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Palladium-Catalysed Construction of All-Carbon Quaternary Centres with Propargylic Electrophiles: Challenges in the Simultaneous Control of Regio-, Chemo- and Enantioselectivity

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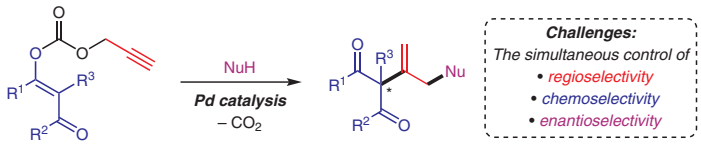

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Abstract This article describes the palladium-catalysed three-component coupling of 1,3-dicarbonyl compounds with nucleophiles and propargylic electrophiles for the generation of quaternary all-carbon centres in a single step, which necessitates the simultaneous control of regio-, chemo- and enantioselectivity. The use of propargyl enol carbonates, the source of two of the components, was found to be essential in maintaining high levels of regiocontrol and chemoselectivity, whereas a careful analysis of pK_a trends of O-, C- and N-nucleophiles as the other coupling partner indicates that the highest levels of selectivity are likely to be obtained with relatively acidic species, such as phenols, 1,3-dicarbonyl compounds and aromatic N-heterocycles. Finally, studies towards the development of the catalytic enantioselective construction of quaternary all-carbon centres by means of alkenylation and allylic alkylation are disclosed.

Key words palladium, enantioselective catalysis, quaternary centres, propargylic electrophiles, 1,3-dicarbonyl compounds

To facilitate drug discovery programmes, the pharmaceutical industry has historically relied upon tapping into compound screening libraries which are strongly biased towards molecules that are rich in aromatic character and flat structural features.[1] These properties are associated with low shape diversity, poorer solubility, higher toxicity and, therefore, higher levels of attrition during drug development.[2] To alleviate this effect, there is currently a strong drive to enhance the efficiency of drug discovery processes by utilising molecules with greater 3D complexity, increased levels of saturation and more chiral centres.[3] These changes can result in better solubility profiles, higher selectivity of binding and lower toxicity,[4] as well as more efficient sampling of larger areas of chemical space.[5] Quaternary all-carbon centres inherently offer scope for maximum exploration of 3D chemical space through chain growth in all four directions from the sp^3 tetrahedral carbon atom. However, quaternary all-carbon centres are severely sterically crowded, making the catalytic enantioselective construction of such centres a formidable synthetic challenge and an active area of research.[6] As such, the development of new catalytic methodologies for the installation of quaternary centres remains essential towards enabling access to novel 3D building blocks for drug discovery.

Our group has had a long-standing interest in the reactivity of propargylic electrophiles under palladium catalysis, the broad reactivity profiles that propargylic electrophiles exhibit, and the opportunities to exploit this type of reactivity in the construction of quaternary all-carbon centres. In reactions with a palladium(0) catalyst (Scheme 1, A), propargylic electrophiles, such as carbonate **1**, lead to the formation of η^3-π-propargylpalladium(II) intermediate **2** via oxidative addition and subsequent decarboxylation.[7] Although species **2** can take part in propargylation and allenylation reactions,[8] the process generating the most complexity is one that allows the coupling of two nucleophiles with **2**.[9] Such a process typically requires the use of soft nucleophiles,[10] the first of which undergoes addition at the central carbon atom in **2** and affords transient palladacyclobutene species **3**.[11] Protonation of **3** by the conjugate acid of the second nucleophile gives rise to η^3-π-allylpalladium(II) intermediate **4**, where the initial palladacyclobutene **3** formation and protonation may be synchronous.[7b] In the final mechanistic step, allylic alkylation at one of the termini in **4** affords product **5**, in which one nucleophile has undergone alkenylation and the second, allylic alkylation. Unfortunately, the direct one-pot coupling of η^3-π-propargylpalladium(II) intermediate **2** with two independent nucleophiles is extremely challenging owing to several selectivity issues (Scheme 1, B).[12] Firstly, the order of addition of the two nucleophiles must be controlled so that only one of the two cross-coupled products **5** or **6** is made (regio-

Biographical Sketches

Miles Kenny was born in Milton Keynes, UK, in 1991. After receiving his MChem degree from the University of East Anglia, UK, Miles embarked on a PhD in the group of Dr Vilius Franckevičius at Lancaster University, UK, working on the development of new palladium-catalysed methodologies for the generation of quaternary carbon centres. Miles successfully completed his PhD in 2017.

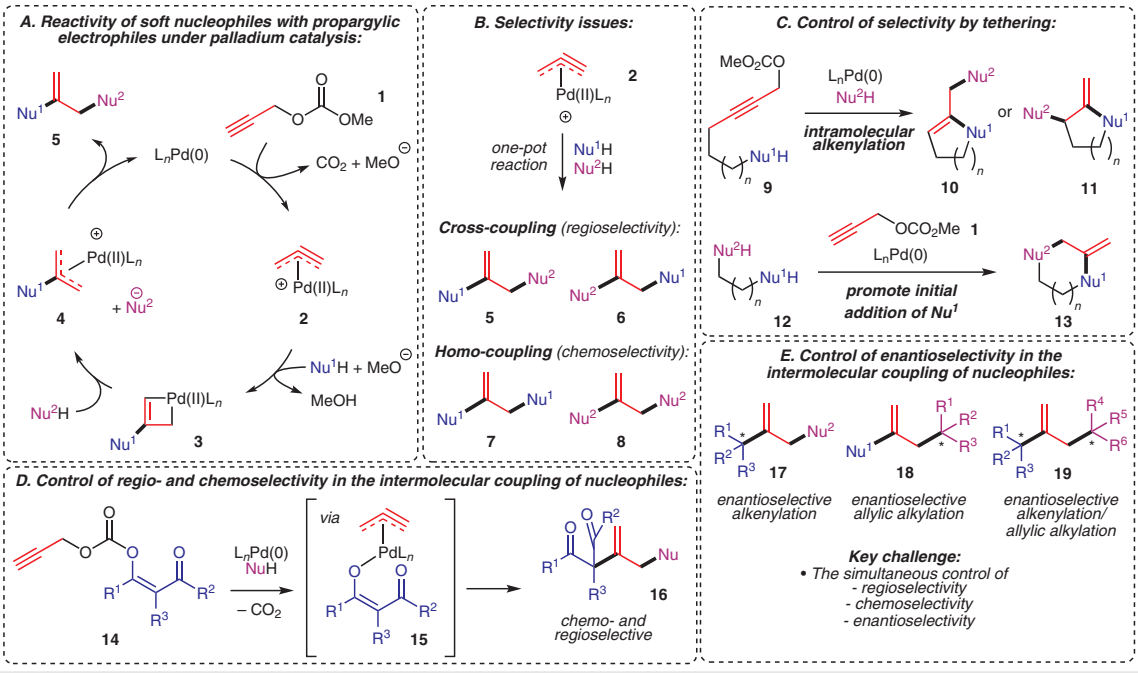
Sybrin P. Schröder was born in the Netherlands in 1989. He received his BSc degree in chemistry from Radboud University Nijmegen, the Netherlands, in 2010, where he also obtained his MSc degree in organic chemistry, in 2012, working in the group of Prof. Floris Rutjes. As part of his master's studies, Sybrin undertook an Erasmus placement at the University of York, UK, working with Dr. Vilius Franckevičius on the development of new methodologies for the palladium-catalysed intermolecular coupling of nucleophiles with propargylic electrophiles. He is currently a PhD student in the group of Prof. Hermen Overkleeft in Leiden, the Netherlands, focusing on the development of activity-based probes for carbohydrate-processing enzymes.

Nicholas J. Taylor was born in Macclesfield, UK, in 1990. He completed his MChem in chemistry at the University of York, UK, during which he undertook a final year project working with Dr. Vilius Franckevičius on the palladium-catalysed coupling of propargylic electrophiles with enolate nucleophiles. He then moved to the University of Oxford, UK, for his DPhil studies, where he worked in the group of Professor Véronique Gouverneur on the copper-mediated nucleophilic ^{18}F-radiolabelling of (hetero)arenes for applications in positron emission tomography. He is currently a postdoctoral research chemist in herbicide chemistry at Syngenta, UK.

Paula Jackson was born in Liverpool, UK, in 1991. She received an integrated MChem degree from the University of York, UK, in 2014, working in the group of Prof. Richard Taylor under the supervision of Dr. William Unsworth. During her studies, Paula successfully secured a Royal Society of Chemistry Undergraduate Research Bursary to undertake a summer placement with Dr. Vilius Franckevičius focusing on the development of new decarboxylative palladium-catalysed coupling methodologies. She is currently a scientist at Redx Pharma Plc., UK, working on the development of novel small-molecule therapies for cancer and fibrosis.

Daniel J. Kitson was born in Manchester, UK, in 1995. In 2015, Danny was awarded a Royal Society of Chemistry Undergraduate Research Bursary, exploring palladium-catalysed methodologies for quaternary carbon centre generation in the group of Dr. Vilius Franckevičius at Lancaster University, UK. Danny graduated with an MChem degree from Lancaster University, UK, in 2017, having undertaken a final year research project in the area of photochemistry under the supervision of Dr. Susannah Coote.

Vilius Franckevičius was born in Lithuania in 1983. Since 2013, he has been a lecturer at the Department of Chemistry at Lancaster University, UK, and has research interests in new synthetic methodology development and enantioselective catalysis. Prior to this, Vilius completed his PhD under the supervision of Prof. Steven V. Ley at the University of Cambridge, UK. This was followed by a postdoctoral position in the group of Prof. Dirk Trauner at Ludwig Maximilians University of Munich, Germany, and a Research and Teaching Fellowship with Prof. Richard Taylor at the University of York, UK.



Scheme 1 Control of selectivity in palladium-catalysed coupling reactions of nucleophiles with propargylic electrophiles

selectivity). Secondly, homo-coupling of just one nucleophile, leading to **7** and **8**, must also be prevented (chemoselectivity).

Typically, these selectivity challenges can be overcome by employing tethering strategies in cyclisation reactions (Scheme 1, C). For example, if one of the nucleophiles is tethered to the propargylic electrophile in **9**,[13] then alkenylation of the tethered nucleophile is likely to occur prior to alkenylation of the external nucleophile due to the intramolecular nature of the cyclisation reaction. Allylic alkylation of the second nucleophile then follows at either the less or the more substituted position to afford **10** or **11**, respectively. An alternative approach is the use of tethered bis-nucleophiles **12**.[14] In such a process, a clear differentiation between the two nucleophiles in **12** must be achieved if the order of addition is to be accurately controlled. If one of the nucleophiles is more acidic than the other, then it should preferentially undergo the initial deprotonation and, therefore, alkenylation, followed by intramolecular allylic alkylation of the second nucleophile to afford **13**. Alternatively, if the acidity is similar, a strong steric bias between the two nucleophiles or a distinct difference in nucleophilicity could favour the initial addition of one nucleophile over the other. Both approaches enable the control of regioselectivity, whereas homo-coupling is prevented through intramolecularity.

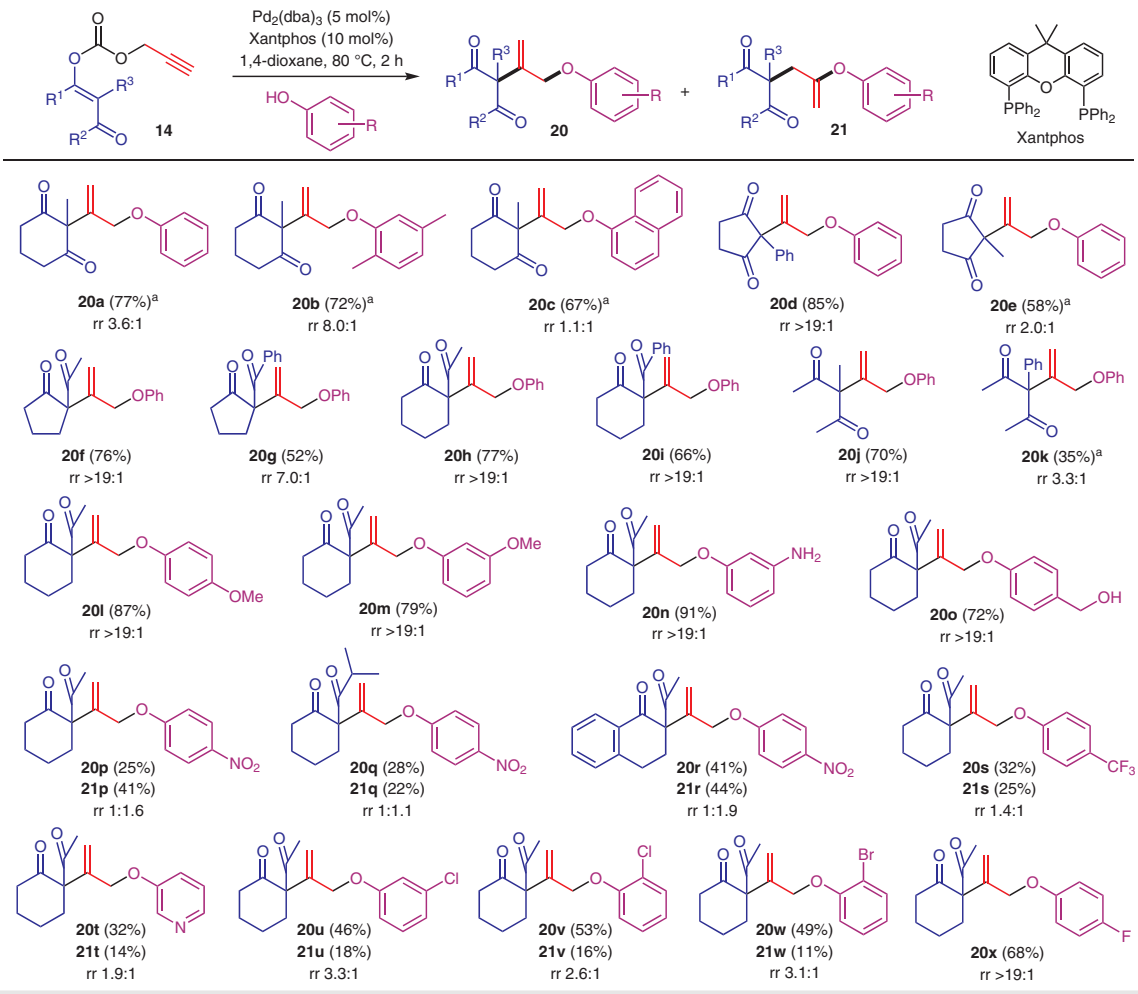
To exploit the use of palladium catalysis in the generation of quaternary all-carbon centres from propargylic electrophiles, our group discovered a method that enables the coupling of nucleophiles to afford *linear* products whilst maintaining high levels of regiocontrol and chemoselectivity. This approach involves the use of propargylic enol carbonates **14** (Scheme 1, D), derived from 1,3-dicarbonyl compounds. The palladium-catalysed reaction proceeds via intermediate **15** following oxidative addition and decarboxylation, in which the η^3-π-propargylpalladium(II) electrophile remains tightly associated with the enolate nucleophile.[15] This process results in the selective intramolecular alkenylation of the enolate and intermolecular allylic alkylation of the external nucleophile to afford linear products of type **16** with high regio- and chemoselectivity, in which a quaternary all-carbon centre has been installed. We surmised that, in the presence of a chiral ligand on palladium, the use of a non-symmetrical enolate could result in the enantioselective construction of a quaternary all-carbon centre in **17** via alkenylation (Scheme 1, E). Similarly, the use of a non-symmetrical external carbon-based nucleophile could lead to the enantioselective installation of a quaternary carbon centre by means of allylic alkylation (**18**). Finally, the use of two non-symmetrical carbon-based nucleophiles could, in principle, pave the way to the enantioselective construction of two all-carbon quaternary centres in a single step (**19**). However, to achieve both high efficiency and stereoselectivity in any of the above enantioselective processes, all control elements, namely, regio-, chemo- and enantioselectivity, must be simultaneously controlled. Indeed, there are very few examples reported of the enantioselective construction of quaternary all-carbon centres by means of alkenylation using the palladium-catalysed coupling reaction of propargylic electrophiles with nucleo-

philes,[16] typically affording only moderate levels of enantioselectivity. The induction of enantioselectivity at the allylic alkylation step of the mechanism has been studied using catechol,[17] and β-ketoester nucleophiles;[18] however, there are no examples in which a quaternary all-carbon centre had been installed enantioselectively.

