

---

This item was submitted to [Loughborough's Research Repository](#) by the author.  
Items in Figshare are protected by copyright, with all rights reserved, unless otherwise indicated.

## Synthesis of 1,3-Dienes via a sequential Suzuki-Miyaura coupling/Palladium-mediated Allene isomerization sequence.

PLEASE CITE THE PUBLISHED VERSION

<http://dx.doi.org/10.1021/acs.orglett.6b01841>

PUBLISHER

© American Chemical Society

VERSION

AM (Accepted Manuscript)

PUBLISHER STATEMENT

This work is made available according to the conditions of the Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International (CC BY-NC-ND 4.0) licence. Full details of this licence are available at: <https://creativecommons.org/licenses/by-nc-nd/4.0/>

LICENCE

CC BY-NC-ND 4.0

REPOSITORY RECORD

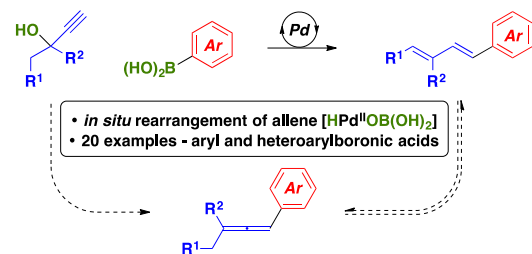
Al-Jawaheri, Yassir, and Marc C. Kimber. 2019. "Synthesis of 1,3-dienes via a Sequential Suzuki-miyaura Coupling/palladium-mediated Allene Isomerization Sequence.". figshare. <https://hdl.handle.net/2134/21992>.

# Synthesis of 1,3-dienes *via* a sequential Suzuki-Miyaura coupling-palladium mediated allene isomerization sequence

Yassir Al-Jawaheri and Marc C. Kimber\*

Department of Chemistry, Loughborough University, LE11 3TU, UK

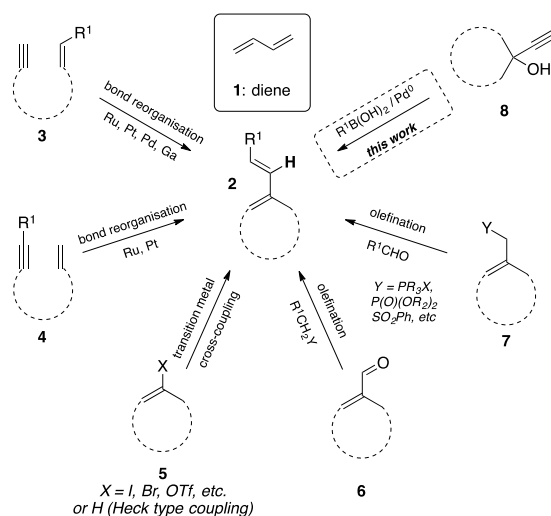
Supporting Information Placeholder



**ABSTRACT:** We report a facile method for the synthesis of 1,3-dienes by a sequential process consisting of a palladium catalyzed, base-free, Suzuki-Miyaura coupling/isomerization sequence. This sequence couples boronic acids with propargyl alcohols, generating the requisite allene *in situ*, followed by conversion of the unactivated allene to its 1,3-diene *via* a hydro-palladation/dehydro-palladation process. This process is general for a range of boronic acids, including boronic acids with electron donating and withdrawing groups, as well as heteroarylboronic acids. Key to this process is the boric acid by-product of the base-free Suzuki-Miyaura coupling, which generates the required palladium-hydrido complex [H-Pd<sup>II</sup>-OB(OH)<sub>2</sub>] required for the isomerization.

