Lewis Acids as Highly Efficient Catalysts for the Decarboxylative Esterification of Carboxylic Acids with Dialkyl Dicarbonates

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Abstract: Mild Lewis acids such as $Mg(ClO_4)_2$ show a new level of catalytic activity for the decarboxylative esterification of carboxylic acids with commercially available dialkyl dicarbonates. In the presence of as little as one mol % $Mg(ClO_4)_2$ catalyst, carboxylic acids can thus easily and near quantitatively be protected at room temperature, e.g., as methyl, benzyl, or *t*-butyl esters. Only volatile by-products are released so that the purification of the products is particularly easy. Many sensitive functionalities are tolerated, including even phenol esters, or free hydroxy and BOC groups.

Keywords: carboxylic acids; catalysis; dialkyl dicarbonate; esterification; esters; Lewis acids

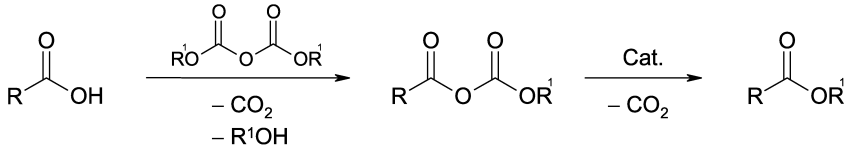
Undoubtedly the most popular way to protect carboxylic acid groups in organic synthesis is their conversion into esters, in particular methyl, benzyl or *t*-butyl esters.[1] Usually, such esterifications are performed using the classical acid-catalyzed reaction of carboxylic acids with excess alcohol.[2] However, problems are encountered as soon as the substrates bear acid-sensitive or basic functional groups. The alternative alkylation of carboxylates, e.g., with dialkyl sulfates,[3] alkyl halides,[4] or dimethyl carbonate/DBU[5] has a higher functional group tolerance but requires the use of toxic reagents and the separation of the product ester from stoichiometric amounts of waste.

Another particularly practical method is the reaction of carboxylic acids with alcohols in the presence of coupling reagents such as DCC/DMAP[6] or DEAD/PPh_3.[7] These reactions generally proceed in excellent yields, even for complex molecules. The only major drawback of this procedure consists of the necessity to separate the products from the waste derived from the coupling reagents. Clearly, if coupling reagents could be employed that would solely produce volatile side products, a significant improvement of this approach might be possible.

We now report a general and practical esterification method based on commercially available dialkyl dicarbonates. These react at room temperature with carboxylic acids to give mixed carbonic carboxylic anhydrides together with one equivalent of the alkyl alcohol. Takeda et al. reported that in the presence of substoichiometric amounts of *N*,*N*-dimethylaminopyridine (DMAP), CO_2 is released from such mixtures and the corresponding alkyl esters are formed (Scheme 1).[8] They showed that this reaction can be used as a method to esterify a limited range of carboxylic acids, in particular amino acids. However, the fact that large quantities of DMAP (10–30 mol %) and long reaction times (up to 96 h) are required for more standard carboxylic acids has precluded the widespread use of this interesting reaction.

While investigating on the use of dialkyl dicarbonates as activating agents for carboxylic acids in palladium-catalyzed reactions,[9] we observed that the addition of Lewis acids to mixed carboxylic-carbonic anhydrides led to rapid formation of carboxylic esters. Intrigued by this observation, we decided to explore its synthetic potential, and chose the reaction of 3-phenylpropionic acid **1** with dimethyl dicarbonate **3a** as a model (Scheme 2) on which to perform systematic studies using different catalysts, solvents and temperatures. Selected results are summarized in Table 1.

In the presence of Brønsted acids almost no ester formation was observed (entries 1 and 2), and DMAP displayed only modest catalytic activity of under the



Scheme 1. Decarboxylative esterification of carboxylic acids with dialkyl dicarbonates.

