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PAPER

Palladium-Catalyzed Allylation of Tautomerizable Heterocycles with Alkynes

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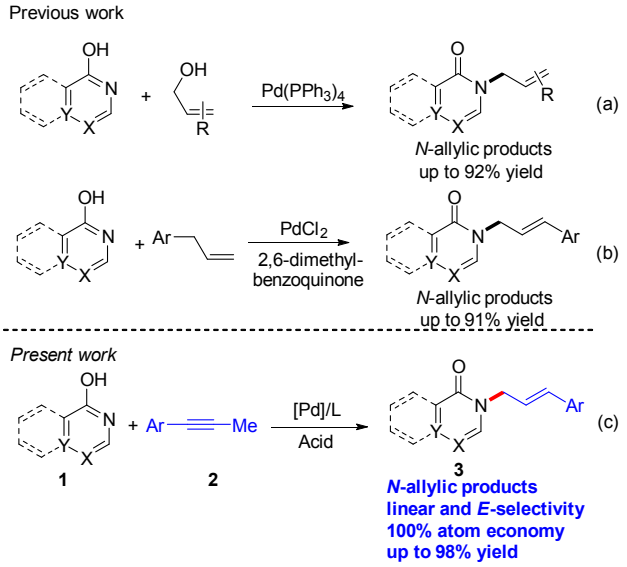
Chuan-Jun Lu,*[a] Dong-Kai Chen,[a] Hong Chen,[a] Hong Wang,[a] Hongwei Jin,[a] Xifu Huang[b] and Jianrong Gao[a]

A method for the allylic amidation of tautomerizable heterocycles was developed by palladium catalyzed allylation reaction with 100% atom economy. A series of structurally diverse *N*-allylic substituted heterocycles can be synthesized in good yields with high chemo-, regio-, and stereoselectivities under mild conditions.

Introduction

Quinazolinones and related tautomerizable heterocycles are found as pharmacophores in a large number of drug candidates, displaying a vast array of biological activities such as anticancer, antimalarial, antidiabetic, and antihypertensive activities.[1] Consequently, their diverse functionalization is highly significant. However, as these nucleophiles exist in two or more tautomeric forms, which in the course of alkylation reactions can lead to mixtures of O- and *N*-substituted products. Control of chemo-selectivity is an important consideration as it poses competitive reaction pathways.[2] The palladium-catalyzed allylic substitution has been instrumental to obtain structural diversity via formation of C-C and C-hetero bonds.[3] However, to date, very limited examples have been documented accessing in a regio- and chemo-selective fashion of these tautomerizable heterocycles.[4,5] Recently, Cook and coworkers reported an elegant palladium-catalyzed regioselective allylation of quinazolinones and relevant heteroarenes with allyl alcohols. Excellent *N*-selectivity was achieved in these allylic substitution reactions, leading to linear *E*-allylated products in high yields (Scheme 1, (a)).[5a] Subsequently, they also reported a regio- and chemo-selective palladium-catalyzed intermolecular oxidative allylic amidation of tautomerizable *N*-heterocycles with allylbenzene derivatives via allylic C-H activation reaction, to afford diverse *N*-heterocycles amenable for medicinal chemistry applications (Scheme 1, (b)).[5b]

On the other hand, after the pioneering work by Yamamoto on the Pd(0)-catalyzed allylation of methylmalononitrile with arylpropyne,[6] arylpropyne has proved to be an ideal precursor to form the π-allylmetal complex due to its highly atom economy. A series of *N*-, O- and C-nucleophiles with these alkynes have been reported to established linear or branched allylated compounds in the presence of palladium[7] or rhodium catalysts.[8] We recently described a highly regioselective palladium-catalyzed allylation of sulfonyl hydrazides with arylpropyne derivatives to construct allyl arylsulfones compounds.[9] We deliberated as to whether this methodology might be successfully transferred to allylation of quinazolinones and relevant heterocycles. If this method works, a stoichiometric amount of leaving group or stoichiometric amounts of oxidant can be avoided. We report herein a palladium catalyzed allylic amidation[10] of tautomerizable heterocycles with simple alkynes for the synthesis of linear allyl heterocycles in good yields with high chemo-, regio-, and stereoselectivities (Scheme 1, (c)).[11]



Scheme 1 Different approaches for the allylic alkylation reactions of tautomerizable heterocycles catalyzed by palladium

Results and discussion

At the beginning of our study, 4-hydroxy quinazoline (4-quinazolinone) **1a** was chosen as a model substrate with three distinct tautomerizable nucleophilic centers (-OH and -NH) to

[a] College of Chemical Engineering, Zhejiang University of Technology, Chaowang Road 18#, Hangzhou 310014, China; E-mail: luchuanjun@zjut.edu.cn
[b] Ningbo Detai Chemical Co., Ltd
[c] †Electronic Supplementary Information (ESI) available: Copies of NMR spectra. See DOI: 10.1039/x0xx00000x

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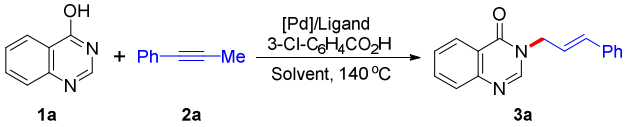
react with 1-phenyl-1-propyne **2a** (Table 1). To our delight, in the presence of 10 mol% $Pd(OAc)_2$ as a catalyst, 24 mol% PPh_3 as a ligand and 1.0 equiv. 3-Cl-$C_6H_4CO_2H$ as the additive in DMSO solvent at 140 °C under N_2 atmosphere for 12 hours, 48% of amide-NH allylation product **3a** was isolated as the only regioisomer in excellent chemo-(amide-NH), regio-(linear), and stereoselectivity (*E*-product) (Table 1, entry 1). Next, the reaction of **1a** with **2a** was investigated in the presence of different Pd catalysts. The formation of **3a** was observed with all Pd catalysts with varying yields (entries 2-6), however $Pd(dba)_2$ was found to be the best catalyst (entry 2). With $Pd_2(dba)_3$ or $Pd(PPh_3)_4$ as the catalyst, a slightly lower yield was achieved (entries 3 and 5). Whereas by switching the palladium catalyst to $PdCl_2$ or $PdCl_2(PPh_3)_2$, the product **3a** was obtained in poor yield (entries 4 and 6). Subsequent ligand screening indicated that in the case of the bidentate ligands such as BINAP, DPPE, DPPB, and DPPF, inferior results were obtained (entries 7-10). And the electro-rich ligand PCy_3 also was not an efficient one (entry 11). To further improve the yield, we investigated the solvent effect on this reaction. The studies revealed that solvent was crucial for this transformation. It showed that reduced yield was observed in toluene and THF (entries 12 and 15). However, to our delight, the desired product was isolated in 82% yield when the reaction was conducted in DMF (entry 13). And in solvents like dioxane and DME, the formation of **3a** was found to be more optimal, with dioxane as the solvent to give the highest yield (entries 14 and 16). Moreover, by reducing the amount of catalyst/ligand (entry 17) or acid (entry 18), the reaction can also occur smoothly to give **3a** in 80% and 60% yield, respectively. Finally, with 3-F-$C_6H_4CO_2H$ as the additive instead of 3-Cl-$C_6H_4CO_2H$, reduced yield was achieved (entry 19). While HOAc or TsOH was used, almost no product **3a** could be detected (entries 20-21).

