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Chiral Phosphoric Acid Catalyzed Enantioselective Synthesis of α-Tertiary Amino Ketones from Sulfonium Ylides

Wengang Guo,[§‡] Yuzheng Luo,[§†] Herman H.-Y. Sung,[‡] Ian D. Williams,[‡] Pingfan Li,[†]* and Jianwei Sun[‡]*

[†] State Key Laboratory of Chemical Resource Engineering, Department of Organic Chemistry, College of Chemistry, Beijing University of Chemical Technology, Beijing 100029, China;

[‡] Department of Chemistry, the Hong Kong University of Science and Technology, Clear Water Bay, Kowloon, Hong Kong SAR, China

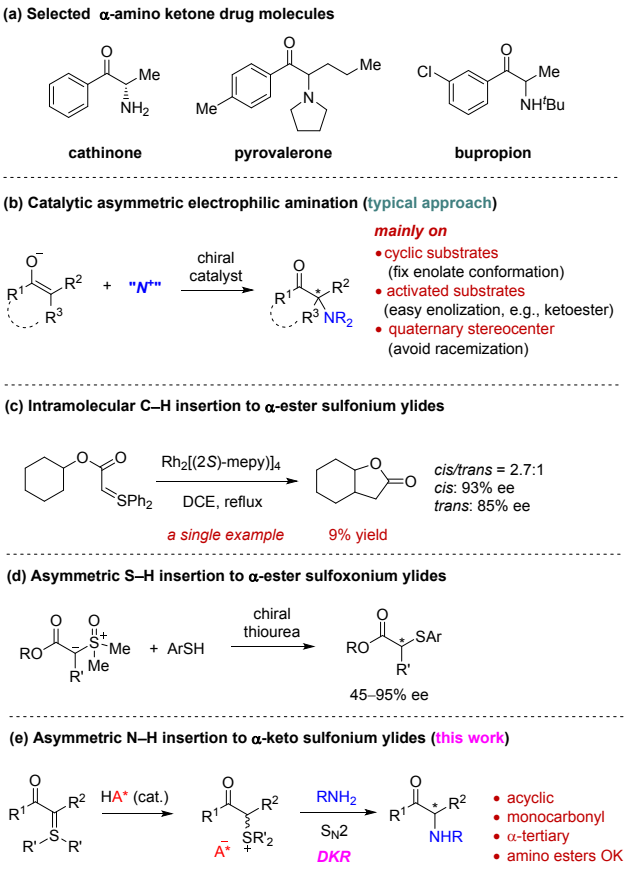
ABSTRACT: Herein we disclose a new catalytic asymmetric approach for the synthesis of chiral α-amino ketones, which is particularly useful for the less accessible acyclic α-tertiary cases. By a protonation-amination sequence, our approach represents a rare asymmetric H−heteroatom bond insertion by α-carbonyl sulfonium ylides, an attractive surrogate of diazocarbonyls. The mild intermolecular C–N bond formation was catalyzed by chiral phosphoric acids with excellent efficiency and enantioselectivity. The products are precursors to other important chiral amine derivatives, including drug molecules and chiral ligands. The enantioselectivity was controlled by dynamic kinetic resolution in the amination step, rather than the initial protonation. This process opens up a new platform for the development of other related insertion reactions.

INTRODUCTION

Chiral α-amino ketones are substructures present in numerous important molecules of pharmaceutical relevance (Scheme 1a).[1] They also serve as important precursors to β-aminol alcohols, widely used as chiral ligands.[2] As a result, efficient asymmetric synthesis of such important chiral amines has been a constant pursuit of organic chemists. In the past decades, a few catalytic enantioselective approaches have been devised for this purpose.[3-5] Among them, direct electrophilic α-amination of ketone enolates represents the most general approach (Scheme 1b).[4] However, this elegant method has its limitations. For example, the majority of current examples dealt with cyclic ketones or activated ketones (such as β-ketoesters), whose stereocontrol might benefit from the restricted conformation of cyclic enolates or interaction with the additional carbonyl group. Moreover, they are mainly limited to the construction of quaternary stereocenters, which likely avoids epimerization of the otherwise labile tertiary stereocenter.[4b-f] Another point probably worthy of note is that currently known approaches rarely employ free amines as the nitrogen source. Instead, masked and protected amines (e.g., diazocarboxylate, azide, amides) were typically needed to be compatible with the catalytic systems.[3-6] While recent progress by other ingenious strategies have been achieved, catalytic asymmetric approaches for the synthesis of *acyclic α-tertiary amino ketones remain scarce*. Herein we introduce a completely different approach to address these challenges.

