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Ni-Catalyzed Denitrogenative Cross-Coupling of Benzotriazinones and Cyclopropanols: An Easy Access to Functionalized β-Aryl Ketones

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Cite This: https://dx.doi.org/10.1021/acs.orglett.0c01579 Read Online

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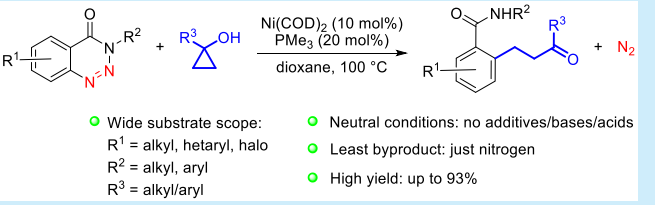
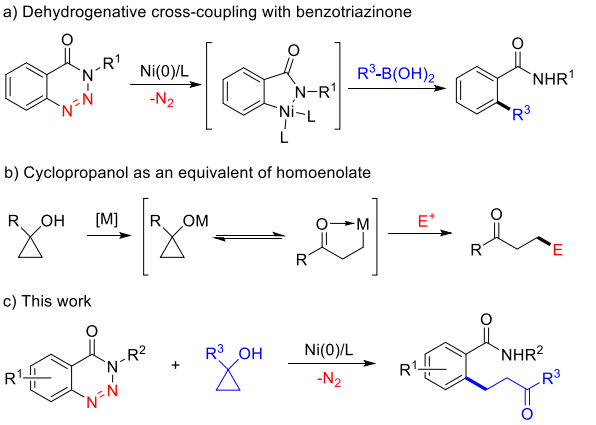
ABSTRACT: A novel Ni-catalyzed denitrogenative cross-coupling between benzotriazinones and cyclopropanols is reported herein. This neoteric reactivity allows for the convenient synthesis of β-(*o*-amido)aryl ketones from readily available starting materials with good yields (up to 93%) and general substrate scope.



The search for new reactivities has long been one fundamental task of organic chemistry. Admittedly, transition-metal-catalyzed cross-coupling reactions harnessed the reactivities of different electrophiles and nucleophiles in a broad and delicate way, which engendered an epochal compilation of synthetically powerful reactions.[1] The exploration of nonclassical electrophiles (those besides organo halides and pseudohalides) and nucleophiles (those besides organometallics) rendered many new possibilities for the facile construction of C−C bonds within various structural motifs. Nitrogen is renowned as an excellent electrofugal leaving group, whereby the employment of aryl diazonium salts and triazenes as electrophiles is experiencing a renaissance in cross-coupling chemistry.[2] Recently, 1,2,3-benzotriazinones, a type of readily available cyclic triazenes de facto, witnessed a series of interesting transformations in the presence of metal catalysts. In 2008, Murakami and co-workers reported the first synthesis of isoquinolones by the Ni-catalyzed denitrogenative alkyne insertion of 1,2,3-benzotriazin-4(3*H*)-ones.[3] Later on, the same group incorporated allenes,[4] 1,3-dienes[5] and isocyanides[6] for the denitrogenative transannulation to form different heterocycles. Other groups achieved the asymmetric,[7] visible-light-promoted,[8] or Pd/Cu catalyzed[9] version of these reactions using alkynes or arynes.[10]

Intrigued by the above denitrogenative transannulation reactions with 1,2,3-benzotriazin-4(3*H*)-ones and our continued interest in the denitrogenative cross-coupling reaction involving aryl triazenes,[11] we envisaged that benzotriazinones might serve as reactive electrophiles to couple with a wide array of nucleophiles to form new C−C bonds in high efficiency. In 2018, the Mannathan and the Cheng group[12] independently reported Ni-catalyzed denitrogenative cross-coupling between 1,2,3-benzotriazin-4(3*H*)-ones and organoboronic acids, which allowed for a facile access to *ortho*-arylated and alkenylated benzamides (Scheme 1a).

