DOI: 10.1002/adsc.200505211

Thiophenol-Mediated 1,5-Hydrogen Atom Abstraction: Easy Access to Mono- and Bicyclic Compounds

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Received: May 22, 2005; Accepted: August 1, 2005-09-01

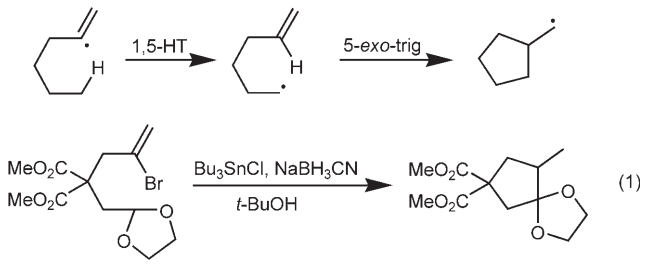
Supporting Information for this article is available on the WWW under http://asc.wiley-vch.de/home/.

Abstract: A thiophenol-mediated method for cyclization of alkynes is described. The reaction cascade involves the intermolecular addition of a phenylthiyl radical to a terminal triple bond generating an alkenyl radical, followed by a 1,5-hydrogen atom transfer and a 5-*exo*-trig radical cyclization. This very efficient tin-free procedure allows one to prepare highly functionalized cyclopentane derivatives as well as fused bicyclic and spirocyclic compounds from easily available precursors. During this cyclization process, a phenylthio moiety is incorporated into the final cyclized products. This functionalization is particularly attractive for further transformation of the products.

Keywords: alkynes; cyclization; hydrogen transfer; radicals; spiro compounds; sulfur

Introduction

Radical reactions represent a valuable tool for organic synthesis.[1] For instance, carbon-carbon bonds can be formed under mild conditions with a unique functional group tolerance. Moreover, radical reactions can be highly regio- and stereoselective and their ability to be involved in cascade reactions makes them particularly attractive. The use of hydrogen atom abstraction is of particular interest since it allows functionalization of remote unreactive positions without using of transition metal catalysts.[2] The highly reactive alkenyl radicals are suitable precursors for efficient intramolecular 1,5-hydrogen abstraction at C–H bonds. After translocation, the new radical species can cyclize to give a cyclopentane derivative (Scheme 1).[3–5]

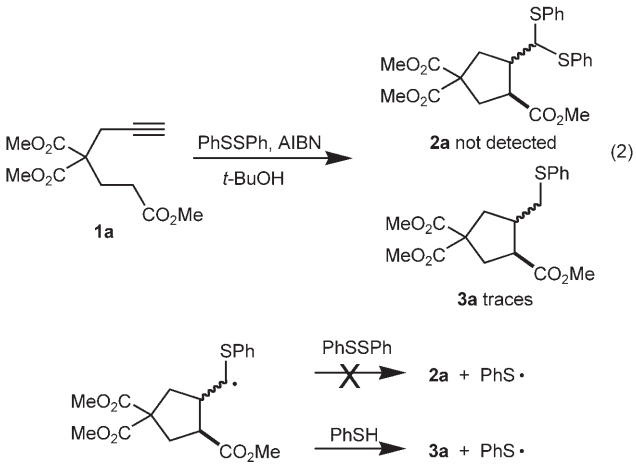


Scheme 1. 1,5-Hydrogen transfer-cyclization process.

The alkenyl radicals are usually prepared by reaction of the corresponding vinyl halide with a stannyl radical.[3–5] The pioneering work of Curran demonstrated the potential of this reaction [see Scheme 1, Eq. (1)] and following this work many applications have been developed.[2,6] However, the practicability of this process is hampered by the use of tin derivatives and by the formation of uncyclized product *via* direct reduction of the intermediate alkenyl radical. Radical addition to terminal or disubstituted alkynes offers an attractive alternative for the generation of alkenyl radicals that undergo 1,5-translocation to alkyl radicals and 5-*exo*-trig cyclization (related reactions involving the formation of heterocycles *via* transient silyl,[7,8] alkoxyl[9,10] and imidyl[11] radicals are also reported). Inter- and intramolecular additions of carbon-centered radicals are utilized to initiate such cascade processes.[4,12–14] Bachi and later Alcaide employed the intermolecular radical addition of tin hydride[15,16] and more recently, in parallel to the present work, we developed a dialkyl phosphite-mediated reaction.[17]

