EDGE ARTICLE

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Switching mesoionic carbene-organocatalysis from radical to ionic pathway through base-controlled formation of Breslow intermediates *versus* Breslow enolates†

Jie Jiao,‡[a] Zengyu Zhang,‡[a] Guangyin Lu,[a] Shiqing Huang,[a] Yajing Bian,[a] Fan Gao,[a] Guy Bertrand [ID] *[b] and Xiaoyu Yan [ID] *[a]

N-heterocyclic carbene (NHC) organocatalysis has experienced significant advancements. Two distinct reaction pathways have been developed, ionic and radical, through Breslow intermediates (BIs) and Breslow enolates (BI⁻s), respectively. The ability to selectively generate these intermediates is crucial for optimizing reaction outcomes. In this paper we show that with mesoionic carbenes (MICs) it is possible to control the formation of BIs *versus* BI⁻s, through the use of weak bases and strong bases, respectively. Of particular interest is the coupling of aldehydes and alkyl halides to yield ketones *via* an ionic pathway.
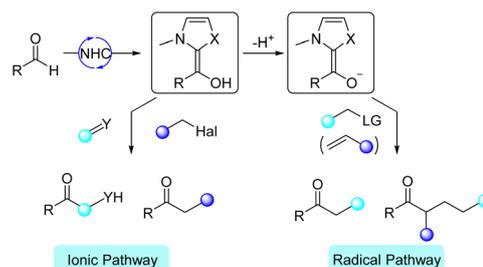
Introduction

Over the past decades, N-heterocyclic carbene (NHC) organocatalysis[1] has witnessed tremendous advancement primarily involving the umpolung of aldehydes through the formation of nucleophilic Breslow intermediates (BIs).[2] A large number of organocatalytic reactions have been developed based on the nucleophilic addition of BIs to $C(sp^2)$-type electrophiles, such as carbonyl compounds,[3] conjugated enones,[4] imines,[5] *etc.* This approach has also been extended to nucleophilic substitutions of BIs with some $C(sp^3)$-type electrophiles,[6] such as benzyl halides,[7] allyl halides,[8] and even unactivated organic halides.[9] In addition to the ionic pathway, NHC-catalyzed radical reactions have also recently been developed.[10] These reactions involve SET between deprotonated Breslow intermediates (BI⁻s, also called Breslow enolates) with single-electron oxidants, such as redox-active esters,[11] pyridinium salts,[12] oxime esters,[13] and activated alkyl halides.[14] This process leads to the formation of NHC-derived ketyl radicals and alkyl radicals which then couple to give ketones (Fig. 1A). In short, ionic pathway involves BIs as intermediates, while radical pathway involves BI⁻s as intermediates.[15] This suggested that it could be possible to switch the

reaction mechanism and therefore the nature of the products by controlling the intermediate involved in the reaction. However, for the catalysts frequently involved in these reactions, *i.e.* thiazol-2-ylidenes,[16] it's still difficult to control the formation of BIs *versus* BI⁻s. Indeed, with these carbenes, both ionic and radical pathway[1,2] are feasible with weak bases[17] such as amines or carbonates, which revealed that either BIs or BI⁻s are formed under these reaction conditions.

[a]Key Laboratory of Advanced Light Conversion Materials and Biophotonics, School of Chemistry and Life Resources, Renmin University of China, Beijing, 100872, China. E-mail: yanxy@ruc.edu.cn

[b]Department of Chemistry and Biochemistry, UCSD-CNR Joint Research Laboratory (IRL3555), University of California, San Diego, La Jolla, CA 92093-0358, USA. E-mail: gbertrand@ucsd.edu

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‡ These authors contributed equally.

Fig. 1 NHC- and MIC-catalyzed ionic and radical coupling reactions.

