Communications to the Editor

Conceptually New Directed Aldol Condensation Using Aluminum Tris(2,6-diphenylphenoxide)

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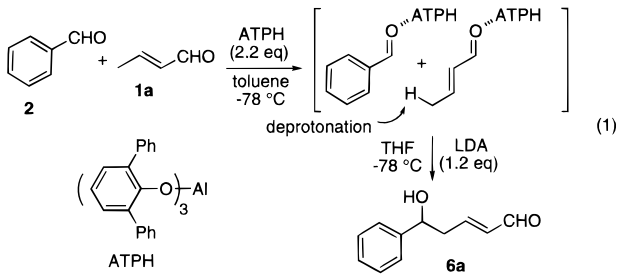
Control of the mixed aldol condensation between two different carbonyl compounds which present several possible sites for enolization is a challenging problem for synthetic chemists.[1] Such reactions are normally carried out by converting the carbonyl compound, which is to serve as a nucleophile, to an enolate. This reactive nucleophile is then allowed to react with the second carbonyl compound. We describe here an entirely different strategy for combining two different carbonyl compounds using lithium diisopropyl amide (LDA), in which both of the substrates are complexed with the bulky aluminum reagent aluminum tris(2,6-diphenylphenoxide) (ATPH).[2,3]

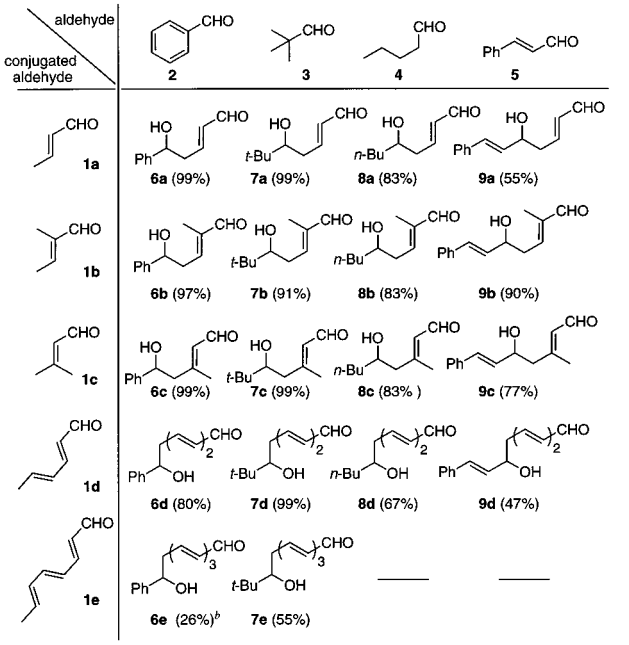
Sequential treatment of a toluene solution of ATPH (2.2 equiv) with crotonaldehyde (**1a**) (1.0 equiv) and benzaldehyde (**2**) (1.0 equiv) at −78 °C under argon was followed by deprotonation with a THF solution of LDA (1.2 equiv). The reaction mixture was stirred for 15 min and quenched with aqueous NH_4Cl to give, after chromatography on silica gel, homoallylic alcohol **6a** in quantitative yield with retention of the olefin configuration. None of the (*Z*)-isomer of **6a** was detected by ^{1}H NMR or GC-MS analyses. It is noteworthy that the deprotonation and subsequent addition occurred exclusively at the γ-position of crotonaldehyde (eq 1).[4]



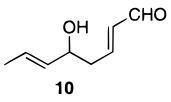
(1)

Other representative examples of various combinations of aldehydes are listed in Table 1. The (*E*)-methyl of **1c** was preferred for deprotonation−alkylation to give (*E*)-alcohols **6**−**9c** exclusively. The reaction also tolerated varelaldehyde (**4**) to give the corresponding products **8a**−**d** in high yields. Thus, LDA reacted with conjugated aldehydes and not with varelaldehyde. The 1,2-addition was predominant, in contrast to the 1,4- and 1,6-selectivity commonly observed in the addition of alkylmetals to the cinnamaldehyde (**5**)− and benzaldehyde−ATPH complexes, respectively.[3d,5] This new approach was also applied to dienyl and trienyl aldehydes **1d** and **1e**. It is important to point out that both the aldehydes must be precomplexed effectively with ATPH. In fact, precomplexation of **1a** (1.0 equiv) with ATPH (1.05 equiv), followed by sequential addition of LDA (1.05 equiv) and benzaldehyde (1.0 equiv) at −78 °C, led to self-dimerization of **1a** to produce 1,2-adduct **10** (30%) along with small amounts of 1,4- addition and other products. Neither starting material **1a** nor desired product **6a** was detected, with **2** (>89%) remaining unchanged. This suggests that the proton abstraction and subsequent bond formation should be a rapid process. Moreover,

Table 1. Reactions of Conjugated Aldehydes with Aldehydes by the Combined Use of ATPH and LDA[a]