This article describes our investigations into the utility of this methodology and the challenges involved in controlling selectivity in the palladium-catalysed coupling of nucleophiles with propargylic electrophiles.

Phenol Nucleophiles

Our investigation began with the coupling of highly stabilised enolates, derived from cyclic 1,3-diketones (1,3-cyclohexanedione, pK_a 10 in DMSO),[19] with phenols as nucleophiles (phenol, pK_a 18 in DMSO),[19] to afford the desired product **20** and/or its regioisomer **21** (Scheme 2). In this one-pot process, an all-carbon quaternary centre is formed along with new C–C and C–O bonds.[15] Upon optimisation, we found that Xantphos, a large-bite-angle ligand, was most suitable in this reaction and, in all cases, no homocoupling of nucleophiles was observed. The use of monodentate or smaller bite-angle bidentate ligands leads to severe erosion of both reaction efficiency and selectivity.[15] In the presence of phenols, 1,3-cyclohexanedione products **20a** and **20b** were formed with moderate to good regioselectivity; however, the reaction with 2-naphthol as the nucleophile was not selective (**20c**). The coupling of five-membered 1,3-diketones with phenol to afford **20d** and **20e** also gave different levels of regioselectivity. It can be reasoned that the highly stabilised nature of cyclic 1,3-diketone enolates can result in lower levels of regioselectivity, either due to the lower nucleophilicity of the enolate inhibiting the required intramolecular alkenylation process in **15** (*vide supra*, Scheme 1), or dissociation of the palladium complex from the highly stabilised enolate, paving the way to an uncontrolled order of addition of the two nucleo-



Scheme 2 Regio- and chemoselective coupling of 1,3-dicarbonyl compounds with phenols. Yields of isolated product in parentheses. Isomer **20** shown. Regioselectivity (rr) ratios of **20**:**21** were determined by ^{1}H NMR analysis of the crude product mixtures. [a] Combined yield of **20** and **21** isolated as a mixture

philes. In contrast, the use of propargyl carbonates, derived from less acidic acyclic 1,3-dicarbonyls (pK_a 13–16 in DMSO),[19] gave excellent regioselectivity in most cases (**20f–k**) in the coupling with phenol, presumably due to the tighter association of the enolate with the intermediate palladium complex following decarboxylation. Excellent regioselectivity was maintained with electron-rich phenols (**20l** and **20m**), and no chemoselectivity issues were observed in the presence of other unprotected nucleophiles (**20n** and **20o**), whereby allylic alkylation of the phenol functionality takes place exclusively owing to its higher acidity. In contrast, regioselectivity was low when electron-deficient phenols were utilised. For example, nitro-, trifluoromethyl- and pyridyl-substituted phenols afforded **20p–t** with low regioselectivity. Similarly, halogenated phenols gave rise to **20u–w** with moderate selectivity, with the surprising exception of fluorine-substituted **20x**, which was isolated with complete regioselectivity. Given that electron-poor phenols are more acidic than their electron-rich counterparts (4-nitrophenol, pK_a 11 in DMSO),[20] and as acidic as, if not more than, acyclic 1,3-dicarbonyl compounds, it is likely that the enolate formed in situ after decarboxylation undergoes protonation by the phenol nucleophile, which leads to the dissociation of the palladium complex and, thus, loss of regiocontrol.

1,3-Dicarbonyl Nucleophiles

Given the success in controlling the regioselectivity in the coupling of acyclic 1,3-diketones with relatively electron-rich phenols, we sought to explore whether the analogous coupling could be extended by replacing the phenol nucleophile with a 1,3-dicarbonyl compound (Scheme 3).[21] Indeed, this reaction process was found to be very efficient using DPEphos as the large-bite-angle ligand, enabling the formation of two all-carbon quaternary carbon centres and two new C–C bonds in a single step with complete regiocontrol and good chemoselectivity (**23a–d**) despite the structural similarities between the two nucleophiles. Given that high levels of regiocontrol are imparted by the tight association of the η^3-π-propargylpalladium(II) intermediate with the enolate after decarboxylation of **14**, this reaction process becomes *regioswitchable* by utilising an enol carbonate of 1,3-dicarbonyl nucleophile **22**, thus paving the way to regioisomeric products **23e–h**. Substitution of the 1,3-diketone nucleophile was tolerated to afford coupled products **23i–k**, as well as regioisomers **23n** and **23o**; only a complex mixture of products was obtained in the formation of **23p**. By analogy to electron-deficient phenols, the use of a significantly more acidic 1,3-cyclohexanedione nucleophile in the formation of **23l** afforded a mixture of products, with nucleophile homo-coupling being the major pathway. However, the selectivity in the formation of regioisomer **23q** in the regioswitched process was higher. When an unsubstituted 1,3-diketone was utilised as a nucleophile, **23m** was isolated in 56% yield, but the synthesis of its regioisomer **23r** was not successful, presumably due to the presence of an acidic proton in the product structure. This process was extended to the use of 1,3-dicarbonyl compounds other than 1,3-diketones, and all products **23s–w** were formed with complete regioselectivity. Since the 1,3-dicarbonyls tested are less acidic than 1,3-diketones, this process is analogous to the use of electron-rich phenols as nucleophiles, which had also afforded products with complete regioselectivity (*vide supra*, Scheme 2). Excellent selectivity was obtained in the formation of regioisomers **23x–aa**, with the exception of **23ab**, which resulted in a complex mixture of products.

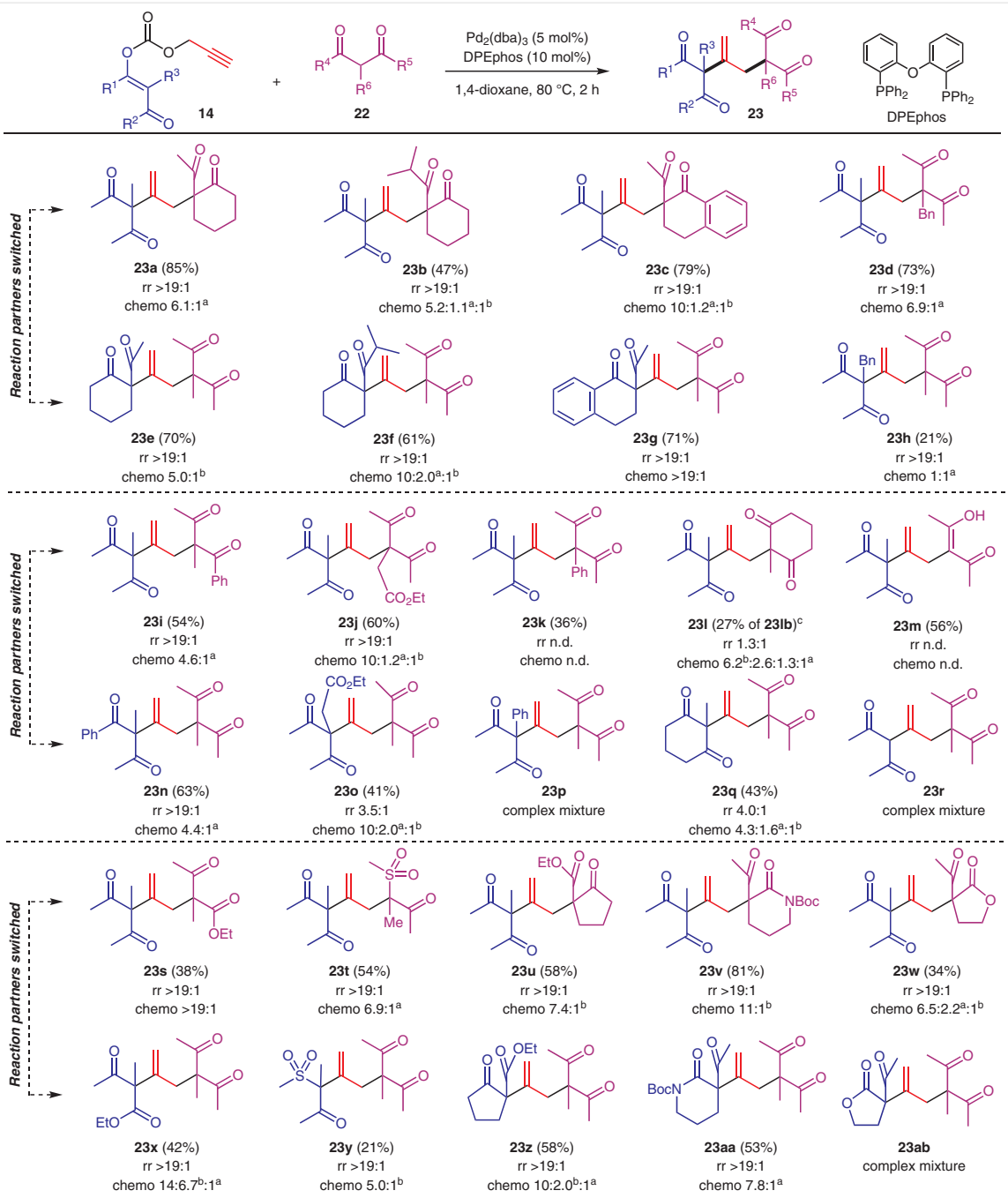
N-Nucleophiles

In addition to O- and C-nucleophiles, we discovered that indole, an aromatic N-heterocycle, can also be readily deprotonated and alkylated as a coupling partner to afford **24a** with complete regio- and chemoselectivity (Scheme 4).[22] However, given that aromatic N-heterocycles are typically less acidic than phenols (indole, pK_a 21; pyrrole, pK_a 23, both in DMSO),[19] a higher reaction temperature was required to facilitate deprotonation. Indeed, product **24b** was obtained in relatively high yield, presumably due to the higher acidity of the indole nucleophile which bears an electron-withdrawing ester substituent. In contrast, electron-donating substitution on the indole unit negatively impacted on the efficiency of the reaction (**24c**). The use of carbazole as the nucleophile was successful (**24d**), and the reaction scope could also be extended to the use of propargyl enol carbonates derived from β-ketoesters (**24e**). The coupling process was broadened to the use of pyrrole as an analogue to indole (**24f**), albeit an electron-withdrawing substituent was essential to obtain a high yield of product (**24g–j**). Crucially, all reactions proceeded with complete regio- and chemoselectivity owing to both the tight association of the η^3-π-propargylpalladium(II) intermediate with the enolate following decarboxylation of **14** and the lack of protonation of the enolate by the N-heterocyclic nucleophile given the substantial difference in pK_a. This methodology was readily extended to other aromatic N-heterocycles, including azaindole, imidazole, benzimidazole and pyrazole, affording **24k–n**, respectively, with complete regiocontrol. Unfortunately, a much less acidic saturated cyclic amine as nucleophile failed to couple (**24o**).

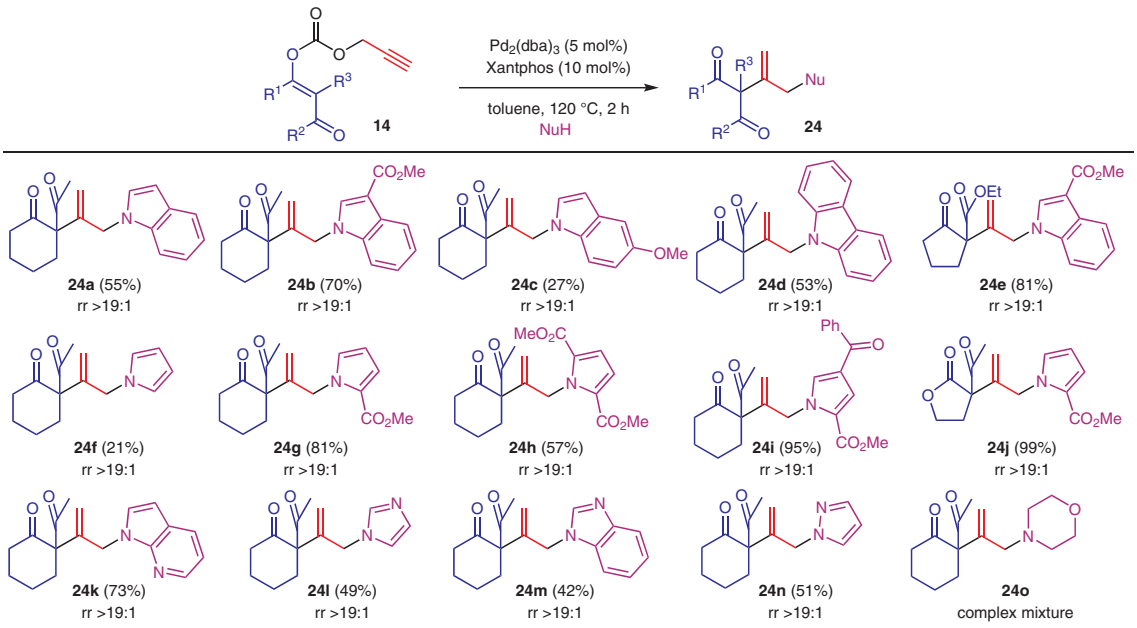
Acidity Trends

The palladium-catalysed coupling of propargyl enol carbonates derived from 1,3-dicarbonyls relied upon the use of phenols (phenol, pK_a 18 in DMSO),[19] 1,3-dicarbonyl compounds (pK_a 13–16),[19] and aromatic N-heterocyclic nucleophiles (pK_a 19–23, in DMSO)[19] to obtain high levels of regiocontrol. As such, we set out to investigate the utility of nucleophiles outside of this pK_a range. Based on the previous cases of low regioselectivity, where the external nucleophile was more acidic than the conjugate acid of the enolate, such as electron-deficient phenols (*vide supra*, Scheme 2), several other acidic species were tested as nucleophiles (Scheme 5). In this context, carboxylic acids as nucleop-

hiles, which display similar acidity to electron-deficient phenols (pK_a 11–12 in DMSO),[19] did afford products **25a–c**, however, regioselectivity was again low and in line with the previous observation that undesired protonation of the enolate occurs prior to the alkenylation step. By increasing the acidity of the external nucleophile further, such as using *p*-toluenesulfonic acid, the reaction process was even more difficult to control (**25d**), leading to a complex mixture of products. On the other side of the pK_a range, the reactivity of C-nucleophiles **27–30**, all less acidic than



Scheme 3 *Regioswitchable* coupling of 1,3-dicarbonyl compounds. Yields of isolated isomer **23** in parentheses. Isomer **23** shown. Regioselectivity (rr) and chemoselectivity (chemo) ratios were determined by ^{1}H NMR analysis of the crude product mixtures. n.d. = not determined due to overlapping signals. [a] Refers to homo-coupling of **14**. [b] Refers to homo-coupling of **22**. [c] Homo-coupled **22** was the major product isolated in 27% yield (**23lb**, see the experimental section)

