

See discussions, stats, and author profiles for this publication at: <https://www.researchgate.net/publication/250310893>

Continuous Flow Organocatalytic C–H Functionalization and Cross–Dehydrogenative Coupling Reactions: Visible Light Organophotocatalysis for Multicomponent Reactions and C–C, C–P Bon...

ARTICLE in ACS CATALYSIS · JUNE 2013

Impact Factor: 9.31 · DOI: 10.1021/cs400350j

CITATIONS

32

READS

68

3 AUTHORS:



Magnus Rueping

RWTH Aachen University

259 PUBLICATIONS 10,018 CITATIONS

SEE PROFILE



Carlos Vila

University of Valencia

44 PUBLICATIONS 891 CITATIONS

SEE PROFILE



Teerawut Bootwicha

University of Bristol

13 PUBLICATIONS 293 CITATIONS

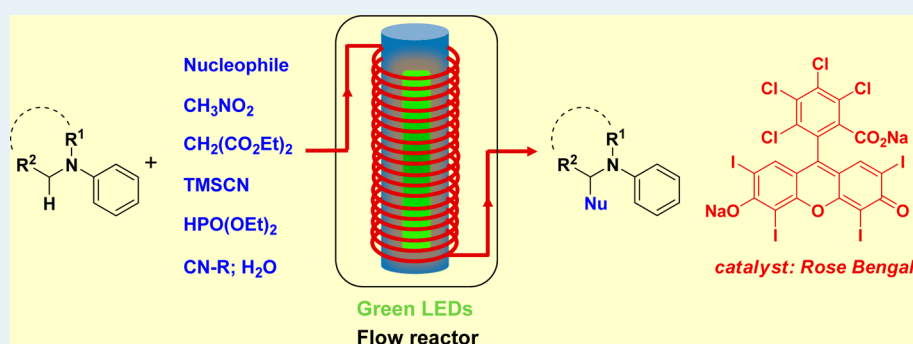
SEE PROFILE

Continuous Flow Organocatalytic C–H Functionalization and Cross-Dehydrogenative Coupling Reactions: Visible Light Organophotocatalysis for Multicomponent Reactions and C–C, C–P Bond Formations

Magnus Rueping,* Carlos Vila, and Teerawut Bootwicha

Institute of Organic Chemistry, RWTH Aachen University, Landoltweg 1, D-52074 Aachen, Germany

S Supporting Information



ABSTRACT: A continuous flow procedure for the efficient metal-free, visible light photoredox-catalyzed α -functionalization of tertiary amines has been developed. Rose Bengal has been identified as an effective organic photocatalyst for continuous flow C–C and C–P bond formations as well as multicomponent reactions.

KEYWORDS: Photocatalysis, Sustainable Catalysis, Organocatalysis, Photoreactor, Rose Bengal

In the past few years, visible light photoredox catalysis has attracted considerable attention in synthetic organic chemistry because visible light is a safe, abundant, inexpensive, renewable, and eco-friendly energy source.^{1–8} In this context, ruthenium and iridium complexes have been used as photoredox catalysts in several chemical transformations.^{9–47} These inorganic complexes are readily available, and their reactivity can be easily tuned by varying the ligands. In addition, organic dyes, which are inexpensive and easy to modify and handle, have been successfully applied in several photoredox reactions.^{48–59} However, only a few C–C bond-forming reactions have been reported. Therefore, we decided to investigate a new oxidative organophotoredox-catalyzed multicomponent reaction of amines, isocyanides, and water to obtain valuable amino acid amides (Scheme 1).

Unfortunately, most of the organic dyes did not result in the desired product or provided satisfactory yields only after long reaction times. Therefore, we decided to examine this new

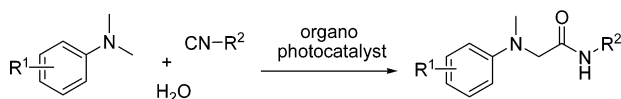
organocatalytic photoredox-catalyzed multicomponent reaction using continuous flow technology.

