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

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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

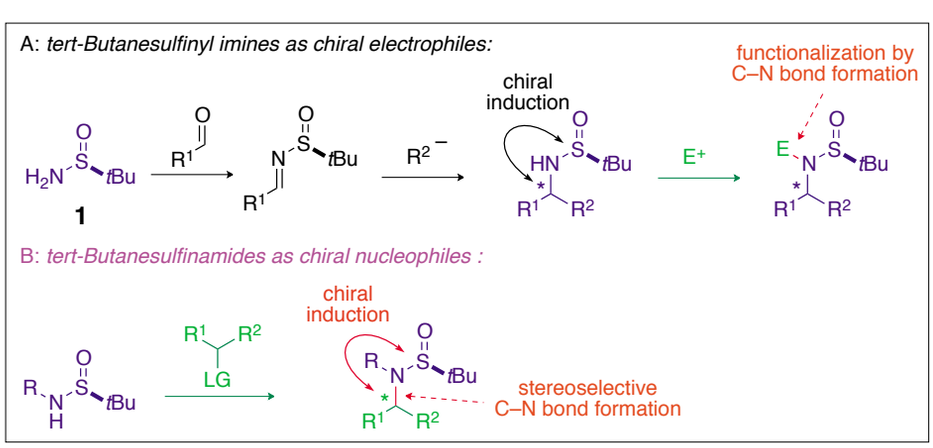
Chiral amine reagent *tert*-butanesulfinamide (**1**) has received massive attention over the last decade and has found applications in an ever-increasing number of research areas.[1] In the field of asymmetric synthesis, it is now a well-established tool for the preparation of chiral non-racemic amines. 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*-butanesulfinamide 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[1] 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 (**1**) and its *N*-substituted congeners react readily with an array of carbon electrophiles. Their good resistance to



Scheme 1. Uses of *tert*-butanesulfinamides as nucleophiles in asymmetric synthesis.

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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,[2] reductive amination approaches are generally preferred.[3] 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.

Metallation of *N*-alkyl *tert*-butanesulfinamides can be carried out conveniently using mainstream strong bases such as KH, NaH, LiHMDS, KHMDS or *n*BuLi. 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.[4]

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[5] are rare.[6] By contrast, allylic and propargylic halides are well-suited electrophiles that permit intermolecular allylation 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-oriented[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]

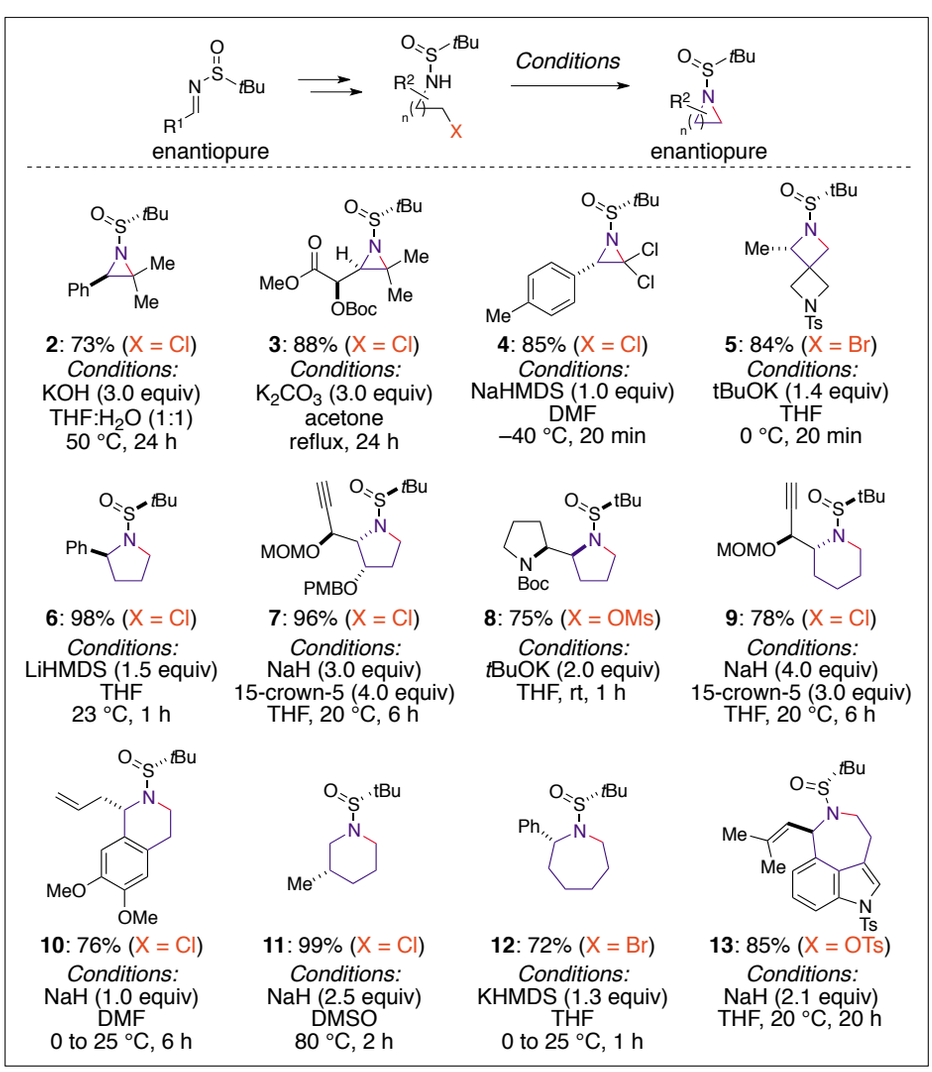
2.1.2 *Intramolecular N-Alkylation Reactions*

