New sulfur-coordinating chiral ligands for the Tsuji—Trost reaction*

E. Schulz and A. Voituriez*

*Laboratory of Molecular Catalysis, Orsay Institute of Molecular Chemistry and Materials, Paris-Sud University, 91405 Orsay, France.***
Fax: 33 (0) 1 6915 4680. E-mail: emmaschulz@ icmo.u-psud.fr

The use of sulfur-coordinating chiral ligands in the palladium-catalyzed asymmetric Tsuji—Trost reaction is reviewed.

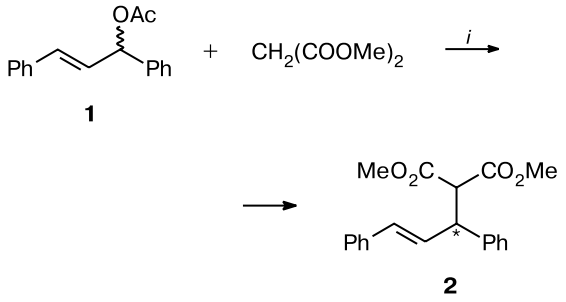
Key words: asymmetric catalysis, chiral sulfur-coordinating ligands, palladium complexes, Tsuji—Trost reaction.

Introduction

The preparation of new and efficient enantiopure ligands for asymmetric catalysis is nowadays a great concern for organic chemists. Highly selective and active catalysts have already been prepared, some of them being used at the industrial scale, mostly in hydrogenation reactions.[1] Many works have already been published and are still in progress to optimize transformations involving C—C bond formations. Recent reviews[2,3] clearly show that nitrogen-containing ligands (and especially with oxazoline moieties) are particularly good candidates to achieve, for example, allylic substitutions, cyclopropanations, Diels—Alder reactions, aldol or Michael-type additions. Sulfur, as potential coordinating atom, has been scarcely used compared to phosphorus or nitrogen, probably because of its known tendency to poison heterogeneous catalysts. Kellog *et al.* reported in the mid-80´s the first investigations to use available chiral sulfides as potential ligands. They prepared various chiral (macrocyclic) sulfides as ligands and tested them, however, with modest success (17% *ee*[4] or 46% *ee*[5]), for the Ni(II)-catalyzed cross-coupling of α-phenylethylmagnesium chloride with vinyl bromide. Since this early work, the efficient use of sulfur-containing ligands has been reported in numerous articles for the preparation of active homogeneous chiral complexes. Most of them deal with asymmetric catalytic C—C bond formations.

We wish to summarize here some of the most recent publications, involving the Pd-catalyzed allylic substitutions, *i.e.*, the Tsuji—Trost reaction,[6] that have been intensively studied with sulfur-containing ligands over the past few years. To evaluate the selectivity of a new chiral ligand for allylic substitutions, the reaction usually performed is the transformation of *rac*-1,3-diphenylprop-2-enyl acetate[1] with dimethyl malonate in the presence of *N*,*O*-bis(trimethylsilyl)acetamide (BSA) and a base (Scheme 1) followed by analysis of product **2**.

Scheme 1



i. [Pd/L*], BSA, KOAc, CH_2Cl_2 or THF.

To perform asymmetric allylic substitution, Trost prepared highly efficient N,N´,P,P´-ligands[7] possessing a C_2-symmetric structure.

This article will deal with homodonor S,S-ligands and heterodonor P,S- and N,S-ligands.

Chiral S,S-ligands

Chiral homodonor ligands such as S,S-chelates (for example, **3**—**5**) gave only modest asymmetric induction for this transformation. Jansat *et al.*,[8] however, published recently high enantioselectivity by using bisthio ether

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** Laboratoire de Catalyse Moléculaire, Institut de Chimie Moléculaire et des Matériaux d´Orsay, Université Paris-Sud UMR CNRS 8075 — Bât 420 — 91405 ORSAY Cedex, France.

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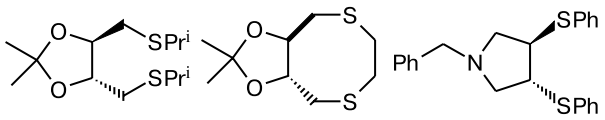
ligands with backbone rigidity. They prepared ligands containing a five-membered heterocyclic backbone such as *O*-isopropylidene or pyrrolidine. Some representative examples are shown below leading to up to 81% *ee*.

