Advanced Synthesis & Catalysis

Accepted Article

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To be cited as: *Adv. Synth. Catal.* 10.1002/adsc.201801490

Link to VoR: http://dx.doi.org/10.1002/adsc.201801490

10.1002/adsc.201801490

FULL PAPER

DOI: 10.1002/adsc.201((will be filled in by the editorial staff))

Domino Synthesis of 3-Alkyliden-2,3-Dihydro-4-Quinolones

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Received: ((will be filled in by the editorial staff))

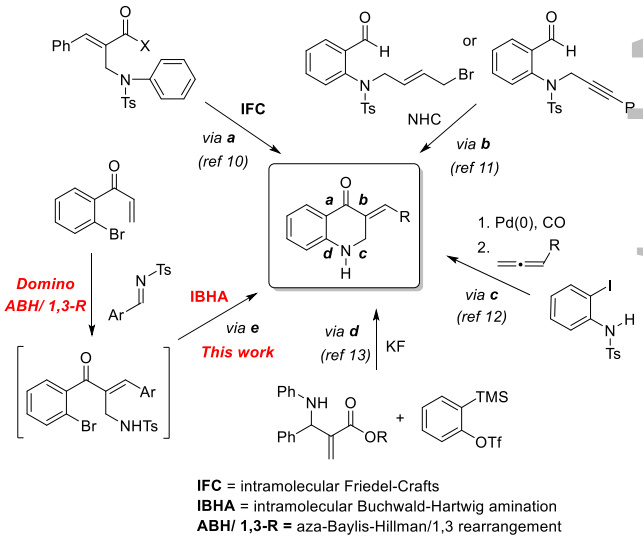
Supporting information for this article is available on the W3, WW under http://dx.doi.org/10.1002/adsc.201#######.((Please delete if not appropriate))

Abstract. The synthesis of 3-alkyliden-2,3-dihydro-4-quinolones has been accomplished in a domino fashion through a three-step sequence that comprised an initial aza-Baylis-Hillman reaction, followed by a 1,3-rearrangement and an intramolecular amination.
Starting from readily available aryl vinyl ketones and *N*-tosyl imines, the reaction with PPh_3, CsOAc and CuI in CH_3CN gave rise, in good overall yields, to final 3-alkyliden-4-quinolone derivatives, valuable scaffolds in medicinal chemistry. The simultaneous addition of two bases, PPh_3 and CsOAc, was found to be crucial for the success of the process.
While PPh_3 promoted the reversible aza-Baylis-Hillman reaction, CsOAc triggered the subsequent 1,3-rearrangement, which shifted the initial equilibrium and allowed to complete the synthetic sequence upon the addition of CuI.

Keywords: 4-quinolones, aza-Baylis Hillman, intramolecular amination, 1,3-rearrangement, domino reactions

Introduction

4-Quinolones are privileged structures in drug discovery due to their ubiquitous presence in natural products and biologically active substances.[1] These scaffolds are present in a large number of marketed antibiotics such as ciprofloxacin and levofloxacin.[2] In addition, suitable functionalization of these nitrogen heterocycles has allowed the shift towards other therapeutic areas, being also present in a wide variety of biologically active molecules with antiviral,[3] anticancer,[4] antimalarial,[5] antimitotic[6] or antidiabetic[7] properties, among others. For this reason, several synthetic methodologies have been devised to access the valuable 4-quinolone skeleton.[8] However, the preparation of 3-alkyliden-2,3-dihydro-4-quinolone derivatives, that contain an exocyclic double bond, is much less common. These compounds have been shown to possess interesting biological activities such as antifertility, antiasmathic or antiarthritic properties.[9] The strategies currently known for their synthesis can be categorized depending on the formation of which bond leads to ring closure. Closure of *bond* ***a*** (Scheme 1) was accomplished by means of an intramolecular Friedel-Crafts type acylation, that created the C-C bond connecting the aromatic ring and the carbonyl functionality (Scheme 1, ***via a***).[10]



Scheme 1. Synthetic strategies to access 3-alkyliden-2,3-dihydro-4-quinolones.

