

Cite this: *RSC Adv.*, 2018, **8**, 4571

Received 6th November 2017

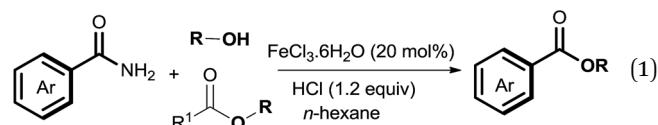
Accepted 6th January 2018

DOI: 10.1039/c7ra12152k

rsc.li/rsc-advances

The amide bond is not only employed as an important natural peptide skeleton in biological systems, but also as a versatile functional group in organic transformations.^{1,2} Among amide transformations,^{3,4} transamidation and esterification of amides have attracted widespread attention from organic chemists.^{5–11} In contrast to transamidation of amides, esterification of amides is relatively difficult because of the low nucleophilicity of alcohols compared with amines.¹² To overcome this shortcoming, various processes for the esterification of amides have been developed, such as using an activating agent,⁶ employing twisted amides,⁷ and forming intramolecular assisted groups.⁸ For increasing the synthetic flexibility of esterification of amides, new catalytic systems $Zn(OTf)_2$ and $Sc(OTf)_3$ were developed by Mashima and Williams for the esterification of amides.⁹ Shimizu *et al.* reported CeO_2 catalyzed esterification of amides.¹⁰ Off late, progress of the significant Ni-catalyzed esterification of amides has gained precedence.¹¹ Although this approach produces satisfactory yield, the drawbacks such as the use of an expensive catalyst, generation of reagent waste, high temperature and the limited scope of the substrate still persists. Herein, under mild reaction conditions, we report a novel and efficient Fe-catalyzed esterification of amides for the synthesis of esters (eqn (1)). Compared to conventional methods, this esterification procedure is distinguished by using a stable, inexpensive, environment-friendly catalyst, *i.e.*, $FeCl_3 \cdot 6H_2O$ with a low toxicity solvent. The catalytic system has wide functional group compatibility. The reactions of several primary, secondary, and tertiary amides with various alcohols have been well tolerated in this process. Moreover, esters were also as effective as esterification reagents for the esterification of amides by the acyl-acyl exchange process. In the course of our present study, a Co-catalyzed amide C–N cleavage to form esters was reported by Danoun *et al.*¹³ However, an additional additive (Bipy) and Mn (3 equiv.) were needed and the scope of

the reaction was limited to only tertiary amides; primary or secondary amides were not compatible with this catalytic oxidation system.



We initially selected benzamide **1a** and ethanol **2a** as model substrates to screen the reaction conditions, and the results are summarized in Table 1. First, in the presence of $FeCl_2$, ethyl benzoate **3a** was afforded in 31% yield (Table 1, entry 1). Next, our catalyst-screening results showed that various iron complexes such as $FeCl_3$, $FeBr_3$, $FeSO_4 \cdot 7H_2O$, $FeCl_3 \cdot 6H_2O$, and $Fe(NO_3)_3 \cdot 9H_2O$ could catalyze the reaction (Table 1, entries 2–6), and $FeCl_3 \cdot 6H_2O$ was the best catalyst for this reaction as ethyl benzoate **3a** was afforded in 35% yield (Table 1, entry 6). Other metal complexes such as $CuCl_2$, $PdCl_2$, and $NiCl_2 \cdot 6H_2O$ did not improve the efficiency of this transformation (Table 1, entries 7–9). In the absence of an iron complex, this reaction could not work and the product was not detected (Table 1, entry 10). Next, in the presence of $FeCl_3 \cdot 6H_2O$, the influence of additives on the reaction was investigated (Table 1, entries 11–18). Among the tested additives, the stronger bidentate ligands such as 1,10-phenanthroline or 2,2-bipyridine did not show any efficiency, while hydrochloric acid gave the best reactive activity as ethyl benzoate **3a** was obtained in 91% yield (Table 1, entry 18). In general, H_2SO_4 or HNO_3 was used as a catalyst for esterification; however, they did not efficiently promote the reaction under the present system (Table 1, entries 16–17). In the absence of $FeCl_3 \cdot 6H_2O$, the product **3a** was afforded in 35% yield (Table 1, entry 19). For the solvents investigated (Table 1, entries 20–23), *n*-hexane was the best choice (Table 1, entry 18).

