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Mild Organocatalytic α-Methylenation of Aldehydes†

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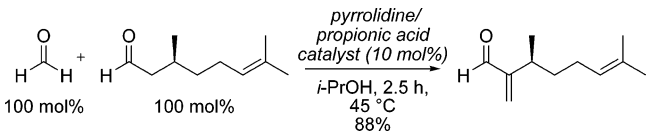

A rapid and extremely convenient method for α-methylenation of aldehydes with aqueous formaldehyde is described. Two optimal catalytic systems are presented that allow short reaction times and afford the functionalized products in good to excellent yields (up to 99%) and chemoselectivity.

α,β-Unsaturated aldehydes, especially those with an α-substituent (α-substituted acroleins), provide a range of possibilities for further transformations such as nucleophilic addition,[1] conjugate addition,[2] Baylis−Hillman reaction,[3] Diels−Alder reaction,[4] and a number of organocatalytic transformations.[5]

Several synthetic methods have been developed for the construction of α-substituted acroleins. Simple alkyl-substituted acroleins, such as methacrolein, can be produced at high temperatures and preferably under high pressure from formaldehyde and propionaldehyde, using variable amounts of secondary amine (typically dimethyl- or diethylamine) and an acid cocatalyst.[6] Although these procedures can be used industrially for the production of simple unsaturated aldehydes, their application in the synthesis of more complex aldehydes present serious problems. With more complex aldehydes, stoichiometric amounts of the amine salt are typically required.[6f−h] As a result of the slow reaction rates and relatively drastic conditions (typically reflux overnight), yields tend to be lower and the reactions are often characterized by the formation of polymeric side products.[7] From an atom economic and process chemistry points of view, the use of a stoichiometric amount of the amine salt and the long reaction time are major disadvantages.

For the synthesis of more complex, functionalized α-substituted acroleins, milder methods have been sought. In these cases, the Horner−Wadsworth−Emmons reaction of phosphorus ylides with paraformaldehyde[8] or the Mannich reaction of aldehydes with methylenedimethylammonium chloride (Eschenmoser's salt) have been the most popular choices.[9,10] The latter has been the method of choice in a total synthesis setting, where the mildness of reaction conditions is most important.[11] A particularly mild method based on dibromomethane has also been described.[12]

Herein we wish to report a very simple and mild *catalytic* protocol for the direct α-methylenation of aldehydes using only 1 equiv of aqueous formaldehyde.[13]

† Dedicated to the memory of Professor Hans Krieger (1929−2005).

(1) For selected examples of aldol reactions with α-substituted acroleins, see: (a) Evans, D. A.; Ratz, A. M.; Huff, B. E.; Sheppard, G. S. *J. Am. Chem. Soc.* **1995**, *117*, 3448−3467. (b) Paterson, I.; Bower, S.; Tillyer, R. D. *Tetrahedron Lett.* **1993**, *34*, 4393−4396. (c) Mann, R. K.; Parsons, J. G.; Rizzacasa, M. A. *J. Chem. Soc., Perkin Trans. 1* **1998**, 1283−1294.

(2) For reviews, see: (a) Perlmutter, P. *Conjugate Addition Reactions in Organic Synthesis*; Pergamon: Oxford, 1992. (b) Rossiter, B. E.; Swingle, N. M. *Chem. Rev.* **1992**, *92*, 771−806. (c) Recently Michael additions of α-substituted α,β-unsaturated aldehydes with α-nitrocycloalkanones have been reported; see: Giorgi, G.; Miranda, S.; López-Alvarado, P.; Avendaño, C.; Rodriguez, J.; Menéndez, J. C. *Org. Lett.* **2005**, *7*, 2197−2200.

(3) For reviews, see: (a) Basavaiah, D.; Dharma Rao, P.; Suguna Hyma, R. *Tetrahedron* **1996**, *52*, 8001−8062. (b) Basavaiah, D.; Jaganmohan Rao, A.; Satyanarayana, T. *Chem. Rev.* **2003**, *103*, 811−891 and references therein.

(4) For a review, see: (a) Kagan, H. B.; Riant, O. *Chem. Rev.* **1992**, *92*, 1007−1019.

