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Palladium-catalysed 5-endo-trig allylic (hetero)arylation†

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A palladium-catalysed intramolecular allylic (hetero)arylation strategy for the synthesis of fused cyclopentenes incorporated with all-carbon quaternary and spiro centres is described. The method is straightforward, shows broad scope, proceeds in synthetically useful yields, and provides a rare means to construct complex cyclopentanoids. The reaction is believed to involve a kinetically unfavourable 5-endo-trig carbocyclisation of the tethered (π -allyl)palladium system. Further, this method was successfully applied as the key step in the total synthesis of diterpene natural products taiwaniaquinone H and dichroanone.

Introduction

Cyclopentannulated arenes and heteroarenes are the primary molecular architectures of many bioactive natural products and drug candidates; they also find potential applications in medicinal chemistry and in materials science.¹ Among them are a sizeable number of bioactive molecules that encompass quaternary carbon atoms on one or more stereogenic centers.² Some of the representative bioactive molecules possessing fused cyclopentane scaffolds and featuring at least one all-carbon quaternary/spiro centre are shown in Fig. 1.³

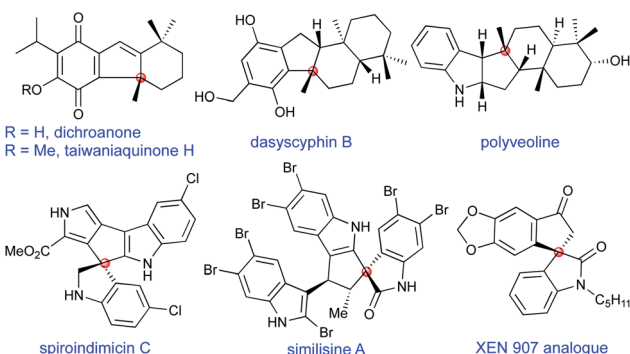


Fig. 1 Some of the representative biologically active molecules under the purview of this work.

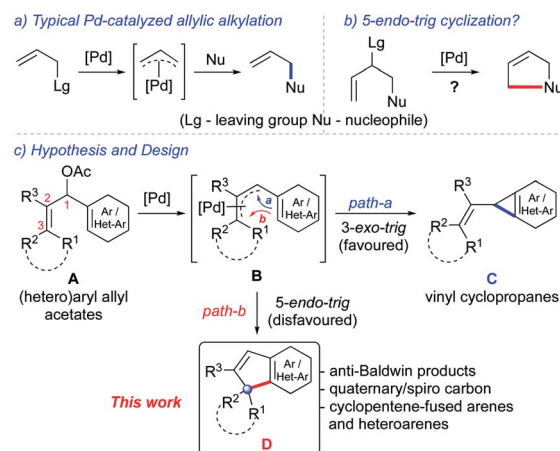
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Among several methods for the synthesis of cyclopenta-fused arenes and heteroarenes, to our knowledge, a disconnection based on 5-endo-trig cyclisation mode is yet to be realised. Baldwin's rules describe 5-endo-trig cyclisation as a stereo-electronically disfavoured pathway owing to the geometric constraints of the reactive functional groups not being able to achieve the Burgi–Dunitz angle.⁴

Palladium-catalysed allylic alkylations have been the subject of intensive investigations subsequent to the seminal contributions of Tsuji and Trost, Scheme 1a.⁵ The construction of nearly all types of rings can be assumed by employing Tsuji–Trost chemistry.⁶ However, Pd-catalysed 5-endo-trig carbocyclisation leading to the formation of cyclopentanes is quite uncommon, Scheme 1b.⁷ Against this background, Malacria in 1998 reported an example depicting Pd-catalysed and silicon-directed 5-endo-trig cyclisation for the formation of a silylated cyclopentene.⁸ Recently, the Tius group demonstrated Pd-



Scheme 1 Pd-catalysed 5-endo-trig allylic arylation for fused cyclopentenes incorporated with a quaternary/spiro centre: this work.



catalysed transformation of diketoesters to 2-hydroxycyclopentenones.⁹ While the reaction is considered to be an intramolecular allylic alkylation reaction,¹⁰ the possibility of Pd-catalysed anionic 5-*endo-trig* cyclisation may not be ruled out.^{7,11} A mechanistically distinct event on a similar substrate design was reported by Oestreich and co-workers, where palladium catalyses 5-*endo-trig* cyclisation of 1-(1*H*-indolyl)prop-2-enones for the formation of 3*H*-pyrrolo[1,2-*a*]indole-3-ones.¹²

