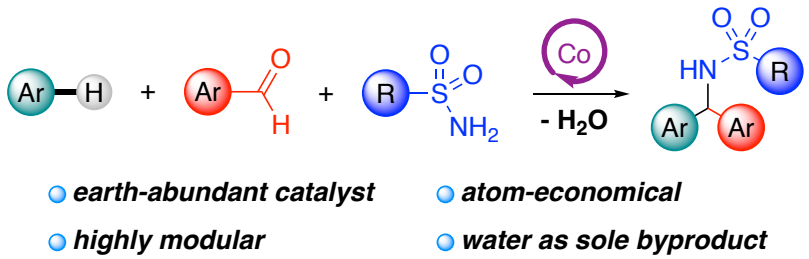
Merging Cobalt-Catalyzed C-H Activation with the Mannich Reaction: An Efficient and Modular Approach to α-Substituted Sulfonamides

Oluwaseun A. Olu-Igbiloba, Helmut Sitzmann, Georg Manolikakes*

Department of Chemistry
RPTU Kaiserslautern-Landau,
Erwin-Schrödinger-Str. Geb. 54
67663 Kaiserslautern
Germany

Table of Content:



Abstract:

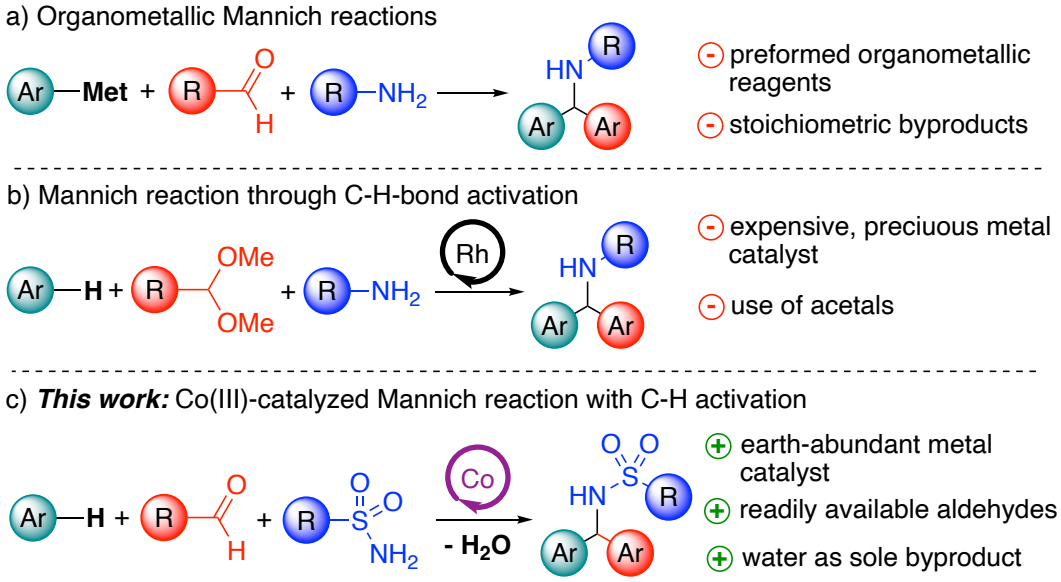
A three-component synthesis of α-substituted sulfonamides from aryl aldehydes, primary sulfonamides and (hetero)arenes is described. This transformation enables a straightforward and modular synthesis of pharmaceutically relevant scaffolds in good yields. The direct functionalization of C(sp^2)-H bonds via cobalt-catalyzed C-H-activation offers an appealing and atom-economical alternative to classical methods for the synthesis of α-arylated amines such as the Petasis or Mannich-type reactions.

