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Palladium-Catalyzed Generation and Reactivity of Allylsulfones

Tingting Chen

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Palladium-Catalyzed Generation and Reactivity of Allylsulfones

Présentée par

Tingting CHEN

Pour obtenir le grade de

Docteur de Sorbonne Université

Soutenance publique prévue le 8 Septembre 2023

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Yours,

Chen

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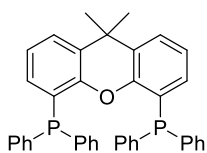
List of abbreviations

2,5-DMBQ	2,5-dimethyl-1,4-benzoquinone
2,6-DMBQ	2,6-dimethyl-1,4-benzoquinone
4Å MS	4Å molecular sieves
acac	acetylacetonate
BINOL	1,1'-bi(2-naphthol)
BMim	1-butyl-3-methylimidazolium
BQ	1,4-benzoquinone
BSA	<i>N,O</i> -bis(trimethylsilyl)acetamide
CMD	concerted metalation deprotonation
DABSO	DABCO- <i>bis</i> (sulfur dioxide)
DAF	4,5-diazafluoren-9-one
dba	dibenzylideneacetone
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCE	1,2-dichloroethane
DIBAL-H	diisobutylaluminium hydride
DIPEA	<i>N,N</i> -diisopropylethylamine
DMAc	<i>N,N</i> -dimethylacetamide
DMF	<i>N,N</i> -dimethylformamide
DMPU	<i>N,N'</i> -dimethylpropylene urea
DMSO	dimethylsulfoxide
DPEPhos	Bis[(2-diphenylphosphino)phenyl]ether
dppb	bis(diphenylphosphino)butane
dppe	bis(diphenylphosphino)ethane
dppf	bis(diphenylphosphino)ferrocene
dppp	bis(diphenylphosphino)propane
DQ	duroquinone (2,3,5,6-tetramethyl-1,4-benzoquinone)
dtbpy	4,4'-di- <i>tert</i> -butyl-2,2'-dipyridyl
hfacac	hexafluoroacetylacetonate
HFIP	1,1,1,3,3,3-hexafluoro-2-propanol (hexafluoroisopropanol)
HMDS	hexamethyldisilazane
HMPA	hexamethylphosphoramide
HWE	Horner-Wadsworth-Emmons (olefination)
L/B	linear vs. branched
LED	light-emitting diode
LG	leaving group
MTBE	methyl <i>tert</i> -butyl ether
MOM	methoxymethyl
NMR	Nuclear Magnetic Resonance
Ns	nosyl

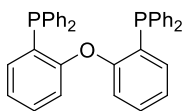
PMB	<i>p</i> -methoxybenzyl
<i>rac</i>	racemic
rt	room temperature
SET	Single Electron Transfer
SM	Starting Material
SOX	sulfoxide oxazoline (ligand)
SPB	sodium perborate tetrahydrate (NaBO ₃ •4H ₂ O)
TBAB	tetra- <i>n</i> -butylammonium bromide
TBAI	tetra- <i>n</i> -butylammonium iodide
TBAT	tetra- <i>n</i> -butylammonium difluorotriphenylsilicate
TBHP	<i>tert</i> -butyl hydroperoxide
TFA	trifluoroacetate
THF	tetrahydrofuran
TLC	thin layer chromatography
TM-DOM	transition-metal catalyzed pure-domino reaction
TM-PDOM	transition-metal catalyzed pseudo-domino reaction
TPPTS	3,3',3''-phosphanetriyltris(benzenesulfonic acid) trisodium salt
Ts	tosyl
VE	valence electrons
XPhos	Dicyclohexyl[2',4',6'-tris(propan-2-yl)[1,1'-biphenyl]-2-yl]phosphane

List of ligands

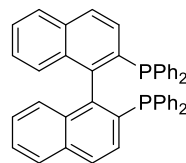
Diphosphines



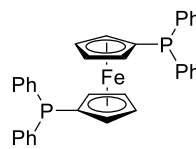
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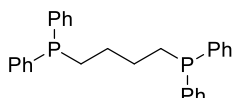
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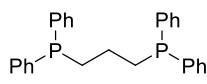
rac-BINAP



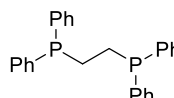
dppf



dppb

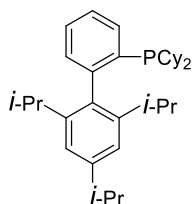


dppp

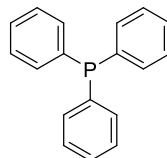


dppe

Monophosphines

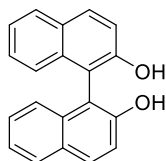


XPhos

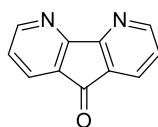


PPh₃

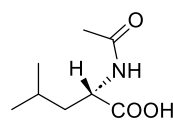
Other ligands



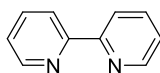
BINOL



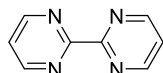
DAF



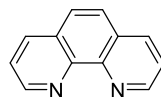
N-Acetyl-L-leucine



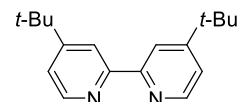
2,2'-Bipyridine



2,2'-Bipyrimidine



1,10-phenanthroline

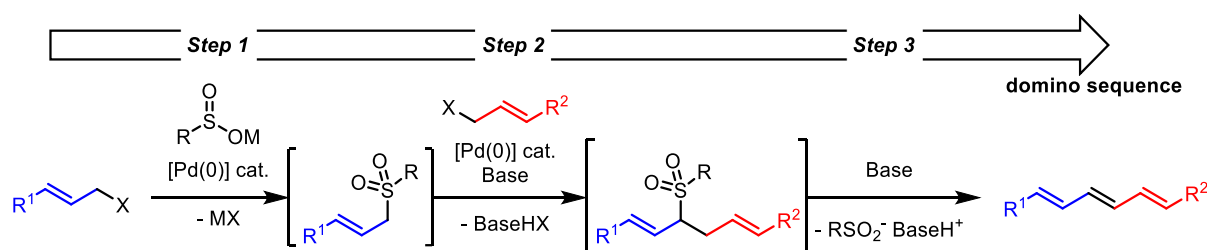


dtbpy

General introduction

Organopalladium chemistry has found a variety of applications in organic synthesis, including cross-coupling reactions, C–H functionalization, asymmetric catalysis, and domino reactions. In particular, the palladium-catalyzed allylation is a very important transformation that allows to build-up complex structures in one or few synthetic operations.^[1] In addition, allylsulfones constitute an extremely useful functional group that plays a key role in a number of important organic reactions. In this context, our group pioneered the palladium chemistry of sulfenate anions (RSO^-),^[2] showing that the palladium-catalyzed allylation of *in situ* generated sulfenate anions provides an efficient route to generate corresponding allyl sulfoxides, and allows the development of interesting pseudo-domino processes.^[3]

My PhD project aimed to develop new transformations involving palladium catalysis and exploring the chemistry of sulfones, and can be divided into two projects. The first one deals with the development of a new domino reaction to access 1,3,5-trienes via a sequence of three consecutive reactions, two of them being catalyzed by palladium complexes. In the event, steps 1 and 2 are both Pd(0)-catalyzed, and, provided that a strong base is added after the first step, all steps could in principle be run in a one-pot mode. The subsequent sulfone elimination is also base promoted (Scheme 1).



Scheme 1. Project 1: Pd-catalyzed synthesis of conjugated trienes by a domino sequence.

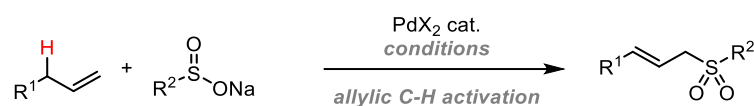
^[1] For a selection of reviews on this topic, see: a) Liron, F.; Oble, J.; Lorion, M. M.; Poli, G. *Eur. J. Org. Chem.* **2014**, 5863-5883; b) Mann, S. E.; Benhamou, L.; Sheppard, T. D. *Synthesis* **2015**, 47, 3079-3117; c) Tang, H.; Huo, X.; Meng, Q.; Zhang, W. *Acta Chim. Sinica* **2016**, 74, 219-233; d) For a chapter review, see: Kammerer-Pentier, C.; Liron, F.; Prestat, G.; Poli, G. *Selectivity in palladium catalyzed allylic substitution*, in: U. Kazmaier (Ed.), *Transition Metal Catalyzed Enantioselective Allylic Substitution in Organic Synthesis*, vol. 38, *Topics in Organometallic Chemistry*; Springer-Verlag, Berlin Heidelberg, **2012**, pp. 1-64.

^[2] a) Maitro, G.; Prestat, G.; Madec, D.; Poli, G. *Tetrahedron: Asym.* **2010**, 21, 1075-1084; b) Aversa, M.C.; Bonaccorsi, P.; Madec, D.; Prestat, G.; Poli, G. In *Innovative Catalysis in Organic Synthesis*, Andersson P. G. Ed., Wiley-VCH Weinheim, **2012**, Chapt. 3, pp 47-76 *The Fabulous Destiny of Sulfenic Acids*.

^[3] a) Maitro, G.; Prestat, G.; Madec, D.; Poli, G. *J. Org. Chem.* **2006**, 71, 7449-7454; b) Bernoud, E.; Le Duc, G.; Bantreil, X.; Prestat, G.; Madec, D.; Poli, G. *Org. Lett.*, **2010**, 12, 320-323; c) Kleimark, J.; Prestat, G.; Poli, G.; Norrby, P.-O. *Chem. Eur. J.* **2011**, 17, 13963-13965.

The second project deals with the preparation of allylsulfones by Pd(II)-catalyzed allylic C–H activation. Direct PdX₂-catalyzed C–H activation/functionalization is a powerful method for the construction of carbon-carbon bonds and carbon-heteroatom bonds.^[4] However, the direct PdX₂-catalyzed C-H sulfonylation procedure for the formation of the C-S bond has never been reported. Considering that the classical method to synthesize allylsulfones has the drawback of lacking economical and environment-friendly properties, it is a necessity to develop more efficient methods to prepare allylsulfones.

Based on previous reports from the literature,^[5] we seek to find out reaction conditions that allow the synthesis of allylsulfones starting from abundant and commercially available terminal alkenes (Scheme 2).



Scheme 2. Project 2: Pd(II)-catalyzed sulfonylation of terminal alkenes.

The structure of the thesis consists of four chapters. In the first chapter, I will give a brief introduction to palladium chemistry and allylsulfones, along with some literature reporting Pd-catalysis in relation to allyl sulfones. The second chapter concerns the study of the Pd-catalyzed domino sequence towards the synthesis of conjugated trienes. The introduction of allylic C–H sulfonylation and PdX₂-catalyzed allylic C-H activation will be presented in Chapter 3. In the last chapter, the optimization and scope of the PdX₂-catalyzed allylic C–H sulfonylation will be described.

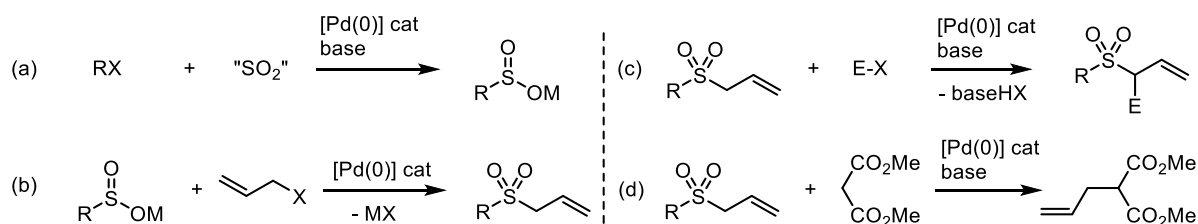
^[4] a) Li, H.; Li, B. J.; Shi, Z. J. *Catal. Sci. Technol.* **2011**, *1*, 191–206; b) Liron, F.; Oble, J.; Lorion, M. M.; Poli, G. *Eur. J. Org. Chem.* **2014**, 5863–5883; c) Tang, H.; Huo, X.; Meng, Q.; Zhang, W. *Acta Chim. Sin.* **2016**, *74*, 219–233; d) Fernandes, R. A.; Nallasivam, J. L. *Org. Biomol. Chem.* **2019**, *17*, 8647–8672.

^[5] a) Chen, M. S.; Narayanasamy, P.; Labenz, N. A.; White, M. C. *J. Am. Chem. Soc.* **2005**, *127*, 6970–6971; b) Diamante, D.; Gabrieli, S.; Benincori, T.; Broggini, G.; Oble, J.; Poli, G. *Synthesis* **2016**, *48*, 3400–3412.

Chapter 1. Introduction to η^3 -allylpalladium chemistry and allylsulfones.

1. Introduction

Among the huge number of transformations associated to sulfones, some of them are palladium-catalyzed processes (Scheme 3). This is the case of the generation of sulfinate anions (RSO_2^-)^[6] from aryl (or heteroaryl) halides and SO_2 sources ($\text{K}_2\text{S}_2\text{O}_5$ or DABSO^[7,8]) (equation a), the formation of allyl sulfones by the reaction between sulfinate anions and allyl esters (equation b);^[9,10] the deprotonation of allyl sulfones by strong bases ($\text{p}K_{\text{a(DMSO)}} \text{PhSO}_2\text{allyl} = 22$) and *in situ* α -alkylation with electrophiles, including η^3 -allylpalladium complexes,^[11] (equation c), and the allylation of malonates with allylsulfones (equation d).^[12]



Scheme 3. Unrelated S-dioxide-based Pd-catalyzed reactions.

The rational combination of the above, unrelated, rather old catalytic transformations may enable the development of smart and unprecedented coupling protocols. The optimization of disjointed catalytic transformations into a single domino sequence is not a simple task and may require a delicate and careful fine-tuning of several reaction parameters.

My initial PhD project aimed to develop a new sequence to access 1,3,5-trienes via a sequence of three consecutive reactions – possibly achievable in domino mode – two of which catalyzed by

^[6] For reviews on sulfonates, see: a) Aziz, J.; Messaoudi, S.; Alami, M.; Hamze, A. *Org. Biomol. Chem.* **2014**, *12*, 9743-9759; b) Liang, S.; Hofman, K.; Friedrich, M.; Manolikakes, G. *Eur. J. Org. Chem.* **2020**, 4664-4667.

^[7] DABSO = DABCO-bis(sulfur dioxide). For a review, see: Hashtroudi, M. S.; Vavsari, V. F.; Balalaie, S. *Org. Biomol. Chem.* **2022**, *20*, 2149-2163.

^[8] a) Shavnya, A.; Coffey, S. B.; Smith A. C. Mascitti, V. *Org. Lett.* **2013**, *15*, 6226-6229; b) Richards-Taylor, C. S.; Blakemore, D. C.; Willis, M. C. *Chem. Sci.* **2014**, *5*, 222-228.

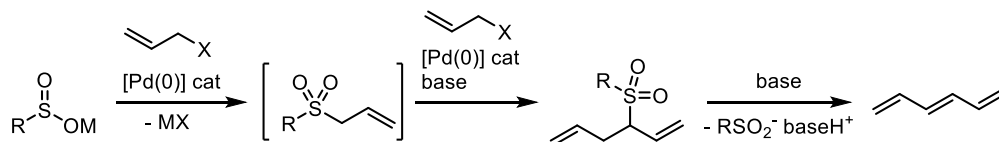
^[9] Julia, M.; Nel, M.; Saussine, L. *J. Organomet. Chem.* **1979**, *181*, C17.

^[10] The reaction takes usually place at the soft sulfur center.

^[11] Trost, B. M.; Weber, L. *J. Org. Chem.* **1975**, *40*, 3617-3619.

^[12] a) Trost, B. M.; Schmuff, N. R.; Miller, J. M. *J. Am. Chem. Soc.* **1980**, *102*, 5979-5981. b) Clayden, J.; Julia, M. *J. Chem. Soc., Chem. Commun.* **1994**, 1905-1906.

palladium.^[13] The sequence is the following: a) a Pd-catalyzed allylation of an aryl sulfinate anion by reaction with an allylic electrophile;^[9,10] b) the subsequent Pd-catalyzed α -allylation of the carbanion of the resulting allyl sulfone by reaction with a second allylic electrophile,^[11] and c) the base promoted elimination of the resulting (3-arylsulfonyl)hexa-1,5-diene, to give the desired 1,3,5-triene (Scheme 4).



Scheme 4. Initial plan of the PhD thesis

As this project is based on palladium catalysis and domino reactions, I will start this manuscript with a brief introduction of palladium catalysis in general. Then, I will describe the state of the art of Pd(0)-catalyzed allylations of sulfur-based nucleophiles, as well as the reactivity of allyl sulfones. Finally, I will disclose some concepts and selected precedents of Pd-catalyzed domino sequences.

2. The Chemistry of Palladium

Organopalladium chemistry has found a variety of applications in organic synthesis, especially in industrial processes. Indeed, the development of palladium-catalyzed cross-coupling reactions has been awarded with the Nobel prize in chemistry in 2010 for Richard F. Heck, Akira Suzuki and Ei-ichi Negishi.^[14] Palladium catalysts are able to favor and accelerate transformations that are hard to perform with more classical techniques. In most cases, palladium-catalyzed reactions take place under mild reaction conditions and tolerate a lot of functional groups. Palladium-catalyzed couplings have proven to be powerful and key reactions for the synthesis of a great number of targets, including carbo- and heterocycles.^[14a,14c,15]

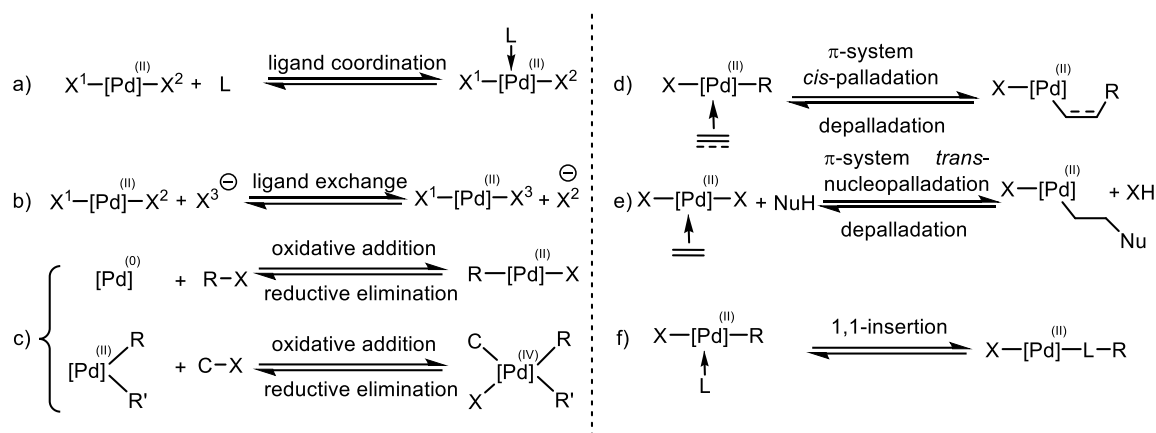
Palladium is a transition metal of the nickel triad, located in the second row of the periodic table.

^[13] For another recent contribution, see: Chen, Y.; Coussanes, G.; Souris, C.; Aillard, P.; Kaldre, D.; Runggatscher, K.; Kubicek, S.; Di Mauro, G.; Maryasin, B.; Maulide, N. *J. Am. Chem. Soc.* **2019**, *141*, 13772-13777.

^[14] For a selection of reviews on Pd-catalyzed cross-coupling reactions, see: (a) Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem. Int. Ed.* **2005**, *44*, 4442-4489; (b) Torborg, C.; Beller, M. *Adv. Synth. Catal.* **2009**, *351*, 3027-3043; (c) Johansson Seechurn, C. C. C.; Kitching, M. O.; Colacot, T. J.; Snieckus, V. *Angew. Chem. Int. Ed.* **2012**, *51*, 5062-5085; (d) Devendar, P.; Qu, R.-Y.; Kang, W.-M.; He, B.; Yang, G.-F. *J. Agric. Food Chem.* **2018**, *66*, 8914-8934.

^[15] a) Bolm, C. *J. Org. Chem.* **2012**, *77*, 5221-5223; b) *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E., Ed.; Wiley: New York, **2002**; c) *Cross-Coupling Reactions. A Practical Guide*; Miyaura, N., Ed. *Top. Curr. Chem.* **2002**, *219*; d) *Metal-Catalyzed Cross-Coupling Reactions, 2nd ed.*; de Meijere, A., Diederich, F., Eds.; Wiley-VCH: Weinheim, **2004**; e) Corbet, J.-P.; Mignani, G. *Chem. Rev.* **2006**, *106*, 2651-2710; f) Jana, R.; Pathak, T. P.; Sigman, M. S. *Chem. Rev.* **2011**, *111*, 1417-1492; g) van Leeuwen, P. W. N. M. and Chadwick, J. C. **2011**, *Metal-Catalyzed Cross-Coupling Reactions* (chapter 9), in *Homogeneous Catalysts: Activity - Stability - Deactivation*, Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim, Germany; h) *Chemical Society Reviews*, themed collection: *Cross coupling reactions in organic synthesis*, **2011**, Issue 10, 4877-5208; i) Colacot, T. (Ed.) *New Trends in Cross-Coupling: Theory and Applications* **2015**, RSC press; j) Tsuji, J. *Palladium Reagents and Catalysts*, J. Wiley and Sons, **2004**; k) Tsuji, J. Ed. *Palladium in Organic Synthesis*, Springer, **2005**.

Its ground-state electronic structure is $[\text{Kr}] 4d^{10}5s^0$. Except rare exceptions, palladium complexes exist in the three oxidation states: Pd(0), Pd(II), Pd(IV),^[16] each oxidation state exhibiting different chemical properties. The main elementary steps involving palladium complexes are: a) dative ligand coordination, b) ligand exchange, c) oxidative addition / reductive elimination [Pd(0)/Pd(II) or Pd(II)/Pd(IV)], d) π -system (alkene/alkyne) *cis*-palladation (migratory insertion), e) π -system *trans*-nucleopalladation and f) dative ligand 1,1-insertion (Scheme 5).^[17]



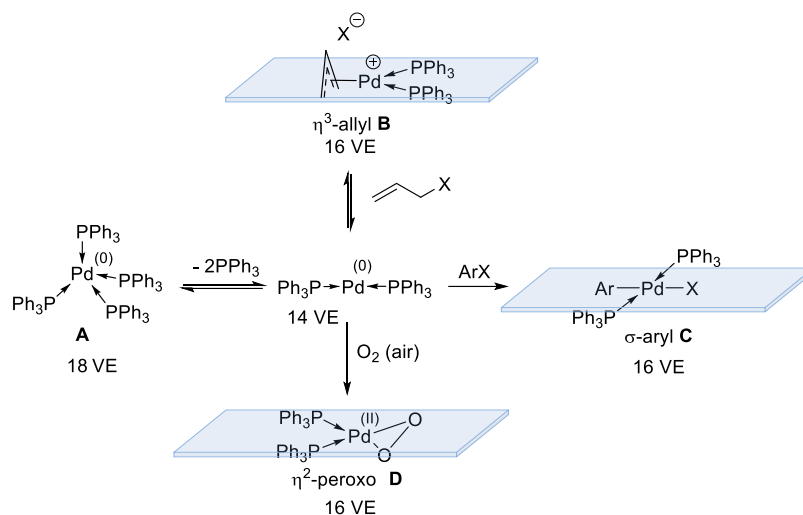
Scheme 5. Main elementary steps involved in Pd-catalyzed reactions.

As a function of the nature of the ligands and reagents involved, the equilibria of these reactions may be more or less displaced to the left or right side, reversible or irreversible. All the Pd-catalyzed reactions feature a combination of the above elementary steps. The starting elementary step of the catalytic cycle can be the oxidative addition, the ligand coordination, or the ligand exchange, while the closing elementary step may be the reductive elimination or the depalladation step (usually dehydropalladation).

Thus, for example, phosphine- or NHC-ligated Pd(0) complexes are d^{10} electron-rich, nucleophilic species and can oxidatively add to electrophilic partners to give square planar Pd(II) 16 valence-electron (VE) complexes. This is for example the case of: a) allylic derivatives, which form η^3 -allylpalladium(II) complexes **B**; b) aryl halides (or pseudo-halides), which form σ -arylpalladium(II) halides **C**; and c) molecular oxygen, which forms the η^2 -peroxopalladium(II) complex **D** (Scheme 6).

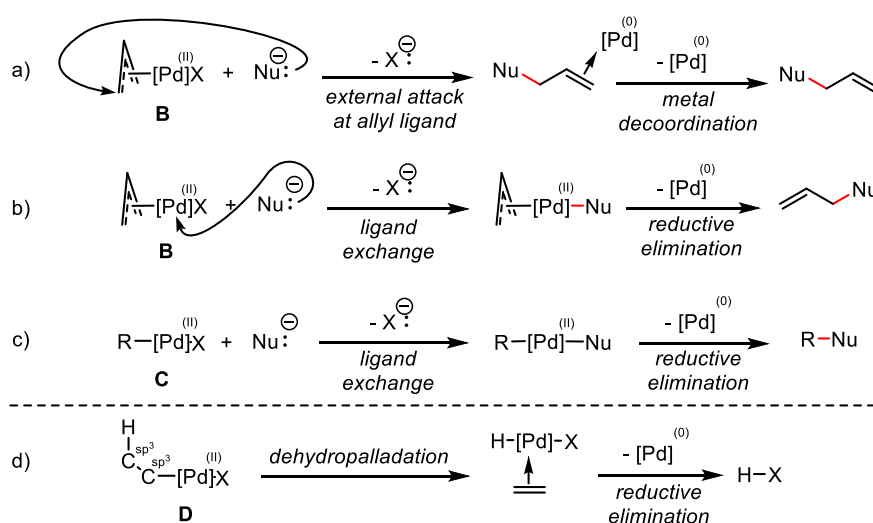
^[16] For selected reviews on the chemistry of Pd(0), Pd(II) and Pd(IV) complexes, see: a) Tsuji, J. *Synthesis* **1990**, *13*, 739–749; b) Sehnal, P.; Taylor, R. J. K.; Fairlamb, I. J. S. *Chem. Rev.* **2010**, *110*, 824–889.

^[17] Throughout the manuscript: a) brackets around palladium atom intend to render implicit the dative ligand(s); b) R: covalent carbon-based ligand, X: covalent heteroatom-based ligand, L: dative ligand.



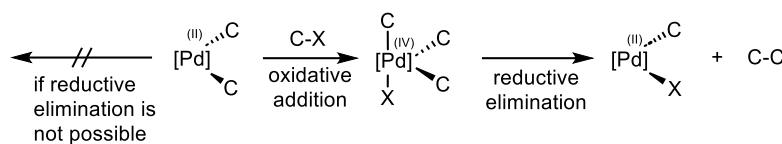
Scheme 6. Oxidative addition of Pd(0) complexes.

The η^3 -allylpalladium(II) complexes **B** and the σ -arylpalladium(II) halides **C** are important electrophilic intermediates in organic chemistry. The former ones, reversibly formed by oxidative addition of Pd(0) complexes and allylic systems (see above), as a function of the nature of the nucleophile, can suffer two types of allylic substitution: a) exterior attack of the nucleophile at the allylic ligand, *anti* to the Pd atom (*alias anti*-reductive elimination) (observed with soft nucleophiles); or b) ligand displacement at Pd atom, followed by *syn*-reductive elimination (observed with hard nucleophiles). σ -Arylpalladium(II) halides **C**, usually irreversibly formed by oxidative addition of Pd(0) to aryl halides or pseudo-halides (see above), also suffer ligand substitution on palladium followed by reductive elimination. On the other hand, $C(sp^3)$ organopalladium complexes bearing a β -H atom **D**, tend to undergo a very easy dehydropalladation (Scheme 7).



Scheme 7. Evolution of organopalladium(II) complexes with nucleophiles.

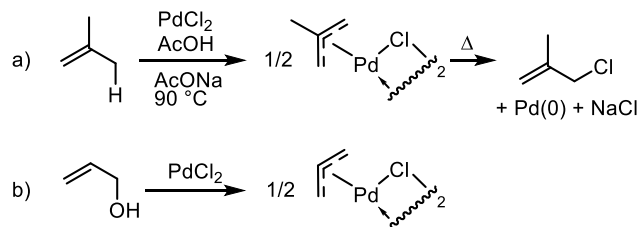
Pd(IV) complexes are quite rare, although a few complexes are known. These complexes have hardly been isolated, but transient Pd(IV) species are increasingly considered as intermediates in palladium-catalyzed reactions (Scheme 8).



Scheme 8. Evolution of transiently formed Pd(IV) complexes.

2.1. η^3 -Allylpalladium Complexes

As early as 1959, Hüttel^[18] and Hafner^[19] independently reported the first preparation of the η^3 -allylpalladium chloride dimer. While the former protocol relied on what we would now call a C–H allylic activation of simple olefin (Scheme 9, top left equation), the second one was likely due to *in situ* reduction of PdCl₂ to Pd(0), followed by oxidative addition of the alcohol (Scheme 9, bottom equation). In a series of subsequent papers Hüttel showed, *inter alia*, the thermally induced reductive elimination of these dimeric complexes to give the corresponding allylic chloride. However, no synthetic application was reported at that time.



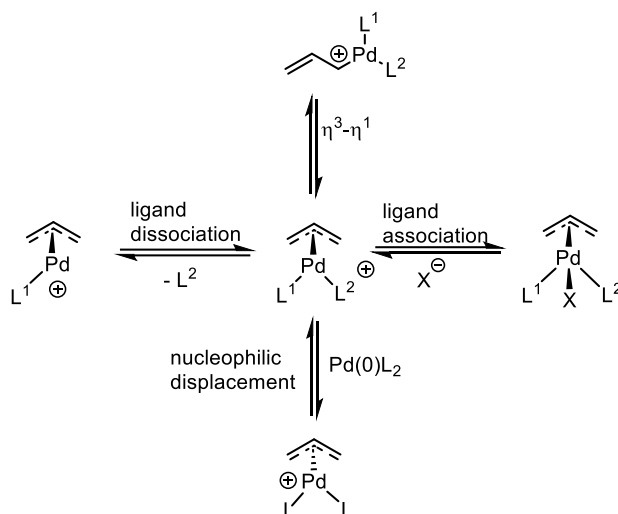
Scheme 9. Pioneering generation of η^3 -allylpalladium complexes.

In solution, these complexes are fluxional molecules and can be engaged in several dynamic equilibrations. In the absence of a nucleophile, or if the trapping step is slow enough, the π -allylpalladium complex may undergo the following four different equilibria: a) $\eta^3 \rightarrow \eta^1$ isomerization, b) ligand association, c) ligand dissociation, d) nucleophilic displacement by a Pd(0)L_n complex. Activation of these equilibria depends on the reaction conditions and can trigger exchange of the allyl face

^[18] a) Hüttel, R.; Kratzer, J. *Angew. Chem.* **1959**, *71*, 456-456; b) Hüttel, R.; Bechter, M. *Angew. Chem.* **1959**, *71*, 456-456; c) Hüttel, R.; Kratzer, J.; Bechter, M. *Chem. Ber.* **1961**, *94*, 766-780; d) Hüttel, R.; Christ, H. *Chem. Ber.* **1963**, *96*, 3101-3104; e) Hüttel, R.; Christ, H. *Chem. Ber.* **1964**, *97*, 1439-1452; f) Hüttel, R.; Dietl, H.; Christ, H. *Chem. Ber.* **1964**, *97*, 2037-2045; g) Hüttel, R.; Christ, H.; Herzog, K. *Chem. Ber.* **1964**, *97*, 2710-2712; h) Hüttel, R.; Dietl, H. *Chem. Ber.* **1965**, *98*, 1753-1760; i) Hüttel, R.; McNiff, M. *Chem. Ber.* **1973**, *106*, 1789-1803; j) Hüttel, R. *Synthesis* **1970**, 225-255; See also: k) Morelli, D.; Ugo, R.; Conti, F.; Donati, M. *Chem. Commun.* **1967**, 801-802; l) Clark, D.; Hayden, P.; Smith, R. D. *Discuss. Faraday Soc.* **1968**, *46*, 98-109.

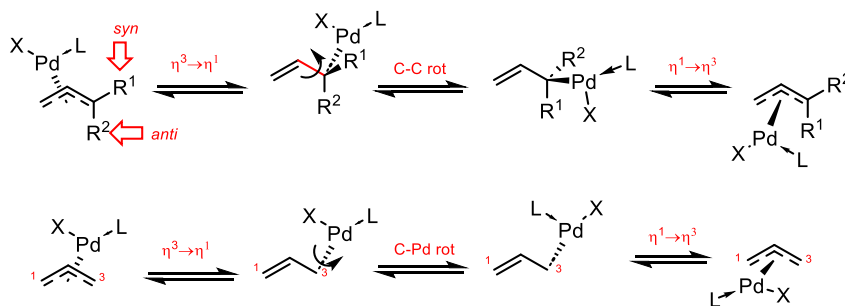
^[19] Smidt, J.; Hafner, W. *Angew. Chem.* **1959**, *71*, 284-284.

complexed by the metal (with or without *syn-anti* switch of the allylic substituents), or the formal rotation of the allyl moiety with respect to the other coordinated ligands (Scheme 10).



Scheme 10. Possible equilibria associated to a generic π -allylpalladium complex.

$\eta^3 \rightarrow \eta^1$ Isomerization followed by C-C bond rotation and $\eta^1 \rightarrow \eta^3$ equilibration leads to a global *syn-anti* exchange of the substituent pair concerned in the rotation, with simultaneous exchange of the complexed allyl face. This equilibrium is very facile when $R^1 = R^2 = H$, and normally displaced toward the *syn* isomer side in the case of monosubstitution (Scheme 11, equation 1).^[20] On the other hand, apparent allyl rotation involves the formal rotation of the allyl moiety around the imaginary Pd-allyl bond axis (Scheme 11, equation 2).

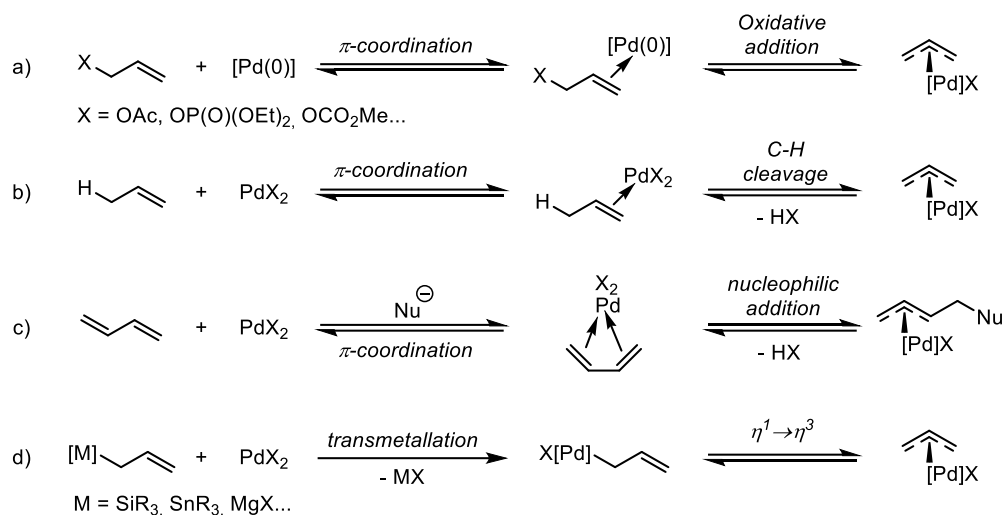


Scheme 11. The isomerization of *syn* and *anti* η^3 -allylpalladium complexes.

η^3 -Allylpalladium complexes can be generated from palladium(II) or palladium(0) complexes according to different reaction processes: (a) oxidative addition of palladium(0) catalysts to C-X bonds of allylic substrates containing a leaving group, (b) PdX_2 promoted allylic C-H cleavage of alkenes, (c)

^[20] a) Faller, J. M.; Thomsen, M. E.; Mattina, M. J. *J. Am. Chem. Soc.* **1971**, *93*, 2642–2653; b) Åkermark, B.; Vitagliano, A. *Organometallics* **1985**, *4*, 1275–1283; c) Ramey, K. C.; Statton, G. L. *J. Am. Chem. Soc.* **1966**, *88*, 4387–4390; d) Pregosin, P.S. Togni, A. et al. *J. Am. Chem. Soc.* **1994**, *116*, 4067.

PdX_2 promoted nucleophilic addition to 1,3-dienes, allenes, or vinyl- and methylenecyclopropanes^[21] and (d) transmetalation of allyl organometallics such as allylmagnesium halides, allylsilanes and allylstannanes with palladium(II) salts (Scheme 12).^[22] Within this manuscript, we will exclusively focus on the generation of η^3 -allylpalladium complexes from allyl esters.

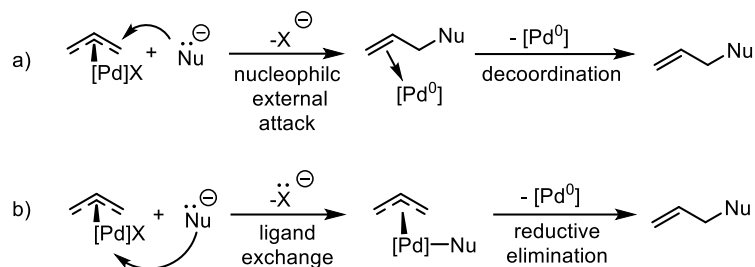


Scheme 12. General methods for the generation of η^3 -allylpalladium complexes.

As anticipated above, a variety of nucleophiles can undergo nucleophilic attack with η^3 -allylpalladium complexes to allow the formation of carbon-carbon bonds and carbon-heteroatom bonds. The most used nucleophiles are those containing nitrogen (amines, amides, sulfonamides), carbon (activated methylene species), sulfur (thiols, sulfonates and sulfinates) and oxygen atoms (carboxylates, alcohols, and water). The nature of the nucleophile has also some importance, since soft nucleophiles attack the π -allyl moiety *anti* with respect to Pd via an outer sphere mechanism, while hard nucleophiles firstly attack the metal center via an inner sphere mechanism and then undergo reductive elimination (Scheme 13).

^[21] On the preparation of η^3 -allylpalladium complexes from conjugated dienes, for an early contribution, see: a) Rowe, J. M.; White, D. A. *J. Chem. Soc. A: Inorg. Phys. Theor.* **1967**, 1451-1455. For a review, see: b) Zenit, G.; Larock, R. C. *Chem. Rev.* **2006**, *106*, 4644-4680. For a selection of examples, see: c) Rosko, R. V.; Larock, R. C. *J. Org. Chem.* **2010**, *75*, 4131-4134; d) Liao, L.; Syngman, M. S. *J. Am. Chem. Soc.* **2010**, *132*, 10209-10211.

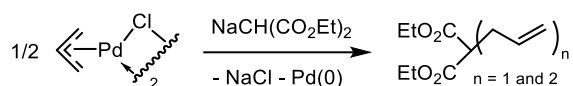
^[22] For a selection of examples, see: a) Golaszewski, A.; Schwartz, J. J. *Am. Chem. Soc.* **1984**, *106*, 5028-5030; b) Nakamura, H.; Iwama, H.; Yamamoto, Y. *J. Am. Chem. Soc.* **1996**, *118*, 6641-6647.



Scheme 13. Reaction of η^3 -allylpalladium complexes with nucleophiles.

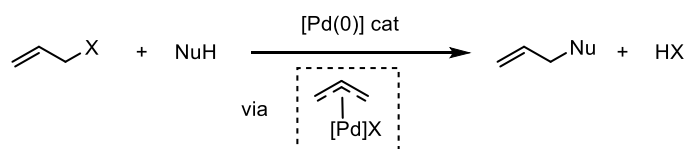
2.2. Pd(0)-catalyzed electrophilic allylations^[21]

A few years after the first preparation of η^3 -allylpalladium complexes, Tsuji reported that ethyl malonate, acetoacetate as well as an enamine derived from cyclohexanone could react smoothly with dimeric η^3 -allylpalladium chloride to afford the corresponding allylated products (Scheme 14).^[23]



Scheme 14. First use of η^3 -allylpalladium complexes as allylating agents.

The first catalytic version was independently reported in 1970 in publications or patents by Atkins,^[24] Hata,^[25] and Shryne, from Union Carbide, Toray Industries, and Shell Oil,^[26] respectively, and concerned the Pd(0)-catalyzed allylation of alcohols, amines and active methylenes. Six years later Trost applied this Pd(0)-catalyzed allylation protocol to the synthesis of desethylbogamin alkaloid, and in 1977 he reported the first asymmetric version.^[27] This redox-neutral Pd(0)-catalyzed protocol, often named Tsuji-Trost reaction or allylic-alkylation (for carbon nucleophiles) or -amination (for nitrogen nucleophiles), gained an enormous success because of its power, mildness, functional group tolerance, and possibility of asymmetric versions (Scheme 15).



Scheme 15. Generic Pd(0)-catalyzed allylation of nucleophiles with allylic electrophiles

^[23] Tsuji, J.; Takahashi, H.; Morikawa, M. *Tetrahedron Lett.* **1965**, *6*, 4387-4388.

^[24] a) Walker, W. E.; Manyik, R. M.; Atkins, K. E.; Farmer, M. L. *Tetrahedron Lett.* **1970**, *43*, 3817-3820. b) Atkins, K. E.; Walker, W. E.; Manyik, R. M. *Tetrahedron Lett.* **1970**, *43*, 3821-3824.

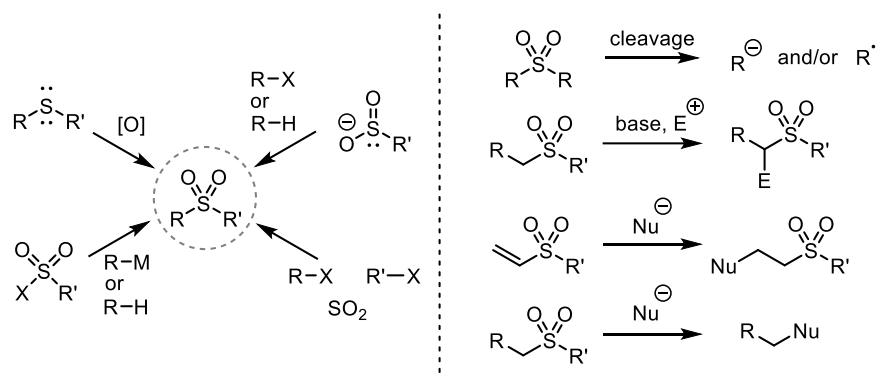
^[25] Hata, G.; Takahashi, K.; Miyake, A. *J. Chem. Soc. D.* **1970**, 1392-1393.

^[26] Shryne, T. S.; Smutny, E. J.; Stevenson, D. P. US Patent, **1970**, 3493617.

^[27] Trost, B. M.; Strege, P. E. *J. Am. Chem. Soc.* **1977**, *99*, 1649-1651.

3. The Chemistry of Sulfones

The extraordinary flexibility of sulfones has been widely exploited in organic synthesis over several decades. Indeed, sulfones are invaluable reagents for organic synthesis^[28] allowing to carry out a number of synthetically useful transformations. Their relevance and versatility is so high^[28,29] that B. M. Trost defined them as *chemical chameleons*,^[30a] and P. L. Fuchs as *pluripotent*.^[30b] Sulfones can be incorporated in an organic molecule in several ways. Oxidation of a thioether is the most popular method. Furthermore, they can be introduced in a nucleophilic fashion by alkylating sulfinate anions, or, electrophilically, by reacting a carbon nucleophile with a sulfonyl halide or anhydride. As to the modification of this functional group, the C–S bond in a sulfone can be cleaved to generate carbanions or carbon-centered radicals. Furthermore, a sulfone can activate an adjacent deprotonation, and π -bonds conjugated to a sulfone can undergo conjugate additions. Finally, the sulfinate ion can behave as leaving group (Scheme 16).



Scheme 16. Main syntheses (left) and reactivities (right) of sulfones

3.1. Sulfonyl α -carbanions

Sulfones can be deprotonated at the α -position, usually by strong bases such as *n*-butyllithium, sodium hydride, Grignard reagents, etc. The resulting sulfonyl α -carbanions can react with halocarbons, introducing alkyl groups at the α -position;^[31] and also ring-opening reaction with epoxides for instance, to form carbon-carbon bonds.^[32] Meanwhile, the sulfonyl α -carbanions can be involved in nucleophilic addition reactions with aldehydes or ketones to form β -hydroxy sulfones, which are generally intermediates for carbon-carbon double bond formation through further removal of the sulfonyl group

[28] Magnus, P. D. *Tetrahedron* **1977**, *33*, 2019–2045.

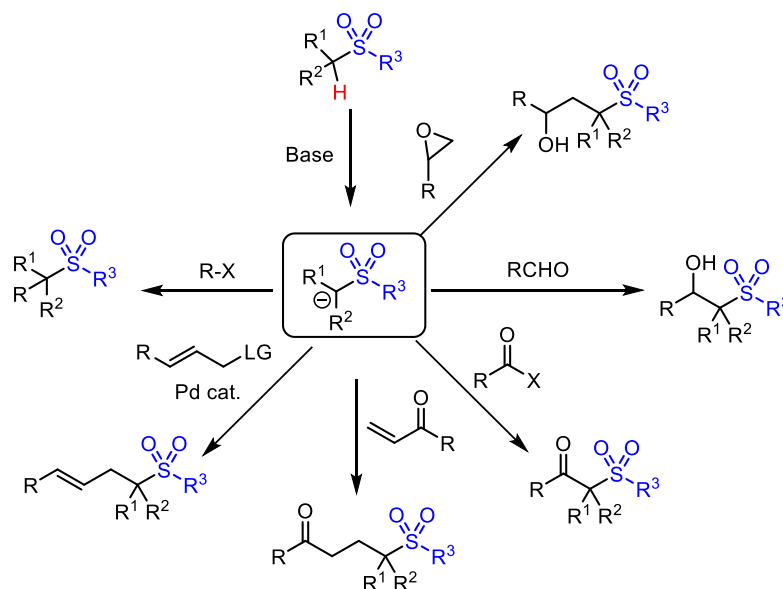
[29] Liu, N.-W.; Liang, S.; Manolikakes, G. *Synthesis*, **2016**, *48*, 1939–1973.

[30] a) Trost, B. M. *Bull. Chem. Soc. Jp.* **1988**, *61*, 107–124; b) El-Awa, A.; Noshi, M. N.; Mollat du Jourdin, X.; Fuchs, P. L. *Chem. Rev.* **2009**, *109*, 2315–2349.

[31] Halm, C.; Evarts, J.; Kurth, M. J. *Tetrahedron Lett.* **1997**, *38*, 7709–7712.

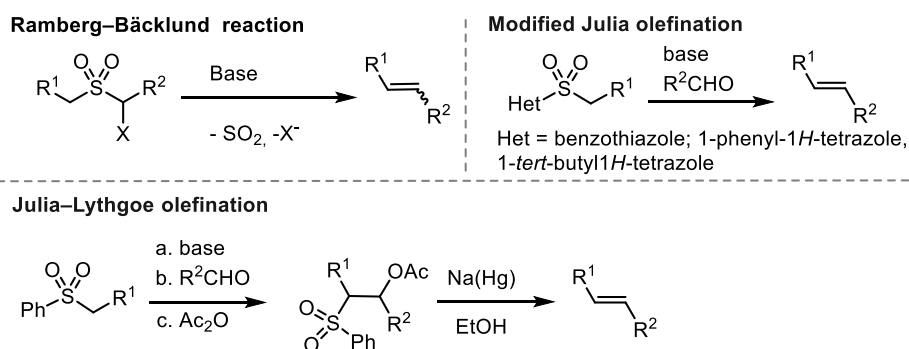
[32] Kondo, K.; Tunemoto, D. *Tetrahedron Lett.* **1975**, *17*, 1397–1400.

(Julia-olefination).^[33] α -carbanions can also add to esters or acyl chlorides to form β -ketosulfones in Claisen-type reactions.^[34] α -Carbanions are also employed in Michael addition reactions with α,β -unsaturated carbonyl compounds.^[35] The sulfonyl α -carbanions can react with allylic substrates bearing a leaving group in the presence of a palladium catalyst for the formation of carbon-carbon bonds (Scheme 17).



Scheme 17. The reactivity of the sulfonyl α -carbanions.

Sulfones are intermediates in synthetically relevant carbon-carbon bond forming reactions, such as the Ramberg–Bäcklund,^[36] the Julia–Lythgoe,^[37] as well as the modified Julia olefination (Scheme 18).^[38]



Scheme 18. Classical reactions of sulfones in organic synthesis.

^[33] Kocienski, P. J.; Bell, A.; Blakemore, P. R. *Synlett* **2000**, 3, 365–366.

^[34] Kondo, K.; Saito, E.; Tunemoto, D. *Tetrahedron Lett.* **1975**, 27, 2275–2278.

^[35] Kraus, G. A.; Frazier, K. *Synth. Commun.* **1978**, 8, 483–486.

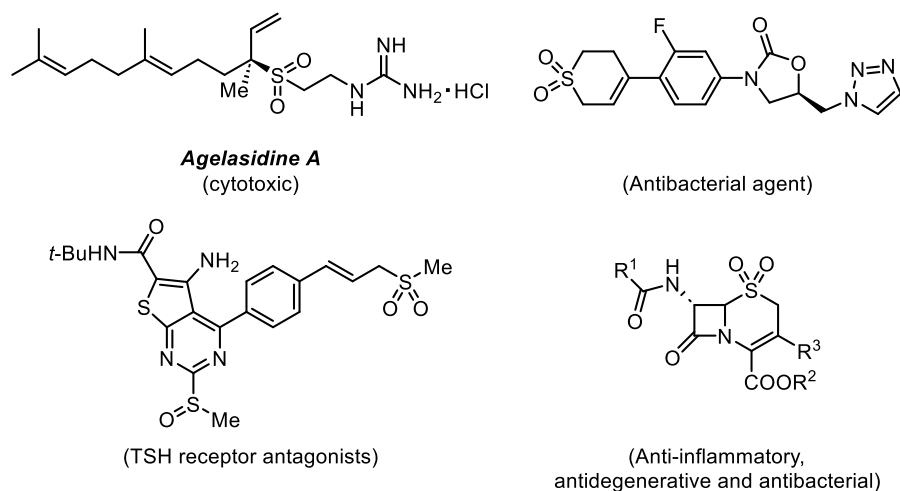
^[36] Chan, T.-L.; Fong, S.; Li, Y.; Man, T.-O.; Poon, C.-D. *J. Chem. Soc., Chem. Commun.* **1994**, 1771–1772.

^[37] Baudin, J. B.; Hareau, G.; Julia, S. A.; Ruel, O. *Tetrahedron Lett.* **1991**, 32, 1175–1178.

^[38] Blakemore, P. R. *J. Chem. Soc. Perkin Trans.* **2002**, 2, 2563–2585.

3.2. Allylsulfones

Allylsulfones represent a very useful subclass of sulfones that has proven to be extremely useful as nucleophilic as well as electrophilic building blocks, following ionic or radical mechanisms depending on the reaction conditions adopted.^[12,39,40,41,42] Furthermore, the allylsulfone motif can be found in a number of molecules that show diverse biological and pharmacological activities,^[43] such as anticancer, antibacterial, antifungal, anti-inflammatory, etc. (Scheme 19).



Scheme 19. Allylsulfones motifs in biologically active molecules.

3.3. Synthesis of allylsulfones

Allylsulfones can be obtained in several different ways. A selection of them is described here below.

^[39] Markovic, T.; Murray, P. R. D.; Rocke, B. N.; Shavnya, A.; Blakemore, D. C.; Willis, M. C. *J. Am. Chem. Soc.* **2018**, *140*, 15916–15923.

^[40] Corpas, J.; Mauleón, P.; Gómez Arrayás, R.; Carretero, J. C. *Chem. Soc. Rev.*, **2022**, *51*, 6774.

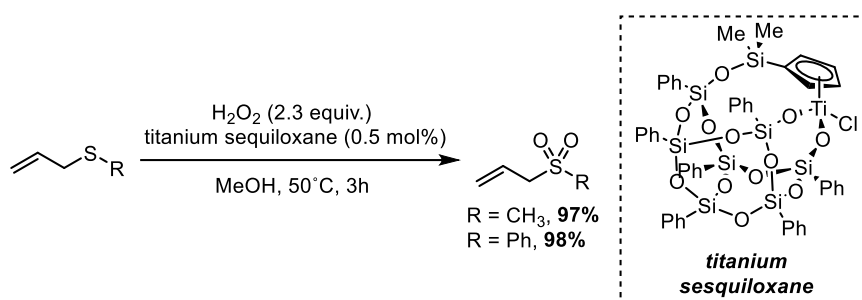
^[41] a) Julia, M.; Righini A.; Verpeaux, J.-N. *Tetrahedron Lett.*, **1979**, *26*, 2393–2396; b) Julia, M.; Righini-Tapie A.; Verpeaux, J.-N. *Tetrahedron*, **1983**, *39*, 3283–3287.

^[42] For selected examples of allyl sulfones involving in radical reactions, see: a) Baralle, A.; Fensterbank, L.; Goddard, J.-P.; Ollivier, C. *Chem. Eur. J.* **2013**, *19*, 10809–10813; b) Corcé, V.; Chamoreau, L.-M.; Derat, E.; Goddard, J.-P.; Ollivier, C.; Fensterbank, L. *Angew. Chem. Int. Ed.* **2015**, *54*, 11414–11418; c) Zhang, J.; Li, Y.; Zhang, F.; Hu, C.; Chen, Y. *Angew. Chem. Int. Ed.* **2016**, *55*, 1872–1875; d) Cai, Y.; Tang, Y.; Fan, L.; Lefebvre, Q.; Hou, H.; Rueping, M. *ACS Catal.* **2018**, *8*, 9471–9476; e) Liu, H.; Ge, L.; Wang, D.-X.; Chen, N.; Feng, C. *Angew. Chem. Int. Ed.* **2019**, *58*, 3918–3962; f) Wu, J.; Grant, P. S.; Li, X.; Noble, A.; Aggarwal, V. K. *Angew. Chem. Int. Ed.* **2019**, *58*, 5697–5757; g) Xia, Y.; Studer, A. *Angew. Chem. Int. Ed.* **2019**, *58*, 9836–9840; h) Uno, M.; Sumino, S.; Fukuyama, T.; Matsuura, M.; Kuroki, Y.; Kishikawa, Y.; Ryu, I. *J. Org. Chem.* **2019**, *84*, 9330–9338; i) Chen, X.; Gong, X.; Li, Z.; Zhou, G.; Zhu, Z.; Zhang, W.; Liu, S.; Shen, X. *Nat. Commun.* **2020**, *11*, 2756; j) Lou, Y.; Qiu, J.; Yang, K.; Zhang, F.; Wang, C.; Song, Q. *Org. Lett.* **2021**, *23*, 4564–4569; k) Sun, K.; Ueno, M.; Imaeda, K.; Ueno, K.; Sawamura, M.; Shimizu, Y. *ACS Catal.* **2021**, *11*, 9722–9728.

^[43] a) Nakamura, H.; Wu, H.; Kobayashi, I.; Ohizumi, Y.; Hiqashijima, T.; Miyazawa, T. *Tetrahedron Lett.* **1983**, *24*, 4105–4108; b) Reck, F.; Zhou, F.; Girardot, M.; Kern, G.; Eyermann, C. J.; Hales, N. J.; Ramsay, R. R.; Gravestock, M. B. *J. Med. Chem.* **2005**, *48*, 499–506; c) Xie, P.; Wang, J.; Liu, Y.; Fan, J.; Wo, X.; Fu, W.; Sun, Z.; Loh, T. P. *Nat. Commun.* **2018**, *9*, 1321.

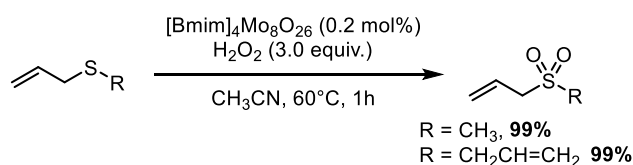
3.3.1. Oxidation of allyl thioethers

The oxidation of thioethers or sulfoxides is the oldest and most common method used to obtain sulfones. Commonly used oxidants to perform this oxidation are as hydrogen peroxide (H₂O₂) or peroxyacids.^[44] Research in recent years has focused on catalytic systems for milder and more efficient oxidation systems. Here below are a couple of modern examples. In 2015, the Royo's group reported that a titanium silsesquioxane complex, which exhibited stability and reusability, was able to catalyze the oxidation of thioethers to sulfones (Scheme 20) in the presence of hydrogen peroxide as terminal oxidant and methanol as solvent.^[45]



Scheme 20. the catalytic oxidation of thioethers to sulfones.

In 2016, Zhou *et al.* reported that alkylimidazolium/alkylpyridinium octamolybdates were efficient catalysts for the oxidation of thioethers to sulfones using hydrogen peroxide as terminal oxidant (Scheme 21).^[46]



Scheme 21. [Bmim]₄Mo₈O₂₆-Catalyzed the oxidation of thioethers to sulfones.

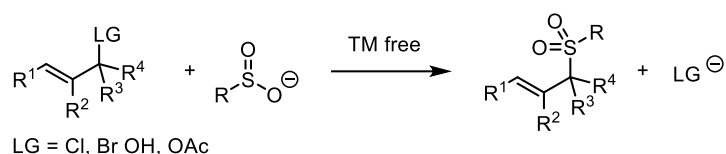
3.3.2. Nucleophilic substitution of allylic substrates with sulfinate anions

Another well-known and straightforward way to access allylsulfones involves the coupling between substrates bearing an allylic leaving group (LG) and sulfinate anions (Scheme 22).

^[44] Liang, S.; Hofman, K.; Friedrich, M.; Keller, J.; Manolikakes, G. *ChemSusChem* **2021**, *14*, 4878–4902.

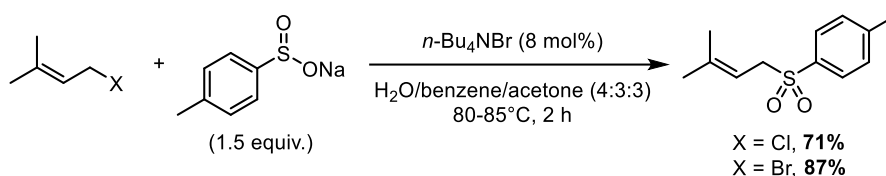
^[45] Postigo, L.; Ventura, M.; Cuenca, T.; Jiménez, G.; Royo, B. *Catal. Sci. Technol.* **2015**, *5*, 320–324.

^[46] Ye, J. X.; Wang, J. Y.; Wang, X.; Zhou, M. D. *Catal. Commun.* **2016**, *81*, 1–3.



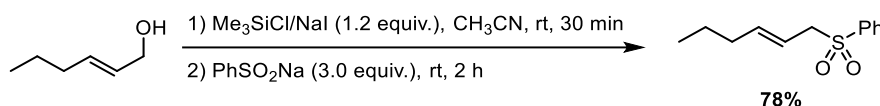
Scheme 22. General coupling between an allylic electrophilic substrate and a sulfinate anion.

In 1985, the Crandall's group reported the preparation of allyl aryl sulfones by reacting sodium aryl sulfonates with an allylic chloride or bromide in the presence of catalytic amounts of *tetra-n*-butylammonium bromide (TBAB) as the phase-transfer catalyst in the ternary medium water, benzene and acetone (Scheme 23).^[47]



Scheme 23. *n*-Bu₄NBr-catalyzed allylation of sodium benzenesulfinate.

In 1990, Ishii and co-workers described the preparation of allylic sulfones from allylic alcohols via iodination (TMS-Cl, NaI) followed by treatment of the resulting allylic iodide by sodium benzenesulfinate (Scheme 24).^[48]



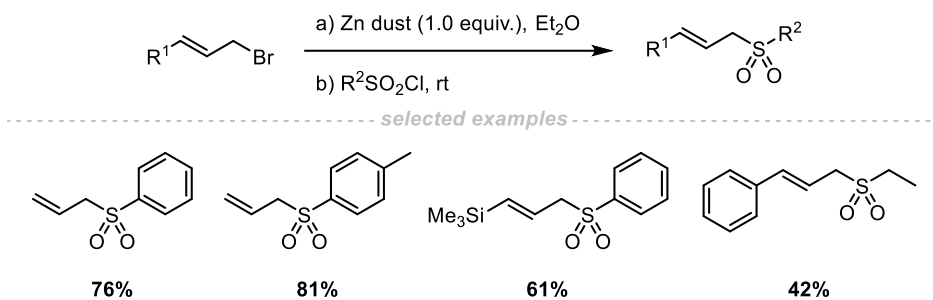
Scheme 24. Domino iodination/nucleophilic substitution of allylic alcohols with sodium sulfonates.

In 1997, Zhang *et al.* described that treatment allylzinc reagents, in turn formed by the interaction between allyl bromides and Zn dust, react with aryl or alkyl sulfonyl chlorides to give the corresponding allylsulfones. However, only small variations of both substrates were studied. (Scheme 25).^[49]

^[47] Crandall, J. K.; Pradat, C. *J. Org. Chem* **1985**, *50*, 1327–1329.

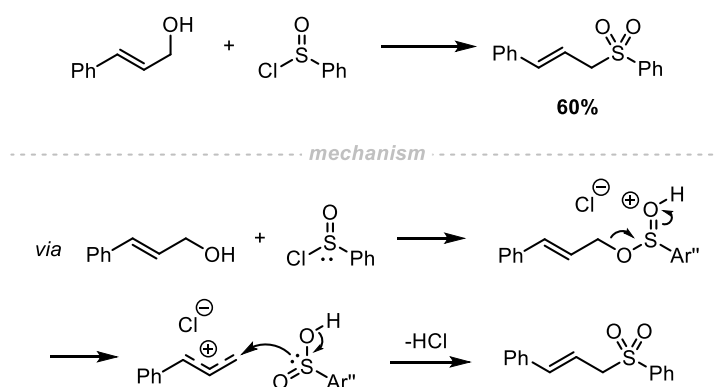
^[48] Kanai, T.; Kanagawa, Y.; Ishii, Y. *J. Org. Chem* **1990**, *55*, 3274–4277.

^[49] Sun, P.; Wang, L.; Zhang, Y. *Tetrahedron Lett.* **1997**, *38*, 5549–5550.



Scheme 25. Zn-promoted allylation of sulfonyl chlorides.

In 2009, Tian *et al.* reported that allylsulfones can be prepared by the reaction between benzylic, or allylic, alcohols and various aryl sulfinyl chlorides, in the absence of external catalysts and additives (Scheme 26).^[50] The mechanism of this reaction is expected to involve the initial formation of the O-protonated allylic sulfonate, which breaks to the corresponding allylic cation and sulfinic acid. Their subsequent S_N1-type interaction generates the corresponding allylic sulfone and HCl.

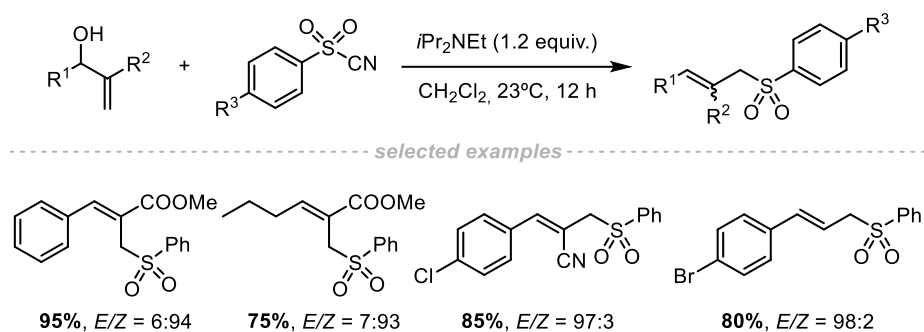


Scheme 26. Synthesis of allylsulfones from allyl alcohols and sulfinyl chlorides.

In the same year, Reddy *et al.* reported that the reaction between arenesulfonyl cyanides and simple allylic alcohols allowed the generation of the corresponding allylsulfones in good yields (Scheme 27).^[51]

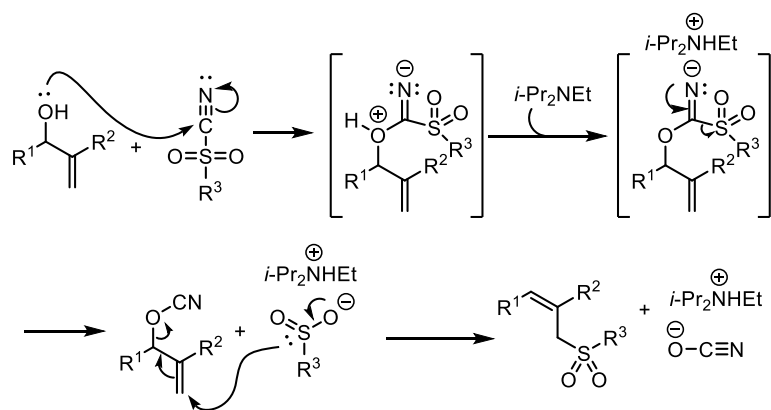
^[50] Li, H. H.; Dong, D. J.; Jin, Y. H.; Tian, S. K. *J. Org. Chem.* **2009**, *74*, 9501–9504.

^[51] Reddy, L. R.; Hu, B.; Prashad, M.; Prasad, K. *Angew. Chem. Int. Ed.* **2009**, *48*, 172–174.



Scheme 27. Baylis–Hillman alcohols react with arenesulfonyl cyanides.

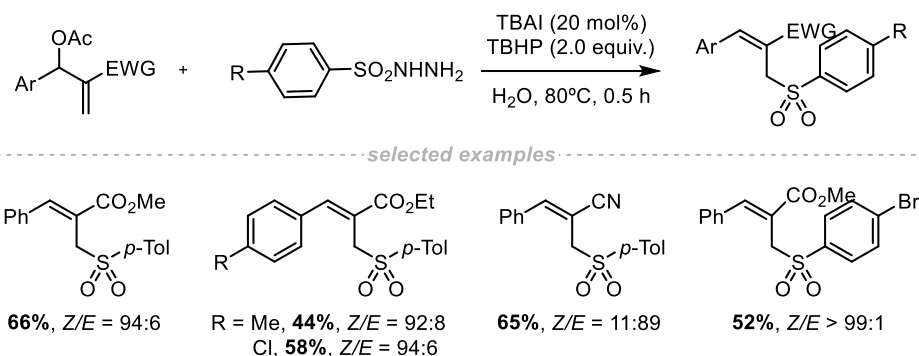
The authors proposed the following mechanism for this transformation. First, the allylic alcohol adds to the nitrile function of the arenesulfonyl cyanide in the presence of a base. Cleavage of the resulting adduct generates a nucleophilic arenesulfinate and an electrophilic 3-cyanatoprop-1-ene derivative, whose S_N2' reaction generates the allylsulfone product with expulsion of cyanate anion (Scheme 28).



Scheme 28. A possible mechanism for the reaction between Baylis–Hillman alcohols and cyanosulfones.

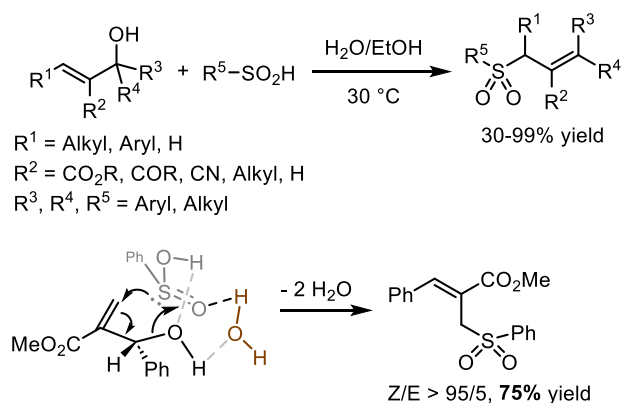
In 2013, Li and Xu obtained allylsulfones in moderate yields by the coupling between Baylis–Hillman acetates and sulfonylhydrazides, in the presence of *tert*-butyl hydroperoxide (TBHP) and catalytic amounts of tetrabutylammonium iodide (TBAI) in water.^[52] In this case the mechanism is radical (Scheme 29).

