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Amide/Iminium Zwitterionic Catalysts for (Trans)esterification: Application in Biodiesel Synthesis

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(China)

ABSTRACT: A class of zwitterionic organocatalysts based on an amide anion/iminium cation charge pair has been developed. The zwitterions are easily prepared by reacting aziridines with aminopyridines. They are catalytically applicable to transesterifications and dehydrative esterifications. Mechanistic studies reveal that the amide anion and iminium cation work synergistically in activating the reaction partners, with the iminium cationic moiety interacting with the carbonyl substrates through non-classical hydrogen bonding. The reaction can be applied to large-scale synthesis of biodiesel under mild conditions.

KEYWORDS**:** biodiesel, esterification, orgnaocatalysis, mechanism, transesterification, zwitterion

1. INTRODUCTION

Bifunctional organocatalysts have emerged in recent decades and play an increasingly important role in organic synthesis. Thanks to the cooperative effect between the functional groups in the bifunctional systems, the substrate reaction partners can be brought into close proximity for efficient chemical transformations. Constitutional components such as Brønsted bases/acids, Lewis bases, dihydrogen bonds and cooperative ion pairing are frequently included in the design of bifunctional organocatalysts.[1-9] An emerging class of bifunctional organocatalysts is zwitterions (also referred to as inner salts),[10] in which an anion and a cation are site-isolated within a single molecule and the ion pair works synergistically to activate the reaction partners. However, catalysis using zwitterions is underexploited, partly because of the difficulties in identifying suitable catalyst architectures and preparation of zwitterionic catalysts.

Among the sporadic reports on zwitterion catalytic systems,[1,11-12] oxide-containing zwitterions are relatively the most studied. For instance, betaines (with oxide and ammonium) derived from a number of skeletons have been utilized in a range of catalytic processes such as CO_2 fixation,[13-16] polymerization,[17] photoredox reactions,[18-19] and Aldol/Mannich-type reactions[20-25] and aziridine opening.[26] Recently, seminal works on asymmetric catalytic reactions using chiral quaternary ammonium betaines were independently reported by Ooi,[27-33] Deng,[34] Gong,[35] and Levacher.[36] In one very recent report, a betaine Co(III) complex was applied in copolymerization.[37] In situ generated oxide/phosphonium zwitterionic catalysts are also applicable in selected reactions. Gong reported in situ generated oxide/phosphonium zwitterions for Mannich-type and Strecker-type reactions.[38-39] Ranocchiari reported that in situ generated oxide/phosphonium zwitterions with the influence of metal-organic frameworks could catalyze the Aldol-Tishchenko reactions.[40] Tado and Suga also reported the use of in situ generated aromatic oxide/phosphonium zwitterions for primary hydroxyl group selective acylation of diols.[41]

In contrast, zwitterionic catalysts containing other ion pairs are very rare. A pioneering work by Brown documented the use of a zwitterionic imidazolium thiolate catalyst to promote the hydrolysis of amides.[42] Structurally unique zwitterionic carbon acids were established by Yanai and Taguchi and have been applied in some acid-catalyzed transformations.[43-46] In 2007, Ishihara reported a seminal work using the sulfide/iminium zwitterion **3** with an anionic sulfide and a cationic imine for transesterification.[47,48] Later, our research team applied the same catalyst in the medium-ring lactonization of olefinic acids and electrophilic halogention of arenes.[49-50] Zwitterion **3** is an attractive catalyst platform because it can be easily prepared through the nucleophilic attack of isothiocyanate **1** by an equal molar amount of 4-aminopyridine **2** (Figure 1A). In addition, the structurally well-defined charge pair system allows effective interaction with the reaction partners. However, sulfide zwitterion **3** was found to exist in equilibrium with its constitutional components **1** and **2** in solution phase, and isothiocyanate **1** would be hydrated gradually in the presence of moisture,[49] which limited its application. Herein, we are pleased to disclose our recent success in the design and preparation of a new class of zwitterionic organocatalysts **5** based on an amide anion/iminium cation pair. Zwitterions **5** could easily be prepared and were found to be structurally stable. In addition, the catalytic protocol has been successfully applied in transesterification and dehydrative esterification. A computational study revealed that the cationic ammonium moiety in zwitterion **5** could interact with the intermediate through non-classical hydrogen bonding. This newly developed methodology was found to be applicable to the scalable synthesis of biodiesel.

2. RESULTS AND DISCUSSION

2.1 Catalyst design and preparation

Our study began with the design and preparation of zwitterion **5**. We rationalized that instead of using isothiocyanate **1**, nucleophilic attack of the bicyclic aziridine system **4** by 4-aminopyridine **2** would release the ring-strain and result in the energetically more favorable zwitterion **5**, which would inhibit the backward reaction (Figure 1B). The *N*-sulfonated aziridines **4** can readily be prepared through literature procedures.[51] To our delight, tosyl aziridine **4a** could be opened by 4-(*N*,*N*-dimethylamino)pyridine (DMAP, **2a**) in refluxing acetonitrile to give zwitterion **5a** in 72% yield (Figure 1B). Changing the *N*-sulfonamide at aziridine **4** (e.g. **4b**) and/or the aminopyridine partner [e.g. 4-pyrrolidylpyridine (PPY), **2b**] yielded the structural analogues **5b–5d**. An X-ray crystallographic study on a single crystal sample of zwitterion **5a** was performed (Figure 1C). It was found that the N(3)-C(9) bond length (1.34 Å, the labeling is based on the X-ray data) was significantly shorter than a typical C-N single bond, suggesting that the bonding had considerable C=N character and the N(3) nitrogen was positively charged. We believe that the electropositivity of the iminium cation was considerably enhanced because the counteranion sulfonamide is effectively dissociated to a large extent as a result of its site isolation in the carbon skeleton. Computational study on the electrostatic potential of **5a** also revealed that the iminium moiety possesses considerable positive charge (Figure 1C). Notably, zwitterions **5** were found to be structurally stable and no decomposition was observed upon heating, which could be attributed to the fact that the pyridinium moiety in **5** sat at the equational position so that they could withstand decomposition through substitution or Hoffmann elimination. In addition, zwitterions **5** were not hygroscopic so that they were easy to handle for catalytic reactions.

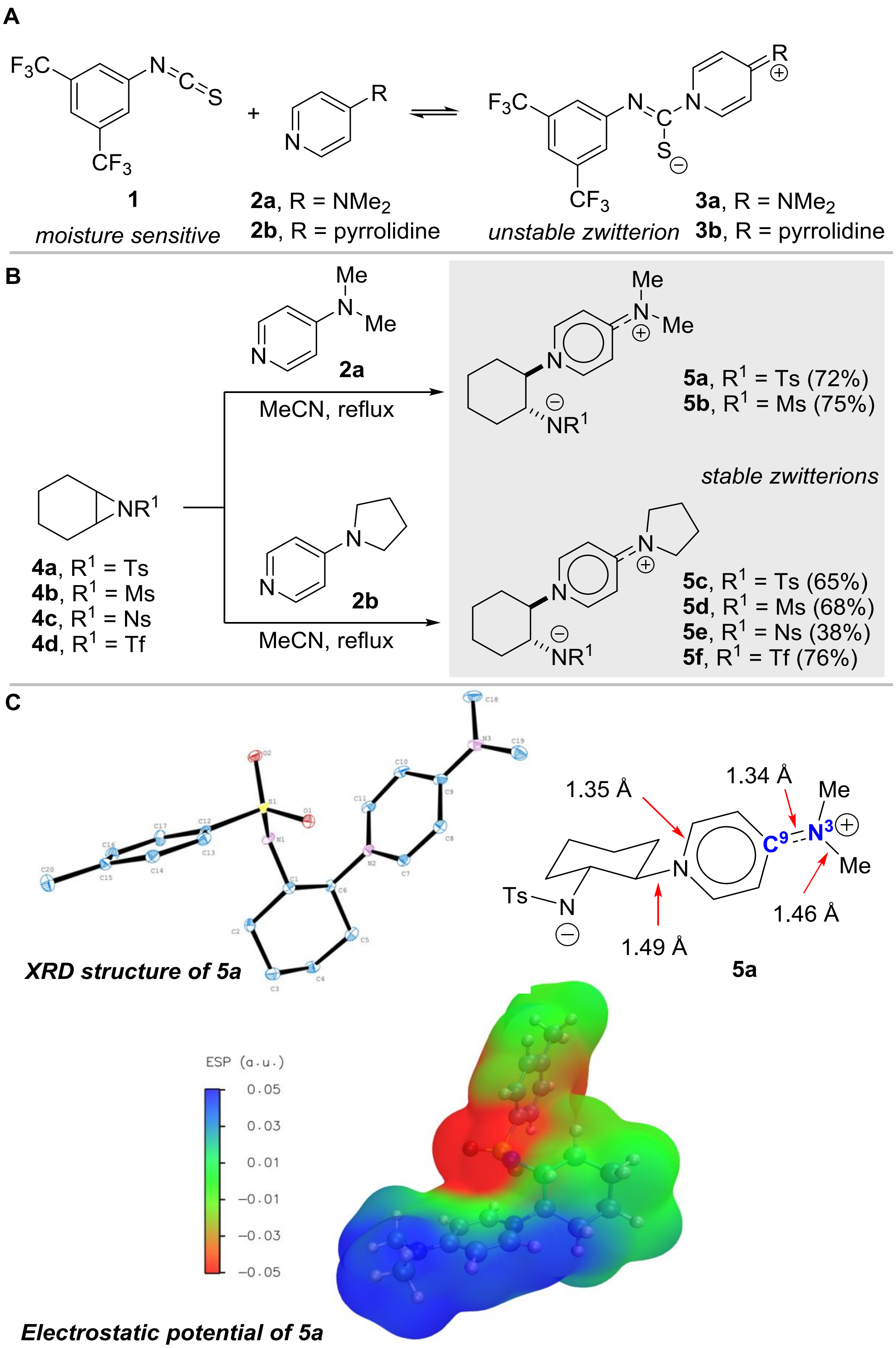
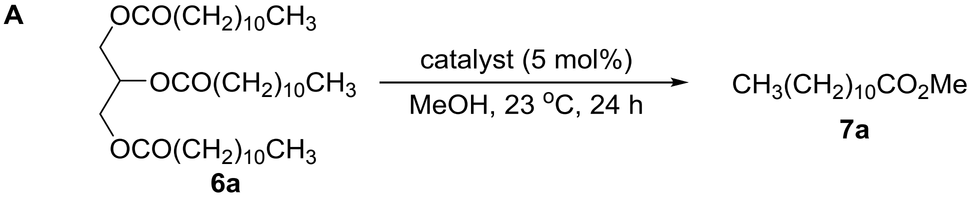


