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New frontiers of *N*-heterocyclic carbene catalysis

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N-heterocyclic carbene (NHC) is both a family of strong σ-donor ligands for transition metals and a privileged class of organocatalysts with synthetic potential that rivals popular amine and phosphoric acid catalysts. NHC was found as a key catalytic species in thiamine diphosphate catalyzed biochemical reactions [1]. However, due to their inherent chemical instability, free NHCs had not been isolated until 1991 by Ardungo *et al*. [2]. Since then, the use of chiral NHC as a versatile organocatalyst has enjoyed tremendous advances and has helped to transform modern synthetic chemistry. There are over 2000 research papers dealing with both "*N*-heterocyclic carbene" and "Catalysis" in the past 15 years [3].

Early exploration of NHC catalysis was primarily centered on the biomimetic Breslow intermediate, an umpolung acyl anion equivalent formed by nucleophilic attack of an aldehyde by NHC. This unique mode of activation distinguishes NHC from other LUMO-lowering and HOMO-raising organocatalysts. Representative examples include benzoin condensation [4] and Stetter reaction [5], which are difficult to accomplish using other types of catalysts. However, only aldehyde carbonyl was reactive against NHC. As a consequence, an overwhelming majority of reported reactions used aldehyde substrates. More recently, research efforts were more oriented towards uncovering hidden activation potential of NHC for functional groups beyond aldehyde carbonyls [6]. This perspective introduces a handful of examples that capture the most recent discovery of novel activation modes by NHC.

Besides aldehydes, NHC can react with other highly electrophilic carbonyls such as ketenes and acid chlorides. Nevertheless, activation of less reactive esters and acids appeared difficult.

Early investigation of ester activation using NHC was reported by Lupton's group [7]. The authors discovered that reactive vinyl esters could react with strong nucleophilic NHCs to form an acyl imidazonium intermediate that undergoes a formal [3+3] cycloaddition reaction. In 2012, Chi and co-workers [8] accomplished activation of stable esters using NHC via a similar mechanism. The key to a facile reaction between ester and NHC is to use a good aryloxy leaving group, such as *p*-nitrophenoxyl. Subsequently, the same group reported a number of enantioselective reactions using this general strategy of ester activation [9–11]. In 2013, they reported direct generation of conjugate Breslow intermediate **5** using esters and NHC through aryloxy displacement, α-deprotonation and β-H transfer (Scheme 1(a)) [9]. The authors found that this species engages in a Michael-aldol-lactonization-decarboxylation cascade with α,β-unsaturated ketones, ketones and hydrazones to yield various five-membered rings with multiple chiral centers. Excellent remote stereocontrol was accomplished.

Compared to esters, acids are even less reactive towards nucleophiles and pre-activation of the OH is required. In 2014, Scheidt and co-workers [12] used carbonyldiimidazole (CDI) as the *in situ* acid activator to promote the coupling between carboxylic acids with NHC (Scheme 1(b)). The resulting acyl azolium **9** functions as a donor-accept species to react with aza-*O*-quinones. This delicate catalytic cycle avoids decomposition of substrates that had been problematic for aldehydes. Very recently, Chi and co-works