α-Carbonyl sulfonium ylides are versatile species in organic synthesis, serving as attractive surrogates to α-diazocarbonyl compounds.[7] However, so far, their application in catalytic asymmetric synthesis has been mainly focused on cycloaddition reactions.[8] Their utilization for asymmetric H–heteroatom bond insertion has been rarely exploited. In 1999, Müller and coworkers reported a single example of Rh-catalyzed asymmetric intramolecular C–H insertion with α-ester sulfonium ylides,

Scheme 1. Introduction and Reaction Design



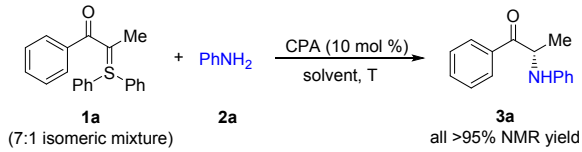
but with very low efficiency (9% yield, Scheme 1c).[9] During the preparation of this manuscript, Burtoloso and coworkers reported an elegant S–H insertion of arylthiols to α-ester sulfoxonium ylides with chiral thiourea catalysis, leading to a range of α-arylthio esters in 45–95% ee.[10] Notably, in contrast to the α-ester sulfur ylides, asymmetric insertion using α-*keto* sulfur ylides has not been realized. We envisioned that these reactions may remedy some of the drawbacks encountered with α-diazo*ketones*.[5e] Specifically, metal carbene complexes generated from diazo*ketones* have poor stability due to easy decomposition (e.g., β-elimination).[11] Moreover, the resulting metal ylides can easily lose enantiocontrol due to facile detachment of the metal/L* part off the molecule.[5e,6c] In this context, an organocatalytic approach with α-keto sulfonium ylides for this purpose would be a highly desirable alternative.

The relative basicity of sulfonium ylide inspired us to envision that protonation with a chiral acid would lead to a chiral sulfonium ion pair, in which the labile α-tertiary stereocenter bearing a good leaving group (organosulfide) would be susceptible to nucleophilic substitution (Scheme 1e). Depending on the relative rates of its epimerization and subsequent substitution, the ultimate asymmetric control could be from either asymmetric protonation[12a] or dynamic kinetic resolution (DKR) in amination.[12b,c] Notably, the nucleophilic nature of the nitrogen source would permit free amines to be directly used.[13]

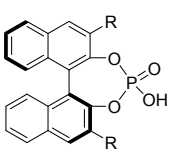
RESULTS AND DISCUSSION

We began our study with sulfonium ylide **1a**, which was readily prepared as a mixture of s-*cis* and s-*trans* isomers.[14] A range of chiral phosphoric acids (CPAs) were examined for the reaction with aniline (Table 1).[15] To our delight, all these reactions proceeded cleanly in DCM to form the desired amino ketone **3a**, albeit with low enantioselectivity. Among them, (*S*)-**A4** exhibited the best performance (44% ee, entry 4). SPINOL-derived CPAs and chiral thioureas proved inferior (see the SI for more details). With (*S*)-**A4**, further condition screening revealed that **3a** could be generated with 83% ee in toluene at –40 °C (entry 12).

