



HAL
open science

Selective C-H Activation of Terpenes

Marco Di Matteo

► **To cite this version:**

Marco Di Matteo. Selective C-H Activation of Terpenes. Organic chemistry. Sorbonne Université, 2024. English. NNT: 2024SORUS001 . tel-04887425

HAL Id: tel-04887425

<https://theses.hal.science/tel-04887425v1>

Submitted on 15 Jan 2025

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Thèse de doctorat de Sorbonne Université

Spécialité : **Chimie Organique**

École Doctorale de Chimie Moléculaire de Paris Centre – ED406

Institut Parisien de Chimie Moléculaire / Équipe CASCH

Selective C–H Activation of Terpenes

Présentée par

Marco DI MATTEO

Pour obtenir le grade de

Docteur de Sorbonne Université

Soutenance publique prévue le 15 Janvier 2024

Devant un jury composé par :

Professeur Jean-François Soulé	Université Paris Saclay	Président du jury
Professeur Daniele Passarella	Università degli Studi di Milano	Rapporteur
Docteur Tatiana Besset	Université de Rouen Normandie	Rapporteur
Docteur M. Ángeles Fernández-Ibáñez	University of Amsterdam	Examineur
Docteur Alexandre PRADAL	Sorbonne Université	Examineur
Professeur Giovanni POLI	Sorbonne Université	Examineur
Docteur Fabrice Gallou	Novartis Pharma	Invité

Acknowledgements

First and foremost, I would like to extend my sincere thanks to the members of the jury: Dr. Tatiana Besset, Prof. Daniele Passarella, Dr. M. Ángeles Fernández-Ibáñez, and Prof. Jean-François Soulé, for agreeing to evaluate my PhD work and for the time dedicated to meticulously reading and reviewing the manuscript.

Furthermore, I wish to express my deepest gratitude to my supervisor, Prof. Giovanni Poli. Although he has often suggested I call him Giovanni, I find myself continuing to address him with the respect due to a professor after these three years. I am grateful for the opportunity to undertake this PhD, for his constant presence whenever I needed guidance, and for the support and assistance he has provided. I am indebted to him for imparting his expertise in palladium chemistry, instilling in me a curiosity about the intricacies of how things work and, at times, why they do not, always striving to understand the mechanisms behind each reaction I studied. I am thankful for his acceptance and for allowing me to have this wonderful experience in such a beautiful city and group.

Alexandre, I am sincerely grateful to you for welcoming me on January 4th, 2021, at Place Jussieu and for accompanying me throughout these past three years. I thank you for all the advice you have given me, in chemistry and beyond, during this time. Your teachings on how to balance stress and pressure have been crucial, especially during my thesis writing. Thank you for showing me the importance of being curious, encouraging me to solve problems through reasoning, and steering me away from unfounded approaches. Your daily help, consistent advice, and practical solutions have been a tremendous support in every moment of doubt or difficulty. I consider myself extremely lucky to have had you as my co-supervisor. As you prepare for your first PhD upon receiving your HDR, I wish you the very best.

Fabrice, thank you for guiding me during my time in Basel, for offering advice about my future, and for teaching me the importance of commitment and the value of hard work. I was very fortunate to have you as my industrial supervisor, even if it was just for three months. I appreciate your efforts in teaching me so much in such a short period, for listening to my concerns, and for providing insightful solutions for my career and future life.

To Federico, a friend first and then a colleague, who has always been there for me. I believe our work, despite our different approaches to chemistry, began and concluded in unison. Before arriving here, I

never imagined I would find such a close friend and cherished colleague with whom I could relate so deeply. Here's to our work, our joint efforts, and all the days we spent together finding solutions and striving for the best. To the value of hard work, which you taught; to those Saturday afternoons doing chromatography columns; to the beers after university; and to all the laughter we shared. I wish you the best in your future, because that is what you deserve.

To Mikael, mon gars, for reminding me what commitment and education mean, and for welcoming me and teaching me so much about your culture, both French and Portuguese. To our days working in unison in the laboratories, each of us listening to our own music, to the lunches in the canteen where I have never seen anyone eat so quickly. Thank you for reminding me of the importance of family and friendship, and for introducing me to this city and this new French experience. To Gredy and Ruben, my elder brothers during this journey. Thank you for the practical solutions you provided me, for the beautiful moments we shared together, and for hosting me in your home without any hesitation. Thank you for all the advice you gave me, both outside and inside the university, always trying to help me throughout these three years. To Ichrak, for teaching me what it means to be kind, sometimes too much so. Thank you for giving me so much, especially during my last year, for helping me with my thesis, with ADUM, and with all the bureaucratic stuff I always procrastinated on. In a few days, you will finish before me and Fede. I wish you all the best for your future in France, and I am sure that everything will turn out well. To Anna and Valentin, my M2s who have helped me in my doctoral journey. I hope that during your PhD, you will have master's students as capable and dedicated as you are. It's not easy to manage students (Alex knows this well), but I am sure that you will do your best. To Julie, who has always helped me from the beginning, even though I didn't understand anything she was saying in French. Thank you for the continuous advice, for cheering me up even on bad days, and for showing me what it means to be professional and human at the same time. I want to especially thank all the members of the ROCS team, or at least what used to be the ROCS team. In particular, Alejandro, for always helping me, teaching me so many practical things in the lab, solving so many bureaucratic problems for me, getting me a new fume hood glass, and for our conversations about Real Madrid. For next year, get ready because Italy-Spain will once again be a match in the European Cup. A huge thank you to all my friends and colleagues. To Alessia, Ting Ting, Jassmin, Simona, Lorenzo, Per, Arturo, Tullio. To Fabrice, Olivier, and Myriam, who have taught me so much over these three years, during our lunches in the canteen or through the stimulating seminars within our group.

I particularly want to thank Claire and Regina for their constant work in maintaining and managing the NMR. For the specific help they provided me, especially when I needed it most. A special thanks to Gilles, for your hard work, your availability, and for conducting HRMS analyses often at short notice.

To Maria Elena, the only person I knew here, for introducing me to her group, for giving me so much, and for the beautiful moments we spent together. To my friends Paolo and Maria, for always being there even from afar, for the support during these years, and for the many adventures we've had and still have to face. To Martina, a wonderful person I met on this journey, and to the many experiences we've shared together. To my Italian friends here in France, Luna, Eleonora, Umberto, Irene, Bianca, Cecilia, Alberto, Matilde.

Ed infine, ai miei genitori, senza i quali non avrei mai immaginato di trovarmi qui.

Questa tesi, è principalmente dedicata a voi, siete dei genitori fantastici. Grazie per avermi insegnato e dato tutto, grazie per avermi ascoltato ogni giorno durante questa mia esperienza. È solo grazie ad i vostri sforzi se mi ritrovo qui, il giorno 4 Dicembre 2023, a completare questo lavoro di tesi.

Spero solo che possiate essere orgogliosi di me quanto io lo sia di voi, per i vostri sforzi, per il vostro sostegno, per il vostro bene.

Table of contents

List of abbreviations	8
General introduction	10
Chapter 1. Introduction to metal-catalyzed C–H activation/functionalization	13
1. Introduction	13
1.1. Seminal work	15
1.2. Reactivity of the isolated C–H bond.....	16
1.3. Redox concepts in C–H activation processes	17
2. Metal-promoted mechanisms for C–H activation	19
2.1. Outer sphere mechanisms	19
2.2. Inner-sphere mechanisms	20
3. Pd-catalyzed coupling reactions involving C(sp²)–H functionalizations	24
3.1. C(sp ²)–H/C(sp ²)–X coupling reactions	25
3.1.1. The classical Mizoroki-Heck reaction ¹	25
3.1.2. The oxidative Heck coupling.....	28
3.1.3. Selectivity of the bimolecular Mizoroki-Heck reactions.....	30
3.1.4. Reverse Mizoroki-Heck coupling.....	32
3.2. C(sp ²)-H / C(sp ²)-H couplings	36
3.2.1. Aryl/Aryl C–H/C–H coupling (a hint).....	37
3.2.2. Aryl/Alkenyl C–H/C–H coupling.....	39
3.3. Alkene / alkene C(sp ²)-H / C(sp ²)-H couplings.....	41
Chapter 2: Cross Dehydrogenative alkene / alkene coupling of terpenes	47
1. Introduction	47
2. Preliminary studies and optimization of the reaction conditions	50
2.1. Optimization of the reaction conditions	51
2.1.1. Variation of the solvent.....	51
2.1.2. Variation of the reaction time.....	52
2.1.3. Variation of the catalyst	53
2.1.4. Variation of the oxidant	54
2.1.5. Introduction of a ligand.....	55
2.1.6. Amount of the oxidant.....	57

2.2.	Configurational Assignment.....	58
2.3.	Racemization/Epimerization studies at the C4 stereocenter	59
2.4.	Study of the scope of the coupling	60
2.5.	Mechanistic studies	66
2.5.1.	Stoichiometric studies.....	66
2.5.2.	DFT Studies.....	68
Chapter 3: Application: Copper free Sonogashira cross coupling in water.....		75
1.	Introduction	75
2.	Optimization of the reaction conditions.....	79
3.	Attempts for scale-up, CDC reaction under micellar regime and comparison with classical conditions	82
Chapter 4: Development of a C(sp²)-H / C(sp²)-X alkene / haloalkene coupling reaction..		85
1.	Introduction	85
2.	Preliminary studies and optimization of the reaction conditions.....	87
2.1.	Preliminary studies	87
2.2.	Optimization of the reaction conditions.....	88
2.2.1.	Geometric configuration and nature of halogen of the haloacrylate	88
2.2.2.	Variation of the solvent.....	89
2.2.3.	Variation of the ionizing agent	90
2.3.	Scope study of the coupling reaction.....	92
2.3.1.	Synthesis of the commercially unavailable β-haloalkenes.....	92
2.3.2.	Coupling of the synthesized β-haloalkenes.....	94
2.4.	Mechanistic proposal.....	96
Chapter 5: Approaches to the Total Synthesis of Cannabidiol		99
1.	Introduction	99
1.1.	Generalities about Cannabidiol.....	99
1.2.	A selection of previously reported synthetic pathways toward CBD.....	101
1.2.1.	Lewis-acid mediated arylation of terpenic allylic cations.	102
1.2.2.	Attempts to increase the regioselectivity	104
1.2.3.	Aromatic coupling mediated by organometallic species	106
1.2.4.	Building of the limonene scaffold by ring closing metathesis.....	107
1.3.	Analogues of (-)-CBD.....	108
1.4.	Planned Project.....	110

2. Results and discussion	112
2.1. Strategy 1: π -allyl Palladium catalysis	112
2.2. Strategy 2: 1,4-addition onto a carvone-derived Michael acceptor	115
2.2.1. Modified Shapiro reaction	115
2.2.2. Synthesis of an α,β -unsaturated nitrile intermediate	120
General Conclusion	123
Experimental Section	126
1. General Remarks	126
2. Chapter 2: Cross Dehydrogenative couplings of terpenes.....	127
2.1. Synthesis and characterization of starting materials	127
2.1.1. Synthesis of acrylates	127
2.1.2. Synthesis of acrylamides	128
2.1.3. Preparation of other terpenes	130
2.2. Synthesis and characterization of ligands.....	131
2.3. Pd(II)-catalyzed cross dehydrogenative coupling	133
3. Chapter 3: Application: Copper free Sonogashira cross coupling in water	150
4. Chapter 4: Development of a C-H / C-X coupling reaction	151
4.1. Synthesis and characterization of starting materials	151
4.1.1. Synthesis of (<i>E</i>)-3-bromoacrylic acid	151
4.1.2. Synthesis of (<i>Z</i>)-3-haloacrylic acid	152
4.1.3. Synthesis of 3-haloacrylates.....	153
4.1.4. Synthesis of (<i>Z</i>)-3-bromoacrylamides.....	155
4.1.5. Synthesis of other (<i>Z</i>)-3-bromo coupling partners	157
4.2. Pd(II)-catalyzed redox neutral coupling	160
5. Chapter 5: Approaches to the Total Synthesis of Cannabidiol	164
5.1. Synthesis and characterization of starting materials	164
5.2. Strategy 1: π -allyl Palladium catalysis	167
5.3. Strategy 2: 1,4-addition onto a carvone-derived Michael acceptor	169
5.3.1. Oxidation of the alcohol 57d	171

List of abbreviations

abn-CBD	abnormal cannabidiol
acac	acetylacetonate
AMLA	ambiphilic metal-ligand activation
API	active pharmaceutical ingredient
BDEs	bond dissociation energies
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
σ-BM	σ -bond metathesis
BTF	benzene trifluoride
σ-CAM	σ -complex assisted metathesis
CBD	cannabidiol
CBDD	cannabidiol dimethylether
CBG	cannabigerol
CB₁R	cannabinoid receptor 1
CB₂R	cannabinoid receptor 2
CDC	cross-dehydrogenative coupling
CMD	concerted metalation deprotonation
Cp	centipoise
CT	charge transfer
CuTC	copper(I) thiophenecarboxylate
DCC	dicyclohexylcarbodiimide
DCE	1,2-dichloroethane
DG	directing group
DIBAL-H	di- <i>iso</i> -propylaluminium hydride
DMA	dimethyl acetamide
DMAP	4-dimethylaminopyridine
DMC	dimethyl carbonate
DME	dimethoxyethane
DMF	dimethylformamide
DMH	dimethylheptyl
DMSO	dimethylsulfoxide
dppe	1,2-bis(diphenylphosphino)ethane
EA	electrophilic activation
ECS	endocannabinoid system
ent	enantiomer
Eq.	equation
equiv.	equivalent
EWG	electron withdrawing group
FDA	Food and Drug Administration
HFIP	1,1,1,3,3,3-hexafluoroisopropanol
HMPV	heteropolymolybdovanadic acid
HPMC	hydroxypropyl methylcellulose
IES	internal electrophilic substitution
MVK	methylvinylketone
NHC	<i>N</i> -heterocyclic carbene
NFSI	<i>N</i> -fluorobenzenesulfonimide
NMP	<i>N</i> -methylpyrrolidone
OA	oxidative addition
PIDA	diacetoxyiodobenzene (phenyliodide diacetate)

PyOx	pyridine-oxazoline ligand
rt	room temperature
TBHP	<i>tert</i> -butyl hydroperoxide
TBPB	<i>tert</i> -butyl perbenzoate
THC	tetrahydrocannabinol
TLC	thin layer chromatography
TMEDA	tetramethylethylenediamine
TPGS	tocofersolan
TS	transition state
XantPhos	(9,9-dimethyl-9 <i>H</i> -xanthene-4,5-diyl)bis(diphenylphosphane)

General introduction

Today's stock of chemical raw materials is heavily dependent on fossil resources such as oil, coal and natural gas. Unfortunately, the use of these natural carbon-based deposits leads to a carbon imbalance in our ecosystem, which in turn is the cause of global warming of the planet. One of the solutions to this issue is to switch from fossil resources to biomass, mainly lignocellulosic, as a source of energy and for synthetic purposes, to produce lubricants, drugs, fertilizers, commodities, plastics, etc. However, the chemical nature of fossil resources and lignocellulosic biomass is fundamentally different. While lignocellulosic biomass consists of heteroatom-containing carbon-based material, fossil resources (which anciently were biomass) lost their functionality during the process of ketogenesis. As a result, the well-established fossil-based synthetic chemistry developed since the birth of industrial chemistry cannot be directly transposed to biomass. For this reason, a great part of modern synthetic chemistry is directed toward the development of a new set of synthetic strategies to transform lignocellulosic biomass into value-added targets.^[1] In this scenario, terpenes^[2] represent a special case in that, in contrast to lignocellulosic biomass, they are hydrocarbons. Consequently, like fossil materials, they are ideal starting molecules for selective C–H functionalization, provided efficient methods of selective C–H activation are available. However, the field of selective C–H activation / functionalization of hydrocarbons is still in its infancy, and is far from satisfactory from the selectivity, yields, and eco-compatibility perspective. For the present project, we focused our attention on (+)-limonene. This monoterpene, possessing a total of eleven allylic C–H bonds and three vinylic C–H bonds, is a prime candidate as a starting synthetic building block. (Figure 1).

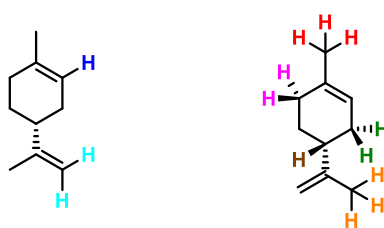


Figure 1. Vinylic (left) and allylic (right) C–H bonds in (+)-limonene.

More precisely, the objective of this thesis was to develop novel C–C couplings between a vinylic C–H bond of (+)-limonene and other alkenes.

^[1] (a) Corma, A.; Iborra, S.; Velty, A. *Chem. Rev.* **2007**, *107*, 2411-2502; (b) Gallezot, P. *Chem. Soc. Rev.* **2012**, *41*, 1538-1558; (c) Ferreira, P. G.; Nicoletti, C. D.; Da Silva, F. de C.; Ferreira, V. F. *Curr. Green Chem.* **2016**, *3*, 259; (d) Wu, L.; Moteki, T.; Gokhale, A. A.; Flaherty, D. W.; Toste, F. D. *Chem.* **2016**, *1*, 32-58; (e) Isikgor, F. H.; Becer C. R. *Polym. Chem.* **2015**, *6*, 4497-4559; (f) Sheldon, R. A. *J. Mol. Catal. A* **2016**, *422*, 3-12; (g) Serrano-Ruiz, J. C.; Luque, R.; Sepúlveda-Escribano, A. *Chem. Soc. Rev.* **2011**, *40*, 5266-5281.

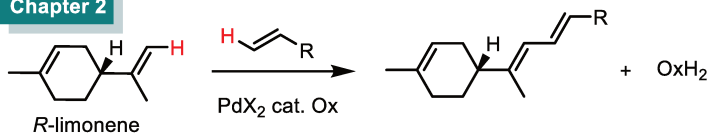
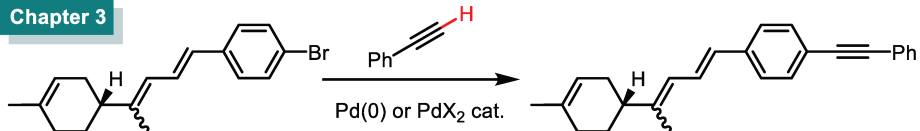
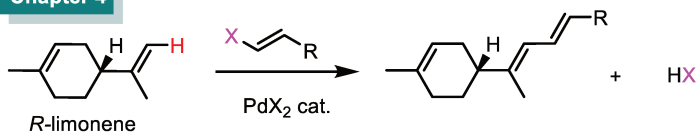
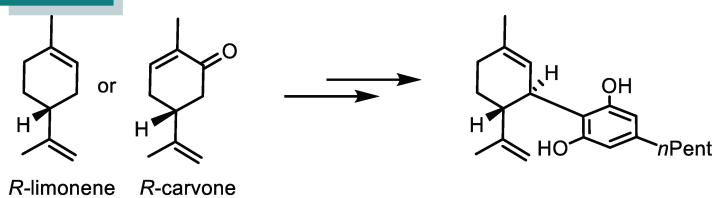
^[2] Brill, Z. G.; Condakes, M. L.; Ting, C. P.; Maimone, T. J. *Chem. Rev.* **2017**, *117*, 11753-11795.

The intermolecular direct C(sp²)-H alkene coupling represents an ideal method for achieving the atom- and step economical direct functionalization of an alkene. This contemporary topic can be in turn conceptually divided into two main sub-fields: the “directed”^[3] and the “undirected”^[4] couplings (see Chapter 2).

The manuscript consists of five chapters. Chapter 1 gives a brief introduction on metal-catalyzed C-H activation/functionalization with special focus on alkenyl/alkenyl C(sp²)-H/C(sp²)-H and C(sp²)-H/C(sp²)-X couplings, along with some literature reporting Pd-catalysis in relation to C-H activation of terpenes. Chapter 2 describes our studies on the development of Pd(II)-catalyzed oxidative C(sp²)-H/C(sp²)-H coupling reactions between limonene and electron poor alkenes, with extensions to other terpenes and terpenoids (Scheme 1, first equation). The coupled product will be subsequently employed as starting material for a Sonogashira coupling through micellar catalysis as described in Chapter 3 (Scheme 1, second equation). An alternative Pd(II)-catalyzed non-oxidative C(sp²)-H/C(sp²)-X coupling between limonene and electron-poor alkenes bearing a leaving group is the topic of Chapter 4 (Scheme 1, third equation). Chapter 5 focuses on our attempts to find new synthetic ways to access the terpenoid Cannabidiol (CBD) via C-H as well as non-C-H activating strategies. The last chapter is dedicated to the experimental part.

[3] Sambigiato, C.; Schönbauer, D.; Blicke, R.; Dao-Huy, T.; Pototschnig, G.; Schaaf, P.; Wiesinger, T.; Zia, M. F.; Wencel-Delord, J.; Besset, T.; Maes, B. U. W.; Schnürch, M. *Chem. Soc. Rev.* **2018**, *47*, 6603-6743.

[4] Shang, X.; Liu, Z.-Q. *Chem. Soc. Rev.* **2013**, *42*, 3253-3260.

Chapter 2**Chapter 3****Chapter 4****Chapter 5**

Scheme 1. General topics treated in the present thesis work.

Chapter 1. Introduction to metal-catalyzed C–H activation/functionalization

1. Introduction

In recent years, there has been significant interest in the concept of step-economical and environmentally friendly synthesis. Simplifying the synthetic process by minimizing the manipulation of functional groups has emerged as a straightforward approach to reducing the number of synthetic steps,^[5] and has significantly transformed the landscapes of synthetic chemistry. The definition of C–H activation is rather vague and is often confused with the related term C–H functionalization. However, there is a certain consensus to define the topic. The C–H bonds of organic molecules can be arbitrarily classified as “inherently reactive” or “inherently unreactive”.^[6,7,8] The first type of bond refers to the C–H bonds, in a substrate or in a reaction intermediate, which can undergo cleavage via traditional organic chemistry methods, either by C–H deprotonation (loss of H⁺) or by C–H homolysis (loss of H·). On the other hand, only specific strategies can trigger some of the “unactivated” C–H bonds and ultimately functionalize them. In this context, the approach that relies on the *in-situ*, often catalytic, conversion of a C–H bond into a C–Metal bond via an inner sphere C–H/Metal interaction *en route* toward its final functionalization, is termed C–H activation. In the initial phase of the C–H activation research, the main focus was on discovering novel catalytic systems that enabled the direct conversion of a specific C–H bond of a substrate into a C–Metal bond, which can be *in situ* converted

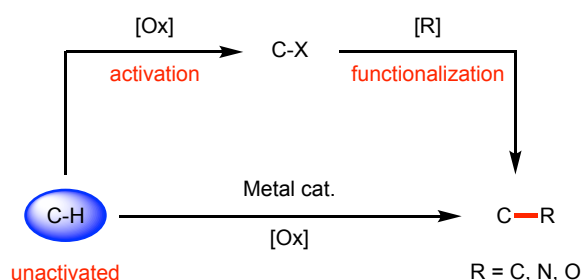
[5] For selected general reviews on C–H activation see: (a) Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010**, *110*, 1147–1169; (b) Yeung, C. S.; Dong, V. M. *Chem. Rev.* **2011**, *111*, 1215–1292; (c) Ackermann, L. *Chem. Rev.* **2011**, *111*, 1315–1345; (d) Zhao, D.; You, J.; Hu, C. *Chem. Eur. J.* **2011**, *17*, 5466–5492; (e) Wencel-Delord, J.; Dröge, T.; Liu, F.; Glorius, F. *Chem. Soc. Rev.* **2011**, *40*, 4740–4761; (f) Colby, D. A.; Tsai, A. S.; Bergman, R. G.; Ellman, J. A. *Acc. Chem. Res.* **2012**, *45*, 814–825; (g) Arockiam, P. B.; Bruneau, C.; Dixneuf, P. H. *Chem. Rev.* **2012**, *112*, 5879–5918; (h) Kuhl, N.; Hopkinson, M. N.; Wencel-Delord, J.; Glorius, F. *Angew. Chem. Int. Ed.* **2012**, *51*, 10236–10254; (i) Engle, K. M.; Yu, J.-Q. *J. Org. Chem.* **2013**, *78*, 8927–8955; (j) Kuhl, N.; Schröder, N.; Glorius, F. *Adv. Synth. Catal.* **2014**, *356*, 1443–1460; (k) Hu, F.; Xia, Y.; Ma, C.; Zhang, Y.; Wang, J. *Chem. Commun.* **2015**, *51*, 7986–7995; (l) Zhao, B.; Shi, Z.; Yuan, Y. *Chem. Rec.* **2016**, *16*, 886–896; (m) Jana, R.; Mamataj-Begam, H.; Dinda, E. *Chem. Commun.*, **2021**, *57*, 10842–10866.

[6] (a) Crabtree, R. H. *Chem. Rev.* **2010**, *110*, 575–575; (b) Labinger, J. A.; Bercaw, J. E. *Nature* **2002**, *417*, 507–514.

[7] For selected books on C–H bond functionalizations, see: (a) Yu, J.-Q. *Catalytic Transformations via C–H Activation Vols 1 and 2, Science of Synthesis*, Thieme, **2016**; (b) Dixneuf, P. H.; Doucet, H. *C–H Bond Activation and Catalytic Functionalization I and II, Topics in Organometallic Chemistry 55 and 56*, Springer, **2016**; (c) Li, J. J. *C–H Bond Activation in Organic Synthesis*, CRC Press, **2015**; (d) Ribas, X. *C–H and C–X Bonds Functionalization: Transition Metal Mediation*, RSC, Publishing, London, **2013**; (e) Pérez, P. J. *Alkane C–H Activation by Single-Site Metal Catalysis, Catalysis by Metal Complexes*, vol. 38, Springer, New York, **2012**; (f) Yu, J.-Q.; Shi, Z. *C–H Activation*, Springer, Berlin, Germany, **2010**; Yu, J.-Q.; Shi, Z. *Top. Curr. Chem.* vol. 292, Springer, **2010**; (h) Dyker, G. *Handbook of C–H Transformations: Applications in Organic Synthesis*, Wiley-VCH, Weinheim, **2005**; (i) Goldberg, K. I.; Goldman, A. S. *Activation and Functionalization of C–H Bond*, in: ACS Symposium Series 885, American Chemical Society, Washington, DC, **2004**.

[8] (a) For special issues on C–H activation, see: (a) Shul’pin, G. B.; Adams, R. D. *J. Organomet. Chem.* **2015**, *793*, 1–268; (b) Neufeldt, S. R.; Sandford, M. S. *Acc. Chem. Res.* **2012**, *45*, 777–958; (d) Davies, H. M. L.; Du Bois, J.; Yu, J.-Q. *Chem. Soc. Rev.* **2011**, *40*, 1845–2040.

into a C–C, C–O or C–N bond. This involves bypassing the need to obtain pre-oxidized substrates through multiple functional group transformations (Scheme 2).^[9]



Scheme 2. C-H activation/functionalization as opposed to the classical approach involving a pre-oxidation step.

The inclusion of C–H bonds alongside conventional functional groups such as halides, alcohols, and carbonyls, greatly expands the synthetic toolbox of the organic chemist (Figure 2).

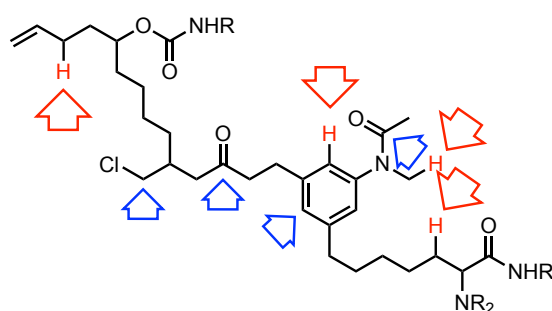


Figure 2. Virtual target with potential reactive sites for classical functional group modifications (blue arrows) and those for C–H activation/functionalization strategy (red arrows).^[10]

C–H activation, while promising, has not yet gained popularity in the late-stage modification of molecules due to the presence of multiple sensitive functionalities, that are intolerant to harsh reaction conditions. The current focus of ongoing research is on creating the next generation of C–H transformations that can truly function as impactful tools for synthesis.

Beyond enhancing the efficiency and selectivity of C–H transformations, research groups have recently concentrated on conceiving protocols that take place under increasingly milder reaction conditions.^[11] In the absence of a clear definition in current literature, the concept of “mild” reaction conditions for C–H activation is generally understood to involve operation at or below ambient temperature, under neutral conditions and without the requirement for strong oxidizing or reducing agents. The

^[9] Roudesly, F.; Oble, J.; Poli, G. *J. Mol. Catal. A Chem.* **2017**, *426*, 275-296.

^[10] Adapted from a personal communication of Prof. Huw Davies (Paris, July, 2014).

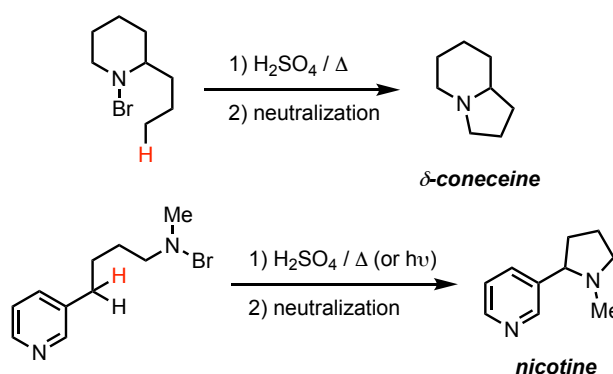
^[11] Gensch, T.; Hopkinson, M. N.; Glorius, F.; Wencel-Delord, J. *Chem. Soc. Rev.* **2016**, *45*, 2900-2936.

integration of mild conditions, selectivity, and efficiency remains fundamental to what constitutes an ideal chemical transformation.^[5e]

An inherent challenge in this field lies in achieving selectivity. Organic molecules, even relatively simple ones, contain various types of distinct C–H bonds. Consequently, designing strategies based on C–H bond activation requires addressing the issues related to selectively activating a specific C–H bond. Of course, this issue holds significance not only in fine chemistry, but also in broader contexts.

1.1. Seminal work

The earliest example of isolated alkyl C–H bond functionalization dates back to 1883 and was reported by August W. Hofmann. This approach relied on generating highly reactive oxygen- and nitrogen-based radicals under strongly acidic conditions. Due to the indiscriminate reactivity of these radicals, achieving selectivity necessitated exploiting the structural proximity between the high-energy radical generated and the target C–H group.^[12] Löffler and Freytag later expanded this strategy to secondary amines, ingeniously utilizing it in the synthesis of nitrogen-heterocyclic derivatives (Scheme 3).^[13]



Scheme 3. Earliest reported functionalization of isolated alkyl C–H bonds.

In 1892, Jacob Volhard reported the first example of metal-promoted C–H activation involving the reaction between thiophene and mercury (II) chloride to yield chloromercurythiophene (Scheme 4, eq. 1).^[14] A few years later, Dimroth described the preparation of various arylmercury acetates by the reaction between $\text{Hg}(\text{OAc})_2$ and different aromatic hydrocarbons (Scheme 4, eq. 2).^[15] Subsequently, Kharasch and Isbell managed to react AuCl_3 with benzene to form chlorobenzene and gold(I) chloride.

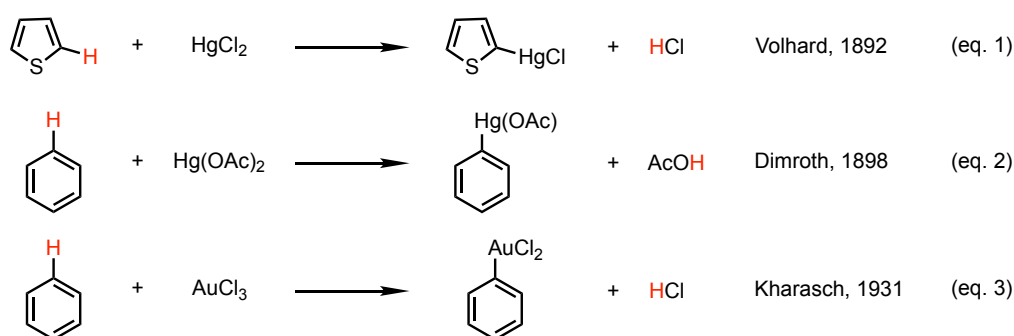
^[12] (a) Hofmann, A. *W. Ber. Dtsch. Chem. Ges.* **1885**, *18*, 5-23; (b) Hofmann, A. *W. Ber. Dtsch. Chem. Ges.* **1883**, *16*, 558-560.

^[13] Löffler, K.; Freytag, C. *W. Ber. Dtsch. Chem. Ges.* **1909**, *42*, 3427-3431.

^[14] Volhard, J. *Justus Liebigs Ann. Chem.* **1892**, *267*, 172-185.

^[15] (a) Dimroth, O. *W. Ber. Dtsch. Chem. Ges.* **1898**, *31*, 758; (b) Dimroth, O. *W. Ber. Dtsch. Chem. Ges.* **1898**, *31*, 2154-2156; (c) Dimroth, O. *W. Ber. Dtsch. Chem. Ges.* **1902**, *35*, 2032-2045; (d) Dimroth, O. *W. Ber. Dtsch. Chem. Ges.* **1902**, *35*, 2853-2873.

The authors managed to isolate the complex PhAuCl_2 , demonstrating that the reaction products could then be obtained from that metalated arene (Scheme 4, eq. 3).^[16]



Scheme 4. Pioneering examples of electrophilic C-H metalations.

1.2. Reactivity of the isolated C–H bond

The reactivity of an isolated C–H bond in a molecule is generally very low when it is non-acidic. This is primarily due to the significant energy barrier associated with breaking the C–H bond. The energy required to homolytically break these bonds, known as bond dissociation energies (BDEs), as well as the acidities of various C-H bonds in seven simple hydrocarbons, are outlined in Table 1.

Type of C-H	C(sp)	C(sp ²) _{arom}	C(sp ²) _{vinyl}	C(sp ³) _{1°}	C(sp ³) _{2°}	C(sp ³) _{3°}	C(sp ³) _{allylic}
Structure	$\text{H}-\text{C}\equiv\text{C}-\text{H}$		$\text{H}_2\text{C}=\text{C}-\text{H}$	$\text{H}_3\text{C}-\text{C}-\text{H}$	$\text{H}_3\text{C}-\text{C}-\text{H}$	$\text{H}_3\text{C}-\text{C}-\text{H}$	$\text{CH}_2=\text{C}-\text{H}$
BDE (kJ/mol)	552.2	473.0	460.2	410.8	397.9	389.9	361.1
pK _a	~25	43	44	~50	~50	~50	43

Table 1. BDE and pK_a values of selected hydrocarbon C-H bonds in DMSO.

Across different types of C–H bonds, BDE decreases in the sequence C(sp)–H → C(sp²)–H → C(sp³)–H, and on moving from primary to secondary to tertiary C(sp³)–H bonds, aligning with the concept that the BDE is inversely proportional to the stability of the radicals formed by homolytic cleavage of the bond. On the contrary, since acidity correlates with the stability of the corresponding deprotonated species, the pK_a trend follows a roughly opposite direction, with the exception of the allylic C–H bond.^[17]

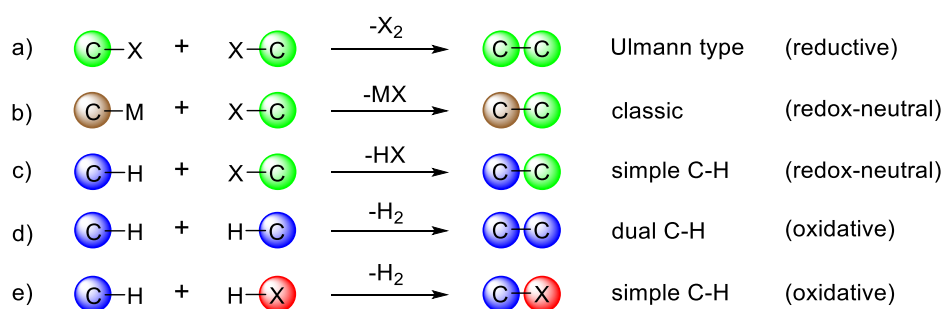
^[16] Kharasch, M. S.; Isbell, H. S. *J. Am. Chem. Soc.* **1965**, 843-855.

^[17] (a) Liron, F.; Oble, J.; Lorion, M. M.; Poli, G. *Eur. J. Org. Chem.* **2014**, 5863-5883; (b) Engelin, C. J.; Fristrup, P. *Molecules* **2011**, 16, 951-969; (c) Liu, G.; Wu, Y. *Top. Curr. Chem.* **2010**, 292, 195-209.

Although establishing direct correlations between homolytic or heterolytic C–H bond dissociation and the reactivity of C–H bonds isn't straightforward, we will discover that the interplay between these closely interconnected factors governs and clarifies this chemistry. In this context, the involvement of transition metals becomes crucial in the chemistry of activating or functionalizing C-H bonds.

1.3. Redox concepts in C–H activation processes

Coupling reactions serve to connect two carbon atoms from distinct substrates or reactants, resulting in the formation of a new C–C bond, plus a secondary product (Scheme 5). In order to be thermodynamically favored, the secondary products of these transformations have sometimes to react with appropriate acceptors: an oxidizing agent if the secondary product is H₂, or a reducing agent if it is X₂. Accordingly, coupling reactions can be systematically categorized on the basis of redox principles. Thus, a coupling involving two organohalides is termed a reductive coupling [Eq. (a)]. Conversely, a coupling between a principal organometallic reagent, or a C–H active substrate, and an organohalide falls into the category of a redox-neutral processes, where the oxidation degree of the metal doesn't change during the course of the reaction [Eqs. (b) and (c)]. Additionally, a coupling between two C–H active substrates constitutes an oxidative process [Eq. (d)]. This conceptual framework can be expanded to include equally pertinent oxidative transformations [C–H → C–X], where X represents a heteroatom [Eq. (e)].

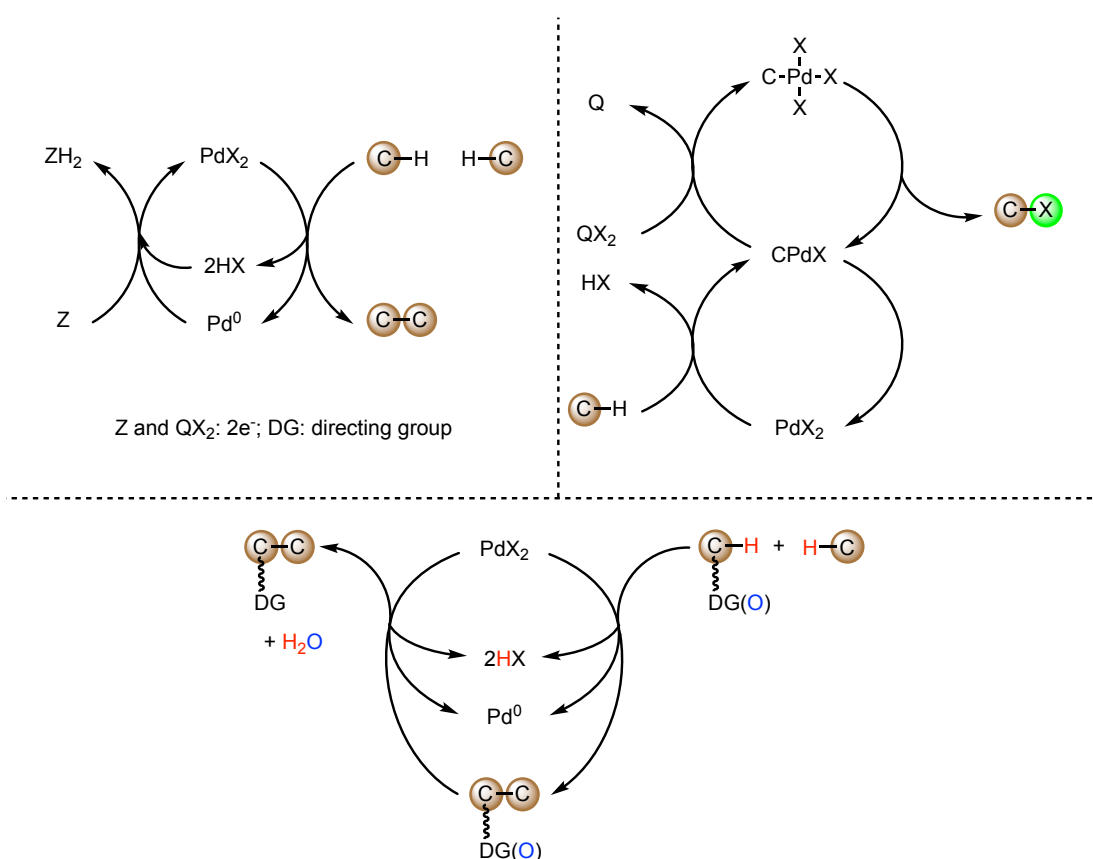


Scheme 5. Redox concepts in coupling reactions and C-H activation processes.

Type a) couplings correspond to the familiar Ulmann-type couplings, for instance. Type b) couplings concerns the well-established cross-coupling reactions catalyzed by transition metals like palladium. While these couplings are highly valuable, they necessitate pre-oxidation to generate the requested activated reactant – the organohalide or the organometallic reagent. On the other hand, type c) and type d) couplings involve one or two C–H activation processes, respectively, and type d) coupling represents a highly atom-economical strategy based on C–H activation, that is also called cross

dehydrogenative coupling (CDC) or dual C-H activation. Lastly, type e) reactivity, although not precisely a cross-coupling, underscores the synthetically significant formation of a carbon-heteroatom bond from a C-H active substrate. In summary, the blue markers in Scheme 5 indicate that redox-neutral or oxidative C-H activation processes have a significant presence within coupling methodologies.

Focusing on Pd chemistry, an oxidative catalytic transformation [Eqs. (d) and (e) in Scheme 5] can either directly yield an oxidized product (Scheme 6, top left), or generate an oxidized intermediate (Scheme 6, top right). In both scenarios, an external oxidizing agent is required to complete the catalytic cycle, either after, or before product formation, respectively. Alternatively, an oxidizing moiety can be covalently tethered to the substrate to obviate the need for an external oxidizing agent (Scheme 6, bottom).^[18] Furthermore, in cases where the oxidizing transformation simultaneously produces a reduced byproduct that can be removed, such as H₂, or if coupling of a redox pair is feasible, the catalytic system might not necessitate a sacrificial oxidant.^[19] Of course, if an oxidizing transformation generates a secondary product that can be evacuated, such as H₂, the thermodynamic system will be no more closed, and the transformation may not need a sacrificial oxidant to go to completion.



^[18] Patureau, F. W.; Glorius, F. *Angew. Chem. Int. Ed.* **2011**, *50*, 1977-1979.

^[19] Guillena, G.; Ramón, D. J.; Yus, M. *Chem. Rev.* **2010**, *110*, 1611-1641.

Scheme 6. Pd-catalyzed oxidative transformations. Top left: Pd(0)/Pd(II) cycle with external oxidant. Top right: Pd(II)/Pd(IV) cycle with external oxidant. Bottom: Pd(0)/Pd(II) cycle with built-in oxidant. Z and QX₂: 2e⁻ sacrificial oxidants. DG: directing group

The deployment of a covalently linked directing group, functioning as an internal oxidant in C–H activation (Scheme 6, bottom), was initially pioneered independently by groups led by Cui and Wu,^[20] Hartwig,^[21] Yu,^[22] as well as Guimond and Fagnou.^[23]

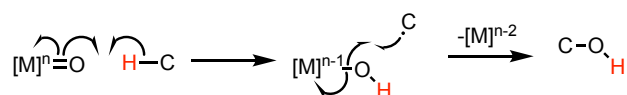
2. Metal-promoted mechanisms for C–H activation

The mechanisms underlying C–H activation/functionalization processes can be divided into two classes. The first class, namely outer-sphere mechanisms, consists in the insertion of a ligand (oxo, peroxy, carbene or nitrene) into a C–H bond. The second class involves the coordination of the C–H bond with the metal center, resulting in the formation of an organometallic complex where the hydrocarbyl species remains within the inner coordination sphere of the metal throughout the C–H cleavage process.

Although the term "C–H activation" and "C–H functionalization" are often used interchangeably, there is a growing consensus to restrict the use of the former term specifically to refer to inner-sphere mechanisms.

2.1. Outer sphere mechanisms

Within the realm of alkane oxidation, enzymatic metal-oxo species, as well as their bioinspired derivatives, facilitate C–H activation via a metalloradical pathway, often referred to as the "rebound" mechanism. This process involves a metal-oxo species abstracting a hydrogen radical from the alkane, followed by the rapid recombination of the radical onto the metal hydroxo intermediate, as depicted in Scheme 7.^[24]



Scheme 7. Radical rebound mechanism.

^[20] Wu, J. Cui, X.; Chen, L.; Jiang, G.; Wu, Y. *J. Am. Chem. Soc.* 2009, *131*, 13888-13889.

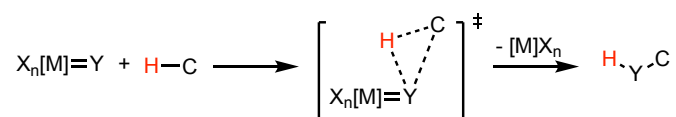
^[21] Tan, Y.; Hartwig, J. F. *J. Am. Chem. Soc.* 2010, *132*, 3676-3677.

^[22] Ng, K.-H.; Chan, A. S. C.; Yu, W.-Y. *J. Am. Chem. Soc.* 2010, *132*, 12862-12864.

^[23] Guimond, N.; Goulliaras, C.; Fagnou, K. *J. Am. Chem. Soc.* 2010, *132*, 6908-6909.

^[24] White, M. C.; Zhao, J. *J. Am. Chem. Soc.* 2018, *140*, 13988-14009.

In a similar manner, interactions involving metal-carbenes and metal-nitrenes result in the establishment of new C–H and C–C bonds, or N–H and N–C bonds with the carbene carbon atom or nitrene nitrogen atom, respectively. These transformations take place concurrently with metal dissociation. Notably, metal-carbenes and metal-nitrenes have showcased remarkable adaptability in effecting both intramolecular and intermolecular C–H functionalization reactions, as outlined in Scheme 8.^[25]



Y = CR₂, RN (metal-carbene or -nitrene)

Scheme 8. Metal-carbene and metal-nitrene insertions into C-H bonds.

2.2. Inner-sphere mechanisms

Three main sub-categories have been proposed for this type of mechanism^[26]: (a) Oxidative Addition (OA) for low-valent electron-rich transition metal complexes; (b) σ -Bond Metathesis (σ -BM) for electrophilic early transition metal complexes; (c) Electrophilic Activation (EA) for late transition metals featuring electron-withdrawing ligands. However, contemporary understanding has rendered these distinctions less definitive.^[9] A more refined approach involves classifying these processes based on the primary direction of charge transfer intrinsic to C–H activation.

Indeed, the interaction between a C–H bond and a transition metal involves a two-fold charge transfer (CT) process (Scheme 9):

- Reverse CT entails a transfer of charge from a metal-based occupied d_π orbital to the antibonding orbital (σ^* orbital) of the coordinated C-H bond.
- Forward CT involves charge transfer from the filled $\sigma_{(C-H)}$ bond to an empty metal-based d_σ orbital.^[26]

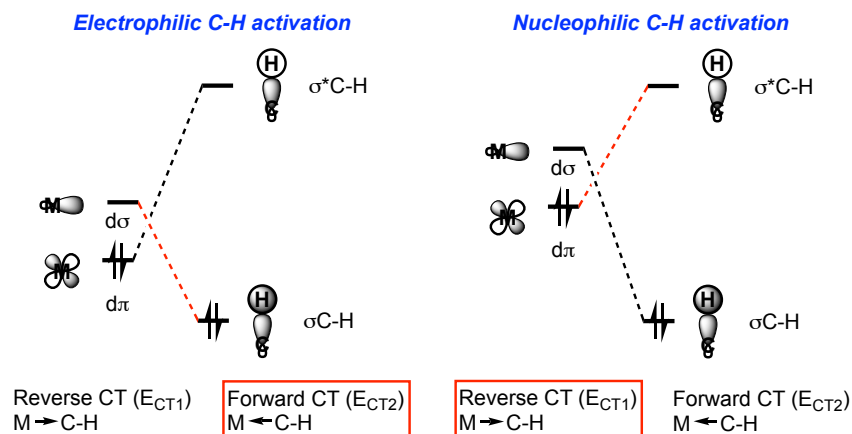
Both of these charge transfers collectively contribute to the gradual weakening and eventual cleavage of the C–H bond.

Accordingly, on the basis of the electronic nature of the resulting transition state during a C–H activation process, we can distinguish between nucleophilic and electrophilic mechanisms. Specifically, electron-deficient late transition metals, including cationic forms, tend to possess lower-

^[25] Davies, H. M. L.; Manning, J. R. *Nature* **2008**, *451*, 417-424.

^[26] Ess, D. H.; Goddard III, W. A.; Periana, R. A. *Organometallics* **2010**, *29*, 6459-6472.

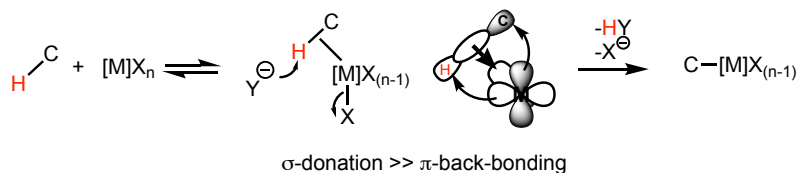
energy d_{π} orbitals with available d_{σ} electrons. Consequently, in their interaction with a C–H bond, the forward CT prevails over the reverse CT. This characterizes such transition metal complexes as electrophilic (Scheme 9, left side).



Scheme 9. Frontier orbital interactions for electrophilic (left) and nucleophilic (right) mechanism.

On the contrary, electron-rich transition metal complexes typically have higher-energy d_{σ} and d_{π} orbitals. In this scenario, the dominant interaction is reverse CT, defining a nucleophilic C–H activation (Scheme 9, right side). Therefore, the type of inner-sphere mechanism hinges on the nature and oxidation state of the metal within the complex.

Hence, late transition metals with low electron density and high oxidation states, like Pd(II), Pt(II), Rh(III), Ir(III), and Ru(II), often engage in electrophilic activation (EA) mechanisms. In such cases, the initial (C–H)-to-metal coordination is characterized by a robust σ -donation and relatively weak π -back-donation, usually followed by heterolytic cleavage (deprotonation) that is facilitated by an external anion (Scheme 10).

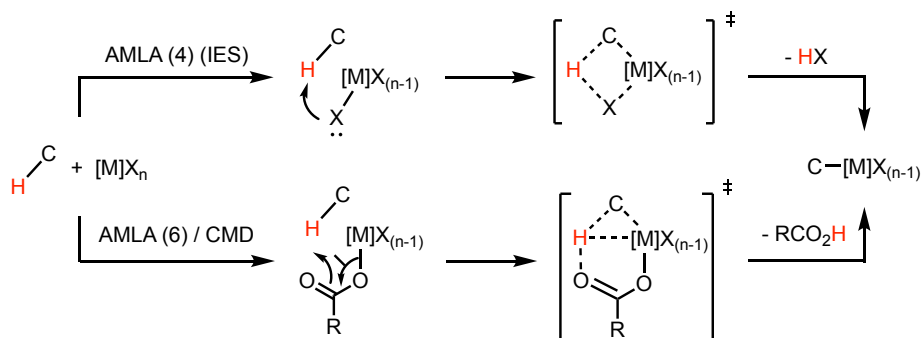


Scheme 10. Electrophilic substitution mechanism.

One of the most prevalent variations of the mechanism outlined above involves an intramolecular deprotonation process facilitated by a heteroatom-based ligand. This ligand could be a halide or an alkoxy anion, or even a bridging ligand like an acyloxy or carbonate anion. This deprotonation occurs through a cyclic and concerted mechanism. These mechanisms go by various names, such as

ambiphilic metal-ligand activation (AMLA),^[27] concerted metalation deprotonation (CMD),^[28] internal electrophilic substitution (IES)^[29] or 1,2-addition.

In these processes, hydrogen bonding typically arises between the lone pair-bearing ligand, often oxygen-based, and the proton of the C–H bond. This interaction influences the basic character of the ligand, promoting cleavage of the C–H bond. This effect raises the electron density in the C–H bond, further enhancing the agostic interaction (Scheme 11).



Scheme 11. Ambiphilic concerted mechanisms.

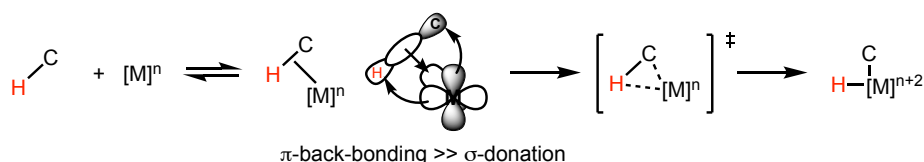
Late transition metals with reduced valence states have the capacity to trigger C–H activation mechanisms ranging from oxidative addition (OA) to σ -bond metathesis (σ -BM), with a plethora of intermediate mechanisms positioned between these two extremities. The selection of a specific mechanism is influenced by factors such as the metal center, the steric and electronic properties of the ligands, and the nature of the substrate involved in the C–H activation process.

In contrast to the electrophilic mechanisms mentioned earlier, nucleophilic mechanisms tend to be favored when electron donor ligands like phosphines, N-heterocyclic carbenes (NHCs), or bidentate nitrogen-based ligands are present. The oxidative addition (OA) mechanism, in particular, represents a nucleophilic process observed in electron-rich, d^8 low-valent, second- and third-row late transition metal complexes. In cases where the enthalpy difference between the C–H bond cleavage and the formation of M–C and M–H bonds, leading to the oxidized d^6 configuration, is not excessively energetically demanding, the OA mechanism becomes significant. This scenario involves an initial (C–H)-to-metal coordination intermediate featuring weak σ -donation and very strong π -back-bonding (Scheme 12).

^[27] Besora, M.; Braga, A. A. C.; Sameera, W. M. C.; Urbano, J.; Fructos, M. R.; Pérez, P. J.; Maseras, F. J. *Organomet. Chem.* **2015**, *784*, 2-12.

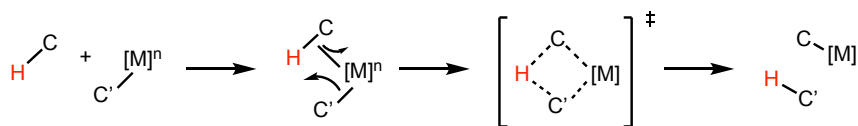
^[28] (a) Gorelsky, S. I.; Lapointe, D.; Fagnou, K. *J. Org. Chem.* **2012**, *77*, 658-668; (b) Lapointe, D.; Fagnou, K. *Chem. Lett.* **2010**, *39*, 1118-1126; (c) Gorelsky, S. I.; Lapointe, D.; Fagnou, K. *J. Am. Chem. Soc.* **2008**, *130*, 10848-10849.

^[29] Ongaard, J.; Tenn III, W. J.; Nielsen, R. J.; Periana, R. A.; Goddard III, W. A. *Organometallics* **2007**, *26*, 1565-1567.



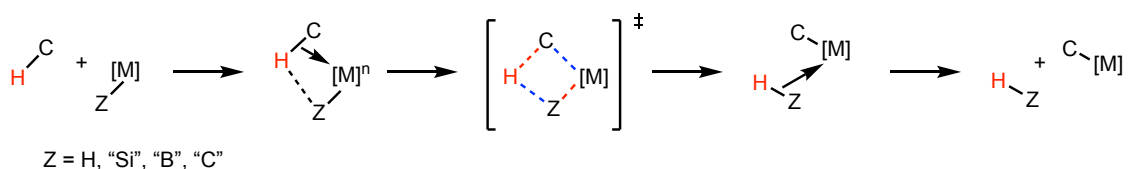
Scheme 12. Oxidative addition mechanism.

Transition metals with early d^0 configurations in high oxidation states, which lack available d electrons, are incapable of undergoing oxidative additions. Nevertheless, they can engage in a C–H bond through four-centered concerted σ -bond metathesis (σ -BM),^[30] involving four electrons, which occurs without altering the metal's oxidation state (Scheme 13).



Scheme 13. σ -Bond metathesis mechanism

Transition metal fragments with d^4 to d^8 configurations also typically participate in σ -bond metathesis (σ -BM) transformations. However, due to their vacant sites, they often tend to form stable σ -adducts prior to and after the actual metathesis. This process is termed σ -complex assisted metathesis (σ -CAM)^[31] and involves a mechanism where σ -adduct formation plays a pivotal role (Scheme 14).

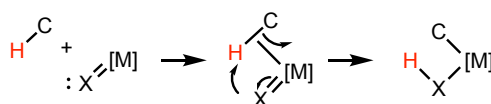


Scheme 14. σ -Complex assisted metathesis mechanism.

Lastly, the C–H bond can undergo a concerted four-centered 1,2-addition across a metal-X bond. This mechanism is similar to σ -bond metathesis (σ -BM), but in this case, the newly formed X–H motif remains connected to the resulting metal complex. This process involves the participation of lone pairs or π -electrons instead of σ -bonds. Early and middle transition metal complexes featuring amido, alkylidene, alkoxy, and alkylidyne ligands often operate through this C–H activation mode (Scheme 15).

^[30] (a) Watson, P. L. *J. Am. Chem. Soc.* **1983**, *105*, 6491-6493; (b) Thompson, M. E.; Baxter, S. M.; Bulls, A. R.; Burger, B. J.; Nolan, M. C.; Santarsiero, B. D.; Schaefer, W. P.; Bercaw, J. E. *J. Am. Chem. Soc.* **1987**, *109*, 203-219; (c) Waterman, R. *Organometallics* **2013**, *32*, 7249-7263.

^[31] Perutz, R. N.; Sabo-Etienne, S. *Angew. Chem. Int. Ed.* **2007**, *46*, 2578-2592.



Scheme 15. 1,2-Addition mechanism.

3. Pd-catalyzed coupling reactions involving C(sp²)-H functionalizations

Organopalladium chemistry has found widespread utility in organic synthesis, particularly in industrial applications. The pioneering advancements in palladium-catalyzed cross-coupling reactions, notably recognized with the 2010 Nobel Prize in Chemistry awarded to Richard F. Heck, Akira Suzuki, and Ei-ichi Negishi,^[32] have been essential. Palladium catalysts have demonstrated their capacity to facilitate and accelerate transformations that are challenging to achieve using conventional methods. A notable advantage is that palladium-catalyzed reactions generally occur under mild reaction conditions and exhibit a remarkable tolerance for various functional groups. The significance of palladium-catalyzed couplings is evident in their pivotal role in synthesizing a diverse range of compounds, including both carbocycles and heterocycles.^[33]

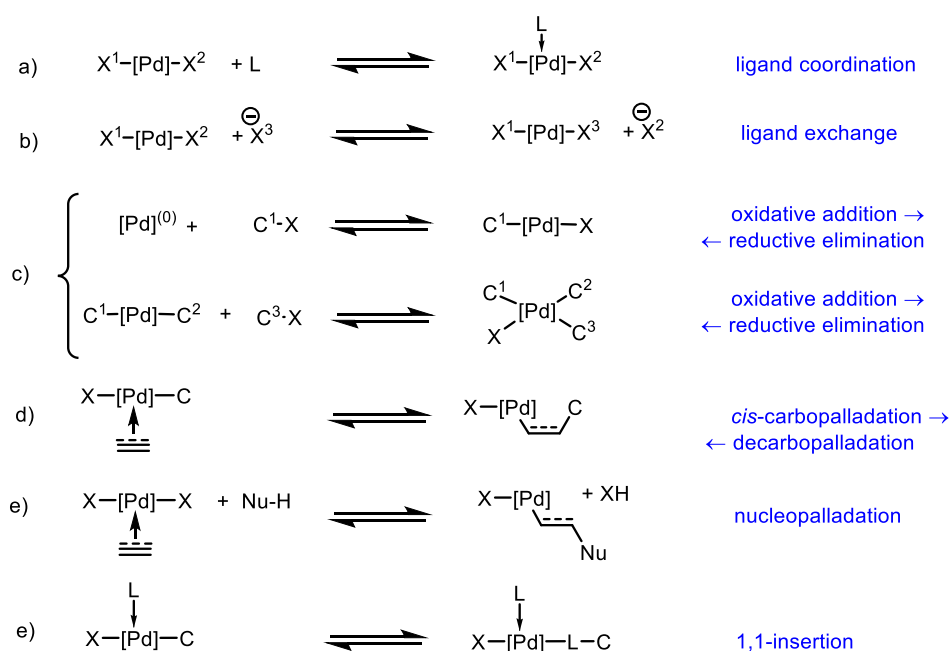
Palladium, a transition metal of the nickel triad, is situated in the second row of the periodic table. Its ground-state electronic configuration is [Kr] 4d¹⁰ 5s⁰. With few exceptions, palladium complexes exist in three oxidation states: Pd(0), Pd(II), and Pd(IV).^[34] Each oxidation state introduces distinct chemical properties. The fundamental steps in palladium chemistry include: a) coordination of dative ligands, b) ligand exchange, c) oxidative addition / reductive elimination, d) *cis*-palladation of π -systems

^[32] 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.

^[33] (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.; 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**.

^[34] 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) Sehnaal, P.; Taylor, R. J. K.; Fairlamb, I. J. S. *Chem. Rev.* **2010**, *110*, 824-889.

(alkenes/alkynes) through migratory insertion, e) trans-nucleopalladation of π -systems, f) dative ligand 1,1-insertion and finally a carbene insertion (Scheme 16).^[35]



Scheme 16. Main elementary steps involved in Pd-catalyzed reactions.

The equilibria of these reactions can be influenced by the nature of ligands and reagents, potentially leading to varying degrees of displacement to the left or right, reversible or irreversible. Pd-catalyzed reactions involve combinations of these elementary steps. The initial step in the catalytic cycle can be oxidative addition, ligand coordination or ligand exchange, while the terminal step might be reductive elimination or depalladation (often dehydropalladation).

3.1. C(sp²)-H/C(sp²)-X coupling reactions

3.1.1. The classical Mizoroki-Heck reaction^[36]

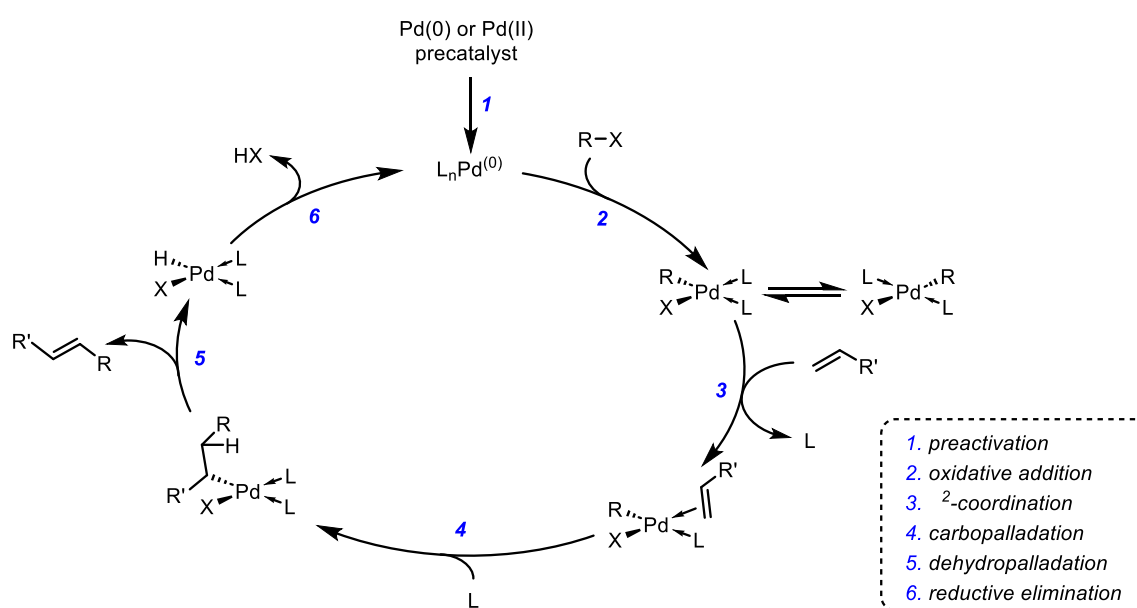
The Mizoroki-Heck coupling involves the Pd(0)-catalyzed reaction between an unsaturated halide (or pseudohalide) and an alkene, to form a substituted alkene. The reaction was first reported by Tsutomu Mizoroki in 1971,^[37] who described the coupling between iodobenzene and styrene, in methanol, to

^[35] 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.

^[36] (a) The Mizoroki-Heck Reaction; Oestreich, M., Ed.; Wiley: Chichester, **2009**; (b) Whitecomb, N. J.; Hii, K. K.; Gibson, S.E. *Tetrahedron*, **2001**, *57*, 7449-7476.

^[37] Mizoroki, T.; Mori, K.; Ozaki, A. *Bull. Chem. Soc. Jpn.* **1971**, *44*, 581.

form stilbene at 120°C, in the presence of potassium acetate base and catalytic amounts of palladium chloride. This work appeared after Fujiwara's report in 1967, which described the Pd(II)-mediated coupling between arenes and alkenes, and of that of Richard F. Heck,^[38] who, in 1968, reported the coupling between arylmercuric halides (ArHgCl) and alkenes (see later). In 1972, Heck independently reported results analogous to those of Mizoroki.^[39] The Mizoroki-Heck reaction is undoubtedly the most popular transformation to carry out a C(sp²)-H/C(sp²)-X coupling.^[40] The schematic representation in Scheme 17 outlines the major steps of this reaction. However, it's important to note that this simplified scheme, while helpful, cannot encompass all the diverse variants of the Mizoroki-Heck chemistry.



Scheme 17. General mechanism for a Heck catalytic cycle.

The catalytic cycle is initiated by reducing Pd(II) complexes to their active Pd(0) forms when using Pd(II) precursors or generating Pd(0) active species through multiple ligand exchanges from commercial Pd(0) complexes. The primary reduction of Pd(II) to Pd(0) can be performed by phosphines when starting from Pd(II) acetate,^[41] although it can also be assisted by hard nucleophiles with other Pd(II)

^[38] Heck, R. F. *J. Am. Chem. Soc.* **1968**, *90*, 5518-5526.

^[39] Heck, R. F.; Nolley, J. P. *J. Org. Chem.* **1972**, *37*, 2320-2322.

^[40] For selected general reviews on the Mizoroki-Heck reaction, see: (a) Beletskaya, I. P.; Cheprakov, A. V. *Chem. Rev.* **2000**, *100*, 3009-3066; (b) Heck, R. F. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds. Pergamon Press: Oxford, **1991**; Vol. 4; (c) Heck, R. F. *Org. React.* **1982**, *27*, 345-390; (d) Crisp, G. T. *Chem. Soc. Rev.* **1998**, *27*, 427-436.

^[41] For a selection of articles, see: (a) Amatore, C.; Jutand, A.; M'Barki, M. A. *Organometallics* **1992**, *11*, 3009-3013; (b) Ozawa, F.; Kubo, A.; Hayashi, T. *Chem. Lett.* **1992**, *11*, 2177-2180; (c) Amatore, C.; Carré, E.; Jutand, A.; M'Barki, M. *Organometallics* **1995**, *14*, 1818-1826.

sources such as Pd(PPh₃)₂Cl₂, for instance. Common nucleophiles include hydroxide (from Pd(OAc)₂)^[42] and alkoxide ions,^[43] water,^[44] and water-acetate ion combinations. In special cases, even fluoride in the presence of water can play a role in this reduction.^[45] Once the active Pd(0) species is formed, it engages in an oxidative addition by the organohalide derivative (aryl halide or vinyl halide).

This step is a concerted process, where the breaking of the C–X bond synchronizes with the formation of M–C and M–X bonds. Unlike stepwise addition-elimination mechanisms operating in nucleophilic aromatic or vinylic substitutions,^[46] oxidative addition is less sensitive to the nature of the alkene but highly sensitive to the nature of the nucleofuge (I > OTf > Br > Cl)^[47] and the strength of the newly formed M–X bonds. Once the oxidative addition has taken place, the alkene coordinates to the metallic center and then engages in a *syn*-carbopalladation, during which a new C–C bond is formed. This step plays often a crucial role in determining regioselectivity, stereoselectivity (see later). The subsequent step is a dehydropalladation (alias β-H elimination), which generates an alkene coordinated to palladium hydride. The mechanism of this step, in which the total electron count of the metal complex increases by 2, is a cyclic, concerted, involving four-centers. Hence, the intermediate after the carbopalladation step has to be able to adopt a conformation wherein the β-H and the palladium atom are in *syn*-coplanar relation. During this step, palladium must have a vacant coordination site that can interact with the β-H atom of the alkyl ligand (Scheme 18). The scheme evidences that the driving force of this step is due to the synergy between a σ-agostic donation (σ_{C-H}→Pd), and π-back donation (Pd→σ*_{C-H}).^[48] In fact, a d⁰ metal complexes lacking the possibility to participate in d-orbital back-bonding, such as Ag⁺ or Hg²⁺, are normally stable to β-hydride elimination. Since the C–H bond in a dehydropalladation is broken due to the inner sphere interaction between the C–H bond and palladium, this step can be regarded as a special case of intramolecular C–H activation wherein an H–Pd bond is formed instead if a C–Pd bond. So, although this is not the common thinking, the Mizoroki-Heck coupling can be classified as a C–H activation coupling reaction wherein the C–H activation step takes place after the C–C forming step.

[42] For a selection of articles, see: (a) Ioele, M.; Ortaggi, G.; Scarsella, M.; Sleiter, G. *Polyhedron* **1991**, *10*, 2475-2476; (b) Grushin, V. V.; Alper, H. *Organometallics* **1993**, *12*, 1890-1901; (c) Grushin, V. V. *J. Am. Chem. Soc.* **1999**, *121*, 5831-5832.

[43] Roffia, P.; Gregorio, G.; Conti, F.; Pregaglia, G. F. *J. Mol. Catal.* **1977**, *2*, 191-201.

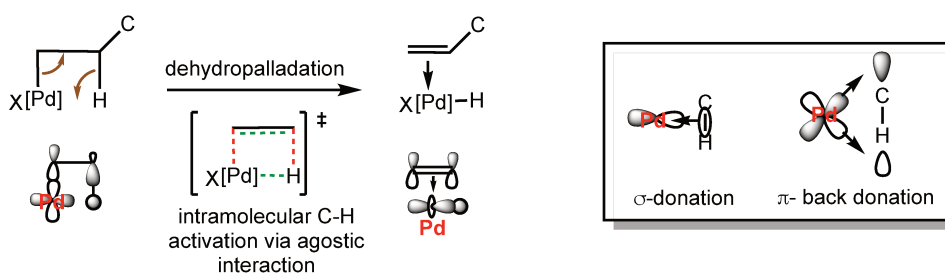
[44] Amatore, C.; Jutand, A.; Medeiros, M. J. *New J. Chem.* **1996**, *20*, 1143-1148.

[45] (a) Mason, M. R.; Verkade, J. G. *Organometallics* **1992**, *11*, 2212-2220; (b) McLaughlin, P. A.; Verkade, J. G. *Organometallics* **1998**, *17*, 5937-5940.