Continuous flow methodologies have attracted considerable interest⁶⁰ because they can have advantages over the traditional batch reactions. These include facile automation, energy efficiency, reproducibility, precise control of reaction parameters, and predictable reaction scale-up. In the case of photoredox catalysis, the productivity in batch reactors may be impeded by limited light penetration through the reaction media. Thus, continuous flow processes in microreactors present an alternative to batch conditions because the small reaction channels and the larger surface-to-volume ratio allow efficient, uniform, and homogeneous irradiation of the reaction mixture.^{61–64} These advantages result in shorter reaction times and may, as such, prevent undesired side reactions. Very recently, initial reports of visible light photoredox catalysis in continuous flow have been reported.^{65–69}

We here report the use of an organophotocatalyst in various continuous flow C–C and C–P bond-forming reactions, including unprecedented visible light organophotoredox catalyzed multicomponent reactions.

To implement a successful continuous flow procedure, we designed our photoreactor using commercially available

Scheme 1. First Organocatalytic Photoredox Multicomponent Reaction



Received: May 13, 2013

Published: June 25, 2013

fluorinated ethylene polymer (FEP) tubes with an internal diameter of 0.8 mm. FEP tubes are chemical-resistant, mechanically flexible, easy to handle, and optically transparent in the visible region of the light spectrum (Figure 1).

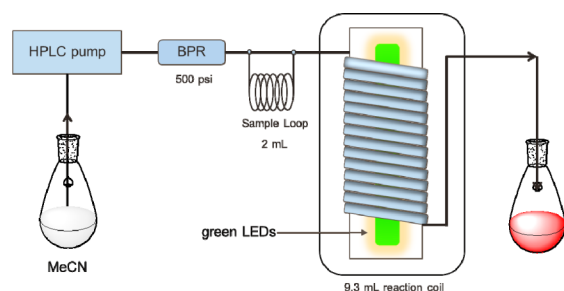


Figure 1. Schematic diagram of the organocatalytic photoredox continuous flow reactor.

The tube (4.6 m, corresponding to a 9.3 mL reactor volume) was wrapped around a glass tube. Inside the glass tube, we placed the strip of green LEDs, and the flow rate was controlled by a HPLC pump. To maintain the temperature, air was allowed to pass between the glass tube and the green LEDs.

We began our studies on the continuous flow α -functionalization of tertiary amines through the cross-dehydrogenative coupling reaction (CDC),⁷⁰ with the examination of Rose Bengal as the organophotocatalyst. We started with the organophotoredox-catalyzed reaction of *N*-phenyl tetrahydroisoquinoline with nitromethane^{32,36,71} to compare the flow procedure with the reported batch procedure.⁵⁰ Applying the same reaction conditions as reported by Tan,⁵⁰ we performed the reaction with a 4 mL reaction coil at a flow rate of 0.1 mL min⁻¹. Unfortunately, only 43% conversion was observed (Table 1, entry 1). Improved conversion was obtained

Table 1. Optimization of Reaction Conditions^a

entry	flow rate (mL min ⁻¹)	catalyst	<i>t</i> (h)	conv (%) ^b
1 ^c	0.1	Rose Bengal	0.75	43
2 ^c	0.05	Rose Bengal	2	72
3 ^{c,d}	0.05	Rose Bengal	2	46
4 ^e	0.1	Rose Bengal	1.5	65
5 ^e	0.1	Eosin Y	1.5	47
6 ^e	0.1	Rhodamine B	1.5	22
7 ^e	0.05	Rose Bengal	3	82 (73) ^f
8 ^e	0.03	Rose Bengal	5	95 (92) ^f

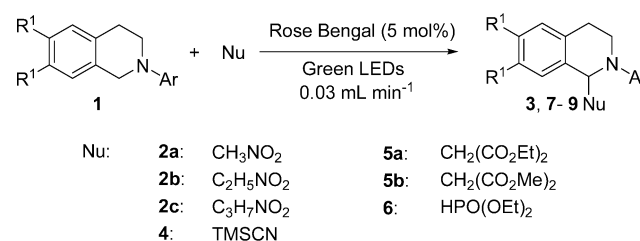
^aReactions performed using 0.15 mmol of **1a** (0.075 M) in a CH₃CN/CH₃NO₂/H₂O mixture (1:0.8:0.2 ratio). ^bConversion was determined by ¹H NMR. ^cUsing 4 mL reaction coil. ^dFlow reactor was cooled by water. ^eUsing 9 mL reaction coil. ^fYield after column chromatography.