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 enantiomerically 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 H_2O/THF,[11] as illustrated with the preparation of **2** (Scheme 2), K_2CO_3 in acetone, as shown with **3**,[12] or *t*BuOK in *i*PrOH.[13]

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 diazaspiro[3.3]heptane **5**[16] by intramolecular alkylation triggered with *t*BuOK 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 H_2O/THF[17] or *t*BuOK in *i*PrOH,[13] or at room temperature in THF using LiHMDS[18] (see the formation of **6**), KHMDS,[19] 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



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 *t*BuOK, as for the formation of **8**, or NaH.

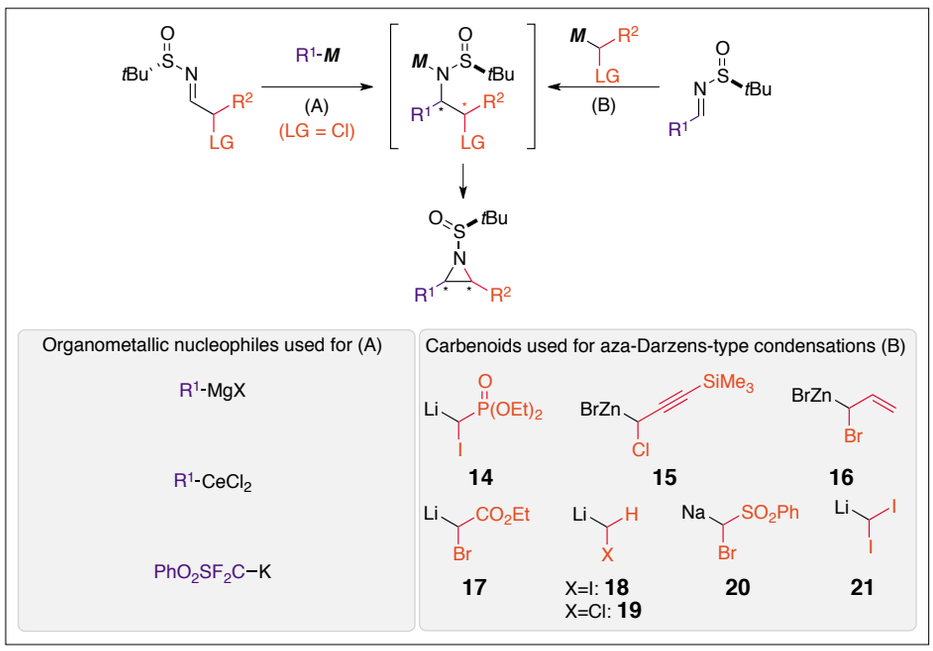
In the case of six-membered ring construction, the use of NaH as base has been privileged (Scheme 2). Again, it has been used in combination with 15-crown-5, in THF at room temperature, to prepare functionalized piperidines like **9**.[23] However, in solvents with higher polarity, similar cyclizations 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,[18b] azepane formation has been reported by intramolecular displacement of a bromide following deprotonation with KHMDS,[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[11a,27] and organocerium[28] reagents, as well as with KCF_2SO_2Ph.[29] On the other hand (B), aza-Darzens-type condensations between carbenoid reagents and *N-tert*-butanesulfinyl imines have been disclosed with a rather large array of carbanions. These include: lithiated halomethylphosphonates like **14**,[30] zincated propargylic and allylic bromides **15**[31] and **16**,[32] a lithiated (chloroethyl)oxazoline,[33] lithiated bromoesters such as **17**,[34] lithiated halomethanes **18** and **19**,[35] the sodium anions 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 aziriridines.