On the other hand, we have recently shown that besides classical NHCs, another type of persistent carbene, namely mesoionic carbenes (MICs),[18] can be successfully used in organocatalysis *via* radical pathway.[19] BI⁻s derived from MICs, are more reducing than classical NHCs, and served as super electron donors (SEDs),[20] enabling the single-electron reduction of unactivated aryl and alkyl halides.[19a,b] The radical coupling reaction of aldehydes and alkyl halides has also been achieved with MIC catalysts. Importantly, in the case of MICs, and in contrast to classical NHCs, it is possible to choose to generate BIs *versus* BI⁻s. Indeed, the formation of MIC-derived BI⁻s required a strong base (typically ^{t}BuOK), whereas the deprotonation of MIC precursors giving BIs is possible with a weak base (*e.g.* Cs_2CO_3).[21] Herein, we report that the coupling reaction of aldehydes and alkyl halides, with Cs_2CO_3 as a base, giving ketones *via* the ionic pathway as shown by the stereochemistry of the reaction (Fig. 1B). The coupling reaction has a broad functional group tolerance, especially for strong-base sensitive β-functionalized alkyl halides. Mechanistic investigations reveal that the reaction involves a tandem benzoin condensation, α-alkylation, retro-benzoin condensation sequence, where α-alkylated benzoin serves as key intermediate. We also found that the retro-benzoin condensation can be inhibited in MeOH, thus, α-alkylated benzoins can be selectively formed in MeOH. Comparison of the ionic pathway with a weak base and the radical pathway with a strong base, demonstrates the ability to control the formation of BIs *versus* BI⁻s through the choice of the base.

Results and discussion

In our previous work, we showed that the deprotonation of MIC conjugate acid can be done with Cs_2CO_3.[21] We firstly tested the coupling reaction of thiophene-2-carbaldehyde **1a** and ^{n}butyl iodide **2a** in CH_3CN with Cs_2CO_3 as a base. Interestingly, beside formation of the coupling product **3aa**, α-alkylated benzoin derivative **4aa** was formed. Optimizations revealed that the reaction works well with 4 equivalents of base at 40 °C (Table 1, entries 2–4). Similar yield was obtained by using a stoichiometric amount of aldehyde and alkyl iodide (entry 5). The reaction also worked well in isopropanol and DMSO, but showed less efficiency in less polar solvents (entries 6–10). Ester substituted triazolium **B**, which was frequently used as catalyst in our previously reported radical MIC-organocatalysis, gave a lower yield (60%) (entry 11). A lower yield was also obtained with 1,2,4-triazolium **D**, and other NHC precursors were even less efficient (entries 12–14). Base screening revealed Cs_2CO_3 was the best choice (see ESI†). Using ^{n}butyl bromide instead of ^{n}butyl iodide afforded the ketone in 85% yield in DMSO as solvent (entry 15). Moreover, the selectivity was reversed in methanol, and the α-alkylated benzoin derivative **4aa** was formed in 89% yield with a minor amount of **3aa**.

With the optimized reaction conditions in hand, the scope of the reaction was investigated (Table 2). A series of arylaldehydes were tested, five-membered hetero-aryl aldehydes gave the desired ketones in 55–86%. For six-membered aryl aldehydes, the electron-deficient substrates afforded the desired products

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**Table 1** Optimization of reaction conditions^a
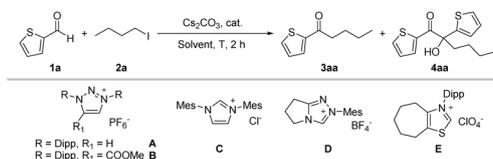
Entry	Cat.	Solvent	Amount of base	T (°C)	Yield^b of **3aa** (%)	Yield^b of **4aa** (%)
1	**A**	CH_3CN	2 equiv.	60	14	25
2	**A**	CH_3CN	4 equiv.	60	41	33
3	**A**	CH_3CN	4 equiv.	40	85	Trace
4	**A**	CH_3CN	4 equiv.	25	75	15
5^c	**A**	CH_3CN	4 equiv.	40	88(86)	Trace
6^c	**A**	^{i}PrOH	4 equiv.	40	68	10
7^c	**A**	DMSO	4 equiv.	40	79	8
8^c	**A**	Dioxane	4 equiv.	40	22	Trace
9^c	**A**	THF	4 equiv.	40	35	6
10^c	**A**	MTBE	4 equiv.	40	8	Trace
11^c	**B**	CH_3CN	4 equiv.	40	60	10
12^c	**C**	CH_3CN	4 equiv.	40	10	31
13^c	**D**	CH_3CN	4 equiv.	40	62	10
14^c	**E**	CH_3CN	4 equiv.	40	6	n.d.
15^d	**A**	DMSO	4 equiv.	60	85(82)	Trace
16	**A**	CH_3OH	4 equiv.	60	10	89(88)

^{a} Reactions were performed with 0.20 mmol of **1a**, 0.10 mmol of **2a** and 20 mol% of protonated NHC in 1.0 mL of solvent for 2 h. ^{b} Yields were determined by ^{1}H NMR with CH_2Br_2 as internal standard. Isolated yields were given in parentheses. ^{c} 0.2 mmol of **2a** were employed. ^{d} ^{n}BuBr was used for 6 h.