(5) α,β-Unsaturated aldehydes are key starting materials for several organocatalytic transformations utilizing iminium catalysis. For representative examples, see the following. Diels−Alder reaction: (a) Northrup, A. B.; MacMillan, D. W. E. *J. Am. Chem. Soc.* **2002**, *124*, 2458−2460. [3 + 2] Cycloaddition: (b) Jen, W. S.; Wiener, J. J. M.; MacMillan, D. W. E. *J. Am. Chem. Soc.* **2000**, *122*, 9874−9875. Hydride reduction: (c) Yang, J. W.; Hechavarria Fonseca, M. T.; Vignola, N.; List, B. *Angew. Chem., Int. Ed.* **2005**, *44*, 108−110. (d) Ouellet, S. G.; Tuttle, J. B.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2005**, *127*, 32−33. Very recently, α-substituted α,β-unsaturated aldehydes have also emerged as viable partners for iminium catalysis: (e) Ishihara, K.; Nakano, K. *J. Am. Chem. Soc.* **2005**, *127*, 10504−10505. (f) King, H. D.; Meng, Z.; Denhart, D.; Mattson, R.; Kimura, R.; Wu, D.; Gao, Q.; Macor, J. E. *Org. Lett.* **2005**, *7*, 3437−3440.

(6) For examples of previous base- and acid-*catalyzed* Mannich-type reactions, see: (b) Deshpande, R. M.; Diwakar, M. M.; Mahajan, A. N.; Chaudhari, R. V. *J. Mol. Catal. A* **2004**, *211*, 49−53. (b) Matsuoka, K. JP 04173757, 1992. (c) Nagareda, K.; Yoshimura, N. JP 06263683, 1994. JP3324820, 2002. (d) Duembge, G.; Fouquet, G.; Krabetz, R.; Lucas, E.; Merger, F.; Nees, F. DE3213681, 1983. (e) Merger, F.; Förster, H. J. EP58927, 1982. (f) Bernhagen, W.; Bach, H.; Brundin, E.; Gick, W.; Springer, H.; Hack, A. DE285504, 1980. (f) For examples of *stoichiometric* Mannich α-methylenations, see: Marvel, C. S.; Myers, R. L.; Saunders: J. H. *J. Am. Chem. Soc.* **1948**, *70*, 1694−1699. (g) Snider, B. B.; Lobera, M.; Marien, T. P. *J. Org. Chem.* **2003**, *68*, 6451−6454. (h) Basu, K.; Richards, J.; Paquette, L. A. *Synthesis* **2004**, 2841−2844. This paper also includes an excellent introduction to the state-of-the-art methods for the synthesis of α-substituted acroleins.

(7) For experimental examples with more complex aldehydes, see: (a) Yoshida, K.; Grieco, P. *J. Org. Chem.* **1984**, *49*, 5257−5260. (b) Heckendorn, R.; Allgeier, H.; Baud, J.; Gunzenhauser, W.; Angst, C. *J. Med. Chem.* **1993**, *36*, 3721−3726. (c) In our hands, these protocols often failed to give any useful yields of the product, especially with aldehydes prone to polymerization.

(8) (a) Boehm, H. M.; Handa, S.; Pattenden, G.; Roberts, L.; Blake, A. J.; Li, W.-S. *J. Chem. Soc., Perkin Trans.* **2000**, 3522−3538. (b) Villiéras, J.; Rambaud, M. *Synthesis* **1984**, 406−408.

(9) Kinast, G.; Tietze, L.-F. *Angew. Chem.* **1976**, *88*, 261−262.

(10) Takano, S.; Inomata, K.; Samizu, K.; Tomita, S.; Yanase, M.; Suzuki, M.; Iwabuchi, Y.; Sugihara, T.; Ogasawara, K. *Chem. Lett.* **1989**, 1283−1284.

(11) (a) Total synthesis of brevetoxin B (second to last step): Nicolaou, K. C.; Rutjes, F. P. J. T.; Theodorakis, E. A.; Tiebes, J.; Sato, M.; Untersteller, E. *J. Am. Chem. Soc.* **1995**, *117*, 1173−1174. See also: Nicolaou, K. C.; Reddy, K. R.; Skokotas, G.; Fuminori, S.; Xiao, X.-Y. *J. Am. Chem. Soc.* **1992**, *114*, 7935−7936. (b) Total synthesis of laulimalide: Crimmins, M. T.; Stanton, M. G.; Allwein, S. P. *J. Am. Chem. Soc.* **2002**, *124*, 5958−5959. (c) Ahmed, A.; Hoegenauer, E. K.; Enev, V. S.; Hanbauer, M.; Kaehlig, H.; Ohler, E.; Mulzer, J. *J. Org. Chem.* **2003**, *68*, 3026−3042. (d) Pinnatoxin A: Ishiwata, A.; Sakamoto, S.; Noda, T.; Hirama, M. *Synlett* **1999**, 692−694.