Introduction:

The Mannich reaction, a three-component reaction between an amine, an aldehyde and an enolizable ketone, is a powerful method for the synthesis of densely substituted amines.[1] It involves the aminoalkylation of an enol or enolate with an in situ formed electrophilic imine species. Over the years various improvements and extensions of the classical Mannich reaction to other nucleophiles have been reported. These “Mannich-type” reactions utilize

electron-rich (hetero)arenes[2] or organometallic species as nucleophilic species (Scheme 1a).[3] The amino- or amidoalkylation of (hetero)arenes proceeds via an electrophilic aromatic substitution pathway. It is therefore limited to electron-rich (hetero)aromatics and delivers specific regioisomers (or mixtures) guided by the inherent reactivity of the arene.[4] Mannich-like reactions with organometallic species, including the Petasis borono-Mannich reaction[5] or A3-couplings,[6] offer a highly modular approach for the preparation of α-substituted amines and α-amino acids in a high structural diversity, even in an enantioselective fashion.[7] However, the utilization of preformed organometallic reagents is associated with several disadvantages. Many organometallic species are very reactive and difficult to handle. More importantly, both the synthesis and the use of organometallic reagents generate large amounts of waste products. The direct functionalization of C-H-bonds using transition metal catalysts has emerged as a greener, more sustainable alternative to classical organometallic chemistry.[8] Therefore, the addition of organometallic complexes, generated via a transition-metal catalyzed C-H-bond activation, to electrophilic imines provides an attractive alternative to preformed organometallic reagents.

Indeed, the regioselective functionalization of C(sp^2)-H bonds with preformed imines has been described both with Rh(II)- and Co(III)-catalysts.[9,10] Yet, merging advances in transition-metal catalyzed C-H-bond functionalization with classical multicomponent reactions is still a sparsely covered research area.[11] There are only a few examples for the functionalization of C-H-bonds with in situ generated imines.[12] The Rh(III)-catalyzed Mannich-type reaction of LeGall and Presset represents an important breakthrough in this field (Scheme 1b).[12e] In this report dimethyl acetals had to be used instead of the parent aldehyde since the Rh-catalyst system is sensitive to water. In addition, the use of expensive and rare Rh(III)-salts is economically and environmentally unfavorable. More recently, earth-abundant metals have emerged as attractive alternative in metal-catalyzed C-H-functionalization reaction.[13] Considering the already described Co(III)-catalyzed addition of (hetero)arenes to preformed imines via C-H-activation,[10] we aimed to explore the utilization of earth-abundant cobalt catalysts in Mannich-type reactions for the synthesis of α-substituted amines via direct C-H functionalization of (hetero)arenes.

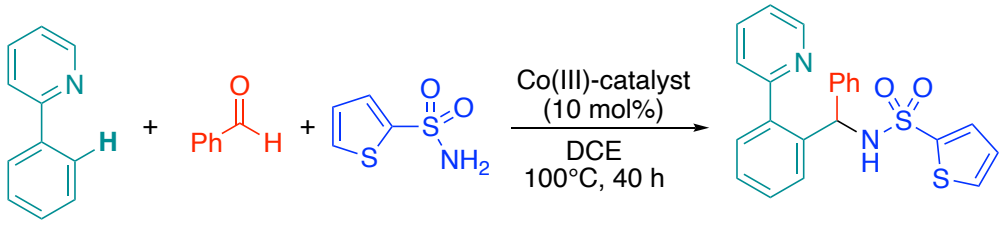


Scheme 1. Mannich-Type Reactions

Results and Discussion

We initiated our studies by selecting the three-component reaction between phenylpyridine (**1a**), benzaldehyde (**2a**) and 2-thiophenesulfonamide (**3a**) as model transformation (Table 1). No product formation was observed in the presence of $Cp^*Co(CO)I_2$ (Cp^* = 1,2,3,4,5-pentamethylcyclopentadienyl), the most common cobalt-based catalyst for C-H-activation reactions (entry 1).[14] Addition of a silver salt ($AgSbF_6$) to generate a cationic Co(III) species resulted in the formation of the desired product **4a** in 28% yield (entry 2). The direct use of the cationic complex $Cp^*Co(CH_3CN)_3][SbF_6]_2$ led to a significant improvement, furnishing the α-arylated sulfonamide **4a** in 91% yield after 40 h at 100 °C in DCE (entry 3). Interestingly, water formed during the reaction did not interfere with the catalyst system and no additional drying agents were necessary. Lower reaction temperatures, shorter reaction times or decreased catalyst loadings resulted in lower yields of product 4a (entries 4-6). DCE proved to be the optimal solvent for this transformation. The use of other solvents, such as acetonitrile, 1,4-dioxane, THF or MeOH did afford sulfonamide **4a** in significantly decreased yields (entry 7).