Table 2 Scope of the coupling reaction of aldehydes and alkyl halides
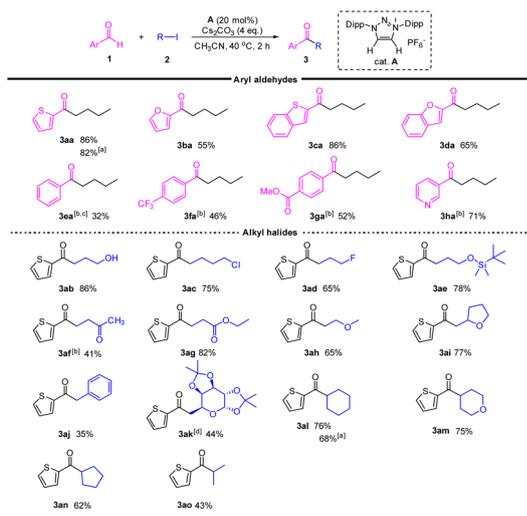
[a] Reaction conditions: aryl aldehydes **1** (0.2 mmol), alkyl halides **2** (0.2 mmol), Cs$_2$CO$_3$ (0.8 mmol), **A** (0.04 mmol) and CH$_3$CN (1 mL) for 2 h at 40 °C. Isolated yields were given. Alkyl bromide was used in DMSO at 60 °C for 6 h. [b] Solvent was changed to ^{i}PrOH. [c] Reaction time was changed to 6 h. [d] Single isomer.[23]

in moderate yields, while electron-rich substrates were unreactive. This is likely due to the fact that electron-rich aldehydes reacted with MICs much slowly and thus the competitive alkylation of MICs led to catalyst decomposition.[22]

The scope of alkyl halides was then investigated. A number of primary alkyl halides bearing different functional groups were employed for this reaction, and the desire ketones were obtained in moderated to high yields. It should be noted that the reaction proceeded well with β-functionalized alkyl halides (products **3af–3ai**), which are unstable under strong base conditions. The reaction was also viable for benzyl iodide, affording ketone **3aj** in 35% yield. The high functional group tolerance of this reaction encouraged us to investigate the acylation of sugar moiety. Reaction of 6-iodo-glucose with thiophene-2-carbaldehyde afforded the 6-acylated glucose in 44% yield. The reaction of secondary alkyl halides also worked well, and the desired ketones were obtained in 43–76% yields.

To further investigate the mechanism of the process, some complex secondary alkyl iodides were investigated as shown in Fig. 2. Reaction of thiophene-2-carbaldehyde **1a** with *cis*-1-iodo-4-methylcyclohexane **2p** gave ketone **3ap** with 11 : 1 *trans*/*cis*. Reaction of **1a** with **2q** with *cis* configuration also gave the product **3aq** with mainly *trans* configuration. Interestingly, Reaction of **1a** with **2r** with *trans* configuration gave a mixture of *trans* and *cis* in 7 : 10 ratio. The partial loss of stereoselectivity is mainly due to slow epimerization under basic condition.[9,24] For 3-iodo-epiandrosterone, only the (3α) isomer **2t** gave the ketone product, while no reaction occurred with (3β) isomer **2s**. The reaction also worked for acyclic alkyl iodide, although the stereoselectivity was low. In addition, no reaction occurred with bulky alkyl iodides, such as menthyl iodide.
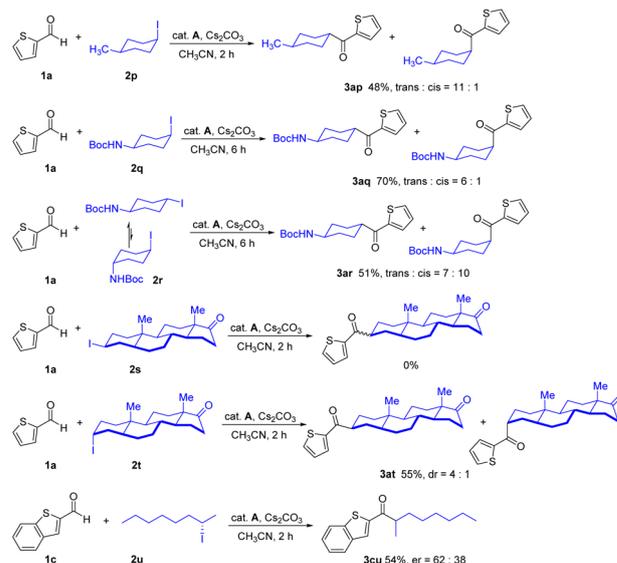
Fig. 2 Reaction of aldehydes with complex secondary alkyl iodides.

