EurJOC
European Journal of Organic Chemistry

Chemistry Europe
European Chemical Societies Publishing

Accepted Article

Title: Copper(I)/Bpy-catalyzed C-2-H benzylation of quinazolin-4(3H)-ones with N-tosylhydrazones

Authors: Fei Li, Xiao-Juan Gu, Chang-E Zeng, Xia Li, Bo Liu, and Guoli Huang

To be cited as: *Eur. J. Org. Chem.* 10.1002/ejoc.202000244

Link to VoR: https://doi.org/10.1002/ejoc.202000244

WILEY-VCH

FULL PAPER WILEY-VCH

Copper(I)/Bpy-catalyzed C-2-H benzylation of quinazolin-4(3*H*)-ones with *N*-tosylhydrazones

Fei Li,[a] Xiao-Juan Gu,[a] Chang-E Zeng,[a] Xia Li,[b] Bo Liu,[a] and Guo-Li Huang*[a]

[a] Dr. G.-L. Huang
School of Chemistry and Chemical Engineering
Yunnan Normal University
Kunming 650500, China
E-mail: hgli2005@126.com
[b] X. Li
Department of Library
Yunnan Normal University
Kunming 650500, China

Supporting information for this article is given via a link at the end of the document.

Abstract: A general and efficient copper-catalyzed C-H benzylation reaction of quinazolin-4(3*H*)-ones with *N*-tosylhydrazones is reported. The formation of new C(sp^3)-C(sp^2) bonds through cross-coupling occurres at the electron-poor C-2 position of quinazolin-4(3*H*)-one, and represents an exceedingly practical method to afford 2-benzylated quinazolin-4(3*H*)-ones in moderate to good yields under mild reaction conditions. A possible reaction mechanism for this transformation was proposed. This catalytic transformation has the potential to be an important synthetic applications for the late-stage functionalization of advanced synthetic intermediates.

Introduction

N-tosylhydrazones, which can be easily prepared from carbonyl compounds, have been widely used as the synthetic intermediates of diazo compounds or carbenes through the transition metal-catalyzed or metal-free reactions.[1] *N*-tosylhydrazone chemistry has widespread application in the construction of different types of C-X (X = C,[2] N,[3] O,[4] S,[5] P,[6] Sn,[7] and B[8]) bonds in organic synthesis and various useful transformations. Recently, direct methods of Csp^3-Csp^2 bonds formation by copper-catalyzed benzylation of arenes and heteroarenes with *N*-tosylhydrazones have been developed as a versatile and efficient technique for C-H bond functionalization.[2b, 2f, 9]

2-Alkylquinazolin-4-ones are a highly significant class of heteroaromatic compounds that are widely found in bioactive molecules, natural products, synthetic drugs, pharmaceuticals, and agrochemicals (Figure 1).[10] Thus, the development of straightforward access to functionalized quinazolin-4-ones has become an attractive area of research. The reported literatures mainly consist of five types of strategies: a) ring-closure condensation of anthranilic acid derivatives or C-H amidation,[11] b) palladium-catalyzed carbonylation of 2-halogenoaniline derivatives or *N*-arylamidines,[12] c) copper-catalyzed coupling reactions of 2-halogenobenzoic acid derivatives with amidines,[13] d) rearrangement or cyclization of other heterocycles,[14] e) the Minisci reaction, radical approaches have been recently developed as a strategy to assemble late-stage alkylation of quinazolinones using carboxylic acids,[15] boronic acids[16], aldehydes,[17] and alkyltrifluoroborates[18] as alkyl radical precursors. Recently, Zhang and colleagues developed $PhI(O_2CCF_3)_2$/NaN_3-promoted cross-dehydrogenative coupling

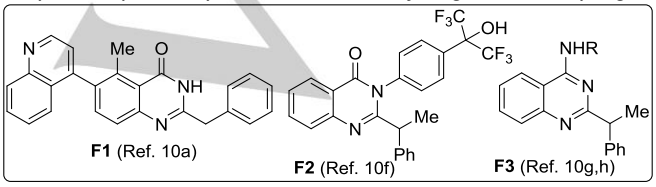


Figure 1. Selected representatives of bioactive 2-alkylquinazolin-4-ones.

of quinazolin-4-one with nonactivated alkanes to carry out 2-alkylation of quinazolinones.[19] Unfortunately, some of these methods suffer from expensive metal catalyst, stoichiometric amount of oxidant or photocatalyst, highly toxic carbon monoxide, excess of the radical precursor or high temperature.

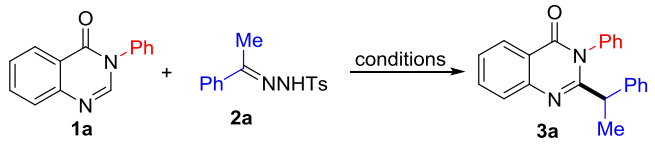
Thus, development of efficient and economical functionalization methodologies of 2-alkylquinazolinones is required and C-2 alkylation remains a challenging goal for organic chemists. Directive late-stage modificated functionalization of quinazolinones is of great value and significance for rapid synthesis of selective 2-alkylquinazolin-4-ones under mild reaction conditions.[20] Following our effort in developing efficient Cu-catalyzated C-H bond functionalization strategies,[21] herein we decided to investigate the direct benzylation of quinazolin-4-ones with *N*-tosylhydrazones.

Results and Discussion

To optimize the reaction conditions, we evaluated various reaction conditions for the direct benzylation of 3-phenylquinazolin-4(3*H*)-one (**1a**) with acetophenone-derived *N*-tosylhydrazone (**2a**). To our delight, the reaction of **1a** with **2a** in the presence of catalytic amount of CuI (10 mol%) with *t*-BuOLi (2.5 equiv.) as the base in toluene for 6 hours under nitrogen atmosphere afforded the C-2 benzylated product **3a** selectively in 26% yield (Table 1, entry 1). To our surprise, the moderate yield (42% of **3a**) was achieved with 0.1 equiv. 1,10-phenanthroline (Phen) as the ligand (Table 1, entry 2). However, the various forms of Cu-containing catalysts, such as CuCl, CuBr, CuCN, $Cu(acac)_2$, $CuCl_2$, and $Cu(OAc)_2$ exhibited a very low catalytic activity, and validated the crucial role of CuI in the reaction (Table 1, entries 3-8). Next, we examined the various ligands, such as Bpy, PPh_3, DMEDA, TED, TMEDA, L-proline, benzil, and Dbm (Table 1, entries 9-13). Pleasingly, the use of Bpy as a ligand significantly improved the catalytic efficiency and gave a good yield (72%). The influence of different base and solvent were also conducted. Various base substituents failed the reaction, using *t*-BuONa, *t*-BuOK, and Cs_2CO_3 as the base gave very poor yield, (Table 1, entries 14-16), K_3PO_4 and K_2CO_3 provided moderate yield (entries 17, 18), while KOH gave a slightly lower yield (entry 19), necessitating the usage of *t*-BuOLi. In addition, switching the solvent to xylene gave comparative yield (Table 1, entry 20), other solvent such as dioxane, THF, DMF, and DCE were found to show less activity. Gratifyingly, when 0.2 equiv. of CuI and Bpy were used, the yield of the C-2 benzylated product in this reaction could noteworthy increase from 72 to 90% (Table 1, entry 21).