[46] (a) Rappoport, Z. *Acc. Chem. Res.* **1981**, *14*, 7-15; (b) Knipe, A. C., Watts, W. E., Eds.; John Wiley & Sons Ltd.: New York, **1997**.

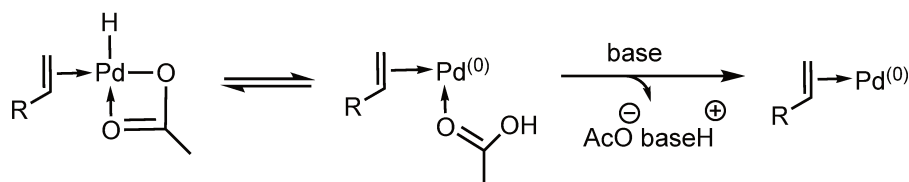
[47] Jutand, A.; Mosleh, A. *Organometallics* **1995**, *14*, 1810-1817.

[48] Thorn, D. L. Hoffman, R. *J. Am. Chem. Soc.* **1978**, *100*, 2079-2090.



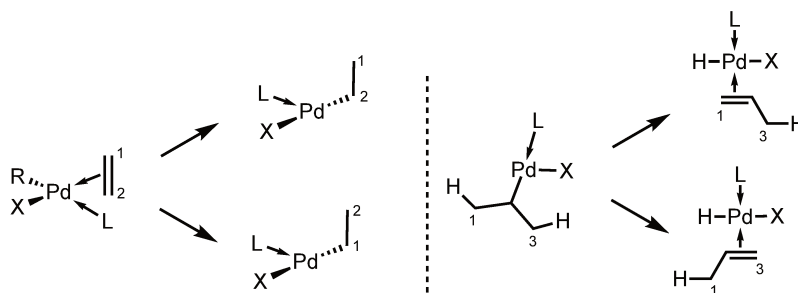
Scheme 18. Left: general mechanism of a dehydropalladation. Right: synergy of σ -agostic donation ($\sigma_{C-H} \rightarrow Pd$), and π -back donation ($Pd \rightarrow \sigma^*_{C-H}$).

The last step of the Mizoroki-Heck coupling is the reductive elimination from the palladium hydride $H[Pd]X$ ($X = OAc$) species. Although this step is normally exergonic,^[49] a base often is used to form the salt of the acid so as to drive the equilibrium to the right side (Scheme 19).



Scheme 19. Reductive elimination of $H[Pd]X$.

It should be noted that the carbopalladation and the dehydropalladation steps may suffer from regioselectivity issues (Scheme 20).



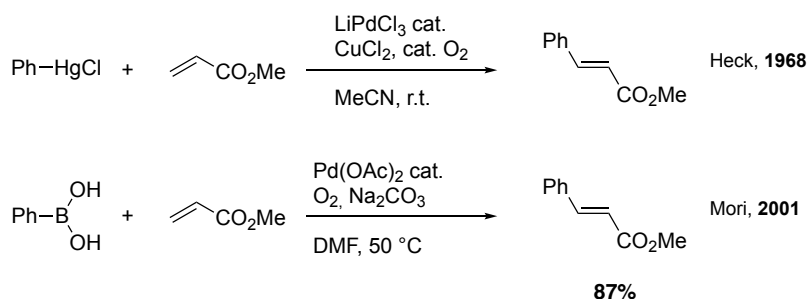
Scheme 20. Possible regioselectivity issues in the carbopalladation and dehydropalladation steps.

3.1.2. The oxidative Heck coupling

As mentioned above, in 1968, Heck^[38] (three years before the first report of the reaction that is known as the classical Mizoroki-Heck coupling) reported the PdX_2 -catalyzed aerobic arylation of olefins from

^[49] Nahra, F. Liron, F.; Prestat, G.; Mealli, C.; Messaoudi, A.; Poli, G. *Chem.-Eur. J.*, **2009**, *15*, 11078-11082.

phenylmercuric chloride in the presence of catalytic amounts of CuCl_2 (Scheme 21). In 1975, Heck and Dieck reported the first palladium(II)-mediated coupling between organoboronic acids and alkenes using stoichiometric $\text{Pd}(\text{OAc})_2$, today known as the oxidative Heck reaction. In 1994, Cho and Uemura^[50] reported the first catalytic version of this reaction (although the proposed mechanism was not correct).

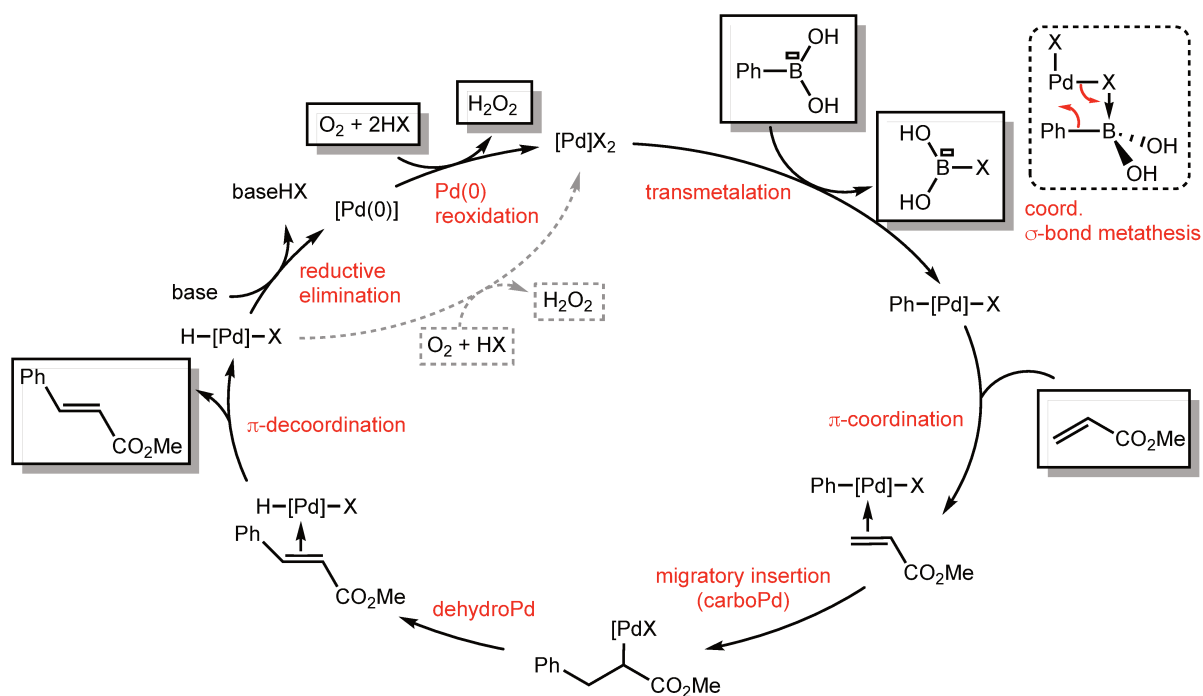


Scheme 21. The oxidative Heck reaction.

Finally, in 2001 Mori et al.^[51] reported this reaction using $\text{Cu}(\text{OAc})_2$ as terminal oxidant (Scheme 21), proposing a plausible mechanism (Scheme 22). It has to be noted that the mechanism of the oxidative Heck reaction differs from the classical Mizoroki-Heck reaction only in the first step (transmetalation of the boronic acid instead of the oxidative addition of the organohalide), and for an additional redox fixing step at the end.

^[50] Cho, C. S.; Uemura, S. *J. Organometal. Chem.* **1994**, 465, 85-92.

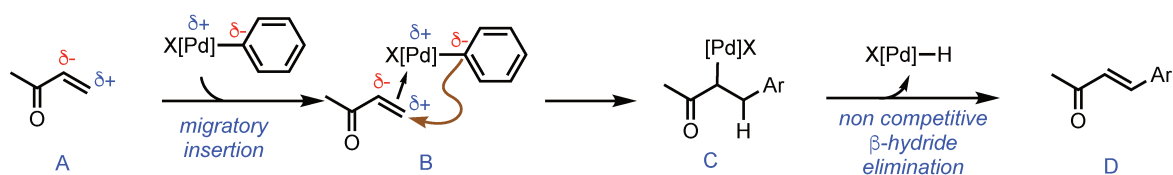
^[51] Du, X. L.; Suguro, M.; Hirabayashi, K.; Mori, A.; Nishikata, T.; Hagiwara, N.; Kawata, K.; Okeda, T.; Wang, H. F.; Fugami, K.; Kosugi, M. *Org. Lett.* **2001**, 3, 3313-3316.



Scheme 22. Mechanism of the oxidative Heck coupling.

3.1.3. Selectivity of the bimolecular Mizoroki-Heck reactions

The simplest way to obtain a regioselective bimolecular Mizoroki-Heck is to use an electron-poor alkene as olefinic partner. In this way, the carbopalladation step strongly favors the interaction between the electron-rich *ipso* carbon atom of the organopalladium species and the electron-poor C(sp²) atom of the alkene β located with respect to the electron-withdrawing group. Furthermore, the subsequent dehydropalladation step can only involve one type of H atom (Scheme 23).^[52,53]

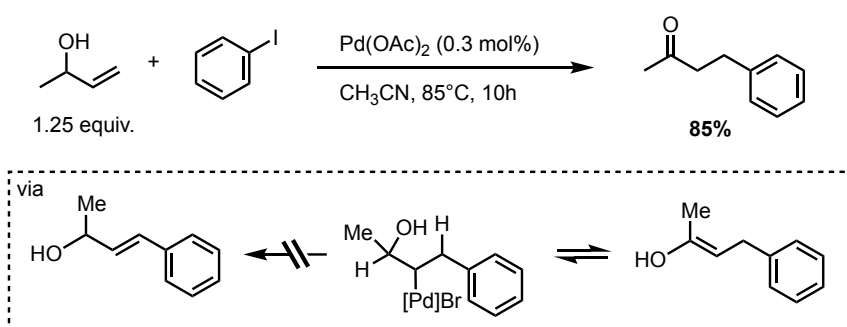


Scheme 23. Classical Mizoroki-Heck reaction with polarized alkenes.

^[52] (a) Mc Cartney, D.; Guiry, P. *J. Chem. Soc. Rev.* **2011**, *40*, 5122-5150; (b) Shibasaki, M.; Vogl, E. M.; Ohshima, T. *Adv. Synth. Catal.* **2004**, *346*, 1533-1552; (c) Dounay, A. B.; Overman, L. E. *Chem. Rev.* **2003**, *103*, 2945-2964.

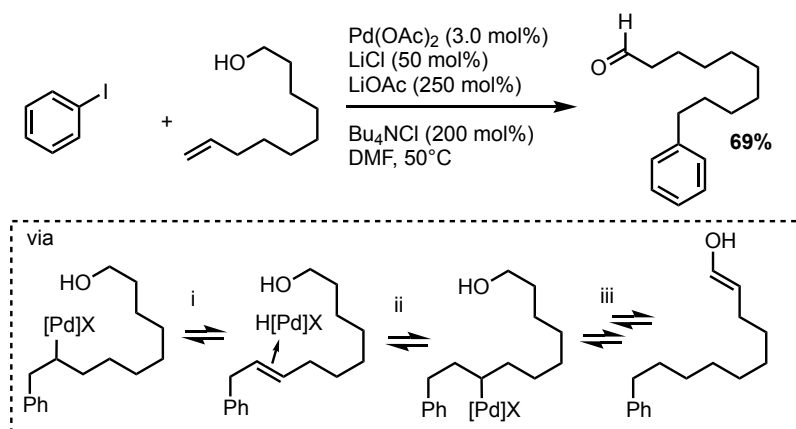
^[53] (a) Sigman, M. S.; Werner, E. W. *Acc. Chem. Res.* **2012**, *45*, 874-884; (b) Yonehara, K.; Mori, K.; Hashizume, T.; Chung, K.-G.; Ohe, K.; Uemura, S. *J. Organomet. Chem.* **2000**, *603*, 40-49; (c) Yoo, K. S.; Park, C.; Yoon, C. H.; Sakaguchi, S.; O'Neil, J.; Jung, K. W. *Org. Lett.* **2007**, *9*, 3933-3935; (d) Yoo, K. S.; O'Neil, J.; Sakaguchi, S.; Giles, R.; Lee, J. H.; Jung, K. W. *J. Org. Chem.* **2010**, *75*, 95-101.

Another method to achieve regioselective bimolecular Mizoroki-Heck coupling is the use of an allylic alcohol as substrate, as pioneered independently by Heck and Chalk in 1976.^[54] With this type of substrates, the carbopalladation is often regioselective and generates a β -hydroxyalkylpalladium intermediate. The subsequent dehydropalladation is also regioselective, involving a β -H atom close to the hydroxyl function. The enol transiently generated promptly equilibrates to the corresponding carbonyl derivative (Scheme 24). These works also observed that homoallylic alcohols afforded arylated carbonyl compounds, which implied the first cases of a chain-walking palladium.



Scheme 24. Mizoroki-Heck reaction with allylic alcohols as substrates.

The above early examples of chain walking were later extended by Larock to the distant functionalization of longer-chain ω -alkenols, to afford the corresponding arylated carbonyls.^[55,56]



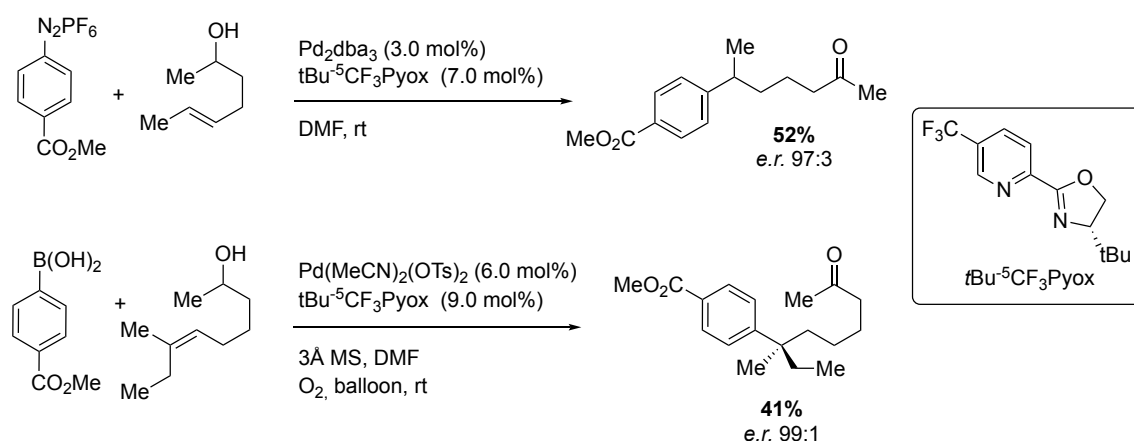
Scheme 25. Mizoroki-Heck with ω -alkenols as substrates. Steps: i: dehydropalladation; ii: hydripalladation; iii: iterative hydripalladation / dehydropalladation sequences.

^[54] (a) Melpolder, J. B.; Heck, R. F. *J. Org. Chem.* **1976**, *41*, 265; (b) Chalk, A. J.; Magennis, S. A. *J. Org. Chem.* **1976**, *41*, 273-278; (c) Chalk, A. J.; Magennis, S. A. *J. Org. Chem.* **1976**, *41*, 1206-1209. See also: (d) Bouquillon, S.; Ganchev, B.; Estrine, B.; Hénin, F.; Muzart, J. *J. Organomet. Chem.* **2001**, *634*, 153-156.

^[55] Larock, R. C.; Leung, W.-Y.; Stolz-Dunn, S. *Tetrahedron Lett.* **1989**, *30*, 6629-6632.

^[56] For a review, see: Sommer, H.; Juliá-Hernández, F.; Martín, R.; Marek, I. *ACS Cent Sci*, **2018**, *4*, 153-165.

More recently, Sigman and his group reported a series of papers on the Mizoroki-Heck coupling on ω -alkenols. The use of the bulky chiral enantiopure N,N' -bidentate $t\text{Bu}^{\text{-5}}\text{CF}_3\text{Pyox}$ ligand allowed these authors to render the carbopalladation step highly enantioselective. At the same time, the use of an electrophilic catalyst system favored the full migration of the alkene function, as opposed to an undesired HPdX decoordination. The strategy allowed to create quaternary carbon centers via classical Mizoroki-Heck as well as oxidative Heck conditions. Since the two hydrogen atoms of the alcohol function (CH-OH) formally moved to saturate the initially formed alkene, this disproportionation was named “redox-relay” (Scheme 26).^[57]



Scheme 26. Examples of enantioselective classical Mizoroki-Heck and oxidative Heck couplings from ω -alkenols.

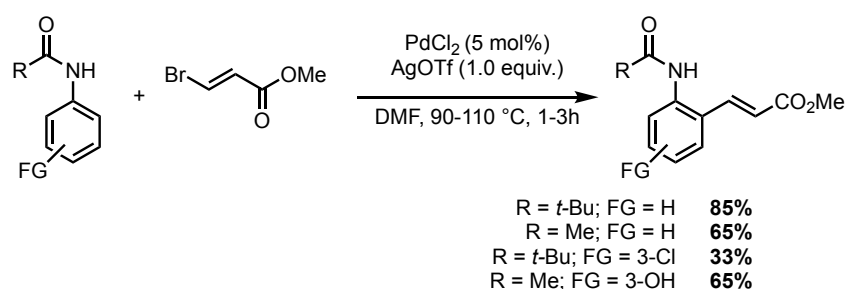
3.1.4. Reverse Mizoroki-Heck coupling

In 2005, Daugulis and coworkers reported an interesting redox-neutral Pd(II)-catalyzed strategy to achieve the *ortho* acryloylation of anilides by the coupling between an anilide and a β -halo acrylate (Scheme 27).^[58] This coupling represents a case of anilide *ortho*-palladation. Since in this $\text{C}(\text{sp}^2)\text{-H}/\text{C}(\text{sp}^2)\text{-X}$ coupling, the chronology of the interaction of the catalyst with the substrate components

^[57] (a) Werner, E. W.; Mei, T.-S.; Burckle, A. J.; Sigman, M. S. *Science* **2012**, *338*, 1455-1458; (b) Mei, T.-S.; Werner, E. W.; Burckle, A. J.; Sigman, M. S. *J. Am. Chem. Soc.* **2013**, *135*, 6830-6833; (c) Hilton, M. J.; Xu, L.-P.; Norrby, P.-O.; Wu, Y.-D.; Wiest, O.; Sigman, M. S. *J. Org. Chem.* **2014**, *79*, 11841-11850; (d) Mei, T.-S.; Patel, H. H.; Sigman, M. S. *Nature* **2014**, *508*, 340-344; (e) Xu, L.; Hilton, M. J.; Zhang, X.; Norrby, P.-O.; Wu, Y.-D.; Sigman, M. S.; Wiest, O. *J. Am. Chem. Soc.* **2014**, *136*, 1960-1967; (f) Patel, H. H.; Sigman, M. S. *J. Am. Chem. Soc.* **2015**, *137*, 3462-3465; (g) Zhang, C.; Santiago, C. B.; Crawford, J. M.; Sigman, M. S. *J. Am. Chem. Soc.* **2015**, *137*, 15668-15671; (h) Zhang, C.; Santiago, C. B.; Kou, L.; Sigman, M. S. *J. Am. Chem. Soc.* **2015**, *137*, 7290-7293; (i) Chen, Z.-M.; Hilton, M. J.; Sigman, M. S. *J. Am. Chem. Soc.* **2016**, *138*, 11461-11464; (j) Patel, H. H.; Sigman, M. S. *J. Am. Chem. Soc.* **2016**, *138*, 14226-14229; (k) Chen, Z.-M.; Nervig, C. S.; DeLuca, R. J.; Sigman, M. S. *Angew. Chem., Int. Ed.* **2017**, *56*, 6651-6654; see also: (l) Singh, S.; Bruffaerts, J.; Vasseur, A.; Marek, I. *Nat. Commun.* **2017**, *8*, 14200; (m) Larionov, E.; Lin, L.; Guénée, L.; Mazet, C. *J. Am. Chem. Soc.* **2014**, *136*, 16882-16894.

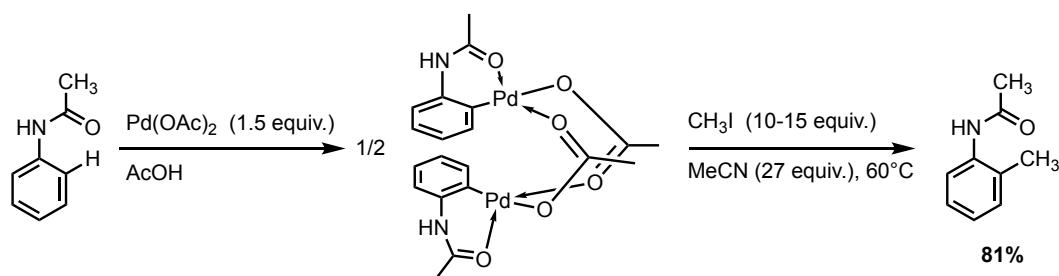
^[58] Zaitsev, V. G.; Daugulis, O. *J. Am. Chem. Soc.* **2005**, *127*, 4156-4157.

is opposite with respect to that of the Mizoroki-Heck (“anilide first” as opposed to “organohalide first”) Daugulis named this type of coupling 'reverse' Heck.



Scheme 27. Selected examples of coupling between anilides and β -haloacrylates reported by Daugulis.

Cyclopalladation chemistry, pioneered by Cope in 1965, involved using azobenzene as the substrate,^[59] is very rich.^[60] In particular, in 1984, Tremont and Rahman^[61] reported that treatment of acetanilides with stoichiometric amounts of Pd(OAc)₂ brought about an ortho-cyclopalladation, and treatment of the resulting palladacycle with excess MeI afforded the methylation of the palladated position. Later studies demonstrated that the intermediate cyclopalladated structure is dimeric (Scheme 28).^[62]



Scheme 28. Stoichiometric Pd(OAc)₂-mediated ortho methylation of acetanilide.

More than twenty years later, Daugulis and Zaitsev^[63] revisited the topic and showed that anilides could be arylated with aryl iodides by treatment with catalytic amounts of Pd(OAc)₂ in the presence AgOAc (Scheme 29).

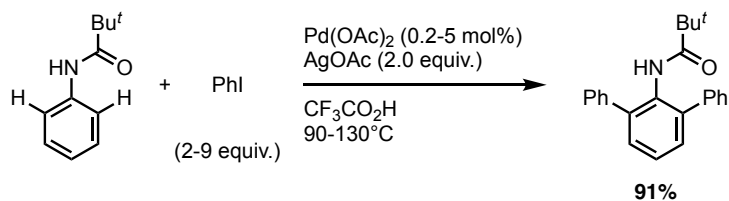
^[59] (a) Cope, A. C.; Siekman, R. W. *J. Am. Chem. Soc.* **1965**, *87*, 3272-3273; (b) Cope, A. C.; Friedrich, E. C. *J. Am. Chem. Soc.* **1968**, *90*, 909-913.

^[60] (a) Ryabov, A. D. *Chem. Rev.* **1990**, *90*, 403-424; (b) Albrecht, M. *Chem. Rev.* **2010**, *110*, 576-623; (c) Tóth, B. L.; Monory, A.; Egyed, O.; Domján, A.; Bényei, A.; Szathury, B.; Novák, Z.; Stirling, A. The ortho effect in directed C–H activation. *Chem. Sci.* **2021**, *12*, 5152-5163.

^[61] (a) Tremont, S. J.; Rahman, H. U. *J. Am. Chem. Soc.* **1984**, *106*, 5759-5760; (b) McCallum, J. S.; Gasdaska, J. R.; Liebeskind, L. S.; Tremont, S. J. *Tetrahedron Lett.* **1989**, *30*, 4085-4088.

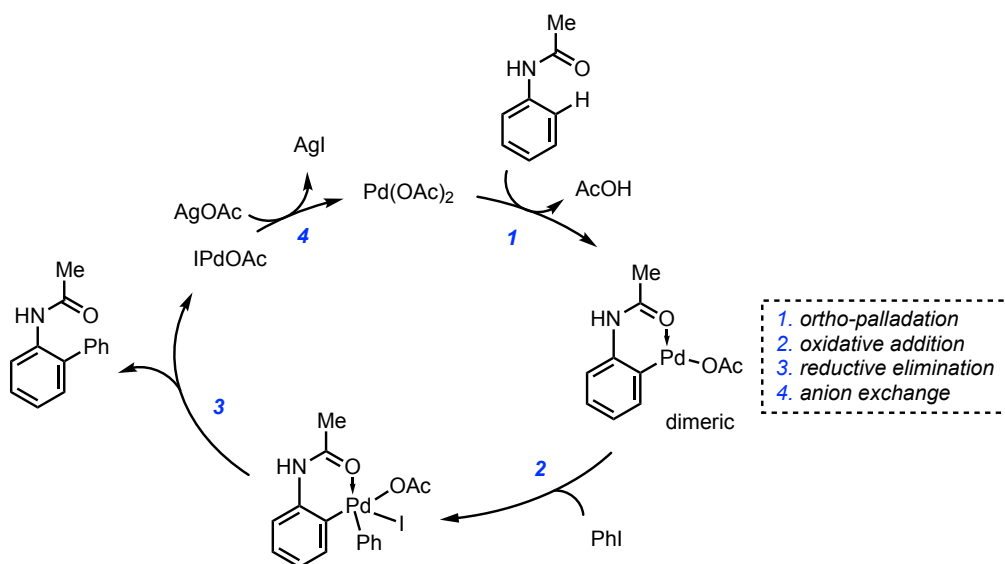
^[62] Yeung, C. S.; Zhao, X.; Borduas, N.; Dong, V. M. *Chem. Sci.* **2010**, *1*, 331-336.

^[63] Daugulis, O.; Zaitsev, V. G. *Angew. Chem. Int. Ed.* **2005**, *44*, 4046-4068.



Scheme 29. $\text{Pd}(\text{OAc})_2$ -catalyzed ortho arylation of anilides using aryl iodides.

The mechanism of the above Pd-catalyzed arylation is expected to involve the initial coordination of $\text{Pd}(\text{OAc})_2$ by the directing group followed by a cyclopalladation. The resulting dimeric Pd(II) complex undergoes oxidative addition by the aryl halide to afford a transient Pd(IV) complex, as postulated by Catellani^[64] in the eponymous reaction. Reductive elimination followed by anion exchange closes the catalytic cycle (Scheme 30).



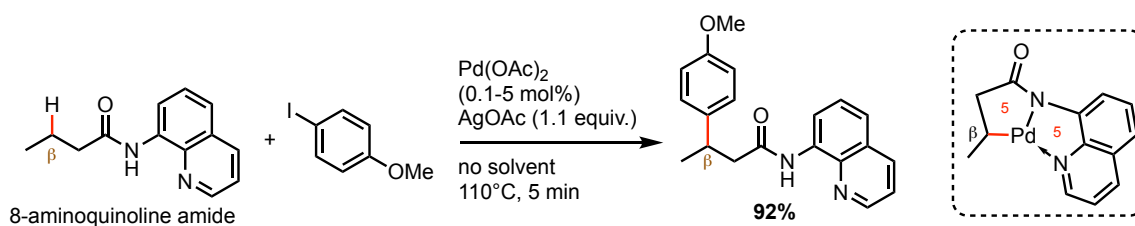
Scheme 30. Postulated mechanism for the PdX_2 -catalyzed ortho arylation of anilides.

Subsequent evolution of this *ortho*-palladation chemistry led the Daugulis group^[65] to the development of the now popular bidentate monoanionic removable auxiliary 8-aminoquinoline, which allowed the Pd-catalyzed $\text{C}(\text{sp}^3)\text{-H}$ arylation of carboxylic acid derivatives at the β position (Scheme 31).^[66]

^[64] Catellani, M.; Frignani, F.; Rangoni, A. *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 119-122.

^[65] Zaitsev, V. G.; Shabashov, D.; Daugulis, O. *J. Am. Chem. Soc.* **2005**, *127*, 13154-13155.

^[66] Nadres, E. T.; Santos, I. G.; Daugulis, D. *J. Org. Chem.* **2013**, *78*, 9689-9714.

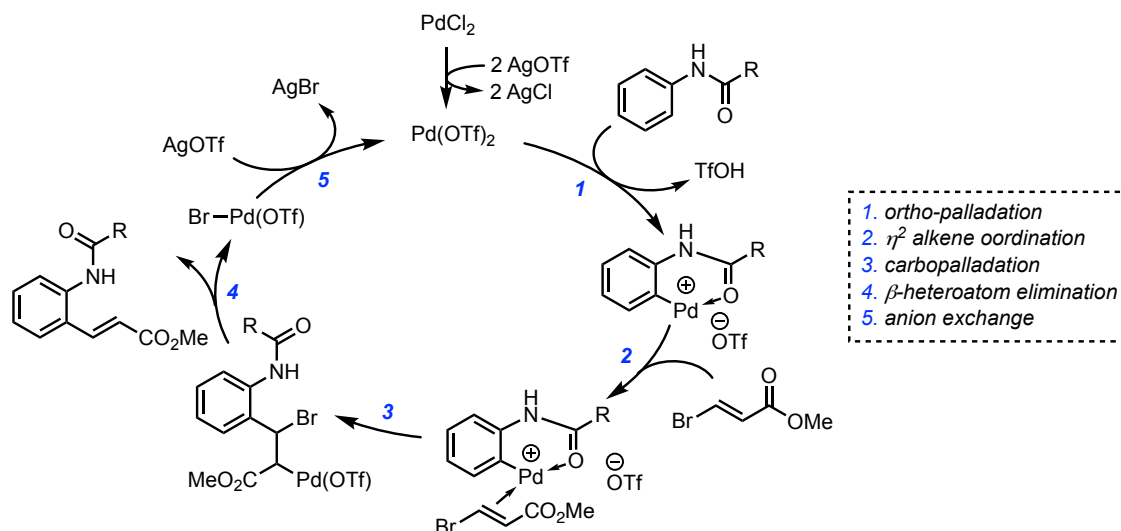


Scheme 31. Pd-catalyzed β -C(sp³)-H arylation of carboxylic acid derivatives.

Along this line, several works by our and other groups later built on the Pd-catalyzed *ortho*-palladation concept to functionalize the *ortho* position of aromatic amino acids such as phenyl alanine and tyrosine.^[67]

Coming back to the above mentioned *ortho* acryloylation of anilides, stoichiometric experiments performed by the authors confirmed that the reaction between preformed *ortho*-palladated anilines and haloalkenes gave efficiently the corresponding coupling products. Addition of silver salts and the use of N,N-dimethylformamide (DMF) proved to be effective for the catalysis, enabling the successful *ortho*-alkenylation of several anilides. However, the reaction is inhibited by the coupling products, and anilides with electron-withdrawing substituents halted at low conversions. Both inter- and intramolecular deuterium isotope effects supported C–H bond cleavage as the turnover-limiting step. The mechanism proposed by the authors involves the initial *ortho*-palladation of the aniline by the Pd(II) catalyst. Following coordination, and regioselective carbopalladation of the bromoacrylate affords a new intermediate, which, after dehalopalladation (in contrast with the dehydropalladation of the classical Mizoroki-Heck reaction) generates the coupled product. Finally, anion exchange by the silver salt regenerates the cationic catalyst (Scheme 32).

^[67] (a) Li, J.-J.; Mei T.-S., Yu, J.-Q. *Angew. Chem. Int. Ed.* **2008**, *47*, 6452-6455; (b) Zhang, S.-Y.; He, G.; Nack, W.A.; Zhao, Y.; Li, Q.; Chen, G. *J. Am. Chem. Soc.*; **2013**, *135*, 2124-2127; (c) Zhao, Y.; Chen, G.; *Org. Lett.* **2011**, *13*, 4850-4853; (d) Wang, X.; Niu, S.; Xu, L.; Zhang, C.; Meng, L.; Zhang, X.; Ma, D. *Org. Lett.* **2017**, *19*, 246-249; (e) Illuminati, D.; Fantinati, A.; De Ventura, T.; Perrone, D.; Sturaro, C.; Albanese, V.; Marzola, E.; Cristofori, V.; Oble, J.; Poli, G.; Trapella, C. *J. Org. Chem.* **2022**, *87*, 5, 2580-2589.



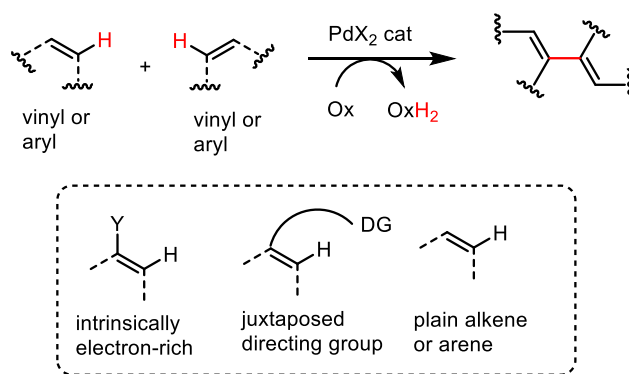
Scheme 32. Postulated mechanism for the PdX_2 -catalyzed *ortho*-acryloylation of anilides.

Alternative mechanisms to the one proposed above have also been considered by the authors. However, the possibility of the involvement of the alkyne generated by elimination of HX from haloalkene was ruled out, as a control experiment substituting bromoalkene for methyl propiolate gave no product. A mechanism based on oxidative addition of the organohalide on the *ortho*-palladated intermediate (Scheme 30) and the one based on a Pd(II)-catalyzed electrophilic aromatic substitution were ruled out as the observed order of reactivity ($\text{RBr} > \text{RI} \sim \text{RCI}$) was inconsistent with either of these possibilities.

3.2. $\text{C}(\text{sp}^2)\text{-H}$ / $\text{C}(\text{sp}^2)\text{-H}$ couplings

Electrophilic $\text{C}(\text{sp}^2)\text{-H}$ / $\text{C}(\text{sp}^2)\text{-H}$ couplings between alkenes or arenes can be conceptually divided into three classes. Those wherein one of the two C–H partners is intrinsically electron-rich,^[68] as a heteroatom-enriched alkene or an electron rich arene; those wherein one of the two coupling partners carries a juxtaposed directing group, and those involving a plain alkene or arene. Coupling of the two first classes is usually, at least mechanistically, simpler, as these coupling partners will be palladated first. More intriguing and challenging is the third case of couplings, wherein none of the coupling partners is activated by an intrinsic electron richness or a strategically placed directing group. For example, when simple arenes are used, like for example benzene, they are employed in large excess, or even as solvents (Scheme 33).

^[68] Brückl, T.; Baxter, R. D.; Ishihara, Y.; Baran, P. S. *Acc. Chem. Res.* **2012**, *45*, 826-839.



Scheme 33. Classification of $C(sp^2)\text{-H} / C(sp^2)\text{-H}$ couplings in the case of Pd(II) catalysis.

3.2.1. Aryl/Aryl C–H/C–H coupling (a hint)

Palladium catalysis has proven effective in the oxidative intermolecular cross C–H coupling between two aromatic substrates^[69] since the pioneering work of Wenjun Lu's in 2006.^[70] The field evolved with Fagnou's cross-coupling of indoles and benzene and DeBoef's hetero-couplings.^[71,72,73] In particular, Fagnou described a cross-coupling reaction between indoles and benzene (Scheme 34), while DeBoef disclosed a hetero-coupling between benzofuran and benzene, employing the heteropolymolybdovanadic acid (HMPV) with molecular oxygen as an external oxidant system (Scheme 34). These two cases are clear examples involving an intrinsically electron-rich (activated) coupling partner.

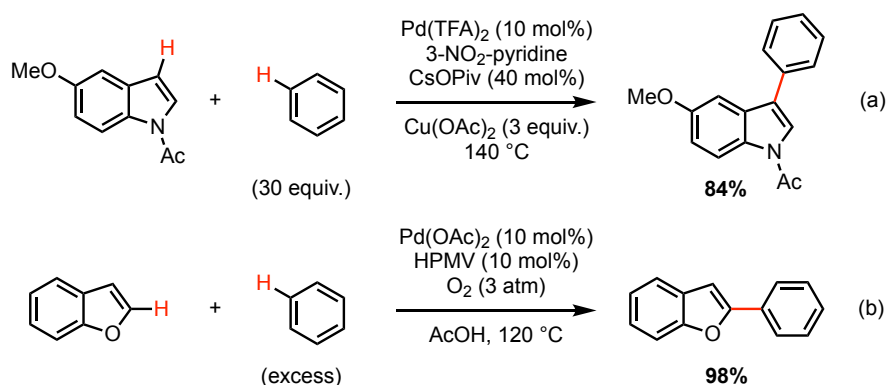
^[69] (a) Liu, C.; Yuan, J.; Gao, M.; Tang, S.; Li, W.; Shi, R.; Lei, A. *Chem. Rev.* **2015**, *115*, 12138–12204; (b) Kuhl, N.; Hopkinson, M. N.; Wencel-Delord, J.; Glorius, F. *Angew. Chem. Int. Ed.* **2012**, *51*, 10236–10254; (c) Cho, S. H.; Kim, J. Y.; Kwak, J.; Chang, S. *Chem. Soc. Rev.* **2011**, *40*, 5068–5083.

^[70] Li, R.; Li, J.; Lu, W. *Organometallics* **2006**, *25*, 5973–5975.

^[71] (a) Stuart, D. R.; Fagnou, K. *Science* **2007**, *316*, 1172–1175; (b) Dwight, T. A.; Rue, N. R.; Charyk, D.; Josselyn, R.; DeBoef, B. *Org. Lett.* **2007**, *16*, 3137–3139; (c) Potavathri, S.; Pereira, K. C.; Gorelsky, S. I.; Pike, A.; LeBris, A. P.; DeBoef, B. *J. Am. Chem. Soc.* **2010**, *132*, 14676–14681.

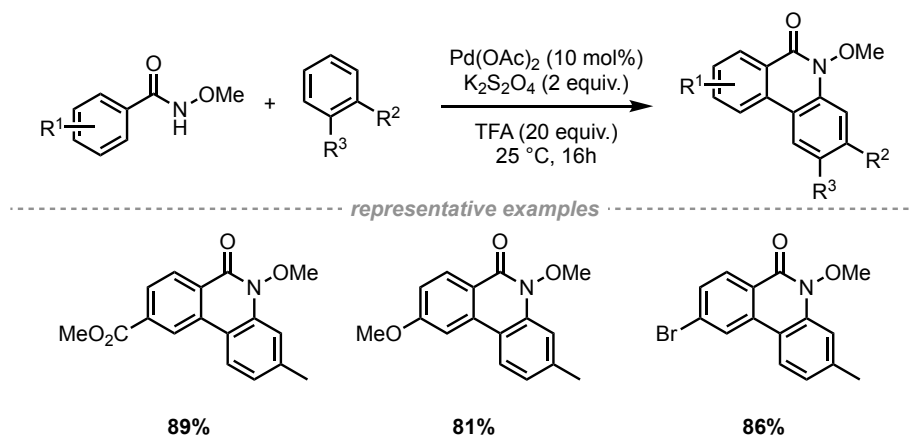
^[72] For other examples of dehydrogenative aryl/aryl cross-coupling see: (a) Liu, B.; Huang, Y.; Lan, J.; Song, F.; You, J. *Chem. Sci.* **2013**, *4*, 2163–2167; (b) Gong, X.; Song, G.; Zhang, H.; Li, X. *Org. Lett.* **2011**, *13*, 1766–1769; (c) Cho, S. H.; Hwang, S. J.; Chang, S. *J. Am. Chem. Soc.* **2008**, *130*, 9254–9256; (d) Potavathri, S.; Dumas, A. S.; Dwight, T. A.; Naumiec, G. R.; Hammann, J. M.; DeBoef, B. *Tetrahedron Lett.* **2008**, *49*, 4050–4053; (e) Li, B.-J.; Tian, S.-L.; Fang, Z.; Shi, Z.-J. *Angew. Chem. Int. Ed.* **2008**, *47*, 1115–1118; (f) Stuart, D. R.; Villemure, E.; Fagnou, K. *J. Am. Chem. Soc.* **2007**, *129*, 12072–12073; (g) Hull, K. L.; Sanford, M. S. *J. Am. Chem. Soc.* **2007**, *129*, 11904–11905.

^[73] For enantioselective examples see: Gao, D.-W.; Gu, Q.; You, S.-L. *J. Am. Chem. Soc.* **2016**, *138*, 2544–2547.



Scheme 34. Pd-catalyzed cross-coupling of aromatic C-H substrates.

As to aryl/aryl directed C(sp²)-H / C(sp²)-H couplings, we can cite as a representative example Cheng's work, who developed a directed palladium-catalyzed cyclization, forming C–C and C–N bonds from C–H bonds using *N*-methoxybenzamides as directing groups for phenanthridinones synthesis (Scheme 35).^[74]



Scheme 35. First directed palladium-catalyzed cyclization reaction.

Meanwhile, Yu's group achieved para-selective C–H arylation of monosubstituted arenes with an electron-poor amide directing group, identifying *N*-Fluoro sulfonimide (NFSI) as a superior oxidant for high para-selectivity.^[75] Sanford's group also contributed with a selective Pd-catalyzed oxidative cross-coupling between benzo[h]quinoline and disubstituted arenes, revealing the influence of quinone oxidant concentration on site-selectivity.^[5a, 76] Itami *et al.* reported a regioselective oxidative coupling

^[74] Karthikeyan, J.; Cheng, C.-H. *Angew. Chem. Int. Ed.* **2011**, *50*, 9880–9883.

^[75] (a) Wang, X.; Leow, D.; Yu, J.-Q. *J. Am. Chem. Soc.* **2011**, *133*, 13864–13867; (b) Wang, X.; Mei, T.-S.; Yu, J.-Q. *J. Am. Chem. Soc.* **2009**, *131*, 7520–7521.

^[76] Sanhueza, I. A.; Wagner, A. M.; Sanford, M. S.; Schoenebeck, F. *Chem. Sci.* **2013**, *4*, 2767–2775.

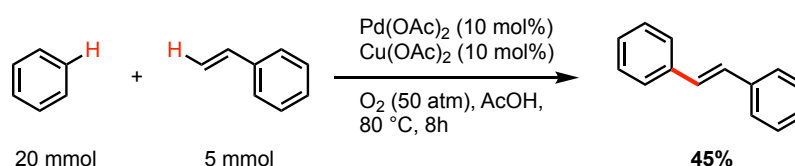
between fluoranthene and simple arenes, predominantly at the C3 position of fluoranthene, even in the absence of directing groups.^[77]

These few examples underscore the essential role played by ligands, oxidants, and reaction conditions in fine-tuning site-selectivity in CDC aryl/aryl C–H couplings.

3.2.2. Aryl/Alkenyl C–H/C–H coupling

Undirected arene/alkene CDC reactions

The undirected aryl / alkenyl C(sp²)-H / C(sp²)-H coupling was the pioneering type of coupling. In a ground-breaking study in 1967, Fujiwara and Moritani reported the stoichiometric Pd(II)-mediated vinylation of arenes.^[78] Soon thereafter, the same researchers developed a catalytic aerobic variant of this dehydrogenative coupling, employing an oxidant system consisting in the combination of copper(II) acetate and molecular oxygen (Scheme 36).



Scheme 36. The Fujiwara coupling.

Sanford's investigation into the effects of pyridine ligands on Pd-catalyzed oxidative cross-coupling between arenes and α,β -unsaturated esters underscored the critical role of ligands,^[79] with 3,5-dichloropyridine improving reaction efficiency.

Directed arene/alkene CDC reactions

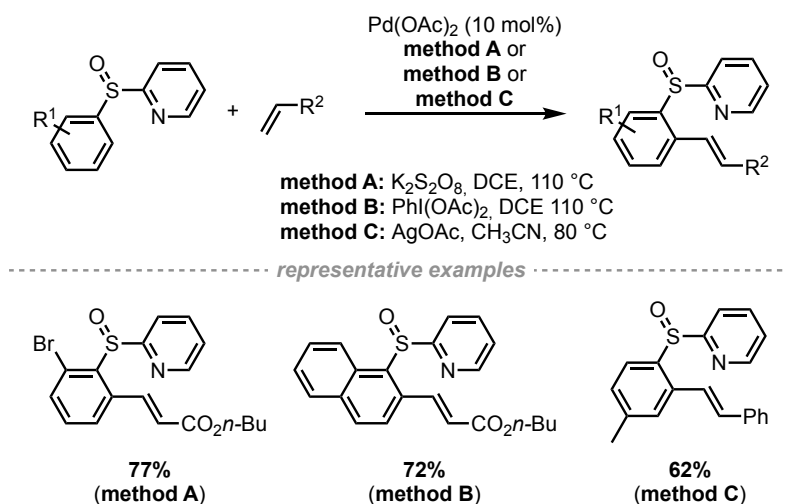
Directed aryl / alkenyl C(sp²)-H / C(sp²)-H couplings came later. These couplings were perceived as conceptual improvements of the previously reported undirected couplings as superstoichiometric amounts of the coupling partner are no more needed. For example, Arrayas and Zhang applied 2-pyridyl sulfoxides as directing groups in Pd-catalyzed oxidative cross-couplings with alkenes, showing excellent compatibility and functional group tolerance (Scheme 37).^[80]

^[77] Kawasumi, K.; Mochida, K.; Kajino, T.; Segawa, Y.; Itami, K. *Org. Lett.* **2012**, *14*, 418–421.

^[78] (a) Moritani, I.; Fujiwara, Y. *Tetrahedron Lett.* **1967**, *8*, 1119–1122; (b) Fujiwara, Y.; Moritani, I.; Danno, S.; Asano, R.; Teranishi, S. *J. Am. Chem. Soc.* **1969**, *91*, 7166–7169; (c) Jia, C.; Lu, W.; Kitamura, T.; Fujiwara, Y. *Org. Lett.* **1999**, *1*, 2097–2100; (d) Jia, C.; W.; Kitamura, T.; Fujiwara, Y. *Acc. Chem. Res.* **2001**, *34*, 633–639. For a review see: (e) Zhou, L.; Lu, W. *Chem. Eur. J.* **2014**, *20*, 634–642.

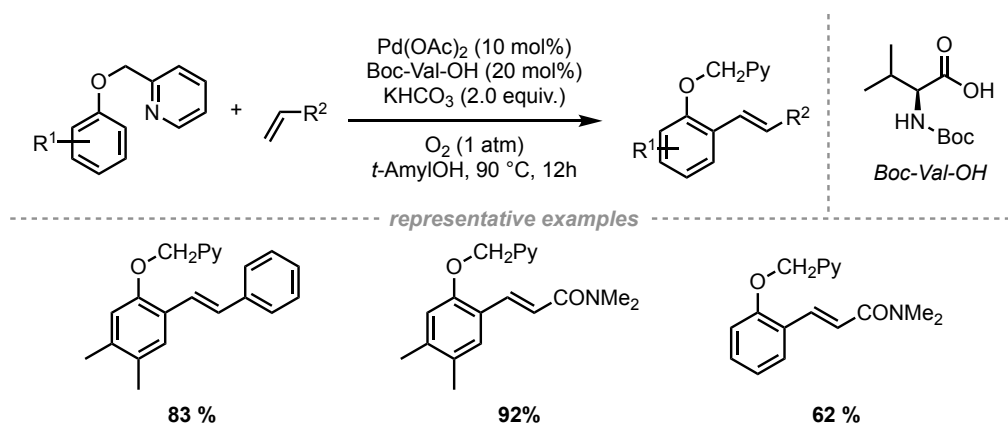
^[79] Kubota, A.; Emmert, M. H.; Sanford, M. S. *Org. Lett.* **2012**, *14*, 1760–1763.

^[80] (a) García-Rubia, A.; Fernández-Ibáñez, M. Á.; Gómez Arrayas, R.; Carretero, J. C. *Chem. Eur. J.* **2011**, *17*, 3567–3570; (b) Yu, M.; Liang, Z.; Wang, Y.; Zhang, Y. *J. Org. Chem.* **2011**, *76*, 4987–4994.



Scheme 37. Pyridyl sulfoxide directed Pd(II)-catalyzed cross-coupling using different oxidants: K₂SO₄ (method A); PhI(OAc)₂ (method B); AgOAc (method C).

You and Lan's use of 2-pyridylmethyl ether directed ortho-alkenylation of arenes, with molecular oxygen as the oxidant, demonstrated the efficiency of Boc-Val-OH in promoting the reaction,^[81] allowing for easy removal of the directing group post-reaction (Scheme 38).^[82]



Scheme 38. Directed palladium-catalyzed C-H activation using Boc-Val-OH as a ligand.

Furthermore, various N-coordinating directing groups, such as imines,^[83] amides,^[84] and amines,^[85] have been developed for diverse aromatic C-H alkenylations.

^[81] Lu, Y.; Wang, D.-H.; Engle, K. M.; Yu, J.-Q. *J. Am. Chem. Soc.* **2010**, *132*, 5916-5921.

^[82] Cong, X.; You, J.; Gao, G.; Lan, J. *Chem. Commun.* **2013**, *49*, 662-664.

^[83] Xu, Z.; Xiang, B.; Sun, P. *Eur. J. Org. Chem.* **2012**, *2012*, 3069-3073.

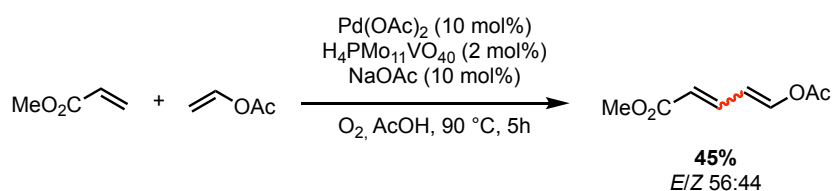
^[84] Liu, Q.; Li, Q.; Ma, Y.; Jia, Y. *Org. Lett.* **2013**, *15*, 4528-4531.

^[85] Pi, C.; Li, Y.; Cui, X.; Zhang, H.; Han, Y.; Wu, Y. *Chem. Sci.* **2013**, *4*, 2675-2679.

3.3. Alkene / alkene C(sp²)-H / C(sp²)-H couplings

Undirected alkene/alkene CDC reactions

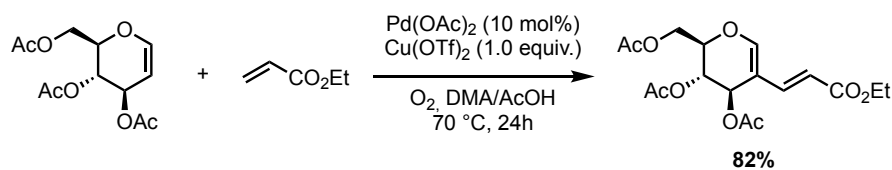
The C(sp²)-H / C(sp²)-H cross-coupling reaction between two different alkenes has been less studied. In 2004, Ishii reported the first example of oxidative cross-coupling between two distinct olefins.^[86] In this ground-breaking study, vinyl acetate – an intrinsically activated alkene – was employed for the coupling with acrylates (Scheme 39).



Scheme 39. First reported cross-coupling between two different olefins.

Palladium(II) acetate was used as the catalyst precursor, and a catalytic amount of H₄PMo₁₁VO₄₀ was introduced as a co-oxidant, with molecular oxygen serving as the terminal oxidant. Sodium acetate was also incorporated to enhance the reaction's efficiency, preventing the deposition of Pd(0) and resulting in the formation of a mixture of *E/Z*-isomers. Following this seminal report, other studies subsequently demonstrated the feasibility of oxidative cross-coupling between different olefins.

In 2011, Liu and colleagues reported the use of peracetylated glucal as a substrate for coupling with acrylates (Scheme 40).^[87]



Scheme 40. Pd-catalyzed coupling between vinyl ether and acrylates via Heck-type alkenylation.

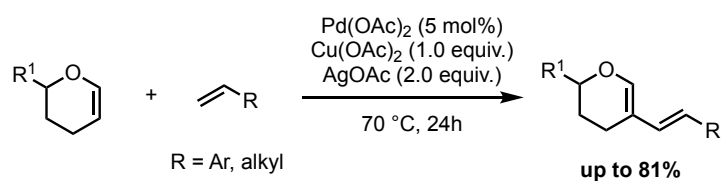
These authors found that palladium(II) acetate was the optimal catalyst, with a stoichiometric amount of copper(II) triflate in combination with molecular oxygen (1 atm) serving as the oxidant. This reaction exhibited selectivity for the β-position of the vinyl ether. It was proposed that the initial step involved

^[86] (a) Hatamoto, Y.; Sakaguchi, S.; Ishii, Y. *Org. Lett.* **2004**, *6*, 4623–4625; (b) For a pioneering work on the oxidative coupling of vinyl acetate with Pd(OAc)₂ to give 1,4-diacetoxy-1,3-butadiene; see: Kohll, C. F.; Van Helden, R. *Rec. Trav. Chim. Pays-Bas* **1967**, *86*, 1930.

^[87] Bai, Y.; Zeng, J.; Cai, S.; Liu, X.-W. *Org. Lett.* **2011**, *13*, 4394–4397.

the interaction between the vinyl ether and the Pd-catalyst, forming a vinyl-palladium intermediate, followed by a Mizoroki-Heck-type alkenylation with acrylate, to yield the final coupling product.

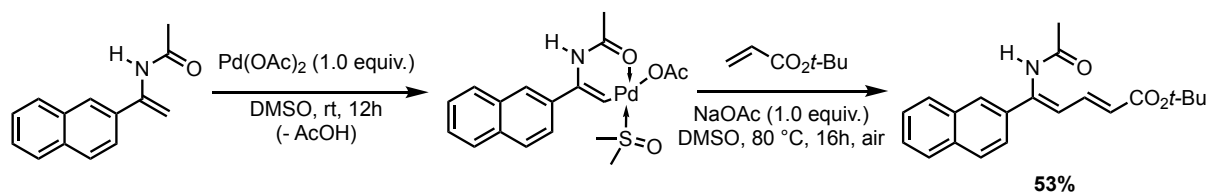
An extension of this work has been reported two years later by Kapur, who employed a combination of copper(II) acetate and silver(I) acetate as oxidants to achieve a Pd-catalyzed oxidative cross-coupling between simple dihydropyrans and unactivated alkenes. This approach allowed for the use of styrene derivatives and aliphatic alkenes as coupling partners in addition to acrylates (Scheme 41).^[88]



Scheme 41. Pd-catalyzed oxidative cross-coupling between dihydropyrans and plain alkenes.

Directed alkene/alkene CDC reactions

In 2011, Loh and co-workers developed an efficient catalytic system for the olefination of enamides.^[89] The authors managed to isolate a palladacycle showing the formation of a C–Pd bond through C–H activation. Its structure, confirmed by ¹H-NMR and X-ray analyses, shows the assistance of the acetamide function in the C–H activation step through coordination of the oxygen with palladium (Scheme 42). Starting from this isolated intermediate, they also demonstrated that by adding *tert*-butylacrylate, the CDC reaction was taking place, which suggests that the palladacycle is a very likely reaction intermediate in the mechanism.

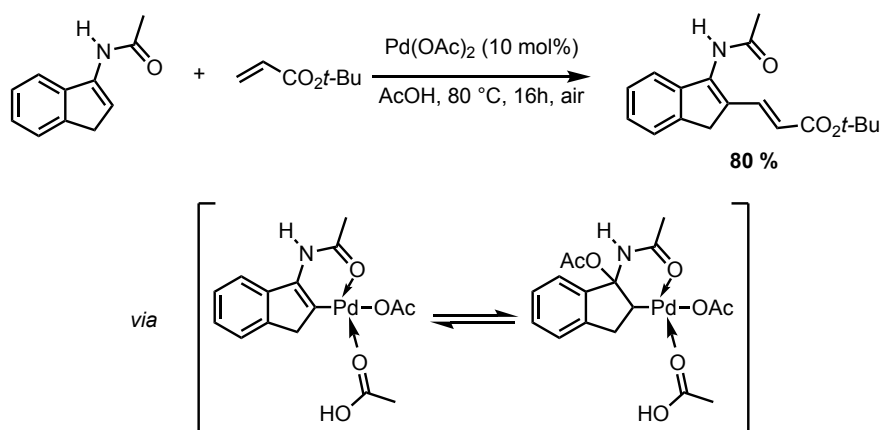


Scheme 42. Evidence of an enamide-directed cyclopalladation and following coupling with an acrylate.

In the same study, the authors demonstrated that the coupling between a trisubstituted enamide and *tert*-butyl acrylate gave the corresponding coupling product in 80% yield using catalytic amounts of palladium(II) acetate with acetic acid as the solvent under air (Scheme 43). In this case, the molecular oxygen of air is expected to oxidize the resulting Pd(0) back into Pd(II).

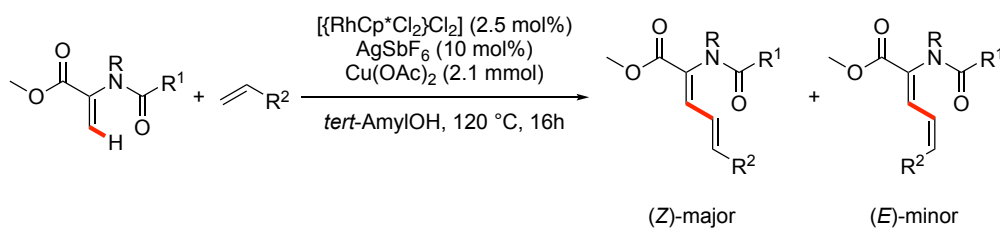
^[88] Pawar, G. G.; Singh, G.; Tiwari, V. K.; Kapur, M. *Adv. Synth. Catal.* **2013**, *355*, 2185–2190.

^[89] Zhu, T.-H.; Zhang, X.-C.; Zhao, K.; Loh, T.-P. *Chem. Sci.* **2011**, *2*, 1822–1825.

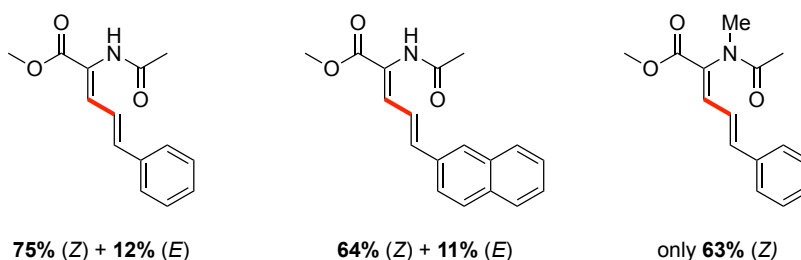


Scheme 43 Directed Pd(II)-catalyzed coupling between an enamide followed and an acrylate ester.

However, most of the reported directed CDCs are based on Rh or Ru catalysts.^[90] In 2011, the Glorius's group focused on the Rh^(III)-catalyzed oxidative olefination of vinylic C-H bonds, presenting a novel approach toward di-unsaturated α -amino acid derivatives and linear 1,3-butadienes.^[91] Acetamidoacrylate, in particular, yielded good results, exhibiting high levels of selectivity in terms of mono-olefination, cross-coupling, and the formation of linear, *Z*-selective products (Scheme 44).



----- representative examples -----



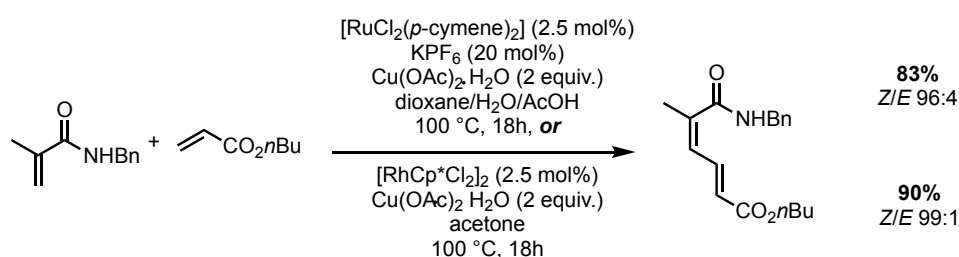
Scheme 44. Directed Rh^(III)-catalyzed C-H oxidative olefination of alkenes.

^[90] For a selection of examples, see for example (a) Hu, X.-H.; Zhang, J.; Yang, X.-F.; Xu, Y.-H.; Loh, T.-P. *J. Am. Chem. Soc.* **2015**, *137*, 3169-3172; (b) Li, F.; Yu, C.; Zhang, J.; Zhong, G. *Org. Biomol. Chem.* **2017**, *15*, 1236-1244; (c) Logeswaran, R.; Jeganmohan, M. *Org. Lett.* **2021**, *23*, 767-771.

^[91] (a) Besset, T.; Kuhl, N.; Patureau, F. W.; Glorius, F. *Chem. Eur. J.* **2011**, *17*, 7167-7171; (b) Bouladakis-Arapinis, M.; Hopkinson, M. N.; Glorius, F. *Org. Lett.* **2014**, *16*, 1630-1633;

Additionally, this process was applied to provide an efficient, atom-economic pathway to synthesize polyfunctionalized $\alpha,\beta,\gamma,\delta$ -unsaturated amino acids, which are crucial building blocks for further complex transformations.

In another study, Loh's group developed a ruthenium- and rhodium-catalyzed directing-group-assisted cross-coupling between acrylamides and a wide range of alkenes possessing various functional groups (Scheme 45).^[92] Thus, an α,β -unsaturated amide could be coupled to *n*-butyl acrylate in the presence of $[\text{RuCl}_2(p\text{-cymene})]_2$ (2.5 mol%) as the catalyst, potassium hexafluorophosphate as an additive and copper(II) acetate as the oxidant in a ternary solvent system (dioxane/water/acetic acid). In these conditions, the corresponding dienic coupling product was obtained in 83% yield and 96:4 *Z/E* selectivity (Scheme 45, top conditions). The same coupling product could be obtained in 90% yield and 99:1 *Z/E* selectivity using $[\text{RhCp}^*\text{Cl}_2]_2$ as the pre-catalyst, copper(II) acetate as the oxidant, in acetone (Scheme 45, bottom conditions). In both cases, the authors propose a mechanism involving an amide-directed cyclometallation.



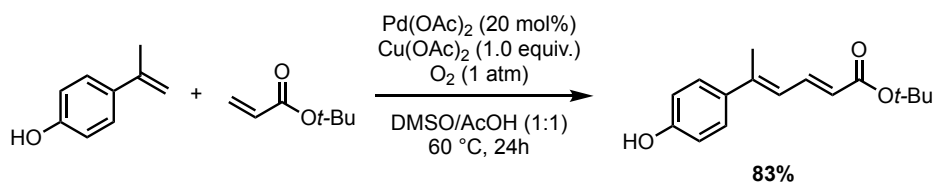
Scheme 45. Ruthenium- and rhodium-catalyzed acrylamide alkenylating coupling with acrylates.

Undirected alkene / alkene couplings between plain aliphatic alkenes and Michael acceptors

The group of Loh developed an efficient Pd(II)-catalyzed $\text{C}(\text{sp}^2)\text{-H} / \text{C}(\text{sp}^2)\text{-H}$ cross-coupling between simple alkenes and acrylates proceeding under mild reaction conditions.^[93] The optimized conditions need palladium(II) acetate as the catalyst, copper(II) acetate and molecular oxygen as the oxidant (to regenerate Pd(II) from the Pd(0) formed during the reaction) in a mixture of DMSO and acetic acid. Under these conditions, the direct coupling reaction between 4-isopropenylphenol and *tert*-butyl acrylate afforded the desired product in 83% yield (Scheme 46).

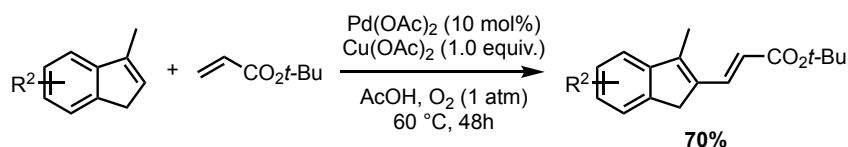
^[92] Zhang, J.; Loh, T.-P. *Chem. Commun.* **2012**, 48, 11232-11234.

^[93] Xu, Y.-H.; Lu, J.; Loh, T.-P. *J. Am. Chem. Soc.*, **2009**, 131, 1372-1373.



Scheme 46. Pd(OAc)₂ catalyzed direct cross-coupling between styrenes and acrylate esters.

This protocol allows the generation of dienoates, which are important building blocks in many natural products.^[94,95] However, the above protocol needed a very high loading of the palladium catalyst (20 mol%) to afford satisfactory yields. Further studies by the same group found that the solvent and the electronic effect of the substituents on the olefin had a very significant influence on the yield in the coupling reaction (Scheme 47).^[96] The best results were obtained with a 10 mol% loading of palladium(II) acetate, 1.0 equiv. of copper(II) acetate under oxygen (1 atm) in acetic acid at 60°C, with a 2:1 ratio of the starting materials (trisubstituted alkene/*tert*-butylacrylate). With these conditions, the desired product was obtained in 70% yield.



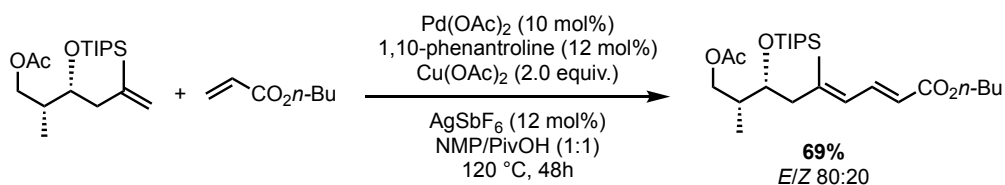
Scheme 47. Pd-catalyzed direct non-directed C–H/C–H cross-coupling with various coupling partners.

In 2012, Loh *et al.* reported a new undirected C(sp²)-H / C(sp²)-H coupling between 1,1-disubstituted aliphatic and electron-poor alkenes for the construction of 1,3-dienes.^[94] The best reaction conditions require palladium(II) acetate (10 mol%), 1,10-phenanthroline (12 mol%) as the ligand, silver(I) hexafluoroantimonate (12 mol%) as an additive and copper(II) acetate (2.0 equiv.) of as oxidant in an equivolumic mixture of N-methylpyrrolidone (NMP) and pivalic acid at 120°C for 24h. These reaction conditions allow to obtain the desired coupling product in 69% yield with an *E/Z* ratio of 80/20 (Scheme 48). The authors also applied their conditions in the total synthesis of the C13-C21 fragment of palmerolide A.

^[94] Wen, Z.-K.; Xu, Y.-H.; Loh, T.-P. *Chem. Eur. J.* **2012**, *18*, 13284-13287.

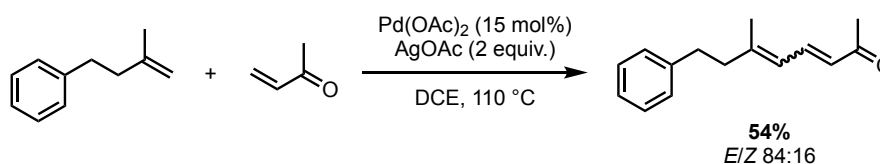
^[95] (a) Hopf, H.; Maas, G. In *The Chemistry of Dienes and Polyenes*; Rappoport, Z., Ed.; Wiley: Chichester, U.K., **1997**; (b) Souris, C.; Frébault, F.; Patel, A.; Audisio, D.; Houk, K. N.; Maulide, N. *Org. Lett.* **2013**, *15*, 3242-4245.

^[96] Xu, Y.-H.; Wang, W.-J.; Wen, Z.-K.; Hartley, J. J.; Loh, T.-P. *Tetrahedron Lett.* **2010**, *51*, 3504-3507.



Scheme 48. Loh's improved Pd-catalyzed direct non-directed C–H/C–H cross-coupling with various coupling partners.

A further protocol for the CDC reaction between aliphatic alkenes and α,β -unsaturated ketones was reported a year later by the same group.^[97] By using palladium(II) acetate (15 mol%) and silver(I) acetate (2.0 equiv.) as the oxidant in 1,2-dichloroethane (DCE), they obtained the conversion of 2-methyl-4-phenylbut-1-ene and methyl vinylketone into the corresponding diene with a moderate yield of 54% and a good diastereoselectivity in favor of the conjugated (*E,E*)-diene (Scheme 49). This protocol was also applied to the synthesis of Vitamin A1 and bornelone starting respectively from β -ionone and camphene.



Scheme 49. $\text{Pd}(\text{OAc})_2$ catalyzed coupling between alkenes and α,β -unsaturated ketones (2013).

Building on the above results, we envisaged to develop a novel $\text{C}(\text{sp}^2)\text{-H} / \text{C}(\text{sp}^2)\text{-H}$ undirected Pd-catalyzed coupling of (+)-limonene.

^[97] Zhang, X.; Wang, M.; Zhang, M.-X.; Xu, Y.-H.; Loh, T.-P. *Org. Lett.* **2013**, *15*, 5531-5533.

Chapter 2: Cross Dehydrogenative alkene / alkene coupling of terpenes.

1. Introduction

Terpenes constitute a large and structurally diverse class of secondary metabolites occurring mainly in plants – particularly in evergreens and conifers – but also in insects, marine microorganism and fungi.^[98] These compounds originate from the assembly of C5 isoprene units in a head-to-tail fashion. Terpenes are categorized into different classes based on their carbon atom count: hemiterpenes (C5), monoterpenes (C10), sesquiterpenes (C15), diterpenes (C20), sesterterpenes (C25), triterpenes (C30), and tetraterpenes (C40). They represent an invaluable biorenewable resource that has the potential to partially replace conventional petroleum-based chemistry for producing essential building blocks.

The biosynthesis of these abundant compounds begins with acetyl-coenzyme A, involving the coupling of C5 2-methylbutane subunits (following the isoprene rule). While terpenes and terpenoids are not as abundant as primary feedstocks like lignin, starch, cellulose, proteins, chitin, or triglycerides, they possess distinctive characteristics. These include an extraordinary structural diversity, including unsaturated hydrocarbons, alcohols, ethers, carbonyls, carboxylic acids, and esters, as well as various functional groups and oxidation states.

The cheapest and most used terpenes are α -pinene, β -pinene, limonene, myrcene, and camphor (Figure 3).

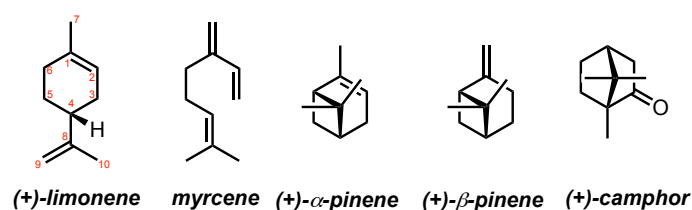


Figure 3. Structures of the most common terpenes.

The first two are extracted from turpentine oil (350000 t/year), a side product of paper pulp industry (coniferous trees) containing mainly α -pinene, β -pinene, camphene, limonene, Δ^3 -carene, and β -myrcene *via* steam distillation of oleoresin, while limonene is extracted from citrus oil (30000 t/year).

^[98] (a) Thurman, M. *Comprehensive Analytical Chemistry*, 2020, Vol. 90, pages 197-233; (b) Breitmaier, E. *Terpenes: Flavors, Fragrances, Pharmaca, Pheromones*, Wiley 2006.

