Aromatic Iodides: Synthesis and Conversion to Heterocycles

Florence MONGIN
florence.mongin@univ-rennes1.fr
William ERB
Frédéric LASSAGNE

Aromatic Iodides: Synthesis and Conversion to Heterocycles

Contents:

- **Selective Introduction of Iodine onto Aromatic Compounds :**

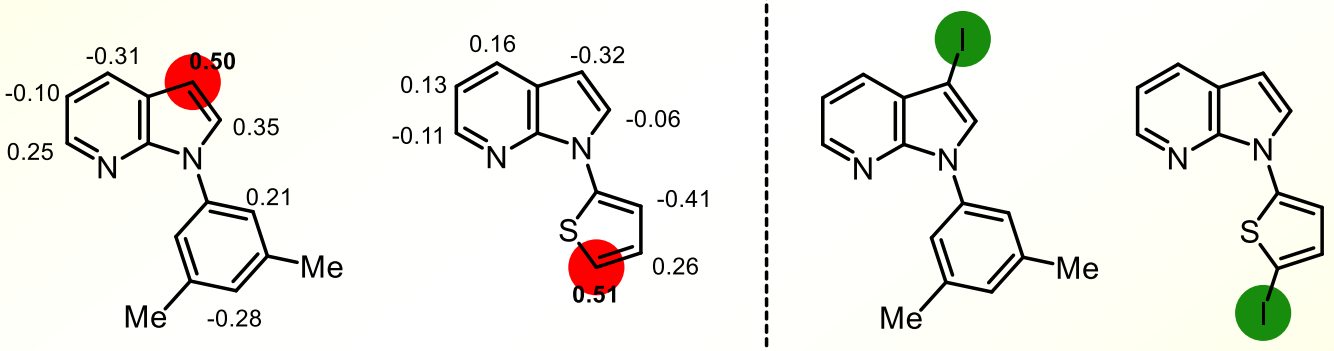
  → **Direct iodination and application to the synthesis of heterocycles of interest**

  → **Deprotometalation with in situ trapping-iodolysis as an alternative to direct iodination**

- **Aromatic Iodides in Copper-mediated *N*-arylation of Anilines**

Direct iodination of 1-aryl/heteroaryl 7-azaindoles

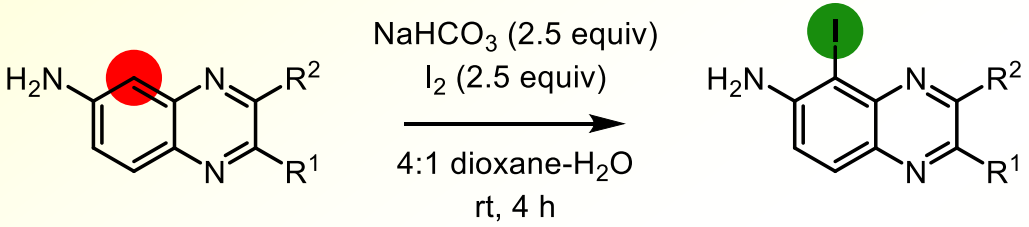
amplitudes of the HOMO coefficients

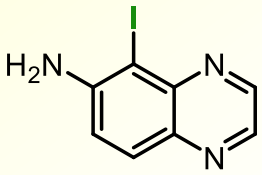


M. Y. Ameur Messaoud, G. Bentabed-Ababsa, Z. Fajloun, M. Hamze, Y. S. Halauko, O. A. Ivashkevich, V. E. Matulis, T. Roisnel, V. Dorcet, F. Mongin, *Molecules* **2021**, *26*, 6314, and references cited therein.

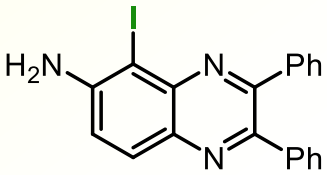
Selective introduction of iodine onto aromatic compounds

Direct iodination of aminoquinoxalines

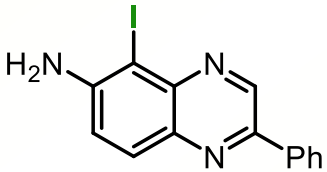




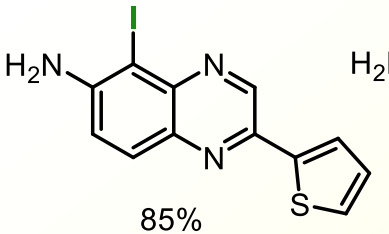
83%



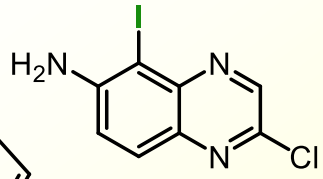
93%



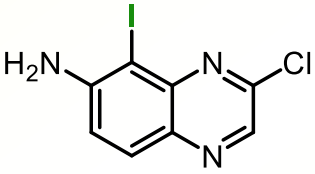
93%



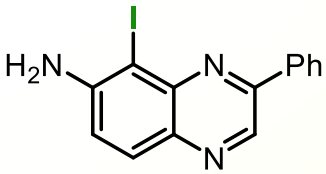
85%



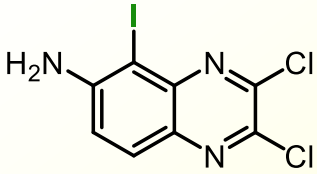
88%



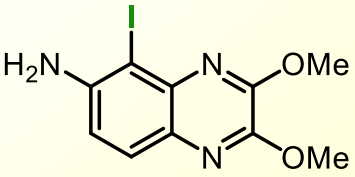
88%



75%



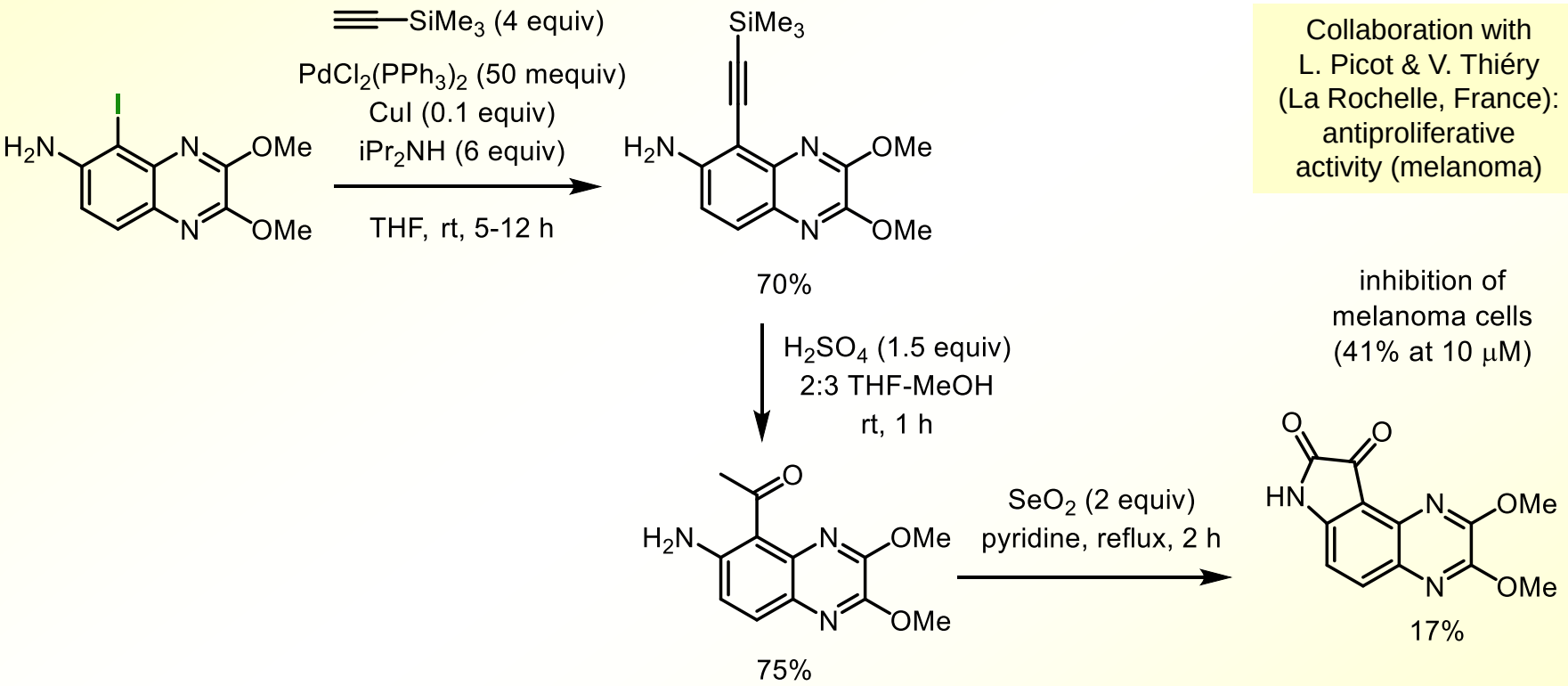
83%



86%

Selective introduction of iodine onto aromatic compounds

Access to pyrazinoisatin



Collaboration with L. Picot & V. Thiéry (La Rochelle, France): antiproliferative activity (melanoma)

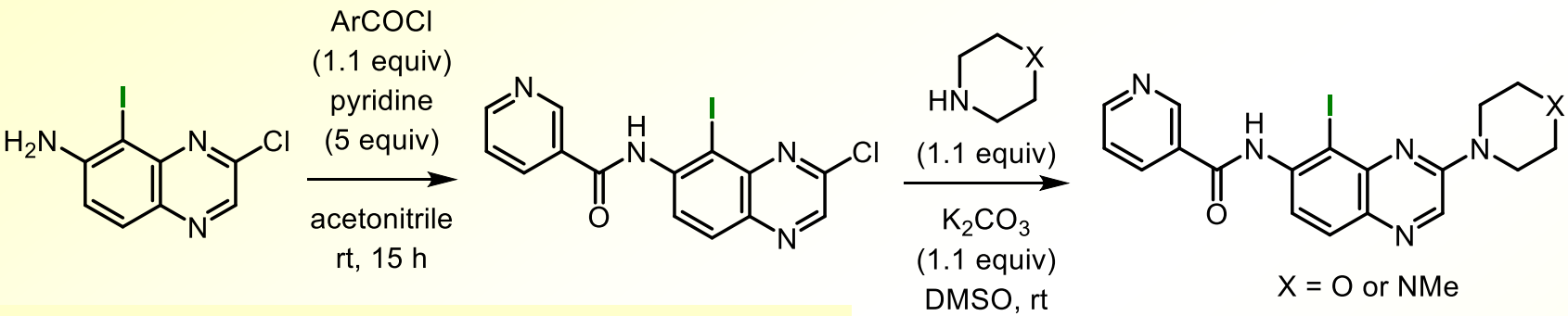
inhibition of melanoma cells (41% at 10 μM)

F. Lassagne, J. M. Sims, W. Erb, O. Mongin, N. Richy, N. El Osmani, Z. Fajloun, L. Picot, V. Thiéry, T. Robert, S. Bach, V. Dorcet, T. Roisnel, F. Mongin, *Eur. J. Org. Chem.* **2021**, 2756, and references cited therein.

