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Metal-Free Cyclocarboamination of *ortho*-Formyl Phenylacetylenes with Secondary Amines: Access to 1, 3-Diamino-1*H*-Indenes and 3-Amino-1-Indanones

Jian-Fang Cui,[a, b] Rishi Tang,[a] Bin Yang,[a] Nathanael Chun-Him Lai,[a] Jia-Jun Jiang,[a] Jie-Ren Deng,[a] and Man-Kin Wong[a]*

[a] State Key Laboratory of Chemical Biology and Drug Discovery, Department of Applied Biology and Chemical Technology, The Hong Kong Polytechnic University, Hong Kong, People's Republic of China. E-mail: mankin.wong@polyu.edu.hk

[b] Department of Chemistry, Southern University of Science and Technology, Shenzhen, People's Republic of China.

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Abstract. This work first discloses a new strategy for amine activation to give reactive amine anion by *in situ* generated amine anion-iminium cation pair through decomposition of sterically hindered aminals. Utilizing this strategy, a highly regio- and chemoselective cyclocarbo-amination of *ortho*-formyl phenylacetylenes with secondary amines has been realized under metal-free mild reaction conditions. The cyclocarboamination with notably tunable product profiles depends on the separation and purification procedure, a diverse range of 1, 3-diamino-1*H*-indenes (essentially reactive enamines) and 3-amino-1-indanones were obtained, respectively. Moreover, using iodine as an electrophile to couple with various *ortho*-formyl phenylacetylenes and secondary amines, a series of 3-amino-2-iodo-1-indanones were efficiently achieved with four bonds (C=O, C-C, C-N and C-I) formation in an one-pot three-component reaction. These results demonstrated an unprecedented methodology for the construction of highly functionalized 1*H*-indene and 1-indanone compounds.

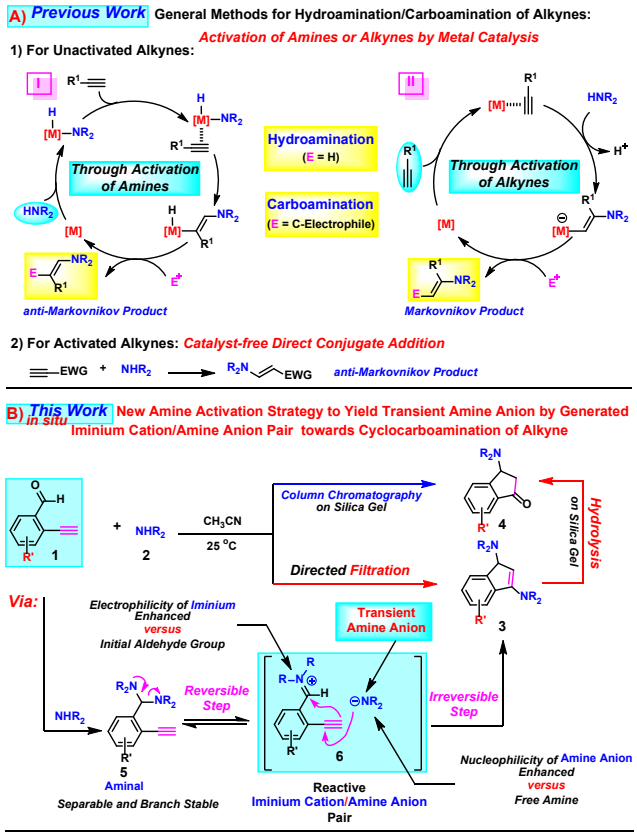
Keywords: Carboamination; Amine activation; Indene; Indanone; Aminal

Introduction

Amines are abundant in biologically active natural products, medicines and functional materials.[1] Selective synthesis of amines from readily available precursors is a significant research direction in chemical research. Efficient methods including transition-metal-catalyzed C-N bond cross-coupling, nucleophilic addition to imines, carbene insertion into N-H bond and enzymatic synthesis for access to various amines have been well developed.[2] Hydroamination and carboamination of alkenes, [3], [4] or alkynes with sequential reduction of enamine or imine intermediates, [5], [6] are potentially the most atom economic process and efficient approaches for the formation of highly functional amines. Over the decades, great progress has been achieved in the hydroamination and carboamination of alkenes due to the direct access to stable desirable amines. However, hydroamination and carboamination of alkynes remains a challenging issue because of the reactive enamines[7] and imines generated are difficult to be isolated and purified. Yet, the formation of the reactive enamine and imine intermediates can be considered as an advantage because it offers high synthetic flexibility for access to various important classes of products. In contrast to hydroamination of alkynes, carboamination of alkynes has attracted more attention in organic synthesis due to simultaneous incorporation of both C−C and C−N bonds across an alkyne in one-step to build complex molecules which possess significant synthetic utility in chemical synthesis.[6]

Generally, catalysts are mandatory for the hydroamination/carboamination of electronically unactivated alkynes through activation of amines by alkali metals or transition-metals with *anti*-Markovnikov selectivity, and through activation of carbon-carbon triple bond by transition-metals (or Brønsted acids) with Markovnikov selectivity.[8] Alternatively, metal-free or catalyst-free hydroamination of alkynes with amines is generally limited to the activated electron-deficient alkynes through direct nucleophilic addition (conjugate addition) and afforded the products with Markovnikov selectivity (Scheme 1A).[9] However, metal-free/catalyst-free

(cyclo)carboamination of alkynes remains rare.[6a, 6b] Herein we report an unprecedented metal-free cyclocarboamination of *ortho*-formyl phenylacetylenes **1** with secondary amines **2** involving a transient iminium cation/amine anion pair **6**[10] which generated *in situ* via reversible equilibrium of aminal **5**[11] to give 3-amino-1*H*-indenes **3** and 3-amino-1-indanones **4** (Scheme 1B).[12]



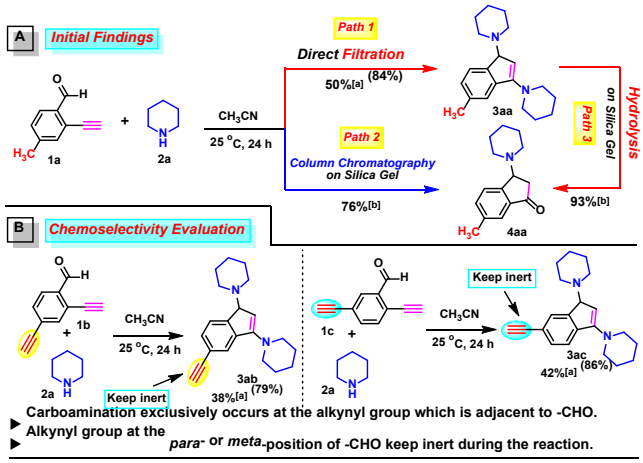
Scheme 1. A) General methods for hydroamination and carboamination of alkynes; B) New amine activation strategy for metal-free cyclocarboamination by *in situ* generated iminium cation/amine anion pair.