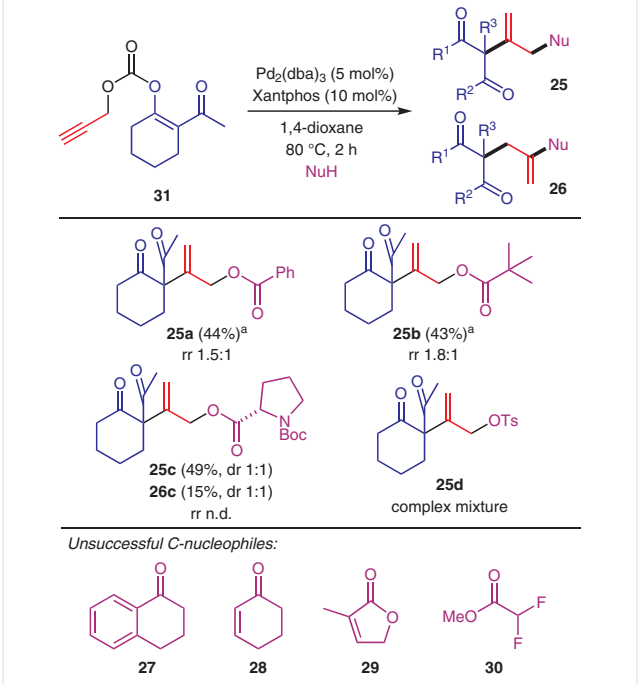


Scheme 4 Regio- and chemoselective coupling of 1,3-dicarbonyl compounds with N-nucleophiles. Yields of isolated isomer **24**. Regioselectivity (rr) ratios were determined by ^{1}H NMR analysis of the crude product mixtures. No homo-coupling (chemoselectivity) of **14** or the N-nucleophile was observed in all cases

phenols and 1,3-dicarbonyl compounds (e.g., cyclohexanone, pK_a 26 in DMSO),[19] was tested. If the reaction were to proceed through the previously postulated mechanism (*vide supra*, Scheme 1), then deprotonation of a much less acidic nucleophile would be required. Unfortunately, the reaction with ketone **27** was unsuccessful and a complex mixture of products was obtained. To enhance the acidity of the carbonyl functionality and attempt to facilitate deprotonation, we explored cyclohexenone (**28**), which had been shown to participate in an intramolecular coupling reaction,[14c] furanone **29**, which would give an aromatic anion upon deprotonation that would be more stable than an enolate of a saturated lactone, and α-difluorinated ester **30**, which is more acidic than a simple ester due to the electron-withdrawing nature of the fluorine atoms. In all three cases, only a complex mixture of products was observed. It was therefore apparent that, overall, in the coupling of 1,3-dicarbonyl compounds with nucleophiles, high reaction efficiency and selectivity is most likely to be achieved with relatively acidic nucleophiles (pK_a ~13–23 in DMSO).

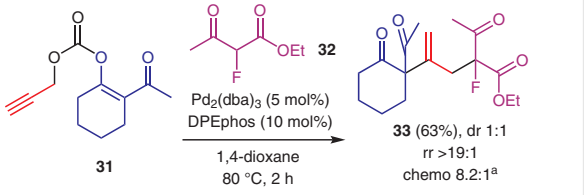
Diastereoselective Synthesis

A crucial aspect of this project was the construction of quaternary all-carbon centres in a stereoselective manner. By utilising propargyl enol carbonate **31** and β-ketoester **32**, two stereogenic quaternary centres were installed in a single step (Scheme 6). However, while the reaction conditions enabled the concerted control of regio- and chemoselectivity in the formation of **33**, no induction of diastereoselectivity was observed, potentially due to the remoteness



Scheme 5 Investigation of acidity trends. Isomer **25** shown. Regioselectivity (rr) and diastereoselectivity (dr) ratios were determined by ^{1}H NMR analysis of the crude product mixtures. n.d. = not determined due to overlapping signals. No homo-coupling (chemoselectivity) of **31** or the external nucleophile was observed in all cases. [a] Combined yield of **25** and **26** isolated as a mixture

of the two chiral centres and the acyclic nature of 1,3-dicarbonyl compound **32**. This observation gave an indication that the enantioselective installation of a stereogenic centre during the alkenylation step of the mechanism while relying on diastereocontrol to construct the second stereogenic centre at the allylic alkylation stage was likely to pose challenges. To avoid this difficulty, the next stage of the investigation focused on the enantioselective installation of a single stereogenic centre, either by means of alkenylation or allylic alkylation. Notwithstanding, such a process was still likely to be extremely demanding because to achieve both high levels of enantioselectivity and yield of the desired product, the simultaneous control of not only stereoselectivity, but also regio- and chemoselectivity is required.



Scheme 6 Diastereoselective coupling. [a] Refers to homo-coupling of **32**

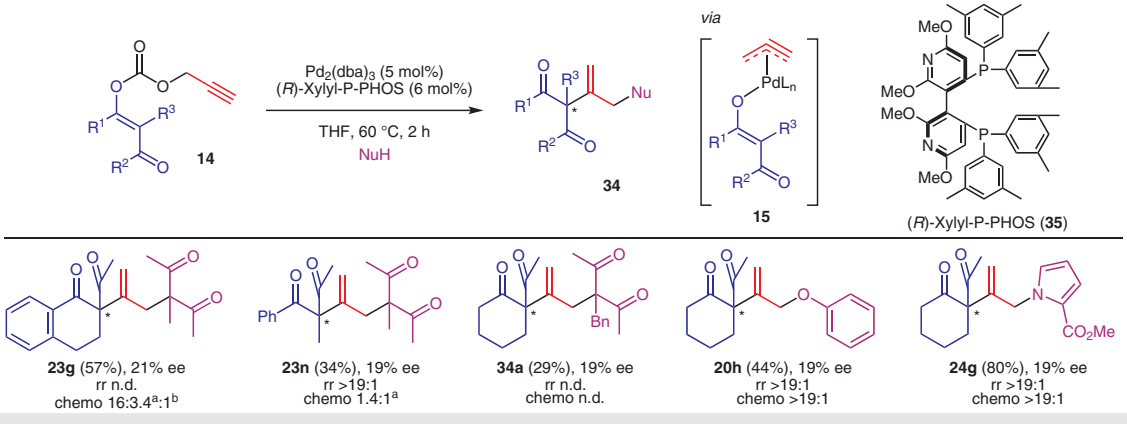
Enantioselective Alkenylation

The enantioselective construction of a stereogenic all-carbon quaternary centre in **34** by means of a chiral ligand sphere around the palladium centre necessitates stereocontrol at the alkenylation step of enolate **15** following decarboxylation (Scheme 7). In this context, 30 chiral bisphosphines were screened, including the BINAP, SEGPHOS, BIPHEP, P-PHOS, PhanePhos, Trost, PHOX and phosphoramidite ligand families, and reaction parameters, including solvent, time and temperature, were carefully optimised (see the Supporting Information for ligand structures and full optimisation details). (*R*)-Xylyl-P-PHOS (**35**) was identified as the optimum ligand in terms of yield and selectivity. Although **23g** was formed in 57% yield, the enantioselectivity was low (21% ee). Similar levels of enantioselectivity were observed in the formation of **23n** and **34a**, but the product yields were low due to inadequate levels of control of either regio- or chemoselectivity. In addition to the use of 1,3-dicarbonyls, phenol and pyrrole nucleophiles were utilised, both of which afforded **20h** and **24g** in 19% ee whilst maintaining full regio- and chemoselectivity.

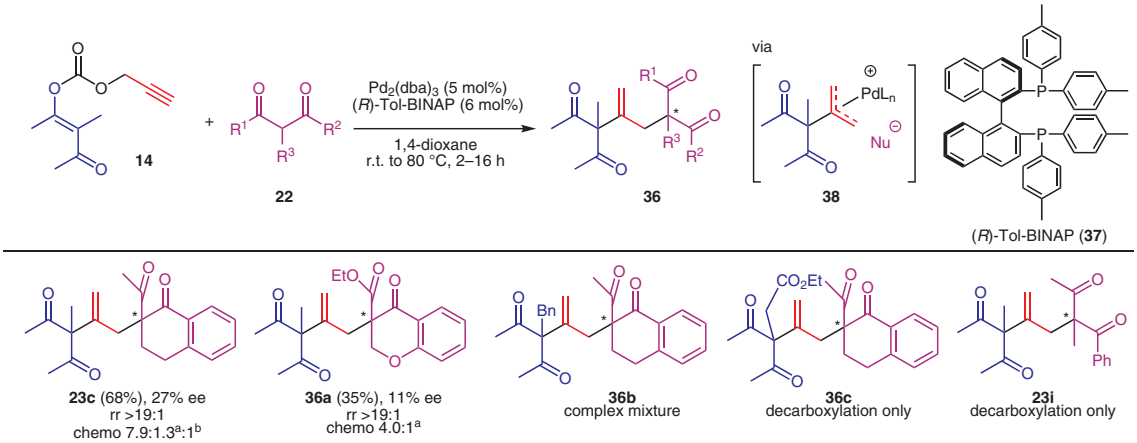
Enantioselective Allylic Alkylation

The enantioselective construction of a quaternary all-carbon centre via the allylic alkylation of intermediate **38** was developed in a fashion analogous to the enantioselective alkenylation process (Scheme 8), where again the simultaneous control of regio-, chemo- and stereoselectivity was essential. Following a screen of chiral ligands for palladium (see the Supporting Information for ligand structures and full optimisation details), (*R*)-Tol-BINAP (**37**) was found to give the best balance of reaction efficiency and enantioselectivity. Using this ligand and 1,3-diketone **22** with a defined enolate geometry upon deprotonation, product **23c** was formed in a good yield owing to complete regiocontrol and good chemoselectivity; however, the enantioselectivity was low (27% ee).

When a β-ketoester was employed as a nucleophile, **36a** was formed with complete regiocontrol, but the yield was low due to modest chemoselectivity; additionally, the enantioselectivity was poor. All attempts to extend this process to a broader range of substrates by exploring substitution led to disappointing results: the attempted formation of **36b** afforded a complex mixture of products, indicating low levels of selectivity, whereas **36c** and **23i** were not formed due to the corresponding propargyl enol carbonates only undergoing decarboxylation and failing to take part in the desired reaction process. Based on these results, it is apparent that the contemporaneous control of regio-,



Scheme 7 Enantioselective alkenylation. Yields of isolated isomer **34**. Isomer **34** shown. Enantiomeric excess (ee) values were determined by chiral HPLC. Regioselectivity (rr) and chemoselectivity (chemo) ratios were determined by ^{1}H NMR analysis of the crude product mixtures. n.d. = not determined due to overlapping signals. [a] Refers to homo-coupling of 14. [b] Refers to homo-coupling of external NuH



Scheme 8 Enantioselective allylic alkylation. Yields of isolated isomer **36**. Isomer **36** shown. Enantiomeric excess (ee) values were determined by chiral HPLC. Regioselectivity (rr) and chemoselectivity (chemo) ratios were determined by ^{1}H NMR analysis of the crude product mixtures. [a] Refers to homo-coupling of **14**. [b] Refers to homo-coupling of **22**

chemo- and stereoselectivity in the palladium-catalysed intermolecular coupling of nucleophiles in the presence of propargylic electrophiles remains notoriously difficult.

In conclusion, this research programme has enabled us to identify and explore the utility of propargyl enol carbonates, derived from 1,3-dicarbonyls, in the palladium-catalysed cross-coupling with nucleophiles for the construction of quaternary all-carbon centres. We have successfully developed chemical processes for the decarboxylative coupling of enolates with a range of nucleophiles with high levels of regio- and chemoselectivity owing to the tight association of the η^3-π-propargylpalladium(II) intermediate with the enolate following decarboxylation. A careful analysis of acidity trends of nucleophiles has indicated that relatively acidic nucleophiles (pK_a ~13–23 in DMSO), such as phenols, 1,3-dicarbonyl compounds and aromatic N-heterocycles, give rise to excellent levels of regiocontrol. The use of more acidic nucleophiles, such as electron-deficient phenols, cyclic 1,3-diketones and carboxylic acids, results in low regioselectivity, presumably owing to the premature protonation of the intermediate enolate and, thus, dissociation of the palladium metal centre from the resulting neutral enol. Similarly, less acidic carbon-based nucleophiles, such as unstabilised enolates derived from ketones and esters, failed to take part in the desired coupling process. Crucially, this approach has enabled us to explore the opportunities for the catalytic enantioselective construction of quaternary all-carbon stereogenic centres. Both enantioselective alkenylation and allylic alkylation processes were explored; however, despite extensive screens of chiral ligands, the need for simultaneous control of regio-, chemo- and stereoselectivity was a formidable challenge to overcome. While it was possible to retain high levels of regiocontrol and chemoselectivity in many cases, the levels of enantioselectivity were generally low. The stereoselective installation of quaternary carbon centres by means of palladium-catalysed coupling of nucleophiles with propargylic electrophiles remains a major challenge for synthetic chemists, yet at the same time offers ample opportunities for its broader development and application.

All commercially available starting materials were used as received without further purification. Solvents were of reagent grade and dried prior to use. Petrol (PE) refers to the fraction of petroleum ether that boils between 40 and 60 °C. All reactions were performed under an argon atmosphere in oven dry glassware. Reactions were monitored by thin-layer chromatography using Fluka precoated silica gel plates with a fluorescent indicator (254 nm) and visualised by UV light (254 nm) and by staining with potassium permanganate or aqueous acidic ammonium molybdate(IV) solutions. Flash column chromatography was carried out using Fisher silica gel (60 Å particle size, 230–400 mesh). Melting points were determined using a Gallenkamp melting point instrument and are uncorrected. Optical rotations were recorded using a Optical Active AA-65 Automatic Polarimeter polarimeter. IR spectra were recorded on a Agilent Technologies Cary 630 FTIR spectrometer as a neat film. NMR spectra were recorded on either Bruker Ultra Shield Plus 400 or 300 MHz instruments (^{1}H NMR at 400 and 300 MHz, respectively, and ^{13}C{^{1}H} NMR at 100 and 75 MHz, respectively) in $CDCl_3$. Residual solvent $CHCl_3$ was referenced at 7.26 ppm for ^{1}H NMR spectra, and the central resonance of $CDCl_3$ was referenced at 77.0 ppm for ^{13}C{^{1}H} NMR spectra. High-resolution mass spectrometry data were recorded using electron spray ionisation on a Shimadzu LCMS-IT-TOF mass spectrometer.

The following compounds have been previously reported in reactions using phenols:[15] **20a**, **20d**, **20f**, **20h–j**, **20l–p** and **20x**; 1,3-dicarbonyl compounds:[21] **23a**, **23c–g**, **23i**, **23j**, **23n**, **23t–v**, **23z**, **23aa**, **33** and **36a**; *N*-heterocycles:[22] **24a–n**. With the exception of **39**, **41** and **43–45**, syntheses of all propargyl enol carbonates **14** and **31** have been reported and appropriate references are provided in each case below.

Palladium-Catalysed Cross-Coupling; Method A

Carbonate **14** (0.24 mmol), $Pd_2(dba)_3$ (11 mg, 0.012 mmol), Xantphos (13.9 mg, 0.024 mmol) and the phenol nucleophile (0.26 mmol) were added to a dried tube under argon. The tube was fitted with a septum and purged further with argon. 1,4-Dioxane (1.5 mL) was added and the sealed tube was placed in an oil bath preheated to 80 °C. The mixture was stirred at 80 °C for 2 h, then cooled to room temperature, concentrated in vacuo and purified by flash column chromatography. The ratio of **20**:**21** was determined by ^{1}H NMR spectroscopy of the crude product mixture prior to purification.

