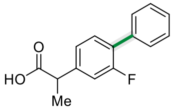
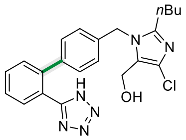
Synthesis of biaryls via oxidative coupling reactions of homoleptic and heteroleptic tetraarylzincate reagents

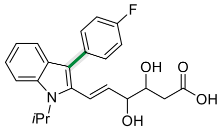
Pharmaceuticals & agrochemicals



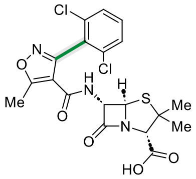
Flurbiprofen
anti-inflammatory



Lorsartan
antihypertensive

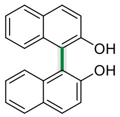


Fluvastatin
cholesterol lowering agent

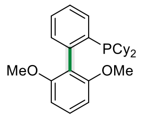


Dicloxacillin
antibiotic

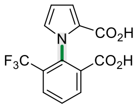
Ligands, catalysts & resolving agents



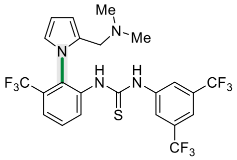
BINOL



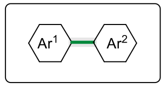
SPhos



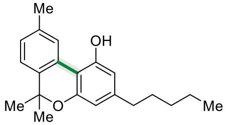
resolving agent



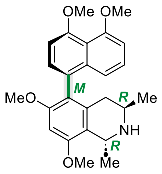
axially chiral organocatalyst



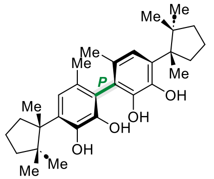
Natural products



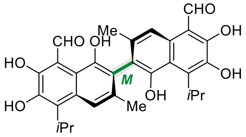
Cannabinol
antibiotic, anti-inflammatory activity



Ancistrolikokine C_2
antimalarial, anticancer activity

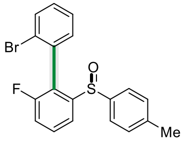


Mastigophorene A
neurological activity

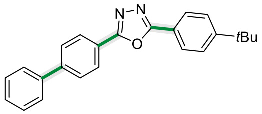


(–)-Gossypol
antimalarial activity

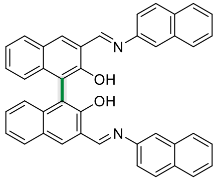
Materials & Miscellaneous



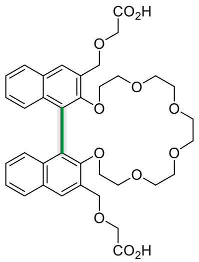
rotarory molecular motor



electron-conducting material

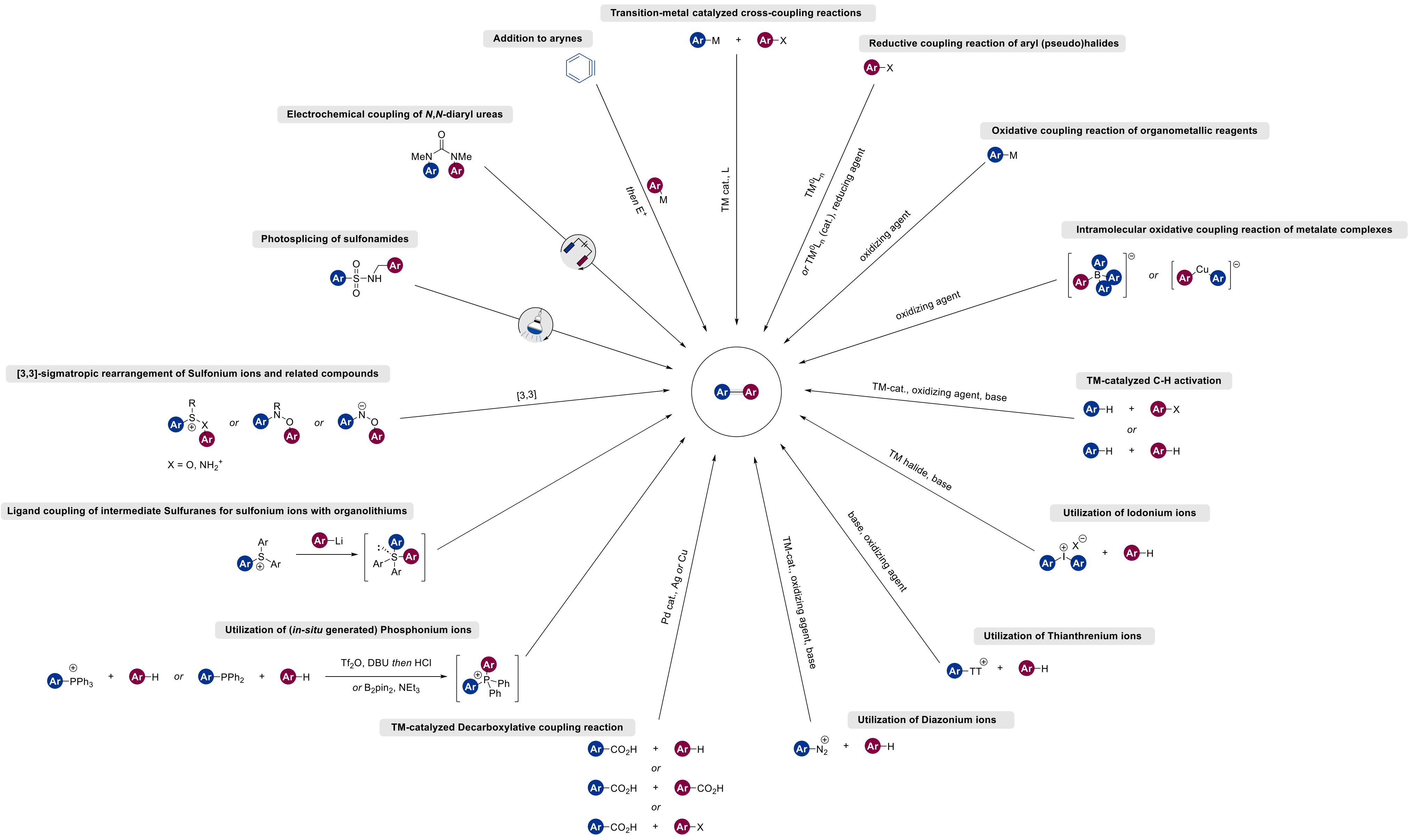


fluorescent sensor

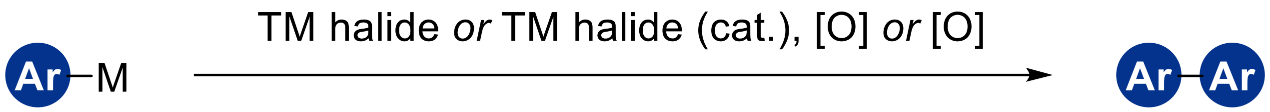


molecular recognition

Preparation of biaryl compounds



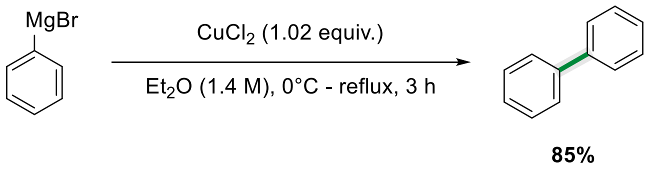
Oxidative homo-coupling reactions of organometallic reagents



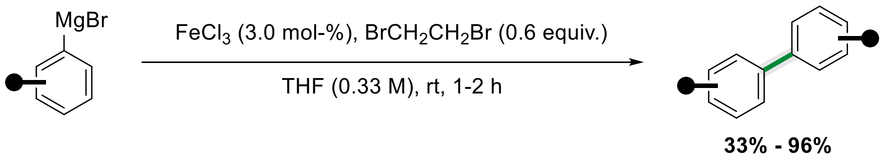
M = Li, MgX, $B(OR)_2$, SiR_3, ZnR, SnR_3

- Oxidative coupling reactions utilizing:
  - Overstoichiometric amount of a transition-metal (TM) halide
  - Catalytic amount of TM halide with an oxidízing agent (O2, dry air, (di)haloalkanes, (imino)quinones), nitroarenes, etc.)
  - TM-free protocols

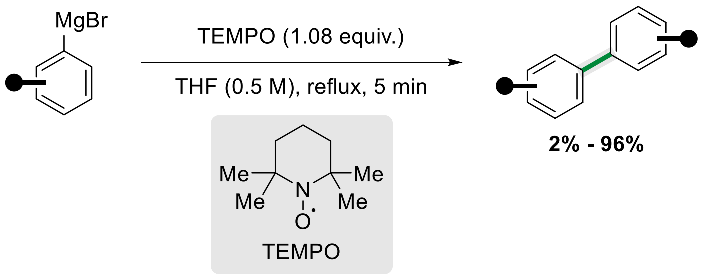
Bennet & Turner (1914):



