The organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified with flash column chromatography on silica gel (eluent: EtOAc/petroleum ether = 7∶2) to afford compound (*S*)-**14a** (89.7 mg, 50% yield) as colorless semi-solid. $[\alpha]_D^{23}$ −14.1 (*c* 2.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 11.2−11.8 (br, 1H), 8.80 (dd, J=8.4, 1.6 Hz, 1H), 8.48−8.58 (br, 1H), 8.45 (dd, J=4.4, 1.4 Hz, 1H), 8.20 (dd, J=8.0, 5.6 Hz, 1H), 7.28−7.73 (m, 7H), 6.41 (s, 1H), 5.45 (s, 1H), 5.11 (s, 2H), 4.40 (t, J=6.8 Hz, 1H), 3.90−4.30 (m, 4H), 1.44 (d, J=6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 171.1, 155.7, 155.3, 147.8, 144.3, 143.7, 137.4, 136.1, 134.7, 134.0, 132.2, 132.1, 131.9, 129.3, 128.6, 128.4, 128.3, 128.2, 123.8, 123.3, 100.2, 67.1, 65.5, 51.7, 18.7; HRMS (ESI) calculated for $C_{24}H_{25}N_4O_5$ ($M+H^+$): 449.1819, found 449.1827.

Benzyl-(*S*)-1-(2-(3-(1,3-dioxolan-2-yl)pyridin-2-yl)-pyridin-3-ylcarbamoyl)-2-phenylethylcarbamate (*S*)-14b (*S*)-**14b** was prepared by following the same procedure as that of (*S*)-**14a**: Compound **12** (60.0 mg, 0.2 mmol, 1.0 equiv.), (*S*)-Cbz-Phe (110.7 mg, 0.37 mmol, 1.5 equiv.) and EDCI (70.9 mg, 0.37 mmol, 1.5 equiv.). The reaction mixture was stirred at room temperature overnight. Purification with flash column chromatography on silica gel (eluent: EtOAc/petroleum ether=8∶5) provided (*S*)-**14b** (83.5 mg, 65% yield) as colorless semi-solid. $[\alpha]_D^{23}$ −27.8 (*c* 3.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 11.2−11.8 (br, 1H), 8.79 (dd, J=8.4, 1.6 Hz, 1H), 8.45 (dd, J=4.4, 1.2 Hz, 1H), 8.36 (s, 1H), 8.18 (dd, J=8.0, 1.2 Hz, 1H), 7.10−7.50 (m, 12H), 6.42 (s, 1H), 5.20−5.40 (br, 1H), 5.09 (s, 2H), 4.60 (s, 1H), 3.90−4.20 (m, 4H), 3.01−3.30 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 169.8, 155.7, 155.2, 147.5, 144.3, 143.7, 137.3, 136.1, 135.9, 134.7, 133.8, 129.4, 129.1, 128.6, 128.5, 128.2, 128.1, 127.2, 123.7, 123.2, 100.2, 67.1, 65.5, 57.1, 38.5; HRMS (ESI) calculated for $C_{30}H_{29}N_4O_5$ ($M+H^+$): 525.2132, found 525.2140.

Axially chiral 2,2'-bipyridine *N*,*N*'-dioxides (−)-5a and (+)-5a Under N_2 to a well stirred solution of **14a** (500 mg, 1.12 mmol, 1.0 equiv.) in dried $CHCl_3$ (2.0 mL) was added a solution of *m*-CPBA (1.6 g, 8.98 mmol, 8.0 equiv.) in 3.0 mL of $CHCl_3$ dropwise. After addition, the reaction mixture was stirred for 3 h at room temperature. The reaction was quenched with saturated $NaHCO_{3(aq)}$ (10 mL) and diluted with 15 mL of CH_2Cl_2. The organic

