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Cornforth Review

Polarity Inversion Catalysis by the 1,4-Addition of N-Heterocyclic Carbenes

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Polarity inversion is the hallmark of N-heterocyclic carbene (NHC) organocatalysis, with the generation and reaction of acyl anion equivalents known for more than 70 years. In contrast, polarity inversion through 1,4-addition of NHCs to conjugate acceptors was first applied in a catalytic reaction in 2006. This sub-field of NHC-organocatalysis has developed steadily over the subsequent years, enabling novel coupling reactions, enantioselective cycloisomerizations, polymerizations, and other reactions. In this review, this emerging area of NHC-organocatalysis is discussed with comprehensive coverage. In addition, notes regarding the use of other Lewis base catalysts for related reactions, and comments regarding NHC selection for this type of catalysis, are provided.

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Introduction

Although catalysis via polarity-inverted intermediates can be achieved with various catalysts and substrates,[1] reactions of acyl anions formed using N-heterocyclic carbenes (NHCs) are some of the most common.[2] Such chemistry was discovered more than 70 years ago by Ukai,[3] with mechanistic clarity introduced by Breslow in 1958.[4] Specifically, a nucleophilic carbene **1** adds to an aldehyde and the resultant alkoxide tautomerizes to give the acyl anion equivalent **2**, colloquially referred to as the Breslow intermediate. Subsequent coupling to an electrophile is followed by elimination of the NHC to complete the catalytic cycle (Scheme 1a). Before the turn of this century, these events were largely limited to the benzoin condensation and Stetter reaction. More recently, Breslow intermediates derived from more sophisticated aldehydes have been accessed, thereby providing access to a range of secondary reactive intermediates, and fuelling the rapid growth in NHC-organocatalysis.[2c]

In little more than the last decade, a parallel field of NHC-organocatalysis has emerged in which the polarity of conjugate

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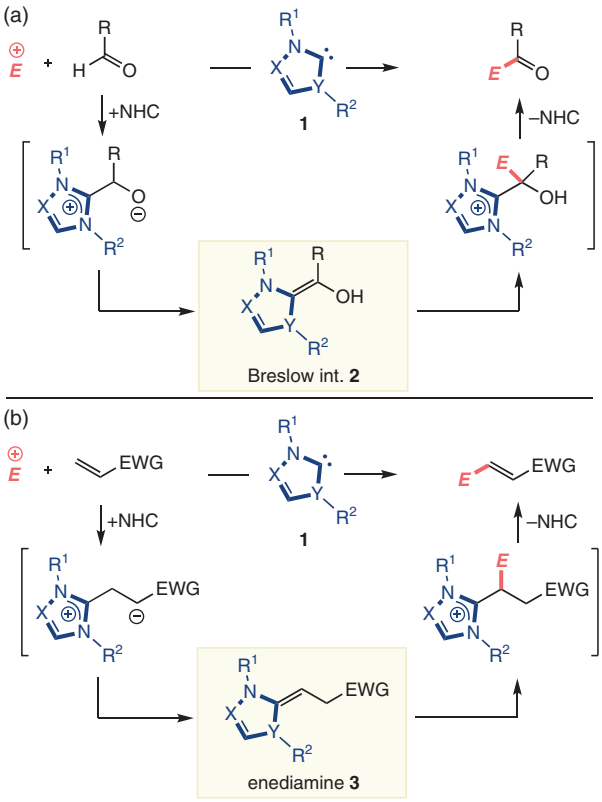
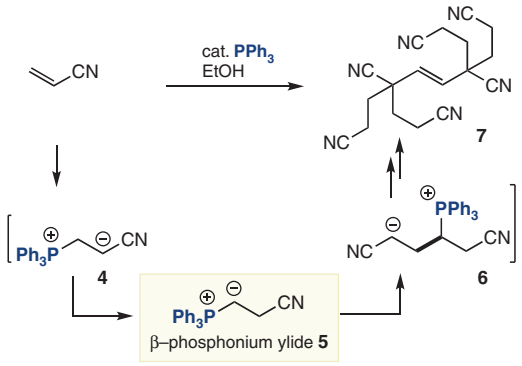
Yuji Nakano completed a Bachelor of Science (Science Scholar Program) at Monash University in 2012 and a Ph.D. in 2017 at Monash University under the supervision of Professor David W. Lupton, where he worked on enantioselective N-heterocyclic carbene catalysis. From there, Yuji moved to Princeton University as an Endeavour Postdoctoral Fellow to conduct post-doctoral research with Professor Todd K. Hyster, investigating photoenzymatic catalyzed processes. In mid-2019, Yuji returned to Melbourne and took up a position as a post-doctoral fellow with Professor Jonathan B. Baell, where he is undertaking medicinal chemistry research at the Monash Institute of Pharmaceutical Sciences.

