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FULL PAPER

Chiral bisdiphenylphosphine dioxides bearing an original bis(triazolyl) backbone as promising Lewis bases for asymmetric organocatalysis

Nicolas Sevrain,[a] Jean-Noel Volle,[a] Jean-Luc Pirat,[a] Tahar Ayad*[a],[b] and David Virieux*[a]

Abstract: Two chiral C_2-symmetric diphenylphosphine dioxides bearing an original bis(triazolyl) backbone were prepared starting from inexpensive and readily available precursors. The key step of our approach involves the simultaneous formation of 5 bonds in one chemical step with 100% atom efficiency through a Copper catalyzed tandem [3+2] cycloaddition/dimerization reaction. Interestingly, these chiral inducers exhibited good to excellent catalytic activities as chiral Lewis base organocatalysts promoting useful stereoselective reactions.

Introduction

The design and synthesis of new chiral Lewis base catalysts that are able to promote enantioselective reactions with high levels of chemical efficiency and stereocontrol is a topic of primary importance in modern organic chemistry. Over the past decade, a wide range of chiral Lewis bases have been developed. Among them, enantiopure phosphoramides,[1] formamides,[2] *N*-oxides,[3] and sulfoxides[4] are probably the most popular and have found widespread applications as organocatalysts promoting stereoselective reactions in good to excellent stereoselectivities.[5] For instance, Lewis base catalyzed asymmetric reactions involving hypervalent silicate intermediates, where both the electrophilicity and nucleophilicity of the adduct are enhanced, have received increasing attention in recent years.[6] Mechanistically, the above-mentioned Lewis bases are thought to activate silicon atom in electron donors such as silane derivatives, while conventional Lewis acid catalysts activate heteroatoms in electron acceptors such as carbonyl groups. Chiral phosphine oxides, thanks to a Lewis base character derived from the highly polarized P=O bond, are also able to coordinate silanes, thereby generating hypervalent silicate species. Quite surprisingly, they have been very scarcely explored as chiral Lewis base organocatalysts in stereoselective reactions. This is even more surprising if, one thinks that enantiomerically pure phosphine oxides can be readily obtained through straightforward oxidation of commercially available chiral phosphines. Indeed, only few examples of chiral phosphine oxide catalysts are known in literature;[7] and these studies mainly rely on the use of bis-(diphenylphosphinoyl)-binaphthyl dioxides (BINAPO) derived from the popular BINAP. To the best of our knowledge, the first true organocatalytic reaction catalyzed by chiral phosphine oxides was disclosed in 2005 by Nakajima and co-workers[8], when (*S*)-BINAPO catalyzed the addition of allyltrichlorosilane to aldehydes. Shortly after this seminal work, a very limited number of chiral phosphine oxides mostly derived from known phosphines have been reported and used as Lewis bases in several chemical processes including asymmetric allylation of aldehydes,[9] aldol reactions,[10] ring-opening of *meso*-epoxides,[11] Abramov−type phosphonylation of carbonyl compounds[12] and Morita-Baylis-Hillman reaction.[13] Despite some notable successes, most of these catalysts resulted in low to moderate catalytic activities. Therefore, the development of more effective chiral phosphine oxides with new structural and/or electronic features remains a challenge.

Recently, we committed to develop a program dedicated to the design and the utilization of new chiral phosphorus ligands, that resulted in the development of a highly convergent and atom economic synthetic route toward enantiopure C_2-symmetric diphenylphosphine dioxides bearing an original bis(triazolyl) backbone. Such derivatives were obtained through a tandem Cu-mediated Huisgen reaction–oxidative coupling.[14] Gratifying, it turned out that those ligands are effective Lewis bases for $SiCl_4$-mediated enantioselective Abramov-type phosphonylation of aldehydes with trialkyl phosphites.[15] Considering these encouraging results, we thus decided to extend the use of this new class of ligands as chiral Lewis bases in other relevant synthetic transformations. In this context, we wish to report herein, the full investigation of our studies regarding the asymmetric allylation and reductive aldol reactions of aldehydes promoted by enantiopure bis(triazolyl)bisphosphine dioxide organocatalysts **3**.

