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Enantioselective synthesis of α-amino ketones through palladium-catalyzed asymmetric arylation of α-keto imines†

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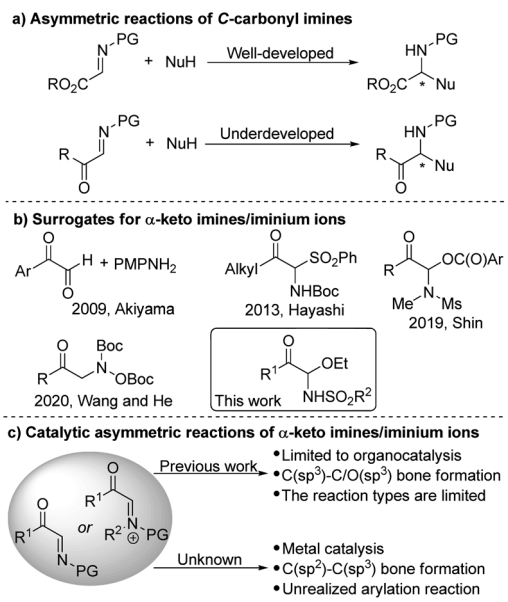
Chiral α-amino ketones are common structural motifs in natural products and pharmaceuticals, as well as important synthons in organic synthesis. Thus, establishing efficient methods for preparing compounds with these privileged scaffolds is an important endeavor in synthetic chemistry. Herein we disclose a new catalytic asymmetric approach for the synthesis of chiral α-amino ketones through a chiral palladium-catalyzed arylation reaction of *in situ* generated challenging α-keto imines from previously unreported *C*-acyl *N*-sulfonyl-*N*,*O*-aminals, with arylboronic acids. The current reaction offers a straightforward approach to the asymmetric synthesis of acyclic α-amino ketones in a practical and highly stereocontrolled manner. Meanwhile, the multiple roles of the chiral Pd(II) complex catalyst in the reaction were also reported.

Introduction

α-Amino ketones are substructures present in numerous important bioactive molecules, natural products and pharmaceuticals.[1] More importantly, α-amino ketones are useful intermediates and versatile building blocks for the synthesis of polyfunctional amino derivatives due to the rich chemistry of the carbonyl groups.[2] For example, they can be reduced into α-amino alcohols or oxidized into α-amino acids, and new carbon–carbon or carbon–hetero bonds can be formed by addition of various nucleophiles to the ketone groups. The design and development of new asymmetric methods and strategies for the preparation of chiral α-amino ketones is thus a critical objective in chemical synthesis. In the past decades, a few catalytic enantioselective approaches have been devised for this purpose.[3–8] Such as the asymmetric electrophilic amination of ketones or enolates,[4] the chiral carbene-catalyzed cross coupling of aldehydes with imines,[5] the asymmetric catalyzed N–H insertion of amines with α-diazoketones or α-keto sulfonium ylides,[6] the asymmetric reduction of α-keto ketimines,[7] through colorful rearrangement reactions to construct enantioenriched α-amino ketones,[8] and so on.[9] Herein we propose a completely different approach to address these challenges.

C-Carbonyl imines/iminium ions are versatile reagents and intermediates in organic synthesis.[10,11] The adjacent carbonyl group not only makes the imine more reactive for electrophilic reaction, but also can undergo beneficial transformations. The metal- or organocatalytic asymmetric addition of many different types of nucleophiles to α-ester imines to synthesize various α-



Scheme 1 Catalytic asymmetric reactions of *C*-carbonyl imines/iminium ions.

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amino acid derivatives and heterocyclic compounds has been studied extensively (Scheme 1a).[10] In contrast, so far, the application of α-keto imines/iminium ions in catalytic asymmetric synthesis is still very few.[11] Recently, several organocatalytic asymmetric reactions of α-keto imines/iminium ions have been developed,[12] but metal-catalyzed asymmetric conversion has not yet been achieved.