Table 1 Optimization of reaction conditions[a]

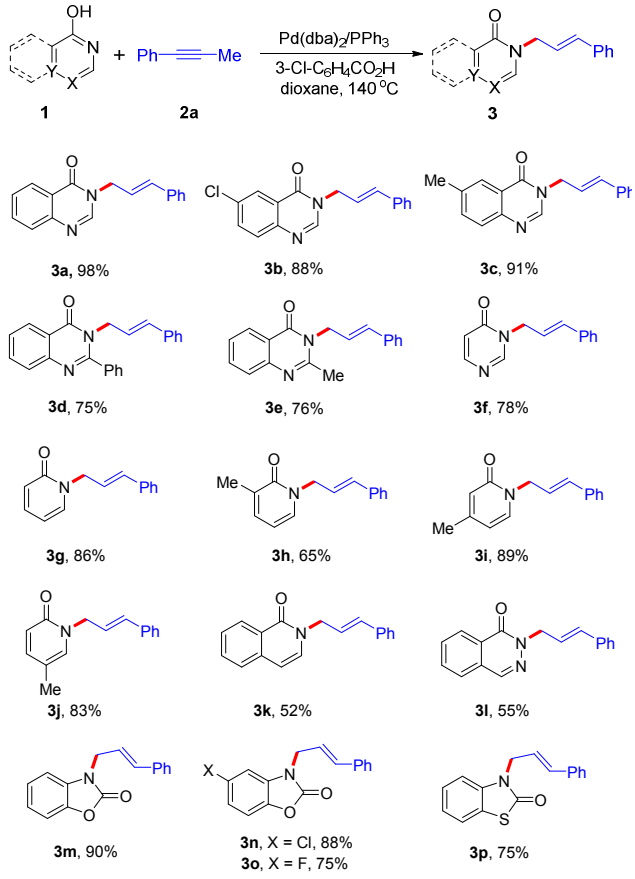


1a **2a** **3a**

Entry	Catalyst	Ligand	Solvent	Yield[b] (%)
1	$Pd(OAc)_2$	PPh_3	DMSO	48
2	$Pd(dba)_2$	PPh_3	DMSO	72
3[c]	$Pd_2(dba)_3$	PPh_3	DMSO	58
4	$PdCl_2$	PPh_3	DMSO	25
5	$Pd(PPh_3)_4$	/	DMSO	64
6	$PdCl_2(PPh_3)_2$	PPh_3	DMSO	32
7[d]	$Pd(dba)_2$	BINAP	DMSO	57
8[d]	$Pd(dba)_2$	DPPE	DMSO	38
9[d]	$Pd(dba)_2$	DPPB	DMSO	45
10[d]	$Pd(dba)_2$	DPPF	DMSO	28
11	$Pd(dba)_2$	PCy_3	DMSO	30
12	$Pd(dba)_2$	PPh_3	toluene	42
13	$Pd(dba)_2$	PPh_3	DMF	82
14	$Pd(dba)_2$	PPh_3	dioxane	98
15	$Pd(dba)_2$	PPh_3	THF	50
16	$Pd(dba)_2$	PPh_3	DME	90
17[e]	$Pd(dba)_2$	PPh_3	dioxane	80
18[f]	$Pd(dba)_2$	PPh_3	dioxane	60
19[g]	$Pd(dba)_2$	PPh_3	dioxane	72
20[h]	$Pd(dba)_2$	PPh_3	dioxane	trace
21[i]	$Pd(dba)_2$	PPh_3	dioxane	trace

[a] Reaction conditions: **1a** (0.3 mmol), **2a** (0.45 mmol), 3-Cl-$C_6H_4CO_2H$ (1.0 equiv.), 10 mol% Pd catalyst, 24 mol% ligand in 0.6 mL solvent at 140 °C for 12 h. [b] isolated yields. [c] 5 mol% $Pd_2(dba)_3$ was used. [d] 12 mol% ligand was used. [e] 5 mol% $Pd(dba)_2$, 12 mol% PPh_3 was used. [f] 0.4 equiv. 3-Cl-$C_6H_4CO_2H$ was used. [g] 3-F-$C_6H_4CO_2H$ was used instead of 3-Cl-$C_6H_4CO_2H$. [h] HOAc was used instead of 3-Cl-$C_6H_4CO_2H$. [i] TsOH was used instead of 3-Cl-$C_6H_4CO_2H$.

Table 2 Scope of tautomerizable heterocycles[a]



1 2a 3

[a] Reaction conditions: **1** (0.3 mmol), **2** (0.45 mmol), 3-Cl-$C_6H_4CO_2H$ (0.3 mmol), $Pd(dba)_2$ (10 mol %), and PPh_3 (24 mol%) in dioxane (0.6 mL) at 140 °C for 12-24 h under N_2 atmosphere.

