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A catalyst system for the reaction of carboxylic acids with aliphatic isocyanates

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In memoriam Professor Dr. Eberhard Steckhan

Abstract—Catalysts have been found for the selective reaction of aliphatic isocyanates with carboxylic acids giving amides after carbon dioxide extrusion. Magnesium and calcium salts lead to a dramatic increase in reaction rates while improving the selectivity when sterically hindered isocyanates and/or carboxylic acids are used.

1. Introduction

The reaction of isocyanates with carboxylic acids is one of the lesser-utilised reactions in isocyanate chemistry. Little has been published[1,2] and these publications almost exclusively deal with the reactions between aromatic isocyanates and acids. Furthermore no catalyst system has been described. However, for the production of raw coating materials the reaction between aliphatic isocyanates and acids appears to be a viable tool that should be further investigated due to the great variety of readily available starting materials. In the production of raw coating materials the starting materials need to react completely because typically no final purification step is involved. The results of this examination may be interesting for a wider variety of applications.

Typically, for the reaction of aliphatic carboxylic acids with aliphatic isocyanates, high reaction temperatures (up to 140 °C) and long reaction times are required. By lowering the reaction temperature and thus allowing more controlled reactions a novel access to polyisocyanate building blocks for coatings could be opened up. Lower temperature would lead to less colouration—which is crucial for coating applications and raw material manufacturing—and would make the incorporation of thermosensitive acids like acrylic acid possible. Very often the prime way to lower reaction temperatures is to make use of a catalytic system and this is the main goal of the efforts described in this paper.

Two reaction pathways are in competition in the reaction of an acid and an isocyanate (Scheme 1). The actual reaction pathways depend on the degree of substitution of the α-carbon of the aliphatic carboxylic acid. For higher substituted carboxylic acids (e.g., pivalic acids) path B occurs almost exclusively, however, with the sterically unhindered acetic acid, path A was found to be preferred giving the corresponding amide. Depending on the conditions and stoichiometry this amide can then further react to form an acyl urea. Thus the catalyst screening was focussed to find a catalyst system that supports reaction path A.

2. Catalyst screening

The catalyst screening was performed in a multiparallel way in a minaturised fashion. Up to 10 reactions could be run at a time on a 5 g scale. The small amounts of catalysts employed made it difficult to reduce further the size of these reactions, and no solvent was used. The stoichiometry of acid to isocyanate was 1:1. Reactions were run for 3 h at 70 °C, the amount of catalyst used was 0.01 mol %. Reactions were repeated several times to confirm the results obtained. The samples were

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Keywords: Aliphatic isocyanates; Coatings; Catalyst screening; Acid–isocyanate reaction.

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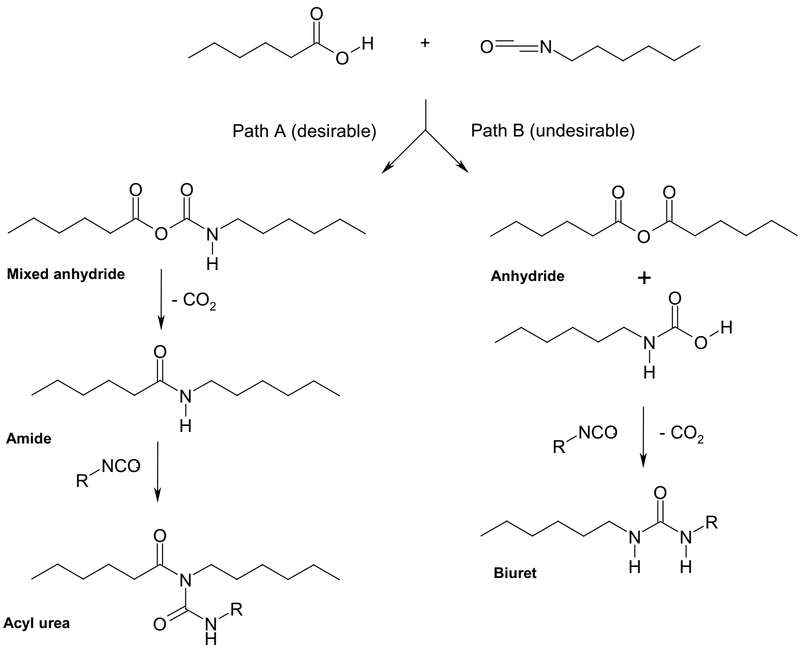


Scheme 1. Reaction pathways for the reaction of carboxylic acids with isocyanates.

investigated using SFC (supercritical fluid chromatography using supercritical CO_2) directly after completion of the reaction to avoid follow up reactions. Nitrobenzene was used as an external standard. For this screening we investigated a representative selection of metals from the periodic table and in a few promising cases we used different salts of the specific metal cation. The first model system investigated was the reaction of hexyl isocyanate with hexanoic acid.

