Chemistry Europe
European Chemical Societies Publishing

WILEY VCH

Excellence in Chemistry Research

Announcing our new flagship journal

- Gold Open Access
- Publishing charges waived
- Preprints welcome
- Edited by active scientists

Meet the Editors of *ChemistryEurope*

Luisa De Cola
Università degli Studi di Milano Statale, Italy

Ive Hermans
University of Wisconsin-Madison, USA

Ken Tanaka
Tokyo Institute of Technology, Japan

ChemistrySelect

Research Article
doi.org/10.1002/slct.202302326

Chemistry Europe
European Chemical Societies Publishing

www.chemistryselect.org

Direct Arylation of Thiophenes in Continuous Flow

Alessandro Petronilli,[a] Tommaso Carofiglio,[a] and Paolo Zardi*[a, b]

Synthetic methodologies involving direct C–H functionalization are promising to improve sustainability in organic synthesis. However, these newly developed strategies may have a scarce appeal for larger scale applications due to the high catalyst loading, harsh conditions or their typically long reaction times that affect severely the process productivity. Flow chemistry technology is a recognized tool to improve both the efficiency and scalability in organic synthesis that can overcome these issues. In the present paper we studied an "in flow" method for the direct arylation of thiophene derivatives with aromatic bromides to promptly afford heteroaromatic biaryls, which are recurrent motifs both in biologically active molecules and in functional materials. By using a packed-bed reactor containing potassium carbonate as the solid base and an automated system, we could develop a reliable methodology for thiophene arylation in flow with yields up to 90% within a residence time of 30–60 minutes. This strategy is suitable for a wide variety of substrates and allowed the reaction to be carried out at gram-scale reaching a productivity value of 1.1 g h^{-1}.

Introduction

The adaptation "in flow" of newly developed synthetic methodologies is relevant in order to launch the achievements of academic research towards practical applications.[1] Continuous flow technology significantly facilitates the scaling of an organic synthetic reaction and can be highly beneficial for the efficiency of a chemical transformation.[2] For instance, mass and energy transfers are consistently accelerated if occurring in a micro- or meso-reactor with a high surface-to-volume ratio. Moreover, the inhomogeneities in heating and concentration in the reaction medium (the so-called "hot spots" which may lead to unwanted side-reactions) are greatly reduced with respect to a batch process.[3] Flow reactors enhance the control over crucial parameters such as temperature and reaction time and give an easy access to a large conditions window without using complex apparatus, e.g. autoclaves, for high pressure operations. Furthermore, the transition from the laboratory-scale to a large production is possible with a reduced effort with respect to batch processes.

In the context of molecules derivatization through C–H bond functionalization, we witnessed the rise of several methods with high potential towards a more sustainable organic synthesis.[4] Among these recently disclosed reactivities, direct arylation of heterocycles is an important transformation