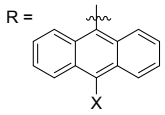
Table 1. Evaluation of Reaction Conditions[a]



1a (7:1 isomeric mixture) **2a** **3a** all >95% NMR yield



A1, R = 1-naphthyl
A2, R = 9-phenanthrenyl
A3, R = 1-pyrenyl
A4, R = 9-anthracenyl
A5, R = 2,4,6-^{i}Pr$_3$C$_6$H$_2$



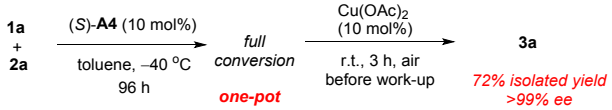
A6 (X = Ph)
A7 (X = 3,5-^{i}Pr$_2$C$_6$H$_3$)

entry	cat.	T/°C	*t*/h	solvent	ee (%)[b]
1	(*S*)-**A1**	25	1	DCM	24
2	(*S*)-**A2**	25	1	DCM	24
3	(*S*)-**A3**	25	1	DCM	0
4	(*S*)-**A4**	25	1	DCM	44
5	(*S*)-**A5**	25	1	DCM	43
8	(*S*)-**A4**	25	1	toluene	54
9	(*S*)-**A4**	25	36	Et_2O	46
10	(*S*)-**A4**	25	1	$CHCl_3$	34
11	(*S*)-**A4**	–30	72	toluene	80
12	(*S*)-**A4**	–40	96	toluene	83

[a] Reaction scale: **1a** (0.10 mmol), **2a** (0.11 mmol), catalyst (0.01 mmol), solvent (1.0 mL). [b] Determined by chiral HPLC.

Aiming to further enhance the product enantiopurity, we then resorted to a post-reaction operation. After complete conversion, a substiochiometric amount of $Cu(OAc)_2$ was added to the reaction mixture (Scheme 2). Stirring the mixture under air atmosphere at room temperature for 3 h led to the isolation of product **3a** in 72% yield in enantiopure form! The minor enantiomer was selectively consumed (oxidized by air), which was catalyzed by the *in-situ* generated Cu/CPA complex.[16] It is remarkable that same (*S*)-**A4** has the matched absolute configuration for the subsequent ee enhancement through kinetic resolution, which is key to the success of this one-pot operation.

Scheme 2. One-pot ee Enhancement with $Cu(OAc)_2$



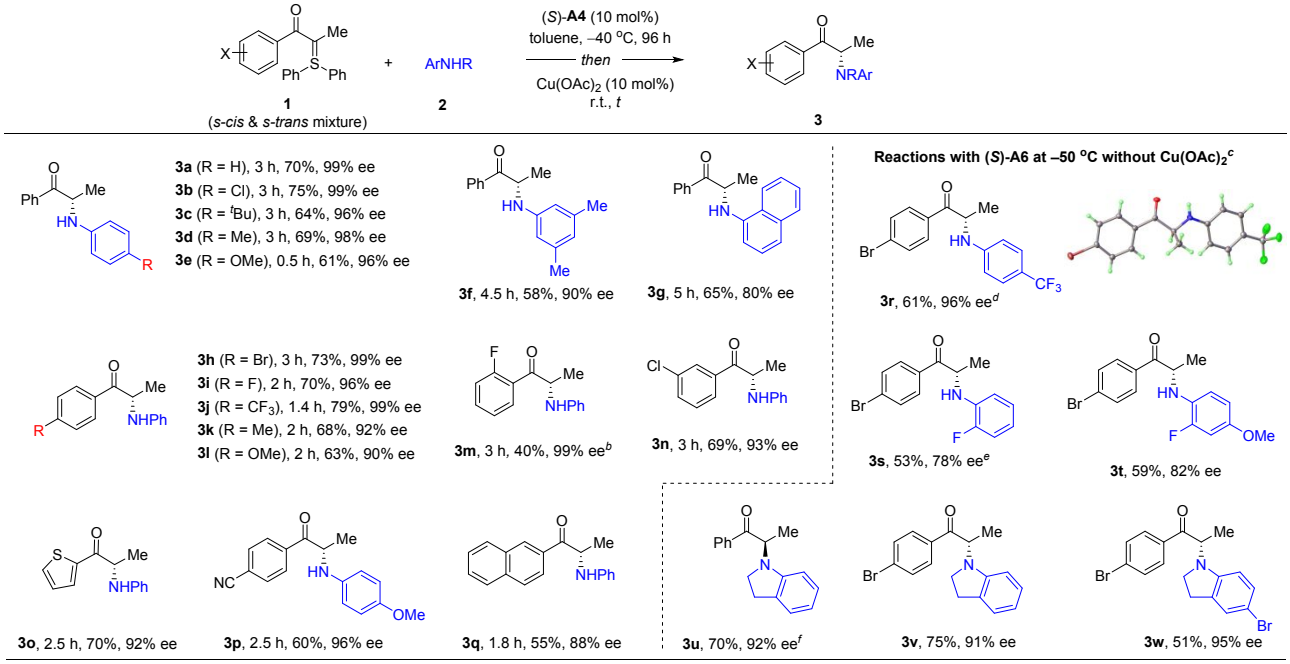
We then examined the scope of this formal N–H insertion process. A range of sulfonium ylides and anilines, including electron-poor and electron-rich examples, all participated in the reaction to form the corresponding α-amino ketone products with excellent enantioselectivity (Table 2). The mild conditions tolerated a range of functional groups. Notably, the late-stage oxidation condition is compatible with the *p*-methoxyphenyl (PMP) and thiophene functionalities, which are known to be labile toward oxidation.