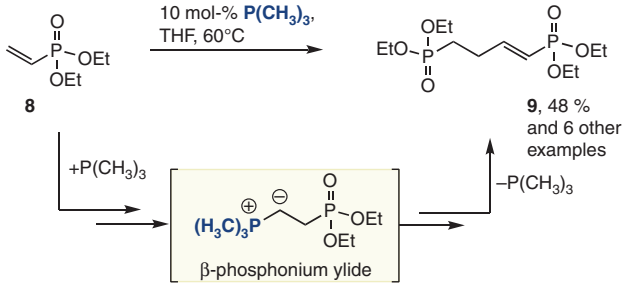
David W. Lupton graduated with a Bachelor of Science (Honours, first class) in 2001 (University of Adelaide) before being awarded a Doctorate of Philosophy for studies under the supervision of Professor Martin G. Banwell (Australian National University) in 2005. Dr Lupton then undertook a post-doctoral fellowship with Professor Barry M. Trost (Stanford University) as a Sir Keith Murdoch fellow of the American Australian Association. In 2007, he returned to Australia to take up an academic appointment at Monash University in Melbourne, receiving an Australian Research Council Future Fellowship in 2011, and promotion to Professor in 2018. In 2010, he received the Athel Beckwith Lectureship of the Royal Australian Chemical Institute (RACI) while in 2013 he received the Rennie Medal of the RACI. Studies under David's supervision are focused on the capacity of catalysis to enable discoveries in chemical synthesis.



Scheme 1. (a) Polarity inversion of aldehydes by 1,2-addition. (b) Polarity inversion of conjugate acceptors by 1,4-addition. EWG = electron-withdrawing group; int. = intermediate.



Scheme 2. Hexamerization of acrylonitrile. cat. = catalyst.



Scheme 3. Trimethylphosphine-catalyzed dimerization of vinyl phosphate.

acceptors is inverted by 1,4-addition of the NHC. As with the formation of the Breslow intermediate, polarity inversion occurs by addition of the NHC and tautomerization of the resultant enolate, resulting in reactive intermediate **3**. Enediamine **3** (also referred to as the β-azolium ylide or deoxy-Breslow intermediate[5]) couples to an electrophile and, after elimination of the NHC, gives a β-alkylated product (Scheme 1b). In the present review, we will examine the development of this chemistry in a comprehensive fashion. In the section *Phosphine Catalysis*, related catalysis achieved with phosphines is discussed. In the section *Stoichiometric Access to the Enediamine*, stoichiometric routes to the enediamine are discussed, with the section *NHC-Catalysis Involving Single C–C Bond Formation* detailing catalytic reactions involving single C–C bond-forming events. Finally, multiple C–C bond formation is discussed in the section *NHC-Catalysis Involving Multiple C–C Bond Formation*, while comments on catalyst selection and concluding remarks are made in the sections *Miscellaneous Reactions of the Enediamine* and *Catalyst Selection*.

Phosphine Catalysis

In 1962, Takashina and Price reported the triphenyl phosphine-catalyzed hexamerization of acrylonitrile (Scheme 2).[6] In contrast to phosphine-catalyzed reactions of the β-phosphonium enolate (i.e. **4**) – a species that would attract significant attention over the following years[6b,7] – this transformation was achieved in the presence of ethanol as a cosolvent. It was postulated that the alcoholic additive allows tautomerization of enolate **4** to give the β-phosphonium ylide **5** that then couples with a second acrylonitrile to give **6**. Four subsequent Michael additions and elimination of the catalyst then gives **7**. Although the utility of such products is not clear, this pioneering report demonstrates the potential of catalysis exploiting polarity inversion of conjugate acceptors.

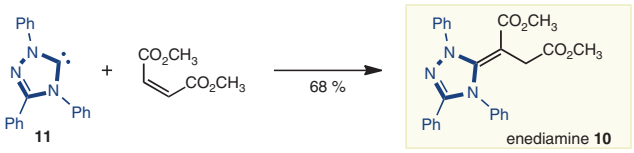
Related phosphine-catalyzed dimerizations of electron-poor olefins have been examined sporadically in the years following this report,[8] often in the context of non-electrochemical routes to adiponitrile. Most recently, Han and coworkers reported the dimerization of vinylphosphonate **8** to give **9** in 48 % yield in the presence of a catalytic trialkyl phosphine (Scheme 3).[8c]

Although these reports demonstrate the viability of phosphine-mediated polarity inversion, the development of reactions beyond commodity chemical dimerization and oligomerization is yet to be demonstrated. The variability and abundance of phosphine catalysts in the literature suggest that this subfield could, in the future, expand into a profitable area of organocatalysis.