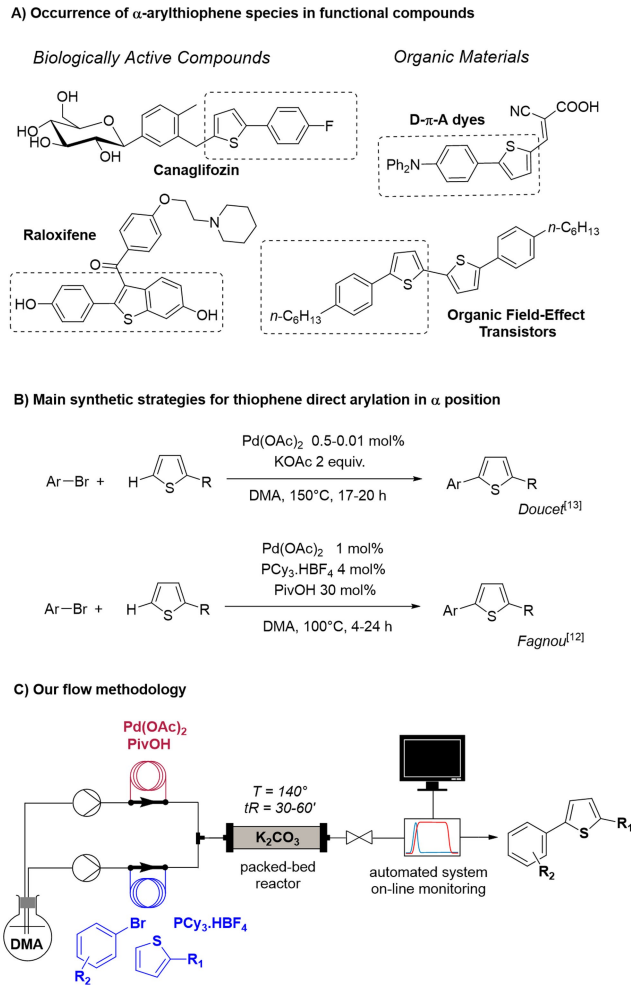


Figure 1. Overview of (A) relevant compounds containing an aryl thiophene fragment, (B) parent methodologies for thiophene arylation in α position, (C) the flow strategy proposed in the present paper.

[a] A. Petronilli, Prof. T. Carofiglio, Dr. P. Zardi
Department of Chemical Sciences,
University of Padova
Via Francesco Marzolo 1, 35131, Padova (Italy)
E-mail: paolo.zardi@unimore.it

[b] Dr. P. Zardi
Department of Chemical and Geological Sciences
University of Modena and Reggio Emilia
Via Giuseppe Campi 103, 41125, Modena (Italy)

Supporting information for this article is available on the WWW under https://doi.org/10.1002/slct.202302326

in view of readily obtaining valuable heteroaromatic biaryls with an increased step and atom economy with respect to the traditional cross-coupling methods.[5] Among the most interesting products, aryl thiophenes are recurrent building blocks in both useful molecules for electronic devices[6] (e.g. light emitting diodes, field effect transistors) and several biologically relevant compounds[7] (Figure 1A).

Aryl thiophenes synthesis through direct arylation usually involves an aryl halide and an unfunctionalized thiophene species reacted in the presence of a transition metal catalyst.[8] Several methodologies exhibiting high yields and regioselectivities with a wide substrate scope have been developed. However, the long reaction times at harsh conditions may reduce the appeal of these reaction for a potential conversion to an industrial process. From this point of view, a cross-coupling protocol using a stoichiometric organometallic reagent can still be a more convenient strategy than C–H functionalization.

In the present paper we aim to overcome these issues by raising the productivity of thiophenes direct arylation through the implementation of flow chemistry technology. Since the direct arylation is usually carried out in a heterogeneous environment due to the presence of an inorganic base (e.g., alkali metal carbonates), we decided to use a packed-bed reactor containing the insoluble reagent. This can improve the reaction efficiency thanks to the presence of a large solid-liquid interphase area and through an easier separation of the base. We present herein the performances obtained in the palladium-catalyzed arylation of thiophene derivatives species using a small column reactor packed with potassium carbonate. A similar strategy involving a solid base confined in a column reactor was also employed in the flow synthesis of polymeric materials by means of direct (hetero)arylation polymerization,[9] however no examples for small molecules synthesis was reported to the best of our knowledge. By using an automated flow setup, the α-arylation of thiophene derivatives was performed with a wide substrate scope and this strategy showed an unchanged efficiency as the methodology was performed at the gram-scale.

Results and Discussion

The most general and effective methodologies for thiophenes direct arylation involve the use of a palladium-based catalytic system in the presence of an inorganic base (e.g. K_2CO_3, Cs_2CO_3, KOAc).[8a,10] Also, the presence of carboxylate salts is beneficial as they act as proton-shuttles assisting the concerted metalation-deprotonation (CMD) in the C–H activation step.[11] As one of the most established examples, Fagnou developed a synthetic strategy employing a palladium/phosphine catalytic system along with pivalic acid (PivOH) and potassium carbonate as co-catalyst and base respectively.[12] On the other hand, Doucet reported a methodology using only potassium acetate as base beside the palladium catalyst.[13] Both protocols employ dimethylacetamide (DMA) as solvent and a heterogeneous base. Therefore, while designing an appropriate flow setup for this transformation, the presence of an insoluble compound in the reaction environment must be considered. This issue can be mitigated, for instance, by confining the solid reagent in a packed bed reactor. Therefore, our strategy relied on the use of a glass column filled with the finely divided inorganic base, in order to maximize the solid-liquid contact, in which the solution containing the substrates and the catalyst precursors was allowed to flow. The Fagnou's methodology was chosen for the present study as potassium carbonate exhibits a low solubility in DMA even at high temperatures. On the other hand, the use of potassium acetate was not convenient since it led to the formation of a slurry mixture in DMA at the operating conditions, which resulted in the salt reprecipitation and clogging at the outlet tubes of the reactor.

