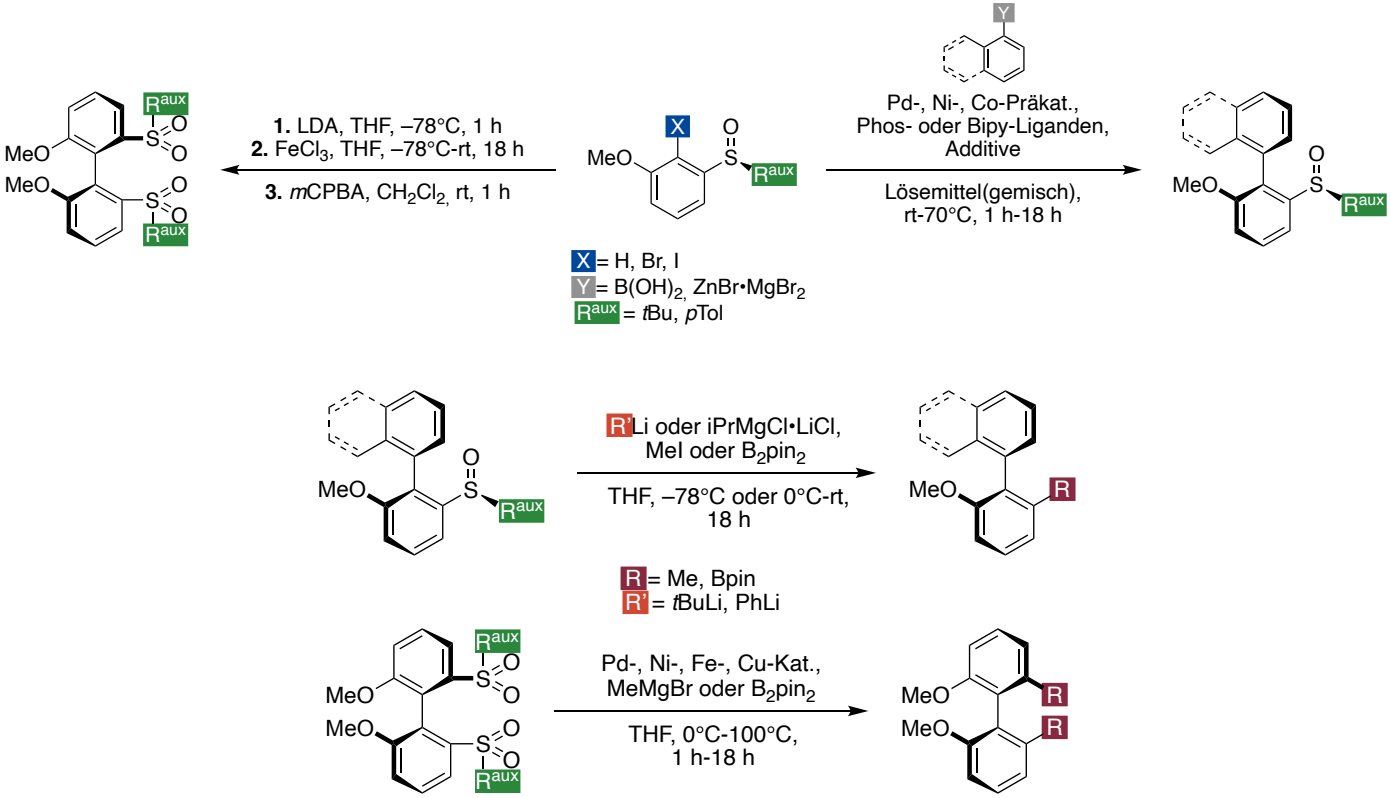
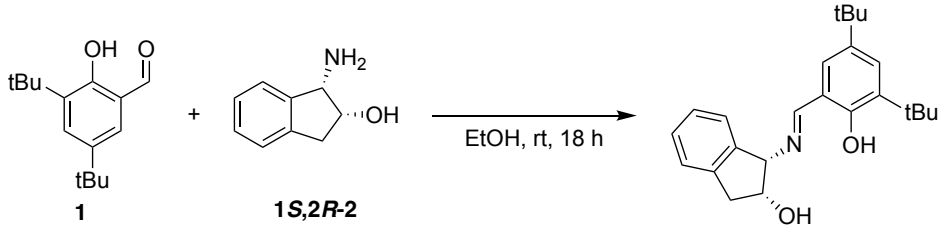
Dirigierende Chirale Sulfoxide in Atropselektiven Kupplungsreaktionen und (De)Funktionalisierungen



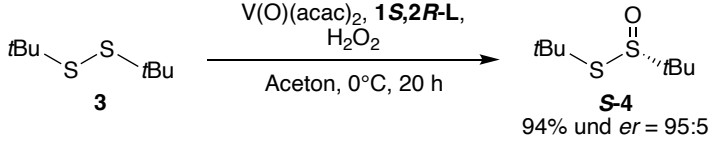
02.06.2025, Lennart Kirchhoff

Präsentation der Masterarbeit unter Aufsicht und Betreuung von Dino Berthold

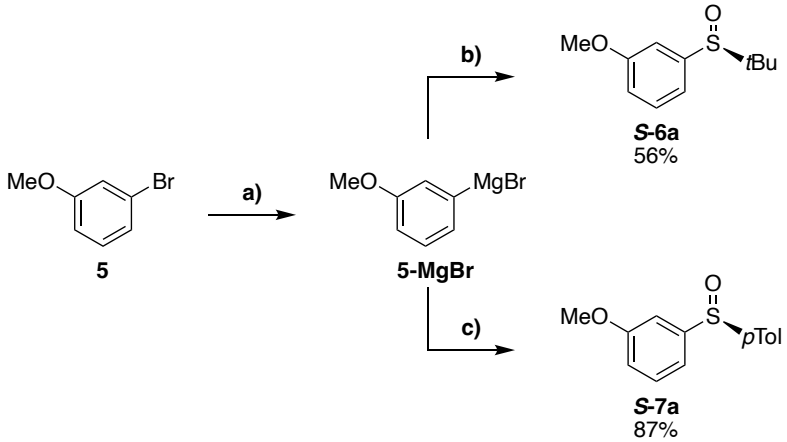
Herstellung der Sulfoxidsubstrate



Reaktionsbedingungen:
1 (1.0 equiv.), **1*S*,2*R*-2** (1.1 equiv.), EtOH (0.16 M), rt, 18 h.



