o-Bromo-*p*-methoxyphenyl Ethers. Protecting/Radical Translocating (PRT) Groups That Generate Radicals from C−H Bonds β to Oxygen Atoms

Dennis P. Curran* and Jinyou Xu

Contribution from the Department of Chemistry, University of Pittsburgh, Pittsburgh, Pennsylvania 15260

Received December 11, 1995[⊗]

Abstract: The *o*-bromo-*p*-methoxyphenyl ether group is introduced as a new protecting/radical translocating (PRT) group. This group protects an alcohol both before and after its use as a translocating group to generate a radical from a C−H bond β to the protected alcohol. All prior PRT groups generate radicals α to the functional group that they protect. The group is introduced by Mitsunobu reaction or Williamson ether synthesis, and removed by oxidation with ceric ammonium nitrate. The efficiency of the radical translocation reaction has been studied by isotopic labeling experiments with tributyltin deuteride. These results were used to design and execute a series of tandem radical translocation/cyclization reactions that illustrate the potential usefulness of the PRT group in synthesis. Secondary radicals are generated with about 50% efficiency due to slow 1,5-hydrogen transfer and competing 1,6-hydrogen transfer. Tertiary radicals are generated with efficiencies of about 80%. Modified PRT groups with added *ortho* substituents (Br, Me) can increase the efficiency of radical generation up to about >80% and >90%, respectively. The results provide only limited support for a rate and selectivity analogy based on radical cyclizations that was used to design the groups.

Introduction

Protecting/radical translocating (PRT) groups[1] are designed to serve a dual function in the synthesis of target molecules: they selectively activate a remote functionality in a molecule for a radical bond-forming reaction and they serve as a protecting group both before and after the radical reaction.[2] Like standard protecting groups,[3] they should be designed with ease of introduction and removal in mind, and they should withstand diverse sets of common reaction conditions. Beyond that, they must function rapidly and selectively in the radical translocation, which is often an intramolecular hydrogen transfer reaction.[4] At one key stage, the PRT group is implemented to activate the C−H bond adjacent to the functional group, which then allows a subsequent radical bond-forming reaction. The synthesis then proceeds to the point where the PRT group is no longer required for protection, at which point it is removed.

A number of PRT groups have been introduced recently from our lab[1,5] and those of De Mesmaeker[6] and others.[7,8] These groups vary both in the nature of the protecting group and in the functional group that is protected. Figure 1 illustrates several PRT groups for alcohols,[1,5a,6a] amides/amines,[5a,6b,8] and carboxylates.[5b,c,7] The target hydrogen that is abstracted when the PRT group is implemented in each structure is highlighted. In all of the groups introduced to date, the target C−H bond is α to the protected functional group. This location for the C−H bond is a convenient one from the standpoint of the structure of typical protecting groups, and it is also advantageous because the functional group may weaken the target C−H bond, and thereby facilitate radical translocation by hydrogen transfer.

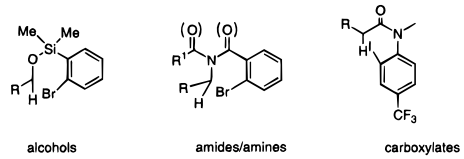


Figure 1.

Our recent detailed study of substituent effects on intramolecular 1,5-hydrogen transfer reactions in a simple model system[9] provides guidelines for the design of PRT groups with new features. In this study, we suggested that there was a qualitative analogy between 5-*exo*-cyclizations and 1,5-hydrogen atom transfer reactions.[9] In other words, radicals that suffered rapid, selective 5-*exo*-cyclizations might also suffer rapid, selective 1,5-hydrogen transfer reactions. This analogy suggests that the importance of locating the target C−H bond α to the functional group in a PRT substrate may be overrated, and that the nature and geometry of the connecting chain between the target C−H bond and the initial radical site on the PRT group

[⊗] Abstract published in *Advance ACS Abstracts,* March 15, 1996.

(1) Curran, D. P.; Kim, D.; Liu, H. T.; Shen, W. *J. Am. Chem. Soc.* **1988**, *110*, 5900.

(2) For a synthetic application of the (*o*-bromophenyl)dimethylsilyl ether group, see: Schwartz, C. E.; Curran, D. P. *J. Am. Chem. Soc.* **1990**, *112*, 9272.

(3) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*; Wiley: New York, 1991.

(4) (a) Beckwith, A. L. J.; Ingold, K. U. In *Rearrangements in the Ground and Excited States*; de Mayo, P., Ed.; Academic: New York, 1980; Vol. 1, p 161. (b) Wilt, J. W. In *Free Radicals*; Kochi, J. K., Ed.; Wiley-Interscience: New York, 1973; Vol. 1, p 333.

