Enantioselective Intermolecular Murai-Type Alkene Hydroarylation Reactions

|  |  |
| --- | --- |
| Timothy P. Aldhousa,b  Raymond W. M. Chungb  Andrew G. Dallinga  John F. Bowerb\*  a*School of Chemistry, University of Bristol, Bristol, BS8 1TS, United Kingdom*  b*Department of Chemistry, University of Liverpool, Liverpool, L69 7ZD, United Kingdom*  John.Bower@liverpool.ac.uk |  |
|  |

Received:   
Accepted:   
Published online:   
DOI:

Abstract. Strategies that enable the efficient assembly of complex building blocks from feedstock chemicals are of paramount importance to synthetic chemistry. Building upon the pioneering work of Murai and co-workers in 1993, C-H activation-based enantioselective hydroarylations of alkenes offer a particularly promising framework for the step and atom economical installation of benzylic stereocenters. This short review presents recent intermolecular enantioselective Murai-type alkene hydroarylation methodologies and the mechanisms by which they proceed.

1. Introduction

2. Enantioselective Hydroarylation Reactions of Strained Bicyclic Alkenes

3. Enantioselective Hydroarylation Reactions of Electron Rich Acyclic Alkenes

4. Enantioselective Hydroarylation Reactions of Electron Poor Acyclic Alkenes

5. Enantioselective Hydroarylation Reactions of Minimally Polarized Acyclic Alkenes

6. Conclusion and Outlook

**Key words** Enantioselective, Hydroarylation, C-H activation, Catalysis, Transition-metal

1. **Introduction**

Tertiary benzylic stereocenters are key structural features in numerous pharmaceutical agents, including Naproxen1 (an anti-inflammatory), Tapentadol2 (an opioid analgesic) and Sertraline3 (an antidepressant, Scheme 1). Large-scale methods to prepare these molecules highlight the challenge of installing enantiomerically pure tertiary benzylic stereocenters; commercial syntheses have required lengthy sequences that rely on chiral auxiliary control or chiral resolution.1,2,4



**Scheme 1:** Examples of pharmaceutical drugs containing tertiary benzylic stereocenters.

A convergent solution to the problem of accessing enantioenriched tertiary benzylic stereocenters lies in methods that can install the key C(sp3)-Ar(sp2) bond in a direct and stereocontrolled manner. Whilst the Suzuki-Miyaura cross-coupling reaction is widely used for the construction of C(sp2)-C(sp2) bonds, it has not generally found application to the formation of tertiary-C(sp3)-C(sp2) bonds, and therefore tertiary benzylic stereocenters, because isomerization of the alkyl-Pd(II) intermediate often leads to isomeric side products.5–8 Methodological advances have emerged that address this issue, and numerous alternate cross-coupling strategies have also been developed. Pd-catalyzed methods that tolerate enantioenriched alkyl nucleophiles, including powerful enantiodivergent processes, have been reported by the groups of Sigman and Biscoe (Scheme2A).9,10 Transition metal-free cross-couplings of enantioenriched alkyl-boronic esters with aryl-lithium reagents have been developed by Aggarwal and co-workers.11–16 Pd-catalyzed processes where enantioenriched alkyl nucleophiles are formed in situ have been disclosed by Buchwald17 and Liao.18 Lu and co-workers have developed enantioselective benzylic C-H arylations that deliver tertiary benzylic stereocenters with moderate to high enantiomer ratios.19 Aryl nucleophiles can be cross-coupled with enantioenriched or racemic alkyl electrophiles to give enantioenriched products, as reported by the groups of Jarvo20, Watson21,22, Tang23 and Fu24 (Scheme2B). Effective methods that harness two electrophiles have been reported.25



**Scheme 2:** Representative methods to construct tertiary stereocenters.

The aforementioned strategies to form tertiary benzylic stereocenters require prefunctionalization of, in some cases, one or, more commonly, both cross-coupling partners. From an atom and step economy perspective, it would be more desirable to reduce the degree of prefunctionalization. In principle, this can be achieved by the enantioselective addition of aryl C-H bonds across alkenes. Friedel-Crafts alkylation offers one approach to this, but, despite advances,26–30 stereocontrolled processes are still rare,31–34 particularly with respect to minimally polarized alkenes (Scheme2C). Additionally, well established problems associated with regiocontrol, polyalkylation and the scope of the arene limit applicability. Recent metal-catalyzed strategies address some, but not all of these issues.35,36 Indeed, prevailing enantioselective methods for the hydroarylation of minimally polarized alkenes do not use aryl C‑H bonds and instead employ a combination of a prefunctionalized arene and an exogenous or internal reductant (Scheme2D).17,37–40

Regiocontrol issues associated with Friedel-Crafts reactions can be circumvented by directing group controlled C-H activation of the arene partner (Scheme3A).41–43 This strategy directs the catalyst into the proximal C-H bond of the aromatic system, thereby providing *ortho*-selectivity for the ensuing alkylation process. For reactions involving mono-substituted alkenes, recent advances have shown that the catalyst can be tuned to enforce the formation of branched (Markovnikov) products over more conventional linear (Anti-Markovnikov) products (vide infra). Further, by employing a chiral ligand, products bearing enantioenriched tertiary benzylic stereocenters can be formed. Accordingly, this Murai-type approach can exert three-fold control over (a) aryl C-H bond selectivity, (b) alkene hydrofunctionalization regioselectivity, and (c) enantioselectivity; importantly, this is all achieved within a step and atom economic framework.

In general, branch selective hydroarylation reactions are proposed to proceed through one of two mechanisms shown in Scheme3B. In both, a directing group reversibly initiates insertion of a metal catalyst into the *ortho*-C-H bond to form **I**. This is followed by either hydrometallation (**I** to **IIa**, left, *Chalk-Harrod*) or carbometallation (**I** to **IIb**, right, *Modified Chalk-Harrod*) of the alkene reactant.44 In certain cases, these pathways have been probed through computational45–48 and experimental studies;49,50 however, a Modified Chalk-Harrod mechanism has been invoked less commonly (vide infra) due to the generally higher activation barrier of alkene migratory insertion into the metal-carbon bond versus the metal-hydride bond of **I**. The final irreversible reductive elimination step gives the desired product and closes the catalytic cycle.



**Scheme 3:** (A) Hydroarylation of alkenes via C-H activation can generate branched or linear products. (B) Common mechanisms by which these hydroarylation reactions proceed.

