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Construction of Carbo- and Heterocycles Using Radical Relay Cyclizations Initiated by Alkoxy Radicals

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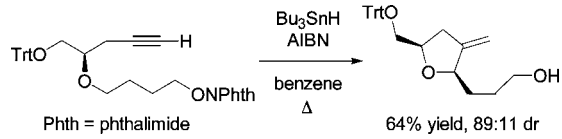
ABSTRACT



An efficient method for the rapid construction of carbo- and heterocycles has been developed using radical relay cyclizations initiated by alkoxy radicals. Linear substrates were cyclized to form a wide range of cyclopentane, pyrrolidine, tetrahydropyran, and tetrahydrofuran derivatives in excellent yields. This methodology was utilized as a key step in the synthesis of the tetrahydrofuran fragment in (−)-amphidinolide K.

In the search for new methods that rapidly increase molecular complexity from simple starting materials, there is increasing emphasis on developing new techniques to convert unactivated C−H bonds into reactive intermediates for the formation of carbon−carbon bonds. Significant advances have been made in this field, particularly with metal-mediated methodologies.[1,2] Radical abstractions of C−H bonds serve as a useful complement to these metal-mediated processes as radicals display excellent functional group tolerance.[3] For example, vinyl and aryl radicals readily undergo a 1,5-hydrogen abstraction[4] followed by cyclization to afford complex carbocycles.[5−7] While these radical relay cyclizations have been utilized in the synthesis of several natural products,[7] the overall versatility of the methodology is limited

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(2) For reviews, see: (a) Davies, H. M.; Manning, J. R. *Nature (London)* **2008**, *451*, 417–424. (b) Kakiuchi, F.; Chatani, N. *Adv. Synth. Catal.* **2003**, *345*, 1077–1101. (c) Davies, H. M.; Beckwith, R. E. *J. Chem. Rev.* **2003**, *103*, 2861–2904. (d) Ritleng, V.; Sirlin, C.; Pfeffer, M. *Chem. Rev.* **2002**, *102*, 1731–1770.

(3) For reviews on carbon−radical cyclizations, see: (a) Ramaiah, M. *Tetrahedron* **1987**, *43*, 3541–3676. (b) Curran, D. P. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 4, Chapter 4.1, pp 715−777. (c) Giese, B.; Kopping, B.; Göbel, T.; Dickhaut, J.; Thoma, G.; Kulicke, K. J.; Trach, F. In *Organic Reactions*; Paquette, L., Eds.; John Wiley & Sons, Inc.: New York, 1996; Vol. 48, Chapter 2, pp 303−856. (d) Gansäuer, A.; Bluhm, H. *Chem. Rev.* **2000**, *100*, 2771–2788. (e) Curran, D. P. *Synthesis* **1988**, 417–439. (f) Curran, D. P. *Synthesis* **1988**, 489–513.

(4) 1,5-Hydrogen abstractions with subsequent functionalizations have been studied extensively by Breslow. For a review, see: Breslow, R. *Acc. Chem. Res.* **1980**, *13*, 170–177.

(5) For early reports on the use of vinyl radicals for radical relay cyclizations, see: (a) Heiba, E. I.; Dessau, R. M. *J. Am. Chem. Soc.* **1967**, *89*, 3772–3777. (b) Chenera, B.; Chuang, C.-P.; Hart, D. J.; Hsu, L.-Y. *J. Org. Chem.* **1985**, *50*, 5409–5410. (c) Bennett, S. M.; Clive, D. L. J. *J. Chem. Soc., Chem. Commun.* **1986**, 878–880. (d) Lathbury, D. C.; Parsons, P. J.; Pinto, I. *J. Chem. Soc., Chem. Commun.* **1988**, 81–82. Curran, D. P.; Kim, D.; Liu, H. T.; Shen, W. *J. Am. Chem. Soc.* **1988**, *110*, 5900–5902. (e) Borthwick, A. D.; Caddick, S.; Parsons, P. J. *Tetrahedron Lett.* **1990**, *31*, 6911–6914.

