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Oxyarylation and Aminoarylation of Styrenes Using Photoredox Catalysis

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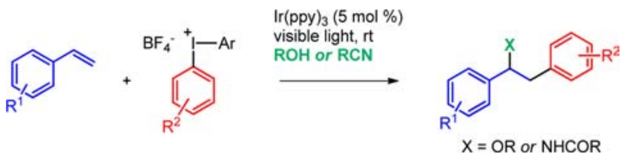
ABSTRACT



A three-component coupling of styrenes is reported, using photoredox catalysis to achieve simultaneous arylation and C–O or C–N bond formation across the styrene double bond.

Photoredox catalysis (PRC) is receiving renewed attention as a powerful method for organic synthesis under mild conditions, with impressively broad application across diverse reaction types.[1,2] Using readily available visible light sources, transition metal complexes or organic dyes are photoactivated to mediate electron transfer to organic substrates. The resulting radical cation and anion intermediates offer lower energy pathways for bond formation, enabling both the discovery of new reactions and the enhancement of classical transformations *via* improved reaction conditions. Application of PRC to [2 + 2] and [4 + 2] photocycloadditions, for example, removes the need for specialized glassware and powerful UV light sources.[3] Excitation of the photoredox catalyst is highly selective, with colorless organic substrates generally being inert to photoexcitation by visible light. As a result, deleterious radical side reactions can be avoided, widening the substrate scope and improving yields.

Photoredox-catalyzed arylation, in particular, has created new approaches to the controlled incorporation of aryl and heteroaryl moieties.[4,5] Proceeding through aryl radicals, as opposed to the aryl organometallics typical of modern arylation reactions, photoredox-catalyzed arylation opens up different and complementary reaction manifolds. Importantly, the PRC approach enables highly reactive aryl radicals to be harnessed in intermolecular couplings, a difficult transformation to achieve using conventional radical-generating methods.

We envisaged that the mild conditions typical of PRC could enable the arylative functionalization of styrenes, **1** (Scheme 1). Styrenes are fundamental building blocks in

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(1) Reviews: (a) Tucker, J. W.; Stephenson, C. R. J. *J. Org. Chem.* **2012**, *77*, 1617. (b) Narayanam, J. M. R.; Stephenson, C. R. J. *Chem. Soc. Rev.* **2011**, *40*, 102. (c) Zeitler, K. *Angew. Chem., Int. Ed.* **2009**, *48*, 9785. (d) Yoon, T. P.; Ischay, M. A.; Du, J. N. *Nat. Chem* **2010**, *2*, 527.

(2) Selected recent examples: (a) Nagib, D. A.; MacMillan, D. W. C. *Nature* **2011**, *480*, 224. (b) Nguyen, J. D.; Tucker, J. W.; Konieczynska, M. D.; Stephenson, C. R. J. *J. Am. Chem. Soc.* **2011**, *133*, 4160. (c) Zou, Y. Q.; Chen, J. R.; Liu, X. P.; Lu, L. Q.; Davis, R. L.; Jorgensen, K. A.; Xiao, W. J. *Angew. Chem., Int. Ed.* **2012**, *51*, 784. (d) Tucker, J. W.; Zhang, Y.; Jamison, T. F.; Stephenson, C. R. J. *Angew. Chem., Int. Ed.* **2012**, *51*, 4144. (e) Cai, S. Y.; Zhao, X. Y.; Wang, X. B.; Liu, Q. S.; Li, Z. G.; Wang, D. Z. G. *Angew. Chem., Int. Ed.* **2012**, *51*, 8050. (f) Yasu, Y.; Koike, T.; Akita, M. *Angew. Chem., Int. Ed.* **2012**, *51*, 9567. (g) Lu, Z.; Yoon, T. P. *Angew. Chem., Int. Ed.* **2012**, *51*, 10329. (h) Kim, H.; Lee, C. *Angew. Chem., Int. Ed.* **2012**, *51*, 12303. (i) Miyake, Y.; Nakajima, K.; Nishibayashi, Y. *J. Am. Chem. Soc.* **2012**, *134*, 3338. (k) DiRocco, D. A.; Rovis, T. *J. Am. Chem. Soc.* **2012**, *134*, 8094. (l) Wallentin, C. J.; Nguyen, J. D.; Finkbeiner, P.; Stephenson, C. R. J. *J. Am. Chem. Soc.* **2012**, *134*, 8875. (m) Ye, Y. D.; Sanford, M. S. *J. Am. Chem. Soc.* **2012**, *134*, 9034. (n) Grandjean, J. M. M.; Nicewicz, D. A. *Angew. Chem., Int. Ed.* **2013**, *52*, 3967. (o) Zhu, S. Q.; Das, A.; Bui, L.; Zhou, H. J.; Curran, D. P.; Rueping, M. *J. Am. Chem. Soc.* **2013**, *135*, 1823. (p) Mizuta, S.; Engle, K. M.; Verhoog, S.; Galicia-Lopez, O.; O'Duill, M.; Medebielle, M.; Wheelhouse, K.; Rassias, G.; Thompson, A. L.; Gouverneur, V. *Org. Lett.* **2013**, *15*, 1250. (q) Yasu, Y.; Koike, T.; Akita, M. *Org. Lett.* **2013**, *15*, 2136.

