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Asymmetric Aminalization via Cation-Binding Catalysis

Sang Yeon Park,[+a] Yidong Liu,[+b] Joong Suk Oh,[a] Yoo Kyung Kweon,[a] Yong Bok Jeong,[a] Mengying Duan,[b] Yu Tan,[b] Ji-Woong Lee,*[c] Hailong Yan*[b] and Choong Eui Song*[a]

Abstract: Asymmetric cation-binding catalysis, in principle, can generate "chiral" anionic nucleophiles, where the counter cations are coordinated within chiral environments. Nitrogen-nucleophiles are intrinsically basic, therefore, its use as nucleophiles is often challenging and limiting the scope of the reaction. Particularly, a formation of configurationally labile aminal centers with alkyl substituents has been a formidable challenge due to the enamine/imine equilibrium of electrophilic substrates. Herein, we report enantioselective nucleophilic addition reactions of potassium phthalimides to Boc-protected alkyl- and aryl-substituted α-amido sulfones. *In-situ* generated imines smoothly reacted with the nitrogen nucleophiles to corresponding aminals with good to excellent enantioselectivitiy under mild reaction conditions. In addition, transformation of aminal products gave biologically relevant pyrrolidinone-fused hexahydropyrimidine scaffold with excellent stereoselectivity and good yield.

Chiral aminals, or geminal diamines, are attractive structural motifs in numerous natural products and pharmaceuticals.[1] For example, pyrrolidine-fused hexahydropyrimidine frameworks with aminal stereogenic centers are found in the skeletons of many natural products (Figure 1a).[2] Acyclic *N*-protected chiral aminals have also often been incorporated into peptide chains to provide partially modified *retro-inverso* (PMRI) peptide mimics, which can alter physical and chemical properties of pharmacologically active peptides (Figure 1b).[3] Chiral Brønsted acid can catalyze aminal formation reactions in high enantioselectivity with aromatic imine substrates and nitrogen nucleophiles (i.e. sulfonamides[4a] and imides[4b]).[4–6] However, aminal stereogenic centers are difficult to access particularly with aliphatic imine substrates due to the acidic α-protons and rapid tautomerization under acidic conditions. Therefore, chiral and strong Brønsted acids are presumably impotent to generating aminal stereogenic centers for aliphatic imines.[7] It is noteworthy that aminals with saturated carbons are more pertinent structural motifs in biologically active molecules, since their predominant aminal stereogenic centers are correspondent to aliphatic substrates (see Fig. 1a). In addition, to the best of our knowledge, there is no examples of functional group transformation with enantioenriched aminal products, which can be highly valuable in syntheses of numerous enanioenriched nitrogen-based heterocycles.

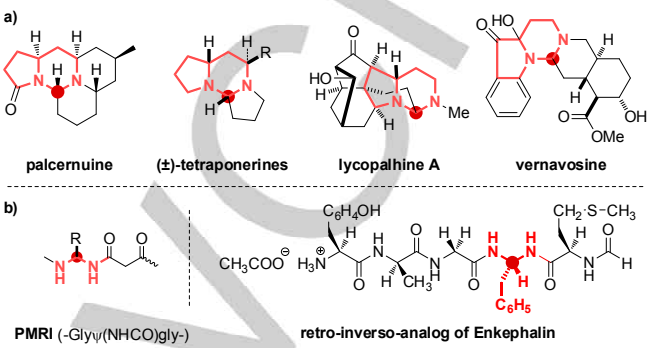

Figure 1. a) Natural products with pyrrolidine-fused hexahydropyrimidines with aminal stereogenic centers. b) Examples of PMRI.