One of the important reasons is that it is restricted due to the difficulty in the synthesis of α-keto imines. The classic method of preparing α-keto imines involves the condensation of glyoxal derivatives and anilines (Scheme 1b).[12a] However, the *N*-aryl α-keto imines prepared by this method were sensitive to moisture and leads to instability, which hinders its application in synthesis. In 2013, Hayashi and co-workers reported an α-*N*-Boc sulfone ketone derivative as a precursor of α-keto imine, but an excess of base is required.[12b] In addition, the potential of α-keto imines in catalytic asymmetric synthesis has not been fully exploited, the scope of applicable nucleophiles and types of chiral catalyst systems are still rather limited to date (Scheme 1c). Thus, we are interested in developing the general method for generating active α-keto imines and studying the application of α-keto imines in catalytic asymmetric synthesis.

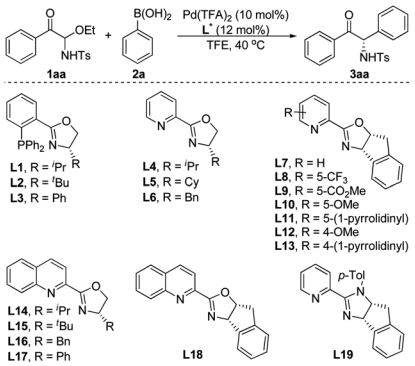
Transition-metal-catalyzed asymmetric additions of arylboron to electron-deficient bonds are well-known for their efficient construction of C–C bonds with the simultaneous generation of stereocenters with high optical purity.[13–16] Additions to imines in particular represent a powerful method for the synthesis of chiral amines.[14–16] Herein, we reported *C*-acyl *N*-sulfonyl-*N*,*O*-aminals as α-keto imines surrogates. And the resulting *C*-acyl *N*-sulfonyl-*N*,*O*-aminals undergone enantioselective addition with arylboronic acids catalyzed by palladium to synthesize acyclic α-amino ketones with good yields and enantioselectivities.[17]

Results and discussion

Reaction condition optimization

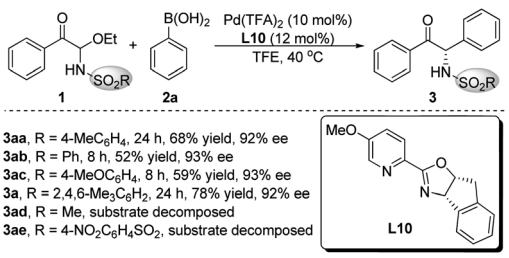
We began our study with the synthesis of active α-keto imine precursor. In the presence of tetraethoxysilane, phenylglyoxal and $TsNH_2$ condensed to form *C*-acyl *N*-Ts *N*,*O*-aminal **1aa**, and the resulting *C*-acyl *N*-Ts *N*,*O*-aminals could be recrystallized and are bench-stable for months. We envisioned that these new *C*-acyl *N*-Ts *N*,*O*-aminals could generate α-keto imines *in situ* and be used in asymmetric catalytic reactions to synthesize α-amino ketones and derivatives. To validate our hypothesis, we used the *C*-acyl *N*-Ts *N*,*O*-aminal **1aa** as the standard substrate, and investigated the reaction conditions of the palladium-catalyzed enantioselective addition of phenylboronic acid **2a** to the α-keto imines (Table 1). Phosphine–oxazoline **L1** was chosen as the initial ligand and formed a complex with $Pd(TFA)_2$ to catalyze the reaction. The reaction proceeded as expected, leading to the corresponding α-amino ketone **3aa** in low yield and good ee at 40 °C using TFE as the solvent (Table 1, entry 1). Subsequently, different chiral phosphine–oxazoline ligands were screened (entries 2 and 3), but the yield of **3aa** has not improved. To our delight, when pyridine–oxazoline **L4** was used as the ligand, the yield was greatly improved and high enantioselectivity was obtained (entry 4). Subsequently, we studied the catalytic effects of a series of pyridine–oxazoline type ligands (entries 5–18). Most of the other ligands with substituents on oxazoline rings or pyridine rings can achieve good enantioselectivities and moderate yields. To our surprise, **L6** gave racemate **3aa** (entry 6). When the pyridine ring in the ligand was replaced by a quinoline ring, the enantioselectivity of **3aa** was greatly reduced (entries 14–17). Interestingly, compared

Table 1 Effect of ligands[a]