3. Results

By using the correct catalyst, the reaction of linear aliphatic isocyanates with aliphatic carboxylic acids could be dramatically accelerated.

The ranking was made depending on the sum of the yield of amide and acyl urea (the follow up product from the reaction of an isocyanate with an amide). Magnesium salts exhibit the highest catalytic activity, followed by lanthanum, ytterbium and calcium salts. Some of the most active catalysts led to complete turnover after 30 min. Surprisingly, we found that magnesium and ytterbium catalysed reactions were complete within less than 10 min. The reaction could be initiated even at room temperature. After completion the reaction was quenched by diluting the reaction mixture with solvent (THF) and immediate analysis by SFC. The yields for some of the catalysts can be found in Table 2. The selectivities obtained after a reaction time of 30 min may differ from those after 3 h (compare Table 1).

Interestingly, in the case of magnesium there was only a small dependence on the anion. However, we obtained different ratios of carboxylic anhydride versus product and dihexyl urea versus product, respectively. We found this for calcium salts as well. With some catalysts, large amounts of urea are formed as a side product. This is not desirable for further applications.

Big, highly charged cations (e.g., Bi^{3+}) and salts of the first group of the periodic table (lithium, sodium and potassium) and group III salts as well as amine bases and ionic liquids showed only limited catalytic activity. This was also true for catalysts, which are used in the coatings area such as DBTL (dibutyltin dilaurate) or zinc 2-ethylhexanoate. Some of the catalysts under investigation led to colouration of the reaction mixture, which is also prohibitive for use in coatings applications. These included acetylacetonates such as zirconium(IV) acetylacetonate and catalysts containing titanium and copper. We suppose that in situ reduction from Ti(IV) to Ti(III) or Zr(III) takes place; these d^1-species are known to be coloured.

All of the tested catalysts activate the carboxylic acid as proved by the increased formation of carboxylic acid anhydride in comparison to the noncatalysed reactions.

The most active catalysts promote the extrusion of CO_2 from the addition product of the isocyanate and carboxylic acid. We have performed NMR studies to prove this (Scheme 2). The extrusion of CO_2 seems to be the rate determining step in the overall reaction, as can be shown with ^{13}C labelled carboxylic acids. The carbon dioxide stems from the isocyanate group.

4. Investigation of the reaction of a sterically hindered isocyanate (cyclohexyl isocyanate) with an aliphatic carboxylic acid

In order to widen the application we had a closer look at the reaction of a cyclic aliphatic isocyanate with a linear

Table 1. Catalyst (selection) screening for the reaction of hexyl isocyanate with hexanoic acid

