



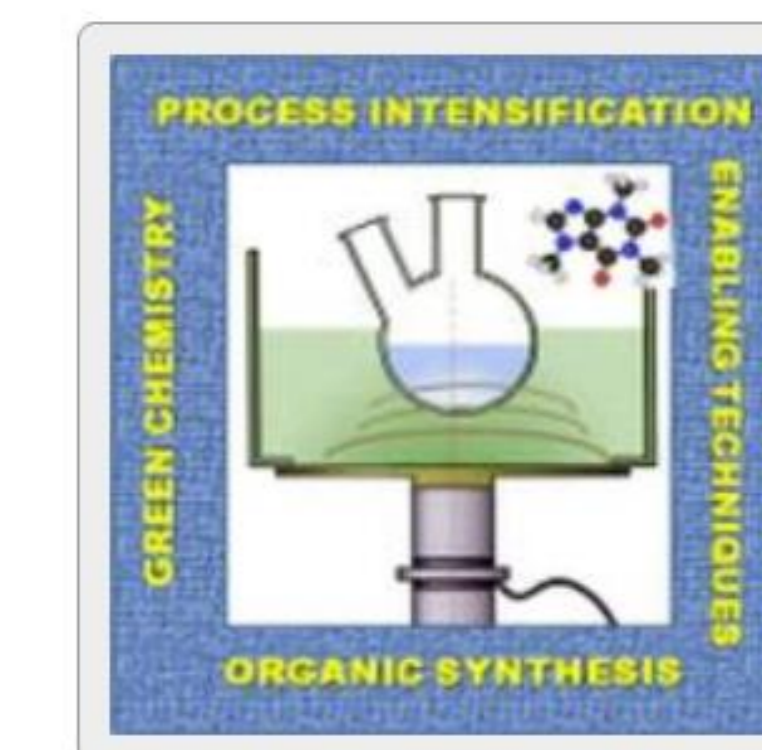
Base and Acid Free copper catalysed C-H amination

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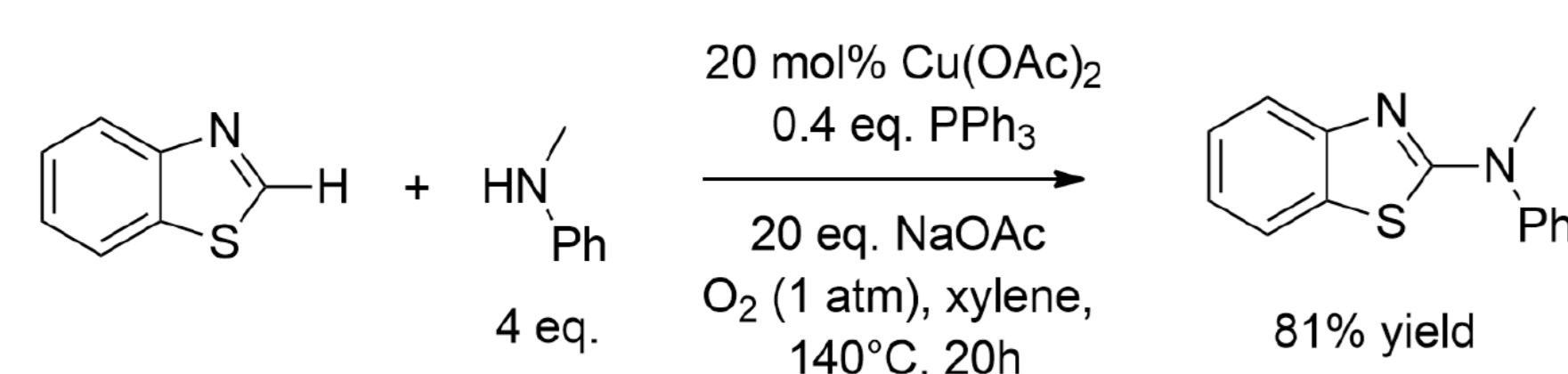
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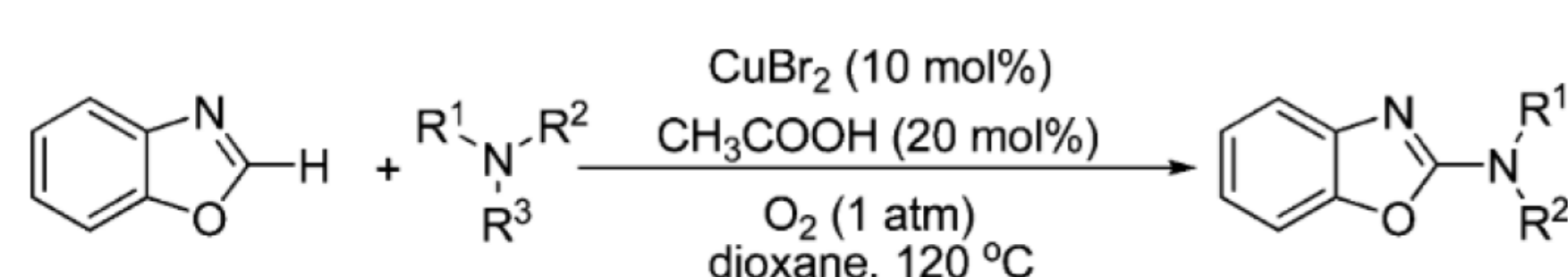
Direct functionalization of generally unreactive C-H bonds is an extremely valuable organic transformation¹ and a green and sustainable method, especially when O₂ is used as stoichiometric oxidant: excellent Atom Economy, avoidance of pre-functionalization steps to increase reactivity are the most important advantages over classical methods. The high versatility and the low cost of the copper make its use favourable among the other catalysts: acid and base additives free procedures were developed and the ultrasounds effect was investigated.