In this study, we describe an asymmetric aminal formation reaction from α-amido sulfones[8] as *in-situ* equivalents of imines[9] with potassium phthalimides using our cation-binding catalyst **1** (Figure 2).[10] The scope of this new catalytic protocol was not limited to aromatic or heteroaromatic imines. Aliphatic substrates, regardless the degree of branching, also provided the desired aminals with excellent yields and ees. To the best of our knowledge, this is the first successful preparation of chiral primary, secondary, and tertiary aliphatic acyclic aminal derivatives in high enantiopurity. Derivatization of enantioenriched aminals were also realized, showing the unprecedented application potential of the enantiopure aminals in asymmetric syntheses of natural products and biologically active molecules.

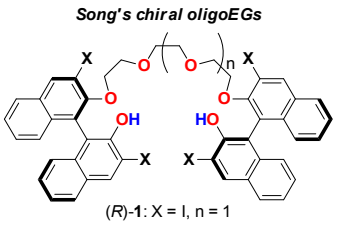

Figure 2. Song's chiral oligo ethylene glycol(EG)s.

Asymmetric cation-binding catalysis is to generate reactive "chiral" anions (nucleophiles) from achiral salts by binding to their counter cations with a catalyst in the "chiral cage" of the catalyst.[11] Recently, we have successfully expanded the scope of cation-binding catalysis by employing Song's chiral oligoEGs (Figure 2),[10] in which the ether oxygens act as Lewis base to coordinate metal ions such as K^+, thus generating a soluble chiral anion in a confined chiral space. Moreover, the terminal phenol groups are capable of simultaneously activating electrophiles by hydrogen bonding interactions. The resulted

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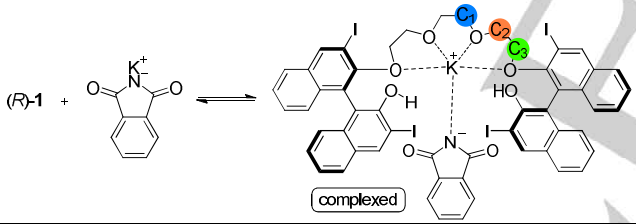
self-assembled transition state leads to excellent stereoinduction in asymmetric reactions; for example, in desilylative kinetic resolution of silyl-protected secondary alcohols,[10b] asymmetric Strecker reaction using potassium cyanide,[10c] kinetic resolution of β-sulfonyl ketones through enantioselective β-elimination,[10d] organocatalytic asymmetric synthesis of chiral dioxazinanes and dioxazepanes with in situ generated nitrones,[10e] enantioselective synthesis of anti−syn-trihalides and anti−syn−anti-tetrahalides via asymmetric β-elimination,[10f] and enantioselective glyoxalase I mimic catalytic isomerization of in-situ generated hemithioacetals,[10g] etc. The vast application potential of this catalytic system stimulated us to explore other challenging asymmetric transformations with nucleophilic anions.[10h] It is worth noted here that there was no cation-binding catalysis with nitrogen-based nucleophiles prior to this study. We presumed that cation-binding catalysis could be suitable for the reaction of potassium phthalimide with α-amido sulfones **2**, in which potassium phthalimide, upon the activation by the chiral cation-binding catalyst, may effectively serve as both the base and the nucleophile for addition reactions.

First, we examined the bimolecular complexation; nitrogen nucleophiles and catalyst (*R*)-**1**. ^{13}C Spin-lattice relaxation time (T_1) decreased dramatically upon the complexation of **1** with potassium phthalimide (Table 1). This indicates that the complexation of the potassium cation with catalyst **1** reduced the mobility of the ether units on the host (**1**).[12] Further evidence of the complexation of the catalyst (**1**) with potassium phthalimide was observed by ESI-HRMS (positive ion mode, calculated for $C_{46}H_{34}I_4KO_6^+$: 1228.8166; observed: 1228.8167) (see Supporting Information, Figure S1).

