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Palladium-catalyzed relay hydroaminocarbonylation of alkenes with hydroxylamine hydrochloride as an ammonia equivalent

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Amides are prevalent in pharmaceuticals, agrochemicals, and materials. Hydroaminocarbonylation of alkenes has emerged as one of the most direct and rapid approaches to amides. Nowadays, these reactions remain largely confined to using alkylamines as nitrogen sources, leading to sluggish reactions due to their strong binding ability and basicity. Here we show the application of abundantly available hydroxylamine hydrochloride ($\text{NH}_2\text{OH}\cdot\text{HCl}$) as a surrogate of ammonia for the relay hydroaminocarbonylation of simple alkenes in the presence of a convenient palladium catalyst system. The in situ formation of alkylamines from hydroxylamine hydrochloride by hydroaminocarbonylation reaction and Lossen rearrangement allows us to establish an efficient relay hydroaminocarbonylation. Notably, this transformation allows the catalytic formation of two C–N bonds with hydroxylamine hydrochloride as an amine source by incorporation of two molecules of alkene and avoids the use of alkylamines.

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Nitrogen atoms are ubiquitous in natural products, pharmaceuticals, polymers, and synthetic functional materials. Therefore, the development of novel catalytic reactions for the efficient construction of C–N bonds that take place with unactivated feedstocks under mild conditions while generating few byproducts has been a theme of modern synthesis^{1,2}. Arguably, the direct synthesis of nitrogen-containing molecules with the inexpensive commodity chemical ammonia as a nitrogen source and simple alkenes as carbon sources represents a highly attractive approach. Unfortunately, many common reactions with simple alkenes as starting materials catalyzed by transition-metal complexes do not occur with ammonia. This observation is probably attributed to its easy formation of unreactive Lewis acid–base adducts with transition metals owing to its basicity, small size, and strong N–H bond^{3,4}. An attractive and complementary approach would use ammonium salts as surrogates of ammonia gas for establishing transition-metal-catalyzed reactions. Some ammonium salts have been utilized as ammonia surrogates for transition metal-catalyzed C–N bond formation reactions^{5,6}, yet catalytic reactions between simple alkenes and ammonium salts remain largely unexplored⁷.

Amides are an important class of nitrogen-containing compounds that constitute the major body of bioactive natural products, pharmaceuticals, and the backbones of all natural peptides and proteins⁸. As such, the construction of amidic C–N bond is of utmost importance in synthetic organic chemistry, and has been the subject of tremendous research activity for many years^{9–11}. Among the numerous strategies for the preparation of amides, transition metal-catalyzed hydroaminocarbonylation of alkenes

has emerged as one of the most promising methods, enabling a rapid access to various amides from abundant and cost-effective feedstock materials^{12–22}. At present, these catalytic hydroaminocarbonylative C–N bond formation reactions remain largely confined to the utilization of primary or secondary amines as amine sources (Fig. 1a). Unfortunately, the higher binding ability of these secondary and primary amines to transition metals coupled with their stronger basicity can inhibit the desired reaction to some extent¹². One potential method to circumvent this problem is using ammonia or its surrogates as amine sources to in situ generate alkylamines (Fig. 1b).

In this context, we have previously established a palladium-catalyzed hydroaminocarbonylation of alkenes to primary amides with simple NH_4Cl as an ammonia surrogate¹⁶. In this process, the reaction was initiated via palladium hydride species to form alkylpalladium **i**, which underwent CO insertion to form acylpalladium species **ii**. Direct aminolysis of the resultant intermediate **ii** with NH_4Cl in the presence of CO and NMP afforded the primary amides in excellent yields under very lower catalyst loading (Fig. 1c). Encouraged by this result, we sought to establish a catalytic sequential hydroaminocarbonylation and hydroamination reaction manifold to access secondary amides with NH_4Cl as a nitrogen source, in which the alkylpalladium species **i** was thought to be intercepted by the newly formed primary amide to construct the second C–N bond. Unfortunately, many attempts to realize the aforementioned sequential reaction were failed, although the palladium-catalyzed hydroamination of alkenes with amides has long been well-established^{23–30}. The underlying reason might be largely stemmed from the inherently

