Cobalt-Catalysed Atroposelective C-H Arylation

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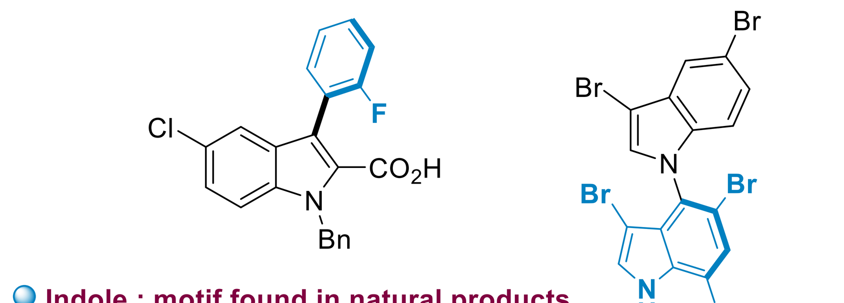
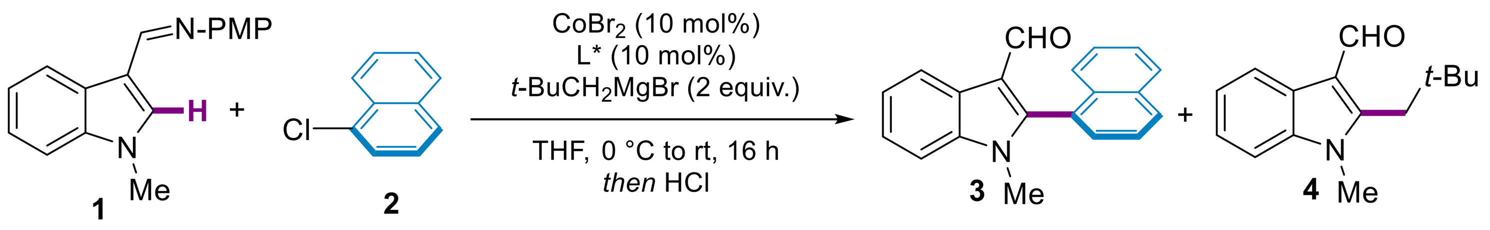
Introduction

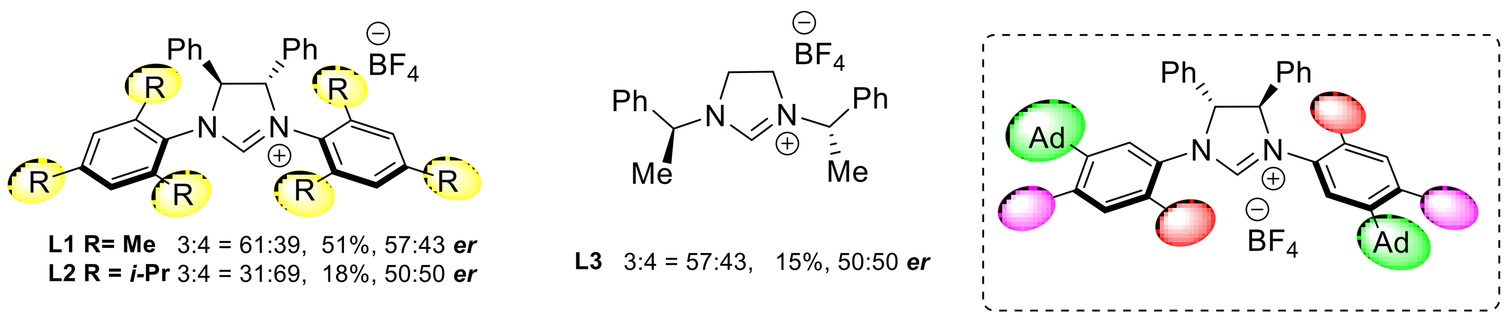
Atropisomeric compounds have been attracting a growing attention over the last decades thanks to their wide applications.[1] C-H activation has become a powerful tool to construct atropisomeric molecules, however this strategy is still limited to the use of noble metals.[2,3] In this work, we report a low valent cobalt(I) catalyzed atroposelective direct arylation, furnishing C2-arylated indoles with excellent enantioselectivities under mild conditions. This approach can also be extended to another type of axial chirality.

