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Dimethylamino-iodine(III)/PPh_3-mediated synthesis of α-ketoamides from glyoxylic acids

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The development of efficient synthetic approaches to α-ketoamides remains a significant objective. Herein, we report a mild and metal-free method for the preparation of α-ketoamides from glyoxylic acids, mediated by a dimethylamino-iodine(III)/PPh_3 system. This method is further utilized for the *in situ* generation of amino-based hypervalent iodine(III) reagents, which enable the formation of diverse α-ketoamides. Mechanistic studies suggest that the transformation proceeds through an ionic pathway, involving the formation of an active dimethylamino-phosphonium species derived from the reaction between the novel dimethylamino-iodine(III) reagent (**DMI**) and PPh_3.

Introduction

α-Ketoamides constitute a distinct and highly valued class of privileged structural motifs characterized by a keto group at the α-position of an amide. Numerous bioactive natural products and marine metabolites, including tacrolimus (FK506),[1] colibrimycin C,[2] cytokine inhibitor[3] and indibulin,[4] feature the α-ketoamide backbone (Fig. 1a).[5] The exceptional biological activity of α-ketoamides arises mainly from the electrophilic α-keto group and has been widely exploited in the design and synthesis of non-natural antiviral agents, such as narlaprevir[6] and leritrelvir,[7] all of which are FDA-approved (Fig. 1b).[8]

Often referred to as activated amides, α-ketoamides combine the reactivity of ketones and amides, possessing two pronucleophilic and two proelectrophilic centers.[9] Therefore, they are highly reactive species that undergo a variety of chemical transformations, including nucleophilic addition,[10] as well as enantioselective and chemoselective reductions.[11] Furthermore, they also act as synthetic equivalents of various organic building blocks, including homoenolates[12] and α-amido silyl enol ethers,[13] thereby serving as versatile precursors to a wide range of heterocycles[14] and structurally diverse scaffolds such as γ-lactams,[15] α-ketoesters, α-ketothioesters and sterically hindered 1,2-diols.[16]

Owing to the importance of the aforementioned factors, numerous methods have been developed for the synthesis of α-ketoamides.[3,17] In particular, various approaches have employed α-hydroxyamides, α-aminoamides,[18] acetophenones,[19] aryl halides,[20] α-ketoaldehydes,[21] styrenes,[22] phenylacetylenes,[23] enaminones,[24] vinyl azides[25] and diazo compounds[26] as key substrates to facilitate this transformation. These methods generally require metal catalysts, photocatalysts or base additives under diverse conditions. Given their broad utility, greener and more direct methods for synthesizing α-ketoamides are still highly desirable.

Recently, glyoxylic acids have been widely utilized as ideal coupling partners in C–N bond-forming reactions to prepare α-ketoamides, offering an attractive alternative to costly organometallic reagents and minimizing toxic metal waste (Fig. 2a).[27] In the electrochemical field, Wei's group reported the synthesis of α-ketoamides *via* a decarboxylative coupling of α-keto acids with isocyanides and water.[28] Later, a carbonyl-

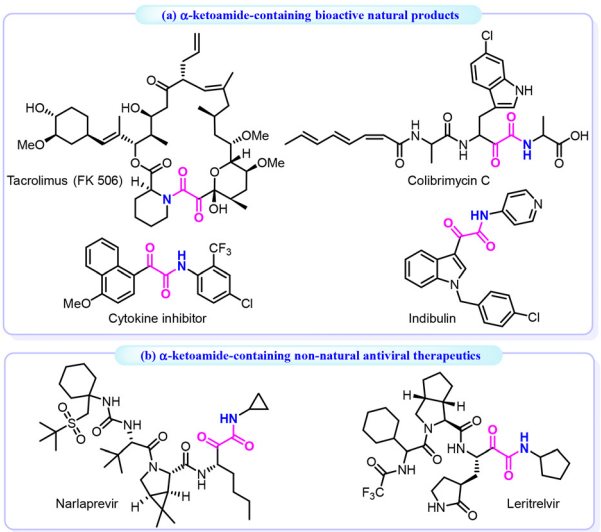

Fig. 1 Representative examples of naturally-occurring and therapeutic α-ketoamides.

