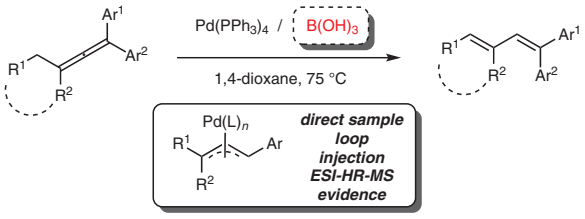
Synthesis Y. Al-Jawaheri et al. Feature

Enabling the Rearrangement of Unactivated Allenes to 1,3-Dienes by Use of a Palladium (0)/Boric Acid System

Yassir Al-Jawaheri[a,b]
Matthew Turner[a]
Marc C. Kimber*[a]

[a] School of Science, Department of Chemistry, Loughborough University, LE11 3TU, U.K.
M.C.Kimber@lboro.ac.uk
[b] College of Education, Department of Chemistry, Mosul University, Iraq



Received: 28.02.2018
Accepted after revision: 04.04.2018
Published online: 17.05.2018
DOI: 10.1055/s-0036-1591580; Art ID: ss-2018-z0138-fa

Abstract A redox neutral rearrangement of an allene to a 1,3-diene by means of a unique palladium hydride complex is reported. The palladium hydride complex is generated from a simple Pd^0 source and boric acid [$B(OH)_3$], which is typically identified as a waste by-product of the Suzuki–Miyaura reaction. A mechanism for this transformation using this novel palladium hydride complex is presented; using a direct sample loop and flow injection ESI-HRMS analysis we have detected and identified key π-allylpalladium complexes that support the addition of the palladium hydride complex to the allene.

Key words allene, 1,3-diene, palladium, boric acid, palladium hydride complex

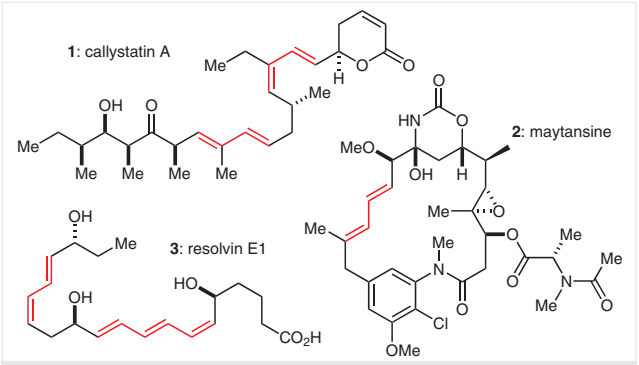
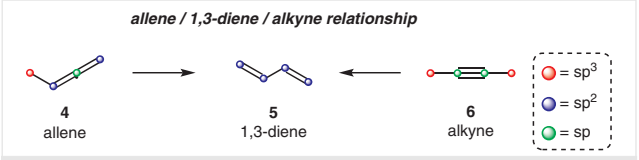


Figure 1 Representative natural products, metabolites, and marketed drugs that contain 1,3-dienes

1,3-Dienes are prominent and ubiquitous motifs in natural products, biosynthetic metabolites, potential drug targets, and functional molecules.[1] It is a core part within polyketide antibiotics such as callystatin A (**1**),[2a] the EPA oxidation anti-inflammatory metabolite resolvin E1 (**3**),[2b] as well as anticancer agents such as maytansine (**2**),[2c] which is currently used within antibody drug conjugates ado-trastuzumab emtansine marketed by Genetech and ImmunoGen under the name Kadcyla® (Figure 1).

Importantly, they have proven value as flexible intermediates in complex target synthesis.[3] The success of staple reactions such as [4+2]-cycloadditions (e.g., Diels–Alder reaction,[1b] $^1O_2$ addition,[4] etc.) are predicated on convenient routes to suitably functionalized 1,3-dienes. Additionally, a number of high profile transition-metal transformations using 1,3-diene have been recently reported that also highlight the need to access these substrates.[5]

The isomerization of an unactivated allene **4** to a 1,3-diene **5** represents a redox neutral, atom-efficient process, where the overall oxidation state of the starting material and product remain unchanged (Scheme 1). Similarly, the rearrangement of an unactivated alkyne **6** to a 1,3-diene **5** also can be seen as a redox neutral process. Yet, although unactivated alkynes have been shown to undergo this arrangement,[6] often facilitated by a transition metal, synthetically useful examples of unactivated allenes undergoing this transformation are far scarcer within the literature.



Scheme 1 Rearrangement of unactivated alkynes and allenes to 1,3-dienes

To date this rearrangement has been accomplished under thermal, acidic, and metal-mediated reaction conditions. In the 1960s and 1970s cyclopropyl-derived allenes were shown to experience thermal rearrangement; while

in the late 1980s, allenic system were shown to give cyclopentyl dienes under high temperatures.[7] Acidic conditions, using both mineral acids and organic Brønsted acids, have also been employed; however, the substrate scope for these processes has been limited and often biased toward more electron-rich allenyl substrates.[8]

More recently, metal-mediated processes, using complexes of palladium and gold, have found prominence (Scheme 2).[9] Following on from initial reports by Tsuji in the 1980s,[10a,b] in 1998 Yamamoto described the use of a palladium hydride complex derived from Pd^0 and acetic acid, H-Pd^{II}-OAc, to affect this rearrangement, although yields were modest, substrate scope limited and the reaction was complicated by a competing hydroalkoxylation pathway.[10c] In 2012, Liu successfully developed a Au^I/PhNO system to efficiently transform a range of allenyl substrates to their 1,3-diene products;[11a,b] while Widenhoefer in 2014 was able to crystallize a Au^I–π-1,3-diene complex derived from the reaction of an allene and a Au^I complex.[11c]