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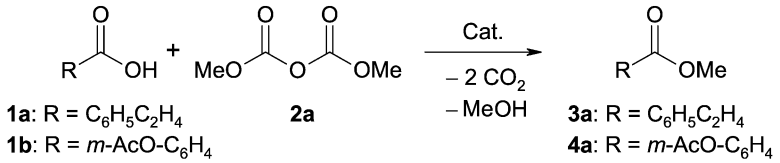


Scheme 2. Model reactions for the decarboxylative esterification.

Table 1. Variation of the catalyst and reaction conditions.

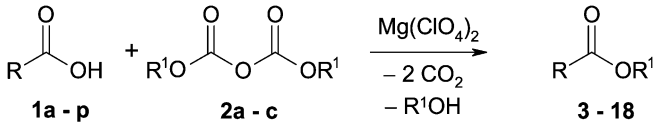
Entry	R	Catalyst	Solvent	Temperature [°C]	Conversion [%]	Selectivity [%]
1	$C_6H_5C_2H_4$	TsOH[a]	CH_3NO_2	25	4	81
2	"	$HClO_4$[a]	"	"	9	70
3	"	DMAP[a]	THF	"	47	>98
4	"	$LiBF_4$	CH_3NO_2	"	0	–
5	"	$FeCl_3$	"	"	97	>98
6	"	$Yb(OTf)_3$	"	"	100	>98
7	"	$Sc(OTf)_3$	"	"	100	>98
8	"	$Hf(OTf)_4$	"	"	100	>98
9	"	$Bi(OTf)_3$	"	"	80	>98
10	"	$Al(OTf)_3$	"	"	69	>98
11	"	$Zn(OTf)_2$	"	"	87	>98
12	"	$Mg(ClO_4)_2$	"	"	100	>98
13	"	$Cu(OTf)_2$	"	"	100	>98
14	"	$Mg(ClO_4)_2$	"	55	100	>98
15	"	"	"	90	100	93
16	"	"	MeOH	25	100	>98
17	"	"	CH_3CN	"	100	>98
18	"	"	CH_2Cl_2	"	100	>98
19	"	"	toluene	"	40	>98
20	"	"	THF	"	69	>98
21	"	"	NMP	"	7	>98
22	m-AcO-C_6H_4	$Yb(OTf)_3$	CH_3NO_2	"	100	89
23	"	$Sc(OTf)_3$	"	"	100	49
24	"	$Hf(OTf)_4$	"	"	100	33
25	"	$Cu(OTf)_2$	"	"	100	>98
26	"	$Mg(ClO_4)_2$	"	"	100	>98

Conditions: 1 mmol carboxylic acid, 1.3 mmol dimethyl dicarbonate, 1 mol % catalyst, 4 mL solvent, 16 h; conversion and selectivity determined by GC using *n*-tetradecane as an internal standard.
[a] 3 mol % catalyst.

conditions reported in the literature (entry 3).[8] In sharp contrast to these findings, several Lewis acidic compounds showed a high catalytic activity for the desired transformation, so that a catalyst loading of 1 mol % was sufficient to obtain excellent conversions within a few hours at room temperature. Not only the expensive early transition metal compounds were found to be suitable, e.g., scandium, hafnium or ytterbium triflate (entries 6–8), but also main group metal salts such as aluminium triflate or magnesium perchlorate (entries 9–12). Even some late transition metal salts, e.g., copper triflate (entry 13), displayed excellent catalytic activity.

The reaction can be performed in various solvents; the best results were obtained with dichloromethane, acetonitrile or nitromethane (entries 12, 16–18). The catalytic activity was significantly lower in more strongly coordinating solvents (entries 20, 21), probably since they inactivate the catalyst. Since the greatest variety of carboxylic acids was soluble in nitromethane, this solvent was used for all further experiments. The reaction can also be performed at higher temperatures within shorter reaction times without a significant loss of selectivity (entries 14, 15).