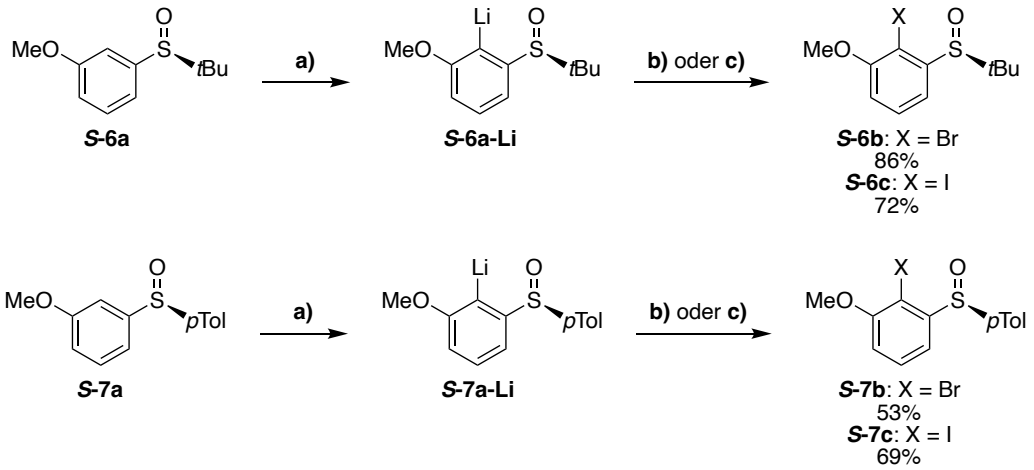
Reaktionsbedingungen:[1]
3 (1.0 equiv.), V(O)(acac)$_2$ (0.5 mol-%), **1*S*,2*R*-L** (0.5 mol-%), Aceton (3.0 M), 0°C, 20 h.



Reaktionsbedingungen:
a) Mg (2.0 equiv.), THF (1.0 M), 80 °C, 2 h.
b) ***S*-4** (1.2 equiv.), THF (1.0 M), 0 °C-rt, 18 h.
c) (*S*)-pTolS(O)(–)menth (1.2 equiv.), THF (1.0 M), 0 °C-rt, 18 h.

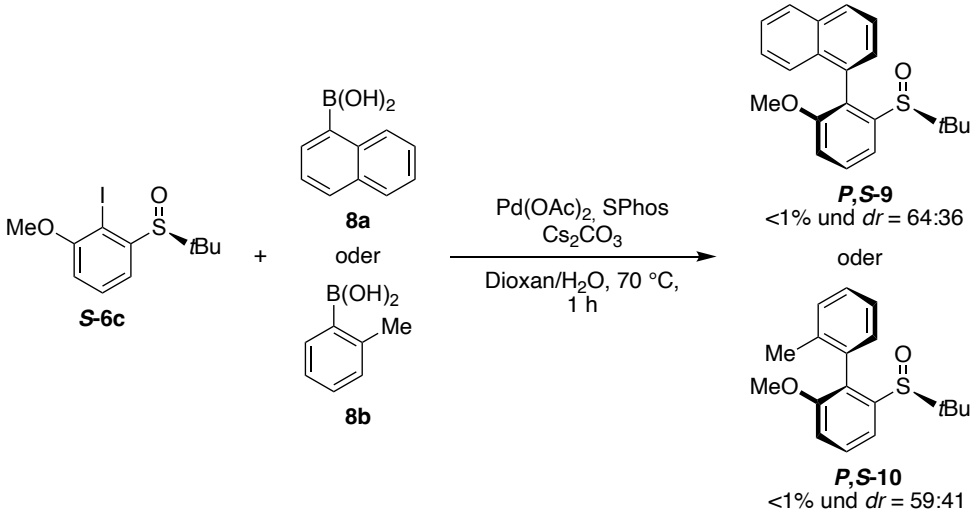
[1] D. J. Weix, J. A. Ellman, *Org. Lett.*, **2003**, 5(8), 1317–1320.

Herstellung der Sulfoxidsubstrate

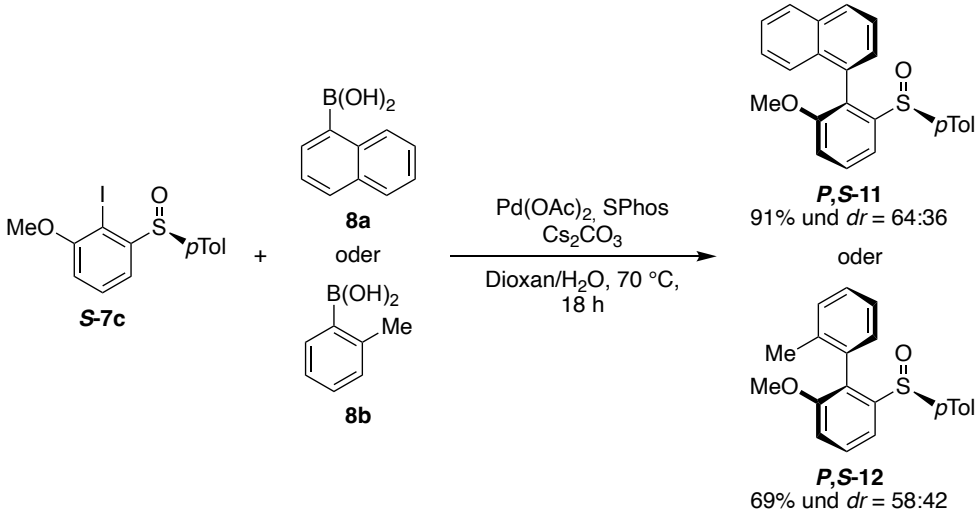


Reaktionsbedingungen:
a) LDA (*n*BuLi (1.2 equiv.), *i*Pr_2NH (1.3 equiv.)), THF (0.6 M), –78 °C, 1 h.
b) $(CCl_2Br)_2$ (1.2 equiv.), THF (0.85 M), –78-rt, 18 h.
c) I_2 (1.2 equiv.), THF (0.85 M), –78-rt, 18 h.

Suzuki-Kreuzkupplungen



Reaktionsbedingungen:[2]
***S*-6c** oder ***S*-7c** (1.0 equiv.), **8a** oder **8b** (2.0 equiv.), $Pd(OAc)_2$ (10 mol-%), SPhos (15 mol-%), Cs_2CO_3 (4.0 equiv.), Dioxan/H_2O (5:1, 0.1 M), 70°C, 1 h.

