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Synthesis and characterization of enantiopure chiral NH_2/SO palladium complexes†

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A series of enantiopure chiral NH_2/SO palladium complexes have been synthesised with high yields by treating the corresponding *tert*-butylsulfinamide/sulfoxide derivatives with $Pd(CH_3CN)_2Cl_2$. The enantiopure chiral ligands were prepared by stereoselective addition of *tert*-butyl or phenyl methylsulfinyl carbanions to different *tert*-butylsulfinylimines. In all cases, coordination occurs with concomitant desulfinylation. X-ray studies of the Pd complexes showed a higher *trans* influence of the phenylsulfinyl group in comparison to that of the *tert*-butylsulfinyl group. Furthermore, we have obtained and characterised two possible palladium amine/sulfonyl complexes, epimers at sulfur, resulting from *N*-desulfinylation and coordination of palladium with both oxygens of the prochiral sulfonyl group. The catalytic activity and enantioselectivity of the new Pd(II) complexes of acetylated amine/*tert*-butyl- and phenylsulfoxides in the carboxylated cyclopropanes arylation reaction has been studied, obtaining the best results with the phenylsulfoxide ligand **25(S_C,S_S)** that produced the final arylated product in a 93 :7 enantiomeric ratio.

Introduction

Homogeneous transition-metal catalysis reactions are essential in various areas of modern synthetic chemistry. Proof of this is the high number of asymmetric catalytic reactions for industrial applications, such as the Takasago isomerization,[1] Sumitomo cyclopropanation,[2] or Sharpless epoxidation,[3] together with the now classic Monsanto asymmetric hydrogenation to produce L-DOPA.[4]

However, for much of the early 20th century, the reactivity and selectivity of all known homogeneous metal catalysts were lower compared to their heterogeneous and biological counterparts.[5] Despite advances made in this field to date, finding a catalyst that combines high catalytic capacity and high enantioselectivity at the same time for a wide range of chemical processes continues to represent a significant synthetic challenge.

Nowadays, palladium catalysts are an important tool in many syntheses because of the enormous versatility of this metal. Specifically, in asymmetric catalysis, palladium-catalyzed reactions have gained a prominent place in the synthesis of products of pharmacological and industrial interest.[6]

A large number of examples can be found in the literature concerning the application of Pd complexes in asymmetric catalysis, such as the reaction of arylboronic acids with *N*-benzylisatin derivatives[7] or cyclic *N*-sulfonyl imines,[8] the Carroll rearrangement,[9] C–H activation,[10] allylic etherification and amination,[11] or decarboxylative [4 + 2] cycloaddition.[12]

For this purpose, a plethora of different chiral ligands have been developed in asymmetric Pd-catalyzed reactions, such as the well-known binaphtyl phosphine, phosphine dioxide and phosphite ligands,[13] or the BINOL-phosphoric acid ligands,[14] chiral mono-*N*-protected aminoacids,[15] the bis-oxazoline ligands[16] or the tridentate P/C/P or N/C/N ligands.[17]

Our contribution in this field was originally focused on the development of carbohydrate-based ligands, such as *C*2-symmetric bis-thioglycoside-type ligands and sulfur–phosphorous mixed ligands, as precursors of chiral Pd complexes, and their applications in Pd-catalyzed allylic substitution reactions (with ee up to 90% and 96%, respectively) (Fig. 1).[18] More recently, in light of the good results obtained with the Sulfisox* ligand, a bidentate sulfinamide/sulfoxide-type ligand (Fig. 1), in the Rh(I) catalyzed enantioselective arylation reactions,[19] we considered the possibility of expanding its range of application in the asymmetric catalysis mediated by other metals such as Pd.

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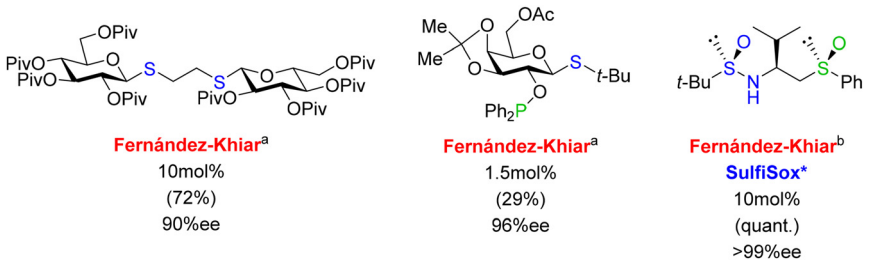


Fig. 1 Chiral bidentate sulfur ligands previously developed in our research group. [a] Allyl substitution reaction catalyzed by Pd. [b] Rh-catalyzed 1,4-addition of arylboronic acids to α,β-unsaturated carbonyl compounds.

Even if sulfinamide/phosphine[20] and sulfinamide/alcohol derivatives[21] have been described as bidentate ligand precursors of chiral Pd complexes, to the best of our knowledge, no sulfinamide/sulfur type bidentate chiral Pd complex, including sulfinamide/sulfoxide, sulfinamide/sulfone or sulfinamide/thioether derivatives, has previously been described, so it is interesting to approach their study.

Other types of bidentate sulfinamide/heteroatom ligands have been developed in Pd catalysis. Thus, among the sulfinamide/phosphine ligands represented in Fig. 2, it is worth highlighting *N*-Me-XuPhos[20a] and its sterically hindered analog *N*-Me-TY-Phos[22] in the enantioselective reductive Heck reaction and in the palladium-catalyzed asymmetric fluoroarylation of *gem*-difluoroalkenes, respectively, or PC-Phos[23] and its analog (PC-Phos analog) in the Pd-mediated enantioselective arylation of aryl and alkyl sulfenates[24] and in the chiral dearomatization of indole,[25] respectively. The Xiao-Phos ligand, previously used as an organocatalyst,[26] has provided high enantioselectivities in the asymmetric P–C cross-coupling reaction of secondary phosphine oxides and aryl bromides.[27] Interestingly, the sulfinamide/phosphanyl Riera–Verdaguer ligand[28] can behave as a P-monodentate or P/O or P/S bidentate ligand, depending on the nature of the Pd precursor and the reaction conditions used.[20d] Regarding the sulfinamide/alcohol derivatives, to our knowledge, there is only one example in the literature as a bidentate ligand, in the asymmetric allylic alkylation of ethyl 2-fluoroacetoacetate catalyzed by Pd, with high ee (94%) and chemical yield (90%).[21a,b]