(5) (a) Snieckus, V.; Cuevas, J. C.; Sloan, C. P.; Liu, H.; Curran, D. P. *J. Am. Chem. Soc.* **1990**, *112*, 896. (b) Curran, D. P.; Abraham, A. C.; Liu, H. T. *J. Org. Chem.* **1991**, *56*, 4335. (c) Curran, D. P.; Liu, H. T. *J. Chem. Soc., Perkin Trans. 1* **1994**, 1377. (d) Curran, D. P.; Yu, H. S.; Liu, H. T.*Tetrahedron* **1994**, *50*, 7343. (e) Yamazaki, N.; Eichenberger, E.; Curran, D. P. *Tetrahedron Lett.* **1994**, *35*, 6623.

(6) (a) Denenmark, D.; Hoffmann, P.; Winkler, T.; Waldner, A.; De Mesmaeker, A. *Synlett* **1991**, 621. (b) Denenmark, D.; Winkler, T.; Waldner, A.; De Mesmaeker, A. *Tetrahedron Lett.* **1992**, *33*, 3613.

(7) (a) Esker, J. L.; Newcomb, M. *Tetrahedron Lett.* **1992**, *33*, 5913. (b) Esker, J. L.; Newcomb, M. *J. Org. Chem.* **1994**, *59*, 2779.

(8) (a) Murakami, M.; Hayashi, M.; Ito, Y. *J. Org. Chem.* **1992**, *57*, 793. (b) Williams, L.; Booth, S. E.; Undheim, K. *Tetrahedron* **1994**, *50*, 13. (c) Undheim, K.; Williams, L. *J. Chem. Soc., Chem. Commun.* **1994**, 883. (d) Brunckova, J.; Crich, D.; Yao, Q. W. *Tetrahedron Lett.* **1994**, *35*, 6619.

(9) Curran, D. P.; Shen, W. *J. Am. Chem. Soc.* **1993**, *115*, 6051.

0002-7863/96/1518-3142$12.00/0

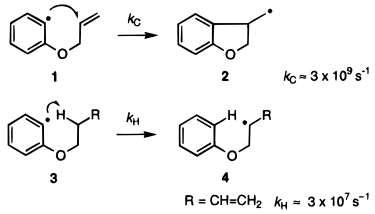


Figure 2.

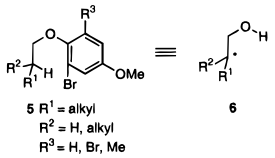


Figure 3.

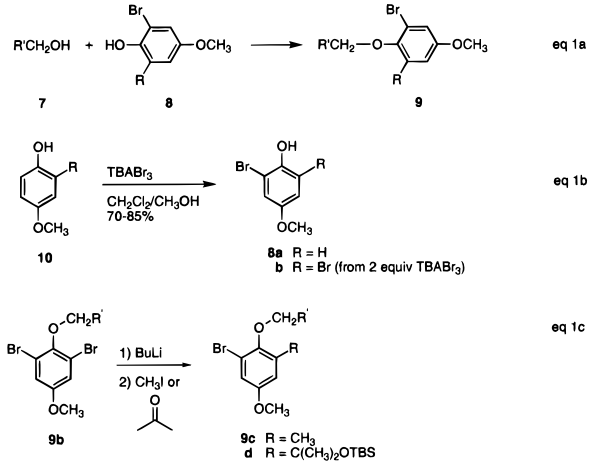
may be more important in promoting rapid 1,5-hydrogen transfer reactions than the bond dissociation energy of the target C−H bond.

We envisioned that it would be useful to develop PRT groups that could generate radicals β to protected functional groups. Such groups could be used to abstract and subsequently functionalize completely unactivated C−H bonds (that is, C−H bonds not adjacent to any heteroatoms or π-conjugating groups) through the intermediacy of simple alkyl radicals. Our design of β-translocating groups was guided by the proposed analogy between 5-*exo*-cyclizations and 1,5-hydrogen transfer reactions. Cyclizations of aryl allyl ether radicals like **1** (Figure 2) are exceptionally rapid and selective.[10] This is presumably due to the high reactivity of the aryl radical coupled with the favorable geometry of the substrate for cyclization. The analogy then suggests that 1,5-hydrogen transfer reactions of radicals like **3** might be sufficiently rapid and selective for use in PRT groups. Beckwith has already observed that this type of 1,5-hydrogen transfer was competitive with 6-*exo*-cyclization when R = vinyl,[10] and we set out to learn if these hydrogen transfers could still occur when R = alkyl.

In this paper, we introduce the first class of PRT group that generates radicals β to the protected functional group. The *p*-methoxy-*o*-bromophenyl group[11] protects alcohols, and it generates secondary alkyl radicals from C−H bonds β to the oxygen atom (see **6**, Figure 3) with 50−55% efficiency and tertiary alkyl radicals with 80−85% efficiency. This efficiency can be increased to >80% for secondary radicals and >90% for tertiary radicals by introducing a second *o*-bromine atom or (better yet) an *o*-methyl group.