While the post-reaction Cu-catalyzed kinetic resolution provided an alternative to boost the product enantiopurity, we also further examined the protocol without this additional operation. For example, with **A6** and a new catalyst **A7** (shown in Table 1), the reactions could directly afford the desired products with good to excellent enantioselectivity (**3r-w**).

The nucleophilicity of the anilines was also important to ensure successful reactivity. Anilines with electron-donating and slightly electron-withdrawing groups, such as *p*-Cl (σ_p^- = +0.19), *p*-CF_3 (σ_p^- = +0.65), were suitable nucleophiles. However, strongly electron-withdrawing groups, such as *p*-NO_2, *p*-CN, led to no reactivity, even at an elevated temperature (see SI for more details). The low nucleophilicity not only directly led to poor amination reactivity, but also resulted in relatively faster catalyst deactivation (*vide infra*). Finally, in addition to primary amine nucleophiles, we found that secondary amines, such as indolines, were also excellent nucleophiles that furnished the desired tertiary amine products with excellent enantioselectivity (**3u-w**). However, aliphatic amines resulted in either low reactivity or low enantioselectivity (see the SI for details), which is likely related to their relatively higher basicity that might be incompatible with the acid catalyst. The absolute configuration of the *p*-trifluoromethylaniline product **3r** was determined by single crystal X-ray crystallography to be (*S*), as

was that of the indoline product **3v** via its indolyl derivative **13** (see Scheme 3).

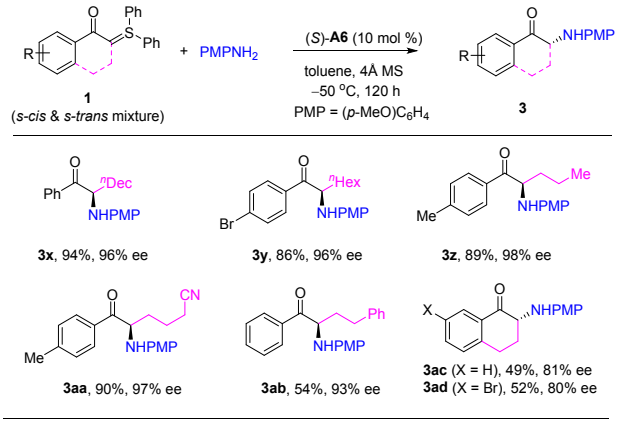
Table 2. Synthesis of α-Amino Propiophenones[a]



[a] Reaction scale: **1** (0.5 mmol, **2** (0.55 mmol), (*S*)-**A4** (10 mol%), toluene (5.0 mL). [b] Run with **A4** (20 mol%), –40 °C, 72 h, followed by 24 h at r.t. after addition of $Cu(OAc)_2$. [c] (*S*)-**A6** (10 mol%), 4 Å MS (100 mg), –50 °C, 120 h. [d] (*S*)-**A6** (15 mol%), –30 °C. [e] (*S*)-**A6** (20 mol %), –40 °C, 120 h. [f] (*R*)-**A7** (10 mol %).

