A Conceptually Different Approach to the Asymmetric Synthesis of α-Substituted Carbonyl Compounds

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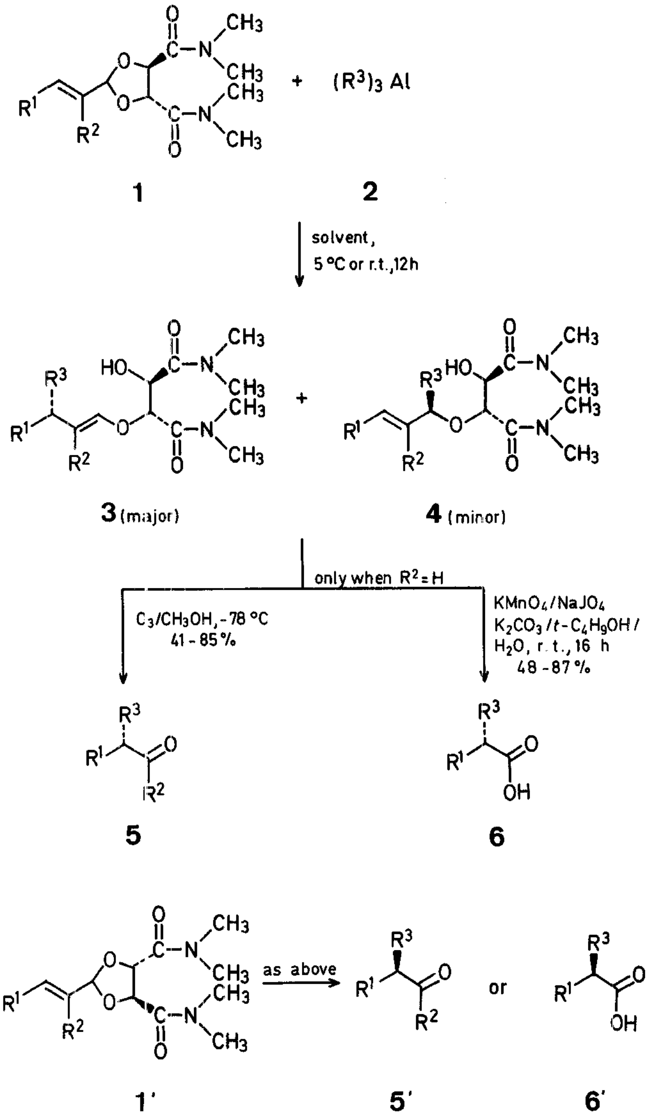
A new approach has been demonstrated for the asymmetric synthesis of α-substituted carbonyl compounds. Thus, the key asymmetric carbon-carbon bond formation is accomplished by the highly diastereoselective addition of organoaluminum reagents to the chiral α,β-unsaturated acetal derived from the α,β-unsaturated aldehyde and (*R,R*)-tartaric acid diamide to furnish the 1,4-adduct preferentially along with the 1,2-adduct as a minor product. Subsequent oxidation of the combined adducts with ozone or the system potassium permanganate/sodium periodate gives rise to the optically active α-substituted aldehyde, ketone, or carboxylic acid, respectively, with high enantioselectivities. The present method has been applied to the facile synthesis of an anti-inflammatory agent and the principal alarm pheromone of the leaf-cutting ant *Atta texana* in optically active forms.

Methods for the asymmetric carbon-carbon bond formation α to the carbonyl group reported[1] so far have utilized electrophilic alkylation of chiral metal enolates or their synthetic equivalents[2]. Here we disclose a nucleophilic counterpart based on the oxidative cleavage of the 1,4-adduct **3**. Thus, the key asymmetric carbon-carbon bond formation step was accomplished by the highly diastereoselective addition of organoaluminum reagents **2** to chiral α,β-unsaturated acetals **1** derived from (*R,R*)-tartaric acid diamide as described previously[3] to furnish the 1,4-adduct **3** preferentially along with 1,2-adduct **4** as a minor product. Subsequent oxidation of the combined products **3** and **4** with ozone or the catalyst system potassium permanganate/sodium periodate gave rise to the optically active α-substituted aldehyde **5** or carboxylic acid **6**, respectively.