Cahiez (2005):



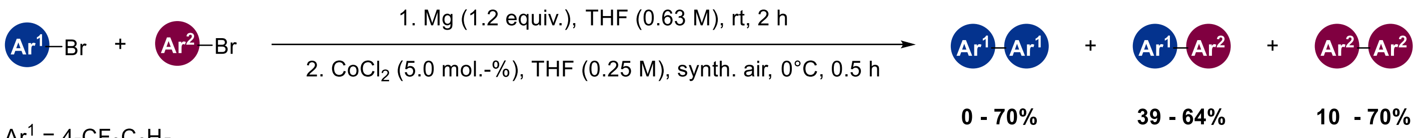
Studer (2009):



Oxidative cross-coupling reactions of organometallic reagents

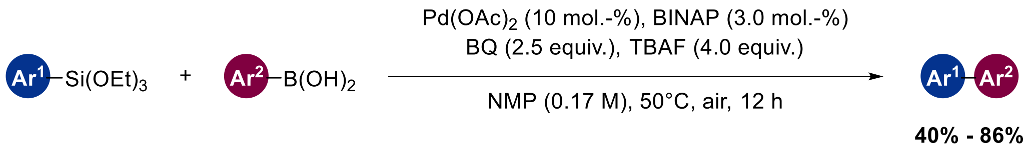
- Few examples on aryl–aryl cross-coupling reactions

Wangelin (2009)

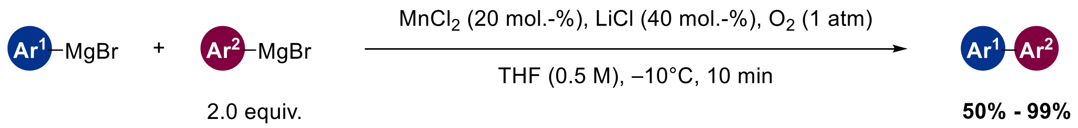


Ar^1 = 4-$CF_3C_6H_5$
Ar^2 = 4-$OMeC_6H_5$

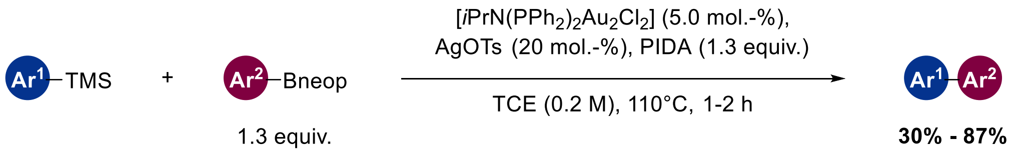
Wang (2015)



Madsen (2017)

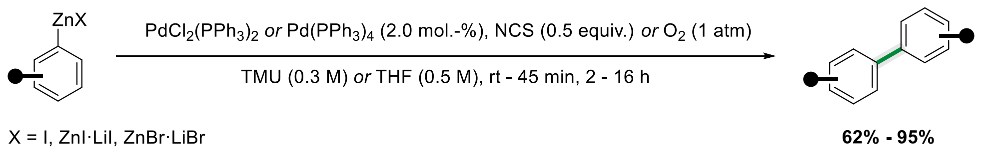


Xie (2019)

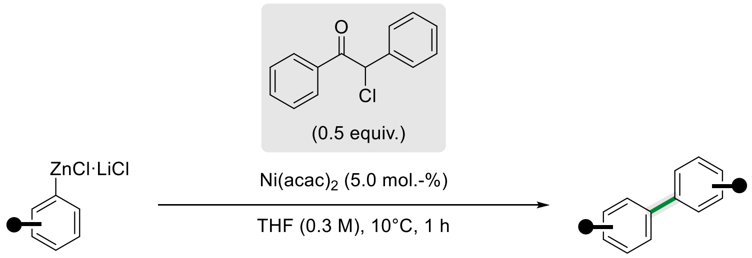


Oxidative coupling reactions of organozinc reagents

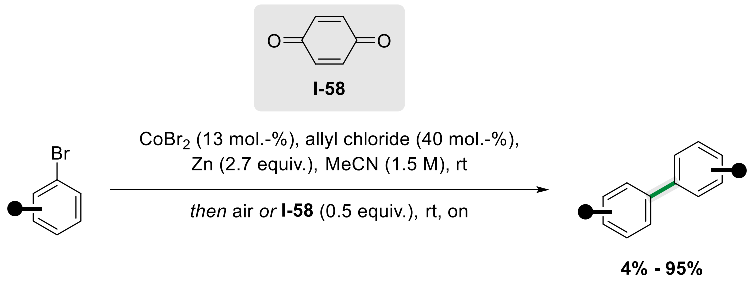
Takagi (2000)



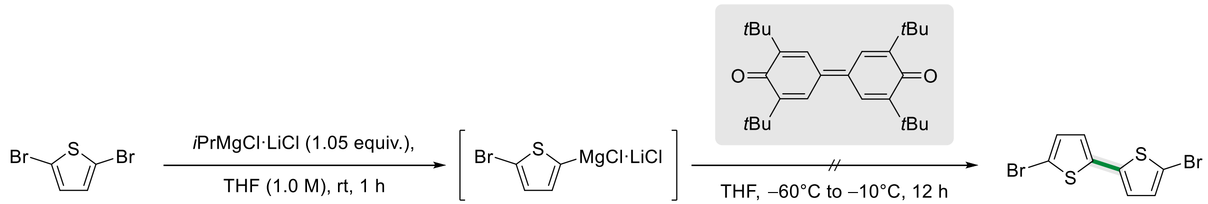
Lei (2010)

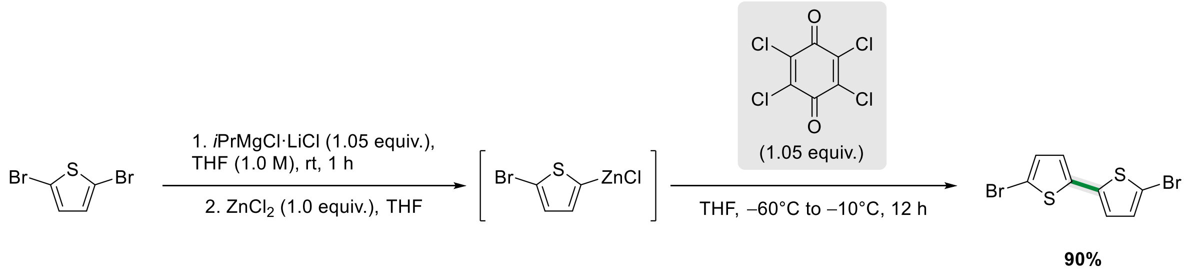


Gosmini (2016)



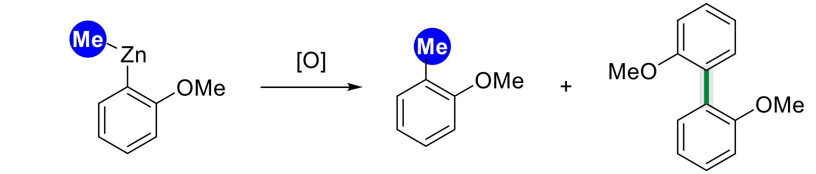
Knochel (2006)



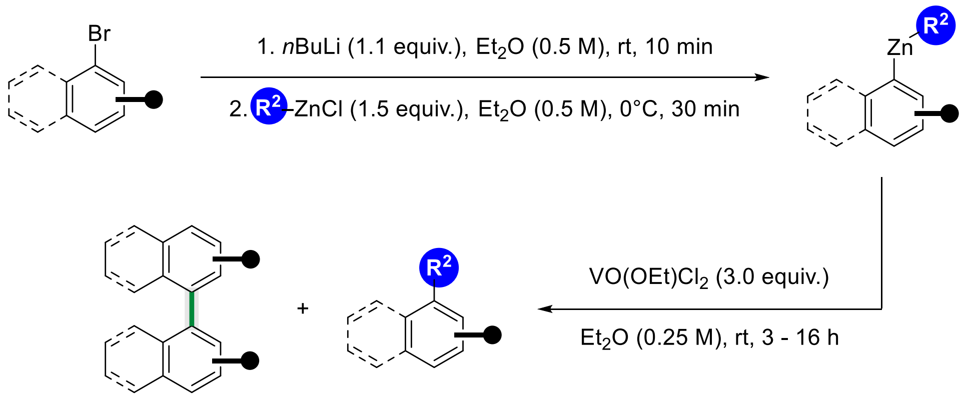


Oxidative coupling reactions of organozinc(ate) reagents

Oxidation of heteroleptic diorganozinc reagents:



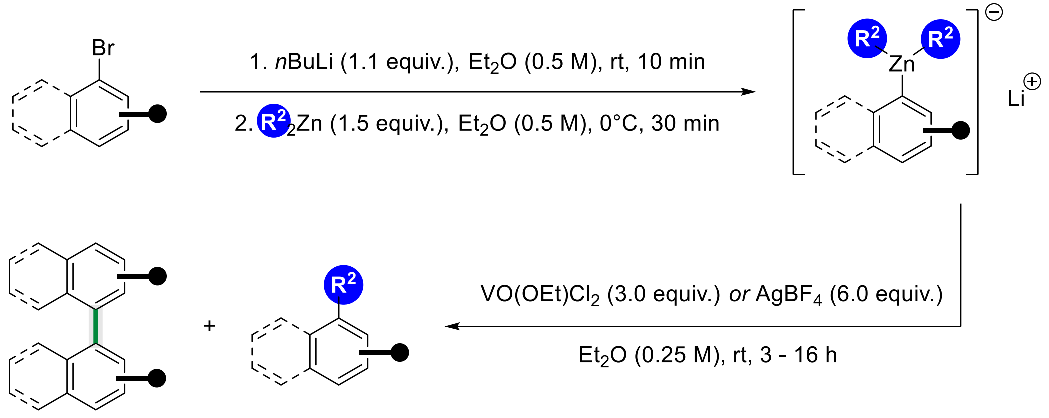
I-49	**I-50**	:	**I-51**
Cp_2FePF_6 (3.0 equiv.): **33%**	0	:	100
$AgBF_4$ (6.0 equiv.): **55%**	31	:	69



6% - 62% **24% - 92%**

R^2 = Me, *n*Bu, Me—≡, *n*Hex—≡, TMS—≡

Oxidation of heteroleptic triorganozincates:



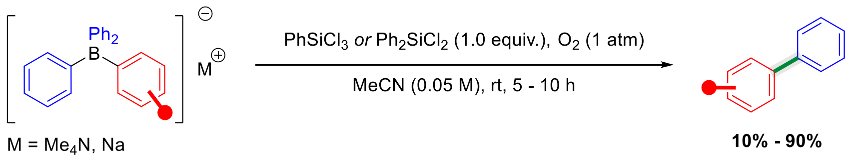
4% - 60% **31% - 92%**

R^2 = Me, Et, *n*Bu

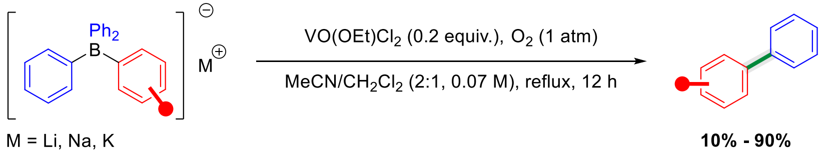
Oxidative coupling reactions of boronate complexes

Hirao (2003 & 2006)

Silylchloride promoted oxidative cross- and homo-coupling reaction

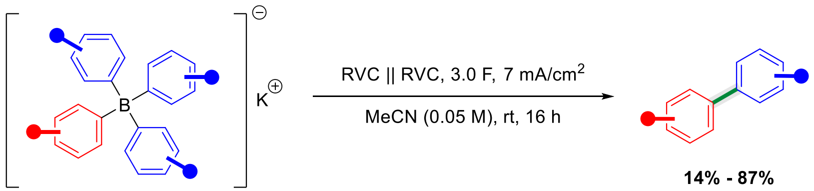


Vanadylchloride promoted oxidative cross and homo-coupling reaction

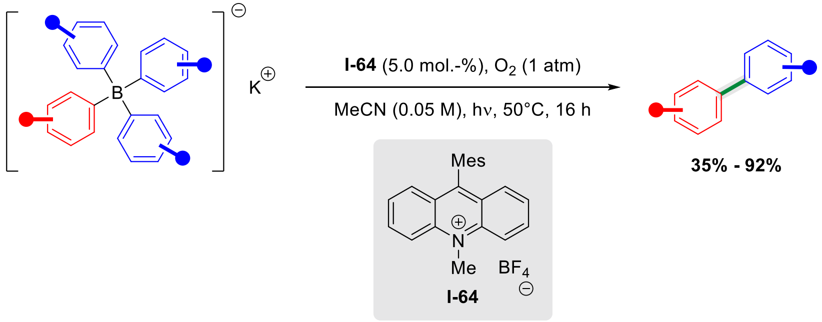


Didier (2020 & 2021)

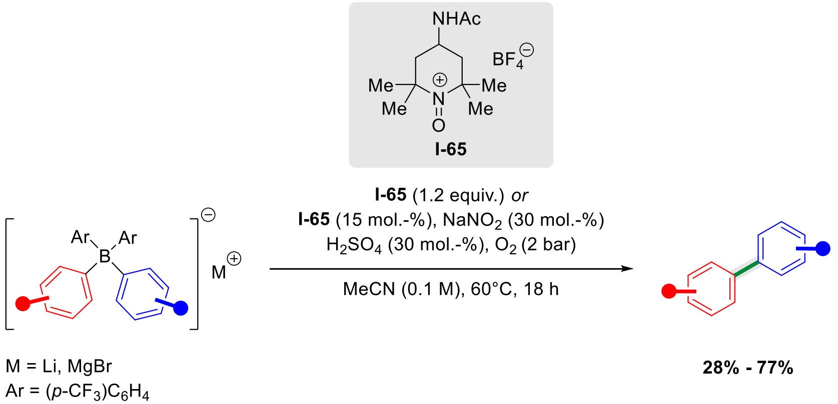
Electrochemical oxidative cross-coupling of heteroleptic tetraarylborates



Photochemical oxidative cross-coupling of heteroleptic tetraarylborates

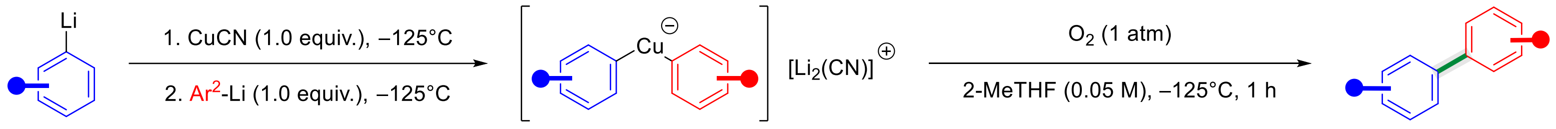


Studer (2020)



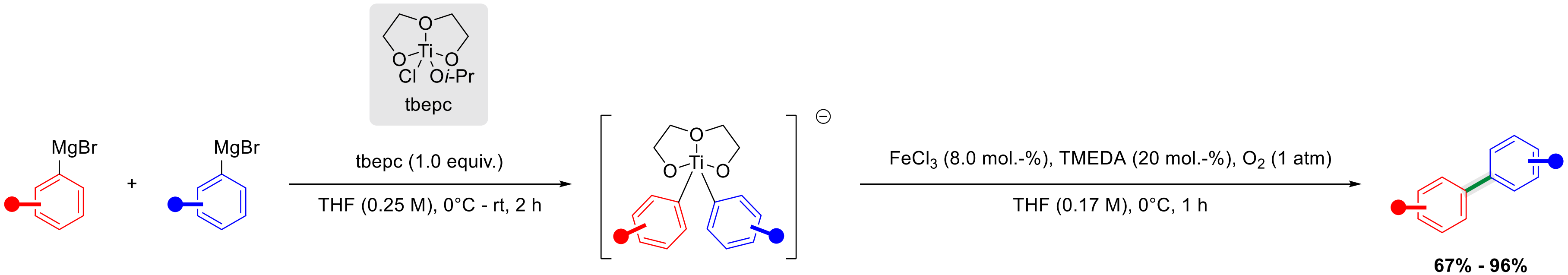
Oxidative coupling reactions of metalate complexes

Lipshutz (1992-94)



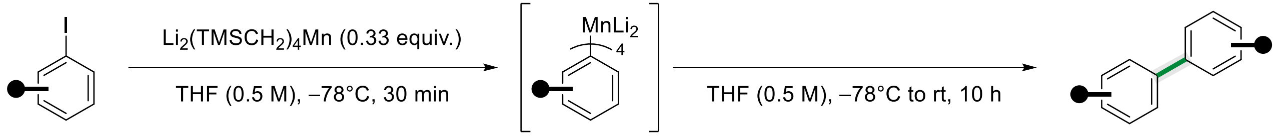
76% - 84%

Duan (2015)



67% - 96%

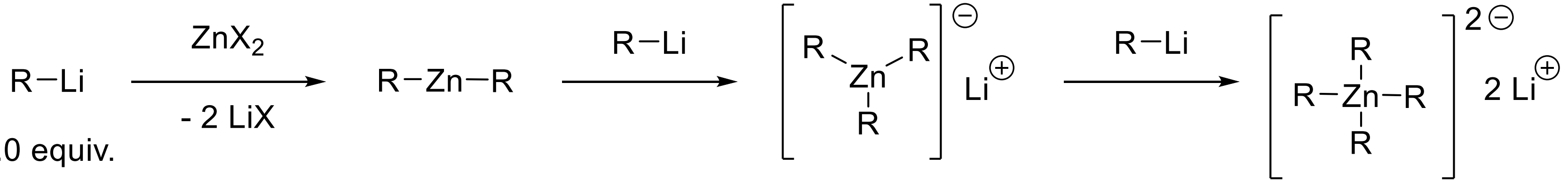
Hevia (2021)



33% - 87%

Synthesis of Tri- and Tetraorganozincates

Addition to diorganozinc reagents:



2.0 equiv.