Having developed several catalytic strategies for the synthesis of various types of cyclopropanoids and cyclopentanoids,¹³ we envisioned that appropriately substituted (hetero)aryl allyl acetates **A** under palladium catalysis will generate (π -allyl)palladium species **B**, which, by undergoing 3-*exo-trig* cyclisation will deliver vinyl cyclopropanes **C** (path-a), Scheme 1c.¹⁴ On the other hand, a possibility for the formation of fused cyclopentenones **D** may also arise if **B** undergoes rather unfavorable 5-*endo-trig* cyclisation (path-b). It is interesting to note that whenever competition arises, palladium catalysis usually favours the 3-*exo-trig* process over 5-*endo-trig* cyclisation; however, this fact may derive from kinetic preference.¹⁵

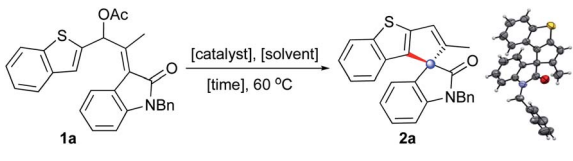
Here, we describe a general and straightforward Pd(II)-catalysed 5-*endo-trig* allylic (hetero)arylation of (hetero)aryl allyl acetates **A** that provides ready access to a wide range of indenes and cyclopentene-fused heteroarenes **D** incorporated with an all-carbon quaternary or a spiro centre, which, to our knowledge, have not been achieved thus far, as shown in Scheme 1c. At the beginning of the study, it was expected that the formation of **C** may outweigh the formation of **D** based on the considerations that the 5-*endo-trig* cyclisation mode is disfavoured (especially over 3-*exo-trig* process)¹⁴⁻¹⁶ and also that the steric encumbrance at C-3 (of **B**) may further discourage the formation of **D**.

Results and discussion

In order to verify the hypothesis presented in Scheme 1c, the oxindole-based allyl acetate **1a** was prepared and the reaction was evaluated with respect to the solvent, temperature, and catalyst, Table 1. Initial screening with Pd(0) catalysts provided mixed results. For example, Pd(PPh₃)₄ showed no reaction while Pd₂(dba)₃ provided encouraging results by generating the desired product **2a**, although in moderate yield (entries 1 and 2). The structure of **2a** was readily deduced from the NMR data, and was eventually confirmed by the single-crystal X-ray diffraction analysis of **2a**.¹⁷

Among Pd(II) catalysts, interestingly, Pd(OAc)₂ provided **2a** in poor yield, but the reaction catalysed by PdCl₂ furnished **2a** in good yield in a short reaction time (entries 3–5). As part of our efforts to improve the efficiency of the reaction, a brief solvent screening was undertaken, which did not provide any better result (entries 6–10). Lowering the catalyst loading to 5 mol% prolonged the reaction time and resulted in less yield of the product (entry 11). Further, no reaction was observed in the absence of any catalyst (entry 12) and the reactions which were performed in the presence of 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP) or *N,N*-dimethylaminopyridine (DMAP), to rule out the possibility of any traces of HCl catalyzing the reaction, delivered **2a** in good yields (entries 13 and 14).

Table 1 Optimisation of the reaction parameters^{a,b,c}



Entry	Catalyst (10 mol%)	Solvent	Time (h)	Yield ^d (%)
1	Pd(PPh ₃) ₄	1,2-DCE	48	—
2	Pd ₂ (dba) ₃	1,2-DCE	48	48
3	Pd(PPh ₃) ₂ Cl ₂	1,2-DCE	48	—
4	Pd(OAc) ₂	1,2-DCE	48	30
5	PdCl ₂	1,2-DCE	8	82
6	PdCl ₂	Toluene	30	43
7 ^e	PdCl ₂	DMF	10	—
8	PdCl ₂	MeCN	48	35
9	PdCl ₂	MeNO ₂	6	73
10	PdCl ₂	1,4-Dioxane	36	63
11 ^f	PdCl ₂	1,2-DCE	18	75
12	—	1,2-DCE	120	—
13 ^g	PdCl ₂	1,2-DCE	22	76
14 ^h	PdCl ₂	1,2-DCE	16	74