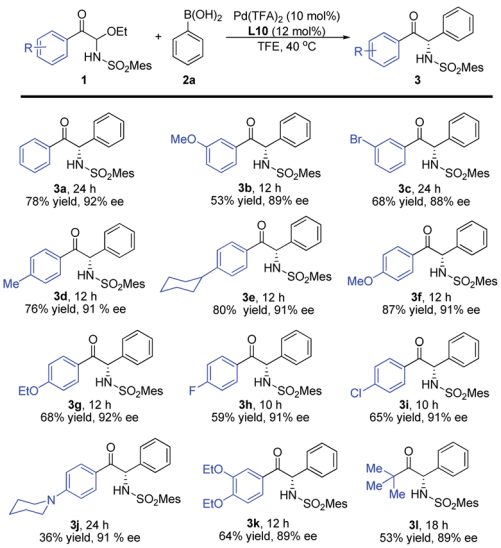
Entry	Ligand (L*)	*t*/h	Yield[b] (%)	ee[c] (%)
1	**L1**	48	10	82
2	**L2**	48	n. d.	n. d.
3	**L3**	48	3	73
4	**L4**	23	52	89
5	**L5**	17	53	90
6	**L6**	8	43	0
7	**L7**	17	59	93
8	**L8**	12	48	88
9	**L9**	7	50	96
10	**L10**	24	68	92
11	**L11**	24	53	89
12	**L12**	24	28	92
13	**L13**	25	38	90
14	**L14**	24	78	12
15	**L15**	48	38	−59
16	**L16**	24	72	6
17	**L17**	48	58	1
18	**L18**	24	55	−38
19	**L19**	10	39	74

[a] Reaction conditions: **1aa** (0.10 mmol), **2a** (0.15 mmol), $Pd(TFA)_2$ (10 mol%) and ligand (12 mol%) in TFE (0.5 mL), carried out in air at 40 °C. [b] Isolated yield. [c] Determined by chiral HPLC. n. d. = not determined. TFA = trifluoroacetic acetate, TFE = 2,2,2-trifluoroethanol.



Scheme 2 Effect of nitrogen protecting groups.

Table 2 Substrate scope of α-keto imines[a]



[a] Reaction conditions: **1** (0.20 mmol), **2a** (0.30 mmol), $Pd(TFA)_2$ (10 mol%) and **L10** (12 mol%) in TFE (1.0 mL), carried out in air at 40 °C. Mes = 2,4,6-trimethylphenyl.

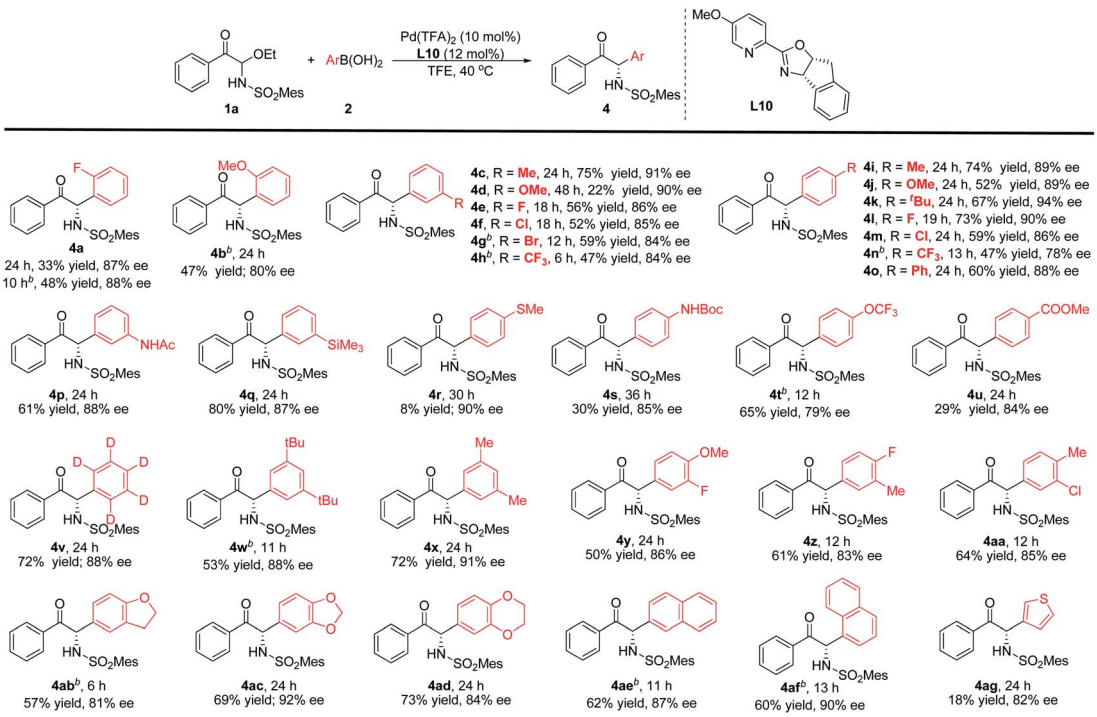
with the other pyridine–oxazoline ligands **L4–L14**, the absolute configuration of **3aa** was reversed when using ligand **L15** or **L18** (entries 15 and 18). Another type of ligand, **L19**, was also tested but gave poor results (entry 19). Considering the yield and enantioselectivity of the reaction, ligand **L10** was selected as the optimal ligand (entry 10).