Under the optimized reaction conditions (Table 1, entry 14), the scope of substituted quinazolinone was first examined with phenylpropyne **2a** as a standard substrate (Table 2). Di□erently substituted quinazolinones reacted well to produce **3** in high yields with excellent chemo-, regio-, and stereoselectivities. It was found that quinazolinones possessing either electron-rich or electron-deficient groups on the phenyl proceeded efficiently to afford the amidation products in good yields (Table 2, **3b-3c**). Additionally, more hindered 2-substituted quinazolinones

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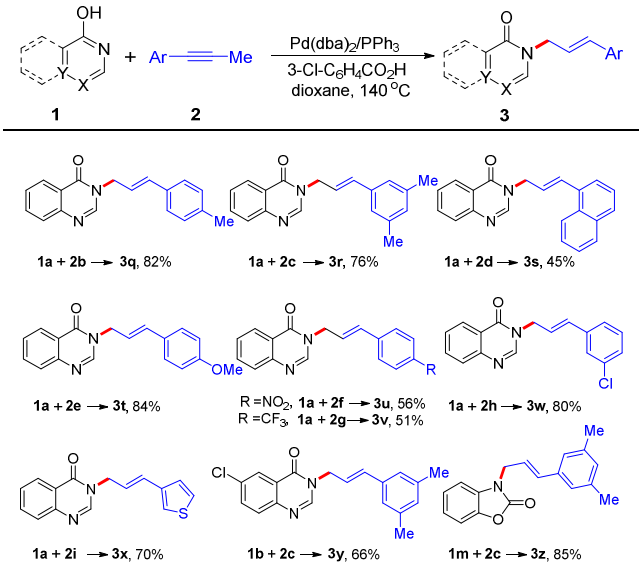
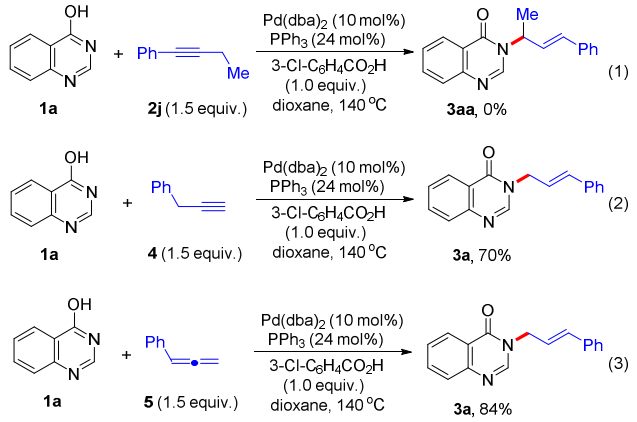
can also react with **2a** to afford the allylic products but with relatively lower yields (Table 2, **3d-3e**). The applicability of this protocol was further extended to other tautomerizable heteroarenes. Gratifyingly, *N*-cinnamylation of a variety of heteroarenes proceeded well with good chemo-, regio-, and stereoselectivities. Six-membered *N*-heterocycles such as pyrimidine (**3f**), and pyridines (**3g-3j**) all reacted well with excellent yields under the optimized conditions. However, for the isoquinolinone (**3k**) or phthalazinone (**3l**), relatively lower yield was afforded. Moreover, five-membered tautomerizable heteroarenes such as benzoxazolinone (**3m-3o**) and benzothiazolinone (**3p**) can also be used as the partner to react with the alkyne **2a**, affording the allylic amidation products.

Table 3 Substrate scope of alkynes[a]



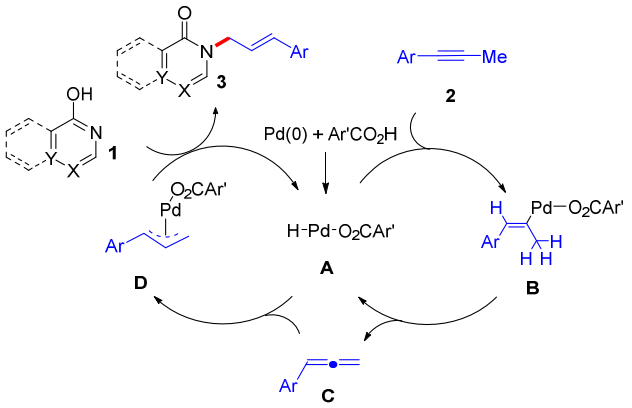
[a] Reaction conditions: **1** (0.3 mmol), **2** (0.45 mmol), 3-Cl-$C_6H_4CO_2H$ (0.3 mmol), $Pd(dba)_2$ (10 mol %), and PPh_3 (24 mol%) in dioxane (0.6 mL) at 140 °C for 12-24 h under N_2 atmosphere.



We then turned to examine the scope of the alkynes for this reaction and the results are summarized in Table 3. Different aromatic substituted internal alkynes were subjected to the allylic amidation reaction. The reactions worked well over different aryl substituents. All of the alkynes were coupled with **1** to give the corresponding linear allylic products in high chemo- and stereoselectivities (**3q-3z**). With 1-naphth substituted alkynes as the substrate, relatively lower yield was achieved (**3s**). 3-(Prop-1-yn-1-yl)thiophene **2i** bearing a heterocycle group can also be used as the partner to react with **1a**, affording the desired allylic product **3x** in 70% yield. However, when the internal alkyne but-1-yn-1-ylbenzene **2j** was employed, no reaction ensued, which may be due to the large steric hindrance (eqn (1)). This reflects the limitation of alkynes in the current method.

Furthermore, terminal alkyne **4** and phenylallene **5** can also work as the partner to react with 4-hydroxy quinazoline **1a**. Under the optimized reaction conditions, the reaction proceeded smoothly to afford amide-NH allylation product **3a** in 70% and 84% yield respectively (eqn (2) and (3)), suggesting that the alkyne is capable of undergoing C-H activation to allene through a *β*-H-elimination.

A reasonable mechanism for the direct allylic amidation can be envisioned (Scheme 2). The catalytic cycle is initiated by the oxidation addition of Pd(0) with 3-Cl-$C_6H_4CO_2H$ (Ar'CO_2H) to generate the hydropalladation intermediate **A**. The following insertion of alkyne **2** affords vinyl palladium intermediate **B**. The resulting vinyl palladium species **B** would produce allene intermediate **C** and the active catalyst **A** via *β*-elimination. Subsequently, reinsertion of hydropalladation intermediate **A** to allene **C** to form the *π*-allylpalladium intermediate **D**. Finally, the palladium-allyl species **D** can be captured by the tautomerizable heterocycle **1** to afford the desired allylic amidation product **3** and regenerated intermediate **A**.



Scheme 2. Plausible reaction mechanism

Conclusions

In summary, we have developed a palladium catalyzed allylic amidation of tautomerizable heterocycles with simple alkynes for the synthesis of *N*-allylation of a variety of heteroarenes in good yields with high chemo-, regio-, and stereoselectivities under mild conditions. This methodology was found to be advantageous in terms of substrate scope, functional group tolerance and with 100% atom economy.

