Review

N-Tosylcarboxamide in C–H Functionalization: More than a Simple Directing Group

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Abstract: C–H activation with transition metal catalysis has become an important tool in organic synthesis for the functionalization of low reactive bonds and the preparation of complex molecules. The choice of the directing group (DG) proves to be crucial for the selectivity in this type of reaction, and several different functional groups have been used efficiently. This review describes recent advances in C–H functionalization of aromatic rings directed by a N-tosylcarboxamide group. Results regarding alkenylation, alkoxylation, halogenation, and arylation of C–H in the ortho position to the tosylcarboxamide are presented. Moreover, the advantage of this particular directing group is that it can undergo further transformation and act as CO or CON fragment reservoir to produce, in sequential fashion or one-pot sequence, various interesting (hetero)cycles such as phenanthridinones, dihydroisoquinolinones, fluorenones, or isoindolinones.

Keywords: C–H functionalization; catalysis; directing group; tosylbenzamide

1. Introduction

Over the last few years, the direct functionalization of C–H bonds has become an essential chemical transformation in organic synthesis. Methodologies based on this mode of activation are now major tools for the generation of molecular diversity and the construction of elaborate molecular architectures. Recent advances in the C–H activation/transformations allow these methodologies to be integrated into multi-step sequences, to be used on poly-substituted substrates, in late-stage functionalization strategies, and even in total synthesis [1–3].

In this context, the functionalization of aromatic rings by the selective activation of carbon–hydrogen bonds has experienced unprecedented growth for two decades. The scientific community has devoted many efforts to address the key aspects in this area that are (i) the control of selectivity when activating a C–H bond and (ii) the expansion of the molecular diversity by installing various functional groups at activated carbon atoms. If the metal-based catalytic system and the substrate topology and substitution pattern crucially impact the C–H functionalization issues [4], the directing group (DG) has become similarly essential. As examples, mono and bis activations in position ortho to the directing group or at remote positions have been extensively studied, requiring the development of especially designed and extended DG or shuttles [4–7]. In most of these cases, the DG is installed at a selected position of the substrate with the unique aim of orientation of the C–H activation. This strategy has gained popularity but suffers from drawbacks and remains neither atom- nor step-economical. Indeed, such an approach requires a costly synthetic sequence to install the DG prior to the C–H activation and, when possible, transformation of the DG into valuable functional groups after the C–H functionalization step. An emerging approach consists in using transient or
transformable DGs (Scheme 1). While the transient DG (tDG) strategy uses a functional group (FG) already installed at the substrate, temporarily transformed into a DG and finally released (e.g., a ketone or carboxaldehyde) [8–15], the transformable DG (TDG) one is characterized by the reuse of the DG or one part of the DG backbone to create molecular diversity such as new functional groups or (hetero)cycles during or after the C–H functionalization step.

**Scheme 1.** Types of directing groups (DGs).

The TDG-based activation/functionalization represents a current challenge towards molecular diversity and complexity in the aromatic series. In this context, the sulphonamide TDG is of appealing interest due, on the one hand, to its ability to promote the formation of various C-functional group bonds after C–H activation and, on the other hand, to the reuse of the CO and CON fragments of this TDG towards molecular diversity through the multiple synthetic transformations.

This review intends to give the reader an overview of the recent advances (until the beginning of 2020) in C–H functionalization using sulphonamides acting as TDGs.

As shown in Scheme 2, this review concentrates first on C–H functionalizations focusing on molecular diversity. Thus, alkenylation, alkoxylation, halogenation, and arylation reactions are covered (Scheme 2 (a–d)). A second part of the review is devoted to the construction of five- and six-membered rings using the N-tosyloxamide (CONHTs) TDG jointly as directing group and as CO or CON fragment reservoir (Scheme 2 (e–h)).
Scheme 2. Scope of the reaction promoted by N-tosylcarboxamide (CONHTs) as directing group.

