Advanced Synthesis & Catalysis

DOI: 10.1002/adsc.201400759

Silver(I)-Mediated C–H Amination of 2-Alkenylanilines: Unique Solvent-Dependent Migratory Aptitude

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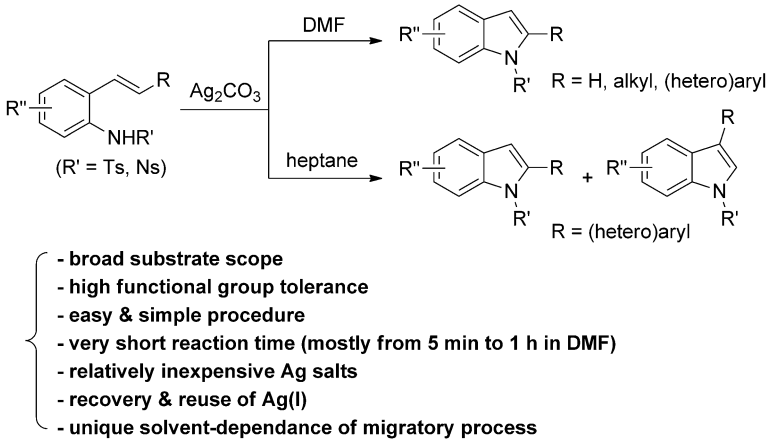
Received: August 1, 2014; Revised: September 18, 2014; Published online: ■■ ■■, 0000

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201400759.

Abstract: A highly effective silver(I)-mediated C–H amination of 2-alkenylanilines has been developed to afford a diverse range of substituted indoles. High functional group tolerance, broad substrate scope, simple/fast/high-yielding reaction, and recovery/reuse of the inexpensive silver oxidant are noteworthy. Furthermore, an uncommon migratory process of β-monosubstituted 2-alkenylanilines with solvent-dependence was demonstrated.

Keywords: cyclization; indoles; migration; oxidation; silver

Intramolecular oxidative C–H amination is one of the straightforward and powerful routes to highly valuable, bioactive nitrogen heterocycles.[1] Among them, Pd(II)-catalyzed C–H amination of 2-alkenylanilines has been considered as an effective pathway toward the indole skeleton, since the pioneering work of the Hegedus group.[2,3] Its rather limited substrate scope has been significantly broadened by the beautiful photocatalytic reaction of Zheng and co-workers.[4] However, its practicality is yet to be solved due to the requirement of a difficult-to-remove *para*-alkoxyphenyl group on the nitrogen atom, expensive transition metal catalysts, and a special experimental set-up. Recently, our group reported a DDQ-mediated metal-free C–H amination of 2-alkenylanilines for the synthesis of a diverse array of substituted indoles in excellent yields.[5] This facile and simple procedure along with the use of easily removable Ts (*para*-toluenesulfonyl) as an *N*-protecting group has significantly improved the efficiency and practicality of indole formation *via* C–H amination of 2-alkenylanilines. However, there was still a limitation which is the incompatibility of alkyl-substituted alkene derivatives ($R \neq$ alkyl in Scheme 1) and a methyl substituent (in some cases when $R = 4\text{-}MeC_6H_4$ or $R'' = Me$) under strong oxidation conditions (i.e., DDQ). Therefore, we were interested in developing a more general and



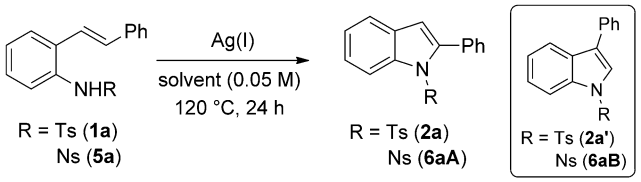
Scheme 1. Ag(I)-mediated oxidative C–H amination of 2-alkenylanilines.

efficient procedure with high functional group tolerance and wide substrate scope.