Selective introduction of iodine onto aromatic compounds

Access to oxazoloquinoxalines

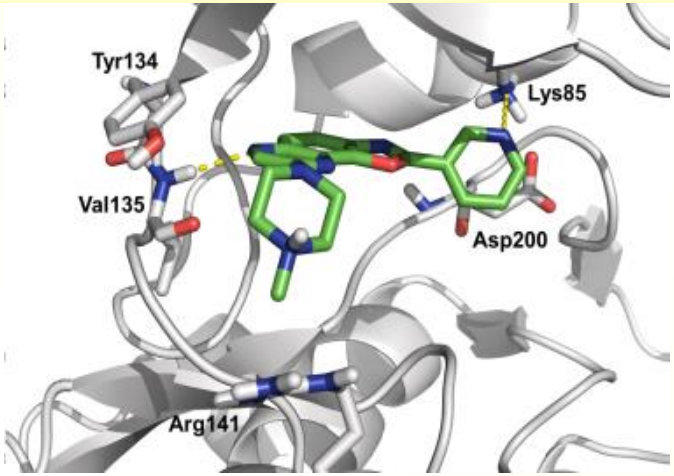
- Collaboration with T. Robert & S. Bach (Roscoff): kinase inhibition
- Collaboration with A. Martinez (Madrid): docking studies (GSK3-β)

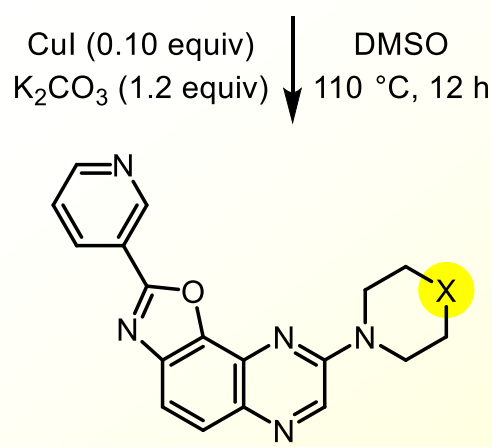


Absorption of FI-290 :
- molar extinction coefficient ε_{max}: 31400 at λ_{abs} = 300 nm (UV)

Fluorescence :
- λ_{em} = 455 nm (blue-violet) - quantum yield: 0.08

Docking of FI-277 in GSK3-β (below)





58-67% yield (3 steps)

X = O: IC_{50} (GSK3-α) = 15 nM; IC_{50} (GSK3-β) = 25 nM

FI-277: X = NMe: IC_{50} (GSK3-α) = 24 nM; IC_{50} (GSK3-β) = 55 nM

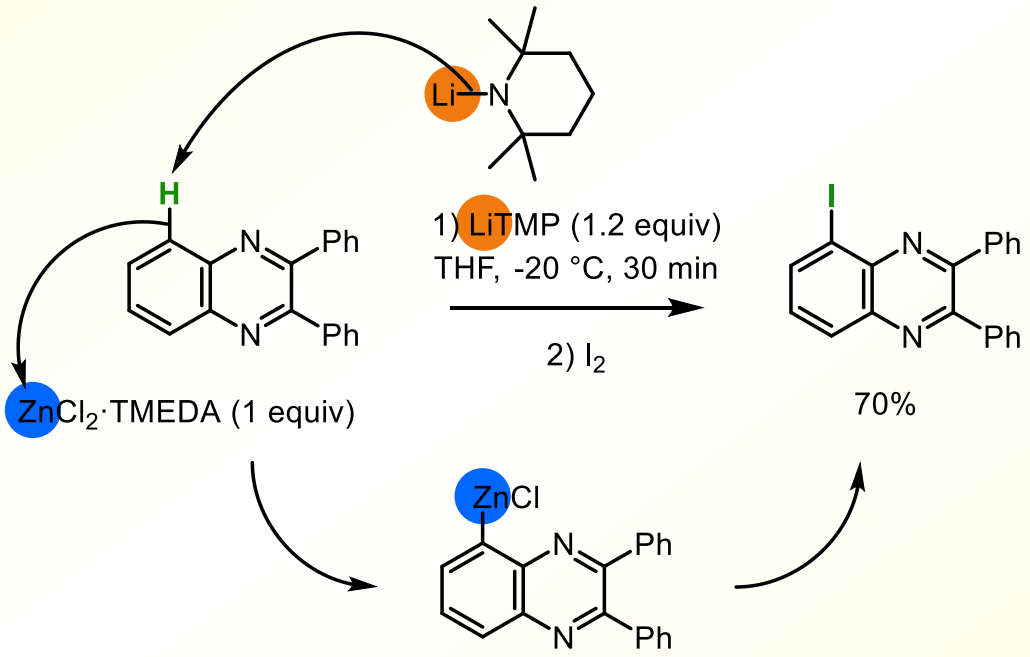
FI-290: X = CH_2: IC_{50} (GSK3-α) = 11 nM; IC_{50} (GSK3-β) = 33 nM

X = S: IC_{50} (GSK3-α) = 5 nM; IC_{50} (GSK3-β) = 22 nM

F. Lassagne, C. Duguépéroux, C. Roca, C. Perez, A. Martinez, B. Baratte, T. Robert, S. Ruchaud, S. Bach, W. Erb, T. Roisnel, F. Mongin, *Org. Biomol. Chem.* **2020**, *18*, 154.

Selective introduction of iodine onto aromatic compounds

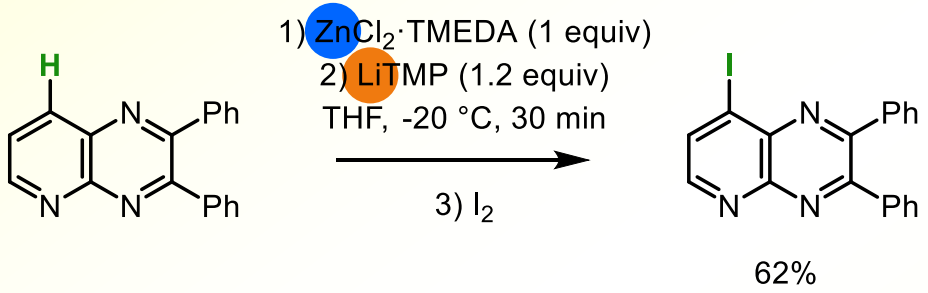
Deprotometalation-trapping using lithium-zinc bases as an alternative to direct iodination

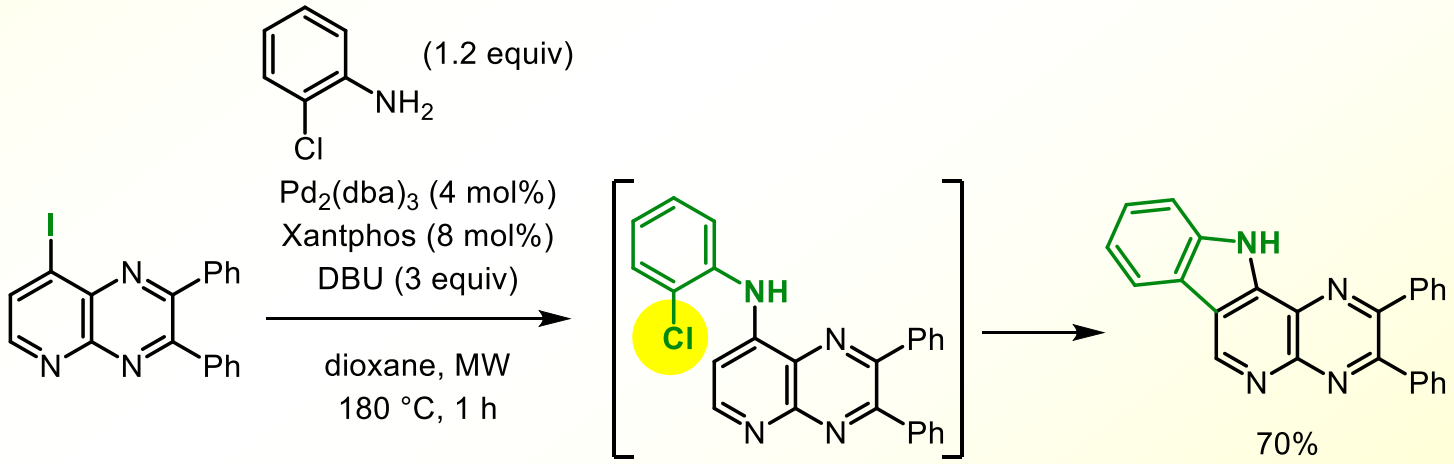


Short review: N. Mokhtari Brikci-Nigassa, G. Bentabed-Ababsa, W. Erb, F. Mongin, *Synthesis* **2018**, *50*, 3615.

Selective introduction of iodine onto aromatic compounds

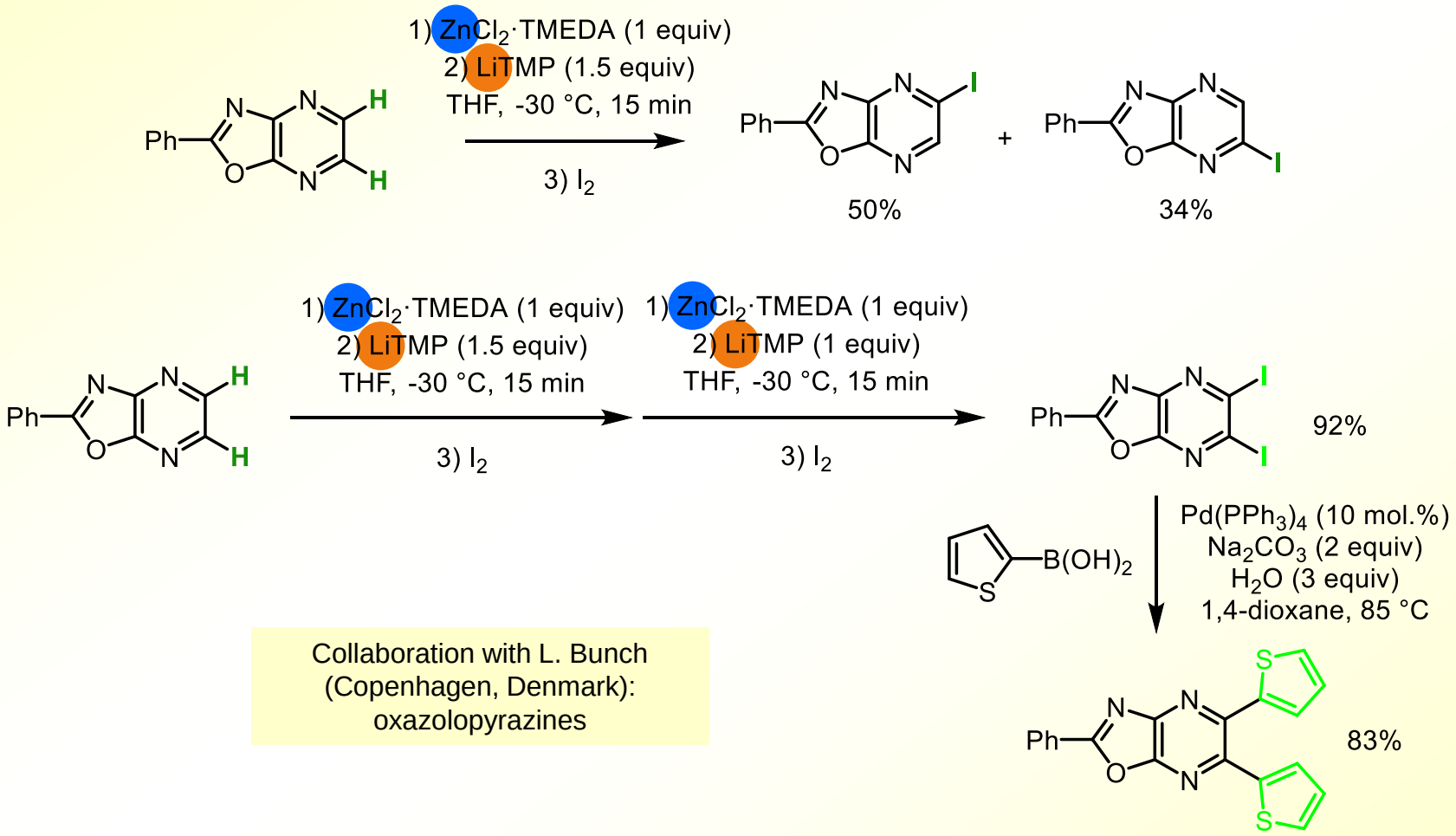
Access to pyrazinocarbolines





F. Lassagne, T. Langlais, E. Caytan, E. Limanton, L. Paquin, M. Boullard, C. Courtel, I. Curbet, C. Gédéon, J. Lebreton, L. Picot, V. Thiéry, M. Souab, B. Baratte, S. Ruchaud, S. Bach, T. Roisnel, F. Mongin, *Molecules* **2018**, *23*, 2961.

