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Asymmetric catalysis with *N*-heterocyclic carbenes as non-covalent chiral templates

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N-heterocyclic carbenes are a class of persistent carbenes stabilized by adjacent heteroatoms that are part of a heterocycle. They play a central role in multiple enzymatic biosynthetic reactions that involve thiamine diphosphate. Inspired by this biocatalysis machinery, *N*-heterocyclic carbenes have emerged as one of the most versatile classes of organocatalysts for organic reactions. However, the asymmetric synthesis of carbon–carbon bonds through a non-covalent interaction mechanism has not been previously established for chiral carbenes. Here, we report an *N*-heterocyclic carbene-catalysed, highly enantioselective process that uses weak hydrogen bonds to relay asymmetric bias. We find that catalytic amounts of hexafluoroisopropanol are the critical proton shuttle that facilitates hydrogen transfer to provide high-reaction rates and high enantioselectivity. We demonstrate that a successful asymmetric reaction of this type can be accomplished through a rational design that balances the pKa values of the substrate, the carbene precursor and the product.

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The use of *N*-heterocyclic carbenes (NHCs) in organic synthesis has led to substantial advances in transition-metal catalysis[1] and organocatalysis[2] over the past decade. Extensive research has shown that chiral NHCs are a class of privileged chiral ligands for transition-metal catalysis[3,4] and that they are versatile chiral organocatalysts[5,6] that can generate one enantiomer preferentially in numerous organic transformations[7,8]. NHCs can catalyse chemical bond synthesis because of several unique chemical characteristics: they are strong σ-donors[1] and good Brønsted bases, and they have moderate π-acidity[9]. For metal catalysis, the strong σ-donor nature of NHCs makes them excellent ligands for late transition metals for asymmetric olefin metathesis[10–12], hydrogenation[13–16] and conjugate additions[17,18]. Typically, an NHC-mediated organocatalytic reaction proceeds through a mechanism similar to the thiamine diphosphate mechanism, wherein a highly nucleophilic acyl-anion equivalent is the key reaction intermediate and is generated by the addition of the NHC catalyst to an aldehyde[19,20]. This umpolung species, also known as the Breslow intermediate, reacts with various electrophiles to form addition products. The hydrolysis of those adducts regenerates the NHC catalyst and generates the acyl addition/substitution products, often with high enantiomeric excess (*ee*) when a chiral NHC is used (Fig. 1a, for example, Benzoin condensation[21] and the Stetter reaction[22,23]). NHCs can also react with acyl halides/anhydrides/esters[24,25], electron-deficient olefins[26,27] and ketenes[28,29], forming either highly reactive acylating agents or Baylis–Hillman-type intermediates through a nucleophilic addition reaction (Fig. 1b,c)[30]. These intermediates can undergo a series of stereoselective nucleophilic and electrophilic reactions to produce functionalized carbonyl compounds. Catalyst turnover is generally achieved by alcoholysis or elimination. All of the aforementioned enantioselective processes utilize strong bond interactions (coordinate or covalent bonds) to ensure the robust communication of chiral information between the NHC and the substrate. Despite the well-established concept of asymmetric hydrogen bond catalysis[31–34], NHCs have yet to identify themselves as good asymmetric Brønsted base catalysts for carbon–carbon bond-forming reactions. Several transesterification reactions using NHCs have been reported, in which the carbene species were believed to exhibit Brønsted base characteristics[35–39]. Although transesterification of unactivated esters has been reported through the use of achiral NHC catalysts[35–38], only highly reactive vinyl esters were successful in the asymmetric versions[39]. Alternative nucleophile catalysis by NHC may occur for these reactions, as supported by recent work by Chi and co-workers[25,40,41]. Presumably, an acyl imidazolium cation intermediate is formed by the substitution of the vinyl alcohol with NHC, which in turn undergoes alcoholysis. Nevertheless, highly selective carbon–carbon bond synthesis utilizing weak H-bond interactions alone remains challenging (Fig. 1d).

In this paper, we describe an enantioselective Michael addition reaction in which NHCs are successfully used as a chiral Brønsted base for the first time. The enantioselectivity for this reaction is accomplished by combining a chiral triazolium salt, a lithium base and an acidic additive that serves as the pivotal proton shuttle to produce a high-reaction rate and high enantioselectivity.

Results

Analysis of NHC-catalysed Michael addition reactions. Relative to amines, NHCs are significantly stronger Brønsted bases, and their conjugate acids have pKa values in the range of 17–25, similar to alkoxides[42–44]. In the case of a Brønsted base-catalysed conjugate addition reaction, the regeneration of the free NHC catalyst in the final step of the catalytic cycle would require a very basic product enolate. The competing retro-Michael could racemize the newly generated stereogenic centre if the final protonation step is not fast enough (Fig. 2a). In addition, a single-point binding mode creates a rather floppy H-bond complex, which further discourages facial discrimination. As a result, a good level of enantioselectivity has not been achieved when using a chiral NHC as an organic base catalyst. A recent study on NHC-catalysed oxy-Michael addition showed that facial discrimination was poor with popular chiral-NHC scaffolds; only 11% enantioselectivity was achieved for an intramolecular addition reaction, possibly as a result of a loosely stacked catalyst/substrate ion pair (Fig. 2b)[45]. In a separate report on carbo-Michael addition, strongly basic NHCs showed excellent catalytic activity. However, an attempt to influence this reaction asymmetrically was unsuccessful, likely due to the two aforementioned reasons (Fig. 2c)[46]. In our opinion, these fundamental obstacles have prevented the development of successful asymmetric Brønsted base catalysis using NHCs.