by decreasing the flow rate to 0.05 mL min⁻¹ (entry 2). When the FEP tube was wrapped around a cooling condenser, a drop in the conversion due to lower irradiation was observed. To improve the conversion, we decided to increase the volume of the flow reactor to 9.3 mL and studied the aza-Henry reaction with different organic dyes employing a 0.1 mL min⁻¹ flow rate (entries 4–6). The best conversion was obtained when Rose

Bengal was used, and the corresponding product was isolated in 92% yield (entry 8).

With the optimal conditions in hand, we explored the substrate scope of the oxidative coupling reaction of *N*-aryl tetrahydroisoquinolines with nitroalkanes (Table 2, entries 1–

Table 2. Substrate Scope for the Flow Photoredox Reaction Catalyzed by Rose Bengal



entry	1	R ¹	Ar	Nu	product	yield % ^a
1 ^b	1a	H	Ph	2a	3a	92
2 ^b	1a	H	Ph	2b	3b	76
3 ^b	1a	H	Ph	2c	3c	78
4 ^b	1b	H	<i>p</i> Tol	2a	3d	85
5 ^b	1c	H	<i>p</i> MeO-Ph	2a	3e	86
6 ^b	1d	MeO	Ph	2a	3f	91
7 ^c	1a	H	Ph	4	7a	87
8 ^c	1b	H	<i>p</i> Tol	4	7b	77
9 ^c	1c	H	<i>p</i> MeO-Ph	4	7c	64
10 ^c	1d	MeO	Ph	4	7d	67
11 ^c	1e	H	<i>p</i> Br-Ph	4	7e	75
12 ^d	1a	H	Ph	5a	8a	71
13 ^d	1a	H	Ph	5b	8b	73
14 ^d	1b	H	<i>p</i> Tol	5a	8c	53
15 ^d	1c	H	<i>p</i> MeO-Ph	5a	8d	51
16 ^d	1e	H	<i>p</i> Br-Ph	5a	8e	55
17 ^e	1a	H	Ph	6	9a	59
18 ^e	1b	H	<i>p</i> Tol	6	9b	56
19 ^e	1c	H	<i>p</i> MeO-Ph	6	9c	60
20 ^e	1d	MeO	Ph	6	9d	49
21 ^e	1e	H	<i>p</i> Br-Ph	6	9e	56

^aYields after column chromatography. ^bReactions performed using 0.12 mmol of **1** (0.075 M) in a mixture CH₃CN/nitroalkane 2/H₂O (1:0.8:0.2 ratio), 5 h. ^cReactions performed using 5 equiv of **4**, 0.15 mmol of **1** (0.075 M) in a CH₃CN/H₂O mixture (1.7:0.2 ratio), 5 h. ^dReactions performed using 0.15 mmol of **1** (0.075 M) in a CH₃CN/malonate 5/H₂O mixture (1:0.8:0.2 ratio), 5 h. ^eReactions performed using 5 equiv of **6**, 0.15 mmol of **1** (0.075 M) in a CH₃CN/H₂O mixture (1.7:0.2 ratio) at 0.05 mL min⁻¹, 3 h.

6). In general, the reactions proceeded smoothly to provide the corresponding products **3a–f** in good to excellent yields (76–92%). It is important to note that the reaction proceeded faster under flow conditions than in the batch conditions reported previously.

