Direct functionalization of 2-phenylquinazoline

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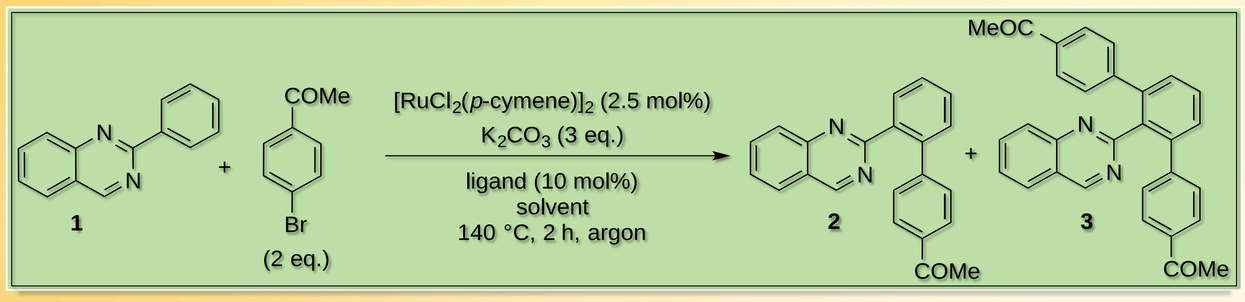
Introduction

Catalytic transformation of carbon–hydrogen (C–H) bonds has recently become one of the most promising and powerful methods for the construction of carbon–carbon (C–C) bond frameworks.[1] The idea of direct functionalization of C–H bonds is appealing, because it presents an elegant way to obtain desired products by shortening and simplifying reaction pathways.

Chelation-assisted transformation has become a common and effective method for selective functionalization of *ortho* C–H bonds.

For example, quinazoline and its derivatives are well known nitrogen heterocycles often found in many alkaloids and bioactive molecules.[2] Their synthesis present an important value in the pharmaceutical industry.[3]

Therefore, the method of C–H functionalization was carried out on 2-phenylquinazoline.



1 **2** **3**

Table 1: C–H activation of 2-phenylquinazoline in the presence of various Ru^{II}-catalytic systems.[a]

ligand				
example		conversion (%)[b]	mono (**2**) (%)	di (**3**) (%)
1	NaOAc	29	25	75
2	PPh_3	41	71	29
3	glycolic acid	50	40	60
4	1-naphthoic acid	69	14	86
5	1-phenyl-1-cyclopentanecarboxylic acid (PCCA)	96	7	93
6	pivalic acid	96	4	96
7	adamantane carboxylic acid	97	3	97

[a] Reaction conditions: **1** (0.5 mmol), 4-bromoacetophenone (1 mmol), $[RuCl_2(p\text{-cymene})]_2$ (0.0125 mmol), K_2CO_3 (1.5 mmol), NaOAc (1.5 mmol), solvent (2 mL), 140 °C, 2 h, argon. [b] Conversion of **1** and the ratio of products was determined by ^1H NMR.

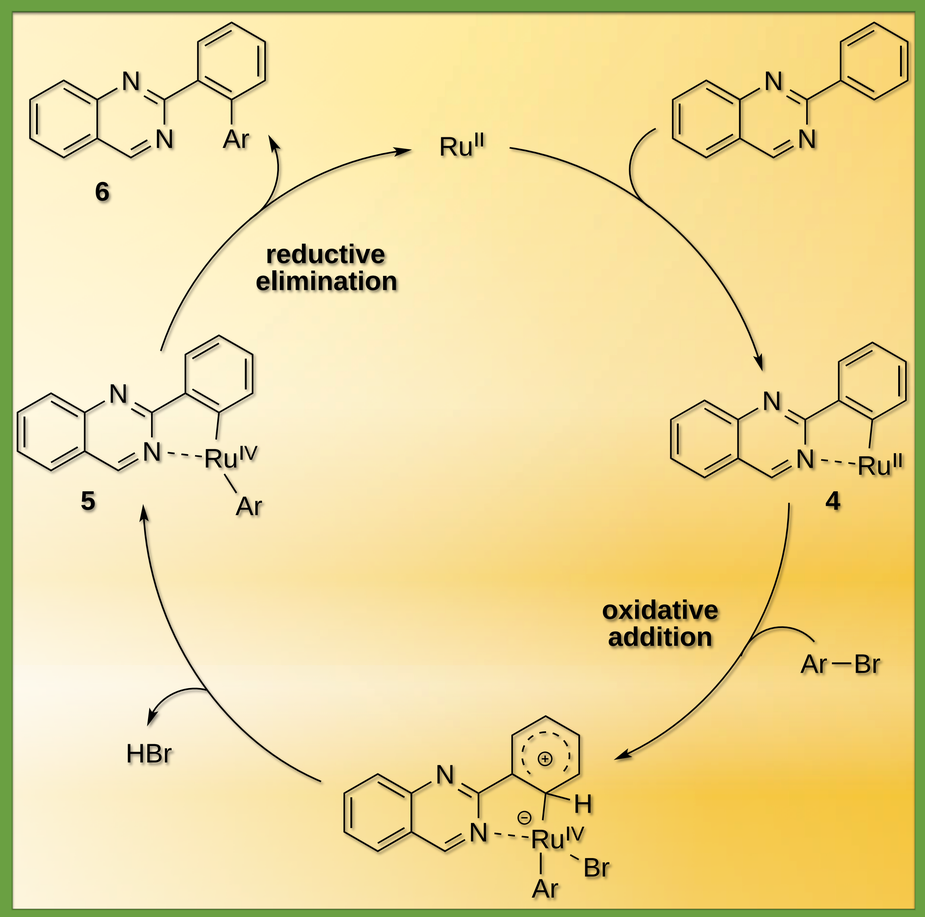
Table 2: C–H activation of 2-phenylquinazoline in different solvents.[a]

