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Generation and exploitation of acyclic azomethine imines in chiral Brønsted acid catalysis

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Successful implementation of a catalytic asymmetric synthesis strategy to produce enantiomerically enriched compounds requires the adoption of suitable prochiral substrates. The combination of an azomethine imine electrophile with various nucleophiles could give straightforward access to a number of synthetically useful chiral hydrazines, but is used rarely. Here we report the exploitation of acyclic azomethine imines as a new type of prochiral electrophile. They can be generated *in situ* by the condensation of *N′*-benzylbenzoylhydrazide with a variety of aldehydes in the presence of a catalytic amount of an axially chiral dicarboxylic acid. By trapping these electrophiles with alkyl diazoacetate or (diazomethyl)phosphonate nucleophiles, we produced a diverse array of chiral α-diazo-β-hydrazino esters and phosphonates with excellent enantioselectivities.

Chiral organic compounds with a hydrazine moiety are found in a variety of natural and synthetic biologically active compounds, as represented by piperazimycins[1,2] (potent cancer-cell cytotoxins) and the antiretroviral drug atazanavir[3,4]. In addition, they have many applications as the synthetic precursors of chiral amines, which can be generated easily by reductive cleavage of the N–N bond. To date, one of the most reliable and flexible methods for the asymmetric synthesis of chiral hydrazines is the catalytic asymmetric addition of nucleophiles to prochiral hydrazones, as a diverse array of enantiomerically enriched hydrazines can be obtained by judiciously choosing nucleophilic reaction partners and catalysts[5–9]. However, hydrazones are intrinsically less electrophilic than the corresponding imines[10], a drawback that means their application in asymmetric catalysis has been limited and has left untouched the possibility of using many mild nucleophiles in the synthetic toolbox. A promising and innovative, but as yet unexplored strategy to overcome this issue is to develop more reactive, highly electrophilic, substrates that are structurally related to hydrazones.

In this context, *N*-acyl azomethine imines, with the key $C{=}N^{+}{-}N^{-}$ 1,3-dipole structure, are powerful candidates because their structural similarity to hydrazones and their inherent ionic property could be beneficial in terms of reactivity (Fig. 1a). In the literature, *N,N′*-cyclic azomethine imines **I** are utilized widely in asymmetric catalysis in the context of 1,3-dipolar cycloadditions[11–13]; a couple of notable examples using these templates for nucleophilic additions were published recently[14,15]. In addition, *C,N*-cyclic azomethine imines **II** emerged as a viable option in our research[16,17]. However, acyclic azomethine imines **III**, which are ideal substrates as hydrazone surrogates of high generality, have not been the subject of asymmetric catalysis.

A straightforward method to access acyclic azomethine imines is the simple condensation of the corresponding aldehydes and *N′*-alkylacylhydrazides **IV** (Fig. 1b)[18–21]. Oppolzer's seminal study indicates that they are reluctant to form azomethine imines by simple condensation and remain at the stage of the hydrates **V** (refs 18–21). Accordingly, it is considered necessary to generate the labile species **III** via the azeotropic removal of water from the reaction flask, in sharp contrast to other *N,N′*-cyclic and *C,N*-cyclic azomethine imines, which are prepared as isolable materials. Although the thus-generated acyclic azomethine imines have some application in 1,3-dipolar cycloadditions[22–24], the requisite harsh reaction conditions are apparently not suitable for use in asymmetric catalysis.

