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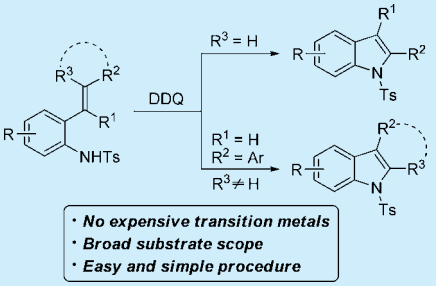
Metal-Free C−H Amination for Indole Synthesis

Young Ho Jang and So Won Youn*

Center for New Directions in Organic Synthesis, Department of Chemistry and Research Institute for Natural Sciences, Hanyang University, Seoul 133-791, Korea

Supporting Information

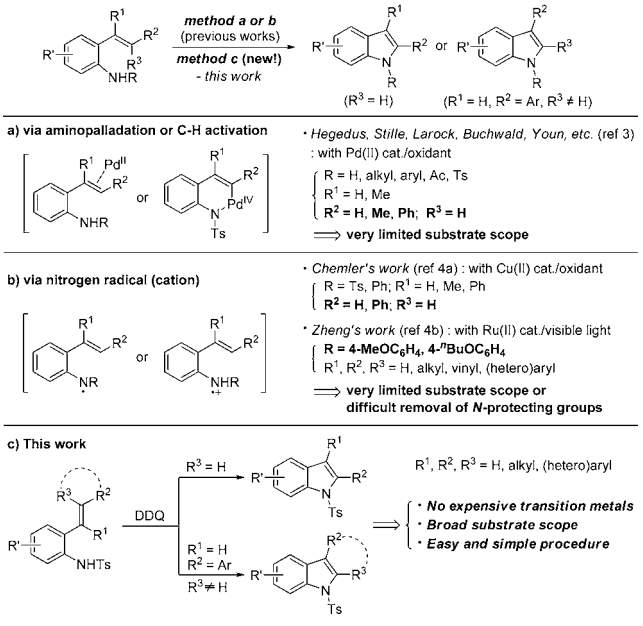
ABSTRACT: An effective metal-free C−H amination of *N*-Ts-2-alkenylanilines by using DDQ as an oxidant has been developed to afford a diverse range of substituted indoles. This protocol is operationally simple and robust, obviates the need of expensive transition-metal catalysts, and offers a broad substrate scope. A mechanism involving a radical cation generated by SET and a migratorial process via a phenonium ion intermediate is proposed.



Due to their ubiquity in nature and broad application in chemistry, biology, and material sciences, indoles are one of the most important and valuable heterocycles.[1] Consequently, numerous methods for the synthesis of indole derivatives have been developed,[2] and new, more efficient synthetic strategies still continue to be pursued. C−H amination of 2-alkenylanilines is one of the straightforward methods for the construction of an indole moiety. Two different approaches have been developed for such a purpose: via (1) Pd(II) catalysis and (2) nitrogen radical (cation). Since pioneered by Hegedus and co-workers, Pd(II)-catalyzed aminopalladation has evolved as one of the most efficient methods for the synthesis of indoles, albeit with very limited substrate scope (Scheme 1a).[3] Recently, our group showed a single example, synthesis of 2-phenylindole, as a vinylic C−H bond activation variant in a Pd-catalyzed oxidative C−H amination of *N*-Ts-2-arylanilines for the synthesis of carbazoles.[3g] In contrast, a radical mechanism has also been implicated in the reactions of the same substrates (Scheme 1b).[4] Very recently, Chemler's group showed a few examples of a Cu-catalyzed intramolecular oxidative amination of alkenes for the synthesis of indoles, suggesting a mechanism involving nitrogen-radical addition to the alkenes.[4a] In addition, Zheng and co-workers reported a photocatalytic synthesis of indoles involving a nitrogen-centered radical cation generated from *N*-*p*-alkoxyphenyl-2-alkenylanilines.[4b] Despite the significant advance with respect to the substrate scope, the requirement of a *p*-alkoxyphenyl group on the nitrogen atom, which could facilitate the generation of a nitrogen radical cation, could limit this practicality due to its difficult removal (R = 4-$MeOC_6H_4$, 4-^{n}$BuOC_6H_4$).