(6) For early reports on the use of aryl radicals for radical relay cyclizations, see: (a) Snieckus, V.; Cuevas, J.-C.; Sloan, C. P.; Liu, H.; Curran, D. P. *J. Am. Chem. Soc.* **1990**, *112*, 896–898. (b) Curran, D. P.; Abraham, A. C.; Liu, H. *J. Org. Chem.* **1991**, *56*, 4335–4337. (c) Beckwith, A. L. J.; O'Shea, D. M.; Gerba, S.; Westwood, S. W. *J. Chem. Soc., Chem. Commun.* **1987**, 666–667.

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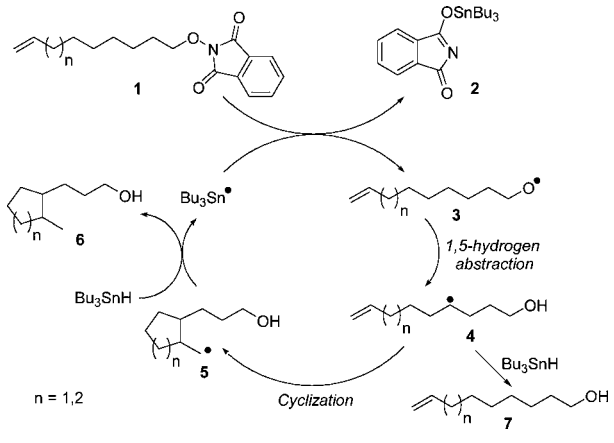
either by cyclization back onto the vinyl group or by the resulting aryl-incorporated products.

Radical relay cyclizations initiated by oxygen-centered radicals are an attractive alternative to carbon-based initiators as the oxygenated product facilitates further synthetic transformations. While oxygen-centered radical promoted 1,5-hydrogen abstractions have been utilized extensively for remote functionalizations,[8,9] there are few examples of the abstraction followed by a subsequent carbon−carbon bond-forming reaction[10−12] and no general solution for the cyclization of linear substrates.

There are only two attempts at cyclizing acyclic substrates.[11a,b] One example employs a radical relay cyclization initiated by a radical epoxide fragmentation.[13] This indirect method for generating oxygen-centered radicals results in the formation of the cyclization acceptor.[11b,c] Directly forming the oxygen-centered radical from homolysis of an oxygen−heteroatom bond would enhance the generality of cyclization from linear substrates as it allows for the incorporation of different cyclization acceptors. The only example of a direct oxygen-centered radical formation in a linear system provided the resulting carbocycles in only 25−32% yield.[11a] We sought to develop a general solution for the cyclization of simple linear precursors to carbo- and heterocycles that allows flexibility in the choice of acceptor.

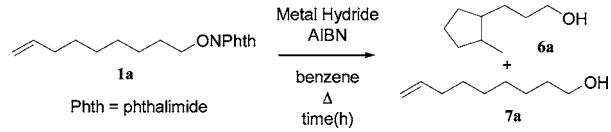
The problem with oxygen-centered radical-initiated relay cyclizations is undesired quenching of the radical prior to cyclization.[11a] We hypothesized that it is crucial to control the concentration of the trapping agent during the course of the radical relay cyclization to maximize the yield of cyclized product. We were, therefore, interested in using *N*-alkoxyphthalimides as oxygen-centered radical precursors (Scheme 1). The reaction of tributyltin hydride with *N*-alkoxyphthalimide **1** results in the formation of alkoxy radical **3** and byproduct **2**,[14] which is completely unreactive under these reaction conditions. The oxygen-centered radical can then undergo a 1,5-hydrogen abstraction to provide radical **4**. If the concentration of tributyltin hydride is kept low, through slow addition, then the rate of the hydrogen-quench to produce **7** should be slower than the rate of cyclization to form cyclized product **5**. Trapping of the primary radical **5** with tributyltin hydride should then provide desired cyclized product **6**.