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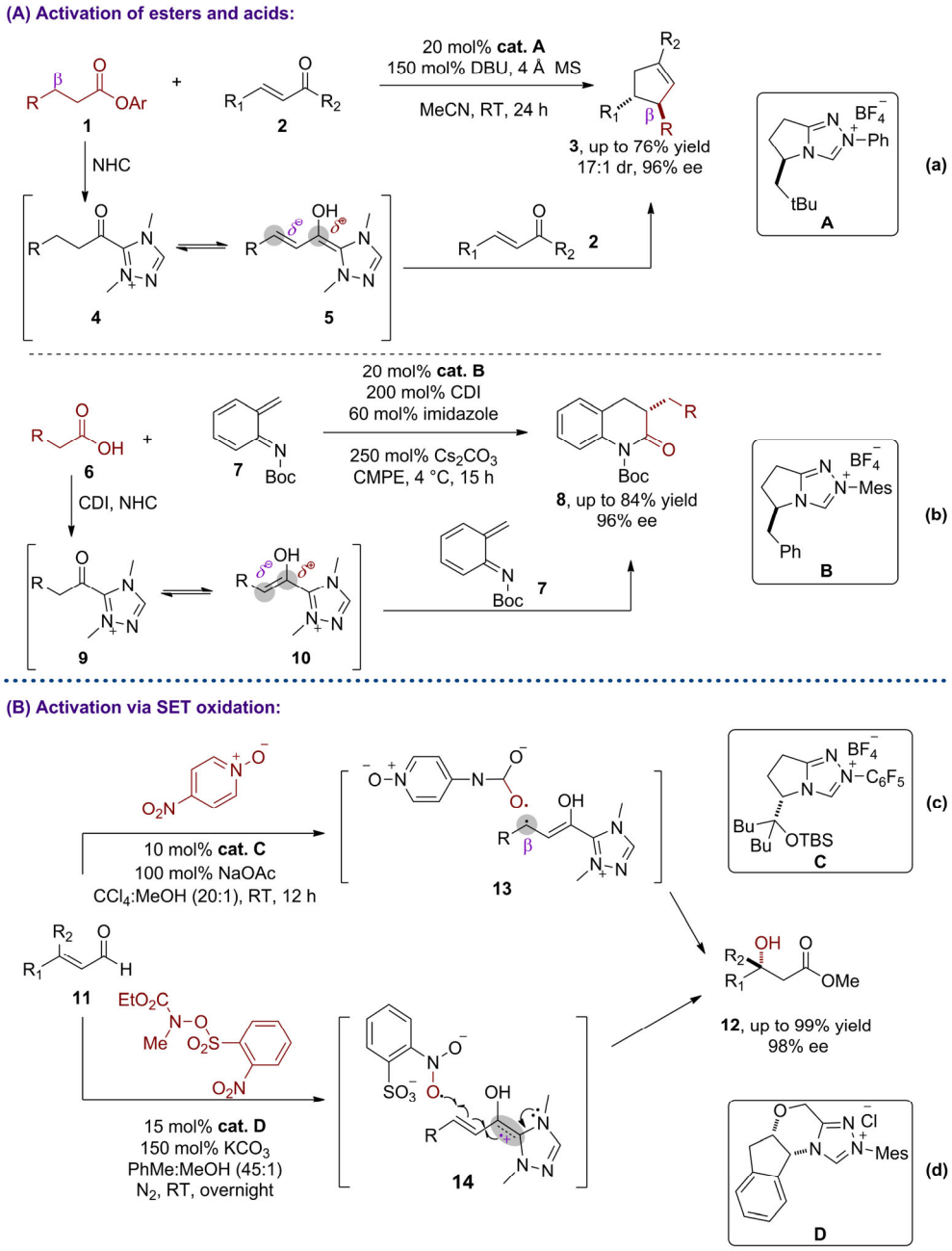