layer was separated and the aqueous layer was extracted with CH_2Cl_2 (10 mL×3). The combined organic layers were washed with water (15 mL×3) and then with brine (15 mL×3) and dried over anhydrous Na_2SO_4. The crude product was purified with flash column chromatography on silica gel (eluent: CH_2Cl_2/MeOH=20:1) to afford chiral 2,2'-bipyridine *N*,*N*-dioxides (–)-**5a** (153.8 mg, 29 % yield) and (+)-**5a** (47.7 mg, 9% yield) as slightly yellow oil. (–)-**5a**: $[\alpha]_D^{23}$ –311.2 (*c* 2.8, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.24 (br, 1H), 8.22 (s, 1H), 8.13 (d, *J*=6.4 Hz, 1H), 7.89 (s, 1H), 7.63 (d, *J*=8.0 Hz, 1H), 7.00−7.50 (m, 7H), 5.95 (s, 1H), 5.65 (d, *J*=6.4 Hz, 1H), 5.00 (dd, *J*=35.2, 12 Hz, 2H), 4.10−4.40 (m, 1H), 3.50−3.95 (m, 4H), 1.31 (d, *J*=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 171.9, 155.9, 140.7, 139.6, 137.6, 136.0, 135.8, 135.6, 134.3, 132.7, 130.0, 129.6, 128.6, 128.3, 128.0, 126.1, 125.9, 125.7, 121.6, 99.6, 66.8, 65.0, 64.7, 53.4, 51.4, 50.5, 29.6, 17.9; HRMS (ESI) calculated for $C_{24}H_{25}N_4O_7$ ($M+H^+$): 481.1718, found 481.1716. (+)-**5a**: $[\alpha]_D^{23}$ +322.9 (*c* 3.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.29 (s, 1H), 8.35 (d, *J*=6.0 Hz, 1H), 8.13 (d, *J*=6.4 Hz, 1H), 7.91 (d, *J*=8.0 Hz, 1H), 7.68 (d, *J*=8.0 Hz, 1H), 7.20−7.50 (m, 7H), 5.96 (s, 1H), 5.26 (d, *J*=4.2 Hz, 1H), 4.99 (s, 2H), 4.10−4.20 (m, 1H), 3.50−3.90 (m, 4H), 1.39 (d, *J*=6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 171.3, 155.7, 141.1, 140.0, 139.9, 138.2, 136.0, 135.8, 135.6, 128.5, 128.2, 128.0, 126.2, 125.9, 125.1, 120.8, 99.8, 66.9, 64.9, 64.8, 51.0, 29.7, 18.0; HRMS (ESI) calculated for $C_{24}H_{25}N_4O_7$ ($M+H^+$): 481.1718, found 481.1717.

Axially chiral 2,2'-bipyridine *N*,*N'*-dioxides (–)-5b and (+)-5b (–)-**5b** and (+)-**5b** were prepared by following the same procedure as that of (–)-**5a** and (+)-**5a**: **14b** (230.0 mg, 0.439 mmol, 1.0 equiv.) in dried $CHCl_3$ (2.0 mL), *m*-CPBA (605.7 mg, 3.511 mmol, 8.0 equiv.) in dried $CHCl_3$ (3.0 mL). The reaction mixture was stirred at room temperature for 3 h. Purification with flash column chromatography on silica gel (eluent: CH_2Cl_2/MeOH=20:1) provided chiral 2,2'-bipyridine *N*,*N*-dioxides (–)-**5b** (140.2 mg, 58 % yield) and (+)-**5b** (53.0 mg, 22% yield) as slightly yellow oil. (–)-**5b**: $[\alpha]_D^{23}$ –126.4 (*c* 3.4, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.40 (br, 1H), 8.17 (d, *J*=6.4 Hz, 1H), 7.90 (t, *J*=8.6 Hz, 1H), 7.64 (d, *J*=7.6 Hz, 1H), 7.00−7.60 (m, 12H), 5.96 (s, 1H), 5.61 (d, *J*=7.6 Hz, 1H), 4.80−5.10 (m, 2H), 4.51 (d, *J*=5.2 Hz, 1H), 4.50 (d, *J*=5.2 Hz, 1H), 3.90−4.00 (m, 2H), 3.60−3.80 (m, 2H), 3.17 (dd, *J*=14.0, 4.8 Hz, 1H), 2.93 (dd, *J*=14.0, 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 170.6, 155.9, 141.2, 139.9, 139.6, 137.9, 136.0, 135.9, 135.7, 134.4, 132,9, 130.0, 129.6, 129.1, 129.0, 128.7, 128.6, 128.2, 128.1, 127.8, 127.1, 126.1, 126.0, 125.3, 121.0, 99.7, 66.9, 65.0, 64.8, 56.7, 53.4, 37.8; HRMS (ESI) calculated for $C_{30}H_{29}N_4O_7$ ($M+H^+$): 557.2031, found 557.2023. (+)-**5b**: $[\alpha]_D^{23}$ +187.5 (*c* 3.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.46 (br, 1H), 8.26 (d, *J*=6.4 Hz, 1H), 8.09 (d, *J*=6.4 Hz, 1H), 7.75 (d, *J*=8.4 Hz, 1H), 7.63 (d, *J*=8.0 Hz, 1H), 6.90−7.49 (m, 12H), 5.98 (s, 1H), 5.34 (d, *J*=7.6 Hz, 1H), 4.90−5.00 (m, 2H), 4.41 (dd, *J*=13.6, 6.4 Hz, 1H), 3.40−4.00 (m, 4H), 2.90−3.20 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 170.2, 155.7, 141.1, 139.7, 139.8, 138.1, 136.0, 135.9, 135.8, 135.7, 129.3, 129.1, 128.7, 128.6, 128.3, 128.0, 127.1, 126.2, 125.9, 125.3, 121.2, 99.8, 66.9, 64.8, 64.7, 56.3, 53.5, 37.5; HRMS (ESI) calculated for $C_{30}H_{29}N_4O_7$ ($M+H^+$): 557.2031, found 557.2022.

