Rhodium-Catalysed Arylative Cyclisations of Malonate Esters By 1,4-Rhodium Migration



Thesis submitted in accordance with the requirement of the University of Nottingham for the degree of Chemistry MSc (by Research)

By

Luke O'Brien

Supervisor: Professor Hon Wai Lam

September 2018

Declaration

I hereby declare that, except for where specific reference is made to other sources, the work contained within this thesis is the original work of my own research since the registration of my MSc by research degree in September 2017, and any collaboration is clearly indicated. This thesis has been composed by myself and has not been submitted, in whole or part, for any other degree diploma or other qualification. I confirm that the work submitted is my own except work which has formed part of jointly-authored publications. The contributions of myself and other authors to this work have been specifically indicated where relevant. I confirm that appropriate credit has been given within the thesis where references have been made to the work of others.

Acknowledgements

Firstly, I would like to thank my supervisor Professor Hon Wai Lam for giving me the opportunity to work within his research group. His feedback and patience throughout the project were greatly appreciated.

Secondly, I will be forever grateful to Dr. S. Karad for teaching me many many laboratory techniques as well as his advice and solutions to various problems I encountered throughout the year. His kindness will never be forgotten.

Many thanks to everyone in the Lam group past and present, for making my time in the group very enjoyable. Particular thanks to Alistair Groves and Connor Yap for their tips and tricks, and for their support over the course of the year.

Finally, I would like to thank my family and friends for their support and understanding throughout my time at the University of Nottingham. I will always remember their kindness, friendship and faith in me.

Contents

Abbreviations v
Abstract vii
Chapter 1: Introduction 1
1.1 C-H Bond Activation 1
1.2 Through Space Metal Migrations 2
1.3 1,4-Rhodium(I) Migrations 5
1.3.1 1,4-Rhodium(I) Migrations to sp^2 Centres 5
1.3.2 1,4-Rhodium(I) Migrations to sp^3 Centres 15
1.4 1,4-Rhodium(III) Migrations 18
1.5 1,4-Iridium(I) Migrations 20
1.6 1,4-Cobalt Migrations 21
1.7 Summary on Remote C-H Activation 24
Chapter 2: Results and Discussion 25
2.1 Aims and Objectives 25
2.2 Reaction Optimisation 26
2.3 Synthesis of Alkynyl Malonate Esters 32
2.4 Malonate Ester Scope 34
2.5 Boronic Acid Scope 40
2.6 Enantioselective Variant 42
2.7 Conclusions and Future Work 47
Chapter 3: Experimental 48
3.1 General Information 48
3.2 Synthesis of Alkynyl Malonate Esters 49
3.3 Racemic Rhodium-Catalysed Desymmetrisation of Malonate Esters 64
3.4 Enantioselective Rhodium-Catalysed Desymmetrisation of Malonate Esters 82
References 86

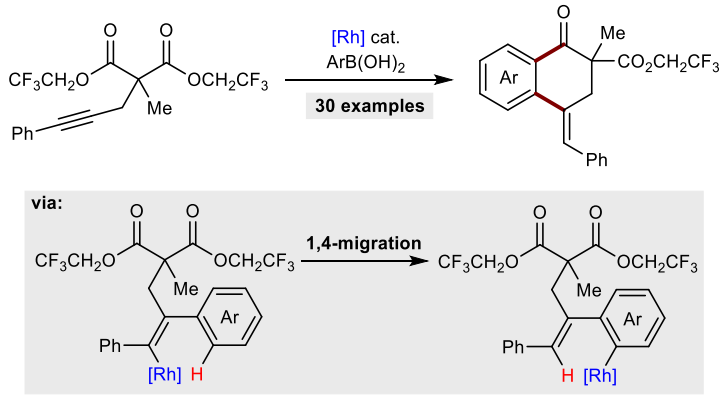
Abbreviations

Ac	acetyl
acac	acetylacetonate
Am	amyl
Ar	aryl
Bn	benzyl
Bu	butyl
cat.	catalyst
cod	cyclooctadiene
Cp*	pentamethylcyclopentadiene
d	doublet
d.r	diastereomeric ratio
DCE	dichloroethane
DFT	density functional theory
DMA	dimethylacetamide
DMF	*N*,*N*-dimethylformamide
ee	enantiomeric excess
equiv.	equivalent
ESI	electrospray ionisation
Et	ethyl
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
i-	iso
IR	infrared
m	multiplet
Me	methyl
mmol	millimol
m.p.	melting point
NMR	nuclear magnetic resonance
NR	no reaction
Ph	phenyl
pin	pinacol
Piv	pivaloyl
R_f	retention factor

RT	room temperature
s	singlet
t	triplet
t-	tert
temp.	temperature
TFE	trifluoroethanol
THF	tetrahydrofuran
TLC	thin layer chromatography
TMP	2,2,6,6-tetramethylpiperidine
UV	ultraviolet

Abstract

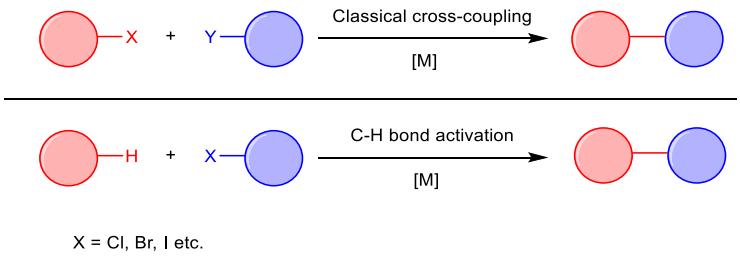
Rhodium-catalysed intramolecular arylative cyclisations of malonate esters, generating highly functionalised bicycles has been described. The key step is a known alkenyl-to-aryl 1,4-rhodium migration. The reaction is considered to proceed through regioselective carbometallation of the tethered alkyne, followed by alkenyl-to-aryl 1,4-migration and subsequence intramolecular 1,2-addition to the ester moiety. Discovery and preliminary results were conducted by Dr. S. Karad. Through the use of a bisphosphine base ligand, good levels of enantiocontrol were achieved.



Chapter 1: Introduction

1.1 C-H Bond Activation

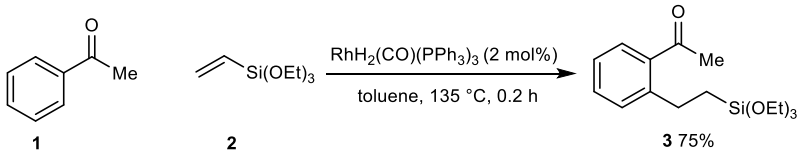
Carbon-carbon bonds form the 'backbone' of the majority of organic compounds. Therefore, forming C-C bonds will always be one of the most valuable and fundamental reactions in the development of synthetic organic chemistry.[1] Classically, C-C bond formation required the use of functional groups, such as halides which interact with a metal to form a new C-M bond. (Scheme 1). These new C-M bonds are further functionalised to form new C-C or C-X (X = heteroatom) bonds, known as cross-coupling reactions. However, substrates require prior functionalisation, and with sustainability at the forefront of most research, these reactions are not environmentally friendly due to the formation of toxic by-product waste.



Scheme 1: *Classical cross-coupling vs. C-H bond activation.*

Among the myriad of synthetic chemical transformations exists the potential to formally use unactivated C-H bonds (Scheme 1). Such transformations represent novel synthetic disconnections accessing otherwise challenging compounds in fewer steps saving time, resources and reducing waste. Therefore, the development of new methods and synthetic strategies in which C-H bonds can be activated represents one of the most promising areas of research in the field of synthetic chemistry.[2]

C-H bonds are abundant within organic compounds. Therefore, activation of these C-H bonds could potentially eliminate the preparation of complex functionalised starting materials. Unfortunately, C-H bonds are generally unreactive, non-polar and are so abundant in organic compounds that regioselectivity issues can arise. These regioselectivity issues can be overcome by using directing groups which through coordination to a metal catalyst allow for selective C-H activation. One of the earliest reported examples was described by Murai *et al*, demonstrating the *ortho*-alkylation of aromatic ketone **1**, using ruthenium catalysis, (Scheme 2).[3]

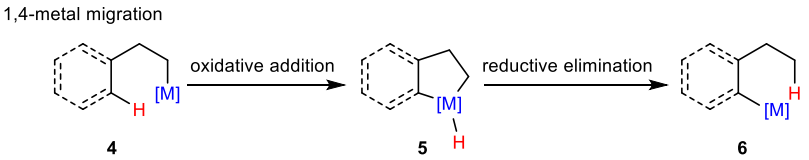


Scheme 2: *Ortho-alkylation of aromatic ketone* ***1****.*

Over the next few decades a wide variety of functional groups have been developed for use as directing groups in the chemical transformation of C-H bonds.[4–7] However, the requirement to incorporate and remove directing groups can be considered a disadvantage, as it often requires harsh reaction conditions and lengthens reaction sequences. One way to overcome the problems associated with the use of directing groups is the incorporation of through space metal migrations.[8]

1.2 Through Space Metal Migrations

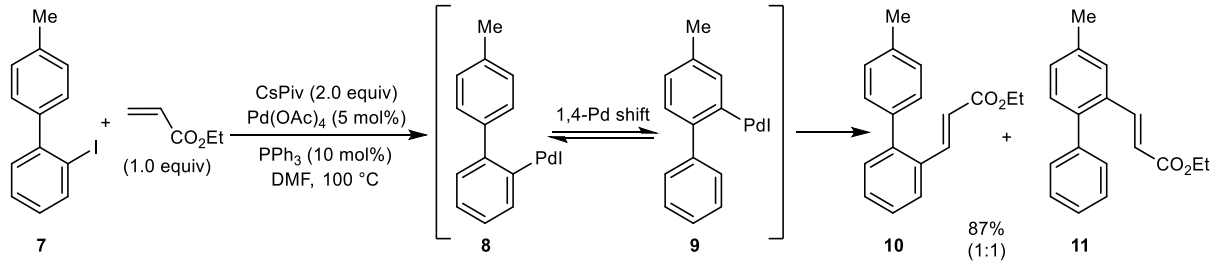
Through space metal migrations are commonly thought to proceed through an initial oxidative addition forming metallacycle **5**, followed by reductive elimination allowing for the relocation of both the metal and hydrogen atom (Scheme 3). Initial formation of a C-M bond occurs, followed by a through space interaction between the metal and a nearby C-H bond (**4**). This leads to the cleavage of the C-H bond and migration of the metal. Simultaneous to this, the hydrogen atom that was residing on the carbon atom has migrated in the opposite direction to the carbon that resided the metal (**6**). The newly activated C-M bond (**6**) can undergo further functionalisation, typically nucleophilic additions.[9] This process introduces a metal into an otherwise unactivated C-H bond within the molecule without the requirement of a directing group.[10]



Scheme 3: *Mechanistic understanding of 1,4-metal migrations.*

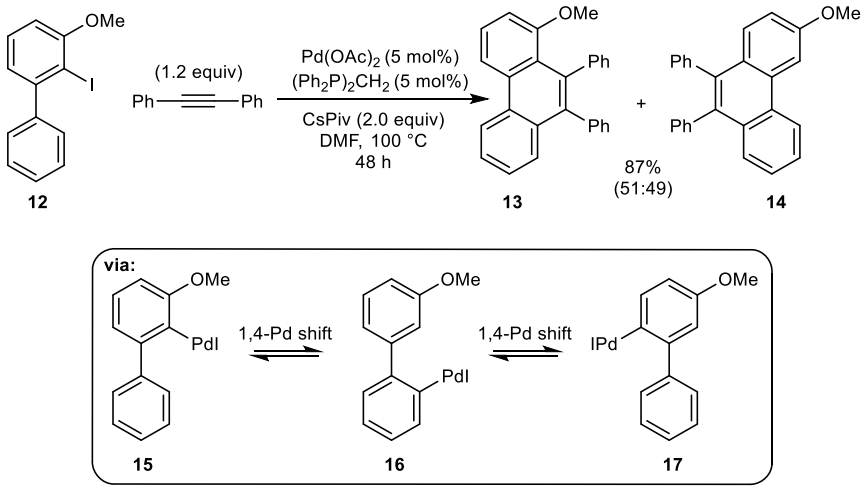
1,4-Migrations are the most common due to the formation of a favoured five membered metallacycle. Palladium and rhodium are the most common metals to perform such migrations; however, more recently 1,4-migrations have been observed for more abundant metals such as iridium,[11] cobalt,[12] nickel [13] and iron.[14]

One of the first examples of catalytic 1,4-metal migration was reported by Larock, demonstrating the olefination of unsymmetrical *o*-iodophenyls (Scheme 4).[15] Two regioisomeric Heck products (**10** and **11**) were observed, which suggested an aryl-to-aryl 1,4-palladium migration. Observing the expected regioisomer (**10**) and observing the mixture of regioisomers (**10** and **11**) was achieved by modification of the reaction conditions. It was observed that leaving the reaction to equilibrate prior to the addition of olefin lead to a 1:1 mixture of both regioisomers.



Scheme 4: *1,4-Palladium migration from o-iodobiaryl **7**.*

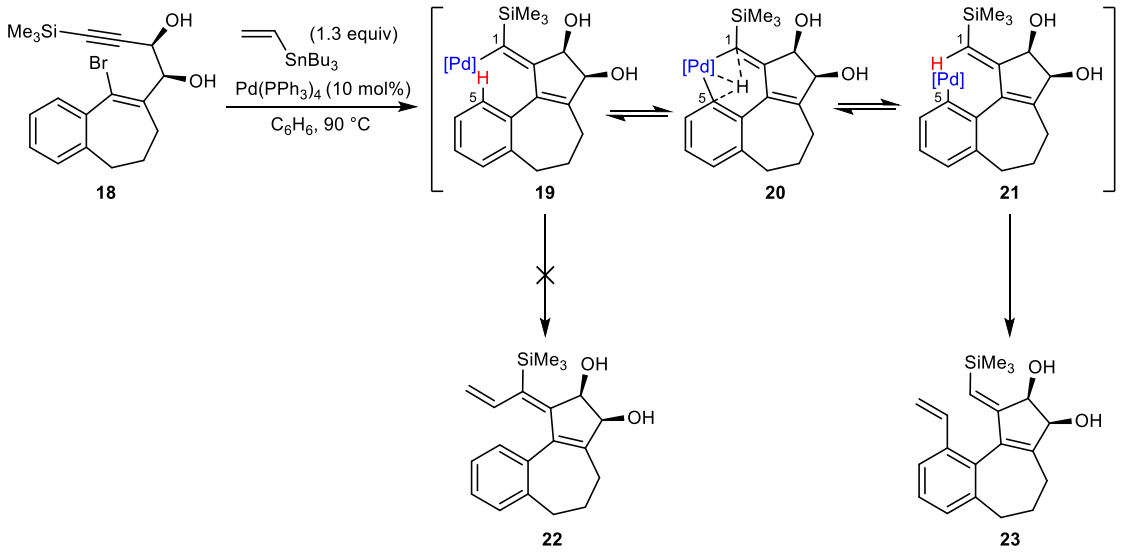
Larock extended this concept to symmetrical alkynes (Scheme 5), which lead to the formation of the mixture of regioisomers **13** and **14**. The mechanism is suggested to involve three aryl-to-aryl 1,4-palladium migrations (**15**, **16** and **17**), which by trapping the reactive intermediates could generate **13** and **14**. Intermediate **16** generates both regioisomers, while intermediates **15** and **17** generate the single regioisomer **13** and **14** respectively.



Scheme 5: *Proposed intermediates in the formation of **13** and **14**.*

In comparison to 1,4-metal migrations the number of reported 1,3 or 1,5-migrations is significantly less well-described due to the formation of an unfavourable metallacycle.[16] One example was reported by Bour and Suffert in 2005 (Scheme 6) who proposed an alkenyl-to-

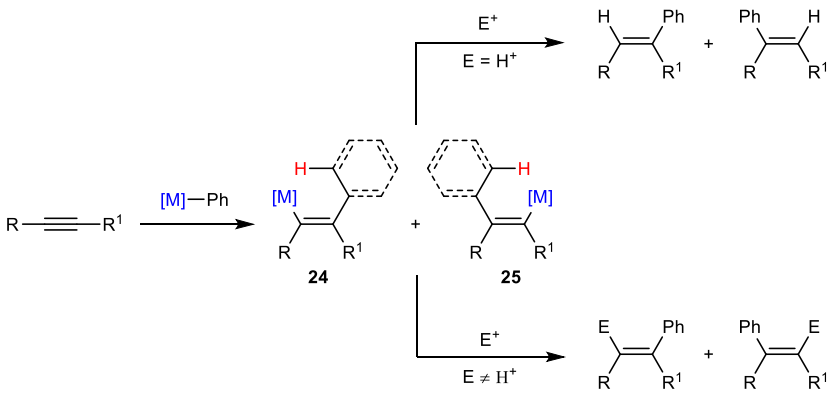
aryl 1,5-palladium shift followed by Stille coupling to yield **23**.[17,18] The expected product (**22**) was not formed under these reaction conditions.



Scheme 6: *Formation of **23** by alkenyl-to-aryl 1,5-palladium migration.*

DFT calculations suggested the alkenyl-to-aryl 1,5-palladium shift is a one-step process, whereby direct hydrogen transfer (**20**) is achieved from the C1 position (**19**) to the C5 position (**21**). Therefore, it is energetically unfavourable to form a palladium (IV) species for this migration process. 1,5-metal migrations are thought to not proceed *via* an oxidative addition reductive elimination pathway, instead by direct hydrogen transfer.

Metal migrations are typically initiated through the carbometallation of an alkyne *via* migratory insertion. This introduces the metal into the molecule affording highly substituted alkenes (Scheme 7). Most commonly, this migratory insertion is *syn*-selective forming alkenylmetal intermediates **24** and **25**, which can then be quenched *via* a proton source, to give tri-substituted alkenes. Alternatively, the alkenylmetal intermediate can be intercepted with an external electrophile to give tetra-substituted alkenes. Controlling the initial migratory insertion when adding across unsymmetrical alkynes forms single regioisomers. In many of the metal migrations discussed, this initial carbometallation (**24** and **25**) is followed by a metal migration and subsequent quenching using an electrophilic source.



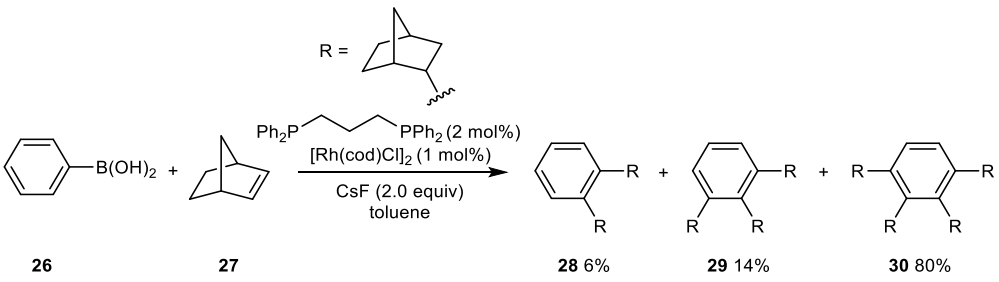
Scheme 7: *Addition of organometallics across alkynes.*

1.3 1,4-Rhodium(I) Migrations

1,4-Rhodium migrations to alkenyl or aryl carbons are the most common type of metal migration. The energy barrier required for migration to a sp^2 carbon is much lower than a migration to a sp^3 carbon. Therefore, migrations to alkyl carbons are far less common.

1.3.1 1,4-Rhodium(I) Migrations to sp^2 Centres

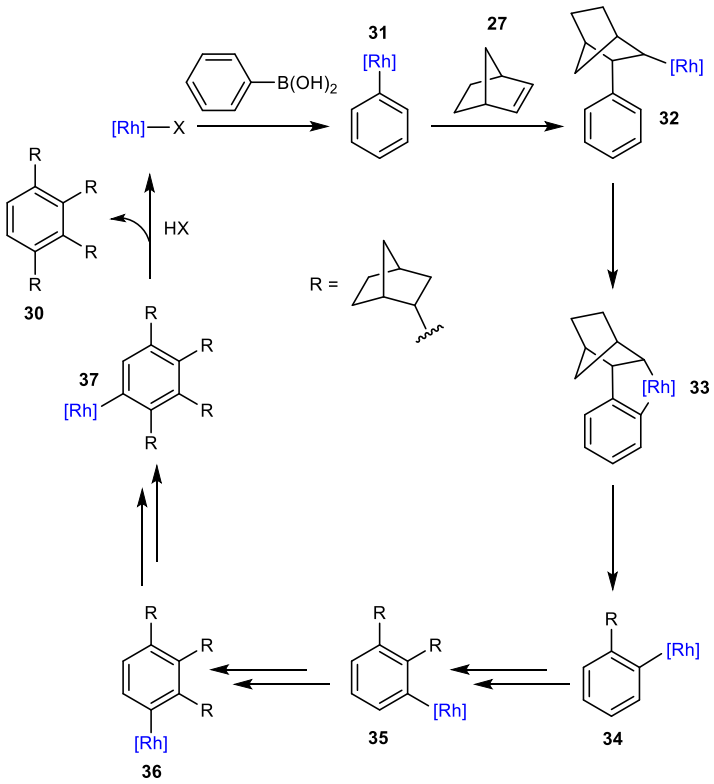
In 2000 Miura reported the very first 1,4-rhodium migration.[19] Using 2-norbornene (**27**), phenylboronic acid along with the rhodium(I) catalyst was found to promote multiple alkylations of an aryl ring by several alkyl-to-aryl 1,4-migrations (Scheme 8). This reaction gave di-substituted product **28**, tri-substituted product **29** and the unexpected major tetra-substituted product **30** in an overall yield of 73%.



Scheme 8: *'Merry-go-around' alkylation of* ***26****.*

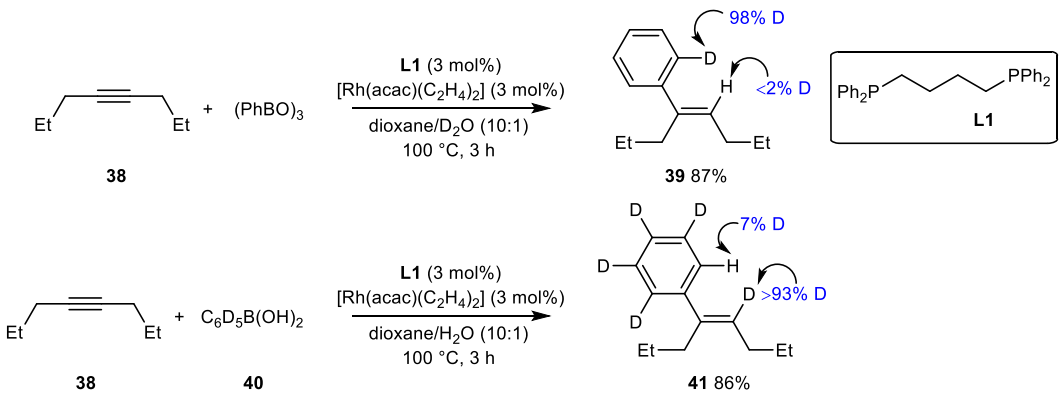
The proposed mechanism is described in Scheme 9, initiating with the transmetalation between the boronic acid and the rhodium catalyst, forming species **31**. This species then undergoes migratory insertion with 2-norbornene (**27**), followed by cyclorhodation *via* C-H cleavage to form intermediate **33**. Intermediate **33** then reductively eliminates generating arylrhodium species **34** having undergone a 1,4-rhodium migration. This process is repeated to form di-

substituted (**35**), tri-substituted (**36**) and tetra-substituted (**37**) arylrhodium species. Termination of the catalytic cycle is thought to proceed through boronic acid induced protonolysis, regenerating the catalyst. Further alkylation is inhibited, due to steric clash arising from bulky substituents. The lack of mono-substituted product is due to the extremely fast initial migratory insertion and reductive elimination.



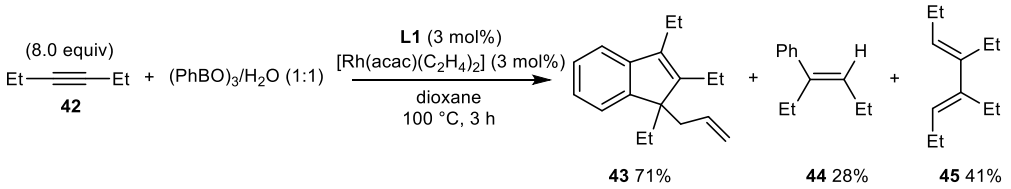
Scheme 9: *Proposed mechanism for the formation of **30** by multiple 1,4-migrations.*

Building on Miura's initial alkenyl-to-aryl 1,4-rhodium migration, Hayashi published the first rhodium-catalysed hydroarylation of alkynes using arylboroxines.[20] The reaction is initiated by *syn*-selective carbometallation of an alkyne, with subsequent alkenyl-to-aryl 1,4-migration. When the hydroarylation of alkyne **38** with phenylboroxine was performed using D_2O instead of H_2O (Scheme 10), only trace amounts of deuterium incorporation (<2%) were observed at the alkenyl position. Instead the majority of deuterium incorporation was primarily observed at the *ortho* position on the phenyl ring (98%). This indicated an alkenyl-to-aryl 1,4-metal migration after the initial carbometallation reaction. This is thought to proceed through an initial oxidative addition forming a rhodium(III) complex, followed by reductive elimination. When deuterated phenylboroxine (**40**) with H_2O was reacted with alkyne **38**, deuterium was primarily incorporated into the alkenyl position (>93%). In both deuterated experiments, protonolysis gives the observed products **39** and **41**.



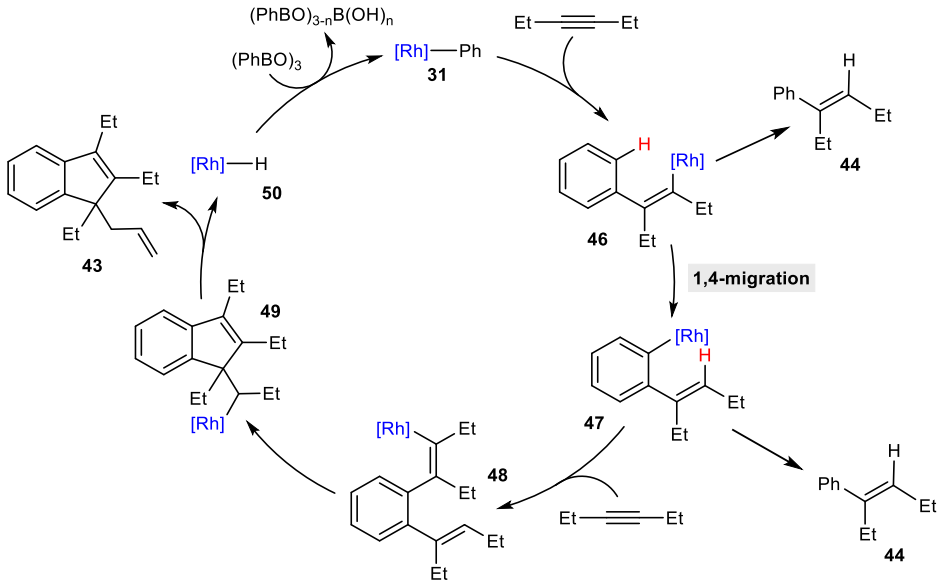
Scheme 10: *Mechanistic studies for 1,4-rhodium migration.*

Using an excess of arylboroxine with a large excess of H_2O prevents a second addition of alkyne (Scheme 10), selectively forming the hydrolysed product. Modification of the reaction conditions using an excess of alkyne and minimising the amount of H_2O allows for a second addition (Scheme 11) to occur forming indene **43**.



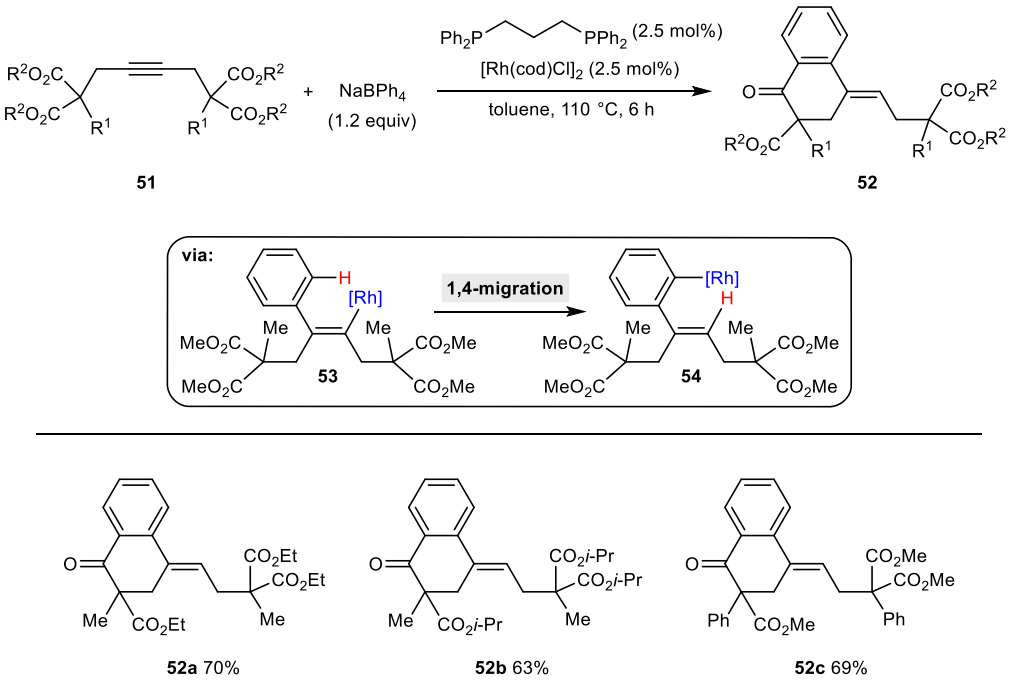
Scheme 11: *Formation of indene **43** via quenching with a second addition of alkyne.*

The formation of indene **43** (Scheme 12) is postulated to proceed by an initial migratory insertion of the alkyne, followed by alkenyl-to-aryl 1,4-rhodium migration, forming species **47**. A second migratory insertion of alkyne **42** forms alkenylrhodium intermediate **48**. This is followed by *β*-hydride elimination and isomerisation to give indene **43**. Hydrolysis before the second addition of alkyne results in the formation of **44**, while the formation of diene **45** suggests the involvement of species **50** by re-entering the catalytic cycle.



Scheme 12: *Catalytic cycle for the formation of indene* ***43****.*

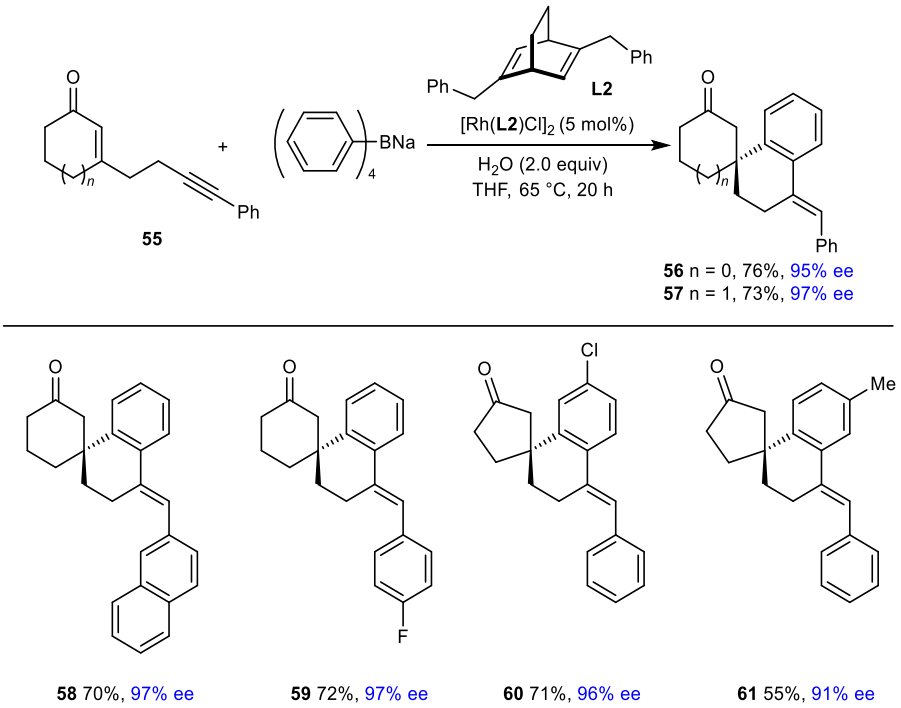
In 2005 Murakami reported a rhodium-catalysed cyclisation cascade forming bicyclic ketones (Scheme 13).[21] The reaction begins by the transmetalation of $NaBPh_4$ with rhodium(I) followed by migratory insertion of the alkyne. Alkenyl-to-aryl 1,4-rhodium migration occurs resulting in intermediate **54**. Intramolecular nucleophilic 1,2-addition of arylrhodium species **54** onto an ester moiety ensues, generating product **52**. The reaction requires anhydrous conditions otherwise protonolysis of the alkenylmetal species **53** and **54** would occur.



Scheme 13: *Rhodium-catalysed formation of bicyclic ketones.*

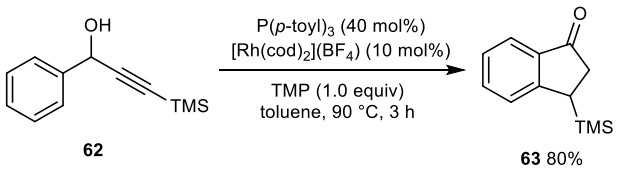
The reaction scope was modest with only symmetrical alkynes tolerated (Scheme 13). Both alkyl and aryl groups were tolerated at the α-position (**52a** and **52c**). No variation of the sodium tetraphenylborate was investigated. However, the reaction did proceed with excellent yields using various ester groups. An enantioselective variant was not investigated.

In 2010 Hayashi and co-workers reported the synthesis of spirocyclic compounds in excellent yields and enantioselectivity, *via* an alkenyl-to-aryl 1,4-rhodium migration (Scheme 14).[22] A similar catalytic cycle to that of Scheme 12 is believed to be generating product **56**, whereby transmetalation with rhodium(I), followed by an alkenyl-to-aryl 1,4-migration and subsequent nucleophilic attack onto the Michael acceptor, forming the desired product (**56**). The substrate evaluation was diverse with five and six membered rings tolerated. Various substituted sodium tetraphenylborates were tolerated, including *meta*-substituted (**60**) and *para*-substituted (**61**). However, electron-withdrawing groups were not tolerated. Aryl, alkenyl, and alkyl substituents were all tolerated on the alkyne group. In all cases, high enantiocontrol was observed.



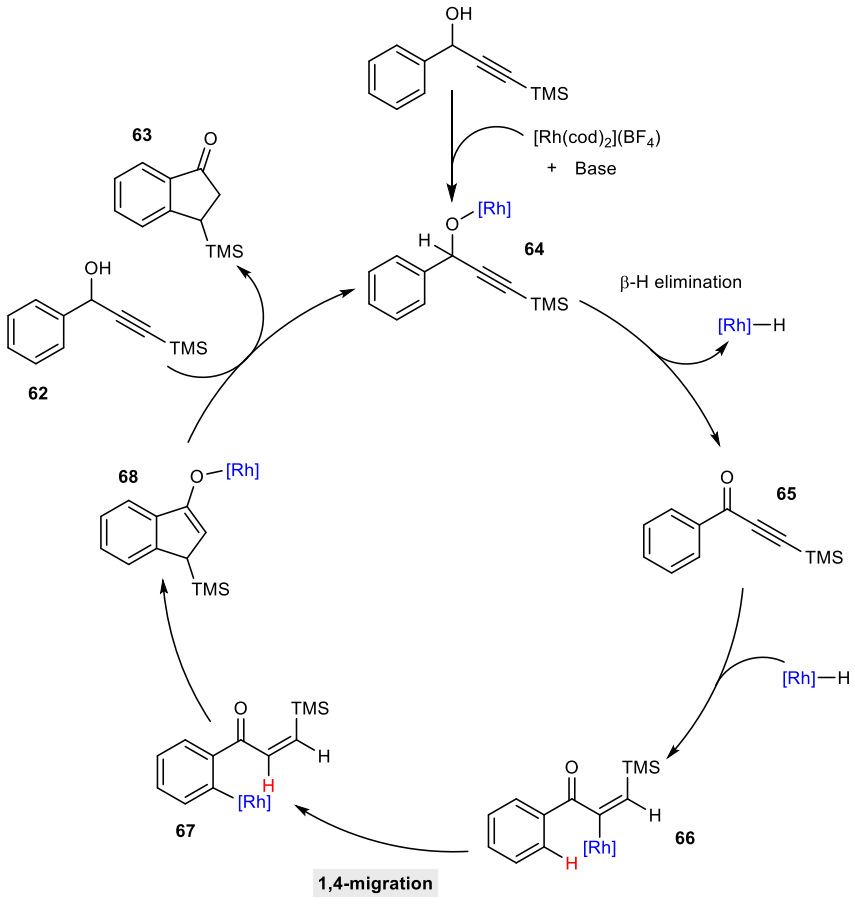
Scheme 14: *Rhodium-catalysed cyclisation of forming spirocyclic compounds.*

In 2005, Iwasawa and co-workers utilised a alkenyl-to-aryl 1,4-rhodium migration to synthesise indanone derivatives (Scheme 15).[23] Arylpropargyl alcohol **62** underwent rhodium-catalysed cyclisation forming bicyclic ketone **63**.



Scheme 15: *Rhodium-catalysed cyclisation of arylpropargyl alcohol* ***62****.*

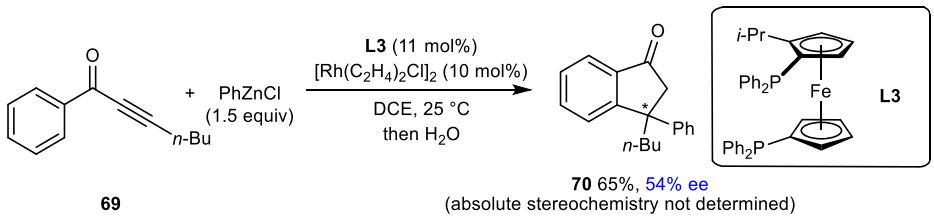
The proposed catalytic cycle (Scheme 16) for the formation of **63** initially involves deprotonation of the arylpropargyl alcohol, followed by coordination to the rhodium catalyst, forming species **64**. *β*-Hydride elimination affords intermediate **65.** This hydride species undergoes hydrometallation onto the alkynyl ketone, followed by an alkenyl-to-aryl 1,4-metal migration. Arylrhodium species **67** undergoes 1,4-addition onto the ketone, forming rhodium enolate species **68**, which after proton exchange with an additional arylpropargyl alcohol generates product **63**, closing the catalytic cycle. An enantioselective variant was not investigated.



Scheme 16: *Catalytic cycle for the formation of* ***63****.*

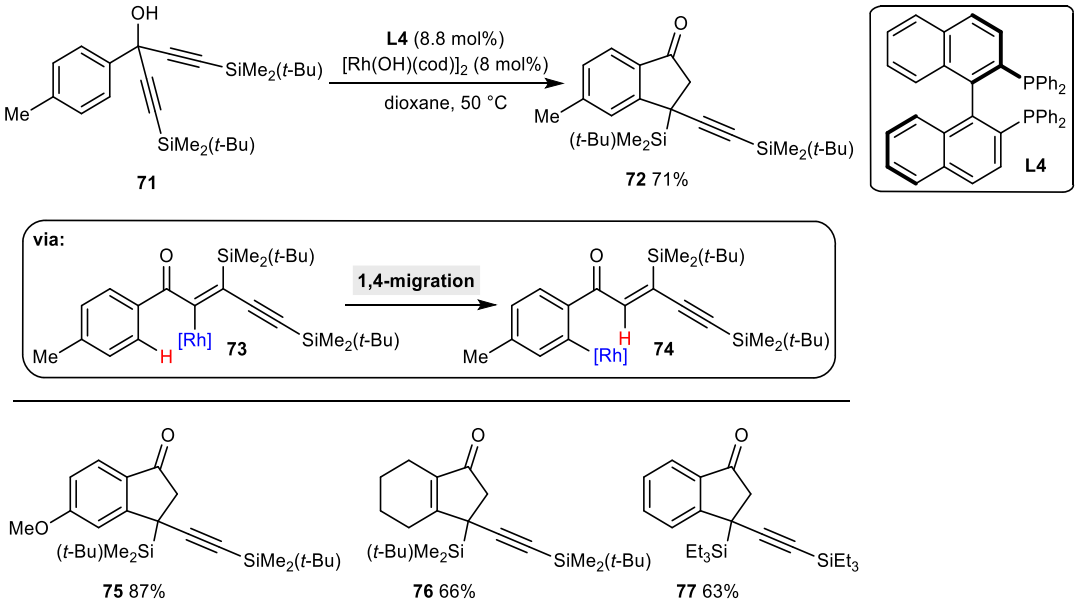
Hayashi reported the carbometallation of alkynyl ketone **69** utilising aryl zinc reagents, generating highly substituted indanones (Scheme 17).[24] A planar-chiral ferrocene bisphosphine

ligand was employed to govern enantiocontrol. Unfortunately, only modest enantioselectivity was obtained (54% *ee*). A similar catalytic cycle to that of Scheme 16 is believed to be generating product **70**. Trapping of the enolate species with an external electrophile generates indanones with one tertiary and one quaternary chiral centre by forming three new carbon-carbon bonds.