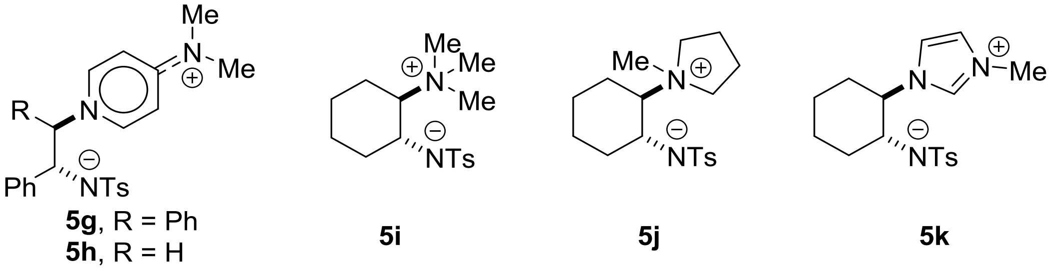
Figure 1. Design and Preparation of Aminopyridinium Zwitterionic Organocatalysts

2.2 Synthesis of biodiesel through transesterification



catalyst	yield of **7a**	catalyst	yield of **7a**	catalyst	yield of **7a**
3b	0%	**5f**	0%	Et_3N	trace[c]
5a	70%	**5g**	0%	DMAP	trace[c]
5b	72%	**5h**	0%	PPY	trace[c]
5c	79%	**5i**	0%	PPh_3	trace
5d	>99%	**5j**	60%	TBAI	trace
5d	99%[a]	**5k**	74%	$[(n\text{-dodec})_3MeN]^+Cl^-$	0%
5d	99%[b] ***50 g scale***	NaOMe	32%[c]	$[Me_4N]^+[OCO_2Me]^-$	trace
5e	0%	*t*BuOK	52%[c]		

[a] Reaction was done using 2 mol% of **5d** at 70 °C for 2 h. [b] Reaction was done using 2.5 mol% of **5d** for 96 h. [c] Reaction was done at 70 °C.

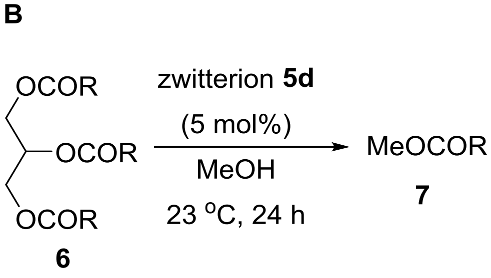


5g, R = Ph
5h, R = H

5i

5j

5k



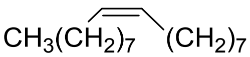
substrate	R	product	yield
6b	CH_3	**7b**	99%
6c	$CH_3(CH_2)_3$	**7c**	99%
6d	$CH_3(CH_2)_6$	**7d**	99%
6e	$CH_3(CH_2)_{12}$	**7e**	99%
6f		**7f**	99%

Figure 2. Transesterification of triglycerides **6** to FAMEs **7**

The catalytic performances of zwitterions **5a-d** in the transesterification of triglycerides **6** to fatty acid methyl esters **7** (FAMEs, commonly known as biodiesel) were evaulated.[52-55] Fatty acid ester **6a** was suspended in a solution of MeOH containing 5 mol% of zwitterionic catalyst **5** at 23 °C (Figure 2A). The transesterification proceeded smoothly and the FAME **7a** was obtained in 70-79% isolated yield when using zwitterions **5a-c**. The efficiency was significantly enhanced when using zwitterion **5d** bearing both a mesyl and a PPY substituents. The reaction could be run with a lower catalyst loading (2 mol% of **5d**) at 70 ^{o}C for 2 h, giving FAME **7a** in 99% yield. In addition, the reaction was readily scalable (50 gram scale) and **7a** was obtained quantitatively. In sharp contrast, no reaction was observed when using zwitterion **3b** as the catalyst, attributed to the decomposition of the catalyst through methanolysis of isothiocyanate **1** (exist in equilibrium with **3b**). Zwitterions **5e-f** (with more electron-deficient sulfonamide), **5g-h** (different skeleton rigidity) and **5i-k** (different distance between the cation and anion), which were prepared using a similar method as that in **5a-d**, were also examined and their performances were inferior to **5d**. These results suggest that the Brønsted basicity, structurally rigidity and cation/anion distance in **5d** might be the determining factors of catalytic performance. It was also found that other catalysts including Brønsted bases (NaOMe, *t*BuOK), Lewis bases (Et_3N, DMAP, PPY, PPh_3), and ammonium salts [tetra-*n*-butylammonium iodide (TBAI), tri-*n*-dodecylmethylammonium chloride,[56] and tetramethylammonium methyl carbonate[57]] were much less effective in promoting the reaction under the same conditions.

The reaction was also found to be applicable to other fatty acid esters **6b-f**. For the case of **6f**, the corresponding FAME **7f** was obtained in quantitative yield with the unsaturated system remaining intact (Figure 2B).

FAME **6a** could be separated simply by aqueous washing to remove the glycerol and zwitterionic catalyst **5d**. In addition, the by-product mixture containing glycerol (a glut by-product from the production of biodiesel) and catalyst **5d** could undergo transesterification with ethyl acetate to give triacetin (99%) (Figure 3), which has various applications such as biodiesel additive, antiknock agent, food additive, and plasticizer.[58] The zwitterionic catalyst **5d** could then be recycled and reused in the next round of FAME **7** synthesis with similar performance.[59] It is noteworthy that unlike some common methods such as base-catalyzed transesterification (which requires anhydrous conditions to avoid hydrolysis of the ester to form carboxylic acid) and catalyst-free transesterification in supercritical MeOH (which requires high temperature/pressure and special equipment),[52-55] this virtually neutral zwitterionic catalyst system could be operated in an open-flask environment without the need of exclusion of moisture or the use of anhydrous alcoholic solvents. In addition, clean conversion was achieved using conventional apparatus at ambient conditions (1 atm and 23 °C). These features provide a solid foundation for the scalable synthesis of biodiesel under mild organocatalytic conditions.

