

# A General Protocol for Robust Sonogashira Reactions in Micellar Medium

Markus Jakobi,<sup>a,b</sup> Fabrice Gallou,<sup>a</sup> Christof Sparr,<sup>\*b</sup> and Michael Parmentier<sup>\*a</sup>

<sup>a</sup> Chemical & Analytical Development, Novartis Pharma AG, 4056 Basel, Switzerland

e-mail: michael.parmentier@novartis.com

<sup>b</sup> Department of Chemistry, University of Basel, St. Johanns-Ring 19, 4056 Basel, Switzerland

e-mail: christof.sparr@unibas.ch

A robust and general protocol for a sustainable copper-free Sonogashira cross coupling under micellar aqueous reaction conditions with high turnover was developed. By using the commercially available catalyst CataCXium A Pd G3 and THF as co-solvent, various alkyne substrates were efficiently cross-coupled with a broad range of aryl halides, providing improved yields and low catalyst loadings. The reaction parameters were optimized to render the process operationally simple, robust and scalable. The method gives access to alkynylated arenes, heterocyclic compounds and monofunctionalized products from dihalogenated substrates with an improved selectivity achieved by the micellar aqueous reaction conditions.

**Keywords:** Micelles • Ligands • Copper-free Sonogashira Cross Coupling • Sustainable Synthesis • Water

## Introduction

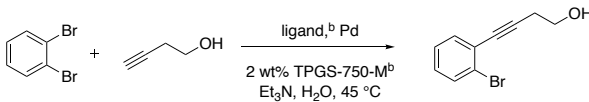
Cross-coupling reactions belong to the most widely utilized transformations in the pharmaceutical industry, ranging from the discovery phase to multi-ton scale production.<sup>[1–6]</sup> Whereas meticulous process optimization reduced the ecological footprint and cost of production, solvents remain a main economic and environmental factor in these reactions. Numerous initiatives from the industrial side therefore aim at replacing problematic solvents, while regulatory legislations have further incentivized the development of sustainable processes by a suitable solvent selection.<sup>[7,8]</sup> The use of aqueous reaction conditions is thereby often considered as ideal medium, taking into account the overall assessment of cost and environmental impact.<sup>[9]</sup>

However, many organic transformations are incompatible with water as solvent, often due to the low solubility of substrates, reagents or catalysts.<sup>[10–12]</sup> Micellar reaction conditions utilizing readily available surfactants allowed to overcome some of these limitations and thus expanded the range of transformations that are amenable to aqueous reaction conditions.<sup>[13–15]</sup> In particular, catalytic cross-coupling reactions under micellar conditions allowed a broad range of application, especially when a small amount of co-solvent is used which increase the size of the micelles and therefore the overall reaction dynamics of the system.<sup>[16,17]</sup> However, for a versatile and robust reaction protocol, the distribution of catalyst and substrates and their mass transfer processes require suitably general reaction conditions and an exceptionally efficient catalytic process. We therefore aimed at increasing the scope of copper-free Sonogashira reactions in aqueous micellar media, which allows to cross-couple hydrophilic alkynes with a broad range of aryl halides and heterocyclic substrates. Furthermore, the procedure was designed to be operationally simple, robust, tolerant to air, amenable to scale-up and directly applicable by using commercially available catalysts and reagents.

## Results and Discussion

To develop a method with improved generality, robustness and scalability, we chose the selective mono-functionalization of 1,2-dibromobenzene with 3-butynol under micellar reaction conditions using an aqueous solution of surfactant TPGS-750-M as our reaction platform. With the HandaPhos ligand known to be effective for other copper-free Sonogashira reactions under micellar conditions,<sup>[18]</sup> we observed a low conversion (Table 1, entry 1, 8%), further underlining the importance of complementary ligands for sustainable Sonogashira reactions. Significant improvements of reactivity were observed with 1 mol% DPEPhos and *t*-BuXPhos (entries 2 and 3).

