Methylene C(sp^3)–H activation enables stereoselective synthesis of Indidene natural products

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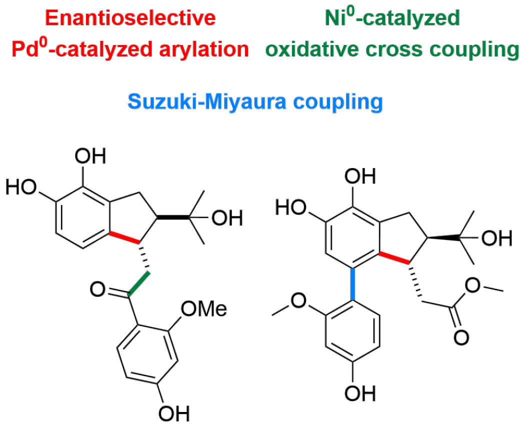
Recently developed C–H activation methodologies have enabled concise and efficient total syntheses of various bioactive natural products[1]. In this context, Pd^0-catalyzed C–H activation has emerged as a method of choice for construction of cyclopentane rings of various complexity[2]. We report our investigations towards racemic and enantioselective synthesis of Indidenes A and C, polyketides isolated from bark of *S. indicus*, as well as other indidene congeners. The construction of the indane scaffold is enabled by implementation of a Pd^0-catalyzed methylene C–H activation[3], which sets the first stereocenter. The installation of the side chain is achieved by a Ni^0-catalyzed oxidative cross-coupling[4] in the case of Indidene A, while Suzuki coupling facilitated formation of a biphenyl system in Indidene C.



***rac*-indidene A** **(–)-Indidene C**

[1] O. Baudoin, *Angew. Chem. Int. Ed*. **2020**, *59*, 17798-17809; C. Tsukano, Y. Takemoto, Handbook of CH-Functionalization, Wiley-VCH, **2022**.

[2] Example of such a synthesis: P. Thesmar, O. Baudoin, *J. Am. Chem. Soc.* **2019**, *141*, 15779-15783.

[3] R. Melot, M. Zuccarello, D. Cavalli, N. Niggli, M. Devereux, T. Bürgi, O. Baudoin, *Angew. Chem. Int. Ed.* **2021**, *60*, 7245-7250.

[4] T. Verheyen, L. von Turnhout, J. K. Vandavasi, E. S. Isbrandt, W. M. De Borggraeve, S. G. Newman, *J. Am. Chem. Soc.,* **2019**, *141*, 6869-6874.