JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY
Article
pubs.acs.org/JACS

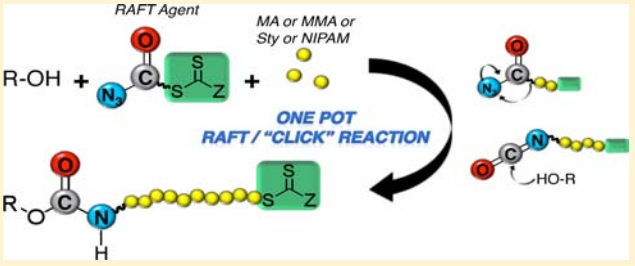
One-Pot RAFT/"Click" Chemistry via Isocyanates: Efficient Synthesis of α-End-Functionalized Polymers

Guillaume Gody,[†] Christian Rossner,[§] John Moraes,[†] Philipp Vana,[§] Thomas Maschmeyer,[‡] and Sébastien Perrier*,[†]

[†]Key Centre for Polymers & Colloids, School of Chemistry, The University of Sydney, New South Wales 2006, Sydney, Australia
[‡]Laboratory of Advanced Catalysis for Sustainability, School of Chemistry, The University of Sydney, New South Wales 2006, Sydney, Australia
[§]Institut für Physikalische Chemie, Georg-August-Universität Göttingen, Tammannstrasse 6, D-37077 Göttingen, Germany

Supporting Information

ABSTRACT: A new methodology has been developed for preparing α-functional polymers in a one-pot simultaneous polymerization/isocyanate "click" reaction. Our original synthetic strategy is based on the preparation of a carbonyl-azide chain transfer agent (CTA) precursor that undergoes the Curtius rearrangement *in situ* during reversible addition−fragmentation chain transfer (RAFT) polymerization yielding well-controlled α-isocyanate modified polymers. This strategy overcomes numerous difficulties associated with the synthesis of a polymerization mediator bearing an isocyanate at the R group and with the handling of such a reactive functionality. This new carbonyl-azide CTA can control the polymerization of a wide range of monomers, including (meth)acrylates, acrylamides, and styrenes (M_n = 2−30 kDa; $Đ$ = 1.16−1.38). We also show that this carbonyl-azide CTA can be used as a universal platform for the synthesis of α-end-functionalized polymers in a one-pot RAFT polymerization/isocyanate "click" procedure.



INTRODUCTION

In recent years, the most significant advances in polymer chemistry have relied on the exploitation of organic chemistry concepts and tools to control the structure of polymeric architectures at the molecular level. Preparation of new nanomaterials with improved properties and applications is still an intense and challenging area for scientists,[1] and the advance of modern synthetic methods has paved the way for new opportunities in the preparation of well-defined materials based on polymeric macromolecules.[2] Among these materials, end-functionalized polymers are receiving considerable attention, due to their wide applications in chemistry, medicine, and material science.[3] To achieve end-functionalized polymers, researchers have widely adopted techniques typically employed in the synthesis of small organic molecules and applied them to macromolecular chemistry.[2] Today, one of the remaining challenges is still to explore and combine these highly efficient organic reactions to respond to the challenges of bringing this chemistry to the macromolecular scale.

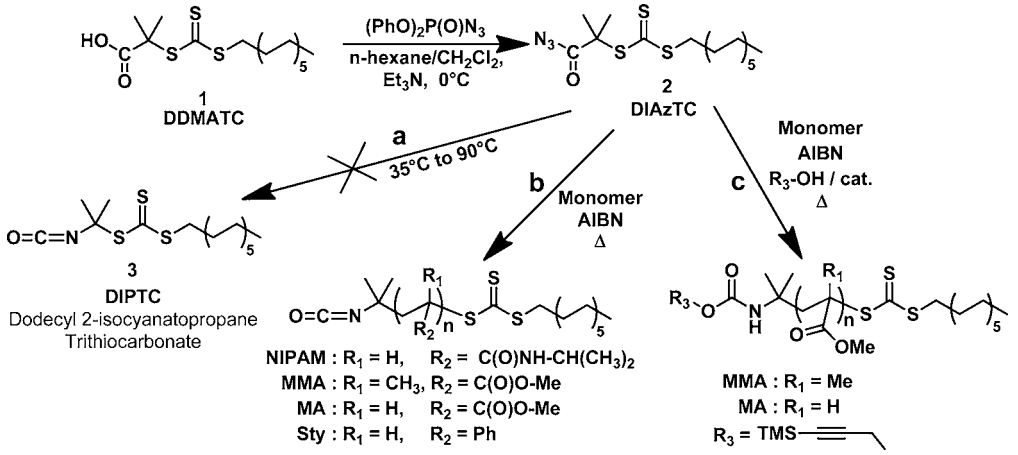
End-functionalized polymers are usually obtained *via* chain growth polymerization using one of the two following strategies: (1) *Pre*polymerization modification, in which a functionalized polymerization initiator carrying the desired functionality is synthesized.[4] This strategy provides a high degree of α-functionalization, if polymerization conditions are carefully chosen. However, this approach is time-consuming, may require several synthetic steps, and lacks versatility, since a different initiator has to be synthesized for each new α-functionalized polymer. (2) *Post*polymerization modification, in which the polymer chain bearing a reactive group reacts with, e.g., a (bio)molecule of interest that possesses a complementary functional group.[5] Such a strategy is challenging, since the coupling reaction has to be very efficient in order to compensate for the low accessibility of the polymer chain-end (due to steric hindrance).

Over the past decade, a growing number of tools has been developed and combined to access controlled and functionalized architectures. Among these tools, the advent of reversible-deactivation radical polymerization (RDRP,[6] also known as controlled radical polymerization or CRP), e.g., reversible addition−fragmentation chain transfer, RAFT,[7] atom transfer radical polymerization, ATRP,[8] aminoxyl-mediated radical polymerization, AMRP (also known as nitroxide mediated polymerization, NMP),[9] as well as ring-opening polymerization (ROP) has allowed for the synthesis of very well-defined polymers with a very precise control of the chain-end. Furthermore, the use of highly efficient coupling chemistries, such as "click chemistry", enables polymer chemists to overcome one of the central difficulties in functionalizing

