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Letter

Differentiating Catalysis in the Dearomative [4 + 2]-Cycloaddition Involving Enals and Heteroaromatic Aldehydes

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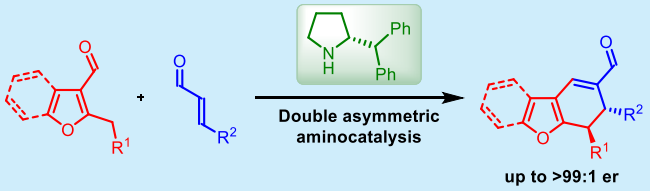
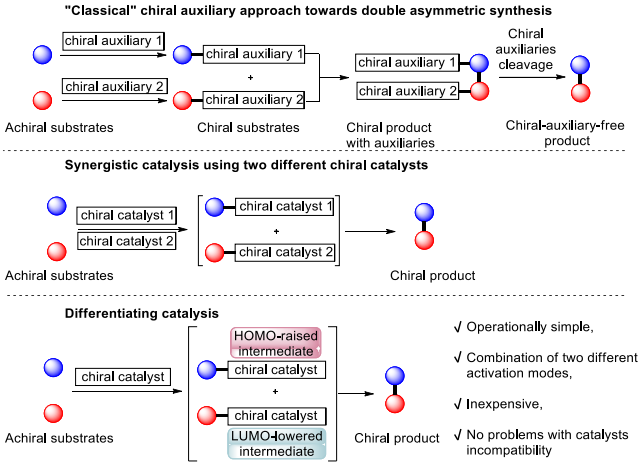
ABSTRACT: In this paper, the application of differentiating catalysis in the [4 + 2]-cycloaddition between 2-alkyl-3-formylheteroarenes and α,β-unsaturated aldehydes is described. Within the developed approach, the same aminocatalyst is employed for the independent activation of both starting materials, differentiating their properties via LUMO-lowering and HOMO-rising principles. By the combination of dearomative dienamine activation with iminium ion chemistry high enantio- and diastereoselectivity of the doubly asymmetric process was accomplished. Selected transformations of products were also demonstrated.



Stereocontrolled synthesis of specific structural motifs is one of the most important tasks in contemporary organic chemistry.[1] Within this area of research, double-asymmetric synthesis constitutes an interesting approach.[2] It leads to the formation of a new stereogenic center by the utilization of two enantiopure substrates bearing a chiral auxiliary unit. When appropriate enantiomers of substrates are employed ("match" case), the chirality of both reagents synergistically enhances the stereochemical reaction outcome (Scheme 1). The main drawback of the approach concerns its atom- and step-economy as chiral auxiliaries are used in stoichiometric amounts and must be introduced and removed in additional, time-consuming procedures. A much easier strategy is based on the catalytic generation of chiral intermediates that participate in the reaction as no additional synthetic protocols are required. The main tool used for this type of asymmetric synthesis is synergistic catalysis where two different catalysts independently activate two substrates, thus providing chiral intermediates capable of participating in a given transformation.[3] On the contrary, the pathway relying on the activation of both substrates by two molecules of the same catalyst is much less explored.[4] In this type of approach, electronic properties of substrates are enhanced and at the same time differentiated via the formation of both LUMO-lowered and HOMO-raised reactive intermediates. Therefore, such catalytic activation can be referred to as differentiating catalysis. This strategy offers many benefits including operational simplicity, yet it is more challenging as substrates employed must possess functional groups of similar properties, thus resulting in competitive reaction pathways.

Scheme 1. Double Asymmetric Synthesis: Classical and Catalytic Approaches



Since the turn of the millennium, aminocatalysis has proven extremely useful in synthetic methodology, allowing for the stereoselective functionalization of numerous types of carbonyl compounds.[5] Among different strategies provided by this methodology, HOMO-raising enamine activation of aldehydes and ketones occupies a prominent position. Identification of polyenamine-mediated processes gave access to novel stereoselective methods of functionalization of unsaturated carbonyl compounds with dienamine and trienamine chemistry providing significant synthetic opportunities.[6] Over the past few years, novel approaches toward generation of polyenamines from (hetero)aromatic compounds have been identi-

