

## Resnick Prize Postdoctoral Fellowship in Sustainable Science

Applicant: Allegra Liberman-Martin

### Design of Efficient Metathesis Catalysts to Transform Nitrile-Containing Monomers

#### Introduction

Organonitriles, which contain the R–C≡N functional group, are versatile reagents for the synthesis of pharmaceuticals, vitamins, synthetic resins, plastics, and dyes.<sup>1</sup> However, the methods currently used to prepare organonitriles (Scheme 1) are energy intensive (*i.e.* require harsh conditions) and wasteful (*i.e.* have poor atom economy).<sup>2</sup> The most material economical option, hydrocyanation, relies on hydrogen cyanide gas, which is extremely toxic, corrosive, and explosive, limiting its industrial application.<sup>3</sup>

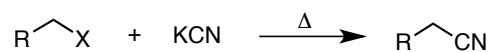
Cross metathesis offers an alternative method to conveniently synthesize organonitriles from a range of olefinic substrates. Instead of relying on hydrogen cyanide, cross metathesis could obtain the nitrile group from acrylonitrile, which can be derived (via ammoxidation) from glycerol, an abundant byproduct of biodiesel production.<sup>4</sup> However, efficient cross metathesis with acrylonitrile remains an unsolved challenge.

The difficulties of acrylonitrile metathesis are apparent upon examining a proposed mechanism (Scheme 2). Previous work suggests that once an N-heterocyclic carbene-supported (NHC-supported) ruthenium alkylidene reacts with acrylonitrile, a ruthenium-cyanocarbene is formed that is readily trapped by donor ligands, such as phosphines, to form stable, catalytically-inactive complexes.<sup>5</sup> I propose that replacement of the NHC with a more highly-donating ligand will destabilize the formation of these off-cycle intermediates and improve the catalyst's efficiency. If successful, this research will streamline, and lower the energy requirements for, the synthesis of nitrile-containing products and also enable the use renewable feedstocks as starting materials.

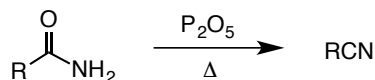
#### Catalyst Design Strategy

Previous strategies to improve acrylonitrile metathesis catalysts have primarily focused on the synthesis of pre-catalysts with

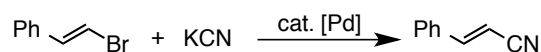
#### Kolbe nitrile synthesis:



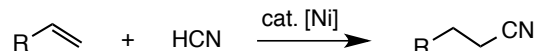
#### Amide dehydration:



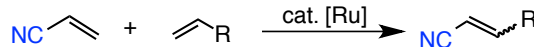
#### Vinyl halide cross-coupling:



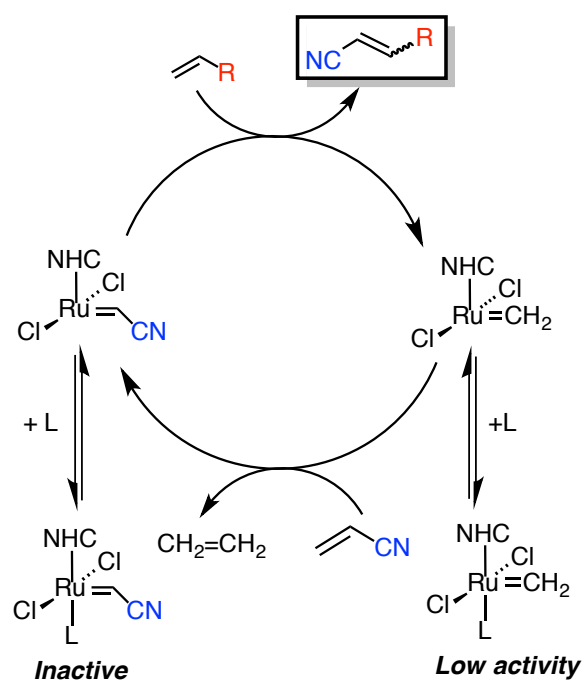
#### Hydrocyanation:



#### Acrylonitrile cross metathesis:



Scheme 1. Synthetic methods to prepare organonitriles.