Palladium-Catalysed Cross-Coupling; Method B

Carbonate **14** (0.24 mmol), $Pd_2(dba)_3$ (11 mg, 0.012 mmol), DPEphos (13.1 mg, 0.024 mmol) and the 1,3-dicarbonyl nucleophile (0.24 mmol) were added to a dried tube under argon. The tube was fitted with a septum and purged further with argon. 1,4-Dioxane (1.5 mL) was added and the sealed tube was placed in an oil bath preheated to 80 °C. The mixture was stirred at 80 °C for 2 h, then cooled to room temperature, concentrated in vacuo and purified by flash column chromatography. Regioselectivity and chemoselectivity ratios were determined by ^{1}H NMR spectroscopy of the crude product mixture prior to purification.

Palladium-Catalysed Cross-Coupling; Method C

Carbonate **14** (0.24 mmol), $Pd_2(dba)_3$ (11 mg, 0.012 mmol), Xantphos (13.9 mg, 0.024 mmol) and the N-heterocyclic nucleophile (0.24 mmol) were added to a dried tube under argon. The tube was fitted with a septum and purged further with argon. Toluene (1.5 mL) was added and the sealed tube was placed in an oil bath preheated to 120 °C. The mixture was stirred at 120 °C for 2 h, then cooled to room temperature, concentrated in vacuo and purified by flash column chromatography.

Palladium-Catalysed Cross-Coupling; Method D

Carbonate **14** (0.24 mmol), $Pd_2(dba)_3$ (11 mg, 0.012 mmol), Xantphos (13.9 mg, 0.024 mmol) and the carboxylic acid nucleophile (0.24 mmol) were added to a dried tube under argon. The tube was fitted with a septum and purged further with argon. 1,4-Dioxane (1.5 mL) was added and the sealed tube was placed in an oil bath preheated to 80 °C. The mixture was stirred at 80 °C for 2 h, then cooled to room temperature, concentrated in vacuo and purified by flash column chromatography. The ratio of **25**:**26** was determined by ^{1}H NMR spectroscopy of the crude product mixture prior to purification.

2-[3-(2,5-Dimethylphenoxy)prop-1-en-2-yl]-2-methylcyclohexane-1,3-dione (20b)

Following method A, carbonate **14**[15] (50 mg, 0.24 mmol) was reacted with 2,5-dimethylphenol (32 mg, 0.26 mmol). Flash column chromatography (PE/EtOAc, 19:1) afforded an inseparable mixture of **20b** and **21b** in a 13:1 ratio (48 mg, 72%) as an orange oil.

R_f = 0.36 (PE/EtOAc, 3:1).

IR (film): 2878, 1703, 1673 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ (resonances due to **20b** quoted) = 7.00 (d, J = 7.4 Hz, 1 H), 6.70 (d, J = 7.5 Hz, 1 H), 6.59 (s, 1 H), 5.52 (t, J = 1.3 Hz, 1 H), 5.13 (s, 1 H), 4.39 (s, 2 H), 2.86 (ddd, J = 16.5, 8.5, 5.4 Hz, 2 H), 2.60 (ddd, J = 16.6, 8.0, 5.0 Hz, 2 H), 2.30 (s, 3 H), 2.19–2.09 (m, 1 H), 2.16 (s, 3 H), 1.90–1.77 (m, 1 H), 1.45 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ (resonances due to **20b** quoted) = 207.9, 156.2, 143.8, 136.8, 130.7, 123.9, 122.0, 116.6, 113.0, 70.0, 68.7, 38.7, 21.4, 19.5, 17.7, 16.0.

HRMS (ESI): m/z [M + Na]$^+$ calcd for $C_{18}H_{22}O_3Na$: 309.1461; found: 309.1448.

2-Methyl-2-[3-(naphthalen-1-yloxy)prop-1-en-2-yl]cyclohexane-1,3-dione (20c) and 2-Methyl-2-[2-(naphthalen-1-yloxy)allyl]cyclohexane-1,3-dione (21c)

Following method A, carbonate **14**[15] (50 mg, 0.24 mmol) was reacted with 2-naphthol (37 mg, 0.26 mmol). Flash column chromatography (PE/EtOAc, 19:1) afforded an inseparable mixture of **20c** and **21c** in a 1.6:1 ratio (50 mg, 67%) as an orange oil.

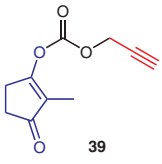
R_f = 0.25 (PE/EtOAc, 3:1).

IR (film): 3348, 1669, 1554 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.26–6.75 (m, 7 H and 7 H*), 5.63 (t, J = 1.3 Hz, 1 H*), 5.26 (s, 1 H*), 4.62 (s, 2 H*), 4.12 (dd, J = 2.3, 1.0 Hz, 1 H), 3.74 (d, J = 2.5 Hz, 1 H), 3.16 (s, 2 H), 2.86–2.65 (m, 4 H and 2 H*), 2.65–2.56 (m, 2 H*), 2.13–2.00 (m, 1 H*), 1.99–1.86 (m, 2 H), 1.87–1.77 (m, 1 H*), 1.51 (s, 3 H*), 1.39 (s, 3 H); isomer **21c** annotated by an asterisk.

^{13}C NMR (100 MHz, $CDCl_3$): δ (mixture of **20c** and **21c**) = 210.4, 208.4, 158.6, 151.9, 150.3, 143.3, 135.0, 134.9, 127.9, 127.7, 126.6 (2 C), 126.4, 126.4, 126.0, 125.9, 125.2, 125.0, 122.1, 121.9, 120.4, 117.5, 117.2, 108.6, 105.8, 89.4, 69.4, 69.2, 62.4, 40.1, 38.7, 38.0, 22.2, 20.1, 17.8, 17.5.

HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{20}H_{21}O_3$: 309.1485; found: 309.1474.



39

3-Oxo-2-methylcyclopent-1-enyl prop-2-ynyl Carbonate (39)

A suspension of sodium hydride (60 wt%, 220 mg, 5.5 mmol) in mineral oil was washed with PE (2 mL). Tetrahydrofuran (25 mL) was added and the mixture was cooled to 0 °C. 2-Methyl-1,3-cyclopentadione (560 mg, 5.0 mmol) was added as a solid. After stirring at 0 °C for 10 min, propargyl chloroformate (539 µL, 5.5 mmol) was added dropwise. The mixture was allowed to warm to room temperature and stirred at this temperature for 1.5 h. The reaction was quenched by addition of aq HCl (10%, 50 mL) and the mixture was extracted with EtOAc (3 × 50 mL). The combined organic phases were washed with aq $NaHCO_3$ (3 × 50 mL), brine (100 mL), dried ($MgSO_4$) and concentrated in vacuo. Flash column chromatography (PE/EtOAc, 4:1) afforded carbonate **39** (590 mg, 61%) as a pale yellow oil.

R_f = 0.17 (PE/EtOAc, 4:1).

IR (film): 3353, 2883, 2097, 1750, 1642 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.81 (d, J = 2.8 Hz, 2 H), 2.87 (ddd, J = 9.2, 4.0, 2.0 Hz, 2 H), 2.61 (t, J = 2.4 Hz, 1 H), 2.53–2.48 (m, 2 H), 1.63 (t, J = 2.0 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 205.5, 174.7, 149.9, 125.8, 76.7, 75.8, 56.3, 34.2, 26.4, 6.3.

HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{10}H_{11}O_4$: 195.0652; found: 195.0654.

2-Methyl-2-(3-phenoxyprop-1-en-2-yl)cyclopentane-1,3-dione (20e) and 2-Methyl-2-(2-phenoxyallyl)cyclopentane-1,3-dione (21e)

Following method A, carbonate **39** (47 mg, 0.24 mmol) was reacted with phenol (25 mg, 0.26 mmol). Flash column chromatography (PE/EtOAc, 9:1) afforded an inseparable mixture of **20e** and **21e** in a 2.0:1 ratio (34 mg, 58%) as a clear oil.

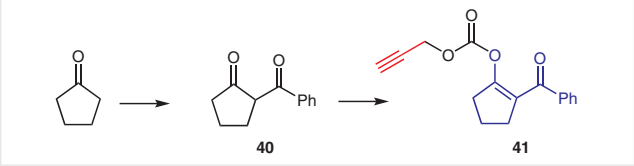
R_f = 0.25 (PE/EtOAc, 4:1).

IR (film): 3017, 2883, 2828, 1739, 1698, 1623, 1572 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$,): δ = 7.30 (t, *J* = 7.6 Hz, 1 H), 7.25–7.21 (m, 2 H), 7.12 (tt, *J* = 7.2, 1.2 Hz, 1 H*), 6.95 (tt, *J* = 7.2, 1.2 Hz, 2 H*), 6.90–6.86 (m, 2 H*), 6.78–6.73 (m, 2 H), 5.48 (t, *J* = 1.6 Hz, 1 H), 5.32 (t, *J* = 0.8 Hz, 1 H), 4.46 (t, *J* = 1.2 Hz, 2 H), 4.15–4.12 (m, 1 H*), 3.82 (d, *J* = 2.4 Hz, 1 H*), 2.85 (s, 4 H), 2.82 (s, 2 H*), 2.75 (dt, *J* = 10.0, 2.4 Hz, 4 H*), 1.32 (s, 3 H), 1.15 (s, 3 H*); isomer **21e** annotated by an asterisk.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 215.8*, 213.3, 157.7*, 157.3, 153.9*, 141.5, 129.7, 129.6, 124.8*, 121.7*, 120.8*, 116.6, 114.2, 89.5*, 68.9, 59.5, 53.9*, 39.6*, 34.8*, 34.7, 20.7*, 18.7; isomer **21e** annotated by an asterisk.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{15}H_{16}O_3Na$: 267.0992; found: 267.0989.



2-Benzoylcyclopentanone (40)[23]

To a stirred solution of cyclopentanone (4.42 mL, 50 mmol) and *p*-toluenesulfonic acid (476 mg, 2.5 mmol) in toluene (100 mL) was added pyrrolidine (6.15 mL, 75 mmol). The mixture was heated to reflux at 110 °C under Dean–Stark conditions for 16 h, then allowed to cool to room temperature. The mixture was concentrated in vacuo to afford the crude enamine (6.31 g) as a dark orange oil.

To a stirred solution of the crude enamine (4.17 g, 30 mmol) in toluene (80 mL) were added triethylamine (5.82 mL, 42 mmol) and benzoyl chloride (4.88 mL, 42 mmol). The mixture was heated to reflux at 110 °C for 1.5 h, then allowed to cool to room temperature. Aq HCl (10%, 30 mL) was added and the mixture was heated to reflux at 110 °C for 30 min, then allowed to cool to room temperature. Another portion of aq HCl (10%, 20 mL) was added and the mixture was extracted with EtOAc (3 × 50 mL). The combined organic phases were washed with brine (100 mL), dried ($MgSO_4$) and concentrated in vacuo. Flash column chromatography (PE/EtOAc, 49:1–9:1) afforded a mixture of three compounds as a yellow solid. The major component was the enol tautomer of diketone **40**.

R_f = 0.66 (PE/EtOAc, 3:1).

IR (film): 2985, 2938, 1717, 1624 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.12 (dd, *J* = 8.3, 1.4 Hz, 2 H), 7.79–7.75 (m, 1 H), 7.48–7.44 (m, 2 H), 2.87 (t, *J* = 7.1 Hz, 2 H), 2.50 (t, *J* = 7.9 Hz, 2 H), 2.01–1.92 (m, 2 H), (signal due to OH not observed).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 210.6, 171.8, 133.8, 130.7, 128.6, 128.4, 109.4, 37.7, 28.4, 21.4.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{12}H_{12}O_2Na$: 211.0730; found: 211.0730.

2-Benzoylcyclopent-1-en-1-yl Prop-2-yn-1-yl Carbonate (41)

A suspension of sodium hydride (60 wt%, 117 mg, 2.93 mmol) in mineral oil was washed with PE (2 mL). Tetrahydrofuran (20 mL) was added and the mixture was cooled to 0 °C. A solution of 2-benzoylcyclopentanone (**40**) (500 mg, 2.66 mmol) in tetrahydrofuran (2 mL) was added dropwise. After stirring at 0 °C for 10 min, propargyl chloroformate (286 µL, 2.93 mmol) was added dropwise. The mixture was allowed to warm to room temperature and stirred at this temperature for 1 h. The reaction was quenched by addition of aq HCl (10%, 20 mL) and the mixture was extracted with EtOAc (3 × 20 mL). The combined organic phases were washed with brine (50 mL), dried ($MgSO_4$) and concentrated in vacuo. Flash column chromatography (PE/EtOAc, 19:1–4:1) afforded carbonate **41** (320 mg, 10% from cyclopentanone) as a brown oil.

R_f = 0.34 (PE/EtOAc, 4:1).

IR (film): 3287, 2967, 2130, 1766, 1715, 1619 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.60–7.56 (m, 2 H), 7.44–7.41 (m, 3 H), 4.83 (d, *J* = 2.5 Hz, 2 H), 2.94 (t, *J* = 7.1 Hz, 2 H), 2.57 (t, *J* = 2.5 Hz, 1 H), 2.40 (t, *J* = 7.8 Hz, 2 H), 1.95 (quin, *J* = 7.4 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 204.9, 151.7, 147.6, 133.5, 130.4, 128.4, 128.1, 124.7, 76.6, 76.0, 56.0, 39.2, 30.3, 20.5.

2-Benzoyl-2-(3-phenoxyprop-1-en-2-yl)cyclopentanone (20g)

Following method A, carbonate **41** (64.8 mg, 0.24 mmol) was reacted with phenol (25 mg, 0.26 mmol). Flash column chromatography (PE/EtOAc, 49:1) afforded an inseparable mixture of **20g** and dibenzylideneacetone (dba) (42 mg, ratio **20g**:dba 13:1, corresponding to 40.0 mg of **20g**, 52%) as a yellow oil.

R_f = 0.66 (PE/EtOAc, 3:1).

IR (film): 3078, 2967, 2926, 2891, 1748, 1667, 1597, 1495 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.08 (dd, *J* = 8.5, 1.3 Hz, 2 H), 7.54 (tt, *J* = 7.4, 1.3 Hz, 1 H), 7.42 (t, *J* = 7.7 Hz, 2 H), 7.24 (dd, *J* = 8.8, 7.4 Hz, 2 H), 6.94 (tt, *J* = 7.4, 1.0 Hz, 1 H), 6.80 (dd, *J* = 8.8, 1.0 Hz, 2 H), 5.54 (t, *J* = 1.4 Hz, 1 H), 5.24 (s, 1 H), 4.77 (d, *J* = 12.7 Hz, 1 H), 4.57 (d, *J* = 12.7 Hz, 1 H), 2.86–2.79 (m, 1 H), 2.53–2.43 (m, 2 H), 2.41–2.30 (m, 1 H), 2.08–1.97 (m, 1 H), 1.95–1.82 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 212.3, 196.8, 158.0, 142.2, 134.6, 133.0, 130.1, 129.4, 128.1, 121.1, 116.8, 114.4, 70.4, 69.0, 37.8, 34.3, 19.4.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{21}H_{20}O_3Na$: 343.1305; found: 343.1293.

2-Acetyl-2-(3-phenoxyprop-1-en-2-yl)cyclohexanone (20h)[15]

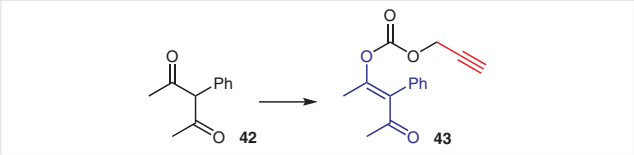
Following method A, carbonate **31**[15] (53.3 mg, 0.24 mmol) was reacted with phenol (25 mg, 0.26 mmol). Flash column chromatography (PE/EtOAc, 19:1) afforded **20h** (50 mg, 77%) as a clear oil.

