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**tert-Butanesulfinamides as Nitrogen Nucleophiles in Carbon–Nitrogen Bond Forming Reactions**

Johana Ramirez Hernandez, Fabrice Chemla, Franck Ferreira, Olivier Jackowski, Julie Oble, Alejandro Perez-Luna*, and Giovanni Poli

Abstract: The use of tert-butanesulfinamides as nitrogen nucleophiles in carbon–nitrogen bond forming reactions is reviewed. This field has grown in the shadow of the general interest in N-tert-butanesulfinyl imines for asymmetric synthesis and occupies now an important place in its own right in the chemistry of the chiral amine reagent tert-butanesulfinamide. This article provides an overview of the area and emphasizes recent contributions wherein the tert-butanesulfinamides act as chiral auxiliaries or perform as nitrogen donors in metal-catalyzed amination reactions.

**Keywords:** Amination · tert-Butanesulfinamide · Chiral nucleophiles

1. Introduction

Chiral amine reagent tert-butanesulfinamide (I) has received massive attention over the last decade and has found applications in an ever-increasing number of research areas. In the field of asymmetric synthesis, it is now a well-established tool for the preparation of chiral non-racemic amines. Rapid access to both enantiomeric forms of tert-butanesulfinamide, high levels of stereodiscrimination and easy removal of the sulfinyl moiety under mild acidic conditions constitute major advantages to the use of the tert-butanesulfinyl group as chiral auxiliary on nitrogen. Asymmetric synthesis of enantiopure chiral amines using tert-butanesulfinamidine usually follows a well-established pattern that entails condensation with a carbonyl derivative and a subsequent reaction at the electrophilic carbon atom of the N-sulfinyl imine thereby produced (Scheme 1, A).[1]

In this context, the performance of tert-butanesulfinamides as nitrogen nucleophiles raises increasing interest. On the one hand it represents a possibility to elaborate further the α-branched amines produced from additions to N-tert-butanesulfinyl imines (Scheme 1, A). On the other hand, a number of recent reports have evidenced that tert-butanesulfinamides can perform as chiral nitrogen nucleophiles in nucleophilic amination reactions producing a new stereocenter, and that stereoinduction is possible with excellent levels of diastereoselectivity (Scheme 1, B). The purpose of this article is to showcase the possibilities offered by the use of tert-butanesulfinamides as nitrogen nucleophiles in asymmetric synthesis and to emphasize the recent contributions wherein the sulfinyl moiety acts as chiral auxiliary.

The combination of the steric bulk of the tert-butyl moiety and the electron-withdrawing effect of the positively charged sulfur atom means that the tert-butanesulfinyl group attenuates considerably the nucleophilicity of the nitrogen atom of tert-butanesulfinamides. Leaving aside the above-mentioned condensation reactions with aldehydes and ketones that have been reviewed previously and will not be discussed here, reactions with carbon electrophiles are essentially of two types: (i) those that rely on the intermediate formation of a main-group metal amide and (ii) those, less common, that involve a transition-metal catalyzed process.

2. Reactions Involving Metallated N-tert-Butanesulfinamides as Nucleophiles

Main-group anions of tert-butanesulfinamide (I) and its N-substituted congeners react readily with an array of carbon electrophiles. Their good resistance to

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*Scheme 1. Uses of tert-butanesulfinamides as nucleophiles in asymmetric synthesis.*
racemization makes them privileged intermediates to carry out N-functionalization without losing the chiral information on the sulfur atom. Strategies for N-alkylation and N-acylation have been developed as well as aza-Michael reactions.

2.1 N-Alkylation of tert-Butanesulfinamides

N-alkylation of tert-butanesulfinamides can be achieved by deprotonation and electrophilic trapping of the corresponding metal amide with alkyl halides. In the case of tert-butanesulfinamide (1), the process is complicated by competitive dialkylation and, even if treatment with KOH can be a solution to obtain N-monoalkylation,[12,13] reductive amination approaches are generally preferred.[17] The strategy is thus most useful for the functionalization of N-substituted tert-butanesulfinamides. Not only are these products widely accessible through nucleophilic addition or reduction of tert-butanesulfinyl imines, but also introduction of a second nitrogen substituent is not possible by reductive amination.