These molecules are at present mainly used for the synthesis of flavors and fragrances. Nevertheless, terpenes lend themselves as a cheap and very differentiated biorenewable platform for their selective upgrading to synthetically valuable synthons or more complex natural products.^[2] For this reason, direct and regioselective C–H activation of terpenes presents a great challenge. In fact, the existing protocols are far from satisfactory from the selectivity, yield, as well as the eco-compatibility viewpoint.

Among the terpenes mentioned above, we decided to focus our attention on (+)-limonene. This aliphatic hydrocarbon is present in about 300 types of plants, and especially in citrus plant. Most importantly, it can be collected in big amounts as a waste product during the harvest. In addition, it is the cheapest terpene, with an average price in 2020 of \$3.5-4.5 per kg. Limonene possesses five allylic C–H bond types (11 C-H bonds in total) and two vinylic C–H bonds (3 C-H bonds in total) (Figure 4).

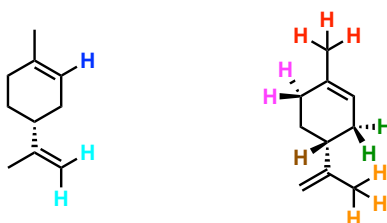
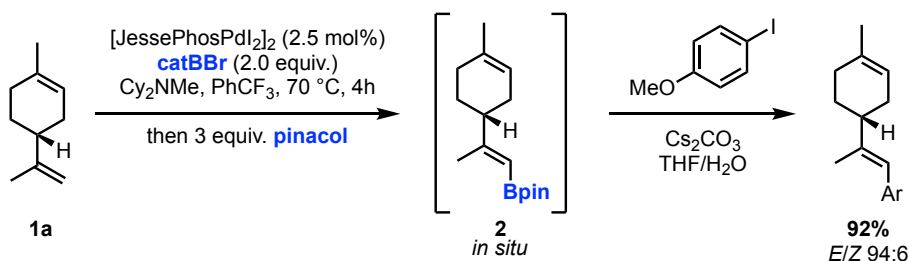


Figure 4. Vinylic C(sp²)-H (left) and allylic C(sp³)-H (right) of limonene.

Our objective is to achieve the coupling of one of the vinylic C–H bond (endocyclic or exocyclic) in order to form a new C–C bond between (+)-limonene and an electron-poor alkene.

To the best of our knowledge, only two examples of vinylic C–H activation of limonene were reported in the literature. The first one, reported by the group of Watson,^[99] consists in the borylation of (+)-limonene **1a** to give the vinylborane **2**, which was then engaged in a Suzuki-Miyaura coupling reaction to form a new C–C bond (Scheme 50). This work was based on prior studies by the same group in related boryl-Heck reactions.^[100]

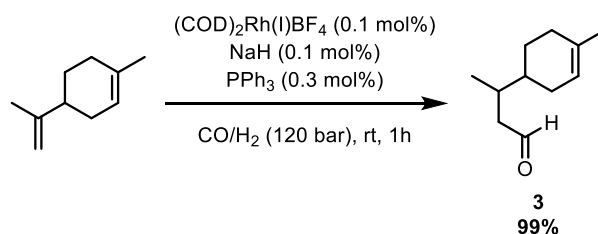


Scheme 50. C–H borylation reaction described by Watson's group.

^[99] Reid, W. B.; Watson, D. A. *Org. Lett.* **2018**, *20*, 6832-6835.

^[100] Reid, W. B.; Spillane, J. J.; Krause, S. B.; Watson, D. A. *J. Am. Chem. Soc.* **2016**, *138*, 5539-5542.

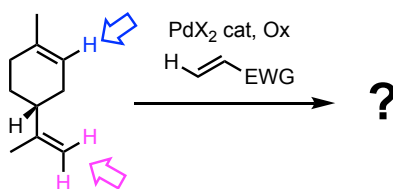
The latter one, pioneered by Kollár^[101] in 1990, and improved first by Gusevskaya in 2012,^[102] then by Rieger in 2020,^[103] consists in Rh-catalyzed hydroformylation of limonene, which afforded the corresponding homologated aldehyde.



Scheme 51. Hydroformylation of limonene as reported by Rieger's group.

As mentioned in Chapter 1, the intermolecular direct C(sp²)-H/C(sp²)-H alkene / alkene coupling represents an ideal atom- and step-economical method to couple two otherwise unactivated C(sp²)-H bonds. As mentioned in the general introduction, this area can be divided into two general sub-categories. The “directed”^[3] and the “undirected”^[4] couplings. In the first type of coupling, a Lewis-base/Lewis-acid interaction between a heteroatom covalently linked to the substrate and a transition metal creates a local concentration effect that enables the selective C-H metalation of the substrate through formation of a metallacycle. In the undirected version, the C-H metalation is due to the intrinsic affinity between the substrate's C-H bond and the transition metal, without the assistance of the aforementioned proximity effect. As terpenes are devoid of heteroatomic functionalities, only the latter, rather challenging, strategy can be devised for limonene.

Accordingly, we decided to explore the non-directed CDC reaction between a C(sp²)-H bond of limonene and electron-poor alkenes (Scheme 52).



Scheme 52. Envisaged strategy for a novel C-H/C-H non-directed Pd-catalyzed coupling of (+)-limonene.

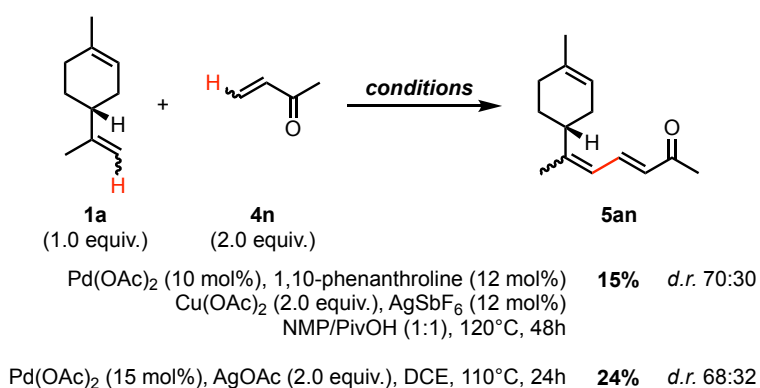
^[101] Kollár, L.; Bakos, J.; Heil, B.; Sándor, P.; Szalontai, G. J. *Organomet. Chem.* **1990**, *385*, 147-152.

^[102] Vieira, C. G.; de Freitas, M. C.; dos Santos, E. N.; Gusevskaya, E. V. *ChemCatChem* **2012**, *4*, 795-801.

^[103] Causero, A.; Troll, C.; Rieger, B. *Ind. Eng. Chem. Res.* **2020**, *59*, 15464-15477.

2. Preliminary studies and optimization of the reaction conditions

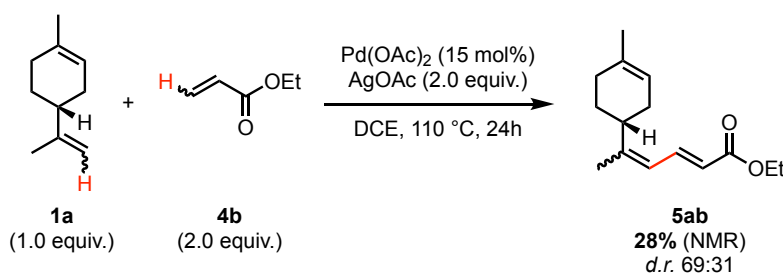
Building on the work of Loh, who recently reported protocols of non-directed C–H/C–H alkene coupling between standard and electron poor alkenes,^[104] we started testing two different conditions for the Pd-catalyzed C–H/C–H undirected coupling between (+)-limonene **1a** and methyl vinyl ketone **4n** (MVK). The first reaction conditions consist in the use of the system [palladium(II) acetate (10 mol%), 1,10-phenanthroline (12 mol%), silver(I) hexafluoroantimonate (12 mol%), copper(II) acetate (2.0 equiv.)], while the second reaction conditions are [palladium(II) acetate (15 mol%), silver(I) acetate]. Gratifyingly, both protocols generated $\alpha,\beta,\gamma,\delta$ -unsaturated ketone **5an** as the sole new product, the result of an alkenylative C9–H_(lim)/C3–H_(MVK) coupling (Scheme 53, equations 1 and 2). Although the conjugated diene was formed in only 15% and 24% spectroscopic (¹H-NMR) yields, the reaction displays a remarkable total selectivity, targeting the C9–H_(lim) while leaving the endocyclic double bond untouched, possibly due to steric hindrance.



Scheme 53. Envisaged strategies for the CDC between limonene and methyl vinyl ketone.

In light of the better yield and more practical reaction conditions, the second protocol was selected for the optimization of the coupling procedure. Furthermore, switch from MVK to ethyl acrylate as the coupling partner was decided (Scheme 54). Indeed, the high toxicity and tendency to polymerize of MVK make this alkene less suitable as a reaction partner for the first optimization study. Accordingly coupling between limonene **1a** and ethyl acrylate **4b** in the presence of the [Pd(OAc)₂/AgOAc]-based catalytic system gave the corresponding alkenylative C9–H_(lim)/C3–H_(acrylate) coupling product **5ab** in 28% ¹H-NMR yield. Again, the coupling was completely regioselective, but not stereoselective, resulting in a 69:31 4E/4Z mixture (see below for the E/Z assignment).

^[104] Wen, Z.-K.; Xu, Y.-H.; Loh, T.-P. *Chem. Eur. J.* **2012**, *18*, 13284-13287.



Scheme 54. Preliminary study of the model coupling.

2.1. Optimization of the reaction conditions

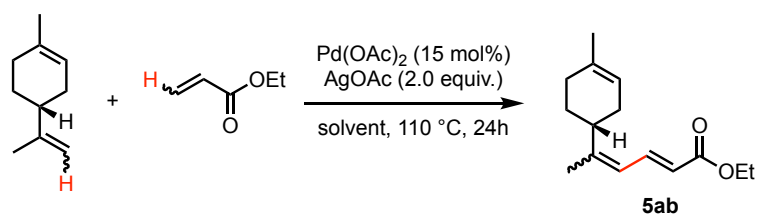
The influence of various parameters (temperature, solvent, palladium source, oxidant and ligand) on the outcome of the reaction was next studied.

2.1.1. Variation of the solvent

The optimization of the reaction conditions was undertaken by varying different parameters. For each experiment, the product yield and the conversion of limonene (the limiting reagent) was determined by quantitative ¹H-NMR spectroscopy, using 1,4-dinitrobenzene as internal standard. A preliminary temperature evaluation revealed that lowering the temperature from 110°C to 80°C significantly affected the yield. Consequently, we decided to maintain a constant temperature of 110°C for all the optimization. Since the reactions were carried out in a closed vial, solvents with bp lower than 110°C could be used. Among ether solvents (1,4-dioxane, THF, diglyme and 2-methyltetrahydrofuran), 1,4-dioxane and THF turned out to be the best compromise in terms of conversion, yield and diastereomeric ratio, the desired product **5ab** being obtained in 37 and 36% yield, respectively (Table 2, entry 2 and 3). However, as 1,4-dioxane is considered a hazardous solvent,^[105] THF was selected as the preferred one for further optimizations. Switch to other polar solvents such as DMSO, acetic acid, HFIP, DMF, or NMP resulted in either low yields or no conversion (Table 2, entry 6-10). Solvent mixtures were tested, too.^[104,106] Unfortunately, when employing a 1:1 v/v mixture of NMP and pivalic acid, no conversion was observed (Table 2, entry 11). Analogously, low yields were observed when using a 1:1 v/v mixture of DMSO and pivalic acid (Table 2, entry 12). The environmentally friendly solvent dimethyl carbonate (DMC) gave a 47% yield of product, prompting its selection alongside THF for subsequent solvent optimization studies (Table 2, entry 13).

^[105] Prat, D.; Hayler, J.; Wells, A. *Green Chem.* **2014**, *16*, 4546-4551.

^[106] Zhang, Y.; Cui, Z.; Li, Z.; Liu, Z.-Q. *Org. Lett.* **2012**, *14*, 1838-1841.



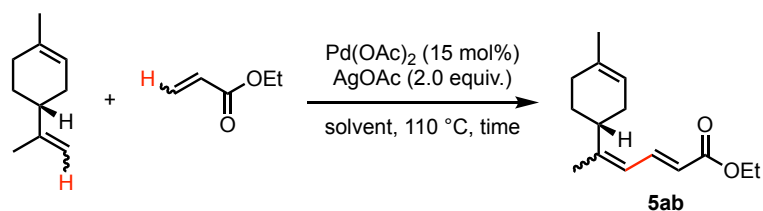
Entry ^[a]	Solvent	5ab (%) ^[b]	Conv.(%) ^[b]	d.r.
1	DCE	28	74	69:31
2	1,4-dioxane	37	65	67:33
3	THF	36	74	68:32
4 ^[c]	Diglyme	-	-	-
5	2-methyl THF	34	71	66:34
6	DMSO	<5	97	50:50
7 ^[c]	AcOH	-	-	-
8	HFIP	<5	91	82:18
9	DMF	12	88	51:49
10	NMP	9	88	66:34
11 ^[c]	NMP/PivOH (1:1)	-	-	-
12	DMSO/PivOH (1:1)	5	89	57:43
13	DMC	47	76	69:31

[a] typical reaction conditions: (+)-limonene **1a** (0.5 mmol), ethyl acrylate **4b** (2.0 equiv.), Pd(OAc)₂ (15 mol%), AgOAc (2.0 equiv.), solvent (0.2 M), 110 °C in a sealed vial; [b] measured by quantitative ¹H-NMR using 1,4-dinitrobenzene as an internal standard; [c] no conversion was observed.

Table 2. Screening of the solvents in the model reaction.

2.1.2. Variation of the reaction time

The influence of the two selected solvents with respect to reaction time was next evaluated (Table 3). After a 24-hour reaction time, dimethylcarbonate (Table 3, entry 1) exhibited superior performance in terms of yield compared to THF (Table 3, entry 3). However, a reversal of this trend occurred after 48 hours (Table 3, entry 4 vs entry 2). Indeed, over an extended time, DMC led to substantial product degradation. Therefore, THF was elected as the solvent of choice, with a 24h reaction time for further optimization studies.



Entry ^[a]	Solvent	Time (h)	5ab (%) ^[b]	Conv. (%) ^[b]	d.r.
1	DMC	24	47	76	69:31
2	DMC	48	39	100	67:33
3	THF	24	36	74	68:32
4	THF	48	48	100	73:27

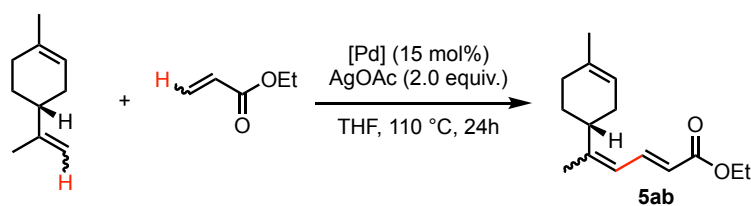
[a] typical reaction conditions: (+)-limonene **1a** (0.5 mmol), ethyl acrylate **4b** (2.0 equiv.), Pd(OAc)₂ (15 mol%), AgOAc (2.0 equiv.), solvent (0.2 M), 110 °C in a sealed vial; [b] measured by quantitative ¹H-NMR using 1,4-dinitrobenzene as an internal standard.

Table 3. Screening of solvents depending on the reaction time.

2.1.3. Variation of the catalyst

Several catalysts (or pre-catalysts) have been examined. With Pd(OAc)₂, the expected product **5ab** was obtained in 36% of yield and a diastereomeric ratio of 68:32 (Table 4, entry 1). Use of the pre-catalyst Pd(PPh₃)₃(OAc)₂ resulted in a lower yield and a lower conversion (Table 4, entry 2). We were aware that a phosphine could be oxidized to the corresponding phosphine oxide in the presence of oxidizing agents such AgOAc. The use of palladium(II) trifluoroacetate [Pd(TFA)₂] instead of Pd(OAc)₂ caused a drop of conversion and yield to 46% and 6%, respectively (Table 4, entry 3). However, palladium(II) pivalate [Pd(Piv)₂] gave similar conversion, yield, and diastereomeric ratio as Pd(OAc)₂ (Table 4, entry 4). Palladium chloride complexes such as bis(acetonitrile)palladium(II) chloride [PdCl₂·(CH₃CN)₂], PEPPSI-IPr and palladium (II) chloride (PdCl₂) resulted in lower yields of product 33%, 10% and 15%, respectively (Table 4, entry 5-7). All the experiments gave a near constant E/Z diastereomeric ratio of the product. In summary, Pd(OAc)₂ and Pd(OPiv)₂ turned out to be the best and almost equally performing catalysts. However, due to reproducibility issues with commercial Pd(OAc)₂, we switched to Pd(OPiv)₂ as the catalyst of choice. Indeed, commercial samples of Pd(OAc)₂ have been reported to contain Pd₃(OAc)₅(NO₂) and polymeric [Pd(OAc)₂]_n as impurities.^[107] Finally, despite much struggling, we were unable to reduce the catalytic loading of the palladium complex without seriously compromising the chemical yield.

^[107] (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.



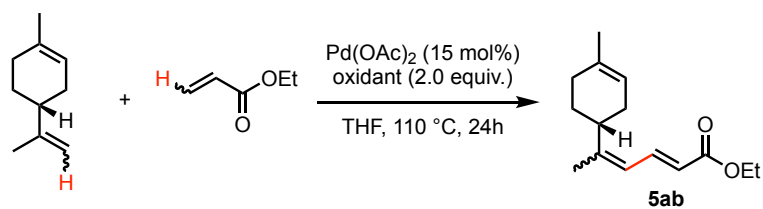
Entry ^[a]	Catalyst	5ab (%) ^[b]	Conv. (%) ^[b]	d.r.
1	Pd(OAc) ₂	36	74	68:32
2	Pd(PPh ₃) ₃ (OAc) ₂	24	37	64:36
3	Pd(TFA) ₂	6	46	<i>n.d.</i> ^[c]
4	Pd(OPiv) ₂	41	76	62:38
5	PdCl ₂ (CH ₃ CN) ₂	33	68	65:35
6	PEPPSI-IPr	10	19	62:38
7	PdCl ₂	15	83	66:34

[a] typical reaction conditions: (+)-limonene **1a** (0.5 mmol), ethyl acrylate **4b** (2.0 equiv.), catalyst (15 mol%), AgOAc (2.0 equiv.), THF (0.2 M), 110 °C (reflux) in a sealed vial; [b] measured by quantitative ¹H-NMR using 1,4-dinitrobenzene as an internal standard.

Table 4. Screening of the catalyst.

2.1.4. Variation of the oxidant

We next investigated the influence of the oxidant, while keeping THF as the solvent and Pd(OPiv)₂ as the catalyst, to find out the most efficient Pd(0)-Pd(II) reoxidation agent for the catalytic cycle (Table 5). The best results were obtained with AgOAc, AgNO₃ and AgCO₃ generating the desired compound **5ab** with 76%, 72% and 69% yield, respectively (Table 5, entries 1-3) while Ag₂O (Table 5, entry 4) led essentially to degradation products. Changing the oxidant to other metal salts such as Cu(OAc)₂ and CuCl₂ (Table 5, entries 5 and 6) led to the formation of only trace amounts of product. Other oxidants such as 1,4-benzoquinone and derivatives (Table 5, entry 7 and 8), (diacetoxyiodo)benzene (PIDA), Oxone[®], H₂O₂, *tert*-butylhydroperoxide, potassium persulfate or Selectfluor[®] led only to degradation being observed (Table 5, entries 9-14). During my secondment at the University of Göttingen, under the supervision of Prof. Lutz Ackermann, I studied the feasibility of an electrochemical variant of coupling that avoided the use of the terminal oxidant. (Table 5, entry 15). Unfortunately, despite numerous attempts, the electrochemical experiments led to intractable mixtures of several oxidation products of limonene and no coupled product. So, AgOAc revealed to be the best oxidant.



Entry ^[a]	Oxidant	5ab (%) ^[b]	Conv. (%) ^[b]	d.r.
1	AgOAc	41	76	62:38
2	AgNO ₃	24	72	64:36
3	AgCO ₃	32	69	71:29
4	Ag ₂ O	– ^[c]	>99	–
5	Cu(OAc) ₂	traces	>99	65:35
6	CuCl ₂	traces	>99	62:38
7	BQ	– ^[c]	>99	–
8	DMBQ	– ^[c]	>99	–
9	PIDA	– ^[c]	>99	–
10	Oxone [®]	– ^[c]	>99	–
11	H ₂ O ₂	– ^[c]	>99	–
12	<i>t</i> -BuOOH	– ^[c]	>99	–
13	K ₂ S ₂ O ₈	– ^[c]	>99	–
14	Selectfluor	– ^[c]	>99	–
15^[e]	EC	– ^[d]	>99	–

[a] typical reaction conditions: (+)-limonene **1a** (0.5 mmol), ethyl acrylate **4b** (2.0 equiv.), Pd(OPiv)₂ (15 mol%), oxidant (2.0 equiv.), THF (0.2 M), 110 °C in a sealed vial; [b] measured by quantitative ¹H-NMR using 1,4-dinitrobenzene as an internal standard; [c] degradation; [d] formation of an isomeric mixture of oxidized byproducts; [e] For more detailed see experimental part.

Table 5. Screening of the terminal oxidants.

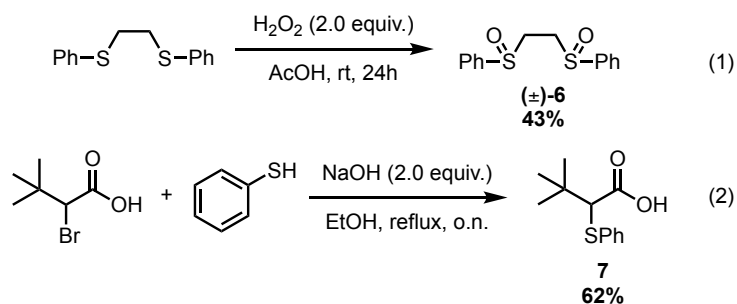
2.1.5. Introduction of a ligand

Since very moderate yields were obtained, we decided to check whether the introduction of a ligand could avoid, or at least moderate, the loss of catalytic activity, and prevent the aggregation of Pd black from the newly generated Pd(0) before its reoxidation.

Most of the ligands shown in this study were commercially available. Furthermore, racemic 1,2-bis(phenylsulfinyl)ethane **6** was prepared according to the protocol described by C. M White^[108] by

^[108] Rice, G. T.; White, M. C. J. *Am. Chem. Soc.* **2009**, *131*, 11707-11711.

treatment of 1,2bis(phenylthio)ethane with hydrogen peroxide in acetic acid (Scheme 55, equation 1).^[109] 3,3-dimethyl-2-(phenylthio)butanoic acid **7** was prepared according to the protocol described by Fernández-Ibáñez,^[110] by reaction between 2-bromo-3,3-dimethylbutanoic acid and sodium benzenethiolate (Scheme 55, equation 2).



Scheme 55. Synthesis of ligands.

The bidentate White sulfoxide ligand (±)-1,2-bis(phenylsulfinyl)ethane **6** (Table 6, entry 2) or the monodentate phenylvinylsulfoxide ligand (Table 6, entry 3) did not give better yields compared to the previously reported ligandless conditions.^[108, 111] Pyridine-type ligands such as 1,10-phenanthroline or 2,2'-bipyridine proved to be much less efficient (Table 6, entry 4 and entry 5).

Remarkably, the Pd/S,O-ligands are known to exhibit great activity and exert a strong influence on site selectivity when compared to the well-established Pd/pyridine-based catalytic system.^[110,112] Unfortunately, in our hands, the use of 3-methyl-2-(phenylthio)butanoic acid **7** did not improve the reaction efficiency (Table 6, entry 6). *N*-protected amino acids are known to favor C–H activation processes via a Concerted Metalation Deprotonation (CMD) mechanism.^[113] However, the use of *N*-acetyl-*L*-leucine (Ac-Leu-OH) and *N*-acetyl-*L*-valine (Ac-Val-OH) did not provide better yields than that the reaction carried out under ligandless conditions (Table 6, entries 7-8). Phosphine ligands were also ineffective (Table 6, entry 9-11).

^[109] The protocol formed some amount of the meso isomer that could be separated and discarded in the isolation phase.

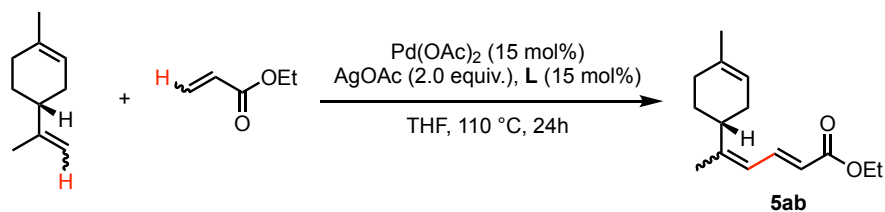
^[110] Naksomboon, K.; Valderas, C.; Gómez-Martínez, M.; Álvarez-Casao, Y.; Fernández-Ibáñez, M. Á. *ACS Catal.* **2017**, *7*, 6342-6346.

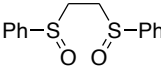
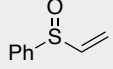
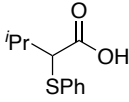
^[111] (a) Chen, M. S.; White, M. C. *J. Am. Chem. Soc.* **2004**, *126*, 1346–1347; (b) Chen, M. S.; Narayanasamy, P.; Labenz, N. A.; White, M. C. *J. Am. Chem. Soc.* **2005**, *127*, 6970–6971.

^[112] For a selection on Pd/S,O-ligand, see: (a) Naksomboon, K.; Álvarez-Casao, Y.; Uiterweerd, M.; Westerveld, N.; Maciá, B.; Fernández-Ibáñez, M. Á. *Tetrahedron Lett.* **2018**, *59*, 379-382; (b) Naksomboon, K.; Poater, J.; Bickelhaupt, F. M.; Fernández-Ibáñez, M. Á. *J. Am. Chem. Soc.* **2019**, *141*, 6719-6725; (c) Lia, W.-L.; Westerveld, N.; Wong, K. M.; Morsch, T.; Hakkennes, M.; Naksomboon, K.; Fernández-Ibáñez, M. Á. *Org. Lett.* **2019**, *21*, 9339-9342.

^[113] 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.; Musaev, 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.

Unfortunately, this modification did not lead to any improvement in yield. In light of the above experiments, we decided to stick to the original ligandless conditions for the rest of the study.



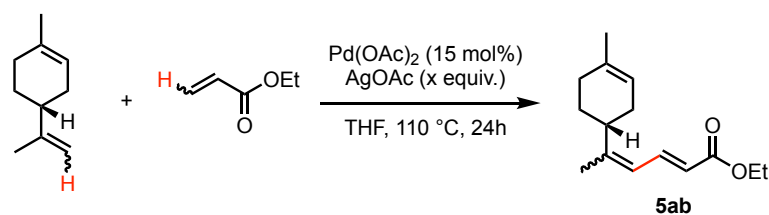
Entry ^[a]	Ligand	5ab (%) ^[b]	Conv. (%) ^[b]	<i>d.r.</i>
1	No ligand	41	76	62:38
2		18	82	67:33
3		21	86	72:28
4	1,10-phenanthroline	traces	>99	_ ^[c]
5	2,2'-bipyridine	traces	>99	_ ^[c]
6		traces	>99	_ ^[c]
7	Ac-Leu-OH	23	>99	62:38
8	Ac-Val-OH	28	>99	73:27
9	BINAP	_ ^[d]	>99	-
10	XantPhos	_ ^[d]	>99	-
11	dppe	_ ^[d]	>99	-

[a] typical reaction conditions: (+)-limonene **1a** (0.5 mmol), ethyl acrylate **4b** (2.0 equiv.), Pd(OPiv)₂ (15 mol%), AgOAc (2.0 equiv.), ligand (15 mol%), THF (0.2 M), 110 °C in a sealed vial; [b] measured by quantitative ¹H-NMR, using 1,4-dinitrobenzene as an internal standard; [c] not determined because of overlapping NMR signals; [d] degradation.

Table 6. Study of the introduction of a ligand.

2.1.6. Amount of the oxidant

The amount of AgOAc was considered next (Table 7, entry 1-4). An increase of the amount of the oxidant increased the yield. Specifically, the use of four equivalents of AgOAc turned out to be the best compromise, affording **5ab** in 85% yield (Table 7, entry 3).



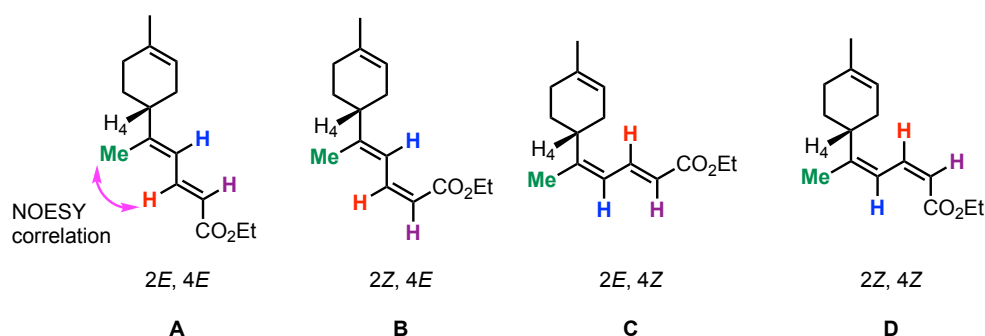
Entry ^[a]	AgOAc (equiv.)	5ab (%) ^[b]	Conv. (%) ^[b]	d.r.
1	2	41	76	62:38
2	3	69	89	64:36
3	4	85	>95	74:26
4	5	85	>95	73:27

[a] typical reaction conditions: (+)-limonene **1a** (0.5 mmol), ethyl acrylate **4b** (2.0 equiv.), Pd(OPiv)₂ (15 mol%), AgOAc (x equiv.), THF (0.2 M), 110 °C in a sealed vial; [b] measured by quantitative ¹H-NMR using 1,4-dinitrobenzene as an internal standard.

Table 7. Influence of the quantity of oxidant on the outcome of the reaction.

2.2. Configurational Assignment

The coupling generates only two out of the four possible geometrical isomers: **A** (2*E*,4*E*), **B** (2*Z*,4*E*), **C** (2*E*,4*Z*), and **D** (2*Z*,4*Z*) (Figure 5). Since, the vicinal coupling constants $J_{(H_{\alpha}/H_{\beta})}$ in the ¹H-NMR spectrum of the two observed isomers is 11.5 Hz, we can rule out isomers **B** and **D**. Furthermore, a NOESY 2D NMR spectrum of an analytically pure sample of the major isomer showed correlation between the methyl group on C8 (limonene numbering) and H_β. This allowed to assign the configuration 2*E*,4*E* to the major isomer **A**, and the 2*E*,4*Z* to the minor isomer **C**.



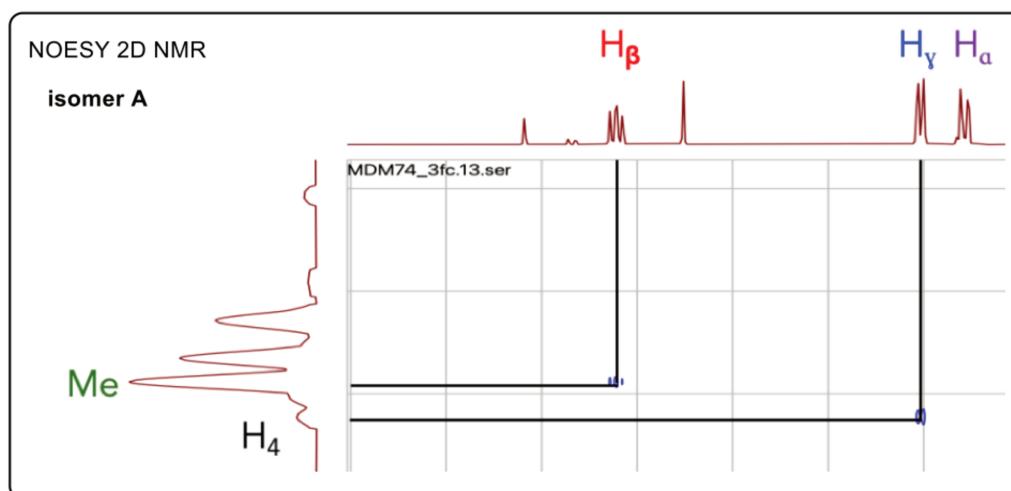
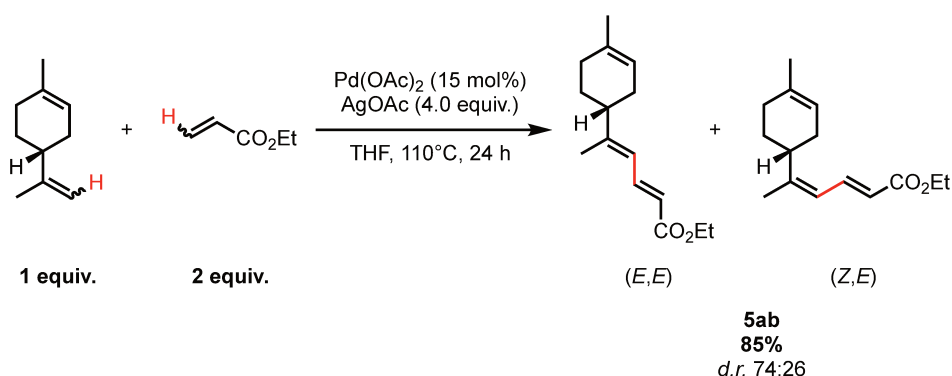


Figure 5. Top: possible geometrical isomers of the coupling reaction. Bottom: selected region of the NOESY 2D NMR spectrum of the major isomer A.

We can thus conclude that the best protocol for the alkenylative coupling implies treatment of limonene with ethyl acrylate (2.0 equiv.) in the presence of Pd(OPiv)₂ (15 mol %) as the catalyst, and AgOAc (4.0 equiv.) as the terminal oxidant in THF (0.2 M) at reflux (110 °C) which affords the cross-coupled product **5ab** as a 74:26 mixture of the geometrical isomers **A** and **C** in a 85% yield (Scheme 56).



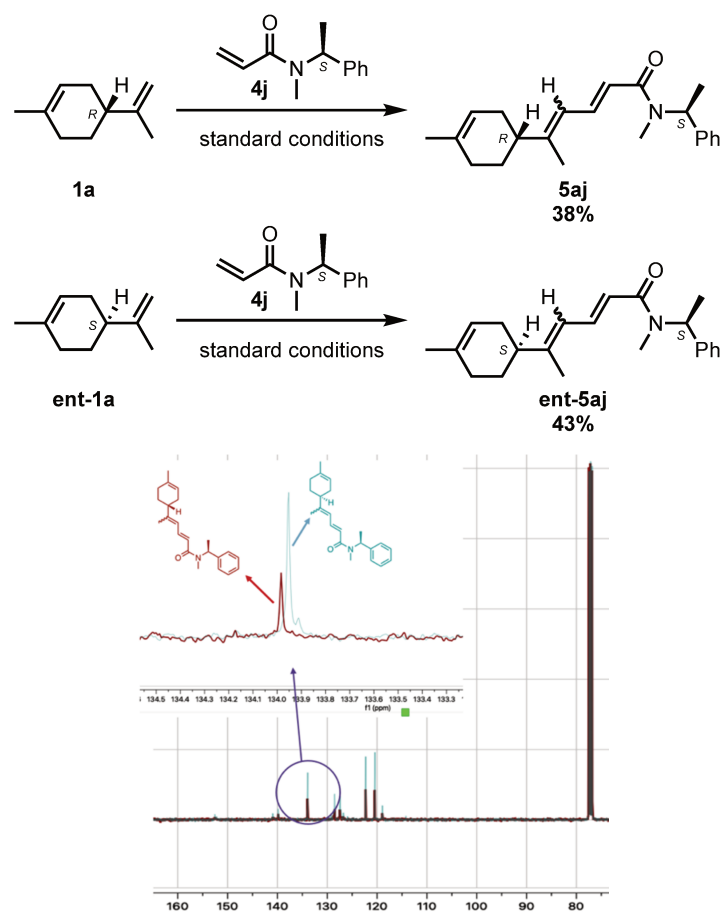
Scheme 56. Dehydrogenative coupling between limonene and ethyl acrylate.

2.3. Racemization/Epimerization studies at the C4 stereocenter

To confirm that the reaction conditions are not affecting (racemizing or epimerizing) the stereogenic allylic center of limonene (C4), we tested and compared the couplings of (*R*)- and (*S*)-limonene with (*S*)-*N*-methyl-*N*-(1-phenylethyl)acrylamide.^[114] We reasoned that in the absence of racemization, each coupling should afford a couple of enantiopure *2E,4E*/*2E,4Z* products **5aj** and **ent-5aj** that are different

^[114] Prepared by acryloylation of (*S*)-*N*-methyl-1-phenylethan-1-amine under standard conditions.

(diastereoisomeric relation) from each other. Contrarily, the four diastereoisomers (as *E/Z* couples) should be produced from each experiment, should the racemization of limonene (or the epimerization of the coupled product) take place (Scheme 57). The two couplings were successful, affording products **5aj** and **ent-5aj** in 38% and 43% yield respectively, and a careful comparison of the ^{13}C NMR spectra of the products (each as *E/Z* mixtures) of the two coupling reactions showed they are not fully superimposable. Hence, we confirmed that this coupling does not affect the stereochemical integrity of the allylic stereocenter of limonene.

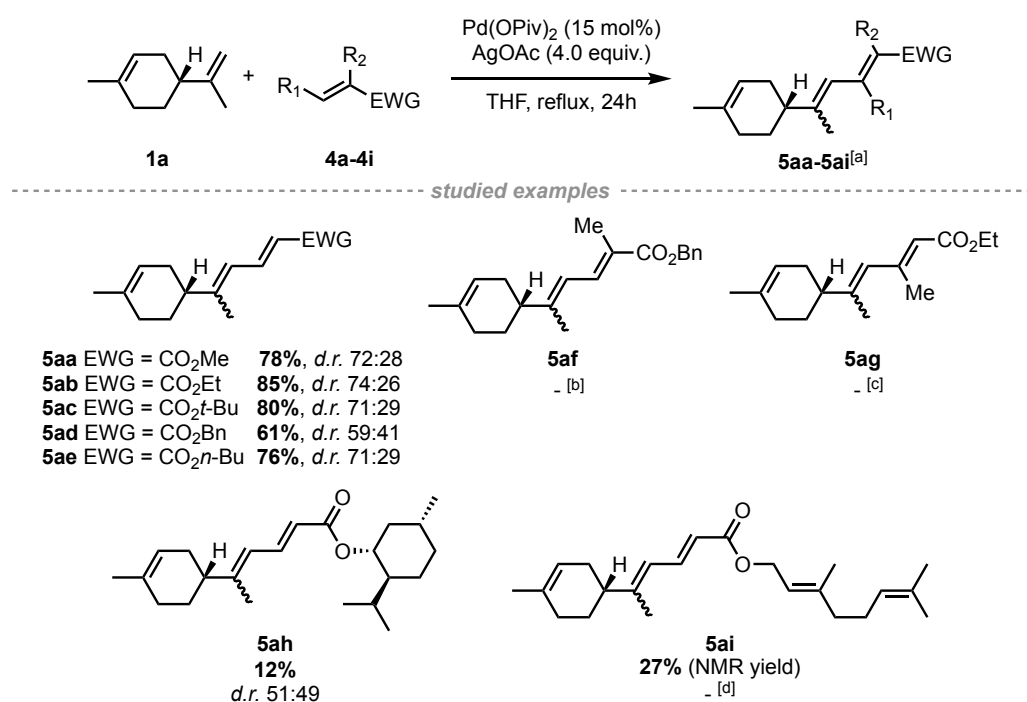


Scheme 57. Top: coupling between (*R*)- or (*S*)-limonene, and (*S*)-*N*-methyl-*N*-(1-phenylethyl)acrylamide. Bottom: comparison of the ^{13}C -NMR spectra of the products **5aj** and **ent-5aj**.

2.4. Study of the scope of the coupling

After having optimized the model reaction between limonene and ethyl acrylate, we passed to evaluate the scope of this dehydrogenative coupling by testing other alkenes as reaction partners for limonene. We first tested the reactivity of (+)-limonene **1a** with different acrylates (Scheme 58). Reacting limonene with methyl, ethyl, *tert*-butyl, benzyl and *n*-butyl acrylates **4a-4e** under the

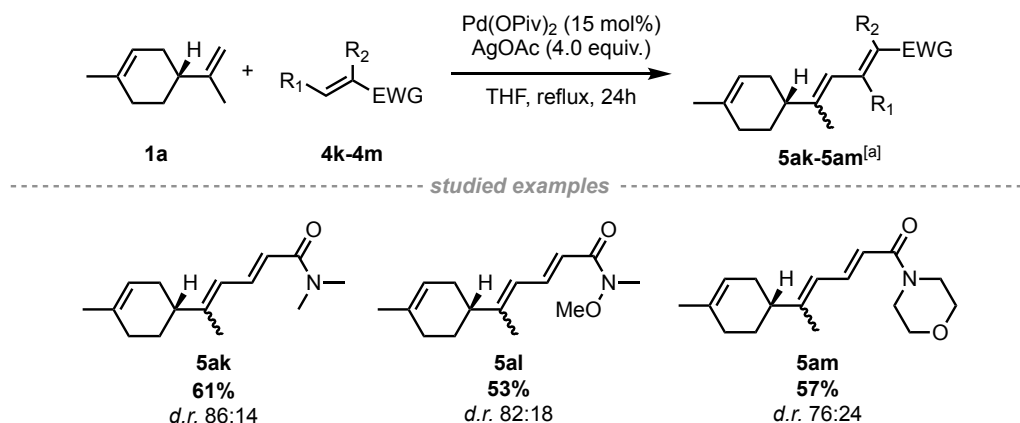
previously optimized reaction conditions gave the expected corresponding dienoates **5aa-5ae** in isolated yields ranging between 61 and 85%. In all cases, except with benzyl acrylate, the reaction was rather diastereoselective forming preferentially the (2*E*,4*E*)-diastereomer with *d.r.* values around 3:1. We then considered the influence of the substitution of the alkene partner. Unfortunately, no conversion was observed with benzyl methacrylate **4f**, while only degradation products were generated with (*E*)-ethyl crotonate **5g**. Thus, the coupling appears to be incompatible with substitutions at the position α as well as β in the electron-poor alkene. More complex acrylate esters such as menthyl acrylate **4h** and geranyl acrylate **4i**, prepared by acryloylation of (-)-menthol and geraniol under standard conditions, proved to be less reactive. In the first case, the desired conjugated diene **5ah** could be isolated with 12% yield (46% NMR yield) and a poor diastereoselectivity. This low yield is due to difficulties during the purification step, because the product is always isolated as a mixture with the excess acrylate. Likewise, diene **5ai** could not be isolated, although we managed to measure a spectroscopic (¹H-NMR) yield of 27%.



[a] reaction conditions: (+)-limonene **1a** (0.5 mmol), acrylate **4a-4i** (2.0 equiv.), Pd(OPiv)₂ (15 mol%), AgOAc (4.0 equiv.), THF (0.2 M), 110°C (reflux); [b] no conversion; [c] only degradation products were observed; [d] yield measured by quantitative NMR using 1,4-dinitrobenzene as internal standard, since no product could be isolated, no *d.r.* was determined.

Scheme 58. Evaluation of acrylates as coupling partners for the Pd-catalyzed CDC reaction of (+)-limonene.

We then tested acrylamides as coupling partners. *N,N*-dimethyl-, *N*-methoxy-*N*-methyl^[115] and morpholine acrylamides **4ak**, **4al** and **4am** were engaged in the optimized reaction conditions affording the desired conjugated dienoates **5ak**, **5al** and **5am** in moderate yields of 61%, 53% and 57% respectively (Scheme 59). These coupling partners appear to be somewhat less efficient but more stereoselective than acrylates. We only considered tertiary acrylamides, as primary^[116] and secondary acrylamides are expected to be incompatible with this undirected coupling.¹¹⁷



[a] reaction conditions: (+)-limonene **1a** (0.5 mmol), acrylamide **4k-4m** (2.0 equiv.), Pd(OPiv)₂ (15 mol%), AgOAc (4.0 equiv.), THF (0.2 M), 110°C (reflux).

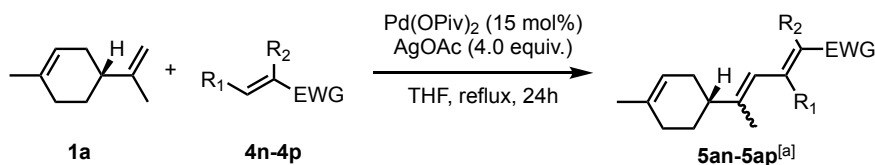
Scheme 59. Evaluation of acrylamides as coupling partners for the Pd-catalyzed CDC reaction with (+)-limonene.

The use of α,β -unsaturated ketones was also investigated (Scheme 60). Methyl vinyl ketone **4n** provided the corresponding conjugated diene **5an** with a low yield of 21%. This yield can be explained by the volatility of the product making it hard to isolate. Ethyl vinyl ketone **4o** was also tested, and the corresponding product **5ao** could be isolated with 54% yield and a diastereomeric ratio of 81:19. On the other hand, cyclohexanone **4p** gave no conversion, which confirmed the incompatibility of β -substituted coupling partners already seen above with acrylates.

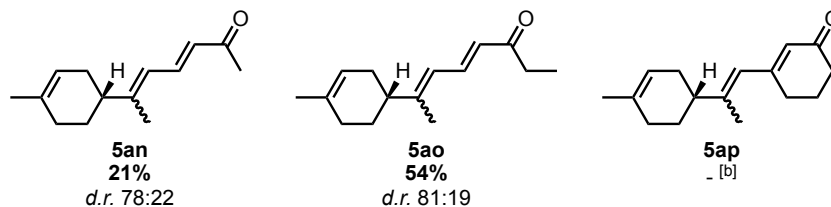
^[115] Prepared by acryloylation of Weinreb amine under standard conditions.

^[116] Xu, Y.-H.; Wang, W.-J.; Wen, Z.-K.; Hartley, J. J.; Loh, T.-P. *Tetrahedron Lett.* **2010**, *51*, 3504-3507.

^[117] This part of project was accomplished in collaboration with Master student Anna Gagliardi.



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

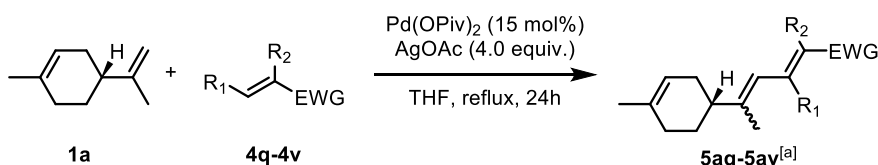


[a] reaction conditions: (+)-limonene **1a** (0.5 mmol), α,β -unsaturated ketone **4n-4p** (2.0 equiv.), Pd(OPiv)₂ (15 mol%), AgOAc (4.0 equiv.), THF (0.2 M), 110°C (reflux); [b] no conversion.

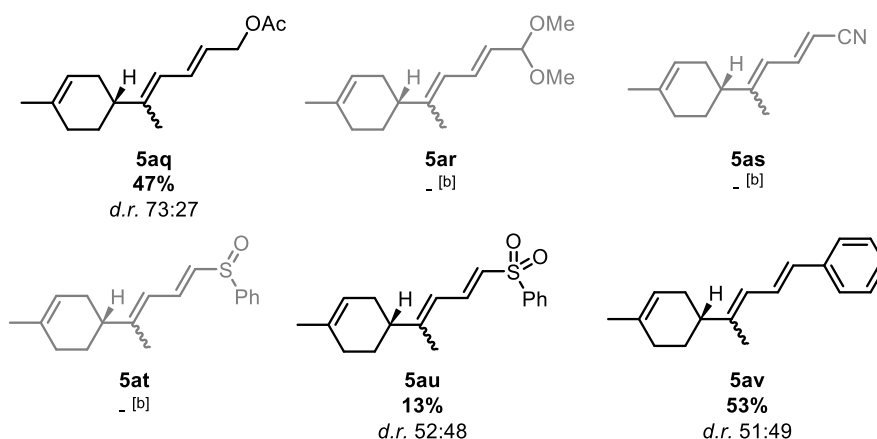
Scheme 60. Evaluation of α,β -unsaturated ketones as coupling partners in the CDC reaction with (+)-limonene.

Surprisingly, acrylonitrile **4s** and 3,3-dimethoxyprop-1-ene **4r** did not lead to the formation of any products. Phenyl vinyl sulfone **4u** provided diene **5au** with a low 13% yield and a poor diastereoselectivity, while phenyl vinyl sulfoxide **4t** was totally unreactive.

Interestingly, allylacetate **4q** gave diene **5aq** in a moderate 47% isolated yield and a fairly good diastereomeric ratio. More electron-rich styrene **4v** was also reactive and provided the desired diene **5av** with a moderate 53% yield and no diastereoselectivity.



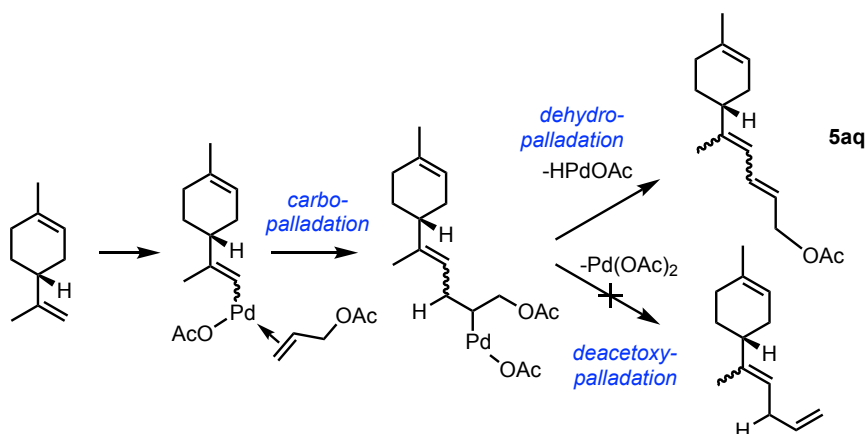
----- studied examples -----



[a] reaction conditions: (+)-limonene **1a** (0.5 mmol), electron-poor alkene **4q-4v** (2.0 equiv.), Pd(OPiv)₂ (15 mol%), AgOAc (4.0 equiv.), THF (0.2 M), 110°C (reflux); [b] no conversion.

Scheme 61. Evaluation of other electron-poor alkenes as coupling partners in the CDC reaction with (+)-limonene.

This last result is interesting from the mechanistic viewpoint, as it shows that the intermediate after the carbopalladation favors dehydropalladation over a potential deacetoxy-palladation.^[118] It is also interesting from a synthetic viewpoint, as the protocol allows the C3 elongation of a terminal alkene with an acetoxymethylene unit generating an allyl acetate (Scheme 62).



Scheme 62. Mechanistic implication in the coupling between limonene and allyl acetate.

To sum up, the reaction conditions appear to be compatible with a number of electron-poor alkene substrates, including acrylates, acrylamides and carbonyl derivatives, provided that the alkene moiety is unsubstituted.

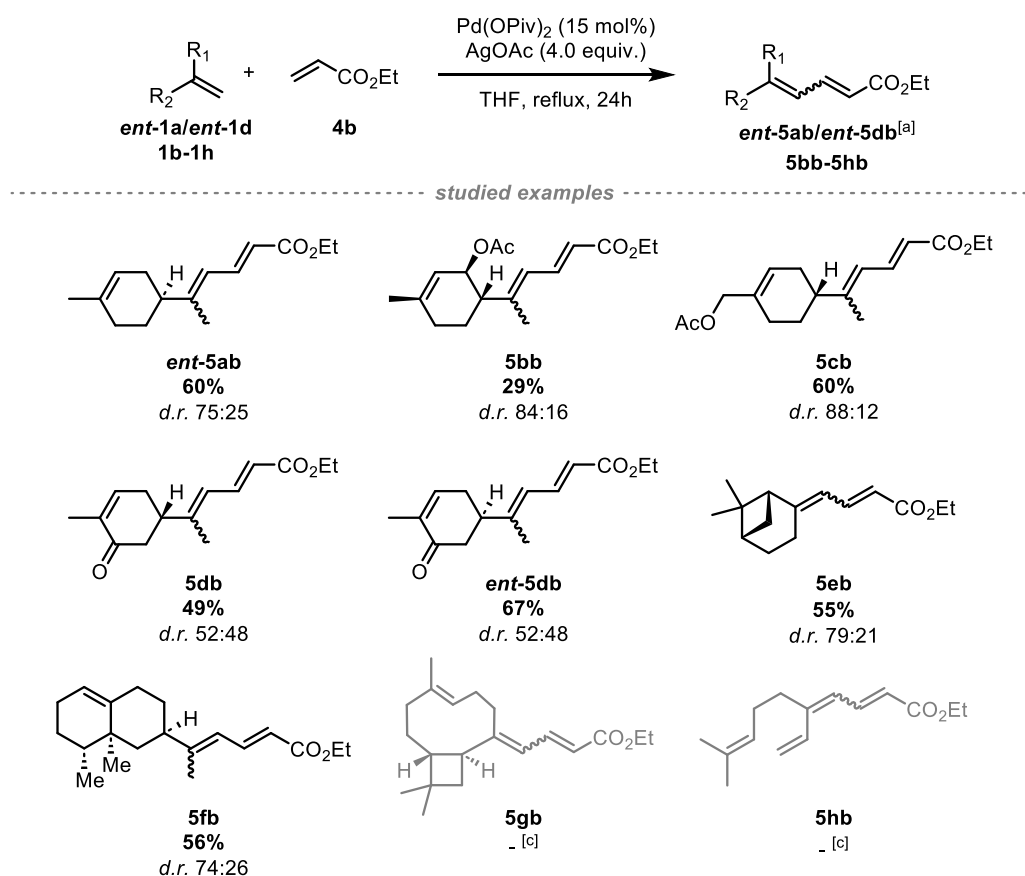
Lastly, keeping ethyl acrylate as the secondary coupling partner, we evaluated the optimized reaction conditions with several terpenes and terpenoids substrates carrying a 1,1-disubstituted terminal alkene (Scheme 63). Accordingly, and as expected, (-)-limonene **ent-1a** led to the corresponding dienoate **ent-5ab** in 60% and 3:1 E/Z ratio.^[119] Acetyl isopulegol **1b** and perillyl acetate **1c**,^[120] could be transformed into the corresponding ethyl sorbates **5bb** and **5bc** in 29% and 60% yield and E/Z ratios \geq 4:1. (+)- and (-)-Carvone **1d** and **ent-1d** also provided the expected coupling products **5db** and **ent-5db** as roughly equimolar E/Z mixtures in 49% and 67% yield. Other structurally different terpenes such as β -pinene **1e** and valencene **1f** could also be successfully converted into their corresponding conjugated E/Z mixtures of dienoates **5eb** and **5fb** in 55% and 56% yield. Caryophyllene **1g** gave only degradation products, and the linear myrcene **1h** gave no conversion. The failure of β -caryophyllene to undergo the coupling might be due to steric hindrance close to the 1,1-disubstituted alkene, while

^[118] (a) Zhao, H.; Ariafard, A.; Lin, Z. *Organometallics* **2006**, *25*, 812-819; (b) Ferber, B.; Prestat, G.; Vogel, S.; Madec, D.; Poli, G. *Synlett* **2006**, *13*, 2133-2135; (c) Bogdos, M. K.; Stepanović, O.; Bismuto, A.; Luraschi, M. G.; Morandi, B. *Nat. Chem.* **2022**, *1*, 787-793.

^[119] The reduced chemical yield with respect to the coupling of (+)-limonene is likely due to purification problems.

^[120] (-)-isopulegol **1b** and (-)-perillyl alcohol **1c** prepared by acetoxylation under standard conditions.

that of myrcene to the presence of multiple double bonds, which might coordinate to Pd(II) and form a catalytically inactive complex.



[a] reaction conditions: terpene **ent-1a/ent-1d**, **1b-1h** (0.5 mmol), ethyl acrylate **4b** (2.0 equiv.), Pd(OPiv)₂ (15 mol%), AgOAc (4.0 equiv.), THF (0.2 M), 110°C (reflux); [b] the configuration of the major diastereomer was not attributed; [c] only degradation products were observed; [d] no conversion.

Scheme 63. Screening of terpenes and terpenoids.

Overall, we can affirm that, in addition to limonene, the coupling protocol is compatible with other types of terpenes containing a 1,1-disubstituted alkene scaffold. Particularly with β -pinene, valencene and carvone the reaction works quite well, even though the yields are not as good as with limonene. Terpenoids such as acetyl isopulegol and perillyl acetate were also reactive.

2.5. Mechanistic studies

2.5.1. Stoichiometric studies

According to our results, only silver-based oxidants were efficient to reoxidize the Pd(0) species formed during the course of the reaction, and a fairly high amount of the silver salt is needed to increase the chemical yield.

Several Pd-catalyzed coupling reactions need the presence of Ag(I) salts, whose role may be manifold.^[121] Indeed, Ag(I) salts: a) are halogenophilic, and abstract halides from palladium(II) complexes by formation of the corresponding insoluble silver halides;^[122] b) are one-electron oxidizing agents that regenerate the transition metal catalyst back to its native oxidation state;^[123] c) can form heterodimeric Pd/Ag complexes species that are catalytically active in CMD processes;^[124] d) can promote arene C–H bond activation, generating an organosilver derivatives, which can in turn undergo transmetallation with an organopalladium(II) intermediate;^[125] e) enable CO₂ release from carboxylic acids, generating the corresponding organosilver intermediate (C–C activation), which can undergo subsequent transmetallation with an organopalladium(II) intermediate (Scheme 64).^[126]

^[121] (a) de Carvalho, R. L.; Diogo, E. B. T.; Homölle, S. L.; Dana, S.; da Silva Júnior, E. N.; Ackermann, L. *Chem. Soc. Rev.* **2023**, *52*, 6359-6378; (b) Pérez-Ortega, I.; Albéniz, A. C. *Dalton Trans.*, **2023**, *52*, 1425-1432; (c) Anand, M.; Sunoj, R. B.; Schaefer, III H. F. *J. Am. Chem. Soc.* **2014**, *136*, 5535-5538; (d) Bhaskararao, B.; Singh, S.; Anand, M.; Verma, P.; Prakash, P.; Athira, C.; Malakar, S.; Schaefer, III H. F.; Sunoj, R. B. *Chem. Sci.*, **2020**, *11*, 208-216; (e) Funes-Ardoiz, I.; Maseras, F. *ACS Catal.* **2018**, *8*, 1161-1172; (f) T. Bhattacharya, S. Dutta, D. Maiti, *ACS Catal.* **2021**, *11*, 9702-9714; (g) Masui, K.; Ikegami, H.; Mori, A. *J. Am. Chem. Soc.* **2004**, *126*, 5074-5075.

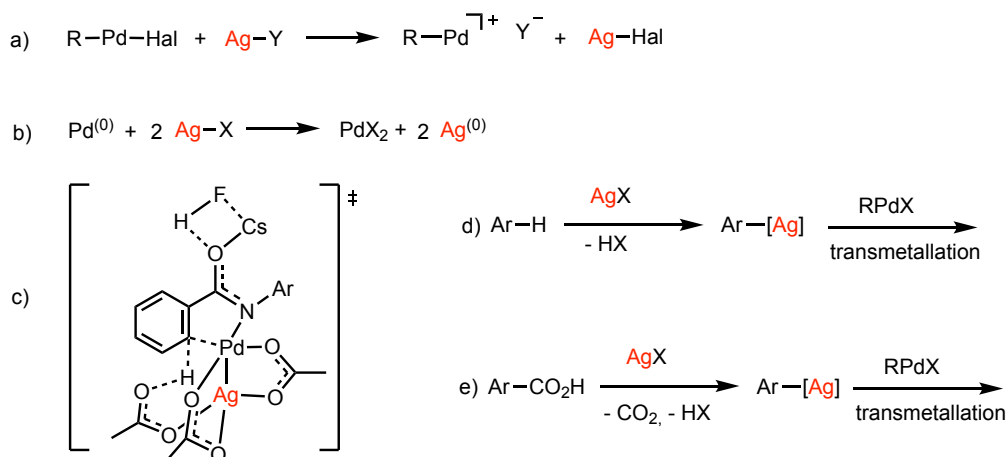
^[122] The solubility product constant of AgI is 8.3×10^{-17} .

^[123] Sivaguru P.; Bi X. *Introduction to Silver Chemistry. In Silver Catalysis in Organic Synthesis*, 1st ed.; Li C. J., Bi X., Eds.; John Wiley & Sons, **2019**; pp 1–32.

^[124] (a) Bay, K. L.; Yang, Y.-F.; Houk, K. N.; *J. Organomet. Catal.*, **2018**, *864*, 19-25; (b) Yang, Y.-F.; Cheng, G.-J.; Liu, P.; Leow, D.; Sun, T.-Y.; Chen, P.; Zhang, X.; Yu, J.-Q.; Wu, Y.-D.; Houk, K. N. *J. Am. Chem. Soc.* **2014**, *136*, 344-355.

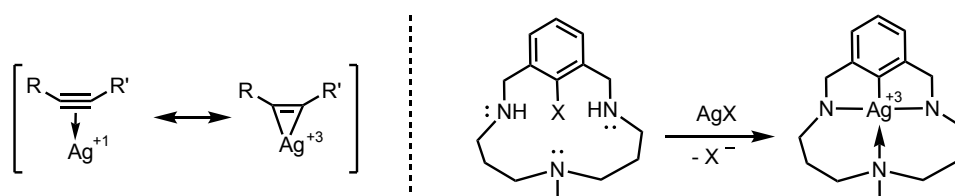
^[125] (a) Lee, S. Y.; Hartwig, J. F. *J. Am. Chem. Soc.* **2016**, *138*, 15278-15284; (b) Colletto, C.; Islam, S.; Julia-Hernandez, F.; Larrosa, I. *J. Am. Chem. Soc.* **2016**, *138*, 1677-1683; (c) Colletto, C.; Panigrahi, A.; Fernández-Casado, J.; Larrosa, I. *J. Am. Chem. Soc.* **2018**, *140*, 9638-9643.

^[126] (a) Gooßen, L. J.; Deng, G.; Levy, L. M. *Science* **2006**, *313*, 662-664; (b) Gooßen, L. J.; Rodríguez, N.; Gooßen, K. *Angew. Chem. Int. Ed.* **2008**, *47*, 3100-3120; (c) Becht, J. M.; Catala, C.; Le Drian, C.; Wagner, A. *Org. Lett.* **2007**, *9*, 1781-1783.



Scheme 64. Possible roles of Ag(I) salts in Pd-catalyzed couplings.

Furthermore, due to the availability of vacant f orbitals on silver, and to the relativistic effects,^[127] silver salts show moderate carbophilic π -Lewis acid character forming π -complexes with unsaturated substrates such as alkenes, allenes and alkynes.^[128] This three-center bonding is due to three different factors: electrostatic (ion-dipole) interactions, electron donation from occupied alkene π -orbitals to empty s-orbitals of the transition metal, and back-donation from filled metal d-orbitals to the unoccupied π^* -orbital of the alkene or alkyne. Finally, Ag(I) salts can undergo oxidative additions by aryl halides possessing a specific environment.^[129]



Scheme 65. Possible roles of Ag(I) salts in catalysis not directly connected to Pd-chemistry.

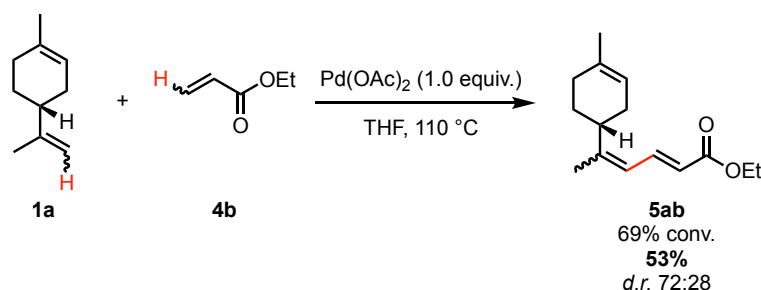
Therefore, in order to get a clue about the role of the Ag(I) salt, we decided to carry out the model coupling reaction in the presence of a stoichiometric amount of the Pd(II) salt and in the absence of the Ag(I) salt. Accordingly, performing the model reaction in the presence of 1.0 equiv. of Pd(OAc)₂,

^[127] Due to the large positive charge of the nucleus, the electrons in especially the 1s-orbitals obtain very large kinetic energies. As a result, the effective mass of the 1s electrons in Ag is ca. 1.08 times the rest mass of the electron. Hence, the 1s-orbitals contract, which results in increased shielding. Other core orbitals (specifically s-type) will also contract, while in contrast, d- and f-type orbitals will expand in space, and rise in energy. For example, the relativistic contribution to the bonding of Ag(I) and ethene has been computed to amount to ca. 10 kcal/mol. See: Kaneti, J.; de Smet, L. C. P. M.; Boom, R.; Zuilhof, H.; Sudhölter, E. J. R., *J. Phys. Chem. A* **2002**, *106*, 11197; see also: Fürstner, A.; Davies, P. W. *Angew. Chem. Int. Ed.* **2007**, *46*, 3410.

^[128] (a) Munoz, M.P. *Chem. Soc. Rev.* **2014**, *43*, 3164-3183; (b) Naodovic, M.; Yamamoto, H. *Chem. Rev.* **2008**, *108*, 3132-3148.

^[129] Font, M.; Acuña-Parés, F.; Parella, T.; Serra, J.; Luis, J. M.; Lloret-Fillol, J.; Costas, M.; Ribas, X. *Nat. Commun.* **2014**, *5*, 4373-4383.

and omitting AgOAc, afforded the expected coupled product in 53% yield (Scheme 66), yet leaving some unreacted limonene. This result suggests that in this coupling the silver salt is likely to merely behave as a H₂ acceptor, and that in the catalytic experiment Pd⁰ aggregation to give catalytically inactive Pd black may compete with the reoxidation step. However, it is possible that an important amount of the metal remains incorporated as an unproductive organometallic complex.



Scheme 66. Stoichiometric tests to elucidate the reaction mechanism.

2.5.2. DFT Studies

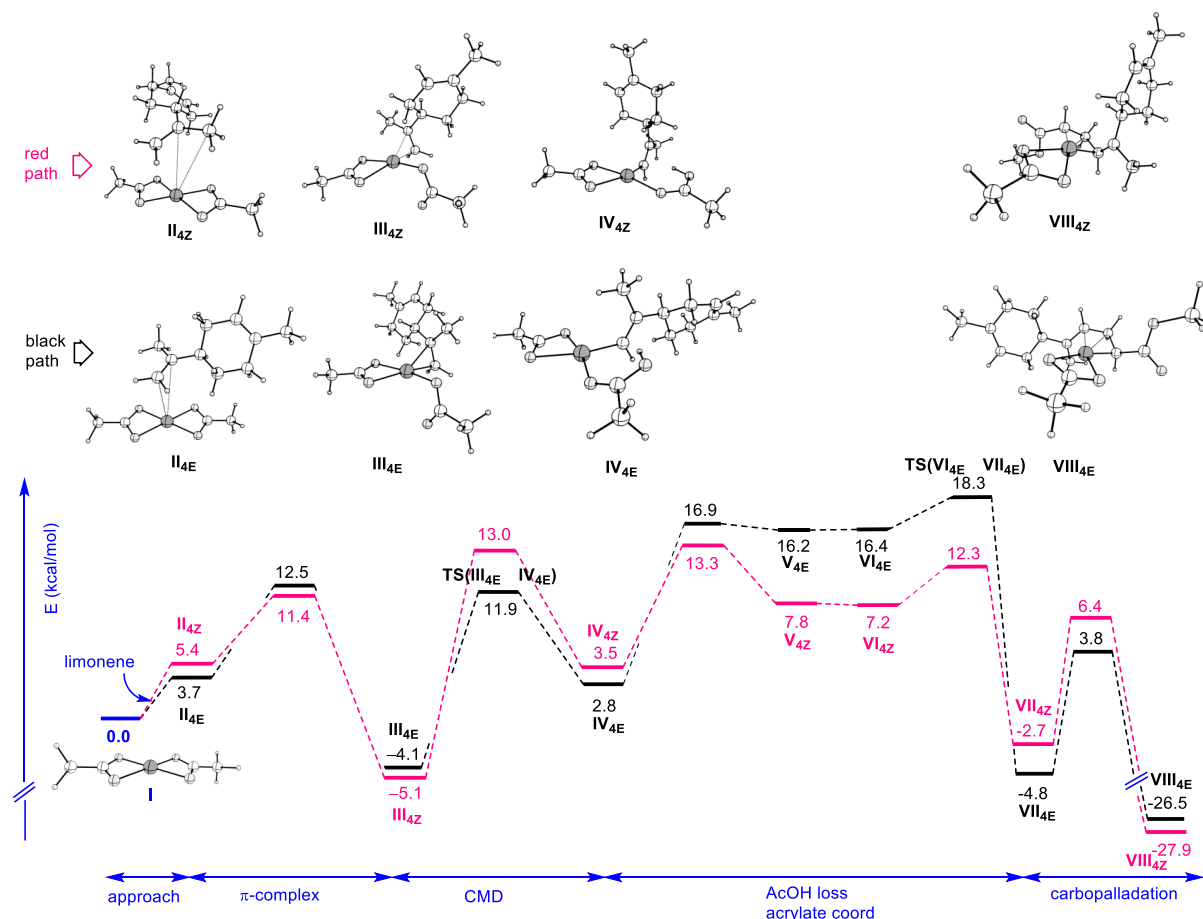
The mechanism of this transformation was studied via DFT calculations made through a collaboration with Prof. Luis F. Veiros, from the University of Lisbon.^[130]

As four geometrical isomers can in principle be generated, two of which are experimentally observed, we computationally studied all the four pathways. The monomeric complex [Pd(II)(bis- κ^2 (OAc)₂] **I** was considered as the starting active catalyst ($\Delta G = 0$ kcal/mol as reference). The first step of the mechanism consists in the formation of an aggregate between [Pd(II)(bis- κ^2 (OAc)₂] and the exocyclic alkene of limonene. This thermodynamically unfavorable step already defines the geometry of the trisubstituted alkene in the final product because the two located complexes **II**_{4E} (3.7 kcal/mol) and **II**_{4Z} (5.4 kcal/mol) lie in the path leading to the 4E and the 4Z trisubstituted alkenes, respectively. For the black path (Scheme 67), following full π coordination of the exocyclic alkene of limonene to palladium generates intermediate **III**_{4E} ($\Delta G = -4.1$ kcal/mol), passing an energetic barrier of 8.8 kcal/mol. In this step, one acetate ligand passes from κ^2 to σ -coordination, to allow the π coordination by the alkene. The next step is a concerted metalation deprotonation (CMD), wherein the σ -bound acetate ligand intramolecularly deprotonates the H atom on the exocyclic alkene located *trans* to the cyclic scaffold of limonene. The step is endergonic, passing an energetic barrier of 16 kcal/mol, and generating the σ -vinylpalladium complex **IV**_{4E} (2.8 kcal/mol), still coordinated by the newly generated

^[130] All calculations were performed at the PBE0-D3/(SDD*,6-311++G(d,p)//PBE0/(SDD*,6-31G(d,p)), level using the GAUSSIAN 09 package. Solvent effects (THF) were considered using the PCM/SMD model.

acetic acid molecule. It is worthy to note the agostic interaction (Pd-H 229 pm) in the corresponding transition state $\text{TS}(\text{III}_{4\text{E}} \rightarrow \text{IV}_{4\text{E}})$, which assists the deprotonation. The step is stereoretentive, because the palladium atom replaces the position of the deprotonated vinylic H atom. Follows a dissociative (two-step) globally thermodynamically favored ligand exchange between the exiting acetic acid and the entering acrylate, which generates complex $\text{VII}_{4\text{E}}$ (-4.8 kcal/mol). The transition state for acrylate coordination $\text{TS}(\text{VI}_{4\text{E}} \rightarrow \text{VII}_{4\text{E}})$ is the turnover frequency (TOF) determining transition state of the cycle (18.3 kcal/mol). The subsequent carbopalladation of the resulting intermediate $\text{VII}_{4\text{E}}$ is quite exergonic, generating complex $\text{VIII}_{4\text{E}}$ (-26.5 kcal/mol), resting state of the catalytic cycle, *via* a barrier of 8.6 kcal/mol.