The substrate scope of esterification with alcohols was investigated under the optimized reaction conditions. As shown in Table 2, esterification of benzamide by primary alcohols,

Hubei University Of Science and Technology, China

† Electronic supplementary information (ESI) available. See DOI: 10.1039/c7ra12152k



Table 1 Optimization of the reaction conditions^a

Entry	Catalyst (20%)	Additive (40%)	Yield ^b	Reaction scheme:	
				<chem>1a</chem>	<chem>2a</chem>
1	FeCl ₂	—	31		
2	FeCl ₃	—	31		
3	FeBr ₃	—	25		
4	FeSO ₄ ·7H ₂ O	—	20		
5	Fe(NO ₃) ₃ ·9H ₂ O	—	20		
6	FeCl ₃ ·6H ₂ O	—	35		
7	CuCl ₂	—	Trace		
8	PdCl ₂	—	Trace		
9	Ni ₂ Cl ₆ ·6H ₂ O	—	Trace		
10	—	—	—		
12	FeCl ₃ ·6H ₂ O	Pyridine	Trace		
13	FeCl ₃ ·6H ₂ O	1,10-Phenanthroline	Trace		
14	FeCl ₃ ·6H ₂ O	Formic acid	Trace		
15	FeCl ₃ ·6H ₂ O	l-Proline	Trace		
16	FeCl ₃ ·6H ₂ O	H ₂ SO ₄	22		
17	FeCl ₃ ·6H ₂ O	HNO ₃	25		
18	FeCl ₃ ·6H ₂ O	HCl	91		
19	—	HCl	35		
20 ^c	FeCl ₃ ·6H ₂ O	HCl	Trace		
21 ^d	FeCl ₃ ·6H ₂ O	HCl	36		
22 ^e	FeCl ₃ ·6H ₂ O	HCl	28		
23 ^f	FeCl ₃ ·6H ₂ O	HCl	40		

^a Reaction conditions: **1a** (0.2 mmol), **2a** (0.1 mL), catalyst (0.04 mmol, 20 mol%), H₂SO₄ (concentrated, 0.24 mmol), HNO₃ (concentrated, 0.24 mmol), HCl (0.24 mmol, 36–38%), *n*-hexane (1.0 mL), 80 °C, 14 h. ^b GC yield using hexadecane as internal standard. ^c DMF was used as a solvent. ^d 1,4-Dioxane was used as solvent. ^e Toluene was used as solvent. ^f CH₃CN was used as solvent.

secondary alcohols, tertiary alcohols, and ring alcohols took place smoothly, and the corresponding esters were afforded in good to high yields. When primary alcohols **2a**, **2b**, **2c** were used as substrates, affording the ester products **3a**–**3c** in high yields, it should be noted that the reactivity of the alcoholysis of amides was independent of the alkyl chain length (Table 2, entries 1–3). Secondary alcohols **2d** and tertiary alcohols **2e** also worked effectively as the substrates, producing the esters in 81–91% yield (Table 2, entries 4–5). Treating **1a** with cyclohexanol **2f** could afford the ester **3f** in 80% yield (Table 2, entry 6). Alcoholysis products **3g** and **3h** were obtained from corresponding alcohols (Table 2, entries 7–8). Substrate alcohol having trifluoromethyl also participated in this catalytic reaction to form the ester **3i** in high yield (Table 2, entry 9). Moreover, when ethane-1,2-diol was treated with **1a**, only one product **3j** was obtained (Table 2, entry 10).

