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Bifunctional NHC-Catalyzed Remote Enantioselective Mannich-type Reaction of 5-(Chloromethyl)furfural via Trienolate Intermediates

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Dedicated to Professor Lin-Xin Dai on the occasion of his 100th birthday.

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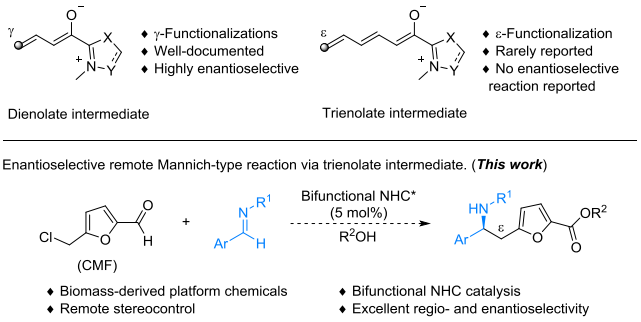
Abstract: The N-heterocyclic carbene (NHC)-catalyzed enantioselective Mannich-type reactions of the biomass-derived platform compound 5-(chloromethyl)furfural (CMF) with imines were developed. A series of high-value-added chiral amines were afforded in good to high yields with excellent regio- and enantioselectivities. The bifunctional NHC derived from L-pyroglutamic acid was efficient to steer the remote addition of trienolate intermediate to imine in a highly stereocontrolled manner. This represents the first example of enantioselective reactions via NHC-bound trienolate intermediate.

Biomass, produced by plants through solar photosynthetic processes, is abundant on the Earth. Chemical conversion of biomass to access useful materials is considered a promising approach to replacing non-renewable fossil resources.[1] Lignocellulose occupies the largest proportion of biomass, and is mainly composed of cellulose, hemicellulose and lignin.[2] Degradation of cellulose and hemicellulose can yield carbonyl compounds, such as glucose, xylose, furfural, 5-hydroxymethyl furfural (HMF), 5-(chloromethyl)furfural (CMF), levulinic acid and lactic acid.[3] Further transformation of biomass-derived platform compounds via asymmetric catalysis to obtain high-value-added chiral chemicals is of great significance.[4]

In the past decades, N-heterocyclic carbenes (NHCs) have emerged as efficient organocatalysts to enable highly enantioselective transformations via versatile intermediates.[5] The umpolung of aldehydes,[6] and α-[7] or β-functionalizations[8] of aldehydes or carboxylic acid derivatives have been well established. In recent years, the NHC-catalyzed enantioselective γ-functionalization via dienolate **I** has been well established (Scheme 1, upper left).[9] In 2011, our group reported the first NHC-catalyzed asymmetric [4+2] annulation reaction via dienolate from β-methyl-α,β-unsaturated acyl chlorides.[10] Chi et al developed an elegant oxidative strategy for the formation of dienolate from β-methyl enals.[11] Since then, studies involving NHC-bound dienolates[12] and (hetero-) *o*-quinodimethane intermediates[13] have been extensively investigated. In addition, the NHC-catalyzed δ-functionalizations via α,β-γ,δ-bisunsaturated acyl azolium intermediates were also reported by Lupton,[14] Chi,[15] and Zhu[16] groups. Compared with the well-developed NHC-catalyzed α-, β-, γ-, and δ-functionalizations, the NHC-catalyzed ε-functionalizations via trienolate have been far less developed (Scheme 1, upper right). During our research on NHC/photo-cocatalyzed alkylation of enals, the ε-alkylated products were afforded via NHC-bound trienolates.[17] Recently, the NHC-catalyzed reactions of 4-(chloromethyl)-benzaldehydes[18] and CMF[19] via trienolates were also developed. However, asymmetric version of these NHC-catalyzed reactions meets little success,[20] compared to the achievements on enantioselective remote functionalization via aminocatalysis.[21]

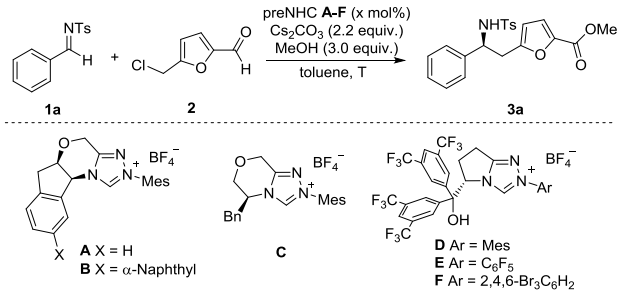


Scheme 1. NHC-bound dienolate and trienolate intermediate, and asymmetric remote Mannich reaction via trienolate.