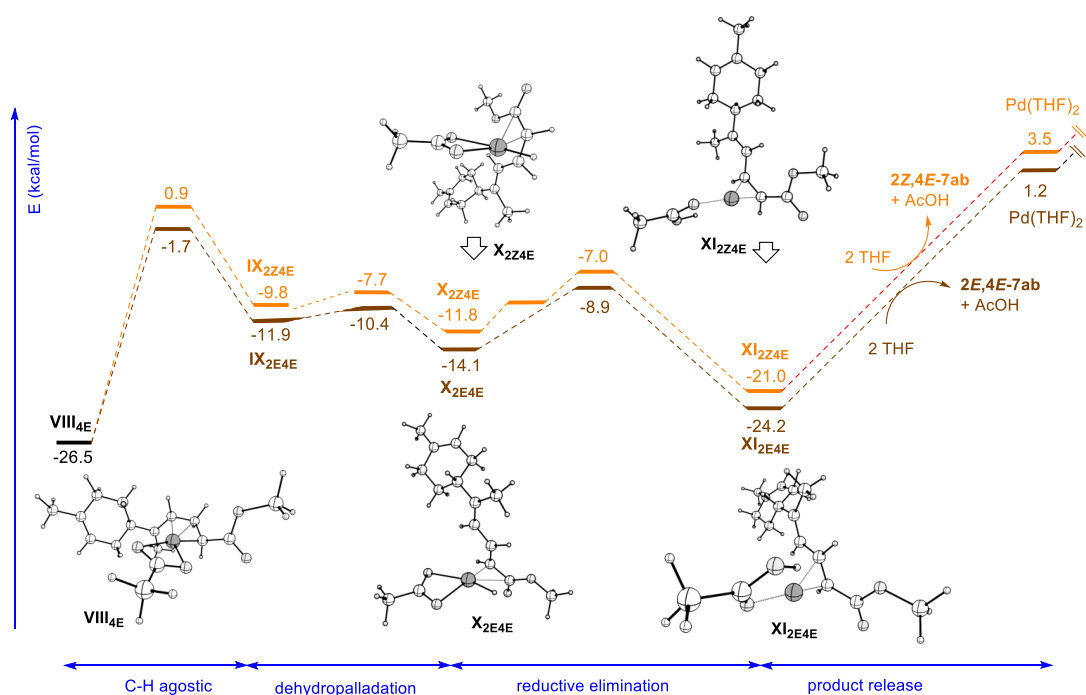
For the pink path (Scheme 67), leading to the minor geometrical isomer, the same steps occur from higher energy intermediate $\text{II}_{4\text{Z}}$ and lead to intermediate $\text{VIII}_{4\text{Z}}$ (-27.9 kcal/mol).



Scheme 67. First part of the energetic profile for the Pd-catalyzed CDC reaction of limonene.

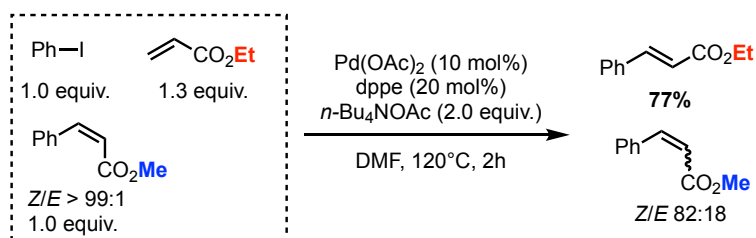
For both paths (black and pink), the following step is a dehydropalladation (β -H elimination). This globally endergonic two-step transformation implies the second bifurcation of the mechanism, which will determine the geometry of the 1,2-disubstituted alkene (Scheme 68). One of the two paths (brown path) generates the hydride complex $\text{X}_{2\text{E}4\text{E}}$ (-14.1 kcal/mol) passing through the “agostic”

intermediate $\text{IX}_{2\text{E}4\text{E}}$, while the other path (orange path) generates the hydride complex $\text{X}_{2\text{E}4\text{Z}}$ (-11.8 kcal/mol), passing through the “agostic” intermediate $\text{IX}_{2\text{E}4\text{Z}}$. The subsequent reductive elimination from $\text{X}_{2\text{E}4\text{E}}$ is thermodynamically favored, affording a Pd(0) complex π -coordinated with the final $2\text{E},4\text{E}$ product and σ -coordinated with acetic acid $\text{XI}_{2\text{E}4\text{E}}$ (-24.2 kcal/mol) passing a barrier of 5.2 kcal/mol. At this point, two molecules of the solvent (THF) enter the Pd coordination sphere, liberating the final $2\text{E},4\text{E}$ product and acetic acid. This step is exergonic, reaching +1.2 kcal/mol and generating the Pd(0)(THF)₂ complex. For the other path of the bifurcation (orange path), the same steps occur from $\text{IX}_{2\text{E}4\text{Z}}$ leading to $\text{XI}_{2\text{Z}4\text{E}}$ (-21.0 kcal/mol). Likewise, from this intermediate, THF enters the coordination sphere of palladium and liberates the final $2\text{E},4\text{Z}$ product and acetic acid reaching an energy of +3.5 kcal/mol. It is important to notice that the barrier for going back from complexes $\text{XI}_{2\text{E}4\text{E}}$ and $\text{XI}_{2\text{Z}4\text{E}}$ to the common resting state $\text{VIII}_{4\text{E}}$ is lower than that for going forward toward product release (Scheme 68, part B), and this is also valid for the equivalent sequence of steps starting from the minor resting state $\text{VIII}_{4\text{Z}}$ (see experimental part). This situation indicates that equilibration between $\text{XI}_{2\text{E}4\text{E}}$ and $\text{XI}_{2\text{Z}4\text{E}}$ occurs before product release. Accordingly, the $2\text{E}/2\text{Z}$ ratios in the products are expected to depend on the energy differences between $\text{XI}_{2\text{E}4\text{E}}$ and $\text{XI}_{2\text{Z}4\text{E}}$ for the major 4E path, and on that between $\text{XI}_{2\text{E}4\text{Z}}$ and $\text{XI}_{2\text{Z}4\text{Z}}$ for the minor 4Z path (not shown in Scheme 68). The computed ΔG s highly favor the 2E stereochemistry in both cases ($\Delta\text{G}_{4\text{E}} = 3.2$ kcal/mol; $\Delta\text{G}_{4\text{Z}} = 5.0$ kcal/mol), which agrees with the fact that only the 2E geometrical isomers are experimentally observed. According to these results, the catalytic cycle is experimentally viable only for the two paths that at the second branching lead to the 2E configured products.



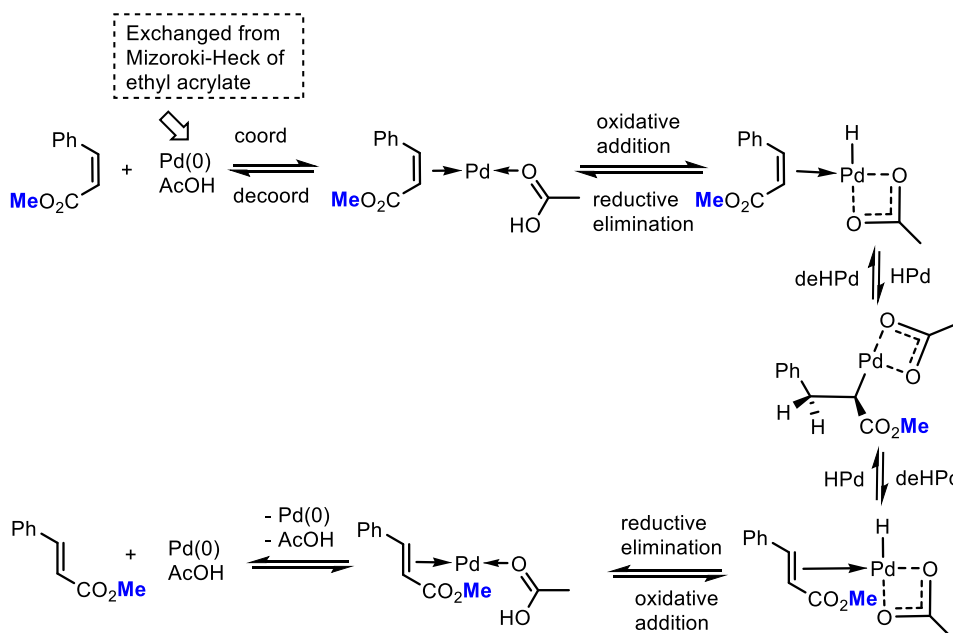
Scheme 68. Second part of the energetic profile for the Pd-catalyzed CDC reaction of limonene.

To validate the above-mentioned equilibration between the isoenergetic intermediates **XI_{2E,4E}** and **XI_{2Z,4E}**, we carried out a classical Mizoroki-Heck coupling^[131] between iodobenzene (1.0 equiv.) and ethyl acrylate (1.3 equiv.) in the presence of 1.0 equiv. of (*Z*)-methyl cinnamate [Pd(OAc)₂ (10 mol%), dppe (20 mol%), *n*-Bu₄NOAc (2.0 equiv.), DMF, 120°C, 2h]. During this reaction, (*E*)-ethyl cinnamate was isolated in 77% yield, accompanied by an 82:18 *Z*/*E* mixture of methyl cinnamate (Scheme 69).



Scheme 69. Experimental evidence for a *Z* to *E* isomerization through formation of a Pd hydride.

The *Z*-to-*E* isomerization of methyl cinnamate, although partial, is ostensibly due to the Pd(0)/AcOH system, in accordance with the reversibility of the dehydropalladation / reductive elimination sequence.^[132]



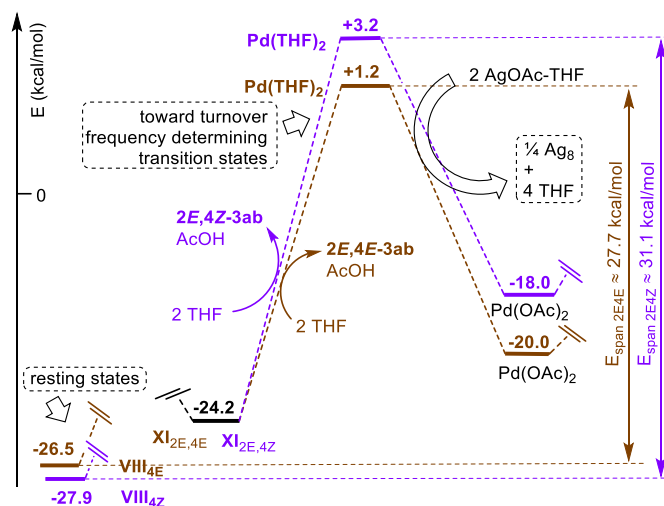
Scheme 70. Proposed mechanism for the *Z*/*E* equilibration of *Z* methyl cinnamate during the Mizoroki-Hack coupling.

Coming back to the computational study, from the two isoenergetic intermediates **XI_{2E,4E}** and **XI_{2E,4Z}** (not shown in Scheme 68) the two isomeric dienates and Pd(THF)₂ are released through a very

^[131] Mingoia, F.; Vitale, M.; Madec, D.; Prestat, G.; Poli, G. *Tetrahedron Lett.* **2008**, *49*, 760-763.

^[132] For an example of transformation of (*Z*)-alkenes into (*E*)-alkenes through catalytic palladium hydride formation, see: Kim, I. S.; Dong, G. R.; Jung, Y. H. *J. Org. Chem.* **2007**, *72*, 5424-5426.

endergonic step that reaches 1.2 and 3.2 kcal/mol through a 25.4 and 27.4 kcal/mol rise. At this point, Pd(0) reoxidation by the silver salt comes into Calculations were made considering the generation of different clusters of metallic silver. Consideration of the simplest aggregate Ag₂^[133], according to the equation [Pd(0)THF₂ + 2 AgOAc-THF → Pd(OAc)₂ + Ag₂ + 4 THF] turns out to be endergonic (Δ_rG° = +2.5 kcal/mol). However, the thermodynamics becomes slightly favorable (Δ_rG° = -11.1 kcal/mol) when the Ag₄ (D_{2h}) aggregate is considered as the silver reduced product, according to the equation [2 Pd(0)-THF₂ + 4 AgOAc-THF → 2 Pd(OAc)₂ + Ag₄ + 8 THF], and clearly favorable (Δ_rG° = -84.6 kcal/mol) when the Ag₈ (D_{2h}, dodecahedron) aggregate is considered as the silver reduced product, according to the equation [4 Pd(0)-THF₂ + 8 AgOAc-THF → 4 Pd(OAc)₂ + Ag₈ + 16 THF]. Thus, using the latter stoichiometry, the reaction free energy changes (Δ_rG°) of the catalytic cycles relative to the formation of **2E,4E-3ab** as well as of **2E,4Z-3ab** become -20.0 and -18.0 kcal/mol, respectively. Therefore, assuming that the states relative to Pd(THF)₂ are very close in energy and geometry to the corresponding transition states leading to and departing from it, we can predict energetic spans close to 27.7 kcal/mol [+1.2 -(-26.5)] for the 2E,4E isomer, and to 31.1 kcal/mol [(+3.2 -(-27.9))] for the 2E,4Z isomer. Here again, the computed energy values are qualitatively in accord with the observed 74:26 2E,4E / 2E,4Z isomer ratio of the coupled products as well as with the experimental conditions (24h of THF reflux) (Scheme 71).



Scheme 71. Calculated energetic diagram for product release and reoxidation of Pd⁰(THF)₂ with silver acetate.

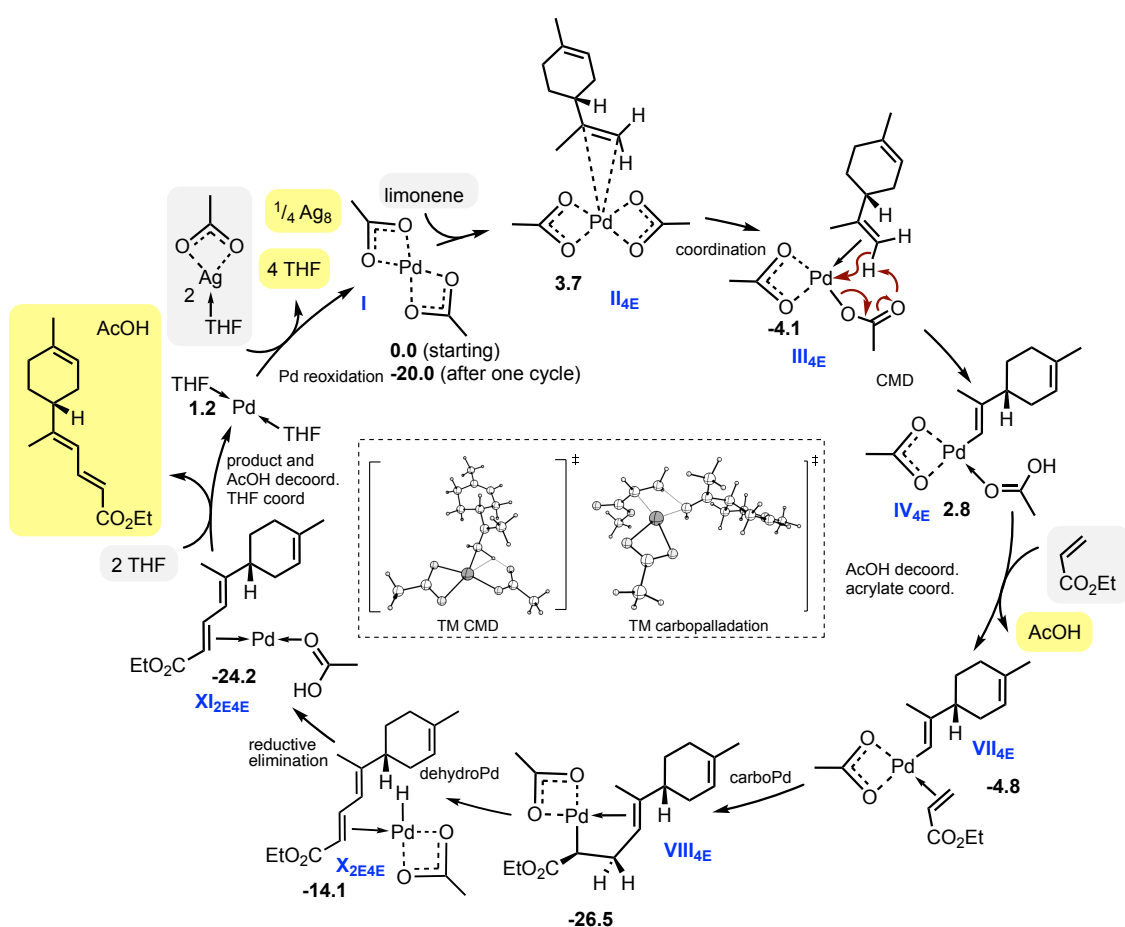
Furthermore, the aggregation state of silver is not the only factor having an influence of the thermodynamics of the reoxidation step. Indeed, considering the bulk transformation, the use of 4.0

^[133] a) M. Pereiro, D. Baldomir, J. E. Arias, *Phys. Rev. A* **2007**, 75, 063204; (b) M. Pereiro, D. Baldomir, *Phys. Rev. A* **2007**, 75, 033202; (c) M. Pereiro, D. Baldomir, *Phys. Rev. A* **2005**, 72, 045201; (d) T. Tsuneda. *J. Comput. Chem.* **2019**, 40, 206–211.

equiv. of silver acetate is crucial to push the equilibrium of the reoxidation to regenerate appropriate amounts of palladium(II) acetate.^[134]

In summary, while the *E/Z* isomeric ratio for the C4-C5 double bond is kinetic in origin, resulting from different energetic spans, the isomeric ratio at the C2-C3 double bond (for each isomer at C4=C5) comes from a local equilibration between **XI_{2Z4E}** and **XI_{2E4E}**, and between **XI_{2Z4Z}** and **XI_{2E4Z}** (not shown in Scheme 68), respectively, before the release of product **5ab**.

With all the above considerations, we can propose the catalytic cycle explaining the CDC reaction between (+)-limonene **1a** and ethyl acrylate **4b** and leading to the dienoate **5ab** (Scheme 72).



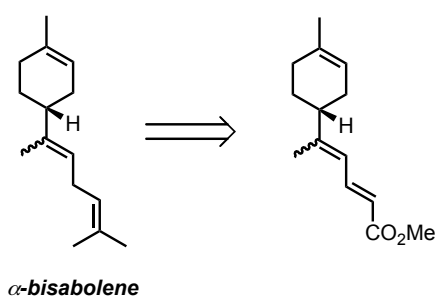
Scheme 72. Proposed mechanism for the Pd-catalyzed coupling between limonene and ethyl acrylate to give the major 2*E*,4*E* product.

^[134] (a) Solel, E.; Tarannam, N.; Kozuch, S. *Chem. Commun.* **2019**, 55, 5306-5322; (b) Besora, M.; Maseras, F. *Wiley Interdiscip. Rev.: Comput. Mol. Sci.* **2018**, 8, e1372.

In summary, in this project, we developed a Pd-catalyzed coupling between (+)-limonene and electron-poor alkenes, extending it to various terpenes and terpenoids. The reaction was totally regioselective, but not stereoselective, affording a mixture of geometrical isomers. While the reaction is elegant and green, using terpenes as bio-renewable starting materials, it has limitations. The coupling is compatible for unsubstituted acrylates, but requires a high catalytic loading and generates significant waste with a large excess (4.0 equiv.) of a silver-based oxidant.

In summary, in this project we have developed the first $C(sp^2)$ - $C(sp^2)$ -H vinyl / vinyl coupling of limonene with several unsaturated partners such as acrylic acid esters and amides, α,β -unsaturated ketones, styrenes and allyl acetate. The coupling was completely regioselective for both the reaction partners, involving exclusively the exocyclic unsaturation of limonene without disturbing the integrity of the absolute stereochemistry of the C4 stereogenic center of limonene. The reaction regularly produced a mixture of the two geometrical isomers 2E,4E and 2E,4Z, out of the four possible, with the former always dominant. The 2Z isomers were never detected. Terpenes other than limonene, possessing an isopropenyl function besides an endocyclic alkene, such as carvone, perillyl acetate, and valencene, could also be satisfactorily coupled. DFT computation gave results in qualitative accord with the observed selectivity, allowing to propose a plausible mechanism for the coupling.

Future improvements could be involving greener oxidants like O_2 or photochemistry. We plan to perform KIE studies to complete the mechanistic study and to apply this methodology to the stereoselective total synthesis of the sesquiterpene α -bisabolene (Scheme 73).



Scheme 73. General idea for the synthesis of α -bisabolene starting from our coupled product.

Chapter 3: Application: Copper free Sonogashira cross coupling in water

During my secondment at Novartis (Basel, Switzerland), in the team of Dr. Fabrice Gallou, I was involved in a project dedicated to the development of Sonogashira cross-couplings in water.

1. Introduction

The carbon–carbon triple bond of alkynes is a very useful functional group that can undergo a number of synthetically useful transformations. Furthermore, the alkyne function is found into a number of value-added organic compounds. For example, Norethynodrel has been the pioneer oral contraceptive, Efavirenz is an antiretroviral agent, Terbinafine is an antifungal agent, and Phorbaside A is an antibacterial agent (Figure 6). Last but not least, alkynes are crucial in the field of π -conjugated oligomers and polymers with applications in photonics, optoelectronics, and molecular electronics. Hence, the interest in the synthesis of alkynes is of fundamental importance. In this context, the Sonogashira-Hagihara coupling (more often simply known as the Sonogashira coupling) is a superior method to incorporate an alkyne function into a substrate.^[135]

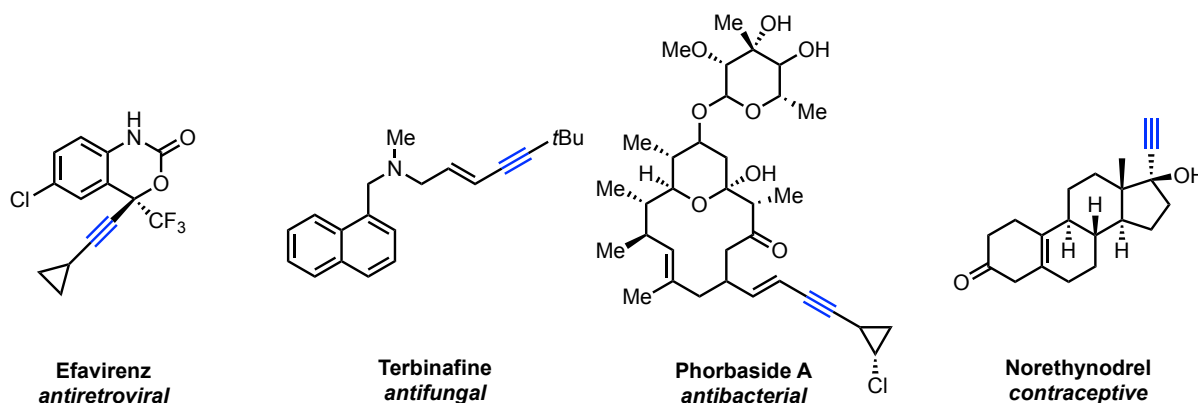
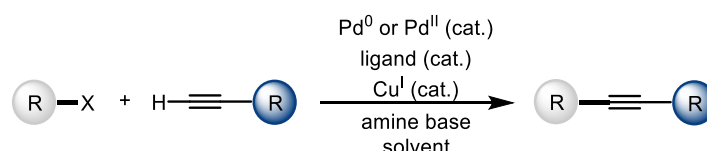


Figure 6. Selected examples of the alkyne-containing drugs and natural products.

^[135] (a) Struwe, J.; Ackermann, L.; Gallou, F. *Chem. Catal.* **2023**, *3*, 100485-100503; (b) Wang, D.; Gao, S. *Org. Chem. Front.* **2014**, *1*, 556-566; (c) Lipshutz, B. H.; Chung, D. W.; Rich, B. *Org. Lett.*, **2008**, *10*, 3793-3796; (d) Jakobi, M.; Gallou, F.; Sparr, C.; Parmentier, M. *Helv. Chim. Acta* **2019**, *102*, e1900024; (e) Braje, W.; Britze, K.; Rich, J. D.; Jolit, A.; Kaschel, J.; Klee, J.; Lindner, T. Patent **2017**, WO 2017/129796.

The alkynylation reaction of aryl halides by terminal alkynes was independently reported in 1975 by Cassar,^[136] Dieck and Heck,^[137] as well as Sonogashira, Tohda and Hagihara.^[138] The three protocols employ a palladium catalyst. However, the protocols of Cassar and Heck use only a palladium catalyst, and require high reaction temperatures. Conversely, the use of copper-cocatalyst in addition to palladium complexes in Sonogashira's procedure allows the reaction to be carried under mild reaction conditions and gives superior yields (Scheme 74).



Scheme 74. Classical Sonogashira reaction.

Traditionally, Sonogashira couplings have been carried out in organic solvents like *N*-methylpyrrolidone (NMP), *N,N*-dimethylformamide (DMF), or THF using amine bases. These reactions typically required high reaction temperatures.

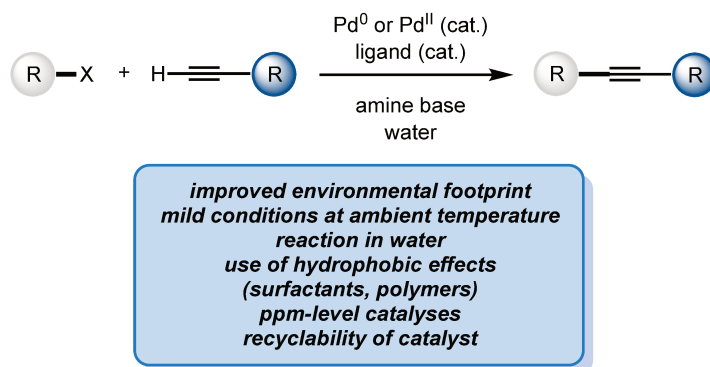
Over the last decade, there has been a shift towards more environmentally friendly reactions conducted in water in the presence of surfactants, polymersomes, dendrimers, or nanogels, which self-assemble in supramolecular architectures that behave as nanoreactors. This trend has led to the development of greener, safer, and more manageable alternatives, including the case of the Sonogashira cross-couplings (Scheme 75).^[139]

^[136] Cassar, L. J. *Organomet. Chem.*, **1975**, *93*, 253-257.

^[137] Dieck, H.A.; Heck, R.F. *J. Organomet. Chem.*, **1975**, *93*, 259-263.

^[138] Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.*, **1975**, *16*, 4467-4470.

^[139] (a) Fabris, F.; Illner, M.; Repke, J.-U.; Scarso, A.; Schwarze, M. *Molecules* **2023**, *28*, 4809-4845; (b) Roschangar, F.; Zhou, Y.; Constable, D. J. C.; Colberg, J.; Dickson, D. P.; Dunn, P. J.; Eastgate, M. D.; Gallou, F.; Hayler, J. D.; Koenig, S. G.; Kopach, M. E.; Leahy, D. K.; Mergelsberg, I.; Scholz, U.; Smith, A. G.; Henry, M.; Mulder, J.; Brandenburg, J.; Dehli, J. R.; Fandrick, D. R.; Fandrick, K. R.; Gnad-Badouin, F.; Zerban, G.; Groll, K.; Anastas, P. T.; Sheldon, R. A.; Senanayake, C. H. *Green Chem.* **2018**, *20*, 2206-2211; (c) Cortes-Clerget, M.; Yu, J.; Kincaid, J. R. A.; Walde, P.; Gallou, F.; Lipshutz, B. H. *Chem. Sci.* **2021**, *12*, 4237-4266; (d) Lipshutz, B. H.; Ghorai, S. *Aldrichim. Acta* **2012**, *45*, 3-16; (e) De Martino, M. T.; Abdelmohsen, L. K. E. A.; Rutjes, F. P. J. T.; van Hest, J. C. M. *Beilstein J. Org. Chem.*, **2018**, *14*, 716-733; (f) Lipshutz, B. H.; Ghorai, S.; Cortes-Clerget, M.; *Chem. Eur. J.* **2018**, *24*, 6672-6695.



Scheme 75. Sustainable Sonogashira-Hagihara coupling in micellar regime.

However, a common challenge with using water as a solvent is the low solubility of organic starting materials and reagents. A solution to this issue emerged a few years ago through the use of surfactants such as the vitamin E derived polyoxyethanyl- α -tocopheryl sebacate (PTS) or the second-generation amphiphile TPGS-750-M, or polymers such as hydroxypropyl methylcellulose (HPMC) (Figure 7).^[140] In a comprehensive study Lipshutz *et al.*, developed several cross couplings under micellar catalysis, including the Sonogashira coupling.

Of particular scientific interest is the recent investigation of the hydrophobic effects associated with select polymers, notably HPMC (system C). This investigation has unveiled a remarkable phenomenon akin to the behavior of micelles, yielding noteworthy rate enhancements across various chemical transformations. This effect has been observed to exhibit efficiency in a diverse variety of reactions.

^[140] Lipshutz, B. H.; Ghorai, S.; Abela, A. R.; Moser, R.; Nishikata, T.; Duplais, C.; Krasovskiy, A.; Gaston, R. D.; Gadwood, R. *C. J. Org. Chem.* **2011**, *76*, 4379-4391.

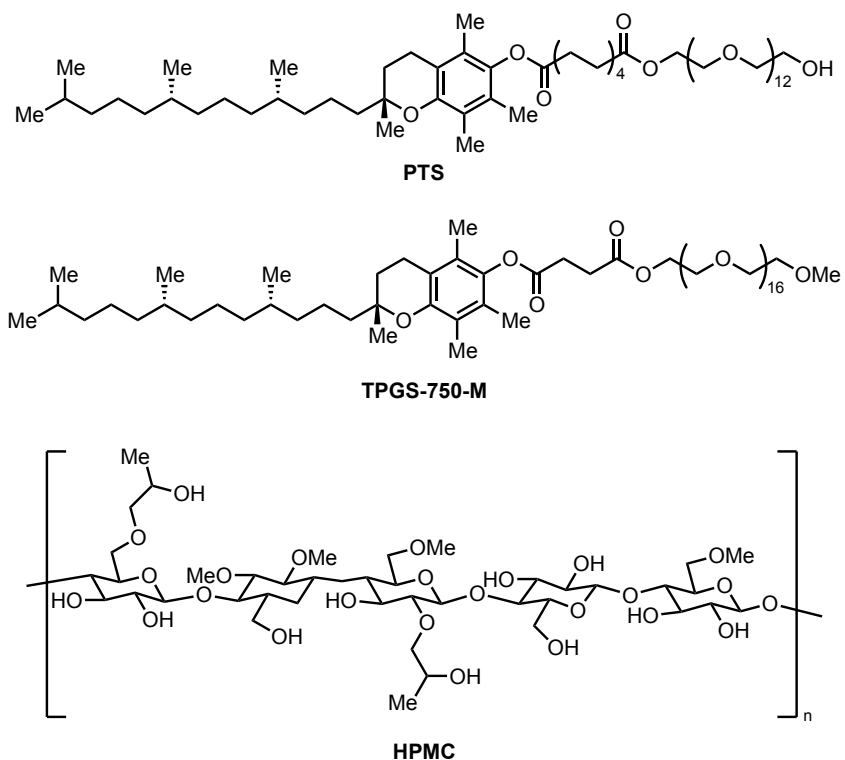


Figure 7. Examples of surfactants (PTS and TPGS-750-M) and polymer (HPMC) for micellar catalysis.

These compounds form stable but dynamic micelles due to the hydrophobic effect. In these micelles, the unfavorable interaction between hydrophobic portions and the aqueous (polar) reaction medium is minimized by exposing the polar head groups of the surfactants to water (Figure 8).

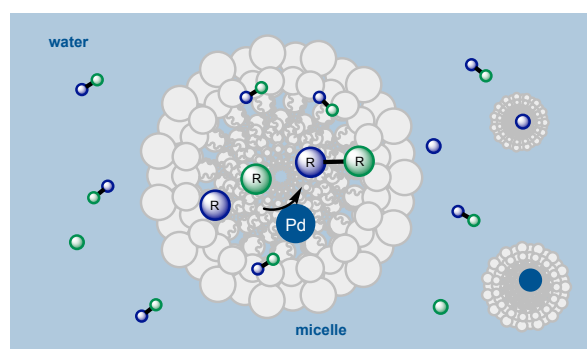


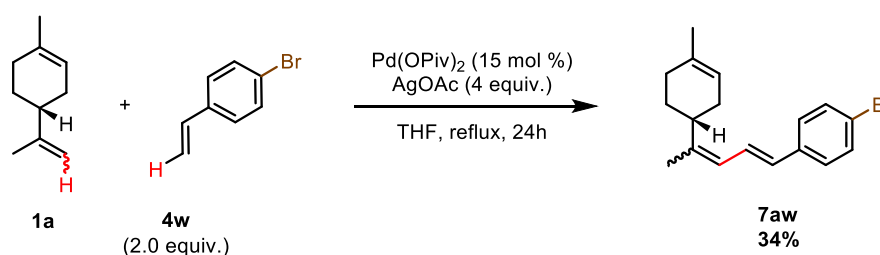
Figure 8. Formation of micelles through the hydrophobic effect. Adapted from Ref 135a

Organic compounds and transition metal catalysts can easily move within the lipophilic cavity of these micelles or at their hydrophilic interface. This process facilitates the partial solubilization of organic compounds within the supramolecular structure of the micelles, enabling catalysis. Additionally, micelles can protect sensitive intermediates from decomposition, as observed in oxidations, reductions, and C–C bond forming processes. By employing micellar catalysis instead of the traditional

homogeneous catalysis in organic solvents, it has been possible to achieve milder reaction conditions characterized by lower reaction temperatures and reduced catalyst loading. This can be attributed to the confinement of the reagents on the inner surface of the micelles, which reduces the degree of freedom on this two-dimensional surface.

2. Optimization of the reaction conditions

In light of the above considerations, and with the aim of strengthening the usefulness of the above-described CDC of limonene, we decided to test a post-functionalization experiment based on micellar catalysis. In particular, we decided to perform a CDC between limonene and *p*-bromostyrene **4w**, and, if successful, to evaluate the resulting coupled product in a Sonogashira coupling under micellar conditions. Accordingly, using the optimized conditions described above, the planned C(sp²)–H/C(sp²)–H coupling gave the expected bromodiene **7aw**, albeit in low yield (Scheme 76).



Scheme 76. CDC between (+)-limonene and 4-bromostyrene in view a subsequent post-functionalization.

The Sonogashira coupling between **5aw** and phenyl acetylene **8** under micellar catalysis was next tackled. To find out the optimum reaction conditions for the desired coupled product, we carried out a comparative study using three different reported Sonogashira coupling (Scheme 77).^[141] A first one based on the [Pd(MeCN)₂Cl₂ (1.0 mol%), XPhos (2.5 mol%), Et₃N (2.0 equiv.), TPGS-750-M (3 wt%)] (protocol A); a second one based on the [CataCXium A Pd G3 (0.30 mol%), Et₃N (3.0 equiv.), TPGS-750-M (2 wt%), H₂O, glucose (5 mol%), THF (15 vol%)] (protocol B), and a third one based on [Pd(MeCN)₂Cl₂ (1.0 mol%), XPhos (1.3 mol%), Et₃N (2.0 equiv.), HPMC 40-60 cPs^[142] (2 wt%)] (protocol C). In the event, system A gave, after a 24h reaction time, the desired product **9** in a 24% yield, while system B gave 54%, again after a 24h reaction (Scheme 77). Incorporation of THF (15 vol%), to enhance reaction

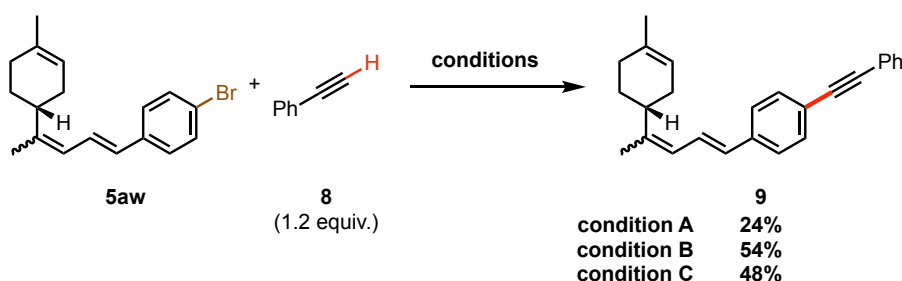
^[141] (a) Lipshutz, B. H.; Chung, D. W.; Rich, B. *Org. Lett.* **2008**, *10*, 3793-3796; (b) Jakobi, M.; Gallou, F.; Sparr, C.; Parmentier, M. *Helv. Chim. Acta* **2019**, *102*, e1900024; (c) Braje, W.; Britze, K.; Diet Rich, J. D.; Jolit, A.; Kaschel, J.; Klee, J.; Linder, T. Patent **2017**, WO 2017/129796.

^[142] "cP" stands for "centipoise", which is a unit to define the viscosity of a fluid.

homogeneity, and the addition of glucose (5 mol%), to sustain catalytic efficiency, were crucial for the better result of this protocol with respect to the first one.^[141b,143]

When applying conditions C, the desired coupled product **9** was obtained with a notable yield of 48% after an overnight reaction (Scheme 77). It is worth noting that these reactions typically exhibit remarkable rapidity, frequently concluding within a timeframe ranging from 2 minutes to 2 hours. Consequently, the observed plateau in reaction progress after an overnight duration can be attributed to the inherently rapid kinetics characterizing these transformations.

Considering the cost-effectiveness of the polymer relative to the surfactant and the demonstrated efficacy of condition B, we have chosen the latter as the starting reaction conditions for the beginning of our optimization studies.

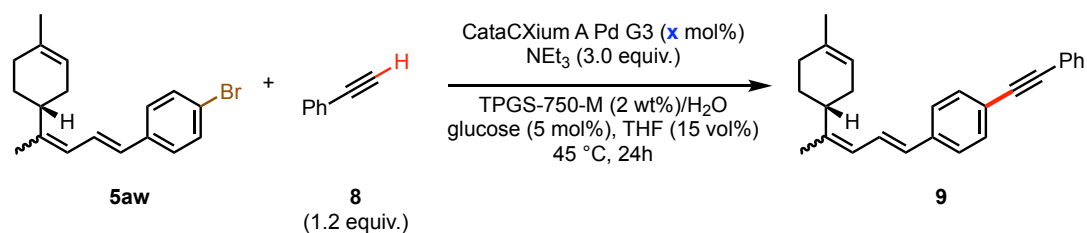


conditions A: Pd(MeCN)₂Cl₂ (1.0 mol%), XPhos (2.5 mol%), Et₃N (2.0 equiv.), TPGS-750-M (3 wt%), H₂O, rt, 24h
conditions B: CataCXium A Pd G₃ (0.30 mol%), Et₃N (3.0 equiv.), TPGS-750-M (2 wt%), H₂O, glucose (5 mol%), THF (15 vol%), 45°C, 24h
conditions C: Pd(MeCN)₂Cl₂ (1.0 mol%), XPhos (1.3 mol%), Et₃N (2.0 equiv.), HPMC 40-60 cps (2 wt%), rt, overnight

Scheme 77. Sonogashira cross-coupling between the limonene-derived aryl bromide **5aw** and phenyl acetylene **8**: three protocols compared.

Our initial investigations involved a systematic examination of the catalytic loadings (Table 8). Although 0.3 mol% (Table 8, entry 1) of the palladium catalyst emerged as the most favorable compromise among all loadings because compound **9** was obtained with 34% and 62% yield respectively with 0.1 and 0.5 mol% (Table 8, entries 2-3), we have selected a catalytic loading of 0.1 mol% for further optimizing the reaction conditions. The decision to retain a catalytic loading of 0.1 mol% is motivated by cost considerations. This choice provides an economically viable starting point for our optimization efforts. As we refine the reaction conditions, we may explore the possibility of increasing the catalytic loading, especially during the scale-up of the reaction, to assess its impact on performance.

^[143] (a) Bollenbach, M.; Wagner, P.; Aquino, P. G. V.; Bourguignon, J.-J.; Bihel, F.; Salomé, C.; Schmitt, M. *ChemSusChem* **2016**, *9*, 3244-3249; (b) Camp, J. E.; Dunsford, J. J.; Cannons, E. P.; Restorick, W. J.; Gadzhieva, A.; Fay, M. W.; Smith, R. J. *ACS Sustainable Chem. Eng.* **2014**, *2*, 500-505.



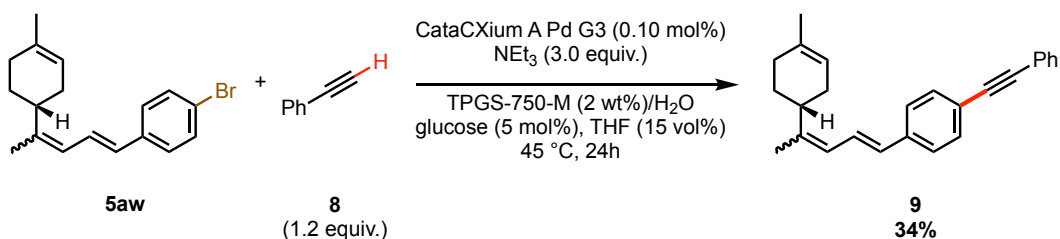
Entry ^[a]	CataCXium A Pd G3 (x mol%)	9 (%) ^[b]
1	0.30	54
2	0.10	34
3	0.50	62

[a] typical reaction conditions: **5aw** (0.1 mmol), phenyl acetylene (1.2 equiv.), CataCXium A Pd G3 (x mol%), NEt_3 (3.0 equiv.), TPGS-750-M (2 wt%)/ H_2O , glucose (5 mol%), THF (15 vol%) at 45°C in a sealed vial; [b] measured by quantitative $^1\text{H-NMR}$ using 1,4-dinitrobenzene as an internal standard.

Table 8. Screening of the catalytic loading of the palladium catalyst.

After the determination of the optimal catalytic loading, our efforts focused on the optimization of reaction conditions (Table 9). Attempts to substitute THF with alternative, more polar co-solvents such as acetone or *tert*-amyl alcohol (Table 9, entry 2 and 3) did not yield any noticeable improvements. Similarly, the exploration of alternative inorganic bases (Table 9, entries 4-5), such as sodium carbonate or cesium carbonate, or the extension of lipophilicity (Table 9, entry 6) within the alkyl chain through the use of *n*- Oct_3N , did not result in enhanced yields.

Interestingly, a substantial increase in yield from 34% to 54% (Table 9, entry 7) was observed upon doubling the concentration of the reaction, prompting our decision to maintain this concentration level for further optimization efforts. Subsequently, we turned our attention to investigating the influence of the temperature on the reaction outcome. However, neither room temperature (rt) nor a higher temperature of 60°C appeared to significantly enhance reaction performance (Table 9, entries 8-9).



Entry ^[a]	Deviation from standard conditions	9 (%) ^[b]
1	None	34
2	acetone instead of THF	12

3	<i>tert</i> -amyl alcohol instead of THF	8
4	Na ₂ CO ₃ instead of Et ₃ N	_[c]
5	Cs ₂ CO ₃ instead of Et ₃ N	_[c]
6	(<i>n</i> -oct) ₃ N instead of Et ₃ N	12
7	0.4M instead of 0.2M	53
8	rt instead of 45°C	23
9	60°C instead of 45°C	52

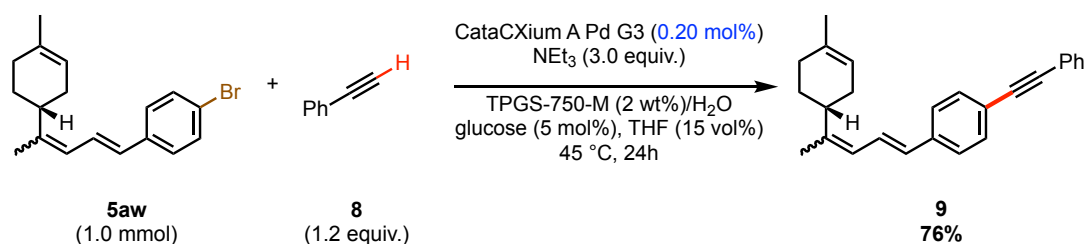
[a] typical reaction conditions: **5aw** (0.1 mmol), phenyl acetylene (1.2 equiv.), CataCXium A Pd G3 (0.10 mol%), base (3.0 equiv.), TPGS-750-M (2 wt%)/H₂O, glucose (5 mol%), co-solvent (15 vol%) at T in a sealed vial; [b] measure by quantitative ¹H-NMR, using 1,4-dinitrobenzene as an internal standard; [c] not determined.

Table 9. Optimization of the reaction conditions.

3. Attempts for scale-up, CDC reaction under micellar regime and comparison with classical conditions

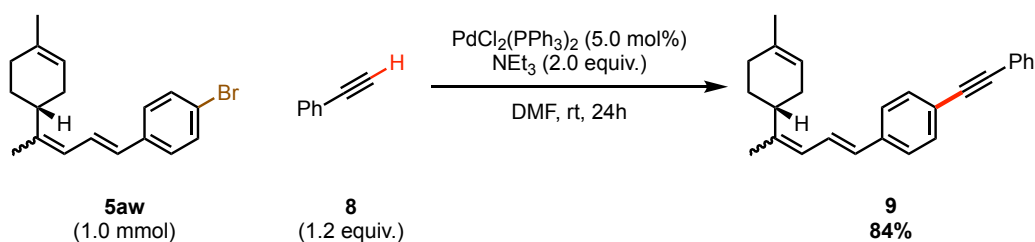
With the optimized reaction conditions at our disposal, we planned to perform a scale-up of the reaction, passing from 0.1 mmol to a 1 mmol scale of the coupled substrate. In this scaled-up scenario, we chose to increase the catalytic loading of the palladium source from 0.1 mol% to 0.2 mol%.

The Sonogashira cross-coupling reaction involving the coupled substrate **5aw** with phenylacetylene **8** was performed under the following optimized conditions: CataCXium A Pd G3 (0.2 mol%), NEt₃ (3.0 equiv.), TPGS-750-M (2 wt%)/H₂O, glucose (5 mol%), and THF (15 vol%) as a co-solvent. The reaction proceeded at 45°C for 24h, with formation of the desired product with a yield of 76% (Scheme 78).



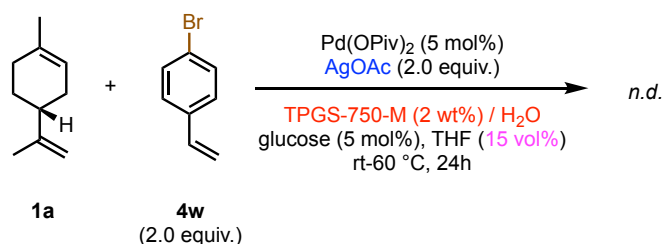
Scheme 78. Final optimized conditions for Sonogashira cross coupling.

Lastly, a comparison between the micellar protocol and a classical copper-free alkylation protocol was carried out. Accordingly, use of the system [PdCl₂(PPh₃)₂ (5 mol%), Et₃N (2.0 equiv.)] in DMF yielded the desired product in 84% yield (Scheme 79).



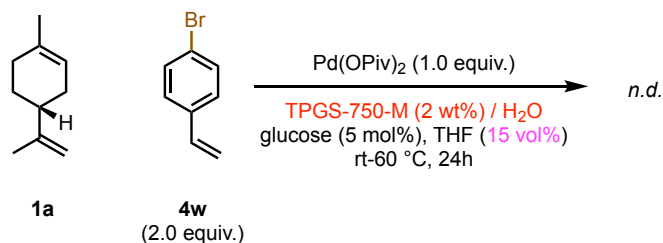
Scheme 79. Classical copper-free Sonogashira cross-coupling protocol.

As a last task, we evaluated the feasibility of conducting also the initial undirected C–H/C–H coupling reaction between (+)-limonene **1a** and 4-bromostyrene **4w** within a micellar environment. Hence, we envisaged to perform the coupling reaction by employing a combination of reaction conditions that took inspiration from both the protocols employed in the CDC coupling reaction and the Sonogashira coupling protocol conducted in an aqueous environment. Regrettably, when using Pd(OPiv)₂ (5 mol%), AgOAc (2.0 equiv.), TPGS-750-M (2 wt%)/H₂O, glucose (5 mol%), and THF (15 vol%) as the cosolvent at reflux for 24h our attempts to obtain the desired product **5aw** were unsuccessful (Scheme 80).



Scheme 80. CDC attempt between limonene and 4-bromostyrene using micellar catalysis.

Due to the limited solubility of silver salts within the reaction mixture, in a second experiment, we opted to avoid their use and instead performed a stoichiometric reaction (Scheme 81). However, even under these conditions, the desired product **5aw** was not formed. This failure may be due to the scarce solubility of the palladium catalyst within the reaction mixture.



Scheme 81. Stoichiometric CDC attempt between limonene and 4-bromostyrene using micellar catalysis.

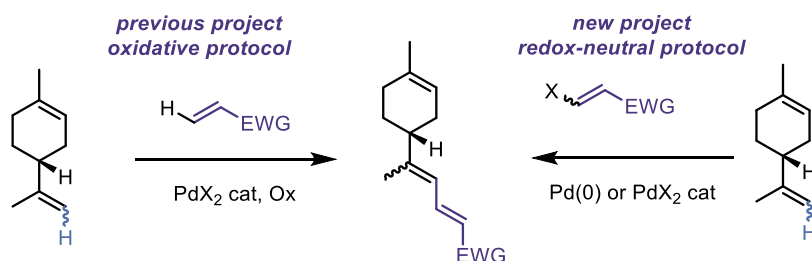
In summary, to further valorize the method developed in the previous chapter, a Sonogashira coupling using a C–H/C–H coupled product as a starting substrate was studied and successfully performed under micellar catalysis conditions, allowing its further selective functionalization. Work is in progress to develop other selective post-functionalizations and new selective catalytic functionalizations of terpenes.

Chapter 4: Development of a C(sp²)-H / C(sp²)-X alkene / haloalkene coupling reaction

1. Introduction

During the first project (Chapter 2), we developed conditions for a regioselective Pd-catalyzed CDC reaction between limonene and electron-poor alkenes, extending this strategy to several terpenes and terpenoids.

The optimized protocol calls for treatment of the terpenes with the electron-poor alkenes (2.0 equiv.) in the presence of palladium(II) pivalate (15 mol%) and a large excess of silver acetate (4.0 equiv.) in THF at reflux for 24h. One of the major problems for this protocol is the use a high catalytic loading of the palladium complex and the large excess of silver salt used as oxidant. In order to solve these problems, we decided to study an alternative Pd-catalyzed protocol, this time exploiting a redox neutral coupling between limonene and 3-heterosubstituted electron poor alkenes (Scheme 82).

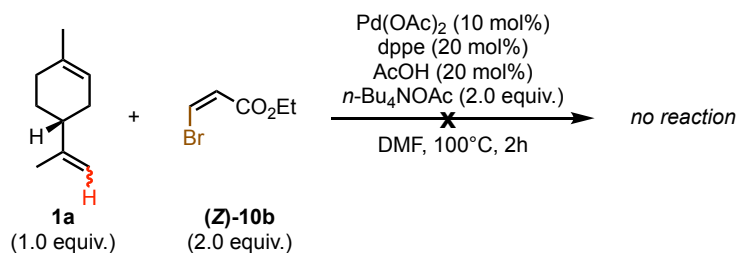


Scheme 82. Alternative strategy to access the coupled product.

Our initial approach in exploring this new redox-neutral coupling of limonene was based on the widely known Mizoroki-Heck reaction, which needs Pd(0) catalysis,^[36,40a,144] using ethyl (*Z*)-3-bromoacrylate as the alkene partner. However, despite numerous attempts, we were unable to obtain the desired coupling product under classical Mizoroki-Heck reaction conditions (Scheme 83).^[145]

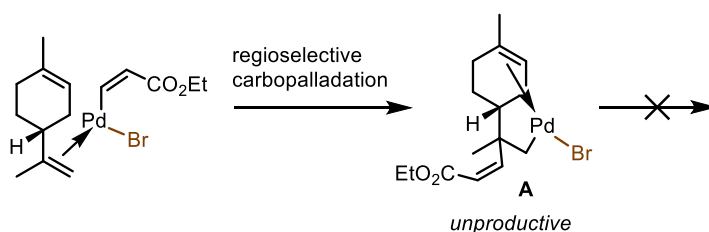
^[144] Murray, P. M.; Tyler, S. N. G.; Moseley, J. D. *Chimica Oggi-Chemistry Today* **2012**, *30*, 15-18.

^[145] Poli, G.; Giambastiani, G. *J. Org. Chem.* **2002**, *67*, 9456-9459.



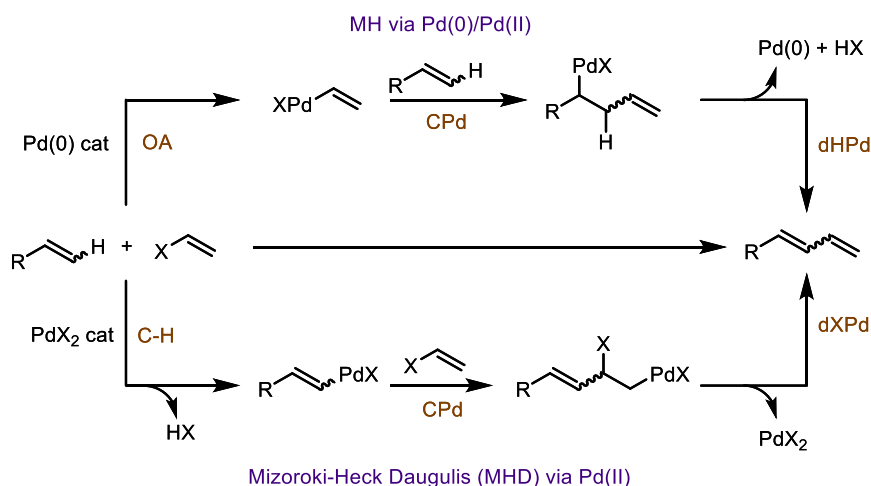
Scheme 83. Envisioned strategy to the coupled product via classical Mizoroki-Heck conditions.

We reasoned that the failure of this coupling may be due to the 1,1-disubstituted nature of the exocyclic alkene of limonene. Indeed, under these reaction conditions, it is conceivable that the carbopalladation step leads regioselectively to the σ -homoallylpalladium complex **A**, which, due to its β,β -disubstitution, cannot undergo dehydropalladation, or evolve otherwise (Scheme 84).



Scheme 84. Hypothesis on the failure of the classical Mizoroki-Heck coupling between limonene and (Z)-3-bromoacrylate.

In view of the above failure, we thought to test this redox neutral C–H / C–X coupling via an unusual Pd(II)-catalyzed protocol. In particular, we reasoned that such a coupling could be in principle be initiated by Pd(II)-catalyzed palladation of limonene rather than an oxidative addition of the heteroalkene to a Pd(0) complex (Scheme 85).



Scheme 85. Alternative Pd(0)- (top) and Pd(II)- (bottom) catalyzed C–H / C–X couplings.

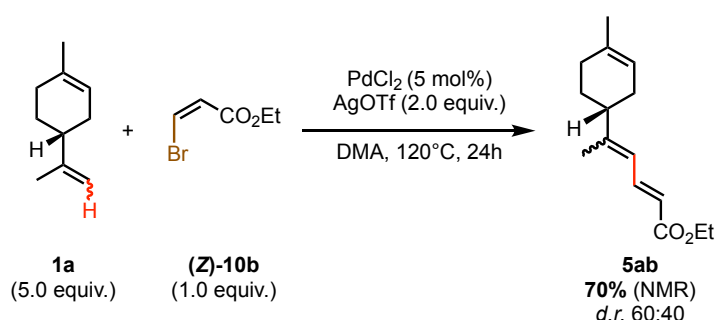
Although, to the best of our knowledge, no such [alkene / haloalkene] coupling has been so far reported in the literature, the elegant work of Daugulis and Zaitsev,^[58] who reported in 2005 a Pd(II)-catalyzed C–H_{ortho} / C–X alkenylative coupling between anilides and a β-halo acrylates, gave us the inspiration to try this strategy. Accordingly, we decided to switch to Pd(II)-catalysis for this C(sp²)–H / C(sp²)–X alkenylative coupling.

2. Preliminary studies and optimization of the reaction conditions

2.1. Preliminary studies

The study of the Pd(II)-catalyzed coupling between limonene **1a** and ethyl (Z)-3-bromoacrylate (**Z**)-**10b** was thus undertaken. Initially, we attempted the optimization of the coupling using a limonene: bromoacrylate ratio of 1:2. However, this approach yielded to unsatisfying results due to the low conversion of limonene. To address this issue and to take advantage of the cost-effectiveness of limonene, we revised the strategy by inverting the ratio, using an excess of limonene (5.0 equiv.) and making bromoacrylate the limiting reagent.

After some experimentation, we were very pleased to find that reacting the two components in a 5:1 ratio with the catalytic system [PdCl₂ (5 mol%), AgOTf, (2.0 equiv.)] in DMA at 120°C for 24h,^[58] generated a 6:4 E/Z mixture of the expected coupled dienoate **5ab** in 70% spectroscopic yield (Scheme 86). So, this redox-neutral coupling generated the same product as the one obtained via the oxidative coupling using the acrylate instead of the 3-bromoacrylate. Again, the coupling is totally regioselective but not stereoselective. As in the oxidative protocol, the 2E double bond geometry has been exclusively observed, the E:Z mixture concerning exclusively position 4.



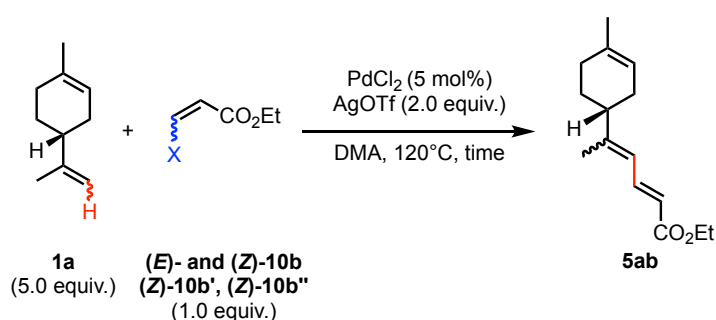
Scheme 86. Preliminary result for the coupling between limonene and ethyl 3-bromoacrylate.

2.2. Optimization of the reaction conditions

The influence of various parameters, such as the (*E*)- or (*Z*)-haloacrylate configuration, the nature of the halide, the solvent, the halide scavenging agent, and the ratio of coupling partners on the outcome of the reaction was next studied.

2.2.1. Geometric configuration and nature of halogen of the haloacrylate

Using the previous reaction conditions, the optimization of the reaction conditions was then continued. Acrylates (**Z**-10b and (*E*)-10b showed similar reactivities, affording 70% and 64% yield of the dienoate, respectively (Table 10, entries 1 and 2). We thus decided to select the (*Z*)-3-haloacrylates for the suite of the study, because they appear to provide slightly better yields, and are also easier to synthesize. Since the conversion of the experiments described above was not complete (81%, Table 10, entry 1), longer reaction times were tested. In the event, a 48h reaction time allowed to isolate the desired dienoate **5ab** with a better yield of 84% (Table 10, entry 3). The nature of the halogen on the acrylate coupling partner was investigated next. Ethyl (*Z*)-3-chloroacrylate (**Z**-10b') provided the desired compound **5ab** with a lower yield of 56% (Table 10, entry 4). This result is in accordance with the observations of Daugulis for the C–H alkenylation of acetanilides with haloacrylates.^[58] On the other hand, ethyl (*Z*)-3-iodoacrylate (**Z**-10b'') showed a reactivity comparable with that of bromoacrylate (**Z**-10b (entry 5). The order of reactivity of haloolefins is thus Br ≈ I > Cl.^[61] Therefore, we decided to continue our studies using the (*Z*)-bromoacrylates as coupling partners.



Entry ^[a]	haloacrylate	time (h)	Conv. (%) ^[b]	5ab (%) ^[b]	<i>d.r.</i>
1	(Z) -10b	24	81	70	60:40
2	(E) -10b	24	86	64	58:42
3	(Z) -10b	48	95	84	72:28
4	(Z) -10b'	48	98	56	58:42

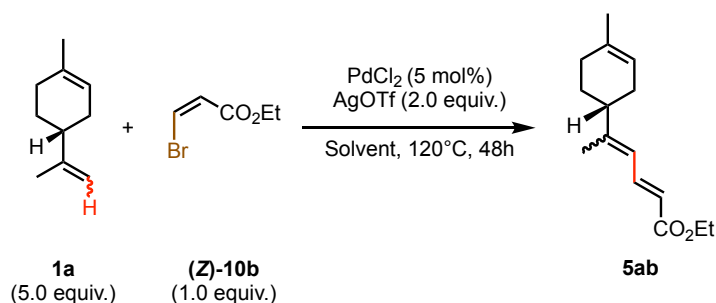
5	(Z)-10b''	48	93	79	60:40
---	-----------	----	----	----	-------

[a] typical reaction conditions: (+)-limonene **1a** (5.0 equiv.), ethyl 3-haloacrylates (*E*)-**10b**, (*Z*)-**10b**, (*Z*)-**10b'** or (*Z*)-**10b''** (0.5 mmol), PdCl₂ (5 mol%), AgOTf (2.0 equiv.), DMA (0.2 M), 120 °C in an ace pressure tube; [b] measured by quantitative ¹H-NMR using 1,4-dinitrobenzene as an internal standard.

Table 10. Variations on the nature of the haloacrylate.

2.2.2. Variation of the solvent

We then screened different solvents. In addition to DMA, other amide polar solvents such as DMF and NMP were tested. Contrary to NMP, who gave no conversion of the bromoacrylate (Table 11, entry 3), the use of DMF allowed the formation of the desired dienoate **5ab** in a lower yield of 61% (Table 11, entry 2). DMA remained the best solvent amongst the amide polar solvents (Table 11, entry 1). THF did not allow any conversion of the bromoacrylate (Table 11, entry 4), whereas 1,4-dioxane provided the desired coupling product **5ab** in 32% (Table 11, entry 5). DCE gave no conversion of the bromoacrylate (Table 11, entry 6). Therefore, we decided to keep DMA as the solvent for further optimization studies. However, as DMA and DMF are considered harmful solvents,^[146] the replacement of these solvents with safer and more eco-friendly solvents^[147] such as cyrene^[148] and dimethyl isosorbide^[149] will be evaluated in the future.



Entry ^[a]	Solvent	Conv. (%) ^[b]	5ab (%) ^[b]	d.r.
1	DMA	95	84	72:28
2	DMF	95	61	66:34
3	NMP	-[c]	-	-
4	THF	-[c]	-	-

^[146] Prat, D.; Hayler, J.; Wells, A. *Green Chem.* **2014**, *16*, 4546-4551.

^[147] Byrne, F. P.; Jin, S.; Paggiola, G.; Petchey, T. H. M.; Clark, J. H.; Farmer, T. J.; Hunt, A. J.; McElroy, C. R.; Sherwood, J. *Sustain Chem. Process* **2016**, *4*, 7, 1-24.

^[148] (a) Sherwood, J.; De bruyn, M.; Constantinou, A.; Moity, L.; McElrouy, C. R.; Farmer, T. J.; Duncan, T.; Raverty, W.; Hunt, A. J.; Clark, J. H. *Chem. Commun.* **2014**, *50*, 9650-9652; (b) Citarella, A.; Amenta, A.; Passarella, D.; Micale, N. *Int. J. Mol. Sci.* **2022**, *23*, 15960-15978.

^[149] Aricó, F.; Tundo, P. *Beil. J. Org. Chem.* **2016**, *12*, 2256-2266.

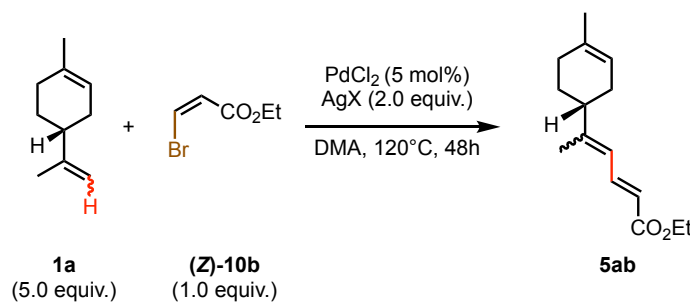
5	1,4-dioxane	89	32	67:33
6	DCE	_[c]	-	-

[a] typical reaction conditions: (+)-limonene **1a** (5.0 equiv.), ethyl (Z)-3-bromoacrylate (**Z**)-**10b** (0.5 mmol), PdCl₂ (5 mol%), AgOTf (2.0 equiv.), solvent (0.2 M), 120 °C in an ace pressure tube; [b] measured by quantitative ¹H-NMR using 1,4-dinitrobenzene as an internal standard; [c] no conversion was observed.

Table 11. Screening of the solvents.

2.2.3. Variation of the ionizing agent

We next investigated the influence of the ionizing agent, while keeping PdCl₂ (5 mol%) as the pre-catalyst and DMA as the solvent. Contrary to silver triflate (Table 12, entry 1), silver carbonate lead to a low yield and a low conversion (Table 12, entry 2), while silver acetate failed to yield any desired product (Table 12, entry 3). Silver tetrafluoroborate and silver trifluoroacetate resulted in lower yields too (Table 12, entries 4-5). Silver bistriflimide proved to be the best additive (Table 12, entry 2), and was selected as the scavenging agent of choice for further optimization.



Entry ^[a]	AgX	Conv. (%) ^[b]	5ab (%) ^[b]	d.r.
1	AgOTf	95	84	72:28
2	Ag ₂ CO ₃	32	6	n.d.
3	AgOAc	_[c]	-	-
4	AgBF ₄	83	60	60:40
5	AgTFA	95	31	57:43
6	AgNTf ₂	95	88	60:40

[a] typical reaction conditions: (+)-limonene **1a** (5.0 equiv.), ethyl (Z)-3-bromoacrylate (**Z**)-**10b** (0.5 mmol), PdCl₂ (5 mol%), scavenger (2.0 equiv.), DMA (0.2 M), 120 °C in an ace pressure tube; [b] measured by quantitative ¹H-NMR using 1,4-dinitrobenzene as an internal standard; [c] no conversion was observed. n.d.: not determined.

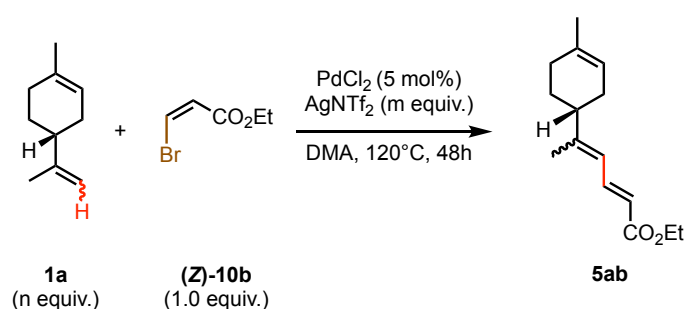
Table 12. Screening of the ionizing agents in the model reaction.

Optimization of the amount of AgNTf₂ was next evaluated. When reducing the amount of the ionizing agent to 1.2 equiv., while keeping the amount of limonene 5.0 equiv., the dienoate **5ab** was obtained

in 84% yield (Table 13, entry 2). Reducing the amount to 10 mol% resulted in a poor yield of the product (Table 13, entry 3). It was thus concluded that 1.2 equiv. of silver bistriflimide represented the best compromise between cost and atom economy.

Passing from 5.0 to 2.0 equiv. of limonene gave the dienoate **5ab** in 83%, when using 1.2 equiv. of silver bistriflimide, and in 86% when using 2.0 equiv. of the ionizing agent (Table 13, entries 4-5).

However, when maintaining 1.2 equiv. of silver bistriflimide and further reducing the limonene amount to 1.0 equiv., a slightly decreased yield of 79% was observed (Table 13, entry 6). In all cases, the coupling product **5ab** was obtained as a 60:40 to a 71:29 mixture of diastereoisomers, the major one being (*E,E*)-configured.

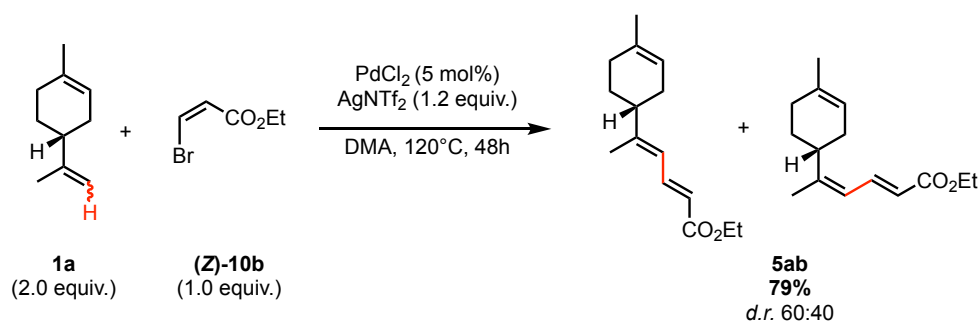


Entry ^[a]	1a (n equiv.)	AgNTF ₂ (m equiv.)	Conv. (%) ^[b]	5ab (%) ^[b]	d.r.
1	5	2	95	88	60:40
2	5	1.2	98	84	71:29
3	5	0.1	_[c]	10	_[c]
4	2	1.2	96	83	60:40
5	2	2	95	86	63:37
6	1	1.2	88	79	61:39

[a] typical reaction conditions: (+)-limonene **1a** (n equiv.), ethyl (*Z*)-3-bromoacrylate (**Z**)-**10b** (0.5 mmol), PdCl₂ (5 mol%), AgNTf₂ (m equiv.), DMA (0.2 M), 120 °C in an ace pressure tube; [b] measured by quantitative ¹H-NMR using 1,4-dinitrobenzene as an internal standard; [c] not determined because of overlapping NMR signals.

Table 13. Study of the amount of scavenger with respect to limonene.

