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Highly Diastereoselective Radical Cyclizations on Soluble Ring Opening Metathesis Supports

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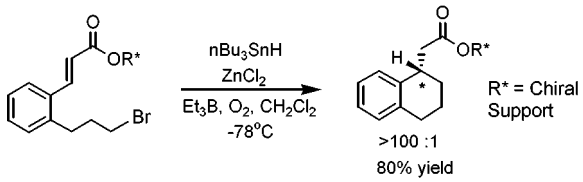
ABSTRACT



This study represents the first examples of stereoselective radical cyclizations on soluble supports. A stereocontrol element consisting of a polymer-imbedded (+)-isosorbide chiral auxiliary was used in each monomer subunit. A survey of various Lewis acids was also examined. The best results gave very high distereoselectivites of >100:1 in a hepa-1,3-dienenyl radical cyclization using zinc chloride as a Lewis acid.

Considerable recent research efforts have enabled a much better understanding of the transition metal catalyzed olefin metathesis reaction.[1] In particular, ring opening metathesis polymerization (ROMP), commonly employing a Grubbs-type ruthenium-based catalyst, has been used extensively in organic materials and macromolecular applications but has seen little use as a support for synthetic organic reactions.[2] When properly constructed, such supports are soluble in a variety of organic solvents and can be readily precipitated as white crystalline-like solids from cold (−78 °C) methanol.

As an alternative to the drawbacks of commonly employed cross-linked resin supports,[3] interest has recently turned to soluble polymers driven by a multitude of benefits, such as direct NMR monitoring of the reaction, rapid product purification, solution-phase reaction rates, and facile removal of harmful solution organometallics by rapid filtration of the precipitated solid support.[4] Our investigations were further motivated by the desire to abate physiologically and environmentally toxic tin byproducts in tributyltin hydride mediated radical reactions.[4d,e] The difficulty of tin removal is considered by many to be the Achilles' heel of synthetic radical methodology, which hinders it use and application in pharmaceutical syntheses.[5]

An important recent goal in radical reactions is in control of stereoselectivity and we recently began a new program involving the attachment of chiral auxiliaries to soluble polymer precursors.[6] Polymer-bound chiral auxiliaries are of particular importance as they can lead to asymmetric radical reactions with concomitant facile recovery and potential recycling of the supported chiral vehicle by simple

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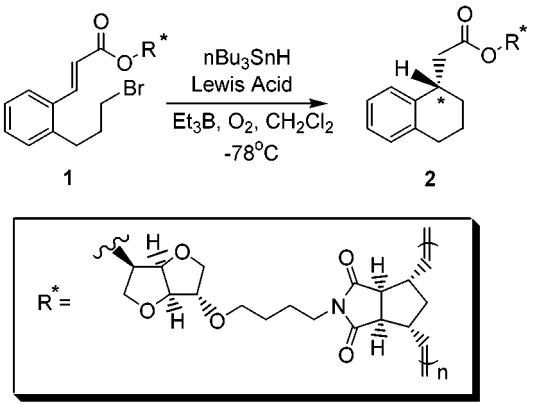
filtration.[7] The increasing demands of higher diastereo- and enantioselectivity in the combinatorial/drug discovery area are now just beginning to lead investigators to seek new methods of incorporating asymmetry into polymer-supported transformations.[7b−d]

In this study, 6-heptenyl radical cyclizations were examined on a new custom-synthesized designer support by mounting each reaction on a soluble succinimide-derived ROMP backbone, shown as **1** → **2** in Scheme 1.[8] A

Scheme 1



stereocontrol element (R*) consisting of a polymer-imbedded (+)-isosorbide chiral auxiliary was used in each monomer subunit. Very high diastereoselectivites of >100:1 were observed in the cyclization using zinc chloride as a Lewis acid and >99% enantiomeric excess was achieved after cleavage from the support. A survey of various solvent systems, radical initiators, temperatures, and Lewis acids resulted in highly diastereoselective cyclic products. It is worth noting that this work contains the first examples of asymmetric radical cyclizations on soluble support.[8]