Nevertheless, there are some indications that the generation of acyclic azomethine imines could be facilitated by the action of acid additives, which resembles the well-known acid-catalysed promotion of imine formation from the corresponding hemiaminals. A study by Kanemasa *et al.* revealed that treatment of a hydrate form of acyclic azomethine imines (**V**) with acetic acid in the presence of a dipolarophile provided the corresponding cycloadduct at room

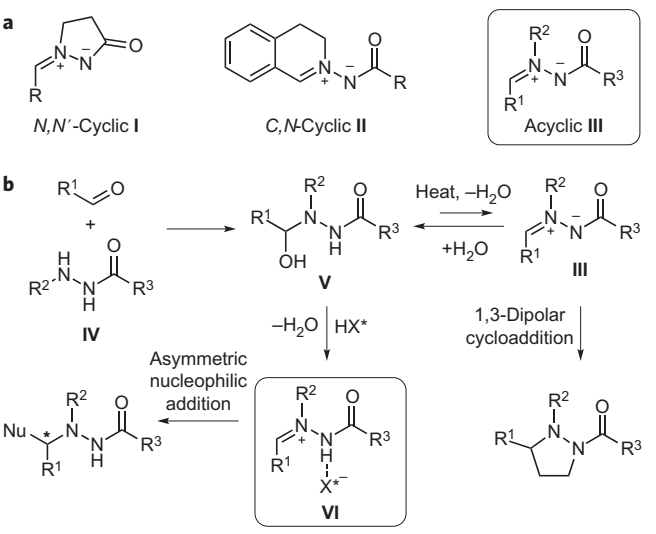

Figure 1 | Classification and reactivity of azomethine imines. a, Azomethine imines can be split into three classes, *N,N′*-cyclic (**I**), *C,N*-cyclic (**II**) and acyclic (**III**). Acyclic azomethine imines (**III**) are difficult to generate and have thus not been explored as electrophiles in asymmetric catalysis. **b**, Acyclic azomethine imines are normally generated under harsh thermal conditions. We assumed that the related acyclic azomethine imminium ion **VI** could be generated in the presence of a chiral Brønsted acid (HX*) and then exploited as prochiral electrophiles for asymmetric nucleophilic addition.

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temperature, which suggests the possibility that an acid additive accelerates the formation of acyclic azomethine imines from their hydrates[25]. Even more clearly, our work and that by Tamura *et al.* on *C*,*N*-cyclic azomethine imines, which are prone to form the corresponding hydrates in the presence of excess water or alcohols, showed that protonation of these azomethine imines or hydrates resulted in the formation of stable azomethine iminium salts[16,26]. In addition, a literature survey revealed a single report by Portlock *et al.* that the Petasis reaction of *N*′-alkyl-*N*-carbamoylhydrazides, glyoxylic acid and arylboronic acids gave racemic α-hydrazino acids. Presumably, this proceeded via the formation of an acyclic azomethine imine and the nucleophilic addition of arylboronic acid, although neither the intermediacy of the azomethine imine nor the effect of acidic conditions derived from the use of glyoxylic acid as substrate was described[27].

Taking these facts into consideration, we set out to investigate the possibility of generating the elusive acyclic azomethine imines in the presence of a catalytic amount of chiral Brønsted acid[28,29] and trapping the thus-activated azomethine iminium salt **VI** by a mild nucleophile in an asymmetric manner to give chiral hydrazines.