After having identified several active catalysts, we probed the functional group compatibility of the most active ones using the phenol ester **1b** as the substrate (Scheme 3). The acetoxy group of this substrate is extremely sensitive towards both acid- and base-catalyzed transesterifications, giving rise to the free phenol and alkyl acetate. Transesterification was indeed observed, especially when using early transition metal catalysts (entries 22–24). To our delight and despite their high activity for the esterification, neither magnesium perchlorate nor copper triflate led to the formation



Scheme 3. Decarboxylative esterification of various carboxylic acids.

of more than trace amounts of the free phenol (entries 25, 26). Hence, these two metal salts promised to be the most versatile catalysts. Out of environmental and economical considerations, we considered magnesium perchlorate ($\approx$30 ct/g)[10] to be the superior choice over the other Lewis acids, and even more so over DMAP especially when taking into account the larger catalyst loading required.[11,12]

In order to explore the scope of this transformation, a variety of carboxylic acids was reacted with dimethyl, dibenzyl and di-*t*-butyl dicarbonate (**2a – c**). Besides these compounds, diethyl, diallyl, and di-*t*-amyl dicarbonate are also commercially available[10] and can be expected to react similarly. Selected results are summarized in Table 2.

The reaction can be performed with aromatic, aliphatic, and heterocyclic carboxylic acids and tolerates a broad variety of functional groups such as esters, ketones, amides, ethers, nitriles and even free hydroxy and phenoxy groups.

Dibenzyl and dimethyl dicarbonate displayed a high reactivity and were thus employed in near stoichiometric quantities. Di-*t*-butyl dicarbonate is less reactive and slowly decomposes under the reaction conditions, so that in order to obtain optimal yields of the *t*-butyl esters, the use of two equivalents of this reagent is recommended.

We only observed one major limitation of the new reaction protocol: while protected α-amino acids were converted in high yields into their methyl and benzyl esters, the *t*-butyl esters of these particularly acidic substrates proved to be unstable under the reaction conditions. Thus, isobutene was formed and the carboxylic acids were recovered. For this particular substrate combination, the reaction protocol with DMAP is recommended.[8]

In the reaction of dimethyl dicarbonate with an acid bearing an unprotected primary hydroxy group, the desired methyl ester is formed in high selectivity (compound **18a**). This finding suggests that the reaction proceeds mainly *via* an intramolecular decarboxylation. If the products arose only in an intermolecular reaction of the mixed anhydride with free alcohol, a statistical mixture of methyl ester and cyclic or oligomeric esters should be expected. In order to confirm this hypothesis, phenylpropionic acid was reacted with dimethyl dicarbonate and $Mg(ClO_4)_2$ in the presence of one equivalent of *n*-butanol. Indeed, mainly the methyl ester was formed (81%), but also a small amount of the *n*-butyl ester (19%). More in-depth investigations on the mechanism of this reaction are underway and will be published in due time.

The work-up of the reaction products is very convenient since residual dicarbonates are easily hydrolyzed, volatile alcohols and CO_2 are the only by-products and these, as well as the catalyst, are water-soluble. Thus, the products are usually obtained in pure form after a simple aqueous work-up.

In summary, several Lewis acids were found to catalyze the decarboxylative esterification of carboxylic acids with carbonic anhydrides much more efficiently than the previously employed DMAP. The tolerance of the new esterification reaction to a wide range of sensitive functionalities in combination with the small required amount of the inexpensive and environmentally benign $Mg(ClO_4)_2$ catalyst make it very attractive for the preparative chemist. Particular advantageous for small-scale applications, e.g., in combinatorial chemistry, is the fact that only volatile or water-soluble by-products are released.