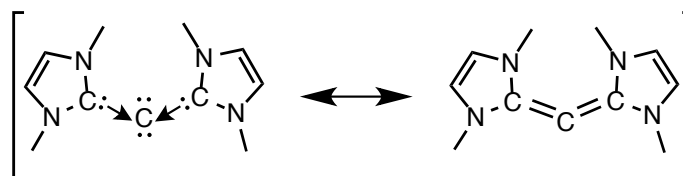


Scheme 2. Acrylonitrile cross metathesis mechanism

more labile L-type donors. Initial studies demonstrated that a  $[(H_2IMes)(PCy_3)(Cl)_2Ru=CHPh]$  complex featuring the strongly coordinated tricyclohexylphosphine ligand displays only low activity for the cross metathesis of acrylonitrile with allylbenzene (21% yield with 2.5% catalyst loading).<sup>5</sup> Moderate improvement of yield was observed under analogous conditions using pre-catalysts with weaker donors, such as the ether-tethered benzylidene derivative  $[(H_2IMes)(Cl)_2Ru=CH(o\text{-}^iPrOC_6H_4)]$  (68% yield) or a catalyst bearing two 3-bromopyridine ligands,  $[(H_2IMes)(3\text{-}Br\text{-}py)_2(Cl)_2Ru=CHPh]$  (67%). Few studies have varied the neutral supporting ligand that is maintained during catalysis, and all known acrylonitrile metathesis catalysts feature saturated, aryl-substituted NHC ligands.<sup>6</sup>

To increase initiation rates and discourage L-type ligand rebinding, I will prepare a series of ruthenium catalysts bearing carbodicarbene (CDC) ligands (Figure 1). These complexes can

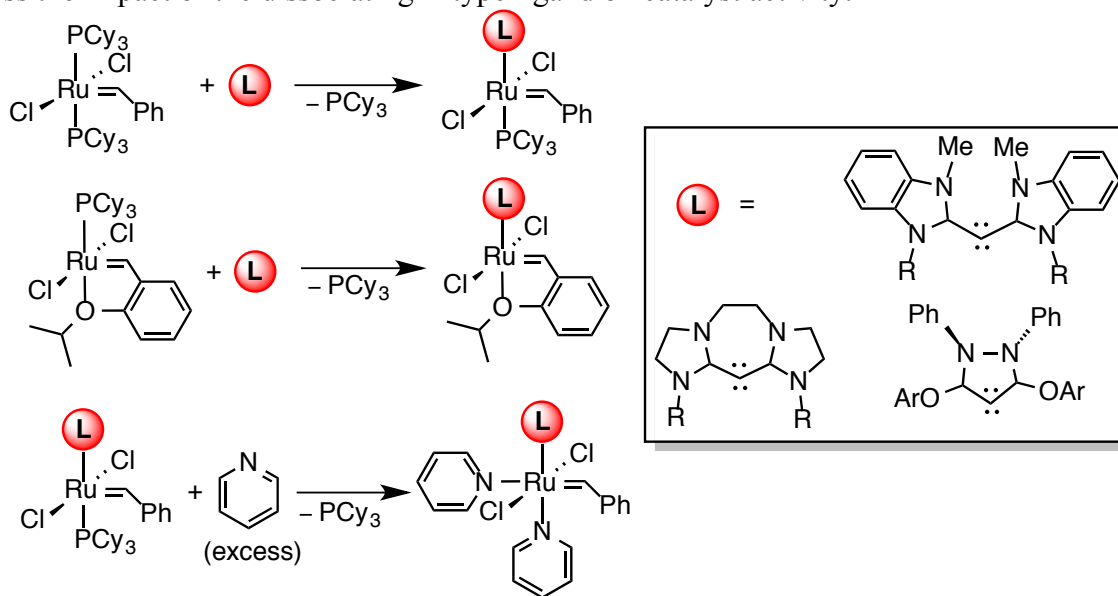
be described as either (i) divalent C(0) carbodicarbene species, with two lone pairs on the central carbon occupying  $\sigma$  and  $\pi$  type orbitals, or (ii) as bent allene species.<sup>7</sup> The very strong donor ability of these ligands has been evidenced by the unusually low