Results and discussion

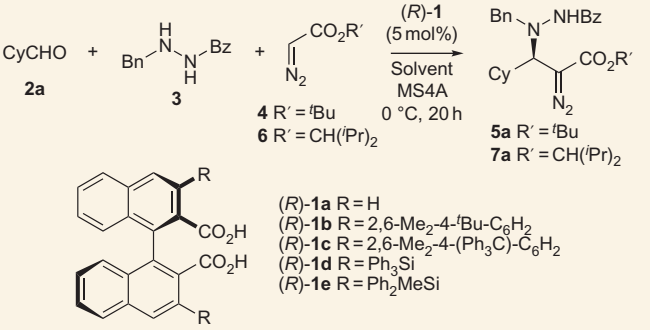
We began our research to realize this unestablished but highly promising synthetic procedure by building on the use of the axially chiral dicarboxylic acid **1**, originally developed in our laboratory as a highly efficient chiral Brønsted acid catalyst[17,30–34]. As a model, we set up a three-component reaction system[35] composed of cyclohexanecarbaldehyde **2a** and *N*′-benzylbenzoylhydrazide **3** to generate a postulated protonated acyclic azomethine imine under the influence of the catalyst (*R*)-**1b** and *t*-butyl diazoacetate as a mild nucleophile (Table 1). Aliphatic aldehyde was chosen because the related Mannich-type reactions, catalysed by chiral Brønsted acid, of diazoacetate with preformed *N*-aryloyl or *N*-*t*-butyloxycarbonyl (*N*-Boc) imines were applicable only to aromatic imines, as reported in both Terada's research and ours[30,31,36]. To our delight, the desired product, α-diazo-β-hydrazino ester **5a**, was isolated in 84% yield with a promising 43% enantiomeric excess (e.e.) (Table 1, entry 1) by carrying out the reaction in CH_2Cl_2 at 0 °C in the presence of 4A molecular sieves (MS4A) as a water scavenger (see Supplementary Information). An effort to identify the optimal catalyst using 3,3′-diaryl dicarboxylic acids failed to attain an acceptable level of enantioselectivity, at most no more than 60% e.e. with (*R*)-**1c** (Table 1, entry 2), so we turned our attention to the use of 3,3′-disilyl-substituted dicarboxylic acids **1d** and **1e** (refs 37,38). Using these sterically demanding catalysts, a drastic increase of the enantioselectivity was observed (Table 1, entries 3 and 4). After establishing (*R*)-**1e**, which bears methyldiphenylsilyl moieties, as the optimal catalyst, we focused on the screening of solvents. Halogenated solvents were preferred with regard to the reaction yield owing to the good solubility of *N*′-benzylbenzoylhydrazide **3**, whereas an aromatic solvent, toluene, was advantageous in terms of the selectivity (Table 1, entries 4–6). We therefore opted for the use of α,α,α-trifluorotoluene as the solvent, with which the α-diazo-β-hydrazino ester **5a** could be produced in 89% yield with 93% e.e. (Table 1, entry 7). Finally, use of diisopropylmethyl diazoacetate **6** in place of *t*-butyl diazoacetate **4** gave rise to α-diazo-β-hydrazino ester **7a** in 84% yield with 96% e.e. (Table 1, entry 8). Although we carried out the reaction routinely in a reaction flask filled with argon in the presence of powdered MS4A, it may be run more conveniently in a glass-stoppered test tube containing Na_2SO_4 as a water scavenger without the deliberate displacement of air and moisture (Table 1, entry 9).

With the optimized conditions in hand, next we explored the substrate scope of this novel synthetic transformation, as shown in Table 2. With regard to other α-branched aldehydes, cyclopentanecarbaldehyde and isobutyraldehyde could be converted into the corresponding α-diazo-β-hydrazino esters in good yields with 96% e.e., respectively (Table 2, entries 2 and 4). For cyclopropanecarbaldehyde, it was found to be advantageous to run the reaction at a lower temperature (−20 °C) to attain high enantioselectivity (Table 2, entry 3). One limitation we faced in this study was the use of pivalaldehyde, with which no appreciable amount of the product was detected (Table 2, entry 5). Our attention then moved to the reactions of α-unbranched aliphatic aldehydes, for which the reaction temperature was generally set to −20 °C to obtain optimal results. Irrespective of the chain length and steric bulk, the desired products were obtained in good yields with e.e. values that ranged from 93% to 99% (Table 2, entries 6–8). Even acetaldehyde could be utilized without significantly compromising the enantioselectivity by carrying out the reaction at −28 °C (Table 2, entry 9). As for functional group tolerance, protected hydroxy and amino functionalities were all tolerated to give densely functionalized β-hydrazino esters with high enantioselectivities (Table 2, entries 10–12). Use of β-ketoaldehyde led to the selective functionalization of the aldehyde, with the keto group unaffected (Table 2, entry 13).

