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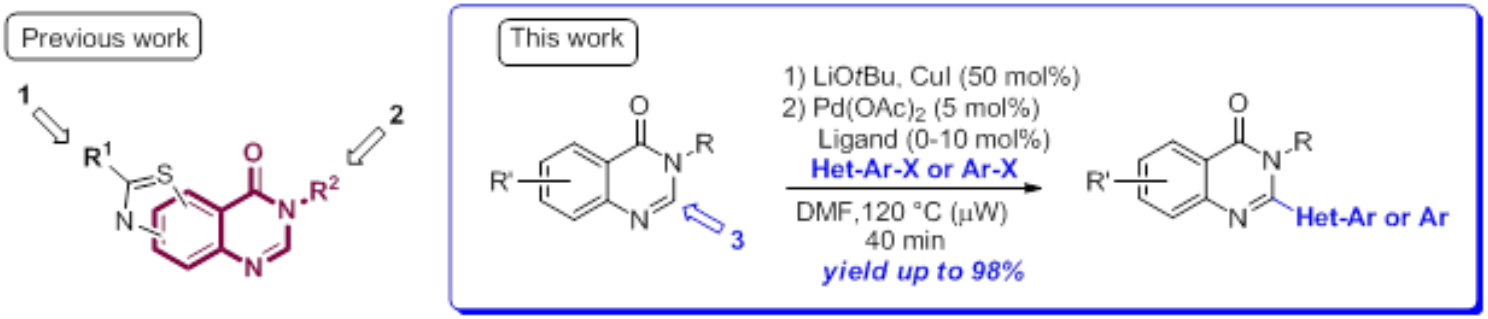
Microwave-assisted C-H arylation of Quinazolin-4-one-type precursors of bioactive heterocycles

Julien Godeau, Marine Harari, Sylvain Laclef, Corinne Fruit* and Thierry Besson

Normandie Univ, COBRA, UMR 6014 & FR 3038; Univ Rouen; INSA Rouen; CNRS, IRCOF, 1 rue Tesnière, 76821 Mont St Aignan Cedex, France;

* Corresponding author: corinne.fruit@univ-rouen.fr

Microwave-assisted C-H arylation of Quinazolin-4-one-type precursors of bioactive heterocycles



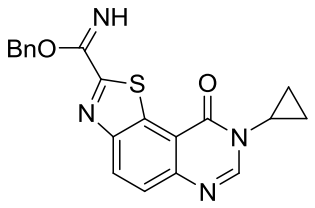
Abstract:
Our group is focused on the synthesis of tricyclic heterocycles precursors of bioactive molecules able to modulate the activity of kinases involved to some extent in Alzheimer's disease. Previous biological results lead us to intensively study thiazoloquinazolin-4-one backbone. Following our effort for the construction of a broad range of substituted thiazoloquinazolin-4-one derivatives as potential kinase inhibitors, we reported the first extensive study of palladium-catalyzed direct C-H (hetero)-arylation of quinazolin-4-ones with various aryl halides under microwave irradiation. This innovative methodology tolerates a broad range of heteroaryl and aryl halides substituted by electronically different groups. The scope of substrates was extended to pyridinopyrimidin-4-ones. This method provides an efficient, versatile and rapid access to biologically relevant *2*-arylquinazolin-4-one backbones and will be extended to our thiazoloquinazolin-4-one derivatives.

Keywords: quinazolin-4(3*H*)-one; microwave; C-H functionalization; catalyse; (hetero)aryl halides

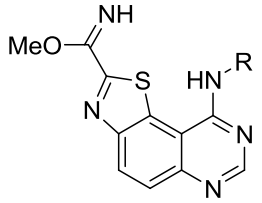
Introduction

Our research groups are invested in the synthesis of polyaromatic heterocyclic molecules able to modulate the activity of kinases in signal transduction, and especially Ser/Thr kinases (CDK5, GSK3, CLK1 and CK1) and dual-specificity kinases (DYRK1A), selected for their strong implication in various human pathologies, especially in Alzheimer disease.

In the course of our work, the multistep synthesis of a novel 9-(aryl)-N-(2-alkyl)thiazolo[5,4-f]quinazoline library was recently described. These compounds were designed as 6,6,5-tricyclic homologs of the basic 4-aminoquinazoline pharmacophore, which is present in approximately 80% of ATP-competitive kinase inhibitors that have received approval for the treatment of cancer. Brief studies of their structure-activity relationships as kinase inhibitors were realized. Among the compounds tested, the most promising series showed submicromolar activities against DYRK1A and GSK3α/β kinases with a marked preference for the first one.