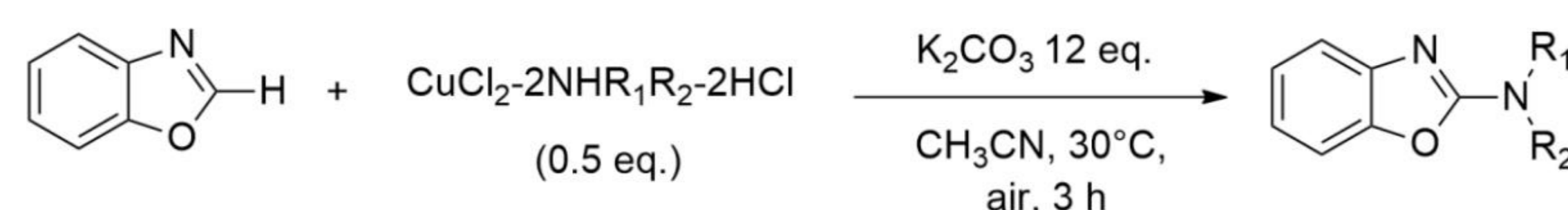
Previous literature:



Mori et al.² (2009): Different amines, 4 eq. Azolic substrates. Use of base.



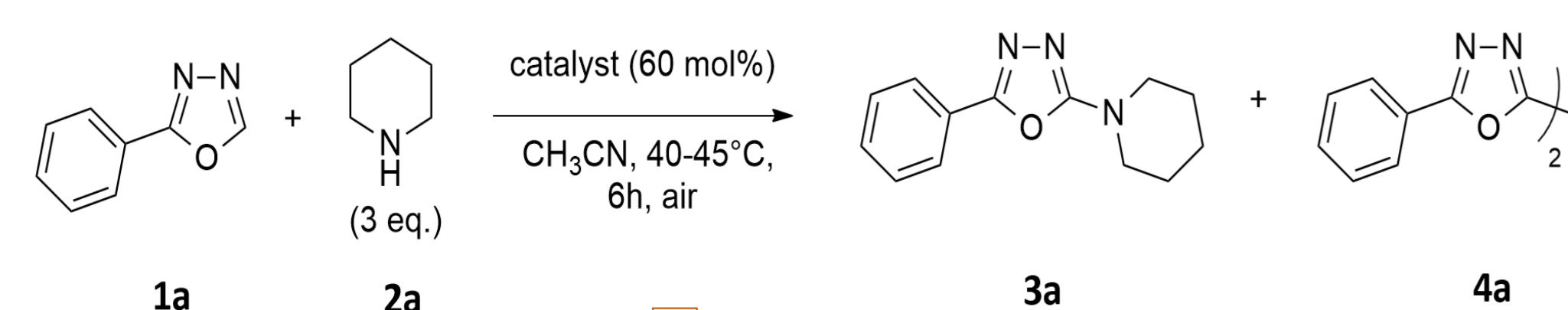
Huang et al.³ (2011): Tertiary amines, 2 eq. Azolic substrates. Use of acid additive.