Access to oxazolopyrazines

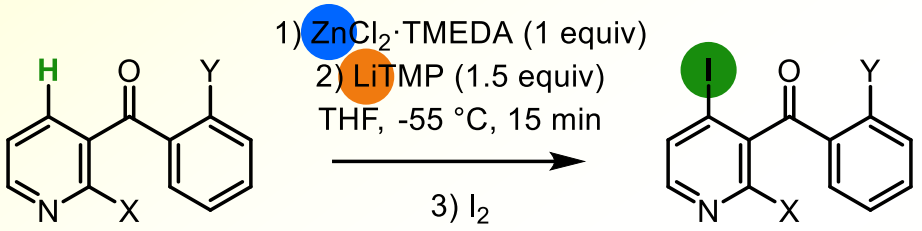


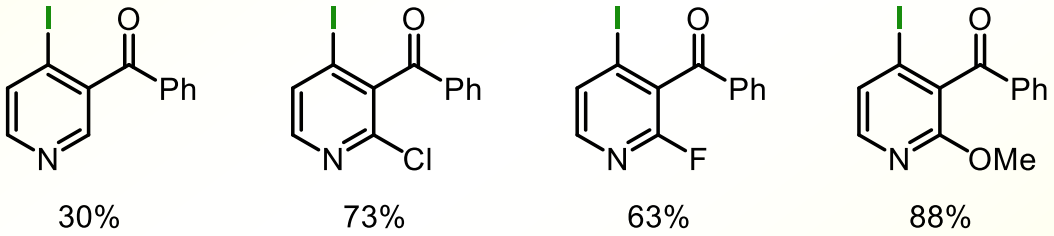
Collaboration with L. Bunch (Copenhagen, Denmark): oxazolopyrazines

N. Bisballe, M. Hedidi, C. S. Demmer, F. Chevallier, T. Roisnel, V. Dorcet, Y. S. Halauko, O. A. Ivashkevich, V. E. Matulis, G. Bentabed-Ababsa, L. Bunch, F. Mongin, *Eur. J. Org. Chem.* **2018**, 3904.

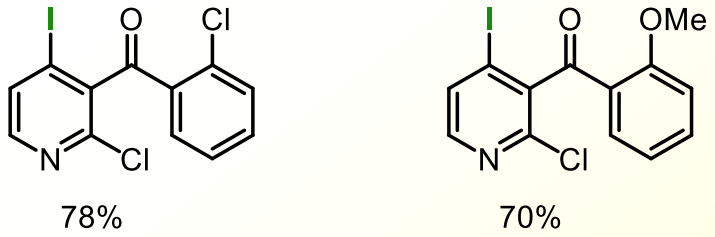
Selective introduction of iodine onto aromatic compounds

Deprotometalation-trapping using lithium-zinc bases as an alternative to direct iodination





30% 73% 63% 88%

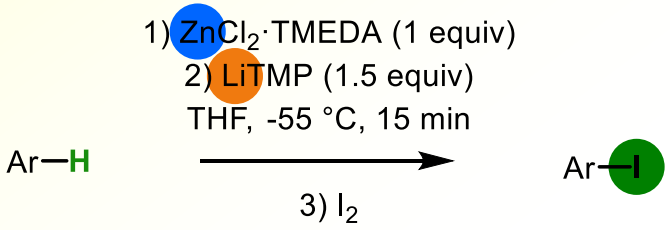


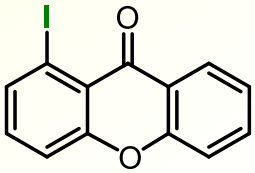
78% 70%

M. Hedidi, W. Erb, F. Lassagne, Y. S. Halauko, O. A. Ivashkevich, V. E. Matulis, T. Roisnel, G. Bentabed-Ababsa, F. Mongin, *RSC Adv*. **2016**, *6*, 63185.

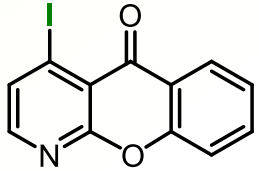
Selective introduction of iodine onto aromatic compounds

Deprotometalation-trapping using lithium-zinc bases as an alternative to direct iodination

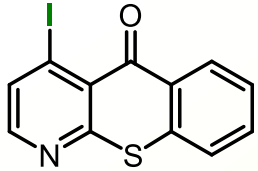




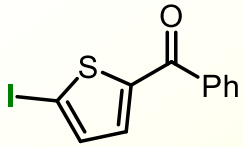
72%



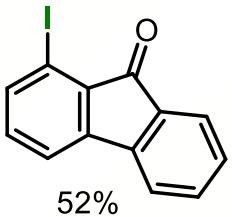
60%



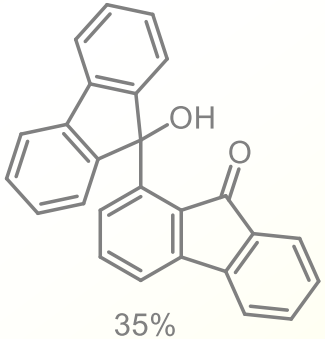
60%



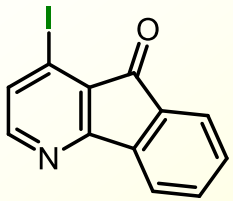
80%



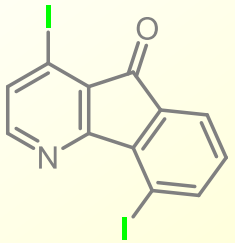
52%



35%



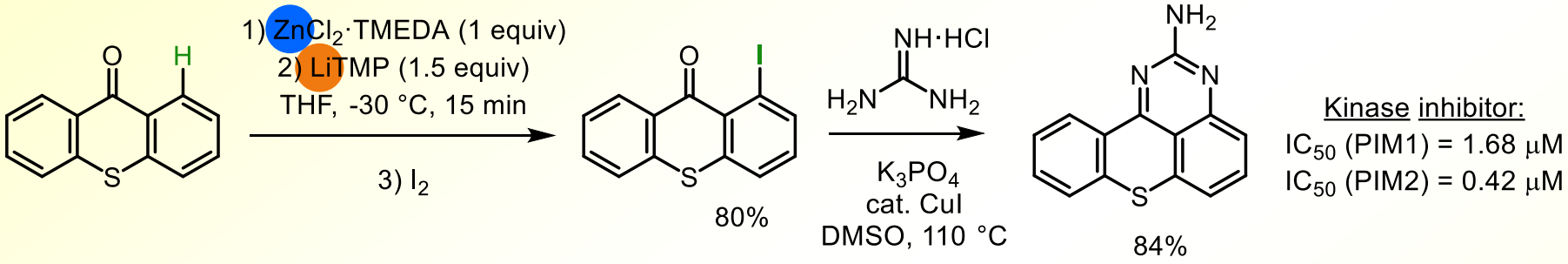
33%



20%

Selective introduction of iodine onto aromatic compounds

Access to benzothiopyranoquinazolines

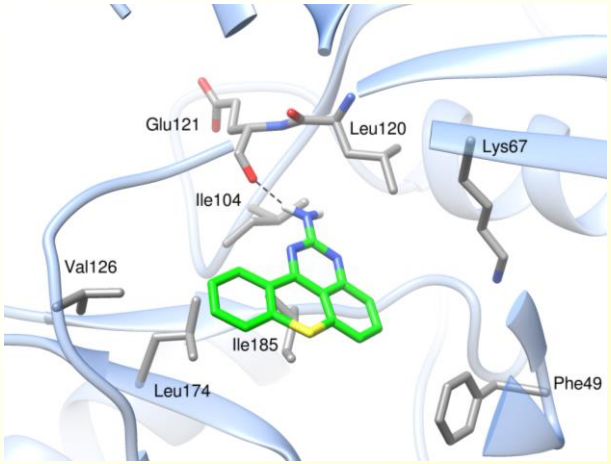


- Collaboration with T. Robert & S. Bach (Roscoff): kinase inhibition
- Collaboration with L. Picot & V. Thiéry (La Rochelle): antiproliferative activity
- Collaboration with L. Nauton & P. Moreau (Clermont): docking studies

PIM kinases: Regulate signaling pathways fundamental to cancer development and progression. Contribute to tumorigenesis.

Overexpressed in cancer cells:
- PIM1: non-Hodgkin's lymphoma, myeloid leukemia, prostate cancer
- PIM2: leukemia, lymphomas
- PIM3: melanoma, pancreatic and gastric tumors

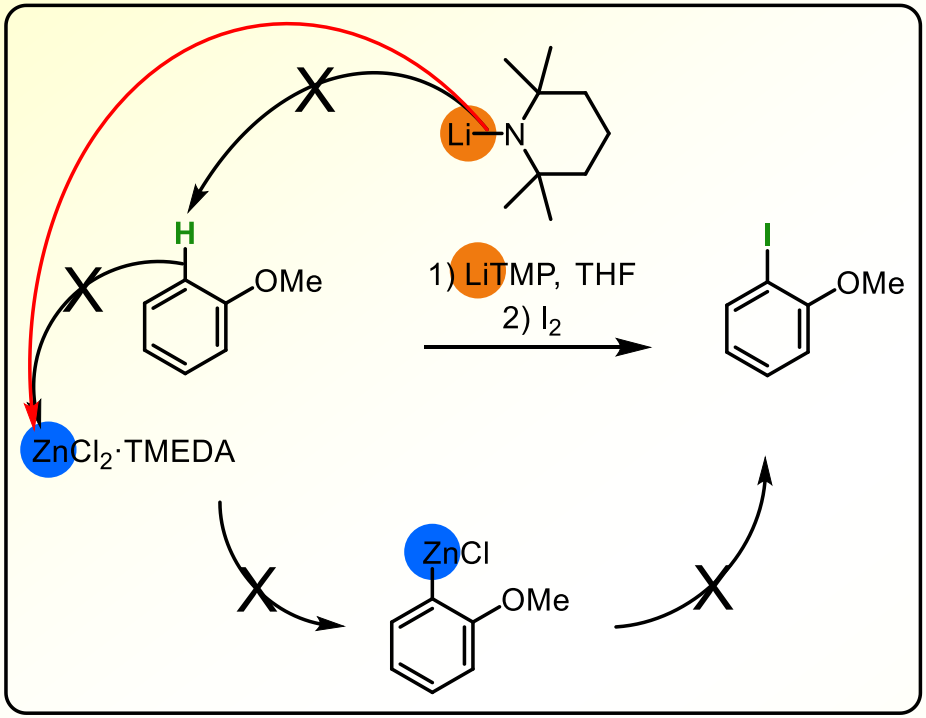
PIM1 mutant responsible for chemoresistance.

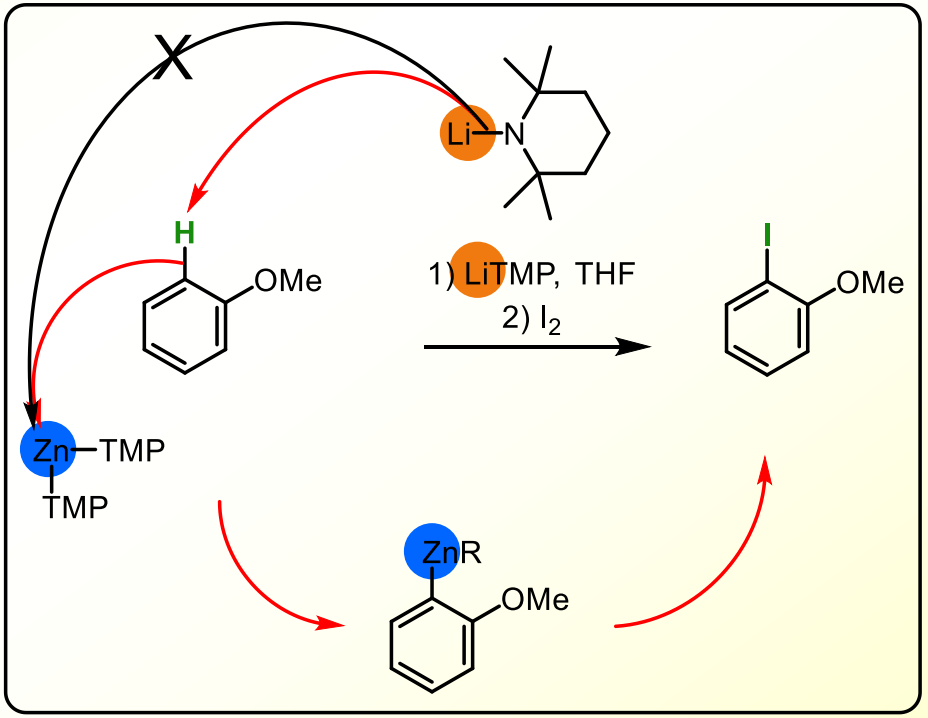


M. Hedidi, J. Maillard, W. Erb, F. Lassagne, Y. S. Halauko, O. A. Ivashkevich, V. E. Matulis, T. Roisnel, V. Dorcet, M. Hamzé, Z. Fajloun, B. Baratte, S. Ruchaud, S. Bach, G. Bentabed-Ababsa, F. Mongin, *Eur. J. Org. Chem.* **2017**, 5903.