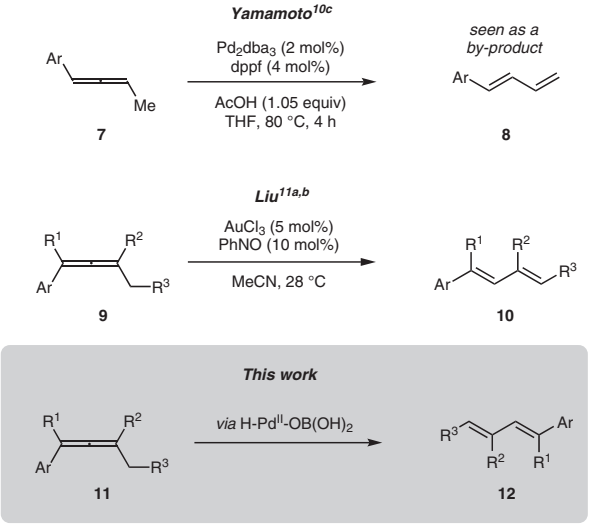
In 2016, we described a direct conversion of propargyl alcohols and aryl/heteroarylboronic acids into 1,3-dienes.[12] This process was expedited by way of a distinctive, and as yet unreported, palladium hydride complex [H-Pd^{II}-$OB(OH)_2$] that derives from Pd^0 and the by-product of the base free Suzuki–Miyaura reaction, boric acid [$B(OH)_3$]. Boric acid is rarely considered as a functional element within catalytic reactions, and there is surprisingly little within the literature describing the use of boric acid as a reagent. This is remarkable given that it is ubiquitous as a by-product in many classical metal-catalysed processes, such as the Suzuki–Miyaura reaction. An exception to this is the work of Watson and co-workers who identified the key role of boric acid within the Cham–Lam amination reaction.[13]

Biographical Sketches

Yassir Al-Jawaheri obtained his Master degree in organic synthesis from Mosul University in 2004 and he was appointed as an Assistant Lecturer in 2006. In 2010 he was promoted to full Lecturer and then in 2013 he was promoted to Assistant Professor. In 2014 he joined the Kimber group at Loughborough University to undertake his Ph.D. studies, where his primary research goals have centred on the synthesis of bioactive natural products utilising singlet oxygen ($^1O_2$) and 1,3-dienes.

Matthew Turner began his career as an analytical chemist in 1996, specializing in the analysis of pesticides, toxins, and veterinary residues in foods and feeds. In 2009 Matthew undertook his Ph.D. at Loughborough University focusing on the detection of volatile organic compounds in human breath. Matthew's current research focuses on volatile organic compound detection for application with *in vitro* and *in vivo* sources. In addition, he was awarded the RSC Tom West fellowship in 2018 for development of a differential ion mobility spectrometry interface as part of his ongoing instrument development research.

Marc C. Kimber studied at the University of Adelaide and received his Ph.D. (1998) on the synthesis of *in vivo* Zn(II) fluorophores. After postdoctoral positions with Prof. Margaret M. Harding (University of Sydney) and Prof. Dennis K. Taylor (University of Adelaide) he moved in 2002 to the UK to take up a postdoctoral position with Prof. J. Stephen Clark (University of Nottingham) working on the total synthesis of gambieric acid A. In 2004 he moved into industry (2004) as a Senior Scientist at Evotec; but returned to academia in 2006 to work on the total synthesis of nosiheptide in the group of Prof. Christopher J. Moody (University of Nottingham). In 2008 he took up a Lectureship in Organic Chemistry at Loughborough University where he was promoted to Senior Lecturer in 2015. His current research interests centre on the use of singlet oxygen ($^1O_2$) in natural product synthesis, and novel innovative synthetic transformations of allenes (and their derivatives!).



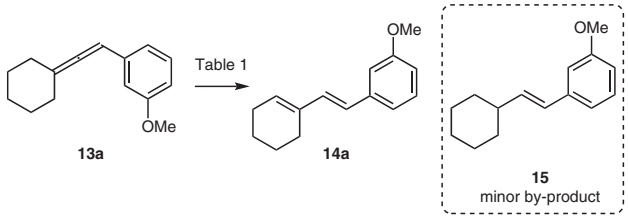
Scheme 2 Rearrangement of unactivated alkynes and allenes to 1,3-dienes

Therefore, herein, we describe the direct conversion of an allene into its 1,3-diene (Scheme 2, 11 to **12**) using this unique palladium hydride complex (H-Pd^{II}-OB(OH)$_2$. Furthermore, we provide ESI-HRMS evidence, utilising a direct sample loop and flow injection system, that supports the proposed mechanism of this rearrangement and formation of the palladium hydride complex.

Mechanistic work on the propargyl alcohol to 1,3-diene transformation had established the pivotal role of boric acid.[12] Therefore, using this as a starting point we treated allene **13a** with 10 mol% of Pd(PPh$_3$)$_4$ in the presence of 200 mol% of boric acid in 1,4-dioxane at 75 °C for 8 h, and this gave the expected 1,3-diene product **14a** in a respectable 66% conversion (Table 1, entry 1). Increasing the reaction time to 24 h increased this conversion of **13a** into **14a** to 90%, and an isolated yield of 70% was also achieved (entry 2). When the rearrangement was conducted at room temperature it proved detrimental, with the conversion to **14a** dropping to 55% (entry 3); and an increase in temperature to 90 °C, resulted in the conversion to **14a** slightly rising to 60%, but we did observed degradation of the product via polymerisation (entry 4). When the amount of boric acid was reduced by 100 mol% the conversion to **14a** fell to 35% and a minor product, **15**, was also observed (entry 5). This product **15** was also detected when B(OH)$_3$ was replaced with BzOH;[14] however, in this case, minimal 1,3-diene was observed.