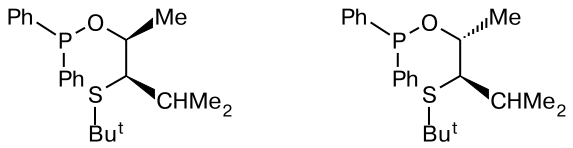


3 **4** **5**

L*	Time /days	Conversion of compound **1**	*ee* for **2**
		%	
3	7	74	27 (*R*)
4	1	100	42 (*S*)
5	7	100	81 (*S*)

Chiral P,S-ligands

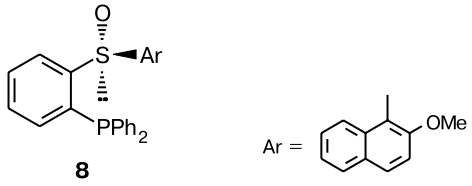
Much more examples are to be found in which S-containing heterodonor ligands are used to perform asymmetric allylic substitution processes. Thus Evans *et al.*[9,10] prepared a new class of mixed phosphorus/sulfur ligands incorporating a thioether and a diarylphosphinite moieties with strong donor heteroatoms. Ligands of the type **6** and **7** led to very efficient structures in terms of activity and enantioselectivity in the test reaction described above (see Scheme 1).



6 **7**

L*	Yield of product **2**	*ee* for **2**
	%	
6	93	91
7	97	98

The authors could furthermore prove the contribution of sulfur in the coordination of the palladium atom by X-ray study of crystals of these chiral organometallic complexes. Hiroi *et al.*[11] prepared and used chiral β-phosphino sulfoxides as ligands for the Tsuji—Trost reaction, the chirality being solely introduced by the chiral sulfoxide moiety. The authors prepared chiral *o*-phosphinophenyl sulfoxides from *o*-fluoroiodobenzene and readily available sulfinates. The chiral sulfoxide **8** was proven to be stable at room temperature, whereas a complete conversion in the corresponding phosphine oxide could be observed in refluxing THF. Performing the palladium-catalyzed asymmetric allylic alkylations (see Scheme 1) at low temperature allowed obtaining of the dimethyl malonate derivative **2** with high enantioselectivity (up to 82% *ee*) and good yield (71%). Here again, X-ray analyses proved the formation of a five-membered chelated palladium complex with coordination between the phosphino function and the sulfinyl group. Mechanism of catalysis by this complex was investigated.



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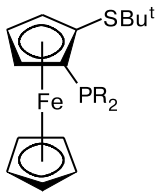
Another class of P,S-containing ligands (**9**) has been used in palladium-catalyzed allylic substitutions, the enantioselectivity being here introduced *via* the planar chirality of ferrocene derivatives.



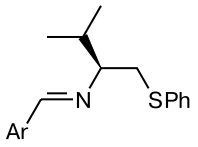
9a—d

L*	R	Yield of product **2**	*ee* for **2**
		%	
9a	Ph	92	93
9b	*p*-FC_6H_4	94	92
9c	*p*-$CF_3C_6H_4$	90	92
9d	2-Furyl	60	90

Carretero *et al.*[12] prepared 2-phosphino-1-sulfenylferrocenes starting from sulfinyl ferrocene by diastereocontrolled *ortho*-lithiation followed by phosphination. Subsequent reduction of the sulfoxide moiety to sulfide led to ligands **9**. These ligands provided the expected product[2] in the test reaction with good to excellent yields and enantioselectivities.

Chiral N,S-ligands

N,S-Chelates have been the most studied to perform the Tsuji—Trost reaction. Thus Anderson *et al.*[13,14] performed this catalytic reaction effectively by palladium complexes containing chiral imine—sulfide chelate ligands of the type **10**. The ligands were obtained easily in two steps from commercial amino alcohols. The ligating sulfur atom has a high affinity towards most metals useful in catalytic reactions, and particularly palladium.



