Organic LETTERS

Letter

Cite This: Org. Lett. XXXX, XXX, XXX−XXX

pubs.acs.org/OrgLett

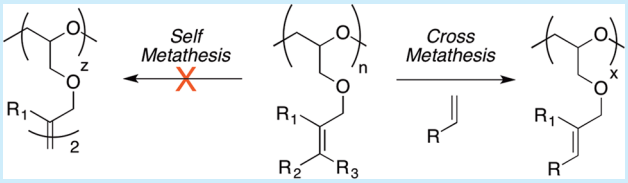
Tailoring Polyethers for Post-polymerization Functionalization by Cross Metathesis

Stephen D. Morrison, Rob M. J. Liskamp, and Joëlle Prunet*

WESTCHEM, School of Chemistry, University of Glasgow, Joseph Black Building, University Avenue, Glasgow G12 8QQ, U.K.

Supporting Information

ABSTRACT: Olefin cross metathesis is reported for the first time to attach small molecules to a range of novel polyethers with a poly(ethylene glycol) backbone and pendent alkene groups, allowing for a loading of up to one compound per monomer unit. These polymers are tailored to prevent the occurrence of self metathesis (reaction of the polymer with itself) by varying the substitution on the pendent alkenes, thus steering their reactivity toward olefin cross metathesis. Efficient functionalization has been observed for a range of coupling partners as a proof of concept for the use of olefin metathesis to graft small and larger molecules to polyethers for drug delivery. This approach also paves the way for the use of olefin cross metathesis as an efficient method to functionalize a wide variety of polymers with pendent olefin groups.



Biocompatible polymers such as poly(ethylene glycol) (PEG) have been widely used for drug conjugation,[1] but they lack functional handles along the polymer backbone. This limits the possible modifications they can undergo. The synthesis of pertinent and useful polymers frequently requires post polymerization modification in order to incorporate architectures bearing functional groups not compatible with the polymerization process.[2] Side-chain functionalization of polymers is commonly achieved by employing azide−alkyne cycloaddition,[3] terminal functional group modification,[4] thiol−ene addition,[5] Michael-type addition,[6] and amidation,[7] among many others.[2] Olefin cross metathesis (CM) is a powerful carbon−carbon bond-forming reaction[8] performed under very mild conditions with catalysts compatible with most heteroatom functional groups and, therefore, could be used for the conjugation of polyethers possessing pendent olefin handles. However, conjugation of polymers by olefin CM remains a relatively unexplored area.[9] Functionalization by CM was pioneered by Coates et al., who showed that moderate conversion could be achieved when reacting various alkene-contining polyolefins with small olefins.[10] Hoogenboom and Meier and co-workers also reported that acrylate derivatives could successfully be coupled to a poly(2-oxazoline) (POx) with pendent olefins.[11] This approach was successful, but the occurrence of self metathesis (SM) was observed, which is the process by which a pendent olefin of the polymer undergoes CM with another pendent olefin, either intramolecularly or intermolecularly. This undesired process was limited by using a large excess (7−12 equiv) of the acrylate coupling partners. Edgar et al. then described CM of cellulose esters with 20 equiv of acrylate derivatives.[12] Our group has performed successful CM reactions of hindered polyesters with several olefinic partners.[13] The Shaver group further reported CM reactions between the polymer of β-heptenolactone and an extensive range of small olefinic partners.[14] In the latter case, self metathesis was minimized with a high loading (8 equiv) of the olefin cross partner.

Polyethers have a flexible backbone and therefore should be prone to SM, as is the case for the POx derivatives.[11] Intermolecular SM is especially deleterious to the efficiency of CM functionalization, as the resulting cross-linking leads to highly increased dispersities in the grafted polymers but using a large excess of an expensive coupling partner is not a sustainable solution. Herein, we report tailoring the polyethers according to the olefinic partners in order to favor CM over SM, by modifying the substitution on the pendent alkene of the polymer.