Radical reactions offer synthetic benefits such as neutral reaction conditions and tolerance of various functional groups and protecting schemes.[9] New studies have shown the diastereoselectivity of free radical reactions is greatly enhanced as a result of the use of a combination of low temperatures, Lewis acids, and appended chiral auxiliaries, scaffolds, and templates.[10] For example, radical cyclizations with chiral auxiliaries such as oxazolidinones, sulfoxides, and chiral esters have investigated.[10d−f] An important objective in our studies was to study radical cyclizations using a removable carbohydrate on designer support as a stereocontrol element.[11] Although carbohydrate auxiliaries not on polymer support have been studied with many varieties of reactions, they have not been systematically studied in radical cyclizations or on support. In general, we hoped that this would offer a well-documented and reliable means of radical carbon−carbon bond formation.

Our studies on stereoselective and polymer-supported radical cyclizations began with the construction of a metathesis monomer. This would then be tethered to polymer-supported norborene imide by a short series of four methylene units. All of the important structural features for the 6-heptenyl radical reaction were to be covalently secured into the polymer backbone before polymerization of the norborene ring system. This is done to ensure that each monomer contains a cyclization precursor and, thus, increase the loading on the polymer to an absolute maximum. In other words, each monomer unit contains a reaction site integrated into the backbone so that this designer polymer essentially has 100% loading capacity. Standard solid-phase resins cannot achieve this level of loading mainly because the substrate is incompletely covalently attached to the polymer. With the methodology discussed herein, the substrate is always completely incorporated into each monomer and then subsequently polymerized.

We decided to use norbornyl monomers in these studies because they polymerize readily by ring-opening metathesis with Grubbs' well-defined ruthenium catalysts.[12] The small amount of strain inherent with norbornenes assists and accelerates the metathesis.[13] Moreover, a wide variety of norbornenes are commercially available or readily prepared by Diels−Alder reactions.

Diol **4** was constructed initially in 79% yield (two steps) from 1,2-dihydronaphthalene (**3**) by ozonolysis and reductive workup with sodium borohydride, as shown in Scheme 2.

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(8) For examples of radical reactions on commercial resin supports, see: (a) Sibi, M. P.; Chandramouli, S. V. *Tetrahedron Lett.* **1997** *38*, 8929−8932. (b) Miyabe, H.; Konishi, C.; Naito, T. *Org. Lett.* **2000**, *2*, 1443−1445. (c) Jia, G. F.; Iida, H.; Lown, J. W. *Synlett* **2000**, 603−606. (d) Wendeborn, S.; De Mesmaeker, A.; Brill, W. K. D.; Berteina, S. *Acc. Chem. Res.* **2000**, 215−224. (e) Jeon, G. H.; Yoon, J. Y.; Kim, S.; Kim, S. S. *Synlett* **2000**, 128−130. (f) Miyabe, H.; Ueda, M.; Yoshioka, N.; Yamakawa, K.; Naito, T. *Tetrahedron* **2000**, *56*, 2413−2420. (g) Miyabe, H.; Tanaka, H.; Naito, T. *Tetrahedron Lett.* **1999**, *40*, 8387−8390. (h) Caddick, S.; Hamza, D.; Wadman, S. N. *Tetrahedron Lett.* **1999**, *40*, 7285−7288. (i) Berteina, S.; De Mesmaeker, A.; Wendeborn, S.; *Synlett* **1999**, 1121−1123. (j) Zhu, X. W.; Ganesan, A. *J. Comb. Chem.* **1999**, *1*, 157−162. (k) Yim, A. M.; Vidal, Y.; Viallefont, P.; Martinez, J.; *Tetrahedron Lett.* **1999**, *40*, 4535−4538. (l) Miyabe, H.; Fujishima, Y.; Naito, T. *J. Org. Chem.* **2000**, *64*, 2174−2175. (m) Watanabe, Y.; Ishikawa, S.; Takao, G.; Toru, T. *Tetrahedron Lett.* **1999**, *40*, 3411−3414. (n) Berteina, S.; Wendeborn, S.; De Mesmaeker, A. *Synlett* **1998**, 1231−1233.

