Letter

Asymmetric Synthesis of P-Stereogenic Compounds via Thulium (III)-Catalyzed Desymmetrization of Dialkynylphosphine Oxides

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Asymmetric Synthesis of *P*-Stereogenic Compounds via Thulium (III)-Catalyzed Desymmetrization of Dialkynylphosphine Oxides

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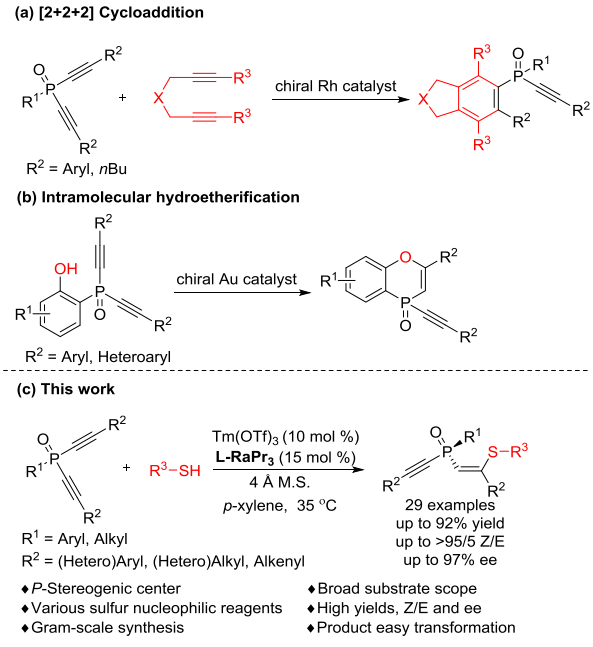
ABSTRACT: A chiral thulium(III) catalyzed sulfur-conjugation addition reaction of dialkynylphosphine oxides to construct *P*-stereogenic centers has been developed. Dialkynylphosphine oxides bearing aryl, alkyl, alkenyl substitution at the alkyne terminus position were tolerated under the reaction conditions. The corresponding *P*,*S*-containing compounds were obtained in moderate to good yields (up to 92% yield) with high Z/E ratios and enantioselectivities (up to >95/5 Z/E and 97% ee), which could be transformed into versatile optically active phosphine oxide derivatives. X-ray single crystal structures of chiral *N*,*N*'-dioxides with rare-earth metal triflates revealed how the center metal and ligand structure affect the enantioselectivity.

KEYWORDS: desymmetrization, dialkynylphosphine oxides, sulfur nucleophiles, P-stereogenic centers, thulium

Chiral phosphorus compounds are widely used as ligands[1] or organocatalysts in asymmetric catalysis.[2] The prominent chiral induction in numerous catalytic asymmetric reactions provides a justification for development of approaches to synthesis of those enantiomerically enriched phosphorus derivatives. Several enantioselective synthetic methods have been developed for this purpose.[3] Traditional methods for the synthesis of *P*-stereogenic phosphorus compounds usually rely on the chiral reagent- or auxiliary group-assisted transformations.[4] Recently, several catalytic enantioselective synthetic methods have been introduced.[5] Among them, the desymmetrization of prochiral phosphorus compounds with two same substituents including dimethyl,[6] dihydroxyl,[7] diphenyl,[8] dialkenyl[9] and dialkynyl[10] groups has been reported. For these reactions, transition metal catalyzed and organocatalyzed processes were frequently utilized. However, the scope and efficiency of most of the approaches await further improvements. There are two examples related to desymmetrization of dialkynylphosphine oxides (Scheme 1). Tanaka firstly reported the desymmetrization of dialkynylphosphine oxides using Rh(I)-catalyzed [2+2+2] cycloaddition with 1,6-diynes (Scheme 1a).[10a] Nevertheless, the methyl group on the phosphorus center and aryl groups at the alkyne terminus were required to get good results. Recently, Zi achieved Au(I)-catalyzed desymmetrization of dialkynylphosphine oxides by an intramolecular hydroetherification reaction (Scheme 1b).[10b] However, the substrate scope focused on *o*-hydroxyphenol groups on the phosphorus center and aryl groups at the alkyne terminus. Therefore, developing new methods as well as novel chiral catalytic systems for synthesis of versatile *P*-stereogenic compounds is meaningful and desirable.