Flow reactions were carried out under inert atmosphere using an automated system (Vapourtec R-Series). Dry DMA was used as solvent while the reagents solutions were loaded using sample loops placed after the pumps and mixed in a T-junction just before entering the heated column reactor packed with potassium carbonate (a detailed scheme of the flow apparatus and the procedure for the reactor preparation are available in Section 2 of the Supporting Information). The reagents were divided between a solution A containing palladium acetate and pivalic acid, and a solution B containing the reaction substrates and the phosphine ligand. The outcome of the reactor was monitored by on-line IR spectroscopy measuring the intensity of a signal at 808 cm^{-1}, which corresponded to a vibrational mode of the model product **3aa**. The use of an IR detector was convenient for checking the dispersion of the reaction plug flowing along the column reactor and therefore to perform a precise sample collection. In fact, the software controlling the automated system was able to predict the concentration profile of the reaction mixture at the collection point by considering the volume and diameter of the reactor and tubings. However, this may not consider the deviations due to multiple pathways in the packed-bed reactors or interactions with the solid phase. The comparison between the concentration profile predicted by Flow Commander software and the actual dispersion of the reaction plug measured with the IR flow cell is reported in the Supporting Information (Figure S3). Slight differences were found in the profiles shape and in the position of the maximum concentration point, proving the necessity of on-line IR monitoring to correct these minor deviations and precisely collect the reaction mixture samples.

The model reaction between **1a** and **2a** was investigated for the optimization of the reaction conditions. By using palladium acetate as the metal source and pivalic acid as co-catalyst, different temperatures, ligands and catalyst loadings were tested.

The first tests showed that a moderate yield could be obtained in only 60 minutes of residence time at a temperature higher than 100 °C. The optimal temperature was found at 140 °C giving a 80% yield in the α-arylated product (Table 1, Entry 4). Encouraged by this result, we tried to reduce the catalyst amount by using 0.5%mol of palladium acetate. A consistent yield decrease was observed, however by using an opportune phosphine ligand the yield value was brought back

Table 1. Optimization of the **1a** arylation in flow[a]

entry	catalyst loading (mol%)	Ligand (mol%)	T (°C)	residence time (min)	Yield (%)[b]
1[c]	1	–	100	60	34
2[c]	1	–	120	60	50
3[c]	1	–	140	60	80
4[c]	1	–	150	60	61
5	0.5	–	140	60	50
6	0.5	dppb (0.5)	140	60	56
7	0.5	PPh_3 (1)	140	60	63
8	0.5	tompp (1)	140	60	<5
9	0.5	XPhos (1)	140	60	30
10	0.5	$PCy_3.HBF_4$ (1)	140	60	84
11[d]	0.5	$PCy_3.HBF_4$ (1)	140	60	94
12[d]	0.5	$PCy_3.HBF_4$ (1)	140	30	81
13[e]	0.5	$PCy_3.HBF_4$ (1)	140	30	70

[a] Experimental Conditions: **2a** (1.0 mmol, 0.25 M), **1a** (1.5 mmol), PivOH (15 mol%). dppb = 1,4-bis(diphenylphosphino)butane. tompp = Tris(o-methoxyphenyl)phosphine. XPhos = 2-Dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl. [b] Yield determined by ^{1}HNMR analysis by using dibromomethane as the internal standard. [c] PivOH (30 mol%). [d] **2a** (3.0 mmol, 0.75 M), **1a** (4.5 mmol). [e] **2a** (6.0 mmol, 1.5 M), **1a** (9.0 mmol).

to 80%. The electronrich monodentate tricyclohexylphosphine was found as the most effective to promote **1a** arylation. At the optimized conditions reported in Entry 9 of Table 1, we also investigated the reaction efficiency by performing the **1a** arylation yield at different flow rates. The yield versus residence time plot is reported in Figure 2. As the curve flattens around 60 minutes of residence time, we did not consider extending further the residence time to maintain a high productivity value.