Selective introduction of iodine onto aromatic compounds

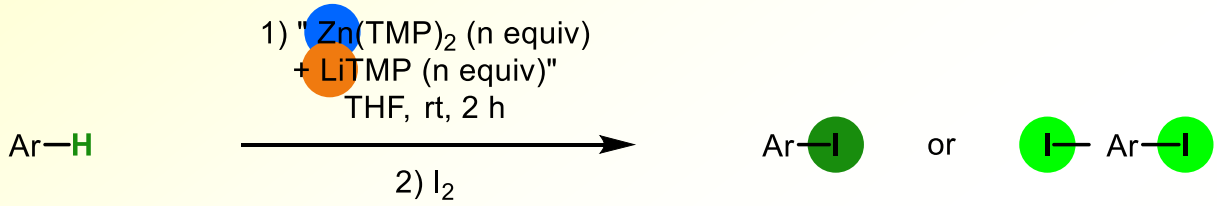
Deprotometalation-trapping using lithium-zinc bases as an alternative to direct iodination

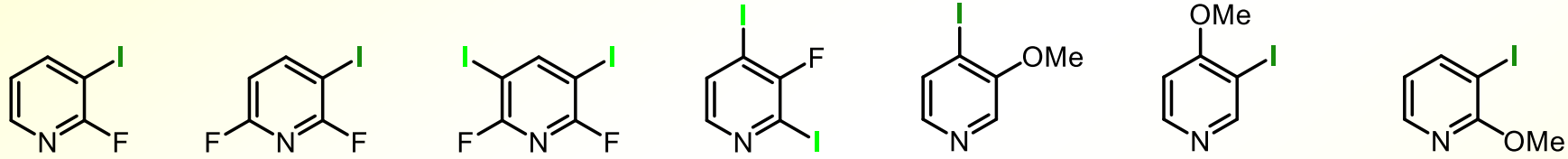




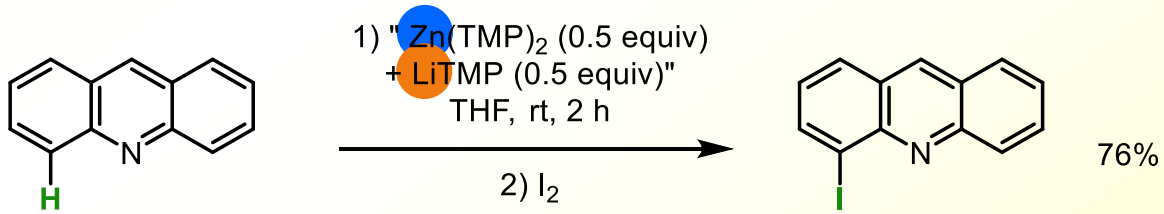
G. Akimoto, M. Otsuka, R. Takita, M. Uchiyama, M. Hedidi, G. Bentabed-Ababsa, F. Lassagne, W. Erb, F. Mongin, *J. Org. Chem.* **2018**, *83*, 13498, and references cited therein.

Functionalization of azines



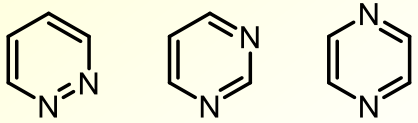


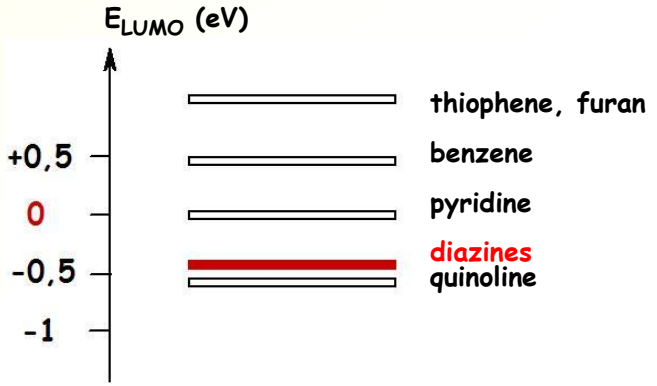
M. Hedidi, G. Bentabed-Ababsa, A. Derdour, Y. S. Halauko, O. A. Ivashkevich, V. E. Matulis, F. Chevallier, T. Roisnel, V. Dorcet, F. Mongin, *Tetrahedron* **2016**, *72*, 2196.

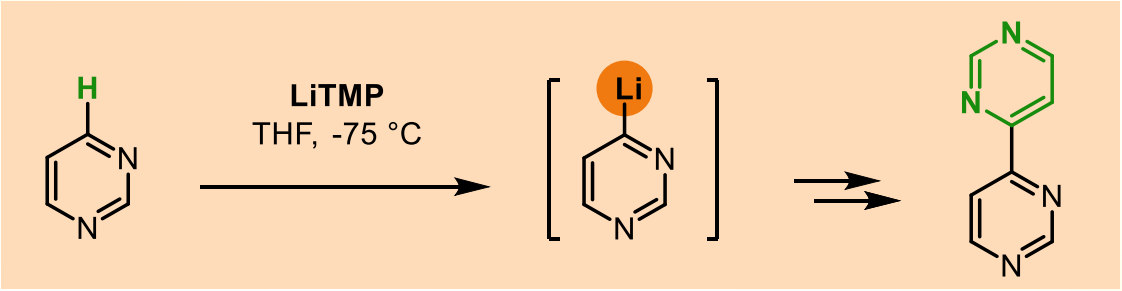


S. Zeghada, G. Bentabed-Ababsa, O. Mongin, W. Erb, L. Picot, V. Thiéry, T. Roisnel, V. Dorcet, F. Mongin *Tetrahedron* **2020**, *76*, 131435.

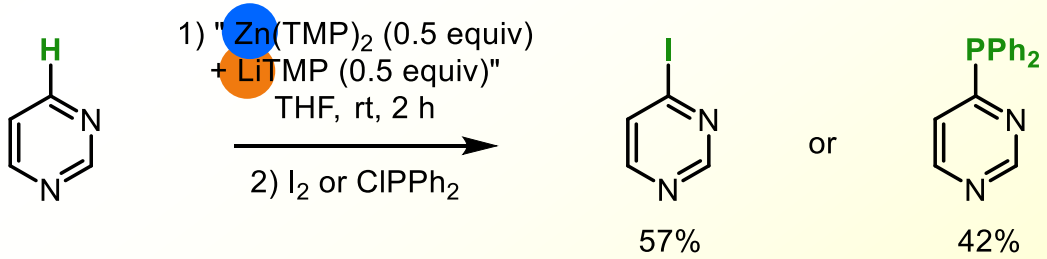
Functionalization of diazines







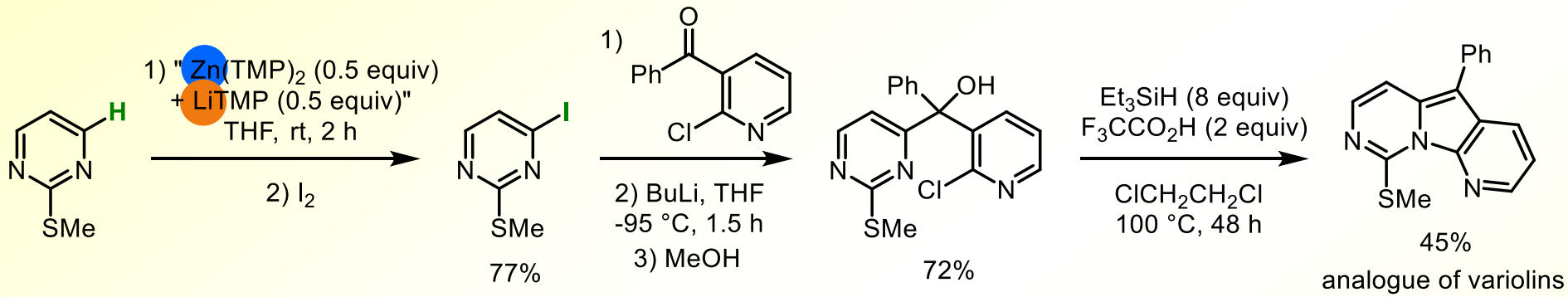
N. Plé, A. Turck, K. Couture, G. Quéguiner, *J. Org. Chem.* **1995**, *60*, 3781.



A. Seggio, F. Chevallier, M. Vaultier, F. Mongin, *J. Org. Chem.* **2007**, *72*, 6602.

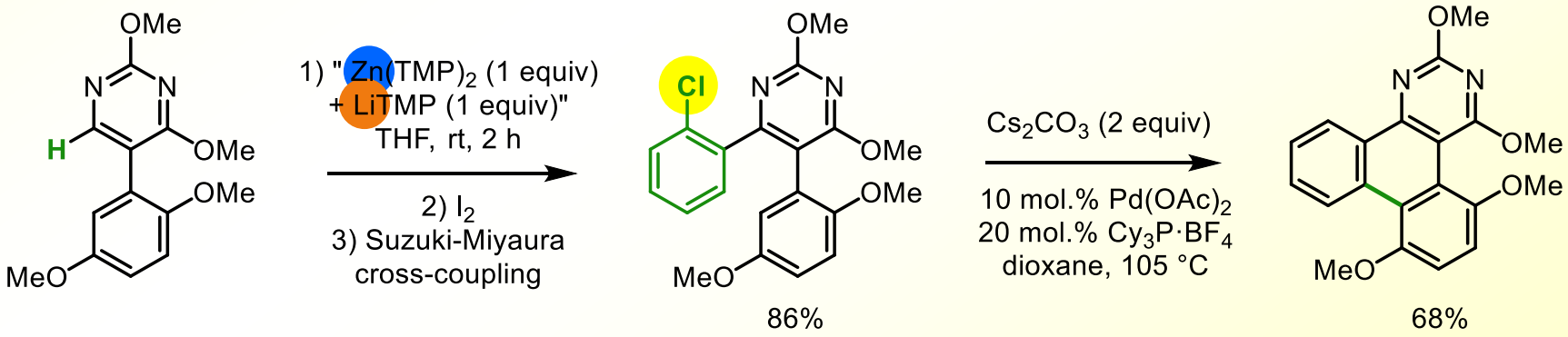
Selective introduction of iodine onto aromatic compounds

Access to analogue of variolins



N. Marquise, T. T. Nguyen, F. Chevallier, L. Picot, V. Thiéry, O. Lozach, S. Bach, S. Ruchaud, F. Mongin, *Synlett* **2015**, *26*, 2811.

Access to nitrogen-containing polyaromatic hydrocarbon



R. R. Kadiyala, D. Tilly, E. Nagaradja, T. Roisnel, V. E. Matulis, O. A. Ivashkevich, Y. S. Halauko, F. Chevallier, P. C. Gros, F. Mongin, *Chem. Eur. J.* **2013**, *19*, 7944.

