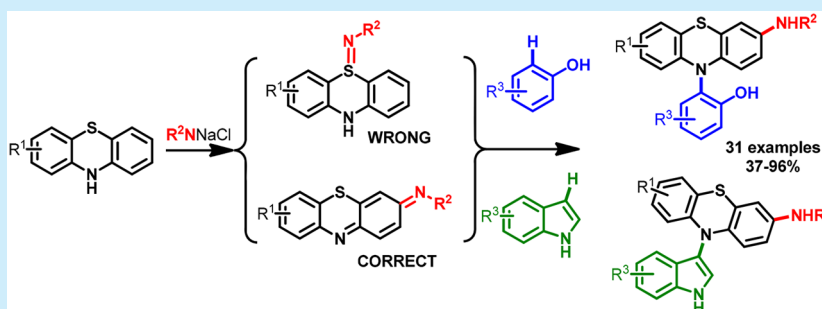


Phenothiazinimides: Atom-Efficient Electrophilic Amination Reagents

Rongwei Jin,[‡] Christina L. Bub,[‡] and Frederic W. Patureau*[§]

Fachbereich Chemie, Technische Universität Kaiserslautern, Erwin-Schrödinger Strasse Geb. 52, 67663 Kaiserslautern, Germany

S Supporting Information



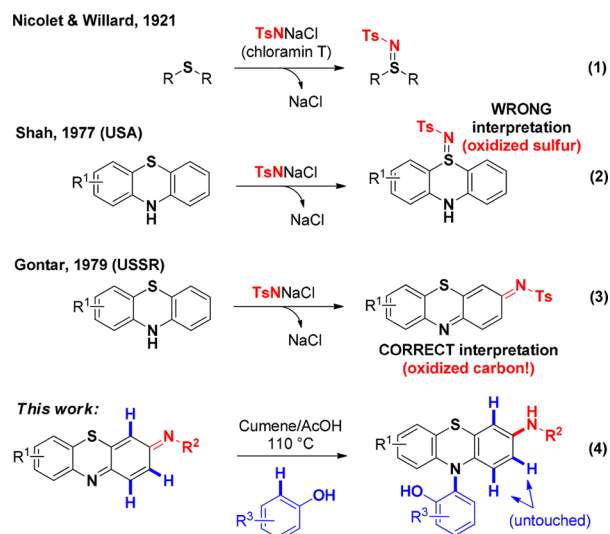
ABSTRACT: Phenothiazinimides, a fairly unknown class of imines, were prepared and found to be very reactive as ultrasimple atom-efficient electrophilic amination reagents for phenols and indoles under metal-free conditions.

“Linkages of the type C–X–C are much easier to make than direct C–C linkages. So why not focus on them?”¹

Chloramines are arguably underappreciated as convenient and relatively sustainable nitrene sources (NaCl as sole byproduct), in particular, for metal-free synthetic methods. The action of chloramine T and related trivial chloramines on thioethers has been known to deliver sulfimides since the pioneering work of Nicolet and Willard in 1921.² Their protocol is very general—sulfur is quite sensitive to nitrene oxidation—and is still utilized nowadays to prepare sulfimides in a single step.³ In 1977, Shah utilized this method to prepare what he thought to be sulfimide–phenothiazines.⁴ Shah’s claim lies solely on an IR band at 920 cm^{-1} , which he attributes to the sulfimide S=N double bond. In 1979, however, Gontar claimed that Shah’s structure could not be correct because of the absence of NH band in the IR spectrum.⁵ Gontar proposed, instead, a carbon-based phenothiazinimide interpretation (Scheme 1). In any case, these compounds are generally very insoluble, and the broadness of the NMR lines forbids a decisive interpretation as to the one structure or the other, or possibly a mixture thereof. In this paper, the reactivity of phenothiazinimides is described for the first time and thus lifts this structural ambiguity, surprisingly, in favor of Gontar’s interpretation (Schemes 1–4).