With the optimized reaction conditions in hand, we investigated the scope of this copper(I)/bpy-catalyzed C-2 benzylation of quinazolin-4(3*H*)-ones with *N*-tosylhydrazones. First of all, as shown in Table 2, the variation in the quinazolin-

Table 1. Optimization of reaction conditions.[a]

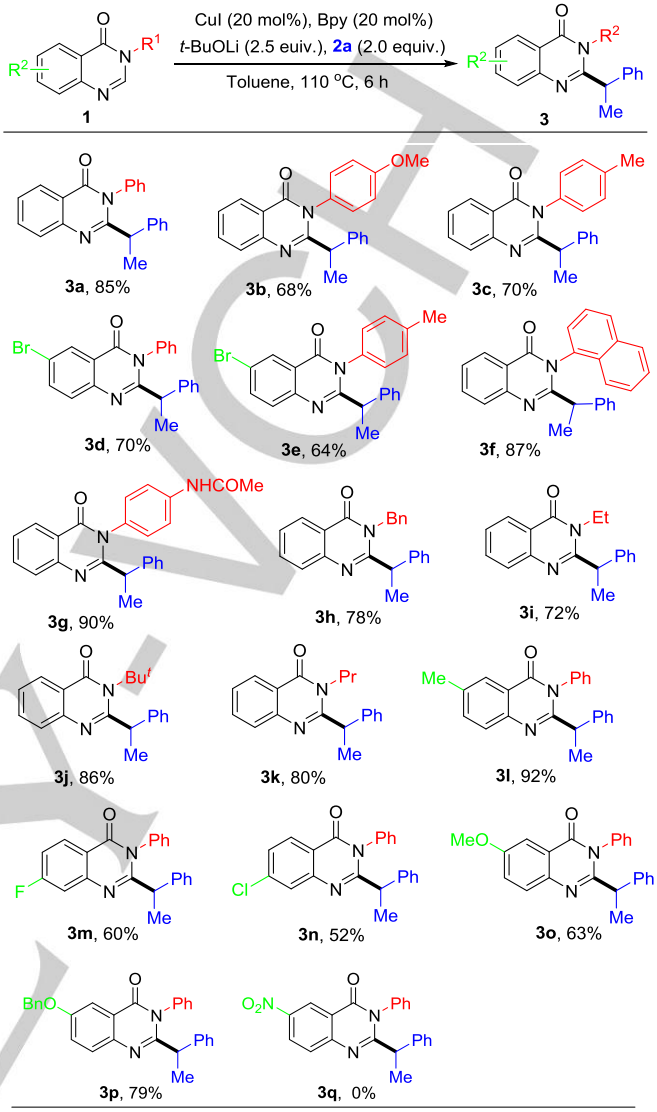


Entry	Cat.	Ligand[b]	Base	Yield[c]
1	CuI	-	*t*-BuOLi	26
2	CuI	Phen	*t*-BuOLi	42
3	CuCl	Phen	*t*-BuOLi	trace
4	CuBr	Phen	*t*-BuOLi	25
5	CuCN	Phen	*t*-BuOLi	10
6	$Cu(acac)_2$	Phen	*t*-BuOLi	7
7	$CuCl_2$	Phen	*t*-BuOLi	trace
8	$Cu(OAc)_2$	Phen	*t*-BuOLi	trace
9	CuI	BPy	*t*-BuOLi	72
10	CuI	PPh_3	*t*-BuOLi	32
11	CuI	DMEDA	*t*-BuOLi	13
12	CuI	TED	*t*-BuOLi	trace
13	CuI	TMEDA	*t*-BuOLi	10
14	CuI	BPy	*t*-BuONa	15
15	CuI	BPy	*t*-BuOK	5
16	CuI	BPy	Cs_2CO_3	trace
17	CuI	BPy	K_3PO_4	31
18	CuI	BPy	K_2CO_3	44
19	CuI	BPy	KOH	26
20[d]	CuI	BPy	*t*-BuOLi	71
21[e]	CuI	BPy	*t*-BuOLi	90

[a] Reaction conditions: **1a** (0.20 mmol), **2a** (0.40 mmol), catalyst (10 mol%), ligand (10 mol%), and base (2.50 mmol) in 2.0 mL of solvent at 110 °C for 6 h.
[b] Phen = 1,10-phenanthroline; Bpy = 2,2'-bipyridine; DMEDA = *N,N'*-dimethylethylene diamine; TED = triethylene diamine; TMEDA = *N,N,N,N'*-tetramethylethylene diamine.
[c] Unless specified, the yield was estimated by ^{1}H NMR.
[d] The solvent was xylene.
[e] The catalyst loading and ligand were 20 mol%

4(3*H*)-ones part of the reaction was studied. We were pleased to observe that a wide range of *N*3-arylated quinazolin-4(3*H*)-ones undergo the reaction successfully, affording the desired products (**3a-c**, **3f**, **3g**) in good to excellent yields. It is noteworthy that compound **3f** was obtained in 87% yield from the large steric effects reaction. To further investigate the functional group tolerance, alkylated substituted substrates on *N*3-positions of quinazolin-4-ones all reacted smoothly to afford the corresponding C-2 benzylated compounds (**3h-k**) in good yields. Additionally, quinazolin-4(3*H*)-ones bearing either electron-donating or electron-withdrawing groups, such as F, Cl, Br, Me, OMe, and OBn, at C6- or C7-positions of the aromatic nucleus were well-tolerated in the reaction system to give the corresponding products (**3d**, **3e**, **3l-p**) in moderate to good yields and provided the possibility for further functionalization of the

Table 2. Substrate scope of quinazolin-4(3*H*)-ones.[a,b]