Catalyst	Hexyl isocyanate	Hexanoic acid	Carboxylic acid anhydride	Amide	Dihexyl urea	Acyl urea	Sum amide plus acyl urea	Turnover based on hexyl isocyanate [%]	Ratio anhydride/product [%]	Ratio urea/product [%]	Total selectivity [%]
Triethyl borate	26.6	32.0	4.9	23.4	0.7	7.5	**30.9**	73.4	15.9	2.1	82.0
Tetraethylammonium tetrafluoroborate	21.3	25.9	6.2	31.9	1.0	9.0	**40.9**	78.7	15.1	2.4	82.5
Tin(II)-laurate	21.8	25.2	6.3	31.9	0.9	9.3	**41.2**	78.2	15.3	2.2	82.6
HMDS (hexamethyldisilazane)	20.5	25.9	6.2	32.8	1.0	9.1	**41.9**	79.5	14.8	2.4	82.8
Without catalyst	20.2	26.6	6.2	32.9	1.0	9.1	**42.0**	79.8	14.7	2.4	83.0
Butylpyridinium tetrafluoroborate	23.7	26.3	5.4	32.4	1.1	9.7	**42.1**	76.3	12.8	2.7	84.5
Aluminium acetylacetonate	22.8	24.0	5.4	32.9	1.3	9.3	**42.2**	77.2	12.9	3.1	84.0
Sodium chloride	21.2	25.3	5.3	33.4	1.3	9.2	**42.6**	78.8	12.5	3.0	84.6
Aluminum triethylate	21.1	23.5	5.3	33.5	1.0	9.9	**43.5**	78.9	12.3	2.3	85.4
Butyl-pyridinium-hexafluorophosphate	22.7	25.0	5.6	33.7	1.2	9.8	**43.5**	77.3	12.8	2.8	84.5
Triethylamine	21.8	24.4	5.6	34.4	1.2	9.7	**44.1**	78.2	12.6	2.6	84.8
Methyl-butyl-imidazolium-tetrafluoroborate	17.5	27.9	5.2	35.6	1.2	8.6	**44.2**	82.5	11.7	2.7	85.6
DBTL (dibutyltin dilaurate)	19.5	22.9	5.5	35.7	1.1	9.7	**45.4**	80.5	12.2	2.5	85.4
Bismuth(III) 2-ethylhexanoate	20.5	20.8	5.5	37.2	1.5	9.4	**46.5**	79.5	11.8	3.2	84.9
DBN (1,5-diazabicyclo[4.3.0]non-5-ene)	18.7	25.5	5.4	37.4	1.3	9.6	**47.0**	81.3	11.6	2.7	85.8
Lithium hexafluorophosphate	21.7	21.5	6.2	35.9	1.0	11.2	**47.1**	78.3	13.1	2.1	84.8
Cesium methylsulfonate	19.8	22.5	5.8	37.1	1.1	10.0	**47.2**	80.2	12.3	2.4	85.3
Potassium triflate	19.6	23.1	5.8	37.5	1.4	9.8	**47.3**	80.4	12.2	2.9	84.9
Methyl-butyl-imidazolium-hexafluorophosphate	20.1	22.6	5.9	37.2	1.4	10.1	**47.3**	79.9	12.5	2.9	84.6
Bismuth(III) acetate	17.4	21.5	5.5	37.4	1.1	10.0	**47.4**	82.6	11.6	2.4	86.1
Sodium methylsulfonate	18.6	23.4	5.8	38.0	1.2	10.2	**48.1**	81.4	12.0	2.5	85.5
Zinc 2-ethylhexanoate	18.2	22.5	5.8	38.0	1.2	10.5	**48.4**	81.8	11.9	2.5	85.6
Lithium tetrafluoroborate	18.5	21.8	6.1	38.1	1.3	10.4	**48.5**	81.5	12.6	2.6	84.8
Pyridinium triflate	19.0	22.7	5.9	38.4	1.2	10.3	**48.7**	81.0	12.1	2.5	85.5
Sodium triflate	18.4	22.7	6.0	39.1	1.2	10.6	**49.7**	81.6	12.0	2.4	85.5
Lithium chloride	17.5	21.3	6.0	40.0	1.2	10.4	**50.4**	82.5	11.9	2.4	85.7
Bismuth(III) neodecanoate	16.2	21.3	5.6	40.7	1.2	10.4	**51.1**	83.8	11.0	2.3	86.7
Zinc triflate	16.1	21.1	6.1	41.3	1.4	10.7	**51.9**	83.9	11.7	2.7	85.6
Lithium triflate	15.6	20.4	6.1	42.4	1.3	11.1	**53.5**	84.4	11.4	2.4	86.2
Calcium phosphate	12.2	20.8	6.9	44.2	1.5	9.5	**53.7**	87.8	12.9	2.7	84.3
Copper(II) triflate	16.9	18.5	4.3	44.0	1.4	9.9	**54.0**	83.1	8.0	2.5	89.5
Titanium(IV) isopropoxide	13.5	18.8	6.5	43.0	2.0	11.2	**54.2**	86.5	12.0	3.8	84.2
Titanium(IV) 2-ethylhexoxide	14.2	18.0	7.0	42.9	1.8	11.7	**54.6**	85.8	12.9	3.2	83.9
Zirconium(IV) trifluoroacetylacetonate	16.0	14.9	6.7	44.0	1.7	12.1	**56.1**	84.0	12.0	3.0	85.0
Zirconium(IV) 2-ethylhexanoate	11.7	14.1	7.2	49.3	2.6	10.5	**59.9**	88.3	12.0	4.3	83.7
Zirconium(IV) acetylacetonate	8.1	12.8	7.0	55.0	2.3	11.2	**66.2**	91.9	10.7	3.4	85.9
Scandium(III) trifluoromethansulfonate	9.2	8.9	7.1	59.8	4.6	7.9	**67.8**	90.8	10.5	6.7	82.7
Calcium chloride	5.2	11.9	7.6	60.5	3.1	10.4	**70.8**	94.8	10.7	4.4	84.9

