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Highly chemo- and regioselective allylic substitution with tautomerizable heteroarenes

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Tautomerizable heteroarenes, bearing multiple interconvertible nucleophilic centers exhibit high chemo- and regio-selective allylation irrespective of allylating agents used under Pd-catalysis. The achieved selectivity may be attributed to the dominant lactam form of heteroarenes and Pd-catalyzed intramolecular allylic substitution. A generalized green protocol for chemo- and regio-selective allylation of biologically relevant heteroarenes with allyl alcohols in dimethyl carbonate (DMC) as solvent was developed. Excellent selectivity was observed during intermolecular competition study demonstrating the differential nucleophilicity of tautomerizable heteroarenes and differential allyl palladium forming ability of a variety of allyl alcohols.

Introduction

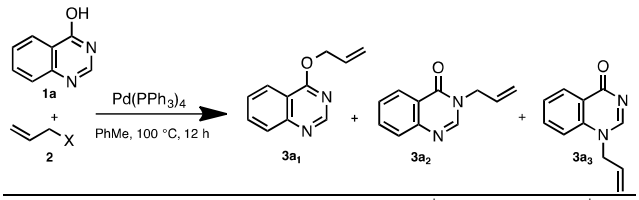
The selective functionalization of heteroarenes is a significant problem in the early drug development process to generate lead molecules.[1] In this context, the Pd-catalyzed allylic substitution reaction is a powerful tool for the construction of C-C and C-X (N, O & S) bonds to obtain structural diversity.[2] One of the general features of this transformation is that allyl substrates with a wide range of activated leaving groups (acetates, carbonates, halides, phosphates, carboxylates etc.) can be utilized to form allylpalladium complexes, which undergo nucleophilic attack to construct C-C/C-X bonds.[2]

Control of regio- and chemoselectivty is an important consideration in the context of medicinal chemistry,[3] and is especially problematic during the direct allylation of tautomerizable heteroarenes as it poses competitive reaction pathways. Thus, the present work aims to delineate the factors that control selectivity during Pd-catalyzed allylic substitution of tautomerizable heteroarenes in the context of allylating reagents, reaction conditions, and substrate. This work also seeks to offer mechanistic insight to rationalize selectivity and develop a generalized green allylation protocol.

Results and discussion

To begin, 4-hydroxy quinazoline **1a** was chosen as a model substrate as it represents a reactant with three distinct tautomerizable nucleophilic centers (-OH and –NH). Apart from that its broad spectrum of biological activities renders the quinazoline framework a highly sought scaffold for drug development.[4] In a model study, the reaction of **1a** with different allylating reagents **2** was performed under base free conditions in the presence of a Pd(0) catalyst (Table 1). Among the different allyl sources examined, chloride **2a**, phenyl ether **2i**, amine **2j**, isothiocyanate **2l**, cyanide **2p**, and benzene **2q** proved ineffective. Other allylic substrates afforded allylated products in modest to good yield. It is important to note that the formation of $\mathbf{3a_2}$ (amide-NH allylation) was observed as the overwhelmingly major product in most of cases. However trifluoroacetate **2f**, isocyanate **2k**, and urea **2m**, the formation of $\mathbf{3a_1}$ was detected along with $\mathbf{3a_2}$. Formation of 1-allyl quinazolin-4(3*H*)-one $\mathbf{3a_3}$ was not observed in any cases. In the absence of the Pd-catalyst, no reaction was observed.

Table 1: Reaction of **1a** with allylating reagents in presence of Pd(0) catalysis under neutral condition.[a]



Entry	Allylating agent	% Conversion[b]			Yield (%)[c, d]
		$\mathbf{3a_1}$	$\mathbf{3a_2}$	$\mathbf{3a_3}$	$\mathbf{3a_2}$
1	**2a**; X = Cl	0	0	0	0
2	**2b**; X = Br	0	76	0	62
3	**2c**; X = I	0	81	0	68
4	**2d**; X = OH	0	82	0	70
5	**2e**; X = OAc	0	85	0	71
6	**2f**; X = $OCOCF_3$	3	85	0	72
7	**2g**; X = OCO_2Me	0	95	0	88
8	**2h**; X = $OP(O)(OEt)_2$	0	100	0	86
9	**2i**; X = OPh	0	0	0	0
10	**2j**; X = NH_2	0	0	0	0

