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Diversity-Orientated Stereoselective Synthesis through Pd-Catalyzed Switchable Decarboxylative C–N/C–S Bond Formation in Allylic Surrogates

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Abstract: Switchable catalytic transformation of reactants can be a powerful approach towards diversity-orientated synthesis from easily available molecular synthons. Herein, an endogenous ligand-controlled, Pd-catalyzed allylic substitution allowing for either selective C–N or C–S bond formation using vinyl ethylene carbonates and *N*-sulfonylhydrazones as coupling partners has been developed. This versatile methodology provides a facile, diversifying route for the highly chemo- and stereoselective synthesis of functional allylic sulfones or sulfonohydrazides. The newly developed protocol features wide substrate scope (nearly 80 examples), broad functional group tolerance and potential for the late-stage functionalization of bioactive compounds. The isolation and crystallographic analysis of a catalytically competent π -allyl Pd complex suggests that the pathway leading to the allylic products proceeds through a different manifold as previously proposed for the functionalization of VECs with nucleophiles.

Diversity-oriented synthesis aims to generate diverse structural motifs with a broad range of biological activities in a concise and efficient manner, and has thus received much attention in synthetic organic and medicinal communities.^[1] Undoubtedly, controllable and switchable strategies have emerged as a powerful tool to significantly increase the diversity and complexity of molecular architectures using reactants with tunable reactivity.^[2] Vinyl ethylene carbonates (VECs)^[3] have become popular substrates in transition metal catalyzed transformations including allylic substitution reactions.^[4] For example, highly regio-, stereo and enantioselective Pd-catalyzed allylic substitutions of VECs with water,^[3a] amines^[3p,3r] or thiols^[3q] to deliver valuable building synthetic blocks have been reported. In addition, Zhang et al. disclosed an elegant approach for the Pd-catalyzed asymmetric allylic substitution of VECs with water or alcohols towards the formation of branched allylic ethers and alcohols featuring chiral tertiary carbon centers.^[3m]

Notably, all these reported protocols exclusively employ the use of single nucleophiles in allylic substitution reactions of which

the regio- and stereo-bias is ligand-controlled (Scheme 1a). To the best of our knowledge, the chemo-switchable and stereoselective Pd-catalyzed allylic substitution of VECs in the presence of substrates incorporating different pro-nucleophilic sites remains elusive to date despite its potential to provide through a single process a much higher degree of molecular diversity (Scheme 1b).

(a) **Previous work:** *single* nucleophiles in allylic substitutions

(b) **Challenge:** *switchable* nucleophiles in allylic substitutions

(c) **This work:**

- Diversity-orientated synthesis of allylic sulfones/sulfonohydrazides
- Ligand directed high chemo-, regio- and stereoselective control
- Mild conditions, operationally simple, broad scope & FG diversity
- Late-stage allylic substitution of drug/bioactive molecules

Scheme 1. (a) Reported Pd-catalyzed allylic substitution reactions using VECs, (b) new conceptual diversity orientated approach, and (c) reaction design applied in this work.

In order to address this challenge (Scheme 2b), we envisioned the use of well-known and robust *N*-sulfonylhydrazones as coupling partners.^[5] From this versatile coupling partner three distinct intermediates can be generated including ambiphilic metal carbenes, sulfur nucleophiles as well as nucleophilic nitrogen species in the presence of suitable metals under basic conditions. Whereas the ambiphilic metal carbene intermediates have been widely utilized in transition metal catalyzed C–C bond formation,^[5b] the use of the S- and N-nucleophilic species in synthetic chemistry is still in its infancy. Therefore, the exploration of such unmapped chemical space can create new opportunities for diversity-orientated synthesis. Based on the previous successful accomplishments with *N*-tosylhydrazones^[5b,6] and VECs^[3i, 3l, 3o-r] in preparative chemistry, we hypothesized that activated *N*-sulfonylhydrazones could trap the allyl-Pd intermediate after decarboxylation of the VEC. By carefully manipulating the reaction conditions and ligands, either S-based or N-based nucleophiles may be generated *in situ*

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thereby creating a useful diversificating approach from a single set of substrates (Scheme 1c). Herein, we report the first example of a conceptually divergent, Pd-catalyzed stereoselective allylic substitution of VECs. This chemo-switchable C–N and C–S bond formation is scrutinized by the presence of simple endogenous ligands. Moreover, this protocol allows for easy access to multifunctional allylic scaffolds of importance in organic synthesis^[7] and being frequently encountered in many bioactive natural products.^[8]

Table 1. Optimization of the reaction conditions towards selective formation of allylic sulfone **3aa** or allylic hydrazone **4aa**.^[a]

