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Organocatalysis

# Carbene-Catalyzed Activation of C–Si Bonds for Chemo- and Enantioselective Cross Brook–Benzoin Reaction

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**Abstract:** The first carbene-catalyzed asymmetric chemoselective cross silyl benzoin (Brook–Benzoin) reaction has been developed. Key steps of this reaction involve activation of the carbon–silicon bond of an acylsilane by a chiral N-heterocyclic carbene (NHC) catalyst to form a silyl acyl anion intermediate. These acyl anions then undergo an addition reaction with indole aldehydes in a highly chemo- and enantioselective manner to afford α-silyloxy ketones with excellent optical purities. The reaction mechanism of this cross Brook–Benzoin reaction was investigated through both experimental and computational methods. The chiral α-hydroxy ketone derivatives obtained by this approach show promising, agrochemically interesting activity against harmful plant bacteria.

## Introduction

Chiral indole and carbazole molecules are widely found in natural products and exhibit proven and potential bioactivities.[1] Especially, chiral pinacol molecules derived from indole and carbazole cores are interesting entities that have shown great significance in the development of drugs (Figure 1a).[2] For example, notoamides E2 and E3 are key metabolites isolated from a marine-derived fungus *Aspergillus sp.*, and are significant in the investigation of the biosynthetic pathways for various bioactive indole alkaloids.[2e,f] Nigrospin A has been found in the culture broth of the fungal strain *Nigrospora oryzae* SCSGAF 0111 isolated from the South China Sea gorgonian *Verrucella umbraculum* that possesses strong antimicrobial activities against a broad spectrum of fungi and bacteria.[2h] (−)-Dihydroxygirinimbine and clausine W are carbazole-derived chiral pinacols isolated from the roots of *Zanthoxylum austrosinense* and have shown promising inhibitory activities against 5 kinds of human cancer cells and the inflammatory NO production.[2g,l] Neocarazostatin A is a bacterial alkaloid

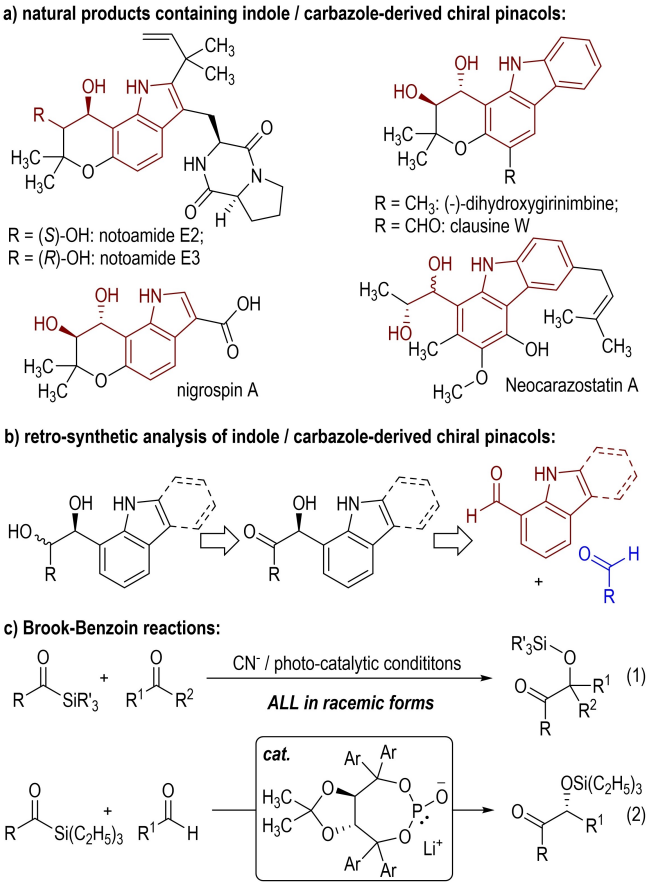


***Figure 1.*** Natural products containing indole/carbazole-derived pinacol motifs and the catalytic cross Brook–Benzoin reactions.

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and has been widely used as a potent free radical scavenger in living cells.[2b,i–k] Therefore, the development of efficient and enantioselective strategy for the construction of indole and carbazole-derived chiral pinacol structures is of great interest.

From the view of the retro-synthetic analysis towards the indole and carbazole-derived chiral pinacol molecule, the optically enriched α-hydroxyl ketone containing the heteroaryl alkaloid core is one of the key precursors (Figure 1b). A most direct method to prepare such α-hydroxyl ketone molecules is perhaps through benzoin reactions.[3] Unfortunately, in typical benzoin reactions with two different aldehydes (or aldehydes and ketones) as the substrates, achieving chemo-selective cross reactions remains challenging.

To address such chemoselectivity issues, one approach is to replace one of the aldehyde substrates with acylsilanes for cross silyl benzoin reactions (Brook–Benzoin reactions, Figure 1c).[4] Metal cyanides[4a,b,d,e] and Lewis acids[4g] have been used as catalysts for this transformation [Figure 1c, Eq. (1)]. However, most of the reported Brook–Benzoin reactions are performed in racemic forms. An elegant exception came from Johnson's group in 2004, in which they realized enantioselective cross Brook–Benzoin reactions using chiral metallophosphite as the catalyst [Figure 1c, Eq. (2)].[5] Scheidt explored N-heterocyclic carbenes (NHCs) as organocatalysts[6] to mediate aza-benzoin[4c] and Stetter reactions[7] using acylsilanes as the nucleophiles, with the corresponding products obtained in racemic forms as well.[8] To the best of our knowledge, enantioselective Brook–Benzoin reactions mediated by NHCs or other organocatalysts have not been achieved.[9] Challenges might come from two main factors: i) the steric hindrance impedes addition of typically bulky chiral NHC catalysts to the relatively bulky acylsilane substrates; and ii) chemo-selective reaction of NHC catalyst with acylsilane over the aldehyde electrophiles. In a general picture, achieving enantioselective cross (silyl) benzoin reactions remains an important problem waiting for effective solutions.

Herein, we disclose the first NHC-catalyzed enantioselective cross Brook-Benzoin reaction between acylsilanes[10] and aldehydes (Figure 2). Chiral NHC catalyst can attack the acylsilanes **1** to give a zwitterionic intermediate **I** and then leads to the formation of the silylated Breslow intermediate **II** via a 1,2-Brook rearrangement process promoted by LiHMDS.[11] To avoid the competing side reactions from the aldehyde substrate and the NHC catalyst, indole aldehyde **2a** bearing a less electrophilic carbonyl carbon is used[12] to react with the silylated Breslow intermediate **II** through a Benzoin condensation process to give the zwitterion intermediate **III**. A 1,4-silyl group migration reaction can be realized with the assistance of LiHMDS to give the intermediate **V** via formation of a 5-membered ring intermediate **IV**. The silylated Benzoin product **3** can be finally afforded after elimination of the NHC catalyst and LiHMDS from the intermediate **V**.