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11	**2k**; X = NCO	4	65	0	52
12	**2l**; X = NCS	0	0	0	0
13	**2m**; X = $NHCONH_2$	6	60	0	49
14	**2n**; X = SMe	0	26	0	15
15	**2o**; X = SO_2Me	0	38	0	25
16	**2p**; X = CN	0	0	0	0
17	**2q**; X = Ph	0	0	0	0

[a]**1a** (0.5 mmol) was treated with **2** (2 equiv, 1 mmol) in toluene (1 mL) at 100 °C (oil bath temp) in presence of $Pd(PPh_3)_4$ (10 mol %) for 12 h. [b]Based on GC-MS. [c] Isolated yield of **3a₂**. [d]No product formation was observed (**1a** was found intact) in absence of catalyst.

To examine the effect of base on chemoselectivity, the entire set of reactions shown in Table 1 were reinvestigated in the presence of K_2CO_3 (see SI-Table 2). No significant difference in the outcomes was observed with the exception that **2a**, **2i**, **2j**, and **2l**, which were ineffective without base, exhibited allylation to form **3a₂** (and **3a₁** in case of **2m**). It is interesting to note the formation of **3a₂** with **2j** under basic conditions. This was likely formed through a nucleophilic ring-opening cascade by allylamine rather than ionization of the allyl group as the reaction also formed **3a₂** in the absence of $Pd(PPh_3)_4$. Further, the inability of **2j**, **2p**, and **2q** to perform allylation with Pd(0) under neutral/basic conditions could be explained on the basis of lack of ionization of the allylic leaving to form a π-allylpalladium complex.

Tautomeric equilibrium is susceptible to various reaction conditions such as solvents, catalysts (metal salts), temperature, p*H* etc. which significantly affect the subsequent reaction outcomes.[5,6] To test whether the selectivity in the reaction of **1a** was vulnerable to changes in the tautomeric composition, the reaction of **1a** with allyl alcohol **2d** was performed in different solvents (see Table 2 & SI-Table 3). No significant difference of the reaction media on selectivity was observed, however in solvents like MeOH, EtOH, TFE, and NO_2Me, the formation of **3a₁** was detected along with **3a₂**. The use of DMSO and DMC was found optimal, however DMC was chosen as the solvent of choice for further studies due of its favorable properties for sustainability (renewable, low toxicity and biodegradability).[7]

Table 2: Investigation of solvent effect on the selectivity control during the reaction of **1a** with **2d** in under $Pd(PPh_3)_4$ catalysis.[a]

Entry	Solvent	% Conversion[b]			Yield (%)[c]
		3a₁	**3a₂**	**3a₃**	**3a₂**
1	MeOH	9	60	0	47
2	EtOH	5	90	0	78
3	TFE	2	97	0	81
4	1,4-Dioxane	0	97	0	84
5	THF	0	37	0	25
6	DMF	0	93	0	82
7	DMSO	0	96	0	85
8	PhMe	0	83	0	70
9	PhH	0	89	0	75
10	DCE	0	79	0	67
11	DMC	0	100	0	92
12	$MeNO_2$	5	46	0	29
13	MeCN	0	93	0	80

[a]**1a** (0.5 mmol) was treated with **2d** (2 equiv, 1 mmol) in various solvents (1 mL) at 100 °C in presence of $Pd(PPh_3)_4$ (10 mol%) for 12 h. [b]Based on GC-MS. [c]Isolated yield of **3a₂**.

A variety of transition metal-catalyzed allylic substitution are known and the choice of metal and ligand can significantly affect the regioselectivity.[6] Thus, the reaction of **1a** with **2d** was investigated in the presence of different Pd catalysts (see Table 3 & SI-Table 4) and other transition metal catalysts (Rh, Ru, Ir, Ni, Fe, Au, and Cu; see Table 3 & SI-Table 6-8). The formation of **3a₂** was observed with all Pd catalysts with varying yield, however $Pd(PPh_3)_4$ was found distinctly superior. Rh, Ir, and Ni catalysts also resulted in the formation of **3a₂** whereas other metals were ineffective. Of particular note, no significant effect of catalysts and ligands was observed on the selectivity (see Table 3, 4 & SI-Table 5 & 8).

