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Lipophilic NHC assisted one-pot synthesis of syncarpamide analogues in aqueous medium†

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Lipophilic NHC catalysis in aqueous medium was reported for the synthesis of biologically relevant (a)symmetrically substituted and unsymmetrically substituted syncarpamide analogues. All the reported reactions were performed in the absence of any expensive metal salts or additives. A diverse array of syncarpamide analogues was obtained in good yields. Lipophilic NHC catalysis was also extended to chemoselective transesterification reactions.

Introduction

Amongst the diverse array of green solvents, water has been well acclaimed as the green solvent par excellence.[1,2] In addition to its environmentally benign nature, water greatly accelerates the reaction between lipophilic reactants through the "hydrophobic hydration effect".[3–5] In spite of such elegance, it would be difficult to perform the reaction in aqueous medium if the reactants have distinctly different solubility in water. One such example is the reaction between hydrophilic aminoethanol and lipophilic cinnamate ester derivatives which results in the formation of biologically relevant syncarpamide analogues. Naturally derived syncarpamide shows good antiplasmodial activity (IC_{50} = 2.04 μM) and hence the synthesis of novel syncarpamide analogue skeletons is essential to combat multidrug-resistant *Plasmodium falciparum* strains (Chart 1).[6,7] Apart from their biological significance, syncarpamide analogues are also distributed in natural products. Tenaglin is a representative example of a symmetrically acylated amino alcohol derivative obtained from plant resources (Chart 1).[8]

The conventional synthesis of syncarpamide analogues was carried out in chlorinated organic solvents in the presence of excess DCC/DMAP reagents under a strictly moisture-free environment.[6] Additionally, unsymmetrically substituted derivatives were synthesized by a multi-step reaction which involves (i) *O*-acylation of azido alcohols, (ii) transformation of azide to amine functionality, followed by (iii) *N*-acylation, in which each step is devoid of aqueous medium.[6] Hence, identification of a catalytic system which performs consecutive amidation and transesterification reactions in an aqueous medium under one-pot operation is highly desirable.

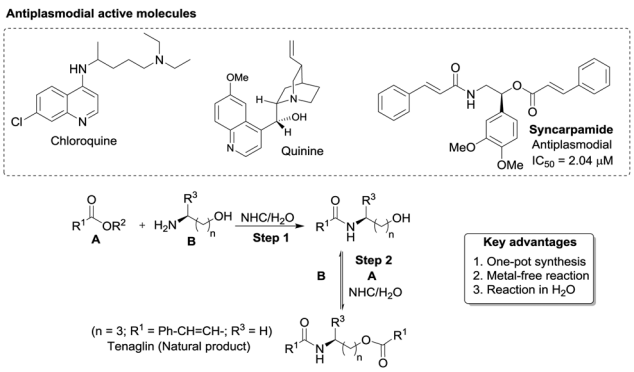

Chart 1 NHC catalyzed syncarpamide analogue synthesis in water.

Though N-heterocyclic carbene (NHC) mediated transesterification[9] and amidation[10] reactions have been previously reported in organic solvents, one-pot, concomitant transesterification and amidation reactions in aqueous medium are challenging. Unlike metal–NHC complexes, the major disadvantage of performing NHC organocatalysis in the aqueous medium is the facile protonation of metal-free naked NHC since the pK_a of the imidazolium cations (23.8) is higher than that of water.[11] Lemcoff and co-workers gave a detailed account on NHC catalysis performed in the aqueous medium and highlighted the difficulty in performing NHC organocatalysis in the aqueous medium.[12] Our proposed scheme is given in Chart 1.

In recent years, "surfactant-like catalysts"[13,14] are increasingly being investigated instead of simple surfactants[15] or emulsion droplets[16,17] to perform organic transformations in the aqueous medium. These surfactant-like catalysts not only catalyze the reaction but also provide a larger interface for the immiscible phases of the reactants and the aqueous medium.

