DOI: 10.1002/adsc.200800268

Domino Catalysis in the Direct Conversion of Carboxylic Acids to Esters

I. Held,[a] P. von den Hoff,[a] D. S. Stephenson,[a] and H. Zipse[a,*]

[a] Department Chemie und Biochemie, LMU München, Butenandtstr. 5–13, 81377 München, Germany
Fax: (+49)-89-2180-77738; e-mail: zipse@cup.uni-muenchen.de

Received: May 2, 2008; Revised: June 19, 2008; Published online: July 24, 2008

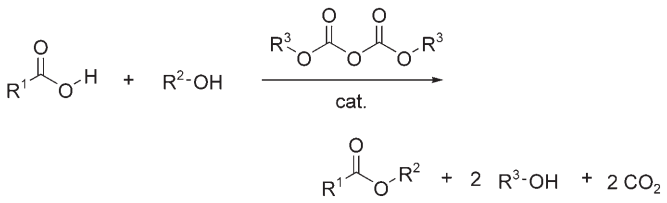
Supporting information for this article is available on the WWW under http://asc.wiley-vch.de/home/.

Abstract: The combined use of high concentration conditions, auxiliary bases, and new catalysts allows for the rapid synthesis of sterically hindered carboxylic acid esters at room temperature. Mechanistic analysis indicates the intermediate formation of acid anhydrides and subsequent rate-limiting transformation to the ester products.

Keywords: *ab initio* calculations; acylation; esterification; nucleophilic catalysis; sterically hindered carboxylates

Introduction

The direct conversion of carboxylic acids to esters through *in situ* activation and subsequent reaction with alcohols represents a well established procedure for the synthesis of esters. Numerous procedures are based on the use of carbodiimides as activating reagents, which generate urea by-products in the course of the reaction.[1] Problems with the separation of these by-products have recently led to attempts to use dialkyl dicarbonates as activating reagents.[2–4] The by-products formed in these reactions are CO_2 and a new alcohol (Scheme 1).

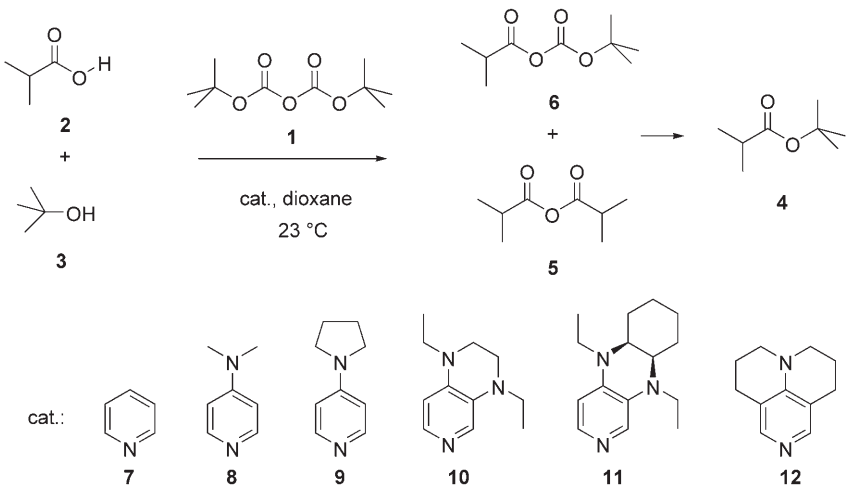


Scheme 1.

Earlier work by Takeda et al. and by Gooßen et al. has shown that this approach has great general value under the condition that the "substrate" alcohol (here R^2-OH) is significantly more reactive than the "reagent" alcohol (here R^3-OH).[2–4] This requirement is easily fulfilled through the use of di-*tert*-butyl dicarbonate (Boc_2O, **1**). It was also found that the reaction can be accelerated by a wide range of Lewis acids[3] as well as by electron-rich pyridines such as *N*,*N*-dimethylpyridine (DMAP).[2,4] The base-catalyzed approach has also found application in the synthesis of amides and peptides.[5,6] The recent development of more potent acylation catalysts based on the DMAP motif[7–10] now prompts us to reinvestigate the Takeda–Gooßen direct esterification procedure, in particular with respect to its utility for the synthesis of sterically highly hindered esters.

Results and Discussion

Recent mechanistic studies of the acylation of alcohols with anhydrides suggest that the rate of these reactions depends linearly on the concentration of all reactants and on that of the catalyst.[11,12] Given the experimentally observed intermediacy of mixed anhydrides in the synthesis of peptides,[13] one may anticipate that the rate of the transformation shown in Scheme 1 will similarly benefit from high reagent and catalyst concentrations. To this end initial studies were performed using the reaction of isobutyric acid (**2**) with *tert*-butanol (**3**) at 23 °C under high concentration conditions[14] to give the corresponding ester **4** (Scheme 2). One equivalent of 1,4-dioxane relative to acid **2** was added to the reaction mixture as an internal standard for ^{1}H NMR spectroscopy and a small excess of 1.3 equiv. of Boc_2O was used in order to achieve complete turnover of acid. In the presence of 0.05 equiv. of DMAP (**8**) as the catalyst the following observations can be made: acid **2** disappears quantita-



Scheme 2.

tively within the first 20 min of the reaction (Figure 1) as indicated by the isopropyl doublet signal at 1.14 ppm in the ^{1}H NMR spectrum. At the same time two new, strongly overlapping doublet signals appear at 1.190 ppm and 1.195 ppm. The former of these signals is identical to isobutyric anhydride **5**, while the latter is most likely that of the mixed anhydride **6** (Scheme 2). The intensity of these two anhydride signals peak at around 20 min reaction time, where both anhydrides combined account for 96% of the substrate concentration. It is only at this time that formation of ester product **4** sets in, detectable through a doublet signal at 1.06 ppm. The reaction is essentially complete after 170 min, illustrating the benefit of high concentration reaction conditions.