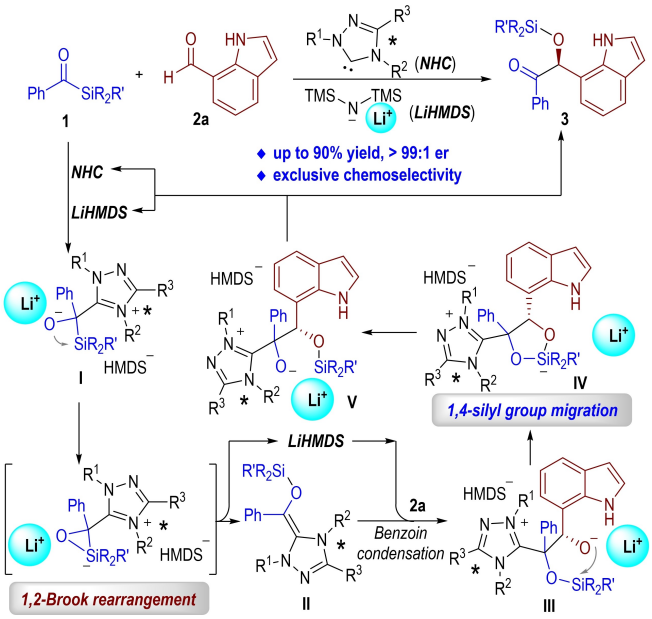
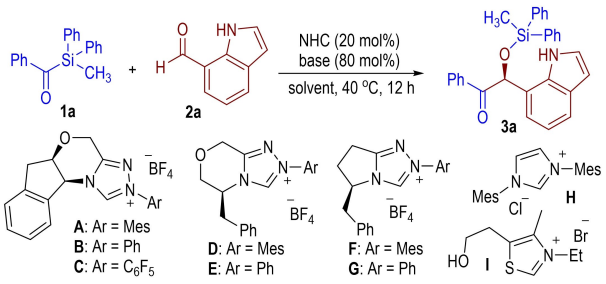



***Figure 2.*** NHC-catalyzed enantioselective cross Brook–Benzoin reaction.

## *Results and Discussion*

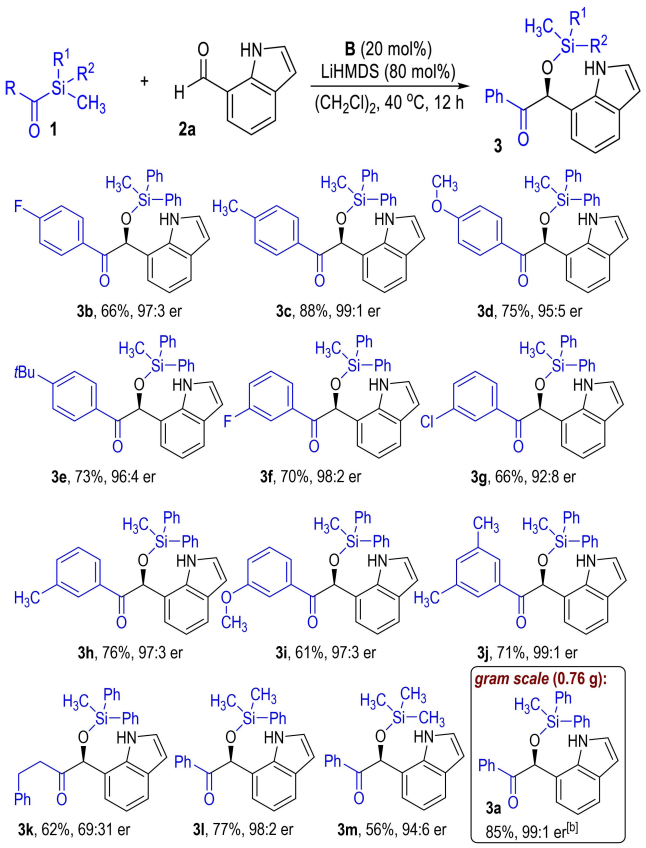
Benzoylsilane **1a** bearing a diphenylmethylsilyl group was chosen as the model substrate to react with the indole aldehyde **2a** under the catalysis of various NHC catalysts in the presence of LiHMDS in $CH_2Cl_2$ (Table 1, entries 1 to 9). Aminoindanol derived NHC catalysts bearing electron-rich N-Mes[13] or N-Ph[14] groups were found efficient for the Brook-Benzoin reaction, with the desired silylated Benzoin product **3a** afforded in promising yields with excellent enantioselectivities (entries 1 to 2). NHC catalysts bearing an electron-deficient N-$C_6F_5$[15] group cannot promote this transformation (e.g., entry 3). The triazolium NHC catalysts bearing chiral morpholine structures cannot promote this reaction (e.g., entries 4 and 5),[16] while the chiral pyrollo-triazolium-derived NHC catalysts can give the desired Brook–Benzoin products in poor to moderate yields with good to excellent enantioselectivities (e.g., entries 6 and 7).[14,17] The triazolium fragment of the NHC catalysts played significant roles in this catalytic transformation, since no isolable products could be observed when using NHC catalysts without the triazolium frameworks (e.g., entries 8 and 9).[18] Switching the LiHMDS to other organic or inorganic bases resulted in no formation of the desired product (e.g., entry 10). This is in accordance with the crucial roles that the strong alkyl metal bases have played in various reported Brook rearrangement reactions.[19] Disilylamide salts other than LiHMDS could give the desired products in lower yields, although the er values of the products were not affected (e.g., KHMDS, entry 11). Non-polar organic solvents could be used as the reaction medium (e.g., entries 12 and 13), and the target product **3a** could be afforded in 70% yield and >99:1 er value when using $(CH_2Cl)_2$ as the reaction solvent (entry 13). Organic solvents

***Table 1:*** Optimization of reaction conditions.[a]




| Entry | NHC | Base | Solvent | Yield [%][b] | er[c] |
|---|---|---|---|---|---|
| 1 | **A** | LiHMDS | $CH_2Cl_2$ | 35 | 98:2 |
| 2 | **B** | LiHMDS | $CH_2Cl_2$ | 53 | 99:1 |
| 3 | **C** | LiHMDS | $CH_2Cl_2$ | <5 | – |
| 4 | **D** | LiHMDS | $CH_2Cl_2$ | <5 | – |
| 5 | **E** | LiHMDS | $CH_2Cl_2$ | 0 | – |
| 6 | **F** | LiHMDS | $CH_2Cl_2$ | 54 | 93:7 |
| 7 | **G** | LiHMDS | $CH_2Cl_2$ | 28 | 99:1 |
| 8 | **H** | LiHMDS | $CH_2Cl_2$ | 0 | – |
| 9 | **I** | LiHMDS | $CH_2Cl_2$ | 0 | – |
| 10 | **B** | DBU/DMAP/$K_2CO_3$/$Cs_2CO_3$ | $CH_2Cl_2$ | 0 | – |
| 11 | **B** | KHMDS | $CH_2Cl_2$ | 21 | 99:1 |
| 12 | **B** | LiHMDS | toluene | 45 | 94:6 |
| 13 | **B** | LiHMDS | $(CH_2Cl)_2$ | 70 | >99:1 |
| 14 | **B** | LiHMDS | THF | <5 | – |
| 15 | **B** | LiHMDS | $CHCl_3$ | 0 | – |
| 16[d] | **B** | LiHMDS | $(CH_2Cl)_2$ | 83 | 99:1 |

[a] Reaction conditions: **1a** (0.12 mmol), **2a** (0.10 mmol), NHC (0.02 mmol), base (0.08 mmol), solvent (1.0 mL) at 40 °C for 12 h. [b] Isolated yield of **3a**. [c] The er values were determined via HPLC on chiral stationary phase. [d] **1a** (0.10 mmol), **2a** (0.15 mmol), **B** (0.02 mmol), LiHMDS (0.08 mmol), $(CH_2Cl)_2$ (2.0 mL), 40 °C, 12 h.