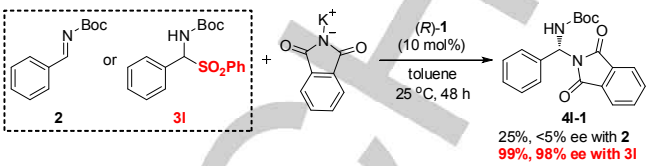
Table 1. ^{13}C Spin-lattice relaxation measurements[a]



Sample (0.075 M)	T_1 [s]		
	C_1	C_2	C_3
(*R*)-**1**	0.364	0.397	0.604
(*R*)-**1**/K^+ salt (1/1)	0.163	0.223	0.203
T_1 ((*R*)-**1**)/T_1 (complex)	**2.23**	**1.78**	**2.97**

[a] The NMR experiments were performed in $CDCl_3$ at 22 °C.

Confirming that a phthalimide anion can be associated within the chiral ologoEGs, we performed catalytic reactions with imine **2** as a model substrate. However, we observed only low yield and disappointing enantioselectivity (25% yield, <5% ee, Scheme 1). Notably, α-amido sulfone **3a** – imine precursor – showed complete conversion and excellent enantioselectivity (99% yield, 98% ee) under same reaction conditions (see Supporting Information for catalyst screening and reaction conditions optimization). This result indicates that the sulfinate leaving group (-SO_2Ph) is critical in both enhancing the reaction rate and the enantioselectivity.[13] Therefore, we decided to use the imine precursor for further study of aminal formation reactions.

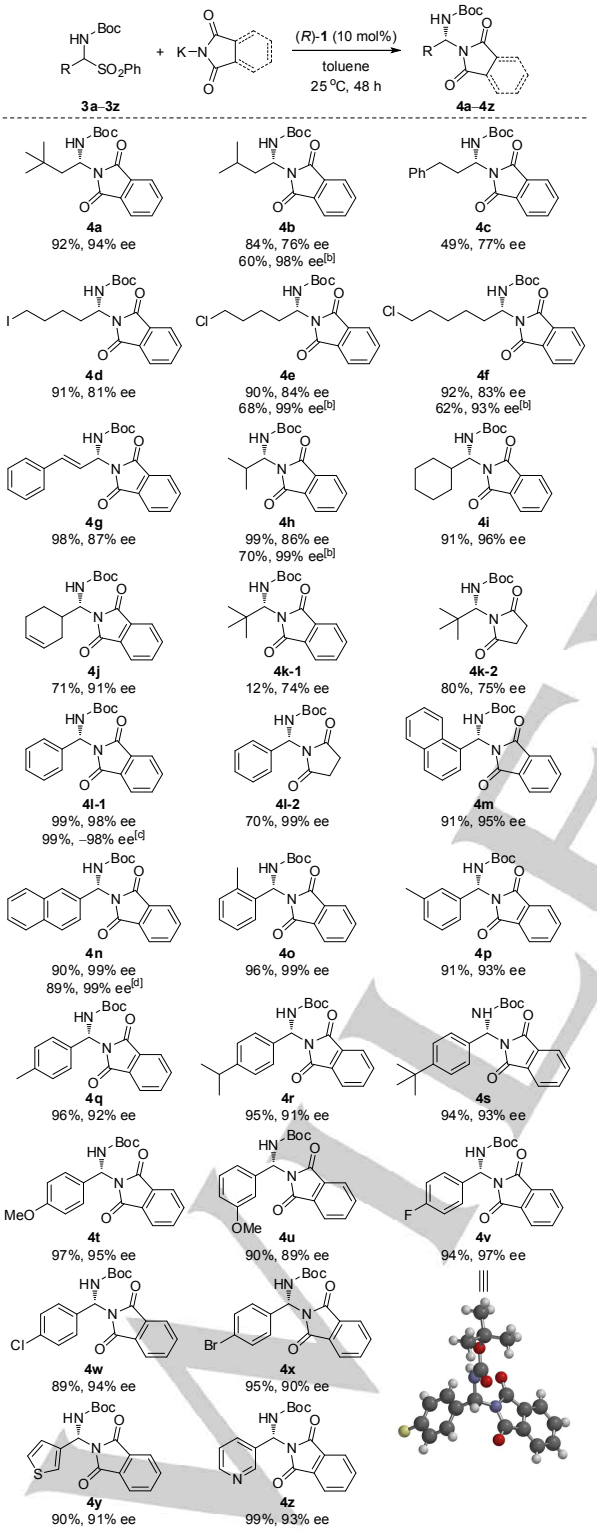


Scheme 1. Catalytic reaction with imine **2** and α-amido sulfone **3l** as substrates.