Aromatic Iodides: Synthesis and Conversion to Heterocycles

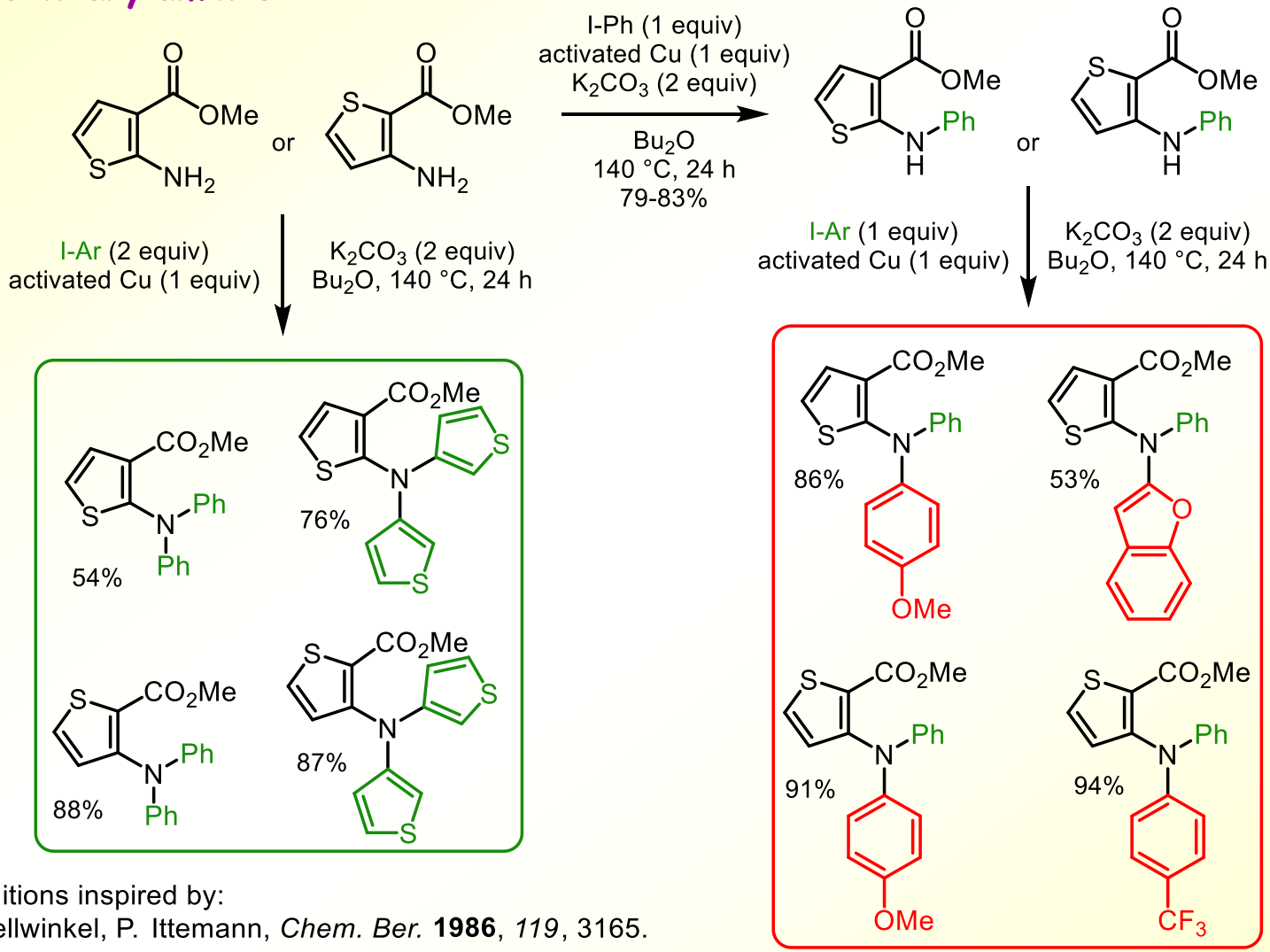
- Selective Introduction of Iodine onto Aromatic Compounds :

  → Direct iodination and application to the synthesis of heterocycles of interest

  → Deprotometalation with in situ trapping-iodolysis as an alternative to direct iodination

- Aromatic Iodides in Copper-mediated *N*-arylation of Anilines

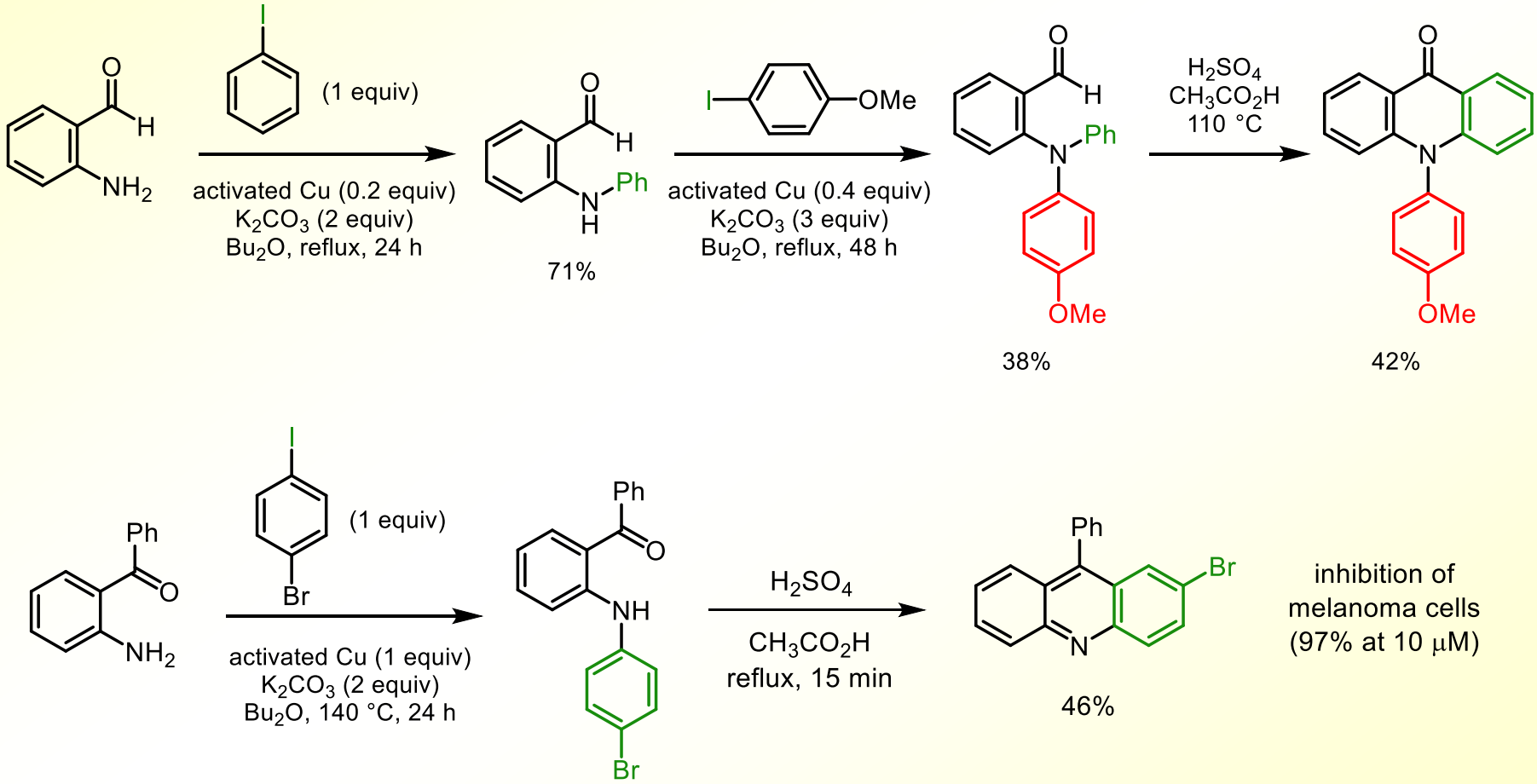
Access to triarylamines



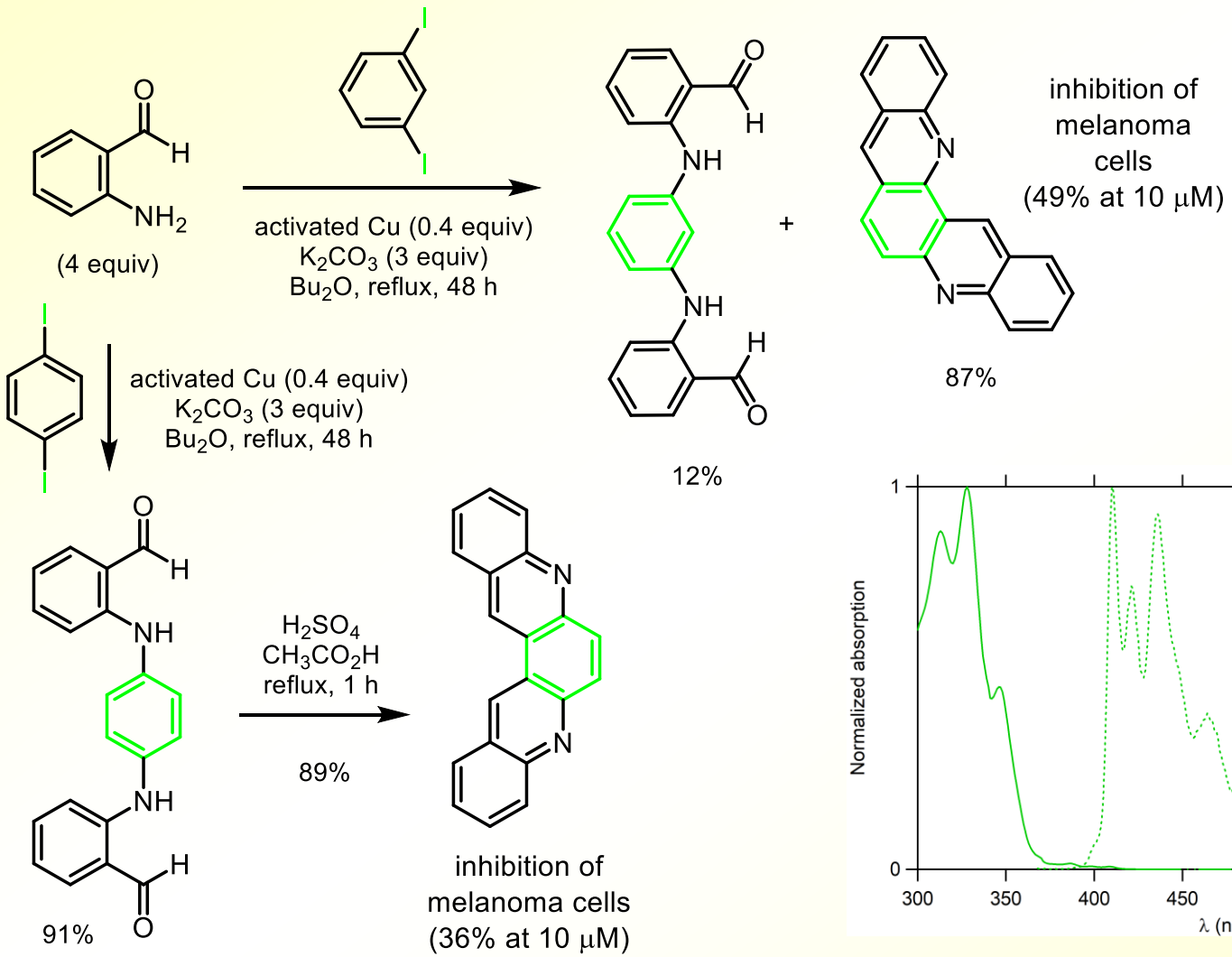
Conditions inspired by:
D. Hellwinkel, P. Ittemann, *Chem. Ber.* **1986**, *119*, 3165.

S. Bouarfa, S. Graβl, M. Ivanova, T. Langlais, G. Bentabed-Ababsa, F. Lassagne, W. Erb, T. Roisnel, V. Dorcet, P. Knochel, F. Mongin, *Eur. J. Org. Chem.* **2019**, 3244.