Table 3: Investigation of different transition metal catalysts on the selectivity control during the reaction of **1a** with **2d** in DMC.[a]

Entry	Catalyst	% Conversion[b]			Yield (%)[c]
		3a₁	**3a₂**	**3a₃**	**3a₂**
1	$PdCl_2$	0	21	0	12
2	$Pd(OAc)_2$	0	18	0	10
3	$(PPh_3)_4Pd$	0	100	0	91
4	$(PPh_3)_2PdCl_2$	0	8	0	traces
5	$(TFA)_2Pd$	0	41	0	28
6	$[PdCl(C_3H_5)]_2$	0	40	0	28
7	$(C_6H_5CN)_2PdCl_2$	0	13	0	traces
8	$Pd_2(dba)_3$	0	12	0	traces
9	$Pd(dppf)Cl_2$	0	5	0	traces
10	$[Ir(1,5\text{-cod})Cl]_2$	0	32	0	20
11	$RhCl(PPh_3)_3$	0	14	0	traces
12	$Ni(PPh_3)_4$	0	15	0	traces
13	$[Ru(p\text{-cymene})Cl_2]_2$	0	0	0	0
14	$Fe(acac)_3$	0	0	0	0
15	$(Ph_3P)AuCl$	0	0	0	0
16	CuI(I)	0	0	0	0
17	Zirconocene	0	0	0	0

[a]**1a** (0.5 mmol) was treated with **2d** (2 equiv, 1 mmol) in DMC (1 mL) at 100 °C in presence of different transition metal catalysts (10 mol%) for 12 h. [b]Based on GC-MS. [c]Isolated yield of **3a₂**.

Table 4: Investigation of different ligands on the selectivity control during the reaction of **1a** with **2d** in DMC under $Pd(PPh_3)_4$ catalysis.[a]

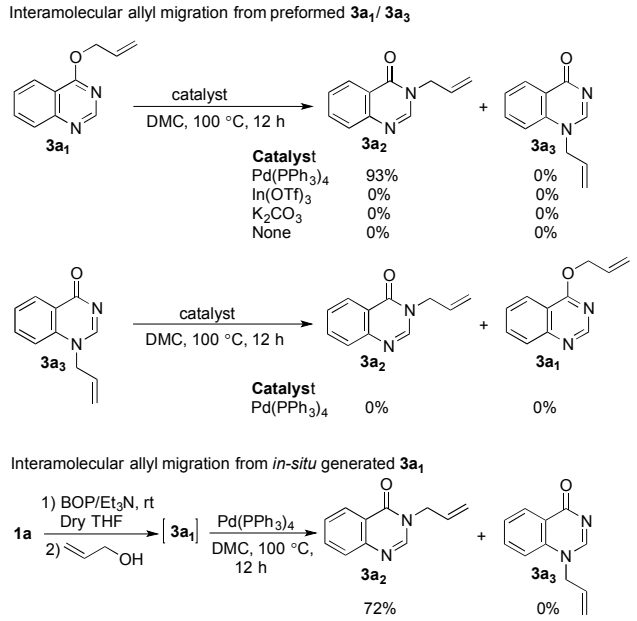
Entry	Ligand	% Conversion[b]			Yield (%)[c]
		3a₁	**3a₂**	**3a₃**	**3a₂**
1	PCy_3	0	96	0	85
2	$P(o\text{-tol})_3$	0	87	0	76
3	TFP	0	91	0	78
4	dppp	3	70	0	67
5	BPhen	4	88	0	92
6	DPFF	0	95	0	83
7	XPhos	0	86	0	72
8	$(DHQD)_2AQN$	5	93	0	84
9	TEP	5	82	0	70

[a]**1a** (0.5 mmol) was treated with **2d** (2 equiv, 1 mmol) in dimethyl carbonate (1 mL) at 100 °C in presence of $Pd(PPh_3)_4$ (10 mol%) and different ligands (20 mol%) for 12 h. [b]Based on GC-MS. [c]Isolated yield of **3a₂**.