Thiyl radicals are easily generated from thiols and disulfides and add efficiently in a reversible manner to carbon-carbon multiple bonds leading to carbon-centered radicals.[18,19] The resulting radicals have been extensive-

ly used for further cyclization onto alkenes,[20,21] oxime ethers and hydrazones.[22] To the best of our knowledge, only one report of a thiophenol-mediated radical addition onto an alkyne followed by a radical translocation-cyclization process has been reported.[23] In this report, Burke described the formation of tetrahydrofuran-2-carboxylic acid derivatives involving the generation of captodative stabilized radicals. Even in this favorable system, the formation of non-cyclized products *via* direct reduction of the alkenyl radical intermediate could not be totally suppressed. We report here that, despite its high radical reducing power, the thiophenol-mediated reaction is far more efficient than initially expected when run under non-chain reaction conditions and generation of non-stabilized alkyl radical is even possible. Expeditious preparation of fused-ring and spirocyclic compounds illustrates the potential of this approach and complements our preliminary results reported recently.[24,25]



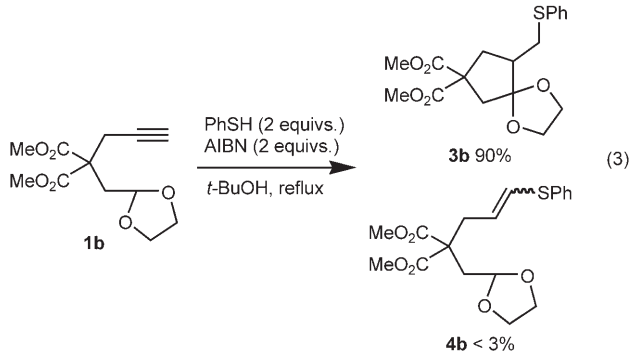
Scheme 2. Attempt to develop a diphenyl disulfide-mediated reaction.

Results and Discussion

Development of the Method

An efficient and preparatively useful procedure for the formation of a 5-membered ring *via* a radical translocation-cyclization process should fulfill the following criteria: 1) the starting material and reagents should be easily available; 2) the direct reduction of the intermediate alkenyl radicals leading to non-cyclized product should be minimized; 3) the final product should be a versatile synthetic intermediate; 4) the toxicity of the reagent should be as low as possible and product contamination (a major drawback of the tin hydride procedure) should be eliminated. With these few criteria in mind, we decided to test the use of terminal alkynes as radical precursors together with a source of thiyl radicals. Preliminary experiments were run with diphenyl disulfide and the terminal alkyne **1a** [Scheme 2, Eq. (2)]. The expected dithioacetal **2a** was not observed, indicating that trapping of the final radical with diphenyl disulfide is not working. However, traces of the reduced product **3a** were isolated and attributed to the presence of a small amount of thiophenol in the reaction mixture.[26]

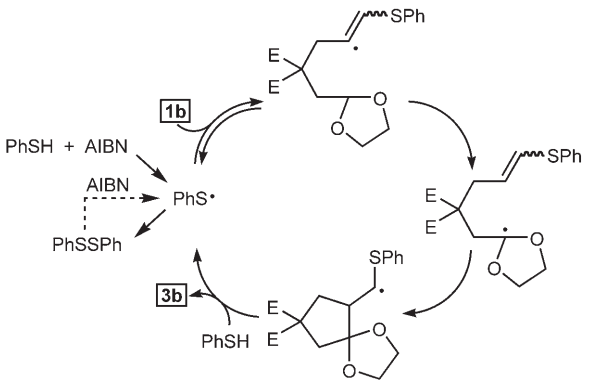
Based on this preliminary result, the use of thiophenol was investigated. Under standard reaction conditions (refluxing benzene, 10 mol % AIBN), only a low conversion was obtained with different substrates. Therefore, a systematic study for the optimization of the reaction conditions was undertaken with substrate **1b** [Scheme 3, Eq. (3)]. Best results are obtained in refluxing *t*-BuOH by using syringe pump addition of thiophenol (2 equivalents) over 20 hours under AIBN initiation. The amount of the initiator plays a crucial role in this process. The use of two equivalents of AIBN gives the



Scheme 3. Optimization of the reaction conditions with thiophenol.

best results and the cyclized product **3b** is isolated in 90% yield. The uncyclized product **4b** is not detected by ^{1}H NMR analysis of the crude product. From a practical point of view, the procedure is particularly simple since no work-up is required. At the end of the reaction, the crude reaction mixture is concentrated by evaporation of the solvent under reduced pressure and directly submitted to purification by flash chromatography.