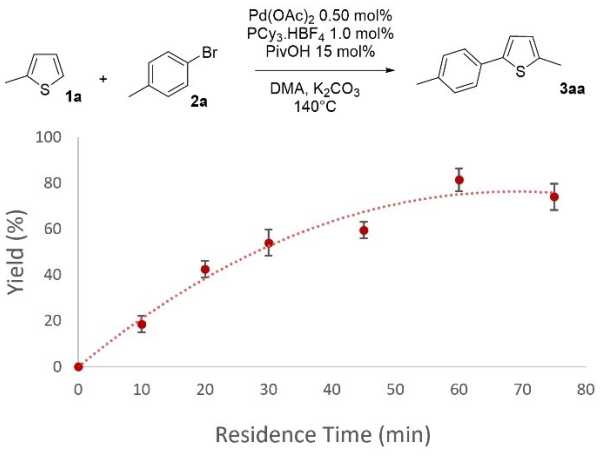


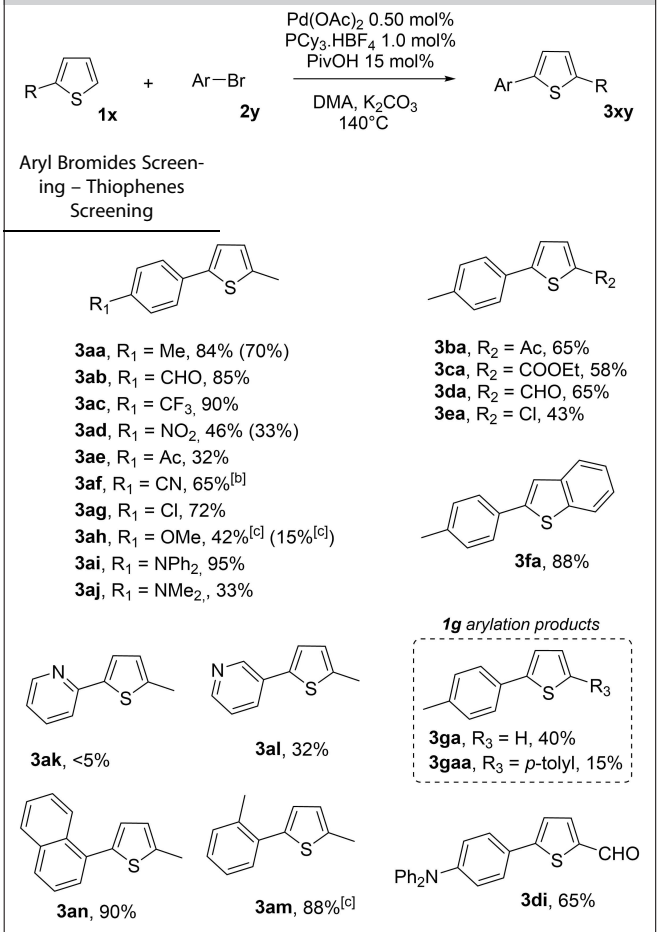
Figure 2. **3aa** yield versus residence time under optimized conditions. Fitting was performed with a third-degree polynomial function, $R^2 = 0.975$.

The optimized conditions were also tested batchwise in order to assess the impact of the continuous flow approach on the reaction efficiency. The model reaction was performed at 140 °C with a 1-hour reaction time in a sealed tube, which was chosen because the boiling point of **1a** (113 °C) is lower than the operating temperature. The yield obtained with the batch system was 70%, which proves a moderate enhancement of the direct arylation yield by using a column flow reactor. However, the use of a pressurized sealed container is intrinsically less safe and reproducible with respect to an operation carried out in a flow system with a stable back-pressure,[2b] and this advantage is worth of additional consideration in the flow-batch comparison.