Experimental Section

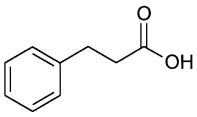
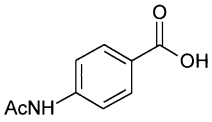
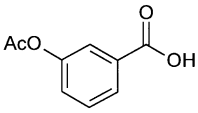
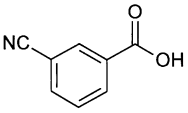
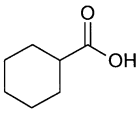
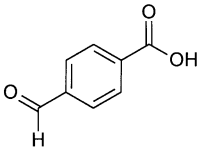
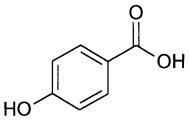
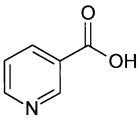
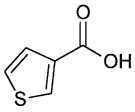
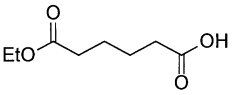
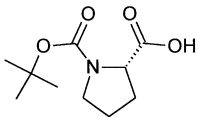
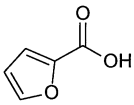
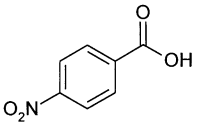
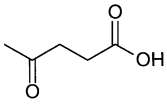
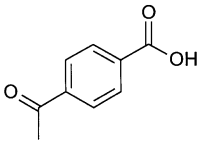
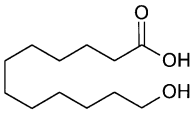
Synthesis of 3-Acetoxybenzoic Acid Methyl Ester (4a)

An oven-dried flask was charged with 3-acetoxybenzoic acid **1b** (180 mg, 1.00 mmol), dimethyl dicarbonate **2a** (180 mg, 1.30 mmol), and magnesium perchlorate (2.20 mg, 0.01 mmol). Dry nitromethane (4 mL) was added by a syringe and the mixture was stirred at 20 °C overnight. After the reaction was complete (TLC), ethyl acetate was added and the organic layer was washed consecutively with aqueous ammonium chloride and sodium bicarbonate solution, water and brine. After drying with magnesium sulfate and removal of the volatiles under vacuum, the product was obtained in high purity. For spectroscopic characterization, the product was filtered through a small plug of silica using hexane/dichloromethane (3:7) as eluent. After removal of the volatiles, **4a** was obtained as a colorless liquid; yield: 186 mg (96%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.92 – 7.88 (m, 1H), 7.76 (m, 1H), 7.46 – 7.26 (m, 2H), 3.89 (s, 3H), 2.28 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 169.1, 166.0, 150.6, 131.6, 129.4, 126.9, 126.2, 122.8, 52.2, 20.9; MS (EI): *m/z* (%) = 194 (20) [M^+], 163 (10), 153 (9), 152 (100), 121 (195), 93 (15), 43 (35); HRMS (EI): calcd. for $C_{10}H_{10}O_4$ [M^+]: 194.05791; found: 194.05786; anal. calcd. for $C_{10}H_{10}O_4$: C 61.85, H 5.19, O 32.96%; found: C 61.73, H 5.24, O 32.89%.

Synthesis of 3-Acetoxybenzoic Acid Benzyl Ester (4b)

Compound **4b** was synthesized accordingly from 3-acetoxybenzoic acid **1b** (180 mg, 1.00 mmol), dibenzyl dicarbonate **2b** (372 mg, 1.30 mmol), and magnesium perchlorate (2.20 mg, 0.01 mmol). The product was obtained as a colorless, viscous oil; yield: 261 mg (97%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.98 – 7.94 (m, 1H), 7.80 (m, 1H), 7.47 – 7.28 (m, 7H), 5.36 (s, 2H), 2.30 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 169.2, 165.5, 150.7, 135.8, 131.7, 129.5, 128.7, 128.4, 128.3, 127.2, 126.6, 123.0,

Table 2. Scope of the decarboxylative esterification.