Herein we disclose a highly effective Ag(I)-mediated C–H amination of 2-alkenylanilines to construct a wide range of substituted indoles (Scheme 1).[6] In particular, this newly developed method offers significantly improved substrate scope and functional group tolerance through the use of Ag_2CO_3 as a relatively inexpensive Ag oxidant which can be easily recovered and reused. The operationally straightforward and simple procedure, notably short reaction time, and unprecedented, unique migratory process with solvent-dependence are also highly noteworthy.

Considering the recent advances of various Ag-mediated oxidative processes in heterocyclic synthesis,[7,8] we envisioned the potential application of such an oxidation system for the desired indole formation. We began our investigations on a variety of Ag salts as an oxidant using **1a** as the test substrate (Table 1). Gratifyingly, it was found that Ag_2CO_3 promoted this C–H amination reaction to afford **2a** along with **2a′** resulting from a phenyl migration in 54% yield (entry 1). Among a variety of Ag salts examined, Ag_2CO_3 was the most effective oxidant for this transformation (entries 1–5). Various solvents were examined, and DMF appeared preferable with regard to reaction time and product yield (entries 6–12). Further optimization of reaction conditions (entries 13–16) secured a high yield of indole **2a** after a very short reaction time (83%, 1.3 equiv. Ag_2CO_3 in 0.025 M DMF at 150 °C for 30 min, entry 16). On the other hand, during the solvent screening study, 1,2-phenyl migration was observed in both dichloroethane (DCE) and heptane, giving the mixture of 2- and 3-phenyl-substituted indole products (**2a**:**2a′** = 1:0.2, entries 1 and 7). This unexpected finding is of great interest since the 1,2-carbon shift has been generally observed in the related reaction of only β,β-disubstituted 2-alkenylaniline derivatives[4,5,9] with the exception of a single example of a β-monosubstituted 2-alkenylaniline bearing an electron-rich substituent (e.g., **1f** with 4-$MeOC_6H_4$) in our previous work.[5] Prompted by this initial result, we subsequently turned our efforts to find more effective reaction conditions for the 1,2-aryl migration. It was found that the use of both heptane as a solvent at higher reaction temperature (150 °C) and Ns (*para*-nitrobenzenesulfonyl) group instead of Ts as the *N*-protecting group was beneficial for both higher chemical yield (**2a** + **2a′**) and ratio of **6aB** to **6aA**, respectively.[10] Finally, optimal reaction conditions were established as entry 20 in Table 1, giving **6a** in good combined yields (88%, **6aA**:**6aB** = 1:0.8), albeit with a longer reaction time than that in DMF. To the best of our knowledge, this represents the first example of 1,2-phenyl migration in the related C–H amination of 2-styrylaniline derivatives bearing one substituent at the β position of alkenes.

Table 1. Optimization studies.[a]

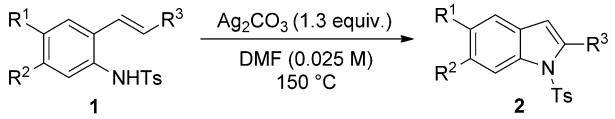


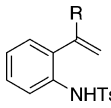
Entry	Ag(I) (equiv.)	Solvent	Yield [%][b]
1	Ag_2CO_3 (1)	$ClCH_2CH_2Cl$	54 (1:0.2)[c]
2	Ag_2O (1)	$ClCH_2CH_2Cl$	26
3	AgOAc (1)	$ClCH_2CH_2Cl$	45
4	$Ag(O_2CCF_3)$ (1)	$ClCH_2CH_2Cl$	19
5	AgOTs (1)	$ClCH_2CH_2Cl$	–
6	Ag_2CO_3 (1)	toluene	31
7	Ag_2CO_3 (1)	heptane	51 (1:0.2)[c]
8	Ag_2CO_3 (1)	1,4-dioxane	(77)
9	Ag_2CO_3 (1)	MeCN	52
10[d]	Ag_2CO_3 (1)	DMF	(78)
11	Ag_2CO_3 (1)	DMSO	79
12	Ag_2CO_3 (1)	*t*-BuOH	39
13[e]	Ag_2CO_3 (0.5)	DMF	(47)
14[f]	Ag_2CO_3 (1.3)	DMF	(82)
15[g]	Ag_2CO_3 (2)	DMF	(77)
16[h]	**Ag_2CO_3 (1.3)**	**DMF**	**(83)**
17[i]	Ag_2CO_3 (1.3)	heptane	(89) (1:0.2)[c]
18[j]	Ag_2CO_3 (1.3)	$ClCH_2CH_2Cl$	(42) (1:0.2)[c]
19[i,k]	Ag_2CO_3 (1.3)	heptane	77 (1:0.2)[c]
20[i,l]	**Ag_2CO_3 (1.3)**	**heptane**	**(88) (1:0.8)[c]**