IC_{50} DYRK1A = 60 nM
IC_{50} GSK3 = 100 nm

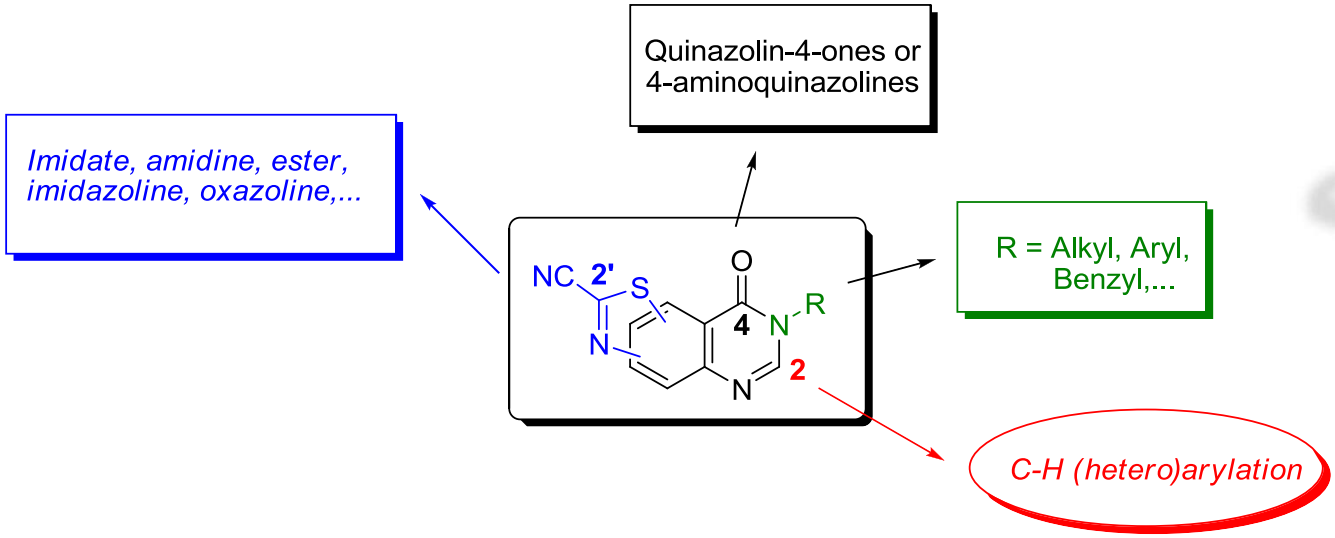


IC_{50} DYRK1A = 0.22-0.99 nM

a) Leblond, B.; Casagrande, A.-S.; Désiré, L.; Foucourt A.; Besson, T. *European Patent* **WO 2013/026806 A1**. b) Besson, T. and coll. *Molecules* **2014**, *19*, 15446. c) Besson, T. and coll. *Molecules* **2014**, *19*, 15411. d) Hédou, D.; Deau, E.; Harari, M.; Sanselme, M.; Fruit, C.; Besson, T. *Tetrahedron* **2014**, *70*, 5541. d) Deau, E.; Hédou, D.; Chosson, E.; Levacher, V.; Besson, T. *Tetrahedron Lett.* **2013**, *54*, 3518.

Introduction

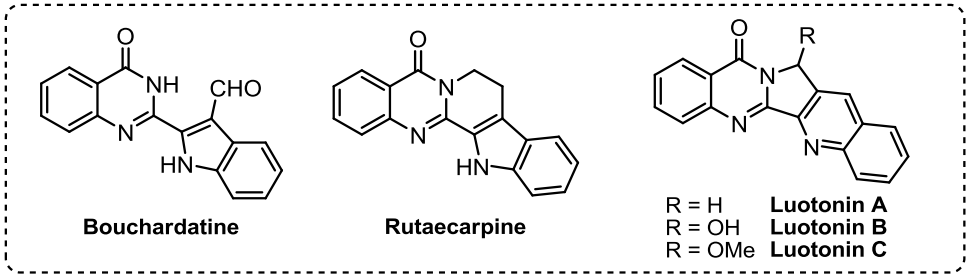
Owing to the importance of DYRK1A inhibitors, structure-activity relationship studies were investigated. Among the potential chemical transformation, C2-functionalization of quinazolin-4(3H)-one core was investigated. In this context, transition metal-catalyzed intermolecular C-C coupling of quinazolin-4(3H)-one scaffolds through direct C-H arylation represents an extremely attractive approach, circumventing tedious multi-step syntheses in structure-activity relationship studies.



Drug Design – Structure-Activity Relationship Studies

Introduction

Quinazolin-4(3*H*)-one scaffolds were chosen as model substrates for the direct C-H functionalization studies. Indeed, C2-arylquinazolin-4(3*H*)-ones are a highly significant class of heteroaromatic compounds that are widely found in bioactive molecules, pharmaceuticals and natural products.[1] Reflecting this, their syntheses have attracted much attention.[2]

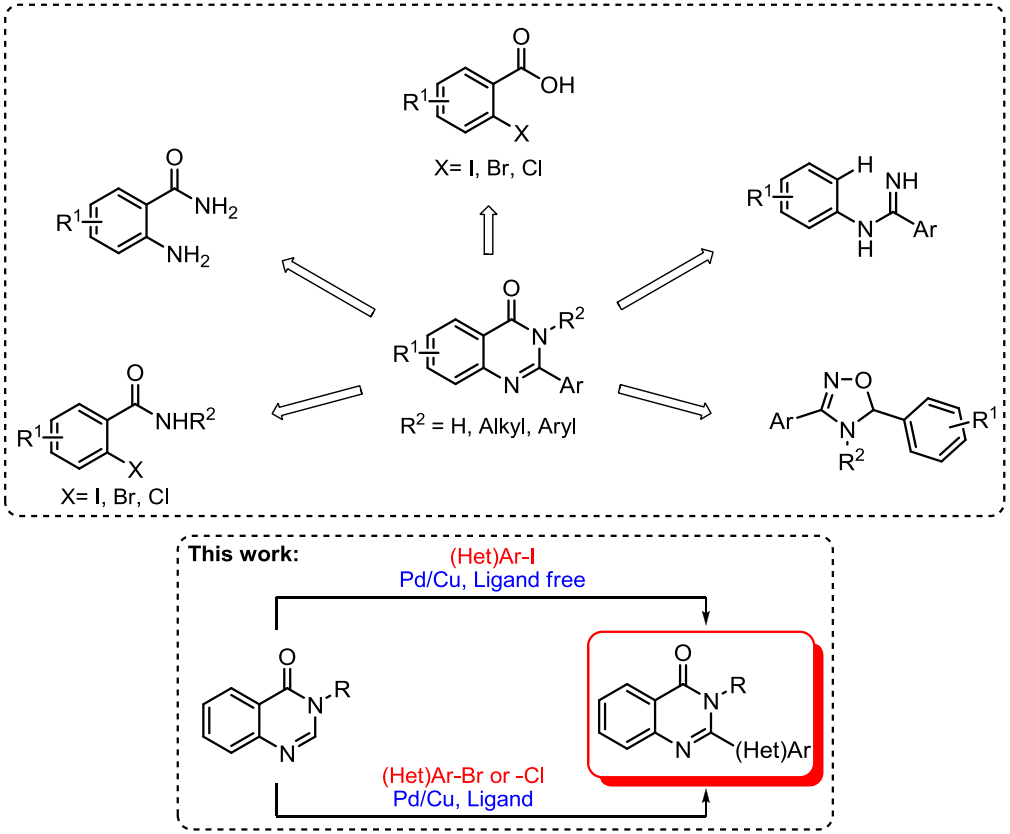


Selected examples of bioactive quinazolin-4(3*H*)-ones

[1] a) Kahn, I.; Ibrar, A.; Abbas, N.; Saeed, A. *Eur. J. Med. Chem.* **2015**, *90*, 124. b) Johannes, J. W. et al. *ACS Med. Chem. Lett.* **2015**, *6*, 254. c) Kahn, I.; Ibrar, A.; Abbas, N.; Saeed, A. *Eur. J. Med. Chem.* **2014**, *76*, 193. d Kahn, K. M.; Saad, S. M.; Shaikh, N. N.; Hussain, S.; Fakhri, M.; Perveen, S.; Taha, M.; Choudhary, M. I. *Bioorg. Med. Chem.* **2014**, *22*, 3449. e) Nathubhai, A.; Wood, M. D.; Thompson, A. S.; Threadgill, M. D. *ACS Med. Chem. Lett.* **2013**, *4*, 1173.