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Experimental section

Materials and methods

Reactions and manipulations involving organometallic or moisture sensitive compounds were carried out under dry nitrogen and glassware heated under oven for two hours prior to use. ^{1}H and ^{13}C spectra were recorded on Bruker AVANCE III 500 MHz using $CDCl_3$ as solvent with TMS as internal standard. Anhydrous dioxane, THF, toluene were freshly distilled over Na and stored under nitrogen. Commercial reagents were used as received without further purification unless otherwise noticed. Melting points (m.p.) were recorded on a SGW Melting Point X-4. IR was recorded on the Thermo Nicolet 6700. HRMS were recorded on Agilent 6210 TOF LC/MS mass spectrometer. Column chromatography was carried out using silica gel (200-300 mesh).

General procedure for the synthesis of alkynes

The alkynes were synthesized according to the known method.[12] A mixture of $Pd(PPh_3)_2Cl_2$ (5 mol%), 1,4-bis(diphenylphosphanyl)butane (10 mol%), 4-iodobenzene (1.1 equiv.), 2-butynoic acid (1.0 equiv.), DBU (3.0 equiv.), and DMSO (1.0 M) was stirred at 80 °C for 12 h under N_2 atmosphere until the reaction was completed (monitored by TLC). The reaction mixture was poured into NH_4Cl (aq.) and extracted with DCM. The organic phase was dried over $MgSO_4$, and solvents were removed in vacuo to give a residue, which was purified by flash column chromatography to give the title compounds. The NMR spectral data of all the alkynes were in agreement with the published data.[12]

1-Methyl-4-(prop-1-yn-1-yl)benzene (2b). 75%, colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31 (d, *J* = 8.1 Hz, 2H), 7.11 (d, *J* = 7.9 Hz, 2H), 2.35 (s, 3H), 2.06 (s, 3H).

1,3-Dimethyl-5-(prop-1-yn-1-yl)benzene (2c). 62%, colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.06 (s, 2H), 6.94 (s, 1H), 2.30 (s, 6H), 2.07 (s, 3H).

1-(Prop-1-yn-1-yl)naphthalene (2d). 56%, colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.48 (d, *J* = 8.3 Hz, 1H), 7.90 (d, *J* = 8.1 Hz, 1H), 7.85 (d, *J* = 8.3 Hz, 1H), 7.73 (d, *J* = 7.1 Hz, 1H), 7.67-7.62 (m, 1H), 7.60-7.56 (m, 1H), 7.47 (dd, *J* = 8.1, 7.3 Hz, 1H), 2.29 (s, 3H).

1-Methoxy-4-(prop-1-yn-1-yl)benzene (2e). 86%, yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35 (d, *J* = 8.8 Hz, 2H), 6.83 (d, *J* = 8.8 Hz, 2H), 3.80 (s, 3H), 2.05 (s, 3H).

1-Nitro-4-(prop-1-yn-1-yl)benzene (2f). 70%, yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.16 (d, *J* = 8.9 Hz, 2H), 7.52 (d, *J* = 8.9 Hz, 2H), 2.11 (s, 3H).

1-(prop-1-yn-1-yl)-4-(trifluoromethyl)benzene (2g). 60%, colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.55 (d, *J* = 8.2 Hz, 2H),7.49 (d, *J* = 8.2 Hz, 2H), 2.09 (s, 3H).

3-(Prop-1-yn-1-yl)thiophene (2i). 68%, colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37-7.35 (m, 1H), 7.26-7.23 (m, 1H), 7.10-7.07 (m, 1H), 2.05 (s, 3H).

Typical procedure for the palladium catalyzed allylation of tautomerizable heterocycles with alkynes

To a mixture of tautomerizable heterocycle **1** (0.30 mmol, 1.0 equiv) and 1-phenyl-1-propyne derivatives **2** (0.45 mmol, 1.5 equiv), $Pd(dba)_2$ (0.03 mmol, 10 mol%), PPh_3 (0.072 mmol, 24 mol%) and *m*-chlorobenzoic acid (0.3 mmol) in a sealed tube was added 0.6 mL dry dioxane under N_2 atmosphere. The resulting mixture was then stirred at 140 °C until the reaction was completed (monitored by TLC). The solvent was then removed under vacuum and the residue was purified by chromatography on silica, eluting with EtOAc/petroleum ether 1:5 (v/v) to afford the desired product**.**

3-Cinnamylquinazolin-4(3*H*)-one (3a). 77 mg, 98%, pale yellow solid, m.p. 108-110°C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.40-8.33 (m, 1H), 8.11 (s, 1H), 7.78-7.71 (m, 2H), 7.52 (s, 1H), 7.39-7.35 (m, 2H), 7.31 (dd, *J* = 8.1, 6.6 Hz, 2H), 7.26 (d, *J* = 7.2 Hz, 1H), 6.66 (d, *J* = 15.9 Hz, 1H), 6.34 (dt, *J* = 15.8, 6.5 Hz, 1H), 4.79 (dd, *J* = 6.5, 1.3 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.8, 148.0, 146.1, 135.7, 134.4, 134.2, 128.6, 128.2, 127.4, 126.7, 126.5, 122.7, 122.1, 48.1. IR (neat) υ (cm^{-1}) 3022, 1677, 1606, 1476, 1367, 1292, 1258, 1167, 782. The recorded NMR spectral data was in agreement with the known compound.[5a]

6-Chloro-3-cinnamylquinazolin-4(3*H*)-one (3b). 78 mg, 88%, off white solid, m.p. 120-121°C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.28 (d, *J* = 1.1 Hz, 1H), 8.14 (s, 1H), 7.68 (d, *J* = 2.1 Hz, 2H), 7.39-7.34 (m, 2H), 7.31 (t, *J* = 7.4 Hz, 2H), 7.28-7.24 (m, 1H), 6.67 (d, *J* = 15.9 Hz, 1H), 6.33 (dt, *J* = 15.8, 6.5 Hz, 1H), 4.78 (dd, *J* = 6.5, 1.1 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.8, 146.4, 135.6, 134.8, 133.2, 128.9, 128.6, 128.3, 126.6, 126.1, 123.1, 122.3, 48.3. IR (neat) υ (cm^{-1}) 3060, 2939, 1671, 1605, 1469, 1359, 1320, 1257, 1158. The recorded NMR spectral data was in agreement with the known compound.[5a]

3-Cinnamyl-6-methylquinazolin-4(3*H*)-one (3c). 75 mg, 91%, white solid, m.p. 125-127°C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.14 (dd, *J* = 1.2, 0.7 Hz, 1H), 8.08 (s, 1H), 7.62 (dd, *J* = 19.8, 5.0 Hz, 2H), 7.41-7.36 (m, 2H), 7.35-7.30 (m, 2H), 7.27 (t, *J* = 3.6 Hz, 1H), 6.66 (d, *J* = 15.9 Hz, 1H), 6.35 (dt, *J* = 15.9, 6.4 Hz, 1H), 4.80 (dd, *J* = 6.4, 1.3 Hz, 2H), 2.52 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.0, 146.1, 145.5, 137.7, 135.8, 134.4, 128.7, 128.3, 127.3, 126.7, 126.3, 122.9, 121.9, 48.2, 21.4. IR (neat) υ (cm^{-1}) 3060, 2936, 1666, 1608, 1488, 1360, 1161, 970. HRMS (ESI) m/z calculated for $C_{18}H_{17}N_2O$ $[M+H]^+$ 277.1335, found 277.1334.