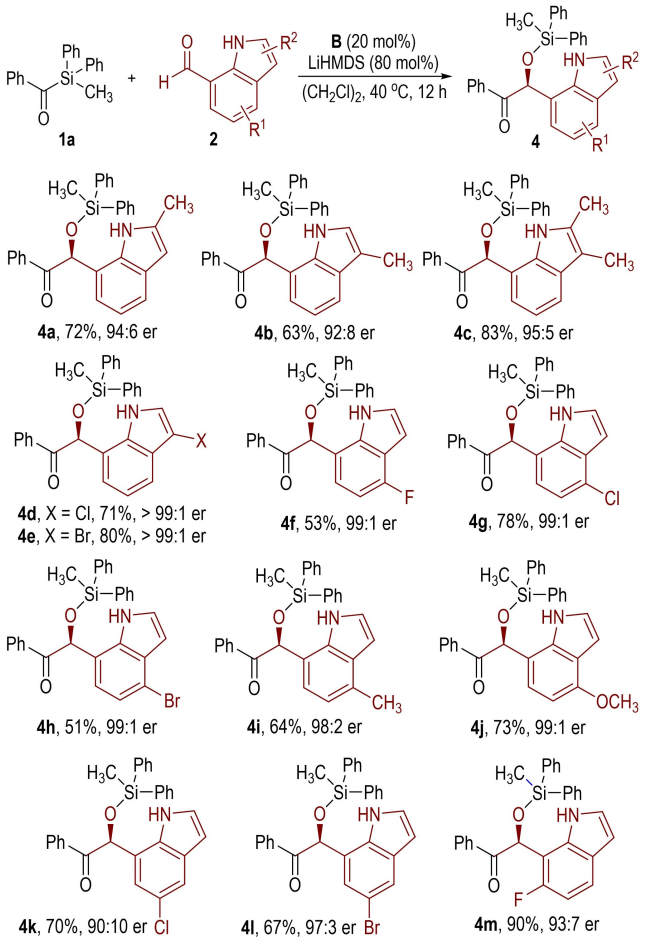

***Scheme 1.*** Scope of acylsilanes **1**.[a] [a] Reaction conditions as stated in Table 1, entry 16. Yields are isolated yields after purification by column chromatography. The er values were determined via HPLC on chiral stationary phase. [b] The reaction was carried out on a 2.0 mmol scale based on **1a**.

with high polarities are not suitable for this transformation (entries 14 and 15). Finally, the yield of **3a** could be further improved to 83 % without obvious erosion on the optical purity when an excess amount of the indole aldehyde **2a** was used in a diluted reaction system (entry 16).

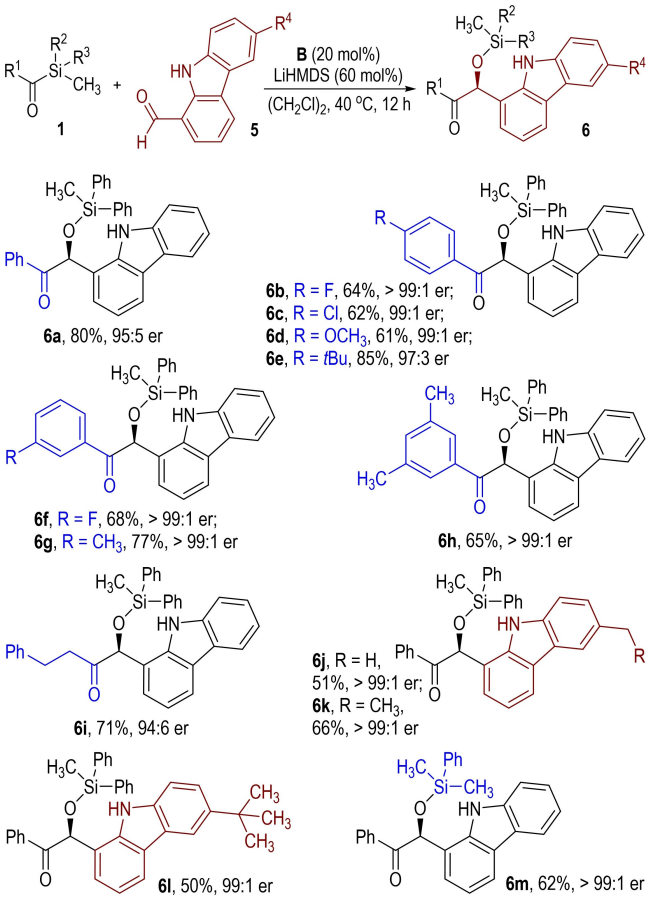
With an optimized reaction condition being identified, we then seek to examine the reaction scope by using both of the acylsilylanes **1** and the indole aldehydes **2** bearing different substituents and substitution patterns (Schemes 1 and 2). Substituents with various electronic properties and steric effects can be installed on the 4- and 3-positions of the benzoyl group of **1a**, with the corresponding silylated benzoin products afforded in good yields with good to excellent enantioselectivities (Scheme 1, **3b** to **3j**). It is worth noting that benzoylsilanes bearing a 2-substituent on the benzoyl moieties cannot work in this Brook–Benzoin reaction, which was probably due to the increased steric hindrance existed in the nucleophilic attack of the NHC catalysts to the acylsilane substrates. An aliphatic acylsilane can also be used for this transformation, although the target product **3k** can only be afforded in a moderate yield and er value under the current reaction condition. Replacing the diphenylmethylsilyl group of the benzoylsilane substrate with a phenyldimethylsilyl group resulted in little erosion on the reaction outcome (**3l**). However, drops on both of the product yield and optical purity were observed when using benzoyltrimethylsilane as the reaction substrate (**3m**). Noteworthy, this NHC-catalyzed asymmetric Brook–Benzoin reaction between **1a** and **2a** can be carried out at gram scales and the chiral product **3a** can be afforded in even higher yield with retention of the optical purity (Scheme 1, **3a**).

The indole aldehydes **2** can also tolerate a variety of functional groups on each position of its aromatic ring (Scheme 2). For example, installations of both electron-donating and electron-withdrawing groups on the 2-, 3- and 4- positions of the indole rings of the aldehydes **2** can give the silylated benzoin products in moderate to good yields with excellent enantioselectivities (**4a** to **4j**). A chloride substituent installed on the 5-position of the indole aldehyde led to drops on the product er values (**4k**). This is probably resulted from the unique electronic effects of the strong electron-negative 5-Cl substituents, since the 5-Br substituted indole aldehyde substrate can give the desired product **4l** in an excellent optical purity. Note that, the yield of the desired product can be dramatically increased when using the indole aldehyde bearing a 6-F substituent (**4m**).

To our great delight, carbazole-1-carbaldehydes **5** can be used as another set of suitable reactants for this chiral NHC-promoted enantioselective Brook-Benzoin reaction under




***Scheme 2.*** Scope of indole aldehydes **2**.[a] [a] Reaction conditions as stated in Table 1, entry 16. Yields are isolated yields after purification by column chromatography. The er values were determined via HPLC on chiral stationary phase.




***Scheme 3.*** Scope of carbazole-1-carbaldehydes **5**.[a] [a] Reaction conditions: **1** (0.10 mmol), **5** (0.15 mmol), **B** (0.02 mmol), LiHMDS (0.06 mmol), $(CH_2Cl)_2$ (2.0 mL), 40 °C, 12 h. Yields are isolated yields after purification by column chromatography. The er values were determined via HPLC on chiral stationary phase.

similar catalytic conditions (Scheme 3). With a slightly less amount of LiHMDS used, the silyl-benzoin products **6** could be afforded in generally excellent optical purities. Both electron-donating and electron-withdrawing groups were well tolerated on the benzoyl group of the acylsilane substrate **1**, with corresponding products afforded in moderate to good yields with excellent er values (**6b** to **6h**). Alkyl substituted acylsilane substrate also worked well in this process, although the target product **6i** was afforded in slightly decreased enantioselectivity. Several alkyl substituents can be installed on the aromatic ring of the carbazole-1-carbaldehyde substrate **5** without much erosion on either the product yields or the enantioselectivities (**6j** to **6l**). The diphenylmethylsilyl group on the reaction substrate **1a** could be changed into a phenyldimethylsilyl group, with the desired product **6m** afforded in 62 % yield with >99:1 er value.