[2] For a review, see: V. Mittapelli, *Der Pharma Chemica* **2014**, *6*, 272.

Introduction



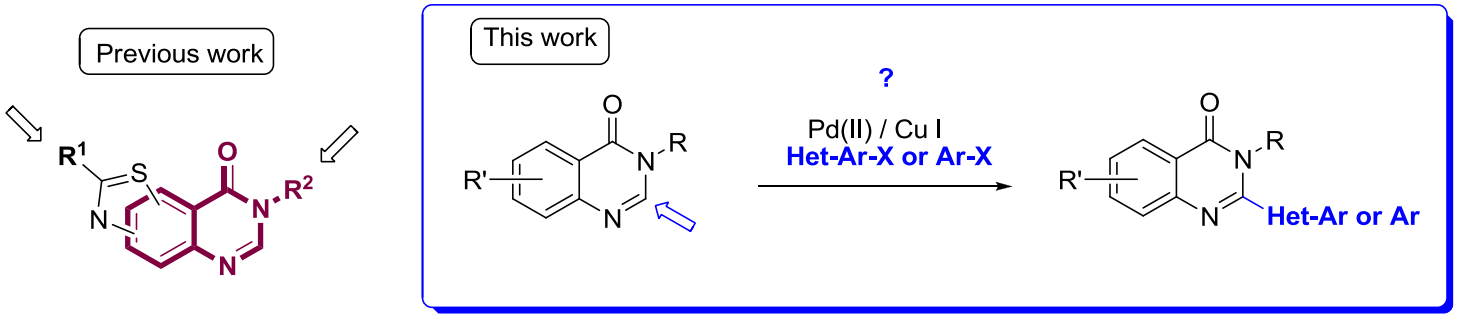
Reported methods and present strategy for synthesis of quinazolin-4(3*H*)-ones.

Despite the practical importance of C2-aryl quinazolin-4(3H)-ones, a unique example of intermolecular palladium-catalyzed C-H arylation of quinazolin-4-ones with aryl chlorides was reported for the synthesis of Bouchardatine, a naturally occurring cytotoxic alkaloid.

Naik, N. H.; Urmode, T. D.; Sikder, A. K.; Kusurkar, R. S. *Aust. J. Chem*. **2013**, *66*, 1112.

Results and discussion

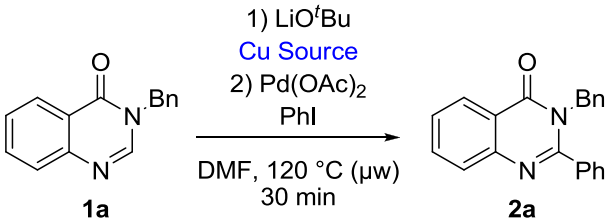
Following our effort for the construction of a broad range of substituted quinazoline derivatives as potential inhibitors of kinases, the first extensive study of palladium-catalyzed direct C-2-H arylation of N^3-protected quinazolin-4-ones was investigated with aryl halides under microwave irradiation*.



* Microwaves (Monowave 300 from Anton-Paar) used in this study worked under pressure in sealed vials (5-20 mL).

Results and discussion

Table 1. Effect of Copper Source

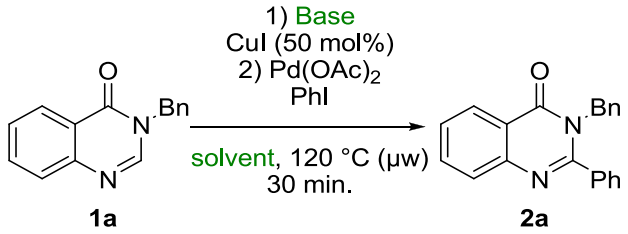


Entry[a]	Copper source	Cu catalyst loading	Yield[b] (%)
1	CuI	1 equiv	96
2	**CuI**	**50%**	**91**
3	CuBr	50%	54
4	CuOAc	50%	0
5	$CuCl_2$	50%	56
6	CuI	30%	78
7	CuI	10%	66
8	none	-	0

[a] Conditions: Reactions were performed in a sealed tube at 0.4 M with premixing **1a** (1 equiv), LiO^{t}Bu (2 equiv), and the copper source in a microwave reactor for 10 min at 120°C, before adding PhI (2 equiv), $Pd(OAc)_2$ (5 mol%). [b] Reported yields are isolated yields.

Results and discussion

Table 2. Effect of Solvent and Base

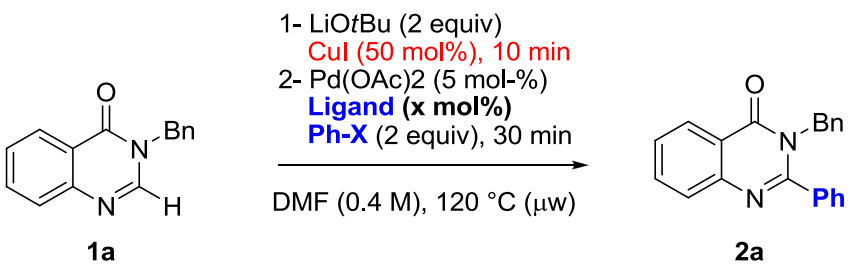


Entry[a]	Solvent	Base	Yield[b] (%)
1	DMF	LiO^{t}Bu	91 (90)[c]
2	DMA	LiO^{t}Bu	43
3	DMPU	LiO^{t}Bu	0
4	DMSO	LiO^{t}Bu	0
5	dioxane	LiO^{t}Bu	0
6	DMF	KO^{t}Bu	14
7	DMF	K_3PO_4	0

[a] Conditions: Reactions were performed in a sealed tube at 0.4 M with premixing **1a** (1 equiv), Base (2 equiv), and CuI (50 mol%) in a microwave reactor for 10 min at 120 °C, before adding PhI (2 equiv), $Pd(OAc)_2$ (5 mol%). [b] Reported yields are isolated yields. [c] Scale up, 8.5 mmol of **1a** under optimized conditions.

Results and discussion

Table 3. Ligand screening in direct 2-arylation of N^3-benzylated quinazolin-4(3*H*)-one **1a** with phenyl halides.