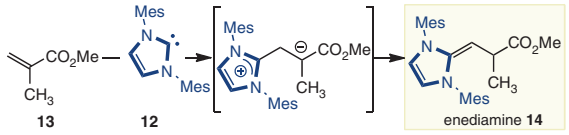
Stoichiometric Access to the Enediamine

Enders and coworkers reported the stoichiometric preparation of an enediamine in 1995.[9] Like the β-phosphonium ylide introduced in the previous section, the formation of enediamine **10** is thought to occur by 1,4-addition of NHC **11** to an electron-poor olefin and subsequent tautomerization (Scheme 4). Further reactions of the enediamine were not explored; however, this report introduced NHCs and substrates that could subsequently be applied in catalytic reactions.

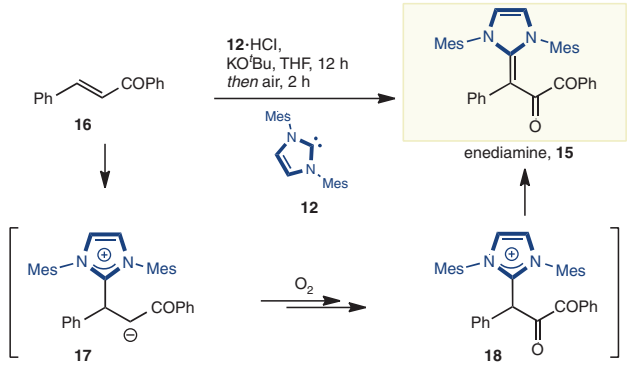
Stoichiometric formation of related enediamines was reported by Chen and coworkers in 2012[10] in their studies of NHC-mediated polymerization reactions. Specifically, they found that the combination of IMes **12** and methyl methacrylate (**13**) afforded enediamine **14**, which was characterized by X-ray



Scheme 4. Formation of enediamine by Enders.



Scheme 5. Isolation of enediamine **14** by Chen.



Scheme 6. Oxidative formation of enediamine **15**.

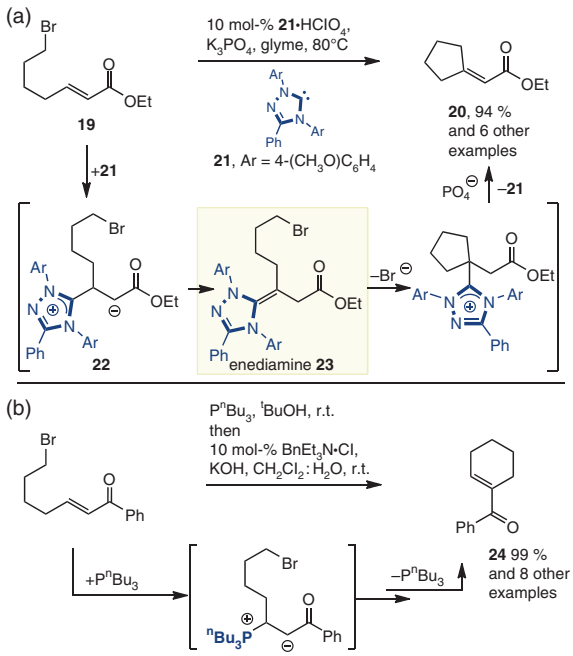
crystallography (Scheme 5). Whether enediamine formation (i.e. **14**), dimerization, or polymerization occurs with methylmethacrylate (**13**) was found to be sensitive to the nature of the azolium.

More recently, Biju and coworkers reported the stoichiometric formation of enediamine **15** when chalcone **16** is exposed to various imidazolium-derived NHCs (i.e. **12**) in the presence of air (Scheme 6).[5e] In this reaction, 1,4-addition provides enolate **17**, which is oxidized to the 1,2-dicarbonyl **18**, which is then deprotonated to give enediamine **15**.

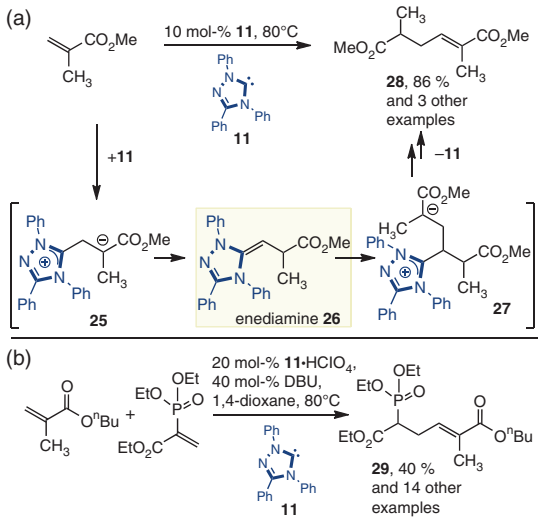
NHC-Catalysis Involving Single C–C Bond Formation

