CHEMISTRY

A European Journal

A Journal of

Accepted Article

Title: Metal-Free Dearomatization: Direct access to Spiroindol(en)ines in Batch and Continuous-Flow

Authors: Prabhat Ranjan, Gerardo M. Ojeda, Upendra K. Sharma, and Erik Van der Eycken

This manuscript has been accepted after peer review and appears as an Accepted Article online prior to editing, proofing, and formal publication of the final Version of Record (VoR). This work is currently citable by using the Digital Object Identifier (DOI) given below. The VoR will be published online in Early View as soon as possible and may be different to this Accepted Article as a result of editing. Readers should obtain the VoR from the journal website shown below when it is published to ensure accuracy of information. The authors are responsible for the content of this Accepted Article.

To be cited as: *Chem. Eur. J.* 10.1002/chem.201805945

Link to VoR: <http://dx.doi.org/10.1002/chem.201805945>

Supported by
ACES

WILEY-VCH

COMMUNICATION

Metal-Free Dearomatization: Direct access to Spiroindol(en)ines in Batch and Continuous-Flow

Prabhat Ranjan,^[a] Gerardo M. Ojeda^[a,b], Upendra K. Sharma,^{*[a]} Erik V. Van der Eycken,^{*[a,c]}

Abstract: We report herein a metal-free, phosphine-catalyzed intramolecular “umpolung Michael addition” on alkynes to form spiroindol(en)ines. This nucleophilic catalysis enables the formation of a wide scope of five- and six-membered spiroindol(en)ines in moderate to excellent yields in batch as well as under continuous-flow conditions. Triphenylphosphine-catalyzed nucleophilic activation of alkynes allows the exclusive formation of exo-product under mild reaction conditions.

Dearomatization^[1] is a robust strategy to synthesize three-dimensional rigid molecular scaffolds from simple planar aromatic molecules. The synthesis of spiroindol(en)ines and related spirocarbocycles through dearomatization of indole and substituted phenols has captured the close attention of chemist due to their widespread presence in various natural products and biologically relevant molecules.^[2-3] Henceforth, greener and atom economical syntheses of these structures have become imperative for synthetic chemists (Scheme 1a-c).^[4-8] Several simple Lewis or π -acidic catalysts were employed in the last decades for the synthesis of spiroindolenines through dearomatization of indole at the C-3 position, including nano-metal catalysts.^[9] In addition, a number of alternative methods for the synthesis of spiroindolenines has also been developed in the last decade, viz. the intramolecular version of the Prins cyclization^[10], a radical-oxidation^[11] and acid-catalyzed reactions.^[12] However, several synthetic procedures are often limited by exo/endo selectivity issues and side reactions such as reopening of the spiro-ring through 1,2-migration to restore the aromaticity, particularly prevalent with spiroindolenines. Apart from these reports, an umpolung Michael-type synthesis of spiroindol(en)ines with catalytic Lewis base (LB) is still elusive.

The uniqueness of nucleophilic phosphine catalysis has already resulted in a plethora of reports in the last two decades^[13] after seminal work appearing in the 1960s.^[14] In 1997, Trost

Scheme 1: Background on spiroindolenines framework.

described the phosphine-catalyzed α -umpolung Michael reaction of alkyl esters with sulfonyl amine or phthalimide to achieve α -amino carbonyl compounds (Scheme 1d).^[15] The reaction proceeds through several intermediates, of which intermediate II could be trapped with different nucleophiles.