2. C–H Functionalization Using N-Tosylcarboxamide as Directing Group

2.1. Alkenylation

In 2017, Nishimura successfully developed the alkenylation of arenes including benzene and naphthalene derivatives using hydroxoiridium complexes [16]. The use of sulfonylamides as ortho directing groups for alkenylation (and alkylation) afforded the desired products with exceptional yields and a broad scope (32 examples, yield > 82%). Both N-mesyl and N-tosylcarboxamide (CONHMs and CONHTs) were shown efficient in such transformation. As an example, diphenylacetylene was successfully hydroarylated using m-tolyl-CONHTs under Ir-catalyzed conditions, leading to a functionalized styryl derivative in a high yield (Scheme 3).

Scheme 3. Alkenylation of benzene.

2.2. Alkoxylation

Arylalkyl ethers are structural motifs widely found in diverse areas of chemistry. The construction of the arene–oxygen bond through C–H activation is thus of broad interest. Interestingly, alkoxylation
of arenes can be achieved at room temperature using Pd(OAc)$_2$ and classical oxidants. If in some cases molecular oxygen may afford good results, PhI(OAc)$_2$ represents a reliable oxidant in this context. The C–H functionalization is of a broad scope, compatible with the presence of electron-withdrawing and -releasing groups in various substitution patterns and the installation of trifluoroalkoxy residues at benzene and naphthalene substrates (Scheme 4) [17,18]. In the latter case, the use of Pd(TFA)$_2$ instead of Pd(OAc)$_2$ was required to ensure optimized transformations [19].

![Alkoxylation of arenes](image)

### Scheme 4. Alkoxylation of arenes.

2.3. Halogenation

Additional C–H functionalizations such as halogenations have proven the general usefulness of sulfonylamides as ortho directing groups. This area has been nicely exemplified allowing the installation of Cl, Br, and I at room temperature using N-chloro, N-bromo and N-iodosuccinimide (NCS, NBS, and NIS), respectively, as halide sources [17]. This methodology has also been recently extended to C–H radioiodination targeting the straightforward synthesis of complex radioiodinated compounds of biological interest (Scheme 5) [20].
Given the prevalence of biaryl structural subunits in complex aromatic architectures, the formation of C-C bonds linking to aromatic fragments through C–H activation is undoubtedly a challenging area of current interest. In this context again, the CONHTs directing group has proven to be quite efficient. The case of benzene-based substrates has been studied since 2012 by Fabis and coworkers, using palladium as a catalyst in acetic acid [21]. In that study, 23 examples of arylated benzene derivatives were obtained with yields up to 84%, with a great variety of substrate and aryl moieties (Scheme 6).

The specific case of naphthalene was only studied more recently by Prim et al. [22]. In that case, the reaction was perfectly regioselective—only the position 2 was attacked with a DG in position 1 and the position 3 with a directing group in position 2 (Scheme 7). The yields observed were comparable to those obtained with benzene derivatives, proving that the CONHTs directing group is also efficient on extended aromatic structures.
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3. Access to Six-Membered Rings through C–H Functionalization and Subsequent Transformation of Tosylbenzamides

If DGs have been shown to be effective in the formation of C-C and C–Heteroatoms, an interesting and emerging perspective relies on the ability of this DG to undergo further transformation after the C–H functionalization step. In this context, a potential reuse of part of the DG's atoms for the creation of fused carbo- or hetero-cycles in one-pot or sequential synthetic sequences is of high and general interest. The next sections are devoted to the synthesis of various five- and six-membered fused aza-heterocycles and fluorenones.

3.1. Sequential Approach

Installing an aryl moiety next to the CONHTs directing group allows an access to various polycyclic structures by using the DG to build additional five- or six-membered rings on various positions of the substrate. Among six-membered rings, phenanthridinones, for instance, are widely

Scheme 6. Arylation of benzene derivatives.