Chiral *N*,*N*'-dioxides (Figure 1) are useful ligands in Lewis acid catalyzed asymmetric reactions,[11] especially employed for the *in situ* formation of rare-earth complex catalysts. Lanthanide complexes are generally quite electropositive, and exhibit high coordination numbers such as 7, 8, or to the maximum 12 because of their large ionic radii. The tetra-dentate *N*,*N*'-dioxides could be assembled around the metal ions, creating variable integrated chiral space for the control of enantioselectivity in the reaction. We anticipated that oxophilic lanthanide metal complexes are appropriate to activate dialknylphosphine oxides compounds by selective coordination at the vacant

Scheme 1. Catalytic desymmetrization of dialkynylphosphine oxides



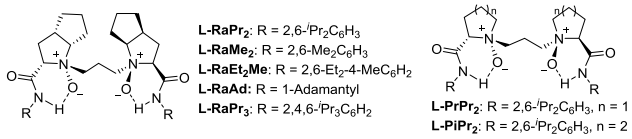


Figure 1. Chiral ligands used in the reaction

positions, enabling a desymmetrization process via an intermolecular conjugation addition reaction (Scheme 1c). Herein, we present an efficient sulfur-addition reaction[12] of dialkynylphosphine oxides catalyzed by a new seven-coordinate chiral *N,N'*-dioxide-thulium (III) complex catalyst with pentagonal bipyramidal geometries. The hard Lewis-acidity of lanthanide metal complex avoided catalyst poison caused by sulfur-containing reagents. A wide range of substituted dialkynylphosphine oxides, as well as sulfur nucleophiles were tolerated under the mild reaction conditions, providing *P*-stereogenic products with moderate to good yields and excellent enantioselectivities. In addition, several dodecahedral coordinations are illustrated by other lanthanide metal ions, such as Pr^{3+}, Gd^{3+}, Ho^{3+}, and Dy^{3+}. The dependency of the enantioselectivity of the reaction on the ionic radii of the rare-earth metal complexes of *N,N'*-dioxide were studied based on their X-ray crystal diffraction analysis data. It would help to rational choose of metal salts for chiral *N,N'*-dioxide ligand-involved asymmetric catalysis.

We began our investigation by choosing dialkynylphosphine oxide **1a** as the model substrate and methyl thioglycolate **2a** as the nucleophile, to optimize the reaction conditions. Firstly, various rare-earth metal triflates [RE(OTf)$_3$] coordinated with *N,N'*-dioxide **L-PiPr$_2$** (Figure 1) *in situ* were examined in toluene at 60 ℃ (Figure 2). There were an interesting phenomenon that the reactivity and enantioselectivity was significantly influenced by the differences in ionic radii of RE(OTf)$_3$ salts. As shown in Figure 2, the desymmetric addition product **3aa** via sulfur-conjugate addition was obtained with 10% yield in a racemic version in the present of Sc(OTf)$_3$ whose metal center has smallest ionic radius. Notably, La(OTf)$_3$ with the largest ionic radius delivered the product with dramatically increased yield (76%) and 21% ee. Moreover, the enantioselectivity enhanced gradually as the ionic radii reduces from La^{3+} to Ho^{3+}, accompanied by high reactivity. However, the yield of the reaction dropped smoothly from Ho^{3+} to Lu^{3+}, whereas the enantioselectivity was generally satisfied. Y^{3+} and Ho^{3+} have similar ion radius, which resulted in similar enantioselectivity and reactivity. Typically, **L-PiPr$_2$**/Tm(OTf)$_3$ enabled the formation of chiral phosphine oxide **3aa** in 52% yield with up to 70% ee. The influence of the rare earth metal ions on the enantioselectivity reflected tunable stereoenvironment raised from the nature of the metal centers.