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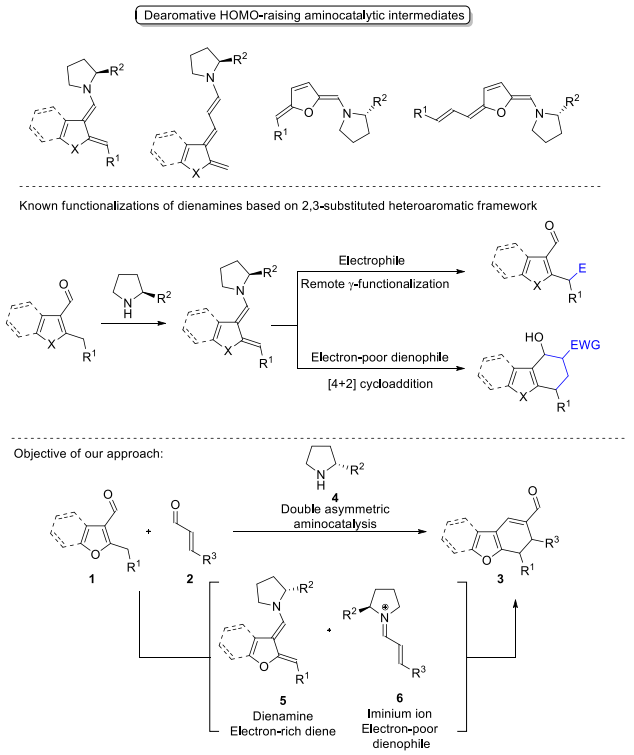
fied with aminocatalytic dearomative strategies paving new directions in the development of the field. Interestingly, diverse heteroaromatic carbonyl compounds can be transformed with dearomatization into polyenamines under aminocatalytic conditions (Scheme 2, top).[7] Notably, dienamines derived

Scheme 2. Polyenamine Species Generated from Heteroaromatic Aldehydes and Their Functionalization



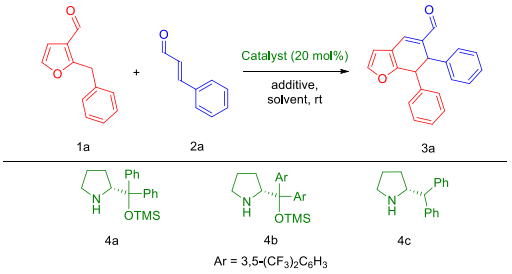
from 2,3-disubstituted heteroaromatic compounds are prone to the reaction with electrophiles providing either alkylation products[7f,i,j] or more rarely undergoing cycloaddition[7e,g] (Scheme 2, middle).

Given the interesting possibilities provided by differentiating catalysis, the task of development of dearomative dienamine-mediated [4 + 2]-cycloaddition was undertaken (Scheme 2, bottom). It was envisioned that catalytically generated iminium ions **6** derived from α,β-unsaturated aldehydes **2** might serve as an appropriate electron-poor dienophile for this reaction. It was anticipated that the utilization of selected aminocatalyst should be beneficial for two independent processes: formation of dearomatized dienamine **5** and the previously mentioned iminium ion **6**. Chiral intermediates thus obtained should be prone to react in the Diels–Alder cycloaddition, and double-asymmetric catalysis concept should result in enhancement of stereoselectivity of the process.[8]

Herein, we present our studies on the aminocatalytic [4 + 2]-cycloaddition between dienamines **5** (generated from heteroaromatic aldehydes **1**) and iminium ions **6** (derived from enals **2**) realized according to differentiating catalysis principles. Dearomative Diels–Alder reaction proceeded efficiently, providing enantioenriched heteroaromatic derivatives **3**. Utilization of the obtained product in selected transformations was also demonstrated.