The key steps of Murai-type processes were realized in 1986 when Lewis and Smith reported an *ortho*-selective alkylation of phenols viadirected Ru-catalyzed C-H activation.51 A phosphite directing group and a high pressure of ethylene were employed to afford alkylated phenols in moderate yield. Building upon this work, Murai and co-workers described Ru-catalyzed linear-selective hydroarylations of mono-substituted alkenes, **2** with (hetero)aryl ketones **1** (Scheme4A).52For ketone-based systems **1**, it was postulated that the carbonyl group coordinates the metal and directs C-H activation at the *ortho*-position, thereby enforcing exquisite regioselectivity with respect to the arene. For example, hydroarylation of triethoxyvinylsilanewith 2,2-dimethylpropiophenone gave solely **3a** in quantitative yield**.** Similarly, furan and thiophenesubstratesgave **3b** and **3c** in 100% and 90% yield, respectively. The key advance in Murai’s report was the discovery that “native” functional groups can be used to enforce very high levels of efficiency in these C-H activation-based processes.

In 2010, Nakao, Hiyama and co-workers established the first general methodology that overrides the usual linear selectivity of Murai hydroarylations to give more sterically-demanding branched products. This was achieved through the development of a Ni-catalyzed hydro*hetero*arylation of vinylarenes with indoles (Scheme 4B).53 Prior to this, branch selective Murai-type hydroarylation processes were limited to isolated examples.54 In Nakao and Hiyama’s study, complete branch selectivity was achieved using Ni(cod)2 with IMes as the ligand; for example, under these conditions, hydroheteroarylation of styrene **5** with indole **4** provided **6** in 90% yield and as solely the branched product. Following this, Yoshikai and co-workers developed a branch selective hydroarylation protocol.55 This was achieved by employing a PCy3-ligated Co catalyst for the coupling of 2-arylpyridines (e.g. **7**) with styrene derivatives (Scheme 4C). For example, hydroarylation of styrene with 2-phenylpyridine gave **8** in 81% yield and 98:2 branched to linear selectivity.

Branch selective Murai hydroarylation reactions set a new stereocenter, and this has stimulated the development of intermolecular enantioselective variants. Cross-couplings of this type are becoming increasingly sophisticated, such that benzylic stereocenters can now be accessed in a direct and by-product free manner. The aim of this review is to give an overview of progress in this area and to highlight key challenges that still remain.



**Scheme 4:** (A) Murai’s hydroarylation protocol, (B) Nakao and Hiyama’s branch selective hydroheteroarylation of styrene with an indole, (C) Yoshikai’s branch selective hydroarylation of styrene with 2-phenylpyridine.

Although not covered in this review, it is important to note that C-H activation triggered alkene hydroarylation and hydroheteroarylation reactions have also been developed in intramolecular settings.56 These processes are relatively well suited to enantioselective processes; this is because regioselectivity with respect to the alkene is usually (although not always)57 under substrate control, and so the development of chiral catalyst systems is simplified. The groups of Ellman and Bergman58–61, Cramer62 and others63–68 have reported enantioselective intramolecular processes that proceed viaC-H activation (Scheme5A**–**B). Enantioselective organocatalytic69 and Friedel-Crafts-type70,71 processes have also been disclosed. Reductive processes, in which a prefunctionalized aryl substrate is used, have been pursued as an alternative approach.72–74 List and co-workers have disclosed intramolecular hydroheteroarylations of non-polarized alkenes with indole moieties (Scheme5C).75 This method uses a chiral Brønsted-acid catalyst (**L2**) to produce tertiary carbocations from alkenes in situ*,* and provides a broad range of tetrahydrocarbazoles possessing quaternary stereocenters.



**Scheme 5:** (A) Ketone directed enantioselective intramolecular hydroarylations, (B) enantioselective intramolecular hydroheteroarylations using benzimidazoles, (C) enantioselective intramolecular hydroheteroarylations of non-polarized alkenes using a chiral acid.

**2. Enantioselective Hydroarylation Reactions of Strained Bicyclic Alkenes**

Early developments into intermolecular enantioselective Murai hydroarylations exploited strained and symmetrical bicyclic alkenes. The symmetry of these systems removes the issue of regiocontrol with respect to the alkene partner (vide supra). Additionally, their high steric bulk facilitates high enantioinduction, and their high reactivity enhances C-C bond forming efficiency.

The first reported example of a highly enantioselective Murai hydroarylation process involving a strained bicyclic alkene was demonstrated in 2000 by Togni and co-workers (Scheme6A).76 Here, a CpIr(I) complex, modified with a chiral bisphosphine ligand, promoted enantioselective intermolecular hydroarylation of norbornene **12** with benzamide **11** to afford **13** in 12% yield and 94% *e.e.* The process was extended further by Shibata and co-workers in 2008 (Scheme6B).77 In this study, the combination of a cationic Ir(I) precatalyst and (*R*)-MeO-BIPHEP promoted the reaction between aromatic ketone **14** and norbornene to provide **15** in 58% yield and 70% *e.e.* Note that, compared to the process in Scheme 6A, the Shibata protocol offers a higher yield and shorter reaction time, while using a weaker ketone directing group.



**Scheme 6:** (A)Togni’s and(B) Shibata’s enantioselective hydroarylations of norbornene.

Building upon the proof-of-concept studies described above, Yamamoto and Shirai developed, and thoroughly exemplified, a highly enantioselective protocol for the hydroarylation of norbornene (Scheme7).78 As with Shibata’s study, a cationic Ir(I) precatalyst was used, but this time modified with (*R*,*R*)-S-Me-BIPAM, a sulfide-linked bis(phosphoramidite) ligand. Under these conditions, various aromatic ketones and *N*,*N*-disubstituted benzamides (**16**) participate to provide the targets with invariably high levels of enantioinduction (**17a–h**). For ketone-based systems, *ortho*-substitution on the starting arene (**17a-b**) is required to prevent uncontrollable formation of bis-*ortho*-alkylated products. Conversely, only mono-*ortho*-alkylated adducts were observed when *N,N*-disubstituted amide directing groups were employed (**17c–h**). For these systems, it was postulated that initial mono-*ortho*-alkylation restricts rotation about the acyl-aryl bond, such that subsequent directed C-H bond activation of the remaining *ortho*-site is prevented.



**Scheme 7:** Enantioselective hydroarylations of norbornene using (*R*,*R*)-S-Me-BIPAM.

The processes described so far are postulated to proceed via carbonyl directed C-H bond activation. An alternative directing approach was reported in 2017 by Nishimura and co-workers, who demonstrated enantioselective hydroarylations of norbornene using an *N*‑sulfonylbenzamide directing group (Scheme8).79 The process employs an Ir(I) precatalyst that can function as a base to deprotonate the *N*‑sulfonylamide directing group with concomitant loss of water. This generates a neutral amidoiridium(I) intermediate (**I**) that undergoes C-H activation and alkylation. Deprotonation of another equivalent of starting amide by the N-Ir moiety enables turnover, such that exogenous base is not required. The use of (*R,R*)-QuinoxP\* as the chiral ligand provided **19** with 81% enantiomeric excess and in excellent yield.