The substrate scope of this reaction was extended further to aromatic aldehydes without difficulty. The electronic property of the aromatic rings had no influence on the selectivity, although use of 2-tolualdehyde resulted in a slight decrease of the enantioselectivity (Table 2, entries 14–17). This reaction system could not be applied to α,β-unsaturated aldehydes, such as cinnamaldehyde, because of the facile 1,4-addition of the hydrazide **3** (ref. 39), but 3-phenylpropiolaldehyde was transformed successfully into the desired product, incorporating an alkynyl moiety in 75% yield with 87% e.e. (Table 2, entry 18).

During the course of this study, we became aware of the intriguing phenomenon that the catalyst structure not only affects the enantioselectivity of the products, but also the entire course of the reaction when α-unbranched aliphatic aldehydes are used as substrates (Fig. 2). As demonstrated above, use of 3,3′-bis(methyldiphenylsilyl)-substituted dicarboxylic acid (*R*)-**1e** in the reaction of 3-phenylpropionaldehyde provided the corresponding β-hydrazino ester **7f** selectively in fairly good yield. In contrast, 3,3′-unsubstituted

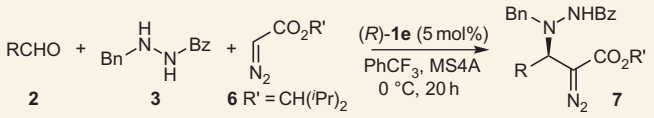
Table 1 | Optimization of reaction conditions.

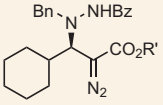
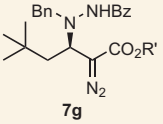
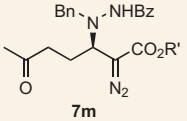
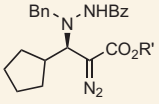
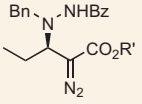
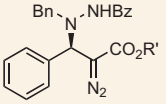
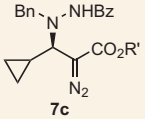
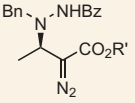
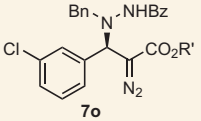
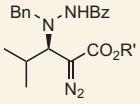
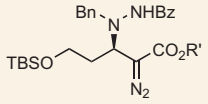
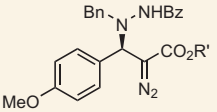
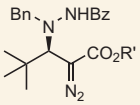
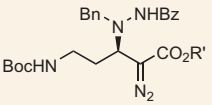
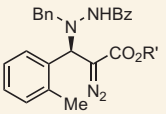
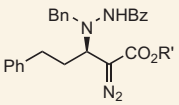
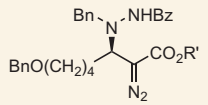
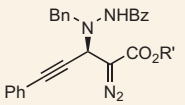


Entry	Catalyst	Solvent	R′	Yield (%)*	e.e. (%)†
1	**1b**	CH_2Cl_2	^{t}Bu	84	43
2	**1c**	CH_2Cl_2	^{t}Bu	74	60
3	**1d**	CH_2Cl_2	^{t}Bu	57	89
4	**1e**	CH_2Cl_2	^{t}Bu	73	90
5	**1e**	$CHCl_3$	^{t}Bu	84	91
6	**1e**	PhMe	^{t}Bu	19	93
7	**1e**	$PhCF_3$	^{t}Bu	89	93
8	**1e**	$PhCF_3$	$CH(^iPr_2)$	84	96
9‡	**1e**	$PhCF_3$	$CH(^iPr_2)$	72	96

Conditions: performed with **2a** (0.15 mmol), *N*′-benzylbenzoylhydrazide **3** (0.10 mmol) and diazoacetate (0.12 mmol) in the presence of 5 mol% (*R*)-**1** (0.005 mmol) and MS4A (100 mg). *Isolated yield. †Determined by chiral high-performance liquid chromatography analysis. ‡Performed in the presence of Na_2SO_4 (300 mg) for 72 h.

