

The role of imine–enamine tautomerism in effecting cross-aldol condensations

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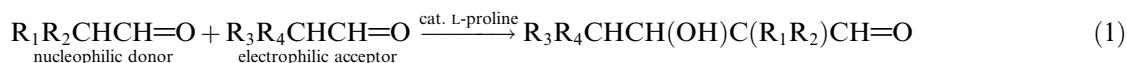
Abstract—An indirect method to effect cross-aldol coupling of two nonequivalent enolizable aldehydes is reported that involves initial conversion of one aldehyde to an imine derivative possessing an *N*-3° alkyl substituent. In sharp contrast to the related couplings (e.g., the use of α -lithiated imines at low temperature), condensation between the imine and several representative aldehydes occurs readily at ambient temperature in the presence of a catalytic amount of cobalt(II) chloride.

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The aldol condensation¹ is arguably considered to be the most important carbon–carbon bond-forming reaction in organic synthesis. During the past several decades, aldol technology has advanced to the stage where the formidable challenge of direct cross-aldol coupling of two nonequivalent enolizable aldehydes (Eq. 1) can be achieved using *L*-proline as a catalyst.² This novel modification of the cross-aldol condensation is not without limitation, since its success is contingent on the aldehydes functioning as two distinct components: a nucleophilic donor and an electrophilic acceptor. The obtention of a single regioisomer of the cross-aldol product, along with the suppression of homodimerization of both the donor and the acceptor aldehydes, would still appear to be a formidable synthetic challenge, especially if the donor aldehyde has a steric environment similar to that of the acceptor aldehyde and both aldehydes are enolizable (e.g., the reactants in the Table 1, entry 4).

with enol silyl ethers in the presence of TiCl_4 ,⁴ and the reaction of carbonyl compounds with an α -lithiated imine at low temperature.⁵ Since enamine derivatives of highly reactive aldehydes (e.g., propanal) are more difficult to obtain in high yield than the corresponding imine derivatives of such aldehydes, we decided to investigate the possible use of imine derivatives of enolizable aldehydes in cross-aldol condensations with carbonyl compounds in the presence of a suitable Lewis acid catalyst. This strategy was based on the knowledge that imines derived from enolizable aldehydes are known to react via their secondary enamine tautomeric form (present in undetectable concentration at equilibrium) with electrophilic olefins to yield Michael adducts.⁶ The present Letter presents the results and limitations of this investigation (Scheme 1).

In order to test the feasibility of a Lewis acid-catalyzed coupling of an imine (**1**) with an aldehyde (**3**), various



Various indirect methods¹ for effecting cross-aldol coupling between two non-identical carbonyl compounds have been reported, including the reaction of aldehydes with enamines,³ the coupling of carbonyl compounds

imine derivatives of propanal were prepared using standard conditions.⁷ Subsequent reaction of imine **1** [$\text{R}^1 = \text{CH}_3$; $\text{R} = (\text{CH}_2)_5\text{CH}_3$ or CH_2Ph] with 2-methylpropanal in the presence of a catalytic amount of cobalt(II) chloride in various organic solvents containing an excess of anhydrous calcium sulfate⁸ at ambient temperature failed to yield the desired coupling product [**4**, $\text{R}^1 = \text{CH}_3$; $\text{R}^2 = \text{CH}(\text{CH}_3)_2$]. This was surprising since

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Table 1. Co⁺²-catalyzed coupling of imine **1a** with representative aldehydes^a

