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Transition Metal-Free Synthesis of 3-Alkynylpyrrole-2-carboxylates *via* Michael Addition/Intramolecular Cyclodehydration

Qing-hu Teng,[+a] Yan-li Xu,[+b] Ying Liang,[c,*] Heng-shan Wang,[a] Ying-chun Wang,[a] and Ying-ming Pan[a,*]

[a] Key Laboratory for the Chemistry and Molecular Engineering of Medicinal Resources (Ministry of Education of China), School of Chemistry and Pharmaceutical Sciences of Guangxi Normal University, Guilin 541004, People's Republic of China
Fax: (+86)-773-580-3930; e-mail: panym@mailbox.gxnu.edu.cn
[b] College of Pharmacy, Guilin Medical University, Guilin 541004, People's Republic of China
[c] School of Life and Environmental Sciences, Guilin University of Electronic Technology, Guilin 541004, People's Republic of China
Fax: (+86)-773-219-1683; e-mail: liangyi0774@guet.edu.cn
[+] These authors contributed equally to this work.

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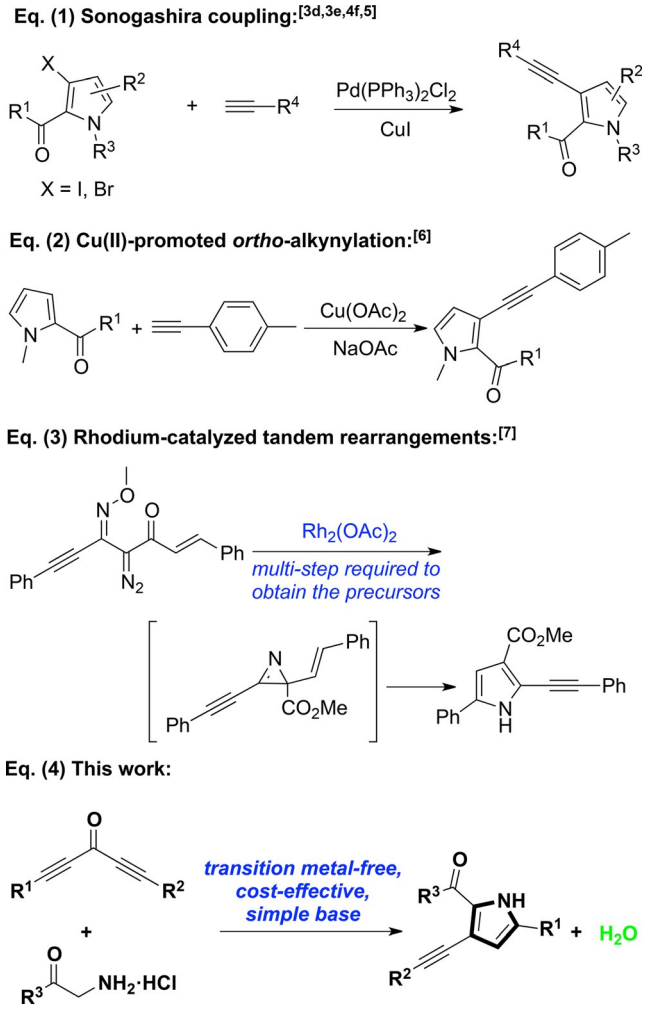
Abstract: A transition metal-free and efficient method for the synthesis of 3-alkynylpyrrole-2-carboxylates from diynones and glycine esters or 2-aminoacetophenone hydrochloride has been developed. This transformation provides a large range of substituted pyrroles in good to excellent yields with the elimination of water as the only by-product. The detailed mechanistic studies elucidated that this transformation involves a Michael addition/intramolecular cyclodehydration process.

Keywords: 3-alkynylpyrrole-2-carboxylates; 2-aminoacetophenones; diynones; glycine esters

