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Palladium-Catalyzed Dual Annulation: A Method for the Synthesis of Norneocryptolepine

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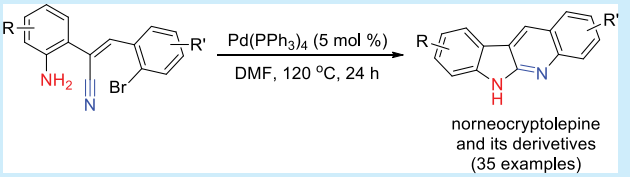
Supporting Information

ABSTRACT: A novel procedure for the Pd-catalyzed dual annulation reaction to synthesize the norneocryptolepine derivatives involving the concerted construction of two central heterocycles is reported. The further methylation of the norneocryptolepine to afford its alkaloid analog neocryptolepine implies that synthesis of various neocryptolepine derivatives is feasible. The oxidative addition of Pd(0) is indicated as the key step to activate the intramolecular addition of nitrile according to the mechanism study.

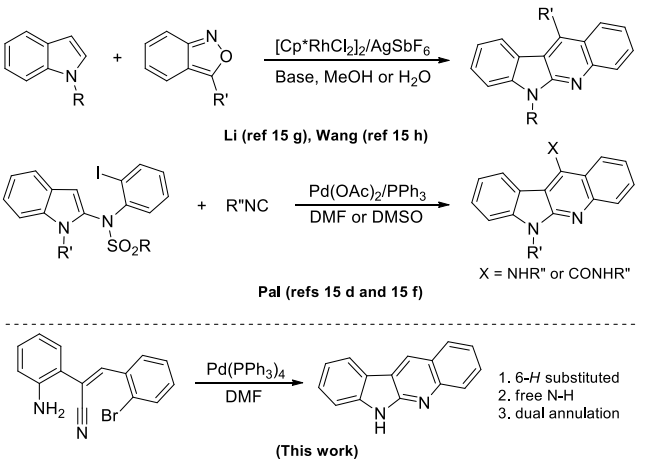


Norneocryptolepine (or norcryptotackieine), a natural alkaloid isolated from the leaves of *Justicia betonica*,[1] is often used as an intermediate for the synthesis of its *N*-methylated derivative, neocryptolepine.[2] The highly structural similarity causes these two alkaloids to share several focused bioactivities, including inhibition of DNA topoisomerase II,[3] antiplasmodial activity,[4] activity against schistosomiasis,[5] antibacterial activity,[6] antitumor activity,[3,7] etc. The source of neocryptolepine (*Cryptolepis sanguinolenta*) was even used as the traditional herbal medicine for the treatment of malaria and other common diseases in West and Central Africa.[8] Because of the importance, many synthetic and pharmaceutical chemists have paid a lot of attention to the synthesis of this quinindoline core structure and its medicinal potential. However, synthesis of this complicated tetra-fused heterocycle is not easy, and still, only limited strategies have been reported to approach the quinindoline derivatives to date.

Construction of a quinindoline scaffold mainly relies on three synthetic pathways. The oldest fashion involved the extension of an indole moiety from a functionalized quinoline through the C−C or the C−N coupling.[9] Although modification toward various coupling processes has been carried out, this strategy has often been reported in synthesizing a solo case of neocryptolepine[10] or with a limited scope of natural alkaloid derivatives.[11] The dual annulation of an *N*-alkynylaryl-*N*-aryl carbodiimide through a diradical pathway is another method for the synthesis of quinindolines that has appeared occasionally in the literature.[12] Despite the progress having been halted for a decade, a very recent paper has revealed that the structural diversity can be effectively broadened by a modified cationic cyclization.[13] The most commonly selected strategy emerging in recent work is the ring expansion of an indole derivative.[14] Due to the continuous development in this strategy, various coupling methods[15] regarding the cyclization to furnish an extended quinoline ring have been afforded in response to the diverse structural requirement.