Scheme 7. Arylation of naphthalene derivatives.
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3.1. Sequential Approach

Installing an aryl moiety next to the CONHTs directing group allows an access to various polycyclic structures by using the DG to build additional five- or six-membered rings on various positions of the substrate. Among six-membered rings, phenanthridinones, for instance, are widely represented in natural compounds and can be easily obtained from arylated aromatic substrates bearing the CONHTs DG. On benzene, one example of such a reaction was reported using Pd(OAc)$_2$ as catalyst [21], and eight additional examples were isolated with good yields by Prim et al. on naphthalene derivatives [22] using PdCl$_2$ as catalyst (Scheme 8).

![Scheme 8. Access to phenanthridinones.](image)

3.2. One-Pot Sequence

Six-membered rings can also be accessed from a two-step one-pot process, as shown by Liang’s research, who reported the intermolecular annulation between aromatic substrates and allenes, leading to dihydroisoquinolinones [23]. In those examples, characteristic features are high regioselectivity, good substrate tolerance, and good functional group tolerance (Scheme 9). This transformation also provides an alternative and attractive route to such compounds, which usually requires multiple steps involving halogenated intermediates.

Recently, Yang [24] developed an elegant C–H functionalization/intramolecular allylation cascade process leading to dihydroisoquinolones. The Pd-catalyzed sequence involved 1,3-diene and
tosylbenzamides. Both aryl groups of the reactants tolerate wide substitution patterns. The catalytic system is based on Pd(TFA)\(_2\) and pyridine–oxazoline-type ligands. An asymmetric version of this transformation has also been reported leading to high yield and enantioselective combinations (Scheme 10).

Scheme 9. Access to dihydroisoquinolines.

Scheme 10. Synthesis of dihydroisoquinolones.
4. Access to Five-Membered Rings through C–H Functionalization and Subsequent Transformation of Tosylbenzamides

N-Tosylcarboxamides have the further advantage of also leading to five-membered rings. Such useful synthetic transformations allow researchers to save at least one part of the TDG and create new fused rings. Fluorenones and isoindolinones are relevant examples of synthetic strategies involving tosylbenzamides. The final cyclization step can occur besides a first C–H functionalization at isolated intermediates or during a C–H functionalization–cyclization one-pot sequence.

4.1. Fluorenones

The transformation of the N-tosylcarboxamide TDG into fluorenones was first reported by Fabis et al. [21]. Activation of the carbonyl group of the TDG in acidic media (TFA) at 120 °C led to the corresponding fluorenone in 81% yield (Scheme 11). In the naphthalene series [22], electrophilic cyclization into benzo-fused fluorenones required the use of TfOH (12 eq) in AcOH (0.1 M) to avoid cleavage and degradation of the directing group. Under such conditions, the construction of angular and linear tetra- and pentacyclic fluorenones was readily achieved. In the latter cases, both the substitution pattern of the aryl group and the position of the TDG at the naphthalene core were shown as key parameters towards selective cyclization. The obtaining of mixtures as well as the reaction pathways and crucial steps of the cyclization processes have been rationalized using density functional theory (DFT) calculations.

Scheme 11. N-Tosylcarboxamide as precursors of fluorenones.
### 4.2. Isoindolinones

The construction of isoindolinones has been studied by several groups within the last decades. In all cases, aromatic N-tosylamides were subjected to ortho C–H activation and functionalization prior to a cyclization step to afford the expected five-membered heterocycle by the consecutive formation of one C-C and one C-N bond. Several coupling partners can be used such as C-C double and triple bonds, aldimines, gem-difluoroolefins, internal alkenes, and alkynes as well as isocyanides or diazoacetates, leading to a large molecular and functional diversity at the isoindolinone architecture (Scheme 12).

![Scheme 12. Access to isoindolinones from sulfonylamides.](image)

Dihydroisoindolinones have been mainly obtained after ortho C–H activation and subsequent addition of alkenes. The overall reaction proceeds through oxidative alkenylation and intramolecular aza-Michael-type cyclization, leading to the formation of a monosubstituted sp³ carbon atom in the last step of the sequence. Common efficient catalytic systems involve Pd(OAc)₂/phenanthroline/O₂ [25] or [[RuCl₂(p-cymene)]₂]/CsOAc/O₂ [26].