Proton-shuttling strategy for Brønsted base catalysis using NHCs. To address the general problem of the lack of asymmetric control for NHCs used as chiral Brønsted base catalysts, we developed a proton-shuttling strategy (Fig. 3)[47]. This design takes advantage of a stable cyclic enol form that predominates in solution with 1,3-dicarbonyl compounds. The NHC catalyst might form a well-organized cyclic intermediate through a hydrogen-bonding interaction, instead of fully deprotonating the substrate. In addition, the acidic nature of the 1,3-dicarbonyl compounds might allow direct proton transfer from the substrate to the product anion without forming a stable NHC acid salt. The NHC would in fact become a proton-shuttle promoter, as opposed to a hard base. Furthermore, this proton-shuttling strategy might favour the use of NHCs derived from less basic triazolium salts, which are the class of scaffold that has been most successful in delivering high enantiomeric control for other types of catalytic mechanisms[48].

Preliminary evaluation of NHCs as Brønsted base catalysts. We used the Michael addition reaction between 1,3-diketones and nitroolefins as a template for testing our design (Fig. 4)[49–52]. Confirming our initial hypothesis, we found that strong Brønsted base NHCs, such as *N*,*N*-dialkylimidazolium-generated NHCs, neither catalysed nor generated appreciable conversion for this reaction. This result is in sharp contrast to previous reports that used NHCs as Brønsted bases for both oxy- and carbo-Micheal addition reactions[45,46]. Those reports primarily used *N*-alkyl imidazolium-derived NHCs because they are strongly basic. We suggest that such NHCs can fully deprotonate a diketone substrate, which triggers the first nucleophilic addition cycle, and that the reaction stalls at the imidazolium stage because the conjugate imidazolium salt has a high pKa and cannot be redeprotonated[42–44]. When a C_2-symmetric imidazolium salt with two identical chiral alkyl chains on both nitrogen atoms was used stoichiometrically, no *ee* was observed for the product, suggesting that the diketone enolate and imidazolium cation ion pair is rather loose and flexible or that the reaction is reversible due to slow protonation of the product anion. In sharp contrast, less basic *N*,*N*-diarylimidazolium- and triazolium-derived NHCs catalysed the reaction smoothly, despite the attenuated deprotonation potential resulting from the reduced basicity of their corresponding NHCs (Supplementary Table 1). It is suggested that this reaction likely operates through a hydrogen-bonded complex, and not a fully charged ion pair. The result

