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Convergent Regiodirected Assembly of 2,3-Disubstituted Furans

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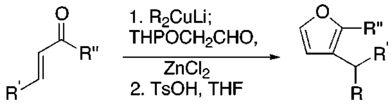
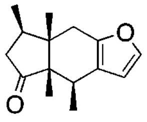
ABSTRACT

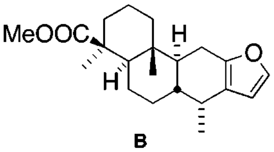


The conjugate addition of organocopper reagents to α,*β*-unsaturated enones results in the regiospecific generation of enolate anions, which can be made to undergo the aldol reaction with (tetrahydropyranyloxy)acetaldehyde under zinc chloride catalysis. Treatment of the resulting product with *p*-toluenesulfonic acid in THF affords the targeted 2,3-disubstituted furan.

For a broadly representative class of biologically significant natural products such as pinguisone (**A**),[1] furodysinin,[2] hippospongin A,[3] and methyl vouacapenate (**B**),[4] a 2,3-disubstituted furan ring constitutes a distinctive structural feature. In recent years, this realization has spawned a number of methods for accessing members of this heterocyclic class. The vast majority of the published routes involve the chemical modification of acyclic precursors.[5] These include, for example, the base-promoted cyclization of 3-alkynyl allylic alcohols,[6] the Ag(I)-catalyzed ring closure of allenyl ketones,[7] a ruthenium-promoted alternative involving *γ*-ethynylallyl alcohols,[8] and 2-fold alkylation of 3-tosylpropanal ethylene ketal with subsequent acidic hydrolysis.[9]



A



B

While these methodologies have seen applicability in a variety of contexts, a need still exists for a short and versatile approach to the construction of these systems. In this Letter, we outline representative examples of a broadly useful new method for assembling 2,3-disubstituted furans. Our investigations in this area are an outgrowth of the earlier development of a general synthesis of 2,3,4-trisubstituted furans by cycloaddition−thermal retrogression reactions involving oxazoles.[10] The present protocol is highly conver-

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(14) For the reaction of lithium enolates with aldehydes, see: (a) Stork, G.; d'Angelo, J. *J. Am. Chem. Soc.* **1974**, *96*, 7114. (b) Stork, G.; Kraus, G. A.; Garcia, G. A. *J. Org. Chem.* **1974**, *39*, 3459. (c) Stork, G.; Kraus, G. *J. Am. Chem. Soc.* **1976**, *98*, 6747. For the effect of $ZnCl_2$ on the aldol condensation of lithium enolates, consult: House, H. O.; Crumrine, D. S.; Teranishi, A. Y.; Olmstead, H. D. *J. Am. Chem. Soc.* **1973**, *95*, 3310.

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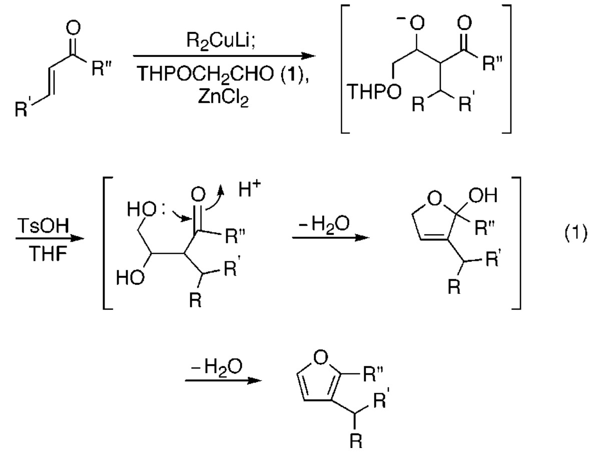
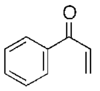
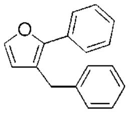
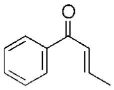
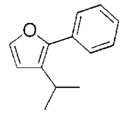
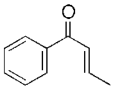
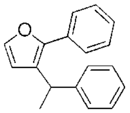
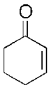
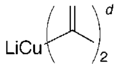
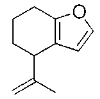
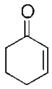
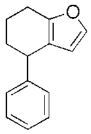
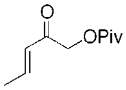
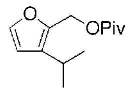
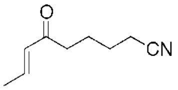
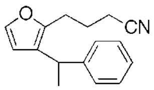
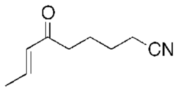
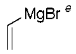
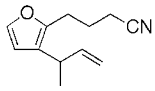
gent and utilizes three previously recognized phenomena. The first is the widespread ease with which organocuprates add to α,β-unsaturated enone systems with regiospecific generation of enolate anions.[11] Also relevant is the ability of these reactive intermediates to add to aldehydes,[12] especially in the presence of zinc chloride as a promoter.[13,14] For the present purposes, (tetrahydropyranyloxy)acetaldehyde (**1**)[15,16] plays the role of a universal intermediate. The final precedent is the susceptibility of terminal β,γ-dihydroxy ketones to acid-promoted cyclization.[17,18] The generalized scheme is outlined in eq 1.