Even though the structure library has been expanded by accumulated research work, the limitation of synthetic methods still restricts the scope to some extent. Therefore, a new route to approach the quinindolines is still desired. In this concern, transition-metal-catalyzed annulation reactions may possess the potential to construct this tetra-fused heterocyclic skeleton in a more flexible manner. However, only a few examples based on Pd[15d,f] and Rh[15g,h] have been reported up to now (Scheme 1).

Scheme 1. Synthesis of Quinindoline via Transition-Metal Catalysis



To increase the examples in the new synthetic pathway via the transition-metal catalysis, we try to explore the new possibility on the basis of our experience. Our continuous interest in the catalytic annulation reactions by utilizing the C−N multiple bonds as the reaction participants[16,17] prompted us to develop a new catalysis for the synthesis of quinindolines with versatile substituents. Herein, we report the Pd-catalyzed dual annulation

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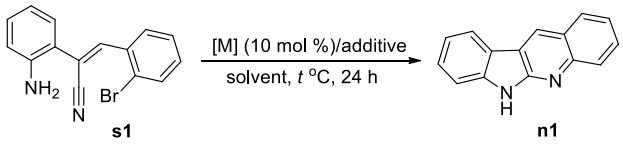
Table 1. Optimization of Reaction Conditions[a]



entry	[M]	additive	solvent	temp (°C)	yield (%)[b]
1	Cu_2O		DMSO	120	27
2	$Cu(CH_3CN)_4BF_4$		DMF	120	36
3[c]	Cu_2O	$BF_3{\cdot}OEt_2$	DMF	100	15
4[c]	Cu_2O	$BF_3{\cdot}OEt_2$	DMF	120	83
5[c]	CuI	$BF_3{\cdot}OEt_2$	DMF	120	63
6	$Ni(cod)_2$		1,4-dioxane	100	19
7[d]	$Ni(cod)_2$	PPh_3	1,4-dioxane	100	26
8[d]	$Ni(cod)_2$	PPh_3	1,4-dioxane	120	28
9[e]	$NiBr_2(PPh_3)_2$	Zn	CH_3CN	100	21
10[e]	$CoI_2(PPh_3)_2$	Zn	DMF	120	trace
11	$Pd(PPh_3)_4$		1,4-dioxane	100	0
12	$Pd(PPh_3)_4$		DMF	100	0
13	$Pd(PPh_3)_4$		DMF	120	86
14	$Pd_2(dba)_3$		DMF	120	42
15[d]	$Pd(OAc)_2$	PPh_3	DMF	120	17
16[f,g]	$Pd(PPh_3)_4$		DMF	120	96 (93)[h]
17[f,i]	$Pd(PPh_3)_4$	PPh_3	DMF	120	92
18			DMF	120	0

[a]Reaction conditions: **s1** (0.2 mmol, 1.0 equiv), [M] (10 mol %), solvent (2.0 mL), indicated temperature, under N_2, 24 h. [b]^{1}H NMR yield based on internal standard mesitylene. [c]40 mol % $BF_3{\cdot}OEt_2$. [d]20 mol % PPh_3. [e]3.0 equiv of Zn. [f]8.0 mL of DMF. [g]5 mol % $Pd(PPh_3)_4$. [h]Isolated yield. [i]3 mol % $Pd(PPh_3)_4$ and 3 mol % PPh_3, 40 h.

reaction through an intramolecular addition of nitrile to synthesize the norneocryptolepine derivatives.