3-Nitro-2-(3-nitropyridin-2-yl)pyridine (16)[12] Under N_2 to a well stirred suspension of freshly activated copper powder (2.0 g, 31.6 mmol) in anhydrous DMF (40 mL) was added 2-chloro-3-nitropyridine (2.0 g, 12.7 mmol) in one portion. The resulted mixture was stirred at 150 ℃ for 45 min. After cooling to room temperature, the excessive copper powder was removed by filtration under reduced pressure. The filtrate was treated with 20.0 mL of con. ammonia$_{(aq)}$, and the resulted blue suspension was extracted with EtOAc (50.0 mL×3). The organic extracts were dried over anhydrous Na_2SO_4, and concentrated under reduce pressure. The crude product was purified by flash chromatography on silica gel (eluent: EtOAc/petroleum ether=1:1.5) to afford compound **16** (1.0 g, 65% yield) as colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.88 (dd, *J*=4.8, 1.2 Hz, 2H), 8.59 (dd, *J*=8.4, 1.6 Hz, 2H), 7.65 (dd, *J*=8.4, 4.8 Hz, 2H).

2-(3-Aminopyridin-2-yl)pyridin-3-amine (17)[13] A suspension of compound **16** (1.1 g, 4.5 mmol) and 10% Pd-C in absolute EtOH (30.0 mL) was hydrogenated under 1.0 atm for 8 h. The reaction mixture was diluted with EtOH (60.0 mL), and filtered through a Celite pad under reduced pressure. The filtrate was concentrated under reduced pressure, and the resulted residue was purified by flash chromatography on silica gel (eluent: EtOAc/petroleum ether=1:2) to afford compound **17** (790.0 mg, 95% yield) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.98 (d, *J*=1.6 Hz, 2H), 7.06−7.01 (m, 4H), 6.28 (br. s, 4H).