Optimization studies were performed using 2-benzylfuran-3-carbaldehyde **1a** and *trans*-cinnamaldehyde **2a** as model reactants (Table 1). The initial experiment, performed with

Table 1. Differentiating Catalysis in the [4 + 2]-Cycloaddition Optimization Studies[a]



entry	cat.	solvent	conv[b] (%)	dr[c]	er[d]
1	**4a**	CH_2Cl_2	34	12:1	>99:1
2	**4b**	CH_2Cl_2	trace		
3	**4c**	CH_2Cl_2	32	>20:1	>99:1
4[e]	**4c**	CH_2Cl_2	25	>20:1	
5[f]	**4c**	CH_2Cl_2	43	>20:1	
6[f,g]	**4c**	CH_2Cl_2	92 (80)	>20:1	>99:1
7[f,h]	**4c**	CH_2Cl_2	32	>20:1	
8[f,i]	**4c**	CH_2Cl_2	85	>20:1	
9[f,g]	**4c**	$CHCl_3$	39	>20:1	
10[f,g]	**4c**	toluene	30	>20:1	
11[f,g]	**4c**	Et_2O	94 (95)	>20:1	>99:1
12[f,g,j]	**4c**	Et_2O	96 (91)	>20:1	>99:1

[a]The reactions were performed in 0.05 mmol scale using equimolar amounts of **1a** and **2a** in 0.2 mL of the solvent. [b]Determined by ^{1}H NMR spectroscopy of a crude reaction mixture after 24 h. The isolated yield is shown in parentheses. [c]Determined by ^{1}H NMR spectroscopy of a crude reaction mixture. [d]Determined by chiral stationary phase UPC.[2] [e]Reaction performed using **1a** (1.2 equiv) and **2a** (1.0 equiv). [f]Reaction performed using **1a** (1.0 equiv) and **2a** (1.2 equiv). [g]Reaction performed with $PhCO_2H$ (40 mol %) as additive. [h]Reaction performed with triethylamine (40 mol %) as additive. [i]Reaction performed with 4-dimethylaminobenzoic acid (40 mol %) as additive. [j]Reaction performed on a 1 mmol scale.

Hayashi–Jørgensen catalyst **4a** in dichloromethane, showed that the desired enantioenriched product **3a** was formed; nevertheless, the conversion and diastereoselectivity of the reaction were unsatisfactory (Table 1, entry 1). Utilization of amine **4b** provided only traces of cycloadduct **3a**; therefore, further organocatalyst screening proved necessary (Table 1, entry 2). Inspired by our previous work,[4f] (*R*)-2-benzhydrylpyrrolidine **4c** was used as catalyst, which gave similar results as **4a**, but with enhancement of diastereoselectivity (Table 1, entry 3). Therefore, **4c** was chosen as the most suited catalyst, and subsequent optimization studies were focused on the influence of the relative ratio of substrates on the cycloaddition outcome (Table 1, entries 3–5). The best results were obtained when 1.2-fold excess of **2a** was used, providing 43% conversion within 24 h (Table 1, entry 5). Therefore, the additive screening covering the effect of basic, acidic, or amphiprotic additives was carried out (Table 1, entries 6–8). The highest reaction enhancement was observed when benzoic acid was used as cocatalyst, providing the desired product in 80% yield after 24 h (Table 1, entry 6). Further optimization studies were devoted to the choice of the most suited solvent for the studied cycloaddition (Table 1, entry 9–11). Et_2O proved the best as it afforded the product **3a** in high chemical yield and with excellent stereoselectivity, thus determining the final reaction conditions (Table 1, entry 11). It is worth mentioning that the developed reaction was

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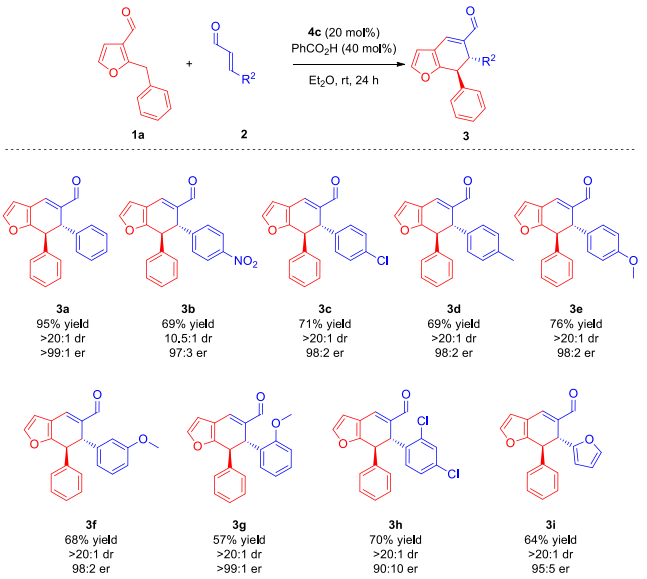
readily realized in a 20-fold higher scale, providing cycloadduct **3a** with similar results (Table 1, entry 12).