We then examined the generality of amides and the results are compiled in Table 3. Under the optimized conditions, both electron-rich and electron-deficient group substituted benzamide could undergo C–N bond cleavage and esterification by ethanol to afford the corresponding ester products in high yields (Table 3, entries 1–7). Various functional groups such as

Table 2 Esterification of primary amide with various alcohols^a

Entry	Alcohol	Products	Yield ^b	Reaction scheme:	
				<chem>1a</chem>	<chem>2a-2j</chem>
1	Ethanol 2a	<chem>3a</chem>	85%		
2	<i>n</i> -Propanol 2b	<chem>3b</chem>	88%		
3	<i>n</i> -Octanol 2c	<chem>3c</chem>	82%		
4	<i>i</i> -Propanol 2d	<chem>3d</chem>	91%		
5	<i>t</i> -Butyl alcohol 2e	<chem>3e</chem>	81%		
6	Cyclohexanol 2f	<chem>3f</chem>	80%		
7	Phenethanol 2g	<chem>3g</chem>	83%		
8	Phenethanol 2h	<chem>3h</chem>	81%		
9	Trifluoroethanol 2i	<chem>3i</chem>	81%		
10	Ethane-1,2-diol 2j	<chem>3j</chem>	85%		

^a Reaction conditions: **1a** (0.2 mmol), **2a** (0.1 mL), **2b**–**2j** (0.24 mmol), FeCl₃·6H₂O (0.04 mmol, 20 mol%), HCl (0.24 mmol, 36–38%), *n*-hexane (1.0 mL), 80 °C, 14 h. ^b Isolated yield.

alkoxy, hydroxyl, amino, halide, and nitro remained intact during the reaction. 2-Naphthamide also served as an efficient substrate and could react with **2a**, furnishing the ester **3r** in 86% yield. Interestingly, heteroaryl substituted esters **3s** and **3t** were obtained from the reaction of 2-thiophenecarboxamide and **3-**

Table 3 Esterification of different amides with ethanol^a

Entry	Amides	Products and yield ^b	Table 3 (Contd.)		
			1b-1l	2a	3k-3u
1		3k, 86%			
2		3l, 85%			
3		3m, 78%			
4		3n, 75%			
5		3o, 86%			
6		3p, 84%			
7		3q, 90%			
8		3r, 86%			
9		3s, 84%			
10		3t, 55%			
11		3u, 88%			
12		3v, 85%			

Table 3 (Contd.)

Entry	Amides	Products and yield ^b	Table 3 (Contd.)		
			1b-1l	2a	3k-3u
13		3w, 81%			

^a Reaction conditions: **1b-1n** (0.2 mmol), **2a** (0.1 mL), $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ (0.04 mmol, 20 mol%), HCl (0.24 mmol, 36–38%), *n*-hexane (1.0 mL), 80 °C, 14 h. ^b Isolated yield.

indoleacetamide with **2a** using the present reaction conditions, indicating that this method will be an efficient approach to introduce an aromatic heterocycle into functional molecules. Substrates containing alkynes such as cinnamamide (**1l**) could also react with ethanol smoothly to give an esterification product **3u** with 88% yield. The reaction was not sensitive to the steric environment of the amide moiety; when *meta*- and *ortho*-substituted amides **1m** and **1n** were subjected to the reaction system, the corresponding ester products were obtained in high yields.

In addition to alcohols, esters were also used as substrates for esterification of amides through the acyl-acyl exchange process under the optimal reaction conditions.¹⁴ As shown in Table 4, in the current catalytic system, formate, acetate and benzoate also served as efficient substrates and could react with amides, furnishing the corresponding esters in high yield (Table 4, entries 1–7).