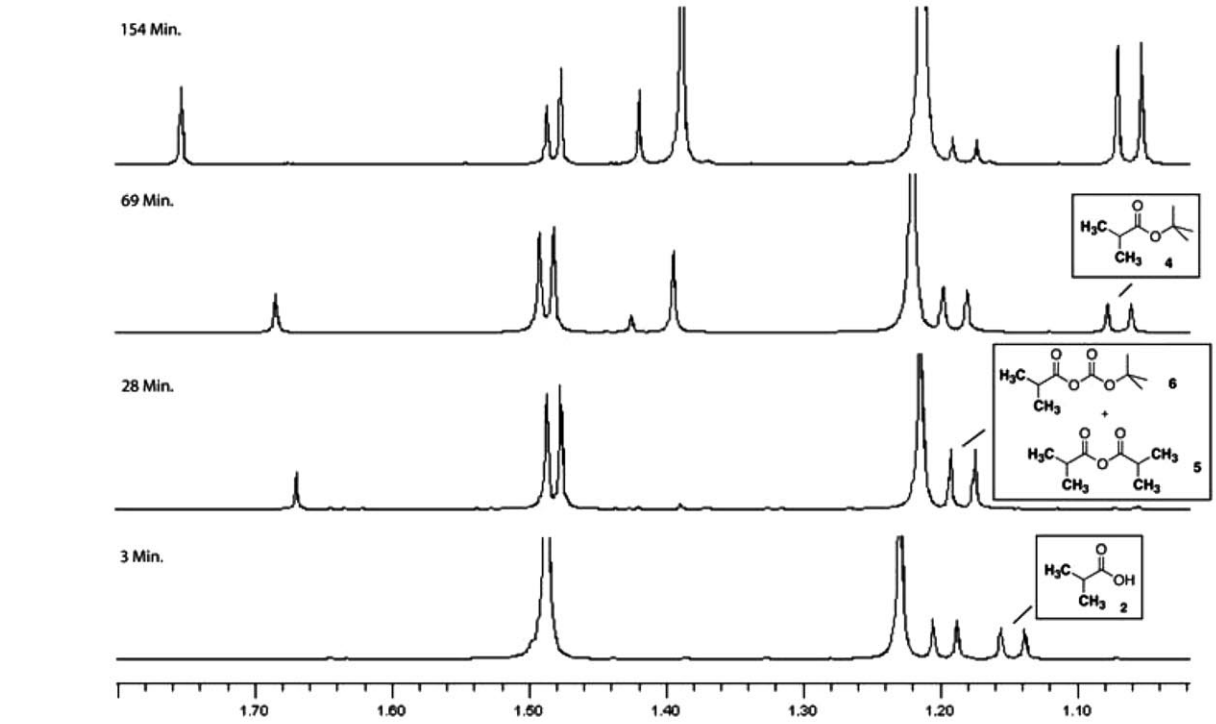
Analysis of the time course of the reactant and product concentrations through monitoring of the isopropyl doublet and *tert*-butyl singlet signals of **1**–**6** also shows that formation of the intermediate anhydrides occurs much more rapidly (approximate $\tau_{1/2}=$ 3 min) than formation of ester product **4** (approximate $\tau_{1/2}=65$ min).

Higher absolute rates are observed when using 0.10 equiv. catalyst (Figure 2a). The initial lag phase for ester formation is significantly reduced under this condition and the half-life for the DMAP-catalyzed process now amounts to $\tau_{1/2}=40$ min. The rate of reaction can be further accelerated by using more electron-rich pyridine derivatives than DMAP such as those shown in Scheme 2. While only a small acceleration is observed for the commercially available PPY (**9**), better results are obtained with the diaminopyridine compounds **10** and **11**. Still, the half-lives observed for DMAP (**8**) and the best catalyst **11** vary by less than a factor of two, a much smaller difference than measured for the reaction of anhydrides with alcohols under basic reaction conditions.[9]

Whether similar rate enhancements can also be achieved through addition of an auxiliary base was explored for the DMAP-catalyzed process through addition of 2 equiv. (relative to acid **2**) of triethylamine (NEt_3). In contrast to the reaction lacking the auxiliary base depicted in Figure 1 and Figure 2a, the reaction now has essentially no lag phase and progresses with $\tau_{1/2}=47$ min in the presence of 0.05 equiv. of DMAP as the catalyst. Complete turnover is achieved after approximately 130 min. Similar observations can be made for the more active catalysts **9**, **11**, and **12**. Best results are obtained for catalyst **11** in the presence of 2 equiv. of NEt_3 with $\tau_{1/2}=19$ min and complete turnover in less than 60 min. (Table 1). An experiment performed at a slightly larger scale with 0.10 equiv. DMAP as catalyst and 2 equiv. NEt_3 turns over with $\tau_{1/2}=21$ min. The final conversion measured by ^{1}H NMR spectroscopy is 98% and only one product can be detected at this stage. The final yield of product **4** amounts to 75% after isolation and purification by distillation (Table 1).

All of the results described above can be accounted for by assuming the domino catalysis mechanism[15–20] shown in Scheme 3.

This mechanism involves formation of mixed anhydride **6** through a first catalytic cycle driven by pyridine catalysts such as DMAP. The mixed anhydride is subsequently transformed in a second catalytic cycle to an ester product such as **4**. In both catalytic cycles one equivalent *t*-BuOH (**3**) is formed through decarboxylation of the *tert*-butylcarbonic ester or its anion. The evolution of CO_2 can be observed right from the beginning of the experiment in form of a steady stream of bubbles escaping from the reaction solution (see Supporting Information). The evolution of CO_2 to the gas phase makes the reaction practically irreversible, but does not necessarily deliver the enthalpic



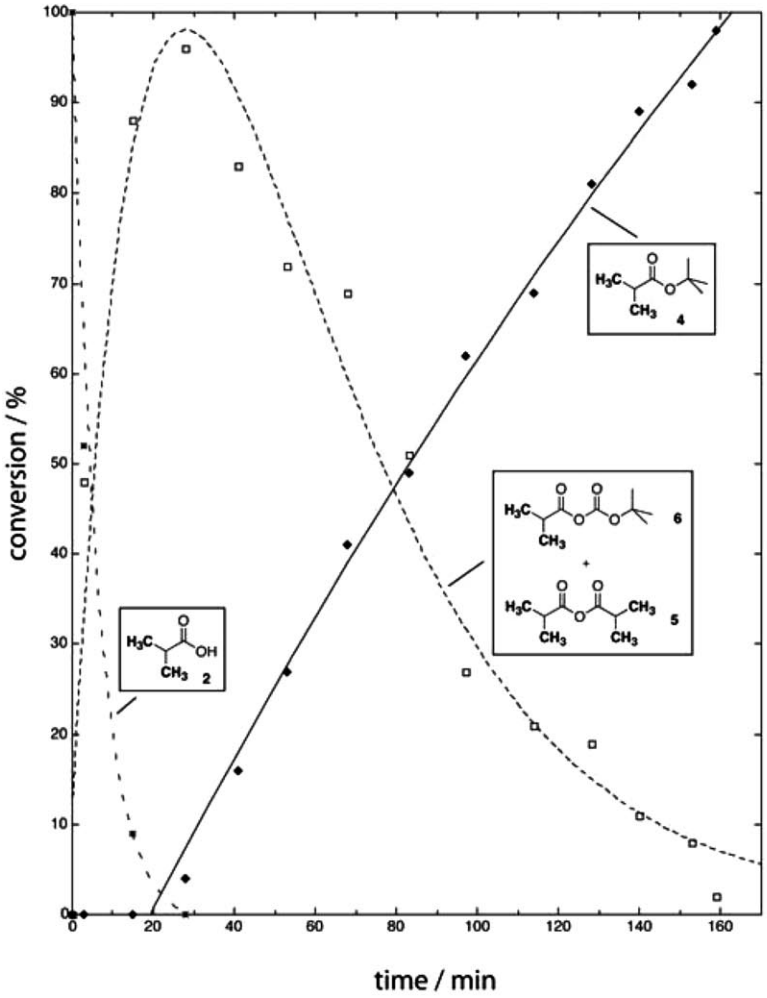


Figure 1. DMAP-catalyzed reaction of isobutyric acid (**2**) with Boc_2O (**1**) and *tert*-butanol (**3**) through intermediate formation of anhydrides **5** and **6**.