The first catalytic reaction implicating the enediamine was reported in 2006 by Fu and coworkers. In studies examining a nickel-catalyzed Mizoroki-Heck reaction, it was discovered that the cyclization of **19** to give **20** (Scheme 7a) could be catalyzed by NHC ligand **21** in the absence of a transition metal.[11] The observed reaction was rationalized as occurring by 1,4-addition of the Lewis base catalyst to give enolate **22**, which then undergoes tautomerization to enediamine **23**. Subsequent displacement of the tethered bromide provides the cyclized material, with elimination of the catalyst giving the observed product **20**. What is striking in this reaction is that enolate **22** does not undergo direct cyclization to give cyclohexene **24** (Ph = OEt). In contrast, with phosphines – Lewis base catalysts also capable of polarity inversion (see above) – cyclization via the enolate is observed to provide the six-membered product **24** (Scheme 7b).[12]

Computational investigations by Wang and coworkers examined the divergent reactivity of NHC and phosphine catalysts, and concluded that formation of enediamine **23** was



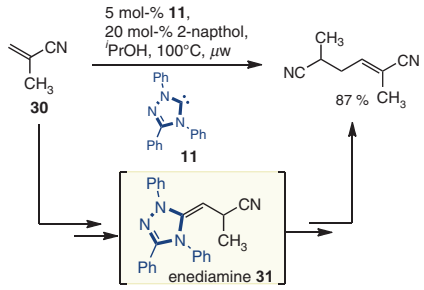
Scheme 7. (a) Catalysis via enedamine **23**. (b) Orthogonal reactivity with phosphine catalysis. r.t. = room temperature.



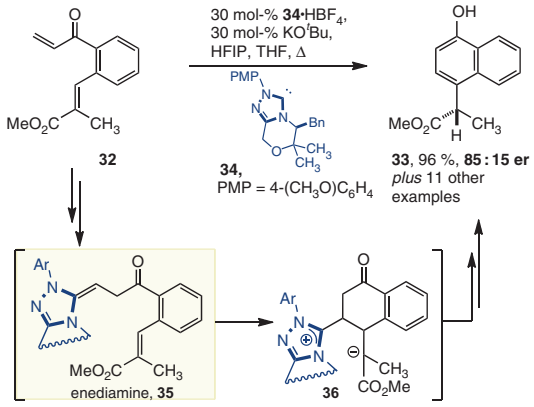
Scheme 8. Tail-to-tail coupling of electron-poor olefins.

thermodynamically favoured over enolate **22**, something that was not the case for the analogous β-phosphonium ylide.[13]

This intriguing report from Fu introduced a new reactive intermediate to the field and demonstrated that NHC-organocatalysis by 1,4-addition is not limited to enolate reactions.[14] Despite this advance, it was some 5 years before the next report of catalysis via the enediamine emerged. In 2011, Matsuoka and coworkers reported the tail-to-tail dimerization of acrylates effected by triazolium-derived NHC **11** (Scheme 8a).[15] The proposed mechanism for this reaction involves addition of the NHC to provide enolate **25**, which then tautomerizes to give the enediamine **26**. Nucleophilic addition to another equivalent of the starting material then installs the new C–C bond in **27**, with elimination of the catalyst by an E1cB mechanism providing the observed product **28**. Independent



Scheme 9. Tail-to-tail dimerization of acrylonitrile derivatives. μw = microwave.



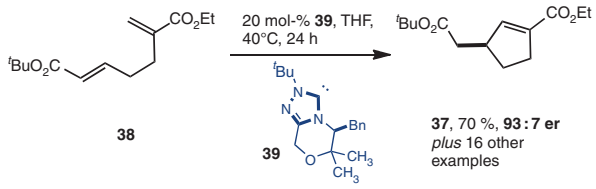
Scheme 10. Cycloisomerization of bis-Michael acceptor **32**.

studies reported concurrently by Glorius and coworkers introduced a similar transformation.[16] In their work, it was also possible to achieve the cross-coupling of acrylates with vinylphosphonates in the presence of triazolium-derived NHC **11** to give, for example, **29** (Scheme 8b). Presumably the dual activation within the vinyl phosphonate allows chemoselective addition of the NHC to this partner.