Fig. 1 Design relay hydroaminocarbonylation with hydroxylamine chloride. **a** Classical hydroaminocarbonylation with alkylamines. **b** Hydroaminocarbonylation via in situ generation of alkylamine. **c** This work: relay hydroaminocarbonylation with hydroxylamine hydrochloride

lower nucleophilicity of the primary amide, as well as the lower concentration of the alkylpalladium species **i** that exists in the presence of CO. Thus, it is highly desirable to identify an alternative strategy that is capable of producing alkylamines from the simple alkenes and further able to transfer the alkylamines into secondary amides. However, to the best of our knowledge, there is currently no reported strategy that is capable of generation of primary amines via hydroamination of unactivated alkenes with simple ammonia in the presence of CO²⁷.

To this end, we envisioned that a relay hydroaminocarbonylation reaction, in which alkylamine would originate from a simple alkene and hydroxylamine hydrochloride salt (NH₂OH·HCl) via consequence hydroaminocarbonylation and Lossen rearrangement^{31–34}, instead of from hydroamination of alkene with ammonia (Fig. 1c). Hydroxylamine hydrochloride salt is an attractive choice of abundant, cost-effective, and stable nitrogen source, which has been widely utilized as an important nucleophilic reagent in organic synthesis. On the basis of our programmatic focus on the development of Pd-catalyzed hydroaminocarbonylation reactions, we hypothesized that the hydroxylamine hydrochloride could be utilized as a nucleophilic amine source for hydroaminocarbonylation reaction and the tandem hydroaminocarbonylation/Lossen rearrangement sequence would yield the desired alkylamine intermediate. Specifically, aminolysis of acylpalladium intermediate **ii** with NH₂OH·HCl would lead to the formation of hydroxamic acid **iii**, which underwent Lossen rearrangement to give the primary alkylamine **iv** by extrusion of CO₂. The resultant primary alkylamine **iv** is nucleophilic in nature, which should be intercepted by the electrophilic acylpalladium intermediate **ii** to give the desired secondary amides. The key to this strategy is the discovery that the combination of hydroaminocarbonylation and Lossen rearrangement as key strategic steps is uniquely effective for transformation of the hydroxylamine hydrochloride salt to primary alkylamines. Such strategy would be considerably more practical and versatile, as it would not require alkylamines as amine sources, which can overcome the basicity barrier imparted by alkylamines.

Herein, we describe the design and development of Pd-catalyzed relay hydroaminocarbonylation of unactivated alkenes, hydroxylamine hydrochloride salt, and CO coupled with Lossen rearrangement. This study demonstrates that an alkylamine is not necessary for the success of the secondary amide synthesis via hydroaminocarbonylation.

Results

Catalytic system and solvent optimization. At the outset, we anticipated several key challenges associated with this transformation (Fig. 1c). First, it was unclear whether such a protocol could be implemented, as the Lossen arrangement has rarely been accomplished under the carbonylation reaction conditions. Second, HCl, a Brønsted acid will be released over the course of this transformation; thus, a suitable acid-binding reagent must be identified and must not be inhibited in the reaction to drive the reaction forward. Third, there were four potential regioisomers to be generated, thus, the catalyst must be highly selective. With these challenges in mind, we started our proposed catalytic protocol by evaluating the relay hydroaminocarbonylation of styrene **1a** with NH₂OH·HCl in the presence of CO.