**Table 1.** Comparison of catalysts for the micellar Sonogashira reaction<sup>a</sup>



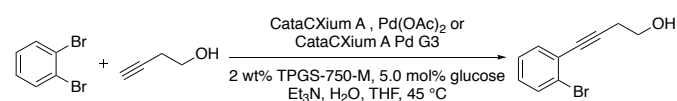
Entry	Ligand <sup>b</sup> /Catalyst	Cat.-Loading	Additive <sup>c</sup>	Yield <sup>d</sup>
1	HandaPhos, Pd(OAc) <sub>2</sub>	1.00 mol%	–	8%
2	Pd(DPEPhos)Cl <sub>2</sub>	1.00 mol%	–	27%
3	<i>t</i> -BuXPhos Pd G3	1.00 mol%	–	28%
4	CataCXium A Pd G3	1.00 mol%	–	53%
5	cBRIDP, Pd(OAc) <sub>2</sub>	3.00 mol%	–	16%
6	Pd(dppf)Cl <sub>2</sub>	3.00 mol%	–	38%
7	CataCXium A Pd G3	3.00 mol%	glucose	52%
8	Tris-Adam-Phosphine, Pd(OAc) <sub>2</sub>	3.00 mol%	glucose	20%
9	EvanPhos, Pd(OAc) <sub>2</sub>	3.00 mol%	glucose	0%

<sup>a</sup> Reactions performed with 420 μmol *o*-dibromobenzene, 504 μmol 3-butynol and 840 μmol Et<sub>3</sub>N in 1.0 mL 2.0 wt% TPGS-750M in HPLC grade water (420mmol<sup>-1</sup>) at 45 °C for 24 hours. <sup>b</sup> See Supporting Information for Structures of TPGS-750-M and ligands <sup>c</sup> 5 mol% glucose was added <sup>d</sup> Yield was determined by calibrated HPLC.

However, the CataCXium A Pd G3 catalyst indicated the significance of ligand structure variation to modulate the reactivity of the copper-free Sonogashira reaction under micellar reaction conditions (entry 4, 53%). We next determined the effect of a higher catalyst-loading and the use of additives by investigating the reaction yield and processability. Inferior results were obtained with cBRIDP or the ferrocenyl dppf-ligand (entries 5 and 6) and interestingly, a similar yield was obtained with 3 mol% of CataCXium A Pd G3 (entries 7–9). However, the use of 5 mol% glucose strongly affected the homogeneity of the reaction mixture, allowing improved robustness, more effective stirring and an ideal processability.<sup>[19,20]</sup>

Having identified CataCXium A Pd G3 as an optimal catalyst and the beneficial effect of glucose, we set out to explore the impact of the size of micelles, the amount of base, Pd/ligand ratio and the minimal catalyst loading. Interestingly, reducing the catalyst loading to 0.50 mol% provided a similar conversion, while the use of THF as co-solvent resulted in substantially increased reactivity and more homogeneous reaction conditions, particularly when 3.00 eq. of Et<sub>3</sub>N is used as base (Table 2, entries 1 and 2, 72%). With this more effective catalytic system, the expected two-fold Sonogashira reaction was also observed, thus reducing the selectivity for the mono-functionalization to 76%. Moreover, further decreasing the catalyst loading to 0.1 mol% sharply effected the reaction outcome (entry 3), while the Pd/ligand ratio afforded only minor improvements of the conversion (entries 4 and 5). Furthermore, we confirmed the impact of the temperature on the active catalyst generation and the conversion by a comparison with reactions at ambient temperature (45°C vs. RT). Ambient temperature thereby resulted in an unsuitably low conversion when CataCXium A was used in combination with Pd(OAc)<sub>2</sub>

**Table 2.** Optimization of the reaction conditions using CataCXium A and co-solvent.<sup>a,b</sup>



Entry	Cat.-Loading [Pd/Ligand ratio]	Et <sub>3</sub> N (eq.)	Co-solvent	Conversion Selectivity <sup>c</sup>
1	0.50 mol% [1.00/1.00]	2.00 eq.	-	55%
2	0.30 mol% [1.00/1.00]	3.00 eq.	15 wt% THF	72% ; 76%
3	0.10 mol% [1.00/1.00]	3.00 eq.	15 wt% THF	10% ; 100%
4	0.30 mol% [0.80/1.00]	3.00 eq.	15 wt% THF	76% ; 68%
5	0.30 mol% [1.20/1.00]	3.00 eq.	15 wt% THF	65% ; 79%
6 <sup>d</sup>	0.30 mol% [1.00/1.00]	3.00 eq.	15 wt% THF	11% ; 100%
7	0.30 mol% [G3]	3.00 eq.	15 wt% THF	81% ; 58%
8 <sup>d</sup>	0.30 mol% [G3]	3.00 eq.	15 wt% THF	62% ; 94%