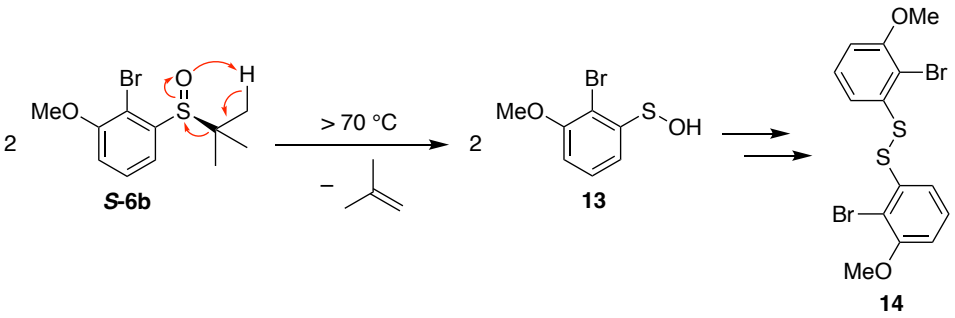


Reaktionsbedingungen:[2]
***S*-6c** oder ***S*-7c** (1.0 equiv.), **8a** oder **8b** (2.0 equiv.), $Pd(OAc)_2$ (10 mol-%), SPhos (15 mol-%), Cs_2CO_3 (4.0 equiv.), Dioxan/H_2O (5:1, 0.1 M), 70°C, 18 h.

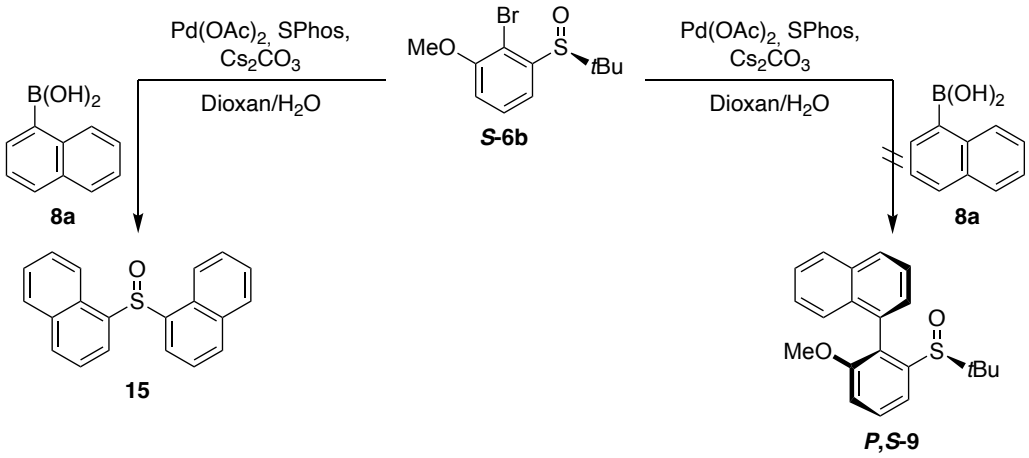
[2] F. Colobert, V. Valdivia, S. Choppin, F. R. Leroux, I. Fernández, E. Álvarez, N. Khiar, *Org. Lett.*, **2009**, 11(22), 5130–5133.

Problematiken beim Einsatz vom *tert*-Butylsulfoxid

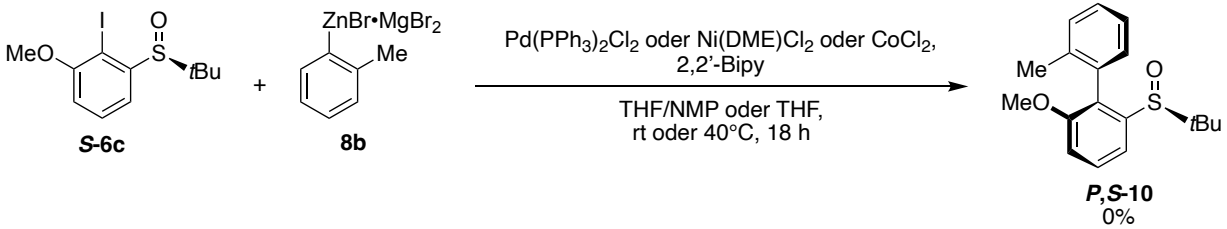
Thermolabilität der *tert*-Butylgruppe:



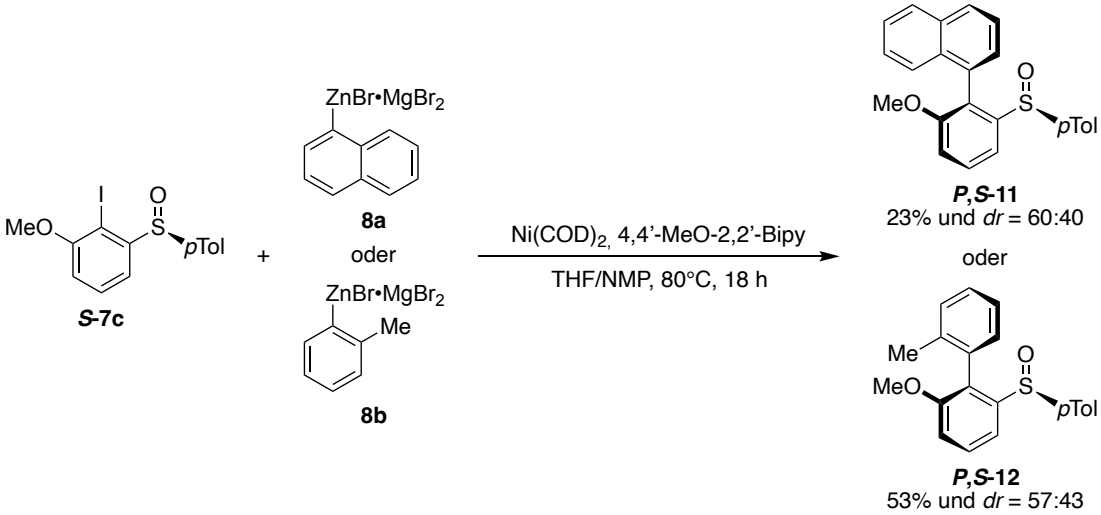
Favorisierte Nebenreaktion:



Negishi-Kreuzkupplungen

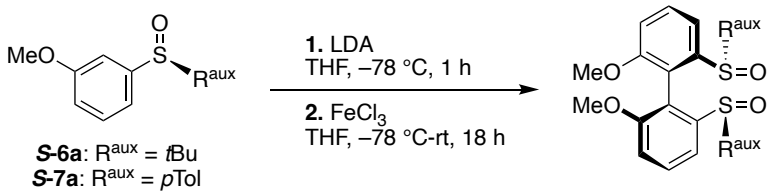


Reaktionsbedingungen:
***S*-6c** (1.0 equiv.), **8b** (2.0 equiv.), $Pd(PPh_3)_2$ (10 mol-%) oder $Ni(DME)Cl_2$ (20 mol-%) oder $CoCl_2$ (30 mol-%), 2,2'-Bipy (30 mol-%), THF/NMP (4:1, 0.2 M) oder THF (0.2 M), rt oder 40°C, 18 h



Reaktionsbedingungen:
***S*-7c** (1.0 equiv.), **8a** oder **8b** (2.0 equiv.), $Ni(COD)_2$ (10 mol-%), 4,4'-MeO-2,2'-Bipy (15 mol-%)
THF/NMP (4:1, 0.2 M), 80°C, 18 h

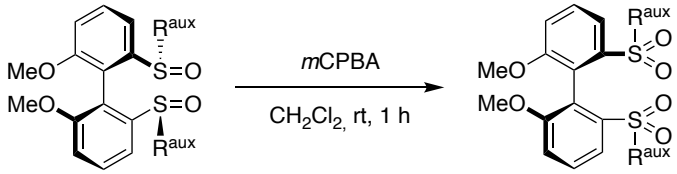
Homokupplungen und Oxidation



***S*-6a**: R^{aux} = *t*Bu
***S*-7a**: R^{aux} = *p*Tol

***M,S*-16**: R^{aux} = *t*Bu
83% und *dr* > 95:5
***M,S*-17**: R^{aux} = *p*Tol
55% und *dr* > 95:5

Reaktionsbedingungen:[3]
***S*-6a** oder ***S*-7a** (1.0 equiv.)
1. LDA (*n*BuLi (1.2 equiv.), *i*Pr_2NH (1.3 equiv.)), THF (0.6 M), –78°C, 1 h.
2. $FeCl_3$ (1.2 equiv.), THF (0.35 M), –78 °C-rt, 18 h.



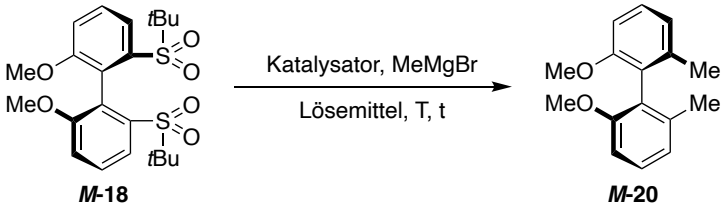
***M,S*-16**: R^{aux} = *t*Bu
***M,S*-17**: R^{aux} = *p*Tol

***M*-18**: R^{aux} = *t*Bu
86% yield
***M*-19**: R^{aux} = *p*Tol
>99% yield

Reaktionsbedingungen:
***S*-16a** oder ***S*-17a** (1.0 equiv.), *m*CPBA (3.0 equiv.), CH_2Cl_2 (0.34 M), rt, 1 h.

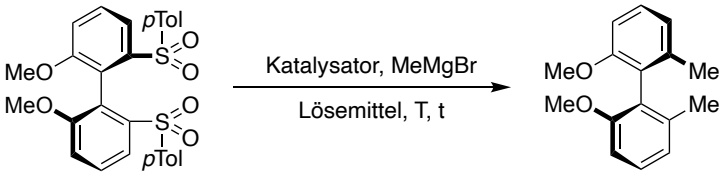
[3] Q.-A. Chen, X. Dong, M.-W. Chen, D.-S. Wang, Y.-G. Zhou, Y.-X. Li, *Org. Lett.*, **2010**, 12(9), 1928–1931.

Funktionalisierung der Disulfonbiaryle



Eintrag	Katalysator	MeMgBr [equiv.]	Lösemittel	T [°C]	t [h]	
1	$Ni(acac)_2$ (20 mol-%)	4.0	THF (0.1 M)	80	1	Weder Edukt noch Produkt isolierbar
2	$Pd(PPh_3)Cl_2$ (10 mol-%)	4.0	THF (0.1 M)	80	1	
3	$FeCl_3$ (10 mol-%)	3.0	THF (0.1 M)	rt	18	
4	$Fe(acac)_3$ (10 mol-%)	3.0	THF (0.1 M)	rt	18	
5	IMesCuCl (10 mol-%)	3.0	Toluol (0.1 M)	100	5	→ Edukt wieder isoliert

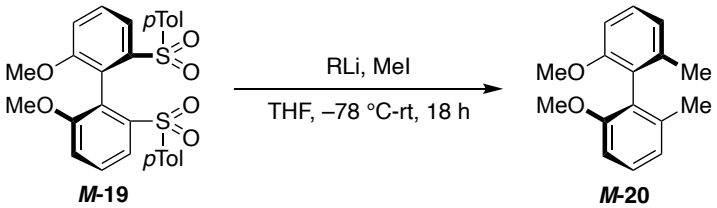
Funktionalisierung der Disulfonbiaryle



***M*-19** **M-20**

Eintrag	Katalysator	MeMgBr [equiv.]	Lösemittel	T [°C]	t [h]	
1	$Ni(acac)_2$ (20 mol-%)	10.0	THF (0.1 M)	80	1	Defunktionalisierung der Sulfone
2	$Pd(PPh_3)Cl_2$ (10 mol-%)	10.0	THF (0.1 M)	80	1	
3	$FeCl_3$ (10 mol-%)	10.0	THF (0.1 M)	rt	18	
4	$Fe(acac)_3$ (10 mol-%)	10.0	THF (0.1 M)	rt	18	
5	IMesCuCl (10 mol-%)	10.0	Toluol (0.1 M)	100	5	Edukt wieder isoliert
6	$Ni(PCy_3)_2Cl_2$ (20 mol-%)	10.0	THF (0.1 M)	80	18	