The generation of the C-C bond between the carbonyl and the exocyclic double bond (*bond* ***b***, Scheme 1) involved the use of a Stetter type reaction catalyzed by an NHC ligand (Scheme 1, ***via b***),[11] while the N-C *bond* ***c*** was assembled by a palladium catalyzed tandem carbonylation/allene insertion of *ortho*-iodo *N*-tosyl anilines (Scheme 1, ***via c***).[12]

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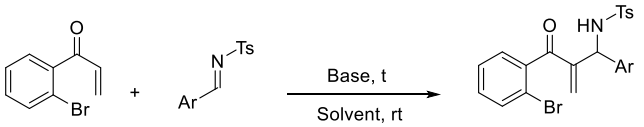
Finally, the construction of both *bonds* ***a*** and ***d*** was recently described through the reaction of Baylis-Hillman adducts with arynes generated from *ortho*-trimethylsilyl triflates with potassium fluoride (Scheme 1, ***via d***).[13]

Herein we report a new strategy for the synthesis of 3-alkyliden-2,3-dihydro-4-quinolone derivatives starting from *ortho*-bromo aryl vinyl ketones and *N*-tosyl imines. It involves a three-step sequence consisting of an initial aza-Baylis-Hillman reaction followed by a 1,3-rearrangement and an intramolecular amination (Scheme 1, ***via e***). This new methodology, that generates the aromatic C-N *bond* ***d*** (Scheme 1) in the final closure, was achieved in a domino fashion, rendering 3-alkyliden-2,3-dihydro-4-quinolones in a very simple manner from readily available starting materials.

Results and Discussion

The initial aza-Baylis-Hillman reaction was evaluated employing aryl vinyl ketone **1a** as a model substrate.[14] The results obtained in the optimization process are compiled in Table 1. The first attempt to perform the reaction of compound **1a** and the *N*-tosyl imine derived from benzaldehyde **2a** was carried out using PPh_3 as a base in THF. After 24h at room temperature, a small amount of the Baylis-Hillman adduct **3a** was detected by ^{1}H-NMR (Table 1, entry 1). Similar result was achieved when CH_3CN was used as the solvent (Table 1, entry 2). However, changing the solvent to diethyl ether led to the precipitation of the aza-Baylis-Hillman adduct, which was isolated by simple filtration in pure form and good yield (Table 1, entry 3). These reaction conditions were tested on *p*-methoxyphenyl imine **2b**, which was not soluble in diethyl ether and the reaction did not proceed (Table 1, entry 4). Likewise the use of THF or more nucleophilic phosphines such as PPh_2Me and $PPhMe_2$ was not effective and decomposition of the starting imine **2b** was detected after stirring the reaction mixture for 24h (Table 1, entries 5-7). Best results were obtained when $P(PMP)_3$ was employed as a Lewis base, either in THF or CH_3CN. Under these conditions the reaction proceeded in a small extent, affording only 20% of the desired compound **3b** together with the decomposition product of imine **2b** (Table 1, entries 8, 9). From these results, it seems that the aza-Baylis-Hillman reaction is reversible and, only when the product precipitates in diethyl ether, the equilibrium is shifted to the right and the Baylis-Hillman adduct **3a** can be isolated in reasonable yield.[15]

Table 1. Optimization conditions for the aza-Baylis-Hillman reaction (ABH).[a]



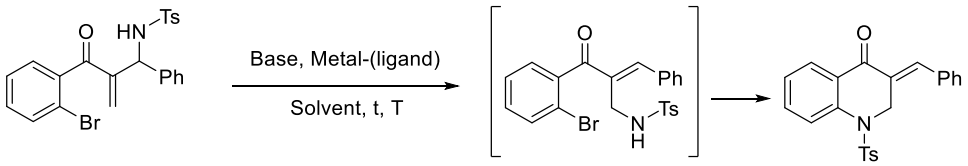
Entry	Ar	2	Solvent	Base	t [h]	3 [%][b]
1	Ph	**2a**	THF	PPh_3	24	**3a** [20]
2	Ph	**2a**	CH_3CN	PPh_3	24	**3a** [20]
3	Ph	**2a**	Et_2O	PPh_3	4	**3a** [57][c]
4	PMP	**2b**	Et_2O	PPh_3	24	---
5	PMP	**2b**	THF	PPh_3	24	---
6	PMP	**2b**	THF	PPh_2Me	24	---
7	PMP	**2b**	THF	$PPhMe_2$	24	---
8	PMP	**2b**	THF	$P(PMP)_3$	24	**3b** [20]
9	PMP	**2b**	CH_3CN	$P(PMP)_3$	24	**3b** [20]

PMP= *p*-methoxyphenyl. [a] Reactions were carried out with **1a** (1 equiv) and **2** (1.2 equiv), base (10 mol%) in the corresponding solvent (0.095M) at room temperature. [b] Yields were determined by ^{1}H-NMR. [c] Yield of isolated compound **3a** after precipitation in diethyl ether.