^[52] Li, X.; Xu, X.; Tang, Y. *Org. Biomol. Chem.* **2013**, *11*, 1739–1742.



Scheme 29. TBAI-catalyzed sulfonylation of Baylis-Hillman acetates.

More recently, Xie, Loh and co-workers reported a highly efficient water-promoted dehydrative cross-coupling between sulfinic acids and allylic alcohols—including Morita-Baylis adducts—at room temperature.^[43c] The desired allylic sulfones were obtained in high yields with excellent selectivity. DFT calculations showed that the crucial role of water is to create an intermolecular H bonding (Scheme 30).

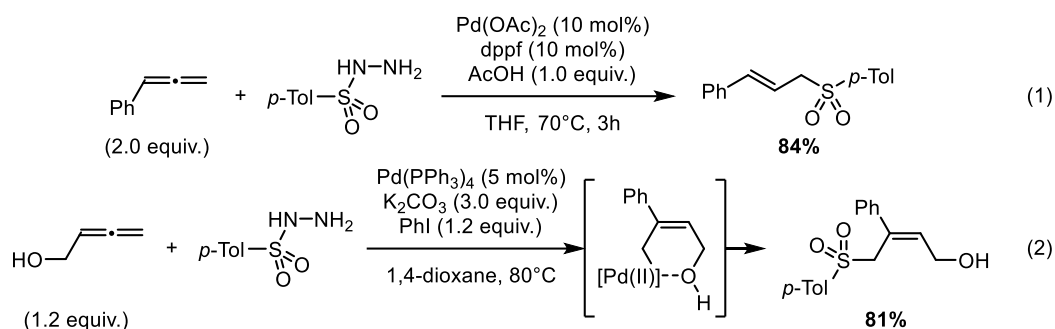


Scheme 30. Water-promoted reaction between allylic alcohols and sulfinic acids.

Sulfonylhydrazones have also been used as sulfinate precursors in palladium-catalyzed hydrosulfination of allenes. While terminal allenes were providing the corresponding (*E*)-allylsulfones in the presence of 10 mol% of palladium(II) acetate, dppf as the ligand and 1.0 equiv. of acetic acid (Scheme 31, equation 1),^[53] allenyl alcohols could generate (*Z*)-allylic sulfones through coordination of the alcohol function with the palladium catalyst during the carbopalladation step on the allene (Scheme 31, equation 2).^[54]

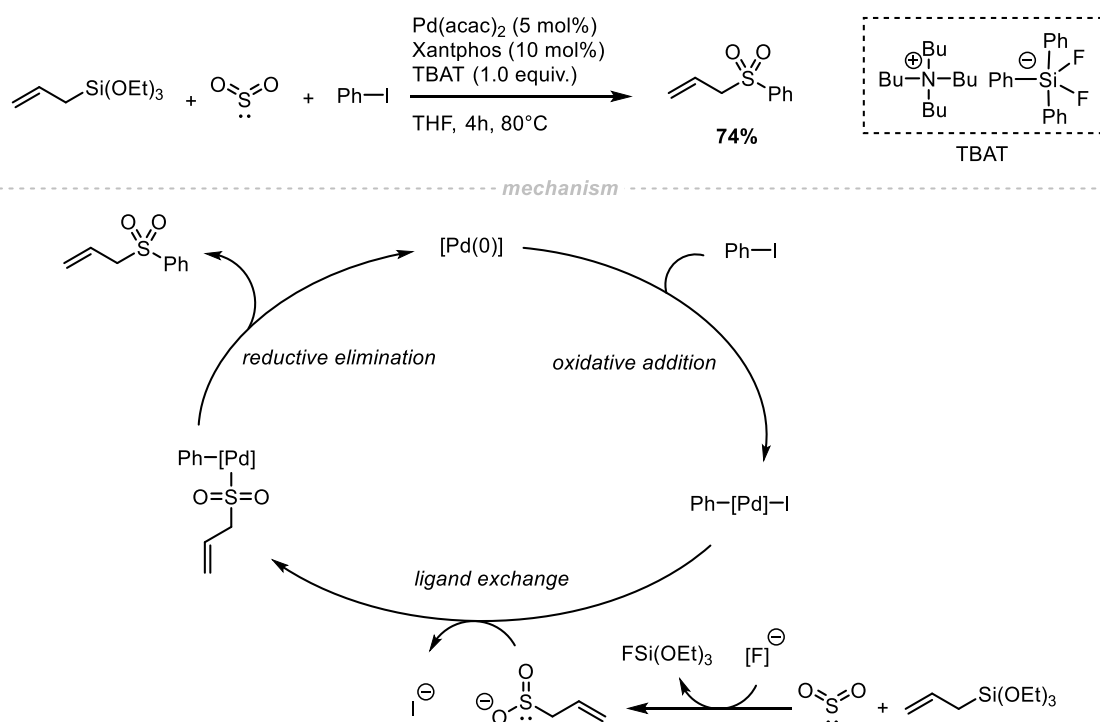
^[53] Kamijo, S.; Al-Masum, M.; Yamamoto, Y. *Tetrahedron Lett.* **1998**, *39*, 691-694.

^[54] Hou, Y.; Shen, Q.; Li, Z.; Chen, S.; Zhao, Y.; Qin, M.; Gong, P. *Adv. Synth. Catal.* **2018**, *360*, 631-636.



Scheme 31. Preparation of allylsulfones from allenes and sulfonylhydrazones with palladium-catalysis.

In 2019, Cantat *et al.* developed a new palladium-catalyzed synthesis of allyl aryl sulfones through coupling between allylsilanes, aryl halides, and sulfur dioxide, in the presence of tetrabutylammonium difluorotriphenylsilicate (TBAT) as the fluoride source.^[55] Experimental and theoretical investigations demonstrated the preformation of allyl sulfinate anion. Accordingly, the authors proposed a mechanism involving the initial oxidative addition of Pd(0) to the aryl halide, followed by ligand exchange of the resulting arylpalladium complex with the preformed sulfinate anion (Scheme 32).

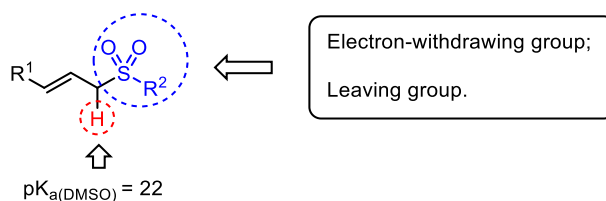


Scheme 32. Allylsulfones via Pd(0)-catalyzed coupling between allylsilanes, SO₂, and aryl iodides.

^[55] Adenot, A.; Char, J.; Von Wolff, N.; Lefevre, G.; Anthore-Dalio, L.; Cantat, T. *Chem. Commun.* **2019**, 55, 12924–12927.

3.4. General reactivity of allylsulfones

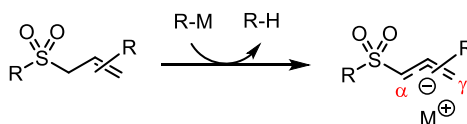
Allylsulfones play a key role in a number of organic reactions, finding applications in various synthetic methods. Being the sulfonyl group a strongly electron-withdrawing group, an allyl sulfone carrying α -H atoms possesses a relatively high acidity (for example, $pK_{a(\text{DMSO})} \text{PhSO}_2\text{CH}_2\text{CHCH}_2 = 22$). Therefore, it can be easily deprotonated by a strong base to afford the corresponding delocalized allyl carbanion.^[44] At the same time, the allylically located sulfonyl group can also behave as a leaving group, thereby generating an allylic electrophile (Scheme 33).



Scheme 33. The reactivity of the sulfonyl group.

3.4.1. Carbanions of allylsulfones

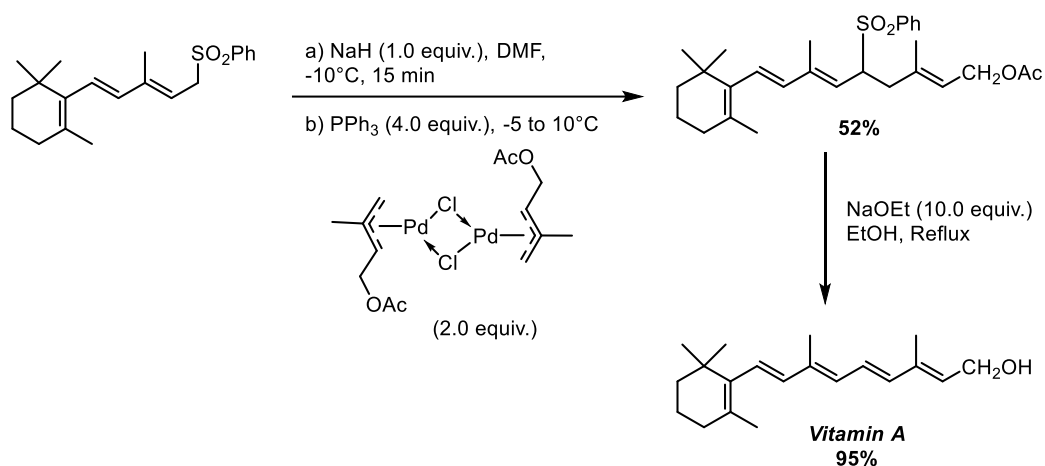
As other alkylsulfones (see above), allylsulfones can be deprotonated at the α position by strong bases. However, they are special in that the resulting carbanion is a delocalized allylanion, which can in principle react with an electrophilic reagent at $C\alpha$ or at $C\gamma$ (Scheme 34).



Scheme 34. Deprotonation of an allylsulfone

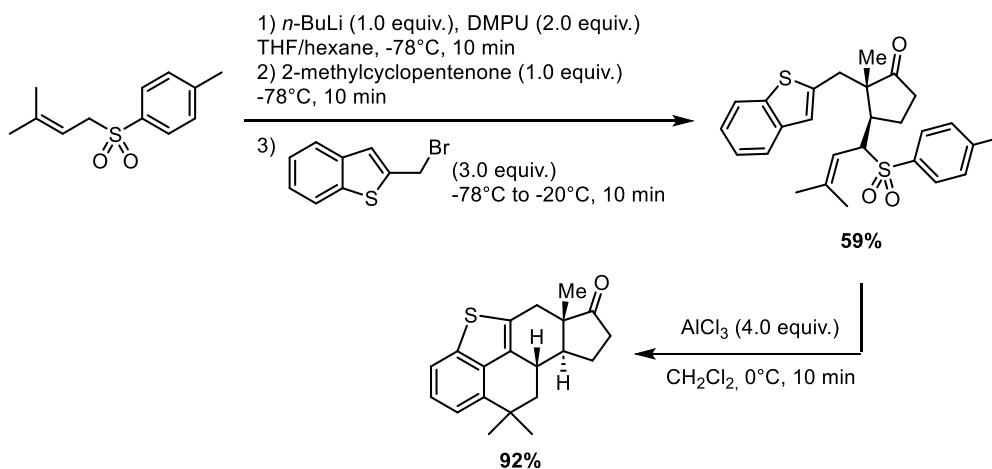
In 1978, Manchand *et al.*, at Hoffmann-La Roche, reported a synthesis of vitamin A involving η^3 -allylpalladium chemistry. An advanced allylsulfone intermediate was deprotonated with sodium hydride, and then reacted with a stoichiometric amount of a dimeric η^3 -allylpalladium chloride, in the presence of triphenylphosphine in DMF. Treatment of the resulting α -allylation product with sodium ethoxide in EtOH at reflux brought about sulfinate anion elimination, generating the targeted all-*trans* Vitamin A as the major product in an 81% yield (Scheme 35).^[56]

^[56] Manchand, P.S; Wong, H. S.; Blount, J. F. *J. Org. Chem.* **1978**, *43*, 4769–4774.



Scheme 35. Synthesis of vitamin A.

In 1990, the Jones' group described a straightforward, convergent approach to 1,11-epithiosteroids. The three-component tandem coupling of 2-methylbut-2-enyl-*p*-tolylsulfone with 2-methylcyclopentenone and 2-bromomethylbenzothiophene in the presence of *n*-butyllithium formed an adduct that underwent Lewis acid-activated cyclization to give a precursor of the 1,11-epithiosteroids (Scheme 36).^[57]

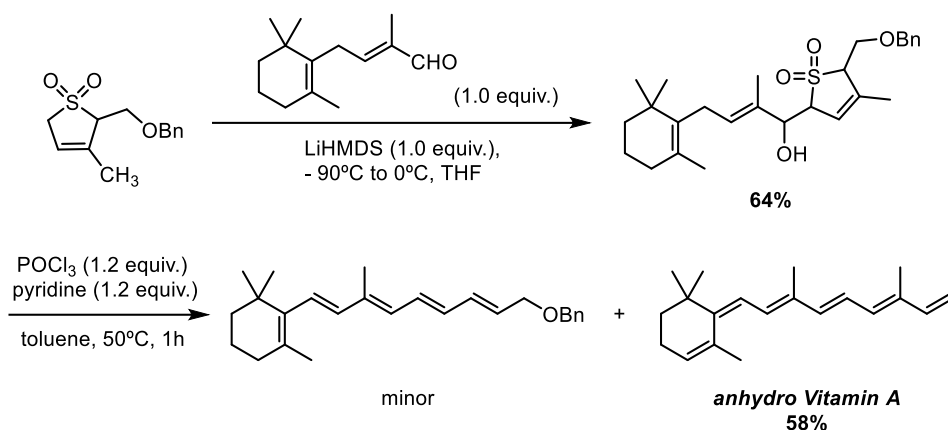


Scheme 36. Synthesis of 1,11-epithiosteroids.

In 2001, an approach to retinol-related anhydro vitamin A was described by the Bhat's group.^[58] A 3-sulfolene derivative was deprotonated, and then added to a C₁₄-aldehyde derived from β-cyclocitral. The resulting α-adduct was desulfonylated and dehydrated by treatment with POCl₃ and pyridine, to generate anhydro vitamin A (Scheme 37).

^[57] Adams, J. P.; Rowler, J.; Collins, M. A.; Jones, D. N.; Swallow, S. *Tetrahedron Lett.* **1990**, *31*, 4355–4358.

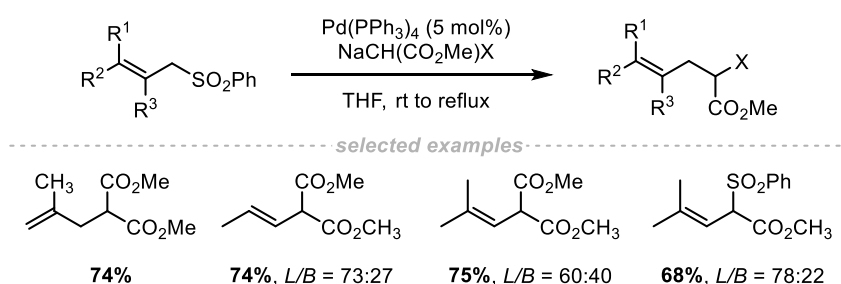
^[58] Subramanian, T.; Chou, T. S.; Bhat, S. V. *Synth. Commun.* **2001**, *31*, 2787–2793.



Scheme 37. Synthesis of anhydro vitamin A.

3.4.2. Allylsulfones as allylic electrophiles

The sulfonyl group of allylsulfones can behave as a leaving group, too. Such a desulfinative reactivity is typically obtained in Pd-catalyzed substitution of allylsulfones using soft carbanions^[59] or hydrides^[60] as nucleophiles (Scheme 38).



Scheme 38. Allylsulfones as allylic electrophiles in Pd(0)-catalyzed reaction with soft carbon nucleophiles

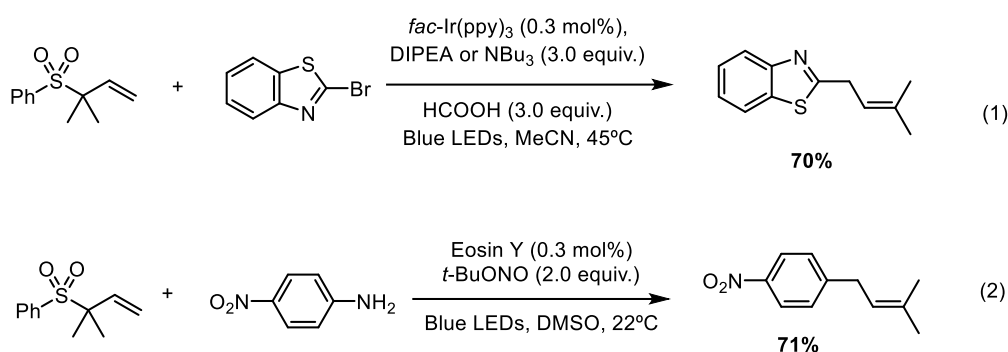
Recently, visible light photocatalysis has proven effective at catalytically generating a variety of radicals under near ambient conditions, often resulting in useful reactions that are remarkably tolerant of functional groups. In 2019, the Weaver's group developed a method based on a visible light photoredox-mediated prenylation of 2-bromo-azoles, aryl iodides, α -bromo-carbonyls and anilines with allylphenylsulfones.^[61] A photocatalytic system consisting in 0.3 mol% of an Ir-photocatalyst and a combination of formic acid and DIPEA and blue LEDs has been developed for 2-bromoazole, aryl iodide and α -carbonyl substrates (Scheme 39, equation 1). Another photocatalytic system with 0.3 mol% of the organic photocatalyst Eosin Y and *tert*-butylnitrite was developed for aniline substrates (Scheme 39, equation 2). The latter are *in situ* transformed into diazonium salts by oxidation with the nitrite

^[59] Alonso, D. A.; Najera, C. In *Organic Reactions*; Denmark, S. E., Ed.; 2008; pp 367–656.

^[60] Tsuji, J.; Mandai, T. *Synthesis* **1996**, 1–24.

^[61] Rathnayake, M. D.; Weaver, J. D. *Eur. J. Org. Chem.* **2020**, 1433–1438.

oxidant which is transformed into the aryl radical by abstraction of N₂.

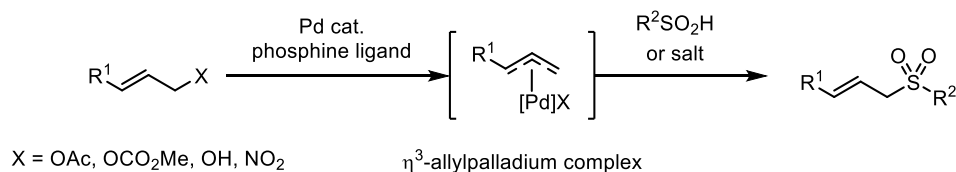


Scheme 39. Photocatalyzed Reductive desulfonation

4. Palladium and Sulfones

4.1. Allylsulfones via Pd(0)-catalyzed sulfinic anions allylation

A commonly used method for the regio- and stereoselective preparation of allylic sulfones consists in a Pd(0)-catalyzed coupling of allylic electrophiles (allylic carboxylates, carbonates, alcohols or nitro compounds) with sulfinic acids. Reactivities and regioselectivities can differ significantly depending on the structure of the allyl electrophile and the catalyst system (Scheme 40).^[62]

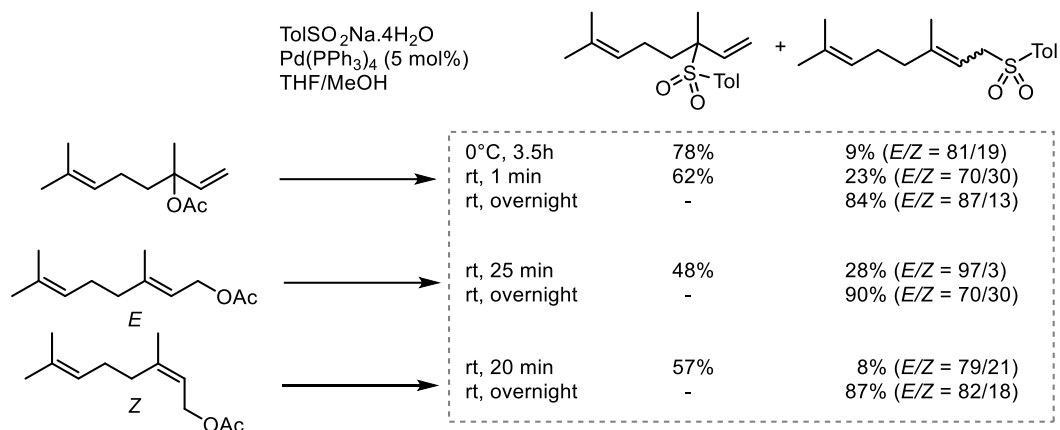


Scheme 40. Palladium-catalyzed allylic sulfonylation.

In 1981, Kotake *et al.* reported that tetrakis(triphenylphosphine) palladium(0) (Pd(PPh₃)₄) was able to catalyze the coupling between sodium *p*-toluenesulfinate and allylic acetates in THF and methanol to give the corresponding allylic sulfones.^[63] The role of methanol was to solubilize the sulfinic anion. In particular, when the reaction mixture was stirred for a short time, branched allylsulfones were the major products. On the other hand, only the linear allylsulfones were obtained after stirring overnight (Scheme 41).

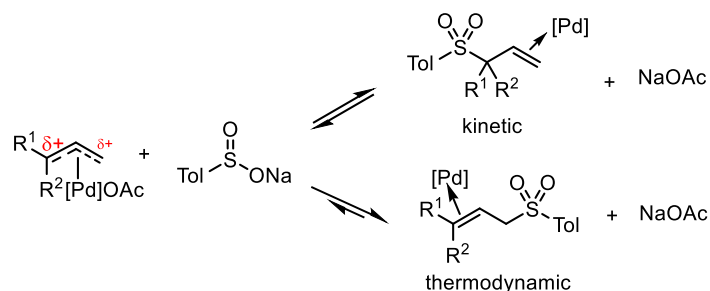
^[62] Tamura, R.; Kai, Y.; Kakihana, M.; Havashi, K.; Tsuji, M.; Nakamura, T.; Oda, D. *J. Org. Chem.* **1986**, *51*, 4375–4385.

^[63] Inomata, K.; Yamamoto, T.; Kotake, H. *Chem. Lett.* **1981**, 1357–1360.



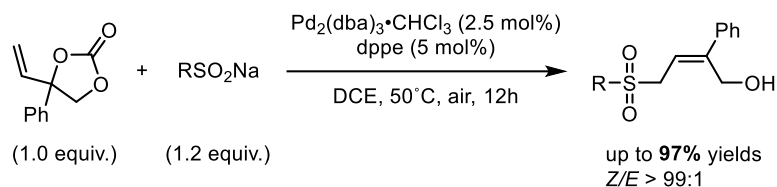
Scheme 41. Pd(0)-catalyzed allylation of *p*-tolylsulfinate with allyl acetates.

The above results clearly indicate that reaction is reversible, the branched allylsulfone being the kinetic product, while the linear is the thermodynamic one. The kinetic preference for the more substituted allyl terminus is undoubtedly due to the fact that the internal allyl terminus stabilizes the positive charge better than the external one (Scheme 42).

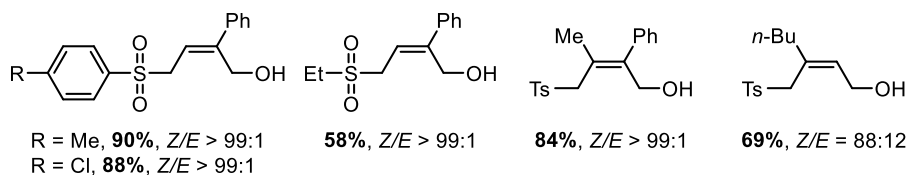


Scheme 42. Kinetic versus thermodynamic allylation of sulfonates.

The general mechanism involves first the formation of a η^3 -allylpalladium intermediate **A** by oxidative addition (Scheme 43). Nucleophilic attack of the sulfinate on the π -allylpalladium intermediate generates then an η^2 -allylsulfone palladium intermediate **B** which decoordinates to regenerate [Pd(0)] active species and liberates the desired allylsulfone. As mentioned above, the reaction is expected to be reversible. Therefore, the interaction between the allylsulfone and [Pd(0)] can regenerate back the corresponding η^3 -allylpalladium intermediate **A**.

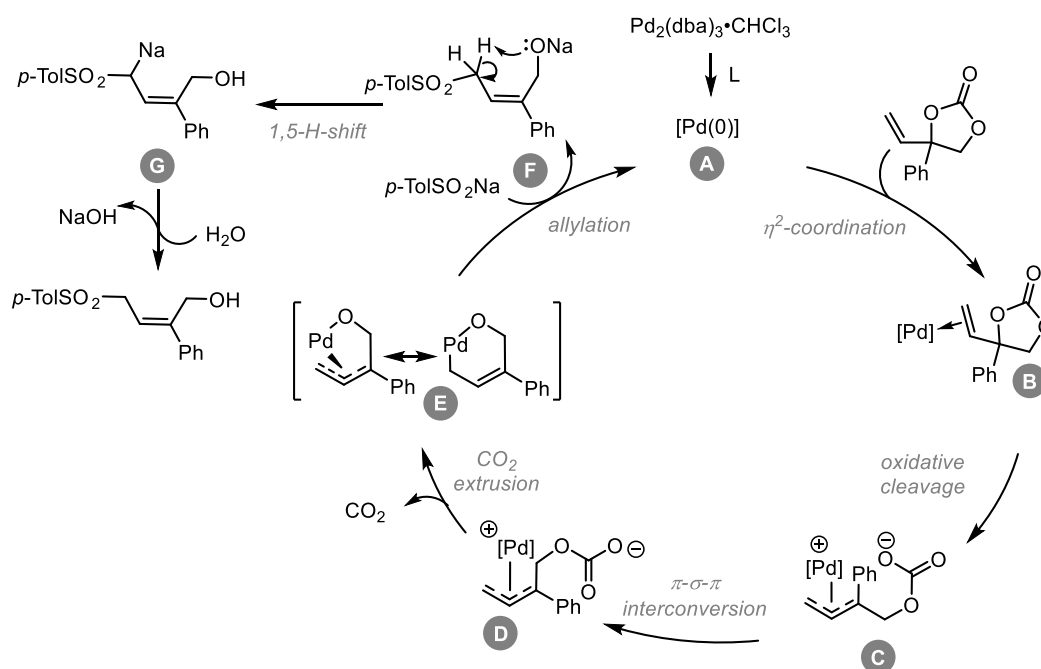


----- *selected examples* -----



Scheme 45. Pd(0)-catalyzed sulfonylation of a substituted vinyl ethylene carbonate.

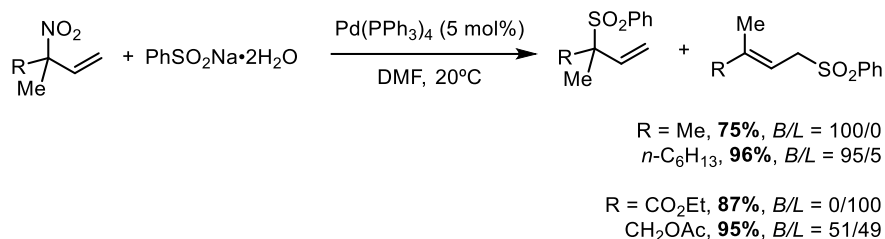
The mechanism proposed by the authors involves the initial η^2 -coordination of the alkene of the substrate to Pd(0) **A**, to afford intermediate **B**. Following oxidative cleavage generates the zwitterionic π -allylpalladium intermediate **C**. After **C**-to-**D** *anti/syn* equilibration through a π - σ - π interconversion, oxapalladacyclohexene **E** is formed with carbon dioxide extrusion. Following sulfinate anion attack generates the allylsulfone **F** and regenerates the catalytic active species **A**. Intermediate **F** undergoes a rapid 1,5-proton shift to form carbanionic intermediate **G**, before being quenched by a protic source (Scheme 46).



Scheme 46. A possible mechanism for the Pd(0)-catalyzed allylic sulfonylation of a substituted vinyl ethylene carbonate.

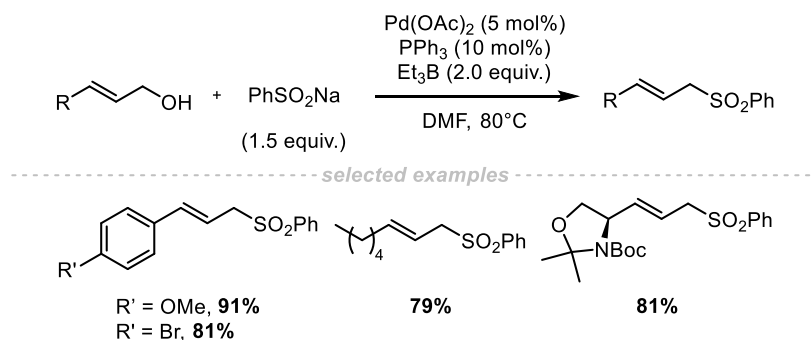
In 1986, Tamura reported that treatment of allylic nitro compounds with sodium benzenesulfinate in the presence of $\text{Pd}(\text{PPh}_3)_4$ catalyst resulted in the formation of allylic sulfones with predominance of

kinetically-controlled products.^[70] When the R group was an electron-donating group such as alkyl groups, the substitution reaction took place at the most hindered site to give the branched allylic sulfones regioselectively. On the contrary, when the R group was an electron-withdrawing group, the reverse regioselectivity was observed and linear allylic sulfones were obtained (Scheme 47).



Scheme 47. Pd(0)-catalyzed coupling between benzenesulfinate and allylic nitro compounds.

In 1986, the Chandrasekhar's group reported the direct Pd(0)-catalyzed reaction between sulfonates and allylic alcohols (Scheme 48). The coupling, which needs the presence of triethylborane, afforded the corresponding linear allyl sulfones in good yields.^[71]

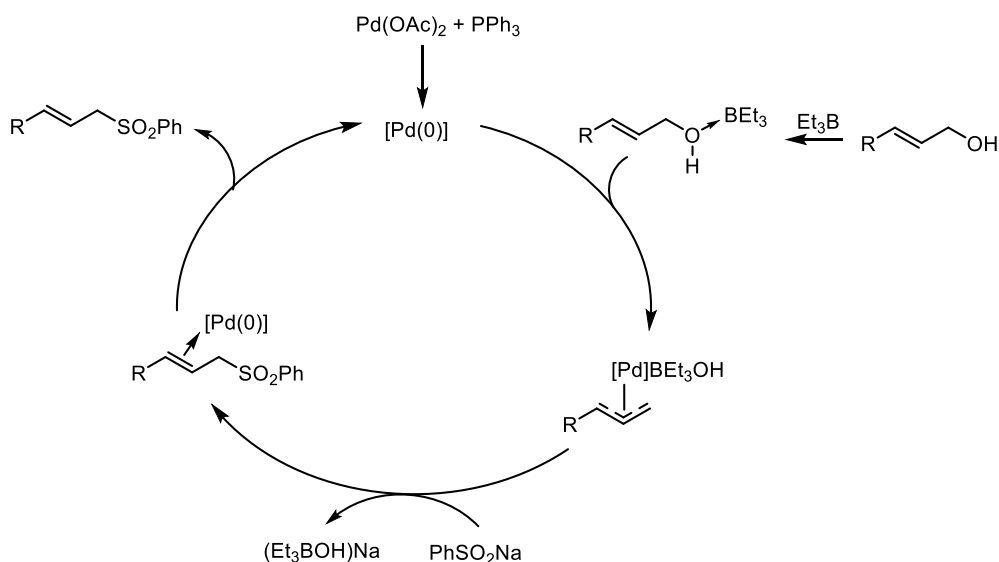


Scheme 48. Pd(0)-catalyzed allylic substitution of allyl alcohols.

The proposed mechanism involves activation the allylic alcohol by the Lewis acid triethylborane (Scheme 49).

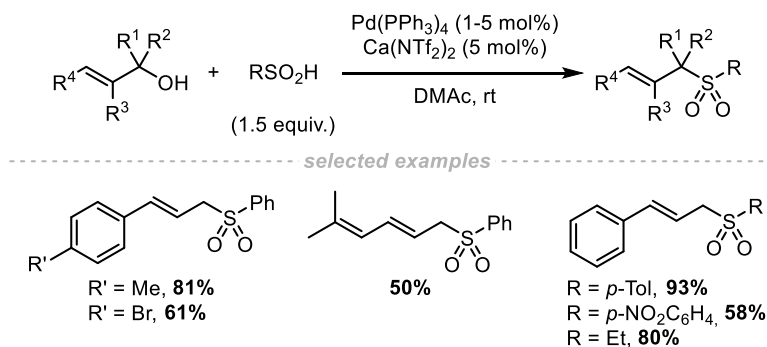
^[70] Ono, N.; Hamamoto, I.; Kawai, T.; Kaji, A.; Tamura, R.; Kakihana, M. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 405–410.

^[71] Chandrasekhar, S.; Jagadeshwar, V.; Saritha, B.; Narsihmulu, C. *J. Org. Chem.* **2005**, *70*, 6506–6507.



Scheme 49. Postulated mechanism for the Pd(0)-catalyzed sulfonylation of allylic alcohols.

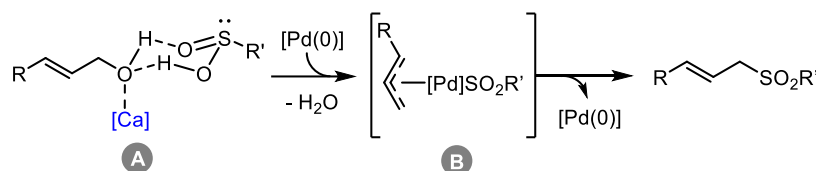
In 2020, Loh and Xie developed a Pd/Ca(NTf₂)₂ co-catalyzed direct cross-coupling between sulfinic acids and allylic alcohols, which allowed to obtain a vast range of allylic sulfones (Scheme 50).^[72]



Scheme 50. Pd/Ca(NTf₂)₂ co-catalyzed allylic substitution of allylic alcohols.

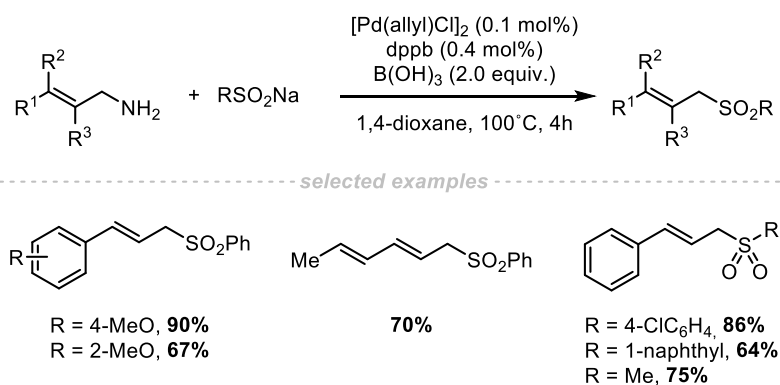
The proposed mechanism involves an oxidative addition step through a 6-membered cyclic mechanism featuring a chair-like transition state with double H-bonding. According to the authors, the calcium salt might facilitate the generation of intermediate **A**, which undergoes oxidative addition to afford the π-allylpalladium intermediate **B** (Scheme 51).

^[72] Xie, P.; Sun, Z.; Li, S.; Cai, X.; Qiu, J.; Fu, W.; Gao, C.; Wu, S.; Yang, X.; Loh, T. P.; Loh, T. P. *Org. Lett.* **2020**, *22*, 4893–4897.



Scheme 51. A brief mechanism for the Pd/Ca-co-catalyzed allylic sulfonylation of allylic alcohols.

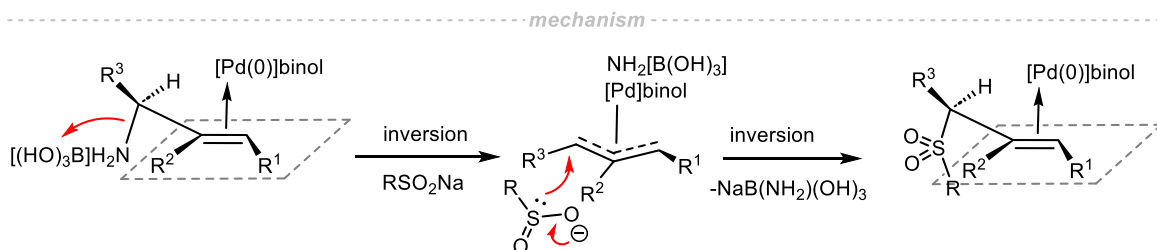
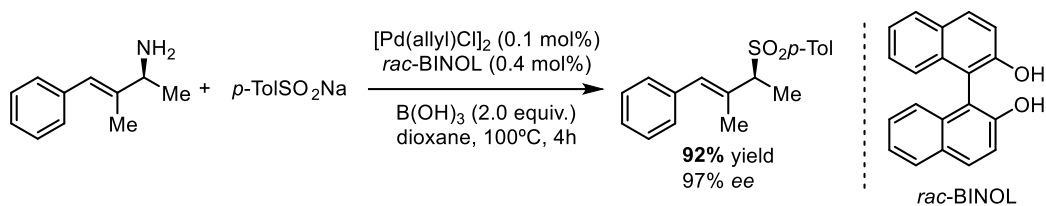
Allylamines are competent precursors of π -allylpalladium complexes, too. In 2012, the Tian's group developed the first Pd-catalyzed direct substitution of primary allylic amines with sulfinate salts to afford the corresponding allylsulfones with (*E*) stereochemistry (Scheme 52).^[73] As to the mechanism, the amine function is expected to coordinate to boric acid, which triggers the oxidative addition step.



Scheme 52. Pd(0)-catalyzed allylic sulfonylation of allylic amines.

When α -stereogenic enantiopure allylic amines were used as substrates, the sulfonylation took place with excellent stereoretention. In this case, the ligand dppb was replaced by *rac*-BINOL as ligand. The stereoretention observed in this reaction when using BINOL as ligand is expected to be the result of two subsequent stereoinversions (Scheme 53).

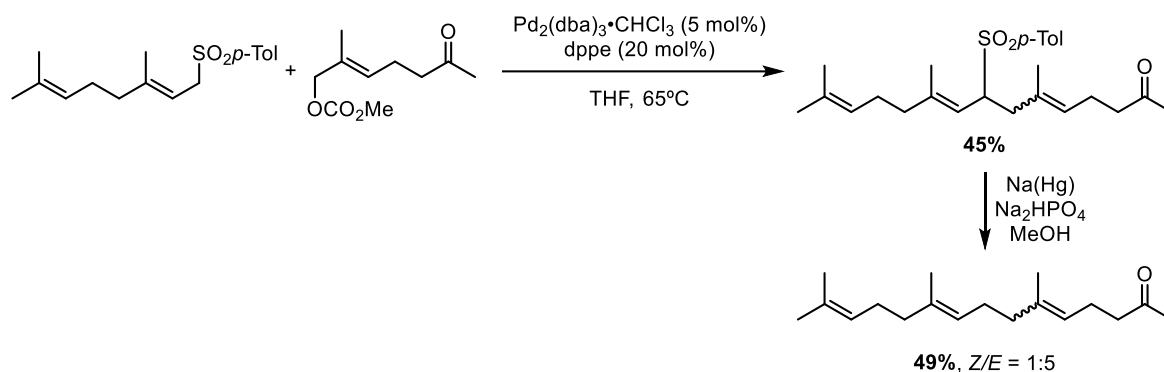
^[73] Wu, X. S.; Chen, Y.; Li, M. B.; Zhou, M. G.; Tian, S. K. *J. Am. Chem. Soc.* **2012**, *134*, 14694–14697.



Scheme 53. Pd-catalyzed-catalyzed sulfonylation of enantioenriched allylic amines, and rationalization of the stereo retention.

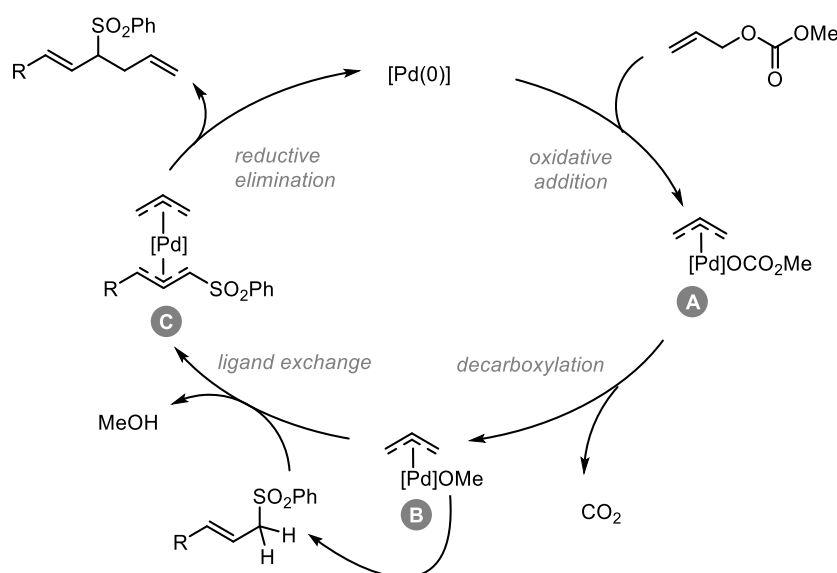
4.2. Pd(0)-catalyzed allylation and elimination of allyl sulfones

In the context of the synthesis of a pre-vitamin A model, in 1980, Trost *et al.* reported a Pd(0)-catalyzed coupling between the carbanion of an allyl sulfone and an allyl acetate, which gave the corresponding α -alkylated allylsulfone in an 85% yield.^[12a] Heating the coupled product with DBU in DMSO failed to produce the desired trienone, which was instead successfully achieved repeating the reaction with the additional presence of the Pd(0) catalyst. The authors speculated that the high acidity of the H α to the sulfone was likely the reason of the failure of the elimination in the sole presence of DBU. On the other hand, the presence of the Pd(0) catalyst solved the issue. Carrying out the same two-step sequence in a one-pot process by using DMSO as solvent, gave directly the trienone in 77% yield (Scheme 54).



Scheme 56. $\text{Pd}_2(\text{dba})_3$ -catalyzed allylation of allyl sulfones with allylcarbonates.

The possibility of carrying out base-free Pd-catalyzed coupling can be explained as follows. Oxidative addition of the Pd(0)-phosphine complex to allylic carbonates generates a η^3 -allylpalladium carbonate **A**, which suffers decarboxylation to the corresponding cationic η^3 -allylpalladium alkoxide **B**. The alkoxide counter-anion deprotonates the allylsulfone bringing about a counterion exchange of the η^3 -allylpalladium complex. Final reductive elimination of the resulting diallylpalladium complex **C** affords the allylated product and regenerates the Pd(0) catalyst (Scheme 57). In 1998, Poli and coworkers showed that even the common acetate leaving group can perform as endogenous deprotonation anion, provided that the pronucleophile is acid enough.^[76]

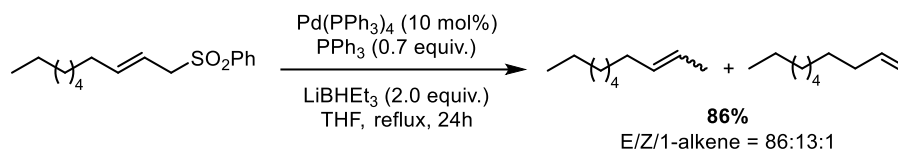


Scheme 57. Commonly accepted mechanism for the Pd(0)-catalyzed base-free allylation of allylsulfones with allylcarbonates.

^[76] Giambastiani, G.; Poli, G. *J. Org. Chem.* **1998**, *63*, 9608–9609.

4.3. Palladium(0)-catalyzed reductive desulfonylation of allyl sulfones.

In 1982, Hutchins and Learn described a Pd(0)-catalyzed allylic reduction using the super hydride LiBH₄Et₃ as the reducing agent (Scheme 58). With this method, which is expected to involve hydride addition to a transient η^3 -allylpalladium intermediate, primary allylic sulfones could be transformed into the corresponding 2-alkenes with good regio- and stereoselectivity.^[77]



Scheme 58. Pd(0)-catalyzed desulfonylation of allylsulfones by Hutchins.

5. Palladium-catalyzed domino reactions Involving η^3 -Allylpalladium Complexes.

The construction of complex molecular structures in a facile and efficient method remains an overarching goal of the chemical sciences. Cascade (or domino) reactions allow improved atom and step economy in organic synthesis and therefore represent significant progress toward this goal.^[78] Transition metal-mediated domino reactions play an important role in organic chemistry, because they allow the formation of complex molecular structures in a single synthetic operation and usually the reaction is performed under mild conditions.

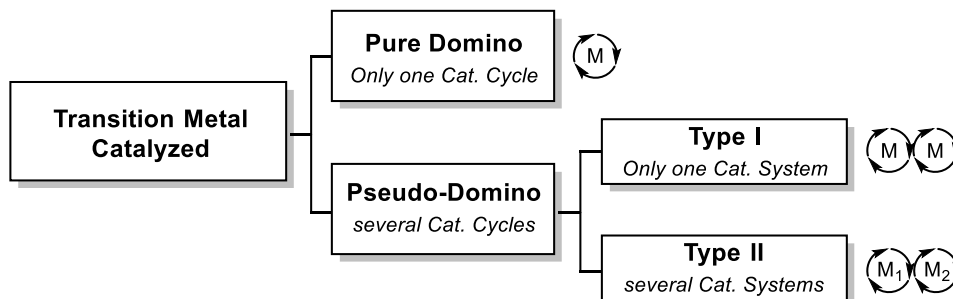
According to the commonly accepted definition by Tietze^[79]: “a domino reaction is a process involving two or more bond-forming transformations which take place under the same reaction conditions without additional reagents and catalysts, and in which the subsequent reactions result as a consequence of the functionality formed in the previous step.” However, when the above domino process is transition metal-catalyzed, three conceptually distinct classes may be further discriminated. The process may either involve a single catalytic cycle driven by a single catalytic system (“M”) and featuring several distinct transition metal-catalyzed transformations, or be made up of sequential, yet mechanistically independent, catalytic cycles, each one involving a simple catalytic transformation. According to the above consideration, our team proposed to distinguish and classify these two transition-metal-catalyzed transformations as pure-domino (TM-DOM) and pseudo-domino (TM-

^[77] a) Hutchins, R. O.; Learn, K. J. *J. Org. Chem.* **1982**, *47*, 4380–4382; b) see also: Mohri, M.; Kinoshita, H.; Inomata, K.; Kotake, H. *Chem. Lett.* **1985**, *14*, 451–454.

^[78] a) Nicolaou, K. C.; Edmonds, D. J.; Bulger, P. G. *Angew. Chem. Int. Ed.* **2006**, *45*, 7134–7186. b) Newhouse, T.; Baran, P. S.; Hoffmann, R. W. *Chem. Soc. Rev.* **2009**, *38*, 3010–3021.

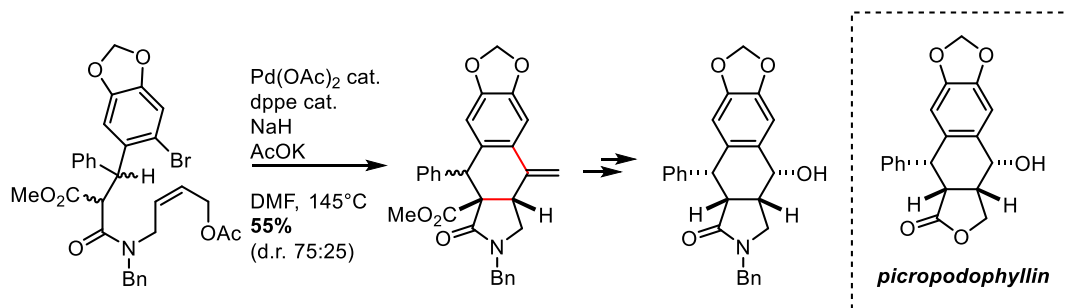
^[79] Tietze, L.F. *Chem. Rev.* **1996**, *96*, 115–136.

PDOM) processes, respectively. Furthermore, the latter type of process may either involve a single “multipurpose” catalytic system (“M”) sharing the sequential cycles (type I), or call for reciprocally compatible catalytic systems of different nature (“M1, M2,..”) (type II) (Scheme 59).^[80]



Scheme 59. Classification of transition metal-catalyzed domino processes.

Our group has a longstanding experience in Pd-catalyzed domino reactions.^[81] Two examples from our team, chosen among several, are presented below. In the context of TM-PDOM sequences, in 2002 we developed a doubly intramolecular Pd-catalyzed allylation / Heck coupling leading to a tetracyclic coupling product.^[82] Further transformations of the coupled product allowed to attain the desired picropodophyllin aza-analog (Scheme 60).



Scheme 60. Doubly intramolecular Pd-catalyzed allylation / Mizoroki-Heck coupling pseudo-domino sequence.

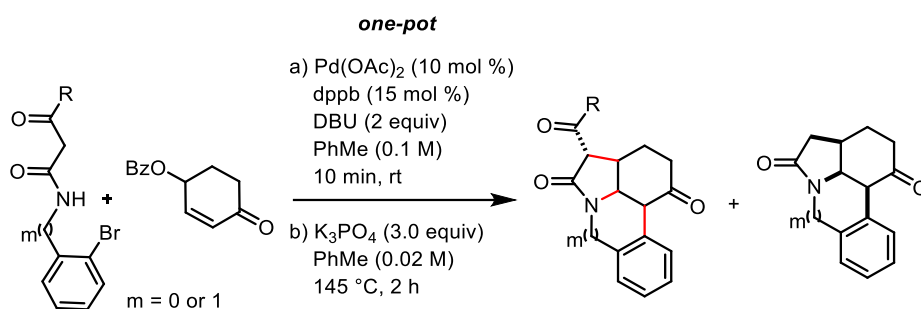
In a more recent study, our group developed a Pd-catalyzed triple domino sequence consisting in an intermolecular Tsuji-Trost allylation / intramolecular nitrogen 1,4-addition sequence / intramolecular keto α -arylation (Scheme 61). This sequence allowed the generation of two new cycles

^[80] a) Lemaire, S.; Prestat, G.; Giambastiani, G.; Madec, D.; Pacini, B.; Poli, G. *J. Organomet. Chem.* **2003**, *687*, 291-300; b) Prestat, G.; Poli, G. *Chemtracts Org. Chem.* **2004**, *17*, 97-103; c) Patil, N. T.; Yamamoto, Y. *Top. Organomet. Chem.* **2006**, *19*, 91-113; d) Liu, Y.; Oble, J.; Pradal, A.; Poli, G. *Eur. J. Inorg. Chem.* **2020**, 942-961.

^[81] For some examples, see: a) Giboulot, S.; Liron, F.; Prestat, G.; Wahl, B.; Sauthier, M.; Castanet, Y.; Mortreux, A.; Poli, G. *Chem. Commun.* **2012**, *48*, 5889; b) Lorion, M. M.; Gasperini, D.; Oble, J.; Poli, G. *Org. Lett.* **2013**, *15*, 3050; c) Rigamonti, M.; Prestat, G.; Brogini, G.; Poli, G. *J. Organomet. Chem.* **2014**, *760*, 149; d) Erray, I.; Rezgui, F.; Oble, J.; Poli, G. *Synlett* **2014**, *25*, 2196; e) Kammerer, C.; Prestat, G.; Madec, D.; Poli, G. *Acc. Chem. Res.* **2014**, *47*, 3439

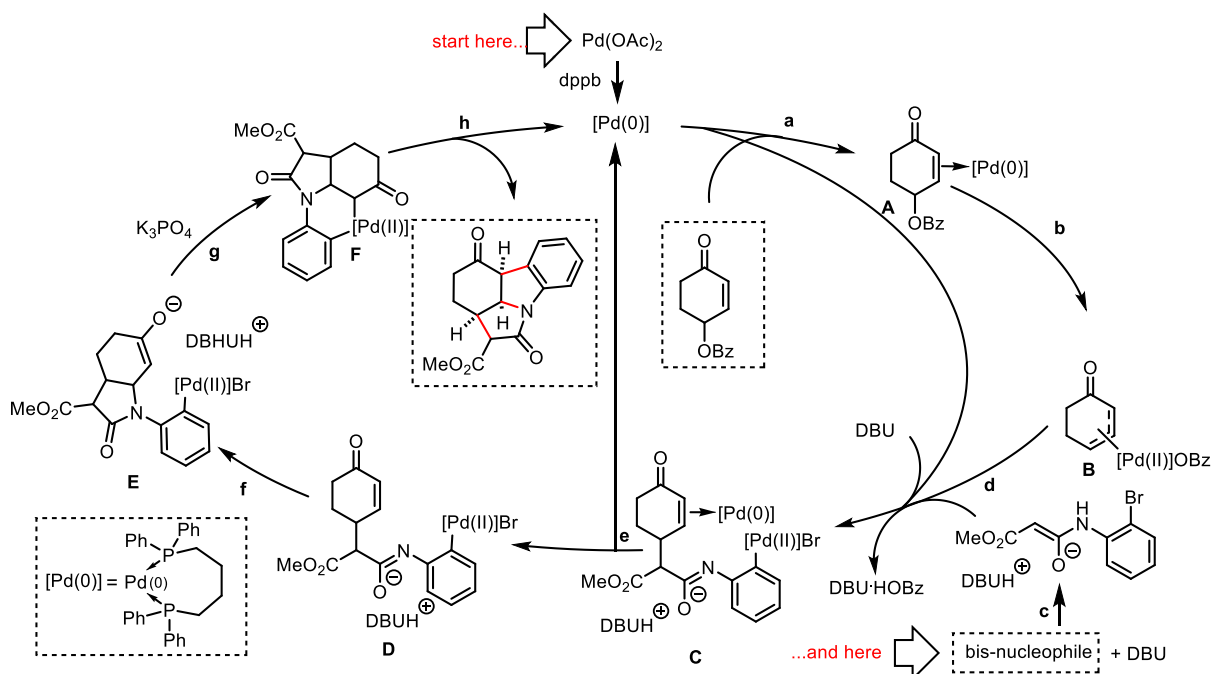
^[82] Poli, G.; Giambastiani, G. *J. Org. Chem.* **2002**, *67*, 9456-9459.

and three new bonds in the same synthetic operation.^[83]



Scheme 61. Triple domino allylation / *N*-conjugate addition / enolate α -arylation.

A plausible mechanism for this annulation is presented in the next scheme (Scheme 62). The sequence starts with an oxidative addition of the bis-electrophile onto the Pd(0) complex to generate the corresponding transient η^3 -allyl-complex **B** through the η^2 -alkene complex **A** (steps a and b). The amidinium-enolate of the bis-nucleophile formed in the meantime (step c), enters the catalytic cycle through C-allylation. Then, a new deprotonation by DBU and an oxidative addition of its aryl halide to Pd(0) generates amidate **C** (step d). Pd(0) decooordination (step e), to form **D**, opens the way to the intramolecular aza-conjugate addition to afford bicyclic enolate **E** (step f). Subsequent enolate-palladation (step g) followed by reductive elimination generates the final tricyclic product and the Pd(0) complex.



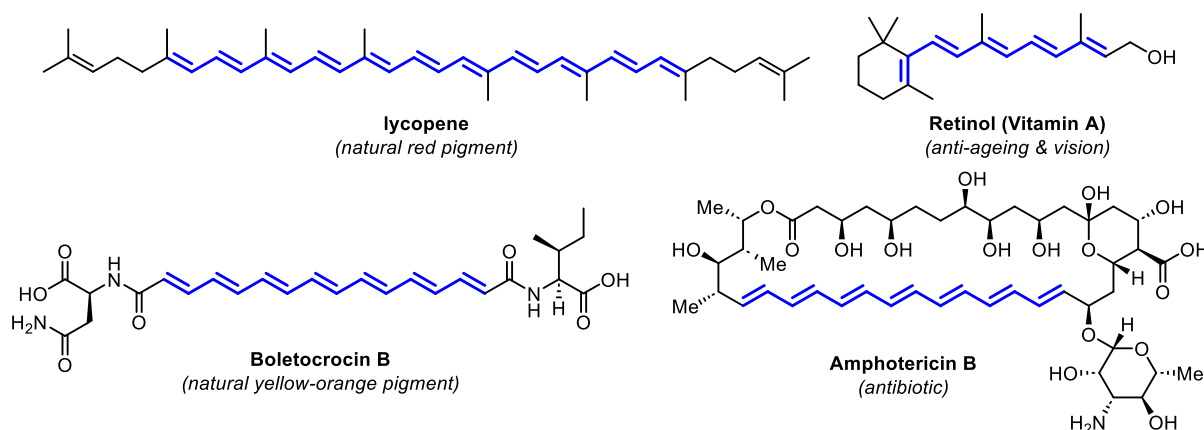
Scheme 62. Plausible mechanism of domino Pd-catalyzed allylation / aza-Michael / Pd-catalyzed keto α -arylation.

^[83] Liu, Y.; Mao, Z. Pradal, A. Huang, P.-Q.; Oble, J.; Poli G. *Org. Lett.* **2018**, *20*, 4057-4061.

Chapter 2. Approach toward the synthesis of conjugated trienes by a Pd-catalyzed domino process involving allyl sulfones.

1. Introduction

Conjugated polyenes are chemical units of great importance in organic chemistry since they can be found in a huge number of natural products (Scheme 63).^[84] This family of molecules can be divided into two main groups. The former group is represented by the polyene antibiotics, whose biological properties depend by their interaction with non-polar molecules such as sterols or liposomes.^[85] The latter group is constituted by pigments, whose color is due the absorption of specific wavelengths of the solar light thanks to the delocalization of the conjugated π -electrons.



Scheme 63. Polyene-containing natural products.

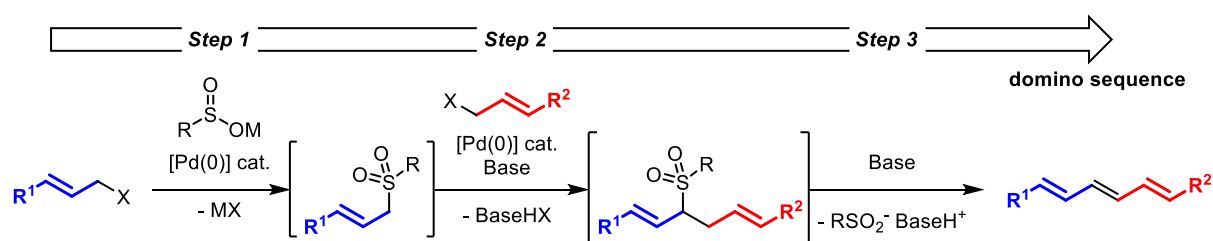
Common methods for the synthesis of polyenes include olefin-generating reactions, such as the Wittig, Horner–Wadsworth–Emmons and Julia olefinations, and the metal-catalyzed crossing-coupling

^[84] For a review, see: Thirsk, C.; Whiting, A. *J. Chem. Soc. Perkin Trans. 1* **2002**, 999-1023.

^[85] For a book chapter, see: Hammond, S. M. Biological Activity of Polyene Antibiotics (Chap. 3). In: *Progress in Medicinal Chemistry*, Vol. 14, Eds: Ellis, G. P.; West G. B., Elsevier, pp.106-164 (1977).

reactions, most notably, the Suzuki–Miyaura reaction, or the Stille reaction.^[14a,86]

As mentioned in Chapter 1, palladium-catalyzed domino sequences represent ideal approaches to the construction of complex molecules. In this context, we envisaged a strategy toward conjugated trienes that involves a sequence of three reactions that could be run in cascade. This strategy involves an initial Pd(0)-catalyzed allylation of a sulfinate anion to produce an allyl sulfone, followed by a second Pd(0)-catalyzed allylation of the anion of the allyl sulfone to produce a 3-sulfonyl-1,5-diene. A final sulfinate elimination is expected to generate the desired conjugated 1,3,5-triene (Scheme 64). The main challenge here is to combine all of these steps in a single process without the palladium catalyst to be deactivated in the course of the reaction. Another challenge consists in the selective addition of only one allyl reagent during step 2.



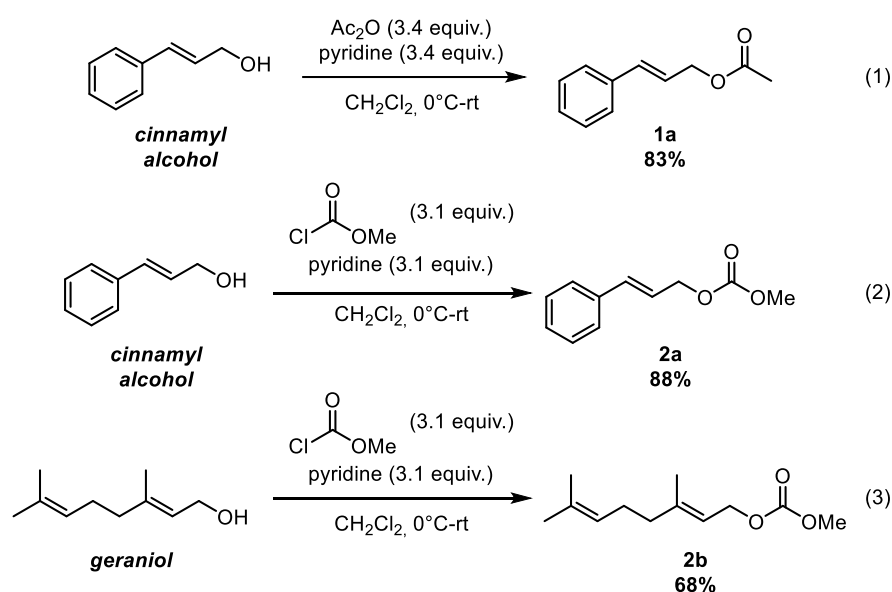
Scheme 64. Proposed strategy for the synthesis of conjugated trienes with palladium and sulfone chemistry.

Our objective was to combine these reactions together and verify if a domino process could allow us an easy access to trienic moieties. In the following paragraphs, step 1 will concern the palladium-catalyzed allylic sulfonylation of allyl acetates or carbonates, step 2 will designate the palladium-catalyzed α -allylation of allyl sulfones and step 3 will apply to the elimination reaction to form the triene. As seen in Chapter 1, taken separately, each of these three steps is a known transformation. So, the challenge of this project resides in the ability to put these transformations in an unprecedented domino sequence. It has to be noted that the optimization of disjointed transformations into a single domino sequence is far from being a simple task and may require a delicate and careful fine-tuning of several reaction parameters.

^[86] Rivas, A.; Areal, A.; Mora, P.; Álvarez, R.; de Lera, A. R. *Chem. Eur. J.* **2020**, *26*, 13543–13567.

2. Synthesis of allyl acetates and allyl carbonates

The first task consisted into the preparation of various allyl acetates and allyl carbonates as the allylating agents for steps 1 and 2. Accordingly, cinnamyl alcohol was acetylated by treatment with acetic anhydride and pyridine in dichloromethane, providing cinnamyl acetate **1a** in 83% isolated yield (Scheme 65, equation 1).^[87] Similarly, treatment of cinnamyl alcohol or geraniol with methyl chloroformate and pyridine in dichloromethane, gave cinnamyl methyl carbonate **2a** and geranyl methyl carbonate **2b** in 88% and 68% yield, respectively (Scheme 65, equations 2 and 3).^[88]



Scheme 65. Preparation of cinnamyl acetate **1a**, cinnamylmethylcarbonate **2a** and geranyl methyl carbonate **2b** from commercially available cinnamyl alcohol and geraniol.

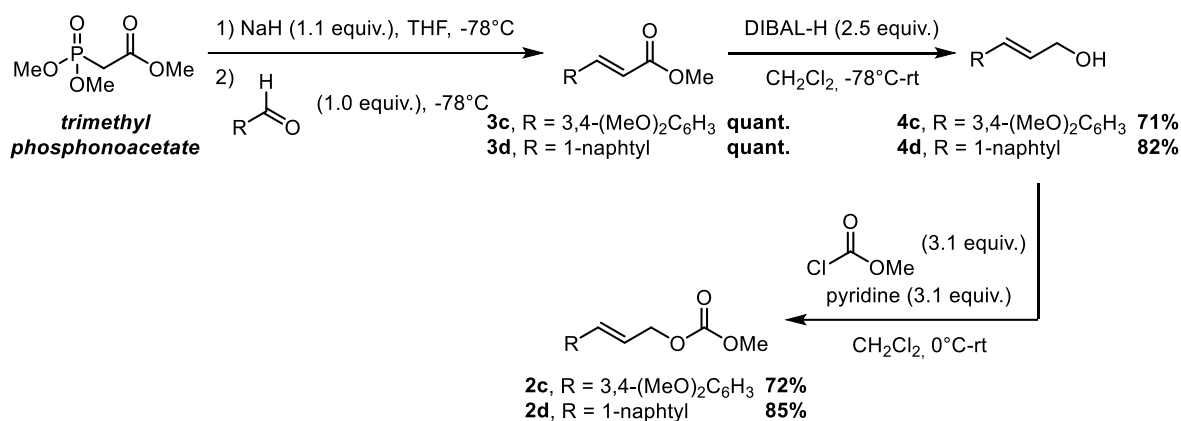
When the aldehyde, instead of the allylic alcohol, was commercially available, the substrate was converted into the corresponding α,β -unsaturated methyl ester by a HWE olefination with trimethyl phosphonoacetate,^[89] and the resulting ester was reduced to the corresponding allylic alcohol with

^[87] Kelly, C. B.; Ovia, J. M.; Cywar, R. M.; Gosselin, T. R.; Wiles, R. J.; Leadbeater, N. E. *Org. Biomol. Chem.* **2015**, *13*, 4255-4259.

^[88] Schlatzer, T.; Schröder, H.; Trobe, M.; Lembacher-Fadum, C.; Stangl, S.; Schlögl, C.; Weber, H.; Breinbauer, R. *Adv. Synth. Catal.* **2020**, *362*, 331-336.

^[89] Jones, B. T.; Avetta, C. T.; Thomson, R. J. *Chem. Sci.* **2014**, *5*, 1794-1798.

DIBAL-H.^[90,91] Finally, the alcohol was converted into the corresponding allyl methyl carbonate under standard conditions.^[88] Using this strategy, 3,4-dimethoxybenzaldehyde and 1-naphthyl aldehyde could be first converted into the corresponding α,β -unsaturated esters **3c** and **3d** in a quantitative yield in each case (Scheme 66). Then, reduction of the ester function with an excess of DIBAL-H lead to allylic alcohols **4c** and **4d** with 71% and 82% yield respectively. Conversion of the alcohols into the methyl carbonates was achieved affording allyl carbonates **2c** and **2d** with 72% and 85% yield, respectively.



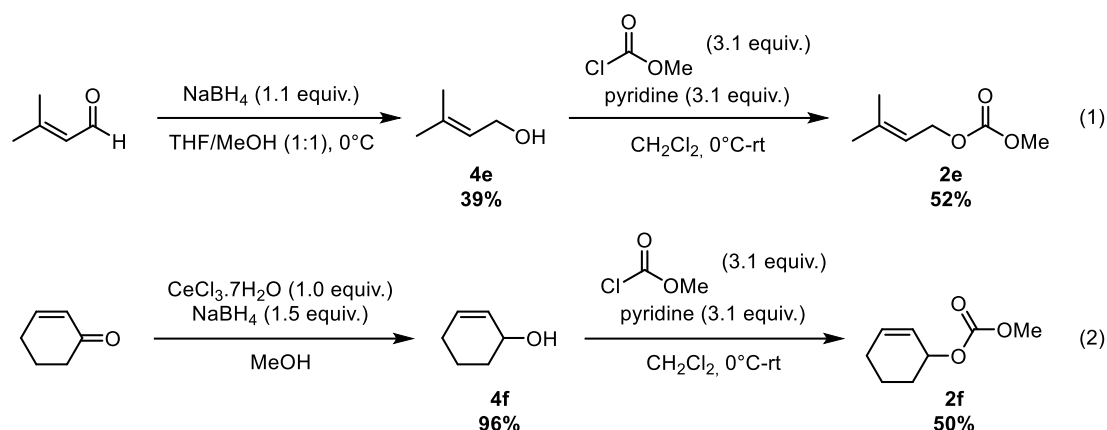
Scheme 66. Three-step synthesis of allyl methyl carbonates **2c** and **2d**.