Entry	Catalyst	Base (equiv)	Solv.	3aa ^[b]	4aa ^[b]
1	Pd ₂ (dba) ₃	K ₂ CO ₃ (2.4)	Diox	47% (87:13)	19%
2	Pd ₂ (dba) ₃	K ₂ CO ₃ (2.4)	DMF	46% (80:20)	–
3	Pd ₂ (dba) ₃	K ₂ CO ₃ (2.4)	MeCN	68% (93:7)	17%
4	Pd ₂ (dba) ₃	Na ₂ CO ₃ (2.4)	MeCN	trace	trace
5	Pd ₂ (dba) ₃	Et ₃ N (2.4)	MeCN	trace	trace
6	Pd ₂ (dba) ₃	Cs ₂ CO ₃ (2.4)	MeCN	39% (82:18)	–
7	Pd ₂ (dba) ₃	CsF (2.4)	MeCN	64% (93:7)	16%
8	Pd ₂ (dba) ₃	K ₂ CO ₃ (2.0)	MeCN	68% (94:6)	17%
9	Pd ₂ (dba) ₃	K ₂ CO ₃ (1.0)	MeCN	69% (94:6)	8%
10	Pd₂(dba)₃	K₂CO₃ (0.8)	MeCN	71% (94:6)	6%
11	Pd ₂ (dba) ₃	K ₂ CO ₃ (2.4)	MeCN	61% (92:8)	14%
12	Pd(OAc) ₂	K ₂ CO ₃ (2.4)	MeCN	56% (89:11)	8%
13	PdCl ₂	K ₂ CO ₃ (2.4)	MeCN	60% (92:8)	21%
14	Pd(PPh₃)₄	K₂CO₃ (2.4)	MeCN	–	94% ^[c]

[a] Reaction conditions: **1a** (0.05 mmol), **2a** (0.1 mmol), [Pd] (5 mol %) in solvent (0.5 mL) at 80 °C for 2 h; Diox stands for 1,4-dioxane, note that Pd₂(dba)₃ here reflects the use of the CHCl₃ solvate. [b] The yield of (*Z*)-**3aa** and (*Z*)-**4aa** was determined by the ¹H NMR using CH₂Br₂ as an internal standard; the *Z/E* ratios were determined from the crude product by ¹H NMR and values are reported in brackets. [c] The *Z/E* ratio of the product was >99:1.

Inspired by the challenge presented in Scheme 1b, we set out to examine the feasibility of this conceptual approach using the model VEC substrate **1a** and *N*-tosylhydrazone **2a**. To our delight, an initial trial (Table 1, entry 1) revealed that a catalytic system comprising Pd₂(dba)₃·CHCl₃ and K₂CO₃ gave rise to both C–S and C–N bond formation products albeit with unsatisfactory chemo- and stereoselectivity. The (*Z*)-configuration of **3aa** and **4aa** were confirmed by NOE analysis. When DMF was utilized as solvent under similar conditions, only **3aa** was produced in excellent chemoselectivity but with moderate stereocontrol (entry 2; 46% yield, *Z/E* = 80:20). Further solvent screening indicated that the overall conversion and stereoselectivity of **3aa** could be significantly enhanced in CH₃CN though some erosion of the

chemoselectivity was noted (Table 1, entry 3; **3aa**:**4aa** = 4:1, for **3aa**, *Z/E* = 93:7). These combined results highlight the challenge of simultaneous achieving high chemo- and stereoselectivity, and encouraged us to investigate the influence of different bases. The use of both Na₂CO₃ and Et₃N was unproductive (entries 4 and 5), and the presence of either Cs₂CO₃ or CsF did not further improve the results (entries 6 and 7). Gratifyingly, decreasing the amount of K₂CO₃ (cf., entries 8–10) to 0.8 equiv provided optimal chemo- and stereoselectivity towards **3aa** (entry 10; yield 71%, *Z/E* = 94:6). Variation of the Pd precursor was also examined (entries 11–14), and when a mixture of **1a** and **2a** was treated with Pd(PPh₃)₄ and K₂CO₃ in CH₃CN (entry 14), exclusively C–N bond formation could be achieved giving allylic hydrazone **4aa** in 94% yield and in excellent stereoselectivity (*Z/E* >99:1). This complete switch in chemoselectivity may be attributed to stronger π–π interactions between the PPh₃ ligand and nucleophilic intermediate obtained from **2a**, and notably no exogenous ligand was required to induce this switch in chemoselectivity.