With compound **3a** in hand, we decided to explore the feasibility of the intramolecular amination in order to access 3-alkyliden-4-quinolone derivatives in a sequential manner. Thus, the reaction was initially tested with $PdCl_2(PPh_3)_2$ and *t*-BuOK or Cs_2CO_3 as bases in refluxing toluene.[16] Unfortunately, very low yields of product **5a** were obtained (Table 2, entries 1, 2). It is important to point out that, before the intramolecular amination, a base-promoted 1,3-rearrangement takes place, which converts the aza-Baylis-Hillman adduct **3a** to the *N*-tosyl amine **4a**.[17]

Other reaction conditions previously employed in the synthesis of 4-quinolone derivatives under Pd catalysis were also tested. Therefore, next attempt was performed with $Pd_2(dba)_3$ and racemic BINAP in the presence of *t*-BuONa as a base.[18] Again under these conditions, 4-quinolone **5a** was isolated in poor yield (Table 2, entry 3). Similarly, when $Pd(OAc)_2$ was employed as the metal promoter and PPh_3 as a ligand, the desired compound **5a** was obtained in only 27% yield (Table 2, entry 4).[19]

Table 2. Optimization of the intramolecular Buchwald-Hartwig amination.[a]



3a **4a** **5a**

Entry	Base	Solvent	Metal-(ligand)	time [h]	T [° C]	Yield **5a** [%][b)]
1	*t*-BuOK	toluene	$PdCl_2(PPh_3)_2$	24	45	10
2	Cs_2CO_3	toluene	$PdCl_2(PPh_3)_2$	24	110	11
3	*t*-BuONa	toluene	$Pd_2(dba)_3$-BINAP[c)]	24	110	17
4	K_2CO_3	Dioxane	$Pd(OAc)_2$-PPh_3	24	110	27
5	CsOAc	DMSO	CuI	24	95	---
6	CsOAc	DMF	CuI	24	95	---
7	CsOAc	CH_3CN	CuI	24	82	47
8	CsOAc	CH_3CN	CuI	12	82	76
9	CsOAc	CH_3CN	CuOAc	24	82	---
10	CsOAc	CH_3CN	CuI-Phen[d)]	24	82	---

[a)] Reactions were carried out by mixing **3a** (1 equiv), with the corresponding base (5 equiv) and metal-(ligand) (2 equiv) in the solvent indicated. [b)] Isolated yields of **5a** after purification by column chromatography. [c)] Racemic BINAP was used as ligand. [d)] Reaction performed with 1,10-phenanthroline as ligand.

It is known that copper salts (more economical than palladium ones) catalyze this type of cross-coupling reactions. The unique combination of copper iodide and cesium acetate was found to mediate intramolecular aminations under mild conditions.[20] Therefore, we tested those conditions with our substrate, although no identifiable product could be detected either in DMSO and DMF as solvents (Table 2, entries 5, 6). When the reaction was carried out in refluxing acetonitrile for 24h, quinolone **5a** was obtained in 47% yield through the domino process 1,3-rearrangement/ intramolecular amination (Table 2, entry 7). We found that lowering the reaction time was crucial in order to improve the chemical yield. Thus, compound **5a** was isolated in 76% yield when the reaction was allowed to proceed for 12h (Table 2, entry 8). The use of other copper salts or additional ligands such as 1,10-phenanthroline resulted in the complete suppression of the process (Table 2, entries 9, 10).

With these data in hand, the optimized conditions to perform the domino 1,3-rearrangement/ intramolecular amination lay in heating the aza-Baylis-Hillman adduct in acetonitrile for 12h in the presence of CuI (2 equiv) and CsOAc (5 equiv) as a base.