The palladium catalysts, solvents and additives were screened using **L10** as the ligand, but the highest yield of product **3aa** was only 68%, when the enantioselectivity persisted above 90% ee (see the ESI† for details). We speculated that the poor yield of product **3aa** was due to that the acyclic *N*-Ts α-keto imines intermediate formed *in situ* was easy to decompose. The bulky SO_2R group would improve the stability of the α-keto imines active intermediate. Therefore, different nitrogen protecting groups (SO_2R) of *C*-acyl *N*,*O*-aminals **1** were investigated employing $Pd(TFA)_2$ as the palladium source and **L10** as the chiral ligand (Scheme 2). The catalytic results demonstrated that substrates **1ad** and **1ae** were not stable under the reaction conditions, and when R = 2,4,6-trimethylphenyl, the best results were provided, and the target product **3a** with 78% yield and 92% ee was obtained.

Substrate scope of α-keto imines and arylboronic acids

With the optimized conditions in hand, we evaluated the substrate scope and generality. As shown in Table 2, different electron-withdrawing and electron-donating groups at different positions on the aromatic ring of the substrates **1** all offered high enantioselectivities (**3b–k**). However, when the *para*-position was substituted by *N*-piperidinyl, the yield of the corresponding product **3j** was significantly reduced. In addition, a *C*-

Table 3 Substrate scope of arylboronic acids[a]

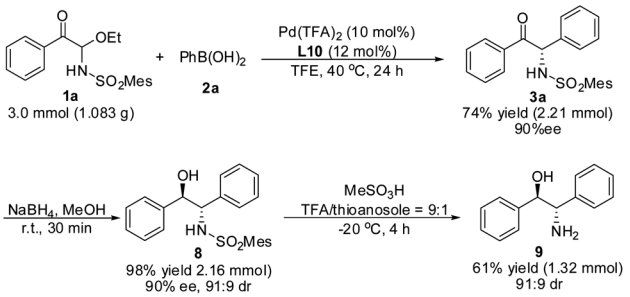


[a] Reaction conditions: **1a** (0.20 mmol), **2** (0.30 mmol), $Pd(TFA)_2$ (10 mol%) and **L10** (12 mol%) in TFE (1.0 mL), carried out in air at 40 °C. [b] The reaction was carried out at 60 °C. Mes = 2,4,6-trimethylphenyl.

acyl *N*,*O*-aminal derived from *tert*-butylglyoxal was also examined, and the desired product was obtained with good yield and enantioselectivity (**3l**).

The arylboronic acid scope was also experimented (Table 3). The results suggest that reactivity could be influenced unfavourably by steric effects. For example, the *ortho*-position fluorine and methoxy groups greatly reduced the reactivity. Nevertheless, increasing the temperature can obtain products with moderate yields and good enantioselectivities (**4a-b**). The *meta*- and *para*-substituted phenylboronic acids have also been investigated. The reaction conditions were compatible with –Me, –OMe, $-CF_3$, $-^tBu$, –Ph and halogens, corresponding products could be obtained with moderate to good yields and good enantioselectivities (**4c–o**). In comparison with the arylboronic acids bearing electron-donating aryl groups, the arylboronic acids with electron-withdrawing substituent provided a slightly lower enantioselectivity. Functional group compatibility was further investigated, such as –NHPG, –TMS, $-OCF_3$ and $-CO_2Me$ were also suitable (**4p–q**, **4s–u**), and the corresponding arylboronic acid reacts with **1a** to provide the target products with 29–80% yields and 79–88% ee. But for the 4-(methylthio)phenylboronic acid, only a small amount of the product was observed with 90% ee (**4r**). When phenyl-*D*5-boronic acid was used in this reaction, the product can be obtained with 72% yield and 88% ee (**4v**). Disubstituted aryl, polycyclic aryl or fused-ring arylboronic acids as nucleophiles could also be used in this reaction to attain high yields and enantioselectivities (**4w–af**). In addition, we also considered a heterocyclic boronic acid (**4ag**). 3-Thiopheneboronic acid could lead to good enantioselectivity, but the reactivity was low.

