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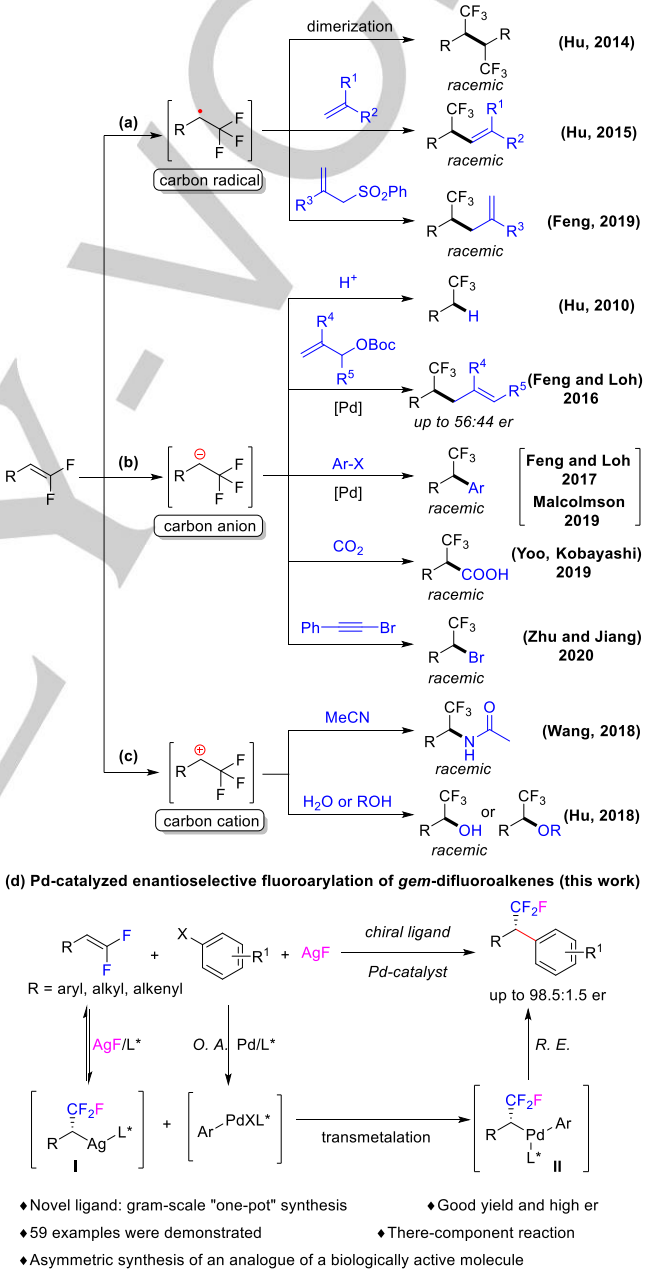
Design, Synthesis of TY-Phos and Application in Palladium-Catalyzed Enantioselective Fluoroarylation of *gem*-Difluoroalkenes

Tao-Yan Lin, Zhangjin Pan, Youshao Tu, Shuai Zhu, Hai-Hong Wu, Yu Liu, Zhiming Li,* and Junliang Zhang*

Dedicated to 70th anniversary of Shanghai Institute of Organic Chemistry, CAS

Abstract: The first example of highly enantioselective fluoroarylation of *gem*-difluoroalkenes with aryl halides is presented by using a new chiral sulfinamide phosphine (**Sadphos**) type ligand **TY-Phos**. *N*-Me-**TY-Phos** can be easily synthesized on a gram scale from readily available starting materials in 3 steps. Salient features of this work including readily available starting materials, good yields, high enantioselectivities as well as broad substrate scope make this approach very practical and attractive. Notably, the asymmetric synthesis of an analogue of a biologically active molecule is also reported.