The 1,3-diene motif is one of the most important and ubiquitous structural units in organic chemistry (Scheme 1, **1**). It has been at the cornerstone of many of the most significant synthetic transformations within the discipline (e.g., Diels-Alder, pericyclic transformations); it is present in numerous natural products and drug candidates, and as such any new synthetic method that can greatly simplify its synthesis is noteworthy.<sup>1</sup>

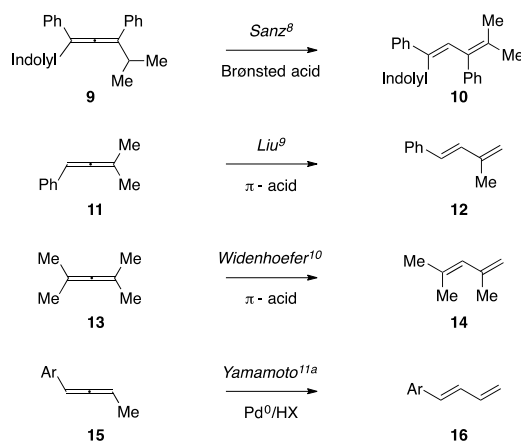
## Scheme 1. Synthesis of 1,3-dienes.



1,3-Dienes (**2**) of the structure shown in scheme 1, whether cyclic or acyclic, can be synthesized *via* a number of methods including (i) bond reorganisation of enyne substrates (**3** and

**4**) using transition or noble metal catalysis,<sup>2</sup> (ii) traditional metal cross coupling of a suitably functionalized precursor (**5**),<sup>3</sup> as well as (iii) olefination methods on substrates such as **6** and **7**.<sup>4</sup> An additional, atom efficient approach, is the rearrangement of an alkyl-substituted allene<sup>5</sup> (**8**) to a diene (**2**), *via* a formal 1,3-hydrogen migratory process (Scheme 1).

## Scheme 2. Reported conversion of allenes to 1,3-dienes.



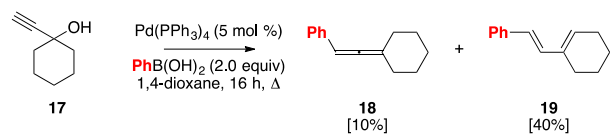
This type of 1,3-hydrogen migratory route, either under kinetic or thermodynamic conditions, is commonly found in activated allenes,<sup>6</sup> however, such transformations on unactivated allenes have been infrequent within the literature.<sup>7</sup> Reported procedures include the use of Brønsted acids by Sanz<sup>8</sup> in 2010; Au(I)  $\pi$ -acids by Liu<sup>9</sup> in 2012 and Widenhoefer in 2014,<sup>10</sup>

where the latter were able to isolate and crystallize the Au(I)  $\pi$ -1,3-diene complex; and Yamamoto in 1998<sup>11a</sup> who demonstrated that aliphatic allenes could be isomerized using a Pd<sup>0</sup>/acetic acid protocol to their 1,3-dienes, but with very limited substrate scope, moderate yields, and with a competing hydrocarboxylation pathway.

With these examples of formal 1,3-hydrogen migration routes to 1,3-dienes from allenes in mind, we would now like to report an operationally simple route to 1,3-dienes such as **2**. This method involves a palladium-mediated, base-free, Suzuki-Miyaura coupling of propargyl alcohols (**8**) and boronic acids to give the required unactivated allene,<sup>12</sup> followed by a novel *in situ* rearrangement of this allene to give the sought after 1,3-diene. Furthermore, the rearrangement of the unactivated allene to the 1,3-diene involves an *in situ* hydropalladation / dehydropalladation step promoted by the formation of boric acid within the base free Suzuki-Miyaura reaction conditions.

Our initial detection of this transformation occurred when **17** was exposed to the adapted conditions of Yoshida and co-workers (Scheme 3),<sup>12</sup> where extended heating of this reaction led not to the exclusive isolation of the allene **18**, but significant amounts of the 1,3-diene **19** in an isolated yield of 40%. The product **19** was confirmed by a combination of <sup>1</sup>H, <sup>13</sup>C NMR and IR spectroscopy, with *inter alia* a coupling of  $J = 16$  Hz between alkene protons at 6.85 and 6.52 ppm, respectively, indicative of an *E*-double bond.