Results and Discussion

Our synthetic approach to enantiopure bis(triazolyl)bisphosphine dioxides **3** is outlined in Scheme 1. Diphenylethynylphosphine oxide **1**[16] and alkyl azides **2**[17] chosen for our study were readily prepared on multigram scale from cheap and commercially available precursors according to known literature procedures. With the aforementioned compounds **1** and **2** in hand, the key copper catalyzed tandem [3+2] cycloaddition/dimerization

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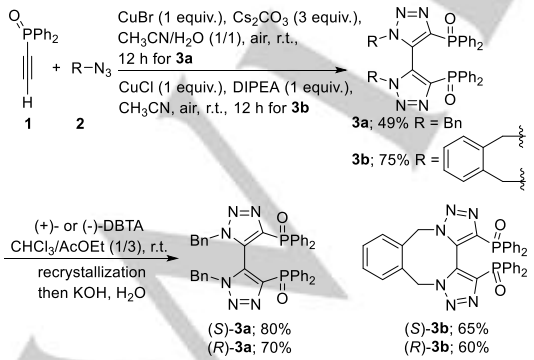
Supporting information for this article containing experimental procedures and characterization data for all new compounds is available on the WWW under http://dx.doi.org/10.1002/cctc.200xxxx.

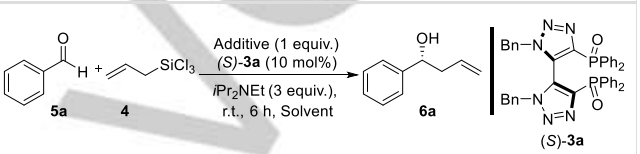
reaction was then explored.[14, 18] We found that the yields of the desired oxidatively coupled bis(triazole) compounds **3**, as well as the product distribution of this Huisgen reaction–oxidative coupling is highly dependent on both the reaction conditions and the nature of the alkyl azide partner employed. Indeed, after considerable screening, bis(triazolyl)bisphosphine dioxide product **3a** was isolated in 49% yield, along with some monotriazole derivatives (not shown)[19] by using 1 equivalent of CuBr in the presence of 3 equivalents of Cs_2CO_3 and benzyl azide at 0.25 M substrate concentration in a 1:1 mixture of acetonitrile/water under air atmosphere at room temperature. Unfortunately, the above-mentioned conditions proved to be not suitable for the synthesis of the more constrained bis(triazolyl)bisphosphine dioxide **3b**, leading to somewhat disappointing results in terms of both yield and product distribution. Therefore, further optimizations were required to maximize yield of **3b**. Gratifyingly, we discovered that performing the [3+2] cycloaddition/dimerization reaction under conditions of high dilution, which favors the intramolecular at the expense of the intermolecular oxidative coupling of the two triazole rings, is a critical parameter for the success of this process. Indeed, diphenylethynylphosphine oxide **1** (1 equiv.) reacted with 1,2-bis(azidomethyl)benzene **2b** (0.5 equiv.) in the presence of a stoichiometric amount of CuCl/DIPEA catalyst in acetonitrile at 0.025 M substrate concentration under air atmosphere at room temperature to give the expected cyclic bis(triazolyl) derivative **3b** in 75% isolated yield along with a tiny amount of the uncyclized bis(triazole) (not shown).[19] It is worth pointing out that our synthetic approach for the preparation of bis(triazolyl)bisphosphine dioxides **3a−b** involves the simultaneous formation of 5 bonds in one chemical step with 100% atom efficiency. Next, the resolution of racemic **3a−b** using (+)- or (−)-2,3-dibenzoyl tartaric acid (DBTA) as resolving reagents was realized (Scheme 1). To this end, a chloroformic solution of racemic **3a−b** was slowly added at room temperature to a molar equivalent amount of DBTA previously dissolved in ethyl acetate. Both enantiomers of **3a** and **3b** were obtained on gram scale in yields ranging from 60 to 80% and *ee* values comprised between 99 to 100% from the recrystallized diastereoisomeric complex by treatment with aqueous potassium hydroxide solution.