R_f = 0.39 (PE/EtOAc, 4:1).

Enantioselective Catalysis: carbonate **14**[15] (35.5 mg, 0.16 mmol), $Pd_2(dba)_3$ (7.3 mg, 0.008 mmol), (*R*)-Xylyl-P-PHOS (**35**) (7.3 mg, 0.0096 mmol) and phenol (15 mg, 0.16 mmol) were added to a dried tube under argon. The tube was fitted with a septum and purged further with argon. Tetrahydrofuran (1 mL) was added and the mixture was stirred at 60 °C for 2 h, then concentrated in vacuo. Flash column chromatography (PE/EtOAc, 19:1–9:1) afforded **20h** (19 mg, 44%).

Chiral HPLC: AD-H column, 1 mL/min, (hexane/IPA, 9:1), t_A (major) = 6.0 min, t_B (minor) = 6.5 min, 19% ee.

$[\alpha]_D^{25}$ +0.8 (*c* 0.1, $CHCl_3$, 19% ee).



4-Oxo-3-phenylpent-2-en-2-yl Prop-2-ynyl Carbonate (43)

A suspension of sodium hydride (60 wt% in mineral oil, 74.8 mg, 1.87 mmol) in tetrahydrofuran (15 mL) was cooled to 0 °C. A solution of **42**[24] (300 mg, 1.70 mmol) in tetrahydrofuran (5 mL) was added dropwise and the mixture was stirred at 0 °C for 10 min. Propargyl chloroformate (182 µL, 1.87 mmol) was added dropwise and the mixture was allowed to warm to room temperature and then stirred at room temperature for 1.5 h. The reaction was quenched by the addition of aq HCl (1 M, 10 mL) and the mixture was extracted with EtOAc (3 × 25 mL). The combined organic phases were washed with brine (30 mL), dried ($MgSO_4$) and concentrated in vacuo. Flash column chromatography (PE/EtOAc, 4:1) afforded **43** (279 mg, 57%) as a pale green solid.

R_f = 0.16 (PE/EtOAc, 2:1); mp 46–48 °C.

IR (film): 3270, 2989, 2126, 1763, 1686, 1612 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.41–7.30 (m, 3 H), 7.25–7.21 (m, 2 H), 4.81 (d, *J* = 2.8 Hz, 2 H), 2.58 (t, *J* = 2.1 Hz, 1 H), 2.11 (s, 3 H), 1.91 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 198.2, 151.1, 150.7, 134.8, 131.1, 129.3, 128.8, 128.0, 76.4, 76.1, 55.9, 30.6, 18.4.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{15}O_4$: 259.0962; found: 259.0965.

3-(3-Phenoxyprop-1-en-2-yl)-3-phenylpentane-2,4-dione (20k) and 3-(2-Phenoxyallyl)-3-phenylpentane-2,4-dione (21k)

Following method A, carbonate **43** (62 mg, 0.24 mmol) was reacted with phenol (25 mg, 0.26 mmol). Flash column chromatography (PE/EtOAc, 19:1) afforded an inseparable mixture of **20k**, dba and **21k** in a 4.0:1.5:1 ratio (29 mg, corresponding to 25.5 mg of **20k** and **21k**, 35%) as a yellow oil.

R_f = 0.48 (PE/EtOAc, 4:1).

IR (film): 3014, 2983, 1681, 1627, 1573 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.44–7.18 (m), 6.94 (tt, *J* = 7.6, 1.2 Hz), 6.89–6.84 (m) (10 H and 10 H*), 5.85 (t, *J* = 1.6 Hz, 1 H), 5.32 (s, 1 H), 4.66 (t, *J* = 0.8 Hz, 2 H), 4.00 (d, *J* = 2.4 Hz, 1 H*), 3.83 (d, *J* = 2.4 Hz, 1 H*), 3.35 (s, 2 H*), 2.21 (s, 6 H and 6 H*); resonances due to **21k** annotated by an asterisk.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 205.1, 204.9, 158.8, 158.2, 143.3, 142.9, 135.6, 134.7, 130.5, 129.5, 129.4, 128.9, 128.4, 128.23, 128.20, 127.5, 125.4, 124.5, 121.5, 121.2, 121.1, 114.6, 74.1, 72.7, 68.9, 38.9, 29.7, 28.1.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{20}H_{20}O_3Na$: 331.1305; found: 331.1292.

2-Isobutyryl-2-[3-(4-nitrophenoxy)prop-1-en-2-yl]cyclohexanone (20q) and 2-Isobutyryl-2-[2-(4-nitrophenoxy)allyl]cyclohexanone (21q)

Following method A, carbonate **14**[15] (60 mg, 0.24 mmol) was reacted with 4-nitrophenol (36 mg, 0.26 mmol). Flash column chromatography (PE/EtOAc, 49:1–19:1) afforded **20q** (23 mg, 28%) and **21q** (18.5 mg, 22%) as clear oils.

20q

R_f = 0.23 (PE/EtOAc, 4:1).

IR (film): 3335, 2896, 2829, 1687, 1569 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.19 (d, *J* = 9.3 Hz, 2 H), 7.00 (d, *J* = 9.3 Hz, 2 H), 5.65 (t, *J* = 1.4 Hz, 1 H), 5.27 (s, 1 H), 4.70 (dt, *J* = 12.9 Hz, 1.3 Hz, 1 H), 4.49 (d, *J* = 12.9 Hz, 1 H), 3.05 (sept, *J* = 6.7 Hz, 1 H), 2.60 (dt, *J* = 14.0, 6.8 Hz, 1 H), 2.54–2.43 (m, 2 H), 2.16–2.08 (m, 1 H), 1.95–1.79 (m, 3 H), 1.79–1.68 (m, 1 H), 1.11 (d, *J* = 6.7 Hz, 3 H), 1.06 (d, *J* = 6.7 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 213.5, 209.4, 163.3, 141.7, 140.3, 125.9, 118.9, 114.7, 72.5, 69.4, 41.2, 36.7, 32.7, 26.8, 22.1, 20.8, 20.7.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{19}H_{23}NO_5Na$: 368.1468; found: 368.1464.

21q

R_f = 0.35 (PE/EtOAc, 4:1).

IR (film): 2895, 2828, 1669, 1622, 1586, 1567 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.22 (d, *J* = 9.3 Hz, 2 H), 7.09 (d, *J* = 9.2 Hz, 2 H), 4.40 (d, *J* = 2.4 Hz, 1 H), 4.18 (d, *J* = 2.5 Hz, 1 H), 3.07 (d, *J* = 15.0 Hz, 1 H), 2.97 (sept, *J* = 6.7 Hz, 1 H), 2.73 (d, *J* = 15.0 Hz, 1 H), 2.67 (dtd, *J* = 13.9, 4.0, 2.5 Hz, 1 H), 2.54 (dtd, *J* = 13.9, 4.3, 1.0 Hz, 1 H), 2.31 (ddd, *J* = 14.4, 12.0, 5.7 Hz, 1 H), 2.05–1.96 (m, 1 H), 1.86–1.77 (m, 2 H), 1.75–1.64 (m, 1 H), 1.55–1.45 (m, 1 H), 1.05 (d, *J* = 6.6 Hz, 3 H), 0.99 (d, *J* = 6.7 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 210.8, 208.9, 160.0, 157.4, 143.8, 125.7, 120.5, 95.4, 66.6, 42.3, 38.7, 36.4, 33.7, 26.9, 22.2, 21.2, 20.1.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{19}H_{23}NO_5Na$: 368.1468; found: 368.1461.

2-Acetyl-2-[3-(4-nitrophenoxy)prop-1-en-2-yl]-3,4-dihydronaphthalen-1(2*H*)-one (20r) and 2-Acetyl-2-[2-(4-nitrophenoxy)allyl]-3,4-dihydronaphthalen-1(2*H*)-one (21r)

Following method A, carbonate **14**[15] (65 mg, 0.24 mmol) was reacted with 4-nitrophenol (36 mg, 0.26 mmol). Flash column chromatography (PE/EtOAc, 19:1–9:1–4:1) afforded **20r** (35.5 mg, 41%) as a dark yellow solid and **21r** (38.5 mg, 44%) as a clear oil.

20r

R_f = 0.15 (PE/EtOAc, 4:1); mp 124–126 °C.

IR (film): 3009, 2908, 1685, 1647, 1571, 1492, 1477, 1320 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.16 (d, *J* = 9.6 Hz, 2 H), 8.12 (d, *J* = 9.2 Hz, 1 H), 7.51 (td, *J* = 5.7, 1.6 Hz, 1 H), 7.32 (td, *J* = 7.6, 0.8 Hz, 1 H), 7.24 (d, *J* = 7.6 Hz, 1 H), 6.87 (d, *J* = 9.2 Hz, 2 H), 5.59 (s, 1 H), 5.21 (s, 1 H), 4.77 (d, *J* = 12.0 Hz, 1 H), 4.69 (dd, *J* = 12.4, 0.8 Hz, 1 H), 3.00 (t, *J* = 13.6 Hz, 2 H), 2.73 (dd, *J* = 14.0, 6.4 Hz, 1 H), 2.43–2.37 (m, 1 H), 2.36 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 205.6, 195.8, 162.9, 143.0, 141.8, 140.2, 134.0, 131.9, 128.7, 127.9, 127.0, 125.9, 119.8, 114.6, 70.2, 67.9, 29.6, 28.2, 25.8.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{21}H_{20}NO_5$: 366.1336; found: 366.1333.

21r

R_f = 0.30 (PE/EtOAc, 4:1).

IR (film): 3029, 2888, 2807, 1683, 1648, 1567, 1495, 1467, 1431 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.21 (d, *J* = 8.4 Hz, 2 H), 8.03 (d, *J* = 8.0 Hz, 1 H), 7.50 (t, *J* = 7.6 Hz, 1 H), 7.32 (t, *J* = 7.6 Hz, 1 H), 7.23 (d, *J* = 7.6 Hz, 1 H), 7.07 (d, *J* = 9.2 Hz, 2 H), 4.52 (d, *J* = 2.4 Hz, 1 H), 4.30 (d, *J* = 2.4 Hz, 1 H), 3.27–3.14 (m, 2 H), 2.93 (dt, *J* = 17.6, 4.0 Hz, 1 H), 2.85 (d, *J* = 14.8 Hz, 1 H), 2.80 (dt, *J* = 14.0, 4.0 Hz, 1 H), 2.14 (s, 3 H), 2.08 (ddd, *J* = 16.4, 11.2, 5.2 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 204.2, 196.2, 160.1, 157.1, 143.8, 143.7, 134.1, 131.8, 129.0, 127.9, 126.8, 125.7, 120.0, 96.8, 62.8, 39.3, 29.4, 27.1, 25.8.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{21}H_{19}NO_5Na$: 388.1155; found: 388.1148.

2-Acetyl-2-{3-[4-(trifluoromethyl)phenoxy]prop-1-en-2-yl}cyclohexan-1-one (20s) and 2-Acetyl-2-{2-[4-(trifluoromethyl)phenoxy]allyl}cyclohexan-1-one (21s)

Following method A, carbonate **31**[15] (53.3 mg, 0.24 mmol) was reacted with 4-(trifluoromethyl)phenol (42 mg, 0.26 mmol). Flash column chromatography (PE/EtOAc, 19:1–9:1) afforded **20s** (26.5 mg, 32%) as a clear oil and an inseparable mixture of **21s** and dba in a 9.4:1 ratio (21.5 mg, corresponding to 20 mg of **21s**, 25%) as a pale yellow oil.

20s

R_f = 0.39 (PE/EtOAc, 4:1).

IR (film): 3037, 2902, 2824, 1687, 1617, 1589, 1566 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.53 (d, *J* = 8.4 Hz, 2 H), 6.95 (d, *J* = 8.4 Hz, 2 H), 5.64 (t, *J* = 1.2 Hz, 1 H), 5.26 (s, 1 H), 4.62 (d, *J* = 12.0 Hz, 1 H), 4.49 (dd, *J* = 12.4, 1.2 Hz, 1 H), 2.63–2.49 (m, 2 H), 2.45 (dddd, *J* = 14.8, 7.2, 3.2, 1.6 Hz, 1 H), 2.24 (s, 3 H), 2.11–2.02 (m, 1 H), 1.98–1.74 (m, 3 H), 1.73–1.61 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 209.2, 206.7, 160.6, 141.5, 126.9 (q, *J* = 3.7 Hz), 123.3 (q, *J* = 32.6 Hz), 119.4, 114.6, 71.6, 69.4, 40.9, 32.8, 27.1, 27.0, 21.8, (signal due to CF_3 not observed).

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{18}H_{19}F_3O_3Na$: 363.1179; found: 363.1175.

21s

R_f = 0.50 (PE/EtOAc, 4:1).

IR (film): 3070, 3018, 2900, 2827, 1670, 1619, 1589 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.59 (d, *J* = 8.4 Hz, 2 H), 7.07 (d, *J* = 8.0 Hz, 2 H), 4.23 (d, *J* = 2.4 Hz, 1 H), 4.00 (d, *J* = 2.4 Hz, 1 H), 3.19 (d, *J* = 14.8 Hz, 1 H), 2.76 (dq, *J* = 14.0, 3.6 Hz, 1 H), 2.52 (dtd, *J* = 13.6, 4.0, 1.6 Hz, 1 H), 2.50 (d, *J* = 14.8 Hz, 1 H), 2.24 (td, *J* = 12.8, 5.6 Hz, 1 H), 2.13 (s, 3 H), 2.09–1.98 (m, 1 H), 1.89–1.74 (m, 2 H), 1.68 (tt, *J* = 12.8, 4.0 Hz, 1 H), 1.43 (ddd, *J* = 13.6, 12.0, 4.4 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 209.0, 204.3, 158.2, 157.2, 127.0 (q, *J* = 3.8 Hz), 126.5 (q, *J* = 32.5 Hz), 121.1, 93.0, 66.7, 41.9, 39.2, 34.3, 27.4, 26.7, 22.2, (signal due to CF_3 not observed).

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{18}H_{19}F_3O_3Na$: 363.1179; found: 363.1169.

2-Acetyl-2-[3-(pyridin-3-yloxy)prop-1-en-2-yl]cyclohexan-1-one (20t) and 2-Acetyl-2-[2-(pyridin-3-yloxy)allyl]cyclohexan-1-one (21t)

Following method A, carbonate **31**[15] (53.3 mg, 0.24 mmol) was reacted with 3-hydroxypyridine (25 mg, 0.26 mmol). Flash column chromatography (PE/EtOAc, 2:1–1:1) afforded **20t** (21 mg, 32%) as a brown oil and **21t** (9 mg, 14%) as a dark orange solid.

20t

R_f = 0.16 (PE/EtOAc, 1:1).

IR (film): 2894, 2822, 1687, 1669, 1550 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.32–8.24 (m, 1 H), 8.21 (dd, *J* = 3.6, 2.4 Hz, 1 H), 7.26–7.21 (m, 2 H), 5.64 (t, *J* = 1.2 Hz, 1 H), 5.27 (s, 1 H), 4.63 (d, *J* = 12.4 Hz, 1 H), 4.49 (dd, *J* = 12.4, 1.2 Hz, 1 H), 2.61–2.50 (m, 2 H), 2.46 (ddq, *J* = 14.0, 6.8, 1.2 Hz, 1 H), 2.23 (s, 3 H), 2.06 (dddd, *J* = 14.4, 9.6, 4.0, 0.8 Hz, 1 H), 1.97–1.86 (m, 1 H), 1.86–1.74 (m, 2 H), 1.72–1.60 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 209.1, 206.8, 154.6, 142.1, 141.4, 137.8, 124.5, 121.5, 119.4, 71.7, 69.5, 40.9, 32.8, 27.0, 26.9, 21.9.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{20}NO_3$: 274.1438; found: 274.1429.