(12) (a) Hon, Y.-S.; Chang, F.-J.; Lu, L. *J. Chem. Soc., Chem. Commun.* **1994**, 2041−2042. (b) Hon, Y.-S.; Chang, F.-J.; Lu, L.; Lin, W.-C. *Tetrahedron* **1998**, *54*, 5233−5246. (c) Hon, Y.-S.; Lin, W.-C. *Tetrahedron Lett.* **1995**, *36*, 7693−7696.

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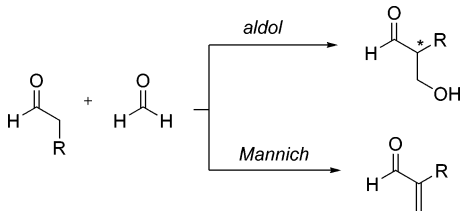
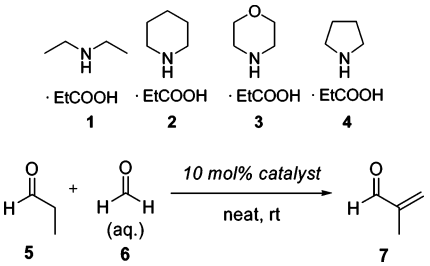


FIGURE 1. Possible reaction modes of formaldehyde with simple aldehydes.

TABLE 1. Screening of Different Amine Salts as Catalysts



		conversion[a] (%)	
entry	catalyst	30 min	135 min
1	**1**	19	37
2	**2**	9	19
3	**3**	8	29
4	**4**	70	75

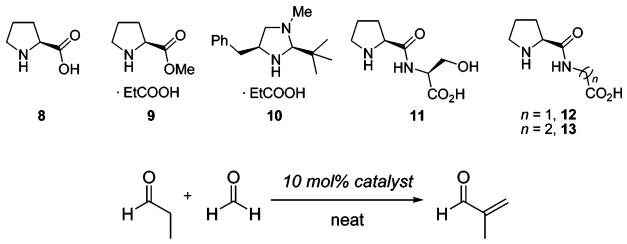
[a] Determined by ^{1}H NMR.

The reaction of formaldehyde with simple α-monosubstituted aldehydes can afford either the aldol product[14] or the dehydrated α-substituted acrolein (Figure 1). The latter product might arise from a Mannich-type reaction with a catalytic amount of secondary amine base.[15]

To prevent any unwanted crossed-aldol or polymerization reactions, we sought to develop conditions that were as mild and neutral as possible. In our initial study, different secondary amine/carboxylic acid combinations were screened (Table 1). Pyrrolidine was found to be the optimal amine component in a reaction between propionaldehyde and formaldehyde in room temperature.

Inspired by these results, we reasoned that pyrrolidine derivatives that would contain also the acid functionality in the molecular structure might be potential catalysts for this reaction.

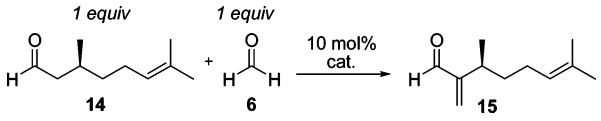
TABLE 2. Proline and Imidazolidinone Derivatives as Catalysts



entry	catalyst	temp	time (h)	conversion[a] (%)
1	**8**	rt	>24	9
2	**9**	rt	4	0
3	**10**	rt	4	0
4	**11**	rt	4	12
5	**12**	rt	24	73
6	**12**	45 °C	4	75
7	**13**	rt	4	78
8	**13**	45 °C	4	90

[a] Determined by ^{1}H NMR.

TABLE 3. Optimization Studies with Citronellal



			conversion[b] (%)	
entry	catalyst	conditions[a]	3 h	24 h
1	**12**	45 °C, neat	14	36
2	**13**	rt, neat	5[c]	35
3	**13**	45 °C, neat	24	54
4	**13**	45 °C, *i*-PrOH[d]	32	100
5	**13**	45 °C, *i*-PrOH[e]	67	100
6	**4**	rt, neat	4	11
7	**4**	45 °C, neat	100	nd[f]

[a] Temperature, solvent. [b] Determined by ^{1}H NMR. [c] 2 h. [d] 200 μL/mmol *i*-PrOH. [e] 100 μL/mmol *i*-PrOH. [f] Not determined.