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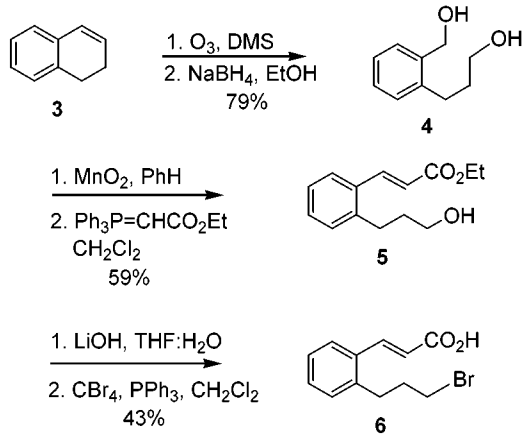
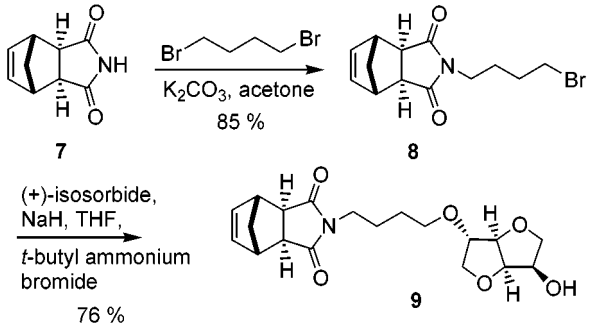
Scheme 2



Next, diol **4** was selectively oxidized in the benzylic position with manganese dioxide, followed by a Wittig reaction, providing α,*β*-unsaturated ester **5** in 59% yield. The ester was saponified with lithium hydroxide and converted to the corresponding bromide **6**.

Starting tricyclic norborene adduct **7**, constructed by the Diels−Alder reaction of maleimide and cyclopentadiene, is shown in Scheme 3. Bromide **8** was obtained in 85% yield

Scheme 3

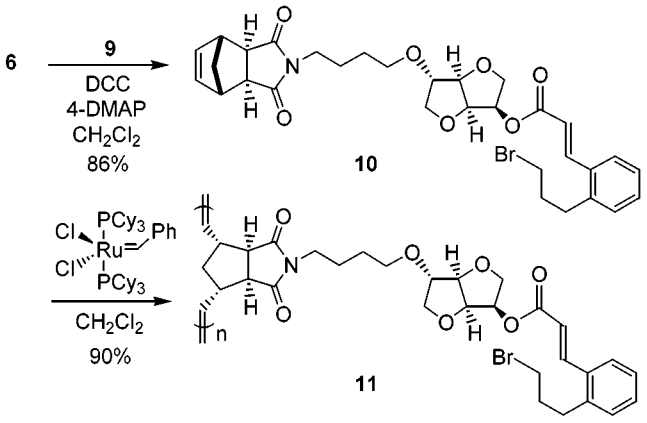


by treatment with base in the presence of 1,4-dibromobutane. The remaining halide was next displaced with (+)-isosorbide in a Williamson ether synthesis, constructing **9** in 76% yield.

Scheme 4 illustrates the final construction of the monomer units and metathesis polymerization. DCC esterification of carboxylic acid derivative **6** with succinimide alcohol **9** gave succinimide ester **10** in 86% yield. Subsequent polymerization of the succinimide ester **10** with Grubbs' ruthenium catalyst yielded modest molecular weight polymers of **11** after a span of 2−3.5 days, as shown in Scheme 4. The brown polymer was precipitated in methanol at ambient temperature and was washed several times with excess solvent to remove unwanted byproducts. Because of the solubility of the polymers generated, ^{1}H NMR techniques were employed to observe reaction completion and success.

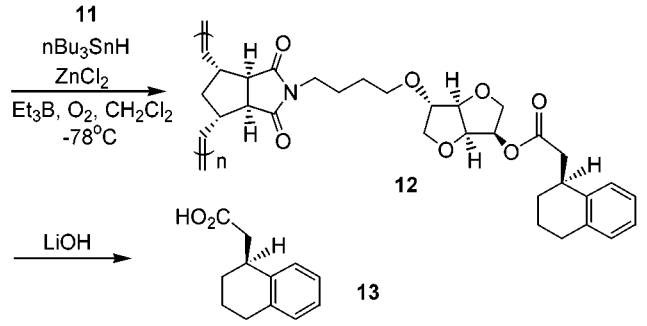
The radical cyclization precursor **11** was next subjected to standard tin hydride conditions to prepare the cyclohexane

Scheme 4



ring in **12**, as shown in Scheme 5. Because soluble polymers behave much like normal solution-phase organic reactions, the reactions discussed here behaved similarly to liquid-phase radical cyclization reactions.[11] After the tin-mediated radical cyclization to **12**, the precipitated polymer was subjected to immediate saponification conditions with LiOH so that enantiomeric excess of the resultant acid derivative could be studied by chiral HPLC using a (*S*)-*tert*-leucine-(*R*)-1-(α-naphthyl)ethylamine column.