Scheme 1



We began our study by optimizing the rate of addition of tributyltin hydride in a radical relay cyclization using *N*-alkoxyphthalimide **1a** (Table 1, entries 1−3). Addition of tributyltin hydride in one portion (entry 1) provided a similar distribution of cyclized (**6a**) to linear product (**7a**) as was obtained with a comparable substrate.[11a] However, decreasing the rate of addition of tributyltin hydride afforded the desired cyclized product to linear alcohol in a ratio of up to 95:5 (entries 2 and 3). Slow addition of triphenyltin hydride also provided the cyclized product (entries 4 and 5), although the effect was not as pronounced as was observed with tributyltin hydride (entry 3 vs entry 5). The same reaction can be affected under tin-free cyclization conditions using tris(trimethylsilyl)silane (entry 6).[15,16] Since the rate of

Table 1. Optimization Studies on the Rate of Addition of the Metal Hydride



entry[a]	metal hydride	addition	reaction time (h)	cyclization/ linear (**6a/7a**)[b]
1	Bu_3SnH	one portion	1	77:23
2	Bu_3SnH	1 mL/h	2	92:8
3	Bu_3SnH	0.5 mL/h	3	95:5
4	Ph_3SnH	one portion	1	67:33
5	Ph_3SnH	0.5 mL/h	3	80:20
6	$(TMS)_3SiH$	one portion	1	90:10

[a] Reactions were carried out on a 0.17 mmol scale. [b] Conversions determined by NMR spectroscopic analyses of crude reaction mixtures.

(7) For a recent review, see: Robertson, J.; Pillai, J.; Lush, R. K. *Chem. Soc. Rev.* **2001**, *30*, 94–103.

(8) For early reports, see: (a) Cainelli, G.; Mihaiovic, M. L.; Arigoni, D.; Jeger, O. *Helv. Chim. Acta* **1959**, *42*, 1124–1127. (b) Barton, D. H. R.; Beaton, J. M.; Geller, L. E.; Pechet, M. M. *J. Am. Chem. Soc.* **1960**, *82*, 2640–2641. (c) Barton, D. H. R.; Beaton, J. M.; Geller, L. E.; Pechet, M. M. *J. Am. Chem. Soc.* **1960**, *82*, 2641–2641.

(9) For recent reviews and representative examples, see: (a) Čeković, Ž. *Serb. J. Chem. Soc.* **2005**, *70*, 287–318. (b) Čeković, Ž. *Tetrahedron* **2003**, *59*, 8073–8090. (c) Hartung, J.; Gottwald, T.; Špehar, K. *Synthesis* **2002**, 1469–1498. (d) Petrović, G.; Čeković, Ž. *Tetrahedron* **1999**, *55*, 1377–1390. (e) Majetich, G.; Wheless, K. *Tetrahedron* **1995**, *51*, 7095–7129. (f) Petrović, G.; Saiič, R. N.; Čeković, Ž. *Tetrahedron* **2003**, *59*, 187–196.

(10) For intermolecular examples, see: (a) Petrović, G.; Čeković, Ž. *Tetrahedron Lett.* **1997**, *38*, 627–630. (b) Tsunoi, S; Ryu, I.; Okuda, T.; Tanaka, M.; Komatsu, M.; Sonoda, N. *J. Am. Chem. Soc.* **1998**, *120*, 8692–8701. (c) Martín, A.; Pérez-Martín, I.; Quintanal, L. M.; Suárez, E. *Tetrahedron Lett.* **2008**, *49*, 5179–5181.

(11) For intramolecular examples, see: (a) Čeković, Ž.; Ilijev, D. *Tetrahderon Lett.* **1988**, *29*, 1441–1444. (b) Rawal, V. H.; Newton, R. C.; Krishnamurthy, V. *J. Org. Chem.* **1990**, *55*, 5181–5183. (c) Rawal, V. H.; Krishnamurthy, V. *Tetrahedron Lett.* **1992**, *33*, 3439–3442. (d) Moman, E.; Nicoletti, D.; Mouriño, A. *Org. Lett.* **2006**, *8*, 1249–1251.

(12) For a single example of a radical relay cyclization initiated by a nitrogen-centered radical, see: Kim, S.; Yeon, K. M.; Yoon, K. S. *Tetrahedron Lett.* **1997**, *38*, 3919–3922.

hydrogen abstraction for the silane is slower than for the stannane, a slow addition rate was not required to obtain good selectivity for cyclized product **6a**.