Results and Discussion

We selected the *o*-bromo-*p*-methoxyphenyl PRT group to integrate with the standard *p*-methoxyphenyl (PMP) ether protecting group for alcohols.[11] The PMP-based PRT groups were introduced by standard *O*-alkylation reactions (either Williamson ether synthesis[12] or Mitsunobu reaction[13]) starting from the appropriate *o*-bromophenol **8a** or **8b** and alcohol **7** or halide (eq 1a; details are provided in the supporting information). In turn, the *o*-bromophenols **8a,b** were synthesized in good yields by standard bromination reactions of the corresponding phenol **10** with $TBABr_3$ or Br_2 (eq 1b).[14] Four different PMP-based groups were surveyed in this study: monobromides **9a** (R = H), **9c** (R = Me), and **9d** (R = CMe_2OTBS) and dibromide **9b** (R = Br). The *o*-alkyl compounds **9c** and **9d** were made from the dibromide **9b** by halogen−metal exchange and quenching, as shown in eq 1c.



Reductions of several substrates were initially conducted under fixed concentration conditions with tributyltin deuteride (0.01 M) to survey the efficiency of 1,5-hydrogen transfer compared to 1,6-hydrogen transfer and direct reduction by tributyltin deuteride. The results of these labeling studies are summarized in eqs 2a−e. The products of the labeling experiments were compared with authentic (fully protio) samples to identify the structures and to locate the deuterium label. The ratios listed in eqs 2a−e were determined by integration of the ^{2}H NMR spectrum of the crude reaction mixture. Isolated yields were not determined in these reactions, but the suspicion that they were high was confirmed by the subsequent preparative experiments.

Reduction of the phenylethanol derivative **11** provided **12** containing 82% of the label in the benzylic position (1,5-hydrogen transfer) and 18% of the label on the aromatic ring (direct reduction). Phenylpropanol homolog **13** (eq 2b) provided mainly the product **14** of 1,6-hydrogen transfer (72%) along with smaller amounts of 1,5-hydrogen transfer (13%) and direct reduction (15%) products. The reduction of cyclopentyl substrate **15** (eq 2c) was especially unselective, providing significant amounts of directly reduced product (35%) along with the products of 1,4,[15] 1,5 (two stereoisomers), and 1,6 (two stereoisomers) hydrogen transfer. Unfortunately, the chemical shifts of the hydrogens of cyclopentyl methylene groups were too close to confidently assign these protons, so we could not quantitate the ratio of 1,5/1,6-hydrogen transfer. However, we suspect that the minor (2%) product should be the *trans* stereoisomer resulting from 1,5-hydrogen transfer.[16] Thus, even if the major product (21%) is the *cis* isomer from 1,5-hydrogen transfer, the total amount of 1,6-hydrogen transfer still exceeds that of 1,5-transfer.

(10) (a) Beckwith, A. L. J.; Gara, W. B. *J. Chem. Soc., Perkin Trans. 2* **1975**, 795. (b) Abeywickrema, A. N.; Beckwith, A. L. J. *J. Chem. Soc., Chem. Commun.* **1986**, 464. (c) Beckwith, A. L. J.; Meijs, G. F. *J. Org. Chem.* **1987**, *52*, 1922. (d) Abeywickrema, A. N.; Beckwith, A. L. J.; Gerba, S. *J. Org. Chem.* **1987**, *52*, 4072.

(11) (a) Fukuyama, T.; Laird, A. A.; Hotchkiss, L. M. *Tetrahedron Lett.* **1985**, *26*, 6291. (b) Petitou, M.; Duchaussoy, P.; Choay, J. *Tetrahedron Lett.* **1988**, *29*, 1389.

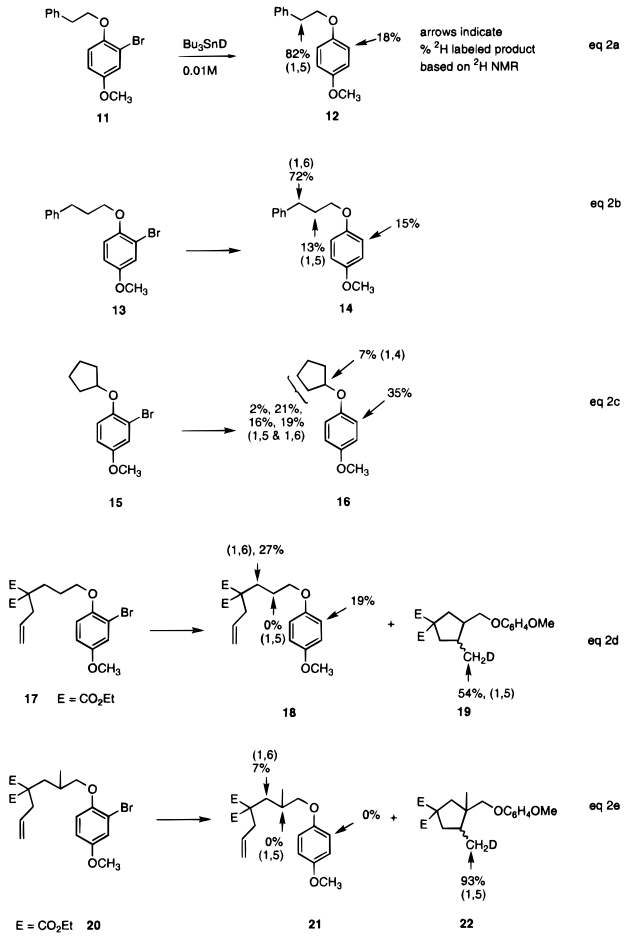
(12) Johnstone, R. A. W.; Rose, M. E. *Tetrahedron* **1979**, *35*, 2169.