Access to acridones or acridines



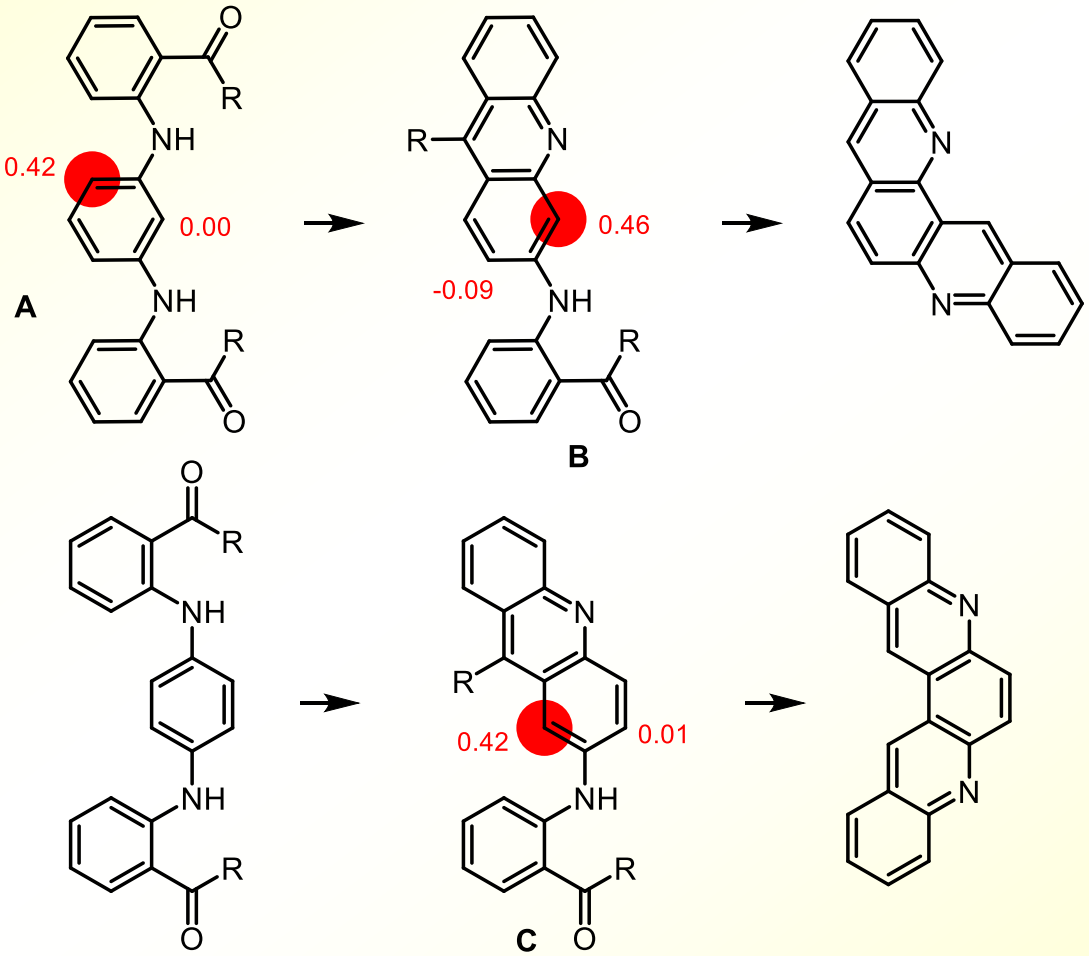
Access to aza-aromatic polycycles



Collaboration with L. Picot & V. Thiéry (La Rochelle, France): antiproliferative activity (melanoma)

S. Zeghada, G. Bentabed-Ababsa, O. Mongin, W. Erb, L. Picot, V. Thiéry, T. Roisnel, V. Dorcet, F. Mongin
Tetrahedron **2020**, *76*, 131435, and references cited therein.

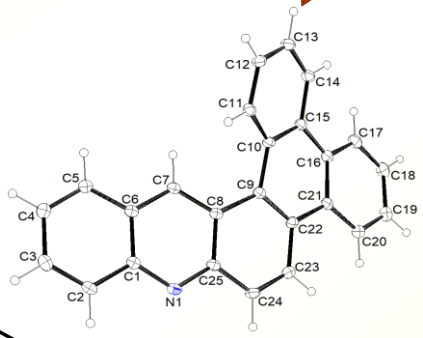
Access to aza-aromatic polycycles

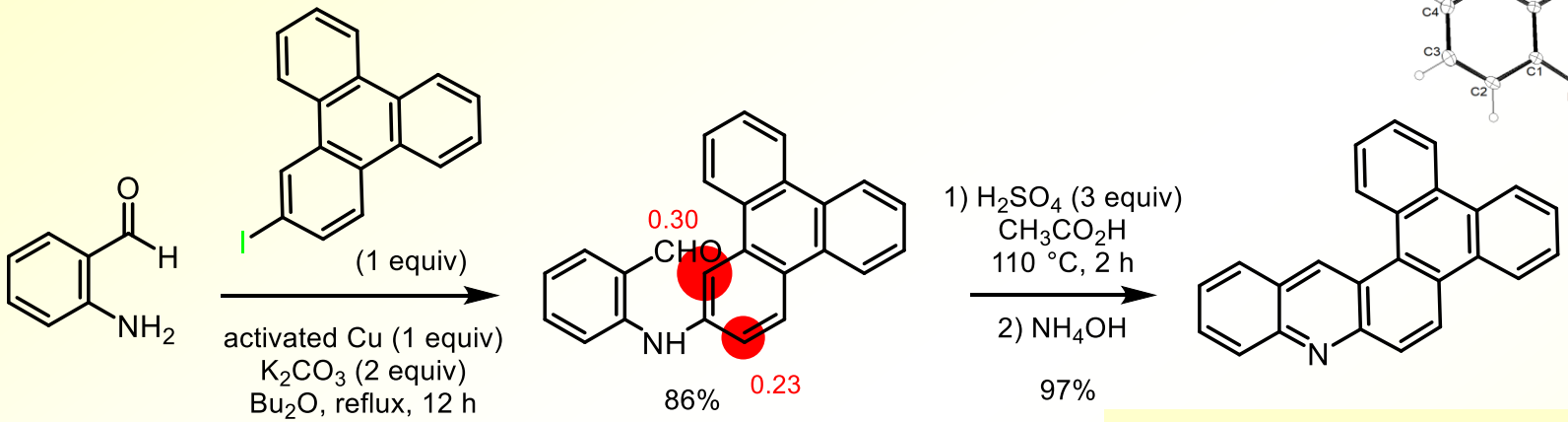


Amplitudes of the HOMO coefficients obtained by using the HuLiS calculator: N. Goudard, Y. Carissan, D. Hagebaum-Reignier and S. Humbel, HuLiS 3.3.4, http://ism2.univ-amu.fr/hulis.

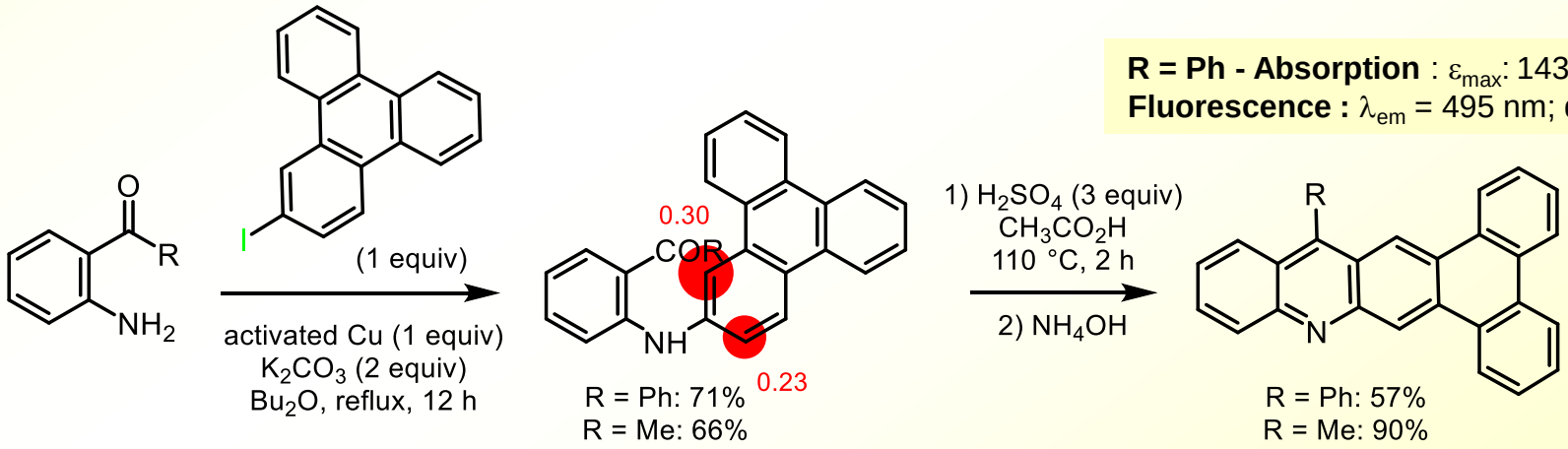
Aromatic iodides in copper-mediated N-arylation of anilines

Access to aza-aromatic polycycles





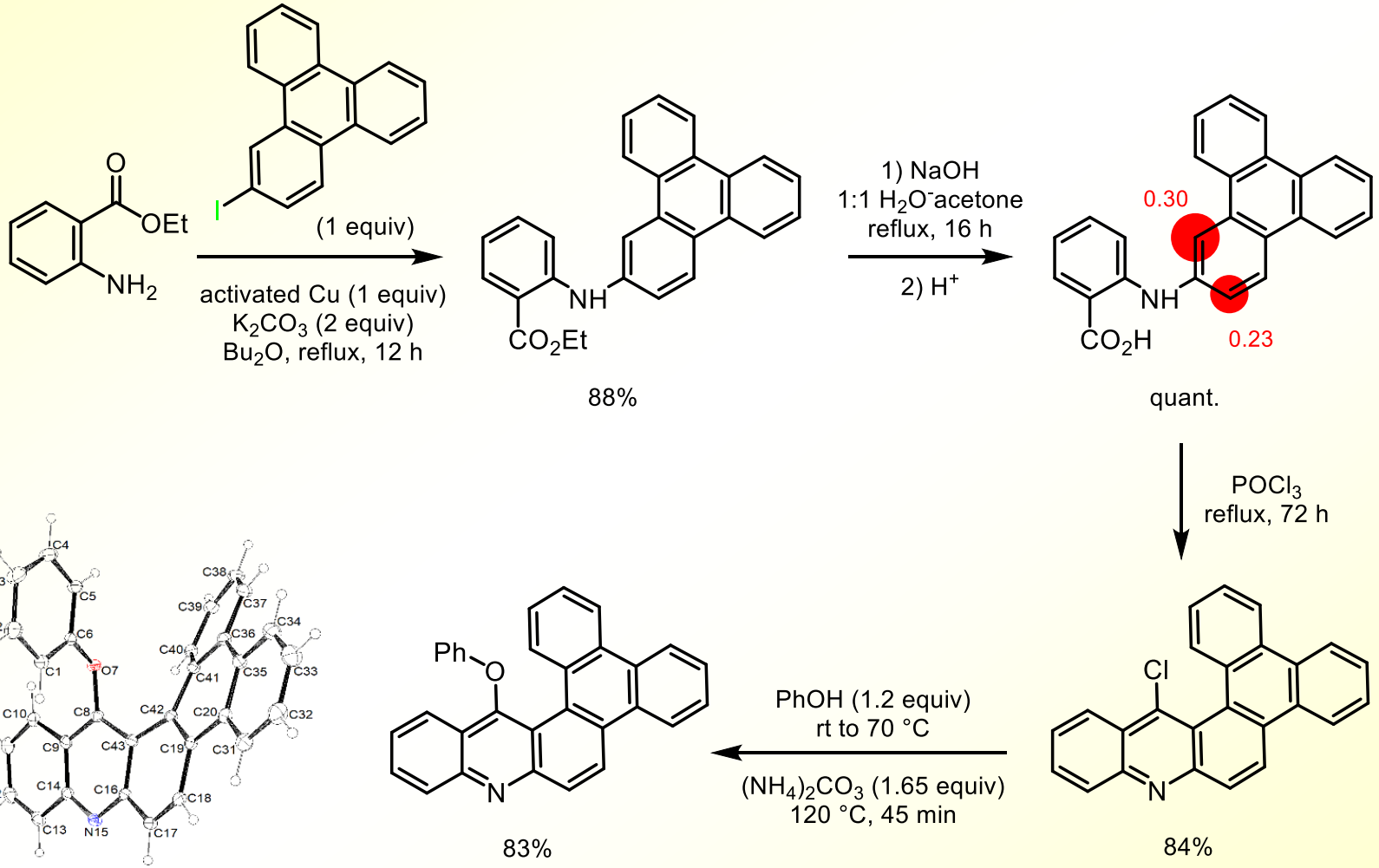
Absorption : ε_{max}: 9480 at λ_{abs} = 392 nm
Fluorescence : λ_{em} = 447 nm; quantum yield: 0.06