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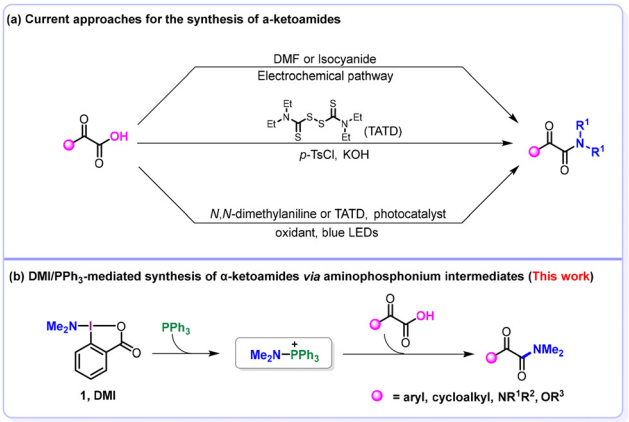
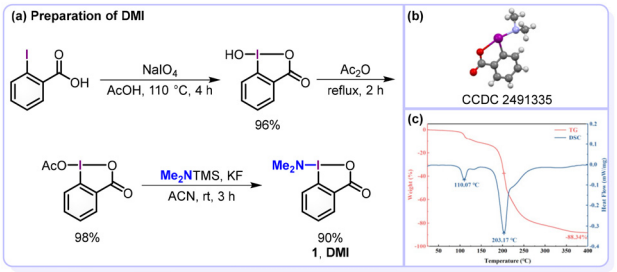


Fig. 2 Different strategies for the synthesis of α-ketoamides from glyoxylic acids.

carbonyl radical electrochemical cross-coupling between a dimethylcarbamoyl radical, generated from DMF, and an acyl radical derived from the electrochemical decarboxylation of α-ketoacids was developed by Gong's group.[29] In 2019, Zhao's group achieved the tosyl chloride-mediated synthesis of aryl thioamides and aryl-α-ketoamides through base-promoted decarboxylative functionalization of α-oxocarboxylic acids with tetraalkylthiuram disulfides (TATD).[30] Additionally, under visible-light irradiation, Jana's group developed a biomimetic strategy for the highly selective monodemethylation of *N*,*N*-dimethylanilines to afford secondary amines, which subsequently coupled with α-ketocarboxylic or alkynyl carboxylic acids to furnish α-ketoamides.[31] In 2024, a visible-light-promoted α-ketoamidation of α-oxocarboxylic acids with TATD, using PIDA as the oxidant through a radical pathway was reported by Majee's group.[32] However, all of the above method required amino agents with additional oxidants, *via* specific electrochemical or photochemical pathway to generate α-ketoamides. Herein, we report a mild and metal-free method for the preparation of α-ketoamides from glyoxylic acids, mediated by a dimethylamino-iodine(III)/PPh_3 system *via* dimethylaminophosphonium intermediates generated *in situ*.

Owing to the low toxicity, mild reactivity, readily availability, high stability, and ease of handling, hypervalent iodine reagents have recently attracted considerable attention as oxidants in diverse coupling reactions.[33] In particular, iodine(III) reagents bearing aliphatic amino groups have been synthesized and shown to exhibit excellent reactivity as amination reagents.[34] Our group has also been engaged in developing diverse methodologies utilizing hypervalent iodine reagents,[35] and we are particularly interested in the development of a novel dimethylamino-iodine(III) reagent (**DMI**), which was synthesized for the first time with straightforward three-step sequence (Scheme 1a) and characterized by NMR spectroscopy and X-ray crystallography (Scheme 1b, CCDC 2491335). Notably, **DMI** could be prepared on a multigram scale (4.9 g) without loss of yield. It is bench stable to air and moisture and could be stored at −20 °C for up to six months without detectable degradation. Thermogravimetric and differential scanning calorimetry (TG-DSC) measurements showed an exothermic decomposition at 203.2 °C with a mass change of 88.3%, which demonstrated that **DMI** had good thermal stability (Scheme 1c). With this newly developed **DMI** in hand, we envisioned that the reaction of glyoxylic acids with **DMI** might directly afford α-ketoamides.

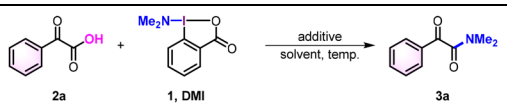


Scheme 1 Preparation and identification of the hypervalent iodine reagent **DMI**.