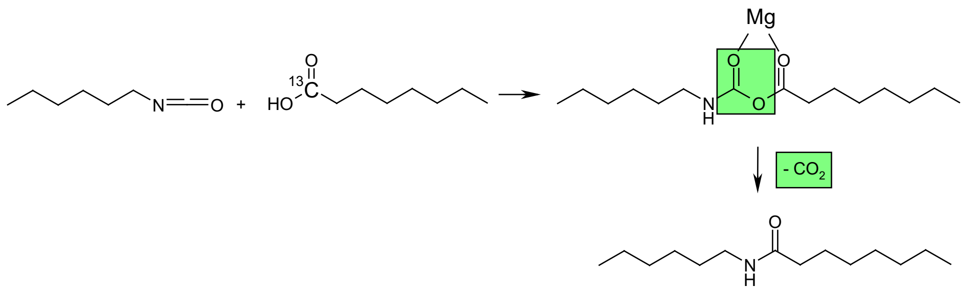
Table 1 (*continued*)

Catalyst	Hexyl isocyanate	Hexanoic acid	Carboxylic acid anhydride	Amide	Dihexyl urea	Acyl urea	Sum amide plus acyl urea	Turnover based on hexyl isocyanate [%]	Ratio anhydride/product [%]	Ratio urea/product [%]	Total selectivity [%]
Scandium(III) acetate hydrate	3.9	8.2	7.7	64.0	4.3	9.5	**73.5**	96.1	10.5	5.8	83.7
Calcium perchlorate	0.4	4.9	8.6	73.9	6.3	4.4	**78.3**	99.6	11.0	8.1	81.0
Calcium bis-(2,2,6,6-tetramethyl-3,5-heptanedionate)	2.0	2.7	7.9	72.1	5.7	6.9	**79.0**	98.0	10.0	7.2	82.9
Calcium stearate	0.0	7.2	8.3	74.3	5.9	4.7	**79.1**	100.0	10.5	7.4	82.1
Lanthanum(III) acetate hydrate	1.1	1.3	8.1	76.1	8.0	4.0	**80.1**	98.9	10.1	10.0	79.9
Magnesium *n*-propoxide	0.0	2.4	6.4	82.2	8.3	0.3	**82.5**	100.0	7.8	10.0	82.2
Magnesium acetylacetonate	0.0	0.0	6.7	82.2	8.8	0.3	**82.6**	100.0	8.1	10.7	81.3
Magnesium stearate	0.0	0.4	6.8	82.9	9.0	0.4	**83.3**	100.0	8.2	10.8	81.1
Magnesium trifluoromethylsulfonate	0.3	1.2	6.4	83.0	9.0	0.4	**83.3**	99.7	7.6	10.8	81.6
Magnesium chloride	0.0	0.8	6.4	83.8	8.4	0.3	**84.1**	100.0	7.6	10.0	82.5
Ytterbium(III) trifluoromethylsulfonate	1.7	2.7	6.0	82.8	6.7	2.4	**85.2**	98.3	7.1	7.9	85.0
Magnesium perchlorate	0.0	2.3	5.3	85.4	6.8	0.3	**85.7**	100.0	6.2	7.9	85.9

Table 2. Reaction within 30 min

Catalyst	Hexyl isocyanate	Hexanoic acid	Acid anhydride	Amide	Dihexyl urea	Acyl urea	Sum amide plus acyl urea	Turnover based on hexyl isocyanate [%]	Ratio anhydride/products [%]	Ratio urea/products [%]	Total selectivity [%]
Without catalyst	37.7	42.5	3	11.5	1.4	3.1	**14.6**	62.3	20.5	9.6	69.9
Butylpyridinium tetrafluoroborate	38.3	72.6	2.8	12.3	1.8	3.7	**16**	61.7	17.5	11.3	71.3
DBTL (dibutyltin dilaurate)	37.3	39.5	3.1	13.7	2	4	**17.6**	62.7	17.6	11.4	71.0
Zinc 2-ethylhexanoate	36.1	40.5	3.1	13.8	2	4.1	**17.9**	63.9	17.3	11.2	71.5
Calcium stearate	15.3	13.1	8.6	51.3	5.3	5.3	**56.5**	84.7	15.2	9.4	75.4
Ytterbium trifluoromethylsulfonate[a]	1.6	18.5	6.3	64.5	6.9	1.7	**66.3**	98.4	9.5	10.4	80.1
Magnesium stearate[a]	2.9	1.9	9.7	74.1	9.3	0.7	**74.9**	97.1	13.0	12.4	74.6