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 $LiBHEt_3$ (Scheme 4).[17,18b] 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 lager rings (azepanes and azocines) was not successful.

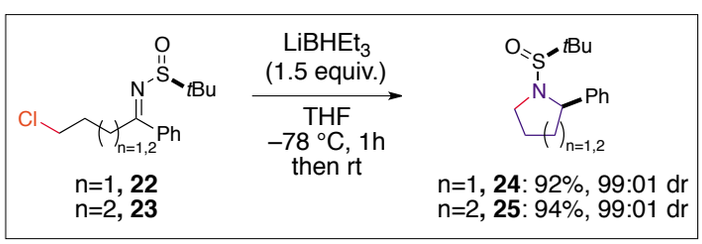


Scheme 3. Aziridine formation by one-pot tandem nucleophilic addition/intramolecular alkylation reactions.

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 enantiomerically 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 pyrrolidones. 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 allylation 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



Scheme 4. Pyrrolidine and piperidine formation by reductive cyclization of γ- or δ-chlorinated *N-tert*-butanesulfinyl ketimines.

a Grignard reagent to *N*-sulfinyl imine **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]

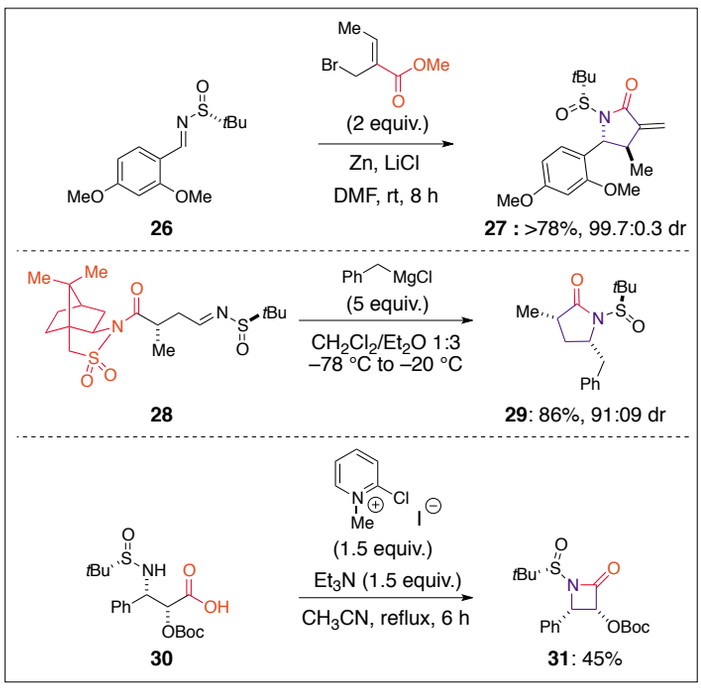
2.3 *Intramolecular aza-Michael Reactions*

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

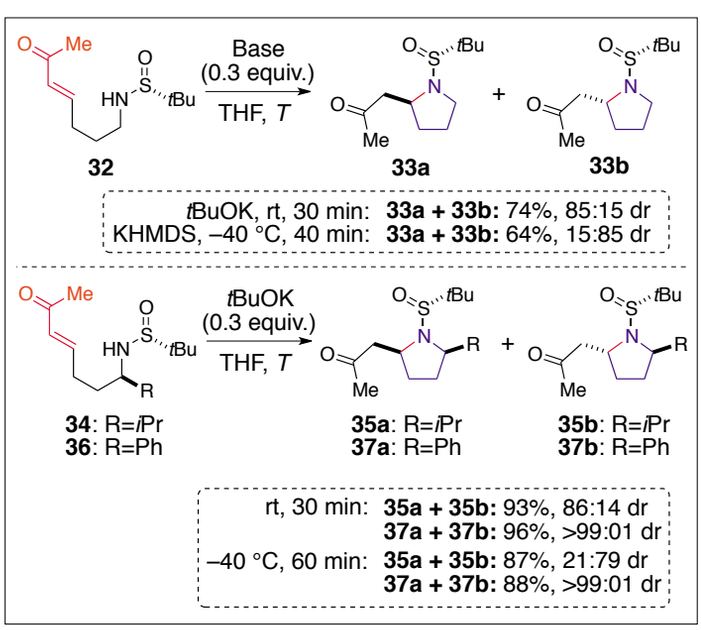
Treatment of *tert*-butanesulfinamide **32**, that has a tethered α-β-unsaturated ketone, with a sub-stoichiometric amount of base afforded a mixture of diastereomeric pyrrolidines **33a** and **33b** (Scheme 6).[51] It was shown that the process was reversible and that the stereoselectivity varied with the reaction conditions. With *t*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 *i*Pr substituent, the stereochemical outcome was governed by the sulfinyl 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.