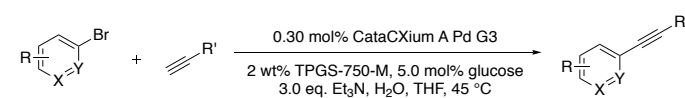
<sup>a</sup> Reactions performed with 420 μmol *o*-dibromobenzene, 504 μmol 3-butynol and 840 μmol or 1.26 mmol Et<sub>3</sub>N in 1.0 mL 2.0 wt% TPGS-750M in HPLC grade water (420mmolL<sup>-1</sup>) and 150 μl THF at 45°C for 24 hours. <sup>b</sup> 5 mol% glucose was added

<sup>c</sup> Conversion and selectivity were determined by calibrated HPLC. <sup>d</sup> Reaction at RT.

(entry 6) or in a reduced reactivity with CataCXium A Pd G3 as compared to the transformation carried out at 45°C (entries 7 vs. 8, 81% vs. 62%). Whereas the selectivity is improved by lowering the reaction temperature, the formation of a substantial amount of double alkylation could not be fully prevented (58% vs. 94%).

Having in hand conditions that allow low catalyst loadings and a high substrate conversion, we next investigated the scope of the optimized protocol for Sonogashira reaction under micellar reaction conditions (Table 3). Compared to *o*-dibromobenzene, a lower selectivity was observed

**Table 3.** Scope of the micellar Sonogashira reaction.<sup>a</sup>

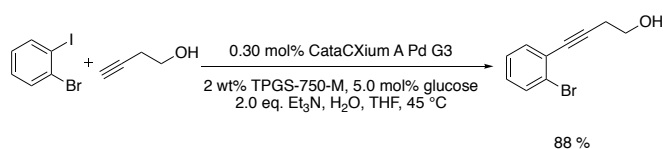


Entry	Substrate	Product	Yield <sup>b</sup>
1			31 %
2			49 %
3			69 %
4			77 %
5			67 %
6			98 %
7			91 %
8			97 %
9			98 %

<sup>a</sup> Reactions performed with 100 mg aryl bromide, 3.00 eq. Et<sub>3</sub>N, 1.20 eq. alkyne, 2.0 wt% TPGS-750M in HPLC grade water (420 mmolL<sup>-1</sup>), 5 mol% glucose and THF as co-solvent at 45°C for 24 hours. <sup>b</sup> Isolated yields.

with the *meta*-substituted congener, resulting in 31% yield (entry 1), whereas a slightly higher selectivity provided a 49% isolated yield of the corresponding product with isomeric *p*-dibromobenzene (entry 2).

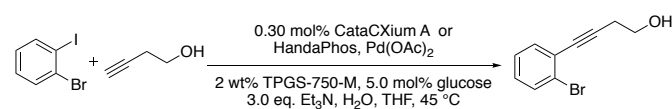
However, when employing substrates without selectivity concerns, the optimized conditions with CataCXium A Pd G3 as catalyst afforded the corresponding alkynylated products with up to 98 % isolated yield (entries 3–9). Various aryl bromides and heterocyclic substrates poised for further functionalization were well tolerated by this versatile transformation and a broad range of alkynes with different lipophilicities, alkyl (entries 1–3 and 5), aryl (entries 6 and 7) or heteroaryl substitution (entries 4, 8 and 9) as well as appropriately protected substrates (2-hydroxyprop-2-yl (HOP), entry 5) were efficiently cross-coupled. We next studied this notable catalytic efficiency by examining the coupling of 2-iodobenzene with 3-butynol, which provided the product in 88% yield on a 5 g scale. Furthermore, the improved stirring with increased reaction scale allowed to reduce the amount of Et<sub>3</sub>N to 2.0 eq (Scheme 1).