In view of the versatility and importance of indoles, we were interested in developing a new, efficient synthetic protocol for the C−H amination of 2-alkenylanilines. Herein we disclose a highly effective, metal-free C−H amination of 2-alkenylanilines (Scheme 1c). The use of DDQ (2,3-dichloro-5,6-dicyanobenzoquinone)[5] allowed the easy preparation of a diverse array of substituted indoles. In sharp contrast to the previously reported,

Scheme 1. Indole Synthesis from 2-Alkenylanilines



related methods (Scheme 1a,b),[3,4] the reaction protocol described herein significantly improved the efficiency and practicality of indole formation via C−H amination of 2-alkenylanilines, overcoming the deficiencies with regard to substrate scope[3,4a] and *N*-protecting group.[4b]

We began our studies using **1a** as the test substrate and examined the reaction parameters to identify optimal conditions (Table 1). Gratifyingly, it was found that DDQ promoted this C−H amination reaction to afford **2a** in 69% yield (entry 1). Various solvents were examined, and CCl_4 appeared preferable

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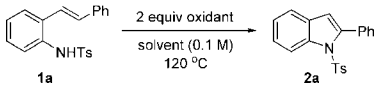
Table 1. Optimization Studies



entry	oxidant	solvent	time (h)	yield (%)[a]
1	DDQ	$ClCH_2CH_2Cl$	24	69
2	DDQ	CCl_4	7	(96)
3	DDQ	CH_3CCl_3	24	(96)
4	DDQ	toluene	24	87
5	DDQ	*c*-hexane	24	90[b]
6	DDQ	1,4-dioxane	24	69
7	DDQ	MeCN	24	40
8	DDQ	DMF	24	6
9	DDQ	*i*PrOH	24	–
10	MnO_2	CCl_4	24	–
11	$Mn(OAc)_3{\cdot}2H_2O$	CCl_4	2	8
12[c]	$PhI(OAc)_2$	CCl_4	13	–
13	$FeCl_3$	CCl_4	24	–[d]
14	$CuBr_2$	CCl_4	24	7
15	I_2	CCl_4	2	41[d]
16[e]	DDQ	CH_3CCl_3	24	57
17[f]	DDQ	CH_3CCl_3	24	(85)
18[g]	DDQ	CH_3CCl_3	21	62
19[h]	DDQ	CH_3CCl_3	24	90–91

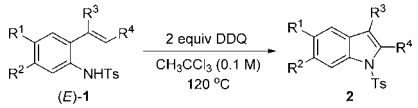
[a]Yields were determined by ^{1}H NMR using trichloroethylene as an internal standard. Value in parentheses indicates an isolated yield. [b]Mixture of 2- and 3-phenyl-substituted *N*-Ts-indoles was obtained (2-Ph:3-Ph = 9:1). [c]At 25 °C. [d]*N*-Ts-2-Phenylindoline was obtained in 17–21%. [e]Using 1 equiv DDQ. [f]At 100 °C. [g]In the presence of 1 equiv LiOMe. [h]In the presence of 1 equiv Na_2CO_3 or K_2CO_3.

with regard to reaction time and product yield (entries 1–9). Due to toxicity and safety issues, however, 1,1,1-trichloroethane (CH_3CCl_3) was selected as the solvent of choice, albeit requiring a little longer reaction time than in CCl_4 (entry 2 vs entry 3). Among a variety of oxidants examined, DDQ was revealed as the most effective oxidant for this transformation (entries 10–15). Reducing either the reaction temperature or the amount of DDQ led to a lower yield of **2a** (entries 16 and 17). We further hypothesized that the introduction of a base could either enhance the nucleophilicitiy of sulfonamide or facilitate the generation of nitrogen radical, thereby increasing the rate of the oxidative cyclization. However, addition of LiOMe was detrimental, while both Na_2CO_3 and K_2CO_3 gave no beneficial effect (entries 18 and 19).

With the optimized conditions in hand, we explored the effect of protecting groups.[6] Considering the susceptibility of 2-alkenylanilines to oxidation at both nitrogen atom and olefin moiety, judicious selection of an *N*-protecting group would be crucial to the success of this oxidative cyclization reaction. As expected, electron density on nitrogen atom exerted a great influence on the reaction outcome, and the effectiveness of the sulfonyl protecting group was immediately apparent. Among sulfonyl groups, the Ts (*p*-toluenesulfonyl) group proved the superior as a protecting group for this reaction, giving a delicately balanced nucleophilicity and oxidation susceptibility of the NH group.