We tested the generality of the flow protocol by using several different aryl bromides and 2-substituted thiophenes. At first, the use of aryl bromides with functional groups at the *para* position with different electronic properties was investigated. Higher yields were generally obtained reacting **1a** with aryl bromides carrying electron-withdrawing groups (EWGs), except when the substrate was equipped with coordinating moieties (e.g. acetyl, cyano groups) and for the nitro-functionalized **3ad**. This is generally observed in most reports, since EWGs on the aryl halide ring facilitate the oxidative addition on the active palladium(0) species.[12] On the other hand, in the presence of aryl bromides with electron-donating functionalities (**3ah**) or sterically hindered ones (**3am**) the catalyst loading was raised to 1% in order to have moderate yields. The comparison between batch and flow processes was performed also for the synthesis of products **3ad** and **3ah**, which confirmed a significantly lower yield for the corresponding batch experiments, especially when aryl bromide **2h** was employed (batch yields are indicated in brackets in Table 2). 3-Bromopyridine (**2n**) was also tested in the arylation of **1a** and gave moderate yields, on the other hand the use of the *ortho* regioisomer gave only a trace amount of product **3ak** (less than 5%). 2-Substituted thiophenes were investigated as coupling partners for **2a**. Generally, the presence of an EWG in α position of the heteroarene substrate, guaranteed good yields, although lower with respect to the model reaction. A high conversion in the product **3fa** was observed in the arylation of benzothiophene. The reaction between thiophene (**1g**) and aryl bromide **2a** gave the monoarylated compound **3ga** in 40% yield while the diarylated **3gaa** was produced in a 15% yield. This is unusual since the direct arylation of a thiophene derivative with both α positions available normally yields a majority of the 2,5-diarylated product even in the presence of a thiophene excess.[15] This occurs because the monoarylated product (i.e., **3ga**) reacts faster than the starting unfunctionalized thiophene. However, **3ga** was obtained as major product by using the flow system, probably as a consequence of the short reaction time and fast thermal quench at the outlet of the column reactor, which limits the occurrence of the consecutive arylation.

Finally, we investigated the synthesis in flow of a useful intermediate for the preparation of the D-π-A dyes type pictured in Figure 1A.[16] This can be achieved through the arylation of 2-formylthiophene (**1d**) with 4-bromotriphenylamine (**2i**) which gave the product **3di** in a 65% yield.

Table 2. Screening of aryl bromides and thiophene species[a]



[a] Experimental Conditions: Aryl bromide (1.0 mmol, 0.25 M), thiophene derivative (1.5 mmol), $Pd(OAc_2)$ (5.0×10^{-3} mmol), $PCy_3.HBF_4$ (1.0×10^{-2} mmol), pivOH-(1.5×10^{-1} mmol), DMA, 140 °C, 1 h residence time. Yield determined by ^{1}H NMR analysis by using dibromomethane as the internal standard. Results obtained by the batch methodology are indicated in brackets. [b] dppb was used instead of $PCy_3.HBF_4$ [c] $Pd(OAc_2)$ (1.0×10^{-2} mmol), $PCy_3.HBF_4$ (2.0×10^{-2} mmol), PivOH (3.0×10^{-1} mmol).

The flow approach usually allows a reaction scale-up with minor efforts with respect to batch transformations. To confirm this, we brought our model reaction up to the gram scale with only a few changes in the flow apparatus employed for the optimization and screening phases. Since the reagents and product of the model reaction exhibit high solubility in DMA, we employed a higher substrates concentration, which is convenient for process intensification. A three-fold increase in the reagent concentration was beneficial for the reaction speed and allowed to obtain an 81% yield of **3aa** in a residence time of 30 minutes (Table 1 Entry 13). A further increase of the substrates concentration brought to a lower yield (Table 1 Entry 14). The scale-up reaction was carried out at a three-fold higher reagent concentration and the volume of the sample loops used to inject the reagents solutions was increased from 2 mL to 10 mL. This allowed a 15-fold increase in the reaction scale which resulted in an NMR yield of 81%, a nearly unchanged value with respect to the results obtained at the optimized conditions. The product **3aa** was purified by column chromatography on silica in a 2.1 g amount, corresponding to a 75% isolated yield. The productivity of the flow process was therefore determined as 1.1 g h^{-1}.

Conclusions

In summary, we developed an "in flow" method for the direct arylation of thiophene derivatives. With respect to the corresponding batch methodology, the use of a packed-bed reactor containing the solid base allowed a moderate increase in the reaction efficiency at improved safety conditions. The scope of the direct arylation was assessed with differently substituted coupling partners showing similar results to those reported in the literature. The flow strategy allowed the development of a multigram-scale synthesis of product **3aa** with minor differences in yield and instrumental setup with respect to the small-scale experiments.