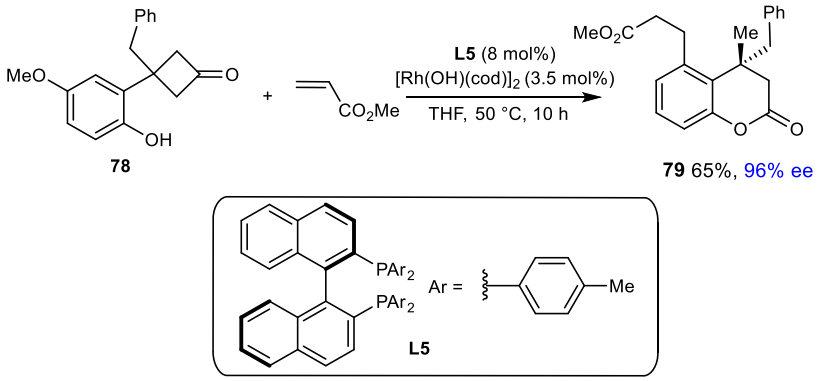
Scheme 17: *Arylative cyclisation of aryl alkynyl ketones.*

Hayashi extended this concept to include *β*-carbon elimination (Scheme 18).[25] Bisphosphine based ligands were required to achieve significant conversion. The proposed catalytic cycle is initiated by the generation of alkoxorhodium species, which undergoes *β*-alkynyl elimination. This is followed by carbometallation of the alkyne and alkenyl-to-aryl 1,4-migration, generating intermediate **74**. 1,4-addition occurs, followed by protonolysis to give indanone **72**. Substrate scope was modest, with electron-donating (**72**) and electron-withdrawing (**76**) substituted aryl bis(alkynyl) carbinols generating products in good yields. Cyclohexenyl groups at the alcohol position gave significant conversion (**77**), involving an alkenyl-to-alkenyl 1,4-migration rather than an alkenyl-to-aryl 1,4-migration.



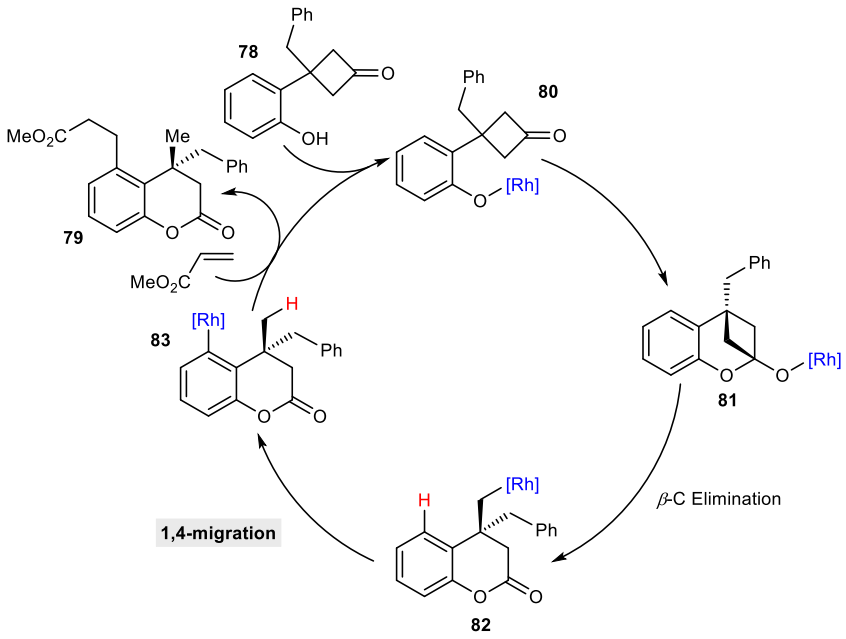
Scheme 18: *Formation of **72** by rhodium-catalysed cyclisation.*

In 2007 Murakami reported the asymmetric synthesis of 3,4-dihydrocouramins utilising cyclobutanones (Scheme 19).[26] Using bisphosphine ligand **L5**, Murakami was able to render this process enantioselective.



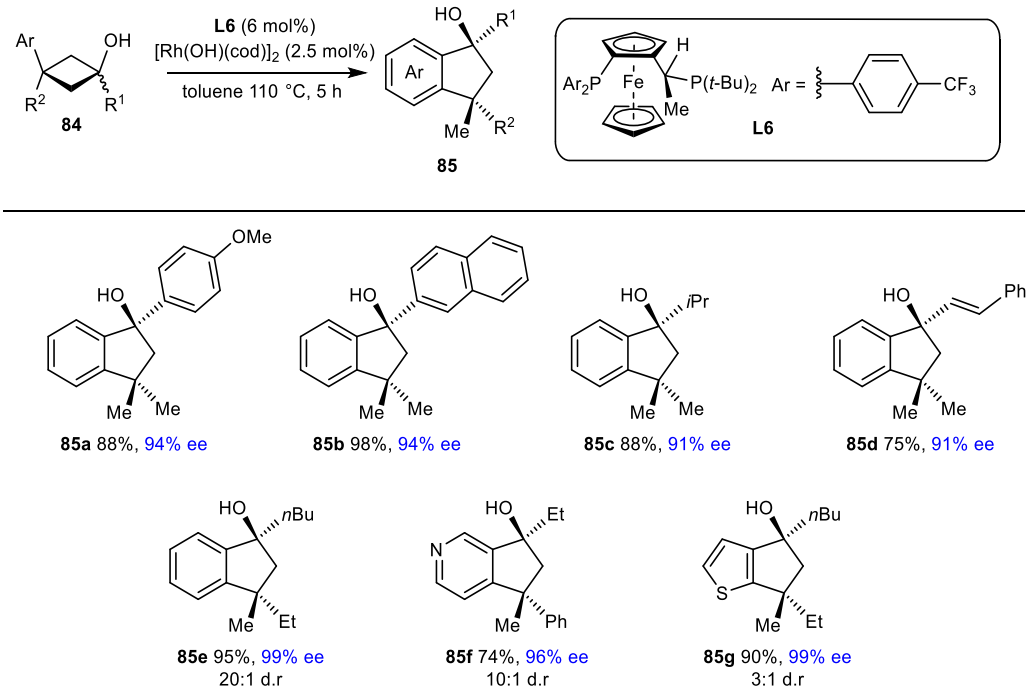
Scheme 19: *Rhodium-catalysed formation of **79** by an alkyl-to-aryl 1,4-migration.*

The proposed mechanism is initiated by the formation of rhodium aryloxide **80** (Scheme 20). Rhodium aryloxide **80** undergoes 1,2-addition to the ketone, forming species **81**. *β*-Carbon elimination causes the ring opening of the cyclobutane skeleton. This is the enantiodifferentiating step, whereby there is a selective insertion into one of the two adjacent C-C bonds of the symmetrical cyclobutane. An alkyl-to-aryl 1,4-rhodium migration occurs, followed by an intermolecular conjugate addition, generating the highly substituted 3,4-dihydrocoumarin **79**.



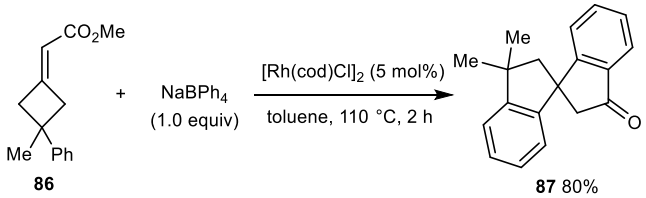
Scheme 20: *Catalytic cycle for the formation of **79**.*

In 2009 Cramer reported the synthesis of indanols from cyclobutanols *via* selective *β*-carbon elimination (Scheme 21).[27] A range of substituted aryl tertiary cyclobutanols were tolerated (**85a** and **85b**) in excellent yields and enantioselectivity. Substrates that contained alkyl groups (**85c**) were tolerated as well as sterically hindered alkyl groups (**85d**). When all substituents on the cyclobutanol skeleton are different, two stereocentres are formed. Selectivity is maintained when alkyl groups are incorporated and heteroaromatic ring systems generated indanols in modest to high diastereoselectivities.



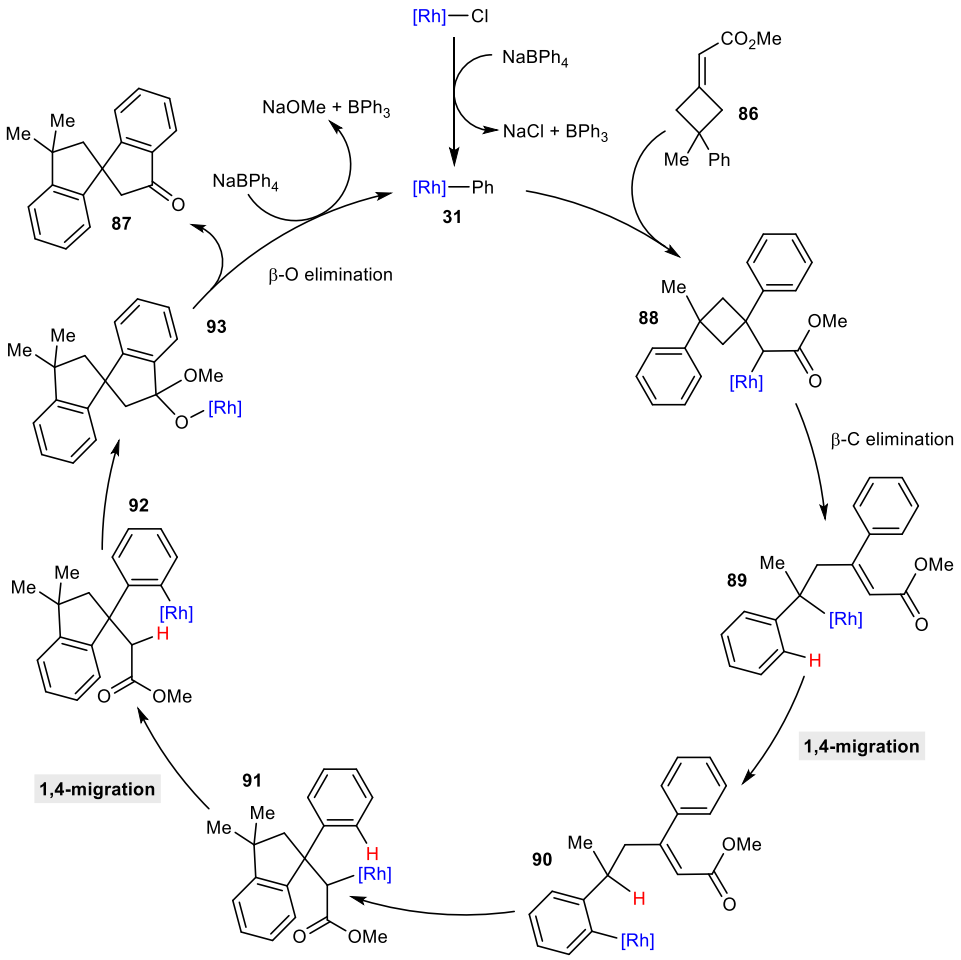
Scheme 21: *Rhodium-catalysed cyclisation of cyclobutanols.*

Matsuda reported the synthesis of spirocycles *via* a double alkyl-to-aryl 1,4-rhodium migration domino cascade which utilises *β*-carbon elimination from cyclobutanes (Scheme 22).[28] During the rhodium-catalysed spirocyclisation of **86**, generation of product **87** involves two 1,4-additions, two *β*-eliminations, two alkyl-to-aryl 1,4-migrations and a 1,2-addition. To avoid unwanted *β*-hydride product, there must be no hydrogen atom at the 3-position in the cyclobutane skeleton.



Scheme 22: *Rhodium-catalysed arylative spirocyclisation of* ***86****.*

The proposed catalytic cycle (Scheme 23) is initiated by the transmetalation of sodium tetraphenylborate with rhodium(I) generating arylrhodium species **31**. Arylrhodium species **31** undergoes 1,4-addition onto **86** forming intermediate **88**. *β*-Carbon elimination occurs, opening the strained cyclobutane ring, generating α,β-unsaturated ester **89**. Subsequence alkyl-to-aryl 1,4-migration occurs, followed by another 1,4-addition to generate indane **91**. Successive alkyl-to-aryl 1,4-migration followed by 1,2-addition with the ester moiety, generates **93**. Finally, *β*-oxygen elimination occurs forming spirocycle **87**, regenerating the rhodium catalyst which can then re-enter the catalytic cycle.



Scheme 23: *Proposed catalytic cyclic for the formation of* ***87****.*

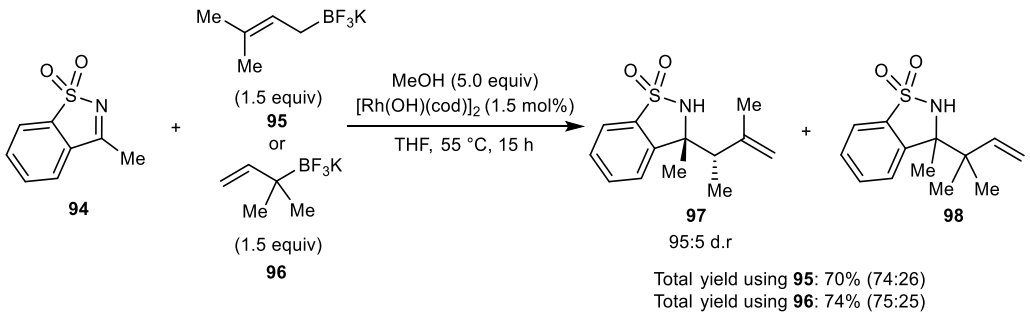
Intermediate **88** can undergo either *β*-carbon elimination or alkyl-to-aryl 1,4-migration. Selectivity towards *β*-carbon elimination occurs due to a potential reduction in ring strain. During the second alkyl-to-aryl 1,4-migration generating **92**, the rhodium has a choice to migrate between two distinct aryl environments. Selective migration towards the phenyl ring occurs due to increased steric hinderance surrounding the indane ring system. The reaction

sequence is highly selective and is a unique example incorporating two alkyl-to-aryl 1,4-rhodium migrations.

1.3.2 1,4-Rhodium(I) Migrations to sp^3 Centres

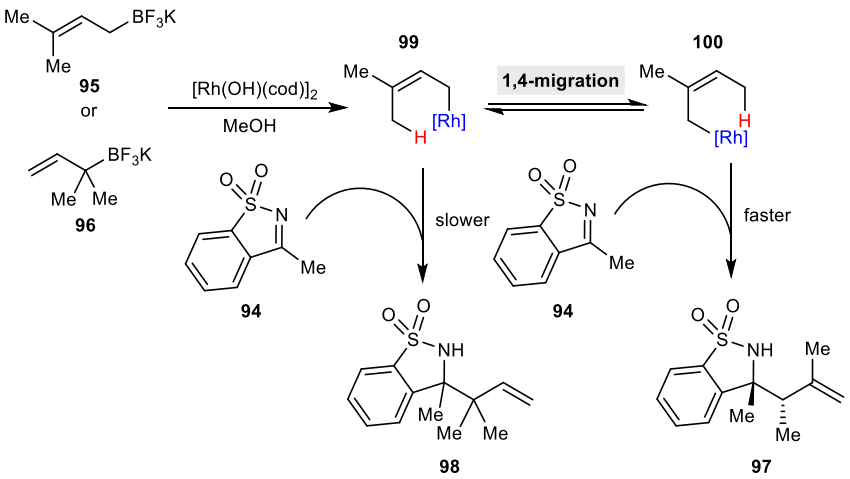
1,4-Rhodium migrations to sp^3 centres are not well-described in comparison to sp^2 migrations. The formation of an alkylrhodium species is less favoured compared to an aryl or vinylrhodium species, most likely due to the energy difference between the intermediates. Recently, this type of migration has been explored more thoroughly and could provide a new route to synthetically challenging molecules.[29]

In 2014 the Lam group reported the rhodium-catalysed allylation of cyclic imines *via* a novel allyl-to-allyl 1,4-rhodium migration (Scheme 24).[30] Interestingly, the reverse prenylation product (**98**) was the minor component, with the major component (**97**) being formed with excellent diastereoselectivity (95:5). Nearly identical results were obtained for both isomers of prenyltrifluoroborate (**95** and **96**).



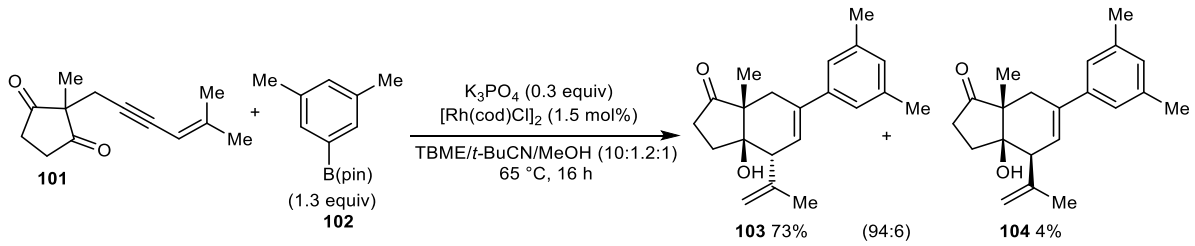
Scheme 24: *Rhodium-catalysed allylation of* ***94****.*

The catalytic cycle (Scheme 25) is initiated by the transmetalation of trifluoroborates (**95** or **96**) with rhodium(I), forming species **99**. Due to the unreactive nature of cyclic imine **94**, direct allylation without involving metal migration is disfavoured. Alternatively, an allyl-to-allyl 1,4-migration can occur, followed by nucleophilic allylation of **94**, forming the less sterically hindered product **97**.



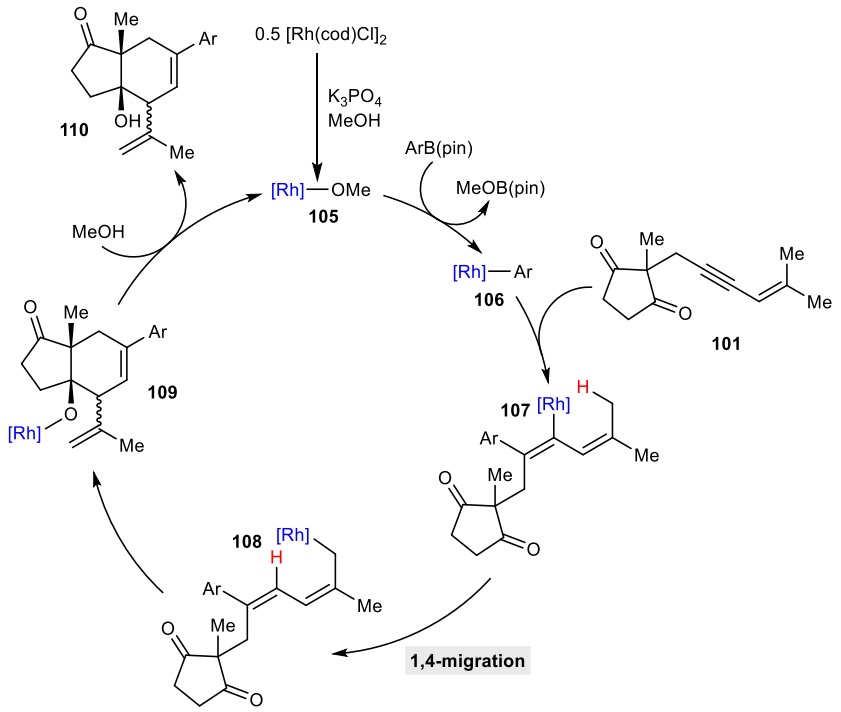
Scheme 25: *Proposed isomerisation of allylrhodium intermediates.*

In 2017 the Lam group reported a novel alkenyl-to-allyl 1,4-rhodium migration to generate bicylces in high diastereoselectivities (Scheme 26).[31] Reacting enynone **101** with pinacol borate **102** generated the major diastereoisomer bicycle **103** in 73% yield. 3,5-Disubstituted pinacol borates were required to prevent alkenyl-to-aryl 1,4-rhodium migration.



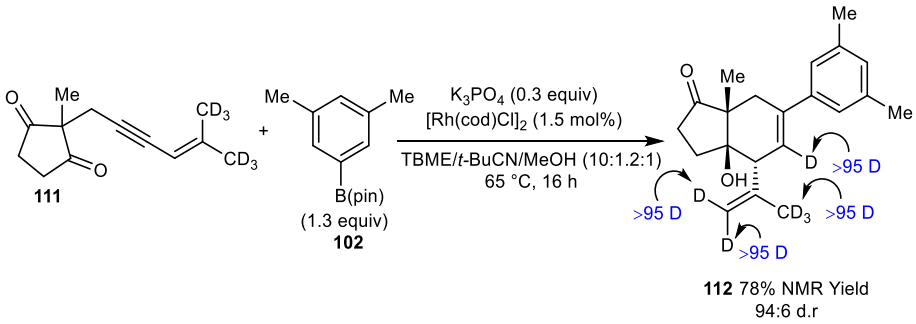
Scheme 26: *Arylative intramolecular allylation of **101**.*

The proposed catalytic (Scheme 27) cycle is initiated with the transmetalation of the pinacol borate with rhodium methoxide, forming species **106**. Migratory insertion of the alkyne in a *syn*-selective fashion affords intermediate **107**. Alkenyl-to-aryl 1,4-migration occurs, followed by 1,2-addition onto a ketone, generating **109**. Methanolysis affords bicycle **110**, regenerating the rhodium alkoxide catalyst.



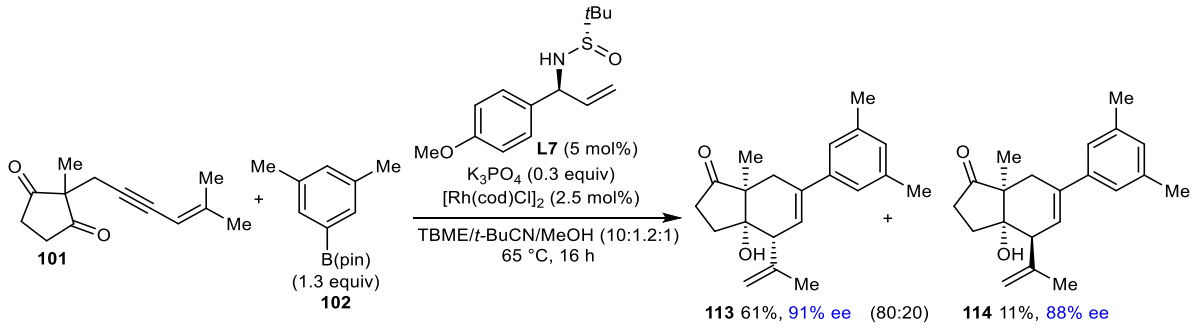
Scheme 27: *Catalytic cycle for the formation of* ***110****.*

Mechanistic studies were performed by subjecting hexadeuterated 1,3-enyne **111** and pinacol borate **102** to the reaction conditions, generating bicycle **112** with a greater than 95% incorporation of deuterium at the akene position on the cyclohexene ring (Scheme 28). This suggests an alkenyl-to-allyl 1,4-migration which is consistent with the proposed catalytic cycle.



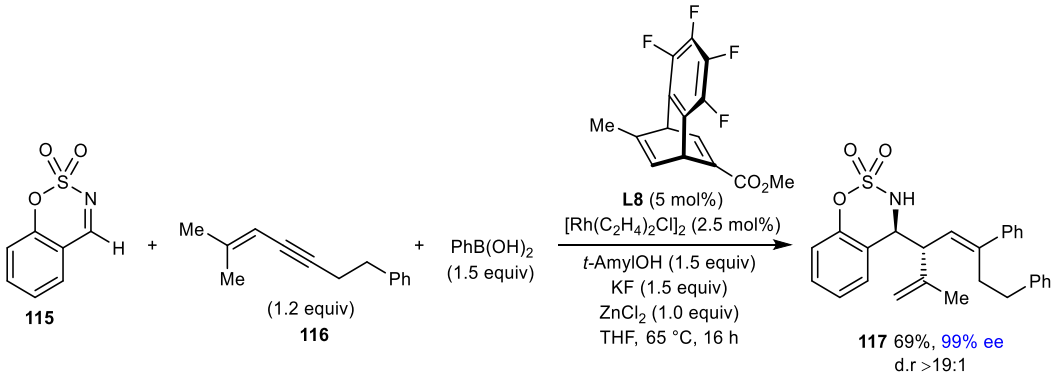
Scheme 28: *Mechanistic study supporting the alkenyl-to-aryl 1,4-migration.*

Enantioselectivity could be induced by employing the chiral sulfur-olefin **L7** (Scheme 29). The major diastereoisomer (**113**) was generated with 91% *ee*, while the minor diastereoisomer (**114**) with 88% *ee.*



Scheme 29: *Enantioselective variant of the arylative intramolecular allylation of* ***101****.*

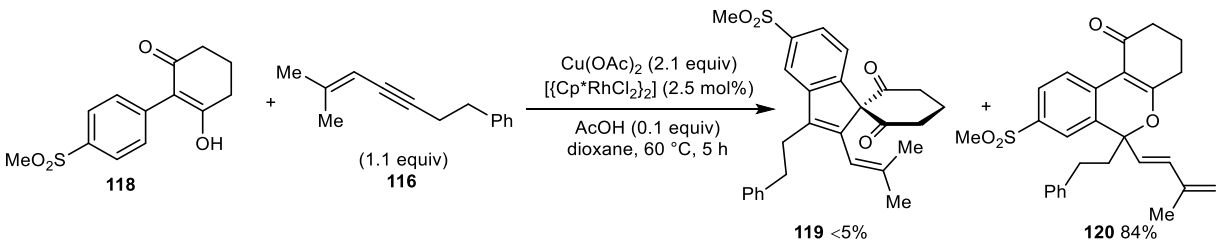
In 2017, the Lam group utilised an alkenyl-to-aryl 1,4-migration in a three-component coupling reaction between arylboronic acids, 1,3-enynes and cyclic imines (Scheme 30).[32] The reaction was rendered enantioselective using chiral diene **L8**.



Scheme 30: *Three-component coupling of* ***115****.*

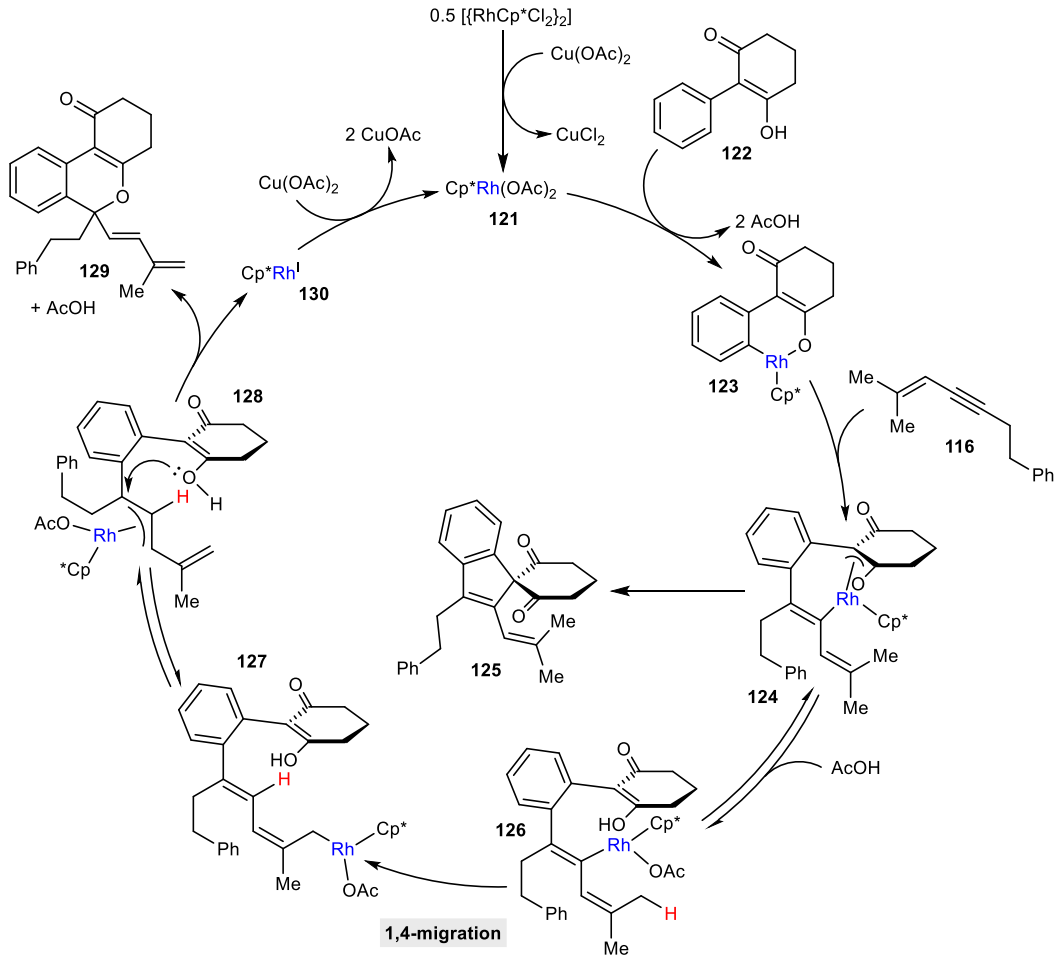
1.4 1,4-Rhodium(III) Migrations

In 2013 Ishii and co-workers described the first 1,4-rhodium(III) migration using a stoichiometric rhodium catalyst.[33] Then in 2014 the Lam group reported the first catalytic alkyl-to-alkenyl 1,4-rhodium (III) migration.[34] An unexpected mode of oxidative annulation was reported using 1,3-enynes which acted as one carbon annulation partners (Scheme 31), resulting in the formation of benzopyran **120** as the major product. For good selectivity towards benzopyran **120**, an electron-withdrawing group must be present on the aryl ring of cyclohexanone **118**. If electron-donating groups are present, the major product is the formation of spiroindene **119**, which occurs *via* reductive elimination.



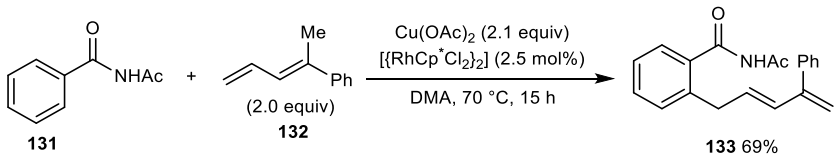
Scheme 31: *Oxidative annulation of using 1,3-enynes.*

Active catalyst **121** is formed by reacting $Cu(OAc)_2$ with $[\{RhCp^*Cl\}_2]$. Cyclorhodation of **122** occurs, followed by migratory insertion of the 1,3-enyne, forming intermediate **124**. Reductive elimination from intermediate **124** generates spiroindene **125**. However, an alternative pathway involves the reversible protonolysis of **124** to produce alkenylrhodium species **126**. Alkyl-to-alkenyl 1,4-rhodium (III) migration occurs, followed by σ-π isomerisation. Nucleophilic attack by the enol oxygen forms benzopyran **129**, resulting in the formation of rhodium(I) catalyst **130**. This is then reoxidised to rhodium(III) by $Cu(OAc)_2$.



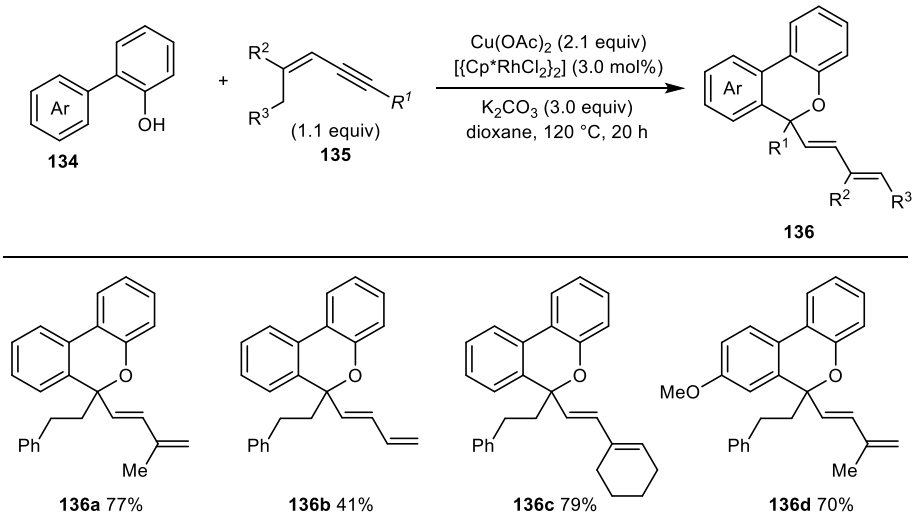
Scheme 32: *Proposed catalytic cycle for the formation of **129**.*

In 2016 the Lam group extended this concept to incorporate N-acetylbenzamides with 1,3-dienes (Scheme 33).[35] This was the first example of allyl-to-allyl 1,4-rhodium(III) migration.



Scheme 33: *Oxidative allylation of N-acetylbenzamide* ***131****.*

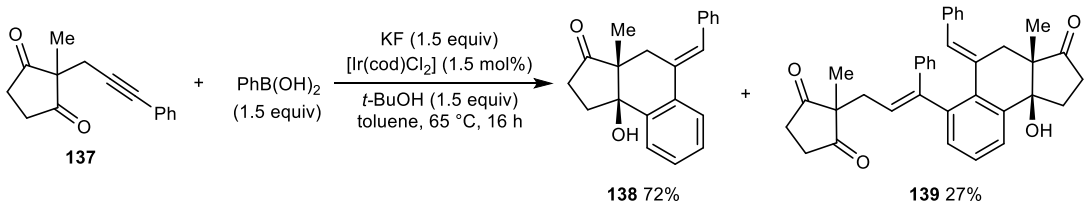
In 2018, the Lam group reported oxidative annulations of 2-phenylphenols using 1,3-enynes *via* a alkyl-to-alkenyl 1,4-rhodium(III) migration (Scheme 34).[36] The substrate scope was diverse with aliphatic substitution at the alkyne (**136a**) generating product in good yield. Various substituted 2-arylphenols were tolerated, including *para*-substituted (**136d**) and *meta*-substituted, incorporating both electron-donating and electron-withdrawing groups. Cyclohexene substitution cis to the alkyne (**136c**) also gave significant conversion.



Scheme 34: *Oxidative annulation of 2-phenylphenol* ***134****.*

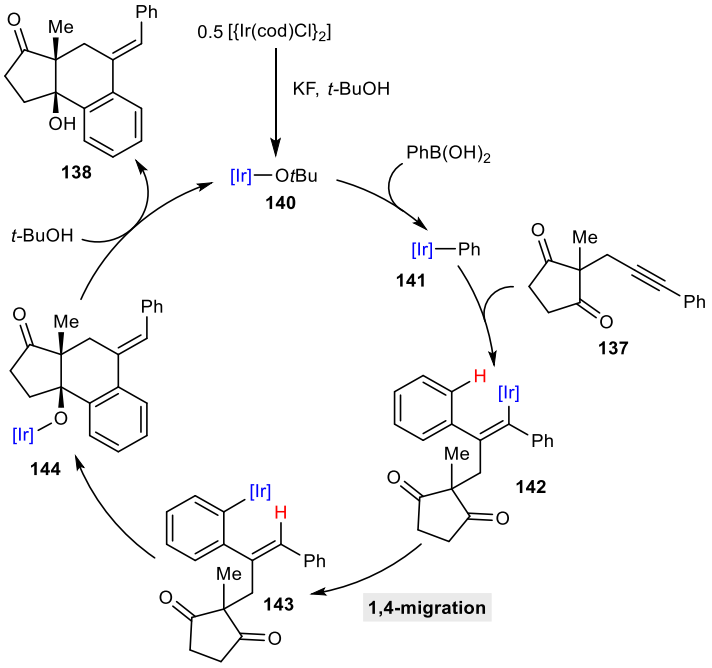
1.5 1,4-Iridium(I) Migrations

The Lam group reported the first iridium(I) migration using cyclic alkynones, forming fused polycyclic structures (Scheme 35).[11] Preliminary results using rhodium catalysis gave modest yields; however, utilising an iridium catalyst formed product **138** in a 72% yield. Side product **139** results from a 2:1 adduct of **137** and the boronic acid, arising from the carbometallation of the alkyne with the opposite regioselectivity to that of **138**.



Scheme 35: *Iridium catalysed cyclisation of alkynone **137**.*

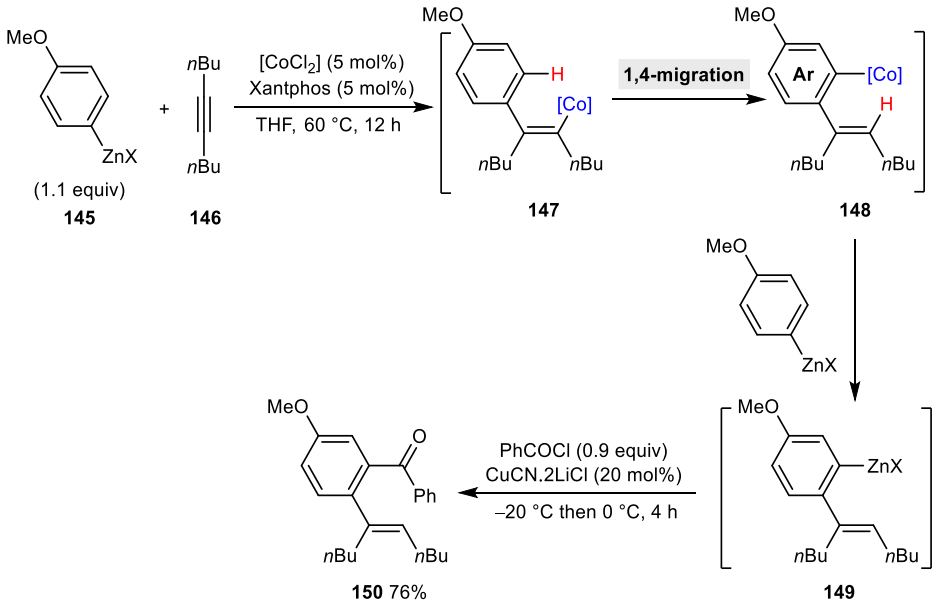
The proposed catalytic cycle is initiated by the transmetalation of the boronic acid with iridium alkoxide (**140**). This iridium complex (**141**) undergoes migratory insertion reaction to give species **142**, which is followed by an alkenyl-to-aryl 1,4-migration. The resulting intermediate (**143**) undergoes 1,2-additon with one of the ketones, followed by protonation to give the fused polycyclic structure **138**.



