Advanced Synthesis & Catalysis

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To be cited as: *Adv. Synth. Catal.* 10.1002/adsc.201701143

Link to VoR: http://dx.doi.org/10.1002/adsc.201701143

DOI: 10.1002/adsc.201((will be filled in by the editorial staff))

Nickel-Catalyzed Denitrogenative Annulation of 1,2,3-Benzotriazin-4-(3*H*)-ones with Benzynes for Construction of Phenanthridinone Scaffolds

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Received: ((will be filled in by the editorial staff))

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201######.((Please delete if not appropriate))

Abstract. The synthesis of phenanthridinones via denitrogenative annulation of 1,2,3-benzotriazin-4-(3*H*)-ones with arynes catalysed by Ni(0)/dppm was successfully developed. A variety of phenanthridinones were prepared in good to excellent yields. Based on this method, nature product, N-methylcrinasidine, was synthesized.

Keywords: nickelacycle; annulation; benzyne; nickel; phenanthridinone

Transition metal-catalyzed reactions have emerged as powerful tools for the construction of C-C, C-N and C-X bonds in organic synthesis.[1] In particular, Rh, Pd, Ni, Co, Ir and Cu catalysis to build nitrogen heterocycles, natural products and complex molecular architectures have gained enormous attention.[1-7] Phenanthridinone alkaloids are an important class of compounds and are well recognized for antimalarial, anti-inflammatory, anticancer and many other pharmacological properties (Figure 1).[3] Considerable efforts have been directed towards the synthesis of phenanthridinone analogues. A Pd-catalyzed homocoupling reaction of *o*-halobenzamide reported by Kan and aminocarbonylation of unprotected *o*-arylaniline with CO was achieved by Zhu.[4a,b] Similarly, Fagnou and Dong developed a Pd-catalyzed intramolecular arylation of prefabricated aryl-substituted amides.[4c,d] Curran and co-workers reported a silane mediated radical cyclization of prefunctionlized aromatic amide.[4e] Our group has succeeded in a Pd-catalyzed multiple C-H/N-H bond activation and annulation of *N*-methoxybenzamides with arenes to give *N*-methoxyphenanthridinone under mild reaction conditions and its application to the synthesis of crinasiadine.[5a] Later, we and Wang *et.al* independently achieved a Rh(III) and Pd-catalyzed dual C-H bond activation of *N*-methoxybenzamides with aryl boronic acids and aryl iodide, respectively, for the synthesis of phenanthridinone derivatives.[5b,c] Recently, Jiao's group disclosed a Pd-catalyzed domino process enabling the transformation of arylcarbamic chlorides and aryl iodides to phenanthridinone scaffolds.[5d] Jaganmohan *et. al* accomplished a Pd-catalyzed cyclization of benzamides and arynes to give phenanthrididone derivatives.[12f]

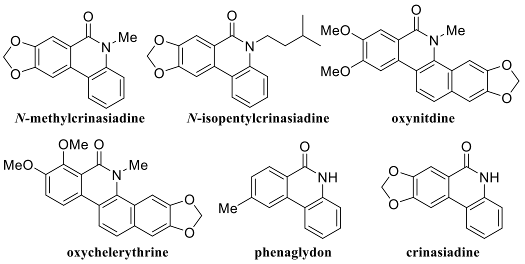
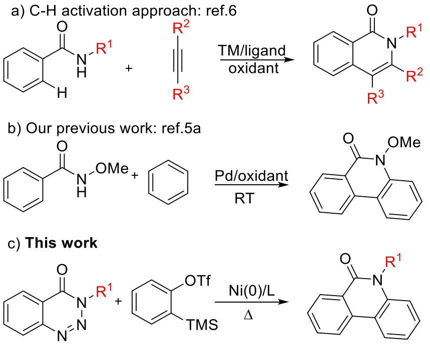


Figure 1. Representative phenanthridinone alkaloids.

In recent years, transition metal-catalyzed denitrogenative annulation of substrates such as 1,2,3-benzotriazin-4-(3*H*)one, triazole, pyridotriazole, *N*-aroylbenzotriazole has drawn considerable attention.[8-11] Similarly the decarboxylation and decarbonylation strategy were employed to obtain various heterocycles by utilizing phthalimides, phthalic anhydride, isatoic anhydrides, triazole and its analogues.[9,10] These triazole derivatives served as precursors for metallocycle formation by the expulsion of gaseous molecules like N_2, CO and CO_2. Upon annulation of the metallocycles with various π-substrates, a diverse heterocycles can be formed.[8-10] Gevorgyan and co-workers reported a heterocyclic scaffold accessible via rhodium-catalyzed denitrogenation of pyridotriazole.[8a,d] The work by