[a] All reactions were carried out 3–5 times repetitively and the average values of both yields and ratios are given. Except for entries 19 and 20, all reactions used **1a** as a substrate.
[b] Yields were determined by ^1H NMR using trichloroethylene as an internal standard. Value in parentheses indicates an isolated yield.
[c] Ratios of inseparable isomers (**2a**:**2a′** or **6aA**:**6aB**) were determined by ^1H NMR.
[d] For 2.5 h.
[e] For 48 h.
[f] For 3 h.
[g] For 1 h.
[h] In DMF (0.025 M) at 150 °C for 0.5 h.
[i] At 150 °C for 12 h.
[j] At 150 °C for 5 h.
[k] Using *N*-Bs-substituted substrate instead of **1a**.
[l] Using *N*-Ns-substituted substrate (**5a**) instead of **1a**. Ts = *para*-toluenesulfonyl, Bs = benzenesulfonyl, Ns = *para*-nitrobenzenesulfonyl.

With the optimized reaction conditions in hand, we first set out to explore the substrate scope of the process in DMF (Table 2). Both terminal (mono- and 1,1-disubstituted, entries 15 and 18–20) and internal (1,2-disubstituted) alkenes were well tolerated for this reaction. Aryl-substituted alkenes (R^3 = aryl) underwent C–H amination smoothly to afford the corresponding indoles in good yields irrespective of the aryl substitu-

Table 2. Substrate scope: mono- or disubstituted alkene derivatives.



Entry	R^1	R^2	R^3	Time [h]	Yield [%][a]
1	H	H	Ph (**1a**)	0.5	83 (72)[b] (**2a**)
2	H	H	4-MeC_6H_4 (**1b**)	0.5	72 (**2b**)
3	H	H	3-MeC_6H_4 (**1c**)	0.5	74 (**2c**)
4	H	H	2-MeC_6H_4 (**1d**)	0.5	72 (**2d**)
5	H	H	2,4,6-$Me_3C_6H_2$ (**1e**)	0.5	96 (**2e**)
6	H	H	4-$MeOC_6H_4$ (**1f**)	0.75	73 (**2f**)
7	H	H	3-$MeOC_6H_4$ (**1g**)	0.5	77 (**2g**)
8	H	H	4-ClC_6H_4 (**1h**)	1	60 (**2h**)
9	H	H	4-$NO_2C_6H_4$ (**1i**)	0.5	79 (**2i**)
10	H	H	3-$CF_3C_6H_4$ (**1j**)	1	68 (**2j**)
11	H	H	1-naphthyl (**1k**)	0.5	76 (**2k**)
12	H	H	3-thienyl (**1l**)	4	75 (**2l**)
13	H	H	3-furanyl (**1m**)	0.5	61 (**2m**)
14	H	H	2-pyridyl (**1n**)	0.5	73 (**2n**)
15	H	H	H (**1o**)	0.5	79 (**2o**)
16	H	H	*n*-Hex (**1p**)	0.5	74 (**2p**)
17	H	H	*c*-Hex (**1q**)	0.5	80 (**2q**)
18			R = Ph (**1r**)	2	92 (**2r**)
19			R = Me (**1s**)	1.5	90 (**2s**)
20			R = *c*-Pr (**1t**)	0.3	96 (**2t**)
21	OMe	H	Ph (**1u**)	0.17	55 (**2u**)
22	Me	H	Ph (**1v**)	1	86 (**2v**)
23	Cl	H	Ph (**1w**)	0.08	71(**2w**)
24	NO_2	H	Ph (**1x**)	0.5	48 (**2x**)
25	H	OMe	Ph (**1y**)	0.5	66 (**2y**)
26	H	Me	Ph (**1z**)	1	84 (**2z**)
27	H	Cl	Ph (**1aa**)	1	88 (**2aa**)
28	H	NO_2	Ph (**1ab**)	2	75 (**2ab**)