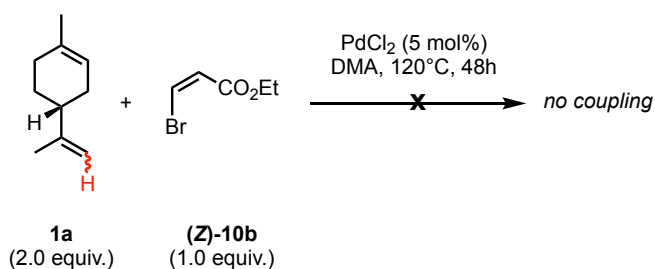
We can thus conclude that the best protocol for the palladium redox neutral [C–H/C–X] coupling implies treatment of (+)-limonene **1a** (2.0 equiv.) with ethyl (*Z*)-3-bromoacrylate (**Z**)-**10b** in the presence of palladium(II) chloride (5 mol%) as the catalyst and silver bistriflimide (1.2 equiv.) as the ionizing agent in DMA (0.2 M) at 120 °C, which affords the desired conjugated diene in 79% isolated yield, and a 60:40 diastereomeric ratio (Scheme 87).



Scheme 87. Optimized reaction conditions for the coupling between (+)-limonene and ethyl (Z)-3-bromoacrylate.

An ad hoc experiment for mechanistic purpose

To gain more information on the mechanism, a model coupling reaction was tested using stoichiometric amounts of PdCl₂ and in the absence of AgNTf₂. The failure to obtain a coupling product under these conditions suggests that a cationic Pd(II) species has to be present from the outset of the catalysis (Scheme 88).



Scheme 88. Attempted stoichiometric coupling in the absence of the ionizing agent.

2.3. Scope study of the coupling reaction

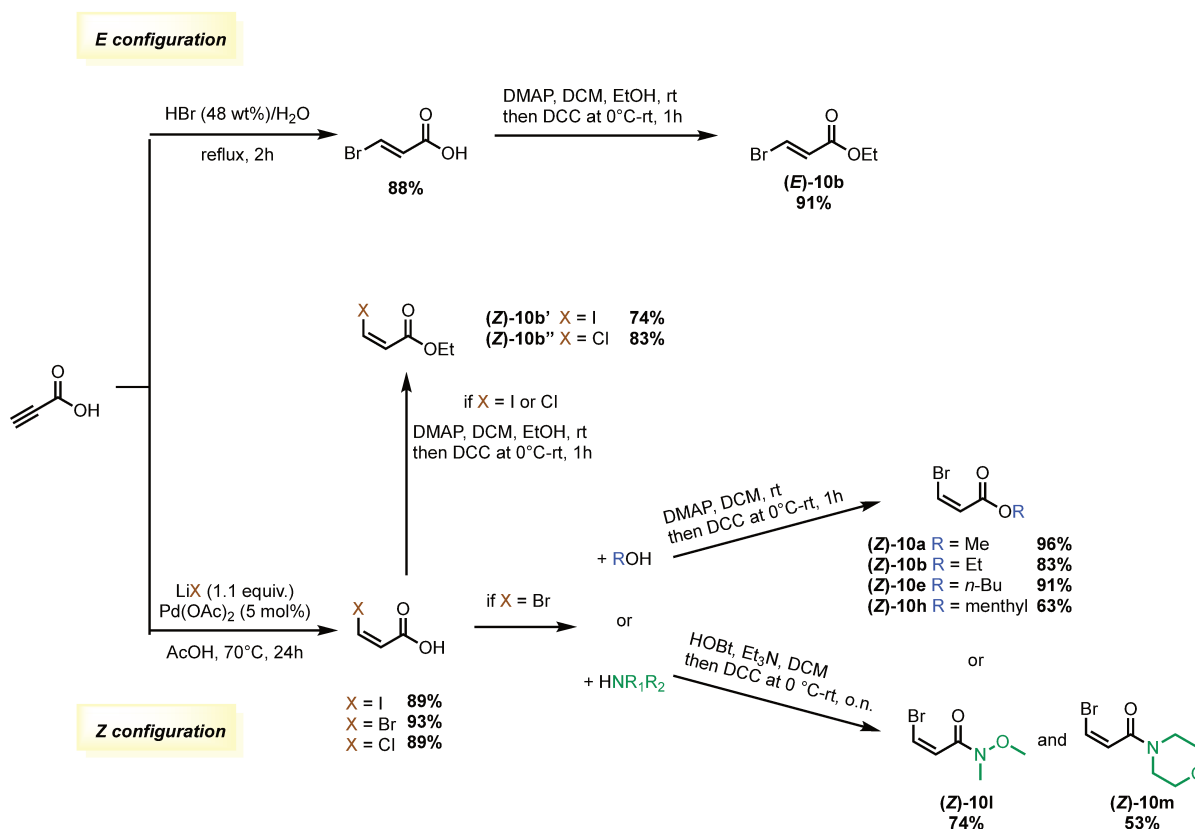
2.3.1. Synthesis of the commercially unavailable β-haloalkenes

Since the model reaction was successful, the synthesis of other haloalkenes was carried out following reported literature, in view of their utilization with the new coupling strategy. Accordingly, (*E*)-3-bromoacrylic acid was prepared by hydrobromination of propiolic acid with HBr (48 wt% aq.) in water at reflux for 2h (Scheme 89, top).^[150] The subsequent esterification with DCC / 4-DMAP (catalytic) and EtOH gave uneventfully the corresponding ester (**E**)-10b in high yield. The (*Z*)-3-haloacrylic acids were obtained in high yields by the reaction between propiolic acid and LiX (X = I, Br, Cl) in acetic acid in the presence of a catalytic amount of palladium(II) acetate (Scheme 89, bottom),^[151] and the subsequent

^[150] Faltracco, M.; Ruijter, E. *Org. Biomol. Chem.* **2021**, *19*, 9641-9644.

^[151] Ma, S.; Lu, X. *J. Chem. Soc., Chem. Commun.* **1990**, 1643-1644.

standard [DCC / cat. 4-DMAP]-mediated esterification with EtOH, MeOH, *n*-BuOH, and menthol gave the corresponding esters (**Z**-10a, **Z**-10b, **Z**-10b', **Z**-10b'', **Z**-10e, and **Z**-10h in moderate to excellent yields (Scheme 89, middle right).^[152] The (**Z**)-3-bromoacrylamides (**Z**-10l and **Z**-10m were prepared by the reaction between (**Z**)-3-bromoacrylic acid and *N,O*-dimethylhydroxylamine, or morpholine, in the presence of triethylamine and catalytic 4-DMAP in dichloromethane (Scheme 89, bottom right).^[153]

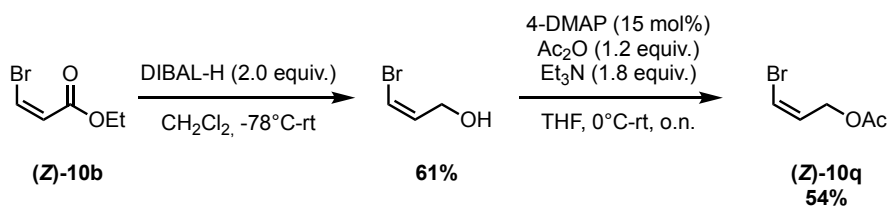


Scheme 89. Synthesis of 3-haloacrylates and acrylamides.

(**Z**)-3-Bromoallyl acetate (**Z**-10q) was obtained by reduction of the ester (**Z**-10b with DIBAL-H in dichloromethane, followed by standard acetylation of the resulting allylic alcohol (Scheme 90).

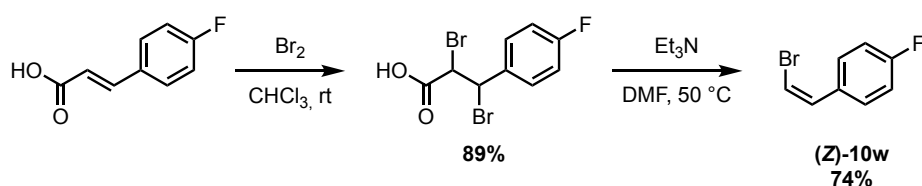
^[152] Kawasaki, T.; Yamamoto, Y. *J. Org. Chem.* **2002**, *67*, 2653-2658.

^[153] Yu, J. I.; Kim, H. R.; Kim, S. K.; Ki, D.; Lee, J. *Tetrahedron* **2012**, *68*, 1177-1184.



Scheme 90. Synthesis of (Z)-3-bromoallyl acetate.

(Z)-1-(2-bromovinyl)-4-fluorobenzene (**Z-10y**) was prepared via dibromination of 3-(4-fluorophenyl)acrylic acid in chloroform, followed by decarboxylative dehydrobromination^[154] (Scheme 91).



Scheme 91. Synthesis of (Z)-1-(2-bromovinyl)-4-fluorobenzene.

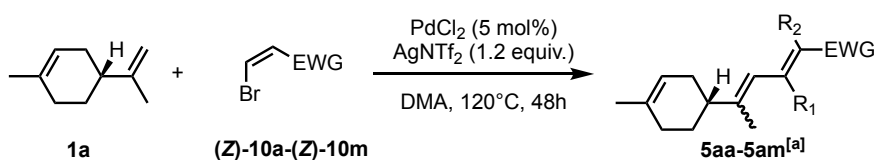
2.3.2. Coupling of the synthesized β -haloalkenes

With the optimized conditions in hand, [(+)-limonene **1a** (2.0 equiv.), (Z)-3-bromoacrylate (**Z-10a**-(**Z-10m**) (0.5 mmol), PdCl₂ (5 mol%), AgNTf₂ (1.2 equiv.), DMA (0.2 M), 120 °C in an ace pressure tube], the scope of this Pd(II)-catalyzed redox neutral coupling was next evaluated, by testing other bromoalkenes as reaction partners for (+)-limonene.

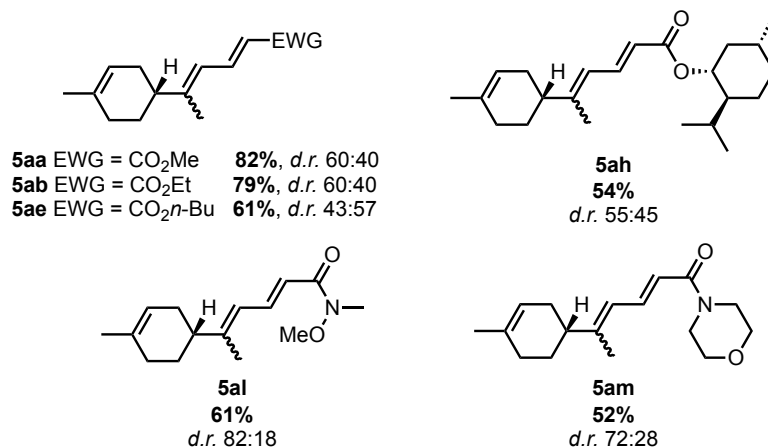
Accordingly, reacting limonene with methyl, ethyl and *n*-butyl 3-bromoacrylates (**Z-10a**, (**Z-10b**) and (**Z-10e**) under the optimized reaction conditions gave the expected corresponding dienoates **5aa**, **5ab** and **5ae** in 82%, 79% and 61% isolated yields respectively. Menthyl (Z)-bromoacrylate (**Z-10h**) also gave the corresponding dienoate **5ah** in 54% yield. Worthy of note, this coupling favorably compares with that of the corresponding dehydrogenative protocol (see Chapter 2), which gave a very low yield (see Chapter 2). The coupling with *N*-methoxy-*N*-methyl and morpholine (Z)-3-bromoacrylamides (**Z-10i**) and (**Z-10m**) afforded the desired conjugated dienes **5al** and **5am** in moderate yields of 61% and 52% respectively. These coupling appear to be less efficient, yet more diastereoselective, than those of the corresponding oxidative coupling. We only considered tertiary acrylamides, as primary^[155] and secondary acrylamides are expected to be incompatible with this coupling.

^[154] Kim, S. H.; Wei, H.-X.; Willis, S.; Li, G. *Synth. Commun.* **1999**, *29*, 4179-4185.

^[155] Xu, Y.-H.; Wang, W.-J.; Wen, Z.-K.; Hartley, J. J.; Loh, T.-P. *Tetrahedron Lett.* **2010**, *51*, 3504-3507.



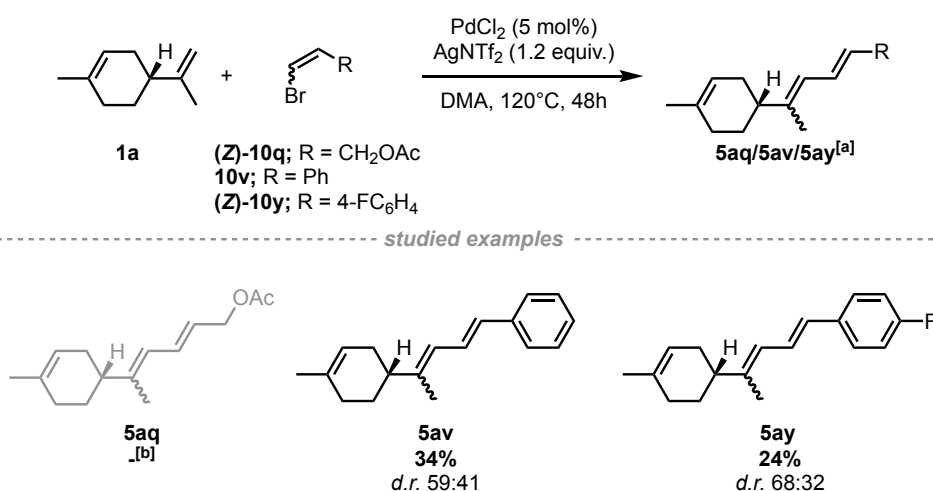
----- studied examples -----



[a] reaction conditions: (+)-limonene **1a** (2.0 equiv.), (Z)-3-bromoacrylate **(Z)-10a-(Z)-10m** (0.5 mmol), PdCl₂ (5 mol%), AgNTf₂ (1.2 equiv.), DMA (0.2 M), 120 °C in an ace pressure tube.

Scheme 92. Evaluation of bromoacrylates as coupling partners for the Pd-catalyzed [C-H/C-X] reaction of (+)-limonene.

Unfortunately, (Z)-3-bromoallyl acetate **(Z)-10q** did not afford a coupling product. This result contrasts with the oxidative coupling between limonene and allyl acetate, which satisfactorily afforded diene **5aq** (see Chapter 2). On the other hand, β-bromostyrene^[156] **10v** and (Z)-β-bromo-4-fluorophenyl)ethylene **(Z)-10y** gave the corresponding dienes **5vv** and **5ay** in 34% and 24% yield, respectively.¹⁵⁷



[a] reaction conditions: (+)-limonene **1a** (2.0 equiv.), (Z)-3-bromoacrylate **(Z)-10q/10v/(Z)-10y** (0.5 mmol), PdCl₂

^[156] Commercially available as a mixture of (E) and (Z) isomers.

^[157] This part of project was accomplished with in collaboration with PhD student Tullio Crovetto.

(5 mol%), AgNTf₂ (1.2 equiv.), DMA (0.2 M), 120 °C in an ace pressure tube [b] no conversion.

Scheme 93. Evaluation of other bromoalkenes as coupling partners in the C–H/C–X coupling with (+)-limonene.

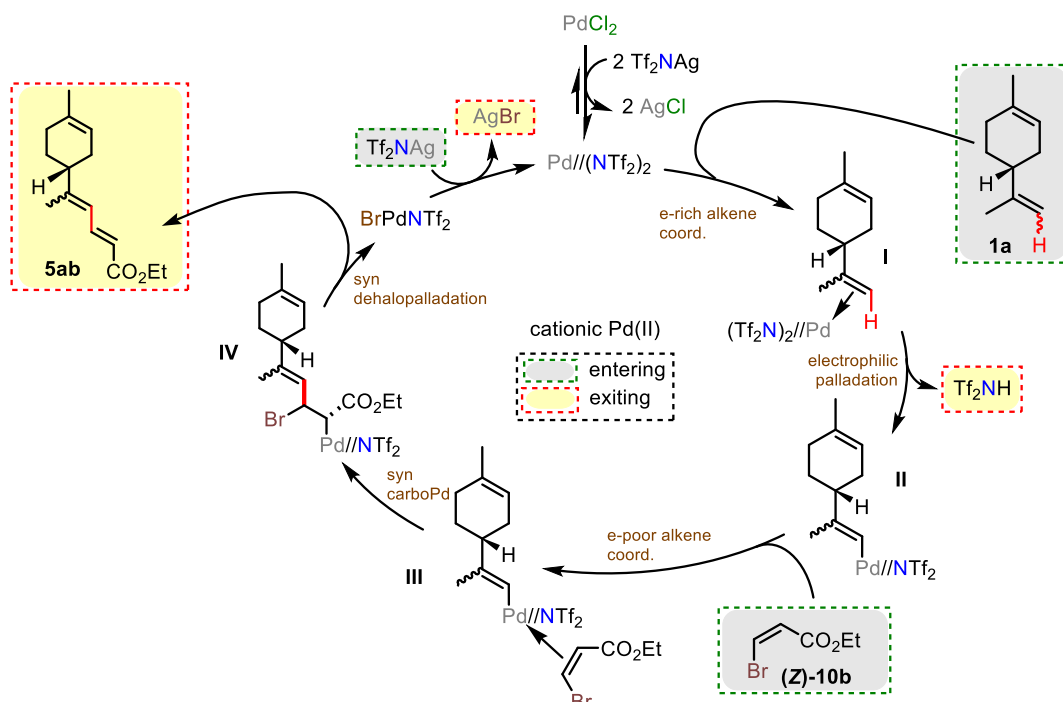
To sum up, the reaction conditions appear to be compatible with alkene substrates, including acrylates, acrylamides and some styrenyl derivatives, albeit with low yields.

2.4. Mechanistic proposal

On the basis of the literature data^[63] and our own results, we propose for this redox neutral Pd(II)-catalyzed C(sp²)–H/C(sp²)–X coupling reaction the following mechanism. The interaction between polymeric PdCl₂ and AgNTf₂ leads to the dicationic catalyst Pd(II)//(NTf₂)₂,^[158] likely coordinated by four molecules of DMF.^[159] After coordination by the electron-rich cyclic alkene of (+)-limonene to Pd(II), the resulting intermediate **I** undergoes electrophilic palladation to generate the vinyl palladium intermediate **II** as an E/Z mixture of geometrical isomers. Coordination by the electron-poor haloalkene followed by a regioselective *syn* carbopalladation of the resulting intermediate **III**, generates intermediate **IV**. Then, *syn* debromopalladation (β-Br elimination) generates the final coupled product. Finally, ionization of the resulting BrPdNTf₂ by AgNTf₂ regenerates the starting cationic Pd(II) catalyst (Scheme 94).

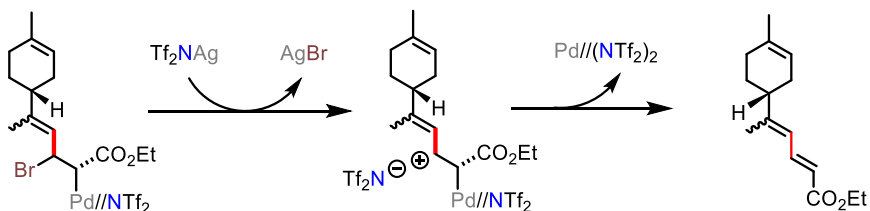
^[158] (a) Stang, P. J.; Cao, D. H. *J. Am. Chem. Soc.* **1994**, *116*, 4981-4982; (b) Stang, P. J.; Cao, D. H.; Poulter, G. T.; Arif, A. M. *Organometallics* **1995**, *14*, 1110-1114.

^[159] For a review on dissociating solvents, see: Muzart, J. *Tetrahedron* **2009**, *65*, 8313-8323.



Scheme 94. Proposed mechanism for the PdX_2 catalyzed coupling between (+)-limonene and ethyl 3-bromoacrylate.

Though, as suggested by Muzart and Le Bras,^[160] the halide scavenging could alternatively take place directly from intermediate **IV** (Scheme 95). Finally, the known Pd(II)-catalyzed 2Z-to-2E equilibration of alkenes rationalizes the fact that only the 2E geometrical isomer is observed in the coupling.^[161]



Scheme 95. Alternative final part of the mechanism of the PdX_2 catalyzed coupling between (+)-limonene and ethyl 3-bromoacrylate.

^[160] Le Bras, J.; Muzart, J. *Chem. Rev.* **2011**, *111*, 1170–1214.

^[161] For reported Pd(II)-catalyzed isomerization of alkenes see: (a) Yu, J. Q.; Gaunt, M. J.; Spencer, J. B. *J. Org. Chem.* **2002**, *67*, 4627–4629; (b) Giles, R. G. F.; Son, V. R. L.; Sargent, M. V. *Aust. J. Chem.* **1990**, *43*, 777–781; (c) Thiery, E.; Chevrin, C.; Le Bras, J.; Harakat, D.; Muzart, J. *J. Org. Chem.* **2007**, *72*, 1859–1862; (d) Fan, J.; Wan, C.; Wang, Q.; Gao, L.; Zheng, X.; Wang, Z. *Org. Biomol. Chem.* **2009**, *7*, 3168–3172; (e) Liron, F.; Fontana, F.; Zirimwabagabo, J.-O.; Prestat, G.; Rajabi, J.; La Rosa, C.; Poli, G. *Org. Lett.* **2009**, *11*, 4378–4381.

In summary, this Pd(II)-catalyzed C(sp²)-H/C(sp²)-X strategy proves to be more efficient than the corresponding Pd(II)-catalyzed C(sp²)-H/C(sp²)-H dehydrogenative coupling described in chapter 2, needing a lower catalytic loading and of the silver salt. In contrast to the well-known Pd(0)-catalyzed C(sp²)-H/C(sp²)-X Mizoroki-Heck protocol, this new coupling features an isohypsic mechanism, all the intermediates along the catalytic cycle staying at +2 formal oxidation state. Both the dehydrogenative (chapter 2) as well as the redox-neutral (this chapter) couplings need important amounts of a silver salt to close the catalytic cycle. However, their role in the two protocols is radically different. While in the oxidative coupling the role of the silver salt is to bring the oxidation state of the palladium complex back from 0 to +2, in the redox-neutral protocol the role is to create (from PdCl₂) and to regenerate (from BrPdNTf₂) a cationic palladium complex. To the best of our knowledge, this is the first example of a Pd(II)-catalyzed C(sp²)-H/C(sp²)-X coupling involving an alkene and a vinyl halide, and is complementary with respect to the Pd(0)-catalyzed Mizoroki-Heck manifold, allowing the coupling of 1,1-disubstituted alkenes, where the Mizoroki-Heck protocol fails. Being limonene a very cheap natural product, and the protocol requiring a tiny amount of palladium catalyst, this regioselective coupling represents an ideal step-economical method that meets some requirements of green chemistry. However, this strategy has two limitations: a) important amounts of a silver salt are needed; b) most of the required halo-alkenes or (pseudo)halo-alkenes are not commercially available.

As to the perspectives, replacement of DMA with an alternative green and non-toxic solvent is planned, as well as adaptation of this strategy to micellar conditions. Also, more 1,1-disubstituted alkenes will be tested as starting alkenes to enlarge the scope of the method. Finally, transposition of the method from Pd- to the less expensive Ni-catalysis is another possible topic for future investigations.

Chapter 5: Approaches to the Total Synthesis of Cannabidiol

1. Introduction

In addition to the main project devoted to the study of new methods for the selective C–H functionalization of terpenes, the thesis plan also included a secondary, synthesis-oriented, project devoted to the study of new approaches toward cannabidiol (CBD). This chapter contains the preliminary studies carried out within this framework.

Accordingly, a brief review of CBD will be presented below, followed by the work carried out to this end.

1.1. Generalities about Cannabidiol

Cannabis sativa L., commonly known as cannabis or marijuana, is a hemp species originating from East Asia.^[162] It has been cultivated for centuries for various purposes, including as a source of fibers, as a recreational substance, and for its medicinal properties. Among the more than 500 compounds identified in *Cannabis sativa L.*, the primary active components are cannabinoids, such as tetrahydrocannabinol (THC) and cannabidiol (CBD).^[163]

In human biology, the regulatory pathway influenced by cannabinoids is known as the endocannabinoid system (ECS).^[164] The ECS consists in two primary receptor types, CB₁R and CB₂R, and is supported by enzymes responsible for synthesizing and breaking down their endogenous ligands.^[165] While THC is notorious for its psychoactive effects, primarily through its agonistic activity on the CB₁ receptor, CBD, on the other hand, does not induce psychotomimetic effects and is more closely examined for its pharmacological potency.^[166]

^[162] Ren, G.; Zhang, X.; Li, Y.; Ridout, K.; Serrano-Serrano, M. L.; Yang, Y.; Liu, A.; Ravikanth, G.; Nawaz, M. A.; Mumtaz, A. S.; Salamin, N.; Fumagalli, L. *Sci. Adv.* **2021**, *7*, eabg2286.

^[163] Aizpurua-Olaizola, O.; Soydaner, U.; Öztürk, E.; Schibano, D.; Simsir, Y.; Navarro, P.; Etxebarria, N.; Usobiaga, A. *J. Nat. Prod.* **2016**, *79*, 324–331.

^[164] Amenta, A.; Caprioglio, D.; Minassi, A.; Panza, L.; Passarella, D.; Fasano, V.; Imperio, D. *Front. Nat. Produc.* **2023**, *2*, 1–14.

^[165] De Petrocellis, L.; Di Marzo, V. *Best. Pract. Res. Clin. Endocrinol. Metabolism* **2009**, *23*, 1–15.

^[166] Hložek, T.; Uttl, L.; Kadeřábek, L.; Balíková, M.; Lhotková, E.; Horsley, R. R.; Nováková, P.; Šichová, K.; Štefková, K.; Tylš, F.; Kuchař, M.; Páleníček, T. *Eur. Neuropsychopharmacol.* **2017**, *27*, 1223–1237.

CBD research has explored its therapeutic potential in various applications, particularly as an anticonvulsant for Dravet and Lennox-Gastaut syndromes, up until the approval of Epidiolex[®] (GW Pharmaceuticals) by the Food and Drug Administration (FDA) in 2018.^[167]

Indeed, the deleterious effects met in THC, such as increased panic, anxiety and psychosis, have not been found in CBD, whose administration does not present any major risk.^[168] Subsequently, cannabidiol and its non-psychotropic analogs have gained considerable attention reaching a market size of \$6.4B in 2022.^[169] In addition, a flourishing variety of CBD-derived products, such as oils, resins, flowers, or cosmetics has emerged on the market.

The first successful reports on CBD isolation and characterization were done in the mid 1940's. Drawing from earlier methods for CBD isolation,^[170] the groups of Adams and Todd separately achieved the first partial characterization of (-)-CBD using oils and resins from *Cannabis sativa* and *C. indica* respectively,^[171] while attempting to isolate cannabinol (CBN, **13**), another cannabinoid from the *Minnesota Wild Hemp* species.^[172] CBD **1** and THC **2** are structural isomers, the latter being a cyclized form of the first one. Indeed, the cyclization from CBD to THC has been first reported by Mechoulam in 1966.^[173]

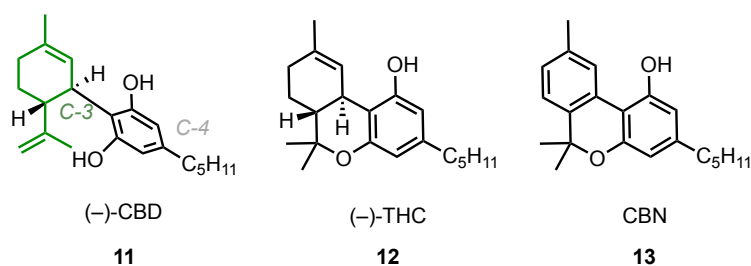


Figure 9. Structures of cannabidiol **1**, tetrahydrocannabinol **2** and cannabinol **3**.

^[167] (a) Devinsky, O.; Patel, A. D.; Thiele, E. A.; Wong, M. H.; Appleton, R.; Harden, C. L.; Greenwood, S.; Morrison, G.; Sommerville, K.; *Neurology* **2018**, *90*, e1204; (b) Devinsky, O.; Cilio, M. R.; Cross, H.; Fernandez-Ruiz, J.; French, J.; Hill, C.; Katz, R.; Di Marzo, V.; Jutras-Aswad, D.; Notcutt, W. G.; Martinez-Orgado, J.; Robson, P. J.; Rohrbach, B. G.; Thiele, E.; Whalley, B.; Friedman, D. *Epilepsia* **2014**, *55*, 791–802; (c) Devinsky, O.; Patel, A. D.; Cross, J. H.; Villanueva, V.; Wirrell, E. C.; Privitera, M.; Greenwood, S. M.; Roberts, C.; Checketts, D.; Van Landingham, K. E.; Zuberi, S. M. *N. Engl. J. Med.* **2018**, *378*, 1888–1897; (d) Santos, A. B.; Scherf, J. R.; Mendes, R. D. C. *Acta Bras.* **2019**, *3*, 30.

^[168] (a) D'Souza, D. C.; Perry, E.; MacDougall, L.; Ammerman, Y.; Cooper, T.; Wu, Y.; Braley, G.; Gueorguieva, R.; Krystal, J. H. *Neuropsychopharmacol.* **2004**, *29*, 1558–1572; (b) Sharma, A. A.; Nenert, R.; Allendorfer, J. B.; Gaston, T. E.; Grayson, L. P.; Hernando, K.; Szaflarski, J. P. *Epilepsy & Behav. Reports* **2019**, *12*, 100341.

^[169] <https://www.grandviewresearch.com/industry-analysis/cannabidiol-cbd-market>

^[170] (a) Cahn, R. S. J. *Chem. Soc.* **1930**, 986–992; (b) Cahn, R. S. J. *Chem. Soc.* **1933**, 1400; (c) Cahn, R. S. J. *Chem. Soc.* **1932**, 1342–1353; (d) Wood, T. B.; Spivey, W. T. N.; Easterfield, T. H. *J. Chem. Soc. Trans.* **1899**, *75*, 20–36; (e) Work, T. S.; Bergel, F.; Todd, A. R. *Biochem. J.* **1939**, *33*, 123–127.

^[171] (a) Jacob, A.; Todd, A. R. *Nature* **1940**, *145*, 350; (b) Todd, A. R. *Experientia* **1946**, *2*, 55–60; (c) Adams, R.; Hunt, M.; Clark, J. H. *J. Am. Chem. Soc.* **1940**, *62*, 196–200; (d) Adams, R.; Baker, B. R.; Wearn, R. B.; *J. Am. Chem. Soc.* **1940**, *62*, 2204–2207; (e) Adams, R.; Baker, B. R. *J. Am. Chem. Soc.* **1940**, *62*, 2405–2408.

^[172] Wood, T. B.; Spivey, W. T. N.; Easterfield, T. H. *J. Chem. Soc., Trans.* **1896**, *69*, 539–546.

^[173] Gaoni, Y.; Mechoulam, R. *Tetrahedron* **1966**, *22*, 1481–1488.

CBD can be isolated through various methods, including solvent or ultrasonic extraction. However, supercritical CO₂ extraction is often the preferred choice due to its efficiency in isolating the desired compound using a non-toxic and safe solvent that leaves no residue.^[174] Furthermore, the therapeutic benefits of using the molecule in combination with its surrounding extracts are suspected to be more effective in treating epilepsy than using the pure compound alone.^[175]

However, with the expanding interest towards CBD for its medicinal, relaxing, or recreational properties, access to this drug *via* organic synthesis may become a competitive alternative, with the added benefit of allowing the synthesis of potentially interesting non-natural analogs.

1.2. A selection of previously reported synthetic pathways toward CBD

Several total syntheses leading to CBD in racemic^[176] as well as in enantioselective form^[177] have been reported in the literature. Although a comprehensive description of these approaches is out of the scope of this manuscript, three main synthetic strategies will be briefly outlined here below. The probably most intuitive synthetic strategy toward CBD is based on the formal coupling between limonene (at the C-3 position) and olivetol (a resorcinol with an n-pentyl chain at the C-4 position). Evolutions of this type of approach are of particular interest to our laboratory, as they can be related to C–H activation approaches. Another approach involves the addition of an olivetol-derived organometallic species to mentha-diene-1-ol, an C₁₀ intermediate deriving from limonene. Yet, another entirely different approach builds the limonene carbocycle by ring closing metathesis (Figure 10).

^[174] Karđılı, U.; Aytacı, E. *J. Supercrit. Fluids.* **2022**, *179*, 105410.

^[175] Pamplona, F. A.; da Silva, L. R.; Coan, A. C. *Frontiers in Neurology* **2018**, *9*, 759.

^[176] For selected examples see: (a) Mechoulam, R.; Gaoni, Y. *J. Am. Chem. Soc.* **1965**, *87*, 3273–3275; (b) Korte, F.; Hackel, E.; Sieper, H. *Justus Liebigs Ann. Chem.* **1965**, *685*, 122-128; (c) Korte, F.; Dlugosch, E.; Claussen, U. *Justus Liebigs Ann. Chem.* **1966**, *693*, 165-170; (d) Kōchi, H.; Matsui, M. *Agric. Biol. Chem.* **1967**, *31*, 625-627; (e) Childers, W. E.; Pinnick, H. W. *J. Org. Chem.* **1984**, *49*, 5276-5277.

^[177] Aguillón, A. R.; Leão, R. A. C.; Miranda, L. S. M.; de Souza, R. O. M. A. *Chem. Eur. J.* **2021**, *27*, 5577-5600.

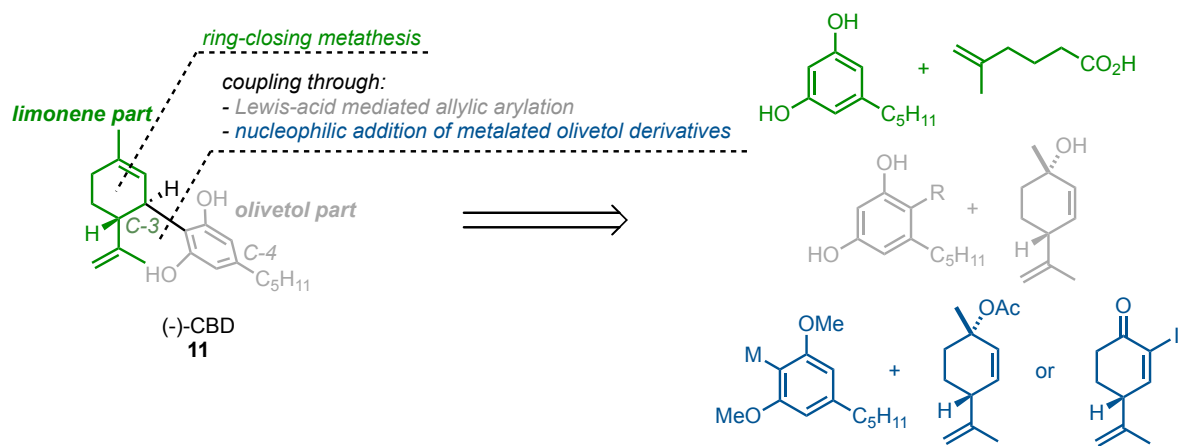
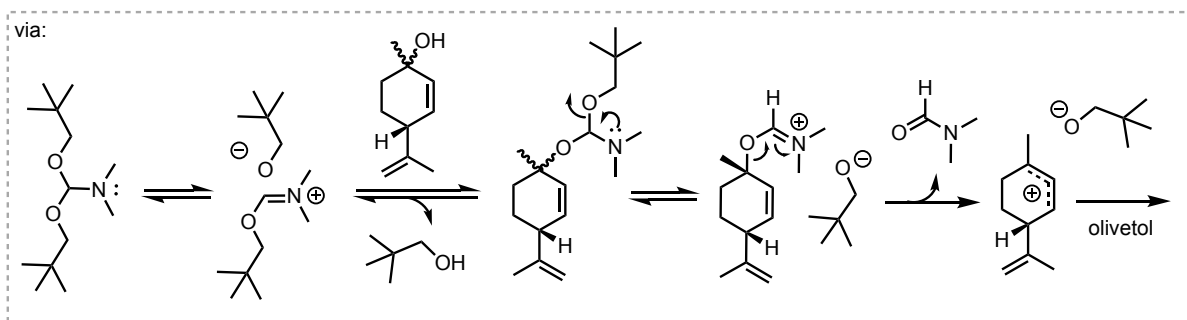
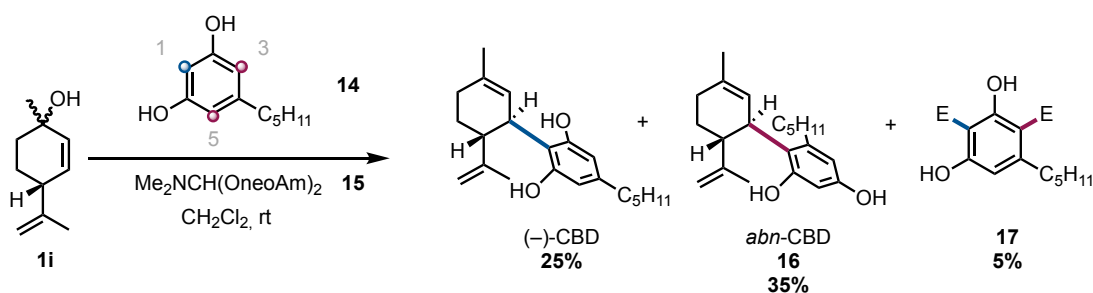


Figure 10. Previously reported main methods for the total synthesis of (-)-CBD.

1.2.1. Lewis-acid mediated arylation of terpenic allylic cations.

In 1969, Petrzilka reported the first stereoselective synthesis of (-)-CBD, whose final step consisted in the treatment of (+)-*p*-mentha-diene-1-ol **1i** (as a mixture of (*R*)-*cis* and (*R*)-*trans* isomers) with *N,N*-dimethylformamide dineopentyl acetal **15** (Meerwein acetal) and olivetol **14**.^[178] The mechanism of the coupling is expected to involve the initial formation of a mixed acetal via ionization of *N,N*-dimethylacetamide dimethyl acetal. Subsequent reionization through formation of a new alkoxyiminium ion intermediate and DMF departure generates an allylic cation, which undergoes the Friedel-Crafts reaction with olivetol producing three products (Scheme 96).

^[178] Petrzilka, T.; Haefliger, W.; Sikemeier, C. *Helv. Chim. Acta* **1969**, *52*, 1102–1134.



Scheme 96. Petrziilka's strategy towards (-)-CBD.

Thus, olivetol **14** exhibits two non-equivalent reactive sites in the electrophilic aromatic substitution. Indeed, reaction at position **1** afforded (-)-CBD in 25% yield (blue bond), while reaction at the equivalent positions **3** and/or **5** (purple bond) gives rise to the "abnormal" CBD isomer *abn*-CBD **16** in 35% yield. Furthermore, a small amount of the 1,3-diallylated product **17** was formed in 5% yield, and 30% of unreacted olivetol was also recovered. On the other hand, the condensation between (+)-*p*-mentha-diene-1-ol **1i** and olivetol **14** in presence of Brønsted acids^[179] (such as *p*-toluenesulfonic acid or hydrochloric acid) or Lewis acids^[180] (such as $\text{BF}_3 \cdot \text{OEt}_2$) leads directly to the structural isomer (-)-THC **12**, which in turn derives from cyclization of CBD. For this reason, several research groups investigated the acid-catalyzed cyclization of (-)-CBD to form the THC skeleton employing various Lewis or protic acids.^[181]

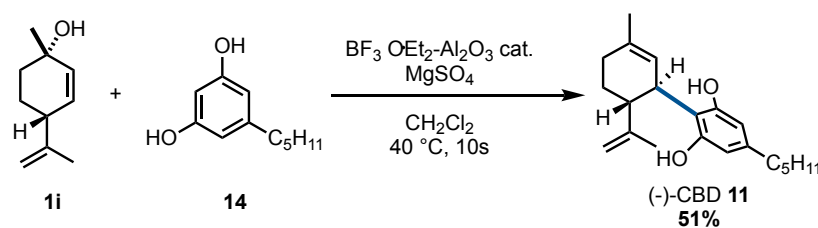
Mechoulam and coworkers^[182] made a significant improvement to the above coupling by replacing the sacrificial Meerwein acetal with basic alumina (Al_2O_3)-supported $\text{BF}_3 \cdot \text{OEt}_2$ as a Lewis acid catalyst (Scheme 97).

^[179] Petrziilka, T.; Haefliger, W.; Sikemeier, C.; Ohloff, G.; Eschenmoser, A. *Helv. Chim. Acta* **1967**, *50*, 719–723.

^[180] (a) Radzan, R. K.; Dalzell, H. C.; Handrick, G. R. *J. Am. Chem. Soc.* **1974**, *96*, 5860–5865; (b) Handrick, G. R.; Uliss, D. B.; Dalzell, H. C.; Razdan, R. K. *Tetrahedron Lett.* **1979**, *20*, 681–684; (c) Razdan, R. K.; Puttick, A. J.; Zitko, B. A.; Handrick, G. R. *Experientia* **1972**, *28*, 121–122.

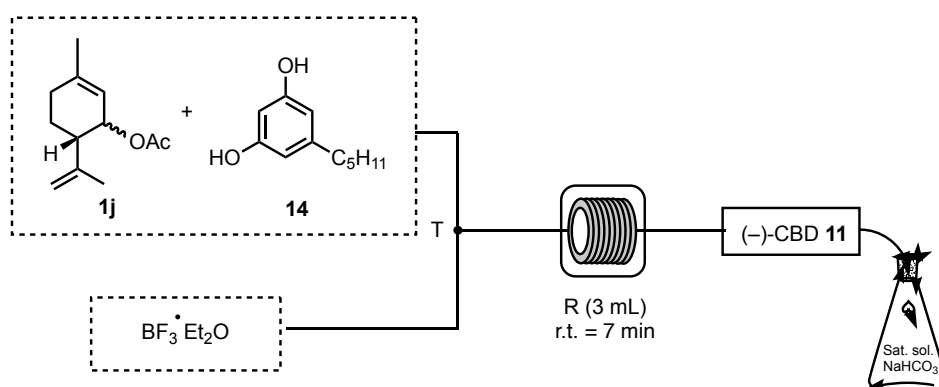
^[181] (a) Marzullo, P.; Foschi, F.; Coppini, D. A.; Fanchini, F.; Magnani, L.; Rusconi, S.; Luzzani, M.; Passarella, D. *J. Nat. Prod.* **2020**, *83*, 2894–2901; (b) Bassetti, B.; Hone, C. A.; Kappe, C. O. *J. Org. Chem.* **2023**, *88*, 6227–6231.

^[182] Baek, S.-H. H.; Srebnik, M.; Mechoulam, R. *Tetrahedron Lett.* **1985**, *26*, 1083–1086.



Scheme 97. Modification of (-)-CBD synthesis proposed by Mechoulam and coworkers.

Recently, the group of Palmieri developed a continuous flow variant of the Mechoulam synthetic strategy towards cannabidiol (and its structural analogs).^[183] Specifically, treatment of *p*-menthadiene-3-ol acetate **1j** with olivetol **14** in presence of boron trifluoride etherate delivered (-)-CBD in 55% yield, together with *abn*-CBD **16** and diallylated olivetol **17** in 19% and 4% yield respectively. Prevention of THC formation (GC <0.4%) could be obtained by direct quench of the outcoming flow with a saturated solution of NaHCO₃ (Scheme 98).



Scheme 98. General apparatus for the continuous flow synthesis of (-)-CBD.

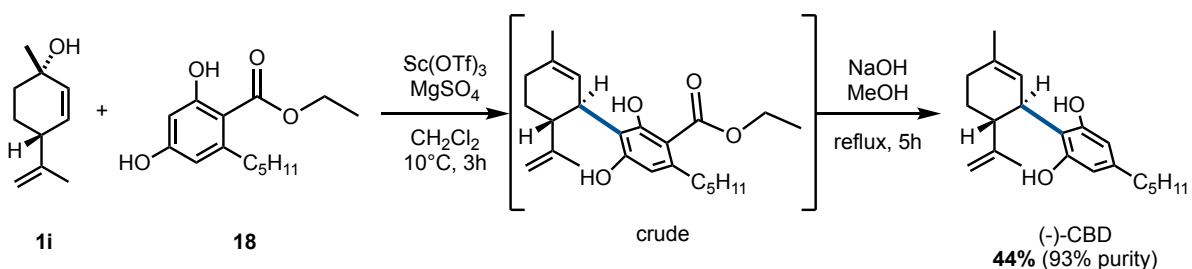
1.2.2. Attempts to increase the regioselectivity

In an effort to increase the yield of the desired product (-)-CBD while minimizing the formation of byproducts *abn*-CBD **16** and **17**, researchers devised different fundamental modifications to enhance both selectivity and efficiency. One approach involved employing the esters of olivetolic acid **18** as a temporarily substituted olivetol surrogate to carry out the Friedel-Crafts allylation in a two-step linear process.^[184] For instance, Burdick and coworkers^[185] achieved this coupling using Sc(OTf)₃ as the catalyst (Scheme 99).

^[183] Chiurchiù, E.; Sampaolesi, S.; Allegrini, P.; Ciceri, D.; Ballini, R.; Palmieri, A. *Eur. J. Org. Chem.* **2021**, 2021, 1286–1289.

^[184] (a) Steup, C.; Herkenroth, T. US2010298579A1, **2009**; (b) Chen, J.; Li, B.; Gu, Z. CN109734591, **2018**.

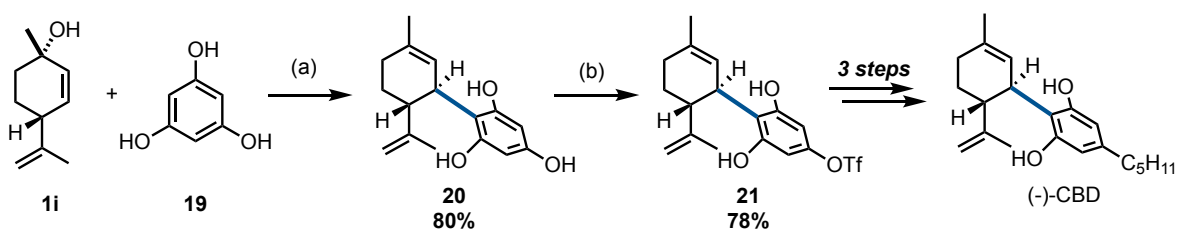
^[185] Burdick, D. C.; Collier, S. J.; Jos, F.; Biolatto, B.; Paul, B. J.; Meckler, H.; Helle, M. A.; Habershaw, A. J. US2007093665-A1, **2005**.



Scheme 99. Lewis acid mediated addition of ethyl cannabidiolate **18** in the presence of $\text{Sc}(\text{OTf})_3$.

While the methodology described by Burdick *et al.* yielded the targeted compound without a significant improvement in terms of yield and purity, the use of scandium(III) triflate as a catalyst offers distinct advantages. Unlike typical Lewis acid such as $\text{BF}_3 \cdot \text{OEt}_2$, which can decompose or deactivate in the presence of water, scandium triflate remains stable in aqueous solutions. Additionally, the catalyst can be recovered almost quantitatively from the aqueous layer upon completing the reaction.

In another approach, Gong and Aisa^[186] successfully employed phloroglucinol **19** and **1i** as key intermediates in a five-step linear strategy (Scheme 100). The intermediate **20** was first prepared by carrying out the Friedel-Crafts allylation between **1i** and an excess (10 equiv.) of **19** in the presence of $\text{BF}_3 \cdot \text{OEt}_2$. After selective conversion of the phenolic hydroxyl group in *para* position into the corresponding triflate **21**, (-)-cannabidiol was obtained by *O*-protection of the two remaining phenolic hydroxy groups as pivalate esters, subsequent Negishi cross-coupling to substitute the triflate group with the *n*-pentyl chain, and final deprotection of the pivalate esters. The elegant point of this approach consists in the use of phloroglucinol, which, thanks to its symmetry, does not imply regioselectivity issues in the Friedel-Crafts allylation.



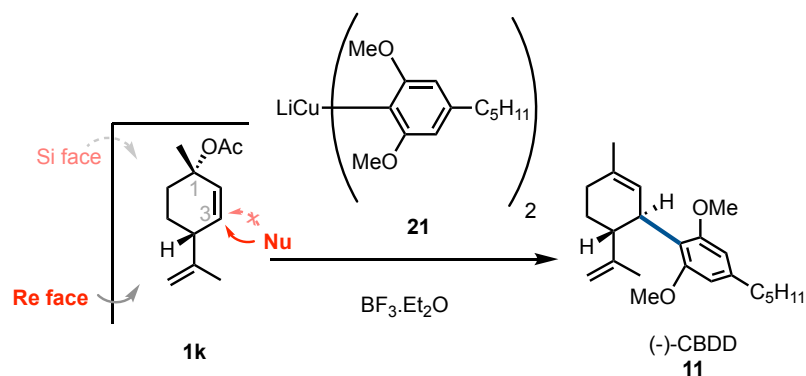
Reagents and conditions: (a) $\text{BF}_3 \cdot \text{Et}_2\text{O}$ (10 mol%), phloroglucinol **19** (10.0 equiv.), THF, -10°C to 0°C , 2h, 80%; (b) Tf_2O (1.0 equiv.), phenol **20** (1.5 equiv.), 2,6-lutidine (2.0 equiv.), CH_2Cl_2 , -30°C to -20°C , 30 min, 78%.

Scheme 100. Total synthesis of (-)-CBD reported by Aisa.^[186]

^[186] Gong, X.; Sun, C.; Abame, M. A.; Shi, W.; Xie, Y.; Xu, W.; Zhu, F.; Zhang, Y.; Shen, J.; Aisa, H. A. *J. Org. Chem.* **2020**, *85*, 2704-2715.

1.2.3. Aromatic coupling mediated by organometallic species

Aiming to circumvent the above mentioned regioselectivity issue in the construction of cannabinoid framework, Rickards reacted the higher order olivetol-derived diaryl cuprate **21** with (1*S*,4*R*)-*p*-mentha-2,8-dien-1-yl acetate **1k**. The boron trifluoride etherate-catalyzed coupling took place cleanly in an S_N2' fashion and was totally stereoselective.^[187] In fact, while the methyl group at position 1 prevents nucleophilic attack via a S_N2 type substitution, the isopropenyl moiety hinders the *Si* side of C-3 position, favoring the approach from the *Re* side. As in the strategy of Mechoulam, CBD was obtained by methylether deprotection with excess of methylmagnesium iodide at 160°C (Scheme 101).

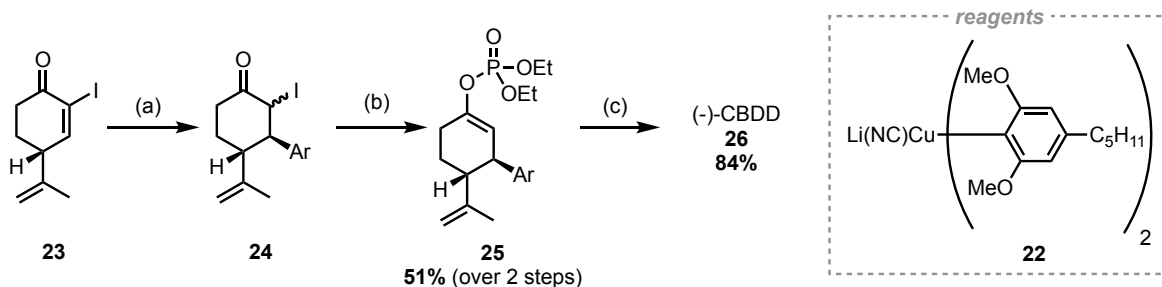


Scheme 101. Key step of diaryl cuprate-based S_N2' reaction in Rickard's synthesis of (-)-CBDD X.

In a related approach, Kobayashi and co-workers reported the conjugate addition of the olivetol-derived higher order cyanocuprate **22** to α -iodocyclohexenone **23**,^[188] which again placed the aryl group *trans* to the isopropenyl moiety. Metal-halogen exchange from the α -iodo ketone **24** was achieved upon treatment with EtMgBr to give the corresponding magnesium enolate (not represented), which was trapped with diethyl chlorophosphate. The resulting enol phosphate **25** provided (-)-CBDD **26**, or (-)-CBD **11** after few synthetic steps, including methylether deprotection. Despite the successful coupling between the terpenoid and the resorcinol moieties, the subsequent steps to the target cannot be considered straightforward (Scheme 102).

^[187] Rickards, R. W.; Roenneberg, H. *J. Org. Chem.* **1984**, *49*, 572–573.

^[188] (a) William, A. D.; Kobayashi, Y. *Org. Lett.* **2001**, *3*, 2017–2020; (b) William, A. D.; Kobayashi, Y. *J. Org. Chem.* **2002**, *67*, 8771–8782; (c) Kobayashi, Y.; Takeuchi, A.; Wang, Y.-G. *Org. Lett.* **2006**, *8*, 2699–2702.



Reagents and conditions: (a) $\text{BF}_3 \cdot \text{Et}_2\text{O}$ (1.0 equiv.), **23** (3.0 equiv.), Et_2O , -78°C , 2h; (b) EtMgBr (1.5 equiv.), THF, 0°C then diethyl chlorophosphonate (2.5 equiv.), 0°C , 2h, 51% from **25** (over 2 steps); (c) $\text{Ni}(\text{acac})_2$ (20 mol%), MeMgCl (2.4 equiv.), THF, rt, overnight, 84%.

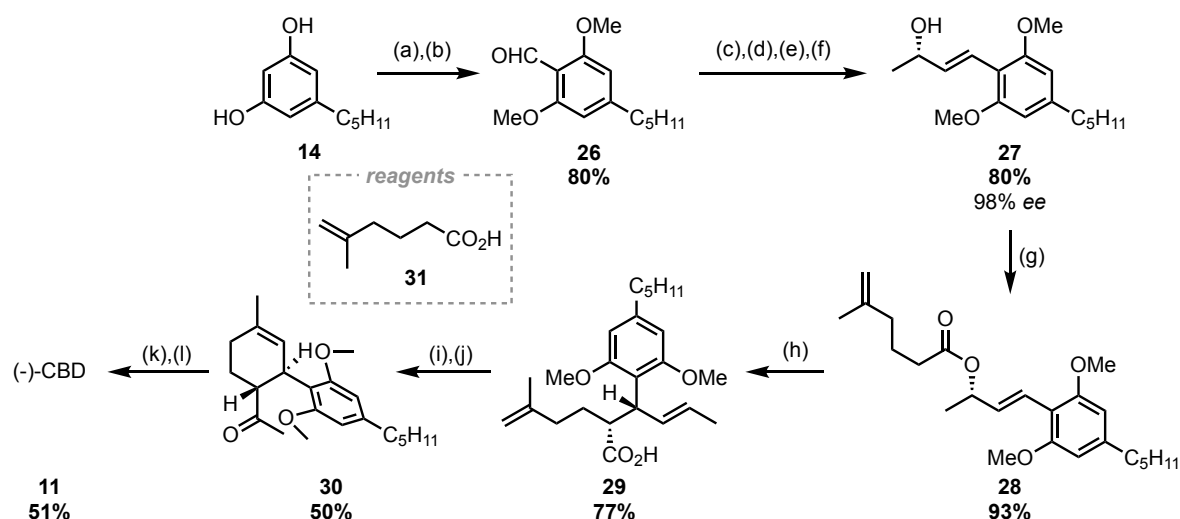
Scheme 102. α -Iodocyclohexenone-based synthesis of (-)-CBDD 11.

1.2.4. Building of the limonene scaffold by ring closing metathesis

Rather than combining olivetol **14** (or its derivative) with monoterpene precursors, other researchers investigated enantioselective cyclizations as a means to build the cyclohexene ring of (-)-CBD.^[189] Leahy recently accomplished a total synthesis of CBD, as outlined in Scheme 103.^[190] The process begins with the conversion of olivetol **14** to aldehyde **26** through a series of steps involving *O*-dimethylation and formylation. Aldol condensation, reduction, and kinetic resolution (or asymmetric reduction) then yielded alcohol **27**. This compound is esterified with acid **31**, and the resulting ester **28** is subjected to an Ireland–Claisen rearrangement, to afford **29** as the sole product. Further steps involve conversion of the acid to the methyl ketone and ring-closing metathesis to generate **30**. A Wittig methylenation of the ketone and deprotection with MeMgI leads to (-)-CBD. While these achievements demonstrate the capabilities of modern organic synthesis to reach CBD, neither of these approaches provides a definitive solution for a large and sustainable supply of CBD as an active pharmaceutical ingredient (API).

^[189] Ballerini, E.; Minuti, L.; Piermatti, O. *J. Org. Chem.* **2010**, *75*, 4251-4260.

^[190] (a) Shultz, Z. P.; Lawrence, G. A.; Jacobson, J. M.; Cruz, E. J.; Leahy, J. W. *Org. Lett.* **2018**, *20*, 381-384; (b) Leahy, J. W.; Shultz, Z. P.; Lawrence, G. A. US2019023680, **2018**.



Reagents and conditions: (a) K_2CO_3 (3.0 equiv.), Me_2SO_4 (3.0 equiv.), acetone, $80^\circ C$, 8h, 98%; (b) *s*-BuLi (1.2 equiv.), TMEDA (1.2 equiv.), THF, $-78^\circ C$ - $0^\circ C$, 1.5h then DMF (1.2 equiv.), THF, $0^\circ C$ -rt, 1.5h, 85%; (c) aq. NaOH (3.4 equiv.), acetone (5.0 equiv.), water, $60^\circ C$, 12h, 89%; (d) $NaBH_4$ (1.1 equiv.), EtOH, rt, 8h, 93%; (e) *Savinase-12T* (100% wt/wt), Et_3N (1.0 equiv.), vinylbutyrate (3.0 equiv.), rt, 3 days, 41%; (f) NaOH (5% in EtOH/ H_2O 5:1 v/v), reflux, 3h, 99%, *ee* > 98%; (g) 4-DMAP (10 mol%), DCC (1.4 equiv.), **31** (1.0 equiv.), CH_2Cl_2 , $0^\circ C$ -rt, 12h, 93%; (h) KHMDS (3.0 equiv.), toluene, $-78^\circ C$, 1h then TMSCl (5.0 equiv.), pyridine (4.5 equiv.), $-78^\circ C$ -rt, 4h, 77%; (i) MeLi (2.5 equiv.), Et_2O , $0^\circ C$ -rt, overnight, 72%; (j) Grubbs II catalyst (2 x 5 mol%), CH_2Cl_2 , reflux, 15h, 70%; (k) $MePPh_3^+Br^-$ (1.2 equiv.), *t*-BuOK (1.2 equiv.), THF, $75^\circ C$, 12h, 82%; (l) MeMgI (3.9 equiv.), Et_2O , $160^\circ C$ at 150 mbar, 1.5h, 62%.

Scheme 103. Total synthesis of (-)-CBD proposed by Leahy and coworkers.

1.3. Analogs of (-)-CBD

The pursuit of (-)-Cannabidiol (CBD) analogs stems from the compound's significant therapeutic potential, paired with a low incidence of adverse psychoactive effects. However, (-)-CBD's clinical viability is compromised by its limited solubility and metabolic resilience. In this scenario, the synthesis of novel CBD analogs is a very important field, as it can enable to refine (-)-CBD's pharmacological profile by enhancing its solubility, stability, and potency (Scheme 104).

The first class of CBD analogs involves resorcinol-modified derivatives. For example, the introduction of halogens on the aromatic ring (**33-39**, Scheme 104), possible according to Yamamoto's protocol,^[191] is expected to enhance potency through electronic modulation, influencing the interaction with biological systems, as demonstrated in various pharmacological studies (Scheme 104, top).^[192]

^[191] (a) Maruyama K.; Yamamoto Y. *J. Am. Chem. Soc.* **1977**, *99*, 8068-8070; (b) Yamamoto Y.; Yamamoto S.; Yatagai H.; Ishihara Y.; Maruyama K. *J. Org. Chem.* **1982**, *47*, 119-126.

^[192] (a) Jung, B.; Lee, J. K.; Kim, J.; Kang, E. K.; Han, S. Y.; Lee, H.-Y.; Choi, I. S. *Chem. Asian J.* **2019**, *14*, 3749-3762; (b) Wilkinson, S. M.; Price, J.; Kassiou, M. *Tetrahedron Lett.* **2013**, *54*, 52-54.

The second class involves limonene-modified analogs, with cannabigerol (CBG) **40** and related compounds showcasing a spectrum of biological activities due to structural diversification. The variations in the limonene moiety, as observed in natural extracts and synthetic metabolites, have been correlated with their pharmacological potency. These include novel bioactivities that may offer therapeutic advantages over the parent molecule, as indicated by Hill *et al.* and Mascal *et al.* in their respective studies (Scheme 104, left).^[193]

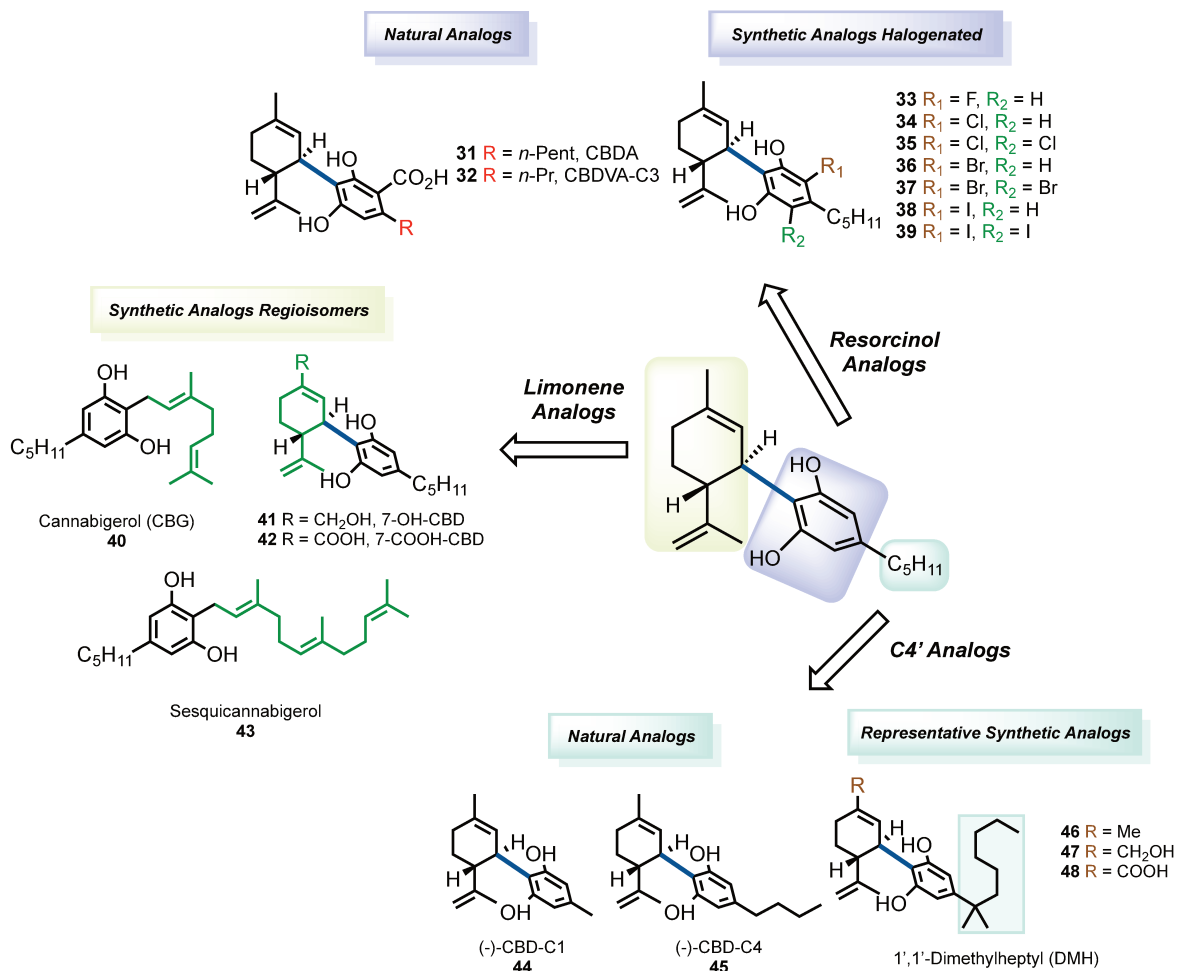
Within the third and final category of analogs, modifications are centered on the *n*-pentyl group at the C4' position of the resorcinol moiety. Both phyto-cannabinoids and synthetic molecules with variations in the C4'-alkyl chain length have been evaluated for their potential to modulate biological activity and improve drug-like properties. Recently, Passarella's group has made a significant contribution to cannabinoid research with the total synthesis of a (–)-Cannabidiol-C4 (CBD-C4) **45**, an analog designed to enhance the compound's pharmacological efficacy.^[194] This synthetic derivative was engineered to improve upon the solubility and metabolic stability issues associated with natural CBD, potentially offering a more potent therapeutic profile. The successful synthesis of CBD-C4 **45** marks a pivotal step in the quest for more efficacious cannabinoid-based treatments.

Synthetic analogs, particularly those featuring a dimethylheptyl (DMH) (**46-48**) side chain as developed by Hanuš *et al.*, have exhibited significant neuroprotective effects and a heightened bioactivity profile, suggesting an increase in potency (Scheme 104, bottom).^[195]

^[193] (a) Hill, A. J.; Mercier, M. S.; Hill, T. D. M.; Glyn, S. E.; Jones, N. A.; Yamasaki, Y.; Futamura, T.; Duncan, M.; Stott, C. G.; Stephens, G. J.; Williams, C. M.; Whalley, B.J.; *Br. J. Pharmacol.* **2012**, *167*, 1629-1642; (b) Mascal, M.; Hafezi, N.; Wang, D.; Hu, Y.; Serra, G.; Dallas, M. L.; Spencer, J. P. E. *Sci. Rep.* **2019**, *9*, 7778.

^[194] Marzullo, P.; Maiocchi, A.; Paladino, G.; Ciriello, U.; Lo Presti, L.; Passarella D. *Eur. J. Org. Chem.* **2022**, e202200392.

^[195] (a) Li, H.; Liu, Y.; Tian, D.; Tian, L.; Ju, X.; Qi, L.; Wang, Y.; Liang, C. *Eur. J. Med. Chem.* **2020**, *192*, 112163; (b) Kinney, W. A.; McDonnell, M. E.; Zhong, H. M.; Liu, C. M.; Yang, L. Y.; Ling, W.; Qian, T.; Chen, Y.; Cai, Z. J.; Petkanas, D.; Brenneman, D. E. *ACS Med. Chem. Lett.* **2016**, *7*, 424–428.



Scheme 104. Selected examples of (-)-CBD analogs: (a) resorcinol analogs (top); (b) limonene analogs (left); (c) C4' analogs (bottom).

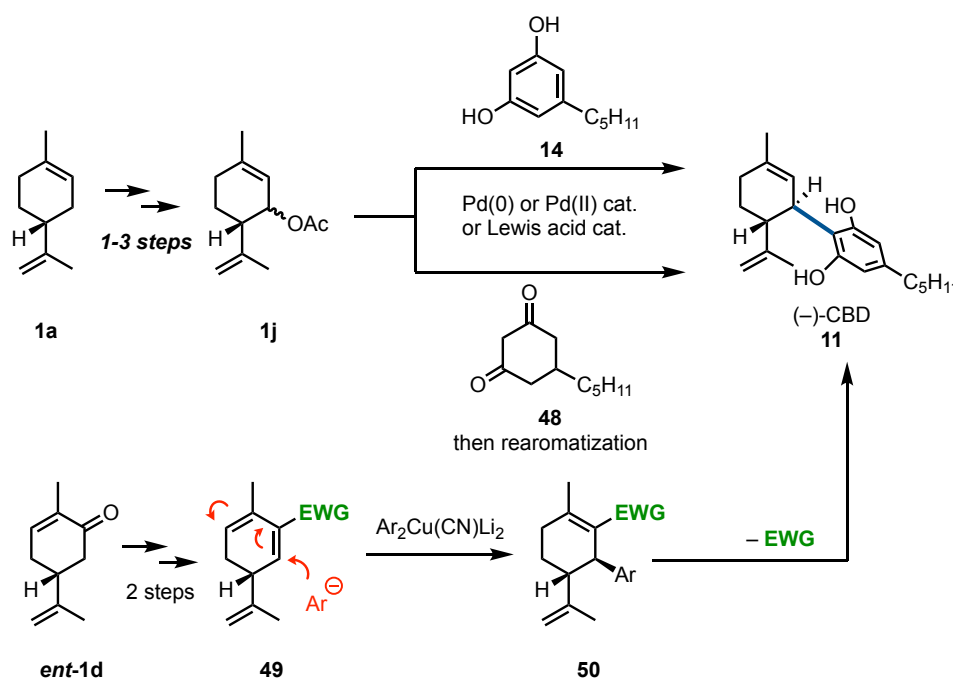
In summary, the search for (-)-CBD analogs is a topic of high importance as it aims at producing molecules of superior therapeutic efficacy. The modification of the C4' alkyl chain, or the resorcinol and limonene moieties on (-)-CBD scaffold is an example of the nuanced interplay between organic synthesis and pharmacological application, as evidenced by the array of referenced research endeavors.

1.4. Planned Project

Considering the current state of the art of the chemical synthesis of CBD, we envisioned to study new synthetic ways of access to (-)-CBD **11** that could be direct, regio- and stereoselective, and that avoid the undesired formation of tetrahydrocannabinol. Given that my PhD project concerns the functionalization of terpenes in the frame of biomass valorization, it has become increasingly intriguing to study novel C–H activation methodologies for the total synthesis of (-)-CBD.

Consequently, we have outlined two distinct synthetic routes for the synthesis of (-)-CBD **11**, both centered around the key coupling between a cyclic monoterpene derivative and the resorcinol moiety. The first approach is based on the initial selective allylic oxidation of (*R*)-(+)-limonene **1a** at position C-3, either to give directly the allyl acetate **1j** or through the formation of the corresponding ketone followed by reduction to give isopiperitenol (not shown) and acylation to give the corresponding allyl acetate **1j**. Subsequent Pd-catalyzed coupling with olivetol **14**, or a diketone-masked olivetol derivative **48**, joins the two components (Scheme 105, top). In the case of the diketone nucleophile, subsequent aromatization should deliver (-)-CBD.^[196] It is assumed that the attack to the transiently formed η^3 -allyl metal complex by the nucleophilic species should take place regioselectively at C-3 because of the steric hindrance imparted by methyl group at C-1. Furthermore, the Pd-catalyzed allylic substitution is also expected to take place stereoselectively leading to the *trans* configuration with respect to the isopropenyl group for steric reasons, as reported in the acid-promoted strategies of Petrzilka and Palmieri.^[178,179,183]

The second approach relies on the conjugate addition of a resorcinol nucleophile to a Michael acceptor derived from *R*-carvone (Scheme 105, bottom).



Scheme 105. General strategy for the synthesis of (-)-CBD from (*R*)-(+)-limonene **1a** and (*R*)-(-)-carvone *ent*-**1d** (Ar = protected resorcinol).

