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Direct Furan Formation by Treatment of Alkynyl Ketones with Strong Potassium Bases

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Abstract

The reaction of keto-alkynes with strong potassium bases such as KOtBu, KHMDS or KH yields substituted furans in moderate to good yields without any special activation of the alkyne required. The method offers both a flexibility and rapid method for the synthesis of di- tri- or tetra-substituted furans, although some yields are only modest at best. © 1999 Elsevier Science Ltd. All rights reserved.

Keywords: Furans; cyclization; alkynes; enolates

Introduction

Furans occur widely throughout nature in a variety of commercially important compounds; including pharmaceuticals (anti-inflammatory properties), flavour and fragrance enhancers.[1,2] In many instances they also play an important role as intermediates in synthetic pathways because they react as a special class of vinyl ethers[3,4] or as dienophiles in the Diels-Alder reaction.[5] Given furans well documented uses, and the considerable synthetic challenge of many furan-containing natural products, it is not surprising that many methods have been devised for the syntheses of these derivatives.[6-12]

We first became interested in the synthesis of these compounds while investigating the chemistry of alkynyl sulfoxides.[13] We have since turned this result into a general process for constructing highly functionalized furans.[14,15] However, to synthesize a substrate required for the above investigation, attempted acylation of alkynyl ketone **1** led not to the expected β-diketone, but to 2-methyl-3,5-diphenylfuran **2**[16] in approximately 30% yield, equation 1. It is well known that γ-alkynyl ketones undergo furan formation under acidic conditions,[17-20]

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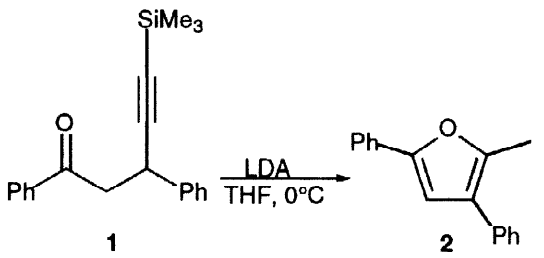
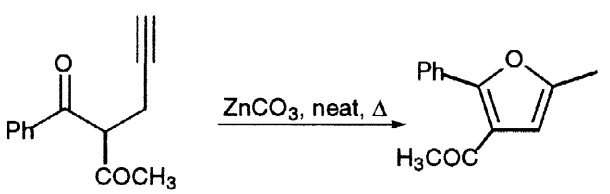
however, the fact that cyclization had occurred under basic conditions was a surprise,[21] especially considering that unactivated alkynes are generally not very electrophilic. Despite



(1)

this truism, however, there are examples that illustrate the contrary.[22-24]

Most closely related to our observation was the work of Mock. In this seminal article they demonstrated that in certain cases γ-alkynyl-β-diketones, and γ-alkynyl-β-keto esters would form furans when neat solutions were heated to reflux in the presence of a catalytic amount of $ZnCO_3$, equation 2. Although the yields were acceptable, the reaction was not of a broad scope. Thus we were struck not only by the ease with which our reaction took place, but also that a "normal" ketone enolate had initiated the process. As a result, we decided to explore the scope and limitations of this reaction.



(2)

Results and Discussion

Before looking at various reactions, it was necessary to develop a protocol that would allow for the cyclization to proceed with a respectable yield. The approximately 30% yield obtained in the initial runs clearly was not acceptable. After much experimentation, three general methods were found to give an acceptable yield of the product (47%-57% depending on the base used). The conditions developed required the use of a strong potassium base (KOtBu, KHMDS, NaH/KH) for a short time (ca. 5 minutes) followed by a rapid and