X = Cl, Br

neutral diorganozinc reagent	triorganozincate lower-order zincates	tetraorganozincate higher-order zincates
$3d^{10}4s^24p^2$	$3d^{10}4s^24p^4$	$3d^{10}4s^24p^6$ = [Kr]
14 electrons	16 electrons	18 electrons

Halogen-zinc exchange & deprotonative metalation:

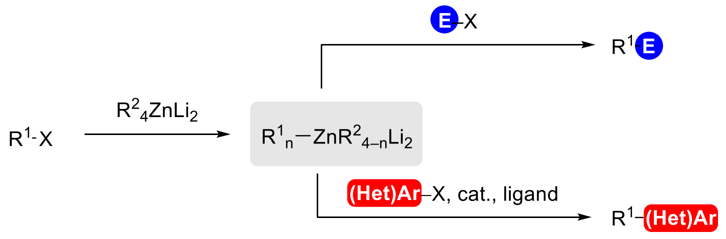
$$R^1{-}X \xrightarrow{R^2_4ZnLi_2} R^1R^2_3ZnLi_2 + R^1_2R^2_2ZnLi_2 + R^1_3R^2ZnLi_2 + R^1_4ZnLi_2$$

R^1 = aryl, alkinyl
R^2 = alkyl, alkoxy
X = Br, I, H

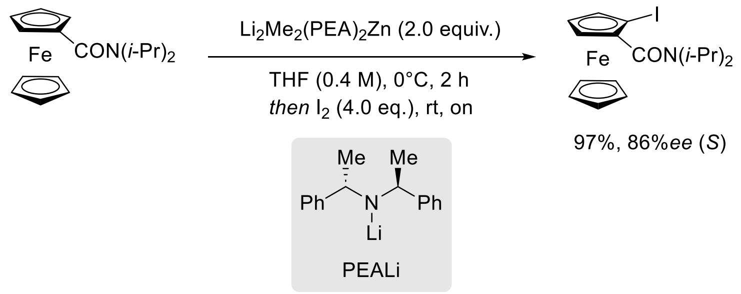
obtained zincate reagent depending on: nature of tetraorganozincate, amount/equivalents of tetraorganozincate

Application of Tetraorganozincates

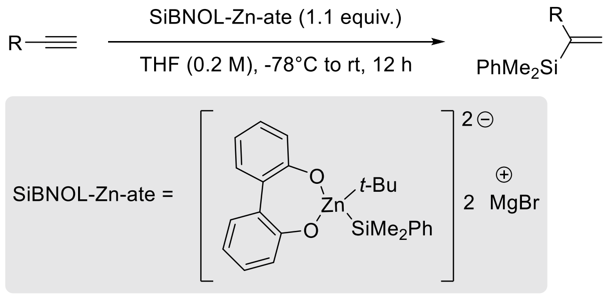
Halogen-Zinc-Exchange & electrophilic trapping:



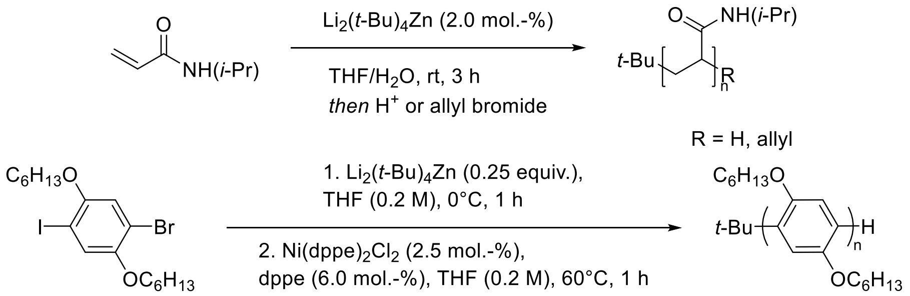
(Asymmetric) directed metalation:



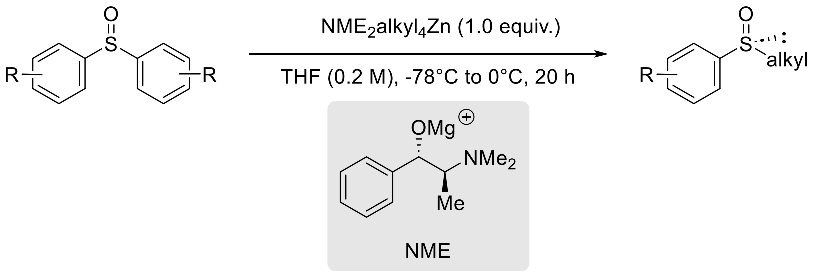
Silylzincation:

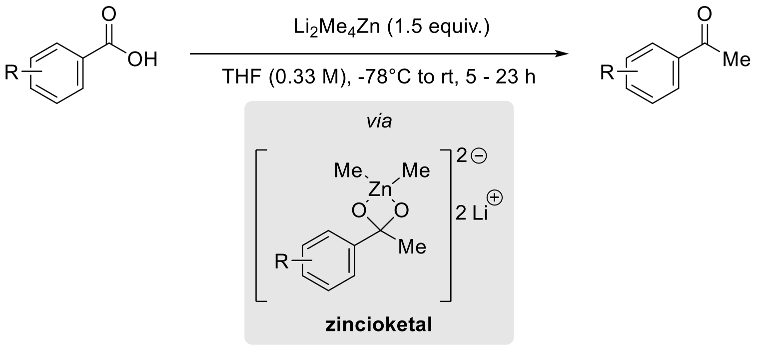


Polymerization:



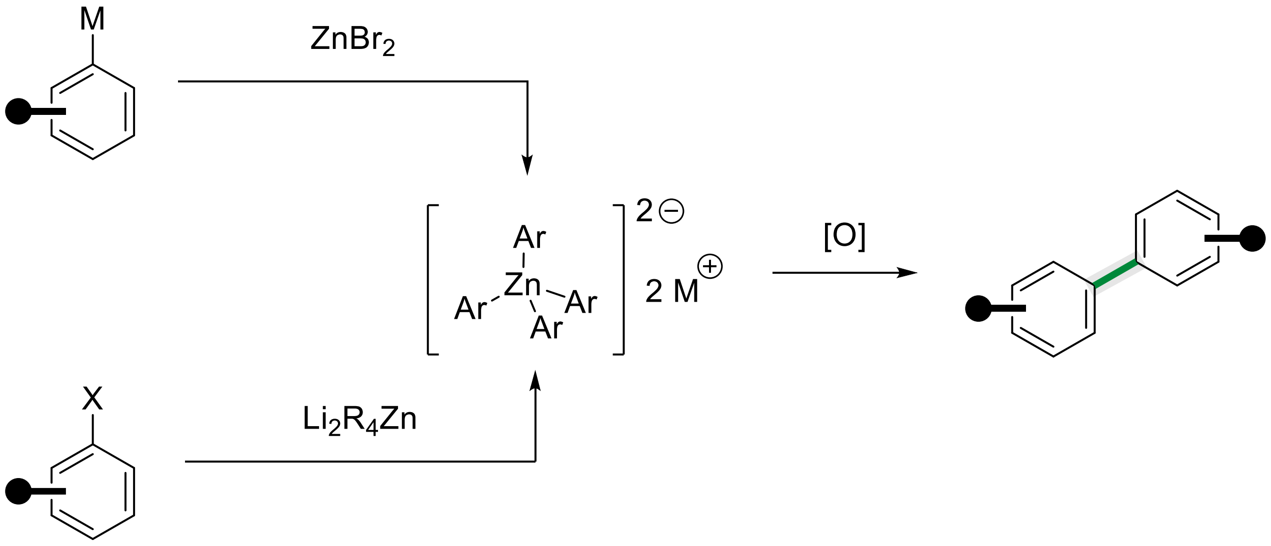
(Asymmetric) substitution reactions:





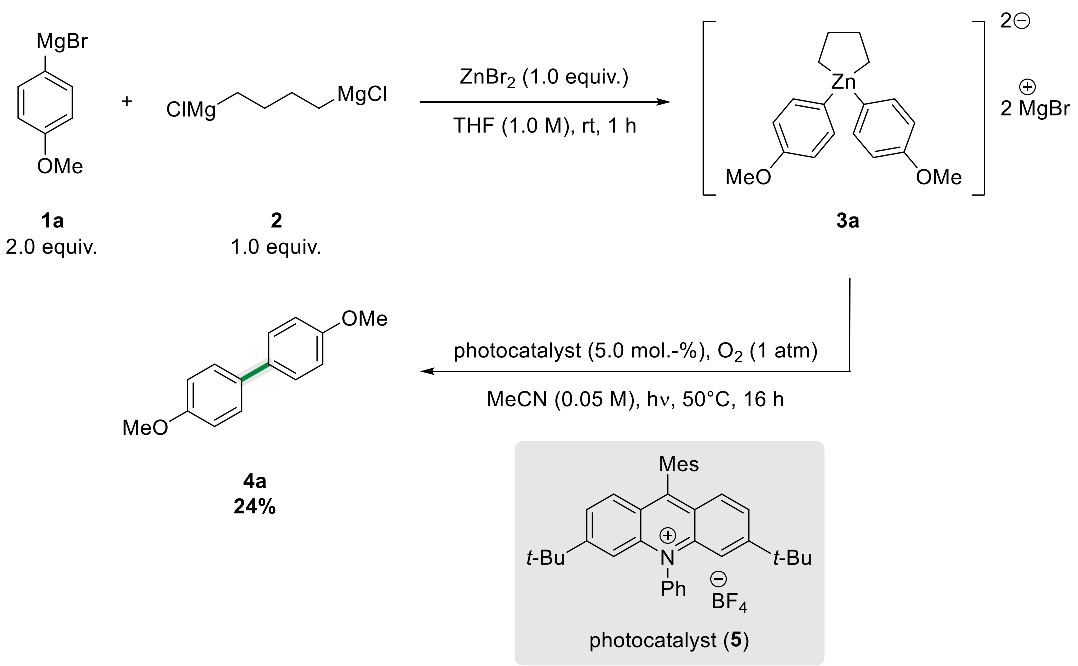
Purpose of this study

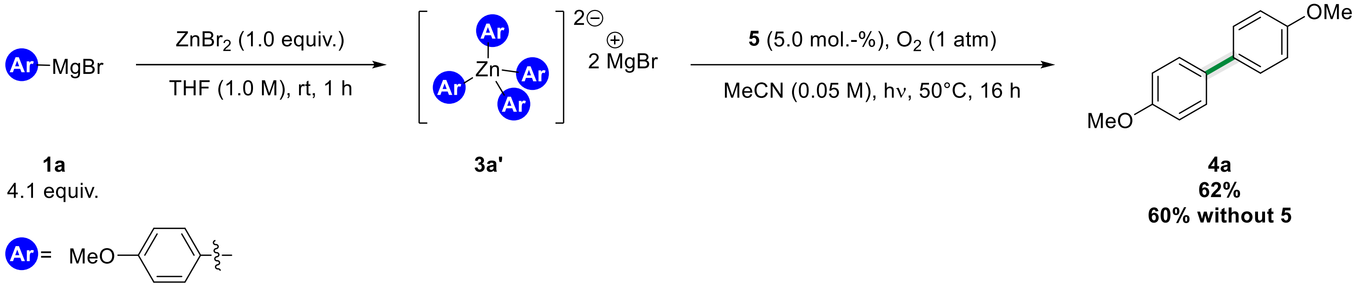
- Synthesis & characterization of tetraarylzincates
- Develop oxidative coupling reaction towards symmetrical biaryls under:
  - Photochemical conditions
  - Thermal conditions
- Testing conditions for cross-coupling reactions & differently hybridized substrates

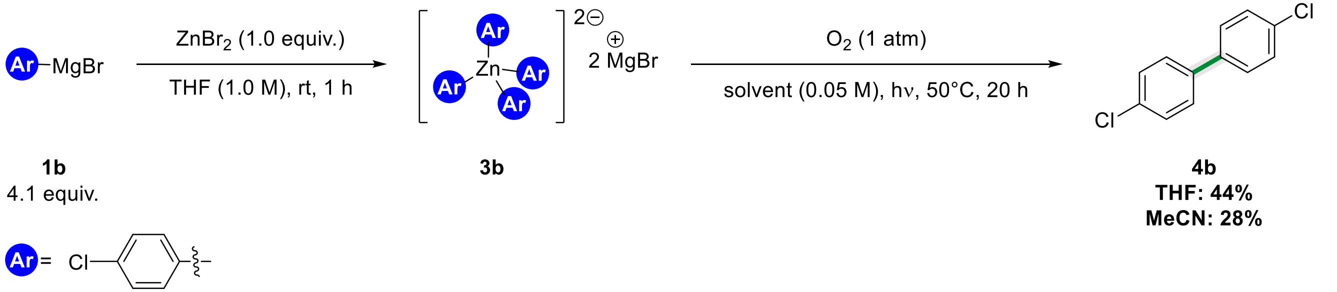


M = Li, MgBr
X = I, Br

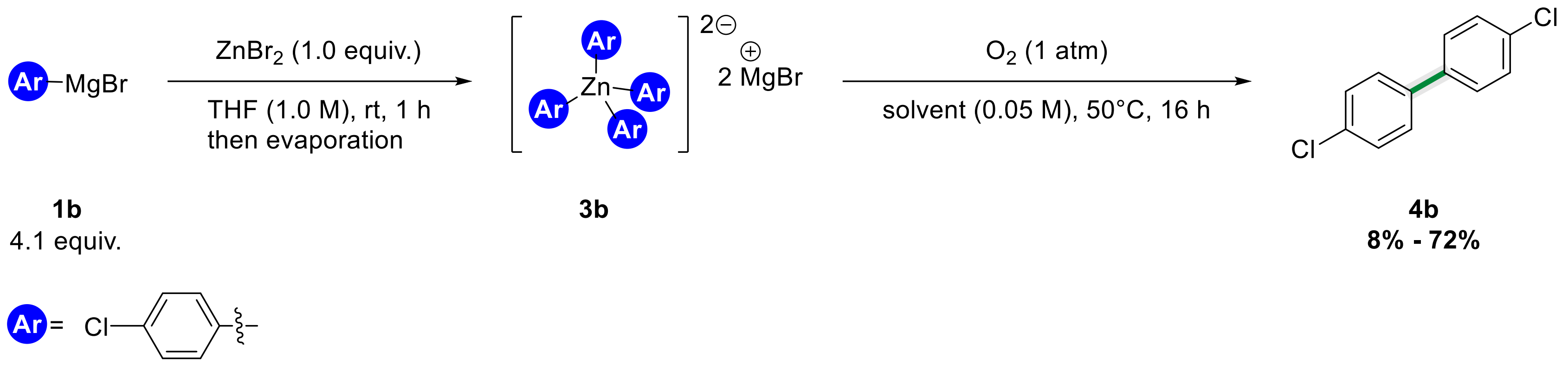
Preliminary photocatalytic experiments







Optimization – solvent



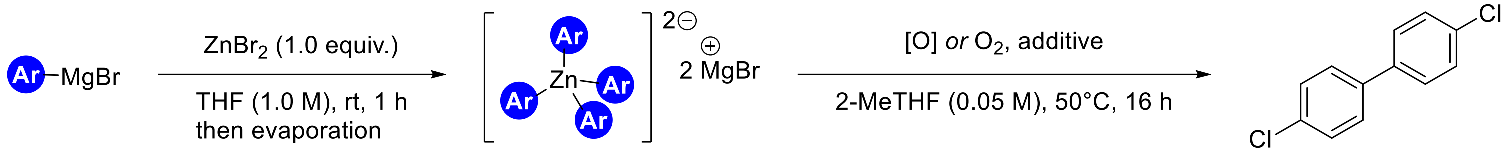
1b
4.1 equiv.

