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Synthesis of Substituted Furan/Pyrrole-3-carboxamides through a Tandem Nucleopalladation and Isocyanate Insertion

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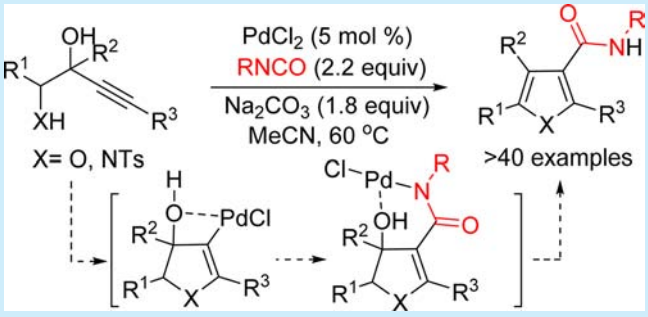
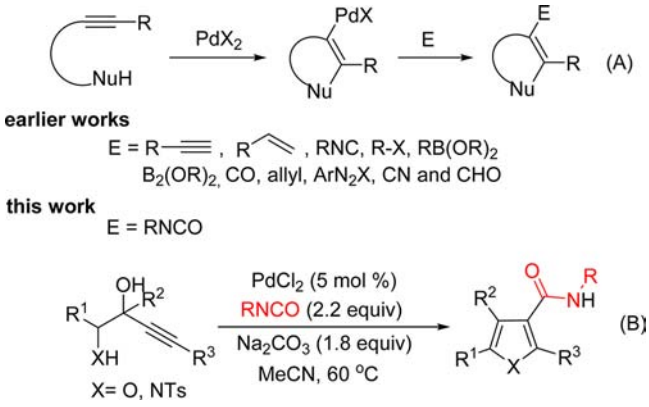
Supporting Information

ABSTRACT: Access to furanyl- and pyrrolyl-3-carboxamides from readily available 3-alkyne-1,2-diols and 1-amino-3-alkyn-2-ols using isocyanate as amido surrogate is demonstrated. The approach constitutes a successful unprecedented combination of heteropalladation and isocyanate insertion, a new avenue for novel amide bond constructions. The mechanism likely involves a 6-membered oxaaminopalladacycle as the key intermediate.



Palladium-catalyzed cyclization of functionalized alkynes opens many otherwise difficult C−Pd avenues which via various couplings in tandem can be materialized for composite outcomes.[1] The approach not only avoids the unnecessary prefunctionalization of the heterocycles, which is usually required in most of the classical coupling reactions, but brings in the high atom and step economies and thus altogether delivers the complex architectures in short pathways. Thus, various groups have explored the heteropalladation and its tandem coupling with various partners like carbon monoxide,[1a,b] alkynes,[1c] boronates,[1d,e] halides/pseudohalides,[1f,g] olefins,[1h−j] allylic alcohols,[1k] cyanides,[1l] aldehydes,[1m] isocyanides,[1n−q] etc. (Scheme 1A). On the similar lines, and in consequent to the enormous importance in biology, amide construction in tandem to nucleopalladation was also recently studied. Thus, Gabriele et al.[1r,s] achieved the installation of an amide group by tethering carbon monoxide followed by amines to the C−Pd bond derived from nucleopalladation of alkynes. Zhu et al.,[1n] followed by us,[2a] revealed the use of isocyanide for the amide construction in tandem to amino/oxypalladation. In continuation of interest in uncovering new activities of functionalized alkynes,[2] we herein present an unprecedented isocyanate coupling[3]/insertion in tandem to intramolecular oxy/amino palladation of alkynes for furanyl- and pyrrolyl-3-carboxamides (Scheme 1B). An interesting mechanism involving an oxyaminopalladacycle is proposed with some evidence.

Scheme 1. Tandem Nucleopalladation and Coupling of Alkynes



Furans and pyrroles are frequently found scaffolds both in drug discovery as well as natural products.[4,5] Particularly, these heterocycles tethered with amide unit were identified as very important subunits in many bioactive compounds.[4,5] For example: atorvastatin and sunitinib are among the best selling drugs; proximicin C, tallimustine, oroidin, dispyrin, (−)-bromophakellin, bromoagelaspongin, (+)-ageliferin, (−)-sceptrin, and kibdelomycin are some of the natural products that contain these subunits. We therefore aimed to synthesize these motifs in an expeditious pathway.

