Counteranion Control

DOI: 10.1002/anie.201300665

Investigation of the Carboxylate Position during the Acylation Reaction Catalyzed by Biaryl DMAP Derivatives with an Internal Carboxylate**

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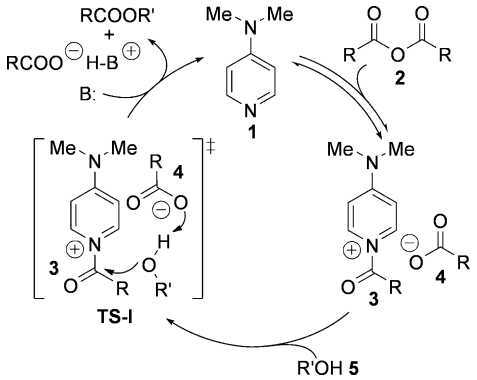
The 4-dimethylaminopyridine (DMAP) (**1**)-catalyzed acylation of an alcohol with acid anhydrides **2** is one of the most fundamental and widely used organic transformation for the synthesis of esters.[1] The currently accepted mechanism underlying the catalytic cycle in the presence of an auxiliary base (B:) is depicted in Scheme 1.[2] The first key step of this

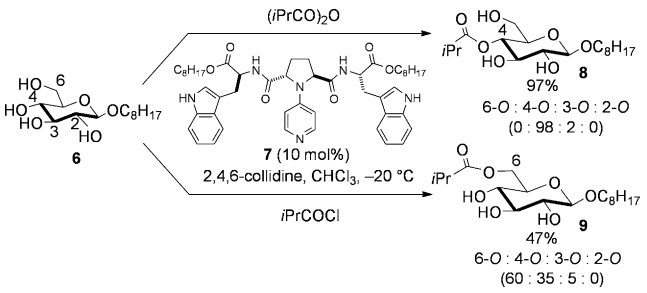


Scheme 1. Catalytic cycle of the DMAP-catalyzed acylation with acid anhydride.

cycle is the establishment of equilibrium between DMAP and its acylpyridinium salt composed of the acylpyridinium ion **3** and its counteranion, carboxylate **4**. The second key step is the irreversible nucleophilic attack of alcohol **5** on the carbonyl group of the acylpyridinium ion via the transition state TS-I. It has been proposed that the rate-determining step of the catalytic cycle is the second key step. Therefore, the efficiency of the DMAP-catalyzed acylation depends not only on the concentration of the acylpyridinium salt, but also on the kinetics of the second step via TS-I.

In the rate-determining TS-I, it has been postulated that the carboxylate ion **4** of the acylpyridinium salt plays a crucial role as a general base catalyst in the deprotonation of the alcohol hydroxy group.[3,4] Steglich and Höfle found that the acylation of a tertiary alcohol with acetic anhydride proceeded faster than acylation by acetyl chloride in the presence of excess DMAP.[3a] Kattnig and Albert also found that the acylation of 1- and 2-propanol with acetic anhydride in the presence of catalytic amounts of DMAP proceeded faster than that with acetyl chloride in the presence of K_2CO_3 as the auxiliary base.[5] These results supported that the acetate, which was more basic than chloride, functioned better as a general base to accelerate the nucleophilic attack of the alcohol on the acylpyridinium ion. Wakselman observed that the acetylation of *t*BuOH proceeded only in the presence of the *N*-acetyl-dimethylaminopyridinium salt with acetate as the counteranion, and the reaction did not proceed if acetate were substituted for other counteranions, such as BF_4^-.[6]

Apart from improving the reaction efficiency, we found that a carboxylate ion also affected the regiochemical outcome of the acylation of glucose derivative **6** in the presence of a DMAP-related nucleophilic catalyst **7** (Scheme 2).[7] Although the acylation of **6** with isobutyric anhydride proceeded at the secondary C4 OH group with high regioselectivity to yield **8**, this regioselectivity was dramatically reduced upon substitution with isobutyryl chloride,



Scheme 2. Regioselectivities of the acylation reactions of **6** with isobutyric anhydride or isobutyryl chloride in the presence of catalyst **7**.

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[**] We are grateful to Prof. Hendrik Zipse (Ludwig-Maximilians-Universität München) for valuable discussion on theoretical aspects for catalyst performance. This work was supported by a Grant-in-Aid for Scientific Research on Innovative Areas "Advanced Molecular Transformations by Organocatalysts" and a Grant-in-Aid for Scientific Research (C) from the Ministry of Education, Culture, Sports, Science and Technology (Japan).
DMAP = 4-dimethylaminopyridine.