Next, we focused our attention on the reaction between *N*-aryl tetrahydroisoquinolines (**1**) and cyanotrimethylsilane (**4**) to obtain α -amino nitriles, which are synthetically useful intermediates in organic synthesis.^{72,73} Their functionalization offers access to various important building blocks, such as α -amino acids, diamines, α -amino aldehydes, and α -amino ketones as well as α -amino alcohols. This versatility makes metal-free synthesis in continuous flow very attractive. Therefore, the standard conditions were directly applied to the cyanation of *N*-aryl tetrahydroisoquinolines, and the results

are summarized in Table 2 (entries 7–11). The reaction times were much shorter compared with the batch conditions,⁵¹ and the products **7a–e** were obtained in good yields. Next, we turned our attention to the continuous flow Mannich reaction with dialkylmalonates (Table 2, entries 12–16).⁷⁴ The corresponding β -amino diesters were obtained in moderate to good yields under the optimized conditions. Finally, the visible light organocatalytic phosphonylation of tertiary amines **1** was studied in continuous flow manner. α -Amino phosphonates are a very interesting structural motif in medicinal and organic chemistry being used as α -amino acid analogues.^{75–78} Hence, their synthesis in a metal-free procedure is highly desirable for their application in medicinal chemistry. As shown in Table 2 (entries 17–21), this methodology can also be applied to C–P bond formation to give the corresponding α -amino phosphonates **9** in moderate yields.

On the basis of this success, the oxidative Ugi multicomponent reaction^{79–83} using *N,N*-dimethylaniline (**10a**), *p*-toluenesulfonyl methyl isocyanide (**11a**), and H₂O was studied; the optimization is shown in Table 3. We started the

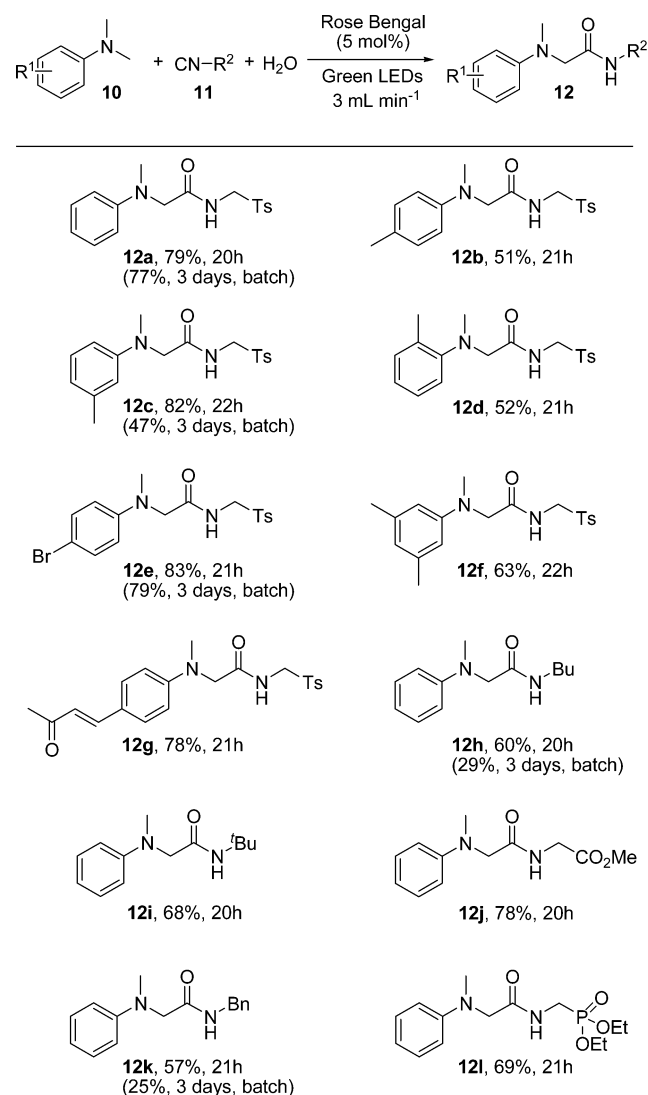
Table 3. Flow Photoredox Multicomponent Reaction with Rose Bengal^a

entry	flow rate (mL min ⁻¹)	catalyst (5 mol %)	<i>t</i> (h)	conv % ^b (yield %) ^c
1	0.5	Rose Bengal	12	22
2	0.5	Rose Bengal	18	42
3	1	Rose Bengal	18	59
4	2	Rose Bengal	18	77
5	3	Rose Bengal	20	81 (79)
6 ^d	1	Rose Bengal	18	17
7	3	Eosin Y	20	54
8	3	Rhodamine B	20	33

