Palladium Catalysis Hot Paper

How to cite: *Angew. Chem. Int. Ed.* **2023**, *62*, e202211167
International Edition: doi.org/10.1002/anie.202211167
German Edition: doi.org/10.1002/ange.202211167

Rapid and Modular Access to Vinyl Cyclopropanes Enabled by Air-stable Palladium(I) Dimer Catalysis

*Marvin Mendel, Lars Gnägi, Uladzislava Dabranskaya, and Franziska Schoenebeck**

Abstract: While vinyl cyclopropanes are valuable functional groups in drugs or natural products as well as established precursors to trigger a rich variety of synthetic transformations, their reactive nature can make their installation via direct catalytic approaches challenging. We herein present a modular access to (di)vinyl cyclopropanes under very mild conditions and full conservation of stereochemistry, allowing access to the *cis* or *trans* cyclopropane- as well as *E* or *Z* vinyl-stereochemical relationships. Our protocol relies on air-stable dinuclear Pd^{I} catalysis, which enables rapid (<30 min) and selective access to a diverse range of vinyl cyclopropane motifs at room temperature, even on gram scale.

Owing to their exquisite bonding properties and privileged structure–activity relationships, vinyl cyclopropanes are key structural motifs in various drugs, agrochemicals and natural products.[1] Notable examples include the antivirals Simeprevir (Hepatitis C treatment) or Danoprevir (against COVID-19).[2] Representative natural products containing the vinyl cyclopropane motif are *Pyrethrines*, the naturally occurring esters of chrysanthemic acid used by the chrysanthemum flower to fight insects, or the *Dictyopterene* pheromones, found in marine brown algae (Figure 1A).[3] Owing to their pronounced reactivity, vinyl cyclopropanes also find numerous applications as versatile synthetic precursors that participate in a broad range of transformations, including ring-openings, cycloadditions and rearrangements (Figure 1B) to access natural products or functional molecules and polymers.[4]

Since they are reactive functional groups, the synthetic installation of mono- and di-vinyl cyclopropanes is more challenging compared to the non-vinylic cyclopropane motifs.[5] The majority of synthetic approaches either rely on indirect access via multistep syntheses or focus on building the cyclopropane ring along with the vinylic motif.[5] While this allows to access desired isomers, the methods tend to be substrate-specific. The direct catalytic and modular installation of the vinyl cyclopropane motif would be advantageous and enhance the accessibility of these valuable compounds and their derivatives (and as such potentially accelerate the discovery of new function). Moreover, it would allow to introduce the desired stereochemistry (*cis/trans* cyclopropane; *E*/*Z* olefin stereochemistry) as a pre-defined entity. In this context, the carbometalation of cyclopropenes, followed by quenching with electrophiles[6] or subsequent functionalization by metal-catalyzed cross-coupling,[7] has greatly advanced the modular access to richly substituted cyclopropanes under stereochemical control.[8] Especially recent work by Marek and co-workers further advanced the coupling repertoire,[9,10] allowing to make highly substituted vinyl cyclopropanes in a stereospecific manner.[11] This was achieved through Pd^{0}-catalyzed coupling at 50–75 °C over 16 h of alkenyl halides with cyclopropyl organometallic reagents, which were accessed through CuI-catalyzed *cis*-selective[8] carbometalation of cyclopropenes. Cross-coupling