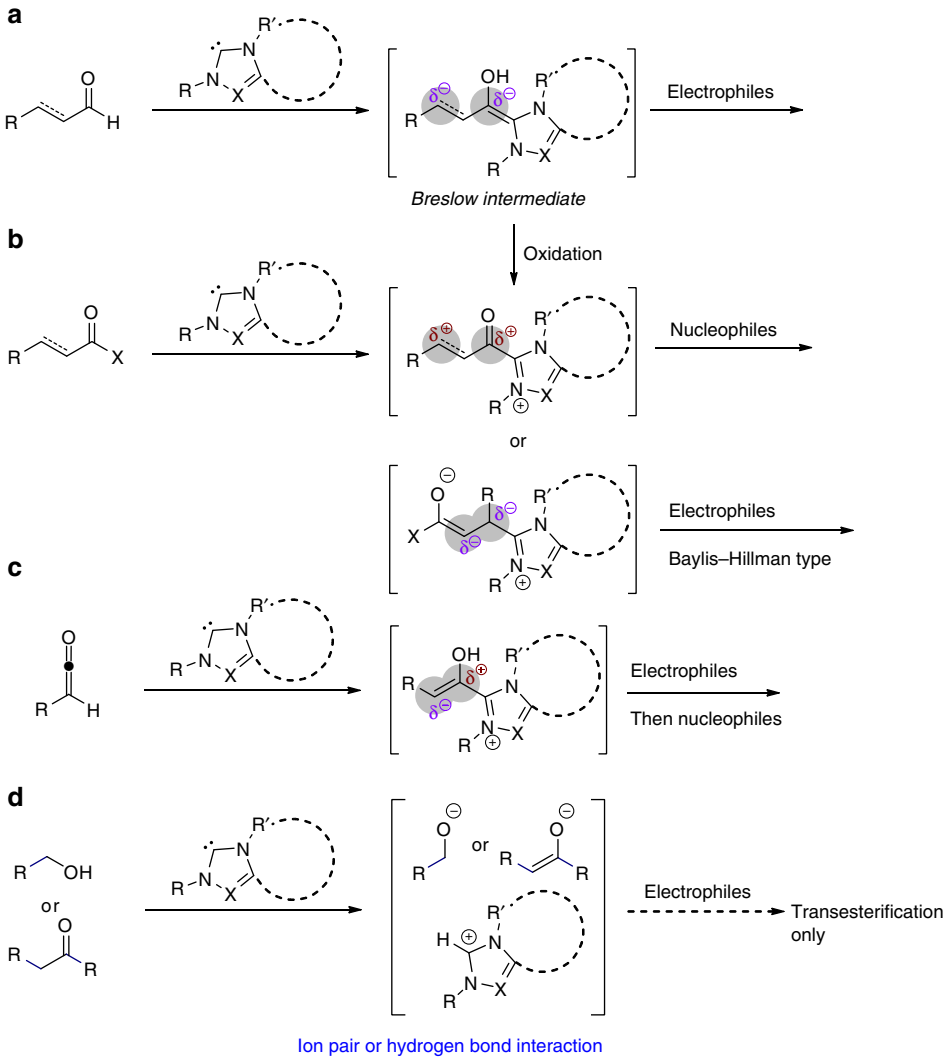


Figure 1 | NHCs as organocatalysts for asymmetric synthesis. (**a**) NHCs nucleophilically add to an aldehyde, generating an umpolung acyl-anion equivalent (Breslow intermediate). (**b**) NHCs react with acyl halides/anhydrides/esters or electron-deficient olefins to generate chiral carbonyl compounds. (**c**) NHCs react with ketenes to form a [1, 2]-dipolar species that undergoes [n + 2] annulation reactions. (**d**) NHCs as asymmetric Brønsted bases remain elusive, except for the transesterification of highly reactive vinyl esters. The shaded area highlights the reactive sites that possess a partial charge.

strongly supports our initial notion of maintaining complementary pKas for the substrate, catalyst and product.

Condition screening and reaction optimization. With these preliminary data in hand, we explored the feasibility of controlling the enantioselectivity of the Michael addition reaction of 1,3-diketone compounds and nitroalkenes catalysed by a chiral triazolium salt-derived NHC (Table 1). The product *ee* was highly sensitive to the structures of chiral NHCs. Aminoindanol-derived catalysts promoted a moderately selective reaction. The base used to generate the free NHC catalyst also had a strong effect on the selectivity of the reaction. Lithium inorganic bases were rapidly identified as the best co-catalysts (Supplementary Table 2). The facial selectivity was strongly influenced by the aryl substituent on the triazolium nitrogen. In contrast to the popular NHC-catalysed acyl-anion reactions, the pentafluorinated phenyl catalyst did not promote the reaction due to its low pKa. A mesityl group showed the highest enantioselectivity. Organic base co-catalysts (for example, 1,8-diazabicyclo[5.4.0]undec-7-ene, DBU) produced moderate yields and *ee*s, likely as a result of interference from their conjugate acid forms, which may disrupt the organization of the transition state. Because the final proton transfer is likely to be the most problematic step, we tested a number of additives bearing an acidic proton that could act as a proton shuttle (Supplementary Table 3). Surprisingly, we found that a highly acidic alcohol, hexafluoroisopropanol (HFIP), afforded both higher yields and improved enantioselectivity. The reaction was also sensitive to solvent, with only ethers affording both high yields and high *ee*s (Supplementary Table 4). Our investigation resulted in the following optimized reaction parameters: 20 mol% NHC precursor, 16 mol% lithium bis(trimethylsilyl)amide (LHMDS), 20 mol% HFIP and 4 Å molecular sieves in methyl *t*-butylether (MTBE) at −40 °C for 48 h. The reaction occurred smoothly when using 5 mol and 10 mol% catalyst loading, but the reaction time was longer. For the sake of easy operation at small scales, 20 mol% catalyst loading was chosen for the substrate scope survey.

Substrate scope. Under the optimized conditions, both aryl and aliphatic nitroalkenes were suitable substrates for this reaction (Table 2). The use of aryl, including heteroaryl substituted nitroalkenes resulted in particularly high reactivity and selectivity, regardless of the substitution pattern and the electronic characteristics of the substituents. Yields greater than 80% and *ee*s of