^aReactions performed using 0.8 mmol of **10a**, 0.4 mmol of **11a** (0.05 M) in a CH₃CN/H₂O mixture (7.4:0.6 mL). ^bConversions were determined by ¹H NMR. ^cYields after column chromatography. ^d0.1 M solution of **11a** was used.

optimization by varying the flow rate, catalyst, and concentration (Table 3). To obtain the best results, a recycling process was run at a flow rate of 3 mL min⁻¹. After 20 h, the corresponding α -amino amide **12a** was isolated in 79% yield (entry 5). The concentration of the solution was crucial for good conversion. When a 0.1 M solution was used instead of 0.05 M, a decrease in the conversion was observed (entry 6). Different organic dyes, such as Eosin Y and Rhodamine B, were tested in the multicomponent reaction in flow, but lower conversions were observed (entries 7 and 8). Under the optimal conditions, the substrate scope of the continuous flow photoredox oxidative Ugi multicomponent type reaction catalyzed by Rose Bengal was investigated. In general, different amines **10** and different isocyanides **11** could be successfully applied, providing the desired α -amino amides **12** in moderate to good yields (Scheme 2). For instance, (*E*)-4-(4-(dimethylamino)phenyl)but-3-en-2-one was subjected to the multicomponent reaction obtaining exclusively the desired α -amino amide **12g** in 78% yield. Furthermore, we were interested in the substrate scope with different isocyanides **11**. Therefore, *N,N*-dimethylaniline **10a** was reacted with

Scheme 2. Substrate Scope for the Photoredox Multicomponent Reaction in Flow with Rose Bengal



different isocyanides under the optimized conditions, which resulted in the desired products **12h–l** in good yields. In addition, for selected examples, we performed the oxidative Ugi multicomponent reaction in batch conditions,^{84,85} confirming the potential of the continuous flow methodology.

In summary, we have developed an environmentally acceptable, metal-free, photo-organocatalytic, continuous flow methodology that has been successfully applied in the α -functionalization of tertiary amines. Nitroalkanes, TMSCN, dialkyl malonates, and dialkyl phosphites were reacted with various *N*-aryl tetrahydroisoquinolines to provide the corresponding products in moderate to excellent yields. Furthermore, *N,N*-dimethylanilines were successfully reacted with different isocyanides in the Ugi-multicomponent reaction in flow, resulting in highly valuable α -amino amides in good yields. However, most importantly, considerably shorter reaction times are necessary if compared with the batch conditions. This is important for further reaction design. In addition, Rose Bengal is an inexpensive, readily available, environmentally benign organic dye that can be used as an efficient visible light photoredox catalyst in continuous flow fashion.

■ ASSOCIATED CONTENT

■ Supporting Information

General procedures, schematic diagram of the flow reactors (Figure S1), and full characterization of the products. This material is available free of charge via the Internet at <http://pubs.acs.org>.

■ AUTHOR INFORMATION

Corresponding Author

*Fax: +49 241 8092665. E-mail: magnus.rueping@rwth-aachen.de.

Notes

The authors declare no competing financial interest.