As we mentioned in the discussion of Table 1, the participation of tosyl imines different than **2a**, derived from benzaldehyde, in the PPh_3 catalyzed aza-Baylis-Hillman reaction is troublesome, probably due to the poor solubility of those imines in diethyl ether and the reversibility of the reaction. This would entail a significant limitation in our synthetic strategy as we would not access compounds different than **3a** in order to extend the scope of our domino 1,3-rearrangement/ intramolecular amination leading to 4-quinolones **5**. On the other hand, from results showed in Table 2, it becomes apparent that CsOAc is responsible for the 1,3-rearrangement. Consequently, we envisioned that the combination of both bases, PPh_3 and CsOAc, would trigger both processes, the reversible aza-Baylis-Hillman and the 1,3-rearrangement in a single step. In this manner, if the rearrangement is an irreversible process, it would push the aza-Baylis-Hillman equilibrium to the right, hence allowing us to synthesize rearranged products **4** in a domino fashion. To test our hypothesis, we treated ketone **1a** and imine **2a** with PPh_3 and CsOAc simultaneously in THF and, after 12h at room temperature, the clean formation of the rearranged product **4a** was observed in 60% isolated yield. This product was then treated with CuI in refluxing acetonitrile, rendering the desired 4-quinolone **5a** in good yield (Scheme 2).

With the aim of improving our three-step synthesis of quinolones, we intended to perform the complete sequence in a one pot manner. To achieve that goal, we conducted the domino 1,3-rearrangement/ intramolecular amination in CH_3CN and, once TLC revealed the total consumption of the starting materials, CuI was added to the reaction mixture and it was heated at reflux for 12h. In this manner, final

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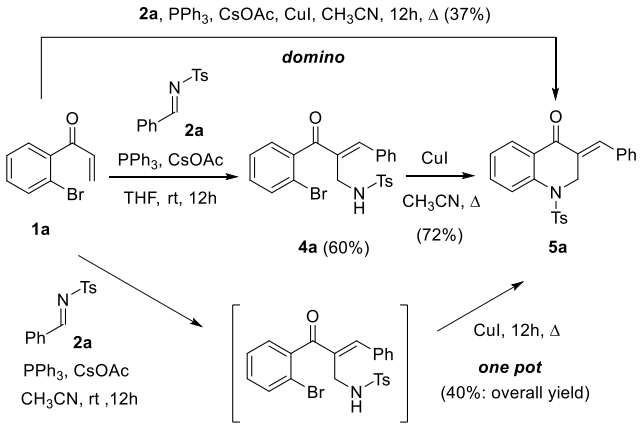
quinolone **5a** was obtained in 40% overall yield, which means that each individual reaction took place in 75% average yield (Scheme 2).

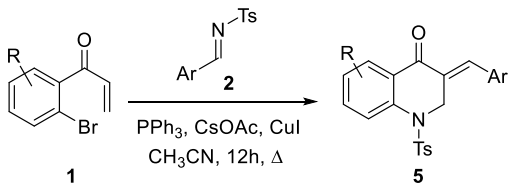
Finally, the whole protocol developed for the synthesis of alkyliden-quinolone **5a** was tested in a domino manner. To this end, PPh_3, CsOAc and CuI were added to a solution of ketone **1a** and tosyl imine **2a** in acetonitrile. The reaction mixture was stirred at reflux for 12h and, after chromatographic purification, final product **5a** was obtained in 37% yield, which is comparable to that of the one pot procedure (Scheme 2).

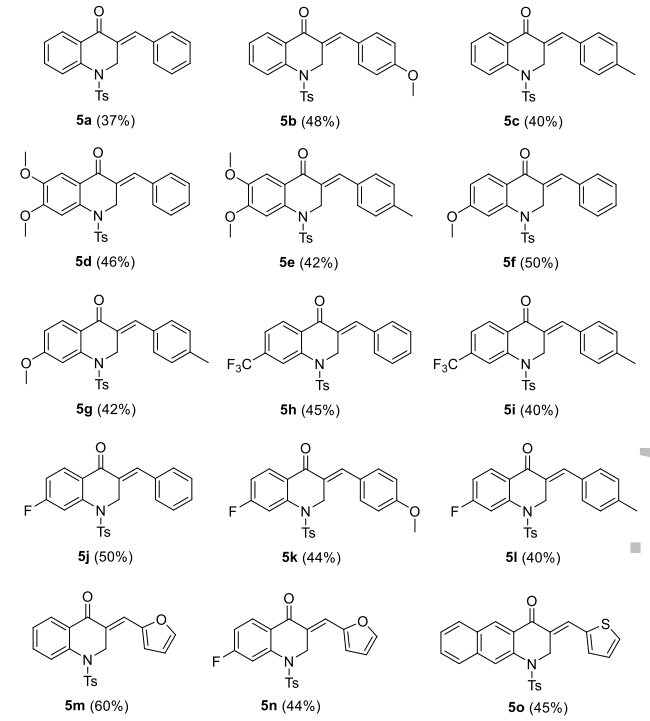


Scheme 2. Domino protocol to access quinolone **5a**.