In the frame of our research interests for the development of ultrasimple direct C–H amination methods,⁶ we decided to investigate the unexplored reactivity of those phenothiazinimides, in particular, as electrophilic amination reagents.⁷ In this context, the intermolecular direct amination of C–H bonds remains a considerable challenge. Indeed, the vast majority of intermolecular C–N bond-forming coupling reactions still operate via prior preactivation of the substrates and usually through precious metal catalysis (Ullmann condensation, Buchwald–Hartwig amination).⁸ To this end, we first prepared

Scheme 1. Sulfimides and Phenothiazinimides



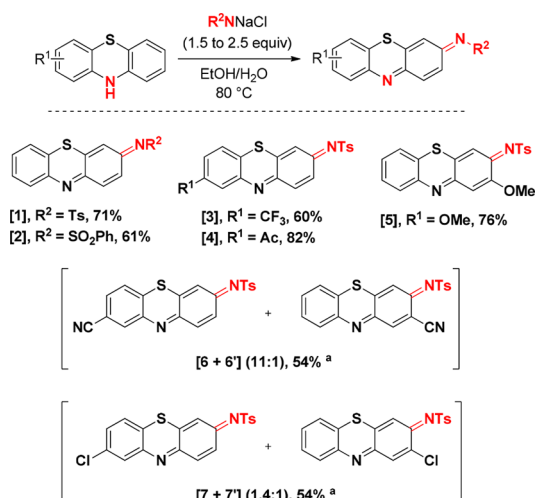
a series of phenothiazinimides according to Shah’s protocol (Scheme 2). As expected, in the case of unsymmetrical phenothiazines (PTZs), the imide is formed preferentially on the more electron-rich side. In most cases, the regioselectivity is excellent (Scheme 2).

We then devised an intrinsically sustainable, ultrasimple, metal-free, atom-efficient condensation method with phenol-coupling partners. The phenothiazinimide (1 mmol) is typically placed in a 180 mL reactor with 3 mmol of phenol-coupling

Received: March 20, 2018

Published: April 27, 2018

Scheme 2. Phenothiazinimides Synthesis, All Compounds Are Isolated by Precipitation as Deep Purple Poorly Soluble Substances



^aRatios of [6]/[6'] and [7]/[7'] were determined a posteriori from the more soluble coupling products [29]/[29'] and [30]/[30'].

partner. Cumene (2.5 mL) and acetic acid (0.5 mL) are then added, the reactor is flushed with O₂, and the reaction is then stirred at 110 °C for 16 h. During the first hours of the reaction, the deep purple suspension typically and progressively turns to a clear light blue or light pink solution.

A new coupling product is thereby obtained that is fortunately more soluble and that we solved by a combination of COSY, NOESY, and natural abundance ¹H–¹⁵N HMBC NMR characterization techniques (crystallization attempts have been unsuccessful so far, Figure 1).⁹ Importantly, control experiments

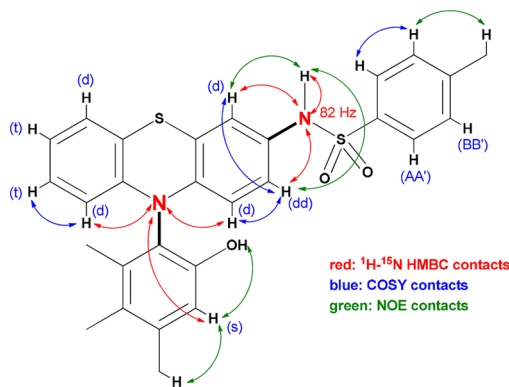
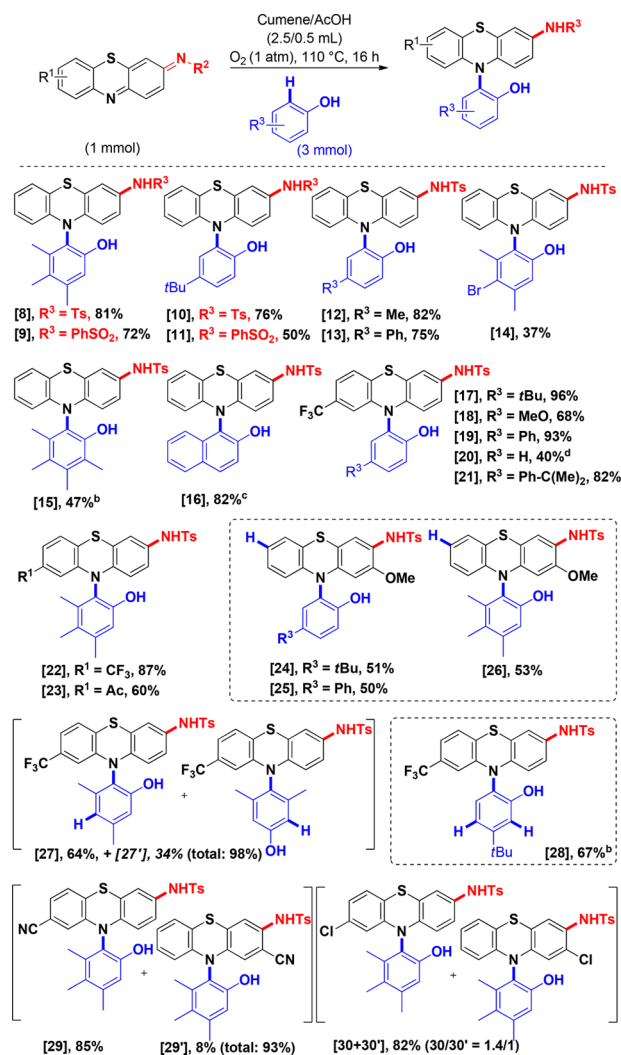