3b

4b
8% - 72%

Entry	Solvent	Isolated yield [%]
1a	THF	30
1b	THF	50
2a	2-MeTHF	72
2b	2-MeTHF	60
3	toluene	28
4	DCE	36
5	Dioxane	8
6	DMSO	16
7	DMF	12
8	EtOAc	8
10	MeCN	18
11	DME	54
12	diglyme	42

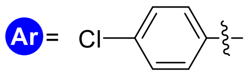
Optimization – oxidizing agent



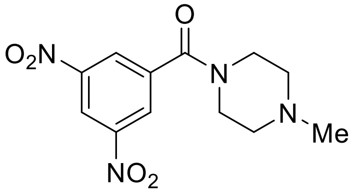
1b
4.1 equiv.

3b

4b



Entry	Oxidizing agent or additives	Isolated yield [%]
1	**6** (5 mol.-%) + O_2 (1 atm)	40
2	**6** (3.0 equiv.)	44
3	**7** (1.5 equiv.)	48
4	**8** (1.5 equiv.)	30
5	**9** (1.5 equiv.)	56
6	**10** (3.0 equiv.)	**66**
7	**Dry air**	**62**
8	TMEDA (1.0 equiv.) + O_2 (1 atm)	22
9	TMEDA (2.0 equiv.) + O_2 (1 atm)	26
10	BDMAEE (1.0 equiv.) + O_2 (1 atm)	30
11	BDMAEE (2.0 equiv.) + O_2(1 atm)	24



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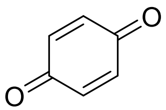

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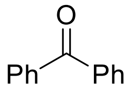

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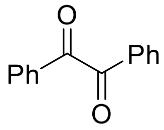

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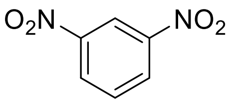

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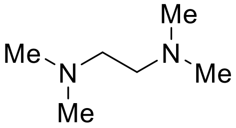
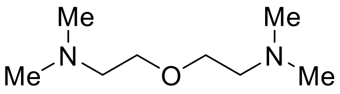
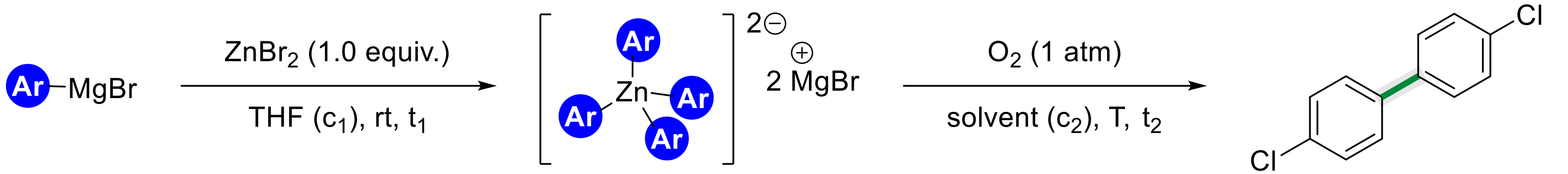


TMEDA



BDMAEE

Optimization – time, temperature & concentration

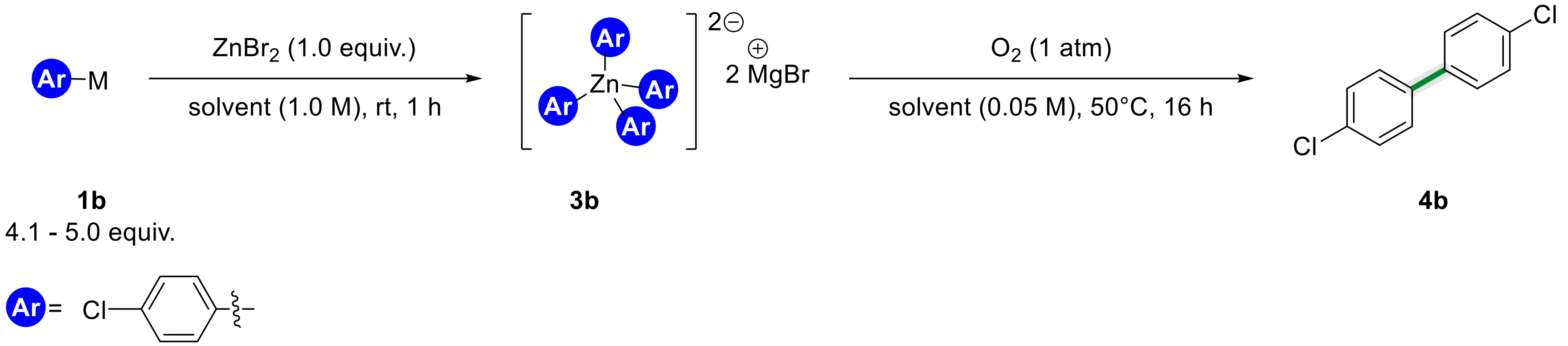


1b 4.1 - 5.0 equiv. **3b** **4b**

Entry	Ar-MgBr [equiv.]	c_1 [M]	Solvent	T [°C]	c_2 [M]	Isolated yield [%]
1	4.50	1.00	2-MeTHF	50	0.05	48
2	5.00	1.00	2-MeTHF	50	0.05	60
3	4.10	1.00	2-MeTHF	50	0.05	52
4	4.10	1.00	2-MeTHF	50	0.10	76
5	4.10	1.00	2-MeTHF	50	0.25	54
6	4.10	1.00	2-MeTHF	60	0.05	65
7	4.10	0.05	THF	rt	0.05	40

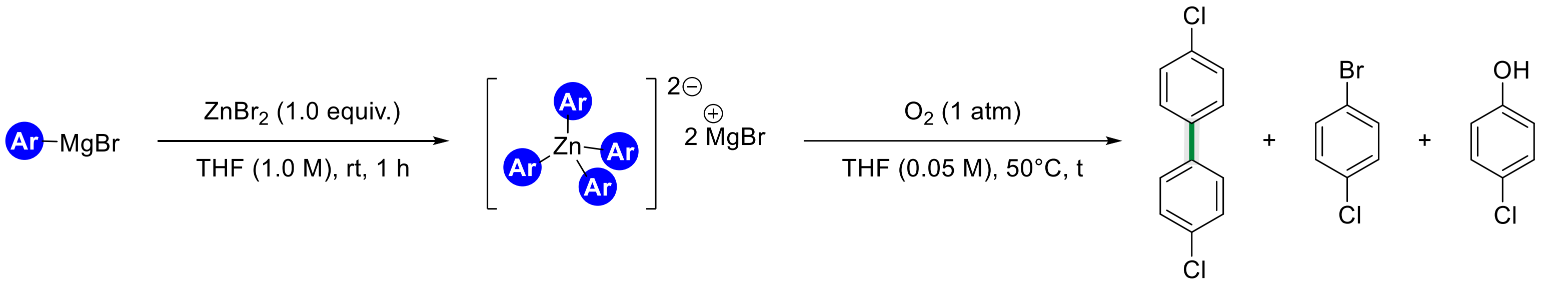
Entry	c_1 [M]	t_1 [h]	T [°C]	t_2 [h]	Isolated yield [%]
1	1.00	1	rt	1	56
2	0.05	16	rt	1	36
3	0.05	5	50	16	48
4	0.05	5	50	1	32
5	0.05	16	50	24	44