Results and Discussion

Ortho-Formyl phenylacetylenes are versatile building blocks for many organic transformations through transition metal catalysis and organocatalysis.[13] The carbon-carbon triple bonds of *ortho*-formyl phenylacetylenes are generally activated by transition metals leading to highly reactive ylide intermediates, which are amendable to subsequent nucleophilic addition, [3+2]-annulation, and [4+2]-cycloaddition, to afford structurally diverse heterocyclic compounds.[13b, 13c] For example, we have reported a chemoselectively gold(III)-catalyzed cyclization of *ortho*-formyl phenylacetylenes with trialkyl orthoformate.[14] Notably, *ortho*-formyl phenylacetylenes readily react with primary amines to give imines in which the nucleophilic nitrogen atom intramolecularly reacts with *ortho*-alkynyl (hydroamination) to yield diverse amines.[13c] Nevertheless, studies on reactions of *ortho*-formyl phenylacetylenes with secondary amines remain sparse.[13a, 13d, 13e] Recently, we found that 5-methyl *ortho*-formyl phenylacetylene (**1a**) reacted smoothly with piperidine (**2a**) in CH_3CN at room temperature and produced an off-white precipitate. The precipitate was isolated and purified by direct filtration and subsequent washing by cold CH_3CN to afford a white solid **3aa** (50% isolated yield) confirmed by ^1H NMR, ^{13}C NMR and HRMS spectroscopy analysis (Scheme 2A, Path 1). Additionally, the residual **3aa** in the filtrate was determined by ^1H NMR in 34% yield. As a result, the total yield of **3aa** is actually 84%. When the reaction mixture was purified by column chromatography on silica gel, instead of **3aa**, another product 3-amino-6-methyl-1-indanone (**4aa**) was afforded in 76% yield (Scheme 2A, Path 2). These results indicated that this transformation with interestingly tunable product profiles depends on the separation and purification procedure.[15] The initially formed reactive enamine **3aa** was readily converted to stable ketone **4aa** upon column chromatography on silica gel owing to its inherent sensitivity to hydrolysis. It was also demonstrated by treatment of pure **3aa** with silica gel upon column chromatography to give **4aa** in 93% yield (Scheme 2A, Path 3). It is noteworthy that the regioselectivity in this Markovnikov cyclocarboamination is not in accord with the results that of the previously reported metal-free hydroamination/carboamination of activated electron-deficient alkynes.[9a-c] We rationalize herein the Markovnikov regioselectivity towards 2-formyl phenylacetylene arised from the LUMO-lowering activation by iminium formation leading to enhanced electrophilicity versus that of the original aldehyde, so that the iminium generated was more readily to accept nucleophilic attack from the *in situ* generated alkenyl anion (intermediate **6'**, see Figure 1).[16] Furthermore, synergetic thermodynamically favorable five-membered ring formation would also be the driving force leading to Markovnikov cyclocarboamination.

Substrates **1b** and **1c** bearing one more alkynyl group at the *para*- or *meta*-position of the aldehyde group, respectively, were employed to react with piperidine in CH_3CN at room temperature for 24 h. The reactions also proceeded smoothly and the expected products **3ab** and **3ac** also precipitated out in CH_3CN and were isolated by filtration in 38% and 42% yield, respectively (Scheme 2B). Notably, the cyclocarboamination exclusively occurs at the alkynyl group which is adjacent to aldehyde group, whereas the alkynyl group at the *para*-

position or *meta*-position of the aldehyde group kept inert during the reaction. The inertness of the alkynyl groups that are not adjacent to the aldehyde group showed that this cyclocarboamination was of high chemoselectivity. Furthermore, we noted that the enamine products **3aa, 3ab** and **3ac** were bench stable for months although they are inherently sensitive to acid medium and moisture for hydrolysis.

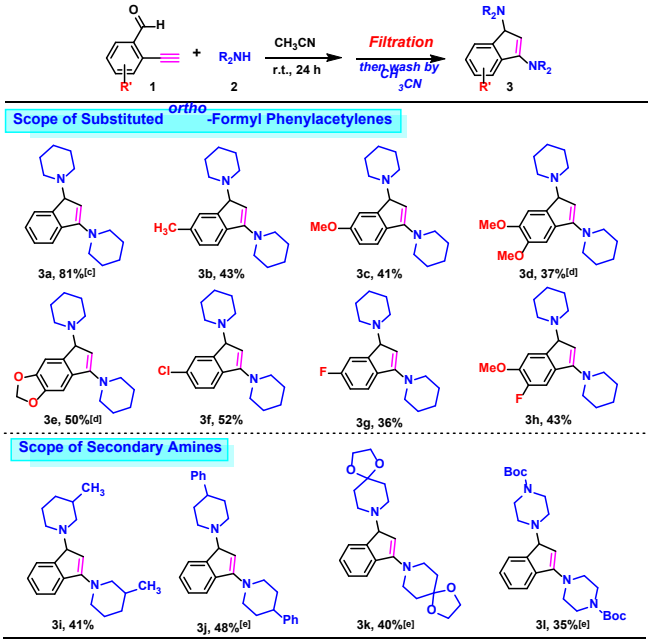


Reaction conditions: **1** (0.5 mmol), **2** (1.5 mmol, 3.0 equiv.), CH_3CN (1.5 mL), 25 °C, 24 h. [a] Isolated yield by filtration, the yield in parentheses is the total yield calculated by combining the isolated yield and the yield of residual product in filtrate which was determined by ^1H NMR using 1,3,5-trimethoxybenzene as the internal reference. [b] Isolated yield by column chromatography on silica gel.

Scheme 2. A) Initial findings of the metal-free cyclocarboamination of **1a** and **2a**; B) Experiments for evaluating the chemoselectivity of the cyclocarboamination between *ortho*-formyl phenylacetylenes and secondary amines.