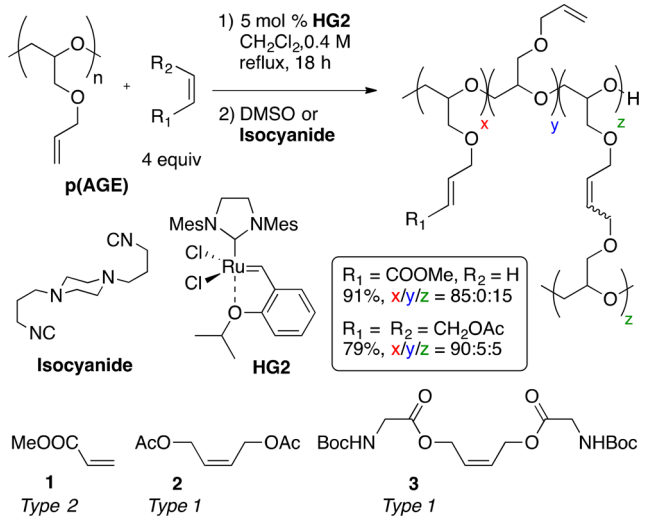
As CM with alkene-containing polyethers had not been reported, preliminary studies were conducted on the known poly(allyl glydidyl ether) p(AGE).[15] Anionic ring-opening polymerization of commercially available allyl glycidyl ether (neat) with potassium benzoxide as initiator produced the desired polymer (M_n = 7990 g/mol, Đ = 1.08). When this polyether was submitted to metathesis with methyl acrylate in the presence of Hoveyda−Grubbs second-generation catalyst **HG2**[16] in refluxing dichloromethane, the desired CM reaction took place (Scheme 1, *x* units), but some unreacted olefins were recovered (*y* units), and a substantial amount of SM was observed (*z* units). Under optimized conditions, the *x*/*y*/*z* ratio was 85:0:15 for methyl acrylate **1** (R_1 = COOMe, R_2 = H) and 90:5:5 for *Z*-1,4-butenediol diacetate **2** (R_1, R_2 = CH_2OAc), which behaves as an allyl acetate surrogate.

These ratios were determined by ^{1}H NMR spectroscopy, which clearly shows the different olefinic protons for each unit (Figure 1). Although the amount of SM is not very high, especially in the case of CM with the dimer of allyl acetate, the

Received: February 19, 2018

DOI: 10.1021/acs.orglett.8b00595
Org. Lett. XXXX, XXX, XXX−XXX

Scheme 1. First Attempt of Olefin CM Reactions with p(AGE)[17]



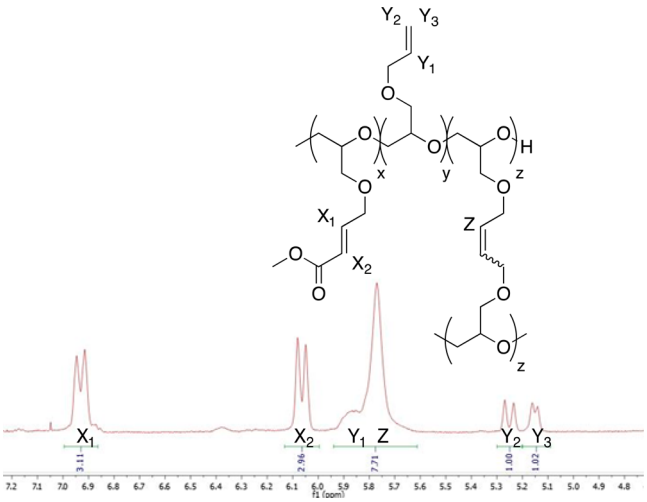


Figure 1. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) showing *x*, *y*, and *z* units.

dramatic increase in dispersity (Đ > 2) indicates mainly intermolecular SM and, hence, formation of branched polymers. Surprisingly, increasing the amount of CM partner up to 8 equiv did not improve the efficiency of the desired CM process.

In order to limit the degree of SM, we designed novel polyethers with additional steric hindrance around the pendent olefin. Using potassium *tert*-butoxide as initiator,[18] which is easier to handle than potassium benzoxide, p(AGE), poly(crotyl glydidyl ether) p(CGE), poly(prenyl glydidyl ether) p(PGE) and poly(methallyl glydidyl ether) p(MAGE) were synthesized in high molar masses and low dispersity (Figure 2) from the corresponding epoxide monomers.[19] It is worth noting that the grafted polymer units resulting from CM with p(AGE), p(CGE) and p(PGE) will be the same, while CM with p(MAGE) will lead to a trisubstituted olefin.