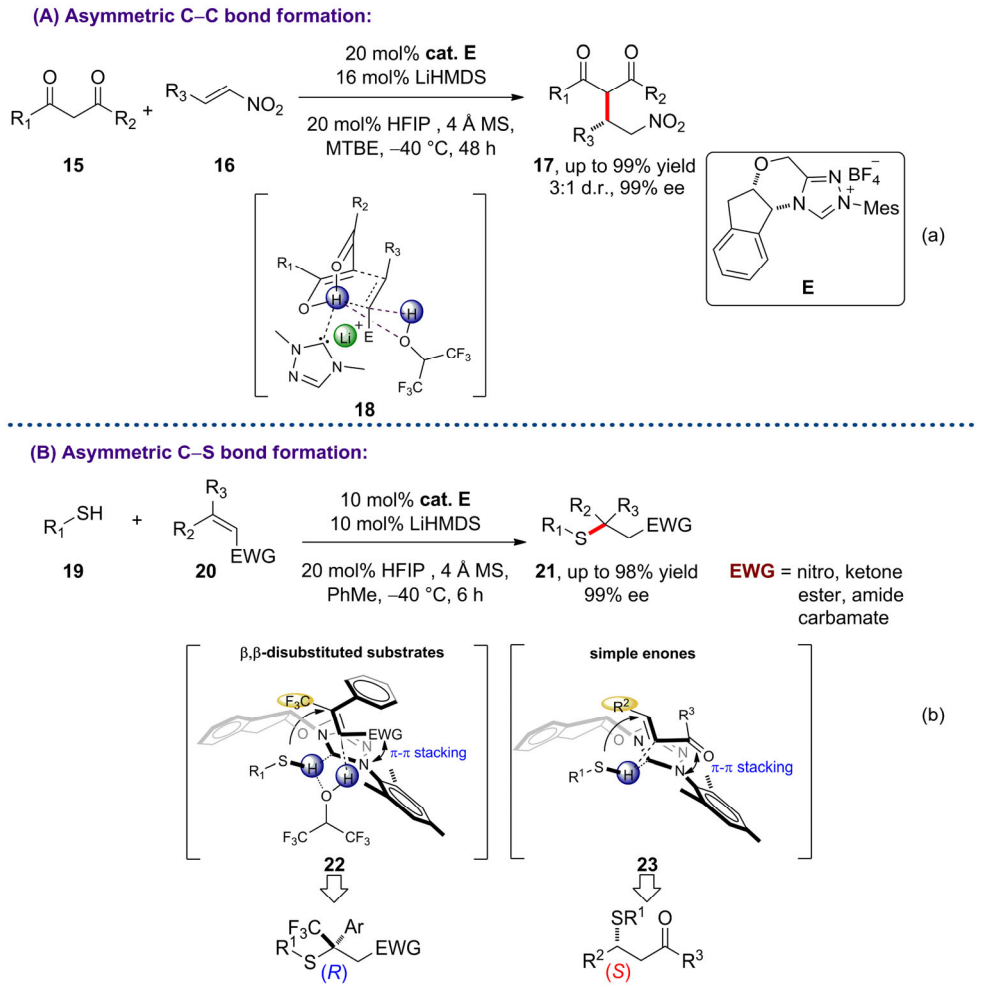
Scheme 1 Novel covalent catalysis using chiral NHC.

[13] reported activation of propionic acid using an analogous strategy.

Orthogonally, NHC-mediated redox catalysis has progressed steadily. Very recently, Rovis's group [14] and Chi's group [15] independently developed protocols for asymmetric synthesis of β-hydroxy esters. Rovis's group [14] judiciously chose 4-nitropyridine *N*-oxide as a single-electron oxidant to convert the classical Breslow intermediate to a β-radical cation **13** that is subsequently oxygenated (Scheme 1(c)). Almost simultaneously, Chi's group [15] discovered nitrobenzenesulfonic carbamate as an effective single-electron oxidant for the same transformation (Scheme 1(d)). In their mechanistic investigation, the authors suggested multiple radical intermediates.

To this extent, the key step of NHC catalysis all involves nucleophilic attack of the catalyst to an electrophilic carbon of the substrate to form a strong, covalent bond. Besides nucleophilicity, NHC is also a strong organic base, which has a conjugate acid pK_a value ranging between 17 and 25 in water [16]. Therefore, new activation mode through non-covalent interaction is also possible.

In the past, the Brønsted base property of NHC was poorly exploited in asymmetric catalysis. We reason that the strong basicity of NHC disfavors catalyst turnover. The



Scheme 2 Novel non-covalent catalysis by NHC.

resulting long half-life, anionic intermediate would lead to reaction reversibility and product racemization [17,18]. In 2014, our group [19] demonstrated the first asymmetric C–C bond formation using NHC as a non-covalent chiral template. The success of this highly enantioselective transformation is a result of pK_a match between the substrate and the product, which assists proton transfer. In addition, an acidic additive, hexafluoroisopropanol (HFIP) was identified as an efficient proton shuttle to facilitate this proton transfer (Scheme 2(a)).