Table 2 | Substrate scope.



Entry	Product	Yield (%)*	e.e. (%)†	Entry	Product	Yield (%)*	e.e. (%)†	Entry	Product	Yield (%)*	e.e. (%)†
1	 **7a**	84	97	7‡	 **7g**	84	99	13‡	 **7m**	87	95
2	 **7b**	89	96	8‡	 **7h**	80	96	14	 **7n**	80	91
3‡	 **7c**	84	89	9§	 **7i**	57	86	15	 **7o**	57	90
4	 **7d**	69	96	10‡	 **7j**	83	95	16	 **7p**	70	92
5	 **7e**	N.R.		11‡	 **7k**	50	91	17	 **7q**	64	81
6‡	 **7f**	85	93	12‡	 **7l**	84	93	18‡	 **7r**	75	87

Conditions: Performed with **2** (0.15 mmol), N′-benzylbenzoylhydrazide **3** (0.10 mmol) and diazoacetate **6** (0.12 or 0.20 mmol) in the presence of 5 mol% (*R*)-**1e** (0.005 mmol) and MS4A (100 mg). *Isolated yield. †Determined by chiral HPLC analysis. ‡Performed at −20 °C. §Performed at −28 °C. N.R. = no reaction.

dicarboxylic acid (*R*)-**1a** furnished, as a major product, a different species with a molecular weight that corresponded to the dimer of the acyclic azomethine imine. The structure was elucidated to be the five-membered heterocycle **8**, which was assumed to be generated via 1,3-dipolar cycloaddition of acid-activated acyclic azomethine imine and its tautomerized *N*′-alkenylbenzoylhydrazide **9** (ref. 40). This unwanted reaction pathway still persisted when the 3,3′-diaryl substituted catalyst (*R*)-**1b** was used to give the homo coupling product **8** in 9% yield in conjunction with the β-hydrazino ester, whereas the use of (*R*)-**1e** minimized the yield of **8** to only 2%. Notably, chiral phosphoric acid (*R*)-**10** with the same 3,3′-disilyl substituents generated a considerable amount of the dimer **8** in addition to **7f** (45% e.e.), which highlights the distinctive catalytic activity of the axially chiral dicarboxylic acid (*R*)-**1e**. Slow tautomerization of acyclic azomethine imine might be the reason for the selective formation of β-hydrazino ester in the case of 3,3′-disilyl substituted dicarboxylic acid catalysis.

The strategy described herein provides a facile organocatalytic method for the asymmetric synthesis of β-hydrazino acids, which are regarded as an analogue of β-amino acids. As a unique extension of this study, we pursued further the synthesis of β-hydrazino phosphoric acids as a second-degree relative of β-amino acids that have both hydrazine and phosphoric acid in lieu of amine and carboxylic acid[41] on the premise that alkyl diazoacetate can be replaced by the corresponding dimethyl (diazomethyl)phosphonate **11** without affecting the selectivity in axially chiral dicarboyxlic acid catalysis (Fig. 3a)[30,31]. This novel three-component reaction actually proceeded smoothly irrespective of the nature of the aldehydes to give the corresponding α-diazo-β-hydrazino phosphonates **12** with excellent enantioselectivities. To the best of our knowledge, this is the first report of success in providing these compounds in a catalytic asymmetric manner.

Next, the reaction with alkyl diazoacetate was performed on a 2.0 mmol scale under more elaborate reaction conditions to show the scalability of this methodology (Fig. 3b). In the presence of 1 mol% (*R*)-**1e** with smaller amounts of the solvent and molecular sieves, the reaction using cyclohexanecarbaldehyde **2a** took place without difficulty to give the adduct **7a** in 74% yield with 96% e.e. (see Supplementary Information).