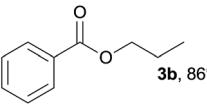
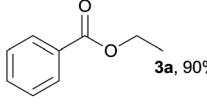
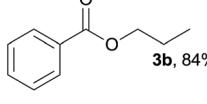
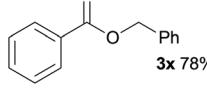
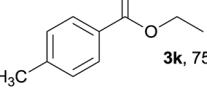
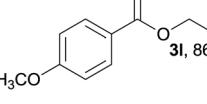
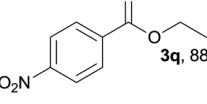
The substrate scope of this iron-catalyzed esterification of secondary and tertiary amides with alcohols was investigated. Remarkably, when a secondary amide, *viz.*, *N*-methylbenzamide (**1o**) and a tertiary amide, *viz.*, *N,N*-diethylbenzamide (**1p**) were used as substrates, the corresponding esters **3a** and **3v** were afforded in high yield (Scheme 1).

In addition to aromatic primary, secondary and tertiary amides, the esterification of aliphatic primary, secondary and tertiary amides was also investigated under the optimal reaction conditions, the corresponding esters were afforded in good to excellent yield and the results are shown in Scheme 2. 2-Phenylacetamide (**1q**) participated in this catalytic reaction to form the ester **3y** in 86% yield. *N*-Acetyl aniline **1r** and *N,N*-dimethylformamide **1s** were also applicable to this catalytic system, and transformed into the corresponding esters **3z** and **3z'** in 79% and 82% yield respectively.

To demonstrate the effect of iron salt in the current catalytic system, several control experiments were carried out as shown in Scheme 3. When 1 equivalent $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ was used as the catalyst in the absence of HCl, **3a** was obtained in 90% yield. This result indicated that the catalytic cycle of the iron salt was

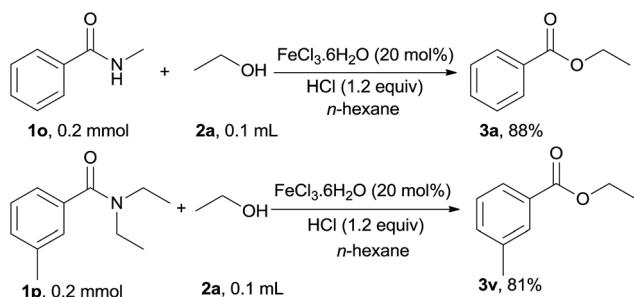


Table 4 Expanded substrate scope of amides and esters^a

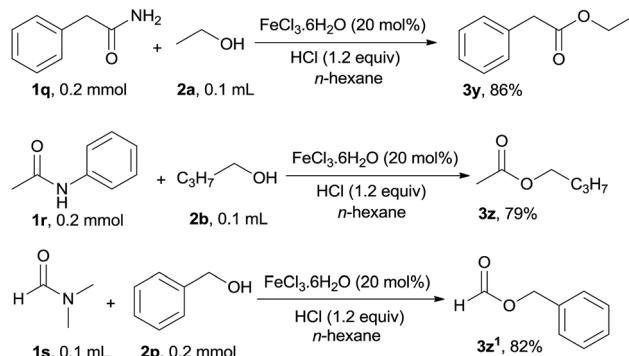
Entry	Amides	Esters	Products and yield ^b	
			2k-2l	3b-3q
1	1a	HCO ₂ CH ₂ CH ₃ (2k)		3b, 86%
2	1a	CH ₃ COCH ₂ CH ₃ (2l)		3a, 90%
3	1a	CH ₃ CH ₂ COCH ₂ CH ₃ (2m)		3b, 84%
4	1a	CH ₃ CH ₂ COCH ₂ Ph (2n)		3x, 78%
5	1b	PhCOCH ₂ CH ₃ (2o)		3k, 75%
6	1c	CH ₃ COCH ₂ CH ₃ (2l)		3l, 86%
7	1h	CH ₃ COCH ₂ CH ₃ (2l)		3q, 88%

^a Reaction conditions: 1a–1h (0.2 mmol), 2k, 2l (0.1 mL), 2m–2o (0.24 mmol), FeCl₃·6H₂O (0.04 mmol, 20 mol%), HCl (0.24 mmol, 36–38%), *n*-hexane (1.0 mL), 80 °C, 14 h. ^b Isolated yield.