The reaction of aldehydes with alkyl iodides in MeOH was also investigated as shown in Table 3. A number of α-alkylated benzoin derivatives can be obtained with different aldehydes and alkyl iodides. Stereo-inversion was observed which revealed that the reaction occurred *via* an S$_N$2 pathway. When 1,*n*-dihalide **2c** and **2d** were used, cyclic ether products **5c** and **5d** were obtained in high yields. It should be noted that, under similar reaction conditions, but with classical NHC **D** as catalyst, only ketones were formed and α-alkylated benzoin derivatives **4** and **5** were not detected.

Our previous work involving MIC-catalyzed coupling of aldehydes and alkyl halides with strong bases supported a radical pathway. For comparison, radical clock and radical trapping experiments were conducted to check whether the reaction proceeded through radical pathway. When (iodomethyl)cyclopropane was employed, only **3aad** was obtained, and the ring-open product was not detected (Fig. 3a). The reaction with Cs$_2$CO$_3$ was not affected with radical trapping reagents such as 1,1-diphenylethylene (DPE), while DPE inhibited the reaction with ^{t}BuOK (Fig. 3b). We also performed competition experiments between primary and secondary alkyl iodides, and the former reacted much faster than the latter (Fig. 3c). All of these experiments were different than those of our previous results[19b] (radical pathway), and similar as Li's results[9] (ionic pathway). Thus, we can conclude that MIC-catalyzed coupling of aldehydes and alkyl halides proceeded through radical pathway with a strong base and ionic pathway with a weak base. To further understand the reaction pathway, we performed the reaction at lower temperature (30 °C) and tracked the formation of products (Fig. 3d). In 30 min, most of the aldehydes were consumed, and α-alkylated benzoin derivative **4aa** was formed as the major product. Then **4aa** decreased with **3aa** increasing. This experiment showed that the aldehyde was first converted to **4aa**, which was then converted to **3aa**. To confirm this hypothesis, treatment of benzoin derivative **6** with

Table 3 Scope of the coupling reaction of aldehydes and alkyl halides
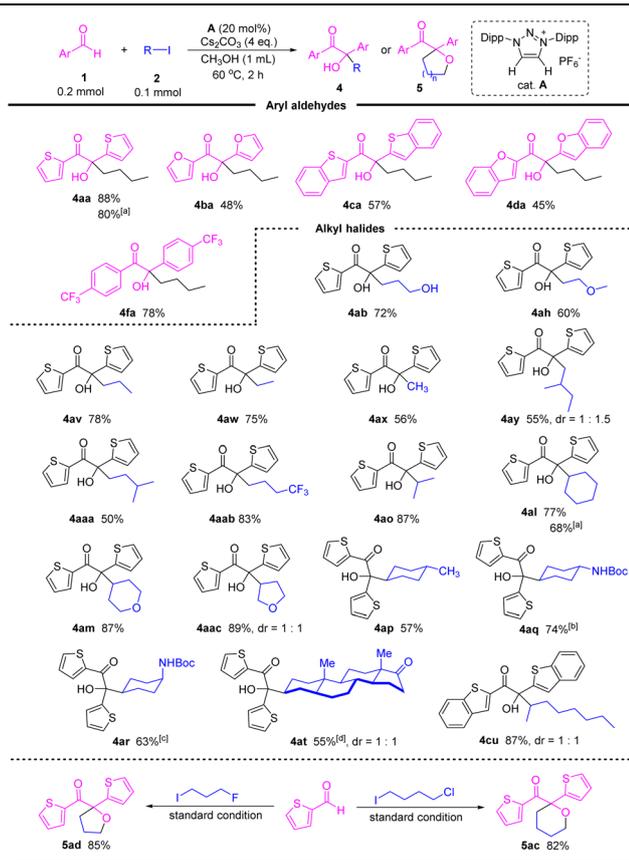
[a] Reaction conditions: aryl aldehydes **1** (0.2 mmol), alkyl halides **2** (0.1 mmol), Cs$_2$CO$_3$ (0.4 mmol), **A** (0.02 mmol) and CH$_3$OH (1 mL) for 2 h at 60 °C. Isolated yields are given. Alkyl bromide was used. [b] **2q** was used. [c] **2r** was used. [d] **2t** was used.