The present methodology[4] provides a new access to a variety of α-substituted carbonyl compounds with high asymmetric induction (Table). Most noteworthy is the operational simplicity of the reaction, since separation of the desired monoalkylation product from unreacted starting material and di- or polyalkylation side products is quite troublesome in the existing methodologies using chiral metal enolate equivalents[1]. Furthermore, even readily enolizable α-phenyl-substituted aldehydes can be prepared without any racemization under mild oxidation conditions (**5dc**)[5]. Since both (*R,R*)- and (*S,S*)-tartaric acid diamide are readily obtainable in optically pure form[6], this method serves as the practical synthesis of both enantiomers of α-substituted carbonyl compounds in a predictable manner (products **6dc** and **6′dc** or **5′gc** and **5′gc**). A simple illustration of the potential utility of this approach can be envisioned by the facile synthesis of an anti-inflammatory agent **6ec**[7], and the principal alarm pheromone **5gc** of the leaf cutting ant *Atta texana*[8] in optically active forms.



Addition of Trialkylaluminum to α,β-Unsaturated Acetal 1d; Typical Procedure:

To a stirred solution of α,β-unsaturated acetal **1d** (318 mg, 1 mmol) in toluene (10 ml) at 0 °C is added a 2 molar hexane solution of trimethylaluminum (**2c**; 5 mmol), and the resulting mixture is stirred at room temperature for 12 h. The mixture is poured into 10% aqueous sodium hydroxide (30 ml) and extracted with dichloromethane (3 x 20 ml). The combined extracts are concentrated and purified by column chromatography on silica gel (methanol/ethyl acetate as eluent) to give a mixture of 1,4-(**3dc**) and 1,2-adducts **4dc** in a ratio of 5.7:1; yield: 304 mg (91%).

(+)-2-Phenylpropanal (5dc); Typical Procedure:

A stream of ozonized oxygen gas is passed into a stirred solution of **3dc** + **4dc** (303 mg, 0.91 mmol) in methanol (10 ml) at – 78 °C, until the color changes to slightly blue. After evaporation of the solvent, dichloromethane (10 ml) and dimethyl sulfide (0.67 ml, 9.1 mmol) are added, and the solution is maintained at room temperature for 12 h. Concentration of the mixture followed by silica gel column chromatography (ether/pentane as eluent) of the residue furnishes the aldehyde **5dc** yield: 100 mg (82%); $[\alpha]_D$: + 192° (*c* 0.69, ether).

To a solution of **5dc** (100 mg, 0.75 mmol) in methanol (2 ml) is added sodium borohydride (31 mg, 0.83 mmol) at 0 °C and the resulting solution is stirred at 0 °C for 30 min. The mixture is poured into 1 normal hydrochloric acid (20 ml) and extracted with ether

Table. Asymmetric Synthesis of α-Substituted Carbonyl Compounds

Acetal No.	R^1	R^2	Aluminium Reagent No.	R^3	Reaction Conditions Solvent/Temperature	Yield [%] of **3**+**4**	Ratio[a] **3**:**4**	Oxidation Product[b] No.	Yield [%]	Optical Yield[c] % e.e. (configuration)
1a	CH_3	H	**2a**	n-C_3H_7	CH_2Cl_2/5°C	96	2.1:1	**6aa**	63	87 (*R*)[12]
1a	CH_3	H	**2b**	n-C_6H_{13}	CH_2Cl_2/5°C	98	1:1	**6ab**	48	91 (*R*)[12]
1b	n-C_3H_7	H	**2c**	CH_3	CH_2Cl_2/25°C	91	3.3:1	**6bc**	64	>95 (*S*)[12]
1c	n-C_6H_{13}	H	**2c**	CH_3	$ClCH_2CH_2Cl$/25°C	85	6.4:1	**5cc**	85	98[d] (*S*)[12]
								6cc	72	>95 (*S*)[12]
1d	C_6H_5	H	**2c**	CH_3	toluene/25°C	91	5.7:1	**5dc**	82	>95 (*S*)[12]
								6dc	84	>95 (*S*)[12]
1′d	C_6H_5	H	**2c**	CH_3	toluene/25°C	74	5.7:1	**6′dc**	77	>95 (*R*)[12]
1e	4-C_6H_5—C_6H_4	H	**2c**	CH_3	toluene/25°C	64	15:1	**6ec**	87	91 (*S*)[7]
1f	—$(CH_2)_4$—		**2c**	CH_3	toluene/25°C	91	1:1	**5fc**	41	82[e] (*S*)[8]
					$ClCH_2CH_2Cl$/25°C	42	14:1	**5fc**	73	79[e] (*S*)[8]
1g[f]	n-C_3H_7	C_2H_5	**2c**	CH_3	$ClCH_2CH_2Cl$/25°C	72	2:1	**5gc**	55	70[g,h] (*S*)[8]
1′g[f]	n-C_3H_7	C_2H_5	**2c**	CH_3	$ClCH_2CH_2Cl$/5°C	64	2:1	**5′gc**	59	64[h] (*R*)[8]

[a] The ratio of **3** and **4** was determined by ^{1}H-N.M.R. analysis, or by chromatographic isolation after conversion to their acetates.