■ REFERENCES

- (1) Zeitler, K. *Angew. Chem., Int. Ed.* **2009**, *48*, 9785.
- (2) Yoon, T. P.; Ischay, M. A.; Du, J. *Nat. Chem.* **2010**, *2*, 527.
- (3) Narayanam, J. M. R.; Stephenson, C. R. J. *Chem. Soc. Rev.* **2011**, *40*, 102.
- (4) Teplý, F. *Collect. Czech. Chem. Commun.* **2011**, *76*, 859.
- (5) Xuan, J.; Xiao, W.-J. *Angew. Chem., Int. Ed.* **2012**, *51*, 6828.
- (6) Shi, L.; Xia, W. *Chem. Soc. Rev.* **2012**, *41*, 7687.
- (7) Prier, C. K.; Rankic, D. A.; MacMillan, D. W. C. *Chem. Rev.* **2013**, DOI: [dx.doi.org/10.1021/cr300503r](https://doi.org/10.1021/cr300503r).
- (8) Ravelli, D.; Fagnoni, M.; Albin, A. *Chem. Soc. Rev.* **2013**, *42*, 97.
- (9) Nicewicz, D. A.; MacMillan, D. W. D. *Science* **2008**, *322*, 77.
- (10) Ischay, M. A.; Anzovino, M. E.; Du, J.; Yoon, T. P. *J. Am. Chem. Soc.* **2008**, *130*, 12886.
- (11) Narayanam, J. M. R.; Tucker, J. W.; Stephenson, C. R. J. *J. Am. Chem. Soc.* **2009**, *131*, 8756.
- (12) Du, J.; Yoon, T. P. *J. Am. Chem. Soc.* **2009**, *131*, 14604.
- (13) Tucker, J. W.; Narayanam, J. M. R.; Krabbe, S. W.; Stephenson, C. R. J. *Org. Lett.* **2010**, *12*, 368.
- (14) Ischay, M. A.; Lu, Z.; Yoon, T. P. *J. Am. Chem. Soc.* **2010**, *132*, 8572.
- (15) Dai, C.; Narayanam, J. M. R.; Stephenson, C. R. J. *Nat. Chem.* **2011**, *3*, 140.
- (16) Andrews, R. S.; Becker, J. J.; Gagné, M. R. *Angew. Chem., Int. Ed.* **2010**, *49*, 7274.
- (17) Nagib, D. A.; MacMillan, D. W. C. *Nature* **2011**, *480*, 224.
- (18) Furst, L.; Narayanam, J. M. R.; Stephenson, C. R. J. *Angew. Chem., Int. Ed.* **2011**, *50*, 9655.
- (19) Lin, S.; Ischay, M. A.; Fry, C. G.; Yoon, T. P. *J. Am. Chem. Soc.* **2011**, *133*, 19350.
- (20) Chen, Y.; Kamlet, A. S.; Steinman, J. B.; Liu, D. R. *Nat. Chem.* **2011**, *3*, 146.
- (21) Courant, T.; Masson, G. *Chem.—Eur. J.* **2012**, *18*, 423.
- (22) Zou, Y.-Q.; Chen, J.-R.; Liu, X.-P.; Lu, L.-Q.; Davis, R. L.; Jørgensen, K. A.; Xiao, W.-J. *Angew. Chem., Int. Ed.* **2012**, *51*, 784.
- (23) Cheng, Y.; Yang, J.; Qu, Y.; Li, P. *Org. Lett.* **2012**, *14*, 98.
- (24) Larraufie, M.-H.; Pellet, R.; Fensterbank, L.; Goddard, J.-P.; Lacôte, E.; Malacria, M.; Ollivier, C. *Angew. Chem., Int. Ed.* **2011**, *50*, 4463.
- (25) Kohls, P.; Jadhav, D.; Pandey, G.; Reiser, O. *Org. Lett.* **2012**, *14*, 672.
- (26) Miyake, Y.; Nakajima, K.; Nishibayashi, Y. *J. Am. Chem. Soc.* **2012**, *134*, 3338.
- (27) Miyake, Y.; Ashida, Y.; Nakajima, K.; Nishibayashi, Y. *Chem. Commun.* **2012**, *48*, 6966.
- (28) Miyake, Y.; Nakajima, K.; Nishibayashi, Y. *Chem.—Eur. J.* **2012**, *18*, 16473.
- (29) McNally, A.; Prier, C. K.; MacMillan, D. W. C. *Science* **2011**, *334*, 1114.
- (30) Ju, X.; Li, D.; Li, W.; Yu, W.; Bian, F. *Adv. Synth. Catal.* **2012**, *354*, 3561.
- (31) Zhu, S.; Das, A.; Bui, L.; Zhou, H.; Curran, D. P.; Rueping, M. *J. Am. Chem. Soc.* **2013**, *135*, 1823.
- (32) Condie, A. G.; González-Gómez, J. C.; Stephenson, C. R. J. *J. Am. Chem. Soc.* **2010**, *132*, 1464.
- (33) Xie, Z.; Wang, C.; deKrafft, K. E.; Lin, W. *J. Am. Chem. Soc.* **2011**, *133*, 2056.
- (34) Xuan, J.; Cheng, Y.; An, J.; Lu, L.-Q.; Zhang, X.-X.; Xiao, W.-J. *Chem. Commun.* **2011**, *47*, 8337.
- (35) Zou, Y.-Q.; Lu, L.-Q.; Fu, L.; Chang, N.-J.; Rong, J.; Chen, J.-R.; Xiao, W.-J. *Angew. Chem., Int. Ed.* **2011**, *50*, 7171.