[a] Isolated yield.
[b] 1.1 g of **1a** was used.

tion, showing little electronic and steric dependence (entries 1–11). Heteroaromatic motifs such as thiophene, furan, and pyridine could be also incorporated as a substituent at the alkene terminus (entries 12–14). Noteworthy is the fact that alkyl-substituted alkenes (R^3 = alkyl) were also well tolerated in this reaction, leading to the desired indole products in good yields (entries 16, 17 and 19, 20). On the other hand, electron-withdrawing substituents at the alkene moiety (e.g., R^3 = ketones, esters, amides, nitrile) resulted in no reaction with mostly recovered starting materials (not shown), alluding to the involvement of an electrophilic addition to a tethered alkene. Both electron-donating and electron-withdrawing substituents residing on the aromatic moiety of *N*-Ts-2-styrylanilines (R^1, R^2) had no significant effect on the reactivity (entries 21–28). It is noteworthy that this process can tolerate various functional groups such as methoxy, halogen, nitro, heteroaryl groups as well as the methyl group which is prone to oxidation.[11]

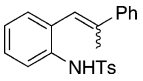
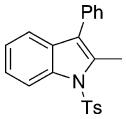
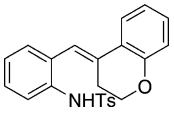
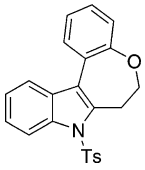
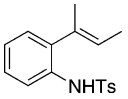
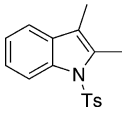
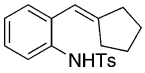
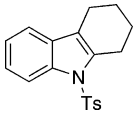
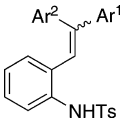
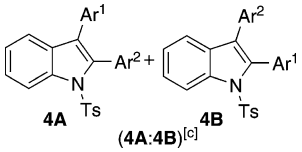
Subsequently, we investigated the reaction of trisubstituted alkenyl derivatives under the standard reaction conditions (Table 3). All reactions proceeded successfully to afford the corresponding 2,3-disubstituted indoles. When the β,β-disubstituted 2-alkenylanilines have an alkyl and an aryl substituent at the β position, a selective migration of the aryl group was observed in good yields (entries 1 and 2). In the case of β,β-dialkyl-substituted substrate **3d**, the ring expansion product **4d** was obtained through an alkyl group migration (entry 4). Meanwhile, β,β-diaryl-substituted substrates showed the higher migratory aptitude of an electron-rich aryl group than an electron-deficient one (entries 5–8). These findings might provide important insights into the reaction mechanism, suggesting that benzylic carbocations and cationic rearrangements are presumably involved.[4,5,9]

Next, we turned our attention to the 1,2-carbon shift reaction of β-monosubstituted *N*-Ns-2-alkenylaniline **5** under the optimized reaction conditions (Table 4). Compared to the reactions in DMF, this protocol generally required longer reaction times. In some cases, DCE was needed as a co-solvent due to the low solubility of the substrates in only heptane which could result in very low conversion. As shown in Table 4, a variety of (hetero)aryl groups could migrate to give the corresponding rearranged 3-substituted indole **6B** along with unrearranged **6A** (entries 1–11 and 13, 14), whereas 1,2-alkyl migration failed to take place (entry 12). While only little steric effect of the migrating group with *ortho* substituents (entries 5–7 and 10) was apparent, its electronic density seems to play an important role to determine the degree of 1,2-aryl migration: electron-rich aryl groups migrate more favorably (entries 1 and 9, 10 *vs.* entries 2–8), providing further evidence for cationic rearrangements *via* a phenonium ion intermediate.[4,5,9]