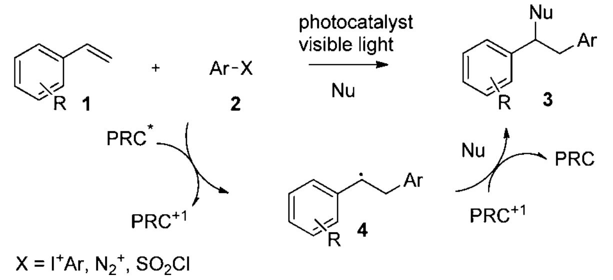
(3) (a) Du, J.; Yoon, T. P. *J. Am. Chem. Soc.* **2009**, *131*, 14604. (b) Lin, S. S.; Ischay, M. A.; Fry, C. G.; Yoon, T. P. *J. Am. Chem. Soc.* **2011**, *133*, 19350. (c) Lu, Z.; Yoon, T. P. *Angew. Chem., Int. Ed.* **2012**, *51*, 10329.

(4) Seminal work on PRC arylation: (a) Cano-Yelo, H.; Deronzier, A. *J. Chem. Soc., Faraday Trans. 1* **1984**, *80*, 3011. (b) Cano-Yelo, H.; Deronzier, A. *J. Chem. Soc., Perkin Trans. 2* **1984**, 1093. (c) Cano-Yelo, H.; Deronzier, A. *Tetrahedron Lett.* **1984**, *25*, 5517. (d) Hamada, T.; Ishida, H.; Usui, S.; Watanabe, Y.; Tsumura, K.; Ohkubo, K. *Chem. Commun.* **1993**, 909.

10.1021/ol401940c

organic and materials chemistry, whose functionalization is hindered by facile polymerization under acidic, basic, or UV photochemical conditions. If PRC could be used to generate aryl radicals from a suitable precursor (**2**), at ambient temperature under neutral conditions, it might be possible to capture the styrene double bond to give **4**, avoiding the undesired polymerization pathway. Oxidation of **4** to close the PRC cycle would then generate a benzylic cation for a second C−X bond forming step with a nucleophile. The resultant three-component coupling would create diverse, doubly functionalized phenylethyl scaffolds that would see broad application in synthesis.

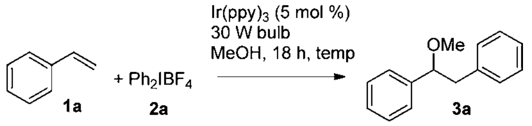
Scheme 1. Proposed Three-Component Coupling of Styrenes



Three-component coupling reactions of styrenes and arenes are rare.[6] Lloyd-Jones and co-workers described a gold-catalyzed methoxarylation of styrenes with aryl silanes in the presence of an iodine(III) oxidant.[7] They observed that oxyarylation systems using Selectfluor,[8,9] previously successful with alkenes, failed with styrenes, reflecting the difficulties in capturing these reactive substrates in simultaneous C−C and C−X bond coupling.[10] Multistep hydroxyarylation was achieved by Studer and co-workers using a diazonium salt with a stoichiometric amount of TEMPO/Na.[11] Subsequent zinc mediated reduction was then required to cleave the TEMP group and produce the hydroxyarylated products.