Subsequent exploration of chiral *N,N'*-dioxide ligands (Figure 1) revealed that the steric hindrance created by the use of different amino acids and amines are also critical to the enantioselectivity (Table 1). With the use of Tm(OTf)$_3$ as the optimal metal salt, ee value of the reaction grew up gradually when the steric hindrance of either the amino acids (entries 1−3) or anilines (entries 3−6) used for the ligand synthesis increased. Nevertheless, when 1-adamantyl amine-derived ligand **L-RaAd** was used, desymmetrization process failed to yield **3aa** as a racemate with a reduced yield (entry 7),

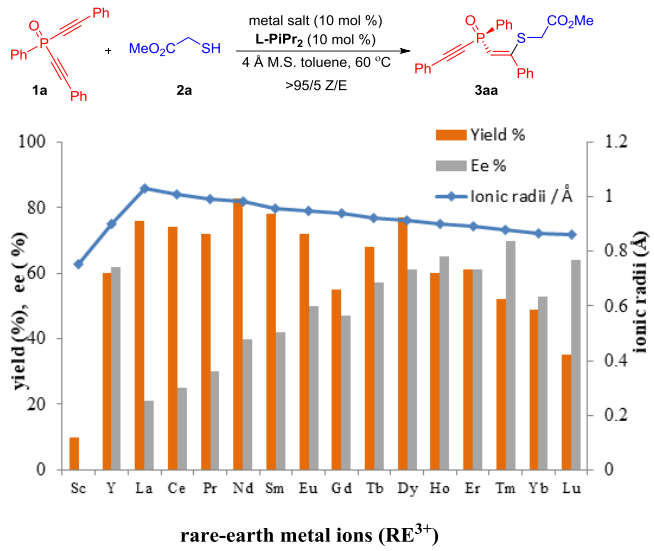
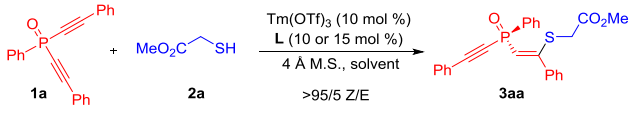


Figure 2. The influence of rare-earth metal ions on the reaction

indicating the amide units of the ligand play an extremely important role for the discrimination of the dialkynyl groups of the substrate **1a**. Thus, **L-RaPr$_3$** was chosen as the optimal ligand in terms of enantioselection (entry 4). When the reaction was performed in *p*-xylene instead of toluene, the enantioselectivity increased to 87% ee (entry 8). Lowering the reaction temperature to 35 ℃ resulted in slightly improved reactivity and enantioselectivity (entry 9). After increasing the ratio of **L-RaPr$_3$** to Tm(OTf)$_3$, and the ratio of sulfur-nucleophile to dialkynylphosphine oxide **1a**, and decreasing the amount of

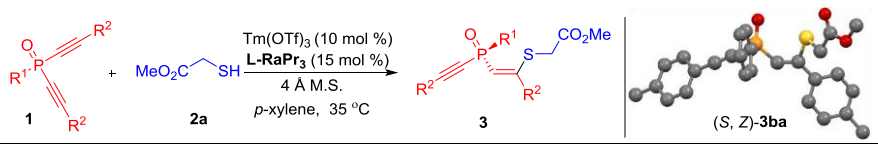
Table 1. Optimization of the reaction conditions[a]