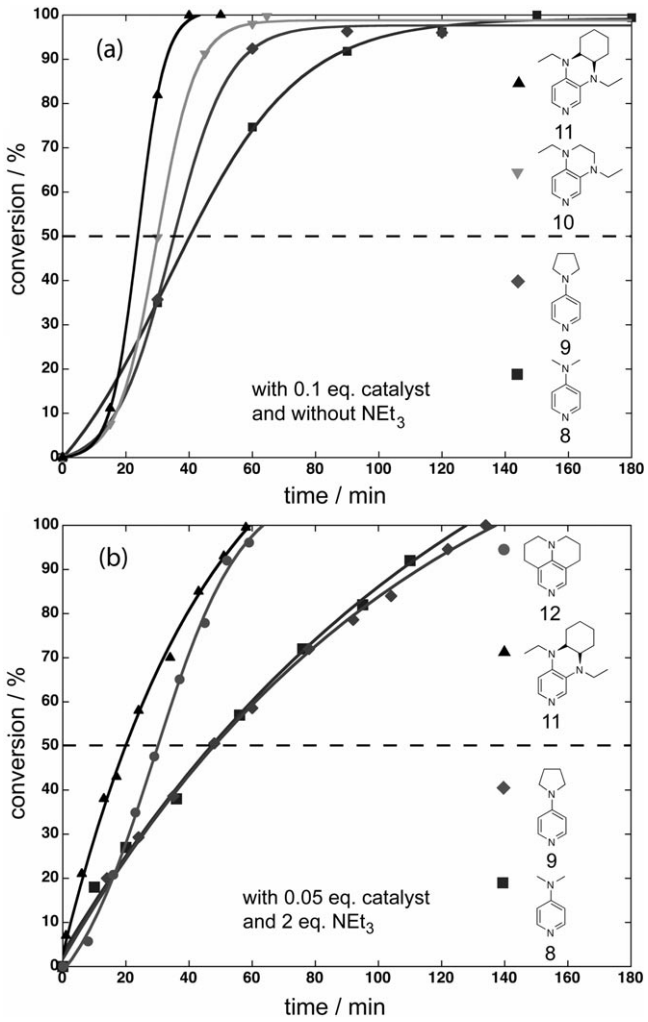


Figure 2. Reaction of isobutyric acid (**2**) with *tert*-butanol (**3**) and Boc_2O (**1**) under high-concentration conditions at room temperature (**a**) in the presence of 0.1 equiv. catalyst, or (**b**) in the presence of 0.05 equiv. catalyst and 2 equiv. NEt_3.

driving force of the reaction. This latter point has been addressed through calculation of the reaction enthalpies at different stages of the overall substrate reaction at the G3(MP2)B3 level of theory (Table 2). The accuracy of the G3(MP2)B3 method in predicting the thermodynamic stability of a variety of small and medium sized molecular systems has been estimated as 5.2 kJ mol^{-1}.[21,22]

The results in Table 2 show that all steps of the overall substrate reaction are exothermic. The most exothermic step along the reaction pathway involves reaction of *tert*-butanol (**3**) with mixed anhydride **6** to yield the ester product **4** and carbonic acid *tert*-butyl ester. This step is exothermic by 44.2 kJ mol^{-1} and thus accounts for slightly more than half of the overall reaction enthalpy. The two decomposition reactions of carbonic acid *tert*-butyl ester to CO_2 and *tert*-butanol (**3**) yield a reaction enthalpy of 15.3 kJ mol^{-1} each, and, if taken together, provide somewhat less than half of the overall reaction enthalpy. The driving force of the overall substrate reaction thus stems to similar parts from the generation of CO_2 as a thermochemically stable by-product and from the formation of a thermodynamically stable ester C–O bond. Evolution of CO_2 from the reaction mixture provides, of course, an additional entropic driving force.

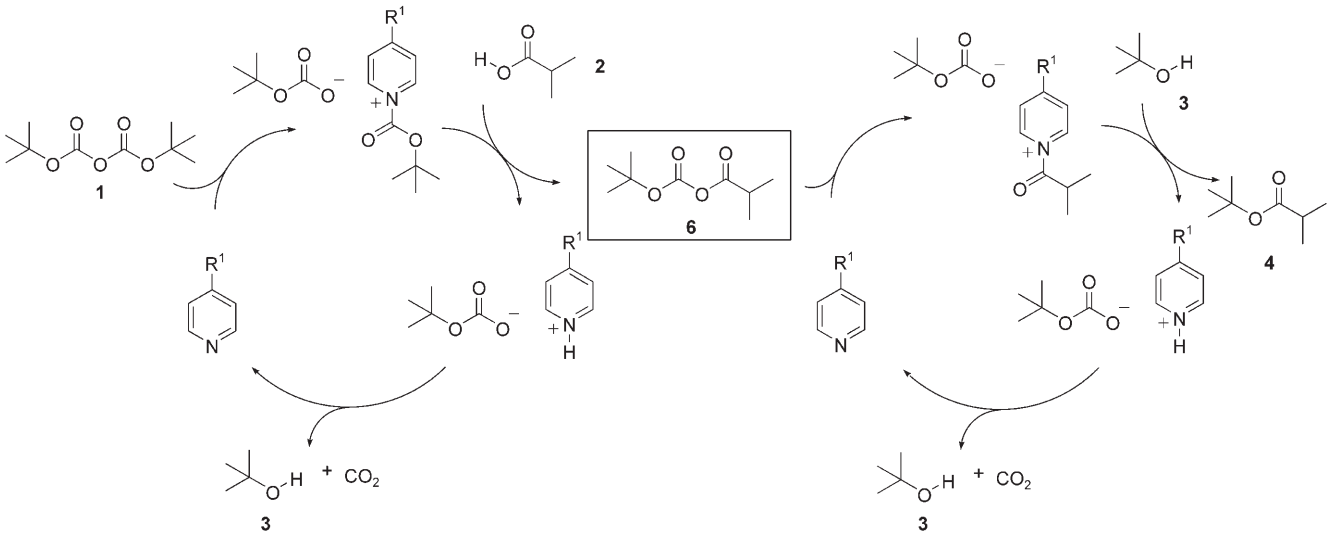
The initial lag phase observed experimentally at low catalyst concentrations and in the absence of auxiliary base may be caused by inactivation of the catalyst within the first cycle (formation of stable ion pairs) or outside of the cycle through complexation with acid substrate (formation of a strong hydrogen bond or even protonation). Elimination of the lag phase through addition of 2 equiv. of NEt_3 is in support of this latter option as the 40-fold excess of auxiliary base over the catalytic base DMAP will lead to a largely reduced extent of complexation/protonation of the latter as described through the competitive complexation equilibria in Scheme 4.