Of special interest is the acetamide/sulfoxide ligand successfully developed by Colobert for the asymmetric C–H activation Pd catalyzed reaction, through a N/S coordination.[10b] This ligand can be considered structurally related to the aminosulfoxides previously developed by Pettinari as bidentate N/S ligands in Pd complexes.[29]

Results and discussion

Stereoselective synthesis of sulfinamide/sulfoxide ligands

In a previous work, we developed a series of sulfinamide/sulfoxide derivatives as chiral ligands in the Rh-catalyzed addition of arylboronic acids to activated ketones.[19] These ligands were obtained, by stereoselective additions of the corresponding racemic methylsulfinyl carbanions to *N*-*tert*-butylsulfinylimines, as pair of epimers at the sulfinyl sulfur, which were subsequently separated by column chromatography. In order to avoid this last chromatographic separation step, which in some cases is complicated and ineffective, in this work we have approached the preparation of this type of bidentate ligands in enantiopure form, by adding the corresponding *R* or

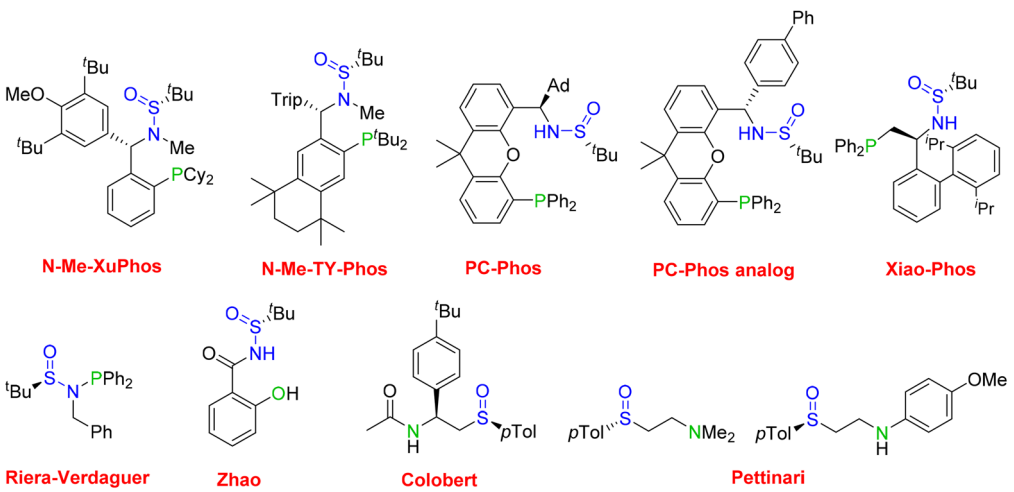
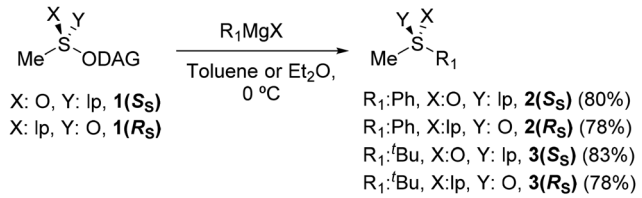


Fig. 2 Bidentate SON/heteroatom and SO/N ligands.

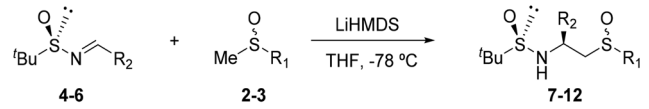


Scheme 1

S enantiopure methyl sulfoxides, previously obtained by applying the DAG methodology (Scheme 1),[30] instead of racemic.

The addition of the corresponding methylsulfinyl carbanions, generated by treating the enantiopure sulfoxides with LHMDS at low temperature in the presence of the sulfinylimines **4–6**, yielded the corresponding sulfinamide/sulfoxides (**7–12**) with good to excellent yields as a single diastereoisomer (Table 1). In order to determine the influence of the different nature of the substituents of the ligand on the formation of its palladium complexes, a series of aryl and alkyl derivatives differently substituted both in the chiral carbon (Ph, 2-Napht and ^{i}Pr) and in the sulfoxide function (Ph and ^{t}Bu) were easily prepared (Table 1).

Table 1 Synthesis of sulfinamide/sulfoxide ligands **7–12**



4-6 **2-3** **7-12**

Entry	Sulfinylimine	R_2	Sulfoxide	R_1	Ligand (SON/SO)	Yield (%)
1	**4**(R_S)	2-Naph	**2**(R_S)	Ph	**7**(R_S,S_C,R_S)	90
2	**4**(R_S)	2-Naph	**2**(S_S)	Ph	**7**(R_S,S_C,S_S)	94
3	**5**(R_S)	Ph	**2**(R_S)	Ph	**8**(R_S,S_C,R_S)	91
4	**5**(R_S)	Ph	**2**(S_S)	Ph	**8**(R_S,S_C,S_S)	89
5	**6**(R_S)	^{i}Pr	**2**(R_S)	Ph	**9**(R_S,S_C,R_S)	81
6	**6**(R_S)	^{i}Pr	**2**(S_S)	Ph	**9**(R_S,S_C,S_S)	91
7	**4**(R_S)	2-Naph	**3**(R_S)	^{t}Bu	**10**(R_S,S_C,R_S)	78
8	**4**(R_S)	2-Naph	**3**(S_S)	^{t}Bu	**10**(R_S,S_C,S_S)	68
9	**5**(R_S)	Ph	**3**(R_S)	^{t}Bu	**11**(R_S,S_C,R_S)	77
10	**5**(R_S)	Ph	**3**(S_S)	^{t}Bu	**11**(R_S,S_C,S_S)	65
11	**6**(R_S)	^{i}Pr	**3**(R_S)	^{t}Bu	**12**(R_S,S_C,R_S)	68
12	**6**(R_S)	^{i}Pr	**3**(S_S)	^{t}Bu	**12**(R_S,S_C,S_S)	66

In the obtained ligands, the configurations at both sulfurs (sulfinamide and sulfoxide) were unequivocally assigned based on the known configuration of both starting chiral products, (*R*)-*N*-*tert*-butylsulfinamide and the added (*R*)- or (*S*)-methyl sulfoxide. The configuration at the new chiral carbon can be predicted as *S* based on the known stereochemical control of the *tert*-butylsulfinyl group of the chiral *N*-*tert*-butylsulfinylimines in the nucleophilic additions to the imino double bond. This configurational assignment was confirmed by X-ray.