The selection of allyl alcohol **2d** for these and subsequent studies was made for sustainability reasons[8] as performing such substitutions with activated allyl substrates generates

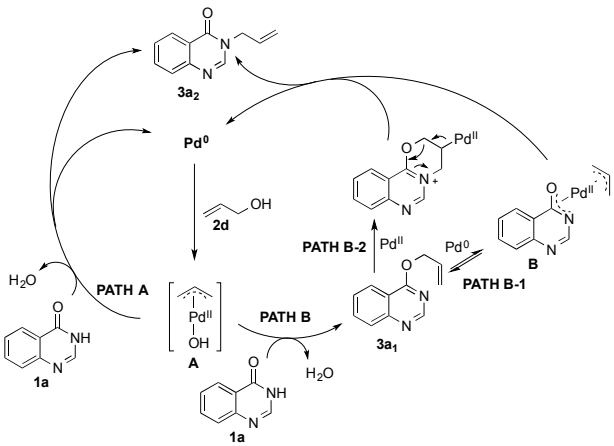
stoichiometric amounts of waste and allyl alcohol forms water as the only by-product. It also negated the need for additional steps to prepare the allyl reagents.[8b]

The predominant formation of **3a$_2$** irrespective of conditions tested (allylating reagent, base, solvent, catalyst, and ligand) indicated the possible intermediacy of **3a$_1$** and/or **3a$_3$**. These could be formed first and undergo rearrangement to form the final product, **3a$_2$**. To investigate this, **3a$_1$** and **3a$_3$** were prepared by an independent route or prepared *in-situ*[9] and subjected to Pd(0) catalysis in DMC at 100 °C. A smooth conversion of **3a$_1$** into **3a$_2$** was observed, however **3a$_3$** failed to react (see scheme 1 & SI page S12). This transformation could proceed *via* a thermal or Lewis acid catalyzed [3,3]-sigmatropic rearrangement.[10] This was ruled out by the heating of **3a$_1$** in DMC at 100 °C for 12 h with or without a Lewis acid [In(OTf)$_3$]. **3a$_1$** was recovered intact indicating the exclusive role of the Pd-catalyst in allylic disposition from **3a$_1$** to **3a$_2$** (see scheme 1 & ESI-Table 9).[11]



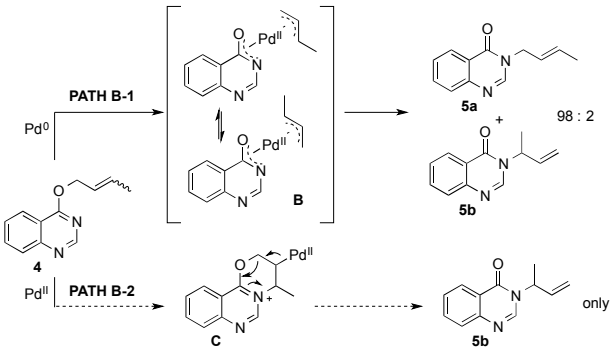
Scheme 1: Investigation of intramolecular allyl migration

Possible mechanistic pathways for the allylation of **1a** with allyl alcohol are presented in Scheme 2. In all cases the first step is likely the oxidative addition of Pd(0) into the allylic alcohol bond to form an allylpalladium hydroxide intermediate (**A**). Direct *N*-allylation of **1a** with loss of water would form the observed product **3a$_2$** (Path A). Alternatively, *O*-allylation could occur to form **3a$_1$** as an intermediate (Path B). This could re-ionize to form intermediate **B** that could produce the product **3a$_2$** (Path B-1). Alternatively, exogenous Pd(II) could catalyze a stepwise [3,3]-sigmatropic rearrangement to produce the final product (Path B-2). It should be noted that Path B-1 may be indistinguishable from Path A.



Scheme 2: Possible routes for the formation of **3a$_2$**

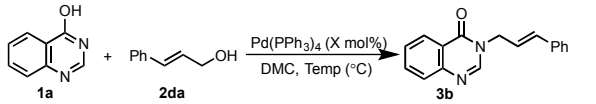
To investigate allylic rearrangement *via* Path B-1 or Path B-2, the crotyl derivative **4** was prepared and examined under the reaction conditions. If the rearrangement were to occur via Path B-1, a mixture of regioisomeric products would be expected. Alternatively, if the reaction proceeds through Path B-2, only the branched product would result. We observed the formation of a mixture of regioisomers **5a** and **5b** (92:8; GC-MS) demonstrating the ionization pathway B-1 was operative (scheme 3).