As mentioned previously, aliphatic substrates are challenging with Brønsted acid catalysis, because of the facile enamine formation and related by-products formed under acidic environments.[7] To our delight, our reaction condition turned out to be highly tolerant to the encarbamate formation. All investigated alkyl chain substituted substrates including highly challenging primary alkyl substituted substrates gave good to excellent chemical yields and enantioselectivities (see **4a**–**4k** in Scheme 2). Moreover, the highly enantiomerically enriched primary alkyl-substituted products (**4b**, **4e** and **4f**) were obtained by a single recrystallization step similar to most of other aminal products **4** (see Supporting Information). However, highly sterically demanding tertiary alkyl substrate **3k** showed slower reaction rates when potassium phthalimide was used (**4k-1**, 12% conversion after 48 h) compared to other aliphatic substrates. The reaction rate, however, was dramatically increased by changing the sterically bulky potassium phthalimide to a sterically less demanding potassium succinimide, (**4k-2**, 80% conversion after 48 h). These results implies that the catalysis proceeds in a sterically congested chiral cage, generated by binding a potassium cation with the polyether backbone, ensuring high enantio-induction. To the best of our knowledge, this is the first catalytic preparation of chiral primary, secondary, and tertiary aliphatic aminal derivatives, presumably due to the mild acidity of the catalyst. The acitidty of the catalyst might be enough to activate the substrates but not to facilitate the tautomerization. For aromatic substrates, both the electron-donating (**3o**–**3u**) and electron-withdrawing substituents (**3v**–**3x**) on the aromatic ring were equally tolerated under the reaction conditions. Electron-donating substituents in ortho-, meta-, or para-positions were all shown to be excellent substrates for the addition. Likewise, the use of electron withdrawing substituents on the para-position of the phenyl-substituted imines also afforded high yields and enantiomeric excess of the addition products. Sterically demanding imine **3m** was also smoothly converted to the corresponding aminal **4m** (91%, 95% ee). Heteroaromatic substrates such as 3-thienyl (**3y**) and 3-pyridyl (**3z**) also gave excellent yields and enantioselectivities. The absolute configuration of **4v** was unambiguously determined by a single crystal X-ray structure analysis.[14] Moreover, X-ray crystal structure can explain the configurational stability of acyclic aminals obtained in this study. The aminals are stabilized by intramolecular hydrogen bonding between BocNH proton and

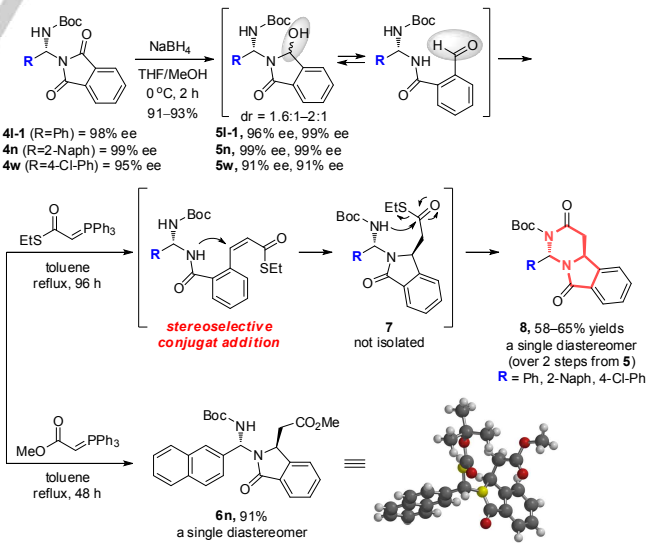
carbonyl oxygen atom of phthaimide group (length: NH---O = 2.705 Å, see SI for structural information of **4v**).[15]

