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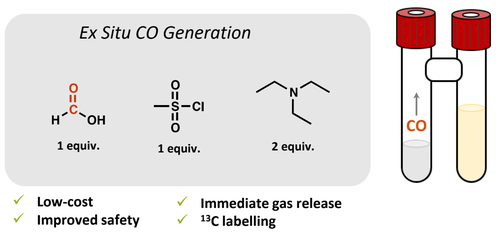
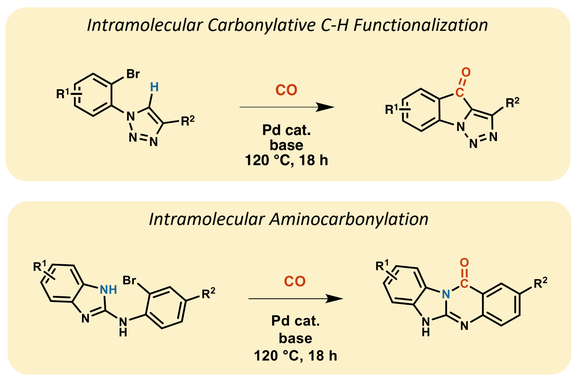
SAFE AND CONVENIENT CO GENERATION AND ITS APPLICATIONS IN ORGANIC CHEMISTRY

Gert Steurs (gert.steurs@kuleuven.be), Sarah Vangrunderbeeck (sarah.vangrunderbeeck@kuleuven.be), Cedrick Veryser (cedrick.veryser@kuleuven.be), Wim M. De Borggraeve (wim.deborggraeve@kuleuven.be) ✉

Abstract

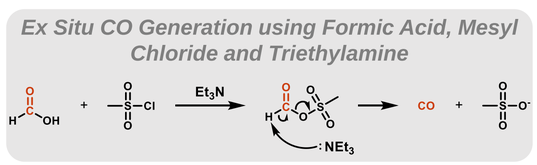
Carbon monoxide is one of the most important C1 building blocks in organic synthesis, as it is abundantly available and highly beneficial in terms of atom economy. Despite its effectiveness, carbonylation chemistry is often hampered in research laboratories by the extreme toxicity of carbon monoxide.

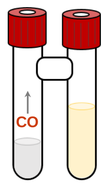




Recently, our group developed a safe and convenient way to generate CO, starting from formic acid, mesyl chloride and triethylamine,[1] by means of a two-chamber reactor system.[2] This methodology gave access to a novel heterocyclic scaffold through intramolecular carbonylative C–H functionalization of 1-(2-bromoaryl)-1,2,3-triazoles.[3] Furthermore, intramolecular aminocarbonylation of various substituted *N*-(2-bromophenyl)-1*H*-benzo[*d*]imidazol-2-amines resulted in a diverse set of benzimidazo[2,1-b]quinazolin-12(*6H*)-ones.

CO Generation

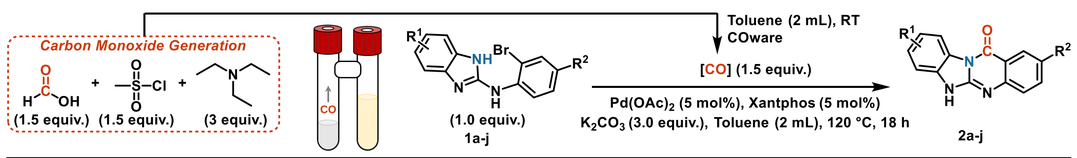


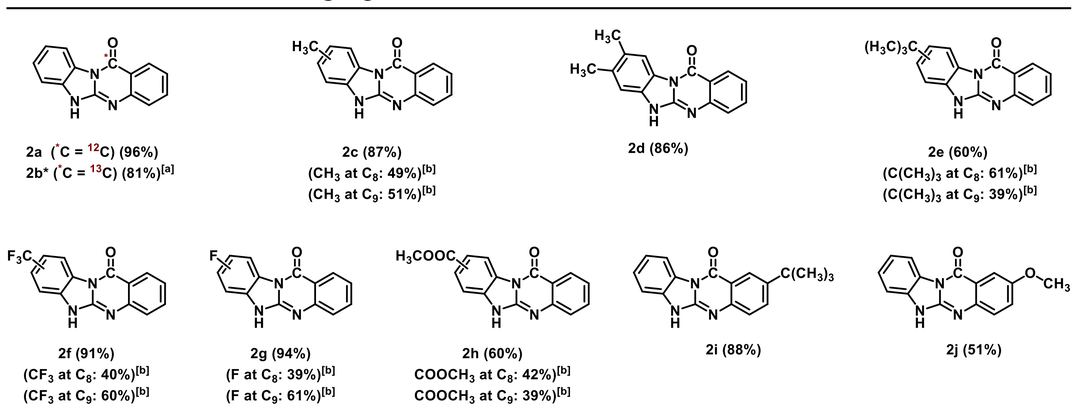


CO Consuming Reaction

- *Aminocarbonylation*
- *Carbonylative Suzuki coupling*
- *Carbonylative Sonogashira coupling*
- *…*