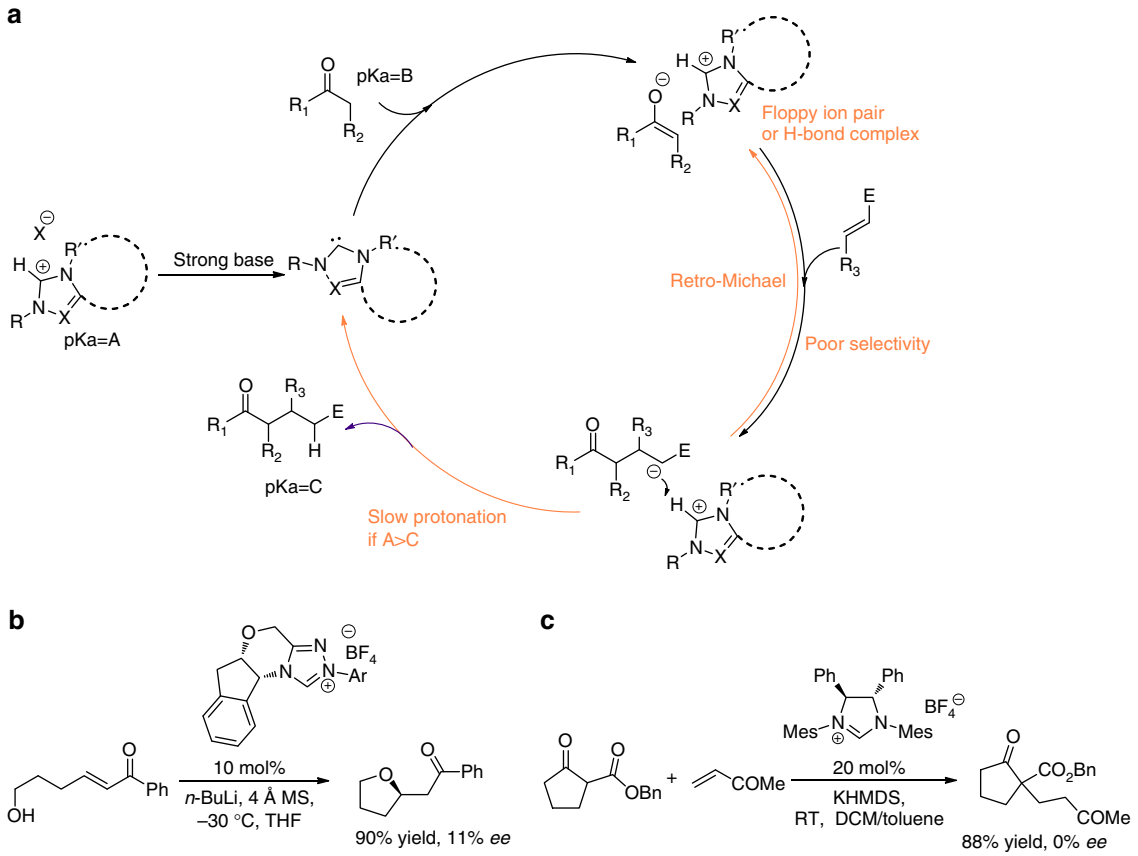


Figure 2 | NHC as a chiral Brønsted base is strategically problematic. (**a**) NHC-catalysed Michael addition reactions lack asymmetric control: (1). typically, pKa A > B ~ C, so the final protonation step is slow, and the retro-Michael reaction becomes competitive. (2). Single-point H-bonding or ion pairing generally lacks enantio-control. (**b**) A chiral triazolium salt-catalysed oxy-Michael reaction provides low enantioselectivity, even for an intramolecular reaction. (**c**) The lack of enantioselective control was also observed for a carbo-Michael addition reaction. DCM, dichloromethane; KHMDS, potassium bis(trimethylsilyl)amide; RT, room temperature; THF, tetrahydrofuran.

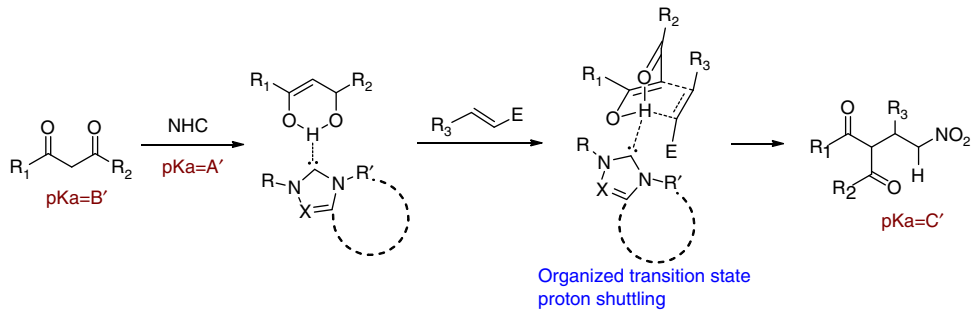


Figure 3 | Proton-shuttling strategy for brønsted base catalysis using NHCs. The use of a 1,3-dicarbonyl substrate has two benefits: it generates an organized catalyst/substrate pair, and it promotes efficient proton transfer from the starting material to the product. Here, pKa A′ ≫ C′ ≫ B′.

95% were uniformly observed. Aliphatic nitroalkenes showed a somewhat attenuated reactivity with moderate enantioselectivity. For example, a nitroalkene with a β-*i*Pr substituent generated the desired product **3k** with 47% yield and 75% *ee*. 1,3-Diketones were the best nucleophiles for this NHC-catalysed asymmetric Michael addition. Moderate diastereoselectivity was observed for asymmetric 1,3-diketones (Fig. 5). Both diastereomers were formed to have good to excellent *ee*s. 1,3-ketoesters were also tolerated. We examined various 1,3-dicarbonyl substrates and found that both the reactivity and selectivity were highly sensitive to the pKa of the substrate; those with significantly higher or lower acidities than 1,3-diketones were poor substrates. This observation supports our original hypothesis that the pKa values of the substrate, product and NHC precursor should be well balanced to obtain sufficient catalytic turnover and facial discrimination.

Enantioselective Michael reaction on a 5 mmol scale. A large-scale reaction using 5 mmol (*E*)-(2-nitrovinyl)benzene was carried out with 20 mol% **5a**. The desired product, **3b**, was isolated with 90% yield and 99% *ee* under the standard conditions described in Table 2.