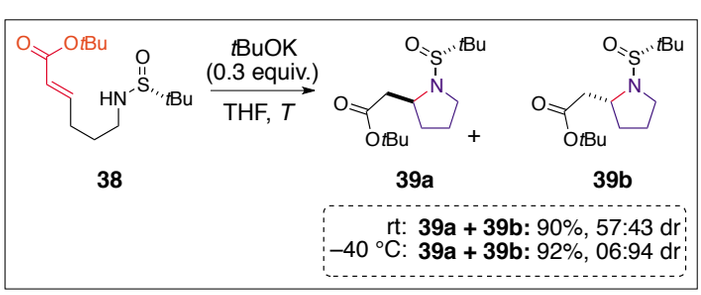
Cyclization on ester Michael-acceptors has proved most useful in the construction of substituted isoindolines (Scheme 8).[52] As shown for substrate **40**, a first set of conditions involving treatment with TBAF at room temperature allowed the formation of product **41b** in good yield and excellent 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 sulfinyl oxygen interacts with the electrophilic carbon of the ester group. **M1** is favored over **M2** because the *tert*-butyl group occupies a *pseudo*-



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.



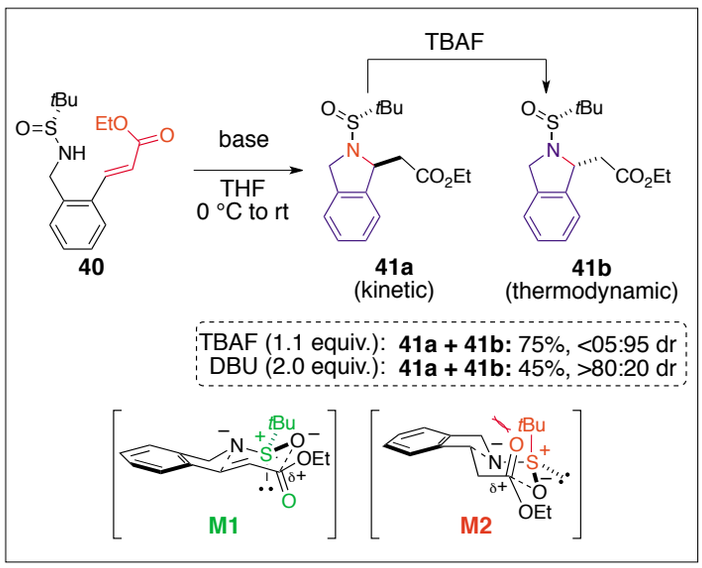
Scheme 7. Asymmetric synthesis of pyrrolidines by diastereoselective intramolecular aza-Michael additions of *tert*-butanesulfinamides on tethered α-β-unsaturated esters.

equatorial position and not a *pseudo*-axial one (Scheme 8).