With our enduring interest in spiroindol(en)ines,^[16] we planned to trap the intermediate II through an intramolecular nucleophilic attack of the C-3 position of the indole (Scheme 1e). This unique approach of LB-catalyzed umpolung reaction could lead to highly functionalized spiroindol(en)ines and related spirocarbocycles under mild reaction conditions. We commenced our investigation on the dearomatization of propargylic amides **1a**, derived from tryptamine and propargylic acid, with triphenylphosphine as nucleophilic catalyst. In the presence of a catalytic amount of phosphine, we observed the regioselective

- [a] P. Ranjan, Gerardo M. Ojeda, Dr. U. K. Sharma, and Prof. E. V. Van der Eycken
Laboratory for Organic & Microwave-Assisted Chemistry (LOMAC), Department of Chemistry, University of Leuven (KU Leuven), Celestijnenlaan 200F, B-3001 Leuven, Belgium.
Email: usharma81@gmail.com; erik.vandereycken@kuleuven.be.
- [b] Center for Natural Products Research, Faculty of Chemistry, University of Havana, Zapata y G, 10400 Havana, Cuba.
- [c] Prof. E. V. Van der Eycken
People's Friendship University of Russia (RUDN University), Miklukho-Maklaya street 6, RU-117198 Moscow, Russia.

Additional data related to this publication is available at the <https://doi.org/> data repository.

COMMUNICATION

Table 1: Optimization of spiroindolenines.^a

Entry	Catalyst	Solvent	t (h)	T(°C)	Yield ^b (%)
1	PPh ₃	Toluene	5	30	10
2	PPh ₃	Toluene	5	80	40
3	PPh ₃	DCM	5	30	12
4	PPh ₃	EtOAc	3	80	78
5	PPh₃	EtOH	3	80	84
6	P(<i>p</i> -MeOPh) ₃	EtOH	3	80	87 ^c
7	P(<i>n</i> -Bu) ₃	EtOAc	2	80	<30
8	P(<i>n</i> -Bu) ₃	EtOH	1.2	80	<30
9	Me ₂ PPh	EtOH	3	80	10
10	(CF ₃ Ph) ₃ P	EtOH	3	80	50
11	P(<i>p</i> -FC ₆ H ₄) ₃	EtOH	3	80	-
12	P(OPh) ₃	EtOH	3	80	-
13	P(<i>p</i> -Tol) ₃	EtOH	3	80	trace
14	DMAP	EtOH	4.5	80	-
15	DBU	EtOH	8	80	-
16	Quinuclidine	EtOH	12	80	-
17	DABCO	EtOH	3	80	-

^aReaction conditions: **1a** (0.10 mmol), and catalyst (20 mol%), ethanol (0.3M).^bDetermined by ¹HNMR using 1,3,5-trimethoxybenzaldehyde as an internal standard. ^cIsolated yield.

formation of the six-membered spiroindolenine as the major product. In view of recent reports on the phosphine-catalyzed conjugate addition on electron-deficient acetylenes, we started optimizing our reaction.^[17] Various potential LB catalysts were investigated under different reaction conditions using amide **1a** as substrate (Table 1). The initial investigation was carried out using toluene as solvent with 20 mol% of triphenylphosphine at 30 °C showing a slight conversion (Table 1, entry 1). On increasing the temperature to 80 °C, we observed the formation of **2a** with 40% yield (entry 2). Considering the previous reports, the product yield was increased to 78% (entry 4) by using the more polar ethyl acetate as solvent. To further increase the yield of the desired product **2a**, we planned to use protic solvents like alcohols, as we reasoned that they could increase the concentration of intermediate **II**, via rapid proton transfer to intermediate **I** (Scheme 1d). This should favour the attack through the C-3 position of the indole. To our delight **2a** was obtained in 84% yield when EtOH was used as solvent (entry 5). Ethanol has the potential to assist [1,2]-proton shift in the intermediate **III** (Scheme 1d).^[18] In addition, we assumed that the rapid protonation of intermediate **I** might avoid the chance of self-oligomerization.^[14,19] In an attempt to further enhance the yield we screened different phosphines. With tris(4-methoxyphenyl)phosphine (*p*-MeOPh)₃P under our optimized reaction conditions, the yield increased to 87% (entry 6).^[20] On the contrary, electron-rich PBu₃ and PMe₂Ph afforded very low yields (entries 7-9). More electron deficient P(*p*-FC₆H₄)₃ gave only 50% yield of the desired product **2a** (entry 10), whereas (CF₃Ph)₃P, P(OPh)₃ and P(*p*-Tol)₃ totally met with failure (entry 11-13). When various amine Lewis bases such as DMAP, DBU, quinuclidine and DABCO were used, no desired product was observed (entry 14-17).^[21] Thereafter, we investigated the effect of the reaction concentration as well as the amount of triphenylphosphine. The yield of the reaction showed a

concentration dependency up to 0.3 M and became almost invariant at higher concentrations. A similar pattern was observed for catalyst loading where yield remained identical past 20 mol% of the catalyst.