Received: March 29, 2012
Published: June 26, 2012

dx.doi.org/10.1021/ja3030643 | J. Am. Chem. Soc. 2012, 134, 12596−12603

Scheme 1. Synthesis of the Carbonyl-azide RAFT Agent DIAzTC, 2; (a) Rearrangement into Isocyanate with Concomitant Degradation; (b) Simultaneous RAFT Polymerization and Rearrangement into Isocyanate; and (c) One-Pot RAFT Polymerization/"Click" Alcohol-Isocyanate *via in-situ* Rearrangement into Isocyanate



macromolecules.[10] However, a critical analysis of the characteristics of the most widely used "click" reactions highlights a few drawbacks.[11] For example, while the copper(I)-catalyzed azide−alkyne cycloaddition (CuAAC) reaction remains a gold standard for "click" reactions,[12] it requires the introduction of one of the entities (azide or alkyne) on the (bio)molecules of interest, as none of these two functional groups exist in natural compounds. This demands preliminary stages of synthesis that can add very significantly to the complexity of the coupling strategy. Moreover, such azide groups may be involved in side reactions during radical polymerization,[13] and the copper catalyst can contaminate the product. For the thiol−ene/yne and Michael-addition type reactions,[14] drawbacks include the necessity to introduce the thiol and ene/yne functionalities on the bio(molecule) of interest for a further "click" reaction, since these groups are reactive in radical chemistry. Likewise, the strict orthogonality of the attractive (hetero)Diels−Alder "click" reaction,[15] coupled to the necessity of using protection/deprotection steps, limits its versatility.

In this context, it would be highly advantageous to employ a functionality that is readily synthesized, is stable in radical polymerization, and is capable of reacting efficiently with a wide range of (naturally occurring) functional groups. In this respect, the isocyanate group is a very promising candidate. Isocyanates can be easily and safely prepared from carboxylic acids *via* a thermal Curtius rearrangement of the carbonyl-azide group.[16] The (re)discovery of diphenylphosphoryl azide (DPPA) has simplified their synthesis,[17] avoiding the use of potentially explosive sodium azide or highly toxic phosgene. Moreover, the stability of isocyanates in radical polymerizations has already been demonstrated in the literature.[18] Isocyanates are also one of the only functionalities, along with epoxides, azlactones,[19] and ketenes[20] which have the unique and attractive property to react rapidly and quantitatively, without formation of side products, under mild reaction conditions with a wide range of nucleophiles (such as amines,[21] thiols,[22] alcohols,[23] and carboxylic acids[24]). Despite the importance of isocyanates (particularly in poly(urethane) chemistry), the synthesis of an α-isocyanate end-functional polymer has not yet been reported, even though a few articles mention the use of isocyanate-modified monomers in radical polymerization, most likely due to the difficulty of introducing and handling such a reactive functionality.[25]

In this article, we describe for the first time the synthesis of α-isocyanate end-functional polymers from acrylate, methacrylate, acrylamide, and styrene derivatives *via* an original and highly efficient strategy based on the use of a carbonyl-azide RAFT agent precursor (see Scheme 1) that rearranges into an isocyanate *in situ* during RAFT polymerization. As elegantly shown by Hawker and co-workers for the generation of highly reactive ketene from Meldrum's acid units via thermolysis,[26] the concept of using a stable prereactive group appears very powerful and circumvents numerous difficulties associated with the synthesis, purification, and storage of a highly reactive functionality. In our case, the carbonyl azide RAFT agent acts as a protected isocyanate RAFT agent that is easier to handle. In addition, we also demonstrate that this RAFT agent is highly effective in the preparation of α-end-functionalized polymers in a one-pot RAFT polymerization/"click" alcohol-isocyanate coupling approach. This one-pot reaction is at the borderline between a domino strategy and an orthogonal tandem reaction. This approach is rapid, is very versatile, and offers important new perspectives in the quest for a fast, simple synthesis of α-end-functionalized polymers.

RESULTS AND DISCUSSION

Synthesis of the Carbonyl-azide RAFT Agent, DIAzTC, 2. One of the drawbacks of isocyanates is their poor stability in the presence of water, which renders them difficult to handle and greatly limits their utility regarding the development of *post*polymerization modification strategies. However, isocyanates show different reactivity depending on their electronic and steric environments. For example, the reactivity of the isocyanate moiety in the monomer dimethyl *meta*-isopropenyl benzyl isocyanate (TMI) appears to be lowered due to steric hindrance, and consequently, it exhibits good stability in the presence of water.[27] With this in mind, our aim was to design a CTA, bearing an isocyanate with a good balance between reactivity and stability. Our initial work showed that an isocyanate group on a secondary carbon is too reactive to offer good control over the addition reaction. We, therefore, focused our research on the RAFT agent *S*-1-dodecyl-*S*′-(α,α′-dimethyl-α′′-acetic acid)trithiocarbonate (DDMATC, **1**, Scheme 1), which possesses a tertiary carboxylic acid in the R group that is likely to give a stable carbonyl-azide and, hence, isocyanate. In a first step, the corresponding carbonyl-azide CTA (dodecyl

dx.doi.org/10.1021/ja3030643 | J. Am. Chem. Soc. 2012, 134, 12596−12603

isobutyryl azide trithiocarbonate, DIAzTC, **2**) was prepared by the reaction of DDMATC with diphenylphosphoryl azide (without the requirement of using anhydrous solvents), which afforded the desired RAFT agent in good yield (83% after column chromatography on silica gel, Supporting Information (SI) Figures S1−2). The carbonyl-azide appears stable at room temperature, making it easy to handle. Indeed, after one week at ambient temperature under air or vacuum, no degradation or rearrangement into isocyanate was observed (SI Figures S3−4).

Synthesis of the Isocyanate RAFT Agent, DIPTC, 3. The next step was to convert the carbonyl-azide CTA 2 into isocyanate CTA 3 *via* the Curtius rearrangement (pathway a in Scheme 1). Attempts to effect a thermally driven rearrangement at different temperatures between 35 and 90 °C revealed that the isocyanate CTA 3 could not be obtained with an acceptable purity. The reaction was monitored by Fourier transform infrared spectroscopy (FTIR) and by proton nuclear magnetic resonance spectroscopy (^{1}H NMR) at 50 and 65 °C, which showed that the carbonyl-azide CTA 2 is relatively stable at 50 °C (low yields in rearrangement into isocyanate observed by FTIR after 4 h 30 min; SI Figure S5). However, at 65 °C, where the rearrangement into isocyanate occurred slowly (50% by ^{1}H NMR after 20 h, SI Figure S6), analysis by ^{1}H NMR and by thin-layer chromatography (TLC) indicated a degradation of the CTA (not visible by FTIR). Increasing the temperature allows the carbonyl-azide to rearrange faster into isocyanate but also leads to degradation of the CTA.

RAFT Polymerization with Carbonyl-azide CTA 2. Since the carbonyl-azide CTA displayed good stability at 50 °C, it was used directly to test the RAFT polymerization of methyl acrylate (MA) at this temperature (pathway b in Scheme 1). The aims were to (1) study the ability of this new carbonyl-azide-based leaving group to control RAFT polymerization and (2) prepare a α-carbonyl-azide end-functional polymer that could be further rearranged into an isocyanate upon heating, thus avoiding the problem of CTA degradation. Low molar mass polymers were initially targeted (3400 g·mol^{-1}) to facilitate the analysis by ^{1}H NMR and FTIR.