That initial deactivation of the pyridine catalysts through complexation with substrate acid **2** is at the heart of the problem is also supported by analysis of the time-dependence of product development. In the presence of the best catalysts **11** and NEt_3 as the auxiliary base, the reaction actually speeds up with increasing turnover (Figure 2b): while the first 50% of the ester is formed after 22 min, complete conversion is achieved already after 40 min. This can most simply be explained by assuming that even with 2 equiv. of auxiliary base added the catalyst still remains partially deactivated through complexation with acid **2** at the beginning of the reaction. With progressive conversion of the substrate acid this deactivation is steadily reduced, freeing up more catalyst as the reaction proceeds. That DMAP (**8**) and PPY (**9**) have almost the same catalytic efficiency in these experiments may also be due to the formation of hydrogen bonded complexes of acid substrate and the pyridine base. Recent determination of nucleophilicity parameters for these two pyridines identified a large solvent effect, leading to higher nucleophilicities for PPY than for DMAP in dichloromethane, but to the reverse order in protic solvents such as H_2O.[23] The combined presence of *t*-BuOH and acidic substrates may lead to a similar reduction of the intrinsically higher nucleophilic activity of PPY in this case. It should be added that the reaction proceeds extremely slowly in the absence of any of the pyridine bases (but with 2 equiv. NEt_3 present) with a half-life of 5 days 16 h. When the auxiliary base NEt_3 is also missing, no product formation can be detected within 16 days.

Table 1. Direct synthesis of sterically hindered esters through Boc_2O-mediated reaction of acids and alcohols at 23 °C.[a]

Acid	Alcohol	Product	Catalyst (equiv.)[b]	NEt_3 [equiv.][b]	$t_{1/2}$ [min]	Conversion [%][c]	Yield [%][d]
2	**3**	**4**	**8** (0.1)	–	40	99	71
			8 (0.05)	–	84	88	–
			9 (0.1)	–	35	100	–
			10 (0.1)	–	30	98	–
			11 (0.1)	–	23	100	–
			8 (0.1)	2.0	21	98	75%
			8 (0.05)	2.0	47	99	–
			8 (0.025)	2.0	121	73	–
			9 (0.05)	2.0	49	100	–
			12 (0.05)	2.0	31	93	–
			11 (0.05)	2.0	19	96	–
			–	2.0	8215	69	–
13	**3**	**14**	**9** (0.05)	2.0		–[e]	93
15	**3**	**16**	**9** (0.05)	2.0	11	100	85
			11 (0.05)	2.0	<2.5	–	–
17	**3**	**18**	**9** (0.05)	2.0	164	99	89
			11 (0.05)	2.0	99	96	–
			-	2.0	10500	58	–

[a] 1.3 equiv. of Boc_2O have been used.
[b] Equivalents relative to acid.
[c] Final conversion to ester product determined by ^1H NMR measurements.
[d] Isolated yield after product purification.
[e] Multiple signal overlaps in the ^1H NMR spectrum.



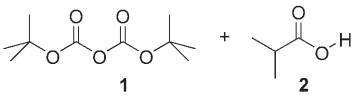
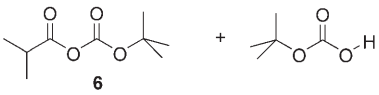
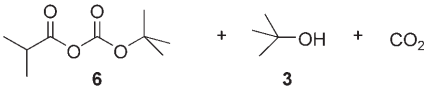
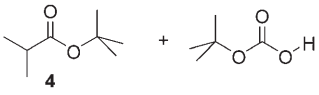
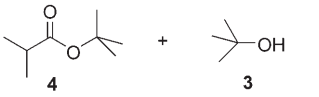
Scheme 3.

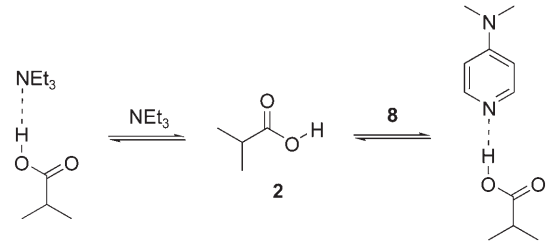
Synthesis of *tert*-Butyl Esters

The optimized reaction conditions for the conversion of isobutyric acid **2** with *t*-BuOH (**3**) offer a very attractive general protocol for the conversion of sterically hindered substrates, the only limitation being alcohols of higher steric hinderance than *t*-BuOH itself. The synthetic value of this protocol was tested for a number of sterically hindered substrates as well as other "difficult" systems (Scheme 5).

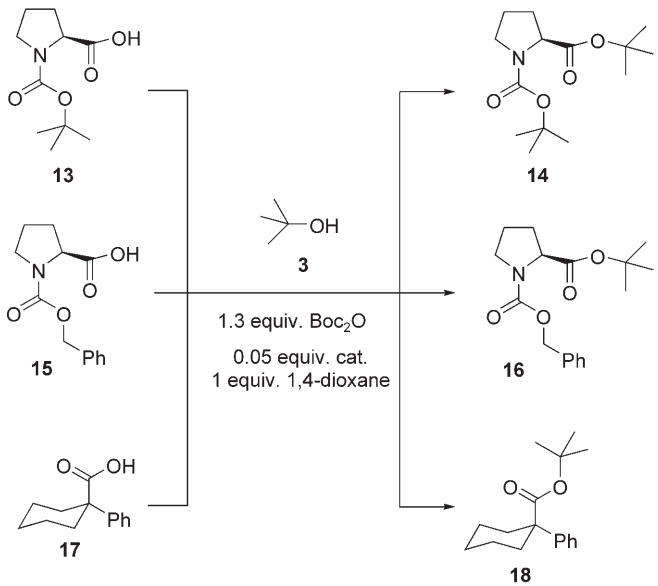
The synthesis of ester **14** is complete within 2 h as determined by TLC and yields 93% product after column chromatography. The time course of this reaction could, unfortunately, not be monitored by ^1H NMR spectroscopy due to multiple signal overlaps. The optical rotation measured for **14** shows no loss of stereochemical integrity. Why formation of **14** is not effective under the original conditions used by Gooßen et al.[4] is not clear at this point. The reaction of Z-protected proline **15** with *t*-BuOH (**3**) is similarly

Table 2. Enthalpy profile at 298 K of the substrate reaction of Boc_2O (**1**) with isobutyric acid (**2**) as determined at the G3(MP2)B3 level of theory.