Murakami *et.al*. demonstrated a nickel-catalyzed denitrogenative reaction of triazole, 1,2,3-benzotriazin-4(3*H*)-ones with internal alkynes and allenes. [10b,8b] Nakamura *et.al.* found a palladium-catalyzed denitrogenative indolization of *N*-aroylbenzotriazole with alkyne.[10c] Recently, Liu's group displayed a Ni(0)-driven chiral denitrogenative transannulation of 1,2,3-benzotriazin-4(3*H*)-ones furnishing axially chiral isoquinolones with excellent enantioselectivity.[11]

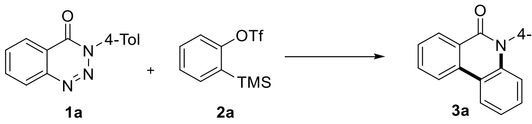


Scheme 1. Synthetic approaches towards phenanthridinones.

Benzyne from o-trimethylsilylphenyl triflate and fluoride was first discovered by Kobayashi and his co-workers.[12a] Studies on the application of benzyne chemistry has gained great attention over the past years.[12] In particular, transition metal-catalyzed aryne transformation has extensively investigated.[12-14] As a part of our research in utilizing aryne as useful substrate for organic synthesis, we report herein an interesting nickel-catalyzed denitrogenative annulation of 1,2,3-benzotriazin-4-(3*H*)-one with aryne.

In this study, *N*-tolyl-1,2,3-benzotriazin-4-(3*H*)-one (**1a**) is selected as the model substrate which can be readily prepared from methyl anthranilate in two steps.[15] The initial investigation was focused on the activation of the triazo core with nickel complexes. We found that Ni(cod)$_2$ and a suitable phosphine ligand is effective for the activation. Thus, treatment of **1a** (0.10 mmol) with benzyne precursor **2a** (0.15 mmol) in the presence of Ni(cod)$_2$ (0.010 mmol), dppm (0.020 mmol), KF (0.30 mmol) and 18-crown-6 (0.20 mmol) in THF at 100˚C for 12 h afforded the desired product **3a** in 94% isolated yield (Table 1, entry 2). Upon switching to dppe ligand, the yield of **3a** decreased to 70% (entry 4). Also, when **1a** was treated with **2a** in acetonitrile (ACN), **3a** was obtained in 80% yield (entry 6). The reaction was completely ineffective without Ni(cod)$_2$ and a phosphine ligand. The NiI$_2$/Zn/dppm system is also active affording **3a** in 43% yield (entry 12). This is because the active Ni(0) was successfully generated in situ using zinc as the reducing agent. The reaction did not give the annulation product without 18-crown-6 which would enhance the benzyne generation rate by increasing the solubility of KF through coordination to K$^+$ and thus the F$^-$ concentration (entry 13). Other monodentate phosphine ligands like PPh$_3$ and P(*o*-tolyl)$_3$ and bidentate ligands like, dppp, dppb and dppf did not provide the desired product (see Supporting Information (SI) for the detailed optimization studies page S4). This reveals that an appropriate ligand with suitable bite angle plausibly plays crucial role during the course of reaction. Based on the optimization studies, It appears that the bidentate ligand, dppm, is important to facilitate the reaction with high yields. Thus, we choose the Ni(cod)$_2$/dppm system as the catalyst for the following denitrogenative annulation reactions.

Table 1. Scope of 1,2,3-benzotriazin-4(3*H*)-one. [a,b]

