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Highly efficient cyclotrimerization of isocyanates using N-heterocyclic olefins under bulk conditions†

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With a catalyst loading as low as 0.005%, high to excellent yields of isocyanurates could be achieved from N-heterocyclic olefin mediated organocatalytic cyclotrimerization of a wide range of isocyanates under bulk conditions. Experimental details coupled with structural characterization of the key intermediates led to comprehensive mechanistic studies of cyclotrimerization.

In recent years, 1,3,5-triazinane-2,4,6-triones (isocyanurates) bearing stable six-membered rings have attracted intense attention since they could be employed as additives to achieve enhanced performance of polyurethane foams, coating materials and composites[1] and polymers[2,3] due to their intriguing properties of excellent rigidity, high thermal stability and hydrolytic stability. Their derivatives are also utilized in the application of chiral discrimination,[4] selective ion bonding,[5] medicine,[6,7] and cross-linker[8] and periodic mesoporous organosilica.[9] Cyclotrimerization of isocyanates provides a facile strategy to readily achieve the synthesis of isocyanurates.[1,10,11] Metal-containing complexes based on Yb, Eu, Sm, Nb, Sn, Pd, Mn, Fe, Na, and Li are reported as pre-catalysts for the cyclotrimerization of isocyanates.[12–16] However, most of them are only applicable for either aryl isocyanates or alkyl isocyanates.[13,14,16,17] Recently, catalyst systems composed of organic Lewis bases have demonstrated their application in different reactions.[17–21] Louie *et al.* discovered that N-heterocyclic carbines can serve as highly efficient organocatalysts for the cyclotrimerization of isocyanates, affording up to 99% yield of trimer products in an hour.[11] Several organocatalysts such as tetrabutylammonium phthalimide-*N*-oxyl, tetraethylammonium 2-(carbamoyl)benzoate, ketene cyclic *N*,*O*-acetal and tetrakis(dimethylamino)ethylene are also found to be active for the cyclotrimerization of isocyanates.[22–25] So far, there are still several unaddressed key issues existing in the cyclotrimerization of isocyanates. First, it is inevitable to yield a dimer, allophanate, urethane or carbodiimide along with the production of a trimer due to poor selectivity.[1,11,26] Second, there is no structural characterization of the key reaction intermediate species yet. Third, a highly efficient catalyst system needs to be developed.[11] To this end, this contribution reports the employment of strong nucleophilic N-heterocyclic olefins (NHOs) as organocatalysts to achieve highly efficient synthesis of isocyanurates from the cyclotrimerization of a wide range of isocyanate substrates under solvent-free conditions at room temperature (RT), with a catalyst loading as low as 0.005 mol%.

As highly polarized molecules with an electron-rich exocyclic C=C double bond, NHOs could serve as ligands to stabilize metals or organocatalysts in the preparation of polyesters, polyethers, and polyacrylates as well as in organic synthesis.[27–37] Previous studies indicated that the substituents on the exocyclic carbon atom of NHO have a great influence on the polymerization activity.[32,36,38] **NHO1–3** bearing different substituents on the exocyclic C=C double bond were synthesized and their efficacies on the cyclotrimerization of a wide range of isocyanates as substrates were examined (Scheme 1).[31,38,39] It turned out that once **NHO1** having two hydrogen atoms on the exocyclic C=C double bond was added to phenyl isocyanate (**1**) in toluene at RT, the reaction mixture immediately turned from orange to colourless, but no trimer product was observed up to 24 h (run 1, Table S1, ESI†). To gain more insights into the reaction, we performed an *in situ* NMR reaction and found that 2 equiv. of 3-methylphenyl isocyanate (**3**) reacted with **NHO1** to yield an addition product $\mathbf{INT_{13}}$ (Fig. S1 and S2, ESI†). Therefore, a possible reaction pathway was proposed for the reaction as shown in Scheme S1 (ESI†), in which, the reaction of **NHO1** with **3** produced a zwitterionic intermediate **A**. The subsequent H transfer from the methylene to the carbamoyl anion of the intermediate **A** generated intermediate **B**, which went through continuous nucleophilic attack and a H-transfer reaction to form $\mathbf{INT_{13}}$. This is similar to what is proposed for the cyclotrimerization of isocyanates catalyzed using *N*,*N*′-dimethyl cyclic ketene, *N*,*N*′-acetals or *N*-methyl cyclic