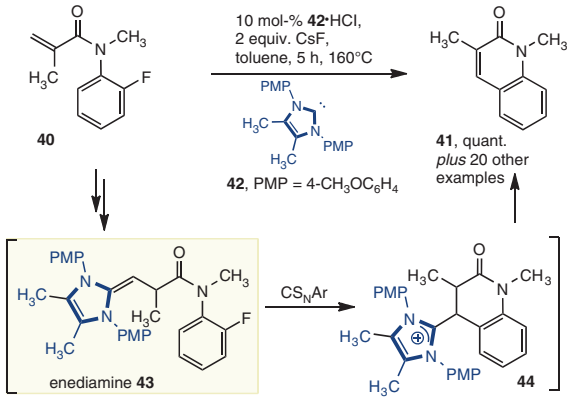
Subsequently, Matsuoka and coworkers expanded on these initial discoveries to include α,β-unsaturated nitrile **30** as a precursor to enediamine **31**. This transformation proved sensitive to H-bond donor additives, with favourable results obtained in the presence of propan-2-ol and 2-naphthol (Scheme 9).[17]

The first enantioselective reaction to exploit the enediamine intermediate was introduced by Nakano and Lupton in 2016. In this work, the cycloisomerization of bis-Michael acceptor **32** was achieved to allow access to enantioenriched aryl propiolate **33** (Scheme 10).[18] Specifically, the reaction starts with polarity inversion of the more electrophilic β-unsubstituted vinyl ketone using the nucleophilic *p*-methoxyphenyl NHC **34** to give enediamine **35**. Subsequent addition into the second Michael acceptor gives rise to enolate **36**. Diastereoselective protonation, to establish the only stereogenic centre retained in the product, is then followed by elimination of the catalyst and keto-enol tautomerism to give **33**. The reaction occurred with moderate levels of enantioselectivity, which could be augmented using hexafluoroisopropanol (HFIP) as an additive. This is likely due to the HFIP serving as a bulky acid for the diastereoselective protonation.

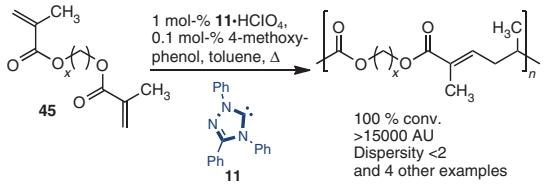
Although enantioselectivity was possible with the previous design, an alternative cycloisomerization was developed by the same group to access more highly enantioenriched materials (Scheme 11).[19] In this transformation, the cyclization sets a



Scheme 11. Cycloisomerization by α-linked bis-Michael acceptor **38**.



Scheme 12. 2-Quinolone synthesis by Tobisu.



Scheme 13. Proton-transfer polymerization exploiting the enediamine intermediate.

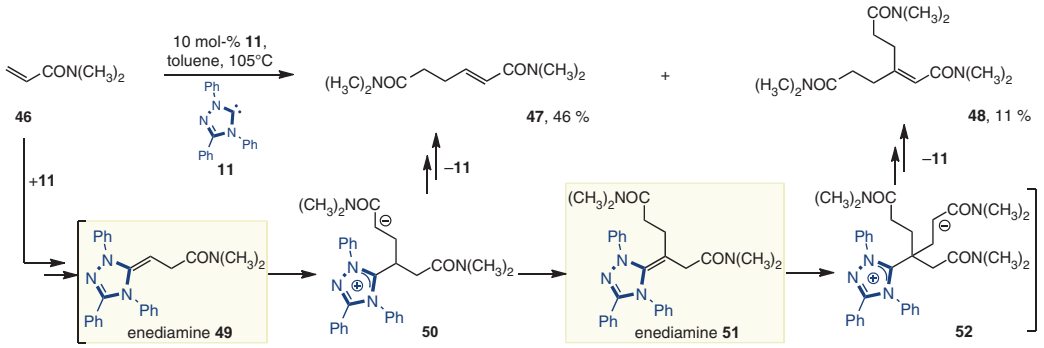
stereocentre that is retained in the product. As a consequence, this design was more robust, allowing a wide array of cyclopentanes (i.e. **37**) to be prepared from bis-Michael acceptors (i.e. **38**) with high levels of enantioselectivity.

Recently, polarity inversion of aryl acrylamide **40** has enabled the preparation of 2-quinolones **41** (Scheme 12).[20] In this report, Tobisu and coworkers exploit bespoke high-nucleophilicity NHCs (i.e. **42**) to give enediamine **43**, which then undergoes a concerted aromatic substitution reaction (CS_NAr, supported by computational studies) to give **44** and ultimately the quinolone **41**. This study is a rare example of the enediamine adding to an electrophile that is not a Michael acceptor.