We began our studies with the optimization of reaction conditions for the conversion of **1a** to **2aa** (Table 1). When $Pd(OAc)_2$ was used as catalyst and Na_2CO_3 as base in CH_3CN, the desired product **2aa** was formed via oxypalladation and isocyanate insertion followed by dehydration in 10% yield (entry 1).

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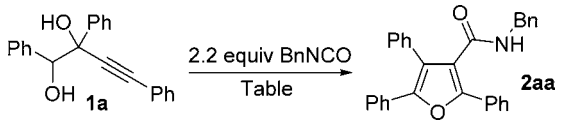
Table 1. Optimization of Reaction Conditions[a]



entry	catalyst	base	solvent	temp (°C)	yield (%)[b]
1	$Pd(OAc)_2$	Na_2CO_3	CH_3CN	60	10
2	PdI_2	Na_2CO_3	CH_3CN	60	30
3	$Pd(PPh_3)_2Cl_2$	Na_2CO_3	CH_3CN	60	40
4	**$PdCl_2$**	**Na_2CO_3**	**CH_3CN**	**60**	**82**
5	$Pd(TFA)_2$	Na_2CO_3	CH_3CN	60	26
6	$PdCl_2$	K_2CO_3	CH_3CN	60	65
7	$PdCl_2$	Cs_2CO_3	CH_3CN	60	35
8	$PdCl_2$	TEA	CH_3CN	60	20
9	$PdCl_2$	DIPEA	CH_3CN	60	15
10	$PdCl_2$	DBU	CH_3CN	60	
11	$PdCl_2$	Na_2CO_3	DMSO	60	10
12	$PdCl_2$	Na_2CO_3	2-BuOH	60	
13	$PdCl_2$	Na_2CO_3	1,4-dioxane	60	25
14	$PdCl_2$	Na_2CO_3	DCE	60	05
15	$PdCl_2$	Na_2CO_3	toluene	60	45
16	$PdCl_2$	Na_2CO_3	THF	60	28

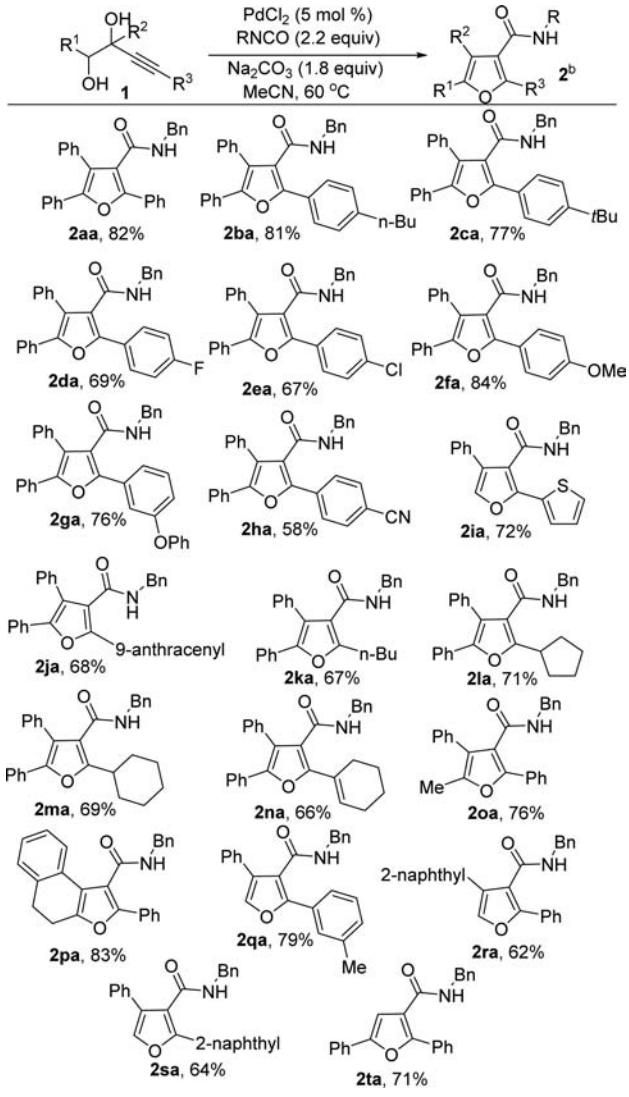
[a]Conditions: **1aa** (0.5 mmol), BnNCO (1.1 mmol), base (0.9 mmol), catalyst (0.025 mmol) in solvent (2.5 mL) at 60 °C under air. [b]Isolated yield.