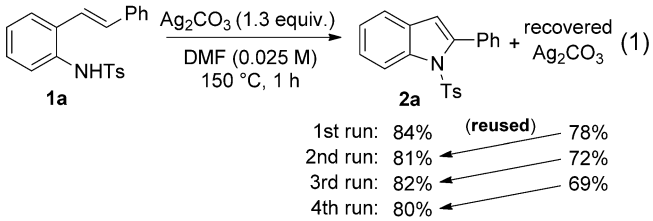
To investigate the synthetic potential of the C–H amination method presented herein, the reaction of **1a** was carried out on a gram scale (Table 2, entry 1). To our delight, the desired product **2a** was obtained in 72% yield. Furthermore, recovery and recycling of Ag_2CO_3 could alleviate the cost and waste problem to use stoichiometric amounts of Ag_2CO_3 in this reaction, albeit the relative low cost of Ag_2CO_3 among silver sources is favorable. The regenerated Ag_2CO_3 could effectively promote this oxidative C–H amination of **1a** without the loss of activity, with four consecutive runs providing comparable yields [Eq. (1)].[12]

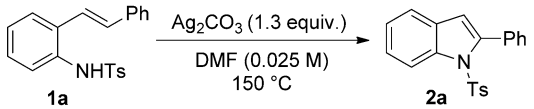
To gain further mechanistic insight into this reaction, a series of control experiments were performed. When substrate **1a** was subjected to the optimal reac-

Table 3. Oxidative cyclization reactions of trisubstituted alkene derivatives.[a]

Entry	Substrate		Time [h]	Product		Yield [%][b]
1	**3a**		0.5	**4a**		82
2	**3b**		0.5	**4b**		92
3	**3c**		0.5	**4c**		93
4	**3d**		0.5	**4d**		63
						
5	**3e**	Ar^1 = 4-$MeOC_6H_4$, Ar^2 = Ph	0.5	**4e**	(6:1)	89
6	**3f**	Ar^1 = 4-MeC_6H_4, Ar^2 = Ph	1	**4f**	(2.5:1)	86
7	**3g**	Ar^1 = Ar^2 = Ph	5	**4g**	–	77
8	**3h**	Ar^1 = 4-ClC_6H_4, Ar^2 = Ph	0.5	**4h**	(1:1.2)	83

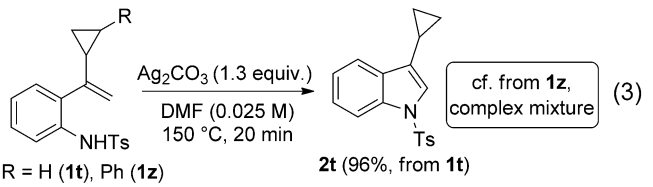
[a] Same reaction conditions as Table 2.
[b] Isolated yield.
[c] Determined by ^{1}H NMR.





Radical scavenger	Time [h]	**1a** [%][a]	**2a** [%][a]
-	0.5	-	83[b]
TEMPO (1 equiv.)	3	-	86
BHT (1 equiv.)	24	80	18

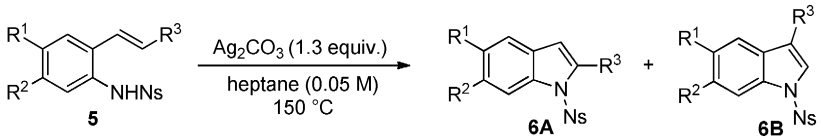
[a] Determined by ^{1}H NMR.
[b] Isolated yields.



tion conditions in the presence of TEMPO (2,2,6,6-tetramethylpiperidine-*N*-oxyl), the reaction proceeded as usual to give **2a** in 86% yield [Eq. (2)]. On the contrary, BHT (3,5-di-*tert*-butyl-4-hydroxytoluene) did exert a deleterious effect on the reaction.[13] We speculated that a radical might be involved but its oxidation to the corresponding benzylic carbocation (**B**→**C**, Scheme 2) could be too fast for TEMPO to inhibit the reaction. Alternatively, it has been also reported that the reaction rate of resonance stabilized benzylic radicals with TEMPO is much slower than that of alkyl radicals and its reaction is reversible even at ambient temperature.[14] While the detrimental effect of BHT could infer that a radical might be involved in this reaction, it cannot be completely excluded that this outcome could be attributed to its direct reaction with Ag_2CO_3, leading to depletion of Ag oxidant and ineffective reaction thus shutting down the indole formation reactions to a large extent.