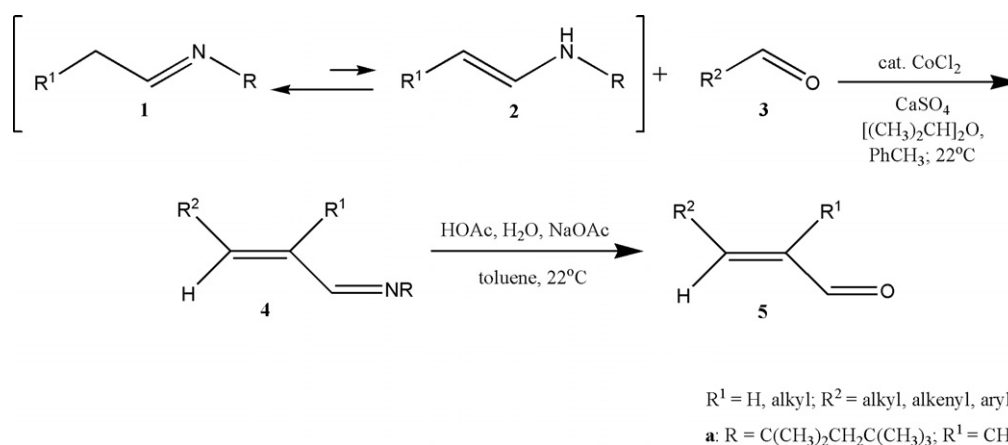
Entry	Aldehyde 3	Representative ¹ H NMR data (CDCl ₃ , 300 MHz) for imine product 4	Overall yield ^b (%) of aldehyde 5
1	2-Methylpropanal ^c	δ 7.73 (s, 1H), 5.62 (d of q, <i>J</i> = 9.3, 1.2 Hz, 1H), 2.75 (m, 1H), 1.84 (d, <i>J</i> = 1.2 Hz, 3H), 1.60 (s, 2H), 1.21 (s, 6H), 1.02 (d, <i>J</i> = 6.6 Hz, 6H), 0.93 (s, 9H)	73
2	Benzaldehyde	δ 7.95 (s, 1H), 7.40 (m, 5H), 6.76 (br s, 1H), 2.15 (br s, 3H), 1.65 (s, 2H), 1.27 (s, 6H), 0.95 (s, 9H)	81 ^d
3	3-Methyl-2-butenal	δ 7.83 (s, 1H), 6.53 (d, <i>J</i> = 12 Hz, 1H), 6.26 (br d, <i>J</i> = 12 Hz, 1H), 1.95 (br s, 3H), 1.89 (br s, 3H), 1.85 (br s, 3H), 1.62 (s, 2H), 1.23 (s, 6H), 0.92 (s, 9H)	61
4	Hexanal	δ 7.26 (s, 1H), 5.81 (t of q, <i>J</i> = 7.2, 1.2 Hz, 1H), 2.22 (m, 2H), 1.84 (d, <i>J</i> = 1.2 Hz, 3H), 1.60 (s, 2H), 1.22 (s, 6H), 0.93 (s, 9H), 0.92 (t, <i>J</i> = 5.7 Hz, 3H)	83

^a See Ref. 21 for the general procedure.

^b Isolated yield. All aldehyde products were characterized by ¹H and ¹³C NMR spectroscopy and compared with available literature data.

^c Distilled prior to use, to remove traces of isobutyric acid (which catalyzes hydrolysis of imines).

^d See Ref. 22 for full spectral characterization of this aldehyde.

**Scheme 1.**

imines possessing an *N*-benzyl group have been shown to be in equilibrium with their secondary enamine tautomer⁹ and thus capable of reacting with electrophiles. Although a similar reaction using *N*-propylidene-cyclohexanamine¹⁰ (**1**, R¹ = CH₃; R = cyclohexyl) and 2-methylpropanal afforded some of the desired cross-coupled imine, a complex mixture of products was obtained. The latter problem was overcome by the use of an imine possessing a bulky *N*-*tert*-octyl group. Indeed, the reaction of 2,4,4-trimethyl-*N*-propylidene-2-pentanamine¹¹ (**1a**) with 2-methylpropanal in a solution of 2:1 (v/v) isopropyl ether: toluene¹² containing an excess of powdered Drierite[®] (CaSO₄ containing CoCl₂ as an indicator) at ambient temperature proceeded smoothly, affording 75% yield of the desired cross-coupled adduct [**4a**, R² = CH(CH₃)₂], substantially free of any impurities.¹³ To confirm the identity of the cross-coupled adduct, the latter imine was hydrolyzed using aqueous acetic acid containing sodium acetate at room temperature¹⁴ to afford the previously reported¹⁵ *E*-2,4-dimethyl-2-pentenal, the identity and purity of which were ascertained by NMR spectroscopy.¹⁶