Scheme 2. The scope of allylic sulfones **3** derived from various VECs and *N*-sulfonylhydrazones using the reaction conditions of Table 1, entry 10. Reported yields are of the isolated product.

With the optimized conditions in hand, first the scope of the Pd-catalyzed allylic sulfone formation was explored varying both the VEC and *N*-sulfonylhydrazone substrate (Scheme 2).^[9] A series of *para*-, *meta*- and *ortho*-monosubstituted aryl groups in the substituted VECs with either electron-donating or electron-withdrawing character are well-tolerated by the developed protocol to afford **3ba–3ka** in moderate to good yields with excellent chemo- (typically >90%) and stereoselectivity (for **3ba** X-ray analysis confirmed the major isomer, see also the Supporting Information, SI).^[10] Particularly, substrates bearing chloro or bromo functional groups were also amenable to the standard conditions (**3ga** and **3la**), thus offering potential for

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further functionalization. The catalytic system also showed compatibility with sulfur-containing VECs allowing to isolate **3ma** in high yield without any sign of catalyst deactivation. The R¹ group of the VEC could be extended to aliphatic substituents such as methyl (**3na**), cyclohexyl (**3oa**) and tetrahydropyranyl (**3pa**) and all provided reasonable yields under high stereoselection. Cycloalkyl groups with fused aromatic rings (**3qa** and **3ra**) could also be introduced in the allylic sulfone product while maintaining high chemo- and stereoselectivity.

Scheme 3. The scope of allylic sulfonohydrazides **4** derived from various VECs and *N*-sulfonohydrazones using the reaction conditions of Table 1, entry 14. Reported yields are of the isolated product.

Subsequently, a series of substituted *N*-tosylhydrazone substrates was tested (Scheme 2, lower part; compounds **3ab–3am**) and those having aryl groups with electron-donating substituents favored higher yields than those with electron-withdrawing groups. Apart from simple aromatic rings, also naphthyl (**3aj**), cyclopropyl (**3al**) and 3-pyridyl (**3am**) could be introduced in the allylic sulfone product being relevant to target-oriented synthesis. For the latter derivative, a lower chemoselectivity was observed, though excellent stereoselectivity could be achieved.

The scope of the Pd-catalyzed formation of allylic sulfonohydrazides was also evaluated (Scheme 3). The substrate scope of these reactions also proved extensive, and in the majority of the cases excellent chemo- and stereoselectivity was observed regardless the electronic and steric properties of the substrates. Aryl groups in the VECs with different types of substitution (*ortho*, *meta* or *para*) were endorsed by the catalytic procedure (*cf.*, compounds **4ba–4la**), while the presence of various heterocyclic, vinyl and alkyl groups also allowed to deliver allylic sulfonohydrazides **4ma–4ra** in good yield and under high stereo-control except for **4ta** (Z/E = 74:26).

The generality of this C–N bond formation protocol could be further illustrated by successful synthesis of various allylic sulfonohydrazides (*cf.*, products **4ab–4at**) that comprise a variety of heterocyclic groups such as naphthyl, pyridyl, (substituted) thiophenyl, furyl, morpholinyl and piperidinyl, and substituted aromatics with potentially useful nitro (**4af**) and halide substituents (**4ae**, **4ah** and **4ak**). In all aforementioned examples, formation of the targeted products was observed with good yields (typically >70%) with excellent Z/E ratios of up to >99:1.

Scheme 4. Late-stage functionalization of biologically important scaffolds with allylic sulfone or sulfonohydrazide groups. Reported yields are of the isolated product.

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Fragment-based drug design has emerged as a crucial strategy to accelerate lead compound identification,^[11] and this encouraged us to use our develop protocol for late-stage functionalization of important drug scaffolds (Scheme 4; see also the SI for further details). We first prepared Erlotinib (used in lung cancer treatment)^[12] and Pregnenolone (neuroprotecting agent)^[13] analogues by incorporating VEC fragments. The late-stage functionalization of these two biologically relevant scaffolds was successfully accomplished (compounds **3ua**, **4ua**, **3va** and **4va**) and allowed the introduction of functionalized allylic sulfone and sulfonylhydrazide groups. Alternatively, Erlotinib, Pregnenolone, Fenofibrate,^[14] and Testosterone^[15] could be easily substituted with *N*-tosylhydrazones which after treatment with VEC **1a** under the optimal conditions (Table 1, entry 14) gave smooth access to the products **4ay**, **4az**, **5aa**, and **5ab** in high yields and with excellent stereocontrol.

Scheme 5. Gram-scale reaction of **3aa** and further transformations furnishing **6a–8a**. All reported yields are from the isolated product. See for details the SI.