While excellent results were obtained with α-methyl sulfonium ylides, further study indicated that those bearing a higher alkyl substituent reacted with moderate enantioselectivity. Importantly, the post-reaction kinetic resolution with $Cu(OAc)_2$ no longer improved the enantiopurity, but became mismatched scenario, leading to ee erosion. More importantly, we found that the sense of asymmetric induction was opposite to the cases in Table 2, which might be the cause of the mismatched kinetic resolution. This observation also indicated that increasing the size of the α-substituent from methyl group had dramatic influence on the enantiodetermining transition state. Next, various catalysts were screened again. Gratifyingly, **A6** (Table 1) was identified as the superior one (Table 3). After slight modification of reaction parameters, these α-amino ketones bearing various alkyl chains could be obtained with good to excellent enantioselectivity without post-reaction kinetic resolution. Cyclic α-amino ketones, such as aminotetralones,[17] could also be synthesized. Some of these products resembles commercial drugs (e.g, **3z** vs. pyrovalerone in Scheme 1a). The absolute configuration of **3ab** was determined by single crystal X-ray crystallography of its derivative (see the SI for details). Notably, α-ethyl substitution also led to 70% ee (see the SI for details).

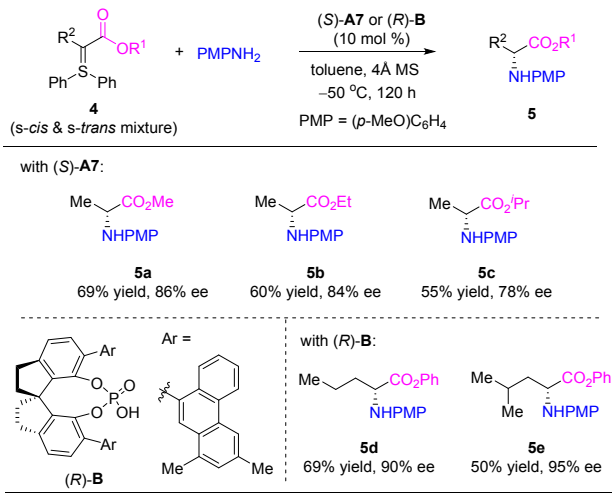
Table 3. Scope for α-Non-methyl Aminoketones[a]



[a] Reaction scale: **1** (0.5 mmol), **2** (0.55 mmol), (*S*)-**A6** (10 mol%), and 4 Å MS (250 mg), toluene (5.0 mL).

With the success on α-amino ketones, we were curious about the potential of this approach for the synthesis of α-amino esters. However, the previous catalysts of choice were not suitable for these substrates. Nevertheless, we managed to achieve good to excellent enantioselectivity with **A7** and another new SPINOL-derived catalyst **B** (Table 4). Similarly, α-methyl and other α-alkyl esters required different catalysts. However, the sense of asymmetric induction of these two types of products remained same, in contrast to the scenario for α-amino ketones.