Dibenzyl((2*R*,2'*S*)-([2,2'-bipyridine]-3,3'-diyl-bis-(azanediyl))bis(1-oxopropane-2,1-diyl))dicarbamate (18) Under N_2 to a well stirred solution of compound **17** (790.0 mg, 4.2 mmol) in anhydrous dichloromethane (10.0 mL) was added *N*-Cbz-(*S*)-Ala (2.8 g, 12.6 mmol) and EDCI (2.4 g, 12.6 mmol) successively. The resulting mixture was stirred at room temperature for 2 h. The reaction mixture was filtered under reduced pressure and the collected yellow solid was recrystallized from chloroform to provide compound **18** (2.0 g, 80% yield) as a white solid. $[\alpha]_D^{15}$ –93.3 (*c* 0.03, $CHCl_3$); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 13.46−13.61 (m, 2H), 9.03 (d, *J*=8.4 Hz, 2H), 8.44−8.30 (m, 2H), 8.14−7.80 (m, 2H), 7.49−7.32 (m, 10H), 7.96 (d, *J*=17.2 Hz, 4H), 5.04−4.96 (m, 4H), 4.17−4.13 (m, 2H), 1.35 (d, *J*=7.2 Hz, 4H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 173.1, 156.5, 141.8, 137.0, 136.0, 129.4, 128.8, 128.5, 124.4, 66.4, 52.7, 17.9; HRMS (ESI) calculated for $C_{32}H_{32}N_6O_6$ ($M+H^+$): 597.2456, found 597.2444.

Axially chiral 2,2'-bipyridine *N*,*N'*-dioxides (−)-6a and (+)-6a Under N_2 to a solution of compound **18** (100.0 mg, 0.17 mmol) in 8.0 mL of HOAc was added 3.0 mL of 30% H_2O_2 aqueous solution. The reaction mixture was stirred at 75 ℃ for 4 h. At room temperature, the reaction mixture was diluted with CH_2Cl_2 (20.0 mL) and washed with sat. $NaHCO_3$ (10.0 mL×3) and brine (10.0 mL×3) successively. The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (eluent: ethyl acetate/methanol=6:1) to furnish the products (−)-**6a** (28.0 mg, 26% yield) as white solid and (+)-**6a** (30.0 mg, 28% yield) as white solid. (−)-**6a**: $[\alpha]_D^{15}$ –402.7 (*c* 0.18, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 10.02−10.24 (br. d, 2H), 8.02−8.27 (br. d, 4H), 7.27−7.39 (m, 12H), 5.52 (br. s, 2H), 5.12 (br. s, 4H), 4.32−4.65 (br. d, 2H), 1.24−1.33 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 171.8, 171.2, 155.8, 139.1, 136.3, 136.1, 134.8, 128.6, 128.4, 128.2, 126.1, 123.6, 67.1, 60.4, 53.5, 51.3, 21.1, 18.1, 14.2. HRMS (ESI) calculated for $C_{32}H_{33}N_6O_8$ ($M+H^+$): 629.2354, found 629.2349. (+)-**6a**: $[\alpha]_D^{15}$ + 360.0 (*c* 0.03, $CHCl_3$); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 9.55 (br. s, 2H), 8.16 (d, J=6.4 Hz, 2H) 7.94 (d, J=8.4 Hz, 2H), 7.67 (d, J=6.8 Hz, 2H), 7.55 (dd, J=8.4, 6.4 Hz, 2H), 7.32−7.40 (m, 10H), 4.97−5.04 (m, 4H), 4.16−4.21 (m, 2H), 1.16 (d, J=7.2 Hz, 4H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 172.7, 156.4, 139.2, 137.4, 136.0, 134.1, 129.1, 128.8, 128.3, 126.9, 121.0, 66.0, 55.4, 51.1, 17.6. HRMS (ESI) calculated for $C_{32}H_{33}N_6O_8$ ($M+H^+$): 629.2354, found 629.2326.

General procedure of asymmetric catalytic allylation of aromatic aldehydes with allyltrichlorosilane Under N_2 to a well stirred solution of catalyst (0.1 equiv.) in anhydrous CH_2Cl_2 (1.0 mL) were added aromatic aldehydes (1.0 equiv.) and DIPEA (1.5 equiv.) successively at room temperature. The resulted reaction mixture was cooled to −78 ℃ and allyltrichlorosilane (1.5 equiv.) was added dropwise via a syringe. The resulted reaction mixture was stirred for 4−12 h at −78 ℃ and then the reaction was quenched with saturated $NaHCO_{3(aq)}$. The reaction mixture was allowed to warm up to room temperature and the reaction mixture was extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and then concentrated *in vacuo*. The crude product was purified with flash column chromatography on silica gel to afford desired product **21**.

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(Pan, B.)