In the presence of 2.5 mol% Pd(*t*-Bu₃P)₂, conducting the reaction in NMP under 20 atm of CO for 12 h failed to give any product (Table 1, entry 1). To our delight, when anisole was employed as the solvent, the desired transformation occurred, thus providing the branched-branched secondary amide **2a** in 40% yield with a trace amount of linear-branched amide **4a** (Table 1, entry 2). Other two potential regioisomers were not

detected. These results suggested that the anisole played a key role, which may act as a weak base to capture the released HCl by formation of oxonium salts to drive the reaction forward^{35,36}. Inspired by this promising result, the effect of palladium-catalyst was systematically investigated (Table 1, entries 2–9). Several commonly used palladium-catalysts, such as Pd(PPh₃)₄, Pd(Xantphos)Cl₂, and Pd(PPh₃)₂Cl₂, were firstly evaluated, however no good results were observed (Supplementary Table 1). Further screening of phosphine ligands with Pd(CH₃CN)₂Cl₂ as a catalyst precursor disclosed that sterically congested monodentate phosphine ligands could deliver the desired amide with good regioselectivity, and among the monophosphines that have been evaluated (Supplementary Table 2), the RuPhos (**L4**) showed highest efficiency (71% yield) and was thus kept for the rest of the study. These results revealed that subtle modifications on the monophosphine ligand backbone led to profound changes on the reaction outcome (entries 6–9), suggesting that a reasonable steric bulk was critical for stabilizing the transient reaction species. Furthermore, subsequently experiments demonstrated that variation of the ratio of alkene/NH₂OH·HCl from 1/2.4 to 2.4/1 resulted in higher reactivity and selectivity (71% vs. 89% yield). In line with our expectations, the nature of the solvent used for this reaction proved to be a crucial parameter (Supplementary Table 3). Reactions conducted in anisole gave the best yield and selectivity. Notably, excellent yield (96% isolated yield) and regioselectivity were achieved when the catalyst loading was increased to 5 mol% (entry 17, Supplementary Table 4). Control experiment revealed that a catalyst is necessary for the reaction to take place (entry 18).

Scope of the reaction. After identifying the optimal reaction conditions, we next shifted our focus to investigating the scope of this transformation (Fig. 2). Styrenes bearing different substituents underwent smooth carbonylation to furnish the corresponding regioisomerically pure amides. A variety of electronically disparate *ortho*-, *meta*-, and *para*-substituted styrenes were found to be suitable for this transformation, affording the corresponding branched-branched amide products in 32–98% yields (**2a–2r**). Notably, no other regioisomers were observed for all of alkenes tested here except 2-methylstyrene (the branched-linear product was isolated in 13% yield, see Supplementary Information (SI)). A good range of functional groups, such as methyl, alkyl, ether, halogen (F, Cl, Br), CF₃, OCF₃, CN and even thioether, were well tolerated, which provided a potential synthetic handle for further coupling reactions. It was noted that the electronic nature on the phenyl ring of the styrene had a strong influence on the reactivities. Styrenes bearing electron-donating groups proceeded smoothly to give the corresponding amides in excellent yields with complete regioselectivities. Compared with the results of the substrates with an electron-donating group, the presence of a strong electron-withdrawing group, such as CN (**2j**) and CF₃ (**2k**) led to moderate yields (32–38% yields). The reactions of 1-vinylnaphthalene and 2-vinylnaphthalene delivered **2s** and **2t** in 54% and 85% yields, respectively. In addition, heteroaromatic 2-vinylthiophene also provided product **2u** in 26% yield with good regioselectivity. To further test the applicability of this method for late-stage functionalization, we examined a family of estrone and testosterone substrates. Alkenes derived from these two compounds underwent the present reaction smoothly, leading to the corresponding amides **2w** and **2y** in good yields with excellent regioselectivities. These transformations indicated that the reaction system was amenable to functionalization and modification of complex alkenes bearing the skeleton of natural products, and showed high potential applications in biological evaluation. In addition, the reaction was applicable to internal