Asymmetric Mannich reaction is one of the most important methodologies to access chiral amine building blocks. The metal- and organo-catalyzed enantioselective classical and vinylogous Mannich reactions have witnessed great success.[22] Given our ongoing interests in asymmetric NHC catalysis,[23] we herein report a bifunctional NHC-catalyzed enantioselective

remote Mannich-type reaction of CMF via trienolate with imines for the construction of chiral amines (Scheme 1, down). H-bonding effect between azolium trienolate and the imine was believed to promote the reaction in an efficient and highly enantiocontrolled manner.

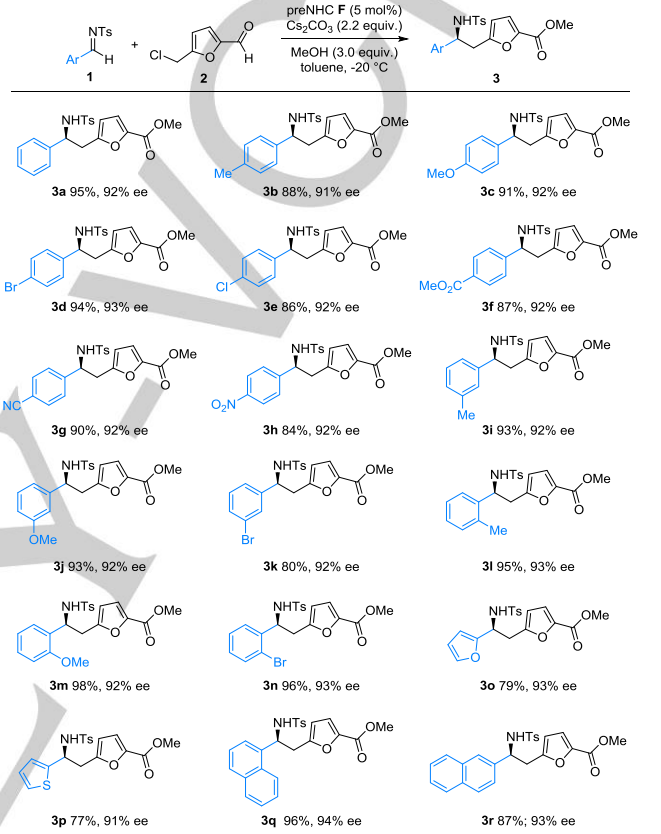
Table 1. Optimization of reaction conditions[a]



entry	preNHC	x	T (°C)	yield (%)[b]	ee (%)[c]
1	**A**	20	RT	64	6
2	**B**	20	RT	73	9
3	**C**	20	RT	49	11
4	**D**	20	RT	68	57
5	**E**	20	RT	33	73
6	**F**	20	RT	45	80
7[d]	**F**	20	RT	75	92
8[d]	**F**	10	RT	73	92
9[d]	**F**	10	-20	93	93
10[d]	**F**	5	-20	95	92
11[d]	**F**	2	-20	70	93

[a] General conditions: **1a** (0.1 mmol), **2a** (2.0 equiv.), preNHC (20 mol%), Cs_2CO_3 (2.2 equiv.), toluene 1 mL (*c* = 0.1 mol/L), 15 h, RT. [b] Isolated yields. [c] Determined by HPLC analysis using a chiral stationary phase. [d] toluene 2 mL (*c* = 0.05 mol/L). Mes = mesityl; RT = room temperature.