CM was then performed between these polymers and various type 1 and type 2 coupling partners (Table 1). Grubbs' classification of olefins according to their reactivity toward metathesis with a specific catalyst states that type 1 olefins undergo fast homodimerization, type 2 olefins dimerize slowly,

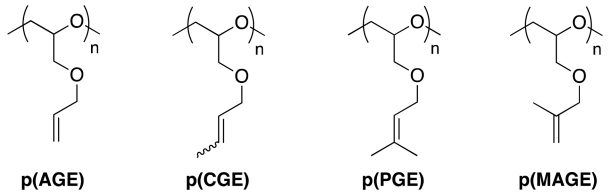


Figure 2. Novel polyethers with varying olefin handles.

and type 3 olefins do not dimerize, although they can participate in CM reactions.[20] Under the previously optimized conditions, coupling of p(CGE) with methyl acrylate **1** (entry 1) saw a slight decrease in conversion in comparison to p(AGE) (entry 2) with an overall increase in SM, indicating that the added methyl group is not efficient in inhibiting formation of the SM product. The reaction of p(PGE) with methyl acrylate (entry 3) led to a significant increase in successful CM (95%). Unsurprisingly, no reaction occurred between p(MAGE) and methyl acrylate (entry 4) due to the low reactivity of both olefin species.

Coupling of the polymer range with the dimer of allyl acetate **2** saw good conversion with p(AGE) (entry 5), p(CGE) (entry 6), and p(PGE) (entry 7) and a strong correlation between the degree of SM and the increase in dispersity. In each case, a substantial degree (up to 30%) of the original pendent olefins remained unreacted, which is probably due to intramolecular SM, resulting in conformations of the polymer chain that makes some olefins less accessible. Most interestingly, p(MAGE) underwent 23% successful CM with no evidence of SM (entry 8). For the first three polymers, the *E*/*Z* ratio of olefin isomers was 10:1, and for p(MAGE), it was 3:1. These numbers are in line with the selectivities observed for CM between small molecules of the same type.[20]

Coupling more complex molecules, such as peptides with the polymer range is of considerable interest, as these peptides moieties could serve as targeting devices in the drug delivery process. Studies were thus conducted on an amino acid substrate. CM of the derivative of Boc-protected glycine **3** (see Scheme 1 for structure) with p(AGE) (entry 9) and p(CGE) (entry 10) yielded similar results with 30% and 40% successful CM, respectively, along with a significant amount of SM. With p(PGE) (entry 11), the same percentage of desired CM was observed, but with 27% unreacted prenyl handles remained. With p(MAGE) (entry 12), a conversion of 30% was achieved, but once again no SM was detected for this polymer, as seen by the maintained dispersity on the GPC trace.

The results observed for the CM reactions can be explained by the different reactivity of the polymers. Both p(AGE) and p(CGE) possess type 1 olefins and, therefore, show good reactivity with any coupling partner. However, a certain degree of SM is seen as a result of their reactivity. The ruthenium catalyst reacts primarily with the pendent olefin to form the metal−polymer complex **4**,[21] which can then undergo successful CM (Scheme 2). Carbene **4** can also react more slowly with another pendent olefin, yielding SM product **6**. In the case of a type 1 olefin coupling partner, the desired product **5** is also a type 1 olefin and can react with the catalyst to regenerate the carbene **4**, thus leading to the SM product **6** by a secondary metathesis reaction. For these two polymers, successful CM is the major outcome of metathesis, along with 10−20% of SM. We had hoped that SM would be slower in the case of p(CGE) because of the additional steric

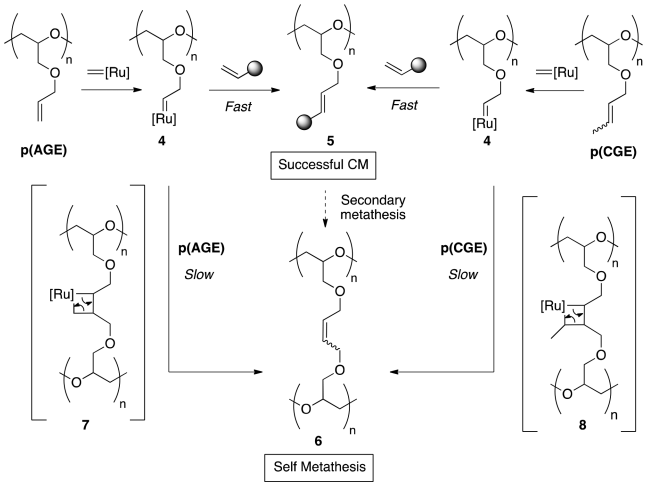
DOI: 10.1021/acs.orglett.8b00595
Org. Lett. XXXX, XXX, XXX−XXX