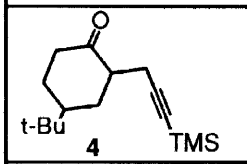
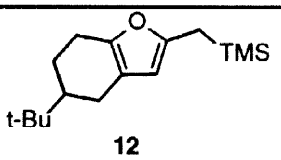
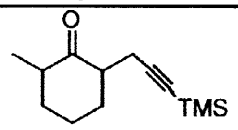
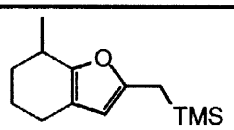
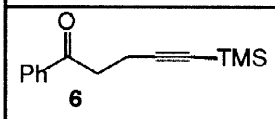
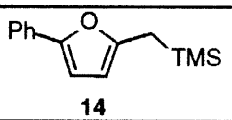
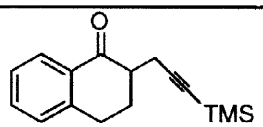
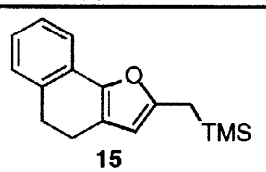
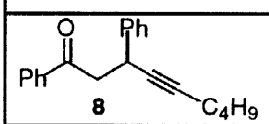
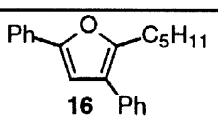
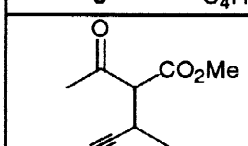
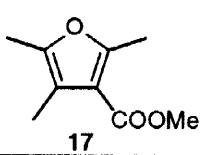
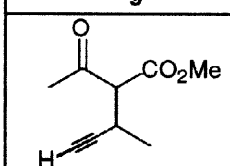
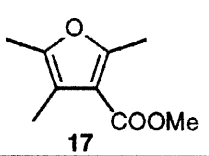
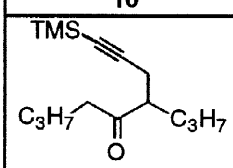
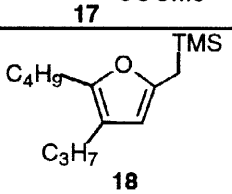
immediate quench with mild acid (0.1 M HCl). It is important to note that the use of other alkali metal bases (e.g., LDA, LiOtBu, NaHMDS) gave vastly inferior results.

This rapid synthesis of 3-methyl-2,5-diphenylfuran posed several questions: (1) Could this cyclization take place without the phenyl group on the ketone? (2) Was the phenyl group β to the ketone required? (3) Would this reaction work without having a silyl group on the acetylene? (4) Could less reactive oxy-anions be used? (5) Could the mechanism for this transformation be delineated?

To suitably answer these questions we needed to generate several precursors by the alkylation of an appropriate ketone with 3-iodo-1-trimethylsilylpropyne **3**[15] (1.1 eq. LDA, THF, 0°C), except **10** in which propargyl bromide was used as the electrophile and **8** which was synthesized according to a literature procedure.[25] To probe the effect of the phenyl ketone (question 1), precursors **4** (52%), **5** (32%) and **11** (43%) were made. To investigate what effect the phenyl group had (if any) α to the alkyne (question 2), alkynyl ketones **6** (48%) and **7** (57%) were constructed. To search the effect of the silyl group (question 3), **8** (64%) and **10** (53%) were synthesized, and to see if less nucleophilic oxy-anions would cyclize ketone **9** (43%) was prepared, Table 1.

Cyclization studies were initiated by treatment of each ketone (**4-11**) with the protocols developed for **2**. After SiO_2 chromatography the corresponding furans **12-18** were obtained in moderate to good isolated yields. The results from this study are presented in Table 1, and several points are worth mentioning. The success of alkyl-ketones **4** and **5** indicates that a phenyl ketone is not required for cyclization, however, the reluctance of ketone **11** to cyclize to furan **18** indicates that not all ketones will undergo cyclization. Attempts to force the reaction (RT, refluxing THF or longer reaction times at 0°C) only resulted in decomposition of the starting material. Since we have observed another substrate bearing bulky substituents fail to cyclize, it may be that the reluctance of this ketone to undergo cyclization is due to entropic, as well as steric reasons and not to the fact that a phenyl ketone is required. The realization that ketones **4-7** all undergo this reaction supports the notion that a phenyl group, or for that matter any substituent, α to the alkyne is not a requirement for cyclization. In addition, it appears that a trimethylsilyl group is not needed to effect a successful reaction since ketones **8** and **10** also cyclized under the reaction conditions.