21t

R_f = 0.34 (PE/EtOAc, 1:1); mp 61–63 °C.

IR (film): 2898, 2824, 1672, 1618 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.41 (br s, 1 H), 8.32 (br s, 1 H), 7.33 (ddd, *J* = 8.4, 2.8, 1.6 Hz, 1 H), 7.30–7.26 (m, 1 H), 4.17 (d, *J* = 2.4 Hz, 1 H), 3.87 (d, *J* = 2.4 Hz, 1 H), 3.21 (d, *J* = 14.8 Hz, 1 H), 2.76 (dq, *J* = 14.0, 3.6 Hz, 1 H), 2.53 (dtd, *J* = 13.6, 4.0, 1.6 Hz, 1 H), 2.51 (d, *J* = 14.8 Hz, 1 H), 2.24 (ddd, *J* = 14.0, 13.2, 6.4 Hz, 1 H), 2.14 (s, 3 H), 2.09–1.99 (m, 1 H), 1.92–1.74 (m, 2 H), 1.68 (qt, *J* = 12.8, 4.0 Hz, 1 H), 1.43 (ddd, *J* = 14.0, 12.0, 4.8 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 209.0, 204.2, 159.0, 150.9, 145.9, 143.8, 128.8, 124.1, 91.7, 66.7, 41.9, 39.5, 34.3, 27.4, 26.7, 22.2.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{20}NO_3$: 274.1438; found: 274.1436.

2-Acetyl-2-[3-(3-chlorophenoxy)prop-1-en-2-yl]cyclohexan-1-one (20u) and 2-Acetyl-2-[2-(3-chlorophenoxy)allyl]cyclohexan-1-one (21u)

Following method A, carbonate **31**[15] (53.3 mg, 0.24 mmol) was reacted with 3-chlorophenol (33.4 mg, 0.26 mmol). Flash column chromatography (PE/EtOAc, 19:1–9:1) afforded **20u** (34 mg, 46%) as a pale yellow oil and an inseparable mixture of **21u** and dba in a 1.6:1 ratio (19 mg, corresponding to 13 mg of **21u**, 18%) as a yellow oil.

20u

R_f = 0.36 (PE/EtOAc, 4:1).

IR (film): 3024, 2899, 2823, 1687, 1618, 1570 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.17 (t, *J* = 8.4 Hz, 1 H), 6.92 (ddd, *J* = 7.6, 1.6, 0.8 Hz, 1 H), 6.87 (t, *J* = 2.0 Hz, 1 H), 6.76 (ddd, *J* = 8.4, 2.4, 0.8 Hz, 1 H), 5.64 (t, *J* = 0.8 Hz, 1 H), 5.24 (s, 1 H), 4.55 (d, *J* = 12.0 Hz, 1 H), 4.44 (dd, *J* = 12.0, 0.8 Hz, 1 H), 2.65–2.47 (m, 2 H), 2.43 (dddd, *J* = 14.4, 7.6, 3.2, 1.2 Hz, 1 H), 2.32 (s, 3 H), 2.06 (dddd, *J* = 14.4, 8.8, 3.2, 1.2 Hz, 1 H), 1.95–1.61 (m, 4 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 209.3, 206.7, 158.8, 141.6, 134.8, 130.2, 121.3, 119.5, 115.0, 113.0, 71.6, 69.4, 40.8, 32.6, 27.1 (2 C), 21.8.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{20}ClO_3$: 307.1095; found: 307.1094.

21u

R_f = 0.46 (PE/EtOAc, 4:1).

IR (film): 2890, 2806, 1671, 1626, 1566 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.25 (t, *J* = 8.4 Hz, 1 H), 7.11 (ddd, *J* = 8.0, 2.0, 1.2 Hz, 1 H), 6.98 (t, *J* = 2.0 Hz, 1 H), 6.87 (ddd, *J* = 8.0, 2.4, 0.8 Hz, 1 H), 4.15 (d, *J* = 2.4 Hz, 1 H), 3.93 (d, *J* = 2.4 Hz, 1 H), 3.18 (d, *J* = 14.8 Hz, 1 H), 2.75 (dq, *J* = 14.0, 3.6 Hz, 1 H), 2.52 (dtd, *J* = 13.6, 3.6, 1.2 Hz, 1 H), 2.47 (d, *J* = 14.8 Hz, 1 H), 2.24 (td, *J* = 13.6, 5.6 Hz, 1 H), 2.13 (s, 3 H), 2.08–1.99 (m, 1 H), 1.90–1.73 (m, 2 H), 1.67 (tt, *J* = 12.8, 4.0 Hz, 1 H), 1.42 (ddd, *J* = 14.0, 12.4, 4.4 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 209.1, 204.2, 158.6, 155.0, 134.8, 130.4, 124.8, 121.7, 119.6, 91.8, 66.7, 41.9, 39.2, 34.2, 27.4, 26.7, 22.2.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{17}H_{19}ClO_3Na$: 329.0915; found: 329.0911.

2-Acetyl-2-[3-(2-chlorophenoxy)prop-1-en-2-yl]cyclohexan-1-one (20v) and 2-Acetyl-2-[2-(2-chlorophenoxy)allyl]cyclohexan-1-one (21v)

Following method A, carbonate **31**[15] (53.3 mg, 0.24 mmol) was reacted with 2-chlorophenol (27 µL, 0.26 mmol). Flash column chromatography (PE/EtOAc, 19:1–9:1) afforded **20v** (39 mg, 53%) as a yellow oil and an inseparable mixture of **21v** and dba in a 1.2:1 ratio (23 mg, corresponding to 12 mg of **21v**, 16%) as a yellow oil.

20v

R_f = 0.28 (PE/EtOAc, 4:1).

IR (film): 3020, 2900, 2822, 1673, 1564 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.33 (dd, *J* = 8.0, 1.6 Hz, 1 H), 7.19 (ddd, *J* = 8.4, 7.6, 1.6 Hz, 1 H), 6.96 (dd, *J* = 8.4, 1.6 Hz, 1 H), 6.88 (td, *J* = 7.6, 1.2 Hz, 1 H), 5.73 (t, *J* = 1.2 Hz, 1 H), 5.26 (s, 1 H), 4.64 (d, *J* = 12.4 Hz, 1 H), 4.47 (dd, *J* = 12.4, 0.8 Hz, 1 H), 2.64–2.43 (m, 3 H), 2.27 (s, 3 H), 2.16–2.07 (m, 1 H), 1.96–1.75 (m, 3 H), 1.73–1.61 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 209.2, 206.8, 153.7, 141.3, 130.2, 127.7, 122.7, 121.6, 119.7, 113.4, 71.8, 69.7, 40.9, 32.7, 27.1, 27.0, 21.9.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{20}ClO_3$: 307.1095; found: 307.1088.

21v

R_f = 0.40 (PE/EtOAc, 4:1).

IR (film): 3015, 2897, 2824, 1672, 1626, 1596, 1567 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.38 (dd, *J* = 8.0, 1.6 Hz, 1 H), 7.23 (ddd, *J* = 8.0, 7.6, 1.6 Hz, 1 H), 7.12–7.06 (m, 1 H), 7.03 (dd, *J* = 8.0, 1.6 Hz, 1 H), 4.11 (d, *J* = 2.4 Hz, 1 H), 3.76 (d, *J* = 2.4 Hz, 1 H), 3.24 (d, *J* = 15.2 Hz, 1 H), 2.80 (dq, *J* = 14.0, 4.0 Hz, 1 H), 2.57 (d, *J* = 14.8 Hz, 1 H), 2.52 (dtd, *J* = 14.0, 4.0, 1.6 Hz, 1 H), 2.25 (ddd, *J* = 13.6, 12.8, 5.6 Hz, 1 H), 2.18 (s, 3 H), 2.08–1.98 (m, 1 H), 1.95–1.75 (m, 2 H), 1.68 (qt, *J* = 12.8, 4.0 Hz, 1 H), 1.50 (ddd, *J* = 14.0, 12.4, 4.4 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 209.0, 204.6, 157.8, 150.2, 130.5, 128.0, 127.0, 125.8, 123.3, 90.6, 66.7, 41.7, 39.1, 34.1, 27.3, 26.7, 22.2.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{17}H_{19}ClO_3Na$: 329.0915; found: 329.0905.

2-Acetyl-2-[3-(2-bromophenoxy)prop-1-en-2-yl]cyclohexan-1-one (20w) and 2-Acetyl-2-[2-(2-bromophenoxy)allyl]cyclohexan-1-one (21w)

Following method A, carbonate **31**[15] (53.3 mg, 0.24 mmol) was reacted with 2-bromophenol (30 µL, 0.26 mmol). Flash column chromatography (PE/EtOAc, 19:1–9:1) afforded **20w** (41 mg, 49%) as a pale yellow oil and an inseparable mixture of **21w** and dba in a 1.8:1 ratio (21 mg, corresponding to 9.5 mg of **21w**, 11%) as a yellow solid.

20w

R_f = 0.29 (PE/EtOAc, 4:1).

IR (film): 2898, 2822, 1673 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.51 (dd, *J* = 8.0, 1.6 Hz, 1 H), 7.24 (ddd, *J* = 8.4, 7.6, 1.6 Hz, 1 H), 6.93 (dd, *J* = 8.4, 1.6 Hz, 1 H), 6.83 (td, *J* = 7.6, 1.6 Hz, 1 H), 5.76 (t, *J* = 1.2 Hz, 1 H), 5.26 (s, 1 H), 4.63 (d, *J* = 12.4 Hz, 1 H), 4.45 (d, *J* = 12.4 Hz, 1 H), 2.64–2.44 (m, 3 H), 2.27 (s, 3 H), 2.17–2.07 (m, 1 H), 1.96–1.75 (m, 3 H), 1.73–1.60 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 209.1, 206.9, 154.6, 141.1, 133.3, 128.4, 122.1, 119.6, 113.3, 111.9, 71.8, 69.6, 40.9, 32.8, 27.1, 27.0, 21.9.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{20}BrO_3$: 351.0590; found: 351.0580.

21w

R_f = 0.40 (PE/EtOAc, 4:1); mp 46–49 °C.

IR (film): 2895, 1672, 1596 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.55 (dd, *J* = 8.0, 1.6 Hz, 1 H), 7.30–7.25 (m, 1 H), 7.06–6.99 (m, 2 H), 4.13 (d, *J* = 2.4 Hz, 1 H), 3.77 (d, *J* = 2.4 Hz, 1 H), 3.26 (d, *J* = 14.8 Hz, 1 H), 2.81 (dq, *J* = 14.0, 3.6 Hz, 1 H), 2.57 (d, *J* = 14.8 Hz, 1 H), 2.52 (dtd, *J* = 14.0, 4.0, 1.6 Hz, 1 H), 2.31–2.19 (m, 1 H), 2.19 (s, 3 H), 2.10–1.98 (m, 1 H), 1.95–1.61 (m, 3 H), 1.51 (ddd, *J* = 14.0, 12.4, 4.4 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 209.0, 204.6, 157.8, 151.4, 133.5, 128.7, 126.1, 123.3, 116.2, 90.8, 66.8, 41.7, 39.2, 34.2, 27.3, 26.8, 22.2.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{17}H_{19}BrO_3Na$: 373.0410; found: 373.0399.

3-[3-(1-Isobutyryl-2-oxocyclohexyl)prop-1-en-2-yl]-3-methylpentane-2,4-dione (23b)

Following method B, carbonate **14**[21] (47.1 mg, 0.24 mmol) was reacted with 2-isobutyrylcyclohexanone (40 µL, 0.24 mmol). Flash column chromatography (PE/EtOAc, 9:1) afforded **23b** (36 mg, 47%) as a yellow solid.

R_f = 0.25 (PE/EtOAc, 4:1); mp 40–42 °C.

IR (film): 2972, 2931, 2875, 1694, 1641 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.02 (q, *J* = 1.2 Hz, 1 H), 4.87 (q, *J* = 1.4 Hz, 1 H), 3.01 (sept, *J* = 6.6 Hz, 1 H), 2.54–2.39 (m, 5 H), 2.18 (s, 3 H), 2.17 (s, 3 H), 1.79–1.60 (m, 5 H), 1.55 (s, 3 H), 1.10 (d, *J* = 7.1 Hz, 3 H), 0.98 (d, *J* = 6.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 214.8, 209.9, 207.6, 207.4, 141.4, 116.9, 71.9, 67.6, 41.5, 36.0, 35.7, 34.3, 27.2, 27.06, 27.05, 22.0, 21.0, 20.6, 18.8.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{19}H_{29}O_4$: 321.2060; found: 321.2047.

3-[3-(2-Acetyl-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)prop-1-en-2-yl]-3-methylpentane-2,4-dione (23c)[21]

Carbonate **14**[21] (23.5 mg, 0.12 mmol), $Pd_2(dba)_3$ (5.5 mg, 0.006 mmol), DPEphos (6.5 mg, 0.012 mmol) and 2-acetyl-1-tetralone (26.7 mg, 0.12 mmol) were added to a dried tube under argon. The tube was fitted with a septum and purged further with argon. 1,4-Dioxane (1.5 mL) was added and the sealed tube was placed in an oil bath preheated to 80 °C. The mixture was stirred at 80 °C for 2 h, then cooled to room temperature and concentrated in vacuo. Flash column chromatography (PE/EtOAc, 4:1) afforded an inseparable mixture of **23c**

and homo-coupled **14** in a 14:1 ratio (34.8 mg, corresponding to 32 mg of **23c**, 79%) as a yellow oil.

R_f = 0.33 (PE/EtOAc, 4:1).

Enantioselective Catalysis: carbonate **14**[21] (31.3 mg, 0.16 mmol), $Pd_2(dba)_3$ (7.3 mg, 0.008 mmol), (*R*)-Tol-BINAP (**37**) (6.5 mg, 0.0096 mmol) and 2-acetyl-1-tetralone (30 mg, 0.16 mmol) were added to a dried tube under argon. The tube was fitted with a septum and purged further with argon. 1,4-Dioxane (1 mL) was added and the mixture was stirred at room temperature for 16 h, then concentrated in vacuo. Flash column chromatography (PE/EtOAc, 9:1–4:1) afforded **23c** (37 mg, 68%).

Chiral HPLC: OD-H column, 1 mL/min, (hexane/IPA, 9:1), t_A (minor) = 11.2 min, t_B (minor) = 12.9 min, 27% ee.

$[\alpha]_D^{25}$ +1.4 (*c* 0.1, $CHCl_3$, 27% ee).

3-[2-(2-Acetyl-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)allyl]-3-methylpentane-2,4-dione (23g)[21]

Following method B, carbonate **14**[21] (64.8 mg, 0.24 mmol) was reacted with 3-methyl-2,4-pentanedione (28 µL, 0.24 mmol). Flash column chromatography (PE/EtOAc, 4:1) afforded **23g** (58 mg, 71%) as a yellow oil.

R_f = 0.34 (PE/EtOAc, 4:1).

Enantioselective Catalysis: carbonate **14**[21] (43.2 mg, 0.16 mmol), $Pd_2(dba)_3$ (7.3 mg, 0.008 mmol), (*R*)-Xylyl-P-PHOS (**35**) (7.3 mg, 0.0096 mmol) and 3-methyl-2,4-pentanedione (19 µL, 0.16 mmol) were added to a dried tube under argon. The tube was fitted with a septum and purged further with argon. Tetrahydrofuran (1 mL) was added and the mixture was stirred at 60 °C for 2 h, then concentrated in vacuo. Flash column chromatography (PE/EtOAc, 9:1–4:1) afforded **23g** (30 mg, 57%).