Entry[a]	PhX	Ligand (mol-%)	Yield (%)[b]
1	**PhI**	**none**	**91 (90)[c]**
2	PhBr	none	trace
3	PhBr	PCy_3 (6)	82
4	PhBr	$PtBu_3$ (6)	83
5	**PhBr**	**PPh_3 (6)**	**80**
6	PhBr	$P(C_6F_5)_3$ (6)	68
7	PhCl	$PtBu_3$ (6)	trace
8	PhCl	PPh_3 (6)	trace
9	PhCl	PPh_3 (10)	trace
10	PhCl	dppp (6)	trace
11	PhCl	dCype (6)	trace
12	PhCl	dippp (6)	5
13	PhCl	dippp (10)	16
14	PhCl	dbpf (6)	trace
15	PhCl	Xantphos (6)	trace
16	PhCl	NiXantphos (6)	37
17	**PhCl**	**NiXantphos (10)**	**93**
18	PhCl	Pd-PEPPSI-IPent	trace

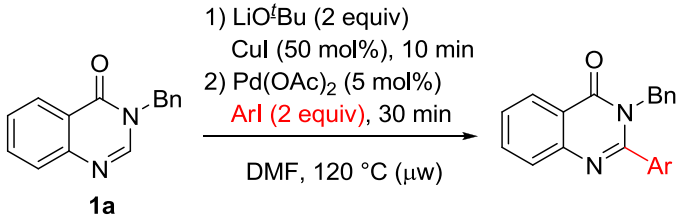
[a] Reactions were performed in a sealed tube at 0.4 M premixing **1a** (1 equiv), LiO*t*Bu (2 equiv), and CuI (50 mol-%) in a microwave reactor for 10 min at 120°C, before adding PhX (2 equiv), $Pd(OAc)_2$ (5 mol-%) and ligand (6-10 mol-%) for 30 min at 120°C.

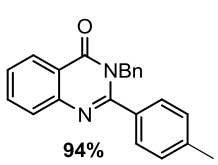
[b] Reported yields are isolated yields.

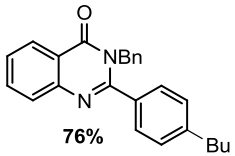
[c] Scale-up, 8.5 mmol of **1a** under optimized conditions.

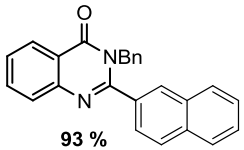
Results and discussion

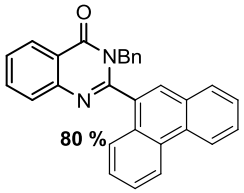
Scheme 1. Direct Arylation of N^3-Benzylated Quinazolin-4-one **1a** with Aryl Iodides