gem-Difluoroalkenes are increasingly being exploited as versatile fluorinated building blocks in organofluorine synthesis[1] via mono-defluorinative[2] or fluorine retentive[3] functionalization reactions. Over the past decade, by taking advantage of easily available *gem*-difluoroalkenes as reliable trifluoromethyl (CF_3) precursors, many chemists reported a conceptually novel protocol for the expedient synthesis of CF_3-containing molecules through an additional fluorine source via a radical pathway or an anion/ cation mechanism (**Scheme 1**), which are supplement to the typical trifluoromethylation reaction.[4] In 2014, Hu and co-workers demonstrated the formation of *α*-trifluoromethylated benzylsilver species from the reaction of *gem*-difluoroalkene with AgF for the first time, and which undergoes rapid C-Ag^{I} bond homolysis in-situ to afforded the *α*-CF_3 benzyl radical[5]. Recently, Feng et al.[6] reported a photoredox-coupled F-nucleophilic addition induced allylic alkylation of *gem*-difluoroalkenes via the *α*-CF_3 benzyl radical intermediate (**Scheme 1**, **a**). In contrast, Feng & Loh group[7] and Malcolmson et al.[8] realized palladium-catalyzed fluorinative allylation and arylation of *gem*-difluoroalkenes via *α*-CF_3 carbanion intermediate, and the first attempt to palladium-catalyzed asymmetric fluoroallylation of *gem*-difluoroalkenes with allyl *tert*-butyl carbonate was done by Feng and Loh group.[7a]



Scheme 1. Trifluoromethylation of *gem*-difluoroalkenes.

However, only up to 56:44 er was achieved in Feng and Loh's catalytic system after examining a variety of chiral ligands. In addition, Kobayashi[9] and Jiang[10] demonstrated that α-CF3 carbanion intermediate could be intercepted by CO_2 or bromoalkyne, furnishing the α-CF_3-carboxylic acids or α-CF_3-

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halides, respectively (**Scheme 1**, **b**). In 2018, α-CF_3 carbocation intermediate was report by Wang[11] and Hu[12], which generated from *gem*-difluoroalkenes with a F^+ source and applied to aminofluorination and fluoro-hydroxylation, respectively (**Scheme 1**, **c**).

Despite that a number of methodologies have been developed for the construction of CF_3-containing molecules from *gem*-difluoroalkenes, none of those method is enantioselective version.[7a] Herein, we wish to report the first example of highly enantioselective fluoroarylation of *gem*-difluoroalkenes with aryl halides enabled by the palladium and a new type of chiral sulfonamide phosphine (**Sadphos**) ligand, so called **TY-Phos** (**Scheme 1, d**), providing an easy access to chiral 1,1,1-trifluoro-2-arylalkanes.[13] The incorporation of a fluoride or trifluoromethyl group in an organic molecule often significantly alters the physical, chemical, and biological properties compared to a nonfluorinated organic molecule.[14] (Bis)arylethanes, in particular, with a hydroxyl group or alkoxyl or hydroxyl group at the *ortho*-posititon of the aryl, are ubiquitous structural motifs found in an array of biologically active natural products and pharmaceuticals (Figure 1).[15] For example, (-)-Curcuphenol is a natural product and has been isolated from the marine sponge Didiscus flavus.[15a] Racemic **1a** and **1b** have been found to have excellent tubulin binding properties and antitumor activity.[15b] Therefore, the development of highly efficient methods for synthesis of chiral 1,1,1-trifluoro-2-arylalkanes is in high demand.

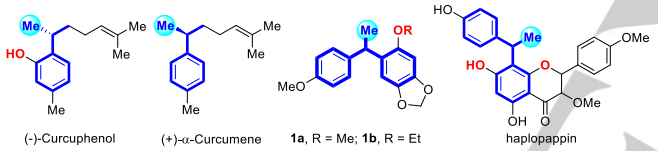
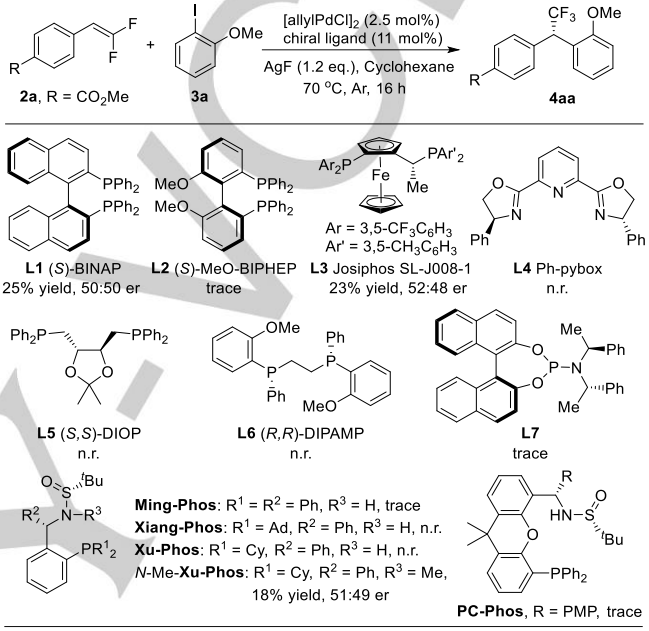