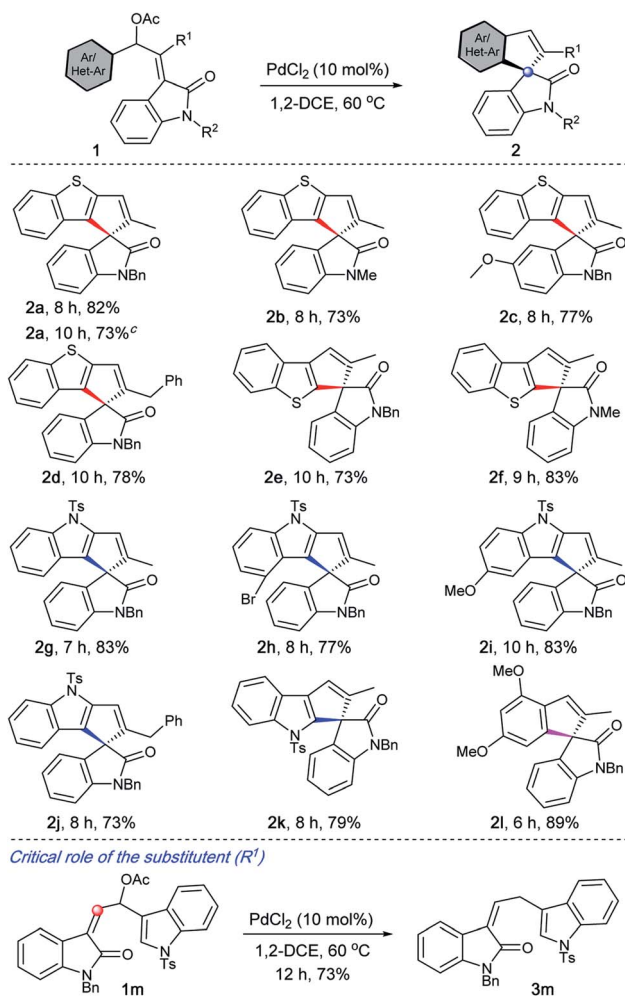
^a Reaction conditions: see the ESI for details. ^b Yield of the reaction at 30 °C (for 36 h) is 53%; yield at 45 °C (for 12 h) is 62%. ^c No reaction was observed with either Ni(cod)₂ or [Ir(cod)Cl]₂. ^d Isolated yield after column chromatography. ^e **1a** decomposed. ^f 5 mol% PdCl₂ was employed. ^g In the presence of 1 equiv. of 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP). ^h In the presence of 1 equiv. of *N,N*-dimethylaminopyridine (DMAP).

Thus, an unusual Pd-catalysed 5-*endo-trig* spirannulation of oxindoles was established based on rational designing of the precursor. Unlike several palladium-catalysed reactions, intriguingly, this reaction does not require any external additives, oxidants, bases, or ligands.¹⁸

Under the optimised conditions, the generality of the method was evaluated. It is evident from Table 2 that a wide range of heteroarene-fused spirocyclopentene oxindoles possessing electronically diverse substituents can be obtained in good to excellent yields (**2a–2k**). The method can also be extended to the synthesis of indeno spirooxindoles such as **2l**. In particular, the reaction works efficiently from both C-2 and C-3 of benzothiophenes (**2a–2d** vs. **2e–2f**), indoles (**2g–2j** vs. **2k**), and arenes (**2l**) indicating that the reaction may not be involving a C–H activation pathway.¹⁹

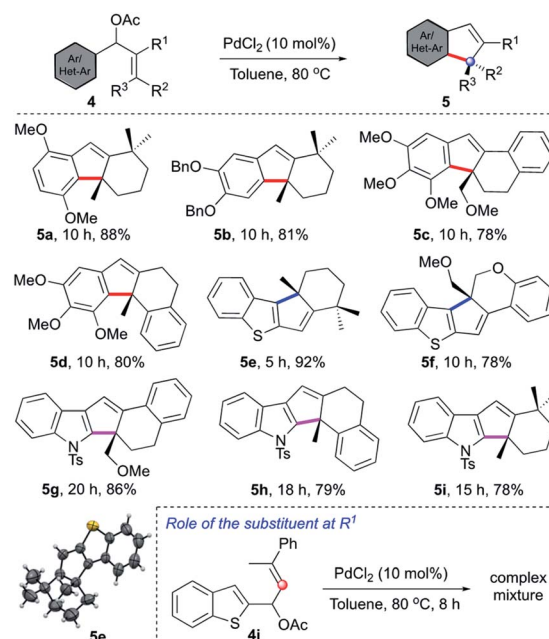
Spirocyclopentane oxindoles are known to be privileged structures with regard to their structural complexity and their biological activity.²⁰ In this context, it is worth highlighting that **2k** represents part of the structure of natural products such as similisines and spiroindimicins (see Fig. 1) whereas **2e** and **2f** serve as their sulphur analogues.³ On the other hand, **2l** represents a XEN 907 analogue.³

A critical role of the substituent (R¹) was realised during the evaluation of the substrate scope, Table 2. For example, when **1m** was treated under the optimised conditions, only the deacylated product **3m** was realised.²¹

Table 2 Generality and scope: spiroindoles^{a,b}

^a Reaction conditions: see the ESI for details. ^b Isolated yield after column chromatography. ^c With the OBoc substrate instead of OAc.