Figure 1. COSY, NOESY, and ¹H–¹⁵N HMBC NMR structural resolution of coupling product [8].⁹

showed that the O₂ atmosphere is not necessary—the reaction is formally redox neutral—however, it affords higher yields of product compared to inert N₂ atmospheric conditions (see mechanistic discussion).

We next explored the substrate scope of the reaction. Gratifyingly, as long as phenols and phenothiazinimides are involved, a good number of functional groups are tolerated (methoxy, halide, ketone, nitrile, CF₃, naphthol, and more, see Scheme 3). We also verified that the *N*-tosyl group of the phenothiazinimide could be replaced by an *N*-benzenesulfonyl group. This is indeed the case, although lower yields are then

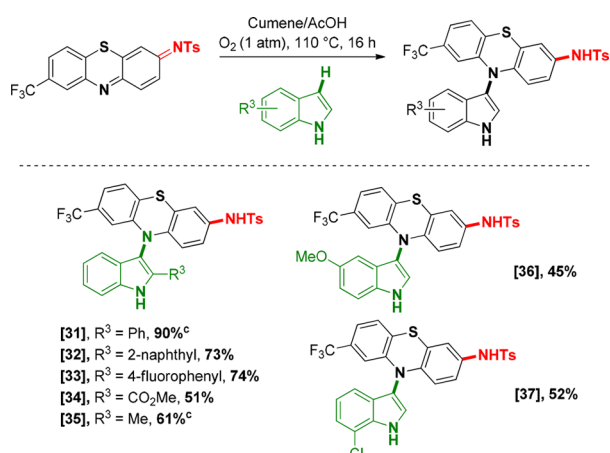
Scheme 3. Phenol Substrate Scope^a



^aIsolated yields. ^b0.5 mmol scale. ^c90 °C reaction temperature. ^dVery minor *para* isomer lost during purification; see also entry [27] for *ortho/para* relative reactivity/selectivity.

typically obtained ([9], [11]). It should be noted that in the case of competing *ortho* and *para* C–H positions very poor regioselectivity is typically observed. For example, 3,5-dimethylphenol affords the *ortho*-aminated product [27] (64%) and the *para*-aminated product [27'] (34%) in a close to statistical ratio. Strong steric repulsion, however, such as in 3-*t*Bu-phenol, afforded a single regioisomeric amination product [28] in 67% yield. In order to explore the applicability of this new electrophilic amination reagent, we then investigated other nucleophilic substrate classes. Gratifyingly, it was found that unprotected indoles are often competent substrates in this reaction, affording typically C3-aminated coupling products in moderate to good yields (Scheme 4). In general, C2-functionalized indoles performed best (for example, [31], 90%). Moreover, even unprotected sensitive indoles afforded the C3-aminated coupling product in encouraging 45–52% yields ([36], [37]). No coupling product occurred, however, with structurally related benzofuran or benzothiophene. The reaction is thus highly specific to phenols and indoles.

We then performed a number of essential mechanistic experiments. We first prepared phenothiazone [38], a