**Figure 1.** Carbodicarbene resonance structures.

carbonyl stretching frequency observed for a  $(CDC)Rh(CO)_2Cl$  complex ( $\nu_{CO} = 2014\text{ cm}^{-1}$ ) compared to NHC analogues ( $\nu_{CO} = 2036\text{--}2058\text{ cm}^{-1}$ ).<sup>8</sup> Despite the unique ability of CDC ligands to serve as neutral four-electron donors, few reports describe the reactivity of CDC-ligated metal complexes.<sup>9</sup>

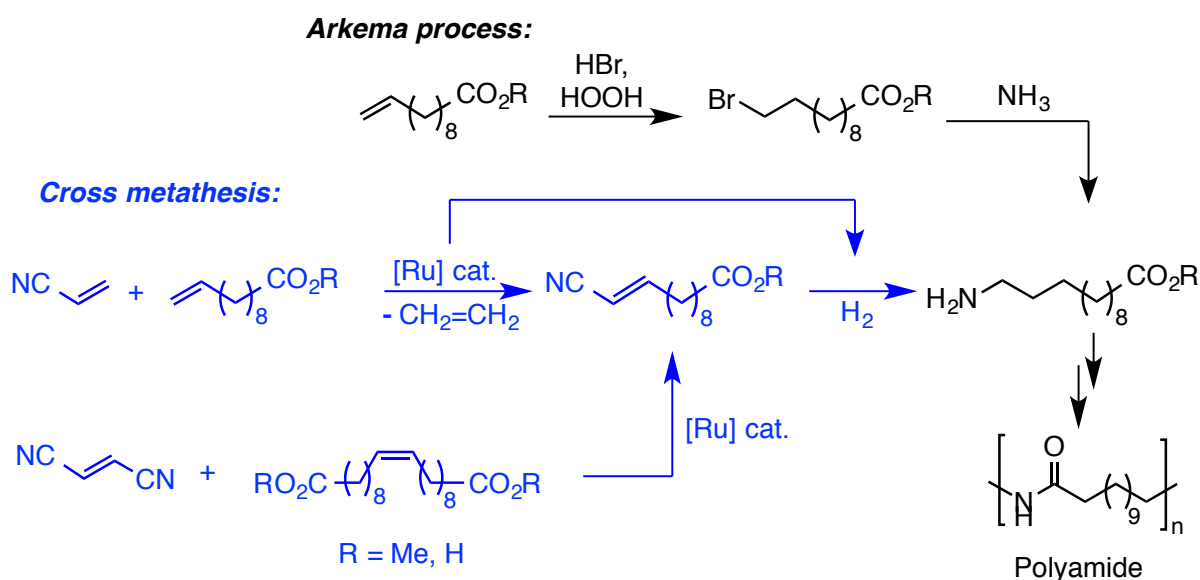
The three previously-reported CDC ligands shown in Scheme 3 were selected for initial study.<sup>9</sup> We anticipate that CDC-supported ruthenium carbene complexes,  $[CDC\text{-}Ru]$ , will be easily prepared from well-known precursors by displacement of tricyclohexylphosphine with free carbodicarbene.<sup>10</sup> Treatment of the CDC-Ru-PCy<sub>3</sub> complexes with an excess of pyridine should allow preparation of bispyridine derivatives.<sup>11</sup> Pre-catalysts featuring tricyclohexylphosphine, ether-tethered benzylidene, and pyridine ligands will be compared to assess the impact of the dissociating L-type ligand on catalyst activity.