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Polarz and co-workers recently reported the synthesis of surfactant-like NHC by anchoring a lipophilic alkyl chain far away from the reactive NHC–metal head to perform interfacial catalysis in aqueous medium.[14] We have decided to tether a lipophilic alkyl chain directly on to the NHC nitrogen atom which could facilitate a reaction between hydrophilic aminoethanol and lipophilic cinnamate ester derivatives. Unlike amphiphilic metal catalyzed reactions,[18,19] investigations on NHC organocatalysis in the aqueous medium are largely confined to benzoin condensation reactions.[20]

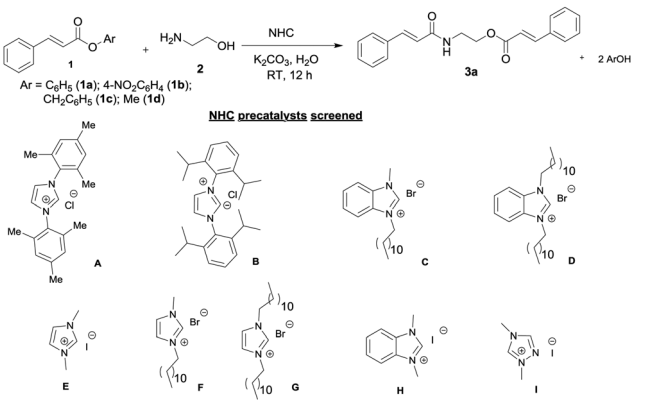
Results and discussion

The choice of NHC is essential for the success of one-pot amidation/transesterification reactions. The use of (benz)imidazolium based NHCs is preferred over triazolium derived NHC since the latter could lead to the LUMO activation of α,β-unsaturated esters.[21,22] The preliminary investigation on one-pot amidation and transesterification reactions performed with aminoethanol **2** and 4-nitrophenylcinnamate ester **1b** with *N*-aryl imidazolium NHC precatalysts **A** and **B** gave the corresponding product **3a** in poor yields (Table 1, entries 1 and 2). Since *N*-alkyl substituted NHCs have higher nucleophilicity[9] and better electron donating ability[23] than the corresponding *N*-aryl counterparts, the *N*-alkylated imidazolium/benzimidazolium NHC precatalysts **C–H** were prepared. Among *N*-alkyl substituents, sterically more demanding lipophilic dodecyl substituted NHCs are unique since they shift the Wanzlick equilibrium towards the free carbene side (Scheme 1).[20] Moreover, the presence of the lipophilic chain greatly assists the performance of the desired organic transformation in aqueous medium. As predicted, the reactions performed with NHC precatalysts **C** and **D** gave the corresponding product in moderate to good yields (entries 3 and 4).

Increasing the reaction temperature from RT to 50 °C or changing the inorganic base to DBU drastically affected the yield of the product (entries 5 and 6). To identify the role of the solvent, the reaction was performed in THF under optimized conditions. However, it gave only the amidation product instead of the desired product **3a** (entry 7). Similarly, the reaction performed with brine solution instead of water also did not yield the desired outcome (entry 8). These results show that the synergetic combination of sterically demanding lipophilic benzimidazolium NHC and water is essential for the success of this reaction. Under optimized reaction conditions, changing the leaving group from 4-nitrophenyl (**1b**) to the phenyl group (**1a**) marginally improved the product yield to 82% (entry 9 *vs.* 4) whilst the use of benzyl cinnamate (**1c**) or methyl cinnamate (**1d**) instead of **1a** did not yield the desired outcome (entry 10). Hence, it was decided to carry out further reactions with phenyl cinnamate ester itself.

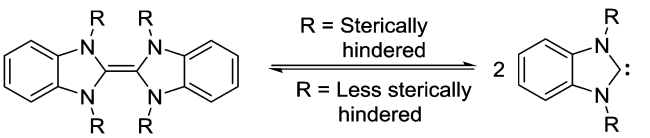
To further understand the role of NHC, the reaction was carried out under optimized conditions with NHC precatalysts **E–H**. Among these, the sterically demanding lipophilic imidazolium NHC precatalyst gave superior yield (entry 13 *vs.* 11 and 12). This shows that the nature of the alkyl group tethered on to the NHC dictates the course of the reaction.