**Scheme 8:** Nishimura’s amidoridium(I) directed enantioselective hydroarylation of norbornene.

Enantioselective Murai-type hydro*hetero*arylations of strained bicycloalkenes were first realized by Hartwig and Sevov in 2013 (Scheme9).80 Here, it was shown that the C2-H bond of indoles, thiophenes, pyrroles and furans will add across norbornene **12** using an Ir(I) precatalyst modified with DTBM-SEGPHOS. The protocol demonstrates good functional group tolerance and provides the targets with generally high levels of enantioinduction. For example, reaction of methyl indole-5-carboxylate with norbornene gave **21a** in 96% yield and 99% *e.e*. The most notable feature of these processes is that a directing group is not required; this demonstrates that electronically controlled C-H activation is feasible if the aromatic partner is sufficiently electron-rich.



**Scheme 9:** Enantioselective hydroheteroarylations of norbornene developed by Hartwig and Sevov.

**3. Enantioselective Hydroarylation Reactions of Electron Rich Acyclic Alkenes**

Enantioselective hydroarylation reactions of acyclic, non-strained alkenes are more challenging. A particular issue is that processes of this type must usually address the additional element of Markovnikov versus anti-Markovnikov regioselectivity. Most advances in enantioselective Murai-type hydroarylations of acyclic alkenes have exploited strongly polarized variants, in which there is a natural bias for the regioselectivity of C-C bond formation. More recently, processes that exploit minimally polarized alkenes have emerged, and these are described later.

In 2015, Nishimura and Ebe disclosed Ir(I)-catalyzed enantioselective and branch selective hydroarylations of vinyl ethers **22** with 2-phenylpyridine **7** (Scheme 10).81 The group employed a cationic Ir(I) catalyst (formed in situ) modified with (*S,S*)-Fc-tfb\*, a chiral diene ligand based on the barrelene framework (Fc = ferrocene). Under these conditions, hydroarylation of ethyl and phenyl vinyl ethers occurred in high yields and promising enantioselectivities. For example, **23a** and **23b** were generated in 77% and 76% *e.e.*, respectively. Importantly, the process offers very high regioselectivity with respect to the alkene, likely due to the strong electron donating properties of the ether oxygen (vide infra)*.* Although this process does not generate demanding tertiary stereocenters (i.e. those bearing 3-carbon-based substituents), it does demonstrate that enantioselective hydroarylation of acyclic alkenes is feasible, and it also provides an interesting approach to benzylic alcohol derivatives.



**Scheme 10:** Nishimura and Ebe’s enantioselective hydroarylation of vinyl ethers.

Deuterium labelling studies showed that reversible hydrometallation occurs in the process shown in Scheme10. This observation stimulated cross-couplings of vinyl ethers that are generated in situ via olefin isomerization of alkenyl ethers **25** (Scheme 11A).82 Optimized conditions employ an in situ generated cationic Ir(I) catalyst modified with (*R*)-BINAP or (*R*)-DM-SEGPHOS. Under these conditions a range of arenes possessing heterocyclic directing groups are tolerated, and this allows access to alkylated 2-phenyl-pyridines (**26a–c**), ‑benzothiazoles (**26d**), -benzoxazoles (**26e**) and ‑benzimidazoles (**26f**). Thorough scope studies revealed that substitution is tolerated at all positions of the aromatic ring. Notably, the methodology was also used to synthesize flavan derivatives by reaction of acetophenone with 2*H*-chromene; this demonstrates that weaker carbonyl based directing groups are effective. The group later expanded the methodology to a broader range of aromatic ketones, in addition to seven- and eight-membered cyclic alkenes. For example, the isomerization-hydroarylation reaction of seven-membered alkene **27** with 2-phenylpyridine **7** gave **28** in 54% yield and 82% *e.e.* (Scheme 11B).83 For the processes in Scheme 11, hydroarylation occurs after isomerization to the enol ether and direct coupling of **25** is usually not observed. However, when terminal alkene **29** was used, linear and branched products **31** and **32** were formed in a 3:1 ratio, in addition to target product **30** (Scheme 11C). This selectivity issue was resolved by exposing alkene **29** to the Ir(I) catalyst for 6 hours prior to addition of 2-phenylpyridine **7**. This modification allowed isomerization to occur fully before hydroarylation, such that **30** could be isolated in 84% yield and 89% *e.e.*



**Scheme 11:** (A) Isomerization-hydroarylation reactions of (A) acyclic and (B) cyclic alkenyl ethers, and (C) key regioselectivity observations.

In 2016, Nishimura and co-workers reported Ir(I)-catalyzed asymmetric alkylations of *N*-sulfonylbenzamides **33** with vinyl ethers **34** that employ the chiral diene ligand (*S,S*)-Me-tfb\* (Scheme 12A).84 Here, a hydroxyiridium(I) complex was used, which, as outlined earlier (cf. Scheme 8), likely forms a catalytically-active neutral amidoiridium(I)-complex in situ. The protocol tolerates a variety of vinyl ethers (**35a–b**), as well as a cyclic variants such as **35c**. Certain heteroaromatic substrates are effective, and this allowed access to **35d** and **35e**. Deuterium-exchange studies using D2O and butyl vinyl ether are consistent with a sequence of reversible oxidative addition of the *ortho*-C-H to the Ir(I) catalyst, followed by reversible and non-selective alkene hydrometallation (Scheme 12B). Based on further control experiments, it was proposed that, in fact, alkene hydrometallation is non-productive and C-C bond formation instead proceedsvia carbometallation (i.e. a modified Chalk-Harrod mechanism). This scenario would nicely rationalize regioselectivity with respect to the alkene – the more electron rich carbon-center of the enol ether interacts with the more electropositive Ir-center during migratory insertion.



**Scheme 12:** (A) Benzamide directed enantioselective hydroarylations of vinyl ethers and (B) associated deuterium-exchange studies.

Subsequently, the scope of the directing group was expanded to include pyrroles, imidazoles, indoles and benzimidazoles, this time using (*R,R*)-QuinoxP\* as the chiral ligand (Scheme 13A).85 The azole N-H unit is essential for the formation of the amidoiridium(I) species, such that *ortho*-alkylation to give **39a** could be achieved even in the presence of a potentially competing 2-pyridyl group. This result shows how careful tuning of properties of the catalyst and directing group can be used to enforce the desired C-H functionalization selectivity. Interestingly, C-C bond formation was not observed when 2-(*m*-tolyl)imidazole **40** was used. A competition experiment showed that **40** inhibits the hydroarylation reaction (Scheme 13B), perhaps because it coordinates too strongly to the Ir catalyst.