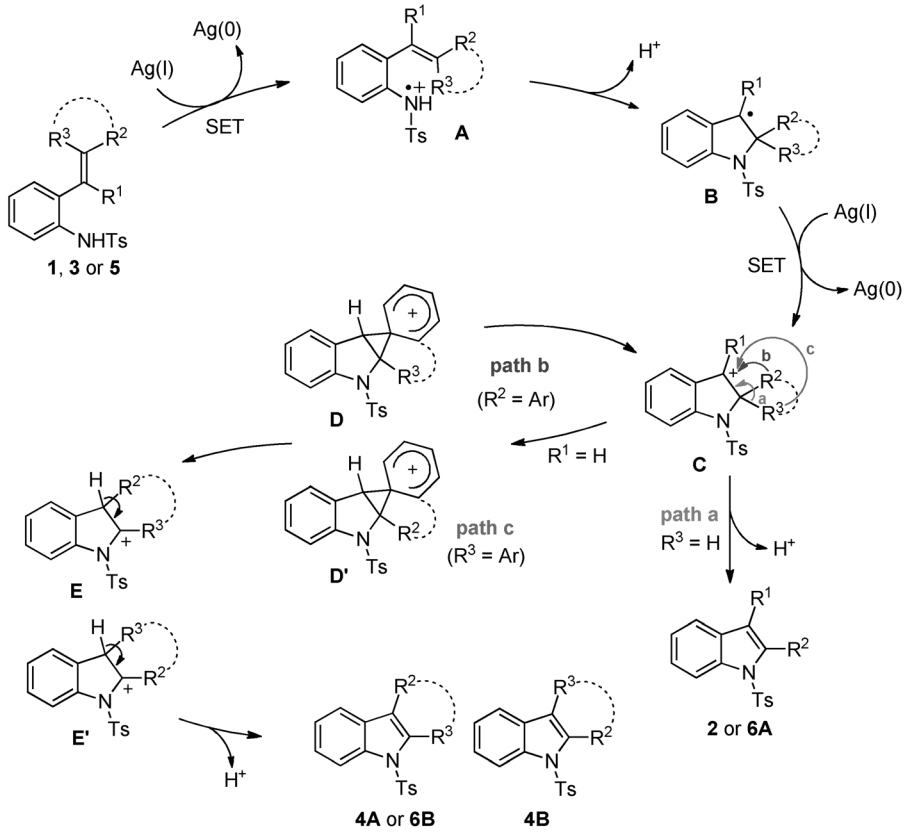
Radical clock experiments[15] using **1t** and **1z** were conducted under the optimized conditions [Eq. (3)]. The first gave indole **2t** in very high yield (96%) as the sole product with the cyclopropyl ring remaining intact, while the latter led to a complex mixture in-

Table 4. Substrate scope of 1,2-migration reaction.



Entry	5	R^1	R^2	R^3	Time [h]	6	Yield [%][a] (6A:6B)[b]
1	**5a**	H	H	Ph	12	**6a**	88 (1:0.8)
2	**5b**	H	H	4-MeC_6H_4	12	**6b**	86 (1:1.5)
3	**5c**	H	H	4-$MeOC_6H_4$	12	**6c**	95 (1:2.1)
4	**5d**	H	H	3,4-$(MeO)_2C_6H_3$	24	**6d**	75 (1:1.9)
5	**5e**	H	H	2,6-$(MeO)_2C_6H_3$	24	**6e**	78 (1:2.4)
6[c]	**5f**	H	H	2,4-$(MeO)_2C_6H_3$	7	**6f**	86 (1:3.1)
7[c]	**5g**	H	H	2,4,6-$(MeO)_3C_6H_2$	7	**6g**	91 (1:3.9)
8[c]	**5h**	H	H	3,4-(-OCH_2O-)C_6H_3	4	**6h**	80 (1:4.5)
9[c]	**5i**	H	H	4-ClC_6H_4	7.5	**6i**	84 (1:0.95)
10	**5j**	H	H	1-naphthyl	24	**6j**	65 (1:0.5)
11[c]	**5k**	H	H	3-thienyl	24	**6k**	87 (1:2.5)
12	**5l**	H	H	*c*-Hex	24	**6l**	70 (1:0)
13	**5m**	Me	H	Ph	24	**6m**	85 (1:1.4)
14[c]	**5n**	H	Cl	Ph	24	**6n**	78 (1:0.8)