Optimization – employed organometallic reagent

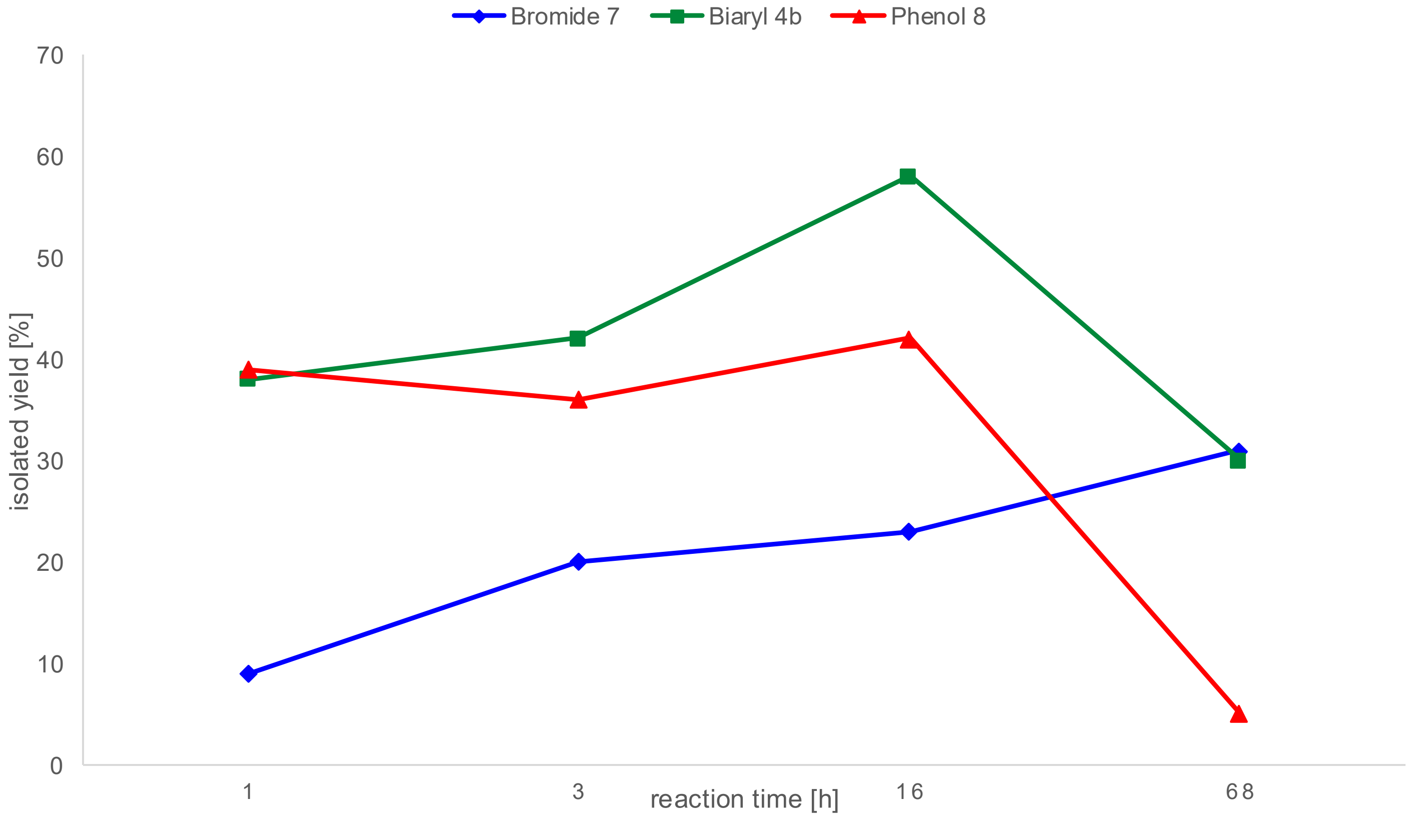


Entry	Ar–M	Solvent	T [°C]	t [h]	Isolated yield [%]
1	Ar–Li	2-MeTHF	50	16	6
2	Ar–Li	THF	50	16	62
3	Ar_2Mg	THF	50	16	48
4	Ar–MgCl·LiCl	THF	50	16	28

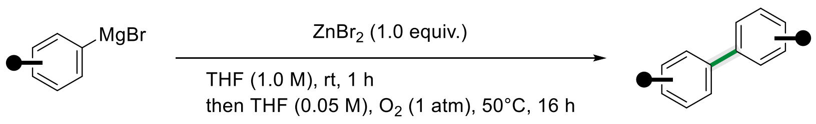
Time dependent analysis of (by)product formation



1b 4.1 equiv. **3b** **4b** **11** **12**



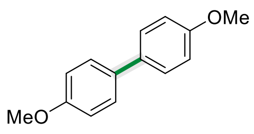
Scope & limitations



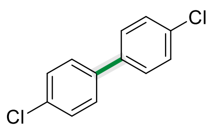
1a - 1q
4.1 equiv.

4a - 4q
n.o. - 72%

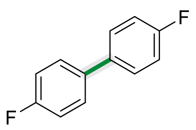
Scope



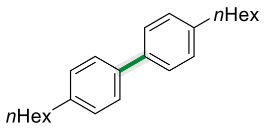
4a
17%



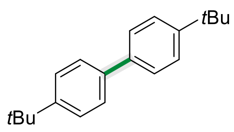
4b
72%



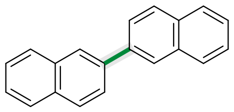
4c
37%



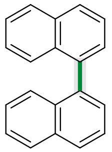
4d
22%



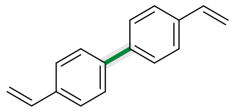
4e
18%



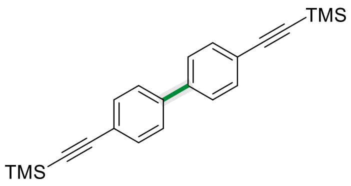
4f
66%



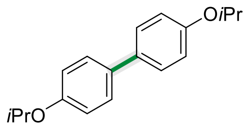
4g
15%



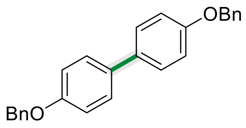
4h
34%



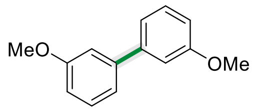
4i
29%



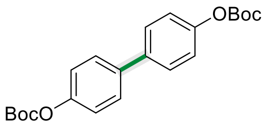
4j
11%



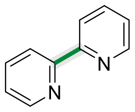
4k
traces



4l
40%[a]



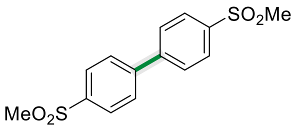
4m
18%



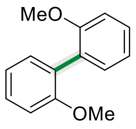
4n
14%

[a] contains impurities

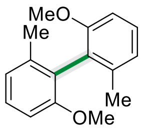
Limitations



4o
n.o.



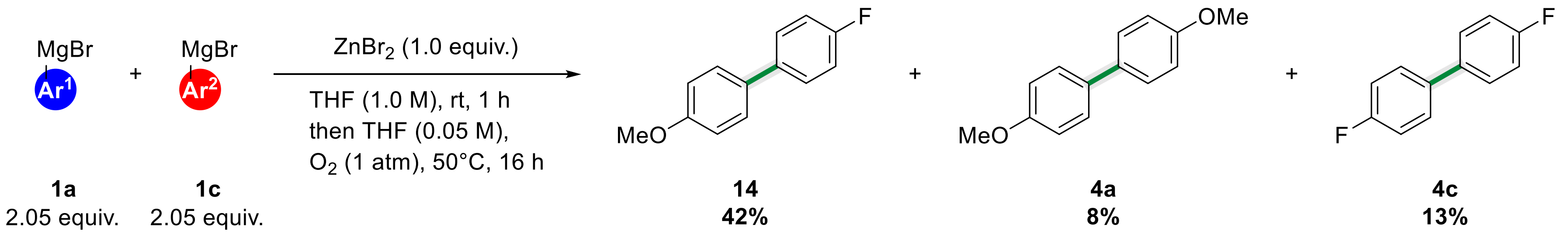
4p
n.o.



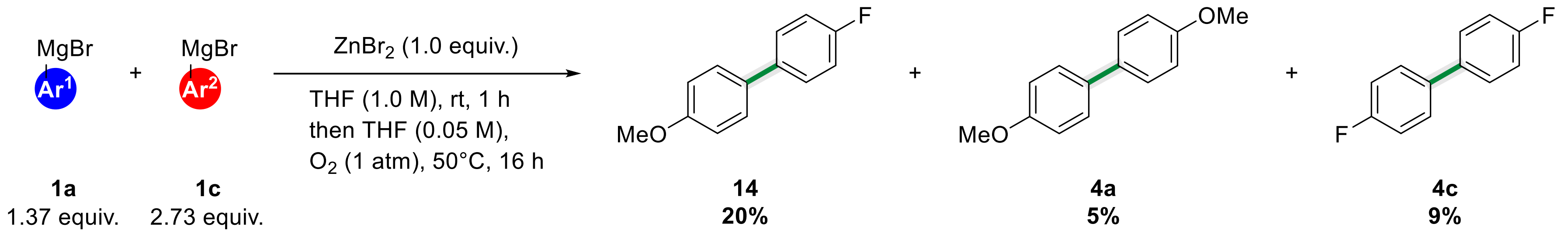
4q
n.o.