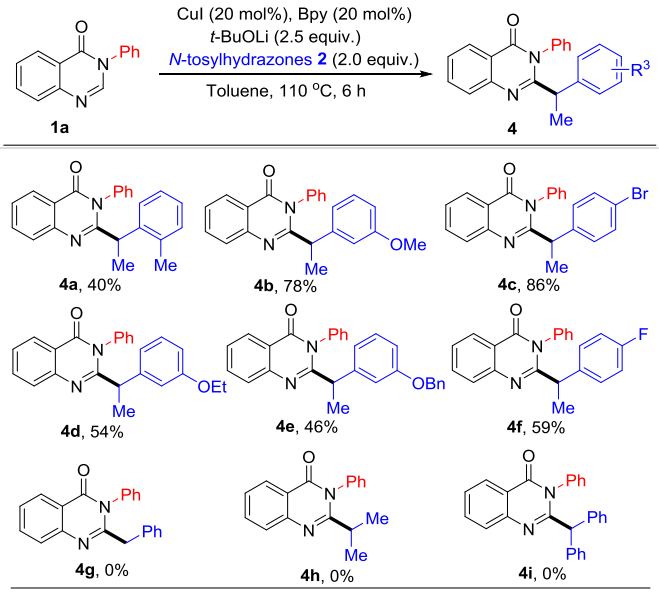
[a] Reaction conditions: **1** (0.20 mmol), **2a** (0.40 mmol), CuI (20 mol%), Bpy (20 mol%), and *t*-BuOLi (0.50 mmol) in tulene (3.0 mL) at 110 °C for 6 h.
[b] Isolated yield.

substituted quinazolin-4(3*H*)-ones. However, the corresponding product **3q** was not detected when the benzylation of **1q** bearing NO_2 group with **2a** was carried out.

After studying the scope of quinazolin-4(3*H*)-ones, we turned our attention toward direct C-2 benzylation of 3-phenylquinazolin-4(3*H*)-one **1a** to investigate the scope of substituted *N*-tosylhydrazones. As shown in Table 3, the reaction was found to work well with a wide range of *N*-tosylhydrazones, affording the desired products (**4a-f**) in moderate to good yields. *N*-tosylhydrazones with electron-donating alkyl and alkoxy groups were well-tolerated, as evidenced by the formation of **4a**, **4b**, **4d**, and **4e** in good yields, ranging from 40% to 78%. Halogen-substituted *N*-tosylhydrazones were also found compatible for this reaction (**4c** and **4f**). Conversely, we found that the *N*-tosylhydrazones derived from benzaldehyde (**4g**), acetone (**4h**) and benzophenone (**4i**) were not tolerated by this transformation.

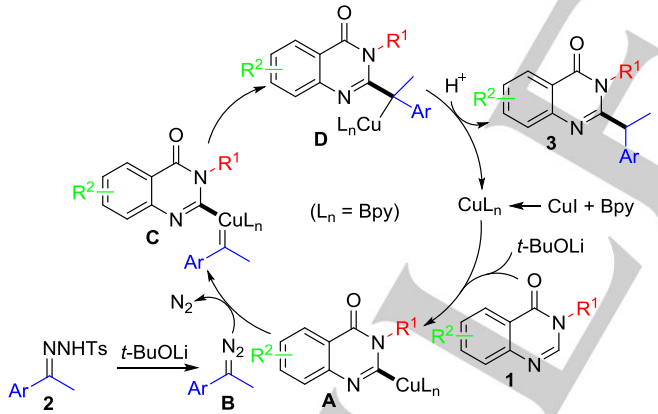
On the basis of the experimental results and previously reported copper(I)-catalyzed C-H benzylation,[1,2b,9] a proposed reaction mechanism is described in Scheme 1. Firstly, the reaction was initiated by deprotonation-metallation of the C-H bond at C-2 position of quinazolin-4(3*H*)-one **1** in presence of

Table 3. Substrate scope of *N*-tosylhydrazones.[a,b]



[a] Reaction conditions: **1** (0.20 mmol), **2** (0.40 mmol), CuI (20 mol%), Bpy (20 mol%), and *t*-BuOLi (0.50 mmol) in tulene (3.0 mL) at 110 °C for 6 h.
[b] Isolated yield.

Bpy-stabilized copper(I) complex (CuL_n) and base (*t*-BuOLi) to generate the intermediate **A**. Sequently **A** possibly would undergo the diazo compound **B** derived from the *N*-tosylhydrazone **2** by *t*-BuOLi, to form a Cu(I) carbene species **C**. The latter was then converted into **D** by 1,2-migration insertion of alkenyl group to the carbenic carbon. Finally by protonation liberated the benzylated product **3** along with regeneration of the copper catalyst.



Scheme 1. Proposed reaction mechanism.

Conclusion

In summary, an efficient copper(I)-catalyzed system for the direct benzylation of quinazolin-4(3*H*)-ones with *N*-tosylhydrazones was developed. A variety of C-2-benzylated quinazolin-4(3*H*)-one derivatives have been successfully synthesized in moderate to good yields. This reaction provides an exceedingly effective, practical, and economical strategy to access C-H bond functionalization of biologically important quinazolin-4-ones by challenging the secondary benzyl group. This methodology features a highly efficient synthetic process, wide substrate scope, and high functional-group tolerance. This discovery can be easily used for the modular synthesis of bioactive quinazolin-4-one libraries.

Experimental Section

General Information: All chemicals were purchased from the Wencai New Material Technology and Merck in high purity and were used directly without any purification. Solvents were freshly distilled prior to use. All reactions were carried out under nitrogen atmosphere unless noted. ^{1}H NMR and ^{13}C NMR spectra were recorded with a Bruker Avance III 500 MHz spectrometer in $CDCl_3$ or DMSO-*d6* solution. High resolution mass (HRMS) spectra were measured with a VG Auto Spec-3000 spectrometer. Melting points (mp) were determined with a digital electrothermal apparatus without further correction. TLC analyses were performed on commercial glass plates bearing a 0.25 mm layer of Merck silica gel 60 F254. Silica gel (200-300 mesh) was used for column chromatography.

General experimental procedure for benzylation of quinazolin-4(3*H*)-ones with *N*-tosylhydrazones: In a 10 mL round bottom flask quinazolin-4(3*H*)-ones **1** (0.20 mmol), *N*-tosylhydrazones **2** (0.40 mmol, 2.0 equiv), CuI (7.8 mg, 0.04 mmol, 0.2 equiv.), Bpy (6.2 mg, 0.04 mmol, 0.2 equiv.), and *t*-BuOLi (40.0 mg, 2.5 equiv.) in toluene (3.0 mL) were taken. The reaction mixture was stirred at 110 °C for 6 h. The progress of the reaction was monitored by TLC. After the consumption of the starting materials, the reaction mixture was allowed to cool, and subsequently extracted with CH_2Cl_2 (2×10 mL). The combined organic extracts were dried over anhydrous $MgSO_4$. Concentration of the material in vacuo followed by flash chromatography on silica gel column afforded a pure benzylated product.