**Scheme 3.** Synthesis of carbodicarbene-ruthenium complexes.

## Olefin metathesis with nitrile-containing substrates

Polyamides represent a widely utilized class of engineering plastics that could be synthesized by acrylonitrile cross metathesis.<sup>12</sup> Industrially, polyamides are commonly prepared from petroleum-derived monomers, such as diamines, diacids, and amino acids.<sup>13</sup> There is considerable interest in the development of new processes that generate polyamide precursors from biomass sources rather than fossil fuels. For example, Arkema has commercialized a method to prepare polyamide products from monomers that are derived from castor oil.<sup>14</sup> Although this method circumvents the need for petroleum-derived monomers, the procedure involves an inefficient bromination/ammoniation sequence that generates bromide-containing byproducts (Scheme 4).



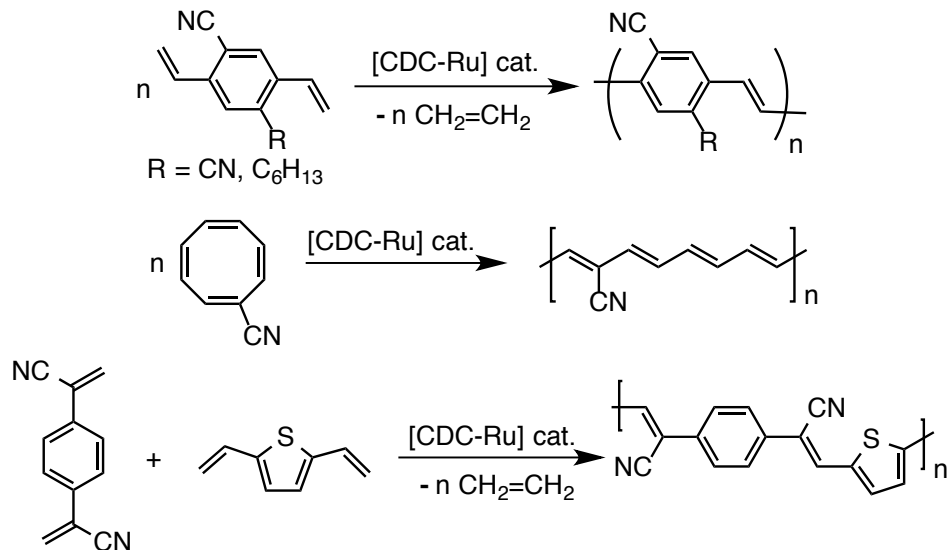
**Scheme 4.** Comparison of traditional and cross metathesis methods for polyamide synthesis.

Cross metathesis between acrylonitrile and castor-oil derived substrates, specifically methyl 11-undecenoate or 11-undecenoic acid, could generate a crucial polyamide precursor in a process that utilizes two bio-derived monomers and produces only ethylene as a recoverable byproduct (Scheme 4).<sup>6</sup> I will therefore focus initial studies of [CDC-Ru] activity on these cross metathesis reactions. Following metathesis, hydrogenation of the vinyl-nitrile intermediate to a saturated, amino acid (or ester) is required. Fortunately, previous work has demonstrated NHC-Ru complexes to be efficient hydrogenation catalysts, so potentially the same Ru-based catalyst that enables cross metathesis could also catalyze the hydrogenation step.<sup>15</sup> To determine if this is possible, the activity of [CDC-Ru] catalysts for sequential metathesis/hydrogenation will be tested. Finally, the amino-acid or -ester products formed upon hydrogenation can be directly polymerized to form polyamide 11 (PA 11). Additional studies of cross metathesis between fumaronitrile and a symmetrical diester substrate will also be performed, as this approach would altogether avoid formation of the ethylene byproduct.