Synthesis of the complexes

Once the ligands were synthesized, we studied their capacity and mode of coordination with Pd(II). Assuming that the sulfoxide function is coordinated through sulfur,[10b,29,31] and taking into account the ambidentate character of the sulfinamido group, the coordination mode of these ligands with the metal in the catalyst, in principle, could take place by one of the three heteroatoms, S, O or N, thus generating bidentate N/S, S/S or O/S type ligands, the ring size of the chelate being 5, 6 or 7 members, respectively (Fig. 3).

In a previous work, we demonstrated that the Rh(I) catalysts obtained with these sulfinamide/sulfoxide ligands are S/S 6-membered type **II** chelates. However, a N/S coordination with a 5-membered type **I** chelates, similar to that described by Colobert group with the carboxamide/sulfoxide ligands, can also be considered in the case of the Pd(II) complexes with our sulfinamide/sulfoxide ligands, which would therefore imply two different coordination modes for them, S/S or N/S, depending on the nature of the metal.

To evaluate the ability of sulfinamide/sulfoxides **7–12** to form palladium complexes, they were treated with $PdCl_2(CH_3CN)_2$ as palladium precursor in methylene chloride as solvent. In all cases, the starting material was consumed after 48 h, and the ^{1}H-NMR spectra of the corresponding palladium complexes formed, which precipitated by adding ether, showed the disappearance of the singlet corresponding to the *tert*-butylsulfinyl group, indicating that the coordination occurs with concomitant *N*-desulfinylation (Table 2).

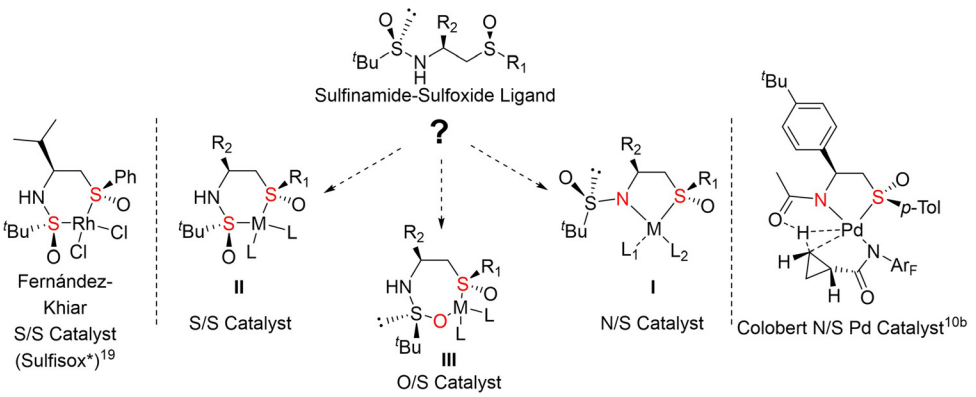
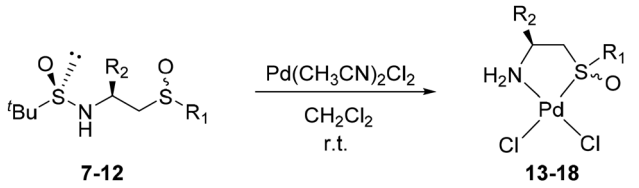


Fig. 3 Bidentate N/S, S/S and O/S ligands.

Table 2 Synthesis of palladium complexes **13–18**



Entry	Ligand (SON/SO)	R_2	R_1	Pd complex	Yield (%)
1	**7**(R_S,S_C,R_S)	2-Naph	Ph	**13**(S_C,S_S)	94
2	**7**(R_S,S_C,S_S)			**13**(S_C,R_S)	Quant.
3	**8**(R_S,S_C,R_S)	Ph	Ph	**14**(S_C,S_S)	96
4	**8**(R_S,S_C,S_S)			**14**(S_C,R_S)	Quant.
5	**9**(R_S,S_C,R_S)	^{i}Pr	Ph	**15**(S_C,S_S)	88
6	**9**(R_S,S_C,S_S)			**15**(S_C,R_S)	96
7	**10**(R_S,S_C,R_S)	2-Naph	^{t}Bu	**16**(S_C,S_S)	92
8	**10**(R_S,S_C,S_S)			**16**(S_C,R_S)	97
9	**11**(R_S,S_C,R_S)	Ph	^{t}Bu	**17**(S_C,S_S)	78
10	**11**(R_S,S_C,S_S)			**17**(S_C,R_S)	Quant.
11	**12**(R_S,S_C,R_S)	^{i}Pr	^{t}Bu	**18**(S_C,S_S)	95
12	**12**(R_S,S_C,S_S)			**18**(S_C,R_S)	80

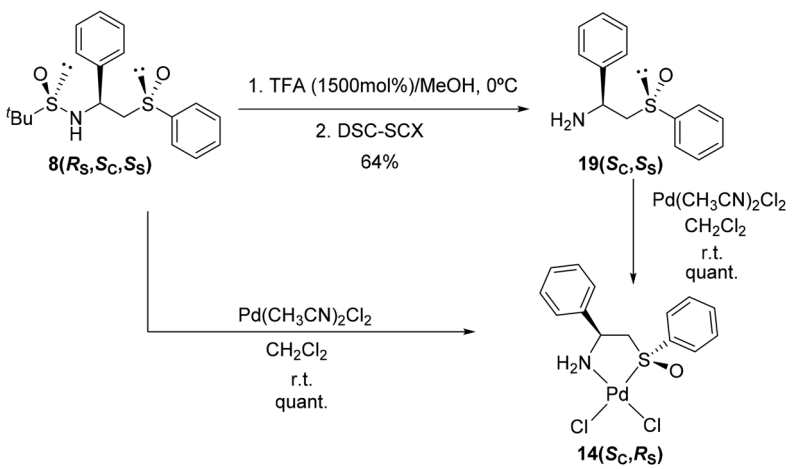
All **13–18** complexes were obtained in good purity with high yields, without the need of purification, by simple filtration. Complex formation also takes place in other solvents such as chloroform, THF and trifluoromethylbenzene, although in the latter case with a decrease in yield. On the contrary, the nature of the palladium precursor turns out to be decisive for the formation of the complexes, in such a way that these were only obtained by treating the ligands with $Pd(CH_3CN)_2Cl_2$, but the coordination does not take place with other palladium precursors such as $Pd(OAc)_2$, $Pd(cod)Cl_2$ or $Pd[(\gamma\text{-}C_3H_5)Cl_2]$. Finally, it was confirmed that the reaction is not affected by the presence of traces of moisture, acid or oxygen.