In order to determine the scope of this cross-coupling, imine **1a** was allowed to react with several representative aldehydes; and, as indicated by the results in the Table 1,

overall yields of conjugated enals **5** were generally quite good. The obtention of a single adduct in this imine-aldehyde cross-coupling process was further confirmed by the coupling of hexanal and imine **1a** (Table 1, entry 4) to afford, after hydrolysis, (*E*)-2-methyl-2-octenal¹⁷ as the sole product in 83% overall yield. The coupling of imine **1a** with an α, β-unsaturated aldehyde (Table 1, entry 3) proved to be rather slow, thereby allowing in situ hydrolysis of **1a** to occur via a competitive reaction pathway. Thus, in contrast to the other systems that were examined, the coupled imine [**4a**, R² = CH=C(CH₃)₂] obtained from 3-methyl-2-butenal and imine **1a** was contaminated with a significant amount (approximately 20% of the product mixture) of the *N*-*tert*-octyl imine derivative of (*E*)-2-methyl-2-pentenal (**4a**, R² = CH₂CH₃)—the product obtained via ‘homodimerization’ of imine **1a**,¹⁸ accompanied by an equivalent amount of the *N*-*tert*-octyl imine derivative of 3-methyl-2-butenal. Subsequent hydrolysis of the crude reaction mixture resulted in a 61% overall yield (based on 3-methyl-2-butenal) of the desired (2*E*)-2,5-dimethyl-2,4-hexadienal.¹⁹

In conclusion, a process has been developed for the cross-coupling of an *N*-*tert*-alkyl imine derivative of an enolizable alkyl aldehyde (**1**) with several types of alde-

hydes (**3**) and offers an efficient methodology to obtain conjugated enals if **3** is a simple aliphatic aldehyde. Not unexpectedly, all efforts to couple imines of general structure **1** to representative ketones (e.g., 2-heptanone and cyclohexanone) failed to yield any coupled adduct. Indeed, various ketones, as well as esters and alcohols,²⁰ were used successfully as co-solvents in this cross coupling process during the preliminary studies. Hence the process may be feasible for a variety of functionalized aldehydes.