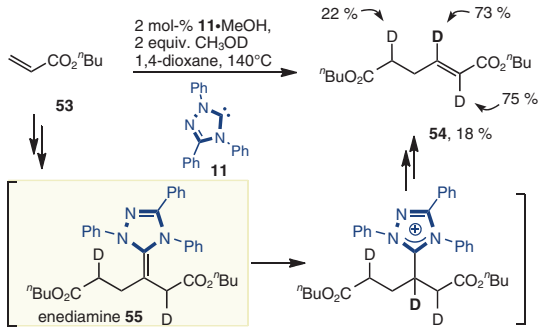
In addition to small-molecule synthesis, the enediamine has been exploited in polymerization studies.[21] For example, Chen and coworkers reported linear chain propagation of dimethacrylate **45** by tail-to-tail dimerization catalyzed by **11**. This reaction furnished polyesters of high atomic weight and narrow dispersity (Scheme 13).

NHC-Catalysis Involving Multiple C–C Bond Formation

Formation of the enediamine proceeds via initial formation of an enolate – the key intermediate for the Morita–Baylis–Hillman and Rauhut–Currier reactions.[7] In addition, mechanistic investigations have revealed how the enediamine can reform following a bond-forming reaction (see below). Thus, reactions



Scheme 14. Dimerization and trimerization of acrylamide **46**.



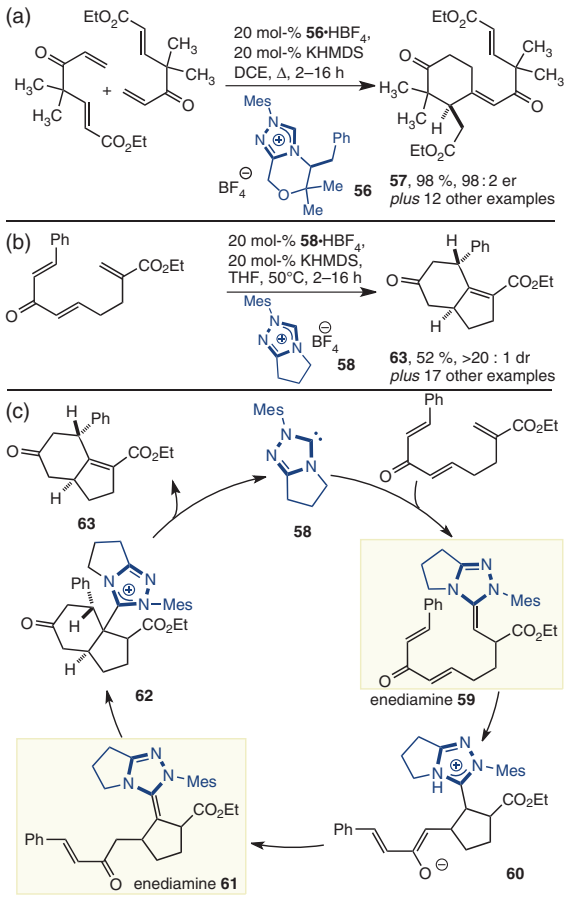
Scheme 15. Matsuoka's deuterium labelling studies.

can be designed that exploit multiple C–C bond-forming events involving either intermediate.

In 2015, Berkessel and coworkers reported studies on the dimerization of dimethyl acrylamide **46** with the Enders triphenyltriazolium (TPT) catalyst **11**. Analogous to adducts formed with acrylates and phosphonates, the tail-to-tail dimer **47** formed, although this was also accompanied by a small amount of trimer **48** (Scheme 14).[22] Mechanistically, it would appear that formation of the first enediamine (i.e. **49**) is followed by coupling to an acrylamide to give enolate **50**. This can then either eliminate the NHC to give the dimer **47**, or tautomerize to the second enediamine (i.e. **51**). The latter pathway then allows a third acrylamide to be incorporated, to give **52**, which then eliminates the NHC to give trimer **48**.

Repeated formation of the enediamine can also be inferred from deuterium labelling studies reported by Matsuoka (Scheme 15).[23] Specifically, when acrylate **53** is dimerized in the presence of deuterated methanol, isotope incorporation is observed in product **54** that is consistent with formation of a second enediamine (i.e. **55**) before elimination of the NHC.