Metalation of N-alkyl tert-butanesulfinamides can be carried out conveniently using mainstream strong bases such as KH, NaH, LiHMDS, KHMD or nBuLi. The most used solvents are THF or DMF and often the reactions are performed at temperatures higher than –30 °C. Regioselective N-alkylation is generally obtained, but the competitive S-alkylation might hamper the process in the case of substrates where the sulfinyl nitrogen is sterically hindered.[14]

2.1.1 Intermolecular N-Alkylation Reactions

Reports on intermolecular N-alkylation reactions of metallated tert-butanesulfinamides with non-activated alkyl halides other than methyl iodide[15] are rare.[6] By contrast, allylic and propargylic halides are well-suited electrophiles that permit intermolecular alkylation and propargylation reactions that are particularly important from an applicative point of view. First they open up possibilities for subsequent rapid construction of nitrogen heterocycles which are useful both for target-orientated[7,8] and diversity-oriented synthesis.[9] Second, N-allyl tert-butanesulfinamides have been recently uncovered as valuable chiral ligands in the context of transition-metal enantioselective catalysis.[10]

2.1.2 Intramolecular N-Alkylation Reactions

Base-mediated intramolecular N-alkylation of tert-butanesulfinamides is a synthetically useful reaction that has received significant attention because it gives straightforward access to chiral substituted nitrogen heterocycles in enantio-merically pure form. For most of the reported examples, the cyclization precursors are α-branched sulfinamides obtained from N-tert-butanesulfinyl imines and, with the notable exception of aziridine formation, the carbon undergoing substitution is primary. Heterocyclizations leading to the formation of rings ranging from 3 to 7 members have been accomplished and a rather large variety of reagents and conditions have been described (Scheme 2).

A possible reason for this is the absence of a truly general cyclization method and the fact that, quite often, ring closure for a given substrate-type or cyclisation mode only proceeds under precise experimental conditions (base, solvent, temperature, …). Thus, the correct choice of these conditions is a key element to achieve the desired transformation.

Cyclization of β-chloro N-tert-butanesulfinamides to aziridines is a favorable reaction that has been achieved at high temperature by treatment with KOH in H2O/THF[11] as illustrated with the preparation of 2 (Scheme 2). K2CO3 in acetone, as shown with 3,[12] or nBuOK in iPrOH[13] leaving

With stronger bases such as NaHMDS[14] or LiHMDS[15] in DMF, ring-closure has been obtained at much lower temperatures (~40 °C) as for the formation of 4.

The preparation of diazaspiron[3,3]heptane 5[16] by intramolecular alkylation triggered with nBuOK in THF, evidences that four-membered heterocyclization is also possible with tert-butanesulfinamide nucleophiles, but such reactions are not common. By contrast, five-membered ring formation by displacement of a halide leaving group is far more usual and has been implemented in several ways (Scheme 2). It has been accomplished either at 50 °C by treatment with KOH in H2O/THF[17] or nBuOK in iPrOH,[18] or at room temperature in THF using LiHMDS[19] (see the formation of 6), KHMD,[9] or a combination of NaH and a crown ether additive (15-Crown-5).[20] As illustrated with 7, the latter conditions are tolerant of functionalized substrates. It is also noteworthy that efficient pyrrolidine formation has been described by intramolecular displacement of mesylate[21] or tosylate[22] leaving

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Scheme 2. Representative examples of heterocyclization by intramolecular N-alkylation of tert-butanesulfinamides with halides and related leaving groups.
groups in the presence of either tBuOK, as for the formation of 8, or NaH.