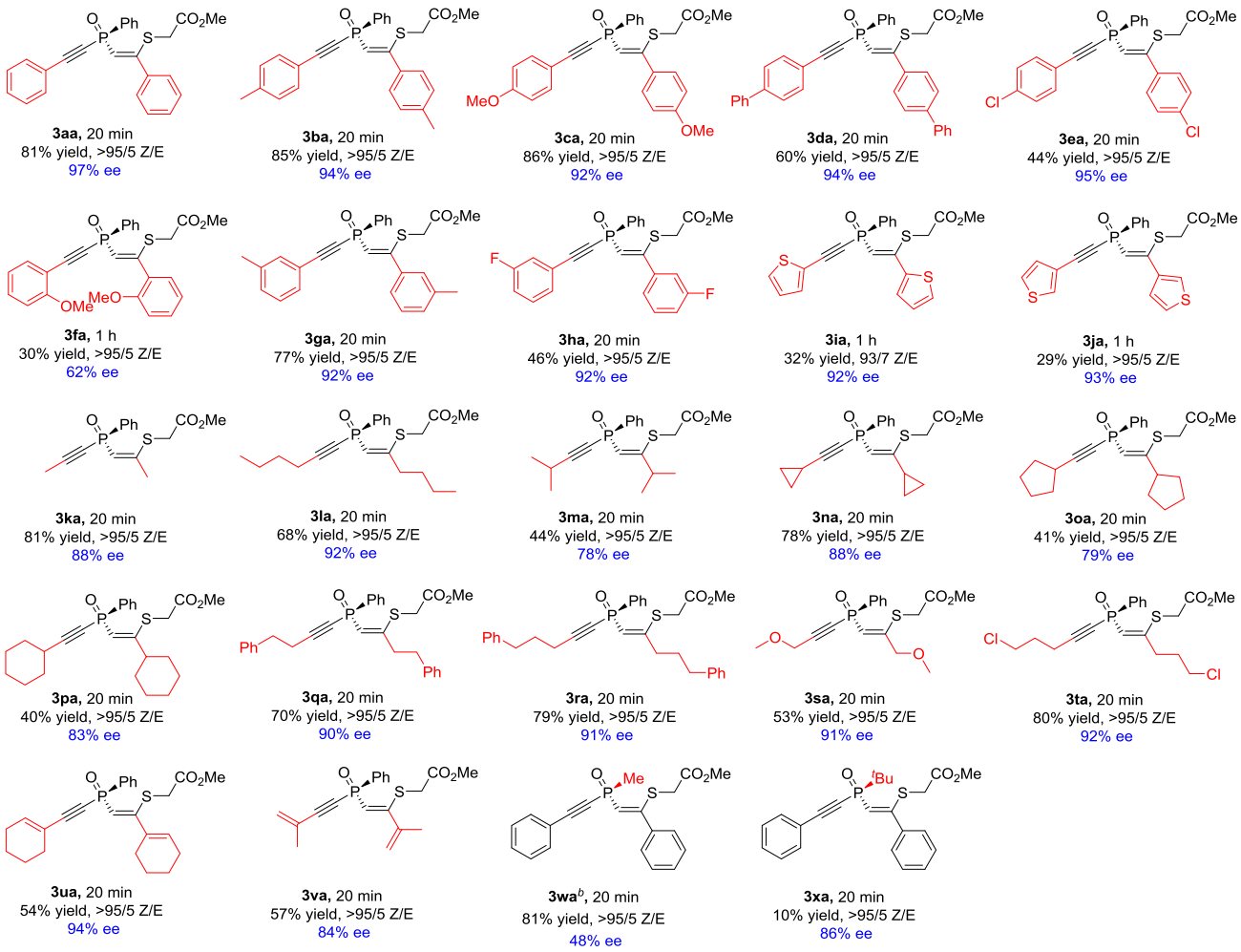


entry	ligand	T (°C)	L/Tm^{3+} (mol%)	yield (%)	ee (%)
1	**L-PrPr$_2$**	60	10/10	54	48
2	**L-PiPr$_2$**	60	10/10	52	70
3	**L-RaPr$_2$**	60	10/10	51	79
4	**L-RaPr$_3$**	60	10/10	52	84
5	**L-RaEt$_2$Me**	60	10/10	58	42
6	**L-RaMe$_2$**	60	10/10	53	35
7	**L-RaAd**	60	10/10	27	0
8[b]	**L-RaPr$_3$**	60	10/10	47	87
9[b]	**L-RaPr$_3$**	35	10/10	50	89
10[b]	**L-RaPr$_3$**	35	10/15	44	95
11[c]	**L-RaPr$_3$**	35	10/15	81	97

[a]Unless otherwise noted, the reaction were carried out with Tm(OTf)$_3$ (10 mol %), ligand (10-15 mol %), **1a** (0.1 mmol), **2a** (1.1 equiv) and 4 Å M.S. (20 mg) in toluene (1.0 mL) at the indicate time for 24 h. Isolated yield of **3aa** by silica gel chromatography. Ee was determined by UPC^2 analysis (Daicel CHIRALPAK IC-3). [b]In *p*-xylene (1.0 mL). [c]**2a** (2.0 equiv) and in *p*-xylene (0.2 mL) for 20 min.