We proceeded to explore the substituent effect at the alkene moiety (Table 2). A variety of *N*-Ts-2-styrylanilines (R^4 = aryl) underwent C–H amination smoothly to afford the corresponding indoles in good to excellent yields irrespective of the aryl substitution, showing little electronic and/or steric dependence

Table 2. Substrate Scope: Mono- or Disubstituted Alkene Derivatives



entry	R^1	R^2	R^3	R^4	time (h)	yield (%)[a]
1	H	H	H	Ph (**1a**)	24	96 (**2a**)
2[b,c]	H	H	H	Ph ((*Z*)-**1a**)	24	76 (**2a**)
3[c]	H	H	H	4-MeC_6H_4 (**1b**)	0.5	42 (**2b**)
4	H	H	H	3-MeC_6H_4 (**1c**)	16	84 (**2c**)
5	H	H	H	2-MeC_6H_4 (**1d**)	16	90 (**2d**)
6	H	H	H	4-$MeOC_6H_4$ (**1e**)	2	99 (**2e**)[d]
7	H	H	H	3-$MeOC_6H_4$ (**1f**)	10	74 (**2f**)
8	H	H	H	4-ClC_6H_4 (**1g**)	12	86 (**2g**)
9	H	H	H	4-$NO_2C_6H_4$ (**1h**)	24	73 (**2h**)
10[c]	H	H	H	3-$CF_3C_6H_4$ (**1i**)	18	94 (**2i**)
11	H	H	H	1-naphthyl (**1j**)	10	99 (**2j**)
12	H	H	H	3-thienyl (**1k**)	5	86 (**2k**)
13[c]	H	H	H	H (**1l**)	5	50 (**2l**)
14[c]	H	H	Ph	H (**1m**)	21	95 (**2m**)
15	H	OMe	H	Ph (**1n**)	2	57 (**2n**)
16	H	Me	H	Ph (**1o**)	24	6 (**2o**)
17	H	Cl	H	Ph (**1p**)	9	87 (**2p**)
18	H	NO_2	H	Ph (**1q**)	24	100 (**2q**)
19	OMe	H	H	Ph (**1r**)	2	100 (**2r**)
20[c]	Me	H	H	Ph (**1s**)	19	20 (**2s**)
21	Cl	H	H	Ph (**1t**)	24	86 (**2t**)
22	CF_3	H	H	Ph (**1u**)	24	99 (**2u**)
23	NO_2	H	H	Ph (**1v**)	22	96 (**2v**)

[a]Isolated yield. [b]*Z*-Isomer of **1a** was used as a substrate. [c]Performed at 150 °C. [d]Mixture of 2- and 3-aryl-substituted *N*-Ts-indoles was obtained (2-:3- = 5.6:1).

(entries 1–10). The reactions of (*Z*)-isomer also proceeded uneventfully to form **2a** in 76% yield (entry 2). Both naphthyl- and heteroaryl-substituted alkenes were well tolerated for this reaction (entries 11 and 12). Noteworthy is the fact that the reaction of **1e** bearing an electron-rich substituent (R^4 = 4-$MeOC_6H_4$) afforded the mixture of 2- and 3-substituted indole products (2-:3- = 5.6:1, entry 6), indicating that a migratorial process occurred via a carbocation intermediate (*vide infra*).[7] Mono- and 1,1-disubstituted terminal alkenes (R^3 = H or Ph, R^4 = H) proved to be suitable substrates (entries 13 and 14). In some cases, interestingly, a few substrates among Me-substituted ones led to complicated mixtures along with the desired products in low yields (entries 3, 16, and 20), probably resulting from the oxidation of the benzylic position (i.e., Me group) by DDQ.[8]

Subsequently, we also investigated the effects of substituents (R^1, R^2) residing on the aromatic moiety of *N*-Ts-2-styrylanilines (entries 15–23). Both electron-donating and -withdrawing substituents were well tolerated with the exception of Me group as mentioned above. An electron-donating substituent (e.g., OMe) *para* to both amino moiety (R^1) and alkene moiety (R^2) accelerated the reaction rate considerably, presumably as a consequence of the increased nucleophilicity of amine and the reduced oxidation potential of alkene (possibly amine as well), respectively (entries 15 and 19). The latter observation is also consistent with the effect of a 4-MeO-phenyl substituent at the alkene moiety (R^4 = 4-$MeOC_6H_4$, entry 6). In sharp contrast, reducing the electron density of olefin through the direct introduction of electron-withdrawing substituents (e.g., R^4 =