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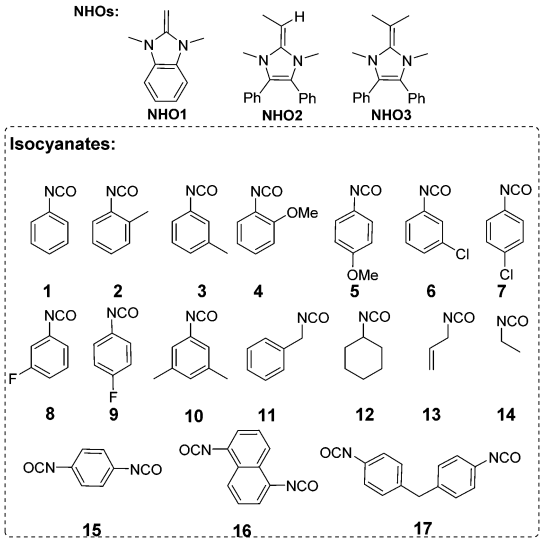


Scheme 1 Structures of NHOs and isocyanates employed in the cyclotrimerization of isocyanates.

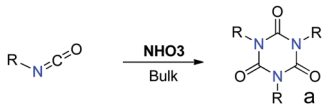
ketene-N,X (X = S, O)-acetals, with no observation of a spiro compound.[24,40] Compared with **NHO1**, $\mathbf{INT_{13}}$ showed a larger steric hindrance that led to its incapability of reacting with isocyanates (run 1, Table S3, ESI†), which also well explains why **NHO1** possessing two H atoms on the exocyclic carbon is ineffective for cyclotrimerization of isocyanates. Previous studies revealed that NHOs with similar structures also exhibited poor activity towards the polymerization of acrylic monomers owing to the occurrence of the H transfer reaction.[36] To verify our assumption, we employed **NHO2** bearing one H atom and one methyl group on the exocyclic carbon to examine the reaction. The stoichiometric *in situ* NMR reaction of isocyanate **3** with **NHO2** in a 1 : 1 ratio generated a single addition product $\mathbf{INT_{23}}$ (Scheme S2 and Fig. S3, S4, ESI†), which could be successfully isolated and utilized for the cyclotrimerization of isocyanates. Interestingly, the isocyanates **1**, **3**, and **5** could be quantitatively converted into the corresponding trimer products within several minutes (run 2–4, Table S3, ESI†), indicating that $\mathbf{INT_{23}}$ is highly effective for the reaction. To our expectations, similar reactivity and product yields could be obtained for the cyclotrimerization of **1**, **3**, and **5** by using **NHO2** as an organocatalyst (run 3–5, Table S1, ESI†).

Since the H transfer reaction that leads to the deactivation of the catalyst accounted for the ineffective polymerization of polar vinyl monomers catalyzed using NHOs,[36] we chose **NHO3** having two methyl groups on exocyclic carbon for the reaction. Isocyanate **1** could be nearly quantitatively converted to isocyanurates **1a** in 97% isolated yield when the reaction was performed in toluene with a 1 mol% catalyst loading of **NHO3** (run 1, Table S2, ESI†) whereas a 98% isolated yield was obtained with an even lower catalyst loading of 0.04 mol% (run 2, Table S2, ESI†). It is noted that we did not observe a dimeric product, a common by-product found in the reaction.[1,11] It turned out that **NHO3** showed high activity towards the cyclotrimerization of a wide range of aromatic isocyanates possessing either an electron donating or electron withdrawing substituent, achieving quantitative monomer conversion within three minutes and a high to excellent product yield (up to 97%) (runs 3 to 8, Table S2, ESI†). It is noted that isocyanates **2** and **4** having a substituent at the *ortho* position exhibited relatively lower activity than other substrates, probably because the substituent at the *ortho* position hindered the nucleophilic attack of the incoming isocyanate by the anionic centre (*vide infra*). Similar results were observed for the Fe and Mn complex-catalyzed cyclotrimerization of secondary and tertiary aliphatic isocyanates.[16] **NHO3** is also effective for the cyclotrimerization of aliphatic isocyanate **12**, furnishing the corresponding trimer **12a** in 90% yield (run 13, Table S2, ESI†). This might be attributed to the higher electron cloud density at the carbon of isocyano in aliphatic isocyanates than that in aromatic isocyanates, which was not conducive to nucleophilic attack and the formation of a stable zwitterionic intermediate (*vide infra*). Previously, Dekamin and co-workers also found that Lewis bases are less active for the cyclotrimerization of aliphatic isocyanates than they are for aromatic isocyanates.[22] We also compared the effectiveness of NHO with the other commonly used, strong organic bases, such as 1,8-diazabicyclo(5.4.0)-undec-7-ene (DBU) and 7-methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene (MTBD), on the cyclotrimerization of **1**. It turns out that DBU did not produce any cyclotrimerization product for up to 48 h whereas MTBD could furnish around 80% yield of the cyclotrimerization product after 3 h (runs 14 and 15, Table S2, ESI†).