Following that, 3-methylbut-2-enal was reduced in the presence of sodium borohydride according to reported conditions leading to 3-methylbut-2-enol **4e** in 39% yield. Likewise, cyclohex-2-en-1-one was reduced to cyclohex-2-en-1-ol **4f** using Luche conditions providing in 96% yield.^[92] Both alcohols were then converted into the corresponding methyl carbonates **2e** and **2f** in 52% and 50% yield, respectively (Scheme 67).^[88]

^[90] a) Kocsis, L. S.; Brummond, K. M. *Org. Lett.* **2014**, *16*, 4158–4161; b) Ren, K.; Zhang, L.; Hu, B.; Zhao, M.; Tu, Y.; Xie, X.; Zhang, T. Y.; Zhang, Z. *ChemCatChem* **2013**, *5*, 1317–1320; c) Naimi-Jamal, M. R.; Mokhtari, J.; Dekamin, M. G.; Kaupp, G. *Eur. J. Org. Chem.* **2009**, 3567–3572.

^[91] For a general procedure for the synthesis of the allylic alcohols from the lab, see: Carlet, F.; Bertarini, F.; Broggin, G.; Pradal, A.; Poli, G. *Eur. J. Org. Chem.* **2021**, 2162–2168.

^[92] Ren, K.; Zhang, L.; Hu, B.; Zhao, M.; Tu, Y.; Xie, X.; Zhang, T. Y.; Zhang, Z. *ChemCatChem* **2013**, *5*, 1317–1320.



Scheme 67. Two-step synthesis of allyl carbonates **2e** and **2f**.

3. First studies on the compatibility of the reaction conditions for the domino process.

In order to accomplish a domino process, we first needed to check if the reaction conditions used for the first step are compatible with those used for the second step.

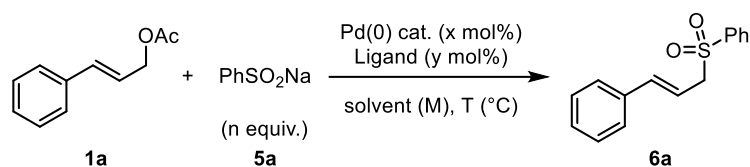
3.1. Studies on cinnamyl acetate **1a**.

3.1.1. Studies on step 1: Sulfonylation of cinnamyl acetate **1a**.

The next task was finding out the most suitable conditions for the first step of the planned domino process, *i.e.* the sulfonylation of cinnamyl acetate **1a**. Accordingly, following the protocol of Kotake,^[63] treatment of cinnamyl acetate **1a** and sodium benzenesulfinate **5a** in the presence of 5 mol% of Pd(PPh₃)₄ in THF/MeOH, at rt, gave the desired cinnamyl sulfone **6a** in 79% (Table 1, entry 1). Since Pd(II) complexes can react with methanol generating Pd(0) and formaldehyde^[93] and because we wished to use the same catalyst for steps 1 and 2 of the domino sequence, other solvents under otherwise similar conditions were screened. When switching to DMF or THF as the sole solvent, the desired product **6a** was obtained in 70% and 86% yield, respectively (Table 1, entries 2-3). In this case, the reaction mixture had to be heated to solubilize completely the sulfinate salt. This resulted in longer

^[93] Marcinkowski, M. D.; Yuk, S. F.; Doudin, N.; Smith, R. S.; Nguyen, M.-T.; Kay, B. D.; Glezakou, V.-A.; Rousseau, R.; Dohnálek, Z. *ACS Catal.* **2019**, *9*, 10977-10982.

reaction times when using THF. Other reported conditions favoring the solubilization of the sulfinate were tested. Treatment of cinnamyl acetate **1a** and sodium benzenesulfinate **5a** with 10% Pd/C and triphenylphosphine in water at 70°C for 18 h resulted in the formation of the desired product **6a** in 87% yield (Table 1, entry 4).^[67] We then selected conditions that were close to those described for the second step of the domino sequence and checked whether they were compatible for the first step.^[74,75] The use of a catalytic system consisting of 5 mol% of Pd₂(dba)₃ and 20 mol% of dppe, working in THF at 65°C for 2.5 h, allowed to obtain the desired cinnamyl sulfone **6a** in an excellent 93% yield (Table 1, entry 5). These conditions have been considered to be the optimal not only because of the high yield of the product, but also because they are close to those reported for the second step of the domino process.



Entry	Pd(0) cat. (x mol%)	Ligand (y mol%)	5a (n equiv.)	Solvent (M)	T (°C)	Reaction time	6a (%) ^[a]
1	Pd(PPh ₃) ₄ (5)	-	1.1	THF/ MeOH (0.25)	rt	5 min	79
2	Pd(PPh ₃) ₄ (1)	-	2.0	DMF (0.38)	70	10 min	70
3	Pd(PPh ₃) ₄ (5)	-	1.1	THF (0.25)	65	3 h	86
4	10% Pd/C (1)	PPh ₃ (4)	2.0	H ₂ O (0.38)	70	18 h	87
5	Pd ₂ (dba) ₃ (5)	dppe (20)	1.1	THF (0.25)	65	2.5 h	93

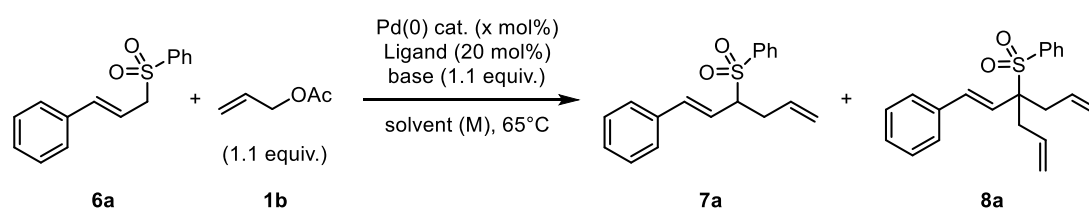
[a] Yields were measured by quantitative ¹H NMR analysis using 1,4-dinitrobenzene as internal standard.

Table 1. Conditions studied for the sulfonation of cinnamyl acetate **1a**.

3.1.2. Studies on step 2: Pd-catalyzed α -allylation of cinnamyl sulfone **6a**.

We then passed to study step 2, the Pd-catalyzed α -allylation of cinnamyl sulfone **6a**, testing first the reaction conditions reported by Trost.^[12a] Thus, treating cinnamyl sulfone **6a** with 1.1 equivalents

of sodium hydride (NaH), to deprotonate the allylic position, and then with 1.1 equivalents of allyl acetate **1b**, in the presence of catalytic amounts of Pd(PPh₃)₄, in THF at 65°C for 30 h, provided the desired monoallylated product **7a** in 38% yield together with 7% yield of byproduct **8a**, resulting from the double α -allylation of cinnamyl sulfone. Under these conditions, the conversion of the substrate was only of 61% (Table 2, entry 1). Performing the reaction in the presence of methanol as a co-solvent (like in step 1), brought about substrate decomposition (Table 2, entry 2). When potassium *tert*-butoxide (*t*-BuOK) was used as the base, the conversion was still not complete, giving and after 27 h the monoallylated product **7a** in 36% yield and the diallylated byproduct **8a** in 12% yield (Table 2, entry 3), and generating palladium black. Introduction of triphenylphosphine (PPh₃), in the hope of stabilizing the palladium catalyst, again gave unsatisfactory results (Table 2, entry 4). Using the best conditions for step 1, and in the presence of NaH as the base, gave only decomposition (Table 2, entry 5). The use of 10 mol% of palladium (II) acetate (Pd(OAc)₂) and dppe (20 mol%) as the catalyst system also failed to improve the result, although gave only the monoallylated product (Table 2, entry 6).



entry ^[a]	Pd(0) (x mol%)	ligand	Base	Solvent (M)	t (h)	Conv. (%) ^[b]	7a (%) ^[b]	8a (%) ^[b]
1	Pd(PPh ₃) ₄ (5)	-	NaH	THF (0.2)	30	61	38	7
2	Pd(PPh ₃) ₄ (5)	-	NaH	THF/MeOH (4:1 v/v, 0.1)	54	0	0	0
3	Pd(PPh ₃) ₄ (5)	-	<i>t</i> -BuOK	THF (0.2)	27	52	36	12
4	Pd(PPh ₃) ₄ (5)	PPh ₃	NaH	THF (0.2)	27	64	38	20
5	Pd ₂ dba ₃ (5)	dppe	NaH	THF (0.2)	30	0	0	0
6	Pd(OAc) ₂ (10)	dppe	NaH	THF/DMF (3:2 v/v, 0.2)	22	55	19	0

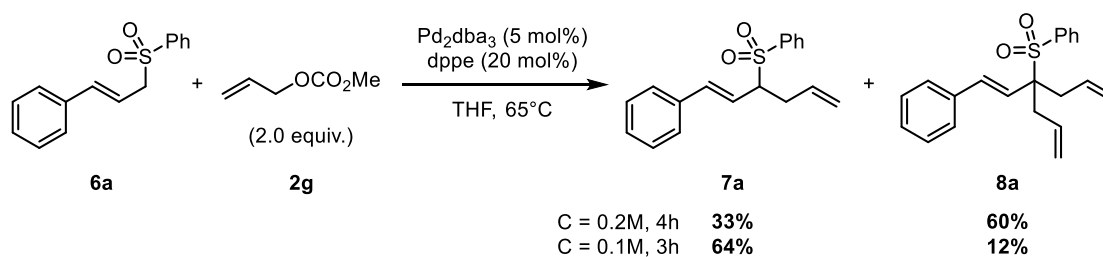
[a] Conditions: cinnamylphenylsulfone **6a** (0.5 mmol), allyl acetate **1b** (1.1 equiv.), Pd(0) catalyst (5-10 mol%), ligand (20 mol%), base (1.1 equiv.), solvent (0.1-0.2M), 65°C; [b] Conversion and yields were measured by quantitative ¹H NMR analysis using 1,4-dinitrobenzene as internal standard.

Table 2. Conditions studied for the α -allylation of cinnamylphenylsulfone **6a**.

The above results suggest that the second allylation tend to compete with the first allylation, thus partially subtracting the allylating agent to the starting allyl sulfone. Given the poor results obtained in terms of conversion and yield of **7a**, and on the basis of the work by Tsuji *et al.*,^[74] we considered the use of allyl carbonates as allylating agents. As described in Chapter 1, they are much more reactive than allyl acetates in Pd-catalyzed allylations, and need no external base.

3.2. Further studies on step 2: on the use of allyl methyl carbonate **2g** in the allylation of cinnamyl sulfone **6a**.

When step 2 was carried out by treating cinnamyl phenyl sulfone **6a** with 2.0 equivalents of allyl methyl carbonate **2g** in the presence of 5 mol% of Pd₂dba₃ and 20 mol% of dppe in THF at 65°C for 4 h, the diallylated byproduct **8a** was obtained in 60% yield together with the monoallylated product **7a** in 33% yield. In another experiment carried out at higher dilution (0.1 M), the α -monoallylated sulfone **7a** was obtained in 64% yield, while the α -diallylated sulfone **8a** was formed in only 12% yield (Scheme 68). These reaction conditions were selected to test step 2, which appear very close to the best conditions previously selected for step 1.

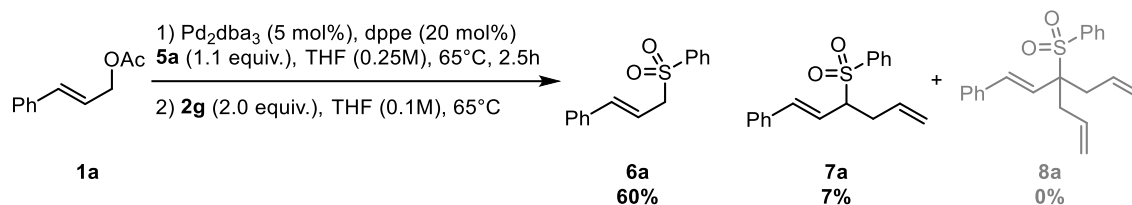


Scheme 68. Use of allyl methyl carbonate **2g** for the α -allylation of cinnamyl phenyl sulfone **6a**.

4. Combination of steps 1 and 2 in a domino process.

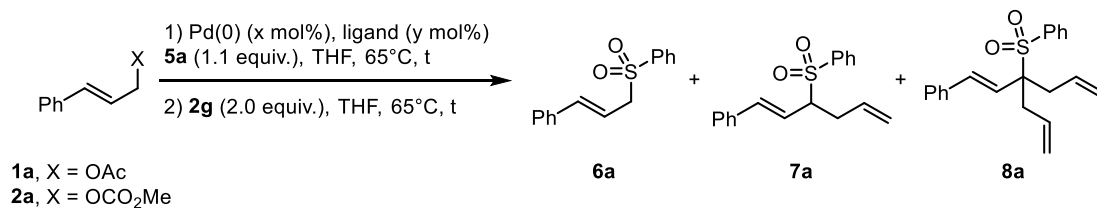
With the aim of finding reaction conditions compatible with the sequential *in situ* achievement of step 1 and 2, we started to test the combination of the two steps. Accordingly, after treatment of

cinnamyl acetate **1a** and sodium benzenesulfinate **5a** with Pd₂dba₃ (5 mol%) and dppe (20 mol%) in THF (0.25 M) at 65°C for 2.5h, the resulting mixture (formation of sulfone **6a** verified by TLC), was treated with 2.0 equivalents of allyl methyl carbonate **2g** at the same temperature. After 49h stirring at this 65°C, this protocol gave the desired monoallylated product **7a** in 7% yield, accompanied by the remaining cinnamyl sulfone **6a** in 60% (Scheme 69).



Scheme 69. First trial on the combination of steps 1 and 2 in the domino sequence.

In the above experiment, precipitation of Pd-black was observed during step 1. Therefore, we surmised that step 2 only barely proceed due to the extensive inactivation of the palladium catalyst. Furthermore, increasing the loading of Pd₂(dba)₃ to 10 mol%, gave only decomposition products (Table 3, entry 2). Accordingly, we envisaged to look for catalytic systems that remain active at the end of step 2. Adding new Pd₂dba₃ (5 mol%) and dppe (20 mol%) after first step was completed, the domino reaction produced the target product **7a** in 58% yield, along with the diallylated byproduct **8a** in 23% yield (Table 3, entry 3). Use of the diphosphines dppp or dppf, instead of dppe, in the reaction did not bring any improvement, too (Table 3, entries 4-5). On the other hand, the use of the large bite-angle ligand XantPhos, gave **7a** and **8a** in 43% and 17% yield, respectively (Table 3, entry 6), without having to add a second batch of catalyst. Gladily, when cinnamylmethylcarbonate **2a** was used as starting material under the same reaction conditions as in entry 1, we obtained the desired monoallylated product **7a** in 50% yield and recovered cinnamylphenylsulfone **6a** in 17% yield (Table 3, entry 7). In this case, fortunately, no diallylated byproduct **8a** was generated.



Entry ^[a]	SM	Pd(0) (x mol%)	Ligand (y mol%)	t (h)	6a (%) ^[b]	7a (%) ^[b]	8a (%) ^[b]
1	1a	Pd ₂ (dba) ₃ (5)	dppe (20)	2.5/ 49	60	7	0
2	1a	Pd ₂ (dba) ₃ (10)	dppe (20)	2.5/ 48	0	0	0
3^[c]	1a	Pd ₂ (dba) ₃ (5+5)	dppe (20+20)	2.5/ 24	6	58	23
4	1a	Pd ₂ (dba) ₃ .CHCl ₃ (5)	dppp (20)	2.5/ 48	54	16	0
5	1a	Pd ₂ (dba) ₃ (5)	dppf (20)	1/48	60	8	0
6	1a	Pd ₂ (dba) ₃ (5)	XantPhos (20)	24/4	13	43	17
7	2a	Pd ₂ (dba) ₃ (5)	dppe (20)	2/29	17	50	0

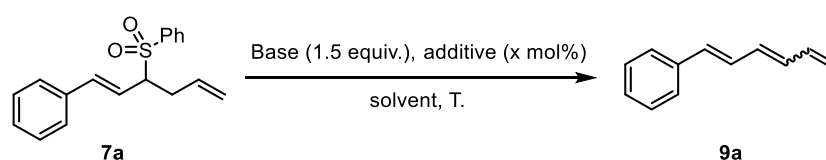
[a] Conditions: cinnamyl acetate **1a** or cinnamylmethylcarbonate **2a** (0.5 mmol), sodium benzenesulfinate **5a** (1.1 equiv.), Pd(0) catalyst (5–10 mol%), ligand (20–40 mol%), THF (0.25M), 65°C, 1–24h then allyl methyl carbonate **2g** (2.0 equiv.), THF (0.1M), 65°C, 4–49h; [b] Yields were measured by quantitative ¹H NMR analysis using 1,4-dinitrobenzene as internal standard; [c] A second batch of palladium catalyst and ligand were added at the beginning of the second step.

Table 3. Optimization of the domino sequence for combined steps 1 and 2.

At this stage, we had two sets of reaction conditions for the preparation of the desired monoallylated sulfone **7a**: a) the double addition of the catalytic system [Pd₂dba₃ (5 mol%) and dppe (20 mol%)] starting from cinnamyl acetate **1a**; b) the use of cinnamyl methyl carbonate **2b**. Next, we turned our attention to the study on the elimination step (step 3 of the domino sequence).

5. Studies on step 3: Synthesis of conjugated trienes by elimination of the sulfone moiety.

As seen in chapter 1, the elimination reaction can take place in the presence of a base, with or without the presence of an additional palladium-catalyst.^[94] In the event, treatment of the monoallylated allyl sulfone **7a** with potassium *tert*-butoxide (*t*-BuOK) or sodium hydride (NaH) in THF at 65°C led to decomposition of the reaction mixture (Table 4, entries 1-2). On the other hand, the use of DBU left the substrate untouched (Table 4, entries 3), which is not surprising given the work reported by Trost.^[12a] In view of these negative results, we decided to screen conditions involving palladium catalysis. However, treatment of **7a** with potassium *tert*-butoxide (*t*-BuOK) in the presence of Pd₂(dba)₃ (5 mol%) and dppe (20 mol%), in THF at 65°C or rt, brought about a rapid decomposition (Table 4, entries 4 and 5), and the same decomposition happened replacing *t*-BuOK with NaH or DBU (Table 4, entries 6 and 7). Finally, following a protocol reported by Koo,^[95] treatment of **7a** with KOH at 80 °C for 4 h in toluene and in the presence of 20 equivalents each of *t*-BuOH/EtOH, gave apparently the desired elimination product, as detected by signals compatible with a 1,3,5-triene on the crude ¹H NMR spectrum. However, due to the low polarity of this product, its chromatographic separation failed. At this point, we should note that no palladium catalyst was required with these conditions.



Entry ^[a]	Base	Additive (x mol%)	Solvent (M)	T (°C)	t (h)	Conv. (%) ^[b]	9a (%) ^[b]
1	<i>t</i> -BuOK	-	THF (0.1)	65	20	100	0
2	NaH	-	THF (0.1)	65	20	100	0
3	DBU	-	THF (0.1)	65	55	0	0
4	<i>t</i> -BuOK	Pd ₂ (dba) ₃ (5 mol%) dppe (20 mol%)	THF (0.1)	65	2	100	0
5	<i>t</i> -BuOK	Pd ₂ (dba) ₃ (5 mol%) dppe (20 mol%)	THF (0.1)	rt	40	100	0

^[94] For a selection of articles on sulfone elimination reactions, see: (a) Wallace, T. J.; Hofmann, J. E.; Schriesheim, A. *J. Am. Chem. Soc.* **1963**, *85*, 2739-2743; (b) Baker-Glenn, C. A.; Barrett, A. G. M.; Gray, A. A.; Procopiou, P. A.; Ruston, M. *Tetrahedron Lett.* **2005**, *46*, 7427-7430; (c) Lim, B.; Oh, E.-T.; Im, J. O.; Lee, K. S.; Jung, H.; Kim, M.; Kim, D.; Oh, J. T.; Bae, S.-H.; Chung, W.-J.; Ahn, K.-H.; Koo, S. *Eur. J. Org. Chem.* **2017**, 6390-6400; (d) Karan, G.; Sahu, S.; Maji, M. S. *Eur. J. Org. Chem.* **2022**, e202200240.

^[95] Alam, M. S.; Koo, S. *Synth. Commun.* **2018**, *48*, 247-254.

6	NaH	Pd ₂ (dba) ₃ (5 mol%) dppe (20 mol%)	THF (0.1)	65	5	100	0
7	DBU	Pd ₂ (dba) ₃ (5 mol%) dppe (20 mol%)	THF (0.1)	65	55	0	0
8	KOH	<i>t</i> -BuOH (20.0 equiv.) EtOH (20.0 equiv.)	Toluene (0.07)	80	4	100	n.d.

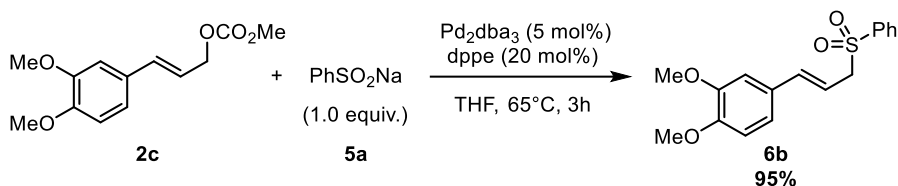
[a] Conditions: allyl sulfone **7a** (0.5 mmol), Base (1.5 equiv.), additives, solvent (0.07-0.1M), rt-65°C, 2-55h; [b] Conversions and yields were measured by quantitative ¹H NMR analysis using 1,4-dinitrobenzene as internal standard. n.d.: not determined.

Table 4. Attempts on the elimination reaction from mono allylated sulfone **7a**.

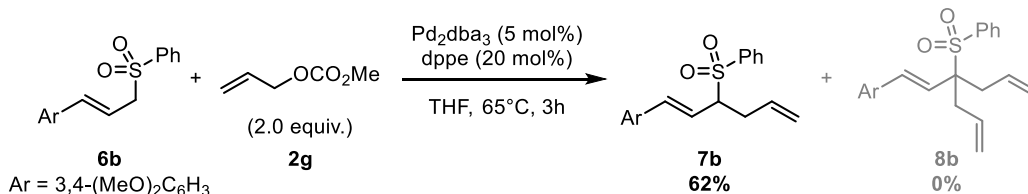
6. Studies on the domino reaction from allyl carbonate **2c**.

Considering the issues met above, we decided to start a new study of domino sequence, this time using (*E*)-3-(3,4-dimethoxycinnamyl) methyl carbonate **2c** as starting allylic electrophile instead of the very apolar cinnamyl methyl carbonate **2a**. This new substrate was prepared under standard conditions from the commercially available (*E*)-3,4-dimethoxybenzaldehyde. With the new substrate **2c** in hand, we first checked if the reaction conditions optimized for the two steps of the domino sequence were still compatible. Accordingly, reacting an equimolar mixture of the carbonate **2c** and sodium benzenesulfinate **5a** in the presence of Pd₂dba₃ (5 mol%) and dppe (20 mol%) in THF at 65°C allowed to isolate 3,4-dimethoxycinnamylsulfone **6b** in 95% yield (Scheme 70). We used precisely 1.0 equivalent of sodium benzenesulfinate **5a** to eliminate any potential impact of an excess of sodium sulfinate on the second reaction. Then, reacting 3,4-dimethoxycinnamylsulfone **6b** with two equivalents of allyl carbonate **2g** in the presence of the same catalytic system as that of step 1, and under the same reaction conditions as those of step 1, gave the desired monoallylated product **7b** in 62% yield, without formation of the diallylated byproduct **8b** (Scheme 70).

■ **Step 1: Pd(0)-catalyzed sulfonylation**



■ **Step 2: Pd(0)-catalyzed allylation of allylsulfone 6b**

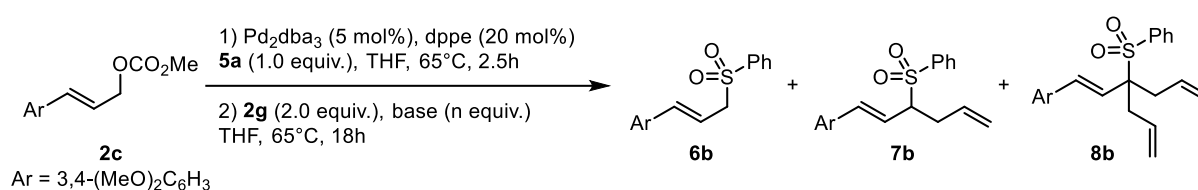


Scheme 70. Application of step 1 and 2 starting from the more polar substrate **2c**.

6.1. Combination of steps 1 and 2 of the domino process and elimination studies

Keeping the same reaction conditions as in the previous experiments, we started to test the domino process. Hence, in a first experiment, after having reacted the 3,4-dimethoxycinnamyl carbonate **2c** with the sulfinate **5a** at 65°C for 2.5 h according to step 1, the resulting reaction mixture containing the newly generated **6b** was directly treated with allyl carbonate **2g** and stirring at 65°C was continued for 18h. However, work up of this experiment gave only the intermediate of the domino process 3,4-dimethoxycinnamylsulfone **6b** in 54% yield, while no target product **7b** was detected (Table 5, entry 1). In a second experiment, the same reaction as above was repeated, except for the addition of sodium methoxide (NaOMe) (1.2 equiv.). However, in this case as well, no desired product **7b** was observed, and **6b** was still produced with 55% yield after 22 hours (Table 5, entry 2). Further experiments using sodium acetate (NaOAc) or sodium hydride (NaH) as bases generated the desired product **7b** in 28% and 42% yield, respectively, together with the intermediate allyl sulfone **6b** in 34% and 10% yield (Table 5, entries 3-4). Other inorganic bases such as cesium carbonate (Cs₂CO₃) and potassium *tert*-butoxide (*t*-BuOK) gave the desired product **7b** in 25% and 40% yield, together with the diallylated byproduct **8b** in 30% and 12% yield, respectively (Table 5, entries 5-6). Use of the organic base DBU resulted only in degradation products (Table 5, entry 7). Finally, using a combination of *N,O*-

bis(trimethylsilyl)acetamide (BSA) with 10 mol% of potassium acetate (AcOK)^[96] led to the exclusive formation of the diallylated product **8b** in 48% isolated yield (Table 5, entry 8). In summary, the results obtained from the above study suggest that the kinetics of the α -allylation of **7b** to **8b** is likely of the same order of magnitude as that of **6b** to **7b**, which renders very hard to stop the allylation to **7b**. However, although we were unable to obtain the desired 1,5-diene **7b** in a synthetically useful yield using a one-pot procedure, we did find a protocol that generated triene **8b**, resulting from a two successive α -allylations of **7b**, in an acceptable yield.



Entry ^[a]	Base (n equiv.)	6b (%) ^[b]	7b (%) ^[b]	8b (%) ^[b]
1	-	54	0	0
2	NaOMe (1.2)	55	0	0
3	AcONa (1.2)	34	28	0
4	NaH (1.2)	10	42	9
5	CS ₂ CO ₃ (1.2)	0	25	30
6	<i>t</i> -BuOK (1.2)	0	40	12
7	DBU (1.2)	0	0	0
8	BSA (1.2equiv.) /AcOK (10 mol%)	0	0	52 ^[c]

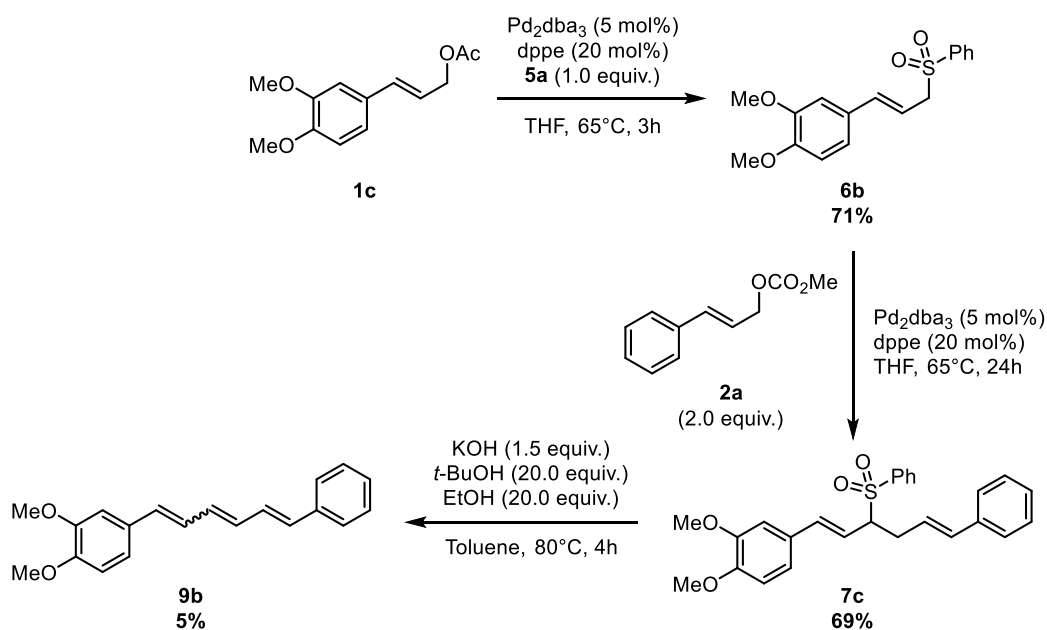
[a] Conditions: allyl carbonate **2c** (0.5 mmol), sodium benzenesulfinate **5a** (1.0 equiv.), Pd₂dba₃ (5 mol%), dppe (20 mol%), THF (0.1M), 65°C, 2.5h then allyl methyl carbonate **2g** (2.0 equiv.), THF (0.1M), 65°C, 18h; [b] Yields were measured by quantitative ¹H NMR analysis using 1,4-dinitrobenzene as internal standard; [c] 48% isolated yield.

Table 5. Study of the domino process from allyl carbonate **2c**.

As the monoallylated product **7b** was not obtained in a synthetically acceptable yield via a one-pot process, we decided to prepare the new targeted 3-sulfonyl hexa-1,5-diene via a stepwise protocol, to test it in the elimination reaction (step 3). Accordingly, treatment of 3,4-dimethoxy cinnamyl acetate

^[96] Trost, B. M.; Murphy, D. J. *Organometallics* **1985**, 4, 1143-1145.

1c with sodium benzenesulfinate **5a** under the previously set up Pd-catalyzed conditions yielded the allyl sulfone **6b** in a 71% yield (Scheme 71). It has to be noted that the same reaction using 3,4-dimethoxycinnamyl carbonate gave 95% yield. The latter was subsequently reacted with cinnamyl carbonate **2a** under Pd(0)-catalysis to produce monoallylated product **7c** with a 69% yield. Treatment of **7c** with KOH at 80 °C for 4 h in toluene, in the presence of 20 equivalents of *t*-BuOH/EtOH, allowed to isolate the desired 1,3,5-triene **9b** in only 5% yield. The exact configuration of the product **9b** could not be determined by NMR analyses (Scheme 71).

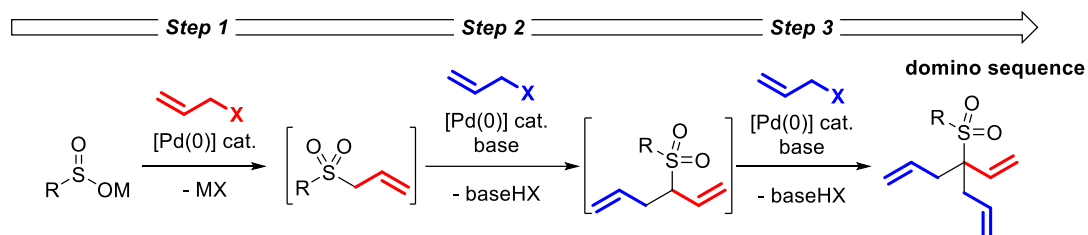


Scheme 71. Study of elimination of the sulfonyl hexa-1,5-diene **7c**.

7. Domino Pd(0)-catalyzed sulfonylation/ α -diallylation

In view of the results obtained in the previous study, we decided to focus on the development of a method to generate 4-sulfonyl 4-vinylhepta-1,6-dienes (α -diallylated allyl sulfones) starting from a sulfinate salt and allylating agents *via* three sequential one-pot Pd(0)-catalyzed allylations (Scheme 72). The importance of this hitherto unknown sequence lies in its potential to have access to densely functionalized polyunsaturated synthons in a single synthetic operation. Given the presence of three unsaturations and a sulfonyl group at specific positions, and in view of the rich chemistry of these functional groups, these synthons may be ideal starting building blocks to important targets, such as

cyclopentenes via ring closure metathesis, for example.^[97] Henceforth, in the following paragraphs, step 1 will concern the Pd(0)-catalyzed coupling between a sulfinate anion and an allyl acetate (or carbonate) to give an allyl sulfone, step 2 will designate the Pd(0)-catalyzed α -allylation of an allyl sulfone to give a 3-sulfonyl hexa-1,5-diene (α -allylated sulfone), and step 3 will apply to the Pd(0)-catalyzed allylation of the α -allylated sulfone to give a 4-sulfonyl 4-vinylhepta-1,6-diene (α -diallylated sulfone) (Scheme 72).



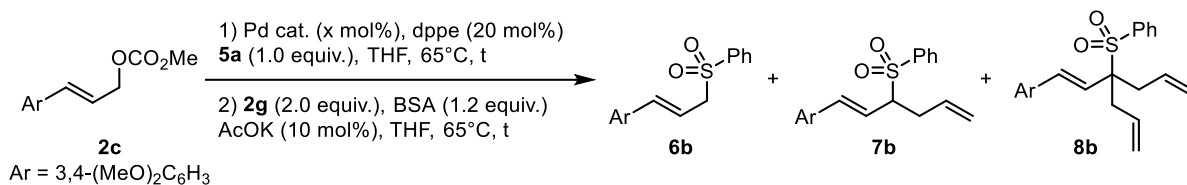
Scheme 72. Triple domino Pd(0)-catalyzed allylation reaction for the synthesis of α -diallylated allyl sulfones.

7.1. Optimization of the triple Pd(0)-catalyzed domino sequence

7.1.1. Screening of palladium catalysts

We started this study by screening several Pd(0) complexes and Pd(II) salts as potential catalyst or pre-catalysts. As described above, the use of the system [Pd₂dba₃ (5mol %)]; dppe (20 mol%); BSA (1.2 equiv.); AcOK (10 mol%)] allowed to obtain the diallylated allylsulfone **8b** in 52% NMR yield (Table 6, entry 1). In the presence of Pd₂dba₃·CHCl₃, Pd(PPh₃)₄ or Pd(dba)₂, the desired product **8b** was obtained in lower yields (Table 6, entries 2-4). When the reaction was carried out with Pd(II) pre-catalysts such as palladium(II) acetate or [Pd(η^3 -C₃H₅)Cl]₂, the yields of diallylated product **8b** did not improve (Table 6, entries 5 and 6). In the end, Pd₂dba₃ proved to be the best palladium catalyst for this domino reaction.

^[97] Kammerer, C.; Prestat, G.; Gaillard, T.; Madec, D.; Poli, G. *Org. Lett.* **2008**, *10*, 405-408.



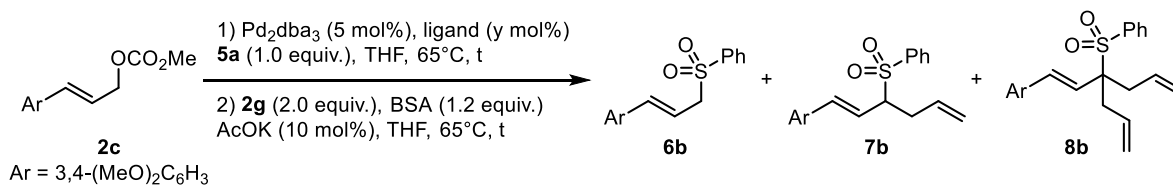
Entry ^[a]	Pd cat. (x mol%)	t (step 1/step 2) (h)	6b (%) ^[b]	7b (%) ^[b]	8b (%) ^[b]
1	Pd ₂ dba ₃ (5)	3/18	0	0	52 ^[c]
2	Pd ₂ dba ₃ ·CHCl ₃ (5)	3/18	0	0	43
3	Pd(PPh ₃) ₄ (10)	3/18	0	0	41
4	Pd(dba) ₂ (10)	3/18	0	0	30
5	Pd(OAc) ₂ (10)	4/18	0	0	22
6	[Pd(C ₃ H ₅)Cl] ₂ (10)	3/18	0	23	31

[a] Conditions: allyl carbonate **2c** (0.5 mmol), sodium benzenesulfinate **5a** (1.0 equiv.), Pd catalyst (5-10 mol%), dppe (20 mol%), THF (0.1M), 65°C, 3-4h then allyl methyl carbonate **2g** (2.0 equiv.), BSA (1.2 equiv.), AcOK (10 mol%), THF (0.1M), 65°C, 18h; [b] Yields were measured by quantitative ¹H NMR analysis using 1,4-dinitrobenzene as internal standard; [c] 48% isolated yield.

Table 6. Screening of palladium catalysts for the triple domino reaction.

7.1.2. Screening of ligands

Following the catalyst screening, the impact of different ligands on the efficiency of the triple Pd(0)-catalyzed domino sequence was evaluated. When dppe was used, the desired diallylated product **8b** was obtained in 52% NMR yield (Table 7, entry 1). When using monophosphine ligands such as triphenylphosphine or XPhos, no improvement was achieved (entries 2 and 3). Other diphosphine ligands like dppf, dppb or dppp proved to be more efficient than monophosphine ligands but less than dppe (Table 7, entries 4-6), the desired diallylated product **8b** being obtained in 34-40% yields with monoallylated product **7b** generated in lower yields. However, using diphosphine ligands with a large bite angle such as DPEPhos or XantPhos proved to be less efficient in promoting this domino reaction (Table 7, entries 7-8). With DPEPhos, mono- and diallylated products **7b** and **8b** were respectively obtained with 15% and 19% yield. With XantPhos, the diallylated product **8b** was generated in 8% yield. Finally, these experiments showed that dppe is the best ligand for this domino reaction.



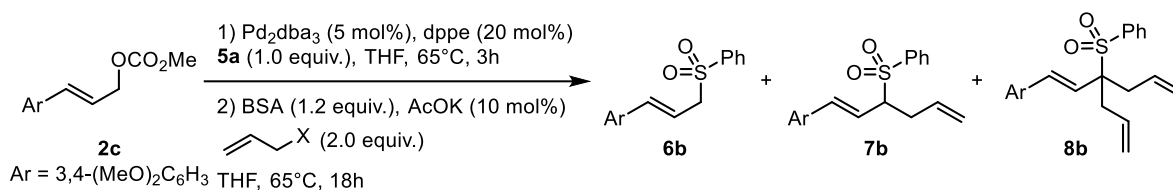
Entry ^[a]	Ligand (y mol%)	Time (step 1/step 2) (h)	6b (%) ^[b]	7b (%) ^[b]	8b (%) ^[b]
1	dppe (20)	3/18	0	0	52 ^[c]
2	PPh ₃ (40)	6/18	0	10	9
3	XPhos (40)	3/18	0	0	0
4	dppf (20)	3/18	0	30	40
5	dppb (20)	3/18	0	19	34
6	dppp (20)	3/18	0	0	36
7	DPEPhos (20)	3/18	0	15	19
8	XantPhos (20)	3/18	0	0	8

[a] Conditions: allyl carbonate **2c** (0.5 mmol), sodium benzenesulfinate **5a** (1.0 equiv.), Pd₂dba₃ (5 mol%), ligand (20–40 mol%), THF (0.1M), 65°C, 3–6h then allyl methyl carbonate **2g** (2.0 equiv.), BSA (1.2 equiv.), AcOK (10 mol%), THF (0.1M), 65°C, 18h; [b] Yields were measured by quantitative ¹H NMR analysis using 1,4-dinitrobenzene as internal standard; [c] 48% isolated yield.

Table 7. Screening of ligands for the triple domino reaction.

7.1.3. Screening of the nature of the second allylic precursor

After the catalyst and ligand screening, a variety of allyl precursors for the second step were investigated. When 3,4-dimethoxycinnamylcarbonate **2c**, sodium benzenesulfinate **5a** and allyl acetate **1b** reacted together under a catalyst system composed of Pd₂(dba)₃ and dppe in THF at 65 °C, the monoallylated product **7b** and diallylated product **8b** were obtained with 32% and 31% yield respectively (Table 8, entry 1). Diallyl carbonate **2h** did not perform much better in this domino sequence (Table 8, entry 2). Moreover, the use of allyl *N,N*-diisopropyl carbamate **2i** or allyl *tert*-butyl carbonate **2j** as alternative allyl reagents did not lead to significant improvements in product yield (Table 8, entries 3 and 4). Additionally, increasing the amount of allyl methyl carbonate **2g** to 2.5 equivalents failed to give a more favorable outcome (Table 8, entry 5) compared to the best conditions found (Table 8, entry 6).



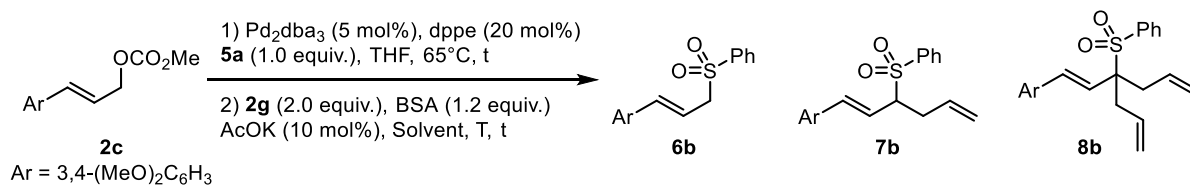
Entry ^[a]	X (n equiv.)	6b (%) ^[b]	7b (%) ^[b]	8b (%) ^[b]
1	1b OAc (2.0)	0	32	31
2	2h OCO ₂ allyl (2.0)	0	15	16
3	2i OCON(<i>i</i> -Pr) ₂ (2.0)	29	5	0
4	2j OBoc (2.0)	19	20	19
5	2g OCO ₂ Me (2.5)	0	0	33
6	2g OCO ₂ Me (2.0)	0	0	52 ^[c]

[a] Conditions: allyl carbonate **2c** (0.5 mmol), sodium benzenesulfinate **5a** (1.0 equiv.), Pd₂dba₃ (5 mol%), dppe (20 mol%), THF (0.1M), 65°C, 3h then allylating reagent **1b** or **2g-2h** (2.0 equiv.), BSA (1.2 equiv.), AcOK (10 mol%), THF (0.1M), 65°C, 18h; [b] Yields were measured by quantitative ¹H NMR analysis using 1,4-dinitrobenzene as internal standard; [c] 48% isolated yield.

Table 8. Screening of the allylic precursors in step 2 of the domino sequence.

7.1.4. Influence of the solvent and temperature on the reaction outcome

Further experimentation revealed that the reactivity of this domino reaction varies with different solvents and temperature. Using highly polar aprotic solvents such as DMSO or DMF only gave 3,4-dimethoxycinnamylsulfone **6b** in 46% and 26% yield respectively, without the desired diallylated product **8b** (Table 9, entries 1 and 2). No improvement was achieved in the presence of 1,4-dioxane (Table 9, entry 3). When THF was used at lower temperatures such as room temperature or 50°C, the product **8b** was obtained with a lower yield (Table 9, entry 5 and 6). Even raising the temperature to 100°C did not result in a higher yield of the desired product **8b** (Table 9, entry 7).



Entry ^[a]	Solvent	T (°C)	t (step 1/step 2) (h)	6b (%) ^[b]	7b (%) ^[b]	8b (%) ^[b]
1	DMSO	65	3/18	46	0	0
2	DMF	65	3/18	26	0	0
3	1,4-dioxane	65	3/18	0	38	15
4	THF	65	3/18	0	0	52 ^[c]
5	THF	RT	4/18	0	26	7
6	THF	50	3/18	0	22	16
7	THF	100	2/17	0	0	16

[a] Conditions: allyl carbonate **2c** (0.5 mmol), sodium benzenesulfinate **5a** (1.0 equiv.), Pd₂(dba)₃ (5 mol%), dppe (20 mol%), THF (0.1M), 65°C, 2-4h then allyl methyl carbonate **2g** (2.0 equiv.), BSA (1.2 equiv.), AcOK (10 mol%), solvent (0.1M), rt-100°C, 17-18h; [b] Yields were measured by quantitative ¹H NMR analysis using 1,4-dinitrobenzene as internal standard; [c] 48% isolated yield.

Table 9. Influence of the solvent and the temperature on the outcome of the triple domino sequence.

All in all, the best conditions we keep for this transformation are the use of a catalyst system consisting of 5 mol% of Pd₂(dba)₃ and 20 mol% of dppe in THF at 65°C for 3 h, followed by the addition of 2.0 equivalents of allyl methyl carbonate **2g**, 2.0 equivalents of BSA and 10 mol% of potassium acetate at 65°C for further 18 h.

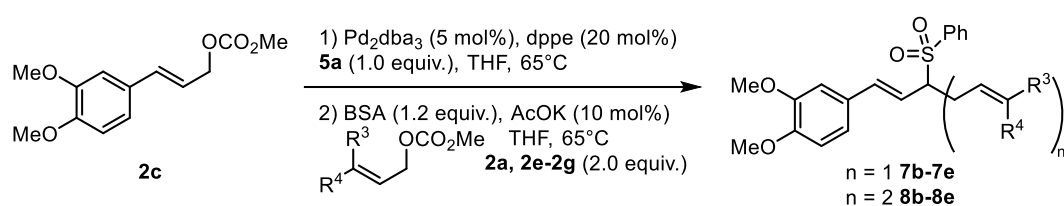
7.2. Scope study on the triple domino sequence

With the best reaction conditions in hand, the scope of the Pd-catalyzed domino sequence was evaluated.

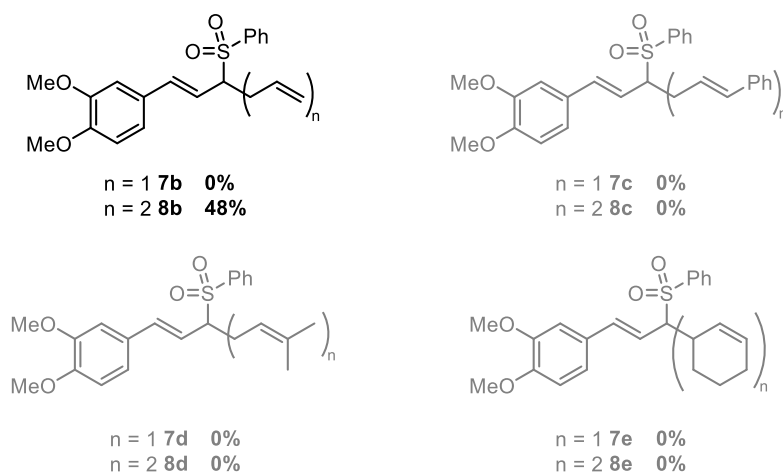
7.2.1. Variation on the second allylic coupling partner

Next, we performed the domino reactions using 3,4-dimethoxycinnamylcarbonate **2c** for the initial sulfinate allylation, with various other allyl methyl carbonates were performed (Scheme 73). We saw previously that the triple Pd-catalyzed domino sequence {[**5a** + **2c** → **6b**] / [**6b** + **2g** → **7b**] / [**7b** + **2g** → **8b**]} gave the α-diallylated allyl sulfone **8b** in 48% isolated yield, without formation of the intermediate

7b. However, repeating the same domino sequence as above, but using cinnamyl methyl carbonate **2a** instead of allyl methyl carbonate **2g** gave only degradation products. Similarly, when prenyl methyl carbonate **2e** was used as the second allylating agent, the corresponding mono- and diallylated products **7d** and **8d** could not be obtained. Using cyclohexyl methyl carbonate **2f** as the second coupling partner was also unsuccessful. In the last two cases, step 2 did not work, and only allyl sulfone **6b** was detected. These reaction outcomes were disappointing and suggest that the reaction may be sensitive to the steric hindrance of the second coupling partner. The sequence seems to be very substrate dependent.



----- studied examples -----

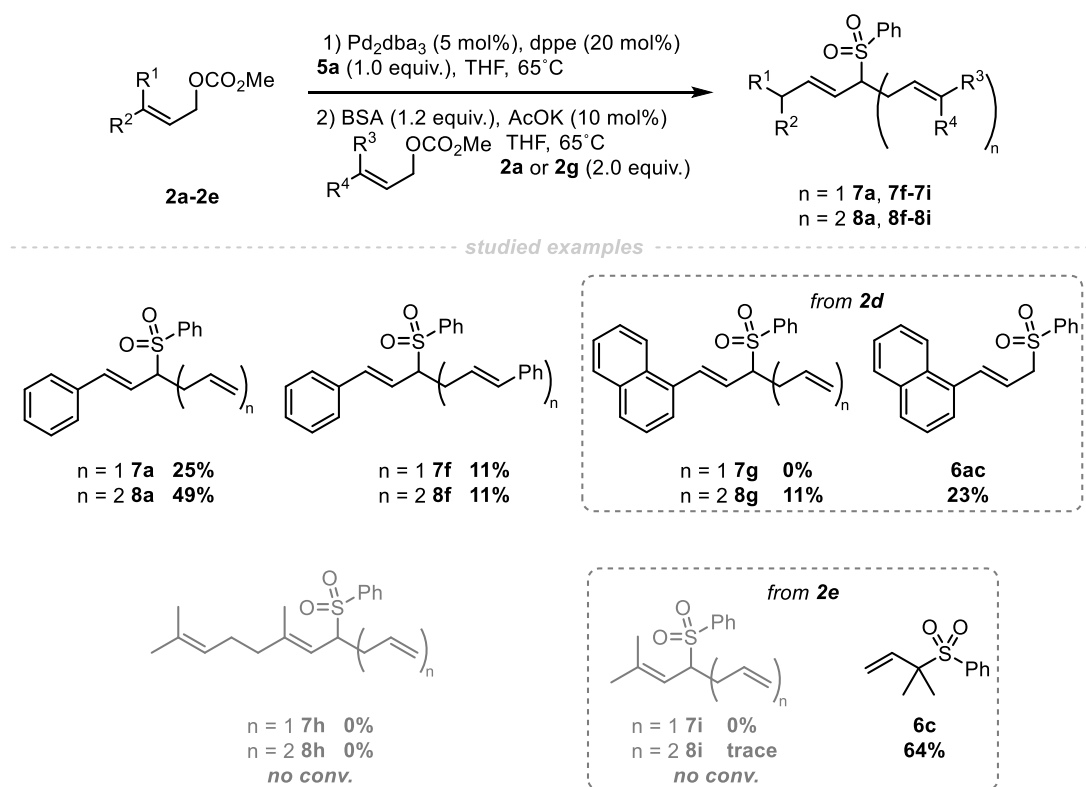


Scheme 73. Variations on allyl methyl carbonates in the domino reactions starting from **2c**.

7.2.2. Variations on the first allylic coupling partner.

We next passed to change the first allylic coupling partner, keeping allyl methyl carbonate as the second coupling partner, under our optimized reaction conditions. Accordingly, applying our domino protocol to cinnamyl methyl carbonate **2a** {planned sequence [**5a** + **2a** → **6a**] / [**6a** + **2a** → **7a**] / [**7a** + **2a** → **8a**]}, the α -allylated sulfone **7a** and the α -diallylated sulfone **8a** were obtained in 25% and 49% yield, respectively. By replacing allyl methyl carbonate **2g** with cinnamyl methyl carbonate **2a**, as the second allylating agent gave the α -allylated sulfone **7f** and α -diallylated sulfone **8f**, each in 11% yield.

This lower yield could possibly be explained by the fact that cinnamyl methyl carbonate is somewhat bulkier than allyl methyl carbonate. Using the (*E*)-3-naphthalen-1-yl-allyl methyl carbonate **2d** as the first allylating agent and allyl methyl carbonate **2g** as the second, completion of the first step was not achieved within 12 h and allylsulfone **6ac** was isolated with 23% yield and diallylated product **8g** was produced with 11% yield after 40 h of reaction. Using of geranyl methyl carbonate **2b** as the first allylating agent and allyl methyl carbonate **2g** as the second did not yield the desired products **7h** and **8h** due to unsuccessful completion of the first step, resulting in no conversion. Finally, reacting prenyl carbonate **2e** as the first allylating agent and **2g** as the second one, the initial allylation with sodium benzenesulfinate **5a** failed to generate a linear allyl sulfone and instead led to the branched allyl sulfone **6c** in 64% yield. These results show that the limitations of this reaction conditions are significant as a very limited number of substrates seem to work (Scheme 74).



Scheme 74. Scope of first allylcarbonate coupling partner in the triple domino sequence.

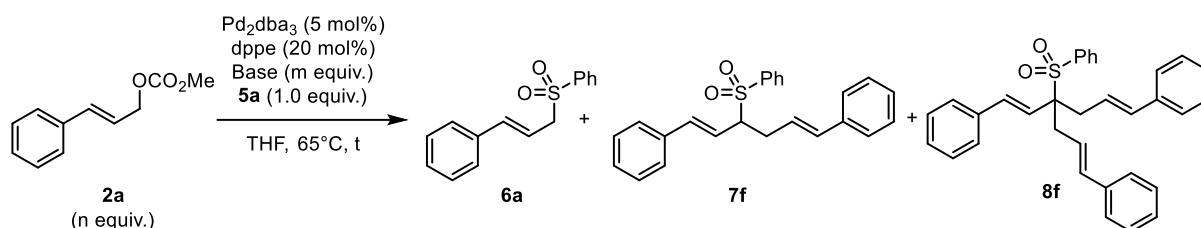
Further exploration and re-optimization of the reaction conditions may be necessary to overcome these challenges and expand the applicability of the reaction to different substrates.

7.3. Study of a pure-domino procedure.

Due to the limited substrate scope observed in the above experimental methods, the construction of S–C/C–C/C–C bonds in a domino sequence remains a significant challenge. In the hope to overcome this issue, we passed to study a triple Pd-catalyzed process that would run not only as a one-pot procedure, but also as a pure domino process. That is to say, eliminating the addition of one component during the process. In a pure domino sequence, all the reactions components have to be present at the outset of the experiment, and this fact may help reducing the risk of Pd-catalyst deactivation.

7.3.1. Development of a pure-domino process from allyl carbonate **2a**.

In the first trial, we reacted 3.0 equivalents of cinnamylmethylcarbonate **2a** and 1.0 equivalent of sodium benzenesulfinate **5a** in the presence of 5 mol% of Pd₂dba₃, 20 mol% of dppe and with the combination of 1.2 equiv. of BSA and 10 mol% of potassium acetate as the base in THF at 65°C for 4 h. Since cinnamyl methyl carbonate **2a** is expected to participate as the first, the second and the third allylating agent, at least 3 equivalents of substrate **2a** are theoretically required. With these conditions, the monoallylated product **7f** and diallylated sulfone **8f** were obtained in 22% and 15% yield, respectively (Table 10, entry 1). Increasing the amount of cinnamyl carbonate **2a** to 4.0 equivalents led to the formation of diallylated product **8f** in 38% yield, while the monoallylated product **7f** was not observed (Table 10, entry 2). However, using cesium carbonate as the base provided both mono- and diallylated products **7f** and **8f** in 30% and 16% yield respectively (Table 10, entry 3). Further attempts to improve the yield by increasing or decreasing the amount of base did not yield better results (Table 10, entries 4 and 5). In addition, the domino reaction could not provide a better yield of the products when no external base was used (Table 10, entry 6).



Entry ^[a]	2a (n equiv.)	Base (m equiv.)	t (h)	6a (%) ^[b]	7f (%) ^[b]	8f (%) ^[b]
1	3.0	BSA(1.2 equiv.) /AcOK (10 mol%)	4	0	22	15
2	4.0	BSA (1.2 equiv.) /AcOK (10 mol%)	4	0	0	38
3	4.0	Cs ₂ CO ₃ (1.2 equiv.)	4	0	30	16
4	4.0	BSA (2.0 equiv.) /AcOK (25 mol%)	4	10	0	0
5	4.0	BSA (0.6 equiv.) /AcOK (5 mol%)	20	0	0	20
6	4.0	-	20	0	17	22

[a] Conditions: cinnamyl methyl carbonate **2a** (3-4 equiv.), sodium benzenesulfinate **5a** (0.1 mmol), Pd₂dba₃ (5 mol%), dppe (20 mol%), Base, THF (0.1M), 65°C, 4-20h; [b] Yields were measured by quantitative ¹H NMR analysis using 1,4-dinitrobenzene as internal standard.

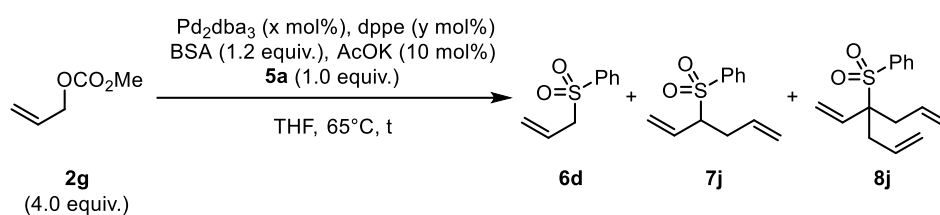
Table 10. Optimization studies on the triple domino process from cinnamylmethylcarbonate **2a**.

As can be seen from the above results, the pure domino sequence did provide the desired diallylated product **8f**, although the yield remained moderate. Since the former study employing cinnamyl methyl carbonate showed poor yield, we decided to study the same kind of pure domino process with allyl methyl carbonate **2g**.

7.3.2. Development of a pure domino process from allyl methyl carbonate **2g**.

Applying our optimal reaction conditions for the pure domino process to allyl carbonate **2g**, after 4 h of heating and stirring, the reaction produced 42% of the monoallylated product **7j** and 14% of the diallylated product **8j** (Table 11, entry 1). Prolonging the reaction time to 18 h resulted in an increase in the yield of the diallylated product **8j** to 37%. However, 23% of allylsulfone **6d** remained unreacted, without undergoing further transformation to the monoallylated product **7j** (Table 11, entry 2). The

addition of 5 mol% of Pd₂(dba)₃ and 20 mol% of dppe to the reaction mixture after 4 h resulted in the major product being the monoallylated product **7j** with 51% yield (Table 11, entry 3). However, despite this improvement, 23% of allylsulfone **6d** remained unreacted. The observation that a significant amount of the starting material and allyl methyl carbonate **2g** remained unreacted despite the use of additional Pd-catalyst and longer reaction times, suggests that the allyl carbonate may undergo decomposition during the reaction progress, highlighting the need for further optimization to improve the yield and selectivity of the domino reaction.



Entry ^[a]	Pd cat.	t (h)	6d (%) ^[b]	7j (%) ^[b]	8j (%) ^[b]
1	Pd ₂ dba ₃ (5 mol%) dppe (20 mol%)	4	25	42	14
2	Pd ₂ dba ₃ (5 mol%) dppe (20 mol%)	18	23	31	37
3 ^[c]	Pd ₂ dba ₃ (5+5 mol%) dppe (20+20 mol%)	4/24	20	51	23

[a] Conditions: allylmethylcarbonate **2g** (4.0 equiv.), sodium benzenesulfinate **5a** (0.1 mmol), Pd₂dba₃ (5 mol%), dppe (20 mol%), BSA (1.2 equiv.), AcOK (10 mol%), THF (0.1M), 65°C, 4-24h; [b] Yields were measured by quantitative ¹H NMR analysis using 1,4-dinitrobenzene as internal standard; [c] A second batch of palladium catalyst and ligand were added at the beginning of the second step.

Table 11. Application of the pure-domino process conditions to allylmethylcarbonate **2g**.

7.3.3. Kinetic studies on the pure domino process.

To investigate the above hypothesis, we followed the kinetics of the above process. Accordingly, we reacted 0.4 mmol of allyl methyl carbonate **2g** with 0.1 mmol of sodium benzenesulfinate **5a** in THF-*d*⁸, at 65°C, using the catalytic system described above and monitoring the reaction progress via ¹H NMR at hourly intervals, using 1,4-dinitrobenzene as an internal standard (Figure 1). The starting material **2g** was rapidly consumed and products **6d**, **7j** and **8j** were all produced within a short period of time (5 hours), then the amount of allyl carbonate **2g** decreases slowly, while products **6d** and **8j**

kept almost unchanged as the reaction proceeded. The rise of the α -allylated sulfone **7j** is pretty fast within the first 2h. Then, its amount decreases to the profit of the α -diallylated sulfone **8j** (from 2 to 3 hours). At the end of the reaction, the formation of the monoallylated product **7j** becomes very slow but increases a little. These results seem to indicate that the starting material is consumed faster than the mono and diallylated allyl sulfones are formed without accumulation of the allyl sulfone **6d**, highlighting a potential degradation or an unidentified side-reaction happening. The slow formation of the products may also suggest that the palladium catalyst deactivates after a certain amount of time (around 5h) and becomes less effective.

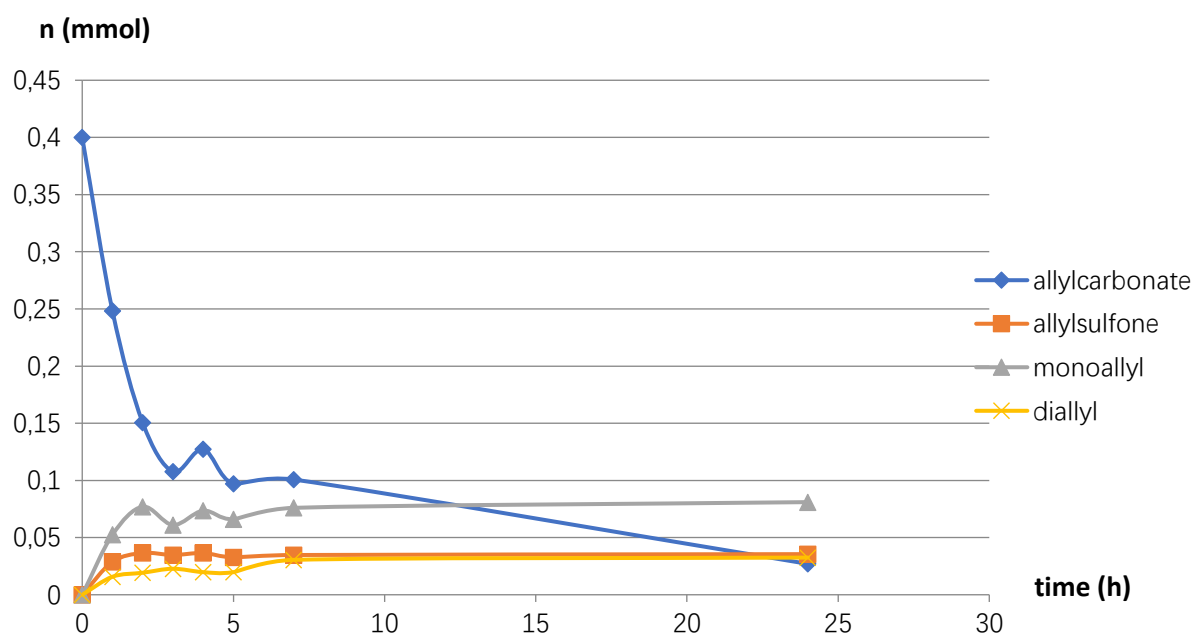
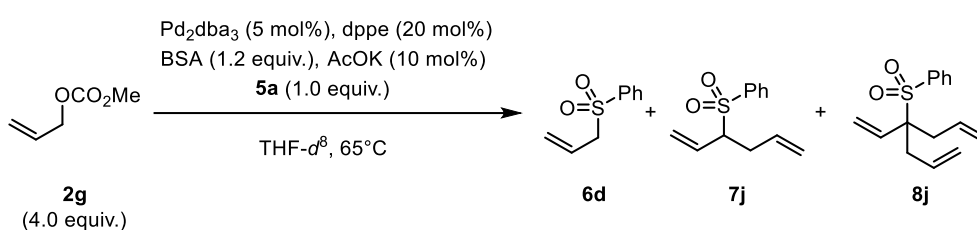


Figure 1. Kinetic study with allyl methyl carbonate **2g**.

Since allyl methyl carbonate **2g** seemed to engage in other transformations than the planned domino reaction, we changed the substrate and selected commercial allyl acetate **1b** for further studies. We followed the kinetics of the reaction by monitoring the reaction of 0.4 mmol of allyl acetate **1b** with

0.1 mmol of sodium benzenesulfinate **5a** by quantitative ^1H NMR with the introduction of 1,4-dinitrobenzene as an internal standard (Figure 2). From this study, we can observe that allyl acetate **1b** was rapidly consumed and allyl sulfone **6d** was rapidly produced in a short period of time (up to 2h), but the mono- and diallylated products **7j** and **8j** were obtained only in small amounts. With the time, the amount of allyl acetate **1b** decreases and remains almost unchanged after 6h of reaction. The yield of allyl sulfone **6d** increased gradually, while the yields of **7j** and **8j** remained almost unchanged. Although the reactivity of allyl acetate **1b** was lower than that of allyl methyl carbonate **2g**, unreacted **1b** remained stable throughout the duration of the experiment. Therefore, further optimization of this reaction was conducted.

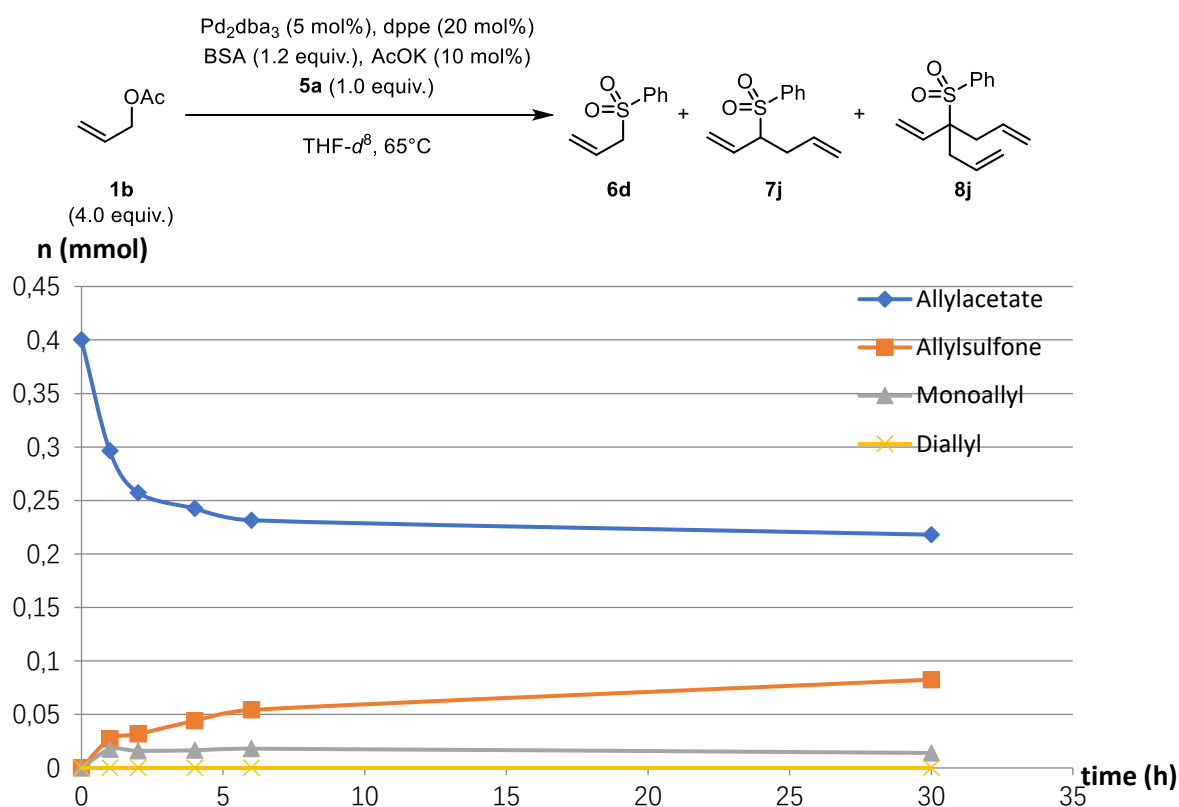
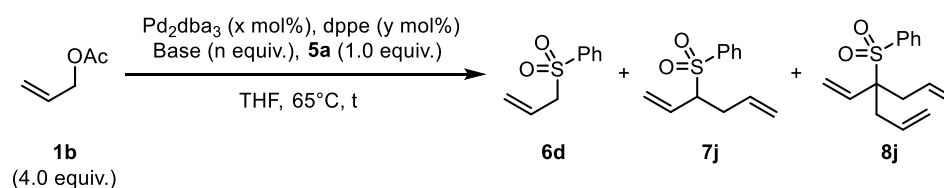


Figure 2. Kinetic study with allyl acetate **1b**.