Scheme 2. Substrate scope of the 1,2-addition of imide with aliphatic and aromatic α-amido sulfones **3a**–**3z**[a]



[a] Unless otherwise indicated, the reactions were performed with **3** (0.1–0.5 mmol), 1.1 equiv. of potassium phthalimide and (*R*)-**1** catalyst (10 mol%) in toluene at 25 °C. See Supporting Information for reaction condition optimization study including catalyst screening. [b] Recrystallization from methylcyclohexane. [c] Using (*S*)-**1** catalyst. [d] Reaction was performed on a 1.2 gram scale.

To demonstrate the synthetic utility of the obtained chiral aminals, we attempted asymmetric syntheses of pyrrolidine-fused hexahydropyrimidine scaffold, which are found in the skeletons of many natural alkaloids (Figure 1a).[2] Chemo-selective reductions of **4l-1**, **4n** and **4w** with $NaBH_4$ afforded *N,O*-hemiaminals **5** with low diastereoselectivity (dr = 1.6:1 – 2:1). However, in the reaction mixture, compounds **5** are in equilibrium between *N,O*-acetal and aldehyde, which will be consumed selectivity when it is in the aldehyde form. Gratifyingly upon the addition of Wittig reagents (Ph_3P=CHC(O)OMe or Ph_3P=CHC(O)SEt) to aldehyde form, the resulting products rapidly underwent tandem diastereoselective 1,4-addition reaction, affording single diastereomeric β-amino ester **6** and β-amino thioesters **7**. In the case of thioesters **7**, we observed simultaneously cyclized *in-situ* to furnish hexahydropyrimidinopyrrolidines **8** as a single diastereomer in good yields (58–65% yields over 2 steps, see Supporting Information for experimental and calculation details) (Scheme 3). Furthermore, we performed the deprotection of Boc group of compound **8n** using 1M HCl in Et_2O solution afforded the free amine compound without epimerization (see Supporting Information for details). The tricyclic core of aminals **8** can be a valuable synthon, recognizing that further derivatization is amenable on two differentiated carbonyls, Boc-protecting group and the secondary amine. The absolute configuration of **6n** was determined to be (*S,S*) by X-ray single crystallography. The absolute configuration of **7** was assigned by analogy.[16]



Scheme 3. Utility of chiral aminals in the enantioselective synthesis of some pyrrolidine-fused hexahydropyrimidines.

Our proposed catalytic mechanism depicted in Fig. 3 involves initial simultaneous activation of potassium phthalimide and amido sulfone by the catalyst. Subsequently, the coordinated phthalimide anion can eliminate the potassium sulfinate from the substrate, generating a catalyst-bound imine (H-bonded). We confirmed the formation of imine by ^{1}H-NMR spectroscopy (see Supporting Information, Figure S2). Subsequently, phthalimide **9** (**HNR$_2$** in Figure 3) is able to react with the imine, with high enantioselectivity, providing aminals (up to 99% ee). The coordination of potassium sulfinate within the catalyst cavity seems vital, based on the experimental data and previous mechanistic studies.