Screening of other Pd catalysts like PdI_2, $Pd(PPh_3)_2Cl_2$, $PdCl_2$, and $Pd(TFA)_2$ revealed that $PdCl_2$ was highly effective for the intended conversion to afford **2aa** in 82% yield (entries 2−5). Other bases (both inorganic and organic) like K_2CO_3, Cs_2CO_3, TEA, DIPEA, and DBU were not as productive as Na_2CO_3 (entries 6−10). MeCN was the best of all the solvents tested (entries 11−16).

With the optimized conditions in hand, we next evaluated the generality of the methodology. We first studied the reaction scope of dihydroxy alkynes. As is evident from Scheme 2, the reaction accommodated substrates with disparate electron properties. Initially, variation of substitution at alkyne terminal was studied. Substrates with alkylated phenyl substitution on the alkyne terminal (**1b,c**) led to similar product yields (77−81%) like **1a**, whereas halo (F and Cl) phenyl substitution (**1d,e**) slightly decreased the productivity (67−69%). The electronic nature of the phenyl substitution has a noticeable influence on the outcome. Thus, electron-rich alkoxy-substituted substrates **1f,g** gave the corresponding adducts **2fa−ga** in 76−84% yields, whereas the electron-deficient counterpart **1h** was transformed to the desired adduct **2ha** in moderate yield of 58%. Substrates with thiophenyl and anthracenyl substitution (**1i,j**) were found to be equally viable substrates for the reaction to furnish the products (**2ia−ja**) in 68−72% yields. We next tested the tolerance of the reaction toward aliphatic substitution. Pleasingly, the substrates with both acyclic (**1k**) and cyclic (**1l,m**) alkyl substitution passed through the reaction smoothly to afford the products in excellent yields (67−71%). Furthermore, the reaction proceeded well with the enyne **1n** to afford product with alkenyl substitution at C2. Products with alkyl substitution at C-5 (**2oa−pa**) were also smoothly accessed (76−83%). Finally, trisubstituted furanamides **2pa−ta** were synthesized in 62−79% yields under the standard conditions.

The scope of this transformation was further investigated with respect to isocyanates (Scheme 3). Phenyl isocyanates

Scheme 2. Synthesis of Furan-3-amides from Alkynediols[a]



[a]Conditions: **1** (0.5 mmol), BnNCO (1.1 mmol), base (0.9 mmol), catalyst (0.025 mmol) in solvent (2.5 mL) at 60 °C under air. [b]Isolated yield.

were initially tested. Alkyl- and halophenyl isocyanates successfully reacted under standard conditions to afford the corresponding products **2ab−ae** in 67−77% yields. Further expanding the scope of the reaction, aliphatic isocyanates were found to be even better partners compared to their aromatic counterpartners. Thus, **2af−am** were obtained in 69−89% yields. Steric factors in the case of isopropyl and *tert*-butyl isocyanates showed no apparent effect on the outcome. Pleasingly, sensitive chloroethyl groups survived successfully through the standard conditions during the synthesis of **2ai**. Setting a limitation, substrates bearing a terminal alkyne did not afford the desired product. The structure of **2ak** was unambiguously confirmed by X-ray crystallography.

We next aimed to screen the amino alkynols to expand the reaction scope for the synthesis of pyrrole-3-amides (Scheme 4). Delightedly, when we subjected **3a** and BnNCO to the standard conditions, the expected product **4a** was obtained in an excellent yield of 79%. The reaction went equally well with toluyl (**3b**) substitution (**4b** in 83% yield) at the alkyne terminal, whereas the chlorophenyl group (**3c**) was found to