The latter approach is based on the idea of converting *R*-carvone into the Michael acceptor **49**, which could undergo a conjugate addition by an appropriate olivetol-derived nucleophile, such as an aryl

^[196] Hurem, D. M., Benjamin J.; Carlini, R.; Lewis, J.; McNulty, J. *SynOpen* **2021**, 5, 86–90.

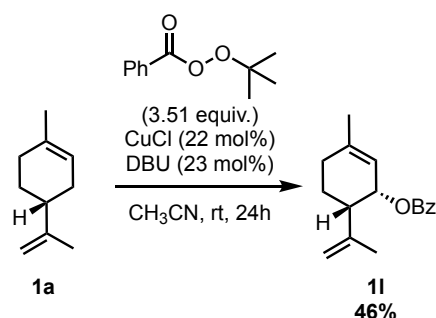
cyanocuprate. The addition of the aryl nucleophile is expected to take place *trans* to the isopropenyl substituent, and the resulting enolate, being at the same time an allyl anion, could be regioselectively protonated at the C-6 position of the terpene backbone, thereby placing the newly formed alkene in conjugation with the EWG. Removal of the electron withdrawing group followed by deprotection should eventually provide (–)-CBD.

2. Results and discussion

2.1. Strategy 1: π -allyl Palladium catalysis

The first strategy envisioned for accessing (–)-CBD is based on the direct coupling between a limonene-derived π -allyl palladium complex and a diketone as masked olivetol or an olivetol-derived nucleophile. This type of connection was already studied by Petrzilka,^[178] and later Palmieri,^[183] under acidic conditions. However, so far, no study has been extended to Pd-catalysis, which is a major topic in our group.^[197]

The allylic oxylation of limonene was thus considered. In 2012, Massanet *et al.* reported that submitting (+)-limonene to the Kharasch-Sosnovsky reaction (*tert*-butyl peroxybenzoate, catalytic CuCl, DBU) in acetonitrile at room temperature afforded benzoyl isopiperitenol **11** in 46% spectroscopic, 30% isolated yield (Scheme 106).^[198]



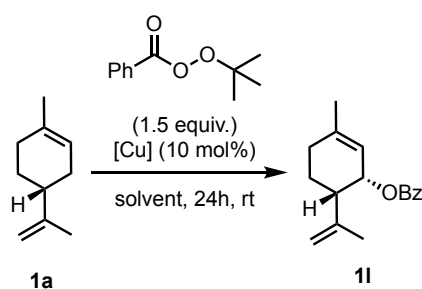
Scheme 106. Kharasch-Sosnovsky allylic oxidation of limonene reported by Massanet and coworkers.

The project started trying to reproduce the protocol by Massanet. However, although under the reported reaction conditions we managed to convert cyclohexene into cyclohex-2-en-1-yl benzoate in 85% yield, we were unable to obtain product **11** from limonene. The related article had a lack of clarity

^[197] Kammerer-Pentier, C.; Liron, F.; Prestat, G.; Poli, G. Selectivity in Palladium Catalyzed Allylic Substitution. In *Transition Metal Catalyzed Enantioselective Allylic Substitution in Organic Synthesis*; Springer-Verlag Berlin Heidelberg Publisher, **2012**; pp 1–64.

^[198] Marín-Barrios, R.; Guerra, F. M.; García-Cabeza, A. L.; Moreno-Dorado, F. J.; Massanet, G. M. *Tetrahedron* **2012**, *68*, 1105–1108.

on the use of DBU as an additive. Sekar *et al.*^[199] speculated that DBU may increase the rate of the oxidation step, probably through coordination to Cu-intermediates, so as to preclude the self-association of the Cu-benzoate complex and/or promoting some steps of the catalytic cycle.^[200] However, in another work, Muzart postulated that the addition of DBU as an additive (0.1 equiv.) resulted in a clean reaction, albeit with a slower reaction rate.^[201] Consequently, we removed DBU and selected the cationic copper complex $\text{Cu}(\text{MeCN})_4\text{BF}_4$ as the catalyst in the hope to make the catalytic system more reactive.^[201] Following these conditions, different solvents were screened (Table 14, entries 1-7). Acetonitrile and acetone lead to no conversion, probably because they strongly coordinated the copper center, shielding it (Table 14, entries 1 and 2). The lower coordinating dichloromethane, dichloroethane and benzotrifluoride allowed the formation of the desired product, albeit in low yields (Table 14, entries 3, 4, and 5), although toluene and cyclohexane gave also no reaction (entries 6 and 7). The protic solvent HFIP did not work, too (entry 8). Other cationic copper(I) and (II) sources were evaluated maintaining BTF as solvent, but unfortunately, no product formation was observed (Table 14, entries 9-11).



Entry ^[a]	[Cu]	Solvent	Conv. (%) ^[b]	1j (%) ^[b]
1	$\text{Cu}(\text{MeCN})_4\text{BF}_4$	MeCN	– ^[c]	–
2	$\text{Cu}(\text{MeCN})_4\text{BF}_4$	acetone	– ^[c]	–
3	$\text{Cu}(\text{MeCN})_4\text{BF}_4$	CH_2Cl_2	90	18
4	$\text{Cu}(\text{MeCN})_4\text{BF}_4$	DCE	81	18
5	$\text{Cu}(\text{MeCN})_4\text{BF}_4$	BTF	90	32
6	$\text{Cu}(\text{MeCN})_4\text{BF}_4$	toluene	– ^[c]	–
7	$\text{Cu}(\text{MeCN})_4\text{BF}_4$	cyclohexane	– ^[c]	–
8	$\text{Cu}(\text{MeCN})_4\text{BF}_4$	HFIP	– ^[c]	–
9	CuTC	BTF	– ^[c]	–
10	$\text{Cu}(\text{OTf})_2$	BTF	– ^[c]	–

^[199] Sekar, G.; DattaGupta, A.; Singh, V. K. *Tetrahedron Lett.* **1996**, *37*, 8435-8436.

^[200] Rawlinson, D. J.; Sosnovsky, G. *Synthesis* **1972**, *1*, 1-28.

^[201] Le Bras, J.; Muzart, J. J. *Mol. Catal. A Chem.* **2002**, *185*, 113-117.

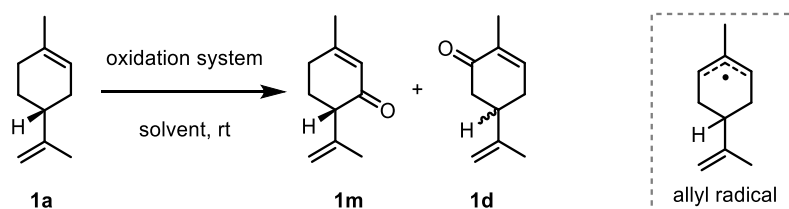
11	Cu(acac) ₂	BTF	_[c]	-
-----------	-----------------------	-----	------	---

[a] typical reaction conditions: (+)-limonene (1.0 mmol), TBPB (1.5 equiv.), [Cu] (10 mol%), solvent (0.25 M) at rt in a sealed vial; [b] measured by quantitative ¹H-NMR using 1,4-dinitrobenzene as an internal standard; [c] no conversion was observed. BTF: benzotrifluoride (trifluorotoluene); HFIP: 1,1,1,3,3,3-hexafluoroisopropanol; DCE: 1,2-dichloroethane, CuTC: copper(I) thiophenecarboxylate; acac: acetylacetonate.

Table 14. Kharasch-Sosnovsky allylic oxidation of (+)-limonene using reported conditions by Muzart.

Given the poor results obtained, we tried to find other ways to reach allylic oxidation of the C-3 position of limonene.

A CrO₃/*t*-BuOOH-based system in CCl₄ has been reported to convert limonene into isopiperitenone **1m** in 40% yield.^[202] However, attempted reproduction of these reaction conditions did not afford the expected oxidation product, neither using CCl₄ (Table 15, entry 1) nor cyclohexane (Table 15, entry 2) as the solvent. On the other hand, treatment of limonene with chromium hexacarbonyl and *tert*-butyl hydroperoxide (TBHP) gave (*R*)-isopiperitenone **1m** in 40% isolated yield,^[203] along with 18% of carvone **1d** (Table 15, entry 3). It has to be noted that the carvone generated by this oxidation turned out to be racemic (null value of its optical rotation, to compare with the specific rotation of enantiomerically pure (*S*)-carvone [α]_D²¹ = +63.3° dm⁻¹ cm³ g⁻¹ in ethanol). This result suggests the radical nature of the mechanism of the Cr-based oxidation protocol.^[204] Indeed, the intermediate allyl radical, possessing a mirror plane, loses the chiral information coming from (*R*)-(+)-limonene.



Entry	Oxidation system	Solvent	1m (%) ^[a]	1d (%) ^[a]
1	CrO ₃ (4.1 equiv.)	CCl ₄ / <i>t</i> -BuOH (3:1)	_[b]	_[b]
2	CrO ₃ (4.1 equiv.)	cyclohexane/ <i>t</i> -BuOH (3:1)	_[b]	_[b]
3	Cr(CO) ₆ (0.5 equiv.) TBHP (2.0 equiv.)	MeCN	40	18

[a] measured by quantitative ¹H-NMR using 1,4-dinitrobenzene as an internal standard; [b] no conversion was observed.

Table 15. Attempts of allylic C–H oxidation at C-3 of limonene **1a** with various oxidation systems.

^[202] Dethe, D. H.; Das, S.; Dherange, B. D.; Mahapatra, S. *Chem. Eur. J.* **2015**, *21*, 8347–8350.

^[203] Guillon, J.; Rioult, J.-P.; Robba, M. *Flavour and Fragr. J.* **2000**, *15*, 223–224.

^[204] Yu, J.-Q.; Corey, E. J. *Org. Lett.* **2002**, *4*, 2727–2730.

In view of the deceiving results obtained, halt of this project was decided and passed to the study of the second planned approach.

2.2. Strategy 2: 1,4-addition onto a carvone-derived Michael acceptor

The second strategy envisioned involves the introduction of an electron withdrawing group – noted **E** (Scheme 105)– to convert (*R*)-(-)-carvone **1d** into a Michael acceptor. As the **E** group is temporary (to modify the electronics of the endocyclic alkene), three important criteria need to be considered. The functional group should: a) be appended without difficulty; b) allow an efficient 1,4-addition reaction; c) be easily removable. With these conditions in mind, two methods were envisaged: a) a modified Shapiro reaction featuring an appropriate electrophilic quenching of the resulting vinyl lithium intermediate; b) accessing a carvone-derived α,β -unsaturated nitrile.

2.2.1. Modified Shapiro reaction^[205]

The Shapiro reaction classically allows the formation of olefins from toluenesulfonyl (tosyl) hydrazones with the use of an excess of a strong base, such as *n*-butyllithium or methyllithium.^[206] While the first equivalent of base deprotonates the hydrazone, consequently giving rise to a nitrogen-centered anion, the second deprotonation takes place at the α position to the carbonyl function. The thus formed dianion then undergoes in sequence an α elimination that releases lithium aryl sulfinate followed by nitrogen gas extrusion that generates the vinyl anion. The latter can either be quenched by a proton donor, as in the classical Shapiro reaction,^[206] or by various electrophiles thus allowing the obtention of the tosyl olefinated/functionalized derivative.

While electrophilic quenching of the vinyl anion produced by the Shapiro reaction has received less attention compared to the more common protonation-based approach, there are notable instances where this strategy has been applied in the total synthesis of natural products. For instance, Nicolaou's total synthesis of taxol[®] incorporates the use of an aldehyde as an electrophile.^[207] Yan's approach to the total synthesis of (-)-isoscopariusin A involves quenching the vinyl lithium species with methyl chloroformate, yielding the corresponding methyl ester.^[208] Additionally, other reported examples use

^[205] This part of project was accomplished in the frame of the Master student Valentin Poirier.

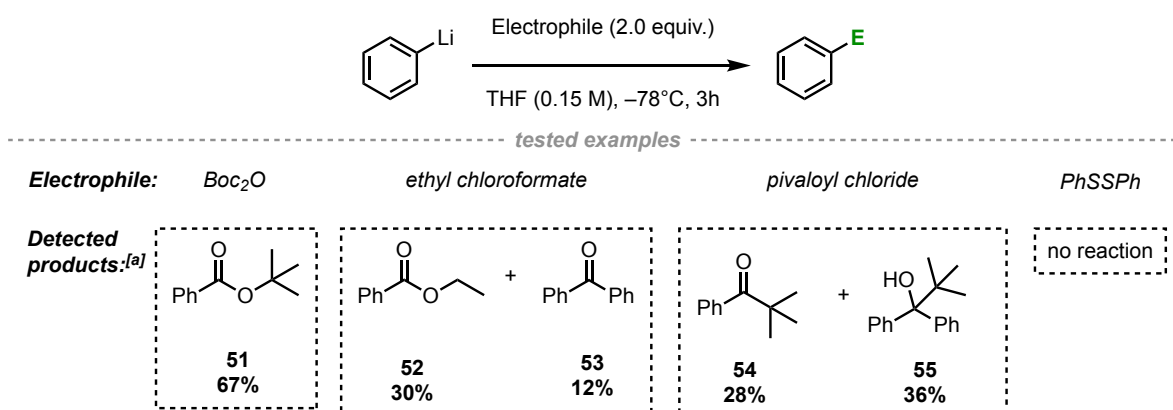
^[206] Shapiro, R. H.; Heath, M. J. *J. Am. Chem. Soc.* **1967**, *89*, 5734–5735.

^[207] Nicolaou, K. C.; Ortiz, A.; Zhang, H.; Dagneau, P.; Lanver, A.; Jennings, M. P.; Arseniyadis, S.; Faraoni, R.; Lizos, D. E. B. *J. Am. Chem. Soc.* **2010**, *132*, 7138–7152.

^[208] Yan, B.-C.; Zhou, M.; Li, J.; Li, X.-N.; He, S.-J.; Zuo, J.-P.; Sun, H.-D.; Li, A.; Puno, P.-T. *Angew. Chem. Int. Ed.* **2021**, *60*, 12859–12867.

electrophiles such as dimethyl formamide^[209] and iodine to generate vinylic aldehyde or iodinated products.^[210]

To investigate the scope of electrophiles compatible with quenching a vinyl lithium species, commercially available phenyllithium was selected as a model substrate and reacted with various electrophilic precursors (Scheme 107). Di-*t*-butyl dicarbonate (Boc₂O) successfully yielded *t*-butyl benzoate **51** with a 67% yield. However, ethyl chloroformate and pivaloyl chloride led to partial over-reactions. In the case of the former, the desired ethyl benzoate **52** was obtained in 30% yield, along with the undesired benzophenone **53** in 12% yield. Pivaloyl chloride resulted in the desired 2,2-dimethyl-1-phenylpropan-1-one **54** with 28% yield, accompanied by the undesired 2,2-dimethyl-1,1-diphenylpropan-1-ol **55** with 36% yield resulting from the double addition of phenyllithium. No reaction occurred with diphenyl disulfide.



[a] All reactions were performed on 0.5 mmol scale. Yield was determined by ¹H-NMR using *p*-dinitrobenzene as internal standard. Boc₂O = Di-*tert*-butyl carbonate; PhSSPh = Diphenyl disulfide.

Scheme 107. Screening of electrophiles for quenching of phenyllithium.

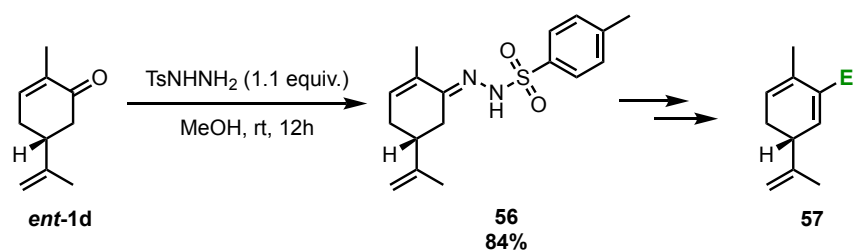
A quick analysis provides a rationalization for these results. The addition of phenyllithium to the aforementioned electrophiles leads to the formation of the corresponding esters or ketone, involving a transient high-energy tetrahedral intermediate. However, phenyllithium can further react with an ester or ketone. If the kinetics of phenyllithium addition to the resulting ester or ketone are comparable to those with the initial electrophile, ketone and/or alkoxide byproducts will be formed to some extent, thus consuming phenyllithium. The high yield observed with di-*tert*-butyl dicarbonate suggests that, unlike the other cases, phenyllithium addition to the bulky *t*-butyl ester does not

^[209] Serra, S.; Fuganti, C. *Tetrahedron Lett.* **2005**, *46*, 4769–4772.

^[210] Garner, C. M.; Mossman, B. C.; Prince, M. E. *Tetrahedron Lett.* **1993**, *34*, 4273–4276.

compete with its addition to Boc_2O . Those preliminary studies shed light on the probable similar reactivity that could be observed while quenching the vinyl lithium species formed on the carvone-derived tosyl hydrazone.

Coming back to the synthesis of (–)-cannabidiol **11**, the required vinyl lithium intermediate may derive from a Shapiro reaction of the tosyl hydrazone of the naturally abundant (*R*)-(–)-carvone **ent-1d**, and its reaction with an appropriate electrophile may generate the required Michael acceptor derivative **57**. While an optimized procedure reported by Zografos describes the preparation of (*R*)-(–)-carvone tosyl hydrazone **56** on gram scale,^[211] Shapiro's reports on the reactivity of the latter proved to be useful for selecting the most appropriate base (Scheme 108).^[212] Accordingly, (*R*)-(–)-carvone **ent-1d** was converted into the corresponding tosyl hydrazone **56** by reaction with tosyl hydrazine in methanol, giving exclusively rise to (*E*)-configured carbon-nitrogen double bond.^[213]



Scheme 108. Preparation of (*R*)-(–)-carvone derived tosyl hydrazone **56** for Shapiro reaction.

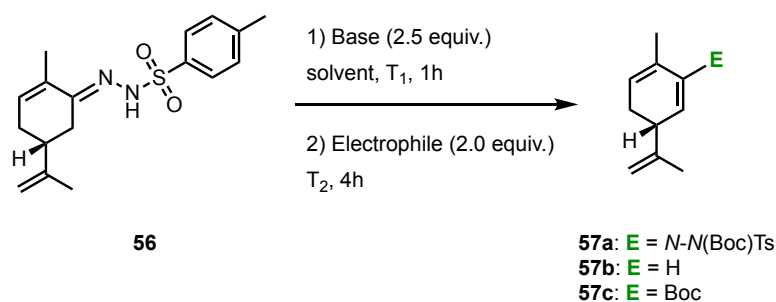
The first experiments of the Shapiro reaction on carvone *N*-tosyl hydrazone **56** were conducted using *n*-butyllithium as a base, in THF. However, as no new product could be identified (Table 16, entry 1), the role of the base was further investigated. According to Shapiro, methyllithium in diethyl ether proved to be the most efficient base to form dienic vinyl lithium species from the carvone hydrazone.^[212] Another parameter that required careful attention was the reaction temperature. Indeed, when, as reported by Yan,^[208] we performed the Shapiro reaction at -78°C , adding methyl chloroformate at that temperature, only the *N*-methoxycarbonylation product **57a** was obtained. This result clearly indicated that at that temperature only the first *N*-deprotonation occurred (Table 16, entry 2). When the same reaction was repeated at higher temperature (0°C to rt), the sole product that could be identified (yet not isolated) was assigned to *p*-mentha-1,5,8-triene **57b**, seemingly coming from an undesired quenching of the vinyl lithium species (Table 16, entry 3). Switching to

^[211] Katsina, T.; Papoulidou, K. E.; Zografos, A. L. *Org. Lett.* **2019**, *21*, 8110–8115.

^[212] Dauben, W. G.; Lorber, M. E.; Vietmeyer, N. D.; Shapiro, R. H.; Duncan, J. H.; Tomer, K. J. *Am. Chem. Soc.* **1968**, *90*, 4762–4763.

^[213] Configuration of hydrazone elucidated via Nuclear Overhauser Effect Spectroscopy.

Boc₂O as electrophile afforded an equimolar mixture of *p*-mentha-1,5,8-triene **57b** and *t*-butyl 6-methyl-3-(prop-1-en-2-yl)cyclohexa-1,5-diene-1-carboxylate **57c** (31% yield), and again, problems of isolation were encountered due to high volatility of the latter (Table 16, entry 4). Repeating the reaction with a larger excess of base and electrophile did not provide any improvement, since the protonation product was still observed and turned out to be major product with a 3:1 ratio towards formation of desired product detected on ¹H-NMR analysis.



Entry ^[a]	Base	Solvent	T ₁ (°C)	T ₂ (°C)	Electrophile	Product	yield(%) ^[b]
1	<i>n</i> -BuLi	THF	-78	-78	MeOCOCl	-	-[c]
2	MeLi	Et ₂ O	-78	0	MeOCOCl	57a	60
3	MeLi	Et ₂ O	0	rt	MeOCOCl	-	-[c]
4	MeLi	Et ₂ O	0 – rt	-78 – rt	Boc ₂ O	57c:57b	31 (31)
5^[d]	MeLi	Et ₂ O	0 – rt	-78 – rt	Boc ₂ O	57c:57b	-[e]

[a] All reactions were performed under Argon atmosphere on a 0.5 mmol scale with respect to tosyl hydrazone **56**; [b] Isolated yield. Yield in protonated vinyl lithium product **57b** showed in parenthesis, estimated by quantitative ¹H-NMR analysis; [c] No product could be identified nor isolated; [d] Reaction was performed with 4.3 equiv. of base and 4.0 equiv. of electrophile; [e] Ratio observed between desired product **57c** and protonated vinyl lithium product **57b** estimated to 1:3 by ¹H-NMR analysis.

Table 16. Optimization of Shapiro reaction on *p*-toluene sulfonyl hydrazone **56**.

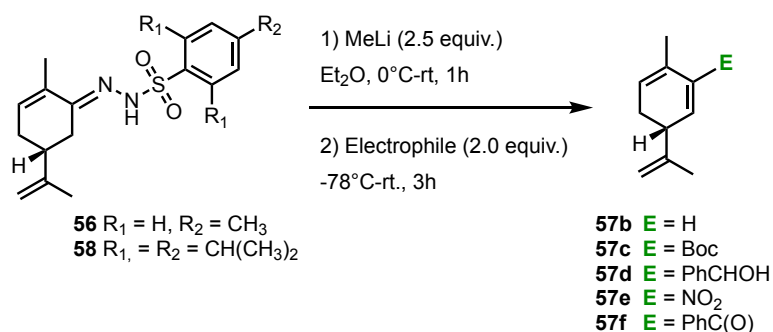
Appearance of the protonated vinyl lithium product **57b**, although undesired, indicated that the successful formation of the vinyl lithium species occurs when the temperature is risen from 0°C to room temperature. This is in accordance with mechanistic studies that indicate that nitrogen extrusion takes place when the temperature is increased.^[214] Nonetheless, the transient vinyl lithium species suffered to a great extent the undesired early protonation to **57b** from an unknown source. Chamberlin and co-workers investigated this side-reaction,^[215] which appears to be an issue only when the vinyl lithium species is quenched with an electrophile other than a protic source. They attributed this premature quenching to a not-totally dry solvent, or to the tolyl moiety, which might undergo an

^[214] Adlington, R. M.; Barrett, A. G. M. *J. Chem. Soc., Perkin Trans. 1* **1981**, No. 0, 2848–2863.

^[215] Chamberlin, A. R.; Stemke, J. E.; Bond, F. T. *J. Org. Chem.* **1978**, *43*, 147–154.

intramolecular *ortho*-metalation reaction. Adlington and co-workers solved this issue using triisopropylbenzene sulfonyl hydrazone (trisyl hydrazone), instead of the tosyl hydrazone, which does not bear acidic hydrogen atoms at the *ortho* position of the aryl sulfonyl group.^[216]

Hence, we envisioned to use (*R*)-carvone trisyl hydrazone **58**, in turn prepared according to Carreira and co-workers from trisyl hydrazide,^[217] using the previously optimized reaction conditions.



Entry ^[a]	Substrate	Electrophile	Product	Yield (%) ^[b]
1	56	Boc ₂ O	57c/57b	31/31
2	58	Boc ₂ O	57c/57b	12/48
3	58	PhCHO	57c/57b	33/21
4	58	NO ₂ BF ₄	-	_[c]
5	58	PhCOCl	57b	65

[a] All reactions were performed under argon atmosphere on a 0.5 mmol scale with respect to hydrazone; [b] Isolated yield. Yield in **57b** was estimated by ¹H-NMR analysis; [c] No product could be identified nor isolated despite full conversion.

Table 17. Screening of arene sulfonyl hydrazone and electrophile for Shapiro reaction.

Switching from tosyl hydrazone **56** to trisyl hydrazone **58** led to a drop of yield from 31% (Table 17, entry 1) to 12% (Table 17, entry 2), along with an increased yield in protonated product **57b** from 31% (entry 1) to 48% (entry 2). Having ruled out the seemingly deleterious role of the tosyl hydrazone **56** as internal protic source, the latter was chosen as precursor of vinyl lithium species in spite of the high ratios of protonated product **57b**, which to date remains of unclear origin. Benzaldehyde, nitronium tetrafluoroborate, and benzoyl chloride were also tested as quenchers for the vinyl lithium intermediate. Benzaldehyde proved to be the most satisfying one, affording the targeted alcohol **57d**

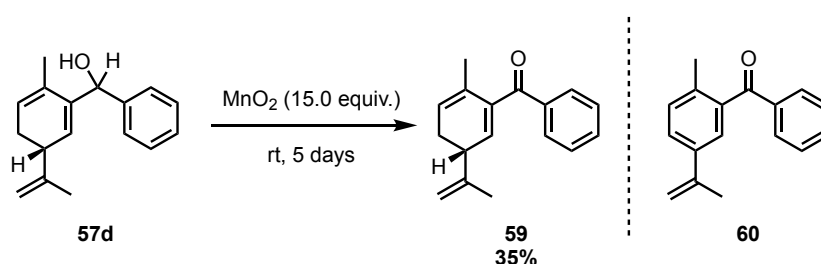
^[216] Adlington, R. M.; Barrett, A. G. M. *Acc. Chem. Res.* **1983**, *16*, 55–59.

^[217] Schreib, B. S.; Son, M.; Aouane, F. A.; Baik, M.-H.; Carreira, E. M. *J. Am. Chem. Soc.* **2021**, *143*, 21705–21712.

in 33% yield (Table 17, entry 3). On the other hand, neither nitronium tetrafluoroborate, nor benzoyl chloride afforded the expected nitroalkene **57e** (Table 17, entry 4) or ketone **57f** (Table 17, entry 5).

In view of the above preliminary results, it was decided to focus on the allylic alcohol **57d**, disregarding the other electrophiles. Accordingly, oxidation of **57d** to the corresponding ketone **59** was needed to reach a Michael acceptor, hopefully ready to undergo a 1,4-addition by a diaryl cyanocuprate.

Considering the allylic and benzylic nature of alcohol **57d**, a classical oxidation with manganese dioxide was firstly envisioned (Scheme 109).^[218] However, treatment of **57d** with manganese dioxide at reflux of dichloromethane unexpectedly afforded rearomatized ketone **60** in 55% yield instead of the wished ketone **59**.^[219] Thus, besides oxidation of alcohol function, aromatization of the cyclohexadiene motif also took place. Repetition of the reaction at room temperature gave the desired ketone **59** in 35% yield after 5 days of reaction. To date, a suitable method for the efficient and selective oxidation of allyl alcohol **57d** has not yet been found.



Scheme 109. Oxidation of allylic alcohol **57d** into corresponding ketone **59**.

2.2.2. Synthesis of an α,β -unsaturated nitrile intermediate

An alternative strategy envisaged for the transformation of carvone into a suitable Michael acceptor involves the conversion of its keto function into an α,β -unsaturated nitrile. Indeed, α,β -unsaturated nitriles are excellent Michael acceptors,^[220,221] and might cleanly undergo 1,4-addition by a higher order cyanocuprate.

Formation of cyanohydrins followed by dehydration is an efficient way for the transformation of ketones to α,β -unsaturated nitriles.^[222] For example, Harusawa and co-workers reported the

^[218] Gritter, R. J.; Wallace, T. J. *J. Org. Chem.* **1959**, *24*, 1051–1056.

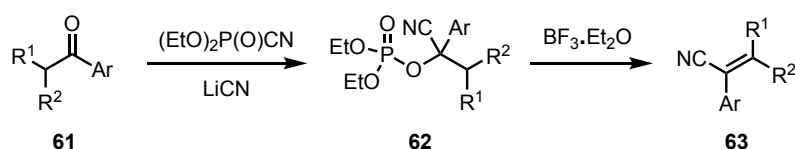
^[219] Ghosh, A. K.; Schiltz, G. E.; Rusere, L. N.; Osswald, H. L.; Walters, D. E.; Amano, M.; Mitsuya, H. *Org. Biomol. Chem.* **2014**, *12*, 6842–6854.

^[220] Das, P.; Devi, N.; Puzari, A. *J. Indian Chem. Soc.* **2022**, *99*, 100411.

^[221] Souza, R. O. M. A. de; Matos, L. M. C.; Gonçalves, K. M.; Costa, I. C. R.; Babics, I.; Leite, S. G. F.; Oestreicher, E. G.; Antunes, O. A. C. *Tetrahedron Lett.* **2009**, *50*, 2017–2018.

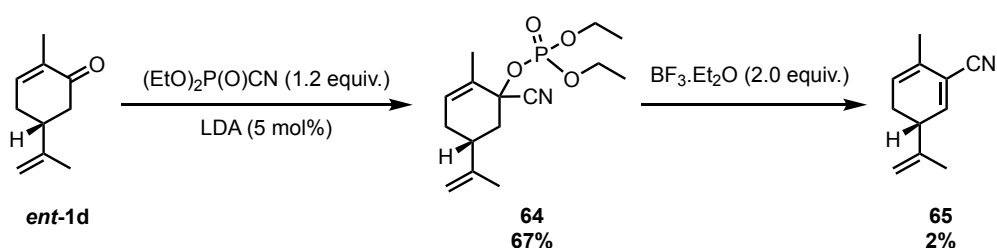
^[222] Fieser L.F. and Fieser, M. "Reagents for Organic Synthesis", Vol. 1. pp 876-881, John-Wiley and Sons, Inc., New York, **1967**.

conversion of aromatic ketone **61** into cyanohydrin diethyl phosphate (cyanophosphate) **62**, and its treatment with boron trifluoride etherate leads to the corresponding α,β -unsaturated nitrile **63** (Scheme 110).^[223] Based on Harusawa's work, Eggleston and Jørgensen also converted aromatic ketones into the corresponding α,β -unsaturated nitriles.^[224, 225]



Scheme 110. Conversion of carbonyl compounds into α,β -unsaturated nitrile via cyanophosphates (R^1, R^2 = Alkyl, Aryl).

Treatment of (*R*)-(-)-carvone **ent-1d** according to the protocol presented below gave a new product whose NMR analysis is compatible with the expected cyanophosphate **64** (67% isolated yield). After boron trifluoride etherate-mediated elimination, only 2% yield of a product supposed to be α,β -unsaturated nitrile **65** derivative was isolated (Scheme 111).



Scheme 111. Formation of α,β -unsaturated nitrile **65** from (*R*)-(-)-carvone **ent-1d** through cyanophosphate **64**.

Unfortunately, the desired product was not detected and further work will be needed to verify if the presented strategy can be viable.

^[223] Harusawa, S.; Yoneda, R.; Kurihara, T.; Hamada, Y.; Shioiri, T. *Tetrahedron Lett.* **1984**, *25*, 427–428.

^[224] Hamilton, C. J.; Fairlamb, A. H.; Eggleston, I. M. *J. Chem. Soc., Perkin Trans. 1* **2002**, No. 8, 1115–1123.

^[225] Donslund, B. S.; Nielsen, R. P.; Mønsted, S. M. N.; Jørgensen, K. A. *Angew. Chem. Int. Ed.* **2016**, *55*, 11124–11128.

In the presented chapter, several strategies aiming at a straightforward access to (-)-CBD without the generation of tetrahydrocannabinol (THC) have been considered.

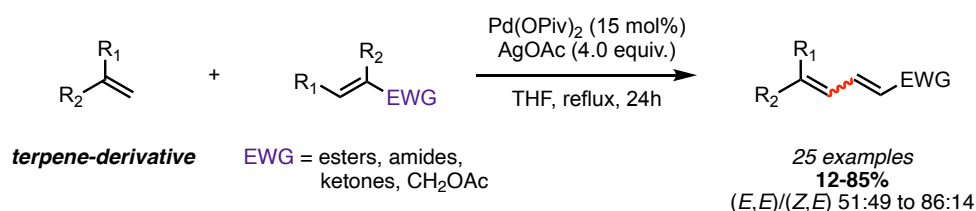
*On one hand, the approach towards (-)-CBD through a Pd-catalyzed coupling between acetate **1j** and olivetol, or a masked equivalent of it, remains possible. While scale-up of the Cr-based oxidation could disclose its potential^[203] the Pd-catalyzed allylic C–H oxidation with t-butyl hydroperoxide as sacrificial oxidant, according to different protocols may give isopiperitenone **1m** in a much more sustainable way.^[204] In conclusion, in this preliminary study, all the different strategies to CBD considered so far remain viable.*

*On the other hand, we managed to obtain two key intermediates through modified Shapiro reactions. Despite the moderate reactivity of esters in conjugate addition reactions, ester **15c** could be a good substrate for the 1,4-addition of a cuprate reagent. Moreover, ketone **59** may also be a suitable candidate for the conjugate addition of a cuprate nucleophile. In this case, removal of the temporary activating group, after coupling with the resorcinol ring, should be possible through a Baeyer-Villiger oxidation.^[226] A final decarboxylation step should then deliver (-)-CBD. On the other hand, the route leading to the α,β -unsaturated nitrile **65** as a Michael acceptor needs further investigation too. In particular, the stepwise formation of the cyanophosphate according to the original procedure of Harusawa, which makes use of diethyl cyanophosphonate with lithium cyanide, is envisaged.*

^[226] Lei, Z.; Ma, G.; Wei, L.; Yang, Q.; Su, B. *Catal. Lett.* **2008**, *124*, 330–333.

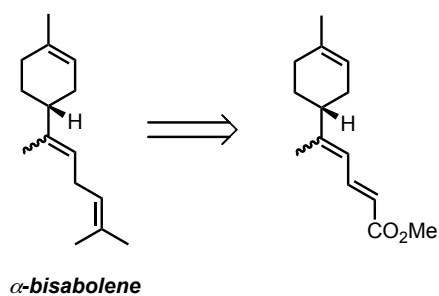
General Conclusion

In the frame of the valorization of renewable natural resources to access higher value-added products, this PhD thesis work focuses on the discovery of new strategies for the C–H activation/functionalization of terpenes, with particular emphasis on (+)-limonene and palladium catalysis. A first project (Chapter 2) describes the dehydrogenative Pd(II)-catalyzed C(sp²)–H/C(sp²)–H coupling between limonene and electron-poor alkenes, with extension to various terpenes and terpenoids bearing an isopropenyl function. This coupling was totally regioselective, enabling the functionalization of the exocyclic double bond of limonene. AgOAc turned out to be the oxidant of choice to close the catalytic cycle. The reaction constantly produced a mixture of the two geometrical isomers 2E,4E and 2E,4Z, out of the four possible, with the former always prevailing, while the 2Z isomers were never detected. An extensive DFT computation gave results in qualitative accord with the observed selectivity, allowing to propose a plausible mechanism. To the best of our knowledge, this protocol represents the first C–H/C–H coupling of limonene. The limitations of this protocol are: a) the chemical yields are not superior; b) a high catalytic loading of the palladium catalyst and superstoichiometric amounts of the silver salt are required; c) the reaction generates a mixture of geometrical isomers; d) α - or β -substituted acrylate esters do not allow the coupling (Scheme 112).



Scheme 112. Developed protocol for the CDC between terpenes and electron poor alkenes.

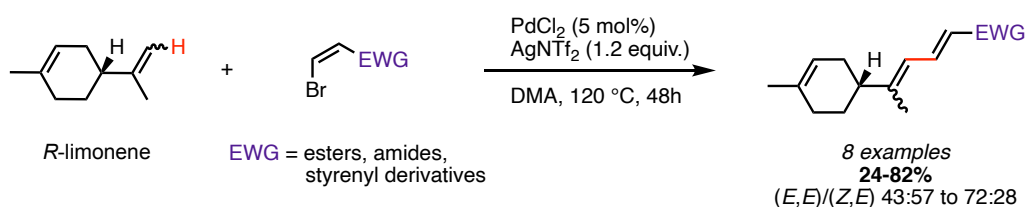
Future improvements could involve the use of greener oxidants like O₂, or photochemistry. We plan to perform KIE studies to complete the mechanistic study and to apply this methodology to the stereoselective total synthesis of the sesquiterpene α -bisabolene (Scheme 113).



Scheme 113. General idea for the synthesis of α -bisabolene starting from our coupled product.

My three-month secondment at Novartis Pharma (Basel, Switzerland) was dedicated to the post-functionalization of a product stemming from the dehydrogenative coupling previously studied in Paris, as described in Chapter 3. The selected post-functionalization was the Sonogashira cross-coupling between a brominated product in turn deriving from the dehydrogenative Pd-catalyzed coupling and ethynylbenzene, which was carried out in water under micellar regime. Proper optimization allowed to successfully obtain the desired coupling in good yield.

Another project of this thesis was dedicated to the Pd(II)-catalyzed redox neutral C(sp²)-H/C(sp²)-X coupling between (+)-limonene and bromoalkenes, as described in Chapter 4. This strategy, which is complementary with respect to the dehydrogenative coupling, needs a lower loading of the palladium catalyst and of the silver salt with respect to the previously studied coupling. In contrast to the well-known Pd(0)-catalyzed C(sp²)-H/C(sp²)-X Mizoroki-Heck protocol, this new coupling features an isohypsic mechanism, all the intermediates along the catalytic cycle staying at +II formal oxidation state. To the best of our knowledge, this is the first example of a Pd(II)-catalyzed C(sp²)-H/C(sp²)-X coupling involving an alkene and a vinyl halide, and is complementary with respect to the Pd(0)-catalyzed Mizoroki-Heck manifold, allowing the coupling of 1,1-disubstituted alkenes, where the Mizoroki-Heck protocol fails (Scheme 114). The limitations of the coupling are: a) important amounts of a silver salt are needed; b) most of the required halo-alkenes or pseudohalo-alkenes are not commercially available.



Scheme 114. Pd(II)-catalyzed non oxidative [C-H/C-X] coupling between limonene and (Z)-bromoacrylates.

Future mechanical studies and DFT calculations are planned for this coupling. As to the perspectives, replacement of DMA for an alternative green and non-toxic solvent is planned, as well as adaptation of this strategy to micellar conditions. Also, more 1,1-disubstituted alkenes will be tested as starting alkenes to extend the scope of the method. Modification of the method from Pd- to the less expensive Ni-catalysis is another possible topic for future investigations.

A secondary, synthesis-oriented, aim of the thesis was the study of new approaches to cannabidiol (CBD). Chapter 5 contains the preliminary studies carried out on this line. Two main approaches were considered. One was based on the coupling between a limonene-derived η^3 -allyl palladium complex (or allyl cation) and an olivetol (or olivetol precursor) nucleophile, while the other strategy was based on the conjugate addition of a resorcinol nucleophile to a carvone-derived Michael acceptor. Of course, more future work will be necessary to evaluate the strategies and reach the target.

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 ($\lambda = 254 \text{ nm}$) 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 ($\delta \text{ } ^1\text{H} = 7.26 \text{ ppm}$; $\delta \text{ } ^{13}\text{C} = 77.16 \text{ ppm}$). 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 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).

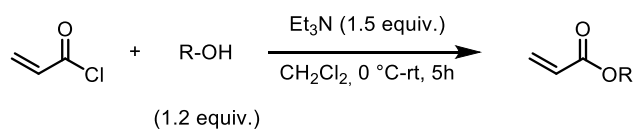
2. Chapter 2: Cross Dehydrogenative couplings of terpenes

2.1. Synthesis and characterization of starting materials

2.1.1. Synthesis of acrylates

Although some acrylates are commercially available, acrylates **4h** and **4i** had to be synthesized according to procedures reported in the literature.^[227]

General procedure A: Synthesis of acrylates

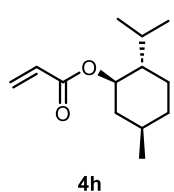


Scheme 115. Synthesis of acrylates.

A round bottom flask purged with argon was charged with a solution of the corresponding alcohol (1.2 equiv.) in dichloromethane (0.5 M). Then, triethylamine (1.5 equiv.) was added dropwise at 0 °C. After stirring at this temperature for 15 min, acryloyl chloride (1.0 equiv.) was slowly added. The solution was allowed to warm to rt and stirred for another 5h. The solution was washed with an aqueous 1M solution of HCl and the resulting organic layer was dried with anhydrous magnesium sulfate, filtered and concentrated under vacuum. The solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography (pentane/ethyl acetate) to give the corresponding compound.

^[227] Chen, H.; Ghiringhelli, F.; van Gemmeren, M. *Angew. Chem. Int. Ed.* **2020**, *59*, 12213-12220.

(1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl acrylate (4h)

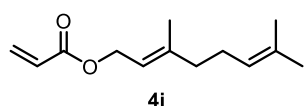


Prepared from the general procedure **A** with 937.6 mg (6.0 mmol, 1.2 equiv.) of (-)-menthol, 1.0 mL (7.5 mmol, 1.5 equiv.) and 0.4 mL (5.0 mmol, 1.0 equiv.) of acryloyl chloride in 10 mL of dry dichloromethane. After work-up, the acrylate **4h** was obtained without further purification as an orange oil (736.2 mg, 70%).

The characterization data are in accordance with the ones reported in the literature.^[228]

¹H NMR (400 MHz, CDCl₃): δ (ppm) 6.35 (dd, *J* = 17.3, 1.6 Hz, 1H), 6.07 (dd, *J* = 17.3, 10.4 Hz, 1H), 5.76 (dd, *J* = 10.4, 1.6 Hz, 1H), 4.73 (td, *J* = 10.9, 4.4 Hz, 1H), 2.02-1.97 (m, 1H), 1.87-1.81 (m, 1H), 1.67-1.62 (m, 2H), 1.52-1.44 (m, 1H), 1.42-1.35 (m, 1H), 1.07-0.93 (m, 3H), 0.88 (d, *J* = 5.6 Hz, 3H), 0.86 (d, *J* = 6.2 Hz, 3H), 0.74 (d, *J* = 7.0 Hz, 3H).

(*E*)-3,7-dimethylocta-2,6-dien-1-yl acrylate (4i)



Prepared according to general procedure **A** using 925.5 mg (6.0 mmol, 1.2 equiv.) of geraniol, triethylamine (1.0 mL, 7.5 mmol, 1.5 equiv.) and 0.4 mL (5.0 mmol, 1.0 equiv.) of acryloyl chloride in 10 mL of dry dichloromethane.

After work-up, the acrylate **4i** was obtained without further purification as an orange oil (941.8 mg, 90%).

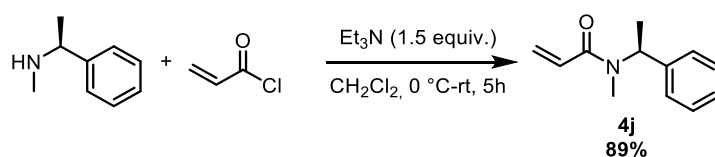
The characterization data are in accordance with the ones reported in the literature.^[229]

¹H NMR (300 MHz, CDCl₃): δ (ppm) 6.37–6.43 (dd, 1H), 6.08–6.17 (m, 1H), 5.79–5.82 (dd, 1H), 5.35–5.39 (m, 1H), 5.05–5.10 (m, 1H), 4.67–4.69 (d, 2H), 2.01–2.12 (m, 4H), 1.72 (s, 3H), 1.68 (s, 3H), 1.60 (s, 3H).

2.1.2. Synthesis of acrylamides

Most of the acrylamides used for the study were commercially available and ready to use, while two of them (**4j** and **4l**) had to be prepared according to reported procedures.

(*S*)-*N*-methyl-*N*-(1-phenylethyl)acrylamide (4j)



^[228] Paul, J.; Xavier, T.; Presset, M.; Le Gall, E.; Léonel, E.; Pichon, C.; Condon, S. *ChemistrySelect* **2018**, *3*, 13480- 13486.

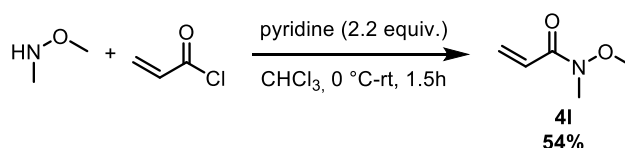
^[229] Worzakowska, M. *J. Term. Anal. Calorim.* **2017**, *127*, 2025-2035.

(*S*)-*N*-methyl-1-phenylethan-1-amine (0,7 mL, 5 mmol, 1.0 equiv.) and dry dichloromethane (20 mL) were placed in a flame-dried flask previously purged with argon and triethylamine (1.0 mL, 7.5 mmol, 1.5 equiv.) was added to the solution. The reaction mixture was then cooled to 0 °C. Acryloyl chloride (0.5 mL, 6 mmol, 1.2 equiv.) was added and then the mixture was stirred at rt overnight under inert atmosphere. The reaction was quenched through the addition of aqueous ammonium chloride; the mixture was extracted with dichloromethane (2 × 10 mL) and the organic layers combined, dried over anhydrous magnesium sulfate and concentrated. The residue was purified by flash column chromatography (pentane/ethyl acetate 70:30) to afford the acrylonitrile **4j** as a pale-yellow oil (842.1 mg, 89%).

The characterization data are in accordance with the ones reported in the literature.^[230]

¹H-NMR (300 MHz, CDCl₃): δ (both rotamers) (ppm) 7.37-7.16 (m, 5H), 6.71–6.52 (m, 1H), 6.39–6.28 (m, 1H), 6.09 (q, *J* = 6.9 Hz, 0.6H), 5.69 (app d, *J* = 8.7 Hz, 1H), 5.23 (q, *J* = 6.0 Hz, 0.4H), 2.69 (s, 3H), 1.58 (d, *J* = 6.0 Hz, 1H), 1.48 (d, *J* = 6.9 Hz, 2H).

N-methoxy-*N*-methylacrylamide (**4i**)



In a round bottom flask was introduced *N,O*-dimethylhydroxylamine (1.0 g, 10.3 mmol, 1.1 equiv.). The flask was placed under vacuum before being backfilled with argon. The vacuum/argon cycles were repeated twice and 20 mL of chloroform were added. The solution was cooled down to 0°C (ice/water bath) and acryloyl chloride (0,75 mL, 9.3 mmol, 1.0 equiv.) was added dropwise followed by anhydrous pyridine (1.65 mL, 20.6 mmol, 2.2 equiv.). After stirring 1.5 h at room temperature, the solvent was evaporated. The residue was dissolved in 1M HCl and the aqueous layer was extracted with dichloromethane (3x15 mL). The combined organic layers were washed with a saturated solution of sodium bicarbonate and brine, dried over anhydrous magnesium sulfate and filtered. The filtrate was evaporated under vacuum to afford the desired acrylonitrile **4i** as a colorless oil (1.16 g, 54% yield).

The characterization data are in accordance with the ones reported in the literature.^[231]

¹H-NMR (400 MHz; CDCl₃): δ (ppm) 6.74 (dd, *J* = 17.3 Hz, 10.4 Hz, 1H), 6.44 (dd, *J* = 17.1 Hz, 2 Hz, 1H), 5.76 (dd, *J* = 10.3 Hz, = 2 Hz, 1H), 3.27 (s, 3H), 3.72 (s, 3H).

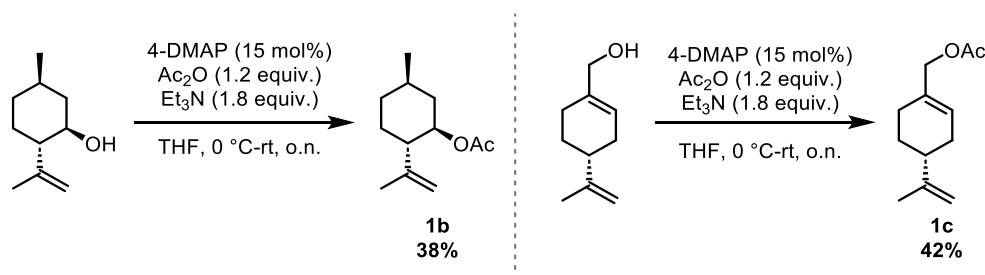
^[230] Khong, S. N.; Kwon, O. *Molecules* **2012**, *17*, 5626-5650.

^[231] Commare, B.; Rigault, D.; Lemasson, I. A.; Deschamps, P.; Tomas, A.; Roussel, P.; Brabet, I.; Goudet, C.; Pin, J.-P.; Leroux, F. R.; Colobert, F.; Acher, F. C. *Org. Biomol. Chem.* **2015**, *13*, 1106-1112.

2.1.3. Preparation of other terpenes

Although most of the terpenes used in this study are commercially available, terpene alcohols had to be protected to avoid any issue with palladium catalysts. Accordingly, **1b** and **1c** had to be synthesized according to procedures reported in the literature.^[232]

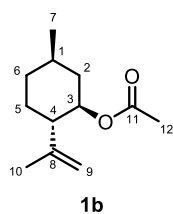
General procedure B: Preparation of terpenes



Scheme 116. Synthesis of terpenes.

In a round bottom flask was placed 4-DMAP (15 mol%). The flask was placed under vacuum before being backfilled with argon. The vacuum/argon cycles were repeated twice and the terpene alcohol (1.0 equiv.) was introduced together with acetic anhydride (1.2 equiv.) and triethylamine (1.8 equiv.) in THF (0.5 M) at 0 °C. The reaction mixture was maintained at 0 °C for 1h and then it was allowed to stir at rt overnight. The solvent was removed under reduced pressure and the resulting material was diluted with ethyl acetate and washed with water and brine. The organic layer was then dried over anhydrous magnesium sulfate. The crude product was purified by flash chromatography on silica gel (pentane/ethyl acetate) to give desired product.

(1R,2S,5R)-5-methyl-2-(prop-1-en-2-yl) cyclohexyl acetate (**1b**)

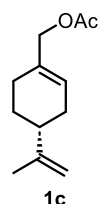


Prepared according to general procedure **B** using (-)-isopulegol (250 mg, 1.55 mmol, 1.0 equiv.), acetic anhydride (185 mg, 1.83 mmol, 1.2 equiv.), triethylamine (0.4 mL, 2.75 mmol, 1.8 equiv.) and 4-DMAP (0.93 mg, 0.15 equiv.) in 3 mL of THF at 0 °C. After work-up, the crude product was purified by flash chromatography on silica gel (pentane/ethyl acetate 7:3) to give isopulegol acetate **1b** as a colourless oil (115.2 mg, 38%).

^[232] Arora, A.; Teegardin, K. A.; Weaver, J. D. *Org. Lett.* **2015**, *17*, 3722-3725.

¹H NMR (400 MHz, CDCl₃): δ (ppm) 4.67 (td, *J* = 10.8, 4.4 Hz, 1H, H-3), 4.61-4.50 (br. s, 2H, H-9), 2.0-0.70 (m, 17H, H-1/H-2, H-4 to H-7 and H-10/H-12) **¹³C NMR** (75 MHz, CDCl₃): δ (ppm) 170.1 (C-11), 146.0 (C-8), 111.5 (C-9), 73.2 (C-3), 50.6 (C-4), 40.4 (C-2), 34.0 (C-6), 31.3 (C-1), 30.2 (C-5), 21.9 (C-7), 20.9 (C-12), 19.3 (C-10). **IR (ATR)** ν (cm⁻¹): 2951, 1736, 1244. **HRMS (ESI)** *m/z*: [M+H]⁺ calcd for C₁₂H₂₀O₂H 197.1536, found 197.1537

(R)-4-(prop-1-en-2-yl)cyclohex-1-en-1-yl)methyl acetate (1c)



Prepared according to general procedure **B** with (-)-perillyl alcohol (245.8 mg, 1.55 mmol, 1.0 equiv.), acetic anhydride (172.4 mg, 1.83 mmol, 1.2 equiv.), triethylamine (0.4 mL, 2.75 mmol, 1.8 equiv.) and 4-DMAP (0.93 mg, 0.15 equiv.) in 3 mL of THF at 0 °C. After work-up, the crude product was purified by flash chromatography on silica gel (pentane/ethyl acetate 7:3) to give perillyl acetate **1c** as a colorless oil (127.1 mg, 42%).

The characterization data are in accordance the ones reported in the literature.^[233]

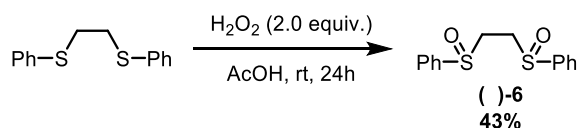
¹H-NMR (CDCl₃, 400 MHz): δ (ppm) 5.73 (s, 1H), 4.73-4.70 (m, 2H). 4.44 (s, 2H), 2.19-2.02 (m, 4H), 2.06 (s, 3H), 1.99-1.92 (m, 1H), 1.87-1.81 (m, 1H), 1.72 (s, 3H), 1.53-1.45 (m, 1H).

2.2. Synthesis and characterization of ligands

Several ligands were evaluated in the optimization of the reaction conditions to see if they could accelerate the reaction and allow us to lower the catalytic loading. Most of the ligands shown in this study were commercially available. However, two of them had to be synthesized in accordance with previously reported procedures.

1,2-bis(phenylsulfinyl)ethane (6)

Ligand (**6**) was prepared following the reported literature.^[234]



A 50 mL flask was charged with 1,2-bis(phenylthio)ethane (2.0 g, 8.12 mmol, 1.0 equiv.). The flask was then placed under vacuum before being backfilled with argon. The vacuum/argon cycles were

^[233] Geoghegan, K.; Evans, P. *Tetrahedron Lett.* **2014**, *55*, 1431-1433.

^[234] Young, A. J.; White, M. C. J. *Am. Chem. Soc.* **2008**, *130*, 14090-14091.

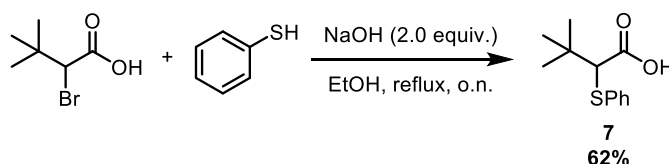
repeated twice and acetic acid (12.2 mL) was introduced. A solution of hydrogen peroxide (50 wt%, 16.24 mmol, 0.94 mL, 2.0 equiv.) in acetic acid (6.7 mL) was added dropwise at room temperature. After approximately 15 min, the solution became homogenous and turned pale yellow. An additional 8 mL of acetic acid was then added and the solution was then allowed to stir for 24h at room temperature. The acetic acid was removed under high vacuum. The pale-yellow solid was emulsified in cold ethanol and cold filtered to yield a mixture of the meso and racemic 1,2-bis(phenylsulfinyl)ethane (976 mg, 43% yield).

The characterization data are in accordance the ones reported in the literature.^[234]

¹H NMR (500 MHz, CDCl₃): δ (ppm) 7.56-7.52 (m, 10H), 3.05 (s, 4H).

3,3-dimethyl-2-(phenylthio)butanoic acid (7)

Ligand (7) was prepared following a reported procedure from the literature.^[235]



A round bottom flask was charged with 2-bromo-3,3-dimethylbutanoic acid (0.49 g, 2.5 mmol, 1.0 equiv.) and NaOH (0.2 g, 5 mmol, 2.0 equiv.). The flask was placed under vacuum before being backfilled with argon. The vacuum/argon cycles were repeated twice and the solids were dissolved in absolute ethanol (7.5 mL). Thiophenol (0.26 mL, 2.5 mmol, 1.0 equiv.) was added at room temperature. The reaction was refluxed overnight and concentrated under reduced pressure. The resulting crude residue was dissolved in water (10 mL) and acidified (6M aqueous HCl solution) until pH = 1. The aqueous layer was extracted with diethyl ether (3 x 10 mL). The combined organic layers were washed with saturated aqueous sodium bicarbonate (3 x 10 mL). Then, the combined aqueous layers were acidified with a 6M aqueous HCl solution until pH = 1. The resulting aqueous layer was extracted with diethyl ether (3 x 20 mL). The combined organic layers were dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure to obtain the desired product as a yellow solid (2.61 g, 62% yield).

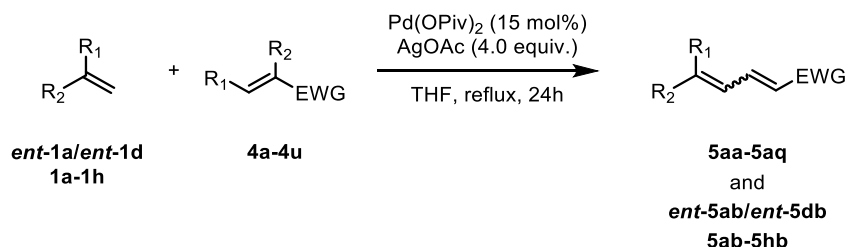
The characterization data are in accordance the ones reported in the literature.^[110]

¹H-NMR (400 MHz, CDCl₃): δ (ppm) 4.10 (s, 1H), 1.15 (s, 9H).

^[235] Yeh, P.-P.; Daniels, D. S. B.; Cordes, D. B.; Slawin, A. M. Z.; Smith, A. D. *Org. Lett.* **2014**, *16*, 964-967.

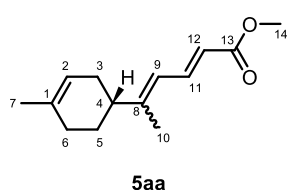
2.3. Pd(II)-catalyzed cross dehydrogenative coupling

General Procedure C for the Pd(II)-catalyzed dehydrogenative coupling



A 10 mL ace pressure tube was charged with 23.2 mg (0.075 mmol, 15 mol%) of palladium (II) pivalate, 333.8 mg (2.0 mmol, 4.0 equiv.) of silver(I) acetate. The tube was placed under vacuum and backfilled with argon. The vacuum/argon cycles were repeated twice and 3.0 mL of freshly distilled THF was added. To this solution was added the terpene/terpenoid **ent-1a/ent-1d** or **1a-1h** (0.5 mmol, 1.0 equiv.) and the electron-poor alkene **4a-4u** (1.0 mmol, 2.0 equiv.). The solution was stirred under inert atmosphere at reflux (heating bath at 110°C) for 24 h. After cooling to rt, the reaction was filtered over a plug of Celite® using 20 mL of dichloromethane. The filtrate was concentrated under reduced pressure and the residue was purified by flash column chromatography on silica gel affording the desired product.

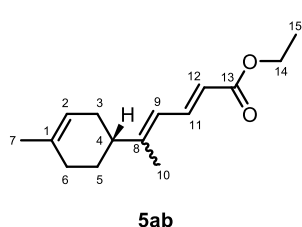
Methyl (R)-5-(4-methylcyclohex-3-en-1-yl)hexa-2,4-dienoate (5aa)



Prepared according to the general procedure **C** from (+)-limonene **1a** (81.0 μL , 0.5 mmol, 1.0 equiv.) and methyl acrylate **4a** (90.6 μL , 1.0 mmol, 2.0 equiv.). The crude product was purified by flash column chromatography over silica gel (pentane/ethyl acetate 99:1) to give *methyl (R)-5-(4-methylcyclohex-3-en-1-yl)hexa-2,4-dienoate* **5aa** as a brown oil (85.9 mg, 78%). ¹H NMR (400 MHz, CDCl₃): δ (ppm) 7.62 (dd, $J = 15.2, 11.6$ Hz, 1H, H-11), 6.02 (d, $J = 11.6$ Hz, 1H, H-9 major isomer), 5.97 (d, $J = 11.8$ Hz, 1H, H-9 minor isomer), 5.79 (d, $J = 15.1$ Hz, 1H, H-12 major isomer), 5.78 (d, $J = 15.2$ Hz, 1H, H-12 minor isomer), 5.40 (br. s, 1H, H-2), 3.74 (s, 3H, H-14), 2.14-1.20 (m, 13H, H-3, H-4, H-5, H-6, H-7, H-10). ¹³C NMR (101 MHz, CDCl₃): δ (ppm) 168.3 (C-13 minor isomer), 168.2 (C-13 major isomer), 154.4 (C-1 major isomer), 148.1 (C-1 minor isomer), 141.5 (C-11 major isomer), 140.3 (C-11 minor isomer), 134.1 (C-8 minor isomer), 134.0 (C-8 major isomer), 123.8 (C-9 minor isomer), 121.9 (C-9 major isomer), 120.4 (C-2 minor isomer), 120.3 (C-2 major isomer), 118.79 (C-12 major isomer), 118.75 (C-12 minor isomer), 51.5 (C-14 both isomers), 43.7 (C-4 major isomer), 36.5 (C-4 minor isomer), 30.5

(2C, C-3 and C-6 both isomers), 30.4 (C-3 or C-6 minor isomer), 30.1 (C-3 or C-6 minor isomer), 27.7 (C-5 major isomer), 27.4 (C-5 minor isomer), 23.65 (C-7 minor isomer), 23.57 (C-7 major isomer), 20.4 (C-10 minor isomer), 15.7 (C-10 major isomer). **IR (ATR)** ν (cm⁻¹): 2914, 1710, 1633, 1434, 1271, 1151, 1137, 979, 887, 793. **HRMS (ESI)** m/z : [M+H]⁺ calcd for C₁₄H₂₀O₂H 221.1536, found 221.1538.

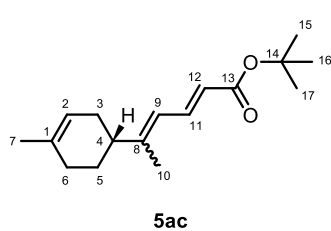
Ethyl (2E)-5-((R)-4-methylcyclohex-3-en-1-yl)hexa-2,4-dienoate (5ab)



Prepared according to the general procedure **C** from (+)-limonene **1a** (81.0 μ L, 0.5 mmol, 1.0 equiv.) and ethyl acrylate **4b** (106.5 μ L, 1.0 mmol, 2.0 equiv.). The crude product was purified by flash column chromatography over silica gel (pentane/ethyl acetate 99:1) to give *ethyl (2E)-5-((R)-4-methylcyclohex-3-en-1-yl)hexa-2,4-dienoate 5ab* as a yellow oil (100.0 mg, 85%).

¹H NMR (400 MHz, CDCl₃): δ (ppm) 7.60 (dd, J = 15.1, 11.6 Hz, 1H, H-11), 6.01 (d, J = 11.7 Hz, 1H, H-9 major isomer), 5.95 (d, J = 12.0 Hz, 1H, H-9 minor isomer), 5.78 (d, J = 15.1 Hz, 1H, H-12 major isomer), 5.76 (d, J = 15.1 Hz, 1H, H-12 minor isomer), 5.39 (br. s, 1H, H-2), 4.19 (q, J = 7.1 Hz, 2H, H-14), 2.17-1.18 (m, 16H, H-3, H-4, H-5, H-6, H-7, H-10, H-15). **¹³C NMR** (101 MHz, CDCl₃): δ (ppm) 167.86 (C-13 minor isomer), 167.76 (C-13 major isomer), 154.0 (C-1 both isomers), 141.2 (C-11 major isomer), 140.0 (C-11 minor isomer), 134.0 (C-8 minor isomer), 133.9 (C-8 major isomer), 123.9 (C-9 minor isomer), 121.9 (C-9 major isomer), 120.4 (C-2 minor isomer), 120.3 (C-2 major isomer), 119.3 (C-12 major isomer), 119.2 (C-12 minor isomer), 60.5 (C-14 minor isomer), 60.2 (C-14 major isomer), 43.7 (C-4 major isomer), 36.4 (C-4 minor isomer), 30.5 (2C, C-3 and C-6 major isomers), 30.4 (C-3 or C-6 minor isomer), 30.0 (C-3 or C-6 minor isomer), 27.6 (C-5 major isomer), 27.4 (C-5 minor isomer), 23.6 (C-7 minor isomer), 23.5 (C-7 major isomer), 20.3 (C-10 minor isomer), 15.7 (C-10 major isomer), 14.4 (C-15 major isomer), 14.3 (C-15 minor isomer). **IR (ATR)** ν (cm⁻¹): 2913, 1714, 1633, 1444, 1367, 1271, 1150, 1134, 1042, 979, 887, 801, 757. **HRMS (ESI)** m/z : [M+H]⁺ calcd for C₁₅H₂₂O₂H 235.1693, found 235.1694.

***Tert*-butyl (2E)-5-((R)-4-methylcyclohex-3-en-1-yl)hexa-2,4-dienoate (5ac)**

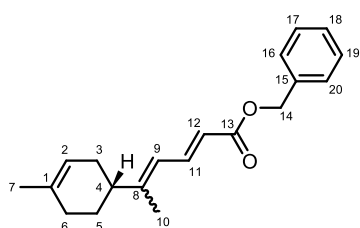


Prepared according to the general procedure **C** from (+)-limonene **1a** (81.0 μ L, 0.5 mmol, 1.0 equiv.) and *tert*-butyl acrylate **4c** (145.2 μ L, 1.0 mmol, 2.0 equiv.). The crude product was purified by flash column chromatography over silica gel (pentane/ethyl acetate 99:1) to give *tert*-butyl (2E)-5-((R)-4-methylcyclohex-3-en-1-yl)hexa-2,4-dienoate **5ac** as a

yellow oil (104.6 mg, 80%). **¹H NMR** (400 MHz, CDCl₃): δ (ppm) 7.52 (dd, J = 15.1, 11.6 Hz, 1H, H-11), 5.99 (d, J = 11.6 Hz, 1H, H-9 major isomer), 5.93 (d, J = 11.5 Hz, 1H, H-9 minor isomer), 5.72 (d, J = 15.1

Hz, 1H, H-12 major isomer), 5.71 (d, $J = 15.1$ Hz, 1H, H-12 minor isomer), 5.39 (br. s, 1H, H-2), 2.02-1.61 (m, 13H, H-3, H-4, H-5, H-6, H-7, H-10), 1.48 (s, 9H, H-15, H-16, H-17). $^{13}\text{C NMR}$ (75 MHz, CDCl_3): δ (ppm) 167.4 (C-13 minor isomer), 167.2 (C-13 major isomer), 153.4 (C-1 minor isomer), 153.2 (C-1 major isomer), 140.2 (C-11 major isomer), 139.2 (C-11 minor isomer), 133.9 (C-8 both isomers), 123.8 (C-9 minor isomer), 121.9 (C-9 major isomer), 121.2 (C-12 major isomer), 121.0 (C-12 minor isomer), 120.5 (C-2 minor isomer), 120.4 (C-2 major isomer), 80.1 (C-14 minor isomer), 80.0 (C-14 major isomer), 43.6 (C-4 major isomer), 36.4 (C-4 minor isomer), 30.5 (2C, C-3 and C-6 major isomers), 30.4 (C-3 or C-6 minor isomer), 30.0 (C-3 or C-6 minor isomer), 28.3 (3C, C-15, C-16, C-17, all 6 isomers), 27.7 (C-5 major isomer) 27.5 (C-5 minor isomer), 23.62 (C-7 minor isomer), 23.56 (C-7 major isomer), 20.3 (C-10 minor isomer), 15.6 (C-10 major isomer). **IR (ATR)** ν (cm^{-1}): 2927, 1708, 1663, 1367, 1284, 1145, 979, 886, 853. **HRMS (ESI)** m/z : $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{17}\text{H}_{26}\text{O}_2\text{Na}$ 285.1825, found 285.1825.

Benzyl (2E)-5-((R)-4-methylcyclohex-3-en-1-yl)hexa-2,4-dienoate (5ad)

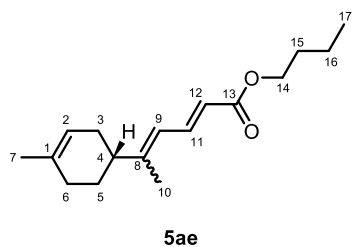


5ad

Prepared according to the general procedure **C** from (+)-limonene **1a** (81.0 μL , 0.5 mmol, 1.0 equiv.) and benzyl acrylate **4d** (153.0 μL , 1.0 mmol, 2.0 equiv.). The crude product was purified by flash column chromatography over silica gel (pentane/ethyl acetate 99:1) to give *benzyl (2E)-5-((R)-4-methylcyclohex-3-en-1-yl)hexa-2,4-dienoate 5ad* as a yellow oil (91.0 mg, 61%). $^1\text{H NMR}$ (300 MHz, CDCl_3): δ (ppm) 7.57

(dd, $J = 15.2, 11.6$ Hz, 1H, H-11), 7.33-7.19 (m, 5H, H-16, H-17, H-18, H-19, H-20), 5.93 (d, $J = 11.6$ Hz, 1H, H-9 major isomer), 5.75 (d, $J = 15.1$ Hz, 1H, H-12), 5.30 (br. s, 1H), 5.10 (s, 2H), 2.17-1.08 (m, 13H). $^{13}\text{C NMR}$ (101 MHz, CDCl_3): δ (ppm) 167.7 (C-13 minor isomer), 167.6 (C-13 major isomer), 154.6 (C-1 both isomers), 141.8 (C-11 major isomer), 140.6 (C-11 minor isomer), 136.5 (C-15 major isomer), 136.5 (C-15 minor isomer), 133.99 (C-8 minor isomer), 133.92 (C-8 major isomer), 128.7 (2C, C-16, C-20 both isomers), 128.3 (2C, C-17, C-19 both isomers), 128.2 (C-18 both isomers), 123.8 (C-9 minor isomer), 121.9 (C-9 major isomer), 120.38 (C-2 minor isomer), 120.27 (C-2 major isomer), 118.8 (C-12 major isomer), 118.7 (C-12 minor isomer), 66.1 (C-14 major isomer), 66.0 (C-14 minor isomer), 43.7 (C-4 major isomer), 36.4 (C-4 minor isomer), 30.4 (2C, C-3 or C-6 both isomers), 30.3 (C-3 or C-6 minor isomer), 30.0 (C-3 or C-6 minor isomer), 27.6 (C-5 major isomer), 27.4 (C-5 minor isomer), 23.63 (C-7 minor isomer), 23.55 (C-7 major isomer), 20.4 (C-10 minor isomer), 15.8 (C-10 major isomer). **IR (ATR)** ν (cm^{-1}) 2963, 1715, 1633, 1270, 1150, 1132, 979, 754, 697. **HRMS (ESI)** m/z : $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{20}\text{H}_{24}\text{O}_2\text{H}$ 297.1849, found 297.1849.