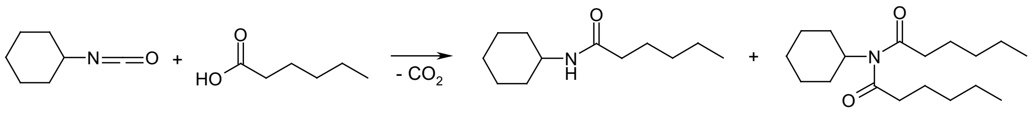
[a] Reaction was complete after 10 min.



Scheme 2. The reaction of carboxylic acids with isocyanates.

aliphatic carboxylic acid using the approach described above (Scheme 3).

The order of catalytic activity as outlined in Table 1 is about the same in this case. Interestingly, the selectivity of the reaction increases strongly with higher reaction rates. The fastest reaction and highest selectivity towards the amide and its follow up product, the acyl urea, was achieved with magnesium perchlorate (or any of the other magnesium catalysts). Other catalysts led to larger amounts of side products. The formation of acyl ureas is unfavoured due to steric hindrance and the stoichiometry used (Table 3).



Scheme 3. Reaction of cyclohexyl isocyanate with hexanoic acid.

Table 3. Reaction of a cyclic isocyanate with a linear aliphatic carboxylic acid

Catalyst	Cyclohexyl isocyanate	Hexanoic acid	Acid anhydride	Amide	Dicyclo-hexyl urea	Acyl urea	Sum amide + acyl urea	Ratio dicyclo-hexyl urea/ product [%]	Ratio anhydride/ products [%]	Total selectivity
Without catalyst	35.9	25.2	5.7	16.7	5.8	3.4	**22.5**	25.8	25.3	48.9
Aluminum triethylate	34.1	26.6	6.2	17.2	5.6	3.5	**22.9**	24.7	26.9	48.4
DBTL (dibutyltin dilaurate)	34.3	25.9	6	17.6	5.6	3.7	**23.2**	24.1	25.9	50
Bismuth(III) acetate	33.6	26.8	5.9	17.7	5.6	3.7	**23.3**	24	25.3	50.7
Sodium triflate	30	30.5	6.7	18.5	5.4	2.8	**23.9**	22.6	27.8	49.6
Potassium triflate	31	30.2	6.3	17.9	6.6	3.1	**24.5**	27	25.6	47.4
Triethyl-amine	27.2	29.9	6.7	20.9	6.4	2.9	**27.3**	23.5	24.6	51.9
Lithium triflate	26.8	23.1	7.2	24.4	7.6	3.3	**32**	23.8	22.5	53.7
Zinc 2-ethyl-hexanoate	24.7	17.3	8.4	30.7	8.1	2.8	**38.8**	20.9	21.6	57.5
Calcium perchlorate	3.9	6.6	11.3	62.1	8.2	1.7	**70.2**	11.6	16.1	72.2
Calcium stearate	5.2	0.6	10.8	65.1	8	1.6	**73.1**	10.9	14.8	74.2
Magnesium stearate	0	0	9.1	79.4	6.6	0.5	**86**	7.6	10.6	81.8
Magnesium perchlorate	0	4.1	5.4	83.5	7.1	0.2	**90.6**	7.9	6	86.2

5. Reaction of a sterically hindered aliphatic carboxylic acid (cyclohexyl carboxylic acid) with an aliphatic isocyanate

From the previous investigations it is known, that sterically crowded carboxylic acids substituted at the α-carbon only react very reluctantly with isocyanates. As a test reaction we chose the reaction of cyclohexane carboxylic acid with butyl isocyanate.

This reaction was also investigated using a multiparallel approach. No additional solvent was added. The reaction was performed at 75 °C for 2 h. The higher temperature was necessary to start the reaction and the results are summarised in Table 4.