We began by screening photoredox catalysts for the reaction of styrene (1 equiv) with diphenyliodonium tetrafluoroborate (2 equiv) in degassed methanol, using a 30 W domestic light bulb (Table 1). While organic dye PRCs (< 5%) and $Ru(bpy)_3Cl_2$ (12%) were largely ineffective (see Supporting Information), we were encouraged to observe that $Ir(ppy)_3$ did effect methoxyarylation, albeit in a modest 27% yield (entry 1). A significant increase in yield was obtained using the iodonium salt as the limiting reagent, with a 5-fold excess of the cheaper and easily accessible styrene reagent affording **3a** in 51% yield (entry 2). Raising the temperature did not lead to significant improvements, with similar yields recorded at 40 °C, 60 °C, and room temperature (entries 4 and 5).

Table 1. Reaction Optimization



entry	temp (°C)	additive (20 mol %)	yield (%)[a]
1[b]	rt	–	27
2[c]	rt	–	51
3[d]	rt	–	32
4	40	–	55
5	60	–	45
6[e]	40	–	50
7	rt	$Zn(OAc)_2$	70
8[f]	rt	$Zn(OAc)_2$	69
9[g]	rt	$Zn(OAc)_2$	0
10[h]	rt	$Zn(OAc)_2$	<5
11[i]	100	$Zn(OAc)_2$	0

[a] Isolated yields. [b] Reaction conditions: styrene (1 equiv), Ph_2IBF_4, **2a** (2 equiv), $Ir(ppy)_3$ (5 mol %), methanol (0.17 M), rt for 18 h. [c] 5 equiv of **1a** and 1 equiv of **2a** used (entries 2−11). [d] 1 M concentration. [e] Distilled styrene. [f] $Ir(ppy)_3$ (1 mol %). [g] Irradiated with no $Ir(ppy)_3$. [h] $Ir(ppy)_3$ (1 mol %) but no irradiation. [i] No irradiation and no $Ir(ppy)_3$.

Reactant concentration was important with respect to maintaining the catalyst and reactants in solution, since at 1 M or above the solutions became cloudy and yields dropped (entry 3). Interestingly, the presence of an inhibitor (4-*tert*-butylcatechol) in commercial samples of styrene did not lead to appreciable differences in reaction yield (entry 6). Finally, to enhance the reaction yield we surveyed a variety of additives and found $Zn(OAc)_2$ (20 mol %) to be effective, affording **3a** in 70% yield (entry 7). Importantly, this level of efficiency was maintained with the $Ir(ppy)_3$ loading reduced to 1 mol % (entry 8). Control reactions without a catalyst or light gave no conversion at both rt and 100 °C, indicating that PRC was essential to the methoxyarylation transformation (entries 9−11).

With optimized conditions established for the three-component methoxyarylation, we surveyed a range of styrenes to explore the substrate scope in this component.

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(5) Recent examples: (a) McNally, A.; Prier, C. K.; MacMillan, D. W. C. *Science* **2011**, *334*, 1114. (b) Kalyani, D.; McMurtrey, K. B.; Neufeldt, S. R.; Sanford, M. S. *J. Am. Chem. Soc.* **2011**, *133*, 18566. (c) Hari, D. P.; Schroll, P.; König, B. *J. Am. Chem. Soc.* **2012**, *134*, 2958. (d) Hering, T.; Hari, D. P.; König, B. *J. Org. Chem.* **2012**, *77*, 10347. (e) Neufeldt, S. R.; Sanford, M. S. *Adv. Synth. Catal.* **2012**, *354*, 3517. (f) Nguyen, J. D.; D'Amato, E. M.; Narayanam, J. M. R.; Stephenson, C. R. J. *Nat. Chem.* **2012**, *4*, 854. (g) Wang, Z. Q.; Hu, M.; Huang, X. C.; Gong, L. B.; Xie, Y. X.; Li, J. H. *J. Org. Chem.* **2012**, *77*, 8705. (h) Zhu, S. Q.; Rueping, M. *Chem. Commun.* **2012**, *48*, 11960. (i) Pirnot, M. T.; Rankic, D. A.; Martin, D. B. C.; MacMillan, D. W. C. *Science* **2013**, *339*, 1593. (j) Sahoo, B.; Hopkinson, M. N.; Glorius, F. *J. Am. Chem. Soc.* **2013**, *135*, 5505. (k) Deng, G. B.; Wang, Z. Q.; Xia, J. D.; Qian, P. C.; Song, R. J.; Hu, M.; Gong, L. B.; Li, J. H. *Angew. Chem., Int. Ed.* **2013**, *52*, 1535.