Experimental Section

General procedure for of thiophenes arylation in flow. The reagents were prepared as stock solutions (A and B) which were loaded in two 2 mL injection loops of the Vapourtec R-Series instrument. The stock solutions had the following composition: Solution A contained $Pd(OAc)_2$ (2.5×10^{-3} M) and pivalic acid (7.5×10^{-2} M) in anhydrous degassed DMA; Solution B contained the aryl bromide (0.50 M), the thiophene derivative (0.75 M) and $PCy_3.HBF_4$ (5.0×10^{-3} M) in anhydrous degassed DMA. Subsequently, A and B were mixed in a T-junction and flowed through a column reactor containing finely ground K_2CO_3 (12.0 g, 87 mmol) at the required temperature. The reaction mixture collection was performed automatically by online IR monitoring at the reactor outlet (detection of a product signal around 810 cm^{-1}). Diethyl ether (70 mL) was added to the collected solution and the mixture was washed with distilled water (3×70 mL). The organic phase was dried over Na_2SO_4 and evaporated under reduced pressure. The crude product was analysed by ^{1}H-NMR using dibromomethane as internal standard and subsequently purified by flash chromatography (SiO_2, hexane/ethyl acetate).

Supporting Information

The authors have cited additional references within the Supporting Information.[17]

Acknowledgements

The authors gratefully acknowledge financial support from the Italian Ministry of University and Research through the Departments of Excellence Program 2018–2022 (NExuS project) and the Department of Chemical Sciences of the University of Padova for the research grant P-DiSC#08BIRD2020-UNIPD. We thank Prof. Michele Maggini for fruitful discussions and insights.

Conflict of Interests

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: Flow Chemistry · Direct Arylation · Thiophene · C–H Functionalization