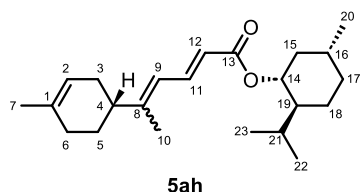
Butyl (2E)-5-((R)-4-methylcyclohex-3-en-1-yl)hexa-2,4-dienoate (5ae)



Prepared according to the general procedure **C** from (+)-limonene **1a** (81.0 μL , 0.5 mmol, 1.0 equiv.) and *n*-butyl acrylate **4e** (142.4 μL , 1.0 mmol, 2.0 equiv.). The crude product was purified by flash column chromatography over silica gel (pentane/ethyl acetate 99:1) to give *butyl (2E)-5-((R)-4-methylcyclohex-3-en-1-yl)hexa-2,4-dienoate* **5ae** as

a yellow oil (101.3 mg, 76%). $^1\text{H NMR}$ (400 MHz, CDCl_3): δ (ppm) 7.60 (dd, $J = 15.0, 11.6$ Hz, 1H, H-11), 6.01 (d, $J = 11.6$ Hz, 1H, H-9 major isomer), 5.96 (d, $J = 11.9$ Hz, 1H, H-9 minor isomer), 5.79 (d, $J = 15.2$ Hz, 1H, H-12 major isomer), 5.77 (d, $J = 15.1$ Hz, 1H, H-12 minor isomer), 5.39 (br. s, 1H, H-2), 4.14 (t, $J = 6.7$ Hz, 2H, H-14), 2.08-1.21 (m, 17H, H-3, H-4, H-5, H-6, H-7, H-10, H-15, H-16), 0.93 (t, $J = 7.4$ Hz, 3H, H-17). $^{13}\text{C NMR}$ (101 MHz, CDCl_3): δ (ppm) 168.0 (C-3 minor isomer), 167.9 (C-3 major isomer), 154.02 (C-1 minor isomer), 154.07 (C-1 major isomer), 141.2 (C-11 major isomer), 140.0 (C-11 minor isomer), 134.1 (C-8 minor isomer), 134.0 (C-8 major isomer), 123.9 (C-9 minor isomer), 121.9 (C-9 major isomer), 120.4 (C-2 minor isomer), 120.3 (C-2 major isomer), 119.3 (C-12 major isomer), 119.2 (C-12 minor isomer), 64.2 (C-14 minor isomer), 64.1 (C-14 major isomer), 43.7 (C-4 major isomer), 35.4 (C-4 minor isomer), 30.9 (C-3 or C-6 major isomer), 30.5 (C-3 or C-6 major isomer), 30.4 (C-3 or C-6 minor isomer), 30.1 (C-3 or C-6 minor isomer), 27.5 (C-5 minor isomer), 27.6 (C-5 major isomer), 23.7 (C-7 minor isomer), 23.6 (C-7 major isomer), 20.4 (C-15 both isomers), 19.3 (C-16 both isomers), 15.7 (C-10 both isomers), 13.9 (C-17 both isomers). **IR (ATR)** ν (cm^{-1}): 2928, 1714, 1633, 1438, 1379, 1273, 1150, 1134, 1066, 979, 887, 794. **HRMS (ESI)** m/z : $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{17}\text{H}_{26}\text{O}_2$ 263.2006, found 263.2006.

(1R,2S,5R)-2-isopropyl-5-methylcyclohexyl (2E)-5-((R)-4-methylcyclohex-3-en-1-yl)hexa-2,4-dienoate (5ah)

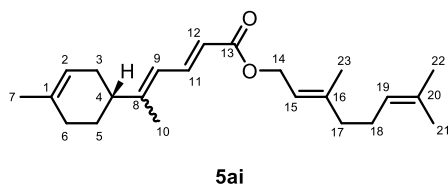


Prepared according to the general procedure **C** from (+)-limonene **1a** (81.0 μL , 0.5 mmol, 1 equiv.) and menthyl acrylate **2h** (223.7 μL , 1.0 mmol, 2.0 equiv.). The crude product was purified by flash column chromatography over silica gel (pentane/ethyl acetate 99:1) to give

(1R,2S,5R)-2-isopropyl-5-methylcyclohexyl (2E)-5-((R)-4-methylcyclohex-3-en-1-yl)hexa-2,4-dienoate **5ah** as a colorless oil (20.6 mg, 12%). $^1\text{H NMR}$ (400 MHz, CDCl_3): δ (ppm) 7.60 (dd, $J = 15.1, 11.6$ Hz, 1H, H-11), 6.02 (d, $J = 11.6$ Hz, 1H, H-9), 5.79 (d, $J = 15.1$ Hz, 1H, H-12), 5.40 (br. s, 1H, H-2), 4.76 (td, $J = 10.9, 4.5$ Hz, 1H, H-14), 1.94-0.85 (m, 28H, H-3, H-4, H-5, H-6, H-7, H-10, H-15, H-16, H-17, H-18, H-19, H-21, H-22, H-23), 0.77 (d, $J = 6.9$ Hz, 3H, H-20). $^{13}\text{C NMR}$ (101 MHz, CDCl_3): δ (ppm) 167.4 (C-3), 153.9 (C-1), 141.1 (C-11), 134.0 (C-8), 122.0 (C-9), 120.4 (C-2), 119.4 (C-12), 73.9 (C-14), 47.4 (C-19),

43.7 (C-4), 41.2 (C-15), 34.5 (C-17 or C-18), 31.6 (C-16), 30.53 (C-3 or C-6), 30.51 (C-3 or C-6), 27.7 (C-5), 26.5 (C-21), 23.8 (C-17 or C-18), 23.6 (C-7), 22.2 (C-22 or C-23), 20.9 (C-22 or C-23), 16.7 (C-20), 15.7 (C-10). **IR (ATR)** ν (cm⁻¹): 2955, 2925, 2360, 1710, 1633, 1455, 1306, 1271, 1193, 1149, 1135, 1014, 981. **HRMS (ESI)** m/z : [M+H]⁺ calcd for C₂₃H₃₆O₂H 345.2788, found 345.2787.

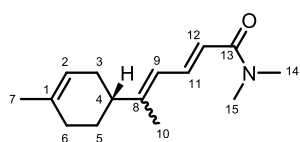
(E)-3,7-dimethylocta-2,6-dien-1-yl (2E)-5-((R)-4-methylcyclohex-3-en-1-yl)hexa-2,4-dienoate (5ai)



5ai

Prepared according to the general procedure **C** from (+)-limonene **1a** (81.0 μ L, 0.5 mmol, 1 equiv.) and geranyl acrylate **4i** (228.9 μ L, 1.0 mmol, 2.0 equiv.). The crude product was purified by flash column chromatography over silica gel (pentane/ethyl acetate 99:1) to give (*E*)-3,7-dimethylocta-2,6-dien-1-yl (*2E*)-5-((*R*)-4-methylcyclohex-3-en-1-yl)hexa-2,4-dienoate **5ai** as a colorless oil (46.2 mg, 27%). **¹H NMR** (400 MHz, CDCl₃): δ (ppm) 7.62 (d, J = 15.1, 11.5 Hz, 1H, H-11), 6.02 (d, J = 11.5 Hz, 1H, H-9), 5.80 (d, J = 15.1 Hz, 1H, H-12), 5.55-5.30 (m, 2H, H-2 and H-15), 5.21-5.02 (m, 1H, H-19), 4.67 (d, J = 6.9 Hz, 2H, H-14), 1.94–0.85 (m, 28H, H-3, H-4, H-5, H-6, H-10, H-17, H-18, H-21, H-22), 0.77 (d, J = 6.9 Hz, 3H, H-20). **¹³C NMR** (101 MHz, CDCl₃): δ (ppm) 167.9 (C-3 both isomers), 154.1 (C-1 both isomers), 142.1 (C-16 both isomers), 141.3 (C-11 both isomers), 134.0 (C-8 both isomers), 131.9 (C-20 both isomers), 124.0, (C-19 both isomers) 122.0 (C-9 both isomers), 120.3 (C-2 both isomers), 119.3 (C-12 both isomers), 118.8 (C-15 both isomers), 61.3 (C-14 both isomers), 43.7 (C-4 both isomers), 39.7 (C-17 both isomers), 30.5 (C-3 or C-6 both isomers), 29.9 (C-3 or C-6 both isomers), 27.7 (C-5 both isomers), 26.5 (C-18 both isomers), 25.8 (C-23 both isomers), 23.6 (C-7 both isomers), 17.8 (C-22 or C-21 both isomers), 16.7 (C-22 or C-21 both isomers), 15.7 (C-10 both isomers). **IR (ATR)** ν (cm⁻¹): 2925, 1717, 1637, 1455, 1377, 1271, 1100, 756. **HRMS (ESI)** m/z : [M+Na]⁺ calcd for C₂₃H₃₆O₂Na 365.2451, found 365.2451.

(2E)-N,N-dimethyl-5-((R)-4-methylcyclohex-3-en-1-yl)hexa-2,4-dienamide (5ak)

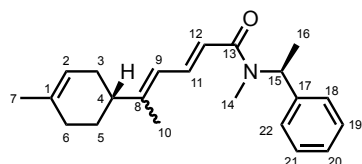


5ak

Prepared according to the general procedure **C** from (+)-limonene **1a** (81.0 μ L, 0.5 mmol, 1.0 equiv.) and *N,N*-dimethylacrylate **4k** (99.5 μ L, 1.0 mmol, 2.0 equiv.). The crude product was purified by flash column chromatography over silica gel (pentane/ethyl acetate 3:7) to give (*2E*)-*N,N*-dimethyl-5-((*R*)-4-methylcyclohex-3-en-1-yl)hexa-2,4-dienamide **5ak** as a colorless oil (71.4 mg, 61%). **¹H NMR** (400 MHz, CDCl₃): δ (ppm) 7.60 (dd, J = 14.6, 11.5 Hz, 1H, H-11), 6.24 (d, J = 14.6 Hz, 1H, H-12), 6.03 (d, J = 11.6 Hz, 1H, H-9), 5.39 (br. s, 1H, H-2), 3.07 (s, 3H, H-14 or H-15), 3.01 (s, 3H, H-14 or H-15), 2.23-1.16 (m, 13H, H-3, H-4, H-5, H-6, H-7, H-10). **¹³C NMR** (101 MHz, CDCl₃): δ (ppm) 167.6 (C-13 both isomers), 152.2 (C-1 both isomers), 139.2 (C-11 both isomers), 134.0 (C-8 both isomers),

122.2 (C-9 both isomers), 120.5 (C-2 both isomers), 118.5 (C-12), 43.6 (C-4 both isomers), 37.4 (C-14 or C-15 both isomers), 35.9 (C-14 or C-15 both isomers), 30.56 (C-3 both isomers), 30.54 (C-6 both isomers), 27.7 (C-5 both isomers), 23.6 (C-7 both isomers), 15.6 (C-10 both isomers). **IR (ATR)** ν (cm⁻¹): 2925, 1648, 1618, 1589, 1494, 1454, 1394, 1267, 1149, 1123, 979, 887. **HRMS (ESI)** m/z : [M+H]⁺ calcd for C₁₅H₂₃NOH 234.1852, found 234.1852.

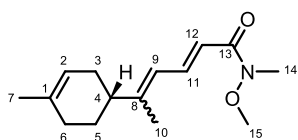
(2E)-N-methyl-5-((R)-4-methylcyclohex-3-en-1-yl)-N-((S)-1-phenylethyl)hexa-2,4-dienamide (5j)



5j

Prepared according to the general procedure **C** from (+)-limonene **1a** (81.0 μ L, 0.5 mmol, 1.0 equiv.) and (S)-N-methyl-N-(1-phenylethyl)acrylamide (189.3 mg, 1.0 mmol, 2.0 equiv.). The crude product was purified by flash column chromatography over silica gel (pentane/ethyl acetate 3:7) to give (2E,4E)-N-methyl-5-((R)-4-methylcyclohex-3-en-1-yl)-N-((S)-1-phenylethyl)hexa-2,4-dienamide (**5j**) as a colorless oil (61.5 mg, 38%). **¹H NMR** (400 MHz, CDCl₃): 7.70 (dd, J = 14.5, 11.5 Hz, 1H, H-11), 7.41-7.17 (m, 5H, H-18, H-19, H-20, H-21, H-22), 6.33-6.24 (m, 1H, H-12), 6.05 (d, J = 11.5 Hz, 1H, H-9), 5.40 (br. s, 1H, H-2), 2.73 (s, 3H, H-14), 2.21 (q, J = 10.4, 5.1 Hz, 1H, H-15), 2.09-1.49 (m, 16H, H-3, H-4, H-5, H-6, H-7, H-10, H-16). **¹³C NMR** (101 MHz, CDCl₃): δ (ppm) 167.4 (C-13 both isomers), 152.5 (C-1 both isomers), 140.9 (C-11 both isomers), 139.8 (C-17 both isomers), 134.0 (C-8 both isomers), 128.5 (C-9 both isomers), 127.4 (C-2 both isomers), 126.7 (C-12 both isomers), 122.3 (2C, C-18 and C-22 both isomers), 120.4 (2C, C-19 and C-21 both isomers), 118.9 (C-20 both isomers), 50.6 (C-15 both isomers), 43.6 (C-4 both isomers), 30.5 (2C, C-3 and C-6 both isomers), 29.7 (C-14 both isomers), 27.7 (C-5 both isomers), 23.6 (C-7 both isomers), 21.1 (C-16 both isomers) 15.7 (C-10 both isomers). **IR (ATR)** ν (cm⁻¹): 3012, 2933, 1632, 1591, 1497, 1113, 977, 845. **HRMS (ESI)** m/z : [M+H]⁺ calcd for C₂₂H₂₉NOH 324.2321, found 324.2320.

(2E)-N-methoxy-N-methyl-5-((R)-4-methylcyclohex-3-en-1-yl)hexa-2,4-dienamide (5al)

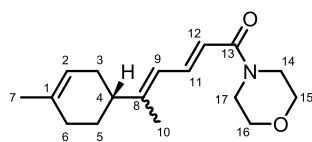


5al

Prepared according to the general procedure **C** from (+)-limonene **1a** (81.0 μ L, 0.5 mmol, 1.0 eq) and N-methoxy-N-methyl acrylamide **4l** (223.7 μ L, 1.0 mmol, 2.0 equiv.). The crude product was purified by flash column chromatography over silica gel (pentane/ethyl acetate 1:1) to give (2E)-N-methoxy-N-methyl-5-((R)-4-methylcyclohex-3-en-1-yl)hexa-2,4-dienamide **5al** as a colorless oil (65.9 mg, 53%). **¹H NMR** (300 MHz, CDCl₃): δ (ppm) 7.64 (dd, J = 14.9, 11.6 Hz, 1H, H-11), 6.37 (d, J = 14.9 Hz, 1H, H-12 major isomer), 6.35 (d, J = 14.9 Hz, 1H, H-12 minor isomer), 6.07 (d, J = 11.5 Hz, 1H, H-9 major isomer), 6.01 (d, J = 11.7 Hz, 1H, H-9 minor isomer), 5.38 (br. s, 1H, H-2), 3.69 (s, 3H, H-15), 3.23 (s, 3H, H-14), 2.22-1.48 (m, 13H, H-3, H-4, H-5, H-6, H-7, H-10). **¹³C NMR** (75 MHz, CDCl₃): δ (ppm)

167.6 (C-13 both isomers), 152.2 (C-1 both isomers), 139.2 (C-11 major isomer), 139.0 (C-11 minor isomer), 133.96 (C-8 minor isomer), 133.91 (C-8 major isomer), 124.4 (C-9 minor isomer), 122.2 (C-9 major isomer), 120.43 (C-2 minor isomer), 120.39 (C-2 major isomer), 117.0 (C-12 major isomer), 116.9 (C-12 minor isomer), 61.8 (C-15 major isomer), 60.5 (C-15 minor isomer), 43.7 (C-4 major isomer), 36.3 (C-4 minor isomer), 32.5 (C-14 both isomers), 30.5 (2C, C-3 and C-6 major isomers), 30.4 (C-3 or C-6 minor isomer), 30.0 (C-3 or C-6 minor isomer), 27.7 (C-5 major isomer), 27.4 (C-5 minor isomer), 23.59 (C-7 minor isomer), 23.54 (C-7 major isomer), 15.6 (C-10 both isomers). **IR (ATR)** ν (cm⁻¹): 2917, 1739, 1655, 1621, 1600, 1412, 1376, 1241, 1175, 1091, 1047, 1004, 886, 801, 704, 618. **HRMS (ESI)** m/z: [M+H]⁺ calcd for C₁₅H₂₃NO₂H 250.1802, found 250.1802.

(2E)-5-((R)-4-methylcyclohex-3-en-1-yl)-1-morpholinohexa-2,4-dien-1-one (5am)

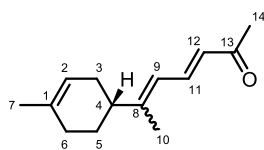


5am

Prepared according to the general procedure **C** from (+)-limonene **1a** (81.0 μ L, 0.5 mmol, 1.0 equiv.) and morpholine acrylamide **4m** (125.8 μ L, 1.0 mmol, 2.0 equiv.). The crude product was purified by flash column chromatography over silica gel (pentane/ethyl acetate 1:1) to give (2E)-5-

((R)-4-methylcyclohex-3-en-1-yl)-1-morpholinohexa-2,4-dien-1-one **5am** as a colorless oil (78.9 mg, 57%). **¹H NMR** (300 MHz, CDCl₃): δ (ppm) 7.62 (dd, J = 14.7, 11.6 Hz, 1H, H-11), 6.19 (d, J = 14.5 Hz, 1H, H-12 major isomer), 6.16 (d, J = 14.5 Hz, 1H, H-12 minor isomer), 6.01 (d, J = 11.4 Hz, 1H, H-9 major isomer), 5.96 (d, J = 10.9 Hz, 1H, H-9 minor isomer), 5.37 (br. s, 1H, H-2), 3.66 (br. s, 8H, H-14, H-15, H-16, H-17), 2.18–1.18 (m, 13H, H-3, H-4, H-5, H-6, H-7, H-10). **¹³C NMR** (75 MHz, CDCl₃): δ (ppm) 166.8 (C-13 minor isomer), 166.3 (C-13 major isomer), 152.9 (C-1 minor isomer), 152.8 (C-1 major isomer), 140.0 (C-11 major isomer), 138.9 (C-11 minor isomer), 133.91 (C-8 major isomer), 133.87 (C-8 minor isomer), 124.1 (C-9 minor isomer), 122.1 (C-9 major isomer), 120.37 (C-2 minor isomer), 120.34 (C-2 major isomer), 117.5 (C-12 major isomer), 117.3 (minor isomer), 66.9 (2C, C-15 and C-16), 43.6 (C-4 major isomer), 36.3 (C-4 minor isomer), 30.48 (2C, C-3 and C-6 both isomers), 30.46 (2C, C-14 and C-17 both isomers), 27.6 (C-5 major isomer), 27.5 (C-5 minor isomer), 23.57 (C-7 minor isomer), 23.53 (C-7 major isomer), 20.2 (C-10 minor isomer), 15.7 (C-10 major isomer). **IR (ATR)** ν (cm⁻¹): 2919, 1737, 1646, 1594, 1430, 1271, 1231, 1115, 1042, 976, 854. **HRMS (ESI)** m/z: [M+H]⁺ calcd for C₁₇H₂₅NO₂H 276.1958, found 276.1958.

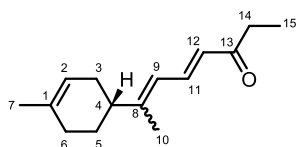
(3E)-6-((R)-4-methylcyclohex-3-en-1-yl)hepta-3,5-dien-2-one (5an)



5an

Prepared according to the general procedure **C** from (+)-limonene **1a** (81.0 μL , 0.5 mmol, 1.0 equiv.) and methylvinylketone **4n** (83.4 μL , 1.0 mmol, 2.0 equiv.). The crude product was purified by flash column chromatography over silica gel (pentane/ethyl acetate 96:4) to give (3E)-6-((R)-4-methylcyclohex-3-en-1-yl)hepta-3,5-dien-2-one **5an** as a colorless oil (21.6 mg, 21%). $^1\text{H NMR}$ (400 MHz, CDCl_3): δ (ppm) 7.47 (dd, $J = 15.3, 11.4$ Hz, 1H, H-11), 6.09 (d, $J = 15.3$ Hz, 1H, H-12 major isomer), 6.08 (d, $J = 15.2$ Hz, 1H, H-12 minor isomer), 6.04 (d, $J = 11.3$ Hz, 1H, H-9 major isomer), 5.98 (d, $J = 12.2$ Hz, 1H, H-9 minor isomer), 5.40 (br. s, 1H, H-2), 2.27 (s, 3H, H-14), 2.10-1.18 (m, 13H, H-3, H-4, H-5, H-6, H-7, H-10). $^{13}\text{C NMR}$ (101 MHz, CDCl_3): δ (ppm) 198.9 (C-13 both isomers), 155.6 (C-1 minor isomer), 155.5 (C-1 major isomer), 139.9 (C-11 major isomer), 138.6 (C-11 minor isomer), 134.2 (C-8 minor isomer), 134.0 (C-8 major isomer), 128.8 (C-12 major isomer), 128.7 (C-12 minor isomer), 124.4 (C-9 minor isomer), 122.4 (C-9 major isomer), 120.4 (C-2 minor isomer), 120.3 (C-2 major isomer), 43.9 (C-4, major isomer), 36.77 (C-4 minor isomer), 30.5 (2C, C-3 and C-6 major isomers), 30.4 (C-3 or C-6 minor isomer), 30.2 (C-3 or C-6 minor isomer), 27.9 (C-5 or C-14 minor isomer), 27.66 (C-5 or C-14 major isomer), 27.65 (C-5 or C-14 major isomer), 27.5 (C-5 or C-14 minor isomer), 23.7 (C-7 minor isomer), 23.6 (C-7 major isomer), 20.6 (C-10 minor isomer), 15.9 (C-10 major isomer). **IR (ATR)** ν (cm^{-1}) 2923, 1666, 1625, 1587, 1437, 1358, 1255, 1155, 974, 885, 802. **HRMS (ESI)** m/z : $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{14}\text{H}_{20}\text{ONa}$ 227.1406, found 227.1407.

(4E)-7-((R)-4-methylcyclohex-3-en-1-yl)octa-4,6-dien-3-one (5ao)

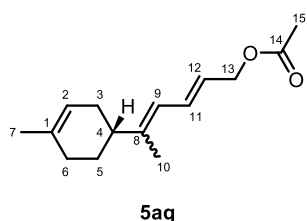


5ao

Prepared according to the general procedure **C** from (+)-limonene **1a** (81.0 μL , 0.5 mmol, 1.0 equiv.) and ethylvinylketone **4o** (99.6 μL , 1.0 mmol, 2.0 equiv.). The crude product was purified by flash column chromatography over silica gel (pentane/ethyl acetate 99:1) to give (4E)-7-((R)-4-methylcyclohex-3-en-1-yl)octa-4,6-dien-3-one **5ao** as a colorless oil (58.9 mg, 54%). $^1\text{H NMR}$ (400 MHz, CDCl_3): δ (ppm) 7.51 (dd, $J = 15.2, 11.4$ Hz, 1H, H-11), 6.11 (d, $J = 15.2$ Hz, 1H, H-12 major isomer), 6.10 (d, $J = 15.1$ Hz, 1H, H-12 minor isomer), 6.03 (d, $J = 11.4$ Hz, 1H, H-9 major isomer), 5.97 (d, $J = 12.1$ Hz, 1H, H-9 minor isomer), 5.40 (br. s, 1H), 2.74-2.44 (m, 2H, H-14), 2.11-1.22 (m, 13H, H-3, H-4, H-5, H-6, H-7, H-10). 1.11 (td, $J = 7.4, 2.8$ Hz, 3H, H-15). $^{13}\text{C NMR}$ (101 MHz, CDCl_3): δ (ppm) 201.4 (C-13 both isomers), 155.3 (C-1 minor isomer), 155.2 (C-1 major isomer), 138.6 (C-11 major isomer) 137.5 (C-11 minor isomer), 134.1 (C-8 minor isomer), 134.0 (C-8 major isomer), 127.7 (C-12 major isomer), 127.5 (C-12 minor isomer), 124.4 (C-9 minor isomer), 122.3 (C-9 major isomer), 120.4 (C-2 minor isomer), 120.2 (C-2 major isomer), 43.7 (C-4 mJOR isomer), 36.6 (C-4 minor isomer), 34.3 (C-14 minor isomer),

34.0 (C-14 major isomer), 30.49 (2C, C-3 and C-6 major isomer), 30.38 (C-3 or C-6 minor isomer), 30.1 (C-3 or C-6 minor isomer), 27.7 (C-5 major isomer), 27.5 (C-5 minor isomer), 23.4 (C-7 major isomer), 23.1 (C-7 minor isomer), 15.8 (C-10 major isomer), 14.2 (C-10 minor isomer), 8.53 (C-15 major isomer), 8.49 (C-15 minor isomer). **IR (ATR)** ν (cm⁻¹): 2921, 1665, 1625, 1591, 1202, 1115, 1033, 976, 887, 756. **HRMS (API)** m/z : [M+H]⁺ calcd for C₁₅H₂₂OH 219.1743, found 219.1744

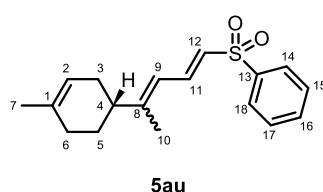
(2E)-5-((R)-4-methylcyclohex-3-en-1-yl)hexa-2,4-dien-1-yl acetate (5aq)



Prepared according to the general procedure **C** from (+)-limonene **1a** (81.0 μ L, 0.5 mmol, 1.0 equiv.) and allyl acetate **4q** (107.9 μ L, 1.0 mmol, 2.0 equiv.). The crude product was purified by flash column chromatography over silica gel (pentane/ethyl acetate 99:1) to give (2E)-5-((R)-4-methylcyclohex-3-en-1-yl)hexa-2,4-dien-1-yl acetate **5aq** as a colorless oil

(53.5 mg, 46%). **¹H NMR** (400 MHz, CDCl₃): δ (ppm) 6.56 (dd, J = 15.0, 10.9 Hz, 1H, H-11), 5.88 (d, J = 10.8 Hz, 1H, H-9 major isomer), 5.82 (d, J = 11.5 Hz, 1H, H-9 minor isomer), 5.66 (dt, J = 14.1, 6.8 Hz, 1H, H-12), 5.40 (br. s, 1H, H-2), 4.60 (d, J = 6.8 Hz, 2H, H-13), 2.06 (s, 3H, H-15), 2.03-1.16 (m, 13H, H-3, H-4, H-5, H-6, H-7, H-10). **¹³C NMR** (101 MHz, CDCl₃): δ (ppm) 171.0 (C-14 both isomers), 145.5 (C-1 major isomer), 145.4 (C-1 minor isomer), 134.1 (C-8 minor isomer), 133.9 (C-8 major isomer), 131.8 (H-11 major isomer), 130.8 (C-11 minor isomer), 124.2 (C-12 major isomer), 124.1 (C-12 minor isomer), 122.2 (C-9 both isomers), 120.8 (C-2 minor isomer), 120.7 (C-2 major isomer), 66.3 (C-13 minor isomer), 65.5 (C-13 major isomer), 43.3 (C-4 major isomer), 37.2 (C-4 minor isomer), 30.69 (C-3 or C-6 major isomer), 30.62 (C-3 or C-6 major isomer), 30.58 (C-3 or C-6 minor isomer), 29.8 (C-3 and C-6 minor isomer), 27.8 (C-5), 237.7 (C-7 minor isomer), 23.6 (C-7 major isomer), 21.2 (C-10 major isomer), 21.1 (C-10 minor isomer), 19.8 (C-15 minor isomer), 15.1 (C-15 major isomer). **IR (ATR)** ν (cm⁻¹): 2919, 2360, 1741, 1438, 1376, 1227, 1023, 964, 798. **HRMS (ESI)** m/z : [M+Na]⁺ calcd for C₁₅H₂₂O₂Na 257.1512, found 257.1513.

((1E)-4-((R)-4-methylcyclohex-3-en-1-yl)penta-1,3-dien-1-yl)sulfonylbenzene (5au)

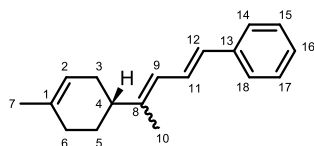


Prepared according to the general procedure **C** from (+)-limonene **1a** (81.0 μ L, 0.5 mmol, 1.0 equiv.) and phenyl vinyl sulfone **4u** (132 μ L, 1.0 mmol, 2.0 equiv.). The crude product was purified by flash column chromatography over silica gel (pentane/ethyl acetate 99:1) to give

((1E)-4-((R)-4-methylcyclohex-3-en-1-yl)penta-1,3-dien-1-yl)sulfonylbenzene **5au** as a colorless oil (20.3 mg, 13%).

¹H NMR (400 MHz, CDCl₃): δ (ppm) 7.92-7.87 (m, 2H, H-14 and H-18), 7.67-7.51 (m, 3H, H-11, H-15, H-16, H-17), 6.24 (d, *J* = 14.6 Hz, 1H, H-12 major isomer), 6.22 (d, *J* = 14.5 Hz, 1H, H-12 minor isomer), 5.95 (d, *J* = 11.6 Hz, 1H, H-9 major isomer), 5.90 (d, *J* = 11.6 Hz, 1H, H-9 minor isomer), 5.38 (br. s, 1H, H-2), 2.29-1.25 (m, 13H, H-3, H-4, H-5, H-6, H-7, H-10). **¹³C NMR** (75 MHz, CDCl₃): δ (ppm) 141.5 (C-1 both isomers), 139.0 (C-13 both isomers), 134.1 (C-8 both isomers), 133.2 (C-16 both isomers), 129.3 (2C, C-15 and C-17 both isomers), 127.6 (2C, C-14 and C-18 both isomers), 127.5 (C-11 both isomers), 121.5 (C-12 both isomers), 120.1 (C-2 both isomers), 119.7 (C-9 both isomers), 43.8 (C-4 both isomers), 30.41 (C-3 or C-6 both isomers), 30.35 (C-3 or C-6 both isomers), 27.5 (C-5 both isomers), 23.5 (C-7 both isomers), 16.0 (C-10 both isomers). **IR (ATR)** ν (cm⁻¹) 2924, 2360, 2342, 1318, 1306, 1145, 1086, 832, 688, 669. **HRMS (ESI)** *m/z*: [M+Na]⁺ calcd for C₁₈H₂₂O₂SNa 325.1233, found 325.1233.

((1*E*)-4-((*R*)-4-methylcyclohex-3-en-1-yl)penta-1,3-dien-1-yl)benzene (5av)

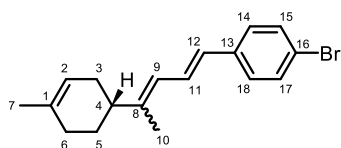


5av

Prepared according to the general procedure **C** from (+)-limonene **1a** (81.0 μL, 0.5 mmol, 1.0 equiv.) and styrene **4v** (115 μL, 1.0 mmol, 2.0 equiv.). The crude product was purified by flash column chromatography over silica gel (pentane 100%) to give ((1*E*)-4-((*R*)-4-methylcyclohex-3-en-1-yl)penta-1,3-dien-1-yl)benzene **5av** as a colorless oil (63.2 mg, 53%).

¹H NMR (400 MHz, CDCl₃): δ (ppm) 7.40 (m, 2H, H-14 and H-18), 7.31 (m, 2H, H-15 and H-17), 7.19 (m, 1H, H-16), 7.05 (dd, *J* = 15.5, 10.9 Hz, 1H, H-11), 6.48 (d, *J* = 15.5 Hz, 1H, H-12 major isomer), 6.45 (d, *J* = 15.4 Hz, 1H, H-12 minor isomer), 6.06 (d, *J* = 10.9 Hz, 1H, H-9 major isomer), 6.01 (d, *J* = 10.5 Hz, 1H, H-9 minor isomer), 5.43 (br. s, 1H, H-2), 2.24-1.48 (m, 13H, H-3, H-4, H-5, H-6, H-7, H-10). **¹³C NMR** (ppm) (101 MHz, CDCl₃): δ 144.6 (C-1 major isomer), 144.4 (C-1 minor isomer), 138.27 (C-13 major isomer), 138.21 (C-13 minor isomer), 134.1 (C-8 minor isomer), 133.9 (C-8 major isomer), 130.4 (C-16 major isomer), 130.3 (C-16 minor isomer), 128.7 (2C, C-14 and C-18 both isomers), 127.08 (C-11 minor isomer), 127.05 (C-11 major isomer), 126.27 (2C, C-15 and C-17 minor isomers), 126.23 (2C, C-15 and C-17 isomers), 125.9 (C-12 major isomer), 125.8 (C-12 minor isomer), 124.9 (C-2 minor isomer), 123.7 (C-2 major isomer), 121.0 (C-9 minor isomer), 120.8 (C-9 major isomer), 43.5 (C-4), 30.76 (2C, C-3 and C-6), 30.74 (2C, C-3 and C-6), 28.0 (C-5), 23.6 (C-7), 15.3 (C-15). **IR (ATR)** ν (cm⁻¹) 3031, 2913, 1596, 1495, 1447, 1072, 959, 914, 801, 747, 691. **GC-MS** (EI, 70 eV): *m/z* 238 (M⁺, 12%).

1-bromo-4-((1E)-4-((R)-4-methylcyclohex-3-en-1-yl)penta-1,3-dien-1-yl)benzene (**5aw**)

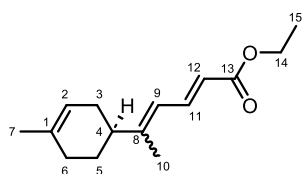


5aw

Prepared according to the general procedure **C** from (+)-limonene **1a** (81.0 μL , 0.5 mmol, 1.0 equiv.) and 4-bromostyrene **4w** (130.8 μL , 1.0 mmol, 2.0 equiv.). The crude product was purified by flash column chromatography over silica gel (cyclohexane 100%) to give 1-bromo-4-

((1E)-4-((R)-4-methylcyclohex-3-en-1-yl)penta-1,3-dien-1-yl)benzene **5aw** as a colorless oil (53.9 mg, 34%). $^1\text{H NMR}$ (400 MHz, CDCl_3): δ (ppm) 7.42 (m, 2H, H-15 and H-17), 7.28 (m, 2H, H-14 and H-18), 7.05 (dd, $J = 15.4, 10.8$ Hz, 1H, H-11), 6.41 (d, $J = 15.5$ Hz, 1H, H-12 major isomer), 6.38 (d, $J = 15.5$ Hz, 1H, H-12 minor isomer), 6.05 (d, $J = 10.9$ Hz, 1H, H-9 major isomer), 6.00 (d, $J = 10.7$ Hz, 1H, H-9 minor isomer), 5.44 (br. s, 1H, H-2), 2.32-1.24 (m, 13H, H-3, H-4, H-5, H-6, H-7, H-10). $^{13}\text{C NMR}$ (101 MHz, CDCl_3): δ (ppm) 145.5 (C-1 major isomer), 145.3 (C-1 minor isomer), 137.2 (C-13 major isomer), 137.1 (C-13 minor isomer), 134.1 (C-8 minor isomer), 134.0 (C-8 minor isomer), 132.0 (C-15 or C-17 minor isomer), 131.8 (2C, C-15 and C-17 major isomer), 131.7 (C-15 or C-17 minor isomer), 129.1 (C-12 minor isomer), 129.0 (C-12 major isomer), 128.0 (C-14 or C-18 minor isomer), 127.8 (C-14 or C-18 minor isomer), 127.7 (2C, C-14 and C-18 major isomers), 126.7 (C-11 minor isomer), 126.6 (C-11 major isomer), 125.5 (C-9 minor isomer), 123.5 (C-9 major isomer), 121.6 (C-2 or C-9 minor isomer), 120.9 (C-2 or C-16 minor isomer), 120.68 (C-2 or C-16 major isomer), 120.62 (C-16 minor isomer), 43.5 (C-4), 30.7 (2C, C-3 and C-6), 27.9 (C-5), 23.6 (C-7), 15.4 (C-10). **IR (ATR)** ν (cm^{-1}): 2922, 1635, 1487, 1437, 1072, 1008, 961, 850, 802, 758. **GC-MS** (EI, 70 eV): m/z 318 (M^+ , 24%), 316 (M^+ , 24%).

Ethyl (2E)-5-((S)-4-methylcyclohex-3-en-1-yl)hexa-2,4-dienoate (**ent-5ab**)



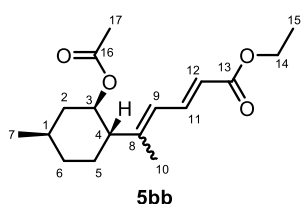
ent-5ab

Prepared according to the general procedure **C** from (-)-limonene **ent-1a** (81.0 μL , 0.5 mmol, 1.0 equiv.) and ethyl acrylate **4b** (106.5 μL , 1.0 mmol, 2.0 equiv.). The crude product was purified by flash column chromatography over silica gel (pentane/ethyl acetate 99:1) to give ethyl (2E)-5-((S)-4-methylcyclohex-3-en-1-yl)hexa-2,4-dienoate **ent-5ab** as a

yellow oil (70.6 mg, 60%). $^1\text{H NMR}$ (400 MHz, CDCl_3): δ (ppm) 7.61 (dd, $J = 15.1, 11.5$ Hz, 1H, H-11), 6.02 (d, $J = 11.6$ Hz, 1H, H-9 major isomer), 5.96 (d, $J = 12.5$ Hz, 1H, H-9 minor isomer), 5.79 (d, $J = 15.1$ Hz, 1H, H-12 major isomer), 5.77 (d, $J = 15.2$ Hz, 1H, H-12 minor isomer), 5.40 (br. s, 1H, H-2), 4.20 (q, $J = 7.1$ Hz, 2H, H-14), 2.37-1.42 (m, 13H, H-3, H-4, H-5, H-6, H-7, H-10), 1.29 (t, $J = 7.1$ Hz, 3H, H-15). $^{13}\text{C NMR}$ (101 MHz, CDCl_3): δ (ppm) 167.86 (C-13 minor isomer), 167.76 (C-13 major isomer), 154.0 (C-1 both isomers), 141.2 (C-11 major isomer), 140.0 (C-11 minor isomer), 134.0 (C-8 minor isomer), 133.9 (C-8 major isomer), 123.9 (C-9 minor isomer), 121.9 (C-9 major isomer), 120.4 (C-2 minor isomer), 120.3 (C-2 major isomer), 119.3 (C-12 major isomer), 119.2 (C-12 minor isomer), 60.5 (C-14 minor

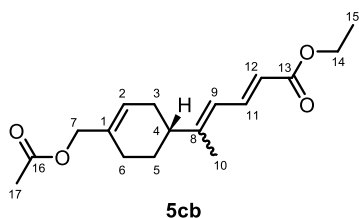
isomer), 60.2 (C-14 major isomer), 43.7 (C-4 major isomer), 36.4 (C-4 minor isomer), 30.5 (2C, C-3 and C-6 major isomers), 30.4 (C-3 or C-6 minor isomer), 30.0 (C-3 or C-6 minor isomer), 27.6 (C-5 major isomer), 27.4 (C-5 minor isomer), 23.6 (C-7 minor isomer), 23.5 (C-7 major isomer), 20.3 (C-10 minor isomer), 15.7 (C-10 major isomer), 14.4 (C-15 major isomer), 14.3 (C-15 minor isomer). **IR (ATR)** ν (cm⁻¹): 2913, 1714, 1633, 1444, 1367, 1271, 1150, 1134, 1042, 979, 887, 801, 757. **HRMS (ESI)** m/z : [M+H]⁺ calcd for C₁₅H₂₂O₂H 235.1693, found 235.1694.

Ethyl (2E)-5-((1S,2R,4R)-2-acetoxy-4-methylcyclohexyl)hexa-2,4-dienoate (5bb)



Prepared according to the general procedure **C** from (-)-isopulegol acetate **1b** (104.5 μ L, 0.5 mmol, 1.0 equiv.) and ethyl acrylate **4b** (106.5 μ L, 1.0 mmol, 2.0 equiv.). The crude product was purified by flash column chromatography over silica gel (pentane/ethyl acetate 95:5) to give *ethyl (2E)-5-((1S,2R,4R)-2-acetoxy-4-methylcyclohexyl)hexa-2,4-dienoate 5bb* as a colorless oil (46.5 mg, 32%). **¹H NMR** (400 MHz, CDCl₃): δ (ppm) 7.55 (dd, J = 15.2, 11.5 Hz, 1H, H-11), 6.01 (d, J = 11.5 Hz, 1H, H-9), 5.78 (d, J = 15.1 Hz, 1H, H-12), 4.84 (td, 1H, H-3), 4.25 (m, 2H, H-14), 2.16 (m, 1H, H-4), 1.92 (s, 3H, H-10 or H-17), 1.81 (s, 3H, H-10 or H-17), 1.77-1.35 (m, 7H, H-1, H-2, H-5, H-6), 1.28 (t, J = 7.2 Hz, 3H, H-15), 0.93 (d, J = 6.4 Hz, 3H, H-7). **¹³C NMR** (101 MHz, CDCl₃): δ (ppm) 170.5 (C-16 both isomers), 167.7 (C-17 both isomers), 149.8 (C-8 both isomers), 140.6 (C-11 both isomers), 124.9 (C-9 both isomers), 119.9 (C-12 both isomers), 73.2 (C-3 both isomers), 60.3 (C-14 both isomers), 53.2 (C-4 both isomers), 40.5 (C-2 both isomers), 34.0 (C-6 both isomers), 31.5 (C-1 both isomers), 29.9 (C-5 both isomers), 22.1 (C-7 both isomers), 21.2 (C-17 both isomers), 14.6 (C-10 both isomers), 14.5 (C-15 both isomers). **IR (ATR)** ν (cm⁻¹): 2928, 2360, 2341, 1736, 1714, 1633, 1368, 1243, 1160, 1928. **HRMS (ESI)** m/z : [M+H]⁺ calcd for C₁₇H₂₆O₄H 295.1904, found 295.1905.

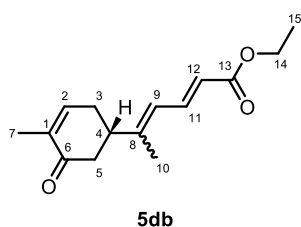
Ethyl (2E)-5-((R)-4-(acetoxymethyl)cyclohex-3-en-1-yl)hexa-2,4-dienoate (5cb)



Prepared according to the general procedure **C** from (-)-perillyl alcohol acetate **1c** (98.9 μ L, 0.5 mmol, 1.0 equiv.) and ethyl acrylate **4b** (106.5 μ L, 1.0 mmol, 2.0 equiv.). The crude product was purified by flash column chromatography over silica gel (pentane/ethyl acetate 95:5) to give *ethyl (2E)-5-((R)-4-(acetoxymethyl)cyclohex-3-en-1-yl)hexa-2,4-dienoate 5cb* as a colorless oil (87.7 mg, 60%). **¹H NMR** (300 MHz, CDCl₃): δ (ppm) 7.59 (dd, J = 15.2, 11.5 Hz, 1H, H-11), 6.00 (d, J = 12.8 Hz, 1H, H-9), 5.81-5.75 (m, 2H, H-12 and H-2), 4.45 (br. s, 2H, H-7), 4.18 (q, J = 7.1 Hz, 2H, H-14), 2.30-1.79 (m, 13H, H-3, H-4, H-5, H-6, H-10, H-17), 1.27 (t, J = 7.1 Hz, 3H, H-15). **¹³C NMR** (75 MHz, CDCl₃): δ (ppm) 171.12 (C-16 minor isomer), 171.09

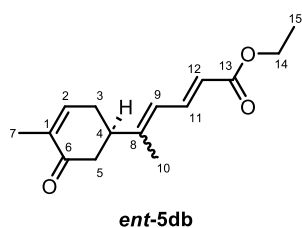
(C-16 major isomer), 167.8 (C-13 minor isomer), 167.7 (C-13 major isomer), 153.12 (C-1 major isomer), 153.05 (C-1 minor isomer), 141.0 (C-11 major isomer), 139.7 (C-11 minor isomer) 133.0 (C-8 minor isomer), 132.9 (C-8 major isomer), 125.7 (C-9 minor isomer), 125.4 (C-9 major isomer), 124.2 (C-2 minor isomer), 122.2 (C-2 major isomer), 119.68 (C-12 major isomer), 119.61 (C-12 minor isomer), 68.6 (C-7 minor isomer), 68.4 (C-7 major isomer), 60.32 (C-14 minor isomer), 60.26 (C-14 major isomer), 43.4 (C-4 major isomer), 36.2 (C-4 minor isomer), 30.2 (C-6 major isomer), 29.8 (C-3 or C-6 minor isomer), 29.7 (C-3 or C-6 minor isomer), 27.1 (C-5 major isomer), 26.9 (C-5 minor isomer), 26.4 (C-3 major isomer), 21.1 (C-17 major isomer), 20.3 (C-17 minor isomer), 15.6 (C-10 both isomers), 14.5 (C-15 both isomers). **IR (ATR)** ν (cm^{-1}): 2926, 1739, 1712, 1633, 1228, 1135, 1026. **HRMS (ESI)** m/z : $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{17}\text{H}_{24}\text{O}_4\text{H}$ 293.1747, found 293.1748.

Ethyl (2E)-5-((S)-4-methyl-5-oxocyclohex-3-en-1-yl)hexa-2,4-dienoate (5db)



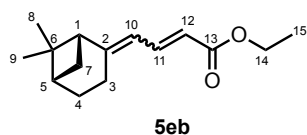
Prepared according to the general procedure **C** from (+)-carvone **1d** (78.2 μL , 0.5 mmol, 1.0 equiv.) and ethyl acrylate **4b** (106.5 μL , 1.0 mmol, 2.0 equiv.). The crude product was purified by flash column chromatography over silica gel (pentane/ethyl acetate 9:1) to give *ethyl (2E)-5-((S)-4-methyl-5-oxocyclohex-3-en-1-yl)hexa-2,4-dienoate* **5db** as a colorless oil (61.3 mg, 49%). **$^1\text{H NMR}$** (400 MHz, CDCl_3): δ (ppm) 7.55 (dd, $J = 15.2, 11.4$ Hz, 1H, H-11), 6.73 (ddd, $J = 5.7, 2.8, 1.5$ Hz, 1H, H-2), 6.01 (d, $J = 11.4$ Hz, 1H, H-9 major isomer), 6.01 (d, $J = 11.5$ Hz, 1H, H-9 minor isomer), 5.82 (d, $J = 15.2$ Hz, 1H, H-12 major isomer), 5.80 (d, $J = 15.1$ Hz, 1H, H-12 minor isomer), 4.18 (q, $J = 7.1$ Hz, 2H, H-14), 2.83-2.75 (m, 1H, H-4), 2.65-2.30 (m, 4H, H-3 and H-5), 1.89 (s, 3H, H-7 or H-10), 1.80-1.76 (m, 3H, H-7 or H-10), 1.27 (t, $J = 7.1$ Hz, 3H, H-15). **$^{13}\text{C NMR}$** (101 MHz, CDCl_3): δ (ppm) 199.1 (C-6 major isomer), 198.8 (C-6 minor isomer), 167.41 (C-13 minor isomer), 167.37 (C-13 major isomer), 149.2 (C-1 major isomer), 148.6 (C-1 minor isomer), 144.4 (C-2 minor isomer), 144.3 (C-2 major isomer), 140.3 (C-11 major isomer), 138.6 (C-11 minor isomer), 135.8 (C-8 minor isomer), 135.7 (C-8 major isomer), 125.5 (C-9 minor isomer), 123.3 (C-9 major isomer), 121.0 (C-12 major isomer), 120.9 (C-12 minor isomer), 60.42 (C-14 minor isomer), 60.36 (C-14 major isomer), 44.9 (C-4 major isomer), 42.8 (C-5 major isomer), 42.2 (C-4 minor isomer), 37.6 (C-5 minor isomer), 31.0 (C-3 major isomer), 30.6 (C-3 minor isomer), 20.4 (C-7 minor isomer), 15.9 (C-7 major isomer), 15.6 (C-10 both isomers), 14.5 (C-15 both isomers). **IR (ATR)** ν (cm^{-1}): 2982, 2923, 2361, 1710, 1674, 1634, 1366, 1274, 1213, 1196, 1160, 1100, 1041, 979, 900, 859. **HRMS (ESI)** m/z : $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{15}\text{H}_{20}\text{O}_3\text{H}$ 249.1485, found 249.1485.

Ethyl (2E)-5-((R)-4-methyl-5-oxocyclohex-3-en-1-yl)hexa-2,4-dienoate (**ent-5db**)



Prepared according to the general procedure **C** from (-)-carvone **1d** (78.2 μL , 0.5 mmol, 1.0 equiv.) and ethyl acrylate **4b** (106.5 μL , 1.0 mmol, 2.0 equiv.). The crude product was purified by flash column chromatography over silica gel (pentane/ethyl acetate 9:1) to give *ethyl (2E)-5-((R)-4-methyl-5-oxocyclohex-3-en-1-yl)hexa-2,4-dienoate ent-5db* as a colorless oil (83.8 mg, 67%). $^1\text{H NMR}$ (400 MHz, CDCl_3): δ (ppm) 7.55 (dd, $J = 15.2, 11.4$ Hz, 1H, H-11), 6.73 (ddd, $J = 5.7, 2.8, 1.5$ Hz, 1H, H-2), 6.01 (d, $J = 11.4$ Hz, 1H, H-9 major isomer), 6.01 (d, $J = 11.4$ Hz, 1H, H-9 minor isomer), 5.82 (d, $J = 15.1$ Hz, 1H, H-12 major isomer), 5.80 (d, $J = 15.1$ Hz, 1H, H-12 minor isomer), 4.18 (q, $J = 7.1$ Hz, 2H, H-14), 2.83-2.75 (m, 1H, H-4), 2.65-2.30 (m, 4H, H-3 and H-5), 1.89 (s, 3H, H-7 or H-10), 1.80-1.76 (m, 3H, H-7 or H-11), 1.27 (t, $J = 7.1$ Hz, 3H, H-15). $^{13}\text{C NMR}$ (101 MHz, CDCl_3): δ (ppm) 199.1 (C-6 major isomer), 198.8 (C-6 minor isomer), 167.41 (C-13 minor isomer), 167.37 (C-13 major isomer), 149.2 (C-1 major isomer), 148.6 (C-1 minor isomer), 144.4 (C-2 minor isomer), 144.3 (C-2 major isomer), 140.3 (C-11 major isomer), 138.6 (C-11 minor isomer), 135.8 (C-8 minor isomer), 135.7 (C-8 major isomer), 125.5 (C-9 minor isomer), 123.3 (C-9 major isomer), 121.0 (C-12 major isomer), 120.9 (C-12 minor isomer), 60.42 (C-14 minor isomer), 60.36 (C-14 major isomer), 44.9 (C-4 major isomer), 42.8 (C-5 major isomer), 42.2 (C-4 minor isomer), 37.6 (C-5 minor isomer), 31.0 (C-3 major isomer), 30.6 (C-3 minor isomer), 20.4 (C-7 minor isomer), 15.9 (C-7 major isomer), 15.6 (C-10 both isomers), 14.5 (C-15 both isomers). IR (ATR) ν (cm^{-1}): 2982, 2923, 2361, 1710, 1674, 1634, 1366, 1274, 1213, 1196, 1160, 1100, 1041, 979, 900, 859. HRMS (ESI) m/z : $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{15}\text{H}_{20}\text{O}_3\text{H}$ 249.1485, found 249.1485.

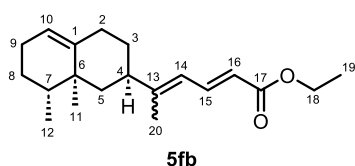
Ethyl 4-((1R,5S)-6,6-dimethylbicyclo[3.1.1]heptan-2-ylidene)but-2-enoate (**5eb**)



Prepared according to the general procedure **C** from (-)- β -pinene **1e** (78.3 μL , 0.5 mmol, 1.0 equiv.) and ethyl acrylate **4b** (106.5 μL , 1.0 mmol, 2.0 equiv.). The crude product was purified by flash column chromatography over silica gel (pentane/ethyl acetate 99:1) to give *ethyl 4-((1R,5S)-6,6-dimethylbicyclo[3.1.1]heptan-2-ylidene)but-2-enoate 5eb* as a colorless oil (64.4 mg, 55%). $^1\text{H NMR}$ (400 MHz, CDCl_3): δ (ppm) 7.56 (dd, $J = 15.2, 11.8$ Hz, 1H, H-11), 5.80 (d, $J = 12.1$ Hz, 1H, H-10), 5.69 (d, $J = 15.2$ Hz, 1H, H-12), 4.22-4.10 (m, 2H, H-14), 2.76-1.87 (m, 6H, H-1, H-3, H-4, H-5), 1.44-1.33 (m, 2H, H-7), 1.27 (m, 9H, H-8, H-9, H-15). $^{13}\text{C NMR}$ (101 MHz, CDCl_3): δ (ppm) 168.1 (C-13 minor isomer), 167.9 (C-13 major isomer), 158.2 (C-2 minor isomer), 158.0 (C-2 major isomer), 140.5 (C-11 major isomer), 140.3 (C-11 minor isomer), 121.1 (C-10 minor isomer), 120.6 (C-10 major isomer), 118.6 (C-12 minor isomer), 117.8 (C-12 major isomer), 60.13 (C-14 major isomer), 60.09 (C-14 minor isomer), 53.6 (C-1 minor isomer), 53.5

(C-1 minor isomer), 40.8 (C-5 minor isomer), 40.6 (C-5 major isomer), 29.8 (C-7 minor isomer), 27.4 (C-7 major isomer), 26.3 (C-8 or C-9 minor isomer), 26.2 (C-8 or C-9 major isomer), 23.9 (C-3 or C-4 minor isomer), 23.6 (C-3 or C-4 major isomer), 22.1 (C-8 or C-9 major isomer), 22.0 (C-8 or C-9 minor isomer), 21.1 (C-3 or C-4 minor isomer), 20.7 (C-3 or C-4 major isomer), 14.5 (C-15 major isomer), 14.3 (C-15 minor isomer). **IR (ATR)** ν (cm^{-1}): 2924, 1712, 1630, 1369, 1309, 1269, 1211, 1202, 1157, 1143, 1127, 1097 1042, 981, 913. **HRMS (ESI)** m/z : $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{15}\text{H}_{22}\text{O}_2\text{H}$ 235.1693, found 235.1694.

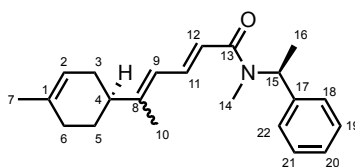
Ethyl (2E)-5-((2R,8R,8aS)-8,8a-dimethyl-1,2,3,4,6,7,8,8a-octahydronaphthalen-2-yl)hexa-2,4-dienoate (5fb)



Prepared according to the general procedure **GP1** from (+)-valencene **1f** (111.1 μL , 0.5 mmol, 1.0 equiv.) and ethyl acrylate **4b** (106.5 μL , 1.0 mmol, 2.0 equiv.). The crude product was purified by flash column chromatography over silica gel (pentane/ethyl acetate 99:1) to give

ethyl (2E)-5-((2R,8R,8aS)-8,8a-dimethyl-1,2,3,4,6,7,8,8a-octahydronaphthalen-2-yl)hexa-2,4-dienoate **5fb** as a colorless oil (84.6 mg, 56%). **$^1\text{H NMR}$** (400 MHz, CDCl_3): δ (ppm) 7.54 (dd, $J = 15.1, 11.6$ Hz, 1H, H-15), 6.01 (d, $J = 12.8$ Hz, 1H, H-14), 5.78 (d, $J = 15.2$ Hz, 1H, H-16), 4.83 (td, $J = 11.0, 4.5$ Hz, 1H, H-10), 4.19 (q, $J = 7.1$ Hz, 2H, H-18), 2.18-0.92 (m, 24H, H-2, H-3, H-4, H-5, H-7, H-8, H-9, H-11, H-12, H-19, H-20). **$^{13}\text{C NMR}$** (101 MHz, CDCl_3): δ (ppm) 167.8 (C-17 both isomers), 154.4 (C-1 both isomers), 142.6 (C-13 both isomers), 141.3 (C-15 both isomers), 121.9 (C-14 both isomers), 120.7 (C-10 both isomers), 119.2 (C-16 both isomers), 60.2 (C-18 both isomers), 44.5 (C-5 both isomers), 43.6 (C-4 or C-7 both isomers), 41.1 (C-4 or C-7 both isomers), 38.0 (C-6 both isomers), 32.7 (C-2 or C-3 both isomers), 32.6 (C-2 or C-3 both isomers), 27.2 (C-8 or C-9 both isomers), 26.0 (C-8 or C-9 both isomers), 18.5 (C-20 both isomers), 15.8 (C-11 or C-12 both isomers), 15.8 (C-11 or C-12 both isomers), 14.5 (C-19 both isomers). **IR (ATR)** ν (cm^{-1}): 2966, 2923, 1714, 1632, 1369, 1306, 1268, 1214, 1148, 1134, 1096, 1045, 979, 887, 844, 809, 732. **HRMS (ESI)** m/z : $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{20}\text{H}_{30}\text{O}_2\text{H}$ 303.2319, found 303.232.

(2E)-N-methyl-5-((S)-4-methylcyclohex-3-en-1-yl)-N-((S)-1-phenylethyl)hexa-2,4-dienamide (ent-5j)



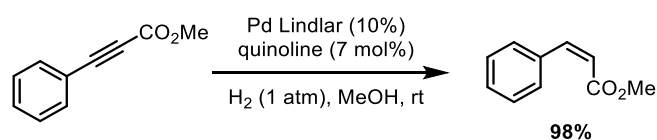
Prepared according to the general procedure **C** from (-)-limonene **ent-1a** (81.0 μL , 0.5 mmol, 1.0 equiv.) and (S)-N-methyl-N-(1-phenylethyl)acrylamide (189.3 mg, 1.0 mmol, 2.0 equiv.). The crude product was purified by flash column chromatography over silica gel

(pentane/ethyl acetate 3:7) to give *(2E)-N-methyl-5-((S)-4-methylcyclohex-3-en-1-yl)-N-((S)-1-phenylethyl)hexa-2,4-dienamide* **ent-5j** as a colorless oil (69.5 mg, 43%). **$^1\text{H NMR}$** (400 MHz, CDCl_3): **$^1\text{H NMR}$** (400 MHz, CDCl_3): 7.69 (dd, $J = 14.4, 11.4$ Hz, 1H, H-11), 7.40-7.19 (m, 5H, H-18, H-19, H-20, H-

21, H-22), 6.31-6.22 (m, 1H, H-12), 6.07 (d, $J = 11.4$ Hz, 1H, H-9), 5.40 (br. s, 1H, H-2), 2.73 (s, 3H, H-14), 2.20 (q, $J = 10.4, 5.1$ Hz, 1H, H-15), 2.10-1.30 (m, 16H, H-3, H-4, H-5, H-6, H-7, H-10, H-16). ^{13}C NMR (101 MHz, CDCl_3): δ (ppm) 168.4 (C-13 both isomers), 152.6 (C-1 both isomers), 141.9 (C-11 both isomers), 140.2 (C-17 both isomers), 139.9 (C-8 both isomers), 128.8 (C-9 both isomers), 127.4 (C-2 both isomers), 126.7 (C-12 both isomers), 122.1 (2C, C-18 and C-22 both isomers), 120.1 (2C, C-19 and C-21 both isomers), 118.7 (C-20 both isomers), 52.1 (C-15 both isomers), 43.7 (C-4 both isomers), 30.5 (2C, C-3 and C-6 both isomers), 29.2 (C-14 both isomers), 27.9 (C-5 both isomers), 23.4 (C-7 both isomers), 20.1 (C-16 both isomers) 15.7 (C-10 both isomers). IR (ATR) ν (cm^{-1}): 3012, 2933, 1632, 1591, 1497, 1113, 977, 845. HRMS (ESI) m/z : $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{22}\text{H}_{29}\text{NOH}$ 324.2321, found 324.2320.

Mechanistic study

Synthesis of (Z)-methyl cinnamate



(Z)-methyl cinnamate was prepared according to a procedure reported in the literature.^[236]

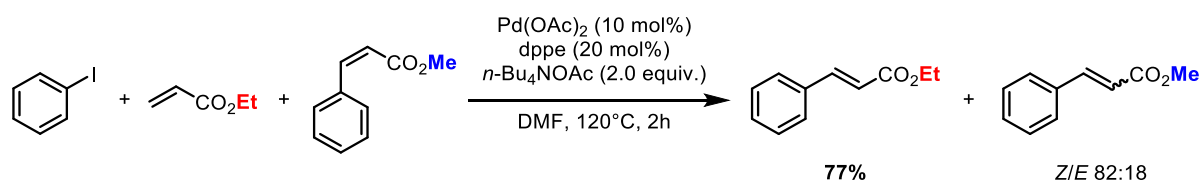
A round bottom flask was charged with Pd Lindlar (660 mg, 6.24 mmol, 1.0 equiv.), quinoline (52 μL , 0.44 mmol, 7 mol%) and methanol (20 mL, 0.3M) was added. To this solution was introduced methyl phenylpropiolate (0.92 mL, 6.24 mmol, 1.0 equiv.) and hydrogen gas was bubbled inside the solution for 10 minutes. The reaction was then stirred overnight at rt under a hydrogen atmosphere. The mixture was then diluted with 100 mL of dichloromethane and filtered over a pad of Celite[®]. The filtrate was concentrated under reduced pressure. The crude residue was then purified by flash column chromatography (cyclohexane/ethyl acetate 20:1) to afford (Z)-methyl cinnamate (985 mg, 98%) as a colorless oil.

The characterization data are in accordance with the ones reported in the literature.^[236]

^1H NMR (400 MHz, CDCl_3): δ (ppm) 7.72-7.47 (m, 2H), 7.47-7.28 (m, 3H), 6.96 (d, $J = 12.6$ Hz, 1H), 5.96 (d, $J = 12.7$ Hz, 1H), 3.72 (s, 3H).

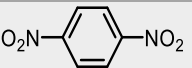
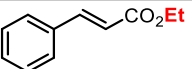
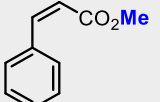
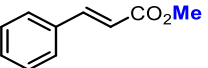
^[236] Kim, I. S.; Dong, G. R.; Jung, Y. H. *J. Org. Chem.* **2007**, *72*, 5424-5426.

Experiment demonstrating the isomerization of (Z)-acrylates with palladium hydride intermediates



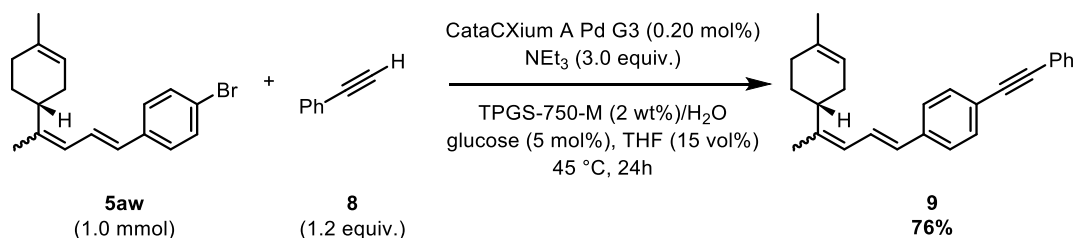
The reaction conditions were taken from a procedure reported in the literature.^[131]

An ace pressure tube was charged with palladium(II) acetate (11.2 mg, 0.05 mmol, 10 mol%), dppe (39.8 mg, 0.1 mmol, 20 mol%), (Z)-methyl cinnamate (81.1 mg, 0.5 mmol, 1.0 equiv.) and tetra-*n*-butylammonium acetate (301.5 mg, 1.0 mmol, 2.0 equiv.). The tube was placed under vacuum before being backfilled with argon. The vacuum/argon cycles were repeated twice and anhydrous DMF (6 mL, 0.08M) was added. To this solution was introduced iodobenzene (72 μL , 0.5 mmol, 1.0 equiv.) and ethyl acrylate (53 μL , 0.65 mmol, 1.3 equiv.). The tube was sealed and the mixture was stirred at 120°C until complete conversion as checked by TLC (2h). The mixture was diluted with 25 mL of ethyl acetate and filtered over a pad of silica gel. The filtrate was concentrated under reduced pressure and the crude mixture was analyzed by quantitative $^1\text{H-NMR}$ using 1,4-dinitrobenzene (8.4 mg, 0.05 mmol, integration I = 4.0) as internal standard. The results are summarized in the following table.

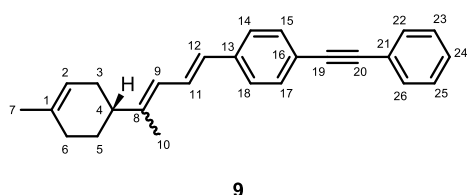
molecule	Integration	n (mmol)	ratio
 internal standard	4.00 (4H)	0.05	-
	15.41 (2H)	0.385	50%
	18.72 (3H)	0.312	41%
	4.21 (3H)	0.070	9%

3. Chapter 3: Application: Copper free Sonogashira cross coupling in water

The desired compound **9** was prepared according to a procedure reported in the literature.^[237]



A round bottom flask was charged with 1-bromo-4-((1*E*)-4-((*R*)-4-methylcyclohex-3-en-1-yl)penta-1,3-dien-1-yl)benzene **5aw** (317.3 mg, 1.0 mmol, 1.0 equiv.) and the flask was placed under vacuum before being backfilled with argon. The vacuum/argon cycles were repeated twice and a 2 wt% aqueous solution of TPGS-750-M (3.0 mL) was added. To this solution was introduced a 0.2 mol% of CataCXium A Pd G3 (145 mg) stock solution in THF (15 vol%), 5 mol% glucose (9.9 mg, 0.05 equiv.), 150 μ L of THF and ethynylbenzene **8** (131 μ L, 1.2 mmol, 1.2 equiv.). The mixture was stirred for 5 min at rt and triethylamine (418 μ L, 3.0 mmol, 3.0 equiv.) was added. The reaction mixture was heated up to 45 °C and the reaction was stirred for 24 h. The reaction mixture was cooled to rt and transferred into a 5 mL syringe filled with 3 g of silica. The silica was washed subsequently with heptane (2 x 2 mL) and ethyl acetate (2 x 2 mL). The combined organic layers were washed with brine (2 x 1 mL), dried over Na₂SO₄ and the solvents were removed *in vacuo*. Crude materials were purified by liquid-liquid extraction (Heptane/AcOEt 7:1) to afford the desired compound 1-((1*E*)-4-((*R*)-4-methylcyclohex-3-en-1-yl)penta-1,3-dien-1-yl)-4-(phenylethynyl)benzene **9** as a colourless oil (257.3 mg, 76%).



¹H NMR (300 MHz, CDCl₃); δ (ppm) 7.59-7.50 (m, 4H, H-14, H-15, H-16, H-17), 7.43-7.34 (m, 5H, H-22, H-23, H-24, H-25, H-26), 6.74 (dd, J = 15.3, 10.9 Hz, 1H, H-11), 6.82 (d, J = 15.5 Hz, 1H, H-12), 6.47 (d, J = 10.9 Hz, 1H, H-9), 5.44 (br. s, 1H, H-2), 2.42-1.11 (m, 13H, H-3, H-4, H-5, H-6, H-7, H-10). ¹³C NMR (75 MHz, CDCl₃); δ (ppm) 147.6 (C-1 both isomers), 143.2 (C-21 both isomers), 140.2 (C-13 both isomers), 136.1 (C-16 both isomers), 133.9 (C-8 both isomers), 131.9 (C-11 both isomers), 131.0 (2C, C-15 and C-17 both isomers), 129.4 (2C, C-

^[237] Jacobi, M.; Gallou, F.; Sparr, C.; Parmentier, M. *Helv. Chim. Acta* **2019**, *102*, e1900024

14 and C-18 both isomers), 128.3 (2C, C-22 and C-26 both isomers), 125.2 (2C, C-23 and C-25 both isomers), 124.4 (C-24 both isomers), 123.1 (C-9 both isomers), 122.6 (C-2 both isomers), 120.4 (C-12 both isomers), 90.4 (C-19 both isomers), 88.5 (C-20 both isomers), 44.6 (C-4 both isomers), 31.2 (C-3 or C-6 both isomers), 30.5 (C-3 or C-6 both isomers), 27.3 (C-5 both isomers), 24.2 (C-7 both isomers), 15.6 (C-10 both isomers). IR (ATR) ν (cm⁻¹): 2978, 1535, 1587, 1427, 1104, 1082, 942, 812, 834, 794. HRMS (ESI) m/z : [M+H]⁺ calcd for C₂₆H₂₆H 339.5020, found 339.5020.

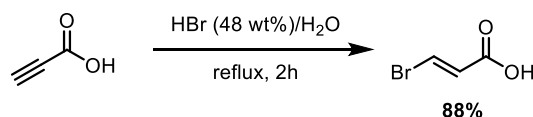
4. Chapter 4: Development of a C-H / C-X coupling reaction

4.1. Synthesis and characterization of starting materials

All the starting materials used for the optimization of the reaction and the evaluation of the scope had to be prepared with the exception of β -bromostyrene **10v**, which was commercially available.

4.1.1. Synthesis of (*E*)-3-bromoacrylic acid

(*E*)-3-bromoacrylic acid was prepared according to a procedure reported in the literature.^[238]



Propiolic acid (1.55 mL, 25.0 mmol, 1.0 equiv.) was dissolved in aqueous HBr (48 wt%, 9.9 mL) and the mixture was refluxed for 2h. The mixture was slowly cooled to room temperature, then to 0 °C. The white crystals obtained were filtered and washed with cold water, dried and used without further purification (3.32 g, 88%).

The characterization data are in accordance with the ones reported in the literature.^[239]

¹H NMR (400 MHz, CDCl₃): δ (ppm) 10.77 (br. s, 1H), 7.77 (d, J = 13.9 Hz, 1H), 6.55 (d, J = 13.9 Hz, 1H).

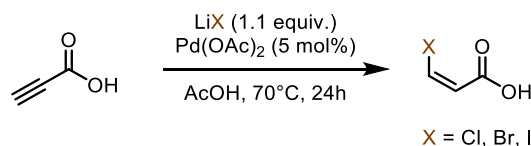
^[238] Faltracco, M.; Ruijter, E. *Org. Biomol. Chem.* **2021**, *19*, 9641-9644.

^[239] Luo, Y.; Roy, I. D.; Madec, A. G. E.; Lam, H. W. *Angew. Chem. Int. Ed.* **2014**, *53*, 4186-4190.

4.1.2. Synthesis of (Z)-3-haloacrylic acid

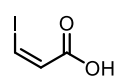
(Z)-3-bromoacrylic acid was prepared according to the reported literature.^[240]

General procedure D: Synthesis of (Z)-haloacrylic acid



A round bottom flask was charged with propiolic acid (10 mmol, 1.0 equiv.), LiX (1.1 equiv.) and Pd(OAc)₂ (5 mol%). The flask was placed under vacuum before being backfilled with argon. The vacuum/argon cycles were repeated twice and acetic acid (10 mL) was introduced. The mixture was then heated to reflux (70 °C) for 24h. It was slowly cooled to rt and the solvent was evaporated under reduced pressure. The resulting crystals were dried and used without any further purification.

(Z)-3-iodoacrylic acid

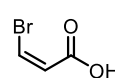


Prepared according to procedure **D** with propiolic acid (0.62 mL, 10.0 mmol, 1.0 equiv.), LiI (1.47 g, 11.0 mmol, 1.1 equiv.), Pd(OAc)₂ (112.3 mg, 5 mol%) in AcOH (10 mL). After work-up, (Z)-3-iodoacrylic acid was obtained as colorless crystals (1.76 g, 89%) that could be used without any further purification.