Table 1 Screening of reaction conditions for NHC catalysis in aqueous medium[a]



S. no	NHC	Substrate	Base	Solvent	Temp (°C)	Time (h)	Yield[b] (%)
1	**A**	**1b**	K_2CO_3	H_2O	RT	12	10
2	**B**	**1b**	K_2CO_3	H_2O	RT	12	37
3	**C**	**1b**	K_2CO_3	H_2O	RT	12	55
4	**D**	**1b**	K_2CO_3	H_2O	RT	12	73
5	**D**	**1b**	K_2CO_3	H_2O	50 °C	12	Impure
6	**D**	**1b**	DBU	H_2O	RT	12	30
7	**D**	**1b**	K_2CO_3	THF	RT	12	—[c]
8	**D**	**1b**	K_2CO_3	Brine	50 °C[d]	12	50
9	**D**	**1a**	$\mathbf{K_2CO_3}$	$\mathbf{H_2O}$	**RT**	**12**[e]	**82**[f]
10	**D**	**1c**/**1d**	K_2CO_3	H_2O	RT	12	Impure
11	**E**	**1a**	K_2CO_3	H_2O	RT	12	—
12	**F**	**1a**	K_2CO_3	H_2O	RT	12	<5
13	**G**	**1a**	K_2CO_3	H_2O	RT	12	76
14	**H**	**1a**	K_2CO_3	H_2O	RT	12	—
15	**I**	**1b**	K_2CO_3	H_2O	RT	12	—

[a] To a mixture of amino alcohol **2** (0.2 mmol), substituted ester **1** (0.2 mmol) in water (2 mL), potassium carbonate (0.3 mmol) and NHC (0.02 mmol) were added. [b] Yields are for the isolated products. [c] Formation of products not observed. [d] At room temperature, formation of products not observed. [e] Presence of unreacted **1** was observed in the reaction medium, if the reaction was performed for less than 12 h; the use of excess amino alcohol **2** (0.2 mmol) is required for the completion of the reaction. [f] The reaction performed in D_2O solvent took 20 h for completion and **3a** was obtained in 80% yield.



Scheme 1 Wanzlick equilibrium.

It was presumed that the presence of electron withdrawing substituents at the aromatic ring would enhance the electrophilicity of the carbonyl carbon and pave the way for facile amidation and transesterification reactions. Hence, after optimizing the reaction conditions, the substrate scope of the reaction was screened with diverse phenyl cinnamate derivatives with electron withdrawing substituents (Fig. 1). Interestingly, irrespective of the nature of the substituents, the syncarpamide analogues **3b–f** were obtained in good yields. The reaction conditions were mild enough to keep the cyano substituent intact in **3e**. The use of the unsubstituted phenyl ester instead of cinnamate ester gave only the amidation product **3g**. Movassaghi *et al.* reported a similar