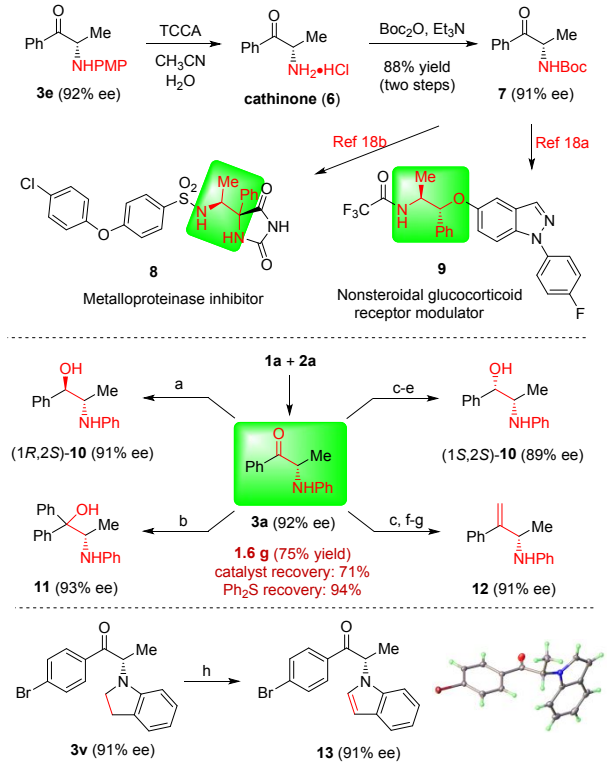
Table 4. Synthesis of Chiral α-Amino Esters[a]



[a] Reaction scale: **1** (0.2 mmol), **2** (0.22 mmol), (*S*)-**A7** or (*R*)-**B** (10 mol%), and 4 Å MS (100 mg), toluene (2.0 mL).

Our products are precursors to other useful chiral amine derivatives (Scheme 3). For example, oxidative PMP-deprotection in **3e** immediately furnished chiral drug cathinone (**6**).[1a] Further Boc-protection delivered **7**, a known precursor toward bioactive molecules **8** and **9**.[18] Next, a gram-scale synthesis of **3a** was performed with recovery of catalyst **A4** and diphenylsulfide. Furthermore, product **3a** were converted to both diastereomers of amino alcohol **10** and alcohol **11**, which are useful chiral ligands.[2] Wittig olefination led to chiral allylamine **12**. Finally, indoline **3v** could be easily oxidized by DDQ to form α-*N*-indolyl ketone **13**. Notably, in all these transformations, no obvious erosion in enantiopurity was observed.

Scheme 3. Product Transformations

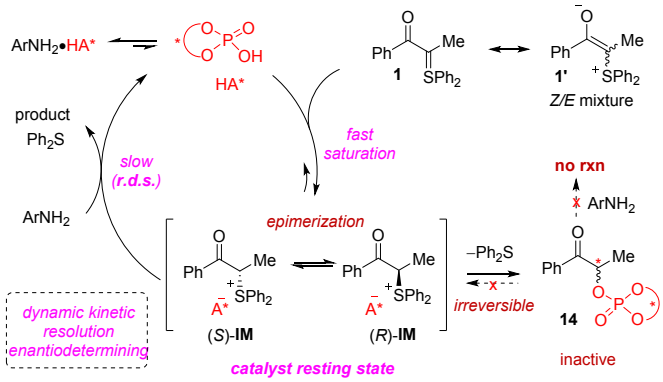


(a) BH_3-SMe_2, THF, 0 °C, 12 h, >50:1 dr, 99% yield; (b) PhMgBr, THF, 0 °C, 15 min, 65% yield; (c) AcCl, THF, 25 °C, 12 h, 75% yield; (d) super-hydride, THF, –20 °C, 1 h; (e) KOH/MeOH, 65 °C, 30 min, 15:1 dr, 65% yield (2 steps); (f) Ph_3PMeBr, ^tBuOK, THF, 0 °C to r.t., 12 h; (g) KOH/MeOH, 65 °C, 30 min, 59% yield (2 steps); (h) DDQ, 0 °C to r.t., 71% yield.