We started our initial study from the survey of transition-metal catalysts by using compound **s1** as the model substrate (Table 1). In the beginning, our research focused on the copper catalysis (entries 1−5); after a series of tests, we found that the $Cu_2O/BF_3{\cdot}OEt_2$ catalytic system can provide the product **n1** in 83% NMR yield (entry 4). However, the catalytic efficiency is insufficient to be considered as a catalytic reaction (20 mol % Cu loading). Further tunings of the reaction conditions were unable to result in any improvement. We then turned our target to other transition-metal catalysts, which have been known to participate in a coupling reaction through activating a carbon−halide bond. Several nickel, palladium, and cobalt complexes were thus selected for the examinations, and the results are summarized in Table 1 (entries 6−17) as well. The nickel complexes showed low efficiency in this reaction; the best performance was accomplished in only 28% yield by using $Ni(cod)_2/PPh_3$ as the catalyst and 1,4-dioxane as the solvent (entry 8). The cobalt complex is inactive; most of the substrate **s1** was not able to be converted, and only a trace amount of desired product **n1** was observed (entry 10). The palladium complexes were found to have higher catalytic efficacy than others, and the $Pd(PPh_3)_4$ was found to be the best catalyst in this reaction (entry 13). In addition, lower concentration and additional phosphine ligand are helpful for this catalysis. A nearly quantitative yield was obtained in the presence of 5 mol % $Pd(PPh_3)_4$ in a quarter concentration of DMF (entry 16). Further decrease of the catalyst loading leads to slightly lower yield even with an additional phosphine ligand (entry 17). The blank reaction in DMF did not exhibit any reactivity (entry 18).

After the optimized condition was established, the substrate scope was then investigated to understand the capacity of this Pd-catalyzed annulation reaction (Scheme 2). As indicated, the reactions proceeded smoothly for a wide range of substrates. Both of the electron-donating and the electron-withdrawing groups are able to be well tolerated, and the yields clearly depend on the electron density of every structural subunit. In general, the products with an electron-deficient group on the quinoline moiety were afforded in higher yields than those with an electron-donating group. Substrates with the groups on the *para* position to bromide affect the yields a lot (**n2**−**n4**), while the yields for the substrates with the groups on the *ortho* position to bromide are not so different (**n5**−**n7**). Notably, the amino groups are also able to be fitted on the scaffold (**n8**, **n9**, and **n17**); these amino derivatives have been reported to possess some focused bioactivities, such as the antiplasmodial activity and the inhibition of β-hematin formation.[15a] The easy access to these structural types will significantly contribute to the development of their structure−activity relationships in the related pharmaceutical research. Products with the dimethoxy groups and an extended dioxole ring on the quinoline moiety (**n10**−**n12**) were generated in good yields. The fused ring system could be extended to the benzoquinoline analog, and the corresponding product **n13** was provided in 83% yield.

The diverse substituents on the indole moiety were carefully examined as well. It is interesting to note that the electron-donating and the weak electron-withdrawing groups did not result in an obvious difference in the reaction yield (**n14**−**n18**), but the strong electron-withdrawing group CF_3 provided a comparably lower yield than others (**n19**). Also, products with the disubstituted electron-donating groups (**n20** and **n21**) were obtained in higher yields than the monosubstituted structures. Moreover, a wide range of structural diversity is available to be established by the free combinations of the substituents on different moieties. Thus, we created several structures (**n22**−