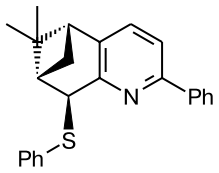
10a—d

L*	Ar	Yield of product **2**	*ee* for **2**
		%	
10a	Ph	86	89
10b	*p*-$NO_2C_6H_4$	77	82
10c	*p*-$MeOC_6H_4$	85	88
10d	*o*-ClC_6H_4	87	94

Up to 94% enantiomeric excess was obtained in this transformation. The authors were able to isolate and characterize a Pd-allyl intermediate by X-ray diffraction.[13,14] They proposed a possible mechanism of chirality transfer.

Chelucci *et al.*[15] significantly contributed to the development of chiral pyridine ligands for applications in asymmetric catalysis. They prepared sulfur-containing pyridine ligands and studied their efficiency to chelate palladium for catalyzed allylic substitution.

The ligands **11** and **12** were readily obtained in a two steps starting from (+)-pinocarvone.[15] Using two molar equivalents of ligands relative to the palladium precursor, the test Tsuji—Trost reaction was performed in good yields and high levels of asymmetric induction. Both epimeric ligands **11** and **12** gave a similar enantioselectivity but the opposite configuration of dimethyl 1,3-diphenylprop-2-enylmalonate, indicating that the stereodifferentiation is highly sensitive to the stereogenic center bonded to the sulfur.



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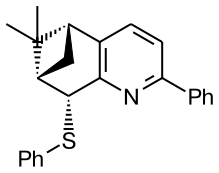
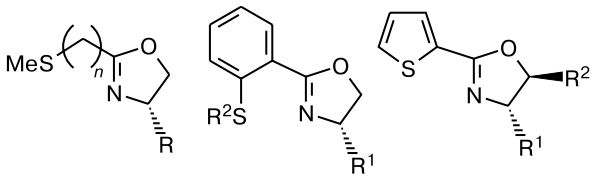


12

L*	Yield of product **2**	*ee* for **2**
	%	
11	90	83 (*R*)
12	85	78 (*S*)

Among N,S-chelates, sulfur-containing oxazoline ligands have been the most studied as regards their potential use in the Tsuji—Trost reaction. Williams prepared various S,N-ligands[16] (structures **13**—**15**) containing oxazoline functionalities and sulfur as an auxiliary donor ligand, in which the sulfur group was an alkyl sulfide,[17] an aryl sulfide[17] and a sulfide within a thiophene ring.[18]

Ligands **13**—**15** were obtained in good yields by the reaction of the appropriate nitriles with homochiral

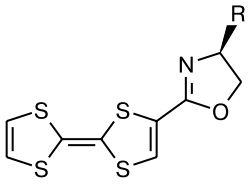


13a—c **14a—c** **15a—c**

L*	R^1	R^2	Yield of product **2**	*ee* for **2**
			%	
13a	Me	—	68	51
13b	Pr^i	—	74	70
13c	Bu^t	—	71	66
14a	Me	Me	91	40
14b	Bu^t	Me	86	80
14c	Bu^t	Ph	92	96
15a	Me	Ph	56	6
15b	CH_2Ph	H	68	24
15c	Pr^i	H	63	68

aminoalcohols. All the sulfanylmethyl-4,5-dihydrooxazoles (see structures **13**) are effective for the palladium-catalyzed allylic substitution. Up to 75% *ee* was obtained by using an excess of ligand **13c** relative to palladium (4 : 1). This suggests that the ligands do not coordinate palladium very strongly. The use of diaryl sulfide (**14c**) afforded the expected product with the maximum enantioselectivity level (96% *ee*) for this series. Variation in the ligand **15c** to Pd ratio increased both the yield and enantioselectivity of the reaction (**15c** : Pd = 10 : 1, 89% yield and 81% *ee*).

Bryce synthesized chiral oxazolines linked to tetrathiafulvalene[19] aiming at their use as redox-active ligands.