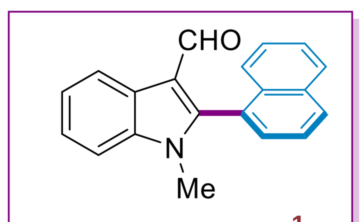


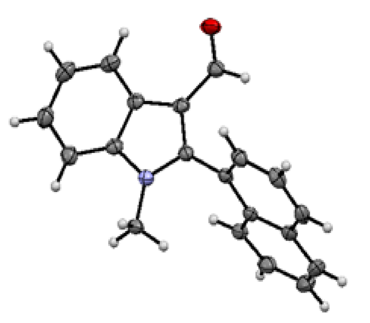
Optimization of the C-H arylation

Yoshikai's pioneering work in the field of cobalt-catalysed C-H activation has provided a ternary catalytic system to access C2-arylated indoles.[4] Inspired by this work, we selected a *N*-methyl indole bearing an imine at the C3 position (to allow the chelation assistance) and 1-chloronaphtalene as coupling partners, targeting the synthesis of the atropostable product. A variety of chiral ligands have been screened to evaluate the yield and enantioselectivity of the transformation.







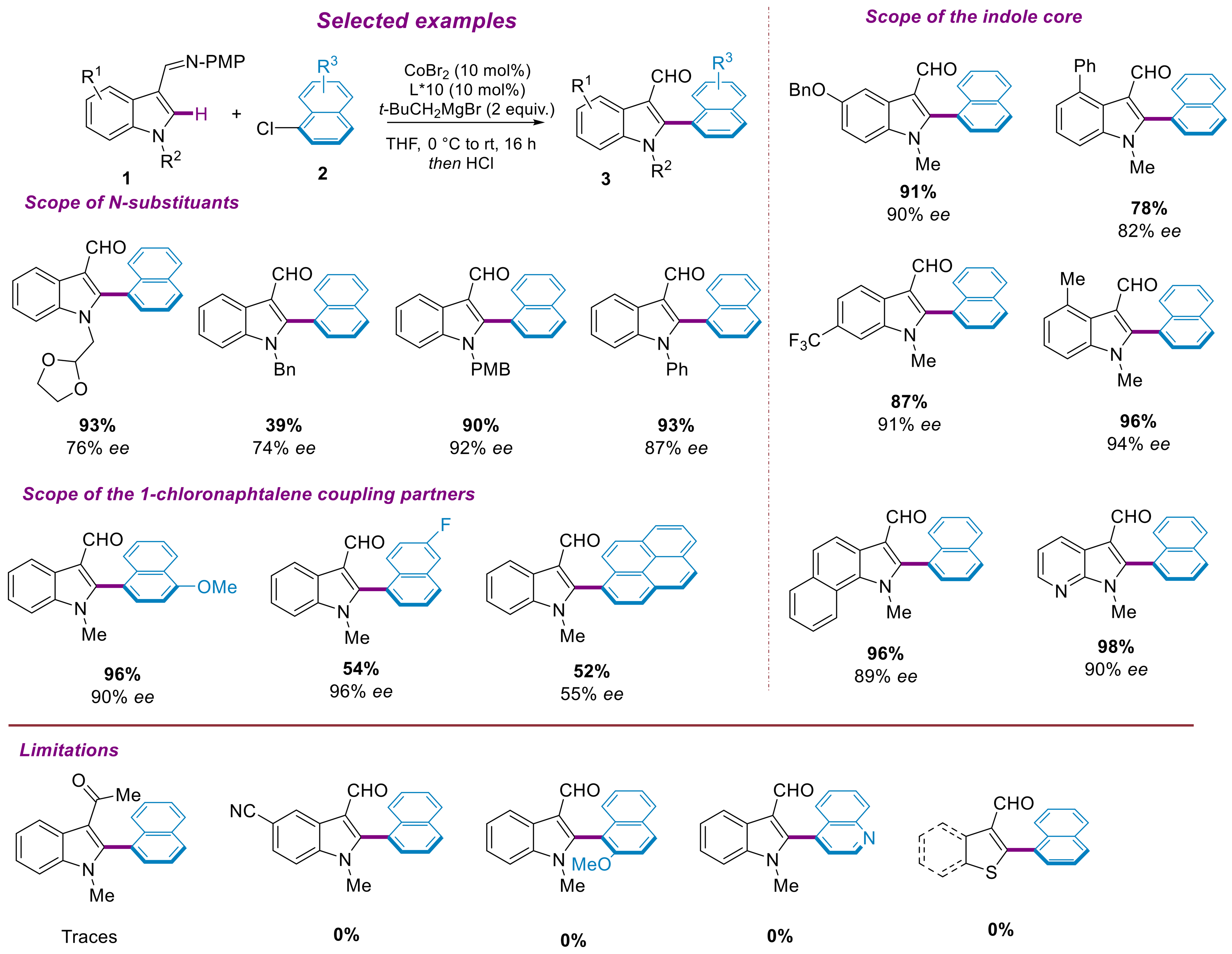


Ligand			3:4	Yield	er
L*4	Me	H	>95:5	70%	93:7
L*5	i-Pr	H	80:20	64%	16:84
L*6	OMe	H	53:47	42%	72:28
L*7	Me	Me	92:8	67%	94:6
L*10	**Me**	**OMe**	**95:5**	**99%**	**96:4**
L*11	Me	Oi-Pr	75:25	61%	85:15