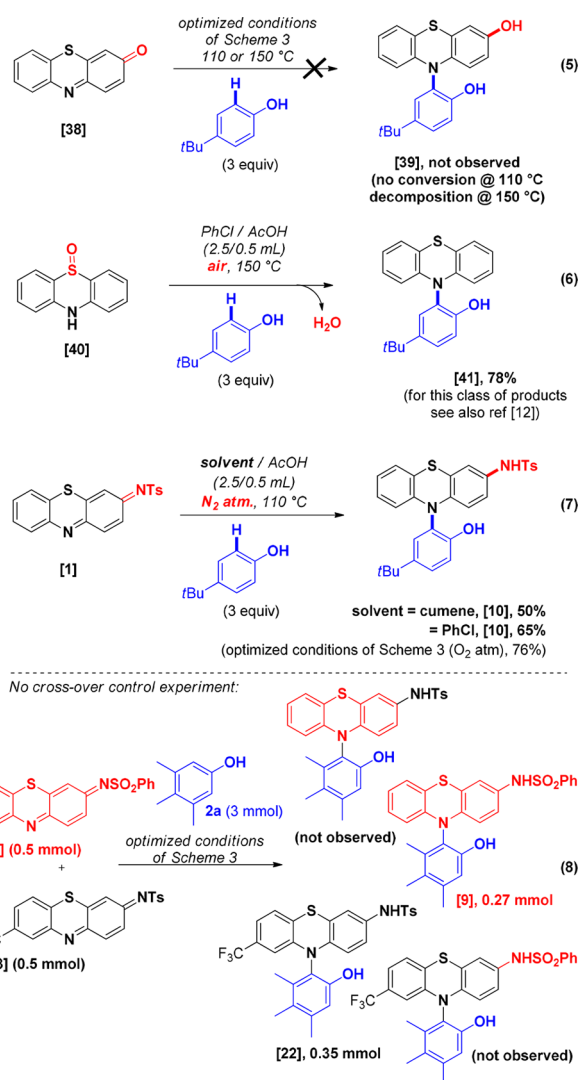
Scheme 4. Indole Substrate Scope^{a,b}

^aIsolated yields. ^b0.5 mmol scale. ^c1 mmol scale.

compound found in the literature.¹⁰ The corresponding condensation product [39] could not be detected. Indeed, no conversion occurred at 110 °C. Increasing the reaction temperature to 150 °C did not yield any expected product either (eq 5, Scheme 5). In contrast, a second control experiment starting with the parent *S*-oxide phenothiazine substrate [40], also a well-known material,¹¹ led to the formation of the known C–N coupling product [41] in which the oxygen atom is not retained (H₂O as leaving group, internal oxidant concept,¹³ eq 6). Some further control experiments (eq 7) show that the reaction also works under strict N₂ atmosphere, albeit with lower yields, thereby proving the internal oxidant character of phenothiazinimides.⁹ Thus, in spite of the formal redox-neutral character of this new C–N bond-forming reaction, utilizing a mild oxidative atmosphere in combination with cumene is useful for maintaining the phenothiazinimide in its oxidized electrophilic active form. Indeed, the cumene/acetic acid/O₂ (re)-oxidizing system has been exemplified by us in a previous method wherein the cumene and its oxidized forms (i.e., cumyl hydroperoxide) may play an active role in radical oxidation processes.^{12a} Moreover, the acetic acid cosolvent may increase the electrophilic character of the phenothiazinimide through H-bonding and/or partial protonation. It should in addition be noted that the reduced phenothiazinimide, i.e., [(1)H₂], is sometimes observed as an undesired byproduct when the oxygen atmosphere is omitted and/or when the arene-coupling partner is not sufficiently nucleophilic (i.e., very electron-poor/acidic phenols).

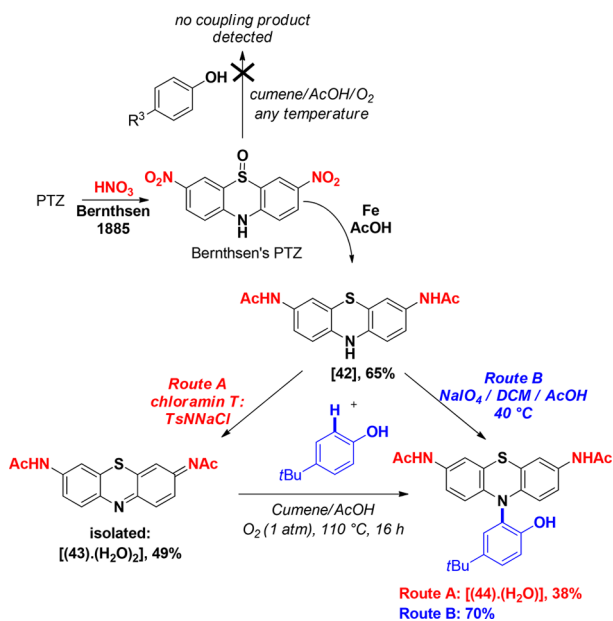
Finally, a cross-over control experiment between substrates [2] and [3], based on two different PTZ backbones and two different chloramines, was attempted (eq 8). Out of the four potential products, only the two noncrossed products [9] and [22] were obtained. Thus, no imine crossover event occurs in this reaction, which arguably constitutes another argument against Shah's structure and in favor of Gontar's. Indeed, Shah's substrate would have involved a 1,4 nitrene sulfur-to-carbon migration, a relatively long distance migration, which might therefore have been susceptible to crossover scrambling. In order to better understand and further confirm the Gontar phenothiazinimide structural interpretation, we then envisioned a different synthetic route. We started from Bernthsen's PTZ, known since 1885 and prepared by nitration of ordinary PTZ.¹⁴ Conversely, we were so far unsuccessful at utilizing Bernthsen's