3-Cinnamyl-2-phenylquinazolin-4(3*H*)-one (3d). 76 mg, 75%, white solid, m.p. 105-106°C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.39 (d, *J* = 7.8 Hz, 1H), 7.81-7.76 (m, 2H), 7.59-7.52 (m, 6H), 7.31-7.26 (m, 4H), 7.26-7.22 (m, 1H), 6.28-6.14 (m, 2H), 4.77 (d, *J* = 5.6 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.1, 156.2, 147.2, 136.1, 135.3, 134.4, 133.5, 130.0, 128.6, 128.0, 127.5, 127.1, 126.8, 126.4, 123.2, 120.9, 47.9. IR (neat) υ (cm^{-1}) 3026, 2924, 2027, 2924, 1677, 1565, 1472, 1125. The recorded NMR spectral data was in agreement with the known compound.[5a]

3-Cinnamyl-2-methylquinazolin-4(3*H*)-one (3e). 63 mg, 76%, white solid, m.p. 127-128°C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.28 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.77-7.69 (m, 1H), 7.65 (d, *J* = 7.9 Hz, 1H), 7.48-7.42 (m, 1H), 7.37-7.32 (m, 2H), 7.28 (dd, *J* = 10.2, 4.7 Hz, 2H), 7.23 (d, *J* = 7.2 Hz, 1H), 6.53 (d, *J* = 16.0 Hz, 1H), 6.29 (dt, *J* = 16.0, 5.8 Hz, 1H), 4.94-4.85 (m, 2H), 2.68 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.8, 154.3, 147.1, 135.8, 134.3, 132.9, 126.8, 126.45, 126.43, 126.4, 122.6, 120.3, 45.9, 22.9. IR (neat) υ (cm^{-1}) 3054, 2925, 1673, 1602, 1472, 1397, 1339, 1301, 1245. The recorded NMR spectral data was in agreement with the known compound.[5a]

3-Cinnamylpyrimidin-4(3*H*)-one (3f). 50 mg, 78%, white solid, m.p. 138-140°C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.17 (s, 1H), 7.89 (d, *J* = 6.6 Hz, 1H), 7.38-7.35 (m, 2H), 7.33-7.29 (m, 2H), 7.28-7.25 (m, 1H), 6.63 (d, *J* = 15.9 Hz, 1H), 6.48 (dd, *J* = 6.6, 0.8 Hz, 1H), 6.29 (dt, *J* = 15.8, 6.6 Hz, 1H), 4.69 (dd, *J* = 6.6, 1.3 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.6, 153.2, 150.9, 135.5, 135.0, 131.9, 128.5, 128.4, 126.5, 122.0, 115.9, 48.3. IR (neat) υ (cm^{-1}) 3027, 1666, 1595, 1524, 1434, 1201, 1134. The recorded NMR spectral data was in agreement with the known compound.[5a]

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1-Cinnamylpyridin-2(1*H*)-one (3g). 55 mg, 86%, pale brown liquid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38-7.33 (m, 2H), 7.33-7.30 (m, 2H), 7.28 (dd, *J* = 8.7, 2.1 Hz, 2H), 7.23 (dt, *J* = 9.4, 4.1 Hz, 1H), 6.61-6.58 (m, 1H), 6.56 (d, *J* = 15.9 Hz, 1H), 6.29 (dt, J = 15.9, 6.5 Hz, 1H), 6.16 (td, *J* = 6.7, 1.3 Hz, 1H), 4.70 (dd, *J* = 6.5, 1.2 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.3, 139.4, 136.9, 135.8, 133.9, 128.4, 128.0, 126.4, 123.5, 120.8, 106.1, 50.5. IR (neat) υ (cm^{-1}) 3033, 1669, 1597, 1520, 1450, 1200. The recorded NMR spectral data was in agreement with the known compound.[5a]

1-Cinnamyl-3-methylpyridin-2(1*H*)-one (3h). 44 mg, 65%, pale brown liquid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40-7.37 (m, 2H), 7.32 (t, *J* = 7.5 Hz, 2H), 7.26 (s, 1H), 7.22 (d, *J* = 6.8 Hz, 2H), 6.60 (d, *J* = 15.8 Hz, 1H), 6.34 (dt, *J* = 15.9, 6.6 Hz, 1H), 6.13 (t, *J* = 6.7 Hz, 1H), 4.75 (dd, *J* = 6.5, 1.0 Hz, 2H), 2.19 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.0, 136.8, 136.2, 134.3, 134.0, 130.1, 128.6, 128.1, 126.6, 124.0, 106.0, 51.0, 17.4. IR (neat) υ (cm^{-1}) 3048, 2912, 1647, 1585, 1487, 1180. HRMS (ESI) m/z calculated for $C_{15}H_{16}NO$ $[M+H]^+$ 226.1226, found 226.1231.

1-Cinnamyl-4-methylpyridin-2(1*H*)-one (3i). 60 mg, 89%, pale brown liquid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40-7.35 (m, 2H), 7.34-7.29 (m, 2H), 7.26 (dd, *J* = 4.8, 3.6 Hz, 1H), 7.21 (d, *J* = 7.0 Hz, 1H), 6.57 (d, *J* = 15.9 Hz, 1H), 6.42 (s, 1H), 6.31 (dt, *J* = 15.9, 6.5 Hz, 1H), 6.04 (dd, *J* = 7.0, 1.8 Hz, 1H), 4.70 (dd, *J* = 6.4, 1.3 Hz, 2H), 2.19 (d, *J* = 0.6 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.4, 151.1, 136.1, 135.8, 133.8, 128.6, 128.0, 126.5, 123.9, 119.4, 108.7, 50.2, 21.2. IR (neat) υ (cm^{-1}) 3058, 3037, 2925, 1649, 1586, 1435, 1180. HRMS (ESI) m/z calculated for $C_{15}H_{16}NO$ $[M+H]^+$ 226.1226, found 226.1233.