Table 2: Substrate scope for spiroindolenine formation.^a

^aReaction conditions: **1a** (0.40 mmol), and catalyst (20 mol%), ethanol (0.3M). PCIB = *para*-chlorobenzyl, PFB = *para*-fluorobenzyl, PMB = *para*-methoxybenzyl. **2g-2j** at 85°C for 6h; **2k** at 90°C for 24h; **2h*** P(*p*-MeOPh)₃ (20 mol%) at 85°C for 4h; **2e** at 85°C for 6h; **2g-2h** at 80°C for 2h.

With the optimized conditions in hand, we explored the substrate scope for the formation of 6-membered spiroindolenines (Table 2). Substrates bearing different electron-donating benzyl groups on the amide nitrogen successfully gave the desired spiroindolenines with good product yields (**2a-2d**,

COMMUNICATION

Table 2). The methoxy- and alkyl substituted (**2f**; 5-OMe, **2o**; 5-Me) indolenines were each formed in high yields. Pleasingly, halogen substitution in indole substrates (**2e**; 6-F, **2g**; 6-Br, **2h**; 5-Br, **2i**; 7-Cl and **2j**; 6-Cl) showed only small influence on the efficiency of the reaction (Table 2). The tryptophan-derived propargylic amide as well as the substrate derived from propargylic amine failed to give the desired products (**2k**, **2p**, Table 2).

Next we employed this protocol to form 5-membered spiroindolenines assuming that the *exo*-dig cyclization was also preserved in this case. Propargylic amides bearing electronically different substituents on the amide-nitrogen were successfully transformed into the desired products (**3a-3h**, Table 2). An additional halogen substituent on the indole (4-Br, 5-Br) resulted in higher yields (**3b** and **3c**, Table 2). The electron-donating 5-OMe-substituent was behaving as in the higher analogous **2f** (**3d**, Table 2). Interestingly, the substrate bearing a strong electron-withdrawing nitro-group gave 57% yield (**3e**, Table 2).^[5] Notably, when indole-based Ugi-adducts were treated with 20 mol% of triphenylphosphine, they gave the tricyclic products (**3g** and **3h**, Table 2).^[16e] These results inspired us to explore the methodology on some phenol-containing propargylic amides to deliver spirocarbocycles (Table 3). With the Ugi four-component reaction, the free hydroxyl containing substrates (**4a-d**) were synthesized conveniently. Here, the post-MCR reaction proceeded with an *ipso* attack on the alkyne, followed by Michael addition to form the tricyclic products (Table 3, **5a-5d**) in moderate to good yields.^[22] As expected, the methoxy-substituted substrate did not result in product formation (**5e**, Table 3).

Table 3: Substrate scope of *ipso* attack.^a

^aReaction conditions: **4a** (0.10 mmol), and catalyst (20 mol%), ethanol (0.3M). **4c**: at 85 °C for 6 h, **4e**: at 85 °C for 24 h.

Encouraged by the above results, we evaluated the reaction of a propargylic amide bearing a γ -proton (alkyl substituted alkynes) under our optimized conditions. The ether appeared to be the major product, resulting from nucleophilic attack of the alcoholic solvent on the γ -position (Scheme 2).^[23] Interestingly, this could be regarded as a remote C-H functionalization. The reaction required a longer time as compared to the spiro-

cyclization. Formation of the ether instead of spiro-product might be due to the rapid isomerization of intermediate **6a** to form the cyclic zwitterion **6b** (Scheme 2). To favour intermediate **6a** we tried different types of phosphines such as DPPP (1,3-bis(diphenylphosphino)propane) and $\text{P}(\text{NMe}_2)_3$ so as to decrease the acidity of the γ -proton.^[24] However, all efforts failed to give the desired spiro-product. To avoid the isomerization in the allenolate product, we tried phenyl substituted propargylic amide in a range of polar and non-polar solvent but unfortunately, we could not achieve the desired spirocyclization (for detail see SI, Table S1).