With the basic reactivity and cyclization selectivity established, we sought to investigate the substrate scope of this transformation (Table 2). Simple cyclopentane derivative **6a** could be isolated in high yields as a 75:25 mixture of *cis* to *trans* isomers (entry 1). The syntheses of cyclohexanes using homologated *N*-alkoxyphthalimides provided only moderate amounts of cyclized product (<30% isolated yield) in poor diastereoselectivity. Analysis of the crude reaction by NMR spectroscopy revealed a 79:21 ratio of cyclohexane to 9-decen-1-ol, presumably arising from quenching the radical prior to cyclization. Attempts to synthesize 8- and 9-membered rings using this methodology were unsuccessful and provided only linear alcohols.

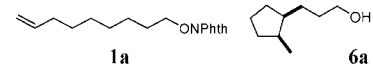
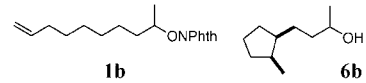
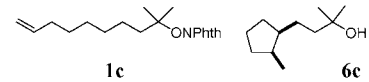
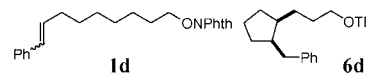
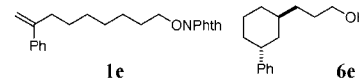
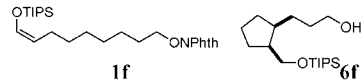
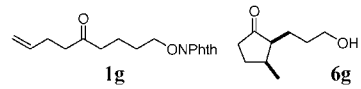
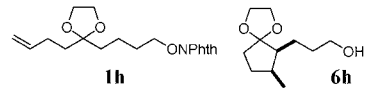
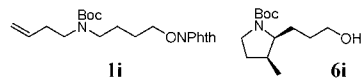
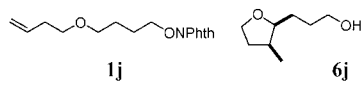
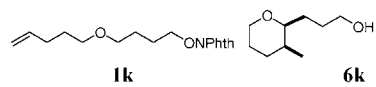
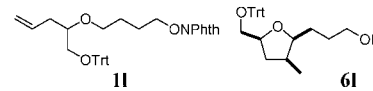
Secondary and tertiary *N*-alkoxyphthalimides (entries 2 and 3) were also viable substrates for the radical relay cyclization. Secondary oxygen-centered radical precursor **1b** provided an 80:20 mixture of *cis* to *trans* cyclopentane isomers in 66% yield. The corresponding tertiary oxygen-centered radical precursor (**1c**) provided comparable ratios of cyclized product to straight-chain alcohol. The yield and diastereoselectivities for both cyclizations were also comparable.

We then studied how the cyclization was affected by aryl substituents on the olefinic acceptor (entries 4 and 5). Cyclization of **1d**, containing a terminally substituted phenyl group (entry 4),[17] afforded cyclopentane derivative **6d** in comparable conversion and diastereoselectivity to cyclizations with terminal alkenes (entries 1−3). The isolated yield is lower because an additional silylation step was needed to allow for separation from tin byproduct **2**. Geminally substituted alkene **1e** (entry 5) resulted in a 6-*endo* cyclization to form cyclohexane **6e** in a 65:35 mixture of *trans* to *cis* isomers.

For this radical relay methodology to have broader synthetic utility, it would be valuable to access additional functional handles after cyclization. One possibility is to cyclize onto silyl enol ethers, as the reaction provides a protected alcohol in the product. Siloxy-substituted olefin **1f** (entry 6) proved to be an excellent acceptor, providing cyclopentane derivative **6f** in 63% yield and moderate diastereoselectivity. Another valuable functionality is a carbonyl group on the cyclopentane ring. Cyclization of ketone **1g** primarily provided the straight-chain hydrogen-quenched product (**7g**); thus, very low yields of cyclopentanone **6g** were obtained. However, the ketal can be readily cyclized to the corresponding protected cyclopentanone (**6h**) in good yield and in a 58:42 ratio of *cis*- to *trans*-fused isomers.