Discussion

The transition state configuration for this reaction and the role of HFIP are complicated. Several experiments were performed to

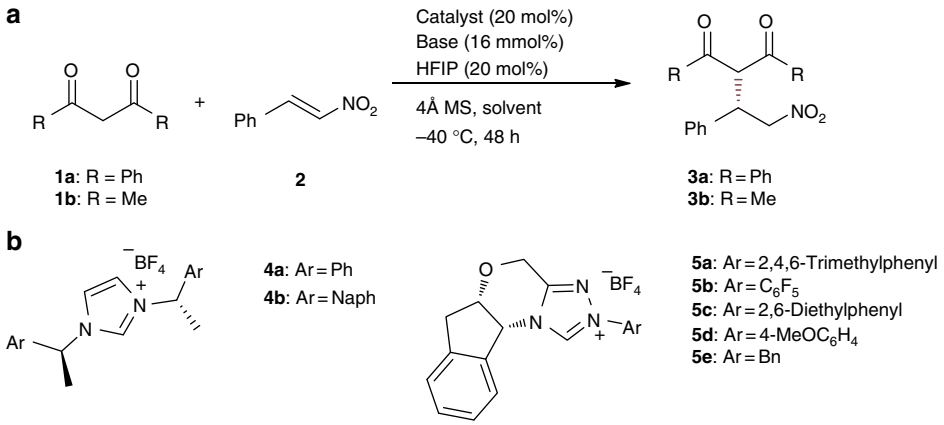


Figure 4 | Survey of NHC catalysts for the Michael addition reaction. (**a**) Reactions were performed using 0.3 mmol of 1,3-dicarbonyl compounds and 0.1 mol nitroalkene in 1.2 ml solvent at −40 °C for 48 h. (**b**) Catalysts evaluated.

Table 1 | Condition screening and reaction optimization*.

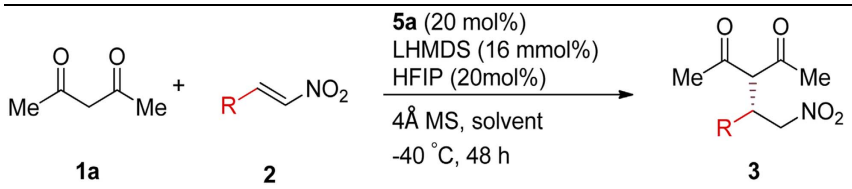
Entry	Catalyst†	Base	Solvent	Product	Yield (%)‡	ee (%)§
1	**4a**	*t*-BuONa	DCM	**3a**	<5	0
2	**4b**	*t*-BuONa	DCM	**3a**	25	0
3	**5a**	*t*-BuONa	DCM	**3a**	86	76
4	**5a**	DBU	DCM	**3a**	61	69
5	**5a**	LHMDS	DCM	**3a**	74	79
6	**5b**	LHMDS	DCM	**3a**	<5	40
7	**5c**	LHMDS	DCM	**3a**	73	69
8	**5d**	LHMDS	DCM	**3a**	80	50
9	**5e**	LHMDS	DCM	**3a**	81	17
10	**5a**	LHMDS	Toluene	**3a**	70	72
11	**5a**	LHMDS	Et_2O	**3a**	63	91
12	**5a**	**LHMDS**	**MTBE**	**3a**	**56**	**96**
13	**5a**	**LHMDS**	**MTBE**	**3b**	**92**	**99**
14‖	**5a**	LHMDS	MTBE	**3b**	50 (67)	91
15¶	**5a**	LHMDS	MTBE	**3b**	20	91

*Reactions were performed using 0.3 mmol of 1,3-dicarbonyl compounds and 0.1 mol nitroalkene in 1.2 ml solvent at −40 °C for 48 h (Fig. 4).
†For the catalyst structures, see Supplementary Table 1.
‡Determined by ^{1}H NMR integration of the crude mixture.
§Determined by chiral HPLC.
‖10 mol% catalyst loading and base, 50% yield for 2 days and 67% yield for 4 days.
¶5 mol% catalyst loading and base, 2 days.

better understand the mechanism underlying this unprecedented NHC-catalysed process. We observed a positive lithium effect. Under otherwise identical reaction conditions, NaHMDS generated a lower yield with significantly decreased enantioselectivity (84% yield, 60% *ee*) relative to LHMDS (92% yield, 99% *ee*). When 12-crown-4 was used together with the lithium cation, a poor yield and low *ee* were obtained (36% and 36%, respectively). These results strongly suggest that lithium is involved in the transition state, possibly as a Lewis acid activator for the electrophile. However, when commercially available lithium acetylacetonate was employed without the NHC catalyst, only trace amounts of product were observed at room temperature (Fig. 6a). Pentane-2,4-dione reacted with (*E*)-(2-nitrovinyl) benzene in a non-selective manner without a catalyst at room temperature, and several products were formed. With the addition of HFIP (20 mol%), the reaction was cleaner, and the major reaction pathway was the Michael addition reaction (Fig. 6b). When catalytic levels of lithium acetylacetonate were introduced with HFIP, the reaction was rapid, and the desired product was isolated quantitatively (Fig. 6c). These data suggest that the final deprotonation step is critical. In the absence of a proton source, the Michael addition reaction is inhibited. The reaction showed a negative non-linear effect (Fig. 7), which suggests that more than one NHC is involved in the carbon–carbon bond formation step, and the NHC pair with opposite absolute stereochemistry resulted in a faster reaction. Such results suggest that there is a delicate, enzyme-like transition state with multiple non-covalent bond interactions.