(13) Mitsunobu, O. *Synthesis* **1981**, 1.

(14) Shoji, K.; Takaaki, T.; Tsuyoshi, O.; Nakamura, H.; Masahiro, F. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 4187.

(15) 1,4-Hydrogen transfers are unusual but not unknown (see ref 4). We cannot rule out the possiblity that part or all of the "1,4-hydrogen transfer product" arises from bimolecular hydrogen transfer reactions.

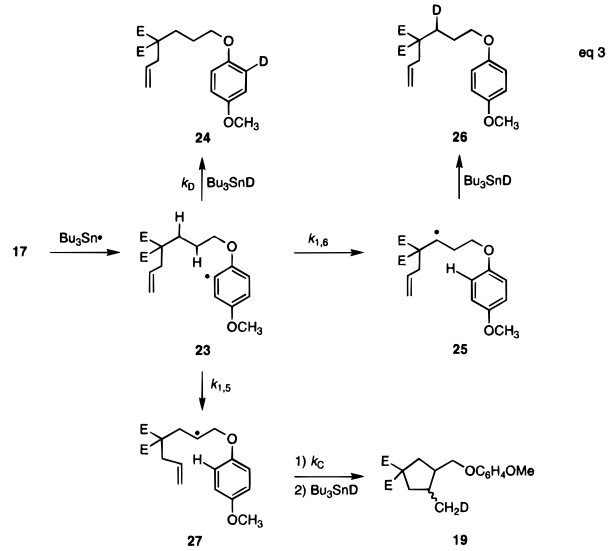
(16) For the radical derived from 1,5-hydrogen transfer, we expect that the deuterium atom will be delivered *trans* to the phenyl ether with a good level of selectivity. For the radical derived from 1,6-hydrogen transfer, we expect low stereoselectivity in the deuterium transfer reaction. See: Giese, B. *Angew. Chem., Int. Ed. Engl.* **1989**, *101*, 993.



Equations 2d,e show the results of labeling experiments coupled with subsequent cyclizations. Reduction of **17** (eq 2d) under the standard conditions now provided two types of products **18** and **19**. The cyclized product **19** (54%) results from 1,5-hydrogen transfer, and this was formed as an 8/1 mixture of *cis*/*trans* isomers that were labeled only in the methyl group. The uncyclized product **18** resulted partly from direct reduction (19%) and partly from 1,6-hydrogen transfer (27%). Significantly better results were obtained with the methyl analog **20** in eq 2e. This provided 93% of the 5-*exo*-cyclized product **22** again bearing the label in the methyl group (as a 1.2/1 mixture of isomers) along with 7% of the reduced product **21** apparently resulting from 1,6-hydrogen transfer. Since resonances in ^{2}H NMR spectra are broad, such experiments could fail to detect small amounts of minor products. Nonetheless, it is clear that there is significantly less directly reduced product in the reduction of **20** compared to **17**.

The proposed mechanism for the reaction of **17** is illustrative of all the substrates, and this is shown in eq 3. Bromine abstraction to generate aryl radical **23** is followed by a competition among direct reduction (leading to **24**), 1,5-hydrogen transfer (leading to **19** after 5-*exo*-cyclization of **27** and deuterium transfer), and 1,6-hydrogen transfer (leading to **26** after deuterium transfer). We conclude from the results in eqs 2a−e that the hydrogen transfer reactions of aryl radicals like **23** are sufficiently rapid to be useful in synthesis.

Intrinsic selectivity between 1,5- and 1,6-hydrogen transfer does not appear to be high, as judged by the result of the relatively unbiased substrate **17**, which provided only a 2/1 ratio of **19** (1,5-transfer product) to **26** (1,6-transfer product). Fortunately, it appears that this bias can be shifted in either direction by substituents. The phenyl group in **13** tips the balance in favor of 1,6-hydrogen transfer by providing a benzyl