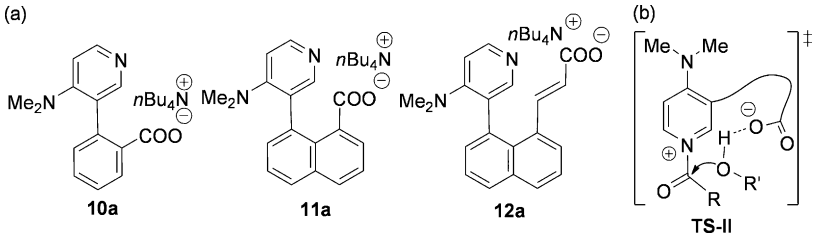
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201300665.

giving the acylate **9** at the primary C6 alcohol as the major product, along with significant amounts of the diacylates. Kattnig and Albert also observed that the regioselectivity depended on the acylating agents in the presence of DMAP.[5] The acylation of **6** with acetyl chloride or acetic anhydride has been reported to predominantly give C6 acetate or C3 acetate, respectively. Burke also found that regioselectivity of acylation of amphotericin B was influenced by the electronic nature of the carboxylate ion.[8]

Recently, the carboxylate ion was also found to act as a pivotal counteranion in asymmetric acylation reactions by virtue of its interaction with chiral thiourea.[9] These results indicated that the carboxylate ion played a crucial role not only in the reactivity, but also in the regio- and stereoselectivity of the acylation reaction.

Recently, Glatthaar, Schreiner, et al. investigated the structures and the dynamics of acetylpyridinium salts by X-ray, spectroscopic, and computational experiments.[10] Based on the results, carboxylate ion **4** interacting with pyridinium C2–H and acetyl H via hydrogen-bonding was proposed as a general base to guide the alcohol towards the carbonyl group of **3**. Zipse and co-workers proposed a model of the TS-I on the basis of results obtained in a computational study.[11] They proposed that the carboxylate ion **4**, positioned proximal to the acylpyridinium ion **3** by a hydrogen-bonding interaction with the C2–H of the pyridinium moiety, acted as a general base; however, experimental evidence supporting the position of the carboxylate, which acts as a general base in TS-I, has not been obtained to date. Determination of the carboxylate position, which affects both reactivity and regioselectivity, would be valuable for a mechanistic understanding as well as for the rational design of DMAP-related nucleophilic catalysts.[12] This context prompted us to experimentally investigate the positioning of the carboxylate ion.

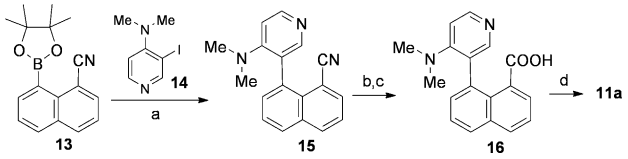
The carboxylate position during DMAP-catalyzed acylation was investigated by designing the relative positions of an ion pair comprising **3** and **4** in TS-I by preparing a series of biaryl DMAP catalysts **10a**–**12a** in the tetrabutyl ammonium salt forms (Scheme 3).



Scheme 3. a) DMAP derivatives having an internal carboxylate group. b) Representation of the transition state (TS-II) involving the internal carboxylate group.

In these catalysts, the internal carboxylate was connected at different distances from and in different geometries relative to the pyridine moiety by a rigid aryl spacer (Scheme 3a). Appropriate positioning of the carboxylate with respect to the acylpyridinium ion was expected to increase the acylation rate by activation of the alcohol by the internal carboxylate group in TS-II (Scheme 3b). Furthermore, the precise positioning of the carboxylate was expected to be verified by the well-defined rigid catalyst structure.[13]

Catalyst **11a**, in which the carboxylate group was linked by a naphthyl spacer, was synthesized as shown in Scheme 4.



Scheme 4. Preparation of catalyst **11a**: a) $[Pd(PPh_3)_4]$, K_3PO_4, DMF, 120 °C, 12 h, 70%; b) diisobutylaluminum hydride, toluene, −78 °C to −45 °C, 1 h, 82%; c) $NaClO_2$, H_2SO_4, 2-methyl-2-butene, CH_3CN, H_2O, 0 °C, 2 h, 55%; d) nBu_4NOH, MeOH, RT, 12 h.