Chiral HPLC: AD-H column, 1 mL/min, (hexane/IPA, 9:1), t_A (minor) = 10.7 min, t_B (major) = 12.6 min, 21% ee.

$[\alpha]_D^{25}$ –1.3 (*c* 0.1, $CHCl_3$, 21% ee).

3,6-Diacetyl-3-benzyl-6-methyl-4-methyleneoctane-2,7-dione (23h)

Following method B, carbonate **14**[15] (65.3 mg, 0.24 mmol) was reacted with 3-methyl-2,4-pentanedione (28 µL, 0.24 mmol). Flash column chromatography (PE/EtOAc, 9:1–4:1) afforded an inseparable mixture of **23h** and homo-coupled **14** in a 6.5:1 ratio (21 mg, corresponding to 17.5 mg of **23h**, 21%) as a yellow solid.

R_f = 0.37 (PE/EtOAc, 4:1); mp 70–72 °C.

IR (film): 3384, 2993, 2927, 1692, 1641, 1500 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.24–7.17 (m, 3 H), 7.06 (dd, *J* = 7.7, 1.5 Hz, 2 H), 5.18 (q, *J* = 1.4 Hz, 1 H), 4.91 (q, *J* = 1.9 Hz, 1 H), 3.47 (s, 2 H), 2.64 (t, *J* = 1.7 Hz, 2 H), 2.15 (s, 6 H), 2.11 (s, 6 H), 1.41 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 206.9, 205.8, 141.2, 136.1, 129.7, 128.4, 127.0, 117.5, 78.0, 66.0, 37.8, 35.6, 28.4, 26.2, 18.0.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{21}H_{27}O_4$: 343.1904; found: 343.1898.

3,6-Diacetyl-3-methyl-4-methylene-6-phenyloctane-2,7-dione (23k)

Following method B, carbonate **14**[21] (47.1 mg, 0.24 mmol) was reacted with 3-phenyl-2,4-pentanedione (42 mg, 0.24 mmol). Flash column chromatography (PE/EtOAc, 9:1–4:1) afforded an inseparable mixture of **23k** and homo-coupled **14** in a 4.8:1 ratio (35 mg, corresponding to 28.2 mg of **23k**, 36%) as a red oil.

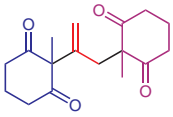
R_f = 0.22 (PE/EtOAc, 4:1).

IR (film): 3058, 2983, 2926, 1692, 1641, 1500 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.36–7.27 (m, 5 H), 5.08 (q, *J* = 1.7 Hz, 1 H), 4.89 (q, *J* = 1.9 Hz, 1 H), 3.03 (t, *J* = 2.0 Hz, 2 H), 2.21 (s, 6 H), 2.20 (s, 6 H), 1.61 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 207.5, 205.8, 141.1, 136.1, 129.0, 128.2, 128.0, 117.1, 72.8, 71.8, 35.2, 28.1, 27.0, 19.0.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{20}H_{25}O_4$: 329.1747; found: 329.1750.



23lb

2,2′-(Prop-2-ene-1,2-diyl)bis(2-methylcyclohexane-1,3-dione) (23lb)

Following method B, carbonate **14**[21] (47.1 mg, 0.24 mmol) was reacted with 2-methyl-1,3-cyclohexadione (30.2 mg, 0.24 mmol). Flash column chromatography (PE/EtOAc, 4:1) afforded an inseparable mixture of homo-coupled **22** (**23lb**), **23l**, its regioisomer **23q**, and homo-coupled **14** in a 9.0:4.0:1.2:1 ratio (39 mg, corresponding to 20 mg of **23lb**, 27%) as an orange solid.

R_f = 0.29 (PE/EtOAc, 9:1–4:1); mp 63–65 °C.

IR (film): 3368, 2939, 1723, 1686, 1638 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ (resonances due to **23lb** quoted) = 4.67 (q, *J* = 1.5 Hz, 1 H), 4.11 (q, *J* = 1.5 Hz, 1 H), 2.96–2.87 (m, 2 H), 2.84–2.75 (m, 2 H), 2.72–2.57 (m, 3 H), 2.54–2.50 (m, 1 H), 2.48 (t, *J* = 1.5 Hz, 2 H), 2.18–2.13 (m, 2 H), 1.60–1.58 (m, 2 H), 1.33–1.31 (m, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ (resonances due to **23lb** quoted) = 209.1, 208.1, 144.9, 113.0, 73.5, 63.2, 38.7, 37.5, 36.0, 26.7, 17.46, 17.45, 17.4.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{23}O_4$: 291.1591; found: 291.1580.

3-Acetyl-6-(1-hydroxyethylidene)-3-methyl-4-methyleneoctane-2,7-dione (23m)

Following method B, carbonate **14**[21] (47.1 mg, 0.24 mmol) was reacted with acetylacetone (25 µL, 0.24 mmol). Flash column chromatography (PE/EtOAc, 4:1) afforded an inseparable mixture of **23m** and homo-coupled **14** in a 10:1 ratio (37 mg, corresponding to 33.6 mg of **23m**, 56%) as a yellow solid.

R_f = 0.27 (PE/EtOAc, 9:1–4:1); mp 63–65 °C.

IR (film): 2983, 2926, 1704, 1639, 1562 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 16.88 (s, 1 H), 5.08 (t, *J* = 2.2 Hz, 1 H), 5.01 (t, *J* = 1.9 Hz, 1 H), 2.83 (t, *J* = 2.0 Hz, 2 H), 2.21 (s, 6 H), 2.06 (s, 6 H), 1.64 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 207.1, 192.3, 144.5, 114.5, 106.0, 71.0, 30.7, 26.9, 22.7, 18.9.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{21}O_4$: 253.1456; found: 253.1442.

6-Acetyl-3-benzoyl-3,6-dimethyl-4-methyleneoctane-2,7-dione (23n)[21]

Following method B, carbonate **14**[21] (61.9 mg, 0.24 mmol) was reacted with 3-methyl-2,4-pentanedione (28 µL, 0.24 mmol). Flash col-

umn chromatography (PE/EtOAc, 4:1) afforded an inseparable mixture of **23n** and homo-coupled **14** in a 5.3:1 ratio (61 mg, corresponding to 50 mg of **23n**, 63%) as a red solid.

R_f = 0.26 (PE/EtOAc, 4:1); mp 73–76 °C.

Enantioselective Catalysis: carbonate **14**[21] (45.8 mg, 0.16 mmol), $Pd_2(dba)_3$ (7.3 mg, 0.008 mmol), (*R*)-Xylyl-P-PHOS (**35**) (7.3 mg, 0.0096 mmol) and 3-methyl-2,4-pentanedione (19 µL, 0.16 mmol) were added to a dried tube under argon. The tube was fitted with a septum and purged further with argon. Tetrahydrofuran (1 mL) was added and the mixture was stirred at 60 °C for 2 h, then concentrated in vacuo. Flash column chromatography (PE/EtOAc, 9:1–4:1) afforded **23n** (18 mg, 34%).

Chiral HPLC: OD-H column, 1 mL/min, (hexane/IPA, 9:1), t_A (major) = 7.7 min, t_B (minor) = 8.5 min, 19% ee.

$[\alpha]_D^{25}$ +1.3 (*c* 0.1, $CHCl_3$, 19% ee).

Ethyl 3,3,6-Triacetyl-6-methyl-4-methylene-7-oxooctanoate (23o)

Following method B, carbonate **14**[15] (50 mg, 0.24 mmol) was reacted with 3-methyl-2,4-pentanedione (28 µL, 0.24 mmol). Flash column chromatography (PE/EtOAc, 4:1) afforded an inseparable mixture of **23o**, homo-coupled **22**, and the regioisomer of **23o** in a 16:1.2:1 ratio (38 mg, corresponding to 33.5 mg of **23o**, 41%) as a green oil.

R_f = 0.31 (PE/EtOAc, 4:1).

IR (film): 2983, 2935, 1697, 1638 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 5.09 (q, *J* = 1.8 Hz, 1 H), 4.87 (q, *J* = 1.9 Hz, 1 H), 4.13 (q, *J* = 4.1 Hz, 2 H), 3.05 (s, 2 H), 2.54 (t, *J* = 1.6 Hz, 2 H), 2.25 (s, 6 H), 2.11 (s, 6 H), 1.40 (s, 3 H), 1.25 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 206.4, 204.8, 170.6, 140.2, 117.2, 73.5, 65.3, 61.2, 37.7, 36.0, 28.1, 26.2, 18.0, 14.0.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{18}H_{26}O_6Na$: 361.1622; found: 361.1606.

2-(4-Acetyl-4-methyl-5-oxohex-1-en-2-yl)-2-methylcyclohexane-1,3-dione (23q)

Following method B, carbonate **14**[15] (50 mg, 0.24 mmol) was reacted with 3-methyl-2,4-pentanedione (28 µL, 0.24 mmol). Flash column chromatography (PE/EtOAc, 9:1–4:1) afforded **23q** (29 mg, 43%) as a yellow solid.

R_f = 0.31 (PE/EtOAc, 4:1); mp 42–44 °C.

IR (film): 3382, 2994, 2950, 2942, 1722, 1692, 1634 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 4.89 (q, *J* = 1.7 Hz, 1 H), 4.73 (q, *J* = 1.7 Hz, 1 H), 2.85–2.74 (m, 2 H), 2.62–2.53 (m, 2 H), 2.47 (t, *J* = 1.2 Hz, 2 H), 2.15–2.12 (m, 1 H), 2.10 (s, 6 H), 1.83–1.80 (m, 1 H), 1.42 (s, 3 H), 1.31 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 208.0, 206.6, 142.8, 114.8, 73.2, 65.9, 38.5, 36.2, 26.2, 18.9, 18.2, 17.4.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{23}O_4$: 279.1591; found: 279.1585.

Ethyl 2,5-Diacetyl-2,5-dimethyl-4-methylene-6-oxoheptanoate (23s)

Following method B, carbonate **14**[21] (47.1 mg, 0.24 mmol) was reacted with ethyl 2-methyl acetoacetate (34 µL, 0.24 mmol). Flash column chromatography (PE/EtOAc, 9:1–4:1) afforded **23s** (27 mg, 38%) as a brown oil.

R_f = 0.29 (PE/EtOAc, 4:1).

IR (film): 2983, 2931, 1701, 1653 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 5.01–4.99 (m, 2 H), 4.18 (q, *J* = 7.1 Hz, 1 H), 4.18 (q, *J* = 7.1 Hz, 1 H), 2.69 (dt, *J* = 18.1, 1.8 Hz, 1 H), 2.49 (dt, *J* = 17.7, 1.5 Hz, 1 H), 2.19 (s, 3 H), 2.11 (s, 3 H), 2.10 (s, 3 H), 1.43 (s, 3 H), 1.39 (s, 3 H), 1.19 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 207.2, 207.1, 205.0, 172.7, 142.4, 116.0, 72.0, 61.8, 58.7, 36.2, 27.3, 27.0, 26.0, 19.0, 18.6, 13.9.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{25}O_5$: 297.1697; found: 297.1684.

3-[3-(3-Acetyl-2-oxotetrahydrofuran-3-yl)prop-1-en-2-yl]-3-methylpentane-2,4-dione (23w)

Following method B, carbonate **14**[21] (47.1 mg, 0.24 mmol) was reacted with α-acetylbutyrolactone (30.8 mg, 0.24 mmol). Flash column chromatography (PE/EtOAc, 9:1–4:1) afforded an inseparable mixture of **23w**, homo-coupled **14** and homo-coupled **22** in a 6.8:2.2:1 ratio (35 mg, corresponding to 23.0 mg of **23w**, 34%) as a yellow oil.

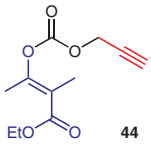
R_f = 0.15 (PE/EtOAc, 4:1).

IR (film): 2981, 2924, 2855, 1759, 1701 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 5.02 (q, *J* = 1.4 Hz, 1 H), 4.89 (q, *J* = 1.8 Hz, 1 H), 4.38–4.24 (m, 2 H), 3.13–3.00 (m, 2 H), 3.01 (dt, *J* = 18.2, 1.6 Hz, 1 H), 2.43–2.33 (m, 1 H), 2.36 (s, 3 H), 2.17 (s, 3 H), 2.16 (s, 3 H), 1.59 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 206.6, 206.4, 203.3, 174.7, 142.1, 115.6, 71.5, 66.9, 60.5, 37.7, 29.7, 27.04, 27.00, 25.7, 18.9.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{21}O_5$: 281.1384; found: 281.1348.



44

Ethyl 2-Methyl-3-[(prop-2-ynyloxy)carbonyloxy]but-2-enoate (44)

A suspension of sodium hydride (60 wt% in mineral oil, 92.3 mg, 2.31 mmol) in tetrahydrofuran (10 mL) was cooled to 0 °C. A solution of 2-methyl ethyl acetoacetate (300 µL, 2.1 mmol) in tetrahydrofuran (5 mL) was added dropwise and the mixture was stirred at 0 °C for 10 min. Propargyl chloroformate (225 µL, 2.31 mmol) was added dropwise and the mixture was allowed to warm to room temperature and stirred at room temperature for 1.5 h. The reaction was quenched by the addition of aq HCl (1 M, 20 mL) and the mixture was extracted with EtOAc (3 × 15 mL). The combined organic phases were washed with brine (20 mL), dried ($MgSO_4$) and concentrated in vacuo. Flash column chromatography (PE/EtOAc, 19:1) afforded **44** (200 mg, 45%) as a clear oil.

R_f = 0.65 (PE/EtOAc, 7:1).

IR (film): 3368, 2939, 2122, 1723, 1686, 1638 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 4.79 (d, *J* = 2.4 Hz, 2 H), 4.18 (q, *J* = 7.3 Hz, 2 H), 2.55 (t, *J* = 2.4 Hz, 1 H), 2.05 (q, *J* = 1.2 Hz, 3 H), 1.90 (q, *J* = 1.2 Hz, 3 H), 1.27 (t, *J* = 6.8 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.2, 152.1, 151.3, 117.0, 76.6, 76.0, 60.9, 55.8, 18.1, 14.5, 14.0.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{11}H_{15}O_5$: 227.0914; found: 227.0916.

Ethyl 2,5-Diacetyl-2,5-dimethyl-3-methylene-6-oxoheptanoate (23x)

Following method B, carbonate **44** (54.3 mg, 0.24 mmol) was reacted with 3-methyl-2,4-pentanedione (28 µL, 0.24 mmol). Flash column chromatography (PE/EtOAc, 9:1–4:1) afforded an inseparable mixture of **23x**, homo-coupled **22** and homo-coupled **14** in a 16:1.3:1 ratio (34 mg, corresponding to 30 mg of **23x**, 42%) as a yellow oil.

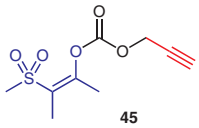
R_f = 0.35 (PE/EtOAc, 4:1).

IR (film): 2935, 2873, 1694, 1641, 1556 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 5.00 (q, *J* = 1.2 Hz, 1 H), 4.76 (q, *J* = 1.4 Hz, 1 H), 4.21 (q, *J* = 7.1 Hz, 2 H), 2.70 (d, *J* = 6.2 Hz, 2 H), 2.21 (s, 3 H), 2.13 (s, 3 H), 2.12 (s, 3 H), 1.55 (s, 3 H), 1.43 (s, 3 H), 1.27 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 207.1, 206.9, 204.8, 171.4, 142.0, 114.7, 66.4, 66.3, 61.6, 36.1, 27.0, 26.3, 26.2, 19.9, 17.8, 14.0.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{16}H_{24}O_5Na$: 319.1516; found: 319.1524.