Results and discussion

Initially, benzoylformic acid **2a** was used as a substrate and **DMI** as the aminating reagent, but the reaction failed to proceed (entry 1, Table 1). In 2018 and 2021, Zhdankin and coworkers reported that alcohols and amines reacted efficiently

Table 1 Optimization of the reaction conditions[a]



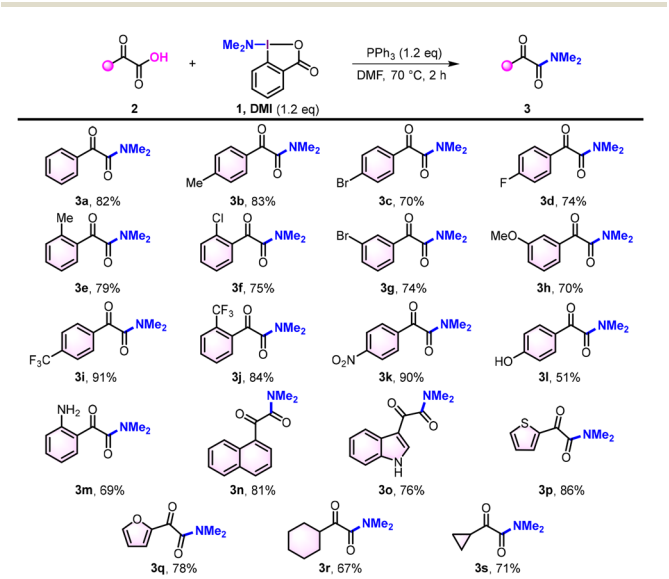
Entry	*x* equiv. of **DMI**	Additive (*y* equiv.)	Solvent	*T* (°C)	Yield[d] (%)
1	1.2	—	DMF	100	NR[e]
2	1.2	PPh_3 (1.2)	DMF	100	66
3	1.2	**PPh_3 (1.2)**	**DMF**	**70**	**82**
4	1.2	PPh_3 (1.2)	DMF	50	68
5	1.2	PPh_3 (1.2)	DMF	rt	42
6	1.2	P(*p*-anisole)$_3$ (1.2)	DMF	70	73
7	1.2	Ph_2POEt (1.2)	DMF	70	15
8	1.2	P(*n*-Bu)$_3$ (1.2)	DMF	70	21
9[b]	1.2	DMS (1.2)	DMF	70	NR
10	1.2	Et_3N (1.2)	DMF	70	NR
11	1.2	PPh_3 (1.2)	DMSO	70	78
12	1.2	PPh_3 (1.2)	Toluene	70	67
13	1.2	PPh_3 (1.2)	Dioxane	70	63
14	1.2	PPh_3 (1.2)	ACN	70	54
15	1.2	PPh_3 (1.2)	DCE	70	65
16	1.2	PPh_3 (1.2)	EtOH	70	NR
17	1.2	PPh_3 (1.2)	HFIP	70	NR
18	3.0	PPh_3 (3.0)	DMF	70	79
19[c]	1.2	PPh_3 (1.2)	DMF	70	80

[a] Reaction conditions: **2a** (0.4 mmol), **DMI** (x equiv.), additive (y equiv.), solvent (2.0 mL), 70 °C, 2 h. [b] Sealed tube. [c] Inert atmosphere. [d] Isolated yield. [e] NR = no reaction.