It is well known that enamines are reactive and usually difficult to isolate and purify.[7] With the newly developed isolation procedure for an easy access to pure enamines, we attempted to extend the scope of using *ortho*-formyl phenylacetylenes and secondary amines to prepare more separable 1,3-diamino-*1H*-indenes. First, the scope of substituted *ortho*-formyl phenylacetylenes was explored by using commercially available piperidine (**2a**) as amine partner. As shown in Table 1, *ortho*-formyl phenylacetylene (**1d**) reacted with **2a** to provide 1,3-dipiperidyl-*1H*-indene (**3a**) in 81% NMR yield. Various *ortho*-formyl phenylacetylenes with electron-neutral group (methyl), electron-donating groups (methoxyl, methylenedioxyl, *ortho*-dimethoxyl), electron-withdrawing groups (Cl, F), as well as two substituents (both methoxyl and F) on the benzene ring were well-tolerated. Separable pure **3b-3h** were afforded in 36-52% yield by filtration of the resulted precipitate and subsequent washing by cold CH_3CN. Then, the scope of secondary amines for this reaction was examined by using *ortho*-formyl phenylacetylene (**1d**) to react with various secondary amines to give **3i-3l** in 35-48% yield. Using 3-methylpiperidine, **3i** was isolated as a white solid in 41% yield. Piperidine derivatives including 4-phenyl piperidine and 1,4-dioxa-8-azaspiro[4.5]decane also afforded the separable pure products **3j** and **3k** in 48% and 40% yield, respectively. Finally 1-Boc-piperazine reacted with **1d** provided product **3j** in 35% isolated yield.

Table 1. Scope of substituted *ortho*-formyl phenylacetylenes **1** and secondary amines **2** for separable 1,3-diamino-1*H*-indenes **3**.[a][b]

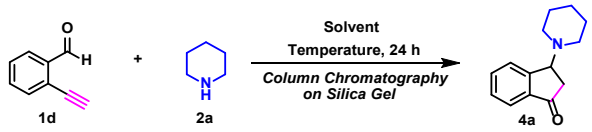


[a] Reaction conditions: **1** (0.5 mmol), **2** (1.5 mmol, 3.0 equiv.), CH_3CN (1.5 mL), room temperature, reaction time: 24 h. [b] Yield of isolated product by filtration. [c] Yield determined by ^1H NMR using 1,3,5-trimethoxybenzene as the internal reference. [d] Reaction time: 48 h. [e] CH_3CN (3.0 mL), reaction time: 72 h.

The access to pure 1,3-diamino-*1H*-indenes **3** depends on whether they could precipitate out in CH_3CN for filtration. Some of the other secondary amines reacted with **1d** to afford the corresponding 1,3-diamino-*1H*-indenes but they could not precipitate out in CH_3CN and hence could not be isolated. As a result, the scope of secondary amines for access to separable products **3** is limited. Note that 1,3-diamino-*1H*-indenes **3** are readily converted to 3-amino-1-indanones **4** by hydrolysis (see Scheme 1A). 1-Indanone derivatives have been widely used in medicine and agriculture research, such as applications in antiviral and antibacterial agents, anticancer drugs, cardiovascular drugs, insecticides and fungicides, owing to their prominent biological activity.[17] Next, we paid attention to the formation of 3-amino-1-indanones **4** and sought to extend the scope for this cyclocarboamination. First, *ortho*-formyl

phenylacetylene (**1d**) and piperidine (**2a**) were employed to investigate the effect of different solvent, temperature and amount of piperidine towards the reaction (Table 2). Solvent screening experiments suggested that CH_3CN provided the best yield (84%) of **4a** for the reaction (Table 2, entries 1–10). Raising the reaction temperature led to the decreased yield of **4a** (Table 2, entries 11–13). Attempt to improve yield by increase or decrease the amount of piperidine was unsuccessful (Table 2, entries 14–16). Therefore, **1d** (0.5 mmol) reacted with 3.0 equivalent of **2a** in CH_3CN (1.5 mL) at room temperature for 24 h was used as the optimized reaction conditions for the synthesis of 3-amino-1-indanones **4a**.

Table 2. Condition Screening Experiments for Synthesis of 3-Amino-1-indanone **4a**. [a]

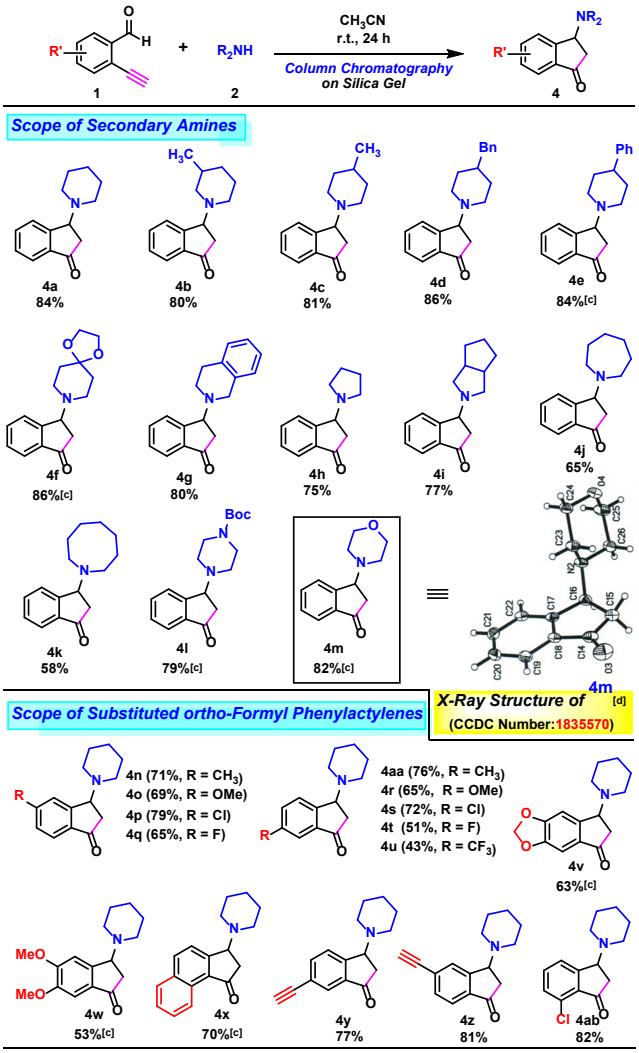


Entry	Solvent	Temp. (°C)	Usage of **2a**	Yield of **4a**[b] (%)
1	CH_3CN	**25**	**3.0 equiv.**	**84 (80)**[c]
2	THF	25	3.0 equiv.	68
3	Dioxane	25	3.0 equiv.	59
4	DCM	25	3.0 equiv.	46
5	DCE	25	3.0 equiv.	60
6	$CHCl_3$	25	3.0 equiv.	46
7	Toluene	25	3.0 equiv.	51
8	Acetone	25	3.0 equiv.	48
9	MeOH	25	3.0 equiv.	75
10	EtOH	25	3.0 equiv.	70
11	CH_3CN	40	3.0 equiv.	77 (72)[c]
12	CH_3CN	60	3.0 equiv.	71
13	CH_3CN	80	3.0 equiv.	63
14	CH_3CN	25	4.0 equiv.	74
15	CH_3CN	25	2.5 equiv.	69
16	CH_3CN	25	2.0 equiv.	56