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7. Imines **1** were prepared in quantitative yield via reaction of the aldehyde with a 1° amine in dichloromethane containing anhydrous sodium sulfate at temperatures of 10–20 °C and were subsequently characterized by ¹H NMR spectroscopy. Imine **1a** exhibited the following data: (CDCl₃, 300 MHz, ppm) δ 7.56 (t, *J* = 4.8 Hz, 1H), 2.25 (q of d, *J* = 7.8, 4.8 Hz, 2H), 1.60 (s, 2H), 1.19 (s, 6H), 1.07 (t, *J* = 7.8 Hz, 3H), 0.92 (s, 9H).
8. An efficient drying agent was essential due to the anticipated ease of hydrolysis of imines **1** and **4** by water liberated during the coupling process.
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12. Other solvent mixtures that were examined led to a lower yield of the desired adduct (**4**), usually arising from in situ hydrolysis of the starting imine (**1a**). It was also important to use a dilute solution (approximately 0.1 M in both imine and reactant aldehyde) to prevent in situ hydrolysis of **1a**, thereby avoiding the formation of propanal (which can react as an electrophilic acceptor) and the imine derivative of the reactant aldehyde. It is noteworthy that a previous study³ of the reaction of enamines with aldehydes in the presence of Lewis acids reported the formation of β-hydroxy carbonyl compounds and the absence of subsequent dehydration even when an excess of the acid catalyst was added to the mixture.
13. Since the unsaturated imines (**4**) were sensitive to heat, light, and atmospheric moisture, after spectroscopic characterization, they were hydrolyzed promptly to afford the known aldehydes (**5**).
14. This hydrolysis procedure was adapted from a similar one reported on page 2074 of the following article: Cummins, C. H.; Coates, R. M. *J. Org. Chem.* **1983**, *48*, 2070–2076.
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16. ¹H NMR (CDCl₃, 300 MHz, ppm) δ 9.38 (s, 1H), 6.29 (d of q, *J* = 9.6, 1.2 Hz, 1H), 2.84 (m, 1H), 1.75 (d, *J* = 1.2 Hz, 3H), 1.09 (d, *J* = 6.6 Hz, 6H).
17. ¹H NMR (CDCl₃, 300 MHz, ppm) δ 9.40 (s, 1H), 6.50 (t of q, *J* = 7.2, 1.2 Hz, 1H), 2.35 (br q, *J* = 7.2 Hz, 2H), 1.75 (d, *J* = 1.2 Hz, 3H), 1.51 (br pentet, *J* = 7.5 Hz, 2H), 1.38–1.28 (m, 4H), 0.91 (br t, *J* = 7 Hz, 3H). For a previous synthesis of (*E*)-2-methyl-2-octenal, see: Ekogha, C. B. B.; Ruel, O.; Julia, S. A. *Tetrahedron Lett.* **1983**, *24*, 4825.
18. This imine was characterized by the following spectral data: ¹H NMR (CDCl₃, 300 MHz, ppm) δ 7.76 (s, 1H), 5.79 (br t, *J* = 7.2 Hz, 1H), 2.25 (m, 2H), 1.84 (br s, 3H), 1.60 (s, 2H), 1.21 (s, 6H), 1.04 (t, *J* = 7.5 Hz, 3H), 0.92 (s, 9H). After hydrolysis of the mixture of imines, (*E*)-2-methyl-2-pentenal can be separated from the desired dienal by evaporative distillation at reduced pressure.
19. This dienal was characterized by the following spectral data: ¹H NMR (CDCl₃, 300 MHz, ppm) δ 9.46 (s, 1H), 7.09 (br d, *J* = 12 Hz, 1H), 6.33 (br d, *J* = 12 Hz, 1H), 1.97 (br s, 3H), 1.96 (br s, 3H), 1.83 (br s, 3H); ¹³C NMR (CDCl₃, 75 MHz) δ 195.4, 147.7, 145.1, 135.4, 121.2, 27.1, 19.0, 9.2. For a previous synthesis of this dienal, see Ref. 22.
20. Among the co-solvents that were successfully used in the coupling reaction were methyl isobutyl ketone, cyclopentanone, ethyl propionate, *tert*-butyl acetate, and 2-methyl-2-butanol.
21. *General procedure for the imine-aldehyde coupling*: A mixture of 1.6 g of powdered Drierite® (CaSO₄ containing CoCl₂ as an indicator, crushed using a mortar and pestle and subsequently dried at 200 °C for 2 days) and 6.0 mL of 2:1 (v/v) isopropyl ether: toluene was stirred for 2 h at 22 °C under a nitrogen atmosphere, after which 0.65 mmol of aldehyde **3** (substantially free of traces of the corresponding carboxylic acid) and 120 μL (approx. 0.63 mmol) of imine **1a** were added to the reaction flask. This reaction mixture was subsequently stirred vigorously at room temperature for 8–10 h, after which it was diluted with 25 mL of hexane and solid material was removed by filtration through a small pad of Hyflo Super-Cel® filtering aid. Removal of the volatile organic solvents by evaporation at reduced pressure, followed by removal of residual traces of toluene under high vacuum, afforded the crude imine product occasionally contaminated with a trace of CoCl₂. The latter was conveniently removed by addition of 25 mL of hexane, and filtration once again through a small pad of Hyflo Super-Cel® filtering aid. Removal of the hexane by evaporation at reduced pressure afforded the imine product (**4**).
22. For full spectral characterization (¹H NMR, ¹³C NMR, IR) of this aldehyde, see: Lahmar, N.; Aatar, J.; Ben Ayed, T.; Amri, H.; Bellassoued, M. *J. Organomet. Chem.* **2006**, *691*, 3018–3026.