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Heterobivalent Library Expansion by "Living Radical" Processes: Thiocarbonyl Addition/Elimination, and Nitroxide-Based Reactions with Fluorous Deconvolution

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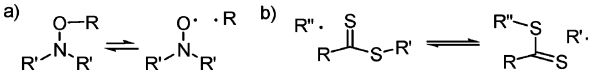
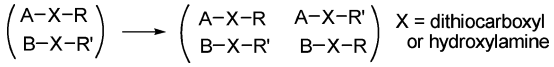
"Living radical" (LR) reactions (Scheme 1) involve the regeneration of masked radicals without loss by simple processes such as heating. The reversible fragmentation of hydroxylamine C−O bonds, giving a persistent nitroxide radical and a carbon-based radical, is a LR based on the persistent radical effect (PRE)[1] that is applied extensively in living radical polymerization (LRP) of alkenes[2] but infrequently in synthesis.[3] The "degenerate" addition of radicals to dithiocarboxyl esters with expulsion of a second radical [reversible addition−fragmentation chain transfer (RAFT)] is an alternative approach to LR chemistry that is used in synthesis[4] and LRP.[5]

Scheme 1. Living Radical Processes in (a) PRE and (b) RAFT



We show that LR is suitable for the combinatorial expansion of small heterobivalent libraries.[6] At the simplest level, a pair of molecules is squared to a matrix of four related ones (Scheme 2) by reversible fragmentation of the A−X−R and B−X−R′ groups. In this chemistry the use of PRE, or the dithioester RAFT reaction, prevents the formation of homobivalent dimers, R−X−R′, A−X−A, and B−X−B, which is unavoidable with most other methods of heterobivalent library expansion.[7,8] We also describe the use of fluorous tagging as a means of deconvolution.

Scheme 2. Squaring of Two-Component Libraries



To prove the principle a 1:1 mixture of dithiocarbamates **1** and **2** was heated to 80 °C in benzene in the presence of 2.5 mol % of AIBN, following which a separable mixture of the four heterobivalent dimers **1**−**4** (Figure 1) was obtained cleanly. An initial five-member library was then similarly expanded to a 25-member library (Figure 1). Examination of the ^{13}C NMR spectrum of this library revealed >20 signals from δ 195−201 (C=S). A combination of GC−MS and ESI-MS enabled the identification of all 25 members of the anticipated library.

Dithiobenzoates were also amenable to library expansion as demonstrated by the formation of a set of four compounds **26**−**29** from **26** and **27**. A more diverse library was obtained when an equimolar mixture of two dithiocarbamates and two dithiobenzoates underwent clean expansion to a 16-member mixed library, as verified mass spectrometrically (Figure 2).

Derivatization of 4-amino-2,2,6,6-tetramethylpiperidine-1-oxyl (4-NH_2-TEMPO) by reaction with acyl chlorides or by standard

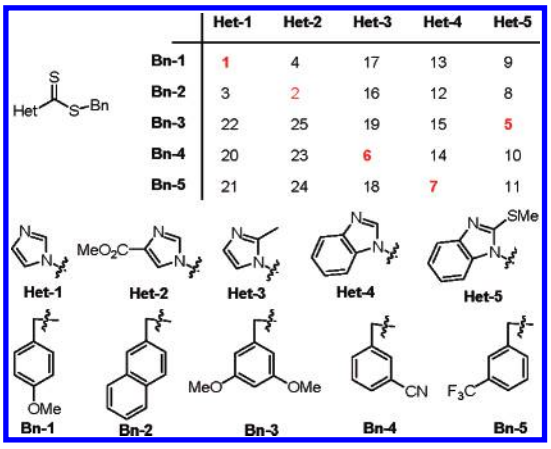


Figure 1. Twenty-five-member RAFT library with initiators in red.

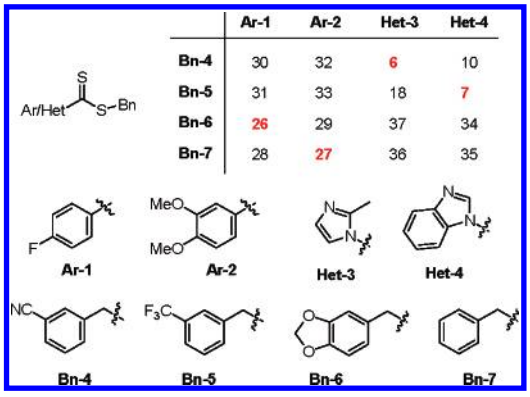
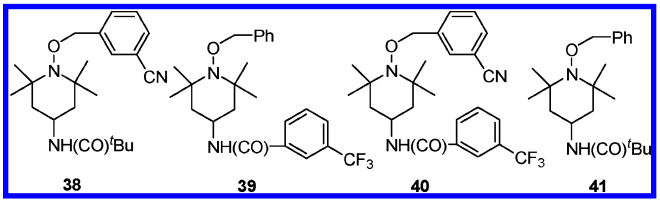


Figure 2. Mixed RAFT library with initiators in red.

peptide coupling methods gave a series of 4-acylamino TEMPOs, which were then benzylated on oxygen in the presence of copper triflate[9] to give a set of hydroxylamines (TEMPOL benzyl ethers). Two of these, **38** and **39**, were heated to reflux in equal proportions in ^{t}BuOH for 24 h, after which four compounds, **38**−**41**, were isolated chromatographically in yields of 86, 88, 80, and 82%, respectively, indicating almost complete equilibration.