Intramolecular Aminocarbonylation

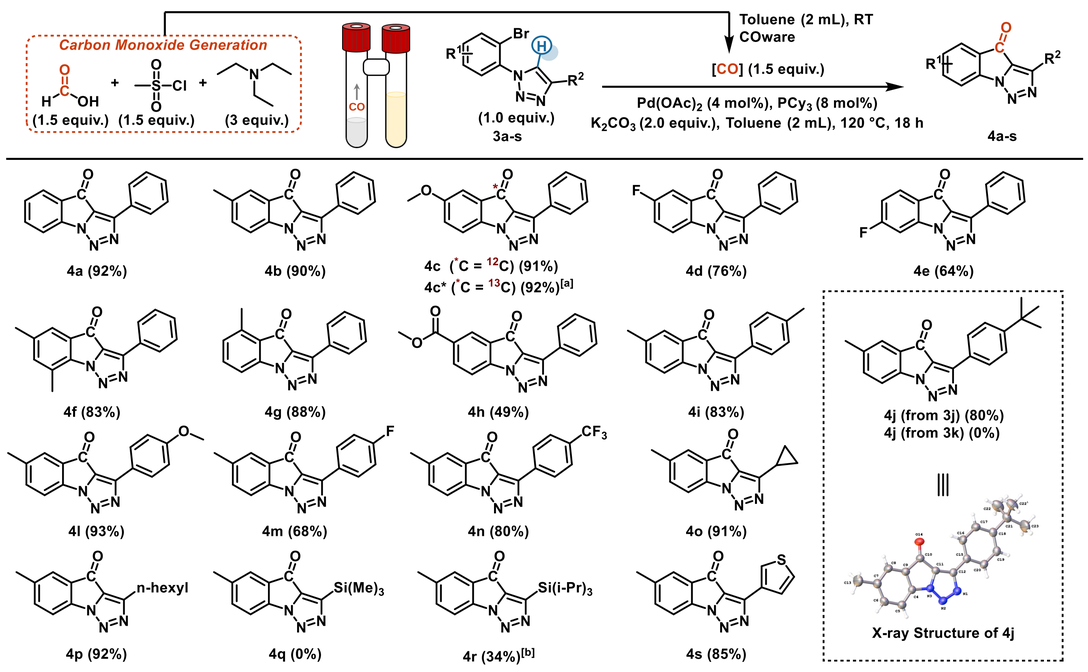




Reaction conditions: *N*-(2-bromophenyl)-1*H*-benzo[*d*]imidazol-2-amine **1** (1.0 mmol), $Pd(OAc)_2$ (5 mol%), Xantphos (5 mol%), K_2CO_3 (3.0 mmol) and CO (1.50 mmol) in 2 mL of dry degassed toluene for 18 h at 120 ° C. Isolated yields. [a] ^{13}C-formic acid was used to generate ^{13}CO. [b] Proportional abundance was determined by NMR.

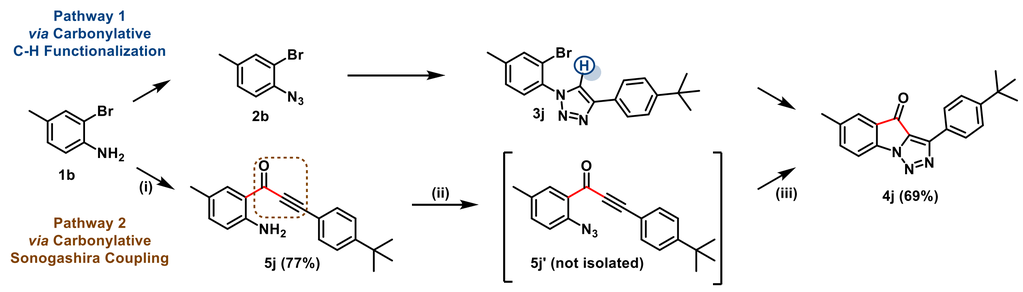
Carbonylative C-H Functionalization[3]

Via C-H Activation of 1-(2-bromophenyl)-1,2,3-triazoles



Reaction conditions: 1-(2-bromophenyl)-1,2,3-triazole **3** (0.40 mmol), $Pd(OAc)_2$ (4 mol%), PCy_3 (8 mol%), K_2CO_3 (0.80 mmol) and CO (0.60 mmol) in 2 mL of dry degassed toluene for 18 h at 120 ° C. Isolated yields. [a] ^{13}C-formic acid was used to generate ^{13}CO. [b] Yield based on ^{1}H NMR.

Via Carbonylative Sonogashira Coupling, Functional Group Interconversion and Ru-catalyzed Azide-Alkyne Cycloaddition



Reaction conditions: (i) 2-bromo-4-methylaniline (1.0 mmol), 4-*tert*-butylphenylacetylene (2.0 mmol), $PdCl_2$ (5 mol%), Xantphos (5 mol%), Et_3N (3.0 mmol) and CO (1.50 mmol) in 2 mL of dry degassed dioxane for 18 h at 100 ° C (ii) compound **5j** (0.40 mmol), *t*-BuONO (0.60 mmol), $TMSN_3$ (0.48 mmol) in 5 mL of acetonitrile for 30 min. at room temperature (iii) intermediate **5j'** (0.40 mmol) and $Cp^*RuCl(PPh_3)_2$ (2 mol%) in 8 mL of dry degassed dioxane for 18 h at 60 ° C.

Conclusion

In conclusion, an efficient CO precursor was developed, which, in combination with the two-chamber reactor setup, proved to be safe and highly efficient for the preparation of carbonyl bearing heterocycles. This strategy was succesfully implemented in the synthesis of both triazolo[1,5-*a*]indolones and benzimidazo[2,1-*b*]quinazolin-12(*6H*)-ones.

References

[1] C. Veryser, S. Van Mileghem, B. Egle, P. Gilles, W. M. De Borggraeve, *React. Chem. Eng*. **2016**, 1, 142. [2] S. D. Friis, A. T. Lindhardt, T. Skrydstrup, *Acc. Chem. Res*. **2016**, 49, 594. [3] C. Veryser, G. Steurs, L. Van Meervelt, W. M. De Borggraeve, *Adv. Synt. Catal*. **2017**, 359, 1271.