Table 1: Cyclization studies on alkynyl ketones using various potassium bases.

Cyclization Precursor	Furan Product[a]	Method A (KOtBu)	Method B (KHMDS)	Method C (KH/NaH)
 4	 12	51%	47%	----
 5	 13	48%	43%	----
 6	 14	67%	61%	----
 7	 15	87%	76%	----
 8	 16	56%	54%	----
 9	 17	NR	NR	71%[b]
 10	 17	NR	NR	67%[b]
 11	 18	<5%	<5%	<5%

a) All new products were fully characterized by ^{1}H and ^{13}C NMR, FT-IR and HRMS.
b) The reaction was refluxed (THF) for 12 hr in order effect efficient cyclization.

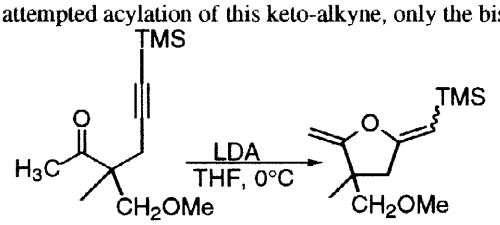
It is noteworthy that acetoacetates **9** and **10** underwent efficient reaction without the need of activating the alkyne, although the reaction temperature had to be elevated. These

results contradict previous studies in which furan formation was only achieved by first transforming the alkyne into a Michael acceptor by addition of an electron withdrawing group,[14] and those where much higher temperatures were required.[23] Despite the positive reactions outlined above, it must be noted that these conditions are far from successful for all β-keto esters or β-diketones. We found that less substituted variants, for instance leading to 2,5-disubstituted furans, either refused to cyclize or decomposed when subjected to more vigorous conditions. It seems that the success achieved with **9** and **10** are a result of balancing subtle steric and electronic factors, and demonstrate a severe limitation to this method.

With the above study completed, a comment on the stability of the products is warranted. It was found that the TMS group in the furan products was more labile than anticipated and if extreme care was not taken in the acidic workup then products that did not contain a trimethylsilyl group were obtained. In two cases, our original example and entry 9, all efforts to isolate material that contained a TMS group failed. Furthermore, we had difficulty isolating and purifying only one compound, **14**. That occurred only when the silyl group had fallen off during work-up. This may suggest that in simpler systems, like **14**, that the presence of a bulky and/or an electron withdrawing group may be required to impart a stability to the products. All the products obtained from this study were stable for several months when stored in benzene under an inert atmosphere at -10°C .

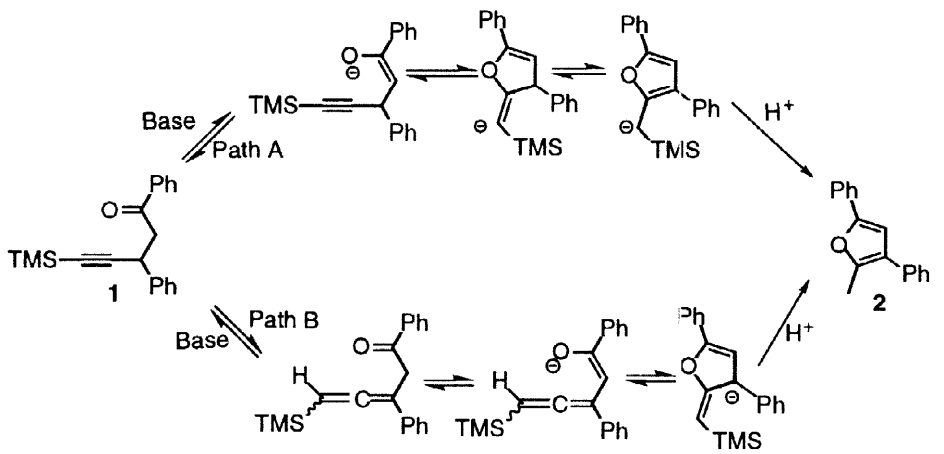
To date there is no conclusive evidence of the reaction pathway, however, several observations are worth note. They are: 1) if a slight deficiency of base is used the reaction still proceeds, but with slightly diminished yields (ca. 5-10% lower than reported); 2) no allene compounds were ever seen in the ^{1}H nmr spectrum of the crude reaction mixtures; 3) in an isolated example a bis-enol ether was isolated and characterized;[1] and 4) all reactions were essentially instantaneous (< 2 minutes) regardless of the base used or the reaction temperature (varying from -78°C to RT). Attempts to garner more information by performing the