(6) Pathak, T. P.; Gligorich, K. M.; Welm, B. E.; Sigman, M. S. *J. Am. Chem. Soc.* **2010**, *132*, 7870. (b) Satterfield, A. D.; Kubota, A.; Sanford, M. S. *Org. Lett.* **2011**, *13*, 1076. (c) Kalyani, D.; Satterfield, A. D.; Sanford, M. S. *J. Am. Chem. Soc.* **2010**, *132*, 8419.

(7) Ball, L. T.; Lloyd-Jones, G. C.; Russell, C. A. *Chem.—Eur. J.* **2012**, *18*, 2931.

(8) Ball, L. T.; Green, M.; Lloyd-Jones, G. C.; Russell, C. A. *Org. Lett.* **2010**, *12*, 4724.

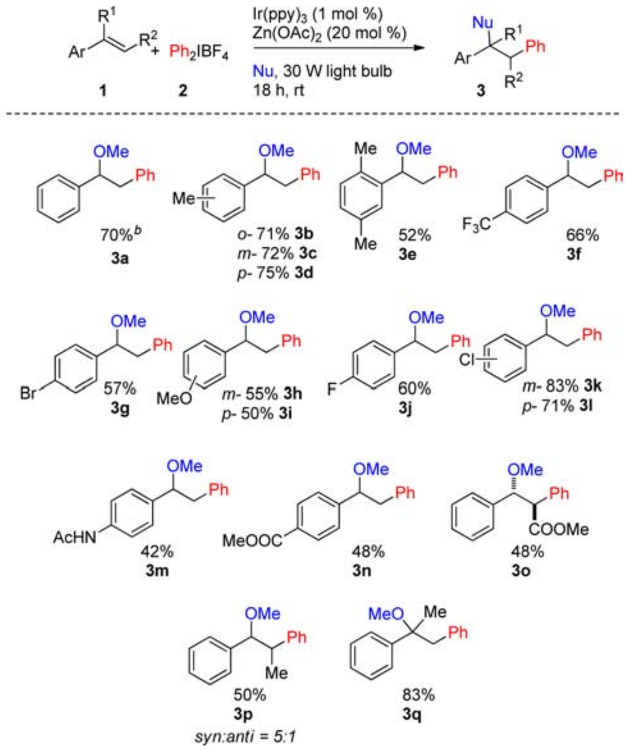
(9) Melhado, A. D.; Brenzovich, W. E.; Lackner, A. D.; Toste, F. D. *J. Am. Chem. Soc.* **2010**, *132*, 8885.

(10) For related studies on alkene oxyarylation and aminoarylation, see: (a) Schultz, D. M.; Wolfe, J. P. *Synthesis* **2012**, 351. (b) Hopkins, B. A.; Wolfe, J. P. *Angew. Chem., Int. Ed.* **2012**, *51*, 9886.

(11) Hartmann, M.; Li, Y.; Studer, A. *J. Am. Chem. Soc.* **2012**, *134*, 16516.

Substitution at the aromatic ring was generally well tolerated across a range of functional groups, both electron donating and withdrawing, with alkyl, trifluoroalkyl, halogen, amide, and ester groups all undergoing successful phenylmethoxyarylation (**3a**−**3n**, Scheme 2). Pleasingly, the reaction was also successful for substituted styrenes. Methyl cinnamate gave a 48% yield of **3o** as a single diastereoisomer, and both α- and *β*-methyl styrenes were productive, the former giving an excellent 83% yield of the tertiary benzylic compound **3q**. Unsuccessful substrates that were screened included simple alkenes such as cyclohexene, vinyl pyridines, and *m*-nitro-substituted styrene, all of which gave no conversion under the reaction conditions.