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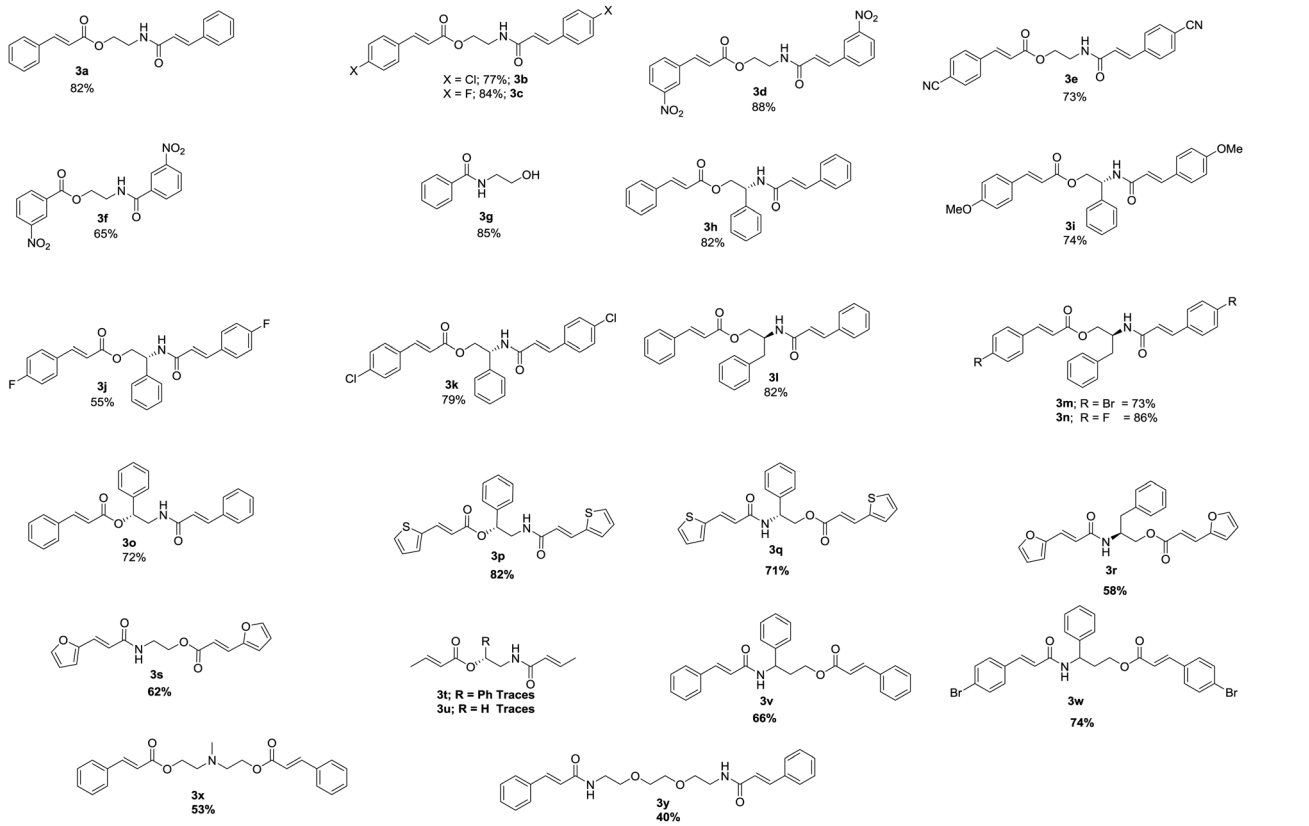

Fig. 1 Substrate scope.

amidation reaction of aromatic ester with amino alcohol derivatives.[10] The scope of the reaction was further extended to chiral amino alcohols such as *R*-(−)-2-phenylglycinol, *S*(−)-2-amino-3-phenyl-1-propanol and *R*(−)-2-amino-1-phenylethanol. For chiral derivatives, the reaction mixture needs to be heated to 60 °C for 5 hours and the reaction gave the products **3h–o** in good yields. Apart from cinnamate esters and β-amino alcohol substrates, the reaction was found to be general for β-heterocyclic esters, γ-amino alcohols, and also dialcohol/diamine derivatives. The products **3p–3s** and **3v–y** were obtained in good yields. However, the reaction carried out with β-alkyl ester did not yield the desired products **3t–u**.

Unlike symmetrical derivatives, one-pot synthesis of unsymmetrically substituted derivatives requires a multi-step reaction, *vide supra*. Caulitenin is a representative example of an unsymmetrically acylated amino alcohol derivative obtained from natural sources.[8] Preliminary investigations on the one-pot synthesis of unsymmetrical derivatives by the reaction of two different esters gave a complex mixture of products. All attempts to enhance the reaction yield failed to yield the desired outcome. Hence, it was decided to perform sequential amidation followed by a transesterification reaction. After careful screening and optimization, we have identified that K_2CO_3 can efficiently carry out the amidation of unactivated methyl benzoate derivatives, which on further NHC mediated transesterification gave the corresponding unsymmetrically substituted derivatives **4a–4d** (Chart 2).