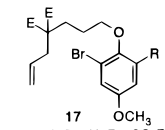
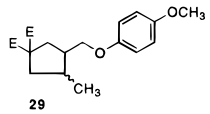
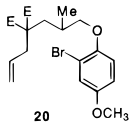
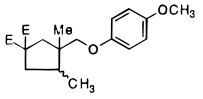
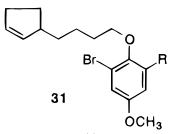
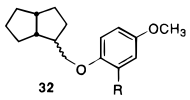
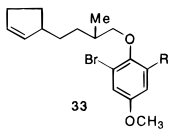
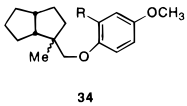
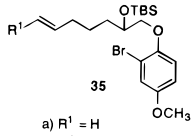
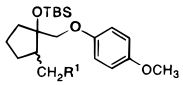
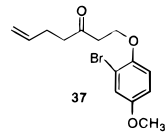
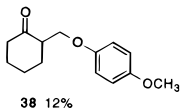
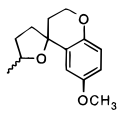
radical, while the methyl group in **20** tips the balance in favor of 1,5-hydrogen transfer by providing a tertiary radical. These two effects appear to have different origins as judged by comparing the total of 1,5- and 1,6-hydrogen transfer products to the directly reduced product. In substrate **13**, this total (85%) is about the same as that for substrate **11** (82%). This implies (somewhat surprisingly) that the increase in the rate of 1,6-hydrogen transfer of the radical derived from **13** is roughly balanced by a decrease in the rate of 1,5-hydrogen transfer. However, in substrate **20**, the significant decrease in the yield of the reduced product **21** implies that the methyl group increases the rate of 1,5-hydrogen transfer. These results suggest that useful radical translocation reactions based on the *o*-bromo-*p*-methoxyphenyl group can be planned by using standard substituent effects to favor 1,5-hydrogen transfer and by using standard reaction techniques to minimize the tin hydride concentration.

To support these suggestions, we conducted a series of preparative experiments with the *o*-bromo-*p*-methoxyphenyl group. These experiments, along with all the subsequent experiments with modified PRT groups, are summarized in Table 1. In these reactions, tributyltin hydride and AIBN were added by syringe pump to a solution of the precursor in refluxing benzene. After DBU workup,[17] ratios of the reduced product (not shown) to the cyclized product were determined by GC analysis. These products were separable in all cases, and Table 1 provides the isolated yields of purified cyclized products as well as the *cis*/*trans* ratio.

Entries 1a and 2 show the preparative experiments that correspond to the labeling experiments in eqs 2d and 2e. For substrate **17a**, pure product **29** was isolated in 44% yield, while substrate **20** gave **30** in 75% yield. Each of these yields was only slightly below the amount of cyclized product present as judged by the cyclized/reduced (C/R) ratio. This shows that total cyclized/reduced yields are high and that product loss during purification is small. The ratios of cyclized/reduced products are similar in the preparative and labeling experiments (for **17a**, 53/47 and 54/46, and for **20**, 85/15 and 93/7). For substrate **17a**, this similarity is disappointing, and it indicates that a significant amount of the reduced product (about 40%) formed in the syringe pump experiment comes from direct reduction of the aryl radical prior to any translocation; the remainder of the reduced product comes from 1,6-hydrogen transfer. The lower tin hydride concentrations used in the

(17) Curran, D. P.; Chang, C.-T. *J. Org. Chem.* **1989**, *54*, 3140.

Table 1. Radical Translocation/Cyclization Reactions

Entry	Precursor	Product Yield, (*cis*/*trans*)[a], cyclized/reduced
1	 **17** a) R = H, E = CO_2Et b) R = Br	 **29** 44% (89/11[b]) 53/47 71% (81/19) 79/21
2	 **20**	 **30** 75% (55/45[c]) 85/15
3	 **31** a) R = H b) R = Br c) R = Me d) R = $C(Me)_2OTBS$	 **32** 48% (50/50) 56/44 76% (60/40[d]) 81/19 (R = H in product) 76% (71/29[d]) 83/17 68% (72/28[d]) 74/26
4	 **33** a) R = H b) R = Me c) R = $C(Me)_2OTBS$	 **34** 74% (55/45[d]) 80/20 85% (55/45[d]) 93/7 87% (60/40[d]) 94/6
5	 **35** a) R^1 = H b) R^1 = CO_2Et	 **36** 48% (80/20[e]) 56/44 84% (58/42[f]) 94/6
6	 **37**	 **38** 12% +  **39** 27% (90/10) 60/40

[a] The *cis* isomer has CH_2OAr *cis* to H. [b] Relative configuration determined by NOE. [c] Relative configuration not assigned. [d] Relative configuration assigned by the γ-gauche effect in ^{13}C NMR. [e] Relative configuration assigned by the analog to entry 5f. [f] Relative configuration assigned by desilylation; the minor isomer gives a lactone, whereas the major isomer does not.

preparative experiments should favor intramolecular hydrogen transfer, but this effect is counterbalanced by the isotope effect of changing from tin deuteride to tin hydride, which favors direct reduction. Under our conditions, these two effects appear to roughly cancel. Lower tin hydride concentrations might be achieved either by slower syringe pumping or by changing the bromide to an iodide,[18] so it might be possible to increase the yield of **29** closer to the maximum limit (73%) imposed by the 1,6-hydrogen transfer.

The results of a another pair of secondary and tertiary substrates shown in entries 3a and 4a closely parallel the results in entries 1a and 2. Reduction of **31a** affords a 48% yield of **32a** (cyclized/reduced ratio 56/44), while the reduction of **33a** affords a 74% yield of **34a** (cyclized/reduced ratio 80/20).

(18) Porter, N. A.; Magnin, D. R.; Wright, B. T. *J. Am. Chem. Soc.* **1986**, *108*, 2787.