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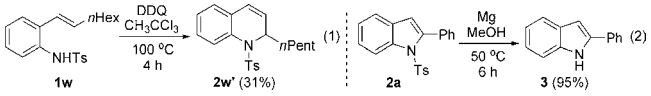
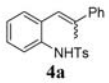
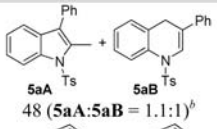
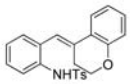
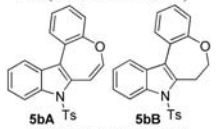
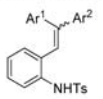
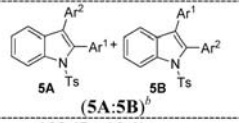
CO_2nBu, $CONMe_2$, CN, $PO(OEt)_2$) at the alkene moiety gave an adverse effect, leading to no reaction with mostly recovered starting materials (not shown). In the case of an alkyl-substituent bearing substrate (R^4 = alkyl) such as **1w**, dihydroquinoline **2w′** instead of indole was obtained as a sole isolable product in a modest yield (eq 1), suggesting a mechanism involving an olefin



radical cation, followed by hydrogen atom transfer to generate the allyl cation.[5,6,9] This is in sharp contrast to the result of Zheng's work in which not dihydroquinoline **2w′** but the corresponding indole product was obtained through electrophilic addition of a nitrogen-centered radical cation to a tethered alkene.[4b] On the other hand, smooth deprotection of the Ts group secured the production of NH free indole **3** in good yield (eq 2).

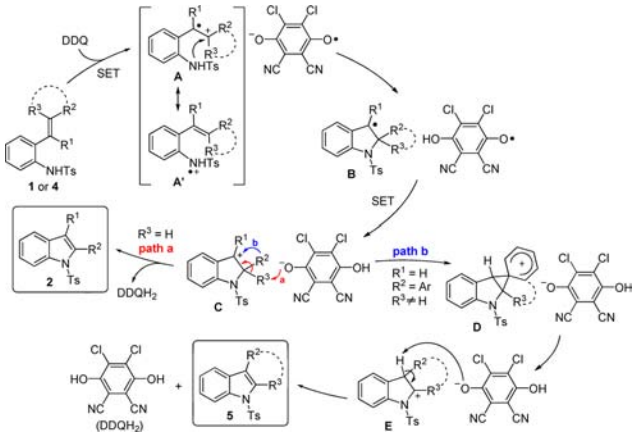
With the speculated carbocation intermediate in mind, we next investigated the reaction of *β*,*β*-disubstituted 2-alkenylanilines (**4**) under the standard reaction conditions. As shown in Table 3, these reactions proceeded uneventfully to generate the corresponding 2,3-disubstituted indoles, showing higher migratory aptitude of an aryl group than an alkyl group (entries 1 and 2). In general, electron-rich aryl groups migrated preferentially (entries 3−8), supporting that cationic rearrangements took place through the formation of phenonium ion intermediate (**D**, Scheme 2).[7] Similarly to the outcome from **1w** in eq 1, dihydroquinoline **5aB** was obtained along with indole **5aA** resulted from a phenyl migration in the reaction of **4a** (entry 1),[5,9] while the formation of the corresponding dihydroquinoline

Table 3. Oxidative Cyclization Reactions of Trisubstituted Alkene Derivatives Involving 1,2-Aryl Migration

entry	substrate	time (h)	product (%)[a]
1	 4a	20	 5aA 5aB 48 (**5aA**:**5aB** = 1.1:1)[b]
2	 4b	18	 5bA 5bB 40 (**5bA**), 17 (**5bB**)[c]
			 5A 5B (**5A**:**5B**)[b]
3	Ar^1 = Ph, Ar^2 = 4-$MeOC_6H_4$ (**4c**)	2	100 (**5c**, 10:1)
4	Ar^1 = Ph, Ar^2 = 4-MeC_6H_4 (**4d**)	18	68 (**5d**, 3.3:1)
5	Ar^1 = Ar^2 = Ph (**4e**)	24	87 (**5e**)
6	Ar^1 = Ph, Ar^2 = 4-ClC_6H_4 (**4f**)	24	79 (**5f**, 1:1.5)[c]
7[d]	Ar^1 = Ph, Ar^2 = 4-$CF_3C_6H_4$ (**4g**)	24	30 (**5g**, 0:1)[c]
8	Ar^1 = 4-$MeOC_6H_4$, Ar^2 = 4-ClC_6H_4 (**4h**)	12	100 (**5h**, 1:13.5)