Table 1. Reaction Optimization

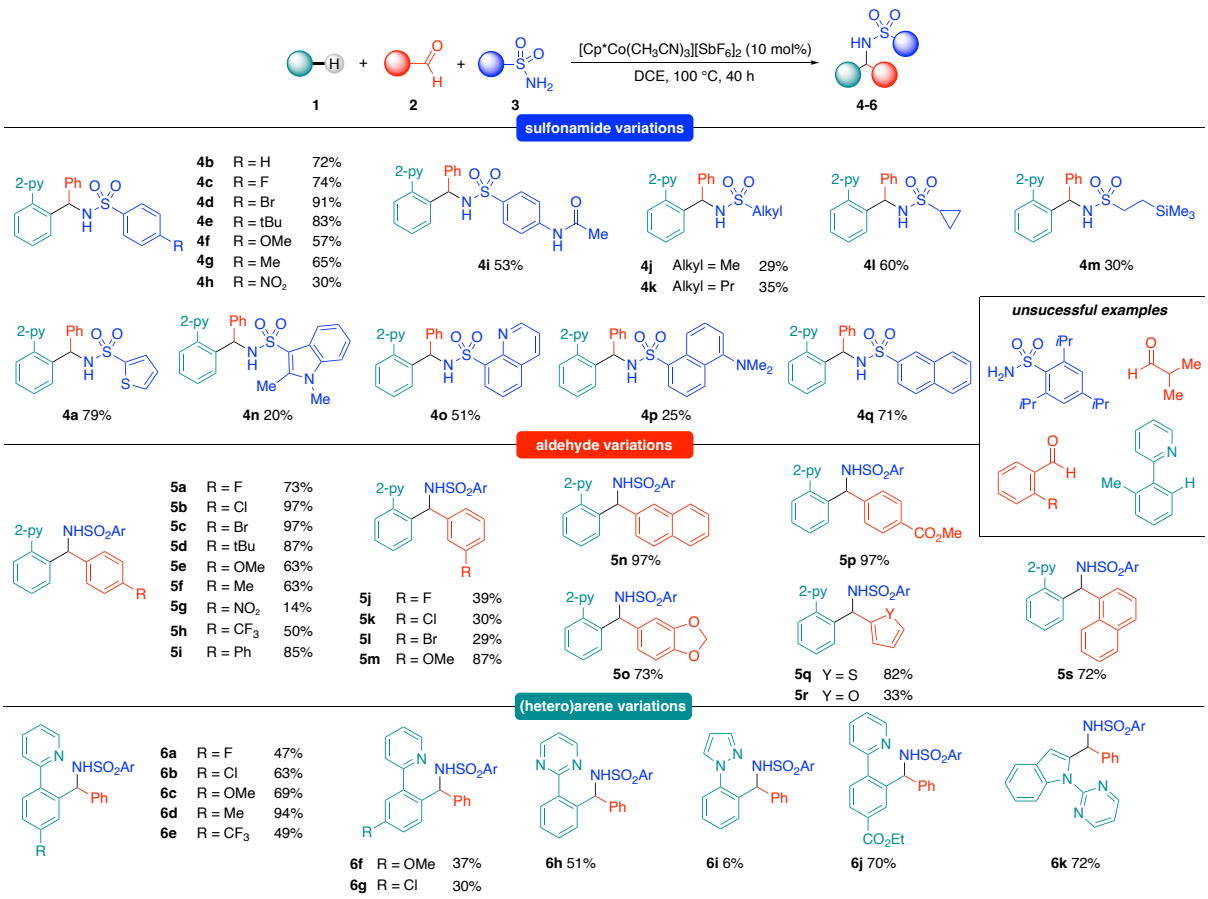


1a **2a** **3a** **4a**

Entry	Conditions	Yield[a]
1	$Cp^*Co(CO)I_2$	-
2	$Cp^*Co(CO)I_2$ + $AgSbF_6$ (20 mol%)	28%
3	$[Cp^*Co(CH_3CN)_3][SbF_6]_2$	91%
4	$[Cp^*Co(CH_3CN)_3][SbF_6]_2$	79%[b]
5	$[Cp^*Co(CH_3CN)_3][SbF_6]_2$	58%[c]
6	$[Cp^*Co(CH_3CN)_3][SbF_6]_2$	46%[d]
7	$[Cp^*Co(CH_3CN)_3][SbF_6]_2$	0 - 38%[e]

[a] Yield of isolated product after purification. [b] reaction time 24 h. [c] reaction temperature 80 °C. [d] with 5 mol% catalyst. [e] with MeCN, 1,4-dioxane, THF or MeOH as solvent.

With the optimized conditions at hand, we investigated the substate scope of this novel 3-component reaction (Scheme 2). A wide range of different sulfonamides were tolerated under the standard reaction conditions, furnishing the α-substituted amides **4a** - **4r** in 20-91% yield. In general, good to high yields were obtained with various para-substituted aromatic sulfonamides bearing electron-donating, electron-withdrawing or halogen residues (**4b – 4i**). Only in the case of 4-nitrobenzenesulfonamide a lower yield was observed (**4h**). Sterically more demanding sulfonamides, such as 2,4,6-triisopropylbenzenesulfonamide did not afforded any desired product. Reactions with simple alkyl sulfonamides proceeded less efficiently, affording the products **4j** and **4k** in only 29% and 35% yield. On the other hand, the cyclopropyl-containing sulfonamide **4l** could be prepared in 60% isolated yield. Using 2-(trimethylsilyl)ethansulfonamide as the amine component furnished the SES-protected[15] amine 4m in 30% yield.



Scheme 2. Substrate Scope[a]

[a] Reactions conditions: (Hetero)arene **1** (0.4 mmol), aldehyde **2** (0.8 mmol), sulfonamide **3** (0.8 mmol) and $[Cp^*Co(CH_3CN)_3][SbF_6]_2$ (0.04 mmol, 10 mol%) in DCE (2 mL, 0.2 M), 100 °C for 40 h; Yields refer to isolated yields of the product after purification; Ar = 2-thiophene.