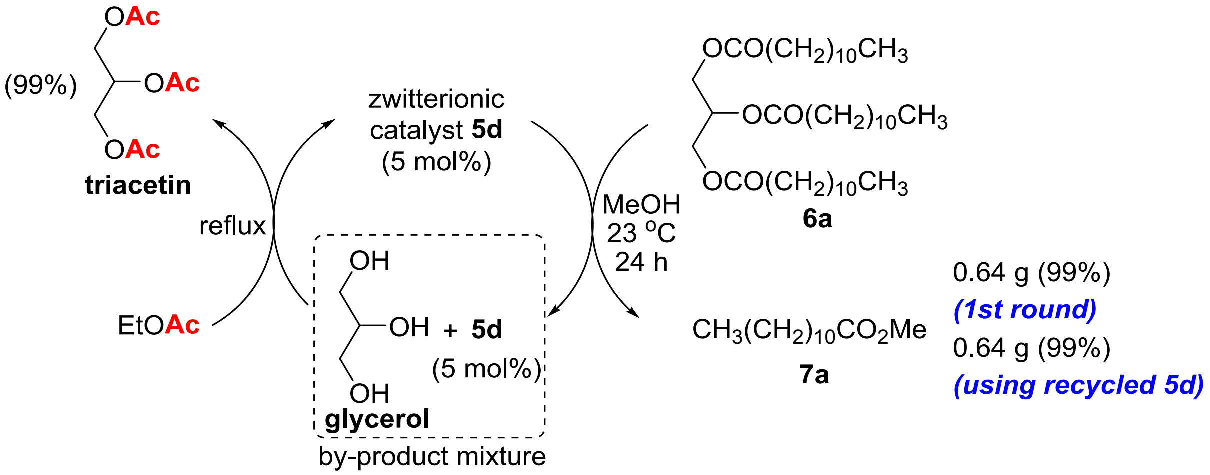


Figure 3. Catalyst recycle and triacetin synthesis

2.3 Transesterification of simple substrates

Next, the catalytic performance of zwitterions **5** in transesterification of other substrates was studied. Benzyl alcohol (**8a**) was used as the model substrate and the reaction was conducted in refluxing ethyl acetate (with 5Å molecular sieves in an additional funnel to remove the ethanol by-product). Similar to the case of biodiesel synthesis, the catalytic performance of zwitterion **5d** remains superior to other structural analogues. (Figure 4A). Further experiments revealed that the reaction could still proceed smoothly with 3 mol% of zwitterion **5d** at a higher concentration.[59]

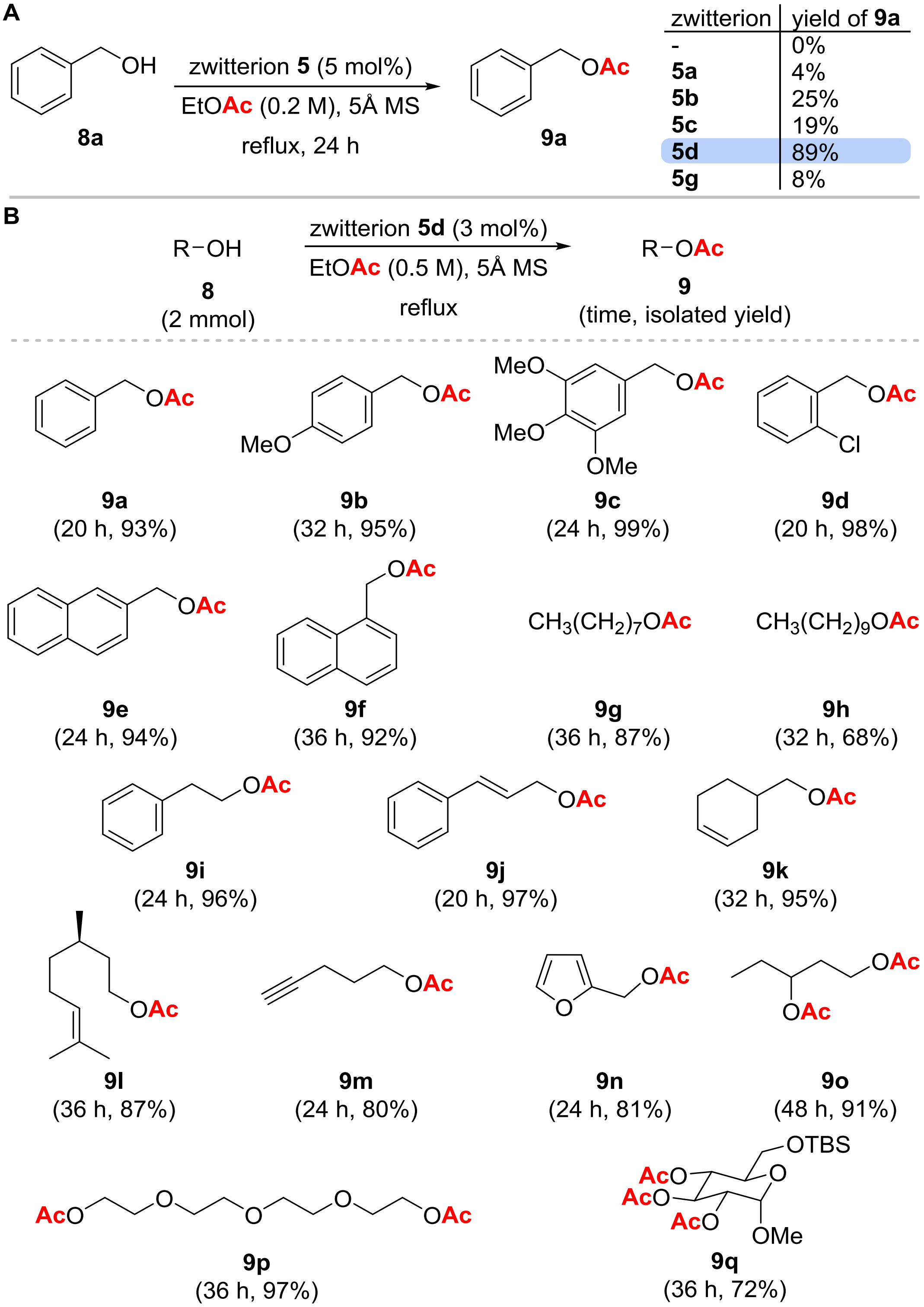
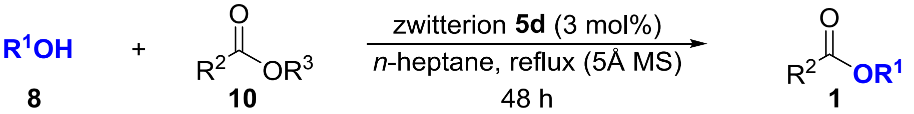


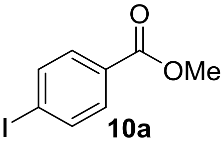
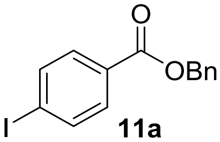
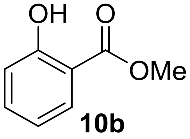
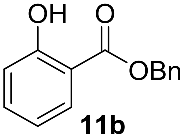
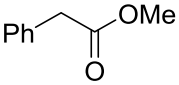
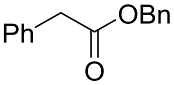
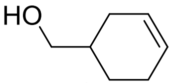
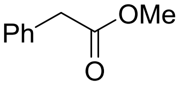
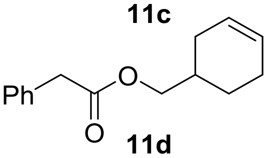
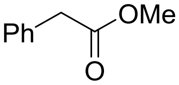
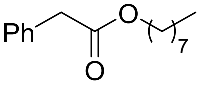
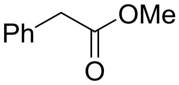
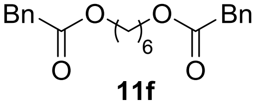
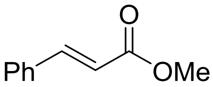
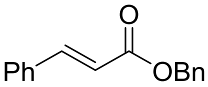
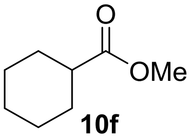
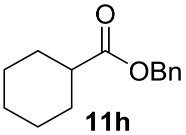
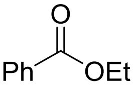
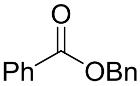
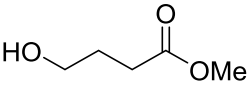
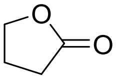
Figure 4. Transesterification with EtOAc

The optimized catalytic protocol was then applied to other alcohols (Figure 4B). In general, the reaction worked well with various aliphatic alcohols **8a-i** with electron-donating or withdrawing substituents. Functionalities including alkene (**8j-l**), alkyne (**8m**), and furan (**8n**), which are sensitive to conventional acid-mediated transesterification conditions,[60] were compatible with the zwitterion-catalyzed system to give the corresponding acetate products **9j-n** in good-to-excellent isolated yields. Acetylation of diols **8o** and **8p** could also be achieved to yield diacetates **9o** (91%) and **9p** (97%) smoothly. Interestingly, triacetylated sugar derivative **9q** was funished in good isolated yield. It is worth mentioning that acetylation of alcohols, which is one of the most common protection methods, typically requires the use of acetyl chloride or acetic anhydride.[61] In contrast, our approach can easily introduce the protecting group acetate into alcohols without acidic conditions.