**Scheme 13:** (A) Heteroarene directed enantioselective hydroarylations of vinyl ethers and (B) a competition experiment to probe reaction inhibition.

In 2020, Lassaletta and co-workers reported a method for the installation of axial chirality by Ir(I)-catalyzed enantioselective hydroarylations with naphthylisoquinolines of type **42** (Scheme 14).86 Here, using (*S*)-Tol-SDP or (*R*)-Tol-BINAP as the chiral ligand, hydroarylation of enol ethers or bicycloalkenes gave a range of demanding targets in high enantioselectivity and diastereopurity. For example, hydroarylation of acyclic vinyl ethers provided **43a–f** in 70–96% yield and 94–99% *e.e.*, whereas cyclic systems generated **43g–i** in 46–76% yield, and 92–97% *e.e.* Hydroarylation of norbornene provided **43j** in 99% yield and 98% *e.e.* Computational studies suggested that the reaction proceeds via a modified Chalk-Harrod mechanism, and that the carbometallation step is stereodetermining.



**Scheme 14:** Enantioselective and diastereoselective hydroarylations of enol ethers and bicycloalkenes to generate axial chirality.

**4. Enantioselective Hydroarylation Reactions of Electron-Poor Acyclic Alkenes**

The processes described in the previous section use electron rich enol ethers where there is a natural preference for C-C bond formation to occur at the α-position. Electron poor alkenes are also predisposed to regioselective hydroarylation and this offers an alternative to conventional conjugate addition chemistry.

Shibata and co-workers used acetanilides as directing groups to develop enantioselective hydroarylations of β-substituted acrylates (Scheme 15A).87 Optimized conditions use a cationic Ir(I) precatalyst modified with (*S,S*)-CHIRAPHOS or (*S*)-DIFLUORPHOS, and these conditions give a range of *ortho*-alkylated products in excellent yield and enantioselectivity. Substitution is tolerated at all positions on the acetanilide, and hydroarylations of (*E*)-methyl crotonate gave **46a-d** in79–98% yield and 81–90% *e.e.* Variations of the β-substituent (R2) and the acrylate ester group (R3) were also explored and uniformly high enantioselectivities were obtained. Mechanistically, it was proposed that reversible and non-selective hydrometallation occurs in advance of irreversible and regioselectivity determining C-C reductive elimination. In contrast to studies described in the previous section, it is noteworthy that the processes in Scheme 15 generate demanding tertiary benzylic stereocenters in a byproduct free manner. In 2018, the Shibata group extended their methodology to hydroarylations with *N*-arylated benzamide substrates **47** (Scheme 15B).88 Here, a pre-formed, cationic Ir(I) catalyst, modified with (*S*)-SEGPHOS, was employed. Although scope studies were limited, it was shown, using β-methyl acrylate, **48**, that the protocol is insensitive to the electronics of the *N*-aryl substituent. The group also presented intramolecular hydroarylations of tethered β-substituted acrylates to obtain γ-lactones possessing all-carbon quaternary stereocenters in high *e.e.*



**Scheme 15:** Enantioselective hydroarylations of β-substituted acrylates with (A) acetanilides and (B) *N*-arylated benzamides.

Yoshino, Matsunaga and co-workers have reported mechanistically distinct β-selective and enantioselective hydroarylations of β-substituted enones (Scheme 16A). Here, an *N*-heteroarene directing group was employed in combination with a Rh(III)Cp\* complex modified with a chiral counterion (**L3**).89 Under these conditions, **52a** and **52b** were obtained in 90% *e.e.* and 80% *e.e.*, respectively. The mechanism is distinct from the options outlined in Scheme 3 because it is isohypsic with respect to the Rh-catalyst. Directed *ortho*-C-H-metallation is proposed to occur via either concerted metallation deprotonation or electrophilic aromatic substitution (rather than by C-H oxidative addition). This generates an aryl-Rh(III) species, which carbometallates the enone, in advance of protodemetallation. By employing a Rh(III) catalyst modified with a chiral Cp unit, Ellman has developed amide directed branch selective and enantioselective hydroarylations of nitroalkenes to generate addition products such as **55a** and **55b** (Scheme 16B).90 The group exemplified this methodology in the total synthesis of (+)-pancratistatin.91



**Scheme 16**: Enantioselective hydroarylations of (A) β-substituted enones and (B) nitroalkenes.

Enantioselective hydro(hetero)arylations of electron poor alkenes can also be used to install tertiary stereocenters at the alkene α-position. Rovis and co-workers have reported Rh(I)-catalyzed processes of this type using acrylates **57** and benzoxazoles **56** (Scheme 17).92 The methodology is mediated by a Rh(I)-acetate complex modified with CTH-(*R*)-xylyl-P-Phos. Through deuterium labelling and competition experiments, a mechanism was proposed where reversible acetate-assisted C-H activation of the benzoxazole gives Rh(I) species **II**. Migratory insertion of the acrylate gives complex **III**,which undergoes β-hydride elimination (to **IV**) and hydrorhodation to provide **V**.Protonation by acetic acid releases the product and regenerates the active Rh-acetate complex. The protocol offers good scope with respect to the acrylate and benzoxazole partner. In many cases, addition of 25 mol% CsOAc was necessary to achieve optimal efficiencies, possibly because this additional acetate source helps to facilitate conversion of **I** to **II**.



**Scheme 17:** Enantioselective hydroheteroarylations of α-substituted acrylates.

**5. Enantioselective Hydroarylation Reactions of Minimally Polarized Acyclic Alkenes**

Enantioselective Murai-type hydroarylations of minimally polarized monosubstituted alkenes (i.e. styrenes and α-olefins) are especially challenging because the catalyst system must be designed to enforce both branch selectivity and enantioselectivity. Additionally, minimally polarized alkenes are not electronically predisposed to C-C bond formation, which, in turn, means that bond forming efficiency can be problematic.

The issues outlined above do not preclude using enantioselective Murai hydroarylation of minimally polarized alkenes in certain specialized contexts. For example, Shibata and Shizuno disclosed *N*-directed enantioselective alkylations of (isoquinolin-1-yl)ferrocene with alkenes (Scheme 18).93 Under Ir-catalyzed conditions, reaction of **59** with **60** gave **61** in 86% yield and 91% *e.e.* (1:2 B:L). In this desymmetrization process, the site of C-H functionalization establishes the planar chirality of the product, whereas branched:linear selectivity is a secondary issue. A range of other alkenes were shown to be suitable and these predominantly offered high linear selectivity.