The model reaction of imine **1a** and CMF **2** was investigated under NHC catalysis (Table 1). After initial assessment of base and solvent, the desired amine **3a** could be afforded in 64% yield albeit with 6% ee when 20 mol% of preNHC **A**[7a] was used, with Cs_2CO_3 as the base and toluene as the solvent (entry 1, for details see the Supporting Information, Table S1). The preNHC **B**[24] with a bulky α-naphthyl was then used, which resulted in a slight increase of the yield but without expected enhancement of the enantioselectivity (entry 2). The reaction using morpholinone-derived triazolium preNHC **C**[25] gave amine **3a** in 49% yield with 11% ee (entry 3). A series of bifunctional *L*-pyroglutamic acid-derived preNHCs with free hydroxyl group were then employed (entries 4-6).[26] We were happy to find that the usage of *N*-Mes bifunctional preNHC **D** dramatically improved the enantioselectivity to 57% ee (entry 4). The *N*-C_6F_5 substituted preNHC **E** showed better enantioselectivity but with decreased yield (entry 5). The reaction using preNHC **F** bearing *N*-2,4,6-tribromophenyl afforded amine **3a** in 45% yield with 80% ee (entry 6). Interestingly, the reaction performed much better to give **3a** in 73% yield with 92% ee when concentration of the reaction was reduced from 0.1 to 0.05 mol/L (entry 7). Decreasing the loading of preNHC **F** to 10 mol% showed no change for the reaction (entry 8 vs 7). The yield of amine **3a** was further increased to 93% when the reaction temperature was lowered to -20 °C (entry 9). Notably, the reaction performed as well with respect to both yield and enantioselectivity when the loading of preNHC **F** was further decreased to 5 mol% (entry 10), while some decreased yield was observed albeit with high ee unchanged when 2 mol% of preNHC **F** was used (entry 11).

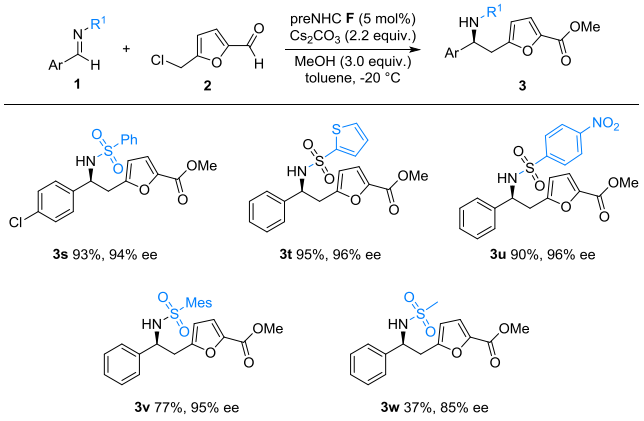


Scheme 2. Scope of *N*-Ts imines.

With the optimized reaction conditions in hand (Table 1, entry 10), we next examined the scope of *N*-Ts imines **1** (Scheme 2). It was found that imines bearing both electron-donating groups (Ar = 4-MeC_6H_4 and 4-OMeC_6H_4) and electron-withdrawing groups (Ar = 4-BrC_6H_4, 4-ClC_6H_4) at the *para*-position of the phenyl ring worked well to give products **3b**-**3e** in excellent yields and enantioselectivities. Functional groups, such as ester, cyano and nitro groups, could be well tolerated (**3f**-**3h**). The reactions of *meta*-substituted imines also proceeded well to give products **3i**-**3k** in excellent yields and enantioselectivities. *ortho*-Substituted aryl imines (Ar = 2-MeC_6H_4, 2-MeOC_6H_4, and 2-BrC_6H_4) performed well under the standard reaction conditions (**3l**-**3n**). 2-Furanyl-substituted and 2-thioenyl-substituted imines resulted in some decreased but still good yields under standard conditions (**3o**-**3p**). High yield and enantioselectivity were achieved for the reaction of α-naphthaldehyde (**3q**) and β-naphthaldehyde (**3r**). Unfortunately, aliphatic imine did not work for the reaction under current conditions.