Scheme 1. Synthesis of enantiopure bis(triazolyl)bisphosphine dioxide organocatalysts **3a** and **3b**.

Having established an efficient route to chiral dioxide ligands **3a-b**, attention was then focused on the evaluation of their catalytic properties as Lewis base organocatalysts in enantioselective processes such as asymmetric allylation[9] and reductive aldol reactions.[20] In the first set of experiments, we studied the effect of the solvent and additives on the stereochemical outcome of the asymmetric addition of allyltrichlorosilane **4** to benzaldehyde **5a** catalyzed by 10 mol% of organocatalyst *(S)*-**3a** in the presence of diisopropylethylamine at room temperature for 6 h.

Table 1. Optimization of the enantioselective addition of allyltrichlorosilane **4** to benzaldehyde **5a**.[a]



Entry	Solvent	Additive	Conversion [%][b]	Yield[%][c]	ee [%][d]
1	DCM	none	80	65	33
2[e]	DCM	none	65	52	22
3	DCM	Bu_4NI	100	91	43
4[f]	DCM	Bu_4NI	75	63	42
5	$CHCl_3$	Bu_4NI	100	87	26
6	Et_2O	Bu_4NI	78	65	29
7	THF	Bu_4NI	60	48	19
8	Toluene	Bu_4NI	70	55	14
9	MeCN	Bu_4NI	100	94	54
10	EtCN	Bu_4NI	100	95	57
11	EtCN	Bu_4NBr	75	55	40
12	EtCN	Bu_4NAc	60	40	6
13	EtCN	LiI	50	27	40
14	EtCN	LiBr	45	22	30
15	EtCN	I_2	100	82	60
16	EtCN	NaI	100	91	55
17	EtCN	KI	100	96	70
18[g]	EtCN	KI	90	82	69

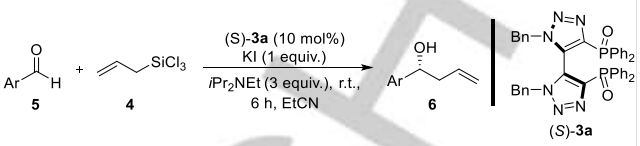
[a] All reactions were run using 10 mol % of (*S*)-**3a** with 0.5 mmol of benzaldehyde, 1.2 equiv. of allyltrichlorosilane and 1 equiv. of additive for 6 h. [b] Determined by ^1H NMR of crude reaction mixture. [c] Isolated yield. [d] Determined by HPLC chromatography using a Chiralcel AS-H column. Absolute configuration was determined to be *R* by comparison with reported

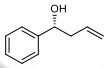
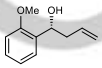
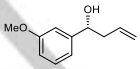
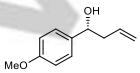
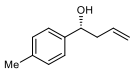
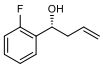
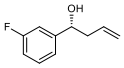
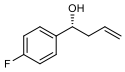
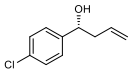
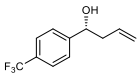
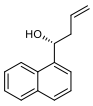
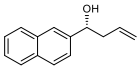
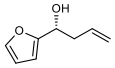
data. [e] Reaction run with 10 mol% of (*S*)-**3b** instead of (*S*)-**3a**. [f] Reaction run at 0 °C for 48 h. [g] Reaction run with 5 mol% of (*S*)-**3a** for 24 h.