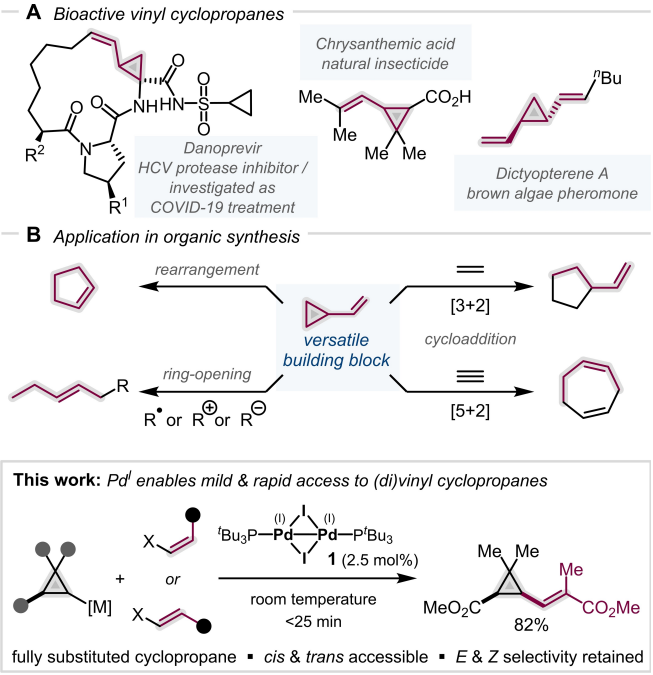


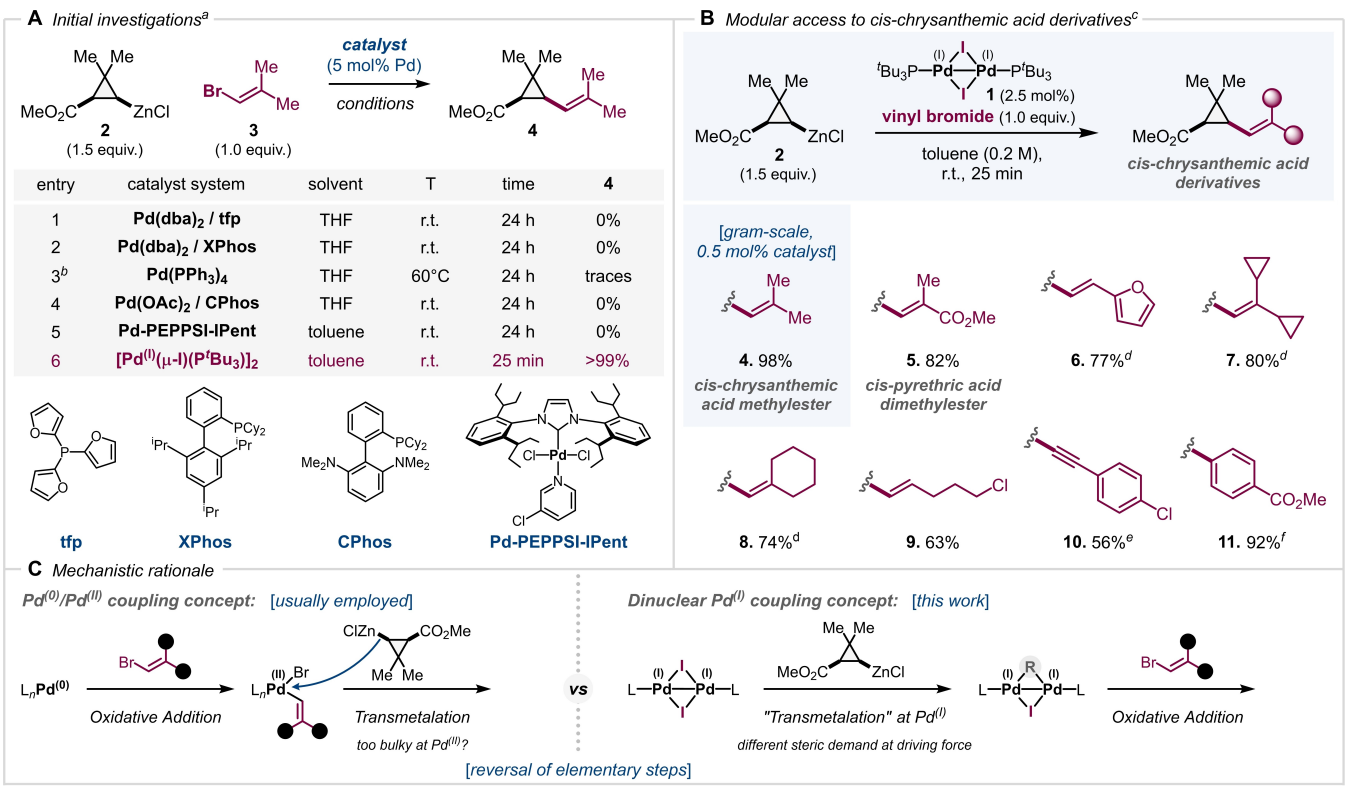
Figure 1. Importance of vinyl cyclopropanes: A) Representative bioactive compounds containing the vinyl cyclopropane scaffold. B) Vinyl cyclopropane in organic synthesis. This work.

[*] M. Mendel, Dr. L. Gnägi, U. Dabranskaya, Prof. Dr. F. Schoenebeck
Institute of Organic Chemistry, RWTH Aachen University
Landoltweg 1, 52074 Aachen (Germany)
E-mail: franziska.schoenebeck@rwth-aachen.de
Homepage: http://www.schoenebeck.oc.rwth-aachen.de