In the case of six-membered ring construction, the use of NaH as base has been privileged (Scheme 2). Again, it has been used in combination with 15-crown-5, in THF at room temperature, to prepare functionalized piperidines like 9.[23] However, in solvents with higher polarity, similar cyclizations have been accomplished without the crown ether additive. For instance, the formation of tetrahydroisoquinolines such as 10 has been achieved in DMF at room temperature.[24] and 3-substituted piperidines like 11 have been prepared in DMSO at 80 °C.[25]

Finally, even though ring closure to afford seven-membered rings is not always straightforward,[186] azepane formation has been reported by intramolecular displacement of a bromide following deprotonation with KHMS,[13] as in the case of 12, as well as by displacement of a tosylate leaving group using NaH (formation of 13).[26]

A notable aspect of these intramolecular N-alkylation reactions is that it is possible to embed them in one-pot tandem sequences that entail the addition of an organometallic reagent on a N-tert-butanesulfinyl imine and the subsequent ring closure of the metal amide produced. Such transformations have been achieved by introducing a suitable leaving group for the alkylation step (usually a halide) either on the imine undergoing the condensation or in the nucleophile used.

Aziridine synthesis has received considerable attention in this context and has been accomplished following the two possible approaches (Scheme 3). On the one hand (A), α-chloro N-tert-butanesulfinyl imines have been reported to provide the corresponding aziridines upon reaction with organomagnesium[14a,27] and organocerium[28] reagents, as well as with KCF₂SO₃Ph.[29] On the other hand (B), aza-Darzens-type condensations between carbendol reagents and N-tert-butanesulfinyl imines have been disclosed with a rather large array of carbamions. These include: lithiated halomethylphosphonates like 14,[30] zinctated propargylalcohols and allylic bromides 15[31] and 16,[32] a lithiated (chloroethyl)oxazoline,[33] lithiated amines such as 17[34] lithiated halomethanes 18 and 19,[35] the sodium amions of bromoform,[36] chloroform[14] and halo methylsulfones (i.e. 20)[37] and the lithium or potassium anions of dihalo methanes (21).[38] It is also important to mention that condensation of sulfur ylides[39] as well as tellurium ylides[40] with N-tert-butanesulfinyl imines is a related process that has also been used to develop some efficient stereoselective synthetic approaches to N-tert-butanesulfinyl aziridines.

Examples in which similar truly one-pot tandem reactions have been implemented to access nitrogen heterocycles other than aziridines are scarce. They concern the asymmetric synthesis of 2-substituted pyrrolidines and piperidines by reductive cyclization of γ- or δ-chlorinated N-tert-butanesulfinyl ketimines on reaction with LiBHEt (Scheme 4).[17,188] As shown with the preparation of 24 from 22 and 25 from 23, the reduction step was carried out at −78 °C, while cyclization by intramolecular alkylation required heating to room temperature. Note that extension of this methodology to prepare larger rings (azepanes and azocines) was not successful.

2.2 N-Acylation of tert-Butanesulfinamides

N-Acylation of tert-butanesulfinamides has also been achieved via the corresponding metal anions. Lithium or potassium anions of tert-butanesulfinamide (1) have been reported to react with carboxylic anhydrides[41] and esters[42,43] to provide the corresponding N-tert-butanesulfinyl amides, and with isocyanates[44] and 1,1’-carbonyldiimidazole[45] to give N-tert-butanesulfinyl ureas. Even though it has been an issue in certain cases,[41] these reactions have been usually carried out without racemization and the acylated derivatives have been obtained in enantio-merically pure form if enantiopure tert-butanesulfinamides were used. The ureas and some of the amides prepared in this way have emerged as valuable organocatalysts for asymmetric catalysis.[42a,44,45]

