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Dearomatization Strategy and Palladium-Catalyzed Domino Reaction: Construction of Azepino[5,4,3-*cd*]indoles from 2-Alkynylanilines

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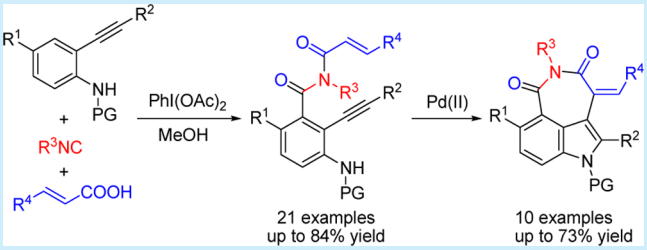
Supporting Information

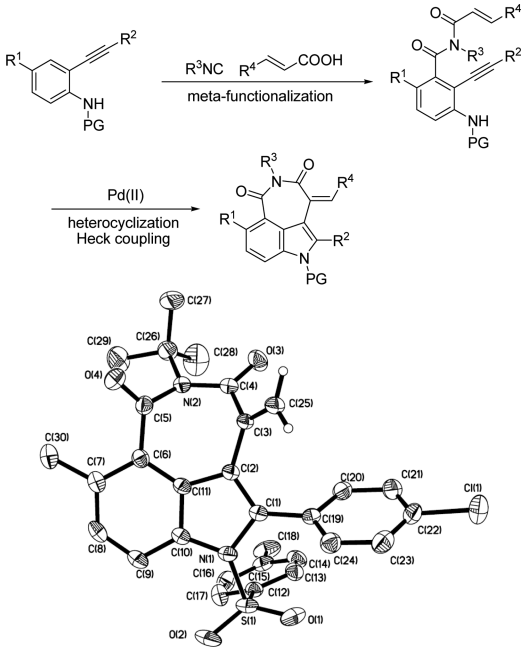
ABSTRACT: A facile approach to construct 3,4-fused tricyclic azepino[5,4,3-*cd*]indoles from 2-alkynyl anilines, isocyanides, and *α,β*-unsaturated acids is reported. This synthetic process involves a regioselective meta-functionalization of 2-alkynylanilines using a dearomatization strategy and a palladium(II)-catalyzed domino heterocyclization/Heck reaction.



3,4-Fused tricyclic indoles constitute a very important class of compounds because of their remarkable medicinal and biological activities.[1] For example, the natural products lysergic acid diethylamide (LSD),[2] hapalindole U,[3] arcyroxocin B,[4] communesin B,[5] decursivine,[6] welwistatin,[7] dehydrobufotenine,[8] and indolactam V[9] have a 3,4-fused tricyclic indole unit as their core structure. Therefore, a number of synthetic approaches toward the construction of 3,4-fused tricyclic indole systems have been developed such as the intramolecular Fischer indole syntheses,[10] Pictet–Spengler reactions,[11] electrocyclizations,[12] photocyclizations,[13] and Diels–Alder reactions.[14] Normally, these strategies involve an introduction of functional groups to the C-3 and the C-4 positions of indoles and a subsequent cyclization. A big challenge in these methods is the selective functionalization of the C-4 position of indoles, which is not a preferred site for the electrophilic substitution reaction. Recently, Jia and co-workers reported an intramolecular Larock indolization reaction, and 2,3-difunctionalized anilines proved to be potential precursors to a variety of 3,4-fused tricyclic indoles.[15] Herein, we report an approach to construct 3,4-fused tricyclic azepino[5,4,3-*cd*]indoles from 2-alkynylanilines, isocyanides, and *α,β*-unsaturated acids. This process involves a regioselective meta-functionalization of 2-alkynylanilines using a dearomatization strategy and a palladium-catalyzed domino heterocyclization/Heck reaction (Scheme 1).

Under oxidizing conditions, the dearomatization[16] of para-substituted 2-alkynylanilines forms 2-alkynylcyclohexadienimines. The reactivity of these products has been shown to allow the regioselective 1,4-addition (Michael-type) of a variety of carbon and heteronucleophiles at the C-3 position.[17,18] We conceived that this dearomatization strategy could be used to achieve the meta-functionalization of 2-alkynylanilines by isocyanides and *α,β*-unsaturated acids (Scheme 2).