**Scheme 18:** Ir-catalyzed *N*-directed enantioselective alkylation of a ferrocene derivative with a styrene.

In recent years, there have been significant developments towards generalizing Murai-type hydro(hetero)arylations of monosubstituted alkenes as an enantioselective method for the construction of tertiary benzylic stereocenters. Typically, reaction development has harnessed electron-rich heteroarenes bearing relatively strong directing groups. These features likely stabilize the cyclometallated intermediate that arises upon C-H activation, thereby facilitating its engagement with the alkene reaction partner.

In 2012, Shibata and co-workers disclosed a protocol for the C2-selective and branch selective alkylation of *N*-acyl indole derivatives with various alkenes (Scheme 19A).94 Under Ir-catalyzed conditions, using (*R*)-SDP as the chiral ligand, hydroarylation of styrene **5** with indole **62** provided **63** in 93% yield and 42% *e.e.* Interestingly, the preference for the linear or branched product could be controlled by employing either an acetyl or benzoyl directing group, respectively. Further, under conditions analogous to those shown in Scheme 19A, but using (*rac*)-BINAP as the ligand, branch selective hydroheteroarylation of non-1-ene occurred in 83% yield, but took 7 days, thereby highlighting the diminished reactivity of α-olefins.

In 2015, Yoshikai and Lee reported a complementary C2-selective alkylation of indoles related to **62** that offers broad scope for styrene derivatives (Scheme 19B).95 Here, by using a PMP*-*imine directing group at C3, a cobalt/phosphoramidite (**L5**) catalyst system was shown to promote the C2-alkylation of *N*-Boc-protected indoles **64** with promising enantioselectivities. Me3SiCH2MgCl was used to reduce a Co(III) precatalyst to an active Co(I) species in situ. Using these conditions, a range of *meta-* and *para*-substituted styrene derivatives participated to provide the corresponding aldehydes **66a–j** after in situ imine hydrolysis. For example, hydroheteroarylation of 4-methoxystyrene with *N*-Boc indole-3-carbaldehyde gave **66a** in 88% yield and 86% *e.e.* whereas a 6-fluoroindole-derived substrate gave **66i** in 72% yield and 87% *e.e.*Through deuterium labelling experiments, the authors proposed a Chalk-Harrod-type mechanism. The process is notable for using a relatively abundant metal as the catalyst, which also provides mild, room temperature reaction conditions. However, the process is limited to styrenes and the requirement for installation of an imine directing group detracts from step efficiency.



**Scheme 19:** (A) *N*-Benzoyl directed enantioselective Ir-catalyzed hydroheteroarylation of styrene with an indole. (B) Co-catalyzed enantioselective hydroheteroarylations of styrene derivatives with indoles.

In 2017, Ackermann and co-workers showed that a similar transformation could be achieved using Fe(I)-catalysis (Scheme 20).96 Key to the reaction was the use of novel *meta*-substituted *N,N*’-diaryl NHC ligand, **L6**. Similar to the examples in Scheme 19B, a stoichiometric equivalent of CyMgCl, as well as TMEDA, were required to form the active Fe(I) catalyst in situ. The process is limited to styrene-like alkenes, but a variety of protecting groups are tolerated on the indole. For example, hydroheteroarylation of vinylferrocene with a benzyl protected indole gave **69a** in 69% yield and 92% *e.e.*



**Scheme 20:** Ackermann’s Fe-catalyzed hydroheteroarylations of styrene-like alkenes via a LLHT mechanism.

A deuterium labelling study showed very high levels of deuterium transfer from the indole C2 position (*deuterio*-**70**) to the methyl group of the product, *deuterio*-**72** (Scheme 20). Based on this, and with the support of computation, it was proposed the C-H cleavage occurs through an inner-sphere, ligand-to-ligand-hydrogen-atom-transfer (LLHT) mechanism. Following imine-directed oxidative addition of the C-H bond of **67** and alkene coordination (**I** to **II**), irreversible carbometallation is induced by ligation of a second equivalent of substrate (**III**). The Fe(I) species then transfers the C2-hydrogen atom from the second equivalent of **67** by a reversible LLHT mechanism (**III** to **IV**).

In a significant advance, Ackermann and co-workers subsequently developed a Co-catalyzed protocol for the C2-selective and enantioselective alkylation of indoles using aliphatic alkenes (Scheme 21).97 In this work, a chiral carboxylic acid **L7** was used to induce asymmetry and an *N*-pyridyl-based directing group was employed on the indole. The protocol offers good scope with respect to the indole and alkene components.Notably, as opposed to other Co-catalyzed processes (cf. Scheme 19B), the developed “Grignard-free” conditions tolerate substrates featuring electrophilic functional groups, such as esters (**75b**, 73% yield, 84% *e.e.*). Reaction efficiency and branch selectivity are reduced when the R2 substituent is moved further from the alkene; for example, **75e** was formed in 34% yield, 34% *e.e.*, and with 4:1 branched:linear selectivity.Deuterium exchange studies using DO2CCD3 revealed deuterium incorporation at the 2-, 3- and 7-positions of the indole substrate (*deuterio*-**76**), and minimal deuterium incorporation at the methyl group of the product, *deuterio*-**77**. With the support of computational studies, it was proposed that **L7** mediates enantioselective protodemetallation (**II** to **III**). This mechanism contrasts the Co-catalyzed hydroheteroarylations in Scheme 19B, where a reductive elimination step completes the catalytic cycle.



**Scheme 21:** Co-catalyzed C2-selective and enantioselective alkylations of indoles using aliphatic alkenes.

The processes described so far in this section tolerate either styrenes or aliphatic alkenes, and are limited to hydroheteroarylations. In 2018, Bower and co-workers reported Ir(I)-catalyzed enantioselective and branch selective hydroarylations of both styrenes and α-olefins using anilide derivatives **78** (Scheme 22A).98 In this work, [Ir(cod)2]BF4 was used in conjunction with chiral bisphosphonite ligand **L8**. Under these conditions a broad range of substrates are tolerated and even challenging α-olefins participate efficiently; for example, hydroarylation of 1-hexene gave **80e** in 96% yield and 88% *e.e.* Further, the anilide unit of the product can easily be derivatized, either by incorporation into an eventual heterocycle (**82**), or via the intermediacy of an aryl diazonium (**83**). Enantioselective hydro*hetero*arylations of styrenes and α-olefins were also developed, this time using ferrocene-based ligand **L9** (Scheme 22B).