The efficiency of this thiophenol-mediated reaction is amazing when compared with the tin hydride reaction. Indeed, thiophenol is a much more powerful reducing agent than tin hydride,[27] however, direct reduction of the alkenyl radical intermediate is in most cases not observed. The assumed mechanism of the thiophenol mediated reaction is depicted in Scheme 4. The phenylthiyl radical is generated from thiophenol and AIBN and adds to the terminal alkyne presumably in a reversible manner. The alkenyl radical undergoes 1,5-hydrogen-transfer followed by 5-*exo* cyclization and reduction of the phenylthio-substituted alkyl radical by thiophenol. The phenylthiyl radical can either start a new chain reaction or dimerize to give the diphenyl disulfide. Un-



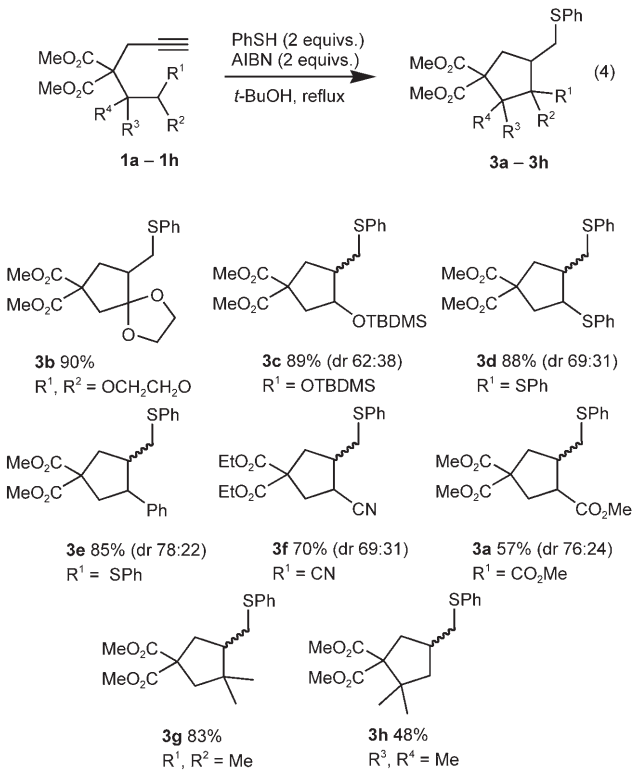
Scheme 4. Proposed mechanism.

der our reaction conditions, the disulfide is inert and does not react with any of the radicals involved in the chain process. The use of a stoichiometric amount of AIBN allows regeneration of the thiyl radical by reaction with either thiophenol or diphenyl disulfide.

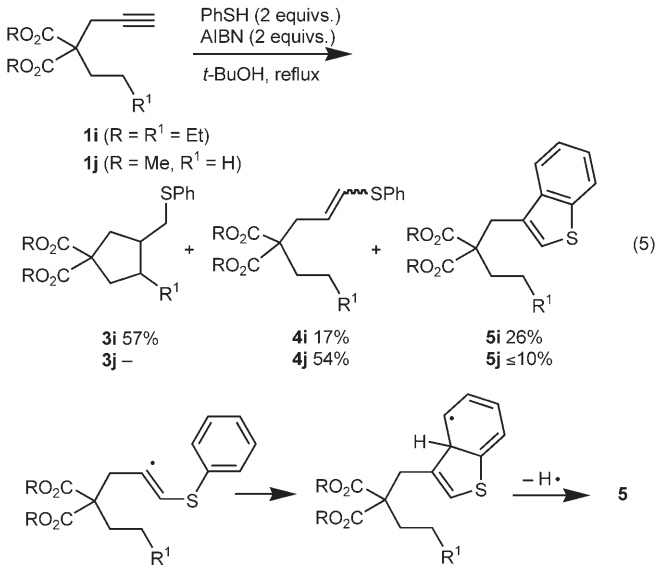
Preparation of Cyclopentane Derivatives

The scope and limitations of the process were investigated next. For this purpose, a series of substrates, easily prepared by alkylation of dimethyl propargylmalonate, were treated under our optimized reaction conditions [Scheme 5, Eq. (4)]. When the translocated radical is stabilized by a heteroatom (substrate **1b**, **1c** and **1d**), excellent yields of cyclic products **3b**, **3c** and **3d** are obtained and no traces of non-cyclized products are detected. Similar results are obtained with translocated radicals stabilized by delocalization (products **3e**, **3f** and **3a**). The relative configurations of the major isomers of **3a** and **3b**–**3f** have not been assigned, however, related systems possessing *gem*-diester substituents are known to give the *cis*-cyclopentanes as major isomers when $R^1 = CO_2R$ or alkyl and $R^2 = H$, and the *trans*-isomer when $R^1 =$ OTBDMS or phenyl and $R^2 = H$.[5,28,29] Interestingly, the formation of non-substituted alkyl radicals is also possible. For instance, the tertiary alkyl radical derived from **1g** affords the cyclic compound **3g** in 83% yield. A primary alkyl radical generated from **1h** affords the cyclic product **3h** as a single product albeit in moderate yield.