Scheme 1. Construction of Azepino[5,4,3-*cd*]indoles



First, we evaluated the reactions of *N*-protected 4-methyl-2-(2-phenylethynyl)benzenamines **1**–**5** with *tert*-butyl isocyanide and cinnamic acid in methanol with (diacetoxyiodo)benzene as oxidant (Scheme 3). The results revealed that the protecting group played a significant role in the transformation. When the

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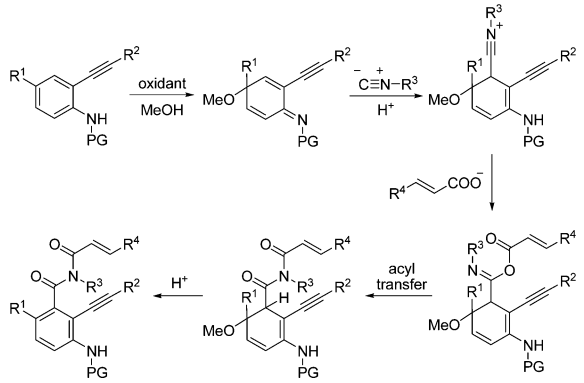
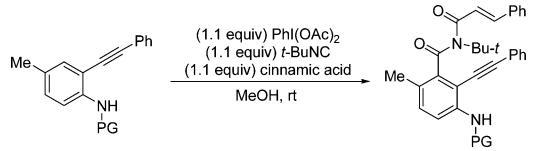
Scheme 2. Meta-Functionalization of 2-Alkynylanilines Using Dearomatization Strategy



Scheme 3

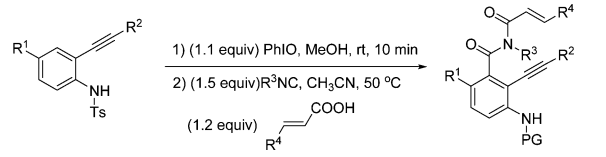


N-$COCF_3$-, *N*-Boc-, or *N*-Bz-protected substrate was used, the oxidative dearomatization proceeded well, but further conversion did not occur. When the *N*-Ms- or *N*-Ts-protected substrate was used, the desired 3-functionalized product **9** or **10** was formed in 31% or 35% yield, respectively.

To avoid the competition between cinnamic acid and acetic acid metabolized from (diacetoxyiodo)benzene, iodosylbenzene (PhIO) was used as oxidant instead.[19] Further optimization showed that the dearomatization had to be conducted in methanol, but acetonitrile was the best reaction medium for the Michael addition and the aromatization steps. Therefore, the meta-functionalization reaction was carried out in a stepwise way: compound **5** was treated with 1.1 equiv of iodosylbenzene in methanol (0.1 M) at room temperature for 10 min. After methanol was removed under a pressure-reducing condition, acetonitrile, 1.5 equiv of *tert*-butyl isocyanide, and 1.2 equiv of cinnamic acid were added, and the resulting mixture was stirred at 50 °C for 48 h. This reaction gave rise to compound **10** in 84% yield. Under the optimized conditions, the reactions of 2-alkynylanilines bearing a range of different substitutions with a variety of isocyanides and *α,β*-unsaturated acids proceeded smoothly leading to the corresponding products in moderate to good yields (Table 1).

We initially investigated the possibility of constructing azepino[5,4,3-*cd*]indole via an iodocyclization[20] and an intramolecular Heck reaction.[21] The desired product **31** was formed, but in a very low yield (Scheme 4). Therefore, we focused our attention on the palladium(II)-catalyzed domino heterocyclization/Heck reaction.[22] We were pleased to observe the formation of compound **31** in the palladium diacetate catalyzed reaction (Table 2, entry 1). To improve the efficiency of this domino reaction, various phosphine ligands, palladium salts, bases, and oxidants were examined (Table 2). When a catalytic amount of palladium diacetate was used together with tris(3-methoxyphenyl)phosphine and a stoichiometric amount

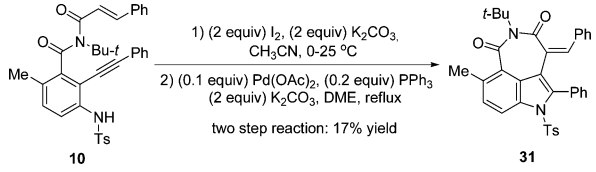
Table 1. Meta-Functionalization of 2-Alkynylanilines