**Scheme 22:** (A)Ir(I)-catalyzed enantioselective and branch selective hydroarylations of styrenes and α-olefins using anilide derivatives, (B) Related enantioselective hydroheteroarylation reactions.

The mechanism of the process in Scheme 22A was probed by in-depth experimental studies, leading to the working hypothesis shown in Scheme 23. Following formation of active catalyst **I**, reversible directed C-H oxidative addition of **II** forms **III**. Reversible alkene coordination (**III** to **IV**) and reversible alkene hydrometallation generates linear and branched intermediates **V** and **VI**. These are non-productive, and instead, natural abundance 13C KIE experiments indicated that reversible carbometallation from **IV** generates **VII** in advance of irreversible and turnover limiting C-H reductive elimination. A key feature of both of the ligands shown in Scheme 22 is that their wide bite angle enhances both reaction efficiency and branch selectivity. Overall, the protocol offers a viable alternative to problematic Friedel-Crafts reactions and sets the stage for the development of related by-product free functionalizations of benzenoid systems.



**Scheme 23:** Proposed mechanism for theIr(I)-catalyzed enantioselective and branch selective hydroarylations of styrenes.

**6. Conclusion and Outlook**

This short review summarizes the development of Murai-type enantioselective hydro(hetero)arylations of cyclic and acyclic alkenes. For cyclic alkenes, sophisticated protocols are now available that provide high enantioselectivity for directing group controlled hydroarylations of strained bicyclic systems. Related enantioselective hydroheteroarylations have also been developed using electron-rich heteroarenes; here, a directing group is not required. Processes involving less reactive acyclic alkenes are more challenging, in part, because Markovnikov versus anti-Markovnikov selectivity must be controlled. The use of polarized alkenes can circumvent this problem, and a variety of useful enantioselective methods have started to emerge. For minimally polarized acyclic alkenes, enantioselective processes are still in their infancy. This is perhaps the area of greatest importance, because the Murai-type framework has significant potential to address deficiencies associated with prevailing cross-coupling protocols. Important recent developments have seen prototype catalyst systems reported that are based on abundant metals and/or sophisticated ligand designs. Going forward, more efficient catalyst systems are required that offer general scope. Within this, it will be important to target processes that tolerate aliphatic alkenes, as these are much more demanding than styrenes. It would also be desirable to promote branch selective and enantioselective hydroarylations of 1,1-disubstituted alkenes, as this would streamline access to challenging quaternary benzylic stereocenters. The development of these new methods should focus on the use of directing groups that can easily be diversified after the hydroarylation step. It may even be possible to develop processes that avoid directing groups or allow “remote” hydroarylation to occur at sites other than the arene *ortho*-position.

Funding Information

We thank the European Research Council (Grant 639594 CatHet and Grant 863799 ChiCC), the University of Bristol, and the University of Liverpool for funding. We also thank the Bristol Chemical Synthesis Centre for Doctoral Training, funded by the EPSRC (EP/L015366/1), and AstraZeneca for a studentship (to T. P. A.).

References

(1) Harrington, P. J.; Lodewijk, E. *Org. Process Res. Dev.* **1997**, *1*, 72.

(2) Zhang, Q.; Li, J. F.; Tian, G. H.; Zhang, R. X.; Sun, J.; Suo, J.; Feng, X.; Fang, D.; Jiang, X. R.; Shen, J. S. *Tetrahedron: Asymmetry* **2012**, *23*, 577.

(3) Lee, S. H.; Kim, I. S.; Li, Q. R.; Dong, G. R.; Jeong, L. S.; Jung, Y. H. *J. Org. Chem.* **2011**, *76*, 10011.

(4) Taber, G. P.; Pfisterer, D. M.; Colberg, J. C. *Org. Process Res.* *Dev.* **2004**, *8*, 385.

(5) Imao, D.; Glasspoole, B. W.; Laberge, V. S.; Crudden, C. M. *J. Am. Chem. Soc.* **2009**, *131*, 5024.

(6) Li, L.; Zhao, S.; Joshi-Pangu, A.; Diane, M.; Biscoe, M. R. *J. Am. Chem. Soc.* **2014**, *136*, 14027.

(7) Swift, E. C.; Jarvo, E. R. *Tetrahedron* **2013**, *69*, 5799.

(8) Leonori, D.; Aggarwal, V. K. *Angew. Chem. Int. Ed.* **2015**, *54*, 1082.

(9) Zhao, S.; Gensch, T.; Murray, B.; Niemeyer, Z. L.; Sigman, M. S.; Biscoe, M. R. *Science* **2018**, *362*, 670.

(10) Li, L.; Wang, C. Y.; Huang, R.; Biscoe, M. R. *Nat. Chem.* **2013**, *5*, 607.

(11) Bonet, A.; Odachowski, M.; Leonori, D.; Essafi, S.; Aggarwal, V. K. *Nat. Chem.* **2014**, *6*, 584.

(12) Llaveria, J.; Leonori, D.; Aggarwal, V. K. *J. Am. Chem. Soc.* **2015**, *137*, 10958.

(13) Odachowski, M.; Bonet, A.; Essafi, S.; Conti-Ramsden, P.; Harvey, J. N.; Leonori, D.; Aggarwal, V. K. *J. Am. Chem. Soc.* **2016**, *138*, 9521.

(14) Aichhorn, S.; Bigler, R.; Myers, E. L.; Aggarwal, V. K. *J. Am. Chem. Soc.* **2017**, *139*, 9519.

(15) Ganesh, V.; Noble, A.; Aggarwal, V. K. *Org. Lett.* **2018**, *20*, 6144.

(16) Wilson, C. M.; Ganesh, V.; Noble, A.; Aggarwal, V. K. *Angew. Chem. Int. Ed*. **2017**, *56*, 16318.

(17) Friis, S. D.; Pirnot, M. T.; Buchwald, S. L. *J. Am. Chem. Soc.* **2016**, *138*, 8372.

(18) Jia, T.; Cao, P.; Wang, B.; Lou, Y.; Yin, X.; Wang, M.; Liao, J. *J. Am. Chem. Soc.* **2015**, *137*, 13760.

(19) Cheng, X.; Lu, H.; Lu, Z. *Nat. Commun.* **2019**, *10*, 3549.

(20) Taylor, B. L. H.; Harris, M. R.; Jarvo, E. R. *Angew. Chem. Int. Ed.* **2012**, *51*, 7790.

(21) Zhou, Q.; Srinivas, H. D.; Dasgupta, S.; Watson, M. P. *J. Am. Chem. Soc.* **2013**, *135*, 3307.

(22) Zhou, Q.; Cobb, K. M.; Tan, T.; Watson, M. P. *J. Am. Chem. Soc.* **2016**, *138*, 12057.