Table 2. Substrate scope of dialkynylphosphine oxides[a]





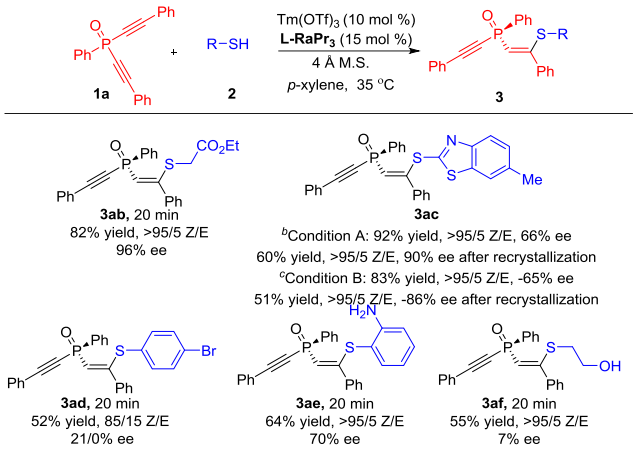
[a]Reaction conditions: the same as entry 11 in table 1. [b]$Yb(OTf)_3$-**L-RaPr$_3$** (1:1.2, 10 mol %).

solvent, the yield improved to 81% with 97% ee (entries 10−11). We therefore chose the reaction conditions in Table 1, entry 11 for further studies.

With the optimized reaction conditions in hand, the substrate scope of dialkynylphosphine oxides was then investigated (Table 2). The alkyne bearing electron-withdrawing and electron-donating substituents at *para*-position of terminus aryl groups could undergo the transformations smoothly, providing the products **3ba**−**3ea** in 44 − 86% yields and 92−95% ee. When increasing the steric hindrance at the *ortho*-position, a moderate yield and enantioselectivity was obtained (**3fa**). *meta*-Substituted substrates were compatible with the reaction conditions, giving *P*-stereogenic alkynylphosphine oxides **3ga** and **3ha** in moderate to good yields and excellent enantioselectivities. Moreover, if dialkynylphosphine oxides containing heteroaromatic groups at the alkyne terminus position were employed, they could produce the corresponding products **3ia**−**3ja** in moderate yields and excellent enantioselectivities. Subsequently, other challenging dialkynylphosphine oxides substrates bearing alkyl group at the alkyne terminus were investigated. Gratifyingly, linear, branched as well as cyclic alkyl substituents could be tolerable, affording **3ka**−**3pa** with moderate to good yields and high enantioselectivities. Those containing functional groups at the end or middle of the alkyl chain, including phenyl (**3qa**, **3ra**), oxygen (**3sa**), chlorine (**3ta**) were well tolerated under catalytic reaction conditions. It was noteworthy that alkenyl substituted substrates did not influence the reaction efficiency and regioselectivity to yield the alkyne-addition products **3ua** and **3va**. Changing the phenyl group on the phosphorus center to

methyl group delivered the desired product **3wa** with high yield and moderate enantioselectivity. The increase of steric hindrance on the phosphorus center shows low reactivity but good enantioselectivity (**3xa**). The absolute configuration of **3ba** was determined to be (*S*, *Z*) by X-ray crystal diffraction analysis.[13] In these cases investigated, *Z*-type alkene substituent on phosphine oxides were generated.

Table 3. Substrate scope of sulfur nucleophiles[a]

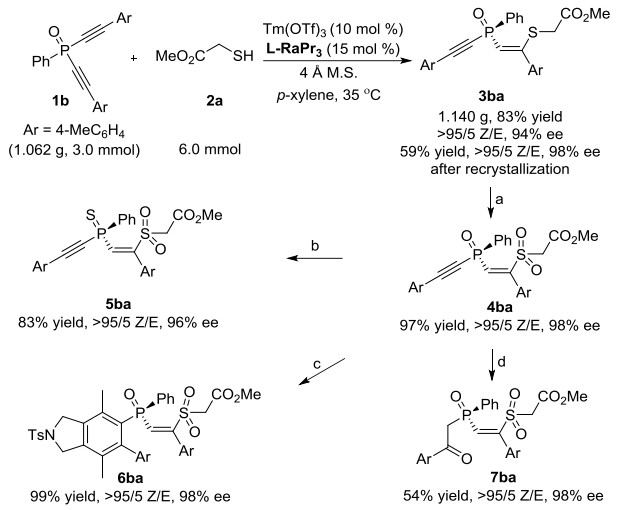


[a]Reaction conditions: the same as entry 11 in table 1. [b]Condition A: Dy(OTf)$_3$-**L-PiPr$_2$** (1:1.2, 10 mol %), **1a** (0.1 mmol), **2** (0.2 mmol) and 4 Å M.S. (20 mg) in toluene (0.2 mL) at 45 °C for 24 h. [c]Condition B: Dy(OTf)$_3$-**L-PiAd** (1:1.2, 10 mol %), **1a** (0.1 mmol), **2** (0.2 mmol) and 4 Å M.S. (20 mg) in toluene (0.2 mL) at 45 °C for 24 h.