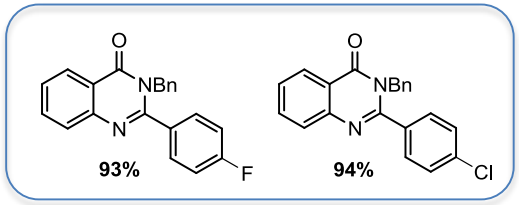


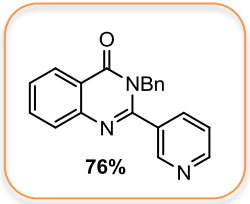


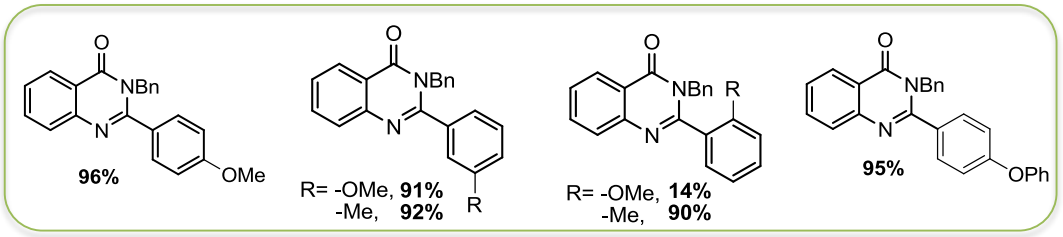


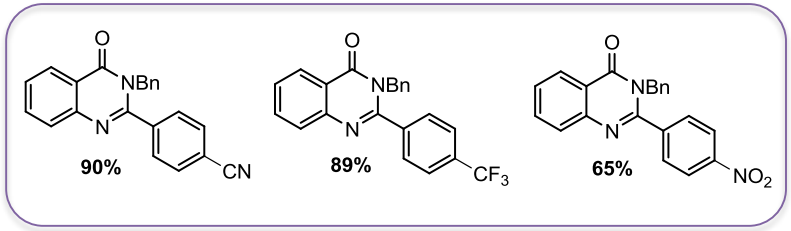








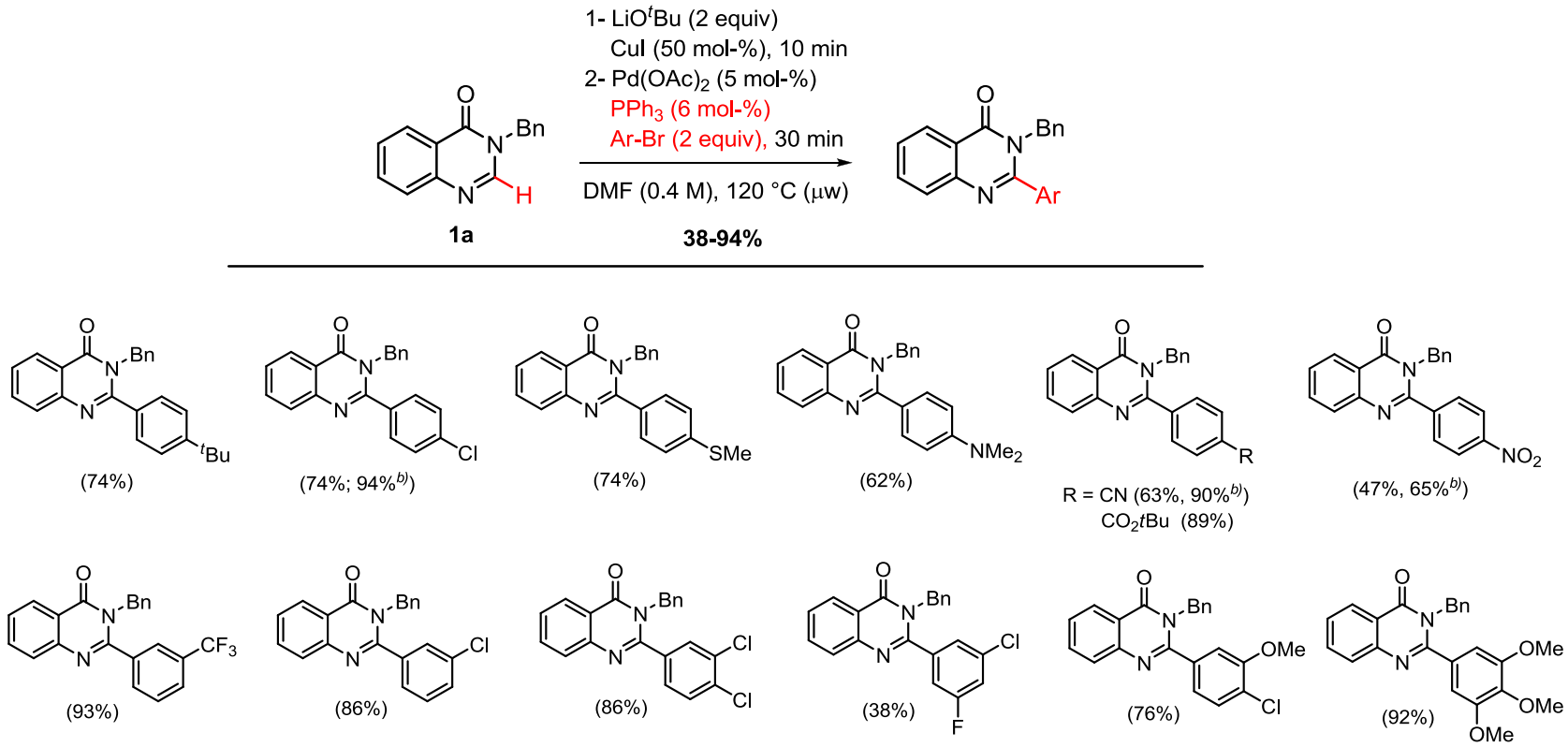




Laclef, S.; Harari, M.; Godeau, J.; Schmitz-Afonso, I.; Bischoff, L.; Hoarau, C.; Levacher, V.; Fruit, C.; Besson, T. *Org. Lett.* **2015**, *17*, 1700.

Results and discussion

Scheme 2. Scope of aryl bromides in direct 2-arylation of N^3-benzylated quinazolin-4(3*H*)-one **1a**.



[b] *Yields obtained with the corresponding aryl iodide as coupling partner, without ligand*

Godeau, J.; Harari, M.; Laclef, S.; Deau, E.; Fruit, C.; Besson, T. *Eur. J. Org. Chem*. **2015**, 10.1002/ejoc.201501129, in press.

Results and discussion

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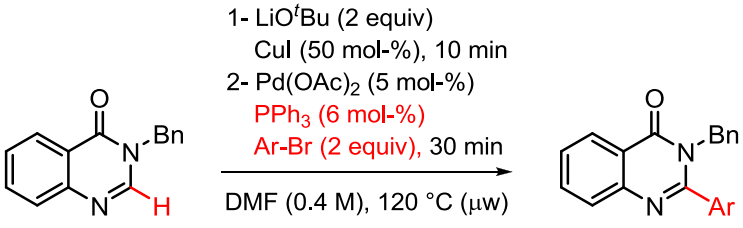
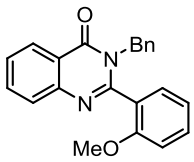
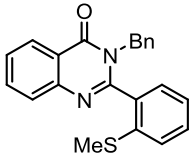
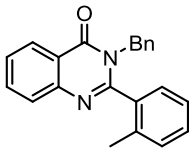




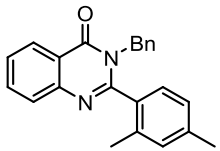
(90%, 14%[b])



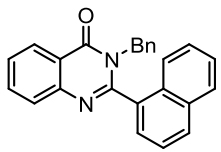
(72%)



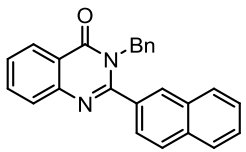
(75%[c], 90%[b])



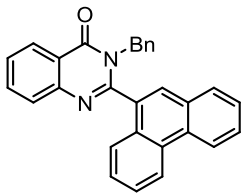
(65%)



(94%, 68%[b])



(93%, 93%[b])



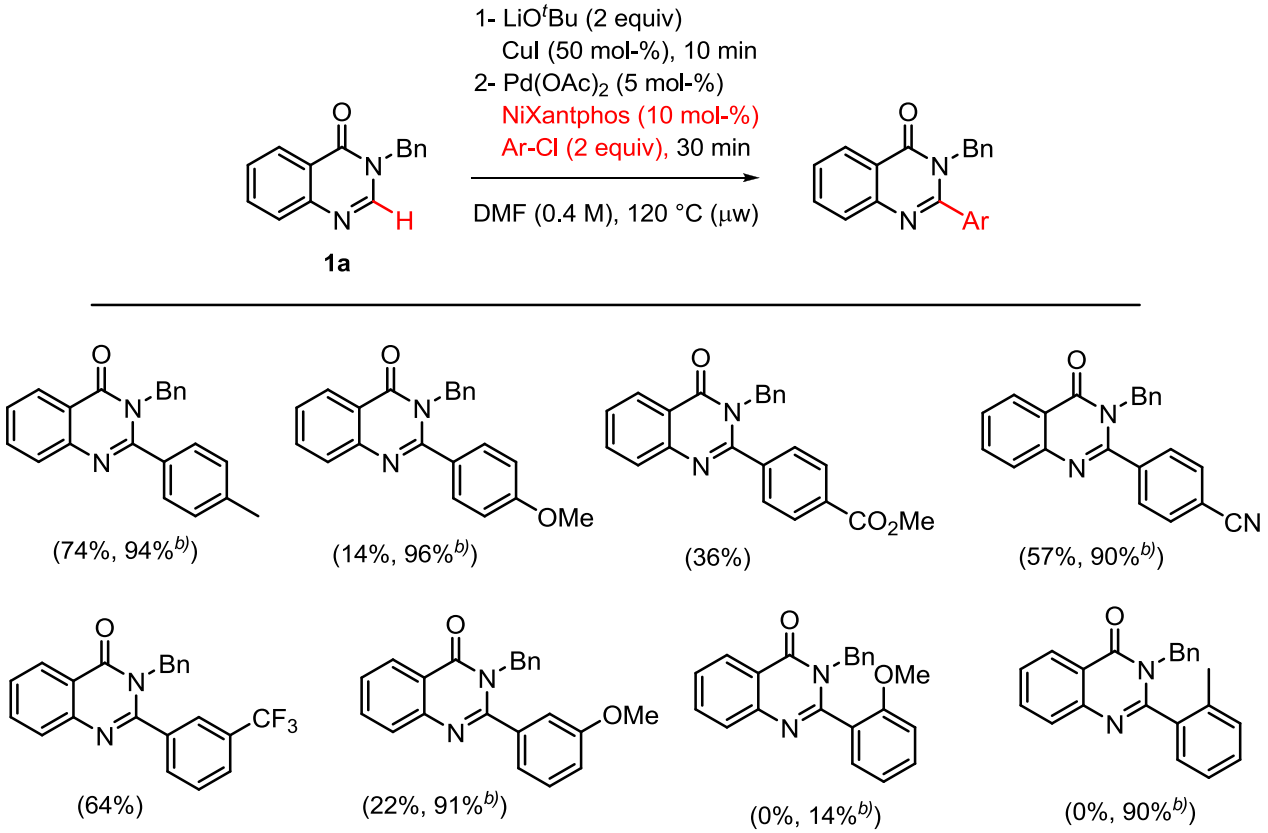
(75%, 80%[b])