(1)

The phenyl-substituted enones **2**[19] and **4**[20] (entries 1−3, Table 1) were readily procurable by previously described routes. An abbreviated approach to the more extensively functionalized substrates **10** and **12** (entries 6−8) took advantage of Schloss' method for the direct conversion of alkenes to homoallylic alcohols.[21] Subsequent oxidation of these intermediates with pyridinium chlorochromate and triethylamine-promoted double bond isomerization gave rise efficiently to these ketonic reagents (eqs 2 and 3).[22]

Table 1. Two-Step Furan Synthesis according to eq 1

entry	α,β-unsaturated ketone	cuprate	product	overall yield, %[a]
1	 **2**	Ph_2CuLi[b]	 **3**	49
2	 **4**	Me_2CuLi[c]	 **5**	53
3	 **4**	Ph_2CuLi[b]	 **6**	65
4	 **7**		 **8**	40
5	 **7**	Ph_2CuLi[b]	 **9**	55
6	 **10**	Me_2CuLi[c]	 **11**	46
7	 **12**	Ph_2CuLi[b]	 **13**	55
8	 **12**	 3% CuI	 **14**	47

[a] The yields of all entries are not optimized. [b] Johnson, C. R.; Dutra, G. A. *J. Am. Chem. Soc.* **1973**, *95*, 7777. [c] Boeckman, R. K.; Blum, D. M.; Ganem, B. *Org. Synth.* **1978**, *58*, 52. [d] Caine, D.; Venkataramu, S. D.; Kois, A. *J. Org. Chem.* **1992**, *57*, 2960. [e] Ito, Y.; Nakatsuka, M; Saegusa, T. *J. Am. Chem. Soc.* **1982**, *104*, 7609.

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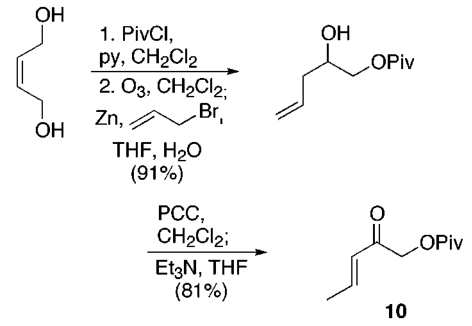
(22) Nitrile **15** has previously been reported by Buchwald, S. L.; Watson, B. L.; Wannamaker, M. W.; Dewan, J. C. *J. Am. Chem. Soc.* **1989**, *111*, 4486.

(23) **Prototypical Procedure:** To a cold (−40 °C), magnetically stirred suspension of purified copper(I) iodide (21 mg, 0.11 mmol) in dry THF (1 mL) containing dimethyl sulfide (0.5 mL) was added vinylmagnesium bromide (3.75 mL of a 1.0 M in THF, 3.75 mmol). Ketone **12** (343 mg, 2.5 mmol) dissolved in dry THF (5.0 mL) was introduced dropwise over 20 min. After an additional 30 min of stirring at −40 °C, the temperature was lowered to −78 °C and aldehyde **1** (900 mg, 6.25 mmol) together with zinc chloride (6.25 mL of 1.0 M in ether, 6.25 mmol) was added. The cooling bath was removed, and after 30 min the reaction mixture was diluted with ether (30 mL) and a saturated NH_4Cl solution (1.0 mL), leading to the formation of a precipitate. After the addition of $MgSO_4$ to this suspension, the solids were removed by filtration. The concentrated filtrate was dissolved in THF (15 mL), *p*-toluenesulfonic acid (47 mg, 0.25 mmol) was introduced, and stirring was maintained for 5 h. Following solvent evaporation, the residue was chromatographed on silica gel (elution with 5% ether in ligroin) to give 221 mg (47%) of **14** as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26 (d, $J = 1.7$ Hz, 1 H), 6.23 (d, $J = 1.7$ Hz, 1 H), 5.96−5.84 (m, 1 H), 4.98 (ddd, $J = 15.9$, 1.5, 1.5 Hz, 1 H), 4.97 (ddd, $J = 11.4$, 1.5, 1.5 Hz, 1 H), 3.34 (quintet, $J = 6.8$ Hz, 1 H), 2.75 (t, $J = 7.0$ Hz, 2 H), 2.32 (t, $J = 7.0$ Hz, 2 H), 1.98 (quintet, $J = 7.0$ Hz, 1 H), 1.27 (d, $J = 6.8$ Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.6, 142.6, 140.7, 123.6, 119.3, 112.8, 109.6, 33.4, 24.5, 24.2, 20.7, 16.3; ES MS $(M + Na)^+$ calcd 212.1051 obsd 212.1056.



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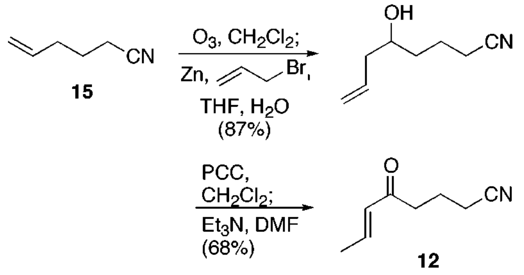

(3)

A key requirement in the implementation of eq 1 was the absence of enolate equilibration which would result in erosion of the overall regioselectivity. Such behavior was not observed. Aldehyde **1** proved to be an extraordinarily serviceable electrophile for our purposes, being highly responsive to the aldol reaction regardless of the structural features of the enolate. Finally, the cyclodehydration of the intermediates so formed proceeded at room temperature and was complete within 4−8 h. A notable aspect of this conversion is that no need to undertake independent removal of the tetrahydropyranyl protecting group exists. The experimental procedure provided in footnote 23 is illustrative of the new, highly convergent pathway to 2,3-disubstituted furans. Many additional applications of this chemistry are, of course, possible, and their deployment for rapid access to this compound class appears meritorious.

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Supporting Information Available: Spectroscopic and analytical data in addition to experimental procedures for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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