Scheme 3: Validation of Path B-1 / B-2

With detailed investigation of factors influencing the selectivity control and mechanistic insight rationalizing the chemo-selectivity, next we explored the feasibility of a generalized green allylation protocol with optimized conditions using cinnamyl alcohol **2da** (see Table 5).

Table 5: Effect of different reaction parameters on the (PPh$_3$)$_4$Pd-catalyzed allylation of **1a** with **2da**.[a]



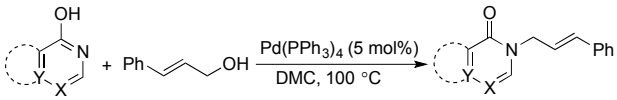
Entry	catalyst (mol%)	equiv (**2da**)	Temp. (°C)	Time (h)	Yield (%)[b]
1	0.5	2	100	24	12
2	1	2	100	24	28
3	2.5	2	100	24	63

4	5.0	2	100	24	90
5	10	2	100	24	90
6	15	2	100	24	90
7	5.0	1	100	24	72
8	5.0	1.2	100	24	90
9	5.0	1.5	100	24	90
10	5.0	1.2	rt	24	traces
11	5.0	1.2	50	24	32
12	5.0	1.2	80	24	51
13	5.0	1.2	100	24	90
14	5.0	1.2	100	4	51
15	5.0	1.2	100	8	69
16	5.0	1.2	100	12	90
17	5.0	1.2	100	16	90

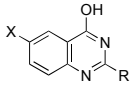
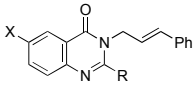
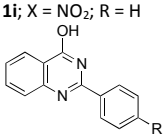
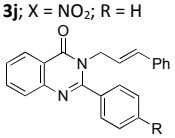
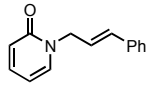
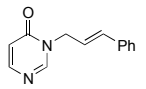
[a]**1a** (0.5 mmol) was treated with **2da** under different reaction conditions in DMC (1 mL). [b]Isolated yield of **3b**.

The scope of tautomerizable heteroarenes was examined first. As summarized in Table 6, a wide range of 4-hydroxy quinazolines bearing alkyl, cycloalkyl, aryl, heteroaryl, and styryl moieties were reacted with cinnamyl alcohol **2da** affording excellent yield of *N*-allylated products (entries 1-15). A wide range of functional groups (-OMe, -NMe_2, -NO_2, -CN, -Cl, CF_3, -CHO, -COMe, -OCH_2O-) were tolerated well, validating the robustness of protocol. The applicability of this protocol was further extended to other biologically relevant tautomerizable heteroarenes. Gratifyingly, *N*-cinnamylation of a variety of heteroarenes proceeded well with excellent yields (entries 16-23).[12]

Table 6: Cinnamylaion of biologically relevant heteroarenes.[a]



X = Y = C or N

Entry	T-heteroarenes	Products	Yield (%)[b]
			
1	**1a**; X = H; R = H	**3b**; X = H; R = H	90
2	**1b**; X = H; R = Me	**3c**; X = H; R = Me	91
3	**1c**; X = H; R = Cy	**3d**; X = H; R = Cy	85
4	**1d**; X = H; R = Ph	**3e**; X = H; R = Ph	88
5	**1e**; X = H; R = furyl	**3f**; X = H; R = furyl	84
6	**1f**; X = H; R = styryl	**3g**; X = H; R = styryl	72
7	**1g**; X = Cl; R = H	**3h**; X = Cl; R = H	84
8	**1h**; X = OMe; R = H	**3i**; X = OMe; R = H	90
9	**1i**; X = NO_2; R = H	**3j**; X = NO_2; R = H	82
			