Additional proton additives were also tested, but only HFIP showed better results than the additive-free reaction. Trifluoroethanol and $(CF_3)_3COH$ inhibited the Michael addition reaction. Stoichiometric HFIP resulted in a fast racemic reaction. Only catalytic levels (0.1–0.3 eq.) of HFIP enhanced both the yield (92% versus 57% without HFIP) and *ee* (99% versus 50% without HFIP). This strong HFIP effect is intriguing. Rovis and co-workers[53,54] showed that less basic triazolium salt-derived NHC catalysts can co-exist with weak Brønsted acids (for example, carboxylic acids). A control experiment was carried out to test the benzoin condensation reaction using benzaldehyde under our standard conditions. The desired benzoin product was isolated with 52% yield and 49% *ee* (Fig. 8), confirming the existence of a free NHC species under these conditions. HFIP is believed to act as a hydrogen bond linker that helps stabilize the transition state of the carbon–carbon bond-forming step. In

Table 2 | Enantioselective Michael addition reactions of 2,4-pentadione*.



Entry	R	Yield† (%)	ee‡ (%)
1	Ph, **3b**	92	99
2	1-Naphthyl, **3c**	95	97
3	4-Me-Ph, **3d**	99	98
4	2-MeO-Ph, **3e**	89	96
5	2-Br-Ph, **3f**	85	95
6	3-Cl-4-F-Ph, **3g**	80	97
7	2-CF_3-Ph, **3h**	94	95
8	3-CF_3-Ph, **3i**	98	99
9	2-thiophenyl, **3j**	80	98
10	*i*Pr, **3k**	47	75
11	C_2H_4Ph, **3l**	87	80

*Reactions were performed under the optimized condition described in Table 2, entry 13.
†Isolated yield.
‡Determined by chiral HPLC.

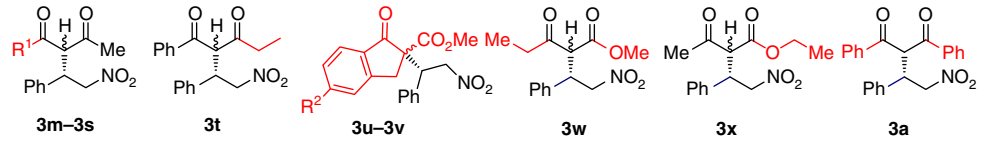


Figure 5 | Substrate scope of the nucleophile. Deviation from 2,4-pentadione is indicated in red. R^1 = Ph, **3m**, (yield: 95%, dr = 1:1, ee: 93%, 97%); R^1 = 2-Me-Ph, **3n** (yield: 77%, dr = 1.4:1, ee: 98%, 98%); R^1 = 4-Cl-Ph, **3o** (yield: 99%, dr = 1.7:1, ee: 91%, 95%); R^1 = 3-F-Ph, **3p** (yield: 88%, dr = 1.2:1, ee: 86%, 91%); R^1 = 4-MeO-Ph, **3q** (yield: 75%, dr = 1.3:1, ee: 90%, 90%); R^1 = 4-Me-Ph, **3r** (yield: 92%, dr = 1.3:1, ee: 94%, 95%); R^1 = 3-CF_3-Ph, **3s** (yield: 76%, dr = 1:1, ee: 90%, 88%); **3t** (yield: 86%, dr = 1.4:1, ee: 96%, 94%); R^2 = H, **3u**, (yield: 97%, dr = 3:1, ee: 92%, 75%); R^2 = F, **3v**, (yield: 95%, dr = 1.7:1, ee: 84%, 77%); **3w** (yield: 90%, dr = 1.2:1, ee: 84%, 82%); **3x** (yield: 79%, dr = 1.4:1, ee: 80%; 80%); **3a** (yield:56%, ee: 96%).

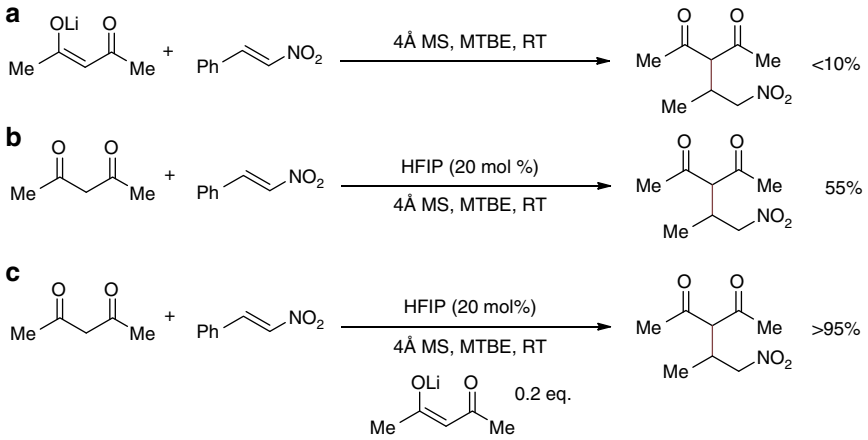


Figure 6 | Control experiments. (**a**) Fully deprotonated 2,4-pentadione failed to react with (*E*)-(2-nitrovinyl)benzene. (**b**) A catalytic amount of HFIP promoted the Michael addition of pentane-2,4-dione to (*E*)-(2-nitrovinyl)benzene. (**c**) A stoichiometric amount of proton source is required to achieve efficient nucleophilic addition.