Reaction stage	ΔH_{rel} (kJ mol^{-1})
	0.0
	−3.7
	−19.0
	−63.2
	−78.6



Scheme 4.



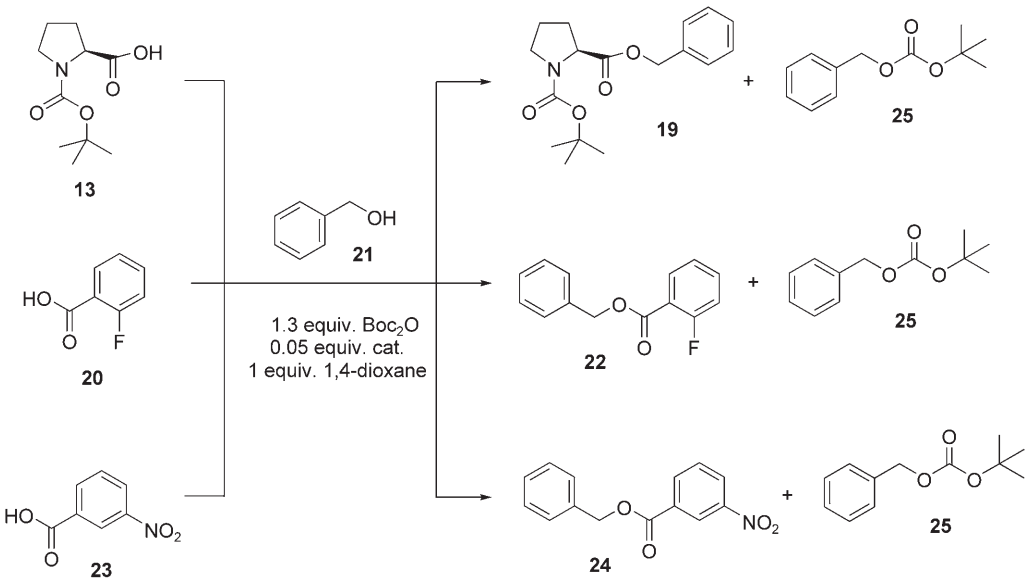
Scheme 5.

efficient as that of Boc-protected proline **13**, leading to ester **16** as the sole product with a half-life of $\tau_{1/2}$ = 11 min using 0.05 equiv. PPY (**9**) as the catalyst. Complete conversion is achieved after 27 min. Use of the more active catalyst **11** leads to complete conversion within 5 min under identical conditions, implying a reaction half-life of less than 2.5 min. The optical rotation measured for product **16** in ethanol at 23 °C is identical to literature values for this compound, indicating no measurable loss of stereochemical information under the reaction conditions used here.[2,24,25] Similar results have been obtained by Takeda et al. in the presence of 0.3 equiv of DMAP (**8**) and *t*-BuOH (**3**) as solvent at room temperature.[2] Complete conversion was achieved under these conditions after 55 min. The newly proposed protocol thus provides a more than 10-fold speedup over the original procedure while using only 0.05 equiv. instead of 0.3 equiv. of catalyst. Under the condition that the reaction rate depends linearly on the catalyst concentration, this represents a more than 60-fold speedup through the new catalyst/reagent combination. The esterification of phenylcyclohexylcarboxylic acid **17** with *t*-BuOH (**3**) was used as a test for the transformation of more sterically demanding substrates. In the absence of any catalyst the reaction is very sluggish and reaches 50% conversion after 10,500 min. In the presence of 0.05 equiv. of PPY (**9**) and 2 equiv. of NEt_3 the reaction is approx. 64 times faster than the background reaction. Using the more potent catalyst **11** the speedup over background amounts to a factor of 106. Using traditional DCC/DMAP conditions in CH_2Cl_2 the conversion of acid **17** to *tert*-butyl ester **18** is not successful and the reaction stops at the stage of the anhydrides.[26]

Synthesis of Benzyl Esters

The successful application of the optimized protocol for the synthesis of *tert*-butyl esters suggests that synthesis of the sterically less hindered benzyl esters should be straightforward and fast. Based on the measured reaction rates for the reaction of primary and tertiary alcohols with acetic anhydride, the reaction with primary alcohols is expected to be approx. 200 times faster than the reaction of a tertiary alcohol.[12] It is therefore surprising that the original Gooßen protocol was reported to fail in coupling benzyl alcohol with either 2-fluorobenzoic acid (**20**) and 3-nitrobenzoic acid (**23**) (Scheme 6 and Table 3).[2]

Repeating these reactions using the new protocol described above with 0.05 equiv. of DMAP (**8**) as the catalyst yields the desired benzyl esters **22** and **24** together with substantial amounts of Boc-protected benzyl alcohol (**25**) (Scheme 6). Monitoring substrate conversion by ^{1}H NMR spectroscopy confirms the ex-



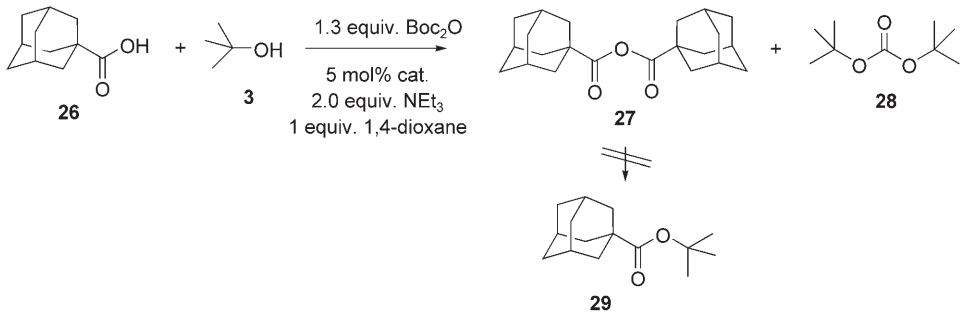
Scheme 6.