Pyrroles are among the most prevalent and important heterocycles in natural products, modern pharmaceuticals, and materials science.[1,2] In particular, 3-alkynylpyrrole-2-carboxylates have been used for the preparation of polyfunctional pyrrole and indole derivatives with distinct structures and properties.[3] They also play significant roles in designing macrocycles that possess a wide variety of biological activities.[4] Indeed, the applications of pyrroles continue to drive the interest in the development of new approaches to the preparation of 3-alkynylpyrrole-2-carboxylates. Among them, the most commonly used method is the well-known Sonogashira coupling reaction of halogenated pyrroles with terminal alkynes in the presence of a palladium catalyst and a copper source (cocatalyst) [Scheme 1 Eq, (1)].[3d,e,4f,5] A more recent strategy for the construction of 3-alkynylpyrrole-2-carboxylates is the Cu(II)-promoted *ortho*-alkynylation of pyrroles with terminal alkynes [Scheme 1 Eq. (2)].[6] However, these reported methods primarily rely on the incorporation of alkynyl groups into pyrrole substrates. Thus, the direct assembly of polysubstituted pyrroles from simple and readily available starting materials remains a challenging and attractive research topic. Recently, Park and co-workers have reported that polysubstituted pyrroles can be formed by rhodium-catalyzed tandem rearrangements of α-diazo oxime ethers [Scheme 1 (Eq. (3)].[7] Although this improvement is a useful complement to the current approaches, the method suffers from several additional drawbacks, such as expensive catalysts and multi-step synthesis of precursors.

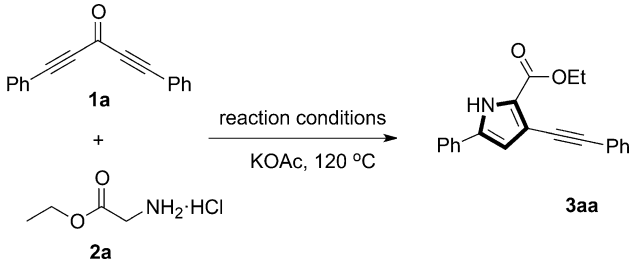
Diynones, symmetrical molecules with multiple reaction sites, are highly nucleophilic acceptors to construct diverse types of attractive cyclization products.[8] To the best of our knowledge, there have been no reports of the preparation of 3-alkynylpyrrole-2-carboxylates from diynones and glycine esters or 2-aminoacetophenone hydrochloride. As part of our continuing efforts in the development of efficient methods for the preparation of N-heterocycles,[9] herein we report a transition metal-free synthesis of 3-alkynylpyrrole-2-carboxylates from diynones and glycine esters or 2-aminoacetophenone hydrochloride *via* a Michael addition/intramolecular cyclodehydration process.



Scheme 1. Approaches to polysubstituted pyrroles.

The reaction of 1,5-diphenylpenta-1,4-diyn-3-one **1a** with ethyl glycinate hydrochloride **2a** was chosen as a model system for the optimization studies (Table 1). Initially, the reaction was carried out in the presence of $KHCO_3$ (1 equiv.) and KOAc (1 equiv.) in DMF at 120 °C for 2 h, affording the desired product **3aa** in 85% yield (Table 1, entry 1). The investigation of various bases [K_2CO_3, Na_2CO_3, Cs_2CO_3, *t*-BuOK, NaOH, KOH, CH_3ONa, $NH_3{\cdot}H_2O$, $(HOCH_2CH_2)_3N$, DMAP, Et_3N] revealed that inorganic bases were more effective than organic amine bases and that $KHCO_3$ was optimal (Table 1, entries 1–12). The control experiments indicated that a combination of $KHCO_3$ and KOAc was indispensable in this reaction (Table 1, entries 13 and 14). When a stronger base, K_2CO_3, was used alone, the reaction afforded the desired product in low yield (Table 1, entry 15). Further experiments demonstrated that a decrease in the loading amount of either $KHCO_3$ or KOAc reduced the yield of **3aa** significantly (Table 1, entries 16 and 17). Moreover, a solvent screening study indicated that DMF was the most suitable solvent for this transformation (Table 1, entry 1 vs. entries 18–20). A decrease in the temperature from 120 °C to 80 °C resulted in the desired product in lower yields (Table 1, entry 1 *vs.* entry 21). Therefore, the optimal conditions for this transformation are $KHCO_3$ (1 equiv.) and KOAc (1 equiv.) in DMF at 120 °C for 2 h.