### Scheme 3. Unexpected formation of 1,3-diene **3**.



The formation of the allene precursor has previously been optimized by Yoshida<sup>12</sup>, however, a small focused optimization for this transformation was performed (Table 1). In line with Yoshida,<sup>12</sup> 1,4-dioxane proved optimal with THF, CH<sub>3</sub>CN and PhMe providing minimal or nil conversion (entries 1-3). Temperature was crucial for this process, with 1,4-dioxane at 75 °C proving ideal (entry 5), with a lower temperature of 60 °C, giving poor conversion (entry 6) and a higher temperature (reflux) in this solvent providing significant amounts of degradation products and therefore lower conversion (entry 4). The number of equivalents of boronic acid was also probed (entries 7 and 8) with 3 proving optimal, unlike Yoshida and co-workers who found two equivalents to be favorable.

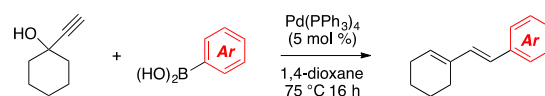
**Table 1.** 1,3-Diene optimization conditions.<sup>a</sup>

entry	PhB(OH) <sub>2</sub> (equiv)	solvent	temp [°C]	conversion to <b>19</b> <sup>b</sup> [%]
1	3	THF	reflux	5
2	3	CH <sub>3</sub> CN	75	-
3	3	PhMe	75	-
4	3	1,4-dioxane	reflux	45
5	3	1,4-dioxane	75	85 [78] <sup>c</sup>
6	3	1,4-dioxane	60	15
7	2	1,4-dioxane	75	45
8	1	1,4-dioxane	75	20

<sup>a</sup>Reactions were performed under N<sub>2</sub> atmosphere at 0.5 M, with 5 mol % of Pd(PPh<sub>3</sub>)<sub>4</sub> for 16 h, unless otherwise stated. <sup>b</sup>Determined by <sup>1</sup>H NMR. <sup>c</sup>Isolated yield.

With conditions for this transformation established, we next looked at the scope of this reaction with regard to the boronic acid coupling partner (Scheme 4 and Table 2). Electron rich boronic acids all participated in the transformation with moderate to high isolated yield (entries 2-4). 1-Naphthylboronic acid performed well, giving the 1,3-diene (**23**) in 94% yield (entry 5), as did 3,4-dimethoxyphenylboronic acid which gave the 1,3-diene (**24**) in 57% yield (entry 6), and 3,5-dimethoxyphenylboronic acid which gave **25** in 62% isolated yield (entry 7). A boronic acid containing an electron-withdrawing group was tolerated under the reaction conditions, giving the 1,3-diene **26** in 70% yield (entry 8). A heterocyclic boronic acid was also tolerant of the reaction conditions with 2-furanylboronic acid giving **27** in 66% isolated yield (entries 9); however 4-bromophenylboronic acid gave limited amounts of the 1,3-diene, with significant amount of starting alkyne and polymeric material being detected (entry 10).

**Table 2.** Variation of the arylboronic acid.



entry	(HO) <sub>2</sub> B-Ar	1,3-diene product	yield [%] <sup>b</sup>
1	Ph	<b>19</b>	78
2	Me	<b>20</b>	99
3	OMe	<b>21</b>	87
4	OMe	<b>22</b>	60
5	1-Naphthyl	<b>23</b>	94
6	3,4-dimethoxyphenyl	<b>24</b>	57
7	3,5-dimethoxyphenyl	<b>25</b>	62
8	4-methoxycarbonylphenyl	<b>26</b>	70
9	2-furanyl	<b>27</b>	66
10	4-bromophenyl	<b>28</b>	<5 <sup>c</sup>

<sup>a</sup>Reactions were performed under N<sub>2</sub> atmosphere at 0.5 M in 1,4-dioxane, with 5 mol % of Pd(PPh<sub>3</sub>)<sub>4</sub> for 16 h, unless otherwise stated. <sup>b</sup>Isolated yields unless otherwise stated. <sup>c</sup>Determined by <sup>1</sup>H NMR spectroscopy.