entry	R^1	R^2	R^3	R^4	product[a] (%)
1	Me	Ph	*t*-Bu	Ph	**10** (84)
2	Et	Ph	*t*-Bu	Ph	**11** (65)
3	*n*-Bu	Ph	*t*-Bu	Ph	**12** (67)
4	Me	4-MeC_6H_4	*t*-Bu	Ph	**13** (66)
5	Me	4-$MeOC_6H_4$	*t*-Bu	Ph	**14** (56)
6	Me	4-ClC_6H_4	*t*-Bu	Ph	**15** (63)
7	Me	*t*-Bu	*t*-Bu	Ph	**16** (62)
8	Me	TMS	*t*-Bu	Ph	**17** (74)
9	Me	H	*t*-Bu	Ph	**18** (63)
10	Me	Ph	*cyclo*-Hex	Ph	**19** (63)
11	Me	Ph	*t*-Bu	4-MeC_6H_4	**20** (82)
12	Me	Ph	*t*-Bu	4-$MeOC_6H_4$	**21** (66)
13	Me	Ph	*t*-Bu	4-ClC_6H_4	**22** (82)
14	Me	Ph	*t*-Bu	4-FC_6H_4	**23** (81)
15	Me	Ph	*t*-Bu	2-furyl	**24** (78)
16	Me	Ph	*t*-Bu	Me	**25** (83)
17	Me	Ph	*t*-Bu	H	**26** (61)
18	Me	TMS	*t*-Bu	H	**27** (63)
19	Me	4-ClC_6H_4	*t*-Bu	H	**28** (50)
20	Et	Ph	*t*-Bu	H	**29** (46)
21	*n*-Bu	Ph	*t*-Bu	H	**30** (48)

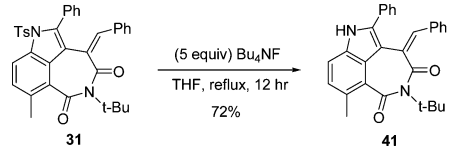
[a]Isolated yield based on 2-alkynylanilines.

Scheme 4



of potassium phosphate, the isolated yield of compound **31** increased to 73%. Molecular oxygen proved to be the best oxidant. The formation of compound **31** was not observed when copper(II) bromide, silver acetate, or *meta*-chloroperbenzoic acid was used.

Azepino[5,4,3-*cd*]indoles with a range of different substitutions were obtained in moderate yields (Scheme 5). The configuration of the double bond of compound **31** was confirmed by its NOESY spectrum. When the double bond in substrates was a terminal alkene, the corresponding reaction was conducted in the absence of phosphine ligand and base, and 2 equiv of acetic acid was added to promote the reaction. The structure of compound **36** was confirmed by its single-crystal diffraction analysis.[23] The treatment of compound **31** with 5 equiv of Bu_4NF in THF at reflux led to the selective deprotection of the Ts group (eq 1).[24]



(1)

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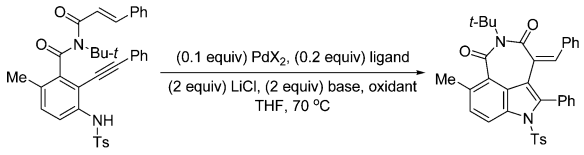
Table 2. Evaluation of Conditions for Palladium(II)-Catalyzed Domino Heterocyclization/Heck Coupling Reaction