Compound	Acid	R^1	Yield [%]	Compound	Acid	R^1	Yield [%]
3a		Me	93	**11a**		Me	93
3b		Bn	92	**11b**		Bn	87
3c		*t*-Bu	91				
4a		Me	96	**12a**		Me	91
4b		Bn	97	**12b**		Bn	98
4c[a]		*t*-Bu	96				
5a		Me	93	**13a**		Me	97
5b		Bn	97	**13b**		Bn	94
5c[a]		*t*-Bu	91				
6a		Me	97	**14a**		Me	92
6b		Bn	93	**15b**		Bn	91
6c[a]		*t*-Bu	90				
7a		Me	95	**15a**		Me	91
7b		Bn	93	**15b**		Bn	93
7c[a]		*t*-Bu	93				
8a		Me	97	**16a**		Me	99
8b		Bn	94	**16b**		Bn	96
8c		*t*-Bu	< 5				
9a		Me	98	**17a**		Me	97
9b		Bn	96				
10a		Me	93	**18a**		Me	92
10b		Bn	94				

Conditions: 1 mmol carboxylic acid, 1.3 mmol dialkyl dicarbonate, 1 mol % $Mg(ClO_4)_2$, 4 mL nitromethane, RT, 16 h; the yields reported are isolated yields.
[a] 2 mmol dialkyl dicarbonate.

67.0, 21.0; MS (EI): *m/z* (%) = 270 (28) [M^+], 228 (46), 210 (25), 183 (7), 121 (100), 91 (61), 43 (22); HRMS (EI): calcd. for $C_{16}H_{14}O_4$ [M^+]: 270.08921; found 270.08931; anal. calcd. for $C_{16}H_{14}O_4$: C 71.10, H 5.22, O 23.68%; found: C 70.85, H 5.30, O 23.48%.

Synthesis of 3-Acetoxybenzoic Acid *t*-Butyl Ester (4c)

An oven-dried flask was charged with 3-acetoxybenzoic acid **1b** (180 mg, 1.00 mmol), di-*t*-butyl dicarbonate **2b** (450 mg, 2.00 mmol), and magnesium perchlorate (2.20 mg, 0.01 mmol). Dry nitromethane (4 mL) was added by a syringe and the mixture was stirred at 40 °C overnight. After the reaction was complete (TLC), ethyl acetate was added and the organic layer was washed consecutively with aqueous ammonium chloride and sodium bicarbonate solution, water and brine. After drying with magnesium sulfate and removal of the volatiles under vacuum, the product was obtained in high purity. For spectroscopic characterization, the product was filtered through a small plug of silica using hexane/dichloromethane (5:5) as eluent. After removal of the volatiles, **4c** was obtained as a colorless liquid; yield: 226 mg (96%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.88–7.85 (d, 1H), 7.68 (s, 1H), 7.45–7.39 (t, 1H), 7.27–7.23 (d, 1H), 2.31 (s, 3H), 1.59 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 169.3, 164.7, 150.5, 133.6, 129.2, 127.9, 126.9, 122.6, 81.4, 28.4, 21.1; MS (EI): *m/z* (%) = 236 (2) [M^+], 194 (24), 138 (100), 121 (20), 57 (38), 43 (24), 41 (26); HRMS (EI): calcd. for $C_{13}H_{16}O_4$ [M^+]: 236.10486; found 236.10500; anal. calcd. for $C_{13}H_{16}O_4$: C 66.09, H 6.83, O 27.09%; found: C 65.87, H 6.78, O 27.26%.

The reactions in Table 2 were performed following the above procedure. All products were isolated and characterized by means of ^{1}H and ^{13}C NMR as well as by GC-MS and HRMS. The analytical data was identical with those reported in the literature.

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[10] See e. g. *Aldrich catalog of laboratory chemicals*, **2003**.

[11] Other magnesium salts with non-coordinating anions, e. g., $Mg(OTf)_2$, gave similar results.

[12] For the activation of acetic anhydride with $Mg(ClO_4)_2$, see: G. Bartoli, M. Bosco, R. Dalpozzo, E. Marcantoni, M. Massaccesi, S. Rinaldi, L. Sambri, *Synlett* **2003**, 35–38.