Next we examined variation of the alkyne coupling partner in this transformation (Table 3). Cyclopentyl propargyl alcohol **29** performed equally well with phenyl, 4-methyl and 4-

methoxyboronic acid giving the 1,3-dienes **30**, **31**, and **32**, respectively (entries 1-3). Furthermore, cycloheptyl- (**33**) and cyclooctyl- (**35**) also behaved as expected to give 1,3-dienes **34** and **36**, in yields of 80% and 75%, respectively (entries 4 and 5).

**Table 3.**<sup>a</sup> Variation of the propargyl alcohol.

entry	propargyl alcohol	1,3-diene product	yield [%] <sup>b</sup>
1		<b>30</b> : R = H	61
2		<b>31</b> : R = Me	67
3		<b>32</b> : R = OMe	78
4		<b>34</b>	80
5		<b>36</b>	75
6		<b>38</b>	43
7		<b>40</b> : R = H	85
8		<b>41</b> : R = Me	47
9		<b>43</b>	74
10 <sup>c</sup>		<b>45</b> Me, Me, E:Z - 85:15	55
11		<b>47</b>	64

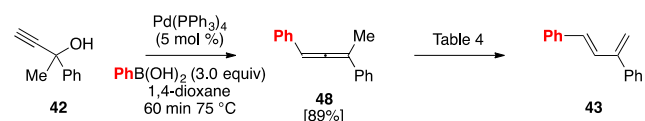
<sup>a</sup>Reactions were performed under N<sub>2</sub> atmosphere at 0.5 M in 1,4-dioxane, with 5 mol % of Pd(PPh<sub>3</sub>)<sub>4</sub> for 16 h, unless otherwise stated. <sup>b</sup>Isolated yields unless otherwise stated. <sup>c</sup>Isolated as a mixture of *E*- and *Z*-isomers in approx. 85:15 ratio.

The 1,4-dioxaspiro-protected propargyl alcohol **37**, when coupled with 3,5-dimethoxyphenylboronic acid gave the 1,3-diene **38** in moderate yield of 47%, demonstrating that the reaction is tolerant of acid sensitive functional groups (entry 6). The acyclic propargyl alcohols 2-methyl-3-butyn-2-ol **39**, when exposed to phenylboronic acid, gave 1,3-diene **40** in 85% yield, while 4-tolylboronic acid gave 1,3-diene **41** in a modest 47% yield (entries 7 and 8). Similarly, 2-phenyl-3-butyn-2-ol **42** gave the 1,3-diene **43** in 74% isolated yield when exposed to phenylboronic acid (entry 9). To investigate the selectivity of this reaction, with regard to 1,3-diene formation, 3-methyl-1-pentyn-3-ol **44** was exposed to 3-methylphenylboronic acid yielding the 1,3-diene **45**<sup>13</sup> as the predominant product in 55% yield (entry 10). The predominance of this 1,3-diene **45** in this

example is presumably due to the formation of the trisubstituted alkene as the thermodynamic product. Finally, 19-norethisterone **46** was exposed to the reaction conditions with 3-methylphenylboronic acid yielding the 1,3-diene **47** in 64% yield, therefore giving an ideal handle for further functionalization of this important steroid (entry 11).

To demonstrate that this process is two-step, i.e., conversion of the alkyne to an allene followed by rearrangement to its 1,3-diene, the reaction was monitored for the formation of allene **48**,<sup>14</sup> which was subsequently isolated in 89% yield (Scheme 6). With **48** in-hand we then exposed it to reaction conditions, mirroring those in Table 1, to promote the formation of 1,3-diene **43** (Scheme 4 and Table 4). The exposure of **48** to 5 mol % of Pd<sup>0</sup> gave no conversion, with only the starting allene being detected (entry 1), while exposure to phenylboronic acid mirrored that of entry 1 (entry 2). Phenylboronic acid in the presence of Pd<sup>0</sup> did give a small conversion to the diene **43**, but with significant degradation of the allene and addition products<sup>11a</sup> being observed (entry 3).