1-Cinnamyl-5-methylpyridin-2(1*H*)-one (3j). 56 mg, 83%, yellow liquid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 (d, J = 7.2 Hz, 2H), 7.31 (dd, *J* =8.2, 6.8 Hz, 2H), 7.26 (d, *J* = 7.2 Hz, 1H), 7.20 (dd, *J* = 9.2, 2.5 Hz, 1H), 7.09 (d, *J* = 0.7 Hz, 1H), 6.61-6.55 (m, 2H), 6.31 (dt, *J* = 15.9, 6.5Hz, 1H), 4.70 (dd, *J* = 6.5, 1.3 Hz, 2H), 2.07 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.74, 142.13, 136.04, 134.32, 133.79, 128.58, 128.02, 126.54, 123.87, 120.60, 115.26, 50.55, 17.07. IR (neat) υ (cm^{-1}) 3029, 1660, 1580, 1514, 1424, 1154. The recorded NMR spectral data was in agreement with the known compound.[5b]

2-Cinnamylisoquinolin-1(2*H*)-one (3k). 41 mg, 52%, yellow solid, m.p. 78-81°C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.51-8.46 (m, 1H), 7.66 (ddd, *J* = 8.2, 5.5, 1.3 Hz, 1H), 7.56-7.49 (m, 2H), 7.39 (dd, *J* = 5.2, 3.5 Hz, 2H), 7.33-7.30 (m, 2H), 7.26 (ddd, *J* = 12.0, 4.9, 3.1 Hz, 1H), 7.14 (d, *J* = 7.4 Hz, 1H), 6.62 (d, *J* = 15.9 Hz, 1H), 6.54 (d, *J* = 7.3 Hz, 1H), 6.37 (dt, *J* = 15.9, 6.4 Hz, 1H), 4.82 (dd, *J* = 6.4, 1.4 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.0, 137.0, 136.2, 133.6, 132.2, 131.0, 128.6, 128.0, 126.9, 126.5, 126.3, 125.9, 124.1, 106.4, 50.3. IR (neat) υ (cm^{-1}) 3060, 2926, 1646, 1597, 1366, 1290, 1179, 1079. HRMS (ESI) m/z calculated for $C_{18}H_{16}NO$ $[M+H]^+$ 262.1226, found 262.1219.

2-Cinnamylphthalazin-1(2*H*)-one (3l). 43 mg, 55%, white solid, m.p. 64-65°C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.47 (dd, *J* = 7.5, 1.1 Hz, 1H), 8.20 (s, 1H), 7.84-7.76 (m, 2H), 7.72-7.69 (m, 1H), 7.41-7.37 (m, 2H), 7.30 (dd, *J* = 10.3, 4.8 Hz, 2H), 7.23 (ddd, *J* = 7.3, 3.7, 1.1 Hz, 1H), 6.72 (d, *J* = 15.9 Hz, 1H), 6.47 (dt, *J* = 15.8, 6.6 Hz, 1H), 5.02 (dd, *J* = 6.6, 1.2 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.2, 138.0, 136.5, 133.7, 133.1, 131.7, 129.7, 128.5, 128.0, 127.7, 126.7, 126.5, 126.0, 123.7, 53.2. IR (neat) υ (cm^{-1}) 3055, 3022, 2933, 1643, 1589, 1494, 1448, 1327, 1290. The recorded NMR spectral data was in agreement with the known compound.[5a]

3-Cinnamylbenzo[*d*]oxazol-2(3*H*)-one (3m). 67 mg, 90%, light brown solid, m.p. 100-102□. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40-7.37 (m, 2H), 7.36-7.32 (m, 2H), 7.29 (dt, *J* = 4.2, 1.6 Hz, 1H), 7.26-7.22 (m, 1H), 7.19-7.12 (m, 2H), 7.06-7.03 (m, 1H), 6.71 (d, *J* = 15.9 Hz, 1H), 6.27 (dt, *J* = 15.9, 6.2 Hz, 1H), 4.64 (dd, *J* = 6.2, 1.5 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.3, 142.67, 135.7, 134.1, 128.61, 128.2, 126.5, 123.8, 122.5, 121.7, 110.0, 108.9, 44.3. IR (neat) υ (cm^{-1}) 3027, 2922, 1747, 1616, 1484, 1349, 1237, 1150. The recorded NMR spectral data was in agreement with the known compound.[5a]

5-Chloro-3-cinnamylbenzo[d]oxazol-2(3*H*)-one (3n). 75 mg, 88%, white solid, m.p. 92-94°C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39 (d, *J* = 7.2 Hz, 2H), 7.34 (t, *J* = 7.3 Hz, 2H), 7.29 (s, 1H), 7.14 (d, *J* = 8.5 Hz, 1H), 7.10 (dd, *J* = 8.5, 2.0 Hz, 1H), 7.03 (d, *J* = 1.9 Hz, 1H), 6.70 (d, *J* = 15.9 Hz, 1H), 6.23 (dt, *J* = 15.9, 6.3 Hz, 1H), 4.59 (dd, *J* = 6.3, 1.4 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.1, 141.0, 135.5, 134.4, 131.8, 129.3, 128.6, 128.3, 126.5, 122.3, 121.0, 110.8, 109.2, 44.4. IR (neat) υ (cm^{-1}) 3033, 1778, 1607, 1486, 1340, 1254, 1057. HRMS (ESI) m/z calculated for $C_{18}H_{16}ClNNaO_2$ $[M+Na]^+$ 308.0449, found 308.0446.