**Scheme 1.** Sonogashira reaction with 2-iodobromobenzene (5 g, mechanic stirrer).

This result was consequently compared to an analogous reaction with HandaPhos, establishing the differences of these two ligands (72% vs. 29%–38% conversion, Table 4).<sup>[21]</sup> Interestingly, an inversed effect of the addition of glucose was observed, providing 29% with and 38% conversion without the use of the additive (entry 2 vs. 3).

**Table 4.** Effect of ligand variation.<sup>a</sup>



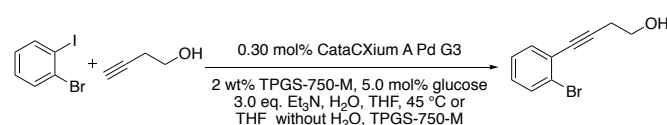
Entry	Variation	Conversion <sup>b</sup>
1	none	72% <sup>c</sup>
2	HandaPhos, with glucose	28%
3	HandaPhos, without glucose	38%

<sup>a</sup> Reactions performed with 420 μmol 2-iodobromobenzene, 504 μmol 3-butynol and 1.26 mmol Et<sub>3</sub>N in 1.0 mL 2.0 wt% TPGS-750M in H<sub>2</sub>O and 150 μl THF at 45°C for 24 hours. <sup>b</sup> Conversion determined by calibrated HPLC. <sup>c</sup> Magnetic stirrer.

The advantages of micellar reaction conditions were further highlighted by comparing the transformation of 2-iodobromobenzene (Table 5, entry 1, magnetic stirring, 80%) with an analogous reaction in THF without the aqueous solution of TPGS-750-M, affording a markedly reduced conversion (Table 5, entry 2, 40%).<sup>[21]</sup> Moreover, the use of micellar reaction conditions provided an improved impurity profile and a suitable mass transfer ideal for scale-up of the process.

To gain further insights into the crucial parameters for catalysis under micellar reaction conditions, we explored the effect of late additions of different reaction components after 5 min. at 45°C. Notably, the late addition of catalyst, base, co-solvent or glucose resulted in inferior conversions (entries 3–6), whereas improved results were obtained by the late addition of the substrates (entries 7 and 8, 81% and 84%). As expected the late addition of the surfactant TPGS-750-M also gave a lower yield, indicating that the formation of micelles is required prior to cross-coupling. Considering the low catalyst loading, the mass transfer of the different components of the reactions is hence considered as a crucial factor for efficient turnover.

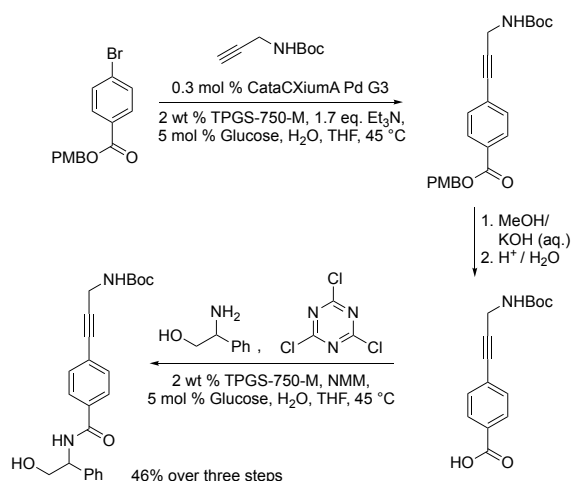
**Table 5.** Comparison of the micellar reaction conditions and study of late additions.<sup>a</sup>



Entry	Variation	Conversion <sup>b</sup>
1	none	80% <sup>c</sup>
2	without H <sub>2</sub> O, TPGS-750-M, THF as solvent	40%
3	late addition <sup>d</sup> of CataCXium A Pd G3	77%
4	late addition <sup>d</sup> of Et <sub>3</sub> N	75%
5	late addition <sup>d</sup> of THF	77%
6	late addition <sup>d</sup> of glucose	77%
7	late addition <sup>d</sup> of 2-iodobromobenzene	81%
8	late addition <sup>d</sup> of 3-butynol	84%
9	late addition <sup>d</sup> of TPGS-750-M	67%

<sup>a</sup> Reactions performed with 420 μmol 2-iodobromobenzene, 504 μmol 3-butynol and 1.26 mmol Et<sub>3</sub>N in 1.0 mL 2.0 wt% TPGS-750M in H<sub>2</sub>O (420 mmol L<sup>-1</sup>) and 150 μl THF at 45°C for 24 hours. <sup>b</sup> Conversion determined by calibrated HPLC. <sup>c</sup> Magnetic stirrer. <sup>d</sup> Addition of the component after 5 min of initial stirring at 45°C.