10	**1j**; R = NMe_2	**3k**; R = NMe_2	85
11	**1k**; R = CF_3	**3l**; R = CF_3	86
12	**1l**; R = CN	**3m**; R = CN	85
13	**1m**; R = C(O)H	**3n**; R = C(O)H	90
14	**1n**; R = C(O)Me	**3o**; R = C(O)Me	85
15	**1o**; R = -OCH_2O-	**3p**; R = -OCH_2O-	83
			
16	**1p**;	**3q**;	81
			
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		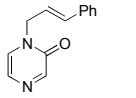	
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		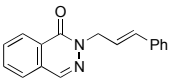	
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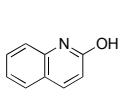
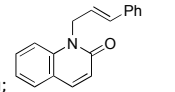
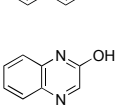
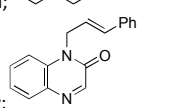
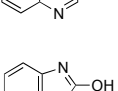
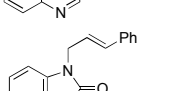
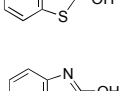
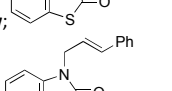
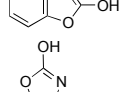
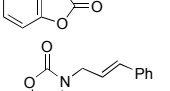
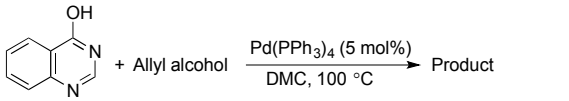
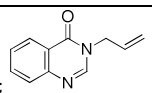
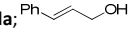
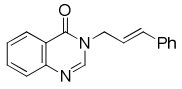
			
19	**1t**;	**3u**;	86
			
20	**1u**;	**3v**;	90
			
21	**1v**;	**3w**;	90
			
22	**1w**;	**3x**;	86
			
23	**1x**;	**3y**;	86

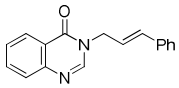
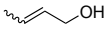
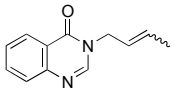
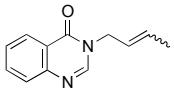
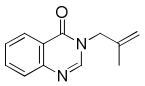
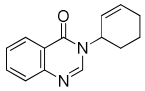
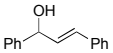
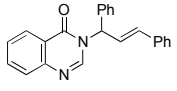
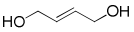
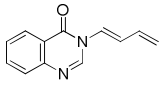
[a]Tautomerizable heteroarenes (0.5 mmol) were treated with **2da** (1.2 equiv, 0.6 mmol) in DMC (1 mL) at 100 °C in the presence of $Pd(PPh_3)_4$ (5 mol %) for 12 h. [b]Isolated yield.

Allylation of **1a** with a variety of allyl alcohols having α-, β-, or γ-substitution proceeded well to produce the allylated products in excellent yields (Table 7).[13] With regards to regioselectivity, allylation with cinnamyl alcohol **2da** or 1-phenylprop-2-en-1-ol **2db** resulted in exclusive formation of the linear product (>99%; GC-MS) whereas a 94:6 isomeric ratio (linear:branched) was observed in the case of **2dc** or **2dd**. The reaction of **1a** with 2-butene-1,4-diol **2dh**, produced the dienamine **6d** in excellent yield. This could serve as model reaction for a generalized one-step synthesis of dienamines, alkenyl oxide/sulfide and conjugated dienes, valuable synthons for pharmaceutical and materials applications. This methodology was found to be advantageous in terms of substrate scope, functional group tolerance and the use of additives or other promoters.[14]

Table 7: Pd-catalyzed reaction of **1a** with different allyl alcohols.[a]

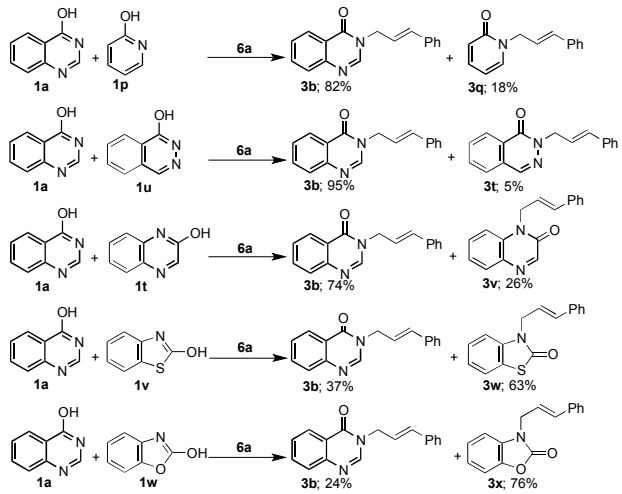


Entry	Allyl alcohol	Product	Yield (%)[b]
1	**2d**; 	**3a$_2$**; 	91
2	**2da**; 	**3b**; 	90