[a] Unless otherwise specified, the reaction was performed in toluene using an unsaturated aldehyde (1.0 equiv), aldehyde (1.0 equiv), ATPH (2.2 equiv), and a THF solution of LDA (1.2 equiv) at -78 °C for 15 min. All yields are of isolated, purified products. [b] **1e** was recovered (> 40%)



10

(1) (a) House, O. H. In *Modern Synthetic Reactions*; Breslow, R., Ed.; W. A. Benjamin, Inc.: Menlo Park, CA, 1972: Chapter 10 and references therein. (b) Heathcock, C. H. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: Oxford, 1991; Vol. 2, Chapter 1.5, and references therein. (c) Heathcock, C. H. In *Modern Synthetic Methods 1992*; Scheffold, R., Ed.; VHCA and VCH: Basel, Weinheim, and New York, 1992; Vol. 6, Chapter 1 and references therein.

(2) For a general review of bulky aluminum reagents, see: Saito, S.; Yamamoto, H. *Chem. Commun.* **1997**, 1585.

(3) ATPH was prepared as follows: To a solution of 2,6-diphenylphenol (3 equiv) in toluene was added a 1 M hexane solution of Me_3Al (1 equiv) at room temperature under argon. The resulting pale yellow solution was stirred at this temperature for 30 min and used without further purification. (a) Maruoka, K.; Ito, M.; Yamamoto, H. *J. Am. Chem. Soc.* **1995**, *117*, 9091. (b) Maruoka, K.; Saito, S.; Yamamoto, H. *Ibid.* **1995**, *117*, 1165. (c) Maruoka, K.; Imoto, H.; Yamamoto, H. *Ibid.* **1994**, *116*, 12115. (d) Maruoka, K.; Imoto, H.; Saito, S.; Yamamoto, H. *Ibid.* **1994**, *116*, 4131. (e) Saito, S.; Ito, M.; Yamamoto, H. *Ibid.* **1997**, *119*, 611.

(4) The alkylation of aldimine dienolates occurred at the α-carbons of the parent imine functionalities: (a) Vedejs, E.; Gapinski, D. M.; McElvain, S. M. *Tetrahedron Lett.* **1981**, *22*, 4913. The aldol condensation of aldehyde dienolates proceeded at the α-carbons of the parent carbonyls: (b) Groenewegen, P.; Kallenberg, H.; van der Gen, A. *Tetrahedron Lett.* **1978**. 491.

(5) The carbanions generated by the present ATPH−LDA method underwent exclusive 1,2-addition. The exact origin of this 1,2-regioselectivity could not be rationalized at this time. However, our possible explanation is that the anion could react with electrophile rapidly enough before complex formation with solvent THF or other possible lithium ligands.

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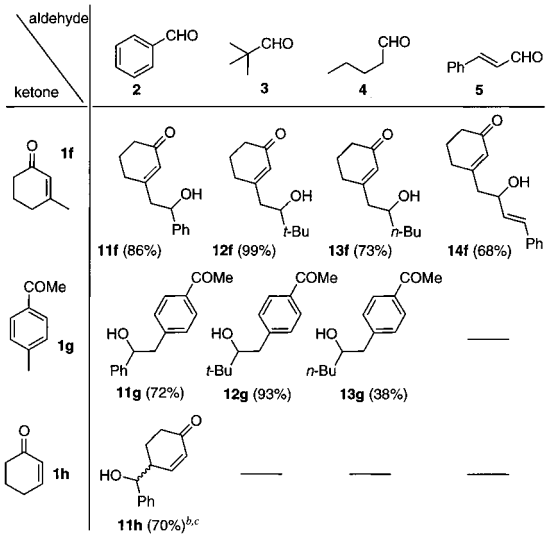
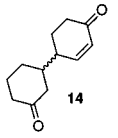
Table 2. Reactions of Conjugated Ketones with Aldehydes by the Combined Use of ATPH and LDA[a]



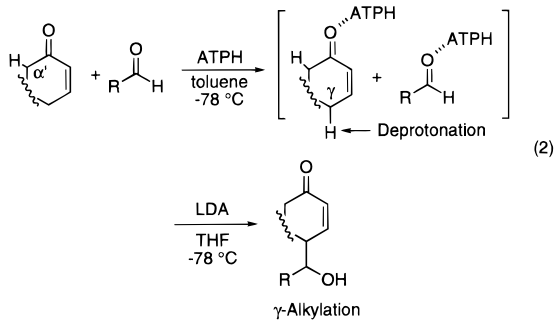
[a] Unless otherwise specified, the reaction was performed in toluene using an unsaturated ketone (1.0 equiv), aldehyde (1.0 equiv), ATPH (2.2 equiv), and a THF solution of LDA (1.2 equiv) at -78 °C for 15 min. All yields are of isolated, purified products. [b] **14** was also obtained in 5% yield. [c] Diastereoselectivity (4 : 1). The relative stereochemistry of **11h** was not assigned.