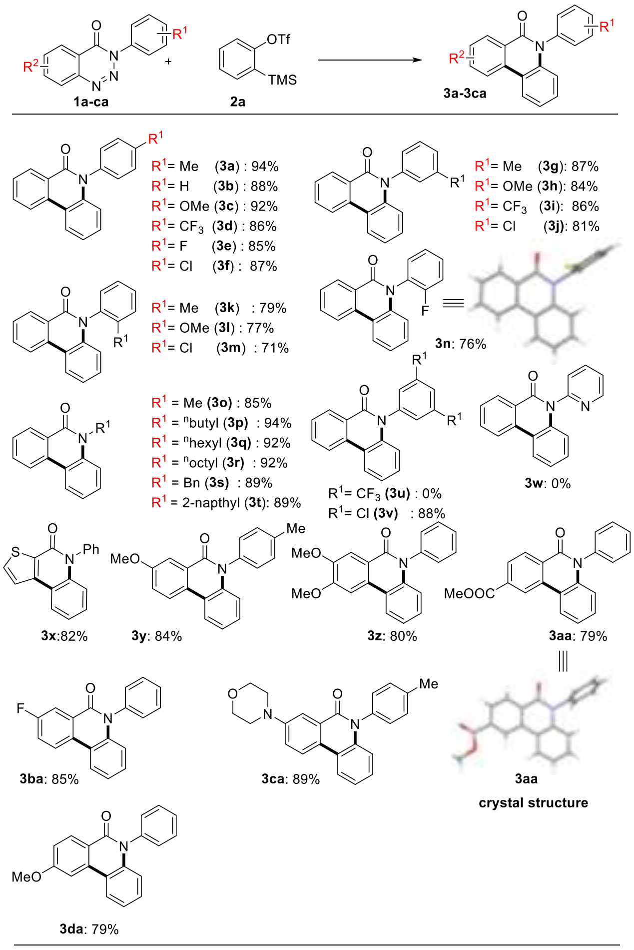


Entry	Catalyst	Ligand	Additives	Solvent	**3a** Yield (%)
1	[Ni(cod)$_2$]	PCy$_3$	KF/18-crown-6	THF	76
2	[Ni(cod)$_2$]	dppm	KF/18-crown-6	THF	95 (94)
3	[Ni(cod)$_2$]	dppm	KF/18-crown 6	THF	80^c
4	[Ni(cod)$_2$]	dppe	KF/18-crown-6	THF	70
5	[Ni(cod)$_2$]	dppp	KF/18-crown-6	THF	trace
6	[Ni(cod)$_2$]	dppm	CsF/-	ACN	80
7	[Ni(cod)$_2$]	dppm	KF/18-crown-6	DMF	80
8	[Ni(cod)$_2$]	dppm	KF/18-crown-6	Dioxane	5
9	[Ni(cod)$_2$]	-	KF/18-crown-6	THF	-
10	--	dppm	KF/18-crown-6	THF	-
11	[Ni(OTf)$_2$]		KF/18-crown-6	THF	-
12	NiI$_2$/Zn	dppm	CsF/-	ACN	43
13	[Ni(cod)$_2$]	dppm	KF/-	THF	-

[a] *Reaction conditions*: Unless otherwise mentioned, all reactions were carried out using **1a** (0.10 mmol), **2a** (0.15 mmol), [Ni(cod)$_2$] (10 mol %), ligand (20 mol %), KF (0.3 mmol), 18-crown-6 (0.2 mmol), solvent (2.0 mL), 100 °C, 12 h, isolated yield. [b] Yields were determined by the ^{1}H NMR integration method using mesitylene as internal standard; the value in the parenthesis was isolated yield. [c]The reaction was carried out at 100 °C, 6 h. NiI$_2$ (0.010 mmol) and Zn (0.3 mmol). Dppm = bis(diphenylphosphino)methane, dppe = bis(diphenylphosphino)-ethane, dppp = bis(diphenylphosphino)propane.

The annulation protocol was successfully applied to a wide range of 1,2,3-benzotriazin-4-(3*H*)-one (**1**) (Scheme 1). We first examined the 1,2,3-benzotriazin-4-(3*H*)-one substrates having *N*-aryl group. Thus, **1a-f** with a *p*-substituted *N*-aryl reacted with benzyne smoothly in the presence of nickel catalyst to give the corresponding phenanthridinones **3a-f** in excellent yields (Table 2). For *meta* and *ortho*-substituted-*N*-aryl 1,2,3-benzotriazin-4-(3*H*)-one, the catalytic reactions with benzyne also proceeded effectively to afford the expected products (**3g-n**) in good to excellent yields. A close examination of the results shows that the product yield decreases in the order: *para*- > *meta*- > *ortho*-substitution. Furthermore, *N*-alkyl and *N*-benzylic 1,2,3-benzotriazin-4-(3*H*)-one substrates (**1o-1s**) also underwent annulation with benzyne smoothly leading to the corresponding phenanthridinones (**3o-3s**) in 85-94% yields. Similar to *N*-aryl substituted 1,2,3-benzotriazin-4-(3*H*)-one (**1**), the *N*-2-naphthyl substituted substrates **1t** reacted smoothly under the standard catalytic conditions to give the corresponding *N*-2-naphthyl product **3t** in 89% yield. Further, we studied the substitution effect at positions 3 and 5 of the *N*-aryl group using electron withdrawing groups CF_3 and Cl as substituents. Substrate **1u** with two *m*-CF_3 groups failed to give the desired product, whereas **1v** with two *m*-Cl afforded the expected product **3v** in 88% good yield. Surprisingly, *N*-2-pyridyl moiety did not give the annulated product **3w**. Further, we focused our attention on the expanding substituents around the backbone of 1,2,3-benzotriazin-4-(3*H*)-one. As expected, a variety of functional groups like fluoro, methoxy and ester did not alter the course of reaction and furnished the expected products **3x-3ba** in 79-85% yields. Also, 4-morpholine substituted substrate **1ca** underwent annulation smoothly affording **3ca** in good yield. Similarly, substrate **1da** reacted effectively to provide the desired product **3da** in 79% yield. Based on the above results, it appears that the catalytic reaction is not much affected by the electronics of substituents around the substrate.