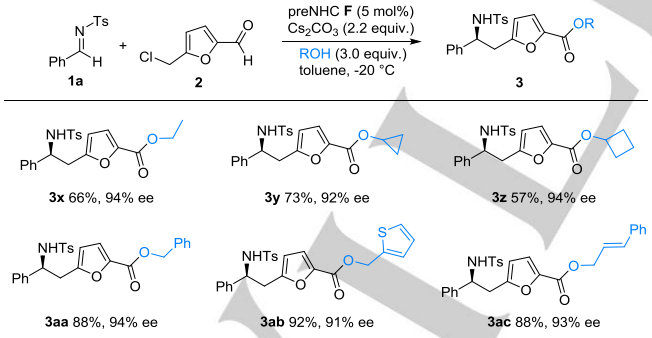
The reaction of imines with different sulfonyl groups were next explored (Scheme 3). Imines with *N*-benzenesulfonyl, *N*-(2-

thienyl)sulfonyl, *N*-(2-thienyl)sulfonyl, and 2-(4-nitrophenyl)sulfonyl all furnished the desired products in high yields and excellent enantioselectivities (**3s**-**3u**). Imine with *N*-mesitylenesulphonyl was also tested to afford **3v** in 77% yield with 95% ee. However, the enantioselectivity decreased when *N*-methylsulfonyl protected imine was used (**3w**), possibly due to the less sterically demanded property. The attempt of using 4-(chloromethyl)benzaldehyde instead of CMF failed under current conditions.



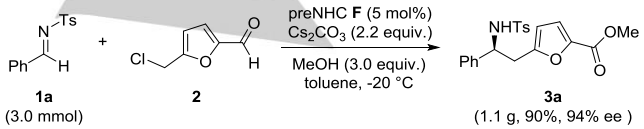
Scheme 3. Variation of *N*-sulfonyl groups of imines.

A variety of nucleophiles were then briefly investigated (Scheme 4). Both primary and secondary alcohols worked well for the reaction (**3x**-**3z**). Benzyl alcohol and 2-thiophenemethanol were tolerated to give the desired products (**3aa**-**3ab**) in high yields. Furthermore, high yield was also achieved for the reaction with cinnamic alcohol (**3ac**). Notably, all of the alcohols furnished the corresponding products in excellent enantioselectivities.



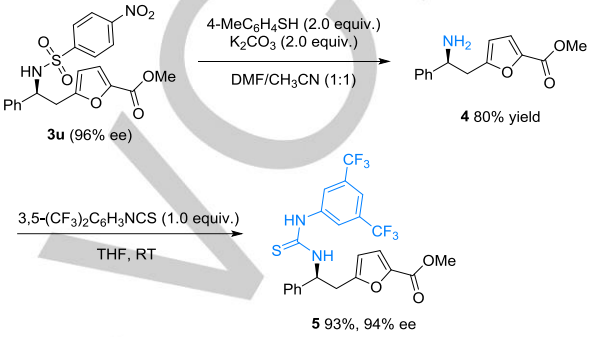
Scheme 4. Scope of the nucleophiles.

The reaction could be easily scaled up to 3.0 mmol to give 1.1 g of the desired amine **3a** in 90% yield with 94% ee under standard conditions (Scheme 5).



Scheme 5. Gram-scale synthesis.

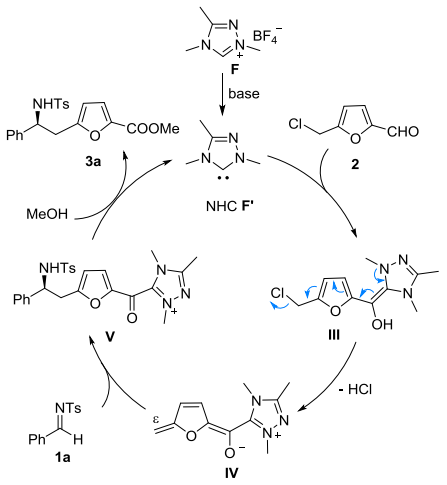
The reaction products were amenable to further transformations through simple procedures (Scheme 6). Removal of the 4-nitrophenylsulfonyl with *p*-toluenethiol afforded chiral amine **4** in 80% yield. Reaction of chiral amine **4** with isothiocyanatoarene gave the corresponding thiourea **5** in excellent yield without apparent erosion of the enantioselectivity (94% ee), which was readily available for potential application in asymmetric transformations as a hydrogen-bonding organocatalyst.