The results described in Scheme 5 (compounds **3b**, **3c**, **3e**, **3f** and **3g)** compare well with the results obtained by Curran starting from alkenyl bromides using tin hydride as reducing agent.[5] The thiophenol method was further investigated with substrate **1i** [Scheme 6, Eq. (5)]. The reaction affords a mixture of three products: the desired cyclic product **3i** (57%), the non-cyclized alkenyl thioether **4i** (17%) and the benzothiophene derivative **5i** resulting from the intramolecular addition of the transient alkenyl radical onto the phenyl ring.[30] The side product

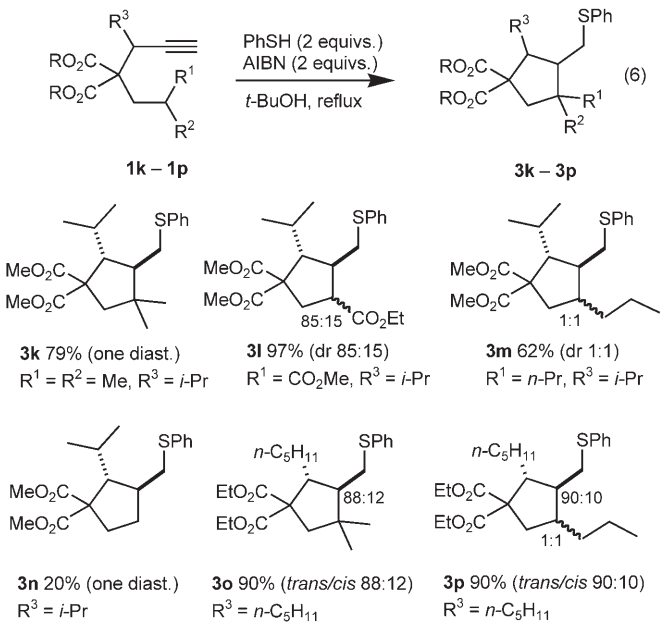


Scheme 5. Reaction with propargylmalonate derivatives.

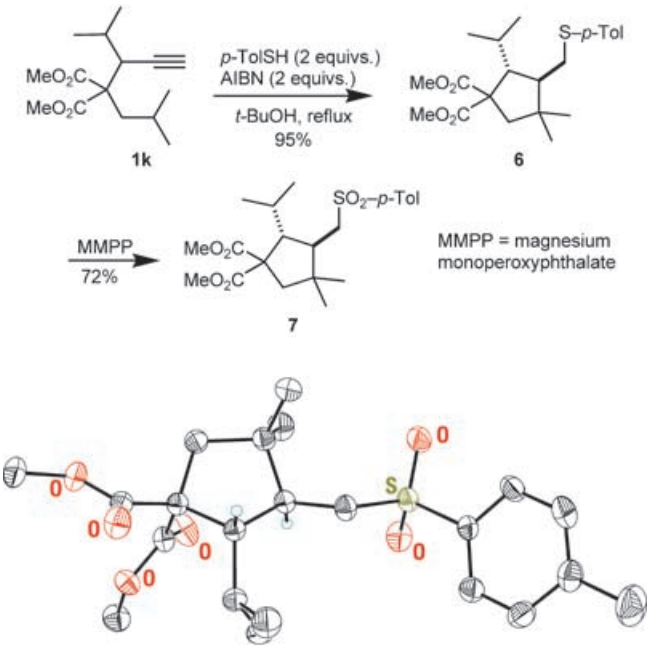


Scheme 6. Limitation of the method: formation of reduced products and benzothiophene derivatives.

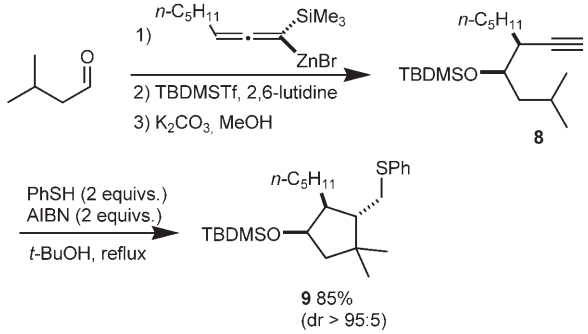
5i defines clearly the limit of the thiophenol method. When the hydrogen abstraction step is too slow (a rate constant of $= 5 \times 10^5\ M^{-1}\ s^{-1}$ can be estimated for this 1,5 H-transfer)[5] the intramolecular addition of the vinyl radical onto the aromatic ring becomes a competitive process and the use of higher dilution will not allow us to enhance the ratio of hydrogen transfer. Attempts to



Scheme 7. Effect of the substitution at the propargylic center.