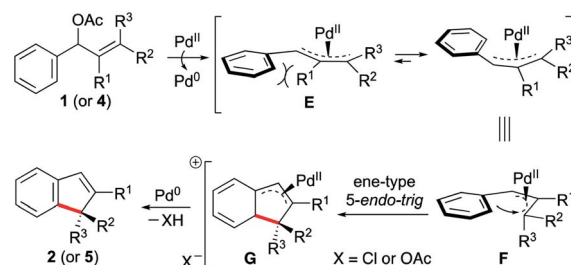
Having established an unprecedented approach for the synthesis of oxindoles bearing a spiro center, we intended to extend the concept for the creation of an all-carbon quaternary center, Table 3. It was expected that the substrate design **4** will provide cyclopentene-fused arenes and heteroarenes **5** having a quaternary carbon. Indeed, after brief optimisation of the reaction conditions, we could achieve the synthesis of natural product-like tri-, tetra- and pentacyclic indenenes (**5a–5d**) and cyclopentannulated heteroarenes (**5e–5i**) in good to excellent yields. The structure of the representative compound (**5e**) was unambiguously confirmed by X-ray diffraction analysis.¹⁷ The reaction of **4j** (where R¹ = H) under the prototypical conditions generated a complex mixture, thereby signifying the role of the substituent (R¹) in the outcome of the reaction. Nevertheless, some of the merits of this strategy are: (i) neutral conditions, (ii) easily accessible starting compounds, (iii) occurrence of numerous natural products and pharmaceutically relevant compounds with the kind of molecular architecture accessed herein.^{1,3}

Table 3 Substrate scope: cyclopentene-fused arenes and heteroarenes^{a,b}

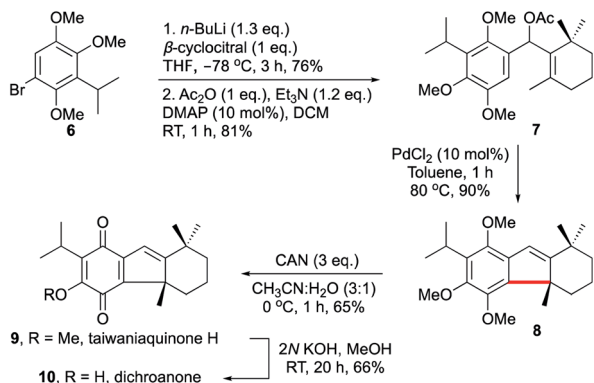
^a Reaction conditions: see the ESI for details. ^b Chromatographic yields.

We then turned our attention to establish the mechanism. Based on the experimental evidence²² and related literature reports,¹⁸ a plausible mechanism is proposed in Scheme 2. The reaction begins with the formation of an (η^3 -allyl)palladium complex **E**,²³ which reorganises itself into **F** owing to steric considerations. The intermediate **F** is now poised to undergo an ene-type 5-*endo-trig* cyclisation to generate another π -allylpalladium species **G**, which upon rearomatisation *via* deprotonation²⁴ delivers **2** (or **5**) and regenerates the active catalyst. The measurement of the kinetic isotope effect (KIE)²⁵ strongly suggested that the new C–C bond-forming cyclisation event most likely involved an ene-type allylic arylation step rather than a C–H activation pathway. Otherwise, typical metal-catalysed C–H functionalisation processes involve C–H bond cleavage in the rate determining step.²⁶

Next, we decided to apply the current strategy in the total synthesis of taiwaniaquinone **9** and dichroanone **10**, Scheme 3.³ Taiwaniaquinoids are a family of diterpenoid natural



Scheme 2 Plausible reaction mechanism.