A variety of amino acids and dipeptides were thus screened (Table 2). We discovered that under the same reaction conditions the dipeptide L-Pro-β-Ala **13** affords the desired product in 78% conversion in 4 h at room temperature (entry 7). Slightly higher yields were obtained by raising the temperature to 45 °C (entry 8).[16] Again, the unsaturated aldehyde was the only product observed.

Further screening of the reaction conditions was then carried out in the reaction between citronellal and formaldehyde by varying the catalyst, temperature, and solvent (Table 3). In this study, citronellal was used as the test aldehyde to probe the generality of the protocol with less water-soluble aldehydes.

Both pyrrolidine/propionic acid **4** as well as L-Pro-β-Ala **13** catalyzed the reaction in neat conditions. However, especially with **13**, the poor solubility of citronellal seemed to limit the reaction rate. This problem was alleviated by the addition of a small amount of isopropyl alcohol. In this case, raising the temperature to 45 °C was essential for good conversions. We were especially delighted that with both catalyst systems, complete conversion of the starting material to the aldehyde

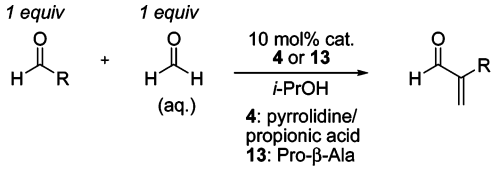
(13) Recently, an organocatalytic method for the synthesis of α,β-unsaturated ketones was reported: (a) Wang, W.; Mei, Y.; Li, H.; Wang, J. *Org. Lett.* **2005**, *7*, 601−604.

(14) (a) Córdova and co-workers have reported that reactions between aldehydes with formaldehyde under proline catalysis afford hydroxymethylated aldehydes enantioselectively. This would suggest that the reaction proceeds via an aldol-dehydration mechanism. However, in our hands reactions of aldehydes with aqueous formaldehyde only afforded the corresponding unsaturated aldehydes. Casas, J.; Sundén, H.; Córdova, A. *Tetrahedron Lett.* **2004**, *45*, 6117−6119. (b) Interestingly, Ishikawa and co-workers have reported a pyrrolidine/benzoic acid catalyzed dimerization of aldehydes that proceeds at room temperature: Ishikawa, T.; Uedo, E.; Okada, S.; Saito, S. *Synlett* **1999**, *4*, 450−452. For related examples, see: (c) Treibs, W.; Krumbholz, K. *Chem. Ber.* **1952**, *85*, 1116−1119. (d) Schreiber, J.; Wermuth, C. G. *Bull. Soc. Chim. Fr.* **1965**, 2242−2249. (e) For an oxa-Michael/aldol/dehydration protocol for the preparation of α,β-substituted aldehydes, see: Habib-Sahmani, H.; Hacini, S.; Bories, C.; Faure, R.; Rodriguez, J. *Synthesis* **2005**, 2151−2156.

(15) (a) List, B.; Pojarliev, P.; Castello, C. *Org. Lett.* **2001**, *3*, 573−575. For a review on the Mannich reaction, see: (b) Arend, M.; Westermann, B.; Risch, N. *Angew. Chem., Int. Ed.* **1998**, *37*, 1045−1070.

(16) With simple amines, raising the temperature afforded higher conversions to the product. However, polymerization and loss of product by evaporation resulted in erratic and irreproducible yields in the case of methacrolein.

TABLE 4. Synthesis of α-substituted Acroleins from Different Aldehydes



entry	substrate	product	catalyst[a]	time (h)	isolated yield (%)
1	**5**	**7**	**13**	4	90[b]
2	**16**	**17**	**4**	4	92
3	**18**	**19**	**4**	4	86
4	**14**	**15**	**4**	2.5	89 (99% ee)[c]
5	**20**	**21**	**4**	1	99
			13	1.5	99
6	**22**	**23**	**4**	1.5	90
			13	4	76
7	**24**	**25**	**4**	24	93
8	**26**	**27**	**4**	1.5	n.d.[d]
			13	1.5	75
9	**28**	**29**	**4**	1	n.d.[d]
			13	1.5	80
10	**30**	**31**	**4**	2	n.d.[d]
			13	2	89
11	**32**	**33**	**4**	4	98
			13	25	64
12	**34**	**35**	**4**	1	85
			13	1.5	86

[a] Reaction conditions: 10 mol % of catalyst, 100 μL of *i*-PrOH/1 mmol of starting material, 45 °C; see Supporting Information for details. [b] Conversion by ^{1}H NMR. [c] Determined by chiral GC (see Supporting Information). [d] Significant decomposition was observed.

could be obtained with both reasonable temperature (45 °C) and reaction time (3−24 h) and therefore selected these two conditions (entries 5 and 7) for further exploration.