[1] Upon attempted acylation of this keto-alkyne, only the bis-enol ether was isolated in 25%-35% yield.



reaction in d_8-THF in a NMR tube, or by performing deuteration experiments proved unreliable and gave inconclusive evidence.

From the observations made above, it is easy to conclude that the reaction proceeds by initial enolate formation, followed by attack onto the alkyne and subsequent isomerization to give the observed product, path A, Scheme 1. Although we favour this pathway, it does not explain the apparent preference for "thermodynamic" enolate formation in compounds like **4** and **5**. An alternative pathway involving isomerization of the alkyne to an allene followed by attack of the enolate on the allene, either in a 5-endo or 5-exo-dig fashion,[26] is also possible, path b, Scheme 1. In a related example, it was shown that cyclization through both "general" pathways shown in Scheme 1 (direct oxy-anion attack on the alkyne, or isomerization to an allene followed by oxy-anion attack) are possible and appear to occur simultaneously.[21] Considering the above study, effort to glean more mechanistic information using deuteration experiments is not warranted, however, it might be possible to investigate compounds that cannot form allenes to see if they will cyclize. Yet, it is important to note that this reaction still will not conclusively prove one pathway over the other.



Scheme 1

Conclusions

A variety of furans containing a diversity of substitution patterns and functionality can be constructed in a very direct fashion and in moderate but usable yields. More specifically, furans can be successfully synthesized from γ-alkynyl ketones without any special activation of the alkyne moiety. The experimental evidence gathered to date suggests that the reaction

proceeds by direct attack of an enolate onto an unactivated alkyne. The utility of this chemistry for natural product synthesis and further insights into the mechanistic pathway is currently being pursued and will be documented when complete.

Acknowledgments

We gratefully thank NSERC Canada (operating grant) and the University of New Brunswick for financial support. Also we would like to thank Dr. Larry Calhoun and May Ling Lee for NMR assistance and Dan Drummond for mass spectral service.

General Experimental Conditions:

All reactions were carried out in a flame or oven dried (140°C) round bottomed flask (RBF) under an argon atmosphere. Temperatures indicated refer to external bath temperatures and all reactions were stirred magnetically. Air sensitive reagents were transferred through rubber septa by syringes. The phrase "removed under reduced pressure" refers to removal of solvent with a Büchi rotary-evaporator using a water aspirator and a bath temperature of 30°C.

All commercial reagents were purchased from Aldrich Chemicals and were used without further purification. Tetrahydrofuran was dried over Na/benzophenone and was transferred by way of syringe. Extraction solvents were purchased in bulk and distilled before use.

Analytical thin layer chromatography was performed using Merck silica gel 60 F254 precoated plates (0.25 mm). Visualization was effected by short wave UV illumination and/or $KMnO_4$-K_2CO_3 solution followed by heating on a hot plate. Column chromatography was performed on Merck silica gel (230-400 mesh) following the procedure of Still.[27] Reagent grade solvents were used without further purification for chromatographic separations.