It is worth to note that the free N–H group in the indole-7-carbaldehyde substrate **2** is crucial to this transformation (Figure 3). No reaction happened when using the N-protected indole carbaldehyde substrates **7**, benzaldehyde or propionic aldehyde as the electrophiles under the current

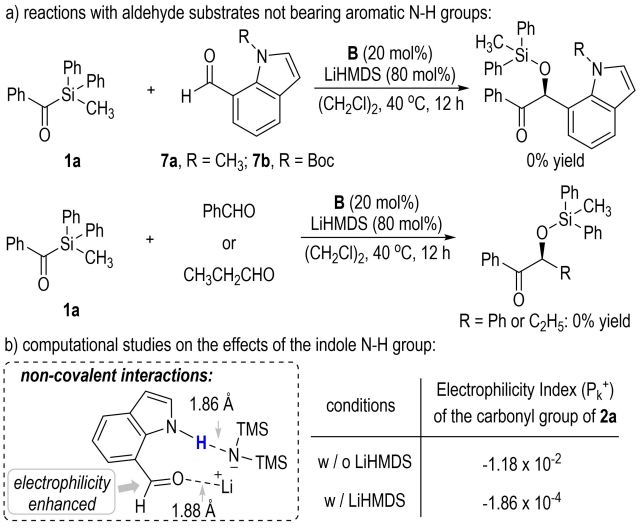



***Figure 3.*** Effects of the indole N–H group on the Brook–Benzoin reaction.

optimized reaction condition (Figure 3a). Computational studies revealed that the indole-7-carbaldehyde **2a** and the ionic LiHMDS are close enough to form substantial non-covalent interactions (Figure 3b, the non-covalent bond length of H···$N^-$ is 1.86 Å, the non-covalent bond length of O···$Li^+$ is 1.86 Å). The electrophilicity of the carbonyl carbon in the indole-7-carbaldehyde substrate **2a** could be greatly enhanced by the non-covalent interactions formed among the free indole N–H group, the strong base of LiHMDS and the O-atom of the carbaldehyde group (Figure 3b, the $P_k^+$ value of **2a** in the presence of LiHMDS is $-1.86\times10^{-4}$, that without LiHMDS is $-1.18\times10^{-2}$).

The relationship between the catalyst ee and the product ee was examined and no deviation from linearity was observed (Figure 4a). The linear relationship indicated that only one of the two reactants was activated by the NHC catalyst in the enantioselective-determining step.[20] The electrophilic affinities of both of the reaction substrates to the NHC catalyst were studied via DFT calculations (Figure 4b).[21] The energy barrier for the addition of the NHC catalyst **B** to the indole-7-carbaldehyde **2a** ($\Delta G = 10.41$ to 15.81 kcal mol$^{-1}$) was much higher than the addition of the catalyst **B** to the benzoylsilane **1a** ($\Delta G = 8.80$ kcal mol$^{-1}$), regardless of whether or not in the presence of the LiHMDS. Therefore, the benzoylsilane substrates are believed to be selectively activated by the NHC catalyst in this Brook–Benzoin reaction system.

To exclude the possibility that a common benzoin reaction was actually taking place with a free silyl group released and transferred during this NHC-catalyzed Brook-Benzoin reaction, we carried out additional control experiments to get further evidence on the reaction process (Figure 5). First of all, neither the cross nor the homo benzoin reaction could happen with the benzaldehyde **8** and the indole-7-carbaldehyde **2a** substrates under our currently optimized reaction condition, although the corresponding benzoin products **9** and **10** could be obtained in 50 % and 40 % yields respectively under reported reaction conditions (Figure 5a).[9f] Moreover, no cross-silyl group transferred product **3a** could be observed when the potential "silyl group shuttle" molecule **11** or **12** was added into the reaction system of **1l** and **2a** (Figure 5b). Therefore, a cross-benzoin reaction between benzaldehyde **8** and the indole-7-carbaldehyde **2a** was unlikely to happen and the silyl group might not be released from any of the possible reaction intermediates during our reaction process. Additionally, we also used the optically pure benzoylsilane **1n** bearing a stereogenic Si center as the substrate for this Brook–Benzoin reaction with the indole-7-carbaldehyde **2a** (Figure 5c). The target prod-

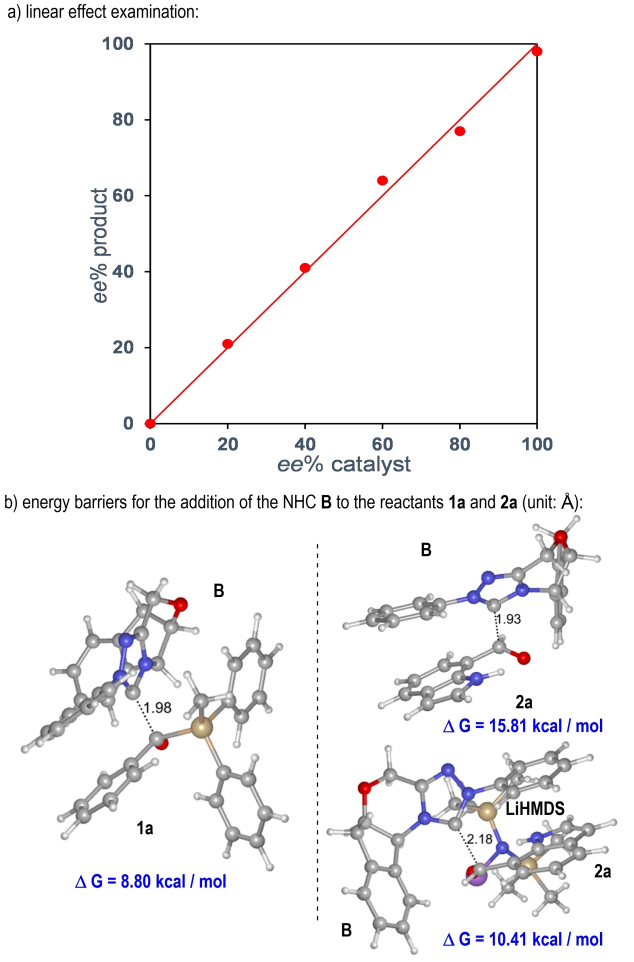



***Figure 4.*** Investigation of the affinities of both reactants to the NHC catalyst.

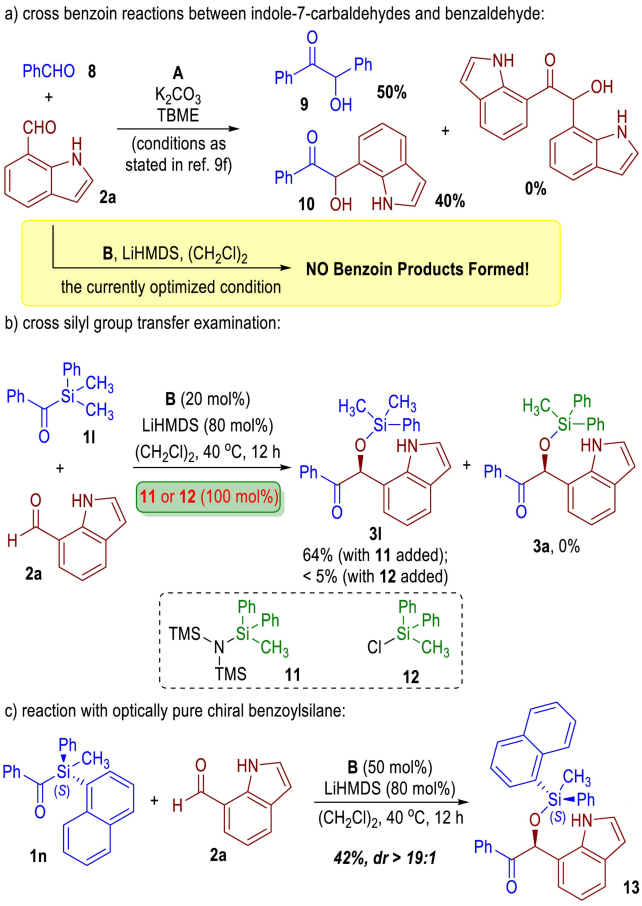



***Figure 5.*** Control experiments on the reaction process.

uct **13** was isolated in 42% yield with an excellent diastereoselectivity, which indicated that no positively charged silicon ions bearing plane-conformations were generated during the intramolecular silyl group-transfer processes.