Suzuki–Miyaura cross-coupling between **13** and aryl iodide **14**[14] gave **15**. After the transformation of the CN group in **15** to carboxylic acid **16**, carboxylate catalyst **11a** was obtained as a tetrabutylammonium salt by treatment of an equivalent amount of tetrabutylammonium hydroxide.

X-ray analysis of **16** indicated that the carboxyl group was positioned proximal to the pyridine ring in a face-to-face geometry with a distance of 2.9 Å between the pyridine C3 and the carbonyl carbon (Figure 1).

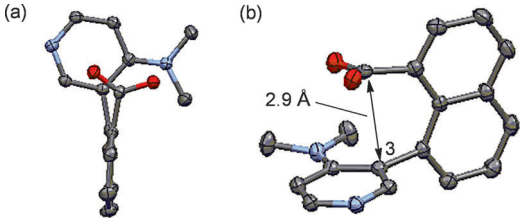


Figure 1. X-ray analysis of **16** (ellipsoids set at 60% probability). C gray, O red, N blue; hydrogen atoms are omitted for clarity. a) View through the carboxyl group to the pyridine moiety. b) Distance between the carbonyl carbon and the C3 position of the pyridine ring.

The catalytic activities of the catalyst **10a** and the corresponding methyl ester **10b** were investigated in a kinetic study. The acetylation of cyclohexanol was carried out in the presence of 5 mol% catalyst under pseudo first-order conditions employing 10 equivalent amounts of acetic anhydride and Et_3N in $CDCl_3$ (Figure 2a). The conversion was monitored by ^1H NMR spectroscopy. Compounds **10a** and **10b** yielded indistinguishable rate constants ($k_{10a} = 1.2 \times 10^{-2}\ min^{-1}$, $k_{10b} = 1.2 \times 10^{-2}\ min^{-1}$; $k_{10a}/k_{10b} = 1.0$; Figure 2b). Therefore, the internal carboxylate in **10a** negligibly affected the acylation efficiency. The catalytic activities of **10a** and **10b** were lower than the activity of DMAP ($k_{DMAP} = 1.3 \times 10^{-1}\ min^{-1}$, $k_{10a}/k_{DMAP} = 0.094$). We also tested the catalytic activity of **10c**,[15] which did not include substituents on the ring. The activity of **10c** ($k_{10c} = 9.6 \times 10^{-3}\ min^{-1}$) was lower than the activity of DMAP

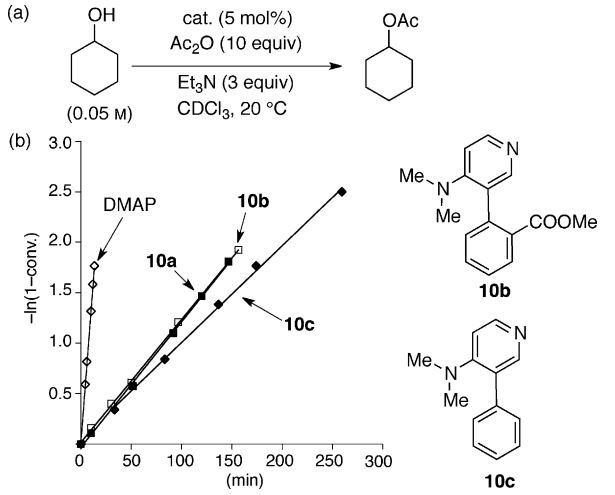


Figure 2. a) Acetylation of cyclohexanol under pseudo first-order conditions: 0.05 M substrate concentration. b) Kinetic profiles of the acetylation of cyclohexanol, catalyzed by **10a–10c** and DMAP.

and comparable with the activities of the catalysts **10a** and **10b**. This result suggested that the activity of a catalyst with a phenyl substituent at the C3 position of the pyridine ring was intrinsically lower than the activity of DMAP.