Fig. 3 Mechanism study.

Fig. 4 Comparison of MIC catalyzed coupling reactions with Cs$_2$CO$_3$ and [t]BuOK.

2a resulted the formation of **4aa**. Then, **4aa** can be converted to **3aa** quantitively in the presence of MIC catalyst via retro-benzoin condensation in CH$_3$CN, while the reaction was pretty slow in MeOH (Fig. 3e), which is in consistence with the reaction results in MeOH. On the basis of the above results, a plausible mechanism is proposed (Fig. 3f). First, MIC reacts with aldehyde giving the Breslow intermediate **7**, which then attacks another molecule of aldehyde via nucleophilic addition to yield benzoin derivative **6** with releasing of MIC. Alkylation of **6** in basic conditions gives α-alkylated benzoin derivative **4**. MIC-catalyzed retro-benzoin condensation of **4** gives ketone product and Breslow intermediate **7**.

To make a detail comparison of MIC-catalyzed coupling reactions of aldehydes and alkyl iodides with weak and strong bases, we listed the different experimental results in Fig. 4. Reaction of aldehydes with (iodomethyl)cyclopropane in the presence of Cs$_2$CO$_3$ gave cyclopropylmethyl ketones, while it gave mixture along with ring-open products in the presence of [t]BuOK. For β-functionalized alkyl iodides (take 2-(iodomethyl) tetrahydrofuran as an example), the reactions only proceeded with Cs$_2$CO$_3$ as a base. In the other hand, for alkyl iodides with
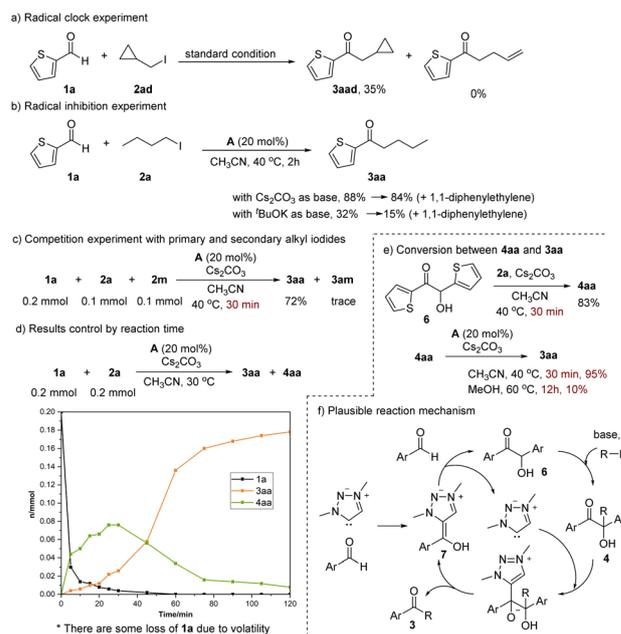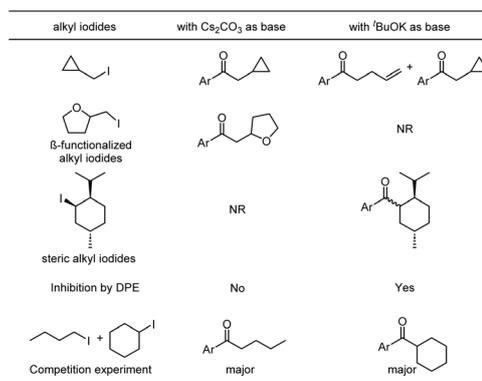
steric hindrance (take menthyl iodide as an example), the reaction only worked with [t]BuOK as a base. Radical inhibition experiments with DPE revealed that the reaction was only inhibited with [t]BuOK as a base. Competition experiments between primary and secondary alkyl iodides also gave different results. These reactions demonstrated that MIC-catalyzed coupling reactions proceeded via ionic pathway with a weak base and radical pathway with a strong base. These two distinct reaction pathways can be further tracked back to different intermediate involved, i.e. BIs for the former and BI$^-$s for the latter, respectively.