Scheme 5. Control/Mechanistic Experiments



PTZ as an electrophilic coupling partner of any kind. Further reduction with Fe⁰ in acetic acid affords the corresponding bis-acetamidophenothiazine [42] (Scheme 6). The latter compound is then oxidized with chloramine T to the corresponding acetylated phenothiazinimide [43].⁹ It should be noted that, in this case, the tosylonitrene moiety does not insert into the substrate and functions solely as an external oxidant. Acetylated phenothiazinimide [43] was found to be a competent electrophilic amination reagent, albeit with moderate yield ([44], 38% yield). Gratifyingly, conducting the reaction in a single step from the bis-acetamidophenothiazine [42] in combination with a strong oxidant such as NaIO₄ (route B, Scheme 6)¹⁵ afforded [44] in 70% yield.

In summary, we solved the 40-year-old disputed structural assignment of phenothiazinimides and validated Gontar's proposal as the dominant species, in which the sulfur atom remains surprisingly unoxidized.¹⁶ We moreover demonstrated the strong electrophilic amination reactivity of those compounds toward phenols and indoles. We expect these new electrophilic amination reagents to impact first the field of phenothiazine centered material synthesis.¹⁷ Moreover, we expect this method to consolidate the intermolecular metal-free C–H oxidative phenothiazination toolbox.⁶

Scheme 6. Alternative Route to the Phenothiazinimide⁹

■ ASSOCIATED CONTENT

S Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b00914.

Experimental procedures and characterization of new compounds (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: patureau@chemie.uni-kl.de.

ORCID

Frederic W. Patureau: 0000-0002-4693-7240

Author Contributions

‡R.J. and C.L.B. contributed equally.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by the DFG-funded Transregional Collaborative Research Center SFB/TRR 88 “Cooperative effects in homo and heterometallic complexes” (<http://3MET.de>), DFG-funded project PA 2395/2-1, COST Action CA15106 (CHAOS), and since March 2017: by ERC project 716136: “2O2ACTIVATION”. We are also thankful to Dr. Alaleh Malekafzali (TU Kaiserslautern) for occasional control experiments in parallel to her research project. Tobias Jost, Patrick Gaß, Benedict Wyrwol, and Ben Teichmann (all from TU Kaiserslautern) are acknowledged for short internships in the group.

■ REFERENCES

- (1) Quote assembled from several sentences in: (a) Ball, P. The click concept. *Chemistry World (RCS)* **2007**, 47. See also: (b) Kolb, H. C.; Finn, M. G.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2001**, 40, 2004. (c) Meldal, M.; Tormøe, C. W. *Chem. Rev.* **2008**, 108, 2952. (d) Worrell, B. T.; Malik, J. A.; Fokin, V. V. *Science* **2013**, 340, 457.
- (2) Nicolet, B. H.; Willard, I. D. *Science* **1921**, 53, 217.

- (3) Selected references: (a) Campbell, M. M.; Johnson, G. *Chem. Rev.* **1978**, 78, 65. (b) Minakata, S. *Acc. Chem. Res.* **2009**, 42, 1172.

- (4) Shah, J. J. *Tennessee Acad. Sci.* **1977**, 52, 19.
- (5) Gontar, S. S.; Karpishchenko, L. S.; Kremlev, M. M.; Markov, V. I. *Russ. J. Org. Chem.* **1978**, 14, 2626.