Table 1 Catalytic system and solvent optimization of palladium-catalyzed relay hydroaminocarbonylation

entry	[Pd]	ligand	solvent	yield (%) ^a	
				2a	4a
1	$\text{Pd}(\text{t-Bu}_3\text{P})_2$	-	NMP	0	0
2	$\text{Pd}(\text{t-Bu}_3\text{P})_2$	-	anisole	40	4
3	$\text{Pd}(\text{PPh}_3)_4$	-	anisole	3	0
4	$\text{Pd}(\text{Xantphos})\text{Cl}_2$	-	anisole	11	9
5	$\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$	-	anisole	13	0
6	$\text{Pd}(\text{CH}_3\text{CN})_2\text{Cl}_2$	L ₁	anisole	30	1
7	$\text{Pd}(\text{CH}_3\text{CN})_2\text{Cl}_2$	L ₂	anisole	58	11
8	$\text{Pd}(\text{CH}_3\text{CN})_2\text{Cl}_2$	L ₃	anisole	0	0
9	$\text{Pd}(\text{CH}_3\text{CN})_2\text{Cl}_2$	L ₄	anisole	71	13
10 ^b	$\text{Pd}(\text{CH}_3\text{CN})_2\text{Cl}_2$	L ₄	anisole	89	4
11 ^b	$\text{Pd}(\text{CH}_3\text{CN})_2\text{Cl}_2$	L ₄	THF	11	1
12 ^b	$\text{Pd}(\text{CH}_3\text{CN})_2\text{Cl}_2$	L ₄	dioxane	18	0
13 ^b	$\text{Pd}(\text{CH}_3\text{CN})_2\text{Cl}_2$	L ₄	DME	18	1
14 ^b	$\text{Pd}(\text{CH}_3\text{CN})_2\text{Cl}_2$	L ₄	toluene	6	1
15 ^b	$\text{Pd}(\text{CH}_3\text{CN})_2\text{Cl}_2$	L ₄	CH_3CN	13	1
16 ^b	$\text{Pd}(\text{CH}_3\text{CN})_2\text{Cl}_2$	L ₄	DMF	0	0
17 ^{b,c}	$\text{Pd}(\text{CH}_3\text{CN})_2\text{Cl}_2$	L ₄	anisole	99(96)	0
18 ^b	-	L ₄	anisole	0	0

^aReaction conditions: **1a** (1.0 mmol), $\text{NH}_2\text{OH}\cdot\text{HCl}$ (2.4 mmol), $[\text{Pd}]$ (2.5 mol%), ligand (5.5 mol%), CO (20 atm), solvent (1.0 mL), 120°C , 12 h. Yield and diastereoisomer ratio (dr) were determined by GC using *n*-hexadecane as the internal standard, dr in all cases is about 1:1, isolated yield in bracket

^b**1a** (1.2 mmol), $\text{NH}_2\text{OH}\cdot\text{HCl}$ (0.5 mmol)

^c $[\text{Pd}]$ (5.0 mol%), **L4** (11 mol%)

alkenes, as exemplified by the reactions of 1H-indene (**1v**) and prop-1-en-1-ylbenzene (**1x**), which provided the corresponding products (**2v** and **2x**) in moderate yields with excellent regioselectivities. Notably, although the diastereoisomer ratio in all cases is about 1:1, nearly all of the two diastereoisomers could be isolated by flash column chromatography (see Supplementary Methods). The structures of **2l** and **4a** were confirmed by X-ray

single-crystal diffraction analysis (Supplementary Figs. 3 and 4, Supplementary Data 1 and 2).