(23) Li, B.; Li, T.; Aliyu, M. A.; Li, Z. H.; Tang, W. *Angew. Chem. Int. Ed.* **2019**, *58*, 11355.

(24) Lundin, P. M.; Fu, G. C. *J. Am. Chem. Soc.* **2010**, *132*, 11027.

(25) Lucas, E. L.; Jarvo, E. R. *Nat. Rev. Chem.* **2017**, *1*, 0065.

(26) Kischel, J.; Jovel, I.; Mertins, K.; Zapf, A.; Beller, M. *Org. Lett.* **2006**, *8*, 19.

(27) Sun, H.-B.; Li, B.; Hua, R.; Yin, Y. *Eur. J. Org. Chem.* **2006**, *2006*, 4231.

(28) Lee, S. Y.; Villani-Gale, A.; Eichman, C. C. *Org. Lett.* **2016**, *18*, 5034.

(29) Poulsen, T. B.; Jørgensen, K. A. *Chem. Rev.* **2008**, *108*, 2903.

(30) Rueping, M.; Nachtsheim, B. J. *Beilstein* *J. Org. Chem.* **2010**, *6*, 6.

(31) Matsuzawa, H.; Miyake, Y.; Nishibayashi, Y. *Angew. Chem. Int. Ed.* **2007**, *46*, 6488.

(32) Vicennati, P.; Cozzi, P. G. *Eur. J. Org. Chem.* **2007**, *2007*, 2248.

(33) Mühlthau, F.; Schuster, O.; Bach, T. *J. Am. Chem. Soc.* **2005**, *127*, 9348.

(34) Mühlthau, F.; Stadler, D.; Goeppert, A.; Olah, G. A.; Prakash, G. K. S.; Bach, T. *J. Am. Chem. Soc.* **2006**, *128*, 9668.

(35) Marcum, J. S.; Roberts, C. C.; Manan, R. S.; Cervarich, T. N.; Meek, S. J. *J. Am. Chem. Soc.* **2017**, *139*, 15580.

(36) Wang, H.; Bai, Z.; Jiao, T.; Deng, Z.; Tong, H.; He, G.; Peng, Q.; Chen, G. *J. Am. Chem. Soc.* **2018**, *140*, 3542.

(37) Podhajsky, S. M.; Iwai, Y.; Cook-Sneathen, A.; Sigman, M. S. *Tetrahedron* **2011**, *67*, 4435.

(38) Chen, Y. G.; Shuai, B.; Xu, X. T.; Li, Y. Q.; Yang, Q. L.; Qiu, H.; Zhang, K.; Fang, P.; Mei, T. S. *J. Am. Chem. Soc.* **2019**, *141*, 3395.

(39) Mei, T. S.; Patel, H. H.; Sigman, M. S. *Nature* **2014**, *508*, 340.

(40) Zhang, C.; Santiago, C. B.; Crawford, J. M.; Sigman, M. S. *J. Am. Chem. Soc.* **2015**, *137*, 15668.

(41) Evano, G.; Theunissen, C. *Angew. Chem. Int. Ed.* **2019**, *58*, 7202.

(42) Dong, Z.; Ren, Z.; Thompson, S. J.; Xu, Y.; Dong, G. *Chem. Rev.* **2017**, *117*, 9333.

(43) Newton, C. G.; Wang, S. G.; Oliveira, C. C.; Cramer, N. *Chem. Rev.* **2017**, *117*, 8908.

(44) Chalk, A. J.; Harrod, J. F. *J. Am. Chem. Soc.* **1965**, *87*, 16.

(45) Matsubara, T.; Koga, N.; Musaev, D. G.; Morokuma, K. *Organometallics* **2000**, *19*, 2318.

(46) Sakaki, S.; Mizoe, N.; Sugimoto, M. *Organometallics* **1998**, *17*, 2510.

(47) Sakaki, S.; Sumimoto, M.; Fukuhara, M.; Sugimoto, M.; Fujimoto, H.; Matsuzaki, S. *Organometallics* **2002**, *21*, 3788.

(48) Zhang, M.; Hu, L.; Lang, Y.; Cao, Y.; Huang, G. *J. Org. Chem.* **2018**, *83*, 2937.

(49) Kakiuchi, F.; Sekine, S.; Tanaka, Y.; Kamatani, A.; Sonoda, M.; Chatani, N.; Murai, S. *Bull. Chem. Soc. Jpn.* **1995**, *68*, 62.

(50) Kakiuchi, F.; Kochi, T.; Mizushima, E.; Murai, S. *J. Am. Chem. Soc.* **2010**, *132*, 17741.

(51) Lewis, L. N.; Smith, J. F. *J. Am. Chem. Soc.* **1986**, *108*, 2728.

(52) Murai, S.; Kakiuchi, F.; Sekine, S.; Tanaka, Y.; Kamatani, A.; Sonoda, M.; Chatani, N. *Nature* **1993**, *336*, 529.

(53) Nakao, Y.; Kashihara, N.; Kanyiva, K. S.; Hiyama, T. *Angew. Chem. Int. Ed.* **2010**, *49*, 4451.

(54) Uchimaru, Y. *Chem. Commun.* **1999**, 1133.

(55) Gao, K.; Yoshikai, N. *J. Am. Chem. Soc.* **2011**, *133*, 400.

(56) Peneau, A.; Guillou, C.; Chabaud, L. *Eur. J. Org. Chem.* **2018**, *2018*, 5777.

(57) Donets, P. A.; Cramer, N. *Angew. Chem. Int. Ed.* **2015**, *54*, 633.

(58) Tsai, A. S.; Wilson, R. M.; Harada, H.; Bergman, R. G.; Ellman, J. A. *Chem. Commun.* **2009**, 3910.

(59) Harada, H.; Thalji, R. K.; Bergman, R. G.; Ellman, J. A. *J. Org. Chem.* **2008**, *73*, 6772.

(60) Watzke, A.; Wilson, R. M.; O’Malley, S. J.; Bergman, R. G.; Ellman, J. A. *Synlett* **2007**, *15*, 2383.

(61) Thalji, R. K.; Ellman, J. A.; Bergman, R. G. *J. Am. Chem. Soc.* **2004**, *126*, 7192.

(62) Diesel, J.; Finogenova, A. M.; Cramer, N. *J. Am. Chem. Soc.* **2018**, *140*, 4489.

(63) Sakamoto, K.; Nishimura, T. *Org. Biomol. Chem.* **2021**, *19*, 684.

(64) Li, G.; Liu, Q.; Vasamsetty, L.; Guo, W.; Wang, J. *Angew. Chem. Int. Ed.* **2020**, *59*, 3475.