Encouraged by the results obtained from methyl thioglycolate **2a**, we extended this catalytic system to desymmetrization of dialkynylphosphine oxide **1a** with various sulfur nucleophiles (Table 3). Ethyl thioglycolate **2b** with variation in the size of the ester group did not affect the outcome, giving **3ab** with excellent yield and enantioselectivity. Besides, 6-methylbenzo[*d*]thiazole-2-thiol **2c** participated in this reaction well when higher temperature and longer time were employed, generating **3ac** with excellent yield and moderate enantioselectivity. Interestingly, an opposite sense of asymmetric induction were found upon homochiral ligand **L-PiPr2** and **L-PiAd** were used in coordination with Dy(OTf)$_3$.[14] Highly optically active phosphine oxide **3ac** could be isolated in good enantioselectivity after recrystallization. A poor result was observed when 4-bromothiophenol **2d** was tested, whereas 2-aminobenzenethiol **2e** underwent the reaction in sharply raised ee value. It implies that a weak coordination functional group might involve in the enantioselective step. The reaction could be extended to 2-mercaptoethanol **2f**, but the corresponding product **3af** was isolated in 55% yield with only 7% ee, maybe because the small hydroxyl group cause the steric hindrance is not obvious in the enantioselective step.

To evaluate the synthetic potential of the current catalytic system, a gram-scale reaction between phenylbis(*p*-tolylethynyl)phosphine oxide **1b** and methyl thioglycolate **2a** was performed, furnishing the product **3ba** in 83% yield, >95/5 Z/E and 94% ee (Scheme 2). Oxidation of the **3ba** by *m*-CPBA generated the corresponding sulfone **4ba** in nearly quantitative yield and 98% ee. Treatment of **4ba** with

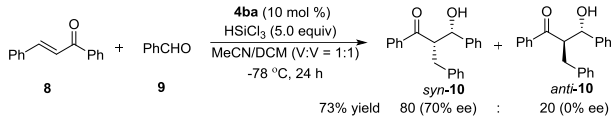
Scheme 2. Gram-scale reaction and transformations of 3ba



Reaction Conditions: a) *m*-CPBA, DCM, RT, 4 h; b) lawen·s reagent, toulene, 60 °C, 1 h; c) [Rh(cod)$_2$]BF$_4$, (±) BiNAP, *N,N*-di(but-2-yn-1-yl)-4-methylbenzenesulfonamide, DCM, RT, 4 h; d) PdCl$_2$, H$_2$O, 1,4-dioxane, 90 °C, 2 h.

Lawesson's reagent afforded *P*-stereogenic alkynylphosphine sulfide **5ba** in excellent yield with slightly reduced chirality. Rh(I)-catalyzed [2+2+2] cycloaddition with 1,6-diynes was also applied to transform optically active **4ba** into diaryl substituted phosphine oxide **6ba** in quantitative yield. Subsequent Pd-catalyzed hydration of **4ba** gave **7ba** with 54% yield without erosion of the enantioselectivity.

Scheme 3. Application of 4ba in an enantioselective reductive aldol reaction



To further investigate the utility of the obtained chiral alkynylphosphine oxides, chiral derivative **4ba** bearing phosphine oxide and sulfone functional groups was subsequently evaluated as potential Lewis base catalyst in enantioselective reductive aldol reaction between chalcone **8** and benzaldehyde **9** (Scheme 3).[15] The desired aldol adduct **10** could be provided with 73% yield, 80/20 *syn/anti* ratio with 70% ee (*syn*-**10**). This indicated that the catalytic products have potential as chiral catalysts in organic chemistry.