We performed a reaction with 4.0 equivalents of allylacetate **1b**, 1.0 equivalent of sodium benzenesulfinate **5a** using a catalytic system consisting of 5 mol% of Pd_2dba_3 and 20 mol% of dppe, with 1.2 equiv. of BSA and 10 mol% of potassium acetate as the base for 20 h. This reaction provided allyl phenyl sulfone **6d**, the monoallylated product **7j** and the diallylated product **8j** in 76%, 14% and 5%

yield respectively (Table 12, entry 1). The use of BSA alone as the base (an acetate anion being formed during the formation of the π -allylpalladium species) could increase the yield of monoallylated product **7j** to 34% yield with a short decrease of the quantity of allyl sulfone **6d** (Table 12, entry 2). Increasing the amount of Pd catalyst and ligand did not lead to an improvement in the reaction (Table 12, entry 3). When 5 mol% of Pd₂dba₃ and 20 mol% of dppe were added after 5h of reaction, the monoallylated product **7j** could be obtained with 65% isolated yield together with 25% of allyl sulfone **6d** and a small amount of diallyl sulfone **8j** (Table 12, entry 4).



Entry ^[a]	Pd cat. (x mol%)	Base (n equiv.)	t (h)	6d ^[b] (%)	7j ^[b] (%)	8j ^[b] (%)
1	Pd ₂ dba ₃ (5) dppe (20)	BSA (1.2) AcOK (10mol%)	20	76	14	5
2	Pd ₂ dba ₃ (5) dppe (20)	BSA (1.2)	20	59	34	7
3	Pd ₂ dba ₃ (10) dppe (40)	BSA (1.2)	25	66	28	6
4 ^[c]	Pd ₂ dba ₃ (5+5) dppe (20+20)	BSA (1.2)	6/40	25	71 ^[d]	< 5

[a] Conditions: allyl acetate **1b** (4.0 equiv.), sodium benzenesulfinate **5a** (0.1 mmol), Pd₂dba₃ (5 mol%), dppe (20 mol%), Base, THF (0.1M), 65°C, 20-46h; [b] Yields were measured by quantitative ¹H NMR analysis using 1,4-dinitrobenzene as internal standard; [c] A second batch of palladium catalyst and ligand were added at the beginning of the second step; [d] 65% isolated yield.

Table 12. Optimization attempt for the pure triple domino reaction with allyl acetate **1b**.

Unfortunately, after several trials, we were not able to obtain a synthetically useful domino sequence. After two years of unsuccessful attempts on this project, we decided to shift our attention toward the Pd-catalyzed generation of allyl sulfones via a C–H activation process.

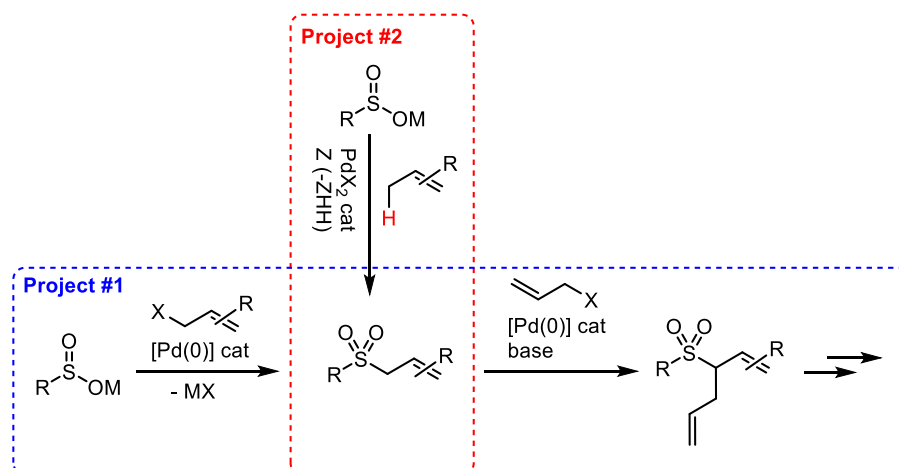
In summary, Pd-catalyzed domino sequences were studied in coupling reactions between allyl

*acetates (or carbonates), and sodium benzenesulfinate. Such planned domino sequences involves three sequential intermolecular Pd-catalyzed allylations generating 4-sulfonyl 4-vinylhepta-1,6-diene motifs through the construction of three new bonds (S–C/C–C/C–C) in a single synthetic operation. Although in some instances we did obtain the desired triene products, the substrate scope for this process remains very limited. A Pd-catalyzed pure domino sequence has been investigated between allyl acetate **1b** (or allyl carbonate **2g**) and sodium benzenesulfinate **5a**. Although this type of protocol has demonstrated improved efficiency compared to the sequential method, it cannot be considered synthetically relevant.*

Chapter 3. Access to allyl sulfones via alkene C–H sulfonylation

1. Introduction

The first project, described in chapter 2, involved the study of the *redox neutral* Pd(0)-catalyzed coupling between a sulfinate anion and an allylically oxidized alkene, coupled with the *in situ* Pd(0)-catalyzed allylation of the resulting allyl sulfone with another allylically oxidized alkene (Scheme 75, blue box). The second project of this thesis work deals with the hitherto unknown alternative generation allyl sulfones via an *oxidative* PdX₂-catalyzed coupling between a sulfinate anion and an alkene (Scheme 75, red box).

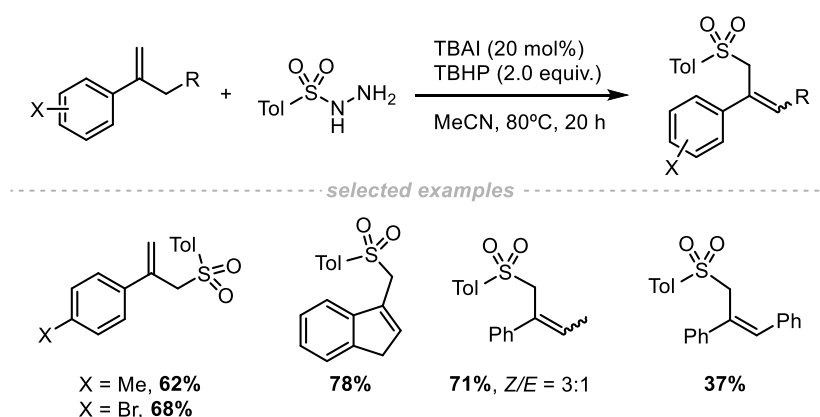


Scheme 75. Project #1 and Project #2 of the thesis and their interconnection. Z = hydrogen acceptor.

This chapter introduces this new project by first presenting the very few reported precedents of allyl sulfone synthesis via alkene C–H sulfonylation. Furthermore, since the planned strategy relies on the direct PdX₂-catalyzed allylic C–H activation / functionalization of alkenes, a brief state of the art of this topic will be also presented.

2. Allylic C–H sulfonation of alkenes

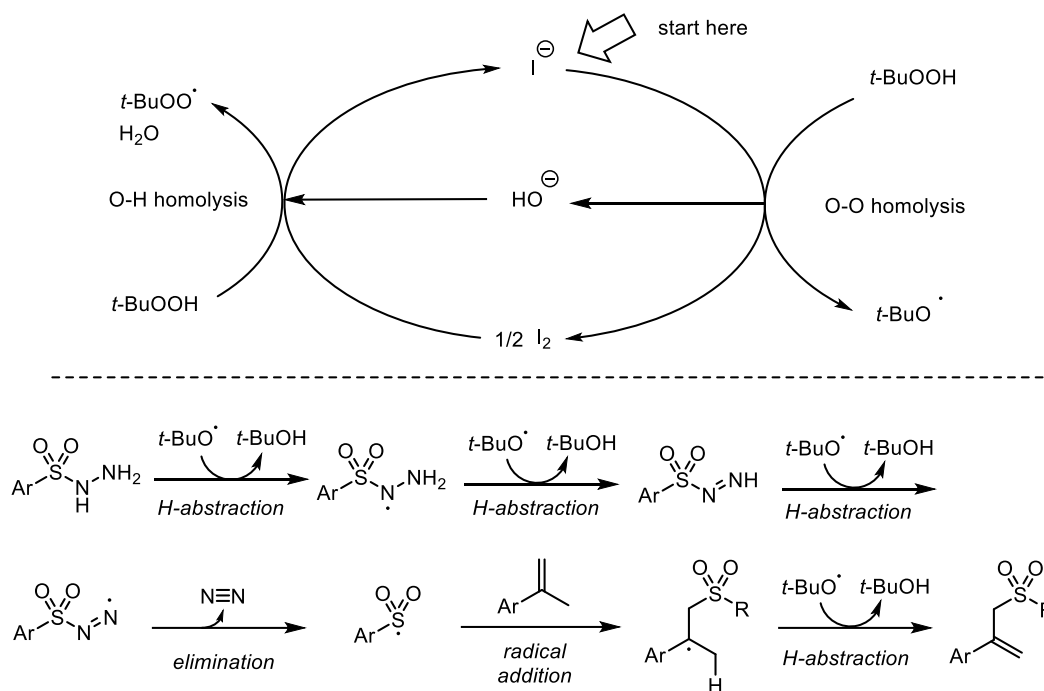
In 2012, Li and co-workers reported that substituted allylic sulfones could be obtained through tetrabutylammonium iodide (TBAI) catalyzed direct allylic C–H coupling between α -methylstyrenes and arylsulfonylhydrazides using *tert*-butyl hydroperoxide (TBHP) as oxidant (Scheme 76).^[98]



Scheme 76. TBAI-catalyzed allylic direct C–H sulfonation.

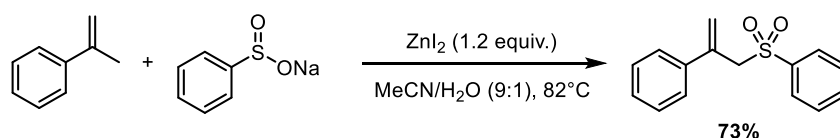
The authors proposed a mechanism for this transformation involving the initial iodide-catalyzed decomposition of TBHP to generate the *tert*-butoxyl and *tert*-butylperoxy radicals (Scheme 77, top). These radicals bring about three consecutive H atom abstractions from the sulfonylhydrazide to generate a sulfonyl radical with the release of molecular nitrogen. Addition of resultant sulfonyl radical to the alkene and subsequent H atom abstraction by *tert*-butoxyl or *tert*-butylperoxy radical affords the allyl sulfone (Scheme 77, bottom).

^[98] Li, X.; Xu, X.; Zhou, C. *Chem. Commun.* **2012**, 48, 12240–12242.



Scheme 77. Postulated mechanism of the TBAI-catalyzed direct allylic C–H sulfonylation. For simplicity H abstraction is indicated only for $t\text{-BuO}^\bullet$.

In 2017, the Chang's group reported that ZnI_2 promoted the C–H sulfonylation of substituted α -methylstyrenes with sodium sulfonates to generate the corresponding α -sulfonyl methylstyrenes (Scheme 78).^[99] Electron-rich α -methylstyrenes did not give the desired products. On the other hand, electron-rich as well as electron-poor aryl sulfonates provided goods yields of the corresponding allyl sulfones. The mechanism postulated by the authors entails the initial interaction between the styrene and ZnI_2 to afford an apparently electrophilic allylzinc intermediate, which undergoes allylic substitution by the sulfinate anion (Scheme 78).

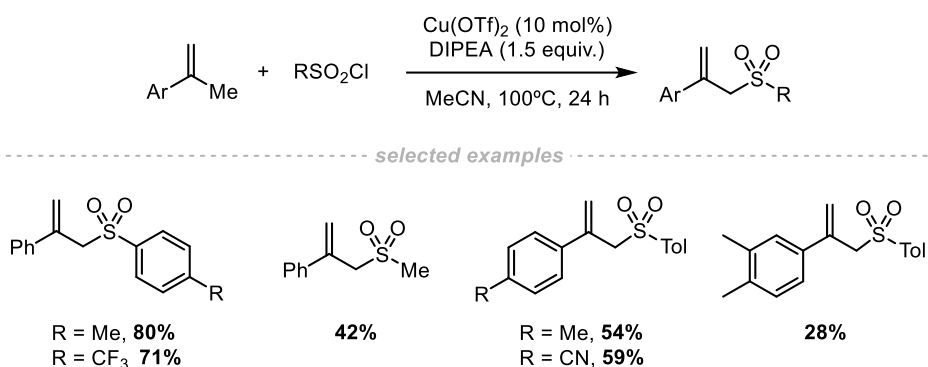


Scheme 78. ZnI_2 -mediated allylic C–H sulfonylation.

Finally last year, Wang *et al.* reported the $\text{Cu}(\text{OTf})_2$ catalyzed C–H coupling between α -

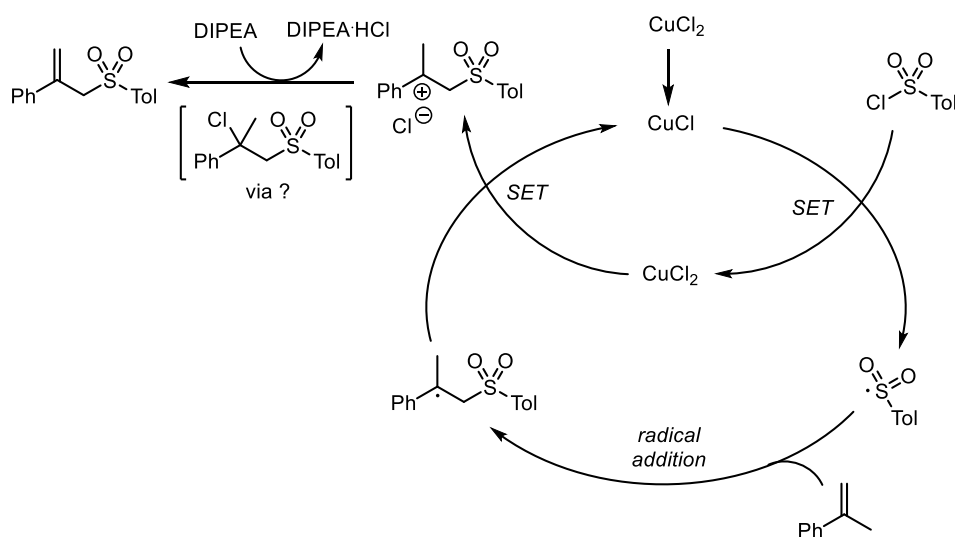
^[99] Chang, M. Y.; Chen, H. Y.; Wang, H. S. *J. Org. Chem.* **2017**, *82*, 10601–10610.

methylstyrenes and arylsulfonyl chlorides, which gave the corresponding allylsulfones in moderate yields (Scheme 79).^[100]



Scheme 79. Copper-catalyzed allylic C–H sulfonylation.

The authors propose for this reaction a radical mechanism involving the initial generation of a CuX active catalyst. A single electron transfer (SET) follows between the Cu(I) species and the sulfonyl chloride, generating a sulfonyl radical and a Cu(II) intermediate. Addition of the sulfonyl radical to α -methylstyrene generates a new benzylic radical intermediate that is oxidized to the corresponding benzylic carbocation by the Cu(II) salt, which in turn reduced to a Cu(I) species. Final elimination gives the α -sulfonyl methylstyrene product (Scheme 80).



Scheme 80. Mechanism postulated for the Cu-catalyzed allylic C–H sulfonylation.

^[100] Liu, L.; Wang, C. *Tetrahedron Lett.* **2022**, *88*, 153553.

3. η^3 -Allylpalladium complexes through direct allylic C-H activation and their reactivity

3.1. Introduction

Recently, the concept of step-economical synthesis has emerged as one of the most challenging topics in organic chemistry. One of the most effective ways to decrease the number of steps of a synthesis is to sidestep the functional group manipulations typically needed to obtain pre-oxidized substrates, to carry out key carbon-carbon or carbon-heteroatom bond formations. One solution to achieve this goal is to realize the direct activation of a C-H bond in an organic substrate. Such an accomplishment allows including the omnipresent C-H bond to the list of the more popular functional groups such as halides, alcohols, carbonyls, etc, thus bypassing intermediate functional group installation.^[101]

A major challenge in this strategy consists in the regio-, chemo- and stereoselective activation of the selected C-H bond, leaving the remaining C-H bonds intact. Reactivity of C-H bonds is highly dependent on the hybridization of the carbon atom. Specifically, while C(sp)-H and C(sp²)-H can be activated more readily, C(sp³)-H are much less reactive, with the notable exception of those in enolizable positions. However, C(sp³)-H bonds in allylic position can be activated more easily than the remaining ones.

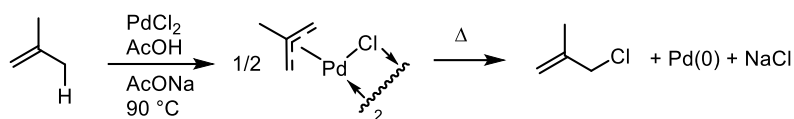
Therefore, the direct functionalization of allylic C-H bonds has been intensely studied. Various transition metals are capable of promoting this activation, and palladium is one of the most interesting metals to accomplish this task, considering both the cost of the metal salt and its reactivity. As a result, several Pd-catalyzed direct allylic oxidations^[102] and aminations^[103] have been published recently.^[1,4b] In 1959, Hüttel^[18] reported the first preparation of the η^3 -allylpalladium chloride dimer via allylic C-H

^[101] For an example of the power of C-H activation to reduce the number of chemical steps in the synthesis of natural molecules, see: Fraunhofer, K. J.; Bachovchin, D. A.; White, M. C. *Org. Lett.* **2005**, *7*, 223-226.

^[102] a) Muzart, J. *Bull. Soc. Chim. Fr.* **1986**, 65-77; b) Rawlinson, D. J.; Sosnovsky, G. *Synthesis* **1973**, 567-603. c) Åkermark, B.; Zetterberg, K. *Handbook of Organopalladium Chemistry for Organic Synthesis* Ed. E.-i. Negishi, John Wiley and Sons, New York, **2002**, 1875-1885; d) Hosokawa, T.; Murahashi, S.-I. Other Intramolecular Oxypalladation-Dehydropalladation Reactions, In: *Handbook of Organopalladium Chemistry for Organic Synthesis*, Ed. E. Negishi, John Wiley & Sons, New York, **2002**, Vol. 2, 2141-2159; e) Henry, P. M. *Palladium Catalyzed Oxidation of Hydrocarbons*, D. Reidel Publishing Co., Dordrecht, **1980**.

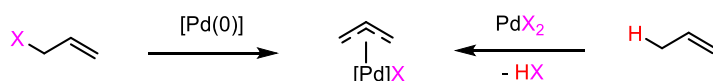
^[103] a) Ramirez, T. A.; Zhao, B.; Shi, Y. *Chem. Soc. Rev.* **2012**, *41*, 931-942. b) Wen, Y.; Zheng, J.; Evans, A. H.; Zhang, Q. *Organics* **2023**, *4*, 289-296.

activation by reacting 2-methylprop-1-ene with palladium(II) chloride, sodium acetate in acetic acid. In a series of subsequent papers, Hüttel showed that heating these complexes brings about reductive elimination to give the corresponding allylic chloride (Scheme 81).



Scheme 81. Pioneering generation of η^3 -allylpalladium complexes.

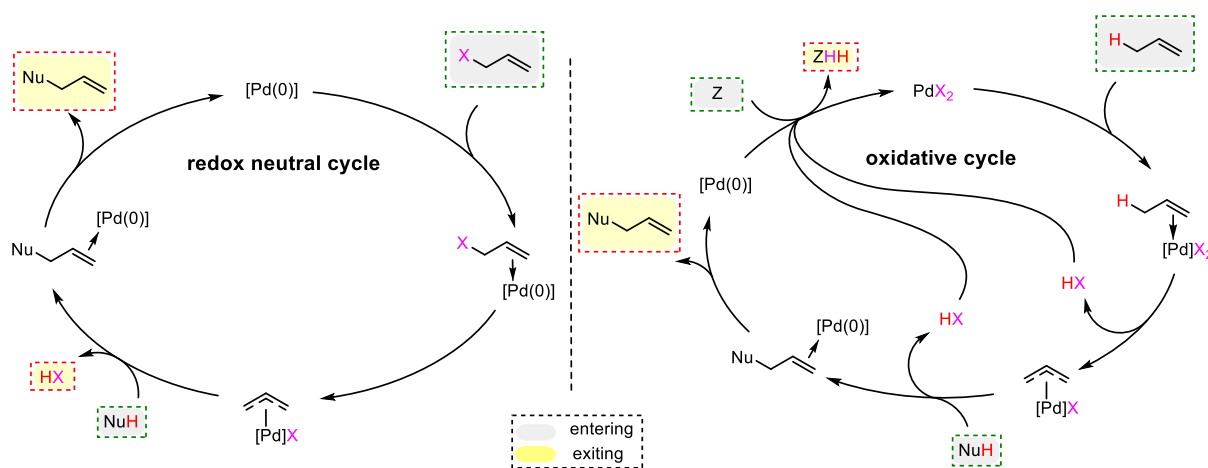
The generation of an η^3 -allylpalladium intermediate from an alkene with a Pd(II) salt implies the C–H activation of the allylic position of an alkene. Therefore, an η^3 -allylpalladium intermediate can be generated either by the interaction between a Pd(0) complex and an allylically oxidized alkene (see chapter 1), or by the interaction between a PdX₂ salt and an alkene having an allylic hydrogen. Therefore, while in the former case the substrate is oxidized and the metal is reduced, the situation is the other way around in the latter case (Scheme 82).



Scheme 82. Two alternative ways to generate η^3 -allylpalladium complexes

In both cases, a Pd-catalysis can be obtained, although under different conditions. Indeed, in the former case, catalysis begins and ends with a [Pd(0)] complex. We already saw several examples of this *redox neutral* catalysis in chapter 1. In the latter case, after the generation of the desired product, the starting Pd(II) salt is reduced to Pd(0). Therefore, a sacrificial oxidant (H₂ acceptor, Z) that brings the metal back to the pristine II oxidation state is here normally^[104] needed (Scheme 83).

^[104] When direct generation of H₂ is possible, the sacrificial oxidant is not needed.



Scheme 83. A generic Pd-catalyzed redox-neutral (left) versus an oxidative (right) Pd-based allylation. Z is the H₂ acceptor.

The possibility of accomplishing oxidative Pd-catalyzed catalytic cycles opened the way to a number of C–H activation-based^[105] allylic functionalizations of alkenes in the presence of several oxygen-, nitrogen- and carbon-based nucleophilic partners.^[106] It should be noted, however, that since these transformations require a sacrificial oxidant, the nucleophile must be compatible with the latter. This chemistry has been recently exploited to generate new C–O (*vide infra*), C–N and C–C bonds by the coupling between alkenes and carboxylic acids, amine derivatives, or carbanions, respectively. On the other hand, the generation of a new C–S bond was unknown before our study. Since the present thesis work required Pd-catalyzed oxidative allyl acyloxylation at some point, a quick state of the art on this C–O bond-forming transformation follows.

3.2. Pd(II)-catalyzed allylic C–H acyloxylation of alkenes

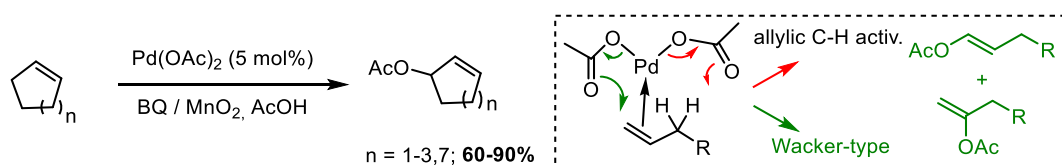
Allylic acetates are useful intermediates in organic synthesis. Traditionally, these substrates can be prepared in one step by esterification of commercially available allylic alcohols with acetic anhydride. However, allylic alcohols are not abundant from commercial sources. For example, the preparation of primary allylic acetates RCH=CHCH₂OAc usually requires three steps from commercially available

^[105] For a selection of recent reviews on C–H activation, see: a) Roudesly, F.; Oble, J.; Poli, G. *J. Mol. Catal. A: Chem.* **2017**, *426*, 275–296; b) Baudoin, O. *Angew. Chem. Int. Ed.* **2020**, *59*, 17798–17809; c) Lam, N. Y. S.; Wu, K.; Yu, J.-Q. *Angew. Chem. Int. Ed.* **2021**, *60*, 15767–15790; d) Rogge, T.; Kaplaneris, N.; Chatani, N.; Kim, J.; Chang, S.; Punji, B.; Schafer, L. L.; Musaev, D. G.; Wencel-Delord, J.; Roberts, C.-A.; Sarpong, R.; Wilson, Z. E.; Brimble, M. A.; Johansson, M. J.; Ackermann, L. *Nat. Rev. Method Primers* **2021**, *1*, 43; e) Dalton, T.; Faber, T.; Glorius, F. *ACS Cent. Sci.* **2021**, *7*, 245–261.

^[106] Transition metals other than palladium allow C–H allylic functionalizations of alkenes.

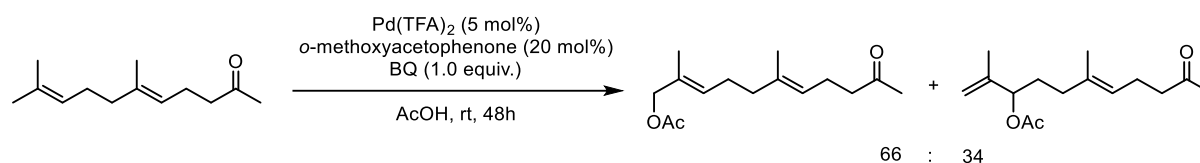
aldehydes. The sequence involves a Horner-Wadsworth-Emmons (HWE) olefination that generates an α,β -unsaturated ester, which is reduced with two equivalents of di-*iso*-butylaluminium hydride (DIBAL-H), to form an allylic alcohol.^[91,107] Finally, the allylic alcohol is transformed into the corresponding allylic acetate by reaction with acetic anhydride. As the above sequence, although of general applicability and efficient, is rather tedious, simpler methods are welcome. The direct allylic acetoxylation of alkenes is a much simpler way to access allylic acetates. In this transformation, a C(sp³)-H bond in an allylic position is formally replaced by an acetate moiety.

In 1984, Åkermark reported that treatment of cycloalkenes with catalytic amounts of Pd(OAc)₂ in the presence of MnO₂ as terminal oxidant afforded the corresponding allylic acetates (Scheme 84).^[108] On the other hand, applying these reaction conditions to terminal alkenes usually produced Wacker oxidation products.



Scheme 84. Catalytic preparation of allylic acetates from cyclic olefins.

The first example of Pd(II)-catalyzed allylic C–H oxidation of a linear alkene was reported by McMurry in 1984.^[109] Treatment of geranyl acetone with the catalytic system [Pd(TFA)₂ (5 mol%)/ *o*-methoxyacetophenone (20 mol%)], in the presence of one equivalent of benzoquinone in acetic acid brought about the allylic acetoxylation of the external alkene with an approximately 66:34 linear / branched ratio. The other examples dealt with cyclic alkenes (Scheme 85).



Scheme 85. First example of Pd(II)-catalyzed allylic C-H acetoxylation of linear alkenes.

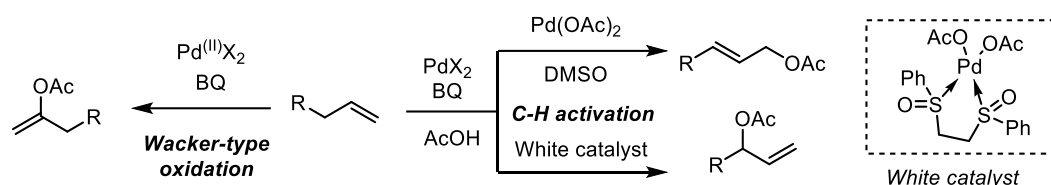
During the following decades, palladium-catalyzed allylic oxidations have been the object of a

^[107] Vermeulen, N. A.; Delcamp, J. H.; White, M. C. *J. Am. Chem. Soc.* **2010**, *132*, 11323-11328.

^[108] Heumann, A.; Åkermark, B. *Angew. Chemie Int. Ed.* **1984**, *23*, 453-454.

^[109] McMurry, J. E.; Kočovský, P. *Tetrahedron Lett.* **1984**, *25*, 4187-4190.

number of studies.^[110] In the early 2000s, White's group disclosed a series of Pd-catalyzed allylic acetoxylation protocols for the selective conversion of monosubstituted olefins into the corresponding linear or branched allylic acetates. The competitive Wacker side reaction could be inhibited when a suitable sulfoxide-based ligand was selected. In particular, use of DMSO (as solvent) in the presence of BQ, acetic acid and catalytic amounts of palladium(II) acetate gave the linear (*E*)-allylic acetates with high regio- and stereoselectivities, whereas the presence of a bis-sulfoxide ligand (White's catalyst) instead of DMSO resulted in the formation of the branched allylic acetates (Scheme 86).^[5a,111]



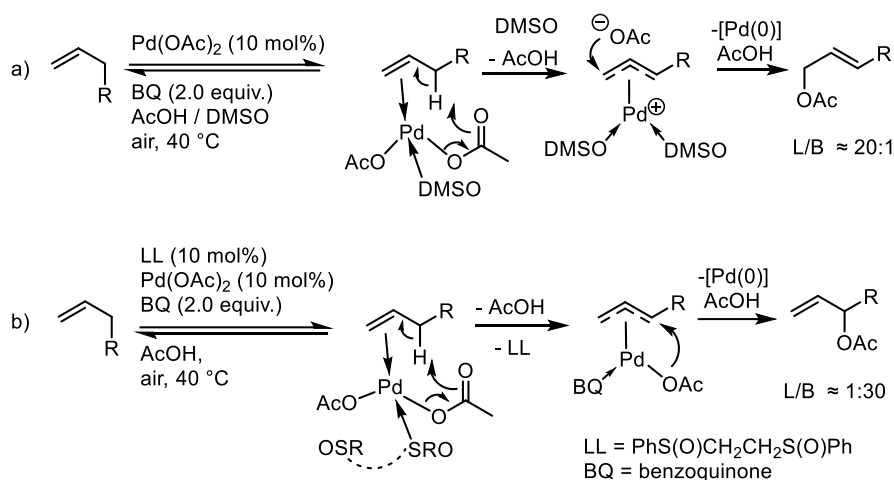
Scheme 86. The Pd(II)/sulfoxide-catalyzed allylic acetoxylation.

The above outcome can be explained as follows. In the presence of DMSO as solvent, abstraction of an allylic proton by the coordinated acetate ligand from the substrate is expected to generate a cationic η^3 -allylpalladium complex (excess DMSO displaces BQ from the Pd coordination sphere). Following trapping by an external acetate anion at the distal allylic position through an outer sphere attack generates a linear allylic acetate. The disulfoxide ligand favors an allylic C–H activation, too. However, in this case, after the C–H activation step, BQ may replace the sulfoxide ligand in the metal coordination sphere (serial ligand catalysis), and the resulting neutral η^3 -allylpalladium complex (with enhanced electrophilicity due to the π -acidic character of BQ) is attacked by an acetate anion at the internal allyl terminus *via* an inner sphere attack generating the branched allylic acetate (Scheme 87).^[112]

^[110] For a selection of other important contributions that will not be discussed here, see: a) Hansson, S.; Heumann, A.; Rein, T.; Åkermark, B. *J. Org. Chem.* **1990**, *55*, 975-984; b) Ferret, N.; Mussate-Mathieu, L.; Zahra, J.-P.; Waegell, B. *J. Chem. Soc., Chem. Commun.* **1994**, 2589-2590; c) Gusevskaya, E.; Gonsalves, J. A. *J. Mol. Catal. A: Chem.* **1997**, *121*, 131-137; d) Kozitsyna, N. Y.; Vargaftik, M. N.; Moiseev, I. I. *J. Organomet. Chem.* **2000**, *593-594*, 274-291; e) Gonçalves, J. A.; Gusevskaya, E. *Appl. Catal. A: Gen.* **2004**, *258*, 93-98; f) Check, C. T.; Henderson, W. H.; Wray, B. C.; Vanden Eynden, M. J.; Stambuli, J. P. *J. Am. Chem. Soc.* **2011**, *133*, 18503-18505; g) von Czapiewski, M.; Meier, M. A. R. *Catal. Sci. Technol.* **2014**, *4*, 2318-2325; h) Li, X.; Sun, B.; Yang, J.; Zhang, X.; Wang, J.; Zhuang, X.; Jin, C.; Yu, C. *Synlett* **2019**, *30*, 1479-1483; i) Zanetti, A.; Schwertz, G.; Nascimento de Oliverira, M.; Gomez Fernandez, M. A.; Amara, Z.; Cossy, J. *J. Org. Chem.* **2021**, *86*, 7603-7608.

^[111] Chen, M. S.; White, M. C. *J. Am. Chem. Soc.* **2004**, *126*, 1346-1347.

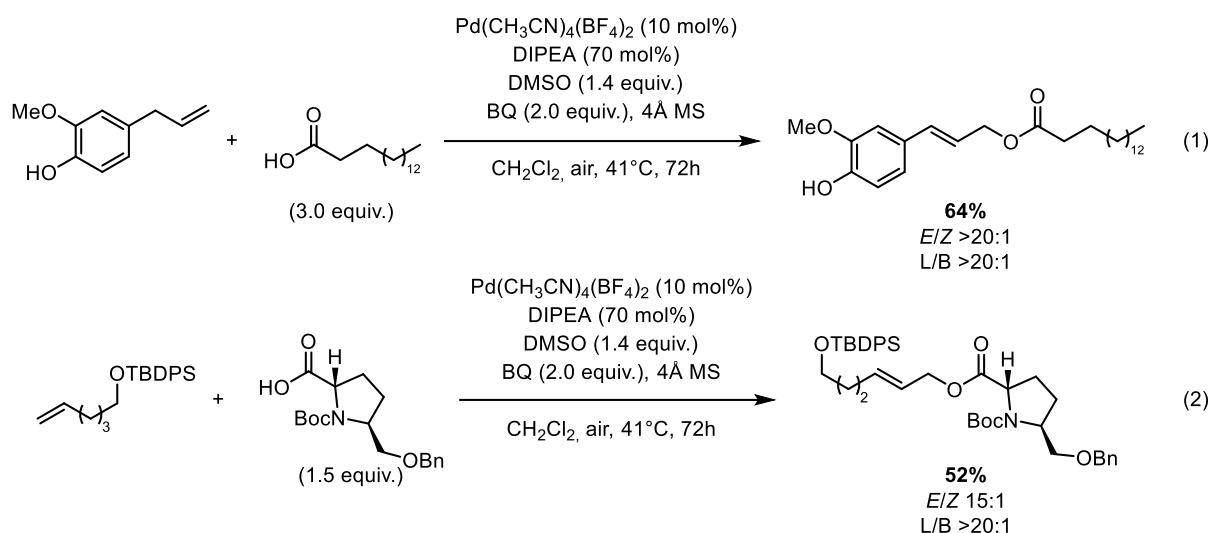
^[112] For an application of this strategy in the total synthesis of D-galactose, see: Covell, D. J.; Vermeulen, N. A.; Labenz, N. A.; White, M. C. *Angew. Chem. Int. Ed.* **2006**, *45*, 8217-8220.



Scheme 87. Proposed scenario for the Pd(II)-catalyzed acetoxylation of terminal alkenes in the presence of sulfoxide ligands.

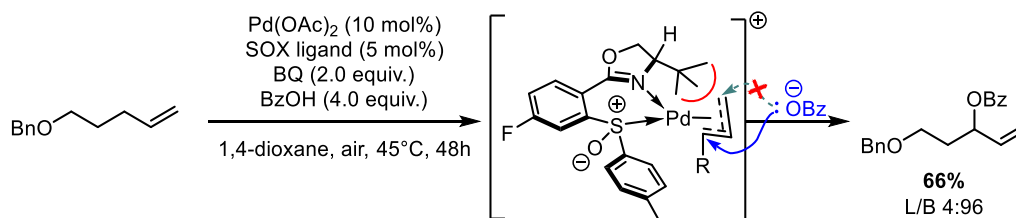
3.2.1. Use of other carboxylic acids for intermolecular allylic C-H acylations.

The PdX₂-catalyzed allylic acetoxylation protocols normally need the presence of acetic acid in a large excess or even as a solvent. This mass effect favors the formation of the products and is easy to implement due to the availability of acetic acid. However, if more complex allylic acyloxylation are desired, the amount of the nucleophile has to be reduced. A general procedure that avoids the use of an excess of carboxylic acid was reported by the group of White in 2010.^[107] This protocol makes use of 1.5 to 3.0 equivalents of carboxylic acids in the presence of the cationic Pd(II) complex (Pd(CH₃CN)₄(BF₄)₂) and DMSO as the ligand. Allylarenes (Scheme 88, equation 1) as well as aliphatic terminal alkenes (Scheme 88, equation 2) could be converted into the corresponding allylic esters in moderate to good yields in excellent linear/branched ratio and diastereoselectivity in favor of the (*E*)-alkene. The reaction was compatible with many carboxylic acids, including aliphatic acids and amino acid derivatives.



Scheme 88. Intermolecular Pd-catalyzed allylic C–H acylation of terminal alkenes.

A couple of years later, Itami *et al.* developed a catalytic system which, thanks to a sterically hindered N,S-bidentate sulfoxide-oxazoline (SOX) ligand, allowed the Pd-catalyzed conversion of monosubstituted terminal alkenes into the corresponding branched allylic esters.^[113] The specific design of the ligand allowed the authors to obtain high selectivities in favor of branched allyl acylates (Scheme 89).



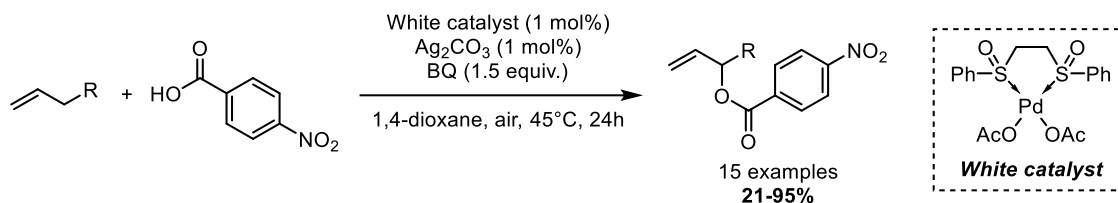
Scheme 89. SOX-ligands for selective formation of branched allyl acylates.

One of the major issues met in Pd-catalyzed allylic acyloxylation is the high catalytic loading of the palladium catalyst needed (usually around 10 mol%). This problem has been partially solved by the group of Tsurugi, Seki and Mashima in 2021, in the acylation of terminal alkenes with *p*-nitrobenzoic acid.^[114] They noticed that the combination of this acid with silver carbonate (Ag_2CO_3) greatly enhanced the kinetics of the Pd(II)-catalyzed allylic C–H acylation of aliphatic terminal as well as cyclic alkenes. In the presence of 1 mol% of Ag_2CO_3 and 1.5 equiv. of BQ, they managed to prepare selectively branched

^[113] Kondo, H.; Yu, F.; Yamaguchi, J.; Liu, G.; Itami, K. *Org. Lett.* **2014**, *16*, 4212-4215.

^[114] Skhiri, A.; Nagae, H.; Tsurugi, H.; Seki, M.; Mashima, K. *Org. Lett.* **2021**, *23*, 7044-7048.

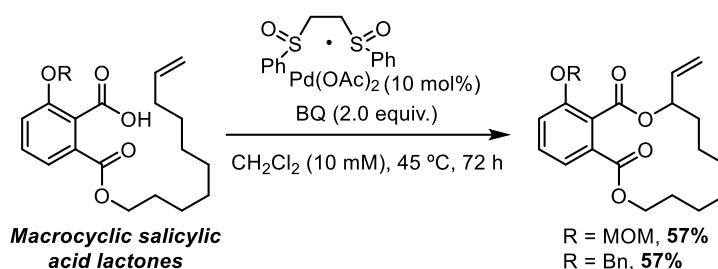
allyl esters using only 1 mol% of commercially available White catalyst for terminal alkenes and 2 mol% of catalyst for cyclic alkenes. The reaction was faster (24h vs 48-72h for other procedures) and proceeded in moderate to excellent yields, depending on the nature of the substrate (Scheme 90).



Scheme 90. Possibility for the reduction of the catalytic loading with *p*-nitrobenzoic acid.

3.2.2. Intramolecular allylic C-H acylation reactions

In 2006, White's group reported the first conversion of linear ω -alkenoic acids into macrolides of different sizes through a Pd/bis-sulfoxide catalyzed intramolecular allylic C–H acetoxylation (Scheme 91).^[115] An application to the total synthesis of 6-deoxyerythronolide B was also later reported by the same group.^[116]



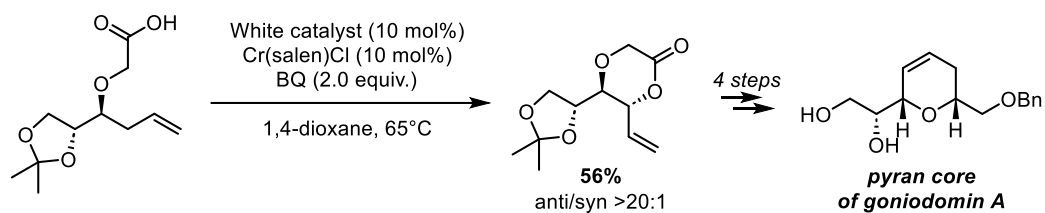
Scheme 91. Synthesis of macrolides through Palladium-catalyzed intramolecular allylic C-H acyloxylation.

In 2011, White's group also reported an intramolecular C–H allylation of a substituted 2-(but-3-en-1-yloxy)acetic acid leading to a 1,4-dioxan-2-one.^[117] The intramolecular C–H acyloxylation was possible in the presence of White's catalyst (10 mol%), Cr(salen)Cl (10 mol%), and benzoquinone in 1,4-dioxane at 65°C. The dioxanones were obtained in good yields and moderate to good diastereomeric ratios, and always highly favoring the *anti* isomer. The resulting products could be converted into several molecular scaffolds such as differentiated *syn* diols, polyoxidized motifs, as well as dihydropyrans (Scheme 92).

^[115] Fraunhofer, K. J.; Prabakaran, N.; Sirois, L. E.; White, M. C. *J. Am. Chem. Soc.* **2006**, *128*, 9032–9033.

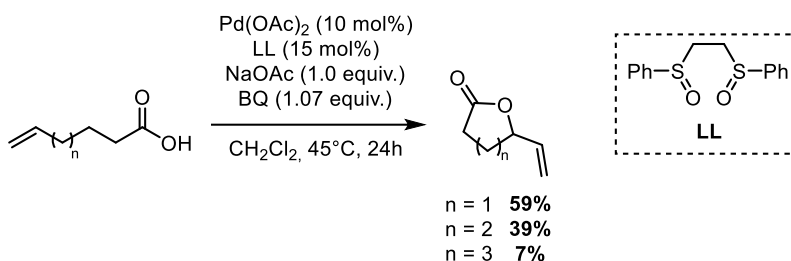
^[116] a) Stang, E. M.; White, M. C. *Nature Chem.* **2009**, *1*, 547–551; b) Stang, E. M.; White, M. C. *Angew. Chem. Int. Ed.* **2011**, *50*, 2094–2097.

^[117] Gormisky, P. E.; White, M. C. *J. Am. Chem. Soc.* **2011**, *133*, 12584–12589.



Scheme 92. Example of synthesis of a 1,4-dioxan-2-one by intramolecular allylic C-H acyloxylation.

In 2015, our group reported the PdX₂-catalyzed intramolecular allylic acyloxylation of unsaturated carboxylic acids, leading to the corresponding lactones.^[118] In particular, a mechanistic study was performed to determine whether the reaction involves a C–H activation or an oxypalladation step (Scheme 93). The study determined that the longer the chain, the lower the yield of the lactone.



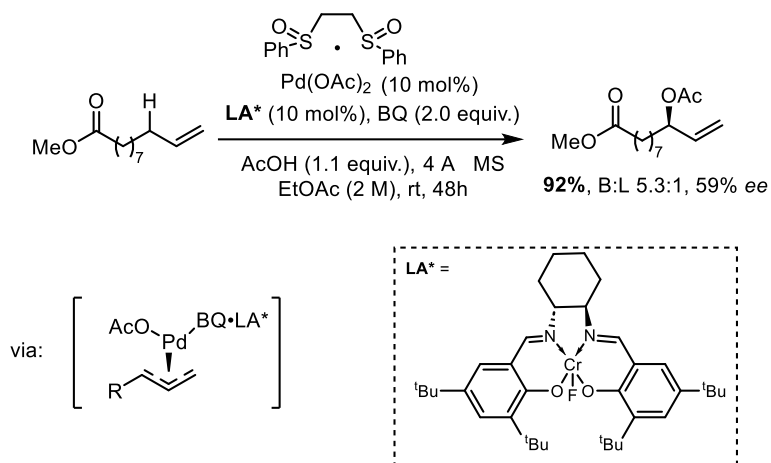
Scheme 93. Synthesis of lactones by intramolecular Pd(II)-catalyzed allylic C-H activation.

3.2.3. Asymmetric direct allylic C-H oxylation

In 2008, White's group managed to perform the direct asymmetric Pd-catalyzed acetoxylation of terminal alkenes working in the presence of catalytic amounts of the chiral enantiopure Cr(III)(salen) complex (Scheme 94).^[119]

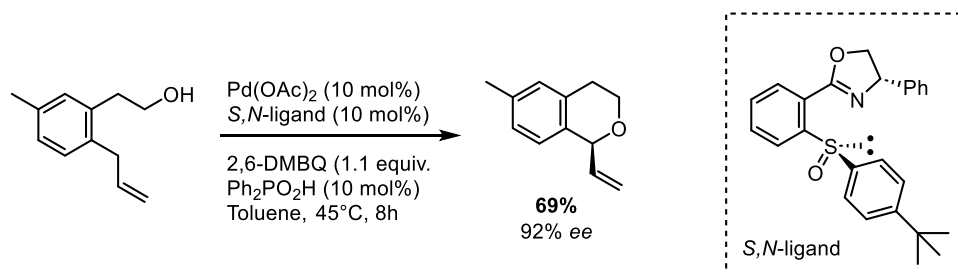
^[118] Louafi, F.; Lorion, M. M.; Oble, J.; Poli, G. *Synlett* **2015**, 26, 2237-2242.

^[119] Covell, D. J.; White, M. C. *Angew. Chem. Int. Ed.* **2008**, 47, 6448-6451.



Scheme 94. The Pd(II)/chiral Cr(III)(salen)-catalyzed enantioselective allylic C-H acetoxylation.

A few years later, White's team developed the asymmetric PdX₂-catalyzed direct intramolecular allylic C-H alkoxylation of a number of terminal alkenes to obtain isochromanes in high ee% using a chiral enantiopure SOX-ligand (Scheme 95).^[120]



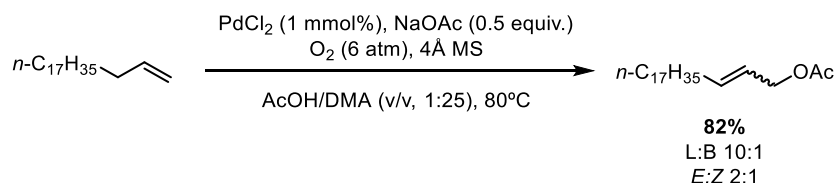
Scheme 95. Direct asymmetric intramolecular allylic C-H alkoxylation of a terminal alkene to access an isochromane.

3.2.4. Use of more environment-friendly oxidants

Many oxidative transformations involving palladium catalysis are accomplished in the presence of stoichiometric amounts of benzoquinones, which, besides of acting as terminal (sacrificial) oxidizing agents, behave also as π -acidic ligands for palladium. However, quinones are rather toxic, normally used in excess, and, once reduced, they form one equivalent of hydroquinone waste. Therefore, the replacement of quinones with more sustainable oxidizing agents is highly desirable. In this context, molecular oxygen is the environmentally friendly oxidant by excellence, being a low-cost molecule, and its only side product is H₂O₂ or H₂O. The reaction conditions for an oxidative transformation using

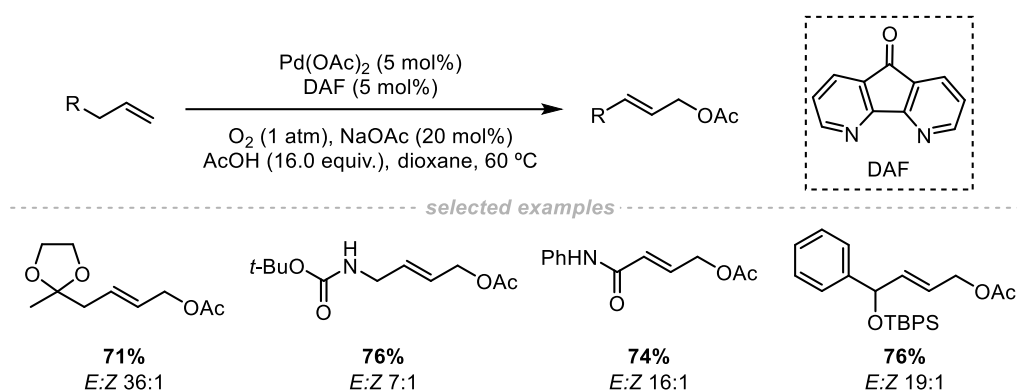
^[120] Ammann, S. E.; Liu, W.; White, M. C. *Angew. Chem. Int. Ed.* **2016**, *55*, 9571-9575.

oxygen as a sacrificial oxidant are termed *aerobic* because they mimic the mechanism of action of *oxidase* enzymes in living cells, which catalyze the transfer of two electrons from the substrate to oxygen, without oxygen incorporation. While the first Pd-catalyzed aerobic transformations were reported by the group of Smidt at the time the Wacker process was unveiled,^[121] Kaneda's group was the first to adopt these reaction conditions in Pd-catalyzed allylic acetoxylation of terminal olefins, which afforded selectively the linear allylic acetates in a poor *E/Z* ratio (Scheme 96).^[122]



Scheme 96. Aerobic allylic acetoxylation of terminal alkenes.

In 2010, Stahl *et al.* performed PdX₂-catalyzed BQ-free aerobic allylic acetoxylation using 4,5-diazafluoren-9-one (DAF) as the ligand. This specially designed ligand allowed the conversion of terminal alkenes into linear allylacetates in good yields and selectivities (Scheme 97).^[123]



Scheme 97. Aerobic allylic acetoxylation of terminal alkenes with diazafluorenone ligand.

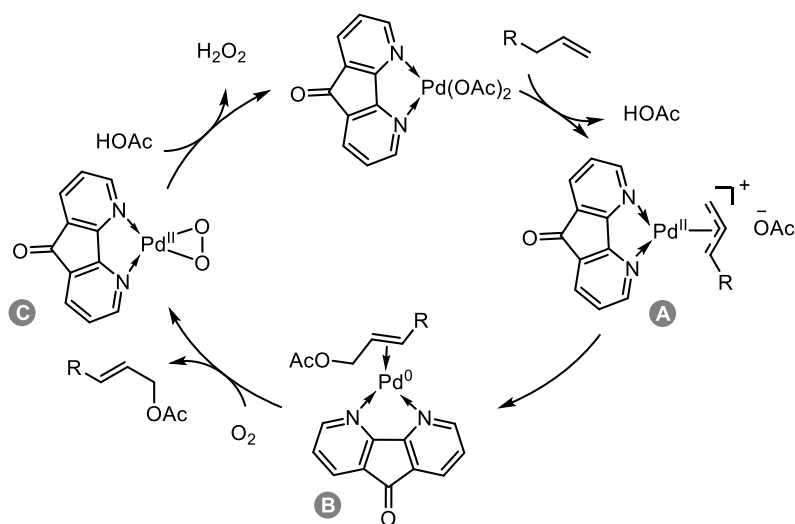
Mechanistic studies revealed that the DAF ligand facilitated the C–O forming reductive elimination

^[121] Smidt, J.; Hafner, W.; Jira, R.; Sedlmeier, J.; Sieber, R.; Ruttinger, R.; Kojer, H. *Angew. Chem.* **1959**, *71*, 176–182.

^[122] Mitsudome, T.; Umetani, T.; Nosaka, N.; Mori, K.; Mizugaki, T.; Ebitani, K.; Kaneda, K. *Angew. Chem. Int. Ed.* **2006**, *45*, 481–485.

^[123] a) Campbell, A. N.; White, P. B.; Guzei, I. A.; Stahl, S. S. *J. Am. Chem. Soc.* **2010**, *132*, 15116–15119; b) Jaworski, J. N.; Kozack, C. V.; Tereniak, S. J.; Knapp, S. M. M.; Landis, C. R.; Miller, J. T.; Stahl, S. S. *J. Am. Chem. Soc.* **2019**, *141*, 10462–10474.

step from the π -allyl-Pd(II) intermediate **A**, thereby eliminating the requirement for benzoquinone as ligand (Scheme 98).



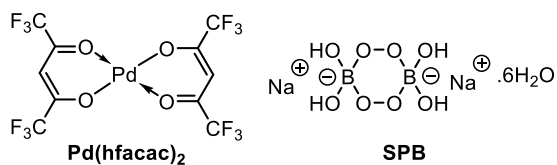
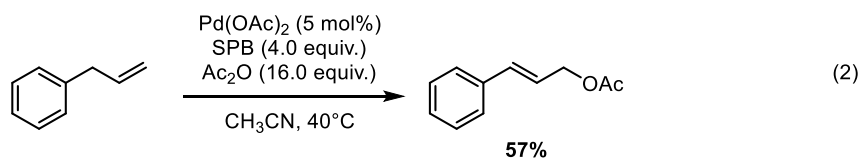
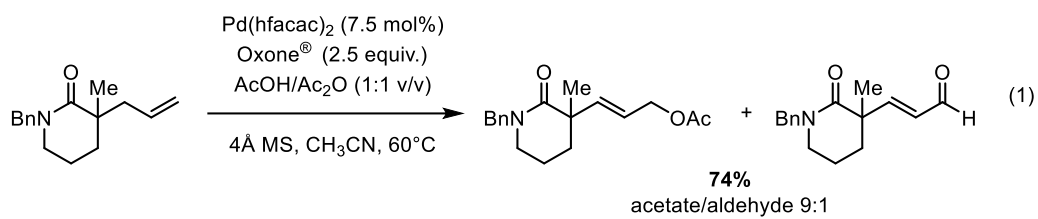
Scheme 98. Proposed mechanism for the PdX₂-catalyzed aerobic allylic acetoxylation.

Other sustainable oxidants such as Oxone[®]^[124] or sodium perborate tetrahydrate (SPB) can be used. On the one hand, the group of Stoltz reported that palladium(II) hexafluoroacetylacetonate (Pd(hfacac)₂) catalyzes the allylic acetoxylation of α -allyllactams in the presence of acetic acid and Oxone[®] as the terminal oxidant (Scheme 99, equation 1).^[125] On the other hand, the group of Szabó described the allylic acetoxylation of terminal alkenes with palladium(II) acetate as the catalyst and SPB as the terminal oxidant (Scheme 99, equation 2).^[126] In both cases, the desired product was obtained in moderate to good yields. In general, the use of these alternative oxidants results in lower yields than molecular oxygen, but they are easier to handle.

^[124] Oxone[®] (KHSO₅·0.5KHSO₄·0.5K₂SO₄) has been widely used as a green, cheap, and safe oxidant because it generates K₂SO₄ as the only by-product.

^[125] Xing, X.; O'Connor, N. R.; Stoltz, B. M. *Angew. Chem. Int. Ed.* **2015**, *54*, 11186-11190.

^[126] Pilarski, L. T.; Janson, P. G.; Szabó, K. J. *J. Org. Chem.* **2011**, *76*, 1503-1506.



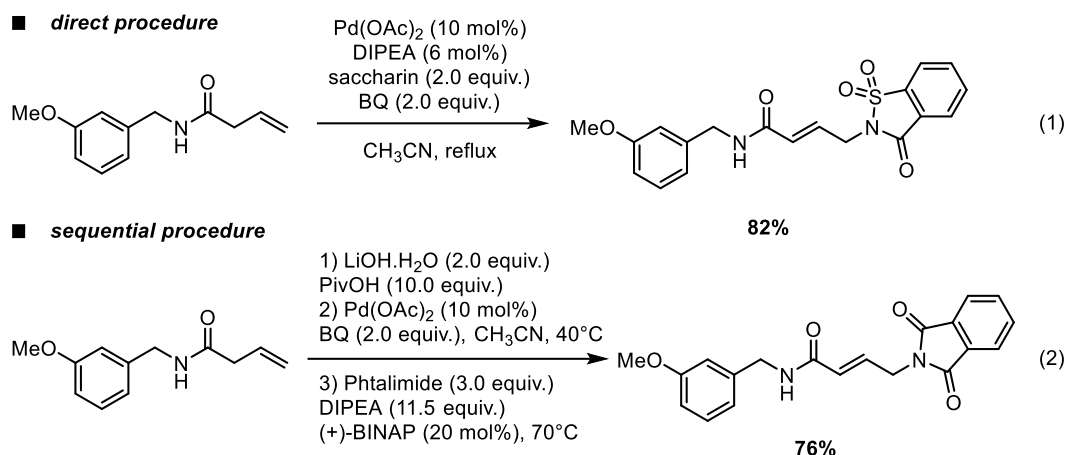
Scheme 99. Use of other sustainable oxidants in selected examples of allylic C-H acetoxylation.

Chapter 4. Synthesis of allylsulfones by palladium-catalyzed C–H activation of terminal alkenes.

1. Introduction

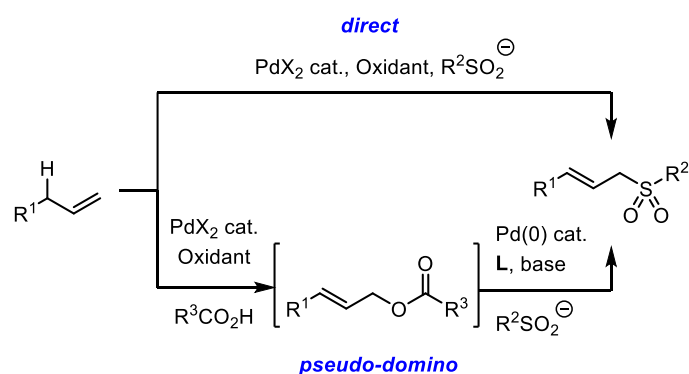
As mentioned earlier, organosulfur compounds are essential molecules in various fields of chemistry, and, in particular, allyl sulfones are very useful building blocks. However, their synthesis using traditional methods requires multiple steps, due to the limited availability of allylic precursors.^[63,64,67,91] Although the direct C–H sulfonylation of alkenes could offer an efficient and elegant route to synthesizing allylsulfones, this approach has been so far limited to a very narrow scope, only allowing for the sulfonylation of methyl styrenes.^[98-100]

Considering the recent studies reported by us and others on the Pd-catalyzed allylic C–H amination^[5b] and acetoxylation of alkenes,^[92,107-112,121-126] we became interested in developing reaction conditions for a Pd-catalyzed allylic C–H sulfonylation of terminal alkenes. Our group reported two complementary strategies for the Pd-catalyzed intermolecular allylic amination of but-3-enoic acid derivatives. The first strategy involves a direct Pd(II)-catalyzed allylic amination, while the second one a palladium(II)-catalyzed allylic pivaloylation, to produce the corresponding α,β -unsaturated- γ -pivaloyloxy butenoic acid derivative, which is submitted *in situ* to a palladium(0)-catalyzed amination. Indeed, with relatively acidic nitrogen nucleophiles such as *N*-tosyl carbamates or saccharin, the direct Pd(II)-catalyzed allylic amination was possible (Scheme 100, equation 1). On the other hand, with the less acidic nitrogen nucleophiles such as *N*-phthalimide, the sequential one-pot Pd(II)-catalyzed pivaloylation/Pd(0)-catalyzed amination reaction was only possible (Scheme 100, equation 2).



Scheme 100. Previous strategies for the Pd-catalyzed allylic C-H amination of but-3-enoic acid derivatives from our group.

Accordingly, we decided to explore the two above-described strategies to obtain the allylic C–H sulfonylation of terminal alkenes (Scheme 101).



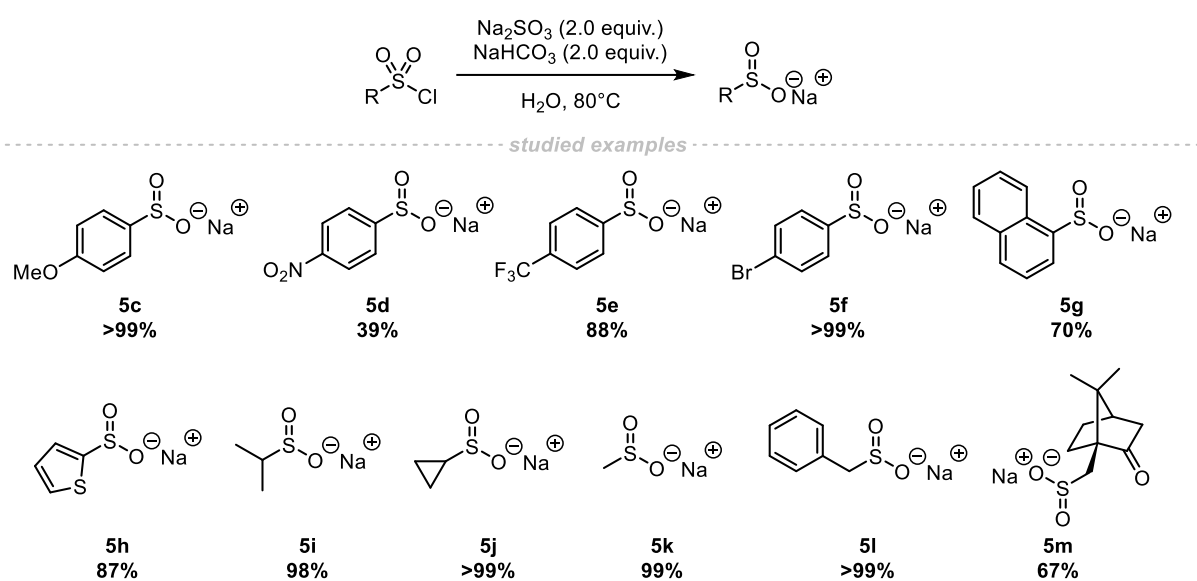
Scheme 101. Envisaged strategies for the Pd-catalyzed allylic C-H sulfonylation of terminal alkenes.

2. Synthesis of substrates.

2.1. Synthesis of sodium sulfonates.

Although some sulfinate salts are commercially available, some others have been synthesized. This was obtained by treatment of commercially available sulfonyl chlorides with sodium bicarbonate and

sodium sulfite in water at 80°C (Scheme 102).^[127] With the exception of *p*-nitrobenzene sulfonyl chloride, which gave the corresponding sulfinate **5d** in a low yield (39%), both, electron-rich and electron-poor aromatic sulfonyl chlorides provided the desired aromatic sodium sulfinate **5c-5g** in excellent yields. 2-Thiophene sulfonyl chloride also gave the corresponding sodium sulfinate **5h** in an excellent yield of 87%. Aliphatic sodium sulfinate **5i-5m** were also prepared efficiently from *iso*-propyl-, cyclopropyl, methyl, benzyl and (+)-10-camphor sulfonyl chlorides with yields ranging between 67% and >99%.



Scheme 102. Synthesis of various sodium sulfinate.

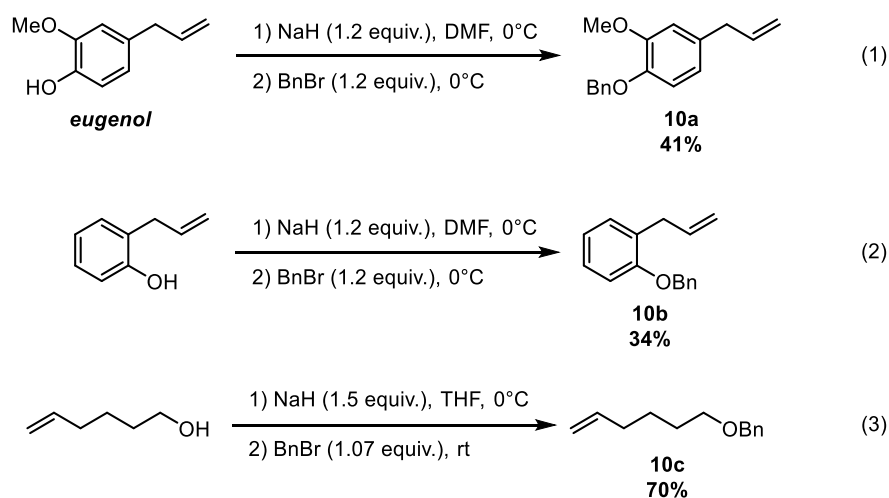
2.2. Synthesis of the terminal alkenes.

Most of the terminal alkenes used for the study were commercially available and ready to use, while a couple of them had to be modified. Accordingly, the phenol functions of *o*-allylphenol and of the naturally occurring eugenol were protected as the benzyl ethers **10a** and **10b** by deprotonation with sodium hydride and reaction with benzyl bromide in DMF^[128] (Scheme 103, equations 1 and 2). Similar conditions, except for the replacement of DMF by THF, were used for the benzylation of the

^[127] a) Liu, L. K.; Chi, Y.; Jen, K.-Y. *J. Org. Chem.* **1980**, *45*, 406-410; b) Liu, J.; Zhou, X.; Rao, H.; Xiao, F.; Li, C.-J.; Deng, G.-J. *Chem. Eur. J.* **2011**, *17*, 7996-7999; c) Meyer, A. U.; Jäger, S.; Hari, D. P.; König, B. *Adv. Synth. Catal.* **2015**, *357*, 2050-2054; d) Meyer, A. U.; Straková, K.; Slanina, T.; König, B. *Chem. Eur. J.* **2016**, *22*, 8694-8699; e) Kim, W.; Kim, H. Y.; Oh, K. *Org. Lett.* **2020**, *22*, 6319-6323.

^[128] Sun, B. F.; Hong, R.; Kang, Y. B.; Deng, L. *J. Am. Chem. Soc.* **2009**, *131*, 10384-10385.

aliphatic terminal alkene hex-5-en-1-ol to generate **10c** (Scheme 103, equation 3).^[129]

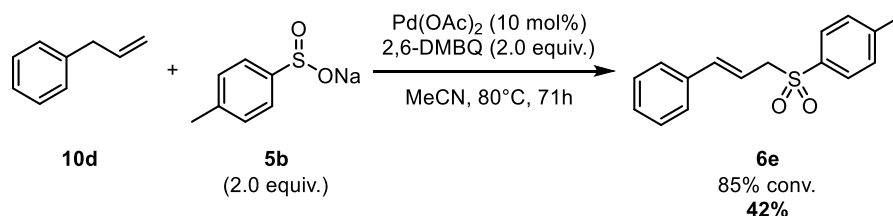


Scheme 103. Synthesis of benzyl-protected terminal alkenes.

3. Preliminary results and optimization of the reaction conditions.

3.1. Preliminary studies.

We first studied the direct C–H sulfonylation strategy, selecting the coupling between allylbenzene **10d** and sodium *p*-toluenesulfinate **5b** as the model reaction. Happily, treatment of 1.0 equivalent of **10d** with 2.0 equivalents of **5b**, in the presence of 10 mol% of palladium acetate and 2.0 equivalents of 2,6-dimethylbenzoquinone (2,6-DMBQ) as the terminal oxidant, in freshly distilled acetonitrile (0.2 M) at 80°C under argon, resulted in the formation of the expected allylsulfone **6e** in 42% yield after 72 hours, with a conversion of 85% (Scheme 104). When we performed the reaction under aerobic conditions (under air), the same result was obtained.



