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Cu(II)-catalyzed enantioselective aldol condensation between malonic acid hemithioesters and aldehydes

Simonetta Orlandi, Maurizio Benaglia and Franco Cozzi*

Dipartimento di Chimica Organica e Industriale, Universita' degli Studi di Milano and CNR-ISTM, Via Golgi 19, I-20133 Milano, Italy

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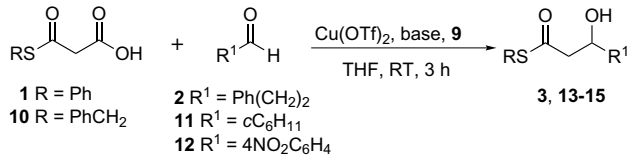
Abstract—A mild, decarboxylative, aldol-type addition of malonic acid hemithioesters to aldehydes has been shown to occur with up to 39% enantioselectivity when the reaction was carried out in the presence of catalytic amounts of a Cu(II) salt, an enantiopure, tartaric acid-derived bis-benzimidazole and an achiral base.

The development of mild, catalytic and enantioselective versions of fundamental C–C bond forming processes is a topic of paramount importance in modern organic chemistry. In this context, the aldol reaction continues to attract a great deal of interest.[1] Very recently,[2] the decarboxylative[3] condensation between *S*-benzylmalonic acid hemithioester and aldehydes catalyzed by a combination of Cu(2-ethylhexanoate)$_2$ (20 mol %) and 5-methoxybenzimidazole (22 mol %) has been described as a new protocol to perform an aldol process under exceptionally mild conditions (wet solvent, air, room temperature), reminiscent of those typical of polyketide biosynthesis. Here, we wish to report some preliminary results obtained while developing an enantioselective version of this reaction.

The condensation between the *S*-phenylthioester **1** (1 mol equiv) and 3-phenylpropanal **2** (1 mol equiv) carried out in the presence of 20 mol % of various Cu(II) salts and 22 mol % of chiral imidazoles to afford aldol adduct **3** (THF, 3 h, room temperature) was used as a model reaction (Scheme 1).

First, it was discovered that Cu(II) salts other than Cu(2-ethylhexanoate)$_2$ could be employed as promoters, with Cu(OAc)$_2$ and Cu(OTf)$_2$ affording satisfactory results (the latter was used in subsequent experiments). Second, the enantiopure mono- and bisbenzimidazoles



Scheme 1. Synthesis of aldol adducts **3**, **13**–**15** from thioesters **1**, **10** and aldehydes **2**, **11**, **12**.

4–**9** collected in Figure 1 were screened to achieve an enantioselective aldol process.[†]

Among these compounds, the use of **9**, derived from inexpensive (2*R*,3*R*)-tartaric acid, led to the higher enantiomeric excess (ee = 21%; Table 1, entry 1), but this was observed for a low yielding reaction (28%). Since it seemed possible that the coordination of Cu(II) ions with **9** could prevent the latter's action as a base, the effect of the addition of different achiral bases to the reaction mixture was investigated with the aim of improving the chemical yield (Table 1, entries 2–8).[‡] It was found that in the presence of diisopropylethylamine

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* Corresponding author. Tel.: +39-02-50314-170; fax: +39-02-50314-159; e-mail: franco.cozzi@unimi.it

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† Benzimidazoles **5**, **6**, **8** and **9** were prepared by reaction of the appropriate aromatic diamines with (*S*)-lactic or (2*R*,3*R*)-tartaric acid. The synthesis of compounds **4** and **7** involved nucleophilic aromatic substitution of 2-fluoronitrobenzene with the enantiopure amines, followed by reduction of the nitro group and reaction with formic acid.[4–6] All new compounds gave analytical and spectral data in agreement with the proposed structures.

‡ A pale green solution was formed upon addition of Cu(OTf)$_2$ to bisbenzimidazole **9**. The subsequent addition of the base did not lead to any significant color change.

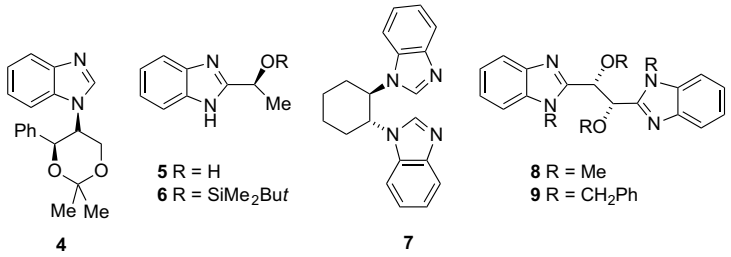

Figure 1. Structures of enantiopure mono- and bisbenzimidazoles **4**–**9**.