Once active catalysts have been identified, polymerization of other nitrile-substituted monomers will be attempted. One potential application of [CDC-Ru] catalysts is for the synthesis of nitrile-containing conjugated polymers. Electron withdrawing substituents, such as nitriles, are of particular interest in the field of organic semiconductors due to their ability to promote electron mobility.<sup>16</sup> Previous reports have demonstrated that nitrile-decorated

polyphenylenevinylene (PPV) polymers can behave as acceptors in polymer–polymer solar cells.<sup>17</sup> For these applications, the ability to produce a well-defined, defect-free polymer is highly desirable.<sup>18</sup> Olefin metathesis polymerizations are an ideal match for these requirements, as the fast rate of polymer chain growth, compared to chain transfer or termination events, often allows for the synthesis of linear polymers with controllable molecular weights and architecture.<sup>19</sup>

Three routes to prepare nitrile-containing conjugated polymers utilizing [CDC-Ru] catalysis are presented in Scheme 5. The polymerization of 1,4-dicyano-2,5-divinylbenzene by ruthenium-catalyzed acyclic diene metathesis (ADMET) to form dicyano-PPV will be attempted. ADMET is driven by the release of ethylene gas, which can be easily recovered.<sup>20</sup> If the dicyano-PPV is insufficiently soluble to allow for a well-controlled polymerization, synthesis of a cyano-alkyl-PPV will be targeted. A second polymer architecture of interest is cyanopolyacetylene, and synthesis will be attempted by ring-opening metathesis polymerization (ROMP). In contrast to ADMET, which is driven by the release of ethylene gas, ROMP produces a single polymeric product, and is driven by the release of ring strain upon opening of the cyclooctatetraene monomer.<sup>21</sup>



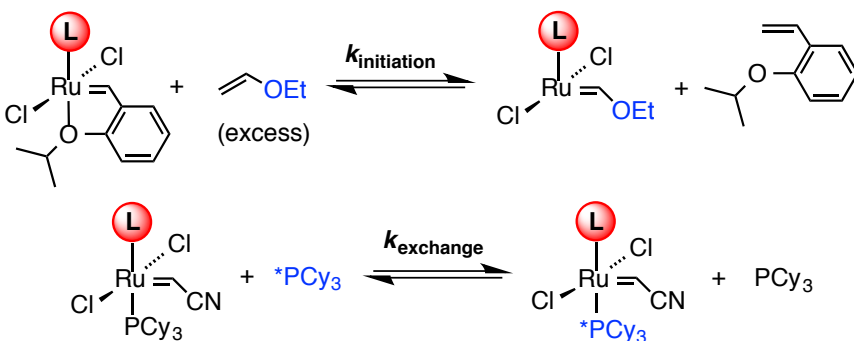
**Scheme 5.** Synthesis of nitrile-containing conjugated polymers.

Lastly, the synthesis of an alternating donor–acceptor conjugated polymer will be attempted by treatment of [CDC-Ru] with a mixture of *p*-phenylenediacrylonitrile and 2,5-divinylthiophene. Both vinyl nitrile and vinyl thiophene substrates have low propensities for self-metathesis (*i.e.* metathesis is more favorable between donor–acceptor than donor–donor or acceptor–acceptor),<sup>22</sup> therefore, an alternating copolymer structure may be favored. Conventional methods for the synthesis of donor–acceptor conjugated polymers have relied on wasteful palladium-catalyzed Stille- or Suzuki-type reactions that generate tin or boron byproducts, respectively.<sup>23</sup> Ruthenium-catalyzed metathesis reactions are appealing as halogen- and salt-free processes that generate only ethylene as a byproduct.

#### Study of catalyst electronic properties

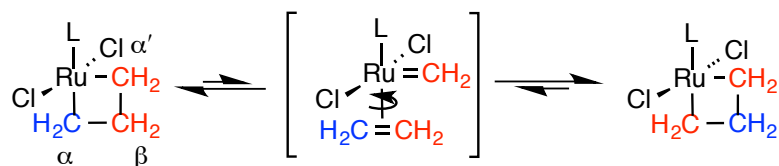
Based on the ability of CDC ligands to behave as both  $\sigma$ - and  $\pi$ -type donors to a metal center, the electronic properties and reactivity of [CDC-Ru] catalysts are expected to differ significantly from the widely studied NHC-supported complexes. Catalyst initiation rates will be

determined by treatment of [CDC-Ru] catalysts with an excess of ethyl vinyl ether (Scheme 6, top).<sup>24</sup> The CDC donor is expected to labilize *trans* ligands, leading to increased initiation rates. In addition, the phosphine exchange rates for cyanocarbene–ruthenium complexes will be measured (Scheme 6, bottom).<sup>25</sup> Previous reports have shown that phosphine dissociation from a NHC-substituted cyanocarbene complex is very slow, which is detrimental to catalyst activity (Scheme 2).<sup>5</sup> The strongly donating CDC ligand is expected to weaken the Ru–PCy<sub>3</sub> bond to facilitate re-entry into the catalytic cycle and improve catalyst efficiency.