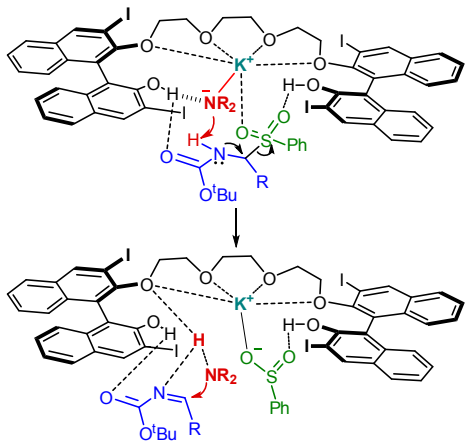
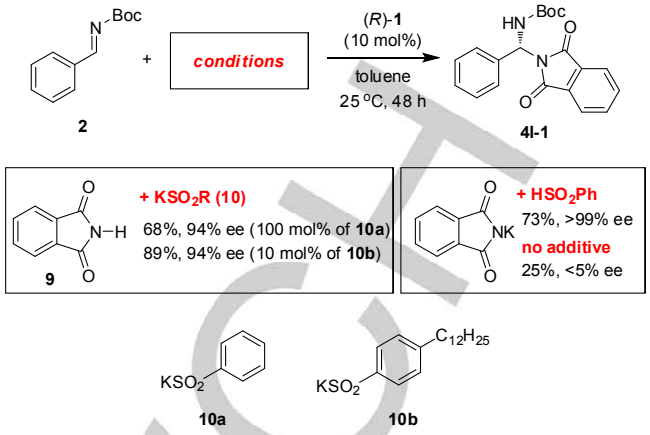


Figure 3. Plausible reaction transition state.

To support this hypothesis, pre-isolated imine **2** were reacted with phthalimide **9** in the presence of additional potassium arene sulfinates **10**. Potassium sulfinate salts are in general not soluble in organic solvents, however, the complexation of cation-binding catalyst **1** and the sulfinate salt is expected in catalytic amounts. We obtained 94% ee of the desired product with 100 mol% of insoluble sulfinate **10a**, mimicking the optimized reaction conditions. In addition, catalytic amounts (10 mol%) of *soluble* sulfinate **10b** was found to be effective to afford identical enantioselectivity (94% ee, Scheme 4). These reactions indicate that the nucleophile of the enantioselective reaction is phthalimide **9**. Also, under otherwise identical reaction conditions, imine **2** failed to give observable conversion and enantioselectivity without the addition of sulfinate ion. Lastly, but not the least, the pre-mixture of potassium phthalimide and sulfinic acid furnished 99% ee of the product (73% yield) under catalytic conditions, which highlight the importance of the sulfinate anion in the enantiodetermining step and catalytic activity as well.



Scheme 4. Critical effects of potassium sulfinate for the catalysis.

According to the above experimental results, an incorporation of the potassium sulfinate is critical. As a cocatalyst, sulfinate anions induced high reactivity and high enantioselectivity, perhaps by increasing the proximity of substrates. The complexation of potassium sulfinate with the catalyst was also confirmed in the measurements of ^{13}C spin-lattice relaxation (T_1) and ESI-HRMS (see Supporting Information, Table S2 and Figure S3). Furthermore, a linear relationship was observed between the optical purity of catalyst (*R*)-**1** and product **4i** (see Supporting Information, Figure S4), indicating that a single catalyst involves in the enantio-determining step, supporting our proposed model shown in Figure 3.

In summary, we developed a new asymmetric nucleophilic addition of potassium phthalimide with α-amido sulfones as imine surrogates, catalyzed by Song's chiral oligoEGs **1** as a cation-binding catalyst. Diverse chiral acyclic aminals were prepared in excellent yields and enatioselectivities (up to 99% ee). In particular, our protocol renders unprecedented and challenging substrate scope, particularly, aliphatic substrates, which are predominant in molecular scaffold of many natural products. A densely confined chiral space can be formed *in-situ* by the incorporation of potassium salt, which enables highly enantio- and chemoselective catalysis. We demonstrated synthetic utility of the current methodology by preparing biologically relevant product, possessing aminal and polyheterocyclic cores.

Experimental Section

General catalytic procedure. An ordinary vial equipped with a magnetic stirring bar, was charged with α-amido sulfone **3** (0.10 mmol), potassium phthalimide (40.7 mg, 0.11 mmol) and the catalyst (*R*)-**1** (11.9 mg, 0.01 mmol). Toluene (1.0 mL) was added at room temperature. After stirring for 48 h, the mixture was filtered and purified by silica gel chromatography (acetone/hexanes = 1/8) to afford the corresponding chiral aminal **4**.