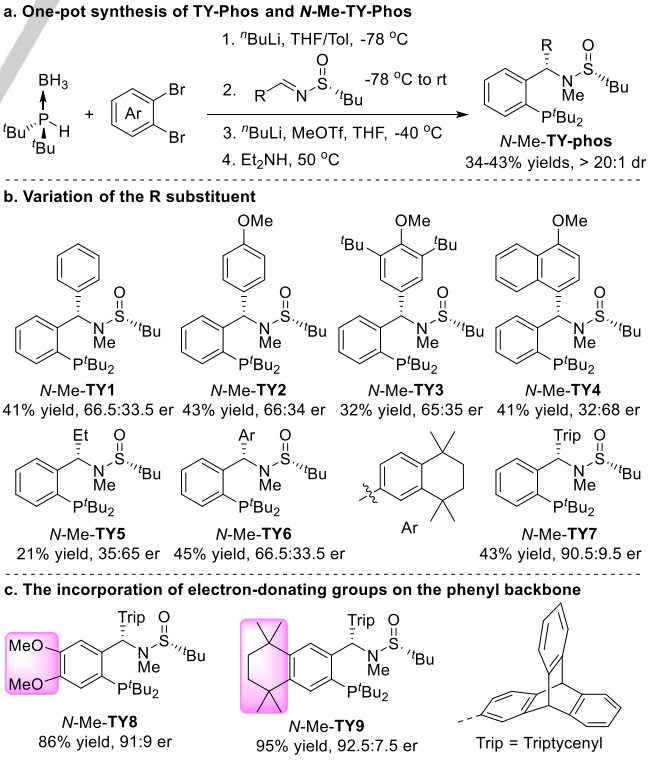
Figure 1. Biologically active compounds and pharmaceuticals bearing (bis)arylethane subunit.

Inspired by the Feng and Loh's elegant work on the racemic synthesis of non-symmetric α,α-disubstituted trifluoroethane derivatives,[7b] we became interested in whether chiral ligands could be applied to the palladium-catalyzed asymmetric fluoroarylation of *gem*-difluoroalkenes with aryl halides. However, this hypothesis faced considerable challenges (Scheme 1, d): (1) catalytic amount of chiral ligand versus an excess amount of AgF will make the intermediate **I** may have no chiral ligand; (2) AgF competitive binding with palladium to chiral ligand,[16] it may weaken or even completely eliminate the enantioselectivity of this reaction; (3) according to Hu's findings,[5] intermediate **I** can generate trifluorobenzyl radical, which will lead to the racemization of intermediate **I**; (4) referring to the work of Tredwell[13c] and Jarvo,[17] the intermediate **II** may also undergo racemization for the same reason; (5) how to avoid hydrofluorination[18] of intermediate **I** rather than the transmetalation; (6) how to avoid β-H elimination of intermediate **II** when the R is alkyl group.

Initially, our investigations began with methyl 4-(2,2-difluorovinyl)benzoate **2a** and 1-iodo-2-methoxybenzene **3a**, and a series of known chiral ligands was screened (Scheme 2). Unfortunately, commercially available ligands **L1-L7** showed low reactivity and enantioselectivity. Meanwhile, our group developed **Sadphos**, such as **Ming-Phos**, [19] **Xiang-Phos**,[20] **Xu-Phos**[21] and **PC-Phos**[22] were not efficient either, but *N*-Me-**Xu-Phos** gave a promising result with 18% yield albeit with only 51:49 er. We found that the substituents on the phosphine have a significant impact on this reaction. Thus, a new chiral sulfinamide phosphine type ligand, named **TY-Phos** was designed by changing the substituent of the phosphine from cyclohexyl of *N*-Me-**Xu-Phos** to the *tert*-butyl to increase the steric hindrance (Scheme 3). To our delight, the *N*-Me-**TY1** showed higher reactivity and enantioselectivity compared to *N*-Me-**Xu1**. Inspired by this promising result, we varied the R group (*N*-Me-**TY2-7**).