The reaction was also monitored in an NMR tube, observing in all cases the disappearance of the signal at 1.3 ppm of the *tert*-butyl of the sulfinamide, at the same time that two new singlets appeared at 2.0 and 1.6 ppm, corresponding to acetonitrile and to the product of desulfinylation, respectively. These last signals disappear when the solvent is removed *in vacuo*.

In order to confirm the structure proposed for the new palladium complexes, complex **14**(S_C,R_S) was also synthesized from the aminosulfoxide **19**(S_C,S_S) with $Pd(CH_3CN)_2Cl_2$ (Scheme 2). The amine ligand was previously obtained by *N*-desulfinylation of **8**(R_S,S_C,S_S) with TFA in methanol. The obtained complex presented identical spectroscopic characteristics to those of the complex **14**(S_C,R_S), obtained directly from the sulfinamide/sulfoxide (Scheme 2).

The X-rays of several of the complexes obtained confirmed the desulfinylation, obtaining in all cases 5-membered chelates where Pd is coordinated to the nitrogen of an amino group NH_2 and to the sulfur of the sulfoxide SOR (R: Ph, ^{t}Bu) (Fig. 4). While the NH signal of starting sulfinamide appears as a doublet at 4.8–4.9 ppm in the C-aryl-substituted ligands (**7**, **8**, **10** and **11**(R_S,S_C,R_S) and (R_S,S_C,S_S)) and above 4.0–4.2 ppm in the C-isopropyl-substituted ligands (**9** and **12** (R_S,S_C,R_S) and (R_S,S_C,S_S)), in the corresponding complexes two non-equivalent NH_2 proton signals are observed with a significant displacement difference, around 100–150 Hz, due to the conformational stiffness imposed by the chelate (Fig. 4).

In the five-membered chelate ring S1–C1–C2–N1–Pd1, the atom C2 occupies a more marked out-of-plane position. In the case of the phenylsulfoxides (**13–15**), regardless of the sulfur configuration, *S* or *R*, the carbon C2 is placed out of the plane in order to leave the substituent, Ph, 2-Napth or ^{i}Pr in a pseudo-equatorial position. However, in the case of the *tert*-butylsulfinyl derivatives (**16–18**), the C2 carbon is located out of the plane depending on the configuration of the sulfoxide, moving towards the opposite plane where the *tert*-butyl group attached to the sulfur is placed to avoid their interaction. This



Scheme 2

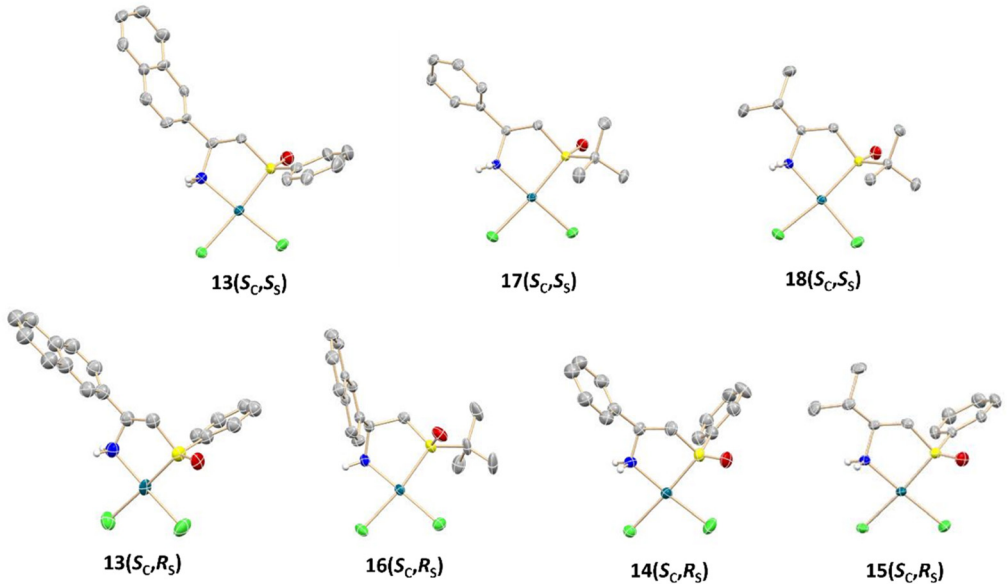


Fig. 4 X-rays of N/S palladium complexes.

forces the naphthyl group at C2 to adopt a pseudoaxial arrangement in the case of the **16(S_C,R_S)** complex, but allows the *tert*-butyl group to always be pseudoequatorial (Fig. 5).

A common feature of these chelates of Pd with the amine/sulfoxide bidentate ligands is to form pseudo-1D-polymeric structures in the crystalline solid state (Fig. 6). Pseudo-polymeric structures are formed through intermolecular hydrogen bonds between the $-NH_2$ of a Pd complex and the chlorine atoms of neighboring complexes, such that each complex binds to its two contiguous neighbors by means of a hydrogen donor group ($-NH_2$) on the one hand and a hydrogen acceptor group (–Cl) on the other. Other interatomic bonding forces likely intervene in crystal packing besides hydrogen bonds, but the latter must be the ones that mainly contribute to the linear pseudo-polymeric structure ordering.

Regarding the IR spectra of the complexes, the SO absorption associated to the sulfinamido group, which is present in the ligand, disappears in all of them and a shift of the absorption associated with the S–O vibration of the sulfoxide towards higher frequencies is observed, due to the coordination of the sulfinyl sulfur with the metal (Table 3). Concerning the ^{1}H-NMR shift of the ABX system, in contrast to the methylene protons which, as expected, are deshielded in all the complexes, methinic protons exhibit a different spectroscopic behavior depending on the sulfinyl configuration. Thus, no change in the chemical shift of methinic proton is observed in