Scheme 3 Acid-free synthesis of bioactive natural products taiwaniaquinone H and dichroanone.

products possessing a [6,5,6]-*abeo*-abietane skeleton with an all-carbon quaternary stereocenter at the pseudobenzyl position. Some of the members of taiwaniaquinoids exhibit potent cytotoxic activity against KB epidermoid carcinoma cancer cells, antitumor activity, aromatase inhibitory activity, to mention a few.²⁷ Owing to their diverse bioactivity profiles and complex structural features, taiwaniaquinoids have attracted the attention of synthetic chemists.^{3b,28}

Our strategy for the synthesis of **9** and **10** involved palladium-catalysed 5-*endo-trig* cyclisation of **7** to **8** as the key step, Scheme 3. Accordingly, the desired acetate **7** was synthesised by the addition of the lithiated **6** to β -cyclocitral followed by acylation of the intermediate alcohol.^{3b} The reaction of **7** under the prototypical conditions described in Table 3 generated **8** in excellent yield. We then accomplished the total synthesis of taiwaniaquinone H **9** in 65% yield by performing ceric ammonium nitrate (CAN)-mediated oxidative transformation of **8**. Subsequently, the total synthesis of dichroanone **10** was also achieved in 66% yield by subjecting **9** to methanolic KOH conditions. As such, the synthesis of **8** also represents the formal synthesis of taiwaniaquinol B.²⁸ The synthetic methodology delineated herein is general and can pave the way for the acid-free synthesis of several other related taiwaniaquinoids as well.

Conclusions

An efficient Pd(II)-promoted 5-*endo-trig* cyclisation of (hetero) aryl allyl acetates to spirocyclopentene oxindoles, indenones and cyclopentene-fused heteroarenes is presented.²⁹ A hallmark of this strategy is its ability to construct a quaternary or a spiro carbon center from easily accessible starting compounds under neutral conditions. Since the method represents one of the very few examples for highly efficient synthesis of complex cyclopentanoids under oxidant, base, additive or ligand-free conditions, it should find practical applications in the synthesis of natural products, pharmaceutically relevant compounds and materials. We are in the process of extending this work for the creation of new spiro structures, and applying the current strategy in the total synthesis of the spiroindimicin and

polyveoline family of natural products. The results will be communicated in due course.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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Notes and references

- (a) M. Somei and F. Yamada, *Nat. Prod. Rep.*, 2005, **22**, 73; (b) S. Cacchi and G. Fabrizi, *Chem. Rev.*, 2005, **105**, 2873; (c) A. J. Kochanowska-Karamyan and M. T. Hamann, *Chem. Rev.*, 2010, **110**, 4489; (d) Y. Ie, K. Nishida, M. Karakawa, H. Tada and Y. Aso, *J. Org. Chem.*, 2011, **76**, 6604; (e) B. Gabriele, R. Mancuso and L. Veltri, *Chem.-Eur. J.*, 2016, **22**, 5056; (f) T. Chanda and M. S. Singh, *Org. Biomol. Chem.*, 2016, **14**, 8895; (g) B. Satpathi, A. Mondal and S. S. V. Ramasastry, *Chem.-Asian J.*, 2018, **13**, 1642; (h) T. Vivekanand, B. Satpathi, S. K. Bankar and S. S. V. Ramasastry, *RSC Adv.*, 2018, **8**, 18576.
- The construction of quaternary/spiro carbon centres is challenging even in the context of modern organic synthesis, see: (a) A. Y. Hong and B. M. Stoltz, *Eur. J. Org. Chem.*, 2013, **14**, 2745; (b) K. W. Quasdorf and L. E. Overman, *Nature*, 2014, **516**, 181; (c) E. V. Prusov, *Angew. Chem., Int. Ed.*, 2017, **56**, 14356; (d) P.-W. Xu, J.-S. Yu, C. Chen, Z.-Y. Cao, F. Zhou and J. Zhou, *ACS Catal.*, 2019, **9**, 1820.
- For dichroanone and taiwaniaquinones, see: (a) G. Majetich and J. M. Shimkus, *J. Nat. Prod.*, 2010, **73**, 284; (b) B. N. Kakde, A. Parida, P. Kumari and A. Bisai, *Tetrahedron Lett.*, 2016, **57**, 3179. For dasyscyphins, see: (c) L. Zhang, X. Xie, J. Liu, J. Qi, D. Ma and X. She, *Org. Lett.*, 2011, **13**, 2956. For polyveoline and similisines, see: (d) S. Dhiman and S. S. V. Ramasastry, *Org. Lett.*, 2015, **17**, 5116. For spiroindimicins, see: (e) W. Zhang, Z. Liu, S. Li, T. Yang, Q. Zhang, L. Ma, X. Tian, H. Zhang, C. Huang, S. Zhang, J. Ju, Y. Shen and C. Zhang, *Org. Lett.*, 2012, **14**, 3364. For XEN 907 and analogues, see: (f) S. Chowdhury, M. Chafeev, S. Liu, J. Sun, V. Raina, R. Chui, W. Young, R. Kwan, J. Fu and J. A. Cadieux, *Bioorg. Med. Chem. Lett.*, 2011, **21**, 3676.
- (a) J. E. Baldwin, *J. Chem. Soc., Chem. Commun.*, 1976, 734; (b) J. E. Baldwin, J. Cutting, W. Dupont, L. Kruse, L. Silberman and R. C. Thomas, *J. Chem. Soc., Chem. Commun.*, 1976, 736; (c) K. Gilmore, M. Manoharan, J. I. Wu, P. V. R. Schleyer and I. V. Alabugin, *J. Am. Chem. Soc.*, 2012, **134**, 10584; (d) I. V. Alabugin and K. Gilmore, *Chem. Commun.*, 2013, **49**, 11246.