Scheme 36: *Proposed catalytic cycle for the formation of **138**.*

1.6 1,4-Cobalt Migrations

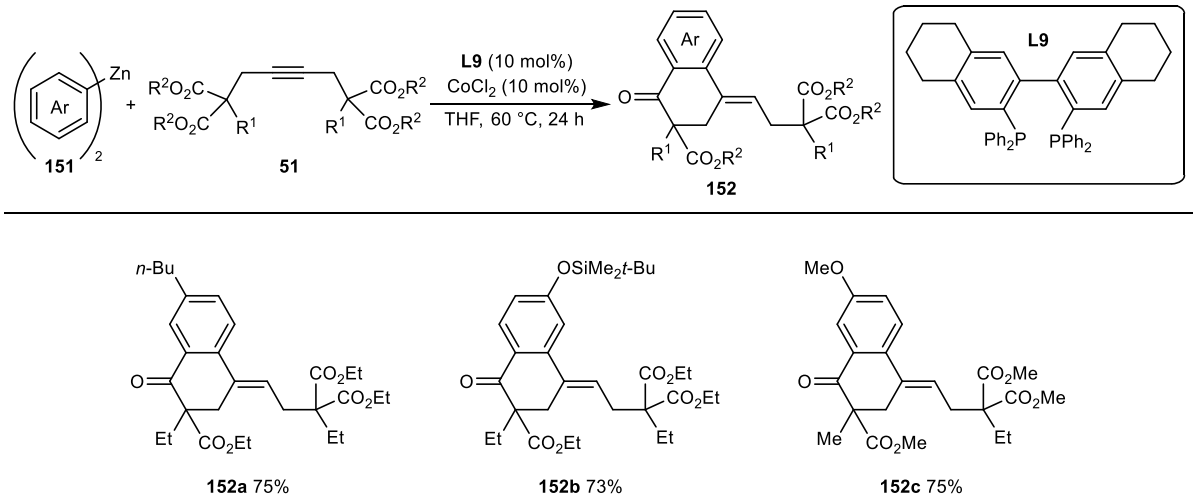
The first 1,4-cobalt migration was reported by Yoshikai in 2012 (Scheme 37).[12] In an analogous process reported by Hayashi arylzinc reagents underwent migratory insertion reactions with alkynes, forming *ortho*-alkenylarylcobalt species **147**.[20] Further transmetalation with arylzinc reagents followed by quenching with an external electrophile afforded product **150**.



Scheme 37: *Alkyne insertion using arylzinc reagents.*

The reaction sequence begins with the transmetalation of the arylzinc reagent with the cobalt catalyst, followed by carbometallation of the alkyne to produce alkenylmetal species **147**. This species then undergoes an alkenyl-to-aryl 1,4-cobalt migration, forming species **148**, followed by subsequent cobalt-zinc transmetalation (**149**). An external electrophile then quenches the reaction generating product **150**.

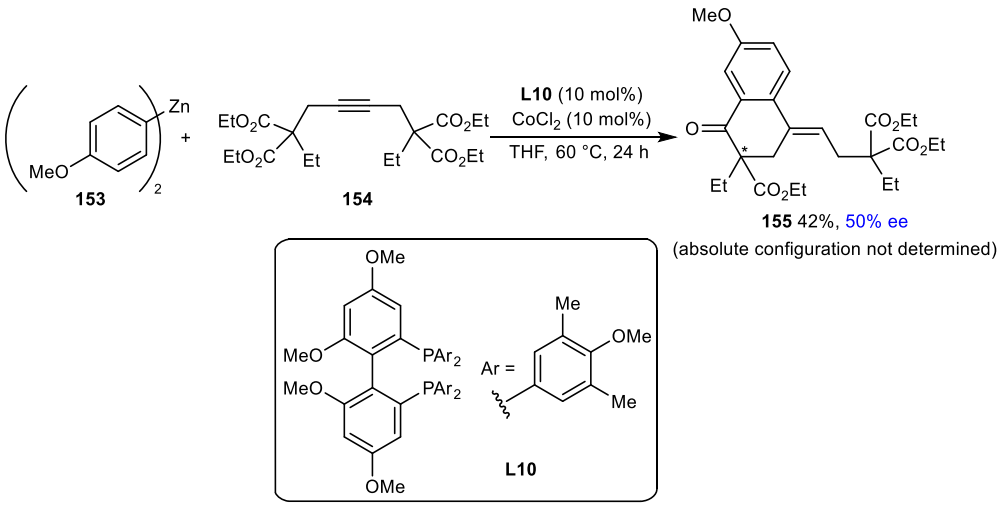
In 2016 Yoshikai extended this concept to symmetrical alkynes, incorporating an alkenyl-to-aryl 1,4-cobalt migration, generating bicyclic ketone **152** (Scheme 38).[37]



Scheme 38: *Arylative cyclisation of **51** via akenyl-to-aryl 1,4-cobalt migration.*

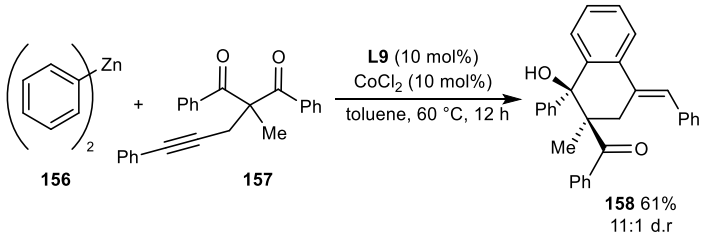
The substrate scope evaluated (Scheme 38) was modest with both electron-donating (**152a**) and electron-withdrawing (**152b**) arylzinc species tolerated. However, only alkyl substituents

were tolerated at the α-position and practically no variation of the ester moiety was investigated. An enantioselective variant was reported using bisphosphine **L10** (Scheme 39). Modest enantioselectivity was observed, with **155** isolated in 42% yield.



Scheme 39: *Enantioselective arylative cyclisation of* ***154****.*

Modification of the solvent and ligand allowed for the arylative cyclisation of homopropargyl diketones (Scheme 40). Cobalt-catalysed carbometallation of tethered unsymmetrical alkynes occurs with regioselective arylation generating product **158** in modest yield. These homopropargyl diketones did not undergo arylative cyclisation using rhodium or iridium catalyst systems.



Scheme 40: *Arylative cyclisation of homopropargyl diketone* ***157*** *via 1,4-cobalt migration.*

1.7 Summary on Remote C-H Activation

In summary, remote C-H activation is a prevailing instrument for synthetic organic chemists. 1,4-Metal migrations, most ubiquitous are palladium and rhodium, enable the remote functionalisation of C-H bonds. 1,4-Metal migrations allow for the generation of molecular complexity without prior functionalisation of starting materials.

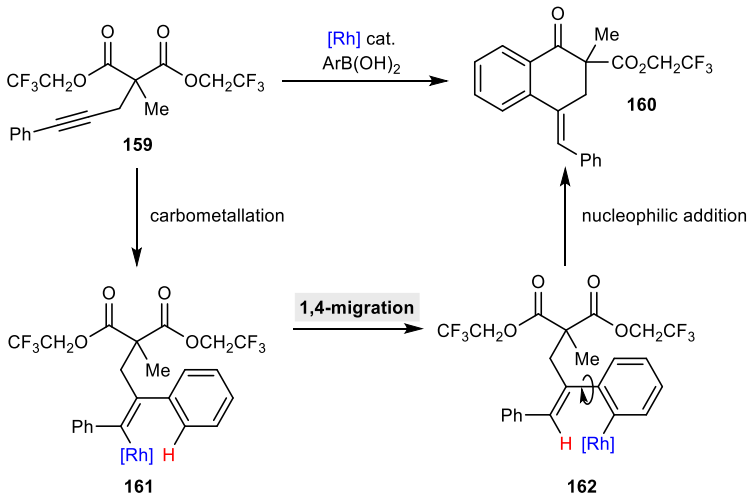
1,4-Metal migrations to sp^2 centres are well described. However, developing new methodologies can further our understanding of 1,4-metal migrations, generating products that would have otherwise been difficult to synthesise. As highlighted, there are limited examples of enantioselective intramolecular rhodium-catalysed cyclisation reactions involving a 1,4-metal migration, with the work done by Hayashi being the most prevalent. Developing methodologies that explore this area could provide access to novel highly functionalised products.

Chapter 2: Results and Discussion

2.1 Aims and Objectives

Intramolecular arylative cyclisations of symmetrical alkynes involving alkenyl-to-aryl 1,4-migrations have been previously reported by Murakami (Scheme 13).[21] Yoshikai extended this concept using cobalt-catalysed cyclisations, forming bicycles of greater complexity (Scheme 38).[37]

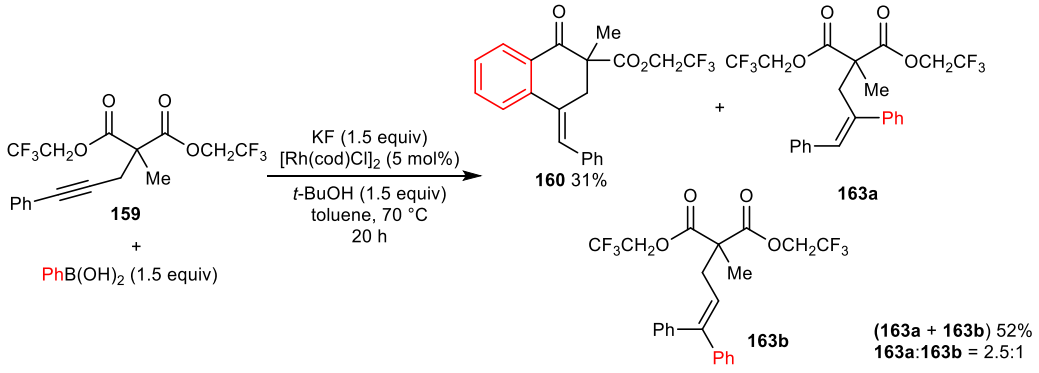
Incorporating these two ideas, the aim of this work was to demonstrate the intramolecular arylative cyclisations of unsymmetrical alkynes, generating greater complexity than previously reported (Scheme 41). We propose an initial regioselective carbometalation of malonate esters **159**, followed by alkenyl-to-aryl 1,4-metal migration, forming nucleophilic arylrhodium species **162**. Cyclisation onto one of the malonate ester moieties would form complex bicycles (**160**). Trifluoroethanol esters were chosen due to their increased electrophilicity, increasing the rate of nucleophilic addition.



Scheme 41: *Reaction principle.*

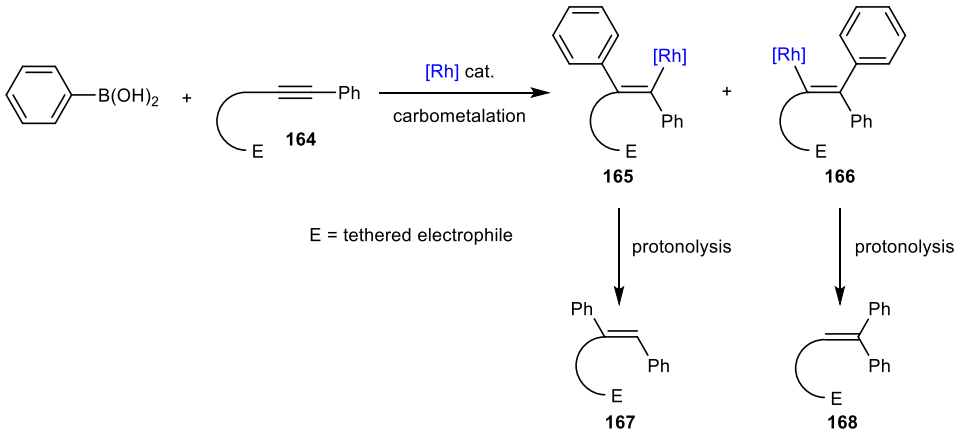
2.2 Reaction Optimisation

As previously discussed, the Lam group published the first 1,4-iridium(I) migration, which involves regioselective carbometalation of an alkyne, followed by alkenyl-to-aryl 1,4-metal migration (Scheme 42).[11] Due to the similarities in the reactivity, Dr. S. Karad subjected substrate **159** to the same conditions, using $[Rh(cod)Cl]_2$ as a catalyst. Pleasingly, he observed the formation of **160** in 31% yield. However, formation of regioisomeric hydroarylation side-products **163a** and **163b** as an inseparable mixture was observed as the major component.



Scheme 42: *Preliminary results using malonate **159** on 0.2 mmol scale. Yields determined by ^1H NMR spectroscopy using 3-bromotoluene as the internal standard. Reaction performed by Dr. S. Karad.*

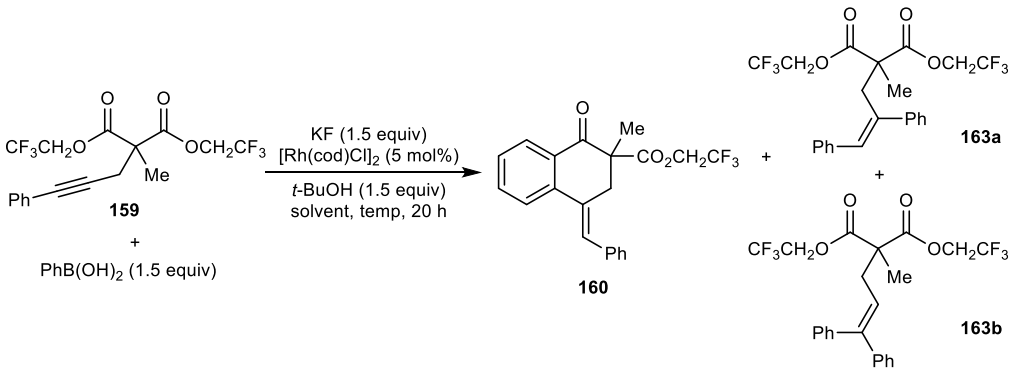
Regioisomeric side-product **167** is thought to arise from the regioselective carbometalation of the tethered alkyne followed by protonolysis, preventing intramolecular cyclisation (Scheme 43). Regioisomeric side-product **168** arises from the opposite regioselective carbometalation of the tethered alkyne followed by protonolysis.



Scheme 43: *Formation of **167** and **168**.*

To optimise yields, the screening of solvent systems was explored (Table 1). Comparing preliminary results (entry 1), xylene (entry 2) gave **160** in 22% yield, while the use of 4Å molecular sieves (entry 3) had no effect on the reaction. Pleasingly, using 1,4-dioxane (entry 4) gave the desired product **160** in 44% yield, with reduction in the formation of side-products **163a** and **163b**. Using a protic solvent (entry 7) gave significant formation of side-product **163a**. 2-MeTHF/MeCN (2.5:1) (entry 6) gave modest yield with low formation of side products. THF (entry 5) shut down reactivity altogether. Therefore, 1,4-dioxane was chosen as the solvent.

Table 1: *Solvent screening.*

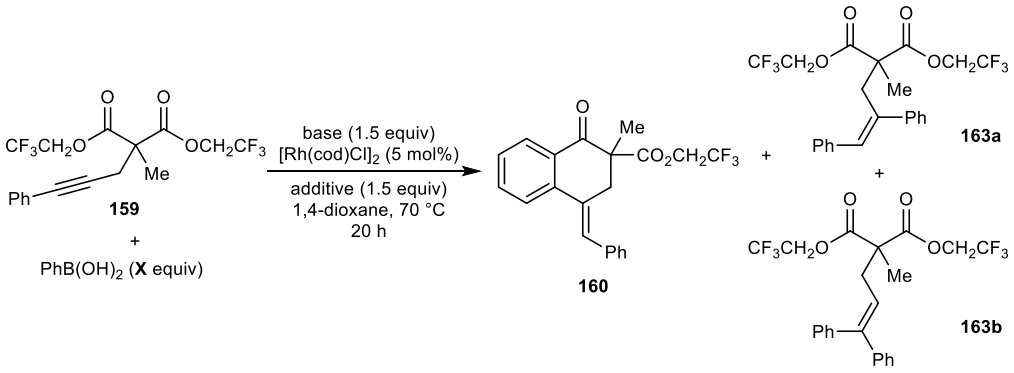


Entry	Solvent	Temperature (°C)	Yield (%)		
			160	**163a**	**163b**
1	toluene	70	31	37	15
2	xylene	100	22	24	9
3	xylene[a]	100	22	22	13
4	1,4-dioxane	70	44	22	13
5	THF	60	9	0	0
6	2-MeTHF/MeCN (2.5:1)	60	31	4	9
7	TFE	90	11	49	33

*Reactions employed 0.05 mmol of **159**. Yields determined by ^{1}H NMR spectroscopy using 1,4-dimethoxybenzene as the internal standard. [a] 4Å Molecular sieves (20 mg).*

Screening of bases and additives was then explored (Table 2). Bases such as Cs_2CO_3 and Et_3N (entries 3 and 4) proved ineffective, decreasing the yield of **160** to 23% and 28% respectively. Using *t*-AmylOH resulted in a slight increase in the formation of **160**. Increasing the equivalents of boronic acid (entry 5) had minimal effect on the reaction. *i*-PrOH (entry 1) gave poor formation of **160**. Therefore, *t*-AmylOH and KF were chosen as they offered the greatest yield.

Table 2: *Base and additive screening.*

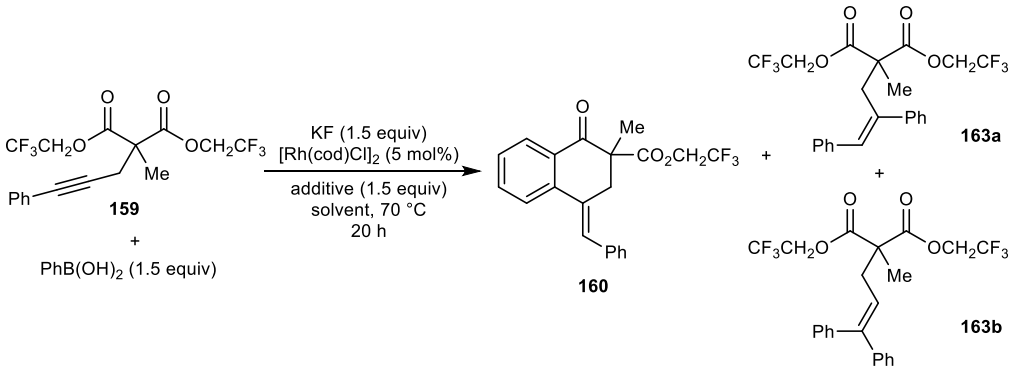


Entry	Base	Additive	(**X** equiv)	Yield (%)		
				160	**163a**	**163b**
1	KF	*i*-PrOH[a]	1.5	23	0	9
2	KF	*t*-AmylOH	1.5	46	19	13
3	Et_3N	*t*-AmylOH	1.5	23	22	9
4	Cs_2CO_3	*t*-AmylOH	1.5	28	0	5
5	KF	*t*-AmylOH	2	40	19	13

*Reactions employed 0.05 mmol of **159**. Yields determined by ^1H NMR spectroscopy using 3-bromotoluene as the internal standard. [a] (5.0 equiv).*

Co-solvent systems were then investigated (Table 3). Using 1,4-dioxane/H_2O (9:1) (entry 1) resulted in a minor increase in the formation of **160** to 47% yield. Pleasingly, removing the additive gave identical results (entry 2), as H_2O can act as the proton source instead of *t*-AmylOH. Modifying the ratio of 1,4-dioxane to H_2O (entries 3 and 4) reduced the formation of product **160**. As expected, increasing the ratio of H_2O increased the formation of regioisomeric side-products **163a** and **163b**. Therefore, for the remainder of our studies 1,4-dioxane/H_2O (9:1) was selected as the solvent system.

Table 3: *Co-solvent screening.*

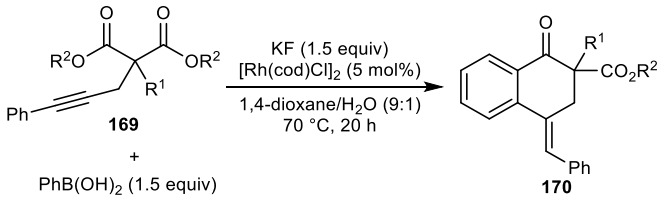


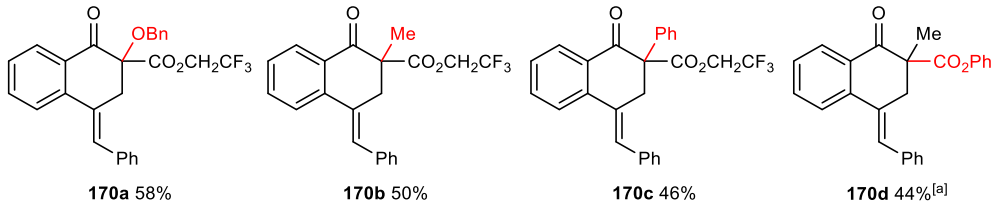
Entry	Solvent	Additive	Yield (%)		
			160	**163a**	**163b**
1	1,4-dioxane/H_2O (9:1)	*t*-AmylOH	47	13	13
2	1,4-dioxane/H_2O (9:1)	none	47	13	13
3	1,4-dioxane/H_2O (10:1)	none	37	9	9
4	1,4-dioxane/H_2O (4:1)	none	39	22	9

*Reactions employed 0.05 mmol of **159**. Yields determined by ^{1}H NMR spectroscopy using 1,4-dimethoxybenzene as the internal standard.*

Initial substrate scope was explored with variations at the α-position and ester moiety (Table 4). Alkyl and aryl substituents at the α-position were tolerated. Bulkier, less electrophilic esters (**170d**) gave good conversion at 44% yield. Bicycle **170a** gave the best reactivity at 58% yield. Therefore, this substrate was utilised for further reaction optimisation.

Table 4: *Substrate screening.*



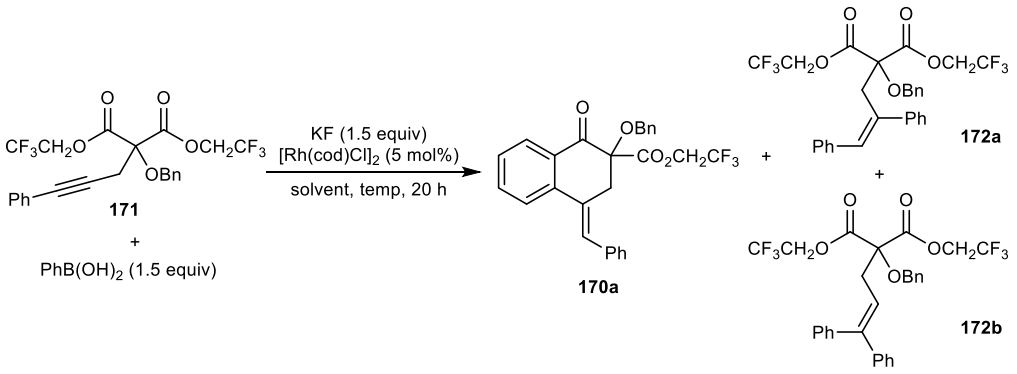


*Reactions employed 0.05 mmol of **169**. Yields determined by ^{1}H NMR spectroscopy using 3-bromotoluene as the internal standard. [a] Substrate prepared by Dr. S. Karad.*

A final solvent screening was conducted (Table 5). Interestingly, the highest yield of 37% was achieved using MeOH and DMA (entries 1 and 5). Various protic solvents (entries 2 and

3) gave poor reactivity. Using DMF (entry 4) generated product **170a** in 25% yield. All co-solvent systems examined (entries 7, 8, 10 and 11) resulted in a decrease in the formation of **170a**. $CHCl_3$ (entry 6) proved ineffective, increasing the formation of regioisomeric side-products **172a** and **172b** to 67%. EtOAc (entry 9) was detrimental for reactivity. In conclusion, deviations from the original solvent systems proved detrimental to the yield. Therefore, 1,4-dioxane/H_2O (9:1) (entry 12) was chosen as the solvent system.

Table 5: *Additional solvent screening.*

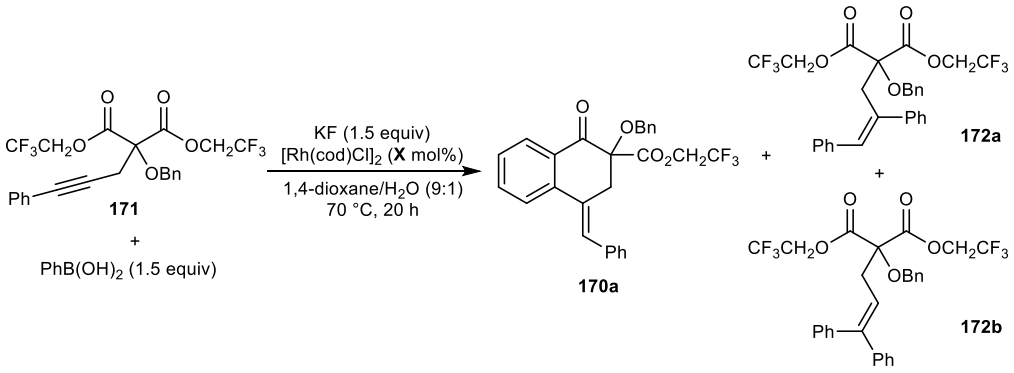


Entry	Solvent	Temperature (°C)	Yield (%)		
			170a	**172a**	**172b**
1	MeOH	60	37	11	11
2	EtOH	70	25	0	5
3	*i*-PrOH	70	16	0	0
4	DMF[a]	80	25	0	9
5	DMA[a]	80	37	5	12
6	$CHCl_3$[a]	60	30	35	32
7	1,4-dioxane/MeOH (9:1)	60	0	0	0
8	THF/H_2O (9:1)	60	30	14	17
9	Ethyl acetate[a]	70	7	23	18
10	1,4-dioxane/MeCN(2:3)[a]	70	28	5	7
11	toluene/H_2O (9:1)	70	7	33	23
12	1,4-dioxane/H_2O (9:1)	70	56	11	11

*Reactions employed 0.05 mmol of **171**. Yields determined by ^1H NMR spectroscopy using 3-bromotoluene as the internal standard. [a] t-AmylOH (1.5 equiv) added.*

Investigation into the catalyst loading was conducted (Table 6). However, the catalyst loading could not be lowered below 5 mol% without detrimental loss in yield and conversion (entries 2 and 3). Therefore, the final set of conditions were maintained (entry 1).

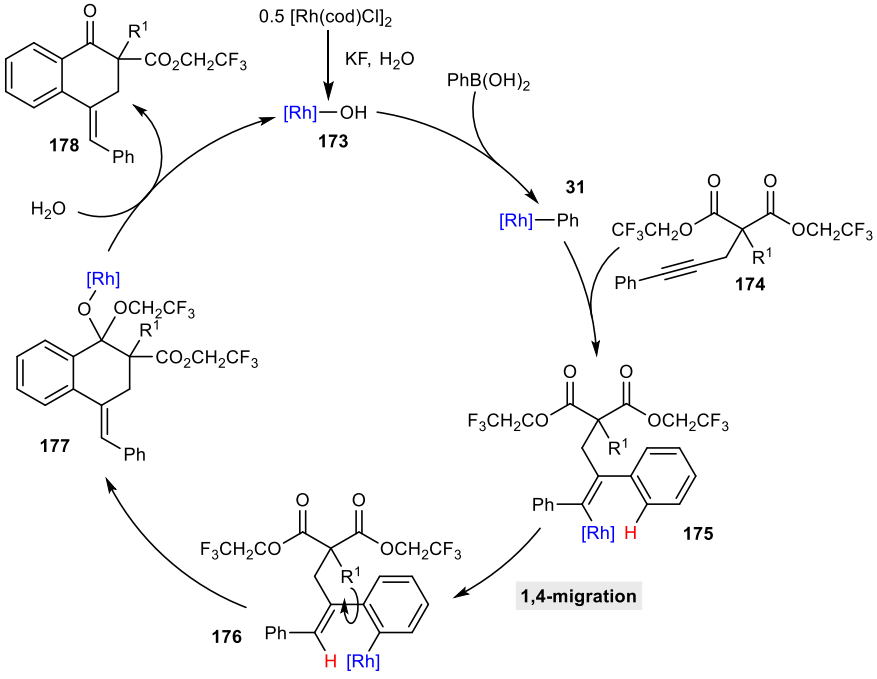
Table 6: *Catalyst loading screening.*



Entry	Catalyst loading (mol%)	Yield (%)		
		170a	**172a**	**172b**
1	5	56	11	11
2	2.5	35	11	14
3	1	30	11	12

*Reactions employed 0.05 mmol of **171**. Yields determined by ^{1}H NMR spectroscopy using 3-bromotoluene as the internal standard.*

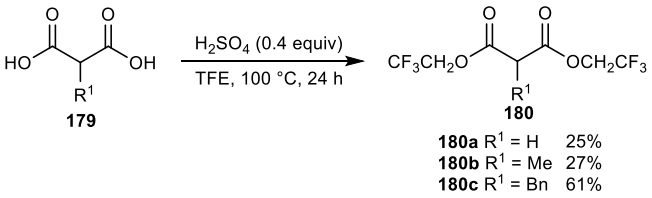
The proposed catalytic cycle (Scheme 44) is initiated by the transmetalation of an arylboronic acid with rhodium hydroxide (**173**). Carbometalation of the alkyne occurs, forming intermediate **175**, followed by alkenyl-to-aryl 1,4-rhodium migration. Subsequent 1,2-addition onto one the ester moieties, forms species **177**, which upon collapsing generates bicycle **178**.



Scheme 44: *Postulated catalytic cycle.*

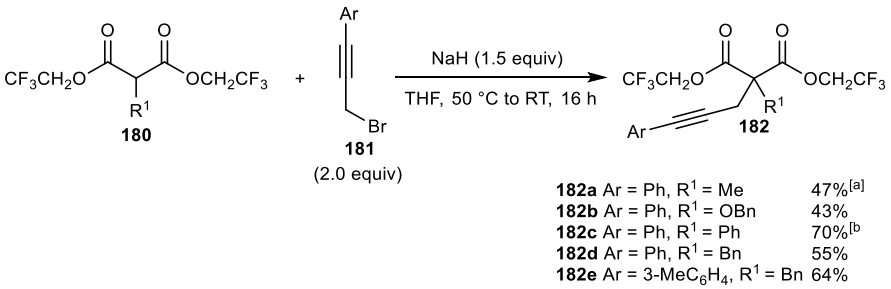
2.3 Synthesis of Alkynyl Malonate Esters

The synthesis of substituted alkynyl malonate esters required various different synthetic routes which proved to be a challenging endeavour. Subjecting substituted malonic acid **179** along with TFE, using sulfuric acid as a catalyst, afforded malonate esters **180a** to **180c** in poor to moderate yields (Scheme 45).



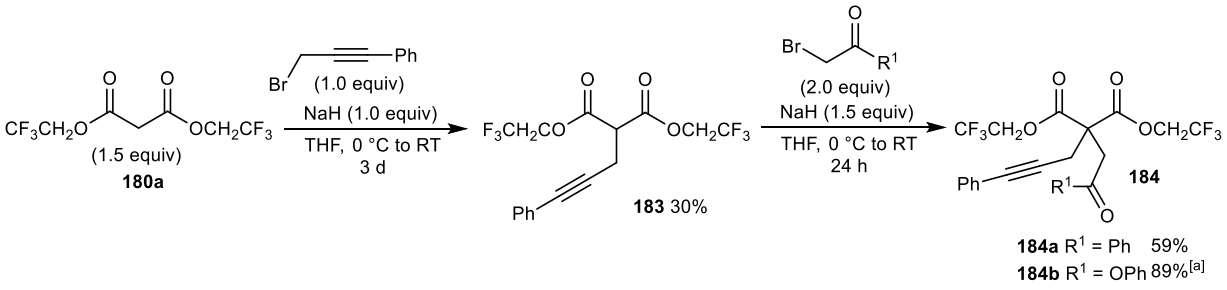
Scheme 45: *Synthesis of malonate esters **180a to 180c**.*

Alkylation of mono-substituted malonate esters afforded alkynyl malonate esters **182a** to **182e** (Scheme 46) in modest to good yields. Increasing the temperature was required to achieve full conversion of **182c**, most likely due to the increased steric hinderance at the α-position.



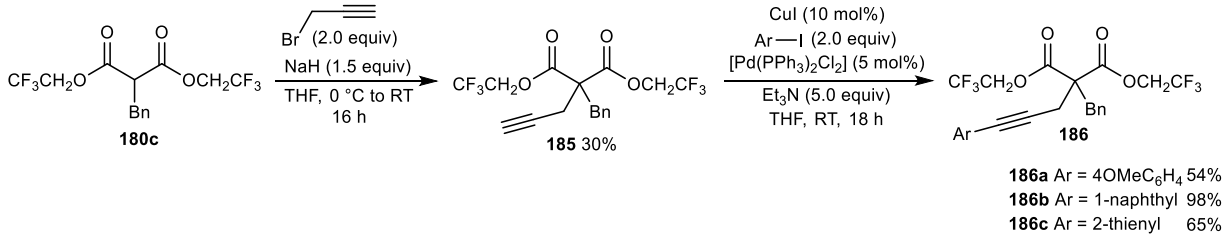
Scheme 46: *Synthesis of alkynyl malonate esters **182a** to **182e**. [a] RT. [b] 60 °C.*

Malonate esters incorporating ketone and ester substituents at the α-position (**184a** and **184b**) were prepared from mono-substituted malonate ester **183** in yields of 59% and 89% respectively (Scheme 47). Mono-substituted malonate ester **183** was prepared by alkylation of **180a**.



Scheme 47: *Synthesis of malonate esters **184a** and **184b**. [a] Left for 16 h.*

Alkynyl malonate esters with variation at the alkyne position (**186**) were prepared in a three-step reaction sequence. Malonate ester **180c** was alkylated with propargyl bromide using sodium hydride to afford alkynyl malonate ester **185**. A Sonogashira coupling using various commercially available aryl halides, generates malonate esters **186a** to **186c** in good to excellent yields.



Scheme 48: *Synthesis of malonate esters **186a** to **186c**.*

Alkynyl malonate esters **187** to **198** were synthesised by Dr. S. Karad and Heena Panchal (Figure 1). Preparation of malonate esters **195**, **196** and **197** proved challenging, requiring ruthenium catalysis to insert heteroatoms at the α-position.

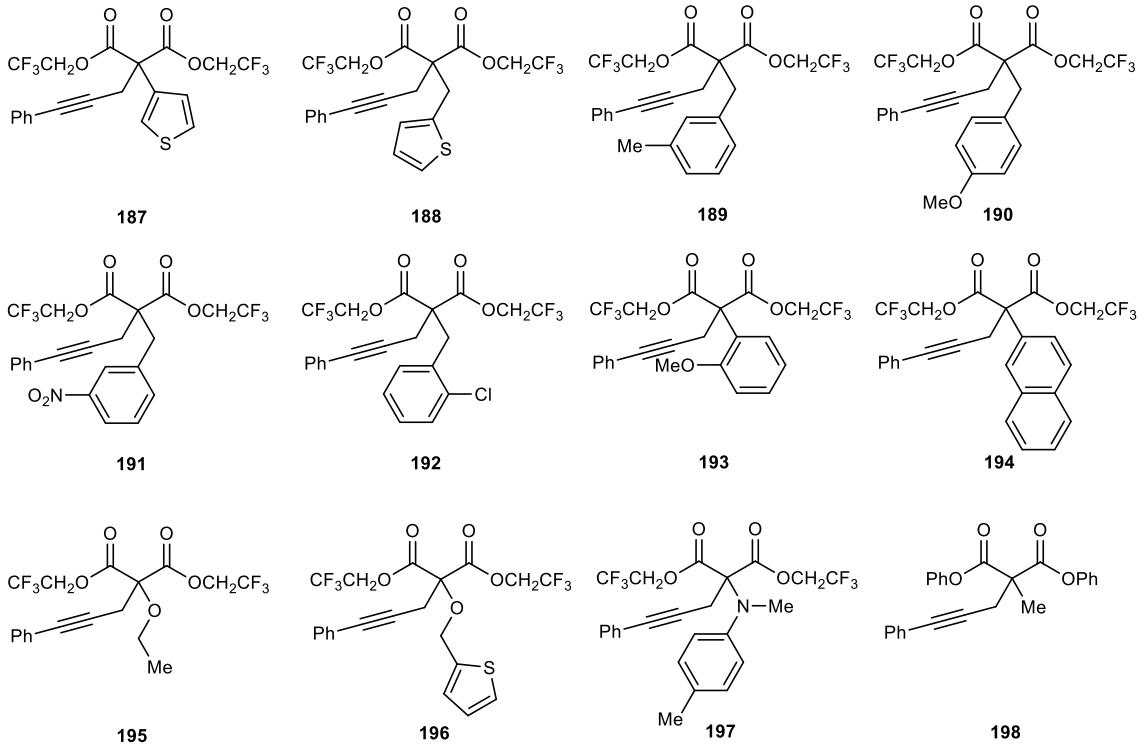
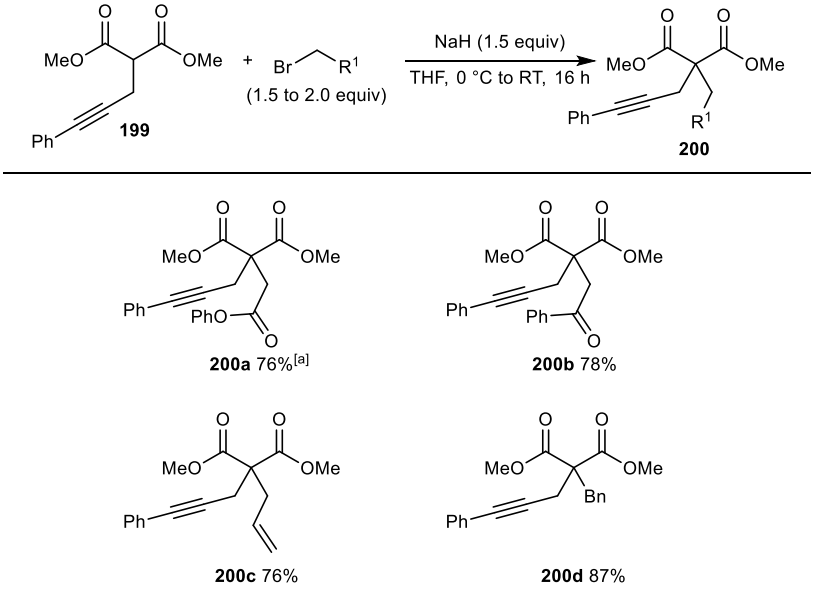


Figure 1: *Synthesis of malonate esters **187** to **198** by Dr. S. Karad and Heena Panchal.*

The preparation of alkynyl methyl malonate esters (**200**) required the alkylation of **199** with various electrophiles to afford the desired product in modest to good yields (Table 7).

Table 7: *Synthesis of methyl malonate esters **200a** to **200d**.*

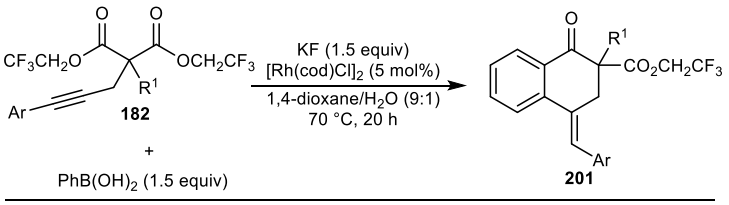


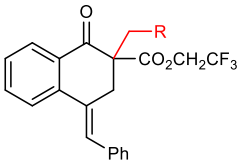
[a] Synthesised by Dr. S. Karad using NaH (1.2 equiv) and left for 2.5 h.

2.4 Malonate Ester Scope

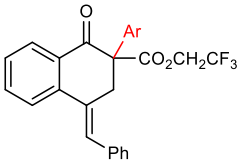
With the optimised conditions in hand, the scope of malonate esters was then investigated (Table 8). Variation at the α-position was well tolerated to give 3,4-dihydronaphthalen-1(*2H*)-ones in modest to good yields (33%-73%). In addition, R^1 could be either an alkyl (**201b**) or aryl (**201h**) group, generating products in modest yields. *Para*-substituted and *meta*-substituted aryl groups at the α-position, incorporating both electron-withdrawing (**201g**) and electron-donating groups (**201f**) afforded bicycles in good yields. *Ortho*-substituted aryl groups gave inferior yields (**201i**), most likely due to steric hinderance. Ketone (**201d**) and ester (**201e**) substituents generated the desired product in 36% and 55% yield respectively. Heteroaromatics at the α-position (**201c** and **201k**) gave significant reactivity. Bulkier naphthyl aryl groups (**201j**) required 10 mol% catalyst loading and 2.0 equivalents of boronic acid to achieve significant conversion. The reaction is not limited to alkyl and aryl substitution, as heteroatom substitution at the α-position (**201p**, **201q** and **201r**) generated 3,4-dihydronaphthalen-1(*2H*)-ones in modest yields. Significant quantities of regioisomeric side-products were formed, accounting for a reduction in yield. Structural diversity at the alkyne position was observed, with *para*-substituted and *meta*-substituted aryl groups (**201l** and **201m**), bulkier naphthyl groups (**201n**) and heteroaromatics (**201o**). Electron-donating groups (**201m**) generated products in greater yields than electron-withdrawing groups (**201l**).