Table 3. Direct synthesis of benzyl esters through Boc_2O-mediated reaction of acids and benzyl alcohol at 23 °C.[a]

Acid	Alcohol	Product	Catalyst (equiv.)[b]	NEt_3 [equiv.][b]	$t_{1/2}$ [min]	Conversion [%][c]	Yield [%][d]
13	**21**	**19**	**8** (0.05)	2	–	–	–
			7 (0.05)	2	–	–	95
20	**21**	**22**	**8** (0.05)	2	~2	66	–
			7 (0.05)	2	108	74	70
			–	2	425	66	–
23	**21**	**24**	**8** (0.05)	2	~1	52	–
			7 (0.05)	2	–	–	84

[a] 1.3 equiv. of Boc_2O have been used.
[b] Equivalents relative to acid.
[c] Final yield of ester product determined by ^1H NMR measurement.
[d] Isolated yield after product purification.

pected high reactivity of benzyl alcohol, leading to reaction half-lifes of 2 min or less. The new protocol was also used for the synthesis of proline benzyl ester **19**, whose formation had previously been completed with the original Gooßen protocol in 89% yield. None of the ester product **19** was detected with the new protocol, which in this case yields Boc-protected benzyl alcohol (**25**) exclusively. Given the extremely short reaction times observed with DMAP (**8**) as the catalyst, all three reactions shown in Scheme 6 were repeated with pyridine (**7**) as the catalyst. Earlier studies of the catalytic potential of pyridine bases have shown that the efficiency of **8** is approx. 10^4 higher than that of **7**.[27] The efficiency difference between these two catalysts found here is somewhat smaller at approx. 5×10^2, but a more accurate determination was not possible due to the very short reaction times for **8**. One remarkable consequence of the use of **7** as a much less reactive catalyst is the retardation of the formation of Boc-protected benzyl alcohol (**25**) and the increased yield of the desired benzyl esters **19**, **22**, and **24**. The optical rotation of ester **19** is in agreement with the literature and implies no loss of stereochemical information.[28] These results are not easily reconciled with the mechanism shown in Scheme 3. Benzyl ester **25** could potentially form through competing reaction of benzyl alcohol with the acylpyridinium cation generated in the first cycle, implying that this competition is favorable for benzyl alcohol in the case of DMAP (**8**, $R^1 = NMe_2$), but not favorable in the case of pyridine (**7**, $R^1 = H$). Considering the differences in basicity of these catalysts it seems more likely that the direct base-catalyzed reaction of **21** with Boc_2O (**1**) competes with the domino catalysis mechanism shown in Scheme 3. The first part of this domino mechanism proceeds without participation of the alcohol, and it should thus be possible to modify the reaction conditions such that



Scheme 7.

enough time is permitted for the initial formation of the mixed anhydride intermediate. This possibility was explored through reaction of proline derivative **13** and Boc_2O (**1**) in the presence of 0.05 equiv. of DMAP (**8**) or PPY (**9**) and 2 equiv. of NEt_3 for 35 min at 23 °C, followed by addition of a benzyl alcohol (**21**), which yields 75% ester **19** after product isolation and purification.

Limitations of the Procedure

In order to test the utility of the new protocol for systems where previous approaches have failed, the direct coupling of adamantanecarboxylic acid (**26**) with *tert*-butanol (**3**) was studied next (Scheme 7). Using 0.05 equiv. of DMAP as catalyst yields anhydride **27** in 50% yield and di(*tert*-butyl) carbonate (**28**) in 29% yield, but none of the desired ester **29** after 12 h reaction time at room temperature. Using more forcing conditions (60 °C, 24 h reaction time) did not alter this result, even when combined with larger concentrations of the most active catalyst **11** (0.20 equiv.).

It thus appears that the acylpyridinium cation generated from carboxylic acid **26** is so sterically hindered that reaction with a tertiary aliphatic alcohol does not proceed at an appreciable rate and that the reaction therefore stops at the stage of the anhydride **27**. Once all the acid **26** has been consumed, the remaining reagent slowly transforms into the carbonate **28**.

Conclusions

A modified version of the Takeda–Gooßen esterification reaction has been developed, in which the use of highly potent catalysts and an auxiliary base has been combined with high concentration reaction conditions in order to reduce reaction times from hours or days to only minutes at room temperature. This facilitates the synthesis of sterically hindered esters dramatically. Recently developed 3,4-diaminopyridine catalysts such as **11** consistently outperform commercially available catalysts such as DMAP (**8**) and PPY (**9**). Side reactions encountered in coupling reactions of benzyl alcohols can be alleviated through simple modification of the reaction conditions or through the use of strongly deactivated catalysts. The direct coupling of adamantanecarboxylic acid with *tert*-butanol is, unfortunately, not successful even under forcing conditions and thus remains as a challenge for the development of new coupling protocols.

Experimental Section

All Schlenk flasks used for the esterification reactions were kept overnight in a 125 °C hot oven and were afterwards dried again under high vacuum with a hot air blower. The flask was cooled down under a nitrogen atmosphere. The ethanol bath for kinetic measurements was tempered at 23 °C with a JULABO F-25 thermostat. Dichloromethane was stirred over concentrated H_2SO_4 for 24 h, then separated from the inorganic phase, washed twice with saturated aqueous $NaHCO_3$ solution, and distilled under nitrogen atmosphere from CaH_2. All deuterated solvents, triethylamine, and pyridine were freshly distilled under a nitrogen atmosphere from CaH_2. Isobutyric acid was distilled from P_2O_5 under nitrogen atmosphere and kept in a Schlenk flask over molecular sieves (4 Å). All other chemicals were purchased from commercial suppliers at the highest available grade and used as such without any further purification.

General Procedure for Kinetic Measurements (a)

In a 10-mL Schlenk flask was added under a nitrogen atmosphere 1 equiv. (5.0 mmol) acid, 1.1 equiv. *tert*-butanol, 1 equiv. dioxane, and 2 equiv. NEt_3. The reaction mixture was stirred until homogenous, cooled to −20 °C and combined with 1.3 equiv. of molten Boc_2O. The reaction mixture was stirred for another 2 min at this temperature, the cooling bath was removed, the flask was equipped with a nitrogen-filled balloon and then immersed in a temperature-controlled ethanol bath held at 23 °C. At this point the reaction visibly starts as indicated through evolution of CO_2 and the reaction mixture turns yellow after some minutes. The moment when the flask was immersed into the thermostat held at 23 °C marks the zero point on the reaction time scale. In defined intervals an aliquot of 0.05 mL was taken

out of the reaction mixture with a syringe and 0.5 mL of dry deuterated solvent was added. The conversion of the reaction was monitored by ^{1}H NMR spectroscopy through comparison of the signal intensities of the *tert*-butyl group of ester product with that of the internal standard dioxane at 3.67 ppm according to Eq. (1). The data points collected in this way were fitted with either a sigmoidal or monoexponential function [Eq. (2) an Eq. (3)]. Half-life times are equal to the time with respect to 50% conversion. For the fitting of the mixed and symmetrical anhydride data points a peak function [Eq. (4)] was used. This function describes the profile of the data points in a reasonable manner.

$$Conv. = \frac{(I_{Ester}/9)}{(I_{dioxane}/8)} \times 100\% \quad (1)$$

$$Conv. = t_0\left(\frac{1}{1+\left(\exp\frac{(-t-t_0)}{k}\right)^c}\right)+c \quad (2)$$

$$Conv. = A\exp(-t-t_0)k)+c \quad (3)$$

$$Conv. = t_0\left(\exp\left(-\frac{(t-t_0)}{k}\right)\right)\cdot\left(\left(\left(\frac{(t-t_0)}{k}\right)+d-1\right)\Big/(d-1)\right)^{d-1}+const. \quad (4)$$

All constants in Eqs. (2)–(4) have no physical meaning and only serve to determine the half-life times as described before. Relevant signals of reactants and products have been collected in Table 4.