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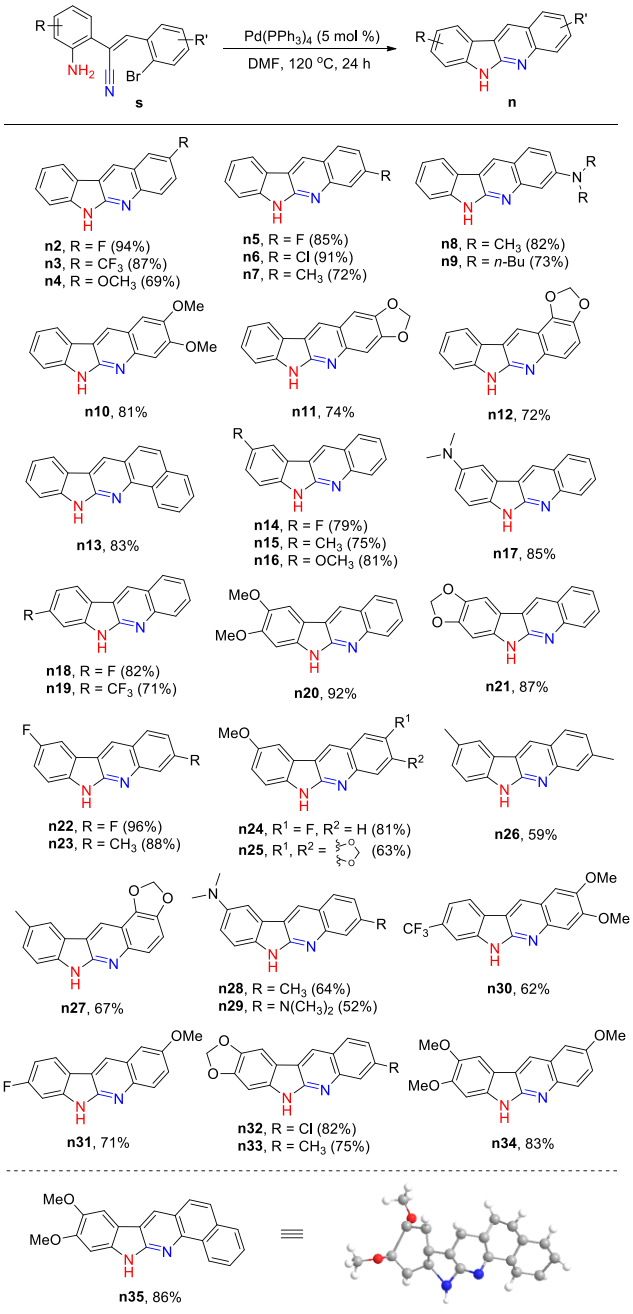
Scheme 2. Scope of the Reaction[a]

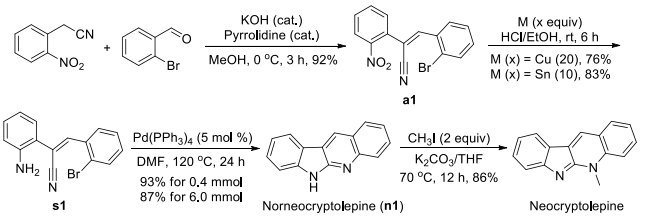


[a]Reactions were carried out using 0.4 mmol (1.0 equiv) **s** with 5 mol % $Pd(PPh_3)_4$ in 16 mL DMF at 120 °C for 24 h. Isolated yield.

n35) to reveal the reaction capacity, and the product **n35** has been verified by the single-crystal X-ray diffraction analysis for additional confirmation.

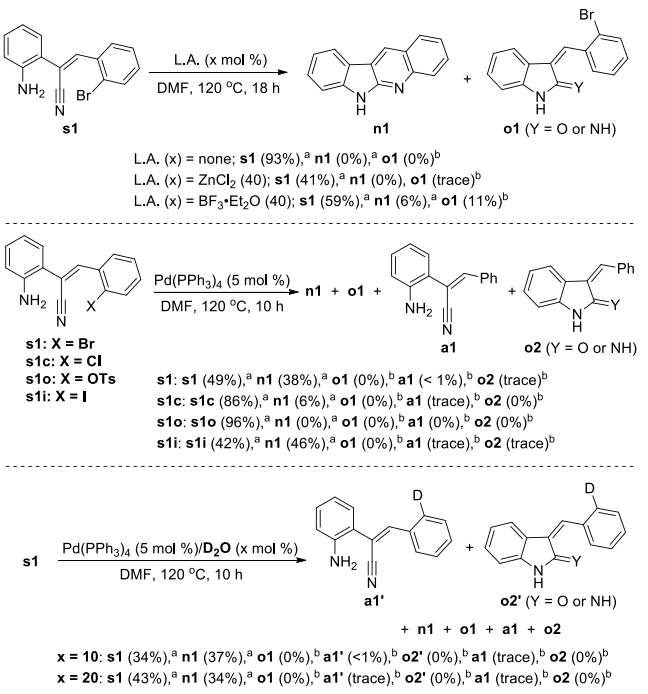
As reported in previous literature,[9a,12a] the neocryptolepine can be obtained by a methylation of the norneocryptolepine (**n1**). Here, we show our synthetic route to lead to these two alkaloids within four steps starting from two commercially available compounds (Scheme 3). This strategy represents an efficient pathway to reach these two alkaloids and implies that all products are feasibly converted to their corresponding neocryptolepine derivatives. Furthermore, the dual annulation reaction can proceed in gram scale without significant loss of the reaction yield.