To briefly probe the effects of other substituents on the radical, we selected the silyl ether and ketone substrates shown in entries 5 and 6. Reduction of terminal alkene **35a** provided a surprisingly low yield of **36a** (48%) and a correspondingly low C/R ratio (56/44) when compared to the results of the tertiary methyl system (entry 2, 75%, C/R = 85/15). This led us to suspect that a significant amount of the reduced product resulted from failed cyclization. A reduced rate of cyclization is not unreasonable because there is no Thorpe/Ingold effect in this substrate and because related alkoxy-substituted radicals are known to cyclize rather slowly.[19] This explanation was supported by reducing the more activated acceptor **35b** to provide an 84% isolated yield of **36b** with a 94/6 C/R ratio. As expected, the silyl ether is even better than a methyl group at promoting 1,5-hydrogen transfer. Reduction of ketone **37** was interesting, though not preparatively useful. In addition to the formation of large amounts of reduced product (C/R = 60/40), this reaction produced the expected product of translocation/6-*endo*-cyclization **38** in 12% yield and the unexpected spirocycle **39** in 27% yield. This last product results from an interesting tandem cyclization where direct closure of the aryl radical to the ketone[20] precedes cyclization of the resulting alkoxy radical to the alkene.[21]

These results suggest that the parent *o*-bromo-*p*-methoxyphenyl ether PRT group will have moderate synthetic utility. Though it may be useful for generating conjugated secondary radicals (see eq 2a), this group does not appear to be useful for generating simple secondary alkyl radicals. Maximum possible yields of secondary radicals generated by 1,5-hydrogen transfer (as limited by 1,6-hydrogen transfer) are in the range of 70−80%, but even these yields are experimentally difficult to obtain due to direct reduction. Actual isolated yields in the range of 40−50% are obtained by standard experimental techniques. The generation of tertiary alkyl radicals with this group is significantly better. Maximum yields of tertiary radicals reach 80−90%, and approaching these maxima is experimentally easier due to the increased rate of 1,5-hydrogen transfer. Actual isolated yields for tertiary substrates are in the 70−80% range.

To improve the 1,5-hydrogen transfer efficiency, we studied several modified PRT groups. One advantage of the PRT method is that the ultimate radical precursor (a C−H bond) is not actually lost during the direct reduction. This means that a given yield could be statistically increased by cleaving the *p*-methoxyphenyl group from the reduced product and reintroducing another *o*-bromo-*p*-methoxyphenyl group. However, such recycling procedures are experimentally tedious. We envisioned that a better alternative would be to use the "double-barreled" [22] *o*,*o*-dibromo-*p*-methoxyphenyl group. If the directly reduced product is formed after abstraction of the first bromine atom and subsequent reduction, then this molecule gets a second chance at cyclization when the second bromine reacts. In effect, this group has one recycle built into it. In such double-barreled applications, these aryl radicals have an advantage over more traditional hydrogen abstracting radical precursors such as hypohalites,[23] which are inherently "single-barreled" (that is, each precursor only gets one shot at hydrogen abstraction).

o,*o*-Dibromo-*p*-methoxyphenyl ethers **17b** and **31b** of two

(19) Keck, G. E.; Tafesh, A. M. *Synlett* **1990**, 257.

(20) Radical additions to ketones: Zhang, W.; Dowd, P. *Chem. Rev.* **1993**, *93*, 2091.

(21) 5-*exo*-Cyclizations of alkoxy radicals are very rapid. Beckwith, A. L. J.; Hay, B. P. *J. Am. Chem. Soc.* **1988**, *110*, 4415.

(22) For examples of the "multiple-barreled" approach to cyclizations, see: (a) Wilcox, C. S.; Gaudino, J. J. *J. Am. Chem. Soc.* **1986**, *108*, 3102. (b) Hirai, Y.; Hagiwara, A.; Terada, T.; Yamazaki, Y. *Chem. Lett.* **1987**, 2417.

(23) Majetich, G.; Wheless, K. *Tetrahedron* **1985**, *41*, 7095.

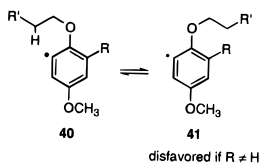
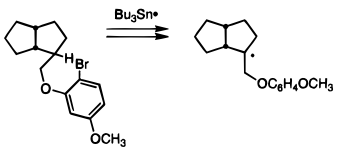


Figure 4.

alcohol precursors of secondary radicals were prepared, and these were reduced under the standard syringe pump conditions, except that 2 equiv of tin hydride was used in place of 1 equiv. In both cases (entries 1b and 3b), the yield of the cyclized product increased significantly (for example, compare entries 1a,b: 44% rises to 71%) as did the C/R ratio (53/47 rises to 79/21). These yields and ratios increased by approximately the statistical amount that is expected if a radical has two equal opportunities to be formed by 1,5-hydrogen transfer rather than one. We also observed noticeable changes in the *cis*/*trans* ratios of the cyclized products **29b** and **32b**. These changes might originate because the translocated monobromoaryl radical cyclizes with a different selectivity than the parent. A second origin for this variation is that the intermediate monobromo product is subject to a second radical translocation that can result in epimerization (see eq 4).[5e,6,8d]