With rearrangement conditions established, we examined the scope of the rearrangement with a number of allenyl substrates [Scheme 3 (a)]. All the allenes in this study were synthesised using known methods.[15] The arylvinylidenecyclohexanes **13a–c** were cleanly converted into [2-(cyclohex-1-enyl)vinyl]arenes **14a–c**; an exception was

Table 1 The Rearrangement of Allene **13a** to 1,3-Diene **14a**[a]

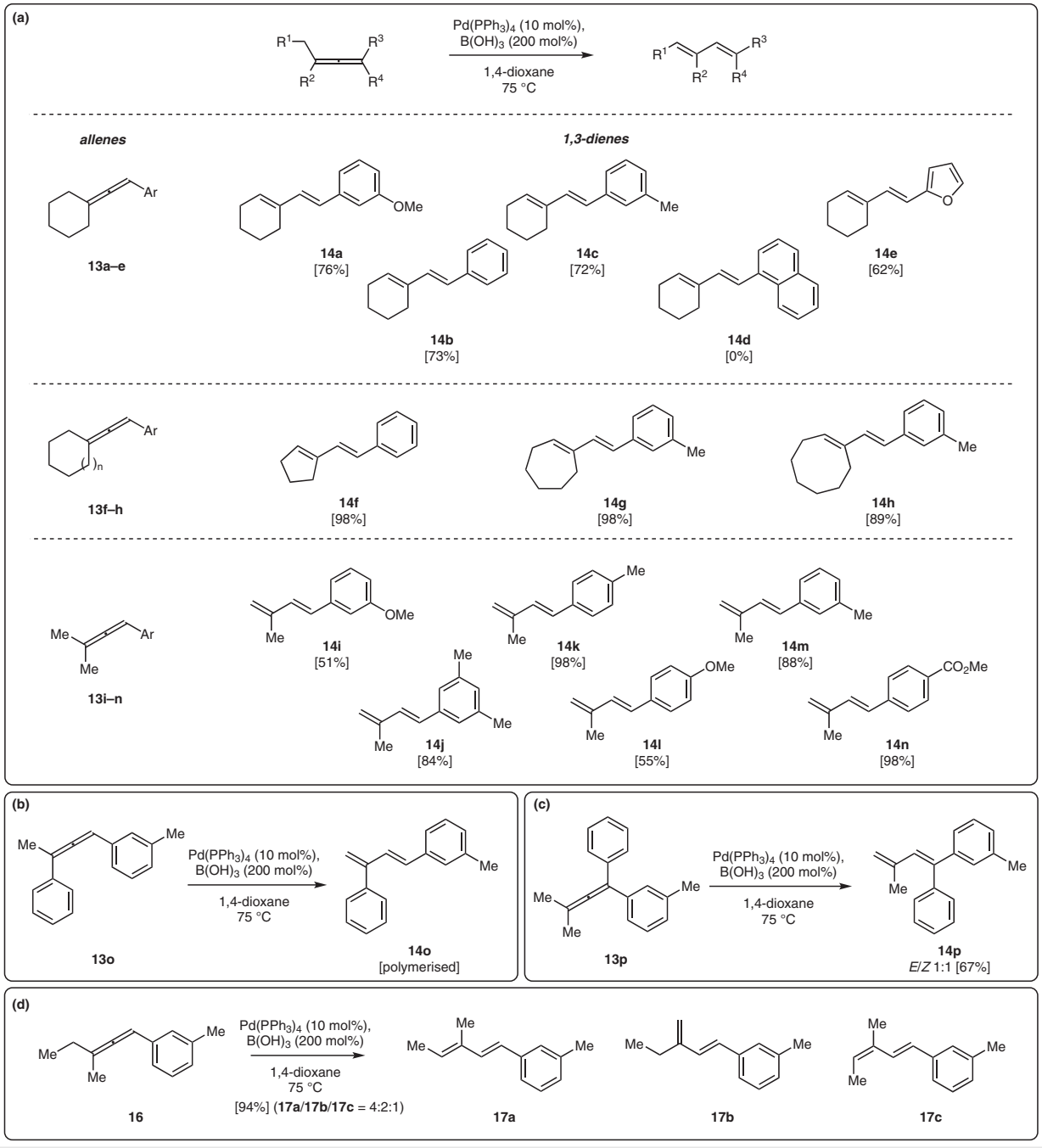


Entry	Temp (°C)	Time (h)	Conversion (%)	
			14a	**15**
1	75	8	66	–
2	75	24	90 (70)[b]	–
3	RT	24	55	–
4	90	24	60[c]	–
5[d]	75	24	35	45
6[e]	75	4.5	>5	40

[a] Reaction conditions: allene (1 equiv), Pd(PPh$_3$)$_4$ (10 mol%), B(OH)$_3$ (200 mol%), 1,4-dioxane, N$_2$ or argon atmosphere, unless otherwise stated. The conversion was determined by ^{1}H NMR analysis.
[b] Isolated yields.
[c] Degradation.
[d] B(OH)$_3$ (100 mol%).
[e] BzOH (100 mol%) instead of B(OH)$_3$.

the naphthyl-substituted allene **13d**, which failed to deliver the expected 1,3-diene **14d**. Yields for the 1,3-diene **14e** were variable due to the instability of the allene; additionally, attempts to synthesise a pyridyl-substituted allene for the rearrangement proved difficult. The arylvinylidenecyclopentane **13f**, -cycloheptane **13g**, and -cyclooctane **13h** all cleanly gave their respective 1,3-diene products **14f–h** in good to excellent isolated yields. As can be seen in these examples, there is no prerequisite in having an activated allene, for example the 3-methylphenyl-substituted allenes **13c**,**f**,**g** all underwent conversion, as do phenyl-substituted allenes **13b**,**f**. The 3-aryl-1,1-dimethylallene series **14i–n** also performed adequately in this rearrangement giving the desired 1,3-dienes in high isolated yields; of note is the performance of relatively electron-poor allene **13n** that gave the anticipated 1,3-diene **14n** in 98% yield. This result shows that both electron-rich and electron-deficient aryl-substituted allenes perform well in this rearrangement in contrast to the acid-mediated processes previously reported.[8]