Scheme 8. Determination of the relative configuration of **7** by X-ray crystal structure analysis.



Scheme 9. Effect of vicinal substituents.

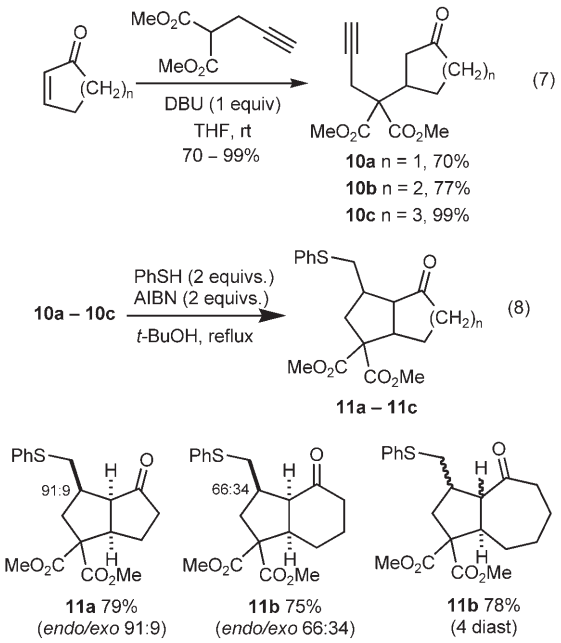
generate a primary radical from **1j** [Scheme 6, Eq. (5)] affords the thioether **4j** in 54% yield together with some benzothiophene **5j** ($\leqslant$5%). In a similar example, the tin hydride method failed also to give the product of radical translocation-cyclization and a rate constant for the 1,5-hydrogen-transfer was estimated to be $<10^5\ M^{-1}\ s^{-1}$.[5]

Substrates bearing an alkyl substituent at the propargylic position were investigated next (Scheme 7). Interestingly, most of these substrates give very high yields of hydrogen transfer. For instance, the generation of tertiary alkyl radicals from **1k** affords the cyclic compound **3k** in 79% yield as single diastereomer. The ester derivative **1l** affords the cyclopentane **3l** in 97% yield. Generation of secondary (from **3m**) and primary (from **3n**) alkyl radicals is also possible and leads to the expected cyclic compounds in 62% and 20% yield, respectively. Similar results are obtained with precursors bearing an *n*-pentyl substituent at the propargylic position. Cyclopentanes **3o** and **3p** are isolated both in 90% yield with a complete regioselectivity. Indeed, a competitive 1,5-hydrogen-transfer involving the propargyl *n*-pentyl side chain is not observed, presumably because of the absence of a Thorpe–Ingold effect. In order to assess the relative configuration of the products, a closely related crystalline sulfone was prepared. The reaction of **1k** was repeated with thiocresol and the *p*-tolyl thioether **6** was isolated in 95% yield as a single diastereomer. Oxidation with magnesium monoperoxyphthalate (MMPP) afforded the sulfone **7** that gave upon recrystallization crystals suitable for X-ray analysis (Scheme 8).[31]

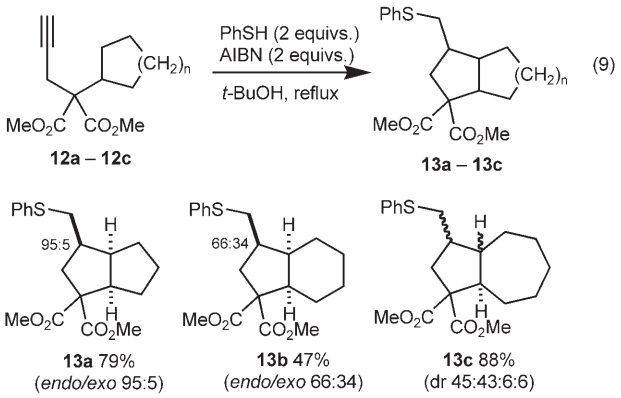
Comparison of the results of Schemes 7 and 6 demonstrates clearly that the propargylic substituent has a very beneficial effect on the rate of hydrogen transfer. The presence of vicinal substituents (the propargylic substituent and the *gem*-diesters) is at the origin of a rate acceleration similar to the one observed by Jung in related *vic*-disubstituted systems.[32] To test further this hypothesis, substrate **8** possessing only vicinal substituents was prepared (Scheme 9). Upon treatment with thiophenol/AIBN, the cyclized product **9** (85% yield, one diastereomer) is obtained. This result supports the presence of *vic*-disubtituent effect enhancing the rate of hydrogen transfer.