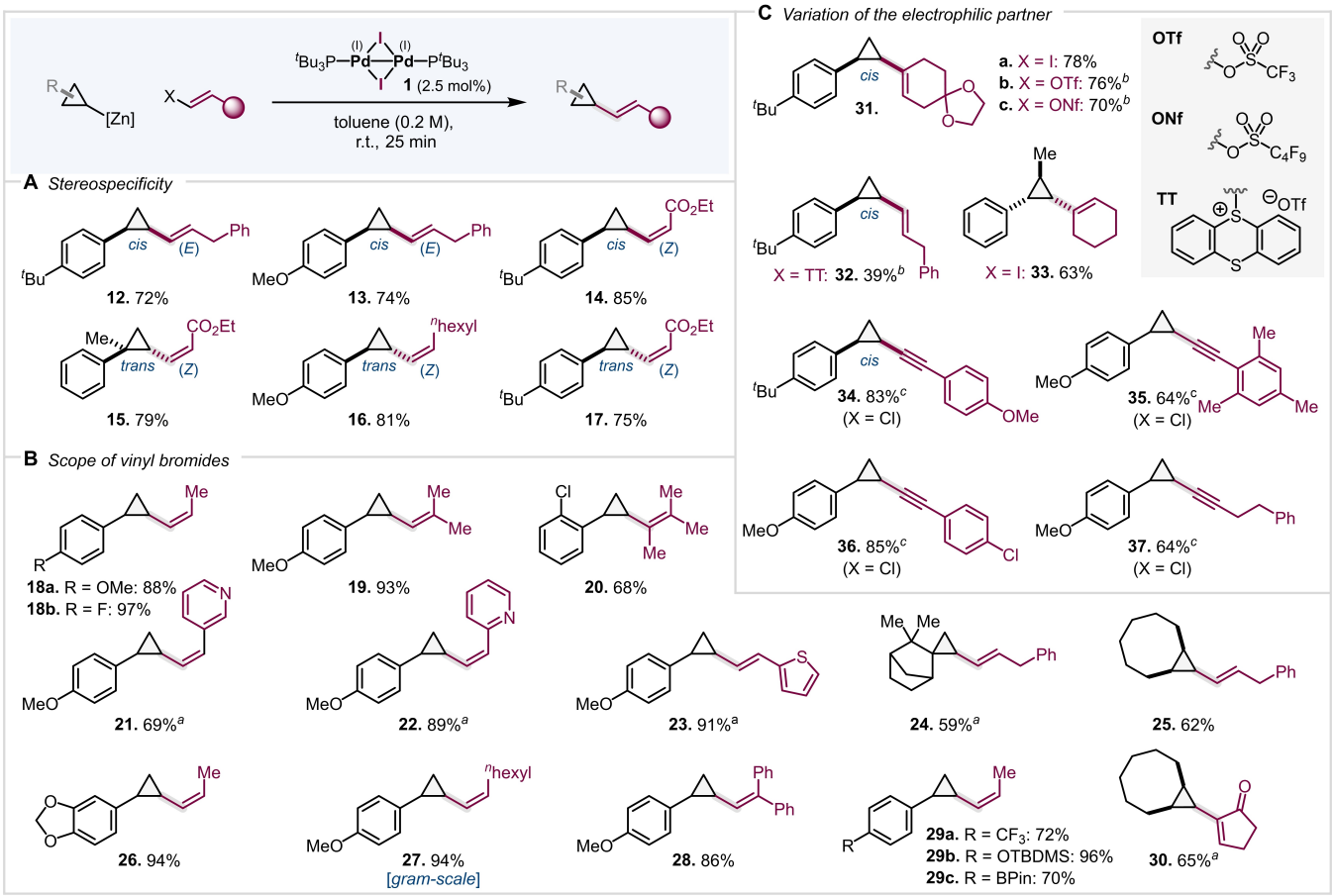
methods, that do not involve prior carbometalation, to make (di)vinyl cyclopropanes[11,12] via cross-coupling of a cyclopropane with a vinyl moiety or, via the alternative disconnection of coupling the vinyl cyclopropane unit with appropriate rests, have frequently one cyclopropane site unsubstituted in the final targets, delivering predominantly the *trans*-cyclopropane and *E*-vinyl relationship.[12]

We envisioned that a milder and more rapid modular access to these structural motifs would be advantageous, especially for more sensitive examples, given their known ring-opening reactivities.

To gain greater insight, we started our investigations by examining a range of cross-coupling protocols, including state-of-the-art alkylation Pd-catalysis methodology,[13] for the possibility to synthesize *cis*-chrysanthemic acid derivatives—a motif that combines several challenges, such as the stereochemistry of the cyclopropane and the vinyl group as well as a richly decorated cyclopropane moiety (see Scheme 1). We envisioned that a useful disconnection would be between the olefin and the vinyl cyclopropane, as this would potentially provide rapid access to previously unknown derivatives and allow to introduce the desired stereochemistry through a pre-made building block. Marek and team showcased such couplings to structurally very similar motifs previously, employing $Pd(PPh_3)_4$/CuI catalysis at 50–75 °C over 16 h.[11] We synthesized the *cis*-cyclopropyl zincate coupling partner (**2**) (see Supporting Information for details) and tested Cu-free methodology to explore the limits of Pd^0 based catalysis in this context. Following $Pd(dba)_2$/tfp catalysis methodology, originally developed by Marek and Knochel for the arylation of cyclopropanes,[13] and applying it to our vinylation challenge of the highly substituted *cis*-cyclopropyl zincate gave no coupling product (**4**). Our closer inspection of the reaction revealed that 80 % of cyclopropyl zincate (**2**) remained untouched. For comparison, using **2** under $Pd(dba)_2$/tfp catalysis with an aryl bromide, instead of vinyl bromide, gave the corresponding aryl cyclopropane in low yield (27 %).[14] Our examinations of alternative Pd-catalysis methodologies that found prior use to make lower substituted vinyl cyclopropanes or represent the state-of-the-art in alkylation methodology,[12,13] also led to no product formation (see Scheme 1, A). Independent quenching examinations revealed that either no reaction took place, with **2** remaining largely untouched (entries 1 and 2),[15] or a complex mixture resulted from side reactions (entries 3–6, with < 5 % of **2** remaining).[14] Consequently, CuI might be a crucial co-catalyst—an additive known to enhance the transmetalation step.[16] Pd^0/Pd^{II} cross-coupling regimes might be confronted with a challenging transmetalation to achieve the desired coupling, likely owing to the steric demands of the transmetalating agent. We envisioned that an alternative coupling regime based on