The cyclotrimerization of isocyanate was also performed under bulk conditions with 0.1 mol% catalyst loading of **NHO3**, by adding the isocyanate into a vial containing predetermined amounts of **NHO3**. Owning to its high efficiency, **NHO3** would be wrapped inside the product and loses its activity upon coming into contact with the isocyanate. Therefore, we employed a stock solution of **NHO3** dissolved in 100 μL toluene to examine the subsequent reactions, achieving a similar high to excellent product yield of aromatic isocyanurates but a much higher polymerization activity (Table 1) than that obtained for cyclotrimerization performed in toluene (Table S2, ESI†). Even a 0.005% catalyst loading of **NHO3** can nearly quantitatively transform 20 000 equiv. of isocyanate **1** into a trimer with 98% isolated yield within 3 minutes (run 2, Table 1). Enhanced polymerization activities were also observed for the cyclotrimerization of other aromatic and aliphatic isocyanates performed under bulk conditions. We also observed a similar trend that aliphatic isocyanates showed lower polymerization activity than aromatic isocyanates (runs 11–14 *vs.* runs 1–10, Table 1).

There are mechanistic studies on the cyclotrimerization of isocyanates catalyzed using Lewis bases reported by other research groups, but experimental evidence is still lacking. Therefore, we performed a series of *in situ* NMR reactions to gain more insights into the reaction. First, the reaction of **NHO3** with isocyanates **1** in 1 : 10 ratio afforded the cyclotrimer **1a** and a zwitterionic species $\mathbf{INT_{31}}$ in a 3 : 1 ratio, without the observation of free **NHO3** (Fig. S9, ESI†). Second, the stoichiometric *in situ* NMR reactions of **NHO3** with isocyanates **1**, **3**, and **9** in a 1 : 1 ratio cleanly yielded the corresponding zwitterionic species $\mathbf{INT_{31}}$, $\mathbf{INT_{33}}$ and $\mathbf{INT_{39}}$, respectively, indicating that these zwitterionic species were readily formed and fairly stable (Fig. S5–S8, ESI†).

Table 1 NHO catalyzed the cyclotrimerization of isocyanates[a]



Run	RNCO	RNCO:NHO3	Time (min)	Product[b]	Yield[c] (%)
1	**1**	1000	<1	**1a**	95
2	**1**	20 000	<3	**1a**	98
3	**2**	1000	120	**2a**	90
4	**3**	1000	<2	**3a**	96
5	**4**	1000	180	**4a**	91
6	**5**	1000	<2	**5a**	97
7	**6**	1000	3	**6a**	97
8	**7**	1000	<1	**7a**	96
9	**8**	1000	3	**8a**	96
10	**10**	200	1	**10a**	98
11	**11**	1000	24 h	**11a**	95
12	**12**	1000	48 h	**12a**	88
13	**13**	1000	48 h	**13a**	89
14	**14**	1000	48 h	**14a**	88

[a] Condition: carried out under bulk conditions, **NHO3** dissolved in 100 μL toluene. [b] Cyclotrimer product. [c] Isolated yield.

We have successfully isolated $\mathbf{INT_{39}}$ generated from the reaction of **NHO3** and isocyanate **9** and characterized its structure by NMR spectroscopy and X-ray crystallography (Fig. 1). Single crystal structural data showed that the angles for O(1)–C(1)–C(2) and N(1)–C(1)–C(2) are 131.60°, 113.82°, and 114.55°, respectively, thus furnishing a sum of 359.97°. Moreover, the dihedral angle of O(1)–C(1)–N(1) and O(1)–C(1)–C(2) is 1.32°. These results indicated that C(1) adopted sp^2 hybridization. On the other hand, the bond length for O(1)–C(1) is 1.256 Å, suggesting a double bond; the bond length for N(1)–C(1) is 1.312 Å, which is close to that for the double bond; and the bond length for C(1)–C(2) is 1.565 Å, which is longer than that for the single bond, thus indicating that it is easy for **NHO3** to leave during cyclization. This information revealed the presence of electron resonance around the C(1) center and N(1) has a negative charge.