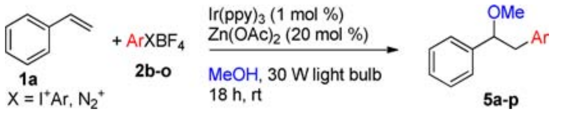
Scheme 2. Styrene Substrate Scope for Methoxyarylation[a]



[a] Isolated yields. [b] Yield is the average of three experiments.

Investigation into the scope of the iodonium species revealed a similarly robust range of functionality (Table 2). Tetrafluoroborates were found to be more effective than the analogous triflate salts,[12] and screening was conducted on this basis. Alkyl, halogen, trifluoromethyl, and ester groups were all well-tolerated (entries 1−12), with a variety of substitution patterns being effective in the reaction. Notably, iodo-substitution on the iodonium salt (**2i**) is tolerated under the photoredox conditions (entry 8), indicating the complementarity of the overall approach with traditional transition metal and radical arylation techniques.

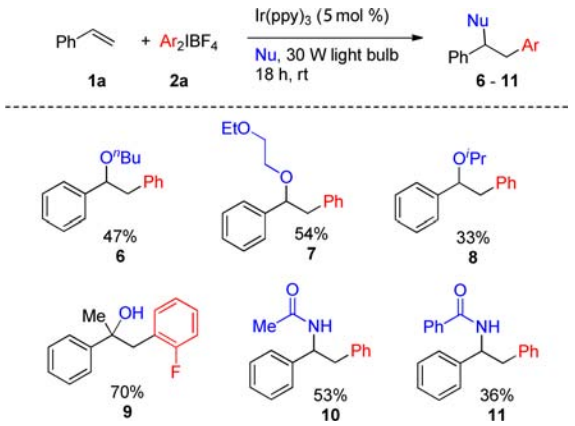
Table 2. Aryl Component Substrate Scope[a]



entry	Ar	compound	yield[a]
1[b]	m-MeC$_6$H$_4$ (**2b**)	**5a**	45%
2[b]	m-,p-(Me)$_2$C$_6$H$_3$ (**2c**)	**5b**	56%
3[b]	o-FC$_6$H$_4$ (**2d**)	**5c**	70%
4[b]	m-FC$_6$H$_4$ (**2e**)	**5d**	61%
5[b]	p-FC$_6$H$_4$ (**2f**)	**5e**	59%
6[b]	p-ClC$_6$H$_4$ (**2g**)	**5f**	50%
7[b]	o-BrC$_6$H$_4$ (**2h**)	**5g**	58%
8[b]	m-IC$_6$H$_4$ (**2i**)	**5h**	68%
9[b]	m-,p-(Cl)$_2$C$_6$H$_3$ (**2j**)	**5i**	71%
10[b]	o-F,p-BrC$_6$H$_3$ (**2k**)	**5j**	65%
11[b]	m-(CF$_3$)C$_6$H$_4$ (**2l**)	**5k**	56%
12[b]	p-(MeO$_2$C)C$_6$H$_4$ (**2m**)	**5l**	81%
13[b]	p-(NHAc)C$_6$H$_4$ (**2n**)	**5m**	25%
14[b]	p-MeOC$_6$H$_4$ (**2o**)	**5n**	27%
15[c]	p-(EtO$_2$C)C$_6$H$_4$ (**2p**)	**5o**	71%
16[c]	p-(NO$_2$)C$_6$H$_4$ (**2q**)	**5p**	45%

[a] Isolated yields. [b] $X = I^+Ar$. [c] $X = N_2^+$.

Scheme 3. Alkoxy- and Aminoarylation



Substitution of electron-donating groups in the *para*-position of the diaryliodonium salt, however, did not prove rewarding, with *p*-NHAc and *p*-MeO returning low yields of methoxyarylated products (entries 13 and 14). We also evaluated diazonium salts in the reaction, as alternative aryl radical precursors, and were pleased to observe successful methoxyarylation of **1a** for p-(EtO$_2$C)C$_6$H$_4$N$_2$BF$_4$ (entry 15) and p-(NO$_2$)-C$_6$H$_4$N$_2$BF$_4$ (entry 16). The complementarity of iodonium and diazonium salts in synthesis has been remarked upon[13] and adds flexibility to the