- 5 (a) J. Tsuji, H. Takahashi and M. Morikawa, *Tetrahedron Lett.*, 1965, **6**, 4387; (b) B. M. Trost and T. J. Fullerton, *J. Am. Chem. Soc.*, 1973, **95**, 292.
- 6 (a) B. M. Trost, *Acc. Chem. Res.*, 1996, **29**, 355; (b) G. Jellerichs, J.-R. Kong and M. J. Krische, *J. Am. Chem. Soc.*, 2003, **125**, 7758; (c) U. Kazmaier, *Curr. Org. Chem.*, 2003, **7**, 317; (d) B. M. Trost and M. L. Crawley, *Chem. Rev.*, 2003, **103**, 2921; (e) H. Miyabe and Y. Takemoto, *Synlett*, 2005, **11**, 1641; (f) S.-L. You and L.-X. Dai, *Angew. Chem., Int. Ed.*, 2006, **45**, 5246; (g) M. Braun and T. Meier, *Angew. Chem., Int. Ed.*, 2006, **45**, 6952; (h) I. Ibrahim and A. Córdova, *Angew. Chem., Int. Ed.*, 2006, **45**, 1952; (i) Z. Lu and S. Ma, *Angew. Chem., Int. Ed.*, 2008, **47**, 258; (j) T. Jensen and P. Fristrup, *Chem.-Eur. J.*, 2009, **15**, 9632; (k) J. D. Weaver, A. Recio III, A. J. Grenning and J. A. Tunge, *Chem. Rev.*, 2011, **111**, 1846; (l) M. J. Wanner, E. Claveau, J. H. van Maarseveen and H. Hiemstra, *Chem.-Eur. J.*, 2011, **17**, 13680; (m) I. D. G. Watsona and F. D. Toste, *Chem. Sci.*, 2012, **3**, 2899; (n) K. C. Majumdar and B. Sinha, *Synthesis*, 2013, **45**, 1271; (o) C. Kammerer, G. Prestat, D. Madec and G. Poli, *Acc. Chem. Res.*, 2014, **47**, 3439; (p) Y. Liu, S.-J. Han, W.-B. Liu and B. M. Stoltz, *Acc. Chem. Res.*, 2015, **48**, 740; (q) B. M. Trost, *Tetrahedron*, 2015, **71**, 5708; (r) R. A. Fernandes and J. L. Nallasivam, *Org. Biomol. Chem.*, 2019, **17**, 8647.
- 7 Pd-catalyzed anionic rearrangement of vinyl cyclopropanes to cyclopentenes, see: (a) Y. Morizawa, K. Oshima and H. Nozaki, *Tetrahedron Lett.*, 1982, 2871; (b) M. Ahmar, B. Gazes and J. Gore, *Tetrahedron*, 1987, **43**, 3453; (c) K. Hiroi and Y. Arinaga, *Tetrahedron Lett.*, 1994, **35**, 153.
- 8 For a single example of silicon-directed Pd-catalyzed 5-*endo-trig* cyclization, see: S. Thorimbert and M. Malacria, *Tetrahedron Lett.*, 1998, **39**, 9659.
- 9 For the Tius-Nazarov reaction, see: (a) C. Bee, E. Leclerc and M. A. Tius, *Org. Lett.*, 2003, **5**, 4927; (b) Z. Cai and M. Harmata, *Org. Lett.*, 2010, **12**, 5668; (c) N. Shimada, C. Stewart, W. F. Bow, A. Jolit, K. Wong, Z. Zhou and M. A. Marcus, *Angew. Chem., Int. Ed.*, 2012, **51**, 5727. For related Pd-catalyzed Nazarov-type reactions, see: (d) S. S. Subramaniam, S. Handa, A. J. Miranda and L. M. Slaughter, *ACS Catal.*, 2011, **1**, 1371; (e) J. Shao, P. Hu, G. Hong, M. Fang, X. Li and X. Xu, *Synlett*, 2014, **25**, 1009.
- 10 T. A. Atesin, G. M. Martinez and D. Flores, *Organometallics*, 2017, **36**, 3589.
- 11 For formal anionic 5-*endo-trig* cyclizations, see: (a) P. Beak and D. A. Burg, *J. Org. Chem.*, 1989, **54**, 1647; (b) W. A. Batson, D. Sethumadhavan and M. A. Tius, *Org. Lett.*, 2005, **7**, 2771; (c) C. P. Johnston, A. Kothari, T. Sergeieva, S. I. Okovytyy, K. E. Jackson, R. S. Paton and M. D. Smith, *Nat. Chem.*, 2015, **7**, 171.
- 12 S. R. Kandukuri, J. A. Schiffner and M. Oestreich, *Angew. Chem., Int. Ed.*, 2012, **51**, 1265.