N-acylation of N-alkyl tert-butanesulfinamides has been achieved in a similar way. There are some intermolecular examples[46] but these reactions have been mostly implemented in the context of heterocycle construction by intramolecular processes. Cyclizations of tert-butanesulfinamides having tethered esters[47] or amides,[48] including lactams,[49] have been used for the preparation of β-lactams and pyrrolidines. It has also been possible to obtain the N-acylation of the metal amides arising from the addition of an organometallic reagent to N-tert-butanesulfinyl imines and this has paved the way for the elaboration of one-pot tandem synthetic strategies (Scheme 5). For instance, 5-methylene 2-pyrrolidones such as 27 have been prepared by a sequence involving the Barbier-type alkylation of 26 followed by intramolecular reaction with the pending ester.[47b,c] Another representative example is the formation of 3,5-disubstituted pyrrolidone 29 by a process initiated by the addition of
a Grignard reagent to N-sulfinylimine 28 that involves a subsequent cyclization on an amide.\[48]\]

Lastly, it is also worthy to note that β-lactam 31, an intermediate used for the semi-synthesis of taxol, has been prepared from 30 by an intramolecular peptide coupling reaction (Scheme 5).\[50]\]

### 2.3 Intramolecular aza-Michael Reactions

**tert-Butanesulfinamides** participate readily as nitrogen nucleophiles in base-mediated intramolecular aza-Michael reactions and the chirality of the sulfynyl moiety has been successfully exploited to develop diastereoselective procedures for the asymmetric synthesis of five- and six-membered nitrogen heterocycles.

Treatment of **tert**-butanesulfinimide 32, that has a tethered α,β-unsaturated ketone, with a sub-stoichiometric amount of base afforded a mixture of diastereomeric pyrrolidines 33a and 33b (Scheme 6).\[51]\] It was shown that the process was reversible and that the stereoselectivity varied with the reaction conditions. With BuOK at room temperature, formation of the thermodynamic product 33a was favored and a 33a/33b = 85:15 ratio was obtained. Conversely, at –40 °C using KHMDS, 33b was produced as major product in a reversed 33a/33b = 15:85 ratio. Related cyclizations with α-branched sulfinamides were also achieved. In the case of 34 having an rPr substituent, the stereochemical outcome was governed by the sulfynyl group: the thermodynamic product 35a was obtained as major product at room temperature, while the kinetic product 35b was favored at –40 °C. By contrast, in the case of 36 with a Ph substituent, product 37a was formed exclusively, regardless of the reaction temperature.

In the presence of base, α,β-unsaturated esters can also undergo intramolecular aza-Michael additions with tethered tert-butanesulfinamides to give five-membered ring closures (Scheme 7).\[51]\] Similarly to the case of α,β-unsaturated ketones, the addition is reversible and the sense of stereoinduction varies with the reaction temperature. Thus, at –40 °C, the cyclization of substrate 38 leads to the kinetic product 39b in an excellent 39a/39b = 06:94 ratio, while at room temperature, 39a is formed as major product, albeit with very low diastereomeric excess.

Cyclization on ester acceptors has proved most useful in the construction of substituted isoindolines (Scheme 8).\[53]\] As shown for substrate 40, a first set of conditions involving treatment with TBAF at room temperature allowed the formation of product 41b in good yield and excellent stereoselectivity. If DBU was used as base, formation of 41a was obtained as major product in a 41a/41b = 80:20 ratio. Product 41a could be readily converted into 41b by equilibration in the presence of TBAF, thereby indicating that 41b was the thermodynamic product and 41a the kinetic one. It was suggested by the authors that the reaction proceeds under kinetic control with DBU because its lower basicity makes the protonation step following addition irreversible and thus precludes equilibration. The model proposed to account for the kinetic stereocontrol during the cyclization step involves two competitive chair-like transition states wherein the negatively charged sulfynyl oxygen interacts with the electrophilic carbon of the ester group. M1 is favored over M2 because the tert-butyl group occupies a pseudo-

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**Scheme 5.** Representative examples of heterocyclization by intramolecular N-acylation of tert-butanesulfinamides.

**Scheme 6.** Asymmetric synthesis of pyrrolidines by intramolecular aza-Michael additions of tert-butanesulfinamides on tethered α,β-unsaturated ketones.