To further demonstrate the utility of the method, a reaction sequence comprised of a Sonogashira cross-coupling, followed by a hydrolysis and an amide coupling of an unprotected amino alcohol under micellar conditions<sup>[22]</sup> was investigated (Scheme 2). With the developed protocol using CataCXium A Pd G3 as catalyst, PMB protected *p*-bromobenzoate was first coupled to *N*-Boc-propargylamine and the liberated acid converted with (±)-2-phenylglycinol to give the corresponding amide in 46% yield over three steps without purification of the intermediates. This sequential synthesis shows the high efficiency not only in terms of chemical yield, but also in a low environmental impact. The Process Mass Intensity (PMI)<sup>[23–25]</sup> for the overall process throughout 3 steps is equal 110 and only 70 if we consider only the organic solvents used (EtOAc for extraction and THF as co-solvent, being both biodegradable with low impact on the environment).



**Scheme 2.** Reaction sequence combining the copper-free Sonogashira reaction under micellar reaction conditions with the hydrolysis and amide coupling step without purification of intermediates.

In conclusion, an efficient general catalytic system for Sonogashira reactions under aqueous micellar conditions was developed. With the surfactant TPGS-750-M in H<sub>2</sub>O, THF as co-solvent and CataCXium A Pd G3 as catalyst, isolated yields of up to 98% were obtained with 0.30 mol% catalyst loading. With glucose as an additive, more homogeneous reaction mixtures were observed throughout our study, rendering the process amenable to scale-up. Considering the low concentration of the intermediates and the mass transfer required for catalyst and substrate species, a catalytic system with synergistic ligand and surfactant properties had to be identified. A precise characterization of relevant ligand features, process parameters, the role of glucose and the characteristics of the external, internal and on-surface processes of the catalytic transformations under micellar aqueous conditions is subject of our current investigation.

## Experimental Section

To a solution of 2-bromoiodobenzene (5.00 g, 17.7 mmol) in 2 wt.% aqueous TPGS-750-M (75.0 mL) were added 0.2 mol % CataCXium A Pd G3 (25.7 mg, 35.4  $\mu$ mol), 5 mol% glucose (159 mg, 884  $\mu$ mol), THF (11.2 mL) and 3-butynol (1.49 g, 21.2 mmol). The mixture was stirred for 5 min at RT and Et<sub>3</sub>N (7.35 mL, 53.0 mmol) was added. The reaction was stirred for 22 h at 45 °C and extracted with EtOAc (50 mL, 25 mL). The combined organic layers were washed with brine (50 mL), dried over Na<sub>2</sub>SO<sub>4</sub> and then concentrated *in vacuo*. The residue was purified by column chromatography (MTBE/heptane, 5:1) to give a yellowish oil (3.52 g, 88%). *R*<sub>f</sub> 0.49 (heptane – MTBE/heptane 5:1); *v*<sub>max</sub> (neat) 3402w, 2886m, 1740w, 1540w, 1470s, 1440m, 1340w, 1096m, 1045s, 849m, 752s; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>):  $\delta$  = 7.67 (1H, dd, <sup>3</sup>*J* 7.7 Hz, <sup>4</sup>*J* 1.7 Hz, C3H), 7.51 (1H, dd, <sup>3</sup>*J* 8.0 Hz, <sup>4</sup>*J* 1.1 Hz, C6H), 7.37 (1H, dt, <sup>3</sup>*J* 7.5 Hz, <sup>4</sup>*J* 1.2 Hz, C5H), (1H, dt, <sup>3</sup>*J* 7.9 Hz, <sup>4</sup>*J* 1.8 Hz, C5H), 3.62 (1H, t, <sup>3</sup>*J* 6.9 Hz, C10H), 2.61 (1H, t, <sup>3</sup>*J* 6.9 Hz, C3H), 4.93 (1H, bs, OH); <sup>13</sup>C-NMR (101 MHz, DMSO-*d*<sub>6</sub>):  $\delta$  = 133.8 (C6), 132.7 (C3), 130.1 (C4), 128.1 (C5), 125.4 (C2), 125.0 (C1), 93.9 (C8), 80.1 (C7), 60.1 (C10), 23.9 (C9).