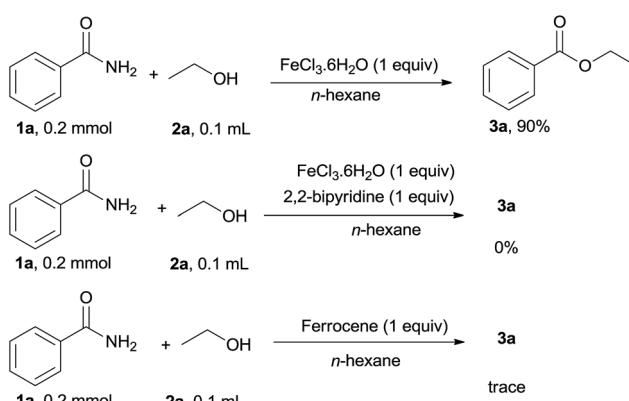
hindered in the present reaction conditions. When the stronger bidentate ligands such as 2,2-bipyridine was used, 3a was not obtained and trace amounts of 3a were detected on using



Scheme 1 Reaction of secondary and tertiary amides 1o and 1p with ethanol.

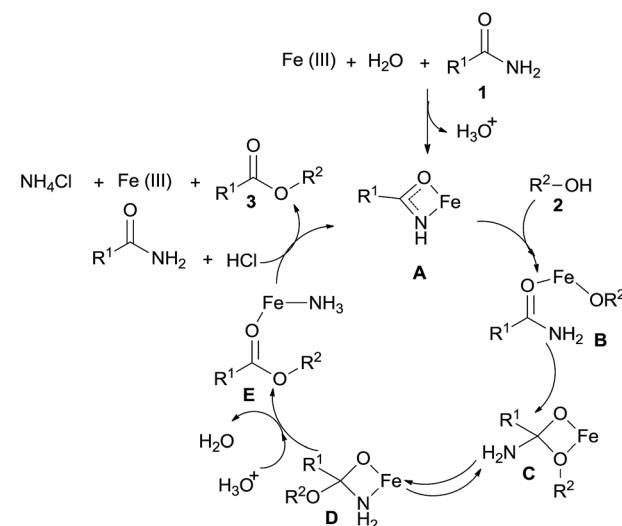


Scheme 2 Reaction of aliphatic amides 1q, 1r and 1s with different alcohols.



Scheme 3 Control experiments.

ferrocene as the catalyst, indicating that the iron salt catalyst showed low efficiency in the presence of the stronger ligand. Thus, it was deduced that free Fe(II or III) was effective for this reaction.



Scheme 4 Plausible reaction mechanism for Fe-catalyzed esterification of amides by alcohols.



According to the reported literature^{5d} and our experimental results, the catalytic reaction pathways for the Fe-catalyzed esterification of amides by alcohols are proposed as shown in Scheme 4. The first step is the generation of the amidate complex **A**, which can be formed from free Fe(III) and amide **1**. The complex **A** reacts with alcohol **2** to produce an unstable intermediate **B**. The interaction between the alcohol oxygen and the carbonyl results in cyclic intermediate **C**, which is in equilibrium with its isomer **D**. Intermediate **E** can also be produced from **D** via C–N bond cleavage. Through the reaction of HCl and a new molecule amide, intermediate **E** produces the desired ester **3**, ammonium chloride (colorless crystal, which was detected after the reaction), and the amidate complex **A**.

Conclusions

In summary, we have discovered a simple, useful and general method for the esterification of amides using inexpensive and readily available iron salts as catalysts. The reaction shows high substrate tolerance as a wide range of aromatic or aliphatic primary, secondary and tertiary amides can be effectively used to produce corresponding esters in good to excellent yields. In addition to alcohol, esters were also used as substrates for esterification of amides through the acyl–acyl exchange process. The present findings not only provide a general and concise method for Fe-catalyzed amide C–N bond cleavage, but also open an avenue for the preparation of esters.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

Financial support by Natural Science Foundation of China (21603068) and research fund for the doctoral program (2016-19XB011 or KY11066) of Hubei University of Science and Technology are gratefully appreciated.