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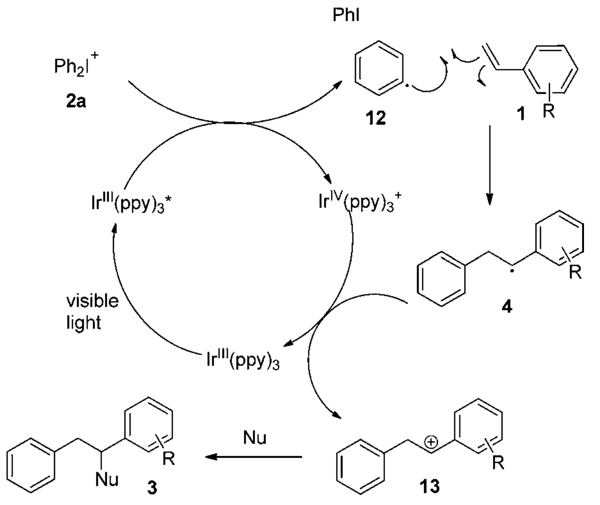
(12) For Cu-catalyzed alkene and alkyne carbofunctionalization using diaryliodonium triflates, see: (a) Phipps, R. J.; McMurray, L.; Ritter, S.; Duong, H. A.; Gaunt, M. J. *J. Am. Chem. Soc.* **2012**, *134*, 10773. (b) Suero, M. G.; Bayle, E. D.; Collins, B. S. L.; Gaunt, M. J. *J. Am. Chem. Soc.* **2013**, *135*, 5332.

(13) Bonin, H.; Fouquet, E.; Felpin, F. X. *Adv. Synth. Catal.* **2011**, *353*, 3063.

(14) Attempted synthesis of bis-4-nitrophenyliodonium tetrafluoroborate according to the Olofsson procedure (Bielawski, M.; Aili, D.; Olofsson, B. *J. Org. Chem.* **2008**, *73*, 4602) was not successful.

Scheme 4. Proposed Reaction Mechanism



current approach in terms of widening the aryl substrate scope. The *p*-NO_2 phenyliodonium tetrafluoroborate salt, for example, could not be readily synthesized in our hands using literature procedures.[14]

We then examined the third component in the reaction, as variation at this position would substantially enhance the scope of the three-component coupling. We could use alternative alcohols in the reaction to afford the ethers **6**, **7**, and **8**, with these reactions being conducted in the absence of $Zn(OAc)_2$ (Scheme 3). Most importantly, we found that water was effective as a nucleophile when used as a cosolvent with THF. The tertiary alcohol **9** was formed in a good 70% yield from α-methylstyrene, with the OH-group available for diverse further functionalizations.

Finally, we explored the scope of Ritter-type reactions to access aminoarylation chemistry. We were pleased to discover the successful formation of the C−N bond using both MeCN and PhCN as solvents in the reaction, accessing the biologically active phenylethylamide scaffolds **10** and **11**, albeit in moderate yields.

A proposed mechanism is outlined in Scheme 4 and involves initial reduction of the iodonium salt **2a** with photoexcited Ir(III)*. The resultant aryl radical is trapped with styrene, present in excess, forming benzylic radical **4** which can be oxidized by Ir(IV) to the cation **13**. Trapping with the appropriate nucleophile then affords the three-component coupled products **3**. The generation of aryl radicals from iodonium salts is known,[15] and their intermediacy was further supported by the observations of TEMPO (2.5 equiv) completely inhibiting the methoxyphenylation of styrene, and degassing of the reaction solvent being necessary for successful reaction. We further trialed $PhI(OAc)_2$ and PhI as aryl sources under the reaction conditions and observed no conversion in either case.

In summary, we have developed a novel three-component, photoredox-catalyzed coupling of styrenes with aryl groups and heteroatom nucleophiles such as alcohols, water, or nitriles. The mild conditions of the reaction allow the reactive styrene moiety to undergo smooth conversion to useful products at ambient temperature, with no polymerization observed under the reaction conditions. The coupling can be extended to diazonium reagents, furthering the range of aryl functionality that may be incorporated into the reaction.

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Supporting Information Available. Optimization tables and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) Lalevee, J.; Blanchard, N.; Tehfe, M. A.; Peter, M.; Morlet-Savary, F.; Fouassier, J. P. *Macromol. Rapid Commun.* **2011**, *32*, 917.

The authors declare no competing financial interest.