Encouraged by our success with aromatic alkenes, the reactions of unactivated aliphatic cyclic alkenes were then explored (Fig. 3). After extensively optimizing the reaction conditions (Supplementary Tables 5–10), we found that the catalytic system composed with $[\text{Pd}(\text{allyl})\text{Cl}]_2$ and Xantphos could catalyze the desired

Fig. 2 Substrate scope of palladium-catalyzed relay hydroaminocarbonylation with aromatic alkenes. Reaction conditions: **1** (1.2 mmol), NH₂OH·HCl (0.5 mmol), Pd(CH₃CN)₂Cl₂ (5.0 mol%), L4 (11 mol%), CO (20 atm), anisole (1.0 mL), 120 °C, 12 h, isolated yield. Diastereoisomer ratio in all cases is about 1:1, which was determined by GC or ¹H NMR analysis of crude reaction mixture. ^a140 °C, 24 h. ^b1 (2.0 mmol), 140 °C, 24 h

reaction with anisole as solvent, allowing for significant expansion of the substrate scope. Under the optimized reaction conditions, a broad range of cyclic alkenes, including cyclopentene (**6a**), cyclohexene (**6b**), cycloheptene (**6c**), and *cis*-cyclooctene (**6d**) were amenable to the desired reaction to give the corresponding amides (**7a–7d**) with moderate to good yields (entries 1–4, 42–74% yields). Other cyclic alkenes, such as norbornene and benzonorbornadiene, as well as its derivatives (**6e**, **6g** and **6h**) were also applicable to give secondary amides in 64–85% yields with good diastereoselectivity. Interestingly, the simple linear aliphatic alkenes and functionalized alkenes proceeded smoothly with slightly modified reaction conditions to afford a series of secondary amides in good yields as well (entries 6, and 9–11). It is worth mentioning that the steric hindrance of the alkenes

strongly affects the regioselectivity, and the linear–linear amides were exclusively formed for the steric congested vinylcyclohexane and *t*-butyl ethylene. Finally, the bulk-scale ethylene was applicable to give the corresponding amides **8** in 54% yield with three molecules of alkene incorporated.

Mechanism study. To gain insight into the reaction mechanism, we performed several experiments (Supplementary Figs. 6–18). To test whether the key palladium hydride species could be formed by the reaction of Pd(0) with acidic hydroxylamine hydrochloride. The reaction of Pd(*t*-Bu₃P)₂ with NH₂OH·HCl was initially investigated and monitored by in situ ¹H NMR and ³¹P NMR. After heating the mixture for 5 min, a new signal at –16.35 ppm appeared in the ¹H NMR spectra (Fig. 4c,

Fig. 3 Substrate scope of palladium-catalyzed relay hydroaminocarbonylation with aliphatic alkenes. Reaction conditions: **6** (2.0 mmol), [Pd(allyl)Cl]₂ (2.5 mol%), Xantphos (6.0 mol%), NH₂OH·HCl (0.5 mmol), anisole (2.0 mL), CO (20 atm) at 140 °C for 24 h, isolated yield. ^a120 °C, ^b48 h. ^cEthylene (5 atm), NH₂OH·HCl (5 mmol), [Pd(allyl)Cl]₂ (0.5 mol%), Xantphos (1.2 mol%), anisole (3.0 mL), CO (20 atm) at 140 °C for 24 h. ^dThe dr ratio was determined by GC or ¹H NMR analysis of crude reaction mixture. ^eThe isomer ratio of (linear-linear)/(linear-branched)/(branched-linear) was determined by GC or ¹H NMR analysis of crude reaction mixture

Supplementary Figure 14), which corresponded to the Pd–H resonance of HPd(*t*-Bu₃P)₂Cl species (Fig. 4a, Supplementary Figure 14)¹³. As prolonging the reaction time, the amount of Pd–H species increased accordingly (Fig. 4d, Supplementary Figure 14). At the same time, the ³¹P NMR analysis of the reaction mixture showed that a signal at 81.84 ppm grew up simultaneously (Fig. 4g–i, Supplementary Figure 15), which was assigned to the HPd(*t*-Bu₃P)₂Cl species (Fig. 4f, Supplementary Figure 15)¹³. In addition, the signal of Pd(*t*-Bu₃P)₂ in ³¹P NMR spectra is at 98.04 ppm (Fig. 4e, Supplementary Figure 15). Moreover, the standard reaction could be catalyzed by HPd(*t*-Bu₃P)₂Cl to afford the desired product with good yield (see Supplementary Methods). These results supported that the Pd–H species was indeed formed by the reaction of Pd(*t*-Bu₃P)₂ and NH₂OH·HCl.