Scheme 3. Synthesis of the Neocryptolepine



To verify the reaction pathway, several control experiments have been conducted to understand the nature of the reaction (Scheme 4), and we can obtain the information via observation

Scheme 4. Control Experiments



[a]NMR yield. [b]Determined by GC-MS after working up.

of different intermediates determined by NMR and GC-MS. First, no reaction can proceed without catalyst or additive; the intramolecular addition of aniline to nitrile can be executed only with Lewis acid. The stronger Lewis acid tends to afford more **o1**. Second, when a reaction proceeded in the presence of the $Pd(PPh_3)_4$, we did not observe **o1** but there was a trace amount of **a1** and **o2**. This result suggests that the oxidative addition of a C−Br bond should be prior to the addition of aniline to nitrile. We then replaced the substrate **s1** with **s1c** and **s1o** and found that, while the oxidative addition of a C−X bond is retarded, the formation of the corresponding hydrogenated intermediates **o1** and **a1** is inhibited as well. However, when a C−I bond (**s1i**) was utilized as the target of oxidative addition, the reaction rate is faster than all other substrates, which indicates that the oxidative addition is the key step to dominate the reaction. Third, addition of D_2O as the deuterium source was conducted as well to monitor the change of intermediates. Interestingly, it was found that the reaction was not affected by additional D_2O; only **s1** and **n1** were observed in the crude NMR spectra, and the GC-MS analysis demonstrated that only **a1** and **a1′** are the detected intermediates.

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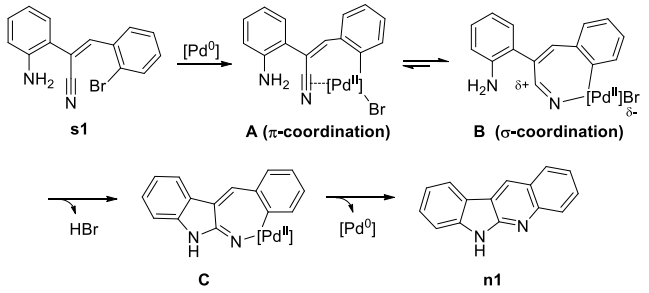
On the basis of the previous reports[16,17] and the above results, a proposed reaction pathway accounting for this Pd-catalyzed dual annulation is shown in Scheme 5. The reaction is initiated

Scheme 5. Proposed Reaction Pathway



from the oxidative addition of $Pd(PPh_3)_4$ to the C−Br bond of **s1**. The resulted Pd(II) species performs as a Lewis acid to activate the nitrile group and produces the corresponding π-coordination complex **A** and σ-coordination complex **B**, which facilitates the intramolecular addition of the aniline moiety to the nitrile group. Reductive elimination of the Pd(II) complex **C** provides desired product **n1** and regenerates the Pd(0).

In conclusion, we have developed a concise method for the Pd-catalyzed synthesis of a wide range of norneocryptolepine derivatives in excellent yields for most cases. Methylation of the norneocryptolepine can afford the neocryptolepine in the shortest synthetic route with the highest overall yield. Study of the reaction mechanism indicates that the Pd(II) species after the oxidative addition performs as a Lewis acid to activate the intramolecular addition of aniline to nitrile and accomplishes the dual annulation. Further studies to explore the applications in pharmaceutical research are currently underway.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b00287.

Experimental procedures, characterization, spectral data, X-ray structure, NMR spectra and X-ray data (PDF)

Accession Codes

CCDC 1888580 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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