All nuclear magnetic resonance spectra (^1H NMR and ^{13}C NMR) were recorded on a Varian Unity 400 (400 MHz) spectrometer, in $CDCl_3$ solution with chemical shifts reported in ppm (δ) relative to tetramethylsilane. ^1H NMR data are reported as follows: chemical shift (multiplicity, number of protons, coupling constant in Hz), and ^{13}C NMR as: chemical shift (number of carbons), which was determined by a heteronuclear multiple quantum coherence

experiment, HMQC. FT-IR spectra were recorded on a Bruker IFS-25 spectrometer using NaCl windows and are reported in wave numbers (cm^{-1}). High resolution mass spectra were run on a Kratos MS50 spectrometer and are reported as m^+/z (% intensity).

General Cyclization Procedures:

Method A: In a 10 mL RBF cooled to 0°C was placed ketone **1** (31 mg, 0.1 mmol) and THF (2 mL). To this was added 1 M potassium *tert.*-butoxide in THF (0.1 mL, 0.1 mmol), the mixture was stirred for 5 minutes and then quenched with cold 0.1 M HCl (1 mL). The mixture was diluted with Et_2O (10 mL), the layers were separated and the organic phase was washed with H_2O (5 mL), brine (5 mL), and dried over $MgSO_4$. Removal of solvent under reduced pressure and purification gave **2**.[16]

Method B: The procedure was exactly as described above except that KHMDS (0.5 M in toluene) was used as base.

Method C: To a 10 mL RBF cooled to 0°C was successively added ketone **9** (18 mg, 0.45 mmol) THF (3 mL), NaH 60% in oil (67 mg, 0.4 mmol) and a catalytic amount of KH. The cold bath was removed and the solution was refluxed overnight, cooled and then quenched with cold 0.1 M HCl (1 mL). The reaction mixture was worked-up as above and purified to give **17**.[28]

*2-Methyl-3,5-diphenyl furan (**2**)*:[16] Purified by SiO_2 chromatography (50:1 hexanes/ethyl acetate as eluant) to give a colourless oil. ^1H NMR: 7.66 (d, 2H, J=8.2), 7.5-7.2 (m, 8H), 6.77 (s, 1H), 2.51 (s, 3H). ^{13}C NMR: 151.6 (1C), 147.6 (1C), 134 (1C), 130.8 (1C), 128.6 (2C), 128.6 (2C), 127.5 (2C), 127 (1C), 126.4 (1C), 123.4 (2C), 123 (1C), 106.4 (1C), 13.2 (1C). FT-IR (neat): 2958, 2924, 2856, 1599. HRMS: calculated for $C_{17}H_{14}O$ 234.1045, found for $C_{17}H_{14}O$ 234.1044 (100).

*5-tert.-Butyl-2-trimethylsilanylmethyl-4,5,6,7-tetrahydro-benzofuran (**12**):* Purified by SiO_2 chromatography (50:1 hexanes/ethyl acetate as eluant) to give a pale yellow oil. ^1H NMR: 5.60 (s, 1H), 2.65-2.00 (m, 4H), 1.98 (s, 2H), 1.55-1.25 (m, 3H), 0.91 (s, 9H), 0.04 (s, 9H). ^{13}C NMR: 152.2 (1C), 147.9 (1C), 117.6 (1C), 104.7 (1C), 45.3 (1C), 32.5 (1C), 27.5 (2C), 27.1 (1C), 24.7 (1C), 23.9 (1C), 23.4 (1C), 18.2 (1C), -1.7 (3C). FT-IR (neat): 2959, 2860, 1562. HRMS: calculated for $C_{16}H_{28}OSi$ 264.1910, found for $C_{16}H_{28}OSi$ 264.1919 (100).

*7-Methyl-2-trimethylsilanylmethyl-4,5,6,7-tetrahydro-benzofuran (**13**):* Purified by SiO_2 chromatography (50:1 hexanes/ethyl acetate as eluant) to give a colourless oil. ^1H NMR: 5.58 (s, 1H), 2.8-2.6 (m, 1H), 2.31 (t, 2H, J=5.2), 1.98 (s, 2H), 2.00-1.08 (m, 4H), 1.15 (d, 3H, J=7), 0.02 (s, 9H). ^{13}C NMR: 152.1 (1C), 151.9 (1C), 116.7 (1C), 104.3 (1C), 32.4 (1C), 31.6 (1C), 22.5 (1C), 22.0 (1C), 19.2 (1C), 18.2 (1C), -1.5 (3C). FT-IR (neat): 2935, 2860. HRMS: calculated for $C_{13}H_{22}OSi$ 222.1441, found for $C_{13}H_{22}OSi$ 222.1454 (100).