solvent				
example		conversion (%)[b]	mono (**2**) (%)	di (**3**) (%)
1	acetonitrile	38	50	50
2	toluene	67	38	62
3	dioxane	80	8	92
4	tetrahydrofuran	82	7	93
5	2-propanol	92	5	95

[a] Reaction conditions: **1** (0.5 mmol), 4-bromoacetophenone (1 mmol), $[RuCl_2(p\text{-cymene})]_2$ (0.0125 mmol), K_2CO_3 (1.5 mmol), NaOAc (1.5 mmol), solvent (2 mL), 140 °C, 2 h, argon. [b] Conversion of **1** and the ratio of products was determined by ^1H NMR.

Proposed mechanism of direct *ortho* arylation of 2-phenylquinazoline

The presumed reaction mechanism is defined as a catalytic cycle. The ruthenium(II) complex chelates on the nitrogen atom of the quinazoline derivative to form a stabile ruthenacycle **4** after which the oxidative addition of the corresponding aryl halide is followed. Elimination of HBr yields the arylated ruthenacycle **5** and the reductive elimination of ruthenium affords the desired product **6**.



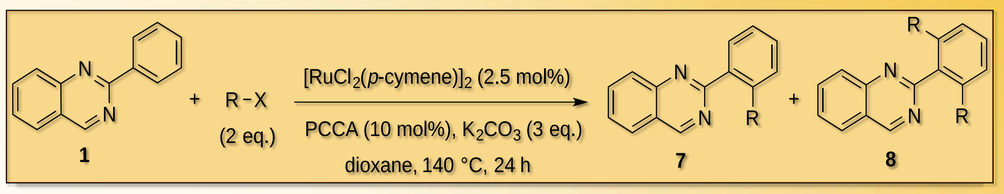
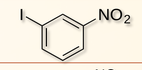
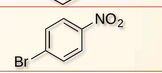
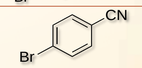
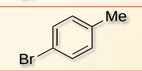
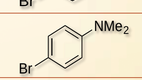
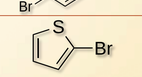
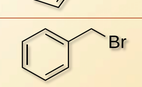


Table 3: C–H functionalization of 2-phenylquinazoline with selected proelectrophiles.[a]

R–X				
example		conversion (%)[b]	mono (**7**) (%)	di (**8**) (%)
1		17	50	50
2		29	50	50
3		94	10	90
4		96	7	93
5		96	9	91
6		90	15	85
7		29	0	100

[a] Reaction conditions: **1** (0.5 mmol), R–X (1 mmol), $[RuCl_2(p\text{-cymene})]_2$ (0.0125 mmol), PCCA (0.05 mmol), K_2CO_3 (1.5 mmol), dioxane (2 mL), 140 °C, 24 h, argon. [b] Conversion of **1** and the ratio of products was determined by ^1H NMR.

Conclusion

- Direct functionalization of sp^2(C)–H bonds of 2-phenylquinazoline was carried out under various reaction conditions.
- In the presence of $[RuCl_2(p\text{-cymene})]_2$, different ligands and potassium carbonate as the base the *ortho* positions of the quinazoline derivative **1** were successfully functionalized in different solvents.
- With PCCA as the selected ligand and dioxane as the chosen solvent, direct functionalization of 2-phenylquinazoline was carried out with several proelectrophiles which gave mono- and di-substituted products in moderate to excellent yields.

References

1. (a) Ackermann, L.; Vicente, R. Ruthenium-Catalyzed Direct Arylations Through C–H Bond Cleavages in Topics in Current Chemistry C–H Activation. Eds.; Yu, J.-Q.; Shi, Z. Springer Heidelberg **2010**, 211–229. (b) Bergman, R.G. C–H Activation. *Nature* **2007**, *446*, 391–393. (c) Yamaguchi, J.; Yamaguchi, A. D.; Itami, K. C–H Bond Functionalization: Emerging Synthetic Tools for Natural Products and Pharmaceuticals. *Angew. Chem. Int. Ed.* **2012**, *51*, 8960–9009.
2. D'yakonov, A. L.; Telezhenetskaya, M. V. Quinazoline alkaloids in nature. *Chem. Nat. Compd.* **1997**, *33*, 221–267.
3. Van Cutsem, E. Raltitrexed (Tomudex™) in combination treatment for colorectal cancer: new perspectives. *Eur. J. Cancer,* **1999**, *35*, S1–S2.