**Scheme 6.** Reactions to determine catalyst initiation and re-entry rates.

Finally, experiments will be performed to understand the electronic effect of the CDC ligand on the [2+2] cycloaddition between the olefin and the alkylidene intermediate. A strongly donating ligand, such as CDC, is expected to favor the formation of a ruthenacyclobutane intermediate, which may prevent catalyst decomposition by protecting the delicate methyldiene intermediate.<sup>26</sup> To test this hypothesis, the preparation of simple ethylene-derived ruthenacycles supported by CDC ligands will be attempted. The rate constant for exchange between protons at the  $\alpha$  and  $\beta$  position of the ruthenacycle can be measured by NMR exchange spectroscopy (EXSY), and should be slower for a more stable Ru(IV) intermediate (Scheme 7). Understanding the relationship between catalyst activity and ruthenacycle stability will guide further catalyst design efforts.



**Scheme 7.** Determination of methylene exchange rates for ruthenacycles.

## Summary

Olefin metathesis offers an atom economical method to efficiently generate more complex organic products and polymers from simple olefinic starting materials. Improved activity for ruthenium metathesis catalysts in the presence of nitrile functional groups would broaden the applicability of these catalysts for the synthesis of a range of polymers, including bio-derived polyamides and electron-deficient conjugated polymers. We propose that use of strongly donating carbodicarbene ligands will improve the activity of ruthenium carbene catalysts by increasing initiation rates, discouraging L-type ligand rebinding, and favoring the formation of a Ru(IV) ruthenacyclobutane intermediate. The successful completion of this proposal could result in more sustainable methods for the preparation of nitrogen-containing polymers.