Protection of 2,2-dimethyl-2-nitroethanol as its TBDMS ether followed by reduction with zinc and NH_4Cl and subsequent condensation with benzaldehyde gave nitrone **42**, which could be

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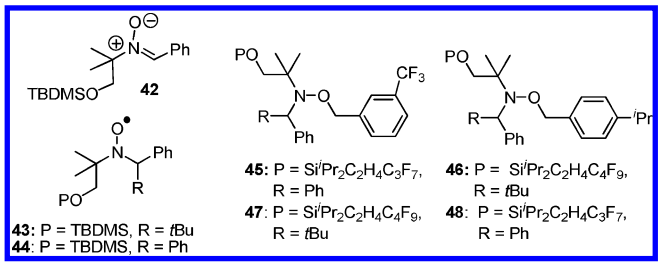
treated with either phenyl or *tert*-butyl Grignard to provide two nitroxides, **43** and **44**. Reductive benzylation in the presence of copper powder then afforded two further alkoxylamines, which were individually tagged to give **45** and **46**. After 24 h at reflux in dichloroethane an equimolar mixture of **45** and **46** was transformed into a library of **45**−**48**, which could be isolated in yields of 96, 95, 92, and 95%, respectively, thereby establishing the validity of the PRE-based hetereobivalent library expansion for a second class of hydroxylamines.



A library of five *N*-acyl TEMPOL ethers was then successfully expanded to a 25-member library in which each component could be readily identified in the ESI-mass spectrum (Figure 3).

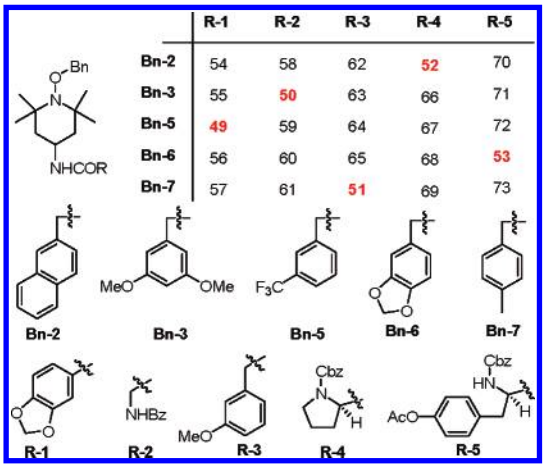


Figure 3. Twenty-five-member PRE library with initiators in red.

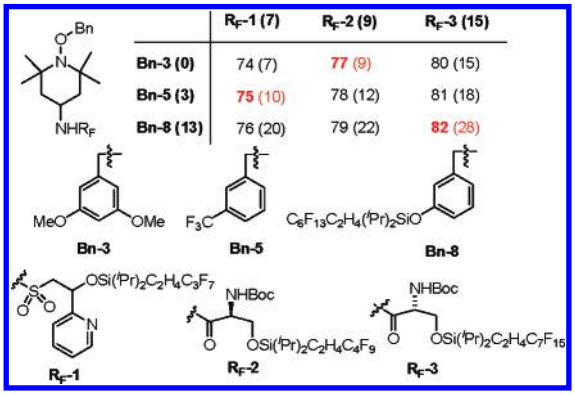


Figure 4. Nine-member fluorous library with initiators in red (number of F atoms in parentheses).

Finally, we investigated the possibility of library deconvolution by a fluorous tagging approach related to the fluorous-mixture synthesis technique.[10] A three-member *N*-functionalized TEMPOL ether library was designed in which both the benzyl ether and TEMPOL moieties carried distinct fluorous tags such that, after heterobivalent expansion, each member of the complete nine compound library would have a different fluorine atom count. Heterobivalent library expansion of these compounds proceeded smoothly in ^{t}BuOH at reflux overnight, and nine compounds were resolved by analytical fluorous HPLC (Figure 4). Preparative HPLC over fluorous silica gel was difficult, presumably owing to the complication of the differing polarities of the various compounds. However, separation was achieved with reasonable efficiency by cutting the library into three fractions of differing polarity on normal silica gel and then subjecting each fraction to fluorous HPLC.[11]

While the temperatures required for heterobivalent library expansion by these methods may preclude their use in a dynamic combinatorial sense for discovery of inhibitors of many enzymes,[12] these systems may prove ideal for targeting thermophilic bacteria.[13,14]

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Supporting Information Available: Experimental details and characterization. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) In an operational setting involving screening of an heterobivalent library separation should not be necessary. For example, if a 25-member library derived by expansion of five compounds shows activity, it should suffice to prepare five 16-member libraries each derived by omitting one of the original five components. Assuming one active compound, a maximum of two of the five-member libraries will be inactive from which the identity of a hit will be readily ascertained.
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