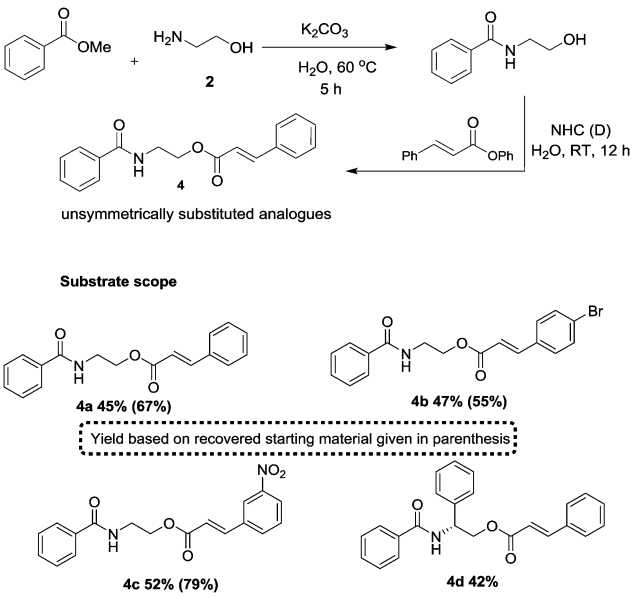

Chart 2 NHC catalyzed unsymmetrically substituted analogue synthesis.

Scope and limitations of NHC organocatalysis in aqueous medium

The NHC organocatalysis was screened with lipophilic/primary/secondary and sterically hindered tertiary alcohol derivatives (Chart 3). The reaction carried out with lipophilic stearyl

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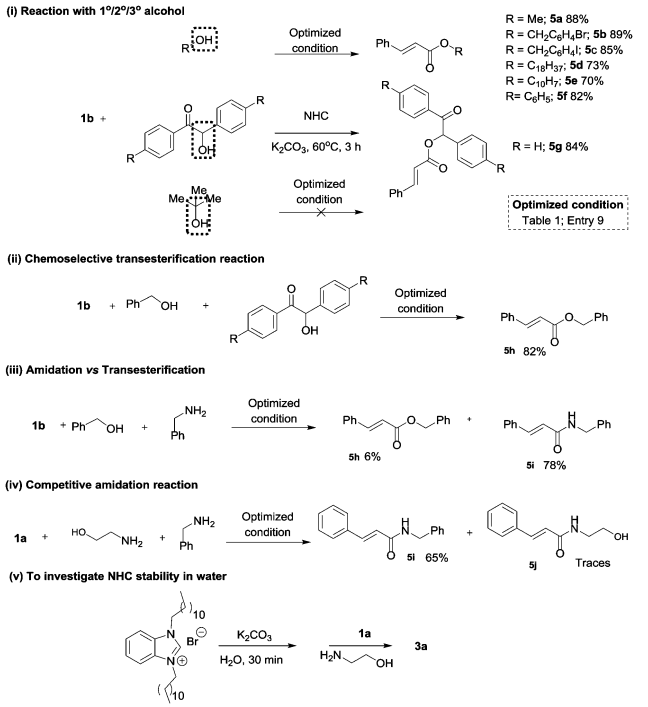

Chart 3 Scope and limitations of NHC organocatalysis in aqueous medium.

alcohol and aromatic naphthol in aqueous medium gave the desired products **5d** and **5e** in good yields (Chart 3(i)). The reaction also proceeded smoothly with the secondary alcohol but not with the tertiary alcohol. Increasing the reaction temperature also did not change the course of the reaction with respect to the tertiary alcohol. The benzoin derivative **5g** obtained by the transesterification of the secondary alcohol is a valuable intermediate for the synthesis of substituted indole derivatives.[24]

Preferential acylation of a primary alcohol in the presence of secondary alcohols or phenols in an aqueous medium is an arduous task. Hence, such transformations are invariably performed in an organic solvent medium under a strictly moisture-free environment.[9,25,26] In our method, the selective acylation of a primary alcohol in the presence of a secondary alcohol derivative was achieved in good yields (Chart 3(ii)). Movassaghi *et al.* reported that NHC mediated amidation of esters with amino alcohols proceeds *via* initial transesterification followed by rapid O to N acyl-transfer.[10] To check this hypothesis, we performed the transesterification/amidation reaction of **1b** in the presence of benzyl alcohol and benzyl amine (Chart 3(iii)). Interestingly, we obtained the corresponding amidation product **5i** in 78% yield with trace amounts of transesterification product **5h**. The preferential formation of the amidation product over the transesterification product could be due to the activation of the amine moiety by the NHC for the nucleophilic addition reaction[27] and/or an uncatalyzed selective amidation reaction over transesterification.[28] A competitive amidation reaction performed with both ethanolamine and benzyl amine resulted in the formation of product **5i** instead of **5j** (Chart 3(iv)). Though