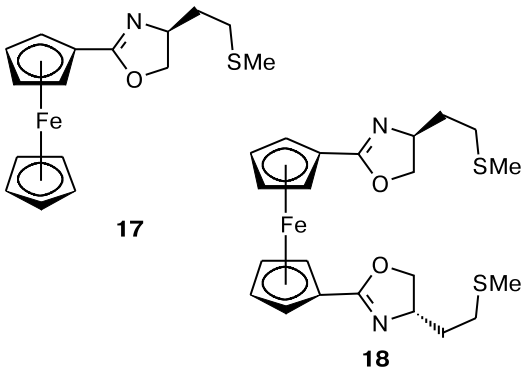


16a—c

L*	R	Yield of product **2**	*ee* for **2**
		%	
16a	Pr^i	29	21
16b	Ph	28	17
16c	Bu^t	Traces	—

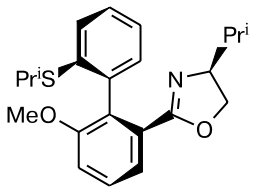
Low enantiomeric excesses were observed for these catalytic systems. A quasi-reversible interaction between a palladium source and **16a** was however proven by cyclic voltammetric measurements indicating that the binding of palladium to this ligand should be controlled electrochemically. However, for ligands **16** only a low level enantiomeric enrichment in **2** was achieved. The same authors improved later the activity, the enantioselectivity, and the electrochemical stability of this type of complex by the

synthesis of chiral ferrocenyloxazolines incorporating thio ether units (**17** and **18**).[20]

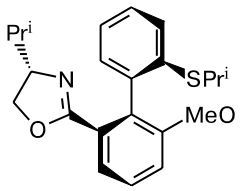


L*	Yield of product **2**	*ee* for **2**
	%	
17	98	93
18	93	91
18	93	91

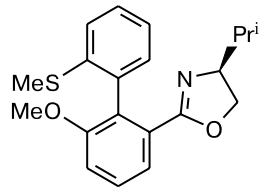
These redox-active ligand systems were successfully used in palladium-catalyzed allylic substitution reactions (up to 93% *ee*). The binding of palladium to these ligands has been successfully studied by cyclic voltammetry and proved to be reversible. This electrochemical behavior seemed promising to apply analogous catalysts in reactions where electrochemical recycling is the main step in the catalytic cycle.



(*S*,a*S*)-**19**



(*S*,a*R*)-**19**



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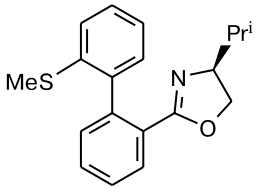


(*S*)-**21**

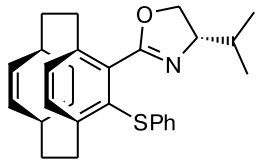
(*S*,a*R*) : (*S*,a*S*) = 17 : 83

L*	Time/h	Yield of product **2**	*ee* for **2**
		%	
(*S*,a*R*)-**19**	48	92	20 (*S*)
(*S*,a*S*)-**19**	96	Traces	—
20	72	90	74 (*S*)
(*S*)-**21**	48	93	82 (*S*)

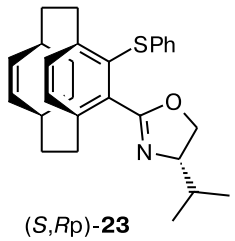
Chiral sulfur-containing oxazoline ligands were introduced by Ikeda *et al.*[21] in which the presence of a biphenyl backbone brought additional axial chirality. Chiral ligands with an axis-fixed (compounds **19** and **20**) and an axis-unfixed (compound **21**) biphenyl backbone were obtained in good yields by coupling reactions of methoxybenzene derivatives, substituted with achiral oxazoline, and sulfur-containing Grignard reagent.

Pure axial chiral ligands were tested in the palladium-catalyzed asymmetric allylic alkylation. Ligand **20**, present as a diastereomeric mixture, showed good yields and 74 % *ee*. Ligand (*S*)-**21** having a free rotation biphenyl axis was proven to afford only one of the two possible diastereomers, determined by ^{1}H NMR, on coordination with bis(acetonitrile)dichloropalladium(II). Consequently, the corresponding complex showed a higher catalytic activity (93%) and enantioselectivity (82%) for the test reaction.

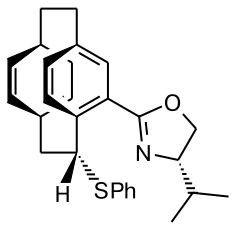
Hou *et al.*[22] reported the preparation of N,S-ligands **22**—**24** possessing planar and central chirality by modifying the paracyclophane backbone with oxazoline moieties.