## Supplementary Material

Supporting information for this article is available on the WWW under <http://dx.doi.org/10.1002/MS-number>.

## Acknowledgements

We gratefully acknowledge Novartis AG for financial support and Prof. Dr. Olivier Baudoïn for helpful discussions. C.S. gratefully thanks the Swiss National Science Foundation (BSSGI0-155902/1), the University of Basel, and the NCCR Molecular Systems Engineering.

## Author Contribution Statement

M.J., F.G., C.S. and M.P. conceived this work, designed the experiments, discussed the results and wrote the manuscript. M.J. performed the experiments described in this manuscript.

## References

- [1] H. C. Shen, 'Selected Applications of Transition Metal-Catalyzed Carbon–Carbon Cross-Coupling Reactions in the Pharmaceutical Industry' in *Applications of Transition Metal Catalysis in Drug Discovery and Development*; Crawley, M. L., Trost, B. M., Eds.; John Wiley&Sons, Inc.: Hoboken, NJ, **2012**; pp 25–95.
- [2] J. A. Marsden, M. M. Haley, 'Cross - Coupling Reactions to sp Carbon Atoms', in *Metal-Catalyzed Cross-Coupling Reactions, 2nd ed.*; de Meijere, A.; Diederich, F., Eds.; Wiley-VCH: Weinheim, Germany, **2004**; pp 317– 394.
- [3] C. C. C. J. Seechurn, M. O. Kitching, T. J. Colacot, V. Sniekus, 'Palladium-Catalyzed Cross-Coupling, A Historical Contextual Perspective to the 2010 Nobel Prize', *Angew. Chem. Int. Ed.* **2012**, *51*, 5062–5085.
- [4] J. Boström, D. G. Brown, R. J. Young, G. M. Keserü, 'Expanding the medicinal chemistry synthetic toolbox', *Nat. Rev. Drug Discov.* **2018**, *17*, 709–727.
- [5] D. G. Brown, J. Boström, 'Analysis of Past and Present Synthetic Methodologies on Medicinal Chemistry: Where Have All the New Reactions Gone?', *J. Med. Chem.* **2016**, *59*, 4443–4458.
- [6] R. W. Dugger, J. A. Ragan, D. H. Brown Ripin, 'Survey of GMP Bulk Reactions Run in a Research Facility between 1985 and 2002', *Org. Process Res. Dev.* **2005**, *9*, 253–258.
- [7] C. P. Ashcroft, P. J. Dunn, J. D. Hayler, A. S. Wells, 'Survey of Solvent Usage in Papers Published in Organic Process Research & Development 1997–2012', *Org. Process Res. Dev.* **2015**, *19*, 740–747.
- [8] D. Prat, A. Wells, J. Hayler, H. Sneddon, C. R. McElroy, S. Abou-Shehata, P. J. Dunn, 'CHEM21 selection guide of classical- and less classical-solvents', *Green Chem.* **2016**, *18*, 288–296.
- [9] For a comprehensive review, see: L. Bergkamp, N. Herbatschek, 'Regulating chemical substances under REACH: the choice between authorization and restriction and the case of dipolar aprotic solvents', *Rev. Euro. Comp. Int. Env. Law* **2014**, *23*, 221–245.
- [10] P. T. Anastas, J.C. Warner, *Green Chemistry : Theory and Practice*. **2014**, Oxford: Oxford University Press.
- [11] C. A. Fleckenstein, H. Plenio, 'Aqueous/Organic Cross Coupling: Sustainable Protocol for Sonogashira Reactions of Heterocycles', *Green Chem.* **2008**, *10*, 563–570.