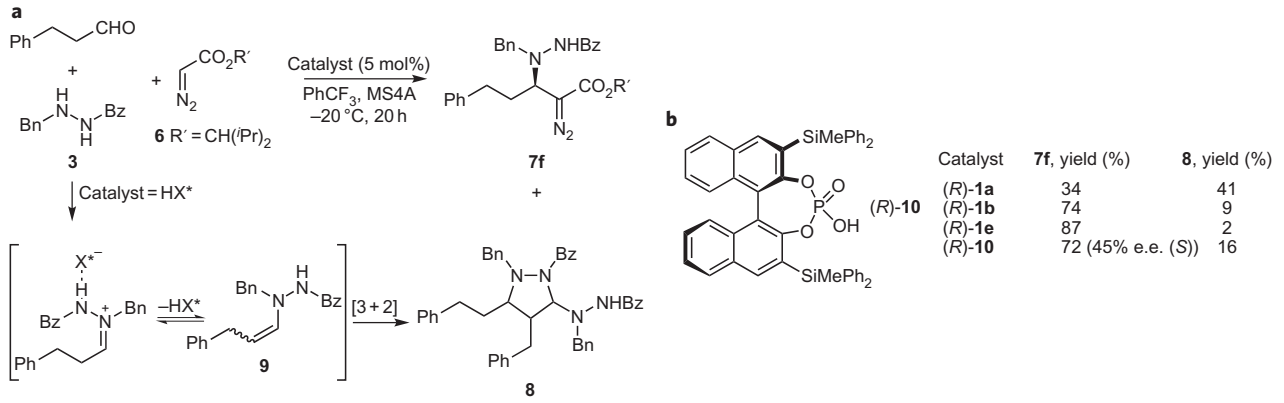


Figure 2 | Influence of the catalyst structure on the reaction pathway. a, After formation of the acyclic azomethine imine, two reaction pathways are possible. Reaction with the diazoacetate **6** leads to the desired product **7f**; alternatively, tautomerization of the azomethine imine produces alkenyl hydrazide **9**, which can undergo a [3 + 2] cycloaddition with a further equivalent of the azomethine imine to produce the dimeric product **8**. **b**, The reaction that predominates is strongly dependent on the catalyst structure.