45

3-(Methylsulfonyl)but-2-en-2-yl Prop-2-ynyl Carbonate (45)

A suspension of sodium hydride (60 wt% in mineral oil, 30.4 mg, 0.76 mmol) in tetrahydrofuran (30 mL) was cooled to 0 °C. A solution of 3-(methylsulfonyl)butan-2-one[25] (104 mg, 0.69 mmol) in tetrahydrofuran (5 mL) was added dropwise and the mixture was stirred at 0 °C for 10 min. Propargyl chloroformate (74 µL, 0.76 mmol) was added dropwise and the mixture allowed to warm to room temperature and stirred at room temperature for 1.5 h. The reaction was quenched by the addition of aq HCl (1 M, 10 mL) and the mixture was extracted with EtOAc (3 × 10 mL). The combined organic phases were washed with brine (10 mL), dried ($MgSO_4$) and concentrated in vacuo. Flash column chromatography (PE/EtOAc, 4:1–1:1) afforded **45** (101 mg, 64%) as a white solid.

R_f = 0.10 (PE/EtOAc, 1:1); mp 75–77 °C.

IR (film): 3293, 2929, 2137, 1763, 1668 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 4.78 (d, *J* = 2.7 Hz, 2 H), 2.99 (s, 3 H), 2.58 (t, *J* = 2.3 Hz, 1 H), 2.13 (q, *J* = 1.2 Hz, 3 H), 2.03 (q, *J* = 1.7 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 152.7, 150.8, 127.7, 76.4, 76.0, 56.3, 42.6, 18.3, 13.5.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_9H_{12}SO_5Na$: 255.0298; found: 255.0291.

6-Acetyl-3,6-dimethyl-4-methylene-3-(methylsulfonyl)octane-2,7-dione (23y)

Following method B, carbonate **45** (55.7 mg, 0.24 mmol) was reacted with 3-methyl-2,4-pentanedione (28 µL, 0.24 mmol). Flash column chromatography (PE/EtOAc, 9:1–1:1) afforded **23y** (15 mg, 21%) as a green oil.

R_f = 0.10 (PE/EtOAc, 4:1).

IR (film): 2927, 2855, 1712, 1695, 1634 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 5.23 (q, *J* = 1.6 Hz, 1 H), 5.07 (q, *J* = 1.9 Hz, 1 H), 3.07 (s, 3 H), 2.96–2.94 (m, 1 H), 2.93–2.91 (m, 1 H), 2.25 (s, 3 H), 2.18 (s, 3 H), 2.17 (s, 3 H), 1.86 (s, 3 H), 1.48 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 207.1, 207.0, 202.7, 137.2, 121.1, 80.2, 65.7, 37.8, 35.7, 27.2, 26.7, 26.2, 18.9, 15.6.

LRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{23}SO_5$: 303.1261; found: 303.0790.

Methyl 1-[2-(1-Acetyl-2-oxocyclohexyl)allyl]-1*H*-pyrrole-2-carboxylate (24g)[22]

Following method C, carbonate **31**[15] (53 mg, 0.24 mmol) was reacted with methyl 1*H*-pyrrole-2-carboxylate (30 mg, 0.24 mmol). Flash column chromatography (PE/EtOAc, 9:1–4:1) afforded **24g** (59 mg, 81%) as a yellow solid.

R_f = 0.43 (PE/EtOAc, 4:1); mp 104–106 °C.

Enantioselective Catalysis: carbonate **31**[15] (35.5 mg, 0.16 mmol), $Pd_2(dba)_3$ (7.3 mg, 0.008 mmol), (*R*)-Xylyl-P-PHOS (**35**) (7.3 mg, 0.0096 mmol) and methyl 1*H*-pyrrole-2-carboxylate (20 mg, 0.16 mmol) were added to a dried tube under argon. The tube was fitted with a septum and purged further with argon. Tetrahydrofuran (1 mL) was added and the mixture was stirred at 60 °C for 2 h, then concentrated in vacuo. Flash column chromatography (PE/EtOAc, 9:1–4:1) afforded **24g** (39 mg, 80%).

Chiral HPLC: OD-H column, 1 mL/min, (hexane/IPA, 19:1), t_A (minor) = 8.7 min, t_B (major) = 9.1 min, 19% ee.

$[\alpha]_D^{25}$ –0.5 (*c* 0.1, $CHCl_3$, 19% ee).

2-(1-Acetyl-2-oxocyclohexyl)allyl Benzoate (25a) and 3-(1-Acetyl-2-oxocyclohexyl)prop-1-en-2-yl Benzoate (26a)

Following method D, carbonate **31** (53.3 mg, 0.24 mmol) was reacted with benzoic acid (29.3 mg, 0.24 mmol). Flash column chromatography (PE/EtOAc, 19:1–9:1) afforded an inseparable mixture of **25a** and **26a** in a 1.7:1 ratio (32 mg, 44%) as a clear oil.

R_f = 0.26 (PE/EtOAc, 9:1).

IR (film): 2931, 2866, 17171, 1698 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.03–7.92 (m, 2 H and 2 H*), 7.62–7.51 (m, 1 H and 1 H*), 7.50–7.38 (m, 2 H and 2 H*), 5.67 (s, 1 H), 5.21 (s, 1 H), 4.96 (s, 1 H*), 4.90 (s, 1 H*), 4.89 (d, *J* = 13.6 Hz, 1 H), 4.83 (d, *J* = 13.6 Hz, 1 H), 3.07 (d, *J* = 15.6 Hz, 1 H*), 2.76 (d, *J* = 15.2 Hz, 1 H*), 2.71–2.57 (m, 1 H and 1 H*), 2.54–2.34 (m, 2 H and 1 H*), 2.23 (s, 3 H), 2.22–2.08 (m, 1 H and 1 H*), 2.03 (s, 3 H*), 2.03–1.93 (m, 1 H*), 1.92–1.57 (m, 4 H and 3 H*), 1.56–1.43 (m, 1 H*); isomer **26a** annotated by an asterisk.

^{13}C NMR (75 MHz, $CDCl_3$): δ = 209.2, 208.4, 206.5, 204.6, 165.9, 164.4, 151.4, 141.4, 133.5, 133.2, 129.9, 129.6, 129.5, 129.3, 128.5, 128.4, 120.0, 106.4, 71.8, 66.6, 65.4, 41.6, 40.6, 38.8, 33.8, 32.3, 27.3, 27.14, 27.08, 26.4, 22.1, 21.7.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{18}H_{20}O_4Na$: 323.1254; found: 323.1251.

2-(1-Acetyl-2-oxocyclohexyl)allyl Pivalate (25b) and 3-(1-Acetyl-2-oxocyclohexyl)prop-1-en-2-yl Pivalate (26b)

Following method D, carbonate **31** (53.3 mg, 0.24 mmol) was reacted with pivalic acid (24.5 mg, 0.24 mmol). Flash column chromatography (PE/EtOAc, 19:1–9:1) afforded an inseparable mixture of **25b** and **26b** in a 1.7:1 ratio (29 mg, 43%) as clear oily crystals.

R_f = 0.62 (PE/EtOAc, 4:1).

IR (film): 2956, 2874, 1732, 1717, 1696 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 5.54 (s, 1 H), 5.14 (s, 1 H), 4.76 (d, *J* = 1.8 Hz, 1 H*), 4.73 (d, *J* = 1.5 Hz, 1 H*), 4.63 (d, *J* = 13.5 Hz, 1 H), 4.50 (d, *J* = 13.5 Hz, 1 H), 2.81 (d, *J* = 15.3 Hz, 1 H*), 2.70 (d, *J* = 15.3 Hz, 1

H*), 2.67–2.21 (m, 3 H and 4 H*), 2.21 (s, 3 H), 2.10 (s, 3 H*), 2.09–1.92 (m, 1 H and 1 H*), 1.92–1.77 (m, 2 H), 1.77–1.57 (m, 2 H and 3 H*), 1.20 (s, 9 H*), 1.16 (s, 9 H); isomer **26b** annotated by an asterisk.

^{13}C NMR (75 MHz, $CDCl_3$): δ = 209.3, 208.4, 206.3, 204.7, 177.9, 176.5, 151.8, 141.7, 120.8, 105.4, 71.6, 66.6, 65.2, 41.7, 40.5, 39.0, 38.7, 38.3, 33.7, 32.0, 27.5, 27.2, 27.01, 26.97, 26.94, 26.5, 22.1, 21.6.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{16}H_{24}O_4Na$: 303.1567; found: 303.1558.

2-[2-(1-Acetyl-2-oxocyclohexyl)allyl] 1-(*tert*-Butyl) (2*S*)-Pyrrolidine-1,2-dicarboxylate (25c) and 2-[3-(1-Acetyl-2-oxocyclohexyl)prop-1-en-2-yl] 1-(*tert*-Butyl) (2*S*)-Pyrrolidine-1,2-dicarboxylate (26c)

Following method D, carbonate **31** (53.3 mg, 0.24 mmol) was reacted with *N*-Boc-L-proline (52 mg, 0.24 mmol). Flash column chromatography (PE/EtOAc, 9:1–4:1) afforded **25c** (46 mg, 49%) as a 1:1 mixture of diastereoisomers as a sticky pale yellow oil, and **26c** (14 mg, 15%) as a 1:1 mixture of diastereoisomers as a sticky pale yellow oil.

25c

R_f = 0.06 (PE/EtOAc, 9:1).

IR (film): 2974, 1752, 1696 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ (mixture of diastereoisomers and rotamers) = 5.61–5.49 (m, 1 H), 5.19–5.10 (m, 1 H), 4.78–4.48 (m, 2 H), 4.39–4.15 (m, 1 H), 3.60–3.30 (m, 2 H), 2.68–2.52 (m, 1 H), 2.52–2.40 (m, 1 H), 2.40–2.29 (m, 1 H), 2.27–2.09 (m, 4 H), 2.07–1.78 (m, 6 H), 1.78–1.61 (m, 2 H), 1.47–1.40 (m, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ (mixture of diastereoisomers and rotamers) = 209.3, 209.2, 209.0, 208.9, 206.7, 206.45, 206.37, 172.39, 172.36, 172.3, 171.0, 170.9, 154.33, 154.28, 153.7, 153.6, 141.4, 141.3, 141.1, 141.0, 120.0, 119.8, 119.7, 119.2, 78.0, 79.8, 71.8, 71.7, 71.6, 59.14, 59.06, 59.01, 58.95, 58.85, 58.78, 46.6, 46.3, 40.8, 40.64, 40.60, 32.5, 32.3, 32.0, 30.8, 30.74, 30.70, 29.8, 29.7, 28.4, 28.3, 27.4, 27.2, 27.15, 27.12, 27.07, 27.00, 26.95, 24.39, 24.37, 24.30, 23.7, 23.6, 21.7, 21.64, 21.58.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{21}H_{31}NO_6Na$: 416.2044; found: 416.2029.

26c

R_f = 0.07 (PE/EtOAc, 9:1).

IR (film): 2942, 2874, 1760, 1696 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ (mixture of diastereoisomers and rotamers) = 4.99–4.91 (m, 1 H), 4.77 (s, 1 H), 4.29–4.14 (m, 1 H), 3.60–3.32 (m, 2 H), 2.93–2.78 (m, 1 H), 2.72–2.43 (m, 4 H), 2.30–2.17 (m, 2 H), 2.17–2.09 (m, 3 H), 2.07–1.81 (m, 4 H), 1.81–1.57 (m, 3 H), 1.51–1.38 (m, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ (mixture of diastereoisomers and rotamers) = 208.6, 208.4, 205.4, 204.6, 170.9, 170.7, 170.6, 154.3, 153.71, 153.67, 151.2, 151.14, 151.07, 105.6, 105.14, 105.11, 80.1, 79.8, 66.7, 66.6, 59.21, 59.17, 59.0, 46.6, 46.4, 41.7, 41.6, 38.8, 38.7, 38.4, 38.2, 33.80, 33.77, 33.6, 30.5, 29.5, 28.40, 28.36, 27.0, 26.5, 26.4, 24.4, 23.6, 22.1.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{21}H_{31}NO_6Na$: 416.2044; found: 416.2045.

3-[2-(1-Acetyl-2-oxocyclohexyl)allyl]-3-benzylpentane-2,4-dione (34a)

Enantioselective Catalysis: carbonate **31**[15] (35.5 mg, 0.16 mmol), $Pd_2(dba)_3$ (7.3 mg, 0.008 mmol), (*R*)-Xylyl-P-PHOS (**35**) (7.3 mg, 0.0096 mmol) and 3-benzylpentane-2,4-dione (30.5 mg, 0.16 mmol) were added to a dried tube under argon. The tube was fitted with a septum and purged further with argon. Tetrahydrofuran (1 mL) was added and the mixture was stirred at 60 °C for 2 h, then concentrated in vacuo. Flash column chromatography (PE/EtOAc, 9:1–4:1) afforded **34a** (17 mg, 29%) as a clear oil.

R_f = 0.44 (PE/EtOAc, 4:1).

Chiral HPLC: AD-H column, 1 mL/min, (hexane/IPA, 9:1), t_A (minor) = 8.4 min, t_B (major) = 9.5 min, 19% ee.

$[\alpha]_D^{25}$ +1.0 (*c* 0.1, $CHCl_3$, 19% ee).

IR (film): 2942, 2206, 1694 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.25–7.19 (m, 3 H), 6.99–6.93 (m, 2 H), 5.04 (q, *J* = 1.7 Hz, 1 H), 4.97 (q, *J* = 1.5 Hz, 1 H), 3.40 (dd, *J* = 19.3, 15.0 Hz, 2 H), 2.56 (dt, *J* = 19.1, 1.6 Hz, 1 H), 2.52–2.36 (m, 3 H), 2.24 (s, 3 H), 2.22 (s, 3 H), 2.17–2.13 (m, 1 H), 2.07 (s, 3 H), 2.07–2.00 (m, 1 H), 1.90–1.80 (m, 1 H), 1.77–1.66 (m, 1 H), 1.57–1.46 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 209.1, 207.4, 206.9, 206.6, 141.2, 135.9, 129.6, 128.4, 127.2, 115.8, 73.4, 70.2, 41.0, 38.0, 33.6, 33.0, 27.7, 27.4, 27.1, 26.7, 21.7.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{23}H_{29}O_4$: 369.2060; found: 369.2050.

Ethyl 3-(3-Acetyl-3-methyl-2-methylene-4-oxopentyl)-4-oxochroman-3-carboxylate (36a)[21]

Enantioselective Catalysis: carbonate **14**[21] (31.3 mg, 0.16 mmol), $Pd_2(dba)_3$ (7.3 mg, 0.008 mmol), (*R*)-Tol-BINAP (**37**) (6.5 mg, 0.0096 mmol) and ethyl 4-oxochroman-3-carboxylate[26] (35 mg, 0.16 mmol) were added to a dried tube under argon. The tube was fitted with a septum and purged further with argon. 1,4-Dioxane (1 mL) was added and the mixture was stirred at room temperature for 16 h, then concentrated in vacuo. Flash column chromatography (PE/EtOAc, 9:1–4:1) afforded **36a** (21 mg, 35%).

R_f = 0.42 (PE/EtOAc, 5:1).

Chiral HPLC: OD-H column, 1 mL/min, (hexane/IPA, 9:1), t_A (major) = 10.1 min, t_B (minor) = 11.2 min, 11% ee.

$[\alpha]_D^{25}$ +0.8 (*c* 0.1, $CHCl_3$, 11% ee).

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Supporting Information

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