[b] The oxidative cleavage of **3** and **4** was carried out by using ozone or catalytic potassium permanganate/sodium periodate.

[c] Unless otherwise specified, the optical yield was determined by ^{1}H-N.M.R. analysis as described in the experimental section.

[d] Determined by G.L.C. on a 25-m PEG-HT capillary column after transformation to the acetal of (−)-2(*R*), 4(*R*)-pentanediol.

[e] Determined by G.L.C. analysis of the (*S*)-(−)-MTPA ester of *cis*-2-methylcyclohexanol which was prepared by reduction of the ketone with L-selectride[11].

[f] The parent α,β-unsaturated aldehyde was readily obtained by the self-condensation of butyraldehyde.

[g] $[\alpha]_D$: +15.47° (*c* 1.0, *n*-hexane). Since optically pure **5gc** has been reported to give $[\alpha]_D$: +22.1° (*c* 1.0, *n*-hexane)[8], the optical yield and absolute configuration of **5gc** were determined as 70% e.e. and (*S*), respectively.

[h] The optical yield was also substantiated by G.L.C. analysis after reduction of the ketone to its alcohol with $LiAlH_4$ followed by transformation to the (*S*)-(−)-MTPA ester.

(3 × 20 ml). The combined extract is dried with anhydrous sodium sulfate and evaporated to give the crude oil which is purified by column chromatography on silica gel (ethyl acetate/hexane as eluent) to give *(+)-2-phenyl-1-propanol*; yield: 98 mg (96%).

A solution of (+)-2-phenyl-1-propanol (68 mg, 0.5 mmol) in dichloromethane (3 ml) is treated successively with pyridine (243 μl, 3 mmol), (*S*)-(−)-α-methoxy-α-(trifluoromethyl)-phenylacetyl chloride [(*S*)-(−)-MTPA chloride] (152 mg, 0.6 mmol), and a catalytic amount of 4-dimethylaminopyridine at room temperature[9]. The mixture is stirred at room temperature for 2 h and worked up with saturated sodium hydrogen carbonate solution (10 ml). The aqueous layer is extracted with ether (3 × 10 ml), and the combined ether extract is dried with anhydrous sodium sulfate. After evaporation of solvent, the crude product is subjected to column chromatography on silica gel (ether/hexane as eluent) to furnish the (*S*)-(−)-MTPA ester of (+)-2-phenyl-1-propanol; yield: 167 mg (95%). ^{1}H-N.M.R. spectroscopy with the chiral shift reagent $Eu(hfc)_3$ indicates the optical purity of the (*S*)-(−)-MTPA ester to be > 95% e.e.

(+)-2-Phenylpropanoic Acid (6dc); Typical Procedure:

To a mixture of **3dc** + **4dc** (303 mg, 0.91 mmol) in *t*-butyl alcohol (24 ml) at room temperature are added a solution of potassium carbonate (377 mg, 2.73 mmol) in water (20 ml) followed by a solution of sodium periodate (1.56 g, 7.3 mmol) and potassium permanganate (189 mg, 1.2 mmol) in water (20 ml)[10]. The solution is then adjusted to pH 8.5 with normal sodium hydroxide, and stirred for 16 h. After evaporation of *t*-butyl alcohol under reduced pressure, the aqueous solution is acidified with concentrated hydrochloric acid to pH 2.5, and sodium hydrogen sulfite is added until the solution becomes off-white. The residue is chromatographed on silica gel (ethyl acetate/hexane as eluent) to give the acid **6dc**; yield: 115 mg (84%); $[\alpha]_D$: + 67.6° (*c* 0.70, ethanol).

Since the optical rotation values of the acid **6dc** are strongly affected by small quantities of impurities, the optical purity is established by ^{1}H-N.M.R. analysis of the methyl ester by combining use of $Eu(hfc)_3$. Thus, a solution of the acid **6dc** (115 mg, 0.76 mmol) and *p*-toluenesulfonic acid monohydrate (10 mg) in methanol (10 ml) is refluxed for 3 h. The solvent is removed under reduced pressure and the residue is taken up in ether (30 ml). The solution is washed with 5% aqueous sodium hydroxide (10 ml), dried with anhydrous sodium sulfate, and evaporated. The residue is purified by column chromatography on silica gel (ethyl acetate/hexane as eluent) to give *methyl 2-phenylpropanoate*; yield: 100 mg (80%) ^{1}H-N.M.R. spectroscopy with $Eu(hfc)_3$ indicated that the methyl ester has > 95% e.e.

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