Scheme 1. Synthesis of chrysanthemic acid derivatives: A) Initial investigations and catalyst comparison. B) Scope of chrysanthemic acid derivatives. [a] yields obtained by quantitative GC-MS analysis; [b] 10 mol % catalyst loading; [c] Reaction conditions for cross-coupling: vinyl bromide (0.5 mmol) and $[Pd^I(\mu\text{-}I)(P^tBu_3)]_2$ **1** (2.5 mol %) in toluene (0.2 M), slow addition of **2** (1.5 equiv) over 15 min via syringe pump, 10 min at r.t.; [d] vinyl bromide (2.0 equiv); [e] alkynyl chloride (2.0 equiv) used as electrophile. [f] aryl bromide (0.5 mmol) used as electrophile. C) Illustration of mechanistic concepts.

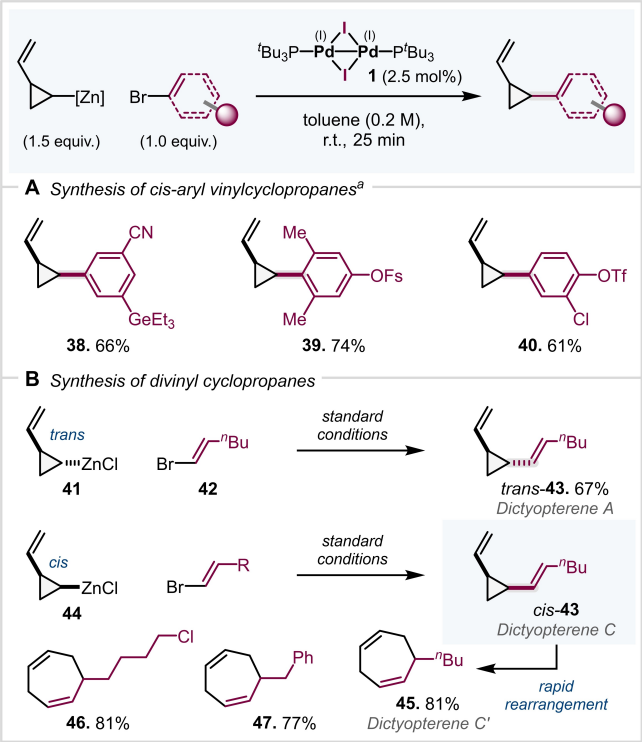


Scheme 2. Scope of the method: A) stereospecificity of the reaction, B) scope of vinyl bromides, C) variation of the electrophilic partner. Reaction conditions: electrophile (0.5 mmol) and **1** (2.5 mol%) in toluene (0.2 M); slow addition of organozincate (1.2–2.0 equiv) over 15 min, 10 min at r.t.; [a] electrophile (0.5 mmol) and **1** (2.5 mol%) in toluene (0.2 M); reverse addition to organozincate (1.5 equiv) over 15 min, 10 min at r.t.; [b] reaction performed in NMP (0.2 M); [c] electrophile (1.0 mmol) and **1** (2.5 mol%) in toluene (0.2 M); slow addition of organozincate (0.5 equiv) over 15 min, 10 min at r.t.; Slow additions were performed using a syringe pump.

dinuclear Pd^{I} might potentially allow for milder coupling conditions. For catalysis involving Pd^{I} dimers[17] the elementary steps are formally reversed with transmetalation taking place initially, which is associated with different driving forces than exchange at Pd^{II} (see Scheme 1, C for a conceptual illustration).[18] The newly formed dinuclear Pd^{I} entity then would react directly with the corresponding coupling partner.[19] Consistent with this view, addition of the cyclopropyl organozincate to Pd^{I} dimer leads to its instantaneous consumption. A structural characterization of the formed species is challenging however, as it is unstable and short-lived at r.t. (less than 2 min).[20] The liberation of a low coordinate Pd^{0} species in this process cannot be unambiguously ruled out and is a mechanistic alternative. While the coupling of vinyl electrophiles under Pd^{I} dimer catalysis has not yet been demonstrated, our previous studies in the area showed that arylations as well as alkylations of aryl halides proceed within minutes at room temperature,[21] even for sterically demanding substrates such as *ortho*-adamantyl arenes.[22] Our calculations suggest that the activation barrier to activate a vinyl bromide with an alkyl bridged Pd^{I} dimer is very similar to that of an aryl bromide.[23]

Using the air-stable Pd^{I} dimer, $[Pd^{I}(\mu\text{-}I)(P^{t}Bu_3)]_2$ (**1**), for the same coupling of **2** with vinyl bromide **3**, pleasingly afforded the vinyl cyclopropane **4** quantitatively at room temperature in a rapid manner: following a slow addition of **2** over 15 min to minimize potential metal-halogen exchange, the reaction mixture was left to stir for another 10 min at room temperature, leading to quantitative formation of the desired product in overall 25 min. To push the limits of this coupling, we also investigated its scalability, and were able to synthesize the *cis*-chrysanthemic acid methyl ester **4** on gram-scale with a catalyst loading of only 0.5 mol % of Pd^{I} dimer **1**.