Towards cross-coupling reactions

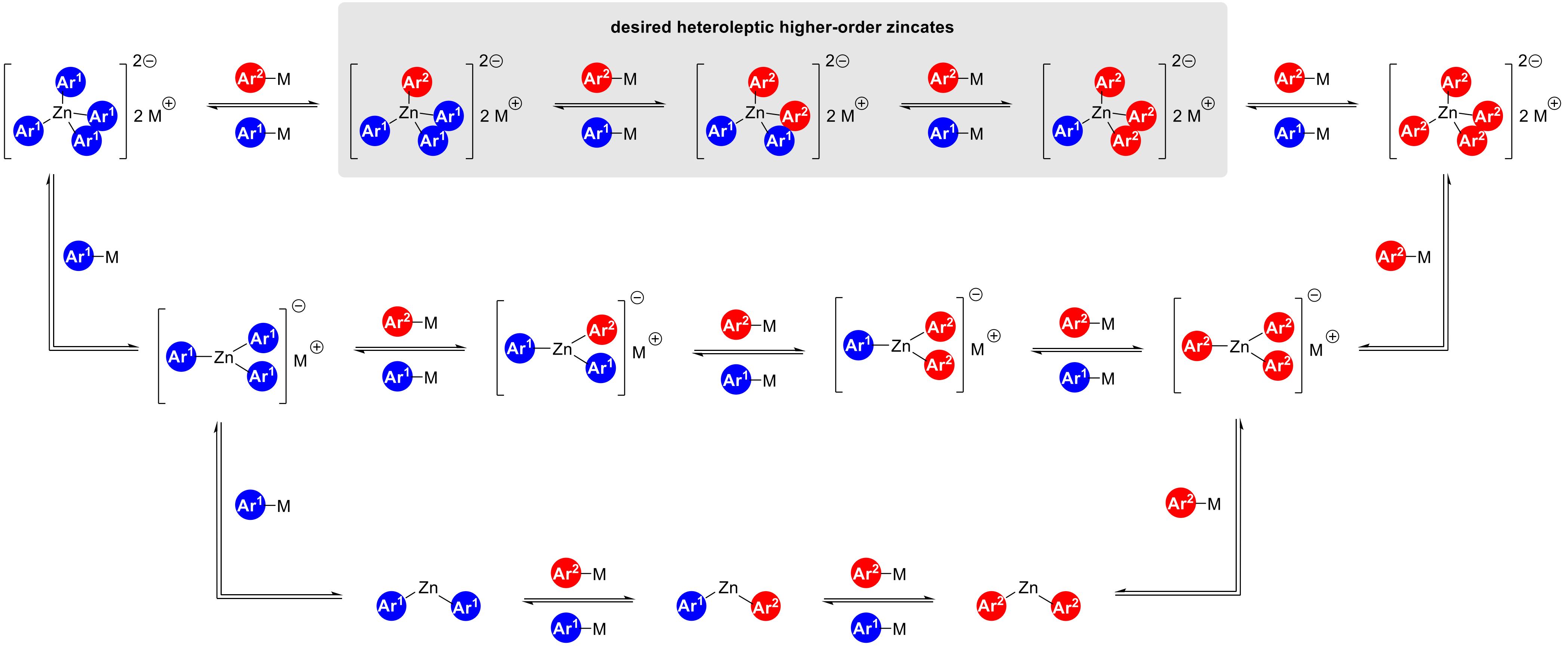
Cross-coupling reaction utilizing a 1:1 ratio of *Grignard* reagents 1a, 1c



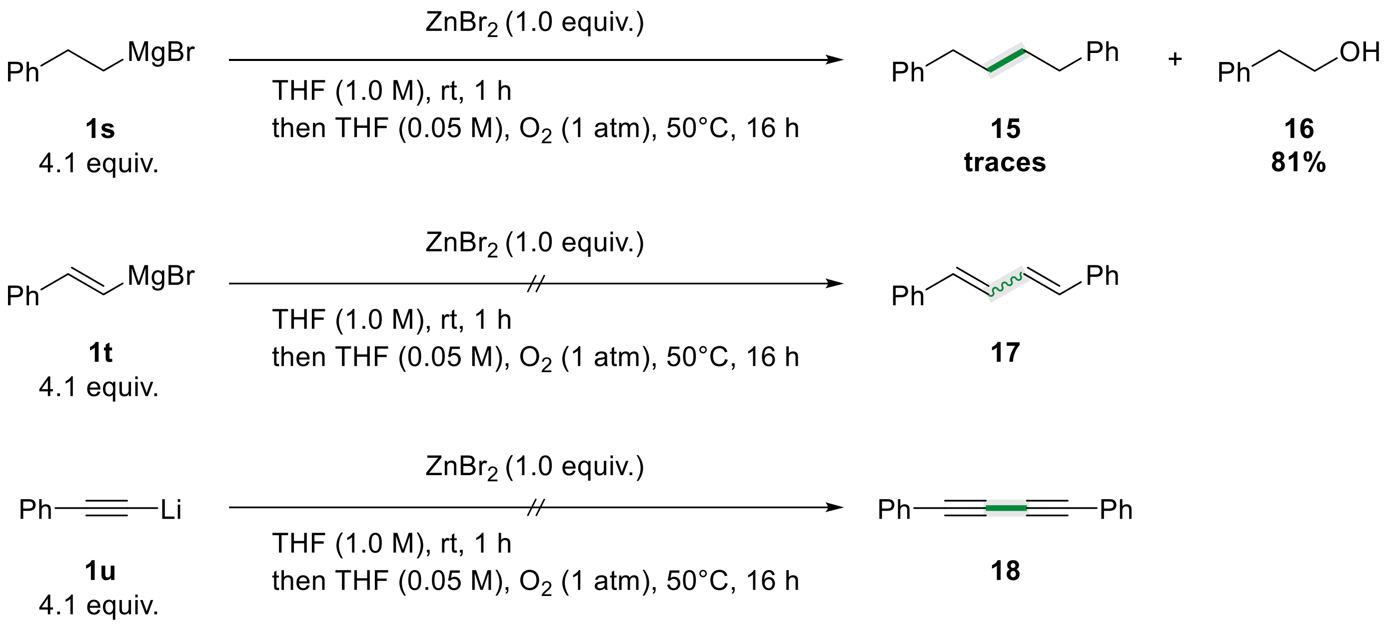
Cross-coupling reaction utilizing a 1:3 ratio of *Grignard* reagents 1a, 1c



Towards cross-coupling reactions

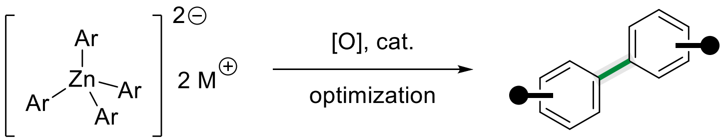


Towards alkyl-, alkenyl- & alkinyl homocoupling reactions

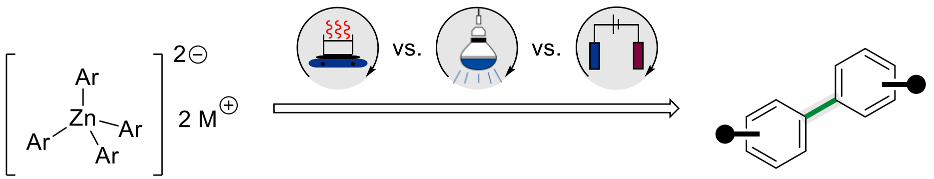


Summary & Outlook

improving developed methods & comparison with electro-/photochemical conditions

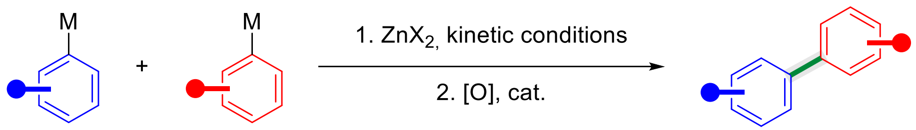


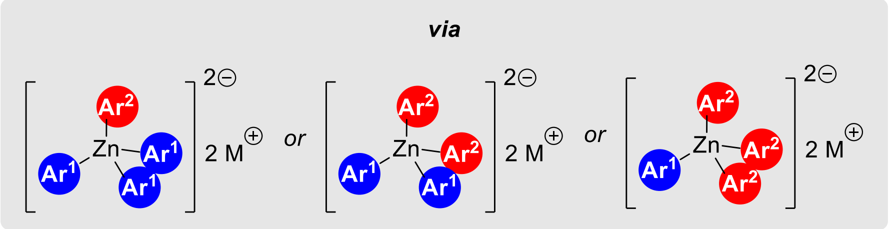
improving: yield · scope · FG tolerance



comparing: reaction conditions · mechanism · yield · scope · FG tolerance

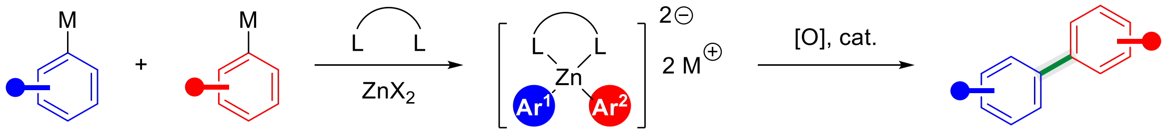
application of (kinetic) heteroleptic higher-order zincates in oxidative cross-coupling





electronically biased arenes · statistical distribution of homo- and cross-coupling products

application of (chiral) anionic ligands in oxidative (atropselective) cross-coupling



potential for (atroposelective) cross-coupling reactions · potential for non-electronically biased arenes

M = Li, MgBr