Next, transesterification of methyl esters with different alcohol partners was studied. Equal molar amounts of alcohols **8** and methyl esters **10** were used and the reactions were conducted in refluxing *n*-heptane to azeotropically remove the methanol by-product (Table 1). Again, the catalytic protocol was found to be compatible with various functionalities. For instance, methyl salicylate (**10b**) readily underwent transesterification with benzyl alcohol (**8a**) to give **11b** in 98% yield with the phenol moiety remaining intact (entry 2). A 2:1 mixture of methyl ester **10d** and diol **8q** gave the transesterified diester product **11f** in 91% yield (entry 6). The catalytic protocol was also found to be compatible with α,β-unsaturated ester **10e**, the bulkier ester **10f**, and ethyl ester **10g** (entries 7-9). Interestingly, lactone **11j** was obtained quantitatively through the intramolecular transesterification of hydroxyl ester **10h** (entry 10). However, the transesterification of methyl benzoate and glycidol,[56] which is a useful but challenging reaction,

Table 1. Transesterification with Other Alcohols[a]



Entry	Alcohol	Ester	Product	Yield[b]
1	BnOH **8a**	 **10a**	 **11a**	98%
2	BnOH **8a**	 **10b**	 **11b**	98%
3	BnOH **8a**	 **10c**	 **11c**	99%
4	 **8k**	 **10d**	 **11d**	90%
5	$CH_3(CH_2)_7OH$ **8g**	 **10d**	 **11e**	99%
6[c]	$HO(CH_2)_6OH$ **8q**	 **10d**	 **11f**	91%
7	BnOH **8a**	 **10e**	 **11g**	90%
8	BnOH **8a**	 **10f**	 **11h**	86%
9	BnOH **8a**	 **10g**	 **11i**	92%
10[d]		 **10h**	 **11j**	99%

[a]Reactions were carried out with **10** (2 mmol), **8** (2.2 mmol) and zwitterion catalyst **5d** (0.06 mmol) in *n*-heptane (4 mL) at reflux under nitrogen atmosphere. [b]Isolated yield. [c]2 equivalents of **10d** were used. [d]The reaction time was 3 h.

was sluggish when using catalyst **5d**. It appears that the reaction scope of **5d** is complementary to that of tri-*n*-dodecylmethylammonium chloride.

2.4 Dehydrative esterification

During our substrate scope evaluation, it was surprising to realize that zwitterion **5d** was able to promote the reaction between succinic anhydride (**12**) and benzyl alcohol (**8a**) to give diester **13a**. The reaction was found to go through a one-pot two-step sequence: (1) ring-opening of **12** by **8a** to yield mono-ester **12'**; (2) dehydrative esterification of **12'** to give diester **13a** (Figure 5A). This result suggests that the catalytic protocol could catalyze the dehydrative esterification between a carboxylic acid and an alcohol, which is known to be challenging due to the high reaction barrier and strongly acidic catalysts are typically required to activate the carboxylic acid substrates.[62] The sulfide zwitterion **3b** was found to be ineffective in catalyzing the reaction, attributed to alcoholysis of isothiocyanate **1** by benzyl alcohol (similar to the case of transesterification of **6a**, Figure 1A).

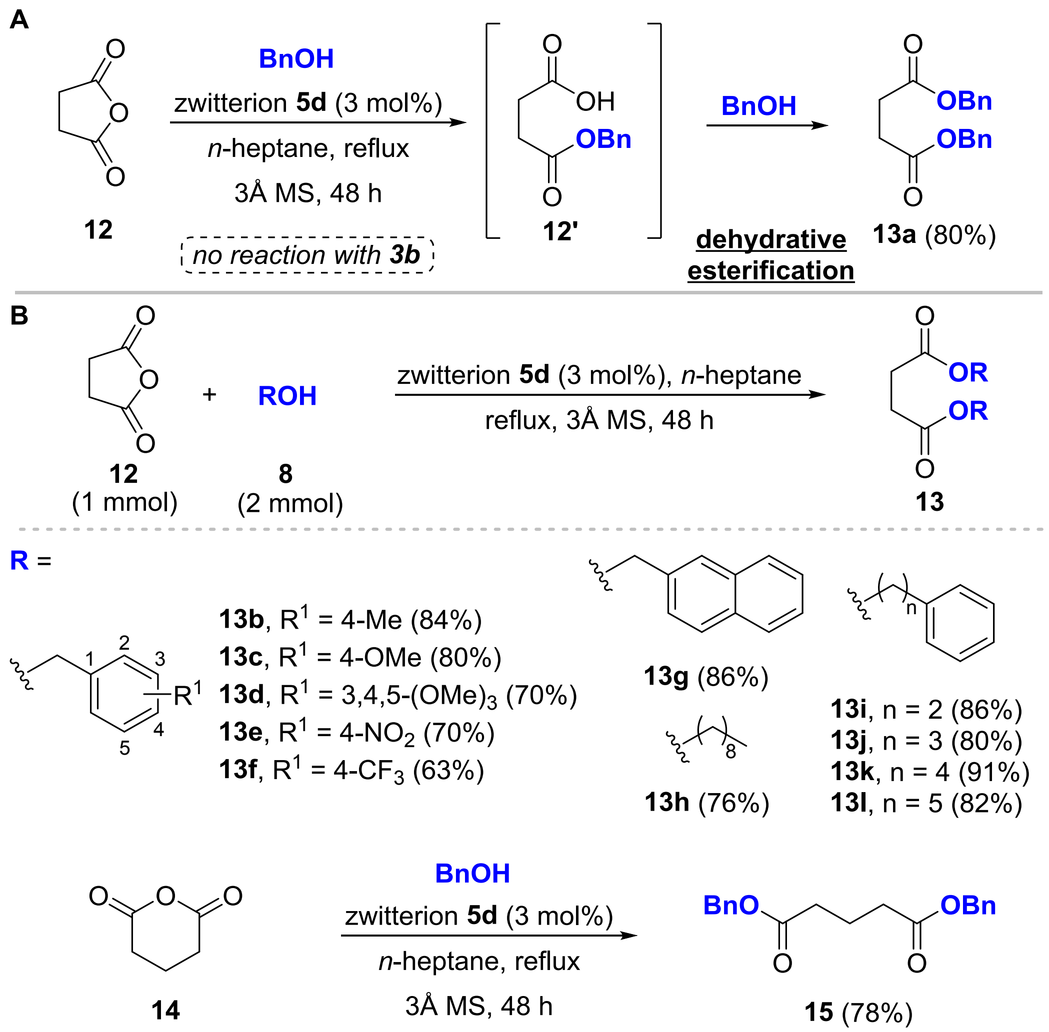


Figure 5. One-step Synthesis of Diesters from Succinic Anhydride

The generality of this reaction system was examined. The reactions were performed in refluxing *n*-heptane with Dean-Stark apparatus to remove the water by-product in the dehydrative esterification process. To our delight, a wide range of alcohols **8** bearing electron-rich or electron-deficient substituents were found to be compatible and the corresponding diester products **13b-13l** could be obtained in good isolated yields under mild conditions (Figure 5B). When replacing succinic anhydride (**12**) with glutaric anhydride (**14**), the corresponding diester **15** could still be obtained in 78% yield. It is noteworthy that diesters are useful starting materials for block co-polymer production but harsh synthetic conditions are often required to synthesize diesters.[66-64] We also examined the dehydrative esterification of other carboxylic acids **16** and alcohols **8**, and the desired ester products **17a-i** were obtained smoothly (Figure 6). Starting from diacids **16j-m**, the corresponding diesters **17j** and **17m** could be obtained in 75%-83% yields.