Acknowledgements

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Keywords: cation-binding catalysis • chiral oligoethylene glycol catalyst • α-amido sulfones • N,N-acetals • chiral acyclic aminals

[1] Book without editor: C. Ko, *Synthesis Methods Using Cyclic Acetals and Aminals*, ProQuest, Ann Arbor, 2011.

[2] a) A. Rouchaud, J.-C. Braekman, *Eur. J. Org. Chem.* **2009**, *16*, 2666–2674; b) I. Bosque, J. C. Gonzalez-Gomez, M. I. Loza, J. Brea, *J. Org. Chem.* **2014**, *79*, 3982–3991; c) C.-E. Nge, C.-Y. Gan, K.-H. Lim, K.-N. Ting, Y.-Y. Low, T.-S. Kam, *Org. Lett.* **2014**, *16*, 6330–6333; d) Y. Tang, J. Xiong, Y. Zou, B. Nay, L.-J. Wang, J.-F. Hu, *Chinese Chemical Letters* **2016**, *27*, 969–973; e) B. M. Williams, D. Trauner, *Angew. Chem. Int. Ed.* **2016**, *55*, 2191–2194; f) Y. Ochi, S. Yokoshima, T. Fukuyama, *Org. Lett.* **2016**, *18*, 1494–1496.

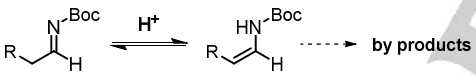
[3] M. D. Fletcher, M. M. Campbell, *Chem. Rev.* **1998**, *98*, 763−795.

[4] a) G. B. Rowland, H. Zhang, E. B. Rowland, S. Chennamadhavuni, Y. Wang, J. C. Antilla, *J. Am. Chem. Soc.* **2005**, *127*, 15696–15697; b) Y. Liang, E. B. Rowland, G. B. Rowland, J. A. Perman, J. C. Antilla, *Chem. Commun.* **2007**, *43*, 4477–4479.

[5] M. Hatano, T. Ozaki, Y. Sugiura, K. Ishihara, *Chem. Commun.* **2012**, *48*, 4986−4988.

[6] Representative examples for catalytic enantioselective synthesis of cyclic aminals, see: a) X. Cheng, S. Vellalath, R. Goddard, B. List, *J. Am. Chem. Soc.* **2008**, *130*, 15786–15787; b) M. Rueping, A. P. Antonchick, E. Sugiono, K. Grenader, *Angew. Chem. Int. Ed.* **2009**, *48*, 908–910.

[7] Spontaneous tautomerization of N-Boc alkyl imines into the corresponding enamines readily occurs even at -20 °C. For the details please see: J. Song, H. W. Shih, L. Deng, *Org. Lett.* **2007**, *9*, 603–606.



[8] For reviews, a) M. Petrini, *Chem. Rev.* **2005**, *105*, 3949–3977; b) B. Yin, Y. Zhang, L. W. Xu, *Synthesis* **2010**, 3583–3595.

[9] For a review on catalytic asymmetric reactions with carbamate-protected imines, see: J. Vaseley, R. Rios, *Chem. Soc. Rev.* **2014**, *43*, 611–630.