We investigated numerous other derivatives of *cis*-chrysanthemic acid and readily accessed derivatives bearing different alkene substituents, such as conjugated alkenes **5** and **6** as well as sterically hindered alkenes **7** and **8**. Also, a primary chloride (**9**) and alkynyl moiety (**10**) were tolerated (Scheme 1B). In addition, the coupling with an aryl bromide gave the corresponding aryl cyclopropane **11** in high yield (92 %). The literature routes[24] to access modifications of



Scheme 3. Use of the vinyl cyclopropane zincate building block. Reaction conditions: electrophile (0.5 mmol) and **1** (2.5 mol%) in toluene (0.2 M); slow addition of organozincate (1.5 equiv) over 15 min via syringe pump, 10 min at r.t.; [a] electrophile (0.5 mmol) and **1** (2.5 mol%) in toluene (0.2 M); reverse addition to organozincate (1.5 equiv) over 15 min via syringe pump, 10 min at r.t.

the vinyl moiety in synthetic chrysanthemic acid derivatives (termed *Pyrethroids*) involve 4–8 step linear sequences, which underscores the advantage of the modular approach.

Next, we set out to synthesize aryl vinyl cyclopropanes. To this end, we studied the coupling of vinyl bromides with cyclopropyl organozincates. We were pleased to find that the transformation is completely stereospecific and neither isomerization of the cyclopropyl unit nor the *Z*-alkenyl counterpart was observed (Scheme 2A). The coupling of diastereomerically pure *cis*- and *trans*-building blocks afforded exclusively diastereomerically pure products (**12**–**17**). For the remaining examples in the scope of vinyl bromides, we employed *cis/trans* mixtures of cylopropyl zincates (Scheme 2B). In these cases, the stereochemical integrity was preserved, too; no change in diastereomeric ratio was observed in the coupling. The method delivers a broad variety of vinyl cyclopropanes independent of the cyclopropane or the alkene coupling partner. Linear (e.g. **18**, **27**, **29**) and branched (e.g. **19**, **20**) alkenyl bromides, (hetero-)aromatic styrene derivatives (**21**–**23**), as well as conjugated alkenyl bromides (**28**, **30**) were all coupled efficiently. No significant influence of the electronic nature of the aryl cyclopropane was observed, since electron-donating (**18a**, **29b**) or electron-withdrawing (**20**, **18b**, **29a**, **29c**) groups did not markedly influence the yield of the reaction. Moreover, highly sterically strained alkyl-substituted vinyl cyclopropanes as in the case of cyclooctane (**25**, **30**) or camphene-derived (**24**) examples were obtained in high yields. Similarly, various additives (arenes containing amine, aldehyde, nitrile, OH functionalities and heterocycles) were also tolerated in the coupling to make **18a** and **19** in our robustness screen,[25] indicating that broad scope would in principle be feasible (see Supporting Information, page S39 for details).

We also examined whether alternative vinyl electrophiles, other than vinyl bromides, could be employed for the coupling (Scheme 2C). We found that alkenyl iodides (**31a**, **33**), triflates (**31b**) and nonaflates (**32c**) give similar results. Vinyl thiantrenium salts[26] (TT, **33**) can also be used as a coupling partner, although the product was formed in lower yield. Beyond the direct coupling of cyclopropyl organozinc with vinyl electrophiles, another option to access the desired products is to couple alkynyl electrophiles, which offers the possibility for further conversion to a vinyl cyclopropane at a later stage. Pleasingly, the coupling of alkynyl chlorides (**34**–**37**) with aryl cyclopropane zincates was found to be possible.

For wider modularity and broader synthetic access to (di)vinyl cyclopropanes, we next assessed the feasibility of coupling a vinyl cyclopropyl organozincate unit with vinyl- or aryl electrophiles. To this end, we examined the challenge of site-selective vinyl-cyclopropanation of polyfunctionalized arenes. To our delight, we saw site-selective coupling of the readily made vinyl cyclopropylzinc reagent with an aryl bromide bearing additional C–CN and C–$GeMe_3$ (**38**), C–OFs (**39**), C–OTf and C–Cl (**40**) sites in 25 min at room temperature. The coupling was exclusively C–Br selective and also independent of steric effects (e.g., *ortho*-dimethyl in **39**). As such, arylated vinyl cyclopropane derivatives can now readily be made in a selective manner, and their rich functionalities (e.g. CN, Ge, OFs, OTf, Cl) allow for further downstream functionalizations of the aryl moiety[21,27] or the vinyl cyclopropane itself. Once again, the stereochemical information of the *cis*-cyclopropane fragment was fully conserved throughout all couplings (Scheme 3A).