Scheme 6. Synthetic applicability.

The absolute (*S*)-configuration of product **3a** was assigned via single-crystal X-ray analysis (see the Supporting Information).[27]

A plausible mechanism for this Mannich-type reaction of CMF is proposed as shown in Scheme 7. Addition of the in situ generated NHC to **2** forms the Breslow intermediate **III**, which undergoes 1,6-elimination of HCl to afford the key trienolate azolium **IV**. The following nucleophilic ε-addition of trienolate **IV** to aldimine **1a** gives adduct **V**, which is trapped by methanol to afford the chiral amine product **3a** and regenerates the NHC catalyst. The possible pathway involving the S_{N2} attack of NHC at Cl-C bond of CMF was ruled out by a control experiment using methyl 5-(chloromethyl)furan-2-carboxylate instead of CMF, which resulting no reaction and full recovery of methyl 5-(chloromethyl)furan-2-carboxylate (see Supporting Information).



Scheme 7. Plausible catalytic cycle.

A weak interaction between the free OH of bifunctional NHC catalyst and aldimine was observed by ^{1}H NMR titration in CD_3CN (see Supporting Information, Figure S1). Based on the control experiments and the stereochemical outcome, a H-bonding directed stereochemical mode is proposed (Figure 1). The imine is pre-positioned with the NHC-CMF adduct via H-bonding, followed by addition of trienolate to the *Si* face of aldimine.

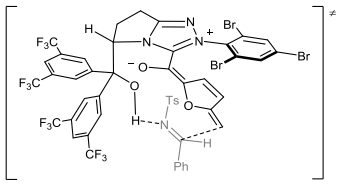


Figure 1. H-Bonding directed stereochemical mode.

In summary, the bifunctional NHC-catalyzed enantioselective Mannich-type reactions of the biomass-derived platform compound CMF with imines were developed, giving a series of high-value-added chiral amines in good to high yields with excellent regio- and enantioselectivities. The L-pyroglutamic acid derived NHC catalyst bearing a free hydroxy group was the key to steer the remote ε-addition of trienolate in a highly stereocontrolled manner. This protocol exemplifies the powerful catalytic activities of NHCs in remote asymmetric transformations. NHC-catalyzed other asymmetric transformations of biomass-derived platform compounds are underway in our laboratory.

Acknowledgements

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Keywords: Mannich-type reactions • N-heterocyclic carbenes • asymmetric catalysis • biomass-derived platform compounds • trienolates

[1] a) J. J. Bozell, *Science* **2010**, *329*, 522; b) H. Kopetz, *Nature* **2013**, *494*, 29; c) Y. Queneau, B. Han, *The Innovation* **2022**, *3*, 100184.

[2] a) C.-H. Zhou, X. Xia, C.-X. Lin, D.-S. Tong, J. Beltramini, *Chem. Soc. Rev.* **2011**, *40*, 5588; b) R. Rinaldi, *Angew. Chem. Int. Ed.* **2014**, *53*, 8559; *Angew. Chem.* **2014**, *126*, 8699; c) Z. Zhang, J. Song, B. Han, *Chem. Rev.* **2017**, *117*, 6834.

[3] a) R.-J. van Putten, J. C. van der Waal, E. de Jong, C. B. Rasrendra, H. J. Heeres, J. G. de Vries, *Chem. Rev.* **2013**, *113*, 1499; b) J. Wang, J. Xi, Y. Wang, *Green Chem.* **2015**, *17*, 737; c) Z. Zhang, K. Deng, *ACS Catal.* **2015**, *5*, 6529; d) M. Mascal, *ChemSusChem* **2015**, *8*, 3391; e) S. Chen, R. Wojcieszak, F. Dumeignil, E. Marceau, S. Royer, *Chem. Rev.* **2018**, *118*, 11023; f) M. Mascal, *ACS Sustain. Chem. Eng.* **2019**, *7*, 5588; g) B. Wozniak, S. Tin, J. G. de Vries, *Chem. Sci.* **2019**, *10*, 6024.