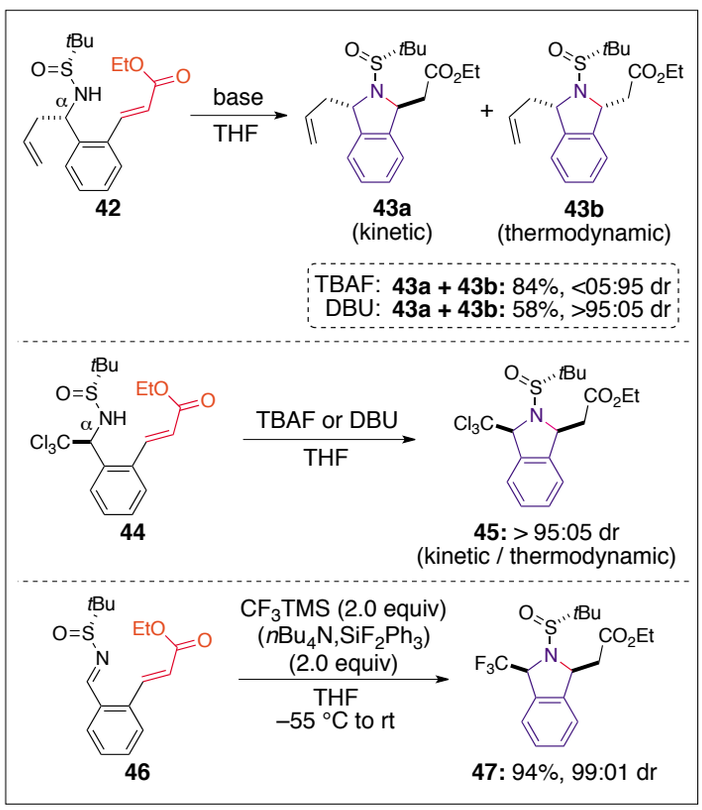
This method has also been used to prepare 2,3-disubstituted isoindolines from α-substituted *N*-*tert*-butanesulfinamides (Scheme 9).[52] It has been found that the stereochemical behavior of the cyclization depends on the relative configuration between the α-carbon and the stereogenic sulfur atom. In 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.[53] 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).[51] Cyclization of **48** occurred most efficiently in the presence of *t*BuOK 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 (in 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.[51]

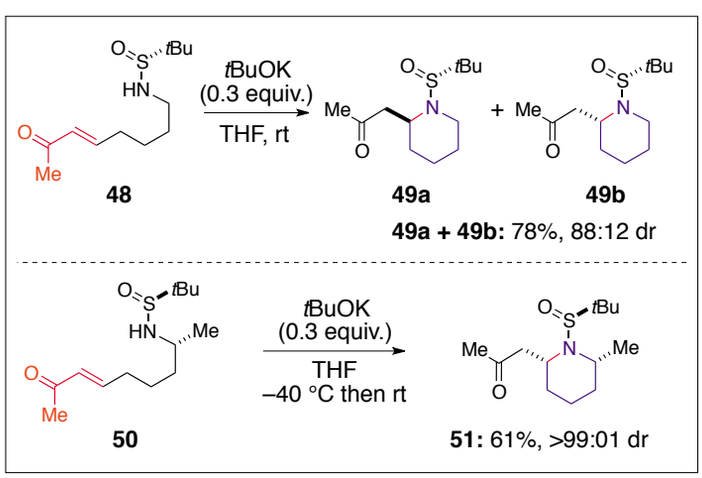
Piperidine formation is also readily achieved by intramolecular aza-Michael reaction of *tert*-butanesulfinamides with tethered acrylates and occurs with excellent



Scheme 8. Isoindoline formation by diastereoselective cyclization of *tert*-butanesulfinamides on tethered α-β-unsaturated esters.