Scheme 2. Screening of known ligands.



Scheme 3. Optimization of the **TY-Phos** ligands.

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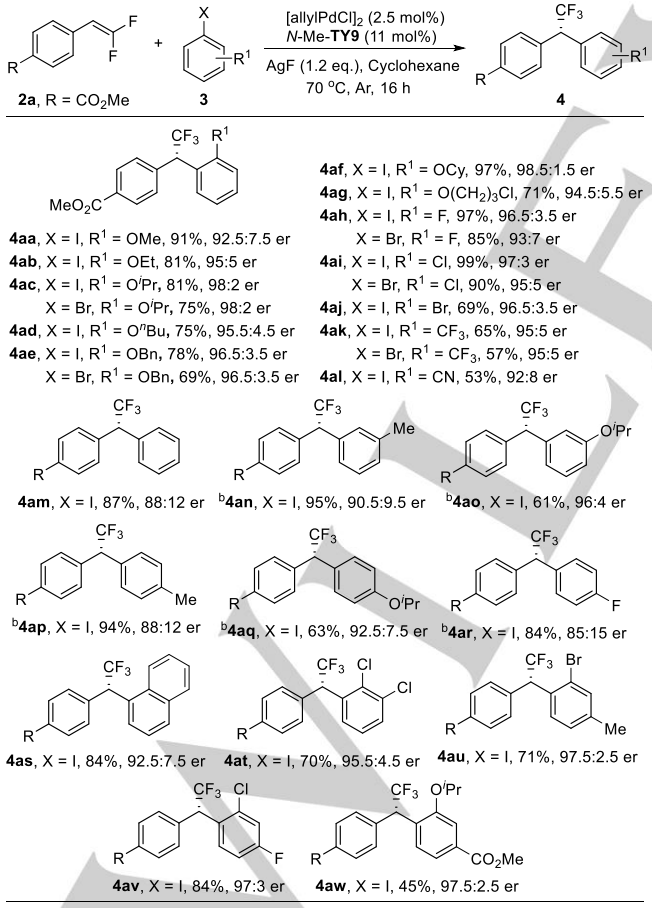
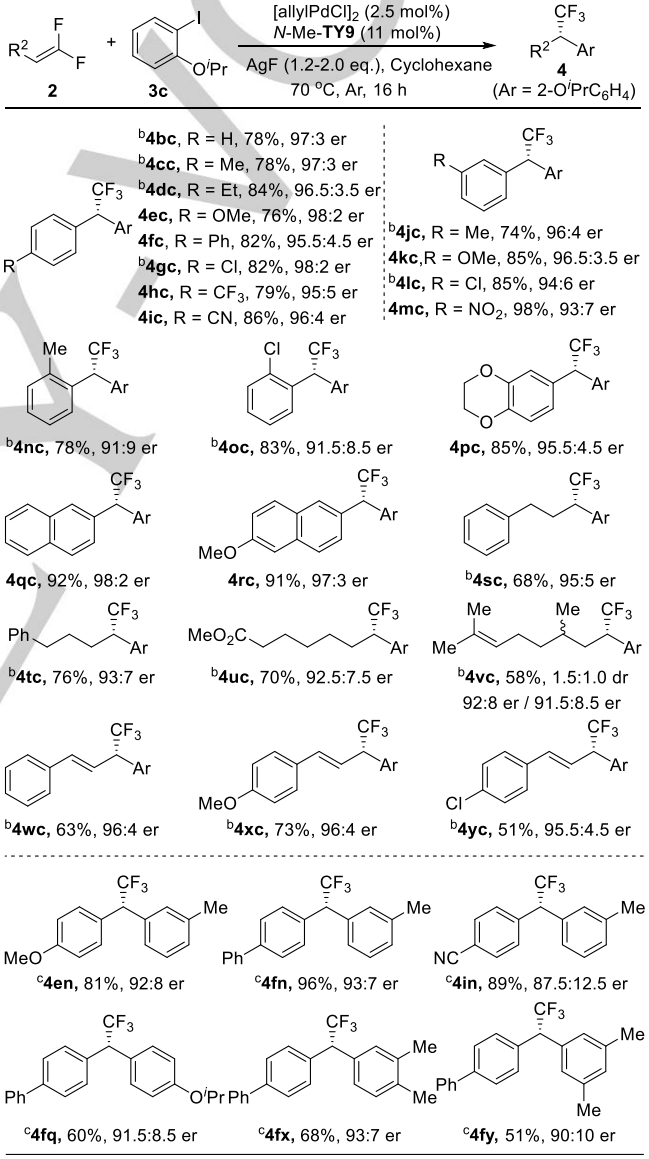
Gratifyingly, the er value can be increased to 90.5:9.5, when the R was triptycenyl group (*N*-Me-**TY7**), but only 43% yield was obtained. We attribute this to the silver intermediate **I** might undergo other transformations (i.e.hydrolysis) before the transmetallation reaction with palladium(II) intermediate generated via the oxidative addition. With the knowledge that electron-rich phosphine ligands could promote the oxidative addition of aryl halides with palladium(0).[23] Therefore, we introduced electron-donating groups into the aryl moiety of *N*-Me-**TY-Phos** structured as *N*-Me-**TY8** and *N*-Me-**TY9** with methoxy and alkyl groups, respectively. Gratifyingly, the product **4aa** was obtained in 95% yield with 92.5:7.5 er with the use of *N*-Me-**TY9** as the chiral ligand. Notably, One-pot and gram scale synthesis of **TY-Phos** and *N*-Me-**TY-Phos** could be achieved from the di-*tert*-butylphosphine borane (for more details, please see the supporting information). The absolute configuration of **TY-Phos** was unambiguously determined via X-ray crystallography analysis.[24] Further screening of the palladium salts, reaction temperatures and solvents failed to give better results either (Table S1, ESI). The optimal reaction conditions are described as follows: $[allylPdCl]_2$ as the catalyst, *N*-Me-**TY9** as the chiral ligand in cyclohexane at 70 °C for 16 h.