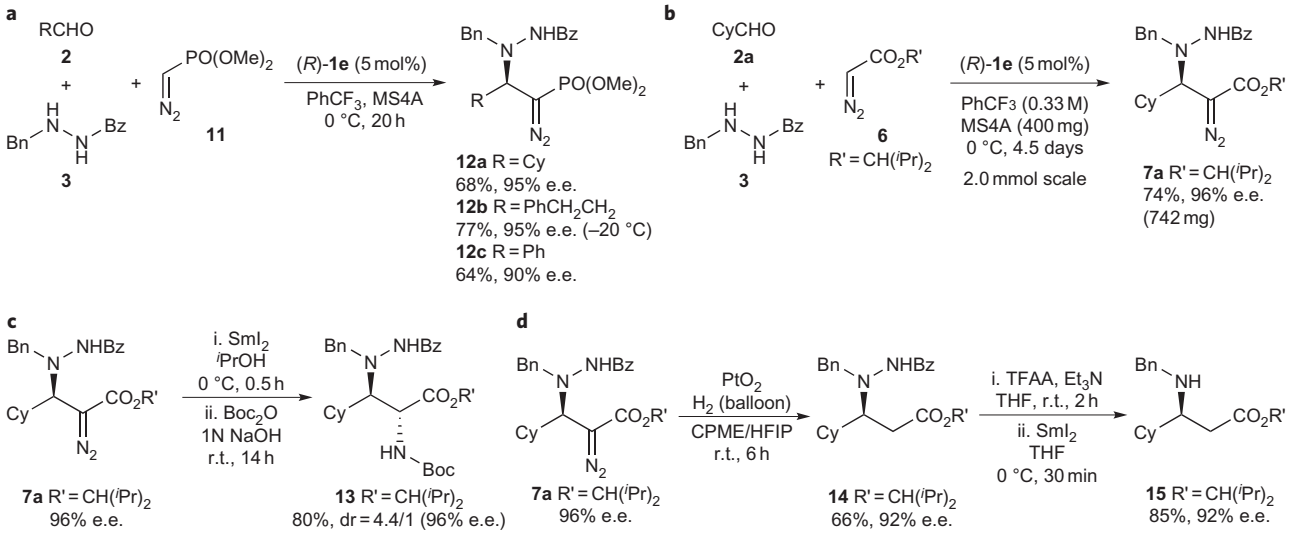


Figure 3 | Applications of axially chiral dicarboxylic acid catalysed reaction of acyclic azomethine imines. a, Use of dimethyl (diazomethyl)phosphonate as the nucleophile in place of alkyl diazoacetate furnished α-diazo-β-hydrazino phosphonates with high enantioselectivities. **b**, An experiment scaled up to 2.0 mmol was conducted using 1 mol% catalyst and a smaller amount of MS4A to exemplify the robustness of the reaction. **c**, The diazo moiety of the α-diazo-β-hydrazino ester can be converted into an amine by SmI_2. **d**, The diazo moiety can be reduced to a methylene by hydrogenation using PtO_2. The N–N bond can be cleaved further by the one-pot trifluoroacetylation/SmI_2-mediated reduction. d.r. = diastereomeric ratio, r.t. = room temperature, TFAA = trifluoroacetic anhydride, THF = tetrahydrofuran.

Two synthetic derivatizations of chiral α-diazo-β-hydrazino ester were then implemented. In one example, the diazo group was converted into the Boc-amino group by a reductive treatment with samarium iodide to give the *trans*-α-amino-β-hydrazino ester **13** in good yield (Fig. 3c). Another application we devised is the complete removal of the diazo moiety via hydrogenation catalysed by platinum oxide as a way to give the α-unsubstituted β-hydrazino ester **14** (Fig. 3d). After the screening of various reaction conditions, we determined that the optimal condition is a co-solvent system that consists of cyclopentyl methyl ether (CPME) and hexafluoroisopropanol (HFIP) at room temperature, both to give **14** and to minimize reduction of the e.e. value. To prove the viability of chiral hydrazine as a protected chiral amine, next we examined the reaction conditions for the detachment of the benzoyl amide moiety of **14**. This can be done via a facile one-pot trifluoroacetylation/SmI_2 reduction sequence to give the β-amino acid ester **15** in 85% yield without deterioration in the enantioselectivity[42].

Conclusion

The field of asymmetric catalysis has grown synergistically with the development of novel catalysts and reaction systems to make available a myriad of enantiomerically enriched materials. However, when we turn our attention to the prochiral substrates employed in these catalyses, it is not hard to recognize that generally only a handful of electrophiles are used, whereas a variety of nucleophiles exist as reaction partners. The research described herein reveals, for the first time, that acyclic azomethine imines can be utilized as a new entry of prochiral electrophiles in association with state-of-the-art chiral Brønsted acid catalysis. From the viewpoint of imine chemistry aimed at chiral amine synthesis, this study could unfold a competitive alternative as acyclic azomethine imines have three major appreciated properties in imine chemistry: no need for the preformation of imines, high reactivity towards mild nucleophiles and applicability to alkyl, aryl and alkynyl aldehydes with high functional group tolerance[43–46]. This discovery will open up operationally simple and environmentally benign organocatalysed

ways to synthesize a diverse array of chiral hydrazines and amines using a variety of readily available mild nucleophiles.

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Author contributions

T.H. conceived the study and wrote the manuscript. H.K. principally performed the experiments. Y.K. assisted preliminary experiments. K.M. organized the research. All authors contributed to designing the experiments, analysing data and editing the manuscript.

Additional information

The authors declare no competing financial interests. Supplementary information and chemical compound information accompany this paper at www.nature.com/naturechemistry. Reprints and permission information is available online at http://www.nature.com/reprints. Correspondence and requests for materials should be addressed to K.M.