From the results depicted in Table 1, it is clear that bis(triazolyl)bisphosphine dioxide **3a** is a more efficient organocatalyst than **3b** for this process leading to **6a** in 65% and 52% isolated yields and 33 and 22% *ee*, respectively (entry 1 *vs* 2). Berrisford and co-workers have reported that tetrabutylammonium salts can dramatically accelerate the allylation of aldehydes with allyltrichlorosilane.[21] As anticipated, the use of Bu_4NI as additive remarkably increased the catalytic activity (entry 3, 91% yield, 43% *ee*). Decreasing the temperature to 0°C provided **6a** in lower yield but with similar enantioselectivity at the expense of a longer reaction time (entry 4). It was also found that the reaction could be performed in all solvents tested, the best catalytic activity in terms of yields and selectivities was obtained in propionitrile giving **6a** in 95% isolated yield with an encouraging optical purity up to 57% (entry 10). Based on those results, we then investigated the effect of other additives that may improve the efficiency of the reaction. For instance, other ammonium salts such as Bu_4NBr and Bu_4NAc turned out to be less effective for this transformation (entries 10 *vs* 11−12). Similar poor results were obtained using LiI and LiBr (entries 13−14), whereas homoallylic alcohol **6a** was obtained in good to excellent yields up to 96% and good enantioselectivities up to 70% using KI as additive (entries 15−17). Reducing the catalyst loading from 10 to 5 mol% was clearly still effective, although a prolonged reaction time was required to maintain a comparable level of selectivity and a satisfying isolated yield of **6a** (entry 17 *vs* 18).

To assess the substrate scope, a wide range of diversely substituted aromatic or heteroaromatic aldehydes were allylated under the optimized conditions using (*S*)-**3a** as organocatalyst (Table 2). Excepting the reaction of 1-naphthaldehyde **2k**, complete conversions were generally reached and chiral homoallylic alcohols **6a−m** were obtained in yields ranging from 86 to 96%. More specifically, for substrates bearing electron-donating substituents on the benzene ring such as a methyl or a methoxy group, the reaction outcomes were negligibly affected by the position of the substituents giving the target adducts **6a−e** in uniformly high yields and acceptable enantiopurities (entries 2−5, 93−96% yield, 59−60% *ee*). For substrates bearing electron-withdrawing substituents such as fluoride, chloride or trifluoromethyl group, the reaction proceeds smoothly, regardless of the position of the substituents, leading to the desired products **6f−i** with slightly higher asymmetric induction but in lower yields (entries 6−10, 86−90% yield, 62−67% *ee*). Similar catalytic activity was reached with 2-naphthyl derivative **2l**, while both chemical and optical yields dropped significantly for 1-naphthyl compound **2k**. This result can presumably be attributed to the increased steric hindrance of the 1-naphthyl over 2-naphthyl group (entries 11 and 12, 96 and 70% yields, 66 and 27% *ee*, respectively). Finally, 2-furaldehyde **2m** proved to be also a suitable partner for this reaction, giving **6m** in high 89% isolated yield and good enantioselectivity up to 81% (entry 13). Although moderated to good enantioselectivities were obtained in this allylation process, those results clearly illustrated that this new class of bis(triazolyl)bisphosphine dioxides can act as efficient chiral Lewis bases in asymmetric catalysis.

Table 2. Substrate scope for the enantioselective addition of allyltrichlorosilane to aldehydes.[a]