Figure 1 shows the kinetics of the polymerization of MA at 50 °C with the carbonyl-azide CTA 2 as well as the evolution of molecular weights with conversion. The polymerization is relatively fast, with 91% conversion reached in 4.5 h; however, an induction period of about 1 h was observed (*vide infra*). Excellent control of the molecular weights, which increase linearly with conversions, and low dispersity values ($Đ$) around 1.16 are achieved. Analysis of ^{1}H NMR spectra during the first hour (SI Figures S7−9) revealed that the CTA is selectively converted into a macro-CTA containing a single monomer unit, i.e. the first monomer adduct. The almost-total consumption of the CTA is observed with the disappearance of the peak corresponding to the six protons of the two methyl groups (R group at 1.67 ppm), the shift from 3.28 ppm to 3.34 ppm of the peak relative to the two protons of the CH_2−S (Z-group), and the appearance of a peak (at 4.89 ppm) that is assigned to proton Hα of the newly formed dormant chains. Once the CTA is fully consumed, the polymerization proceeds rapidly *via* the main equilibrium of the RAFT process. This induction period, although typical for dithiobenzoate RAFT agents,[28] is not common with trithiocarbonate CTAs, and we attribute it to an initialization period[29] arising from slow reinitiation by the carbonyl-azide leaving group. Monitoring the RAFT kinetics by FTIR reveals a fascinating and extremely useful effect: as the polymerization proceeds, the Curtius rearrangement from the

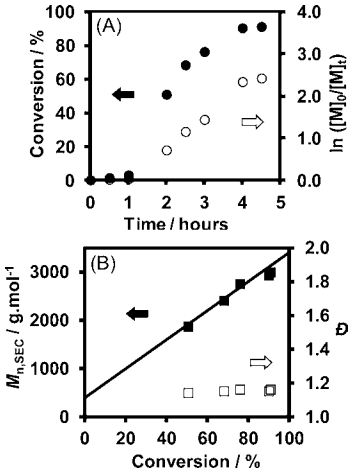


Figure 1. (A) Conversion and pseudo-first-order kinetic plots of MA vs time and (B) evolution of number average molecular weights and dispersity values with conversion in the DIAzTC-mediated RAFT polymerization of MA at 50 °C. The black line represents the theoretical molecular weights. $[MA]_0$ = 6.4 M; $[MA]_0/[DIAzTC]_0/[AIBN]_0$ = 35:1:1.

carbonyl-azide into isocyanate occurs simultaneously. Indeed, after 10 h (SI Figure S13), α-isocyanate end-functional polymers are obtained with conversion of monomer of ca. 99% ($M_{n,theo}$ = 3370 g·mol^{-1}, $M_{n,SEC}$ = 3400 g·mol^{-1}, $Đ$ = 1.13). By comparing this result to the observation made when the CTA DIAzTC was heated alone at the same temperature (i.e., no rearrangement observed), it is clear there is a very strong influence of the electronic environment on the stability of the carbonyl-azide. FTIR and ^{1}H NMR spectra (SI Figures S7−12) show that the rearrangement begins to occur during the first hour, which coincides with the consumption of the CTA (i.e., reinitiation step by the carbonyl-azide leaving group). This observation strongly suggests that as soon as the covalent bond between carbon and sulfur is broken (fragmentation step of the initial CTA) and replaced by a carbon−carbon bond (reinitiation step), the stability of the carbonyl-azide decreases sufficiently to allow the Curtius rearrangement to occur. Based on this observation, and with the aim of polymerizing more activated monomers such as methacrylics and styrenics, the carbonyl-azide CTA 2 was tested at higher temperature (65 °C). Heating the carbonyl-azide CTA alone at 65 °C showed its degradation, possibly due to the close proximity between the carbonyl-azide and the thiocarbonyl-thio group (the mechanism of degradation is yet to be elucidated). However, if the reinitiation of the carbonyl-azide leaving group is faster than the rearrangement/degradation of the CTA, it would be possible to limit or suppress this side reaction. This hypothesis was then examined by monitoring the control of the polymerization of MA at 65 °C by FTIR and ^{1}H NMR. Similar control over the molecular weights distribution is obtained at 65 °C in comparison with the polymerization at 50 °C (linear evolution of the molecular weights with conversion, and dispersity values around 1.15, SI Figure S13), thus confirming our hypothesis. The degradation of the CTA 2 seems to be avoided during the RAFT polymerization. Kinetics also shows that the initialization period appears slightly shorter (around 45 min). As observed at 50 °C, FTIR (Figure 2 A) and ^{1}H NMR spectra (SI Figures S15−16) from experiments at 65 °C reveal that the rearrangement occurs as soon as the first monomer unit is added. However, the Curtius rearrangement takes place much

dx.doi.org/10.1021/ja3030643 | J. Am. Chem. Soc. 2012, 134, 12596−12603

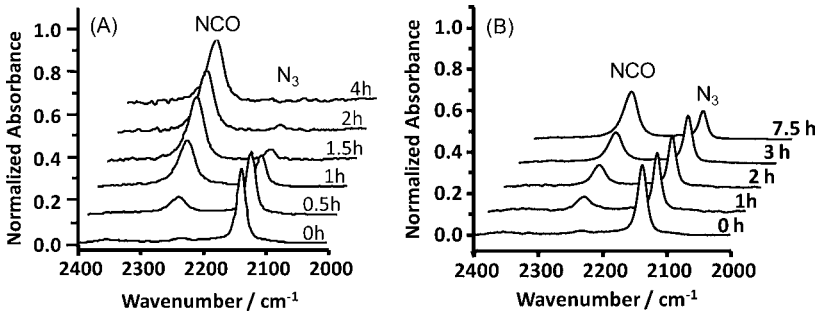


Figure 2. Time evolution of normalized FTIR absorption spectra of (A) RAFT polymerization of MA at 65 °C and (B) DIAzTC CTA alone at 65 °C, showing the rearrangement of the carbonyl-azide into isocyanate.

faster than either the polymerization at 50 °C or when the CTA is reacted alone under the same conditions (Figure 2B). After 2 h (72% of monomer conversion), the majority of polymer chains already bear an isocyanate at the α-chain end (SI Figures S17−18), in contrast to the slow rearrangement observed at 50 °C. After 3 h, the Curtius rearrangement is complete (SI Figure S19). The structure of the resulting α-isocyanate end-functional polymers was confirmed by ^{13}C NMR (SI Figure S20), with the disappearance of the peak corresponding to the carbonyl-azide of the initial CTA 2 at 180.8 ppm (SI Figure S2) and the appearance of the peak at 118.9 ppm assigned to the isocyanate formed.