Table 8: *Malonate scope.*

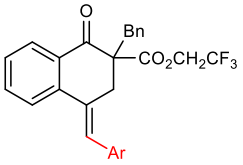




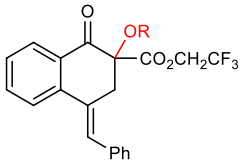
201a	R^1 = Ph	68%
201b	R^1 = H	58%
201c	R^1 = 2-thienyl	50%
201d	R^1 = COPh	36%
201e	R^1 = CO_2Ph	55%
201f	R^1 = 3-MeC_6H_4	73%
201g	R^1 = 4-$OMeC_6H_4$	72%



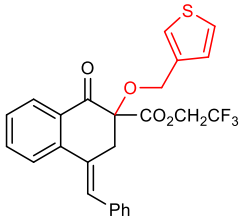
201h	Ar = Ph	62%
201i	Ar = 2-$OMeC_6H_4$	54%
201j	Ar = 2-naphthyl	56%[a]
201k	Ar = 3-thienyl	57%



201l	Ar = 4-$MeOC_6H_4$	64%
201m	Ar = 3-MeC_6H_4	74%
201n	Ar = 1-naphthyl	68%
201o	Ar = 2-thienyl	66%



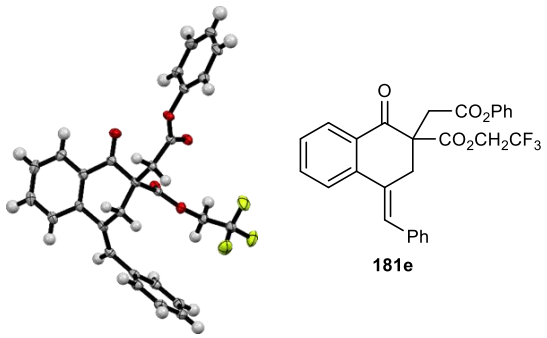
201p	R^1 = Et	36%[a]
201q	R^1 = Bn	51%



201r		33%[a]

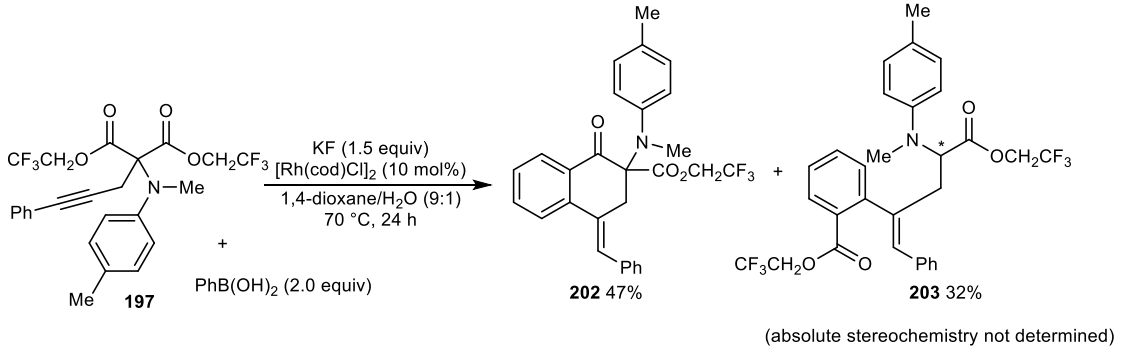
Reactions conducted on a 0.30 mmol scale. Isolated yields.
[a] using $[Rh(cod)Cl]_2$ (10 mol%), $PhB(OH)_2$ (2.0 equiv) and left for 24 h.

X-ray crystallographic data was collected for **201e** (Scheme 49) confirming the geometry of the substituted olefin.



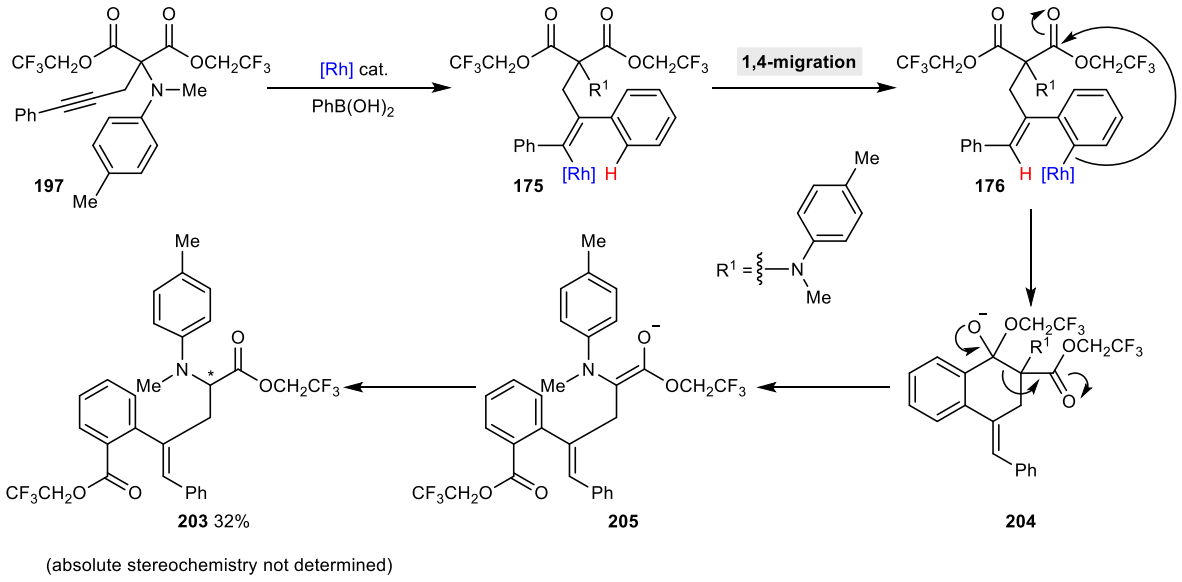
Scheme 49: *X-ray crystal structure for **201e** at 50% atomic probability distributions for ellipsoids.*

Interestingly, when anilino groups (**197**) at the α-position were subjected to the reaction conditions, formation of **202** in 47% yield was observed (Scheme 50). However, complex amino acid derivative **203** was isolated in 32% yield. For significant conversion, 10 mol% catalyst loading and 2.0 equivalents of boronic acid were required.



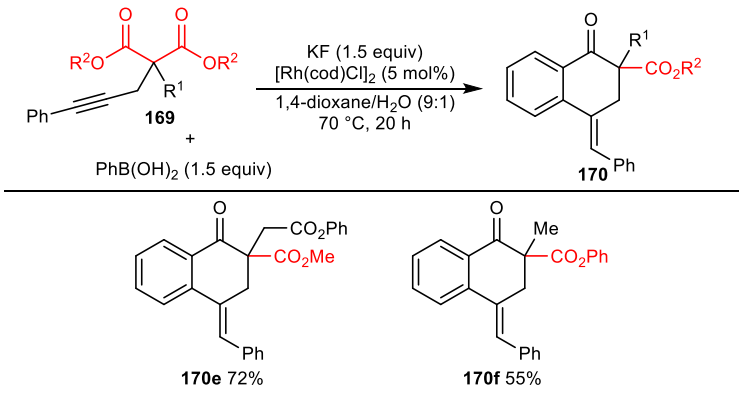
Scheme 50: *Rhodium-catalysed cyclisation of **197**. Isolated yield. Substrate prepared by Dr. S. Karad.*

The proposed mechanism (Scheme 51) for the formation of **203** is initiated by the transmetalation of arylboronic acid with rhodium(I) catalyst. Regioselective migratory insertion with the tethered alkyne occurs, forming intermediate **175**. Alkenyl-to-aryl 1,4-migration occurs, followed by subsequent 1,2-addition onto one of the ester moieties, forming species **204**. Ring-opening of the bicycle occurs, generating enolate species **205**. Finally, proton transfer forms product **203**. An enantioselective proton transfer could induce chirality. However, manipulation of a small proton atom and avoiding product racemisation is a challenging endeavour.[38] This was not investigated further.



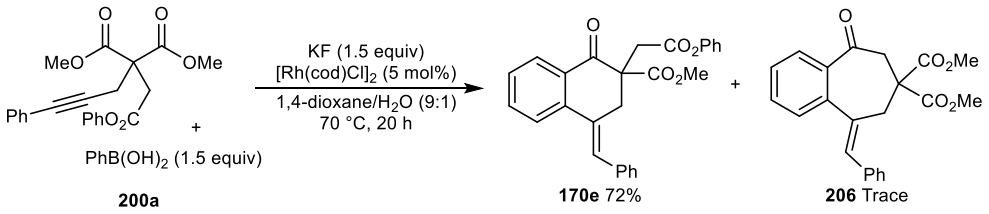
Scheme 51: *Proposed mechanism for the formation of **203**.*

Next, the scope of the reaction with respect to the ester group was investigated (Scheme 52). Methyl esters (**170e**) and bulky phenyl esters (**170f**) generated 3,4-dihydronaphthalen-1(*2H*)-ones in modest to good yields.



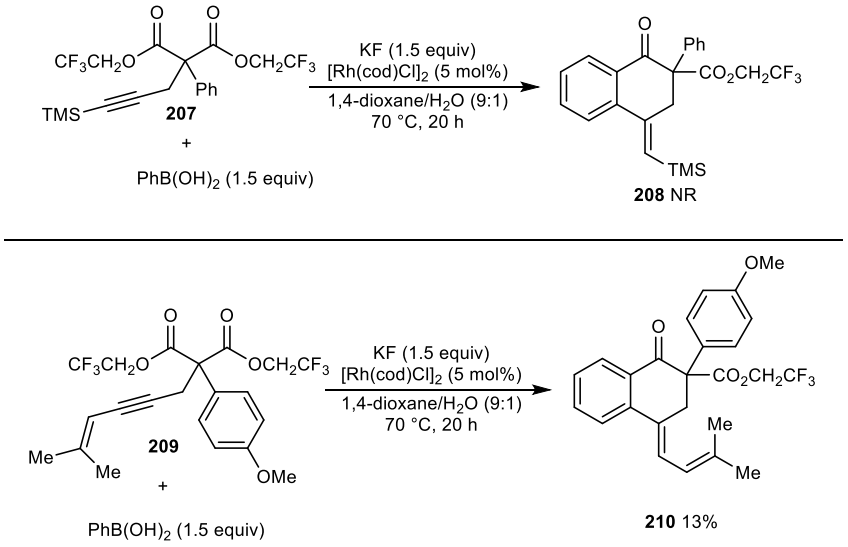
Scheme 52: *Malonate ester scope. Reactions conducted on a 0.30 mmol scale. Isolated yields.*

Interestingly, substrate **200a** (Scheme 53) selectively generates product **170e** with trace amounts of side-product **206** detected by mass spectrometry. 1,2-Addition with the less reactive methyl ester forms 3,4-dihydronaphthalen-1(*2H*)-one **170e**, whilst 1,2-addtion with the more reactive phenyl ester forms 6,7,8,9-tetrahydro-5*H*-benzo[*7*]annulene **206**.



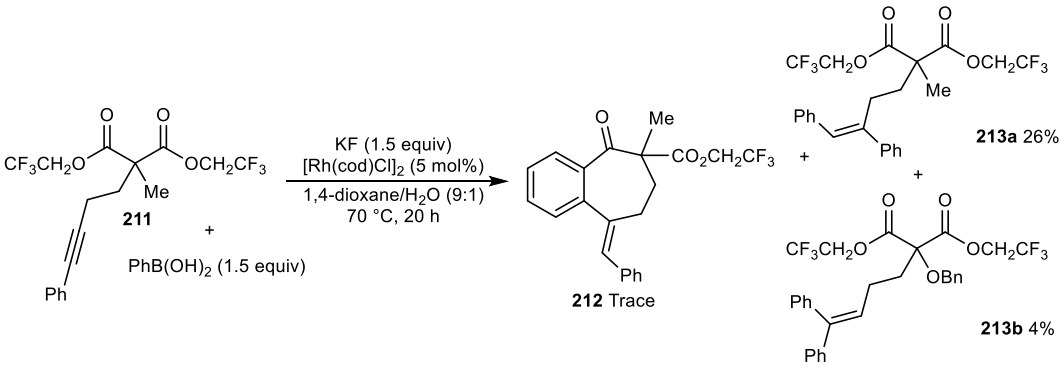
Scheme 53: *Rhodium-catalysed cyclisation of **200a**. Isolated yield. Substrate prepared by Dr. S. Karad.*

While exploring the scope of the alkyne position, several substrates were synthesised containing non aryl substituents (Scheme 54). However, this proved detrimental for reactivity. Silylalkyne **207** was subjected to the reaction conditions and gave no conversion most likely due to steric hindrance. 1,3-Enyne **209** was also subjected to the reaction conditions; however, poor yields were obtained. This could be due to competitive alkenyl-to-alkyl 1,4-migration or alkene coordination to the rhodium catalyst shutting down reactivity.



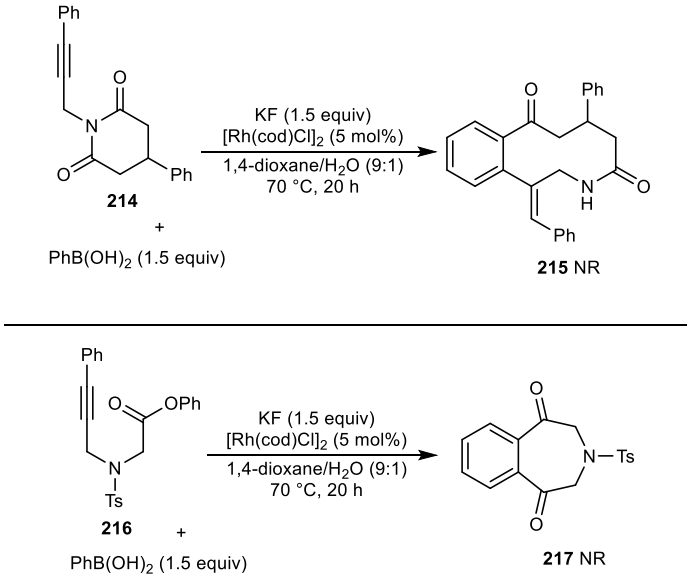
Scheme 54: *Rhodium-catalysed cyclisation of **207** and **209**. Yield determined by ^{1}H NMR spectroscopy using 1,4-dimethoxybenzene as the internal standard. Substrate prepared by Dr. S. Karad.*

It was hypothesised that extending the tethered alkyne chain could form 6,7,8,9-tetrahydro-5*H*-benzo[*7*]annulene **212** (Scheme 55). Substrate **211** was synthesised and subjected to the reaction conditions. However, bicycle **212** was formed in trace amounts, with significant formation of regioisomeric side-products.



Scheme 55: *Rhodium-catalysed cyclisation of **211**. Yield determined by ^{1}H NMR spectroscopy using 1,4-dimethoxybenzene as the internal standard.*

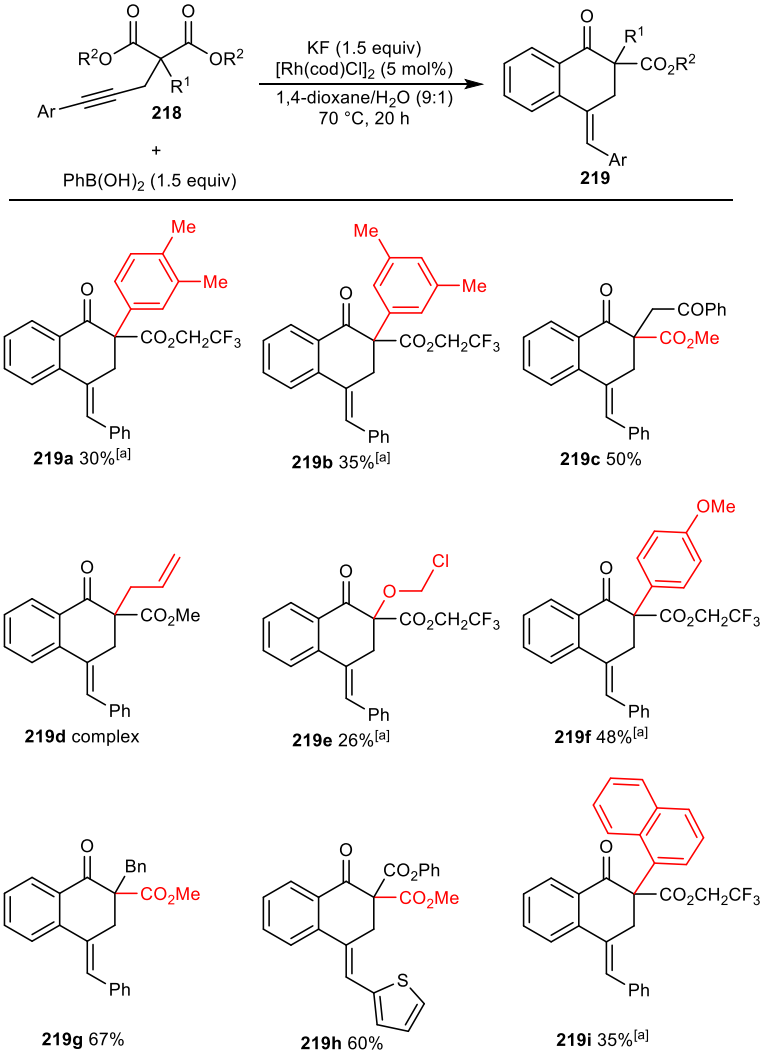
It was also hypothesised that the reaction could be extended beyond tethered malonates. (Scheme 56). Both substrates (**214** and **216**) were subjected to the reaction conditions; however, no reactivity was observed in both cases, with only starting material being recovered.



Scheme 56: *Rhodium-catalysed cyclisation of **214** and **216**. Substrates prepared by Dr. S. Karad.*

A range of additional substrates were screened (Table 9) but were incompatible with this transformation, most likely due to steric constraints and electronic effects. Various di-substituted aryl rings at the α-position (**219a** and **219b**) were tolerated in poor to modest yields. Several methyl esters were screened; however, purification proved challenging as the retention factor of both the 3,4-dihydronaphthalen-1(*2H*)-one product and regioisomeric side-products were the same, resulting in co-elution. Allyl-substituted malonate esters (**219d**) gave a complex mixture of compounds, most likely due to coordination between the alkene and rhodium catalyst.

Table 9: *Rhodium-catalysed cyclisation of malonates.*



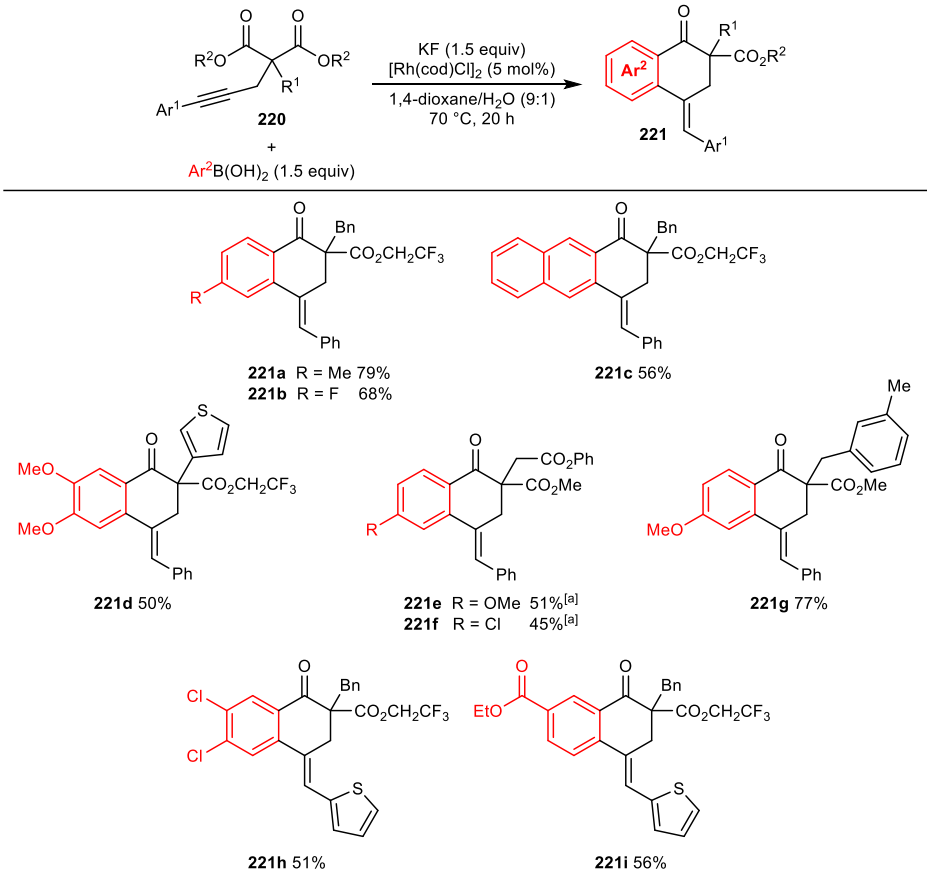
Reactions conducted on a 0.05 mmol scale. Yields determined by ^{1}H NMR spectroscopy using 1,4-dimethoxybenzene as the internal standard. [a] Substrate prepared by Dr. S. Karad.

2.5 Boronic Acid Scope

With the malonate scope explored, we turned our attention to variation of boronic acids. Various electron-donating (**221a**) and electron-withdrawing (**221g**) *para*-substituted boronic acids were tolerated, in modest to good yields (Table 10). *Meta*-substituted boronic acids were also tolerated, however in reduced yield (**221i**), most likely resulting from increased steric hinderance. 3,4-Disubstitued boronic acids (**221d** and **221h**) gave modest conversion. The range of substrates that react with various arylboronic acids, generating products in modest yields, demonstrate the utility of this reaction. Variation of the alkyne and ester moiety gave

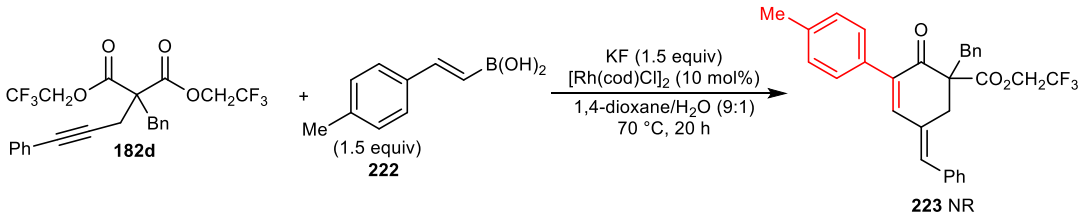
modest yields, due to difficult purification. Various substituents at the α-position tolerated a wide range of boronic acids, including bulkier naphthyl boronic acid (**221c**).

Table 10: *Boronic acid scope.*



Reactions conducted using 0.30 mmol of. Isolated yields. [a] Reactions performed by Dr. S. Karad.

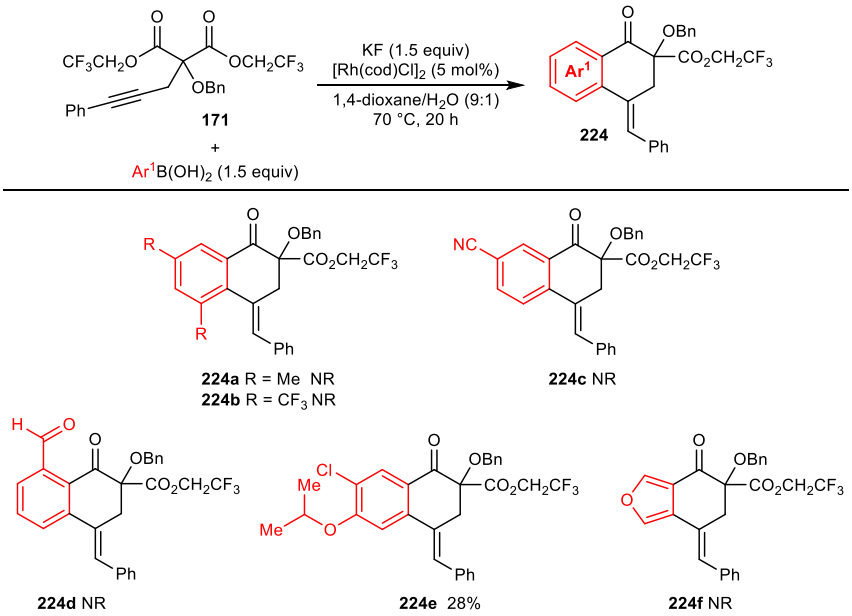
The range of boronic acids subjected to the reaction conditions was extensive (Table 10). However, all boronic acids screened were arylboronic acids. Therefore, the reaction between substrate **222** and trans-2-(4-methylphenyl)vinylboronic acid (**223**) was investigated (Scheme 57), which involves an alkenyl-to-alkenyl 1,4-migration. Unfortunately, no product formation was observed, with only starting material being recovered.



Scheme 57: *Rhodium-catalysed cyclisation using an alkenyl boronic acid.*

A range of additional boronic acids were screened (Table 11) but were incompatible with this reaction. 3,5-Disubstituted boronic acids (**224a** and **224b**) gave no reactivity. This was expected since this substitution pattern is known to inhibit alkenyl-to-aryl 1,4-metal migration.[31] Heteroaromatic boronic acids did not participate in the reaction, possibly due to their instability at higher temperatures. Cyano-substituted (**224c**) and *ortho*-substituted (**224d**) boronic acids were unsuccessful.

Table 11: *Additional boronic acid scope.*

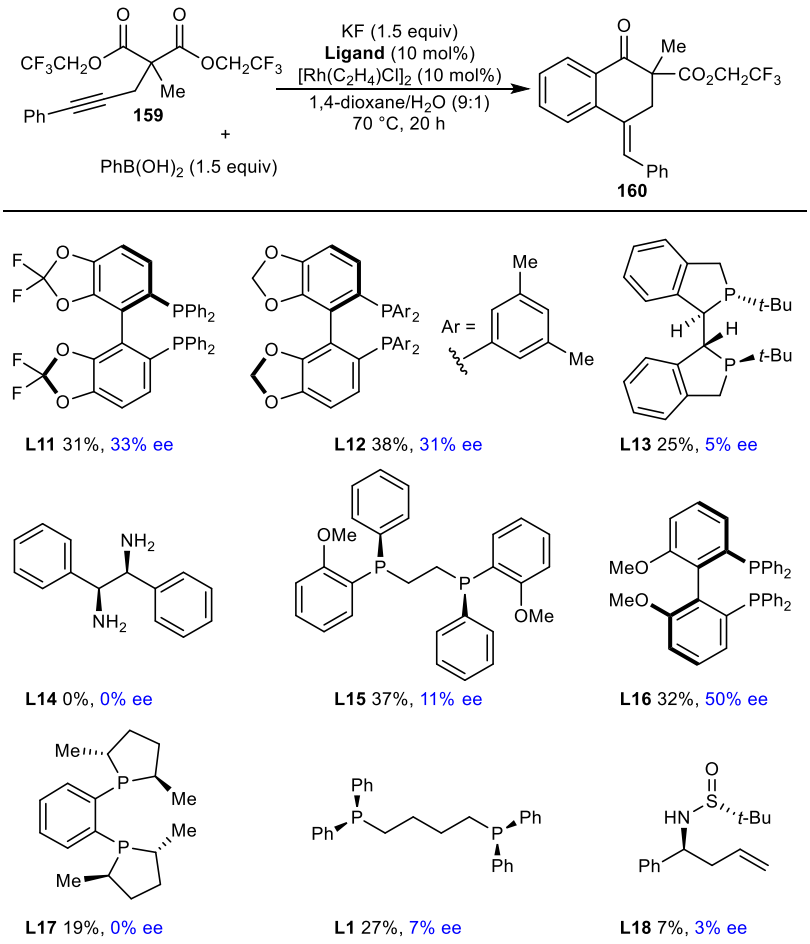


*Yields determined by ^{1}H NMR spectroscopy using 1,4-dimethoxybenzene as the internal standard. Reactions conducted using 0.05 mmol of **171**.*

2.6 Enantioselective Variant

Having optimised the racemic intramolecular arylative cyclisation of malonate esters, attempts to develop an enantioselective variant were investigated. Yoshikai reported modest levels of enantiocontrol in the cobalt-catalysed cyclisations of symmetrical alkynes, utilising phosphine-based ligands.[37] Therefore, various phosphine based ligands were investigated (Table 12). Pleasingly, modest levels of enantiocontrol were observed, with **L16** giving the best results, with 50% enantiomeric excess. Chiral sulfur-olefins (**L18**) were investigated, unfortunately poor levels of enantiocontrol were detected. Nitrogen based chiral ligands (**L14**) gave no conversion.

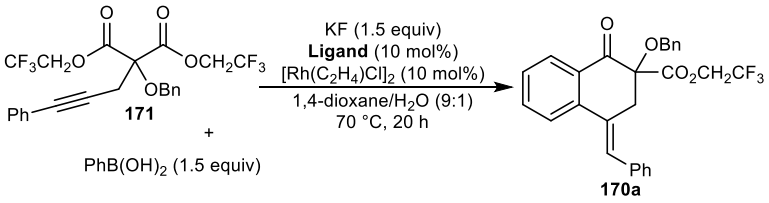
Table 12: *Ligand screening using **159**.*

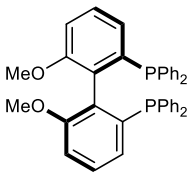


*Yields determined by ^{1}H NMR spectroscopy using 1,4-dimethoxybenzene as the internal standard. Reactions conducted using 0.05 mmol of **159**.*

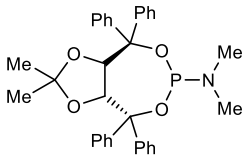
It was envisioned that increasing the steric bulk at the α-position of the malonate ester could increase enantiocontrol. Pleasingly, heteroatom aromatic substitution gave an increase in enantiocontrol to 65% *ee*, when utilising **L16**. Therefore, various other chiral ligands were screened using this substrate (Table 13). Interestingly, using ligands with similar structural features (**L20**) gave poor enantiocontrol. No enantiocontrol was observed when using *P,N* based ligands (**L19**) and *P,O* based ligands (**L23**). Several chiral dienes were investigated (**L24**-**L26**); however, poor to modest levels of enantiocontrol was observed in all cases. From the above, **L16** was selected for the remainder of our studies.

Table 13: *Ligand screening using **172**.*

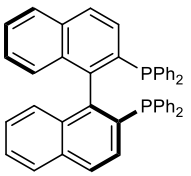




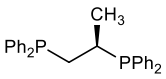
L16 70%[a], 65% ee



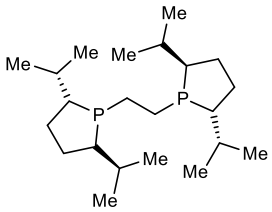
L19 28%, 43% ee



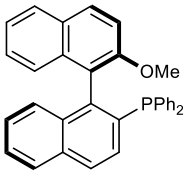
L20 23%, 5% ee



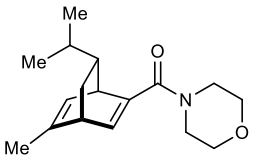
L21 45%, 7% ee



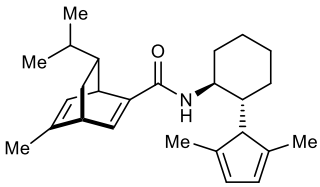
L22 38%, 16% ee



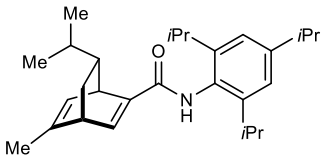
L23 9%, 0% ee



L24 5%, 9% ee



L25 20%, 32% ee

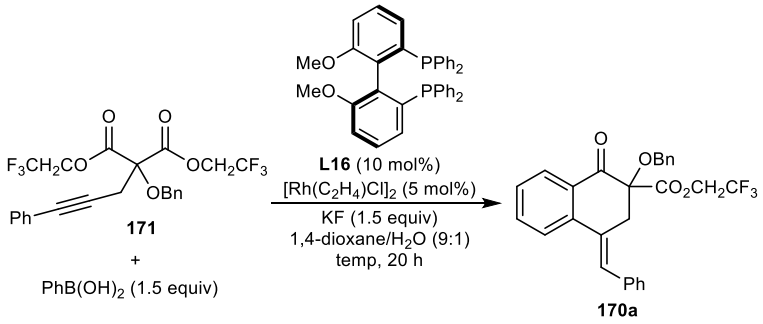


L26 5%, 31% ee

*Yields determined by ^{1}H NMR spectroscopy using 1,4-dimethoxytoluene as the internal standard. Reactions conducted using 0.05 mmol of **171**. [a] Isolated yield.*

Next, a temperature screen was performed (Table 14). The yield of **170a** at 70 °C was 75% with 62% *ee* (entry 3). Lowering the temperature had detrimental effect on the yield and enantioselectivity (entries 1 and 2). Raising the temperature (entries 4 and 5) gave a reduction in yield and enantioselectivity, most likely due to degradation of **170a**. Therefore, 70 °C was selected as the temperature.

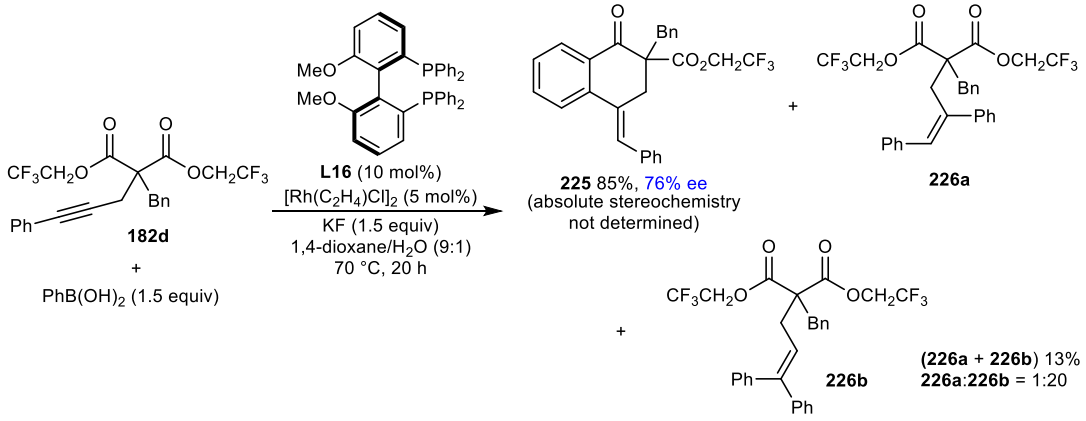
Table 14: *Temperature screening.*



Entry	Temperature (°C)	Yield (%)	*ee*(%)
1	25	11	ND
2	60	23	45
3	70	75	62
4	80	71	58
5	90	54	53

*Yields determined by ^{1}H NMR spectroscopy using 3-bromotoluene as the internal standard. Reactions conducted using 0.05 mmol of **171**.*

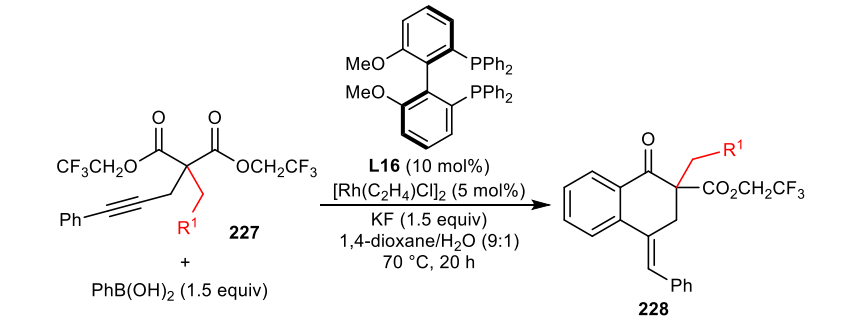
Interestingly, when a benzyl moiety was incorporated at the α-position (**182d**), excellent yield and good enantioselectivity was observed (Scheme 58). Formation of regioisomeric side-products (**226a** and **226b**) was observed with excellent regioselectivity (**226a**:**226b** 1:20).

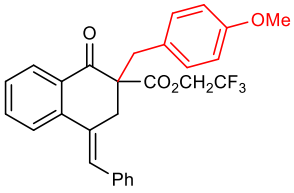


Scheme 58: *Enantioselective rhodium-catalysed cyclisation of malonate **182d** on 0.30 mmol scale. Isolated yields. Regioisomer ratio determined by crude ^{1}H NMR spectroscopy.*

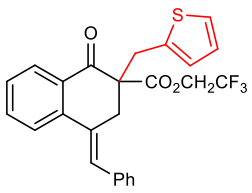
Encouraged by this result, several substituent benzyl groups at the α-position were subjected to the reaction conditions (Table 15). However, no dramatic increase in enantioselectivity was observed. Having a substituent at the 3-position on the aryl ring (**228c** and **228d**) increases enantiocontrol. However, no clear conclusion can be drawn about why these substitution patterns worked the best.

Table 15: *Enantioselective scope.*

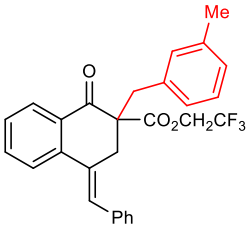




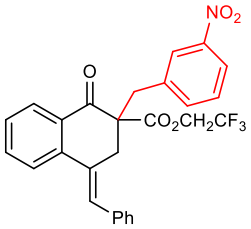
228a 56%, 75% ee



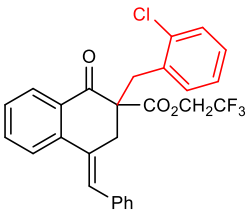
228b 42%, 78% ee



228c 60%, 80% ee



228d 42%, 82% ee



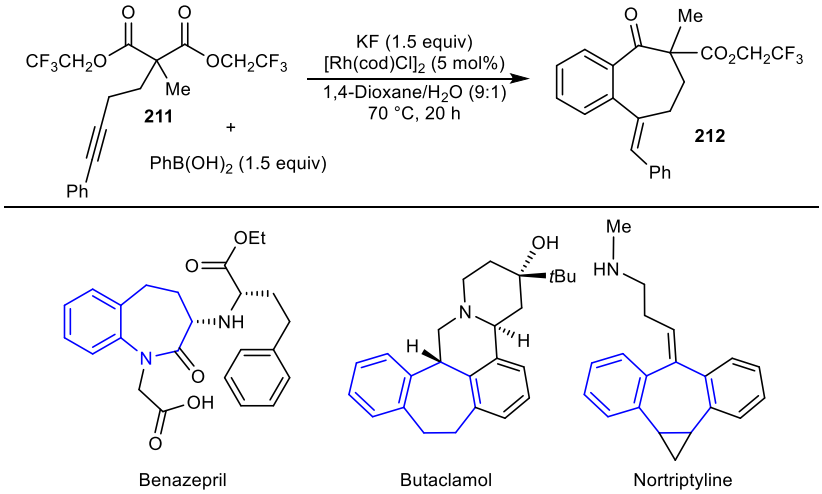
228e 64%, 65% ee

Reactions conducted on a 0.05 mmol scale. Yields determined by ^{1}H NMR spectroscopy using 1,4-dimethoxybenzene as the internal standard. Reactions performed by Dr. S. Karad.

2.7 Conclusions and Future Work

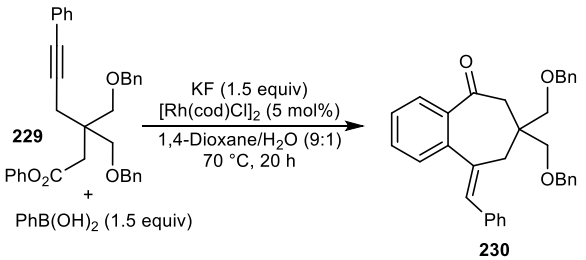
In summary, we have utilised a known alkenyl-to-aryl 1,4-rhodium migration and applied this concept to substrates incorporating unsymmetrical alkynes, generating highly functionalised products. This reaction generates the desired products in modest to good yields. However, inducing enantiocontrol proved challenging, with modest to good enantioselectivities obtained. This methodology precluded the requirement to use symmetrical alkynes, which limited the viability of the previous methodology. It has greater synthetic utility than previously reported examples.[21,37]

Highly functionalised 6,7,8,9-tetrahydro-5*H*-benzo[*7*]annulenes (**194**) are prevalent within biologically active compounds. (Scheme 59). Therefore, further development upon initial results (Scheme 59) could provide a new synthetic pathway to access such bicycles.