14

following the above procedure except that benzaldehyde was exposed to the ATPH−crotonaldehyde complex (−78 °C, 5 min) prior to treatment with LDA, the reaction proceeded with a similar ineffectiveness (recovery of **2** 70%; **6a** 17%.).

For α,β-unsaturated ketones, however, not only γ-protons but also α′-protons are capable of being deprotonated with strong bases to form alkylation products (eq 2).[6,7] Fortunately, the



(2)

reaction proceeded with equal selectivity in these cases to generate γ-alkylation[8] products as outlined in Table 2. Regiocontrolled generation of the exocyclic carbanion was thus achieved with 3-methyl-2-cyclohexene-1-one (**1f**) to give (*E*)-olefinic products **11**−**14f**. These results are consistent with those obtained with **1c**. Since the base attack was unfavorable at the acetyl moiety, nucleophilic addition of *p*-methylacetophenone (**1g**) proceeded through activation at the benzylic methyl with LDA to give **11**−**13 g** as sole products. 2-Cyclohexen-1-one (**1h**), which contains (*Z*)-olefin, similarly underwent effective cross-coupling with benzaldehyde to give a diastereomixture of **11h** (4:1)[9] in 70% yield. The observed γ-selectivities upon deprotonation can best be explained by the steric effect of ATPH, which inhibits base attack at the α′-carbon by encapsulating the carbonyl substrates in its cavity.[3d,e]

In summary, we have developed a directed aldol condensation of conjugated carbonyl substrates with aldehydes initiated with LDA using ATPH as a key reagent. Three outstanding features of this system are (1) the two different carbonyl reactants and ATPH should be mixed together prior to treatment with LDA to give effective cross-coupling, (2) high regioselectivities upon consecutive deprotonation and aldol condensation, which were rarely attained by previous methods,[7,8] and (3) its experimental simplicity and generality. In addition, this procedure should be convenient for elaborating elongated conjugated systems in many important classes of natural products.[10,11]

Supporting Information Available: Representative experimental procedures and spectral data for all new compounds (11 pages). See any current masthead page for ordering and Internet access instructions.

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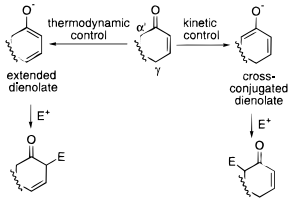
(6) Under kinetic control, cross-conjugated dienolates are the dominant species, whereas extended dienolates are produced preferentially under thermodynamic conditions, such as when using MOBu^t or MH (M = Na, K). These dienolates are generally prone to undergo α-alkylation.



(a) Caine, D. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: Oxford, 1991; Vol. 3, Chapter 1.1, p 21, and references therein. For *O*-silylation of extended dienolates with TMSCl, see: (b) Stork, G.; Hudrlik, P. F. *J. Am. Chem. Soc.* **1968**, *90*, 4464. (c) Kharash, M. S.; Tawney, P. O. *Ibid.* **1941**, *63*, 2308; **1945**, *67*, 128. (d) Kawanishi, M.; Itoh, Y.; Hieda, T.; Kozima, S, Kitoni, T.; Kobayashi, K. *Chem. Lett.* **1985**, 647. (e) Krafft, M. E.; Holton, R. A. *J. Am. Chem. Soc.* **1984**, *106*, 7619.

(7) (a) Nakadaira, Y.; Hayashi, J. *J. Chem. Soc., Chem. Commun.* **1972**, 282. (b) Stratford, E. S.; Aggarwal, N. D. *J. Org. Chem.* **1979**, *44*, 1570. For the α-alkylation of extended dienolates, see: (c) Stork, G.; Benaim, J. *J. Am. Chem. Soc.* **1971**, *93*, 5938.

(8) There are numerous examples of intramolecular γ-alkylations of ketone dienolates: (a) Caine, D. In *Carbon−Carbon Bond Formation*; Augustine, R. L., Ed.; Dekker: New York, 1979; Vol. 1, Chapter 2, p 85, and references therein. See also refs 1b and 1 in the Supporting Information.

(9) See footnote *c* of Table 2.

(10) (a) Williams, J. M.; McGarvey, G. L. *Tetrahedron Lett.* **1985**, *26*, 4891. (b) Ley, S. V.; Smith, S. C.; Woodward, P. R. *Tetrahedron* **1992**, *48*, 1145. (c) Smith, A. B., III; Ott, G. R. *J. Am. Chem. Soc.* **1996**, *118*, 13095. (d) Lampe, T. F. J.; Hoffmann, H. M. R. *Chem. Commun.* **1996**, 1931.

(11) (a) Duhamel, L.; Ancel, J.-E. Tetrahedron **1992**, *48*, 9237.