The characterization data are in accordance with the ones reported in the literature.^[241]

¹H NMR (400 MHz, CDCl₃): δ (ppm) 7.64 (d, *J* = 9.0 Hz, 1H), 6.96 (d, *J* = 9.0 Hz, 1H)

(Z)-3-bromoacrylic acid



Prepared according to procedure **D** with propiolic acid (0.62 mL, 10 mmol, 1.0 equiv.), LiBr (955.3 mg, 11 mmol, 1.1 equiv.), Pd(OAc)₂ (112.3 mg, 5 mol%) in AcOH (10 mL). After work-up, (Z)-3-bromoacrylic acid was obtained as colorless crystals (1.40 g, 93%) that could be used without any further purification.

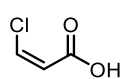
The characterization data are in accordance with the ones reported in the literature.^[240]

¹H NMR (400 MHz, CDCl₃): δ (ppm) 11.31 (br. s, 1H), 7.23 (d, *J* = 8.60 Hz, 1H), 6.66 (d, *J* = 8.60 Hz, 1H)

^[240] Ma, S.; Lu, X. *J. Chem. Soc., Chem. Commun.* **1990**, 1643-1644.

^[241] Zoller, T.; Uguen, D. *Tetrahedron Lett.* **1998**, 39, 6719-6720.

(Z)-3-chloroacrylic acid



Prepared according to procedure **D** with propiolic acid (0.62 mL, 10.0 mmol, 1.0 equiv.), LiCl (466.3 mg, 11.0 mmol, 1.1 equiv.), Pd(OAc)₂ (112.3 mg, 5 mol%) in AcOH (10 mL). After work-up, (Z)-3-chloroacrylic acid was obtained as colorless crystals (947.9 mg, 89%) that could be used without any further purification.

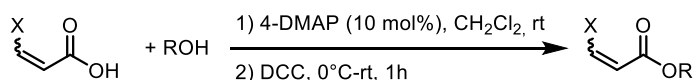
The characterization data are in accordance with the ones reported in the literature.^[242]

¹H NMR (400 MHz, CDCl₃): δ (ppm) 6.84 (d, *J* = 8.0 Hz, 1H), 6.28 (d, *J* = 8.0 Hz, 1H).

4.1.3. Synthesis of 3-haloacrylates

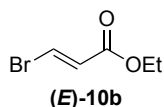
3-haloacrylates were prepared according to a procedure reported in the literature.^[243]

General procedure E: Synthesis of 3-haloacrylates



A round bottom flask was charged with 3-haloacrylic acid (1.0 equiv.) and 4-DMAP (0.1 equiv.). The flask was placed under vacuum before being backfilled with argon. The vacuum/argon cycles were repeated twice and dry dichloromethane (1M) was added. To this solution was introduced a 3M solution of the alcohol (1.0 equiv.) in dichloromethane and the reaction was stirred under an argon atmosphere at rt. The reaction mixture was cooled to 0 °C and DCC (1.2 equiv.) was added. The mixture was stirred for 5 min. After stirring for additional 1 h at room temperature, the reaction mixture was filtered with Celite® and the residue was washed with diethyl ether. The organic layer was washed with a 0.5 N aqueous solution of hydrochloric acid and an aqueous saturated solution of sodium bicarbonate. The resulting organic layer was dried over anhydrous magnesium sulfate and filtered. The filtrate was concentrated under reduced pressure and the residue was purified by flash column chromatography on silica gel to afford the desired product.

Ethyl (E)-3-bromoacrylate ((E)-10b)



Prepared according to the general procedure **E** from (E)-3-bromoacrylic acid (452.9 mg, 3.0 mmol, 1.0 equiv.) and EtOH (175 μL, 3.0 mmol, 1.0 equiv.). The crude product

^[242] Kurtz, A. N.; Billups, W. E.; Greenlee, R. B.; Hamil, H. F.; Pace, W. T. *J. Org. Chem.* **1965**, *30*, 3141-3147.

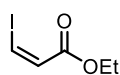
^[243] Kawasaki, T.; Saito, S.; Yamamoto, Y. *J. Org. Chem.* **2002**, *67*, 2653-2658.

was purified by flash column chromatography on silica gel (pentane/ethyl acetate 98:2) to afford *ethyl (E)-3-bromoacrylate (E)-10b* as a yellow oil (488.7 mg, 91%).

The characterization data are in accordance with the ones reported in the literature.^[244]

¹H NMR (400 MHz, CDCl₃): δ (ppm) 6.98 (d, *J* = 8.3 Hz, 1H), 6.61 (d, *J* = 8.3 Hz, 1H), 4.24 (q, *J* = 7.2 Hz, 2H), 1.31 (t, *J* = 7.1 Hz, 3H).

Ethyl (Z)-3-iodoacrylate ((Z)-10b')



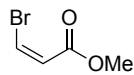
(Z)-10b'

Prepared according to the general procedure **E** from (Z)-3-iodoacrylic acid (593.9 mg, 3.0 mmol, 1.0 equiv.) and EtOH (175 μL, 3.0 mmol, 1.0 equiv.). The crude product was purified by flash column chromatography on silica gel (pentane/ethyl acetate 98:2) to afford *ethyl (Z)-3-iodoacrylate (Z)-10b'* as a colorless oil (501.7 mg, 74%).

The characterization data are in accordance with the ones reported in the literature.^[245]

¹H NMR (400 MHz, CDCl₃): δ (ppm) 7.43 (d, *J* = 9.0 Hz, 1H), 6.87 (d, *J* = 9.0 Hz, 1H), 4.19 (q, *J* = 7.2 Hz, 2H), 1.30 (t, *J* = 6.9 Hz, 3H).

Methyl (Z)-3-bromoacrylate ((Z)-10a)



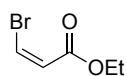
(Z)-10a

Prepared according to the general procedure **E** from (Z)-3-bromoacrylic acid (452.9 mg, 3.0 mmol, 1.0 equiv.) and MeOH (123 μL, 3.0 mmol, 1.0 equiv.). The crude product was purified by flash column chromatography on silica gel (pentane/ethyl acetate 98:2) to afford *methyl (Z)-3-bromoacrylate (Z)-10a* as a white solid (475.2 mg, 96%).

The characterization data are in accordance with the ones reported in the literature.^[246]

¹H NMR (400 MHz, CDCl₃): δ (ppm) 7.03 (d, *J* = 8.3 Hz, 1H), 6.65 (d, *J* = 8.3 Hz, 1H), 3.78 (s, 3H).

Ethyl (Z)-3-bromoacrylate ((Z)-10b)



(Z)-10b

Prepared according to the general procedure **E** from (Z)-3-bromoacrylic acid (452.9 mg, 3.0 mmol, 1.0 equiv.) and EtOH (175 μL, 3.0 mmol, 1.0 equiv.). The crude product was purified by flash column chromatography on silica gel (pentane/ethyl acetate 98:2) to afford *ethyl (Z)-3-bromoacrylate (Z)-10b* as a colorless oil (445.7 mg, 83%).

The characterization data are in accordance with the ones reported in the literature.^[247]

¹H NMR (400 MHz, CDCl₃): δ (ppm) 6.93 (d, *J* = 8.4 Hz, 1H), 6.55 (d, *J* = 8.4 Hz, 1H), 4.16 (q, *J* = 7.0 Hz, 2H), 1.24 (t, *J* = 7.0 Hz, 3H)

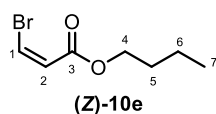
^[244] Bai, Y.; Lin, Z.; Ye, Z.; Dong, D.; Wang, J.; Chen, L.; Xie, F.; Li, Y.; Dixneuf, P. H.; Zhang, M. *Org. Lett.* **2022**, *24*, 7988-7992.

^[245] Dieter, K. R.; Kai, L. *J. Org. Chem.* **2002**, *67*, 847-855.

^[246] Bäckström, P.; Jacobsson, U.; Norin, T.; Unelius C. R. *Tetrahedron* **1988**, *44*, 251-2548.

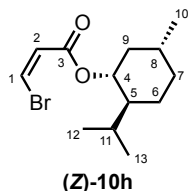
^[247] Salazar, J.; Fernández, F.; Restrepo, J.; López, S. E. *J. Chem. Res.* **2007**, *3*, 170-172.

Butyl (Z)-3-bromoacrylate ((Z)-10e)



Prepared according to the general procedure E from (Z)-3-bromoacrylic acid (452.9 mg, 3.0 mmol, 1.0 equiv.) and *n*-BuOH (274 μ L, 3.0 mmol, 1.0 equiv.). The crude product was purified by flash column chromatography on silica gel (pentane/ethyl acetate 98:2) to afford *butyl (Z)-3-bromoacrylate* ((Z)-10e) as a pale pale-yellow oil (565.3 mg, 91%). ¹H-NMR (400 MHz, CDCl₃): δ (ppm) 6.96 (d, *J* = 8.3 Hz, 1H, H-1), 6.60 (d, *J* = 8.4 Hz, 1H, H-2), 4.17 (t, *J* = 6.6 Hz, 2H, H-4), 1.65 (dq, *J* = 8.5, 6.7 Hz, 2H, H-5), 1.40 (dq, *J* = 8.5, 7.3 Hz, 2H, H-6), 0.93 (t, *J* = 7.4 Hz, 3H, H-7). ¹³C-NMR (400 MHz, CDCl₃): δ (ppm) 164.1 (C-3), 124.7 (C-2), 121.1 (C-1), 64.8 (C-4), 30.7 (C-5), 19.3 (C-6), 13.8 (C-7). IR (ATR) ν (cm⁻¹): 2961, 1730, 1614, 1333, 1208, 1168. HRMS (ESI) *m/z*: [M+Na]⁺ calcd for C₇H₁₁BrO₂Na 228.9835, found 228.9835.

(1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl (Z)-3-bromoacrylate ((Z)-10h)



Prepared according to the general procedure E from (Z)-3-bromoacrylic acid (452.9 mg, 3.0 mmol, 1.0 equiv.) and menthol (468.8, 3.0 mmol, 1.0 equiv.). The crude product was purified by flash column chromatography on silica gel (pentane/ethyl acetate 98:2) to afford *(1R,2S,5R)-2-isopropyl-5-methylcyclohexyl (Z)-3-bromoacrylate* ((Z)-10h) as a pale-yellow solid (546.6 mg, 63%).

¹H-NMR (400 MHz, CDCl₃): δ (ppm) 6.95 (d, *J* = 8.3 Hz, 1H, H-1), 6.60 (d, *J* = 8.3 Hz, 1H, H-2), 4.80 (td, *J* = 10.9, 4.4 Hz, 1H, H-4), 2.11-0.98 (m, 9H, H-5, H-6, H-7, H-8, H-9 and H-11), 0.90 (app t, *J* = 6.7 Hz, 6H, H-12 and H-13), 0.77 (d, *J* = 7.0 Hz, 3H, H-10). ¹³C-NMR (400 MHz, CDCl₃): δ (ppm) 163.8 (C-3), 125.1 (C-1), 120.7 (C-2), 75.1 (C-4), 47.1 (C-5), 41.0 (C-9), 34.4 (C-6 or C-7), 31.6 (C-8), 26.4 (C-11), 23.6 (C-6 or C-7), 22.2 (C-12 or C-13), 20.9 (C-12 or C-13), 16.5 (C-10). IR (ATR) ν (cm⁻¹): 2033, 2870, 1719, 1616, 1575, 1330. HRMS (ESI) *m/z*: [M+Na]⁺ calcd for C₁₃H₂₁BrO₂Na 311.0617, found 311.0618

4.1.4. Synthesis of (Z)-3-bromoacrylamides

(Z)-3-bromoacrylamides were prepared according to procedures reported in the literature.^[248]

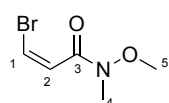
General procedure F: Synthesis of (Z)-3-haloacrylamides

^[248] Oakdale, J. S.; Sit, R. K.; Fokin, V. V. *Chem. Eur. J.* **2014**, *20*, 1-11.



A round-bottom flask was charged with 4-DMAP (0.07 equiv.) The flask was placed under vacuum before being backfilled with argon. The vacuum/argon cycles were repeated twice and dry dichloromethane (0.8M) was introduced. The flask was then cooled to 0°C (ice/water bath) and the corresponding amine HNR_1R_2 (1.02 equiv.) was added directly to the reaction vessel, followed by DCC (1.0 equiv.). Finally, (Z)-3-bromoacrylic acid (1.0 equiv.) was added dropwise and the reaction mixture was allowed to warm to room temperature overnight with stirring. The crude reaction mixture was filtered to remove the urea formed and the filtrate was purified column chromatography on silica gel affording the desired product.

(Z)-3-bromo-N-methoxy-N-methylacrylamide ((Z)-10l)



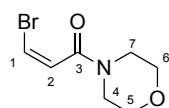
(Z)-10l

Prepared according to the general procedure **F** from (Z)-3-bromoacrylic acid (452.9 mg, 3.0 mmol, 1.0 equiv.) and *N,O*-dimethylhydroxylamine hydrochloride (298.5 mg, 3.1 mmol, 1.02 equiv.). The crude product was purified by flash column

chromatography on silica gel (pentane/ethyl acetate 7:3) to afford (Z)-3-bromo-N-methoxy-N-methylacrylamide **(Z)-10l** as a white solid (430.7 mg, 74%).

¹H NMR (400 MHz, CDCl₃): δ (ppm) 7.04 (d, *J* = 8.3 Hz, 1H, H-1), 6.81 (d, *J* = 8.3 Hz, 1H, H-2), 3.71 (s, 3H, H-5), 3.26 (s, 3H, H-4). ¹³C-NMR (400 MHz, CDCl₃): δ (ppm) 160.1 (C-3), 124.5 (C-2), 117.4 (C-1), 61.9 (C-5), 32.1 (C-4). IR (ATR) ν (cm⁻¹): 3083, 2937, 1664, 1621. HRMS (ESI) *m/z*: [M+Na]⁺ calcd for C₅H₈BrNO₂Na 215.9631, found 215.9632.

(Z)-3-bromo-1-morpholinoprop-2-en-1-one ((Z)-10m)



(Z)-10m

Prepared according to the general procedure **F** from (Z)-3-bromoacrylic acid (452.9 mg, 3.0 mmol, 1.0 equiv.) and morpholine (264 μL, 3.1 mmol, 1.02 equiv.). The crude product was purified by flash column chromatography on silica gel (pentane/ethyl

acetate 7:3) to afford (Z)-3-bromo-1-morpholinoprop-2-en-1-one **(Z)-10m** as a white solid (349.9 mg, 53%).

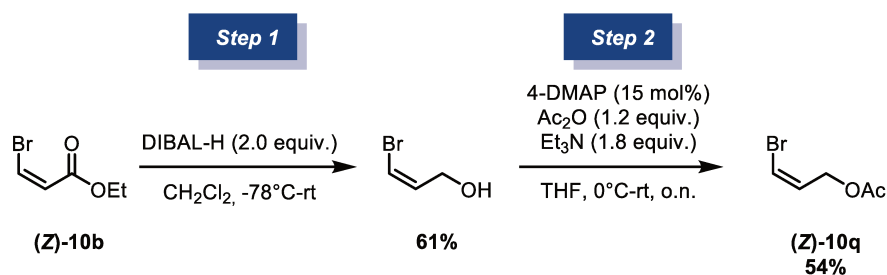
¹H NMR (400 MHz, CDCl₃): δ (ppm) 6.64 (d, *J* = 8.1 Hz, 1H, H-1), 6.49 (d, *J* = 8.1 Hz, 1H, H-2), 3.57 – 3.50 (m, 6H), 3.46 – 3.28 (m, 2H). ¹³C-NMR (400 MHz, CDCl₃): δ (ppm): 164.5 (C-3), 128.3 (C-2), 113.0 (C-1),

67.2 (C-5 or C-6), 66.8 (C-5 or C-6), 46.8 (C-4 or C-7), 41.9 (C-4 or C-7). IR (ATR) ν (cm⁻¹): 2852, 1631, 1435, 1233, 1113. HRMS (ESI) m/z: [M+H]⁺ calcd for C₇H₁₀BrNO₂Na 241.9787, found 241.9788.

4.1.5. Synthesis of other (Z)-3-bromo coupling partners

Synthesis of (Z)-3-bromoallylacetate ((Z)-10q)

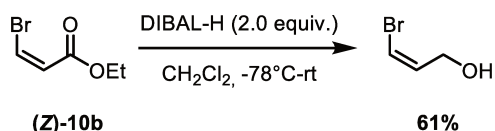
(Z)-3-Bromoallyl acetate ((Z)-10q) was obtained by reduction of the ester ((Z)-10b) with DIBAL-H in dichloromethane (Step 1), followed by standard acetylation of the resulting allylic alcohol (Step 2).



Scheme 117. Synthesis of (Z)-3-bromoallylacetate.

STEP 1

The reduction of the ester ((Z)-10b) into the corresponding β-bromoallyl alcohol was obtained adapting reported conditions from the literature.^[249]



In a round bottom flask was added ethyl (Z)-3-bromoacrylate ((Z)-10b) (450 mg, 2.51 mmol, 1.0 equiv.). The flask was placed under vacuum before being backfilled with argon. The vacuum/argon cycles were repeated twice and dry dichloromethane was added. The stirred solution was cooled to -78 °C (acetone/liquid N₂ bath) and a 1M solution of DIBAL-H (5.0 mL, 2.0 equiv.) was added dropwise. The cooling bath was removed and the reaction mixture was allowed to warm to room temperature. After 2h, the conversion was monitored by TLC and the reaction was quenched at -60 °C with a saturated solution of Rochelle salt (9 mL). The reaction mixture was allowed to warm to room temperature overnight. The organic layer was separated, the aqueous layer was extracted with dichloromethane (2x 10 mL). The combined organic layers were washed with water (10 mL), brine (10 mL) and dried

^[249] Beruben, D.; Marek, I.; Normant, J. F.; Platzer, N. *J. Org. Chem.* **1995**, *60*, 2488-2501.

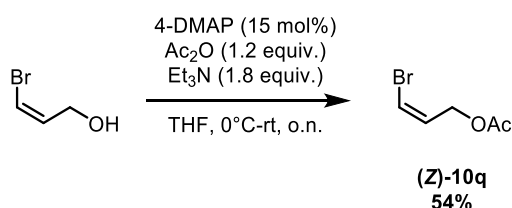
over anhydrous magnesium sulfate. The desired (*Z*)-bromoallyl alcohol was obtained as a colorless oil (209.7 mg, 61%) without any further purification.

The characterization data are in accordance with the ones reported in the literature.^[250]

¹H NMR (400 MHz, CDCl₃): δ (ppm) 6.73 (dt, *J* = 7.3, 5.8 Hz, 1H), 6.26 (dt, *J* = 7.3, 1.4 Hz, 1H), 4.32 (dd, *J* = 5.8, 1.4 Hz, 1H), 1.70 (s, 1H).

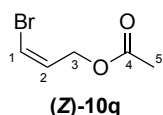
STEP 2

The acetylation of the corresponding (*Z*)-bromoallyl alcohol into the (*Z*)-3-bromoallyl acetate (**(Z)-10q**) was obtained adapting reported conditions from the literature.^[232]



A round bottom flask was charged with (*Z*)-3-bromoallyl alcohol (166.2 mg, 1.22 mmol, 1.0 equiv.) and the flask was placed under vacuum before being backfilled with argon. The vacuum/argon cycles were repeated twice and dichloromethane (2.5 mL) was added. To this solution was introduced acetic anhydride (140 μL, 1.46 mmol, 1.2 equiv.), triethylamine (310 μL, 2.19 mmol, 1.8 equiv.) and 4-DMAP (22.3 mg, 0.15 equiv.). The reaction mixture was cooled to 0°C maintained at this temperature for 1h and stirred at room temperature overnight.

The solvent was removed under reduced pressure and the resulting material was diluted with ethyl acetate and washed with water and brine. The resulting organic layer was dried over anhydrous magnesium sulfate and filtered. The filtrate was concentrated under reduced pressure to afford (*Z*)-3-bromoallylacetate (**(Z)-10q**) as a yellow oil (117.9 mg, 54%) without any further purification.



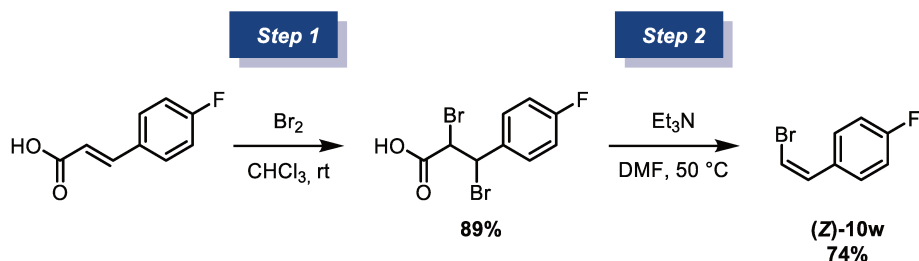
¹H-NMR (300 MHz, CDCl₃): δ (ppm) 6.38 (dt, *J* = 7.3, 1.5 Hz, 1H, H-1), 6.29 (dt, *J* = 7.3, 5.9 Hz, 1H, H-2), 4.73 (dd, *J* = 5.9, 1.5 Hz, 2H, H-3), 2.08 (s, 3H, H-5). ¹³C-NMR (75 MHz, CDCl₃): δ (ppm) 170.9 (C-4), 129.6 (C-2), 111.2 (C-1), 61.9 (C-3), 32.1.

IR (ATR) ν(cm⁻¹): (pending). HRMS (ESI) *m/z*: [M+H]⁺ calcd for C₅H₇BrO₂Na 200.9522, found 200.9519.

Synthesis of (*Z*)-1-(2-bromovinyl)-4-fluorobenzene (**(Z)-10w**)

^[250] Wei, X.; Taylor, R. J. K. *J. Org. Chem.* **2000**, *65*, 616-620.

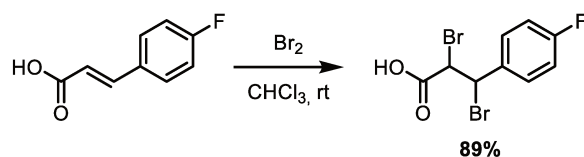
(Z)-1-(2-bromovinyl)-4-fluorobenzene (**Z**-10w) was prepared *via* dibromination of 3-(4-fluorophenyl)acrylic acid in chloroform (Step 1), followed by decarboxylative dehydrobromination (Step 2).



Scheme 118. Synthesis of (Z)-1-(2-bromovinyl)-4-fluorobenzene.

STEP 1

The dibromination of 3-(4-fluorophenyl)acrylic acid into the corresponding 2,3-dibromo-3-(4-fluorophenyl)propanoic acid was obtained according to a reported procedure.^[251]



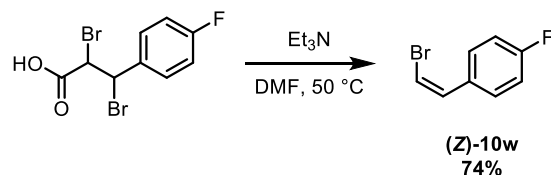
A round bottom flask was charged with 4-fluorocinnamic acid (160 mg, 0.60 mmol, 1.0 equiv.). The flask was placed under vacuum before being backfilled with argon. The vacuum/argon cycles were repeated twice and chloroform (1M) was added. After 5 min, bromine (34 μ L, 0.66 mmol, 1.1 equiv.) was added and the reaction was left stirring for 2h at room temperature. The crude product was filtered over a pad of silica and the filtrate was concentrated under reduced pressure. The desired product was obtained as white solid (169.6 mg, 86%) and directly used for Step 2 without any further purification.

STEP 2

The decarboxylative dehydrobromination of the 2,3-dibromo-3-(4-fluorophenyl)propanoic acid into the corresponding (Z)-1-(2-bromovinyl)-4-fluorobenzene (**Z**-10w) was obtained according to a procedure reported in the literature.^[252]

^[251] Kim, S. H.; Wei, H.-X.; Willis, S.; Li, G. *Synth. Comm.* **1999**, *29*, 4179-4185.

^[252] Kuang, C.; Yang, Q.; Senboku, H.; Tokuda, M. *Tetrahedron* **2005**, *61*, 4043-4052.



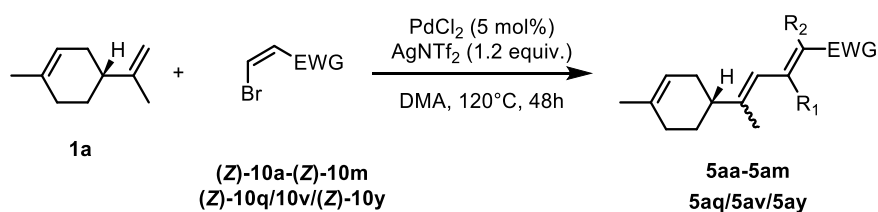
A round bottom flask was charged with 2,3-dibromo-3-(4-fluorophenyl)propanoic acid (163.6 mg, 0.51 mmol, 1.0 equiv.) previously obtained in Step 1 and the flask was placed under vacuum before being backfilled with argon. The vacuum/argon cycles were repeated twice and dry DMF (0.5M) was added. To this solution was introduced triethylamine (140 μL , 1.02 mmol, 2.0 equiv.) at room temperature and the reaction was heated at 50 $^\circ\text{C}$ for 3h. The reaction was finally cooled back to 0 $^\circ\text{C}$ and quenched by the slow addition of a 1N aqueous hydrochloric acid solution (2mL). The two layers were separated, and the aqueous layer was extracted with ethyl acetate (3 x 3mL). The combined organic layers were washed with water three times and then with brine, dried over anhydrous magnesium sulfate and filtered. The filtrate was then concentrated under reduced pressure to afford (Z)-1-(2-bromovinyl)-4-fluorobenzene **(Z)-10w** (71.8 mg, 70%) without any further purification.

The characterization data are in accordance the ones reported in the literature.^[252]

$^1\text{H NMR}$ (400 MHz, CDCl_3): δ (ppm) 6.38 (d, $J = 8.2$ Hz, 1H), 6.97–7.07 (m, 3H), 7.61–7.67 (m, 2H).

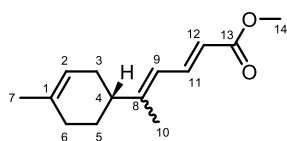
4.2. Pd(II)-catalyzed redox neutral coupling

General Procedure G for the Pd(II)-catalyzed redox neutral coupling



A 10 mL sealed tube was charged with 4.4 mg (0.025 mmol, 5 mol%) of palladium (II) chloride, 257.4 mg (0.6 mmol, 1.2 equiv.) of silver bistriflimide. The tube was placed under vacuum and backfilled with argon. The vacuum/argon cycles were repeated twice and 2.5 mL of DMA was added. To this solution was added (+)-limonene **1a** (1.0 mmol, 2.0 equiv.) and the (Z)-bromoalkene (0.5 mmol, 1.0 equiv.). The solution was stirred under inert atmosphere at reflux (heating bath at 120 $^\circ\text{C}$) for 48 h. After cooling to room temperature, the organic layer was washed with water (3 x 5 mL). The combined organic layers were concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel affording the desired product.

Methyl (*R*)-5-(4-methylcyclohex-3-en-1-yl)hexa-2,4-dienoate (**5aa**)



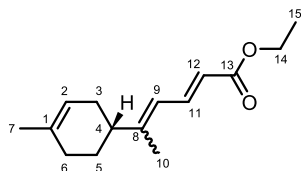
5aa

Prepared according to the general procedure **G** from (+)-limonene **1a** (162 μ L, 1.0 mmol, 2.0 equiv.) and methyl (*Z*)-3-bromoacrylate (**Z**)-**10a** (82.5 mg, 0.5 mmol, 1.0 equiv.). The crude product was purified by flash column chromatography on silica gel (pentane/ethyl acetate 99:1) to give *methyl (R)*-5-(4-methylcyclohex-3-en-1-yl)hexa-2,4-dienoate **5aa** as a brown oil (90.3 mg, 78%).

The characterization data are in accordance with the ones reported in Exp. Section Chapter 2.

¹H NMR (400 MHz, CDCl₃): δ (ppm) 7.62 (dd, $J = 15.2, 11.6$ Hz, 1H, H-11), 6.02 (d, $J = 11.6$ Hz, 1H, H-9 major isomer), 5.97 (d, $J = 11.8$ Hz, 1H, H-9 minor isomer), 5.79 (d, $J = 15.1$ Hz, 1H, H-12 major isomer), 5.78 (d, $J = 15.2$ Hz, 1H, H-12 minor isomer), 5.40 (br. s, 1H, H-2), 3.74 (s, 3H, H-14), 2.14-1.20 (m, 13H, H-3, H-4, H-5, H-6, H-7, H-10).

Ethyl (*2E*)-5-((*R*)-4-methylcyclohex-3-en-1-yl)hexa-2,4-dienoate (**5ab**)



5ab

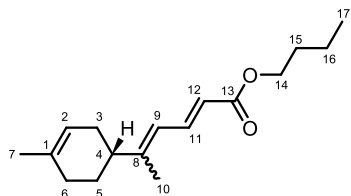
Prepared according to the general procedure **G** from (+)-limonene **1a** (162 μ L, 1.0 mmol, 2.0 equiv.) and ethyl (*Z*)-3-bromoacrylate (**Z**)-**10b** (89.5 mg, 0.5 mmol, 1.0 equiv.). The crude product was purified by flash column chromatography on silica gel (pentane/ethyl acetate 99:1) to give *ethyl (R)*-5-(4-methylcyclohex-3-en-1-yl)hexa-2,4-dienoate **5ab** as a brown oil

(92.9 mg, 79%).

The characterization data are in accordance with the ones reported in Exp. Section Chapter 2.

¹H NMR (400 MHz, CDCl₃): δ (ppm) 7.60 (dd, $J = 15.1, 11.6$ Hz, 1H, H-11), 6.01 (d, $J = 11.7$ Hz, 1H, H-9 major isomer), 5.95 (d, $J = 12.0$ Hz, 1H, H-9 minor isomer), 5.78 (d, $J = 15.1$ Hz, 1H, H-12 major isomer), 5.76 (d, $J = 15.1$ Hz, 1H, H-12 minor isomer), 5.39 (br. s, 1H, H-2), 4.19 (q, $J = 7.1$ Hz, 2H, H-14), 2.17-1.18 (m, 16H, H-3, H-4, H-5, H-6, H-7, H-10, H-15).

Butyl (*2E*)-5-((*R*)-4-methylcyclohex-3-en-1-yl)hexa-2,4-dienoate (**5ae**)



5ae

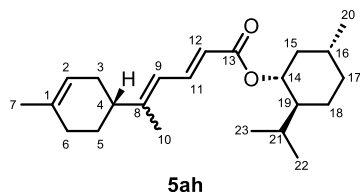
Prepared according to the general procedure **G** from (+)-limonene **1a** (162 μ L, 1.0 mmol, 2.0 equiv.) and ethyl (*Z*)-3-bromoacrylate (**Z**)-**10e** (75.0 mg, 0.5 mmol, 1.0 equiv.). The crude product was purified by flash column chromatography on silica gel (pentane/ethyl acetate 99:1) to give *butyl (2E)*-5-((*R*)-4-methylcyclohex-3-en-1-yl)hexa-2,4-

dienoate **5ae** as a yellow oil (81.3 mg, 61%).

The characterization data are in accordance with the ones reported in Exp. Section Chapter 2.

$^1\text{H NMR}$ (400 MHz, CDCl_3): δ (ppm) 7.60 (dd, $J = 15.0, 11.6$ Hz, 1H, H-11), 6.01 (d, $J = 11.6$ Hz, 1H, H-9 major isomer), 5.96 (d, $J = 11.9$ Hz, 1H, H-9 minor isomer), 5.79 (d, $J = 15.2$ Hz, 1H, H-12 major isomer), 5.77 (d, $J = 15.1$ Hz, 1H, H-12 minor isomer), 5.39 (br. s, 1H, H-2), 4.14 (t, $J = 6.7$ Hz, 2H, H-14), 2.08–1.21 (m, 17H, H-3, H-4, H-5, H-6, H-7, H-10, H-15, H-16), 0.93 (t, $J = 7.4$ Hz, 3H, H-17).

(1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl (2*E*)-5-((*R*)-4-methylcyclohex-3-en-1-yl)hexa-2,4-dienoate (5ah)



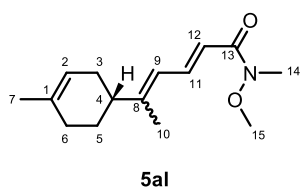
Prepared according to the general procedure **GP5** from (+)-limonene **1a** (162 μL , 1.0 mmol, 2.0 equiv.) and (1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl (*Z*)-3-bromoacrylate (**Z**)-**10h** (144.6 mg, 0.5 mmol, 1.0 equiv.). The crude product was purified by flash chromatography

on silica gel (pentane/ethyl acetate 99:1) to give (1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl (2*E*)-5-((*R*)-4-methylcyclohex-3-en-1-yl)hexa-2,4-dienoate **5ah** as a colorless oil (92.7 mg, 54%).

The characterization data are in accordance with the ones reported in Exp. Section Chapter 2.

$^1\text{H NMR}$ (400 MHz, CDCl_3): δ (ppm) 7.60 (dd, $J = 15.1, 11.6$ Hz, 1H, H-11), 6.02 (d, $J = 11.6$ Hz, 1H, H-9), 5.79 (d, $J = 15.1$ Hz, 1H, H-12), 5.40 (br. s, 1H, H-2), 4.76 (td, $J = 10.9, 4.5$ Hz, 1H, H-14), 1.94–0.85 (m, 28H, H-3, H-4, H-5, H-6, H-7, H-10, H-15, H-16, H-17, H-18, H-19, H-21, H-22, H-23), 0.77 (d, $J = 6.9$ Hz, 3H, H-20).

(2*E*)-*N*-methoxy-*N*-methyl-5-((*R*)-4-methylcyclohex-3-en-1-yl)hexa-2,4-dienamide (5al)



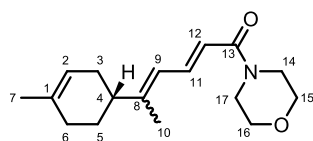
Prepared according to the general procedure **G** from (+)-limonene **1a** (162 μL , 1.0 mmol, 2.0 equiv.) and (*Z*)-3-bromo-*N*-methoxy-*N*-methylacrylamide (**Z**)-**10i** (97.0 mg, 0.5 mmol, 1.0 equiv.). The crude product was purified by flash column chromatography on silica gel

(pentane/ethyl acetate 3:7) to give (2*E*)-*N*-methoxy-*N*-methyl-5-((*R*)-4-methylcyclohex-3-en-1-yl)hexa-2,4-dienamide **5al** as a colorless oil (75.8 mg, 61%).

The characterization data are in accordance with the ones reported in Exp. Section Chapter 2.

$^1\text{H NMR}$ (300 MHz, CDCl_3): δ (ppm) 7.64 (dd, $J = 14.9, 11.6$ Hz, 1H, H-11), 6.37 (d, $J = 14.9$ Hz, 1H, H-12 major isomer), 6.35 (d, $J = 14.9$ Hz, 1H, H-12 minor isomer), 6.07 (d, $J = 11.5$ Hz, 1H, H-9 major isomer), 5.38 (br. s, 1H, H-2), 3.69 (s, 3H, H-15), 3.23 (s, 3H, H-14), 2.22–1.48 (m, 13H, H-3, H-4, H-5, H-6, H-7, H-10).

(2E)-5-((R)-4-methylcyclohex-3-en-1-yl)-1-morpholinohexa-2,4-dien-1-one (5am)



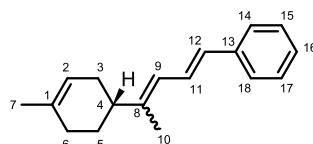
5am

Prepared according to the general procedure **G** from (+)-limonene **1a** (162 μ L, 1.0 mmol, 2.0 equiv.) and (Z)-3-bromo-1-morpholinoprop-2-en-1-one (**Z**)-**10m** (110.0 mg, 0.5 mmol, 1.0 equiv.). The crude product was purified by flash column chromatography on silica gel (pentane/ethyl acetate 3:7) to give (2E)-5-((R)-4-methylcyclohex-3-en-1-yl)-1-morpholinohexa-2,4-dien-1-one **5am** as a colorless oil (72.0 mg, 52%).

The characterization data are in accordance with the ones reported in Exp. Section Chapter 2.

$^1\text{H NMR}$ (300 MHz, CDCl_3): δ (ppm) 7.62 (dd, $J = 14.7, 11.6$ Hz, 1H, C-11), 6.19 (d, $J = 14.5$ Hz, 1H, H-12 major isomer), 6.16 (d, $J = 14.5$ Hz, 1H, H-12 minor isomer), 6.01 (d, $J = 11.4$ Hz, 1H, H-9 major isomer), 5.96 (d, $J = 10.9$ Hz, 1H, H-9 minor isomer), 5.37 (br. s, 1H, H-2), 3.66 (br. s, 8H, H-14, H-15, H-16, H-17), 2.18–1.18 (m, 13H, H-3, H-4, H-5, H-6, H-7, H-10).

((1E)-4-((R)-4-methylcyclohex-3-en-1-yl)penta-1,3-dien-1-yl)benzene (5av)



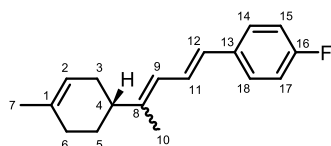
5av

Prepared according to the general procedure **G** from (+)-limonene **1a** (162 μ L, 1.0 mmol, 2.0 equiv.) and commercially available β -bromostyrene **10v** (64 μ L, 0.5 mmol, 1.0 equiv.) The crude product was purified by flash column chromatography on silica gel (pentane 100%) to give ((1E)-4-((R)-4-methylcyclohex-3-en-1-yl)penta-1,3-dien-1-yl)benzene **5av** as a colorless oil (40.5 mg, 34%).

The characterization data are in accordance with the ones reported in Exp. Section Chapter 2.

$^1\text{H NMR}$ (400 MHz, CDCl_3): δ (ppm) 7.40 (m, 2H, H-14 and H-18), 7.31 (m, 2H, H-15 and H-17), 7.19 (m, 1H, H-16), 7.05 (dd, $J = 15.5, 10.9$ Hz, 1H, H-11), 6.48 (d, $J = 15.5$ Hz, 1H, H-12 major isomer), 6.45 (d, $J = 15.4$ Hz, 1H, H-12 minor isomer), 6.06 (d, $J = 10.9$ Hz, 1H, H-9 major isomer), 6.01 (d, $J = 10.5$ Hz, 1H, H-9 minor isomer), 5.43 (br. s, 1H, H-2), 2.24-1.48 (m, 13H, H-3, H-4, H-5, H-6, H-7, H-10).

1-fluoro-4-((1E)-4-((R)-4-methylcyclohex-3-en-1-yl)penta-1,3-dien-1-yl)benzene (5ay)



5ay

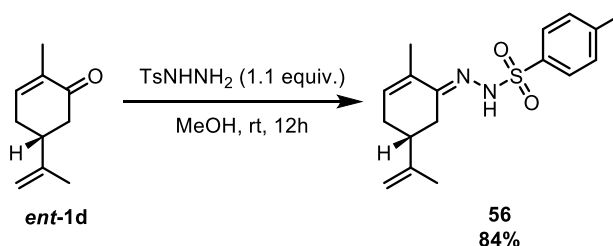
Prepared according to the general procedure **G** from (+)-limonene **1a** (162 μ L, 1.0 mmol, 2.0 equiv.) and (Z)-1-(2-bromovinyl)-4-fluorobenzene (**Z**)-**10w** (100.5 mg, 0.5 mmol, 1.0 equiv.). The crude product was purified by flash column chromatography on silica gel (pentane 100%) to give 1-fluoro-4-((1E)-4-((R)-4-methylcyclohex-3-en-1-yl)penta-1,3-dien-1-yl)benzene **5ay** as a colorless oil (30.5 mg, 24%). $^1\text{H NMR}$ (400 MHz, CDCl_3): δ (ppm) 7.39-7.32 (m, 2H, H-14 and H-18), 7.04-6.91 (m, 3H, H-11, H-15 and H-17), 6.43 (d, $J = 15.5$ Hz, 1H, H-12 major isomer),

6.40 (d, $J = 15.4$ Hz, 1H, H-12 minor isomer), 6.03 (d, $J = 10.8$ Hz, 1H, H-9 major isomer), 5.98 (d, $J = 10.8$ Hz, 1H, H-9 minor isomer), 5.42 (br. s, 1H, H-2), 2.38-1.22 (m, 13H, H-3, H-4, H-5, H-6, H-7, H-10). ^{13}C NMR (101 MHz, CDCl_3): δ (ppm) 144.6 (C-1 both isomers), 134.1 (C-8 both isomers), 129.0 (C-12 both isomers), 127.7 (2C, C-14 and C-18 both isomers), 127.6 (C-13 both isomers), 125.6 (C-9 both isomers), 124.7 (C-11 both isomers), 121.0 (C-2 both isomers), 115.7 (C-15 and C-17 both isomers), 115.5 (C-16 both isomers), 43.5 (C-4 both isomers), 30.7 (2C, C-3 and C-6 both isomers), 27.9 (C-5 both isomers), 23.6 (C-7 both isomers), 15.2 (C-10 both isomers). IR (ATR) ν (cm^{-1}): 2928, 2360, 1665, 1626, 1506, 1209, 967. HRMS (ESI) m/z : $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{18}\text{H}_{21}\text{F}$

5. Chapter 5: Approaches to the Total Synthesis of Cannabidiol

5.1. Synthesis and characterization of starting materials

Synthesis of (*R,E*)-4-methyl-*N'*-(2-methyl-5-(prop-1-en-2-yl)cyclohex-2-en-1-ylidene)benzenesulfonylhydrazide (**56**)

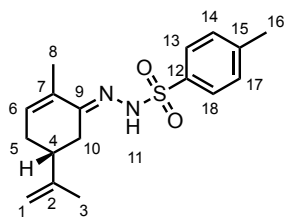


Compound **56** was prepared according to conditions reported in the literature.^[211]

A round bottom flask was charged with *p*-toluenesulfonyl hydrazide (2.05 g, 11.0 mmol, 1.1 equiv.). The flask was placed under vacuum and backfilled with argon. The vacuum/argon cycles were repeated twice and methanol (50 mL) was added. To this suspension was introduced (*R*)-(-)-carvone (1.56 mL, 10.0 mmol, 1.0 equiv.) and the reaction mixture was stirred at room temperature overnight. After removal of the solvent by filtration, and evaporation of the filtrate under reduced pressure, the desired product **56** was obtained as a colorless solid (2.89 g, 84%) and could be used without further purification.

(*R,E*)-4-methyl-*N'*-(2-methyl-5-(prop-1-en-2-yl)cyclohex-2-en-1-ylidene)benzenesulfonylhydrazide

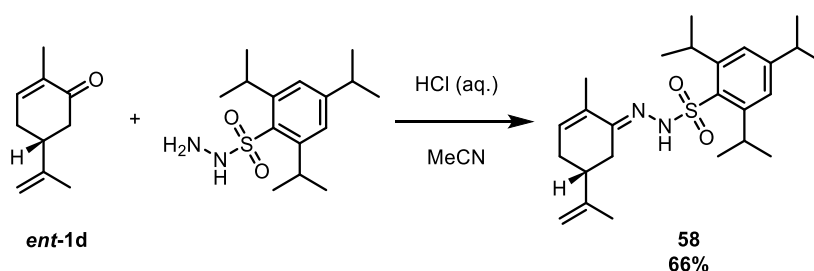
(56)



56

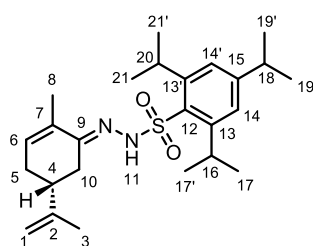
$^1\text{H NMR}$ (300 MHz, CDCl_3): δ (ppm) 7.88 (dd, $J = 8.4$ Hz, 2H, H-13 and H-18), 7.54 (s, 1H, H-11), 7.31 (dd, $J = 8.4$ Hz, 2H, H-14 and H-17), 6.07 (m, 1H, H-6), 4.74 (d, $J = 20.7$ Hz, 2H, H-1), 2.59 (dd, $J = 15.7, 4.2$ Hz, 1H, H-10), 2.43 (s, 3H, H-16), 2.35 (tt, $J = 11.8, 4.2$ Hz, 1H, H-4), 2.23–1.97 (m, 2H, H-5), 1.91 (dd, $J = 15.8, 12.2$ Hz, 1H, H-10'), 1.79 (s, 3H, H-8), 1.72 (s, 3H, H-3). $^{13}\text{C NMR}$ (101 MHz, CDCl_3): δ (ppm) 154.9 (C-9), 147.2 (C-2), 144.1 (C-15), 135.3 (C-12), 133.7 (C-6), 132.6 (C-7), 129.5 (2C, C-14 and C-17), 128.4 (2C, C-13 and C-18), 110.5 (C-1), 40.5 (C-4), 30.1 (C-5), 29.2 (C-10), 21.7 (C-16), 20.8 (C-3), 17.7 (C-8).

Synthesis of (*R,E*)-2,4,6-triisopropyl-*N'*-(2-methyl-5-(prop-1-en-2-yl)cyclohex-2-en-1-ylidene)benzenesulfonylhydrazide (58**)**



Compound **58** was prepared according to conditions reported in the literature.^[217] A round bottom flask was charged with 2,4,6-triisopropylbenzene sulfonyl hydrazide (985 mg, 3.30 mmol, 1.1 equiv.) and the flask was placed under vacuum before being backfilled with argon. The vacuum/argon cycles were repeated twice, and 3 mL of dry acetonitrile was added along with (*R*)-(-)-carvone **ent-1d** (0.50 mL, 3.0 mmol, 1.0 equiv.) and aqueous HCl 37% (0.40 mL, 1.2 equiv.). The resulting solution was stirred at room temperature for 30 min, cooled down to -20°C and filtered to give a colorless solid that was dissolved in dichloromethane. After filtration and evaporation under reduced pressure, a white solid corresponding to the desired product **58** (859 mg, 66%) was obtained. The product could be used without further purification.

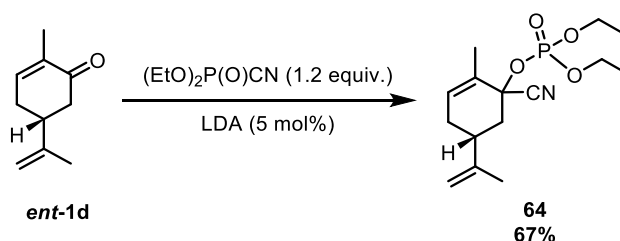
(R,E)-2,4,6-triisopropyl-N'-(2-methyl-5-(prop-1-en-2-yl)cyclohex-2-en-1-ylidene)benzenesulfonylhydrazide (58)



58

¹H NMR (300 MHz, CDCl₃): δ(ppm) 7.16 (s, 2H, H-14 and H-14'), 6.06 (m, 1H, H-6), 4.81 (s, 1H, H-1), 4.74 (s, 1H, H-1), 4.21 (hept, *J* = 6.8 Hz, 2H, H-16 and H-20), 2.90 (hept, *J* = 6.9 Hz, 1H, H-18i), 2.60 (dd, *J* = 16.1, 4.0 Hz, 1H, H-10), 2.36 (m, 1H, H-4), 2.25 (dt, *J* = 17.4, 5.0 Hz, 1H, H-5), 2.14–2.01 (m, 1H, H-5), 1.94 (m, 1H, H-10), 1.74 (s, 3H, H-3), 1.71 (s, 3H, H-8), 1.29–1.23 (m, 18H, H-17/H-17'/H-19/H-19'/H-21/H-21'). **¹³C NMR** (101 MHz, CDCl₃): δ(ppm) 153.4 (C-15), 151.4 (2C, C-13/C-13'), 147.2 (C-2), 132.7 (C-6), 131.5 (C-12), 130.5 (C-9), 123.8 (2C, C-14/C-14'), 110.7 (C-1), 40.7 (C-4), 34.3 (C-18), 30.2 (2C, C-16/C-20), 30.1 (C-5), 29.1 (C-10), 25.0 (2C, C-17/C-21), 24.9 (2C, C-17'/C-21'), 23.7 (2C, C-19/C-19'), 20.8 (C-3), 17.8 (C-8). **IR** (ATR): 1327, 1192 cm⁻¹ **HRMS** (ESI) *m/z*: [M+H]⁺ Calculated for C₂₅H₃₈N₂O₂SH⁺ 431.2727, found 431.2727.

Synthesis of (1-cyano-2-methyl-5-(prop-1-en-2-yl)cyclohex-2-en-1-yl diethyl phosphate (64)

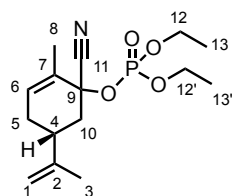


Compound **64** was prepared according to conditions reported in the literature.^[225]

A round bottom flask was charged with (*R*)-(-)-carvone **ent-1d** (0.834 mL, 5.00 mmol, 1.0 equiv.) and diethyl cyanophosphonate (0.91 mL, 6 mmol, 1.2 equiv.). The flask was placed under vacuum before being backfilled with argon. The vacuum/argon cycles were repeated twice and 5 mL dry THF were added. The mixture was cooled to -10°C. To this solution was introduced dropwise a commercial solution of lithium diisopropylamide (0.25 mL, 1.06 M, 0.25 mmol, 5 mol%) in THF/heptane/ethylbenzene. The reaction mixture was allowed to stir up to room temperature overnight before being quenched with water (2 mL). After extraction of the aqueous layer with ethyl acetate (3 x 5 mL), the combined organic layers were dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. Purification *via* flash column chromatography (*n*-pentane/ethyl acetate 3:1) afforded 1-cyano-2-methyl-5-(prop-1-en-2-yl)cyclohex-2-en-1-yl diethyl phosphate **64** (1.05 g, 69%) as light brown oil.

(Due to high toxicity of diethyl cyanophosphonate – HCN precursor – all the glassware and equipment used was thoroughly quenched with bleach after use).

(1-cyano-2-methyl-5-(prop-1-en-2-yl)cyclohex-2-en-1-yl diethyl phosphate (64))

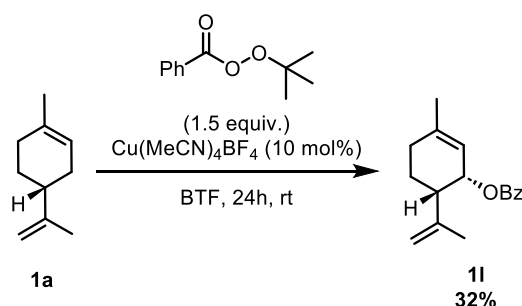


64

¹H NMR (300 MHz, CDCl₃): δ(ppm) 5.77 (d, *J* = 4.4 Hz, 1H, H-6), 4.79 (d, *J* = 10.5 Hz, 1H, H-1), 4.20 (m, 4H, H-12/H-12'), 2.81 (dt, *J* = 12.4, 2.1 Hz, 1H, H-10), 2.54 (m, 1H, H-4), 2.31–2.16 (m, 1H, H-5), 2.10 (d, *J* = 12.8 Hz, 1H, H-10), 2.03 (m, 1H, H-5), 1.89 (s, 3H, H-8), 1.76 (s, 3H, H-3), 1.37 (m, 6H, H-13/H-13'). **¹³C NMR** (75 MHz, CDCl₃): δ(ppm) 146.4 (C-2), 130.8 (C-7), 130.0 (C-6), 118.1 (C-11) 110.7 (C-1), 76.3 (C-9), 76.2 (C-9), 64.6 (2C, C-12/C-12'), 39.3 (C-10), 39.1 (C-4), 30.5 (C-5), 20.6 (C-3), 17.5 (C-8), 16.3 (C-13 or C-13'), 16.2 (C-13 or C-13'). **IR** (ATR): 1326, 1165, 1027, 667 cm⁻¹ **HRMS**: needs to be reinvestigated.^[253]

5.2. Strategy 1: π -allyl Palladium catalysis

Protocol for the Kharasch-Sosnovsky reaction



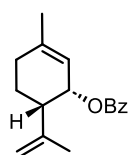
(1*S*,6*S*)-3-methyl-6-(prop-1-en-2-yl)cyclohex-2-en-1-yl benzoate **1l** was synthesized following similar conditions as some reported in the literature.^[254]

A round bottom flask was charged with Cu(MeCN)₄BF₄ (31.5 mg, 0.1 mmol). The flask was placed under vacuum before being backfilled with argon. The vacuum/argon cycles were repeated twice and BTF (3 mL) was added. To this solution was introduced (+)-limonene **1a** (162 μ L, 1.0 mmol, 1.0 equiv.) and *tert*-butyl perbenzoate (285 μ L, 1.5 mmol, 1.5 equiv.). After stirring at room temperature for 24 h, the reaction was worked up by adding 15 mL of ethyl acetate. The organic layer was washed with 2x10 mL of a saturated aqueous solution of ammonium chloride. The aqueous layer was then extracted

^[253] HRMS Sample was prepared and analyzed but no match with the expected structure could be detected.

^[254] Marín-Barrios, R.; Guerra, F. M.; García-Cabeza, A. L.; Moreno-Dorado, F. J.; Massanet, G. M. *Tetrahedron* **2012**, *68*, 1105–1108.

with 2x10 mL of dichloromethane. The organic layers were combined and dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure. The yellow oily crude was purified by flash column chromatography on silica gel (pentane/ethyl acetate 99:1) to afford the desired product **1l** as a colorless oil (82.0 mg, 32%).

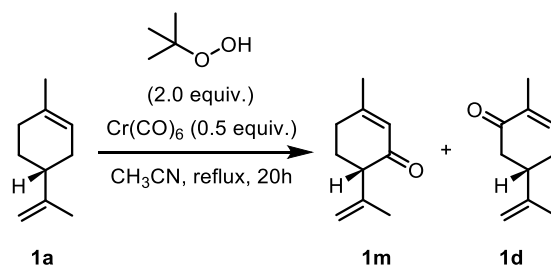


1l

The characterization data are in accordance the ones reported in the literature.^[254]

1H-NMR (400 MHz, CDCl₃): δ (ppm) 8.08 (dd, $J = 8.4, 1.4$ Hz, 2H), 7.58-7.53 (m, 1H), 7.47-7.42 (m, 2H), 5.86-5.75 (m, 1H), 5.59-5.50 (m, 1H), 4.80-4.68 (m, 2H), 2.49-2.37 (m, 1H), 2.31-2.27 (m, 1H), 2.27-2.22 (m, 1H), 2.11 (ddd, $J = 14.2, 4.1, 2.4$ Hz, 1H), 1.99-1.87 (m, 1H), 1.78-1.75 (m, 3H), 1.75-1.73 (m, 3H).

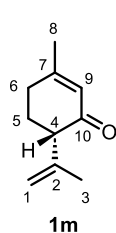
Protocol for the Cr(0)/*t*-BuOOH oxidation of (+)-limonene



Compound **1m** was prepared according to conditions reported in the literature.^[203]

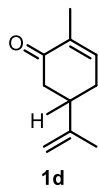
A round bottom flask was charged with chromium hexacarbonyl (110 mg, 0.5 mmol, 0.5 equiv.). the flask was placed under vacuum before being backfilled with argon. The vacuum/argon cycles were repeated twice and 4 mL dry acetonitrile were added. To this solution was introduced (*R*)-(+)-limonene **1a** (0.16 mL, 1.00 mmol, 1.00 equiv.) and *t*-butyl hydroperoxide (5.5 M solution in decane, 0.35 mL, 2.00 mmol, 2.00 equiv.). The reaction mixture was refluxed for 20 h and cooled down in an ice bath. The resulting solution was filtered and washed with cold toluene (3 mL). Diethyl ether was added (5 mL), and the filtrate was washed with a saturated aqueous solution of sodium metabisulfite (5 mL). The organic layers were dried over anhydrous magnesium sulfate, filtered, and the solvents were evaporated under reduced pressure. Purification *via* flash column chromatography (pentane/ethyl acetate 95:5) gave isopiperitenone **1m** (61 mg, 41%) as a yellow oil and (\pm)-carvone **1d** (28 mg, 18%) as a colorless oil.

Isopiperitenone (**1m**)



¹H NMR (300 MHz, CDCl₃): δ(ppm) 5.89 (s, 1H, H-9), 4.99 (s, 1H, H-1), 4.74 (s, 1H, H-1'), 2.92 (dd, *J* = 10.7, 5.1 Hz, 1H, H-4), 2.33 (m, 2H, H-6), 2.10–2.01 (m, 2H, H-5), 1.93 (s, 3H, H-8), 1.72 (s, 3H, H-3). **¹³C NMR** (101 MHz, CDCl₃) δ(ppm) 199.5 (C-10), 162.0 (C-7), 143.5 (C-2), 126.9 (C-9), 113.7 (C-1), 53.9 (C-4), 30.5 (C-6), 27.8 (C-5), 24.3 (C-8), 20.7 (C-3).

(±)-carvone (**1d**)

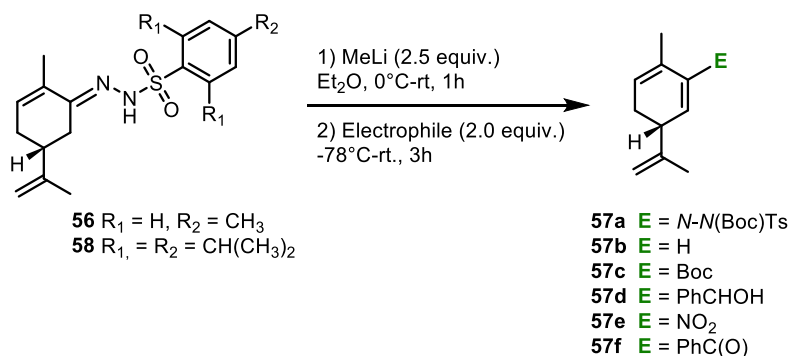


The characterization data are in accordance with the analysis of a commercial sample of *rac*-carvone.

¹H NMR (300 MHz, CDCl₃): δ(ppm) 6.75 (s, 1H), 4.80–4.75 (d, *J* = 14.2 Hz, 2H), 2.68 (m, 1H), 2.28–2.41 (m, 4H), 1.79 (s, 3H), 1.75 (s, 3H).

5.3. Strategy 2: 1,4-addition onto a carvone-derived Michael acceptor

General Procedure H for the Shapiro reaction

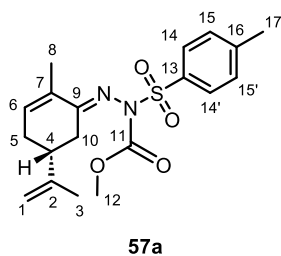


Scheme 119. General protocol for Shapiro reaction.

A round bottom flask was charged with the corresponding carvone-derived hydrazone **56-58** (1.0 equiv.) and the flask was placed under vacuum before being backfilled with argon. The vacuum/argon cycles were repeated twice and dry diethylether (0.2 M) was introduced. After cooling down at -78°C , methyllithium (3.1 M solution in diethoxymethane, 2.5 equiv.) was slowly added and stirred. The temperature was slowly risen to rt, and once bubbling had ceased, the solution of vinylolithium formed was transferred to a solution of the desired electrophile (2.0 equiv.) in anhydrous diethylether (0.1M) at -78°C . After 1 h of stirring at that temperature, an aqueous saturated solution of ammonium chloride (2 mL per mmol of ketone used) was added to quench the reaction mixture. The biphasic mixture was separated, and the aqueous layer was extracted with diethylether (3 x 10 mL per mmol

of ketone used). Washing of the combined organic layers with brine, drying over anhydrous magnesium sulfate, filtration, and evaporation of the solvents under reduced pressure afforded the desired products that were purified *via* flash column chromatography over silica gel.

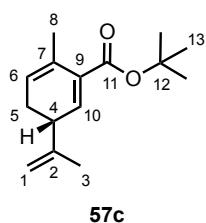
Methyl (*R,E*)-2-(2-methyl-5-(prop-1-en-2-yl)cyclohex-2-en-1-ylidene)-1-tosylhydrazine-1-carboxylate
(57a)



This side-product was prepared according to the general procedure **H** from tosyl hydrazone **56** (159 mg, 0.50 mmol, 1.0 equiv) and methyl chloroformate (76 μ L, 1.00 mmol, 2.0 equiv.), without increase of temperature before addition of methyl chloroformate. Purification *via* flash column chromatography (pentane/ethyl acetate gradient) gave *methyl (R,E)-2-(2-methyl-5-(prop-1-en-2-yl)cyclohex-2-en-1-ylidene)-1-tosylhydrazine-1-carboxylate* **57a** (114 mg, 60%) as an off-white solid. $^1\text{H NMR}$ (300 MHz, CDCl_3): δ (ppm) 7.92 (d, $J = 8.2$ Hz, 2H, H-14/H-14'), 7.32 (d, $J = 8.3$ Hz, 1H, H-15/H-15'), 6.42 (s, 1H, H-6), 4.80 (d, $J = 8.5$ Hz, 2H, H-1), 3.69 (s, 3H, H-12), 3.17 (dd, $J = 16.0, 1.5$ Hz, 1H, H-10), 2.43 (s, 3H, H-17), 2.34 – 2.15 (m, 4H, H-4, H-5, H-10), 1.97 (s, 3H, H-8), 1.75 (s, 3H, H-3).

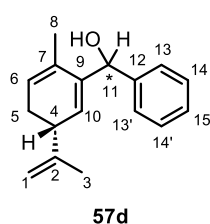
$^{13}\text{C NMR}$ (101 MHz, CDCl_3): δ (ppm) 179.7 (C-11), 152.0 (C-9), 147.0 (C-2), 145.0 (C-16), 140.5 (C-13), 134.7 (C-6), 132.5 (C-7), 129.5 (2C, C-15/C-15'), 129.0 (2C, C-14/C-14'), 110.7 (C-1), 54.2 (C-12), 41.0 (C-4), 32.4 (C-5), 31.3 (C-10), 21.8 (C-17), 20.6 (C-3), 18.0 (C-8). IR (ATR): 1778, 1374, 1277, 1050, 918 cm^{-1} .

tert-butyl 6-methyl-3-(prop-1-en-2-yl)cyclohexa-1,5-diene-1-carboxylate (**57c**)



Prepared according to the general procedure **H** from tosyl hydrazone **56** (159 mg, 0.50 mmol, 1.0 equiv.) and di-*t*-butyl dicarbonate (218 mg, 1.00 mmol, 2.0 equiv.). Purification *via* flash column chromatography (pentane/ CH_2Cl_2 95:5) gave *tert-butyl 6-methyl-3-(prop-1-en-2-yl)cyclohexa-1,5-diene-1-carboxylate* **57c** (37 mg, 31%). $^1\text{H NMR}$ (300 MHz, CDCl_3): δ (ppm) 6.60 (d, $J = 3.8$ Hz, 1H, H-10), 5.67-5.60 (dd, $J = 4.1$ Hz, 1H, H-6), 4.97-4.69 (m, 2H, H-1), 2.86 (ddd, $J = 13.3, 9.6, 3.5$ Hz, 1H, H-4), 2.24-2.06 (m, 2H, H-5), 1.93 (d, $J = 1.9$ Hz, 3H, H-8), 1.77 (s, 3H, H-3), 1.51 (s, 9H, H-13). $^{13}\text{C NMR}$ (75 MHz, CDCl_3): δ (ppm) 166.6 (C-11), 146.4 (C-2), 138.8 (C-10), 130.1 (C-9), 124.0 (C-6), 111.4 (C-6), 80.8 (C-12), 42.2 (C-4), 28.5 (C-13), 28.3 (C-5), 27.5 (C-5), 21.3 (C-3), 20.6 (C-8).

(R)-6-methyl-3-(prop-1-en-2-yl)cyclohexa-1,5-dien-1-yl(phenyl)methanol (**57d**)

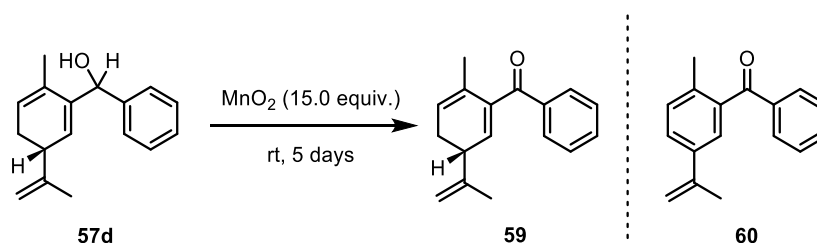


Prepared according to the general procedure **H** from tosyl hydrazone **56** (159 mg, 0.50 mmol, 1.0 equiv.) and benzaldehyde (0.10 mL, 1.00 mmol, 2.0 equiv.). Purification *via* flash column chromatography (pentane/CH₂Cl₂ 95:5) gave *(R)*-6-methyl-3-(prop-1-en-2-yl)cyclohexa-1,5-dien-1-yl(phenyl)methanol **57d** (40 mg, 32%). ¹H NMR (400 MHz, CDCl₃): δ(ppm) (as a mixture of diastereomers 1:1 noted X and X*): δ (ppm) 7.40-7.29 (m, 5H, H13/H-14/H15/H-13'/H-14'), 5.88 (d, 1H, *J* = 2.8 Hz, H-6), 5.74 (d, 1H, *J* = 3.9 Hz, H-6*), 5.60-5.56 (m, 1H, H-10), 5.42 (br. s, 1H, H-11), 4.93-4.56 (m, 2H, H-1), 3.02-2.93 (m, 2H, H-4), 2.30 – 2.14 (m, 4H, H-5), 1.97-1.88 (m, 1H, OH), 1.79 (s, 3H, H-8), 1.76 (s, 3H, H-8*), 1.68 (d, *J* = 1.1 Hz, 3H, H-3), 1.64 (d, *J* = 1.9 Hz, 3H, H-3*).

¹³C NMR (100 MHz, CDCl₃): δ(ppm) 148.0 (C-7) 147.6 (C-7*), 142.5 (C-12), 142.5 (C-12*), 139.8 (C-9), 139.5 (C-9*), 131.5 (C-2), 131.4 (C-2*), 128.6 (2C, C-14/C-14'), 128.5 (2C, C-14*/C-14'*), 127.9 (C-6*), 127.7 (C-15), 127.6 (C-15*), 127.3 (2C, C-13/C-13'), 127.1 (2C, C-13*/C-13'*), 126.5 (C-6), 123.8 (C-10), 123.7 (C-10*), 110.6 (2C, C-1 and C-1*), 74.6 (C-11), 74.2 (C-11*), 42.0 (C-4), 41.7 (C-4*), 28.3 (C-5), 28.2 (C-5*), 21.1 (C-8), 21.1 (C-8*), 19.6 (C-3), 19.4 (C-3*).^[255] IR (ATR): 1157, 703, 665, 650, 623 cm⁻¹.

HRMS: analysis is pending

5.3.1. Oxidation of the alcohol **57d**

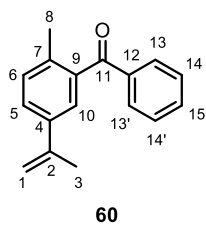


The reaction conditions were inspired from a procedure reported in the literature.^[219]

A round bottom flask was charged with the allylic alcohol **57d** (24 mg, 0.1 mmol, 1.0 equiv.). 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 (100 mL). Manganese dioxide (60 mg, 0.7 mmol, 7.0 equiv.) was then added and stirred overnight at room temperature. The reaction mixture was heated under reflux for 3 h and after cooling to room temperature, 8.0 additional equivalents of manganese dioxide (69.6 mg, 0.8 mmol, 8.00 equiv.) were added. The mixture was

^[255] Available NMR experiments were not sufficient for precise characterization of aromatic protons so arbitrary assignments are reported.

stirred for 4 h at the same temperature. After filtration over silica, all volatiles were removed under reduced pressure to afford (2-methyl-5-(prop-1-en-2-yl)phenyl)(phenyl)methanone **60** (13 mg, 55%) as a colorless oil.



60

¹H NMR (300 MHz, CDCl₃): δ(ppm) 7.75 (m, 2H, H-13/H-13'), 7.61 (m, 1H, H-15), 7.50 (m, 1H, H-5), 7.47 (m, 2H, H-14/H-14'), 7.43 (d, *J* = 2.1 Hz, H-10), 7.29 (s, 1H, H-6), 5.27 (s, 1H, H-1), 4.99 (s, H-1), 2.22 (s, 3H, H-8), 2.04 (s, 3H, H-3). **¹³C NMR**

(101 MHz, CDCl₃): δ(ppm) 198.8 (C-11), 142.4 (C-4), 138.7 (C-9), 138.5 (C-2), 137.8 (C-12), 135.8 (C-7), 133.4 (C-15), 131.0 (C-6), 130.3 (2C, C-13/C-13'), 128.6 (C-5),

127.3 (2C, C-14/C-14'), 125.5 (C-10), 112.7 (C-1), 21.8 (C-3), 19.8 (C-8).

Selective C–H Activation of Terpenes

This thesis work is dealing with the discovery of new strategies for the C–H activation/functionalization of terpenes, with particular emphasis on (+)-limonene and palladium catalysis. Firstly, we studied the dehydrogenative Pd(II)-catalyzed C(sp²)–H/C(sp²)–H coupling between limonene and electron-poor alkenes, with extension to various terpenes and terpenoids. Then, we studied the post-functionalization (Sonogashira under micellar regime) of one product stemming from the dehydrogenative coupling. In another project, we successfully developed the Pd(II)-catalyzed redox neutral C(sp²)–H/C(sp²)–X coupling between (+)-limonene and bromoalkenes. This strategy, which is complementary with respect to the dehydrogenative coupling, needs a lower loading of the palladium catalyst and of the silver salt with respect to the previously studied coupling. Finally, we investigated new synthetic approaches toward cannabidiol (CBD).

Keywords: Palladium; Catalysis; Limonene; C–H Activation; Terpenes; Cannabidiol; Sonogashira.

Activation C–H sélective des terpènes

Ce travail de thèse porte sur la découverte de nouvelles stratégies pour l'activation/fonctionnalisation C–H des terpènes, avec un accent particulier sur le (+)-limonène et la catalyse au palladium. Tout d'abord, nous avons étudié le couplage C(sp²)–H/C(sp²)–H déshydrogénant catalysé par le Pd(II) entre le limonène et des alcènes pauvres en électrons, avec une extension à divers terpènes et terpénoïdes. Ensuite, nous avons étudié la post-fonctionnalisation (Sonogashira en conditions micellaires) d'un produit issu du couplage déshydrogénant. Par la suite, nous avons développé un couplage redox neutre C(sp²)–H/C(sp²)–X entre le (+)-limonène et des bromoalcènes. Cette stratégie, qui est complémentaire par rapport au couplage déshydrogénant, nécessite d'une charge plus faible du catalyseur au palladium et du sel d'argent par rapport au couplage étudié précédemment. Enfin, nous avons étudié de nouvelles voies synthétiques vers le cannabidiol (CBD).

Mots-clés : Palladium ; Catalyse ; Limonène ; Activation C–H ; Terpènes ; Cannabidiol ; Sonogashira.