In sharp contrast to the results obtained using catalysts **10a** and **10b**, catalyst **11a**, with a carboxylate group at the *peri* position of the naphthyl ring, showed a higher catalytic activity than the corresponding methyl ester **11b** ($k_{11a} = 1.3 \times 10^{-1}\ \mathrm{min}^{-1}$, $k_{11b} = 1.0 \times 10^{-2}\ \mathrm{min}^{-1}$; $k_{11a}/k_{11b} = 13$) or **11c**[15] without an internal carboxyl group ($k_{11c} = 1.4 \times 10^{-2}\ \mathrm{min}^{-1}$; $k_{11a}/k_{11c} = 9.6$), under the conditions employed for Figure 2 (Figure 3a).[16] Although the activities of the catalysts **11b** and **11c** were lower than the activity of DMAP ($k_{11b}/k_{DMAP} = 0.077$, $k_{11c}/k_{DMAP} = 0.10$),[17] the activity of **11a** approached that of DMAP ($k_{11a}/k_{DMAP} = 1.0$). Given that **11b**, **11c**, and **10c** showed comparable activities (Figure 3a, $k_{10c} = 9.6 \times 10^{-3}\ \mathrm{min}^{-1}$), the relatively low activities of **11b** and **11c** does not appear to have arisen from the steric effects of the carboxymethyl group at the *peri* position and/or the naphthyl ring itself.

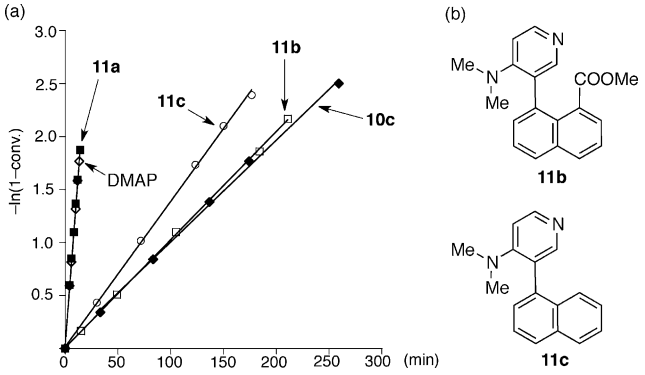
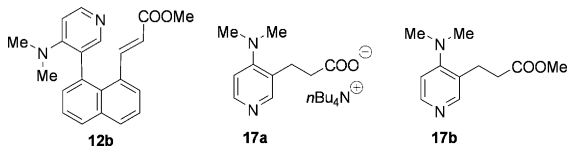


Figure 3. a) Kinetic profiles of the acetylation of cyclohexanol catalyzed by **11a–11c** under the identical conditions employed for Figure 2. The kinetic activities of **10c** and DMAP, shown in Figure 2, are also included. b) Structures of **11b** and **11c**.

Instead, the low activities reflected the intrinsic properties of the C3-substituted DMAP derivative. This clearly indicated that a carboxylate at the *peri* position in **11a** enhanced the activity of the intrinsically low-potency DMAP derivatives that included a naphthyl skeleton.

Next, we evaluated the catalytic activities of **12a** (Scheme 3) and **12b** (Scheme 5), in which the carboxylate groups were linked to the naphthyl ring through an alkene



Scheme 5. Structures of **12b**, **17a**, and **17b**.

spacer. The activities of the catalysts were similar ($k_{12a} = 5.4 \times 10^{-3}\ \mathrm{min}^{-1}$, $k_{12b} = 8.1 \times 10^{-3}\ \mathrm{min}^{-1}$; $k_{12a}/k_{12b} = 0.7$; see the Supporting Information). Thus, a carboxylate group tethered by a two-carbon spacer to the naphthyl ring did not accelerate the reaction, even though **11a**, with a carboxylate group linked directly to the naphthyl ring, was highly active ($k_{11a}/k_{12a} = 25$). This indicated that only a carboxylate positioned appropriately, as found in **11a**, could accelerate the acylation reaction.

Catalyst **17a** (Scheme 5), possessing an alkyl spacer, was prepared, and its catalytic activity was measured. No significant differences between the activities of **17a** ($k_{17a} = 4.8 \times 10^{-3}\ \mathrm{min}^{-1}$) and the corresponding methyl ester **17b** ($k_{17b} = 5.9 \times 10^{-3}\ \mathrm{min}^{-1}$, $k_{17a}/k_{17b} = 0.8$) were observed (see the Supporting Information). This indicated that a carboxylate ion connected by a flexible two-carbon spacer did not affect the acylation efficiency. The activities of **17a** and **17b** were lower than the activity of DMAP ($k_{17a}/k_{DMAP} = 0.036$, $k_{17b}/k_{DMAP} = 0.045$). Therefore, the catalytic activities of catalysts with a substituent at the C3 position of the pyridine ring were generally low,[18] except for **11a**.