With the optimized reaction conditions in hand, studies on the scope and limitations of the method were undertaken. In the first part, the influence of the substitution pattern of α,β-unsaturated aldehydes **2** on the developed cycloaddition was investigated (Scheme 3). Transformation was unbiased toward

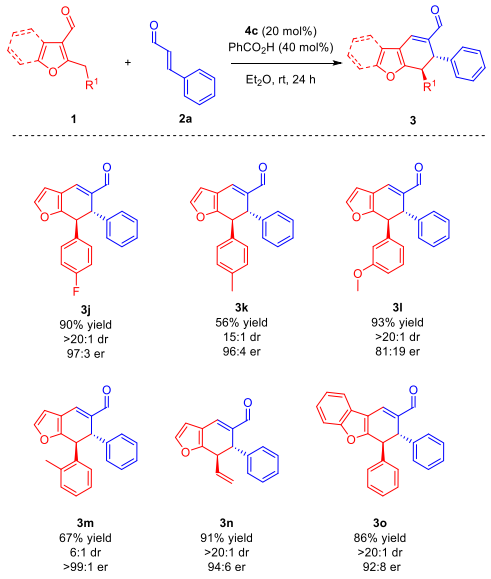
Scheme 3. Differentiating Catalysis in the [4 + 2]-Cycloaddition: α,β-Unsaturated Aldehyde 2 Scope



the presence of both electron-withdrawing and electron-donating substituents on the aromatic ring in **2** (Scheme 3, compounds **3b**–**d**). Interestingly, aldehyde **2b** bearing a nitro group in the *para* position gave access to cycloadduct **3b** in good yield and with excellent enantioselectivity, but with diminished diastereoselection. Substitution of the aromatic ring in **2c** with the chlorine atom and in **2d** with methyl group was also well-tolerated in the transformation affording product **3c** and **3d** with satisfactory results. Further examples showed that the stereoselectivity of the method is not influenced by the position of substituents on the aromatic ring in enals **2** (Scheme 3, products **3e**–**g**) as various methoxy-functionalized aldehydes **2e**–**g** reacted smoothly, providing cycloadducts **3e**–**g** with excellent enantio- and diastereocontrol. It is worth noting that introduction of the double substitution pattern on the aryl ring in **2h** was also possible, but product **3h** was obtained with lower enantioselectivity. Furthermore, the *trans*-3-(2-furyl)acrolein **2i** was also utilized in this transformation, yielding product **3i** decorated with a heteroaryl substituent. Unfortunately, hex-2-enal did not participate in the reaction, indicating that aliphatic α,β-unsaturated aldehydes were difficult substrates for the process.

The next step of scope studies was focused on the utilization of structurally diversified heteroaryl aldehydes **1** (Scheme 4). Aldehyde **1b**, containing an electron-acceptor substituent at the *para* position of the phenyl ring, led to the product **3j** with satisfactory yield, diastereoselectivity, and very good enantioselectivity. In the case of aldehydes **3k** and **3m** bearing methyl groups on the phenyl ring, the substituent position had a slight effect on the reaction results - for both 2- and 4-substituted substrates **1c** and **1e**, a significant decrease in the diastereoselectivity and yield was observed, while the