Scheme 59: *Natural products containing 7 membered bicycles.*

Highly functionalised 6,7,8,9-tetrahydro-5*H*-benzo[*7*]annulenes could also be accessed *via* subjecting homopropargyl monoester substrate **229** to the reaction conditions, generating product **230** (Scheme 60).



Scheme 60: *Formation of 6,7,8,9-tetrahydro-5H-benzo[7]annulene **230**.*

Further investigations are ongoing within the Lam group to extend this methodology.

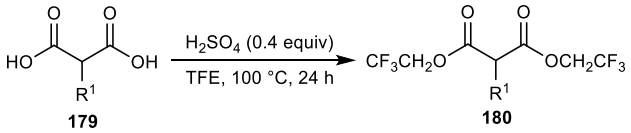
Chapter 3: Experimental

3.1 General Information

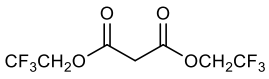
All air-sensitive reactions were carried out under an inert atmosphere using oven-dried apparatus. Anhydrous 1,4-dioxane was purchased from Acros Organics and deoxygenated before use, using a stream of argon gas (30 min). All commercially available reagents were used as received unless otherwise stated. Petroleum ether refers to Sigma-Aldrich product 24587 (petroleum ether boiling point 40-60 °C). Thin layer chromatography (TLC) was performed on Merck DF-Alufoilien 60F254 0.2 mm precoated plates. Compounds were visualized by exposure to UV light or by dipping the plates into solutions of potassium permanganate or vanillin followed by gentle heating. Flash column chromatography was carried out using silica gel (Fisher Scientific 60 Å particle size 35-70 micron or Fluorochem 60 Å particle size 40-63 micron). Melting points were recorded on a Gallenkamp melting point apparatus and are uncorrected. The solvent of recrystallization is reported in parentheses. Infrared (IR) spectra were recorded on Bruker platinum alpha FTIR spectrometer on the neat compound using the attenuated total refraction technique. NMR spectra were acquired on Bruker AV500, Bruker AV500(III)HD, Bruker AV400, Bruker AV(III)400HD, or Bruker DPX400 spectrometers. ^{1}H and ^{13}C NMR spectra were referenced to external tetramethylsilane via the residual protonated solvent (^{1}H) or the solvent itself (^{13}C). All chemical shifts are reported in parts per million (ppm). For $CDCl_3$, the shifts are referenced to 7.26 ppm for ^{1}H NMR spectroscopy and 77.16 ppm for ^{13}C NMR spectroscopy. Coupling constants (*J*) are quoted to the nearest 0.1 Hz. High-resolution mass spectra were recorded using electrospray ionization (ESI) techniques. X-ray diffraction data were collected at 120 K on an Agilent SuperNova diffractometer using CuKα radiation. Chiral HPLC analysis was performed on an Agilent 1290 series or Agilent 1260 series instrument using 4.6 x 250 mm columns.

3.2 Synthesis of Alkynyl Malonate Esters

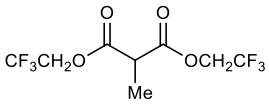
General Procedure A: Esterification of Malonic Acids



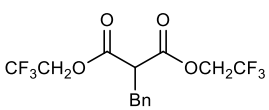
A high pressure flask was charged with the appropriate malonic acid (1 equiv) and a stirrer bar. TFE and concentrated H_2SO_4 (0.4 equiv) were added and the resulting solution was heated at 100 °C for 24 h. The solution was cooled to room temperature and diluted with petroleum ether/Et_2O (7:3), (150 mL), washed with saturated aqueous $NaHCO_3$ solution (3 × 100 mL), water (50 mL) and brine (50 mL). The organic layer was then dried ($MgSO_4$), filtered and concentrated under reduced pressure to give the *malonate ester product*.



Bis(2,2,2-trifluoroethyl) malonate (180a). The title compound was prepared according to General Procedure A, using malonic acid (10.0 g, 96.1 mmol), TFE (50 mL) and concentrated H_2SO_4 (2.05 mL, 38.4 mmol) to give a pale-yellow oil (6.48 g, 25%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.54 (4H, q, J = 8.3 Hz, 2 × C**H**$_2$CF$_3$), 3.61 (2H, s, C**H**$_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.2 (2 × C), 122.6 (q, $J_{C\text{-}F}$ = 277.2 Hz, 2 × C), 61.3 (q, $J_{C\text{-}F}$ = 37.2 Hz, 2 × CH_2), 40.3 (CH_2). Data consistent with previously reported literature.[39]



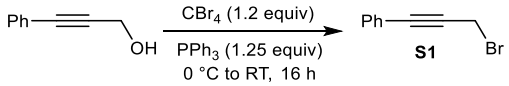
Bis(2,2,2-trifluoroethyl) 2-methylmalonate (180b). The title compound was prepared according to General Procedure A, using methylmalonic acid (8.00 g, 67.7 mmol), TFE (40 mL) and concentrated H_2SO_4 (1.44 mL, 27.1 mmol) to give a colourless oil (5.21 g, 27%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.57-4.50 (4H, m, 2 × C**H**$_2$CF$_3$), 3.67 (1H, q, J = 7.3 Hz, CH$_3$C**H**), 1.52 (3H, d, J = 7.3 Hz, C**H**$_3$CH); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.9 (2 × C), 122.7 (q, $J_{C\text{-}F}$ = 277.3 Hz, 2 × C), 61.2 (q, $J_{C\text{-}F}$ = 37.2 Hz, 2 × CH_2), 45.4 (CH), 13.5 (CH_3). Data consistent with previously reported literature.[40]



Bis(2,2,2-trifluoroethyl) 2-benzylmalonate (180c). The title compound was prepared according to General Procedure A, using

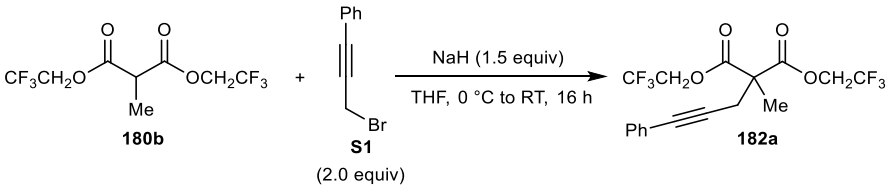
benzylmalonic acid (5.00 g, 25.7 mmol), TFE (25 mL) and concentrated H_2SO_4 (548 µL, 10.3 mmol) to give a colourless oil (5.65 g, 61%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32-7.23 (3H, m, Ar**H**), 7.21-7.18 (2H, m, Ar**H**), 4.56-4.40 (4H, m, 2 × C**H**$_2$CF$_3$), 3.89 (1H, t, *J* = 7.8 Hz, CH$_2$C**H**), 3.29 (2H, d, *J* = 7.8 Hz, C**H**$_2$CH); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.6 (2 × C), 136.5 (C), 128.9 (2 × CH), 128.8 (2 × CH), 127.4 (CH), 122.6 (q, J_{C-F} = 277.3 Hz, 2 × C), 61.3 (q, J_{C-F} = 37.3 Hz, 2 × CH$_2$), 53.0 (CH), 34.6 (CH$_2$). Data consistent with previously reported literature.[40]

(3-Bromoprop-1-yn-1-yl)benzene (S1)



A flask was charged with 3-phenylprop-2-yn-1-ol (12.5 mL, 103 mmol), purged with argon for 30 mins and then suspended in anhydrous CH_2Cl_2 (250 mL). A solution of CBr_4 (40.8 g, 123 mmol) in CH_2Cl_2 was added and the reaction mixture was cooled to 0 ºC. A solution of PPh_3 (33.6 g, 128 mmol) in CH_2Cl_2 was added slowly and the resulting solution was stirred at room temperature for 16 h. Ethanol (200 ml) was added and the reaction mixture was stirred for an additional 30 min. The solvent was removed under reduced pressure and the residue was purified by column chromatography (100% petroleum ether) to give the titled compound (**S1**) (17.4 g, 87%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51-7.43 (2H, m, Ar**H**), 7.38-7.29 (3H, m, Ar**H**), 4.17 (2H, s, C**H**$_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 132.0 (2 × CH), 129.0 (CH), 128.5 (2 x CH), 122.3 (C), 86.9 (C), 84.4 (C), 15.4 (CH$_2$). Data consistent with previously reported literature.[41]

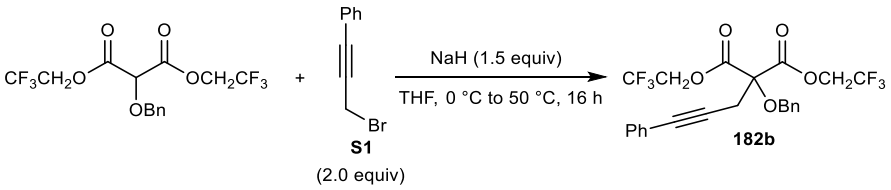
Bis(2,2,2-trifluoroethyl) 2-methyl-2-(3-phenylprop-2-yn-1-yl)malonate (182a)



A flask was charged with NaH (60% dispersion in mineral oil, 356 mg, 14.9 mmol), purged with argon for 30 mins and then suspended in THF (30 mL) at 0 °C. A solution of malonate **180b** (2.00 g, 7.08 mmol) in THF was added to the ice-cooled suspension. The resulting solution was stirred at 0 °C for 45 mins. Alkynyl bromide **S1** (80 wt. % in toluene, 921 µL,

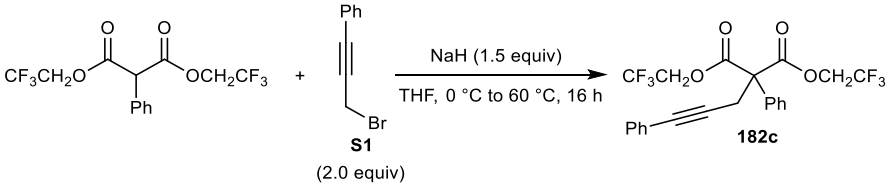
14.2 mmol) was added dropwise and the resulting solution was stirred at room temperature for 16 h. The reaction mixture was quenched with water (30 mL), extracted with Et_2O (3 × 30 mL) and the combined organic layer was washed with brine (40 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by column chromatography (0% to 1% EtOAc/petroleum ether) to give the title compound (**182a)** (1.31 g, 47%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38-7.33 (2H, m, Ar**H**), 7.31-7.27 (3H, m, Ar**H**), 4.56 (4H, q, J = 8.2 Hz, 2 × C**H**$_2$CF$_3$), 3.08 (2H, s, C**H**$_2$C≡C), 1.71 (3H, s, C**H**$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.9 (2 × C), 131.8 (2 × CH), 128.4 (3 × CH), 122.9 (C), 122.7 (q, $J_{C\text{-}F}$ = 277.3 Hz, 2 × C), 84.4 (C), 82.9 (C), 61.3 (q, $J_{C\text{-}F}$ = 37.3 Hz, 2 × CH_2), 53.7 (C), 26.8 (CH_2), 20.0 (CH_3). Data consistent with previously reported literature.[40]

Bis(2,2,2-trifluoroethyl) 2-(benzyloxy)-2-(3-phenylprop-2-yn-1-yl)malonate (182b)



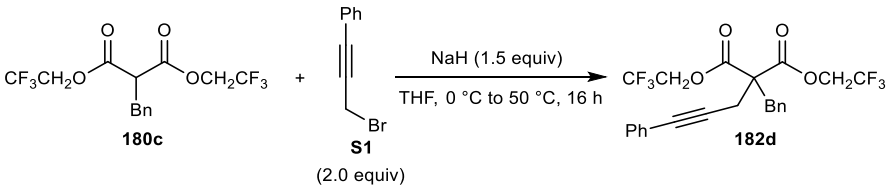
A flask was charged with NaH (60% dispersion in mineral oil, 269 mg, 11.2 mmol), purged with argon for 30 mins and then suspended in THF (30 mL) at 0 °C. A solution of bis(2,2,2-trifluoroethyl) 2-(benzyloxy)malonate (2.00 g, 5.34 mmol) in THF was added to the ice-cooled suspension. The resulting solution was stirred at 0 °C for 45 mins. Alkynyl bromide **S1** (80 wt. % in toluene, 694 µL, 14.2 mmol) was added dropwise and the resulting solution was stirred at 50 °C for 16 h. The reaction mixture was quenched with water (30 mL), extracted with Et_2O (3 × 30 mL) and the combined organic layer was washed with brine (40 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by column chromatography (0% to 2% EtOAc/petroleum ether) to give the title compound (**182b**) (1.11 g, 43%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43-7.28 (10H, m, Ar**H**), 4.81 (2H, s, OC**H**$_2$), 4.57 (4H, qd, J = 8.1, 1.0 Hz, 2 × C**H**$_2$CF$_3$), 3.35 (2H, s, C**H**$_2$C≡C); ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.8 (2 × C), 136.8 (C), 131.9 (2 × CH), 128.5 (2 × CH), 128.4 (CH), 128.3 (2 × CH), 128.2 (CH), 128.0 (2 × CH), 122.9 (C), 122.5 (q, $J_{C\text{-}F}$ = 277.4 Hz, 2 × C), 84.7 (C), 83.6 (C), 81.5 (C), 69.4 (CH_2), 61.5 (q, $J_{C\text{-}F}$ = 37.4 Hz, 2 × CH_2), 26.6 (CH_2). Data consistent with previously reported literature.[40]

Bis(2,2,2-trifluoroethyl) 2-phenyl-2-(3-phenylprop-2-yn-1-yl)malonate (182c)



A flask was charged with NaH (60% dispersion in mineral oil, 147 mg, 6.11 mmol), purged with argon for 30 mins and then suspended in THF (20 mL) at 0 °C. A solution of bis(2,2,2-trifluoroethyl) 2-phenylmalonate (1.00 g, 2.91 mmol) in THF was added to the ice-cooled suspension. The resulting solution was stirred at 0 °C for 45 mins. Alkynyl bromide **S1** (80 wt. % in toluene, 376 µL, 5.82 mmol) was added dropwise and the resulting solution was stirred at 60 °C for 16 h. The reaction mixture was quenched with water (30 mL), extracted with Et_2O (3 × 30 mL) and the combined organic layer was washed with brine (40 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by column chromatography (0% to 1% EtOAc/petroleum ether) to give the title compound (**182c**) (932 mg, 70%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53-7.50 (2H, m, Ar**H**), 7.43-7.36 (3H, m, Ar**H**), 7.31-7.24 (5H, m, Ar**H**), 4.59 (4H, qd, *J* = 8.3, 2.5 Hz, 2 × C**H**$_2$CF$_3$), 3.51 (2H, s, C**H**$_2$C≡C); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.6 (2 × C), 134.1 (C), 131.7 (2 × CH), 128.9 (CH), 128.7 (2 × CH), 128.4 (CH), 128.3 (2 × CH), 127.9 (2 × CH), 122.9 (C), 122.6 (d, $J_{C\text{-}F}$ = 277.4 Hz, 2 × C), 84.8 (C), 83.4 (C), 62.5 (C), 61.6 (q, $J_{C\text{-}F}$ = 37.3 Hz, 2 × CH_2), 27.1 (CH_2). Data consistent with previously reported literature.[40]

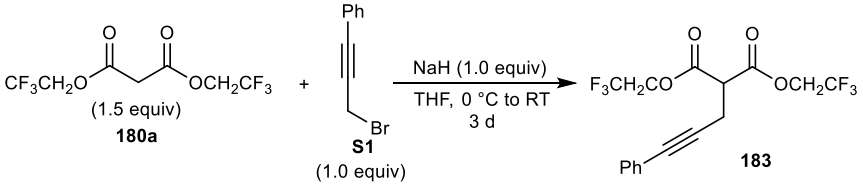
Bis(2,2,2-trifluoroethyl) 2-benzyl-2-(3-phenylprop-2-yn-1-yl)malonate (182d)



A flask was charged with NaH (60% dispersion in mineral oil, 141 mg, 5.86 mmol), purged with argon for 30 mins and then suspended in THF (25 mL) at 0 °C. A solution of malonate **180c** (1.00 g, 2.79 mmol) in THF was added to the ice-cooled suspension. The resulting solution was stirred at 0 °C for 45 mins. Alkynyl bromide **S1** (80 wt. % in toluene, 363 µL, 5.58 mmol) was added dropwise and the resulting solution was stirred at 50 °C for 16 h. The reaction mixture was quenched with water (20 mL), extracted with Et_2O (3 × 30 mL) and the combined organic layer was washed with brine (25 mL), dried ($MgSO_4$), filtered and

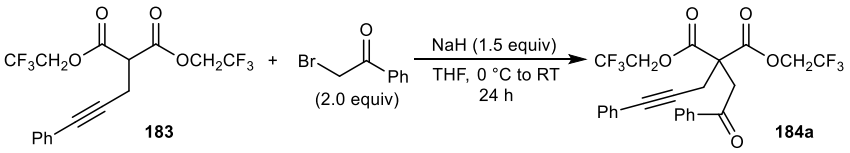
concentrated under reduced pressure. The residue was purified by column chromatography (0% to 1% EtOAc/petroleum ether) to give the title compound (**182d**) (721 mg, 55%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47-7.42 (2H, m, Ar**H**), 7.36-7.27 (6H, m, Ar**H**), 7.23-7.18 (2H, m, Ar**H**), 4.54 (4H, qd, *J* = 8.2, 1.8 Hz, 2 × C**H**$_2$CF$_3$), 3.52 (2H, s, ArC**H**$_2$), 2.98 (2H, s, C**H**$_2$C≡C); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.7 (2 × C), 134.4 (C), 131.9 (2 × CH), 129.9 (2 × CH), 128.9 (2 × CH), 128.54 (CH), 128.48 (2 × CH), 127.8 (CH), 122.9 (C), 122.7 (q, J_{C-F} = 277.3 Hz, 2 × C), 85.3 (C), 83.0 (CH), 61.4 (q, J_{C-F} = 37.4 Hz, 2 × CH_2), 58.8 (C), 37.6 (CH_2), 23.4 (CH_2). Data consistent with previously reported literature.[40]

Bis(2,2,2-trifluoroethyl) 2-(3-phenylprop-2-yn-1-yl)malonate (183)



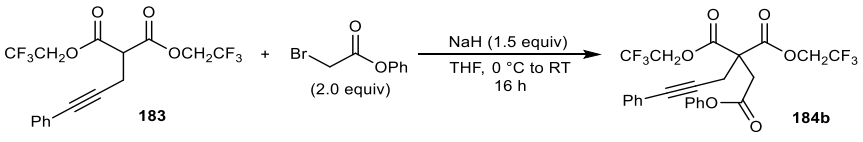
A flask was charged with NaH (60% dispersion in mineral oil, 251 mg, 7.47 mmol), purged with argon for 30 mins and then suspended in THF (25 mL) at 0 °C. A solution of malonate **180a** (3.00 g, 11.19 mmol) in THF was added to the ice-cooled suspension. The resulting solution was stirred at 0 °C for 45 mins. Alkynyl bromide **S1** (80 wt. % in toluene, 491 µL, 7.47 mmol) was added dropwise and the resulting solution was stirred at room temperature for 3 d. The reaction mixture was quenched with water (30 mL), extracted with Et_2O (3 × 30 mL) and the combined organic layer was washed with brine (50 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by column chromatography (0% to 1% EtOAc/petroleum ether) to give the title compound (**183**) (978 mg, 34%) as a yellow oil. R_f = 0.26 (10% EtOAc/petroleum ether); IR 1756 (C=O), 1492, 1280, 1158, 1067, 965, 757, 691, 659, 535 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38-7.34 (2H, m, Ar**H**), 7.31-7.27 (3H, m, Ar**H**), 4.58 (4H, q, *J* = 8.2 Hz, 2 × C**H**$_2$CF$_3$), 3.91 (1H, t, *J* = 7.6 Hz, CC**H**C), 3.09 (2H, d, *J* = 7.6 Hz, C**H**$_2$C≡C); ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.9 (2 × C), 131.8 (2 × CH), 128.4 (CH), 128.4 (2 x CH), 122.8 (C), 122.6 (q, J_{C-F} = 277.3 Hz, 2 × C), 83.7 (C), 83.5 (C), 61.5 (q, J_{C-F} = 37.4 Hz, 2 × CH_2), 50.7 (CH), 19.5 (CH_2); ^{19}F NMR (376 MHz, $CDCl_3$) δ –73.5 (t, *J* = 8.3 Hz, 6 × F); HRMS (ESI) Exact mass calculated for $[C_{16}H_{12}F_6NaO_4]^+$ $[M+Na]^+$: 405.0537, found 405.0535.

Bis(2,2,2-trifluoroethyl) 2-(2-oxo-2-phenylethyl)-2-(3-phenylprop-2-yn-1-yl)malonate (184a)



A flask was charged with NaH (60% dispersion in mineral oil, 66 mg, 2.75 mmol), purged with argon for 30 mins and then suspended in THF (15 mL) at 0 °C. A solution of malonate **183** (500 mg, 1.31 mmol) in THF was added to the ice-cooled suspension. The resulting solution was stirred at 0 °C for 45 mins. A solution of 2-bromoacetophenone (521 mg, 2.62 mmol) in THF was added dropwise and the resulting solution was stirred at room temperature for 24 h. The reaction mixture was quenched with water (20 mL), extracted with Et_2O (3 × 20 mL) and the combined organic layer was washed with brine (25 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by column chromatography (0% to 5% EtOAc/petroleum ether) to give the title compound (**184a**) (385 mg, 59%) as a white solid. R_f = 0.31 (20% EtOAc/petroleum ether); m.p. 91-92 °C (Et_2O); IR 2921, 1754 (C=O), 1681 (C=O), 1434, 1283, 1165, 1065, 973, 751, 692 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.02-7.99 (2H, m, Ar**H**), 7.64-7.59 (1H, m, Ar**H**), 7.51-7.47 (2H, m, Ar**H**), 7.31-7.24 (5H, m, Ar**H**), 4.68-4.49 (4H, m, 2 × C**H**$_2$CF$_3$), 4.02 (2H, s, CC**H**$_2$C), 3.38 (2H, s, C**H**$_2$C≡C); ^{13}C NMR (101 MHz, $CDCl_3$) δ 196.4 (C), 167.5 (2 × C), 136.3 (C), 134.0 (CH), 131.8 (2 × CH), 129.0 (2 × CH), 128.5 (CH), 128.4 (2 × CH), 128.3 (2 × CH), 122.7 (C), 122.7 (q, J_{C-F} = 277.4 Hz, 2 × C), 84.9 (C), 83.0 (C), 61.7 (q, J_{C-F} = 37.4 Hz, 2 × CH_2), 55.2 (C), 41.4 (CH_2), 24.6 (CH_2); ^{19}F NMR (376 MHz, $CDCl_3$) δ –73.8 (t, J = 8.2 Hz, 6 × F); HRMS (ESI) Exact mass calculated for $[C_{24}H_{18}F_6NaO_5]^+$ $[M+Na]^+$: 523.0951, found 523.0951.

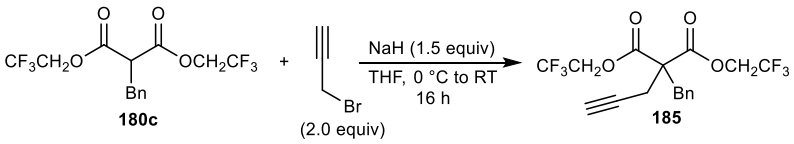
1-Phenyl 2,2-bis(2,2,2-trifluoroethyl) 5-phenylpent-4-yne-1,2,2-tricarboxylate (184b)



A flask was charged with NaH (60% dispersion in mineral oil, 53 mg, 2.21 mmol), purged with argon for 30 mins and then suspended in THF (15 mL) at 0 °C. A solution of malonate **183**

(400 mg, 1.05 mmol) in THF was added to the ice-cooled suspension. The resulting solution was stirred at 0 °C for 45 mins. A solution of phenyl bromoacetate (452 mg, 2.10 mmol) in THF was added dropwise and the resulting solution was stirred at room temperature for 16 h. The reaction mixture was quenched with water (30 mL), extracted with Et_2O (3 × 20 mL) and the combined organic layer was washed with brine (25 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by column chromatography (0% to 4% EtOAc/petroleum ether) to give the title compound (**184b**) (481 mg, 89%) as a pale-yellow oil. R_f = 0.28 (20% EtOAc/petroleum ether); IR 1755 (C=O), 1593 (C=O), 1411, 1281, 1160, 1065, 973, 756, 689, 496 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.41-7.36 (4H, m, Ar**H**), 7.33-7.30 (3H, m, Ar**H**), 7.25-7.22 (1H, m, Ar**H**), 7.10-7.07 (2H, m, Ar**H**), 4.58 (4H, qt, *J* = 8.3, 4.4 Hz, 2 × C**H**$_2$CF$_3$), 3.56 (2H, s, CC**H**$_2$C), 3.35 (2H, s, C**H**$_2$C≡C); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.8 (C), 167.0 (2 x C), 150.3 (C), 131.9 (2 × CH), 129.7 (2 × CH), 128.7 (CH), 128.5 (2 × CH), 126.4 (CH), 122.6 (q, J_{C-F} = 277.3 Hz, 2 × C), 122.6 (C), 121.5 (2 × CH), 85.2 (C), 82.2 (C), 61.9 (q, J_{C-F} = 37.2 Hz, 2 × CH_2), 55.5 (C), 37.4 (CH_2), 25.0 (CH_2); ^{19}F NMR (376 MHz, $CDCl_3$) δ –73.8 (t, *J* = 8.2 Hz, 6 × F); HRMS (ESI) Exact mass calculated for $[C_{24}H_{18}F_6NaO_6]^+$ $[M+Na]^+$: 539.0905, found 539.0906.

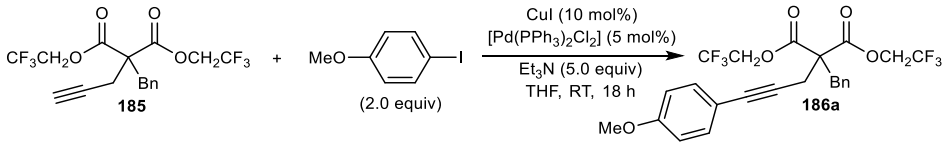
Bis(2,2,2-trifluoroethyl) 2-benzyl-2-(prop-2-yn-1-yl)malonate (185)



A flask was charged with NaH (60% dispersion in mineral oil, 844 mg, 35.18 mmol), purged with argon for 30 mins and then suspended in THF (200 mL) at 0 °C. A solution of malonate **180c** (6.00 g, 16.75 mmol) in THF was added to the ice-cooled suspension. The resulting solution was stirred at 0 °C for 45 mins. Propargyl bromide (3.58 mL, 33.5 mmol) was added dropwise and the resulting solution was stirred at room temperature for 16 h. The reaction mixture was quenched with water (150 mL), extracted with Et_2O (3 × 120 mL) and the combined organic layer was washed with brine (150 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by column chromatography (0% to 1% EtOAc/petroleum ether) to give the title compound (**185**) (2.01 g, 30%) as a pale-yellow oil. R_f = 0.33 (10% EtOAc/petroleum ether); IR 1756 (C=O), 1412, 1281, 1155, 1086, 994,

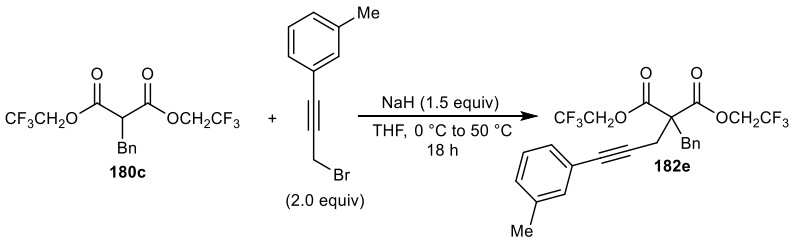
908, 742, 702, 648 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32-7.27 (3H, m, Ar**H**), 7.28-7.15 (2H, m, Ar**H**), 4.61-4.43 (4H, m, 2 × C**H**$_2$CF$_3$), 3.47 (2H, s, CC**H**$_2$C), 2.76 (2H, d, *J* = 2.7 Hz, C**H**$_2$C≡C), 2.21 (1H, t, *J* = 2.6 Hz, C≡C**H**); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.4 (2 × C), 134.1 (C), 129.7 (2 × CH), 128.7 (2 × CH), 127.7 (CH), 122.5 (q, J_{C-F} = 277.2 Hz, 2 × C), 77.7 (C), 73.1 (CH), 61.3 (q, J_{C-F} = 37.4 Hz, 2 × CH_2), 58.3 (C), 37.2 (CH_2), 22.3 (CH_2); ^{19}F NMR (376 MHz, $CDCl_3$) δ –73.6 (t, *J* = 8.2 Hz, 6 × F); HRMS (ESI) Exact mass calculated for $[C_{17}H_{14}F_6NaO_4]^+$ $[M+Na]^+$: 419.0688, found 419.0678.

Bis(2,2,2-trifluoroethyl) 2-benzyl-2-(3-(4-methoxyphenyl)prop-2-yn-1-yl)malonate (186a)



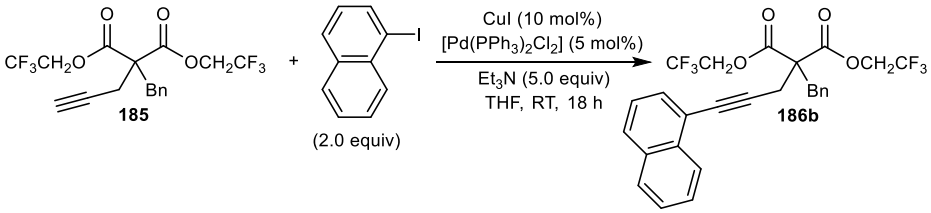
A flask was charged with CuI (24.0 mg, 0.13 mmol), $[Pd(PPh_3)_2Cl_2]$ (44.2 mg, 0.06 mmol), 4-iodoanisole (591 mg, 2.52 mmol) and purged with argon for 20 mins. THF (25 mL) which was freshly deoxygenated (purging with argon for 30 mins) and Et_3N (1.05 mL, 6.30 mmol) were added and the mixture was deoxygenated with a stream of argon for 15 mins. Malonate **185** (500 mg, 1.26 mmol) was added and the mixture was stirred at RT for 18 h. The reaction was quenched with saturated aqueous NH_4Cl (10 mL), extracted with EtOAc (3 x 20 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by column chromatography (0% to 3% EtOAc/petroleum ether) to give the titled compound (**186a**) (345 mg, 54%) as a yellow oil. R_f = 0.29 (10% EtOAc/petroleum ether); IR 2969, 1757 (C=O), 1510, 1443, 1284, 1157, 973, 907, 742, 535 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39-7.35 (2H, m, Ar**H**), 7.32-7.28 (3H, m, Ar**H**), 7.21-7.19 (2H, m, Ar**H**), 6.87-6.83 (2H, m, Ar**H**), 4.53 (4H, dq, *J* = 8.3, 2.2 Hz, 2 × C**H**$_2$CF$_3$), 3.82 (3H, s, OC**H**$_3$), 3.51 (2H, s, CC**H**$_2$C), 2.96 (2H, s, C**H**$_2$C≡C); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.8 (2 × C), 159.8 (C), 134.5 (C), 133.3 (2 × CH), 130.0 (2 × CH), 128.9 (2 × CH), 127.8 (CH), 122.6 (q, J_{C-F} = 277.4 Hz, 2 × C), 115.0 (C), 114.1 (2 × CH), 85.2 (C), 81.5 (C), 61.4 (q, J_{C-F} = 37.3 Hz, 2 × CH_2), 58.8 (C), 55.5 (CH_3), 37.6 (CH_2), 23.4 (CH_2); ^{19}F NMR (376 MHz, $CDCl_3$) δ –73.7 (t, *J* = 8.2 Hz, 6 × F); HRMS (ESI) Exact mass calculated for $[C_{24}H_{20}F_6NaO_5]^+$ $[M+Na]^+$: 525.1107, found 525.1108.

Bis(2,2,2-trifluoroethyl) 2-benzyl-2-(3-(m-tolyl)prop-2-yn-1-yl)malonate (182e)



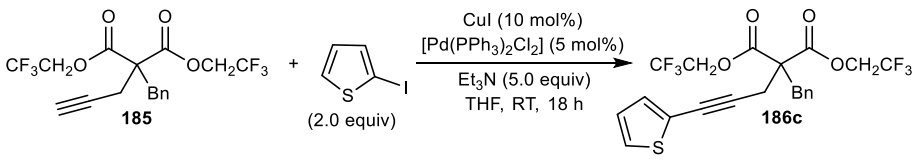
A flask was charged with NaH (60% dispersion in mineral oil, 141 mg, 5.86 mmol), purged with argon for 30 mins and then suspended in THF (15 mL) at 0 °C. A solution of malonate **180c** (1.00 g, 2.79 mmol) in THF was added to the ice-cooled suspension. The resulting solution was stirred at 0 °C for 45 mins. 1-(3-Bromoprop-1-yn-1-yl)-3-methylbenzene (80 wt. % in toluene, 1.48 g, 5.58 mmol) was added dropwise and the resulting solution was stirred at 50 °C for 18 h. The reaction mixture was quenched with water (20 mL), extracted with Et_2O (3 × 20 mL) and the combined organic layer was washed with brine (25 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by column chromatography (0% to 1% EtOAc/petroleum ether) to give the title compound (**182e**) (870 mg, 64%) as a pale-yellow oil. R_f = 0.36 (10% EtOAc/petroleum ether); IR 1757 (C=O), 1486, 1282, 1155, 1085, 974, 784, 742, 702, 651 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.34-7.28 (3H, m, Ar**H**), 7.25-7.19 (5H, m, Ar**H**), 7.15 (1H, d, *J* = 7.4 Hz, Ar**H**), 4.54 (4H, dq, *J* = 8.7, 2.3 Hz, 2 × C**H**$_2$CF$_3$), 3.53 (2H, s, CC**H**$_2$C), 2.98 (2H, s, C**H**$_2$C≡C), (3H, s, C**H**$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.7 (2 × C), 138.2 (C), 134.4 (C), 132.4 (CH), 130.0 (2 × CH), 129.4 (CH), 129.0 (CH), 128.9 (2 × CH), 128.4 (CH), 127.8 (CH), 122.7 (C), 122.7 (q, J_{C-F} = 277.3 Hz, 2 x C), 85.5 (C), 82.56 (C), 61.4 (q, J_{C-F} = 37.4 Hz, 2 × CH_2), 58.8 (C), 37.6 (CH_2), 23.4 (CH_2), 21.4 (CH_3); ^{19}F NMR (376 MHz, $CDCl_3$) δ –73.7 (t, *J* = 8.2 Hz, 6 × F); HRMS (ESI) Exact mass calculated for $[C_{24}H_{20}F_6NaO_4]^+$ $[M+Na]^+$: 509.1158, found 509.1158.

Bis(2,2,2-trifluoroethyl) 2-benzyl-2-(3-(naphthalen-1-yl)prop-2-yn-1-yl)malonate (186b)



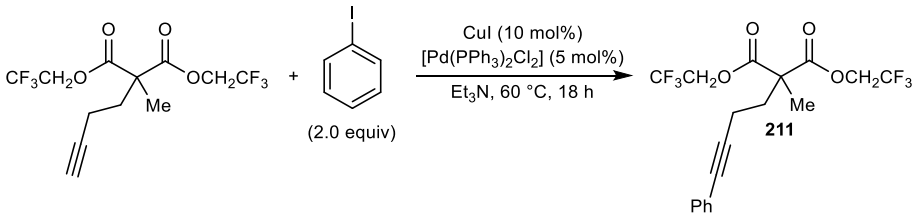
A flask was charged with CuI (24.0 mg, 0.13 mmol), $[Pd(PPh_3)_2Cl_2]$ (44.2 mg, 0.06 mmol) and purged with argon for 20 mins. THF (25 mL) which was freshly deoxygenated (purging with argon for 30 mins) and Et_3N (1.05 mL, 6.30 mmol) were added and the mixture was deoxygenated with a stream of argon for 15 mins. Malonate **185** (500 mg, 1.26 mmol) and 1-iodonaphthalene (0.37 mL, 2.52 mmol) were added and the mixture was stirred at RT for 18 h. The reaction was quenched with saturated aqueous NH_4Cl (10 mL), extracted with EtOAc (3 x 20 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by column chromatography (0% to 5% EtOAc/petroleum ether) to give the titled compound (**186b**) (426 mg, 65%) as a yellow oil. R_f = 0.39 (10% EtOAc/petroleum ether); IR 1755 (C=O), 1281, 1148, 1085, 968, 841, 800, 701, 652, 523 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.32-8.29 (1H, m, Ar**H**), 7.88-7.83 (2H, m, Ar**H**), 7.69 (1H, dd, *J* = 7.2, 1.2 Hz, Ar**H**), 7.60 (1H, ddd, *J* = 8.3, 6.9, 1.4 Hz, Ar**H**), 7.53 (1H, ddd, *J* = 8.2, 6.8, 1.4 Hz, Ar**H**), 7.44 (1H, dd, *J* = 8.3, 7.1 Hz, Ar**H**), 7.35-7.29 (3H, m, Ar**H**), 7.25-7.23 (2H, m, Ar**H**), 4.56 (4H, qd, *J* = 8.2, 4.7 Hz, 2 × C**H**$_2$CF$_3$), 3.62 (2H, s, CC**H**$_2$C), 3.16 (2H, s, C**H**$_2$C≡C); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.8 (2 × C), 134.4 (C), 133.5 (C), 133.3 (C), 130.9 (CH), 130.0 (2 x CH), 129.0 (CH), 128.9 (2 x CH), 128.5 (CH), 127.9 (CH), 127.0 (CH), 126.6 (CH), 126.1 (CH), 125.3 (CH), 122.7 (q, $J_{C\text{-}F}$ = 277.3 Hz, 2 × C), 120.5 (C), 87.9 (C), 83.4 (C), 61.5 (q, $J_{C\text{-}F}$ = 37.4 Hz, 2 × CH_2), 58.8 (C), 37.8 (CH_2), 23.8 (CH_2); ^{19}F NMR (376 MHz, $CDCl_3$) δ –73.6 (t, *J* = 8.1 Hz, 6 × F); HRMS (ESI) Exact mass calculated for $[C_{27}H_{24}F_6NO_4]^+$ $[M+H_4N]^+$: 540.1604, found 540.1606.

Bis(2,2,2-trifluoroethyl) 2-benzyl-2-(3-(thiophen-2-yl)prop-2-yn-1-yl)malonate (186c)



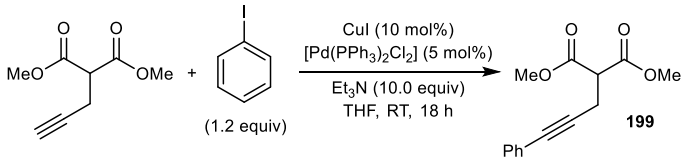
A flask was charged with CuI (24.0 mg, 0.13 mmol), $[Pd(PPh_3)_2Cl_2]$ (44.2 mg, 0.06 mmol) and purged with argon for 20 mins. THF (25 mL) which was freshly deoxygenated (purging with argon for 30 mins) and Et_3N (1.05 mL, 6.30 mmol) were added and the mixture was deoxygenated with a stream of argon for 15 mins. Malonate **185** (500 mg, 1.26 mmol) and 2-iodothiophene (0.28 mL, 2.52 mmol) were added and the mixture was stirred at RT for 18 h. The reaction was quenched with saturated aqueous NH_4Cl (10 mL), extracted with EtOAc (3 × 20 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by column chromatography (0% to 1% EtOAc/petroleum ether) to give the titled compound (**186c**) (591 mg, 98%) as an orange oil. R_f = 0.35 (10% EtOAc/petroleum ether); IR 1754 (C=O), 1443, 1279, 1159, 1073, 972, 958, 838, 700, 528 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.34-7.28 (3H, m, Ar**H**), 7.26-7.24 (1H, m, Ar**H**), 7.22-7.17 (3H, m, Ar**H**), 6.98 (1H, dd, *J* = 5.2, 3,6 Hz, Ar**H**), 4.54 (4H, dq, *J* = 8.3, 2.4 Hz, 2 × C**H**$_2$CF$_3$), 3.50 (2H, s, CC**H**$_2$C), 3.00 (2H, s, C**H**$_2$C≡C); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.6 (2 × C), 134.3 (C), 132.3 (CH), 130.0 (2 × CH), 128.9 (2 × CH), 127.9 (CH), 127.2 (CH), 127.1 (CH), 122.7 (C), 122.6 (q, J_{C-F} = 277.4 Hz, 2 × C), 87.1 (C), 78.4 (C), 61.5 (q, J_{C-F} = 37.4 Hz, 2 × CH_2), 58.7 (C), 37.7 (CH_2), 23.7 (CH_2); ^{19}F NMR (376 MHz, $CDCl_3$) δ –73.6 (t, *J* = 8.3 Hz, 6 × F); HRMS (ESI) Exact mass calculated for $[C_{21}H_{16}F_6NaO_4S]^+$ $[M+Na]^+$: 501.0566, found 501.0565.