To gain a further understanding of the base-controlled formation of BIs versus BI$^-$s, we conducted density functional theory (DFT) investigations at the DLPNO-CCSD(T)/cc-pVTZ// M06-2X/6-31+G** level of theory, employing four different types of NHC-derived BIs (Fig. 5). Thiazol-2-ylidene-derived BI has
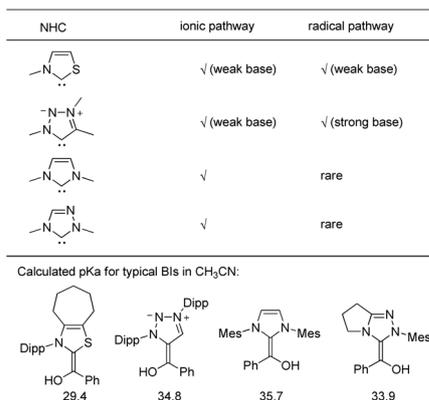
Fig. 5 NHC-catalyzed coupling reaction of aldehydes and the calculated pKa of BIs.

a calculated pKa of 29.4, while the MIC-derived BI has a calculated pKa of 34.8. The difference of pKa revealed that, thiazol-2-ylidene-derived BIs could be deprotonated by a weak base, while MIC-derived BI can only be deprotonated by a strong base. We also calculated the ΔG for the deprotonation process of MIC-derived BI using either a weak base (Me$_3$N and DBU as examples) or strong base (^{t}BuOK). This process is endergonic for weak bases (ΔG = +26.5 and +20.0 kcal mol^{-1}) and exergonic with strong bases (ΔG = −31.3 kcal mol^{-1}). This is in consistence with the experiment results that DBU works for ionic reaction (H/D exchange reaction)[18c] and does not work for radical reactions.[19] In addition, imidazolylidene and 1,2,4-triazol-2-ylidene-derived BIs have pKa values of 35.7 and 33.9. Indeed, imidazolylidenes and 1,2,4-triazol-2-ylidenes were rarely employed in radical coupling reaction of aldehydes, probably due to the instability or bulkiness of their BI$^-$s.[25]

Conclusion

NHC-based organocatalysis usually involves dual pathways—ionic and radical—highlighting the challenges associated with controlling the formation of BIs and deprotonated Breslow intermediates (BI$^-$s). The ability to selectively generate these intermediates is crucial for optimizing reaction outcomes. This work presents a novel approach to control the formation of BIs versus BI$^-$s through basicity-tuning, enabling the coupling of aldehydes and alkyl halides to yield ketones via two distinct reaction pathways. Of particular interest is the coupling of aldehydes and alkyl halides to yield ketones via an ionic pathway through the use of weak bases. The reaction shows broad functional group tolerance and can be used for the acylation of sugar moieties. Mechanistic investigations reveal a tandem benzoin condensation, α-alkylation, and retro-benzoin condensation sequence, where α-alkylated benzoin serves as a key intermediate. It should be noted that the mechanism was different with previous reported ionic coupling reactions of aldehydes with alkyl halides, in which nucleophilic substitutions of BIs with electrophiles were proposed. This work showcases the potential of MIC catalysis in synthetic organic chemistry, paving the way for the development of new

methodologies and applications. The ability to selectively form BIs versus BI$^-$s through basicity tuning represents a significant advancement in NHC catalysis, opening up new possibilities for the umpolung of aldehydes and the synthesis of valuable organic compounds. Further studies on the organocatalysis by MICs are under current investigation.

Data availability

The data supporting this article have been included as part of the ESI.†

Author contributions

J. J., Z. Z., G. L. and F. G. developed the reaction and conducted the experiments. S. H. and Y. B. conducted DFT calculations. G. B. and X. Y. analysed the data and wrote the paper. G. B. and X. Y. directed the project.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

Notes and references

1 (a) A. T. Biju, *N-Heterocyclic Carbenes in Organocatalysis*, Wiley-VCH, Weinheim, 2019; (b) D. Enders, O. Niemeier and A. Henseler, *Chem. Rev.*, 2007, **107**, 5606–5655; (c) V. Nair, R. S. Menon, A. T. Biju, C. R. Sinu, R. R. Paul, A. Jose and V. Sreekumar, *Chem. Soc. Rev.*, 2011, **40**, 5336–5346; (d) S. J. Ryan, L. Candish and D. W. Lupton, *Chem. Soc. Rev.*, 2013, **42**, 4906–4917; (e) M. N. Hopkinson, C. Richter, M. Schedler and F. Glorius, *Nature*, 2014, **510**, 485–496; (f) D. M. Flanigan, F. Romanov-Michailidis, N. A. White and T. Rovis, *Chem. Rev.*, 2015, **115**, 9307–9387; (g) M. Pareek, Y. Reddi and R. B. Sunoj, *Chem. Sci.*, 2021, **12**, 7973–7992; (h) P. Bellotti, M. Koy, M. N. Hopkinson and F. Glorius, *Nat. Rev. Chem*, 2021, **5**, 711–725.