We further evaluated the robustness and practicality of allylic sulfone formation reactions (Scheme 5) using **3aa** as a representative case, which could be easily prepared on gram scale. The alcohol fragment in **3aa** could be conveniently oxidized to an aldehyde through a Dess-Martin oxidation, whereas the double bond in **3aa** could be reduced using a Pd/C catalyst under H₂ to give product **7a** in 87% yield. Treatment of **3aa** under standard Mitsunobu reaction conditions afforded **8a**, whereas the allylic sulfone could also be a viable starting point for the formation of 1,3-oxazolines based on [3+2] cycloaddition reaction recently reported by Terada and coworkers.^[16]

Several experiments were conducted to gain insight into the mechanism of this Pd-catalyzed switchable allylic C–N/C–S bond formation process (Scheme 6, top). Treatment of a stoichiometric combination of [Pd₂(dba)₃·CHCl₃] and VEC **1a** in CH₃CN while adding 2-acetylpyridine resulted in decarboxylation and afforded unexpectedly the π -allyl Pd complex **9** in 45% isolated yield. Complex **9** was fully characterized by ¹H and ¹³C NMR, and X-ray crystallography.^[10] The structure of **9** reveals that the Pd center is η^3 -ligated by the allyl fragment and the hydromethyl group is orientated *syn* to the metal center. Such a π -allyl Pd complex is rather distinct from the DFT-computed six-membered palladacycle recently determined in the functionalization of VECs with various nucleophiles.^[3f,i,q,v] To examine whether this Pd-complex **9** is catalytically competent, it was subjected to the optimized conditions reported in Table 1. First, **9** was combined with substrates **1a** and **2a**, and allylic sulfone **3aa** could be

isolated in 83% yield. When the same substrates were treated in the presence of a catalytic amount of PPh₃, the chemoselectivity was completely reversed towards the formation of the allylic sulfonylhydrazide **4aa** (90% yield). Both yields obtained for **3aa** and **4aa** in the presence of **9** were improved compared to those experiments relying on *in situ* preparation of the active catalyst, and indeed suggest that a Pd(allyl) intermediate similar to **9** may be a catalytic intermediate with the presence of the phosphine ligand exerting a crucial role in the switching of the chemoselectivity.^[17]

Scheme 6. Mechanistic control experiments (top) and proposed manifolds for the formation of the allylic sulfones and sulfonylhydrazides (bottom).

On the basis of these mechanistic control reactions and previous reports, we propose that the synthesis of the allylic products starts off with the decarboxylative oxidative addition of the VEC (here **1a** used as a representative case) to the Pd(0) precursor generating a π -allyl palladium intermediate similar to **9**. From here the reaction proceeds via nucleophilic attack onto this Pd(allyl) intermediate involving either C–S or C–N bond formation providing selectively the allylic sulfone (via Nu²) or sulfonylhydrazide (via Nu¹) and regenerating the requisite Pd(0) catalyst for subsequent turnover. The type of nucleophile that is generated *in situ* can be regulated under basic conditions.

In summary, we have developed the first example of a chemo-switchable allylic C–N or C–S bond formation reaction through an endogenous ligand-controlled, Pd-catalyzed conversion of versatile vinyl-ethylene carbonate and *N*-sulfonylhydrazone substrates. This developed protocol exhibits broad substrate scope and excellent functional group tolerance important for diversity-orientated synthesis and drug discovery. The catalytic methodology can also be applied to late-stage functionalization of bioactive scaffolds by introduction of various allylic fragments. Further diversity-oriented transition metal mediated transformations are currently targeted to further expand this conceptual approach.

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Keywords: allylic substitution • decarboxylation • *N*-sulfonylhydrazones • Pd catalysis • vinyl-ethylene carbonates

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- [17] 2-Acetylpyridine addition (5 mol%) during the catalytic reaction leads to product **3aa** (68%, *Z/E* = 91:9). The result is similar compared with the optimized protocol provided in Table 1, entry 10 (yield of **3aa**: 71%, *Z/E* = 94:6). This may further indicate the existence of an allyl-Pd intermediate as suggested in Scheme 6.

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Nucleophilic Switch: A conceptually attractive and switchable Pd-catalyzed allylic substitution of vinyl-ethylene carbonates with sulfonylhydrazones has been developed in the context of diversity-orientated synthesis. The chemo-switchable C–S and C–N bond formation reactions are highly versatile, and allow for broad scope under high regio- and stereocontrol. Examples of late-stage modification of biologically relevant scaffolds with functional allylic groups add further synthetic value to the developed catalytic protocol.

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