Table 1. CM of Polymer Range with Diverse Coupling Partners[a]

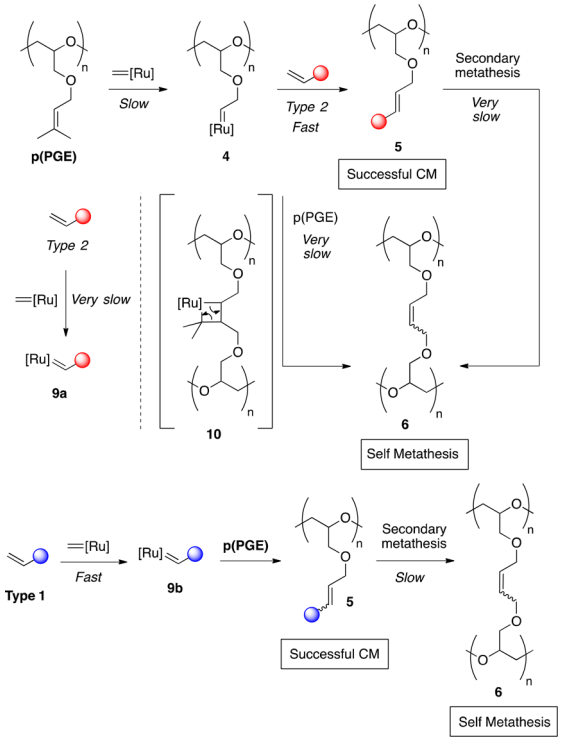
entry	polymer	M_n before CM (by GPC)	Đ before CM	coupling partner	yield (%)	$x/y/z$	M_n after CM (by GPC)	Đ after CM
1	p(AGE)	10000	1.16	1	92	85:5:10	13900[b]	2.11
2	p(CGE)	9200	1.28	1	95	80:0:20	13900[b]	2.21
3	p(PGE)	10000	1.35	1	84	95:2:3	10300[b]	2.00
4	p(MAGE)	15800	1.15	1		0:100:0		
5	p(AGE)	10000	1.16	2	90	87:4:9	12300[c]	1.46
6	p(CGE)	9200	1.28	2	83	73:12:15	15600[c]	1.98
7	p(PGE)	10000	1.35	2	95	60:30:10	12800[c]	1.76
8	p(MAGE)	15800	1.15	2	95	23:77:0	15900[b]	1.09
9	p(AGE)	10000	1.16	3	94	30:7:63	22700[c]	1.81
10	p(CGE)	9200	1.28	3	82	40:7:53	17100[c]	1.72
11	p(PGE)	10000	1.35	3	95	38:27:35	16400[c]	1.84
12	p(MAGE)	15800	1.15	3	97	30:70:0	19000[b]	1.09

[a]All reactions were performed with 5 mol % of **HG2** in refluxing dichloromethane for 18 h at 0.4 M with 4 equiv of coupling partner. [b]Monomodal. [c]Multimodal.

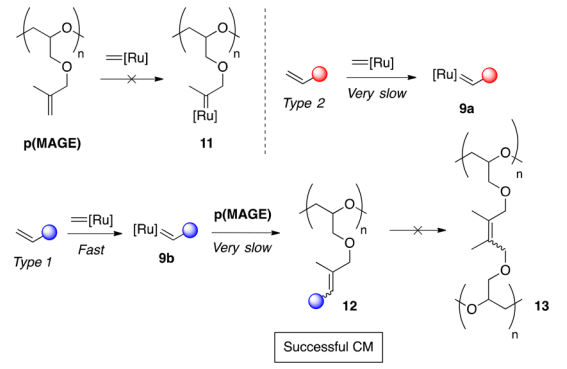
Scheme 2. Metathesis Pathways for p(AGE) and p(CGE)



Scheme 3. Metathesis Pathways for p(PGE)



Scheme 4. Metathesis Pathways for p(MAGE)



hindrance in metallacyclobutane **8** compared to that of **7**, but this hypothesis was not validated.