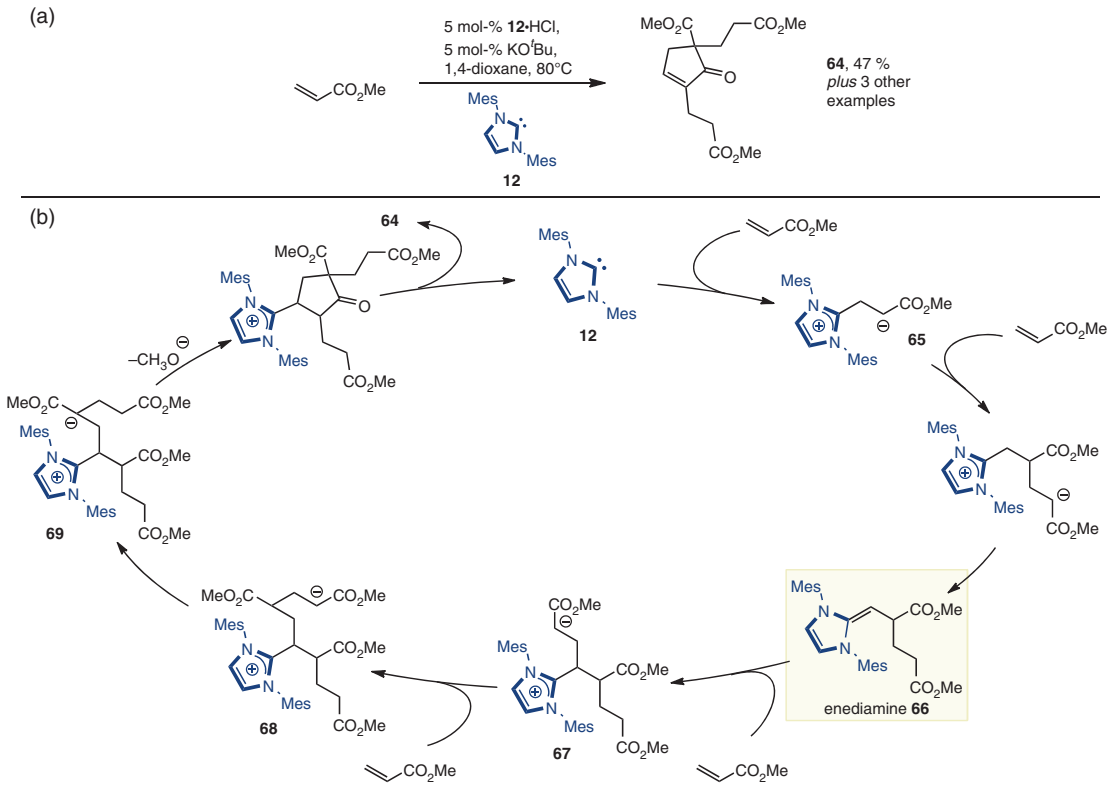
The potential utility of multiple enediamine formation was recently exploited with the development of dimerizing/cycloisomerization, and cycloisomerization, reactions by Lupton and coworkers (Scheme 16).[24] The former reaction design was possible using homochiral NHC **56**, allowing several cyclohexanones (i.e. **57**) to be prepared (Scheme 16a) with high levels of enantioselectivity. The second reaction design was achieved with achiral catalysts **58**. A lack of reactivity with chiral NHCs was attributed to the decreased nucleophilicity of these catalysts,[25] thus making them unsuitable for substrates in which the three electrophiles are linked through the α-position of the first conjugate acceptor (Scheme 16b). Mechanistically, these reactions are related. If we consider the latter reaction it likely commences by 1,4-addition and tautomerization to provide



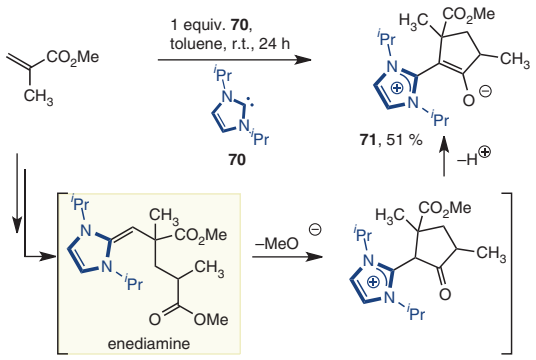
Scheme 16. (a) Dimerizing cycloisomerization via multiple enediamines. (b) Cycloisomerization via multiple enediamines. (c) Proposed mechanism. KHMDS = potassium hexamethyldisilazide; DCE = dichloroethane.

enediamine **59** (Scheme 16c). This species then undergoes an intramolecular conjugate addition to give enolate **60**, which tautomerizes to give the second enediamine **61**. This species undergoes the second cyclization to give **62**, which following elimination of the catalyst, provides the bicyclic product **63**.

The fine lines between dimerization, oligomerization, and polymerization as outcomes in reactions involving the enediamine were exemplified in studies by Matsuoka reported in 2013. Using methyl acrylate in the presence of imidazolium-derived NHC **12**, the tetramer **64** was produced (Scheme 17a).[26] A mechanism was postulated in which enolate **65** is initially formed and undergoes a Michael addition, followed by tautomerization



Scheme 17. Cyclotetramerization via β-azolium enolate and enediamine intermediates.



Scheme 18. Formation of ylide **71** via enolate and enediamine intermediates.

to yield enediamine **66** (Scheme 17b). Its addition into a third acrylate then gives enolate **67**, which adds to a fourth acrylate in a second Michael addition to give **68**. Finally, tautomerization to give **69**, followed by Dieckmann reaction and elimination of the NHC, gives cyclopentenone **64**.