Scheme 1. Conception of Ni-Catalyzed Denitrogenative Cross-Coupling of Benzotriazenones with Cyclopropanol



Unmasked cyclopropanols are a class of easily accessible small ring building blocks which have found versatile applications in organic synthesis.[13] They have received considerable attention because the catalytically formed cyclopropoxides can easily tautomerize to homoenolates which could be trapped by various electrophiles to afford diverse β-functionalized ketones (Scheme 1b).[14] On the basis of the burgeoning applications of 1,2,3-benzotriazin-4(3*H*)-ones and cyclopropanols, we speculated that the Ni(0) catalyst may activate both partners to forge new C−C bonds in the

Received: May 8, 2020

https://dx.doi.org/10.1021/acs.orglett.0c01579
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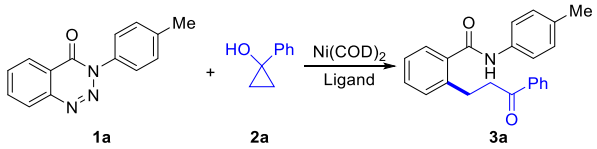
framework of β-(*o*-amido)aryl ketones (Scheme 1c). Of note, these valuable frameworks had only been constructed via Ru, Rh or Co-catalyzed C−H activation procedures with limited substrate scope or involving less stable starting materials.[15]

Initially, *N*-(*p*-tolyl)benzotriazinone (**1a**) and 1-phenylcyclopropan-1-ol (**2a**) were reacted in dioxane at 80 °C in the presence of 10 mol % of $Ni(COD)_2/PPh_3$. After 18 h, the desired product **3a** was obtained with 34% yield (Table 1, entry 1). Increasing the temperature to 100 °C or changing the solvent to toluene improved the yield modestly to 52% and 63%, respectively (Table 1, entries 2 and 3). To further improve the yield of **3a**, the ligand effect was examined. Other monophosphines like P(*t*-Bu)$_3$ and P(*n*-Bu)$_3$ gave no better results than PPh_3 (Table 1, entries 4−6). Diphosphine ligands like dppb and BINAP blocked the cross-coupling reaction wherein the decomposition of **1a** to *N*-tolylbenzamide became the main side reaction (Table 1, entries 7 and 8). Omitting the ligand resulted in the production of **3a** with only 15% yield (Table 1, entry 9). To our delight, when PMe_3 was used, the yield of **3a** was optimized up to 91% at 100 °C (Table 1, entries 10−12). The reaction in other solvents like toluene, acetonitrile, THF, and DMF was much less efficient than in dioxane. In a control experiment, only a trace of **3a** was detected in the presence of $Pd(OAc)_2/PPh_3$. However, using $Pd(PPh_3)_4$ afforded **3a** in 15% yield (Table 1, entry 18). CuI was totally inert for this reaction (Table 1, entry 19). These observations indicated that nickel was the unique metal for this denitrogenative cross-coupling.

Table 1. Optimization of the Reaction Conditions[a]



