SEPTEMBER 23-27 2024
19BMOS
BRAZILIAN MEETING ON ORGANIC SYNTHESIS
BENTO GONÇALVES, RS - BRAZIL

Enantioselective palladium-catalyzed Heck-Matsuda reaction for desymmetrization of N-protected 2,5-dihydro-1-H-pyrroles with aryldiazonium salts

Arnaldo G. de Oliveira Jr., Martí F. Wang, Rafaela C. Carmona, Danilo M. Lustosa, Sergei A. Gorbatov*, Carlos R. D. Correia

Department of Organic Chemistry, Chemistry Institute, University of Campinas, Rua Josué de Castro, 13083-970 Campinas, São Paulo, Brazil

***e-mail:** gorbatov@unicamp.br*

Keywords: *Desymmetrization, enantioselective Heck-Matsuda reaction, lactam synthesis*

ABSTRACT

Desymmetrization reactions are a powerful and refined strategy for asymmetric synthesis, enabling many valuable chemical modifications to increase the complexity of molecules.[1] The Heck-Matsuda reaction has an important role in this strategy, involving the desymmetrization of cyclic systems.[2] Despite previous results in this area, the desymmetrization of 2,5-dihydro-1*H*-pyrroles led to some challenges due to substrate instability and undesirable side reactions. Herein, we report the palladium-catalyzed Heck-Matsuda desymmetrization of *N*-protected 2,5-dihydro-1*H*-pyrroles with aryldiazonium salts using the *N*,*N*-ligand (*S*)-PyraBOx to provide several 4-substituted lactams in an enantioselective fashion, with yields up to 85% and *er* up to 93:7 (**Figure 1**). The methodology was shown to be robust, allowing the use of different protecting groups of the nitrogen of the 4-pyrroline substrate. Two of the chiral aryl-lactams were further derivatized to provide phosphodiesterase-4-inhibitor (*R*)-rolipram[3] (61% overall yield, 3 steps, 82:18 *er*), and the commercial drug (*R*)-baclofen[4] (49% overall yield, 4 steps, 90:10 *er*).

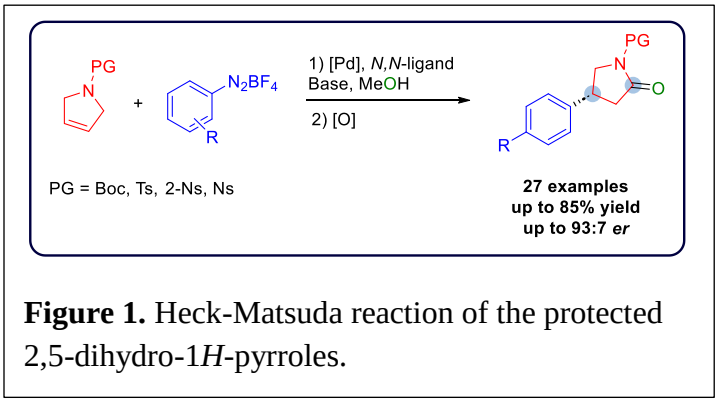

Figure 1. Heck-Matsuda reaction of the protected 2,5-dihydro-1*H*-pyrroles.

ACKNOWLEDGEMENTS

This study was supported by São Paulo Research Foundation (FAPESP, grants: 2017/21494-2 [MFW]; 2023/00025-5 [SAG]; 2014/25770-6, 2013/07600-3, 2014/25770-6 [CRDC], and 2018/00271-8 [RCC]) and the Brazilian National Research Council (CNPq, grants 406643/2018-0, 306773/2018-0 [CRDC]).

REFERENCES

1. Kotani, S.; Nakajima, M., *2012*; Vol. 6, pp 506–517.
2. Angnes, R. A.; Thompson, L. M.; Mashuta, M. S.; Correia, C. R. D.; Hammond, G. B. *Adv. Synth. Catal.* **2018**, *360*, 3760–3767.
3. Krause, W.; Kühne, G.; Sauerbrey, N. *Eur. J. Clin. Pharmacol.* **1990**, *38*, 71–75.
4. Draulans, N.; Vermeersch, K.; Degraeuwe, B.; Meurrens, T.; Peers, K.; Nuttin, B.; Kiekens, C. *Clin. Rehabil.* **2013**, *27*, 1137–1143.