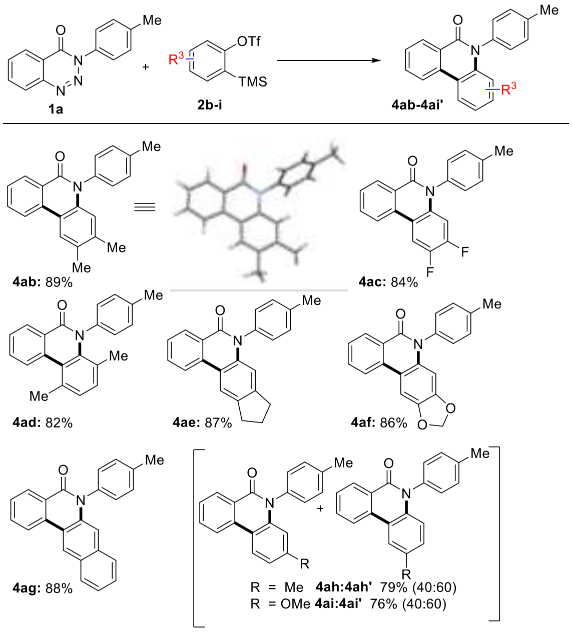
Table 2. The scope of 1,2,3-benzotriazin-4(3*H*)-one in the annulation reaction. [a,b]



[a]Reaction conditions: **1a** (0.10 mmol), **2a** (0.15 mmol), $[Ni(cod)_2]$ (10 mol %), dppm (20 mol %), KF (0.30 mmol), and 18-crown-6 (0.20 mmol) in THF (2.0 mL) at 100 °C for 12 h. [b]isolated yield.

Subsequently, we examined the effect of substitution on the aryne group on the yield of the present nickel-catalyzed reaction (Table 3). Both electron-donating and –withdrawing 4,5-disubstituted symmetrical benzyne **2b** and **2c** offered products **4ab** and **4ac** in high 89 and 84% yields, respectively. Interestingly, the sterically congested 3,6-dimethyl benzyne (**2d**) also reacts smoothly with **1a** affording product **4ad** in 82%. The indanyl derivative **2e** and 1,3-benzodioxole derivatives **2f** furnished products **4ae** and **4af** in excellent yields. Furthermore, 2,3-naphthyne precursor **2g** also proceeded well under the reaction conditions to give **4ag** in 88% yield. As expected, the reaction of **1a** with unsymmetrical aryne precursors **3h** and **3i** afforded two regioisomeric products **4ah/4ah'** and **4ai/4ai'** in moderate combined yields.

Table 3. Scope of 1,2,3-benzotriazin-4(3*H*)-one in the annulation reaction. [a,b]

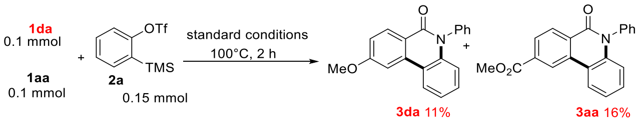


[a]Reaction conditions: **1a** (0.10 mmol), **2a** (0.15 mmol), $[Ni(cod)_2]$ (10 mol %), dppm (20 mol %), KF

(0.30 mmol), and 18-crown-6 (0.20 mmol) in THF (2.0 mL) at 100 °C for 12 h. ^{b}isolated yield.

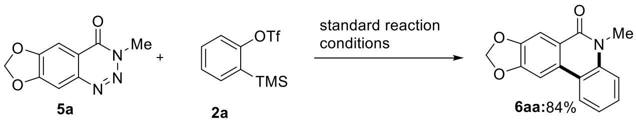
We also conducted a competition experiment between electron-rich substrate **1z** and electron-deficient **1aa** (Scheme 2). Substrate **1aa** reacted with benzyne slightly faster than **1da** under the standard conditions. In agreement with the product yields of **3da** and **3aa** in Table 2, the result reveals that the electronics factor hardly affects the reaction progress.