Table 1. Stereoselective synthesis of adducts **3** and **13**–**15**

Entry	Thioester	Aldehyde	Base[a] (mol%)	Product	Yield (%)[b]	Ee%[c]
1	**1**	**2**	None	(*S*)-**3**	28	21
2	**1**	**2**	NMBI (20)	(*S*)-**3**	33	31
3	**1**	**2**	NMBI (10)	(*S*)-**3**	53	24
4	**1**	**2**	NMBI (5)	(*S*)-**3**	39	23
5	**1**	**2**	DBU (20)	(*S*)-**3**	45	22
6	**1**	**2**	DIPEA (20)	(*S*)-**3**	58	20
7	**1**	**2**	Pyridine (20)	(*S*)-**3**	34	28
8	**1**	**2**	2,6-Lutidine (20)	(*S*)-**3**	53	28
9	**1**	**2**	**9** (20)	(*S*)-**3**	51	24
10	**1**	**11**	2,6-Lutidine (20)	**13**	36	18
11	**10**	**2**	2,6-Lutidine (20)	**14**	25	35
12[d]	**10**	**12**	2,6-Lutidine (20)	**15**	41	39

[a] Abbreviations: NMBI = *N*-methylbenzimidazole; DBU = 1,8-diazabicyclo[5,4,0]undec-7-ene; DIPEA = diisopropylethylamine.
[b] Isolated yields after flash chromatography.
[c] As determined by HPLC on a Chiracel OD column with hexane–isopropanol 90:10 as eluting mixture; flow rate: 1 mL/min; λ: 254 nm.
[d] Reaction time 24 h.

(entry 6) the product could be obtained in up to 58% yield while the ee remained almost unchanged (20%). Other bases gave rise to a slightly increased ee, that reached 31% when 20 mol% of *N*-methylbenzimidazole was employed (entry 2). Lower amounts of this base (entries 3 and 4) increased the yield but depressed the ee. Perhaps the best combination was offered by the use of 2,6-lutidine (20 mol%). With this base, compound **3** was isolated in 53% yield and 28% ee (entry 8). When **9** was employed as the added base, the observed ee was 24% (entry 9). The absolute configuration of compound **3** was established to be (*S*) by $LiAlH_4$ reduction to (−)-(*S*)-5-phenylpentane-1,3-diol.[7]

The extension of the conditions of entry 8 to the additions of thioesters **1** and **10** to the branched aliphatic aldehyde **11** and the aromatic aldehyde **12** to afford adducts **13**–**15** was then attempted (Table 1, entries 10–12). As can be seen from the reported data, the ee remained moderate and reached a maximum of 39% in the case of the condensation of *S*-benzylthioester **10** with 4-nitrobenzaldehyde **12**, which led to product **15** in 41% yield.

In conclusion, a catalytic, enantioselective version of a very mild aldol condensation process has been developed. The reaction relies on the unprecedented use of a combination of 20 mol% each of a Cu(II) salt, an achiral base, and a readily available and inexpensive tartaric acid-derived enantiopure bisbenzimidazole.

Work is in progress to improve the chemical and stereochemical efficiency of the reaction and to extend the use of enantiopure benzimidazoles to other catalytic enantioselective processes.[8,9]

Acknowledgements

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9. Typical experimental procedure for the synthesis of compound **3**: To a stirred solution of bisimidazole **9** (29 mg, 0.04 mmol) and $Cu(OTf)_2$ (14.5 mg, 0.04 mmol) in THF (5 mL), thioester **1** (39.2 mg, 0.2 mmol), aldehyde **2** (26.3 μL, 0.2 mmol), and 2,6-lutidine (4.6 μL, 0.04 mmol) were added in this order. The mixture was stirred for 3 h at RT and the reaction was quenched by the addition of 2 mL of 0.5 M aqueous HCl. Ethyl acetate (5 mL) was then added, the organic phase was separated, washed with a saturated aqueous solution of $NaHCO_3$ and with brine. Evaporation of the solvent gave the crude product that was purified by flash chromatography with an 80:20 hexanes–ethyl acetate mixture as eluant to give **3** (30.5 mg) in 53% yield.