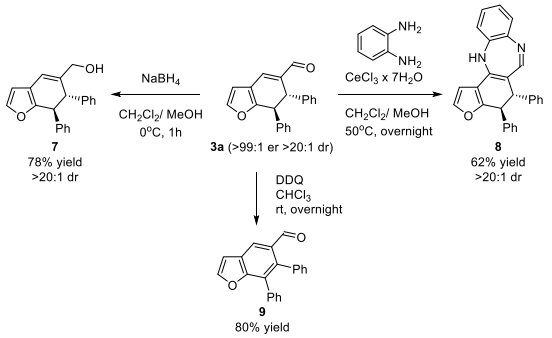
Scheme 4. Differentiating Catalysis in the [4 + 2]-Cycloaddition: Heteroaromatic Aldehyde 1 Scope



enantioselectivity was not affected. Nevertheless, substrate **1d** with a strongly electron-donating methoxy group at the *meta*-position of the phenyl ring gave access to product **3l** with decreased enantioselectivity. It is worth noting that allyl-substituted aldehyde **1f** was also employed in the cycloaddition providing **3n** as a single diastereoisomer in high yield. To our delight, further scope expansion was possible by the utilization of benzofuran-based aldehyde **1g**, which reacted smoothly to give cycloadduct **3o** with good enantioselectivity. Unfortunately 2-butyl-3-furfural and 2-methyl-3-formylbenzofuran were not reactive under the optimal reaction conditions. Moreover, attempts toward utilization of Boc-protected 2-methylindole-3-carbaldehyde and 2-benzylindole-3-carbaldehyde as dienamine precursors were undertaken, but no reactivity was observed in these cases.

Subsequent investigations were focused on the synthetic applications of the obtained product **3a** (Scheme 5).

Scheme 5. Selected Transformations of the Product 3a



Reduction using $NaBH_4$ provided alcohol **7** in 78% yield. Moreover, cerium chloride promoted the reaction with *o*-phenylenediamine, affording chiral diazepine **8**. In these two cases, reactions proceeded with full preserevation of the stereochemical composition of **3a**, as products **7** and **8** were obtained as single diastereomers. It was also demonstrated that cycloadduct **3a** can be transformed using DDQ as an oxidant

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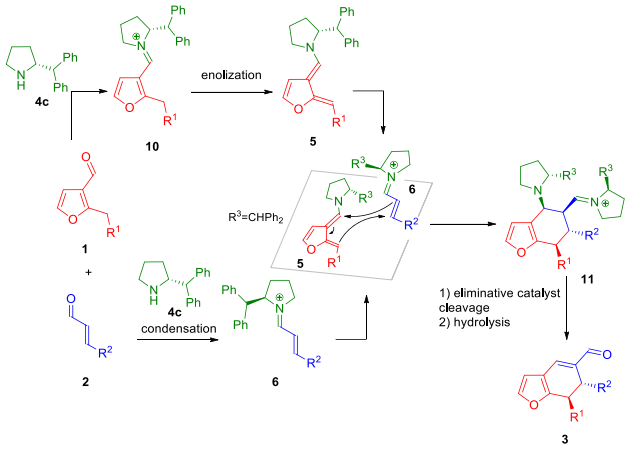
into a highly functionalized benzofuran-5-carbaldehyde **9** with loss of all stereogenic centers.

The absolute configuration of **3a** was determined by the X-ray analysis of a single crystal as (6*S*,7*S*) (see the Supporting Information for further details). The stereochemistry of products **3b**–**o** was assigned by analogy given the assumption that changes in the substitution pattern of products do not have any impact on the mechanism of the cycloaddition. With the knowledge of the stereochemical reaction outcome, the possible reaction mechanism was proposed (Scheme 6).

Scheme 6. Differentiating Catalysis in the [4 + 2]-Cycloaddition: Mechanistic Considerations



The main role is played by the aminocatalyst **4c** which is responsible for the activation and differentiation of both substrates: (1) it forms the dienamine **5** by dearomatization of heteroaryl aldehyde **1** (HOMO-rising differention) and (2) it independently activates α,β-unsaturated aldehyde **2** through LUMO-lowering iminium ion differentiation. Intermediates **5** and **6** subsequently participate in the *endo*-selective Diels–Alder cycloaddition with the steric interactions between bulky groups in the 2-position of the pyrrolidine units present in both diene **5** and dienophile **6** governing the approach. In the next step, after aromative cycloaddition, iminium ion **11** undergoes eliminative cleavage of catalyst and hydrolysis to obtain target product **3**. Moreover, the postulated mechanism involving two molecules of the catalyst was confirmed by the nonlinear effects studies, which indicated the positive nonlinear effect (for more information, see the Supporting Information).