- (36) Rueping, M.; Vila, C.; Koenigs, R. M.; Poschary, K.; Fabry, D. C. *Chem. Commun.* **2011**, *47*, 2360.
- (37) Wang, C.; Xie, Z.; deKrafft, K. E.; Lin, W. *J. Am. Chem. Soc.* **2011**, *133*, 13445.
- (38) Rueping, M.; Zhu, S.; Koenigs, R. M. *Chem. Commun.* **2011**, *47*, 8679.
- (39) Rueping, M.; Zhu, S.; Koenigs, R. M. *Chem. Commun.* **2011**, *47*, 12709.
- (40) Rueping, M.; Leonori, D.; Poisson, T. *Chem. Commun.* **2011**, *47*, 9615.
- (41) Maity, S.; Zhu, M.; Shinabery, R. S.; Zheng, N. *Angew. Chem., Int. Ed.* **2012**, *51*, 222.
- (42) Freeman, D. B.; Furst, L.; Condie, A. G.; Stephenson, C. R. J. *Org. Lett.* **2012**, *14*, 94.
- (43) Rueping, M.; Koenigs, R. M.; Poschary, K.; Fabry, D. C.; Leonori, D.; Vila, C. *Chem.—Eur. J.* **2012**, *18*, 5170.
- (44) Cai, S.; Zhao, X.; Wang, X.; Liu, Q.; Li, Z.; Wang, D. Z. *Angew. Chem., Int. Ed.* **2012**, *51*, 8050.
- (45) Zhao, G.; Yang, C.; Guo, L.; Sun, H.; Chen, C.; Xia, W. *Chem. Commun.* **2012**, *48*, 2337.
- (46) Zhu, S.; Rueping, M. *Chem. Commun.* **2012**, *48*, 11960.
- (47) DiRocco, D. A.; Rovis, T. *J. Am. Chem. Soc.* **2012**, *134*, 8094.
- (48) Liu, H.; Feng, W.; Kee, C. W.; Zhao, Y.; Leow, D.; Pan, Y.; Tan, C.-H. *Green Chem.* **2010**, *12*, 953.
- (49) Lechner, R.; König, B. *Synthesis* **2010**, 1712.
- (50) Pan, Y.; Kee, C. W.; Chen, L.; Tan, C.-H. *Green Chem.* **2011**, *13*, 2682.
- (51) Pan, Y.; Wang, S.; Kee, C. W.; Dubuisson, E.; Yang, Y.; Loh, K. P.; Tan, C.-H. *Green Chem.* **2011**, *13*, 3341.
- (52) Neumann, M.; Földner, S.; König, B.; Zeitler, K. *Angew. Chem., Int. Ed.* **2011**, *50*, 951.
- (53) Hari, D. P.; König, B. *Org. Lett.* **2011**, *13*, 3852.
- (54) Liu, Q.; Li, Y.-N.; Zhang, H.-H.; Chen, B.; Tung, C.-H.; Wu, L.-Z. *Chem.—Eur. J.* **2012**, *18*, 620.
- (55) Fidal, K.; Ceballos, C.; Falguières, A.; Veitia, M. S.-I.; Guy, A.; Ferroud, C. *Green Chem.* **2012**, *14*, 1293.
- (56) Fu, W.; Guo, W.; Zou, G.; Xu, C. *J. Fluorine Chem.* **2012**, *140*, 88.
- (57) Hari, D. P.; Schroll, P.; König, B. *J. Am. Chem. Soc.* **2012**, *134*, 2958.
- (58) Schroll, P.; Hari, D. P.; König, B. *ChemistryOpen* **2012**, *1*, 130.
- (59) Ravelli, D.; Fagnoni, M. *ChemCatChem* **2012**, *4*, 169.
- (60) *Microreactors in Organic Synthesis and Catalysis*; Wirth, T., Ed.; Wiley-VCH: Weinheim, 2008.
- (61) Wiles, C.; Watts, P. *Electrochemical and Photochemical Applications of Micro Reaction Technology*. In *Microreaction Technology in Organic Synthesis*; CRC Press, Taylor & Francis Group: Boca Raton, FL, 2011; pp 289–321.
- (62) Knowles, J. P.; Elliott, L. D.; Booker-Milburn, K. I. *Beilstein J. Org. Chem.* **2012**, *8*, 2025.
- (63) Oelgemöller, M.; Shvydkiv, O. *Molecules* **2011**, *16*, 7522.
- (64) Shvydkiv, O.; Oelgemöller, M. *Microphotochemistry: photochemical synthesis in microstructured flow reactors*. In: *CRC Handbook of Organic Photochemistry and Photobiology*; Griesbeck, A., Oelgemöller, M., Ghetti, F., Eds.; CRC Press: Boca Raton, FL, 2012; pp 49–72.
- (65) Bou-Hamdan, F. R.; Seeberger, P. H. *Chem. Sci.* **2012**, *3*, 1612.
- (66) Tucker, J. W.; Zhang, Y.; Jamison, T. F.; Stephenson, C. R. J. *Angew. Chem., Int. Ed.* **2012**, *51*, 4144.
- (67) Andrews, R. S.; Becker, J. J.; Gagné, M. R. *Angew. Chem., Int. Ed.* **2012**, *51*, 4140.