Bis(2,2,2-trifluoroethyl) 2-methyl-2-(4-phenylbut-3-yn-1-yl)malonate (211)



A flask was charged with CuI (28.6 mg, 0.15 mmol), [Pd(PPh$_3$)$_2$Cl$_2$] (52.6 mg, 0.075 mmol) and purged with argon for 20 mins. Et$_3$N (25 mL) was added and the mixture was deoxygenated with a stream of argon for 15 mins. Bis(2,2,2-trifluoroethyl) 2-methyl-2-(but-3-yn-1-yl)malonate (500 mg, 1.50 mmol) and iodobenzene (336 μL, 3.00 mmol) were added and the mixture was stirred at 60 °C for 18 h. The reaction was quenched with saturated aqueous NH$_4$Cl (20 mL), extracted with EtOAc (3 × 20 mL), dried (MgSO$_4$), filtered and concentrated under reduced pressure. The residue was purified by column chromatography (0% to 2% EtOAc/petroleum ether) to give the titled compound (**211**) (580 mg, 79%) as a pale-yellow oil. R_f = 0.32 (10% EtOAc/petroleum ether); IR 1752 (C=O), 1411, 1280, 1157, 1103, 1027, 975, 756, 692, 650 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.40-7.35 (2H, m, Ar**H**), 7.30-7.27 (3H, m, Ar**H**), 4.59-4.41 (4H, m, 2 × C**H**$_2$CF$_3$), 2.52-2.48 (2H, m, C**H**$_2$C≡C), 2.33-2.28 (2H, m, C**H**$_2$C), (3H, s, C**H**$_3$); ^{13}C NMR (101 MHz, CDCl$_3$) δ 169.7 (2 × C), 131.6 (2 x CH), 128.4 (2 x CH), 128.1 (CH), 123.5 (C), 122.7 (q, J_{C-F} = 277.3 Hz, 2 × C), 88.0 (C), 81.7 (C), 61.3 (q, J_{C-F} = 37.2 Hz, 2 × CH$_2$), 53.3 (C), 34.4 (CH$_2$), 19.9 (CH$_2$), 15.0 (CH$_3$); ^{19}F NMR (376 MHz, CDCl$_3$) δ –73.9 (t, J = 8.2 Hz, 6 × F); HRMS (ESI) Exact mass calculated for [C$_{18}$H$_{16}$F$_6$NaO$_4$]$^+$ [M+Na]$^+$: 433.0845, found 433.0844.

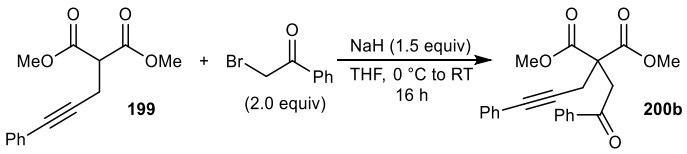
Dimethyl 2-(3-phenylprop-2-yn-1-yl)malonate (199)



A flask was charged with CuI (728 mg, 3.82 mmol), [Pd(PPh$_3$)$_2$Cl$_2$] (1.34 g, 1.91mmol) and purged with argon for 30 mins. THF (300 mL) which was freshly deoxygenated (purging with argon for 30 mins) and Et$_3$N (53.0 mL, 382 mmol) were added and the mixture was deoxygenated with a stream of argon for 20 mins. Dimethyl 2-(prop-2-yn-1-yl)malonate (6.50 g, 38.2 mmol) and iodobenzene (5.11 mL, 45.8 mmol) were added and the mixture was stirred at room temperature for 18 h. The reaction was quenched with saturated aqueous NH$_4$Cl (200 mL), extracted with EtOAc (3 × 150 mL), dried (MgSO$_4$), filtered and concentrated under reduced pressure. The residue was purified by column chromatography (5% to 12% EtOAc/petroleum ether) to give the titled compound (**199**) (6.96 g, 74%) as a yellow oil. ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.37-7.33 (2H, m, Ar**H**), 7.26-7.23 (3H, m, Ar**H**), 3.77 (6H, s, 2 x

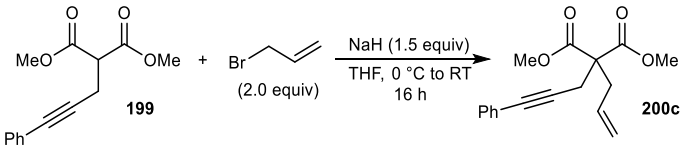
OC**H**$_3$), 3.67 (1H, t, *J* = 7.7 Hz, C**H**CH$_2$C≡C), 2.99 (2H, d, *J* = 7.8 Hz, C**H**$_2$C≡C); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.6 (2 × C), 131.8 (2 x CH), 128.3 (2 x CH), 128.2 (CH), 123.3 (C), 85.3 (C), 82.7 (C), 53.0 (2 x CH_3), 51.3 (CH), 19.7 (CH_2). Data consistent with previously reported literature.[42]

Dimethyl 2-(2-oxo-2-phenylethyl)-2-(3-phenylprop-2-yn-1-yl)malonate (200b)



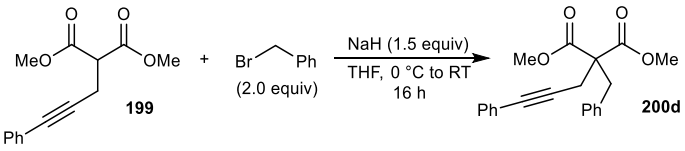
A flask was charged with NaH (60% dispersion in mineral oil, 205 mg, 8.53 mmol), purged with argon for 30 mins and then suspended in THF (25 mL) at 0 °C. A solution of malonate **199** (1.00 g, 4.06 mmol) in THF was added to the ice-cooled suspension. The resulting solution was stirred at 0 °C for 45 mins. A solution of 2-bromoacetophenone (1.61 g, 8.12 mmol) in THF was added dropwise and the resulting solution was stirred at room temperature for 16 h. The reaction mixture was quenched with water (20 mL), extracted with Et_2O (3 × 20 mL) and the combined organic layer was washed with brine (25 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by column chromatography (5% to 10% EtOAc/petroleum ether) to give the title compound (**200b**) (1.15 g, 78%) as a white solid. R_f = 0.38 (10% EtOAc/petroleum ether); m.p. 76-77 °C (Et_2O); IR 3030, 1752 (C=O), 1731 (C=O), 1288, 1178, 1060, 752, 698, 534, 506 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04-8.01 (2H, m, Ar**H**), 7.61-7.56 (1H, m, Ar**H**), 7.49-7.45 (2H, m, Ar**H**), 7.31-7.22 (5H, m, Ar**H**), 3.98 (2H, s, C**H**$_2$COPh), 3.80 (6H, s, 2 x OC**H**$_3$), 3.33 (2H, s, C**H**$_2$C≡C); ^{13}C NMR (101 MHz, $CDCl_3$) δ 197.0 (C), 170.1 (2 × C), 136.5 (C), 133.7 (CH), 131.8 (2 × CH), 128.8 (2 × CH), 128.33 (2 x CH), 128.32 (2 × CH), 128.2 (CH), 123.1 (C), 84.7 (C), 84.1 (C), 55.2 (C), 53.3 (2 x CH_3), 41.4 (CH_2), 24.5 (CH_2); HRMS (ESI) Exact mass calculated for $[C_{22}H_{20}NaO_5]^+$ $[M+Na]^+$: 387.1203, found 387.1203.

Dimethyl 2-allyl-2-(3-phenylprop-2-yn-1-yl)malonate (200c)



A flask was charged with NaH (60% dispersion in mineral oil, 205 mg, 8.53 mmol), purged with argon for 30 mins and then suspended in THF (25 mL) at 0 °C. A solution of malonate **199** (1.00 g, 4.06 mmol) in THF was added to the ice-cooled suspension. The resulting solution was stirred at 0 °C for 45 mins. A solution of allyl bromide (703 μL, 8.12 mmol) in THF was added dropwise and the resulting solution was stirred at room temperature for 16 h. The reaction mixture was quenched with water (20 mL), extracted with Et_2O (3 × 20 mL) and the combined organic layer was washed with brine (25 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by column chromatography (0% to 5% EtOAc/petroleum ether) to give the title compound (**200c**) (878 mg, 76%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36-7.32 (2H, m, Ar**H**), 7.28-7.22 (3H, m, Ar**H**), 5.66 (1H, ddt, *J* = 16.9, 10.1, 7.5 Hz, **H**C=CH_2), 5.21-5.16 (1H, m, HC=C**H**$_a$H$_b$), 5.14-5.11 (1H, m, HC=CH$_a$**H$_b$**), 3.73 (6H, s, 2 × OC**H**$_3$), 3.00 (2H, s, C**H**$_2$C≡C), 2.88-2.83 (2H, m, C**H**$_2$HC=C); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.4 (2 × C), 132.0 (CH), 131.7 (2 x CH), 128.3 (CH), 128.1 (2 × CH), 123.3 (C), 120.0 (CH_2), 84.3 (C), 83.4 (C), 57.4 (C), 52.9 (2 x CH_3), 36.9 (CH_2), 23.8 (CH_2). Data consistent with previously reported literature.[43]

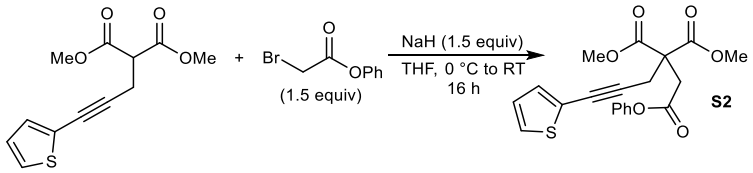
Dimethyl 2-benzyl-2-(3-phenylprop-2-yn-1-yl)malonate (200d)



A flask was charged with NaH (60% dispersion in mineral oil, 205 mg, 8.53 mmol), purged with argon for 30 mins and then suspended in THF (25 mL) at 0 °C. A solution of malonate **199** (1.00 g, 4.06 mmol) in THF was added to the ice-cooled suspension. The resulting solution

was stirred at 0 °C for 45 mins. A solution of benzyl bromide (966 μL, 8.12 mmol) in THF was added dropwise and the resulting solution was stirred at room temperature for 16 h. The reaction mixture was quenched with water (20 mL), extracted with Et_2O (3 × 20 mL) and the combined organic layer was washed with brine (25 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by column chromatography (0% to 5% EtOAc/petroleum ether) to give the title compound (**200d**) (1.19 g, 87%) as a yellow oil. R_f = 0.39 (20% EtOAc/petroleum ether); IR 2951, 1732 (C=O), 1492, 1434, 1279, 1177, 1084, 756, 690, 537 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.48-7.44 (2H, m, Ar**H**), 7.34-7.25 (6H, m, Ar**H**), 7.21-7.18 (2H, m, Ar**H**), 3.78 (6H, s, 2 × OC**H**$_3$), 3.48 (2H, s, CC**H**$_2$C), 3.00 (2H, s, C**H**$_2$C≡C); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.3 (2 × C), 135.6 (C), 131.8 (2 x CH), 130.0 (2 x CH), 128.6 (2 × CH), 128.4 (2 x CH), 128.2 (CH), 127.3 (CH), 123.3 (C), 84.7 (C), 84.5 (C), 58.8 (C), 52.9 (2 x CH_3), 37.8 (CH_2), 23.2 (CH_2); HRMS (ESI) Exact mass calculated for $[C_{21}H_{20}NaO_4]^+$ $[M+Na]^+$: 359.1254, found 359.1258.

2,2-Dimethyl 1-phenyl 5-(thiophen-2-yl)pent-4-yne-1,2,2-tricarboxylate (S2)

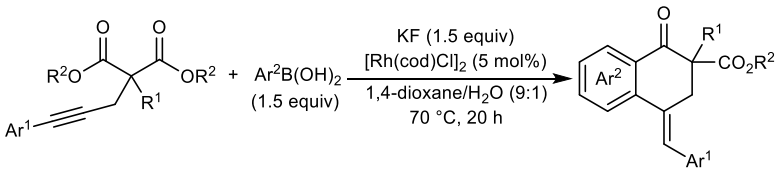


A flask was charged with NaH (60% dispersion in mineral oil, 399 mg, 16.6 mmol), purged with argon for 30 mins and then suspended in THF (30 mL) at 0 °C. A solution of dimethyl 2-(3-(thiophen-2-yl)prop-2-yn-1-yl)malonate (2.00 g, 7.92 mmol) in THF was added to the ice-cooled suspension. The resulting solution was stirred at 0 °C for 45 mins. A solution of phenyl bromoacetate (2.54 g, 11.9 mmol) in THF was added dropwise and the resulting solution was stirred at room temperature for 16 h. The reaction mixture was quenched with water (30 mL), extracted with Et_2O (3 × 30 mL) and the combined organic layer was washed with brine (40 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by column chromatography (3% to 10% EtOAc/petroleum ether) to give the title compound (**S2**) (1.40 g, 62%) as a yellow oil. R_f = 0.37 (20% EtOAc/petroleum ether); IR 2954, 1732 (C=O), 1434, 1289, 1147, 1048, 906, 848, 753, 688 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.40-7.35 (2H, m, Ar**H**), 7.25-7.21 (2H, m, Ar**H**), 7.17 (1H, dd, *J* = 3.6, 1,2 Hz, Ar**H**), 7.12-7.09 (2H, m, Ar**H**), 6.95 (1H, dd, *J* = 5.2, 3.6 Hz, Ar**H**), 3.81 (6H, s, 2 × OC**H**$_3$), 3.49

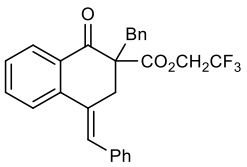
(2H, s, CC**H**$_2$CO$_2$Ph), 3.34 (2H, s, C**H**$_2$C≡C); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.3 (2 × C), 169.1 (C), 150.4 (C), 132.0 (CH), 129.5 (2 x CH), 127.0 (CH), 126.9 (CH), 126.1 (CH), 122.9 (C), 121.5 (2 x CH), 87.9 (C), 77.4 (C), 55.3 (C), 53.4 (2 x CH_3), 37.5 (CH_2), 25.1 (CH_2); HRMS (ESI) Exact mass calculated for $[C_{20}H_{18}NaO_6S]^+$ $[M+Na]^+$: 409.0722, found 409.0710.

3.3 Racemic Rhodium-Catalysed Desymmetrisation of Malonate Esters

General Procedure B: Rhodium-Catalysed Desymmetrisation of Malonate Esters

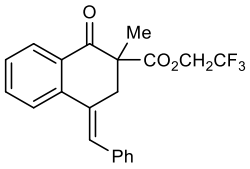


An oven-dried microwave vial fitted with a stirrer bar was charged with the appropriate malonate ester (0.3 mmol), the appropriate arylboronic acid (0.45 mmol), KF (26.1 mg, 0.45 mmol) and $[Rh(cod)Cl]_2$ (7.4 mg, 0.015 mmol). The vial was sealed with a septum-lined cap and purged with argon for 30 mins. Anhydrous 1,4-dioxane (2.7 mL) and water (0.3 mL) both of which were freshly deoxygenated separately (purging with argon for 30 mins) were added. The mixture was stirred at 70 °C for 20 h. The reaction was cooled to room temperature, water (15 mL) was added and the mixture was extracted with EtOAc (3 × 15 mL). The combined organic phases were washed with brine (20 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by column chromatography using EtOAc/*n*-pentane to give the *arylative cyclization product*.

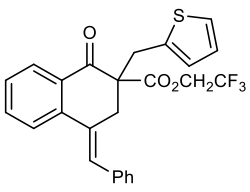


2,2,2-Trifluoroethyl (*E*)-2-benzyl-4-benzylidene-1-oxo-1,2,3,4-tetrahydronaphthalene-2-carboxylate (201a). The title compound was prepared according to General Procedure B, using malonate ester **182d** (141.7 mg, 0.30 mmol) and phenylboronic acid (54.9 mg, 0.45 mmol) which was purified by column chromatography (0% to 1.5% EtOAc/*n*-pentane) to give a pale-yellow oil (92.1 mg, 68%). R_f = 0.32 (10% EtOAc/petroleum ether); IR 2922, 1742 (C=O), 1685 (C=O), 1454, 1273, 1156, 925, 848, 760, 656 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (1H, dd, *J* = 7.9, 1.5 Hz, Ar**H**), 7.76 (1H, dd, *J* = 8.1, 1.1 Hz, Ar**H**), 7.59 (1H, ddd, *J* = 8.2, 7.3, 1.5 Hz, Ar**H**), 7.44-7.39 (4H, m, Ar**H**), 7.34-7.30 (3H, m, Ar**H**), 7.14-7.07 (5H, m, Ar**H**), 4.47

(1H, dq, J = 12.6, 8.4 Hz, C**H**$_a$H$_b$CF$_3$), 4.23 (1H, dq, J = 12.6, 8.4 Hz, CH$_a$**H**$_b$CF$_3$), 3.63 (1H, dd, J = 14.6, 1.4 Hz, =CC**H**$_a$H$_b$), 3.38 (1H, d, J = 13.7 Hz, CC**H**$_a$H$_b$CC), 3.22 (1H, d, J = 13.7 Hz, CCH$_a$**H**$_b$CC), 3.02 (1H, dd, J = 14.6, 1.4 Hz, =CCH$_a$**H**$_b$); ^{13}C NMR (101 MHz, CDCl$_3$) δ 193.6 (C), 170.0 (C), 141.1 (C), 136.7 (C), 135.4 (C), 134.3 (CH), 131.0 (C), 130.9 (2 x CH), 130.3 (C), 129.8 (CH), 129.2 (2 × CH), 128.7 (2 x CH), 128.6 (CH), 128.5 (CH), 128.2 (2 x CH), 127.8 (CH), 127.0 (CH), 124.5 (CH), 122.7 (q, J_{C-F} = 277.4 Hz, C), 61.0 (q, J_{C-F} = 37.1 Hz, CH$_2$), 60.3 (C), 38.9 (CH$_2$), 34.1 (CH$_2$); ^{19}F NMR (376 MHz, CDCl$_3$) δ –73.5 (t, J = 8.3 Hz, 3 × F); HRMS (ESI) Exact mass calculated for [C$_{27}$H$_{21}$F$_3$NaO$_3$]$^+$ [M+Na]$^+$: 473.1335, found 473.1332.

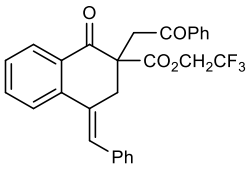


2,2,2-Trifluoroethyl (*E*)-4-benzylidene-2-methyl-1-oxo-1,2,3,4-tetrahydronaphthalene-2-carboxylate (201b). The title compound was prepared according to General Procedure B, using malonate ester **182a** (118.9 mg, 0.30 mmol) and phenylboronic acid (54.9 mg, 0.45 mmol) which was purified by column chromatography (0% to 1.5% EtOAc/*n*-pentane) to give a pale-yellow oil (65.5 mg, 58%). R$_f$ = 0.30 (10% EtOAc/petroleum ether); IR 2956, 1744 (C=O), 1684 (C=O), 1452, 1270, 1156, 920, 850, 758, 659 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.09 (1H, dd, J = 7.9, 1.5 Hz, Ar**H**), 7.74 (1H, dd, J = 8.1, 1.1 Hz, Ar**H**), 7.62 (1H, ddd, J = 8.0, 7.3, 1.5 Hz, Ar**H**), 7.46-7.31 (7H, m, Ar**H**), 4.55 (1H, dq, J = 12.6, 8.4 Hz, C**H**$_a$H$_b$CF$_3$), 4.30 (1H, dq, J = 12.6, 8.4 Hz, CH$_a$**H**$_b$CF$_3$), 3.59 (1H, dd, J = 14.1, 1.5 Hz, =CC**H**$_a$H$_b$), 3.07 (1H, dd, J = 14.1, 1.2 Hz, =CCH$_a$**H**$_b$) 1.46 (3H, s, C**H**$_3$); ^{13}C NMR (101 MHz, CDCl$_3$) δ 195.1 (C), 171.0 (C), 141.5 (C), 136.7 (C), 134.4 (CH), 131.3 (C), 130.2 (CH), 129.6 (C), 129.1 (2 × CH), 128.7 (2 × CH), 128.7 (CH), 128.3 (CH), 127.8 (CH), 124.7 (CH), 122.7 (q, J_{C-F} = 277.5 Hz, C), 60.9 (q, J_{C-F} = 36.9 Hz, CH$_2$), 55.4 (C), 37.4 (CH$_2$), 19.8 (CH$_3$); ^{19}F NMR (376 MHz, CDCl$_3$) δ –73.8 (t, J = 8.3 Hz, 3 × F); HRMS (ESI) Exact mass calculated for [C$_{21}$H$_{18}$F$_3$O$_3$]$^+$ [M+H]$^+$: 375.1203, found 375.1202.

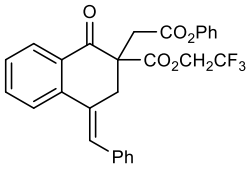


2,2,2-Trifluoroethyl (*E*)-4-benzylidene-1-oxo-2-(2-thienylmethyl)-1,2,3,4-tetrahydronaphthalene-2-carboxylate (201c). The title compound was prepared according to General Procedure B, using malonate ester **188** (143.5 mg, 0.30 mmol) and phenylboronic acid (54.9 mg, 0.45 mmol) which was purified by column chromatography (0%

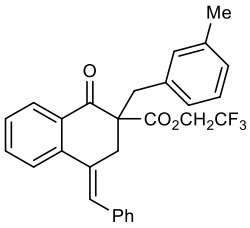
to 1.5% EtOAc/*n*-pentane) to give a yellow oil (68.8 mg, 50%). R_f = 0.46 (10% EtOAc/petroleum ether); IR 2925, 1751 (C=O), 1684 (C=O), 1595, 1278, 1155, 1070, 972, 758, 697, 510 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.12 (1H, dd, *J* = 7.9, 1.4 Hz, Ar**H**), 7.75 (1H, dd, *J* = 8.1, 1.1 Hz, Ar**H**), 7.60 (1H, ddd, *J* = 8.2, 7.3, 1.5 Hz, Ar**H**), 7.45-7.29 (7H, m, Ar**H**), 7.05 (1H, dd, *J* = 5.1, 1.3 Hz, Ar**H**), 6.73-6.69 (2H, m, Ar**H**), 4.53 (1H, dq, *J* = 12.7, 8.4 Hz, C**H**$_a$H$_b$CF$_3$), 4.25 (1H, dq, *J* = 12.7, 8.4 Hz, CH$_a$**H**$_b$CF$_3$), 3.65-3.59 (2H, m, =CC**H**$_a$H$_b$ and CC**H**$_a$H$_b$CS), 3.43 (1H, d, *J* = 14.7 Hz, CCH$_a$**H**$_b$CS), 3.06 (1H, dd, *J* = 14.5, 1.6 Hz, =CCH$_a$**H**$_b$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 193.4 (C), 169.8 (C), 141.4 (C), 136.9 (C), 136.6 (C), 134.4 (CH), 130.8 (C), 130.2 (CH), 130.1 (C), 129.2 (2 × CH), 128.8 (CH), 128.6 (3 × CH), 128.4 (CH), 127.8 (CH), 126.6 (CH), 125.3 (CH), 124.6 (CH), 122.6 (q, $J_{C\text{-}F}$ = 277.6 Hz, C), 61.1 (q, $J_{C\text{-}F}$ = 37.0 Hz, CH_2), 60.3 (C), 34.1 (CH_2), 33.4 (CH_2); ^{19}F NMR (376 MHz, $CDCl_3$) δ –73.5 (t, *J* = 8.3 Hz, 3 × F); HRMS (ESI) Exact mass calculated for $[C_{25}H_{19}F_3NaO_3S]^+$ $[M+Na]^+$: 479.0899, found 479.0900.



2,2,2-Trifluoroethyl (*E*)-4-benzylidene-1-oxo-2-(2-oxo-2-phenylethyl)-1,2,3,4-tetrahydronaphthalene-2-carboxylate (201d). The title compound was prepared according to General Procedure B, using malonate ester **184a** (150.1 mg, 0.30 mmol) and phenylboronic acid (54.9 mg, 0.45 mmol) which was purified by column chromatography (0% to 4% EtOAc/*n*-pentane) to give a pale-yellow oil (52.3 mg, 36%). R_f = 0.26 (10% EtOAc/petroleum ether); IR 1751 (C=O), 1682 (C=O), 1598, 1452, 1156, 1079, 909, 727, 694, 657 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.10 (1H, dd, *J* = 7.9, 1.5 Hz, Ar**H**), 7.81-7.79 (2H, m, Ar**H**), 7.73 (1H, dd, *J* = 8.0, 1.1 Hz, Ar**H**), 7.64-7.60 (1H, m, Ar**H**), 7.58-7.54 (1H, m, Ar**H**), 7.47-7.40 (3H, m, Ar**H**), 7.34-7.27 (4H, m, Ar**H**), 7.20-7.17 (2H, m, Ar**H**), 4.55 (1H, dq, *J* = 12.6, 8.4 Hz, C**H**$_a$H$_b$CF$_3$), 4.29 (1H, dq, *J* = 12.6, 8.4 Hz, CH$_a$**H**$_b$CF$_3$), 3.66-3.54 (4H, m, =CC**H**$_2$C and CC**H**$_2$COPh); ^{13}C NMR (101 MHz, $CDCl_3$) δ 195.8 (C), 193.8 (C), 169.9 (C), 141.8 (C), 136.4 (2 x C), 134.4 (CH), 133.5 (CH), 131.6 (C), 130.4 (CH), 130.3 (C), 129.0 (2 × CH), 128.7 (3 x CH), 128.6 (2 × CH), 128.3 (CH), 128.1 (2 × CH), 127.7 (CH), 124.7 (CH), 122.7 (q, $J_{C\text{-}F}$ = 277.4 Hz, C), 61.1 (q, $J_{C\text{-}F}$ = 36.9 Hz, CH_2), 57.0 (C), 41.7 (CH_2), 35.0 (CH_2); ^{19}F NMR (376 MHz, $CDCl_3$) δ –73.7 (t, *J* = 8.4 Hz, 3 × F); HRMS (ESI) Exact mass calculated for $[C_{28}H_{25}NF_3O_4]^+$ $[M+H_4N]^+$: 501.1290, found 501.1122.

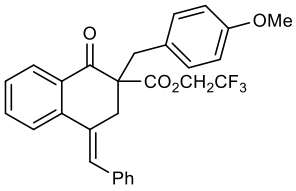


2,2,2-Trifluoroethyl (*E*)-4-benzylidene-1-oxo-2-(2-oxo-2-phenoxyethyl)-1,2,3,4-tetrahydronaphthalene-2-carboxylate (201e). The title compound was prepared according to General Procedure B, using malonate ester **184b** (154.9 mg, 0.30 mmol) and phenylboronic acid (54.9 mg, 0.45 mmol) which was purified by column chromatography (0% to 3% EtOAc/*n*-pentane) to give a white solid (81.6 mg, 55%). R_f = 0.31 (20% EtOAc/petroleum ether); m.p. 138-140 °C (Et_2O); IR 3062, 1754 (C=O), 1687 (C=O), 1594, 1278, 1145, 958, 758, 698, 496 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.12 (1H, dd, *J* = 7.9, 1.5 Hz, Ar**H**), 7.75 (1H, dd, *J* = 8.0, 1.1 Hz, Ar**H**), 7.65-7.61 (1H, m, Ar**H**), 7.47-7.29 (9H, m, Ar**H**), 7.22-7.17 (1H, m, Ar**H**), 6.94-6.90 (2H, m, Ar**H**), 4.53 (1H, dq, *J* = 12.6, 8.3 Hz, C**H**$_a$H$_b$CF$_3$), 4.22 (1H, dq, *J* = 12.6, 8.3 Hz, CH$_a$**H**$_b$CF$_3$), 3.71 (1H, dd, *J* = 14.2, 1.0 Hz, =CC**H**$_a$H$_b$), 3.46 (1H, dd, *J* = 14.2, 1.6 Hz, =CCH$_a$**H**$_b$), 3.18-3.09 (2H, m, CC**H**$_2$CO$_2$Ph); ^{13}C NMR (101 MHz, $CDCl_3$) δ 193.2 (C), 169.3 (C), 168.8 (C), 150.4 (C), 141.6 (C), 136.4 (C), 134.6 (CH), 130.0 (C), 129.4 (2 × CH), 129.1 (2 × CH), 128.8 (2 × CH), 128.8 (CH), 128.3 (CH), 127.9 (CH), 126.0 (CH), 124.7 (CH), 122.6 (q, J_{C-F} = 277.4 Hz, C), 121.5 (2 x CH), 61.2 (q, J_{C-F} = 36.9 Hz, CH_2), 57.1 (C), 38.1 (CH_2), 35.7 (CH_2), [1 x C and 1 x CH concealed within the peak at 130.7]; ^{19}F NMR (376 MHz, $CDCl_3$) δ –73.7 (t, *J* = 8.4 Hz, 3 × F); HRMS (ESI) Exact mass calculated for $[C_{28}H_{21}F_3NaO_5]^+$ $[M+Na]^+$: 517.1233, found 517.1233.

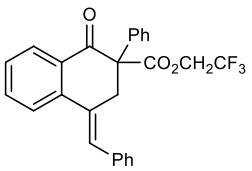


2,2,2-Trifluoroethyl (*E*)-4-benzylidene-2-(3-methylbenzyl)-1-oxo-1,2,3,4-tetrahydronaphthalene-2-carboxylate (201f). The title compound was prepared according to General Procedure B, using malonate ester **189** (145.9 mg, 0.30 mmol) and phenylboronic acid (54.9 mg, 0.45 mmol) which was purified by column chromatography (0% to 1.5% EtOAc/*n*-pentane) to give a colourless oil (101.0 mg, 73%). R_f = 0.34 (10% EtOAc/petroleum ether); IR 2923, 1749 (C=O), 1686 (C=O), 1444, 1279, 1156, 909, 759, 731, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.10 (1H, dd, *J* = 7.9, 1.2 Hz, Ar**H**), 7.76 (1H, d, *J* = 8.0 Hz, Ar**H**), 7.59 (1H, ddd, *J* = 8.1, 7.3, 1.5 Hz, Ar**H**), 7.44-7.30 (7H, m, Ar**H**), 6.99-6.86 (4H, m, Ar**H**), 4.45 (1H, dq, *J* = 12.6, 8.4 Hz, C**H**$_a$H$_b$CF$_3$), 4.24 (1H, dq, *J* = 12.6, 8.4 Hz, CH$_a$**H**$_b$CF$_3$), 3.64 (1H, dd, *J* = 14.7, 1.4 Hz, =CC**H**$_a$H$_b$), 3.33 (1H, d, *J* = 13.8 Hz, CC**H**$_a$H$_b$CC), 3.20 (1H, d, *J* = 13.8 Hz, CCH$_a$**H**$_b$CC), 3.05 (1H, dd, *J* = 14.7, 1.6 Hz, =CCH$_a$**H**$_b$), 2.17 (3H, s, C**H**$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 193.8 (C), 170.0 (C), 141.0 (C), 137.8 (C), 136.7 (C), 135.3 (C), 134.3 (CH), 131.5 (CH), 131.0 (C), 130.3 (C), 129.7 (CH), 129.3 (2 x CH), 128.7

(2 × CH), 128.6 (CH), 128.5 (CH), 128.1 (CH), 127.9 (CH), 127.8 (CH), 127.8 (CH), 124.4 (CH), 122.7 (q, $J_{C\text{-}F}$ = 277.9 Hz, C), 61.0 (q, $J_{C\text{-}F}$ = 36.9 Hz, CH_2), 60.2 (C), 38.8 (CH_2), 34.1 (CH_2), 21.4 (CH_3); ^{19}F NMR (376 MHz, $CDCl_3$) δ –73.5 (t, *J* = 8.3 Hz, 3 × F); HRMS (ESI) Exact mass calculated for $[C_{28}H_{24}F_3O_3]^+$ $[M+H]^+$: 465.1672, found 465.1683.

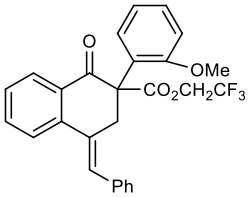


2,2,2-Trifluoroethyl (*E*)-4-benzylidene-2-(4-methoxybenzyl)-1-oxo-1,2,3,4-tetrahydronaphthalene-2-carboxylate (201g). The title compound was prepared according to General Procedure B, using malonate ester **190** (150.7 mg, 0.30 mmol) and phenylboronic acid (54.9 mg, 0.45 mmol) which was purified by column chromatography (0% to 2% EtOAc/*n*-pentane) to give a yellow oil (104.1 mg, 72%). R_f = 0.29 (10% EtOAc/petroleum ether); IR 2928, 1749 (C=O), 1685 (C=O), 1511, 1279, 1248, 1156, 1032, 908, 759 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (1H, dd, *J* = 7.9, 0.5 Hz, Ar**H**), 7.76 (1H, d, *J* = 7.6 Hz, Ar**H**), 7.59 (1H, ddd, *J* = 8.0, 7.2, 1.5 Hz, Ar**H**), 7.44-7.39 (4H, m, Ar**H**), 7.35-7.30 (3H, m, Ar**H**), 7.04-7.00 (2H, m, Ar**H**), 6.63-6.59 (2H, m, Ar**H**), 4.48 (1H, dq, *J* = 12.6, 8.4 Hz, C**H**$_a$H$_b$CF$_3$), 4.26 (1H, dq, *J* = 12.6, 8.4 Hz, CH$_a$**H**$_b$CF$_3$), 3.71 (3H, s, OC**H**$_3$), 3.61 (1H, dd, *J* = 14.6, 1.4 Hz, =CC**H**$_a$H$_b$), 3.31 (1H, d, *J* = 13.9 Hz, CC**H**$_a$H$_b$CC), 3.16 (1H, d, *J* = 13.9 Hz, CCH$_a$**H**$_b$CC), 3.04 (1H, dd, *J* = 14.6, 1.5 Hz, =CCH$_a$**H**$_b$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 193.8 (C), 170.0 (C), 158.6 (C), 141.1 (C), 136.7 (C), 134.3 (CH), 131.8 (2 x CH), 131.1 (CH), 130.2 (C), 129.8 (CH), 129.3 (2 x CH), 128.7 (2 x CH), 128.6 (CH), 128.4 (CH), 127.8 (CH), 127.3 (C), 124.5 (CH), 122.7 (q, $J_{C\text{-}F}$ = 277.4 Hz, C), 113.6 (2 x CH), 61.4 (q, $J_{C\text{-}F}$ = 37.2 Hz, CH_2), 60.5 (C), 55.2 (CH_3), 38.0 (CH_2), 34.0 (CH_2); ^{19}F NMR (376 MHz, $CDCl_3$) δ –73.5 (t, *J* = 8.4 Hz, 3 × F); HRMS (ESI) Exact mass calculated for $[C_{28}H_{24}F_3O_4]^+$ $[M+H]^+$: 481.1621, found 481.1631.

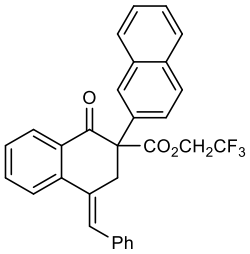


2,2,2-Trifluoroethyl (*E*)-4-benzylidene-1-oxo-2-phenyl-1,2,3,4-tetrahydronaphthalene-2-carboxylate (201h). The title compound was prepared according to General Procedure B, using malonate ester **182c** (137.4 mg, 0.30 mmol) and phenylboronic acid (54.9 mg, 0.45 mmol) which was purified by column chromatography (0% to 1.5% EtOAc/*n*-pentane) to give a yellow oil (81.0 mg, 62%). R_f = 0.42 (10% EtOAc/petroleum ether); IR 2919, 1749 (C=O), 1682 (C=O), 1596, 1447, 1280, 1158, 972, 732, 696 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (1H, dd, *J* = 7.9, 1.4 Hz, Ar**H**), 7.65 (1H, dd, *J* = 8.0, 1.1 Hz, Ar**H**), 7.58-

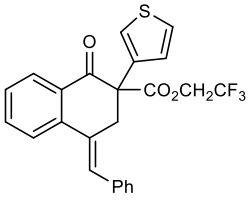
7.53 (1H, m, Ar**H**), 7.48-7.29 (6H, m, Ar**H**), 7.24-7.15 (4H, m, Ar**H**), 6.96-6.93 (2H, m, Ar**H**), 4.54 (1H, dq, *J* = 12.7, 8.4 Hz, C**H**$_a$H$_b$CF$_3$), 4.39 (1H, dq, *J* = 12.7, 8.4 Hz, CH$_a$**H**$_b$CF$_3$), 3.92 (1H, dd, *J* = 14.5, 0.8 Hz, =CC**H**$_a$H$_b$), 3.82 (1H, dd, *J* = 14.5, 1.9 Hz, =CCH$_a$**H**$_b$); ^{13}C NMR (101 MHz, CDCl$_3$) δ 193.5 (C), 169.9 (C), 141.1 (C), 136.9 (C), 134.4 (CH), 134.0 (C), 131.1 (C), 130.3 (CH), 130.2 (C), 129.1 (2 × CH), 128.8 (2 × CH), 128.7 (CH), 128.5 (CH), 128.3 (2 x CH), 128.2 (CH), 128.0 (CH), 127.9 (2 × CH), 124.6 (CH), 122.7 (q, J_{C-F} = 277.5 Hz, C), 64.3 (C), 61.2 (q, J_{C-F} = 36.9 Hz, CH$_2$), 35.2 (CH$_2$); ^{19}F NMR (376 MHz, CDCl$_3$) δ –73.7 (t, *J* = 8.3 Hz, 3 × F); HRMS (ESI) Exact mass calculated for [C$_{26}$H$_{20}$F$_3$O$_3$]$^+$ [M+H]$^+$: 437.1359, found 437.1343.



2,2,2-Trifluoroethyl (*E*)-4-benzylidene-2-(2-methoxyphenyl)-1-oxo-1,2,3,4-tetrahydronaphthalene-2-carboxylate (201i). The title compound was prepared according to General Procedure B, using malonate ester **193** (146.5 mg, 0.30 mmol) and phenylboronic acid (54.9 mg, 0.45 mmol) which was purified by column chromatography (0% to 1.5% EtOAc/*n*-pentane) to give a pale-yellow oil (75.1 mg, 54%). R$_f$ = 0.29 (10% EtOAc/petroleum ether); IR 2923, 1751 (C=O), 1682 (C=O), 1596, 1494, 1157, 1029, 973, 774, 698 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.19 (1H, dt, *J* = 7.8, 1.1 Hz, Ar**H**), 7.61-7.57 (2H, m, Ar**H**), 7.49-7.43 (1H, m, Ar**H**), 7.34-7.29 (2H, m, Ar**H**), 7.26-7.22 (1H, m, Ar**H**), 7.17 (1H, ddd, *J* = 8.2, 6.9, 2.2 Hz, Ar**H**), 7.04-6.99 (3H, m, Ar**H**), 6.70-6.63 (2H, m, Ar**H**), 6.58-6.56 (1H, m, Ar**H**), 4.66 (1H, dq, *J* = 12.7, 8.4 Hz, C**H**$_a$H$_b$CF$_3$), 4.36 (1H, dq, *J* = 12.7 8.4 Hz, CH$_a$**H**$_b$CF$_3$), 4.27 (1H, d, *J* = 13.8 Hz, =CC**H**$_a$H$_b$), 3.52 (1H, dd, *J* = 13.8, 1.8 Hz, =CCH$_a$**H**$_b$), 3.15 (3H, s, OC**H**$_3$); ^{13}C NMR (101 MHz, CDCl$_3$) δ 194.8 (C), 170.2 (C), 156.9 (C), 142.5 (C), 137.0 (C), 134.4 (CH), 132.8 (C), 131.0 (C), 130.1 (CH), 129.1 (CH), 129.0 (2 × CH), 128.6 (CH), 128.3 (2 × CH), 128.1 (CH), 128.0 (CH), 127.3 (CH), 124.9 (C), 124.8 (CH), 122.9 (q, J_{C-F} = 277.7 Hz, C), 120.0 (CH), 110.4 (CH), 63.2 (C), 60.8 (q, J_{C-F} = 36.7 Hz, CH$_2$), 54.3 (CH$_3$), 34.8 (CH$_2$); ^{19}F NMR (376 MHz, CDCl$_3$) δ –73.7 (t, *J* = 8.5 Hz, 3 × F); HRMS (ESI) Exact mass calculated for [C$_{27}$H$_{22}$F$_3$O$_4$]$^+$ [M+H]$^+$: 467.1465, found 467.1464.