MECHANISTIC STUDIES

It is proposed that the reaction begins with protonation of sulfonium ylide **1**, typically a mixture of s-*cis* and s-*trans* isomers with the enolate resonance form **1′**. The ratio of s-*cis* and s-*trans* isomers varies with temperature (see the SI for details). The resulting **IM** is a diastereomeric mixture of sulfonium ions paired with a chiral phosphate anion. Its labile α-stereogenic center makes these two isomers in rapid equilibrium. Subsequent amine substitution delivers the product and regenerates the catalyst (Scheme 4). Indeed, **IM** was found to be the catalyst resting state, which permits extensive epimerization of the labile tertiary stereocenter in **IM**. Thus, even though the initial protonation step could be highly enantioselective, the established chirality is lost during epimerization. This is also consistent with the excellent enantioselectivity even with an isomeric mixture of substrates. Thus, the enantioselectivity is controlled during amination by pseudo dynamic kinetic resolution.[19]

Scheme 4. Proposed Mechanism



To further understand the ion pair intermediate **IM**, we mixed substrate **1** and catalyst (*S*)-**A4** in toluene-d_8. This immediately generated **IM**, whose broad peak at 4.2 ppm in ^{31}P NMR matched that observed in the standard reaction (Figure 1b).[19b] Interestingly, in the absence of amine, this intermediate gradually turned into phosphate ester **14** (Figure 1c). **14** was ultimately obtained as a 1.3:1 diastereomeric mixture (Figure 1d), whose identity was confirmed by isolation and full characterization (eq. 1). The formation of **14** is a result of phosphate *O*-substitution of the sulfonium motif in **IM**. This prompted us to speculate **14** as a potential intermediate, which might be substituted by amine to form the same product.[20] However, treating **14** with $PhNH_2$ resulted in no reaction, even with additional (*S*)-**A4**. Similarly, treating **14** with Ph_2S (with or without **A4**) also did not reverse to **IM**, thus excluding its role as either an active catalyst or a viable intermediate. Although it is an off-cycle dead end, fortunately, its generation in the standard reaction was very slow relative to the substitution of **IM** by amine, which is the key to successful turnover (Figure 1e). We also carried out a competition experiment with deuterated anilines. The absence of kinetic

isotope effect ((k_H/k_D = 1.0) indicated that the protonation step is not rate-determining, which is consistent with the proposed mechanism (eq. 2)

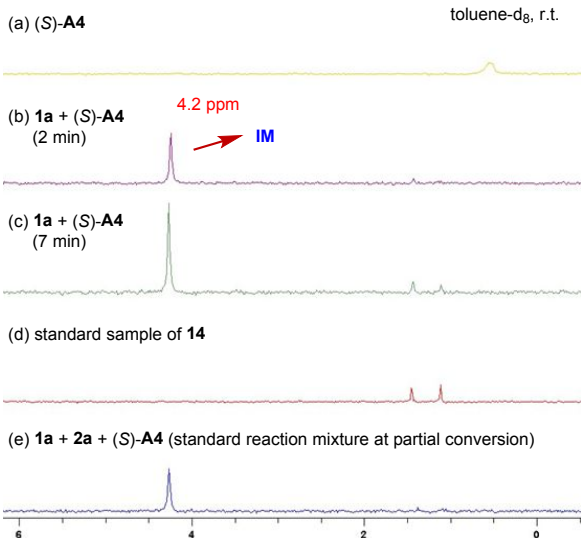
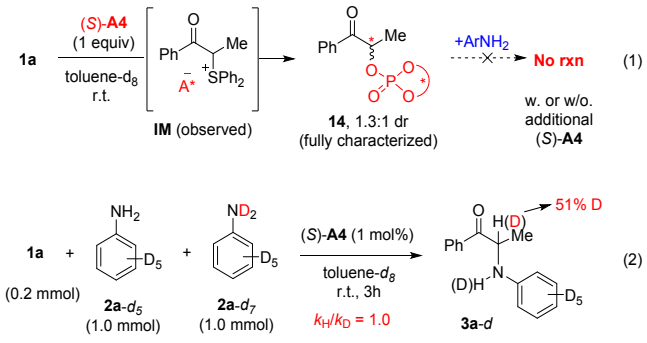


Figure 1. ^{31}P NMR study of the reaction species involved (all with 10 mol% of **A4**).