**Scheme 7.** Asymmetric synthesis of pyrrolidines by diastereoselective intramolecular aza-Michael additions of tert-butanesulfinamides on tethered α,β-unsaturated esters.
equatorial position and not a pseudo-axial one (Scheme 8).

This method has also been used to prepare 2,3-disubstituted isoindolines from α-substituted N-tert-butanesulfinamides (Scheme 9). It has been found that the stereocchemical behavior of the cyclization depends on the relative configuration between the α-carbon and the stereogenic sulfur atom. In the case of substrates having the same relative configuration as 42, a stereodivergent process was observed and the choice of appropriate reaction conditions made it possible to access, in good yields and excellent stereoselectivity, the corresponding 2,3-disubstituted isoindolines either as trans isomers (43a – kinetic control) or cis isomers (43b – thermodynamic control). By contrast, for substrates having the same relative configuration as 44, the cis isomer 45 was favored under both thermodynamic and kinetic control and was thus obtained under all of the reaction conditions. It is also worthy of mention, that in the latter case, stereoselective isoindoline formation was obtained directly from the parent N-tert-butanesulfinyl imines by a tandem sequence involving nucleophilic addition and cyclization through intramolecular aza-Michael reaction. The preparation of 47 from 46 illustrates well this sequence.

Formation of six-membered rings by base-mediated intramolecular aza-Michael addition of tert-butanesulfinamides has also been reported and it has been used for the asymmetric synthesis of 2-substituted and 2,3-disubstituted piperidines (Scheme 10). Cyclization of 48 occurred most efficiently in the presence of tBuOK at room temperature and yielded a mixture of diastereomeric piperidines 49a and 49b in 49a/49b = 88:12 ratio. By contrast with the above-described five-membered ring closure leading to pyrrolidines 33a/33b, no variation of the stereoselectivity was observed upon modification of the reaction conditions (temperature, base or solvent). Such was not the case for α-branched substrates, since reactions at room temperature gave very high selectivity (but moderate yields), while reactions at ~40 °C led to moderate stereoselectivity (good yields). Taking advantage of the reversibility of the process, an optimized procedure combining high stereoselectivity and good yields could eventually be obtained by adding the base at ~40 °C and then letting the reaction temperature rise to room temperature. The synthetic value of this method is well evidenced with the cyclization of 50 to obtain 51 that has been used in natural product synthesis.

Piperidine formation is also readily achieved by intramolecular aza-Michael reaction of tert-butanesulfinamides with tethered acrylates and occurs with excellent selectivity. This method has also been used to prepare 2,3-disubstituted isoindolines from α-substituted N-tert-butanesulfinamides (Scheme 9). It has been found that the stereocchemical behavior of the cyclization depends on the relative configuration between the α-carbon and the stereogenic sulfur atom. In the case of substrates having the same relative configuration as 42, a stereodivergent process was observed and the choice of appropriate reaction conditions made it possible to access, in good yields and excellent stereoselectivity, the corresponding 2,3-disubstituted isoindolines either as trans isomers (43a – kinetic control) or cis isomers (43b – thermodynamic control). By contrast, for substrates having the same relative configuration as 44, the cis isomer 45 was favored under both thermodynamic and kinetic control and was thus obtained under all of the reaction conditions. It is also worthy of mention, that in the latter case, stereoselective isoindoline formation was obtained directly from the parent N-tert-butanesulfinyl imines by a tandem sequence involving nucleophilic addition and cyclization through intramolecular aza-Michael reaction. The preparation of 47 from 46 illustrates well this sequence.