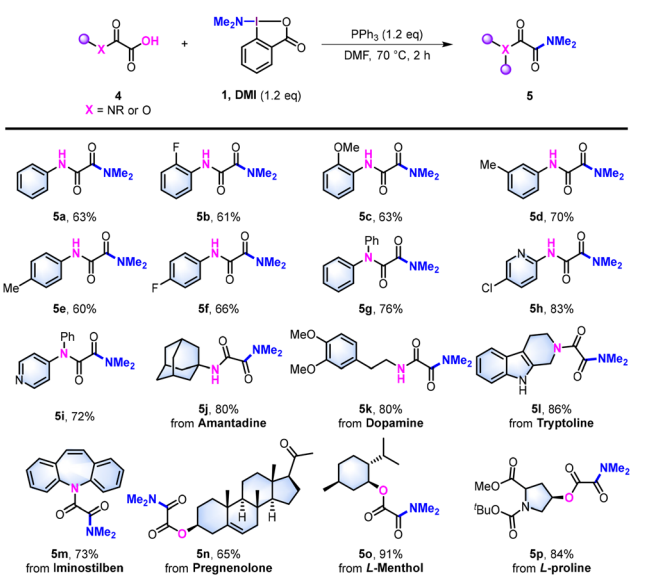
with various benziodazolones in the presence of PPh_3 to afford corresponding esters and amides.[36] Inspired by these work, we employed PPh_3 as an additive in this transformation. Fortunately, the reaction proceeded smoothly with 1.2 equivalents of PPh_3 as an additive in DMF at 100 °C for 2 h, affording the desired *N*,*N*-dimethyl-2-oxo-2-phenylacetamide **3a** in 66% yield (entry 2, Table 1). The optimal yield of 82% was achieved at 70 °C, whereas higher temperatures decreased the yield, and room-temperature conditions also resulted in lower conversions (entries 3–5, Table 1). Furthermore, alternative organophosphorus reagents were tested, such as tris(4-methoxyphenyl)phosphine [P(*p*-anisole)$_3$], ethyl diphenylphosphinite (Ph_2POEt) and tributylphosphine [P(*n*-Bu)$_3$], but all of them gave significantly lower yields (entries 6–8, Table 1). Notably, the use of dimethyl sulfide (DMS) and triethylamine (Et_3N) as a reductant, completely suppressed the reaction (entries 9 and 10, Table 1). Various solvent was also performed. DMSO, toluene, dioxane, ACN and DCE enabled the transformation to afford **3a** in 54–80% yields (entries 11–15, Table 1), whereas protonic solvents such as EtOH and HFIP, completely suppressed the reaction (entries 16 and 17, Table 1). We tentatively proposed that the outcome could possibly be caused by the instability of dimethylaminophosphonium **Int. 1** in EtOH and HFIP, based on the results of some control experiments (see SI, Scheme S2). Further improvement using 3.0 equivalents of **DMI** and PPh_3 gave **3a** in 79% yield (entry 18, Table 1). Moreover, a comparable result of an 80% yield was obtained under an inert atmosphere, implying this transformation was insensitive to air and moisture (entry 19, Table 1).

With the optimal reaction conditions in hand (entry 3, Table 1), we next examined the substrate scope using various aromatic, aliphatic and heteroaryl glyoxylic acids (Scheme 2). Specifically, phenylglyoxylic acids bearing electron-donating groups (–Me, –OMe) or halogen substituents (–F, –Cl, –Br) at the *ortho*-, *meta*- or *para*-positions of the phenyl ring reacted efficiently, affording the corresponding products (**3b–h**) in moderate to good yields. Notably, this protocol was also compatible with electron-withdrawing groups (–NO_2, –CF_3) and reactive groups (–OH, –NH_2) at the *ortho*- and *para*-positions of the phenyl ring, affording the desired products (**3i–m**) in 51–91% yields. Furthermore, phenylglyoxylic acids bearing a 1-naphthyl substituent, as well as heteroaryl glyoxylic acids containing indole, thiophene or furan units, also delivered the desired products **3n–q** smoothly in yields of 76–86%. In addition, cyclohexyl- and cyclopropyl-substrates afforded the corresponding α-ketoamide **3r** and **3s** in 67% and 71% yield, respectively. We also attempted to extend the present reaction system to benzoic acid and 2-naphthylacetic acid as substrates. Unfortunately, the corresponding experimental results demonstrated that they were not compatible with the established transformation (not shown).

Encouraged by these results, we next examined the dimethylamination of N(O)-substituted glyoxylic acid substrates using this newly established **DMI**/PPh_3 system (Scheme 3). This protocol efficiently furnished *N*-substituted unsymmetric α-ketoamide **5a** in a 63% yield. Substrates bearing either electron-withdrawing (–F) or electron-donating (–Me, –OMe) substituents on the phenyl ring were well tolerated, affording the desired products **5b–f** with 60–70% yields. Phenol-protected substrate also reacted smoothly to afford product **5g** in a yield of 76%. In addition, 2-((5-chloropyridin-2-yl)amino)- and 2-(phenyl(pyridin-4-yl)amino)-substituted 2-oxoacetic acids afforded the corresponding products **5h** and **5i** in 83% and 72% yields, respectively. Furthermore, the mild conditions and excellent functional group tolerance enabled the application of this method to the dimethylamination of drugs and natural



Scheme 2 Scope of various aromatic, aliphatic and heteroaryl glyoxylic acids. Reaction conditions: **2** (0.4 mmol), **DMI** (1.2 equiv.), PPh_3 (1.2 equiv.), DMF (2.0 mL), 70 °C, 2 h.