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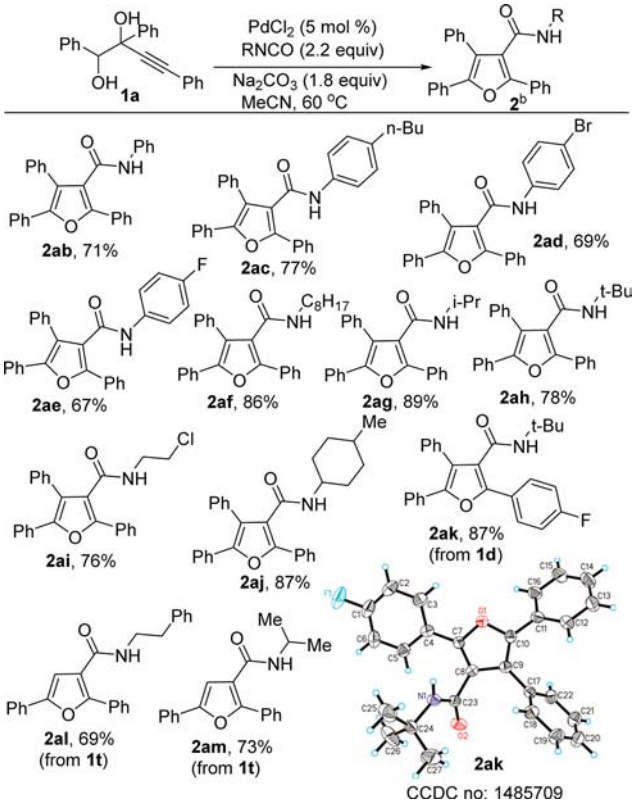
Scheme 3. Scope of Isocyanates[a]

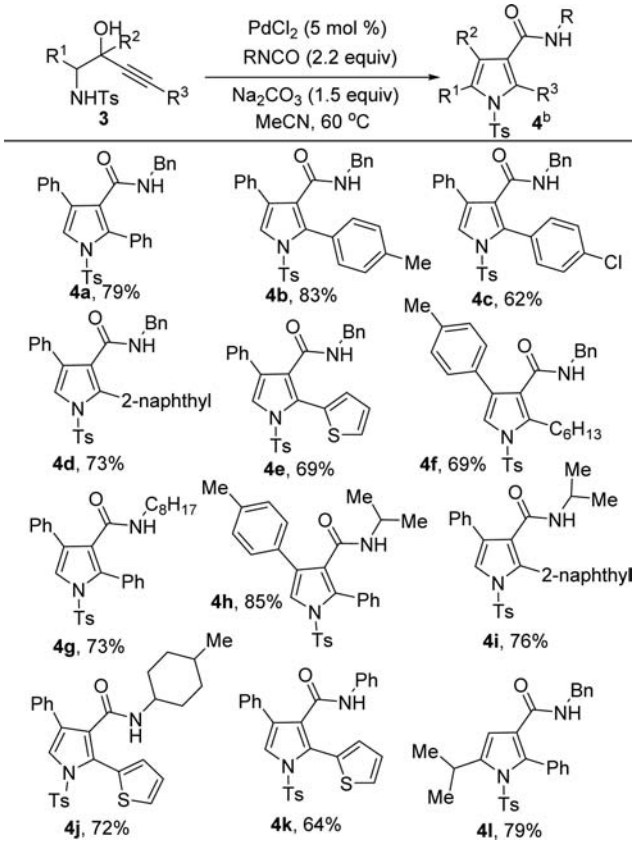


[a]Conditions: **1a** (0.5 mmol), RNCO (1.1 mmol), base (0.9 mmol), catalyst (0.025 mmol) in solvent (2.5 mL) at 60 °C under air. [b]Isolated yield.

slightly deactivate the reaction (**4c** in 62% yield). Next, naphthyl and thiophene-yl substrates (**3d,e**) were cleanly transformed to the products (**4d,e**) in 69−73% yield. Alkyl substitution at alkyne (**3f**) also showed no disparity in undergoing cyclization/amidation cascade. We then tested the scope of isocyanates. Linear or branched aliphatic isocyanates all reacted well to produce the desired products (**4g−j**) in excellent yields (72−85%), whereas phenyl isocyanate showed relatively low productivity (**4k** in 64% yield). A secondary hydroxyl bearing homopropargyl amine **3l** was also found to be feasible in the reaction to afford the corresponding product in excellent yield (**4l** in 79% yield). However, substrates with NHBoc instead of NHTs were found to be incompatible with the reaction.

