Organic LETTERS

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A Tandem Approach to Functionalized Carbazoles from Indoles via Two Successive Regioselective Oxidative Heck Reactions Followed by Thermal Electrocyclization

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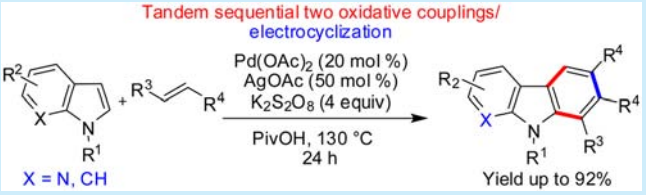
Supporting Information

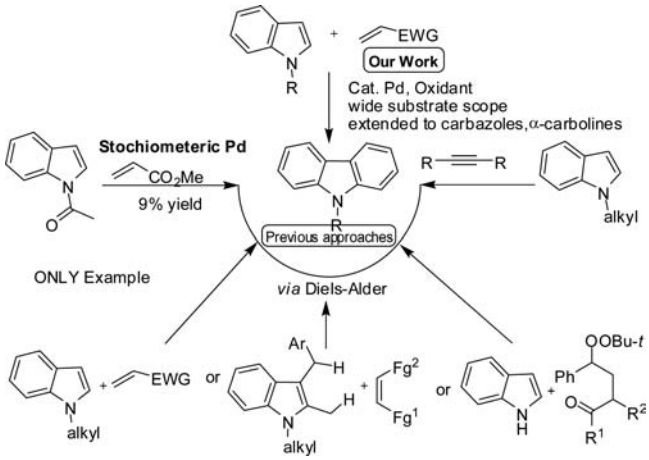
ABSTRACT: A direct one-pot approach to the synthesis of carbazoles (mono-, di-, and trisubstituted) and α-carbolines from readily available indoles or 7-azaindoles and alkenes is described. Based on mechanistic studies, the tandem reaction follows the sequence: palladium-catalyzed regioselective C-3 alkenylation/palladium-catalyzed C-2 alkenylation/thermal electrocyclization.



Carbon−carbon (C−C) direct bond formation involving two C−H bonds, traditionally known as oxidative or cross-dehydrogenative coupling, has received great attention over the C−C bond formation utilizing prefunctionalized substrates, featuring higher atom economy and efficiency.[1] In particular, the oxidative coupling between unfunctionalized arenes and alkenes, first discovered by Fujiwara−Moritani in 1967,[2a] is a beneficial alternative to the classical Heck reaction, although the oxidative Heck reactions remained largely unexplored until recently due to lack of regiocontrol.[2] Pioneering studies on regiocontrol by Stoltz,[3] later by Gaunt,[4] and more recently by others[5] are examples of successful execution of regioselective alkenylations on indoles. However, successive regioselective alkenylations on indoles yielding 2,3-dialkenylated indoles, often with a desired substitution pattern, have scarcely been reported.[4] Furthermore, subsequent benzoannulation of 2,3-dialkenylated indoles to form carbazoles could demonstrate further synthetic applications of 2,3-dialkenylated indoles.

Carbazoles are privileged molecular structures ubiquitously found in biologically active natural and unnatural products, and functional organic materials.[6] Among the various celebrated strategies reported for the synthesis of carbazoles,[7] a direct convergent synthesis of carbazoles from the commercial feedstock indoles is especially attractive. Alkenylation of *N*-acetylindole using methyl acrylate in the presence of a stoichiometric amount of palladium is reported to give 2,3-dialkenylated *N*-acetylindole, which subsequently undergoes electrocyclization thermally[8a] yielding 2,3-disubstituted *N*-acetylcarbazole only in 9% yield (*only* example, Scheme 1).[8b] Reactions of *N*-alkylindoles and alkenes or its synthetic equivalent to form 1,3-disubstituted carbazoles under trimetallic (Pd−Cu−Ag)[9] or bimetallic (Pd−Cu)[10] catalyzed conditions are described to occur through a Diels−Alder reaction of 3-alkenyated indoles and alkenes. Very recently, Zhang has reported a similar approach to the synthesis of highly substituted carbazoles that involves Diels−Alder reaction of dienes, generated in situ from 2-methyl-3-alkylindoles by reaction with DDQ, and tri- or tetrasubstituted alkenes.[11] Subsequently, Diels−Alder reactions of dienes, generated *in situ* from an acid-catalyzed rearrangement of γ-carbonyl *tert*-butylperoixdes, and NH-free indoles as dienophiles were developed leading to the synthesis of 1,2-disubstituted carbazoles.[12] Miura reported that Pd-catalyzed oxidative couplings of *N*-alkylindoles with diarylacetylenes gave 1,2,3,4-tetrasubstituted carbazoles.[13] While Fujiwara's approach to the synthesis of carbazoles utilizing a stoichiometric palladium deserves credit as a pioneering depiction, implementation of a catalytic version that could result in an expanded scope of the