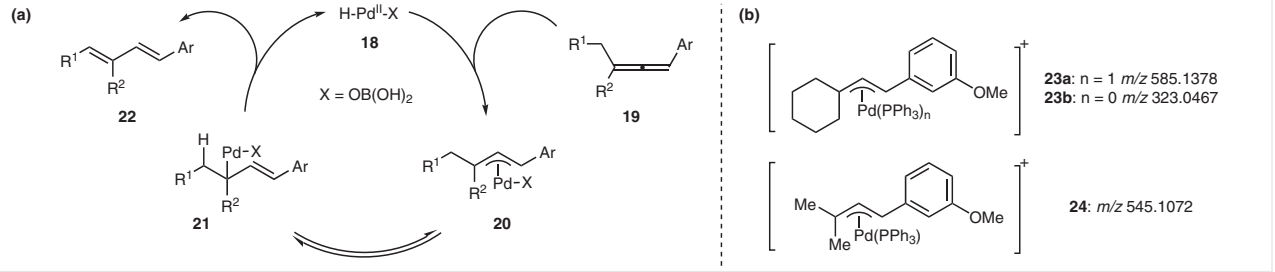
A 1,3-diarylallene **13o** was rearranged [Scheme 3 (b)] to give its 1,3-diene **14o** as indicated by crude ^{1}H NMR, but its isolation proved very problematic, as it readily polymerised upon standing. The 1,1-diaryl-3,3-dimethylallene **13p** could also be rearranged under these conditions, giving its 1,3-diene **14p** as a 1:1 mixture of *E*/*Z* geometric isomers and in an isolated yield of 67% [Scheme 3 (c)].



Scheme 3 (a) Rearrangement of unactivated allenes to 1,3-dienes; (b) formation of a 1,3-diaryl-1,3-diene; (c) rearrangement of tetrasubstituted allenes; (d) product distribution observed from the rearrangement of 3-methyl-1-(3-methylphenyl)penta-1,2-diene.

1-Aryl-3-methylpenta-1,2-diene **16** was exposed to the rearrangement conditions [Scheme 3 (d)]. Again, this allenyl-substrates performed very well, but gave a mixture of 1,3-diene products **17a–c** in good isolated yields. The thermodynamically stable *E,E*-1-aryl-1,3-diene **17a** proved to be the predominant product, together with small amount of its *E,Z*-isomer **17c**; however, the *exo*-1,3-diene **17b** was also detected and subsequently isolated.

The mechanism of this transformation can be adequately described in Scheme 4 (a). Following formation of the hydridopalladium species H-Pd^{II}-OB(OH)$_2$ (**18**),[12] hydropalladation of **19** can occur to give the π-allylpalladium complex **20**. Of the two plausible structures, **21** is the only one that



Scheme 4 (a) Plausible mechanism for $Pd^0/B(OH)_3$-mediated allene to 1,3-diene rearrangements; (b) the detected palladium complexes by direct sample loop and flow injection ESI-HRMS analysis.

can undergo *syn*-β-hydride elimination to give the thermodynamic 1,3-diene product **22**. This mechanism is, in part, supported by the hydroalkoxylation of alkynes described by Yamamoto,[14] but importantly in the case shown in Scheme 4 (a) the absence of an external nucleophile adding to the π-allylpalladium complex **21** leads to the formation **22**. Furthermore, unlike benzoic acid, which also can also lead to 1,3-diene formation,[14] boric acid does not undergo reductive coupling, possibly due to the significant difference in pK_a.[16] It is entirely plausible that the by-product observed in Table 1, entries 5 and 6, derives from intermediate **21**.

To give further support to this mechanistic hypothesis, and particularly the formation of the key π-allylpalladium complex **20**, we utilised the ESI-FTMS approach of Guo and Ma.[17] We selected two arylallenes **13a** and **13i** as substrates for this study; where the substitution on the aryl ring on each allene was selected to ensure adequate ionization, via the use of a protonatable group. However, to reduce the electron-donating ability of each allene, and to impede any adventitious protonation, a *meta*-substitution pattern was also selected. Firstly, the rearrangement of allene **13a** was monitored by direct sample loop and flow injection analysis by ESI-HRMS. After 10 minutes, we were able to intercept, detect, and characterize a number of significant palladium complexes. Two distinct complexes can be observed[18] which correspond well to the π-allylpalladium complex **20** described in Scheme 4 (a); complex **23a** where one phosphine is attached to the Pd centre (*m*/*z* 585.1378; calcd for $[C_{33}H_{34}OP^{108}Pd]^+$: *m*/*z* 585.1386) and complex **23b** (*m*/*z* 323.0467; calcd for $[C_{15}H_{19}O^{108}Pd]^+$: *m*/*z* 323.0470) where there are no phosphines attached to the Pd centre [Scheme 4 (b)]. To further support the formation of the π-allylpalladium complex **20** shown in Scheme 4 (a), allene **13i** was also analysed where an ion corresponding to complex **24** where one phosphine is attached to the Pd centre (*m*/*z* 545.1072; calcd for $C_{30}H_{30}OP^{108}Pd^+$: *m*/*z* 545.1072) was observed [Scheme 4 (b)].[18]

These MS results firmly support the formation of the Pd^{II}–hydride complex, as the key π-allylpalladium complex can only result from addition of the Pd^{II} to the allene as described by Yamamoto.[14] However, unlike Yamamoto's report the poor nucleophilicity of boric acid results in β-hydride elimination instead of undergoing reductive elimination to give the addition product.

In summary, we have demonstrated that a palladium hydride complex derived from simple $Pd(PPh_3)_4$ and boric acid ($B(OH)_3$) can rearrange allenes to their respective 1,3-dienes in good isolated yields. The mechanism of this rearrangement has been supported by the identification of key π-allylpalladium complexes via direct sample loop and flow injection analysis by ESI-HRMS. Importantly, this rearrangement demonstrates that boric acid can play a significant role within an established palladium-catalysed reaction.

All reagent chemicals were purchased from Sigma-Aldrich Chemical Company Ltd. and Lancaster Chemical Synthesis Ltd. Commercially available reagents were used and without further purification. Palladium reagents were obtained from Sigma-Aldrich Chemical Company Ltd and were handled under argon. All solvents were directly used commercially except THF which was distilled from Na/benzophenone prior to use. Petroleum ether (PE) refers to the fractions with bp 40–60 °C. Air-sensitive reactions were carried out using oven-dried glassware under N_2 atmosphere. ^{1}H NMR and ^{13}C NMR were recorded at 400 MHz and 100 MHz respectively using a Bruker Avance 400 MHz spectrometer as solutions in $CDCl_3$. TLC analysis was carried out on aluminium-backed silica plates, and plates were visualized by UV light (254 nm) or vanillin stain.