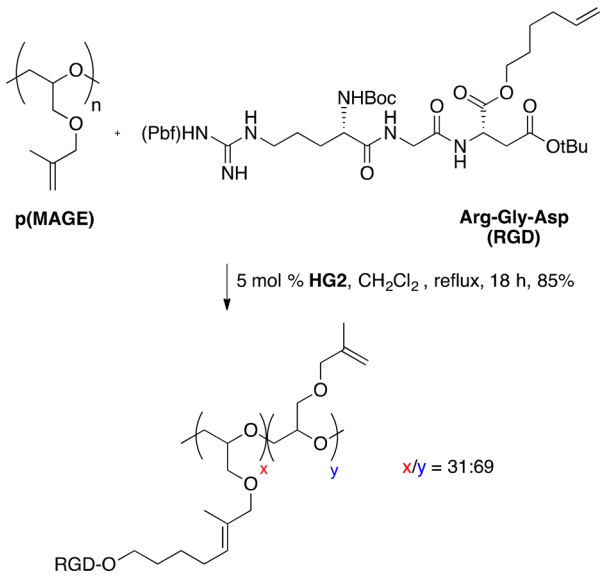
Polyether p(PGE) bears type 2 pendent olefins, so formation of carbene **4** is slow, but in the case of a type 2 olefin partner such as methyl acrylate, formation of carbene **9a** is even slower (Scheme 3). The catalyst reacts first with p(PGE), and unhindered carbene **4** undergoes rapid CM reaction. SM is very slow because of the high steric hindrance of metallacyclobutane **10**, and since the desired product **5** is a type 2 olefin, no secondary metathesis is observed. This explains why p(PGE) is the optimal polymer for coupling with a type 2 olefin.

In the case of a type 1 coupling partner, the catalyst reacts first with the small molecule giving carbene **9b**. This carbene can then couple with a polymer olefin to give the desired product **5**. No SM metathesis product is formed by this pathway, but the CM product **5** is a type 1 olefin that can lead to the SM product **6** by secondary metathesis reaction, which explains why p(PGE) produces the same amount of SM product as the less hindered p(AGE) and p(CGE) polymers with type 1 olefin partners. Polymer p(MAGE) is a type 3 olefin and does not react with the catalyst, so carbene **11** cannot be formed (Scheme 4). With a type 2 olefin, formation of carbene **9a** is very slow, and no metathesis reaction is observed. With a type 1 coupling partner, formation of carbene **9b** is fast, followed by a slow reaction with p(MAGE) to give the desired CM product **12**. Secondary SM cannot occur at all, as this product is also a type 3 olefin.

DOI: 10.1021/acs.orglett.8b00595
Org. Lett. XXXX, XXX, XXX−XXX

Having established that the best candidate in terms of preventing SM in the presence of type 1 olefins is p(MAGE), we then turned to a more challenging coupling partner, such as the protected tripeptide RGD. When using the same linker as for Boc-glycine, the conversion was only 9%, but with only 1 equiv of the hexenyl ester of RGD, 31% successful CM was observed, with no trace of SM products (Scheme 5).

Scheme 5. Successful CM between p(MAGE) and Protected RGD[22]



In conclusion, we have synthesized three novel polymers with pendent alkenes, where these handles are designed for optimum CM with various olefinic compounds, avoiding undesired SM without using a large excess of the small molecule partner. The best polymer for coupling with type 2 olefins is the p(PGE), while no SM occurs during CM of p(MAGE) with type 1 olefins, maintaining a good dispersity throughout the functionalization process. Furthermore, we report the first successful CM between a polymer and a coupling partner of biological relevance, RGD, which is commonly used for targeting tumor cells.[23] Further studies for conjugation of p(MAGE) with drugs such as paclitaxel are in progress.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b00595.

Experimental procedures for preparation of polymers and CM partners and for CM reactions, NMR spectra, and GPC chromatograms (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: joelle.prunet@glasgow.ac.uk.

ORCID

Rob M. J. Liskamp: 0000-0001-8897-8975
Joëlle Prunet: 0000-0002-9075-971X

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The authors thank Prof. Craig Hawker (UC Santa Barbara) and Prof. Karol Grela (University of Warsaw) for a generous gift of polymer samples and isocyanide scavenger, respectively, as well as Prof. Michael Shaver (University of Edinburgh) and Prof. Dave Adams (University of Glasgow) for helpful discussions. Financial support for this work was provided by the University of Glasgow, the EPSRC (Doctoral Training Allocation for S.M. EP/K503058/1), and Tenovus Scotland (Project S17-04).