- (6) Selected reviews on oxidative C–H aminations: (a) Kim, H.; Chang, S. *ACS Catal.* **2016**, 6, 2341. (b) Jiao, J.; Murakami, K.; Itami, K. *ACS Catal.* **2016**, 6, 610. (c) Louillat, M.-L.; Patureau, F. W. *Chem. Soc. Rev.* **2014**, 43, 901. (d) Cho, S. H.; Kim, J. Y.; Kwak, J.; Chang, S. *Chem. Soc. Rev.* **2011**, 40, 5068. (e) Dick, A. R.; Sanford, M. S. *Tetrahedron* **2006**, 62, 2439. See also electrochemical C–H aminations, for example: (f) Waldvogel, S. R.; Möhle, S. *Angew. Chem., Int. Ed.* **2015**, 54, 6398. (g) Morofuji, T.; Shimizu, A.; Yoshida, J.-I. *J. Am. Chem. Soc.* **2015**, 137, 9816.

- (7) For a recent illustration of imino-quinone derived N-electrophile, see: Raju, S.; Annamalai, P.; Chen, P.-L.; Liu, Y.-H.; Chuang, S.-C. *Org. Lett.* **2017**, 19, 4134.

- (8) (a) Surry, D. S.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2008**, 47, 6338. (b) Hartwig, J. F. *Acc. Chem. Res.* **2008**, 41, 1534 and references cited therein.

- (9) See the SI for details.

- (10) Phenothiazone synthesis. See, for example: Barret, R.; Daudon, M. *Monatsh. Chem.* **1991**, 122, 323.

- (11) Sulfoxide–phenothiazine synthesis. See, for example: Kano, H.; Fujimoto, M. *Pharm. Bull.* **1957**, 5, 389.

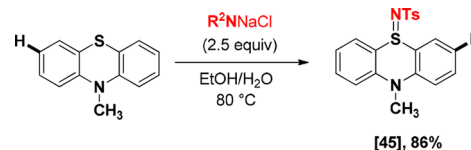
- (12) (a) Louillat-Habermeyer, M.-L.; Jin, R.; Patureau, F. W. *Angew. Chem., Int. Ed.* **2015**, 54, 4102. (b) Zhao, Y.; Huang, B.; Yang, C.; Xia, W. *Org. Lett.* **2016**, 18, 3326.

- (13) Internal oxidant concept. See, for example: Patureau, F. W.; Glorius, F. *Angew. Chem., Int. Ed.* **2011**, 50, 1977.

- (14) Bernthsen, A. *Annalen der Chemie* **1885**, 230, 73.

- (15) Jin, R.; Patureau, F. W. *Org. Lett.* **2016**, 18, 4491.

- (16) However, when the nitrogen atom is protected, Shah’s proposed structure remains valid (see the SI):



- (17) N-Functionalized PTZs are of crucial importance for material sciences, notably as photocatalysts, as electroluminescent organic semiconductors for OLED devices, or as hole-transporting compounds for solar cells. Their efficient synthesis is thus of strategic importance. See, for example: (a) Pan, X.; Lamson, M.; Yan, J.; Matyjaszewski, K. *ACS Macro Lett.* **2015**, 4, 192. (b) Pan, X.; Fang, C.; Fantin, M.; Malhotra, N.; So, W. Y.; Peteanu, L. A.; Isse, A. A.; Gennaro, A.; Liu, P.; Matyjaszewski, K. *J. Am. Chem. Soc.* **2016**, 138, 2411. (c) Treat, N. J.; Sprafke, H.; Kramer, J. W.; Clark, P. G.; Barton, B. E.; Read de Alaniz, J.; Fors, B. P.; Hawker, C. J. *J. Am. Chem. Soc.* **2014**, 136, 16096. (d) Salunke, J. K.; Wong, F. L.; Feron, K.; Manzhos, S.; Lo, M. F.; Shinde, D.; Patil, A.; Lee, C. S.; Roy, V. A. L.; Sonar, P.; Wadgaonkar, P. *J. Mater. Chem. C* **2016**, 4, 1009. (e) Kumar, S.; Singh, M.; Jou, J.-H.; Ghosh, S. *J. Mater. Chem. C* **2016**, 4, 6769. (f) Grisorio, R.; Roose, B.; Colella, S.; Listorti, A.; Suranna, G. P.; Abate, A. *ACS Energy Lett.* **2017**, 2, 1029. (g) Shinde, D. B.; Salunke, J. K.; Candeias, N. R.; Tinti, F.; Gazzano, M.; Wadgaonkar, P. P.; Priimagi, A.; Camaioni, N.; Vivo, P. *Sci. Rep.* **2017**, 7, 46268.