Notes and references

- (a) N. Sewald and H. D. Jakubke, *Peptides: Chemistry and Biology*, Wiley-VCH: Weinheim, 2002; (b) B. L. Bray, *Nat. Rev. Drug Discovery*, 2003, **2**, 587; (c) T. Cupido, J. Tulla-Puche, J. Spengler and F. Albericio, *Curr. Opin. Drug Discovery Dev.*, 2007, **10**, 768; (d) J. W. Bode, *Curr. Opin. Drug Discovery Dev.*, 2006, **9**, 765; (e) J. M. Humphrey and A. R. Chamberlin, *Chem. Rev.*, 1997, **97**, 2243; (f) A. Greenberg, C. M. Breneman and J. F. Liebman, *Amide Linkage: Selected Structural Aspects in Chemistry, Biochemistry, and Materials Science*, Wiley-Interscience, New York, 2000.
- (a) G. W. Wang, T. T. Yuan and D. D. Li, *Angew. Chem., Int. Ed.*, 2011, **50**, 1380; (b) X. X. Zhang, W. T. Teo and P. W. H. Chan, *J. Organomet. Chem.*, 2011, **696**, 331; (c) E. Valeur and M. Bradley, *Chem. Soc. Rev.*, 2009, **38**, 606.
- For reviews in C–N bond activation, see: (a) K. Ouyang, W. Hao, W.-X. Zhang and Z. Xi, *Chem. Rev.*, 2015, **115**, 12045; (b) Q. Wang, Y. Su, L. Li and H. Huang, *Chem. Soc. Rev.*, 2016, **45**, 1257.
- For a review about amide reactivity see: (a) M. C. Whisler, S. MacNeil, V. Snieckus and P. Beak, *Angew. Chem., Int. Ed.*, 2004, **43**, 2206; (b) V. Snieckus, *Chem. Rev.*, 1990, **90**, 879; (c) V. Pace, W. Holzer and B. Olofsson, *Adv. Synth. Catal.*, 2014, **356**, 3697.
- For transamidation of amides see: (a) T. B. Nguyen, J. Sorres, M. Q. Tran, L. Ermolenko and A. Al-Mourabit, *Org. Lett.*, 2012, **14**, 3202; (b) N. A. Stephenson, J. Zhu, S. H. Gellman and S. S. Stahl, *J. Am. Chem. Soc.*, 2009, **131**, 10003; (c) S. N. Rao, D. C. Mohan and S. Adimurthy, *Org. Lett.*, 2013, **15**, 1496; (d) L. Becerra-Figueroa, A. Ojeda-Porras and D. Gamba-Sanchez, *J. Org. Chem.*, 2014, **79**, 4544; (e) Y. Liu, S. Shi, M. Achtenhagen, R. Liu and M. Szostak, *Org. Lett.*, 2017, **19**, 1614; (f) G. Meng, P. Lei and M. Szostak, *Org. Lett.*, 2017, **19**, 2158.
- (a) S. Yamada, *Angew. Chem., Int. Ed.*, 1995, **34**, 1113; (b) S. Yamada, *J. Org. Chem.*, 1996, **61**, 941; (c) M. Hutchby, C. E. Houlden, M. F. Haddow, S. N. G. Tyler, G. C. Loyd-Jones and K. I. Booker-Milburn, *Angew. Chem., Int. Ed.*, 2012, **51**, 548; (d) J. Aubé, *Angew. Chem., Int. Ed.*, 2012, **51**, 3063.