2 (a) R. Breslow, *J. Am. Chem. Soc.*, 1958, **80**, 3719–3726; (b) A. Berkessel, S. Elfert, K. Etzenbach-Effers and J. H. Teles, *Angew. Chem., Int. Ed.*, 2010, **49**, 7120–7124; (c) A. Berkessel, V. R. Yatham, S. Elfert and J. M. Neudörfl, *Angew. Chem., Int. Ed.*, 2013, **52**, 11158–11162; (d) M. Paul, J. M. Neudörfl and A. Berkessel, *Angew. Chem., Int. Ed.*, 2019, **58**, 10596–10600; (e) A. Wessels, M. Klussmann, M. Breugst, N. E. Schlörer and A. Berkessel, *Angew. Chem., Int. Ed.*, 2022, **61**, e202117682.

3 (a) Y. Hachisu, J. W. Bode and K. Suzuki, *J. Am. Chem. Soc.*, 2003, **125**, 8432–8433; (b) T. Ema, Y. Oue, K. Akihara,

Y. Miyazaki and T. Sakai, *Org. Lett.*, 2009, **11**, 4866–4869; (*c*) M.-Q. Jia and S.-L. You, *ACS Catal.*, 2013, **3**, 622–624.

4 J. Read de Alaniz and T. Rovis, *Synlett*, 2009, **8**, 1189–1207.

5 (*a*) J. A. Murry, D. E. Frantz, A. Soheili, R. Tillyer, E. J. J. Grabowski and P. J. Reider, *J. Am. Chem. Soc.*, 2001, **123**, 9696–9697; (*b*) G.-Q. Li, L.-X. Dai and S.-L. You, *Chem. Commun.*, 2007, 852–854; (*c*) L.-H. Sun, Z.-Q. Liang, W.-Q. Jia and S. Ye, *Angew. Chem., Int. Ed.*, 2013, **52**, 5803–5806; (*d*) D. A. DiRocco and T. Rovis, *Angew. Chem., Int. Ed.*, 2012, **51**, 5904–5906.

6 (*a*) F. Gao, Z. Zhang and X. Yan, *ChemCatChem*, 2024, **16**, e202301331; (*b*) Z.-Z. Zhang, R. Zeng, Y.-Q. Liu and J.-L. Li, *ChemCatChem*, 2024, **16**, e202400063.

7 M. Padmanaban, A. T. Biju and F. Glorius, *Org. Lett.*, 2011, **13**, 98–101.

8 M. Zhao, H. Yang, M.-M. Li, J. Chen and L. Zhou, *Org. Lett.*, 2014, **16**, 2904–2907.

9 Q.-Z. Li, R. Zeng, P.-S. Xu, X.-H. Jin, C. Xie, Q.-C. Yang, X. Zhang and J.-L. Li, *Angew. Chem., Int. Ed.*, 2023, **62**, e202309572.

10 (*a*) S. W. Ragsdale, *Chem. Rev.*, 2003, **103**, 2333–2346; (*b*) A. V. Bay and K. A. Scheidt, *Trends Chem.*, 2022, **4**, 277–290; (*c*) T. Ishii, K. Nagao and H. Ohmiya, *Chem. Sci.*, 2020, **11**, 5630–5636; (*d*) X. Chen, H. Wang, Z. Jin and Y. R. Chi, *Chin. J. Chem.*, 2020, **38**, 1167–1202; (*e*) L. Dai and S. Ye, *Chin. Chem. Lett.*, 2021, **32**, 660–667; (*f*) K. Q. Chen, H. Sheng, Q. Liu, P. L. Shao and X. Y. Chen, *Sci. China Chem.*, 2021, **64**, 7–16; (*g*) K. Liu, M. Schwenzer and A. Studer, *ACS Catal.*, 2022, **12**, 11984–11999.

11 (*a*) T. Ishii, Y. Kakeno, K. Nagao and H. Ohmiya, *J. Am. Chem. Soc.*, 2019, **141**, 3854–3858; (*b*) T. Ishii, K. Ota, K. Nagao and H. Ohmiya, *J. Am. Chem. Soc.*, 2019, **141**, 14073–14077; (*c*) Y. Kakeno, M. Kusakabe, K. Nagao and H. Ohmiya, *ACS Catal.*, 2020, **10**, 8524–8529.