Analysis of gas phase of reaction mixture of the standard reaction by using mass spectrometer demonstrated that carbon dioxide (CO₂) was produced (Supplementary Figure 7), which revealed that the oxygen contained in NH₂OH converted into CO₂ and indicated that the Lossen rearrangement was most likely involved in the present reaction. Moreover, monitoring the

standard reaction by ESI-MS disclosed that the hydroxamic acid **9** and α-methylbenzylamine **10** were produced when the reaction was stopped in 2 h (Supplementary Figure 9). However, the *N*-(1-phenylethyl)hydroxylamine, which could be potentially generated from the alkene and hydroxylamine via Cope-type hydroamination reaction³⁷, could not be detected. These results supported the intermediates of hydroxamic acid and primary amine in the catalytic cycle.

It was reported that hydroxamic acids can be converted into secondary amides via Lossen rearrangement and transamidation along with extrusion of NH₂OH^{38,39}. Thus, we considered the possibility that the desired amide **2a** might be produced from the above self-transformation of hydroxamic acids. However, only <10% conversion to **2a** was observed when the hydroxamic acid **9** was heated at 120 °C in the presence of palladium catalyst or not (Fig. 5, Eqs. (1) and (2)), which indicated that self-propagative Lossen rearrangement of hydroxamic acids might be invoked in the transformation of hydroxamic acids into amines. In contrast, treatment of hydroxamic acid **9** with styrene **1a** in the presence of CO and stoichiometric amount of Et₂O·HCl under other identical reaction conditions affords the desired **2a** in 85% yield (Eq. (3)).

Fig. 4 Monitoring the formation of Pd-H species. In situ NMR spectra (**a-i**) of $\text{Pd}(\text{t-Bu}_3\text{P})_2$ with $\text{NH}_2\text{OH}\cdot\text{HCl}$ in benzene- d_6 and anisole supports the formation of $\text{HPd}(\text{t-Bu}_3\text{P})_2\text{Cl}$

These results support that the above self-transformation of hydroxamic acid **9** to **2a** is not the major reaction pathway, but the aminolysis of acylpalladium species with primary amine **10** generated via Lossen rearrangement is likely the major pathway. Moreover, a crossover reaction between hydroxamic acid **9** and 4-methylstyrene **1b** was carried out under the standard carbonylation conditions, and the products **2a** and **2b** were obtained together with the crossover products **11** and **12**. This result together with the fact that relatively higher yields obtained for the 4-methylstyrene-derived amides (**2b**, **11** and **12**) further supports our original mechanistic hypothesis.

Although the detailed mechanism of the present reaction is not clear, we suggest the following catalytic cycle (Fig. 6) based on our preliminary observations and previous work on hydroaminocarbonylation of alkenes with NH_4Cl ¹⁵. Initially, the palladium-hydride species would be generated in situ from the oxidative addition of $\text{Pd}(0)$ and $\text{NH}_2\text{OH}\cdot\text{HCl}$. Reversible coordination and insertion of alkene into the palladium-hydride yields a Pd-alkyl intermediate **A**, which undergoes CO insertion to form intermediate **B**. Aminolysis of **B** with $\text{NH}_2\text{OH}\cdot\text{HCl}$ under the assistance of anisole leads to hydroxamic acid **C** along with palladium hydride species, in which the released HCl might

be trapped by anisole. Finally, Lossen rearrangement of hydroxamic acid **C** takes place to give the primary amine **D**, which was then intercepted by acylpalladium complex **B**, leading to the desired amide **2** and regeneration of the palladium hydride species. Alternatively, the minor reaction pathway by transamidation of hydroxamic acid **C** with amine **D** to afford **2** might be also involved in the catalytic reaction.