Scheme 1. Synthetic Approaches to the Synthesis of Carbazoles from Indoles



Received: August 4, 2015
Published: September 24, 2015

DOI: 10.1021/acs.orglett.5b02265
Org. Lett. 2015, 17, 4742−4745

protocol including improved yields of various substituted carbazoles, a wide substrate scope, and broad applications to the synthesis of related heterocycles could present an excessive challenge.

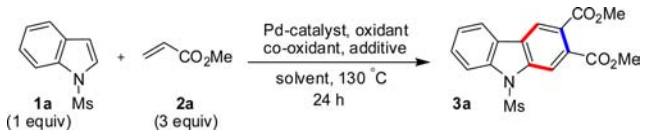
Recently, we developed a palladium-catalyzed intramolecular oxidative coupling involving double C(sp^2)−H bonds in sulfonanilides providing a workable access to biaryl sultams annulated into a six-membered ring.[14] Subsequently, a tactic for the installation of sulphonamide pharmacophores on heterobiaryls has been developed via a palladium-catalyzed oxidative coupling in *N*-arylsulfonyl heterocycles followed by a novel nucleophilic ring opening of heterobiaryl sultams with amines.[15] Based on our recent experiences on oxidative couplings in the synthesis of nitrogen-containing heterocycles, we reasoned that successive multiple C−H functionalizations of indoles with alkenes under one set of reaction conditions might be brought to fruition to obtain functionalized carbazoles in a single operation. Notably, during the preparation of this manuscript, a palladium-catalyzed alkenylation of free (NH) indoles and subsequent conversion to the 1,3-disubstituted carbazoles has appeared.[16] Herein, we describe, distinct from the recent report,[16] a direct synthesis of 2,3-disubstituted carbazoles from indoles via two successive regioselective oxidative Heck reactions on *N*-protected indoles followed by thermal electrocyclization. The optimized conditions in our study is quite resourceful warranting broad applications to the synthesis of carbazoles and α-carbolines.

We began investigation of the reaction of *N*-mesyl indole (**1a**) and methyl acrylate (**2a**) directed to the synthesis of carbazoles. Unlike *N*-alkyl indoles, **1a** and **2a** under the optimized conditions reported for the Diels−Alder reaction[9,10] did not give any carbazole (Table 1, entry 1). However, replacing the solvent from DMSO to pivalic acid resulted in the formation of 2,3-disubstituted carbazole **3a** that is structurally different from the 1,3-disubstituted carbazole reported in the literature (entry 2). Heating **1a** and **2a** in the presence of 15 mol % $Pd(OAc)_2$, 3 equiv of AgOAc, and 30 mol % CsOPiv in pivallic acid at 130 °C improved the formation of carbazole substantially affording **3** in 68% yield together with a significant amount of C3-alkenylated *N*-mesyl indole (**11**) (entry 3). A different oxidant such as Ag_2O exerts a comparable effect to that of AgOAc in the formation of **3a** (entry 4). However, *p*-benzoquinone has a deleterious effect (entry 5). While a strong oxidant $K_2S_2O_8$ (4 equiv) alone could form **3a** although in reduced yield (58%), $K_2S_2O_8$ (4 equiv) together with an optimized substoichiometric amount of AgOAc (50 mol %) resulted in the excellent conversion of starting materials into products yielding **3a** in 80% yield (entries 6−7). A reaction excluding CsOPiv produces **3a** in comparable yield (83%) suggesting that CsOPiv is not essential in this reaction (entry 8). Further optimization showed that increasing the loading of the catalyst improved the yield of carbazole **3a** to 86% (entry 9). No further improvement was observed by changing the palladium source (entry 10). The crucial role of palladium in this reaction was realized when carbazole **3a** did not form in a reaction carried out in the absence of any palladium catalyst (entry 11).