Fused Bicyclic Compounds

The preparation of fused bicyclic compounds was envisaged next. For this purpose, the cycloalkanones **10a**–**10c** were prepared in 70–77% yield by conjugate addition of



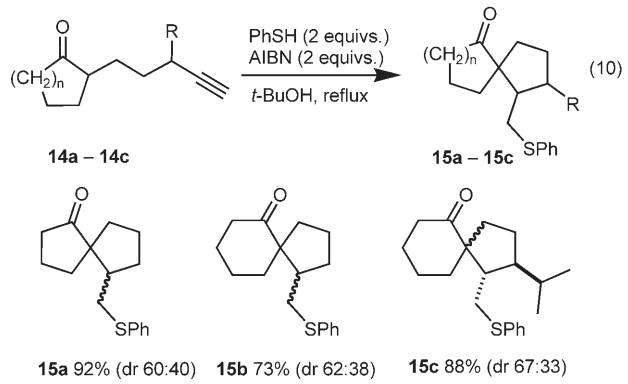
Scheme 10. Fused bicyclic ketones.



Scheme 11. Fused bicyclic alkanes.

the commercially available dimethyl propargylmalonate onto the corresponding cycloalkenones in the presence of DBU [Scheme 10, Eq. (7)].

Treatment with thiophenol and AIBN under standard conditions affords the expected fused bicyclic derivatives in good yields as a single regioisomer [Scheme 10, Eq. (8)]. As planned, hydrogen abstraction is only taking place at the α-position of the ketone leading to a stabilized enolate radical. In case of the cyclopentanone **10a**, the process is very efficient and the fused bicyclic compound **11a** is obtained as an *endo/exo* 91:9 mixture of diastereomers in 79% yield after flash chromatography (entry 1). Cyclohexanone **10b** and cycloheptanone **10c** derivatives give similar results (**11b** 75%, **11c** 78%) with a lower stereoselectivity control in the cyclization step. The relative *endo* configuration of the major isomers of **11a** and **11b** is not proven but tentatively attributed according to well documented literature precedents.[33–36]



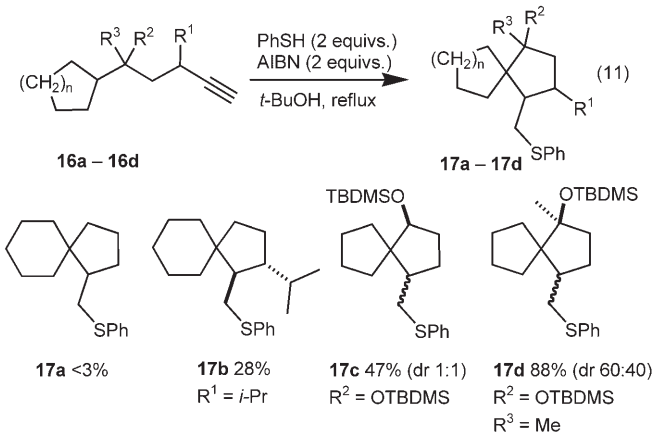
Scheme 12. Spirocyclic ketones.

Encouraged by these results, we decided to investigate the more challenging case of 1,5-hydrogen shift in non-functionalized cycloalkanes. The substituted cycloalkanes **12a**–**12c** were treated with thiophenol/AIBN under the standard conditions [Scheme 11, Eq. (9)]. The [3.3.0]- and [5.3.0]fused bicyclic products **13a** and **13c** were obtained in 79% and 88% yield. Preparation of the [4.3.0]bicyclic species **13b** was less efficient (47% yield).

Spirocyclic Compounds

Standard procedures for spirocyclization of alkynes are intramolecular carbomercuration,[37–40] and iodocarbocyclization of α-iodocycloalkanones using Lewis acids such as $AlCl_3$.[41] Free radical cyclizations have emerged as a powerful method of carbocyclization. For instance, Clive has reported the use of α-(phenylseleno) ketones as radical precursors in 5-*exo* cyclizations.[42] Sha and co-workers have demonstrated that α-carbonyl radicals generated from α-iodo ketones cyclize efficiently in a 5-*exo*-dig mode in the presence of tributyltin hydride and AIBN.[43,44] Only few reports deal with the use of 1,5-hydrogen transfer for the preparation of spiroalkanes.[44–47] The thiophenol-mediated hydrogen transfer-cyclization process represents a very attractive procedure for the preparation of spirocyclic systems since the precursors are easily available and the generation of tertiary alkyl radical *via* 1,5-hydrogen transfer is particularly efficient (*vide supra*). A first series of experiments was run with the easily available cyclic ketones **14a**–**14c** according to Scheme 12 [Eq. (10)]. The spirocyclic ketones **15a**–**15c** are obtained in good yield (73%–92%) and moderate stereoselectivity.[48]

Substituted 5-cycloalkylpent-1-yne derivatives **16a**–**16d** were investigated next according to Scheme 13 [Eq. (11)]. The non-substituted precursor **16a** affords none of the desired spirocyclic derivative **17a**. Substrate



Scheme 13. Spirocyclic alkanes.