R = Ph - Absorption : ε_{max}: 14300 at λ_{abs} = 414 nm
Fluorescence : λ_{em} = 495 nm; quantum yield: 0.30

R = Me - Absorption : ε_{max}: 12000 at λ_{abs} = 412 nm
Fluorescence : λ_{em} = 485 nm; quantum yield: 0.14

Access to aza-aromatic polycycles



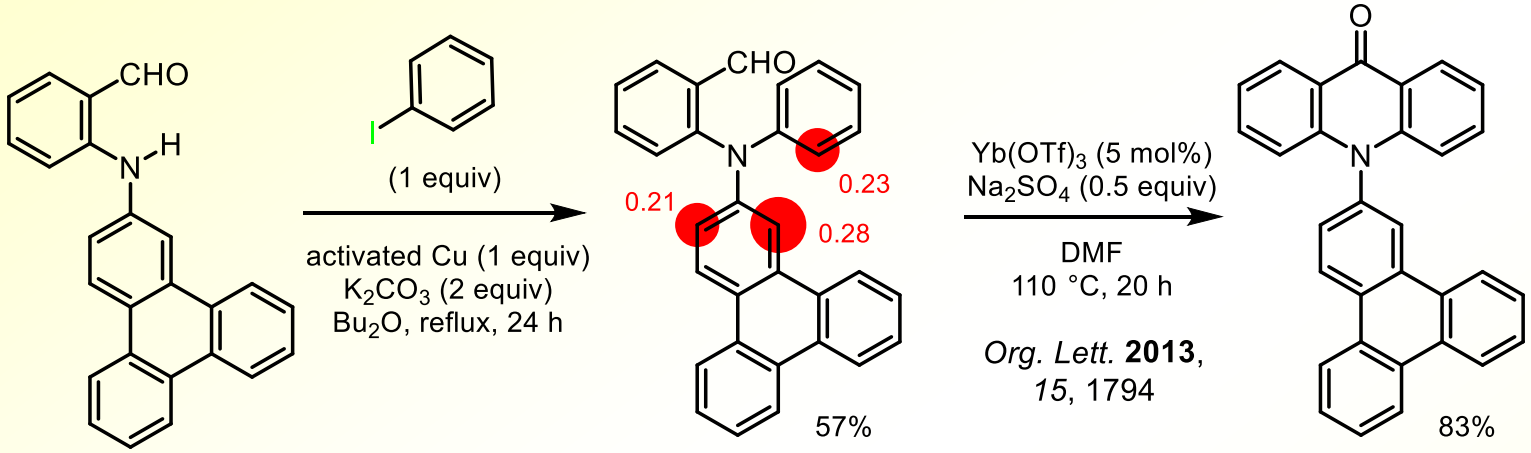
Absorption : ε_{max}: 11000 at λ_{abs} = 399 nm
Fluorescence : λ_{em} = 463 nm; quantum yield: 0.05

Absorption : ε_{max}: 11500 at λ_{abs} = 406 nm
Fluorescence : λ_{em} = 467 nm; quantum yield: 0.02

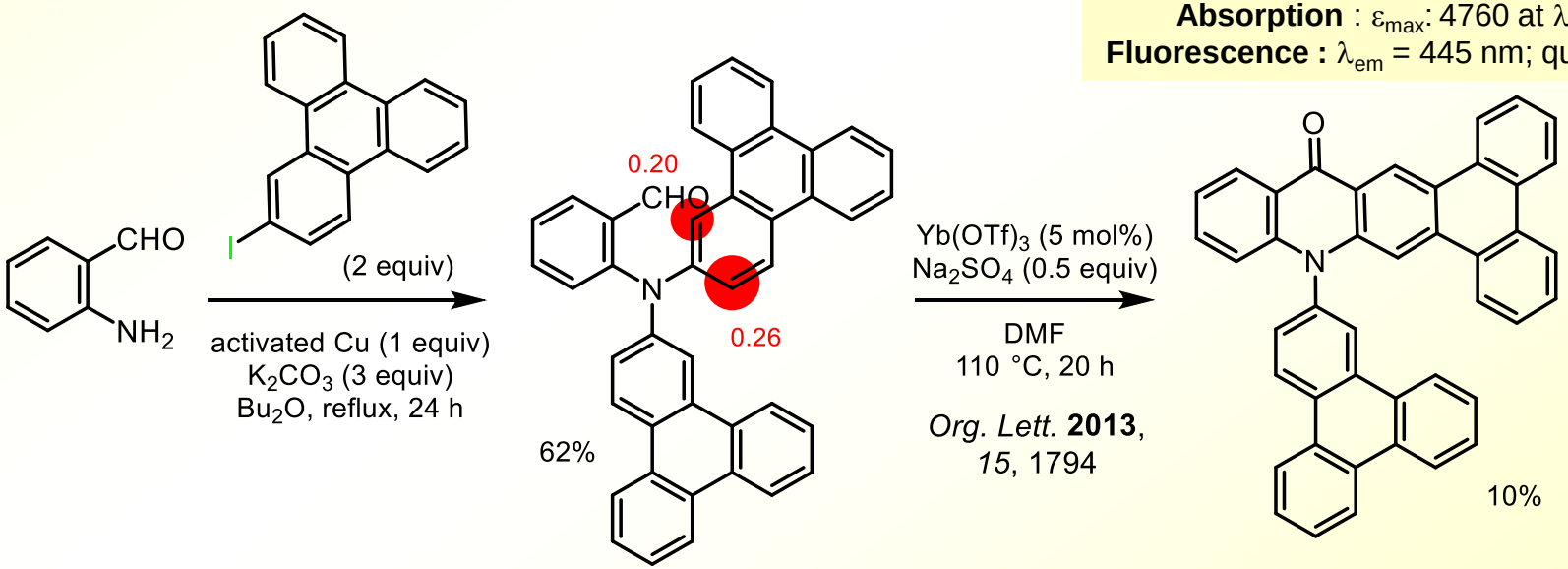
Aromatic iodides in copper-mediated *N*-arylation of anilines

Access to new acridones

Absorption : ε_{max}: 8940 at λ_{abs} = 391 nm
Fluorescence : λ_{em} = 398 nm; quantum yield: 0.03



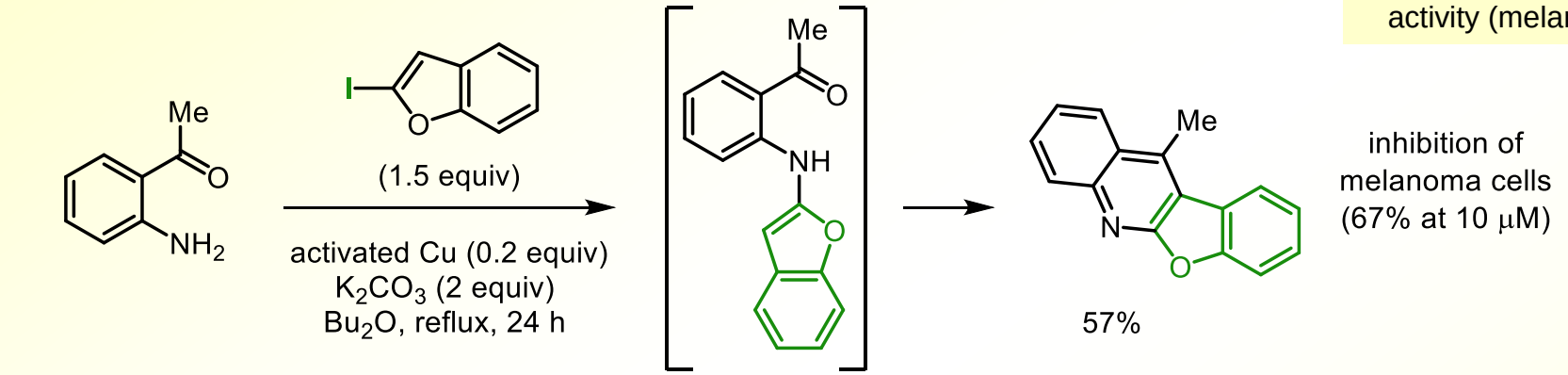
Absorption : ε_{max}: 4760 at λ_{abs} = 436 nm
Fluorescence : λ_{em} = 445 nm; quantum yield: 0.08

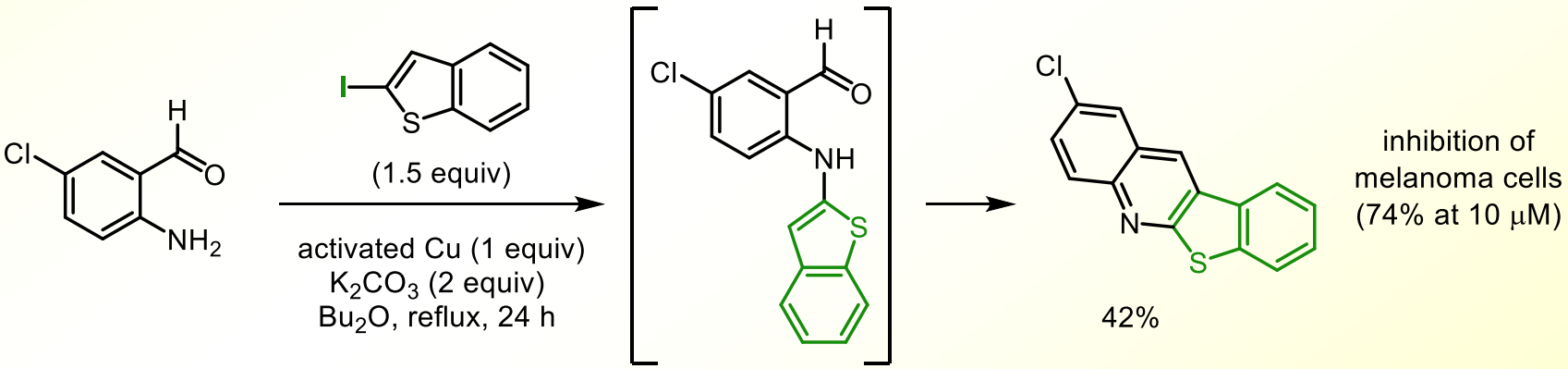


S. Bouarfa, P. Jéhan, W. Erb, O. Mongin, F.-H. Porée, T. Roisnel, G. Bentabed-Ababsa, N. Le Yondre, F. Mongin
New J. Chem. **2021**, *45*, 14414, and references cited therein.