Table 1. Optimization of the reaction conditions.[a]

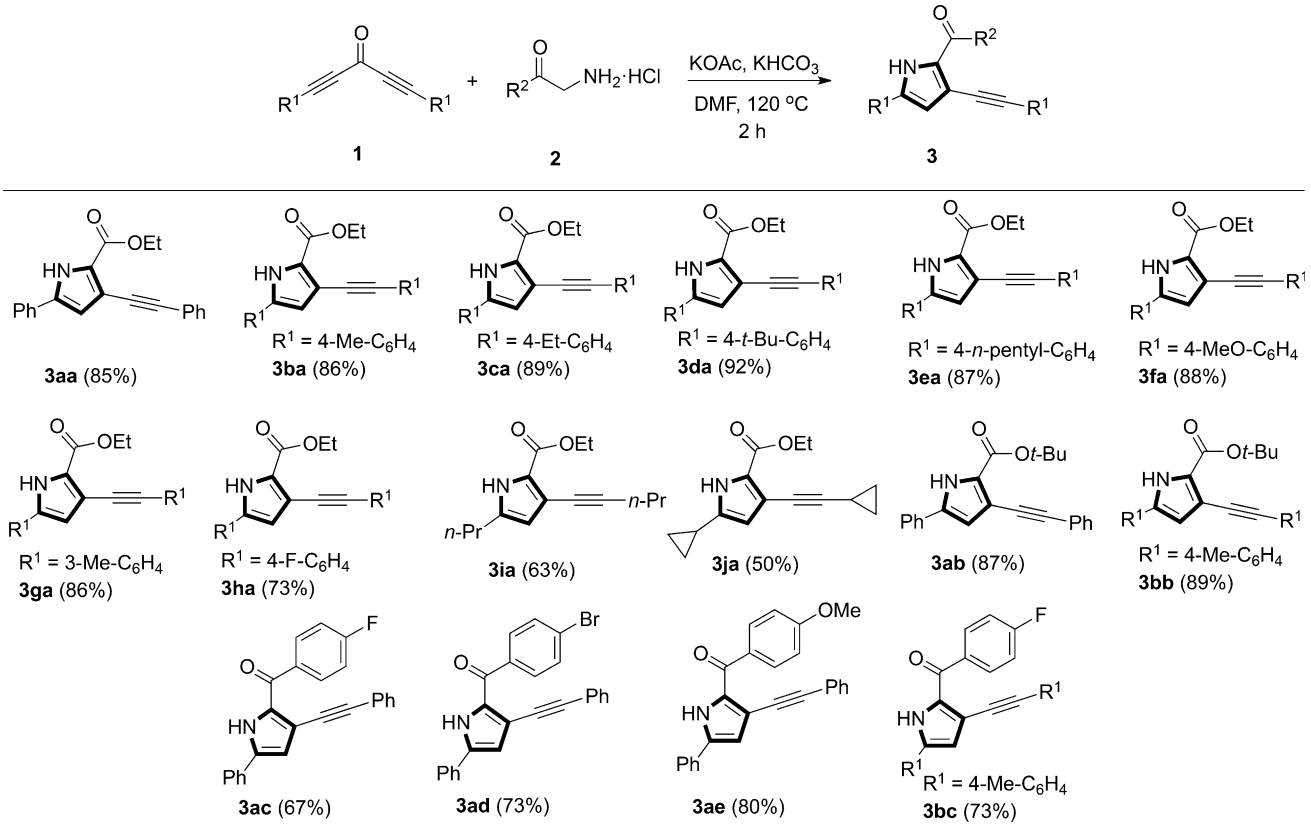


Entry	Base	Solvent	Yield [%][b]
1	**$KHCO_3$**	**DMF**	**85**
2	K_2CO_3	DMF	80
3	Na_2CO_3	DMF	78
4	Cs_2CO_3	DMF	30
5	*t*-BuOK	DMF	60
6	NaOH	DMF	55
7	KOH	DMF	32
8	CH_3ONa	DMF	43
9	$NH_3{\cdot}H_2O$	DMF	trace
10	$(HOCH_2CH_2)_3N$	DMF	trace
11	DMAP	DMF	trace
12	Et_3N	DMF	25
13[c]	$KHCO_3$	DMF	trace
14[d]	–	DMF	trace
15[e]	K_2CO_3	DMF	40
16[f]	$KHCO_3$	DMF	48
17[g]	$KHCO_3$	DMF	46
18[h]	$KHCO_3$	toluene	0
19[h]	$KHCO_3$	CH_3OH	20
20[h]	$KHCO_3$	CH_3CN	0
21[i]	$KHCO_3$	DMF	59

[a] *Reaction conditions*: **1a** (0.5 mmol), **2a** (0.6 mmol), base (1 equiv.), KOAc (0.5 mmol), solvent (2 mL), 2 h, 120 °C.
[b] Isolated yields (based on **1a**).
[c] Using $KHCO_3$ (2 equiv.), without KOAc.
[d] Using KOAc (2 equiv.).
[e] Using K_2CO_3 (2 equiv.), without KOAc.
[f] Using $KHCO_3$ (0.5 equiv.).
[g] Using $KHCO_3$ (0.5 equiv.), KOAc (0.5 equiv.).
[h] The reaction was carried out in a sealed tube.
[i] At 80 °C.