[b] *Yields obtained with the corresponding aryl iodide as coupling partner, without ligand*

Godeau, J.; Harari, M.; Laclef, S.; Deau, E.; Fruit, C.; Besson, T. *Eur. J. Org. Chem*. **2015**, 10.1002/ejoc.201501129, in press.

Results and discussion

Scheme 4. Direct arylation of N^3-benzylated quinazolin-4(3*H*)-one **1a** with aryl chlorides[a].

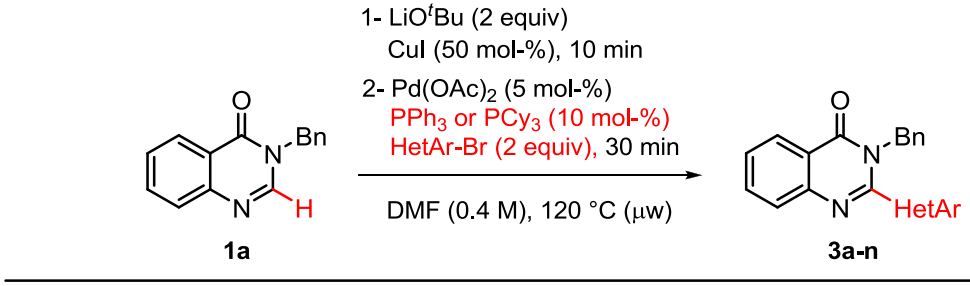


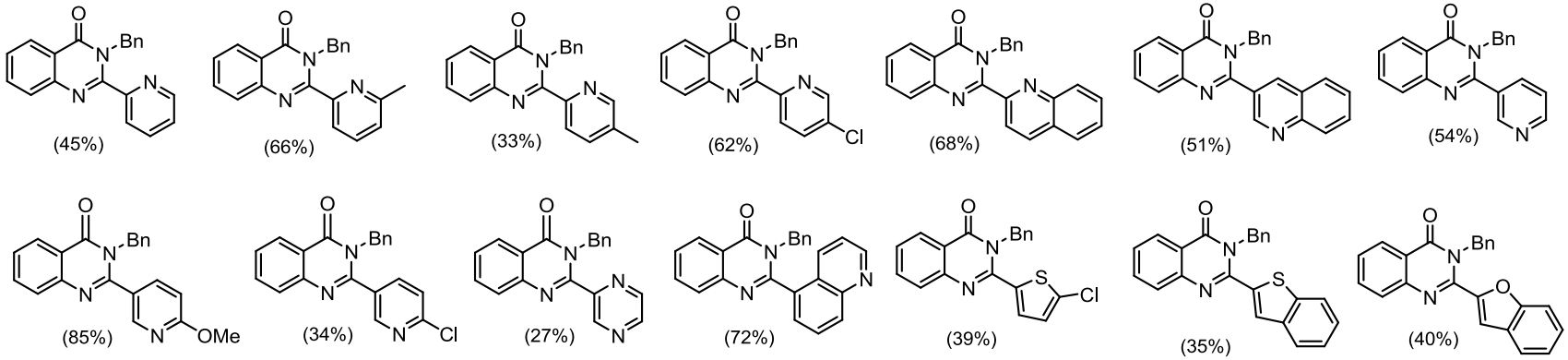
[b] *Yields obtained with the corresponding aryl iodide as coupling partner, without ligand*

Godeau, J.; Harari, M.; Laclef, S.; Deau, E.; Fruit, C.; Besson, T. *Eur. J. Org. Chem*. **2015**, 10.1002/ejoc.201501129, in press.

Results and discussion

Scheme 5. Direct arylation of N^3-benzylated quinazolin-4(3*H*)-one **1a** with heteroaryl bromides[a].