The above-mentioned results suggested two possible reaction pathways (Scheme S3, ESI†): in path a, **NHO3** nucleophilically attacks the carbon atom of –N*C*O of isocyanate generating the zwitterionic species **INT**, which will attack the second isocyanate to form **INT1**. During the subsequent attack of the third isocyanate by **INT1**, the resulting N anion attacks the carbon

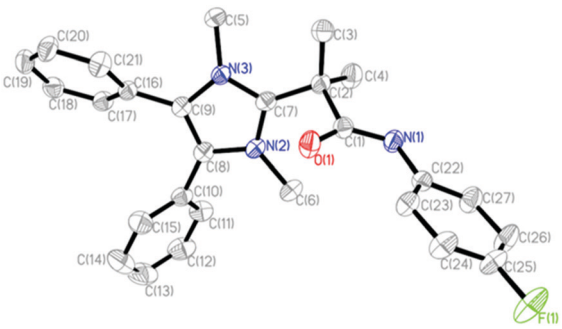
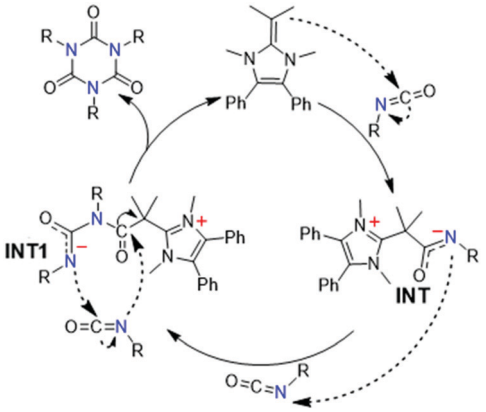


Fig. 1 X-ray crystal structure of $\mathbf{INT_{39}}$. Hydrogen atoms and solvent molecules are omitted for clarity, and ellipsoids are drawn at 50% probability.



Scheme 2 Reaction mechanism proposed for **NHO3** catalyzed the cyclotrimerization of isocyanates.

atom of –N*C*O of the first isocyanate to generate a trimer through cyclization, along with the release of **NHO3** for the next catalytic cycle (Scheme 2). In path b (Scheme S3, ESI†), the zwitterionic species generated from the reaction of NHO with isocyanate could serve as the real catalyst to continuously attack the next three incoming isocyanates and the resulting N anion attacks the carbon atom of –N*C*O of the first isocyanate generating a trimer through the cyclization and release the active zwitterionic species for the next catalytic cycle.

Thanks to the stability of these zwitterionic species, it enables us to employ them to perform the following control experiments to verify the reaction pathway. It turned out that $\mathbf{INT_{39}}$ could rapidly convert isocyanate **1** into 95% yield of **1a** within 2 min ($\mathbf{1}/\mathbf{INT_{39}}$ = 200/1, run 5, Table S3, ESI†), indicating that such zwitterionic species are the real active intermediates for the cyclotrimerization of isocyanates. On the other hand, the *in situ* NMR reaction of $\mathbf{INT_{33}}$ with isocyanate **1** in a 1 : 10 ratio clearly revealed the exclusive generation of $\mathbf{INT_{31}}$, without the formation of $\mathbf{INT_{33}}$ (Fig. S10, ESI†), which suggested that during the reaction, $\mathbf{INT_{33}}$ would release **NHO3** to react with isocyanate **1** to generate a new zwitterionic compound $\mathbf{INT_{31}}$, thus indicating that the zwitterionic $\mathbf{INT_{33}}$ was the real active intermediate rather than the catalyst for the cyclotrimerization of isocyanates. The above-mentioned discussion provided more evidence to support that pathway a is more preferable for the NHO-catalyzed cyclotrimerization of isocyanates (Scheme 2).