The relative catalytic activities on acetylation of all catalysts with respect to the simple biphenyl catalyst **10c** are summarized in Figure 4. This diagram clearly shows that the activity of **11a** was particularly high. The carboxylate position

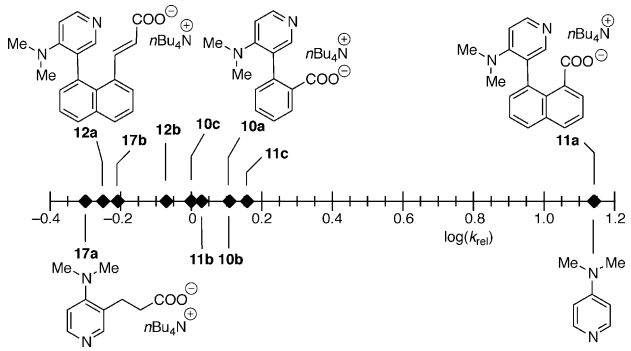


Figure 4. Relative catalytic activities of the catalysts and DMAP with respect to the biphenyl catalyst **10c** on the cyclohexanol acetylation.

that enhanced the acylation rate most efficiently was determined to be as shown in **11a**.

The effects of the acylating agent were further investigated in the presence of benzoic anhydride (Figure 5a). The benzoylation rate of cyclohexanol was evaluated in the

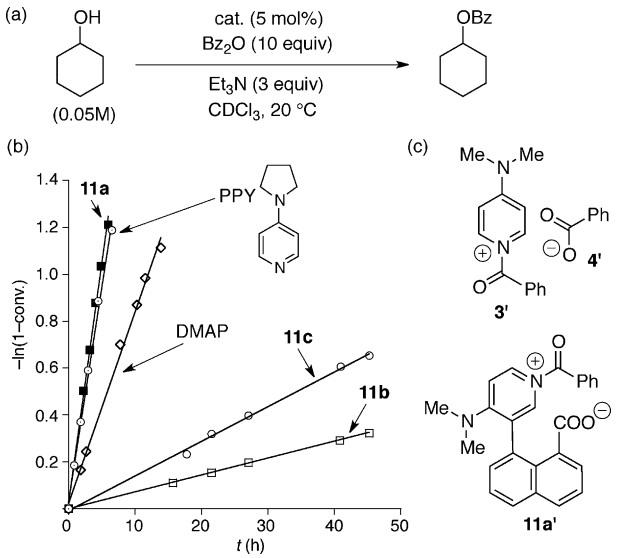


Figure 5. a) Benzoylation of cyclohexanol under pseudo first-order conditions using 10 equivalents of Bz_2O at the substrate concentration of 0.05 M. b) Kinetic profiles of the cyclohexanol benzoylation, catalyzed by **11a**–**11c**, DMAP, or PPY. c) Structures of the acylpyridinium salts generated from benzoic anhydride and DMAP or **11a**.

presence of 5 mol% of the catalysts **11a**–**11c** or DMAP under pseudo first-order conditions employing 10 equivalents of benzoic anhydride (Figure 5a). The relative activity of **11a** with respect to **11b** or **11c** increased beyond the acetylation activity given in Figure 3.

The relative benzoylation rate constants employing **11a** ($k_{11a} = 2.0 \times 10^{-1}\ h^{-1}$) versus **11b** ($k_{11b} = 7.2 \times 10^{-3}\ h^{-1}$), and **11a** versus **11c** ($k_{11c} = 1.5 \times 10^{-2}\ h^{-1}$) were found to be 28 and 14, respectively, both of which were larger than the relative acetylation rates reported in Figure 3 ($k_{11a}/k_{11b} = 13$, $k_{11a}/k_{11c} = 9.6$).