In conclusion, we demonstrated that differentiating catalysis constitutes a powerful tool for the stereoselective synthesis functionalization of carbonyl compounds. The cycloaddition reaction between **1** and α,β-unsaturated aldehydes **2** was realized through the combination of dearomative dienamine **5** and iminium ion activations, thus providing high enantio- and diastereoselectivity of the transformation. The scope and limitations of the process were carefully studied and the stereochemical model of the reaction was proposed. Moreover, useful synthetic transformations of product **3a** were elaborated.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c04328.

Complete experimental procedures, characterization of the products, X-ray data for **3a**, NMR data, and UPC^2 traces (PDF)

Accession Codes

CCDC 2103952 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) Schreiber, S. L. Target-oriented and diversity-oriented organic synthesis in drug discovery. *Science* **2000**, *287*, 1964–1968.

(2) (a) Masamune, S.; Choy, W. Advances in Stereochemical Control: The 1, 2- and 1, 3-Diol Systems. *Aldrichimica Acta* **1982**, *15*, 47–63. (b) Masamune, S. Recent Advances in Stereochemical Control: Multiple Asymmetric Induction. *Heterocycles* **1984**, *21*, 107–136. (c) Masamune, S.; Choy, W.; Petersen, J. S.; Sita, L. R. Double Asymmetric Synthesis and a New Strategy for Stereochemical Control in Organic Synthesis. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 1–30. (d) Sato, T.; Abiko, A.; Masamune, S. Double Asymmetric Synthesis: a New Strategy for Stereochemical Control in Organic Synthesis. *J. Synth. Org. Chem. Jpn.* **1986**, *44*, 309–384.

(3) (a) Du, Z.; Shao, Z. Combining Transition Metal Catalysis and Organocatalysis − an Update. *Chem. Soc. Rev.* **2013**, *42*, 1337–1378. (b) Chen, D.-F.; Han, Z.-Y.; Zhou, X.-L.; Gong, L.-Z. Asymmetric Organocatalysis Combined with Metal Catalysis: Concept, Proof of Concept, and Beyond. *Acc. Chem. Res.* **2014**, *47*, 2365–2377. (c) Kim, U. B.; Jung, D. J.; Jeon, H. J.; Rathwell, K.; Lee, S. Synergistic Dual Transition Metal Catalysis. *Chem. Rev.* **2020**, *120*, 13382–13433.

(d) Martínez, S.; Veth, L.; Lainer, B.; Dydio, P. Challenges and Opportunities in Multicatalysis. *ACS Catal.* **2021**, *11*, 3891−3915.

(4) For representative examples involving aminocatalysis, see: (a) Hong, B.-C.; Wu, M.-F.; Tseng, H.-C.; Liao, J.-H. Enantioselective Organocatalytic Formal [3 + 3]-Cycloaddition of α,β-Unsaturated Aldehydes and Application to the Asymmetric Synthesis of (−)-Isopulegol Hydrate and (−)-Cubebaol. *Org. Lett.* **2006**, *8*, 2217−2220. (b) Bench, B. J.; Liu, C.; Evett, C. R.; Watanabe, C. M. H. Proline Promoted Synthesis of Ring-Fused Homodimers: Self-Condensation of α,β-Unsaturated Aldehydes. *J. Org. Chem.* **2006**, *71*, 9458−9463. (c) de Figueiredo, R. M.; Frohlich, R.; Christmann, M. Amine-Catalyzed Cyclizations of Tethered α,β-Unsaturated Carbonyl Compounds. *Angew. Chem., Int. Ed.* **2008**, *47*, 1450−1453. (d) McLeod, D.; Izzo, J. A.; Jørgensen, D. K. B.; Lauridsen, R. F.; Jørgensen, K. A. Development and Investigation of an Organocatalytic Enantioselective [10 + 2] Cycloaddition. *ACS Catal.* **2020**, *10*, 10784−10793. (e) Curti, C.; Rassu, G.; Lombardo, M.; Zambrano, V.; Pinna, L.; Battistini, L.; Sartori, A.; Pelosi, G.; Zanardi, F. Unlocking Access to Enantiopure Fused Uracils by Chemodivergent [4 + 2] Cross-Cycloadditions: DFT-Supported Homo-Synergistic Organocatalytic Approach. *Angew. Chem., Int. Ed.* **2020**, *59*, 20055−20064. (f) Lu, J.-B.; Shi, C.-H.; Hu, D.; Gao, X.-Y.; Chen, Z.-C.; Du, W.; Chen, Y.-C. Regioselectivity Umpolung in Asymmetric Diels−Alder Reaction of ortho-Formyl-Substituted Cinnamates and Dienals via Double Aminocatalysis. *Org. Lett.* **2021**, *23*, 145−149.