We next extended this approach to the challenging synthesis of divinyl cyclopropanes, i.e. the *Dictyopterene* natural product family (Scheme 3B).[4c,12a,28] To our delight, our rapid and mild conditions allowed us to prepare Dictyopterene A (*trans*-**43**) through the coupling of *trans*-vinyl cyclopropane zincate (**41**) with (*E*)-1-bromohex-1-ene (**42**) in a selective fashion. We were also able to prepare the corresponding *cis*-vinyl cyclopropane zincate (**44**), which yielded exclusively Dictyopterene C′ (**45**). This compound arises from divinyl cyclopropane rearrangement of the *cis*-divinyl cyclopropane intermediate *cis*-**43** (termed Dictyopterene C). This rearrangement is reported to happen within seconds already at room temperature.[4c,29] The divinyl cyclopropane rearrangement was also observed in the case of **46** and **47** in similar yields. However, given that we observed exclusively the product originating from the rearrangement in case of the *cis*-isomer, or the desired *trans*-divinyl cyclopropane for the *trans*-isomer, our coupling clearly was stereospecific in these cases also; no isomerisation occurred during the coupling process.

In conclusion, we have developed a mild and rapid method for the modular synthesis of vinyl cyclopropanes via stereospecific cross-couplings employing an air-stable Pd^{I} dimer catalyst. The method is characterized by operational simplicity, scalability, proceeding at room temperature and high speed (<30 min). A diverse range of cyclopropane organozincates were demonstrated to couple to the corresponding vinylated, arylated or alkynylated derivatives in a fully stereospecific and/or regioselective manner. This also allowed access to hitherto unknown derivatives of the natural insecticide chrysanthemic acid in less than 30 min at room temperature (on gram-scale). Owing to the mildness and speed, we anticipate this methodology to be especially useful for the construction of more reactive vinyl cyclopropanes motifs.

Please note: At the authors' request, significant changes have been made to this publication since its publication as an Accepted Article, in particular regarding the discussion of Ref. [11] (previously Ref. [6f]) and through additional mechanistic studies, which were confirmed by additional peer review. The Editor.

Acknowledgements

We thank RWTH Aachen University, the European Research Council (ERC-637993), the German Merit Foundations (scholarship to M.M.), and the Swiss National Science Foundation (SNSF fellowship P2BEP2_199986 to L.G.) for funding. We are grateful to Jiri Dolezel for experimental assistance and Gourab Kundu for helpful discussions. Open Access funding enabled and organized by Projekt DEAL.

Conflict of Interest

The authors declare no conflict of interests.

Data Availability Statement

The data that support the findings of this study are available in the Supporting Information of this article.

Keywords: Chemoselectivity · Cross-Coupling · Dinuclear Pd^{I} · Stereoselectivity · Vinyl Cyclopropanes

[1] a) J. Salaün in *Small Ring Compounds in Organic Synthesis VI, Vol. 207* (Ed.: A. de Meijere), Springer, Berlin, **2000**, pp. 1–67; b) T. T. Talele, *J. Med. Chem.* **2016**, *59*, 8712–8756.

[2] a) H. Chen, Z. Zhang, L. Wang, Z. Huang, F. Gong, X. Li, Y. Chen, J. J. Wu, *Medicine* **2020**, *99*, e23357; b) Z. Zhang, S. Wang, X. Tu, X. Peng, Y. Huang, L. Wang, W. Ju, J. Rao, X. Li, D. Zhu, H. Sun, H. Chen, *J. Med. Virol.* **2020**, *92*, 2631–2636.

[3] a) R. E. Moore, J. A. Pettus, M. S. Doty, *Tetrahedron Lett.* **1968**, *9*, 4787–4790; b) F. Jüttner, K. Wurster, *Limnol. Oceanogr.* **1984**, *29*, 1322–1324.

[4] For reviews, see: a) M. Rubin, M. Rubina, V. Gevorgyan, *Chem. Rev.* **2007**, *107*, 3117–3179; b) T. Hudlicky, J. W. Reed, *Angew. Chem. Int. Ed.* **2010**, *49*, 4864–4876; *Angew. Chem.* **2010**, *122*, 4982–4994; c) S. Krüger, T. Gaich, *Beilstein J. Org. Chem.* **2014**, *10*, 163–193; d) G. Fumagalli, S. Stanton, J. F. Bower, *Chem. Rev.* **2017**, *117*, 9404–9432; e) M. Meazza, H. Guo, R. Rios, *Org. Biomol. Chem.* **2017**, *15*, 2479–2490.

[5] For a recent review, see: V. Ganesh, S. Chandrasekaran, *Synthesis* **2016**, *48*, 4347–4380.

[6] a) M. Rubin, M. Rubina, V. Gevorgyan, *Synthesis* **2006**, *2006*, 1221–1245; b) H. Lehmkuhl, K. Mehler, *Justus Liebigs Ann. Chem.* **1978**, 1841–1853.