With the optimal conditions in hand, we next extensively evaluated the substrate scope and functional group tolerance of this reaction (Table 2). Gratifyingly, the desired products were obtained in excellent yields from the reactions of diynone substrates with various substitutes. This reaction is relatively tolerant of both electron-withdrawing and electron-donating groups on the phenyl ring. Specifically, diynones featuring electron-donating groups on the phenyl ring

Table 2. Synthesis of 3-alkynylpyrrole-2-carboxylates.[a,b]



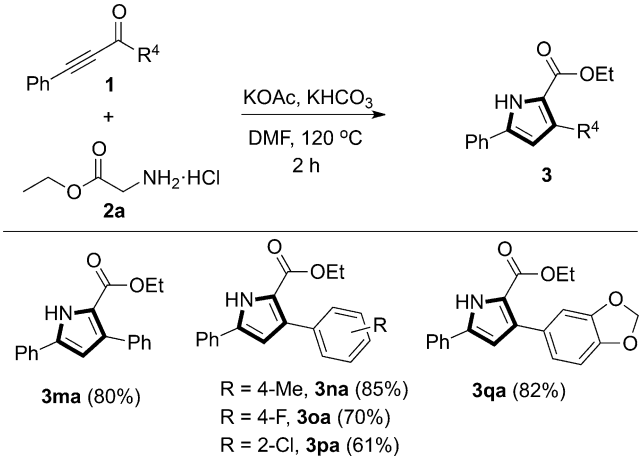
[a] *Reaction conditions*: **1** (0.5 mmol), **2** (0.6 mmol), $KHCO_3$ (1 equiv.), KOAc (1 equiv.), DMF (2 mL), at 120 °C, 2 h.
[b] Isolated yields (based on **1**).

typically provided higher yields of the pyrroles than those bearing electron-withdrawing groups (**3aa**–**3ga** *vs.* **3ha**). Recrystallization of **3ha** in a mixture of hexane and CH_2Cl_2 resulted in single crystals, the molecular structure of which was further confirmed by X-ray crystallographic analysis.[10] To our delight, the diynone **1g** possessing an electron-donating group at the *meta*-position of phenyl ring ($R^1 = R^2 = 3$-Me-C_6H_4) reacted readily to afford the desired product **3ga** in 86% yield. This reaction is also compatible with aliphatic diynones, furnishing the desired product in good yields (**3ia** and **3ja**). In addition, 67–89% yields of the corresponding products (**3ab**–**3bc**) were obtained when R^2 was *t*-BuO-, 4-F-C_6H_4, 4-Br-C_6H_4, or 4-MeO-C_6H_4. Unfortunately, when R^2 was a chain structure, such as ethyl 5-amino-4-oxopentanoate and ethyl 2-(2-aminoacetamido)acetate, the reaction failed to yield the desired products under the typical reaction conditions.