Funktionalisierung der Disulfonbiaryle

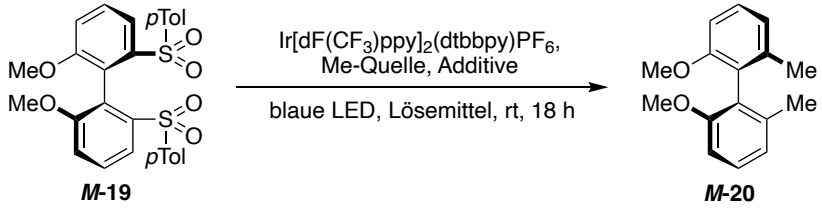


***M*-19** **M-20**

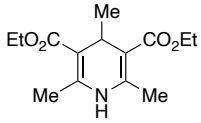
Eintrag	RLi	MeI [equiv.]	Konzentration [M]
1	*t*BuLi	10.0	0.05
2	PhLi	10.0	0.2

Weder Edukt noch Produkt isolierbar

Methylierung der *para*-Tolylgruppe



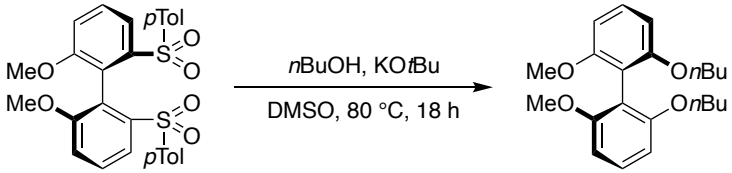
***M*-19** **M-20**

Eintrag	Me-Quelle	Additive	Lösemittel
1[4]	MeI (3.0 equiv)	K_2CO_3 (2.0 equiv.), $(TMS)_3SiH$ (1.2 equiv.)	MeCN (0.05 M)
2[5]	$MeB(OH)_2$ (4.0)	K_3PO_4 (1.5 equiv.)	CH_2Cl_2/EtOAc (2:1, 0.1 M)
3[6]	 **21** (1.2 equiv.)	---	EtOAc (0.1 M)

Edukt wieder isoliert

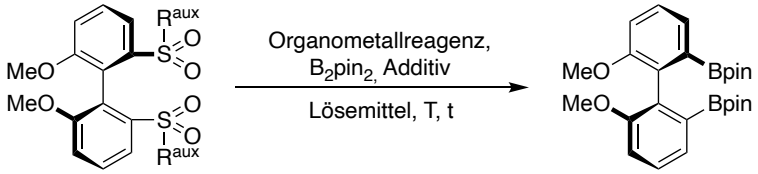
[4] Q.-Q. Zhou, S. J. S. Düsel, L.-Q. Lu, B. König, W.-J. Xiao, *Chem. Commun.*, **2019**, 55, 107–110.
[5] F. Yue, J. Dong, Y. Liu, Q. Wang, *Org. Lett.*, **2021**, 23, 2477–2481.
[6] F. Yue, J. Dong, Y. Liu, Q. Wang, *Org. Biomol. Chem.*, **2021**, 19, 8924–8928.

Funktionalisierung der Disulfonbiaryle



***M*-19** **M-23** 0%

Reaktionsbedingungen:[7]
***M*-19** (1.0 equiv.), *n*BuOH (4.0 equiv.), KO*t*Bu (4.0 equiv.), DMSO (1.0 M), 80°C, 18 h.



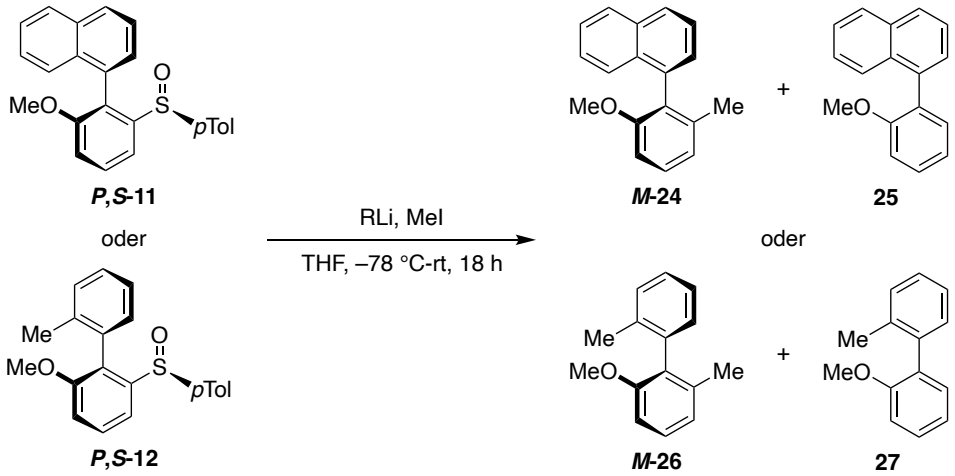
***M*-18**: R^{aux} = *t*Bu
***M*-19**: R^{aux} = *p*Tol

***M*-22**

Eintrag	R^{aux}	Organometall-reagenz	B_2pin_2	Additiv	Lösemittel	T [°C]	t [h]	
1	*t*Bu	IMesCuCl (10 mol-%)	3.0	KO*t*Bu (3.0 equiv.)	Toluol (0.1 M)	100	5	→ Weder Edukt noch Produkt isolierbar
2	*p*Tol	IMesCuCl (20 mol-%)	3.0	KO*t*Bu (3.0 equiv.)	Toluol (0.2 M)	100	5	Edukt wieder isoliert
3	*p*Tol	*i*PrMgCl·LiCl (4.0 equiv.)	10.0	---	THF (0.2 M)	25	18	