Scheme 104. Preliminary studies on the Pd-catalyzed allylic C-H sulfonylation of allylbenzene **10d**.

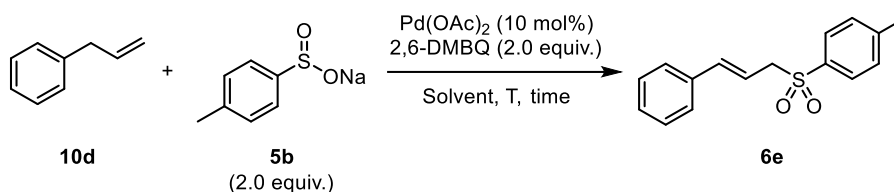
^[129] Florence, G. J.; Fraser, A. L.; Gould, E. R.; King, E. F. B.; Menzies, S. K.; Morris, J. C.; Tulloch, L. B.; Smith, T. K. *ChemMedChem* **2014**, *9*, 2548-2556.

3.2. Optimization of the direct allylic C-H sulfonylation procedure.

The influence of various parameters (temperature, solvent, oxidant, ligand, and palladium source) on the outcome of the reaction was studied next.

3.2.1. Variation of the solvent.

A screening of polar solvents (propionitrile, DMSO, DMF, THF, 1,4-dioxane, MTBE, HFIP, dimethyl carbonate) showed that none of them gave a better yield than acetonitrile (Table 13, entries 2-9). With propionitrile, a similar result was obtained when the reaction was performed at 110°C (Table 13, entry 2). Suspecting that the moderate yield and the long reaction time could be due to a poor solubility of the sulfinate salt in acetonitrile, we tested methanol or *tert*-butanol as a cosolvents. However, performing the reaction in a 4:1 v/v mixture of acetonitrile and MeOH gave a poor yield of 29%, while in a 4:1 v/v mixture of acetonitrile and *tert*-butanol gave a similar yield of 34% (Table 13, entries 10 and 11). In the end, acetonitrile proved to be the best solvent for the reaction.



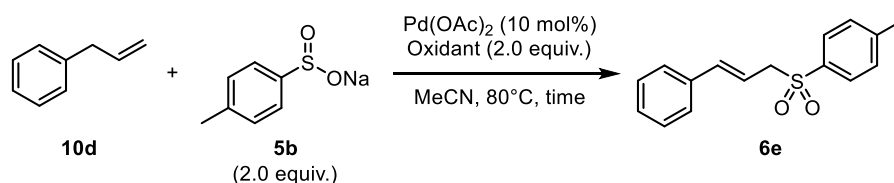
Entry ^[a]	Solvent	T (°C)	time (h)	Conv. (%) ^[b]	6e (%) ^[b]
1	MeCN	80	71	85	42
2	EtCN	110	46	84	35
3	DMSO	80	45	>99	13
4	DMF	80	45	>99	13
5	THF	80	66	95	12
6	1,4-dioxane	80	66	>99	2
7	MTBE	80	66	>99	1
8	HFIP	80	68	>99	26
9	dimethyl carbonate	80	68	>99	9
10	MeCN/MeOH (4:1)	80	66	96	29
11	MeCN/ <i>t</i> BuOH (4:1)	80	66	91	34

[a] typical reaction conditions: Allylbenzene **10d** (0.2 mmol), Pd(OAc)₂ (0.02 mmol), sodium *p*-toluenesulfinate **5b** (0.4 mmol), 2,6-DMBQ (0.4 mmol) in the solvent (0.2 M); [b] Conversions and yields were determined by quantitative ¹H NMR using 1,4-dinitrobenzene as an internal standard.

Table 13. Study of the variation of the solvent.

3.2.2. Variation of the oxidant.

We next investigated the influence of the oxidant, while keeping acetonitrile as the solvent, to find out the most efficient Pd(0)-to-Pd(II) reoxidation in the catalytic cycle. The best results were obtained with 1,4-benzoquinone derivatives, especially with the dimethylated quinone oxidants (2,5- and 2,6-DMBQ) (Table 14, entries 1 and 4). Simple 1,4-benzoquinone led essentially to degradation products, with only trace amount of the desired product **6e** (Table 14, entry 2). DDQ also proved to be unsuccessful to provide allylsulfone **6e** (Table 14, entry 3). Duroquinone (DQ) led to a very low yield (10%) of allylsulfone **6e** (Table 14, entry 5). Changing the oxidant to metal acetates such as silver acetate and copper(II) acetate led to the formation of trace amounts of products accompanied by various amounts of an isomeric mixture of the desulfonylated product (Table 14, entries 6-7).^[130] Switch to other oxidants such as manganese dioxide, molecular oxygen (1 atm), diacetoxyiodobenzene or *tert*-butylhydroperoxide, gave no product, only degradation or byproducts being observed (Table 14, entries 8-11). So, 2,6-DMBQ revealed to be the best oxidant.



Entry ^[a]	Oxidant	Time (h)	Conv.(%) ^[b]	6e (%) ^[b]
1	2,6-DMBQ	71	85	42
2	BQ	66	>99	Trace ^[c]
3	DDQ	66	97	0
4	2,5-DMBQ	70	96	36
5	DQ	70	68	10
6	AgOAc	68	85	Trace ^[d]
7	Cu(OAc) ₂	68	>99	Trace ^[d]
8	MnO ₂	64	>99	0 ^[c]
9	O ₂ (1 atm)	48	>99	0 ^[d]
10	PhI(OAc) ₂	71	>99	0
11	<i>t</i> -BuOOH	71	>99	0 ^[c]

[a] typical reaction conditions: Allylbenzene **10d** (0.2 mmol), Pd(OAc)₂ (0.02 mmol), sodium *p*-toluenesulfinate **5b** (0.4 mmol), Oxidant (0.4 mmol) in acetonitrile (0.2 M) at 80°C; [b] Conversions and yields were determined by quantitative ¹H NMR using 1,4-dinitrobenzene as an internal standard; [c] degradation; [d] formation of an

^[130] a) Zhou, X.; Luo, J.; Liu, J.; Peng, S.; Deng, G. J. *Org. Lett.* **2011**, *13*, 1432–1435; b) Wang, G. W.; Miao, T. *Chem. Eur. J.* **2011**, *17*, 5787–5790; c) Hu, S.; Xia, P.; Cheng, K.; Qi, C. *Appl. Organomet. Chem.* **2013**, *27*, 188–190; For a recent review, see: d) Ortgies, D. H.; Hassanpour, A.; Chen, F.; Woo, S.; Forgione, P. *Eur. J. Org. Chem.* **2016**, 408–425.

isomeric mixture of by-products resulting from the desulfonation of **6e**.

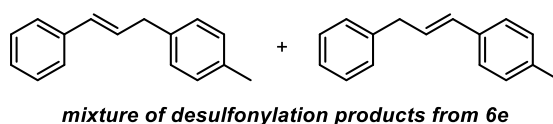
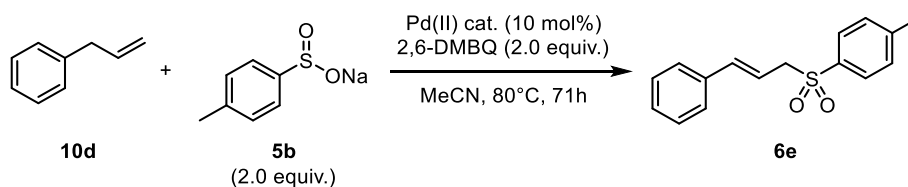


Table 14. Study on the variation of the oxidant.

3.2.3. Variation of the palladium source.

A variety of palladium(II) sources were investigated next. When palladium(II) pivalate, which carries a bulky carboxylate ligand, was tested, the allylsulfone **6e** was obtained in only 12% yield after 71h (Table 15, entry 1), and the electron-poor palladium(II) trifluoroacetate did not improve the yield of **6e**, too (Table 15, entry 2). Palladium(II) acetylacetonate gave results similar to palladium(II) acetate (Table 15, entry 4). Palladium(II) chloride and dichlorobis(acetonitrile)palladium(II) also failed to produce better yields (Table 15, entries 5 and 6). We finally decided to retain palladium(II) acetylacetonate, as with palladium(II) acetate some reproducibility problems due to the variable purity of commercial batches were encountered.^[131]



Entry ^[a]	Pd(II) cat.	Conv.(%) ^[b]	6e (%) ^[b]
1	Pd(OPiv) ₂	79	12
2	Pd(TFA) ₂	93	27
3	Pd(OAc) ₂	85	42
4	Pd(acac) ₂	92	42
5	PdCl ₂	95	15
6	Pd(CH ₃ CN) ₂ Cl ₂	97	23

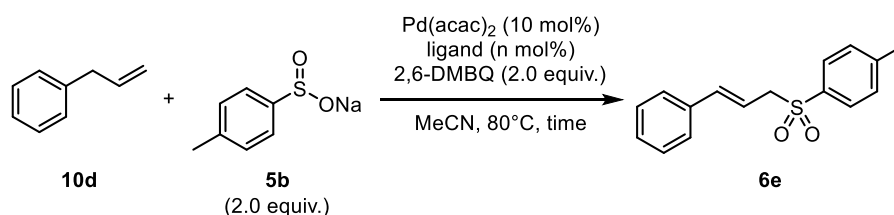
[a] typical reaction conditions: Allylbenzene **10d** (0.2 mmol), Pd(II) cat. (0.02 mmol), sodium *p*-toluene sulfinate **5b** (0.4 mmol), 2,6-DMBQ (0.4 mmol) in acetonitrile (0.2 M) at 80°C; [b] Conversions and yields were determined by quantitative ¹H NMR using 1,4-dinitrobenzene as an internal standard.

Table 15. Study on the variation of the palladium source.

^[131] a) Carole, W. A.; Bradley, J.; Sarwar, M.; Colacot, T. J. *Org. Lett.* **2015**, *17*, 5472-5475; b) Carole, W. A.; Colacot, T. J. *Chem. Eur. J.* **2016**, *22*, 7686-7695.

3.2.4. Introduction of a ligand.

Hypothesizing that the moderate yields of the allylic sulfonylation might be due to catalyst deactivation, we decided to check whether the introduction of a ligand could avoid, or at least moderate, the loss of catalytic activity. The bidentate White sulfoxide ligand 1,2-bis(phenylsulfinyl)ethane,^[5a,111] or the monodentate ligand like phenylvinylsulfoxide and DMSO did not give better yields compared to the previously reported ligandless conditions (Table 16, entries 2-4). 4,5-Diazafluoren-9-one (DAF), known for dehydrogenation reactions,^[132] and pyridine provided the desired product **6e** in comparable yields of 37 and 38% (Table 16, entries 5-6). Other pyridine-type ligands such as 1,10-phenanthroline, 2,2'-bipyridine, 2,2'-bipyrimidine and dtbpy proved to be much less effective (Table 16, entries 7-10). N-acetylamino acids are known to favor C–H activation processes via a Concerted Metalation Deprotonation (CMD) mechanism.^[133] However, the use of *N*-acetyl-*L*-leucine as the ligand did not provide a better yield than that carried out under ligandless conditions (Table 16, entry 11). Phosphine ligands were also ineffective (Table 16, entries 12-13). In light of the above experiments, we decided to stick to the original ligandless conditions for the rest of the study.



Entry ^[a]	Ligand	n (mol%)	Time (h)	Conv. (%) ^[b]	6e (%) ^[b]
1	No ligand	-	71	92	42
2		15	65	87	19
3		30	71	93	13
4	DMSO	30	68	95	30
5	DAF	15	65	76	37
6	Pyridine	30	71	93	38
7	1,10-Phenanthroline	15	24	72	0
8	2,2'-Bipyridine	15	20	81	<5

^[132] Diao, T.; Wadzinski, T. J.; Stahl, S. S. *Chem. Sci.* **2012**, *3*, 887-891.

^[133] For a review, see: a) Engle, K. *Pure Appl. Chem.* **2016**, *88*, 119-138; For a selection of contributions involving palladium-catalysis, see: b) Haines, B. E.; Musaei, D. G. *ACS Catal.* **2015**, *5*, 830-840; c) Hu, L.; Shen, P.-X.; Shao, Q.; Hong, K.; Qiao, J. X.; Yu, J.-Q. *Angew. Chem. Int. Ed.* **2019**, *58*, 2134-2138; d) Chen, H.; Mondal, A.; Wedi, P.; van Gemmeren, M. *ACS Catal.* **2019**, *9*, 1979-1984.

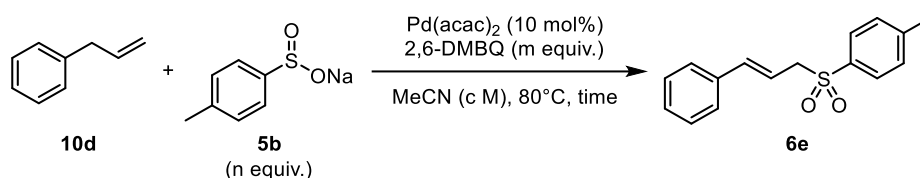
9	2,2'-Bipyrimidine	15	44	89	21
10	dtbpy	15	45	75	14
11	<i>N</i> -Acetyl- <i>L</i> -leucine	15	44	92	10
12	PPh ₃	20	44	>99	25
13	rac-BINAP	15	68	74	<5

[a] typical reaction conditions: Allylbenzene **10d** (0.2 mmol), Pd(acac)₂ (0.02 mmol), ligand (n mol%), sodium *p*-toluenesulfinate **5b** (0.4 mmol), 2,6-DMBQ (0.4 mmol) in acetonitrile (0.2 M) at 80°C; [b] Conversions and yields were determined by quantitative ¹H NMR using 1,4-dinitrobenzene as an internal standard.

Table 16. Study on the introduction of a ligand.

3.2.5. Molarity and amounts of oxidant and sulfinate.

The impact of the concentration on the coupling was studied next. Decrease of the concentration to 0.1M reduced the yield of **6e** to 28% (Table 17, entry 2), while increase to 0.66M raised it to 47% (Table 17, entry 4). Hence, we decided to pursue the study with the latter molarity. Reduction of the amount of sulfinate salt and of the oxidant was also investigated. Unfortunately, all the experiments carried out failed to achieve better yields than the original one, which calls for 2.0 equiv. of 2,6-DMBQ and 2.0 equiv. of sodium sulfinate (Table 17, entries 6-9).



Entry ^[a]	5b (n equiv.)	2,6-DMBQ (m equiv.)	Conc. (M)	time (h)	Conv. (%) ^[b]	6e (%) ^[b]
1	2.0	2.0	0.2	71	92	42
2	2.0	2.0	0.1	43	82	28
3	2.0	2.0	0.5	65	94	34
4	2.0	2.0	0.66	67	93	47
5	2.0	2.0	1.0	43	94	31
6	2.0	1.5	0.66	47	96	45
7	2.0	2.5	0.66	65	90	43
8	2.5	2.0	0.66	65	88	37
9	1.5	2.0	0.66	65	92	28

[a] typical reaction conditions: Allylbenzene **10d** (0.2 mmol), Pd(acac)₂ (0.02 mmol), sodium *p*-toluenesulfinate **5b** (n equiv.), 2,6-DMBQ (m equiv.) in acetonitrile (c M) at 80°C; [b] Conversions and yields were determined by quantitative ¹H NMR using 1,4-dinitrobenzene as an internal standard.

Table 17. Influence of the concentration as well as the quantity of sulfinate and oxidant on the outcome of the reaction.

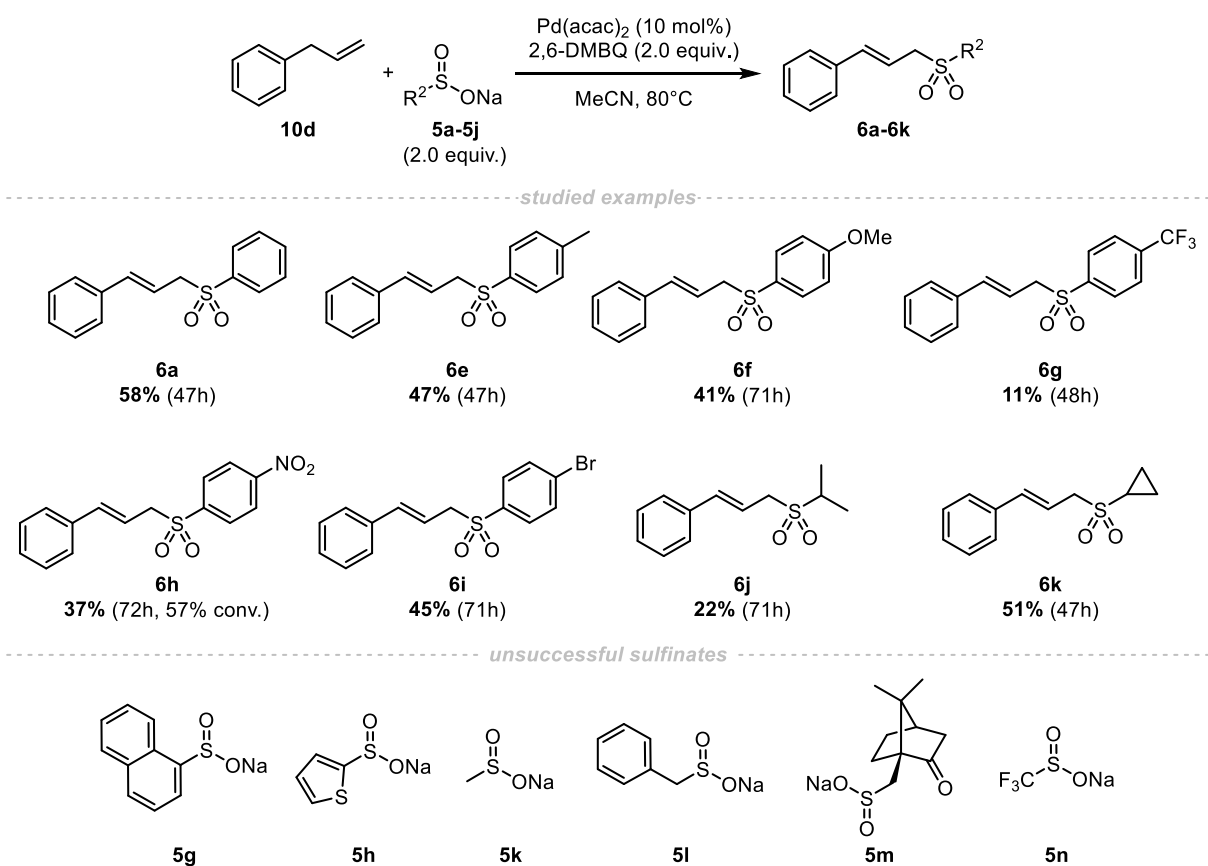
In summary, the final conditions we kept for the coupling between allyl arenes and sodium sulfonates (2.0 equiv.) consist in Pd(acac)₂ (10 mol%) as the catalyst, and 2,6-DMBQ (2.0 equiv.) as the terminal oxidant, in acetonitrile (0.66M) at 80°C. In the following paragraphs, these conditions will be named “method A”.

3.3. Scope of the direct sulfonylation procedure.

3.3.1. Aryl- and alkyl sulfonates.

With the optimized reaction conditions in hand, the scope of the reaction was then evaluated, starting with the coupling between allylbenzene **10d** and various sulfinate salts (Scheme 105). Electron-rich phenyl-, *p*-toluene-, and 4-methoxyphenylsulfonates **5a**, **5b** and **5c** provided the corresponding allylsulfones **6a**, **6e** and **6f** in 58%, 47% and 41% isolated yield respectively. Electron-poor aryl sulfonates reacted too, although their coupling turned out to be much more sluggish. For example, only 57% conversion was detected by quantitative ¹H NMR analysis after 72h reaction between sodium 4-nitrobenzenesulfinate **5d** and allylbenzene **10d**. Nevertheless, the desired allylsulfones **6g** and **6h** could be obtained with 11% and 37% yield, respectively. Sodium 4-bromophenylsulfinate **5f** gave the corresponding allylsulfone **6i** in 45% isolated yield. Worthy of note, the C–Br bond was not affected by the transient formation of Pd(0) in the catalytic cycle (Scheme 105).

Alkyl sulfonates proved also to be reactive. Indeed, reaction between sodium propane-2-sulfinate **5i**, or sodium cyclopropane sulfinate **5j** gave allyl sulfones **6j** and **6k** in 22% and 51% yield, respectively. Unfortunately, sodium α -naphthyl sulfinate **5d**, 2-thiophenylsulfinate **5h**, methyl sulfinate **5k**, benzyl sulfinate **5l** and camphor sulfinate **5m** gave no conversion or degradation products (Scheme 105). The reaction was also totally ineffective with the very electron-poor sodium trifluoromethyl sulfinate (Langlois' reagent) **5n**.

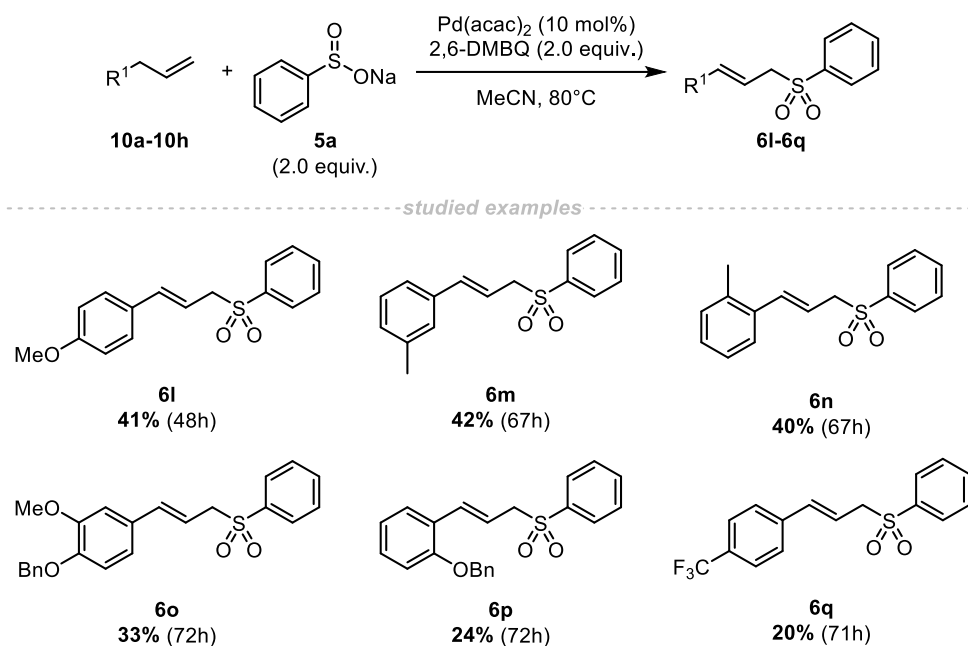


Scheme 105. Evaluation of the reactivity of aryl- and alkyl sulfonates.

3.3.2. Allyl arenes as terminal alkenes

We then studied the influence of the nature of the alkene on the reaction outcome with the developed conditions (method A). For this study, sodium benzenesulfinate **5a** was chosen as the reaction partner, because it is the nucleophile that gave the best results. Moreover, the corresponding allyl sulfones can be considered as synthetic intermediates in the Julia olefinations.

The coupling between the electron-rich allyl arenes **10e** and **10f** and sodium benzenesulfinate **5a** provided the corresponding allylsulfones **6l** and **6m** in 41% and 42% yield respectively (Scheme 106). When the *ortho*-substituted allylbenzene **10g** was tested, the corresponding allylsulfone **6n** was obtained in 40% yield. However, the phenolic derivatives benzyl eugenol **10a** and 2-*O*-benzylallylbenzene **10b** gave the corresponding allylsulfones **6o** and **6p** in lower yields of 33% and 24% respectively. The electron-poor allylarene **10h** bearing a *para*-trifluoromethyl group afforded the expected allylsulfone **6q** in 20% yield (Scheme 106).

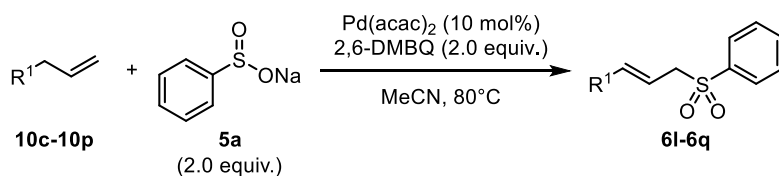


Scheme 106. Evaluation of the reactivity of allylarenes as substrates with method A.

3.3.3. Aliphatic terminal alkenes as substrates.

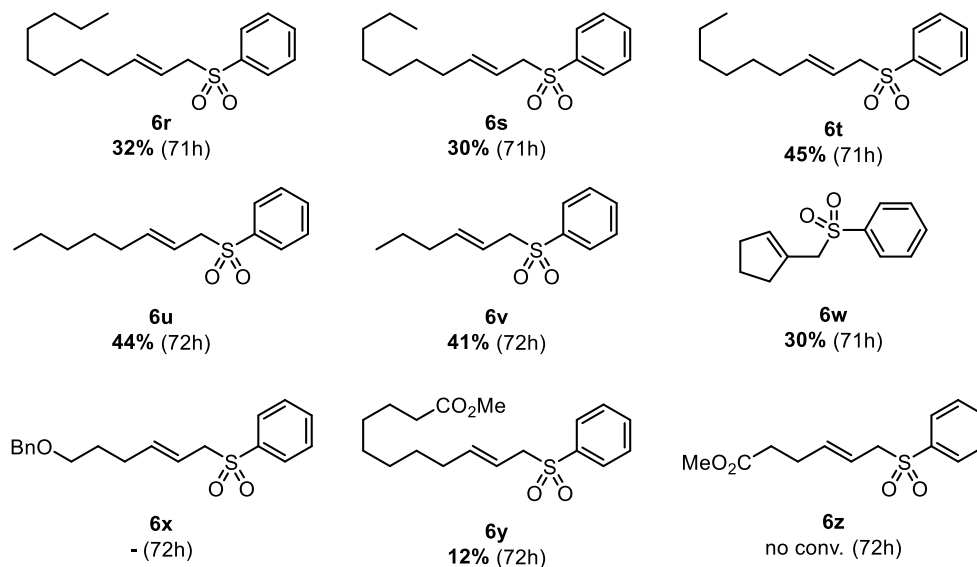
We next evaluated terminal aliphatic alkene substrates in the developed reaction conditions (method A). Undec-1-ene **10i**, dec-1-ene **10j**, non-1-ene **10k**, oct-1-ene **10l** and hex-1-ene **10n** were engaged in the presence of sodium benzenesulfinate **5a**, providing the linear allylsulfones **6r-6v** with total regioselectivity and with yields ranging between 30% and 45%. In most cases, the pure (*E*)-configured allylsulfones were isolated, although trace amounts of the (*Z*) isomers could be detected in the ¹H NMR spectra of the crude reaction products. Only in the case of allylsulfone **6t**, both (*E*)- and (*Z*)-isomers could be isolated separately (Scheme 107).

Methylenecyclopentane **10n** could also be converted into allylsulfone **6w** in a moderate 30% yield. Further studies were conducted on various Pd-functionalized aliphatic alkenes. Among them, the benzyl ether derivative **10c** led to its degradation, whereas the ester **10o** gave the allylsulfone **6y** in a low yield of 12% and only 40% conversion for the reaction. However, no conversion was observed for the alkene **10p** under the reaction conditions (Scheme 107).



$\text{R}^1 = (\text{CH}_2)_3\text{OBn}$ (**10c**)
 $\text{R}^1 = (\text{CH}_2)_n\text{CH}_3$; $n = 8$ (**10i**), $n = 7$ (**10j**)
 $n = 6$ (**10k**), $n = 5$ (**10l**), $n = 3$ (**10m**)
 exomethylenecyclopentane (**10n**)
 $\text{R}^1 = (\text{CH}_2)_n\text{CO}_2\text{Me}$; $n = 8$ (**10o**), $n = 3$ (**10p**)

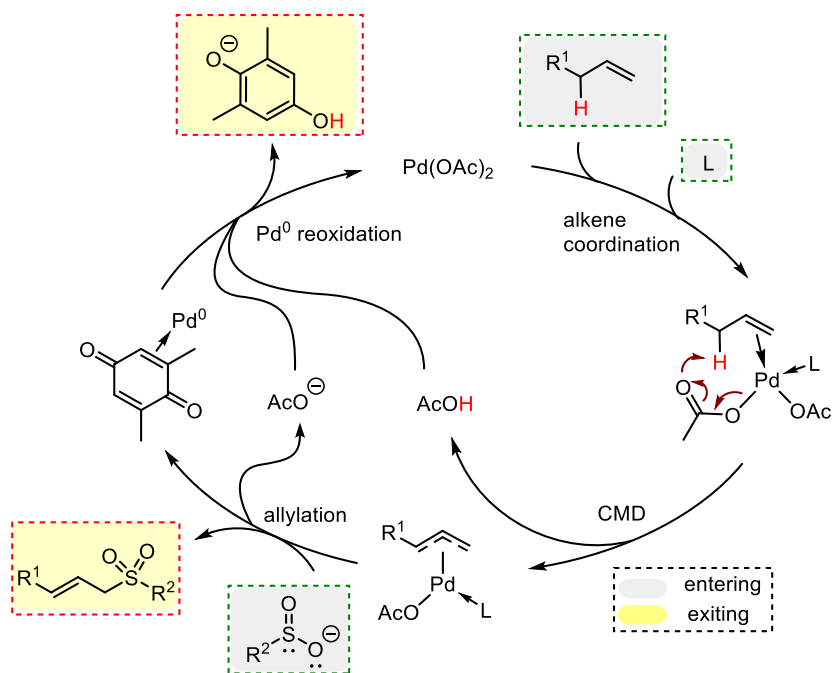
-----studied examples-----



Scheme 107. Evaluation of aliphatic terminal alkenes as substrates with method A.

On the basis of previous reports on Pd-catalyzed allylic C–H activation reactions, a tentative mechanism is proposed (Scheme 108).^[1a,4b,5a,134] After coordination of the alkene to the Pd(II) catalyst, an allylic proton is abstracted *via* a probable concerted metalation deprotonation (CMD) mechanism, and the thus generated η^3 -allylpalladium intermediate undergoes substitution by the sulfinate anion. Finally, after product decoordination, the generated Pd(0) complex, is reoxidized by the coordinated benzoquinone.

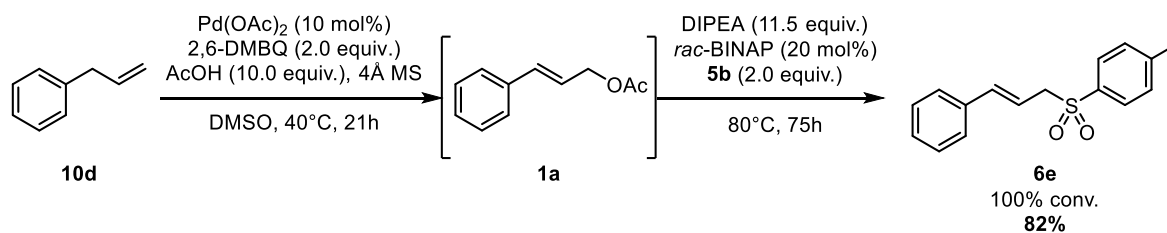
^[134] Reed, S. A.; Mazzotti, A. R.; White, M. C. J. *Am. Chem. Soc.* **2009**, *131*, 11701–11706.



Scheme 108. Proposed mechanism for the direct allylic C-H sulfonation.

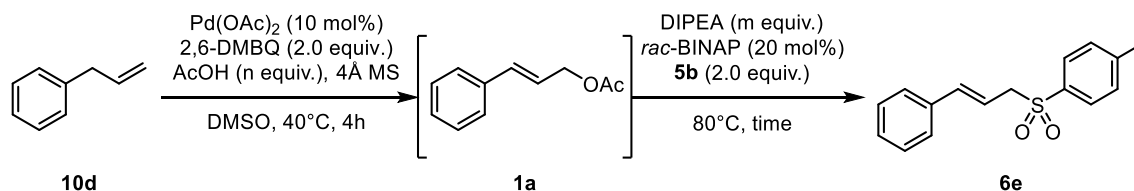
3.4. Optimization of the *in situ* sequential sulfonation procedure (Method B).

Due to the moderate yields obtained with method A in some cases, a variation of the protocol was also considered. Specifically, based on previous reports from our group,^[5b] we decided to attempt an *in situ* sequential protocol consisting in an initial oxidative Pd(II)-catalyzed allylic C–H alkene acetoxylation, followed by an *in situ* redox-neutral Pd(0)-catalyzed allylic sulfonation of the resulting allylic acetate. The major challenge of this process consists in the use of the same palladium source for both transformations. In the event, reacting allylbenzene **10d** (1.0 equiv.) with acetic acid (10.0 equiv.) in the presence of 2,6-DMBQ (2.0 equiv.) and Pd(OAc)₂ (10 mol%) in DMSO (0.2M) at 80°C gave the corresponding allylic acetate **1a**. The latter was not isolated but its formation was checked by TLC. After that, *in situ* addition of *rac*-BINAP (20 mol%), *N,N*-di-isopropylethylamine (11.5 equiv.) and sodium *p*-toluenesulfonate **5b** (2.0 equiv.) with further stirring at 80°C under air gave the desired allylsulfone **6e** in 82% yield (Scheme 109).



Scheme 109. First attempt on a pseudo-domino procedure for the preparation of allylsulfones.

Given that the amount of acetic acid and base introduced (to quench the acid) is very high, we tried to see whether it was possible to reduce it. We first conducted experiments with 10.0 equivalents of both reagents and observed that the allylsulfone **6e** was obtained with a similar yield (83%), but with a significantly longer reaction time for the second step (Table 18, entry 2). However, reducing the amount of acetic acid and DIPEA to 7.0, 5.0, or 3.0 equivalents resulted in generally longer reaction times for the second step and lower yields (Table 18, entries 3-5). We thus decided to keep the conditions used during the preliminary investigations of the *in situ* sequential protocol. In the following paragraphs, these conditions will be named “method B”.



Entry ^[a]	AcOH (n equiv.)	DIPEA (m equiv.)	time step 2 (h)	6e (%) ^[b]
1	10.0	11.5	25	82
2	10.0	10.0	48	83
3	7.0	7.0	38	64
4	5.0	5.0	38	56
5	3.0	3.0	66	48

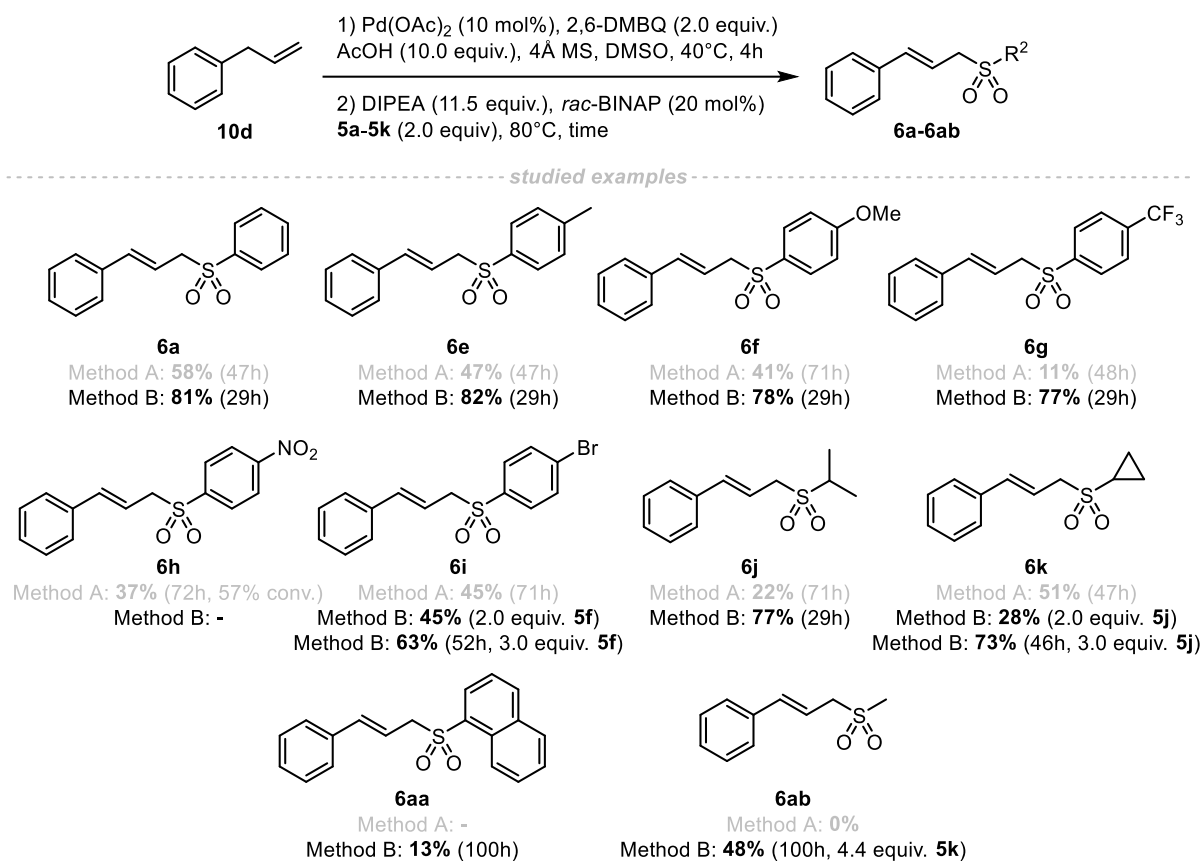
[a] Reaction conditions: allylbenzene **10d** (0.2 mmol), Pd(OAc)₂ (10 mol%), AcOH (n equiv.), 2,6-DMBQ (2.0 equiv.), 4Å MS (50 mg), DMSO (0.2M) were heated at 80°C in a sealed tube for 4h (until complete conversion) then were introduced DIPEA (m equiv.), sodium *p*-toluenesulfinate **5b** (2.0 equiv.), *rac*-BINAP (20 mol%) and the mixture was heated at 80°C until complete conversion of the cinnamyl acetate intermediate; [b] Yields were determined by quantitative ¹H NMR analysis, using 1,4-dinitrobenzene as an internal standard.

Table 18. Optimization attempt for the pseudo-domino procedure.

3.5. Scope of the *in situ* sequential sulfonylation procedure.

3.5.1. Aryl- and alkyl sulfinates.

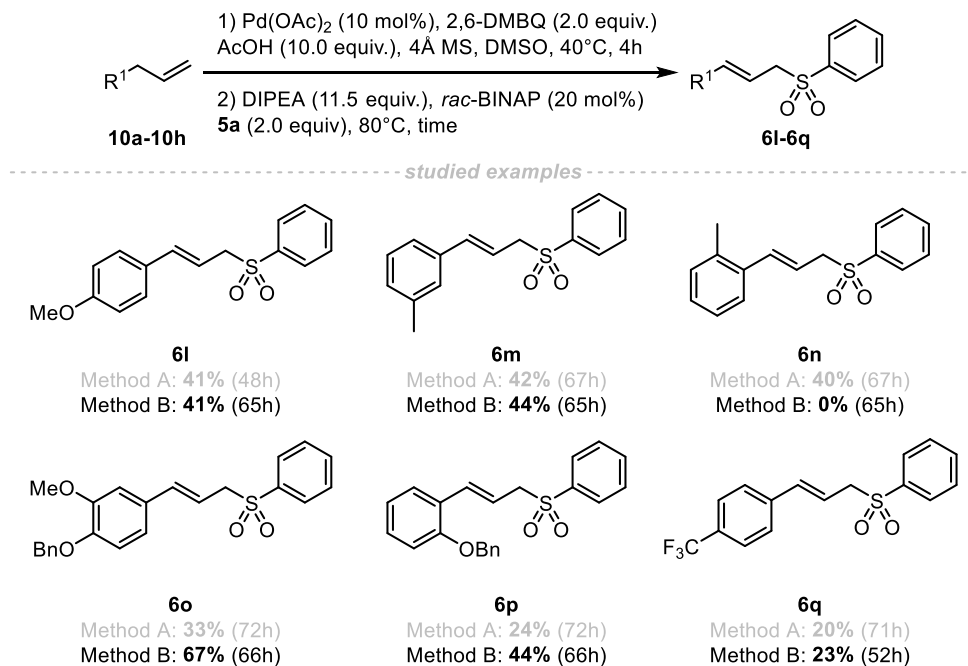
With the new protocol (Method B) in hand for the benchmark reaction between **10d** and **5b**, we re-evaluated the sulfonylation of allylbenzene **10d** with the other sulfinate salts previously used with method A (Scheme 110, yields obtained with method A are indicated for comparison). The reaction turned out to be equally efficient with electron-rich sulfinates **5a-5c** as well as with electron poor sulfinate **5f**, affording satisfactory isolated yields of the desired allylsulfone, ranging from 77% to 82%. In these cases, much higher yields were obtained with method B in comparison to method A. Such increases in yield when switching from method A to method B with reduced reaction times underscore the synthetic importance of the *in situ* sequential procedure, although this strategy is less elegant than the previous one. Contrary to what was observed with method A, sodium 4-nitrobenzenesulfinate **5d** did not react with the intermediate cinnamyl acetate **1a**, which was recovered in 75% yield. With sodium 4-bromophenylsulfinate **5f**, only a partial conversion of intermediate cinnamyl acetate **1a** was detected (40% recovered) and the final allylsulfone **6i** was isolated in only 45% yield. Such a low reactivity is likely due to competitive oxidative addition of the C-Br bond of the sulfinate to Pd(0) formed during the second step of the sequential process. However, increasing the amount of sulfinate **5f** to 3.0 equivalents resulted in the completion of the second step of the sequential procedure and the formation of allylsulfone **6i** with 63% isolated yield. Alkyl sulfinates **5i** and **5j** were also efficient with this protocol, affording the corresponding allylsulfones **6j** and **6k** in 77% and 73% yield respectively. In the case of sodium cyclopropyl sulfinate **5j**, 3.0 equivalents were also needed to obtain a satisfactory yield of cinnamyl sulfone **6k**, as only 28% isolated yield was obtained when using 2.0 equivalents of the sulfinate. In addition, and in contrast to method A, sodium α -naphthyl sulfinate **5d** gave 13% of cinnamyl sulfone **6aa**, while sodium methyl sulfinate **5k** provided the corresponding allylsulfone **6ab** in a moderate 48% yield. In this case, 4.4 equivalents of sodium methyl sulfinate **5k** were necessary to obtain cinnamyl methylsulfone **6ab** (Scheme 110).



Scheme 110. Evaluation of the reactivity of aryl- and alkyl sulfonates with method B.

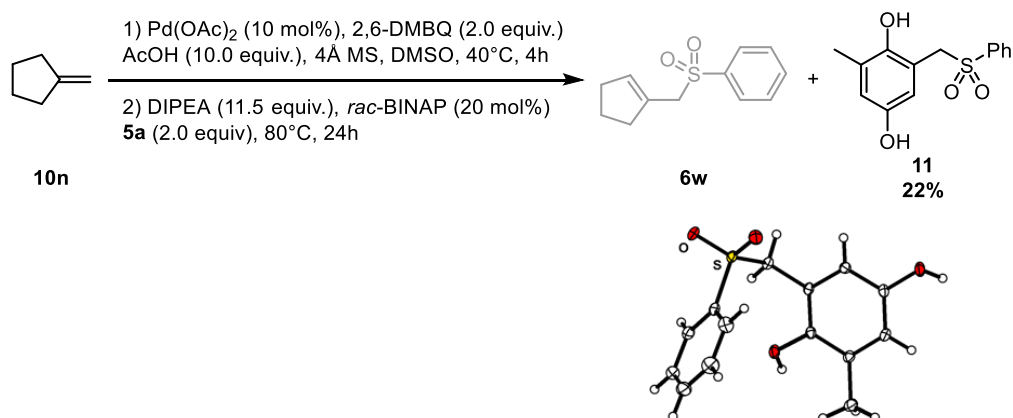
3.5.2. Allylarenes as substrates.

To further investigate the impact of the nature of the alkene on the reaction outcome, we re-evaluated these couplings using the *in situ* sequential reaction conditions (Method B). Notably, when the electron-rich allylarenes **10e** and **10f** were employed in the reaction with sodium benzenesulfinate **5a**, the corresponding allylsulfones **6l** and **6m** were obtained in yields comparable to those obtained with method A (48% and 44% yield respectively) (Scheme 111). Interestingly, when the *ortho*-substituted allylbenzene **10g** was subjected to method B, it failed to yield the corresponding allylsulfone **6n** and produced (*E*)-4-methylcinnamyl acetate **1c** with 26% yield. Furthermore, benzyl eugenol **10a** and 2-*O*-benzylallylbenzene **10b** showed higher yields of the corresponding allylsulfones **6o** and **6p** with method B (67% and 44% yield respectively) as compared to method A. The electron-poor allylarene **10h**, bearing a *para*-trifluoromethyl group, yielded the expected allylsulfone **6q** in 23% isolated yield. However, in this case, the reaction does proceed pretty well, as testified by the 68% NMR yield, the low isolated yield being due to difficulties during the purification process.



Scheme 111. Evaluation of allylarenes as substrates with method B.

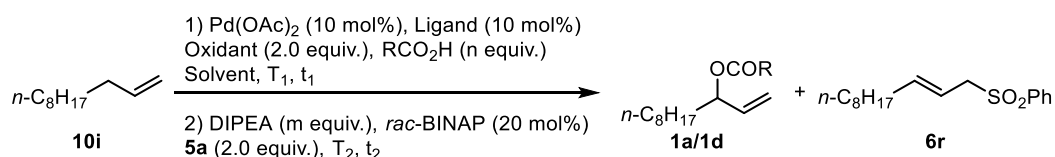
Unfortunately, none of the aliphatic terminal alkenes reacted with method B, due to the failure in the generation the allylacetate intermediates. However, a new product was unexpectedly generated when reacting exomethylenecyclopentane **10n**. Careful analysis, including single crystal X-ray diffraction analysis and IR analysis, showed the product to be hydroquinone **11**, which was formed in 22% isolated yield (Scheme 112).



Scheme 112. Formation of a by-product during the coupling between **10n** and **5a** using method B.

3.6. Reoptimization of method B for aliphatic terminal alkenes.

Since the Pd(II)-catalyzed C–H allylic acetoxylation of aliphatic terminal alkenes has been reported by the group of White,^[5a,111] we considered these reaction conditions to the first step of the *in situ* sequential procedure. Following a variant of White’s protocol, undecene **10i** was treated with Pd(OAc)₂ (10 mol%) in the presence of 1,2-bis(phenylsulfinyl)ethane (10 mol%) as the ligand, benzoic acid (1.5 equiv.), benzoquinone (2.0 equiv.) as the oxidant and 4Å MS (50 mg) in 1,4-dioxane. After 48h stirring at 43°C, treatment of the resulting branched allyl benzoate **1d** (TLC and ¹H NMR verification) with DIPEA (2.5 equiv.), sodium benzenesulfinate **5a** (2.0 equiv.) and *rac*-BINAP (20 mol%) with heating at 80°C, didn’t afford the desired allylsulfone **6r**. The branched allyl benzoate **1d** was detected instead by quantitative ¹H NMR (48% yield) (Table 19, entry 2). We speculate that the bis-sulfoxide ligand may prevent the phosphine promoted Pd(II)-to-Pd(0) reduction, thus halting the second, Pd(0)-catalyzed, step. However, the use of phenylvinylsulfoxide (10 mol%) instead of 1,2-bis(phenylsulfinyl)ethane allowed the formation of the desired allyl sulfone **6r** in 23% NMR yield together with the branched allyl benzoate intermediate **1d** in 27% yield (Table 19, entry 3). When increasing the amount of benzoic acid to 10.0 equivalents and the amount of DIPEA to 11.5 equivalents, only the desired allylsulfone **6r** could be obtained in 43% NMR yield (Table 19, entry 4). The new conditions set up are named Method B’ in the following paragraphs.



Entry ^[a]	Ligand	RCO ₂ H (n equiv.)	DIPEA (m equiv.)	Oxidant	Solvent	T ₁ /T ₂ (°C)	t ₁ /t ₂ (h)	1d (%) ^[b]	6r (%) ^[b]
1	-	AcOH (10.0)	11.5	2,6-DMBQ	DMSO	80/80	4/24	0	0
2		BzOH (1.5)	2.5	BQ	1,4-Dioxane	43/80	68/48	48	0
3		BzOH (1.5)	2.5	BQ	1,4-Dioxane	43/80	72/48	27	23
4		BzOH (10.0)	11.5	BQ	1,4-Dioxane	43/80	45/48	0	43

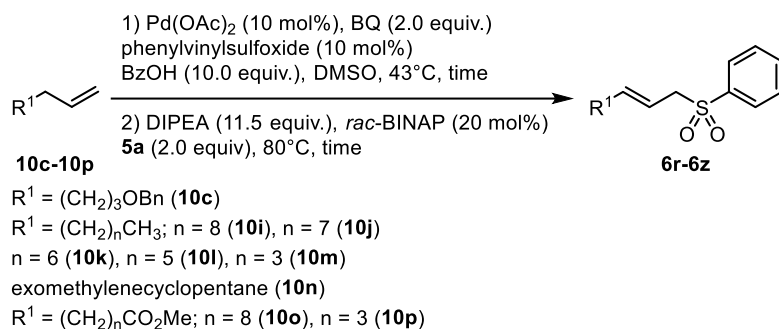
[a] typical reaction conditions: 1) undec-1-ene **10i** (0.2 mmol), Pd(OAc)₂ (10 mol%), ligand (10 mol%), RCO₂H (n equiv.), 2,6-DMBQ (2.0 equiv.) in Solvent (0.33M) at T₁ then 2) *rac*-BINAP (20 mol%), DIPEA (m equiv.), **5a** (2.0 equiv.) at T₂ for the indicated time; [b] yields were determined by quantitative ¹H NMR using 1,4-dinitrobenzene

as an internal standard.

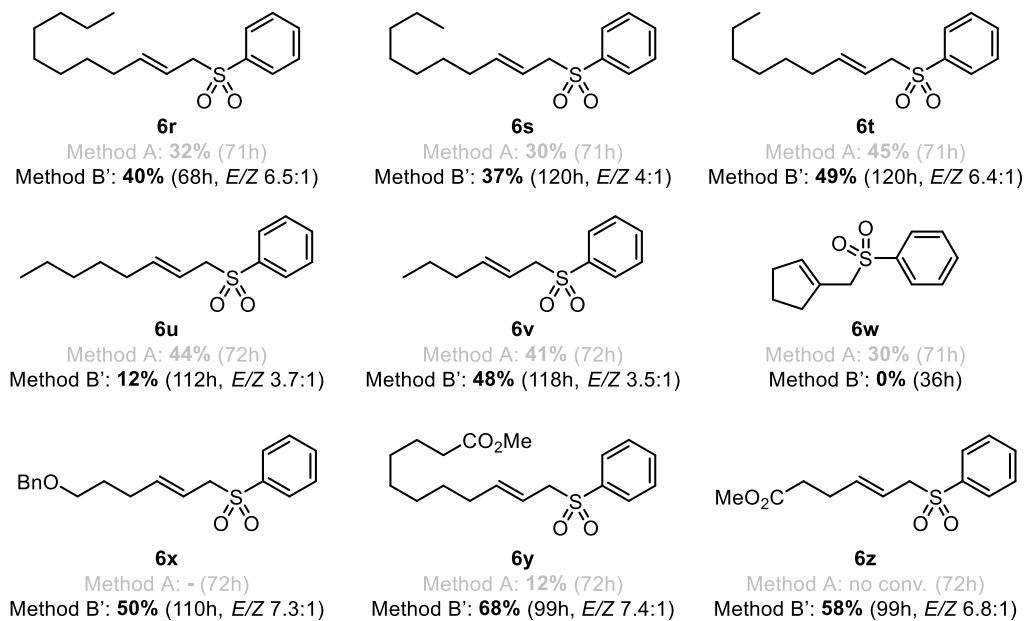
Table 19. Development of reaction conditions for a pseudo-domino process from undecene **10i**.

Using the newly established conditions, re-evaluation of the reactivity of aliphatic terminal alkenes **10c-10p** for the synthesis of their corresponding allylsulfones **6r-6z**, was carried out, as depicted in Scheme 113. Allylsulfone **6r** was obtained in 40% yield from undec-1-ene **10i**. Other aliphatic allylsulfones **6s**, **6t**, **6u** and **6v** were obtained from dec-1-ene **10j**, non-1-ene **10k**, oct-1-ene **10l** and hex-1-ene **10m**, in isolated yields of 37%, 49%, 12%, and 48%, respectively. These results are similar to those observed with method A. Here again, ¹H NMR spectra of the crude reaction products revealed the presence of *E/Z* isomer mixtures, the former isomers being always the major ones.

Methylenecyclopentane **10n** could not be converted into the corresponding allylsulfone **6w** with Method B' and no hydroquinone by-product **11** could be formed in this case. More functionalized aliphatic alkenes such as benzylether **10c** and esters **10o** and **10p**, which gave no or trace amounts of sulfonated products with method A or B, provided the desired allylsulfones **6x**, **6y**, and **6z** in 51%, 68 and 58% yields, respectively using method B'. In all these cases, *E/Z* mixtures were constantly obtained, with the (*E*)-isomer prevailing. This protocol, though requiring a long reaction time (4-5 days), is to date the only way to afford such allyl sulfones via allylic C–H functionalization (Scheme 113).

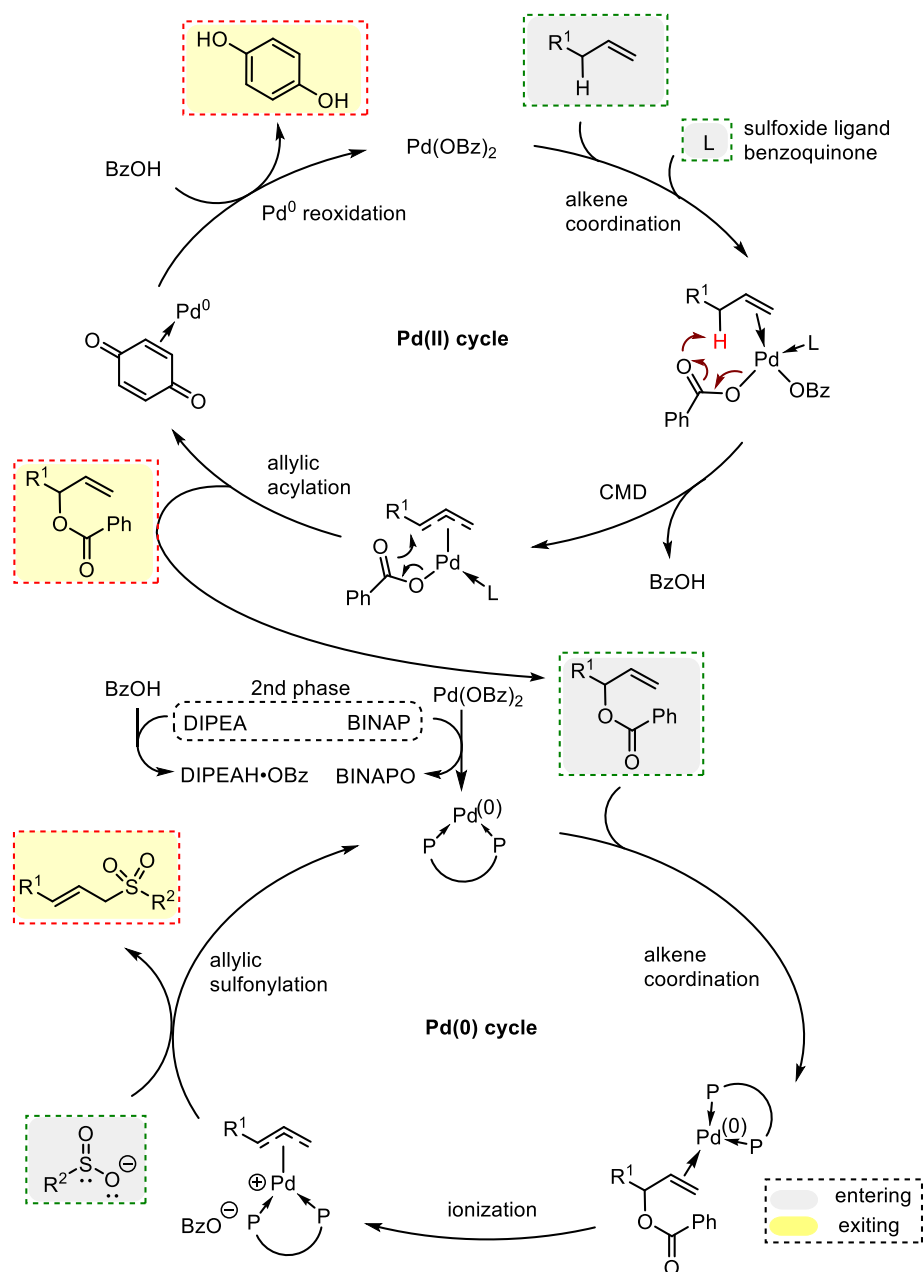


----- studied examples -----



Scheme 113. Evaluation of aliphatic terminal alkenes as substrates with method B'.

The mechanism associated to the conditions in method B' is expected to contain two different, yet connected, catalytic cycles.



Scheme 114. Proposed mechanism for the *in situ* sequential Pd-catalyzed allylic C-H sulfonylation of terminal alkenes using method B'.

Coordination of the terminal alkene and the sulfoxide ligand to the palladium atom of the *in situ* formed palladium dibenzoate generates the corresponding η^3 -allylpalladium complex via a likely CMD mechanism. Following inner sphere benzoate ligand transfer to the internal terminus of the π -complexed allyl fragment generates the branched allylic benzoate and a BQ-complexed Pd(0) intermediate, which regenerates palladium dibenzoate after oxidation with BQ.^[1a,5a] Once the

formation of the allylic benzoate is complete, addition of DIPEA and *rac*-BINAP to the reaction mixture sets the stage for the second catalytic cycle. Indeed, the amine quenches the excess of benzoic acid making the corresponding salt, while the diphosphine reduces the palladium dibenzoate and complexes the thus generated Pd(0) via κ^2 -coordination.^[Erreur ! Signet non défini.] After coordination of the alkene function of the allylic benzoate to the Pd(0) complex, a new, ionic, η^3 -allylpalladium complex is formed. The latter is intercepted by the sulfinate anion, which generates the allylic sulfone product and regenerates the Pd(0) complex (Scheme 114).

4. Attempted optimization of the synthesis of the hydroquinone byproduct 11.

As an ancillary project, we decided to optimize the synthesis of the by-product hydroquinone 11. This work has been performed in collaboration with Dr. Filipa Siopa and Prof. Carlos Afonso from the Faculty of Pharmacy of the University of Lisbon, in Portugal. As previous reports suggest, the conjugate addition on quinones predominantly occurs at the 3- or 5-position of the aromatic ring.^[135] Despite this, there is a lack of reports on "side-chain" conjugate addition of alkyl quinones. Consequently, there is a growing interest in studying the "side-chain" functionalization of substituted quinones.

This side-chain reactivity was pioneered by the group of Smith in 1936, in the reaction between trimethyl quinone and sodium acetoacetic ester/sodium malonic ester.^[136] The formation of a C-C bond on the side-chain of the quinone gave access to coumarins and coumarones. Methyl quinones were later used in Diels-Alder cycloadditions for the synthesis of polycyclic scaffolds.^[137] More recently, Clift *et al.* reported the successful synthesis of benzylamines through the side-chain amination of alkyl quinones.^[138] Based on this finding, we can hypothesize that in our case, a base-promoted tautomerization of the alkyl quinone resulted in the formation of a key quinone methide intermediate,

^[135] a) Bruce, J. M.; Lloyd-Williams, P. J. *Chem. Soc., Perkin Trans. 1*, **1992**, 2877–2884; b) Allgeier, D. E.; Herbert, S. A.; Nee, R.; Schlecht, K. D.; Finley, K. T. *J. Org. Chem.* **2003**, *68*, 4988–4990; c) Yadav, J. S.; Reddy, B. V. S.; Swamy, T.; Ramireddy, N. *Synthesis* **2004**, *11*, 1849–1853.

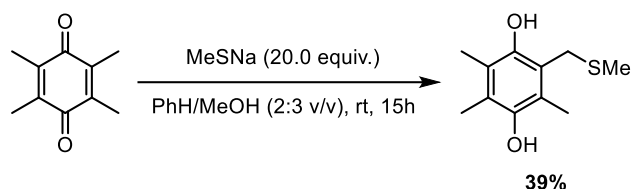
^[136] a) Smith, L. I.; MacMullen, C. W. *J. Am. Chem. Soc.* **1936**, *58*, 629–635; b) Smith, L. I.; Webster, I. M. *J. Am. Chem. Soc.* **1937**, *59*, 662–667; c) Smith, L. I.; Tenenbaum, D. *J. Am. Chem. Soc.* **1937**, *59*, 667–672.

^[137] Lin, C.; Du, H.-J.; Zhao, H.; Yan, D.-F.; Liu, N.-X.; Sun, H.; Wen, X.; Xu, Q.-L. *Org. Biomol. Chem.* **2017**, *15*, 3472–3478.

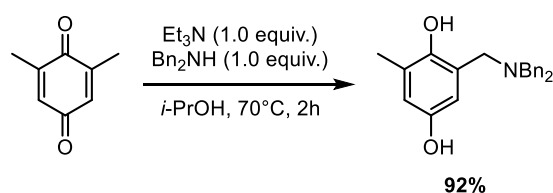
^[138] a) Mori-Quiroz, L. M.; Clift, M. D. *Org. Lett.* **2016**, *18*, 3446–3449; b) Mori-Quiroz, L. M.; Dekarske, M. M.; Prinkki, A. B.; Clift, M. D. *J. Org. Chem.* **2017**, *82*, 12257–12266; c) Mori-Quiroz, L. M.; Dekarske, M. M.; Prinkki, A. B.; Clift, M. D. *J. Org. Chem.* **2018**, *83*, 6243–6243.

which subsequently underwent a rapid reaction with the sodium aryl sulfonic acid nucleophile to yield the desired product **11** (Scheme 115). Worthy of note, formation of C-S bonds using this strategy was reported in 1980 by Thomson and Worthington for the preparation of thioethers.^[139]

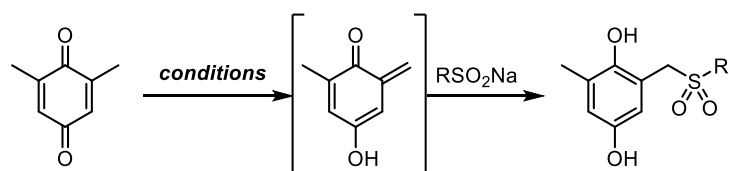
■ **C-S bond formation (ref 139)**



■ **C-N bond formation (ref 138)**



■ **This project**



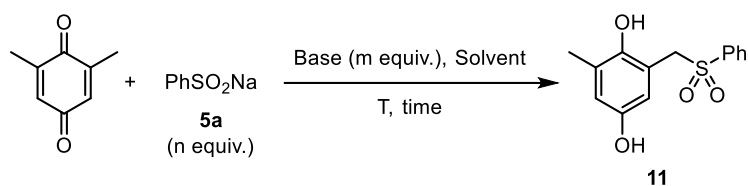
Scheme 115. Functionalization of the side-chain of quinones.

4.1. Optimization of the reaction conditions.

4.1.1. Preliminary experiments.

We investigated the influence of various parameters on the reaction outcome. The reaction of 2,6-DMBQ with sodium benzenesulfinate **5a**, using DIPEA as the base and working in DMSO at 80°C, resulted in degradation products (Table 20, entries 1-2). Lowering the reaction temperature to room temperature did not yield the desired product **11** (Table 20, entry 3). Following the work of Clift,^[138a] we also tested *iso*-propanol as the solvent and triethylamine as the base. However, in our case the starting material underwent decomposition (Table 20, entry 4).

^[139] a) Thomson, R. H.; Worthington, R. D. *J. Chem. Soc. Perkin Trans. 1* **1980**, 282-288; b) Thomson, R. H.; Worthington, R. D. *J. Chem. Soc. Perkin Trans. 1* **1980**, 289-292.



Entry ^[a]	5a (n equiv.)	Base (m equiv.)	Solvent	T (°C)	time (h)	11 (%)
1	1.0	DIPEA (1.0)	DMSO	80	2	0
2	2.0	DIPEA (11.5)	DMSO	80	2	0
3	1.0	DIPEA (1.0)	DMSO	rt	24	0
4	1.0	Et ₃ N (1.0)	<i>i</i> -PrOH	70	2	0

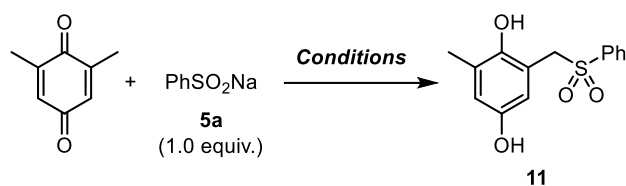
[a] Reaction conditions: 2,6-DMBQ (0.2 mmol), **5a** (1.0 equiv.), base and solvent (0.33M) were stirred in a sealed tube under argon.

Table 20. Preliminary studies for the optimization of the reaction conditions.

We then repeated the initial reaction conditions that generated by-product **11**, to verify the reproducibility of the coupling and in the hope to find out the key parameters that favor this reaction. In fact, we predicted that not all the reagents used in the initial experiment were likely to be needed for its formation.

In the event, adding all the reaction components and reagents at the outset of the reaction, and allowing the reaction to proceed for 24 hours at 80°C, we were able to obtain the desired benzylic sulfone **11** in 48% yield (Table 21, entry 1).

To determine the essential reagents required for the formation of the desired benzylic sulfone **11**, a series of experiments were conducted, wherein the different reagents were removed one by one. Significantly, when 2,6-DMBQ (1.0 equiv.) and sodium benzenesulfinate **5a** (1.0 equiv.) were reacted in the absence of DIPEA, the formation of the desired product **11** was achieved in a yield of 10% after 24 hours (Table 21, entry 2). In the absence of *rac*-BINAP, of 1-hexene, or of palladium(II) acetate, the desired product **11** was obtained in 27%, 16%, and 18% yield respectively (Table 21, entries 3-5). Notably, when acetic acid was removed, the desired product could not be obtained (Table 21, entry 6). This result indicates that acetic acid is an essential reagent for the synthesis of the benzylic sulfone **11**.

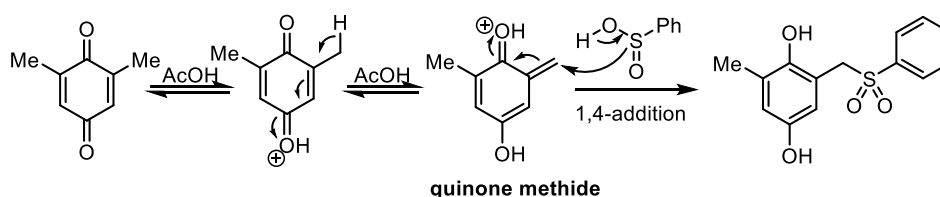


Entry ^[a]	Conditions	11 (%) ^[b]
1	Condition a: 1-hexene (0.5 equiv.), Pd(OAc) ₂ (5mol%), <i>rac</i> -BINAP (10 mol%), AcOH (5.0 equiv.), DIPEA (5.75 equiv.), 5a (1.0 equiv.), DMSO (0.66 M), 4Å MS, 80°C, 24h	48
2	Condition a without DIPEA, 24h	10
3	Condition a without <i>rac</i> -BINAP, 24h	27
4	Condition a without 1-hexene, 24h	16
5	Condition a without Pd(OAc) ₂ , 24h	18
6	Condition a without AcOH, 24h	0

[a] Reaction conditions a: 2,6-DMBQ (0.2 mmol), **5a** (1.0 equiv.), 1-hexene (0.5 equiv.), Pd(OAc)₂ (5mol%), *rac*-BINAP (10 mol%), AcOH (5.0 equiv.), DIPEA (5.75 equiv.), DMSO (0.66 M), 4Å MS, DMSO (0.66M) were heated at 80°C in a sealed tube under argon; [b] Yields were determined by quantitative ¹H NMR using 1,4-dinitrobenzene as an internal standard.