With the optimized conditions in hand, we further investigated the scope of substrates that could participate in the reaction. Similar to **1a**, *N*-Ts indole**1b** gave carbazole **3b** in 75% yield (Table 2, entry 1). The indole substrates **1c−e** with a substitution at the 5-position participated eventfully yielding carbazoles **3c−e** in 72−81% yield (entries 2−4). Styrenes **2b−c** were also viable alkene substrates affording carbazoles **3e** and **3f** in 65% and 60% yields, respectively (entries 5−6). Pleasingly, *N*-benzoylindole **1f** also participated in the reaction affording carbazoles **3h−i** in 75−88% yield (entries 7−8). Similarly, *N*-propionyl indole **1g** gave **3j** in 70% yield together with NH-free carbazole **4**, obtained after concomitant *N*-deacylation under the optimized conditions (entry 9). A NH-free indole did not react with alkenes to produce any carbazole under the optimized conditions (entry 10). Pivotal to this observation (cf. entry 10) was the realization that our optimized conditions referred to conditions distinct from a recent report.[16] Notably, the report does not include any *N*-substituted indole as a starting substrate.

Incongruent to the literature,[9,10] *N*-alkyl indoles **1i−j** under our optimized conditions gave 2,3-disubstituted carbazoles **3l−3m** as a major product together with minor 1,3-disubstituted

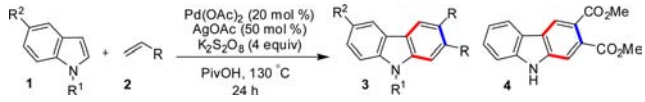
Table 1. Optimization Study for the Synthesis of Carbazole 3a from *N*-Mesyl Indole (1a) and Methyl Acrylate (2a)[a]



entry	catalyst	oxidant/ co-oxidant	additive	solvent	3a, yield (%)[b]
1	$Pd(OAc)_2$	$AgOCOCF_3$/ $Cu(OAc)_2$		DMSO	0
2	$Pd(OAc)_2$	$AgOCOCF_3$/ $Cu(OAc)_2$		PivOH	35
3	$Pd(OAc)_2$	AgOAc	CsOPiv	PivOH	68
4	$Pd(OAc)_2$	Ag_2O	CsOPiv	PivOH	69
5	$Pd(OAc)_2$	BQ	CsOPiv	PivOH	0
6	$Pd(OAc)_2$	$K_2S_2O_8$	CsOPiv	PivOH	58
7	$Pd(OAc)_2$	$K_2S_2O_8$/AgOAc	CsOPiv	PivOH	80
8	$Pd(OAc)_2$	$K_2S_2O_8$/AgOAc		PivOH	83
9[c]	$Pd(OAc)_2$	$K_2S_2O_8$/AgOAc		PivOH	**86**
10	$Pd(TFA)_2$	$K_2S_2O_8$/AgOAc		PivOH	50
11[d]		$K_2S_2O_8$/AgOAc		PivOH	0

[a]**1a** (0.5 mmol), **2a** (1.5 mmol), $Pd(OAc)_2$ (15 mol %), primary oxidant [$Cu(OAc)_2$, 20 mol %; AgOAc, 50 mol %; or other oxidants, 4 equiv], co-oxidant (4 equiv), additive (CsOPiv, 30 mol %), solvent (2.5 mL), 130 °C, 24 h. [b]Isolated yield. [c]$Pd(OAc)_2$ (20 mol %). [d]Without a palladium catalyst.