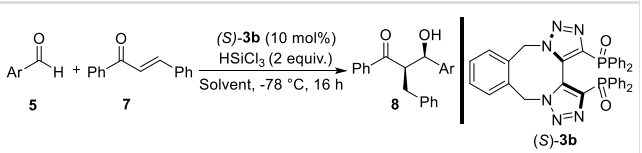


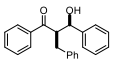
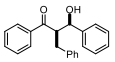
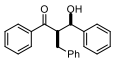
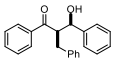
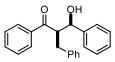
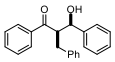
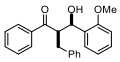
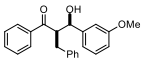
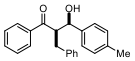
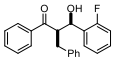
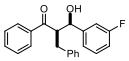
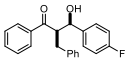
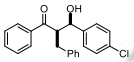
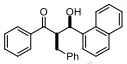
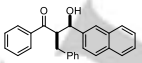
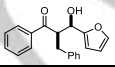
Entry	Product		Yield [%][b]	ee [%][c]
1	**6a**		94	70
2	**6b**		93	59
3	**6c**		95	59
4	**6d**		96	60
5	**6e**		94	60
6	**6f**		86	65
7	**6g**		89	65
8	**6h**		87	62
9	**6i**		90	62
10	**6j**		88	67
11[d]	**6k**		70	27
12	**6l**		96	66
13	**6m**		89	81

[a] All reactions were run using 10 mol % of (*S*)-**3a** with 0.5 mmol of aldehyde derivatives, 1.2 equiv. of allyltrichlorosilane and 1 equiv. of KI for 6 h. [b] Isolated yield. [c] Determined by HPLC chromatography using a Chiralcel AS-H or IA columns (see the Supporting Information for details). Absolute configuration was determined to be *R* by comparison with reported data. [d] 80% conversion was reached.

Inspired by the report of Nakajima and co-workers,[8] and to further demonstrate the potential application of (*S*)-**3** as Lewis base organocatalysts, we next decided to investigate the diastereo- and enantioselective reductive aldol reaction of chalcone **7** and various aldehydes **5** in presence of trichlorosilane. Results from these experiments are presented in Table 3.

Table 3. Optimization and substrate scope for the asymmetric reductive aldol reaction of chalcone **7** and various aldehydes **5**.[a]



Entry	Solvent	Product		Yield [%][b]	d.r. syn:anti[c]	ee [%][d]
1[e]	DCM	**8a**		78	93:7	57
2	DCM	**8a**		84	93:7	85
3	EtCN	**8a**		85	93:7	91
4	THF	**8a**		52	92:8	88
5	Et_2O	**8a**		48	91:9	78
6	Toluene	**8a**		76	90:10	74
7	EtCN	**8b**		71	72:28	71
8	EtCN	**8c**		80	93:7	92
9	EtCN	**8d**		72	78:22	75
10	EtCN	**8e**		90	90:10	94
11	EtCN	**8f**		92	90:10	93
12	EtCN	**8g**		91	86:14	88
13	EtCN	**8h**		90	88:12	91
14	EtCN	**8i**		79	91:9	89
15	EtCN	**8j**		90	95:5	94
16	EtCN	**8k**		92	94:6	99

[a] All reactions were performed using 10 mol % of (*S*)-**3b**, 0.5 mmol of chalcone, 1.2 equiv. of aldehyde and 2 equiv. of trichlorosilane (1 M solution in DCM) for 16 h. [b] Isolated yield. [c] Determined by ^{1}H NMR of crude reaction mixture. [d] Determined by HPLC chromatography using a Chiralcel ID or IB columns (see the Supporting Information for details). [e] 10 mol% of (*S*)-**3a** was used instead of (*S*)-**3b**.