3-Phenyl-2-(1-phenylethyl)quinazolin-4(3*H*)-one (3a): White solid, yield: 85%, m.p. 128 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.16 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.62-7.56 (m, 2H), 7.53-7.48 (m, 3H), 7.47-7.39 (m, 4H), 7.32 (dd, *J* = 16.3, 7.7 Hz, 3H), 7.25 (t, *J* = 7.6 Hz, 1H), 4.20 (s, 1H), 1.58 (s, 3H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ = 159.9, 145.7, 141.1, 139.4, 133.7, 129.3, 128.7, 127.5, 127.1, 126.1, 126.1, 125.1, 125.1, 122.7, 63.4, 43.1, 12.0 ppm. HRMS (ESI): Calcd for $C_{22}H_{19}N_2O$ [M+H$^+$]: 327.1492, Found 327.1495.

3-(4-Methoxyphenyl)-2-(1-phenylethyl)quinazolin-4(3*H*)-one (3b): White solid, yield: 68%, m.p. 162 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.13 (dd, *J* = 7.8, 1.5 Hz, 1H), 7.56 (dd, *J* = 8.3, 1.2 Hz, 2H), 7.49 (td, *J* = 7.7, 1.6 Hz, 1H), 7.40 (dd, *J* = 10.5, 8.2 Hz, 4H), 7.33-7.27 (m, 2H), 7.24 (td, *J* = 7.7, 1.1 Hz, 1H), 6.99-6.94 (m, 2H), 4.17 (s, 1H), 3.82 (s, 3H), 1.56 (s, 3H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ = 160.1, 158.5, 145.7, 141.2, 133.6, 132.2, 128.6, 128.5, 127.4, 126.7, 126.2, 126.1, 125.0, 122.7, 114.6, 63.7, 55.5, 43.0, 12.1 ppm. HRMS (ESI): Calcd for $C_{23}H_{21}N_2O_2$ [M+H$^+$]: 357.1598, Found 357.1603.

2-(1-Phenylethyl)-3-(*p*-tolyl)quinazolin-4(3*H*)-one (3c): White solid, yield: 70%, m.p. 162-164 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.14 (d, *J* = 7.8 Hz, 1H), 7.57 (d, *J* = 7.7 Hz, 2H), 7.52-7.47 (m, 1H), 7.42-7.35 (m, 4H), 7.30 (dd, *J* = 15.0, 7.6 Hz, 2H), 7.26-7.21 (m, 3H), 4.18 (s, 1H), 2.37 (s, 3H), 1.56 (s, 3H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ = 160.0, 145.7, 141.2, 137.0, 136.8, 133.6, 129.9, 128.6, 127.4, 126.2, 126.1, 125.1, 125.0, 122.7, 63.5, 43.0, 21.1, 12.1 ppm. HRMS (ESI): Calcd for $C_{23}H_{21}N_2O$ [M+H$^+$]: 341.1648, Found 341.1645.

6-Bromo-3-phenyl-2-(1-phenylethyl)quinazolin-4(3*H*)-one (3d): White solid, yield: 70%, m.p. 128-129 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.28 (d, *J* = 2.3 Hz, 1H), 7.60 (dd, *J* = 8.4, 2.3 Hz, 1H), 7.56 (d, *J* = 7.7 Hz, 2H), 7.49-7.40 (m, 6H), 7.33 (dd, *J* = 13.9, 7.0 Hz, 2H), 7.18 (d, *J* = 8.4 Hz, 1H), 4.19 (s, 1H), 1.58 (s, 3H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ = 158.7, 144.7, 140.7, 139.1, 136.6, 131.4, 129.4, 128.7, 127.9, 127.7, 127.3, 126.1, 125.0, 124.3, 118.2, 63.5, 43.6, 12.0 ppm. HRMS (ESI): Calcd for $C_{22}H_{18}BrN_2O$ [M+H$^+$]: 405.0597, Found 405.0603.

6-Bromo-2-(1-phenylethyl)-3-(*p*-tolyl)quinazolin-4(3*H*)-one (3e): White solid, yield: 64%. m.p. 172-174 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.25 (d, *J* = 2.3 Hz, 1H), 7.59 (dd, *J* = 8.4, 2.4 Hz, 1H), 7.54 (dd, *J* = 8.3, 1.0 Hz, 2H), 7.42-7.39 (m, 2H), 7.35-7.30 (m, 3H), 7.25 (d, *J* = 8.4 Hz, 2H), 7.17 (d, *J* = 8.4 Hz, 1H), 4.17 (s, 1H), 2.37 (s, 3H), 1.57 (s, 3H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ = 158.7, 144.8, 140.8, 137.3, 136.5, 136.4, 131.4, 130.0, 128.7, 127.9, 127.6, 126.1, 125.0, 124.3, 118.2, 63.6, 43.5, 21.1, 12.1 ppm. HRMS (ESI): Calcd for $C_{23}H_{20}BrN_2O$ [M+H$^+$]: 419.0754, Found 419.0760.

3-(Naphthalen-1-yl)-2-(1-phenylethyl)quinazolin-4(3*H*)-one (3f): Colorless oil, yield: 87%. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.30 (d, *J* = 2.2 Hz, 1H), 7.94 (d, *J* = 7.7 Hz, 3H), 7.66 (dd, *J* = 8.4, 2.3 Hz, 1H), 7.59-7.53 (m, 4H), 7.49-7.46 (m,

3H), 7.34 (t, *J* = 7.6 Hz, 2H), 7.27-7.25 (m, 2H), 4.26 (s, 1H), 1.76 (s, 3H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ = 159.4, 145.4, 140.8, 136.7, 135.7, 134.9, 131.5, 129.6, 129.2, 128.8, 128.6, 128.2, 127.5, 127.5, 126.8, 126.2, 125.8, 125.5, 124.1, 122.3, 118.3, 64.2, 43.8, 12.8 ppm. HRMS (ESI): Calcd for $C_{26}H_{21}N_2O$ [M+H$^+$]: 377.1648, Found 377.1650.