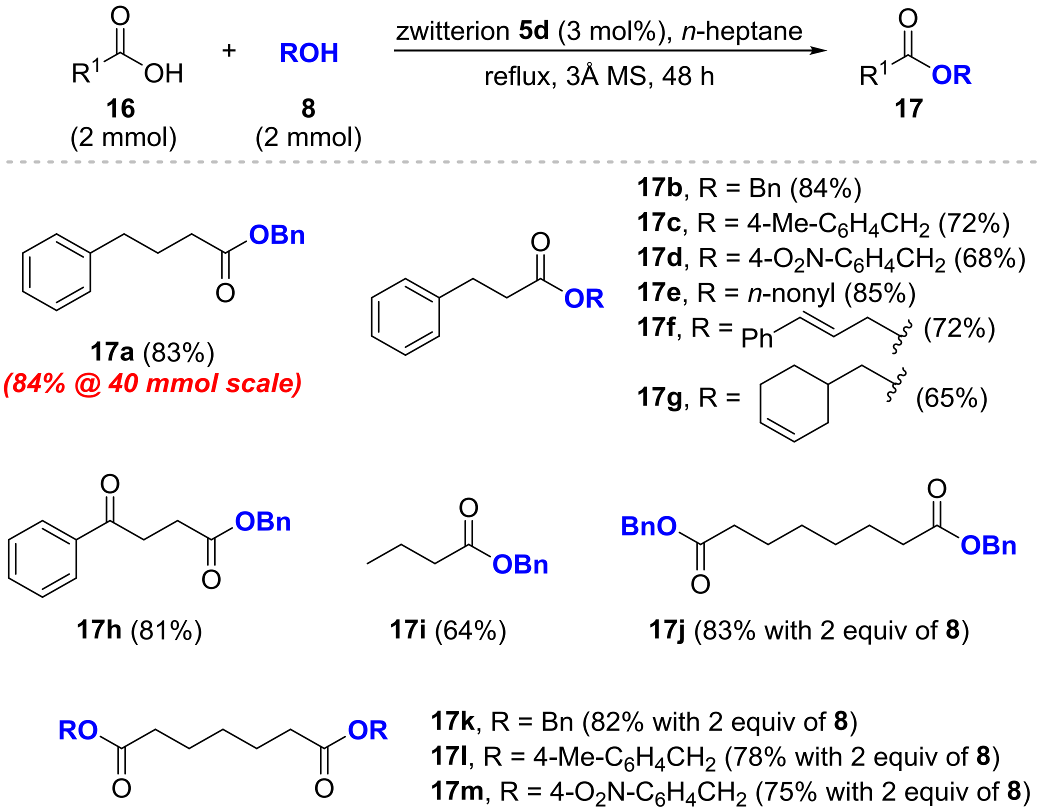


Figure 6. Dehydrative Esterification of Alcohols and Carboxylic Acids

2.5 Mechanistic studies

The mechanism for the dehydrative esterification is particularly remarkable in that the reaction could be promoted with a non-acidic catalyst.[62] ^{1}H NMR experiments on two mixtures, benzyl alcohol (**8a**)/**5d** and acetic acid/**5d**, were conducted and it appears that both the alcohol and the carboxylic acid could interact with the zwitterion **5d**.[59] Density functional theory (DFT) calculations at the level of M06-2X (with Grimme D3)[65-68]/6-311G(d,p) for the reaction between butyric acid (**16i**) and benzyl alcohol (**8a**) were carried out to get a better understanding on the reaction (Figure 7A). On the basis of the NMR studies, two reaction pathways were considered: (1) the sulfonamide deprotonates the carboxylic acid or (2) the sulfonamide deprotonates the alcohol. The calculation results indicated that zwitterion **5d** interacts with carboxylic acid **16i** to form intermediate **Acid-R**, which is more stable than the adduct **5d-R** (formed by the deprotonation of **8a** by zwitterion **5d**) by 3.2 kcal/mol. However, the subsequent step of nucleophilic attack of the carbonyl carbon by the alcohol (**Acid-TS1**) is highly disfavored because of the high free energy barrier ($\Delta G^{\ddagger}$ = 42.2 kcal/mol). From studying the optimized geometry, the zwitterion/alcohol adduct **5d-R** undergoes the nucleophilic substitution at the carbonyl carbon to give the ortho-ester intermediate **5d-IM** through **5d-TS1**, with a significantly smaller free energy barrier ($\Delta G^{\ddagger}$ = 28.7 kcal/mol). As predicted by the Eyring equation, the rate constant associated with this small barrier is about 10^8 times larger than that of the barrier of 42.2 kcal/mol in **Acid-TS1**. The interconversion barrier between **Acid-R** and **5d-R** is likely to be significantly smaller than the energy barriers of 42.2 kcal/mol and 28.7 kcal/mol. Therefore, **Acid-R** appears to be a trap in the catalytic cycle, and the reaction likely proceeds to the final product via the rate-determining step **5d-R→5d-TS1**. Subsequent collapse of the orthoester **5d-IM** through **5d-TS2** gives the ester product **17i** and water together with the regeneration of the zwitterionic catalyst **5d**. Continuous removal of the water by-product from the reaction system favors the product formation.

In the optimized geometry of **5d-TS1**, the pyrrolidine protons adjacent to the iminium cation in zwitterion **5d** are positioned in close proximity to the oxygen of the carbonyl of **16i** with distances at 2.40 and 2.63 Å (average = 2.51 Å, Figure 7B). These values are within the range of a typical hydrogen bond interaction. Thus, we believe that a non-classical hydrogen bond[69-72] might stabilize the intermediate and reduce the energy barrier. This result is also consistent with our NMR study in which the pyrrolidine's proton signals shifted up-field upon the addition of alcohol,[59] potentially due to the interaction of the alkoxide anion with the pyrrolidine's protons through the non-classical hydrogen bonds. The system with the DMAP-derived catalyst **5b** was also analyzed by DFT (the free energy profile is provided in SI). We found that the reaction encounters a considerably higher barrier ($\Delta G^{\ddagger}$ = 30.4 kcal/mol) at the rate-determining step **5b-TS1** as compared with **5d-TS1**. We hypothesize that the movement of the pyrrolidine's protons in **5d** is restricted as a result of the rigid PPY moiety, which can provide a better stabilization effect to the carboxylic acid. In contrast, the rotatable methyl groups in the DMAP moiety of zwitterion **5b** might be less effective in stabilizing the transition state **TS1** through the non-classical hydrogen bond. Indeed, the closest distances between the carbonyl oxygen and the methyl protons in **5b-TS1** were calculated to be 3.72 Å and 2.38 Å (average = 3.05 Å), whose average is considerably longer than that in **5d-TS1**. These computational studies reveal the cooperative nature of the charge pair in zwitterion **5d** in the dehydrative esterification.

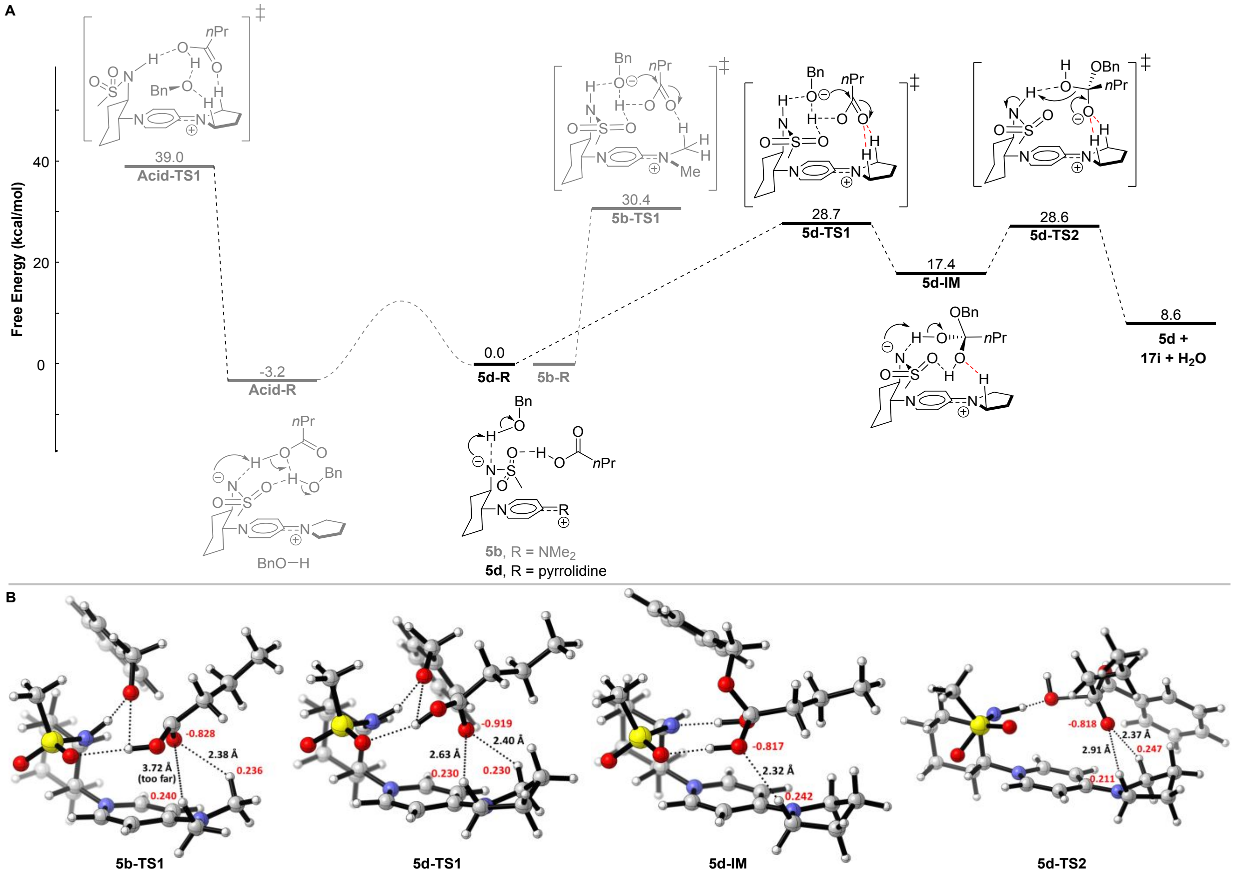


Figure 7. (A) Calculated free energy profile of the proposed dehydrative esterification mechanism. The zero of each free energy profile is defined to be the energy of the **R** state. (B) Snapshots of the transition states. The distances between atoms (angstrom) are shown in black dashed lines. The red numbers next to the atoms are the nitrogen and oxygen NBO atomic charges from the catalyst and the acid.