16b, possessing a substituent at the propargylic position, gives the desired spiro compound **17b** in low yield (28%). The presence of an alkoxy substituent at position 4 in **16c** has a positive effect and the spiro derivative **17c** is obtained in 47% yield (29% starting material recovered). Finally, 4,4-disubstituted pentyne **16d** affords the spirocyclic compound **17d** in 88% yield demonstrating further the importance of *gem*-disubstituents.

Conclusion

We have developed an efficient procedure to run cascade reactions involving 1,5-hydrogen atom abstraction followed by a radical cyclization. Such reactions are classically run under tin hydride conditions starting from haloalkenes. In the procedure presented here, alkenyl radicals are generated from easily available terminal alkynes and thiophenol. This tin-free procedure gives high yields of radical translocation products. By proper design of *gem*- and *vic*-disubstituents effects, it is possible to generate efficiently non-stabilized radicals *via* 1,5-hydrogen transfer. This efficient and convenient procedure allows the formation of fused rings and spiro derivatives under tin-free conditions. Interestingly, the products bear a phenylthio substituent that offers many opportunities for further transformations. Application in the total synthesis of active compounds containing fused ring or spiro-bicyclic skeletons are currently under investigation and will be reported in due course.[49]

Experimental Section

General information, full experimental procedures and analytical data are available as Supporting Information.

General Procedure for the Thiophenol-Mediated Reaction

To a solution of the alkyne (1.0 mmol) and AIBN (1.0 mmol, 164 mg) in refluxing *t*-BuOH (100 mL) was added over 20 h a solution of AIBN (1 mmol, 164 mg) in benzene (2 mL) and a solution of thiophenol (2.0 mmol, 220 mg) in benzene (2 mL) through a syringe pump (the needles were placed in the condenser). After completion of the reaction (TLC monitoring), the solution was cooled down and *t*-BuOH evaporated under reduced pressure. The residue was filtered through a short pad of silica gel (AcOEt/hexane). The filtrate was evaporated under reduce pressure and flash chromatography (AcOEt/hexane) of the residue afforded the desired cyclized products. The ratio of isomers was determined by GC-MS analysis of the crude reaction mixture.

***2-Isopropyl-4,4-dimethyl-3-phenylsulfanylmethylcyclopentane-1,1-dicarboxylic acid dimethyl ester* (3k):** According to the general procedure, from **1k** (268 mg, 1 mmol). Flash chromatography (hexane/AcOEt, 9:1) gave **3k** as a single product; yield: 299 mg (79%); ^{1}H NMR (300 MHz): δ = 7.35–7.25 (m, 4H), 7.19–7.15 (m, 1H), 3.72 (s, 3H), 3.69 (s, 3H), 3.09 (dd, *J* = 12.2, 3.8 Hz, 1H), 2.93 (dd, *J* = 12.2, 10.0 Hz, 1H), 2.72 (dd, *J* = 10.4, 2.6 Hz, 1H), 2.41 (d, *J* = 13.9 Hz, 1H), 2.08–1.98 (m, 2H), 1.95 (d, *J* = 13.9 Hz, 1H), 1.26 (s, 3H), 0.99 (d, *J* = 7.2 Hz, 3H), 0.95 (s, 3H), 0.83 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (75 MHz): δ = 174.0, 172.2, 137.7 (C_q), 129.3 (2CH), 129.0 (2CH), 126.0, 62.4 (C_q), 55.2, 52.8, 52.6, 50.4 (CH_2), 48.1, 40.0 (C_q), 35.9 (CH_2), 30.7, 27.7, 24.0, 23.4, 17.7; HR-MS: calcd. for $C_{21}H_{30}O_4S$ [M^+]: 378.1864; found: 378.1863.