Allene to 1,3-Diene Isomerization; General Procedure

To a solution of allene (1.00 mmol) in 1,4-dioxane (5.00 mL) was added boric acid (123 mg, 2.00 mmol) and $Pd(PPh_3)_4$ (116 mg, 0.10 mmol, 10 mol%) in one portion. The resultant mixture was stirred and heated to 75 °C under a N_2 or argon atmosphere for 24 h. After this time, the mixture was cooled, diluted with Et_2O (50 mL), and transferred to a separating funnel and washed with $NaHCO_3$ (50 mL). The aqueous layer was then extracted with Et_2O (50 mL), and the combined organic layers washed with brine (50 mL), dried ($MgSO_4$), and filtered, and the solvent was removed under reduced pressure. The crude residue was then purified by column chromatography.

1-[(*E*)-2-(Cyclohex-1-enyl)vinyl]-3-methoxybenzene (14a)[12]

Colourless oil; yield: 162 mg (76%); R_f = 0.54 (EtOAc/PE 1:10).

IR (neat): 3010, 2931, 1651, 1157, 771 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.23 (t, *J* = 8.0 Hz, 1 H), 6.99 (d, *J* = 16.0 Hz, 1 H), 6.93 (s, 1 H), 6.79–6.71 (m, 2 H), 6.39 (d, *J* = 16.0 Hz, 1 H), 5.91 (t, *J* = 4.4 Hz, 1 H), 3.81 (s, 3 H), 2.26–2.24 (m, 2 H), 2.19–2.18 (m, 2 H), 1.72–1.70 (m, 2 H), 1.64–1.61 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.9, 139.6, 135.9, 133.0, 131.2, 129.5, 124.6, 119.0, 112.6, 111.4, 55.3, 26.2, 24.6, 22.6, 22.6.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{19}O$: 215.1430; found: 215.1436.

1-[(*E*)-2-(Cyclohex-1-enyl)vinyl]benzene (14b)[11a]

Colourless oil; yield: 133 mg (72%); R_f = 0.29 (PE).

IR (neat): 3082, 2933, 1641, 1493, 739 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.40–7.38 (m, 2 H), 7.31–7.24 (m, 2 H), 7.18 (t, *J* = 7.6 Hz, 1 H), 6.78 (d, *J* = 16.0 Hz, 1 H), 6.45 (d, *J* = 16.0 Hz, 1 H), 5.89 (t, *J* = 4.0 Hz, 1 H), 2.27–2.25 (m, 2 H), 2.19–2.18 (m, 2 H), 1.78–1.69 (m, 2 H), 1.69–1.60 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 137.7, 135.6, 132.7, 131.2, 128.6, 127.2, 126.2, 124.5, 26.5, 24.5, 22.6.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{17}$: 185.1325; found: 185.1321

1-[(*E*)-2-(Cyclohex-1-enyl)vinyl]-3-methylbenzene (14c)[12]

Colourless oil; yield: 145 mg (73%); R_f = 0.45 (PE).

IR (neat): 3045, 2965, 1640, 732 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.20–7.16 (m, 3 H), 7.00 (d, *J* = 4.8 Hz, 1 H), 6.77 (d, *J* = 16.0 Hz, 1 H), 6.42 (d, *J* = 16.0 Hz, 1 H), 5.88 (t, *J* = 4.0 Hz, 1 H), 2.33 (s, 3 H), 2.30–2.21 (m, 2 H), 2.21–2.13 (m, 2 H), 1.78–1.68 (m, 2 H), 1.65–1.61 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.4, 136.0, 132.5, 130.7, 128.7, 127.6, 127.0, 124.8, 123.1, 25.7, 24.8, 22.8, 21.5.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{19}$: 199.1418; found: 199.1421.

2-[(*E*)-2-(Cyclohex-1-enyl)vinyl]furan (14e)[12]

Colourless oil; yield: 106 mg (62%); R_f = 0.85 (10% EtOAc/PE).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.30 (d, *J* = 16.0 Hz, 1 H), 6.79 (d, *J* = 16.0 Hz, 1 H), 6.45–6.43 (m, 1 H), 6.21–6.18 (m, 1 H), 6.20–6.17 (m, 1 H), 5.88 (t, *J* = 3.2 Hz, 1 H), 2.16–2.12 (m, 4 H), 1.70–1.60 (m, 2 H), 1.60–1.54 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 154.0, 141.4, 135.5, 131.2, 131.0, 113.0, 111.4, 106.9, 26.2, 24.2, 22.6, 22.1.

HRMS (ESI): *m*/*z* [M – H]$^+$ calcd for $C_{12}H_{13}O$: 173.0961; found: 173.0981.

1-[(*E*)-2-(Cyclopent-1-enyl)vinyl]benzene (14f)[19a]

Colourless oil; yield: 166 mg (98%); R_f = 0.29 (PE).

IR (neat): 3054, 2986, 1598, 1420, 738 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.42 (d, *J* = 8.0 Hz, 2 H), 7.32 (t, *J* = 5.6 Hz, 2 H), 7.20 (t, *J* = 7.6 Hz, 1 H), 7.02 (d, *J* = 16.0 Hz, 1 H), 6.42 (d, *J* = 16.0 Hz, 1 H), 5.86–5.84 (m, 1 H), 2.58–2.54 (m, 2 H), 2.50–2.46 (m, 2 H), 2.05–1.94 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 142.9, 137.9, 132.2, 128.8, 128.7, 127.2, 126.3, 125.9, 33.2, 31.3, 23.3.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{15}$: 171.1174; found: 171.1168.

1-[(*E*)-2-(Cyclohept-1-enyl)vinyl]-3-methylbenzene (14g)

Colourless oil; yield: 206 mg (98%); R_f = 0.46 (PE).