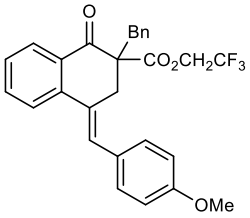


2,2,2-Trifluoroethyl (*E*)-4-benzylidene-1-oxo-3,4-dihydro-[2,2'-binaphthalene]-2(1*H*)-carboxylate (201j). The title compound was prepared according to a slight modification of General Procedure B (in that 2.0 equivalents of boronic acid and 10 mol% catalyst loading was used), using malonate ester **194** (152.5 mg, 0.30 mmol) and phenylboronic acid (73.2 mg, 0.60 mmol) which was purified by column chromatography (0% to 1% EtOAc/*n*-pentane) to give a yellow oil (82.3 mg, 56%). R_f = 0.41 (10% EtOAc/petroleum ether); IR 2924, 1745 (C=O), 1682 (C=O), 1596, 1278, 1157, 1081, 967, 777, 699 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.25 (1H, dt, *J* = 7.8, 1.2 Hz, Ar**H**), 7.77-7.70 (2H, m, Ar**H**), 7.64-7.59 (2H, m, Ar**H**), 7.50 (1H, ddd, *J* = 8.3, 5.9, 2.6 Hz, Ar**H**), 7.31-7.27 (2H, m, Ar**H**), 7.17 (1H, dd, *J* = 8.2, 7.3 Hz, Ar**H**), 7.09-6.93 (6H, m, Ar**H**), 6.57-6.54 (2H, m, Ar**H**), 4.60-4.43 (2H, m, C**H**$_2$CF$_3$), 4.27 (1H, d, *J* = 14.0 Hz, =CC**H**$_a$H$_b$), 3.74 (1H, dd, *J* = 14.0, 1.7 Hz, =CCH$_a$**H**$_b$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 194.8 (C), 170.9 (C), 141.7 (C), 136.3 (C), 134.6 (CH), 134.2 (C), 132.4 (C), 131.6 (C), 131.0 (C), 130.9 (C), 130.5 (CH), 129.2 (CH), 129.2 (CH), 128.8 (CH), 128.3 (CH), 128.2 (2 × CH), 128.1 (2 × CH), 127.0 (CH), 126.2 (CH), 125.9 (CH), 125.5 (CH), 124.8 (CH), 124.5 (CH), 123.7 (CH), 122.6 (q, $J_{C\text{-}F}$ = 277.8 Hz, C), 65.2 (C), 61.2 (q, $J_{C\text{-}F}$ = 36.9 Hz, CH_2), 36.6 (CH_2); ^{19}F NMR (376 MHz, $CDCl_3$) δ –73.3 (t, *J* = 8.4 Hz, 3 × F); HRMS (ESI) Exact mass calculated for $[C_{30}H_{25}F_3NO_3]^+$ $[M+H_4N]^+$: 504.1781, found 504.1783.

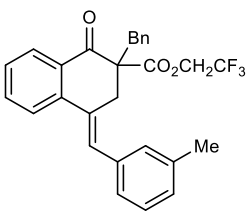


2,2,2-Trifluoroethyl (*E*)-4-benzylidene-1-oxo-2-(3-thienyl)-1,2,3,4-tetrahydronaphthalene-2-carboxylate (201k). The title compound was prepared according to General Procedure B, using malonate ester **187** (139.3 mg, 0.30 mmol) and phenylboronic acid (54.9 mg, 0.45 mmol) which was purified by column chromatography (0% to 2% EtOAc/*n*-pentane) to give a yellow oil (75.7 mg, 57%). R_f = 0.25 (10% EtOAc/petroleum ether); IR 2924, 1749 (C=O), 1682 (C=O), 1596, 1445, 1280, 1156, 908, 731, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.15 (1H, ddd, *J* = 7.9, 1.5, 0.5 Hz, Ar**H**), 7.69 (1H, dd, *J* = 8.1, 1.2 Hz, Ar**H**), 7.58 (1H, ddd, *J* = 8.0, 7.2, 1.5 Hz, Ar**H**), 7.48-7.33 (6H, m, Ar**H**), 7.30 (1H, s, **H**C=C), 7.16 (1H, dd, *J* = 5.1, 3.0 Hz, Ar**H**), 6.89 (1H, dd, *J* = 3.0, 1.4 Hz, Ar**H**), 6.76 (1H, dd, *J* = 5.1, 1.4 Hz, Ar**H**), 4.57 (1H, dq, *J* = 12.6, 8.3 Hz, C**H**$_a$H$_b$CF$_3$), 4.40 (1H, dq, *J* = 12.6, 8.3 Hz, CH$_a$**H**$_b$CF$_3$), 3.89-3.80 (2H, m, =CC**H**$_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 192.4 (C), 169.5 (C), 141.1 (C), 136.7 (C), 134.5 (CH), 134.4 (C), 131.0 (C), 130.4 (CH), 129.7 (C), 129.2 (2 × CH), 128.9 (2 × CH),

128.7 (CH), 128.6 (CH), 128.0 (CH), 127.6 (CH), 125.4 (CH), 124.7 (CH), 123.9 (CH), 122.7 (q, $J_{C\text{-}F}$ = 277.5 Hz, C), 61.3 (q, $J_{C\text{-}F}$ = 36.8 Hz, CH_2), 35.6 (CH_2), [1 x C concealed within the peak at 61.5]; ^{19}F NMR (376 MHz, $CDCl_3$) δ –73.7 (t, *J* = 8.3 Hz, 3 × F); HRMS (ESI) Exact mass calculated for $[C_{24}H_{18}F_3O_3S]^+$ $[M+H]^+$: 443.0923, found 443.0923.

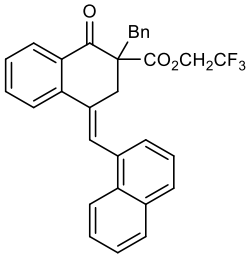


2,2,2-Trifluoroethyl (*E*)-2-benzyl-4-(4-methoxybenzylidene)-1-oxo-1,2,3,4-tetrahydronaphthalene-2-carboxylate (201l). The title compound was prepared according to General Procedure B, using malonate ester **186a** (150.7 mg, 0.30 mmol) and phenylboronic acid (54.9 mg, 0.45 mmol) which was purified by column chromatography (0% to 2% EtOAc/*n*-pentane) to give a yellow oil (91.8 mg, 64%). R_f = 0.31 (10% EtOAc/petroleum ether); IR 2964, 1750 (C=O), 1686 (C=O), 1605, 1510, 1279, 1249, 1157, 1031, 701 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (1H, dd, *J* = 7.9, 1.5 Hz, Ar**H**), 7.73 (1H, dd, *J* = 8.1, 1.1 Hz, Ar**H**), 7.60-7.55 (1H, m, Ar**H**), 7.39 (1H, ddd, *J* = 8.1, 7.2, 1.1 Hz, Ar**H**), 7.34 (1H, s, **H**C=C), 7.29-7.26 (3H, m, Ar**H**), 7.14-7.10 (4H, m, Ar**H**), 6.96-6.92 (2H, m, Ar**H**), 4.47 (1H, dq, *J* = 12.6, 8.4 Hz, $\mathbf{H}_a\mathrm{H}_b\mathrm{CF}_3$), 4.27 (1H, dq, *J* = 12.6, 8.4 Hz, $\mathrm{H}_a\mathbf{H}_b\mathrm{CF}_3$), 3.86 (3H, s, C$\mathbf{H}_3$), 3.63 (1H, dd, *J* = 14.6, 1.4 Hz, =CC$\mathbf{H}_a\mathrm{H}_b$), 3.37 (1H, d, *J* = 13.7 Hz, CC$\mathbf{H}_a\mathrm{H}_b$CCH), 3.24 (1H, d, *J* = 13.7 Hz, CCH$_a\mathbf{H}_b$CCH), 3.02 (1H, dd, *J* = 14.7, 1.5 Hz, =CCH$_a\mathbf{H}_b$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 193.8 (C), 170.0 (C), 159.2 (C), 141.4 (C), 135.4 (C), 134.3 (CH), 130.9 (2 × CH), 130.7 (2 × CH), 130.0 (C), 129.6 (CH), 129.4 (C), 129.3 (C), 128.4 (CH), 128.3 (CH), 128.2 (2 × CH), 127.0 (CH), 124.4 (CH), 122.7 (q, $J_{C\text{-}F}$ = 277.5 Hz, C), 114.1 (2 × CH), 61.0 (q, $J_{C\text{-}F}$ = 36.9 Hz, CH_2), 60.3 (C), 55.5 (CH_3), 38.8 (CH_2), 34.1 (CH_2); ^{19}F NMR (376 MHz, $CDCl_3$) δ –73.5 (t, *J* = 8.4 Hz, 3 × F); HRMS (ESI) Exact mass calculated for $[C_{28}H_{24}F_3O_4]^+$ $[M+H]^+$: 481.1621, found 481.1616.

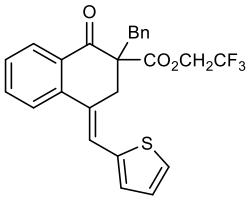


2,2,2-trifluoroethyl (*E*)-2-benzyl-4-(3-methylbenzylidene)-1-oxo-1,2,3,4-tetrahydronaphthalene-2-carboxylate (201m). The title compound was prepared according to General Procedure B, using malonate ester **182e** (145.9 mg, 0.30 mmol) and phenylboronic acid (54.9 mg, 0.45 mmol) which was purified by column chromatography (0% to 1.5% EtOAc/*n*-pentane) to give a yellow oil (102.6 mg, 74%). R_f = 0.31 (10% EtOAc/petroleum ether); IR 1752 (C=O), 1695 (C=O), 1602, 1455, 1281, 1153, 1060, 913, 729, 698 cm^{-1}; ^{1}H NMR (400

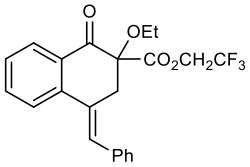
MHz, $CDCl_3$) δ 8.11 (1H, dd, *J* = 7.9, 1.4 Hz, Ar**H**), 7.76 (1H, dd, *J* = 8.1, 1.1 Hz, Ar**H**), 7.59 (1H, ddd, *J* = 8.3, 7.2, 1.5 Hz, Ar**H**), 7.42 (1H, ddd, *J* = 8.2, 7.3, 1.1 Hz, Ar**H**), 7.37 (1H, s, **H**C=C), 7.31-7.27 (1H, m, Ar**H**), 7.13-7.10 (8H, m, Ar**H**), 4.47 (1H, dq, *J* = 12.6, 8.4 Hz, $\mathbf{H}_aH_bCF_3$), 4.31-4.20 (1H, m, $H_a\mathbf{H}_bCF_3$), 3.65 (1H, dd, *J* = 14.7, 1.4 Hz, =CC$\mathbf{H}_a$$H_b$), 3.38 (1H, d, *J* = 13.8 Hz, CC$\mathbf{H}_a$$H_b$CCH), 3.26 (1H, d, *J* = 13.8 Hz, CC$H_a\mathbf{H}_b$CCH), 3.01 (1H, dd, *J* = 14.7, 1.7 Hz, =CC$H_a\mathbf{H}_b$), 2.39 (3H, s, C$\mathbf{H}_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 193.7 (C), 169.9 (C), 141.1 (C), 138.2 (C), 136.6 (C), 135.4 (C), 134.3 (CH), 130.8 (2 × CH), 130.7 (C), 130.3 (C), 130.0 (CH), 129.9 (CH), 128.6 (CH), 128.5 (CH), 128.5 (CH), 128.4 (CH), 128.2 (2 × CH), 127.0 (CH), 126.3 (CH), 124.4 (CH), 122.7 (q, $J_{C\text{-}F}$ = 277.6 Hz, C), 61.0 (q, $J_{C\text{-}F}$ = 36.9 Hz, CH_2), 60.2 (C), 38.9 (CH_2), 34.2 (CH_2), 21.6 (CH_3); ^{19}F NMR (376 MHz, $CDCl_3$) δ –73.5 (t, *J* = 8.4 Hz, 3 × F); HRMS (ESI) Exact mass calculated for $[C_{28}H_{24}F_3O_3]^+$ $[M+H]^+$: 465.1672, found 465.1669.



2,2,2-Trifluoroethyl (*E*)-2-benzyl-4-(naphthalen-1-ylmethylene)-1-oxo-1,2,3,4-tetrahydronaphthalene-2-carboxylate (201n). The title compound was prepared according to General Procedure B, using malonate ester **186b** (156.7 mg, 0.30 mmol) and phenylboronic acid (54.9 mg, 0.45 mmol) which was purified by column chromatography (0% to 1.5% EtOAc/*n*-pentane) to give a yellow oil (102.0 mg, 68%). R_f = 0.38 (10% EtOAc/petroleum ether); IR 3061, 1757 (C=O), 1683 (C=O), 1282, 1152, 974, 908, 778, 752, 663 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (1H, dd, *J* = 7.9, 1.4 Hz, Ar**H**), 7.98 (1H, dd, *J* = 7.8, 1.7 Hz, Ar**H**), 7.94 (1H, dd, *J* = 7.6, 1.8 Hz, Ar**H**), 7.89-7.86 (3H, m, Ar**H**), 7.65 (1H, td, *J* = 7.7, 1.5 Hz, Ar**H**), 7.58-7.45 (4H, m, Ar**H**), 7.38 (1H, d, *J* = 7.0 Hz, Ar**H**), 7.04-7.00 (3H, m, Ar**H**), 6.90-6.86 (2H, m, Ar**H**), 4.45 (1H, dq, *J* = 12.7, 8.4 Hz, C$\mathbf{H}_a$$H_b$$CF_3$), 4.00 (1H, dq, *J* = 12.7, 8.4 Hz, $CH_a\mathbf{H}_bCF_3$), 3.50 (1H, dd, *J* = 14.6, 1.3 Hz, =CC$\mathbf{H}_a$$H_b$), 3.37 (1H, d, *J* = 13.7 Hz, CC$\mathbf{H}_a$$H_b$CCH), 3.12 (1H, d, *J* = 13.7 Hz, CC$H_a\mathbf{H}_b$CCH), 2.96 (1H, dd, *J* = 14.6, 1.5 Hz, =CC$H_a\mathbf{H}_b$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 193.7 (C), 170.0 (C), 140.9 (C), 135.3 (C), 134.4 (CH), 133.8 (C), 133.6 (C), 132.6 (C), 132.2 (C), 130.9 (2 × CH), 130.4 (C), 128.9 (CH), 128.8 (CH), 128.6 (CH), 128.5 (CH), 128.0 (2 × CH), 127.8 (CH), 126.9 (2 × CH), 126.5 (CH), 126.2 (CH), 125.5 (CH), 124.6 (2 × CH), 122.6 (q, $J_{C\text{-}F}$ = 277.5 Hz, C), 60.9 (q, $J_{C\text{-}F}$ = 36.9 Hz, CH_2), 60.5 (C), 38.6 (CH_2), 34.7 (CH_2); ^{19}F NMR (376 MHz, $CDCl_3$) δ –73.7 (t, *J* = 8.3 Hz, 3 × F); HRMS (ESI) Exact mass calculated for $[C_{31}H_{24}F_3O_3]^+$ $[M+H]^+$: 501.1672, found 501.1667.

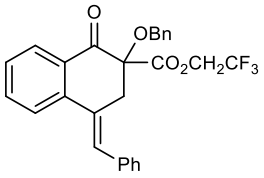


2,2,2-Trifluoroethyl (*E*)-2-benzyl-1-oxo-4-(thiophen-2-ylmethylene)-1,2,3,4-tetrahydronaphthalene-2-carboxylate (201o). The title compound was prepared according to General Procedure B, using malonate ester **186c** (143.5 mg, 0.30 mmol) and phenylboronic acid (54.9 mg, 0.45 mmol) which was purified by column chromatography (0% to 1.5% EtOAc/*n*-pentane) to give a yellow oil (91.7 mg, 66%). R_f = 0.29 (10% EtOAc/petroleum ether); IR 2930, 1759 (C=O), 1681 (C=O), 1283, 1148, 974, 923, 857, 750, 690 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.08 (1H, dd, *J* = 7.9, 1.5 Hz, Ar**H**), 7.73 (1H, dd, *J* = 8.1, 1.0 Hz, Ar**H**), 7.57 (1H, ddd, *J* = 8.3, 7.2, 1.5 Hz, Ar**H**), 7.45 (1H, s, =CC**H**), 7.41-7.35 (2H, m, Ar**H**), 7.22-7.14 (6H, m, Ar**H**), 7.06 (1H, dd, *J* = 5.1, 3.6 Hz, Ar**H**), 4.45 (1H, dq, *J* = 12.6, 8.3 Hz, C$\mathbf{H}_a$H$_b$CF$_3$), 4.29 (1H, dq, *J* = 12.6, 8.3 Hz, CH$_a$$\mathbf{H}_bCF_3$), 3.80 (1H, dd, *J* = 14.8, 1.3 Hz, =CC$\mathbf{H}_a$H$_b$), 3.43-3.36 (2H, m, CC$\mathbf{H}_2$CCH), 3.02 (1H, dd, *J* = 14.8, 1.7 Hz, =CCH$_a$$\mathbf{H}_b$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 193.5 (C), 169.7 (C), 140.9 (C), 139.8 (C), 135.4 (C), 134.3 (CH), 130.8 (2 × CH), 130.2 (C), 130.0 (CH), 128.7 (C), 128.6 (CH), 128.4 (3 × CH), 127.3 (CH), 127.2 (CH), 126.9 (CH), 123.9 (CH), 122.7 (q, $J_{C\text{-}F}$ = 277.5 Hz, C), 122.1 (CH), 61.0 (q, $J_{C\text{-}F}$ = 36.9 Hz, CH_2), 60.0 (C), 39.2 (CH_2), 34.3 (CH_2); ^{19}F NMR (376 MHz, $CDCl_3$) δ –73.6 (t, *J* = 8.3 Hz, 3 × F); HRMS (ESI) Exact mass calculated for $[C_{25}H_{19}F_3NaO_3S]^+$ $[M+Na]^+$: 479.0899, found 479.0903.

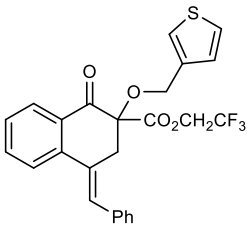


2,2,2-Trifluoroethyl (*E*)-4-benzylidene-2-ethoxy-1-oxo-1,2,3,4-tetrahydronaphthalene-2-carboxylate (201p). The title compound was prepared according to a slight modification of General Procedure B (in that 2.0 equivalents of boronic acid and 10 mol% catalyst loading was used), using malonate ester **195** (127.9 mg, 0.30 mmol) and phenylboronic acid (73.2 mg, 0.60 mmol) which was purified by column chromatography (0% to 1.5% EtOAc/*n*-pentane) to give a yellow oil (43.5 mg, 36%). R_f = 0.27 (10% EtOAc/petroleum ether); IR 2979, 1768 (C=O), 1688 (C=O), 1596, 1282, 1226, 1162, 1041, 755, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.08 (1H, dd, *J* = 7.8, 1.5 Hz, Ar**H**), 7.79 (1H, d, *J* = 8.0 Hz, Ar**H**), 7.63 (1H, ddd, *J* = 8.1, 7.2, 1.5 Hz, Ar**H**), 7.46-7.30 (7H, m, Ar**H**), 4.62 (1H, dq, *J* = 12.6, 8.3 Hz, $\mathbf{H}_a$H$_b$CF$_3$), 4.43 (1H, dq, *J* = 12.6, 8.3 Hz, H$_a$$\mathbf{H}_bCF_3$), 3.65-3.56 (2H, m, OC$\mathbf{H}_aH_b$ and =CC$\mathbf{H}_a$H$_b$), 3.50-3.41 (2H, m, OCH$_a$$\mathbf{H}_b$ and =CCH$_a$$\mathbf{H}_b$), 1.10 (3H, t, *J* = 7.0 Hz, CH$_2$C$\mathbf{H}_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 191.4 (C), 169.0 (C), 141.5 (C), 136.6 (C), 134.6 (CH), 130.5 (CH), 130.0 (C), 129.3 (C), 129.2 (2 × CH), 128.7 (2 × CH), 128.6 (CH), 128.4 (CH), 127.9 (CH), 124.5 (CH), 122.7 (q, $J_{C\text{-}F}$ =

277.3 Hz, C), 84.0 (CH_2), 63.2 (C), 61.0 (q, $J_{C\text{-}F}$ = 37.0 Hz, CH_2), 36.3 (CH_2), 15.5 (CH_3); ^{19}F NMR (376 MHz, $CDCl_3$) δ –73.7 (t, J = 8.3 Hz, 3 × F); HRMS (ESI) Exact mass calculated for $[C_{22}H_{20}F_3O_4]^+$ $[M+H]^+$: 405.1308, found 405.1311.



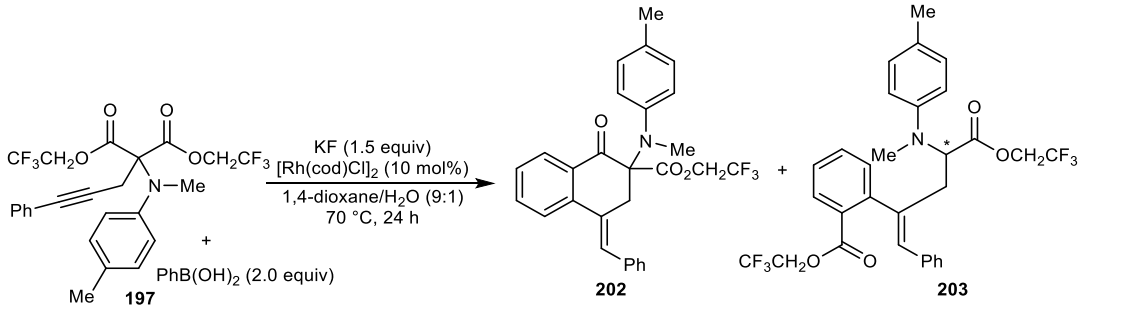
2,2,2-Trifluoroethyl (*E*)-4-benzylidene-2-(benzyloxy)-1-oxo-1,2,3,4-tetrahydronaphthalene-2-carboxylate (201q). The title compound was prepared according to General Procedure B, using malonate ester **182b** (146.5 mg, 0.30 mmol) and phenylboronic acid (54.9 mg, 0.45 mmol) which was purified by column chromatography (0% to 2.5% EtOAc/*n*-pentane) to give a yellow oil (72.0 mg, 51%). R_f = 0.25 (10% EtOAc/petroleum ether); IR 2952, 1762 (C=O), 1692 (C=O), 1433, 1280, 1156, 1052, 972, 752, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.05-8.03 (1H, m, Ar**H**), 7.78 (1H, d, J = 8.8 Hz, Ar**H**), 7.65-7.60 (1H, m, Ar**H**), 7.43-7.32 (7H, m, Ar**H**), 7.22-7.19 (5H, m, Ar**H**), 4.69-4.60 (2H, m, C$\mathbf{H}_a$$H_b$$CF_3$ and OC$\mathbf{H}_a$$H_b$C), 4.53-4.42 (2H, m, $CH_a\mathbf{H}_b CF_3$ and $OCH_a\mathbf{H}_b C$), 3.69 (1H, dd, J = 14.6, 0.8 Hz, =CC$\mathbf{H}_a$$H_b$), 3.52 (1H, dd, J = 14.6, 1.9 Hz, =$CCH_a\mathbf{H}_b$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 191.3 (C), 168.8 (C), 141.6 (C), 137.5 (C), 136.6 (C), 134.7 (CH), 130.8 (CH), 130.0 (C), 129.3 (C), 129.2 (2 × CH), 128.8 (2 x CH), 128.7 (CH), 128.5 (CH), 128.3 (2 x CH), 127.9 (CH), 127.77 (CH), 127.75 (2 x CH), 124.5 (CH), 122.8 (q, $J_{C\text{-}F}$ = 277.4 Hz, C), 83.9 (C), 69.2 (CH_2), 61.1 (q, $J_{C\text{-}F}$ = 37.4 Hz, CH_2), 36.5 (CH_2); ^{19}F NMR (376 MHz, $CDCl_3$) δ –73.5 (t, J = 8.3 Hz, 3 × F); HRMS (ESI) Exact mass calculated for $[C_{27}H_{21}F_3NaO_4]^+$ $[M+Na]^+$: 489.1284, found 489.1287.



2,2,2-Trifluoroethyl (*E*)-4-benzylidene-1-oxo-2-(thiophen-3-ylmethoxy)-1,2,3,4-tetrahydronaphthalene-2-carboxylate (201r). The title compound was prepared according to a slight modification of General Procedure B (in that 2.0 equivalents of boronic acid and 10 mol% catalyst loading was used), using malonate ester **196** (148.3 mg, 0.30 mmol) and phenylboronic acid (73.2 mg, 0.60 mmol) which was purified by column chromatography (0% to 2% EtOAc/*n*-pentane) to give a pale-yellow oil (47.4 mg, 33%). R_f = 0.28 (10% EtOAc/petroleum ether); IR 2924, 1766 (C=O), 1684 (C=O), 1596, 1282, 1162, 1070, 908, 731, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.04 (1H, dd, J = 7.9, 1.5 Hz, Ar**H**), 7.78 (1H, d, J = 8.1 Hz, Ar**H**), 7.65-7.61 (1H, m, Ar**H**), 7.44-7.30 (7H, m, Ar**H**), 7.15 (1H, dd,

J = 5.0, 3.0 Hz, Ar**H**), 7.06 (1H, m, Ar**H**), 6.93 (1H, dd, J = 4.9, 1,2 Hz, Ar**H**), 4.71 (1H, d, *J* = 11.2 Hz, OC**H**$_a$H$_b$), 4.64 (1H, dq, *J* = 12.5, 8.3 Hz, **H**$_a$H$_b$CF$_3$), 4.55 (1H, d, *J* = 11.2, OCH$_a$**H**$_b$), 4.46 (1H, dq, *J* = 12.5, 8.3 Hz, H$_a$**H**$_b$CF$_3$) 3.67 (1H, dd, *J* = 14.7, 0.8 Hz, =CC**H**$_a$H$_b$), 3.51 (1H, dd, *J* = 14.7, 1.9 Hz, =CCH$_a$**H**$_b$); ^{13}C NMR (101 MHz, CDCl$_3$) δ 191.3 (C), 168.8 (C), 141.5 (C), 138.5 (C), 136.5 (C), 134.7 (CH), 130.7 (CH), 129.9 (C), 129.3 (C), 129.2 (2 × CH), 128.8 (2 × CH), 128.7 (CH), 128.4 (CH), 127.9 (CH), 127.3 (CH), 125.6 (CH), 124.5 (CH), 122.9 (CH), 122.7 (q, $J_{C\text{-}F}$ = 277.3 Hz, C), 83.8 (CH$_2$), 65.0 (C), 61.1 (q, $J_{C\text{-}F}$ = 37.0 Hz, CH$_2$), 36.5 (CH$_2$); ^{19}F NMR (376 MHz, CDCl$_3$) δ –73.5 (t, *J* = 8.3 Hz, 3 × F); HRMS (ESI) Exact mass calculated for [C$_{25}$H$_{23}$F$_3$NSO$_4$]$^+$ [M+H$_4$N]$^+$: 490.1294, found 490.1295.

2,2,2-Trifluoroethyl (*E*)-4-benzylidene-2-(methyl(p-tolyl)amino)-1-oxo-1,2,3,4-tetrahydronaphthalene-2-carboxylate (202) and 2,2,2-trifluoroethyl (*E*)-4-(2-((l3-oxidaneyl)carbonyl)phenyl)-2-(methyl(p-tolyl)amino)-5-phenylpent-4-enoate compound with 1,1,1-trifluoro-2l1-ethane (1:1) (203)

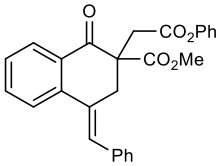


The title compounds were prepared according to a slight modification of General Procedure B (in that 2.0 equivalents of boronic acid and 10 mol% catalyst loading was used), using malonate ester **197** (150.4 mg, 0.30 mmol) and phenylboronic acid (73.2 mg, 0.60 mmol) which was purified by column chromatography (0% to 2% EtOAc/*n*-pentane) to give *bicycle product* **202** (67.2 mg, 47%) as a yellow oil and *product* **203** (55.7 mg, 32%) as an orange oil.

2,2,2-Trifluoroethyl (*E*)-4-benzylidene-2-(methyl(p-tolyl)amino)-1-oxo-1,2,3,4-tetrahydronaphthalene-2-carboxylate (202). R$_f$ = 0.37 (20% EtOAc/petroleum ether); IR 2922, 1749 (C=O), 1688 (C=O), 1513, 1280, 1161, 1062, 908, 732, 698 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.99-7.96 (1H, m, Ar**H**), 7.74 (1H, d, *J* = 8.0 Hz, Ar**H**), 7.59 (1H, ddd, *J* = 8.0, 7.2, 1.5 Hz, Ar**H**), 7.43-7.39 (2H, m, Ar**H**), 7.25-7.19 (3H, m, Ar**H**), 6.96-6.92 (2H, m, Ar**H**), 6.71-6.67 (2H, m, Ar**H**), 6.61-6.58 (2H, m, Ar**H**), 4.71-4.51 (2H, m, C**H**$_2$CF$_3$) 3.91 (1H, d, *J* =

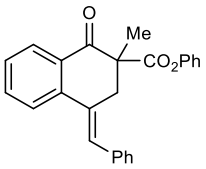
15.3 Hz, =CC**H**$_a$H$_b$), 3.47 (1H, dd, *J* = 15.3, 2.1 Hz, =CCH$_a$**H**$_b$), 2.84 (3H, s, CC**H**$_3$), 2.13 (3H, s, NC**H**$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 194.5 (C), 171.0 (C), 145.8 (C), 140.7 (C), 136.1 (C), 134.1 (CH), 132.2 (C), 130.1 (C), 129.8 (CH), 129.0 (2 × CH), 128.8 (2 × CH), 128.4 (CH), 128.4 (CH), 128.1 (2 × CH), 127.2 (CH), 124.0 (CH), 123.6 (2 × CH), 122.9 (q, $J_{C\text{-}F}$ = 277.3 Hz, C), 114.3 (C), 74.4 (C), 61.0 (q, $J_{C\text{-}F}$ = 37.0 Hz, CH_2), 40.8 (CH_3), 35.1 (CH_2), 20.8 (CH_3); ^{19}F NMR (376 MHz, $CDCl_3$) δ –73.3 (t, *J* = 8.4 Hz, 3 × F); HRMS (ESI) Exact mass calculated for $[C_{28}H_{25}F_3NO_3]^+$ $[M+H]^+$: 480.1781, found 480.1784.

2,2,2-trifluoroethyl (*E*)-4-(2-((l3-oxidaneyl)carbonyl)phenyl)-2-(methyl(p-tolyl)amino)-5-phenylpent-4-enoate compound with 1,1,1-trifluoro-2l1-ethane (1:1) (203). R_f = 0.32 (20% EtOAc/petroleum ether); IR 2923, 1751 (C=O), 1721 (C=O), 1518, 1282, 1156, 1110, 974, 805, 701 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37-7.29 (3H, m, Ar**H**), 7.25-7.20 (3H, m, Ar**H**), 7.13-7.09 (2H, m, Ar**H**), 7.05-7.03 (2H, m, Ar**H**), 7.01-6.97 (2H, m, Ar**H**), 6.71-6.67 (2H, m, Ar**H**), 4.91 (1H, dd, *J* = 10.3, 4.4 Hz, (O)CC**H**N), 4.50 (1H, dq, *J* = 12.7, 8.4 Hz, NCHCO$_2$C**H**$_a$H$_b$CF$_3$) 4.33 (1H, dq, *J* = 12.7, 8.4 Hz, NCHCO$_2$CH$_a$**H**$_b$CF$_3$), 4.15-3.95 (2H, m, CCO$_2$C**H**$_2$CF$_3$), 3.17 (1H, dd, *J* = 14.6, 10.4 Hz, =CC**H**$_a$H$_b$), 2.97 (1H, dd, *J* = 14.6, 4.4 Hz, =CCH$_a$**H**$_b$), 2.46 (3H, s, CC**H**$_3$), 2.27 (3H, s, NC**H**$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.3 (C), 168.6 (C), 153.1 (C), 147.5 (C), 142.0 (C), 140.3 (C), 129.7 (2 x CH), 129.1 (2 x CH), 128.6 (2 x CH), 128.33 (3 × CH), 128.25 (2 × CH), 128.2 (CH), 128.0 (C), 126.3 (C), 122.8 (q, $J_{C\text{-}F}$ = 277.5 Hz, C), 122.7 (q, $J_{C\text{-}F}$ = 277.7 Hz, C), 114.5 (2 x CH), 62.6 (CH), 60.6 (q, $J_{C\text{-}F}$ = 36.8 Hz, CH_2), 60.4 (q, $J_{C\text{-}F}$ = 36.8 Hz, CH_2), 33.3 (CH_3), 31.6 (CH_2), 20.4 (CH_3); ^{19}F NMR (376 MHz, $CDCl_3$) δ –73.5-(–73.6) (m, 6 × F); HRMS (ESI) Exact mass calculated for $[C_{30}H_{28}F_6NO_4]^+$ $[M+H]^+$: 580.1923, found 580.1931.

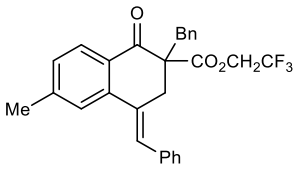


Methyl (*E*)-4-benzylidene-1-oxo-2-(2-oxo-2-phenoxyethyl)-1,2,3,4-tetrahydronaphthalene-2-carboxylate (170e). The title compound was prepared according to General Procedure B, using malonate ester **200a** (114.1 mg, 0.30 mmol) and phenylboronic acid (54.9 mg, 0.45 mmol) which was purified by column chromatography (0% to 7.5% EtOAc/*n*-pentane) to give a white solid (91.2 mg, 71%). R_f = 0.38 (20% EtOAc/petroleum ether); m.p. 136-137 °C (Et_2O); IR 2938, 1756 (C=O), 1685 (C=O), 1593, 1280, 1224, 1156, 1064, 973, 698 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (1H, dd, *J* = 8.0, 1.3 Hz, Ar**H**), 7.73 (1H, dd, *J* = 8.0, 1.1 Hz, Ar**H**), 7.60 (1H, ddd, *J* = 8.0, 7.3, 1.5 Hz, Ar**H**), 7.45-7.29 (9H, m, Ar**H**), 7.20-7.16 (1H, m, Ar**H**),

6.97-6.93 (2H, m, Ar**H**), 3.69 (1H, dd, *J* = 14.0, 0.9 Hz, =CC**H**$_a$H$_b$), 3.59 (3H, s, OC**H**$_3$), 3.38 (1H, dd, *J* = 14.0, 1.6 Hz, =CCH$_a$**H**$_b$), 3.18 (1H, d, *J* = 16.6 Hz, CC**H**$_a$H$_b$CO$_2$Ph), 3.06 (1H, d, *J* = 16.6 Hz, CCH$_a$**H**$_b$CO$_2$Ph); ^{13}C NMR (101 MHz, CDCl$_3$) δ 194.0 (C), 171.1 (C), 169.1 (C), 150.6 (C), 141.8 (C), 136.7 (C), 134.3 (CH), 131.7 (C), 130.4 (C), 130.1 (C), 129.4 (2 × CH), 129.1 (2 × CH), 128.7 (2 × CH), 128.6 (CH), 128.3 (CH), 127.8 (CH), 125.9 (CH), 124.7 (CH), 121.6 (2 × CH), 57.2 (C), 52.8 (CH$_3$), 38.5 (CH$_2$), 35.9 (CH$_2$); HRMS (ESI) Exact mass calculated for [C$_{27}$H$_{23}$O$_5$]$^+$ [M+H]$^+$: 427.1540, found 427.1541.

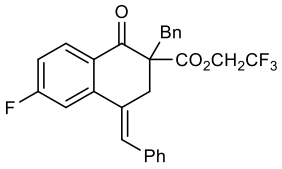


Phenyl (*E*)-4-benzylidene-2-methyl-1-oxo-1,2,3,4-tetrahydronaphthalene-2-carboxylate (170f). The title compound was prepared according to General Procedure B, using malonate ester **198** (115.3 mg, 0.30 mmol) and phenylboronic acid (54.9 mg, 0.45 mmol) which was purified by column chromatography (0% to 1.5% EtOAc/*n*-pentane) to give a white solid (60.5 mg, 55%). R$_f$ = 0.32 (10% EtOAc/petroleum ether); m.p. 95-96 °C (Et$_2$O); IR 2968, 1758 (C=O), 1682 (C=O), 1514, 1412, 1282, 1156, 974, 808, 758 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.15 (1H, dd, *J* = 7.9, 1.4 Hz, Ar**H**), 7.78 (1H, dd, *J* = 8.0, 1.3 Hz, Ar**H**), 7.62 (1H, ddd, *J* = 8.0, 7.2, 1.5 Hz, Ar**H**), 7.47-7.28 (9H, m, Ar**H**), 7.20-716 (1H, m, Ar**H**), 6.97-6.94 (2H, m, Ar**H**), 3.77 (1H, dd, *J* = 14.0, 1.5 Hz, =CC**H**$_a$H$_b$), 3.15 (1H, dd, *J* = 14.0, 1.3 Hz, =CCH$_a$**H**$_b$), 1.57 (3H, s, C**H**$_3$); ^{13}C NMR (101 MHz, CDCl$_3$) δ 195.7 (C), 171.2 (C), 150.7 (C), 141.6 (C), 136.8 (C), 134.3 (CH), 131.8 (C), 130.0 (C), 129.9 (CH), 129.4 (2 × CH), 129.3 (2 × CH), 128.7 (2 × CH), 128.6 (CH), 128.3 (CH), 127.8 (CH), 126.0 (CH), 124.7 (CH), 121.5 (2 × CH), 55.4 (C), 37.7 (CH$_2$), 20.1 (CH$_3$); HRMS (ESI) Exact mass calculated for [C$_{25}$H$_{21}$O$_3$]$^+$ [M+H]$^+$: 369.1485, found 369.1484.