**Scheme 4 and Table 4.**<sup>a</sup> Allene isomerization.



entry	additive <sup>b</sup>	catalyst <sup>c</sup>	product <sup>d</sup> [%]	
			<b>48</b>	<b>43</b>
1	-	Pd(PPh <sub>3</sub> ) <sub>4</sub>	90	-
2	PhB(OH) <sub>2</sub>	-	90	-
3	PhB(OH) <sub>2</sub>	Pd(PPh <sub>3</sub> ) <sub>4</sub>	52	15
4	B(OH) <sub>3</sub>	-	90	-
5	B(OH) <sub>3</sub>	Pd(PPh <sub>3</sub> ) <sub>4</sub>	>5	92 [86] <sup>e</sup>
6	BzOH	Pd(PPh <sub>3</sub> ) <sub>4</sub>	>5	60 <sup>e</sup>

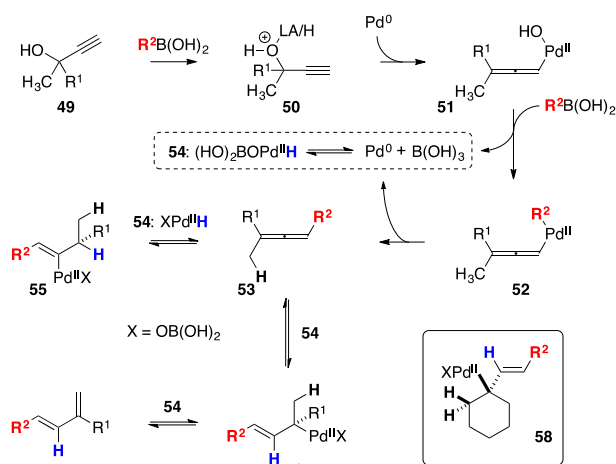
<sup>a</sup>Reactions were performed under N<sub>2</sub> atmosphere at 0.5 M in 1,4-dioxane for 16 h unless otherwise stated. <sup>b</sup>100 mol %. <sup>c</sup>5 mol %. <sup>d</sup>Determined by <sup>1</sup>H NMR. <sup>e</sup>Isolated yield.

In the acid mediated rearrangement of allenes, reported by Sanz and co-workers,<sup>8</sup> pTSA was used to facilitate the rearrangement of the allene. To investigate this, **48** was exposed to 1 equiv B(OH)<sub>3</sub>, the only other significantly acidic by-product of the Suzuki-Miyaura reaction, but this failed to deliver the 1,3-diene (entry 3). This is unsurprising given the pK<sub>a</sub> of boric acid compared to pTSA. However, when **48** was exposed to Pd<sup>0</sup> and 1 equiv of B(OH)<sub>3</sub>, conversion to the 1,3-diene was significant, giving **43** in 86% conversion presumably *via* the formation of a H-Pd<sup>II</sup>-OB(OH)<sub>2</sub> complex (entry 5). Yamamoto and co-workers<sup>11a,15</sup> have reported a similar hydroalkoxylation / isomerization of allenes and alkynes using analogous H-Pd<sup>II</sup>-OBz and H-Pd<sup>II</sup>-OAc complexes, but with limited selectivity and scope. As a consequence, we exposed allene **48** to H-Pd<sup>II</sup>-OBz, derived from Pd<sup>0</sup> and BzOH, and this gave the 1,3-diene **43**, but with significant hydroalkoxylation by-product (entry 6).

Given the results in Table 3, coupled with the reported mechanism<sup>12</sup> for the formation of the allene, we have proposed a plausible mechanism for the formation of the 1,3-diene (Scheme 5). Activation of **49** *via* a proton or the Lewis acidic boronic acid delivers **50**, which in the presence of Pd<sup>0</sup> undergoes nucleophilic addition to give the allenylpalladium species **51**, followed by a subsequent Suzuki-Miyaura coupling to

deliver the intermediate allene **53**. We then propose, based on the results within Table 3, that the boric acid oxidizes the resultant Pd<sup>0</sup> to give the Pd<sup>II</sup> species H-Pd<sup>II</sup>-OB(OH)<sub>2</sub> **54**. Allene **53** can then undergo hydropalladation with **54** to deliver either **55** or **56**: with **55** experiencing a dehydropalladation to regenerate the allene **53**. However, unlike **55**, **56** can undergo two possible dehydropalladations, either regenerating the allene **53**, or more significantly delivering the observed 1,3-diene **57**.