[a] Isolated yield of inseparable isomers (**6A**+**6B**).
[b] Ratios of inseparable isomers were determined by ^1H NMR.
[c] In heptane/$ClCH_2CH_2Cl$ (4:1, 0.05 M). Substrate was dissolved in $ClCH_2CH_2Cl$ first and then heptane was added in the mixture.



Scheme 2. Proposed mechanism.

cluding a couple of unidentified compounds. Different reaction outcomes of **1t** and **1z** may be understood on the basis of literature precedents reporting that the presence of a phenyl substituent exerts a strong influence on the ring opening reaction rates of cyclopropyl-containing radicals (cyclopropylmethyl: $1.2\times10^8\ s^{-1}$, cyclopropylbenzyl: $2.7\times10^5\ s^{-1}$, (2-phenylcyclopropyl)benzyl: $3.6\times10^8\ s^{-1}$): the cyclopropylbenzyl radical undergoes a reversible ring opening reaction with the ring-closed form being thermodynamically preferred, while resonance stabilization of the ring-opened radical by another phenyl group on the cylcopropyl ring skeleton [e.g., (2-phenylcyclopropyl)benzyl radical] facilitates the ring opening reaction.[15] We surmised that a ring opening reaction of the cyclopropylbenzyl radical derived from **1t** might be slower than its competitive oxidation to benzylic cation (**B**→**C**, Scheme 2),[4,15c–e] whereas the reaction using **1z**, in which a phenyl group would allow for a faster ring cleavage to result in a benzyl radical,[15b,e] led to a complicated mixture.

Although clearly detailed mechanistic studies are needed to clarify the mechanism in these reactions, a plausible mechanistic proposal is presented in Scheme 2.[7,8] Nitrogen radical cation **A** generated from the substrate (**1**, **3**, or **5**) with Ag(I) salt undergoes an electrophilic addition to the tethered alkene to afford a benzylic radical **B** with the loss of a proton. Subsequently, single-electron transfer (SET) from **B** to Ag(I) to produce the benzylic carbocation **C** followed by the deprotonation forms the desired indole product **2** *via* path a (when $R^3=H$). Note that a silver mirror is observed during reaction.

In the case of β,β-disubstituted 2-alkenylanilines (R^2 or R^3 = aryl), a migratorial process can occur *via* a phenonium ion intermediate **D** or **D′** through path b or c to give carbocation intermediate **E** or **E′**, respectively. Finally, loss of a proton produces the desired product **4A**/**4B**.[16] While the reason for different reaction pathways of **5** (R^2 = aryl, $R^3=H$) in heptane or DCE solvent remains unclear and difficult to explain at this stage, rearranged indole **6B** can be formed similarly through **C**→**D**→**E** along with unrearranged indole **6A**, which might form directly from **C** or bypassing through **C**→**D**→**C**. An alternative mechanistic pathway involving a nitrogen-centered radical in the initial step could also be invoked.

In summary, we have developed a highly effective Ag(I)-mediated C–H amination of 2-alkenylanilines to construct a diverse range of substituted indoles, one of the most significant heterocycles found in numerous natural products, pharmaceuticals, and other functional molecules.[6] This enabling protocol offers a notably simple and straightforward approach with high functional group tolerance, broad substrate scope, high efficiency and practicality, and short reaction time (in DMF) for indole synthesis *via* C–H amination of 2-alkenylanilines using an inexpensive and reusable Ag oxidant, demonstrating that the method presented herein arguably surpasses other related C–H amination processes. Noteworthy is that a unique 1,2-(hetero)aryl group migration of β-monosubstituted 2-alkenylanilines was observed to give the corresponding rearranged 3-substituted indoles along with the unrearranged 2-substituted ones, depending on the reaction medium. 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. Further investigations to construct other privileged heterocyclic scaffolds with detailed mechanistic studies are currently underway in our laboratory.