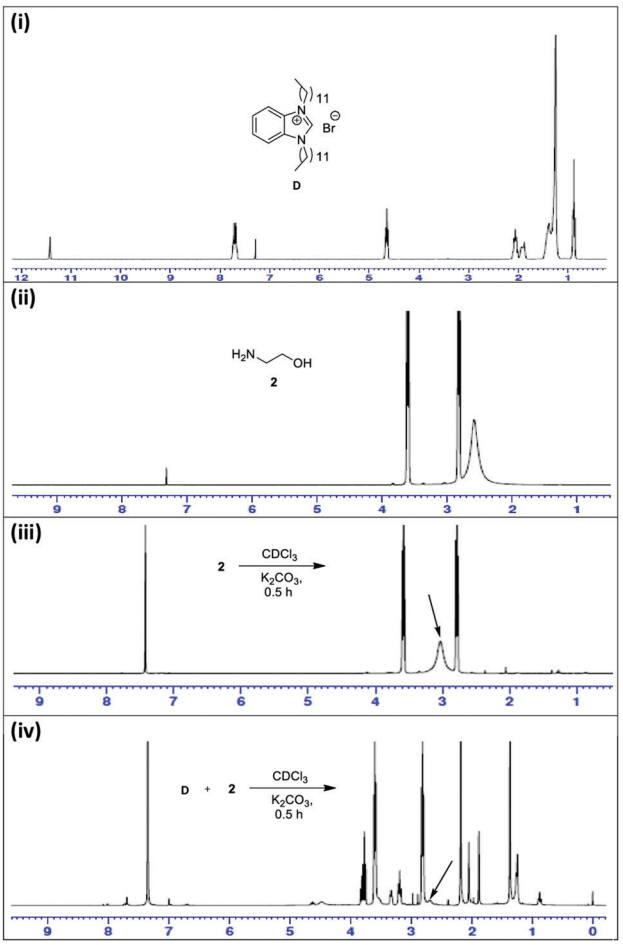

Fig. 2 NMR investigations of one-pot amidation/transesterification.

ethanolamine has higher reactivity than benzyl amine,[10] the highly soluble nature of the former in water could have suppressed the formation of **5j**. In addition, due to the presence of the lipophilic aromatic moiety, facile amidation of benzyl amine takes place with lipophilic NHC. To confirm the stability of the lipophilic NHC in the aqueous medium, we performed the representative **3a** synthesis, by generating NHC in H_2O, followed by the addition of substrates after a 30 minute interval (Chart 3(v)). As expected, the desired amidation/transesterification product was formed, albeit in marginally lesser yields. This shows that the lipophilic dodecyl NHC is not much affected by the presence of water.

Mechanistic investigations

To further confirm the activation of exchangeable NH_2/OH protons by the NHC, we carried out the following NMR experiment. The addition of K_2CO_3 to the ethanolamine solution in $CDCl_3$ shows the presence of an exchangeable protons peak at 3.1 ppm (Fig. 2(iii)). The combined addition of both NHC **D** and the K_2CO_3 base resulted in the disappearance of the exchangeable protons peak (Fig. 2(iv)). This confirms that NHC **D** activates both NH_2/OH groups for the nucleophilic substitution reaction. Based on the results obtained a detailed mechanism is given in the ESI.†

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Conclusions

A versatile and convenient method was developed for the one-pot synthesis of syncarpamide analogues. All the reactions were carried out in the aqueous medium and the products were obtained in good yields. In addition, the lipophilic NHC was utilized to perform chemoselective amidation reactions in the presence of alcohols and esterification of a primary alcohol in the presence of a secondary alcohol.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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Notes and references