The benzoylation activity of **11a** was 2.5 times greater than the activity of DMAP ($k_{DMAP} = 8.2 \times 10^{-2}\ h^{-1}$, $k_{11a}/k_{DMAP} = 2.5$), although the acetylation activities of **11a** and DMAP were almost identical. The superior activity of **11a** was further established by substituting the acylating agent (Ac_2O) with Bz_2O. In the benzoylation reaction, the counteranion of *N*-benzoylpyridinium ion **3′** derived from DMAP was benzoate **4′** (Figure 5c), which was a less-effective (lower basicity) general base than the acetate ion. The DMAP-catalyzed benzoylation reaction could, therefore, be decelerated by reducing the reactivity of the acylpyridinuim salt in TS-I by the less basic external base **4′** (Scheme 1). On the other hand, the activity of the acylpyridinium ion **11a′** derived from **11a** was not influenced by the external benzoate **4′** because the internal carboxylate preferentially acted as a general base. Therefore, the larger relative benzoylation rates of **11a** versus DMAP ($k_{11a}/k_{DMAP} = 2.5$), as compared to the relative acetylation rates ($k_{11a}/k_{DMAP} = 1.0$), may arise from the deceleration of the DMAP (**1**)-catalyzed benzoylation reaction. This observation supported the notion that the higher acylation rate by **11a** arose from general base catalysis of the internal carboxylate, as expected in the TS-II (Scheme 3b).

4-Pyrrolidinopyridine (PPY) has been known to be a more potent nucleophilic catalyst than DMAP.[19] The benzoylation activity of **11a** approached the activity of PPY ($k_{PPY} = 1.8 \times 10^{-1}\ h^{-1}$, $k_{11a}/k_{PPY} = 1.1$; Figure 5b). The high activity of **11a** indicated that the catalytic potential of DMAP-type nucleophilic catalysts may be controlled by the positioning of the counteranion.

The most stable structures of the *N*-acetylpyridinium salts derived from **10a**–**12a** and **17a** at the B3LYP/6-31G* level are shown in Figure 6 (ac-**10a**–ac-**12a** and ac-**17a**).[20] In each of

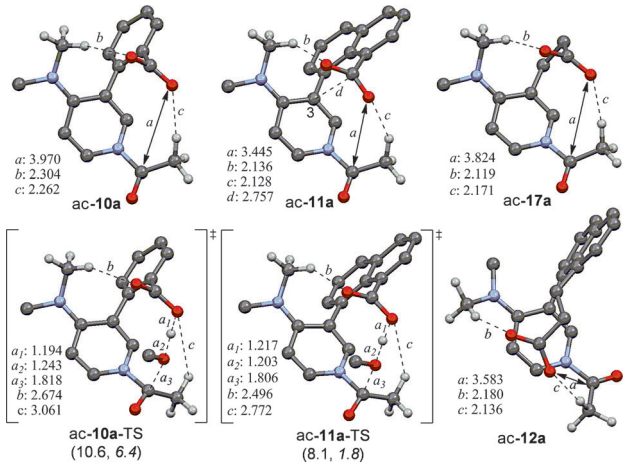


Figure 6. 3D structures of ac-**10a**–ac-**12a**, ac-**17a**, ac-**10a**-TS, and ac-**11a**-TS optimized at the B3LYP/6-31G* level (C gray, O red, N blue). Distances between the atoms are in Å. Hydrogen atoms are partially omitted for clarity. Relative energy differences [kcal mol^{-1}] between TS and *N*-acetylpiridinium salt–MeOH complex (RC is depicted in the Supporting Information) are shown in parentheses. Relative energy differences [kcal mol^{-1}] between TS and RC in the catalyst moiety (**10a** and **11a**) at the B3LYP/6-31+G* level are shown in italics.

the structures, the anionic carboxylate groups are oriented parallel to the *N*-acylpyridinium moiety to interact with both the positive NMe_2 group[21] and the acetyl group by the electrostatic interaction. Focusing on the conformational space of the reactive site, the shorter distance between the carboxylate group and the reacting carbonyl carbon of the acylpyridinium ion is found in ac-**11a** (3.445 Å). The distance between C3 of the pyridinium moiety and the carbonyl carbon in ac-**11a** was 2.757 Å, which is comparable to the distance (2.9 Å) observed in the crystal structure of **16** (Figure 1). To verify the ideal linker structure in the highly active **11a**, the activation energies and the transition structures with MeOH as a model alcohol were compared between **10a** and **11a**, which contain relatively similar and rigid linker structure but exhibit much different activity. In agreement with the experimental catalyst activities, the activation energy is higher in ac**10a**-TS (10.6 kcal mol^{-1}) than ac-**11a**-TS (8.1 kcal