These results at 50 and 65 °C prove that this *in situ* rearrangement from carbonyl-azide into isocyanate during the RAFT polymerization is intimately linked with the electronic environment of the structures created. Given the excellent control of the RAFT polymerization, even at 65 °C, it seems that the degradation of the CTA 2 is prevented at high temperatures due to a fast reinitiation in comparison with the Curtius rearrangement. The proof for this nondegradation of the thiocarbonyl-thio end group was obtained *via* a chain extension experiment with MA at 65 °C. An α-isocyanate end-functional poly(methyl acrylate) synthesized at 65 °C (conversion =93%, $M_{n,theo}$ = 3600 g·mol^{-1}, $M_{n,SEC}$ = 3450 g·mol^{-1}, $Đ$ = 1.17), used as macro-CTA, shows a perfect reinitiation of the polymer chain with no apparent tailing and gives a final block-type homopolymer with an excellent control (conversion = 93%, $M_{n,theo}$ = 19 600 g·mol^{-1}, $M_{n,SEC}$ = 18 900 g·mol^{-1}, $Đ$ = 1.17) (SI Figure S21).

Although analysis by FTIR and ^1H NMR confirms that the rearrangement into isocyanate is successful, it is difficult to estimate how quantitative the conversion of the carbonyl-azide into isocyanate is. Indeed, it could be that the carbonyl-azide degrades in parallel to its rearrangement, with no impact on the thiocarbonyl-thio functionality. In order to assess the retention of end group functionality, *post*polymerization modifications of the new α-isocyanate end-functional polymers with model compounds were carried out.

***Post*polymerization Modification of α-Isocyanate Poly(methyl acrylate).** In order to confirm the high degree of retention of the isocyanate in the α-chain end, alcohol- and amine-isocyanate reactions were both tested on two isocyanate-poly(methyl acrylate)s prepared by RAFT polymerization at 65 °C. As a proof-of-concept for our strategy, propargyl-alcohol and benzylamine were chosen as model compound due to their characteristic chemical shifts before and after coupling that do not interfere with any of the other peaks from the polymer chain.

Both reactions were realized at room temperature, in air and in nondistilled dichloromethane or chloroform to test the robustness of our isocyanate *post*-polymerization modification strategy.

For the alcohol-isocyanate coupling (3 equiv of alcohol), dibutyltin dilaurate (DBTDL) was used as a catalyst, and after 48 h, complete consumption of the isocyanate group is obtained, as proven by the FTIR spectra (Figure 3A) with the

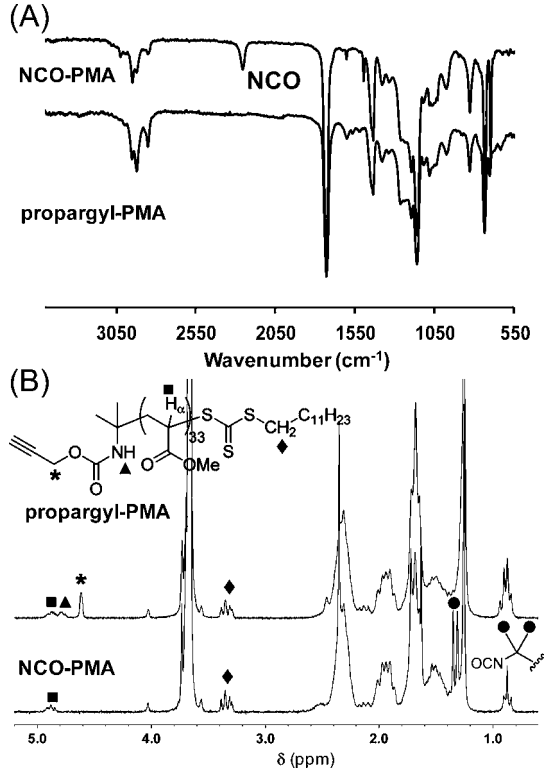


Figure 3. (A) FTIR and (B) ^1H NMR spectra ($CDCl_3$, 200 MHz) showing the *post*polymerization modification of α-isocyanate-end PMA (run 2, Table 1) with propargyl alcohol.

complete disappearance of the associated peak at 2243 cm^{-1}. The ^1H NMR spectra (Figure 3B) also confirmed the efficiency of the alcohol−isocyanate coupling with the disappearance of the two peaks corresponding to the two methyl groups in the α-position with respect to the isocyanate at 1.34 and 1.31 ppm, and the shift of the two protons of the propargyl alcohol (from 4.27 ppm to 4.62 ppm, SI Figures S22−23). Integration of these two protons reveals an almost quantitative coupling with the isocyanate (around 95%, SI Figure S24) and confirms that

dx.doi.org/10.1021/ja3030643 | J. Am. Chem. Soc. 2012, 134, 12596−12603

Table 1. Polymerization Conditions and Macromolecular Characteristics of Polymers Synthesized by RAFT Polymerization Using DIAzTC as Chain Transfer Agent

run	polymer	solvent	$[M]_0$ (mol·L^{-1})	$[M]_0/[DIAzTC]_0/[AIBN]_0$	temp (°C)	time (h)	conv[a] (%)	$M_{n,theo}$[b] (g·mol^{-1})	$M_{n,SEC}$[c] (g·mol^{-1})	$Đ$[c]
1	NCO-PMA	toluene	6.4	35:1:1	50	4.5	91	3 100	3 000[d]	1.16
2	NCO-PMA	toluene	6.4	35:1:0.1	65	4	94	3 200	3 000[d]	1.16
3	NCO-PMA	toluene	6.4	500:1:0.1	60	15	83	35 700	25 300[d]	1.35
4	NCO-PNIPAM	dioxane	2	27:1:0.1	65	4	74	2 650	2 200	1.33
5	NCO-PMMA	toluene	5.5	32:1:0.1	60	13	85	3 100	3 000[e]	1.18
6	NCO-PMMA	toluene	5.5	200:1:0.1	60	13	49	9 900	9 900[e]	1.38
7	NCO-PMMA	toluene	5.5	400:1:0.1	65	20	80	31 800	27 700[e]	1.37
8	NCO-PSty	toluene	8.1	60:1:0.1	65	15	44	3 150	3 700	1.23
9	NCO-PSty	bulk	8.7	200:1:0.1	65	19	41	8 900	6 700	1.24
10	NCO-PSty	bulk	8.7	400:1:0.1	70	16	28	11 700	9 000	1.28

[a]Determined by ^{1}H NMR in $CDCl_3$. [b]$M_{n,theo} = [M]_0 \times Conv\ M_M/[DIAzTC]_0 + M_{DIAzTC} - M_{N2}$. [c]Determined by SEC/RI in THF with PSty used as molecular weight standards. [d]Molecular weight values corrected using the Mark–Houwink–Sakurada parameters K_{PSty} = 14.1 ($\times 10^3$ mL·g^{-1}), α_{PSty} = 0.700 and K_{PMA} = 19 ($\times 10^3$ mL·g^{-1}), α_{PMA} = 0.660. [e]Molecular weight values corrected using the Mark–Houwink–Sakurada parameters K_{PSty} = 14.1 ($\times 10^3$ mL·g^{-1}), α_{PSty} = 0.700 and K_{PMMA} = 10.4 ($\times 10^3$ mL·g^{-1}), α_{PMMA} = 0.697.

no side-reaction of the isocyanate group takes place during the entire process (polymerization, purification, and coupling) despite using nondistilled solvents.