An elegant alternative consists in using aldimines instead of alkenes. The transformation is catalyzed by [[RuCl₂(p-cymene)]₂]/NaHCO₃ and assumed to proceed through cleavage of the TDG and intramolecular cyclization from the nucleophilic nitrogen atom of the aldimine precursor. This method was revealed to be useful in introducing aromatic groups at the sp³ carbon atom of the heterocycle (Scheme 13, first line) [27].

Vinyldene-substituted isoindolinones can be readily obtained from two main approaches. The first involves oxidative alkenylation using styryl derivatives followed by aza-Wacker-type cyclization. Similarly to the classical Wacker reaction, Pd/Cu catalytic combination efficiently promotes (Scheme 13, second line) such a transformation [28]. The second method is based on a two-fold C-F bond cleavage-driven annulation that occurs when using gem-difluoro vinyl derivatives as coupling partner and [RhCp⁺Cl₂]₂/Na₂CO₃ as the catalytic system [29,30]. The formation of isoindolinones bearing a quaternary carbon center has also been evaluated (Scheme 13, third line). Interestingly, several coupling partners can be employed to this end. Maleimides afford spiroindolinones using [RhCp⁺Cl₂]₂/Cu(OAc)₂ as the catalytic system [31]. Symmetrical as well as unsymmetrical disubstituted alkenes may be used allowing the installation of various functional groups at the sp³ carbon center [31,32] using the same catalytic combination. Interestingly, symmetrical alkenes can be replaced by diazo derivatives such as diazoacetate. As shown by Zhu, the diazoacetate is first converted into the corresponding symmetrical alkene under Rh catalysis. The alkene is further subjected to the C–H olefination–cyclization process [31]. Using RuCl₃ as catalyst, internal alkynes can also produce isoindolinones with a quaternary center [33].
Finally, Zhu developed an interesting alternative by using isocyanates instead of classical C-C multiple bonds. [RhCp*Cl₂]₂/Cu(OAc)₂ promoted the formation of a C-N double bond that arises from C–H activation and formation of C-Rh bond, followed by 1,1-insertion of the isocyanide into the Rh-C bond (Scheme 13, last example). Subsequently, the product is obtained through a last reductive elimination step [34].

Scheme 13. Molecular and functional diversity at the isoindolinone architecture: selected examples.

4.3. Naphthalene-Fused Isoindolinones

Due to the unusual reactivity of naphthalene [4], only 2,3 fused naphthoisoindolinones had been obtained using CONHTs as a DG until Prim et al. described a two-step process leading to 1,2 fused naphthoisoindolinones. In that study, the authors showed that, when the position 3 of the naphthalene scaffold is already occupied, the DG can be fused on the remaining adjacent position, using a rhodium catalyst (Scheme 14). This synthetic pathway allows the obtaining of diversely substituted...
trifunctionalized naphthalene with good yields. The two steps of this process are compatible, and the transformation leading to the isoindolin-3-one from the naphthalene bearing only the DG can be performed through the one-pot sequential pathway [19].

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\text{NHTs} \quad \text{[Cp*RhCl₂(5mol%)]} \quad \text{AgOAc (2 eq.)} \quad \text{MeOH/AcOH} \quad \text{NTs}
\]

Scheme 14. Isoindolinones in the naphthalene series.

5. Conclusions

C–H activation and functionalization processes have now incorporated the chemist’s tool box. In this short review, the ability of N-tosylcarboxamide to serve as an efficient DG, orientate C–H activation, and further promote C–H functionalization has been highlighted. Alkenylation, alkoxylation, halogenation, and arylation reactions exemplify this first section. In addition to this classical role of a DG, this review focused on the beneficial use of N-tosylcarboxamide to further generate molecular diversity. Indeed, such a TDG can also act as CO or CON fragment reservoir that can be advantageously used for the construction of more elaborated architectures. In this context, fused five- and six-membered rings have been efficiently obtained. Variously substituted fluorenones obtained from such an approach account for the use of the CO fragment of the DG. Heterocycles such as phenanthridinones and isoindolinones could be prepared from the CON fragment of the TDG.

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