3-Cinnamyl-5-fluorobenzo[d]oxazol-2(3*H*)-one (3o). 60 mg, 75%, white solid, m.p. 95-96°C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40-7.37 (m, 2H), 7.34 (t, *J* = 7.4 Hz, 2H), 7.31-7.27 (m, 1H), 7.16 (dd, *J* = 8.7, 4.2 Hz, 1H), 6.87-6.77 (m, 2H), 6.71 (d, *J* = 15.9 Hz, 1H), 6.24 (dt, *J* = 15.9, 6.3 Hz, 1H), 4.61 (dd, *J* = 6.3, 1.4 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.5 (d, *J* = 240.0 Hz), 154.7, 138.6, 135.6, 134.7, 131.7 (d, *J* = 12.5 Hz), 128.8, 128.5, 126.7, 121,2, 110.6 (d, *J* = 10.0 Hz), 108.7 (d, *J* = 23.8 Hz), 97.6 (d, *J* = 30.0 Hz), 44.7. IR (neat) υ (cm^{-1}) 3062, 1775, 1624, 1489, 1384, 1344, 1253, 1174, 1083. HRMS (ESI) m/z calculated for $C_{18}H_{16}FNNaO_2$ $[M+Na]^+$ 292.0744, found 292.0732.

3-Cinnamylbenzo[*d*]thiazol-2(3*H*)-one (3p). 60 mg, 75%, pale yellow solid, m.p. 46-47°C. ^{1}H NMR (500 MHz, $CDCl_3$) *δ* 7.46 (dd, *J* = 7.8, 1.2 Hz, 1H), 7.38-7.25 (m, 6H), 7.21-7.13 (m, 2H), 6.65 (d, *J* = 15.9 Hz, 1H), 6.26 (dt, *J* = 15.9, 6.0 Hz, 1H), 4.76 (dd, *J* = 6.0, 1.6 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.8, 137.0, 136.0, 133.5, 128.7, 128.1, 126.6, 126.4, 123.3, 122.7, 122.1, 111.16, 44.6. IR (neat) υ (cm^{-1}) 3054, 3023, 2921, 1648, 1590, 1470, 1327, 1181. The recorded NMR spectral data was in agreement with the known compound.[5a]

3-(3-(p-Tolyl)allyl)quinazolin-4(3*H*)-one (3q). 68 mg, 82%, pale yellow solid, m.p. 127-128°C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.34 (d, *J* = 7.9 Hz, 1H), 8.16 (s, 1H), 7.75 (q, *J* = 7.9 Hz, 2H), 7.51 (t, *J* = 6.4 Hz, 1H), 7.26 (d, *J* = 7.9 Hz, 2H), 7.11 (d, *J* = 7.8 Hz, 2H), 6.64 (d, *J* = 15.8 Hz, 1H), 6.29 (dt, *J* = 15.7, 6.5 Hz, 1H), 4.77 (d, *J* = 6.4 Hz, 2H), 2.32 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.8, 147.8, 146.3, 138.1, 134.4, 134.2, 132.9, 129.2, 127.2, 126.7, 126.4, 122.0, 121.5, 48.2, 21.1. IR (neat) υ (cm^{-1}) 3017, 2937, 1679, 1610, 1472, 1365, 1252, 1159. The recorded NMR spectral data was in agreement with the known compound.[5b]

3-(3-(3,5-Dimethylphenyl)allyl)quinazolin-4(3*H*)-one (3r). 66 mg, 76%, white solid, m.p. 127-129°C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.35 (d, *J* = 8.1 Hz, 1H), 8.15 (s, 1H), 7.81-7.66 (m, 2H), 7.52 (d, *J* = 8.0 Hz, 1H), 7.00 (s, 2H), 6.90 (s, 1H), 6.61 (d, *J* = 15.8 Hz, 1H), 6.33 (dt, *J* = 15.8, 6.5 Hz, 1H), 4.78 (d, *J* = 6.5 Hz, 2H), 2.28 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.8, 147.8, 146.3, 138.0, 135.6, 134.7, 134.3, 129.9, 127.3, 126.7, 124.4, 122.2, 122.0, 48.2, 21.1. IR (neat) υ (cm^{-1}) 3011, 2916, 1665, 1610, 1473, 1370, 1160. HRMS (ESI) m/z calculated for $C_{19}H_{18}N_2O$ $[M+H]^+$ 291.1492, found 291.1491.

3-(3-(Naphthalen-1-yl)allyl)quinazolin-4(3*H*)-one (3s). 42 mg, 45%, pale brown solid, m.p. 119-121°C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.41-8.37 (m, 1H), 8.28 (s, 1H), 8.08 (d, *J* = 8.3 Hz, 1H), 7.88-7.84 (m, 1H), 7.82-7.77 (m, 3H), 7.61-7.48 (m, 5H), 7.45 (d, *J* = 7.8 Hz, 1H), 6.39 (dt, *J* = 15.5, 6.5 Hz, 1H), 4.94 (dd, *J* = 6.5, 1.3 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.9, 147.8, 146.4, 134.4, 133.5, 132.1, 131.0, 128.6, 127.5, 127.3, 126.9, 126.3, 125.9, 125.5, 124.3, 123.5, 122.1, 48.5. IR (neat) υ (cm^{-1}) 3008, 2926, 1667, 1612, 1516, 1477, 1378, 1248, 1120. The recorded NMR spectral data was in agreement with the known compound.[5b]

3-(3-(4-Methoxyphenyl)allyl)quinazolin-4(3*H*)-one (3t). 72 mg, 82%, white solid, m.p. 122-124°C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.34 (dd, *J* = 8.0, 1.0 Hz, 1H), 8.14 (s, 1H), 7.82-7.69 (m, 2H), 7.54-7.50 (m, 1H), 7.31 (d, *J* = 8.7 Hz, 2H), 6.84 (d, *J* = 8.8 Hz, 2H), 6.63

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(d, *J* = 15.8 Hz, 1H), 6.20 (dt, *J* = 15.8, 6.6 Hz, 1H), 4.77 (dd, *J* = 6.6, 1.3 Hz, 2H), 3.80 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.9, 159.7, 148.0, 146.3, 134.3, 134.1, 128.5, 127.9, 127.4, 127.3, 126.8, 122.1, 120.4, 114.0, 55.2, 48.3. IR (neat) υ (cm^{-1}) 3002, 2924, 1666, 1602, 1512, 1243, 1030, 768. The recorded NMR spectral data was in agreement with the known compound.[5b]

3-(3-(4-Nitrophenyl)allyl)quinazolin-4(3*H*)-one (3u). 52 mg, 56%, yellow solid, m.p. 170-172°C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.35 (dd, *J* = 8.0, 1.2 Hz, 1H), 8.20-8.15 (m, 2H), 8.11 (s, 1H), 7.83-7.72 (m, 2H), 7.55 (ddd, *J* = 8.2, 7.2, 1.3 Hz, 1H), 7.51 (d, *J* = 8.8 Hz, 2H), 6.69 (d, *J* = 16.0 Hz, 1H), 6.54 (dt, *J* = 15.9, 6.1 Hz, 1H), 4.85 (dd, *J* = 6.1, 1.3 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.9, 148.1, 147.4, 146.0, 142.1, 134.5, 131.9, 127.8, 127.6, 127.2, 126.8, 124.0, 122.1, 48.0. IR (neat) υ (cm^{-1}) 2941, 1675, 1612, 1513, 1347, 1109. HRMS (ESI) m/z calculated for $C_{17}H_{13}N_3NaO_3$ $[M+Na]^+$ 330.0849, found 330.0845.