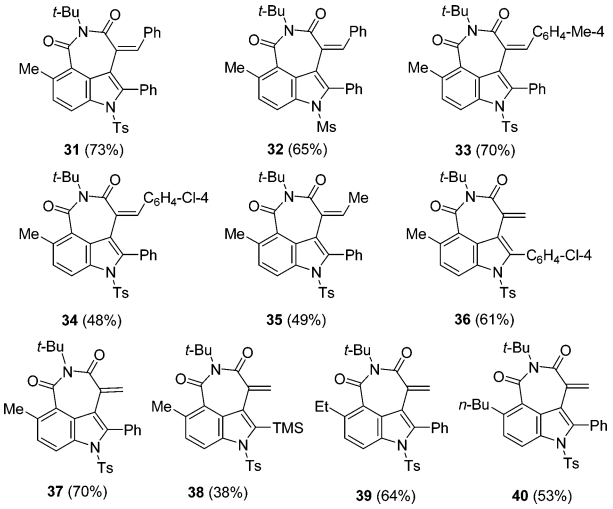
10 31

entry	Pd(II)	R_3P	base	oxidant	31 (%)
1	$Pd(OAc)_2$	Ph_3P	K_2CO_3	O_2	15
2	$Pd(OAc)_2$	$(2\text{-}MeC_6H_4)_3P$	K_2CO_3	O_2	31
3	$Pd(OAc)_2$	$(3\text{-}MeC_6H_4)_3P$	K_2CO_3	O_2	32
4	$Pd(OAc)_2$	$(2\text{-}MeOC_6H_4)_3P$	K_2CO_3	O_2	<5
5	$Pd(OAc)_2$	$(3\text{-}MeOC_6H_4)_3P$	K_2CO_3	O_2	48
6	$Pd(OAc)_2$	$(4\text{-}MeOC_6H_4)_3P$	K_2CO_3	O_2	18
7	$Pd(OAc)_2$	$(C_6F_5)_3P$	K_2CO_3	O_2	23
8	$Pd(OAc)_2$	$(cyclo\text{-}C_6H_{11})_3P$	K_2CO_3	O_2	20
9	$Pd(OAc)_2$	$(2\text{-furyl})_3P$	K_2CO_3	O_2	15
10	$Pd(OAc)_2$	$(n\text{-Bu})_3P$	K_2CO_3	O_2	<5
11	$Pd(OAc)_2$	$(t\text{-Bu})_3P$	K_2CO_3	O_2	<5
12	$PdCl_2$	$(3\text{-}MeOC_6H_4)_3P$	K_2CO_3	O_2	<5
13	$PdBr_2$	$(3\text{-}MeOC_6H_4)_3P$	K_2CO_3	O_2	16
14	$Pd(OCOCF_3)_2$	$(3\text{-}MeOC_6H_4)_3P$	K_2CO_3	O_2	43
15	$Pd(OAc)_2$	$(3\text{-}MeOC_6H_4)_3P$	Li_2CO_3	O_2	<5
16	$Pd(OAc)_2$	$(3\text{-}MeOC_6H_4)_3P$	Cs_2CO_3	O_2	67
17	$Pd(OAc)_2$	$(3\text{-}MeOC_6H_4)_3P$	NaOMe	O_2	30
18	$Pd(OAc)_2$	$(3\text{-}MeOC_6H_4)_3P$	KOBu-*t*	O_2	<5
19	$Pd(OAc)_2$	$(3\text{-}MeOC_6H_4)_3P$	KOAc	O_2	<5
20	$Pd(OAc)_2$	$(3\text{-}MeOC_6H_4)_3P$	K_3PO_4	O_2	73
21	$Pd(OAc)_2$	$(3\text{-}MeOC_6H_4)_3P$	K_3PO_4	BQ	25
22	$Pd(OAc)_2$	$(3\text{-}MeOC_6H_4)_3P$	K_3PO_4	*m*-CPBA	0
23	$Pd(OAc)_2$	$(3\text{-}MeOC_6H_4)_3P$	K_3PO_4	$CuBr_2$	0
24	$Pd(OAc)_2$	$(3\text{-}MeOC_6H_4)_3P$	K_3PO_4	AgOAc	0

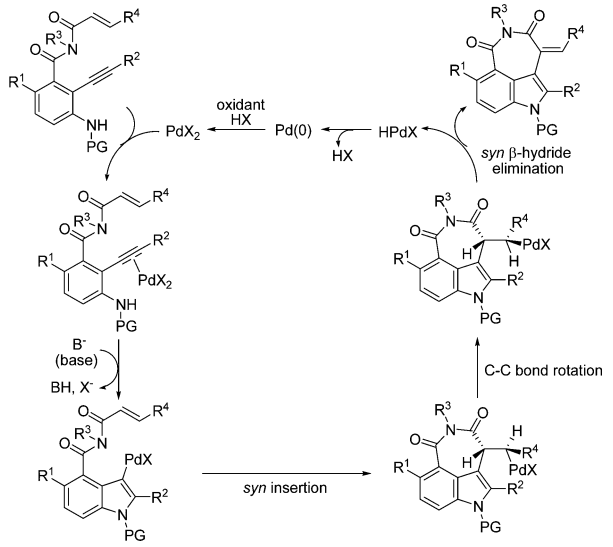
A plausible reaction pathway for the domino reaction is depicted in Scheme 6. The formation of π-alkynepalladium complex induces the intramolecular nucleophilic attack of the nitrogen to the activated carbon−carbon triple bond. The generated σ-indolylpalladium intermediate is trapped by the electron-poor double bond via *syn* insertion. After C−C bond rotation and *syn* β-hydride elimination, azepino[5,4,3-*cd*]indole structure is built, and palladium(0) is formed. The catalytically active palladium(II) is regenerated by oxidation of palladium(0).

In conclusion, we have developed a method to construct 3,4-fused tricyclic azepino[5,4,3-*cd*]indole derivatives form 2-alkynylanilines, isocyanides, and α,β-unsaturated acids. This synthetic process involves a regioselective meta-functionalization of 2-alkynylanilines using a dearomatization strategy, and a palladium-catalyzed domino heterocyclization/Heck reaction. A current effort has also been made to extend its scope and to explore its reaction mechanism and possible synthetic applications, and these results will be reported in due course.

Scheme 5



Scheme 6. Plausible Reaction Pathway of Domino Reaction



■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, characterization data, NOESY spectrum of compound **31**, copies of ^1H NMR and ^{13}C NMR of new compounds, and crystallographic data of compound **36** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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