***N*-(4-(4-oxo-2-(1-phenylethyl)quinazolin-3(4*H*)-yl)phenyl)acetamide (3g):** Yellow solid, yield: 90%. m.p. 169-171 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.16 (dd, *J* = 7.8, 1.4 Hz, 1H), 8.03 (d, *J* = 8.7 Hz, 2H), 7.68 (d, *J* = 8.7 Hz, 2H), 7.61 (d, *J* = 8.0 Hz, 2H), 7.53 (td, *J* = 7.8, 1.5 Hz, 1H), 7.44 (t, *J* = 7.7 Hz, 2H), 7.35 (t, *J* = 7.4 Hz, 1H), 7.30 (d, *J* = 7.9 Hz, 1H), 7.28-7.25 (m, 1H), 4.17 (s, 1H), 2.60 (s, 3H), 1.53 (s, 3H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ = 196.9, 160.0, 145.4, 143.6, 140.7, 134.9, 134.1, 129.3, 128.8, 128.8, 127.7, 126.1, 126.0, 125.2, 123.8, 122.3, 62.9, 43.5, 26.6, 11.7 ppm. HRMS (ESI): Calcd for $C_{24}H_{22}N_3O_2$ [M+H$^+$]: 384.1707, Found 384.1702.

3-Benzyl-2-(1-phenylethyl)quinazolin-4(3*H*)-one (3h): Colorless oil, yield: 78%. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.10 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.46-7.41 (m, 1H), 7.40-7.31 (m, 7H), 7.29-7.26 (m, 1H), 7.24 (dt, *J* = 5.9, 2.1 Hz, 2H), 7.22-7.17 (m, 2H), 5.49 (d, *J* = 14.3 Hz, 1H), 4.18 (d, *J* = 14.3 Hz, 1H), 3.89 (s, 1H), 0.89 (s, 3H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ = 160.1, 145.6, 141.3, 136.2, 133.4, 129.4, 128.7, 128.4, 128.2, 127.2, 126.2, 126.0, 124.9, 122.2, 61.9, 48.7, 43.0, 12.1 ppm. HRMS (ESI): Calcd for $C_{23}H_{21}N_2O$ [M+H$^+$]: 341.1648, Found 341.1652.

3-Ethyl-2-(1-phenylethyl)quinazolin-4(3*H*)-one (3i): Colorless oil, yield: 72%. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.05 (d, *J* = 7.8 Hz, 1H), 7.55 (d, *J* = 7.9 Hz, 2H), 7.45-7.39 (m, 3H), 7.32 (t, *J* = 7.3 Hz, 1H), 7.20 (dd, *J* = 15.1, 7.9 Hz, 2H), 4.16 (dq, *J* = 14.5, 7.3 Hz, 1H), 3.89 (s, 1H), 3.26 (dq, *J* = 14.2, 7.2 Hz, 1H), 1.37 (s, 3H), 1.26 (t, *J* = 7.2 Hz, 3H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ = 160.0, 145.5, 141.6, 133.2, 128.6, 128.1, 127.3, 126.1, 126.0, 124.9, 122.4, 61.8, 42.4, 39.8, 12.6, 12.2 ppm. HRMS (ESI): Calcd for $C_{18}H_{19}N_2O$ [M+H$^+$]: 279.1492, Found 279.1490.

3-(*Tert*-butyl)-2-(1-phenylethyl)quinazolin-4(3*H*)-one (3j): White solid, yield: 86%, m.p. 120-122 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.96 (dd, *J* = 7.8, 1.2 Hz, 1H), 7.53 (d, *J* = 7.2 Hz, 2H), 7.39 (dt, *J* = 9.4, 4.5 Hz, 3H), 7.31 (t, *J* = 7.3 Hz, 1H), 7.12 (m, 2H), 4.00 (s, 1H), 1.54 (s, 9H), 1.47 (s, 3H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ = 161.5, 144.7, 141.3, 133.0, 128.6, 128.0, 127.2, 125.9, 124.4, 124.3, 123.6, 60.4, 57.3, 42.5, 28.2, 12.4 ppm. HRMS (ESI): Calcd for $C_{20}H_{23}N_2O$ [M+H$^+$]: 307.1805, Found 307.1809.

2-(1-Phenylethyl)-3-propylquinazolin-4(3*H*)-one (3k): Colorless oil, yield: 80%. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.05 (dd, *J* = 7.7, 1.2 Hz, 1H), 7.54 (d, *J* = 7.2 Hz, 2H), 7.46-7.39 (m, 3H), 7.32 (t, *J* = 7.3 Hz, 1H), 7.23-7.17 (m, 2H), 4.01 (m, 1H), 3.89 (s, 1H), 3.18 (m, 1H), 1.67 (m, 2H), 1.37 (s, 3H), 1.00 (t, *J* = 7.4 Hz, 3H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ = 160.2, 145.5, 141.6, 133.2, 128.6, 128.2, 127.3, 126.1, 126.0, 124.9, 122.4, 62.3, 47.0, 42. 4, 20.9, 12.2, 11.6 ppm. HRMS (ESI): Calcd for $C_{19}H_{21}N_2O$ [M+H$^+$]: 293.1648, Found 293.1652.

6-Methyl-3-phenyl-2-(1-phenylethyl)quinazolin-4(3*H*)-one (3l): Yellow oil, yield: 92%. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.96 (d, *J* = 1.2 Hz, 1H), 7.61-7.55 (m, 2H), 7.49 (d, *J* = 8.2 Hz, 2H), 7.47-7.38 (m, 4H), 7.31 (q, *J* = 7.6 Hz, 3H), 7.19 (d, *J* = 8.0 Hz, 1H), 4.17 (s, 1H), 2.39 (s, 3H), 1.55 (s, 3H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ = 160.1, 142.9, 141.3, 139.5, 134.9, 134.6, 129.2, 128.8, 128.6, 127.4, 127.0, 126.2,126.1, 125.1, 122.2, 63.4, 42.6, 21.0, 11.9 ppm. HRMS (ESI): Calcd for $C_{23}H_{21}N_2O$ [M+H$^+$]: 341.1648, Found 341.1654.

7-Fluoro-3-phenyl-2-(1-phenylethyl)quinazolin-4(3*H*)-one (3m): Colorless oil, yield: 60%. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.15 (dd, *J* = 8.7, 6.3 Hz, 1H), 7.55 (d, *J* = 7.3 Hz, 2H), 7.49-7.39 (m, 6H), 7.36-7.29 (m, 2H), 6.99 (m, 1H), 6.94 (m, 1H), 4.20 (s, 1H), 1.60 (s, 3H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ = 167.1, 165.1, 159.3, 148.1 (J_{CF} = 12.1 Hz), 140.6, 139.1, 131.2 (J_{CF} = 10.5 Hz), 129.3, 128.7, 127.7, 127.3, 126.1, 125.1, 119.1, 113.0, 112.8 (J_{CF} = 12.6 Hz), 112.7, 63.8, 44.0, 12.1 ppm. HRMS (ESI): Calcd for $C_{22}H_{18}FN_2O$ [M+H$^+$]: 345.1398, Found 345.1404.