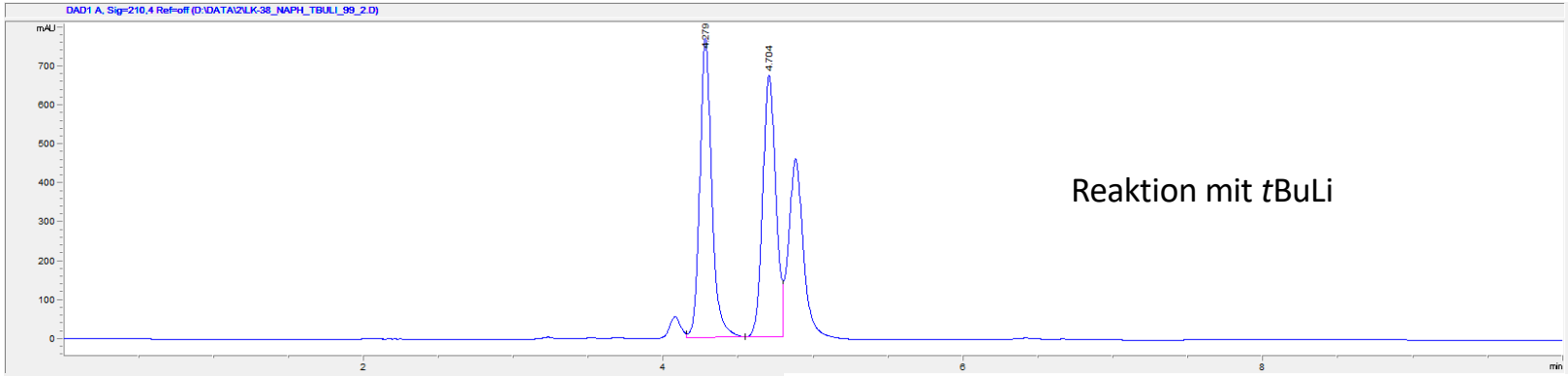
[7] J. Bai, T. Wang, B. Dai, Q. Liu, P. Yu, T. Jia, *Org. Lett.*, **2021**, 23, 5761–5765.

Funktionalisierung der Sulfoxidbiaryle



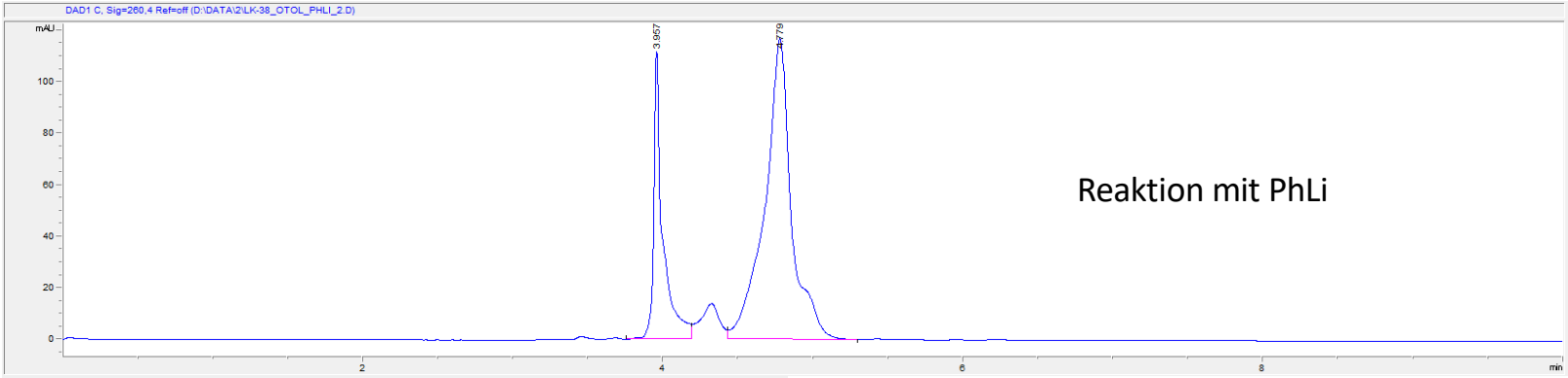
Eintrag	***P,S*-11** oder ***P,S*-12** (*dr*)	RLi	MeI [equiv.]	Konzentration [M]	Produktverhältnis [***M*-24**:**25**] oder [***M*-26**:**27**]	*er*
1	***P,S*-11** (64:36)	*t*BuLi (4.0 equiv.)	10.0	0.05	2.5:1	n.d.
2	***P,S*-12** (58:42)	*t*BuLi (4.0 equiv.)	10.0	0.05	2.1:1	61:39
3	***P,S*-11** (64:36)	PhLi (4.0 equiv.)	10.0	0.05	11.5:1	n.d.
4	***P,S*-12** (58:42)	PhLi (4.0 equiv.)	10.0	0.05	12.0:1	66:34