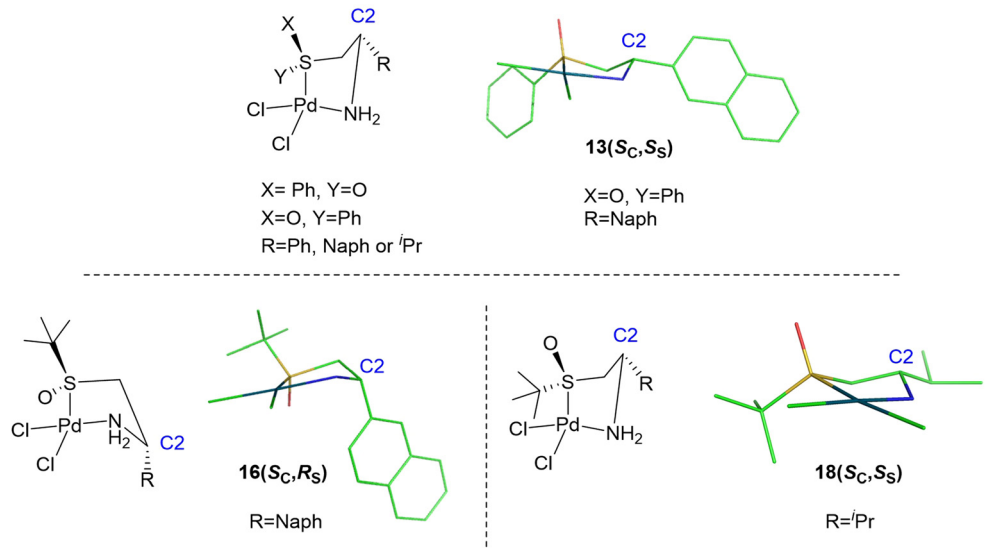


Fig. 5 C2 position at plane in the five-membered chelate ring S1–C1–C2–N1–Pd1.

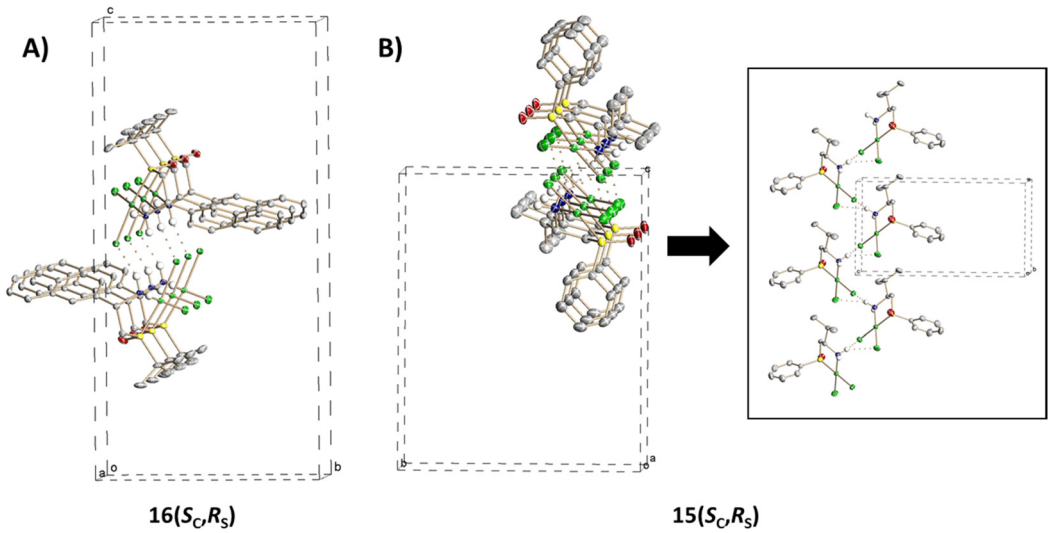


Fig. 6 Pseudo-polymeric structures formed by **16**(S_C,R_S) (A) and **15**(S_C,R_S) (B) complexes in the crystalline state.

Table 3 Differences between ligands (**7–12**) and the corresponding Pd complexes (**13–18**) in IR and ^{1}H-NMR spectrum

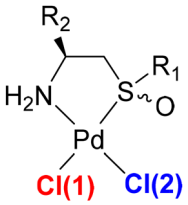
					$\Delta\nu$ (Hz) in ^{1}H-NMR		$\Delta\nu_{SO}$ (cm^{-1}) in IR		
							Ligand		Complex
Entry	R_2	R_1	Ligand (SON/SO)	Pd complex	Ligand	Complex	$\Delta\nu_{SON}$	$\Delta\nu_{SOX}$	$\Delta\nu_{SOX}$
1	2-Naph	Ph	**7**(R_S,S_C,R_S)	**13**(S_C,S_S)	157	77	1065	1020	1133
2			**7**(R_S,S_C,S_S)	**13**(S_C,R_S)	66	139	1064	1016	1133
3	Ph	Ph	**8**(R_S,S_C,R_S)	**14**(S_C,S_S)	150	61	1054	1016	1138
4			**8**(R_S,S_C,S_S)	**14**(S_C,R_S)	79	144	1074	1020	1125
5	^{i}Pr	Ph	**9**(R_S,S_C,R_S)	**15**(S_C,S_S)	56	128	1062	1017	1141
6			**9**(R_S,S_C,S_S)	**15**(S_C,R_S)	40	0	1066	1032	1129
7	2-Naph	^{t}Bu	**10**(R_S,S_C,R_S)	**16**(S_C,S_S)	171	169	1066	1002	1124
8			**10**(R_S,S_C,S_S)	**16**(S_C,R_S)	33	115	1071	1024	1102
9	Ph	^{t}Bu	**11**(R_S,S_C,R_S)	**17**(S_C,S_S)	172	156	1067	1026	1124
10			**11**(R_S,S_C,S_S)	**17**(S_C,R_S)	26	132	1056	1004	1115
11	^{i}Pr	^{t}Bu	**12**(R_S,S_C,R_S)	**18**(S_C,S_S)	60	0	1061	1026	1121
12			**12**(R_S,S_C,S_S)	**18**(S_C,R_S)	169	88	1064	1025	1121

the complexes of (S_C,R_S) configuration but it appears significantly shielded in the epimeric (S_C,S_S) complexes. Regarding the non-equivalence of the methylene protons, the same trend is observed in the protons of the AB system of the 1-aryl-substituted derivatives, both in the *tert*-butyl and in the phenyl sulfoxides, decreasing the non-equivalence in the complexes with *S* configuration in the sulfur, **13**(S_C,S_S), **14**(S_C,S_S), and **18**(S_C,S_S), (entries 1, 3 and 11, Table 3) and increasing in complexes with *R* configuration at the sulfinyl group, (**13**(S_C, R_S), **14**(S_C,R_S), **16**(S_C,R_S) and **17**(S_C,R_S), (entries 2, 4, 8, and 10, Table 3).

It can also be observed in these complexes the greater "*trans* influence" of the phenylsulfoxide on the chlorine in *trans*, with a slightly longer Pd–Cl(1) bond length (less strong bond), than that exerted by the amine on its chlorine in *trans* Pd–Cl(2) (stronger bond) (entries 1–4, Table 4).