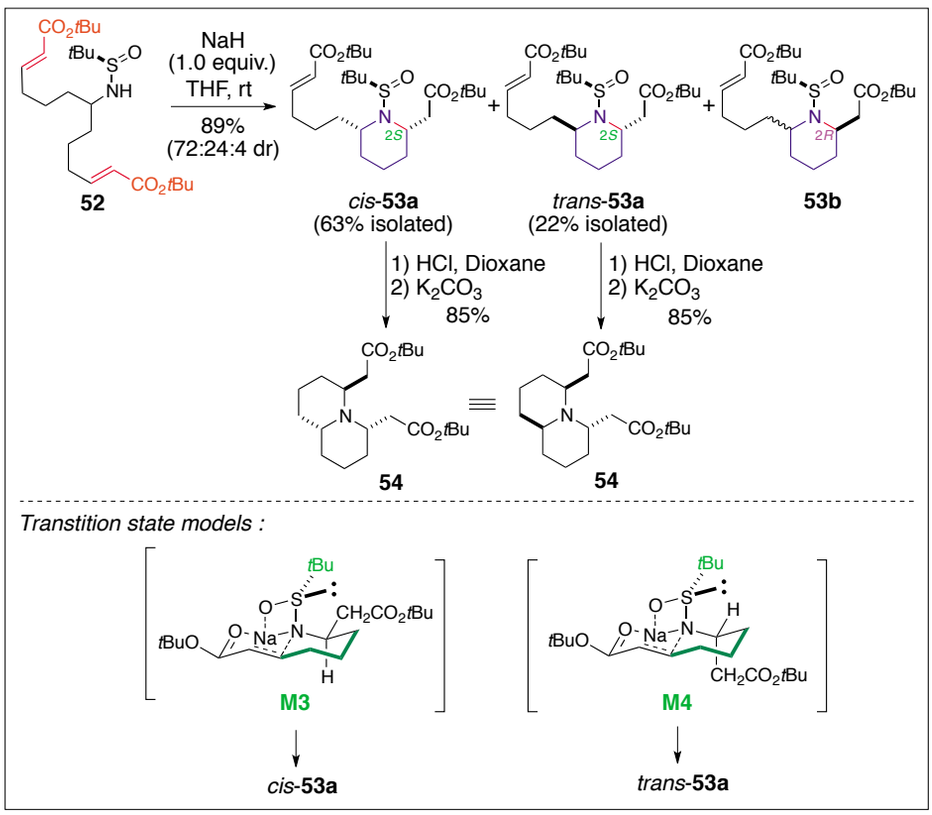


Scheme 9. Asymmetric synthesis of 2,3-disubstituted isoindolines by intramolecular aza-Michael reaction.



Scheme 10. Asymmetric synthesis of piperidines by intramolecular aza-Michael reaction.

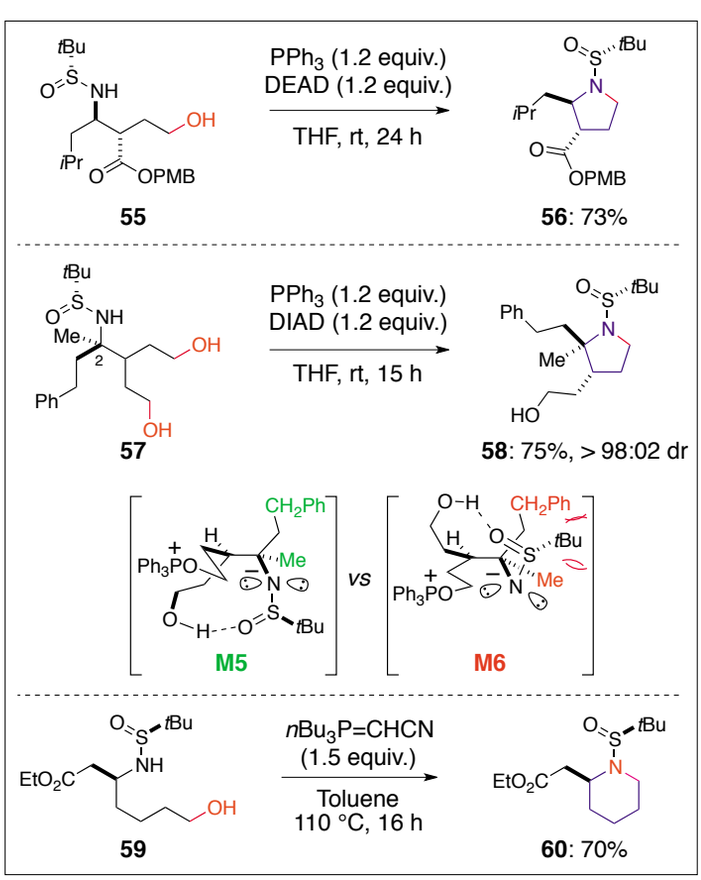
levels of stereoinduction.[51] This approach has been very recently used to develop an asymmetric synthesis of quinolizidine **54**, which was used for natural product synthesis (Scheme 11).[54] The approach involved as the first step the cyclization of diacrylate **52** in the presence of NaH that induced a desymmetrization process wherein two stereocenters were created. The intramolecular aza-Michael reaction afforded a mixture of diastereomers in which isomers having a 2*S* 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 *Si* 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**.



Scheme 11. Asymmetric synthesis of **54**.