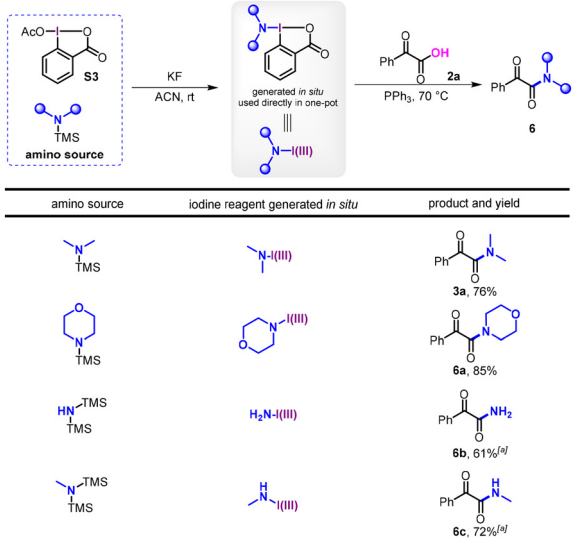
Scheme 3 Dimethylamination of *N*(*O*)-substituted glyoxylic acid substrates. Reaction conditions: **2** (0.4 mmol), **DMI** (1.2 equiv.), PPh_3 (1.2 equiv.), DMF (2.0 mL), 70 °C, 2 h.

products containing glyoxylic acid moieties. *N*-Substituted drugscaffolds, such as adamantane, dopamine, tryptoline and iminostilbene were successfully converted into the corresponding dimethylaminated products **5j–m** in good yields of 73–86%. Moreover, a range of *O*-substituted natural compounds were also examined. All tested molecules, including pregnenolone, L-menthol, and L-proline, were well tolerated under the standard conditions, affording the desired products **5n–p** in 65–91% yields. All of these drug molecules underwent initial modification using α-ketoamides with this method, offering an innovative strategy for introducing biologically active electrophilic α-keto groups into drug molecules.

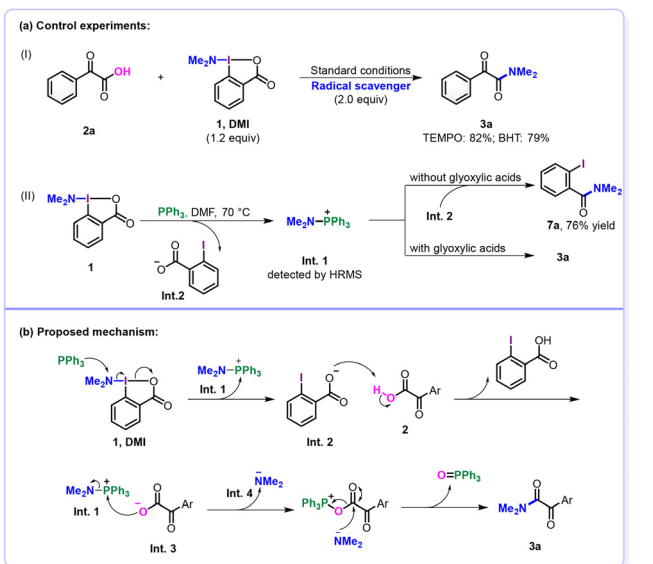
With above results in hand, we investigated whether the aminated hypervalent iodine reagent could be generated *in situ*, thereby enabling the introduction of diverse amino functional groups in a one-pot reaction under mild conditions (Scheme 4). To test this hypothesis, **DMI** was first prepared using *N*,*N*-dimethyltrimethylsilylamine and catalytic KF in ACN. After 2 h of reaction, the crude mixture containing **DMI** was used directly without any purification. Substrate **2a** and PPh_3 were added and the mixture was stirred at 70 °C for an additional 2 h. Gratifyingly, this one-pot protocol afforded the desired product **3a** in a yield of 66%. Furthermore, various amino sources [4-(trimethylsilyl)morpholine], hexamethyldisilazane and heptamethyldisilazane were employed, affording the corresponding products **6a–c** in 61–85% yields, respectively. Notably, when hexamethydisilazane was used as the amino source, the reaction generated NH_2-substituted species *in situ* and the primary amine product **6b** was obtained successfully in a yield of 61%. Unfortunately, the results indicated that amino sources, such as aniline, benzylamine, and *N*-methylaniline, are not compatible with this protocol, as no desired products were detected in all cases (see SI, Scheme S1). This unfavorable outcome could plausibly be ascribed to the instability of the corresponding amino-iodine(III) intermediates under the standard reaction conditions.