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levels of stereoinduction.\textsuperscript{[53]} This approach has been very recently used to develop an asymmetric synthesis of quinolizidine 54, which was used for natural product synthesis (Scheme 11).\textsuperscript{[54]} The approach involved as the first step the cyclization of diacrylate 52 in the presence of NaH that induced a desymmetrization process wherein two stereocenters were created. The intramolecular aza-Michael reaction afforded a mixture of diastereomers in which isomers having a $2S$ configuration predominated as the result of the chiral induction exerted by the tert-butanesulfinyl group. Products cis-53a and trans-53a, isolated in 63% and 22% yields respectively, could then be both engaged in a second intramolecular aza-Michael addition that provided quinolizidine 54 in enantiomerically pure form. Thus, because of the C2-symmetry of 54, the lack of stereocontrol of the relative configuration of the C(2) and C(6) substituents in the first step was not a problem. The authors rationalized the remarkable chiral induction achieved for the desymmetrization step on kinetic bases. It was suggested that the cyclization takes place through a rigid chair-like transition state involving a chelate between the sodium amide, the sulfoxide and the ester carbonyl. The nitrogen nucleophile attacks the $S_i$ face of the acrylate to avoid steric interactions with the bulky tert-butyl group. This induction mode operates regardless of the position occupied by the C(6) substituent that can be either equatorial (favored) as in M3 that gives cis-53a or axial as in M4 that gives trans-53a.

3. Mitsunobu Cyclizations of tert-Butanesulfinamides

In the context of heterocyclization reactions, another important feature of $N$-alkyl tert-butanesulfinamides is that they can be used as nucleophiles for Mitsunobu-type intramolecular alkylations (Scheme 12). Typical Mitsunobu conditions (PPh$_3$ and diethylzodicarboxylate (DEAD) or diisopropylazodicarboxylate (DIAD)) are well suited to achieve pyrrolidine ring closure. This reactivity was first evidenced serendipitously with the unexpected cyclization of 55 to 56\textsuperscript{[55]} and has later provided synthetic solutions in target-oriented-synthesis for cases in which other cyclization conditions were not applicable or failed.\textsuperscript{[56]} Interestingly, this chemistry has been used to develop a very elegant access to stereodefined 2,2,3-trisubstituted pyrrolidines through a highly diastereoselective Mitsunobu cyclization governed by the chiral tert-butanesulfinyl group. Starting from diols such as 57, differentiation of the diastereotopic hydroxyethyl groups was observed, and pyrrolidines like 58 were formed in good yields and excellent diastereoselectivity.\textsuperscript{[57]} To account for the observed stereoinduction, the authors proposed a kinetic-based model involving cyclization via two competitive transition states (M5 versus M6) wherein the sulfinyl group and the free hydroxyethyl group are hydrogen-bonded. Cyclization through transition state model M5 was proposed to be favored because non-bonding interac-

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\caption{Scheme 11. Asymmetric synthesis of 54.}
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\caption{Scheme 12. Representative examples of Mitsunobu-type heterocyclization reactions.}
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tions between the tert-butyl and the C(2) substituents are avoided.

Heterocyclization of tert-butanesulfinamides using the classical Mitsunobu conditions to give nitrogen heterocycles other than pyrrolidines is less favorable and has only been reported for very specific substrates.\textsuperscript{[58]} In order to circumvent this limitation, the use of cyanomethylenetri- 
butylphosphorane, a reagent that performs better for more demanding cyclizations, has been considered. \( \alpha \)-Substituted azetidines, pyrrolidines and piperidines such as \( 60 \) have been prepared with this method that requires nevertheless rather harsh re-
action conditions (toluene, 110 °C).\textsuperscript{[59]}

4. Transition Metal-catalyzed Amination Reactions with tert-
Butanesulfinamides as Nitrogen Donors

The potential of tert-butanesulfinamides as nitrogen donors in metal-cata-
lyzed amination reactions has only started to be investigated very recently but it has already been demonstrated that they can be suitable partners for \( N \)-arylation and \( N \)-heteroarylation reactions, for \( N \)-allylation reactions, including transformations where they act as chiral inductors, and for hy-
droamination reactions.