- (68) Neumann, M.; Zeitler, K. *Org. Lett.* **2012**, *14*, 2658.
- (69) Nguyen, J. D.; Reiß, B.; Dai, C.; Stephenson, C. R. J. *Chem. Commun.* **2013**, *49*, 4352.
- (70) Li, C.-J. *Acc. Chem. Res.* **2009**, *42*, 335.
- (71) Rueping, M.; Zoller, J.; Fabry, D. C.; Poscharny, K.; Koenigs, R. M.; Weirich, T. E.; Mayer, J. *Chem.—Eur. J.* **2012**, *18*, 3478.
- (72) Rueping, M.; Vila, C.; Szadkowska, A.; Koenigs, R. M.; Fronert, J. *ACS Catal.* **2012**, *2*, 2810.
- (73) Enders, D.; Shilvock, J. P. *Chem. Soc. Rev.* **2000**, *29*, 359.
- (74) The excess of dialkyl malonates was distilled using Kugelrohr distillation.
- (75) Kafarski, P.; Lejczak, B. *Phosphorus, Sulfur, Silicon Relat. Elem.* **1991**, *63*, 193.
- (76) Allen, J. G.; Atherton, F. R.; Hall, M. J.; Hassall, C. H.; Holmes, S. W.; Lambert, R. W.; Nisbet, L. J.; Ringrose, P. S. *Nature* **1978**, *272*, 56.
- (77) Hiratake, J.; Oda, J. *Biosci., Biotechnol., Biochem.* **1997**, *61*, 211.
- (78) Hirschmann, R.; Smith, A. B.; Taylor, C. M.; Benkovic, P. A.; Taylor, S. D.; Yager, K. M.; Sprengeler, P. A.; Benkovic, S. J. *Science* **1994**, *265*, 234.
- (79) Ugi, I.; Meyr, R.; Fetzer, U.; Steinbruckner, C. *Angew. Chem.* **1959**, *71*, 386.
- (80) Ugi, I.; Steinbruckner, C. *Angew. Chem.* **1960**, *72*, 267.
- (81) Ugi, I. *Angew. Chem., Int. Ed.* **1962**, *1*, 8.
- (82) Dömling, A.; Ugi, I. *Angew. Chem., Int. Ed.* **2000**, *39*, 3168.
- (83) Dömling, A. *Chem. Rev.* **2006**, *106*, 17.
- (84) Vila, C.; Rueping, M. *Green Chem.* **2013**, DOI: 10.1039/c3gc40587g.
- (85) Rueping, M.; Vila, C. *Org. Lett.* **2013**, *15*, 2092.