(*S*,*S*p)-**22**



(*S*,*R*p)-**23**



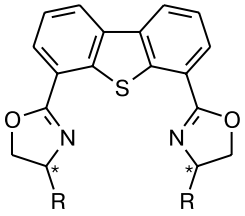
2-(*R*)-19-(*S*)-(*S*p)-**24**

L*	Time/h	Yield of product **2**	*ee* for **2**
		%	
22	32	98	54 (*R*)
23	21.5	98	63 (*S*)
24	1.5	98	94 (*S*)

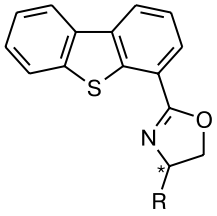
These new ligands catalyzed the Tsuji—Trost reaction to afford the substitution product in almost quantitative yield. Ligand **24** with two substituents at benzylic and benzene ring position gave the highest *ee* value (94%) and the highest reactivity.

We attempted to introduce new sulfur-containing oxazoline compounds[23,24] with dibenzothiophene and benzothiophene as backbones.

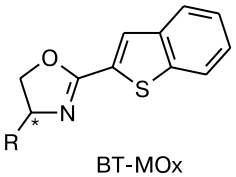
DBT-BOx **25** has been synthesized to allow potential *trans*-chelating tridentate ligands. DBT-MOx **26** and BT-MOx **27** provide different possibilities: the former can afford a six-membered chelate with the metal, whereas the latter may yield a five-membered chelate. All these new sulfur-oxazoline ligands have been prepared in overall good yields starting from the corresponding dibenzothiophene- or benzothiophene- (mono- or di-) carboxylic acids and commercially available amino alcohols: (*S*)-(+)-2-amino-3-methylbutan-1-ol (L-valinol), (*R*)-(−)-2-phenyl-glycinol and (*S*)-*tert*-leucinol.



DBT-BOx
25

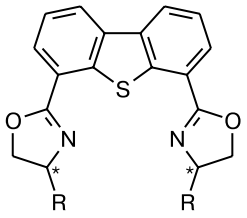


DBT-MOx
26



BT-MOx
27

Allylic substitution of *rac*-1,3-diphenylprop-2-enyl acetate with dimethyl malonate (see Scheme 1) was first investigated under various reaction conditions with DBT-BOx(Pr^i) **25a** as a chiral ligand. This ligand induced a high level of enantioselectivity (77% *ee*) and activity in the transformation, when the nucleophile was prepared in refluxing dichloromethane from BSA (*N*,*O*-bis(trimethylsilyl)acetamide) using allylpalladiumchloride dimer as a catalyst precursor. Under these conditions, (*R*)-dimethyl-1,3-diphenylprop-2-enyl malonate was isolated in 90% yield. Analogous ligands **25b** and **25c** were both less efficient and selective when the transformation was performed under these optimized conditions. We furthermore noticed that DBT-BOx **25a** containing chiral fragments with (*S*)-configuration led to the substitution product with (*R*)-configuration as the major isomer.

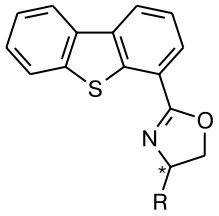


25a—c

L*	R	Time/h	Conversion of compound **1**	*ee* for **2**
			%	
25a	(*S*)-Pr^i	70	100	77 (*R*)
25b	(*R*)-Ph	120	39	28 (*S*)
25c	(*S*)-Bu^t	70	50	51 (*R*)

This is in contrast with results obtained by using other C_2-symmetric bis(oxazolines),[25—27] where (*S*)-configuration in the chiral ligand led to the (*S*)-product as the major compound. However, compared with the inefficiency of the dibenzofuran analogue to perform this palladium-catalyzed reaction,[28] we assume a probable participation of the sulfur atom for stabilizing the complex involved in the selective transformation.

These catalytic systems involving DBT-MOx compounds allowed the preparation of the desired product, albeit with a lower activity and enantioselectivity than those of the analogous bis(oxazoline) system **25**.