IR (neat): 3028, 2921, 1603, 1444, 1264 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.21–7.17 (m, 3 H), 7.00–6.98 (m, 1 H), 6.74 (d, *J* = 16.0 Hz, 1 H), 6.44 (d, *J* = 16.0 Hz, 1 H), 6.04–6.01 (m, 1 H), 2.44–2.41 (m, 2 H), 2.33 (s, 3 H), 2.30–2.23 (m, 2 H), 1.83–1.76 (m, 2 H), 1.57–1.50 (m, 4 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 143.3, 138.1, 135.4, 133.2, 128.5, 127.7, 127.0, 124.9, 123.4, 32.4, 28.8, 27.3, 26.9, 26.4, 21.5.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{21}$: 213.1643; found: 2213.1640.

1-[(*E*)-2-(Cycloocta-1-enyl)vinyl]-3-methylbenzene (14h)

Colourless oil; yield: 200 mg (89%); R_f = 0.46 (PE).

IR (neat): 3024, 2919, 1702, 1601, 1444 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.23–7.17 (m, 3 H), 7.01–6.99 (m, 1 H), 6.74 (d, *J* = 16.4 Hz, 1 H), 6.47–6.43 (d, *J* = 16.0 Hz, 1 H), 5.86 (t, *J* = 8.8 Hz, 1 H), 2.52–2.49 (m, 2 H), 2.33 (s, 3 H), 2.26–2.23 (m, 2 H), 1.62–1.47 (m, 8 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 139.5, 138.1, 138.1, 133.7, 132.1, 128.5, 128.0, 127.0, 125.3, 123.1, 30.6, 28.5, 27.5, 27.1, 26.4, 24.4, 21.5.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{23}$: 227.1800; found: 227.1788.

1-Methoxy-3-[(1*E*)-3-methylbuta-1,3-dienyl]benzene (14i)

Colourless oil; yield: 88 mg (51%); R_f = 0.55 (5% EtOAc/PE).

IR (neat): 2939, 1603, 1464, 1156 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.25–7.21 (m, 1 H), 7.04–7.02 (m, 1 H), 6.96–6.94 (m, 1 H), 6.85 (d, *J* = 16.4 Hz, 1 H), 6.78–6.76 (m, 1 H), 6.49 (d, *J* = 16.4 Hz, 1 H), 5.11 (s, 1 H), 5.07 (s, 1 H), 3.81 (s, 3 H), 1.96 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.9, 142.1, 138.9, 132.1, 129.6, 128.7, 119.3, 117.6, 113.3, 111.7, 55.3, 18.7.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{15}O$: 175.1123; found: 175.1114.

1,3-Dimethyl-5-[(1*E*)-3-methylbuta-1,3-dienyl]benzene (14j)

Colourless oil; yield: 144 mg (84%); R_f = 0.56 (PE).

IR (neat): 2916, 1598, 1445, 1162, 840 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.05 (s, 2 H), 6.88 (s, 1 H), 6.85 (d, *J* = 16.0 Hz, 1 H), 6.48 (d, *J* = 16.0 Hz, 1 H), 5.10 (s, 1 H), 5.04 (s, 1 H), 2.30 (s, 6 H), 1.95 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 142.3, 138.1, 137.4, 131.4, 129.3, 128.9, 124.6, 124.5, 117.1, 21.4, 20.4, 18.7.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{17}$: 173.1330; found: 173.1328.

1-Methyl-4-[(1*E*)-3-methylbuta-1,3-dienyl]benzene (14k)[19b]

Colourless oil; yield: 155 mg (98%); R_f = 0.56 (PE).

IR (neat): 2986, 1603, 1513, 1265, 908 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.34 (d, *J* = 3.6 Hz, 2 H), 7.14 (d, *J* = 8.0 Hz, 2 H), 6.85 (d, *J* = 16.0 Hz, 1 H), 6.50 (d, *J* = 16.0 Hz, 1 H), 5.10 (s, 1 H), 5.05 (s, 1 H), 2.34 (s, 3 H), 1.98 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 142.3, 137.2, 134.9, 131.0, 129.4, 128.7, 126.1, 116.7, 21.3, 18.7.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{15}$: 159.1174; found: 159.1163.

1-Methoxy-4-[(1*E*)-3-methylbuta-1,3-dienyl]benzene (14l)

Colourless oil; yield: 96 mg (55%); R_f = 0.55 (5% EtOAc/PE).

IR (neat): 2959, 1604, 1509, 1172, 827 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.39–7.37 (d, *J* = 8.0 Hz, 2 H), 6.85 (d, *J* = 8.0 Hz, 2 H), 6.78 (d, *J* = 16.0 Hz, 1 H), 6.51 (d, *J* = 16.0 Hz, 1 H), 5.09–5.05 (m, 2 H), 3.81 (s, 3 H), 1.98 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.2, 142.6, 130.2, 129.7, 128.2, 127.7, 116.3, 114.1, 55.3, 18.7.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{15}O$: 175.1123 found: 175.1119.

1-Methyl-3-[(1*E*)-3-methylbuta-1,3-dienyl]benzene (14m)

Colourless oil; yield: 138 mg (88%); R_f = 0.56 (PE).

IR (neat): 3022, 2919, 1605, 1449, 1264 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.26–7.21 (m, 3 H), 7.06–7.05 (m, 1 H), 6.87 (d, *J* = 16.0 Hz, 1 H), 6.50 (d, *J* = 16.0 Hz, 1 H), 5.11 (s, 1 H), 5.06 (s, 1 H), 2.33 (s, 3 H), 1.99 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 202.4, 138.1, 136.1, 128.3, 124.4, 105.3, 94.5, 27.3, 21.4, 19.0, 12.4.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{15}$: 159.1174; found: 159.1171.

Methyl 4-[(1*E*)-3-Methylbuta-1,3-dienyl]benzoate (14n)

Colourless solid; yield: 198 mg (98%); mp 94.5–95.5 °C; R_f = 0.61 (5% EtOAc/PE).