Scheme 2. Remote C-H functionalization.

In order to develop a reusable catalytic-system we moved our attention towards the application of polymer supported triphenylphosphine. This resulted in a yield of 40% for **2a** after 18h. This encouraged us to employ continuous-flow technology^[25] to further improve the reaction efficiency under heterogeneous conditions (Scheme 3). A 0.1M solution of **1a** in a mixture of toluene/ethanol (1:1) was passed through a 3 mm diameter packed bed reactor with 120 mg of polymer bound catalyst (loading 3 mmol/g, corresponding to 94 mg of triphenylphosphine) at a flow rate of 0.025 mL/min. After optimization (for details see SI Table S2) the reaction worked very efficiently, resulted in 88 % of **2a** (gram-scale reaction gave 79 % isolated yield).

Scheme 3: Spirocyclization of propargylamides under continuous-flow conditions with a packed bed reactor using polymer supported triphenylphosphine.

A plausible mechanism is described in scheme 5. The catalytic cycle starts with the Michael addition of PPh_3 to propargylamide **1a** to generate a phosphonium intermediate **1b**, followed by protonation, resulting in intermediate **1d**. Thereafter, **1d** undergoes umpolung Michael addition at the α -position, which is induced by the electron withdrawing ability of the phosphonium entity. The resultant ylide **1e** undergoes proton transfer and

COMMUNICATION

elimination of phosphine from **1f**, generating the final product **2a**. To gain more insight, we followed the ^{31}P NMR spectrum in ethanol for 2h (for detail see SI). Formation of closely associated downfield peaks to triphenylphosphine might support the formation of suitable intermediates during the catalytic cycle. In addition, there was no decrease in the intensity of the triphenylphosphine peak, which confirms the regeneration of the catalyst.^[26]

Scheme 4: Proposed mechanism for phosphine-catalysed alkyne hydroarylation.^[26]

In summary, we have developed a phosphine catalyzed “anti-Michael addition” on alkynes to form the spiroindolines and spiroindolenines in batch as well as continuous-flow heterogeneous conditions. Over 28 examples of structurally and functionally diverse products were successfully synthesized. This nucleophilic catalysis enables a wide scope of six- and five-membered spiroindolenines as well as *ipso*-cyclized products with yields ranging from 56% to 98%. Moreover, triphenylphosphine catalysed nucleophilic activation of alkynes allows us to form the *exo*-product regioselectively. This new activation method should enable the mild synthesis of these biologically relevant molecules in a more sustainable manner.

Acknowledgements

This project has received funding from the European Union's Horizon 2020 research and innovation Programme under the Marie Skłodowska-Curie grant agreement No 721290. This publication reflects only the author's view, exempting the Community from any liability. Project website: <http://cosmic-etn.eu/>. PR is thankful to Marie-Curie action. GMO acknowledges VLIR-UOS for financial support of a TEAM project (project code CU2018TEA458A101) involving Flemish and Cuban institutions and providing a doctoral scholarship. We acknowledge the support of “RUDN University Program 5-100”. We are grateful to Prof. Dr. Wim M. De Borggraeve for valuable suggestions (KU

Leuven) and to Karel Duerinckx (KU Leuven) for the assistance with NMR measurements.

Conflicts of interest

The authors declare no conflict of interest.

Keywords: Dearomatization • Spiroindolenine • Organocatalysis • Indoles • Flow chemistry.