Experimental Section

General Procedure

Substrate **1**, **3** or **5** (0.065 mmol, 1 equiv.) and Ag_2CO_3 (23.4 mg, 0.084 mmol, 1.3 equiv.) were dissolved in DMF (2.6 mL, 0.025 M) or heptane (1.3 mL, 0.05 M) under an argon atmosphere. The resulting mixture was stirred at 150 °C for the reported time under an argon atmosphere. After the reaction was completed, the reaction mixture was concentrated under vacuum. The residue was purified by column chromatography on silica gel to give the corresponding product.

Acknowledgements

This work was supported by both Basic Science Research Program and Nano·Material Technology Department Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Education and MSIP (Nos. 2012R1A1A2041471, 2012M3A7B4049654, and 2014-011165).

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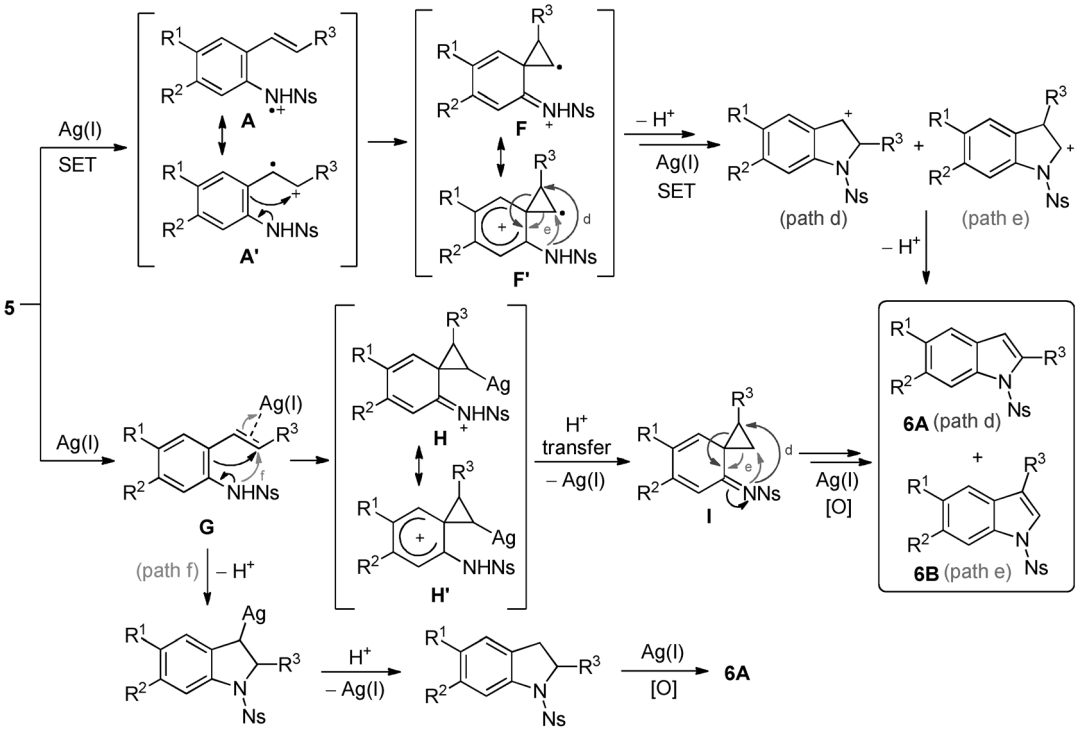

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Silver(I)-Mediated C–H Amination of 2-Alkenylanilines: Unique Solvent-Dependent Migratory Aptitude

Adv. Synth. Catal. **2014**, *356*, 1 – 9

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