The cyclotrimerization of diisocyanates[26,41] can also be utilized to synthesize microporous polyisocyanurate materials having potential applications in heterogeneous catalysis[42] and absorption of lipophilic compounds.[43] With this highly efficient **NHO3** catalyst system for the cyclotrimerization of isocyanates in hand, we further expanded the monomer scope of this method by using three diisocyanates with different distances between two –NCO groups as substrates (Scheme 1). The observation of gel formation (Fig. S11, ESI†) indicated that **NHO3** transformed the diisocyanates into microporous polymer networks (Scheme S4 and Table S4, ESI†). Compared with the previous results,[42,43] **NHO3** exhibited higher polymerization activity under mild conditions. Investigation of the properties and

applications of the resulting microporous polymer networks is still in progress.

In summary, we represented the first example that strong nucleophilic NHOs can serve as highly efficient organocatalysts to achieve rapid cyclotrimerization of both aryl and alkyl isocyanates into isocyanurates with high to excellent yields under mild conditions and even higher polymerization activity under bulk conditions. This NHO catalyst system exhibited higher polymerization activity towards the cyclotrimerization of aromatic isocyanates than for aliphatic isocyanates. We proposed a possible reaction mechanism on the basis of the experimental details and the structural characterization of the active intermediate species. Moreover, this method can be utilized to synthesize a fully covalent-organic-framework, microporous polyisocyanurates, at room temperature. This will definitely stimulate future efforts in expanding the application scope of both NHOs and isocyanurates.

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Conflicts of interest

The authors declare no competing financial interest.