We got several X-ray single crystal structures of chiral *N,N'*-dioxide with rare-earth metal triflates,[16] which help to understand how did the center metal and ligand structure affect the enantioselectivity. Our previous study has showed that chiral *N,N'*-dioxide could act as a tetra-oxygen ligand to coordinate with Sc(III) in a octahedral version.[11] It was found that the complexes of **L-RaPr2** with Pr(OTf)$_3$, Gd(OTf)$_3$ and Ho(OTf)$_3$, a square antiprismatic geometry version is established (Figure 3a–c). Interestingly, a seven-coordinate state is formed when Tm(OTf)$_3$ is used as the metal precursor (Figure 3e). It is obvious that the coordination numbers and steric bias is inherent in the rare-earth metal ions. (1) The coordination

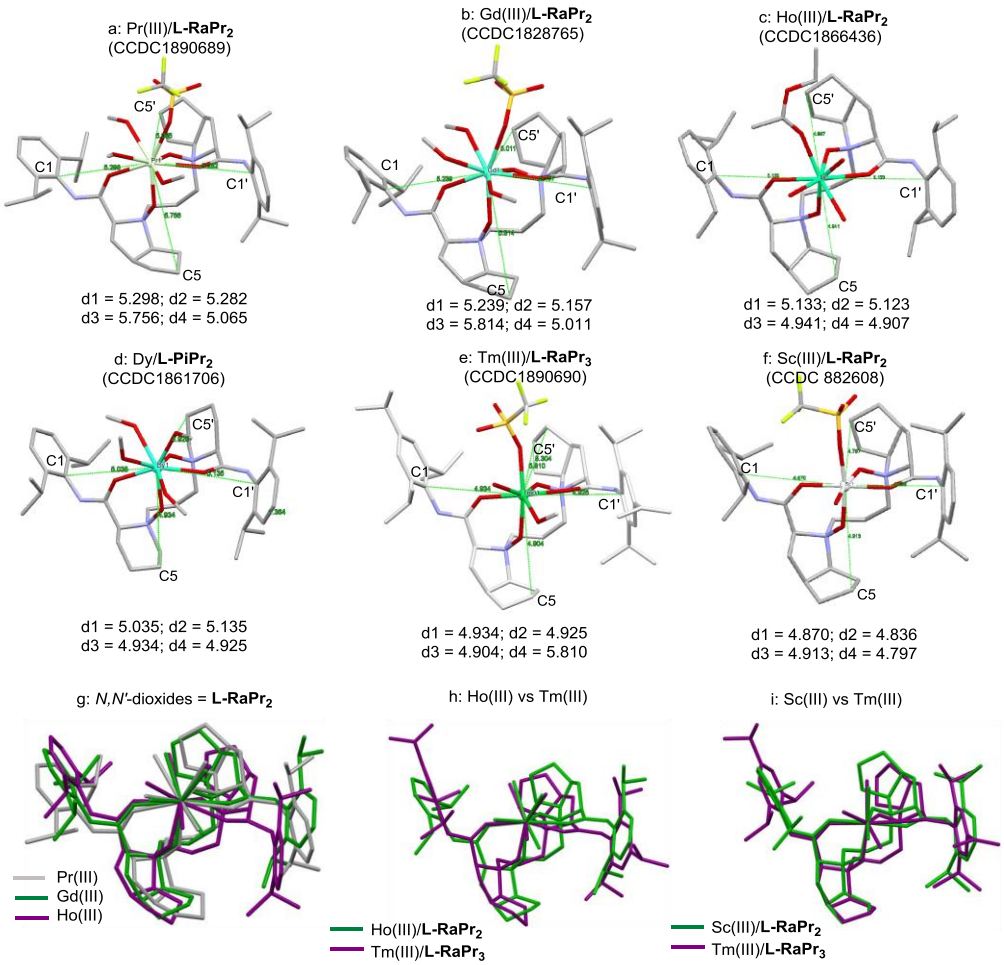


Figure 3. X-ray single crystal structures of chiral *N,N'*-dioxides with rare-earth metal triflates

numbers increased with the increasement of the ionic radii of the rare-earth metal ions, thus vacant sites that can be attached or recognized upon binding of the substrate molecules varied accordingly. (2) The cavity around the metal center is created by the units of both the aniline substituents and the aza-cyclic structure of the amino acid: the larger ionic radii of the RE(III), the larger space, observing from the distance of the C1-RE(III) (d1 and d2) and C5-RE(III) (d3 and d4) in Figure 3a−c, e−f. (3) In connection with the enantioselection shown in Figure 2, it could be concluded that larger or smaller cavity in the catalyst [Pr, Gd or Ho, Sc vs. Tm (Figure 3g−i)] is not beneficial to the discrimination of the dialkyne groups of the phosphine oxide with thioglycolate. The moderate space from Tm(III) catalyst