**Scheme 5. Proposed mechanism for the formation 1,3-dienes from propargyl alcohols and boronic acids under palladium mediated catalysis.**



It should be noted, that while the proposed H-Pd<sup>II</sup>-OB(OH)<sub>2</sub> complex parallels related complexes (e.g., H-Pd<sup>II</sup>-OBz and H-Pd<sup>II</sup>-OAc) as reported by Yamamoto,<sup>11a,15</sup> it displays a *significant* divergence in reactivity. Whereas the latter complex when reacted with allenes gives the hydroalkoxylation product, presumably due to the nucleophilicity of the benzoate conjugate base, the former H-Pd<sup>II</sup>-OB(OH)<sub>2</sub> complex gives predominantly the rearranged 1,3-diene product.

In summary, we have developed a two-step sequential synthesis of 1,3-dienes from propargyl alcohols and arylboronic acids. This sequence gives an initial intermediary unactivated allenyl precursor, *via* a base free Suzuki-Miyaura coupling, which undergoes a subsequent rearrangement to its 1,3-diene, facilitated by the *in situ* formation of a H-Pd<sup>II</sup>-OB(OH)<sub>2</sub> complex. The reaction is general for a range of boronic acids and propargyl substrates, and exhibits moderate to high chemical yields. Further efforts will be directed toward understanding and utilizing this H-Pd<sup>II</sup>-OB(OH)<sub>2</sub> complex in alkenyl, allenyl and alkylnyl rearrangements.

## ASSOCIATED CONTENT

### Supporting Information

Experimental procedures, NMR spectra and characterization for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

## AUTHOR INFORMATION

### Corresponding Author

Email: M.C.Kimber@lboro.ac.uk, Tel. +44 (0) 1509 22 2570

### Funding Sources

No competing financial interests have been declared. We wish to acknowledge funding from the Higher Education of Iraq (YA).

## ACKNOWLEDGMENT

The authors thank Loughborough University for financial support and Dr. Mark Edgar (Department of Chemistry, Loughborough University) for NMR analysis.