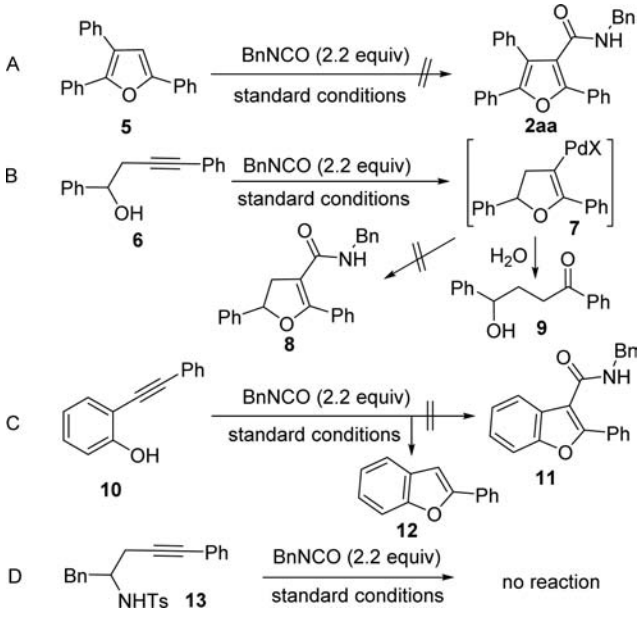
To probe the mechanism, some support experiments were carried out as shown in Scheme 5. Thus, **5** (obtained in the absence of isocyanate) was treated under the standard conditions. No reaction occurred, suggesting that **5** was not an intermediate in the cascade process. When a substrate without the propargyl hydroxyl group (**6**) was subjected to the reaction conditions a simple regioselectively hydrolyzed product **9** was obtained likely via intermediate **7**. No addition product **8** was obtained, indicating that the adjacent hydroxyl group is essential for the desired transformation. Similarly, 2-alkynylphenol **10** also yielded a simple cyclized product **12** without amidation (**11**), emphasizing the importance of the neighboring hydroxyl group. Surprisingly, homopropargyl amine **13**, which is devoid of an adjacent hydroxyl group, did not even cyclize under the standard conditions, suggesting that the hydroxyl group is not only assisting in the isocyanate

Scheme 4. Synthesis of Pyrrole 3-carboxamides[a]



[a]Conditions: **3** (0.5 mmol), BnNCO (1.1 mmol), base (0.75 mmol), catalyst (0.025 mmol) in solvent (2.5 mL) at 60 °C under air [b]Isolated yield.

Scheme 5. Supporting Experiments for Mechanism



insertion but also being partially responsible for initial nucleopalladation. In this case, perhaps due to weak nucleophilicity of NHTS group, the initial cyclization also needed the stronger activation of alkyne group with the help of coordination with adjacent hydroxyl group.

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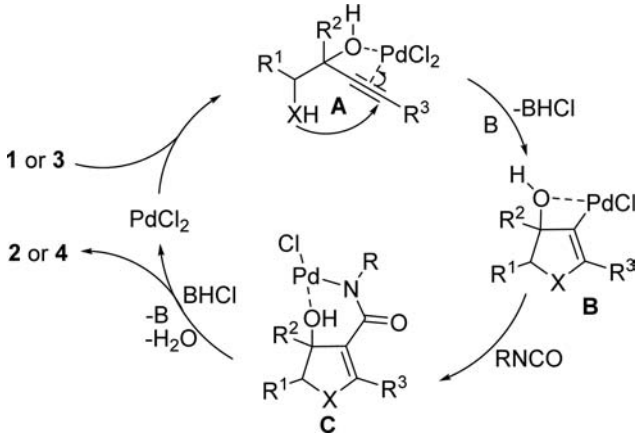
On the basis of these results, a probable mechanism is proposed in Scheme 6. Thus, $PdCl_2$ activates the alkyne group

Scheme 6. Proposed Mechanism



while coordinating with a hydroxyl group (**A**), which leads to nucleopalladation to yield intermediate **B**. This palladium complex does not immediately undergo protodepalladation due to coordination with the hydroxyl group and provides enough room for isocyanate insertion, which probably gives the oxaaminopallada cyclic intermediate **C**. When the water molecule is expelled, subsequent reaction of **C** with liberated HCl releases $PdCl_2$ for the next cycle.

In summary, we have illustrated a general approach for the synthesis of highly substituted furan/pyrrolamides from readily available alkynols/alkynamines using isocyanate as an amino surrogate. The reaction likely proceeds via vicinal hydroxyl-assisted nucleopalladation of alkynes followed by unprecedented isocyanate insertion/dehydration, opening a new avenue for amide bond constructions. Further, a high reaction scope with respect to both partners of the coupling along with excellent product yields makes it a practical approach for the highly privileged scaffolds.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02077.

Experimental procedures, characterization data, and ^1H and ^{13}C NMR spectra, crystallographic data for compound **2ak** (PDF)

X-ray data for compound **2ak** (CIF)

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Notes

The authors declare no competing financial interest.

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