With the successful application of this radical relay methodology to the formation of cyclopentane derivatives, we next focused on the formation of heterocycles. Nitrogen-containing substrate **1i** readily cyclized to pyrrolidine **6i** in 63% yield and in moderate diastereoselectivity (entry 9). Uncyclized aminoalcohol **7i** was not observed by ^{1}H NMR spectroscopic analysis of crude reaction mixtures. Similar

Table 2. Radical Relay Carbo- and Heterocyclizations

entry	substrate[a]	product[b]	yield (%)[c]	dr[d]
1	 **1a**	**6a**	79	75:25
2	 **1b**	**6b**	66	80:20
3[e]	 **1c**	**6c**	64	75:25
4[f]	 **1d**	**6d**	52[g]	75:25
5[e]	 **1e**	**6e**	64	65:35
6	 **1f**	**6f**	63	60:40
7	 **1g**	**6g**	<5	nd
8	 **1h**	**6h**	55	58:42
9	 **1i**	**6i**	63	56:44
10	 **1j**	**6j**	62	90:10
11	 **1k**	**6k**	41	60:40
12	 **1l**	**6l**	64	86:14

[a] Reactions were carried out on a >0.25mmol scale. [b] The relative stereochemistry was determined by NOE experiments. [c] Isolated yields of the mixture of diastereomers after flash chromatography. [d] The diastereomeric ratio was determined by ^{1}H NMR spectroscopy. [e] Ph_3SnH was used as a metal hydride source to facilitate purification of the cyclized product. [f] Substrate **1d** was cyclized using the standard procedure and then converted to the silyl ether. See the Supporting Information for details. [g] The isolated yield corresponds to a two-step cyclization/silylation procedure.

(13) The cyclized product was obtained in 50% yield. The diastereomeric ratio was not reported. See ref 11b.

(14) (a) Kim, S.; Lee, T. A.; Song, Y. *Synlett* **1998**, 471–472. (b) Okada, K.; Okamoto, K.; Oda, M. *J. Am. Chem. Soc.* **1998**, *110*, 8736–8738. (c) Barton, D. H. R.; Blundell, P.; Jaszberenyl, J. C. *Tetrahedron Lett.* **1989**, *30*, 2341–2344.

(15) For the development of tris(trimethylsilyl)silane as a radical reducing agent, see: Chatgilialoglu, C.; Griller, D.; Lesage, M. *J. Org. Chem.* **1988**, *53*, 3641–3642.

(16) For the use of tris(trimethylsilyl)silane in the generation of oxygen-centered radicals, see ref 14a.

(17) The *E*/*Z* ratio is 3:1. See the Supporting Information for details.

to the carbon analogue, piperidine derivatives could only be isolated in poor selectivity.

Oxygen-containing heterocycles could also be accessed using this new cyclization methodology. Ether **1j** cyclized to afford tetrahydrofuran derivative **6j** in 62% yield and a 90:10 ratio of diastereomers (entry 10). The yield of the 6-*exo* cyclization for oxygen-containing substrate **1k** (41% yield) was higher than for the carbon analog (<30% yield), although the diastereoselectivity was still modest (entry 11). Cyclization of racemic substrate **1l**, containing an existing stereocenter, provided trisubstituted tetrahydrofuran **6l** in 64% yield and a 86:14 ratio of the *cis* isomer to all other diastereomers (entry 12).

Substituted tetrahydrofurans are common substitution patterns in many bioactive polyketide natural products.[18] One example is amphidinolide K (Figure 1, **8**), isolated from the

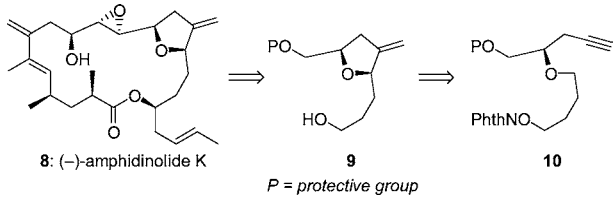


Figure 1. Retrosynthetic analysis of (−)-amphidinolide K.