DFT calculations for the reaction between benzyl alcohol (**8a**) and ethyl acetate with zwitterionic catalyst **5d** were also carried out (Figure 8). A stable complex **Ester-R** originated from the hydrogen bond interaction between **5d** and **8a** was identified, which is consistent with the NMR study.[59] Based on the optimized energy profile, **8a** attacks the ester (**Ester-TS1**) to give the tetrahedral intermediate **Ester-IM1** (stabilized by 7.2 kcal/mol). Similar to the case of dehydrative esterification, the carbonyl group of ethyl acetate is activated by the non-classical hydrogen bond originated from the pyrrolidine's protons (**Ester-TS1**, average distance of the O···H = 2.493 Å). The step **Ester-R→Ester-TS1** is the rate-determining step ($\Delta G^{\ddagger}$ = 21.2 kcal/mol). Re-organization of the complex (**Ester-IM1→Ester-IM2**) followed by collapse of the tetrahedral intermediate through **Ester-TS2** gives transesterification product benzyl acetate (**9a**).

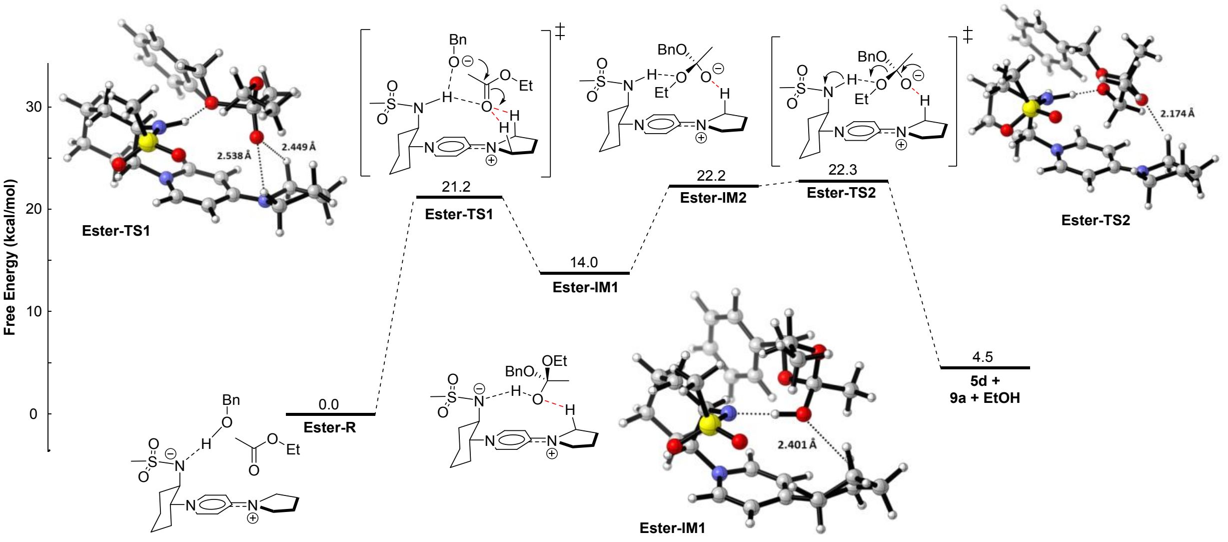


Figure 8. Calculated free energy profile of the proposed transesterification mechanism. The zero of each free energy profile is defined to be the energy of the **R** state.

Although the zwitterion is not Brønsted acidic, the non-classical hydrogen bond in **5d** appears to play an important role in activating the carbonyl group of carboxylic acid and ester in the dehydrative esterification and transesterification, respectively. In addition, a suitable catalyst pocket size (which is defined by the distance between the anion and the cation in the zwitterionic system) seems to be crucial in accommodating the reaction partners for high catalytic performance.

3. CONCLUSIONS

In summary, a new zwitterionic organocatalytic protocol has been developed and applied in (trans)esterification reactions. Mechanistic studies revealed that the catalyst can activate the carbonyl substrates through non-classical hydrogen bonds. Further applications of this novel catalytic protocol in other reactions are underway.

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Notes

The authors declare no competing financial interest.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge.

Experimental details, CIF files, spectroscopic and analytical data for new compounds. (PDF)

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REFERENCES

(1) Waser, M.; Novacek, J.; Gratzer, K. Cooperative Catalysis Involving Chiral Ion Pair Catalysts. In *Cooperative catalysis: Designing efficient catalysts for synthesis*; Peters, R., Ed.; Wiley-VCH: Germany, 2015; pp 197–226.

(2) Tian, S.; Chen, Y.; Hang, J.; Tang, L.; Mcdaid, P.; Deng, L., Asymmetric Organic Catalysis with Modified Cinchona Alkaloids. *Acc. Chem. Res.* **2004**, *37*, 621–631.

(3) Chauhan, P.; Mahajan, S.; Kaya, U.; Hack, D.; Enders, D., Bifunctional Amine-Squaramides: Powerful Hydrogen-Bonding Organocatalysts for Asymmetric Domino/Cascade Reactions. *Adv. Synth. Catal.* **2015**, *357*, 253–281.

(4) Liu, X.; Lin, L.; Feng, X., Amide-based bifunctional organocatalysts in asymmetric reactions. *Chem. Commun.* **2009**, 6145–6158.

(5) Siau, W.; Wang, J., Asymmetric organocatalytic reactions by bifunctional amine-thioureas. *Catal. Sci. Technol.* **2011**, *1*, 1298–1310.

(6) Brière, J.; Oudeyer, S.; Dalla, V.; Levacher, V. Recent Advances in Cooperative Ion Pairing in Asymmetric Organocatalysis. *Chem. Soc. Rev*. **2012**, *41*, 1696-1707.

(7) Brak, K.; Jacobsen, E. N. Asymmetric Ion-Pairing Catalysis. *Angew. Chem. Int. Ed.* **2012**, *2*, 534-561.

(8) Qian, D.; Sun, J. Recent Progress in Asymmetric Ion-pairing Catalysis with Ammonium Salts. *Chem. Eur. J.* **2019**, *15*, 3740-3751.

(9) Phipps, R. J.; Hamilton, G. L.; Toste, F. D. The Progression of Chiral Anions from Concepts to Applications in Asymmetric Catalysis. *Nat. Chem.* **2012**, *4*, 603-614.

(10) McNaught, A. D.; Wilkinson, A. *IUPAC. Compendium of Chemical Terminology (2nd ed.)*; Blackwell Scientific Publications: Oxford, 1997.

(11) Legros, F.; Oudeyer, S.; Levacher, V., New Developments in Chiral Cooperative Ion Pairing Organocatalysis by Means of Ammonium Oxyanions and Fluorides: From Protonation to Deprotonation Reactions. *Chem. Rec.* **2017**, *17*, 429–440.

(12) Godemert, J.; Oudeyer, S.; Levacher, V. Chiral Ammonium Aryloxides: Efficient Multipurpose Basic Organocatalysts. *ChemCat Chem.* **2016**, *8*, 74–85.

(13) Xie, C.; Song, J.; Wu, H.; Zhou, B.; Wu, C.; Han, B., Natural Product Glycine Betaine as an Efficient Catalyst for Transformation of CO_2 with Amines to Synthesize *N*-Substituted Compounds *ACS Sustainable Chem. Eng.* **2017**, *5*, 7086–7092.

(14) Tsutsumi, Y.; Yamakawa, K.; Yoshida, M.; Ema, T.; Sakai, T., Bifunctional Organocatalyst for Activation of Carbon Dioxide and Epoxide To Produce Cyclic Carbonate: Betaine as a New Catalytic Motif. *Org. Lett.* **2010**, *12*, 5728–5731.

(15) Liu X.-F.; Li, X.-Y.; Qiao, C.; Fu, H.-C.; He, L.-N., Betaine Catalysis for Hierarchical Reduction of CO_2 with Amines and Hydrosilane To Form Formamides, Aminals, and Methylamines. *Angew. Chem. Int. Ed.* **2017**, *56*, 7425–7429.

(16) Zhou, Y.; Hu, S.; Ma, X.; Liang, S.; Jiang, T.; Han, B., Synthesis of cyclic carbonates from carbon dioxide and epoxides over betaine-based catalysts. *J. Mol. Catal. A: Chem.* **2008**, *284*, 52–57.

(17) Guillerm, B.; Lemaur, V.; Cornil, J.; Lazzaroni, R.; Dubois, P.; Coulembier, O., Ammonium betaines: efficient ionic nucleophilic catalysts for the ring-opening polymerization of L-lactide and cyclic carbonates. *Chem. Commun.* **2014**, *50*, 10098–10101.

(18) Uraguchi, D.; Torii, M.; Ooi, T., Acridinium Betaine as a Single-Electron-Transfer Catalyst: Design and Application to Dimerization of Oxindoles. *ACS Catal.* **2017**, *7*, 2765–2769.