Access to benzofuro- and benzothienoquinolines

Collaboration with L. Picot & V. Thiéry (La Rochelle, France): antiproliferative activity (melanoma)

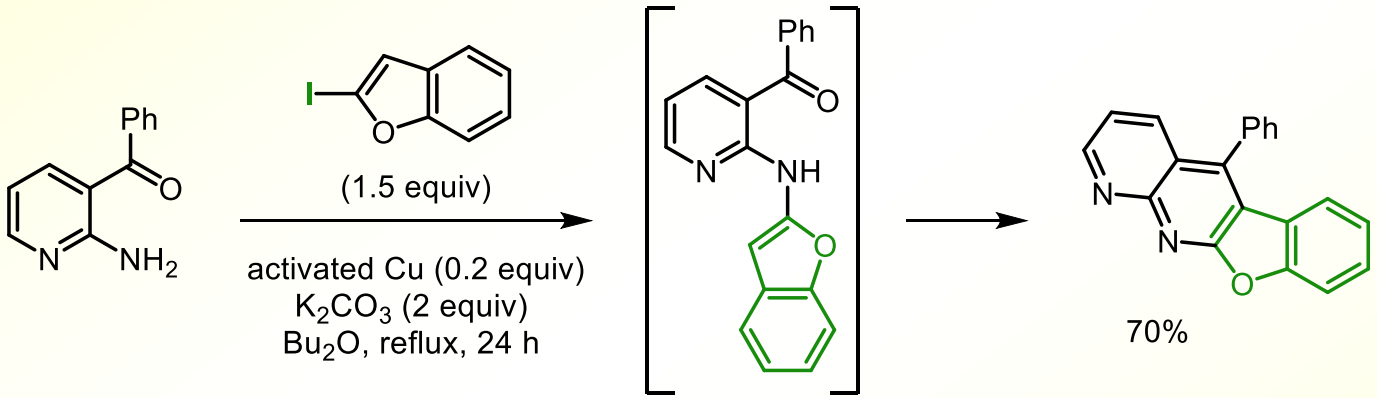




S. Bouarfa, G. Bentabed-Ababsa, W. Erb, L. Picot, V. Thiéry, T. Roisnel, V. Dorcet, F. Mongin, *Synthesis* **2021**, *53*, 1271.

Access to benzofuro- and benzothienoquinolines

Collaboration with T. Robert & S. Bach (Roscoff, France): kinase inhibition



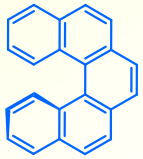
70%

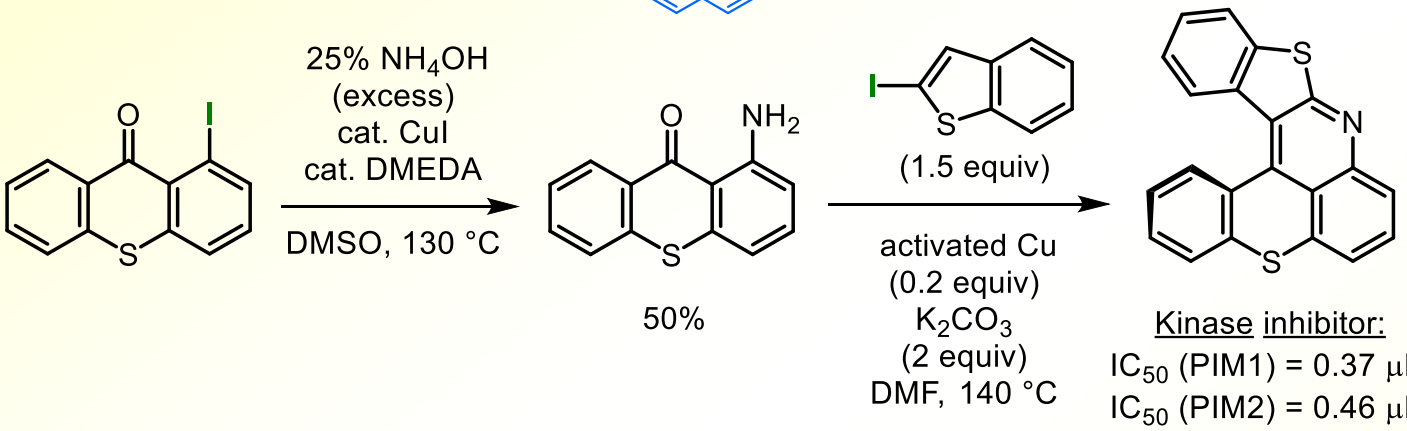
inhibition of PIM1 kinase (44% remaining activity at 1 μM)

N. Mokhtari Brikci-Nigassa, G. Bentabed-Ababsa, W. Erb, F. Chevallier, L. Picot, L. Vitek, A. Fleury, V. Thiéry, M. Souab, T. Robert, S. Ruchaud, S. Bach, T. Roisnel, F. Mongin, *Tetrahedron* **2018**, *74*, 1785.

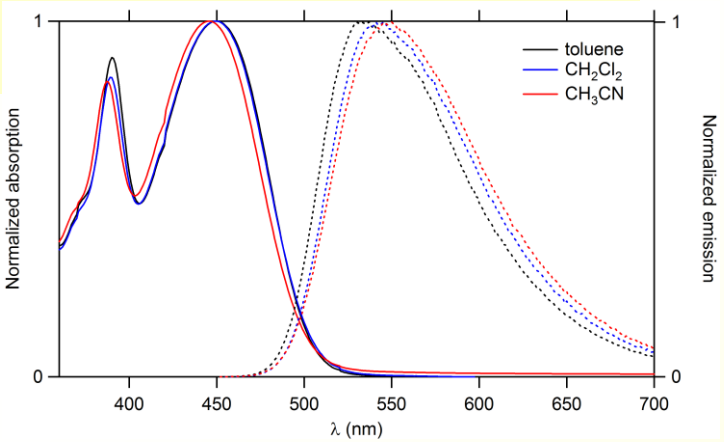
Aromatic iodides in copper-mediated N-arylation of anilines

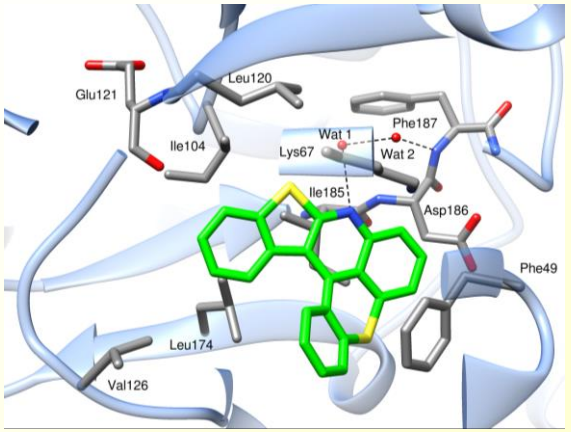
Access to new helicene-like structure





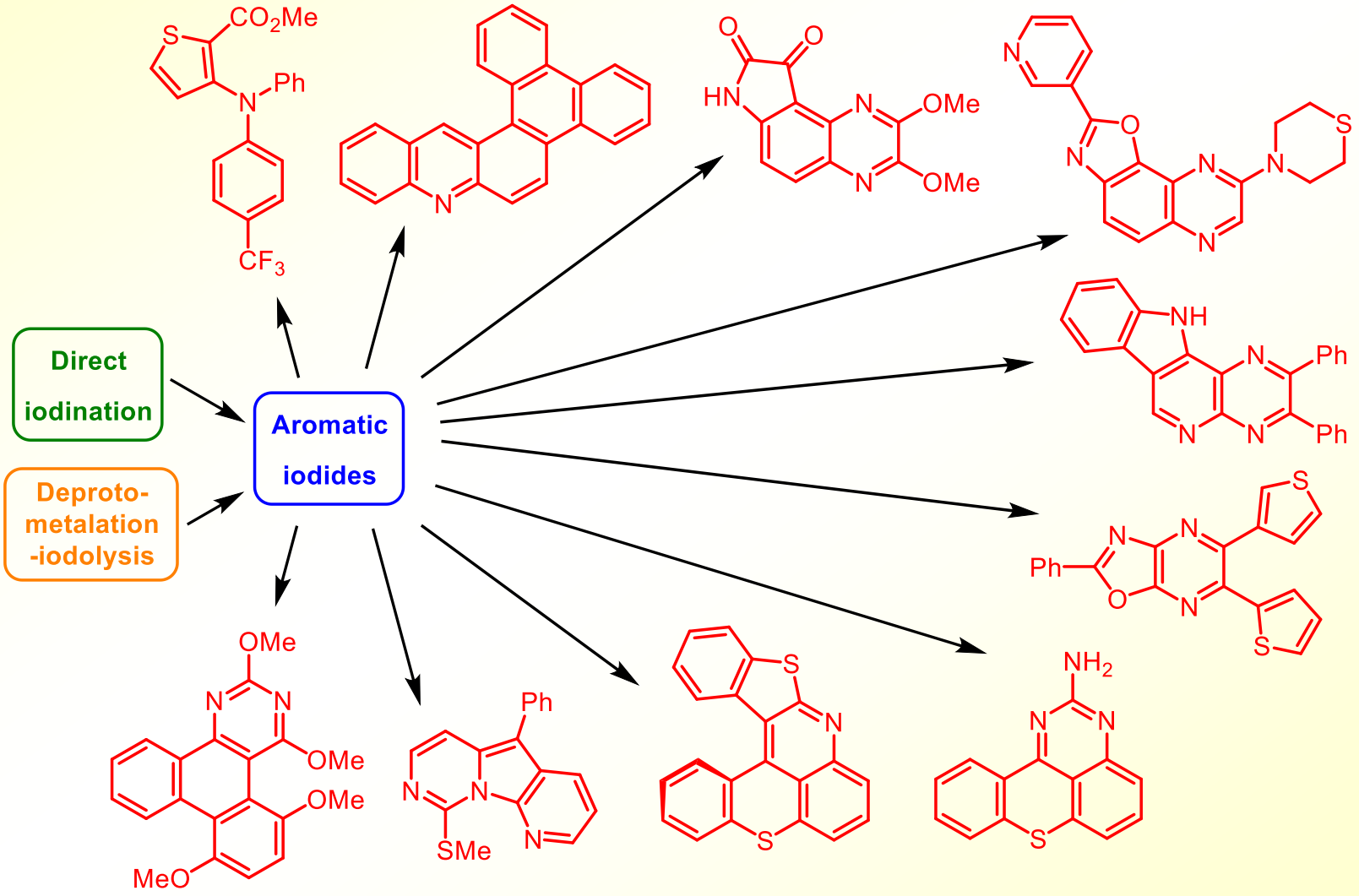
Absorption :
molar extinction coefficient ε_{max}: 6800 at λ_{abs} = 449 nm (blue-violet)
Fluorescence :
- λ_{em} = 532 nm (green)
- quantum yield: 0.50





N. Mokhtari Brikci-Nigassa, L. Nauton, P. Moreau, O. Mongin, R. E. Duval, L. Picot, V. Thiéry, M. Souab, S. Ruchaud, B. Baratte, S. Bach, R. Le Guevel, G. Bentabed-Ababsa, W. Erb, T. Roisnel, V. Dorcet, F. Mongin, *Bioorg. Chem.* **2020**, *94*, 103347.

Aromatic Iodides: Synthesis and Conversion to Heterocycles



Acknowledgements

Mohammed-Yacine AMEUR MESSAOUD (PhD)
Salima BOUARFA (PhD)
Madani HEDIDI (PhD, Postdoc)
Nada MARQUISE (PhD)
Nahida MOKHTARI BRIKCI-NIGASSA (PhD)
Elisabeth NAGARADJA (PhD)
Anne SEGGIO (PhD)

Dr Raghuram KADIYALA (Postdoc)
Dr David TILLY (Postdoc)
Dr Sarah ZEGHADA (Postdoc)

Niels BISBALLE
Camille DUGUEPEROUX
Timothy LANGLAIS
Joshua M. SIMS

Dr William ERB (Ass. Prof.)
Frédéric LASSAGNE (Tech.)
Dr Floris CHEVALLIER (Ass. Prof.)

Collaborations in Rennes:

V. Dorcet, T. Roisnel (X-ray diffraction)
N. Richy, O. Mongin (fluorescence)
E. Limanton, L. Paquin (microwaves)

Other collaborations:

G. Bentabed-Ababsa (Oran, Algeria)
L. Bunch (Copenhagen, Denmark)
A. Martinez (Madrid, Spain)
L. Nauton, P. Moreau (Clermont-Ferrand)
L. Picot, V. Thiéry (La Rochelle, France)
T. Robert, S. Bach (Roscoff, France)