The $^1$H NMR analyses on the crude mixtures of the catalytic system have shown that a catalytic amount of unidentifiable silyl species was generated from the reaction between the benzoylsilane **1a** and the NHC catalyst **B** in the presence of the LiHMDS (Figure 6). The newly generated silyl peaks were believed to belong to silyl-containing intermediates related to the silyl-Breslow intermediate **I**, since stoichiometric or sub-stoichiometric amount of the silyl peaks should be expected if the silyl group could be released under the current catalytic conditions. Moreover, the generation of benzaldehyde-related intermediates was not observed from the mixture of **1a** and the NHC **B** under identical reaction conditions (Figure 6c vs. d).

DFT calculations have been carried out to further rationalize the reaction process and the enantioselective discrimination of this chiral NHC-catalyzed Brook–Benzoin transformation (Figure 7). Gaussian 16[22] with DFT method M06-2X[23] has been employed to explore the energy variations of different transition states and intermediates throughout the catalytic process (Figure 7a). The normal level 6-31G(d,p) was used for geometry optimization and the high level 6-311++G(2d,2p) was calculated energies of single point.[24] Moreover, all calculations were under the condition of dispersion correction (D3).[25] The formation of the Si-Breslow intermediate **II** was greatly favored from addition of the NHC catalyst **B** to the acylsilane substrate **1a** ($\Delta G = -31.54$ kcal mol$^{-1}$). Nucleophilic addition of the intermediate **II** to the indole aldehyde substrate **2a** gave the diastereomeric intermediates **III-1** and **III-2** via the formation of the transition states **TS3-1** and **TS3-2** (Figure 7b). The formation of the **TS4-1** was disfavored due to a high energy barrier and the chiral intermediate **IV** could therefore be exclusively generated via formation of the transition state **TS4-2**. Finally, the target chiral Brook–Benzoin product **3a** could be obtained in an excellent er value from the intermediate **IV** via formation of the transition state **TS5**.

The silylated Benzoin products obtained from our approach are rich in functionalities and can be used in a variety of synthetic transformations (Figure 8). For instance, the ketone group on the chiral silylbenzoin product **3a** can be reduced by $BH_3$ to give the chiral alcohol **14** in a 73% yield as a single enantio- and diastereoisomer.[26] The silyl group on **3a** can be removed by HF under basic conditions to give the chiral α-hydroxyl ketone **15** in a good yield with an excellent optical purity.[27] The chiral pinacol **16** can be afforded as a single diastereomer from reduction of **15** in an excellent yield and enantioselectivity.[28] Moreover, the free NH group incorporate in the aromatic indole ring of **3a** can be efficiently protected by a Boc group to give the product **17** without erosion on its optical purity.[29] An α-diketone compound **18** can also be afforded in a good yield through an oxidative elimination of the silyl group from **3a**.[30]

The afforded indole- and carbazole-derived chiral α-hydroxyl ketone compounds also exhibit promising antimicrobial activities against various harmful plant pathogens (Table 2). For instance, 14 of the chiral molecules obtained from our approach showed better inhibition rates than the commercial bactericides thiodiazole copper (TC) and bismerthiazol (BT) against *Pseudomonas syringae* pv. *actinidiae* (*Psa*).[31] Especially, 2 of the chiral α-silyloxyl ketone compounds containing carbazole cores displayed the best anti-bacterial activities against *Psa* under the concentrations of 100 μg mL$^{-1}$ and 50 μg mL$^{-1}$ respectively (**6b**, **6c**). It is worth noting that *Psa* can colonize *Actinidia* flowers and lead to their browning and fall. It can eventually cause death of the whole plant after its systematic invasion. Therefore, the chiral α-hydroxyl ketone molecules containing indole or

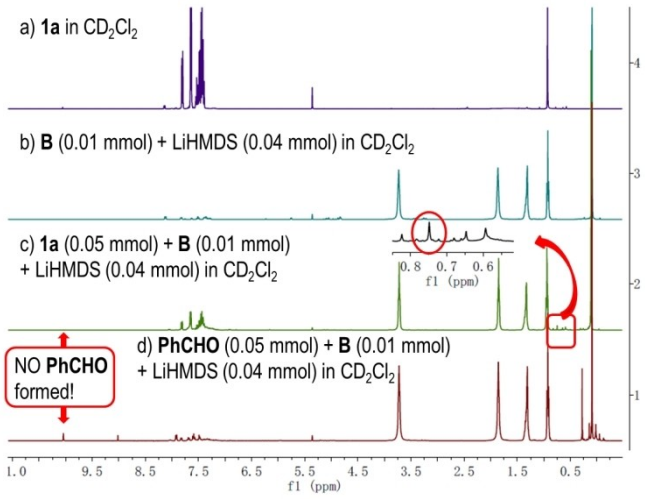



***Figure 6.*** $^1$H NMR analyses of reaction mixtures.

***Table 2:*** Inhibitive activities of the target compounds against *Psa*.

| Compounds | Inhibition Rate [%][a] | |
|---|---|---|
| | 100 μg mL$^{-1}$ | 50 μg mL$^{-1}$ |
| **4j** | 67.1±4.6 | 44.8±0.4 |
| **6a** | 76.8±2.2 | 71.0±1.5 |
| **6b** | 82.5±5.5 | 62.2±2.6 |
| **6c** | 77.3±1.0 | 74.1±1.0 |
| **6e** | 73.3±3.7 | 55.7±5.5 |
| **6g** | 65.9±2.9 | 47.6±2.3 |
| **6h** | 78.6±3.0 | 68.1±2.3 |
| **6i** | 71.7±1.4 | 67.0±2.5 |
| **6j** | 69.7±2.6 | 60.3±5.6 |
| **6k** | 72.6±5.9 | 55.4±2.7 |
| **6l** | 75.3±2.3 | 70.2±0.4 |
| **6m** | 66.9±2.2 | 63.4±3.4 |
| **15** | 66.7±3.6 | 60.5±2.4 |
| **16** | 69.4±3.8 | 61.5±2.5 |
| **TC**[b] | 51.6±2.6 | 27.7±2.3 |
| **BT**[c] | 52.1±1.1 | 30.9±2.5 |

[a] Average of three replicates. [b] TC = Thiodiazole coppers. [c] BT = Bismerthiazol.