3	**2db**; 	**3b**; 	88
4	**2dc**; 	**5a**; 	82[c]
5	**2dd**; 	**5a**; 	81[c]
6	**2de**; 	**6a**; 	86
7	**2df**; 	**6b**; 	78
8	**2dg**; 	**6c**; 	71
9	**2dh**; 	**6d**; 	82

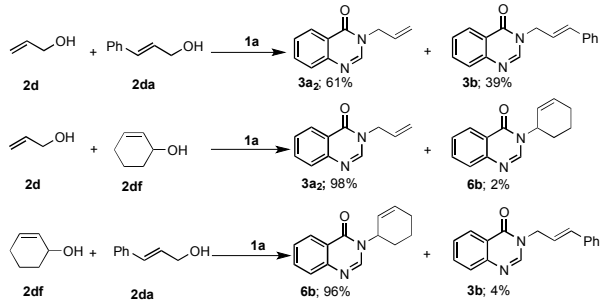
[a]**1a** (0.5 mmol) was treated with allyl alcohol (1-1.5 equiv) in DMSO (1 mL) at 100 °C in the presence of $Pd(PPh_3)_4$ (5 mol %) for 12 h. [b]Isolated yield. [c]E/Z mixture (10:1). A small amount of the branched regioisomer (not shown) was also formed (94:6 linear: branched).

Anticipating differential nucleophilicity of aromatic-OH and/or amide-NH among different heteroarenes, we undertook a competition study and the results are illustrated in Scheme 4. An equimolar mixture of **1a** & 2-hydroxy pyridine **1p**, **1a** & 2-hydroxy phthalazine **1s**, **1a** & 2-hydroxy quinoxaline **1u**, **1a** & 2-hydroxy benzothiazole **1v** as well **1a** & 2-hydroxy benzoxazole **1w** was treated with equimolar amounts of **2da**. Selective cinnamylayion of **1a** took place in preference to **1p**, **1s**, and **1u**. However, the reverse selectivity was observed in the case of **1v** and **1w**.



Scheme 4. Intermolecular competition study involving two different tautomerizable heteroarenes with variable nucleophilicity for a given allyl alcohol (**2da**).

To gain insight into the relative reactivity of allylic alcohols in the allylation reaction, an equimolar mixture of **2d** and **2da**, **2d** and 2-cyclohexeneyl alcohol **2df**, and **2da** and **2df** was treated with **1a** (Scheme 5). Selective incorporation of allyl group took place in preference to cinnamyl and 2-cyclohexeneyl, however in the case of competition between **2da** and **2df**, selective incorporation of cinnamyl group took place in preference to 2-cyclohexeneyl indicating a distinct difference in reactivity with either allylpalladium formation or nucleophilic addition to the allyl complex.



Scheme 5. Intermolecular competitions study involving two different allyl alcohols for a given tautomerizable heteroarenes (**1a**).

The reaction was also performed on a gram scale. 3-(3-Phenyl-allyl)-3*H*-quinazolin-4-one **3b** was obtained in 84% yield, thus demonstrating the scalability and utility of this protocol.

Conclusions

In conclusion, the present work reports the investigation of a wide range of allylating reagents, solvents, metal catalysts, and ligands for the chemo- and regioselective allylation of heteroarenes bearing multiple interconvertible nucleophilic sites. The process was developed as a generalized green protocol for allylation of biologically relevant heteroarenes with allyl alcohols using DMC as solvent with wide range of functional groups tolerance. The differential nucleophilicity of heteroarenes was examined through intermolecular competition studies involving two different heteroarenes and excellent selectivity was observed. Similarly, an excellent selectivity was observed during intermolecular competition involving two different allyl alcohols demonstrating the differential ability of allyl alcohols to form allylpalladium complexes and react with the nucleophile. The direct use of allyl alcohol as an allylating reagent, DMC as solvent, the lack of a requirement for additional additives/promoters, and the feasibility of scale up represent a green protocol for the selective allylation of medicinally relevant tautomerizable *N*-heteroarenes and are an important addition to the tool box of medicinal chemists.