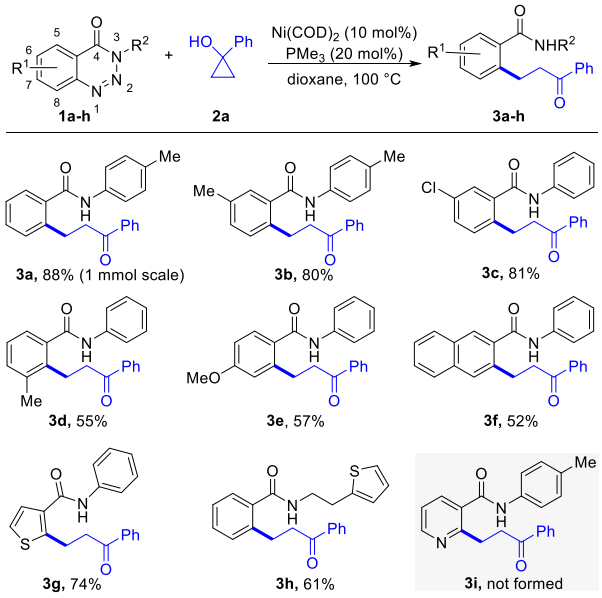
1a 2a 3a

entry	ligand	solvent	*T* (°C)	yield[b] (%)
1	PPh_3	dioxane	80	34
2	PPh_3	dioxane	100	52
3	PPh_3	toluene	100	63
4	P(*t*-Bu)$_3$	dioxane	80	23
5	P(*n*-Bu)$_3$	dioxane	80	25
6	P(*n*-Bu)$_3$	dioxane	100	35
7	dppb	dioxane	100	<5[c]
8	BINAP	dioxane	100	<5[c]
9	–	dioxane	80	15
10	PMe_3	dioxane	80	67
11	PMe_3	dioxane	90	78
12	PMe_3	dioxane	100	91
13	PMe_3	toluene	100	76
14	PMe_3	MeCN	100	64
15	PMe_3	THF	100	57
16	PMe_3	DMF	100	23
17	$Pd(OAc)_2/PPh_3$	dioxane	100	trace
18	$Pd(PPh_3)_4$	dioxane	100	15
19	CuI/PPh_3	dioxane	100	nr

[a]Reaction conditions: **1a** (0.2 mmol), **2a** (0.3 mmol), $Ni(COD)_2$ (0.02 mmol), ligand (0.04 mmol for monophisphines; 0.02 mmol for diphosphines); 2.0 mL of solvent, 18 h. [b]Isolated yield. [c]*N*-Tolylbenzamide was the main side product. nr = no reaction.

With the optimized conditions in hand, we tried to broaden the substrate scope to other substituted 1,2,3-benzotriazinones (Scheme 2). It was found that 6-methyl- and 6-chloro-substituted 1,2,3-benzotriazinones (**1b** and **1c**) were coupled with **2a** to afford 5-chloro-2-(3-oxo-3-phenylpropyl)-*N*-phenylbenzamide (**3b**) and 5-methyl-2-(3-oxo-3-phenylpropyl)-*N*-(*p*-tolyl)benzamide (**3c**) in 80% and 81% yield, respectively. A methyl group on the 8-position depressed the efficiency of this transformation, and **3d** was isolated in 55% yield, which might be caused by the steric hindrance near the reaction site. 7-Methoxybenzotriazinone (**1e**) also gave the product **3e** in 57% yield. In addition, naphthotriazenone (**1f**) and thienotriazenone (**1g**) were also amenable to the denitrogenative cross-coupling to form the corresponding functionalized β-aryl ketones **3g** and **3h** in preparatively meaningful yield. R^2 in the triazinones are not necessarily to be aryl groups. For instance, 61% yield of aliphatic amide (**3h**) was obtained when R^2 is a 2-(2-thienyl)ethyl group (**1h**). It is worth mentioning that pyridotriazinone (**1i**) did not offer the corresponding product (**3i**).

Scheme 2. Substrate Scope of 1,2,3-Benzotriazinones



Encouraged by the wide scope of benzotriazinones, we next examined the denitrogenative cross-coupling reaction with various cyclopropanols (Scheme 3), which can be easily synthesized by Kulinkovich cyclopropanation of esters.[16] Gratifyingly, alkyl-substituted cyclopropanols smoothly participated in the reaction to afford the β-(*o*-amido)aryl ketones in good to excellent yields (65−91%, **4a**−**e**), among which the linear alkyl cyclopropanol (R^3 = *n*-butyl) gave the highest yield (**4a**, 91%). 4-*tert*-Butylbenzylcyclopropanol also reacted with **1a** to form the functionalized dialkyl ketone in 65% yield (**4e**). Several other aryl cyclopropanols were subjected to the optimal conditions to define the substitution effect on the denitrogenative cross-coupling reaction. To our delight, 1-(*p*-tolyl)cyclopropan-1-ol reacted with **1a** to give **4f** in almost quantitative yield (93%). However, *p*-methoxy and *tert*-butyl substituents led to lower yields of **4g** and **4h**, i.e., 85% and 47%, respectively. 1-(4-Fluorophenyl)cyclopropan-1-ol reacted with **1a** to form **4i** in 74% yield, whereas its chloro counterpart led to **4j** in only 40% yield, which may be attributed to the higher reactivity of aryl C−Cl bond toward nickel catalyst.[17]