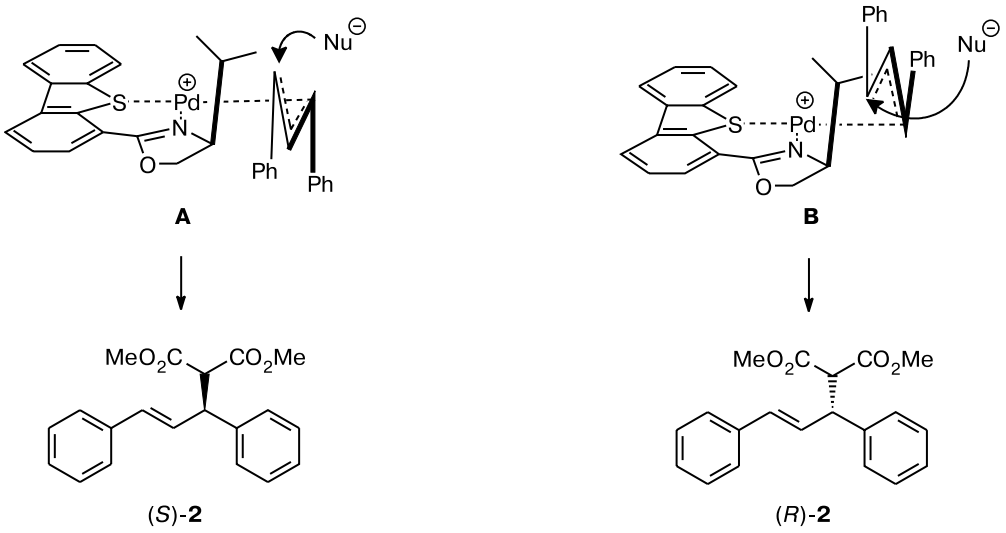
26a—c

L*	R	Time/h	Conversion of compound **1**	*ee* for **2**
			%	
26a	(*S*)-Pr^i	88	100	32 (*S*)
26b	(*R*)-Ph	112	80	34 (*R*)
26c	(*S*)-Bu^t	86	36	56 (*S*)

It was furthermore noticed that, contrary to DBT-BOx(Pr^i) **25a**, the monooxazoline **26a** led mainly to the (*S*)-enantiomer with 32% *ee*. We assumed steric and electronic effects to be both responsible for the observed configuration. Regarding the steric hindrance generated by the isopropyl substituent on the oxazoline group, the substrate was thus placed on the square-planar palladium complex, as depicted in Scheme 2. In such a context, the intermediate **A** would be favored compared to **B**, where the steric hindrance is greater between the substituent of the oxazoline ring and the phenyl group of the substrate.

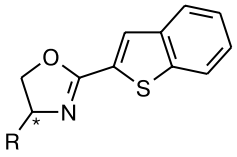
The incoming nucleophile is supposed to attack on the opposite face of the π-allyl system, *i.e.*, on the less-sterically hindered face. Dibenzothiophene acts as a π-donor. It is assumed that this electronic information would be transferred *via* the *trans*-effect to the allyl moiety. In our particular case, the nucleophile would thus preferentially attack the allylic system on the carbon possessing a greater positive charge character, *i.e.*, on the carbon situated *trans* to the nitrogen atom of the oxazoline moi-

Scheme 2



ety (DBT-MOx **26a**). DBT-MOx **26a** led indeed to (*S*)-**2** as the major enantiomer. On the contrary, and as expected by the above-mentioned mechanism, DBT-MOx **26b** possessing a phenyl group with (*R*)-configuration on the oxazoline, allowed the preparation of **2** with a similar enantiomeric excess (34 %) but with (*R*)-configuration.

Ligands BT-MOx **27** lead, however, generally to catalysts slightly less active than DBT-MOx.



27a—c

L*	R	Time/h	Conversion of compound **1**	*ee* for **2**
			%	
27a	(*S*)-Pr^i	115	100	13 (*R*)
27b	(*R*)-Ph	111	71	30 (*S*)
27c	(*S*)-Bu^t	115	78	13 (*S*)

Conclusion

Hence, the present review related to the use of chiral sulfur-coordinating ligands in the Tsuji—Trost reaction allows one to conclude that these ligands, first of all, S,S-, P,S-, or N,S-chelates, are effective to perform catalytic enantioselective C—C bond formations. Key advantages of these new types of ligands are their easy synthesis, mostly starting from readily available commercial compounds, and their stability, which facilitates the catalytic procedures. Moreover, the catalytic C—C bond formations remain a challenge in terms of activity, enantioselectivity, and catalyst loading and recycling. We may imagine that chiral sulfur-containing ligands have future for the development of the asymmetric heterogeneous or homogeneous-supported version of these reactions.

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