[a] Reactions were performed with **1d** (0.5 mmol) and **2a** in solvent (1.5 mL) for 24 h. [b] Yield determined by ^1H NMR using 1,3,5-trimethoxybenzene as the internal reference. [c] Isolated yield by column chromatography on silica gel.

With the optimized reaction conditions in hand, a diverse range of substituted *ortho*-formyl phenylacetylenes and various secondary amines was evaluated for the reaction (Table 3). The coupling reactions of *ortho*-formyl phenylacetylene (**1d**) with a variety of cyclic secondary amines proceeded smoothly to give **4a**-**4m** in good to excellent yields. The reaction was well tolerated of piperidine and its derivatives that bearing 3-methyl, 4-methyl, 4-phenyl and 4-benzyl group, generating **4a**-**4e** in 80–86% yields. Piperidine derivatives including 1,4-dioxa-8-azaspiro[4.5]decane and 1,2,3,4-tetrahydro-isoquinoline afforded the corresponding products **4f** and **4g** in 86% and 80% yield, respectively. 5-, 7- or 8-Membered ring amines (including pyrrolidine, azepane, azacyclooctane) also successfully gave **4h**-**4i** in 58-77% yield. Moreover, heteroatom piperidine derivatives such as 1-Boc-piperazine and morpholine afforded the expected **41** and **4m** in 79% and 82% yield, respectively. The structure of **4m** was further confirmed by X-ray crystallographic analysis.[18]

Table 3. Scope of secondary amines and substituted *ortho*-formyl phenylacetylenes for 3-amino-1-indanones **4**. [a][b]

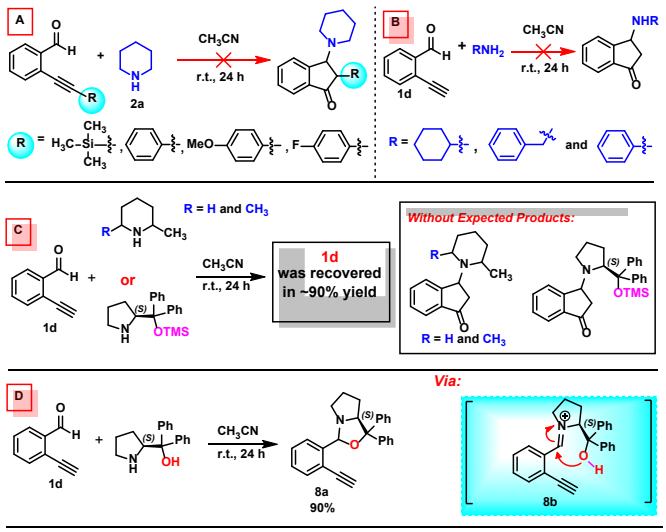


[a] Reaction conditions: **1** (0.5 mmol), **2** (1.5 mmol, 3 equiv.), CH_3CN (1.5 mL), room temperature, reaction time: 24 h. [b] Yield of isolated product. [c] Reaction time: 48 h, CH_3CN (1.5 mL) and $CHCl_3$ (1.5 mL). [d] Structure of **4m** validated by X-ray crystallographic analysis, for details of the crystallographic data, see SI.

However, the use of acyclic secondary amines (including diethylamine, dibenzylamine and diphenylamine) failed to give the desired products. Then, transformations of 3- and 4-substituted as well as 3,4-disubstituted *ortho*-formyl phenylacetylene derivatives reacted with piperidine (**2a**) were also successful to give **4n**-**4w** in 43%-79% yields. A naphthalene-derived

substrate reacted with **2a** in $CH_3CN/CHCl_3$ for 48 h afforded **4x** in 70% yield. Substrates **1b** and **1c** gave **4y** and **4z** in 77% and 81% yield, respectively, with the alkynyl group not at the *ortho*-position of the CHO group remaining intact. Furthermore, a 3-substituted substrate, 3-chloro-2-ethynylbenzaldehyde, reacted with piperidine to give the corresponding product **4ab** in 82% yield. However, when a 6-substituted substrate (6-chloro-2-ethynylbenzaldehyde) was used to react with piperidine under the same reaction conditions, the reaction failed to give the corresponding 3-amino-1-indanone product. The reason would be that the sterically hindered aldehyde group is unfavorable for the formation of aminal.

To further investigate the substrate scope of this transformation, the following control experiments have been carried out (Scheme 3). Internal alkynes (R = trimethylsilyl, phenyl, 4-methoxyphenyl and 4-fluorophenyl) were unreactive with **2a** in CH_3CN at room temperature after stirring for 24 h (Scheme 3A). No expected 3-amino-1-indanones were found when primary amines (such as cyclohexylamine, benzylamine and aniline) reacted with *ortho*-formyl phenylacetyle (**1d**) in CH_3CN for 24 h (Scheme 3B). Notably, sterically hindered secondary amines such as 2,6-dimethylpiperidine, 2-methylpiperidine and (*S*)-α,α-diphenylprolinol *tert*-butyldimethylsilyl ether remained inert towards **1d** under the same reaction conditions (Scheme 3C). Interestingly, using (*S*)-α,α-diphenylprolinol that bearing a free hydroxyl group under the same reaction conditions, an oxazolidine product **8a** was isolated in 90% yield.[19] We propose that the transformation might go through the formation of iminium **8b** which is preferred to be attacked by the adjacent hydroxyl group to form a 5-membered-ring compound **8a** prior to the cyclocarboamination process (Scheme 3D).