1 R. N. Butler and A. G. Coyne, *Chem. Rev.*, 2010, **110**, 6302–6337.
2 A. Chanda and V. V. Fokin, *Chem. Rev.*, 2009, **109**, 725–748.
3 H. Y. Bae, S. Some, J. S. Oh, Y. S. Lee and C. E. Song, *Chem. Commun.*, 2011, **47**, 9621–9623.
4 S. Höfinger and F. Zerbetto, *Chem. Soc. Rev.*, 2005, **34**, 1012–1020.
5 P. Suresh, S. Thamotharan and S. S. Ganesan, *Catal. Commun.*, 2018, **111**, 47–51.
6 E. K. Aratikatla, T. R. Valkute, S. K. Puri, K. Srivastava and A. K. Bhattacharya, *Eur. J. Med. Chem.*, 2017, **138**, 1089–1105.
7 S. A. Ross, G. N. N. Sultana, C. L. Burandt, M. A. ElSohly, J. P. J. Marais and D. Ferreira, *J. Nat. Prod.*, 2004, **67**, 88–90.
8 H. Greger, M. Hofer, K. Teichmann, J. Schinnerl, C. M. Pannell, S. Vajrodaya and O. Hofer, *Phytochemistry*, 2008, **69**, 928–938.
9 G. A. Grasa, R. M. Kissling and S. P. Nolan, *Org. Lett.*, 2002, **4**, 3583–3586.
10 M. Movassaghi and M. A. Schmidt, *Org. Lett.*, 2005, **7**, 2453–2456.
11 T. L. Amyes, S. T. Diver, J. P. Richard, F. M. Rivas and K. Toth, *J. Am. Chem. Soc.*, 2004, **126**, 4366–4374.
12 E. Levin, E. Ivry, C. E. Diesendruck and N. G. Lemcoff, *Chem. Rev.*, 2015, **115**, 4607–4692.
13 Q. Jochyms, E. Mignard and J.-M. Vincent, *J. Fluorine Chem.*, 2015, **177**, 11–18.
14 A. Donner, K. Hagedorn, L. Mattes, M. Drechsler and S. Polarz, *Chem. – Eur. J.*, 2017, **23**, 18129–18133.
15 C. J. Li, *Chem. Rev.*, 2005, **105**, 3095–3165.
16 P. Ghosh, B. Kar, S. Bardhan, K. Kundu, S. K. Saha, B. K. Paul and S. Das, *J. Surf. Sci. Technol.*, 2016, **32**, 8–16.
17 A. Ganesan, J. Kothandapani and S. G. Subramaniapillai, *RSC Adv.*, 2016, **6**, 20582–20587.
18 G. Hamasaka, T. Muto and Y. Uozumi, *Angew. Chem.*, 2011, **123**, 4978–4980.
19 A. F. Mingotaud, M. Krämer and C. Mingotaud, *J. Mol. Catal. A: Chem.*, 2007, **263**, 39–47.
20 K. Iwamoto, M. Hamaya, N. Hashimoto, H. Kimura, Y. Suzuki and M. Sato, *Tetrahedron Lett.*, 2006, **47**, 7175–7177.
21 J. Cheng, Z. Huang and Y. R. Chi, *Angew. Chem., Int. Ed.*, 2013, **52**, 8592–8596.
22 C. Mou, J. Wu, Z. Huang, J. Sun, Z. Jin and Y. R. Chi, *Chem. Commun.*, 2017, **53**, 13359–13362.
23 D. J. Nelson and S. P. Nolan, *Chem. Soc. Rev.*, 2013, **42**, 6723–6753.
24 C. Yao, D. Wang, J. Lu, B. Qin, H. Zhang, T. Li and C. Yu, *Tetrahedron Lett.*, 2011, **52**, 6162–6165.
25 P. A. Procopiou, S. P. D. Baugh, S. S. Flack and G. G. A. Inglis, *J. Org. Chem.*, 1998, **63**, 2342–2347.
26 A. Orita, A. Mitsutome and J. Otera, *J. Org. Chem.*, 1998, **63**, 2420–2421.
27 H. Guo, Y. Wang, G.-F. Du, B. Dai and L. He, *Tetrahedron*, 2015, **71**, 3472–3477.
28 S. D. Sarkar, S. Grimme and A. Studer, *J. Am. Chem. Soc.*, 2010, **132**, 1190–1191.