For the amine-isocyanate coupling (1.2 equiv of amine), the reaction was undertaken without a catalyst in less than 1 h to obtain complete consumption of the isocyanate, as seen from FTIR (SI Figure S25). The ^{1}H NMR spectra (SI Figure S26), before and after precipitation in *n*-hexane, confirmed the high and fast efficiency of the amine–isocyanate coupling (% α-functionalization ≈98%). Remarkably, no side reaction (aminolysis) of the trithiocarbonate end group was observed. The retention of the trithiocarbonate end group was also proved by a successful block extension with butyl acrylate (SI Figure S27).

These results prove that the *in situ* Curtius rearrangement from the carbonyl-azide CTA 2 into isocyanate during the RAFT polymerization is quantitative even at 65 °C, in contrast to the isolated CTA 2, which was unstable at that temperature. This means that the reinitiation step of the carbonyl-azide leaving group occurs more quickly than the rearrangement/degradation of the CTA. This *post*-polymerization modification strategy based on isocyanate is a powerful method and meets key requirements of a "click" reaction, such as room temperature, high efficiency, robustness, and the absence of side-products.

RAFT Polymerization of a Variety of Vinyl Monomers Mediated by DIAzTC. This new carbonyl-azide CTA was further tested in the RAFT polymerization of a range of monomers to evaluate its potential for preparing a large range of α-isocyanate end-functional polymers. *N*-Isopropyl acrylamide (NIPAM) and styrene (Sty) were selected as acrylamide and styrenic derivatives, respectively. The polymerization of methyl methacrylate (MMA) was also attempted, even though trithiocarbonates are known to be less efficient CTAs in the mediation of the RAFT polymerization of methacrylate derivatives. Polymerization conditions and results are reported in Table 1. Good control of the molecular weights and low dispersity values are observed with this new CTA for all monomers. Interestingly, a substantial difference in dispersity values is observed depending on the targeted molecular weight. Excellent control is exhibited when low molecular weight poly(methyl (meth)acrylate) and poly(styrene) are targeted with $Đ$ between 1.16 and 1.23 (runs 1, 2, 5, and 8, Table 1, and SI Figures S28–29). It is particularly remarkable to note that this CTA enables very good control of poly(methyl methacrylate). Analysis by FTIR shows the complete disappearance of the carbonyl-azide group and the formation of α-isocyanate end-functional polymers (SI Figures S30–31). The polymerization seems less controlled for NIPAM ($Đ$ = 1.33, run 4) and when higher molecular weights poly((meth)-acrylate) and poly(styrene) are targeted ($Đ$ increases from 1.16 to 1.38; runs 3, 6, 7, and 10). This can be explained by the competition during the initialization step between reinitiation of the carbonyl-azide leaving group (e.g., preventing the degradation) and the rearrangement/degradation of the CTA. Indeed, when higher molecular weights are targeted, the polymerization is slower due to lower concentration in AIBN (since $[CTA]_0/[AIBN]_0$ is kept constant), thus increasing the time of the initialization period. In all cases, chromatograms obtained by size exclusion chromatography (SEC) in tetrahydrofuran (THF) show a monomodal distribution, but with a tail toward lower molecular weights when high molecular weights are targeted (SI Figures S32–33). For polymers with higher molecular weights, the intensity of the isocyanate peak at 2243 cm^{-1} in FTIR spectra decreases (with the intensity being very low for polymers with ca. 10 000 g·mol^{-1}) and the isocyanate peak could not be observed for polymers with molecular weights higher than 20 000 g·mol^{-1} (SI Figures S33–35). Since the polymerization appears controlled and the SEC chromatograms do not show any degradation of the polymers, we conclude that the isocyanate peak intensity is below the detection limit of the FTIR spectrometer. This is confirmed by ^{1}H NMR spectra that always show the characteristic peaks of the two methyl groups in the α-position with respect to the isocyanate (at 1.30 and 1.34 ppm, Figure S33) but, as expected, with a very low intensity for higher molecular weights.

One-Pot RAFT/Alcohol-isocyanate "Click" Reaction. Despite the very high levels of control attained in the field of polymer synthesis, only a few articles report one-pot strategies that combine simultaneous polymerization and α- or side-chain functionalization. In this area, we can cite the works of Ranjan and Brittain combining CuAAC reaction and RAFT polymerization with the simultaneous attachment of the azido-RAFT agent onto the alkyne-functionalized surface of silica nanoparticles and the polymerization of styrene (orthogonal tandem reactions).[30] Another interesting one-pot strategy has been

dx.doi.org/10.1021/ja3030643 | J. Am. Chem. Soc. 2012, 134, 12596–12603

Table 2. Polymerization Conditions and Macromolecular Characteristics of the One-Pot RAFT Polymerization, Rearrangement into Isocyanate, and Simultaneous "Click" Reaction with TMS-propargyl Alcohol in Toluene at 65°C for 20 h

samples	$[M]_0$ ($mol \cdot L^{-1}$)	$[M]_0/[DIAzTC]_0/[AIBN]_0/[TMS\text{-}prop.alc.]_0/[DBTL]_0$	conv.[a] (%)	$M_{n,theo.}$[b] ($g \cdot mol^{-1}$)	$M_{n,SEC}$[c] ($g \cdot mol^{-1}$)	$Đ$[c]	functionalization (%)
TMS-prop.PMA	6.4	40:1:0.1:3:0.18	99	3900	3800[d]	1.26	>95 ± 5
TMS-prop.PMMA	5.5	35:1:0.1:3:0.22	99	3900	5300[e]	1.23	>95 ± 5

[a]Determined by ^1H NMR in $CDCl_3$. [b]$M_{n,theo} = [M]_0 \times$ Conv $M_M/[DIAzTC]_0 + M_{DIAzTC} - M_{N_2} + M_{TMS-prop.alc.}$. [c]Determined by SEC/RI in THF with PSty used as molecular weights standards. [d]Molecular weights values corrected using the Mark–Houwink–Sakurada parameters K_{PSty} = 14.1 ($\times 10^3$ $mL \cdot g^{-1}$), α_{PSty} = 0.700 and K_{PMA} = 19 ($\times 10^3$ $mL \cdot g^{-1}$), α_{PMA} = 0.660. [e]Molecular weights values corrected using the Mark–Houwink–Sakurada parameters K_{PSty} = 14.1 ($\times 10^3$ $mL \cdot g^{-1}$), α_{PSty} = 0.700 and K_{PMMA} = 10.4 ($\times 10^3$ $mL \cdot g^{-1}$), α_{PMMA} = 0.697.

