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Enantioselective addition of carbon acids to α-nitroalkenes: the first asymmetric aminocatalytic reaction in liquefied carbon dioxide

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ABSTRACT

Carbon acids, in particular malonates, malononitrile, and anthranone, react enantioselectively with α-nitroalkenes in the presence of Takemoto's organocatalyst in liquid carbon dioxide medium (100 bar, rt), under homogeneous conditions, to afford the corresponding Michael adducts in moderate to high yields and with enantioselectivities comparable with those obtained in organic solvents.

Asymmetric catalysis by small, metal-free chiral organic molecules, the so called 'organocatalysts', is a rapidly developing area of modern organic chemistry.[1] Various chiral amines are among the most popular organocatalysts.[2] Primary and secondary amines activate reagents and result in stereoinduction through reversible formation of enamines[3] or iminium cations,[4] their geometry being dictated by the stereocenters present in the catalyst. Tertiary amines, being incapable of forming such intermediates, coordinate reagents in the transition state by means of ion pairing or, in the presence of an auxiliary H-donor group, by hydrogen-bonding.[5] This is the method by which fairly simple catalysts (α-amino acids, alkaloid derivatives, chiral 1,2-diamines, and some others) promote conversion of prochiral compounds into chiral products of high enantiomeric purity in a single step.[6] A number of organocatalytic reactions proceed well both in conventional organic solvents and in neoteric solvents, including ionic liquids[7] and water.[8]

Among solvents for green chemistry,[9] considerable interest has been devoted to carbon dioxide as it is a simple, readily available, nontoxic, nonflammable, and stable natural compound that can be obtained either as a liquid or in a supercritical state.[10] Over the last decade, liquid and supercritical CO_2 have been widely studied as solvents in various chemical reactions[11–13] including asymmetric synthesis promoted by organometallics[12] or biocatalysts.[13] However, to the best of our knowledge, no cases of asymmetric aminocatalysis in this medium have been communicated. The problem is associated with the formation of carbamic acid salts as by-products from primary or secondary amines and carbon dioxide, which removes the catalyst from the catalytic cycle.[14] On the other hand, tertiary amines such as Et_3N or DABCO do not react with CO_2 over broad temperature and pressure ranges and were shown to be capable of promoting racemic Henry[15] or Baylis–Hillman[16] reactions under these conditions.

Herein we report the first example of an asymmetric organocatalytic reaction, that is the enantioselective Michael addition of carbon acids to α-nitroalkenes in liquid CO_2 medium. The reaction is used for the enantioselective synthesis of γ-nitrocarbonyl compounds, which are intermediates for preparing valuable pharmaceutical analogs of γ-amino butyric acid (GABA)—an important natural neuromediator.[17]

Reactions of carbon acids with α-nitroalkenes in organic solvents are catalyzed efficiently by Takemoto's bifunctional tertiary amine–thiourea derivatives.[18] The amino group of catalyst **1** activates the carbon acid while the neighbouring thiourea unit locates the substrate nitroalkene at a position favorable for nucleophilic attack by virtue of the formation of hydrogen bonds with the oxygen atoms of the nitro group in the transition state (Scheme 1, $\mathbf{TS_1}$).[19] The key role of hydrogen bonding in these reactions is in agreement with their specific solvent dependence: high enantioselectivity was observed in aprotic solvents (toluene, THF) whereas in methanol, which may form 'parasitic' hydrogen bonds with a nitroalkene, it was much lower (Table 1, entries 1–3).[18a,18b] It might be expected that carbon dioxide would force the nitroalkene out of the reaction 'zone' due to concurrent hydrogen bonding with the thiourea fragment of the catalyst (Scheme 1, $\mathbf{TS_2}$).[20]

We were happy to discover that the stereoselectivity of the model reaction between diethyl malonate (**2a**) and nitrostyrene (**3a**) in liquid CO_2 (100 bar) at ambient temperature was similar

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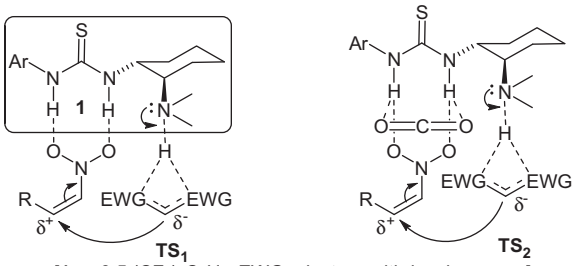


Scheme 1. Tentative transition states of the bifunctional catalyst **1** promoted Michael reactions between carbon acids and nitroalkenes in aprotic organic solvents (**TS_1**) and in CO_2 (**TS_2**).

to that in toluene or THF, and much better than that in methanol (Table 1). The yield of Michael adduct **4a** was moderate when the reaction was run for 24 h, however it improved significantly when the time was reduced to 2–8 h (Table 1, entries 4–8). In these cases, the undesired by-products, in particular β-nitrostyrene oligomers, were generated in negligible amounts. Moreover, the catalyst loading could be reduced to 5 mol % though at the expense of product yield (entry 9). A further reduction of the catalyst amount to 2.5 mol % resulted in lower enantioselectivity (entry 10). Reactions performed at higher (300 bar) or lower (55 bar) CO_2 pressure had no positive effect in terms of enantioselectivity (entries 11 and 12).