The scope of the reaction was then assessed with a representative selection of aldehydes (Table 4).

As shown in Table 4, a wide variety of α-monosubstituted aldehydes can be converted reliably to the corresponding α-substituted acroleins in good to excellent yields with both catalysts. Considerable latitude in both steric demands of the aldehyde (entries 1−5) as well as choice of alcohol and amine protecting groups (benzyl, silyl, Boc, acetonide) and functionalities (ketone, carbamate, alkene) are tolerated (entries 6−12). Further, no isomerization of the double bond was detectable even with aromatic β-substituents (entries 5 and 6), and no epimerization at the β carbon was observed with citronellal (entry 4). In the case of aldehydes **26**, **28**, and **30**, the dipeptide

catalyst **13** gave significantly cleaner reactions and superior yields (entries 8−10). Catalyst **13** would thus appear to be a catalyst of choice with particularly sensitive aldehydes. Finally, α-oxy and α-amino substituents are readily tolerated, giving access to protected enol and enamine derivatives (entries 11 and 12) in high yields (85−98% with catalyst **4**). Hydroxy groups are, of course, also tolerated by these aqueous conditions; however, 5-hydroxyvaleraldehyde and unprotected 2-deoxyribose, both existing predominantly in the hemiacetal form, did not perform well under these conditions.[17] As such, at present the method is limited to aldehydes that exist in the open-chain form.

In summary, a mild, chemoselective, and catalytic method for the synthesis of α-substituted acroleins has been developed, and two different optimized catalysts are described. The mildness of the reaction conditions and the high chemoselectivity of the reaction allows the rapid and easy preparation of functionalized α-substituted acroleins in high yields under very benign reaction conditions. In comparison with previously reported Mannich methods,[6f−h,7] drastic cuts in the amount of amine salt (10 vs 100 mol %, reaction time (typically 2 vs 12−18 h), temperature (45 vs 80−100 °C), and the amount of solvent were realized in this study. The ease with which these reactions can be performed facilitates their use in tandem processes. Studies along these lines will be reported in due course.

(17) With catalyst **4**, 5-hydroxyvaleraldehyde gave ca. 55−60% yield of the α-methylenation product after 24 h reaction time, accompanied by significant decomposition. 2-Deoxyribose afforded less than 5% of the product under similar conditions.

Experimental Section

General Procedure A for the α-Methylenation of Aldehydes. To a mixture of aqueous formaldehyde solution (37% formaldehyde in water, 1.0 mmol, 100 mol %) and aldehyde (1.0 mmol) in *i*-PrOH (100 μL) were added propionic acid (0.1 mmol, 10 mol %) and pyrrolidine (0.1 mmol, 10 mol %). The reaction mixture was stirred at 45 °C for 1−25 h. $NaHCO_3$ was added, and the mixture was extracted with CH_2Cl_2 (3 × 5 mL). The combined extracts were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. If necessary, the crude product thus obtained was purified by a passage through a short pad of silica gel using Et_2O as the eluent.

General Procedure B for the α-Methylenation of Aldehydes. To catalyst **13** (L-Pro-*β*-Ala) (0.1 mmol, 10 mol %) in *i*-PrOH (100 μL) in a 5-mL vial were added aqueous formaldehyde solution (37% formaldehyde in water, 1.0 mmol, 100 mol %) and aldehyde (1.0 mmol, 100 mol %) at room temperature. The mixture was stirred at 45 °C for 1−25 h. H_2O (5 mL) was then added, and the mixture was extracted with CH_2Cl_2 (3 × 5 mL). The combined extracts were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. If necessary, the crude product thus obtained was purified by a passage through a short pad of silica gel using Et_2O as the eluent.

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Supporting Information Available: Experimental procedures for the preparation of the starting materials and the catalysts, characterization data, and copies of NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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