It's important to note that the *trans* influence of the phenylsulfinyl group is just one factor among many that influence the catalytic activity and enantioselectivity of Pd(II) complexes, but it can have significant implications. In general, by understanding and leveraging the *trans* influence, you can design catalysts that promote specific reactions with high selectivity for a desired enantiomer. In our case, the *trans* influence of the phenylsulfinyl group can affect the ligand coordination and stability of the complex. The phenylsulfinyl ligand coordinates to the Pd(II) center forming a coordination complex where the *trans* influence of the phenylsulfinyl group can strengthen the metal–ligand bond, enhancing the stability of the complex.

Table 4 Pd-heteroatom bond lengths in synthesized Pd complexes **13–18**



				Bond lengths (Å)				
Entry	R_2	R_1	Pd complex	Pd–N	Pd–S	*d*1 Pd–Cl(1)	*d*2 Pd–Cl(2)	*d*1 − *d*2
1	2-Naph	Ph	**13**(S_C,S_S)	2.0780	2.1929	2.3380	2.2989	0.0391
2			**13**(S_C,R_S)	2.0700	2.2020	2.3070	2.2820	0.0250
3	Ph	Ph	**14**(S_C,R_S)	2.0450	2.2060	2.3260	2.2870	0.0390
4	^{i}Pr	Ph	**15**(S_C,R_S)	2.0470	2.1993	2.3177	2.2953	0.0224
5	2-Naph	^{t}Bu	**16**(S_C,R_S)	2.0340	2.2265	2.2965	2.3042	−0.0077
6	Ph	^{t}Bu	**17**(S_C,S_S)	2.0426	2.2333	2.3090	2.3014	0.0076
7	^{i}Pr	^{t}Bu	**18**(S_C,S_S)	2.0441	2.2336	2.3086	2.3046	0.004

This effect is not maintained in the case of the sterically hindered *tert*-butylsulfinyl group, where both Pd–Cl bond lengths present more similar values (entries 5–7, Table 4). As expected, the Pd–S bond lengths are shorter in the phenylsulfinyl derivatives than in the *tert*-butylsulfinyl analogs (entries 1–4 *vs.* 5–7, Table 4). It can be explained by considering the electronic and steric effects of the ligands on the metal center.

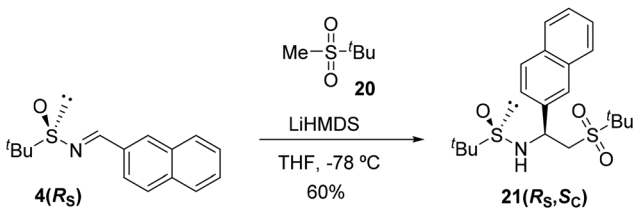
The observed higher *trans* influence of the phenylsulfinyl group could be attributed to its stronger electron-donating ability compared to the *tert*-butylsulfinyl group. The electron-donating nature of the phenyl group can result in increased electron density around the metal center, stabilizing the metal–ligand bond and enhancing the *trans* influence. Thus, the Pd–Cl bond *anti* to the PhSO group is longer than the other one in the complex.

It's important to consider that the *trans* influence can also be affected by various factors, including steric factors. The bulky *tert*-butylsulfinyl group may hinder the approach of sulfur to the metal center, generating a weaker long Pd–S bond consequently. Thus, the *trans* influence of the *t*BuSO group turns out to be like that of the NH_2 group and therefore the Pd–Cl bond lengths for both Cl are also similar.

Sulfinamide/sulfone: ability and coordination mode

In order to determine the influence of the ligand structure on the *N*-desulfinylation process observed during the coordination of the sulfinamide/sulfoxide ligands with the Pd(II) precursor, we prepared other sulfinamide/sulfur derivatives as an analog bidentate ligand with a sulfur function in different oxidation state (sulfone, **21**(R_S,S_C)) as the second coordinating element to the metal, as indicated in Scheme 3.

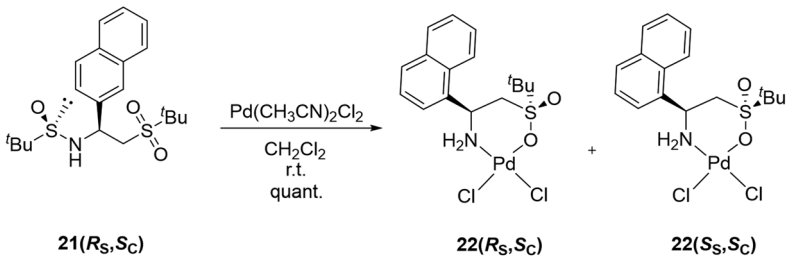
The addition of the methyl sulfonyl carbanion was carried out under identical conditions to those previously described for the sulfinyl carbanion, by dissolving the imine **4**(R_S) and the methyl *tert*-butyl sulfone **20** in THF in the presence of LHMDS at −78 °C. The reaction also occurs in this case in a completely stereoselective manner, obtaining the product of the addition of the nucleophile through the least hindered side of the C=N double bond of the *N*-sulfinylimine (Scheme 3).



Scheme 3

Treatment of the sulfinamide/sulfone ligand **21**(R_S,S_C) with $Pd(CH_3CN)_2Cl_2$ yielded, after stirring for 3 days, a 65 : 35 mixture of two diastereoisomeric palladium complexes, epimers in the sulfur, **22**(R_S,S_C) and **22**(S_S,S_C) (Scheme 4), resulting from the coordination by each one of the sulfonylic oxygens. The coordination was found to proceed again with concomitant desulfinylation, as previously confirmed by monitoring the course of the reaction by NMR, thus eliminating the possibility of *N*-desulfinylation because of the process of treating the reaction and isolating the complex. The high-resolution mass spectrum confirmed the structure of both complexes.

In contrast to the well-known donor properties of the sulfinyl group, sulfones are very weak donors and show very limited coordination chemistry. In this sense, only a few examples of sulfone complexes have been described and structurally characterized.[32] Interestingly, the preferential coordination of one of the sulfonyl oxygens from sulfonamides to magnesium and copper has also been described (Fig. 7).[33] This coordination proved to be not strong enough to allow the isolation of the corresponding complexes.