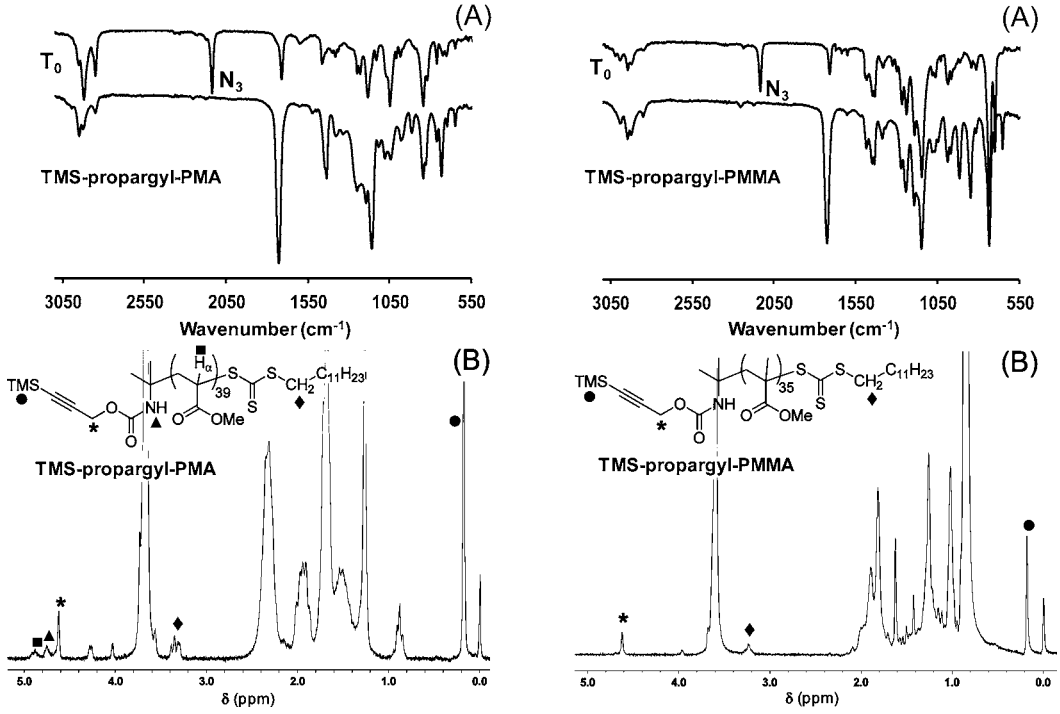


Figure 4. (A) FTIR and (B) ^1H NMR spectra ($CDCl_3$, 200 MHz) showing the one-pot RAFT polymerization at 65 °C for 20 h of MA (left) and MMA (right); rearrangement into isocyanate and simultaneous "click" reaction with TMS-propargyl alcohol.

reported by Barner-Kowollik and co-workers for the preparation of ω-cyclopentadienyl poly(2-ethyl-2-oxazoline) (PEtOx–Cp) *via* cationic ring-opening polymerization utilizing sodium cyclopentadienide as a termination agent (nontandem reaction, multicatalytic strategy).[31] Du Prez et al.[32] also described the *in situ* generation of thiols by nucleophilic ring-opening of a thiolactone with amines, followed by a UV-initiated radical thiol–ene reaction in a one-pot fashion (nontandem reaction, domino strategy). In this context, we were interested in probing as to whether the carbonyl-azide CTA could rearrange into an isocyanate during the polymerization and simultaneously undergo a *post*modification reaction in a one-pot procedure (pathway c in Scheme 1). As a proof of concept, we tested the alcohol-isocyanate coupling since, contrary to amines and thiols that give rise to side reactions in RAFT polymerization, alcohols are relatively inert during the RAFT process. Two one-pot RAFT/alcohol-isocyanate "click" reactions were performed with MA and MMA, using the model compound: trimethylsilyl propargyl alcohol (TMS-prop.alc.) (Table 2). The protected version of the propargyl alcohol was used as a marker in ^1H NMR analyses, and low molecular weights were targeted to follow the reaction by FTIR and to facilitate the quantification of the coupling by ^1H NMR. The two polymerizations were carried out in the presence of the catalyst DBTDL, with trimethylsilyl propargyl alcohol in nonanhydrous toluene (as a proof of the robustness of the process), and at 65 °C, at which temperature degradation of the CTA 2 was observed previously (SI Figure S6). After 20 h, quantitative conversions are obtained for both acrylate and methacrylate monomers. Molecular weights are in very good agreement with theory for PMA and slightly higher than expected for PMMA. For both, dispersity values are low with values around 1.25 (SI Figures S37–39). These results show that the catalyst DBTDL does not interfere with the RAFT process. Results of α-functionalization appear excellent, with a yield above 95% (as determined by ^1H NMR; SI Figures S36–38). Comparison of FTIR spectra before and after polymerization (Figure 4) shows that the azide peak at 2150 cm^{-1} (carbonyl-azide CTA) has completely disappeared and that no isocyanate peak is present. It is therefore clear that the vast majority of polymer chains reacted with the TMS-propargyl alcohol during the RAFT polymerization in this one-pot fashion regime.

■ CONCLUSION

In summary, we have developed a simple and efficient methodology for the preparation of either α-isocyanate end-

dx.doi.org/10.1021/ja3030643 | J. Am. Chem. Soc. 2012, 134, 12596–12603

functional polymers or α-end-functionalized polymers based on the synthesis of a novel carbonyl-azide chain transfer agent. Our carbonyl-azide RAFT agent undergoes the Curtius rearrangement, while mediating the RAFT process and allowing for the easy preparation of α-isocyanate polymers without the usual problems associated with handling an isocyanate-bearing RAFT agent. We also showed that a one-pot RAFT polymerization/"click" alcohol-isocyanate coupling can be performed simply by adding an alcohol and the catalyst DBTDL to the polymerization medium, enabling the preparation of well-defined α-end-functionalized polymers. A catalyst is however not needed when using amines, which leads to a quantitative functionalization at ambient conditions, notably without side-reaction on the trithiocarbonate end group (aminolysis).