To gain insight into the reaction mechanism, control experiments were carried out to explore the possible pathway of this α-ketoamidation reaction (Scheme 5a). First, the reaction proceeded smoothly in the presence of radical scavengers such as TEMPO and BHT (Scheme 5a, I), indicating that a radical pathway was unlikely. Strickingly, when **DMI** and PPh_3 were reacted in the absence of glyoxylic acids, a dimethylaminophosphonium **Int. 1** could be detected by HRMS, and 2-iodo-*N*,*N*-dimethylbenzamide **7a** was isolated in a 76% yield. This result suggested that, in the absence of glyoxylic acid, **Int. 1** further reacted with *ortho*-iodobenzoate **Int. 2**, which was derived from the reduction of **DMI**, giving dimethylbenzamide **7a** (Scheme 5a, II). However, in the presence of glyoxylic acids, the *ortho*-iodobenzoate preferentially reacted with the substrates to generate the 2-oxo-2-phenylacetate, which subsequently coupled with **Int. 1** to afford the desired product **3a**. In addition, ammonium chloride and dimethylamine were separately reacted with glyoxylic acid in the presence of triphenylphosphine. The experimental results showed that no desired product was obtained, thereby demonstrating the unique role of **DMI** in this transformation (see SI, Scheme S2, d).

Based on the above experimental results, a plausible mechanistic pathway was proposed in Scheme 5b. Initially, the hypervalent iodine(III) reagent **DMI** reacts with PPh_3 to generate a dimethylaminophosphonium **Int. 1**, together with *ortho*-iodobenzoate **Int. 2**. Subsequently, iodobenzoate **Int. 2** acts as a base to deprotonate acetoacetic acid **2**, affording the 2-oxo-2-phenylacetate **Int. 3**. This nucleophilic anion then attacks the



Scheme 4 Introduction of diverse amino functional groups in one-pot protocol. Reaction conditions: **S3** (2.0 mmol, 1.0 equiv.), nitrogen source (1.5 equiv.), KF (0.1 equiv.), ACN (10 mL), rt, 2 h; then **2a** (2.0 mmol), PPh_3, 70 °C, 2 h. [a]EtOH (1.5 equiv.) was added.



Scheme 5 Mechanistic experiments and proposed reaction mechanism.

phosphonium center of **Int. 1**, releasing the dimethyl anion **Int. 4**. The latter species subsequently attacks the carbonyl carbon, furnishing the desired α-ketoamide **3a** along with triphenylphosphine oxide as a byproduct, which was detected by TLC analysis.

Conclusions

In summary, we have developed a mild and metal-free method for the preparation of α-ketoamides from glyoxylic acids, mediated by a **DMI**/PPh_3 system *via* dimethylaminophosphonium intermediates generated *in situ*. This methodology is applicable to the dimethylamination of *N*(*O*)-substituted glyoxylic acid substrates and active drug molecules, highlighting its potential for synthesizing more complex α-ketoamide derivatives. The utility of this method is further demonstrated by the *in situ* generation of amino-based hypervalent iodine(III) reagents, which enable the formation of diverse α-ketoamides. Broad substrate scope, aerobic conditions, and excellent functional-group tolerance render this protocol a practical approach for accessing various a-ketoamide derivatives.

Author contributions

D. X. and Y. D. conceived and designed the experiments. D. X. carried out most of experiments. J. H., K. Y., Z. W. and C. L. analyzed data; D. X. and Y. D. wrote the paper and directed the project.

Conflicts of interest

There are no conflicts to declare.

Data availability

The data supporting this article have been included as part of the SI: General procedures for the synthesis of starting materials, characterization of products, control experiments, and NMR spectra of products can be found in the SI. See DOI: **https://doi.org/10.1039/d5qo01675d**.

CCDC 2491335 contains the supplementary crystallographic data for this paper.[37]

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