Scheme 4

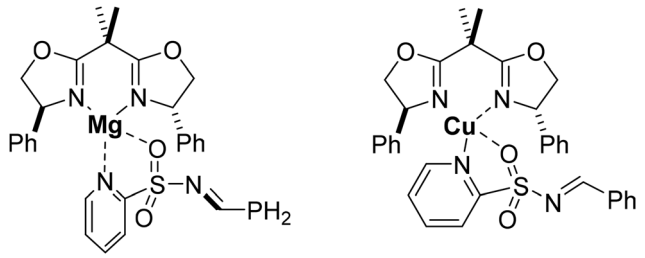


Fig. 7 Proposed structures for magnesium sulfonamide (left) and copper sulfonamide complexes (right).[32]

In our case, due to the low coordination ability of the sulfonyl group, the complexes obtained from sulfone **21**(R_S,S_C) were relatively labile and readily hydrolyzed by moisture with release of the free ligand. Thus, attempts to crystallize the complex were unsuccessful. Instead, crystals of the ammonium salt of the free ligand were obtained (Fig. 8). It should be noted that the counterion of this ammonium salt is the *tert*-butane sulfonate, which implies a sulfinamide sulfur oxidation and not a simple hydrolysis during the desulfinylation process.

Desulfinylation of sulfinamides–sulfoxides *via* palladium complexes as key intermediates. Available methods described in the literature for carrying out the removal of the sulfur-containing fragment in sulfinamides often deal with severe reaction conditions, like acidic[34] or basic[35] hydrolysis, acid catalyzed alcoholysis to sulfinates[36] or through nucleophilic displacement with amides or organolithium reagents.[37] Some milder methods, as the use of a periodinane reagent, the reaction with thiols associated to Lewis acid[38] or the halogenating action of the oxophilic phosphorus reagent $(PhO)_3PCl_2$ have been developed as an option for performing the *N*-desulfinylation when sensitive functionalities are present everywhere in the substrates.

In view of the observed desulfinylation promoted by Pd in the coordination of our ligands, the possibility of applying these conditions as a *N*-desulfinylation method of sulfinamides aroused our interest. A comparative study between the classic desulfinylation conditions by treatment with TFA in methanol (method A) and by treatment with $PdCl_2(CH_3CN)_2$ followed by TMEDA (method B) was achieved, and the results are collected in Table 5.

In the so-called "method A", after stirring for several days, the corresponding amines were obtained in moderate to good yields (46 to 88% yield, Table 5). The results obtained show the influence of steric effects of the R_2 substituent on the reaction yield, obtaining the lowest yield in the case of the bulkier alkyl substituent ^{i}Pr, with a longer reaction time (entry 4, Table 5).

Regarding "method B", it consists of the treatment with TMEDA of the desulfinylated palladium complex, obtained in a first stage, to release the corresponding amino sulfoxide through a ligand exchange. Even though it is a two-step process, the overall yields are higher in all cases than those obtained with the classical method A, ranging between good (78%, entry 1, Table 5) and quantitative (entry 3, Table 5) yields.

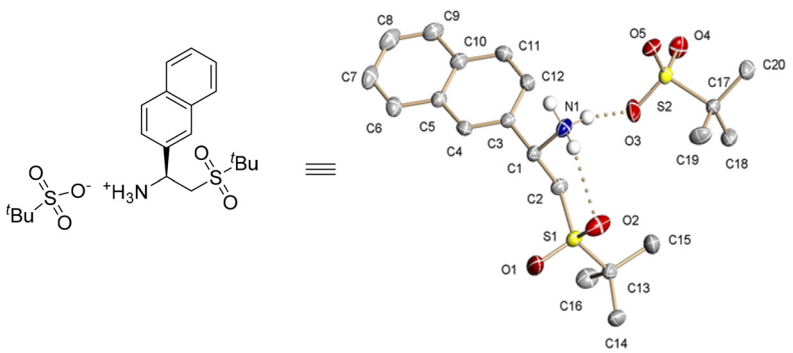
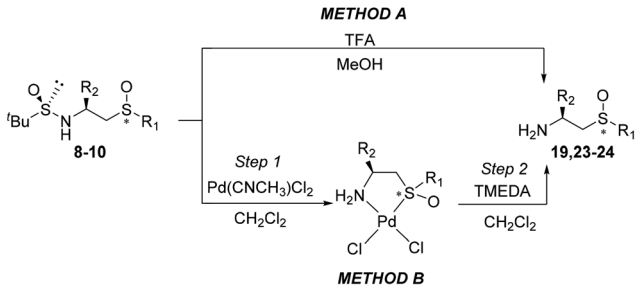


Fig. 8 Crystals of the ammonium salt obtained from desulfinylation of **21**(R_S,S_C).

Table 5 Synthesis of amine/sulfoxides (**19, 23–24**) by *N*-desulfinylation of sulfinamide/sulfoxides (**8–10**)



				Method A		Method B			
						Step 1		Step 2	
Entry	R_2	R_1	Product (NH_2/SO)	t_R (h)	Yield (%)	t_R (h)	Yield (%)	t_R (h)	Yield (%)
1	2-Naph	^{t}Bu	**24(S_C,R_S)**	120	62	48	92	1	85
2	2-Naph	^{t}Bu	**24(S_C,S_S)**	120	88	24	97	1	Quant.
3	Ph	Ph	**19(S_C,S_S)**	48	64	48	Quant.	1	Quant.
4	^{i}Pr	Ph	**23(S_C,R_S)**	168	46	48	88	1	Quant.

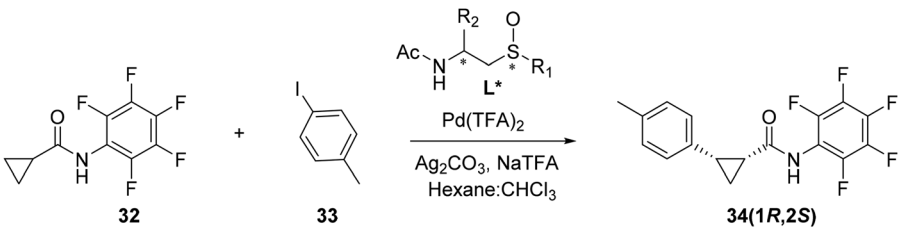
Asymmetric Pd-catalyzed arylation of cyclopropane carboxylic acid derivative

Given the versatility of our synthetic approach, it has been possible to prepare a wide range of amino/sulfoxides with different steric and electronic characteristics. These, through simple acetylation, lead us to the corresponding acetamido/sulfoxides whose catalytic capacity in the reaction of arylation of cyclopropane carboxylic acid derivative mediated by Pd has been previously demonstrated (Table 6).