✓ *Importance of Adamantyl in meta position*
✓ *Large scale synthesis*

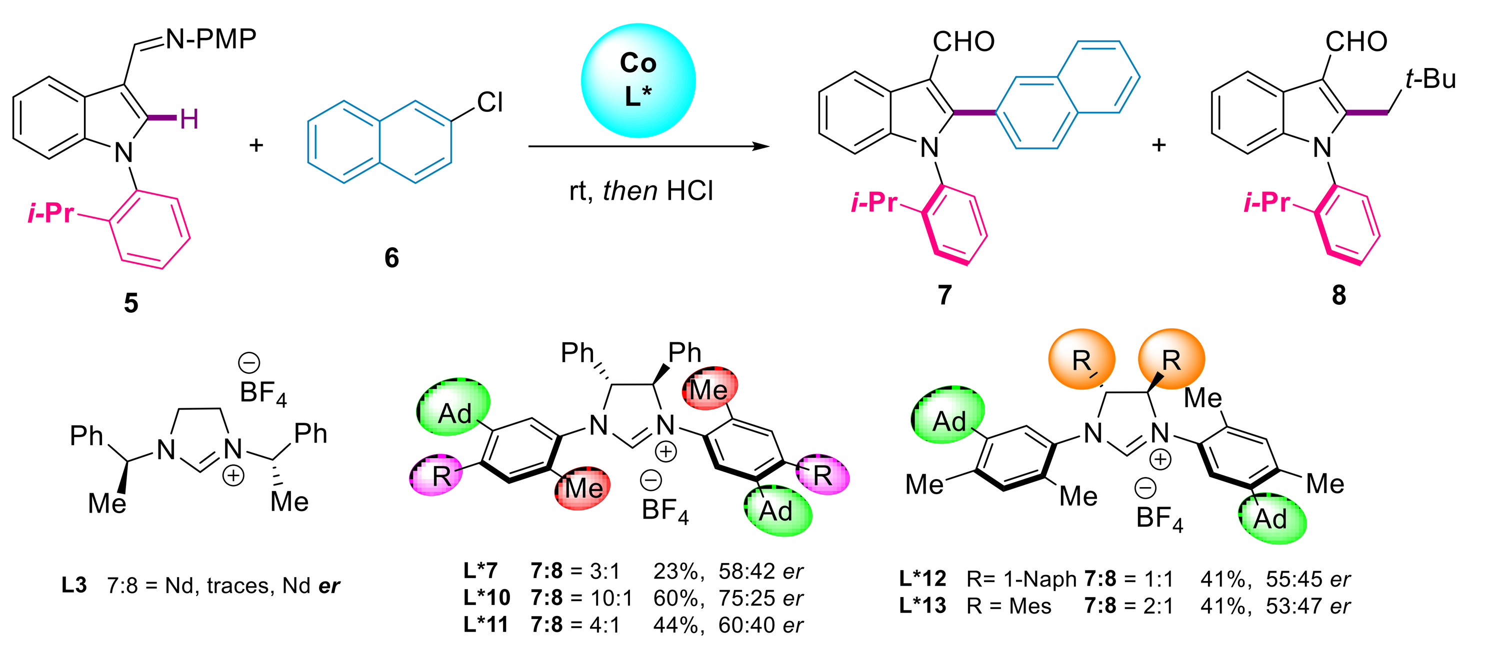
Scope of the reaction

Once the reaction was optimized, the scope of this reaction was evaluated furnishing C2-arylated indoles with high yields and enantioselectivities (up to 99% yield and up to 98:2 *er*). The reaction tolerates a large variety of indoles but some limitations are observed.



Towards C-N axial chirality ?

This work encouraged us to extend this atropoenantioselective arylation of C2-indoles towards the synthesis of C-N axially chiral indoles. Different chiral ligands allowing the C2 arylation of *N*-arylated indoles were screened to reach moderate yields and enantioselectivities.