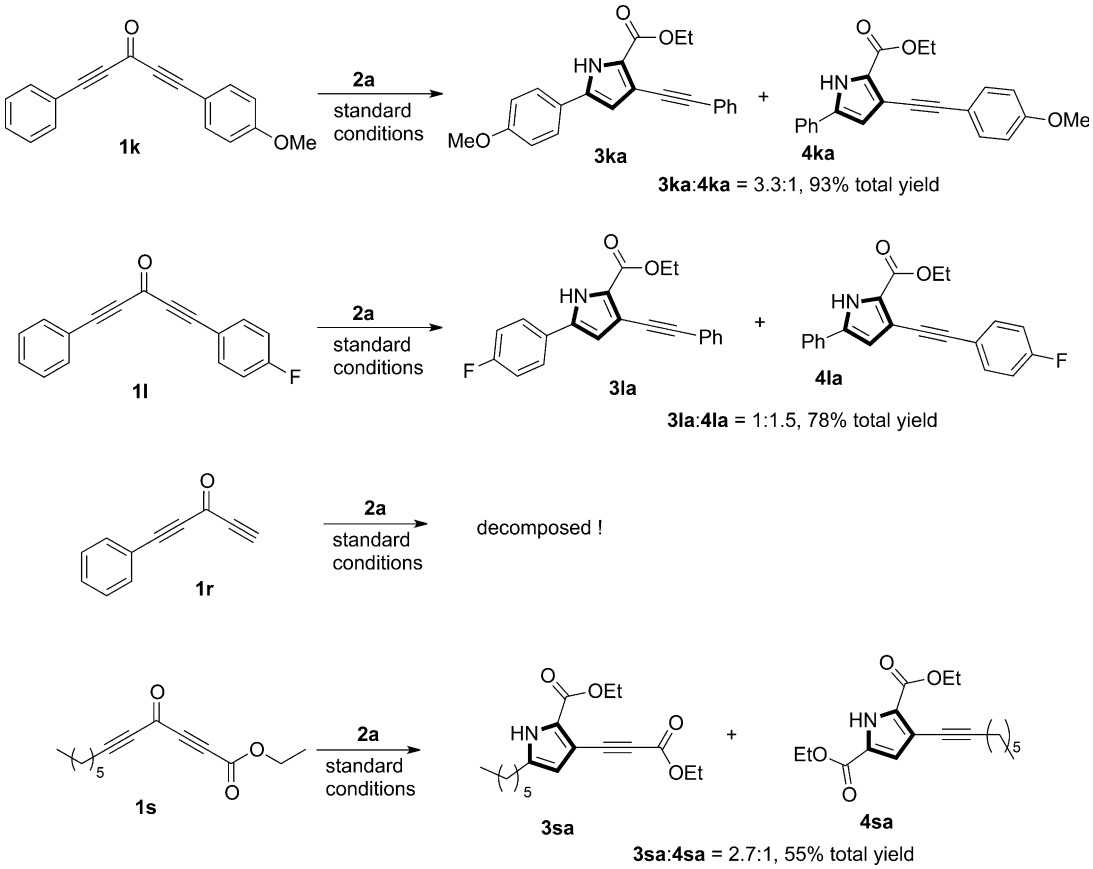
Furthermore, it was also found that this reaction was applicable to aryldiynones. As expected, the reaction of aryldiynones with ethyl glycinate hydrochloride (**2a**) afforded the corresponding pyrroles **3ma**–**3qa** in good yields under the standard conditions (Table 3).

Having investigated the reaction substrate scope and functional group tolerance, we next examined the cycloaddition selectivity of diynones with asymmetri-

Table 3. Synthesis of pyrrole derivatives.[a,b]



[a] *Reaction conditions*: **1** (0.5 mmol), **2a** (0.6 mmol), $KHCO_3$ (1 equiv.), KOAc (1 equiv.), DMF (2 mL), at 120 °C, 2 h.
[b] Isolated yields (based on **1**).



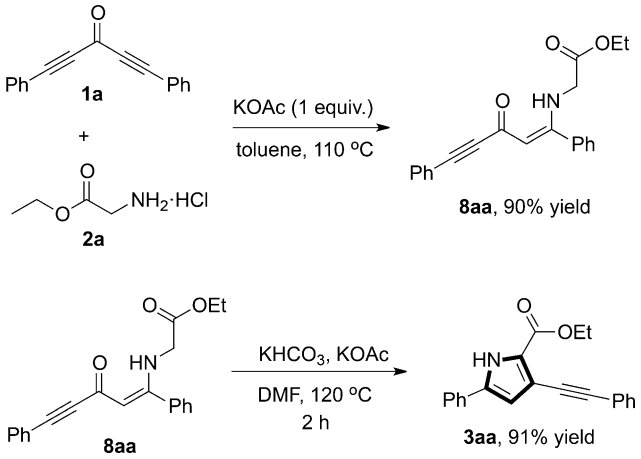
Scheme 2. Competition experiments.

cal structures, in which two different substituents are attached to the two sides of the alkynyl groups. The intramolecular competition experiments employing asymmetrical diynones **1k**, **1l** and **1s** predominantly yielded isomers **3ka**, **4la** and **3sa**, respectively (Scheme 2), which can be rationalized as the diynones featuring electron-donating groups on the phenyl ring provided higher yields of the pyrroles than those bearing electron-withdrawing groups did. In contrast, 1-phenylpenta-1,4-diyn-3-one (**1r**) did not yield the expected pyrrole products under the typical reaction conditions.

