Continuous flow methodologies oriented to drug discovery involving organozinc agents

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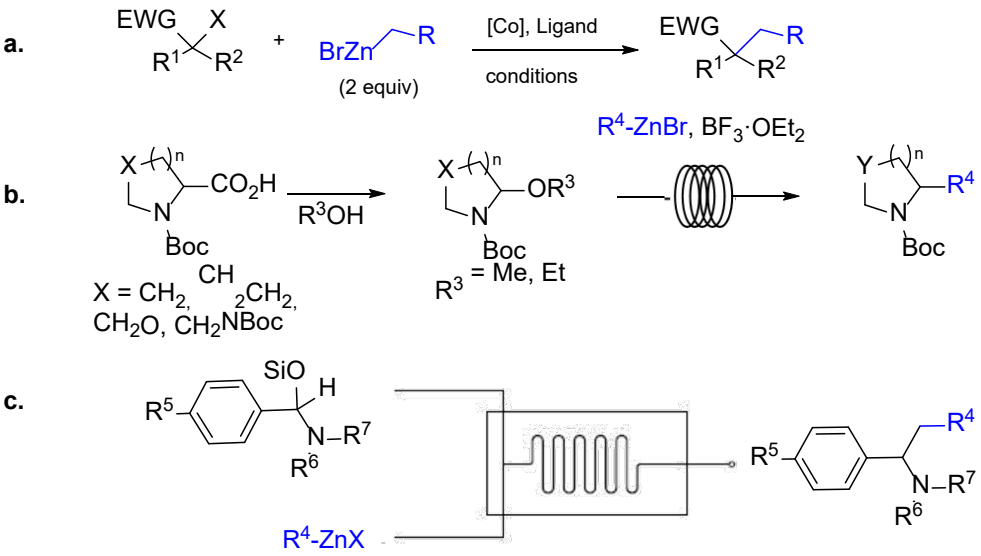
Organozinc halides have been demonstrated to be useful coupling agents in several transformations (e.g. Reformansky and Negishi cross-coupling reactions). They are specially useful in introducing C(sp3)-fractions in drug discovery programs which allows to increase the biological activity of the drug candidates. In order to prepare organozinc halides, a continuous flow version was developed in 2014 by showing several advantages comparing with the traditional batch approach [1]. In this regard, subsequent transformations have been achieved to demonstrate the synthetic value of these organometallic agents [2].

In this work, we demonstrate how these continuous flow generated organozinc agents can be used to achieve C(sp3)-C(sp3) bond formations. First, a new Negishi cross-coupling catalyzed by cobalt is selective over C(sp2)-halides for the generation of quaternary centres (**Scheme 1a**) [3]. Then, we disclose how electrochemistry can be combined with Lewis acids and organozinc agents to achieve the α-functionalization of amines (**Scheme 1b**) [4]. Finally, we show how automated platforms can also we suitable for the coupling of organozinc agents and amides in continuous flow to generate α-functionalized amine derivatives (**Scheme 1c**) [5].



Scheme 1: C(sp3)-C(sp3) bond formation reactions using organozinc halides.

References:

1. a) N. Alonso, L. Zane Miller, J. M. Muñoz, J. Alcázar, T. McQuade, *Adv. Synth. Catal.* **2014**, 356, 3685; b) M. Berton, L. Huck, J. Alcázar, *Nat. Protoc.* **2018**, 13, 324.
2. E. Palao, J. Alcázar, Organometallic Chemistry in flow in the pharmaceutical industry. In book: Flow Chemistry: Integrated approaches for practical aplications. **2020**. RSC. Pp 86-128.
3. E. Palao, E. López, I. Torres-Moya, A. de la Hoz, A. Díaz-Ortiz, J. Alcázar, *Chem. Commun*. **2020**, *56*, 8210.
4. E. López, C. Van Melis, R. Martín, A. Petti, A. de la Hoz, A. Díaz-Ortíz, A. P. Dobbs, K. Lam, J. Alcázar, *Adv. Synth. Catal.* **2021**, *363*, 4521.
5. B. Pijper, R. Martín, A. J. Huertas-Alonso, L. Linares, E. López, J. Llavería, A. Díaz-Ortíz, D. J. Dixon, A. de la Hoz, J. Alcázar, *Org. Lett*. **2023**, **DOI:** 10.1021/acs.orglett.3c01390.