mol^{-1}). This energy difference could be explained by the energies required to deform *N*-acetylpiridinium salt–MeOH complexes (RC) into the corresponding transition states (ac-**10a**-TS and ac-**11a**-TS). The deformation energies estimated at the B3LYP/6-31 + G* level single point energy calculations of the catalyst unit (**10a**, **11a**) between RC and TS is higher in ac-**10a**-TS (6.4 kcal mol^{-1}) than ac-**11a**-TS (1.8 kcal mol^{-1}; for details, see the Supporting Information). This indicates that the larger structural deformation during the deprotonation of the alcohol hydroxy group is required in ac-**10a**-TS rather than ac-**11a**-TS. In conclusion, a carboxylate group positioned in close proximity to the pyridine ring in a face-to-face geometry was found to act as an effective general base to accelerate the acylation reaction.

In summary, we determined the position of the carboxylate ion that accelerates the DMAP-catalyzed acylation by preparing a series of DMAP derivatives with an internal carboxylate. The ability to accelerate the acylation reaction by introducing an internal carboxylate group offers new possibilities for the design of further potent nucleophilic catalysts. Applications to asymmetric acylation by virtue of the axial chirality of **11a** and related carboxylate catalysts are under investigation.[22]

Received: January 25, 2013
Revised: March 18, 2013
Published online: May 6, 2013

Keywords: acylation · base catalysis · counteranions · ion pairs · organocatalysis

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[16] **11a** yielded a higher activity relative to **11c** in the presence of 5 mol% catalyst with two equivalents of Ac_2O. In this experiment, the acetylation of cyclohexanol was monitored until full conversion (see the Supporting Information).

[17] The low activity of **11c** was consistent with the results obtained in the acetylation of 1-methylcyclohexanol by Spivey and co-workers, see Ref. [15].

[18] This may arise from the unfavorable equiliblium formation of acylpyridinium ion owing to less delocalization of positive charge by nitrogen lone pair caused by steric repulsion between the substituent at C3 position of pyridine and the dimethylamino group; see Ref. [3b]. Potent DMAP-type catalysts were developed by securing overlap between the nitrogen lone pair and the pyridine π*-orbital; see: a) M. R. Heinrich, H. S. Klisa, H. Mayr, W. Steglich, H. Zipse, *Angew. Chem.* **2003**, *115*, 4975; *Angew. Chem. Int. Ed.* **2003**, *42*, 4826; b) S. Singh, G. Das, O. V. Singh, H. Han, *Org. Lett.* **2007**, *9*, 401; c) N. D. Rycke, G. Berionni, F. Couty, H. Mayr, R. Goumont, O. R. P. David, *Org. Lett.* **2011**, *13*, 530.

[19] G. Höfle, W. Steglich, *Synthesis* **1972**, 619.

[20] M06-2X/6-31G** and B3LYP/6-31G** calculations were also employed for ac-**10a** and ac-**11a**. The gross structures optimized at these levels were almost the same as the structures depicted in Figure 6 (see the Supporting Information). Therefore, B3LYP/6-31G* was employed for optimization of all of the structures in Figure 6.

[21] The X-ray structures of several *N*-acyl-4-dialkylaminopyridinium ions also suggested an iminium N^+=C substructure; see: a) P. G. Jones, K. Linoh, A. Blaschette, *Z. Naturforsch. B* **1990**, *45*, 267; b) C. Lohse, S. Hollenstein, T. Laube, *Angew. Chem.* **1991**, *103*, 1678; *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 1656; c) S. Hollenstein, C. Lohse, T. Laube, *Croat. Chem. Acta* **1992**, *65*, 727; d) B. Tao, J. C. Ruble, D. A. Hoic, G. C. Fu, *J. Am. Chem. Soc.* **1999**, *121*, 5091.

[22] Spivey and co-workers reported pioneering studies of an asymmetric acylation employing axially chiral biaryl DMAP catalysts; for examples, see: a) A. C. Spivey, T. Fekner, H. Adams, *Tetrahedron Lett.* **1998**, *39*, 8919; b) A. C. Spivey, T. Fekner, S. E. Spey, *J. Org. Chem.* **2000**, *65*, 3154; c) A. C. Spivey, A. Maddaford, D. P. Leese, A. J. Redgrave, *J. Chem. Soc. Perkin Trans. 1* **2001**, 1785; d) E. Larionov, M. Mahesh, A. C. Spivey, Y. Wei, H. Zipse, *J. Am. Chem. Soc.* **2012**, *134*, 9390; e) See also Ref. [15].