The carbon dioxide medium is applicable to Michael reactions of α-nitroalkenes with other C nucleophiles (Table 2). Dialkylmalonates **2a**–**c** (entries 1–11), malononitrile (**2d**) (entry 12), and anthranone (**2e**) (entry 13) reacted enantioselectively with β-nitrostyrene derivatives **3a**–**d** bearing electron-donating or electron-withdrawing groups on the aromatic ring, in liquid CO_2, to afford the corresponding Michael adducts **4**. The aliphatic α-nitroalkene, 1-nitro-4-methylpent-1-ene (**3e**) also served as an electrophile for this reaction (entry 10). The duration of the reaction was dependent on the structure of the reagent: reactions of dialkyl malonates **2a**,**b** or malononitrile (**2d**) with β-nitrostyrene (**3a**) or 4-chloro-β-nitrostyrene (**3b**) required 4–8 h to complete, whereas the reaction time for less active carbon acids **2c**,**e** required 12–60 h. The experiments in an autoclave equipped with sapphire windows showed that the reactions were homogeneous under the conditions used (rt, CO_2 pressure of 100 bar). As a rule, the yields and enantiomeric purities of adducts **4** in the CO_2 medium were comparable with, or somewhat lower than those in toluene. However, compounds **4e**, **4f**, **4i,** and especially **4k** were synthesized in liquid CO_2 with higher enantioselectivities than in conventional organic solvents (entries 6, 7, 10, and 12).

Some of the prepared compounds are of practical interest. Adducts **4b** and **4f** are used as intermediates for the synthesis of the most active (*R*)-enantiomer of the therapeutically useful $GABA_B$ receptor agonist baclofen,[18b] and adduct **4i** for the synthesis of the chiral anticonvulsant, pregabalin.[22] The procedure is convenient: after decompression, the products can be isolated from the residue by conventional methods and volatile carbon dioxide can be, if necessary, recycled.[23] The method is scalable (Table 2, entry 2) and applicable to the preparation of target compounds in amounts needed for biological applications.

In summary, we have shown for the first time that liquefied carbon dioxide is a suitable reaction medium for tertiary chiral amine **1** catalyzed asymmetric Michael reactions. The results may be useful for developing novel environmentally friendly organocatalytic processes.

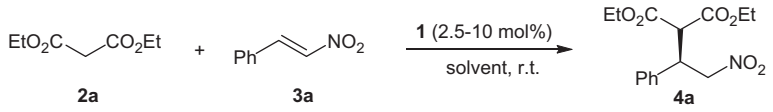
CAUTION: Reactions in supercritical carbon dioxide involve high pressures and should only be carried out with appropriate equipment.

(1*R*,2*R*)-*N*′,*N*′-dimethylcyclohexane-1,2-diamine was prepared according to the literature procedure.[24a] Takemoto's catalyst **1**,[18a] nitrostyrenes **3a**–**d**,[24b] and nitroalkene **3e**[22] were synthesized by reported methods.

Enantioselective Michael reaction in liquid CO_2 (typical procedure)

Under an argon atmosphere, diethyl malonate (**2a**) (64 mg, 0.40 mmol), *trans*-β-nitrostyrene (**3a**) (29.8 mg, 0.20 mmol), and thiourea-catalyst **1** (4.1 mg, 0.01 mmol) were placed in a 2 ml stainless steel autoclave equipped with a magnetic stir bar. The

Table 1
Michael addition of **2a** to **3a** in the presence of **1** in liquid CO_2 and organic solvents[a]



2a 3a 4a

Entry	Solvent (bar)	**1** (mol %)	Time (h)	Yield[b] (%)	*ee*[c,d] (%)
1[e]	Toluene (1)	10	24	60	92
2[e]	THF (1)	10	24	29	88
3[e]	CH_3OH (1)	10	24	33	29
4	CO_2 (100)	10	24	49	86
5[f]	CO_2 (100)	10	24	32	86
6	CO_2 (100)	10	8	84	86
7	CO_2 (100)	10	4	85	85
8	CO_2 (100)	10	2	91	83
9	CO_2 (100)	5	4	59	87
10	CO_2 (100)	2.5	12	60	79
11	CO_2 (300)	5	4	79	87
12	CO_2 (55)	5	4	60	85

[a] Unless otherwise noted, the reactions in liquid CO_2 were carried out in a 2 ml autoclave with **2a** (64 mg, 0.4 mmol), **3a** (30 mg, 0.2 mmol), and catalyst **1**.
[b] Isolated yield.
[c] Enantiomeric excess was determined by HPLC analysis of **4a** using a chiral column.
[d] The absolute configuration was determined by comparing the specific rotation of **4a** with literature data.[18a]
[e] The data are taken from ref. 18b
[f] 0.2 mmol of **2a** was used.