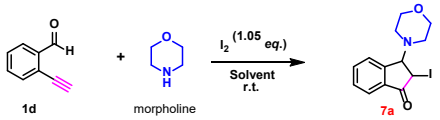


Reactions were performed with *ortho*-formyl phenylacetylenes (0.5 mmol) and amines (1.5 mmol, 3.0 equiv.) in CH_3CN (1.5 mL) at room temperature for 24 h.

Scheme 3. A) Experiments by using internal alkynes reacted with piperidine (**2a**); B) Experiments by using primary amines reacted with *ortho*-formyl phenylacetylene (**1d**); C) Experiments by using sterically hindered secondary amines reacted with **1d**; D) Access to oxazolidine **8a** by using **1d** reacted with (*S*)-α,α-diphenylprolinol.

Enamines are versatile intermediates which generally act as nucleophiles to attack various electrophiles by contributing its lone pair electrons on nitrogen, and subsequent hydrolysis to give α-substituted carbonyl compounds.[7] Initially, we found that adding iodine to the reaction of **1d** and morpholine in CH_3CN at room temperature for 1 h gave a highly functionalized indane derivatives **7a** in 41% isolated yield with excellent *trans* selectivity (*trans/cis* >20:1, Table 4, entry 1). Solvent screening experiments suggested that $CHCl_3$ provided the best yield (82%) of **7a** for the reaction (Table 4, entries 2–7). Furthermore, the yield of **7a** was improved to 91% by prolonging the reaction time to 3 h when using $CHCl_3$ as solvent (Table 4, entry 8).

Table 4. Condition screening experiments for synthesis of 3-amino-2-iodo-1-indanone **7a**. [a]



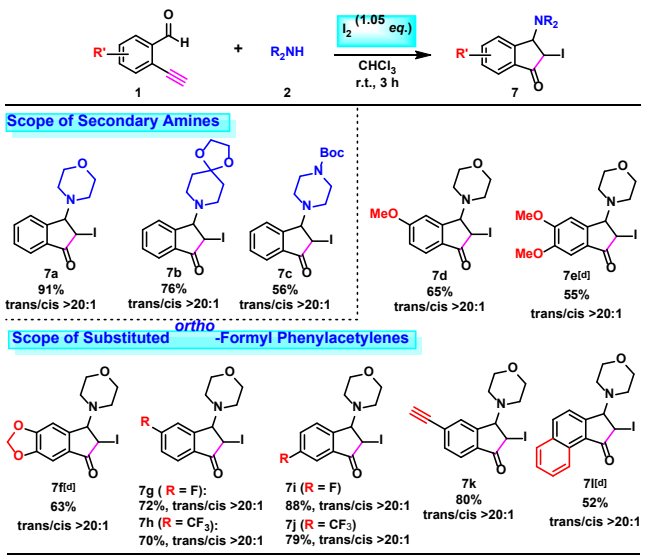
Entry	Solvent	Time (h)	Yield of **7a** (%)[b]	trans/cis[d]
1	CH_3CN	1	41	>20:1
2	Dioxane	1	50	>20:1
3	THF	1	60	>20:1
4	Et_2O	1	30	>20:1
5	DCE	1	72	>20:1
6	CH_2Cl_2	1	77	>20:1
7	$CHCl_3$	1	82	>20:1
8[c]	**$CHCl_3$**	**3**	**91**	>20:1

[a] Reactions were performed with **1d** (0.5 mmol) and morpholine (1.5 mmol, 3.0 equiv.) in solvent (1.5 mL) for 1 h. [b] Isolated yield by column chromatography on silica gel. [c] Reaction time: 3 h. [d] Detected by ^1H NMR analysis.

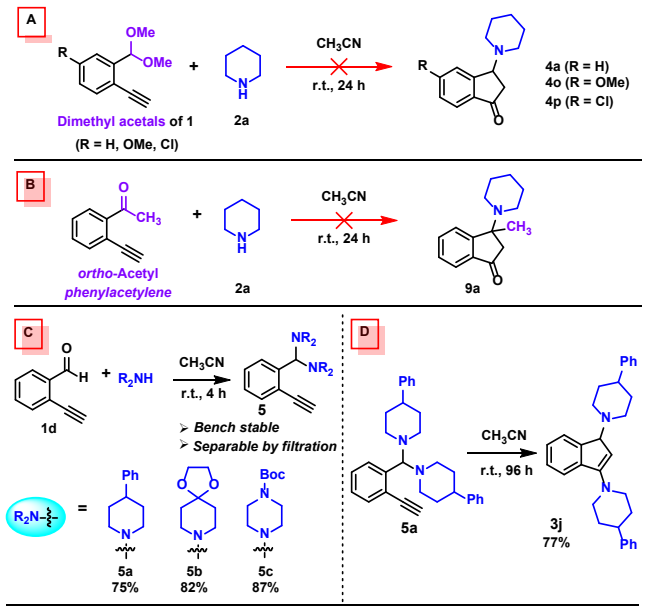
Encouraged by this result, we used iodine as an electrophile to couple with various secondary amines and *ortho*-formyl phenylacetylenes in $CHCl_3$, and a variety of 3-amino-2-iodo-1-indanones **7** were obtained with moderate to excellent yields and excellent stereoselectivity (Table 5). Apart from morpholine, 1,4-dioxa-8-azaspiro[4.5]decane and 1-Boc-piperazine smoothly afforded **7b** and **7c** in good isolated yields (76% and 56%, respectively). A diversity of 3-amino-2-iodo-1-indanones **7d**–**7j** with good isolated yields (55-88%) were also obtained from various electron-donating groups (methoxyl, methylenedioxyl, *ortho*-dimethoxyl) and electron-withdrawing groups (F, trifluoromethyl)

substituted *ortho*-formyl phenylacetylenes. An ethynyl-substituted (*meta*-position towards -CHO group) substrate (**1c**) proceeded smoothly and the *meta*-ethynyl kept inert during this transformation, thus giving the corresponding 3-amino-5-ethynyl-2-iodo-1-indanone **7k** in 80% yield. Furthermore, the naphthalene-derived substrate also afforded the corresponding product **7l** in moderate yield (52%) under the same reaction conditions.

Table 5. Scope of substituted *ortho*-formyl phenylacetylenes **1** and secondary amines **2** for synthesis of 3-amino-2-iodo-1-indanones **7**. [a][b][c]



[a] Reactions were performed with **1** (0.5 mmol) and secondary amine (1.5 mmol) in $CHCl_3$ (1.5 mL) for 3 h. [b] Isolated yield by column chromatography on silica gel. [c] The ratio of trans/cis was detected by ^1H NMR analysis. [d] Reaction time: 24 h.