3. Mitsunobu Cyclizations of *tert*-Butanesulfinamides

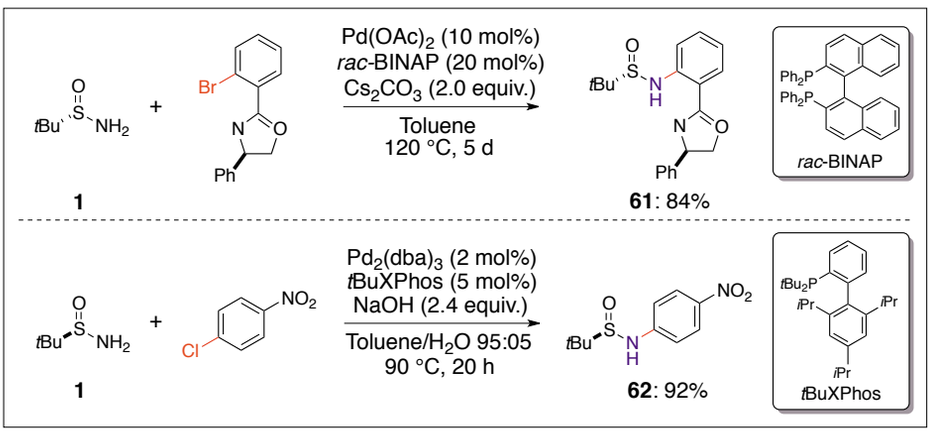
In the context of heterocyclization reactions, another important feature of *N*-alkyl *tert*-butanesulfinamides is that they can be used as nucleophiles for Mitsunobu-type intramolecular alkylations (Scheme 12). Typical Mitsunobu conditions (PPh_3 and diethylazodicarboxylate (DEAD) or diisopropylazodicarboxylate (DIAD)) are well suited to achieve pyrrolidine ring closure. This reactivity was first evidenced serendipitously with the unexpected cyclization of **55** to **56**[55] and has later provided synthetic solutions in target oriented-synthesis for cases in which other cyclization conditions were not applicable or failed.[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.[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-



Scheme 12. Representative examples of Mitsunobu-type heterocyclization reactions.

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.[58] In order to circumvent this limitation, the use of cyanomethylenetributylphosphorane, a reagent that performs better for more demanding cyclizations, has been considered. α-Substituted azetidines, pyrrolidines and piperidines such as **60** have been prepared with this method that requires nevertheless rather harsh reaction conditions (toluene, 110 °C).[59]



Scheme 13. Representative examples of Pd(0)-catalyzed *N*-arylation of *tert*-butanesulfinamides.

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

The potential of *tert*-butanesulfinamides as nitrogen donors in metal-catalyzed 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 hydroamination reactions.

4.1 *N-Arylation and N-Heteroarylation of tert-Butanesulfinamides*

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

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

More general methods have been disclosed with palladium catalysts (Scheme 13). As illustrated with the preparation of **61**, the system obtained by combining $Pd(OAc)_2$ and *rac*-BINAP, catalyzed, in the presence of Cs_2CO_3 in toluene at 120 °C, the reaction between *tert*-butanesulfinamide (**1**) and arylbromides with oxazolidines as *ortho*-substituents.[62] Excess sulfinamide and long reaction times were however necessary. The same catalytic system was used to obtain tetrahydroquinoline formation by intramolecular cross coupling of a secondary *tert*-butanesulfinamide with a tethered aryl bromide, but in this case the *tert*-butanesulfinyl group was concomitantly removed (likely after cyclization).[63]

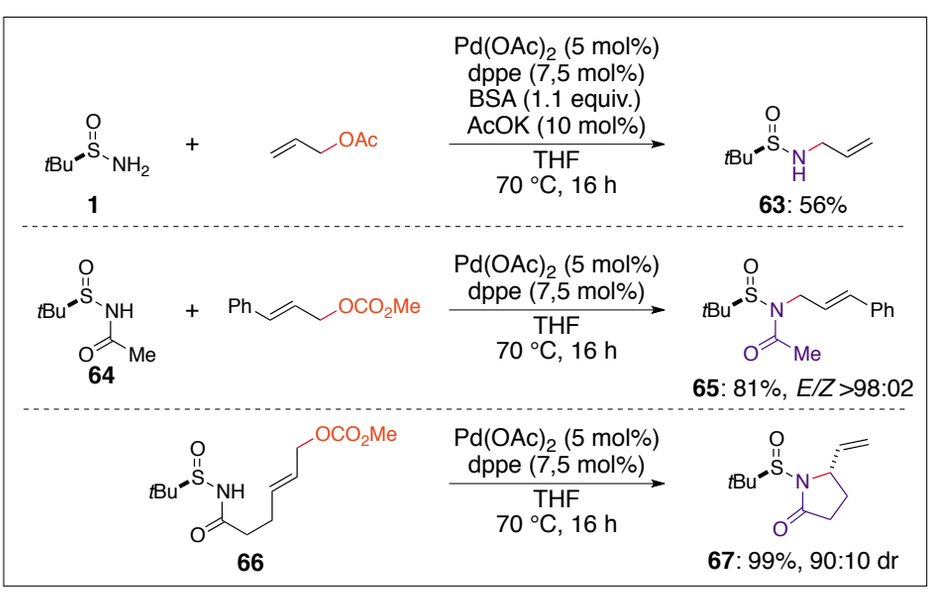
A second system that has proved more efficient for the *N*-arylation of *tert*-butanesulfinamide (**1**) involves $Pd_2(dba)_3$ as palladium source, *t*BuXPhos as ligand and NaOH as base.[64] In this case, cross coupling has been achieved in toluene at 90 °C, provided that a small amount of water was added to the reaction medium. Arylbromides could be used as electrophiles, but also arylchlorides, as shown with the preparation of **62**. Importantly, for both of the catalytic systems disclosed, no racemization was noted.