12 I. Kim, H. Im, H. Lee and S. Hong, *Chem. Sci.*, 2020, **11**, 3192–3197.

13 (*a*) Y. Gao, Y. Quan, Z. Li, L. Gao, Z. Zhang, X. Zou, R. Yan, Y. Qu and K. Guo, *Org. Lett.*, 2020, **23**, 183–189; (*b*) L. Chen, S. Jin, J. Gao, T. Liu, Y. Shao, J. Feng, K. Wang, T. Lu and D. Du, *Org. Lett.*, 2020, **23**, 394–399; (*c*) S. Jin, X. Sui, G. C. Haug, V. D. Nguyen, H. T. Dang, H. D. Arman and O. V. Larionov, *ACS Catal.*, 2021, **12**, 285–294.

14 J.-L. Li, Y.-Q. Liu, W.-L. Zou, R. Zeng, X. Zhang, Y. Liu, B. Han, Y. He, H. J. Leng and Q. Z. Li, *Angew. Chem., Int. Ed.*, 2020, **59**, 1863–1870.

15 V. Regnier, E. A. Romero, F. Molton, R. Jazzar, G. Bertrand and D. Martin, *J. Am. Chem. Soc.*, 2019, **141**, 1109–1117.

16 A. J. Arduengo, J. R. Goerlich and W. J. Marshall, *Liebigs Ann.-Recl.*, 1997, 365–374.

17 The basic strength (strong or weak) is relative. In this manuscipt, weak bases refered to bases such as carbonates and amines, while strong bases refered to alkoxides.

18 (*a*) G. Guisado-Barrios, M. Soleilhavoup and G. Bertrand, *Acc. Chem. Res.*, 2018, **51**, 3236–3244; (*b*) G. Guisado-Barrios, J. Bouffard, B. Donnadieu and G. Bertrand, *Angew. Chem., Int. Ed.*, 2010, **49**, 4759–4762; (*c*) W. Liu, L.-L. Zhao, M. Melaimi, L. Cao, X. Xu, J. Bouffard, G. Bertrand and X. Yan, *Chem*, 2019, **5**, 2484–2494.

19 (*a*) W. Liu, A. Vianna, Z. Zhang, S. Huang, L. Huang, M. Melaimi, G. Bertrand and X. Yan, *Chem Catal.*, 2021, **1**, 196–206; (*b*) C. Liu, Z. Zhang, L.-L. Zhao, G. Bertrand and X. Yan, *Angew. Chem., Int. Ed.*, 2023, **62**, e202303478; (*c*) Z. Zhang, S. Huang, C.-Y. Li, L.-L. Zhao, W. Liu, M. Melaimi, G. Bertrand and X. Yan, *Chem Catal.*, 2022, **2**, 3517–3527; (*d*) F. Su, F. Lu, K. Tang, X. Lv, Z. Luo, F. Che, H. Long, X. Wu and Y. R. Chi, *Angew. Chem., Int. Ed.*, 2023, **62**, e202310072; (*e*) B. Huang, Z. Zhang, J. Jiao, W. Liu and X. Yan, *Org. Lett.*, 2024, **26**, 7419–7424; (*f*) T. Wang, Z. Zhang, F. Gao and X. Yan, *Org. Lett.*, 2024, **26**, 6915–6920.

20 (*a*) J. Broggi, T. Terme and P. Vanelle, *Angew. Chem., Int. Ed.*, 2014, **53**, 384–413; (*b*) J. A. Murphy, *J. Org. Chem.*, 2014, **79**, 3731–3746.

21 M. Abdellaoui, K. Oppel, A. Vianna, M. Soleilhavoup, X. Yan, M. Melaimi and G. Bertrand, *J. Am. Chem. Soc.*, 2024, **146**, 2933–2938.

22 C. E. I. Knappke, A. J. Arduengo, H. Jiao, J.-M. Neudörfl and A. J. von Wangelin, *Synthesis*, 2011, **23**, 3784–3795.

23 The absolute configuration of the chiral centers of **3ak** have been assigned based on the reasonable assumption that they inherit from glucose.

24 The epimerization of **3as** under basic condition was given in ESI†

25 (*a*) L. Delfau, S. Nichilo, F. Molton, J. Broggi, E. Tomás-Mendivil and D. Martin, *Angew. Chem., Int. Ed.*, 2021, **60**, 26783–26789; (*b*) N. Assani, L. Delfau, P. Smits, S. Redon, Y. Kabri, E. Tomás-Mendivil, P. Vanelle and D. Martin, *Chem. Sci.*, 2024, **15**, 14699–14704.