For A and B, reactions were performed with phenylacetylene substrates (0.5 mmol) and piperidine (1.5 mmol, 3.0 *equiv.*) in CH_3CN (1.5 mL) at room temperature for 24 h; For C, reactions were performed with **1d** (0.5 mmol) and amines (1.5 mmol, 3.0 *equiv.*) in CH_3CN (3.0 mL) at room temperature for 4 h; For D, reaction was performed with **5a** (0.3 mmol) in CH_3CN (3.0 mL) at room temperature for 96 h.

Scheme 4. A) Control experiments by using dimethyl acetals of **1** as substrates reacted with piperidine; B) Control experiment by using *ortho*-acetyl phenylacetylene reacted with piperidine; C) Synthesis of separable aminal intermediates **5** by using **1d** reacted with various secondary amines; D) Synthesis of 1,3-diamino-1*H*-indene **3j** from separable aminal **5a**.

We have conducted mechanistic studies to provide support for a proposed reaction mechanism (Scheme 4). Using dimethyl acetals that come from the corresponding *ortho*-formyl phenylacetylenes to react with piperidine (**2a**) in CH_3CN for 24 h, the expected 3-piperidyl-1-indanones were not obtained (Scheme 4A). Moreover, the use of *ortho*-acetyl phenylacetylene[20] reacted with **2a** in CH_3CN for 24 h failed to afford the proposed product **9a** (Scheme 4B). To demonstrate the aminal **5** act as the key intermediate for this transformation, the following control experiments have been carried out. Using **1d** reacted with 4-phenylpiperidine, 1,4-dioxa-8-azaspiro[4.5]decane and 1-Boc-piperazine in CH_3CN at room temperature for 4 h, the corresponding aminals **5a**, **5b** and **5c** (well-characterized by ^1H NMR and ^{13}C NMR spectroscopy, high-resolution ESI-MS) were isolated in 75%, 82% and 87% yield, respectively (Scheme 4C). We also checked the possibility of the formation of aminals by using acyclic amines, such as diethylamine and dibenzylamine, with 2-ethynylbenzaldedhyde, respectively. However, the corresponding aminals were not isolated or detected by ^1H NMR analysis from the reaction mixture. Furthermore, we observed that **5a** was readily converted to the 1,3-diamino-1*H*-indene **3j** in 43% yield upon prolong reaction time (96 h) in CH_3CN (Scheme 4D). Cross over experiment between aminal **5d** and 4-phenylpiperidine was performed, products **4ac** and **4ad** were isolated in 37% and 29% yield, respectively. The results indicated that the carboamination step would be an intermolecular process (see details of the reaction procedures and conditions in the Supporting Information on pages S5-S6).

Based on the observed results, a proposed reaction pathway accounting for this metal-free cyclocarboamination is outlined in Figure 1. Initially, the reaction of *ortho*-formyl phenylacetylene **1** and secondary amine **2** leads to an aminal intermediate **5**, which then undergoes reversible equilibrium to give an iminium cation/amine anion pair **6**. Subsequent nucleophilic attack by the transient reactive amine anion towards carbon-carbon triple bond (at this step, transient intermediate **6'** presumably generated *in situ*) and simultaneous nucleophilic attack to the proximal iminium to complete the

cyclocarboamination process and give versatile enamine products **3**. The enamines **3** are reactive to electrophiles. So 3-amino-indanones **4** were obtained by column chromatography on silica gel, and 3-amino-2-iodo-1-indanones **7** were obtained when I_2 was used as an electrophile for the reaction. Therefore, we consider that the driving force for the metal-free cyclocarboamination process are both the LUMO-lowering activation (iminium **6** formation) and HOMO-rising activation (enamine **3** formation), as well as the enhanced nucleophilicity of the transient amine anion, which comes from the *in situ* generated iminium cation/amine anion pair **6**, versus the free amine.

To demonstrate the practical synthetic utility of our new protocol for synthesis of 3-amino-indanones, a gram-scale cyclocarboamination reaction of **1d** (1.30 g, 10.0 mmol) with 1,2,3,4-tetrahydro-isoquinoline (4.0 g, 30.0 mmol) was conducted at room temperature in CH_3CN for 48 h. The reaction proceeded smoothly and afforded 2.16 g of product **4g** in 82% yield (Scheme 5A). Visible-light-mediated alkynylation of **4g** with trimethylsilylacetylene was carried out under irradiation of 5W LED at room temperature by using Rose Bengal and CuI as co-catalysts and subsequent desilylation to furnish **10a** with 34% yield.[21] The photo-reaction of **4g** with phenylacetylene gave **10b** in 63% yield (Scheme 5B). The resulting alkynyl-containing carbonyl compounds **10a** and **10b** are versatile synthetic blocks for our on-going research work.

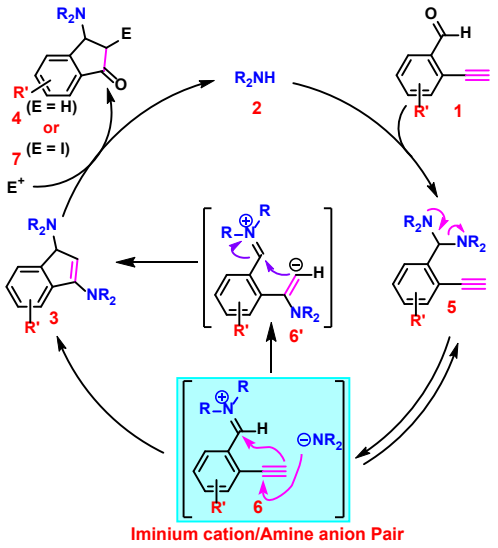
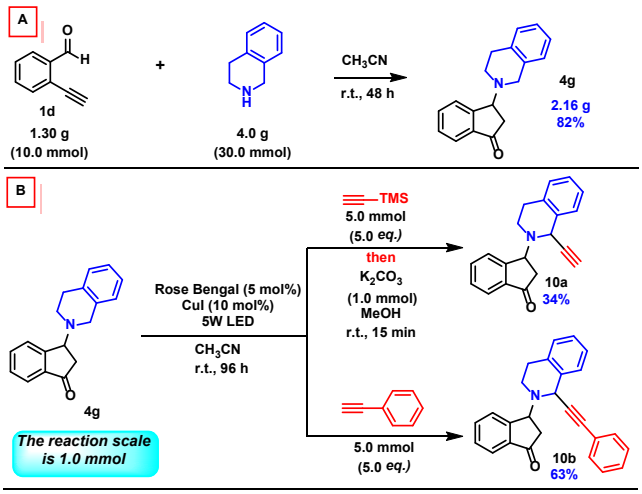


Figure 1. Proposed reaction pathway for this metal-free cyclocarboamination.