3-(3-(4-(Trifluoromethyl)phenyl)allyl)quinazolin-4(3*H*)-one (3v). 51 mg, 51%, pale yellow solid, m.p.123-125°C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.36 (dd, *J* = 8.0, 1.2 Hz, 1H), 8.17 (s, 1H), 7.83-7.75 (m, 2H), 7.58 (d, *J* = 8.2 Hz, 3H), 7.48 (d, *J* = 8.2 Hz, 2H), 6.69 (d, *J* = 15.9 Hz, 1H), 6.46 (dt, *J* = 15.9, 6.3 Hz, 1H), 4.84 (dd, *J* = 6.3, 1.1 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.9, 147.9, 146.3, 139.2, 134.5, 132.9, 130.0, 127.6, 127.3, 126.8, 126.7, 125.7, 125.5, 122.1, 48.1. IR (neat) υ (cm^{-1}) 2951, 1655, 1611, 1487, 1371, 1121. The recorded NMR spectral data was in agreement with the known compound.[5b]

3-(3-(3-Chlorophenyl)allyl)quinazolin-4(3*H*)-one (3w). 71 mg, 80%, white solid, m.p. 131-133°C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.35 (dd, *J* = 8.0, 1.2 Hz, 1H), 8.13 (s, 1H), 7.81-7.73 (m, 2H), 7.56-7.52 (m, 1H), 7.36 (s, 1H), 7.23 (s, 3H), 6.60 (d, *J* = 15.9 Hz, 1H), 6.37 (dt, *J* = 15.9, 6.3 Hz, 1H), 4.80 (dd, *J* = 6.3, 1.2 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.8, 148.0, 146.1, 137.6, 134.6, 134.4, 133.0, 129.8, 128.2, 127.5, 127.4, 126.8, 126.6, 124.8, 124.4, 122.1, 48.1. IR (neat) υ (cm^{-1}) 3048, 2940, 1670, 1611, 1473, 1362, 1159, 771. HRMS (ESI) m/z calculated for $C_{17}H_{13}ClN_2NaO$ $[M+Na]^+$ 319.0609, found 319.0605.

3-(3-(Thiophen-3-yl)allyl)quinazolin-4(3*H*)-one (3x). 56 mg, 70%, light yellow solid, m.p. 104-106°C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.35 (dd, *J* = 8.0, 0.9 Hz, 1H), 8.15 (s, 1H), 7.80-7.74 (m, 2H), 7.55-7.52 (m, 1H), 7.28-7.27 (m, 1H), 7.21-7.19 (m, 2H), 6.70 (d, *J* = 15.8 Hz, 1H), 6.20 (dt, *J* = 15.8, 6.5 Hz, 1H), 4.77 (dd, *J* = 6.5, 1.2 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.9, 147.9, 146.3, 138.4, 134.4, 128.7, 127.4, 127.3, 126.8, 126.4, 124.9, 123.4, 122.5 122.1, 48.2. IR (neat) υ (cm^{-1}) 3102, 2924, 1686, 1606, 1470, 1359, 1161, 768. HRMS (ESI) m/z calculated for $C_{15}H_{12}N_2NaOS$ $[M+Na]^+$ 291.0563, found 291.0574.

6-Chloro-3-(3-(3,5-dimethylphenyl)allyl)quinazolin-4(3*H*)-one (3y). 64 mg, 66%, white solid, m.p. 117-119°C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.30 (dd, *J* = 2.0, 0.6 Hz, 1H), 8.13 (s, 1H), 7.73-7.65 (m, 2H), 7.00 (s, 2H), 6.91 (s, 1H), 6.62 (d, *J* = 15.8 Hz, 1H), 6.31 (dt, *J* = 15.8, 6.6 Hz, 1H), 4.77 (dd, *J* = 6.6, 1.2 Hz, 2H), 2.29 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.8, 146.4, 138.1, 135.5, 135.1, 134.7, 133.2, 130.0, 129.0, 126.1, 124.5, 123.1, 121.9, 48.4, 21.2. IR (neat) υ (cm^{-1}) 2922, 1673, 1605, 1469, 1361, 1252. HRMS (ESI) m/z calculated for $C_{19}H_{18}ClN_2O$ $[M+H]^+$ 325.1101, found 325.1102.

3-(3-(3,5-Dimethylphenyl)allyl)benzo[d]oxazol-2(3*H*)-one (3z). 71 mg, 85%, white solid, m.p. 91-92°C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.24 (dd, *J* = 7.7, 1.0 Hz, 1H), 7.15 (dqd, *J* = 15.3, 7.7, 1.3 Hz, 2H), 7.09-7.04 (m, 1H), 7.02 (s, 2H), 6.94 (s, 1H), 6.66 (d, *J* = 15.9 Hz, 1H), 6.25 (dt, *J* = 15.8, 6.3 Hz, 1H), 4.63 (dd, *J* = 6.3, 1.4 Hz, 2H), 2.32 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.3, 142.6, 138.1, 135.6, 134.3, 129.9, 124.4, 123.8, 122.4, 121.2, 109.9, 108.9, 44.4, 21.1. IR (neat) υ (cm^{-1}) 2915, 1757, 1467, 1369, 1238, 1021. HRMS (ESI) m/z calculated for $C_{18}H_{18}NO_2$ $[M+H]^+$ 280.1332, found 280.1342.

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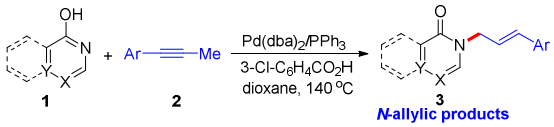

***N*-allylic products**
linear and *E*-selectivity
100% atom economy
up to 98% yield

A palladium-catalyzed allylic amidation of tautomerizable heterocycles was developed in high selectivity with 100% atom economy.