The functional group compatibility and broad substrate scope of this method can also be demonstrated by the reaction of substrate **1a** with arylboronic acids with biologically active moieties. As shown in Scheme 3, when estrone- or Zetia-derived arylboronic acids were employed, the products could be obtained with good yields and diastereoselectivities. It was worth noting that when **L10** or its enantiomer *ent*-**L10** was used as ligand, diastereomeric products were produced respectively, indicating that the stereoselectivity was determined by the chiral catalyst rather than the substrates. In consequence, the system had good functional group compatibility and could be used for the late-stage modification of complex molecules.



Scheme 4 Gram-scale synthesis of (1*R*, 2*S*)-2-amino-1,2-diphenylethanol **9**.

Gram-scale reaction and transformations of products

A gram–scale reaction using substrate **1a** and phenylboronic acid **2a** was carried out, the yield and enantioselectivity of product **3a** did not decrease (Scheme 4). Moreover, compound

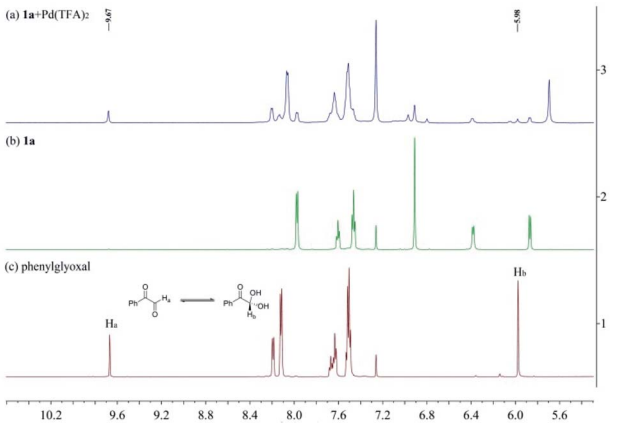
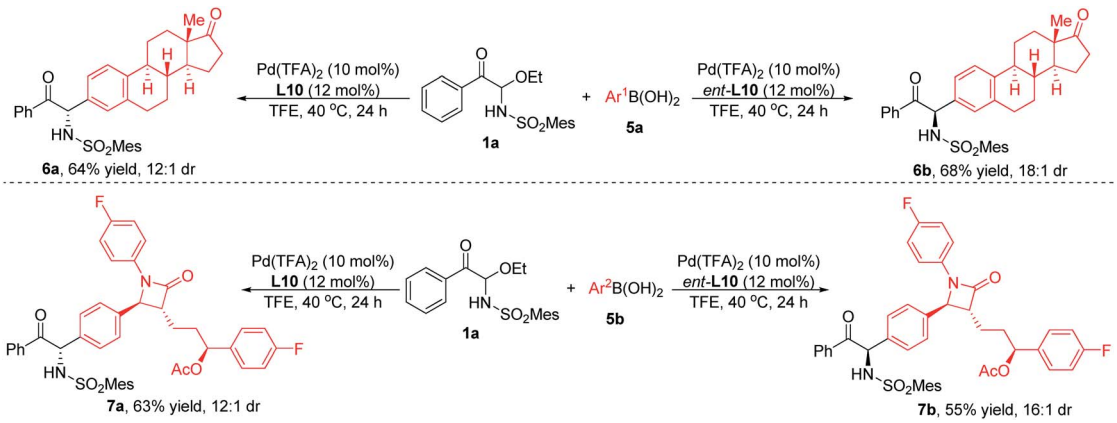


Fig. 1 (a) ^{1}H-NMR spectrum of **1a** (0.02 mmol) and $Pd(TFA)_2$ (0.02 mmol) in $CDCl_3$ (0.5 mL) after stirring for 12 hours at 40 °C. (b) ^{1}H-NMR spectrum of **1a** (0.02 mmol) in $CDCl_3$ (0.5 mL) after stirring for 12 hours at 40 °C. (c) ^{1}H-NMR spectrum of phenylglyoxal.