Discussion

In summary, we have disclosed an approach to secondary amides via Pd-catalyzed relay hydroaminocarbonylation of simple alkenes with the simple and abundant $\text{NH}_2\text{OH}\cdot\text{HCl}$ as an ammonia surrogate. In this process, the requisite alkylamine coupling partner for secondary amide preparation is produced in situ via hydroaminocarbonylation/Lossen rearrangement sequence, which enables two molecules of alkene to be incorporated into the functionalized amides. This approach allows for the facile and highly regioselective formation of C–N bonds from various aromatic alkenes, cyclic aliphatic alkenes, and $\text{NH}_2\text{OH}\cdot\text{HCl}$, where an hydroxylamine hydrochloride salt can now be thought of as a surrogate of ammonia in

Fig. 5 Control experiments. Transformation of the proposed reaction intermediate

Fig. 6 Plausible reaction mechanism. The proposed mechanism involves a palladium-hydride species and a Lossen rearrangement sequence

alkene-functionalization reactions. This study lays a foundation for the use of hydroxylamine chloride as versatile ammonia equivalent in transition metal-catalyzed reactions.

Methods

General procedure for the palladium-catalyzed relay hydroaminocarbonylation. In a glove box, NH₂OH·HCl (35.0 mg, 0.5 mmol), Pd(CH₃CN)₂Cl₂ (6.6 mg, 0.025 mmol), RuPhos (25.8 mg, 0.055 mmol), styrene (124.8 mg, 1.2 mmol), and anisole (1.0 mL) were added into a glass tube which was placed in an autoclave. The autoclave was taken out from the glove box and then the autoclave was purged and charged with CO (20 atm). The resulting reaction mixture was then stirred at 120 °C for 12 h. After the reaction finished, the autoclave was cooled to room temperature and the gas was carefully released in the fume hood. The diastereoisomer ratio of the secondary amide was determined by GC or ¹H NMR analysis of the crude reaction mixture. Then the corresponding reaction mixture was purified by flash column chromatography on a silica gel column (petroleum ether/ethyl acetate = 100/1 – 1/1) to give the desired product **2a**.

Synthesis and characterization. Full synthetic procedures and characterization for products are available in the Supplementary Methods. Full synthetic procedures for **2a** and **7j** are available in Supplementary Figs. 1 and 2. The ORTEP drawing of products **4a** and **2l'** are available in Supplementary Figs. 3 and 4. Full procedures for the synthesis of **8** are available in Supplementary Figure 5.

Mechanistic study. Full procedures for the mechanism study are available in the Supplementary Methods and Supplementary Figs. 6–18.

Synthetic transformations. Full procedures for synthetic transformations of compounds **2a** and **2n** are available in the Supplementary Methods and Supplementary Figs. 19 and 20.

NMR spectra. ¹H, ¹³C, and ¹⁹F NMR spectra of purified compounds are available in Supplementary Figs. 21–87.

Crystallography. X-ray crystallographic CIF files for compounds **4a** and **2l'** are available in Supplementary Data 1 and 2. X-ray-derived ORTEP representations of **4a** and **2l'** are available in Supplementary Figs. 3 and 4.

Data availability

The X-ray crystallographic data for this paper have been deposited at the Cambridge Crystallographic Data Centre (CCDC) with the accession code CCDC 1863093 (**2l**) and 1863095 (**4a**). These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB21EZ, UK; fax: (+44)1223-336-033; or deposit@ccdc.cam.ac.uk). The authors declare that all other data supporting the findings of this study are available within the article and Supplementary Information files, and also are available from the corresponding author upon reasonable request.

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Author contributions

H.H. designed the project and wrote the paper. J.L., S.W. and S.Z. carried out the experimental work. All authors analyzed the data and discussed the results and commented on the manuscript.

Additional information

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