- 13 Some selected references: (a) S. Dhiman and S. S. V. Ramasastry, *Chem. Commun.*, 2015, **51**, 557; (b) S. Dhiman and S. S. V. Ramasastry, *Org. Lett.*, 2015, **17**, 5116; (c) B. Satpathi and S. S. V. Ramasastry, *Angew. Chem., Int. Ed.*, 2016, **55**, 1777; (d) M. Raghu, J. Grover and S. S. V. Ramasastry, *Chem.-Eur. J.*, 2016, **22**, 18316; (e) S. K. Bankar, B. Singh, P. Tung and S. S. V. Ramasastry, *Angew. Chem., Int. Ed.*, 2018, **57**, 1678; (f) A. Mondal, R. Hazra, J. Grover, M. Raghu and S. S. V. Ramasastry, *ACS Catal.*, 2018, **8**, 2748; (g) U. K. Mishra, K. Patel and S. S. V. Ramasastry, *Org. Lett.*, 2019, **21**, 175; (h) B. Satpathi, L. Dutta and S. S. V. Ramasastry, *Org. Lett.*, 2019, **21**, 170; (i) K. Patel, U. K. Mishra, D. Mukhopadhyay and S. S. V. Ramasastry, *Chem.-Asian J.*, 2019, **14**, 4568.
- 14 3-*Exo-trig* closures have extremely low activation barriers, see: B. Fiser, J. M. Cuerva and E. Gomez-Bengoia, *Organometallics*, 2018, **37**, 390.
- 15 According to Trost, cyclopropanes are normally preferred with carbon nucleophiles, but this may be a kinetic preference and does not test the feasibility of five-membered ring formation *via* a 5-*endo-trig* cyclization, for details see: B. M. Trost and T. S. Scanlan, *J. Am. Chem. Soc.*, 1989, **111**, 4988.
- 16 For a recent example where the 3-*exo-trig* mode is preferred over 5-*endo-trig*, see: J. Braun, M. I. Ariens, B. T. Matsuo, S. de Vries, E. D. H. van Wordragen, B. D. Ellenbroek, C. M. L. V. Velde, R. V. A. Orru and E. Ruijter, *Org. Lett.*, 2018, **20**, 6611.
- 17 X-ray crystallographic data of compounds **2a** and **5e** are provided in the ESI.† CCDC 1965370 (**2a**) and 1965374 (**5e**).
- 18 (a) F.-Q. Yuan, L.-X. Gao and F.-S. Han, *Chem. Commun.*, 2011, **47**, 5289; (b) F.-Q. Yuan, F.-Y. Sun and F.-S. Han, *Tetrahedron*, 2012, **68**, 6837.
- 19 Considering the comparable efficiency with arenes and heteroarenes, the reaction can be better described as an ene-type process. Further, it is well-established that heteroarenes respond differently (from C-2 and C-3) under C-H activation conditions. For example, see: (a) B. S. Lane and D. Sames, *Org. Lett.*, 2004, **6**, 2897; (b) N. P. Grimster, C. Gauntlett, C. R. A. Godfrey and M. J. Gaunt, *Angew. Chem., Int. Ed.*, 2005, **44**, 3125; (c) D. R. Stuart, E. Villemure and K. Fagnou, *J. Am. Chem. Soc.*, 2007, **129**, 12072; (d) X. C. Cambeiro, N. Ahlsten and I. Larrosa, *J. Am. Chem. Soc.*, 2015, **137**, 15636; (e) S. Zhang, Y.-H. Niu and X.-S. Ye, *Org. Lett.*, 2017, **19**, 3608.
- 20 Some selected recent studies: (a) J.-N. Desrosiers, L. Hie, S. Biswas, O. V. Zatochnaya, S. Rodriguez, H. Lee, N. Grinberg, N. Haddad, N. K. Yee, N. K. Garg and C. H. Senanayake, *Angew. Chem., Int. Ed.*, 2016, **55**, 11921; (b) R. Samineni, J. Madapa, P. Srihari and G. Mehta, *Org. Lett.*, 2017, **19**, 3119; (c) L. Wang, S. Li, M. Blümel, R. Puttreddy, A. Peuronen, K. Rissanen and D. Enders, *Angew. Chem., Int. Ed.*, 2017, **56**, 8516; (d) C.-C. Wang, J. Huang, X.-H. Li, S. Kramer, G.-Q. Lin and X.-W. Sun, *Org. Lett.*, 2018, **20**, 2888; (e) P. D. Chaudhari, B.-C. Hong, C.-L. Wen and G.-H. Lee, *ACS Omega*, 2019, **4**, 655.
- 21 Mass analysis of the crude reaction mixture also did not indicate the formation of the required product. See the ESI† for details.
- 22 Experimental observations indicated the pronounced effect of the substitution at R¹ (see Tables 2 and 3). We believe that R¹ plays a dual role – electronic and steric. R¹