[10] a) J.-W. Lee, H. Yan, H. B. Jang, H. K. Kim, S. W. Park, S. Y. Lee, D. Y. Chi, C. E. Song, *Angew. Chem., Int. Ed.* **2009**, *48*, 7683–7686; b) H. Yan, H. B. Jang, J.-W. Lee, H. K. Kim, S. W. Lee, J. W. Yang, C. E. Song, *Angew. Chem., Int. Ed.* **2010**, *49*, 8915–8917; c) H. Yan, J. S. Oh, J.-W. Lee, C. E. Song, *Nat. Commun.* **2012**, *3*, 1212; d) L. Li, Y. Liu, Y. Peng, L. Yu, X. Wu, H. Yan, *Angew. Chem., Int. Ed.*, **2016**, *55*, 331–335; e) Y. Liu, J. Ao, S. Paladhi, C. E. Song, H. Yan, *J. Am. Chem. Soc.*, **2016**, *138*, 16486–16492; f) Y. Tan, S. Luo, D. Li, N. Zhang, S. Jia, Y. Liu, W. Qin, C. E. Song, H. Yan, *J. Am. Chem. Soc.*, **2017**, *139*, 6431–6436; g) S. Y. Park, I. S. Hwang, H. J. Lee, C. E. Song, *Nat. Commun.* **2017**, *8*, 14877; h) S. Y. Park, J. W. Lee, C. E. Song, *Nat. Commun.* **2015**, *6*, 7512; i) V. Vaithiyanathan, M. J. Kim, Y. Liu, H. Yan, C. E. Song, *Chem. Eur. J.*, **2017**, *23*, 1268–1272; j) M. J. Kim, L. Xue, Y Liu, S. Paladhi, S. J. Park, H. Yan, C. E. Song, *Adv. Synth. Catal.*, **2017** *359*, 811–823; k) L. Yu, X. Wu, M. J. Kim, V. Vaithiyanathan, Y. Liu, Y. Tan, W. Qin, C. E. Song, H. Yan, *Adv. Synth. Catal.*, **2017**, *359*, 1879–1891; l) M. Duan, Y. Liu, J. Ao, L. Xue, S. Luo, Y. Tan, W. Qin, C. E. Song, H. Yan, *Org. Lett.*, **2017**, *19*, 2298–2301; m) S. Paladhi, Y. Liu, B S. Kumar, M.-J. Jung, S. Y. Park, H. Yan, C. E. Song, *Org. Lett.*, **2017**, *19*, 3279–3282.

[11] K. Brak, E. N. Jacobsen, *Angew. Chem. Int. Ed.* **2013**, *52*, 534–561.

[12] Y. Li, L. Echegoyen, *J. Org. Chem.* **1994**, *59*, 6539–6542.

[13] Similar results were also observed in the asymmetric Strecker reactions. See the reference [9c].

[14] CCDC 1556761 contains the supplementary crystallographic data for compound **4v**. (see Supporting Information).

[15] For examples for acyclic aminals stabilized by intramolecular hydrogen bonding, see: a) G. Koz, D. Astley, S. T. Astley, *Z. Naturforsch.* **2013**, *68b*, 57–63; b) E. Galvez, I. Iriepa, A. Lorente, J. M. Mohedano, F. Florencio, S. Garcia-Blanco, *Can. J. Chem.* **1987**, *65*, 687–692; c) E. Galvez, A. Lorente, I. Iriepa, F. Florencio, S. Garcia-Blanco, *J. Mol. Struct.* **1986**, *142*, 447–450.

[16] CCDC 1555424 contains the supplementary crystallographic data for compound **6n**. (see Supporting Information).

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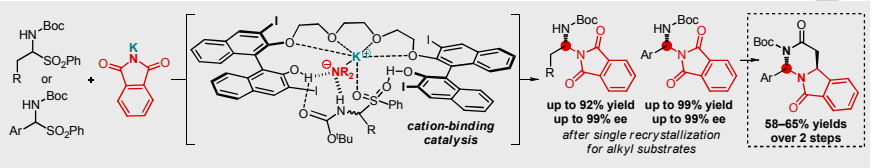

Diverse chiral acyclic aminals were prepared in excellent yields and enatioselectivities (up to 99% ee) via cation-binding catalysis. In particular, the present protocol renders unprecedented and challenging substrate scope, particularly, aliphatic substrates, which are predominant in molecular scaffold of many natural products. The synthetic utility of the current methodology was also demonstrated by preparing biologically relevant product, possessing aminal and polyheterocyclic cores.

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