Scheme 3 The reaction of **1a** with arylboronic acids bearing biologically active moieties.

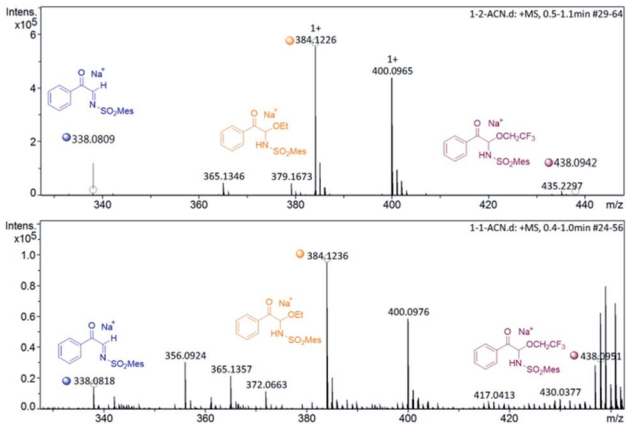


Fig. 2 (a) HRMS spectrum of **1a** (0.1 mmol) in CF_3CH_2OH (0.5 mL) after stirring for 4 hours at 40 °C. (b) HRMS spectrum of **1a** (0.1 mmol), $Pd(TFA)_2$ (10 mol%) and **L10** (12 mol%) in CF_3CH_2OH (0.5 mL) after stirring for 4 hours at 40 °C.

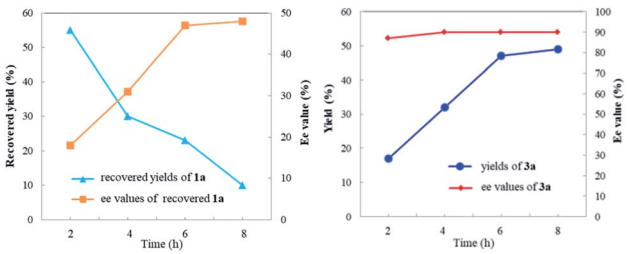


Fig. 3 (a) Recovered yields and ee values of **1a** at different reaction times. (b) Yields and ee values of **3a** at different reaction times.

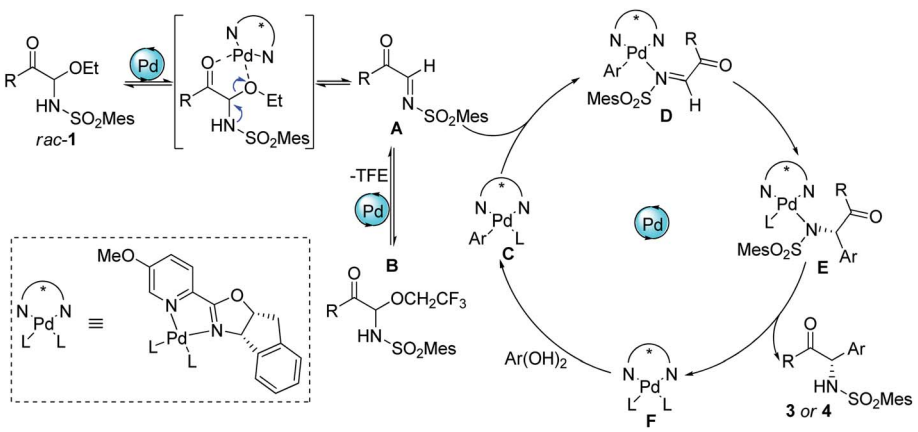
3a could be reduced by $NaBH_4$ to obtain **8** without a reduction in ee value. After removal of the $MesSO_2$– group, the important 2-amino-1,2-diphenylethanol **9** in asymmetric synthesis was obtained.