Subsequently, the same concept was applied to asymmetric sulfa-Michael addition reactions [20]. This novel HOMO-raising activation mechanism of NHC has a very broad tolerance for both thiols and electron-deficient olefins (Scheme 2(b)). Notably, simple aliphatic mertaptans and simple enones, which were unsuccessful substrates in previous reports, reacted with excellent yield and ee. Linear free-energy relationship (LFER) study suggested dual non-covalent interaction: hydrogen bonding and π-π stacking.

In summary, the multidimensional electronic characteristics of NHC offer great opportunities for catalysis innovation. The synthetic potential of many recently discovered new aspects of NHC remains to be further explored. Deep mechanistic understanding of NHC activation will inevitably lead to invention of new synthetic processes, new catalysts with higher efficiency and selectivity, and novel generic modes of catalysis. We expect this field will continue to blossom and remain at the center of synthetic innovation.

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Conflict of interest The authors declare that they have no conflict of interest.

1 Breslow R. *J Am Chem Soc*, 1958, 80: 3719–3726
2 Arduengo AJ III, Harlow RL, Kline MA. *J Am Chem Soc*, 1991, 113: 361–363
3 Web of Science search using both “N-heterocyclic carbene” and “Catalysis” as key words, 2134 hits.
4 Enders D, Niemeier O, Balensiefer T. *Angew Chem Int Ed*, 2006, 45: 1463–1467
5 Read de Alaniz J, Kerr MS, Moore JL, Rovis T. *J Org Chem*, 2008, 73: 2033–2040

6 Ryan SJ, Candish L, Lupton DW. *Chem Soc Rev*, 2013, 42: 4906–4917
7 Ryan SJ, Candish L, Lupton DW. *J Am Chem Soc*, 2009, 131, 14176–14177
8 Hao L, Du Y, Lv H, Chen X, Jiang H, Shao Y, Chi YR. *Org Lett*, 2012, 14: 2154–2157
9 Fu Z, Xu J, Zhu T, Leong WW, Chi YR. *Nat Chem*, 2013, 5: 835–839
10 Cheng J, Huang Z, Chi YR. *Angew Chem Int Ed*, 2013, 52: 8592–8596
11 Fu ZQ, Jiang K, Zhu TS, Torres J, Chi YR. *Angew Chem Int Ed*, 2014, 53: 6506–6510
12 Lee A, Younai A, Price CK, Izquierdo J, Mishra RK, Scheidt KA. *J Am Chem Soc*, 2014, 136: 10589–10592
13 Jin ZC, Jiang K, Fu ZQ, Torres J, Zheng PC, Yang S, Song BA, Chi YR. *Chem Eur J*, 2015, 21: 9360–9363
14 White NA, Rovis T. *J Am Chem Soc*, 2014, 136: 14674–14677
15 Zhang Y, Du Y, Huang Z, Xu J, Wu X, Wang Y, Wang M, Yang S, Webster RD, Chi YR. *J Am Chem Soc*, 2015, 137: 2416–2419
16 Massey RS, Collett CJ, Lindsay AG, Smith AD, O'Donoghue AC. *J Am Chem Soc*, 2012, 134: 20421–20432
17 Phillips EM, Riedrich M, Scheidt KA. *J Am Chem Soc*, 2010, 132, 13179–13181
18 Boddaert T, Coquerel Y, Rodriguez J. *Chem Eur J*, 2011, 17: 2266–2271
19 Chen JA, Huang Y. *Nat Comm*, 2014, 5: 3437–3444
20 Chen JA, Meng SX, Wang LM, Tang HM, Huang Y. *Chem Sci*, 2015, 6: 4184–4189