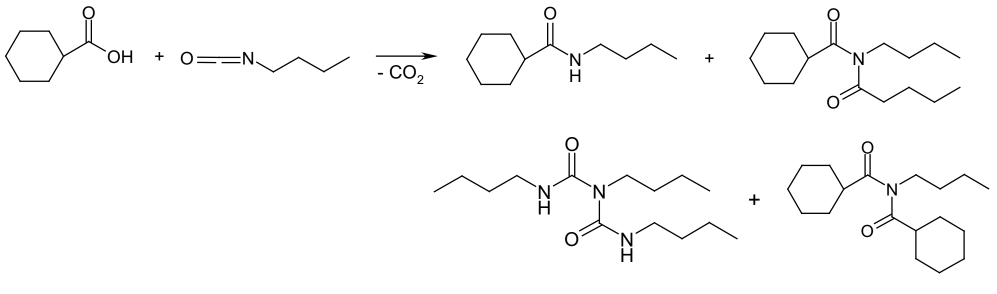
As in the reactions previously described, magnesium salts showed the greatest catalytic activity, followed by calcium salts. In addition, they contributed to a remarkable increase in selectivity towards the formation of the (desired) amide. However, the acylation reaction of cyclohexyl butylamide with cyclohexane carboxylic acid is also catalysed (Scheme 4).

A certain amount of cyclohexane carboxylic acid anhydride is formed as a side product. As a background reaction of the noncatalysed reaction, the reaction of dibutyl urea with butyl isocyanate to give the corresponding biuret takes place. Catalysts that had some activity in the reaction between a linear aliphatic isocyanate with a linear aliphatic carboxylic acid are almost nonactive in the reaction outlined above.

Table 4. Reaction of cyclohexane carboxylic acid with butyl isocyanate

Catalyst	Butyl isocyanate	Cyclohexane carboxylic acid	Amide	Dibutyl urea	Cyclohexane carboxylic acid anhydride	Dibutyl urea biuret	Acyl urea	*N*-Butyl-di cyclohexyl imide	Ratio anhydride/product [%]
Butyl-pyridinium-tetrafluoroborate[a]	12.7	29.3	**26.1**		12.6	12.6	0.3	0.2	48.2
Bismuth(III) acetate[a]	12.4	28.4	**26.7**		12.4	12.4	0.3	0.2	46.3
Triethylamine[a]	13.1	28.7	**27**		12.6	12	0.3	0.2	46.6
DBTL (dibutyltin dilaurate)[a]	12.3	28.9	**27.1**		12.3	12.9	0.3	0.2	45.5
DBU[a]	12.8	29.6	**27.2**		12.5	12.2	0.3	0.2	46.1
Zinc 2-ethylhexanoate[a]	12	28.4	**27.3**		12.8	12.7	0.3	0.2	46.7
Tin(II) laurate[a]	12.6	29.2	**27.5**		12.4	12.2	0.3	0.2	45.1
Aluminium triethylate[a]	11.4	27.9	**28.4**		13.1	12.9	0.3	0.2	46.2
Without catalyst[a]	11	27.5	**28.7**		13.1	12.9	0.3	0.2	45.6
Sodium triflate[a]	12	28	**28.8**		12.5	11.7	0.3	0.2	43.6
Potassium triflate[a]	11.9	28	**29.1**		12.8	11.9	0.3	0.2	43.9
Lithium triflate[a]	10.6	26.8	**29.5**		13	13.2	0.3	0.3	44.2
Calcium chloride	0.9	10.9	**56.2**	4.1	16.9	7.6	0.3	0.5	30
Ytterbium trifluoromethylsulfonate	1.5	9.1	**59.3**	3.8	15.1	6.2	0.3	0.4	25.5
Calcium perchlorate	0.8	9.1	**59.5**	5.2	16.7	5.5	0.5	0.7	28
Calcium stearate	0.2	9	**59.8**	5.2	16.8	5.5	0.4	0.8	28
Magnesium stearate	0	4.6	**66.7**	7.5	14.4	0.6	1.5	2.4	21.6
Magnesium perchlorate	0	4.6	**74.5**	5.2	12.1	0.6	1.1	1.9	16.2

[a] In these cases a comprehensive interpretation of the experimental results was difficult since the amide and the dibutyl urea cannot be separated using SFC. The figures are therefore approximate.



Scheme 4. Reaction of butyl isocyanate with cyclohexane carboxylic acid.

6. Conclusion

In an investigation of the reaction of isocyanates with aliphatic carboxylic acids highly active catalysts could be identified. In particular, magnesium and calcium salts exhibited considerable catalytic activity. These catalysts are equally active in the reaction of linear aliphatic isocyanates with secondary aliphatic carboxylic acids and in the reaction of secondary aliphatic isocyanates with linear aliphatic carboxylic acids. In these cases a remarkable increase in selectivity was observed. The amount of side products produced by each catalyst for each reaction also has to be taken into account.

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