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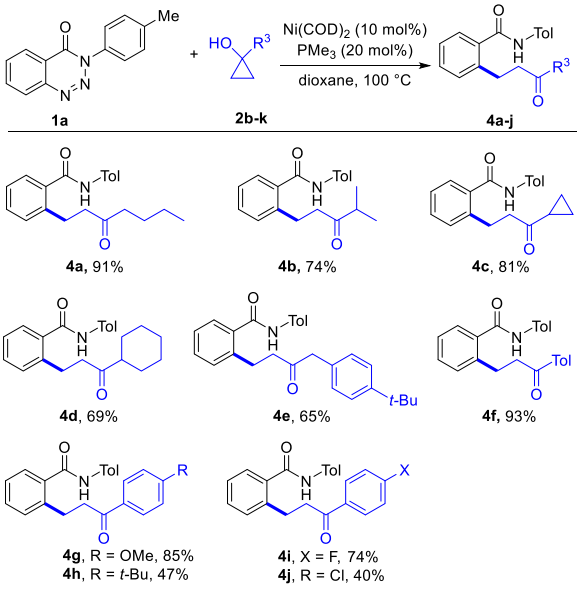
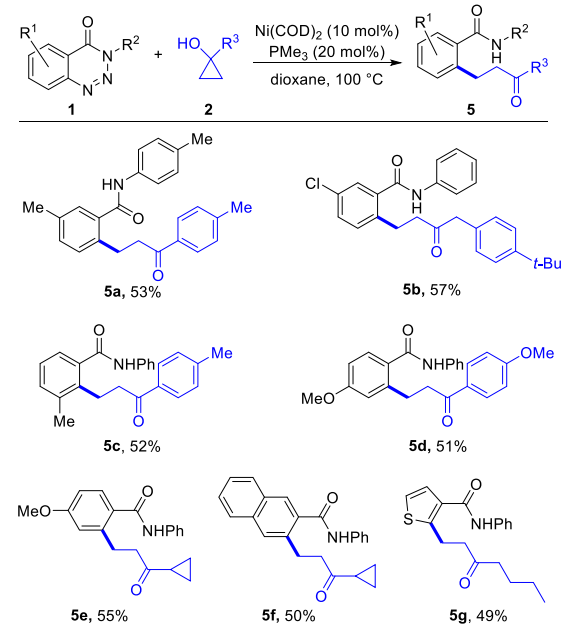
Scheme 3. Substrates Scope of Cyclopropanols



The above screening experiments show that this nickel-catalyzed denitrogenative cross-coupling between benzotriazinones and cyclopropanols tolerated a wide range of substituents on both reaction partners. To further demonstrate the efficiency of this new method for the facile access to β-(*o* amido)aryl ketones, we performed several crossover couplings of the two components (Scheme 4). Moderate to good yields

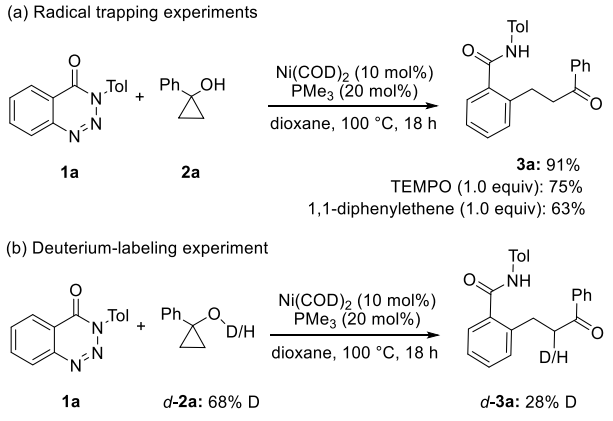
Scheme 4. Further Exploration of the Substrate Scope



were obtained for all of the examples. These pharmaceutically interesting scaffolds,[18] however, still lack some general and practical methods for their synthesis.