7-Chloro-3-phenyl-2-(1-phenylethyl)quinazolin-4(3*H*)-one (3n): White solid, yield: 52%, m.p. 120-122 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.07 (d, *J* = 8.4 Hz, 1H), 7.55 (d, *J* = 7.3 Hz, 2H), 7.45 (m, 6H), 7.35-7.29 (m, 3H), 7.22 (dd, *J* = 8.4, 2.0 Hz, 1H), 4.20 (s, 1H), 1.60 (s, 3H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ = 159.3, 147.0, 140.5, 139.8, 139.1, 130.0, 129.4, 128.7, 127.7, 127.3, 126.1, 125.6, 125.1, 121.2, 63.7, 44.0, 12.1 ppm. HRMS (ESI): Calcd for $C_{22}H_{18}ClN_2O$ [M+H$^+$]: 361.1102, Found 361.1105.

6-Methoxy-3-phenyl-2-(1-phenylethyl)quinazolin-4(3*H*)-one (3o): Colorless oil, yield: 63%. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.65 (d, *J* = 2.9 Hz, 1H), 7.57 (d, *J* = 8.1 Hz, 2H), 7.49 (d, *J* = 7.8 Hz, 2H), 7.44 (t, *J* = 7.3 Hz, 2H), 7.41 (t, *J* = 7.4 Hz, 2H), 7.31 (td, *J* = 7.5, 0.9 Hz, 2H), 7.23 (d, *J* = 8.6 Hz, 1H), 7.08 (dd, *J* = 8.7, 3.0 Hz, 1H), 4.16 (s, 1H), 3.86 (s, 3H), 1.54 (s, 3H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ = 160.0, 157.1, 141.3, 139.4, 138.4, 129.3, 128.6, 127.4, 127.3, 127.1, 126.1, 125.1, 123.2, 121.5, 111.1, 63.5, 55.7, 42.0, 11.7 ppm. HRMS (ESI): $C_{23}H_{21}N_2O_2$ [M+H$^+$]: 357.1598, Found 357.1592.

6-(Benzyloxy)-3-phenyl-2-(1-phenylethyl)quinazolin-4(3*H*)-one (3p): Yellow oil, yield: 79%. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.75 (d, *J* = 2.9 Hz, 1H), 7.57 (d, *J* = 7.9 Hz, 2H), 7.50-7.45 (m, 6H), 7.43-7.39 (m, 4H), 7.34-7.30 (m, 3H), 7.24 (d, *J* = 8.7 Hz, 1H), 7.16-7.13 (m, 1H), 5.11 (s, 2H), 4.16 (s, 1H), 1.55 (s, 3H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ = 159.9, 156.2, 141.2, 139.4, 138.7, 136.6, 129.4, 129.3, 129.2, 128.7, 128.4, 128.2, 127.7, 127.5, 127.4, 127.1, 126.1, 125.1, 123.2, 122.2, 112.2, 70.5, 63.5, 42.1, 11.8 ppm. HRMS (ESI): $C_{29}H_{25}N_2O_2$ [M+H$^+$]: 433.1911, Found 433.1919.

3-Phenyl-2-(1-(*o*-tolyl)ethyl)quinazolin-4(3*H*)-one (4a): Colorless oil, yield: 40%. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.14 (d, *J* = 7.7 Hz, 1H), 7.57-7.51 (m, 3H), 7.50-7.45 (m, 4H), 7.42 (t, *J* = 7.4 Hz, 1H), 7.25 (d, *J* = 7.9 Hz, 1H), 7.19 (t, *J* = 9.6 Hz, 2H), 7.11 (d, *J* = 6.7 Hz, 1H), 4.47 (s, 1H), 2.16 (s, 3H), 1.48 (s, 3H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ = 160.5, 145.7, 139.7, 139.6, 135.7, 133.7, 130.7, 129.8, 128.7, 128.2, 128.2, 127.8, 127.4, 126.2, 126.1, 125.1, 122.5, 62.9, 44.3, 19.2, 13.6 ppm. HRMS (ESI): $C_{23}H_{21}N_2O$ [M+H$^+$]: 341.1648, Found 341.1652.

2-(1-(3-Methoxyphenyl)ethyl)-3-phenylquinazolin-4(3*H*)-one (4b): Colorless oil, yield: 78%. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.15 (d, *J* = 7.8 Hz, 1H), 7.53-7.47 (m, 3H), 7.44 (t, *J* = 7.8 Hz, 2H), 7.31 (dd, *J* = 17.0, 8.4 Hz, 3H), 7.24 (d, *J* = 7.6 Hz, 1H), 7.18-7.12 (m, 2H), 6.86 (d, *J* = 8.2 Hz, 1H), 4.18 (s, 1H), 3.85 (s, 3H), 1.55 (s, 3H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ = 160.0, 145.6, 142.8, 139.4, 133.7, 129.7, 129.3, 128.7, 127.1, 126.1, 125.1, 125.0, 122.6, 118.5, 112.5, 112.2, 63.4, 55.3, 43.0, 11.9 ppm. HRMS (ESI): $C_{23}H_{21}N_2O_2$ [M+H$^+$]: 357.1598, Found 357.1600.

2-(1-(4-Bromophenyl)ethyl)-3-phenylquinazolin-4(3*H*)-one (4c): White solid, yield: 86%. m.p. 144-146 °C .^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.15 (d, *J* = 8.1 Hz, 1H), 7.54-7.48 (m, 3H), 7.44 (m, 6H), 7.30 (t, *J* = 6.8 Hz, 1H), 7.28-7.25 (s, 1H), 4.13 (s, 1H), 1.54 (s, 3H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ = 159.8, 145.2, 140.2, 139.3, 133.8, 131.8 129.3, 128.7, 127.9, 127.2, 126.1, 125.3, 125.0, 122.6, 121.5, 63.4, 42.6, 11.7 ppm. HRMS (ESI): $C_{22}H_{18}BrN_2O$ [M+H$^+$]: 405.0597, Found 405.0607.