- [1] Selected reports on dearomatization: a) A. R. Pape, K. P. Kaliappan, E. P. Kündig, *Chem. Rev.* **2000**, *100*, 2917–2940. b) M. J. James, P. O'Brien, R. J. K. Taylor, W. P. Unsworth, *Chem. - a Eur. J.* **2016**, *22*, 2856–2881. c) C. Zheng, S. You, *CHEMPR* **2016**, *1*, 830–857. d) J. Bariwal, L. G. Voskressensky, E. V. Van der Eycken, *Chem. Soc. Rev.* **2018**, 3831–3848.
- [2] Selected reports on spiro-compounds: a) M. J. James, J. D. Cuthbertson, P. O'Brien, R. J. K. Taylor, W. P. Unsworth, *Angew. Chem. Int. Ed.* **2015**, *54*, 7640–7643. b) C.-X. Zhuo, Y. Zhou, Q. Cheng, L. Huang, S.-L. You, *Angew. Chem. Int. Ed.* **2015**, *54*, 14146–14149. c) V. Magné, F. Blanchard, A. Marinetti, A. Voituriez, X. Guinchard, *Adv. Synth. Catal.* **2016**, *358*, 3355–3361. d) J. T. R. Liddon, A. K. Clarke, R. J. K. Taylor, W. P. Unsworth, *Org. Lett.* **2016**, 28–31. e) J. T. R. Liddon, M. J. James, A. K. Clarke, P. O. Brien, R. J. K. Taylor, W. P. Unsworth, *Chem. - a Eur. J.* **2016**, 8777–8780. f) A. K. Clarke, M. J. James, P. O. Brien, R. J. K. Taylor, W. P. Unsworth, *Angew. Chem. Int. Ed.* **2016**, 13798–13802. g) Q.-F. Wu, C. Zheng, C.-X. Zhuo, S.-L. You, *Chem. Sci.* **2016**, *7*, 4453–4459. h) Q.-F. Wu, C. Zheng, C.-X. Zhuo, S.-L. You, *Chem. Sci.* **2016**, *7*, 4453–4459. i) R.-D. Gao, Q.-L. Xu, L.-X. Dai, S.-L. You, *Org. Biomol. Chem.* **2016**, 8044–8046. j) V. Magné, A. Marinetti, V. Gandon, A. Voituriez, X. Guinchard, *Adv. Synth. Catal.* **2017**, *359*, 4036–4042. k) J. T. R. Liddon, J. A. Rossi-ashton, R. J. K. Taylor, W. P. Unsworth, *Org. Lett.* **2018**, *20*, 3349–3353.
- [3] a) C.-T. Liu, Q.-W. Wang, C.-H. Wang, *J. Am. Chem. Soc.* **1981**, *103*, 4634–4635. b) P. Siengalewicz, T. Gaich, J. Mulzer, *Angew. Chem.* **2008**, *120*, 8290–8296. c) W.-T. Wu, R.-Q. Xu, L. Zhang, S.-L. You, *Chem. Sci.* **2016**, *7*, 3427–3431. d) Q. Cheng, Y. Wang, S.-L. You, *Angew. Chem. Int. Ed.* **2016**, *55*, 3496–3499. e) C. Z. Zhu, Y. L. Sun, Y. Wei, M. Shi, *Adv. Synth. Catal.* **2017**, *359*, 1263–1270.
- [4] V. A. Peshkov, O. P. Pereshivko, E. V. Van der Eycken, *Adv. Synth. Catal.* **2012**, *354*, 2841–2848.
- [5] F. Schröder, U. K. Sharma, M. Mertens, F. Devred, D. P. Debecker, R. Luque, E. V. Van der Eycken, *ACS Catal.* **2016**, *6*, 8156–8161.
- [6] Q.-F. Wu, H. He, W.-B. Liu, S.-L. You, *J. Am. Chem. Soc.* **2010**, *132*, 11418–11419.
- [7] Y. Wang, C. Zheng, S.-L. You, *Angew. Chem. Int. Ed.* **2017**, *56*, 15093–15097.
- [8] K. J. Wu, L. X. Dai, S.-L. You, *Org. Lett.* **2012**, *14*, 3772–3775.
- [9] a) A. K. Clarke, M. J. James, P. O. Brien, R. J. K. Taylor, W. P. Unsworth, *Angew. Chem. Int. Ed.* **2016**, 13798–13802. b) Y. Zhou, Z. L. Xia, Q. Gu, S.-L. You, *Org. Lett.* **2017**, *19*, 762–765.
- [10] R. Chandrashekar, S. P. B. Vemulapalli, B. Sridhar, B. V. Subba Reddy, *Eur. J. Org. Chem.* **2018**, 1693–1698.
- [11] H. Zuleta-Prada, L. D. Miranda, *Tetrahedron Lett.* **2009**, *50*, 5336–5339.
- [12] a) P. Fedoseev, E. V. Van der Eycken, *Chem. Commun.* **2017**, 53, 7732–7735. b) P. D. Fedoseev, G. A. Coppola, G. M. Ojeda, E. V. Van der Eycken, *Chem. Commun.* **2018**, DOI 10.1039/C8CC01474D.
- [13] For selected reports: a) J. L. Methot, W. R. Roush, *Adv. Synth. Catal.* **2004**, *346*, 1035–1050. b) B. J. Cowen, S. J. Miller, *Chem. Soc. Rev.* **2009**, *38*, 3102–3116. c) Y. C. Fan, O. Kwon, *Chem. Commun.* **2013**, 49, 11588.