Initial reactions were carried out in dichloromethane at −78 °C for 16 h using 10 mol% of bis(triazolyl)bisphosphine dioxides **3a**–**b** as organocatalysts and 2 equivalents of trichlorosilane as reductant. As outlined in Table 3, the cyclic bis(triazole) diphenylphosphine dioxide (*S*)-**3b** exhibits significantly higher catalytic activity than (*S*)-**3a** for this transformation, leading to the formation of the *syn* aldol product **8a** as the major diastereoisomer in good yield, high diastereo- and enantiomeric excesses (entry 1 *vs* 2, 78 and 84% yield, 93:7 d.r., 57 and 85% ee, respectively). A brief solvent screening revealed that the stereochemical outcome of this reductive aldol process is highly sensitive to the nature of the solvent. Indeed, reaction in propionitrile gave adduct **8a** in good 85% yield, with a high diastereomeric ratio of 93:7 and an excellent enantioselectivity of 91%, while the use of other solvents such as, THF, ether and toluene led to much lower catalytic activity (entries 3 *vs* 4–6). Thus, propionitrile was selected as the optimal solvent. Remarkably, it should be noted that the catalytic activities obtained with this system are in a similar range than those observed with the most popular chiral diphosphine dioxide BINAPO for the same transformation.[8] Next, we set out to investigate the substrate scope of the reaction of chalcone **7** with a wide range of diversely substituted aldehydes **5**. The reaction proceeds well in most cases, giving the corresponding *syn* aldol products **8a**–**k** in good to excellent yields, with good to high diastereomeric ratios and, good to excellent enantiomeric excesses (entries 7–16). The data in Table 3 also show that the outcomes of the reaction is largely influenced by the substitution pattern on the benzene ring of the aldehyde substrates. For instance, the electron-donating substituents such as a methoxy or a methyl group at the *ortho*- or *para*-position altered the catalytic activity to a significant extent as seen from the moderate yields and selectivities observed (entries 7 and 9, 71 and 72% yields, 72:28 and 78:22 d.r., 71 and 75% ee, respectively). In contrast, and for unknown reasons, significantly better results were obtained for substrate bearing a methoxy group at the *meta* position (entry 8, 80% yield, 93:7 d.r., 92% ee). A marked increase in the reaction efficiency was observed with aldehydes bearing an electron-withdrawing groups such as chlorine or fluorine atoms, giving the desired *syn* *β*-hydroxyl ketones in excellent yields (90 to 92%), high diastereoselectivities (86:14 and 90:10 d.r.) and excellent enantioselectivities (88 to 93% ee), irrespectively of the substituents' position (entries 10–13). Finally, naphthyl derivatives can also be used as partners, as demonstrated by the good to excellent results depicted in Table 3. Due to steric constraints, the 1-naphthyl aldol adduct **8i** was produced in lower yield and selectivities compared to the 2-naphthyl adduct **8j** (entries 14 and 15). Even more impressive results were obtained from 2-furanaldehyde, providing the expected aldo **8k** in high 92% yield, with an excellent diastereoselectivity of 95:5 and an enantioselectivity greater than 99% (entry 16).

Conclusions

In summary, we have developed an efficient, straightforward, and atom-economic protocol for the synthesis of a new family of chiral C_2-symmetric diphenylphosphine dioxides bearing an original bis(triazolyl) backbone. The potential of these novel ligands as

Lewis bases in organocatalytic stereoselective reactions have been demonstrated. While organocatalyst **3a** was able to promote the allylation of aldehydes in up to 96% yield and up to 81% *ee*, organocatalyst **3b** was more efficient in the formation of optically active *β*-hydroxyl ketones in high yields (up to 92%) with good to excellent diastereo- and enantioselectivities (up to 95:5 d.r., 99% ee) through the reductive aldol reaction of chalcone and aldehydes in presence of trichlorosilane. Further studies aimed at expanding the synthetic utility of these new bis(triazolyl)bisphosphine dioxides as Lewis base organocatalysts in other relevant enantioselective transformations are currently ongoing in our laboratory and will be reported in due course.