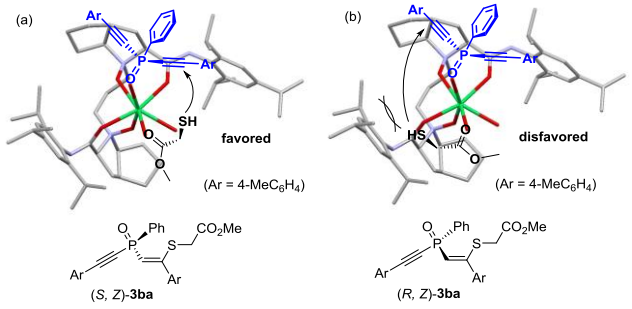


Figure 4. The proposed transition states

prefers the coordination of both phosphine oxide and thioglycolate for enantioselective nucleophilic addition.

The relationship between the ee values of ligand **L-RaPr3** and the product **3aa** was explored.[17] A nonlinear effect was not observed, which suggests that **L-RaPr3** coordinated with the Tm^{3+} ions in a 1:1 ratio (for details see the Supporting Information). The HRMS spectrum of a mixture of $Tm(OTf)_3$/**L-RaPr3** and **1a** (1/1/1) confirmed coordination of the phosphine oxide to the catalyst. Peaks at *m/z* 714.2794 and 1577.5344 were assigned to $[Tm^{3+}$ + **L-RaPr3** + **1a** + $TfO^-]^{2+}$ and $[Tm^{3+}$ + **L-RaPr3** + **1a** + $2TfO^-]^+$ respectively (for details see the Supporting Information). Based on the studies above and the absolute configuration of products and **L-RaPr3**/$Tm(OTf)_3$ complex, a transition state was proposed to rationalize the stereoinduction (Figure 4). Preliminarily, the four oxygen atoms of ligand **L-RaPr3** coordinate to Tm^{3+} in a tetradentate manner. The dialkynylphosphine oxide coordinates to the metal center at one of the vacant sites, with the two alkyne groups stretching along the opening band between the two amide-amine oxide units. The vacant position towards the L-ramipril backbone might be occupied by the thioglycolate. As shown in Figure 4b, the left alkyne group is blocked by the 2,4,6-triisopropylphenyl group left-handed, and the sulfur-nucleophile preferably attacks the right alkynyl group with

less steric hindrance (Figure 4a) to generate the corresponding (*S*, *Z*)-configured product **3ba**.

In summary, we have demonstrated the first Lewis acid catalyzed desymmetrization of prochiral dialkynylphosphine oxides with various sulfur nucleophiles. The desired substituted alkynylphosphine oxides with *P*-stereogenic center were afforded with high reactivity, Z/E selectivities and enantioselectivities (up to 92% yield, >95/5 Z/E and 97% ee). The functionalized alkynylphosphine oxides can be easily transformed to other useful chiral building blocks. The center metal and ligand structure play an important role for the discrimination of the dialkynyl groups of the substrate. Tm(III) catalyst having the moderate cavity prefers concise coordination of both phosphine oxide and thioglycolate for enantioselective nucleophilic addition. Further investigations on the other type of desymmetrization of prochiral phosphorus compounds are underway.

ASSOCIATED CONTENT

Supporting Information.
The Supporting Information is available free of charge on the ACS Publications website.

Experimental procedures, full spectroscopic data for all new compounds, and copies of ^{1}H, ^{13}C, ^{31}P NMR, and HPLC spectra (PDF)

X-ray crystallographic data for **3ba** (CIF)

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Notes

The authors declare no competing financial interest.

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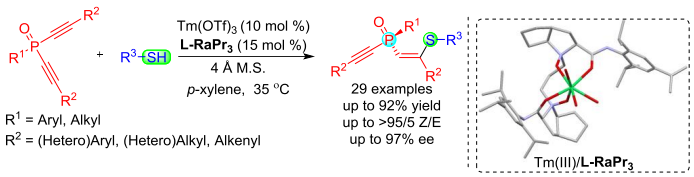

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