COMMUNICATION

- [14] a) M. Rauhut, H. Currier (American Cyanamide Co.), *U. S. Patent* 3,074,999, **1963**; *Chem. Abstr.* **1963**, 58, 11224a. b) J. D. McClure, *U. S. Patent* 3,225,083, **1965**.
- [15] B. M. Trost, G. R. Dake, *J. Am. Chem. Soc.* **1997**, 119, 7595–7596.
- [16] a) A. Kumar, D. D. Vachhani, S. G. Modha, S. K. Sharma, V. S. Parmar, E. V. Van der Eycken, *Angew. Chem. Int. Ed.* **2013**, 9, 2097–2102. b) H. Butani, D. D. Vachhani, U. C. Bhoya, A. K. Shah, E. V. Van der Eycken, *Eur. J. Org. Chem.* **2014**, 2014, 6634–6638. c) N. Sharma, Z. Li, U. K. Sharma, E. V. Van der Eycken, *Org. Lett.* **2014**, 16, 3884–3887. d) F. Schröder, M. Ojeda, N. Erdmann, J. Jacobs, R. Luque, T. Noël, L. Van Meervelt, J. Van der Eycken, E. V. Van der Eycken, *Green Chem.* **2015**, 17, 3314–3318. e) Z. Li, N. Sharma, U. K. Sharma, J. Jacobs, L. Van Meervelt, E. V. Van der Eycken, *Chem. Commun.* **2016**, 52, 5516–5519. f) Y. He, Z. Li, G. Tian, L. Song, L. Van Meervelt, E. V. Van der Eycken, *Chem. Commun.* **2017**, 53, 6413–6416.
- [17] a) V. Sriramurthy, G. A. Barcan, O. Kwon, *J. Am. Chem. Soc.* **2007**, 129, 12928–12929. b) S. Khong, O. Kwon, *J. Org. Chem.* **2012**, 77, 8257–8267. c) L. Liang, E. Li, P. Xie, Y. Huang, *Chem. - An Asian J.* **2014**, 9, 1270–1273. d) J. Saha, C. Lorenc, B. Surana, M. W. Peczu, *J. Org. Chem.* **2012**, 77, 3846–3858. e) Z. Lian, M. Shi, *European J. Org. Chem.* **2012**, 2012, 581–586. f) C. T. Mbofana, S. J. Miller, *ACS Catal.* **2014**, 4, 3671–3674. g) H. Mao, A. Lin, Y. Tang, Y. Shi, H. Hu, Y. Cheng, C. Zhu, *Org. Lett.* **2013**, 15, 4062–4065. h) C. Lu, X. Lu, *Org. Lett.* **2002**, 4, 4677–4679. i) J. Ametovski, U. Dutta, L. Burchill, D. Maiti, D. W. Lupton, J. F. Hooper, *Chem. Commun.* **2017**, 53, 13071–13074. j) Z. Liu, C. Patel, J. N. Harvey, R. B. Sunoj, *Phys. Chem. Chem. Phys.* **2017**, 19, 30647–30657. k) C. Z. Zhu, Y. L. Sun, Y. Wei, M. Shi, *Adv. Synth. Catal.* **2017**, 359, 1263–1270. l) J. Wu, Y. Tang, W. Wei, Y. Wu, Y. Li, J. Zhang, Y. Zheng, S. Xu, *Angew. Chem. Int. Ed.* **2018**, DOI 10.1002/anie.201800555.