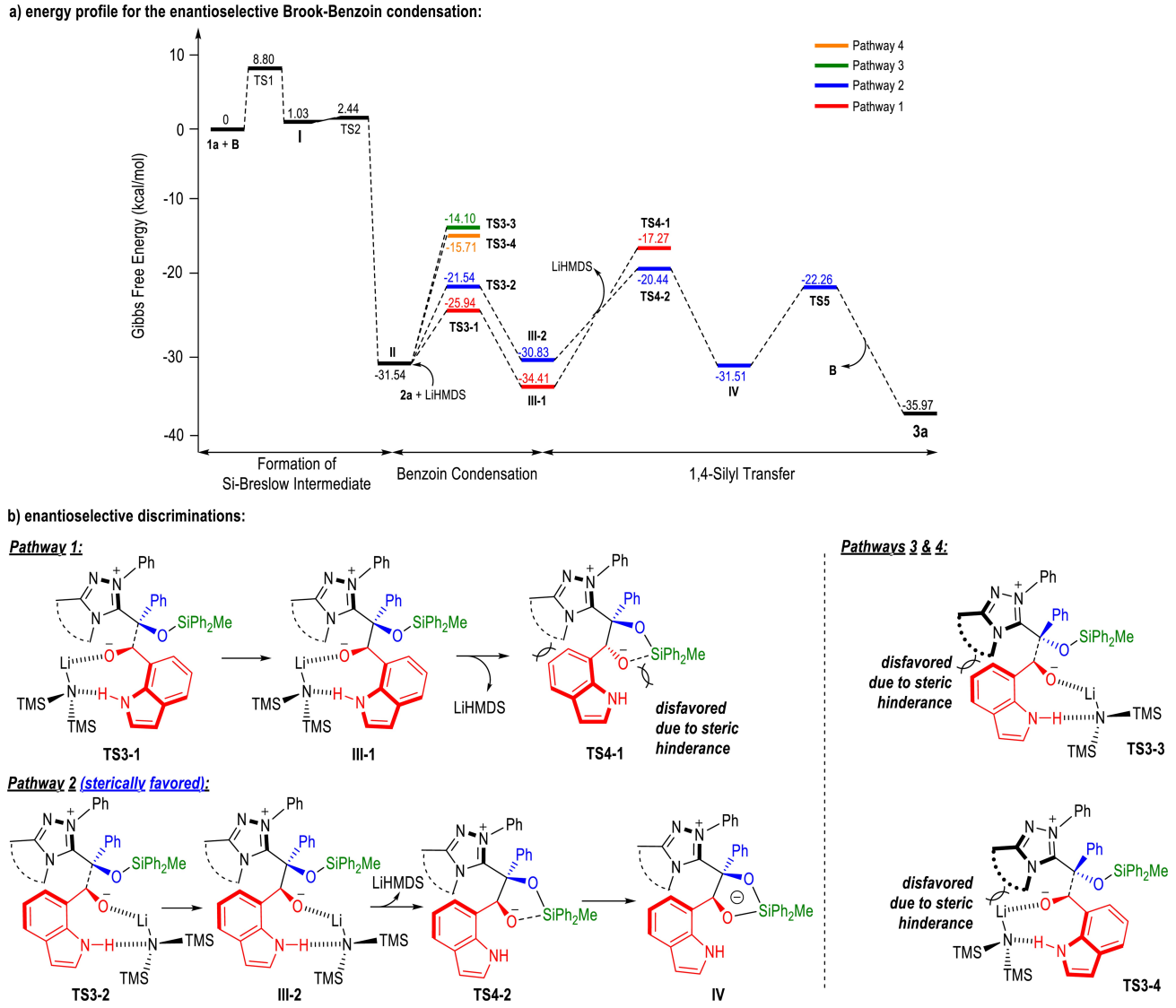



***Figure 7.*** Energy profile for the enantioselective discrimination of the Brook–Benzoin reaction via DFT calculations.

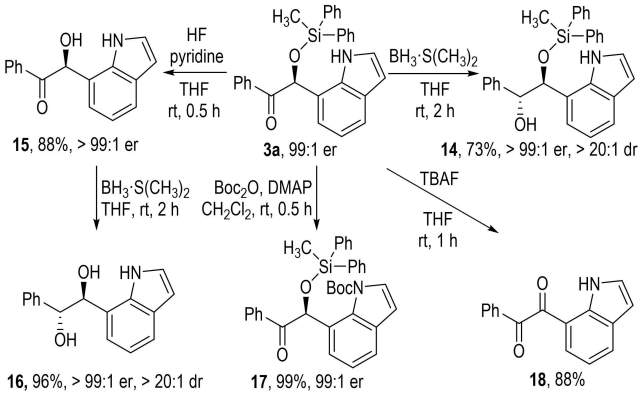



***Figure 8.*** Synthetic transformations of the chiral product **3 a**.

carbazole cores are promising structures in the development of new agrichemicals.

## Conclusion

In summary, we have developed the first NHC-catalyzed enantioselective Brook–Benzoin reaction. α-Silyloxyketone products bearing various substituents and substitution patterns are efficiently afforded from our approach in generally good to excellent yields and enantioselectivities. Mechanistic studies have provided clear evidence that the NHC organocatalyst can selectively activate the acylsilane substrates over the indole aldehydes presented in the reaction systems. Both experimental and computational studies have supported that multiple intramolecular silyl-group transfer processes take place during the reaction without any free silyl species being released. A variety of chiral functional molecules can be efficiently obtained from the silylbenzoin products via simple transformations. Many of the afforded indole- and carbazole-derived chiral α-hydroxyl ketone molecules have been discovered to possess promising inhibition activities against various plant patho-

gens such as *Psa.* Investigations into further synthetic and bioactive applications of the chiral molecules afforded from our approaches are in progress in our laboratories.

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## Conflict of Interest

The authors declare no conflict of interest.

## Data Availability Statement

The data that support the findings of this study are available in the Supporting Information of this article.

**Keywords:** Acylsilanes · Benzoin Condensation · Brook Rearrangement · Chemoselectivity · N-Heterocyclic Carbenes

[1] a) K. Shin-ya, T. Kunigami, J.-S. Kim, K. Furihata, Y. Hayakawa, H. Seto, *Biosci. Biotechnol. Biochem.* **1997**, *61*, 1768; b) A. J. Kochanowska-Karamyan, M. T. Hamann, *Chem. Rev.* **2010**, *110*, 4489; c) A. Głuszyńska, *Eur. J. Med. Chem.* **2015**, *94*, 405; d) N. Netz, T. Opatz, *Mar. Drugs* **2015**, *13*, 4814; e) Y.-X. Yuan, Y. Zhang, L.-L. Guo, Y.-H. Wang, M. Goto, S. L. Morris-Natschke, K.-H. Lee, X.-J. Hao, *Org. Lett.* **2017**, *19*, 4964; f) V. Garg, R. K. Maurya, P. V. Thanikachalam, G. Bansal, V. Monga, *Eur. J. Med. Chem.* **2019**, *180*, 562; g) P. Tang, H. Wang, W. Zhang, F.-E. Chen, *Green Synth. Catal.* **2020**, *1*, 26; h) E. O. N'Nang, P. L. Pogam, T. N. Mba, C. S. Obiang, E. Mouray, P. Grellier, B. Kumulungui, P. Champy, M. A. Beniddir, *J. Nat. Prod.* **2021**, *84*, 1409; i) X.-Y. Liu, Y. Qin, *Green Synth. Catal.* **2022**, *3*, 25.

[2] a) L. G. Humber, E. Ferdinandi, C. A. Demerson, S. Ahmed, U. Shah, D. Mobilio, J. Sabatucci, B. D. Lange, F. Labbadia, P. Hughes, J. DeVirgilio, G. Neuman, T. T. Chau, B. M. Weichman, *J. Med. Chem.* **1988**, *31*, 1712; b) S. Kato, K. Shindo, Y. Kataoka, Y. Yamagishi, J. Mochizuki, *J. Antibiot.* **1991**, *44*, 903; c) N. Orihara, K. Furihata, H. Seto, *J. Antibiot.* **1997**, *50*, 979; d) M. R. Koupai-Abyazani, B. Esaw, B. Laviolette, *J. Anal. Toxicol.* **1999**, *23*, 200; e) S. Tsukamoto, H. Kato, T. J. Greshock, H. Hirota, T. Ohta, R. M. Williams, *J. Am. Chem. Soc.* **2009**, *131*, 3834; f) J. M. Finefield, T. J. Greshock, D. H. Sherman, S. Tsukamoto, R. M. Williams, *Tetrahedron Lett.* **2011**, *52*, 1987; g) C. Auranwiwat, S. Laphookhieo, K. Trisuwan, S. G. Pyne, T. Ritthiwigrom, *Phytochem. Lett.* **2014**, *9*, 113; h) J.-J. Dong, J. Bao, X.-Y. Zhang, X.-Y. Xu, X.-H. Nong, S.-H. Qi, *Tetrahedron Lett.* **2014**, *55*, 2749; i) S. Huang, S. S. Elsayed, M. Lv, J. Tabudravu, M. E. Rateb, R. Gyampoh, K. Kyeremeh, R. Ebel, M. Jaspars, Z. Deng, Y. Yu, H. Deng, *Chem. Biol.* **2015**, *22*, 1633; j) L. Su, R. Zhang, K. Kyeremeh, Z. Deng, H. Deng, Y. Yu, *Org. Biomol. Chem.* **2017**, *15*, 3843; k) Y. Liu, L. Su, Q. Fang, J. Tabudravu, X. Yang, K. Rickaby, L. Trembleau, K. Kyeremeh, Z. Deng, H. Deng, Y. Yu, *J. Org. Chem.* **2019**, *84*, 16323; l) Y.-H. Fu, J.-M. Guo, Y.-T. Xie, J. Hua, Y.-Y. Dai, W. Zhang, T.-C. Lin, Y.-P. Liu, *Bioorg. Chem.* **2020**, *102*, 104101.