Scheme 5



Several Lewis acids, such as magnesium bromide etherate, zinc chloride, and ytterbium(III) triflate, were employed in the reaction and are shown in Table 1. As predicted, the (+)-isosorbide sugar gave excellent diastereomeric ratios using zinc chloride in the 6-heptenyl radical closure.[11] More than

Table 1

entry	Lewis acid	temp (°C)	solvent	yield (%)	ee
1	none	0	CH_2Cl_2	87	0
2	none	−78	CH_2Cl_2	84	40
3	$MgBr_2(OEt_2)$	−78	CH_2Cl_2/Et_2O(1:1)	84	86
4	$ZnCl_2$	−78	CH_2Cl_2/THF (1:1)	80	>90
5	$Yb(OTf)_3$	−78	CH_2Cl_2/Et_2O (1:1)	72	75

99% enantiomeric excess was achieved with zinc chloride. Ytterbium triflate and magnesium bromide etherate were less successful in enhancing the diastereoselectivity of the cyclization, with enantiomeric excesses of 75% and 86%, respectively.

In related reactions off-support, we achieved diastereomeric excesses of >100:1 for both $ZnCl_2$ and $MgBr_2$ for radical cyclizations.[11] These reactions lacked the imide polymer backbone and four-carbon linker but were otherwise the same. It appears that the polymer backbone here provides a new microenvironment for the reaction that is not conducive to high diastereomeric ratios with $MgBr_2$.

The diastereoselectivity for the cyclization on soluble support is particularly high when (+)-isosorbide is used with zinc chloride, and thus this moiety possesses a high affinity for certain Lewis acids.[11] One explanation for this behavior is that the high selectivity may result from the cup-like highly oxygenated endo-surface of the sugar, providing several sites for chelation for the Lewis acid (see Figure 1). Avidity rather than affinity for a single pair of electrons from a Lewis acid are likely a contributing factor for this efficient asymmetric radical cyclization. A minor disfavored geometry has been proposed for a transition state for the cyclization, leading to the (*R*)-enantiomer. It is characterized by important nonbonded interactions between the ring methylene and the phenyl ring. A major favored transition state showing a much reduced steric interaction between the cyclizing radical center and the tetrahydrofuran oxygen is much better and the reaction likely proceeds via this intermediate. The favored transition state leads to the (*S*)-antipode as shown in Scheme 5.

In conclusion, a new study was discussed that represents the first examples of stereoselective radical cyclizations on soluble supports. A stereocontrol element (R*) consisting of a polymer-imbedded (+)-isosorbide chiral auxiliary was used in each monomer subunit. A survey of various Lewis acids was also examined. The best results gave very high distereoselectivites of >100:1 in a 6-heptenyl radical cyclization using zinc chloride as a Lewis acid. Each step using the soluble support gave crystallinelike intermediates readily separated by filtration from toxic tin compounds.

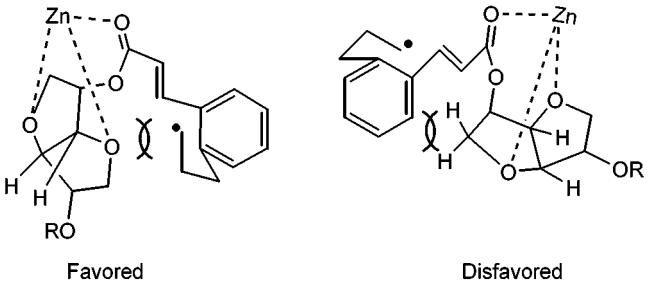


Figure 1. Radical cyclization transition states.

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Supporting Information Available: Spectral information for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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