*2-Phenyl-5-trimethylsilanylmethyl-furan (**14**):* Purified by SiO_2 chromatography (50:1 hexanes/ethyl acetate as eluant) to give a pale yellow oil. ^1H NMR: 7.57 (d, 2H, J=6.6), 7.4-7.1 (m, 3H), 6.51 (d, 1H, J=3), 5.88 (d, 1H, J=3.4), 2.11 (s, 2H), 0.07 (s, 9H). ^{13}C NMR: 154.7 (1C), 151.4 (1C), 131.4 (1C), 128.6 (2C), 126.3 (1C), 123.0 (2C), 106.0 (1C), 105.8 (1C), 18.7 (1C), -1.6 (3C). FT-IR (neat): 2934, 2871. HRMS: calculated for $C_{14}H_{18}OSi$ 230.1127, found for $C_{14}H_{18}OSi$ 230.1116 (100).

*2-Trimethylsilanylmethyl-4,5-dihydro-naphtho[1,2-b]furan (**15**):* Purified by SiO_2 chromatography (50:1 hexanes/ethyl acetate as eluant) to give a pale yellow oil. ^1H NMR: 7.33 (d, 1H, J=7.2), 7.25-6.95 (m, 2H), 7.03 (d, 1H, J=7.2), 5.77 (s, 1H), 2.91 (t, 2H, J=7.8), 2.64 (t, 2H, J=7.8), 2.09 (s, 2H), 0.07 (s, 9H). ^{13}C NMR: 154.7 (1C), 147.4 (1C), 133.7 (1C), 128.5 (1C), 126.5 (1C), 125.2 (1C), 120.6 (1C), 118.1 (1C), 105.3 (1C), 29.1 (1C), 21.0 (1C), 18.8 (1C), -3.6 (3C). FT-IR (neat): 2905, 2850, 1647, 1615, 1606. HRMS: calculated for $C_{16}H_{20}OSi$ 256.1284, found for $C_{16}H_{20}OSi$ 256.1284 (100).

*2-Pentyl-3,5-diphenylfuran (**16**):* Purified by SiO_2 chromatography (50:1 hexanes/ethyl acetate as eluant) to give a pale yellow oil. ^1H NMR: 7.68 (d, 2H, J=7.2), 7.45-7.23 (m, 8H), 6.76 (s, 1H), 2.83 (t, 2H, J=8), 1.85-1.75 (m, 2H), 1.4-1.2 (m, 4H), 0.90 (t, 3H, J=6.8). ^{13}C NMR: 151.8 (1C), 151.5 (1C), 134.2 (1C), 130.9 (1C), 128.6 (2C), 128.6 (2C), 127.7 (2C), 127 (1C), 126.5 (1C), 123.4 (2C), 122.9 (1C), 106.5 (1C), 31.5 (1C), 28.3 (1C), 27.0 (1C), 22.4 (1C), 14.0 (1C). FT-IR (neat): 2905, 2850, 1647, 1615, 1606. HRMS: calculated for $C_{21}H_{22}O$ 290.1672, found for $C_{21}H_{22}O$ 290.1661 (100).

*2,4,5-Trimethyl-furan-3-carboxylic acid methyl ester (**17**):*[28] Purified by SiO_2 chromatography (50:1 hexanes/ethyl acetate as eluant) to give a pale yellow oil. ^1H NMR: 6.21 (s, 1H), 3.78 (s, 3H), 2.51 (s, 3H), 2.22 (s, 3H). ^{13}C NMR: 165.4 (1C), 157.3 (1C), 145.7 (1C), 114.5 (1C), 113.5 (1C), 50.8 (1C), 14.1 (1C), 10.9 (1C), 9.8 (1C). FT-IR (neat): 2980, 2922, 2859, 1705, 1565. HRMS: calculated for $C_9H_{12}O_3$ 168.0787, found for $C_9H_{12}O_3$ 168.0789 (100).