General Procedure for the Synthesis of *tert*-Butyl Esters (b)

In a 20-mL Schlenk flask was added 1 equiv. (5.0 mmol) acid, 0.5 mL (5.5 mmol) *tert*-butanol, 0.427 mL (5 mmol) 1,4-dioxane, 1.39 mL (10 mmol) NEt_3, and 0.05 equiv. PPY. The reaction mixture was stirred until homogeneous and cooled to −20 °C. Afterwards 1.39 mL (6.5 mmol) of molten Boc_2O was added, stirred for 2 min at this temperature and then allowed to warm to room temperature. Stirring was continued depending on the substrate for 4 to 24 h and then worked-up as specified.

Table 4. ^{1}H NMR signals (in ppm) of reactants and products for the reaction shown in Scheme 2.

Compound	δ *t*-Bu (9H, s)	δ *i*-Pr (6H, s)	δ *i*-Pr (1H, sep)	Other
1	1.49	–	–	–
2	–	1.14	2.52	–
3	1.22	–	–	1.88 (1H, s, OH)
4	1.39	1.06	2.39	–
5	–	1.190	2.62	–
6	1.48	1.195	2.59	–

tert-Butyl Isobutyrate (4)

The reaction was carried out as described in procedure (**b**) with 10 mmol of isobutyric acid. After stirring for 6 h the reaction mixture was diluted with 10 mL of DCM and transferred to a separatory funnel, then washed with 10 mL of 2N HCl, 10 mL saturated aqueous $NaHCO_3$ and 10 mL demineralized water. The organic phase was dried over Na_2SO_4 and afterwards fractionally distilled (41 °C, 26 mbar). This furnishes **4** as a colorless liquid; yield: 1.07 g (7.45 mmol, 75%).

tert-Butyl 1-Phenylcyclohexanecarboxylate (18)

The reaction was carried out as described in general procedure (**b**) with 5 mmol 1-phenylcyclohexanecarboxylic acid. The reaction mixture was stirred for 24 h, then diluted with 10 mL DCM and directly purified by flash chromatography on silica gel (10% EtOAc/isohexane) to afford a white solid; yield: 1.15 g (4.45 mmol, 89%).

(*S*)-*tert*-Butyl Benzyl Pyrrolidine-1,2-dicarboxylate (16)

The reaction was carried out on a 5-mmol scale of **15** according to procedure (**b**), except for the additional use of 2 mL dry DCM. The reaction mixturewas stirred for 5 h, diluted with 10 mL DCM, transferred into a separatory funnel, washed with 10 mL 2N HCl and 10 mL saturated aqueous $NaHCO_3$ solution. The organic phase was dried over $MgSO_4$ and the solvent distilled off *via* rotary evaporation. The crude product was purified by flash chromatography on silica gel (3/10, EtOAc/isohexane) to afford a white solid; yield: 1.29 g (4.22 mmol, 85%).

(*S*)-Di-*tert*-butyl Pyrrolidine-1,2-dicarboxylate (14)

The reaction was carried out as described in general procedure (**b**) with 5 mmol (*S*)-1-[(*tert*-butoxy)carbonyl]pyrrolidine-2-carboxylic acid (**13**). The reaction mixture was stirred for 2 h, then diluted with 10 mL DCM and transferred into a separatory funnel. The organic layer was washed with 10 mL 2N HCl and 10 mL aqueous $NaHCO_3$ solution. The organic phase was dried over $MgSO_4$, filtered and the organic solvent distilled off. The crude product obtained was purified on silica gel (10% EtOAc in isohexane) to afford a clear oil; yield: 1.18 g (93%).

(*S*)-*tert*-Butyl Benzyl Pyrrolidine-1,2-dicarboxylate (19), Procedure A

A 25-mL two-necked flask with stopcock was charged with 1.076 g (5 mmol) (*S*)-1-[(*tert*-butoxy)carbonyl]pyrrolidine-2-carboxylic acid (**13**), 1.39 mL (10 mmol) NEt_3, 0.57 mL (5.5 mmol) benzyl alcohol (**21**), and 0.05 equiv. (0.25 mmol, 20 μL) dry pyridine (**7**). The reaction solution was cooled to −20 °C and 1.39 mL (6.5 mmol) molten Boc_2O added *via* syringe. After stirring for 2 min at this temperature the cooling bath was removed and the flask was allowed to warm to room temperature. Stirring was continued for 4 h and the re-

action solution then diluted with 10 mL DCM and transferred to a separatory funnel. The organic phase was washed with 10 mL 2 N HCl and 10 mL aqueous $NaHCO_3$ solution. The organic phase was dried over $MgSO_4$, filtered and the organic solvent distilled off. The crude product was diluted with a small amount of eluent (10% isohexane in EtOAc) and filtered through a frit charged with silica gel. Washing was continued with 30 mL of eluent. The collected eluate was distilled off under reduced pressure to afford of **19** as a clear oil; yield: 1.07 g (4.19 mmol, 84%).

(S)-*tert*-Butyl Benzyl Pyrrolidine-1,2-dicarboxylate (19), Procedure B

A 25-mL two necked flask with stop cock was charged with 1.076 g (5 mmol) *(S)*-1-[(*tert*-butoxy)carbonyl]pyrrolidine-2-carboxylic acid (**13**), 1.39 mL (10 mmol) NEt_3, 0.427 mL (5 mmol) 1,4-dioxane, and 6.10 mg (0.05 equiv.) DMAP. The reaction solution obtained was cooled to −20 °C and 1.39 mL (6.5 mmol) molten Boc_2O added *via* syringe. The flask was allowed to warm to room temperature and then immersed in an ethanol bath held at 23 °C. After 35 min stirring at this temperature 0.57 mL (5.5 mmol) benzyl alcohol (**21**) was added. Stirring was continued for 40 min and the reaction then worked up as described in procedure A. After chromatography on silica gel (20% EtOAc in isohexane) **19** was obtained as a clear oil; yield: 74% 1.13 g (74%).