Funktionalisierung der Sulfoxidbiaryle



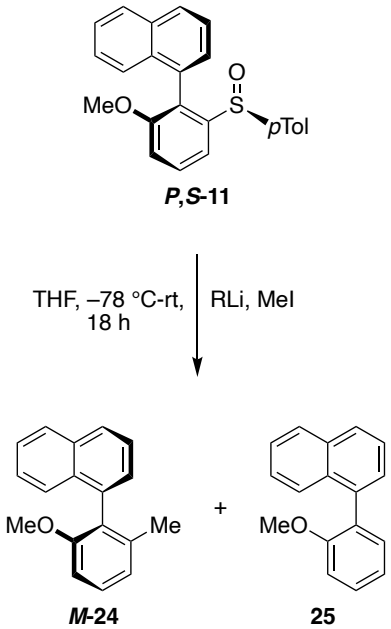
Reaktion mit *t*BuLi

#	Time	Area	Height	Width	Area%	Symmetry
1	4.279	4274.7	769.2	0.0838	51.062	0.82
2	4.704	4096.9	673.1	0.093	48.938	0.889

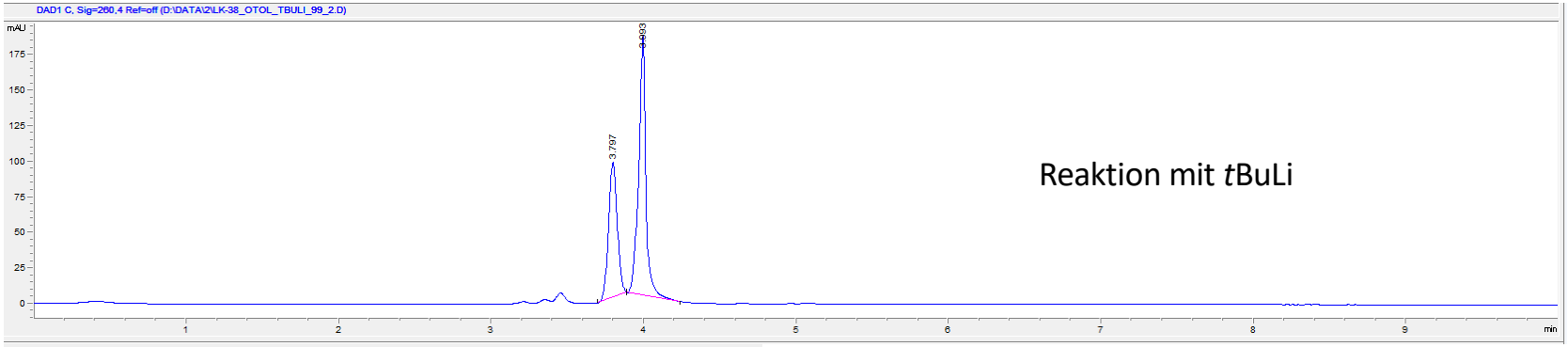


Reaktion mit PhLi

#	Time	Area	Height	Width	Area%	Symmetry
1	3.957	462.3	112.1	0.0551	24.261	0.415
2	4.779	1443.3	116.9	0.1701	75.739	1.235

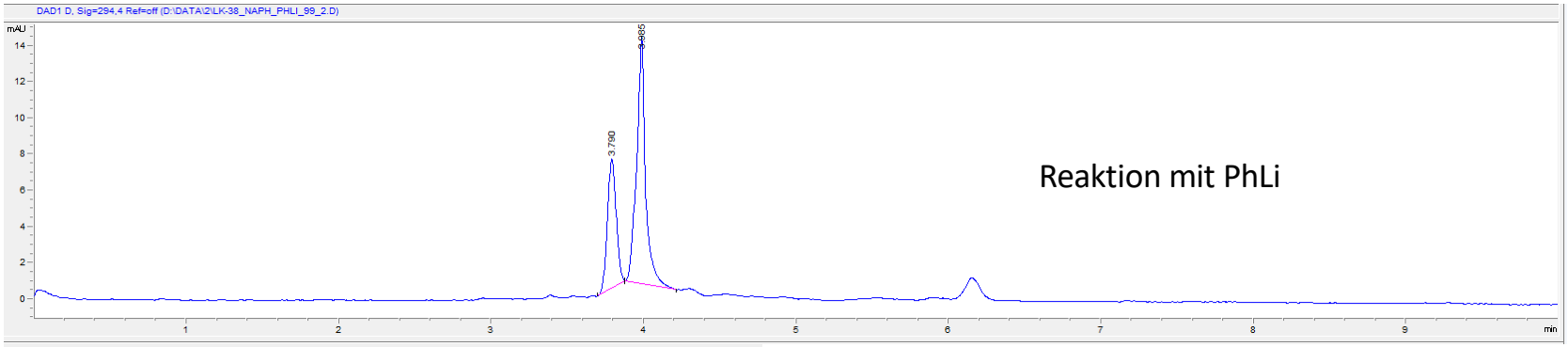


Funktionalisierung der Sulfoxidbiaryle



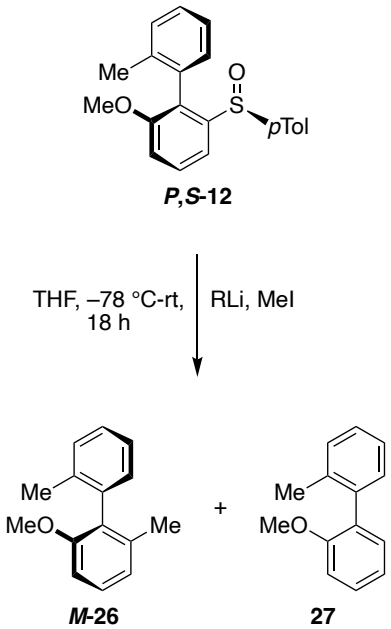
Reaktion mit *t*BuLi

#	Time	Area	Height	Width	Area%	Symmetry
1	3.797	382.4	95.3	0.0618	38.769	0.942
2	3.993	603.9	182.6	0.0466	61.231	1.234

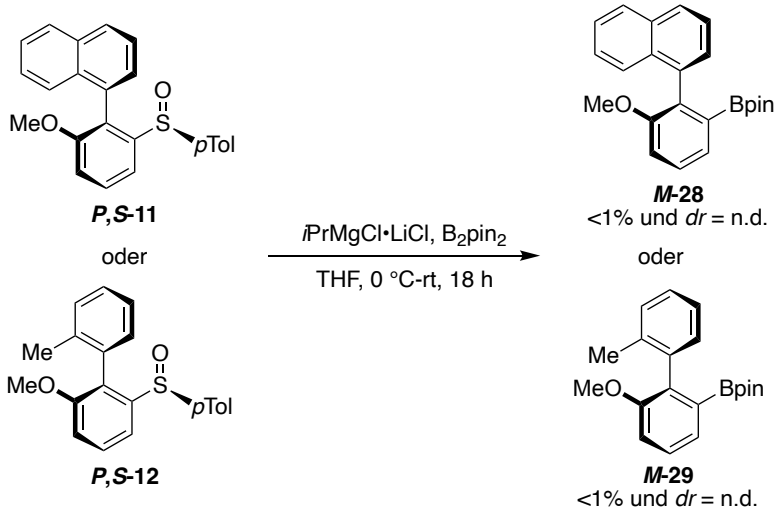


Reaktion mit PhLi

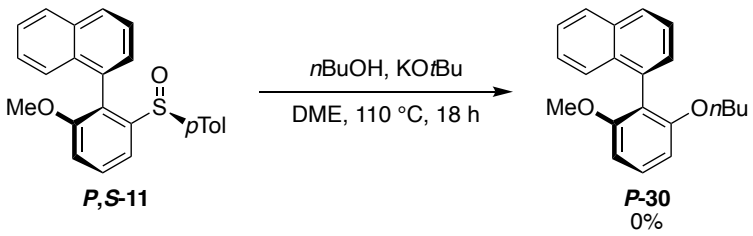
#	Time	Area	Height	Width	Area%	Symmetry
1	3.79	28.7	7.1	0.0619	34.053	0.946
2	3.985	55.6	13.6	0.0566	65.947	1.071



Funktionalisierung der Sulfoxidbiaryle



Reaktionsbedingungen:[8]
***P,S*-11** oder ***P,S*-12** (1.0 equiv.), *i*PrMgCl·LiCl (2.0 equiv.), B_2pin_2 (5.0 equiv.), THF (0.25 M), 0°C-rt, 18 h.