Shi et al.⁴ (2013): CuCl₂ complexes of amines (1 eq amine, 50 mol% Cu). Azolic substrates. Base additive.

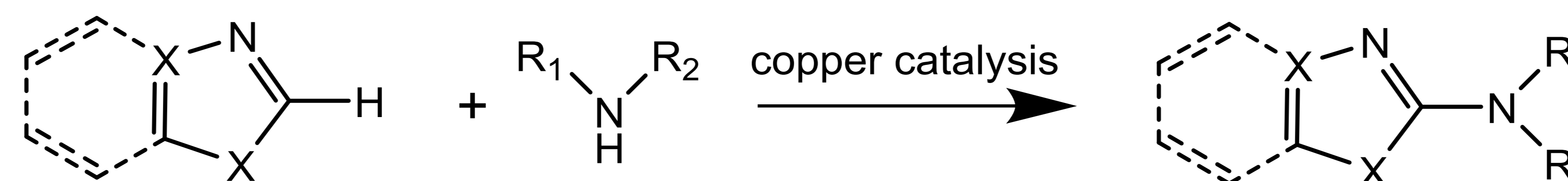
Experimental research:

1 2-phenyl-1,3,4-oxadiazole and piperidine were taken as reactants in a model reaction to screen a number of copper catalysts in different oxidation states.



Cu I species performed better than Cu II ones, in contrast to what reported by previous literature on C-H amination of azoles.

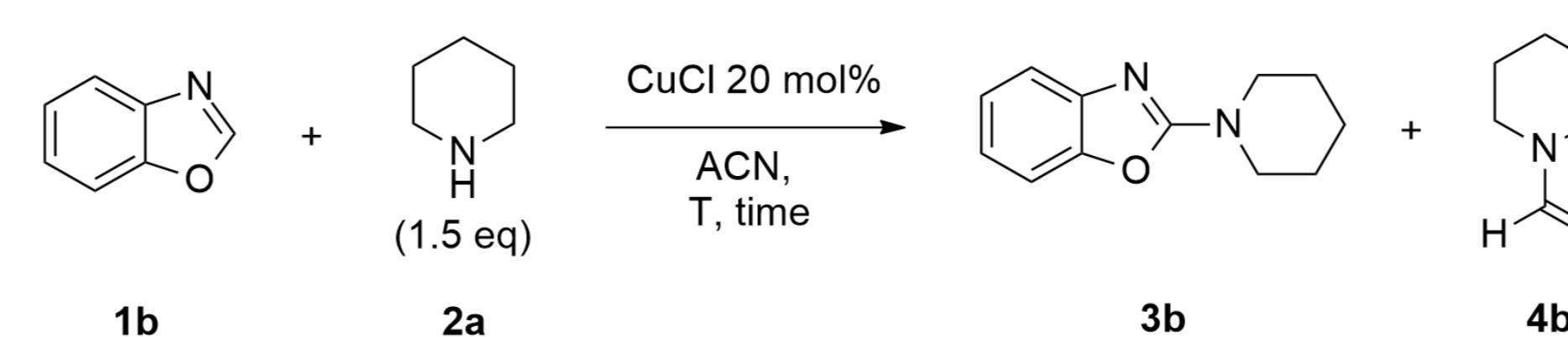
Entry	Catalyst (60 mol %)	Conversion (%) ^a	Selectivity (%) ^a 3a/4a
1	Cu(OAc) ₂	10	-/100
2	CuBr	50	32/24
3	Cu ₂ S	40	75/25
4	CuCl	70	62/17



- Excess of nucleophiles to increase selectivity.
- A/B additives.
- High catalyst loading.
- Low versatility.