Mechanism studies

To investigate the nature of *C*-acyl *N*,*O*-aminals as new imine precursors *in situ* generation of α-keto imines, the following experiments were conducted. First, we designed an experiment to capture the highly reactive α-keto imine intermediate by H_2O and monitored it with ^{1}H-NMR (Fig. 1). In the coexistence system of **1a** and $Pd(TFA)_2$, the generated phenylglyoxal after the hydrolysis reaction of α-keto imine intermediate and H_2O was monitored (Fig. 1a). In the absence of $Pd(TFA)_2$, only trace amounts of phenylglyoxal were generated (Fig. 1b). We also monitored the intermediates by in *situ* HRMS (Fig. 2). In the presence of $Pd(TFA)_2$ and ligand, the α-keto imines and the compound by **1a** exchanged with CF_3CH_2OH were monitored (Fig. 2b). These experimental results indicated that palladium effectively promoted the production of α-keto imines, and the elimination of EtOH was reversible.

Since racemic *N*,*O*-aminals **1** were employed as the precursor of the α-keto imines, we questioned whether potential kinetic resolution occurred in Pd-catalyzed arylation reactions. Accordingly, we monitored the reaction of phenylboronic acid **2a** and *rac*-**1a** over different reaction times, and determined yields and enantiomeric ratios for both the generated product **3a** and the recovered substrate **1a** (Fig. 3). We found that the ee of the recovered starting material **1a** gradually increased with the progress of the reaction. After 8 h, **1a** was recovered in 10% yield and reached 48% ee (Fig. 3a). At the same time, product **3a** could always be obtained with high enantioselectivity at all stages of the reaction (Fig. 3b). The results indicated that (*R*)-**1a** and (*S*)-**1a** were consumed together and the amount of one of the enantiomers decreased more rapidly. The kinetic resolution process also shed some light on the Pd catalyst and *N*,*O*-aminal substrate interactions in this catalytic system. Remarkably, the unfavorable enantiomer could still be fully converted to the products after longer reaction times. Hence, this chiral Pd-catalyzed arylation reaction could be achieved in high yield and enantioselectivity *via* dynamic kinetic asymmetric transformation (DyKAT).

Based on the above experimental results and inferred mechanism of palladium-catalyzed arylation of imines,[15] a catalytic cycle was proposed (Scheme 5). First, the palladium complex **F** acted as a Lewis acid to promote the formation α-keto imines **A** *in situ* from racemic *C*-acyl *N*,*O*-aminals **1**. Simultaneously, α-keto imines **A** could be converted into *N*,*O*-aminals **1**



Scheme 5 Proposed catalytic cycle.

and **B** again by the addition of ethanol and 2,2,2-trifluoroethanol, and **1** and **B** could also form intermediate **A** again under the action of Pd(II). Afterwards, α-keto imines **A** was coordinated with palladium Ar–Pd complex **C** to form intermediate **D**. Complex **C** was formed by the metal transfer of palladium complex **F** and arylboronic acid. Intermediate **D** allowed insertion of the C=N bond into the Pd–C bond to form **E**. The ligand exchange of intermediate **E** afforded the addition product and regenerated the active Pd(II) complex **F**.

Conclusions

In summary, we have developed an efficient method for the synthesis of chiral α-amino ketones through the Pd-catalyzed asymmetric arylation of α-keto imines. The chiral Pd(II) complex catalyst played multiple roles in the reaction: (1) cooperatively activating *C*-acyl *N*,*O*-aminal electrophile to generate α-keto imines active intermediates, and in the process undergoes kinetic resolution of racemic **1**. (2) By synergistically activating α-keto imine and arylboronic acid, the subsequent enantioselective insertion of the C=N bond into Pd–C bond was promoted. The investigation of the potential applications of these *C*-acyl *N*,*O*-aminals as new imine precursors in other asymmetric transformations are underway in our laboratory.

Data availability

Data for this work, including optimization tables, general experimental procedures and characterization data for all new compounds are provided in the ESI.†

Author contributions

W. W. and Q.-X. G. conceived and directed the project. W. W. and Z.-P. A. carried out the experiments. C.-L. Y. and C.-X. L. participated in the preparation of substrates. Z.-L. W. and T. C. performed the HRMS analysis. W. W. and Z.-L. W. wrote the paper. All authors discussed the results.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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