Table 21. Study of the reagents required for the reaction.

Based on the above results, it can be hypothesized that acetic acid is an acidic catalyst for this reaction, and a possible mechanism could involve the initial AcOH promoted enolization the quinone, followed by the conjugate addition of sulfinic acid to the resulting protonated *ortho*-quinone methide (Scheme 116).



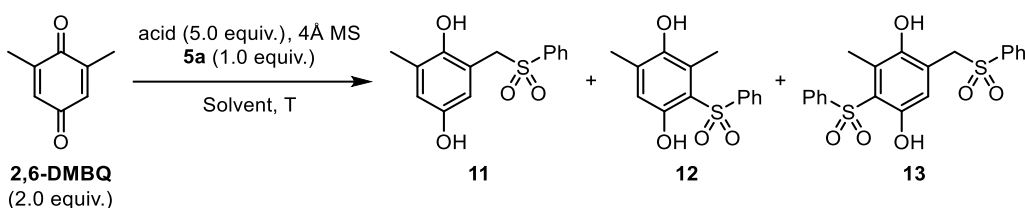
Scheme 116. A possible mechanism for this reaction.

4.1.2. Influence of the amount of 2,6-DMBQ and sulfinate.

Additional experiments were carried out in the hope to find out the optimal reaction conditions generating by-product **11**. In particular, the reaction of 2,6-DMBQ (1.0 equiv.) and sodium

4.1.3. Variation of the solvent.

A screening of various reaction solvents as also carried out. THF, acetonitrile, DMF, HFIP, 1,4-dioxane and ethanol, did not provide better yields than the previously studied AcOH or DMSO (Table 23, entries 1-6). Interestingly, when water or dichloromethane was used as solvent, the byproduct **12** became the major product, with 66% and 79% yield respectively, but no desired product **11** was obtained (Table 23, entries 7-8). Therefore, DMSO was found to be the most effective solvent for this reaction.



Entry ^[a]	Solvent	T (°C)	11 (%) ^[b]	12 (%) ^[b]	13 (%) ^[b]
1	THF	80	5	0	7
2	MeCN	80	9	0	13
3	DMF	80	7	0	8
4	HFIP	80	16	0	15
5	1,4-dioxane	80	18	0	12
6	EtOH	80	16	15	10
7	H ₂ O	80	0	66	0
8	CH ₂ Cl ₂	40	0	79	0

[a] Reaction conditions: 2,6-DMBQ (2.0 equiv.), **5a** (0.2 mmol), solvent (0.66M) were stirred in a sealed tube under argon; [b] Yields were determined by quantitative ¹H NMR using 1,4-dinitrobenzene as an internal standard.

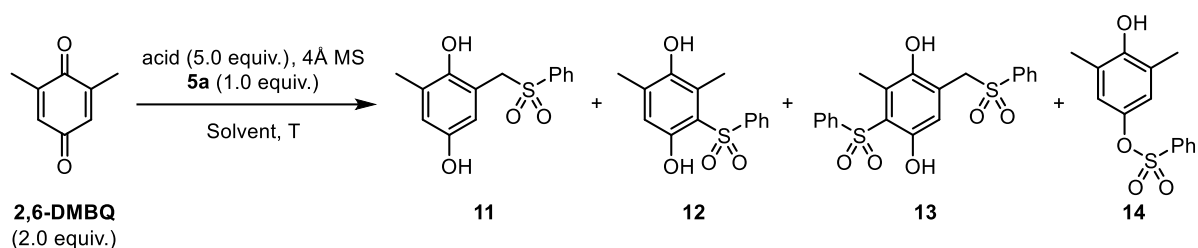
Table 23. Study on the variation of the solvent.

4.1.4. Variation of the acid.

Following the solvent screening, we further investigated the role of the acid in the reaction. We hypothesized that both Brønsted and Lewis acids could be used. Initially, we tried the reaction between 2,6-DMBQ and sodium benzenesulfinate **5a** in the presence of iron(III) chloride as the catalyst and trimethylsilyl chloride as an additive according to reported conditions.^[140] Unfortunately, this reaction condition only provided the by-product **12** in 96% yield, without the formation of the desired product

^[140] Sreedhar, B.; Reddy, M. A.; Reddy, P. S. *Synlett* **2008**, 13, 1949–1952.

11 (Table 24, entry 1). We also tested the Lewis acids copper(II) triflate and ytterbium(III) triflate, which gave the new product **14** in 31% and 46% yield respectively (Table 24, entries 2-3). When palladium(II) acetate was used as an additive and acetic acid was used as the acid, the reaction provided by-product **14** in 24% yield (Table 24, entry 4). Interestingly, the use of benzoic acid as the acid resulted in the formation of the targeted by-product **11**, but in a yield of 30% (Table 24, entry 5).



Entry ^[a]	Acid (n equiv.)	T (°C)	time (h)	11 (%) ^[b]	12 (%) ^[b]	13 (%) ^[b]	14 (%) ^[b]
1 ^[c]	FeCl ₃ (20mol%), TMSCl (1.2 equiv.)	rt	2	0	96 (65) ^[d]	0	0
2	Cu(OTf) ₂ (20mol%)	80	15	0	0	0	31
3	Yb(OTf) ₃ (20mol%)	80	15	0	0	0	46 (19) ^[d]
4	AcOH (5.0 equiv.), Pd(Oac) ₂ (10 mol%)	80	14	0	0	0	24
5	BzOH (5.0 equiv.)	80	24	30	0	0	0

[a] Reaction conditions: 2,6-DMBQ (2.0 equiv.), **5a** (0.2 mmol), acid (m equiv.) and DMSO (0.66M) were stirred in a sealed tube under argon; [b] Yields were determined by quantitative ¹H NMR using 1,4-dinitrobenzene as an internal standard; [c] dichloromethane as the solvent; [d] isolated yields are indicated in parentheses.

Table 24. Study on the variation of the acid.

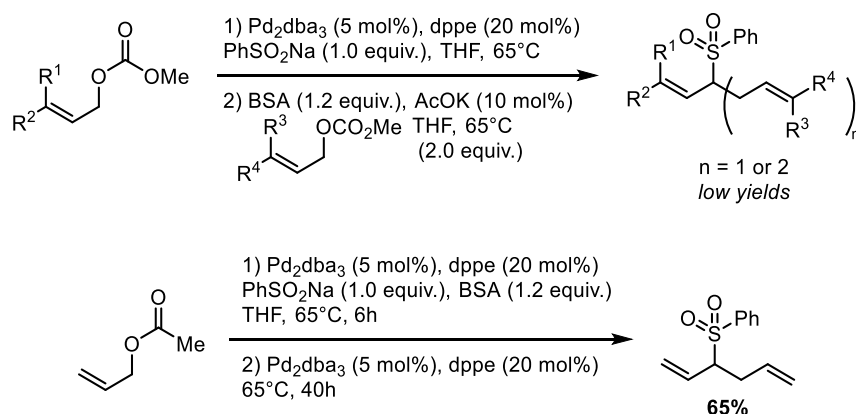
In summary, the targeted by-product **11** could not be obtained in satisfactory yields, rendering further studies of limited value.

In this study, we have successfully developed and compared two distinct and effective protocols for the preparation of allylsulfones from commercially available alkenes via palladium-catalyzed allylic C–H activation. The first method is involving a direct allylic C–H sulfonylation and the second procedure is involving a one-pot sequential Pd(II)-catalyzed allylic C–H acetoxylation followed by a Pd(0)-catalyzed sulfonylation. While the direct sulfonylation protocol is more straightforward and appealing, the

sequential acetoxylation-sulfonylation protocol exhibits a broader substrate scope and often higher yields. In addition, we propose plausible mechanisms for both protocols. Further research on this topic will be worthy. As an ancillary investigation, we tried to optimize the synthesis of a sulfonyl hydroquinone by-product obtained during the coupling when using 2,6-dimethylbenzoquinone . Our findings showed that acetic acid played a crucial role in facilitating the side chain sulfonylation of 2,6-dimethylbenzoquinone. However, despite an extensive screening of the reaction conditions, we failed to improve the yield of formation of this product. Further investigation will be necessary to improve the yield of this side product.

General conclusion

On the one hand, our research group has devoted over two decades to investigating the chemistry of η^3 -allylpalladium complexes, which offers a number of ways to constructing complex molecular frameworks with atom- as well as step economy. On another hand, allylsulfones are functional groups of particular significance, serving as building blocks for many organic reactions. In the present PhD thesis, I focused my research on the discovery of new domino or C–H activation strategies involving Pd-catalysis and sulfones. In the first part of my work, I tackled a one-pot Pd-catalyzed C-S/C-C/C-C bond forming triple intermolecular allylation sequence involving allyl carbonates and benzenesulfinate salts as reaction partners (Scheme 117, top). Unfortunately, despite the good potential, the substrate scope turned out to be rather limited. As an alternative, I explored a one-step Pd-catalyzed domino sequence with allyl acetate or carbonate and sodium benzenesulfinate, but reproducibility problems appeared (Scheme 117, bottom).

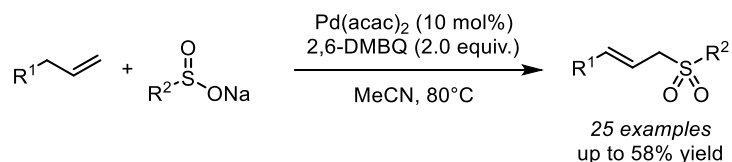


Scheme 117. Development of domino procedures involving sulfone chemistry and palladium catalysis.

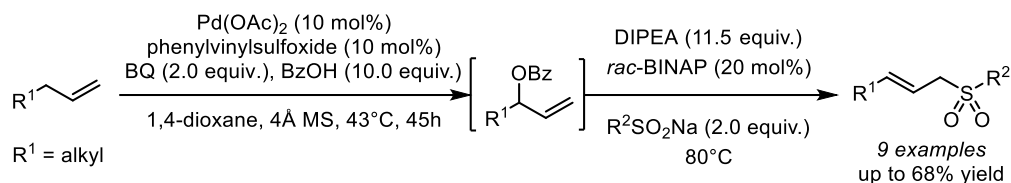
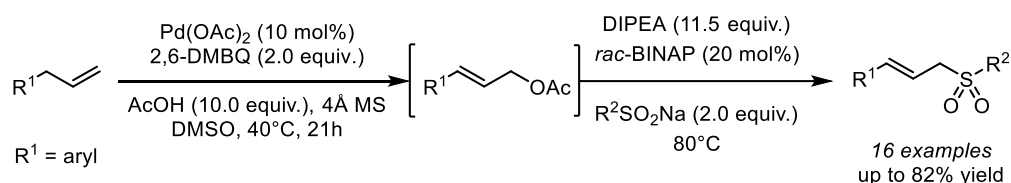
The second part of this thesis is dedicated to the Pd-catalyzed synthesis of allyl sulfones starting from terminal alkenes and sulfinate anions. Specifically, two new protocols have been developed. The first one involved the direct PdX₂-catalyzed allylic C-H sulfonylation, while the second consisted in a one-pot sequential process entailing a first oxidative PdX₂-catalyzed allylic C–H acetoxylation, followed by a redox neutral Pd(0)-catalyzed allylic sulfonylation of the intermediate allylic acetate (Scheme 118). While the direct sulfonylation protocol is more straightforward and appealing, the sequential

acetoxylation-sulfonylation protocol offers a wider substrate scope and often achieves higher conversion rates.

■ **Direct Pd(II)-catalyzed allylic sulfonylation procedure**

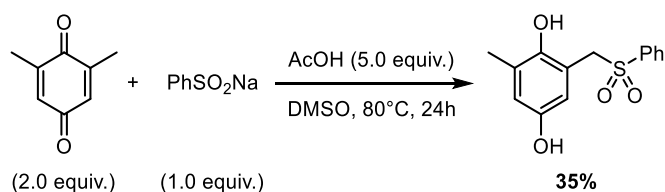


■ **Sequential Pd(II)-catalyzed acylation/Pd(0)-catalyzed sulfonylation procedure**



Scheme 118. Developed protocols for the preparation of allylsulfones by Pd-catalyzed allylic C-H activation.

Finally, I investigated a side-reaction that occurred within the latter project. Namely, the reaction between 2,6-dimethyl benzoquinone and sodium benzenesulfinate, which resulted in the formation of a sulfonyl dihydroquinone. The studies accomplished found that acetic acid was necessary to promote the side-chain sulfonylation of 2,6-dimethylbenzoquinone (Scheme 119). However, it was impossible to obtain the targeted product in a synthetically useful yield.



Scheme 119. Brønsted acid-mediated sulfonylation of 2,6-DMBQ.

Experimental Section

1. General Remarks

Reactions: All reactions were carried out under an argon atmosphere by standard syringe and septa techniques. Glassware was flame-dried under vacuum or taken directly from the oven (100 °C) and let cool under vacuum prior to use. Purifications by flash column chromatography were performed using silica gel Merck Geduran® SI 60 (40-63 µm). Yields refer to chromatographically and spectroscopically pure compounds, unless otherwise mentioned.

Reagents and solvents: Reagents and solvents were purchased from commercial sources and generally used as received. Commercially available reagents were purchased at Alfa Aesar, Acros Organics, Sigma Aldrich, TCI Chemicals and Fluorochem suppliers. Solvents were purchased at Carlo Erba. Dichloromethane and THF were dried on a Mbraun purification system MB SPS-800. Acetonitrile was dried and then distilled over calcium hydride. DMSO, methanol, propionitrile and 1,4-dioxane were purchased anhydrous, dried appropriately and kept under inert atmosphere.

TLC: Reactions were magnetically stirred and monitored by thin layer chromatography using Merck-Kieselgel 60F₂₅₄ plates and analyzed with either an ultra-violet lamp ($\lambda = 254$ nm) and using potassium permanganate or *p*-anisaldehyde as a stain.

NMR: NMR spectra (¹H, ¹³C and ¹⁹F) were recorded on a Bruker AM 300 MHz or on a Bruker AVANCE 400 MHz spectrophotometer. NMR experiments were carried out at room temperature in CDCl₃. Chemical shifts are given in parts per million (ppm) using the CDCl₃ residual non-deuterated signals as reference (δ ¹H = 7.26 ppm; δ ¹³C = 77.16 ppm). The terms m, s, d, t and q correspond to multiplet, singlet, doublet, triplet and quartet, respectively. The term br. and app. are respectively used when the peak is broad or apparent, and in the latter case when the correct real multiplicity cannot be surely assigned. Coupling constants (J) are given in Hertz (Hz). When mixtures of diastereoisomers were found, we indicated the assignable signals to one of the diastereoisomers with the terms “major” and “minor” respectively for the major and minor diastereoisomers. For known compounds, a reference where the characterization can be found was indicated. In addition, ¹H NMR data for these products was shown.

IR: IR spectra were recorded with a Tensor 27 (ATR Diamond) Bruker spectrophotometer and a

Spectrum Two (ATR diamond) PerkinElmer spectrometer. IR spectra were reported as characteristic bands (cm^{-1}).

HRMS: High resolution mass spectra (HRMS) were obtained using a mass spectrometer MicroTOF from Bruker with an electron spray source (ESI) or an atmospheric pressure chemical ionization (APCI) source and a TOF detector at Institut Parisien de Chimie Moléculaire (FR 2769).

Melting points: Melting points were measured in capillary tubes on a Stuart Scientific SMP3 apparatus and are uncorrected.

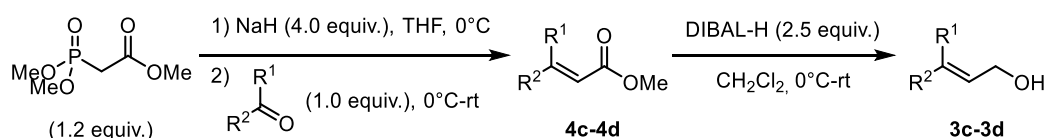
2. Chapter 2: Towards the synthesis of conjugated trienes by a Pd-catalyzed domino process involving allylsulfones.

2.1. Synthesis and characterization of starting materials

2.1.1. Synthesis of allyl acetates and allyl carbonates

Allylic alcohols **4a**, **4b** and **4g** are commercially available. Allylic alcohols **4c** and **4d** were prepared following a slightly modified version of a reported procedure.^[141] Allylic alcohols **4e** and **4f** were reported according to reported procedures.^[142]

General procedure: Synthesis of allylic alcohols



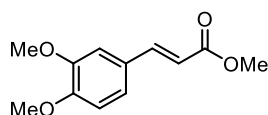
^[141] Salih, M. Q.; Zakharov, L. N.; Beaudry, C. M. *Tetrahedron Lett.* **2020**, *61*, 151988.

^[142] For allylic alcohol **4e**, see: (a) Taylor, P.; Ookawa, A.; Yokoyama, S.; Soai, K. *Synth. Commun.* **1985**, *15*, 985–990. For allylic alcohol **4f**, see: (b) Ren, K.; Zhang, L.; Hu, B.; Zhao, M.; Tu, Y.; Xie, X.; Zhang, T. Y.; Zhang, Z. *ChemCatChem* **2013**, *5*, 1317–1320.

Step 1: General procedure for the HWE olefination of aldehydes.

A round bottom flask was charged with sodium hydride (60 wt% in mineral oil, 4.0 equiv.) and the flask was placed under vacuum. It was then backfilled with argon and the vacuum/argon cycles were repeated twice. The base was suspended in dry THF (C = 1.0M) and the suspension was cooled to 0°C (ice/water bath). Trimethyl phosphonoacetate (1.2 equiv.) was added dropwise. The mixture was stirred for 10 min, and a solution of carbonyl substrate (1.0 equiv.) in THF (C = 1.0M) was added. The mixture was stirred for 15 min at 0°C, then slowly warmed to rt and stirred for an additional 2 h. The advancement of the reaction was checked by ¹H NMR of an aliquot of the reaction mixture. The reaction was quenched by addition of a saturated aqueous solution of ammonium chloride (2 mL/mmol of limiting reagent) and ethyl acetate (5 mL/mmol of limiting reagent) was added. The biphasic mixture was separated and the aqueous layer was extracted with ethyl acetate (3 x 3 mL/mmol of limiting reagent). The combined organic layers were dried over anhydrous magnesium sulfate, filtered and the filtrate was concentrated under reduced pressure. The crude product was purified by silica-gel column chromatography to give desired product.

Methyl *trans*-3,4-dimethoxycinnamate (3c)

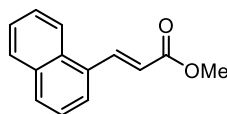


Prepared from trimethyl phosphonoacetate (16.0 mL, 96.0 mmol, 2.5 equiv.), 3,4-dimethoxybenzaldehyde (13.7 g, 80.0 mmol, 1.2 equiv.) and sodium hydride (4.4 g, 110 mmol, 60 wt% in paraffin oil, 1.4 equiv.) in 200 mL of dry THF. After workup, and purification by flash column chromatography on silica gel (cyclohexane/ethyl acetate 1:2), the methyl *trans*-3,4-dimethoxycinnamate **3c** was obtained as a yellowish oil (18.3 g, quantitative yield). The characterization data are in accordance with the ones reported in the literature.^[143]

¹H NMR (300 MHz, CDCl₃) δ 7.63 (d, *J* = 15.9 Hz, 1H), 7.15-6.95 (m, 2H), 6.86 (d, *J* = 8.3 Hz, 1H), 6.30 (d, *J* = 15.9 Hz, 1H), 3.90 (s, 3H), 3.79 (s, 3H).

^[143] Šebestík, J.; Marques, S. M.; Falé, P. L.; Santos, S.; Arduíno, D. M.; Cardoso, S. M.; Oliveira, C. R.; Serralheiro, M. L. M.; Santos, M. A. *J. Enzyme Inhib. Med. Chem.* **2011**, *26*, 485–497.

Methyl (2E)-3-(1-naphthalenyl)-2-propenoate (3d)



Prepared from trimethyl phosphonoacetate (16.0 mL, 24.0 mmol, 1.2 equiv.), 1-naphthalenecarboxaldehyde (13.7 g, 20.0 mmol, 1.0 equiv.) and sodium hydride (960 mg, 24.0 mmol, 60 wt% in paraffin oil, 1.2 equiv.) in 100 mL of dry THF. After workup, and purification by flash column chromatography on silica gel (cyclohexane/ethyl acetate 2:1), methyl (2E)-3-(1-naphthalenyl)-2-propenoate **3d** was obtained as a yellowish oil (4.24 g, quantitative yield). The characterization data are in accordance with the ones reported in the literature.^[144]

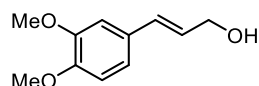
¹H NMR (400 MHz, CDCl₃) δ 8.54 (d, *J* = 15.8 Hz, 1H), 8.20 (d, *J* = 8.3 Hz, 1H), 7.92-7.83 (m, 2H), 7.76 (d, *J* = 7.2 Hz, 1H), 7.63-7.42 (m, 3H), 6.54 (d, *J* = 15.7 Hz, 1H), 3.86 (s, 3H).

Step 2: General procedure for the reduction of the α,β-unsaturated ester.

A round bottom flask was charged with the α,β-unsaturated ester (1.0 equiv.) and the flask was placed under vacuum. It was then backfilled with argon and the vacuum/argon cycles were repeated twice. The ester was dissolved in dry dichloromethane (C = 0.2M) and at the solution was cooled to 0°C. To this cold solution was added dropwise DIBAL-H (1.5-2.5 equiv., 1.0-1.2M in toluene). After stirring for 1 h at 0°C, the reaction mixture was warmed to rt. The reaction mixture was stirred until complete conversion of the ester as observed by TLC. The reaction was slowly quenched with a saturated aqueous solution of Rochelle salt and diluted with water. The biphasic mixture was separated and the aqueous layer was extracted three times with dichloromethane. The combined organic layers were dried with anhydrous magnesium sulfate and filtered. The filtrate was concentrated under reduced pressure. The crude product was purified by silica-gel column chromatography to give the desired allylic alcohol.

^[144] Krätzschmar, F.; Kaßel, M.; Delony, D.; Breder, A. *Chem. Eur. J.* **2015**, *21*, 7030–7034.

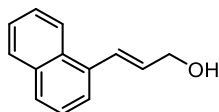
(*E*)-3-(3,4-dimethoxyphenyl)prop-2-en-1-ol (**4c**)



Prepared from methyl *trans*-3,4-dimethoxycinnamate **3c** (17.8 g, 80.0 mmol, 1.0 equiv.) and DIBAL-H (100 mL, 120 mmol, 1.2 M in toluene, 1.5 equiv.) in 200 mL of dry dichloromethane. After workup and purification by flash column chromatography on silica gel (cyclohexane/ethyl acetate 1:1), (*E*)-3-(3,4-dimethoxyphenyl)prop-2-en-1-ol **4c** was obtained as a yellowish oil (18.3 g, 71% yield). The characterization data are in accordance with the ones reported in the literature.^[145]

¹H NMR (400 MHz, CDCl₃) δ 7.00-6.85 (m, 2H), 6.86-6.74 (m, 1H), 6.53 (dd, *J* = 15.9, 1.8 Hz, 1H), 6.32-6.11 (m, 1H), 4.29 (t, *J* = 5.3 Hz, 2H), 3.88 (s, 3H), 3.86 (s, 3H).

(2*E*)-3-(1-Naphthalenyl)-2-propen-1-ol (**4d**)



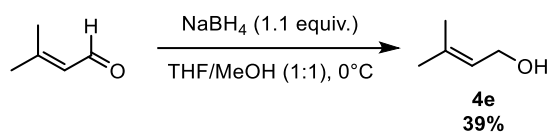
Prepared from methyl (2*E*)-3-(1-naphthalenyl)-2-propenoate **3d** (3.05 g, 14.4 mmol) and DIBAL-H (36.0 mL, 36.0 mmol, 2.5 equiv.) in 100 mL of dry dichloromethane. After workup and purification by flash column chromatography on silica gel (cyclohexane/ethyl acetate 1:1), (2*E*)-3-(1-Naphthalenyl)-2-propen-1-ol **4d** was obtained as a colorless oil (3.90 g, 82% yield). The characterization data are in accordance with the ones reported in the literature.^[146]

¹H NMR (300 MHz, CDCl₃) δ 8.18-8.08 (m, 1H), 7.93-7.82 (m, 1H), 7.78 (d, *J* = 8.2 Hz, 1H), 7.60 (d, *J* = 7.2 Hz, 1H), 7.55-7.34 (m, 4H), 6.40 (dtd, *J* = 15.6, 5.6, 1.0 Hz, 1H), 4.63-4.34 (m, 2H), 1.66-1.54 (m, 1H).

^[145] Kocsis, L. S.; Brummond, K. M. *Org. Lett.* **2014**, *16*, 4158–4161.

^[146] Jiao, K. J.; Li, Z. M.; Xu, X. T.; Zhang, L. P.; Li, Y. Q.; Zhang, K.; Mei, T. S. *Org. Chem. Front.* **2018**, *5*, 2244–2248.

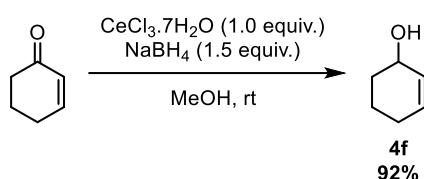
Synthesis of 3-methylbut-2-en-1-ol (4e)



To a solution of 3-methylcrotonaldehyde (2.89 mL, 30.0 mmol, 1.0 equiv.) in 30 mL of a 1:1 v/v mixture of methanol and THF was added sodium borohydride (1.24 g, 33.0 mmol, 1.1 equiv.) over a 10 min period of time at 0°C (ice/water bath). The reaction mixture was stirred until complete conversion of 3-methylcrotonaldehyde as seen by TLC (20 min). The reaction was then quenched by the addition of 50 mL of ice-cold brine and organoaqueous mixture was extracted with diethyl ether (3 x 50 mL). The combined organic layers were washed with brine, dried with MgSO₄ and filtered. The filtrate was concentrated under reduced pressure. The crude mixture was purified by flash column chromatography on silica gel (cyclohexane/ethyl acetate 10:1) to give 3-methylbut-2-en-1-ol **4e** as a colorless oil (1.10 g, 39% yield). The characterization data are in accordance with the ones reported in the literature.^[147]

¹H NMR (300 MHz, CDCl₃) δ 5.52-5.32 (m, 1H), 4.16-4.09 (m, 2H), 1.74 (d, *J* = 1.3 Hz, 3H), 1.68 (d, *J* = 1.3 Hz, 3H).

Synthesis of 2-Cyclohexen-1-ol (4f)



To a solution of cyclohexenone (960 mg, 10.0 mmol, 1.0 equiv.) and cerium(III) chloride heptahydrate (3.72 g, 10.0 mmol, 1.0 equiv.) in 10 mL of methanol was added sodium borohydride (570 mg, 15.0 mmol, 1.5 equiv.) portionswise over a 10 min period of time. The reaction mixture was stirred for 3 h at rt. When conversion of cyclohexanone was complete, as checked by TLC, the reaction mixture was quenched with 10 mL of water and the organoaqueous layer was extracted with diethyl ether (3 x 10

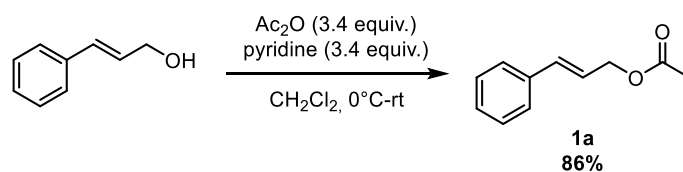
^[147] Rösler, S.; Obenauf, J.; Kempe, R. *J. Am. Chem. Soc.* **2015**, *137*, 7998–8001.

mL). The combined organic layers were washed with water, dried with anhydrous magnesium sulfate and filtered. The filtrate was concentrated under reduced pressure. The crude mixture was purified by flash column chromatography on silica gel (cyclohexane/ethyl acetate 1:1) to give 2-cyclohexen-1-ol **4f** as a colorless oil (0.91 g, 92% yield). The characterization data are in accordance with the ones reported in the literature.^[148]

¹H NMR (400 MHz, CDCl₃) δ 5.88-5.79 (m, 1H), 5.79-5.70 (m, 1H), 4.24-4.15 (m, 1H), 2.02-1.95 (m, 1H), 1.95-1.82 (m, 1H), 1.80-1.68 (m, 1H), 1.67-1.52 (m, 2H), 1.51-1.36 (m, 1H).

2.1.2. Synthesis of cinnamyl acetate (1a).

Cinnamyl acetate **1a** was prepared following a reported procedure.^[149] Allyl acetate **1b** is commercially available.



A round bottom flask was charged with cinnamyl alcohol (6.50 mL, 50.0 mmol) and the flask was placed under vacuum before being backfilled with argon. The vacuum/argon cycles were repeated twice and the alcohol was dissolved in 10 mL of dry dichloromethane. The mixture was cooled to 0°C (ice/water bath) and acetic anhydride (16.0 mL, 170 mmol, 3.4 equiv.) and pyridine (13.5 mL, 170 mmol, 3.4 equiv.) were successively added dropwise. The mixture was warmed at rt and stirred at this temperature until starting material was fully consumed, as checked by TLC (18h). The reaction mixture was hydrolyzed with 100 mL of water and the biphasic mixture was separated. The aqueous layer was extracted with dichloromethane (2 × 100 mL). The combined organic layers were washed with 100 mL of brine, dried over anhydrous magnesium sulfate and filtered. The filtrate was concentrated under reduced pressure. The crude mixture was purified by flash column chromatography (cyclohexane/ethyl acetate 9:1) to give *trans*-cinnamyl acetate **1a** as a colorless liquid (7.61 g, 86% yield). The characterization data are in accordance with the ones reported in the literature.^[149]

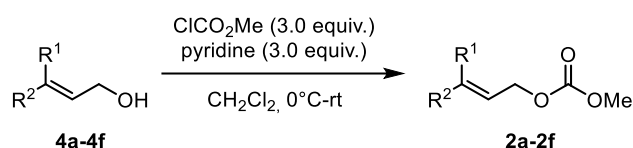
^[148] Abernethy, C. D.; Cole, M. L.; Davies, A. J.; Jones, C. *Tetrahedron Lett.* **2000**, 41, 7567–7570.

^[149] Álvarez-Calero, J. M.; Jorge, Z. D.; Massanet, G. M. *Org. Lett.* **2016**, 18, 6344–6347.

¹H NMR (300 MHz, CDCl₃) δ 7.47-7.21 (m, 5H), 6.66 (dt, *J* = 15.9, 1.4 Hz, 1H), 6.29 (dt, *J* = 15.9, 6.4 Hz, 1H), 4.73 (dd, *J* = 6.4, 1.3 Hz, 2H), 2.11 (s, 3H).

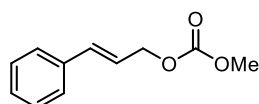
2.1.3. Synthesis of allyl carbonates and carbamates

Allyl methyl carbonates were prepared following a reported procedure.^[150] Allyl methyl carbonate **2g** and diallyl carbonate **2h** are commercially available.



A round bottom flask was charged with the allylic alcohol (1.0 equiv.) and the flask was placed under vacuum before being backfilled with argon. The vacuum/argon cycles were repeated twice and the allylic alcohol was dissolved in dry dichloromethane (C = 0.2M). The flask was cooled to 0°C (ice/water bath) and to this cold solution was successively introduced dropwise pyridine (3.0 equiv.) and methyl chloroformate (3.0 equiv.). The resulting suspension was warmed to rt. Upon complete consumption of the starting material, as checked by TLC, the reaction mixture was quenched by addition of water and stirred vigorously for at least 15 min. The biphasic mixture was separated. The organic layer was washed twice with a 1M aqueous solution of hydrochloric acid and once with a saturated solution of sodium bicarbonate. The resulting organic layer was dried over anhydrous magnesium sulfate and filtered. The filtrate was concentrated under reduced pressure. The crude mixture was then purified by silica gel chromatography to give the desired allyl carbonates.

Methyl (2E)-3-phenyl-2-propen-1-yl carbonate (**2a**)



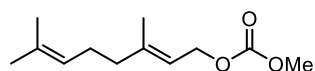
Prepared from cinnamyl alcohol (4.00 g, 30.0 mmol, 1.0 equiv.), methyl chloroformate (6.95 mL, 90.0 mmol, 3.0 equiv.) and pyridine (7.30 mL, 90.0 mmol, 3.0 equiv.). After workup, the crude mixture was

^[150] Schlätzer, T.; Schröder, H.; Trobe, M.; Lembacher-Fadum, C.; Stangl, S.; Schlögl, C.; Weber, H.; Breinbauer, R. *Adv. Synth. Catal.* **2020**, *362*, 331–336.

purified by flash column chromatography (cyclohexane/ethyl acetate 10:1) to give methyl (2*E*)-3-phenyl-2-propen-1-yl carbonate **2a** as a colorless liquid (5.10 g, 88% yield). The characterization data are in accordance with the ones reported in the literature.^[150]

¹H NMR (300 MHz, CDCl₃) δ 7.45-7.24 (m, 5H), 6.76-6.62 (m, 1H), 6.38-6.21 (m, 1H), 4.80 (dd, *J* = 6.4, 1.3 Hz, 2H), 3.81 (s, 3H).

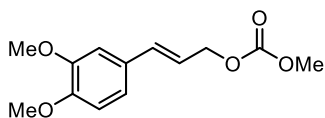
(*E*)-3,7-Dimethylocta-2,6-dien-1-yl methyl carbonate (**2b**)



Prepared from geraniol (1.85 g, 12.0 mmol, 1.0 equiv.), methyl chloroformate (2.78 mL, 36.0 mmol, 3.0 equiv.) and pyridine (2.91 mL, 36.0 mmol, 3.0 equiv.). After workup, the crude mixture was purified by flash column chromatography (cyclohexane/ethyl acetate 10:1) to give (*E*)-3,7-dimethylocta-2,6-dien-1-yl methyl carbonate **2b** as a colorless liquid (1.73 g, 68% yield). The characterization data are in accordance with the ones reported in the literature.^[150]

¹H NMR (400 MHz, CDCl₃) δ 5.45-5.27 (m, 1H), 5.08 (t, *J* = 6.8 Hz, 1H), 4.65 (d, *J* = 7.2 Hz, 2H), 3.77 (s, 3H), 2.16-2.04 (m, 4H), 1.72 (d, *J* = 1.3 Hz, 3H), 1.68 (s, 3H), 1.60 (s, 3H).

(*E*)-3-(3,4-dimethoxyphenyl)allyl methyl carbonate (**2c**)

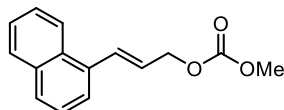


Prepared from (*E*)-3-(3,4-dimethoxyphenyl)prop-2-en-1-ol **4c** (71.3 mg, 30.0 mmol, 1.0 equiv.), methyl chloroformate (6.95 mL, 90.0 mmol, 3.0 equiv.) and pyridine (7.30 mL, 90.0 mmol, 3.0 equiv.). After workup, the crude mixture was purified by flash column chromatography (cyclohexane/ethyl acetate 5:1) to give (*E*)-3-(3,4-dimethoxyphenyl)allyl methyl carbonate **2c** as a colorless liquid (5.40 g, 72% yield).

¹H NMR (300 MHz, CDCl₃) δ 7.01-6.88 (m, 2H), 6.87-6.74 (m, 1H), 6.63 (d, *J* = 15.8 Hz, 1H), 6.17 (dt, *J* = 15.8, 6.6 Hz, 1H), 4.77 (dd, *J* = 6.6, 1.3 Hz, 2H), 3.89 (s, 3H), 3.88 (s, 3H), 3.80 (s, 3H); ¹³C NMR (101 MHz, CDCl₃) δ 155.6, 149.2, 148.9, 134.7, 128.9, 120.2, 120.0, 110.9, 108.8, 68.5, 55.8, 55.7, 54.6; MS (EI, 70

eV) m/z: 252 (M⁺, 77%), 193 (29%), 177 (100%), 161 (43%), 146 (53%), 91 (45%); IR: ν (cm⁻¹) 3015, 2916, 1789, 1545, 1467, 1267, 1168, 987, 856, 787, 612, 403.

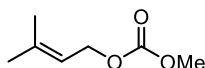
Methyl (2E)-3-(1-naphthalenyl)-2-propen-1-yl carbonate (2d)



Prepared from (2E)-3-(1-naphthalenyl)-2-propen-1-ol **4d** (2.00 g, 11.8 mmol, 1.0 equiv.), methyl chloroformate (2.73 mL, 35.4 mmol, 3.0 equiv.) and pyridine (2.86 mL, 35.4 mmol, 3.0 equiv.). After workup, the crude mixture was purified by flash column chromatography (cyclohexane/ethyl acetate 5:1) to give methyl (2E)-3-(1-naphthalenyl)-2-propen-1-yl carbonate **2d** as a colorless liquid (2.44 g, 85% yield). The characterization data are in accordance with the ones reported in the literature.^[151]

¹H NMR (400 MHz, CDCl₃) δ 8.14-8.02 (m, 1H), 7.88-7.83 (m, 1H), 7.83-7.77 (m, 1H), 7.63-7.58 (m, 1H), 7.56-7.40 (m, 4H), 6.34 (dt, J = 15.6, 6.4 Hz, 1H), 4.91 (dd, J = 6.3, 1.4 Hz, 2H), 3.84 (s, 3H).

Methyl (3-methylbut-2-en-1-yl) carbonate (2e)

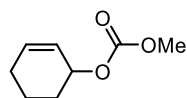


Prepared from 3-methyl-2-buten-1-ol **4e** (1.03 g, 12.0 mmol, 1.0 equiv.), methyl chloroformate (2.78 mL, 36.0 mmol, 3.0 equiv.) and pyridine (2.91 mL, 36.0 mmol, 3.0 equiv.). After workup, the crude mixture was purified by flash column chromatography (cyclohexane/ethyl acetate 10:1) to give methyl (3-methylbut-2-en-1-yl) carbonate **2e** as a colorless liquid (951 mg, 55% yield). The characterization data are in accordance with the ones reported in the literature.^[150]

¹H NMR (300 MHz, CDCl₃) δ 5.38 (t, J = 1.5 Hz, 1H), 4.63 (d, J = 1.5 Hz, 2H), 3.77 (s, 3H), 1.76 (s, 3H), 1.73 (s, 3H).

^[151] Bai, X. dan; Wang, J.; He, Y. *Adv. Synth. Catal.* **2019**, *361*, 496–501.

2-Cyclohexen-1-yl methyl carbonate (2f)

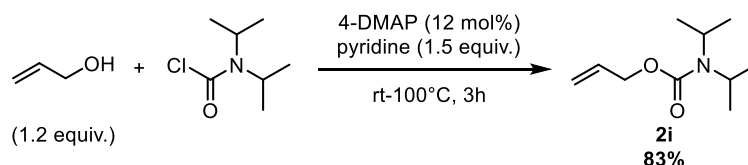


Prepared from 2-cyclohexen-1-ol **4f** (71.3 mg, 9.37 mmol, 1.0 equiv.), methyl chloroformate (2.17 mL, 28.1 mmol, 3.0 equiv.) and pyridine (2.27 mL, 28.1 mmol, 3.0 equiv.). After workup, the crude mixture was purified by flash column chromatography (cyclohexane/ethyl acetate 5:1) to give 2-cyclohexen-1-yl methyl carbonate **2f** as a colorless liquid (721 mg, 49% yield). The characterization data are in accordance with the ones reported in the literature.^[152]

¹H NMR (400 MHz, CDCl₃) δ 6.05-5.89 (m, 1H), 5.81-5.71 (m, 1H), 5.19-5.01 (m, 1H), 3.77 (s, 3H), 2.17-1.93 (m, 2H), 1.91-1.69 (m, 3H), 1.68-1.59 (m, 1H).

Synthesis of allyl *N,N*-di-*iso*-propylcarbamate (2i)

Allyl *N,N*-di-*iso*-propyl carbamate **2i** was prepared according to a procedure reported in the literature.^[153]



A round bottom flask was charged with allyl alcohol (0.38 mL, 4.80 mmol, 1.2 equiv.) and 4-DMAP (4.00 mg, 0.48 mmol, 12 mol%). The flask was placed under vacuum and backfilled with argon. The vacuum/argon cycles were repeated twice and pyridine (0.50 mL, 6.00 mmol, 1.5 equiv.) was added. *N,N*-di-*iso*-propyl carbamoyl chloride (655 mg, 4.00 mmol, 1.0 equiv.) was then introduced in one portion at rt and the mixture was heated to 100°C. After complete conversion as checked by TLC, the mixture was cooled to rt and quenched with 12 mL of an aqueous 1M solution of hydrochloric acid. The organoaqueous layer was extracted with 2 x 16 mL of ethyl acetate. The resulting organic layer was washed with 2x16 mL of water, dried over anhydrous magnesium sulfate and filtered. The filtrate was

^[152] Hatano, M.; Kamiya, S.; Ishihara, K. *Chem. Commun.* **2012**, *48*, 9465–9467.

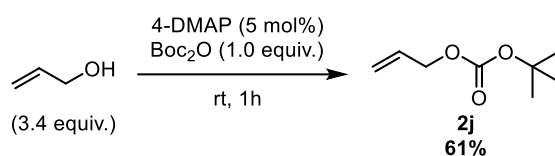
^[153] Sakakura, A.; Yamada, H.; Ishihara, K. *Asian J. Org. Chem.* **2012**, *1*, 133-137.

concentrated under reduced pressure to give pure allyl *N,N*-di-*iso*-propyl carbamate **2i** (619 mg, 83%) as a colorless oil. The characterization data are in accordance with the ones reported in the literature.^[75]

¹H NMR (300 MHz, CDCl₃) δ 5.95 (ddt, *J* = 17.2, 10.7, 5.5 Hz, 1H), 5.30 (dq, *J* = 17.2, 1.7 Hz, 1H), 5.19 (dq, *J* = 10.5, 1.4 Hz, 1H), 4.59 (dt, *J* = 5.5, 1.5 Hz, 2H), 3.92 (br. s, 2H), 1.21 (d, *J* = 6.8 Hz, 12H).

Synthesis of allyl *tert*-butyl carbonate (**2j**)

Allyl *tert*-butyl carbonate **2j** was prepared according to a procedure reported in the literature.^[154]



A two-neck round bottom flask equipped with a reflux condenser was charged with di-*tert*-butyl dicarbonate (10.0 g, 47.5 mmol, 1.0 equiv.). The flask was placed under vacuum and then backfilled with argon. The vacuum/argon cycles were repeated twice and allylic alcohol (10.0 mL, 147 mmol, 3.2 equiv.) was added. 4-DMAP (275 mg, 2.25 mmol, 5 mol%) was then introduced in one portion. Gas evolution started and lasted for about 1h. The reaction mixture was stirred at rt until conversion was found to be complete as checked by TLC. The crude mixture was directly purified by flash column chromatography on silica gel (cyclohexane/ethyl acetate 95:5) to give allyl *tert*-butyl carbonate **2j** (4.58 g, 61% yield) as a colorless oil. The characterization data are in accordance with the ones reported in the literature.^[154]

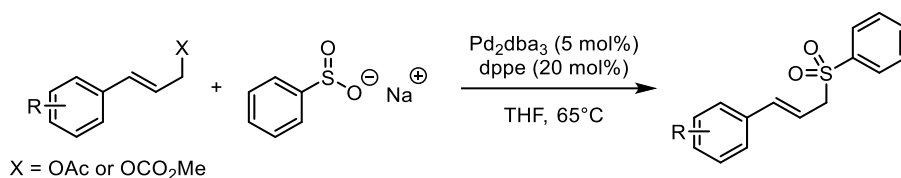
¹H NMR (300 MHz, CDCl₃) δ 5.93 (ddt, *J* = 17.2, 10.4, 5.8 Hz, 1H), 5.33 (dq, *J* = 17.2, 1.5 Hz, 1H), 5.24 (dq, *J* = 10.4, 1.3 Hz, 1H), 4.55 (dt, *J* = 5.8, 1.4 Hz, 2H), 1.49 (s, 9H).

^[154] Kraus, J. M.; Gits, H. C.; Silverman, R. B. *Tetrahedron Lett.* **2012**, 53, 1319-1322.

2.2. Pd(0)-catalyzed domino sulfonylation/allylation of allylacetates and - carbonates.

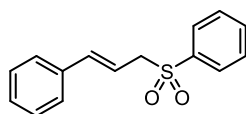
2.2.1. Studies on the sulfonylation and α -allylation of the domino sequence.

General procedure for the synthesis of cinnamyl sulfones



A sealed tube equipped with a stirring bar was charged with Pd₂dba₃ (22.9 mg, 2.50 x 10⁻² mmol, 5 mol%), dppe (39.8 mg, 0.10 mmol, 20 mol%) and sodium benzenesulfinate **5a** (0.50-0.55 mmol, 1.0-1.1 equiv.). The tube was placed under vacuum and then backfilled with argon. The vacuum/argon cycles were repeated twice and 2 to 5 mL of distilled THF (0.10-0.25M) was introduced. To this suspension was introduced cinnamyl acetate **1a** or (*E*)-3-(3,4-dimethoxyphenyl)allyl methyl carbonate **2c** (0.50 mmol, 1.0 equiv.) and the mixture was stirred at 65°C until conversion was complete as checked by TLC. After cooling to rt, the mixture was filtered over a pad of silica gel with 50 mL of ethyl acetate. The filtrate was concentrated under reduced pressure and the residue was purified by flash column chromatography on silica gel to give the desired product.

trans-Cinnamyl phenyl sulfone (**6a**).

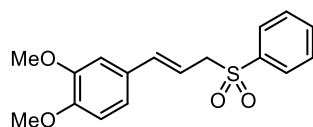


Prepared from cinnamyl acetate **1a** (88.1 mg, 0.50 mmol, 1.0 equiv.) and sodium benzenesulfinate **5a** (90.3 mg, 0.55 mmol, 1.1 equiv.). After workup, the crude mixture was purified by flash column chromatography (cyclohexane/ethyl acetate 5:1) to give *trans*-cinnamyl phenyl sulfone **6a** as a colorless solid (25.4 mg, 93% yield). The characterization data are in accordance with the ones reported in the literature.^[72]

¹H NMR (300 MHz, CDCl₃) δ 7.94-7.82 (m, 2H), 7.64 (t, *J* = 7.3 Hz, 1H), 7.54 (dd, *J* = 8.3, 6.9 Hz, 2H),

7.36-7.21 (m, 5H), 6.37 (d, $J = 15.9$ Hz, 1H), 6.10 (dt, $J = 15.6, 7.5$ Hz, 1H), 3.95 (dd, $J = 7.6, 1.1$ Hz, 2H).

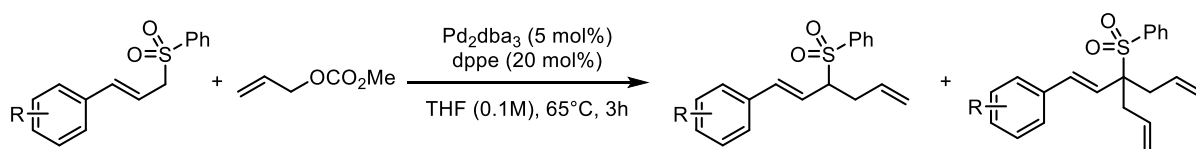
***trans*-3,4-Dimethoxycinnamyl phenyl sulfone (6b).**



Prepared from 2-propen-1-ol, (*E*)-3-(3,4-dimethoxyphenyl)allyl methyl carbonate **2c** (82.1 mg, 0.50 mmol, 1.0 equiv.) and sodium benzenesulfinate **5a** (82.1 mg, 0.50 mmol, 1.0 equiv.). After workup, the crude mixture was purified by flash column chromatography (cyclohexane/ethyl acetate 2:1) to give *trans*-3,4-dimethoxyl cinnamyl phenyl sulfone **6b** as a colorless solid (151 mg, 95% yield).

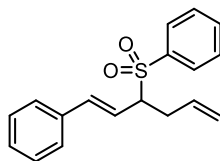
$^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.92-7.77 (m, 2H), 7.68-7.53 (m, 1H), 7.53-7.32 (m, 2H), 6.84-6.71 (m, 3H), 6.34-6.20 (m, 1H), 5.95 (dt, $J = 15.5, 7.6$ Hz, 1H), 3.91 (dd, $J = 7.6, 1.2$ Hz, 2H), 3.83 (s, $2 \times 3\text{H}$); $^{13}\text{C NMR}$ (101 MHz, CDCl_3) δ 149.4, 148.9, 138.8, 138.3, 133.5, 128.9 (2C), 128.7, 128.3 (2C), 120.0, 112.6, 110.9, 108.7, 60.3, 55.70, 55.67; **HRMS** (ESI) m/z : $[\text{M}+\text{Na}]^+$ Calcd for $\text{C}_{17}\text{H}_{18}\text{O}_4\text{SNa}$ 341.0818. Found 341.0819.

General procedure for the α -allylation of allyl sulfones



A sealed tube equipped with a stirring bar was charged with Pd_2dba_3 (22.9 mg, 2.50×10^{-2} mmol, 5 mol%), dppe (39.8 mg, 0.10 mmol, 20 mol%) and the allylic sulfone **6a** or **6b** (0.50 mmol, 1.0 equiv.). The tube was placed under vacuum and then backfilled with argon. The vacuum/argon cycles were repeated twice and 5 mL of distilled THF (0.1M) was introduced. To this suspension was added 110 μL of allyl methyl carbonate **2g** (1.00 mmol, 2.0 equiv.) and the mixture was stirred at 65°C until conversion was complete as checked by TLC. The mixture was filtered over a pad of silica gel with 50 mL of ethyl acetate. The filtrate was concentrated under reduced pressure and the residue was purified by flash column chromatography on silica gel to give the desired products.

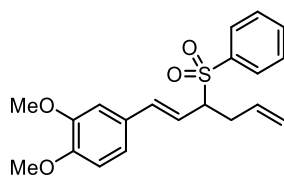
(E)-((1-phenylhexa-1,5-dien-3-yl)sulfonyl)benzene (7a)



Prepared from cinnamyl sulfone **6a** (129.1 mg, 0.50 mmol, 1.0 equiv.) was reacted with allyl methyl carbonate **2g** (113 μ L, 1.00 mmol, 2.0 equiv.). After workup, the crude mixture was purified by flash column chromatography (cyclohexane/ethyl acetate 8:1) to give *(E)*-((1-phenylhexa-1,5-dien-3-yl)sulfonyl)benzene **7a** as a colorless liquid (95.4 mg, 64% yield).

$^1\text{H NMR}$ (300 MHz, CDCl_3) δ 7.92-7.77 (m, 2H), 7.67-7.56 (m, 1H), 7.55-7.42 (m, 2H), 7.35-7.19 (m, 5H), 6.23 (d, $J = 15.9$ Hz, 1H), 5.99-5.85 (m, 1H), 5.80-5.58 (m, 1H), 5.24-4.97 (m, 2H), 3.72 (td, $J = 10.1, 3.6$ Hz, 1H), 2.98 (ddd, $J = 14.2, 7.0, 3.7$ Hz, 1H), 2.63-2.50 (m, 1H); $^{13}\text{C NMR}$ (75 MHz, CDCl_3) δ 138.3, 137.3, 135.7, 133.7, 132.9, 129.2 (2C), 128.8 (2C), 128.6 (2C), 128.4, 126.5 (2C), 120.7, 118.5, 68.9, 31.9; **HRMS** (ESI) m/z : $[\text{M}+\text{NH}_4]^+$ Calcd for $\text{C}_{18}\text{H}_{18}\text{O}_2\text{SNH}_4$ 316.1366. Found 316.1371.

(E)-1,2-dimethoxy-4-(3-(phenylsulfonyl)hexa-1,5-dien-1-yl)benzene (7b)

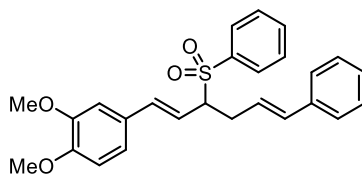


Prepared from *trans*-3,4-dimethoxyl cinnamyl phenyl sulfone **6b** (159 mg, 0.50 mmol, 1.0 equiv.) was reacted with allyl methyl carbonate **2g** (113 μ L, 1.00 mmol, 2.0 equiv.). After workup, the crude mixture was purified by flash column chromatography (cyclohexane/ethyl acetate 5:1) to give *(E)*-1,2-dimethoxy-4-(3-(phenylsulfonyl)hexa-1,5-dien-1-yl)benzene **7b** as a colorless liquid (111 mg, 62% yield).

$^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.92-7.78 (m, 2H), 7.70-7.58 (m, 1H), 7.55-7.46 (m, 2H), 6.87-6.70 (m, 3H), 6.19 (d, $J = 15.8$ Hz, 1H), 5.92-5.64 (m, 2H), 5.22-5.03 (m, 2H), 3.91 (s, 3H), 3.90 (s, 3H), 3.72 (td, $J = 10.2, 3.6$ Hz, 1H), 3.05-2.90 (m, 1H), 2.64-2.47 (m, 1H); $^{13}\text{C NMR}$ (101 MHz, CDCl_3) δ 153.2, 149.5, 149.1, 138.1, 137.4, 133.6, 133.0, 129.3 (2C), 128.9 (2C), 120.1, 118.4, 118.3, 111.0, 108.8, 69.1, 55.9, 55.9, 32.1; **HRMS** (ESI) m/z : $[\text{M}+\text{Na}]^+$ Calcd for $\text{C}_{20}\text{H}_{22}\text{O}_4\text{SNa}$ 381.1131. Found 381.1132.

2.2.2. Studies for the elimination of the allylsulfone 7c

1,2-dimethoxy-4-((1E,5E)-6-phenyl-3-(phenylsulfonyl)hexa-1,5-dien-1-yl)benzene (7c)

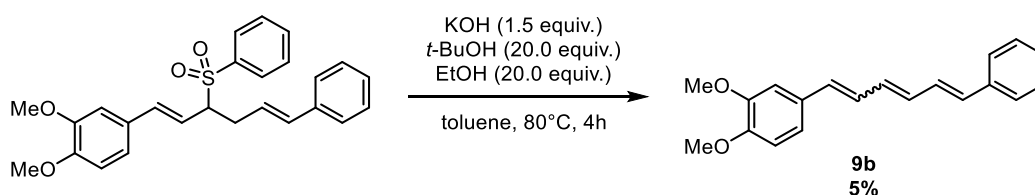


Prepared from *trans*-3,4-dimethoxyl cinnamyl phenyl sulfone **6b** (159 mg, 0.50 mmol, 1.0 equiv.) and cinnamyl methyl carbonate **2a** (192 mg, 1.00 mmol, 2.0 equiv.). After workup, the crude mixture was purified by flash column chromatography (cyclohexane/ethyl acetate 4:1) to give *1,2-dimethoxy-4-((1E,5E)-6-phenyl-3-(phenylsulfonyl)hexa-1,5-dien-1-yl)benzene 7c as a colorless liquid (149.8 mg, 69% yield).*

¹H NMR (400 MHz, CDCl₃) δ 7.96-7.85 (m, 2H), 7.65-7.58 (m, 1H), 7.55-7.47 (m, 2H), 7.33-7.18 (m, 5H), 6.91-6.74 (m, 3H), 6.50 (d, *J* = 15.8 Hz, 1H), 6.24 (d, *J* = 15.8 Hz, 1H), 6.19-6.01 (m, 1H), 5.97-5.78 (m, 1H), 3.87 (d, *J* = 2.6 Hz, 6H), 3.25-3.03 (m, 1H), 2.87-2.53 (m, 1H), 2.07-2.03 (m, 1H); ¹³C NMR (101 MHz, CDCl₃) δ 149.5, 149.0, 138.2, 137.4, 136.8, 133.7, 133.4, 129.2 (2C), 128.9 (2C), 128.8, 128.5 (2C), 127.5, 126.2 (2C), 124.4, 120.1, 118.2, 111.0, 108.9, 69.4, 55.9, 55.8, 31.4; HRMS (ESI) *m/z*: [M+Na]⁺ Calcd for C₂₆H₂₆O₄SNa 457.1444. Found 457.1444.

2-dimethoxy-4-((5E)-6-phenylhexa-1,3,5-trien-1-yl)benzene (9b)

2-dimethoxy-4-((5E)-6-phenylhexa-1,3,5-trien-1-yl)benzene **9b** was prepared according to a procedure reported in the literature.^[95]



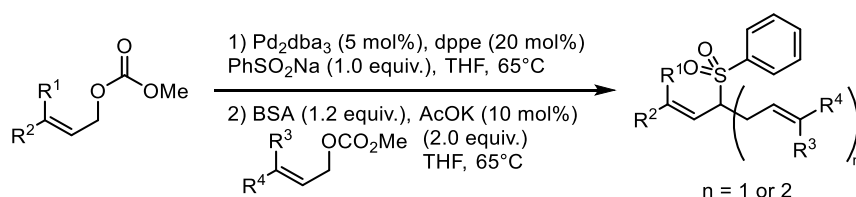
A round bottom flask was charged with **7c** (217.1 mg, 0.5 mmol, 1.0 equiv.) and KOH (42.1 mg, 0.75

mmol, 1.5 equiv.). The flask was placed under vacuum and backfilled with argon. The vacuum/argon cycles were repeated twice and toluene (7 mL) was then introduced in one portion at rt. *Tert*-butanol (1.00 mL, 10.0 mmol, 20.0 equiv.) and ethanol (0.60 mL, 10.0 mmol, 20.0 equiv.) were then added and the mixture was heated at 80°C. After complete conversion as checked by TLC, the mixture was cooled to rt and most of solvent was removed under reduced pressure. The residue was dissolved in ethyl acetate and washed with a 1 M aqueous hydrochloric acid solution. The aqueous layer was extracted with ethyl acetate (15 mL x 4). The combined organic layers were dried over anhydrous magnesium sulfate and filtered. The filtrate was concentrated under reduced pressure and the residue was purified by flash column chromatography (cyclohexane/ethyl acetate 50:1) to give *2-dimethoxy-4-((5E)-6-phenylhexa-1,3,5-trien-1-yl)benzene 9b* (7.3 mg, 5%) as a colorless oil.

¹H NMR (400 MHz, CDCl₃) δ 7.45-7.38 (m, 2H), 7.35-7.29 (m, 2H), 7.24-7.18 (m, 1H), 6.96 (d, *J* = 8.2 Hz, 2H), 6.93-6.85 (m, 1H), 6.83 (d, *J* = 8.3 Hz, 1H), 6.80-6.73 (m, 1H), 6.61-6.54 (m, 2H), 6.54-6.46 (m, 2H), 3.96-3.86 (m, 6H); ¹³C NMR (101 MHz, CDCl₃) δ 149.1, 149.0, 137.5, 133.7, 132.7, 132.5, 132.2, 130.6, 129.3, 128.6 (2C), 127.4, 127.3, 126.3 (2C), 119.8, 111.3, 108.6, 55.9, 55.8; HRMS (ESI) *m/z*: [M+H]⁺ Calcd for C₂₀H₂₁O₂ 293.1536. Found 293.1536.

2.2.3. Synthesis and characterization of diallylated allylsulfones

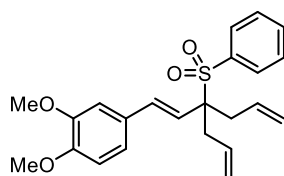
General procedure for the Pd(0)-catalyzed triple allylation domino sequence



A sealed tube equipped with a stirring bar was charged with Pd₂dba₃ (22.9 mg, 2.50 x 10⁻² mmol, 5 mol%), dppe (39.8 mg, 0.10 mmol, 20 mol%) and sodium benzenesulfinate **5a** (82.1 mg, 0.50 mmol, 1.0 equiv.). The tube was placed under vacuum and then backfilled with argon. The vacuum/argon cycles were repeated twice and 5 mL of distilled THF (0.1 M) was introduced. To this suspension was added the first allyl carbonate (1.00 mmol, 2.0 equiv.) and the mixture was stirred at 65°C until conversion was complete as checked by TLC. The mixture was cooled to rt and the second allyl carbonate (1.00 mmol, 2.0 equiv.) was introduced followed by BSA (145 μL, 0.60 mmol, 1.2 equiv.) and

potassium acetate (4.50 mg, 0.05 mmol, 10 mol%). The mixture was stirred at 65°C until conversion of the allylsulfone intermediate was complete as checked by TLC. The mixture was filtered over a pad of silica gel with 50 mL of ethyl acetate. The filtrate was concentrated under reduced pressure and the residue was purified by flash column chromatography on silica gel to give the desired products.

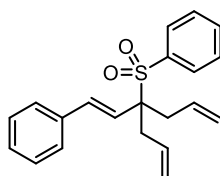
(*E*)-4-(3-allyl-3-(phenylsulfonyl)hexa-1,5-dien-1-yl)-1,2-dimethoxybenzene (8b)



Prepared from (*E*)-3-(3,4-dimethoxyphenyl)allyl methyl carbonate **2c** (126 mg, 0.50 mmol, 1.0 equiv.) was reacted with sodium benzenesulfinate **5a** (82.1 mg, 0.50 mmol, 1.0 equiv.) and allyl methyl carbonate **2g** (113 μ L, 1.00 mmol, 2.0 equiv.). After workup, the crude mixture was purified by flash column chromatography (cyclohexane/ethyl acetate 4:1) to give (*E*)-4-(3-allyl-3-(phenylsulfonyl)hexa-1,5-dien-1-yl)-1,2-dimethoxybenzene **8b** as a colorless liquid (95.5 mg, 48% yield).

$^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.83-7.72 (m, 2H), 7.63-7.57 (m, 1H), 7.50-7.41 (m, 2H), 6.82 (d, $J = 1.1$ Hz, 3H), 6.20 (d, $J = 16.4$ Hz, 1H), 6.02-5.84 (m, 3H), 5.23-5.08 (m, 4H), 3.89 (s, 6H), 2.89-2.79 (m, 2H), 2.74-2.63 (m, 2H); $^{13}\text{C NMR}$ (101 MHz, CDCl_3) δ 149.5, 149.1, 135.7, 134.8, 133.6, 131.8 (2C), 130.8 (2C), 129.0, 128.3 (2C), 123.7, 119.9, 119.4 (2C), 111.1, 108.9, 69.4, 55.9, 55.9, 35.6 (2C); **HRMS** (ESI) m/z : $[\text{M}+\text{Na}]^+$ Calcd for $\text{C}_{23}\text{H}_{26}\text{O}_4\text{SNa}$ 421.1444. Found 421.1443.

(*E*)-(3-allyl-3-(phenylsulfonyl)hexa-1,5-dien-1-yl)benzene (8a)

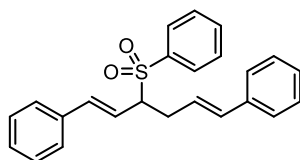


Prepared from cinnamyl methyl carbonate **2a** (96.1 mg, 0.50 mmol, 1.0 equiv.), sodium benzenesulfinate **5a** (82.1 mg, 0.50 mmol, 1.0 equiv.) and allyl methyl carbonate **2g** (113 μ L, 1.00 mmol,

2.0 equiv.). After workup, the crude mixture was purified by flash column chromatography (cyclohexane/ethyl acetate 8:1) to give (*E*)-3-allyl-3-(phenylsulfonyl)hexa-1,5-dien-1-yl)benzene **8a** as a colorless liquid (82.8 mg, 49% yield).

¹H NMR (400 MHz, CDCl₃) δ 7.78 (dt, *J* = 8.1, 1.1 Hz, 2H), 7.65-7.58 (m, 1H), 7.50-7.42 (m, 2H), 7.35-7.24 (m, 5H), 6.27 (d, *J* = 16.5 Hz, 1H), 6.10 (d, *J* = 16.5 Hz, 1H), 6.00-5.86 (m, 2H), 5.32-5.03 (m, 4H), 2.86 (ddt, *J* = 14.7, 7.2, 1.3 Hz, 2H), 2.70 (ddt, *J* = 14.7, 7.0, 1.5 Hz, 2H); ¹³C NMR (101 MHz, CDCl₃) δ 143.3, 136.0, 135.6, 135.1, 133.7, 131.7, 130.8 (2C), 129.0, 128.7 (2C), 128.4, 128.4 (2C), 126.6 (2C), 126.1, 119.5, 69.3, 35.6(2C); HRMS (ESI) *m/z*: [M+NH₄]⁺ Calcd for C₂₁H₂₂O₂SNH₄ 356.1679. Found 356.1691.

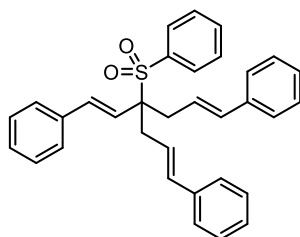
((1*E*,5*E*)-3-(phenylsulfonyl)hexa-1,5-diene-1,6-diyl)dibenzene (7f)



Prepared from cinnamyl methyl carbonate **2a** (96.1 mg, 0.50 mmol, 1.0 equiv.), sodium benzenesulfinate **5a** (82.1 mg, 0.50 mmol, 1.0 equiv.) and again cinnamyl methyl carbonate **2a** (192 mg, 1.00 mmol, 2.0 equiv.) during step 2 of the domino sequence. After workup, the crude mixture was purified by flash column chromatography (cyclohexane/ethyl acetate 5:1) to give ((1*E*,5*E*)-3-(phenylsulfonyl)hexa-1,5-diene-1,6-diyl)dibenzene **7f** as a colorless liquid (20.6 mg, 11% yield).

¹H NMR (300 MHz, CDCl₃) δ 7.97-7.77 (m, 2H), 7.68-7.56 (m, 1H), 7.56-7.49 (m, 2H), 7.37-7.19 (m, 10H), 6.51 (dd, *J* = 15.7, 1.5 Hz, 1H), 6.29 (d, *J* = 16.0 Hz, 1H), 6.12 (ddd, *J* = 15.3, 7.1, 7.1 Hz, 1H), 6.06-5.96 (m, 1H), 3.87-3.73 (m, 1H), 3.21-3.06 (m, 1H), 2.86-2.59 (m, 1H); ¹³C NMR (101 MHz, CDCl₃) δ 138.5, 137.4, 136.8, 135.7, 133.8, 133.6, 129.3 (2C), 128.9 (2C), 128.7 (2C), 128.5 (2C), 128.5, 127.5, 126.6 (2C), 126.3 (2C), 124.4, 120.7, 69.3, 31.4; HRMS (ESI) *m/z*: [M+NH₄]⁺ Calcd for C₂₄H₂₂O₂SNH₄ 392.1679. Found 392.1676.

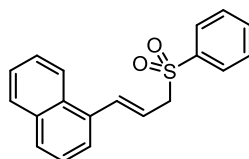
((1E,5E)-3-cinnamyl-3-(phenylsulfonyl)hexa-1,5-diene-1,6-diyl)dibenzene (8f)



Prepared from cinnamyl methyl carbonate **2a** (96.1 mg, 0.50 mmol, 1.0 equiv.), sodium benzenesulfinate **5a** (82.1 mg, 0.50 mmol, 1.0 equiv.) and again cinnamyl methyl carbonate **2a** (192 mg, 1.00 mmol, 2.0 equiv.) during step 2 of the domino sequence. After workup, the crude mixture was purified by flash column chromatography (cyclohexane/ethyl acetate 5:1) to give ((1E,5E)-3-cinnamyl-3-(phenylsulfonyl)hexa-1,5-diene-1,6-diyl)dibenzene **8f** as a colorless liquid (27.0 mg, 11% yield).

¹H NMR (400 MHz, CDCl₃) δ 7.85 (d, *J* = 8.1 Hz, 2H), 7.69-7.61 (m, 1H), 7.50 (t, *J* = 7.7 Hz, 2H), 7.41-7.22 (m, 15H), 6.51 (d, *J* = 15.7 Hz, 2H), 6.44-6.29 (m, 3H), 6.23 (d, *J* = 16.4 Hz, 1H), 3.08 (dd, *J* = 14.7, 7.3 Hz, 2H), 2.93 (dd, *J* = 14.7, 6.9 Hz, 2H); ¹³C NMR (101 MHz, CDCl₃) δ 137.0, 136.0, 135.7, 135.5, 134.6 (2C), 133.8, 130.9, 128.8 (2C), 128.7, 128.6 (4C), 128.5 (2C), 128.4, 128.3, 127.5 (2C), 126.7 (2C), 126.3 (4C), 125.8, 123.3 (2C), 70.1, 35.3 (2C); HRMS (ESI) *m/z*: [M+NH₄]⁺ Calcd for C₃₃H₃₀O₂SNH₄ 508.2305. Found 508.2305.