2 Coordinating properties of the solvent demonstrated to be fundamental for the reactivity: the best conversion and selectivity rates were obtained with the use of acetonitrile at reflux, using an excess of amine (3 eq.).

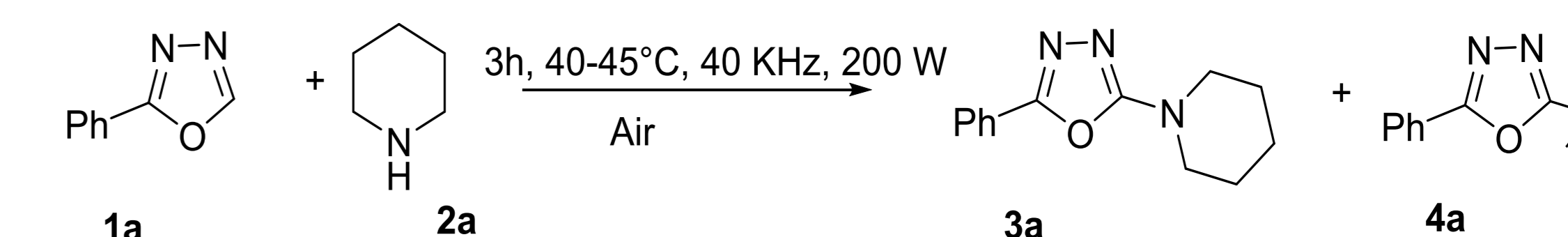
3 The scope was extended studying the reactivity of different amines on different substrate, and remarkable results were achieved reacting the benzoxazole with piperidine under mild conditions.



Entry	Ratio 1b/2a	Catalyst (mol%)	T(°C)	Time	Conversion (%) ^a	Selectivity (%) ^a 3a/4a
1	1/1.5	CuCl 20	reflux	6 h	97	91/9
2	1/1.5	CuCl 20	45	24 h	100	93/7

Entry	Ratio 1a/2a	Catalyst (mol%)	Solvent	T(°C)	Conversion (%) ^a	Selectivity (%) ^a 3a/4a
1	1/3	CuCl 60	DMF	50	19	57/42
2	1/3	CuCl 60	DMSO	50	38	65/35
3	1/3	CuCl 60	ACN	50	52	67/33
4	1/3	CuCl 60	ACN	reflux	100	91/9
5	1/3	CuCl 40	ACN	reflux	95	84/16
6	1/3	CuCl 35	ACN	reflux	89	82/18

4 The role of the ultrasounds effect with Cu I catalyst and a series of solvents with coordinating properties was investigated on 2-phenyl-1,3,4-oxadiazole.



Entry	Ratio 1a/2a	Catalyst (mol%)	Solvent	Conversion (%) ^a	Selectivity (%) ^a 3a/4a
1	1/3	CuCl 60	DMSO (0.5 M)	80	75/25
2	1/3	CuCl 60	DMF (0.5 M)	66	76/24
3	1/3	CuCl 60	DMA (0.5 M)	68	79/21
4	1/3	CuCl 60	ACN (0.5 M)	64	100/-
5	1/3	CuCl 20	ACN (0.5 M)	42	71/29



References:

1. Yeung, C. S.; Dong, V. M., Catalytic Dehydrogenative Cross-Coupling: Forming Carbon-Carbon Bonds by Oxidizing Two Carbon-Hydrogen Bonds. *Chemical Reviews* 2011, 111 (3), 1215-1292.
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