Having found suitable conditions to synthesize quinolone **5a** employing the three-step sequence in a domino manner, the scope of the process was evaluated next. Table 3 summarizes the results obtained in the extension of our strategy to different aryl vinyl ketones **1** and tosyl imines **2**. Good overall yields were achieved starting from aryl ketones **1** bearing electron donating or electron withdrawing substituents and either aromatic or heteroaromatic tosyl imines **2**.[21]

Table 3. Scope of the domino protocol for the synthesis of 4-quinolones **5**. [a), b)]

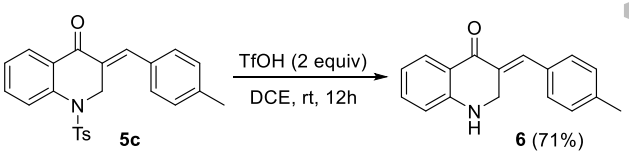




[a)] Reactions were carried out with ketones **1** (1 equiv) and imines **2** (1 equiv) in the presence of PPh_3 (10 mol%), CsOAc (5 equiv) and CuI (2 equiv) in CH_3CN (0.1M) at reflux for 12h. [b)] Yields of quinolones **5** after purification by *flash* column chromatography.

In order to examine the efficiency of the process, a gram-scale reaction was performed. Thus, starting from 2.16 g of ketone **1a** and 1.73 g of imine **2c**, 1.06 g of quinolone **5c** were obtained (42% yield), showing the feasibility of the process for scaling-up.

Finally, the deprotection of the sulfonamide moiety was attempted. Very recently, it was described that chemoselective acidic hydrolysis of sulfonamides can be effected with trifluoromethanesulfonic acid (triflic acid) in a wide variety of examples of practical importance.[22] Those conditions, that involve the treatment of the sulfonamide with 2 equiv of triflic acid in dichloroethane at room temperature for 12 h, were applied to substrate **5c**, affording the deprotected quinolone **6** in 71% yield (Scheme 3).



Scheme 3. Deprotection of quinolone **5c**.

Conclusion

In conclusion, we have developed a domino protocol for the synthesis of 3-alkyliden-2,3-dihydro-4-quinolones **5**. Starting from readily available aryl vinyl ketones **1** and tosyl imines **2**, the sequence aza-Baylis Hillman/ 1,3-rearrangement/ intramolecular amination was performed in the presence of PPh_3, CsOAc, and CuI, giving rise to final products **5** in good overall yields in a domino fashion. The key for the success of this three-step synthesis is the simultaneous addition of PPh_3 and CsOAc, which allows to perform the aza-Baylis-Hillman and the subsequent 1,3-rearrangement in a domino fashion, avoiding the low extension in which the first step takes place as an individual reaction.

Experimental Section

General procedure for the domino synthesis of quinolones 5. To a solution of ketone **1** (1 equiv) and imine **2** (1 equiv) in acetonitrile (0.1 M), PPh_3 (10 % mol), CsOAc (5 equiv) and CuI (2 equiv) were added. The reaction mixture was stirred at reflux for 12 hours under N_2 atmosphere (monitored by TLC). Then, it was cooled to room temperature and filtered through a short pad of Celite®, washing with small portions of EtOAc. The filtrate was concentrated under reduced pressure and the crude mixture was purified by flash chromatography to afford quinolones **5**.