(19) Hasegawa, E.; Izumiya, N.; Miura, T.; Ikoma, T.; Iwamoto, H.; Takizawa, S.; Murata, S., Benzimidazolium Naphthoxide Betaine Is a Visible Light Promoted Organic Photoredox Catalyst. *J. Org. Chem.* **2018**, *83*, 3921–3927.

(20) Kundu, D.; Debnath, R. K.; Majee, A.; Hajra, A., Zwitterionic-type molten salt-catalyzed *syn*-selective aza-Henry reaction: solvent-free one-pot synthesis of β-nitroamines. *Tetrahedron Lett.* **2009**, *50*, 6998–7000.

(21) Kundu, D.; Majee, A.; Hajra, A., Zwitterionic-type molten salt: An efficient mild organocatalyst for synthesis of 2-amidoalkyl and 2-carbamatoalkyl naphthols. *Catal. Commun.* **2010**, *11*, 1157–1159.

(22) Kundu, D.; Bagdi, A. K.; Majee, A.; Hajra, A., Zwitterionic-Type Molten Salt: A Mild and Efficient Organocatalyst for the Synthesis of 3-Aminoalkylated Indoles via Three-Component Coupling Reaction. *Synlett* **2011**, 1165–1167.

(23) Rahman, M.; Bagdi, A. K.; Kundu, D.; Majee, A.; Hajra, A., Zwitterionic-Type Molten Salt-Catalyzed Multicomponent Reactions: One-Pot Synthesis of Substituted Imidazoles Under Solvent-Free Conditions. *J. Heterocycl. Chem.* **2012**, *49*, 1224–1228.

(24) Rahman, M.; Roy, A.; Ghosh, M.; Mitra, S.; Majee, A.; Hajra, A., Organocatalysis by an aprotic imidazolium zwitterion: a dramatic anion–cation cooperative effect on azide–nitrile cycloaddition. *RSC Adv.* **2014**, *4*, 6116–6119.

(25) Qiao, Y.; Zhang, L.; Luo, S.; Cheng, J.-P., Chiral Zwitterions from Vicinal Diamines: Effective and Recoverable Asymmetric Enamine Catalysts. *Synlett* **2011**, *4*, 495–498.

(26) Ghosal, N. C.; Santra, S.; Das, S.; Hajra, A.; Zyryanov, G. V.; Majee, A., Organocatalysis by an aprotic imidazolium zwitterion: regioselective ring-opening of aziridines and applicable to gram scale synthesis. *Green Chem.* **2016**, *18*, 565–574.

(27) Uraguchi, D.; Koshimoto, K.; Ooi, T., Chiral Ammonium Betaines: A Bifunctional Organic Base Catalyst for Asymmetric Mannich-Type Reaction of α-Nitrocarboxylates. *J. Am. Chem. Soc.* **2008**, *130*, 10878–10879.

(28) Uraguchi, D.; Koshimoto, K.; Miyake, S.; Ooi, T., Chiral Ammonium Betaines as Ionic Nucleophilic Catalysts. *Angew. Chem. Int. Ed.* **2010**, *49*, 5567–5569.

(29) Uraguchi, D.; Koshimoto, K.; Ooi, T., Flexible synthesis, structural determination, and synthetic application of a new C_1-symmetric chiral ammonium betaine. *Chem. Commun.* **2010**, *46*, 300–302.

(30) Uraguchi, D.; Koshimoto, K.; Sanada, C.; Ooi, T., Performance of C_1-symmetric chiral ammonium betaines as catalysts for the enantioselective Mannich-type reaction of α-nitrocarboxylates. *Tetrahedron: Asymmetry* **2010**, *21*, 1189–1190.

(31) Uraguchi, D.; Koshimoto, K.; Ooi, T., Ionic Nucleophilic Catalysis of Chiral Ammonium Betaines for Highly Stereoselective Aldol Reaction from Oxindole-Derived Vinylic Carbonates. *J. Am. Chem. Soc.* **2012**, *134*, 6972–6975.

(32) Uraguchi, D.; Oyaizu, K.; Ooi, T., Nitroolefins as a Nucleophilic Component for Highly Stereoselective Aza Henry Reaction under the Catalysis of Chiral Ammonium Betaines. *Chem. Eur. J.* **2012**, *18*, 8306–8309.

(33) Uraguchi, D.; Oyaizu, K.; Noguchi, H.; Ooi, T., Chiral Ammonium Betaine-Catalyzed Highly Stereoselective Aza-Henry Reaction of α-Aryl Nitromethanes with Aromatic *N*-Boc Imines. *Chem. Asian J.* **2015**, *10*, 334–337.

(34) Zhou, X.; Wu, Y.; Deng, L., Cinchonium Betaines as Efficient Catalysts for Asymmetric Proton Transfer Catalysis: The Development of a Practical Enantioselective Isomerization of Trifluoromethyl Imines. *J. Am. Chem. Soc.* **2016**, *138*, 12297–12302.

(35) Zhang, W.-Q.; Cheng, L.-F.; Yu, J.; Gong, L.-Z., A Chiral Bis(betaine) Catalyst for the Mannich Reaction of Azlactones and Aliphatic Imines. *Angew. Chem. Int. Ed.* **2012**, *51*, 4085–4088.

(36) Claraz, A.; Landelle, G.; Oudeyer, S.; Levacher, V., Asymmetric Organocatalytic Protonation of Silyl Enolates Catalyzed by Simple and Original Betaines Derived from *Cinchona* Alkaloids. *Eur. J. Org. Chem.* **2013**, 7693–7696.

(37) Chen, K.; Shi, G.; Li, H.; Wang, C.; Darensbourg, D. J., Design of Betaine Functional Catalyst for Efficient Copolymerization of Oxirane and CO_2. *Macromolecules* **2018**, *51*, 6057–6062.

(38) Wang, H.-Y.; Zheng, C.-W.; Chai, Z.; Zhang, J.-X. Zhao, G., Asymmetric cyanation of imines via dipeptide-derived organophosphine dual-reagent catalysis. *Nat. Commun.* **2016**, *7*, 12720.

(39) Wang, H.-Y.; Zhang, K.; Zheng, C.-W.; Chai, Z.; Cao, D.-D.; Zhang, J.-X.; Zhao, G., Asymmetric Dual-Reagent Catalysis: Mannich-type Reactions Catalyzed by Ion Pair. *Angew. Chem. Int. Ed.* **2015**, *54*, 1775–1779.

(40) Bauer, G.; Ongari, D.; Xu, X.; Tiana, D.; Smit, B.; Ranocchiari, M., Metal–Organic Frameworks Invert Molecular Reactivity: Lewis Acidic Phosphonium Zwitterions Catalyze the Aldol-Tishchenko Reaction. *J. Am. Chem. Soc.* **2017**, *139*, 18166–18169.

(41) Toda, Y.; Sakamoto, T.; Komiyama, Y.; Kikuchi, A.; Suga, H. A Phosphonium Ylide as an Ionic Nucleophilic Catalyst for Primary Hydroxyl Group Selective Acylation of Diols. *ACS Catal*. **2017**, *7*, 6150-6154.

(42) Keillor, J. W.; Neverov, A. A.; Brown, R. S., Catalysis of Amide Hydrolysis and Formation under Neutral Conditions by a Zwitterionic Imidazolium Thiolate. *J. Am. Chem. Soc.* **1994**, *116*, 4669–4673.

(43) Yanai, H.; Kobayashi, O.; Takada, K.; Isono, T.; Satoh, T.; Matsumoto, T., Sequential Mukaiyama–Michael reaction induced by carbon acids. *Chem. Commun.* **2016**, *52*, 3280–3283.

(44) Yanai, H.; Yoshino, T.; Fujita, M.; Fukaya, H.; Kotani, A.; Kusu, F.; Taguchi, T., Synthesis, Characterization, and Applications of Zwitterions Containing a Carbanion Moiety. *Angew. Chem. Int. Ed.* **2013**, *52*, 1560–1563.

(45) Yanai, H.; Ishii, N.; Matsumoto, T.; Taguchi, T., Organic Acid Catalysts in Reactions of Lactones with Silicon Enolates. *Asian J. Org. Chem.* **2013**, *2*, 989–996.

(46) Yanai, H.; Sasaki, Y.; Yamamoto, Y.; Matsumoto, T. Chemoselective Two-Directional Reaction of Bifunctionalized Substrates: Formal Ketal-Selective Mukaiyama Aldol Type Reaction *Synlett* **2015**, *26*, 2457–2461.

(47) Ishihara, K.; Niwa, M.; Kosugi, Y., Zwitterionic Salts as Mild Organocatalysts for Transesterification. *Org. Lett.* **2008**, *10*, 2187–2190.

(48) Hatanoa, M.; Ishihara, K., Lanthanum(III) catalysts for highly efficient and chemoselective transesterification. *Chem. Commun.* **2013**, *49*, 1983−1997.

(49) Cheng, Y. A.; Chen, T.; Tan, C. K.; Heng, J. J.; Yeung, Y.-Y., Efficient Medium Ring Size Bromolactonization Using a Sulfur-Based Zwitterionic Organocatalyst. *J. Am. Chem. Soc.* **2012**, *134*, 16492–16495.