A related trimerization exploiting both enolate and enediamine intermediates was reported by Taton and coworkers when methyl methacrylate was exposed to an equivalent of NHC **70** (Scheme 18).[27] In this case, the ylide **71** was isolated in 51 % yield.

Miscellaneous Reactions of the Enediamine

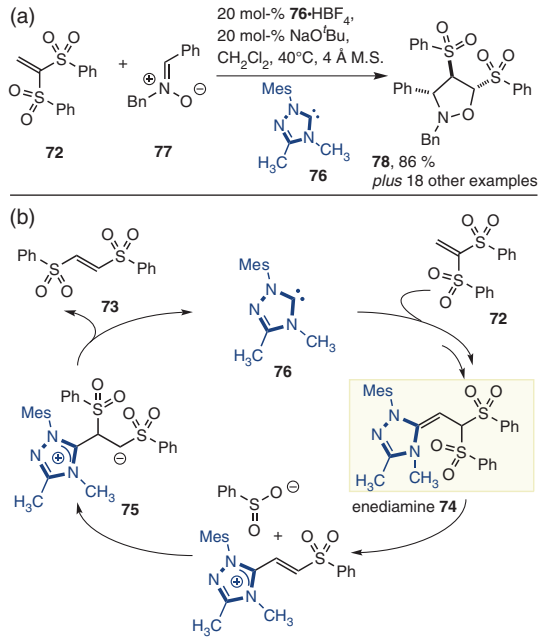
The intermediacy of the enediamine was exploited by Scheidt and coworkers in the rearrangement of 1,1-disulfone **72** to 1,2-disulfone **73**, within the context of a [3 + 2] annulation.[28] Crossover experiments confirmed the formation of the enediamine intermediate **74**, followed by ejection of the sulfonate and recombination to give **75**. Finally, elimination of NHC **76** provided the substrate for the [3 + 2]-dipolar cycloaddition with nitrone **77** to give **78** (Scheme 19).

Arylogous acrylonitrile **79** has been shown to undergo tail-to-tail dimerization reactions to give dinitrile product **80** (Scheme 20). The groups of Glorius[29] and Matsuoka,[23] using conditions similar to those already reported (Scheme 8), were able to execute this coupling reaction with good yields.

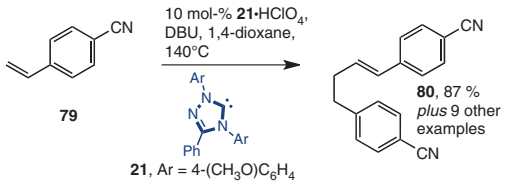
Catalyst Selection

As is common in studies on NHC-organocatalysis, a broad array of catalysts have been reported. In some cases, it can be seen that a systematic investigation into the NHC suited to the reaction design has been undertaken, although this is not always the case. Limiting factors such as accessibility can influence catalyst selection. With this said, a few general comments to guide NHC selection for this type of reaction can be made. First, the use of triazolium-derived NHCs bearing electron-withdrawing *N*-substituents, such as *N*-C_6F_5 or *N*-2,4,6-$Cl_3C_6H_2$, has not been reported. These are common NHCs used in the polarity inversion of aldehydes. Their absence is likely related to a higher degree of nucleophilicity required for the 1,4-addition. In our studies, we have examined a range of NHCs in all enantioselective reaction designs and found that in most, but not all, designs, higher-nucleophilicity carbenes are ideal.

Another feature evident in the studies presented herein is that β-unsubstituted Michael acceptors are most common, with only a limited number of reactions with a β-substituent reported. In



Scheme 19. (a) NHC-catalyzed (3 + 2) cycloaddition. (b) Proposed mechanism. M.S. = molecular sieves.



Scheme 20. Dimerization of benzonitrile **79**.

these cases, more nucleophilic triazolium (or indeed imidazolium)-derived NHCs or forcing conditions are required. Presumably, this correlates with a decrease in electrophilicity of substrate bearing β-substituents.[30]

Conclusions

Catalysis via polarity inversion of conjugate acceptors was reported little more than a decade ago and, after an induction period, is beginning to receive attention within the community. Trends in catalyst selection and substrate suitability are becoming clear, allowing new reaction designs to be established. There are still several limitations in this field, with only tentative forays into enantioselective catalysis reported, and a limited number of reaction designs that exploit electrophilic partners that are not a Michael acceptor. The next stage of development for this type of reaction is likely to involve an expansion of the range of electrophilic partners, and the creation of more general solutions to enantioselectivity.

Conflicts of Interest

The authors declare no conflicts of interest.

Acknowledgements

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