Next, we also studied non-linear effects and observed significant chirality amplification (Figure 2a). This prompted us to examine the catalyst solubility. Surprisingly, stirring the solution of racemic **A4** in toluene at –40 °C resulted in obvious precipitation over time, but the solution from enantiopure **A4** remained clear (Figure 2b). It is believed that the formation of less soluble hetero-aggregates in the racemic sample resulted in precipitation. This might be responsible for the observed dramatic chirality amplification, since the precipitation of a racemic (or low ee) aggregate would enhance the catalyst enantiopurity in solution.[21]

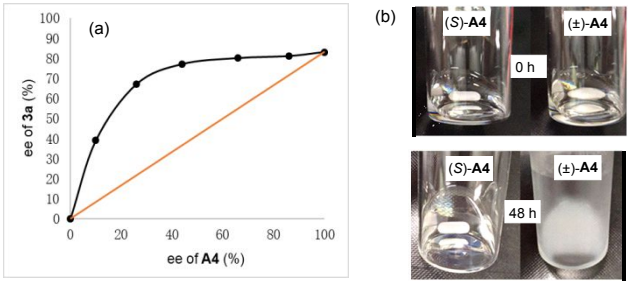


Figure 2. (a) Non-linear effects. (b) Catalyst solubility in toluene (–40 °C) over time.

CONCLUSION

In summary, we have developed a new catalytic asymmetric synthesis of chiral α-amino ketones, whose access has been limited and challenging particularly for acyclic α-tertiary cases. This is also a rare demonstration of asymmetric insertion reactions of α-carbonyl sulfonium ylides, a family of versatile and safe surrogates of diazocarbonyl compounds. With the proper choice of chiral phosphoric acids, the mild intermolecular C–N bond formation process proceeds efficiently with free amines to provide a wide range of highly enantioenriched α-amino ketones. Post-reaction enhancement of the product enantiopurity was also demonstrated by an operationally simple, stereochemically matched, Cu-CPA-catalyzed kinetic resolution. The design of new chiral catalysts also enabled the extension to α-amino esters. The products are precursors to a range of important chiral amine derivatives, including drug molecules and chiral ligands. Mechanistic studies indicated that the enantioselectivity is controlled by dynamic kinetic resolution in the rate-determining amination step, rather than the initial protonation. Finally, the privileged chiral phosphoric acids are now being applied to a new type of substrates and reactions. This process also opens up a new platform for the development of other related insertion reactions.

ASSOCIATED CONTENT

Supporting Information.

The Supporting Information is available free of charge on the ACS Publications website.

Experimental procedures and compound characterization (PDF)
X-ray crystallography data (CIF)

AUTHOR INFORMATION

Corresponding Author

*lipf@mail.buct.edu.cn, sunjw@ust.hk.

Author Contributions

§These authors contributed equally to this work.

Notes

The authors declare no competing financial interests.

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ABBREVIATIONS

Super-hydride, lithium triethylborohydride; TCCA, trichloroisocyanuric acid; DDQ, 2,3-dichloro-5,6-dicyano-1,4-

benzoquinone; TEA, triethyl amine; DCM, dichloromethane; THF, tetrahydrofuran.

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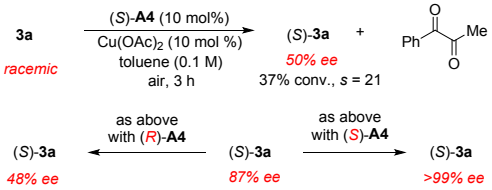

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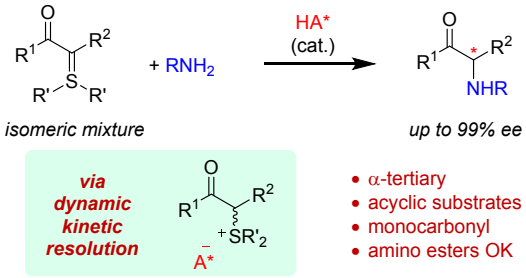
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+ RNH2
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