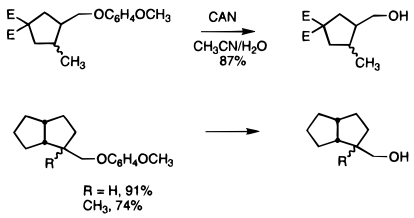


eq 4

On the basis of the rationale shown in Figure 4, we had hoped that these dibromides would actually provide better than statistical increases in the C/R ratio. Introduction of an *o*-substituent larger than hydrogen might raise the energies of unproductive conformers like **41** relative to **40**, and in so doing increase the efficiency of radical translocation relative to bimolecular reduction. It is less obvious whether such a substituent effect would alter the ratio of 1,5/1,6-hydrogen transfer. If such an effect exists with the dibromides, it is not very large, and it cannot be discerned from our data.

To better probe this idea, we prepared and reduced two *o*-bromo-*o*′-methyl-*p*-methoxyphenyl ethers (**31c** and **33b**). In generation of a secondary radical, this group provides a significantly higher yield of cyclized product and a higher C/R ratio than the parent (entry 3c). Indeed, the isolated yield of translocation/cyclization product **32c** from this experiment is a serviceable 76% and the C/R ratio is 83/17. This group also proved superior for generating tertiary radicals (entry 4b), and product **34b** was isolated from **33b** in 85% yield (C/R ratio 93/7). The *o*-methyl-substituted group is about as efficient as the dibromide at hydrogen transfer despite its statistical handicap. Larger *o*-substituents than methyl do not appear to be advantageous, as reflected by the reductions of substrates **31d** and **33c**. The bulky 2-((*tert*-butyldimethylsilyl)oxy)-2-propyl group gives about the same yields and C/R ratios as the simple methyl group (entries 3d and 4c). This probably means that these groups accelerate hydrogen transfer reactions enough to significantly suppress direct reduction and that most of the residual reduced product comes from the 1,6-hydrogen transfer pathway. These results suggest that the *o*-methyl PRT group should be superior to the parent for most applications. It is about as good as the dibromide in efficiency, and it is significantly simpler to use (only 1 equiv of tin hydride is needed, and radical translocation after cyclization is not possible).

After the radical translocation reaction is complete, the PRT group becomes a standard *p*-methoxyphenyl ether. These groups are typically removed under mild oxidative conditions with ceric ammonium nitrate. To demonstrate that removal was possible, we treated three of our products under standard conditions with CAN[10a] (acetonitrile/water, 0 °C, 15 min). In each case, a good yield of the expected primary alcohol was isolated (eq 5).



eq 5

Conclusions

The results described in this paper show that it is possible to invent PRT groups whose purpose is to generate radicals β to the functional groups that they protect. The *o*-bromo-*p*-methoxyphenyl ether PRT groups for generating radicals β to alcohols have excellent protecting group characteristics. They are easy to introduce and are removed under mild conditions. They are superior protecting groups after translocation, being among the most stable of any class of protecting groups for alcohols.[24] Due to the aryl bromide, they have increased liability as protecting groups prior to the radical translocation step (especially toward reductive debromination or halogen−metal exchange); however, even with the bromine present, these groups will exhibit a good protection profile.

With respect to radical translocation reactions, the groups are already useful, but further improvements are desirable. Problems arise due to relatively slow 1,5-hydrogen transfer, and due to competing 1,6-hydrogen transfer. The problems with slow 1,5-hydrogen transfer can be minimized by lowering the tin hydride concentration, but those with competing 1,6-hydrogen transfer cannot. The parent *o*-bromo-*p*-methoxyphenyl group shows low potential for generating simple secondary radicals (efficiencies ∼50%), but better potential for generating conjugated secondary and tertiary radicals (efficiencies ∼75%). The *o*-substituted dibromo and *o*-bromo-*o*′-methyl analogs show improved efficiencies for generating secondary radicals (≥75%) and quite good efficiencies for generating tertiary radicals (≥85%). It is not yet clear how these efficiencies in simple acyclic systems will translate into more complex, conformationally restricted systems.

The original design premise of this group was our rate and selectivity analogy between 5-*exo*-cyclization and 1,5-hydrogen transfer shown in Figure 2. In retrospect, the results suggest that this design premise was only partially correct. The estimated rate constants of intramolecular hydrogen transfer reactions[25] of this class of radicals are at the lower end of the useful scale for aryl radicals,[26] and are considerably lower than the rate constant for 5-*exo*-cyclization of the analogous radical **1** in Figure 2. However, the reduced rate of hydrogen transfer relative to cyclization was anticipated on the basis of the earlier

(24) Greene and Wuts (ref 2) list this group as stable to the following conditions: 3 N HCl, 100 °C; 3 N NaOH, 100 °C; H_2, 1200 psi; O_3, MeOH, −78 °C; $LiAlH_4$; Jones reagent, and PCC.