[4] a) A. Corma, S. Iborra, A. Velty, *Chem. Rev.* **2007**, *107*, 2411; b) C. O. Tuck, E. Pérez, I. T. Horváth, R. A. Sheldon, M. Poliakoff, *Science* **2012**, *337*, 695; c) M. Besson, P. Gallezot, C. Pinel, *Chem. Rev.* **2014**, *114*, 1827; d) L. Wu, T. Moteki, Amit A. Gokhale, David W. Flaherty, F. D. Toste, *Chem* **2016**, *1*, 32; e) T. A. Bender, J. A. Dabrowski, M. R. Gagné, *Nat. Rev. Chem.* **2018**, *2*, 35.

[5] a) D. Enders, O. Niemeier, A. Henseler, *Chem. Rev.* **2007**, *107*, 5606; b) S. De Sarkar, A. Biswas, R. C. Samanta, A. Studer, *Chem. - Eur. J.* **2013**, *19*, 4664; 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) M. H. Wang, K. A. Scheidt, *Angew. Chem. Int. Ed.* **2016**, *55*, 14912; *Angew. Chem.* **2016**, *128*, 15134; g) K. J. R. Murauski, A. A. Jaworski, K. A. Scheidt, *Chem. Soc. Rev.* **2018**, *47*, 1773; h) P. Bellotti, M. Koy, M. N. Hopkinson, F. Glorius, *Nat. Rev. Chem.* **2021**, *5*, 711.

[6] a) J. C. Sheehan, D. H. Hunneman, *J. Am. Chem. Soc.* **1966**, *88*, 3666; b) D. Enders, U. Kallfass, *Angew. Chem. Int. Ed.* **2002**, *41*, 1743; *Angew. Chem.* **2002**, *114*, 1822; c) S. M. Mennen, J. D. Gipson, Y. R. Kim, S. J. Miller, *J. Am. Chem. Soc.* **2005**, *127*, 1654; d) J. Read de Alaniz, T. Rovis, *J. Am. Chem. Soc.* **2005**, *127*, 6284; e) H. Takikawa, Y. Hachisu, J. W. Bode, K. Suzuki, *Angew. Chem. Int. Ed.* **2006**, *45*, 3492; *Angew. Chem.* **2006**, *118*, 3572; f) X. Huang, S. Ye, *Chin. Sci. Bull.* **2010**, *55*, 1753; g) I. Piel, M. Steinmetz, K. Hirano, R. Fröhlich, S. Grimme, F. Glorius, *Angew. Chem. Int. Ed.* **2011**, *50*, 4983; *Angew. Chem.* **2011**, *123*, 5087; h) L.-H. Sun, Z.-Q. Liang, W.-Q. Jia, S. Ye, *Angew. Chem. Int. Ed.* **2013**, *52*, 5803; *Angew. Chem.* **2013**, *125*, 5915; i) M.-Q. Jia, S.-L. You, *ACS Catal.* **2013**, *3*, 622.

[7] a) M. He, J. R. Struble, J. W. Bode, *J. Am. Chem. Soc.* **2006**, *128*, 8418; b) Y.-R. Zhang, L. He, X. Wu, P.-L. Shao, S. Ye, *Org. Lett.* **2008**, *10*, 277; c) N. Duguet, C. D. Campbell, A. M. Z. Slawin, A. D. Smith, *Org. Biomol. Chem.* **2008**, *6*, 1108; d) X. Zhao, K. E. Ruhl, T. Rovis, *Angew. Chem. Int. Ed.* **2012**, *51*, 12330; *Angew. Chem.* **2012**, *124*, 12496; e) L. Hao, Y. Du, H. Lv, X. Chen, H. Jiang, Y. Shao, Y. R. Chi, *Org. Lett.* **2012**, *14*, 2154.