Having the optimal reaction conditions in hand, we first investigated the generality of the aryl halides (Scheme 4). A good tolerance towards both electron-donating substituents (**4aa**-**4ag**) and electron-withdrawing substituents (**4ah**-**4al**) at the *ortho*-position of the aryl iodides delivered the corresponding products



Scheme 4. Substrate scope of aryl halides. [a] Unless otherwise noted, all reactions were carried out with 0.2 mmol of **2a**, 0.4 mmol of **3**, AgF (1.2 equiv), 2.5 mol% $[allylPdCl]_2$ and 11 mol% *N*-Me-**TY9** in 2.0 mL of cyclohexane, 70 °C under Ar for 16 h. [b] *N*-Me-**TY10** was used as chiral ligand (for *N*-Me-**TY10**, please see the supporting information).

in 53-99% yields with 91:9-98.5:1.5 er. The absolute configuration of (*S*)-**4ae** was unambiguously determined via X-ray crystallography analysis.[24] Notably, the aryl bromides are also suitable for this reaction (**4ac**, **4ae**, **4ah**, **4ai** and **4ak**). The reaction showed a high chemoselectivity when the aryl halides contain both iodide and bromide (**4aj**, **4ar**), in which the reaction selectively take place at the iodide position. There is an obvious substituent effect on the enantioselectivity of this reaction. The **4am**-**4ar** were obtained in 61-95% yields with 85:15-96:4 er values when no substituent at the *ortho*-position of the aryl iodides, indicating that the steric hindrance at *ortho*-position is beneficial to the enantioselectivity. Gratifyingly, the disubstituted aryl iodide (**3at**-**3aw**) delivered the corresponding products (**4at**-**4aw**) in moderate to good yields with high er.



Scheme 5. Substrate scope of *gem*-difluoroalkenes. [a] Unless otherwise noted, all reactions were carried out with 0.2 mmol of **2**, 0.4 mmol of **3c**, AgF (1.2 equiv), 2.5 mol% $[allylPdCl]_2$ and 11 mol% *N*-Me-**TY9** in 2.0 mL of cyclohexane, 70 °C under Ar for 16 h. [b] The reaction was conducted with **2** (0.4 mmol), **3c** (0.2 mmol), AgF (0.4 mmol). [c] *N*-Me-**TY10** was used as chiral ligand.