## References

1. Pollack, P.; Romeder, G.; Hagedorn, F.; Gelbke, H.-P. "Nitriles," in Ullman's Encyclopedia of Industrial Chemistry; Wiley-VCH: Weinheim, 1985; Vol. A17, p. 363.
2. (a) Kim, D. W.; Song, C. E.; Chi, D. Y. *J. Org. Chem.* **2003**, *68*, 4281; (b) Kuo, C.-W.; Zhu, J.-L.; Wu, J.-D.; Chu, C.-M.; Yao, C.-F.; Shia, K.-S. *Chem. Commun.* 2007, 301; (c) Bini, L.; Müller, C.; Vogt, D. *ChemCatChem*, **2010**, *2*, 590; (d) Yamamura, K.; Murahashi, S.-I. *Tetrahedron Lett.* 1977, 4429.
3. Romeder, G. Hydrogen Cyanide. *e-EROS Encyclopedia of Reagents for Organic Synthesis*, 2001.
4. Calvino-Casilda, V.; Guerrero-Pérez, M. O.; Bañares, M. A. *Green Chem.* **2009**, *11*, 939.
5. Love, J. A.; Morgan, J. P.; Trnka, T. M.; Grubbs, R. H. *Angew. Chem. Int. Ed.* **2002**, *41*, 4035.
6. Bruneau, C.; Fischmeister, C.; Miao, X.; Malacea, R.; Dixneuf, P. H. *Eur. J. Lipid Sci. Tech.* **2010**, *112*, 3.
7. Martin, D.; Soleilhavoup, M.; Bertrand, G. *Chem. Sci.* **2011**, *2*, 389.
8. Dyker, C. A.; Lavallo, V.; Donnadiou, B.; Bertrand, G. *Angew. Chem. Int. Ed.* **2008**, *47*, 3206.
9. (a) Chen, W.-C.; Hsu, Y.-C.; Lee, C.-Y.; Yap, G. P. A.; Ong, T.-G. *Organometallics* **2013**, *32*, 2435; (b) Schwesinger, R. *Angew. Chem. Int. Ed. Engl.* **1987**, *26*, 1164; (c) Goldfogel, M. J.; Roberts, C. C.; Meek, S. J. *J. Am. Chem. Soc.* **2014**, *136*, 6227; (d) Fernández, I.; Dyker, C. A.; DeHope, A.; Donnadiou, B.; Frenking, G.; Bertrand, G. *J. Am. Chem. Soc.* **2009**, *131*, 11875; (e) Prankevicus, C.; Fan, L.; Stephan, D. W. *J. Am. Chem. Soc.* **2015**, *137*, 5582.
10. (a) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953; (b) Gessler, S.; Randl, S.; Blechert, S. *Tetrahedron Lett.* **2000**, *41*, 9973.
11. Sanford, M. S.; Love, J. A.; Grubbs, R. H. *Organometallics* **2001**, *20*, 5314.
12. Rulkens, R.; Koning, C. "Chemistry and Technology of polyamides." In *Polymer Science: A Comprehensive Reference*; Matyjaszewski, K.; Möller, M., Eds.; Elsevier: Amsterdam, 2012; pp 431–467.
13. Weber, J. M. "Polyamides," in *Kirk-Othmer Encyclopedia of Chemical Technology*; John Wiley & Sons; Hoboken, 2011.
14. Kuciel, S.; Kuźniar, P.; Liber-Kneć, A. *Polimery* **2012**, *57*, 627.
15. Miao, X.; Fischmeister, C.; Bruneau, C.; Dixneuf, P. H.; Dubois, J.-L.; Couturier, J.-L. *ChemSusChem* **2012**, *5*, 1410.
16. Gillissen, S.; Lutsen, L.; Vanderzande, D.; Gelan, J. *Synth. Metals* **2001**, *119*, 137.
17. (a) Sang, G.; Zou, Y.; Huang, Y.; Zhao, G.; Yang, Y.; Li, Y. *Appl. Phys. Lett.* **2009**, *94*, 193302; (b) Granström, M.; Petritsch, K.; Arias, A. C.; Lux, A.; Andersson, M. R.; Friend, R. H. *Nature* **1998**, *395*, 257.
18. Becker, H.; Spreitzer, H.; Kreuder, W.; Kluge, E.; Vestweber, H.; Schenk, H.; Treacher, K. *Synth. Metals* **2001**, *122*, 105.
19. Bielawski, C. W.; Grubbs, R. H. *Prog. Polym. Sci.* **2007**, *32*, 1.
20. (a) Mutlu, H.; de Espinosa, L. M.; Meier, M. A. R. *Chem. Soc. Rev.* **2011**, *40*, 1404; (b) Schulz, M. D.; Wagener, K. B. *Macromol. Chem. Phys.* **2014**, *215*, 1936.
21. Leitgeb, A.; Wappel, J.; Slugovc, C. *Polymer* **2010**, *51*, 2927.
22. (a) Chatterjee, A. K.; Choi, T.-L.; Sanders, D. P.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 11360; (b) Kawai, T.; Shida, Y.; Yoshida, H.; Abe, J.; Iyoda, T. *J. Mol. Catal. A: Chem.* **2002**, *190*, 33.
23. Burke, D. J.; Lipomi, D. J. *Energy Environ. Sci.* **2013**, *6*, 2053.
24. Sanford, M. S.; Love, J. A.; Grubbs, R. H. *J. Am. Chem. Soc.* **2001**, *123*, 6543.
25. Sanford, M. S.; Ullman, M.; Grubbs, R. H. *J. Am. Chem. Soc.* **2001**, *123*, 749.
26. Keitz, B. K.; Grubbs, R. H. *J. Am. Chem. Soc.* **2011**, *133*, 16277.