[3] For selected reviews, see: a) K. Zeitler, *Angew. Chem. Int. Ed.* **2005**, *44*, 7506; *Angew. Chem.* **2005**, *117*, 7674; b) N. Marion, S. Díez-González, S. P. Nolan, *Angew. Chem. Int. Ed.* **2007**, *46*, 2988; *Angew. Chem.* **2007**, *119*, 3046; c) D. Enders, A. A. Narine, *J. Org. Chem.* **2008**, *73*, 7857; d) R. Kluger, K. Tittmann, *Chem. Rev.* **2008**, *108*, 1797; e) X. Bugaut, F. Glorius, *Chem. Soc. Rev.* **2012**, *41*, 3511; f) J. Douglas, G. Churchill, A. D. Smith, *Synthesis* **2012**, *44*, 2295; g) S. De Sarkar, A. Biswas, R. C. Samanta, A. Studer, *Chem. Eur. J.* **2013**, *19*, 4664; h) R. S. Menon, A. T. Biju, V. Nair, *Beilstein J. Org. Chem.* **2016**, *12*, 444; For selected examples, see: i) F. Wöhler, J. Liebig, *Ann. Pharm.* **1832**, *3*, 249; j) P. Dünkelmann, D. Kolter-Jung, A. Nitsche, A. S. Demir, P. Siegert, B. Lingen, M. Baumann, M. Pohl, M. Müller, *J. Am. Chem. Soc.* **2002**, *124*, 12084; k) Y. Hachisu, J. W. Bode, K. Suzuki, *J. Am. Chem. Soc.* **2003**, *125*, 8432; l) J. Rehbein, S.-M. Ruser, J. Phan, *Chem. Sci.* **2015**, *6*, 6013.

[4] a) X. Linghu, J. S. Johnson, *Angew. Chem. Int. Ed.* **2003**, *42*, 2534; *Angew. Chem.* **2003**, *115*, 2638; b) C. C. Bausch, J. S. Johnson, *J. Org. Chem.* **2004**, *69*, 4283; c) A. E. Mattson, K. A. Scheidt, *Org. Lett.* **2004**, *6*, 4363; d) X. Linghu, C. C. Bausch, J. S. Johnson, *J. Am. Chem. Soc.* **2005**, *127*, 1833; e) J. C. Tarr, J. S. Johnson, *Org. Lett.* **2009**, *11*, 3870; f) A. Gliga, B. Goldfuss, J. M. Neudörfl, *Beilstein J. Org. Chem.* **2011**, *7*, 1189; g) K. Ishida, F. Tobita, H. Kusama, *Chem. Eur. J.* **2018**, *24*, 543.

[5] X. Linghu, J. R. Potnick, J. S. Johnson, *J. Am. Chem. Soc.* **2004**, *126*, 3070.

[6] For selected reviews on NHC organocatalysis, see: a) D. Enders, O. Niemeier, A. Henseler, *Chem. Rev.* **2007**, *107*, 5606; b) V. Nair, S. Vellalath, B. P. Babu, *Chem. Soc. Rev.* **2008**, *37*, 2691; c) S. J. Ryan, L. Candish, D. W. Lupton, *Chem. Soc. Rev.* **2013**, *42*, 4906; d) M. N. Hopkinson, C. Richter, M. Schedler, F. Glorius, *Nature* **2014**, *510*, 485; e) D. M. Flanigan, F. Romanov-Michailidis, N. A. White, T. Rovis, *Chem. Rev.* **2015**, *115*, 9307; f) X. Chen, Q. Liu, P. Chauhan, D. Enders, *Angew. Chem. Int. Ed.* **2018**, *57*, 3862; *Angew. Chem.* **2018**, *130*, 3924; g) K. J. R. Murauski, A. A. Jaworski, K. A. Scheidt, *Chem. Soc. Rev.*

**2018**, *47*, 1773; h) A. T. Biju, *N-Heterocyclic Carbenes in Organocatalysis*, Wiley-VCH, Weinheim, **2018** i) X. Chen, H. Wang, Z. Jin, Y. R. Chi, *Chin. J. Chem.* **2020**, *38*, 1167.

[7] a) A. R. Bharadwaj, K. A. Scheidt, *Org. Lett.* **2004**, *6*, 2465; b) A. E. Mattson, A. R. Bharadwaj, K. A. Scheidt, *J. Am. Chem. Soc.* **2004**, *126*, 2314; c) A. E. Mattson, A. R. Bharadwaj, A. M. Zuhl, K. A. Scheidt, *J. Org. Chem.* **2006**, *71*, 5715.

[8] In the sillyl-Stetter reactions reported by Scheidt and co-workers, one enantioselective example with a 74% ee value was realized by using chiral thiourea as the catalyst for chiral inductions, see: A. E. Mattson, A. M. Zuhl, T. E. Reynolds, K. A. Scheidt, *J. Am. Chem. Soc.* **2006**, *128*, 4932.

[9] For examples of enantioselective intermolecular benzoin reactions, see: a) D. Enders, U. Kallfass, *Angew. Chem. Int. Ed.* **2002**, *41*, 1743; *Angew. Chem.* **2002**, *114*, 1822; b) D. Enders, A. Henseler, *Adv. Synth. Catal.* **2009**, *351*, 1749; c) D. Enders, A. Grossmann, J. Fronert, G. Raabe, *Chem. Commun.* **2010**, *46*, 6282; d) D. Enders, A. Grossmann, H. Huang, G. Raabe, *Eur. J. Org. Chem.* **2011**, 4298; e) C. A. Rose, S. Gundala, C.-L. Fagan, J. F. Franz, S. J. Connon, K. Zeitler, *Chem. Sci.* **2012**, *3*, 735; f) C. G. Goodman, J. S. Johnson, *J. Am. Chem. Soc.* **2014**, *136*, 14698; g) S. M. Langdon, M. M. D. Wilde, K. Thai, M. Gravel, *J. Am. Chem. Soc.* **2014**, *136*, 7539; h) K. Iwai, M. Ono, Y. Nanjo, T. Ema, *ACS Omega* **2020**, *5*, 10207.

[10] a) A. F. Patrocínio, P. J. S. Moran, *J. Braz. Chem. Soc.* **2001**, *12*, 7; b) H.-J. Zhang, D. L. Priebbenow, C. Bolm, *Chem. Soc. Rev.* **2013**, *42*, 8540.

[11] For selected reviews, see: a) A. G. Brook, *Acc. Chem. Res.* **1974**, *7*, 77; b) W. H. Moser, *Tetrahedron* **2001**, *57*, 2065; c) G. Eppe, D. Didier, I. Marek, *Chem. Rev.* **2015**, *115*, 9175; d) N. Lee, C.-H. Tan, D. Leow, *Asian J. Org. Chem.* **2019**, *8*, 25.

[12] a) M. Giardinetti, X. Moreau, V. Coeffard, C. Greck, *Adv. Synth. Catal.* **2015**, *357*, 3501; b) X. Yang, G. Luo, L. Zhou, B. Liu, X. Zhang, H. Gao, Z. Jin, Y. R. Chi, *ACS Catal.* **2019**, *9*, 10971.