References

1. Trost, B.; Flygare, J. *J. Org. Chem.* **1994**, *59*, 1078.
2. Look, A. A.; Burch, M. T.; Fenical, W.; Qi-Tai, Z.; Clardy, J. *J. Org. Chem.* **1985**, *50*, 5741.
3. March, J. *Advanced Organic Chemistry, 3'rd edition*, John Wiley and Sons: Toronto, 1985; p. 332.
4. Tsai, T.; Jin, H.; Wiesner, K. *Can. J. Chem.* **1984**, *62*, 1403.
5. Woo, S.; Keay, B. *Tetrahedron: Asymmetry* **1994**, *5*, 1411.
6. Padwa, A.; Ishida, M.; Muller, C.; Murphree, S. *J. Org. Chem.* **1992**, *57*, 1170.
7. Kataoka, Y.; Tezuka, M.; Takai, K.; Utimoto, K. *Tetrahedron* **1992**, *48*, 3495.
8. Wakabayashi, Y.; Fukuda, Y.; Shiragami, H.; Nozaki, H.; Utimoto, K. *Tetrahedron* **1985**, *41*, 3655.
9. Okura, K.; Furuune, M.; Miara, M.; Nomura, M. *J. Org. Chem.* **1992**, *57*, 4754.
10. Minami, I.; Yuhara, M.; Wantanabe, H.; Tsuji, J. *J. Organometallic Chem.* **1987**, *334*, 225.
11. Marshall, J. A.; Robinson, E. *J. Org. Chem.* **1990**, *55*, 3450.
12. Ji, J.; Lu, X. *J. Chem. Soc., Chem. Commun.* **1993**, 764.
13. Kabanyane, S. T.; MaGee, D. I. *Can. J. Chem.* **1992**, *70*, 2758.
14. MaGee, D. I.; Leach, J. D. *Tetrahedron Lett.* **1997**, *38*, 8129.
15. MaGee, D. I.; Leach, J. D.; Mallais, T. C. *Tetrahedron Lett.* **1997**, *38*, 1289.
16. Rio, G.; Lecas-Nawrocka, A. *Bull. Chem. Soc. Fr.* **1974**, 2824
17. Saunders, J.; Tipney, D. C.; Robins, P. *Tetrahedron Lett.* **1982**, *23*, 4147.
18. Cooke, S.; Henderson, D.; Richardson, K. A.; Taylor, R. J. K.; Saunders, J.; Strange, P. G. *J. Chem. Soc., Perkin Trans. 1* **1987**, 1825.
19. Schulte, K. E.; Reisch, J.; Bergenthal, D. *Chem. Ber.* **1968**, *101*, 1540.
20. Reisch, J. *Arch. Pharm.* **1965**, *198*, 591.
21. Although this transformation is reminiscent of recently published work by Marshall, his reactions took advantage of an S_N2' process to initiate ring formation. See: Marshall, J. A., Dubay, W. *J. Org.Chem.* **1993**, *58*, 3435.
22. Funk, R. L.; Bolton, G. L.; Brummond, K. M.; Ellestad, K. E.; Stallman, J. B. *J. Am. Chem. Soc.* **1995**, *115*, 7023.
23. Schulte, K. E.; Reisch, J.; Mock, A. *Arch. Pharm.* **1962**, *295*, 627.
24. Radchenko, S. I.; Petrov, A. A. *Russ. Chem. Rev.* **1989**, *58*, 948.
25. Hooz, J.; Layton, R. *J. Am. Chem. Soc.* **1971**, *93*, 7320.
26. Baldwin, J. *J. Chem. Soc., Chem. Commun.* **1976**, 734.
27. Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.
28. Minami, I.; Yuhara, M.; Watanabe, H.; Tsuji, J. *J. Organometallic Chem.* **1987**, *334*, 225.