IR (neat): 2947, 1708, 1600, 1455, 1275 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.98 (d, *J* = 6.4 Hz, 2 H), 7.47 (d, *J* = 8.4 Hz, 2 H), 6.96 (d, *J* = 16.0 Hz, 1 H), 6.52 (d, *J* = 16.0 Hz, 1 H), 5.18 (s, 1 H), 5.12 (s, 1 H), 3.89 (s, 3 H), 1.97 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.0, 142.0, 141.84, 134.2, 130.0, 128.8, 127.7, 126.4, 119.1, 52.2, 18.6.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{15}O_2$: 203.1072; found: 203.1065.

3-Methyl-1-(3-methylphenyl)-1-phenylbuta-1,3-diene (14p)

Colourless oil; yield: 156 mg (67%); *E*/*Z* isomers approx. 1:1; R_f = 0.37 (PE).

IR (neat): 3021, 2914, 1599, 1489, 1180, 883 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.42–7.01 (m, 9 H), 6.67 (s, 1 H), 5.04–4.98 (m, 2 H), 2.44 (s, 3 H), 2.36 (d, *J* = 14 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 141.7, 141.4, 138.3, 131.0, 130.4, 128.6, 128.2, 128.1, 128.0, 127.8, 127.2, 124.8, 124.3, 119.1, 22.1, 21.6.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{19}$: 235.1487; found: 235.1486.

Isomerisation of 1-Methyl-3-(3-methylpenta-1,2-dienyl)benzene (16)

Compound **16** was isomerized using the general procedure giving a mixture of three compounds **17a**/**17b**/**17c** in a ratio of 4:2:1; **17a** was isolated as a single product, but **17b** and **17c** were isolated and subsequently characterized as a mixture:

1-Methyl-3-[(1*E*,3*E*)-3-methylpenta-1,3-dienyl]benzene (17a)

Colourless oil; yield: 100 mg (58%); R_f = 0.39 (PE).

IR (neat): 3025, 2980, 1640, 1442, 732 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.24–7.18 (m, 3 H), 7.01 (d, *J* = 6 Hz, 1 H), 6.81 (d, *J* = 16.4 Hz, 1 H), 6.43 (d, *J* = 16.0 Hz, 1 H), 5.71 (m, 1 H), 2.35 (s, 3 H), 1.85 (s, 3 H), 1.78 (d, *J* = 6.0 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.0, 138.0, 133.8, 128.3, 128.0, 127.8, 127.0, 125.0, 123.0, 21.8, 14.0, 12.0.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{17}$: 173.1325; found: 173.1323.

1-Methyl-3-[(1*E*)-3-methylenepenta-1,3-dienyl]benzene (17b) and 1-Methyl-3-[(1*E*,3*Z*)-3-methylpenta-1,3-dienyl]benzene (17c)

Inseparable mixture of **17b** and **17c**; yield: 60 mg (35%).

IR (neat): 3025, 2980, 1640, 1442, 732 cm^{-1}.

17b:

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.26–7.19 (m, 3 H), 7.03 (d, *J* = 8 Hz, 1 H), 6.82 (d, *J* = 16.0 Hz, 1 H), 6.56 (d, *J* = 16 Hz, 1 H), 5.10 (d, *J* = 2 Hz, 2 H), 2.36 (m, *J* = 6.8 Hz, 2 H), 2.38 (s, 3 H), 1.16 (m, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 147.8, 139.9, 128.5, 128.1, 127.1, 125.9, 123.6, 115.0, 24.8, 21.5, 18.8.

17c:

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.26–7.19 (m, 3 H), 7.03 (d, *J* = 8 Hz, 1 H), (d, *J* = 8 Hz, 1 H), 6.52 (d, *J* = 12 Hz, 1 H), 5.54 (m, 1 H), 2.36 (s, 3 H), 1.91 (s, 3 H), 1.84 (d, *J* = 6.8 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.2, 133.0, 131.2, 128.1, 127.1, 125.6, 123.6, 22.7, 13.3.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{17}$: 173.1325; found: 173.1322.

Funding Information

This work was financially supported by Loughborough University. Y.A. acknowledges the Ministry of Higher Education of Iraq for funding.

Acknowledgments

We acknowledge Dr. Mark Edgar (Loughborough) for detailed NMR structure determination for compounds **17a–c**; and Dr. Jim C. Reynolds (Loughborough) for helpful discussions on the direct loop injection ESI-HR-MS.

Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0036-1591580.

References

(1) (a) Deagostino, A.; Prandi, C.; Zavattaro, C.; Venturello, P. *Eur. J. Org. Chem.* **2006**, 2463. (b) Nicolaou, K. C.; Synder, S. A.; Montagnon, T.; Vassilikogiannakis, G. *Angew. Chem. Int. Ed.* **2002**, *41*, 1668. (c) Negishi, E.-I.; Huang, Z.; Wang, G.; Mohan, S.;

Wang, C.; Hattori, H. *Acc. Chem. Res.* **2008**, *41*, 1474. (d) De Paolis, M.; Chataigner, I.; Maddaluno, J. *Top. Curr. Chem.* **2012**, *327*, 87.

(2) (a) Kobayashi, M.; Higuchi, K.; Murakami, N.; Tajima, H.; Aoki, S. *Tetrahedron Lett.* **1997**, *38*, 2859. (b) For a review see: Serhan, C. N. *Nature (London)* **2014**, *510*, 92. (c) Morris Kupchan, S.; Komoda, Y.; Court, W. A.; Thomas, G. J.; Smith, R. M.; Karim, A.; Gilmore, C. J.; Haltiwanger, R. C.; Bryan, R. F. *J. Am. Chem. Soc.* **1972**, *94*, 1354.

(3) For a comprehensive review on the synthesis of 1,3-dienes see: *Science of Synthesis*; Georg Thieme Verlag: Stuttgart, **2009**.

(4) Ghogare, A. A.; Green, A. *Chem. Rev.* **2016**, *116*, 9994.