2-(1-(3-Ethoxyphenyl)ethyl)-3-phenylquinazolin-4(3*H*)-one (4d): Colorless oil, yield: 54%. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.15 (d, *J* = 7.8 Hz, 1H), 7.52-7.47 (m, 3H), 7.46-7.41 (m, 2H), 7.31 (dd, *J* = 17.4, 8.4 Hz, 3H), 7.24 (d, *J* = 7.7 Hz, 1H), 7.17-7.13 (m, 2H), 6.87-6.81 (m, 1H), 4.18 (s, 1H), 4.08 (q, *J* = 7.0 Hz, 2H), 1.55 (s, 3H), 1.44 (t, *J* = 7.0 Hz, 3H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ = 159.9, 159.3, 145.6, 142.8, 139.4, 133.7, 129.7, 129.3, 128.7, 127.1, 126.1, 125.1, 125.0, 122.6, 118.4, 112.9, 63.5, 63.4, 43.0, 14.9, 11.9 ppm. HRMS (ESI): $C_{24}H_{23}N_2O_2$ [M+H$^+$]: 371.1754, Found 371.1758.

2-(1-(3-(Benzyloxy)phenyl)ethyl)-3-phenylquinazolin-4(3*H*)-one (4e): Colorless oil, yield: 46%. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.14 (d, *J* = 7.8 Hz, 1H), 7.52-7.37 (m, 9H), 7.37-7.29 (m, 3H), 7.28-7.25 (m, 2H), 7.24-7.21 (m, 1H), 7.18 (d, *J* = 7.8 Hz, 1H), 6.93 (dd, *J* = 8.1, 2.4 Hz, 1H), 5.10 (s, 2H), 4.17 (s, 1H), 1.54 (s, 3H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ = 159.9, 159.1, 145.5, 142.8, 139.3, 136.8, 133.7, 129.7, 129.3, 128.7, 128.1, 127.6, 127.1, 126.1, 125.1, 125.1, 122.6, 118.7, 113.3, 113.2, 70.1, 63.4, 42.9, 11.9 ppm. HRMS (ESI): $C_{29}H_{25}N_2O_2$ [M+H$^+$]: 433.1911, Found 433.1918.

2-(1-(4-Fluorophenyl)ethyl)-3-phenylquinazolin-4(3*H*)-one (4f): Colorless oil, yield: 59%.^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.15 (d, *J* = 7.7 Hz, 1H), 7.56-7.50 (m, 3H), 7.50-7.43 (m, 4H), 7.32 (d, *J* = 6.9 Hz, 1H), 7.30-7.26 (m, 2H), 7.09 (t, *J* = 8.6 Hz, 2H), 4.15 (s, 1H), 1.55 (s, 3H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ = 163.1, 161.1, 159.9, 145.4, 139.3, 136.9, 133.8, 129.3, 128.7, 127.8 (J_{CF} = 8.1 Hz), 127.2, 126.1, 125.2 (J_{CF} = 6.2 Hz), 122.5, 115.5 (J_{CF} = 8.1 Hz) , 63.4, 42.5, 12.1 ppm. HRMS (ESI): $C_{22}H_{18}FN_2O$ [M+H$^+$]: 345.1398, Found 345.1405.

Acknowledgements

We are thankful for the Natural Science Foundation of China (21861043), the Basic Research Projects of Yunnan Province (2019FB016), and the Science Research Foundation Teacher Projects of Yunnan Education Department (2018JS145) for partial support of this work.

Disclosure statement

We confirm that none of the authors have any conflict of interest in the context of this article.

Supplementary information

Full experimental details, ^{1}H and ^{13}C NMR spectra can be found in the supplementary content section of this article's web page.

Keywords: Copper • Quinazolin-4(3*H*)-ones • Benzylation • C-H bond functionalization

[1] a) Z. Shao, H. Zhang, *Chem. Soc. Rev.* **2012**, *41*, 560-572; b) J. Barluenga, C. Valdés, *Angew. Chem. Int. Ed.* **2011**, *50*, 7486-7500.

[2] a) Q. Zhou, S. Li, Y. Zhang, J. Wang, *Angew. Chem. Int. Ed.* **2017**, *56*, 16013-16017; b) A. K. Jha, N. Jain, *Chem. Commun.* **2016**, *52*, 1831-1834; c) Z. Liu, H. Tan, L. Wang, T. Fu, Y. Xia, Y. Zhang, J. Wang, *Angew. Chem. Int. Ed.* **2015**, *54*, 3056-3060; d) S. Xu, G. Wu, F. Ye, X. Wang, H. Li, X. Zhao, Y. Zhang, J. Wang, *Angew. Chem. Int. Ed.* **2015**, *54*, 4669-4672; e) F. Ye, X. Ma, Q. Xiao, H. Li, Y. Zhang, J. Wang, *J. Am. Chem. Soc.* **2012**, *134*, 5742-5745; f) X. Zhao, G. Wu, Y. Zhang, J. Wang, *J. Am. Chem. Soc.* **2011**, *133*, 3296-3299.

[3] a) L. Ling, J. Cao, J. Hu, H. Zhang, *RSC Adv.* **2017**, *7*, 27974-27980; b) P. Xu, F.-L. Qi, F.-S. Han, Y.-H. Wang, *Chem. Asian J.* **2016**, *11*, 2030-2034; c) X. Zeng, G. Cheng, J. Shen, X. Cui, *Org. Lett.* **2013**, *15*, 3022-3025; d) J. Aziz, J.-D. Brion, A. Hamze, M. Alami, *Adv. Synth. Catal.* **2013**, *355*, 2417-2429.

[4] J. Barluenga, M. Tomás-Gamasa, F. Aznar, C. Valdés, *Angew. Chem. Int. Ed.* **2010**, *49*, 4993-4996.

[5] Q. Ding, B. Cao, J. Yuan, X. Liu, Y. Peng, *Org. Biomol. Chem.* **2011**, *9*, 748-751.

[6] Z.-S. Chen, Z.-Z. Zhou, H.-L. Hua, X.-H. Duan, J.-Y. Luo, J. Wang, P.-X. Zhou, Y.-M. Liang, *Tetrahedron* **2013**, *69*, 1065-1068.

[7] D. Qiu, S. Wang, H. Meng, S. Tang, Y. Zhang, J. Wang, *J. Org. Chem.* **2017**, *82*, 624-632.

[8] H. Li, L. Wang, Y. Zhang, J. Wang, *Angew. Chem. Int. Ed.* **2012**, *51*, 2943-2946.

[9] a) N. Salvanna, G. C. Reddy, B. R. Rao, B. Das, *RSC Adv.* **2013**, *3*, 20538-20544; b) M. Reddy Lonka, J. Zhang, T. Gogula, H. Zou, *Org. Biomol. Chem.* **2019**, *17*, 7455-7460.