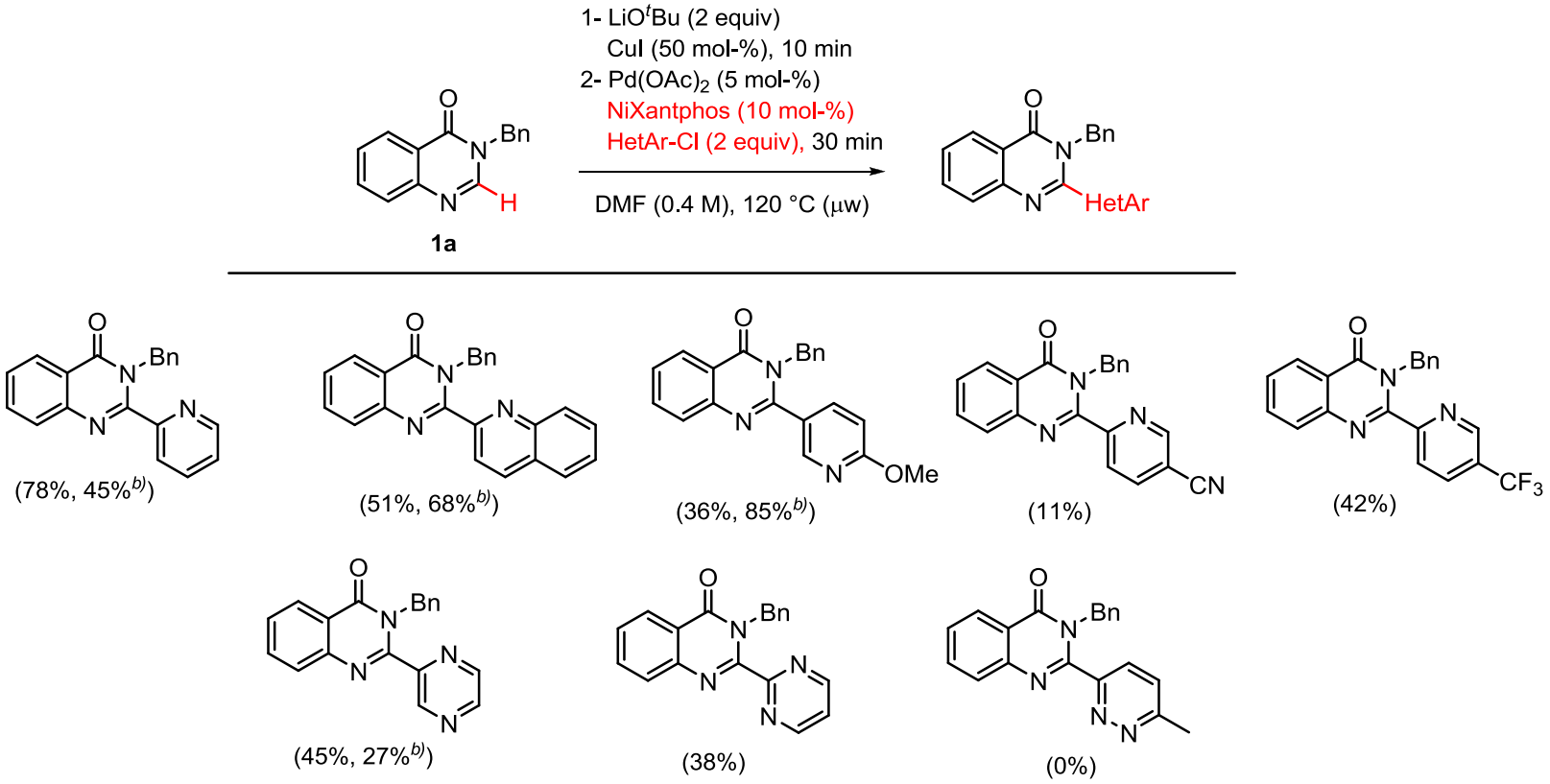




Godeau, J.; Harari, M.; Laclef, S.; Deau, E.; Fruit, C.; Besson, T. *Eur. J. Org. Chem*. **2015**, 10.1002/ejoc.201501129, in press.

Results and discussion

Scheme 6. Heteroaryl chloride scope in direct arylation of N^3-benzylated quinazolin-4(3*H*)-one **1a**.[a]

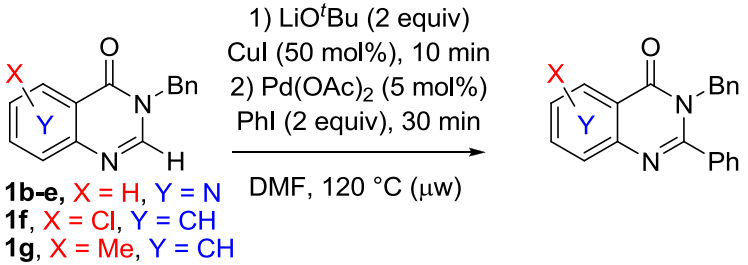


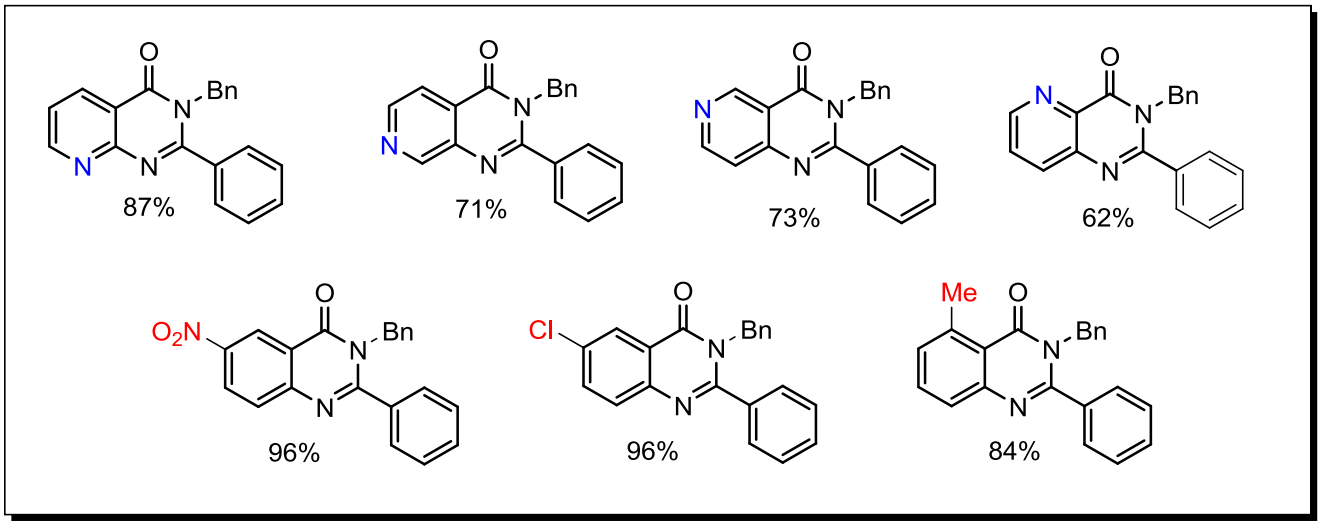
[a] Reported yields are isolated yields.

[b] Reactions performed using the corresponding aryl bromide as coupling partner, with PPh_3 or PCy_3 as ligands.

Results and discussion

Scheme 7. Arylation of N^3-Benzylated Pyrido-Pyrimidin-4-ones **1b-e** and Quinazolin-4-ones **1f-g** with Phenyl Iodide

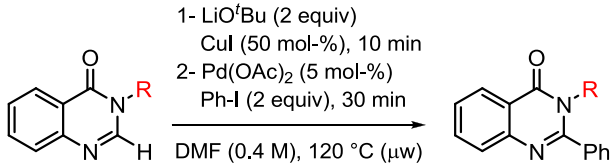




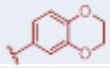
Laclef, S.; Harari, M.; Godeau, J.; Schmitz-Afonso, I.; Bischoff, L.; Hoarau, C.; Levacher, V.; Fruit, C.; Besson, T. *Org. Lett.* **2015**, *17*, 1700.