4.1 \( N \)-Arylation and \( N \)-Heteroary-
lization of tert-Butanesulfinamides

The prospect to carry out \( N \)-(hetero) 
arylation of tert-butanesulfinamides has a two-fold interest. On the one hand, it of-
ers a convenient solution for the synthesis of \( N \)-(hetero)aryl tert-butanesulfinamides in enantio-merically pure form, which is otherwise difficult to achieve. On the other hand, the ease of deprotection of the tert-
butanesulfinyl group makes tert-butane-
sulfinamide (in racemic form) an interesting ammonia surrogate in carbon–nitrogen bond forming cross-coupling reactions.\textsuperscript{[60]}

\( N \)-(hetero)arylation of tert-butanesulfinamide \( 1 \) was first reported under copper catalysis.\textsuperscript{[61]} However, only the cross coupling with 2-bromopyridine was de-
scribed and, in spite of >90% conversion, no isolated yield nor characterization data were given. This method has not been de-
veloped further.

More general methods have been disclo-
closed with palladium catalysts (Scheme 13). As illustrated with the preparation of \( 61 \), the system obtained by combin-
ing \( \text{Pd(OAc)}_2 \) and \( \text{rac-BINAP} \), catalyzed, in the presence of \( \text{Cs}_2\text{CO}_3 \) in toluene at 120 °C, the reaction between tert-butanesulfinamide \( 1 \) and arylobromides with ox-
azolides as \( ortho \)-substituents.\textsuperscript{[62]} Excess sulfinamide and long reaction times were however necessary. The same catalytic system was used to obtain tetrahydroquin-
one formation by intramolecular cross coupling of a secondary tert-butanesulfin-
amide with a tethered aryl bromide, but in this case the tert-butanesulfinyl group was concomitantly removed (likely after cycli-
zation).\textsuperscript{[63]} A second system that has proved more efficient for the \( N \)-arylation of tert-
butanesulfinamide \( 1 \) involves \( \text{Pd}(\text{dba})_2 \) as palladium source, \( \text{BuXPhos} \) as ligand and \( \text{NaOH} \) as base.\textsuperscript{[64]} In this case, cross coupling has been achieved in toluene at 90 °C, provided that a small amount of wa-
ter was added to the reaction medium. Ar-
yl bromides could be used as electrophiles, but also arylchlorides, as shown with the preparation of \( 62 \). Importantly, for both of the catalytic systems disclosed, no racemi-
zation was noted.

4.2 Allylic Amination Reactions with tert-Butanesulfinamides

The use of tert-butanesulfinamide \( 1 \) as partner in \( \text{Pd}(0) \)-catalyzed allylic ami-
nation reactions was envisaged at a quite early stage as a route to chiral allylic amines but met with only limited success. \( N \)-allylation of the lithium anion of \( 1 \) with racemic cyclic allylic carbonates in the presence of \( \text{Pd}(\text{PPh}_3)_2 \) was reported to be low yielding and moderately stereoselec-
tive.\textsuperscript{[65]}

This reaction has been recently rein-
vestigated by us using \( \text{Pd(OAc)}_2 / \text{diphe-
nylphosphino-ethane} \) (dppe) as catalytic system in order to gain insight on the in-
fluence of \( N \)-substitution.\textsuperscript{[43]} Unlike metal-
ated tert-butanesulfinamide \( 1 \), anions of \( N \)-benzyl tert-butanesulfinamide and \( N \)-acetyl tert-butanesulfinamide \( 64 \) were found to react readily with allyl acetate. In the presence of \( \text{BSA} \) (\( \text{N,O-bis(trimethyl) acetamide} \) and a catalytic amount of \( \text{AcOK} \), the use of a strong base could be avoided and \( N \)-allylation of \( 1 \) to afford \( 63 \) was achieved in reasonable yield, despite competitive diallylation (Scheme 14).