addition, the strong acidity of HFIP may also further facilitate the final proton-transfer step and disfavour the retro-Michael reaction.

In summary, we have rationally designed a reaction in which chiral NHCs catalyse a highly enantioselective carbon–carbon bond-forming reaction through a non-covalent bonding interaction. The intellectual considerations were focused on the final catalytic step, the proton transfer, which was critical and potentially problematic. Through careful balancing of the pKas of the substrate, catalyst and product, a highly enantioselective process for Michael addition to nitroolefins was developed. The acidic co-catalyst HFIP was found to significantly enhance this

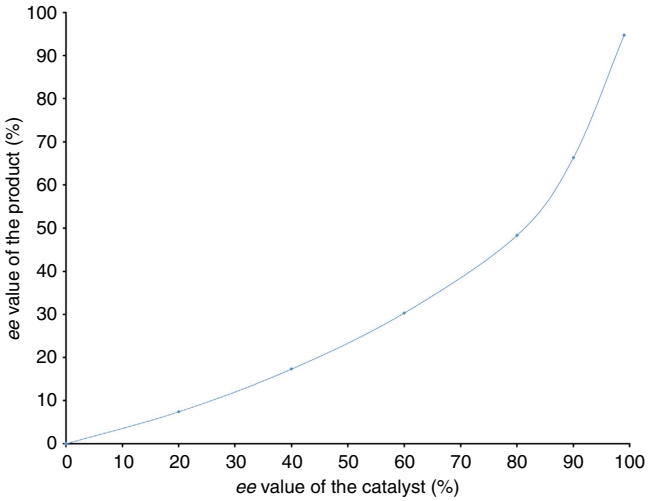


Figure 7 | Non-linear effects. The *ee* of the product was lower than predicted for an ideal linear situation when the optical purity of the catalyst was compromised.

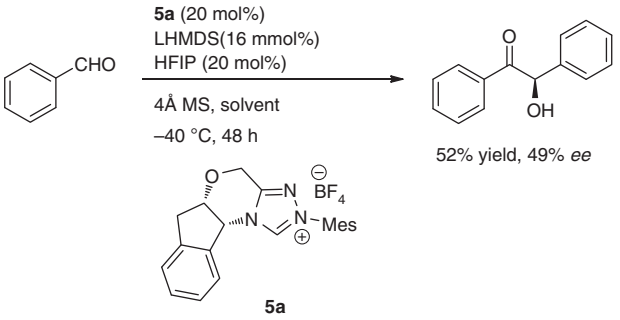


Figure 8 | Benzoin condensation under Brønsted base conditions. A facile benzoin condensation proceeded smoothly when benzaldehyde was used under otherwise identical conditions as those used for the Michael addition reaction. This result demonstrates the existence of free NHC in the reaction system.

reaction in terms of both yield and enantioselectivity. We expect that this concept will be widely used to design new enantioselective organic transformations that use NHCs as a new class of Brønsted bases and ion pair organocatalysts.

Methods

Materials. All solvents were distilled according to general practice before use. All reagents were purchased and used without further purification unless otherwise specified. Solvents for flash column chromatography were technical grade and distilled before use. Analytical thin-layer chromatography was performed using silica gel plates with HSGF 254 (0.15–0.2 mm) manufactured by Shandong Huanghai Chemical Company (Qingdao, China). Visualization of the developed chromatogram was performed by measuring UV absorbance (254 nm) and using appropriate stains. Flash column chromatography was performed using Qingdao Haiyang Chemical HG/T2354-92 silica gel (45–75 μm) with the indicated solvent system according to standard techniques.

General spectroscopic methods. ^{1}H NMR and ^{13}C NMR data were recorded on Bruker 400 MHz (100 MHz for ^{13}C) nuclear resonance spectrometers unless otherwise specified. Chemical shifts (δ) in ppm are reported relative to the residual signals of chloroform (^{1}H 7.26 p.p.m. and ^{13}C 77.16 p.p.m.). Multiplicities are described as follows: s (singlet), bs (broad singlet), d (doublet), t (triplet), q (quartet) and m (multiplet). Coupling constants (*J*) are reported in Hertz (Hz). ^{13}C NMR spectra were recorded with total proton decoupling. Chiral high-performance liquid chromatography (HPLC) was recorded on a Shimadzu LC-20A spectrometer using Daicel Chiralcel columns. HRMS (ESI) analysis was performed by the Analytical Instrumentation Center at Peking University, and HRMS data were reported as ion mass/charge (m/z) ratios in atomic mass units. ^{1}H NMR, ^{13}C NMR and HPLC spectra are provided for all compounds; see Supplementary Figures 1–96. See the Supplementary Methods for the characterization data for compounds not listed in this section.