- stabilises cationic π -allylpalladium intermediates such as **E** and **G**. Especially, the carbon connected to R^1 bears a formal positive charge in **G**; therefore the tertiary carbocation is stabilized. The steric role of R^1 is also shown in Scheme 2. We believe that R^1 is responsible in converting **E** to **F**. In order for this reaction to happen, the attainment of form **F** is necessary.
- 23 The substrate itself may reduce Pd(II) to Pd(0) during the reaction (analogous to Wacker-type process), and consequently, the *in situ* formed Pd(0) serves as the active metal center to promote the subsequent allylation reaction. The formation of Pd black in our reactions is an indicative of this proposition. For a discussion on substrate-induced reduction of Pd(II), see: I. P. Beletskaya and A. V. Cheprakov, *Chem. Rev.*, 2000, **100**, 3009 and references cited therein.
- 24 For deprotonation pathways in Pd-catalyzed reactions, see: (a) D. Garcia-Cuadrado, P. de Mendoza, A. A. C. Braga, F. Maseras and A. M. Echavarren, *J. Am. Chem. Soc.*, 2007, **129**, 6880; (b) S. I. Gorelsky, D. Lapointe and K. Fagnou, *J. Am. Chem. Soc.*, 2008, **130**, 10848; (c) B. Liegault, I. Petrov, S. I. Gorelsky and K. Fagnou, *J. Org. Chem.*, 2010, **75**, 1047.
- 25 The k_H/k_D was found to be 0.51. See the ESI† for details.
- 26 For the study of kinetic isotope effects in organometallic reactions, see: (a) W. D. Jones, *Acc. Chem. Res.*, 2003, **36**, 140; (b) J.-J. Li, R. Giri and J.-Q. Yu, *Tetrahedron*, 2008, **64**, 6979; (c) A. García-Rubia, B. Urones, R. G. Arrayas and J. C. Carretero, *Chem.-Eur. J.*, 2010, **16**, 9676; (d) M. Gomez-Gallego and M. A. Sierra, *Chem. Rev.*, 2011, **111**, 4857; (e) E. M. Simmons and J. F. Hartwig, *Angew. Chem., Int. Ed.*, 2012, **51**, 3066.
- 27 (a) T. Minami, M. Iwamoto, H. Ohtsu, H. Ohishi, R. Tanaka and A. Yoshitake, *Planta Med.*, 2002, **68**, 742; (b) C. I. Chang, J. Y. Chang, C. C. Kuo, W. Y. Pan and Y. H. Kuo, *Planta Med.*, 2005, **71**, 72; (c) T. Katoh, T. Akagi, C. Noguchi, T. Kajimoto, M. Node, R. Tanaka, M. Nishizawa, H. Ohtsu, N. Suzuki and K. Saito, *Bioorg. Med. Chem.*, 2007, **15**, 2736.
- 28 G. Majetich and J. M. Shimkus, *Tetrahedron Lett.*, 2009, **50**, 3311 and references cited therein.
- 29 To rule out PdCl₂ acting as a Lewis acid, the reaction of **1e** was performed with Lewis acids such as MgBr₂, InCl₃, and ZnCl₂. These reactions hardly gave any desired product. See the ESI† for details.