Heterocyclic sulfonamides could be incorporated into the final α-arylated products **4o** and **4p** in 20% and 51% yield respectively. The low yield obtained for indole sulfonamide **4o** is most probably associated with the lability of this group towards acidic reaction conditions.[16] Interestingly, sulfonamides bearing basic residues, such as a quinoline or aniline moiety, did not interfere in the reaction and the desired sulfonamides **4p** or **4q** could be obtained in moderate yields. Replacing benzaldehyde with other aromatic aldehydes afforded the α-arylated sulfonamides of type **5** in 14-97% yield (Scheme 2). In general, good to excellent yields were obtained with para-substituted benzaldehyde derivatives. Electron-donating and electron-withdrawing groups, as halogen substituents (**5a – 5i**) or even a sensitive ester functionality (**5p**) were well tolerated. Only for para-nitrobenzaldehyde the desired product 5g was isolated in a low yield of 14%. On the other hand, reactions with meta-substituted benzaldehydes proceeded not as efficiently, affording the sulfonamide products **5j** – **5m** in lower yields of 29-87%. Unfortunately, no desired products could be obtained in reactions with ortho-substituted benzaldehydes. Reactions with heterocyclic aldehydes furnished the sulfonamides **5o** – **5r** in 33-82% yield. So far, this 3-component reaction is limited to (hetero)aromatic aldehydes. No product formation was observed with simple aliphatic aldehydes, such as formaldehyde or isobutyraldehyde. Finally, we performed reactions with substituted 2-phenylpyridine derivatives as arene component. Again electron-donating, electron-withdrawing groups (**6a – 6e**) or a sensitive ester functionality (**6j**) in para-position were well tolerated, furnishing the functionalized arenes in 47-91% yield. Reactions with meta-substituted 2-phenylpyridines delivered the expected products **6f** and **6g** with complete