(5) For representative examples see (a) Luo, S. X.; Cannon, J. S.; Taylor, B. L. H.; Engle, K. M.; Houk, K. N.; Grubbs, R. H. *J. Am. Chem. Soc.* **2016**, *138*, 14039. (b) Laio, L.; Guo, R.; Zhao, X. *Angew. Chem. Int. Ed.* **2017**, *56*, 3201. (c) Jiang, L.; Cao, P.; Wang, M.; Chen, B.; Wang, B.; Liao, J. *Angew. Chem. Int. Ed.* **2016**, *55*, 13854. (d) Srinnivas, V.; Nakajima, Y.; Ando, W.; Sato, K.; Shimada, S. *J. Organomet. Chem.* **2016**, *809*, 57. (e) Sleet, C. E.; Tambar, U. K. *Angew. Chem. Int. Ed.* **2017**, *56*, 5536. (f) Iwasaki, T.; Min, X.; Fukuoka, A.; Kuniysau, H.; Kambe, N. *Angew. Chem. Int. Ed.* **2016**, *55*, 5550. (g) Yang, X.-H.; Dong, V. M. *J. Am. Chem. Soc.* **2017**, *139*, 1774.

(6) (a) Hirai, K.; Suzuki, H.; Moro-Oka, Y.; Ikawa, T. *Tetrahedron Lett.* **1980**, *21*, 3413. (b) Shiotsuki, M.; Ura, Y.; Ito, T.; Wada, K.; Kondo, T.; Mitsudo, T. *J. Organomet. Chem.* **2004**, *689*, 3168. (c) Shintani, R.; Duan, W.-L.; Park, S.; Hayashi, T. *Chem. Commun.* **2006**, 3646. (d) Yasui, H.; Yorimitsu, H.; Oshima, K. *Synlett* **2006**, 1783.

(7) (a) Crandall, J. K.; Paulson, D. R. *J. Am. Chem. Soc.* **1966**, *88*, 4302. (b) Bloch, R.; Le Perchec, P.; Conia, J.-M. *Angew. Chem. Int. Ed.* **1970**, *9*, 798. (c) Jones, M. Jr.; Hendrick, M. E.; Hardie, J. A. *J. Org. Chem.* **1971**, *36*, 3061. (d) Patrick, T. B.; Haynie, E. C.; Probst, W. J. *Tetrahedron Lett.* **1971**, *12*, 423. (e) Lehric, F.; Hopf, H. *Tetrahedron Lett.* **1987**, *28*, 2697. (f) Meier, H.; Schmitt, M. *Tetrahedron Lett.* **1989**, *30*, 5873.

(8) (a) Jacobs, T. L.; Johnson, R. N. *J. Am. Chem. Soc.* **1960**, *82*, 6397. (b) Werkert, E.; Leftin, M. H.; Michelotti, E. L. *J. Org. Chem.* **1985**, *50*, 1122. (c) Sanz, R.; Miguel, D.; Martínez, A.; Gohain, M.; García-García, P.; Fernández-Rodríguez, M. A.; Álvarez, E.; Rodríguez, F. *Eur. J. Org. Chem.* **2010**, 7027.

(9) $Fe_2(CO)_9$ can convert tetramethylallene into its 1,3-diene via oxidative treatment of the complex, see: Ben-Shoshan, R.; Pettit, R. *J. Am. Chem. Soc.* **1987**, *89*, 2231.

(10) (a) Shimizu, I.; Tsuji, J. *Chem. Lett.* **1984**, 233. (b) Shimizu, I.; Sugiura, T.; Tsuji, J. *J. Org. Chem.* **1985**, *50*, 537. (c) Al-Masum, M.; Yamamoto, Y. *J. Am. Chem. Soc.* **1998**, *120*, 3809.

(11) (a) Ting, C.-M.; Hsu, Y.-L.; Liu, R.-S. *Chem. Commun.* **2012**, *48*, 6577. (b) Chen, J.-M.; Chang, C.-J.; Ke, Y.-J.; Liu, R.-S. *J. Org. Chem.* **2014**, *79*, 4306. (c) Brown, T. J.; Robertson, B. D.; Widenhoefer, R. A. *J. Organomet. Chem.* **2014**, *758*, 25.

(12) Al-Jawaheri, Y.; Kimber, M. C. *Org. Lett.* **2016**, *18*, 3502.

(13) Vantourout, J. C.; Miras, H. N.; Isidro-Llobet, A.; Sproules, S.; Watson, A. J. B. *J. Am. Chem. Soc.* **2017**, *139*, 4769.

(14) Benzoic acid was utilised to generate a H–Pd^{II}–OBz complex in the hydroalkoxylation of alkynes see: Kadota, I.; Lutete, L. M.; Shibuya, A.; Yamamoto, Y. *Tetrahedron Lett.* **2001**, *42*, 6207.

(15) See the Supporting Information for details of the preparation of the allenyl substrates.

(16) Benzoic acid pK_a = 4.20; boric acid pK_a = 9.24.

(17) (a) Qian, R.; Guo, H.; Liao, Y.; Guo, Y.; Ma, S. *Angew. Chem. Int. Ed.* **2005**, *44*, 4771. For a review on the use of ESI-MS to probe reactive intermediates see: (b) Zhu, W.; Yuhan, Y.; Zhou, P.; Zeng, L.; Wang, H.; Tang, L.; Guo, B.; Chen, B. *Molecules* **2012**, *17*, 11507. Also see: (c) Wright, V. E.; Castro-Gomez, F.; Jurneczko, E.; Reynolds, J. C.; Poulton, A.; Christie, S. D. R.; Barran, P.; Bo, C.; Creaser, C. S. *Int. J. Ion. Mobility Spectrom.* **2013**, *16*, 61.

(18) Please see the Supporting Information for details.

(19) (a) Tamura, R.; Rui, M.; Saegusa, K.; Kakihana, M.; Oda, D. *J. Org. Chem.* **1987**, *52*, 4121. (b) Dubbaka, R.; Vogel, P. *Tetrahedron* **2005**, *61*, 1523.