[1] a) M. Baumann, T. S. Moody, M. Smyth, S. Wharry, *Org. Process Res. Dev.* **2020**, *24*, 1802–1813; b) M. Baumann, T. S. Moody, M. Smyth, S. Wharry, *Eur. J. Org. Chem.* **2020**, 7398–7406; c) M. Baumann, T. S. Moody, M. Smyth, S. Wharry, *Synthesis* **2021**, *53*, 3963–3976.
[2] a) S. Govaerts, A. Nyuchev, T. Noel, *J. Flow Chem.* **2020**, *10*, 13–71; b) M. B. Plutschack, B. Pieber, K. Gilmore, P. H. Seeberger, *Chem. Rev.* **2017**, *117*, 11796–11893; c) L. Capaldo, Z. Wen, T. Noël, *Chem. Sci.* **2023**; d) C. A. Hone, C. O. Kappe, *Chem. Methods* **2021**, *1*, 454–467.
[3] T. Westermann, L. Mleczko, *Org. Process Res. Dev.* **2016**, *20*, 487–494.
[4] a) J. C. K. Chu, T. Rovis, *Angew. Chem. Int. Ed.* **2018**, *57*, 62–101; b) T. Dalton, T. Faber, F. Glorius, *ACS Cent. Sci.* **2021**, *7*, 245–261; c) P. Gandeepan, T. Müller, D. Zell, G. Cera, S. Warratz, L. Ackermann, *Chem. Rev.* **2019**, *119*, 2192–2452; d) T. Gensch, M. N. Hopkinson, F. Glorius, J. Wencel-Delord, *Chem. Soc. Rev.* **2016**, *45*, 2900–2936; e) T. Gensch, M. J. James, T. Dalton, F. Glorius, *Angew. Chem. Int. Ed.* **2018**, *57*, 2296–2306; f) J. Grover, G. Prakash, N. Goswami, D. Maiti, *Nat. Commun.* **2022**, *13*, 1085; g) A. Mondal, M. van Gemmeren, *Angew. Chem. Int. Ed.* **2022**, *61*, e202210825.
[5] F. Popowycz, E. Métay, M. Lemaire, *C. R. Chim.* **2011**, *14*, 621–628.
[6] a) F. Zhang, D. Wu, Y. Xu, X. Feng, *J. Mater. Chem.* **2011**, *21*, 17590–17600; b) P. Kumaresan, S. Vegiraju, Y. Ezhumalai, S. L. Yau, C. Kim, W.-H. Lee, M.-C. Chen, *Polymer* **2014**, *6*, 2645–2669; c) P.-Y. Ho, Y. Wang, S.-C. Yiu, Y.-Y. Kwok, C.-H. Siu, C.-L. Ho, L. T. Lin Lee, T. Chen, *J. Photochem. Photobiol. A* **2021**, *406*, 112979; d) F. A. Larik, M. Faisal, A. Saeed, Q. Abbas, M. A. Kazi, N. Abbas, A. A. Thebo, D. M. Khan, P. A. Channar, *J. Mater. Sci. Mater. Electron.* **2018**, *29*, 17975–18010.
[7] a) R. Shah, P. K. Verma, *Chem. Cent. J.* **2018**, *12*, 137; b) R. M. D. da Cruz, F. J. B. Mendonça-Junior, N. B. de Mélo, L. Scotti, R. S. A. de Araújo, R. N. de Almeida, R. O. de Moura, *Pharmaceuticals* **2021**, *14*, 692.
[8] a) C. B. Bheeter, L. Chen, J.-F. Soulé, H. Doucet, *Catal. Sci. Technol.* **2016**, *6*, 2005–2049; b) B. Zhao, B. Prabagar, Z. Shi, *Chem* **2021**, *7*, 2585–2634.
[9] a) N. S. Gobalasingham, J. E. Carlé, F. C. Krebs, B. C. Thompson, E. Bundgaard, M. Helgesen, *Macromol. Rapid Commun.* **2017**, *38*, 1700526; b) F. Grenier, B. R. Aïch, Y.-Y. Lai, M. Guérette, A. B. Holmes, Y. Tao, W. W. H. Wong, M. Leclerc, *Chem. Mater.* **2015**, *27*, 2137–2143.
[10] F. Bellina, *C–H Bond Activation and Catalytic Functionalization I* (Eds.: P. H. Dixneuf, H. Doucet), Springer International Publishing, Cham, **2016**, pp. 77–102.
[11] M. Lafrance, K. Fagnou, *J. Am. Chem. Soc.* **2006**, *128*, 16496–16497.
[12] a) B. Liégault, D. Lapointe, L. Caron, A. Vlassova, K. Fagnou, *J. Org. Chem.* **2009**, *74*, 1826–1834; b) D. J. Schipper, K. Fagnou, *Chem. Mater.* **2011**, *23*, 1594–1600.
[13] a) F. Požgan, J. Roger, H. Doucet, *ChemSusChem* **2008**, *1*, 404–407; b) J. Roger, F. Požgan, H. Doucet, *Green Chem.* **2009**, *11*, 425–432.
[14] a) S. R. Tamang, A. J. Achazi, H. S. Rust, P. Dhungana, P. Miró, J. D. Hoefelmeyer, *Tetrahedron* **2019**, *75*, 2365–2370; b) M. Portnoy, D. Milstein, *Organometallics* **1993**, *12*, 1665–1673.
[15] a) Y. Li, J. Wang, M. Huang, Z. Wang, Y. Wu, Y. Wu, *J. Org. Chem.* **2014**, *79*, 2890–2897; b) S. I. Gorelsky, D. Lapointe, K. Fagnou, *J. Org. Chem.* **2012**, *77*, 658–668.
[16] D. P. Hagberg, T. Marinado, K. M. Karlsson, K. Nonomura, P. Qin, G. Boschloo, T. Brinck, A. Hagfeldt, L. Sun, *J. Org. Chem.* **2007**, *72*, 9550–9556.
[17] a) D.-Z. Zheng, D.-H. Li, H. Liu, Y. Shao, Z. Ke, F.-S. Liu, *Organometallics* **2022**, *41*, 948–961; b) H.-K. Lu, T. Liu, Z. Shi, H. Yan, Z. Li, K.-Y. Ye, *Eur. J. Org. Chem.* **2023**, *26*, e202200963; c) S. Tanaka, D. Tanaka, A. Sugie, A. Mori, *Tetrahedron Lett.* **2012**, *53*, 1173–1176.

Manuscript received: June 19, 2023