Subsequently, we turned our attention to investigate the scope of the current reaction with respect to the *gem*-

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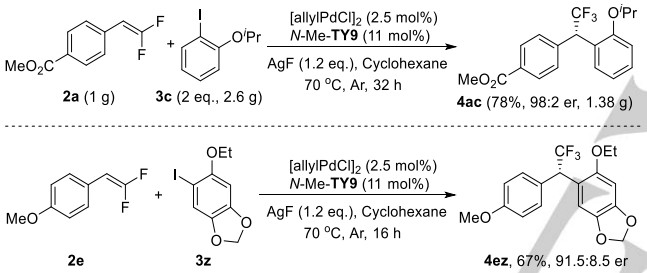
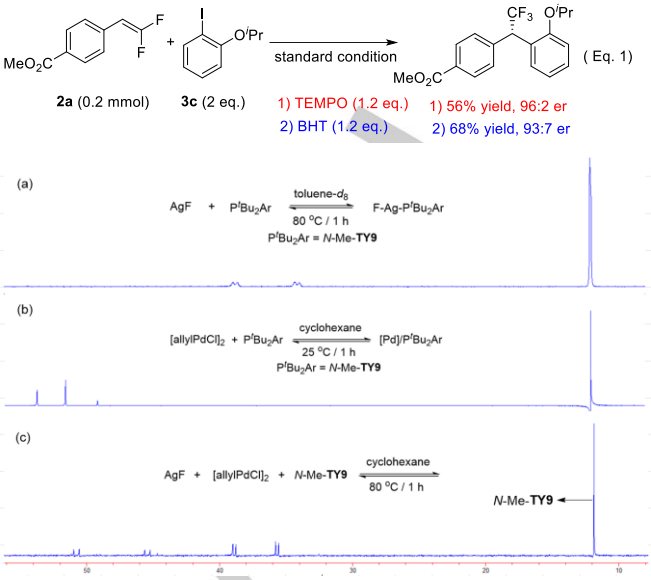
difluoroalkenes (Scheme 5). To our delight, a good tolerance to both electron-donating groups (**4cc**-**4ec**) and electron-withdrawing groups (**4gc**-**4ic**) at the *para*-position of the *gem*-difluoroalkenes was observed, delivering the desired products in 76-86% yields with 95:5-98:2 er. Whereas the substrates with an electron- donating groups (**4jc**-**4kc**) delivered higher er value than those with an electron-withdrawing groups (**4lc**-**4mc**) at the *meta*-position of the *gem*-difluoroalkenes. The **4nc** and **4oc** were obtained with relatively lower er value due to a steric hindrance. The *gem*-difluoroalkenes **3pc**-**3rc** were compatible to produce the desired products (**4pc**-**4rc**) with excellent yields and enantioselectivities. Notably, the aliphatic *gem*-difluoroalkene also successfully gave the desired products **4sc**-**4vc** in 58-76% yields with 91.5:8.5-95:5 er. Moreover, the *gem*-difluoroalkenes **3tc**-**3vc** derived from cinnamaldehyde also participated in this reaction to afford the desired products **4wc**-**4yc** in 51-63% yields with 95.5:4.5-96:4 er. Finally, the examples of across coupling partner (**4en**-**4fy**) were obtained in 51-96% yields with 87.5:12.5-93:7 er.

Finally, in order to show the practicability of this method, a gram-scale reaction was carried out, producing the desired product **4ac** in 78% yield with 98:2 er. Additionally, **4ez**, which is an analogue of biologically active molecule **1b**, could be made in 67% yield with 91.5:8.5 er.



Scheme 6. Gram-scale reaction and asymmetric synthesis of a biologically active molecule **1b**'s analogue **4eu**.