(5) For selected reviews, see: (a) List, B. The ying and yang of asymmetric aminocatalysis. *Chem. Commun.* **2006**, 819−824. (b) Erkkila, A.; Majander, I.; Pihko, P. M. Iminium Catalysis. *Chem. Rev.* **2007**, *107*, 5416−5470. (c) Mukherjee, S.; Yang, J. W.; Hoffmann, S.; List, B. Asymmetric Enamine Catalysis. *Chem. Rev.* **2007**, *107*, 5471−5569. (d) Melchiorre, P.; Marigo, M.; Carlone, A.; Bartoli, G. Asymmetric Aminocatalysis−Gold Rush in Organic Chemistry. *Angew. Chem., Int. Ed.* **2008**, *47*, 6138−6171. (e) Jiang, L.; Chen, Y.-C. Recent advances in asymmetric catalysis with cinchona alkaloid-based primary amines. *Catal. Sci. Technol.* **2011**, *1*, 354−365. (f) Melchiorre, P. Cinchona-based Primary Amine Catalysis in the Asymmetric Functionalization of Carbonyl Compounds. *Angew. Chem., Int. Ed.* **2012**, *51*, 9748−9770.

(6) (a) Li, J.-L.; Liu, T.-Y.; Chen, Y.-C. Aminocatalytic asymmetric Diels-Alder reactions *via* HOMO activation. *Acc. Chem. Res.* **2012**, *45*, 1491−1500. (b) Ramachary, D. B.; Reddy, Y. V. Dienamine Catalysis: An Emerging Technology in Organic Synthesis. *Eur. J. Org. Chem.* **2012**, *2012*, 865−887. (c) Kumar, I.; Ramaraju, P.; Mir, N. A. Asymmetric trienamine catalysis: new opportunities in amine catalysis. *Org. Biomol. Chem.* **2013**, *11*, 709−716. (d) Jiang, H.; Albrecht, Ł.; Jørgensen, K. A. Aminocatalytic remote functionalization strategies. *Chem. Sci.* **2013**, *4*, 2287−2300. (e) Jurberg, I. D.; Chatterjee, I.; Tannert, R.; Melchiorre, P. When asymmetric aminocatalysis meets the vinylogy principle. *Chem. Commun.* **2013**, *49*, 4869−4883. (f) Hepburn, H. B.; Dell'Amico, L.; Melchiorre, P. Enantioselective Vinylogous Organocascade Reactions. *Chem. Rec.* **2016**, *16*, 1787−1806. (g) Marcos, V.; Alemán, J. Old tricks, new dogs: organocatalytic dienamine activation of α,β-unsaturated aldehydes. *Chem. Soc. Rev.* **2016**, *45*, 6812−6832. (h) Pawar, T. J.; Mitkari, S. B.; Peña-Cabrera, E.; Villegas Gómez, C. V.; Cruz Cruz, D. Polyenals and Polyenones in Aminocatalysis: A Decade Building Complex Frameworks from Simple Blocks. *Eur. J. Org. Chem.* **2020**, *2020*, 6044−6061.