It was further shown that \( N \text{-acetyl tert-}
butanesulfinamides undergo \( N \)-allylation
with allylic carbonates with the same Pd(OAc)$_2$/dppe catalytic system and in the absence of additional base. Cross-coupling reactions between $^{64}$ and 2- or 3-substituted allylic carbonates were achieved in high yields. As illustrated with the formation of $^{65}$, in the case of 3-substituted carbonates, complete regio- and stereoselectivity in favor of the $E$-configured linear allylic sulfinamides was obtained.

Since it was demonstrated that the sulfur atom remains configurationally stable throughout the allylation process, the possibility to achieve chiral induction with the tert-butanesulfinyl chiral auxiliary was also considered. The intermolecular reaction with racemic secondary allylic carbonates was sluggish and the levels of diastereoselectivity only moderate. However, the intramolecular $N$-allylation of $N$-acyl sulfinamide $^{66}$ to provide pyrrolidinone $^{67}$ occurred in excellent yield and with very good stereoselectivity.$^{[66]}$

Another Pd-catalyzed process for which 1-tert-butanesulfinamides have proved to be competent nitrogen nucleophiles is the Pd(II)-catalyzed aerobic oxidative cyclization of alkenes (Scheme 15).$^{[67]}$ For instance, the cyclization of sulfinamide $^{68}$ having a tethered Z-alkene and no $\alpha$-substituent leads in good yields to the formation of 2-vinyl pyrrolidinone $^{69}$ on treatment with Pd(TFA)$_2$ (10 mol%) and LiOAc (1 equiv.) under an oxygen atmosphere in DMSO at 50 °C. A diastereomeric ratio of 88:12 is obtained, thereby evidencing that the tert-butanesulfinyl group can act efficiently as chiral auxiliary. The method is applicable to the cyclization of $\alpha$-branched sulfinamides, as illustrated with the formation of $^{71}$ and $^{73}$. In this case the stereoselectivity is governed by the $\alpha$-stereocenter and cis-2,5-disubstituted pyrrolidines are formed in excellent yields and stereoselectivities regardless of the relative configuration between the sulfur atom and the $\alpha$-stereocenter.

### 4.3 Hydroamination Reactions of tert-Butanesulfinamides

Very recently, the possibility to use tert-butanesulfinamides as nitrogen nucleophiles for intramolecular hydroamination reactions under Ag(I) catalysis has been established (Scheme 16).$^{[68]}$ The cyclizations of alkyne $^{74}$ to produce spiro indole $^{75}$ in the presence of a catalytic amount of AgOAc,$^{[64a]}$ and of allene $^{76}$ to obtain $^{77}$ by treatment with a stoichiometric amount of AgBF$_4$,$^{[68b]}$ provide a proof-of-concept for this chemistry for which the scope is yet to be established.

### 5. Conclusion

The collection of reactions described in this review shows that a fertile area of the chemistry of tert-butanesulfinamide has grown in the shade of N-tert-butanesulfinyl imines.

In asymmetric synthesis, carbon–nitrogen bond forming reactions using tert-butanesulfinamides as nitrogen nucleophiles were initially implemented to further elaborate adducts obtained from stereoselective additions of nucleophiles to N-tert-butanesulfinyl imines and have proved particularly useful for the construction of nitrogen heterocycles by heterocyclization reactions. In the last five years, important seminal contributions have unveiled new aspects of this reactivity that will certainly pave the way for new applications in synthesis. On the one hand, it has been demonstrated that chiral induction can be obtained using tert-butanesulfinamides as chiral nucleophiles in a range of transformations. On the other hand, tert-butanesulfinamides have proved suitable nitrogen donors for a variety of metal-mediated carbon–nitrogen cross-coupling reactions.

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**Scheme 15. Pd(i)-catalyzed aerobic oxidative cyclization of alkenes with tert-butanesulfinamide nucleophiles.**

**Scheme 16. Ag(i)-catalyzed intramolecular hydroamination reactions.**

**Scheme 17. Ag(i)-catalyzed intramolecular hydroamination reactions.**

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