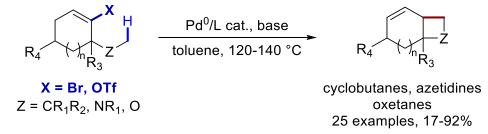
1,4-Pd Migration-Enabled Synthesis of Fused 4-Membered Rings

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1,4-Palladium migration has been established as an elegant approach towards the functionalization of remote C–H bonds.^{1,2} However, its application has been restricted to aryl halide precursors.³ In this work, we are expanding the application of 1,4-Pd migration to alkenyl (pseudo)halides and we report an unprecedented Pd⁰-catalysed cyclobutanation protocol towards fused cyclobutanes.⁴ This reaction takes place via alkenyl-to-alkyl 1,4-Pd shift, followed by intramolecular Heck coupling. The method performs best with cyclohexenyl precursors giving access to a variety of substituted bicyclo[4,2,0]octenes, and also shows a potential for accessing smaller ring systems starting from cyclopentenyl halides. Precursors containing an *N*-methyl or methoxy group lead to fused azetidines or oxetanes, respectively, via the same mechanism. Determination of orders for the reaction using variable time normalization analysis (VTNA)⁵ and deuterium-labelling studies (k_H/k_D 3.1) point towards a rate-limiting C(sp³)–H activation step.



[1] R. F. Heck, J. Organomet. Chem. 1972, 37, 389–398.

[2] F. Shi, R. C. Larock, Top. Curr. Chem. 2010, 292, 123-164.

- [3] (a) R. Rocaboy, I. Anastasiou, O. Baudoin, Angew. Chem. Int. Ed. 2019, 58, 14625–14628. (b) Antonin Clemenceau, Pierre Thesmar, Maxime Gicquel, Alexandre Le Flohic, Olivier Baudoin, J. Am. Chem. Soc. 2020, 142, 15355–15361. (c) Takeru Miyakoshi, Nagja E. Niggli, Olivier Baudoin, Angew. Chem. Int. Ed. 2022, 61, e2021161.
- [4] M. Tsitopoulou, A. Clemenceau, P. Thesmar, O. Baudoin. J. Am. Chem. Soc. 2024, 146, 18811–18816.
- [5] (a) Jordi Burés, Angew. Chem. Int. Ed. 2016, 55, 16084–16087. (b) Christian D.-T. Nielsen, Jordi Burés, Chem. Sci. 2019, 10, 348–353.