- (a) L. M. Berreau, M. M. Makowsak-Grzyska and A. M. Arif, *Inorg. Chem.*, 2000, **39**, 4390; (b) S. Kawaguchi and K. Araki, *Inorg. Chim. Acta*, 2005, **358**, 947; (c) E. Szajna-Fuller, G. K. Lingle, R. W. Watkins, A. M. Arif and L. M. Berreau, *Inorg. Chem.*, 2007, **46**, 2353; (d) M. C. Böhmer and W. Bannwarth, *Eur. J. Org. Chem.*, 2008, 4412; (e) M. C. Bröhmer, S. Mundinger, S. Bräse and W. Bannwarth, *Angew. Chem., Int. Ed.*, 2011, **50**, 6175; (f) M. A. R. Raycroft, C. I. Maxwell, R. A. A. Oldham, A. S. Andrea, A. A. Neverov and R. S. Brown, *Inorg. Chem.*, 2012, **51**, 10325; (g) M. Hutchby, C. E. Houlden, M. F. Haddow, S. N. G. Tyler, G. C. Loyd-Jones and K. I. Booker-Milburn, *Angew. Chem., Int. Ed.*, 2012, **51**, 548.
- (a) S. Yamada, *Angew. Chem., Int. Ed.*, 1993, **32**, 1083; (b) S. Yamada, *Angew. Chem., Int. Ed.*, 1995, **34**, 1113; (c) S. Yamada, *J. Org. Chem.*, 1996, **61**, 941; (d) S. Yamada, *J. Org. Chem.*, 1996, **61**, 5932; (e) M. Hutchby, C. E. Houlden, M. F. Haddow, S. N. G. Tyler, G. C. Loyd-Jones and K. I. Booker-Milburn, *Angew. Chem., Int. Ed.*, 2012, **51**, 548; (f) S. Yamada, *J. Org. Chem.*, 1992, **57**, 1591; (g) M. Hutchby, C. E. Houlden, M. F. Haddow, S. N. G. Tyler, G. C. Loyd-Jones and K. I. Booker-Milburn, *Angew. Chem., Int. Ed.*, 2012, **51**, 548.
- (a) Y. Kita, Y. Nishii, T. Higuchi and K. Mashima, *Angew. Chem., Int. Ed.*, 2012, **51**, 5723; (b) Y. Kita, Y. Nishii, A. Onoue and K. Mashima, *Adv. Synth. Catal.*, 2013, **355**, 3391; (c) B. N. Atkinson and J. M. J. Williams, *Tetrahedron Lett.*, 2014, **55**, 6935; (d) Y. Nishii, S. Akiyama, Y. Kita and K. Mashima, *Synlett*, 2015, **26**, 1831.
- S. M. A. H. Siddiki, A. S. Touchy, M. Tamura and K. Shimizu, *RSC Adv.*, 2014, **4**, 35803.



11 (a) L. Hie, N. F. Fine Nathel, T. K. Shah, E. L. Baker, X. Hong, Y. F. Yang, P. Liu, K. N. Houk and N. K. Garg, *Nature*, 2015, **524**, 79; (b) L. Hie, E. L. Baker, S. M. Anthony, J. N. Desrosiers, C. Senanayake and N. K. Garg, *Angew. Chem., Int. Ed.*, 2016, **55**, 15129; (c) T. Deguchi, H. L. Xin, H. Morimoto and T. Ohshima, *ACS Catal.*, 2017, **7**, 3157.

12 Based on Mayr's reactivity parameters, the difference of nucleophilicity between amines and alcohols is ~ 105 orders of magnitude, for details, see: <http://www.cup.lmu.de/oc/mayr/reaktionsdatenbank/>, accessed Dec. 15, 2016.

13 Y. Bourne-Branchu, C. Gosmini and G. Danoun, *Chem.-Eur. J.*, 2017, **23**, 10043.

14 Acyl-acyl exchange between amides and esters was reported by Bian and co-worker, however the scope of amide was limited to primary amides. Y. Bian and X. Qu, *Org. Biomol. Chem.*, 2016, **14**, 3869.