Scheme 2. Competition Experiment

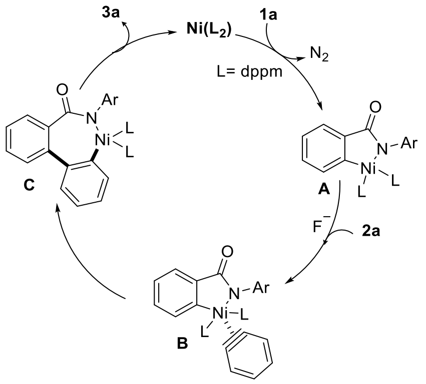


The present annulation can be effectively applied to the synthesis of medicinally interesting compounds as well as naturally occurring bioactive molecules. We have successfully synthesized *N*-methylchrinasidine (**6aa**, Scheme 3) in 84% yield from triazinone **5a** and aryne precursor **2a** under the standard reaction conditions. Since **5a** was prepared in one step from the corresponding commercially available 2-aminoamide in 80% (see SI), the overall yield of **6aa** is 67%. A traditional method for the synthesis of nature product **6aa** was achieved by Cahiez and his coworkers using piperonal as the starting material in 8 steps and 39% overall yield.[16a,b] Our approach appears to give higher yield with less steps compared with above method. It is noteworthy that several other reports for the synthesis of *N*-methylcrinasidine employing metal-catalyed reactions have appeared previously.[4d,12f,16]

Scheme 3. Synthesis of natural product



A possible mechanistic pathway for the present nickel-catalyzed annulation using substrates **1a** and **2a** as the examples is shown in Scheme 4. Initially, **1a** reacts with Ni(0) to form a five-membered azanickelacycle intermediate **A** by extrusion of a molecular nitrogen.



Scheme 4. Proposed Reaction Mechanism

Coordination of benzyne, generated in situ from **2a** and fluoride, to intermediate **A** gives intermediate **B**. Insertion of the coordinated benzyne to the nickel-carbon bond of **A** leading to the formation of a seven membered nickelacycle **C**. Finally reductive elimination provides the final product **3a** and regeneration of the catalyst.[17]

In summary, we have demonstrated the first nickel-catalyzed denitrogenative annulation of 1,2,3-benzotriazin-4-(3*H*)-one with aryne species providing an easy access to structurally diverse phenanthridinones. The highlights of the present approach are one pot synthesis, a wide range of functional group tolerance and the application of the methodology to nature product synthesis. Further investigation on the application of 1,2,3-benzotriazin-4-(3*H*)-one and its related analogues is underway in our laboratory.

Experimental Section

General procedure for Ni-catalyzed annulations of 3-(*p*-tolyl)benzo[d][1,2,3]triazin-4(3*H*)-one (1a) with benzyne (2a): A sealed tube containing 3-(p-tolyl)benzo[d][1,2,3]triazin-4(3*H*)-one **1a** (0.10 mmol), Ni(cod)$_2$ (0.010 mmol), dppm (0.020 mmol), KF (0.30 mmol) and 18-crown-6 (0.20 mmol) was evacuated and purged with nitrogen gas three times. Then, freshly distilled THF (1 mL) was added and benzyne precursor **2a** (0.15 mol) in THF (1 mL) was added via syringe under nitrogen atmosphere and the reaction mixture was stirred at 100 °C for 12 h. After 12 h, the mixture was cooled and diluted with CH$_2$Cl$_2$ (10 mL). The mixture was filtered through a Celite pad and the Celite pad was washed with CH$_2$Cl$_2$ (3 × 10 mL). The filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography using hexane/ethyl acetate as eluent to afford the desired pure product **3a** (26.8 mg; 94%).

Acknowledgements

We thank the Ministry of Science and Technology of the Republic of China (MOST 103-2633-M-007-001) for support of this *research. V.T thank Ministry of Education for Taiwan Government scholarship.*

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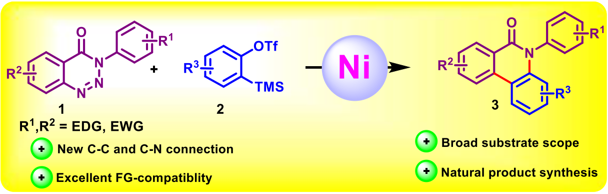
[18] CCDC 1495525 **(3n)**, CCDC 1495723 **(3aa)** and CCDC 1495724 **(4ab)** contain the supplementary crystallographic data for this paper. The data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

COMMUNICATION

Nickel-Catalyzed Denitrogenative Annulation of 1,2,3-Benzotriazin-4-(3*H*)-ones with Benzynes for Construction of Phenanthridinone Scaffolds



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