Synthesis of (*S*) 2-(2-nitro-1-phenylethyl)-1, 3-diphenyl-propane-1, 3-dione 3a. NHC catalyst **5a** (8.4 mg, 0.2 equiv.) and 4-Å oven-dried molecular sieves (100 mg) were dissolved in dry MTBE (0.3 ml) in a 15-ml test tube. The mixture was degassed and back-filled with argon (3 ×) before LHMDS (1 M in tetrahydrofuran/ethylbenzene, 16 μl, 0.16 equiv.) was slowly added. The reaction vessel was degassed and back-filled with argon, and HFIP (2.2 μl, 0.2 equiv.) was added from a micro-syringe. The test tube was sealed with a rubber septum and stirred at −40 °C for 1 h. A solution of **1a** (0.3 mmol, 3.0 equiv.) in MTBE (0.3 ml) was slowly added, and the mixture was stirred for 1 h at −40 °C. A solution of **2a** (0.1 mmol, 1.0 equiv.) in MTBE (0.6 ml) was slowly added over the course of 30 min, and the resulting mixture was stirred at −40 °C for 48 h. When compound **2a** was completely consumed, the reaction was filtered through a short plug of silica gel and concentrated. The residue was purified by silica gel flash column chromatography (eluent: hexane/EtOAc = 8:1) to yield **3a** (21 mg, 56%) as a white solid. ^{1}H NMR (400 MHz, CD_2Cl_2): δ 7.88 (d, J = 7.6 Hz, 2H), 7.79 (d, J = 7.6 Hz, 2H), 7.63–7.50 (m, 2H), 7.41 (dt, J = 15.5, 7.7 Hz, 4H), 7.23 (m, 5H), 5.87 (d, J = 8.2 Hz, 1H), 5.06–4.92 (m, 2H), 4.62 (dd, J = 13.9, 8.3 Hz, 1H); ^{13}C NMR (100 MHz, CD_2Cl_2): δ 194.07, 193.55, 136.81, 136.18, 135.81, 134.01, 133.73, 128.90, 128.81, 128.77, 128.62, 128.48, 128.29, 128.03, 77.40, 59.47 and 44.08. HPLC (IA-H, 10% EtOH in hexanes, 1 ml min^{-1}, 254 nm): t_{major} = 14.8 min, t_{minor} = 17.1 min, 96% *ee*; $^{25}[\alpha]_D$ = +7.4 ° (c = 0.40 in $CHCl_3$)[55].

5 mmol-scale synthesis of (*S*) 3-(2-nitro-1-phenylethyl)-pentane-2,4-dione 3b. NHC Catalyst **5a** (418 mg, 0.2 equiv.) and 4-Å oven-dried molecular sieves (5 g) were dissolved in dry MTBE (30 ml) in a 100 ml round bottom flask. The mixture was degassed and back-filled with argon (5 ×) before LHMDS (1 M in tetrahydrofuran/ethylbenzene, 0.8 ml, 0.16 equiv.) was slowly added. The reaction vessel was degassed/back-filled with argon (5 ×) and stirred at room temperature (25 °C) for 10 min before HFIP (105 μl, 0.2 equiv.) was added from a syringe. The flask was sealed with a rubber septum and stirred at −40 °C for 1 h. Then, **1b** (15 mmol, 3.0 equiv.) was slowly added, and the mixture was stirred for another 1 h at −40 °C. A solution of (*E*)-(2-nitrovinyl)benzene (5 mmol, 1.0 equiv) in MTBE (30 ml) was slowly added over the course of 40 min, and the resulting mixture was stirred at −40 °C for 48 h. Upon the complete consumption of (*E*)-(2-nitrovinyl)benzene, the reaction was filtered through a short plug of silica gel and concentrated. The residue was purified by silica gel flash column chromatography (eluent: hexane/EtOAc = 8:1) to yield the desired addition product **3b** (1.120 g, 90%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.31 (dt, J = 23.1, 8.1 Hz, 3H), 7.19 (d, J = 7.1 Hz, 2H), 4.72–4.57 (m, 2H), 4.37 (d, J = 10.7 Hz, 1H), 4.30–4.17 (m, 1H), 2.29 (s, 3H), 1.94 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 201.75, 200.99, 136.04, 129.33, 128.55, 127.95, 78.18, 70.72, 42.81, 30.42 and 29.56. HPLC (IA-H, 10% EtOH in hexanes, 1 ml min^{-1}, 210 nm): t_{major} = 14.0 min, t_{minor} = 21.4 min, 99% ee; $^{25}[\alpha]_D$ = +172.9 ° (c = 0.95 in $CHCl_3$)[52].

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Author contributions

Y.H. directed the research. Y.H. and J.C. designed the proton-shuttling strategy for NHC-catalysed Michael addition reactions. J.C. performed the experiments. Y.H. analysed the data. The paper was written by Y.H. with the assistance of J.C.

Additional information

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