[13] M. He, J. R. Struble, J. W. Bode, *J. Am. Chem. Soc.* **2006**, *128*, 8418.

[14] M. S. Kerr, J. R. Alaniz, T. Rovis, *J. Am. Chem. Soc.* **2002**, *124*, 10298.

[15] M. S. Kerr, T. Rovis, *J. Am. Chem. Soc.* **2004**, *126*, 8876.

[16] a) M. Wadamoto, E. M. Phillips, T. E. Reynolds, K. A. Scheidt, *J. Am. Chem. Soc.* **2007**, *129*, 10098; b) C. D. Campbell, C. J. Collett, J. E. Thomson, A. M. Z. Slawin, A. D. Smith, *Org. Biomol. Chem.* **2011**, *9*, 4205.

[17] P.-C. Chiang, M. Rommel, J. W. Bode, *J. Am. Chem. Soc.* **2009**, *131*, 8714.

[18] a) H. Stetter, R. Y. Rämsch, H. Kuhlmann, *Synthesis* **1976**, 733; b) A. J. A. Arduengo, R. L. Harlow, M. Kline, *J. Am. Chem. Soc.* **1991**, *113*, 361.

[19] For selected examples, see: a) S. H. Kleinfeld, E. Wegelius, D. Hoppe, *Helv. Chim. Acta* **1999**, *82*, 2413; b) G. Liu, S. M. Sieburth, *Org. Lett.* **2003**, *5*, 4677; c) S. M. Sieburth, H. K. O'Hare, J. Xu, Y. Chen, G. Liu, *Org. Lett.* **2003**, *5*, 1859; d) T. Matsumoto, H. Masu, K. Yamaguchi, K. Takeda, *Org. Lett.* **2004**, *6*, 4367; e) S. Okugawa, K. Takeda, *Org. Lett.* **2004**, *6*, 2973; f) J. Clayden, D. W. Watson, M. Chambers, *Tetrahedron* **2005**, *61*, 3195; g) M. Sasaki, M. Higashi, H. Masu, K. Yamaguchi, K. Takeda, *Org. Lett.* **2005**, *7*, 5913; h) A. B. Smith III, M. Xian, W.-S. Kim, D.-S. Kim, *J. Am. Chem. Soc.* **2006**, *128*, 12368; i) Y. Nakai, M. Kawahata, K. Yamaguchi, K. Takeda, *J. Org. Chem.* **2007**, *72*, 1379; j) Y. Mori, Y. Futamura, K. Horisaki, *Angew. Chem. Int. Ed.* **2008**, *47*, 1091; *Angew. Chem.* **2008**, *120*, 1107; k) M. Sasaki, Y. Kondo, M. Kawahata, K. Yamaguchi, K. Takeda, *Angew. Chem. Int. Ed.* **2011**, *50*, 6375; *Angew. Chem.* **2011**, *123*, 6499; l) M. Sasaki, M. Fujiwara, Y. Kotomori, M. Kawahata, K. Yamaguchi, K. Takeda, *Tetrahedron* **2013**, *69*, 5823; m) M. Sasaki, Y. Kondo, T.-i. Moto-ishi, M. Kawahata, K. Yamaguchi, K. Takeda, *Org. Lett.* **2015**, *17*, 1280; n) J. F. Collados, P. Ortiz, J. M. Pérez, Y. Xia, M. A. J. Koenis, W. J. Buma, V. P. Nicu, S. R. Harutyunyan, *Eur. J. Org. Chem.* **2018**, 3900.

[20] a) T. Satyanarayana, S. Abraham, H. B. Kagan, *Angew. Chem. Int. Ed.* **2009**, *48*, 456; *Angew. Chem.* **2009**, *121*, 464; b) X. Peng, J. Xu, T. Li, Y. R. Chi, Z. Jin, *Chem. Sci.* **2020**, *11*, 12533.

[21] a) E. Chamorro, P. Pérez, L. R. Domingo, *Chem. Phys. Lett.* **2013**, *582*, 141; b) L. R. Domingo, P. Pérez, *Org. Biomol. Chem.* **2013**, *11*, 4350.

[22] Gaussian 16, Revision B.01, M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, B. Mennucci, G. A. Petersson, H. Nakatsuji, M. Caricato, X. Li, H. P. Hratchian, A. F. Izmaylov, J. Bloino, G. Zheng, J. L. Sonnenberg, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, J. A. Montgomery, Jr., J. E. Peralta, F. Ogliaro, M. Bearpark, J. J. Heyd, E. Brothers, K. N. Kudin, V. N. Staroverov, R. Kobayashi, J. Normand, K. Raghavachari, A. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, N. Rega, J. M. Millam, M. Klene, J. E. Knox, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, R. L. Martin, K. Morokuma, V. G. Zakrzewski, G. A. Voth, P. Salvador, J. J. Dannenberg, S. Dapprich, A. D. Daniels, Ö. Farkas, J. B. Foresman, J. V. Ortiz, J. Cioslowski, D. J. Fox, Gaussian, Inc., Wallingford CT, **2016**.

[23] a) Y. Zhao, D. G. Truhlar, *J. Chem. Theory Comput.* **2006**, *2*, 1009; b) Y. Zhao, D. G. Truhlar, *Theor. Chem. Acc.* **2008**, *120*, 215.

[24] a) A. D. McLean, G. S. Chandler, *J. Chem. Phys.* **1980**, *72*, 5639; b) M. M. Francl, W. J. Pietro, W. J. Hehre, J. S. Binkley, M. S. Gordon, D. J. DeFrees, J. A. Pople, *J. Chem. Phys.* **1982**, *77*, 3654; c) G. A. Petersson, A. Bennett, T. G. Tensfeldt, M. A. AlLaham, W. A. Shirley, J. Mantzaris, *J. Chem. Phys.* **1988**, *89*, 2193; d) R. C. Binning, Jr., L. A. Curtiss, *J. Comput. Chem.* **1990**, *11*, 1206; e) G. A. Petersson, M. A. Al-Laham, *J. Chem. Phys.* **1991**, *94*, 6081.

[25] S. Grimme, S. Ehrlich, L. Goerigk, *J. Comb. Chem.* **2011**, *32*, 1456.

[26] C. Kong, N. Jana, T. G. Driver, *Org. Lett.* **2013**, *15*, 824.

[27] M. Deligny, F. Carreaux, B. Carboni, *Synlett* **2005**, *9*, 1462.

[28] Deposition Numbers 2008358 (for **4g**), 2165904 (for **6d**), 2067952 (for **14**), and 2067953 (for **16**) contain the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service.

[29] J. A. Leitch, C. L. McMullin, M. F. Mahon, Y. Bhonoah, C. G. Frost, *ACS Catal.* **2017**, *7*, 2616.

[30] K. C. Nicolaou, B. Zou, D. H. Dethe, D. B. Li, D. Y.-K. Chen, *Angew. Chem. Int. Ed.* **2006**, *45*, 7786; *Angew. Chem.* **2006**, *118*, 7950.

[31] a) K. K. Bastas, A. Karakaya, *Plant Dis.* **2012**, *96*, 452; b) P. Liu, S. Xue, R. He, J. Hu, X. Wang, B. Jia, L. Gallipoli, A. Mazzaglia, G. M. Balestra, L. Zhu, *Eur. J. Plant Pathol.* **2016**, *145*, 743; c) S. Prencipe, M. L. Gullino, D. Spadaro, *Eur. J. Plant Pathol.* **2018**, *150*, 191; d) W. A. Wicaksono, E. E. Jones, S. Casonato, J. Monk, H. J. Ridgway, *Biol. Control* **2018**, *116*, 103; e) I. Donati, A. Cellini, G. Buriani, S. Mauri, C. Kay, G. Tacconi, F. Spinelli, *Hortic. Res.* **2018**, *5*, 56.

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