Regrettably, the precursor sulfinamide/sulfoxides ligands have not shown significant catalytic activity in these reactions, obtaining the cyclopropane arylation product in racemic form, with low conversion percentage.

According to the previous published results,[10b] the stereochemical course of the reaction is controlled by the configuration of the chiral carbon present in these ligands (compare entries 1 and 2, Table 6), and the best stereoselectivity is obtained with the ligand being substituted on said carbon with a *p-tert*-butylphenyl group (entry 3, Table 6). Regarding

Table 6 Pd catalyzed arylation of cyclopropane carboxylic acid derivative **32**



Entry[a]	Ligand (AcNH/SO)	R_2	R_1	T (°C)	Conversion (%)	er (1*R*,2*S*)/(1*S*,2*R*)
1	**28(S_C,R_S)**	Ph	*p*-Tol	110	80	85 : 15
2	**29(R_C,R_S)**	Ph	*p*-Tol	110	85	15 : 85
3	**30(S_C,R_S)**	*p*-^{t}Bu-C_6H_4	*p*-Tol	80	75	94 : 6
4	**31(S_C,R_S)**	2-Naph	*p*-Tol	110	80	90 : 10
5	**31(S_C,R_S)**	Ph	^{t}Bu	110	15	nd
6	**25(S_C,S_S)**	Ph	Ph	80	42	93 : 7
7				110	54	91 : 9
9	**26(S_C,R_S)**	^{i}Pr	Ph	80	28	75 : 25
10				110	46	81 : 19
11	**27(S_C,R_S)**	2-Naph	^{t}Bu	110	36	57 : 43
12	**27(S_C,S_S)**	2-Naph	^{t}Bu	80	nc	—
13				110	34	65 : 35

[a] Entries 1–5: data extracted from ref. 10*b*.

the influence of the substituent on sulfur, the enantiomer ratio obtained with different *p*-tolylsulfinyl derivatives as chiral ligands has been described and a single example of *tert*-butylsulfoxide is mentioned but the stereoselectivity of the process, which occurs with low conversion percentage (15%, entry 5, Table 6), is not indicated. Therefore, in order to determine the influence of sterically hindered sulfinyl groups, as the *tert*-butyl sulfinyl group, on the stereochemical course of the process, we decided to explore our chiral ligands on the enantioselectivity of the Pd-catalyzed arylation and optimize the conversion percentage as much as possible. The results obtained using the acetamide/sulfoxides **25**(S_C,S_S), **26**(S_C,R_S), **27**(S_C,S_S) and **27**(S_C,R_S) as chiral ligands, obtained by acetylation of the amino/sulfoxides **19** (S_C,R_S), **23**(S_C,S_S), **24**(S_C,S_S) and **24**(S_C,R_S) respectively, are indicated in Table 6.

Given that in our ligands, the configuration of the stereogenic carbon is maintained as *S*, the enantioselectivity obtained in the catalytic arylation process always runs in the same sense, in favor of the (1*R*,2*S*) stereoisomer, as confirmed by HPLC.

An increase in temperature, from 80 to 110 °C, leads to an increase in conversion and the enantioselectivity is not significantly modified (compare entries 6 *vs.* 7, Table 6) or slightly increases (compare entries 9 *vs.* 10, Table 6). The Pd(II) complexes with the phenylsulfinyl ligand can activate substrates for catalytic reactions. The *trans* influence can affect the activation process by modulating the electron density and electronic properties of the metal center. This activation step is crucial for facilitating the desired chemical transformation and, in our case, a π-stacking interaction of the phenyl group with the aromatic ring of the substrate must also be considered. Moreover, the *trans* influence of the phenylsulfinyl ligand can bias the orientation and reactivity of the substrates, favoring the cyclopropane ring to be arranged in *anti* with respect to the PhSO group in the Pd(II) complex. Thus, the cyclopropane ring of the substrate is located in the vicinity of the carbonyl of the ligand amide that should exert its effect as a base. This arrangement is necessary for activation of the CH bond of the cyclopropane ring to take place.

Thus, yields and enantioselectivities obtained with the complexes derived from *tert*-butyl sulfoxides are lower than those previously described with the *p*-tolyl sulfoxides, but the reaction proceeds with higher stereoselectivity in the case of the phenylsulfinyl ligand **25**(S_C,S_S) (compare entries 6 and 7 *vs.* entry 1, Table 6).

With regard to the influence of the chiral carbon, an increase in steric volume associated with changing the Ph by an ^{i}Pr group in ligand **26**(S_C,R_S) leads to a decrease in enantioselectivity (compare entries 9 and 10 *vs.* 6 and 7, respectively, Table 6). Finally, it should be noted that er very similar are obtained with ligands **30**(S_C,R_S) and **25**(S_C,S_S), (entries 3 and 6 respectively in Table 6), so the substitution at position 4 of the aromatic ring (^{t}Bu *vs.* H, respectively) does not seem to be a determining factor in the enantioselectivity of the process.

Conclusions

This paper describes the preparation and structural characterizations of a series of enantiopure amine/sulfoxide palladium complexes obtained by treatment of sulfinamide/sulfoxides with $PdCl_2(CH_3CN)_2$. In all cases coordination took place with concomitant desulfinylation. A similar behavior was observed in the case of the sulfone precursor, obtaining the two possible amine/sulfone palladium complexes, epimers at sulfur. These were spectroscopically characterized, and the structure of both complexes confirmed by the high-resolution mass spectrum.

Starting from the *N*-sulfinamide/sulfoxide, a simple ligand exchange of its *N*-desulfinylated palladium complex enables us to obtain the corresponding free aminosulfoxide, thus offering a potentially interesting choice for performing *N*-desulfinylation when sensitive functionalities are present in the substrates.

The acetylated ligands were applied to the Pd-catalyzed arylation reaction, and the influence of temperature and steric factors were studied. The best results were obtained with the phenylsulfoxide ligand **25**(S_C,S_S) which yielded the final arylated product in a 93 : 7 enantiomeric ratio.

X-ray crystallographic studies have shown a higher *trans* influence of the phenylsulfinyl group compared to that of the *tert*-butylsulfinyl group which is very similar to that of the amine group. This finding is important for our ongoing work aimed at designing effective and selective catalysts, where the modulation of the *trans* influence can be decisive for achieve an enantioselective catalytic process. Finally, a common feature of these chelates of Pd with the amine/sulfoxide bidentate ligands is to form pseudo-1D-polymeric structures in the crystalline solid state.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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