The advantages of this strategy include (1) the carbonyl-azide CTA can be readily prepared in a good yield and is easily handled at room temperature (with no rearrangement/degradation); (2) a wide range of monomers can be polymerized (acrylates, acrylamides, methacrylates, and styrenics) at up to 70 °C to give well-defined α-isocyanate end-functional polymers, and (3) no exclusion of air or anhydrous solvent in *post*polymerization modification is required due to the stability of the tertiary isocyanate.

The concept was demonstrated using RAFT polymerization and can clearly be extended to other types of polymerization, radical- or nonradical-based, and permit reaction with a wider range of functional groups (e.g., amines, thiols). This original approach, which is both rapid and very versatile, offers tantalizing opportunities by expanding the current toolbox available to material scientists in the realm of facile end-group modification of macromolecular architectures.

■ ASSOCIATED CONTENT

Supporting Information

Detailed experimental data (organic synthesis and kinetics), ^{1}H and ^{13}C NMR spectra, FTIR spectra, and size exclusion chromatography traces. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

sebastien.perrier@sydney.edu.au

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The authors thank Ignite Energy Resources Ltd, Licella Pty Ltd, and the Australian Research Council for funding the Linkage Project (LP100200339) and (T.M.) for the Future Fellowship (FT0990485), The Gritton Scholarship administered by The University of Sydney (J.M.). P.V. acknowledges receipt of a Heisenberg-Professorship (DFG). C.R. is recipient of a scholarship of the Studienstiftung des deutschen Volkes. Neil Mallo is acknowledged for the preparation of 3-(trimethylsilyl) propargyl alcohol.

■ REFERENCES

(1) (a) Balazs, A. C.; Emrick, T.; Russell, T. P. *Science* **2006**, *314*, 1107−1110. (b) Kiick, K. L. *Science* **2007**, *317*, 1182−1183. (c) Jones, R. *Nat. Nanotechnol.* **2008**, *3*, 699−700.

(2) (a) Hawker, C. J.; Wooley, K. L. *Science* **2005**, *309*, 1200−1205. (b) Barner-Kowollik, C.; Inglis, A. J. *Macromol. Chem. Phys.* **2009**, *210*, 987−992.

(3) (a) Pasut, G.; Veronese, F. M. *Prog. Polym. Sci.* **2007**, *32*, 933−961. (b) Nie, Z. H.; Kumacheva, E. *Nat. Mater.* **2008**, *7*, 277−290. (c) Le Droumaguet, B.; Nicolas, J. *Polym. Chem.* **2010**, *1*, 563−598. (d) Beija, M.; Marty, J. D.; Destarac, M. *Prog. Polym. Sci.* **2011**, *36*, 845−886. (e) Boyer, C.; Stenzel, M. H.; Davis, T. P. *J. Polym. Sci., Part A: Polym. Chem.* **2011**, *49*, 551−595. (f) Dehn, S.; Chapman, R.; Jolliffe, K. A.; Perrier, S. *Polym. Rev.* **2011**, *51*, 214−234. (g) Xu, F. J.; Yang, W. T. *Prog. Polym. Sci.* **2011**, *36*, 1099−1131.

(4) (a) Perrier, S.; Takolpuckdee, P.; Westwood, J.; Lewis, D. M. *Macromolecules* **2004**, *37*, 2709−2717. (b) Heredia, K. L.; Bontempo, D.; Ly, T.; Byers, J. T.; Halstenberg, S.; Maynard, H. D. *J. Am. Chem. Soc.* **2005**, *127*, 16955−16960. (c) Nicolas, J.; San Miguel, V.; Mantovani, G.; Haddleton, D. M. *Chem. Commun.* **2006**, 4697−4699.

(5) (a) Binder, W. H.; Sachsenhofer, R. *Macromol. Rapid Commun.* **2007**, *28*, 15−54. (b) Gauthier, M. A.; Gibson, M. I.; Klok, H. A. *Angew. Chem., Int. Ed.* **2009**, *48*, 48−58.

(6) Jenkins, A. D.; Jones, R. G.; Moad, G. *Pure Appl. Chem.* **2010**, *82*, 483−491.

(7) Chiefari, J.; Chong, Y. K.; Ercole, F.; Krstina, J.; Jeffery, J.; Le, T. P. T.; Mayadunne, R. T. A.; Meijs, G. F.; Moad, C. L.; Moad, G.; Rizzardo, E.; Thang, S. H. *Macromolecules* **1998**, *31*, 5559−5562.

(8) (a) Kamigaito, M.; Ando, T.; Sawamoto, M. *Chem. Rev.* **2001**, *101*, 3689−3745. (b) Matyjaszewski, K.; Xia, J. H. *Chem. Rev.* **2001**, *101*, 2921−2990.

(9) (a) Moad, G.; Rizzardo, E. *Macromolecules* **1995**, *28*, 8722−8728. (b) Hawker, C. J.; Bosman, A. W.; Harth, E. *Chem. Rev.* **2001**, *101*, 3661−3688.

(10) (a) Kolb, H. C.; Finn, M. G.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2001**, *40*, 2004−2021. (b) Iha, R. K.; Wooley, K. L.; Nystrom, A. M.; Burke, D. J.; Kade, M. J.; Hawker, C. J. *Chem. Rev.* **2009**, *109*, 5620−5686. (c) Sumerlin, B. S.; Vogt, A. P. *Macromolecules* **2010**, *43*, 1−13. (d) Chapman, R.; Jolliffe, K. A.; Perrier, S. *Polym. Chem.* **2011**, *2*, 1956−1963. (e) Harvison, M. A.; Lowe, A. B. *Macromol. Rapid Commun.* **2011**, *32*, 779−800. (f) Kempe, K.; Krieg, A.; Becer, C. R.; Schubert, U. S. *Chem. Soc. Rev.* **2012**, *41*, 176−191.

(11) Barner-Kowollik, C.; Du Prez, F. E.; Espeel, P.; Hawker, C. J.; Junkers, T.; Schlaad, H.; Van Camp, W. *Angew. Chem., Int. Ed.* **2011**, *50*, 60−62.

(12) (a) Fournier, D.; Hoogenboom, R.; Schubert, U. S. *Chem. Soc. Rev.* **2007**, *36*, 1369−1380. (b) Besanceney-Webler, C.; Jiang, H.; Zheng, T. Q.; Feng, L.; del Amo, D. S.; Wang, W.; Klivansky, L. M.; Marlow, F. L.; Liu, Y.; Wu, P. *Angew. Chem., Int. Ed.* **2011**, *50*, 8051−8056.