## REFERENCES

- (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.
- (a) Diver, S. T.; Giessert, A. J. *Chem. Rev.* **2004**, *104*, 1317. (b) Zhang, L.; Sun, J.; Kozmin, S. A. *Adv. Synth. Catal.* **2006**, *348*, 2271. (c) Poulsen, C. S.; Madsen, R. *Synthesis* **2003**, 1. (d) Trost, B. M.; Frederiksen, M. U.; Rudd, M. T. *Angew. Chem. Int. Ed.* **2005**, *44*, 6630.
- (a) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457. (b) Lemhadri, M.; Battace, A.; Berthiol, F.; Zair, T.; Doucet, H.; Santelli, M. *Synthesis* **2008**, 1142. (c) Hanson, A. L.; Ebran, J. -E.; Ahlquist, M.; Noorby, P. -O.; Skrydstrup, T. *Angew. Chem. Int. Ed.* **2006**, *45*, 3349. (d) Molander, G. A.; Feliz, L. A. *J. Org. Chem.* **2005**, *70*, 3950. (e) Zheng, C.; Wang, D.; Stahl, S. S. *J. Am. Chem. Soc.* **2012**, *134*, 16496. (f) Delcamp, J. H.; Gormisky, P. E.; White, M. C. *J. Am. Chem. Soc.* **2013**, *135*, 8460.
- (a) Maryanoff, B. E.; Reitz, A. B. *Chem. Rev.* **1989**, *89*, 863. (b) Ager, D. *J. Org. React.* **1990**, *38*, 1. (c) Dong, D. -J.; Li, H. -H.; Tian, S. -K. *J. Am. Chem. Soc.* **2010**, *132*, 5018. (d) Borg, T.; Tuzina, P.; Somfai, P. *J. Org. Chem.* **2011**, *76*, 8070. (e) Billard, F.; Robiette, R.; Pospisil, J. *J. Org. Chem.* **2012**, *77*, 6358. (f) Zhou, R.; Wang, C.; Song, H.; He, Z. *Org. Lett.* **2010**, *12*, 976.
- (a) Zimmer, R.; Dinesh, C. U.; Nandan, E.; Khan, F. A. *Chem. Rev.* **2000**, *100*, 3067. (b) Lechel, T.; Pfrengle, F.; Reissig, H. -U.; Zimmer, R. *ChemCatChem.* **2013**, *5*, 2100. (c) Le Bras, J.; Muzart, J. *Chem. Soc. Rev.* **2014**, *43*, 3003.
- (a) Zhang, X.; Fu, C.; Ma, S. *Org. Lett.* **2011**, *13*, 1920. (b) Krafft, M. E.; Hallal, K. M.; Vidahani, D. V.; Cran, J. W. *Org. Biomol. Chem.* **2011**, *9*, 7535. (c) Tsuboi, S.; Masuda, T.; Takeda, A. *J. Org. Chem.* **1982**, *47*, 4478. (d) Trost, B.; Kazmaier, U. *J. Am. Chem. Soc.* **1992**, *114*, 7933. (e) Hayashi, R.; Hsung, R. P.; Feltenberg, J. B.; Lohse, A. G. *Org. Lett.* **2009**, *11*, 2125. (f) Hayashi, R.; Feltenberger, J. B.; Hsung, R. P. *Org. Lett.* **2010**, *12*, 1152.
- (a) For a theoretical study, see: Jenson, F. *J. Am. Chem. Soc.* **1995**, *117*, 7487. (b) For a pyrolysis example, see: Meier, H.; Schmitt, M. *Tetrahedron Lett.* **1989**, *30*, 5873.
- (a) Sanz, R.; Miguel, D.; Martinez, A.; Gohain, M.; Garcia-Garcia, P.; Fernandez-Rodriguez, M. A.; Alvarez, E.; Rodriguez. *Eur. J. Org. Chem.* **2010**, 7027. (b) For an earlier report using 12 M HCl in methanol, see: Wenkert, E.; Leftin, M. H.; Michelotti, E. L. *J. Org. Chem.* **1985**, *50*, 1122.
- (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.
- Brown, T. J.; Robertson, B. D.; Widenhoefer, R. A. *J. Organomet. Chem.* **2014**, *758*, 25.
- (a) Al-Masum, M.; Yamamoto, Y. *J. Am. Chem. Soc.* **1998**, *120*, 3809. For examples of the palladium rearrangement of activated allenes, see: (b) Warvin, L.; Nicolas, C.; Viala, J.; Rodrigues, J. *Synlett* **2004**, 1820. (c) Ghobsi, A.; Hacini, S.; Wavrin, L.; Gaudel-Siri, A.; Corberes, A.; Nicolas, C.; Bonne, D.; Viala, J.; Rodriguez, J. *Eur. J. Org. Chem.* **2008**, 4446. For an example of dimerization, see: (d) Oh, C. H.; Yoo, H. S.; Jung, S. H. *Chem. Lett.* **2001**, *30*, 1288. For addition of boronic acids to allenols, see: (e) Yoshida, M.; Shoji, Y.; Shishido, K. *Org. Lett.* **2009**, *11*, 1441.
- Yoshida, M.; Gotou, T.; Ihara, M. *Tetrahedron Lett.* **2004**, *45*, 5573.
- Isolated as a mixture of *E*- and *Z*-isomers in approx. 85:15 ratio.
- Conversion to the allene **48** was monitored by TLC and was achieved after 1 h.

15. (a) Kadota, I.; Lutete, L. M.; Shibuya, A.; Yamamoto, Y. *Tetrahedron Lett.* **2001**, *42*, 6207. For a review, see: (b) Grushin, V. V.

*Chem. Rev.* **1996**, *96*, 2011.