[8] a) C. Burstein, F. Glorius, *Angew. Chem. Int. Ed.* **2004**, *43*, 6205; *Angew. Chem.* **2004**, *116*, 6331; b) S. S. Sohn, E. L. Rosen, J. W. Bode, *J. Am. Chem. Soc.* **2004**, *126*, 14370; c) A. Chan, K. A. Scheidt, *J. Am. Chem. Soc.* **2008**, *130*, 2740; d) S. De Sarkar, A. Studer, *Angew. Chem. Int. Ed.* **2010**, *49*, 9266; *Angew. Chem.* **2010**, *122*, 9452; e) F.-G. Sun, L.-H. Sun, S. Ye, *Adv. Synth. Catal.* **2011**, *353*, 3134; f) L. Candish, D. W. Lupton, *J. Am. Chem. Soc.* **2013**, *135*, 58; g) J. Cheng, Z. Huang, Y. R. Chi, *Angew. Chem. Int. Ed.* **2013**, *52*, 8592; *Angew. Chem.* **2013**, *125*, 8754; h) X.-Y. Chen, Z.-H. Gao, C.-Y. Song, C.-L. Zhang, Z.-X. Wang, S. Ye, *Angew. Chem. Int. Ed.* **2014**, *53*, 11611; *Angew. Chem.* **2014**, *126*, 11795.

[9] a) X.-Y. Chen, Q. Liu, P. Chauhan, D. Enders, *Angew. Chem. Int. Ed.* **2018**, *57*, 3862; *Angew. Chem.* **2018**, *130*, 3924; b) J. Gao, J. Feng, D. Du, *Org. Chem. Front.* **2021**, *8*, 6138.

[10] L.-T. Shen, P.-L. Shao, S. Ye, *Adv. Synth. Catal.* **2011**, *353*, 1943.

[11] J. Mo, X. Chen, Y. R. Chi, *J. Am. Chem. Soc.* **2012**, *134*, 8810.

[12] a) X.-Y. Chen, F. Xia, J.-T. Cheng, S. Ye, *Angew. Chem. Int. Ed.* **2013**, *52*, 10644; *Angew. Chem.* **2013**, *125*, 10838; b) Z. Xiao, C. Yu, T. Li, X.-S. Wang, C. Yao, *Org. Lett.* **2014**, *16*, 3632; c) B.-S. Li, Y. Wang, Z. Jin, P. Zheng, R. Ganguly, Y. R. Chi, *Nat. Commun.* **2015**, *6*, 6207; d) Z. Wu, F. Li, J. Wang, *Angew. Chem. Int. Ed.* **2015**, *54*, 1629; *Angew. Chem.* **2015**, *127*, 1649.

[13] a) X. Chen, S. Yang, B.-A. Song, Y. R. Chi, *Angew. Chem. Int. Ed.* **2013**, *52*, 11134; *Angew. Chem.* **2013**, *125*, 11340; b) D. Janssen-Müller, S. Singha, T. Olyschläger, C. G. Daniliuc, F. Glorius, *Org. Lett.* **2016**, *18*, 4444; c) D.-F. Chen, T. Rovis, *Synthesis* **2017**, *49*, 293; d) A. Przydacz, A. Topolska, A. Skrzyńska, Ł. Albrecht, *Adv. Synth. Catal.* **2022**, *364*, 1434.

[14] a) M. Kowalczyk, D. W. Lupton, *Angew. Chem. Int. Ed.* **2014**, *53*, 5314; *Angew. Chem.* **2014**, *126*, 5418; b) R. M. Gillard, J. E. M. Fernando, D. W. Lupton, *Angew. Chem. Int. Ed.* **2018**, *57*, 4712; *Angew. Chem.* **2018**, *130*, 4802.

[15] T. Zhu, C. Mou, B. Li, M. Smetankova, B.-A. Song, Y. R. Chi, *J. Am. Chem. Soc.* **2015**, *137*, 5658.

[16] a) K. Xu, W. Li, S. Zhu, T. Zhu, *Angew. Chem. Int. Ed.* **2019**, *58*, 17625; *Angew. Chem.* **2019**, *131*, 17789; b) K. Xu, Z. Wang, T. Zhu, *Synlett* **2020**, *31*, 925.