(E)-1-(3-(phenylsulfonyl)prop-1-en-1-yl)naphthalene (6ac)

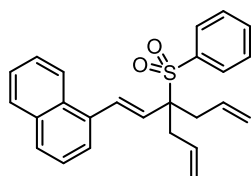


Prepared from methyl (2E)-3-(1-naphthalenyl)-2-propen-1-yl carbonate **2d** (121 mg, 0.50 mmol, 1.0 equiv.) and sodium benzenesulfinate **5a** (82.1 mg, 0.50 mmol, 1.0 equiv.). After workup, the crude mixture was purified by flash column chromatography (cyclohexane/ethyl acetate 4:1) to give (E)-1-(3-(phenylsulfonyl)prop-1-en-1-yl)naphthalene **6ac** as a colorless solid (35.4 mg, 23% yield). The characterization data are in accordance with the ones reported in the literature.^[155]

^[155] Dana, D.; Davalos, A. R.; Subramaniam, G.; Afzal, N.; Hersh, W. H.; Kumar, S. *Tetrahedron Lett.* **2013**, *54*, 2717–2721.

$^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.96-7.89 (m, 1H), 7.86-7.76 (m, 2H), 7.72-7.62 (m, 2H), 7.59-7.52 (m, 2H), 7.52-7.38 (m, 5H), 7.09 (d, $J = 15.6$ Hz, 1H), 6.14 (dt, $J = 15.4, 7.6$ Hz, 1H), 4.08 (dd, $J = 7.6, 1.3$ Hz, 2H).

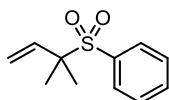
(*E*)-1-(3-allyl-3-(phenylsulfonyl)hexa-1,5-dien-1-yl)naphthalene (8g)



Prepared from methyl (*2E*)-3-(1-naphthalenyl)-2-propen-1-yl carbonate **2d** (121mg, 0.50 mmol, 1.0 equiv.), sodium benzenesulfinate **5a** (82.1 mg, 0.50 mmol, 1.0 equiv.) and allyl methyl carbonate **2g** (113 μL , 1.00 mmol, 2.0 equiv.). After workup, the crude mixture was purified by flash column chromatography (cyclohexane/ethyl acetate 4:1) to give (*E*)-1-(3-allyl-3-(phenylsulfonyl)hexa-1,5-dien-1-yl)naphthalene **8g** as a colorless liquid (21.3 mg, 11% yield).

$^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.90-7.79 (m, 4H), 7.72 (d, $J = 8.3$ Hz, 1H), 7.66-7.58 (m, 2H), 7.53-7.40 (m, 5H), 7.06 (d, $J = 16.0$ Hz, 1H), 6.18 (d, $J = 16.2$ Hz, 1H), 6.03 (ddt, $J = 17.3, 10.4, 7.1$ Hz, 2H), 5.28-5.20 (m, 4H), 2.94 (dd, $J = 14.8, 7.0$ Hz, 2H), 2.82 (dd, $J = 14.8, 7.2$ Hz, 2H); $^{13}\text{C NMR}$ (101 MHz, CDCl_3) δ 135.6, 134.0, 133.7, 133.5, 132.7, 131.8, 131.0, 130.8 (2C), 129.3, 128.7, 128.6, 128.6 (3C), 126.2, 126.0, 125.6, 124.1, 123.5, 119.7 (2C), 69.7, 35.8 (2C); **HRMS** (ESI) m/z : $[\text{M}+\text{Na}]^+$ Calcd for $\text{C}_{25}\text{H}_{24}\text{O}_2\text{SNa}$ 411.1389. Found 411.1389.

(2-Methyl-but-3-ene-2-sulfonyl)-benzene (6c)

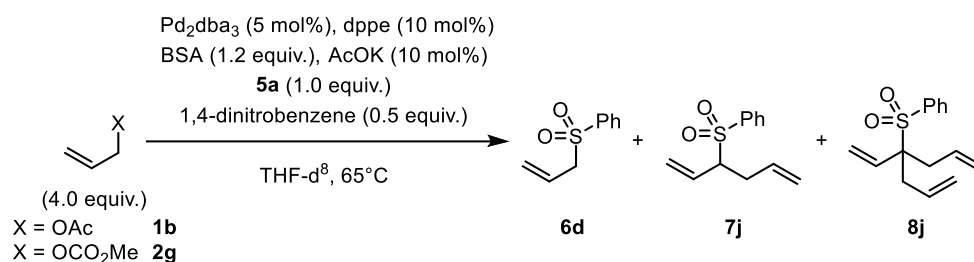


Prepared from methyl (3-methylbut-2-en-1-yl) carbonate **2e** (72.1 mg, 0.50 mmol, 1.0 equiv.) and sodium benzenesulfinate **5a** (82.1 mg, 0.50 mmol, 1.0 equiv.). After workup, the crude mixture was purified by flash column chromatography (cyclohexane/ethyl acetate 7:1) to give (2-methyl-but-3-ene-2-sulfonyl)-benzene **6c** as a colorless solid (67.2 mg, 64% yield). The characterization data are in

accordance with the ones reported in the literature.^[156]

¹H NMR (400 MHz, CDCl₃) δ 7.87-7.77 (m, 2H), 7.63 (t, *J* = 7.4 Hz, 1H), 7.51 (t, *J* = 7.7 Hz, 2H), 6.03 (dd, *J* = 17.4, 10.7 Hz, 1H), 5.27 (d, *J* = 10.7 Hz, 1H), 5.08 (d, *J* = 17.4 Hz, 1H), 1.45 (s, 6H).

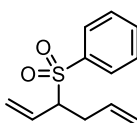
2.2.4. Description of the kinetic study and characterization of the products obtained from the pure domino sequence.



A sealed tube equipped with a magnetic stirrer was charged with 9.2 mg (0.01 mmol, 5 mol%) of Pd₂(dba)₃, 15.9 mg (0.04 mmol, 20 mol%) of dppe, 1.8 mg (0.02 mmol, 10 mol%) of AcOK, 16.4 mg (0.20 mmol, 1.0 equiv.) of sodium benzenesulfinate **5a** and 8.4 mg (0.05 mmol, 0.5 equiv.) of 1,4-dinitrobenzene. The tube was placed under vacuum and then backfilled with argon. The vacuum/argon cycles were repeated twice and 2.0 mL of dry THF-d⁸ (0.1 M) were introduced. To this suspension was added allyl methyl carbonate or acetate **2g** or **1b** (0.8 mmol, 4.0 equiv.) followed by BSA (59 μL, 0.24 mmol, 1.2 equiv.) and the mixture was stirred at 65°C. The progress of the reaction was monitored every hour by quantitative ¹H NMR using the 1,4-dinitrobenzene introduced as an internal standard.

In addition, for their characterization, allylated products resulting from the pure domino sequence were isolated and characterized. Allyl phenyl sulfone is commercially available and its detection on ¹H NMR could be done by comparison with a ¹H NMR of a commercial sample.

(Hexa-1,5-dien-3-ylsulfonyl)benzene (**7j**)

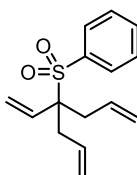


^[156] Jegelka, M.; Plietker, B. *Org. Lett.* **2009**, *11*, 3462–3465.

Prepared from allyl methyl carbonate **2g** (92.9 mg, 0.80 mmol, 4.0 equiv.) and sodium benzenesulfinate **5a** (32.8 mg, 0.20 mmol, 1.0 mmol). After workup, the crude mixture was purified by flash column chromatography (cyclohexane/ethyl acetate 10:1) to give (hexa-1,5-dien-3-ylsulfonyl)benzene **7j** as a colorless liquid (18.6 mg, 42% yield). The characterization data are in accordance with the ones reported in the literature.^[157]

¹H NMR (400 MHz, CDCl₃) δ 7.89-7.76 (m, 2H), 7.71-7.58 (m, 1H), 7.58-7.47 (m, 2H), 5.71-5.56 (m, 2H), 5.29 (d, *J* = 10.2 Hz, 1H), 5.17-4.92 (m, 3H), 3.57 (ddd, *J* = 12.8, 9.4, 3.6 Hz, 1H), 2.95-2.77 (m, 1H), 2.56-2.14 (m, 1H).

((4-vinylhepta-1,6-dien-4-yl)sulfonyl)benzene (**8j**)



Prepared from allyl methyl carbonate **2g** (92.8 mg, 0.80 mmol, 4.0 equiv.) and sodium benzenesulfinate **5a** (32.8 mg, 0.20 mmol, 1.0 equiv.). After workup, the crude mixture was purified by flash column chromatography (cyclohexane/ethyl acetate 10:1) to give ((4-vinylhepta-1,6-dien-4-yl)sulfonyl)benzene **8j** as a colorless liquid (7.30 mg, 14% yield).

¹H NMR (300 MHz, CDCl₃) δ 7.89-7.81 (m, 2H), 7.65 (dd, *J* = 7.9, 1.9 Hz, 1H), 7.54 (dd, *J* = 8.4, 7.0 Hz, 2H), 6.01-5.77 (m, 3H), 5.40 (d, *J* = 11.0 Hz, 1H), 5.23-5.02 (m, 5H), 2.74 (dd, *J* = 14.7, 7.2 Hz, 2H), 2.60 (dd, *J* = 14.8, 7.1 Hz, 2H); ¹³C NMR (101 MHz, CDCl₃) δ 135.5, 134.9, 133.7, 131.6 (2C), 130.8 (2C), 128.4 (2C), 120.8, 119.4 (2C), 69.4, 34.9 (2C); HRMS (ESI) *m/z*: [M+Na]⁺ Calcd for C₁₅H₁₈O₂SNa 285.0920, Found 285.0920.

^[157] Jiajing, T.; Tianyu, Z.; Kun, X.; Changyao, L. *Org. Biomol. Chem.* **2017**, *15*, 4946–4950.

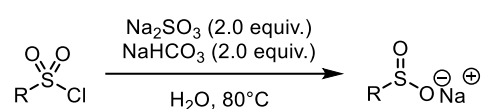
3. Chapter 4: Synthesis of allylsulfones by palladium-catalyzed allylic C-H activation

3.1. Synthesis and characterization of starting materials.

3.1.1. Synthesis of sodium sulfinates.

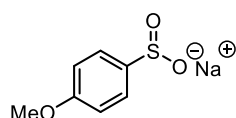
Langlois' reagent (sodium trifluoromethanesulfinate) **5n** and sulfinates **5a** and **5b** were purchased from commercial sources. Sodium sulfinates were prepared according to a procedure reported in the literature.^[158]

General procedure for the synthesis of sodium sulfinates.



A round bottomed flask equipped with a magnetic stirring bar was charged with 5.04 g (40.0 mmol, 2.0 equiv.) of sodium sulfite, 3.36 g (40.0 mmol, 2.0 equiv.) of sodium bicarbonate, the sulfonyl chloride (20.0 mmol, 1.0 equiv.) and 20 mL of water. The flask was then equipped with a condenser and the reaction mixture was heated to 80°C for 4h. The crude mixture was then cooled to rt and the solvent was concentrated under reduced pressure. The resulting residue was suspended in 25 mL of ethanol and the suspension was filtered over Büchner. The solid was washed with 25 mL of ethanol. The filtrate was then concentrated under reduced pressure to give the desired sulfinates.

Sodium 4-methoxybenzene sulfinate (**5c**).



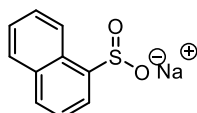
Prepared from 4-methoxybenzenesulfonyl chloride (4.13 g, 20.0 mmol), sodium sulfite (5.04 g, 40.0 mmol) and sodium bicarbonate (3.36 g, 40.0 mmol) in 20 mL of water. After workup, sodium 4-

^[158] a) Meyer, A. U.; Straková, K.; Slanina, T.; König, B. *Chem. Eur. J.* **2016**, *22*, 8694-8699; b) Kim, W.; Kim, H. Y.; Oh, K. *Org. Lett.* **2020**, *22*, 6319-6323.

methoxybenzene sulfinate **5c** was obtained as a colorless solid (3.90 g, quantitative yield). The characterization data are in accordance with the ones reported in the literature.^[158a]

¹H NMR (D₂O, 400 MHz) δ 7.45 (d, *J* = 8.7 Hz, 2H), 6.94 (d, *J* = 8.8 Hz, 2H), 3.72 (s, 3H).

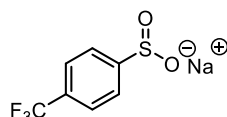
Sodium α-naphtalene sulfinate (**5g**).



Prepared from α-naphtalene sulfonyl chloride (1.13 g, 5.00 mmol), sodium sulfite (1.26 g, 10.0 mmol) and sodium bicarbonate (840 mg, 10.0 mmol) in 5 mL of water. After workup, sodium α-naphtalene sulfinate **5g** was obtained as a colorless solid (375 mg, 70% yield). The characterization data are in accordance with the ones reported in the literature.^[159]

¹H NMR (D₂O, 400 MHz) δ 8.65 (d, *J* = 8.4 Hz, 1H), 8.17-7.96 (m, 3H), 7.76-7.63 (m, 3H).

Sodium 4-trifluoromethylbenzene sulfinate (**5e**)

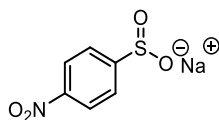


Prepared from 4-trifluoromethylbenzene sulfonyl chloride (2.21 g, 10.0 mmol), sodium sulfite (2.52 g, 20.0 mmol) and sodium bicarbonate (1.68 g, 20.0 mmol) in 10 mL of water. After workup, sodium 4-trifluorobenzene sulfinate **5e** was obtained as a colorless solid (2.05 g, 88% yield).

m.p. 297°C (begins to become a brown solid); ¹H NMR (CD₃OD, 300 MHz) δ 7.83 (d, *J* = 8.0 Hz, 2H), 7.72 (d, *J* = 8.1 Hz, 2H); ¹³C NMR (CD₃OD, 75 MHz), δ 161.5, 132.3 (q, *J* = 32.0 Hz), 126.4 (q, *J* = 3.9 Hz, 2C), 126.0 (2C), 125.6 (q, *J* = 271.3 Hz); ¹⁹F NMR (CD₃OD, 282.2 MHz) δ -63.92; **IR:** ν (cm⁻¹) 3401, 1323, 1139, 1012, 837; **HRMS** (ESI): *m/z* calculated for C₇H₄F₃O₂S [M]⁻ 208.9890, found: 208.9894.

^[159] Higham, J. I.; Bull, J. A. *Chem. Commun.* **2020**, 56, 4587-4590.

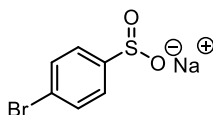
Sodium 4-nitrobenzene sulfinate (**5d**).



Prepared from 4-nitrobenzene sulfonyl chloride (4.43 g, 20.0 mmol), sodium sulfite (5.04 g, 40.0 mmol) and sodium bicarbonate (3.36 g, 40.0 mmol) in 20 mL of water. After workup, sodium 4-nitrobenzene sulfinate **5d** was obtained as a colorless solid (1.64 g, 39% yield). The characterization data are in accordance with the ones reported in the literature.^[158b]

¹H NMR (D₂O, 300 MHz) δ 8.41 (d, *J* = 8.2 Hz, 2H), 7.89 (d, *J* = 8.1 Hz, 2H).

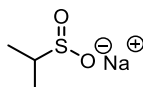
Sodium 4-bromobenzene sulfinate (**5f**).



Prepared from 4-bromobenzene sulfonyl chloride (2.56 g, 10.0 mmol), sodium sulfite (2.52 g, 20.0 mmol) and sodium bicarbonate (1.68 g, 20.0 mmol) in 10 mL of water. After workup, sodium 4-bromobenzene sulfinate **5f** was obtained as a colorless solid (4.98 g, >99% yield). The characterization data are in accordance with the ones reported in the literature.^[158a]

¹H NMR (D₂O, 300 MHz) δ 7.72 (d, *J* = 7.9 Hz, 2H), 7.56 (d, *J* = 8.3 Hz, 2H).

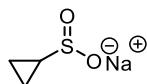
Sodium *iso*-propyl sulfinate (**5i**).



Prepared from *iso*-propyl sulfonyl chloride (1.43 g, 10.0 mmol), sodium sulfite (2.52 g, 20.0 mmol) and sodium bicarbonate (1.68 g, 20.0 mmol) in 10 mL of water. After workup, sodium *iso*-propyl sulfinate **5i** was obtained as a colorless solid (1.28 g, 98% yield). The characterization data are in accordance with the ones reported in the literature.^[158a]

¹H NMR (DMSO-*d*⁶, 300 MHz) δ 1.53 (hept, *J* = 6.9 Hz, 1H), 0.84 (d, *J* = 6.9 Hz, 6H).

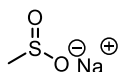
Sodium cyclopropyl sulfinate (5j).



Prepared from cyclopropyl sulfonyl chloride (1.41 g, 10.0 mmol), sodium sulfite (2.52 g, 20.0 mmol) and sodium bicarbonate (1.68 g, 20.0 mmol) in 10 mL of water. After workup, *sodium cyclopropyl sulfinate* **5j** was obtained as a colorless solid (1.30 g, >99% yield).

m.p. 282°C; **¹H NMR** (D₂O, 400 MHz) δ 1.98 (tt, *J* = 8.1, 5.1 Hz, 1H), 0.85-0.51 (m, 4H); **¹³C NMR** (D₂O, 100 MHz), δ 36.0, 0.6; **IR:** ν (cm⁻¹) 3342, 3024, 2993, 1011, 952; **HRMS** (ESI): *m/z* calculated for C₃H₅O₂S [M]⁻ 105.0016, found: 105.0017.

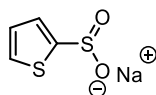
Sodium methyl sulfinate (5k).



Prepared from methyl sulfonyl chloride (0.78 mL, 10.0 mmol), sodium sulfite (2.52 g, 20.0 mmol) and sodium bicarbonate (1.68 g, 20.0 mmol) in 10 mL of water. After workup, *sodium methyl sulfinate* **5k** was obtained as a colorless solid (1.01 g, 99% yield).

m.p. 125°C (the sulfinate is very hygroscopic); **¹H NMR** (DMSO-*d*⁶, 300 MHz) δ 1.93 (s, 3H); **¹³C NMR** (DMSO-*d*⁶, 75 MHz), δ 50.3; **IR:** ν (cm⁻¹) 2906; **HRMS** (ESI): *m/z* calculated for CH₃O₂S [M]⁻ 78.9859, found: 78.9862.

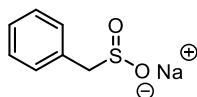
Sodium thiophene-2-sulfinate (5h).



Prepared from 2-thiophenesulfonyl chloride (0.91 g, 5.0 mmol), sodium sulfite (1.26 g, 10.0 mmol) and sodium bicarbonate (0.84 g, 10.0 mmol) in 5 mL of water. After workup, *sodium thiophene-2-sulfinate* **5h** was obtained as a colorless solid (0.74 g, 87% yield). The characterization data are in accordance with the ones reported in the literature.^[158]

$^1\text{H NMR}$ (400 MHz, CD_3OD) δ 7.48 (d, $J = 4.8$ Hz, 1H), 7.26 (d, $J = 3.5$ Hz, 1H), 7.08-7.00 (m, 1H).

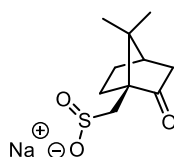
Sodium benzylsulfinate (**5l**).



Prepared from phenylmethanesulfonyl chloride (1.91 g, 10.0 mmol), sodium sulfite (2.52 g, 20.0 mmol) and sodium bicarbonate (1.68 g, 20.0 mmol) in 10 mL of water. After workup, *sodium benzyl sulfinate* **5l** was obtained as a colorless solid (1.78 g, 100% yield). The characterization data are in accordance with the ones reported in the literature.^[160]

$^1\text{H NMR}$ (D_2O , 400 MHz) δ 7.46-7.42 (m, 3H), 7.35-7.33 (m, 2H), 3.66 (s, 2H).

Sodium (1*S*,4*R*)-(7,7-dimethyl-2-oxobicyclo[2.2.1]-hept-1-yl)methanesulfinate (**5m**).



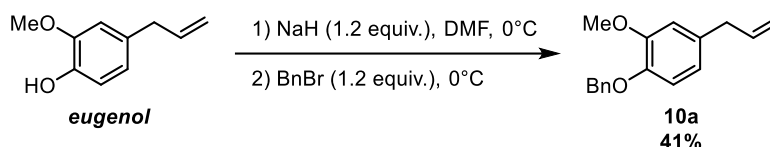
Prepared from (1*S*)-(+)-10-Camphorsulfonyl chloride (1.25 g, 5.0 mmol), sodium sulfite (1.26 g, 10.0 mmol) and sodium bicarbonate (0.84 g, 20.0 mmol) in 5 mL of water. After workup, *sodium (1*S*,4*R*)-(7,7-dimethyl-2-oxobicyclo[2.2.1]-hept-1-yl)methanesulfinate* **5m** was obtained as a colorless solid (0.80 g, 67% yield). The characterization data are in accordance with the ones reported in the literature.^[158]

$^1\text{H NMR}$ (400 MHz, CD_3OD) δ 2.78 (d, $J = 14.9$ Hz, 1H), 2.72-2.67 (m, 1H), 2.41-2.36 (m, 1H), 2.35-2.31 (m, 1H), 2.25-2.15 (m, 1H), 2.09-2.03 (m, 1H), 1.95-1.84 (m, 1H), 1.71-1.57 (m, 1H), 1.38-1.28 (m, 1H), 1.15 (s, 3H), 0.88 (s, 3H).

^[160] Day, J. D.; Neill, D. L.; Xu, S.; Xian, M. *Org. Lett.* **2017**, *19*, 3819-3822.

3.1.2. Synthesis of terminal alkenes

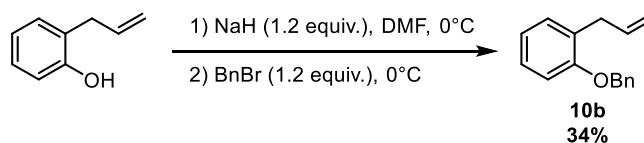
Synthesis of *O*-benzyleugenol (**10a**).



O-benzyleugenol **10a** was prepared according to a procedure reported in the literature.^[161] A round bottom flask was charged with 1.64 g (10.0 mmol, 1.0 equiv.) of eugenol. The flask was placed under vacuum before being backfilled with argon. The vacuum/argon cycles were repeated twice and 20 mL of anhydrous DMF were introduced. The solution was cooled down to 0°C (ice/water bath) and 288 mg (12.0 mmol, 1.2 equiv., 60 wt% in paraffin oil) of sodium hydride was added portionswise. The suspension was stirred at 0°C until gas evolution stopped and 2.05 g (12.0 mmol, 1.2 equiv.) of benzyl bromide were then introduced dropwise. The resulting mixture was stirred until conversion was complete as checked by TLC. Then the reaction was quenched by a slow addition of saturated aqueous NH₄Cl (50 mL) and then ethyl acetate (50 mL). The organic layer was collected, and the aqueous layer was extracted with ethyl acetate (3×50 mL). The combined extracts were washed with water (4×50 mL), brine (40 mL), dried over MgSO₄ and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (Cyclohexane/ethyl acetate 1:0 then 8:2), *O*-benzyleugenol **10a** was obtained as a yellowish oil (1.05 g, 41% yield). The characterization data is in accordance with the ones reported in the literature.^[162]

¹H NMR (CDCl₃, 400 MHz) δ 7.56-7.49 (m, 2H), 7.46-7.39 (m, 2H), 7.39-7.31 (m, 1H), 6.91 (d, *J* = 8.1 Hz, 1H), 6.83 (d, *J* = 2.1 Hz, 1H), 6.76 (dd, *J* = 8.1, 2.0 Hz, 1H), 6.05 (ddt, *J* = 16.8, 10.1, 6.7 Hz, 1H), 5.25-5.12 (m, 4H), 3.92 (s, 3H), 3.41 (d, *J* = 6.7 Hz, 2H).

Synthesis of 1-allyl-2-benzyloxybenzene (**10b**).



^[161] Sun, B. F.; Hong, R.; Kang, Y. B.; Deng, L. *J. Am. Chem. Soc.* **2009**, *131*, 10384-10385.

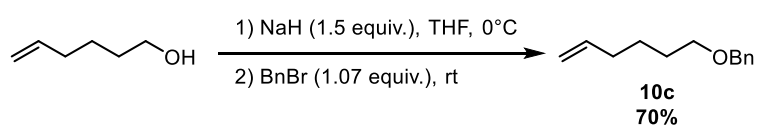
^[162] Eey, S. T. C.; Lear, M. J. *Org. Lett.* **2010**, *12*, 5510-5513.

1-allyl-2-benzyloxybenzene **10b** was prepared according to a procedure reported in the literature.^[161]

A round bottom flask was charged with 1.13 g (10.0 mmol, 1.0 equiv.) of 2-allylphenol. The flask was placed under vacuum before being backfilled with argon. The vacuum/argon cycles were repeated twice and 20 mL of anhydrous DMF were introduced. The solution was cooled down to 0°C (ice/water bath) and 288 mg (12.0 mmol, 1.2 equiv., 60 wt% in paraffin oil) of sodium hydride was added portionswise. The suspension was stirred at 0°C until gas evolution stopped and 2.05 g (12.0 mmol, 1.2 equiv.) of benzyl bromide were then introduced dropwise. The resulting mixture was stirred until conversion was complete as checked by TLC. Then the reaction was quenched by a slow addition of saturated aqueous NH₄Cl (50 mL) and then ethyl acetate (50 mL). The organic layer was collected and the aqueous layer was extracted with ethyl acetate (3×50 mL). The combined extracts were washed with water (4×50 mL), brine (40 mL) and dried over anhydrous MgSO₄ and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (Cyclohexane/ethyl acetate 1:0 then 9:1) to give 1-allyl-2-benzyloxybenzene **10b** as a yellowish oil (762 mg, 34% yield). The characterization data is in accordance with the ones reported in the literature.^[163]

¹H NMR (CDCl₃, 300 MHz) δ 7.60-7.34 (m, 5H), 7.32-7.20 (m, 2H), 7.08-6.92 (m, 2H), 6.12 (ddt, *J* = 16.9, 10.2, 6.7 Hz, 1H), 5.22-5.08 (m, 4H), 3.56 (d, *J* = 6.6 Hz, 2H).

Synthesis of 6-benzyloxyhex-1-ene (**10c**)



6-benzyloxyhex-1-ene **10c** was prepared according to a procedure reported in the literature.^[164] To a suspension of 360 mg of NaH (15.0 mmol, 1.5 equiv., 60%wt% in paraffin oil,) in distilled THF (10 mL) at 0 °C was added a solution of 5-hexen-1-ol (1.2 mL, 10.0 mmol, 1.0 equiv.) in distilled THF (10 mL) *via* cannula. After 5 min, 1.28 mL of benzyl bromide (10.7 mmol, 1.07 equiv.) was added and the reaction mixture allowed to warm to RT. The resulting mixture was stirred until conversion was complete as checked by TLC. The reaction mixture was quenched by slow addition of methanol (2 mL), followed by

^[163] Das, S. K.; Panda, G. *Tetrahedron* **2008**, *64*, 4162-4173.

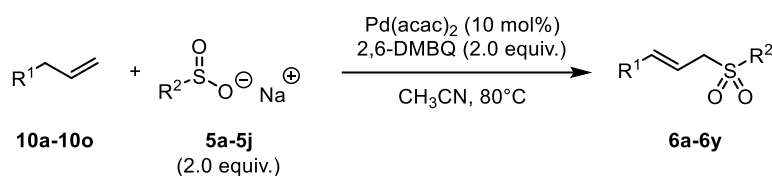
^[164] Florence, G. J.; Fraser, A. L.; Gould, E. R.; King, E. F. B.; Menzies, S. K.; Morris, J. C.; Tulloch, L. B.; Smith, T. K. *ChemMedChem* **2014**, *9*, 2548-2556.

addition of a saturated aqueous solution of ammonium chloride (10 mL). The biphasic mixture was separated and the aqueous layer was extracted with Et₂O (3 × 50 mL). The combined organic layers were washed with water (25 mL), brine (25 mL), dried over anhydrous MgSO₄ and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (pentane/ethyl acetate 1:0 to 5:1) to give 6-benzyloxyhex-1-ene **10c** as a colorless oil (1.32 g, 70% yield). The characterization data is in accordance with the ones reported in the literature.^[165]

¹H NMR (CDCl₃, 400 MHz) δ 7.59-7.36 (m, 5H), 6.01 (ddt, *J* = 16.9, 10.2, 6.7 Hz, 1H), 5.30-5.10 (m, 2H), 4.65 (s, 2H), 3.63 (t, *J* = 6.4 Hz, 2H), 2.27 (q, *J* = 7.0 Hz, 2H), 1.88-1.77 (m, 2H), 1.77-1.63 (m, 2H).

3.2. Palladium-Catalyzed allylic C-H sulfonylation

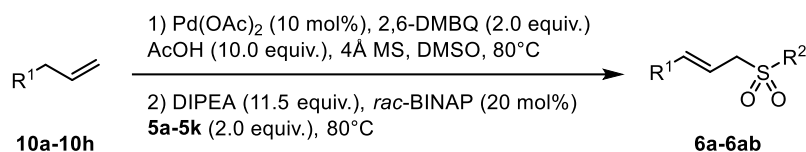
General procedure for direct allylic C-H sulfonylation of alkenes (method A):



An ace pressure tube equipped with a magnetic stirrer was charged with 15.2 mg (0.05 mmol, 10 mol%) of palladium(II) acetylacetonate, 136 mg (1.00 mmol, 2.0 equiv.) of 2,6-dimethyl-1,4-benzoquinone and the sulfinate **5a-5j** (1.00 mmol, 2.0 equiv.). The tube was placed under vacuum and then backfilled with argon. The vacuum/argon cycles were repeated twice and 0.75 mL of distilled acetonitrile (0.66 M) was introduced. To this suspension was introduced the alkene **10a-10o** (0.50 mmol, 1.0 equiv.) and the mixture was heated to 80 °C under stirring until conversion was complete as checked by TLC. The mixture was then cooled to rt and filtered over a pad of silica gel with 50 mL of ethyl acetate. The filtrate was concentrated under reduced pressure and the residue was purified by flash column chromatography on silica gel to give the desired products.

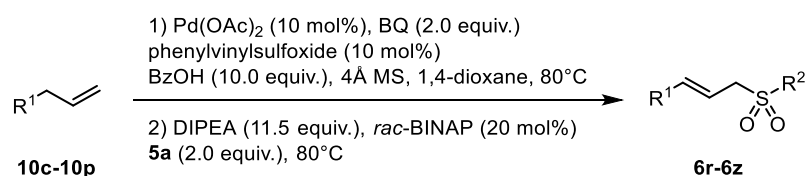
^[165] Lebel, H.; Paquet, V. *Organometallics* **2004**, *23*, 1187-1190.

General procedure for one-pot sequential allylic C-H sulfonation of alkenes (method B):



An ace pressure tube equipped with a magnetic stirrer was charged with 11.2 mg (0.05 mmol, 10 mol%) of palladium(II) acetate, 136.2 mg (1.00 mmol, 2.0 equiv.) of 2,6-dimethylbenzo-1,4-quinone and 50 mg of 4 Å molecular sieves. The solids were suspended in 1.5 mL of anhydrous DMSO and 0.29 mL (5.00 mmol, 10.0 equiv.) of acetic acid was introduced followed by the alkene **10a-10h** (0.50 mmol, 1.0 equiv.). The mixture was heated to 80°C until complete conversion of the alkene was reached as checked by TLC. The mixture was cooled to rt and 62.0 mg (0.10 mmol, 20 mol%) of *rac*-BINAP followed by 1.0 mL (7.25 mmol, 11.5 equiv.) of *N,N*-diisopropylethylamine were added to the reaction mixture. The sulfinate **5a-5k** (1.00 mmol, 2.0 equiv.) was then introduced and the ace pressure tube was closed. The reaction mixture was then heated to 80°C until complete conversion of the intermediate allylacetate was seen by TLC. The mixture was then cooled to rt and filtered over a pad of silica gel with 50 mL of ethyl acetate to remove the salts. The filtrate was placed into a separatory funnel and washed with 50 mL of water. The aqueous layer was extracted with 2 × 20 mL of ethyl acetate. The combined organic layers were dried over anhydrous MgSO₄ and filtered. The filtrate was concentrated under reduced pressure and the residue was purified by flash column chromatography on silica gel to give the desired products.

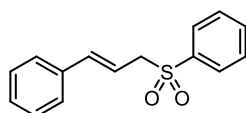
General procedure for one-pot sequential allylic C-H sulfonation of aliphatic terminal alkenes (method B'):



An ace pressure tube equipped with a magnetic stirrer was charged with 4.5 mg (0.02 mmol, 10 mol%) of palladium(II) acetate, 2.7 μL (0.02 mmol, 10 mol%) of phenylvinylsulfoxide and 43.3 mg (0.4 mmol, 2.0 equiv.) of 1,4-benzoquinone. The solids were suspended in 0.6 mL of anhydrous 1,4-dioxane and

244.2 mg (2.00 mmol, 10.0 equiv.) of benzoic acid was introduced followed by the alkene **10c-10p** (0.2 mmol, 1.0 equiv.). The mixture was heated to 43°C until complete conversion of the alkene was reached as checked by TLC or ¹H NMR (usually 66–72 h). The mixture was cooled to rt and 25.0 mg (0.04 mmol, 20 mol%) of *rac*-BINAP followed by 0.4 mL (2.30 mmol, 11.5 equiv.) of *N,N*-diisopropylethylamine were added to the reaction mixture. To this mixture was introduced 65.4 mg (0.40 mmol, 2.0 equiv.) of sodium benzenesulfinate **5a** and the sealed tube was closed. The reaction mixture was then heated to 80°C until complete conversion of the intermediate allylbenzoate was seen by TLC. The mixture was then cooled to rt and filtered over a pad of silica gel with 25 mL of ethyl acetate to remove the salts. The filtrate was concentrated under reduced pressure and the residue was purified by flash column chromatography on silica gel to give the desired products.

***trans*-Cinnamylphenyl sulfone (6a).**



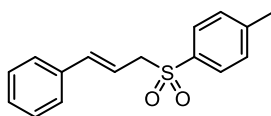
Prepared according to **method A** from sodium benzene sulfinate **5a** (164 mg, 1.00 mmol) and allylbenzene **10d** (59.1 mg, 0.50 mmol). After workup, the crude mixture was purified by flash column chromatography (cyclohexane/ethyl acetate 5:1) to give *trans*-cinnamylphenyl sulfone **6a** as a colorless solid (74.8 mg, 58% yield).

Prepared according to **method B** from sodium benzene sulfinate **5a** (164 mg, 1.00 mmol) and allylbenzene **10d** (59.1 mg, 0.50 mmol). After workup, the crude mixture was purified by flash column chromatography (pentane/ethyl acetate 5:1) to give *trans*-cinnamylphenyl sulfone **6a** as a colorless solid (104.9 mg, 81% yield). The characterization data are in accordance with the ones reported in the literature.^[72]

The characterization data can be found page 129.

¹H NMR (300 MHz, CDCl₃) δ 7.97-7.79 (m, 2H), 7.69-7.58 (m, 1H), 7.59-7.47 (m, 2H), 7.40-7.20 (m, 5H), 6.37 (dd, *J* = 15.9, 1.3 Hz, 1H), 6.10 (dt, *J* = 15.6, 7.5 Hz, 1H), 3.96 (dd, *J* = 7.5, 1.1 Hz, 2H).

***trans*-Cinnamyl-*p*-tolyl sulfone (6e).**

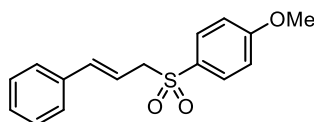


Prepared according to **method A** from sodium 4-methylbenzene sulfinate **5b** (71.3 mg, 0.40 mmol) and allylbenzene **10d** (23.6 mg, 0.20 mmol). After workup, the crude mixture was purified by flash column chromatography (cyclohexane/ethyl acetate 5:1) to give *trans*-cinnamyl-*p*-tolylsulfone **6e** as a colorless solid (25.4 mg, 47% yield).

Prepared according to **method B** from sodium 4-methylbenzene sulfinate **5b** (178 mg, 1.00 mmol) and allylbenzene **10d** (59.1 mg, 0.50 mmol). After workup, the crude mixture was purified by flash column chromatography (cyclohexane/ethyl acetate 5:1) to give *trans*-cinnamyl-*p*-tolylsulfone **6e** as a colorless solid (111.6 mg, 82% yield). The characterization data are in accordance with the ones reported in the literature.^[72]

¹H NMR (400 MHz, CDCl₃) δ 7.76 (d, *J* = 8.3 Hz, 2H), 7.43–7.09 (m, 7H), 6.39 (dt, *J* = 15.8, 1.2 Hz, 1H), 6.10 (dt, *J* = 15.8, 7.6 Hz, 1H), 3.93 (dd, *J* = 7.6, 1.2 Hz, 2H), 2.43 (s, 3H).

***trans*-Cinnamyl-4-methoxyphenyl sulfone (6f).**



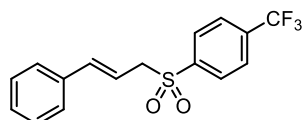
Prepared according to **method A** from sodium 4-methoxybenzene sulfinate **5c** (194 mg, 1.00 mmol) and allylbenzene **10d** (59.1 mg, 0.50 mmol). After workup, the crude mixture was purified by flash column chromatography (dichloromethane) to give *trans*-cinnamyl-4-methoxyphenyl sulfone **6f** as a colorless solid (60.0 mg, 41% yield).

Prepared according to **method B** from sodium 4-methoxybenzene sulfinate **5c** (194 mg, 1.00 mmol) and allylbenzene **10d** (59.1 mg, 0.50 mmol). After workup, the crude mixture was purified by flash column chromatography (pentane/ethyl acetate 4:1) to give *trans*-cinnamyl-4-methoxyphenyl sulfone **6f** as a colorless solid (112.5 mg, 78% yield). The characterization data are in accordance with the ones

reported in the literature.^[166]

¹H NMR (400 MHz, CDCl₃) δ 7.86-7.74 (m, 2H), 7.46-7.10 (m, 5H), 7.10-6.76 (m, 2H), 6.38 (dd, *J* = 15.8, 1.2 Hz, 1H), 6.11 (dt, *J* = 15.9, 7.6 Hz, 1H), 3.93 (dd, *J* = 7.6, 1.2 Hz, 2H), 3.87 (s, 3H).

***trans*-Cinnamyl-4-trifluoromethylphenyl sulfone (6g).**

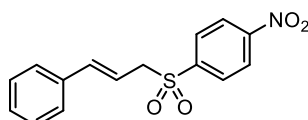


Prepared according to **method A** from sodium 4-trifluoromethylbenzene sulfinate **5e** (232 mg, 1.00 mmol) and allylbenzene **10d** (59.1 mg, 0.50 mmol). After workup, the crude mixture was purified by flash column chromatography (pentane/ethyl acetate 5:1) to give *trans*-cinnamyl-4-trifluoromethylphenyl sulfone **6g** as a colorless solid (17.9 mg, 11% yield).

Prepared according to **method B** from sodium 4-trifluoromethylbenzene sulfinate **5e** (232 mg, 1.00 mmol) and allylbenzene **10d** (59.1 mg, 0.50 mmol). After workup, the crude mixture was purified by flash column chromatography (pentane/ethyl acetate 3:1) to give *trans*-cinnamyl-4-trifluoromethylphenyl sulfone **6g** as a colorless solid (125 mg, 77% yield).

m.p. 147°C; ¹H NMR (CDCl₃, 400 MHz) δ 8.02 (d, *J* = 8.2 Hz, 2H), 7.81 (d, *J* = 8.2 Hz, 2H), 7.46–7.20 (m, 5H), 6.39 (d, *J* = 15.9 Hz, 1H), 6.10 (dt, *J* = 15.5, 7.6 Hz, 1H), 3.99 (dd, *J* = 7.6, 1.2 Hz, 2H); ¹³C NMR (CDCl₃, 100 MHz), δ 141.9, 139.8, 135.5 (q, *J* = 33.1 Hz), 135.4, 129.2 (2C), 128.8, 128.7 (2C), 126.7 (2C), 126.2 (q, *J* = 3.7 Hz, 2C), 123.1 (q, *J* = 273.1 Hz), 114.3, 60.4; ¹⁹F NMR (376 MHz, CDCl₃) δ -63.19; **IR:** ν (cm⁻¹) 3059, 2930, 1495, 1449, 1317, 1128, 1061, 1014, 837, 738, 718, 699; **HRMS** (ESI): *m/z* calculated for C₁₆H₁₂F₃O₂S [M]⁻ 325.0516, found: 325.0513.

***trans*-Cinnamyl-4-nitrophenyl sulfone (6h).**

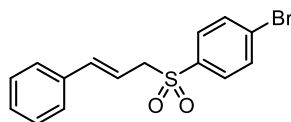


^[166] Shavnya, A.; Hesp, K. D.; Mascitti, V.; Smith, A. C. *Angew. Chem. Int. Ed.* **2015**, *54*, 13571-13575.

Prepared according to **method A** from sodium 4-nitrobenzene sulfinate **5d** (209 mg, 1.00 mmol) and allylbenzene **10d** (59.1 mg, 0.50 mmol). After workup, the crude mixture was purified by flash column chromatography (pentane/ethyl acetate 3:1) to give *trans*-cinnamyl-4-nitrophenyl sulfone **6h** as a colorless solid (58.0 mg, 37% yield). The characterization data are in accordance with the ones reported in the literature.^[72]

¹H NMR (400 MHz, CDCl₃) δ 8.52-8.21 (m, 2H), 8.21-7.86 (m, 2H), 7.45-7.17 (m, 5H), 6.40 (dd, *J* = 15.9, 1.3 Hz, 1H), 6.10 (dt, *J* = 15.6, 7.6 Hz, 1H), 4.02 (dd, *J* = 7.6, 1.2 Hz, 2H).

***trans*-Cinnamyl-4-bromophenyl sulfone (6i).**

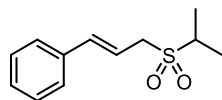


Prepared according to **method A** from sodium 4-bromobenzene sulfinate **5f** (242 mg, 1.00 mmol) and allylbenzene **10d** (59.1 mg, 0.50 mmol). After workup, the crude mixture was purified by flash column chromatography (cyclohexane/ethyl acetate 5:1) to give *trans*-cinnamyl-4-bromophenyl sulfone **6i** as a colorless solid (68.2 mg, 45% yield).

Prepared according to **method B** from sodium 4-bromobenzene sulfinate **5f** (363 mg, 1.50 mmol) and allylbenzene **10d** (59.1 mg, 0.50 mmol). After workup, the crude mixture was purified by flash column chromatography (pentane/ethyl acetate 5:1) to give *trans*-cinnamyl-4-bromophenyl sulfone **6i** as a colorless solid (95.5 mg, 63% yield).

m.p. 106°C; ¹H NMR (CDCl₃, 400 MHz) δ 7.79-7.69 (m, 2H), 7.69-7.58 (m, 2H), 7.39-7.27 (m, 5H), 6.40 (d, *J* = 15.8 Hz, 1H), 6.09 (dt, *J* = 15.8, 7.6 Hz, 1H), 3.95 (dd, *J* = 7.6, 1.2 Hz, 2H); ¹³C NMR (CDCl₃, 100 MHz), δ 139.5, 137.4, 135.5, 132.4 (2C), 130.1 (2C), 129.2, 128.7 (2C), 128.7, 126.6 (2C), 114.7, 60.5; **IR:** ν (cm⁻¹) 3064, 3027, 2999, 2948, 1571, 1469, 1449, 1320, 1146, 1085, 1064, 1008, 969, 741, 721, 695; **HRMS** (ESI): *m/z* calculated for C₁₅H₁₄BrO₂S [M+H]⁺ 336.9892 and 338.9872, found: 336.9891 and 338.9871.

***trans*-Cinnamyl-isopropyl sulfone (6j).**

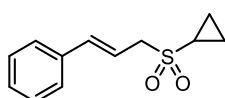


Prepared according to **method A** from sodium isopropyl sulfinat **5i** (130 mg, 1.00 mmol) and allylbenzene **10d** (59.1 mg, 0.50 mmol). After workup, the crude mixture was purified by flash column chromatography (hexane/ethyl acetate 5:1) to give *trans*-cinnamyl-isopropyl sulfone **6j** as a yellow oil (24.6 mg, 22% yield).

Prepared according to **method B** from sodium isopropyl sulfinat **5i** (130 mg, 1.00 mmol) and allylbenzene **10d** (59.1 mg, 0.50 mmol). After workup, the crude mixture was purified by flash column chromatography (pentane/ethyl acetate 9:1) to give *trans*-cinnamyl-isopropyl sulfone **6j** as a yellow oil (86.5 mg, 77% yield).

¹H NMR (CDCl₃, 400 MHz) δ 7.44-7.38 (m, 2H), 7.38-7.27 (m, 3H), 6.70 (dd, *J* = 16.0, 1.4 Hz, 1H), 6.26 (dt, *J* = 16.0, 7.6 Hz, 1H), 3.87 (dd, *J* = 7.6, 1.3 Hz, 2H), 3.22 (hept, 1H), 1.41 (d, *J* = 6.9 Hz, 6H); ¹³C NMR (CDCl₃, 100 MHz), δ 138.6, 135.7, 128.9 (2C), 128.8, 126.8 (2C), 115.6, 54.5, 51.6, 15.3 (2C); IR: ν (cm⁻¹) 2926, 1597, 1495, 1448, 1313, 1257, 1125, 1058, 972, 764, 731, 700; HRMS (ESI): *m/z* calculated for C₁₂H₁₇O₂S [M+H]⁺ 225.0944, found: 225.0944.

***trans*-Cinnamyl-cyclopropyl sulfone (6k).**



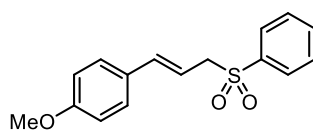
Prepared according to **method A** from sodium cyclopropyl sulfinat **5j** (128 mg, 1.00 mmol) and allylbenzene **10d** (59.1 mg, 0.50 mmol). After workup, the crude mixture was purified by flash column chromatography (cyclohexane/ethyl acetate 5:1) to give *trans*-cinnamyl-cyclopropyl sulfone **6k** as a colorless solid (56.6 mg, 51% yield).

Prepared according to **method B** from sodium cyclopropyl sulfinat **5j** (192 mg, 1.50 mmol) and allylbenzene **10d** (59.1 mg, 0.50 mmol). After workup, the crude mixture was purified by flash column chromatography (cyclohexane/ethyl acetate 5:1) to give *trans*-cinnamyl-cyclopropyl sulfone **6k** as a

colorless solid (81.1 mg, 73% yield). The characterization data are in accordance with the ones reported in the literature.^[72]

¹H NMR (400 MHz, CDCl₃) δ 7.49-7.35 (m, 2H), 7.35-7.19 (m, 3H), 6.72 (d, *J* = 15.8 Hz, 1H), 6.28 (dt, *J* = 15.5, 7.6 Hz, 1H), 3.91 (dd, *J* = 7.6, 1.3 Hz, 2H), 2.43 (tt, *J* = 8.0, 4.8 Hz, 1H), 1.32-1.15 (m, 2H), 1.05-0.92 (m, 2H).

(*E*)-1-methoxy-4-(3-(phenylsulfonyl)prop-1-en-1-yl)benzene (6I).



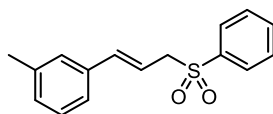
Prepared according to **method A** from sodium benzene sulfinate **5a** (164 mg, 1.00 mmol) and 1-allyl-4-methoxybenzene **10e** (74.1 mg, 0.50 mmol). After workup, the crude mixture was purified by flash column chromatography (pentane/ethyl acetate 4:1) to give (*E*)-1-methoxy-4-(3-(phenylsulfonyl)prop-1-en-1-yl)benzene **6I** as a colorless solid (59.1 mg, 41% yield).

Prepared according to **method B** from sodium benzene sulfinate **5a** (164 mg, 1.00 mmol) and 1-allyl-4-methoxybenzene **10e** (74.1 mg, 0.50 mmol). After workup, the crude mixture was purified by flash column chromatography (dichloromethane) to give (*E*)-1-methoxy-4-(3-(phenylsulfonyl)prop-1-en-1-yl)benzene **6I** as a colorless solid (68.4 mg, 48% yield). The characterization data are in accordance with the ones reported in the literature.^[167]

¹H NMR (400 MHz, CDCl₃) δ 7.97-7.78 (m, 2H), 7.68-7.59 (m, 1H), 7.59-7.47 (m, 2H), 7.26-7.17 (m, 2H), 6.94-6.77 (m, 2H), 6.30 (d, *J* = 15.8 Hz, 1H), 5.95 (dt, *J* = 15.6, 7.6 Hz, 1H), 3.93 (dd, *J* = 7.6, 1.2 Hz, 2H), 3.81 (s, 3H).

^[167] Chandrasekhar, S.; Jagadeshwar, V.; Saritha, B.; Narsihmulu, C. *J. Org. Chem.* **2005**, *70*, 6506-6507.

(E)-1-methyl-3-(3-(phenylsulfonyl)prop-1-en-1-yl)benzene (6m).

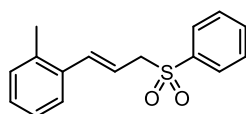


Prepared according to **method A** from sodium benzene sulfinate **5a** (164 mg, 1.00 mmol) and 1-allyl-3-methylbenzene **10f** (66.1 mg, 0.50 mmol). After workup, the crude mixture was purified by flash column chromatography (pentane/ethyl acetate 5:1) to give (E)-1-methyl-3-(3-(phenylsulfonyl)prop-1-en-1-yl)benzene **6m** as a colorless solid (57.2 mg, 42% yield).

Prepared according to **method B** from sodium benzene sulfinate **5a** (164 mg, 1.00 mmol) and 1-allyl-3-methylbenzene **10f** (66.1 mg, 0.50 mmol). After workup, the crude mixture was purified by flash column chromatography (cyclohexane/ethyl acetate 8:2) to give (E)-1-methyl-3-(3-(phenylsulfonyl)prop-1-en-1-yl)benzene **6m** as a colorless solid (60.5 mg, 44% yield). The characterization data are in accordance with the ones reported in the literature.^[72]

¹H NMR (400 MHz, CDCl₃) δ 7.98-7.82 (m, 2H), 7.70-7.59 (m, 1H), 7.57-7.45 (m, 2H), 7.23-7.15 (m, 1H), 7.12-6.99 (m, 3H), 6.33 (d, *J* = 15.9 Hz, 1H), 6.09 (dt, *J* = 15.5, 7.6 Hz, 1H), 3.95 (dd, *J* = 7.6, 1.2 Hz, 2H), 2.33 (s, 3H).

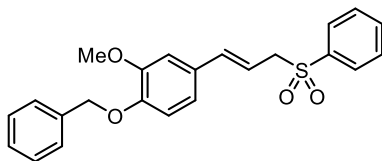
(E)-1-methyl-2-(3-(phenylsulfonyl)prop-1-en-1-yl)benzene (6n).



Prepared according to **method A** from sodium benzene sulfinate **5a** (164 mg, 1.00 mmol) and 1-allyl-2-methylbenzene **10g** (66.1 mg, 0.50 mmol). After workup, the crude mixture was purified by flash column chromatography (cyclohexane/ethyl acetate 5:1) to give (E)-1-methyl-2-(3-(phenylsulfonyl)prop-1-en-1-yl)benzene **6n** as a colorless solid (54.4 mg, 40% yield). The characterization data are in accordance with the ones reported in the literature.^[155]

¹H NMR (400 MHz, CDCl₃) δ 7.97-7.83 (m, 2H), 7.70-7.59 (m, 1H), 7.59-7.49 (m, 2H), 7.34 (dd, *J* = 6.7, 2.3 Hz, 1H), 7.21-7.08 (m, 3H), 6.56 (d, *J* = 15.6 Hz, 1H), 5.98 (dt, *J* = 15.5, 7.6 Hz, 1H), 3.98 (dd, *J* = 7.6, 1.2 Hz, 2H), 2.14 (s, 3H).

(E)-1-(benzyloxy)-2-methoxy-4-(3-(phenylsulfonyl)prop-1-en-1-yl)benzene (6o).

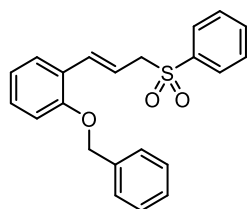


Prepared according to **method A** from sodium benzene sulfinate **5a** (164 mg, 1.00 mmol) and *O*-benzyleugenol **10a** (127 mg, 0.50 mmol). After workup, the crude mixture was purified by flash column chromatography (pentane/ethylacetate 2:1) to give *(E)*-1-(benzyloxy)-2-methoxy-4-(3-(phenylsulfonyl)prop-1-en-1-yl)benzene **6o** as a colorless solid (72.0 mg, 33% yield).

Prepared according to **method B** from sodium benzene sulfinate **5a** (164 mg, 1.00 mmol) and *O*-benzyleugenol **10a** (127 mg, 0.50 mmol). After workup, the crude mixture was purified by flash column chromatography (dichloromethane/ethyl acetate 95:5) to give *(E)*-1-(benzyloxy)-2-methoxy-4-(3-(phenylsulfonyl)prop-1-en-1-yl)benzene **6o** as a colorless solid (132 mg, 67% yield).

m.p. 104°C; **¹H NMR** (400 MHz, CDCl₃) δ 7.84-7.75 (m, 2H), 7.59-7.50 (m, 1H), 7.45 (m, 2H), 7.38-7.17 (m, 5H), 6.83-6.57 (m, 3H), 6.21 (d, *J* = 15.8 Hz, 1H), 5.89 (dt, *J* = 15.6, 7.6 Hz, 1H), 5.06 (s, 2H), 3.84 (dd, *J* = 7.6, 1.1 Hz, 2H), 3.80 (s, 3H); **¹³C NMR** (101 MHz, CDCl₃) δ 149.6, 148.7, 138.9, 138.4, 136.8, 133.7, 129.2, 129.0 (2C), 128.5 (2C), 128.4 (2C), 127.9, 127.2 (2C), 120.0, 113.6, 112.8, 109.4, 70.9, 60.5, 55.9; **IR:** ν (cm⁻¹) 2924, 1598, 1581, 1509, 1468, 1449, 1382, 1324, 1265, 1228, 1134, 1008, 976, 887, 806, 741, 730; **HRMS** (ESI): *m/z* calculated for C₂₃H₂₃O₄S [M+H]⁺ 395.1311, found: 395.1312.

(E)-1-(benzyloxy)-2-(3-(phenylsulfonyl)prop-1-en-1-yl)benzene (6p).

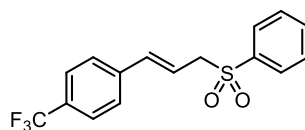


Prepared according to **method A** from sodium benzene sulfinate **5a** (164 mg, 1.00 mmol) and 1-allyl-2-benzyloxybenzene **10b** (112 mg, 0.50 mmol). After workup, the crude mixture was purified by flash column chromatography (pentane/ethyl acetate 3:1) to give *(E)*-1-(benzyloxy)-2-(3-(phenylsulfonyl)prop-1-en-1-yl)benzene **6p** as a colorless oil (47.3 mg, 24% yield).

Prepared according to **method B** from sodium benzene sulfinate **5a** (164 mg, 1.00 mmol) and 1-allyl-2-benzyloxybenzene **10b** (112 mg, 0.50 mmol). After workup, the crude mixture was purified by flash column chromatography (dichloromethane) to give (*E*)-1-(benzyloxy)-2-(3-(phenylsulfonyl)prop-1-en-1-yl)benzene **6p** as a colorless oil (104 mg, 44% yield).

¹H NMR (400 MHz, CDCl₃) δ 7.89-7.84 (m, 2H), 7.60-7.53 (m, 1H), 7.52-7.45 (m, 2H), 7.42-7.30 (m, 6H), 7.22 (ddd, *J* = 8.3, 7.4, 1.7 Hz, 1H), 6.96-6.86 (m, 2H), 6.73 (d, *J* = 16.0 Hz, 1H), 6.16 (dt, *J* = 16.0, 7.6 Hz, 1H), 5.03 (s, 2H), 3.96 (dd, *J* = 7.6, 1.2 Hz, 2H); ¹³C NMR (101 MHz, CDCl₃) δ 156.1, 138.6, 136.9, 134.0, 133.8, 129.7, 129.0 (2C), 128.7 (4C), 128.1, 127.4 (3C), 125.4, 121.2, 115.9, 112.6, 70.4, 61.2; IR: ν (cm⁻¹) 2922, 2854, 1567, 1453, 1373, 1195, 1029, 1018, 751; HRMS (ESI): *m/z* calculated for C₂₂H₂₄O₃SN [M+NH₄]⁺ 382.1471, found: 382.1471.

(*E*)-1-(3-(phenylsulfonyl)prop-1-en-1-yl)-4-(trifluoromethyl)benzene (6q).

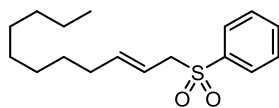


Prepared according to **method A** from sodium benzene sulfinate **5a** (164 mg, 1.00 mmol) and 1-allyl-4-trifluoromethylbenzene **10h** (93.1 mg, 0.50 mmol). After workup, the crude mixture was purified by flash column chromatography (dichloromethane) to give (*E*)-1-(3-(phenylsulfonyl)prop-1-en-1-yl)-4-(trifluoromethyl)benzene **6q** as a colorless solid (32.6 mg, 20% yield).

Prepared according to **method B** from sodium benzene sulfinate **5a** (164 mg, 1.00 mmol) and 1-allyl-4-trifluoromethylbenzene **10h** (93.1 mg, 0.50 mmol). After workup, the crude mixture was purified by flash column chromatography (dichloromethane) to give (*E*)-1-(3-(phenylsulfonyl)prop-1-en-1-yl)-4-(trifluoromethyl)benzene **6q** as a colorless solid (74.5 mg, 23% yield). The characterization data are in accordance with the ones reported in the literature.^[72]

¹H NMR (400 MHz, CDCl₃) δ 7.92-7.75 (m, 2H), 7.71-7.61 (m, 1H), 7.59-7.49 (m, 4H), 7.38 (d, *J* = 8.1 Hz, 2H), 6.42 (d, *J* = 15.9 Hz, 1H), 6.21 (dt, *J* = 15.6, 7.5 Hz, 1H), 3.97 (dd, *J* = 7.6, 1.1 Hz, 2H); ¹⁹F NMR (376 MHz, CDCl₃) δ -62.67.

(E)-(undec-2-en-1-ylsulfonyl)benzene (6r).

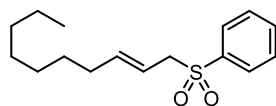


Prepared according to **method A** from sodium benzene sulfinate **5a** (164 mg, 1.00 mmol) and undec-1-ene **10i** (103 μ L, 0.50 mmol). After workup, the crude mixture was purified by flash column chromatography (pentane/ethyl acetate 8:1) to give *(E)*-(undec-2-en-1-ylsulfonyl)benzene **6r** as a colorless oil (47.0 mg, 32% yield).

Prepared according to **method B'** from sodium benzene sulfinate **5a** (65.4 mg, 0.40 mmol) and undec-1-ene **10i** (30.9 mg, 0.20 mmol). After workup, the crude mixture was purified by flash column chromatography (pentane/ethyl acetate 8:1) to give *(E)*-(undec-2-en-1-ylsulfonyl)benzene **6r** as colorless oil (24.0 mg, 40% yield).

$^1\text{H NMR}$ (CDCl_3 , 400 MHz) δ 7.89-7.79 (m, 2H), 7.68-7.60 (m, 1H), 7.57-7.46 (m, 2H), 5.66-5.44 (m, 1H), 5.44-5.20 (m, 1H), 3.74 (dd, $J = 7.2, 1.0$ Hz, 2H), 1.98 (q, $J = 6.7$ Hz, 2H), 1.34-1.14 (m, 12H), 0.88 (t, $J = 6.9$ Hz, 3H); $^{13}\text{C NMR}$ (CDCl_3 , 100 MHz), δ 141.9, 138.4, 133.5, 128.9 (2C), 128.5 (2C), 115.8, 60.2, 32.5, 31.8, 29.3, 29.2, 29.0, 28.6, 22.6, 14.1; **IR**: ν (cm^{-1}) 2956, 2924, 2855, 1464, 1447, 1378, 1320, 1307, 1143, 1086, 1071, 969, 731, 688; **HRMS** (ESI): m/z calculated for $\text{C}_{17}\text{H}_{27}\text{O}_2\text{S}$ $[\text{M}+\text{H}]^+$ 295.1726, found: 295.1726.

(E)-(dec-2-en-1-ylsulfonyl)benzene (6s).



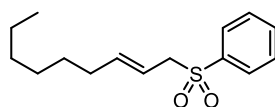
Prepared according to **method A** from sodium benzene sulfinate **5a** (164 mg, 1.00 mmol) and dec-1-ene **10j** (95.0 μ L, 0.50 mmol). After workup, the crude mixture was purified by flash column chromatography (pentane/ethyl acetate 10:1) to give *(E)*-(dec-2-en-1-ylsulfonyl)benzene **6s** as a colorless oil (42.0 mg, 30% yield).

Prepared according to **method B'** from sodium benzene sulfinate **5a** (65.4 mg, 0.40 mmol) and dec-1-ene **10j** (28.1 mg, 0.20 mmol). After workup, the crude mixture was purified by flash column

chromatography (cyclohexane/ethyl acetate 9:1) to give (*E*)-(dec-2-en-1-ylsulfonyl)benzene **6s** as a colorless oil (22.1 mg, 39% yield, *E/Z* 3:1). The characterization data are in accordance with the ones reported in the literature.^[168]

¹H NMR (400 MHz, CDCl₃) δ 7.94-7.77 (m, 2H), 7.68-7.59 (m, 1H), 7.59-7.44 (m, 2H), 5.80-5.65 (m, 2H, minor), 5.55-5.29 (m, 2H, major), 3.85 (dd, *J* = 7.8, 1.2 Hz, 2H, minor), 3.74 (dd, *J* = 7.1, 0.9 Hz, 2H, major), 1.97 (q, *J* = 7.2 Hz, 2H, major), 1.71 (q, *J* = 7.2 Hz, 2H, minor), 1.35-1.04 (m, 10H), 0.92-0.80 (m, 3H).

(*E*)-(non-2-en-1-ylsulfonyl)benzene (6t).



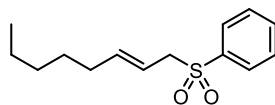
Prepared according to **method A** from sodium benzene sulfinate **5a** (164 mg, 1.00 mmol) and non-1-ene **10k** (87 μL, 0.50 mmol). After workup, the crude mixture was purified by flash column chromatography (pentane/ethyl acetate 10:1) to give (*E*)-1-(non-2-en-1-ylsulfonyl)benzene **6t** as a yellow oil (60.0 mg, 45% yield).

Prepared according to **method B'** from sodium benzene sulfinate **5a** (65.4 mg, 0.40 mmol) and non-1-ene **10k** (25.2 mg, 0.20 mmol). After workup, the crude mixture was purified by flash column chromatography (cyclohexane/ethyl acetate 4:1) to give (*E*)-1-(non-2-en-1-ylsulfonyl)benzene **6t** as a yellow oil (26.3 mg, 49% yield). The characterization data are in accordance with the ones reported in the literature.^[73]

¹H NMR (400 MHz, CDCl₃) δ 7.90-7.80 (m, 2H), 7.64 (td, *J* = 7.3, 1.5 Hz, 1H), 7.54 (td, *J* = 7.6, 1.6 Hz, 2H), 5.59-5.45 (m, 1H), 5.44-5.31 (m, 1H), 3.74 (d, *J* = 7.1 Hz, 2H), 1.98 (q, *J* = 6.9 Hz, 2H), 1.30-1.19 (m, 8H), 0.88 (td, *J* = 7.0, 1.6 Hz, 3H).

^[168] Kim, K.; Park, S.; Lee, Y. *Eur. J. Org. Chem.* **2021**, 125-137.

(E)-(oct-2-en-1-ylsulfonyl)benzene (6u).

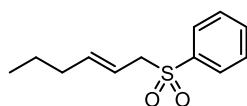


Prepared according to **method A** from sodium benzene sulfinate **5a** (164 mg, 1.00 mmol) and oct-1-ene **10l** (56.1 mg, 0.50 mmol). After workup, the crude mixture was purified by flash column chromatography (pentane/ethyl acetate 5:1) to give (E)-(oct-2-en-1-ylsulfonyl)benzene **6u** as a colorless oil (55.8 mg, 44% yield).

Prepared according to **method B'** from sodium benzene sulfinate **5a** (65.4 g, 0.40 mmol) and oct-1-ene **10l** (22.4 mg, 0.20 mmol). After workup, the crude mixture was purified by flash column chromatography (cyclohexane/ethyl acetate 87:13) to give (E)-(oct-2-en-1-ylsulfonyl)benzene **6u** as a colorless oil (6.0 mg, 12% yield, *E/Z* 6.1:1). The characterization data are in accordance with the ones reported in the literature.^[72]

¹H NMR (400 MHz, CDCl₃) δ 7.92-7.79 (m, 2H), 7.68-7.60 (m, 1H), 7.58-7.47 (m, 2H), 5.56-5.45 (m, 1H), 5.39 (dt, *J* = 15.5, 7.3, 1.2 Hz, 1H), 3.74 (dd, *J* = 7.2, 0.9 Hz, 2H), 1.98 (q, *J* = 7.3 Hz, 2H), 1.34-1.19 (m, 6H), 0.86 (td, *J* = 8.1, 4.3 Hz, 3H).

(E)-(hex-2-en-1-ylsulfonyl)benzene (6v).



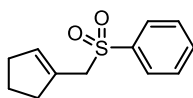
Prepared according to **method A** from sodium benzene sulfinate **5a** (164 mg, 1.00 mmol) and hex-1-ene **10m** (63 μL, 0.50 mmol). After workup, the crude mixture was purified by flash column chromatography (pentane/ethyl acetate 10:1) to give (E)-(hex-2-en-1-ylsulfonyl)benzene **6v** as a brown solid (46.0 mg, 41% yield).

Prepared according to **method B'** from sodium benzene sulfinate **5a** (164 mg, 1.00 mmol) and hex-1-ene **10m** (42.1 mg, 0.50 mmol). After workup, the crude mixture was purified by flash column chromatography (dichloromethane/ethyl acetate 95:5) to give (E)-(hex-2-en-1-ylsulfonyl)benzene **6v** as a brown solid (53.6 mg, 48% yield, *E/Z* 78:22). A pure fraction of the major isomer could be isolated for

characterization.

m.p. 154°C; **¹H NMR** (CDCl₃, 400 MHz) δ 7.89-7.83 (m, 2H), 7.67-7.61 (m, 1H), 7.58-7.51 (m, 2H), 5.56-5.46 (m, 1H), 5.45-5.36 (m, 1H), 3.75 (dd, *J* = 7.1, 0.9 Hz, 2H), 1.97 (q, *J* = 7.1 Hz, 2H), 1.35-1.23 (m, 2H), 0.81 (t, *J* = 7.4 Hz, 3H); **¹³C NMR** (CDCl₃, 100 MHz), δ 141.8, 138.6, 133.7, 129.1 (2C), 128.7 (2C), 116.2, 60.4, 34.7, 22.0, 13.7; **IR**: ν (cm⁻¹) 3276, 2925, 1507, 1461, 1447, 1363, 1341, 1184, 1084, 729; **HRMS** (ESI): *m/z* calculated for C₁₂H₁₇O₂S [M+H]⁺ 225.0944, found: 225.0946.