Okinawan flatworm *Amphiscolops* sp,[19−22] which contains a 2,3,5-trisubstituted tetrahydrofuran in the macrocyclic core. Our synthesis of trisubstituted tetrahydrofuran **6l** (entry 12) suggests that we can utilize our radical methodology for the synthesis of the tetrahydrofuran in amphidinolide K as they both contain the same 2,5-*cis*-substitution pattern. Tetrahydrofuran fragment **9** can easily be accessed using our methodology by replacing the alkene acceptor with an alkyne (**10**). Furthermore, the resulting functionality provides handles for future fragment couplings.

(18) For representative reviews, see: (a) Rupprecht, J. K.; Hui, Y.-H.; McLaughlin, J. L. *J. Nat. Prod.* **1990**, *53*, 237–278. (b) Kobayashi, J.; Tsuda, M. *Nat. Prod. Rep.* **2004**, *21*, 77–93.

(19) Ishibashi, M.; Sato, M.; Kobayashi, J. *J. Org. Chem.* **1993**, *58*, 6928–6929.

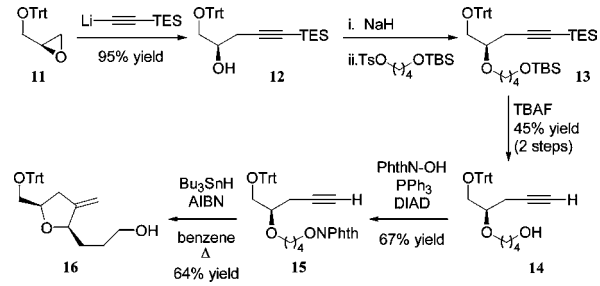
(20) For a synthesis of (+)-amphidinolide K, see: Williams, D. R.; Meyer, K. G. *J. Am. Chem. Soc.* **2001**, *123*, 765–766.

(21) For a synthesis of (−)-amphidinolide K, see: Ko, H. M.; Lee, C. W.; Kwon, H. K.; Chung, H. S.; Choi, S. Y.; Chung, Y. K.; Lee, E. *Angew. Chem. Int. Ed.* **2009**, *48*, 2364–2366.

(22) For synthetic efforts toward the synthesis of (−)-amphidinolide K, see: (a) Williams, D. R.; Meyer, K. G. *Org. Lett.* **1999**, *1*, 1303–1305. (b) Andreou, T.; Costa, A. M.; Esteban, L.; Gonzàlez, L.; Mas, G.; Vilarrasa, J. *Org. Lett.* **2005**, *7*, 4083–4086.

Synthesis of (−)-amphidinolide K fragment **9** began with the epoxide ring-opening of commercially available, enantiomerically enriched trityl-protected glycidol **11** to afford chiral alcohol **12** in 95% yield (Scheme 2). Ether formation,

Scheme 2. Concise Synthesis of the Tetrahydrofuran Fragment within (−)-Amphidinolide K



followed by TBAF-mediated removal of the silyl protecting groups, resulted in free alcohol **14** in 45% yield over two steps. Installation of the phthalimide was achieved using a Mitsunobu reaction to provide *N*-alkoxyphthalimide **15** in 67% yield. The key radical relay cyclization gave (−)-amphidinolike K fragment **16** in 64% yield and an 89:11 ratio of *cis* to *trans* isomers. Overall, the core was synthesized in only five steps from commercially available material.

In summary, we have demonstrated a general and versatile radical methodology for the rapid construction of carbo- and heterocycles from simple linear precursors. The cyclizations are effective for the synthesis of a wide range of cyclopentane, pyrrolidine, tetrahydropyran, and tetrahydrofuran derivatives. The synthetic generality of these new heterocyclizations was demonstrated in the synthesis of the tetrahydrofuran fragment in (−)-amphidinolide K. Studies toward the construction of new, complex heterocyclic frameworks are currently underway. We are also currently investigating the use of this methodology in several natural product syntheses.

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Supporting Information Available: Complete experimental procedures and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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