[7] a) M. Nakamura, H. Isobe, E. Nakamura, *Chem. Rev.* **2003**, *103*, 1295–1326; b) E. Nakamura, M. Isaka, S. Matsuzawa, *J. Am. Chem. Soc.* **1988**, *110*, 1297–1298; c) M. Isaka, E. Nakamura, *J. Am. Chem. Soc.* **1990**, *112*, 7428–7430.

[8] For a review, see: D. S. Müller, I. Marek, *Chem. Soc. Rev.* **2016**, *45*, 4552–4566.

[9] a) Y. Cohen, I. Marek, *Acc. Chem. Res.* **2022**, *55*, 2848–2868; b) A. Cohen, A. Kaushansky, I. Marek, *JACS Au* **2022**, *2*, 687–696; c) Y. Cohen, I. Marek, *Angew. Chem. Int. Ed.* **2021**, *60*, 26368–26372; *Angew. Chem.* **2021**, *133*, 26572–26576; d) Y. Cohen, A. U. Augustin, L. Levy, P. G. Jones, D. B. Werz, I. Marek, *Angew. Chem. Int. Ed.* **2021**, *60*, 11804–11808; *Angew. Chem.* **2021**, *133*, 11910–11914; e) A. Cohen, J. Chagneau, I. Marek, *ACS Catal.* **2020**, *10*, 7154–7161; f) D. S. Müller, V. Werner, S. Akyol, H.-G. Schmalz, I. Marek, *Org. Lett.* **2017**, *19*, 3970–3973.

[10] See also: S. Jerhaoui, P. Poutrel, J. P. Djukic, J. Wencel-Delord, F. Colobert, *Org. Chem. Front.* **2018**, *5*, 409–414.

[11] J. Bruffaerts, D. Pierrot, I. Marek, *Nat. Chem.* **2018**, *10*, 1164–1170.

[12] a) E. Piers, M. Jean, P. S. Marrs, *Tetrahedron Lett.* **1987**, *28*, 5075–5078; b) S.-M. Zhou, M.-Z. Deng, L.-J. Xia, M.-H. Tang, *Angew. Chem. Int. Ed.* **1998**, *37*, 2845–2847; *Angew. Chem.* **1998**, *110*, 3061–3063; c) S. Löhr, A. de Meijere, *Synlett* **2001**, *2001*, 0489–0492; d) S. J. Chawner, M. J. Cases-Thomas, J. A. Bull, *Eur. J. Org. Chem.* **2017**, 5015–5024; e) T. G. Chen, L. M. Barton, Y. Lin, J. Tsien, D. Kossler, I. Bastida, S. Asai, C. Bi, J. S. Chen, M. Shan, H. Fang, F. G. Fang, H.-w. Choi, L. Hawkins, T. Qin, P. S. Baran, *Nature* **2018**, *560*, 350–354.

[13] For selected examples, see: a) V. A. Vu, I. Marek, K. Polborn, P. Knochel, *Angew. Chem. Int. Ed.* **2002**, *41*, 351–352; *Angew. Chem.* **2002**, *114*, 361–362; b) C. Han, S. L. Buchwald, *J. Am. Chem. Soc.* **2009**, *131*, 7532–7533; c) M. Pompeo, R. D. J. Froese, N. Hadei, M. G. Organ, *Angew. Chem. Int. Ed.* **2012**, *51*, 11354–11357; *Angew. Chem.* **2012**, *124*, 11516–11519; d) Y. Yang, K. Niedermann, C. Han, S. L. Buchwald, *Org. Lett.* **2014**, *16*, 4638–4641.

[14] For more details, see the Supporting Information.

[15] Remaining organozincate **2** was quenched by the addition of iodine and the resulting iodinated cyclopropane quantified by GC-MS using mesitylene as an internal standard.

[16] For a review, see: M. H. Pérez-Temprano, J. A. Casares, P. Espinet, *Chem. Eur. J.* **2012**, *18*, 1864–1884.

[17] C. Fricke, T. Sperger, M. Mendel, F. Schoenebeck, *Angew. Chem. Int. Ed.* **2021**, *60*, 3355–3366; *Angew. Chem.* **2021**, *133*, 3395–3406.

[18] X.-Y. Chen, M. Pu, H.-G. Cheng, T. Sperger, F. Schoenebeck, *Angew. Chem. Int. Ed.* **2019**, *58*, 11395–11399; *Angew. Chem.* **2019**, *131*, 11517–11521.

[19] For further demonstrations of the concept, see: a) K. J. Bonney, F. Proutiere, F. Schoenebeck, *Chem. Sci.* **2013**, *4*, 4434–4439; b) G. Yin, I. Kalvet, F. Schoenebeck, *Angew. Chem. Int. Ed.* **2015**, *54*, 6809–6813; *Angew. Chem.* **2015**, *127*, 6913–6917; c) M. Aufiero, T. Sperger, A. S.-K. Tsang, F. Schoenebeck, *Angew. Chem. Int. Ed.* **2015**, *54*, 10322–10326;

Angew. Chem. **2015**, *127*, 10462–10466; d) T. Scattolin, E. Senol, G. Yin, Q. Guo, F. Schoenebeck, *Angew. Chem. Int. Ed.* **2018**, *57*, 12425–12429; *Angew. Chem.* **2018**, *130*, 12605–12609.