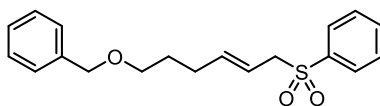
((cyclopent-1-en-1-ylmethyl)sulfonyl)benzene (6w).



Prepared according to **method A** from Sodium benzene sulfinate **5a** (164 mg, 1.00 mmol) and exomethylenecyclopentane **10n** (41.1 mg, 0.50 mmol). After workup, the crude mixture was purified by flash column chromatography (cyclohexane/ethyl acetate 10:1) to give ((cyclopent-1-en-1-ylmethyl)sulfonyl)benzene **6w** as a yellow oil (33.3 mg, 30% yield). The characterization data are in accordance with the ones reported in the literature.^[169]

¹H NMR (400 MHz, CDCl₃) δ 7.94-7.75 (m, 2H), 7.72-7.59 (m, 1H), 7.54 (ddt, *J* = 8.2, 6.6, 1.2 Hz, 2H), 5.50 (tt, *J* = 2.3, 1.2 Hz, 1H), 3.90 (q, *J* = 1.2 Hz, 2H), 2.44-2.31 (m, 2H), 2.31-2.22 (m, 2H), 1.95-1.78 (m, 2H).

(E)-((6-(benzyloxy)hex-2-en-1-yl)sulfonyl)benzene (6x).



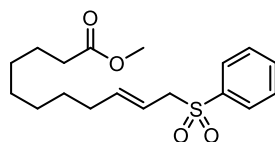
Prepared according to **method B'** from sodium benzene sulfinate **5a** (164 mg, 1.00 mmol) and 6-(benzyloxy)hex-1-ene **10c** (95.2 mg, 0.50 mmol). After workup, the crude mixture was purified by flash column chromatography (dichloromethane/ethyl acetate 95:5) to give (E)-((6-(benzyloxy)hex-2-en-1-

^[169] a) Roy, S.; Das, I.; Bhanuprakash, K. *Tetrahedron* **1994**, *50*, 1847-1858; b) Brandänge, S.; Leijonmarck, H. *Chem. Commun.* **2004**, 292-293.

yl)sulfonyl)benzene **6x** as a colorless oil (84.0 mg, 51% yield, *E/Z* 76:24).

¹H NMR (CDCl₃, 400 MHz) δ 7.84-7.70 (m, 2H), 7.58-7.49 (m, 1H), 7.49-7.39 (m, 2H), 7.31-7.17 (m, 5H), 5.51-5.38 (m, 1H), 5.38-5.27 (m, 1H), 4.39 (s, 2H, major), 4.36 (s, 2H, minor), 3.77 (d, *J* = 7.8 Hz, 2H, minor), 3.66 (d, *J* = 7.2 Hz, 2H, major), 3.32 (t app., *J* = 6.5 Hz, 2H, major), 3.25 (t app., *J* = 6.3 Hz, 2H, minor), 2.03 (q, *J* = 7.2 Hz, 2H, major), 1.78 (q, *J* = 7.6 Hz, 2H, minor), 1.59-1.45 (m, 2H, major), 1.43-1.32 (m, 2H, minor); ¹³C NMR (CDCl₃, 100 MHz), δ 141.1, 138.9, 138.6, 133.7, 129.1 (2C), 128.6 (2C), 128.5 (3C), 127.8 (2C), 116.5, 73.0, 69.4, 60.2, 29.3, 28.9; IR: ν (cm⁻¹) 2929, 2855, 1585, 1496, 1479, 1447, 1305, 1141, 1085, 969, 730, 688; HRMS (ESI): *m/z* calculated for C₁₉H₂₆NO₃S [M+NH₄]⁺ 348.1628, found: 348.1626.

Methyl (*E*)-11-(phenylsulfonyl)undec-9-enoate (**6y**).



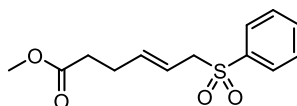
Prepared according to **method A** from sodium benzene sulfinate **5a** (164 mg, 1.00 mmol) and methyl 1-undecenoate **10o** (99.2 mg, 0.50 mmol). After workup, the crude mixture was purified by flash column chromatography (dichloromethane/ethyl acetate 95:5) to give methyl (*E*)-11-(phenylsulfonyl)undec-9-enoate **6y** as a colorless oil (20.2 mg, 12% yield).

Prepared according to **method B'** from sodium benzene sulfinate **5a** (164 mg, 1.00 mmol) and methyl 1-undecenoate **10o** (99.2 mg, 0.50 mmol). After workup, the crude mixture was purified by flash column chromatography (dichloromethane/ethyl acetate 95:5) to give methyl (*E*)-11-(phenylsulfonyl)undec-9-enoate **6y** as a colorless oil (114.5 mg, 68% yield, *E/Z* 77:23).

¹H NMR (CDCl₃, 400 MHz) δ 7.91-7.77 (m, 2H), 7.67-7.58 (m, 1H), 7.58-7.48 (m, 2H), 5.55-5.44 (m, 1H), 5.44-5.32 (m, 1H), 3.84 (dd, *J* = 7.8, 1.2 Hz, 2H, minor), 3.73 (dd, *J* = 7.1, 0.9 Hz, 2H, major), 3.66 (s, 3H, major), 3.65 (s, 3H, minor), 2.33-2.25 (m, 2H), 1.97 (q, *J* = 6.9 Hz, 2H, major), 1.62 (q, *J* = 7.7 Hz, 2H, minor), 1.58-1.54 (m, 4H), 1.33-1.14 (m, 6H); ¹³C NMR (CDCl₃, 100 MHz), δ 174.4, 141.9, 138.8, 133.7, 129.1 (2C), 128.6 (2C), 116.0, 60.3, 51.6, 34.2, 32.6, 29.1 (2C), 28.9, 28.7, 25.0; IR: ν (cm⁻¹) 2928, 2855, 1733, 1447, 1306, 1243, 1144, 1085, 969, 729, 689; HRMS (ESI): *m/z* calculated for C₁₈H₃₀NO₄S

[M+NH₄]⁺ 356.1890, found: 356.1889.

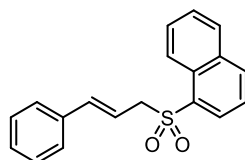
Methyl (*E*)-6-(phenylsulfonyl)hex-4-enoate (6z**).**



Prepared according to **method B'** from sodium benzene sulfinate **5a** (164 mg, 1.00 mmol) and methyl 1-hexenoate **10p** (64.1 mg, 0.50 mmol). After workup, the crude mixture was purified by flash column chromatography (dichloromethane/ethyl acetate 95:5) to give *Methyl (E)-6-(phenylsulfonyl)hex-4-enoate* **6z** as a colorless oil (77.7 mg, 58% yield, *E/Z* 4:1).

¹H NMR (CDCl₃, 400 MHz) δ 7.89 (d, *J* = 7.1 Hz, 2H minor), 7.84 (d, *J* = 7.2 Hz major), 7.67-7.61 (m, 1H), 7.58-7.51 (m, 2H), 5.76-5.67 (m, 1H, minor), 5.57-5.40 (m, 2H), 3.89 (d, *J* = 7.9 Hz, 2H minor), 3.73 (d, *J* = 6.4 Hz, 2H major), 3.65 (s, 3H, major), 3.63 (s, 3H, minor), 2.38-2.25 (m, 4H, major), 2.20-2.12 (m, 2H, minor), 2.12-2.06 (m, 2H, minor); ¹³C NMR (CDCl₃, 100 MHz), δ 173.0, 139.4 (major), 138.5, 137.3 (minor), 133.8, 129.2 (2C), 128.6 (2C), 117.5 (major), 116.9 (minor), 60.1 (major), 55.2 (minor), 51.8, 33.1 (major), 33.0 (minor), 27.8 (major), 22.8 (minor); IR: ν (cm⁻¹) 2953, 2923, 2853, 1732, 1447, 1305, 1148, 1135, 1085, 970, 731, 689; HRMS (ESI): *m/z* calculated for C₁₃H₂₀NO₄S [M+NH₄]⁺ 286.1108, found: 286.1108.

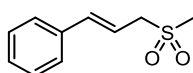
***trans*-Cinnamyl-α-naphthyl sulfone (**6aa**).**



Prepared according to **method B** from sodium α-naphthalene sulfinate **5g** (214 mg, 1.00 mmol) and allylbenzene **10d** (59.1 mg, 0.50 mmol). After workup, the crude mixture was purified by flash column chromatography (pentane/ethyl acetate 4:1) to give *trans*-cinnamyl-α-naphthyl sulfone **6aa** as a colorless solid (20.0 mg, 13% yield). The characterization data are in accordance with the ones reported in the literature.^[73]

¹H NMR (400 MHz, CDCl₃) δ 8.83 (dd, *J* = 8.6, 1.0 Hz, 1H), 8.26 (dd, *J* = 7.4, 1.3 Hz, 1H), 8.12 (d, *J* = 8.2 Hz, 1H), 8.01-7.93 (m, 1H), 7.72 (ddd, *J* = 8.5, 6.9, 1.5 Hz, 1H), 7.64 (ddd, *J* = 8.1, 6.9, 1.2 Hz, 1H), 7.56 (dd, *J* = 8.2, 7.3 Hz, 1H), 7.32–7.21 (m, 3H), 7.17 (dd, *J* = 7.5, 2.0 Hz, 2H), 6.27 (d, *J* = 15.8 Hz, 1H), 6.04 (dt, *J* = 15.6, 7.5 Hz, 1H), 4.16 (dd, *J* = 7.5, 1.1 Hz, 2H).

trans-Cinnamyl-methyl sulfone (**6ab**).

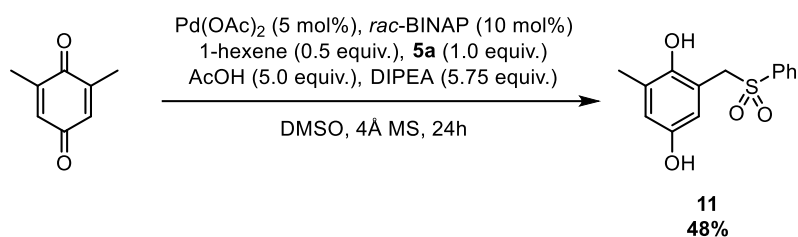


Prepared according to **method B** from Sodium methyl sulfinat **5k** (204 mg, 2.00 mmol) and allylbenzene **10d** (59.1 mg, 0.50 mmol). After workup, the crude mixture was purified by flash column chromatography (pentane/ethyl acetate 1:1) to give *trans*-cinnamyl-methyl sulfone **6ab** as a colorless solid (47.0 mg, 48% yield). The characterization data are in accordance with the ones reported in the literature.^[72]

¹H NMR (400 MHz, CDCl₃) δ 7.46-7.39 (m, 2H), 7.40-7.27 (m, 3H), 6.72 (dt, *J* = 15.9, 1.4 Hz, 1H), 6.29 (dt, *J* = 15.9, 7.6 Hz, 1H), 3.88 (dd, *J* = 7.6, 1.0 Hz, 2H), 2.89 (d, *J* = 0.8 Hz, 3H).

3.3. Studies on the synthesis of the hydroquinone byproduct **11**.

3.3.1. Side-chain Sulfonylation of 2,6-dimethyl-1,4-benzoquinone

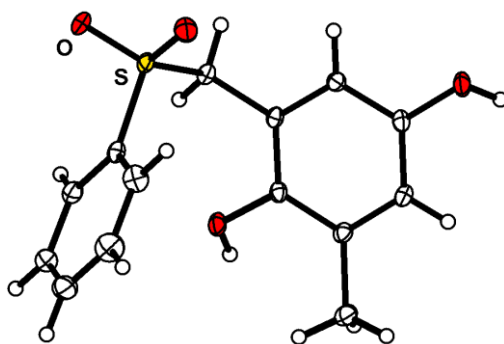


A sealed tube equipped with a magnetic stirring bar was charged with 27.6 mg (0.20 mmol, 1.0 equiv.) of 2,6-dimethyl-1,4-benzoquinone, 9.2 mg (0.01 mmol, 5 mol%) of palladium(II) acetate, 15.9 mg (0.04 mmol, 20 mol%) of *rac*-BINAP, 8.4 mg (0.10 mmol, 0.5 equiv.) of 1-hexene, 23.0 mg of 4Å MS and 32.8 mg (0.20 mmol, 1.0 equiv.) of sodium benzenesulfinate **5a**. The tube was placed under vacuum and then backfilled with argon. The vacuum/argon cycles were repeated twice and 0.3 mL of DMSO (0.66

M), 58 μL (1.00 mmol, 5.0 equiv.) of AcOH and 200 μL (1.15 mmol, 5.75 equiv.) of DIPEA was introduced. The mixture was stirred at 80°C until conversion was complete as checked by TLC. The reaction was quenched by addition of a saturated aqueous sodium bicarbonate (3 mL) and then diluted with ethyl acetate (5 mL). The layers were separated and the aqueous layer was extracted with ethyl acetate (3 x 10 mL). The combined organic layers were dried over anhydrous magnesium sulfate, filtered and the filtrate was concentrated under reduced pressure. The crude product was purified by flash column chromatography (cyclohexane/ethyl acetate 2:1) to give *2-methyl-6-((phenylsulfonyl)methyl)benzene-1,4-diol* **11** as a yellow solid (26.7 mg, 48% yield).

$^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.81-7.69 (m, 2H), 7.68-7.61 (m, 1H), 7.56-7.45 (m, 2H), 6.63 (d, $J = 3.0$ Hz, 1H), 6.36 (s, 1H), 6.09 (d, $J = 3.0$ Hz, 1H), 4.48 (s, 1H), 4.36 (s, 2H), 2.24 (s, 3H); $^{13}\text{C NMR}$ (101 MHz, CDCl_3) δ 149.3, 147.6, 137.2, 134.2, 129.5, 129.1 (2C), 128.5 (2C), 119.1, 116.6, 115.9, 59.3, 16.4; **HRMS** (ESI) m/z : $[\text{M}+\text{Na}]^+$ Calcd for $\text{C}_{14}\text{H}_{14}\text{O}_4\text{SNa}$ 301.0505. Found 301.0506; **IR**: ν (cm^{-1}) 3369, 1653, 1448, 1401, 1262, 1231, 1177, 1156, 1144, 984, 931, 891.

X-ray analysis (recrystallization by slow diffusion of cyclohexane in the product dissolved in the minimum amount of acetone)



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should always be used as a source of symmetry information in preference to the above space-group names.

They are only intended as comments.

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SADABS : Krause, L., Herbst-Irmer, R., Sheldrick G.M. & Stalke D. *J. Appl. Cryst.* **2015**, *48*, 3-10.

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O2 3 0.494461 0.429293 0.184199 11.00000 0.02617 0.02609 =
0.04333 -0.01047 -0.00578 -0.01146

O3 3 0.800914 0.786909 0.178457 11.00000 0.01713 0.02233 =
0.05053 -0.01787 -0.00626 -0.00340

AFIX 147

H3 2 0.840023 0.864916 0.166962 11.00000 -1.50000

AFIX 0

O4 3 -0.008782 1.006881 0.143025 11.00000 0.01696 0.02133 =
0.05182 -0.01575 -0.00847 -0.00106

AFIX 147

H4 2 -0.054403 1.108287 0.127426 11.00000 -1.50000

AFIX 0

C1 1 0.664319 0.657239 0.047982 11.00000 0.02223 0.01710 =
0.02185 -0.00765 -0.00084 -0.00449

AFIX 23

H1A 2 0.797508 0.671430 0.026853 11.00000 -1.20000

H1B 2 0.616685 0.681630 -0.035134 11.00000 -1.20000

AFIX 0

C2 1 0.523280 0.778553 0.111917 11.00000 0.02039 0.01344 =
0.01999 -0.00429 -0.00159 -0.00403

C3	1	0.598790	0.842987	0.174015	11.00000	0.01754	0.01478 =
		0.02420	-0.00455	-0.00284	-0.00451		
C4	1	0.469247	0.957781	0.232361	11.00000	0.02315	0.01740 =
		0.02561	-0.00839	-0.00238	-0.00714		
C5	1	0.267376	1.012347	0.219886	11.00000	0.02114	0.01731 =
		0.02640	-0.00978	0.00058	-0.00445		
AFIX	43						
H5	2	0.178286	1.092208	0.256825	11.00000	-1.20000	
AFIX	0						
C6	1	0.193084	0.952484	0.154465	11.00000	0.01738	0.01645 =
		0.02569	-0.00476	-0.00300	-0.00415		
C7	1	0.319422	0.832698	0.103227	11.00000	0.02251	0.01741 =
		0.02307	-0.00647	-0.00491	-0.00597		
AFIX	43						
H7	2	0.267451	0.787742	0.062427	11.00000	-1.20000	
AFIX	0						
C8	1	0.544666	1.017441	0.310507	11.00000	0.02870	0.03651 =
		0.05041	-0.02847	-0.00674	-0.00629		
AFIX	137						
H8A	2	0.603670	1.102020	0.251137	11.00000	-1.50000	
H8B	2	0.645894	0.925901	0.362888	11.00000	-1.50000	
H8C	2	0.433450	1.063176	0.368286	11.00000	-1.50000	

AFIX	0						
C9	1	0.791629	0.408563	0.286550	11.00000	0.02486	0.01474 =
		0.02672	-0.00747	-0.00448			
C10	1	0.679803	0.370310	0.407439	11.00000	0.03438	0.03117 =
		0.03058	-0.00376	-0.00097			
AFIX	43						
H10	2	0.547300	0.370902	0.414243	11.00000	-1.20000	
AFIX	0						
C11	1	0.765344	0.331058	0.518538	11.00000	0.05596	0.03553 =
		0.02574	-0.00105	-0.00497			
AFIX	43						
H11	2	0.690528	0.305532	0.602015	11.00000	-1.20000	
AFIX	0						
C12	1	0.957756	0.329135	0.507785	11.00000	0.05427	0.03032 =
		0.03529	-0.00941	-0.02142			
AFIX	43						
H12	2	1.016020	0.300268	0.584152	11.00000	-1.20000	
AFIX	0						
C13	1	1.067742	0.369027	0.386240	11.00000	0.03020	0.03583 =
		0.04878	-0.02239	-0.01271			
AFIX	43						
H13	2	1.200316	0.368106	0.379727	11.00000	-1.20000	

AFIX 0
C14 1 0.984525 0.410052 0.274787 11.00000 0.02503 0.02844 =
0.03322 -0.01682 -0.00152 -0.00481

AFIX 43

H14 2 1.058341 0.438872 0.191279 11.00000 -1.20000

AFIX 0

HKLF 4

REM tc593 in P-1

REM wR2 = 0.0849, GooF = S = 1.048, Restrained GooF = 1.048 for all data

REM R1 = 0.0322 for 2172 Fo > 4sig(Fo) and 0.0338 for all 2294 data

REM 176 parameters refined using 0 restraints

END

WGHT 0.0447 0.2765

REM Highest difference peak 0.332, deepest hole -0.312, 1-sigma level 0.046

Q1 1 0.7417 0.4396 0.2235 11.00000 0.05 0.33

Q2 1 0.6768 0.5595 0.0937 11.00000 0.05 0.33

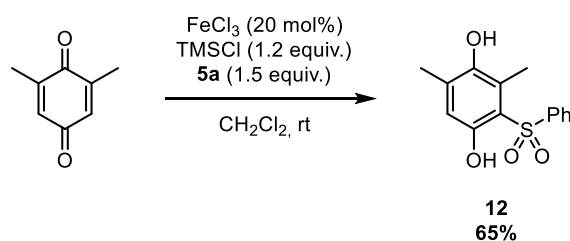
Q3 1 0.5600 0.8090 0.1461 11.00000 0.05 0.21

Q4 1 0.7322 0.2803 0.4776 11.00000 0.05 0.20

Q5 1 0.6850 1.0074 0.3045 11.00000 0.05 0.19

Q6	1	0.2351	0.9854	0.1826	11.00000	0.05	0.18
Q7	1	0.4297	0.8140	0.0970	11.00000	0.05	0.18
Q8	1	0.5824	0.7158	0.0906	11.00000	0.05	0.18
Q9	1	0.4689	1.1371	0.3019	11.00000	0.05	0.17
Q10	1	0.5277	0.8801	0.2191	11.00000	0.05	0.17

3.3.2. Reductive sulfonylation of 2,6-DMBQ on the endocyclic position.



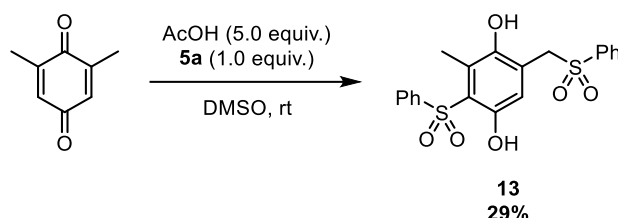
A sealed tube equipped with a magnetic stirring bar was charged with 27.6 mg (0.20 mmol, 1.0 equiv.) of 2,6-dimethyl-1,4-benzoquinone, 6.5 mg (0.04 mmol, 20 mol%) of iron(III) chloride and 49.2 mg of sodium benzenesulfinate **5a** (0.30 mmol, 1.5 equiv.). The tube was placed under vacuum and then backfilled with argon. The vacuum/argon cycles were repeated twice and 0.3 mL of distilled dichloromethane (0.66 M) followed by 30 μL of chlorotrimethylsilane (0.24 mmol, 1.2 equiv.) were introduced. The mixture was stirred at room temperature until conversion was complete as checked by TLC. The reaction was quenched by addition of a saturated aqueous solution of sodium bicarbonate (3 mL) and diluted with ethyl acetate (5 mL). The layers were separated and the aqueous layer was extracted with ethyl acetate (3 x 10 mL). The combined organic layers were dried over anhydrous magnesium sulfate and filtered. The filtrate was concentrated under reduced pressure. The crude product was purified by flash column chromatography (cyclohexane/ethyl acetate 3:1) to give 3,5-dimethyl-2-(phenylsulfonyl)benzene-1,4-diol **12** as a yellow solid (36.2 mg, 65% yield). The characterization data are in accordance with the ones reported in the literature.^[170]

$^1\text{H NMR}$ (400 MHz, CDCl_3) δ 9.99 (s, 1H), 7.90-7.81 (m, 2H), 7.64-7.56 (m, 1H), 7.55-7.46 (m, 2H), 6.76

^[170] Yuan, J. W.; Liu, S. N.; Qu, L. B. *Tetrahedron* **2017**, *73*, 6763–6772.

(s, 1H), 4.28 (s, 1H), 2.39 (s, 3H), 2.15 (s, 3H).

3.3.3. Bis-sulfonylation of 2,6-DMBQ.



A sealed tube equipped with a magnetic stirring bar was charged with 27.6 mg (0.20 mmol, 1.0 equiv.) of 2,6-dimethyl-1,4-benzoquinone, 32.8 mg (0.20 mmol, 1.0 equiv.) of sodium benzenesulfinate **5a**. The tube was placed under vacuum and then backfilled with argon. The vacuum/argon cycles were repeated twice and 0.3 mL of DMSO (0.66 M) followed by 58 μ L (1.00 mmol, 5.0 equiv.) of acetic acid were introduced. The mixture was stirred at room temperature until conversion was complete as checked by TLC. The mixture was filtered over a pad of silica gel with 25 mL of ethyl acetate. The filtrate was concentrated under reduced pressure and the residue was purified by flash column chromatography (cyclohexane/ethyl acetate 1:1) to give *3-methyl-2-(phenylsulfonyl)-5-((phenylsulfonyl)methyl)benzene-1,4-diol 13* as a yellow solid (24.2 mg, 29% yield).

$^1\text{H NMR}$ (300 MHz, CDCl_3) δ 7.91-7.78 (m, 3H), 7.79-7.72 (m, 2H), 7.60-7.47 (m, 5H), 6.94 (d, $J = 0.9$ Hz, 1H), 5.00 (s, 2H), 2.34 (s, 3H); $^{13}\text{C NMR}$ (101 MHz, CDCl_3) δ 152.4, 149.3, 142.3, 139.8, 137.3, 135.1, 129.4 (2C), 129.1 (2C), 128.8 (2C), 128.3, 125.9 (2C), 122.9, 118.2, 114.3, 54.8, 17.4; **HRMS** (ESI) m/z : $[\text{M}+\text{Na}]^+$ Calcd for $\text{C}_{20}\text{H}_{18}\text{O}_6\text{S}_2\text{Na}$ 441.0437. Found 441.0436.

3.3.4. O-Sulfonylation of 2,6-DMBQ.



A sealed tube equipped with a magnetic stirring bar was charged with 55.2 mg (0.40 mmol, 2.0 equiv.) of 2,6-dimethyl-1,4-benzoquinone, 24.8 mg (0.04 mmol, 20 mol%) of ytterbium(III) triflate and 32.8 mg of sodium benzenesulfinate **5a** (0.20 mmol, 1.0 equiv.). The tube was placed under vacuum and then backfilled with argon. The vacuum/argon cycles were repeated twice and 0.3 mL of dry DMSO (0.66 M) was introduced. The mixture was stirred at 80°C until conversion was complete as checked by TLC. The mixture was filtered over a pad of silica gel with 25 mL of ethyl acetate. The filtrate was concentrated under reduced pressure and the residue was purified by flash column chromatography (cyclohexane/ethyl acetate 5:1) to give *4-hydroxy-3,5-dimethylphenyl benzenesulfonate* **14** as a yellow solid (10.6 mg, 19% yield).

¹H NMR (400 MHz, CDCl₃) δ 8.02-7.88 (m, 2H), 7.76-7.63 (m, 1H), 7.61-7.51 (m, 2H), 6.47 (s, 2H), 2.05 (s, 6H); **¹³C NMR** (101 MHz, CDCl₃) δ 153.6 (2C), 141.1, 137.2, 134.0, 133.5, 129.2 (2C), 128.1 (2C), 115.5 (2C), 17.3 (2C), **HRMS** (ESI) m/z: [M+Na]⁺ Calcd for C₁₄H₁₄O₄SNa 301.0505. Found 301.0506.

Allylsulfones through Palladium-Catalyzed Allylic C–H Sulfonylation of Terminal Alkenes

Tingting Chen,^[a] Jassmin Lahbi,^[a, b] Gianluigi Brogginì,^[b] Alexandre Pradal,^{*,[a]} and Giovanni Poli^{*,[a]}*In memory of Professor Gaetano Zecchi*

Two previously unknown protocols for Pd-catalyzed allylic C–H sulfonylation of terminal alkenes have been developed. While the former consists of a direct Pd(II)-catalyzed oxidative C–H allylic sulfonylation in the presence of sulfinate anions, the

latter involves a sequential one-pot Pd(II)-catalyzed C–H allylic acetoxylation followed by a Pd(0)-catalyzed sulfonylation. The scope of both protocols was studied on 25 examples.

Introduction

Organosulfur compounds represent an important class of molecules that play a key role in a number of organic reactions, and find applications in various fields of chemistry. In particular, the relevance and versatility of sulfones^[1] is so high that B. M. Trost^[2] defined them as chemical *chameleons*, and P. L. Fuchs^[3] as *pluripotent*. In addition, sulfones are intermediates in synthetically relevant reactions such as the Julia-Lythgoe olefination, the modified Julia,^[4] and the Julia-Kociensky olefination,^[5] the Ramberg-Bäcklund reaction,^[6] as well as a number of other desulfonylative transformations.^[7]

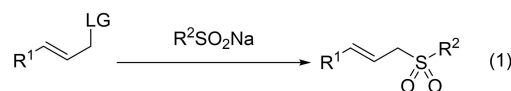
In the course of a project directed toward the synthesis of conjugated polyenes, we became interested in the preparation of allylsulfones. The classic way to access these compounds involves the coupling between substrates bearing an allylic leaving group (LG) and sulfinate anions.^[8,9] This well-known strategy (Scheme 1, equation 1), although normally effective, often implies several synthetic steps, as the required allylic precursors are not always commercially available. Conversely, the direct C–H sulfonylation of alkenes, which, thanks to its step-economy and the abundance of the alkenes would represent a much more elegant access to allylsulfones, has

been so far reported only for the very restricted case of α -methylstyrenes (Scheme 1, equation 2).^[10]

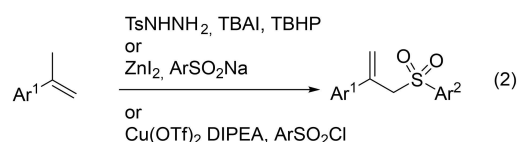
Considering the recent studies by us and others on the Pd-catalyzed allylic C–H activation of alkenes to form C–O,^[11] C–N^[12] and C–C bonds (Scheme 1, equation 3),^[13] we decided to investigate the direct C–H sulfonylation of terminal alkenes.^[14]

We describe in this article the development of two protocols of Pd-catalyzed direct C–H sulfonylation of terminal alkenes (Scheme 1, equation 4).

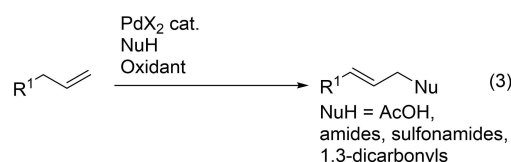
■ Traditional synthesis of allylsulfones (refs 1, 2)



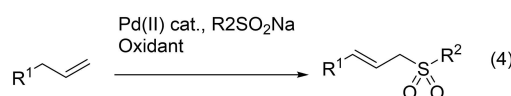
■ C–H sulfonylation of α -methyl styrenes (refs 10a-c)



■ C–H-to-C–O, C–N and C–C bond formation (refs 11–13)



■ This work - C–S bond formation



Scheme 1. Previous works related to the synthesis of allylsulfones (equations 1–3), and this work (equation 4).

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Supporting information for this article is available on the WWW under <https://doi.org/10.1002/ejoc.202201493>

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Results and Discussion

We started our study choosing for our model reaction the coupling between allylbenzene (**1a**) and sodium *p*-toluenesulfinate (**2a**). Gratifyingly, reacting **1a** (1.0 equiv.) with **2a** (2.0 equiv.) in the presence of palladium acetate (10 mol%) and 2,6-dimethylbenzoquinone (2,6-DMBQ) (2.0 equiv.) as the terminal oxidant, in freshly distilled acetonitrile (0.2 M), at 80 °C under argon, gave after 72 h of reaction the expected allylsulfone **3aa** in 42% yield (Table 1, entry 1). Performing the reaction under aerobic conditions led to the same result.

We then studied the influence of several parameters on the outcome of the reaction. A screening of polar solvents (propionitrile, DMF, DMSO, THF, 1,4-dioxane, MTBE, HFIP) showed that none of them gave a better yield than acetonitrile (Table 1, entries 2–8). With propionitrile, a similar result was obtained when the reaction was performed at 110 °C (Table 1, entry 2, note c). Suspecting that the moderate yield and the long reaction time could be due to a poor solubility of the sulfinate salt in acetonitrile, we tested methanol as a cosolvent. However, performing the reaction in CH₃CN/MeOH 4:1 v/v gave a poor yield of 29% (Table 1, entry 9). We next investigated the influence of the oxidant while keeping acetonitrile as the solvent. The use of other quinones such as benzoquinone (BQ), 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ), duroquinone (DQ) and 2,5-dimethyl-1,4-benzoquinone (2,5-DMBQ) proved to be unfruitful (Table 1, entries 10–13).^[15] We thus decided to keep 2,6-DMBQ as the oxidant and screened other palladium(II) sources. However, except for palladium(II) acetylacetonate, which gave results similar to palladium(II) acetate (Table 1, entry 16), none of the other catalysts provided better yields (Table 1, entries 14–18). We finally decided to retain palladium(II) acetylacetonate, as some reproducibility problems were encountered with palladium(II) acetate due to the variable purity of commercial batches. The use of ancillary ligands was also evaluated. However, none of those tested (bis-sulfoxide,

pyridine-type, phenanthroline, pyridones, *N*-acetyl amino acids) gave allylsulfone **3aa** with a better yield than without ligands (See Supporting Information). Finally, changing the concentration of the reaction to 0.66 M increased slightly the yield of **3aa** to 47% (Table 1, entry 19).

With the optimized reaction conditions in hand (Method A), the scope of the reaction was then evaluated, starting with the couplings between allylbenzene **1a** and various sulfonates (Scheme 3). Electron-rich *p*-toluene-, phenyl- and 4-methoxyphenylsulfonates **2a**, **2b** and **2c** provided the corresponding allylsulfones **3aa**, **3ab** and **3ac** in 47%, 58% and 41% isolated yield. Sodium α -naphthylsulfinate gave only degradation products. Electron-poor arylsulfonates reacted too, although their coupling was much more sluggish. For example, only 57% conversion was measured by quantitative ¹H NMR analysis after 72 h of reaction of sodium 4-nitrobenzenesulfinate **2f**. Nevertheless, the desired allylsulfones **3ae** and **3af** could be obtained with 11% yield and 37% yield, respectively. Sodium 4-bromophenylsulfinate **2g** gave the corresponding allylsulfone **3ag** with 45% isolated yield. Worthy of note, the C–Br bond was not affected. Sodium thiophene-2-sulfinate gave only degradation products.

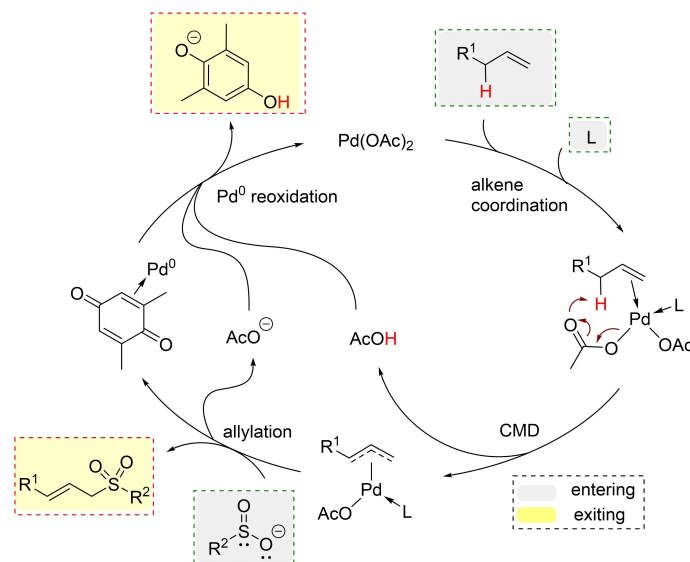
Alkylsulfonates proved also to be reactive. Indeed, reaction between sodium propane-2-sulfinate **2h**, or sodium cyclopropanesulfinate **2i**, gave allylsulfones **3ah** and **3ai** in 22% and 51% yield, respectively. Sodium methylsulfinate, sodium camphorsulfinate and sodium benzylsulfinate, gave no conversion or degradation products. Therefore, cyclopropylsulfinate **2i** turned out to be the only alkylsulfinate able to give the coupling. The reaction was also totally ineffective with very electron-poor sulfonates such as sodium trifluoromethylsulfinate (Langlois' reagent).

On the basis of previous reports on Pd-catalyzed allylic C–H activation reactions, a tentative mechanism is proposed (Scheme 2).^[11e,12d,14] After coordination of the alkene to the Pd(II) catalyst, an allylic proton is abstracted via a likely concerted

Table 1. Optimization of the reaction conditions.^[a]

entry ^[a]	PdX ₂	Oxidant	Solvent	Yield 3aa [%] ^[b]	entry ^[a]	PdX ₂	Oxidant	Solvent	Yield 3aa [%] ^[b]
1	Pd(OAc) ₂	2,6-DMBQ	CH ₃ CN	42	10	Pd(OAc) ₂	BQ	CH ₃ CN	3
2	Pd(OAc) ₂	2,6-DMBQ	EtCN	35 ^[c]	11	Pd(OAc) ₂	DDQ	CH ₃ CN	< 2
3 ^[d]	Pd(OAc) ₂	2,6-DMBQ	DMF	13	12	Pd(OAc) ₂	DQ	CH ₃ CN	10
4 ^[d]	Pd(OAc) ₂	2,6-DMBQ	DMSO	13	13	Pd(OAc) ₂	2,5-DMBQ	CH ₃ CN	36
5	Pd(OAc) ₂	2,6-DMBQ	THF	12	14	Pd(OPiv) ₂	2,6-DMBQ	CH ₃ CN	12
6	Pd(OAc) ₂	2,6-DMBQ	1,4-dioxane	2	15	Pd(TFA) ₂	2,6-DMBQ	CH ₃ CN	26
7	Pd(OAc) ₂	2,6-DMBQ	MTBE	< 2	16	Pd(acac) ₂	2,6-DMBQ	CH ₃ CN	42
8	Pd(OAc) ₂	2,6-DMBQ	HFIP	26	17	PdCl ₂ (CH ₃ CN) ₂	2,6-DMBQ	CH ₃ CN	23
9	Pd(OAc) ₂	2,6-DMBQ	MeCN/MeOH (4:1)	29	18	PdCl ₂	2,6-DMBQ	CH ₃ CN	15
					19 ^[e]	Pd(acac) ₂	2,6-DMBQ	CH ₃ CN	47

[a] Reaction conditions: allylbenzene **1a** (0.2 mmol), sodium *p*-toluenesulfinate **2a** (2.0 equiv.), Pd(OAc)₂ (10 mol%), 2,6-DMBQ (2.0 equiv.), CH₃CN (0.2 M) were heated at 80 °C in a sealed tube under Ar. [b] Yields were determined by quantitative ¹H NMR analysis, using 1,4-dinitrobenzene as an internal standard. [c] Allylsulfone **3aa** was obtained with 33% NMR yield when heating at 110 °C instead of 80 °C. [d] The reaction was finished after 45 h. [e] CH₃CN (0.66 M); 2,6-DMBQ: 2,6-dimethyl-1,4-benzoquinone; BQ: 1,4-benzoquinone; DDQ: 2,3-dichloro-5,6-dicyano-1,4-benzoquinone; DQ: duroquinone (2,3,5,6-tetramethyl-1,4-benzoquinone); 2,5-DMBQ: 2,5-dimethyl-1,4-benzoquinone; acac: acetylacetonate.



Scheme 2. Proposed mechanism for the direct Pd-catalyzed allylic C–H sulfonation of terminal alkenes. L = 2,6-DMBQ.

metalation deprotonation (CMD) mechanism, and the thus generated η^3 -allylpalladium intermediate undergoes substitution by the sulfinate anion. Finally, after product decoordination, the generated Pd(0) complex, is reoxidized by the coordinated benzoquinone.

Given the moderate yields associated to some of the direct C–H sulfonations, we decided to study an alternative protocol. Accordingly, on the basis of our previous work on the amination of but-3-enoic acids,^[12h] we envisioned to perform a sequential one-pot doubly Pd-catalyzed procedure consisting in an initial oxidative Pd(II)-catalyzed allylic C–H alkene acetoxylation, followed by a redox-neutral Pd(0)-catalyzed allylic sulfonation. The major challenge of this process consists in the use of the same palladium source for both the transformations. In the event, reacting allylbenzene (1.0 equiv.) with acetic acid (10.0 equiv.), in the presence of 2,6-DMBQ (2.0 equiv.) and Pd(OAc)₂ (10 mol%), in DMSO (0.2 M) at 80 °C gave the corresponding allylic acetate, which was not isolated (TLC

verification). Subsequent *in situ* addition of *rac*-BINAP (20 mol%), DIPEA (11.5 equiv.), and sodium *p*-toluenesulfinate (2.0 equiv.) with further stirring at 80 °C under air gave the desired allylsulfonate **3aa** in 82 % yield (Table 2, entry 1). When 10.0 equivalents of both acetic acid and base were used, the allylsulfone **3aa** was obtained with a similar yield (83 %), but in a much longer reaction time for the second step (Table 2, entry 2). Reducing this amount to 7.0, 5.0 or 3.0 equivalents resulted in generally longer reaction times for the second step accompanied with lower yields (Table 2, entries 3–5). We thus decided to keep our first conditions for the one-pot sequential protocol (Method B).

With the new one-pot sequential protocol in hand for the model coupling **1a**+**2a**, we re-evaluated the sulfonation of allylbenzene with the sulfinate salts previously used in the direct procedure (method A). The couplings turned out to be equally efficient with electron-rich sulfonates **2a–2c** as well as with electron poor sulfinate **2e**, affording satisfactory isolated

Table 2. Optimization attempt for the one-pot sequential C–H acetoxylation/sulfonation.^[a]

entry	AcOH (n equiv.)	DIPEA (m equiv.)	Time step 2 [h]	Yield 3aa [%] ^[b]
1	10.0	11.5	25	82
2	10.0	10.0	48	83
3	7.0	7.0	38	64
4	5.0	5.0	38	56
5	3.0	3.0	66	48

[a] Reaction conditions: allylbenzene **1a** (0.2 mmol), Pd(OAc)₂ (10 mol%), AcOH (n equiv.), 2,6-DMBQ (2.0 equiv.), 4 ÅMS (50 mg), DMSO (0.2 M) were heated at 80 °C in a sealed tube for 4 h (until complete conversion) then were introduced DIPEA (m equiv.), sodium *p*-toluenesulfinate **2a** (2.0 equiv.), *rac*-BINAP (20 mol%) and the mixture was heated at 80 °C until complete conversion of the cinnamylacetate intermediate. [b] Yields were determined by quantitative ¹H NMR analysis, using 1,4-dinitrobenzene as an internal standard; 2,6-DMBQ: 2,6-dimethyl-1,4-benzoquinone; DIPEA: N,N-di-isopropylethylamine; BINAP: 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl.

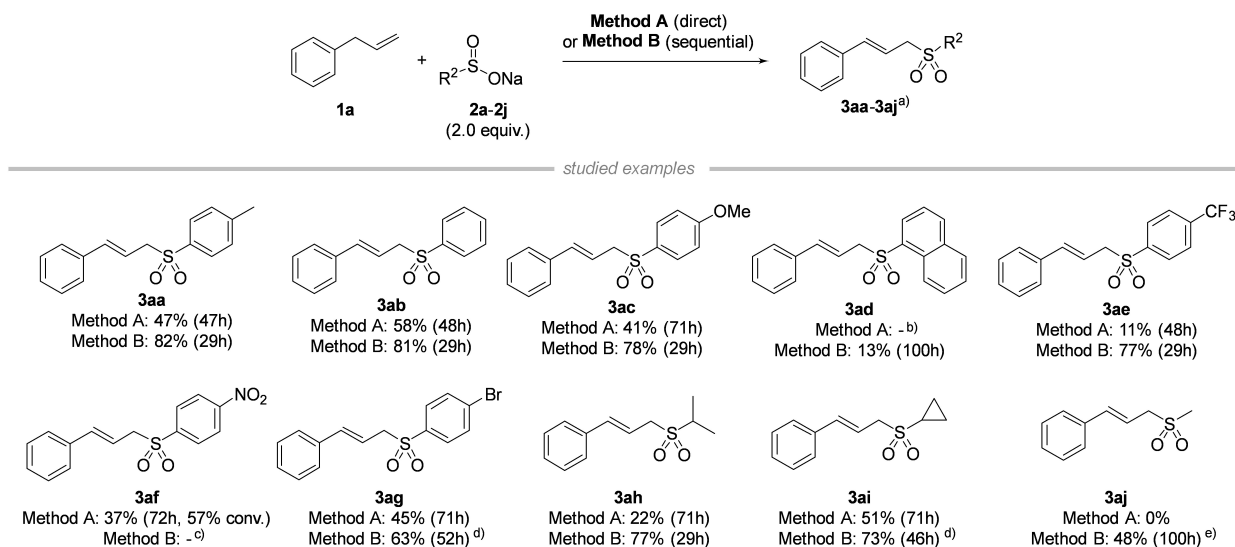
yields, ranging from 77% to 82% (Scheme 3). Such increases in yield when switching from Method A to Method B with reduced reaction times underscore the synthetic importance of the sequential one-pot procedure. However, with this protocol sodium α -naphthylsulfinate **2d** gave a low yield of cinnamylsulfone **3ad**, and sodium 4-nitrobenzenesulfinate **2f** did not sulfonate the intermediate cinnamylacetate **4**, which was recovered in 75% yield. When utilizing 2.0 equivalents of sodium 4-bromophenylsulfinate **2g**, only a partial conversion of intermediate cinnamylacetate **4** was detected (40% recovered) and the allylsulfone **3ag** was isolated with 45% yield. Such a low reactivity might be due to competitive oxidative addition of the carbon-bromine bond of the sulfinate to Pd(0). However, increasing the amount of sulfinate **2g** to 3.0 equivalents, the second step of the sequential procedure was complete and allylsulfone **3ag** was isolated with 63% yield. Alkylsulfonates **2h**, **2i** and **2j** were also relatively efficient with this one-pot protocol, affording the corresponding allylsulfones **3ah**, **3ai** and **3aj** in 77%, 73% and 48% yield, respectively (Scheme 3). In the case of sodium cyclopropylsulfinate **2i**, 3.0 equivalents were also needed to obtain a satisfactory yield of cinnamylsulfone **3ai**, as only 28% yield was obtained when using 2.0 equivalents of the sulfinate. Also, 4.4 equivalents of sodium methylsulfinate **2j** were necessary to obtain cinnamylmethylsulfone **3aj**.

We next studied the influence of the nature of the alkene on the reaction outcome with the two sets of conditions. For this study, sodium benzenesulfinate **2b** was chosen as the reaction partner, because it is the nucleophile that gave the best results and the corresponding allylsulfones are synthetic intermediates for Julia olefinations. Thus, submission of the

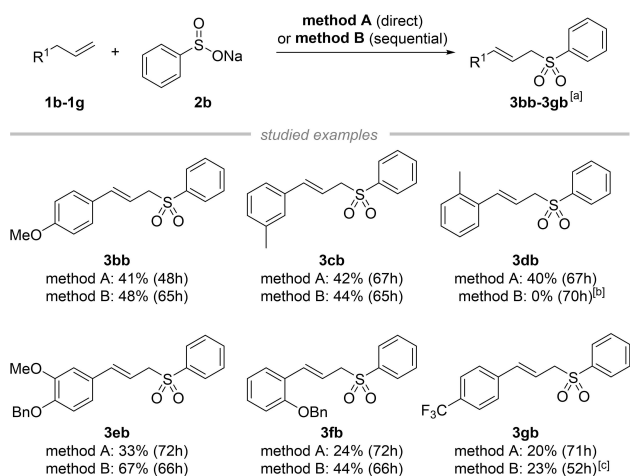
electron-rich allylarenes **1b** and **1c** to the coupling with sodium benzenesulfinate provided the corresponding allylsulfones **3bb** and **3cb** in 41% and 42% yield by Method A, and 48% and 44% yield by Method B (Scheme 4), respectively. *Ortho*-substituted allylbenzene **1d** gave allylsulfone **3db** in 40% yield with Method A, while no product was observed when using the sequential procedure of Method B. The phenolic derivatives benzyleugenol **1e** and 2-*O*-benzylallylbenzene **1f** gave the corresponding allylsulfones **3eb** and **3fb** in 33% and 24% yields with Method A, and in 67% and 42% yields with Method B. The electron-poor allylarene **1g** bearing a *para*-trifluoromethyl substituent afforded the expected allylsulfone **3gb** in 20% yield with Method A and in 23% yield with Method B (Scheme 4).^[16]

We next evaluated terminal aliphatic alkenes in the developed reaction conditions (Scheme 5). Undec-1-ene **1h**, dec-1-ene **1i**, non-1-ene **1j**, oct-1-ene **1k**, and hex-1-ene **1l** were engaged in the presence of sodium benzenesulfinate **2b**, providing with total regioselectivity the linear allylsulfones **3hb**–**3lb** with yields ranging between 30% and 45% with Method A. In most cases, the pure (*E*)-configured allylsulfones were isolated, although minor amounts of the (*Z*) isomers could be detected in the ¹H NMR spectra of the crude reaction products. Only in the case of allylsulfone **3jb**, both (*E*)- and (*Z*)-isomers could be isolated separately.

Unfortunately, with these aliphatic substrates the reaction conditions of Method B do not allow the generation of the intermediate allylacetate. Since the Pd(II)-catalyzed C–H allylic acetoxylation of terminal alkenes has been reported,^[11e] we decided to adopt these reaction conditions



Scheme 3. Evaluation of the reactivity of aryl- and alkylsulfonates in the developed reaction conditions (Methods A and B). [a] Typical reaction conditions: Method A: allylbenzene **1a** (0.5 mmol), **2a–2j** (2.0 equiv.), Pd(acac)₂ (10 mol%), 2,6-DMBQ (2.0 equiv.), CH₃CN (0.66 M), 80 °C in a sealed tube under Ar, 48–72 h. Method B: allylbenzene **1a** (0.5 mmol), Pd(OAc)₂ (10 mol%), AcOH (10.0 equiv.), 2,6-DMBQ (2.0 equiv.), 4 Å MS (50 mg), DMSO (0.2 M) were heated at 80 °C under air in a sealed tube for 4 h (until complete conversion of allylbenzene into the allylic acetate, TLC check). Then DIPEA (11.5 equiv.), **2a–2j** (2.0 equiv.), *rac*-BINAP (20 mol%) were introduced, and the mixture was heated at 80 °C until disappearance (TLC check) of the cinnamylacetate **4** intermediate. Reaction time for Method B corresponds to the sum of the reaction times for the two steps. Indicated yields refer to isolated, after silica gel column chromatography purification. [b] Only degradation products were formed. [c] No allylsulfone was formed. The intermediate cinnamylacetate **4** was obtained with 75% yield (measured by quantitative ¹H NMR with 1,4-dinitrobenzene as internal standard). [d] 3.0 equivalents of sodium 4-bromophenylsulfinate **2f** or sodium cyclopropylsulfinate **2i** were used. [e] 4.4 equivalents of sodium methylsulfinate **2j** were used.



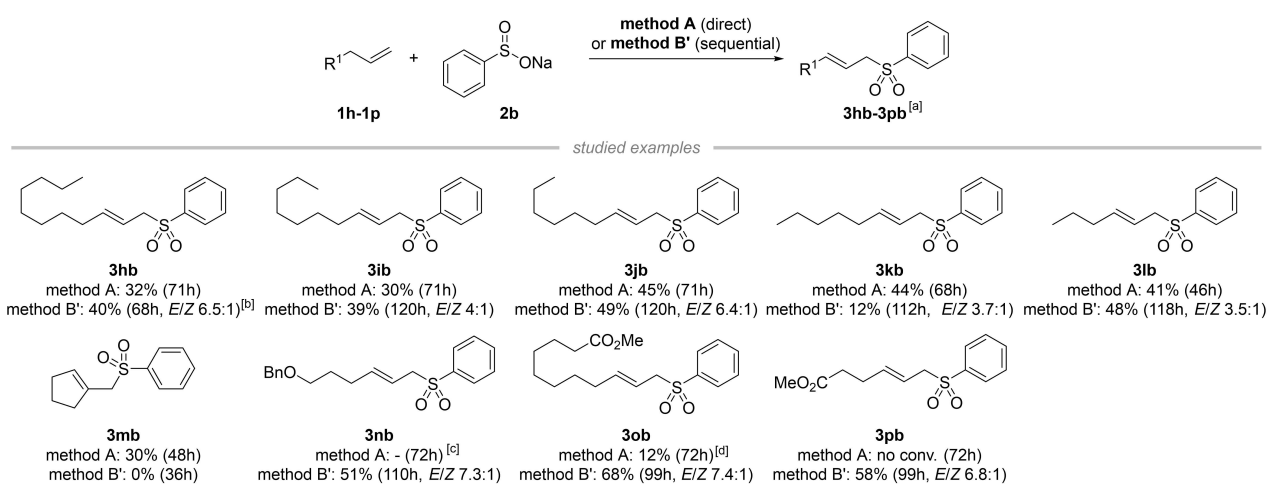
Scheme 4. Evaluation of allylarenes as substrates in the optimized reaction conditions. [a] Typical reaction conditions: **Method A:** allyl-derivative **1b–1g** (0.5 mmol), **2b** (2.0 equiv.), Pd(acac)₂ (10 mol%), 2,6-DMBQ (2.0 equiv.), CH₃CN (0.66 M), 80 °C in a sealed tube, 48–72 h. **Method B:** allyl-derivative **1b–1g** (0.5 mmol), Pd(OAc)₂ (10 mol%), AcOH (10.0 equiv.), 2,6-DMBQ (2.0 equiv.), 4 Å MS (50 mg), DMSO (0.2 M) were heated at 80 °C under air in a sealed tube until complete conversion of the allyl-derivative. Then DIPEA (11.5 equiv.), sodium benzenesulfinate **2b** (2.0 equiv.), *rac*-BINAP (20 mol%) were introduced, and the mixture was heated at 80 °C until complete conversion of the allylacetate intermediate. Reaction time for Method B corresponds to the sum of the reaction times for the two steps. Indicated yields refer to isolated, after silica gel column chromatography purification. [b] (*E*)-4-methylcinnamyl acetate was obtained with 26% yield as measured by ¹H quantitative NMR with 1,4-dinitrobenzene as internal standard. [c] The cinnamylsulfone **3gb** was obtained with 67% NMR yield, as measured by ¹H quantitative NMR with 1,4-dinitrobenzene as internal standard.

as the first step of Method B. In the event, following a variant of White's protocol, undec-1-ene **1h** was treated with Pd(OAc)₂ (10 mol%), in the presence of phenylvinylsulfonide

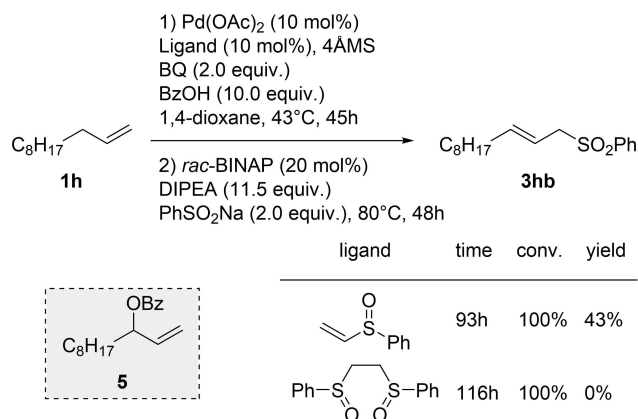
(10 mol%) BzOH (10.0 equiv.), benzoquinone (2.0 equiv.), and 4 Å MS (50 mg), in 1,4-dioxane (0.2 M). After 45 h stirring at 43 °C, treatment of the resulting branched allylic allylbenzoate **5** (TLC and ¹H NMR verification) with DIPEA (11.5 equiv.), sodium benzenesulfinate **2b** (2.0 equiv.), *rac*-BINAP (20 mol%) with heating at 80 °C, afforded the desired allylsulfone **3hb** in 43% NMR yield (Scheme 6). On the other hand, use of 1,2-bis(phenylsulfinyl)ethane (10 mol%) instead of phenylvinylsulfonide, did not allow the formation of the allyl sulfone, giving only allylbenzoate **5** in 48% spectroscopic yield. We speculate that the disulfonide ligand may prevent the phosphine promoted Pd(II)-to-Pd(0) reduction, thus halting the second, Pd(0)-catalyzed, step.

With these new conditions in hand, aliphatic terminal alkenes **1h–1p** were evaluated for the synthesis of the corresponding allylsulfones **3hb–3pb** (Scheme 5). Besides allylsulfone **3hb** which was isolated with 40% isolated yield, aliphatic allylsulfones **3ib**, **3jb**, **3kb** and **3lb** were obtained from dec-1-ene **1i**, non-1-ene **1j**, oct-1-ene **1k** and hex-1-ene **1l** respectively with 39%, 49%, 12% and 48% isolated yield. Here again, *E/Z* mixtures of isomers were detected in the NMR spectra of the crude reaction products, the (*E*)-isomers being always the major ones.

Methylenecyclopentane **1m** could also be converted into allylsulfone **3mb** with Method A in a moderate 30% yield, while Method B and B' failed. More functionalized aliphatic alkenes such as benzylether **1n** and esters **1o** and **1p** gave no or trace amounts of sulfonated product with Methods A or B. Besides, Method B' allowed to obtain the corresponding allylsulfones **3nb**, **3ob**, and **3pb** and in 51%, 68% and 58% yields, respectively. In all these cases, *E/Z* mixtures were constantly obtained, with the (*E*)-isomer prevailing. This protocol, though requiring a long reaction time (4–5 days), is



Scheme 5. Evaluation of aliphatic terminal alkenes as substrates in the optimized reaction conditions. [a] Typical reaction conditions: **Method A:** allyl-derivative **1h–1p** (0.5 mmol), **2b** (2.0 equiv.), Pd(acac)₂ (10 mol%), 2,6-DMBQ (2.0 equiv.), CH₃CN (0.66 M), 80 °C in a sealed tube, 48–72 h. **Method B':** allyl-derivative **1h–1p** (0.2 or 0.5 mmol), Pd(OAc)₂ (10 mol%), phenylvinylsulfonide (10 mol%), BzOH (10.0 equiv.), BQ (2.0 equiv.), 4 Å MS (50 mg), 1,4-dioxane (0.2 M) were heated at 43 °C under air in a sealed tube until complete conversion of the allyl-derivative (48–72 h). Then, DIPEA (11.5 equiv.), sodium benzenesulfinate **2b** (2.0 equiv.), *rac*-BINAP (20 mol%) were introduced, and the mixture was heated at 80 °C until complete conversion of the allylbenzoate intermediate (usually 48 h). Reaction time for Method B' corresponds to the sum of the reaction times for the two steps. Indicated yields refer to isolated, after silica gel column chromatography purification. [b] *E/Z* ratios were calculated on the ¹H-NMR spectra of the crude reaction mixtures. [c] only degradation products were formed. [d] Conversion was 40% (as measured by quantitative ¹H NMR using 1,4-dinitrobenzene as internal standard) after 72 h of reaction.



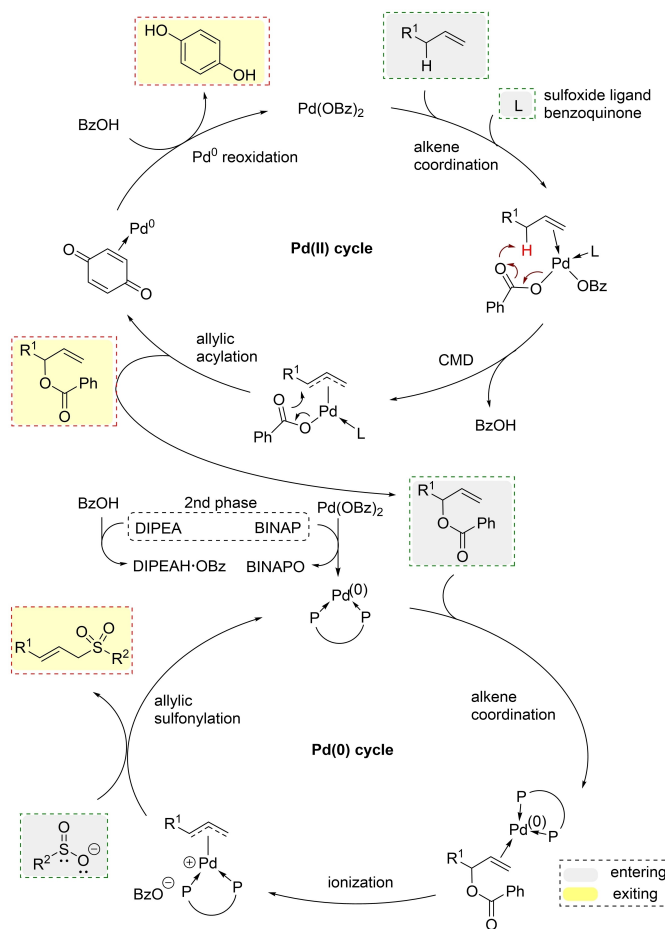
Scheme 6. Adapted sequential conditions for the reaction of undecene **1h** (Method B').

to date the only way to afford such allylsulfones via allylic C–H functionalization.^[17]

The mechanism associated to Method B' is expected to entail two different, but connected, catalytic cycles. Coordination of the terminal alkene and of the sulfoxide ligand to the palladium atom of the in situ formed palladium dibenzoate generates the corresponding η^3 -allylpalladium complex via a likely CMD mechanism. Following inner sphere benzoate ligand transfer to the internal terminus of the π -complexed allyl fragment generates the branched allylic benzoate and BQ-complexed Pd(0), which regenerates palladium dibenzoate.^[11e,14a] Once the formation of the allylic benzoate is complete, addition of DIPEA and *rac*-BINAP to the reaction mixture sets the stage for the second catalytic cycle. Indeed, the amine quenches the excess of benzoic acid making the corresponding salt, while the diphosphine reduces^[18] the palladium diacetate and complexes the thus generated Pd(0) via κ^2 -coordination. After coordination of the alkene function of the allylic benzoate to the Pd(0) complex, a new, ionic, η^3 -allylpalladium complex is formed. This latter is intercepted by the sulfinate anion, which generates the allylic sulfone product and regenerates the Pd(0) complex (Scheme 7).

Conclusion

In summary, we developed two distinct protocols for the preparation of allylsulfones from commercially available alkenes through allylic C–H activation. The first method consists in the palladium-catalyzed direct allylic C–H sulfonylation of terminal alkenes, while the second procedure deals with a one-pot sequential Pd(II)-catalyzed allylic C–H acetoxylation, followed by a Pd(0)-catalyzed sulfonylation. While the first protocol is more straightforward, the second one gave often higher yields with a broader substrate scope, yet allowing to use the same palladium pre-catalyst for the two steps. A plausible mechanism is proposed in both cases. Future work will be dedicated to the improvement of the



Scheme 7. Proposed mechanism for the sequential Pd-catalyzed allylic C–H sulfonylation of terminal alkenes according to Method B'.

above studied protocols as well as the in situ further reaction of the resulting allylsulfones.

Experimental Section

General procedure for direct allylic C–H sulfonylation of alkenes (Method A): An ace pressure tube equipped with a magnetic stirrer was charged with 15.2 mg (0.05 mmol, 10 mol%) of palladium(II) acetylacetonate, 136 mg (1.0 mmol, 2.0 equiv.) of 2,6-dimethyl-1,4-benzoquinone and the sulfinate **2a–2j** (1.0 mmol, 2.0 equiv.). The tube was placed under vacuum and then backfilled with argon. The vacuum/argon cycles were repeated twice and 0.75 mL of distilled acetonitrile (0.66 M) was introduced. To this suspension was introduced the alkene **1b–1q** (0.5 mmol, 1.0 equiv.) and the mixture was heated to 80 °C under stirring until conversion was complete as checked by TLC. The mixture was then cooled to rt and filtered over a pad of silica gel with 50 mL of ethyl acetate. The filtrate was concentrated under reduced pressure and the residue was purified by flash column chromatography on silica gel to give the desired products.

General procedure for one-pot sequential allylic C–H sulfonylation of allylarenes (Method B): An ace pressure tube equipped with a magnetic stirrer was charged with 11.2 mg (0.05 mmol, 10 mol%) of palladium(II) acetate, 136.2 mg (1.0 mmol, 2.0 equiv.)

of 2,6-dimethylbenzo-1,4-quinone and 50 mg of 4 Å molecular sieves. The solids were suspended in 1.5 mL of anhydrous DMSO and 0.29 mL (5.0 mmol, 10.0 equiv.) of acetic acid was introduced followed by the alkene **1b–1g** (0.5 mmol, 1.0 equiv.). The mixture was heated to 80 °C until complete conversion of the alkene was reached as checked by TLC. The mixture was cooled to rt and 62.0 mg (0.1 mmol, 20 mol%) of *rac*-BINAP followed by 1.0 mL (7.25 mmol, 11.5 equiv.) of *N,N*-diisopropylethylamine were added to the reaction mixture. The sulfinate **2a–2j** (1.0 mmol, 2.0 equiv.) was then introduced and the ace pressure tube was closed. The reaction mixture was then heated to 80 °C until complete conversion of the intermediate allylacetate was seen by TLC. The mixture was then cooled to rt and filtered over a pad of silica gel with 50 mL of ethyl acetate to remove the salts. The filtrate was placed into a separatory funnel and washed with 50 mL of water. The aqueous layer was extracted with 2 × 20 mL of ethyl acetate. The combined organic layers were dried over anhydrous MgSO₄ and filtered. The filtrate was concentrated under reduced pressure and the residue was purified by flash column chromatography on silica gel to give the desired products.

General procedure for one-pot sequential allylic C–H sulfonation of terminal aliphatic alkenes (Method B’): An ace pressure tube equipped with a magnetic stirrer was charged with 4.5 mg (0.02 mmol, 10 mol%) of palladium(II) acetate, 2.7 μL (0.02 mmol, 10 mol%) of phenylvinylsulfoxide and 43.3 mg (0.4 mmol, 2.0 equiv.) of 1,4-benzoquinone. The solids were suspended in 0.6 mL of anhydrous 1,4-dioxane and 244.2 mg (2.0 mmol, 10.0 equiv.) of benzoic acid was introduced followed by the alkene **1h–1q** (0.2 mmol, 1.0 equiv.). The mixture was heated to 43 °C until complete conversion of the alkene was reached as checked by TLC or ¹H NMR (usually 66–72 h). The mixture was cooled to rt and 25.0 mg (0.04 mmol, 20 mol%) of *rac*-BINAP followed by 0.4 mL (2.3 mmol, 11.5 equiv.) of *N,N*-diisopropylethylamine were added to the reaction mixture. To this mixture was introduced 65.4 mg (0.4 mmol, 2.0 equiv.) of Sodium benzenesulfinate **2b** and the sealed tube was closed. The reaction mixture was then heated to 80 °C until complete conversion of the intermediate allylbenzoate was seen by TLC. The mixture was then cooled to rt and filtered over a pad of silica gel with 25 mL of ethyl acetate to remove the salts. The filtrate was concentrated under reduced pressure and the residue was purified by flash column chromatography on silica gel to give the desired products.

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Keywords: allylsulfones · C–H activation · one-pot sequential reactions · palladium catalysis · sulfonation

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Palladium-Catalyzed Generation and Reactivity of Allylsulfones

This thesis work is dealing with the study of synthetic opportunities offered by allylsulfones and palladium in chemistry. Firstly, we attempted to develop a new domino sequence, which involves the reaction between allyl carbonates/allyl acetates and sodium sulfinates. This domino reaction involves a triple intermolecular Pd-catalyzed allylation reaction and allows the construction of C-S/C-C/C-C bonds. Secondly, we have successfully developed and compared two distinct and effective protocols for the preparation of allylsulfones from commercially available alkenes via PdX₂-catalyzed allylic C-H activation/sulfonylation. The first protocol is involving a direct PdX₂-catalyzed allylic C-H sulfonylation and the second protocol a one-pot sequential PdX₂-catalyzed allylic C-H acetoxylation followed by a Pd(0)-catalyzed sulfonylation.

Lastly, we tried to improve the generation of a dihydroquino-sulfone side product, studying the reaction conditions for its synthesis.

Keywords: Palladium; Catalysis; Allylation; Domino; C-H Activation; Sulfonylation; Allylsulfone.

Génération et Réactivité des Allylsulfones par Catalyse au Palladium

Ce travail de thèse porte sur l'étude des opportunités synthétiques offertes par les allylsulfones et la chimie du palladium. Tout d'abord, une nouvelle séquence domino a été développée, qui implique la réaction entre les carbonates/acétates d'allyle et des sulfinates de sodium. Cette réaction domino implique une triple réaction d'allylation intermoléculaire catalysée par le Pd et permet la construction de liaisons C-S/C-C/C-C.

Deuxièmement, nous avons développé et comparé avec succès deux protocoles distincts et efficaces pour la préparation d'allylsulfones à partir d'alcènes disponibles dans le commerce via l'activation/sulfonylation C-H allylique catalysée par PdX₂. Le premier protocole implique une sulfonylation C-H allylique catalysée directement par PdX₂ et le second protocole implique une acétoxylation C-H allylique « one-pot » catalysée par PdX₂ suivie d'une sulfonylation catalysée par du Pd(0).

Enfin, nous avons essayé de préparer un produit secondaire de type dihydroquino-sulfone et étudié les conditions de réaction pour sa synthèse.

Mots-clés: Palladium; Catalyse; Allylation; Domino; Activation C-H; Sulfonylation; Allylsulfone.