regioselectivity, albeit in lower yields of 30% and 37%. As for the other components, ortho-substitution on the arene was not tolerated. Overall, steric bulk next to the reactive site on each component seems to shut down the 3-compoenet reaction completely. Replacing the pyridine group with a pyrimidyl- or pyrazolyl-moiety, two other common directing groups for cobalt-catalyzed C-H-functionalization, afforded the sulfonamide products **6h** and **6i** in 51% and 6% yield respectively. By using the 2-pyrimidyl directing group extension of our 3-component process to the functionalization of different heterocyclic scaffolds, such as indoles (**6k**) is possible.

Conclusions:

In conclusion we have developed a novel cobalt-catalyzed three-component synthesis of α-substituted sulfonamides from aryl aldehydes, primary sulfonamides and (hetero)arenes. This reaction enables a modular and efficient construction of pharmaceutically relevant scaffolds from three readily available building blocks via a direct C(sp^2)-H-functionalization. Overall, this method offers an offers an appealing and atom-economical alternative to classical methods for the synthesis of α-aryl amines, such as the Petasis reaction or other organometallic Mannich-type reactions. Further studies towards the extension of the scope of this transformation as well as for the development of an asymmetric version are currently underway in our laboratories.

Acknowledgements:

Generous financial support by the Research Unit NanoKat at the RPTU Kaiserslautern-Landau and the DAAD (PhD scholarship to O. A. O.-I.) is gratefully acknowledged.

Author Contributions

The manuscript was written through contributions of all authors.

Keywords: multicomponent reaction • sulfonamide • C-H functionalization • earth-abundant metal catalysis • Mannich reaction

References:

(1) Allochio Filho, J. F.; Lemos, B. C.; de Souza, A. C.; Pinheiro, S.; Greco, S. J. Multicomponent Mannich reactions: General aspects, methodologies and applications. *Tetrahedron* **2017**, *73*, 6977, DOI: 10.1016/j.tet.2017.10.063.

(2) Hadj Mohamed, A.; Masurier, N. Recent advances in aza Friedel–Crafts reaction: strategies for achiral and stereoselective synthesis. *Org. Chem. Front.* **2023**, *10*, 1847, DOI: 10.1039/D2QO02018A

(3) For two representative examples from our group, see: a) Schneider, A. E.; Manolikakes, G. $Bi(OTf)_3$-Catalyzed Multicomponent α-Amidoalkylation Reactions. *J.Org. Chem.* **2015**, *80*, 6196, DOI: 10.1021/acs.joc.5b00662; b) Halli, J.; Schneider, A. E.; Beisel, T.; Kramer, P.; Shemet, A.; Manolikakes, G. Bismuth- and Iron-Catalyzed Three-Component Synthesis of α-Amino Acid Derivatives: A Simple and Convenient Route to α-Arylglycines. *Synthesis* **2017**, *49*, 849, DOI: 10.1055/s-0035-1561499.