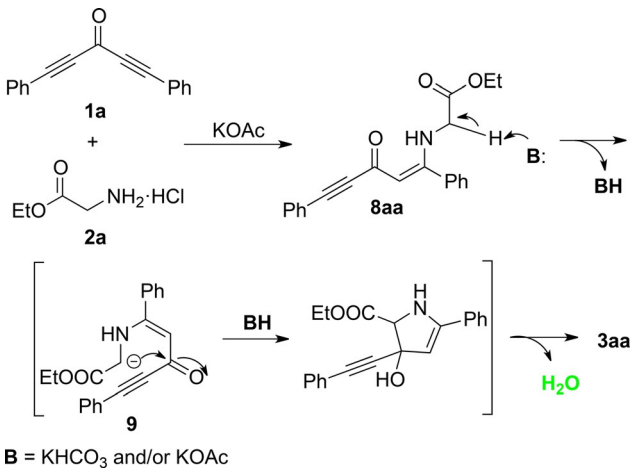
To elucidate the reaction mechanism of diynones with glycine esters, we performed some control experiments and present the results in Scheme 3. The reaction of 1,5-diphenylpenta-1,4-diyn-3-one **1a** with ethyl glycinate hydrochloride **2a** in the presence of 1 equiv. KOAc in toluene at 110 °C afforded the product **8aa** in 90% isolated yield. Subsequently, **8aa** underwent an intramolecular cyclodehydration reaction to provide **3aa** in 91% yield under the standard conditions.

On the basis of above results, a plausible mechanism is proposed in Scheme 4. At first, the Michael addition of **2a** onto **1a** generated the α,β-enaminone intermediate **8aa**,[11] which converted *in situ* into a reactive intermediate **9** under the basic conditions. Subsequently, an intramolecular cyclodehydration reaction of **9** resulted in the formation of the desired product **3aa**.[12]

In conclusion, we have developed a simple, cost-effective, and transition metal-free cascade reaction for the synthesis of 3-alkynylpyrrole-2-carboxylates. This transformation features easy accessibility of starting



Scheme 3. Control experiments.



Scheme 4. Plausible mechanism.

materials, relatively wide functional group tolerance, and a broad range of substrates, thus enabling the formation of 3-alkynylpyrrole-2-carboxylates that cannot be accessed effectively by other means. Moreover, the simple experimental manipulation makes this process an excellent alternative to the preparation of 3-alkynylpyrrole-2-carboxylates under air. Further studies on the applications of 3-alkynylpyrrole-2-carboxylates in drug discovery are currently ongoing in our laboratory.

Experimental Section

General Information

All reactions were performed under air unless otherwise stated. Column chromatography was carried out on silica gel (300–400 mesh). NMR spectra were obtained using a Bruker Avance 500 spectrometer (^{1}H at 500 MHz and ^{13}C at 125 MHz). High-resolution mass spectra (HR-MS) were recorded on an Exactive Mass Spectrometer (Thermos Scientific, USA) equipped with ESI or APCI ionization source.

General Procedure for the Synthesis of Compound 3

The reaction mixture of **1** (0.5 mmol), **2** (0.6 mmol), $KHCO_3$ (1 equiv.), KOAc (1 equiv.), and DMF (2 mL) in a 15-mL test tube was stirred at 120 °C for 2 h. The reaction was monitored periodically by TLC. Upon completion, the reaction mixture was diluted with water (30 mL) and extracted with ethyl acetate (3 × 30 mL). The combined organic layers were washed with water and brine successively, dried over $MgSO_4$, and filtered. The solvent was removed under vacuum. The residue was purified by flash column chromatography to afford **3**.

General Procedure for the Synthesis of Compound 8aa

The reaction mixture of **1a** (1 mmol), **2a** (1.2 mmol), KOAc (1 equiv.), and toluene (4 mL) in a 15-mL test tube was stirred at 110 °C for 2 h. The reaction was monitored periodically by TLC. Upon completion, the solvent was removed under vacuum. The residue was purified by flash column chromatography to afford **8aa** (90%).

Supporting Information

General experimental procedures, spectral data, NMR spectra, high-resolution mass spectra for all compounds, and the X-ray crystal structure of **3ha** are provided in the Supporting Information.

Acknowledgements

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[10] CCDC 1416804 (**3ha**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif. The single crystal X-ray structure of product **3ha** is included in the Supporting Information.
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