(7) For reviews, see: (a) Xiao, B.-X.; Gao, X.-Y.; Du, W.; Chen, Y.-C. Asymmetric Reactions involving Lewis Base Catalyst Tethered Dearomatized Intermediates. *Chem. − Eur. J.* **2019**, *25*, 1607−1613. (b) Przydacz, A.; Skrzyńska, A.; Albrecht, Ł. Breaking Aromaticity with Aminocatalysis: A Convenient Strategy for Asymmetric Synthesis. *Angew. Chem., Int. Ed.* **2019**, *58*, 63−73. For selected examples, see: (c) Liu, Y.; Nappi, M.; Arceo, E.; Vera, S.; Melchiorre, P. Asymmetric Catalysis of Diels−Alder Reactions with in Situ Generated Heterocyclic ortho-Quinodimethanes. *J. Am. Chem. Soc.* **2011**, *133*, 15212−15218. (d) Skrzyńska, A.; Przydacz, A.; Albrecht, Ł. Organocatalytic Nonclassical Trienamine Activation in the Remote Alkylation of Furan Derivatives. *Org. Lett.* **2015**, *17*, 5682−5685. (e) Duan, C.-Q.; He, X.-L.; Du, W.; Chen, Y.-C. Asymmetric [4 + 2] cycloadditions with 3-furfural derivatives and α-cyano-α,β-unsaturated ketones. *Org. Chem. Front.* **2018**, *5*, 2057−2060. (f) He, X.-L.; Zhao, H.-R.; Duan, C.-Q.; Han, X.; Du, W.; Chen, Y.-C. Asymmetric Benzylic Allylic Alkylation Reaction of 3-Furfural Derivatives by Dearomatizative Dienamine Activation. *Chem.—Eur. J.* **2018**, *24*, 6277−6281. (g) Bojanowski, J.; Skrzyńska, A.; Albrecht, A. Dearomatizative and Decarboxylative Reaction Cascade in the Aminocatalytic Synthesis of 3,4-Dihydrocoumarins. *Asian J. Org. Chem.* **2019**, *8*, 844−848. (h) Dyguda, M.; Przydacz, A.; Krzemińska, A.; Albrecht, Ł. On the origins of stereoselectivity in the aminocatalytic remote alkylation of 5-alkylfurfurals. *Org. Biomol. Chem.* **2019**, *17*, 6025−6031. (i) Hu, D.; Gao, Y.; Song, X.; Du, W.; Chen, Y.-C. Asymmetric Remote Addition Reactions of Heterocycle-Based Dearomative Dienamine or Trienamine Species to 1-Azadienes: Application to Construct Chiral Azocanes and Azecanes. *Eur. J. Org. Chem.* **2020**, *2020*, 514−518. (j) Przydacz, A.; Dyguda, M.; Topolska, A.; Skrzyńska, A.; Xu, C.-J.; Chen, Y.-C.; Albrecht, Ł. Doubly vinylogous and doubly rearomative functionalization of 2-alkyl-3-furfurals. *Org. Biomol. Chem.* **2020**, *18*, 5816−5821. (k) Skrzyńska, A.; Frankowski, S.; Topolska, A.; Dyguda, M.; Gao, X.-Y.; Xu, C. J.; Chen, Y.-C.; Albrecht, Ł. Enantioselective H-bond-directed vinylogous iminium ion strategy for the functionalization of vinyl-substituted heteroaryl aldehydes. *Chem. Commun.* **2021**, *57*, 1667−1670. For related Brønsted base-catalyzed dearomative reaction of heteroaromatic aldehydes, see: (l) Wang, Y.; Lin, J.-B.; Xie, J.-K.; Lu, H.; Hu, X.-Q.; Xu, P.-F. Dearomative Dienolate-Mediated Catalysis: A Remote Activation Strategy for Asymmetric Functionalization of Benzylic C − H Bonds of Heteroaryl Aldehydes. *Org. Lett.* **2018**, *20*, 5835−5839.

(8) During the preparation of this manuscript, a complementary approach involving [4 + 2] cycloaddition between dearomative trienamine and iminium ion was reported: Ming, Y.-C.; Lv, X.-J.; Liu, M.; Liu, Y.-K. Synthesis of Chiral Polycyclic Tetrahydrocarbazoles by Enantioselective Aminocatalytic Double Activation of 2-Hydroxycinnamaldehydes with Dienals. *Org. Lett.* **2021**, *23*, 6515−6519.

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