In order to gain insights of the reaction mechanism, we performed some control experiments. A well-known radical-trapping reagent such as TEMPO or BHT was added to the current reaction (Eq. 1). The yield and er only slightly decreased, which might exclude the radical pathway.[5] In addition, we discovered that both silver fluoride and palladium can be coordinated with *N*-Me-**TY9**. As observed by ^{31}P NMR spectroscopy, it appeared two new phosphine peaks ($J^{109}Ag^{31}P$ = 968.8 Hz, $J^{107}Ag^{31}P$ = 840.9 Hz) when AgF and *N*-Me-**TY9** were stirred in toluene-d_8 at 80 °C for 1 h (Scheme 7, a). It was similar to the result reported by Malcolmson and co-workers.[8] The ^{31}P NMR spectrum showed three new phosphine peaks at 54.3, 52.1 and 49.6 ppm after palladium catalyst and *N*-Me-**TY9** stirred in cyclohexane at 25 °C for 1 h (Scheme 7, b). However, the ^{31}P NMR spectrum showed two new doublet of doublets peaks after palladium catalyst, AgF and *N*-Me-**TY9** stirred in cyclohexane at 80 °C for 1 h, indicating the formation of a new [Pd-Ag-*N*-Me-**TY9**] species (Scheme 7, c).[25] The relationship between the ee value of *N*-Me-**TY9** and that of (*S*)-**4ac** was investigated (Figure 2). A linear effect was observed, which indicates that an active catalyst/ligand being of a monomeric nature and the reaction possessing a first-order dependence on catalyst.



Scheme 7. NMR spectroscopic studies.

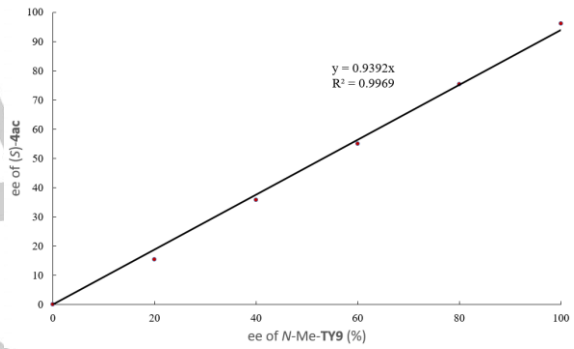


Figure 2. Linear effects syudy.

In summary, we have developed a highly enantioselective palladium-catalyzed fluoroarylation of *gem*-difluoroalkenes with aryl halides by using of a newly designed **Sadphos** type ligand *N*-Me-**TY9** as the chiral ligand, which provides an efficient method for the synthesis of chiral 1,1,1-trifluoro-2-arylalkanes. The salient features of this reaction include readily available starting materials, high yields and enantioselectivity and broad substrate scope. The mechanism of this palladium-catalyzed asymmetric fluoroarylation of *gem*-difluoroalkenes has been investigated by NMR spectroscopy. However, the nature of the reaction mechanism on how to control enantioselectivity remain unclear. Further studies including DFT calculations and synthetic applications of this reaction, and the application of **TY-Phos** or *N*-Me-**TY-Phos** in other transition metal-catalyzed asymmetric transformations are underway and will be reported in the due course.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: *gem*-Difluoroalkene • Fluoroarylation • Palladium • TY-Phos • Ligand Design

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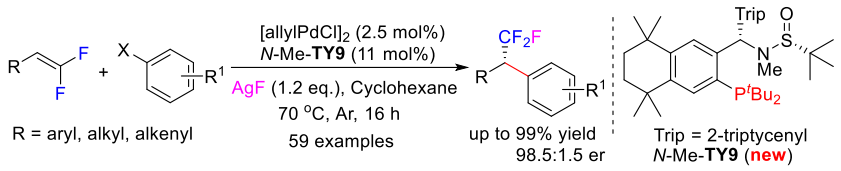

♦New ligand design ♦There-component reaction ♦Good yield and high stereoselectivity

The first example of highly enantioselective fluoroarylation of *gem*-difluoroalkenes with aryl halides is presented by using a new chiral sulfinamide phosphine (**Sadphos**) type ligand (**TY-Phos**). The salient features of this reaction include readily available starting materials, high yields and enantioselectivity and broad substrate scope.

Tao-Yan Lin, Zhangjin Pan, Youshao Tu, Shuai Zhu, Hai-Hong Wu, Yu Liu, Zhiming Li, and Junliang Zhang**

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Design, Synthesis of TY-Phos and Application in Palladium-Catalyzed Enantioselective Fluoroarylation of *gem*-Difluoroalkenes