(4) Paul, J.; Presset, M.; Le Gall, E. Multicomponent Mannich-Like Reactions of Organometallic Species. *Eur. J. Org. Chem.* **2017**, *2017*, 2386, DOI:10.1002/ejoc.201700038

(5) Wu, P. Givskov, M.; Nielsen, T. E. Reactivity and Synthetic Applications of Multicomponent Petasis Reactions. *Chem. Rev.* **2019**, *119*, 11245, DOI: 10.1021/acs.chemrev.9b00214

(6) Farhi, J.; Lykakis, I.N.; Kostakis, G.E. Metal-Catalysed A^3 Coupling Methodologies: Classification and Visualisation. *Catalysts* **2022**, **12,** 660. https://doi.org/10.3390/catal12060660

(7) For some representative examples see: a) List, B. The Direct Catalytic Asymmetric Three-Component Mannich Reaction. *J. Am. Chem. Soc.* **2000**, *122*, 9336, DOI: 10.1021/ja001923x; b) Zani, L.; Eichhorn, T.; Bolm, C. Dimethylzinc-Mediated, Enantioselective Synthesis of Propargylic Amines. *Chem. Eur. J.* **2007**, *13*, 2587, DOI:

10.1002/chem.200601347; c) Beisel, T.; Diehl, A. M.; Manolikakes, G. Palladium-Catalyzed Enantioselective Three-Component Synthesis of α-Arylglycines. *Org. Lett.* **2016**, *18*, 4116. DOI: 10.1021/acs.orglett.6b02045

(8) For some representative reviews, see: a) Dalton, T.; Faber, T.; Glorius, F. C–H Activation: Toward Sustainability and Applications. *ACS Cent. Sci.* **2021**, *7*, 245, DOI: 10.1021/acscentsci.0c01413; b) Rogge, T.; Kaplaneris, N.; Chatani, N.; Kim, J.; Chang, S.; Punji, B.; Schafer, L.; Musaev, D. G.; Wencel-Delord J.; Roberts, C. A.; Sarpong, R.; Wilson, Z. E.; Brimble, M. A.; Johansson, M. J.; Ackermann, L. C–H activation. *Nat. Rev. Methods Primers* **2021**, 1, 43, DOI: 10.1038/s43586-021-00041-2 c) de Jesus, R.; Hiesinger, K.; van Gemmeren, M.; *Angew. Chem. Int. Ed.* **2023**, *62*, e202306659, DOI: 10.1002/anie.202306659;

(9) a) Tsai, A. S.; Tauchert, M. E.; Bergman, R. G.; Ellman, J. A. Rhodium(III)-Catalyzed Arylation of Boc-Imines via C−H Bond Functionalization, *J. Am. Chem. Soc.* **2011**, *13*, 1248, DOI: 10.1021/ja109562x; b) Li, Y.; Li, B.-J.; Wang, W.-H.; Huang, W.-P.;, Zhang, X.-S.; Chen, K.; Shi, Z.-J. Rhodium-Catalyzed Direct Addition of Aryl C-H Bonds to N-Sulfonyl Aldimines. *Angew. Chem. Int. Ed.***2011**, *50*, 2115, DOI: 10.1002/anie.201007464; c) Hesp, K.D.; Bergman, R. G.; Ellman, J. A. Rhodium-Catalyzed Synthesis of Branched Amines by Direct Addition of Benzamides to Imines. *Org. Lett.* **2012**, *14*, 2304, DOI: 10.1021/ol300723x.

(10) a) Yoshino, T.; Ikemoto, H.; Matsunaga, S.; Kanai, M. A Cationic High-Valent Cp*CoIII Complex for the Catalytic Generation of Nucleophilic Organometallic Species: Directed C-H Bond Activation. *Angew. Chem. Int. Ed.* **2013**, *52* 2207, DOI: 10.1002/anie.201209226; b) Yoshino, T.; Ikemoto, H.; Matsunaga, S.; Kanai, M. Cp*CoIII-Catalyzed C2-Selective Addition of Indoles to Imines. *Chem. Eur. J.* 2013, *19*, 9142, DOI: 10.1002/chem.201301505

(11) a) Wan, J.; Gan, L.; Liu, Y. Transition metal-catalyzed C–H bond functionalization in multicomponent reactions: a tool toward molecular diversity. *Org. Biomol. Chem.* **2017**, *15*, 9031. DOI: 10.1039/C7OB02011B b) Brandes, D. S.; Ellman, J. A. C–H bond activation and sequential addition to two different coupling partners: a versatile approach to molecular complexity. *Chem. Soc. Rev*. **2022**, *51*, 6738, DOI: 10.1039/D2CS00012A.