- [18] Y. Xia, Y. Liang, Y. Chen, M. Wang, L. Jiao, F. Huang, S. Liu, Y. Li, Z. X. Yu, *J. Am. Chem. Soc.* **2007**, 129, 3470–3471.
- [19] B. M. Trost, U. Kazmaier, *J. Am. Chem. Soc.* **1992**, 114, 7933–7935.
- [20] K. Kishi, S. Takizawa, H. Sasai, *ACS Catal.* **2018**, 8, 5228–5232.
- [21] a) J. Inanaga, Y. Baba, T. Hanamoto, *Chem. Lett.* **1993**, 22, 241–244. b) V. K. Aggarwal, A. Mereu, *Chem. Commun.* **1999**, 2311–2312. c) C. A. Evans, S. J. Miller, *J. Am. Chem. Soc.* **2003**, 125, 12394–12395. d) J. E. Murtagh, S. H. McCooley, S. J. Connon, *Chem. Commun. (Camb)* **2005**, 227–229.
- [22] Y. He, Z. Li, K. Robeyns, L. Van Meervelt, E. V. Van der Eycken, *Angew. Chem. Int. Ed.* **2018**, 57, 272–276.
- [23] a) Y. K. Chung, G. C. Fu, *Angew. Chem. Int. Ed.* **2009**, 48, 2225–2227. b) R. J. Lundgren, A. Wilsily, N. Marion, C. Ma, Y. K. Chung, G. C. Fu, *Angew. Chem. Int. Ed.* **2013**, 52, 2525–2528. c) D. T. Ziegler, G. C. Fu, *J. Am. Chem. Soc.* **2016**, 138, 12069–12072. d) Y. Q. Fang, P. M. Tadross, E. N. Jacobsen, *J. Am. Chem. Soc.* **2014**, 136, 17966–17968.
- [24] Y. S. Tran, O. Kwon, *J. Am. Chem. Soc.* **2007**, 129, 12632–12633.
- [25] Selected review/book on flow: a) T. Noël, Y. Su, V. Hessel, *Top. Organomet. Chem.* **2016**, 57, 1–41. b) H. P. L. Gemoets, Y. Su, M. Shang, V. Hessel, R. Luque, T. Noël, *Chem. Soc. Rev.* **2016**, 45, 83–117; c) R. Porta, M. Benaglia, A. Puglisi, *Org. Process Res. Dev.* **2016**, 20, 2–25; d) S. V. Ley, D. E. Fitzpatrick, R. M. Myers, C. Battilocchio, R. J. Ingham, *Angew. Chem. Int. Ed.* **2015**, 54, 10122–10136. e) B. Gutmann, D. Cantillo, C. O. Kappe, *Angew. Chem. Int. Ed.* **2015**, 54, 6688–6728. f) Upendra K. Sharma, E. V. Van der Eycken, *Flow Chemistry for the Synthesis of Heterocycles*, Springer International Publishing, Cham, **2018**.
- [26] The absence of the $\text{Ph}_3\text{P}=\text{O}$ peak was confirmed by comparing the ^{31}P -NMR spectrum with this of an authentic sample. For more details about NMR and deuterium labelling experiments, see the SI.

COMMUNICATION

Prabhat Ranjan, Gerardo M. Ojeda, Dr.
Upendra K. Sharma,* Prof. Erik V. Van
der Eycken*