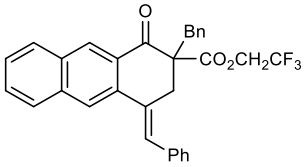


2,2,2-Trifluoroethyl (*E*)-2-benzyl-4-benzylidene-6-methyl-1-oxo-1,2,3,4-tetrahydronaphthalene-2-carboxylate (221a). The title compound was prepared according to General Procedure B, using malonate ester **182d** (141.7 mg, 0.30 mmol) and 4-methylboronic acid (61.2 mg, 0.45 mmol) which was purified by column chromatography (0% to 1% EtOAc/*n*-pentane) to give a yellow oil (110.4 mg, 79%). R$_f$ = 0.32 (10% EtOAc/petroleum ether); IR 2924, 1751 (C=O), 1686 (C=O), 1495, 1280, 1158, 963, 732, 698, 513 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.92 (1H, dd, *J* = 2.0, 0.9 Hz, Ar**H**), 7.66 (1H, d, *J* = 8.1 Hz, Ar**H**), 7.42-

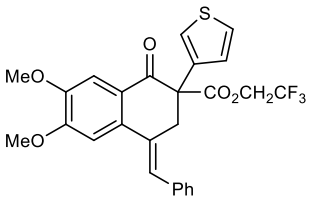
7.38 (3H, m, Ar**H**), 7.35-7.28 (4H, m, Ar**H**), 7.14-7.07 (5H, m, Ar**H**), 4.46 (1H, dq, *J* = 12.6, 8.4 Hz, C**H**$_a$H$_b$CF$_3$), 4.27 (1H, dq, *J* = 12.6, 8.4 Hz, CH$_a$**H**$_b$CF$_3$), 3.62 (1H, dd, *J* = 14.6, 1.4 Hz, =CC**H**aH$_b$), 3.37 (1H, d, *J* = 13.7 Hz, CC**H**$_a$H$_b$CCH), 3.23 (1H, d, *J* = 13.7 Hz, CCH$_a$**H**$_b$CCH), 3.01 (1H, dd, *J* = 14.6, 1.6 Hz, =CCHa**H**$_b$), 2.42 (3H, s, C**H**$_3$); ^{13}C NMR (101 MHz, CDCl$_3$) δ 193.9 (C), 170.0 (C), 138.7 (C), 138.5 (C), 136.8 (C), 135.4 (C), 135.4 (CH), 131.0 (C), 130.8 (2 x CH), 130.0 (C), 129.2 (2 x CH), 128.9 (CH), 128.6 (2 x CH), 128.4 (CH), 128.2 (2 x CH), 127.6 (CH), 127.0 (CH), 124.4 (CH), 122.7 (q, J_{C-F} = 277.5 Hz, C), 61.0 (q, J_{C-F} = 37.0 Hz, CH$_2$), 60.3 (C), 38.8 (CH$_2$), 34.1 (CH$_2$), 21.2 (CH$_3$); ^{19}F NMR (376 MHz, CDCl$_3$) δ –73.5 (t, *J* = 8.3 Hz, 3 × F); HRMS (ESI) Exact mass calculated for [C$_{28}$H$_{24}$F$_3$O$_3$]$^+$ [M+H]$^+$: 465.1675, found 465.1672.



2,2,2-Trifluoroethyl (*E*)-2-benzyl-4-benzylidene-6-fluoro-1-oxo-1,2,3,4-tetrahydronaphthalene-2-carboxylate (221b). The title compound was prepared according to General Procedure B, using malonate ester **182d** (141.7 mg, 0.30 mmol) and 4-fluorobenzeneboronic acid (63.0 mg, 0.45 mmol) which was purified by column chromatography (0% to 1% EtOAc/*n*-pentane) to give a yellow solid (95.1 mg, 68%). R_f = 0.31 (10% EtOAc/petroleum ether); m.p. 135-136 °C (Et$_2$O); IR 3022, 1743 (C=O), 1686 (C=O), 1493, 1270, 1156, 971, 824, 767, 700 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.78-7.72 (2H, m, Ar**H**), 7.43-7.39 (2H, m, Ar**H**), 7.35-7.29 (5H, m, Ar**H**), 7.15-7.10 (5H, m, Ar**H**), 4.48 (1H, dq, *J* = 12.6, 8.4 Hz, C**H**$_a$H$_b$CF$_3$), 4.23 (1H, dq, *J* = 12.6, 8.4 Hz, CH$_a$**H**$_b$CF$_3$), 3.63 (1H, dd, *J* = 14.6, 1.2 Hz, =CC**H**aH$_b$), 3.42 (1H, d, *J* = 13.7 Hz, CC**H**$_a$H$_b$CCH), 3.20 (1H, d, *J* = 13.7 Hz, CCH$_a$**H**$_b$CCH), 2.98 (1H, dd, *J* = 14.6, 1.5 Hz, =CCHa**H**$_b$); ^{13}C NMR (101 MHz, CDCl$_3$) δ 192.6 (C), 169.7 (C), 162.8 (d, J_{C-F} = 250.2 Hz, C), 137.5 (d, J_{C-F} = 3.3 Hz, C), 136.5 (C), 135.2 (CH), 132.0 (d, J_{C-F} = 6.4 Hz, C), 130.8 (2 × CH), 130.1 (C), 129.8 (d, J_{C-F} = 1.5 Hz, C), 129.2 (2 × CH), 128.7 (2 × CH), 128.3 (2 x CH), 127.9 (CH), 127.1 (CH), 126.9 (d, J_{C-F} = 7.3 Hz, CH), 122.6 (q, J_{C-F} = 277.4 Hz, C), 121.9 (d, J_{C-F} = 22.6 Hz, CH), 114.1 (d, J_{C-F} = 22.5 Hz, CH), 61.0 (q, J_{C-F} = 37.1 Hz, CH$_2$), 60.0 (C), 38.8 (CH$_2$), 34.2 (CH$_2$); ^{19}F NMR (376 MHz, CDCl$_3$) δ –73.6 (t, *J* = 8.3 Hz, 3 × F), –112.1 (td, *J* = 8.3, 5.0 Hz, 1 x F); HRMS (ESI) Exact mass calculated for [C$_{27}$H$_{24}$F$_4$NO$_3$]$^+$ [M+H$_4$N]$^+$: 486.1687, found 486.1684.

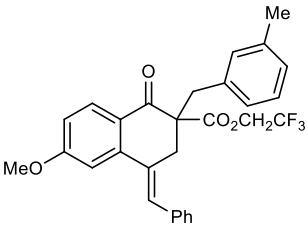


2,2,2-Trifluoroethyl (*E*)-2-benzyl-4-benzylidene-1-oxo-1,2,3,4-tetrahydroanthracene-2-carboxylate (221c). The title compound was prepared according to General Procedure B, using malonate ester **182d** (141.7 mg, 0.30 mmol) and 2-naphthylboronic acid (77.4 mg, 0.45 mmol) which was purified by column chromatography (0% to 1% EtOAc/*n*-pentane) to give a yellow oil (84.5 mg, 56%). R_f = 0.33 (10% EtOAc/petroleum ether); IR 2924, 1749 (C=O), 1687 (C=O), 1586, 1443, 1281, 1156, 972, 734, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.70 (1H, s, Ar**H**), 8.16 (1H, s, Ar**H**), 7.98 (1H, dd, *J* = 8.3, 1.2 Hz, Ar**H**), 7.89 (1H, dd, *J* = 8.3, 1.1 Hz, Ar**H**), 7.60 (1H, ddd, *J* = 8.2, 6.8, 1.3 Hz, Ar**H**), 7.54-7.50 (2H, m, Ar**H**), 7.45-7.41 (2H, m, Ar**H**), 7.39-7.33 (3H, m, Ar**H**), 7.17-7.11 (5H, m, Ar**H**), 4.49 (1H, dq, *J* = 12.6, 8.4 Hz, C**H**$_a$H$_b$CF$_3$), 4.23 (1H, dq, *J* = 12.6, 8.4 Hz, CH$_a$**H**$_b$CF$_3$), 3.70 (1H, dd, *J* = 14.4, 1.3 Hz, =CC**H**aH$_b$), 3.49 (1H, d, *J* = 13.8 Hz, CC**H**$_a$H$_b$CCH), 3.26 (1H, d, *J* = 13.8 Hz, CCH$_a$**H**$_b$CCH), 3.09 (1H, dd, *J* = 14.4, 1.6 Hz, =CCHa**H**$_b$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 193.9 (C), 170.1 (C), 136.9 (2 x C), 136.3 (C), 135.4 (C), 132.6 (C), 131.4 (C), 130.9 (2 x CH), 130.3 (CH), 130.0 (CH), 129.3 (2 × CH), 129.3 (CH), 129.2 (CH), 128.7 (2 x CH), 128.5 (C), 128.2 (2 x CH), 128.1 (CH), 127.7 (CH), 127.0 (2 x CH), 123.5 (CH), 122.7 (q, J_{C-F} = 277.4 Hz, C), 61.0 (q, J_{C-F} = 37.1 Hz, CH_2), 60.7 (C), 38.8 (CH_2), 34.1 (CH_2); ^{19}F NMR (376 MHz, $CDCl_3$) δ –73.5 (t, *J* = 8.3 Hz, 3 × F); HRMS (ESI) Exact mass calculated for $[C_{31}H_{24}F_3O_3]^+$ $[M+H]^+$: 501.1672, found 501.1670.

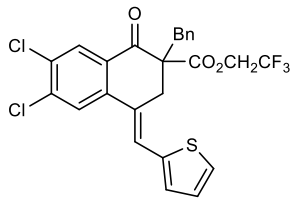


2,2,2-Trifluoroethyl (*E*)-4-benzylidene-6,7-dimethoxy-1-oxo-2-(3-thienyl)-1,2,3,4-tetrahydronaphthalene-2-carboxylate (221d). The title compound was prepared according to General Procedure B, using malonate ester **187** (139.3 mg, 0.30 mmol) and 3,4-dimethoxyphenylboronic acid (81.9 mg, 0.45 mmol) which was purified by column chromatography (0% to 10% EtOAc/*n*-pentane) to give a yellow oil (74.6 mg, 50%). R_f = 0.29 (10% EtOAc/petroleum ether); IR 2941, 1737 (C=O), 1668 (C=O), 1594, 1509, 1241, 1209, 1154, 763, 729 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.58 (1H, s, Ar**H**), 7.48-7.43 (2H, m, Ar**H**), 7.38-7.32 (3H, m, Ar**H**), 7.17-7.14 (2H, m, Ar**H**), 7.06 (1H, s, Ar**H**), 6.87 (1H, dd, *J* = 2.9, 1.4 Hz, Ar**H**), 6.77 (1H, dd, *J* = 5.1, 1.4 Hz, Ar**H**), 4.58 (1H, dq, *J* = 12.7, 8.4 Hz, C**H**$_a$H$_b$CF$_3$), 4.39 (1H, dq, *J* = 12.7, 8.4 Hz, CH$_a$**H**$_b$CF$_3$), 3.98 (3H, s, OC**H**$_3$), 3.96 (3H, s, OC**H**3), 3.82-3.81 (2H, m, =CC**H**$_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 191.3 (C), 169.8 (C), 154.5 (C), 150.0 (C), 136.8 (C), 136.2 (C), 134.8 (C), 131.3 (C), 129.1 (2 x CH), 129.0 (CH), 128.9 (2 × CH),

127.9 (CH), 127.6 (CH), 125.2 (CH), 123.7 (CH), 123.2 (C), 122.8 (q, $J_{C\text{-}F}$ = 277.4 Hz, C), 109.2 (CH), 106.1 (CH), 61.3 (q, $J_{C\text{-}F}$ = 36.8 Hz, CH_2), 61.2 (C), 56.3 (2 x CH_3), 36.1 (CH_2); ^{19}F NMR (376 MHz, $CDCl_3$) δ –73.6 (t, *J* = 8.3 Hz, 3 × F); HRMS (ESI) Exact mass calculated for $[C_{26}H_{22}F_3O_5S]^+$ $[M+H]^+$: 503.1135, found 503.1135.

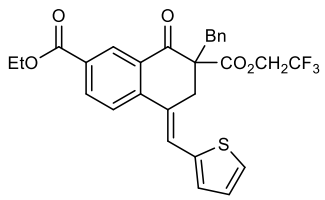


2,2,2-Trifluoroethyl (*E*)-4-benzylidene-7-methoxy-2-(3-methylbenzyl)-1-oxo-1,2,3,4-tetrahydronaphthalene-2-carboxylate (221g). The title compound was prepared according to General Procedure B, using malonate ester **189** (145.9 mg, 0.30 mmol) and 4-Methoxyphenylboronic acid (68.4 mg, 0.45 mmol) which was purified by column chromatography (0% to 1.5% EtOAc/*n*-pentane) to give a colourless oil (114.2 mg, 77%). R_f = 0.32 (10% EtOAc/petroleum ether); IR 2928, 1749 (C=O), 1684 (C=O), 1603, 1281, 1158, 972, 875, 760, 698 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (1H, d, *J* = 8.9 Hz, Ar**H**), 7.54 (1H, d, *J* = 2.9 Hz, Ar**H**), 7.40-7.36 (2H, m, Ar**H**), 7.33-7.27 (4H, m, Ar**H**), 7.16 (1H, dd, *J* = 8.8, 2.9 Hz, Ar**H**), 6.99-6.86 (4H, m, Ar**H**), 4.44 (1H, dq, *J* = 12.6, 8.4 Hz, C**H**$_a$H$_b$CF$_3$), 4.27 (1H, dq, *J* = 12.7, 8.4 Hz, CH$_a$**H**$_b$CF$_3$), 3.89 (3H, s, OC**H**$_3$), 3.62 (1H, dd, *J* = 14.8, 1.4 Hz, =CC**H**$_a$H$_b$), 3.30 (1H, d, *J* = 13.7 Hz, CC**H**$_a$H$_b$CC), 3.20 (1H, d, *J* = 13.7 Hz, CCH$_a$**H**$_b$CC), 3.03 (1H, dd, *J* = 14.7, 1.5 Hz, =CCH$_a$**H**$_b$), 2.17 (3H, s, C**H**$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 193.8 (C), 170.0 (C), 160.0 (C), 137.8 (C), 136.9 (C), 135.3 (C), 134.2 (C), 131.5 (CH), 131.3 (C), 130.6 (C), 129.3 (2 x CH), 128.6 (2 x CH), 128.1 (CH), 128.0 (CH), 127.9 (CH), 127.8 (CH), 127.5 (CH), 126.1 (CH), 123.0 (CH), 122.6 (q, $J_{C\text{-}F}$ = 277.8 Hz, C), 109.7 (CH), 60.9 (q, $J_{C\text{-}F}$ = 36.4 Hz, CH_2), 60.2 (C), 55.8 (CH_3), 38.8 (CH_2), 34.2 (CH_2), 21.4 (CH_3); ^{19}F NMR (376 MHz, $CDCl_3$) δ –73.5 (t, *J* = 8.3 Hz, 3 × F); HRMS (ESI) Exact mass calculated for $[C_{29}H_{26}F_3O_4]^+$ $[M+H]^+$: 495.1778, found 495.1779.



2,2,2-Trifluoroethyl (*E*)-2-benzyl-6,7-dichloro-1-oxo-4-(thiophen-2-ylmethylene)-1,2,3,4-tetrahydronaphthalene-2-carboxylate (221h). The title compound was prepared according to General Procedure A, using malonate ester **186c** (143.5 mg, 0.30 mmol) and 3,4-dichlorophenylboronic acid (96.5 mg, 0.45 mmol) which was purified by column chromatography (0% to 1% EtOAc/*n*-pentane) followed by a preparative TLC (8% EtOAc/*n*-pentane) to give a yellow oil (80.4 mg, 51%). R_f = 0.32 (10% EtOAc/petroleum

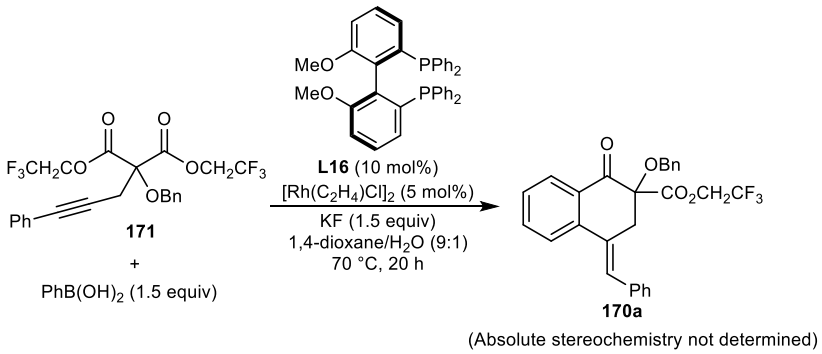
ether); IR 2927, 1749 (C=O), 1691 (C=O), 1579, 1455, 1282, 1160, 907, 732, 700 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 (1H, s, Ar**H**), 7.79 (1H, s, Ar**H**), 7.40 (1H, dd, *J* = 5.1, 1.2 Hz, Ar**H**), 7.37 (1H, s, **H**C=C), 7.21-7.17 (6H, m, Ar**H**), 7.08 (1H, dd, *J* = 5.1, 3.6 Hz, Ar**H**), 4.43 (1H, dq, *J* = 12.6, 8.4 Hz, C**H**$_a$H$_b$CF$_3$), 4.28 (1H, dq, *J* = 12.6, 8.4 Hz, CH$_a$**H**$_b$CF$_3$), 3.81 (1H, dd, *J* = 15.0, 1.2 Hz, =CC**H**aH$_b$), 3.43 (1H, d, *J* = 13.8 Hz, CC**H**$_a$H$_b$CCH), 3.35 (1H, d, *J* = 13.8 Hz, CCH$_a$**H**$_b$CCH), 2.94 (1H, dd, *J* = 15.0, 1.7 Hz, =CCHa**H**$_b$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 191.6 (C), 169.3 (C), 140.4 (C), 139.0 (C), 139.0 (C), 135.0 (C), 132.8 (C), 130.9 (CH), 130.8 (2 x CH), 130.1 (CH), 129.5 (C), 128.5 (2 x CH), 127.7 (CH), 127.5 (CH), 127.4 (CH), 126.4 (C), 125.9 (CH), 123.6 (CH), 122.5 (q, $J_{C\text{-}F}$ = 277.4 Hz, C), 61.1 (q, $J_{C\text{-}F}$ = 37.1 Hz, CH_2), 59.7 (C), 39.2 (CH_2), 34.2 (CH_2); ^{19}F NMR (376 MHz, $CDCl_3$) δ –73.6 (t, *J* = 8.3 Hz, 3 × F); HRMS (ESI) Exact mass calculated for $[C_{25}H_{21}Cl_2F_3NO_3S]^+$ $[M+H_4N]^+$: 542.0566, found 542.0557.



7-ethyl 2-(2,2,2-trifluoroethyl) (E)-2-benzyl-1-oxo-4-(thiophen-2-ylmethylene)-1,2,3,4-tetrahydronaphthalene-2,7-dicarboxylate (221i). The title compound was prepared according to General Procedure A, using malonate ester **186c** (143.5 mg, 0.30 mmol) and 3-ethoxycarbonylphenylboronic acid (87.3 mg, 0.45 mmol) which was purified by column chromatography (0% to 2.5% EtOAc/*n*-pentane) to give a yellow solid (88.9 mg, 56%). R_f = 0.24 (10% EtOAc/petroleum ether); m.p. 117-118 °C (Et_2O); IR 2938, 1754 (C=O), 1724 (C=O), 1695 (C=O), 1433, 1272, 1253, 1052, 771, 690 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.41 (1H, d, *J* = 1.5 Hz, Ar**H**), 8.11 (1H, dd, *J* = 8.2, 0.5 Hz, Ar**H**), 7.98 (1H, dd, *J* = 8.2, 1.5 Hz, Ar**H**), 7.55 (1H, s, **H**C=C), 7.39 (1H, dd, *J* = 5.1, 1.1 Hz, Ar**H**), 7.22-7.17 (6H, m, Ar**H**), 7.08 (1H, dd, *J* = 5.1, 3.6 Hz, Ar**H**), 4.48-4.38 (3H, m, C**H**$_a$H$_b$CF$_3$ and OC**H**$_2$), 4.32-4.22 (1H, m, CH$_a$**H**$_b$CF3), 3.83 (1H, dd, *J* = 15.1, 1.2 Hz, =CC**H**$_a$H$_b$), 3.40 (2H, m, CC**H**$_2$CCH), 3.00 (1H, dd, *J* = 15.1, 1.7 Hz, =CCH$_a$**H**$_b$), 1.43 (3H, t, *J* = 7.1 Hz, CH$_2$C**H**$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 193.2 (C), 169.5 (C), 165.8 (C), 140.9 (C), 139.4 (C), 135.3 (C), 135.2 (C), 132.8 (C), 130.8 (2 x CH), 130.6 (CH), 128.7 (CH), 128.5 (CH), 128.4 (2 x CH), 127.5 (C), 127.4 (CH), 127.3 (2 x CH), 125.5 (CH), 123.2 (CH), 122.6 (q, $J_{C\text{-}F}$ = 277.4 Hz, C), 61.9 (CH_2), 61.1 (q, $J_{C\text{-}F}$ = 37.0 Hz, CH_2), 60.0 (C), 39.2 (CH_2), 34.3 (CH_2), 14.4 (CH_3); ^{19}F NMR (376 MHz, $CDCl_3$) δ –73.6 (t, *J* = 8.3 Hz, 3 × F); HRMS (ESI) Exact mass calculated for $[C_{28}H_{27}F_3NO_5S]^+$ $[M+H_4N]^+$: 546.1557, found 546.1547.

3.4 Enantioselective Rhodium-Catalysed Desymmetrisation of Malonate Esters

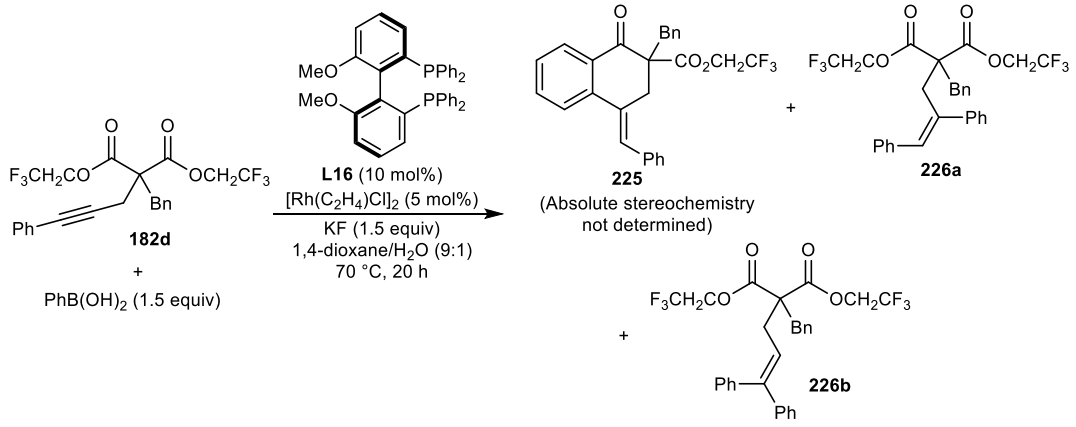
2,2,2-Trifluoroethyl (*E*)-4-benzylidene-2-(benzyloxy)-1-oxo-1,2,3,4-tetrahydronaphthalene-2-carboxylate (170a)



An oven-dried microwave vial was fitted with a stirrer bar and charged with $[Rh(C_2H_4)_2Cl]_2$ (7.8 mg, 0.02 mmol) and **L16** (23.3 mg, 0.04 mmol). The vial was sealed with a septum-lined cap and purged with argon for 30 mins. Anhydrous 1,4-dioxane (2.7 mL) and water (0.3 mL) both of which were freshly deoxygenated separately (purging with argon for 30 mins) were added. The mixture was stirred at room temperature for 30 mins. Meanwhile, a separate oven-dried microwave vial was fitted with a stirrer bar and charged with malonic ester **171** (195.4 mg, 0.4 mmol), phenylboronic acid (73.2 mg, 0.60 mmol) and KF (34.9 mg, 0.60 mmol). The vial was sealed with a septum-lined cap and purged with argon for 30 mins. Deoxygenated anhydrous 1,4-dioxane (0.9 mL), deoxygenated water (0.1 mL) and the solution of catalyst (see above) were added. The mixture was stirred at 70 °C for 20 h. The reaction was cooled to room temperature, water (20 mL) was added and the mixture was extracted with EtOAc (3 × 20 mL). The combined organic phases were washed with brine (25 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by column chromatography using EtOAc/*n*-pentane (0% to 5% EtOAc/*n*-pentane) to give the titled compound (**170a**) (130.1 mg, 70%) as a yellow oil. R_f = 0.28 (10% EtOAc/petroleum ether); IR 2954, 1762 (C=O), 1691 (C=O), 1433, 1282, 1157, 1052, 972, 752, 699 cm^{-1}; $[\alpha]_D^{23}$ +16.0 (*c* 1.00, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 8.04 (1H, dd, *J* = 7.9, 1.6 Hz, Ar**H**), 7.78 (1H, d, *J* = 8.1 Hz, Ar**H**), 7.63 (1H, ddd, *J* = 8.0, 7.2, 1.5 Hz, Ar**H**), 7.44-7.32 (7H, m, Ar**H**), 7.23-7.19 (5H, m, Ar**H**), 4.70-4.61 (2H, m, C**H**$_a$H$_b$CF$_3$ and OC**H**$_a$H$_b$C), 4.53-4.42 (2H, m, CH$_a$**H**$_b$CF$_3$ and OCH$_a$**H**$_b$C), 3.69 (1H, dd, *J* = 14.7, 0.8 Hz, =CC**H**$_a$H$_b$), 3.52 (1H, dd, *J* = 14.7, 1.9 Hz, =CCH$_a$**H**$_b$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 191.3 (C), 168.8 (C), 141.6 (C), 137.5 (C), 136.6 (C), 134.7 (CH), 130.8 (CH), 130.0 (C), 129.3 (C), 129.2 (2 × CH), 128.8 (2 x CH), 128.7

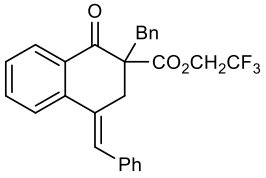
(CH), 128.5 (CH), 128.3 (2 x CH), 127.9 (CH), 127.77 (CH), 127.75 (2 x CH), 124.5 (CH), 122.8 (q, $J_{C\text{-}F}$ = 277.8 Hz, C), 83.9 (C), 69.2 (CH_2), 61.1 (q, $J_{C\text{-}F}$ = 37.3 Hz, CH_2), 36.5 (CH_2); ^{19}F NMR (376 MHz, $CDCl_3$) δ –73.5 (t, J = 8.3 Hz, 3 × F); HRMS (ESI) Exact mass calculated for $[C_{27}H_{22}F_3O_4]^+$ $[M+H]^+$: 467.1465, found 465.1466. Enantiomeric excess was determined by HPLC using a Chiralpak AD-H column (95:5 *iso*-hexane:*i*-PrOH, 1.0 mL/min, 254 nm, 25 °C); t_r (minor) = 12.9 min, t_r (major) = 14.9 min, 65% ee.

2,2,2-Trifluoroethyl (*E*)-2-benzyl-4-benzylidene-1-oxo-1,2,3,4-tetrahydronaphthalene-2-carboxylate (225)

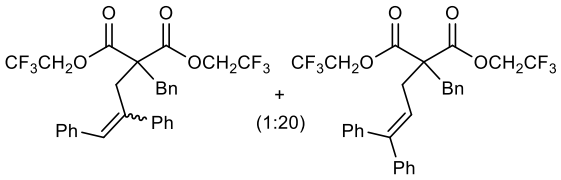


An oven-dried microwave vial was fitted with a stirrer bar and charged with $[Rh(C_2H_4)_2Cl]_2$ (5.8 mg, 0.015 mmol) and **L16** (17.5 mg, 0.03 mmol). The vial was sealed with a septum-lined cap and purged with argon for 30 mins. Anhydrous 1,4-dioxane (1.8 mL) and water (0.2 mL) both of which were freshly deoxygenated separately (purging with argon for 30 mins) were added. The mixture was stirred at room temperature for 30 mins. Meanwhile, a separate oven-dried microwave vial was fitted with a stirrer bar and charged with malonic ester **182d** (141.7 mg, 0.3 mmol), phenylboronic acid (54.9 mg, 0.45 mmol) and KF (26.1 mg, 0.45 mmol). The vial was sealed with a septum-lined cap and purged with argon for 30 mins. Deoxygenated anhydrous 1,4-dioxane (0.9 mL), deoxygenated water (0.1 mL) and the solution of catalyst (see above) were added. The mixture was stirred at 70 °C for 20 h. The reaction was cooled to room temperature, water (15 mL) was added and the mixture was extracted with EtOAc (3 × 15 mL). The combined organic phases were washed with brine (20 mL), dried ($MgSO_4$), filtered and concentrated in *vacuo*. The residue was purified by column chromatography using EtOAc/*n*-pentane (0% to 1.5% EtOAc/*n*-pentane) to give the *arylative cyclization product* **225** (114.6

mg, 85%) as a yellow oil and the mixture of inseparable *hydro-arylative products* **226a** and **226b** (20.9 mg, 13%, (**226a**:**226b** 1:20) as a yellow oil.



2,2,2-Trifluoroethyl (*E*)-2-benzyl-4-benzylidene-1-oxo-1,2,3,4-tetrahydronaphthalene-2-carboxylate (225). R_f = 0.31 (10% EtOAc/petroleum ether); IR 3029, 1748 (C=O), 1685 (C=O), 1595, 1276, 1156, 1081, 760, 729, 698 cm^{-1}; $[\alpha]_D^{25}$ +36.0 (*c* 1.00, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 8.13 (1H, dd, *J* = 7.9, 1.4 Hz, Ar**H**), 7.77 (1H, dd, *J* = 8.0, 1.1 Hz, Ar**H**), 7.60 (1H, ddd, *J* = 8.3, 7.2, 1.5 Hz, Ar**H**), 7.45-7.40 (4H, m, Ar**H**), 7.36-7.31 (3H, m, Ar**H**), 7.16-7.08 (5H, m, Ar**H**), 4.48 (1H, dq, *J* = 12.6, 8.4 Hz, C**H**$_a$H$_b$CF$_3$), 4.26 (1H, dq, *J* = 12.6, 8.4 Hz, CH$_a$**H**$_b$CF$_3$), 3.65 (1H, dd, *J* = 14.6, 1.4 Hz, =CC**H**aH$_b$), 3.40 (1H, d, *J* = 13.7 Hz, CC**H**$_a$H$_b$CCH), 3.25 (1H, d, *J* = 13.7 Hz, CCH$_a$**H**$_b$CCH), 3.04 (1H, dd, *J* = 14.6, 1.6 Hz, =CCHa**H**$_b$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 193.6 (C), 169.9 (C), 141.1 (C), 136.7 (C), 135.4 (C), 134.3 (CH), 131.0 (C), 130.8 (2 × CH), 130.2 (C), 129.8 (CH), 129.2 (2 × CH), 128.6 (2 × CH), 128.6 (CH), 128.4 (CH), 128.2 (2 × CH), 127.8 (CH), 127.0 (CH), 124.5 (CH), 122.7 (q, $J_{C\text{-}F}$ = 277.4 Hz, C), 61.0 (q, $J_{C\text{-}F}$ = 36.9 Hz, CH_2), 60.3 (C), 38.8 (CH_2), 34.0 (CH_2); ^{19}F NMR (376 MHz, $CDCl_3$) δ –73.5 (t, *J* = 8.4 Hz, 3 × F); HRMS (ESI) Exact mass calculated for $[C_{27}H_{22}F_3O_3]^+$ $[M+H]^+$: 451.1516, found 451.1517. Enantiomeric excess was determined by HPLC using a Chiralpak AD-H column (95:5 *iso*-hexane:*i*-PrOH, 1.0 mL/min, 254 nm, 25 °C); t_r (minor) = 8.9 min, t_r (major) = 16.3 min, 76% ee.



Bis(2,2,2-trifluoroethyl) 2-benzyl-2-(3,3-diphenylallyl)malonate (226a) and bis(2,2,2-trifluoroethyl) 2-benzyl-2-(2,3-diphenylallyl)malonate (226b). R_f = 0.39 (10% EtOAc/petroleum ether); IR 3030, 1752 (C=O), 1411, 1281, 1159, 1084, 975, 759, 699, 650 cm^{-1}; ^{19}F NMR (376 MHz, $CDCl_3$) δ –73.6 (t, *J* = 8.2 Hz, 6 × F); HRMS (ESI) Exact mass calculated for $[C_{29}H_{28}F_6NO_4]^+$ $[M+H_4N]^+$: 568.1917, found 568.1919.

*Data for major regioisomer **226a***: ^1H NMR (400 MHz, $CDCl_3$) 7.41-7.28 (6H, m, Ar**H**), 7.24-7.13 (7H, m, Ar**H**), 6.94-6.91 (2H, m, Ar**H**), 5.95 (1H, t, *J* = 7.2 Hz, **H**C=C), 4.56-4.34 (4H, m, 2 x C**H**$_2$CF$_3$), 3.33 (2H, s, CC**H**$_2$CCH), 2.84 (2H, d, *J* = 7.2 Hz, CC**H**$_2$CH); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.6 (2 x C), 146.5 (C), 142.6 (C), 139.2 (C), 134.5 (C), 130.0 (2 x CH), 129.9 (2 x CH), 128.6 (2 x CH), 128.5 (2 x CH), 128.4 (2 × CH), 127.8 (4 x CH), 127.5 (CH),

122.7 (q, $J_{C\text{-}F}$ = 277.4 Hz, 2 x C), 121.3 (CH), 61.2 (q, $J_{C\text{-}F}$ = 37.3 Hz, 2 x CH_2), 59.3 (C), 38.2 (CH_2), 32.0 (CH_2).

Characteristic signals for minor regioisomer ***226b***: ^{1}H NMR (400 MHz, $CDCl_3$) 6.82 (1H, s, **H**C=C), 6.76-6.73 (2H, m, Ar**H**), 3.93-3.84 (2H, m, C**H**$_2$$CF_3$), 3.80-3.73 (2H, m, C**H**$_2$$CF_3$), 3.69 (2H, s, CC**H**$_2$CCH), 3.05 (2H, s, CC**H**$_2$C=CH).

References

(1) Brahmachari, G. *RSC Adv.* **2016**, *6* (69), 64676.

(2) Chen, X.; Engle, K. M.; Wang, D. H.; Jin-Quan, Y. *Angew. Chem. Int. Ed.* **2009**, *48* (28), 5094.

(3) Murai, S.; Kakiuchi, F.; Sekine, S.; Tanaka, Y.; Kamatani, A.; Sonoda, M.; Chatani, N. *Nature* **1993**, *366* (6455), 529.

(4) Li, D. D.; Yuan, T. T.; Wang, G. W. *J. Org. Chem.* **2012**, *77* (7), 3341.

(5) Gao, K.; Yoshikai, N. *J. Am. Chem. Soc.* **2013**, *135* (25), 9279.

(6) Thirunavukkarasu, V. S.; Kozhushkov, S. I.; Ackermann, L. *Chem. Commun.* **2014**, *50* (1), 29.

(7) Wan, L.; Dastbaravardeh, N.; Li, G.; Yu, J. Q. *J. Am. Chem. Soc.* **2013**, *135* (48), 18056.

(8) Rouquet, G.; Chatani, N. *Angew. Chem. Int. Ed.* **2013**, *52* (45), 11726.

(9) *Topics in Current Chemistry: C-H Activation*; Jin-Quan, Y., Zhangjie, S., Eds.; Springer, 2010; Vol. 292.

(10) Ma, S.; Gu, Z. *Angew. Chem. Int. Ed.* **2005**, *44* (46), 7512.

(11) Partridge, B. M.; Solana González, J.; Lam, H. W. *Angew. Chem. Int. Ed.* **2014**, *53* (25), 6523.

(12) Boon-Hong, T.; Dong, J.; Yoshikai, N. *Angew. Chem. Int. Ed.* **2012**, *51* (38), 9610.

(13) Keen, A. L.; Doster, M.; Johnson, S. A. *J. Am. Chem. Soc.* **2007**, *129* (4), 810.

(14) Mo, J.; Müller, T.; Oliveira, J. C. A.; Ackermann, L. *Angew. Chem. Int. Ed.* **2018**, *57* (26), 7719.

(15) Campo, M. A.; Larock, R. C. *J. Am. Chem. Soc.* **2002**, *124* (48), 14326.

(16) Kerr, J. A. *Chem. Rev.* **1966**, *66* (5), 465.

(17) Salem, B.; Delort, E.; Klotz, P.; Suffert, J. *Org. Lett.* **2003**, *5* (13), 2307.

(18) Mota, A. J.; Dedieu, A.; Bour, C.; Suffert, J. *J. Am. Chem. Soc.* **2005**, *127* (19), 7171.

(19) Oguma, K.; Miura, M.; Satoh, T.; Nomura, M. *J. Am. Chem. Soc.* **2000**, *122* (42), 10464.

(20) Hayashi, T.; Inoue, K.; Taniguchi, N.; Ogasawara, M. *J. Am. Chem. Soc.* **2001**, *123* (40), 9918.

(21) Miura, T.; Sasaki, T.; Nakazawa, H.; Murakami, M. *J. Am. Chem. Soc.* **2005**, *127* (5), 1390.

(22) Shintani, R.; Isobe, S.; Takeda, M.; Hayashi, T. *Angew. Chem. Int. Ed.* **2010**, *49* (22), 3795.

(23) Yamabe, H.; Mizuno, A.; Kusama, H.; Iwasawa, N. *J. Am. Chem. Soc.* **2005**, *127* (10), 3248.

(24) Shintani, R.; Hayashi, T. *Org. Lett.* **2005**, *7* (10), 2071.

(25) Shintani, R.; Takatsu, K.; Katoh, T.; Nishimura, T.; Hayashi, T. *Angew. Chem. Int. Ed.* **2008**, *47* (8), 1447.

(26) Matsuda, T.; Shigeno, M.; Murakami, M. *J. Am. Chem. Soc.* **2007**, *129* (40), 12086.

(27) Sciser, T.; Roth, O. A.; Cramer, N. *Angew. Chem. Int. Ed.* **2009**, *48* (34), 6320.

(28) Matsuda, T.; Suda, Y.; Takahashi, A. *Chem. Commun.* **2012**, *48* (24), 2988.

(29) *Topics in Organometallic Chemistry: Activation of Unreactive Bonds and Organic Synthesis*; Murai, S., Alper, H., Gossage, R. A., Grushin, V. V., Hidai, M., Ito, Y., Jones, W. D., Kakiuchi, F., van Koten, G., Lin, Y.-S., Mizobe, Y., Murai, S., Murakami, M., Richmond, T. G., Sen, A., Suginome, M., Yamamoto, A., Eds.; Springer Berlin Heidelberg, 1999; Vol. 3.

(30) Hepburn, H. B.; Lam, H. W. *Angew. Chem. Int. Ed.* **2014**, *53* (43), 11605.

(31) Partridge, B. M.; Callingham, M.; Lewis, W.; Lam, H. W. *Angew. Chem. Int. Ed.* **2017**, *56* (25), 7227.

(32) Callingham, M.; Partridge, B. M.; Lewis, W.; Lam, H. W. *Angew. Chem. Int. Ed.* **2017**, *56* (51), 16352.

(33) Ikeda, Y.; Takano, K.; Kodama, S.; Ishii, Y. *Chem. Commun.* **2013**, *49* (94), 11104.

(34) Burns, D. J.; Lam, H. W. *Angew. Chem. Int. Ed.* **2014**, *53* (37), 9931.

(35) Korkis, S. E.; Burns, D. J.; Lam, H. W. *J. Am. Chem. Soc.* **2016**, *138* (37), 12252.

(36) Dooley, J. D.; Lam, H. W. *Chem. Eur. J.* **2018**, *24* (34), 8692.

(37) Yan, J.; Yoshikai, N. *ACS Catal.* **2016**, *6* (6), 3738.

(38) Mohr, J. T.; Hong, A. Y.; Stoltz, B. M. *Nat. Chem.* **2009**, *1* (5), 359.

(39) De Nanteuil, F.; Loup, J.; Waser, J. *Org. Lett.* **2013**, *15* (14), 3738.

(40) Karad, S. N.; Panchal, H.; Clarke, C.; Lewis, W.; Lam, H. W. *Angew. Chem. Int. Ed.* **2018**, *57* (29), 9122.

(41) Oliva, A. I.; Christmann, U.; Font, D.; Cuevas, F.; Ballester, P.; Buschmann, H.; Torrens, A.; Yenes, S.; Perics, M. A. *Org. Lett.* **2008**, *10* (8), 1617.

(42) Gasperini, D.; Maggi, L.; Dupuy, S.; Veenboer, R. M. P.; Cordes, D. B.; Slawin, A. M. Z.; Nolan, S. P. *Adv. Synth. Catal.* **2016**, *358* (23), 3857.

(43) Kang, H. P.; Young, K. C. *Adv. Synth. Catal.* **2005**, *347* (6), 854.