- [12] Y. He, C. Cai, 'Heterogeneous copper-free Sonogashira coupling reaction catalyzed by a reusable palladium Schiff base complex in water', *J. Organomet. Chem.* **2011**, *696*, 2689–2692.
- [13] F. Gallou, N. A. Isley, A. Ganic, U. Onken, M. Parmentier, 'Surfactant Technology Applied Toward an Active Pharmaceutical Ingredient: More than a Simple Green Chemistry Advance', *Green Chem.* **2016**, *18*, 14–19.
- [14] M. Parmentier, C. M. Gabriel, P. Guo, N. A. Isley, J. Zhou, F. Gallou, 'Switching from organic solvents to water at an industrial scale', *Curr. Opin. Green Sustain. Chem.* **2017**, *7*, 13 – 17.
- [15] F. Gallou, P. Guo, M. Parmentier, J. Zhou, 'A General and Practical Alternative to Polar Aprotic Solvents Exemplified on an Amide Bond Formation', *Org. Process Res. Dev.* **2016**, *20*, 1388–1391.
- [16] B. H. Lipshutz, D. W. Chung, B. Rich, 'Sonogashira Couplings of Aryl Bromides: Room Temperature, Water Only, No Copper', *Org. Lett.* **2008**, *10*, 3793–3796.
- [17] C. M. Gabriel, N. R. Lee, F. Bigorne, P. Klumphu, M. Parmentier, F. Gallou, B. H. Lipshutz, 'Effects of Co-solvents on Reactions Run under Micellar Catalysis Conditions', *Org. Lett.* **2017**, *19*, 194–197 and references cited therein.
- [18] S. Handa, J. D. Smith, Y. Zhang, B. S. Takale, F. Gallou, B. H. Lipshutz, 'Sustainable HandaPhos-ppm Palladium Technology for Copper-Free Sonogashira Couplings in Water under Mild Conditions', *Org. Lett.* **2018**, *20*, 542–545.
- [19] M. Bollenbach, P. Wagner, P. G. V. Aquino, J.-J. Bourguignon, F. Bihel, C. Salomé, M. Schmitt, 'D-Glucose: An Efficient Reducing Agent for a Copper(II)-Mediated Arylation of Primary Amines in Water', *ChemSusChem* **2016**, *9*, 3244–3249.
- [20] J. E. Camp, J. J. Dunsford, E. P. Cannons, W. J. Restorick, A. Gadzhieva, M. W. Fay, R. J. Smith, 'Glucose-Derived Palladium(0) Nanoparticles as in Situ-Formed Catalysts for Suzuki-Miyaura Cross-Coupling Reactions in Isopropanol', *ACS Sust. Chem. Eng.* **2014**, *2*, 500–505.
- [21] Further details are provided in the Supporting Information of this manuscript.
- [22] M. Parmentier, M. K. Wagner, K. Magra, F. Gallou, 'Selective Amidation of Unprotected Amino Alcohols Using Surfactant-in-Water Technology: A Highly Desirable Alternative to Reprotoxic Polar Aprotic Solvents', *Org. Process Res. Dev.* **2016**, *2*, 1104–1107.
- [23] B. H. Lipshutz, N. A. Isley, J. C. Fennewald, E. D. Slack, 'On the Way Towards Greener Transition-Metal-Catalyzed Processes as Quantified by E Factors', *Angew. Chem. Int. Ed.* **2013**, *52*, 10952–10958, and references cited therein.
- [24] For an overview of various metrics, see: F. Roschangar, R. A. Sheldon, C. H. Senanayake, 'Overcoming barriers to green chemistry in the pharmaceutical industry – the Green Aspiration Level concept', *Green Chem.* **2015**, *17*, 752–768.
- [25] C. Jimenez-Gonzalez, C. S. Ponder, Q. B. Broxterman, J. B. Manley, 'Using the Right Green Yardstick: Why Process Mass Intensity Is Used in the Pharmaceutical Industry To Drive More Sustainable Processes', *Org. Process Res. Dev.* **2011**, *15*, 912–917.

### Entry for the Table of Contents