To gain some insight into the reaction pathway, we first performed the model reaction in the presence of 1 equiv of TEMPO and 1,1-diphenylethene as the radical scavengers, and the yield of **3a** was lowered to 75% and 63%, respectively (Scheme 5a). Based on these observations and the previous

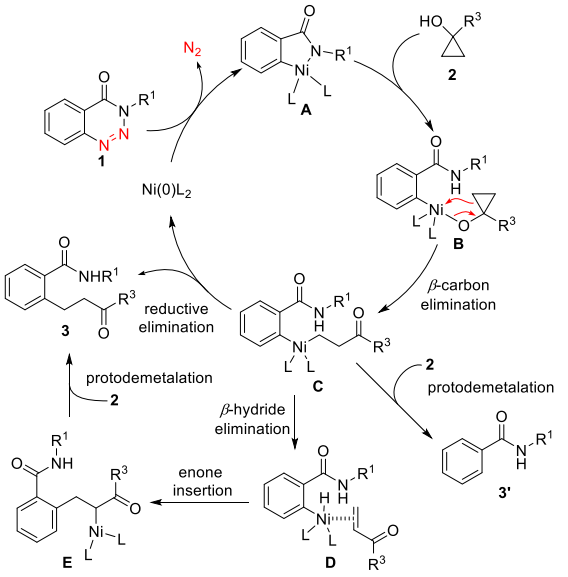
Scheme 5. Mechanistic Studies



reports,[12] we assumed that this reaction may probably not involving a radical process. In addition, when **1a** was reacted with 68% deuterated cyclopropanol **2a**[19] under the standard conditions, the deuterium was found to be partially incorporated at α-position **3a** (Scheme 5b; see the Supporting Information for analysis).

On the basis of the above experiments and the literature reports, a possible reaction pathway is proposed (Scheme 6).

Scheme 6. Plausible Catalytic Cycle



At first, oxidative addition benzotriazinone with Ni(0) and subsequent extrusion of gaseous N_2 affords the five-membered azanickelacycle **A**.[20] Then the nickel−nitrogen bond is cleaved by the cyclopropanol (**2**) to form nickel cyclopropanoxide **B**, which automatically tautomerizes to form aryl alkyl nickel species **C**. At this junction, **C** can undergo ensuing reductive elimination to release the β-aryl ketone product (**3**) and regenerate the Ni(0). Alternatively, it undergoes β-hydride elimination to form enone-complexed nickel hydride **D**,[21] wherein reinsertion of the enone would lead to intermediate **E**. The final product (**3**) is then released by the protodemetalation by the cyclopropanol (**2**), which also accounts for the incorporation of 28% deuterium at the α-position of the ketone in *d*-**3a**. In some cases, the intermediate **C** directly undergoes

https://dx.doi.org/10.1021/acs.orglett.0c01579
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off-cycle protodemetalation to give the denitrogenated side product (**3′**).

In summary, we have discovered a new denitrogenative cross-coupling reaction between benzotriazinones and cyclopropanols catalyzed by simple nickel complex, furnishing a facile access to the valuable building block of *β*-(*o*-amido)aryl ketones. The innovation of this new transformation utilizes the oxidative formation of azanickelacycle between Ni(0) and triazinones after extrusion of nitrogen and the homoenolate nature of the cyclopropanols. This work extended the scope of the nickel catalysis in the double activation of unconventional electrophiles and nucleophiles and will find some useful applications for the construction of some building blocks that require otherwise lengthy or detoured synthetic routes. Further investigations into the new reactivities based on this strategy are underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c01579.

Details of experimental procedures, characterization data for the products **3**−**5**, NMR spectra for compounds **3**−**5** (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We are grateful for the financial support provided by the National Natural Science Foundation of China (21901163). We also acknowledge the generous help from Prof. Kaiwu Dong (East China Normal University) and Prof. Zhaoguo Zhang and Prof. Xiaomin Xie (Shanghai Jiao Tong University).

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(20) See ref 3. The postulated azanickelacycle complex was characterized by X-ray structure by reaction of **1a** with equimolar amounts of $Ni(COD)_2$ and 1,2-bis(diphenylphosphino)benzene (Dppbenz).

(21) We did not observe the dissociation product of enone (phenyl vinyl ketone) in the model reaction. In a separate experiment as

https://dx.doi.org/10.1021/acs.orglett.0c01579
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suggested by the reviewer, we carried out an enone additive experiment by adding 0.3 equiv of 2-naphthalenyl vinyl ketone to the reaction between **1a** and **2a**. However, the 2-naphthalenyl vinyl ketone was not incorporated into the product.

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