Benzyl 2-Fluorobenzoate (22)

A 25-mL two-necked flask with stopcock was charged with 1.076 g (5 mmol) 2-flourobenzoic acid (**20**), 1.39 mL (10 mmol) NEt_3, 0.57 mL (5.5 mmol) benzyl alcohol (**21**), and 0.05 equiv. (0.25 mmol, 20 μL) dry pyridine (**7**). The reaction solution obtained was cooled to −20 °C and 1.39 mL (6.5 mmol) molten Boc_2O added *via* syringe. After stirring for 2 min at this temperature the cooling bath was removed and the flask was allowed to warm to room temperature. After stirring for 3 h at this temperature the reaction mixture was diluted with 10 mL DCM and worked-up as usual. Column chromatography on silica gel affords the ester as a clear oil; yield: 805 mg (70%).

As by-products, a 1:2 mixture of the 2-fluorobenzoic acid *tert*-butyl ester and *tert*-butyl benzyl carbonate (**25**) in a total amount of 600 mg was isolated, implying an additional yield of 20% of 2-fluorobenzoic acid *tert*-butyl ester; R_f = 0.63 (10% EtOAc in isohexane).

Benzyl 3-Nitrobenzoate (24)

A 25-mL two-necked flask with stopcock was charged with 1.076 g (5 mmol) 3-nitrobenzoic acid (**23**), 1.39 mL (10 mmol) NEt_3, 0.57 mL (5.5 mmol) benzyl alcohol (**21**) and 0.05 equiv. (0.25 mmol, 20 μL) dry pyridine (**7**). The reaction solution obtained was cooled to −20 °C and 1.39 mL (6.5 mmol) molten Boc_2O added *via* syringe. After stirring for 2 min at this temperature the cooling bath was removed and the flask was allowed to warm to room temperature. Stirring was continued at this temperature for 4 h and then 10 mL DCM added. After usual work-up the crude material was purified with chromatography on silica gel (isohexane/EtOAc, 9/1) to afford a white solid; yield: 1.07 g (84%).

References

[1] J. Otera, *Esterification: Methods, Reactions and Applications*, Wiley-VCH, Weinheim, **2003**.
[2] K. Takeda, A. Akiyama, H. Nakamura, S. Takizawa, Y. Mizuno, H. Takayanagi, Y. Harigaya, *Synthesis* **1994**, 1063.
[3] L. J. Gooßen, A. Döhring, *Adv. Synth. Catal.* **2003**, *345*, 943.
[4] L. J. Gooßen, A. Döhring, *Synlett* **2004**, 263.
[5] D. K. Mohaptra, A. Datta, *J. Org. Chem.* **1999**, *64*, 6879–6880.
[6] a) V. F. Podnez, *Tetrahedron Lett.* **1995**, *36*, 7115–7118; b) V. F. Podnez, *Int. J. Pept. Protein Res.* **1992**, *40*, 407–414; c) V. F. Podnez, *Int. J. Pept. Protein Res.* **1994**, *44*, 36–48.
[7] M. R. Heinrich, H. S. Klisa, H. Mayr, W. Steglich, H. Zipse, *Angew. Chem.* **2003**, *115*, 4975; *Angew. Chem. Int. Ed.* **2003**, *42*, 4826.
[8] I. Held, A. Villinger, H. Zipse, *Synthesis* **2005**, 1425.
[9] I. Held, S. Xu, H. Zipse, *Synthesis* **2007**, 1185.
[10] a) S. Singh, G. Das, O. V. Singh, H. Han, *Org. Lett.* **2007**, *9*, 401; b) S. Singh, G. Das, O. V. Singh, H. Han, *Tetrahedron Lett.* **2007**, *48*, 1983.
[11] S. Xu, I. Held, B. Kempf, H. Mayr, W. Steglich, H. Zipse, *Chem. Eur. J.* **2005**, *11*, 4751.
[12] C. B. Fischer, S. Xu, H. Zipse, *Chem. Eur. J.* **2006**, *12*, 5779.
[13] F. M. F. Chen, N. L. Benoiton, *Can. J. Chem.* **1987**, *65*, 619–625.
[14] a) S. A. Sikchi, P. G. Hultin, *J. Org. Chem.* **2006**, *71*, 5888; b) R. Varala, S. Nuvala, S. R. Adapa, *J. Org. Chem.* **2006**, *71*, 8283; c) X. Jia, Q. Huang, J. Li, S. Li, Q. Yang, *Synlett* **2007**, 806.
[15] L. F. Tietze, U. Beifuss, *Angew. Chem.* **1993**, *105*, 137; *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 131; *Angew. Chem.* **1993**, *105*, 137.
[16] L. F. Tietze, *Chem. Rev.* **1996**, *96*, 115.
[17] A. Bruggink, R. Schoevaart, T. Kieboom, *Org. Process Res. Dev.* **2003**, *7*, 622.
[18] D. E. Fogg, E. N. dos Santos, *Coord. Chem. Rev.* **2004**, *248*, 2365.
[19] J.-C. Wasilke, S. J. Obrey, R. T. Baker, G. C. Bazan, *Chem. Rev.* **2005**, *105*, 1001.
[20] C. J. Chapman, C. G. Frost, *Synthesis* **2007**, 1.
[21] A. G. Baboul, L. A. Curtiss, P. C. Redfern, K. Raghavachari, *J. Chem. Phys.* **1999**, *110*, 7650.
[22] Gaussian 03, Revision C.02. Gaussian, Inc. Wallingford CT, **2004**. For full citation see Supporting Information.
[23] F. Brotzel, B. Kempf, T. Singer, H. Zipse, H. Mayr, *Chem. Eur. J.* **2007**, *13*, 336–345.
[24] P. Chevallet, P. Garrouste, B. Malawska and J. Martinez, *Tetrahedron Lett.* **1993**, *34*, 7409.
[25] G. W. Anderson, F. M. Callahan, *J. Am. Chem. Soc.* **1960**, *82*, 3359.
[26] B. Neises, W. Steglich, *Angew. Chem.* **1978**, *90*, 556; *Angew. Chem. Int. Ed. Engl.* **1978**, *17*, 522.
[27] G. Höfle, W. Steglich, H. Vorbrüggen, *Angew. Chem.* **1978**, *90*, 602; *Angew. Chem. Int. Ed. Engl.* **1978**, *17*, 569.
[28] A. M. M. Marquet, M. A. Gaudry, S. Boru, French Patent 2585354 A1, **1987**.