(13) Ladmiral, V.; Legge, T. M.; Zhao, Y. L.; Perrier, S. *Macromolecules* **2008**, *41*, 6728−6732.

(14) (a) Kakwere, H.; Perrier, S. *J. Am. Chem. Soc.* **2009**, *131*, 1889−1895. (b) Kade, M. J.; Burke, D. J.; Hawker, C. J. *J. Polym. Sci., Part A: Polym. Chem.* **2010**, *48*, 743−750. (c) Roth, P. J.; Boyer, C.; Lowe, A. B.; Davis, T. P. *Macromol. Rapid Commun.* **2011**, *32*, 1123−1143.

(15) Tasdelen, M. A. *Polym. Chem.* **2011**, *2*, 2133−2145.

(16) Curtius, T. *Chem. Ber* **1890**, *23*, 3023.

(17) Shioiri, T.; Yamada, S.; Ninomiya, K. *J. Am. Chem. Soc.* **1972**, *94*, 6203−6205.

(18) Barner, L.; Barner-Kowollik, C.; Davis, T. P. *J. Polym. Sci., Part A: Polym. Chem.* **2002**, *40*, 1064−1074.

(19) Buck, M. E.; Lynn, D. M. *Polym. Chem.* **2012**, *3*, 66−80.

(20) Tidwell, T. T. *Eur. J. Org. Chem.* **2006**, 563−576.

(21) Yoon, J.; Lovell, P. A. *Macromol. Chem. Phys.* **2008**, *209*, 279−289.

(22) (a) Dyer, E.; Glenn, J. F. *J. Am. Chem. Soc.* **1957**, *79*, 366−369. (b) Smith, J. F.; Friedrich, E. C. *J. Am. Chem. Soc.* **1959**, *81*, 161−163. (c) Iwakura, Y.; Okada, H. *Can. J. Chem.-Rev. Can. Chim.* **1960**, *38*, 2418−2424. (d) Klemm, E.; Stockl, C. *Macromol. Chem. Phys.* **1991**, *192*, 153−158. (e) Li, H. B.; Yu, B.; Matsushima, H.; Hoyle, C. E.; Lowe, A. B. *Macromolecules* **2009**, *42*, 6537−6542. (f) Matsushima, H.; Shin, J.; Bowman, C. N.; Hoyle, C. E. *J. Polym. Sci., Part A: Polym. Chem.* **2010**, *48*, 3255−3264. (g) Hensarling, R. M.; Rahane, S. B.; LeBlanc, A. P.; Sparks, B. J.; White, E. M.; Locklin, J.; Patton, D. L. *Polym. Chem.* **2011**, *2*, 88−90.

(23) (a) Baker, J. W.; Gaunt, J. *J. Chem. Soc.* **1949**, 19−24. (b) Dyer, E.; Taylor, H. A.; Mason, S. J.; Samson, J. *J. Am. Chem. Soc.* **1949**, *71*, 4106−4109. (c) Biedermann, F.; Appel, E. A.; del Barrio, J.; Gruendling, T.; Barner-Kowollik, C.; Scherman, O. A. *Macromolecules* **2011**, *44*, 4828−4835. (d) Flores, J. D.; Treat, N. J.; York, A. W.; McCormick, C. L. *Polym. Chem.* **2011**, *2*, 1976−1985. (e) Mansur, A. A. P.; do Nascimento, O. L.; Orefice, R. L.; Mansur, H. S. *Surf. Interface Anal.* **2011**, *43*, 738−743.

(24) (a) Schuemacher, A. C.; Hoffmann, R. W. *Synthesis* **2001**, 243−246. (b) Sudarshan, N. S.; Narendra, N.; Hemantha, H. P.; Sureshbabu, V. V. *J. Org. Chem.* **2007**, *72*, 9804−9807. (c) Sasaki, K.; Crich, D. *Org. Lett.* **2011**, *13*, 2256−2259.

(25) (a) Barner, L.; Pereira, S.; Sandanayake, S.; Davis, T. P. *J. Polym. Sci., Part A: Polym. Chem.* **2006**, *44*, 857−864. (b) Beck, J. B.; Killops, K. L.; Kang, T.; Sivanandan, K.; Bayles, A.; Mackay, M. E.; Wooley, K. L.; Hawker, C. J. *Macromolecules* **2009**, *42*, 5629−5635. (c) Flores, J. D.; Shin, J.; Hoyle, C. E.; McCormick, C. L. *Polym. Chem.* **2010**, *1*, 213−220. (d) Kyulavska, M.; Kostov, G.; Ameduri, B.; Mateva, R. *J. Polym. Sci., Part A: Polym. Chem.* **2010**, *48*, 2681−2697. (e) Moraes, J.; Maschmeyer, T.; Perrier, S. *J. Polym. Sci., Part A: Polym. Chem.* **2011**, *49*, 2771−2782. (f) Moraes, J.; Maschmeyer, T.; Perrier, S. *Aust. J. Chem.* **2011**, *64*, 1047−1053.

(26) Leibfarth, F. A.; Kang, M.; Ham, M.; Kim, J.; Campos, L. M.; Gupta, N.; Moon, B.; Hawker, C. J. *Nat. Chem.* **2010**, *2*, 207−212.

(27) Dexter, R. W.; Saxon, R.; Fiori, D. E. *J. Coat. Technol.* **1986**, *58*, 43−47.

(28) (a) Drache, M.; Schmidt-Naake, G.; Buback, M.; Vana, P. *Polymer* **2005**, *46*, 8483−8493. (b) Nguyen, D. H.; Vana, P. *Aust. J. Chem.* **2006**, *59*, 549−559.

(29) (a) McLeary, J. B.; Calitz, F. M.; McKenzie, J. M.; Tonge, M. P.; Sanderson, R. D.; Klumperman, B. *Macromolecules* **2004**, *37*, 2383−2394. (b) van den Dungen, E. T. A.; Matahwa, H.; McLeary, J. B.; Sanderson, R. D.; Klumperman, B. *J. Polym. Sci., Part A: Polym. Chem.* **2008**, *46*, 2500−2509.

(30) Ranjan, R.; Brittain, W. J. *Macromol. Rapid Commun.* **2007**, *28*, 2084−2089.

(31) Glassner, M.; Kempe, K.; Schubert, U. S.; Hoogenboom, R.; Barner-Kowollik, C. *Chem. Commun.* **2011**, *47*, 10620−10622.

(32) Espeel, P.; Goethals, F.; Du Prez, F. E. *J. Am. Chem. Soc.* **2011**, *133*, 1678−1681.