Notes and references

1 G. Wegener, M. Brandt, L. Duda, J. Hofmann, B. Klesczewski, D. Koch, R.-J. Kumpf, H. Orzesek, H.-G. Pirkl, C. Six, C. Steinlein and M. Weisbeck, *Appl. Catal., A*, 2001, **221**, 303–335.
2 J. Tang, T. Mohan and J. G. Verkade, *J. Org. Chem.*, 1994, **59**, 4931–4938.
3 S. J. Peters, J. R. Klen and N. C. Smart, *Org. Lett.*, 2008, **10**, 4521–4524.
4 H. Sugimoto, Y. Yamane and S. Inoue, *Tetrahedron: Asymmetry*, 2000, **11**, 2067–2075.
5 M. Mascal, I. Yakovlev, E. B. Nikitin and J. C. Fettinger, *Angew. Chem., Int. Ed.*, 2007, **46**, 8782–8784.
6 A. Bosco, L. Rinaldi, G. Cappelli, A. Saratsis, L. Nisoli and G. Cringoli, *Vet. Parasitol.*, 2015, **212**, 408–410.
7 P. Gibbons, D. Love, T. Craig and C. Budke, *Vet. Parasitol.*, 2016, **218**, 1–4.
8 H. Ni, A. D. Skaja, R. A. Sailer and M. D. Soucek, *Macromol. Chem. Phys.*, 2000, **201**, 722–732.
9 O. Olkhovyk and M. Jaroniec, *J. Am. Chem. Soc.*, 2005, **127**, 60–61.
10 A. L. Silva and J. C. Bordado, *Catal. Rev.: Sci. Eng.*, 2004, **46**, 31–51.
11 H. A. Duong, M. J. Cross and J. Louie, *Org. Lett.*, 2004, **6**, 4679–4681.
12 X. Zhu, J. Fan, Y. Wu, S. Wang, L. Zhang, G. Yang, Y. Wei, C. Yin, H. Zhu, S. Wu and H. Zhang, *Organometallics*, 2009, **28**, 3882–3888.
13 S. R. Foley, Y. Zhou, G. P. A. Yap and D. S. Richeson, *Inorg. Chem.*, 2000, **39**, 924–929.
14 F. Paul, S. Moulin, O. Piechaczyk, P. L. Floch and J. A. Osborn, *J. Am. Chem. Soc.*, 2007, **129**, 7294–7304.
15 D. Liu, X. Wei, J. Shi, Z. Guo and M. Lappert, *Synlett*, 2011, 1937–1939.
16 H. R. Sharpe, A. M. Geer, H. E. L. Williams, T. J. Blundell, W. Lewis, A. J. Blake and D. L. Kays, *Chem. Commun.*, 2017, **53**, 937–940.
17 A. G. Giuglio-Tonolo, C. Spitz, T. Terme and P. Vanelle, *Tetrahedron Lett.*, 2014, **55**, 2700–2702.
18 M. Fevre, J. Pinaud, Y. Gnanou, J. Vignolle and D. Taton, *Chem. Soc. Rev.*, 2013, **42**, 2142–2172.
19 Y. Bai, J. He and Y. Zhang, *Angew. Chem., Int. Ed.*, 2018, **57**, 17230–17234.
20 Y. Zhang, G. M. Miyake and E. Y. Chen, *Angew. Chem., Int. Ed.*, 2010, **49**, 10158–10162.
21 Y. Zhang, M. Schmitt, L. Falivene, L. Caporaso, L. Cavallo and E. Y. Chen, *J. Am. Chem. Soc.*, 2013, **135**, 17925–17942.
22 M. G. Dekamin, K. Varmira, M. Farahmand, S. Sagheb-Asl and Z. Karimi, *Catal. Commun.*, 2010, **12**, 226–230.
23 D. Heift, Z. Benko, H. Grutzmacher, A. R. Jupp and J. M. Goicoechea, *Chem. Sci.*, 2015, **6**, 4017–4024.
24 A. Zhou, L. Cao, H. Li, Z. Liu, H. Cho, W. P. Henry and J. C. U. Pittman, *Tetrahedron*, 2006, **62**, 4188–4200.
25 Z. Pusztai, G. Vlad, A. Bodor, I. T. Horvath, H. J. Laas, R. Halpaap and F. U. Richter, *Angew. Chem., Int. Ed.*, 2006, **45**, 107–110.
26 M. Moritsugu, A. Sudo and T. Endo, *J. Polym. Sci., Part A: Polym. Chem.*, 2012, **50**, 4365–4367.
27 M. M. D. Roy and E. Rivard, *Acc. Chem. Res.*, 2017, **50**, 2017–2025.
28 C. Hering-Junghans, P. Andreiuk, M. J. Ferguson, R. McDonald and E. Rivard, *Angew. Chem., Int. Ed.*, 2017, **56**, 6272–6275.
29 S. Naumann, A. W. Thomas and A. P. Dove, *Angew. Chem., Int. Ed.*, 2015, **54**, 9550–9554.
30 Y. B. Wang, Y. M. Wang, W. Z. Zhang and X. B. Lu, *J. Am. Chem. Soc.*, 2013, **135**, 11996–12003.
31 Q. Wang, W. Zhao, S. Zhang, J. He, Y. Zhang and E. Y. X. Chen, *ACS Catal.*, 2018, **8**, 3571–3578.
32 Q. Wang, W. Zhao, J. He, Y. Zhang and E. Y. Chen, *Macromolecules*, 2017, **50**, 123–136.
33 C. Hering-Junghans, I. C. Watson, M. J. Ferguson, R. McDonald and E. Rivard, *Dalton Trans.*, 2017, **46**, 7150–7153.
34 H. Wang, Q. Wang, J. He and Y. Zhang, *Polym. Chem.*, 2019, **10**, 3597–3603.
35 P. Walther, A. Krauß and S. Naumann, *Angew. Chem., Int. Ed.*, 2019, **58**, 10737–10741.
36 S. Naumann, K. Mundsinger, L. Cavallo and L. Falivene, *Polym. Chem.*, 2017, **8**, 5803–5812.
37 S. Naumann and D. Wang, *Macromolecules*, 2016, **49**, 8869–8878.
38 W. Zhao, Q. Wang, J. He and Y. Zhang, *Polym. Chem.*, 2019, **10**, 4328–4335.
39 W. C. Chen, J. S. Shen, T. Jurca, C. J. Peng, Y. H. Lin, Y. P. Wang, W. C. Shih, G. P. Yap and T. G. Ong, *Angew. Chem., Int. Ed.*, 2015, **54**, 15207–15212.
40 G. Ye, S. Chatterjee, M. Li, A. Zhou, Y. Song, B. L. Barker, C. Chen, D. J. Beard, W. P. Henry and C. U. Pittman, *Tetrahedron*, 2010, **66**, 2919–2927.
41 M. Moritsugu, A. Sudo and T. Endo, *J. Polym. Sci., Part A: Polym. Chem.*, 2013, **51**, 2631–2637.
42 Y. Zhang, S. N. Riduan and J. Y. Ying, *Chem. – Eur. J.*, 2009, **15**, 1077–1081.
43 E. Preis, N. Schindler, S. Adrian and U. Scherf, *ACS Macro Lett.*, 2015, **4**, 1268–1272.