Table 2. Substrate Scope for the Synthesis of Carbazoles

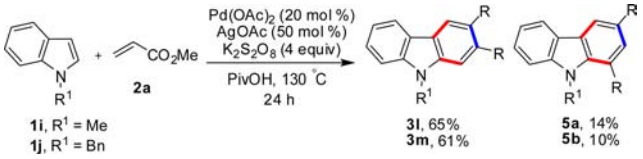


entry	1, R^1, R^2	2, R	3, 4 yield (%)
1	**1b**, Ts, H	**2a**, CO_2Me	**3b**, 75
2	**1c**, Ms, Cl	**2a**, CO_2Me	**3c**, 81
3	**1d**, Ms, OMe	**2a**, CO_2Me	**3d**, 72
4	**1e**, Ms, F	**2a**, CO_2Me	**3e**, 80
5	**1a**, Ms, H	**2b**, Ph	**3f**, 65
6	**1a**, Ms, H	**2c**, 4-$CH_3C_6H_4$	**3g**, 60
7	**1f**, Bz, H	**2a**, CO_2Me	**3h**, 88
8	**1f**, Bz, H	**2b**, Ph	**3i**, 75
9	**1g**, COEt, H	**2a**, CO_2Me	**3j**, 70, **4**, 13
10	**1h**, H, H	**2a**, CO_2Me	**3k**, 0

DOI: 10.1021/acs.orglett.5b02265
Org. Lett. 2015, 17, 4742−4745

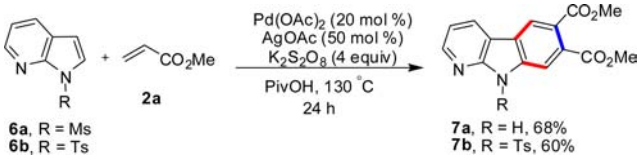
carbazoles **5a**–**5b** via a Diels–Alder reaction (Scheme 2). Evidently, *N*-alkyl indoles produced different results in our study.

Scheme 2. Synthesis of Carbazoles from *N*-Alkyl Indoles



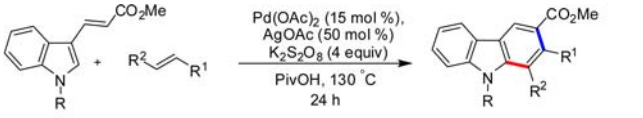
α-Carbolines, both natural and synthetic, have demonstrated an array of biological properties including anxiolytic, anti-inflammatory, and central nervous system stimulating activities.[17] Although the synthesis of α-carbolines, developed earlier by others[18] and us,[19] merits extensive discussion, a tandem one-pot approach via oxidative Heck reactions, to the best our knowledge, has never been explored. Due to inspiration by the above-mentioned successful results and consideration of the high preparative value of α-carbolines, 7-azaindoles **6a**–**b** were subjected to the optimized reaction conditions, which resulted in the formation of α-carbolines**7a**–**7b** in 68–60% yield (Scheme 3). Notably, the preparation of (NH)-free α-carboline **7a**, obtained directly from the reaction of **6a** and **2a**, demonstrated an additional benefit of our protocol.

Scheme 3. Synthesis of α-Carbolines from 7-Azaindoles



To understand the sequence of the reactions that lead to tandem carbazole synthesis, additional experiments were carried out. Under the optimized conditions, the reaction of C-3 alkenylated indole, methyl 3-(1-tosyl-1*H*-indol-3-yl)-acrylate (**8a**), and methyl acrylate **2a** gave carbazole **3b** in excellent yield (92%, Scheme 4). Similarly, an unsymmetrically

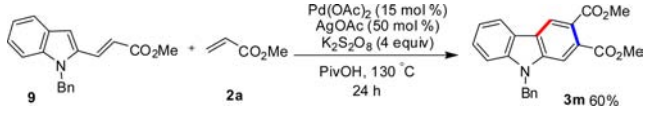
Scheme 4. Synthesis of Carbazoles from C-3 Alkenylated Indoles



substituted carbazole **3n** was prepared from **8b** and **2b**. These reactions suggest that the second oxidative Heck reaction occurs at the C-2 position of indole, not on the terminal alkene attached to the C-3 position of indole.[16] Clearly, our protocol follows a sequence of reactions different from the recent report. Pleasingly, reactions of **8b** and various other electron-deficient mono- or 1,2-disubstituted alkenes gave mono-, di-, or trisubstituted carbazoles in varying yields (Scheme 4).