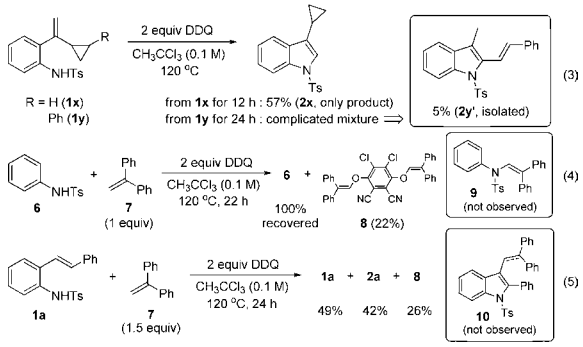
Reaction conditions: Substrate (1 equiv) and DDQ (2 equiv) in CH_3CCl_3 (0.1 M) at 120 °C. [a]Isolated yield. [b]Determined by ^1H NMR. [c]Starting materials were recovered (**4b**: 12%, **4f**: 20%, **4g**: 68%). [d]Performed at 150 °C.

Scheme 2. Proposed Mechanism



was not observed in the reaction of **4b** (entry 2). In sharp contrast to the reaction of **1b** (Table 2, entry 3), interestingly, a *p*-tolyl substituent was well tolerated in the reaction of **4d** (Table 3, entry 4).

To gain insight into this reaction, a series of control experiments were performed.[6] Radical clock experiments using **1x** and **1y** were conducted under the optimized conditions and gave very different outcomes (eq 3).[10] The first afforded **2x** as the



sole product of which cyclopropyl ring remained intact, presumably because a ring opening reaction of the cyclopropyl benzyl radical is slower than its competitive oxidation to benzylic cation (**B** → **C**, Scheme 2).[4b,10c] In sharp contrast, the latter using **1y**, in which a phenyl group would allow for a fast ring cleavage to result in a benzyl radical,[10b] led to a complicated mixture and **2y′** could be isolated, albeit in a low yield. This product is likely to be formed through a cyclopropane ring opening, suggesting that a carbon radical intermediate was involved during the reaction. Inclusion of BHT (3,5-di-*tert*-butyl-4-hydroxytoluene) or TEMPO (2,2,6,6-tetramethylpiperidine-*N*-oxyl) as an additive had deleterious effect on the efficiency of the indole formation, while the corresponding trapping products were not observed in both cases.[6] When DDQ was added to a solution of stilbene, we observed the immediate color change to deep green, whereas a solution of **6** turned to brown by the addition of DDQ. Apparently, a radical ion pair complex might be generated through a single-electron transfer process between the stilbene double bond and DDQ.[6] In stark contrast to the Chemler's work wherein C−H amination products such as **9** were formed through nitrogen-radical addition to various radical acceptors (e.g., **7**),[4a] an intermolecular variant of our protocol did not proceed, giving fully recovered **6** and a byproduct **8** derived from **7** and DDQ (eq 4). The introduction of a radical acceptor **7** to

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our standard reaction conditions using **1a** as the substrate afforded **2a** and the same byproduct **8** as in eq 4 without **10**, which could be formed through interception of a radical intermediate by alkene **7** in domino C−H amination/intermolecular Heck-type coupling reaction (eq 5).[11]

While a clear mechanistic picture is elusive at this juncture, these findings suggest that oxidation of the carbon radical (**B**, Scheme 2), resulted from the intramolecular nucleophilic attack by the *o*-sulfonamide group toward an olefin radical cation (via **A**),[12] to the corresponding benzylic carbocation intermediate (**C**) followed by the deprotonation (**B** → **C** → **2**) is much faster than intermolecular addition of the radical (**B**) to an alkene (e.g., **7**). In addition, intermolecular C−N and C−C bond formations under our conditions appear to be unfavorable.

In summary, we have developed an effective metal-free C−H amination of *N*-Ts-2-alkenylanilines by using DDQ as an oxidant. This new protocol represents an attractive route for a straightforward access to a diverse range of substituted indoles, a privileged motif found in a number of natural and designed compounds with important biological and physical implications. Our experimental findings suggest that this oxidative cyclization reaction implicates a radical cation generated by SET and a phenonium ion intermediate for a subsequent migratorial process, following a postulated mechanistic route as depicted in Scheme 2.

Despite its potential utility and efficiency in indole synthesis, the narrow substrate scope of C−H amination of 2-alkenylanilines seems to have encumbered its application in organic synthesis.[3,4] The reaction presented herein could overcome the longstanding deficiencies and, furthermore, offer high efficiency and facilitation as well as a broad substrate scope without using expensive transition-metal catalysts and a special equipment/experimental setup. Further investigations to extend to an intermolecular version of this protocol together with detailed mechanistic studies are currently underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

Full experimental details and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: sowony73@hanyang.ac.kr.

Notes

The authors declare no competing financial interest.

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