4.2 *Allylic Amination Reactions with tert-Butanesulfinamides*

The use of *tert*-butanesulfinamide (**1**) as partner in Pd(0)-catalyzed allylic amination 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 $Pd(PPh_3)_4$ was reported to be low yielding and moderately stereoselective.[65]

This reaction has been recently reinvestigated by us using $Pd(OAc)_2$/diphenylphosphino-ethane (dppe) as catalytic system in order to gain insight on the influence of *N*-substitution.[43] Unlike metallated *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 BSA (*N,O*-bis(trimethyl) acetamide) and a catalytic amount of 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*-acyl *tert*-butanesulfinamides undergo *N*-allylation

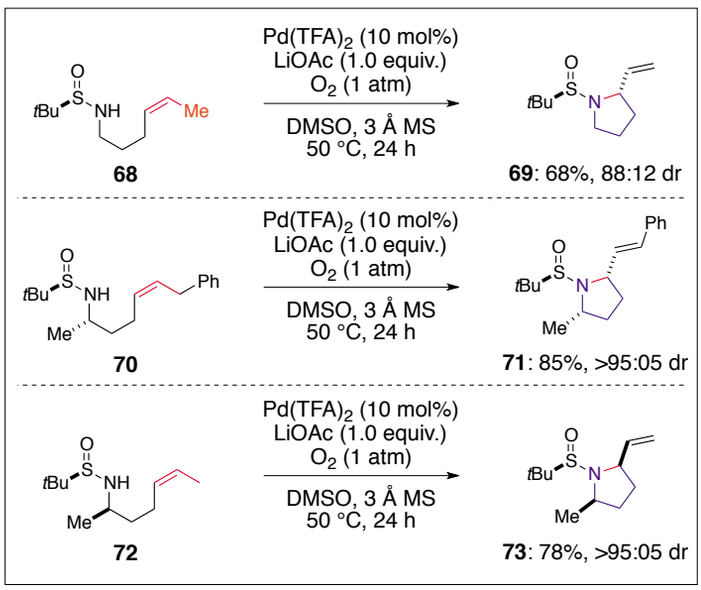


Scheme 14. Representative examples of Pd(0)-catalyzed allylic substitutions with *tert*-butanesulfinamides.

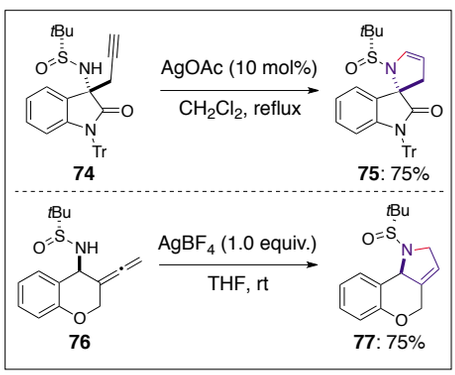
with allylic carbonates with the same $Pd(OAc)_2$/dppe catalytic system and in the absence of additional base. Cross-coupling reactions between **64** and 2- or 3-substituted allylic carbonates were achieved in high yields. As illustrated with the formation of **65**, in the case of 3-substituted carbonates, 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 *N*-alkyl *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 α-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 α-branched sulfinamides, as illustrated with the formation of **71** and **73**. In this case the stereoselectivity is governed by the α-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 α-stereocenter.



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



Scheme 16. Ag(I)-catalyzed intramolecular hydroamination reactions.

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,[68a] 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 heterocyles by heterocylization 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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