Scheme 5. A) Gram-scale synthesis of **4g**; and B) Synthetic utility of **4g**.

Conclusion

In conclusion, we have developed an efficient metal-free cyclocarboamination of *ortho*-formyl phenylacetylenes with secondary amines. This new protocol is distinguished by easy operation, readily available starting materials, good functional-group compatibility, excellent atom economy and high chemo- and regioselectivity, which provide a new attractive access to the construction of highly functionalized indenes and indanones complementary to the existing methods. Experimental results suggested that the *in situ* generated transient iminium cation/amine anion pair **6** plays an important role in the reaction.

Experimental Section

General Procedure for Synthesis of 1,3-Diamino-1*H*-Indenes 3

To a solution of *ortho*-formyl phenylacetylene **1** (0.5 mmol) in CH_3CN was added secondary amine **2** (1.5 mmol, 3.0 equiv.) at room temperature (25 °C). The mixture was stirred at 25 °C for 24 h (or indicated time, monitored by TLC). The resulting precipitate was collected by suction filtration and quickly washed by cold CH_3CN to give the corresponding pure 1,3-diamino-1*H*-indene **3**.

General Procedure for Synthesis of 3-Amino-1-Indaones 4

To a solution of *ortho*-formyl phenylacetylene **1** (0.5 mmol) in CH_3CN was added secondary amine **2** (1.5 mmol, 3.0 equiv.) at room temperature (25 °C). The mixture was stirred at 25 °C for 24 h (or indicated time, monitored by TLC). The solvent was removed under vacuum and the residue was purified by column chromatography (EA/Hexane as eluent) to give the corresponding 3-amino-1-indaones **4**.

General Procedure for Synthesis of 3-Amino-2-Iodo-1-Indaones 7

To a solution of *ortho*-formyl phenylacetylene **1** (0.5 mmol) and secondary amine **2** (1.5 mmol, 3.0 equiv.) in CH_3CN was added iodine (0.525 mmol, 1.05 equiv.) at room temperature (25 ºC). The mixture was stirred at 25 ºC for 3 h (or indicated time, monitored by TLC). The solvent was removed under vacuum and the residue was purified by flash column chromatography (EA/Hexane as eluent) to give the corresponding 3-amino-2-iodo-1-indaones **7**.

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References

[1] a) S. D. Roughley, A. M. Jordan, *J. Med. Chem.* **2011**, *54*, 3451-3479; b) M. Liang, J. Chen, *Chem. Soc. Rev.* **2013**, *42*, 3453-3488.

[2] a) D. S. Surry, S. L. Buchwald, *Chem. Sci.* **2011**, *2*, 27-50; b) G. Sreenilayam, R. Fasan, *Chem. Commun.* **2015**, *51*, 1532-1534; c) L. Chen, H. Cui, Y. Wang, X. Liang, L. Zhang, C.-Y. Su, *Dalton Trans.* **2018**, *47*, 3940-3946; d) A. Zubia, F. P. Cossío, I. Morao, M. Rieumont, X. Lopez, *J. Am. Chem. Soc.* **2004**, *126*, 5243-5252; e) B. Westermann, *Angew. Chem. Int. Ed.* **2003**, *42*, 151-153.

[3] a) S. Hong, T. J. Marks, *Acc. Chem. Res.* **2004**, *37*, 673-686; b) L. Huang, M. Arndt, K. Gooßen, H. Heydt, L. J. Gooßen, *Chem. Rev.* **2015**, *115*, 2596-2697; c) T. E. Müller, K. C. Hultzsch, M. Yus, F. Foubelo, M. Tada, *Chem. Rev.* **2008**, *108*, 3795-3892.

[4] a) Z. Liu, Y. Wang, Z. Wang, T. Zeng, P. Liu, K. M. Engle, *J. Am. Chem. Soc.* **2017**, *139*, 11261-11270; b) W. Zeng, S. R. Chemler, *J. Am. Chem. Soc.* **2007**, *129*, 12948-12949; c) S. N. Gockel, T. L. Buchanan, K. L. Hull, *J. Am. Chem. Soc.* **2018**, *140*, 58-61; d) B. Qian, S. Chen, T. Wang, X. Zhang, H. Bao, *J. Am. Chem. Soc.* **2017**, *139*, 13076-13082; e) Y.-Y. Liu, X.-H. Yang, R.-J. Song, S. Luo, J.-H. Li, *Oxidative 1,2-carboamination of alkenes with alkyl nitriles and amines toward γ-amino alkyl nitriles, Vol. 8*, **2017**; f) J. E. Ney, J. P. Wolfe, *Angew. Chem. Int. Ed.* **2004**, *43*, 3605-3608.

[5] a) F. Pohlki, S. Doye, *Chem. Soc. Rev.* **2003**, *32*, 104-114; b) R. Severin, S. Doye, *Chem. Soc. Rev.* **2007**, *36*, 1407-1420; c) M. Patel, R. K. Saunthwal, A. K. Verma, *Acc. Chem. Res.* **2017**, *50*, 240-254; d) T. Mahdi, D. W. Stephan, *Angew. Chem. Int. Ed.* **2013**, *52*, 12418-12421; e) M. T. Pirnot, Y.-M. Wang, S. L. Buchwald, *Angew. Chem. Int. Ed.* **2016**, *55*, 48-57; f) K. D. Hesp, M. Stradiotto, *J. Am. Chem. Soc.* **2010**, *132*, 18026-18029.