(50) Xiong, X.; Tan, F.; Yeung, Y.-Y., Zwitterionic-Salt-Catalyzed Site-Selective Monobromination of Arenes. *Org. Lett.* **2017**, *19*, 4243–4246.

(51) Watson, I. D. G.; Afagh, N.; Yudin, A. K., Cyclohexene imine (7-aza-bicyclo[4.1.0]heptane). *Org. Synth*. **2010**, *87*, 161–169.

(52) Crocker, M., *Thermochemical conversion of biomass to liquid fuels and chemicals*; RSC Publishing: Cambridge, 2010.

(53) Talebian-Kiakalaieh, A.; Amin, N. A. S.; Mazaheri, H., A review on novel processes of biodiesel production from waste cooking oil. *Appl. Energy* **2013**, *104*, 683–710.

(54) Leung, D. Y. C.; Wu, X.; Leung, M. K. H., A review on biodiesel production using catalyzed transesterification. *Appl. Energy* **2010**, *87*, 1083–1095.

(55) Lin, L.; Zhou, C.; Vittayapadung, S.; Shen, X.; Dong, M., Opportunities and challenges for biodiesel fuel. *Appl. Energy* **2011**, *88*, 1020–1031.

(56) Tanaka, S.; Nakashima, T.; Maeda, T.; Ratanasak, M.; Hasegawa, J.; Kon, Y.; Tamura, M.; Sato, K., Quaternary Alkyl Ammonium Salt-Catalyzed Transformation of Glycidol to Glycidyl Esters by Transesterification of Methyl Esters. *ACS Catal.* **2018**, *8*, 1097−1103.

(57) Hatano, M.; Tabata, Y.; Yoshida, Y.; Toh, K.; Yamashita, K.; Ogura, K.; Ishihara, K., Metal-Free Transesterification Catalyzed by Tetramethylammonium Methyl Carbonate. *Green Chem.* **2018**, *20*, 1193−1198.

(58) Gupta, M.; Kumar, N., Scope and opportunities of using glycerol as an energy source. *Renewable Sustainable Energy Rev.* **2012**, *16*, 4551–4556.

(59) The details appear in SI.

(60) Otera, J., Transesterification. *Chem. Rev.* **1993**, *93*, 1449–1470.

(61) Wuts, P. G. M.; Greene, T. W. *Greene's Protective Groups in Organic Synthesis* (4th ed.); Wiley, New Jersey, **2007**.

(62) Matsumoto, K.; Yanagi, R.; Oe, Y. in *Carboxylic Acid-Key Role in Life Sciences* (Badea, G.-I.; Radu, G. L. eds.), InTechOpen; Ch 2, pp 7-34, **2018**.

(63) Otera, J.; Nishikido, J. *Esterification: Methods, Reactions, and Applications*; Wiley-VCH, Weinheim, 2010.

(64) Feng, H.; Lu, X.; Wang, W.; Kang, N.-G.; Mays, J. W. Block Copolymers: Synthesis, Self-Assembly, and Applications. *Polymers* **2017**, *9*, 494.

(65) The level of the calculations was M06-2X (with Grimme D3)/6-311G(d,p) using Gaussian 09 (ver. D.01). The transition states were verified by frequency calculations. All the thermodynamic properties were evaluated at 373K. The atomic charges shown were NBO charges.

(66) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Petersson, G. A.; Nakatsuji, H.; Li, X.; Caricato, M.; Marenich, A.; Bloino, J.; Janesko, B. G.; Gomperts, R.; Mennucci, B.; Hratchian, H. P.; Ortiz, J. V.; Izmaylov, A. F.; Sonnenberg, J. L.; Williams-Young, D.; Ding, F.; Lipparini, F.; Egidi, F.; Goings, J.; Peng, B.; Petrone, A.; Henderson, T.; Ranasinghe, D.; Zakrzewski, V. G.; Gao, J.; Rega, N.; Zheng, G.; Liang, W.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.;

Nakai, H.; Vreven, T.; Throssell, K.; Montgomery, Jr., J. A.; Peralta, J. E.; Ogliaro, F.; Bearpark, M.; Heyd, J. J.; Brothers, E.; Kudin, K. N.; Staroverov, V. N.; Keith, T.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Millam, J. M.; Klene, M.; Adamo, C.; Cammi, R.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Farkas, O.; Foresman, J. B.; Fox, D. J. Gaussian 09 Revision D. 01. *Gaussian Inc. Wallingford CT* 2009.

(67) Zhao, Y.; Truhlar, D. G., The M06 suite of density functionals for main group thermochemistry, thermochemical kinetics, noncovalent interactions, excited states, and transition elements: two new functionals and systematic testing of four M06-class functionals and 12 other functionals. *Theor. Chem. Acc.* **2008**, *120*, 215–241.

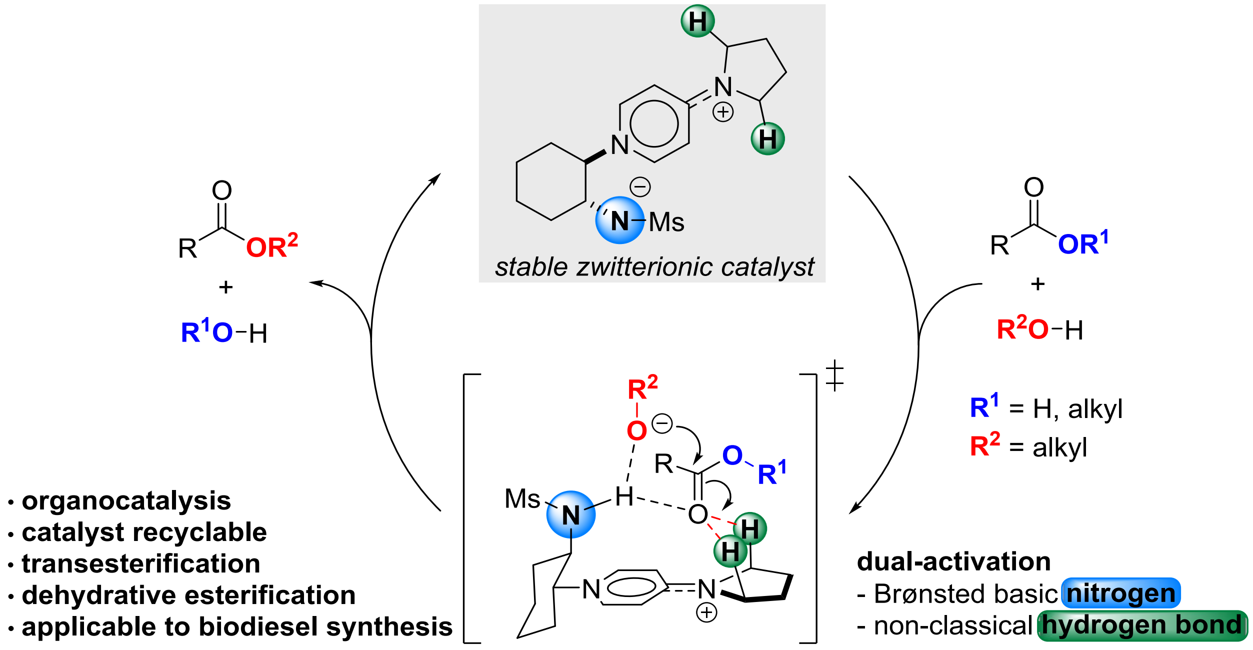
(68) Grimme, S.; Ehrlich, S.; Goerigk, L., Effect of the damping function in dispersion corrected density functional theory. *J. Comput. Chem.* **2011**, *32*, 1456–1465.

(69) Johnston, R. C.; Cheong, P. H.-Y., C–H···O non-classical hydrogen bonding in the stereomechanics of organic transformations: theory and recognition. *Org. Biomol. Chem.* **2013**, *11*, 5057–5064.

(70) Berg, L.; Mishra, B. K.; Andersson, C. D.; Ekström, F.; Linusson, A., The Nature of Activated Non-classical Hydrogen Bonds: A Case Study on Acetylcholinesterase–Ligand Complexes. *Chem. Eur. J.* **2016**, *22*, 2672–2681.

(71) Molina, P.; Zapata, F.; Caballero, A., Anion Recognition Strategies Based on Combined Noncovalent Interactions. *Chem. Rev.* **2017**, *117*, 9907–9972.

(72) Desiraju, G.; Steiner, T. *The Weak Hydrogen Bond: In Structural Chemistry and Biology*; Oxford University Press, **2001**.


stable zwitterionic catalyst
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R OR1
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R1 = H, alkyl
R2 = alkyl
‡
• organocatalysis
• catalyst recyclable
• transesterification
• dehydrative esterification
• applicable to biodiesel synthesis
dual-activation
- Brønsted basic nitrogen
- non-classical hydrogen bond