Acknowledgements

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Notes and references

General procedure for the cinnamylaion of tautomerizable heteroarenes: In a glove box, to an oven dried 4 mL glass vial equipped with a stirring bar, 4-hydroxy quinazoline **1a** (0.731 g, 0.5 mmol), cinnamyl alcohol **2da** (0.067 g, 0.5 mmol, 1 equiv), Pd $(PPh_3)_4$ (0.029 g, 0.025 mmol, 5 mol%) followed by DMC (1 mL) were added and the reaction mixture was stirred at 100 °C. After stipulated time period, the reaction mixture was cooled to rt, diluted with MeOH (2 x 10 mL) and passed through bed of celite to remove catalyst. The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude products were adsorbed on to silica gel and passed through the column (eluent: Hexane/EtOAc) to get analytically pure product **3b** as white solid (0.118 g, 90%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.36 (d, *J* = 7.9 Hz, 1H), 8.12 (s, 1H), 7.73-7.79 (m, 2H), 7.51-7.55 (m, 2H), 7.26-7.39 (m, 5H), 6.68 (d, *J* = 15.8 Hz, 1H), 6.32-6.39 (m, 1H), 4.81 (d, *J* = 2.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.9, 148.2, 146.1, 135.8, 134.5, 134.3, 128.6, 128.3, 127.5, 127.3, 126.8, 126.6, 122.8, 122.2, 48.2; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{17}H_{15}N_2O$ 263.1184, Found 263.1178.

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12 For tautomerizable heteroarenes, the lactam (oxo) form is generally more favored over lactim (hydroxy) form in both solid and solution phase. High temperature, bases and other additives can accelerate the tautomerization from the former to the later. The formation of *N*-allylated product in different tautomerizable heteroarenes in high yields [especially in case of 2-hydroxypyridine **1p**, 4-hydroxypyrimidine **1q** (nonbenzo-annelated analogue of **1a**), and 2-hydroxypyrazine **1r** where the oxo-hydroxy equilibrium is more labile] suggests the existence of more than one pathway for the chemoselective *N*-allylation.

13 Possible facilitation in the formation of the allylpalladium complexes via in-situ formation of mixed carbonates was ruled out by performing a blank reaction in the absence of **1a** under optimized condition. No formation of mixed carbonate was observed See: S. B. Lang, T. M. Locascio and J. A. Tunge, *Org. Lett*., 2014, **16**, 4308.

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Graphical abstract

Highly chemo- and regioselective allylic substitution with tautomerizable heteroarenes

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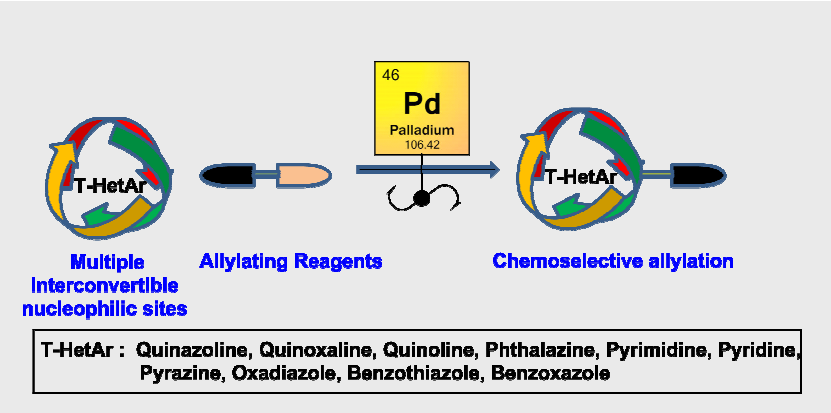

Investigation and exploration of chemo- and regioselective allylic substitution with tautomerizable heteroarenes under variable conditions with mechanistic insight and substrate scope.