Experimental Section

General Procedure for the Asymmetric Allylation of Aldehydes with Allyltrichlorosilane Catalyzed by (*S*)-3a: Diisopropylethylamine (0.32 mL, 1.8 mmol), allyltrichlorosilane **4** (0.087 mL, 0.60 mmol), and a solution of the desired aldehydes **5** (0.5 mmol) in anhydrous propionitrile (0.5 mL) were successively added to a solution of (*S*)- bis(triazolyl)bisphosphine dioxide **3a** (35.8mg, 0.05 mmol, 10 mol%), and potassium iodide (83mg, 0.5 mmol) in anhydrous propionitrile (2 mL) at room temperature. The reaction progress was monitored by TLC (hexane/AcOEt, 80:20). Upon completion (*e.g.* 6 h), the reaction was quenched by 10% of aqueous NaOH (3 mL) and the mixture was extracted with AcOEt (2x10 mL). The combined organic layers were successively washed with 5% HCl (10mL), saturated aqueous $NaHCO_3$ (10 mL), brine (10 mL), dried over anhydrous $MgSO_4$, filtered, and evaporated under reduced pressure. The residue was purified by flash column chromatography (silica gel, hexane/AcOEt gradient from 100:0 to 70:30) to give the corresponding allylic alcohols **6**. The enantiomeric ratios were determined by HPLC using IA or AS-H Chiralpak columns.

General Procedure for Asymmetric Reductive Aldol Reaction of Chalcone and Aldehydes with Trichlorosilane Catalyzed by (*S*)-3b: To a solution of (*S*)- bis(triazolyl)bisphosphine dioxide organocatalyst **3b** (32 mg, 0.05 mmol, 10 mol%), the desired aldehydes **5** (0.6 mmol), and chalcone **7** (104 mg, 0.5 mmol) in anhydrous propionitrile (2 mL) was added dropwise trichlorosilane (ca. 1M CH_2Cl_2 solution, 1 mmol) at −78 °C. The reaction was monitored by TLC analysis (hexane/AcOEt, 80:20). After the chalcone was consumed or no significant change was observed, the reaction was quenched with saturated aqueous $NaHCO_3$ solution (3 mL). After addition of AcOEt (5 mL), the mixture was stirred for 1 h, filtered through a Celite pad and extracted with AcOEt (3x10 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous $MgSO_4$, filtered, and evaporated under reduced pressure. The diastereomeric ratio syn/anti was determined by ^{1}H NMR spectrum of crude reaction mixture. The residue was then purified by flash column chromatography on silica gel using hexane/AcOEt (gradient from 100:0 to 70:30) as eluting solvents to give the desired *syn* aldol products **8** as the major products. The enantiomeric excesses were determined by HPLC using IB or ID Chiralpak columns.

Supporting information: Experimental procedures, characterization data, and copies of the ^{1}H NMR, ^{13}C NMR and HPLC spectra.

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Keywords: Allylation • Reductive Aldol Reaction • Lewis Bases • Organocatalysts • Asymmetric catalysis

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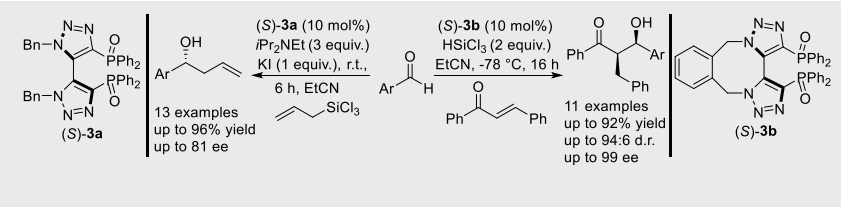

Two new chiral diphenylphosphine dioxides bearing an original bis(triazolyl) backbone were prepared through a two-step sequence. The key reaction of our approach involves a copper catalyzed [3+2] cycloaddition/dimerization reaction leading to the formation of 5 bonds in one chemical step with 100% atom efficiency. Interestingly, these ligands exhibited good to excellent catalytic activities as chiral Lewis base organocatalysts promoting useful stereoselective reactions.

*Asymmetric organocatalysis

Key Topic*

Nicolas Sevrain, Jean-Noel Volle, Jean-Luc Pirat, Tahar Ayad and David Virieux**

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Chiral bisdiphenylphosphine dioxides bearing an original bis(triazolyl) backbone as promising Lewis bases for asymmetric organocatalysis