[10] a) L. Hudson, J. Mui, S. Vázquez, D. M. Carvalho, E. Williams, C. Jones, A. N. Bullock, S. Hoelder, *J. Med. Chem.* **2018**, *61*, 7261-7272; b) R. FerrESIra de FrESItas, R. J. Harding, I. Franzoni, M. Ravichandran, M. K. Mann, H. Ouyang, M. Lautens, V. Santhakumar, C. H. Arrowsmith, M. Schapira, *J. Med. Chem.* **2018**, *61*, 4517-4527; c) V. Alagarsamy, K. Chitra, G. Saravanan, V. R. Solomon, M. T. Sulthana, B. Narendhar, *Eur. J. Med. Chem.* **2018**, *151*, 628-685; d) M. Badolato, F. Aiello, N. Neamati, *RSC Adv.* **2018**, *8*, 20894-20921; e) J. P. Michael, *Nat. Prod. Rep.* **2007**, *24*, 223-246. f) S. Kaneko, T. Watanabe, K. Oda, R. Mohan, E. J. SchwESIger, R. Martin, **2003**, WO 2003106435; g) T. C. Gahman, D. J. Thomas, H. Lang, M. E. Massari, **2008**, WO 2008157500; h) N. K. Lee, J. W. Lee, S. Lee, G.-J. Im, H. Y. Han, T. K. Kim, Y. H. Kim, W.-J. Kwak, S. W. Kim, J. Ha, K. E. Kim, J. K. Lee, C. Y. Yoo, D. Y. Lee, **2006**, WO 2006071095.

[11] a) N. Y. Kim, C.-H. Ch eon, *Tetrahedron Lett.* **2014**, *55*, 2340-2344; b) K. M. Shakhidoyatov, B. Z. Elmuradov, *Chem. Nat. Comd.* **2014**, *50*, 781-800; c) A. Patil, O. Patil, B. Patil, J. Surana, *Mini-Rev. Med. Chem.* **2011**, *11*, 633; d) K. Upadhyaya, R. K. Thakur, S. K. Shukla, R. P. Tripathi, *J. Org. Chem.* **2016**, *81*, 5046-5055; e) T. Kotipalli, V. Kavala, D. Janreddy, V. Bandi, C.-W. Kuo, C.-F. Yao, *Eur. J. Org. Chem.* **2016**, 1182-1193.

[12] a) J. E. R. Sadig, R. Foster, F. Wakenhut, M. C. Willis, *J. Org. Chem.* **2012**, *77*, 9473-9486; b) B. Ma, Y. Wang, J. Peng, Q. Zhu, *J. Org. Chem.* **2011**, *76*, 6362-6366; c) Z. Zheng, H. Alper, *Org. Lett.* **2008**, *10*, 829-832.

[13] X. Liu, H. Fu, Y. Jiang, Y. Zhao, *Angew. Chem. Int. Ed.* **2009**, *48*, 348-351.

[14] a) Y.-F. Wang, F.-L. Zhang, S. Chiba, *Org. Lett.* **2013**, *15*, 2842-2845; b) J. Wang, S. Zha, K. Chen, F. Zhang, C. Song, J. Zhu, *Org. Lett.* **2016**, *18*, 2062-2065.

[15] a) D. R. Sutherland, M. Veguillas, C. L. Oates, A.-L. Lee, *Org. Lett.* **2018**, *20*, 6863-6867; b) T. C. Sherwood, N. Li, A. N. Yazdani, T. G. M. Dhar, *J. Org. Chem.* **2018**, *83*, 3000-3012.

[16] a) L. Zhang, Z.-Q. Liu, *Org. Lett.* **2017**, *19*, 6594-6597; b) G.-X. Li, C. A. Morales-Rivera, Y. Wang, F. Gao, G. He, P. Liu, G. Chen, *Chem. Sci.* **2016**, *7*, 6407-6412.

[17] Á. Gutiérrez-Bonet, C. Remeur, J. K. Matsui, G. A. Molander, *J. Am. Chem. Soc.* **2017**, *139*, 12251-12258.

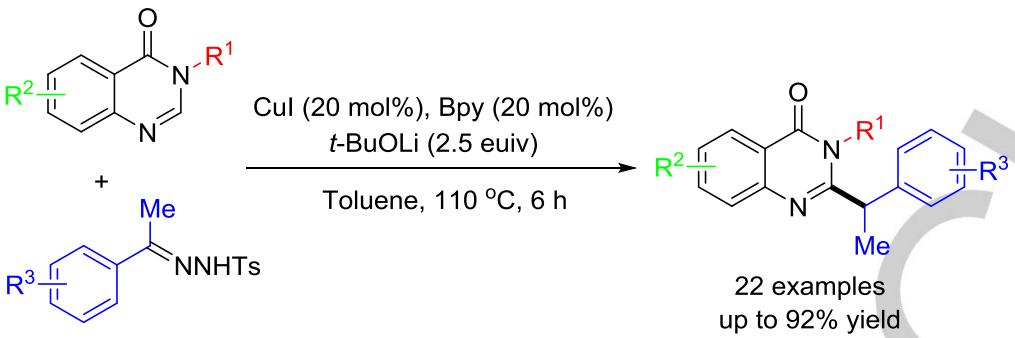
[18] J. K. Matsui, D. N. Primer, G. A. Molander, *Chem. Sci.* **2017**, *8*, 3512-3522.

[19] S. Mao, K. Luo, L. Wang, H.-Y. Zhao, A. Shergalis, M. Xin, N. Neamati, Y. Jin, S.-Q. Zhang, *Org. Lett.* **2019**, *21*, 2365-2368.

[20] a) T. Cernak, K. D. Dykstra, S. Tyagarajan, P. Vachal, S. W. Krska, *Chem. Soc. Rev.* **2016**, *45*, 546-576; b) J. Wencel-Delord, F. Glorius, *Nat. Chem.* **2013**, *5*, 369-375.

[21] a) G. Huang, H. Sun, X. Qiu, C. Jin, C. Lin, Y. Shen, J. Jiang, L. Wang, *Org. Lett.* **2011**, *13*, 5224-5227; b) Y. Ma, M. Na, Y. Gu, G. Huang, X. Li, Y. Chen, *Appl. Organometal. Chem.* **2015**, *29*, 165-169.

Copper(I)/Bpy-catalyzed C-2-H benzylation of quinazolin-4(3*H*)-ones with *N*-tosylhydrazones



The regioselective C-2-H benzylation of quinazolin-4(3*H*)-ones with *N*-tosylhydrazones in ligand dependent copper system was studied. Under the optimized conditions, an array of substituted quinazolin-4(3*H*)-ones could couple effectively with a wide variety of *N*-tosylhydrazones derived from aryl ketones toafford the alkylated products in moderate to good yields. This useful and scalable procedure promotes the construction of C(sp^2)-C(sp^3) bonds from quinazolin-4(3*H*)-ones and *N*-tosylhydrazones in a time-efficient strategy.