***(E)*-3-(4-Methylbenzylidene)-1-tosyl-2,3-dihydroquinolin-4(1H)-one (5c).** By means of the general procedure described above, quinolone **5c** (31 mg, 40% yield) was obtained as a yellow solid starting from 40 mg (0.189 mmol) of ketone **1a** and 52 mg (0.189 mmol) of imine **2c** after flash chromatography with 6:1 *n*-hexanes: ethyl acetate. Mp= 140-145 °C.^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.95 (d, *J* = 9.3 Hz, 1H), 7.82 (d, *J* = 8.1 Hz, 1H), 7.66 – 7.60 (m, 1H), 7.44 – 7.28 (m, 4H), 7.22 (d, *J* = 8.0 Hz, 2H), 7.02 (d, *J* = 8.4 Hz, 2H), 6.97 (d, *J* = 8.2 Hz, 2H), 5.06 (d, *J* = 1.5 Hz, 2H), 2.45 (s, 3H), 2.34 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 182.6 (s), 144.2 (s), 141.3 (s), 140.4 (s), 138.6 (s), 134.5 (s), 134.1 (s), 133.1 (s), 133.0 (s), 131.4 (s), 130.2 (s), 129.7 (s), 129.5 (s), 129.0 (s), 128.8 (s), 128.2 (s), 127.4 (s), 127.4 (s), 48.0 (s), 21.6 (s). HRMS (ESI/Q-TOF): m/z $[M + H]^+$ calcd for $C_{24}H_{21}NO_3S$ 404.1320; found 404.1327.

General procedure for the deprotection of quinolone 5c. To a solution of quinolone **5c** (140 mg, 0.35 mmol) in dichloroethane (3.5 mL, 0.1M), TfOH (62µL, 0.7 mmol, 2 equiv) was added. The reaction mixture was stirred at room temperature for 12 hours under nitrogen atmosphere. Then, saturated aqueous $NaHCO_3$ solution was added and the mixture was extracted with dicloromethane three times. The combined organic layers were dried over anhydrous Na_2SO_4, filtered and evaporated. Finally, solvents were removed and the crude mixture was purified by flash chromatography with 5:1 *n*-hexane: ethyl acetate as eluent to afford quinolone **6** (61 mg, 71 % yield) as an orange solid. Mp= 121-123 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.98 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.80 (t, *J* = 2.3 Hz, 1H), 7.33 – 7.27 (m, 1H), 7.23 (brs, 4H), 6.81 – 6.73 (m, 1H), 6.62 (d, *J* = 8.2 Hz, 1H), 4.61 (brs, 2H), 4.35 (brs, 1H), 2.39 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 183.8, 151.2, 139.3, 135.9, 135.4, 132.5, 131.2, 130.1, 129.4, 128.7, 119.3, 118.4, 115.6, 44.8, 21.6. HRMS (ESI/Q-TOF): m/z $[M + H]^+$ calcd for $C_{17}H_{15}NO$ 250.1232 ; found 250.1238.

Acknowledgements

We gratefully thank the Spanish Ministerio de Economía y Competitividad (CTQ-2017-85026-R to C. P.) M. E. and F. R.-A. thank the Spanish Ministerio de Educación, Cultura y Deporte for a predoctoral fellowship (FPU16/04533 and FPU14/03520 respectively). J. T. thanks Generalitat Valeniana for a predoctoral fellowship (ACIF/2018/078).

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10.1002/adsc.201801490

FULL PAPER

Domino Synthesis of 3-Alkyliden-2,3-Dihydro-4-Quinolones

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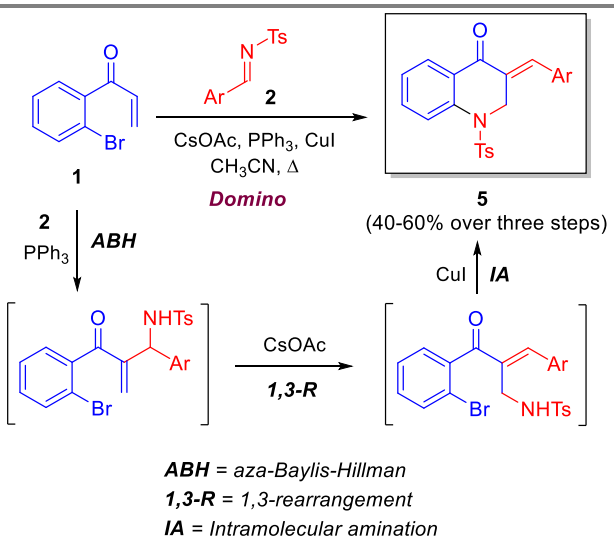

ABH = *aza-Baylis-Hillman*
1,3-R = *1,3-rearrangement*
IA = *Intramolecular amination*