(25) (a) Estimated rate constants (50 °C) for transfer of secondary hydrogens are in the range of $(1-5) \times 10^6$ s^{-1}, and those of tertiary hydrogens are $>10^7$ s^{-1}. (b) The estimates are arrived at by using 2×10^8 M^{-1} s^{-1} as the rate constant for reaction of tributyltin deuteride with aryl radicals. See ref 10b,d.

(26) Aryl radical/solvent reactions are quite fast, so rates of 10^6 s^{-1} or better are needed for reactions to be preparatively useful.

observations of Beckwith (see **3** → **4**),[10] and these relative rates must be taken in context. Carbon−carbon π-bonds are much weaker than carbon−hydrogen σ-bonds, so simple exothermicity considerations suggest the guideline that cyclizations to alkenes will usually be faster than analogous hydrogen transfer reactions. Within the context of intramolecular hydrogen transfer reactions in flexible substrates to aryl or vinyl radicals, we submit that the rate constants for these radicals are quite high.

Though the rate analogy holds reasonably well, the selectivity analogy does not. This analogy suggested that high 5-*exo*/6-*endo* ratios in cyclizations would translate to analogously high ratios of 1,5/1,6-hydrogen atom transfer. Substrate **1** cyclizes exclusively by the 5-*exo* pathway, but its analog **3** gives only about a 2/1 ratio of 1,5/1,6-hydrogen transfer. The selectivity analogy is probably more tenous than the rate analogy because the stereoelectronic effects that operate in cyclizations and hydrogen transfers have different trends and origins. Radicals prefer to attack alkenes with an approach angle of 109°,[27] and this angle is more easily attained in 5-*exo*-cyclizations than in 6-*endo*-cyclizations. In contrast, intramolecular hydrogen transfer reactions can only occur in an "*endo*" sense, and the favored angle of 180° can be approached better in a 1,6-hydrogen transfer than in a 1,5-hydrogen transfer.[28] This analysis seems to suggest that the ratio of rate constants for 5-*exo*/6-*exo*-cyclization might be a better predictor for the 1,5/1,6-hydrogen transfer rather than a 5-*exo*/6-*endo* cyclization ratio. However, this is also not supported by the rates of cyclization **1**/**3** because the 5-*exo*/6-*exo* (**1**/**3**) ratio rate constant[10] is again considerably higher than the 1,5/1,6-hydrogen transfer of our secondary substrates.

The problem of competing 1,6-hydrogen transfer is not unique to these PRT groups,[5d,6a] and this problem constitutes a potentially serious limitation that, depending on substituents, may be difficult to overcome in some cases. Turning this problem around, there is reasonable hope for using substituent effects to increase the rate of 1,6-hydrogen transfer over 1,5-hydrogen transfer.[5d] One could then invent PRT groups that reach even further down the chain to abstract hydrogens and generate radicals.

The groups reported in this paper could become charter members of a club of protecting groups that generate radicals β to functional groups. Variations on the aryl group might allow new options for introduction and cleavage or alter the stability of the protecting group. Variations of the functional group might allow for the generation of other classes of radicals, for example, those β to amines or amides.

Experimental Section

General Procedure for Radical Cyclization Reactions. Tributyltin hydride (1.3−1.5 equiv containing 0.3 equiv of AIBN dissolved in benzene) was added by syringe pump over a period of 10−15 h to a solution of the substrate (1.0 equiv, 0.01 M) and AIBN (0.1 equiv) in refluxing benzene. After evaporation of most of the solvent, wet ether was added followed by addition of DBU (2.0 equiv) and a 1 M solution of I_2 in ether.[17] A white precipitate formed, and stirring was continued for 20 min. The mixture was filtered through a pad of silica gel. The ether solution was concentrated, and the residue was purified by flash chromatography.

General Procedures for Deuterium Labeling Experiments. The substrate (1.0 equiv, 0.01 M), tributyltin deuteride (1.5 equiv), and AIBN (0.2 equiv) were refluxed in benzene for 8 h. The crude mixture was treated with DBU/I_2 as described in the general procedure. The ether solution was concentrated, and the residue was subjected to ^{2}H NMR analysis without further purification to determine the sites of deuteration.

Acknowledgment. We thank the National Institutes of Health for funding this work.

Supporting Information Available: Text describing the experimental details and characterization of all compounds reported in the paper (13 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

JA954150Z

(27) (a) Beckwith, A. L. J.; Schiesser, C. H. *Tetrahedron* **1985**, *41*, 3925. (b) Spellmeyer, D. C.; Houk, K. N. *J. Org. Chem.* **1987**, *52*, 959.

(28) This angle is much softer than the favored angle for radical addition: (a) Dorigo, A. E.; Houk, K. N. *J. Am. Chem. Soc.* **1987**, *109*, 2195. (b) Huang, X. L.; Dannenberg, J. J. *J. Org. Chem.* **1991**, *56*, 5421.