(12) a) Huang, J.-R.; Song, Q.; Zhu, Y.-Q.; Qin, L.; Qian, Z.-Y.; Dong, L. Rhodium(III)-Catalyzed Three-Component Reaction of Imines, Alkynes, and Aldehydes through C-H Activation. *Chem. Eur. J.* **2014**, *20*, 16882. DOI: 10.1002/chem.201404576; b) Boerth, J. A.; Hummel, J. R.; Ellman, J. A. Highly Stereoselective Cobalt(III)-Catalyzed Three-Component C−H Bond Addition Cascade. *Angew. Chem. Int. Ed.* **2016**, *55*, 12650, DOI: 10.1002/anie.201603831; c) Beisel, T.; Kirchner, J.; Kaehler, T.; Knauer, J.; Soltani, Y.; Manolikakes, G. 3-Component synthesis of α-substituted sulfonamides via Brønsted acid-catalyzed C(sp3)–H bond functionalization of 2-alkylazaarenes. *Org. Biomol. Chem*. **2016**, 14, 5525, DOI: 10.1039/C6OB00108D d) Gia Hoang, L.; Zoll, A. J.; Ellman, J. A. Three-Component Coupling of Aldehydes, 2-Aminopyridines, and Diazo Esters via Rhodium(III)-Catalyzed Imidoyl C–H Activation: Synthesis of Pyrido[1,2-a]pyrimidin-4-ones. *Org. Lett.* **2019**, *21*, 3886, DOI: 10.1021/acs.orglett.9b00779; e) Xavier, T.; Rayapin, C.; Le Gall, E.; Presset, M. Multicomponent Aromatic and Benzylic Mannich Reactions through C−H Bond Activation. *Chem. Eur. J.* **2019**, *25*, 13824, DOI: https://doi.org/10.1002/chem.201903414; f) Lin, M.; Wu, Y.; Liu, Z.; Liang, C.; Li, Q.; Liu, T. Rhodium(III)-catalyzed three-component C(sp2)–H activation for the synthesis of amines. *Chem. Commun.* **2023**, *59*, 14431, DOI: 10.1039/D3CC04665F.

(13) a) Gandeepan, P.; Müller, T.; Zell, D.; Cera, G.; Warratz, S.; Ackermann, L. 3d Transition Metals for C–H Activation. *Chem. Rev.* **2019**, *119*, 2192. DOI: 10.1021/acs.chemrev.8b00507; b) Ilies, L. C–H Activation Catalyzed by Earth-Abundant Metals. *Bull. Chem. Soc. Jpn.* **2021**, *94*, 404, DOI: https://doi.org/10.1246/bcsj.20200349.

(14) Chirila P. G.; Whiteoak, C. J. Recent advances using [Cp*Co(CO)I2] catalysts as a powerful tool for C–H functionalization. *Dalton Trans*. **2017**, *46*, 9721. DOI: 10.1039/C7DT01980G

(15) Ribière, P.; Declerck, V.; Martinez, J.; Lamaty, F. 2-(Trimethylsilyl)ethanesulfonyl (or SES) Group in Amine Protection and Activation. *Chem. Rev.* **2006**, *106*, 2249, DOI: 10.1021/cr0300587.

(16) Isidro, A.; Latassa, D.; Giraud, M.; Álvarez, M.; Albericio, F. 1,2-Dimethylindole-3-sulfonyl (MIS) as protecting group for the side chain of arginine. *Org. Biomol. Chem*. **2009**, *7*, 2565, DOI: 10.1039/B904836G.