Results and discussion

Table 4. C-H phenylation of various N^3-substituted quinazolin-4(3*H*)-ones **1h-m** with phenyl iodide.



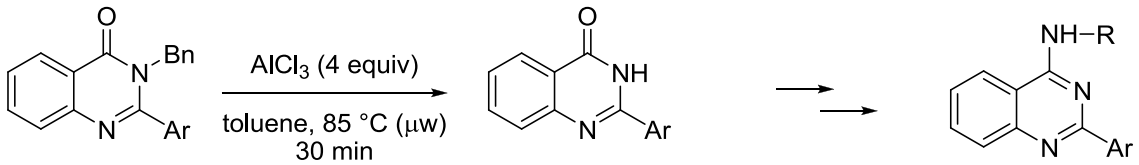
1h-m **4a-f**

Entry	R-	-X	Ligand	Yield[b] (%)
1	4-Me-Ph-	-I -Br -Cl	- PPh_3 NiXantphos	86 45 31
2		-I	-	82
3[a]	-Me	-I -Br -Cl	- PPh_3 NiXantphos	91 74 61
4[a]	-Pr	-I	-	72
5[a]	-^{i}Pr	-I	-	68
6[a]		-I -Br -Cl	- PPh_3 NiXantphos	84 74 63

[a] Reactions performed using 1 equiv of CuI

Results and discussion

Scheme 8. Deprotection of Arylated Quinazolinones **2a-c**



2a, Ar = Ph
2b, Ar = 4-$MeOC_6H_4$
2c, Ar = 4-ClC_6H_4

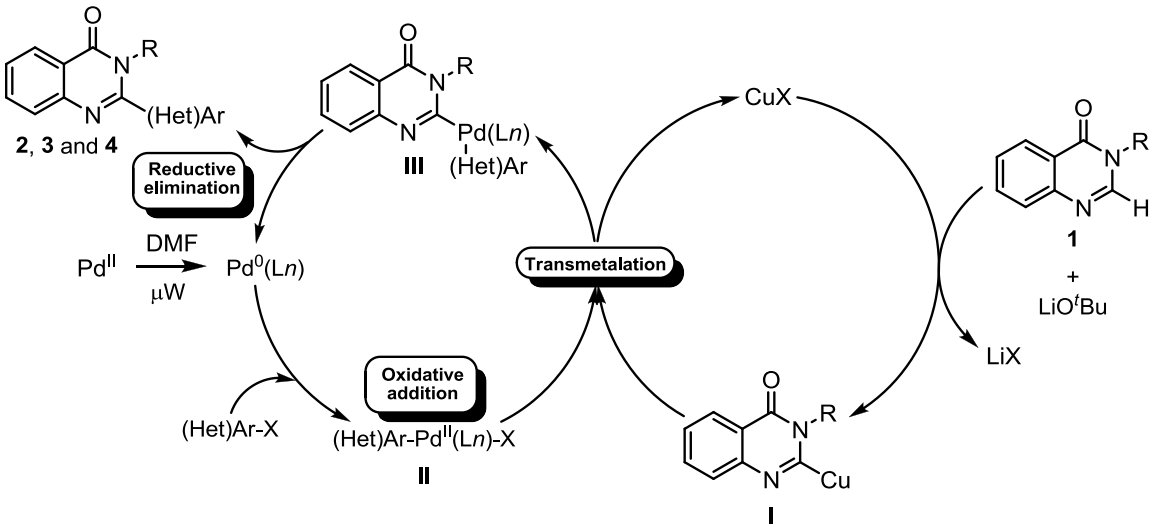
3a, Ar = Ph 94%
3b, Ar = 4-HOC_6H_4 88%
3c, Ar = 4-ClC_6H_4 92%

*Compounds **3** are well-known key intermediates in the classical synthesis of 4-amino-2-aryl-quinazoline derivatives via a two-step synthesis (chlorination/SNAr procedure).*

Laclef, S.; Harari, M.; Godeau, J.; Schmitz-Afonso, I.; Bischoff, L.; Hoarau, C.; Levacher, V.; Fruit, C.; Besson, T. *Org. Lett.* **2015**, *17*, 1700.

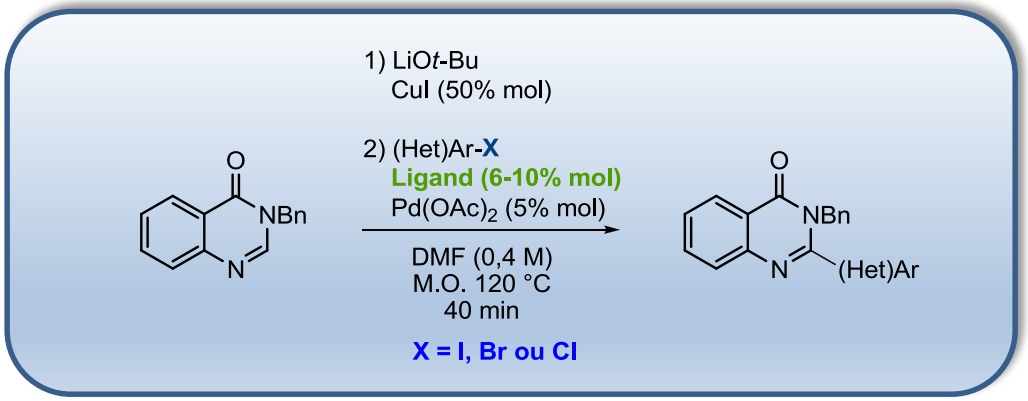
Results and discussion

Scheme 9. Proposed mechanism for C2-(hetero)arylation of N^3-substitued quinazolin-4(3*H*)-ones.



Conclusions

- *Synthesis of more than 50 compounds in 14-96% range yield.*



We have developed the first Cu/Pd-catalyzed microwave-enhanced C-H (hetero)arylation of quinazolin-4-ones with aryl halides in high yields. This innovative methodology tolerates a broad range of aryl halides substituted by electronically different groups. Pyridine derivatives, thiophenes and diazines were also readily introduced at the C2 position of quinazolin-4(3*H*)-ones, a notable feature with respect to the development of medicinal agent synthesis.

The scope of substrate model was also successfully extended to pyridinopyrimidin-4-ones and N^3-, C5- or C6-substituted quinazolin-4(3*H*)-ones. This method provides an efficient, versatile, and rapid access to important 2-arylquinazolin-4-ones, which are potentially active compounds or key intermediates for the synthesis of kinases inhibitors.

Acknowledgments

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