■ REFERENCES

(1) Banerjee, S. S.; Aher, N.; Patil, R.; Khandare, J. *J. Drug Delivery* **2012**, *2012*, 1.
(2) Gauthier, M.; Gibson, M.; Klok, H.-A. *Angew. Chem., Int. Ed.* **2009**, *48*, 48−58.
(3) Delaittre, G.; Guimard, N. K.; Barner-Kowollik, C. *Acc. Chem. Res.* **2015**, *48*, 1296−1307.
(4) Willcock, H.; O'Reilly, R. K. *Polym. Chem.* **2010**, *1*, 149−157.
(5) Hoyle, C. E.; Bowman, C. N. *Angew. Chem., Int. Ed.* **2010**, *49*, 1540−1573.
(6) Rieger, J.; Van Butsele, K.; Lecomte, P.; Detrembleur, C.; Jérôme, R.; Jérôme, C. *Chem. Commun.* **2005**, 274−276.
(7) Singha, N. K.; Gibson, M. I.; Koiry, B. P.; Danial, M.; Klok, H. *Biomacromolecules* **2011**, *12*, 2908−2913.
(8) For a review on metathesis, see: Prunet, J. *Eur. J. Org. Chem.* **2011**, *2011*, 3634−3647.
(9) For reviews, see: (a) Sinclair, F.; Alkattan, M.; Prunet, J.; Shaver, M. P. *Polym. Chem.* **2017**, *8*, 3385−3398. (b) Dong, Y.; Matson, J. B.; Edgar, K. J. *Biomacromolecules* **2017**, *18*, 1661−1676.
(10) Mathers, R. T.; Coates, G. W. *Chem. Commun.* **2004**, 422−423.
(11) de Espinosa, L. M.; Kempe, K.; Schubert, U. S.; Hoogenboom, R.; Meier, M. A. R. *Macromol. Rapid Commun.* **2012**, *33*, 2023−2028.
(12) Meng, X.; Matson, J. B.; Edgar, K. J. *Polym. Chem.* **2014**, *5*, 7021−7033.
(13) Fournier, L.; Robert, C.; Pourchet, S.; Gonzalez, A.; Williams, L.; Prunet, J.; Thomas, C. M. *Polym. Chem.* **2016**, *7*, 3700−3704.
(14) Sinclair, F.; Chen, L.; Greenland, B. W.; Shaver, M. P. *Macromolecules* **2016**, *49*, 6826−6834.
(15) Lee, B. F.; Kade, M. J.; Chute, J. A.; Gupta, N.; Campos, L. M.; Fredrickson, G. H.; Kramer, E. J.; Lynd, N. A.; Hawker, C. J. *J. Polym. Sci., Part A: Polym. Chem.* **2011**, *49*, 4498−4504.
(16) First- and second-generation Grubbs catalysts were also investigated but gave lower percentages of the desired CM (*x* unit).
(17) DMSO or the isocyanide is used to deactivate the metathesis catalyst. For the isocyanide scavenger, see: Szczepaniak, G.; Urbaniak, K.; Wierzbicka, C.; Kosiński, K.; Skowerski, K.; Grela, K. *ChemSusChem* **2015**, *8*, 4139−4148.
(18) Kuhlmann, M.; Groll, J. *RSC Adv.* **2015**, *5*, 67323−67326.
(19) See the Supporting Information for the synthesis of the monomers.
(20) Chatterjee, K.; Choi, T.-L.; Sanders, D. P.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 11360−11370.
(21) The catalyst may also react with the coupling partner if it is a type 1 olefin, resulting in successful CM when coupling with the polymer.
(22) Pbf = 2,2,4,6,7-pentamethyldihydrobenzofuran-5-sulfonyl.
(23) Wang, F.; Li, Y.; Shen, Y.; Wang, A.; Wang, S.; Xie, T. *Int. J. Mol. Sci.* **2013**, *14*, 13447−13462.

DOI: 10.1021/acs.orglett.8b00595
Org. Lett. XXXX, XXX, XXX−XXX