However, the reaction of C-2 alkenylated indole, **9**, and methyl acrylate **2a** gave carbazole **3m** in significantly reduced yield (60%, Scheme 5). The apparent sluggish reactivity of C-2

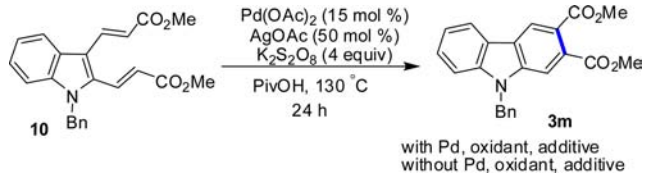
Scheme 5. Synthesis of Carbazole from C-2 Alkenylated Indole



alkenylated indole **9** compared to C-3 alkenylated indoles (**8a**–**b**) toward carbazole formation may explain the fact that palladium-catalyzed alkenylation occurs initially at the 3-position of *N*-sulfonylindoles.

Finally, 2,3-divinyl indole **10** participated in the intramolecular cyclization under the optimized conditions to yield carbazole **3m** (Scheme 6).

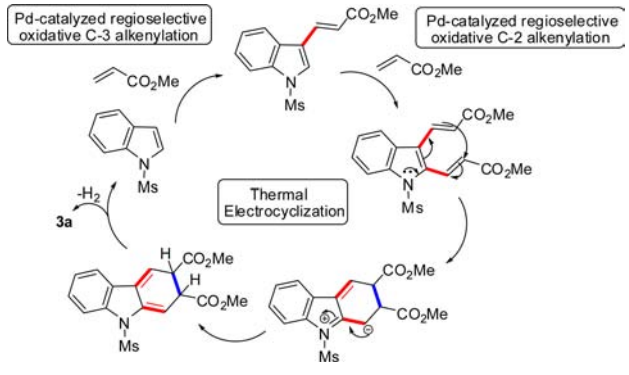
Scheme 6. Synthesis of Carbazole from 2,3-Dialkenylated Indole



A control experiment that involved heating **10** in pivalic acid at 130 °C for 24 h also resulted in nearly complete conversion of **10** to **3m**. A similar observation was documented when **10** was heated in a different solvent, such as DMF. These experiments suggest that intramolecular cyclization to **3m** occurs via thermal electrocyclization of **10** followed by dehydrogenation. The palladium catalyst, oxidant, or additive does not have any apparent role in the conversion of **10** to **3m**. Based on these limited studies, a mechanism is proposed for the conversion of indoles to carbazoles. Initially, an oxidative Heck reaction could occur at the C-3 position of indole,[4] which subsequently could undergo another oxidative Heck reaction at the C-2 position followed by intramolecular ring closure to form carbazoles (Scheme 7).

In conclusion, we have developed a one-pot tandem approach to the synthesis of functionalized carbazoles from

Scheme 7. Proposed Reaction Sequence to Carbazole



DOI: 10.1021/acs.orglett.5b02265
Org. Lett. 2015, 17, 4742–4745

readily available indoles via successive triple C−H functionalizations. Unlike the previous study that uses a stoichiometric amount of a palladium catalyst, the protocol described herein uses only a catalytic amount of a palladium catalyst together with an oxidant. Compared to the *only* example prepared earlier in the previous study, a handful of examples of mono-, di-, and trisubstituted carbazoles have been prepared. Furthermore, an extension of this protocol to the synthesis of α-carbolines, a study described for the first time, warranted a broad application. Further applications of this chemistry to the synthesis of functionalized indoles and pyrroles are under current investigation.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02265.

Experimental procedures, characterization data of new compounds, and copies of ^{1}H and ^{13}C NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We greatly appreciate the financial support from the NIPER, S. A. S. Nagar and SERB of DST, New Delhi.

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