[6] a) S. J. Gharpure, S. K. Nanda, P. A. Adate, Y. G. Shelke, *J. Org. Chem.* **2017**, *82*, 2067-2080; b) T. Stopka, M. Niggemann, *Chem. Commun.* **2016**, *52*, 5761-5764; c) R. T. Ruck, R. L. Zuckerman, S. W. Krska, R. G. Bergman, *Angew. Chem. Int. Ed.* **2004**, *43*, 5372-5374; d) P. A. Wender, D. Strand, *J. Am. Chem. Soc.* **2009**, *131*, 7528-7529; e) D. S. Ryabukhin, A. V. Vasilyev, *Mendeleev Commun.* **2016**, *26*, 500-501; f) Z. W. Davis-Gilbert, L. J. Yao, I. A. Tonks, *J. Am. Chem. Soc.* **2016**, *138*, 14570-14573; g) L. B. Wolf, K. C. M. F. Tjen, H. T. ten Brink, R. H. Blaauw, H. Hiemstra, H. E. Schoemaker, F. P. J. T. Rutjes, *Adv. Synth. Catal.* **2002**, *344*, 70-83; h) A. Fürstner, P. W. Davies, *J. Am. Chem. Soc.* **2005**, *127*, 15024-15025.

[7] a) D. A. Bock, C. W. Lehmann, B. List, *P. Natl. Acad. Sci.* **2010**, *107*, 20636-20641; b) S. Mukherjee, J. W. Yang, S. Hoffmann, B. List, *Chem. Rev.* **2007**, *107*, 5471-5569; c) B. List, *Acc. Chem. Res.* **2004**, *37*, 548-557; d) B. Kempf, N. Hampel, A. R. Ofial, H. Mayr, *Chem.–Eur. J.* **2003**, *9*, 2209-2218.

[8] H. M. Senn, P. E. Blöchl, A. Togni, *J. Am. Chem. Soc.* **2000**, *122*, 4098-4107.

[9] a) M. Inman, C. J. Moody, *Eur. J. Org. Chem.* **2013**, *2013*, 2179-2187; b) A. K. Ogawa, C. A. Willoughby, R. Bergeron, K. P. Ellsworth, W. M. Geissler, R. W. Myers, J. Yao, G. Harris, K. T. Chapman, *Bioorg. Med. Chem. Lett.* **2003**, *13*, 3405-3408; c) N. R. Irlapati, J. E. Baldwin, R. M. Adlington, G. J. Pritchard, A. Cowley, *Org. Lett.* **2003**, *5*, 2351-2354; d) Y. Wang, C. Latouche, A. Rapakousiou, C. Lopez, I. Ledoux-Rak, J. Ruiz, J.-Y. Saillard, D. Astruc, *Chem.–Eur. J.* **2014**, *20*, 8076-8088.

[10] a) C. Luo, J. S. Bandar, *J. Am. Chem. Soc.* **2018**, *140*, 3547-3550; b) V. V. Levin, A. D. Dilman, P. A. Belyakov, M. I. Struchkova, V. A. Tartakovsky, *Tetrahedron Lett.* **2006**, *47*, 8959-8963; c) W. Huang, C. Ni, Y. Zhao, B. Gao, J. Hu, *J. Fluorine Chem.* **2012**, *143*, 161-166.

[11] a) N. Sakai, H. Hori, Y. Yoshida, T. Konakahara, Y. Ogiwara, *Tetrahedron* **2015**, *71*, 4722-4729; b) T. Kano, T. Yurino, D. Asakawa, K. Maruoka, *Angew. Chem. Int. Ed.* **2013**, *52*, 5532-5534.

[12] a) J. F. Gilmer, A. L. Simplício, J. M. Clancy, *Eur. J. Pharm. Sci.* **2005**, *24*, 315-323; b) A. L. s. Simplício, J. F. Gilmer, N. Frankish, H. Sheridan, J. J. Walsh, J. M. Clancy, *J. Chromatogr. A* **2004**, *1045*, 233-238.

[13] a) S. Samala, G. Singh, R. Kumar, R. S. Ampapathi, B. Kundu, *Angew. Chem. Int. Ed.* **2015**, *54*, 9564-9567; b) J.-R. Chen, X.-Q. Hu, W.-J. Xiao, *Angew. Chem. Int. Ed.* **2014**, *53*, 4038-4040; c) H. Wang, Y. Kuang, J. Wu, *Asian J. Org. Chem.* **2012**, *1*, 302-312; d) H. Tsukamoto, T. Ueno, Y. Kondo, *Org. Lett.* **2007**, *9*, 3033-3036; e) Y. Ohta, S. Oishi, N. Fujii, H. Ohno, *Chem. Commun.* **2008**, 835-837.

[14] J.-F. Cui, H.-M. Ko, K.-P. Shing, J.-R. Deng, N. C.-H. Lai, M.-K. Wong, *Angew. Chem. Int. Ed.* **2017**, *56*, 3074-3079.

[15] E. Haak, I. Bytschkov, S. Doye, *Angew. Chem. Int. Ed.* **1999**, *38*, 3389-3391.

[16] a) Y. Huang, A. M. Walji, C. H. Larsen, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2005**, *127*, 15051-15053; b) M. J. Gaunt, C. C. C. Johansson, A. McNally, N. T. Vo, *Drug Discov. Today* **2007**, *12*, 8-27; c) A. Erkkilä, I. Majander, P. M. Pihko, *Chem. Rev.* **2007**, *107*, 5416-5470.

[17] a) S. A. Patil, R. Patil, S. A. Patil, *Eur. J. Med. Chem.* **2017**, *138*, 182-198; b) M. Turek, D. Szczęsna, M. Koprowski, P. Bałczewski, *Beilstein J. Org. Chem.* **2017**, *13*, 451-494.

[18] CCDC 1835570 (**4m**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

[19] M. Periasamy, N. Sanjeevakumar, M. Dalai, R. Gurubrahamam, P. O. Reddy, *Org. Lett.* **2012**, *14*, 2932-2935.

[20] H. Shen, J. Fu, J. Gong, Z. Yang, *Org. Lett.* **2014**, *16*, 5588-5591.

[21] a) W. Fu, W. Guo, G. Zou, C. Xu, *J. Fluorine Chem.* **2012**, *140*, 88-94; b) Q. Xue, J. Xie, H. Jin, Y. Cheng, C. Zhu, *Org. Biomol. Chem.* **2013**, *11*, 1606-1609.

Metal-Free Cyclocarboamination of *ortho*-Formyl Phenylacetylenes with Secondary Amines: Access to 1, 3-Diamino-1*H*-Indenes and 3-Amino-1-Indanones

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Jian-Fang Cui,[a, b] Rishi Tang,[a] Bin Yang,[a] Nathanael Chun-Him Lai,[a] Jia-Jun Jiang,[a] Jie-Ren Deng,[a] and Man-Kin Wong[a]*