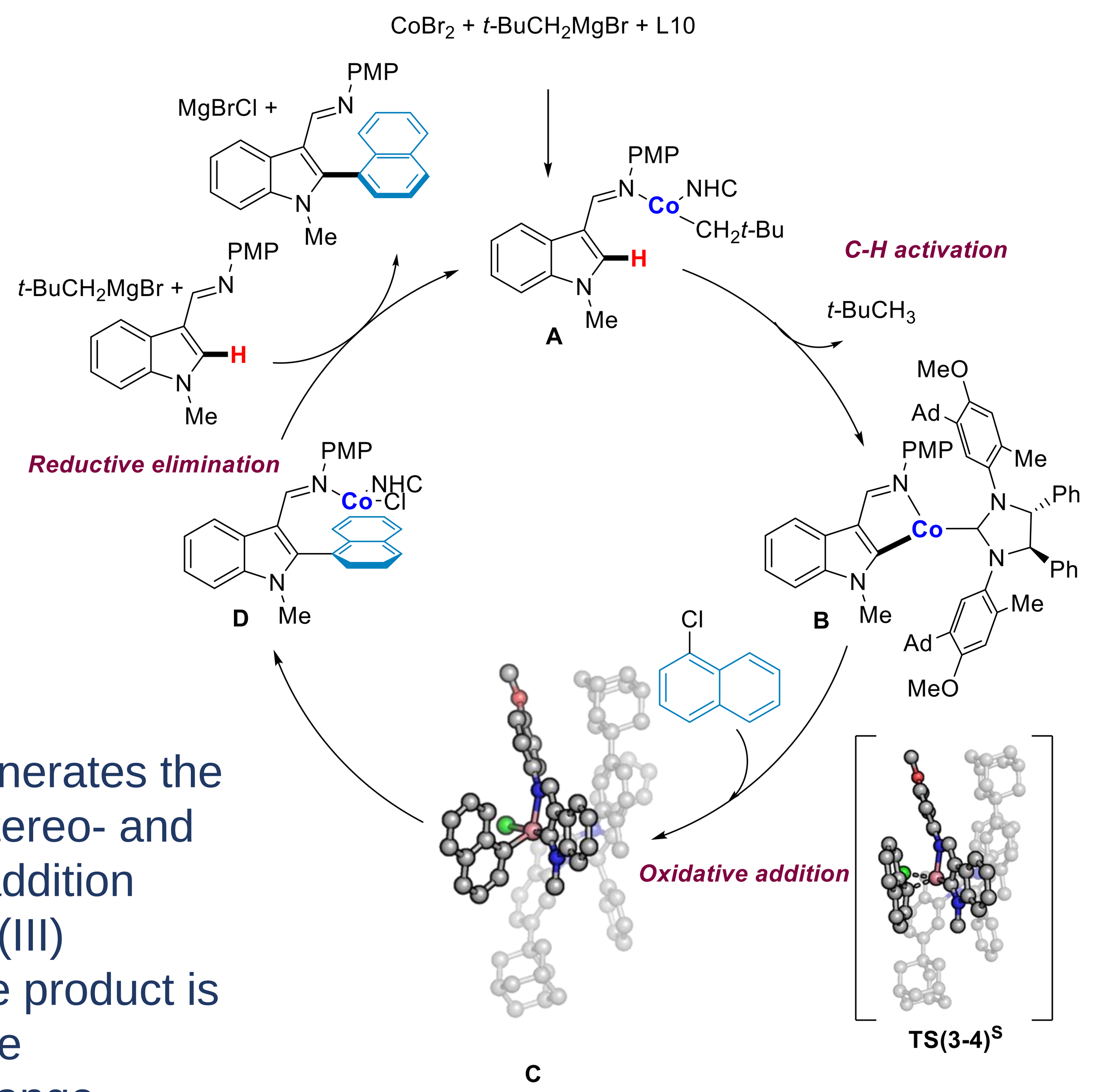


Mechanism

❖ KIE value close to 1,
→ C-H activation step is not the rate determining step.

❖ Experimental studies combined with DFT calculations suggest that a cobalt(I) species is generated *via* reduction of Grignard reagent to form intermediate **A.**

The C-H metalation step generates the metallacycle **B**. Then, the stereo- and rate-determining oxidative addition leads to intermediate cobalt(III) complex **C**. The enantiopure product is then released *via* a reductive elimination with ligand exchange.



Conclusion & future work

We have reported the first atropoenantioselective cobalt-catalyzed C−H arylation affording C2-arylated indoles with high enantioselectivity, and high functional group tolerance.[5] We have demonstrated that a well-defined NHC ligand bearing *meta*-dispersion donor motifs is essential for the stereoselectivity, as rationalized by detailed DFT calculations. This enantioselective arylation has been further extended towards the synthesis of C-N axially chiral compounds and promising results have been obtained.

The authors acknowledge ANR and DFG collaborative project ANR PRCI (grant ANR-17-CE07-0049-01) and the European Commission for the ERC Starting Grant "ALCHIMIE" n° 949804.

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