[17] a) L. Dai, Z.-H. Xia, Y.-Y. Gao, Z.-H. Gao, S. Ye, *Angew. Chem. Int. Ed.* **2019**, *58*, 18124; *Angew. Chem.* **2019**, *131*, 18292; b) Y.-Y. Xu, L. Dai, Z.-H. Gao, S. Ye, *J. Org. Chem.* **2022**, *87*, 14970.

[18] L. Dai, S. Ye, *ACS Catal.* **2020**, *10*, 994.
[19] L. Dai, Y. Qiu, Y.-Y. Xu, S. Ye, *Cell Rep. Phys. Sci.* **2020**, *1*, 100071.
[20] a) L. Bernardi, J. López-Cantarero, B. Niess, K. A. Jørgensen, *J. Am. Chem. Soc.* **2007**, *129*, 5772; b) D. Uraguchi, K. Yoshioka, Y. Ueki, T. Ooi, *J. Am. Chem. Soc.* **2012**, *134*, 19370; c) L. Dell'Amico, Ł. Albrecht, T. Naicker, P. H. Poulsen, K. A. Jørgensen, *J. Am. Chem. Soc.* **2013**, *135*, 8063; d) R. Deng, S. Wu, C. Mou, J. Liu, P. Zheng, X. Zhang, Y. R. Chi, *J. Am. Chem. Soc.* **2022**, *144*, 5441.
[21] a) A. Przydacz, A. Skrzyńska, Ł. Albrecht, *Angew. Chem. Int. Ed.* **2019**, *58*, 63; *Angew. Chem.* **2019**, *131*, 64; b) B.-X. Xiao, X.-Y. Gao, W. Du, Y.-C. Chen, *Chem. - Eur. J.* **2019**, *25*, 1607.
[22] a) J. M. M. Verkade, L. J. C. v. Hemert, P. J. L. M. Quaedflieg, F. P. J. T. Rutjes, *Chem. Soc. Rev.* **2008**, *37*, 29; b) A. Ting, S. E. Schaus, *Eur. J. Org. Chem.* **2007**, *2007*, 5797; c) B. Karimi, D. Enders, E. Jafari, *Synthesis* **2013**, *45*, 2769; d) M. S. Roselló, C. del Pozo, S. Fustero, *Synthesis* **2016**, *48*, 2553; e) S. Saranya, N. A. Harry, K. K. Krishnan, G. Anilkumar, *Asian J. Org. Chem.* **2018**, *7*, 613; f) I. Bagheri, L. Mohammadi, V. Zadsirjan, M. M. Heravi, *ChemistrySelect* **2021**, *6*, 1008.
[23] X.-Y. Chen, Z.-H. Gao, S. Ye, *Acc. Chem. Res.* **2020**, *53*, 690.
[24] C. Zhao, F. Li, J. Wang, *Angew. Chem. Int. Ed.* **2016**, *55*, 1820; *Angew. Chem.* **2016**, *128*, 1852.
[25] M. Wadamoto, E. M. Phillips, T. E. Reynolds, K. A. Scheidt, *J. Am. Chem. Soc.* **2007**, *129*, 10098.
[26] L. He, Y.-R. Zhang, X.-L. Huang, S. Ye, *Synthesis* **2008**, *2008*, 2825.
[27] CCDC 2237090 (**3a**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

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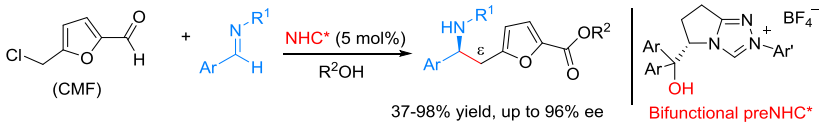

- Biomass-derived platform chemicals
- Remote stereocontrol
- Bifunctional NHC catalysis
- Excellent regio- and enantioselectivity

The NHC-catalyzed enantioselective Mannich-type reactions of 5-(chloromethyl)furfural (CMF), an important biomass-derived platform compound, with aldimines were developed. High-value-added chiral amines were afforded in good yields with excellent regio- and enantioselectivities. The bifunctional NHC bearing a free hydroxy group was efficient to steer the remote addition of trienolate intermediate to imine in a highly stereocontrolled manner.

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