[20] Consistent with the short-lived nature of the key intermediate, our stoichiometric reactivity studies of mixing Pd^{I} dimer with 1.0 equiv of cyclopropyl organozincate led to consumption of the Pd^{I} dimer and formation of a new (unknown) species, as judged by ^{31}P NMR, which rapidly converts to $Pd^{0}(PtBu_3)_2$ within 2 min at room temperature. Once $Pd^{0}(PtBu_3)_2$ is visibly formed, addition of 1.0 equiv of vinyl bromide to this mixture does not lead to its consumption; no reaction takes place [when 5.0 equiv of organozincate were used in the same experiment, low conversion of vinyl bromide was seen (17 %)]. However, if the vinyl bromide is present from the start in this stoichiometric experiment (with 1.0 equiv of each component), full conversion of the vinyl bromide to the corresponding coupled product is seen. These data are in line with a mechanistic scenario in which a short-lived and highly reactive species is formed upon reaction of the Pd^{I} dimer with the organometallic reagent.

[21] a) I. Kalvet, G. Magnin, F. Schoenebeck, *Angew. Chem. Int. Ed.* **2017**, *56*, 1581–1585; *Angew. Chem.* **2017**, *129*, 1603–1607; b) I. Kalvet, T. Sperger, T. Scattolin, G. Magnin, F. Schoenebeck, *Angew. Chem. Int. Ed.* **2017**, *56*, 7078–7082; *Angew. Chem.* **2017**, *129*, 7184–7188; c) S. T. Keaveney, G. Kundu, F. Schoenebeck, *Angew. Chem. Int. Ed.* **2018**, *57*, 12573–12577; *Angew. Chem.* **2018**, *130*, 12753–12757; d) G. Magnin, J. Clifton, F. Schoenebeck, *Angew. Chem. Int. Ed.* **2019**, *58*, 10179–10183; *Angew. Chem.* **2019**, *131*, 10285–10289; e) M. Mendel, I. Kalvet, D. Hupperich, G. Magnin, F. Schoenebeck, *Angew. Chem. Int. Ed.* **2020**, *59*, 2115–2119; *Angew. Chem.* **2020**, *132*, 2132–2136.

[22] I. Kalvet, K. Deckers, I. Funes-Ardoiz, G. Magnin, T. Sperger, M. Kremer, F. Schoenebeck, *Angew. Chem. Int. Ed.* **2020**, *59*, 7721–7725; *Angew. Chem.* **2020**, *132*, 7795–7799.

[23] Barriers for oxidative addition of phenyl and vinyl bromide at a mixed alkyl-iodo-bridged Pd^{I} dimer are 18.2 and 16.6 kcal mol^{-1}, respectively (at the CPCM (toluene) M06L/def2-TZVP//wB97XD/6-31G(d) (LANL2DZ for Pd, I) level of theory). For details see the Supporting Information.

[24] a) Z. Zheng, J. Wang, D. Zhang, X. Guan, S. Gao, Z. Chen, X. Zou, *J. Agric. Food Chem.* **2011**, *59*, 1171–1177; b) P. L. Johnson, *J. Labelled Compd. Radiopharm.* **2007**, *50*, 47–53; c) K. Naumann, *Synthetic Pyrethroid Insecticides: Chemistry and Patents*, Springer, Berlin, **2012**.

[25] K. D. Collins, F. Glorius, *Nat. Chem.* **2013**, *5*, 597–601.

[26] J. Chen, J. Li, M. B. Plutschack, F. Berger, T. Ritter, *Angew. Chem. Int. Ed.* **2020**, *59*, 5616–5620; *Angew. Chem.* **2020**, *132*, 5665–5669.

[27] a) A. Dahiya, C. Fricke, F. Schoenebeck, *J. Am. Chem. Soc.* **2020**, *142*, 7754–7759; b) G. J. Sherborne, A. G. Gevondian, I. Funes-Ardoiz, A. Dahiya, C. Fricke, F. Schoenebeck, *Angew. Chem. Int. Ed.* **2020**, *59*, 15543–15548; *Angew. Chem.* **2020**, *132*, 15673–15678; c) C. Fricke, G. J. Sherborne, I. Funes-Ardoiz, E. Senol, S. Guven, F. Schoenebeck, *Angew. Chem. Int. Ed.* **2019**, *58*, 17788–17795; *Angew. Chem.* **2019**, *131*, 17952–17959.

[28] E. Piers, P. D. G. Coish, *Synthesis* **2001**, *2001*, 0251–0261.

[29] T. Kim, J. Y. Kim, K. Y. Park, D. H. Ryu, *Bull. Korean Chem. Soc.* **2021**, *42*, 675–678.

Manuscript received: July 29, 2022
Accepted manuscript online: October 13, 2022
Version of record online: January 11, 2023