***4-Oxo-3-phenylsulfanylmethylhexahydropentalene-1,1-dicarboxylic acid dimethyl ester* (11a):** According to general procedure, from **10a** (252 mg, 1 mmol). Flash chromatography (hexane/AcOEt, 6:1) gave **11a** as a mixture of 2 diastereomers in a 91:9 ratio; yield: 286 mg (79%). The ratio of the isomers was determined by ^{1}H NMR analysis of the crude reaction mixture before flash chromatography. Major isomer (*endo*-**11a**): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.12–7.40 (m, 5H), 3.75 (s, 3H), 3.72 (s, 3H), 3.42–3.55 (m, 2H), 2.88 (dd, 1H, *J* = 8.82, 10.67), 2.65 (dd, 1H, *J* = 9.93, 12.93), 2.53 (dd, 1H, *J* = 6.25, 12.87), 2.43 (m, 1H), 2.25 (m, 3H), 2.06 (m, 1H), 1.54 (dd, 1H, *J* = 9.19, 13.24); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.6 (CH_2), 36.2 (CH_2), 38.4 (CH_2), 39.9 (CH_2), 40.1 (CH), 47.1 (CH), 53.0 (CH_3), 53.2 (CH), 53.4 (CH_3), 63.7 (C), 126.3 (CH), 128.9 (2*CH), 129.7 (2*CH), 136.1 (C), 169.8 (C), 171.8 (C), 218.9 (C); HR-MS: calcd. for $C_{19}H_{22}O_5S$ [M^+]: 362.1188; found: 362.1188.

***3-Phenylsulfanylmethylhexahydropentalene-1,1-dicarboxylic acid dimethyl ester* (13a):** According to the general procedure, from **12a** (238 mg, 1 mmol). Flash chromatography (hexane/AcOEt, 9:1) gave **13a** as a mixture of diastereomers in a 94:6 ratio; yield: 268 mg (77%). Major isomer (*endo*-**13a**): ^{1}H NMR (300 MHz): δ = 7.36–7.26 (m, 4H), 7.22–7.16 (m, 1H), 3.71 (s, 3H), 3.70 (s, 3H), 3.27 (q, *J* = 9.2 Hz, 1H), 3.01–2.89 (m, 2H), 2.66 (m, 1H), 2.29–2.17 (m, 1H), 2.16–2.05 (m, 2H), 1.86–1.68 (m, 3H), 1.41–1.14 (m, 2H), 1.03–0.86 (m, 1H); ^{13}C NMR (75 MHz): δ = 172.6, 170.9, 136.8 (C_q), 129.5 (2CH), 128.9 (2CH), 126.1 (CH), 63.4 (C_q), 52.8, 52.3, 47.8, 45.1, 38.8, 36.6 (CH_2), 34.9 (CH_2), 30.5 (CH_2), 28.0 (CH_2), 27.2 (CH_2); HR-MS: calcd. for $C_{19}H_{22}O_4S$ [M^+]: 346.1239; found: 346.1239.

***2-Isopropyl-1-phenylsulfanylmethylspiro[4.5]decan-6-one* (15c):** According to the general procedure, from **14c** (206 mg, 1 mmol). Flash chromatography (cyclohexane/*t*-BuOMe, 95:5) gave **15c** as a mixture of diastereomers in a 67:33 ratio; yield: 277 mg (88%). Major diastereomer: ^{1}H NMR (400 MHz): δ = 7.33–7.25 (m, 4H), 7.16–7.12 (m, 1H), 3.01 (dd, *J* = 10.7, 4.1 Hz, 1H), 2.91–2.82 (m, 1H), 2.82 (dd, *J* = 10.7, 9.2 Hz, 1H), 2.49–2.35 (m, 2H), 2.03–1.92 (m, 1H), 1.90–1.59 (m, 10H), 1.41–1.32 (m, 1H), 0.91 (d, *J* = 6.8 Hz, 3H), 0.81 (d, *J* = Hz, 3H); ^{13}C NMR (100 MHz): δ = 213.7, 138.1, 128.9 (2C), 128.6 (2C), 125.6, 58.7 (C_q), 49.8, 43.2, 39.8, 36.3, 35.0, 31.2, 29.4, 26.0, 24.4, 22.5, 21.6, 17.0; HR-MS: calcd. for $C_{20}H_{28}OS$ [M^+]: 316.1861; found: 316.1862.

tert-Butyl-(dimethylsilyl) 1-Methyl-4-[(phenylsulfanyl)methyl]spiro[4.4]non-1-yl Ether (17d)

To a solution of **16d** (140 mg, 0.5 mmol) and AIBN (41 mg, 0.25 mmol) in *t*-BuOH (50 mL) were added during 24 h PhSH (55 mg, 0.5 mmol) and AIBN (123 mg, 0.75 mmol) both *via* syringe pump as two solutions in benzene (2 × 2 mL). *t*-BuOH was evaporated and the residue purified by flash chromatography (hexane/EtOAc, 100:1) to afford **17d** as a 60:40 mixture of two diastereomers; yield: 160 mg (82%); colorless oil; anal. calcd. for $C_{23}H_{38}OSSi$ (390.70): C 70.71, H 9.80; found: C 70.76, H 9.78.

Acknowledgements

We thank the Swiss national science foundation (Grant 20–103627), the Roche Foundation (post-doctoral fellowship to FD) and the University of Berne for supporting this work.

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