(65) Li, Z. Y.; Lakmal, H. H. C.; Qian, X.; Zhu, Z.; Donnadieu, B.; McClain, S. J.; Xu, X.; Cui, X. *J. Am. Chem. Soc.* **2019**, *141*, 15730.

(66) Wang, Y.-X.; Qi, S.-L.; Luan, Y.-X.; Han, X.-W.; Wang, S.; Chen, H.; Ye, M. *J. Am. Chem. Soc.* **2018**, *140*, 5360.

(67) Shibata, T; Ryu, N.; Takano, H. *Adv. Synth. Catal.* **2015**, *357*, 1131.

(68) Shinde, V. S.; Mane, M. V.; Cavallo, L.; Rueping, M. *Chem. Eur. J.* **2020**, *26*, 8308.

(69) Lu, H.-H.; Liu, H.; Wu, W.; Wang, X.-F.; Lu, L.-Q.; Xiao, W.-J. *Chem. Eur. J.* **2009**, *15*, 2742.

(70) Huang, H.; Peters, R. *Angew. Chem. Int. Ed.* **2009**, *48*, 604.

(71) Han, X.; Widenhoefer, R. A. *Org. Lett.* **2006**, *8*, 3801.

(72) Liu, C.; Zhu, X.; Zhang, P.; Yang, H.; Zhu, C.; Fu, H. *iScience* **2018**, *10*, 11.

(73) Zhang, Z.-M.; Xu, B.; Qian, Y.; Wu, L.; Wu, Y.; Zhou, L.; Liu, Y.; Zhang, J. *Angew. Chem. Int. Ed.* **2018**, *57*, 10373.

(74) Jang, Y. J.; Larin, E. M.; Lautens, M. *Angew. Chem. Int. Ed.* **2017**, *56*, 11927.

(75) Zhang, P.; Tsuji, N.; Ouyang, J.; List, B. *J. Am. Chem. Soc.* **2021**, *143*, 675.

(76) Aufdenblatten, R.; Diezi, S.; Togni, A. *Monatsh. Chem.* **2000**, *131*, 1345.

(77) Tsuchikama, K.; Kasagawa, M.; Hashimoto, Y. K.; Endo, K.; Shibata, T. *J. Organomet. Chem.* **2008**, *693*, 3939.

(78) Shirai, T.; Yamamoto, Y. *Angew. Chem. Int. Ed.* **2015**, *54*, 9894.

(79) Nagamoto, M.; Fukuda, J. I.; Hatano, M.; Yorimitsu, H.; Nishimura, T. *Org. Lett.* **2017**, *19*, 5952.

(80) Sevov, C. S.; Hartwig, J. F. *J. Am. Chem. Soc.* **2013**, *135*, 2116.

(81) Ebe, Y.; Nishimura, T. *J. Am. Chem. Soc.* **2015**, *137*, 5899.

(82) Ebe, Y.; Onoda, M.; Nishimura, T.; Yorimitsu, H. *Angew. Chem. Int. Ed.* **2017**, *56*, 5607.

(83) Sakamoto, K.; Nishimura, T. *Adv. Synth. Catal.* **2019**, *361*, 2124.

(84) Hatano, M.; Ebe, Y.; Nishimura, T.; Yorimitsu, H. *J. Am. Chem. Soc.* **2016**, *138*, 4010.

(85) Yamauchi, D.; Nishimura, T.; Yorimitsu, H. *Chem. Commun.* **2017**, *53*, 2760.

(86) Romero-Arenas, A.; Hornillos, V.; Iglesias-Sigüenza, J.; Fernández, R.; López-Serrano, J.; Ros, A.; Lassaletta, J. M. *J. Am. Chem. Soc.* **2020**, *142*, 2628.

(87) Shibata, T.; Michino, M.; Kurita, H.; Tahara, Y. K.; Kanyiva, K. S. *Chem. Eur. J.* **2017**, *23*, 88.

(88) Shibata, T.; Kurita, H.; Onoda, S.; Kanyiva, K. S. *Asian J. Org. Chem.* **2018**, *7*, 1411.

(89) Satake, S.; Kurihara, T.; Nishikawa, K.; Mochizuki, T.; Hatano, M.; Ishihara, K.; Yoshino, T.; Matsunaga, S. *Nat. Catal.* **2018**, *1*, 585.

(90) Potter, T. J.; Kamber, D. N.; Mercado, B. Q.; Ellman, J. A. *ACS Catal.* **2017**, *7*, 150.

(91) Potter, T. J.; Ellman, J. A. *Org. Lett.* **2017**, *19*, 2985.

(92) Filloux, C. M.; Rovis, T. *J. Am. Chem. Soc.* **2015**, *137*, 508.

(93) Shibata, T.; Shizuno, T. *Angew. Chem. Int. Ed.* **2014**, *53*, 5410.

(94) Pan, S.; Ryu, N.; Shibata, T. *J. Am. Chem. Soc.* **2012**, *134*, 17474.

(95) Lee, P.-S.; Yoshikai, N. *Org. Lett.* **2015**, *17*, 22.

(96) Loup, J.; Zell, D.; Oliveira, J. C. A.; Keil, H.; Stalke, D.; Ackermann, L. *Angew. Chem. Int. Ed.* **2017**, *56*, 14197.

(97) Pesciaioli, F.; Dhawa, U.; Oliveira, J. C. A.; Yin, R.; John, M.; Ackermann, L. *Angew. Chem. Int. Ed.* **2018**, *57*, 15425.

(98) Grélaud, S.; Cooper, P.; Feron, L. J.; Bower, J. F. *J. Am. Chem. Soc.* **2018**, *140*, 9351.

**Biosketch**

|  |  |
| --- | --- |
|  | **John F. Bower** obtained his MSci degree in Chemistry from the University of Bristol (2003), where he remained for his PhD studies (2007) with Professor Timothy Gallagher. He then undertook postdoctoral appointments with Professor Michael Krische (University of Texas at Austin, 2007-2008) and Professor Timothy Donohoe (University of Oxford, 2008-2010). In 2010, he was awarded a Royal Society University Research Fellowship and commenced his independent career at the University of Bristol, where he was promoted to Professor in 2017. In 2020, he was appointed to the Regius Chair of Chemistry at the University of Liverpool. The group's research has been recognised by a number of awards, including the 2013 RSC Harrison-Meldola Memorial Prize, the 2015 RSC Hickinbottom Award and a 2016 Philip Leverhulme Prize. Since 2015, the group has been supported by the ERC (2014 Starter Grant, 2019 Consolidator Grant). |