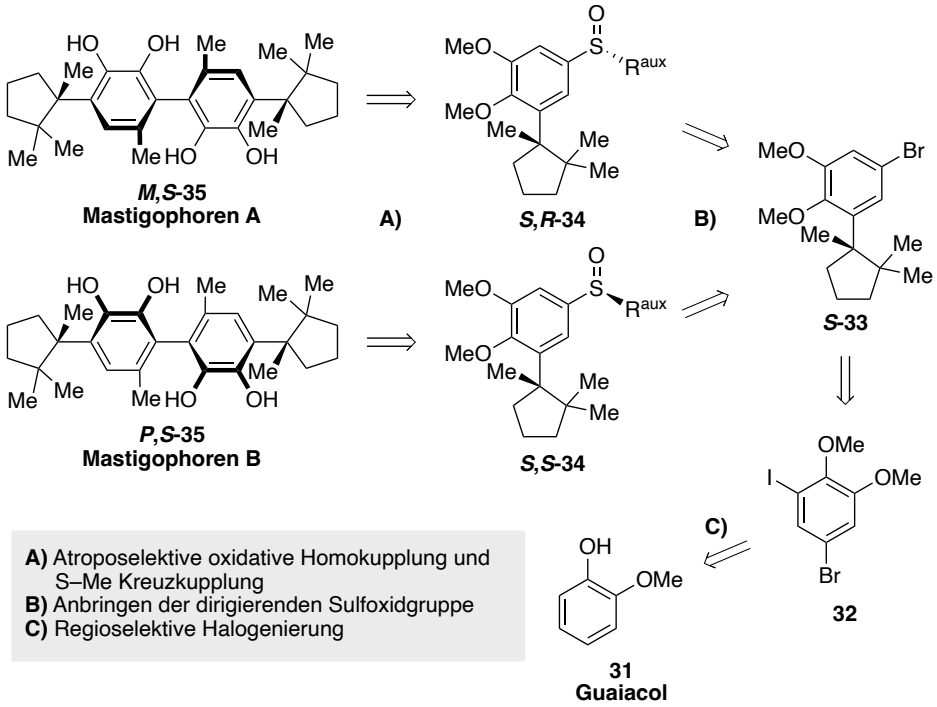


Reaktionsbedingungen:[7]
***P,S*-11** (1.0 equiv.), *n*BuOH (2.0 equiv.), KO*t*Bu (2.0 equiv.), DME (0.5 M), 110°C, 18 h.

[7] J. Bai, T. Wang, B. Dai, Q. Liu, P. Yu, T. Jia, *Org. Lett.*, **2021**, 23, 5761–5765.
[8] J. Bortoluzzi, V. Jha, G. Levitre, M. J. Fer, J. Berreur, G. Masson, A. Panossian, F. R. Leroux, *J. Org. Chem.*, **2018**, 83, 7751–7761.

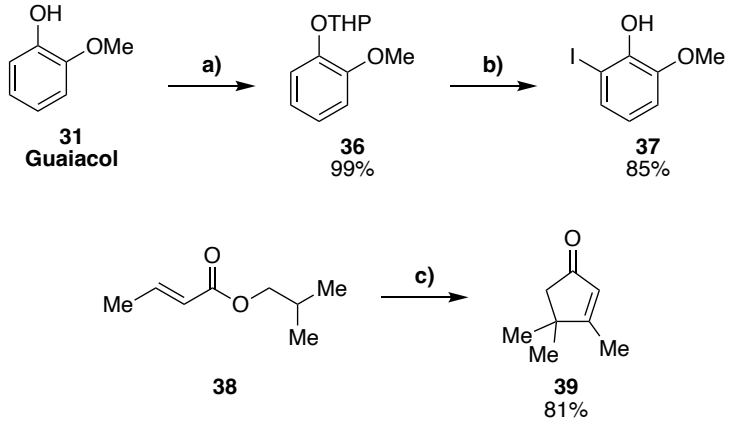
Fortschritt in der Totalsynthese von Mastigophoren

Retrosynthetische Überlegung:



A) Atroposelektive oxidative Homokupplung und S–Me Kreuzkupplung
B) Anbringen der dirigierenden Sulfoxidgruppe
C) Regioselektive Halogenierung

Bisheriger Fortschritt:

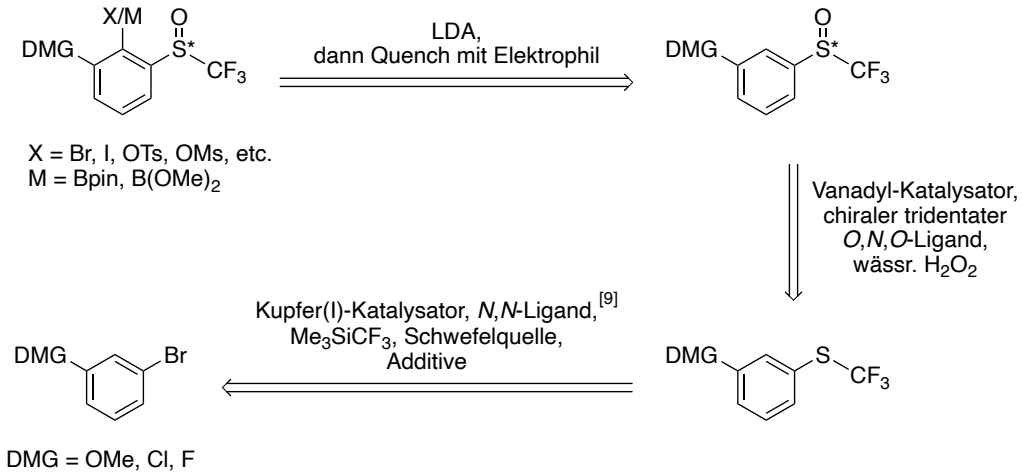


Reaktionsbedingungen:
a) DHP (10.0 equiv.), PPTS (10 mol-%), CH_2Cl_2 (1.1 M), rt, 4 h.
b) *n*BuLi (1.5 equiv.), I_2 (2.0 equiv.), THF (0.5 M), –78°C-rt, 18 h.
c) PPA (1.0 M), 120°C, 4 h.

Ausblick und zukünftige Ambitionen

Trifluormethylgruppe als Alternative

Herstellung der Substrate:

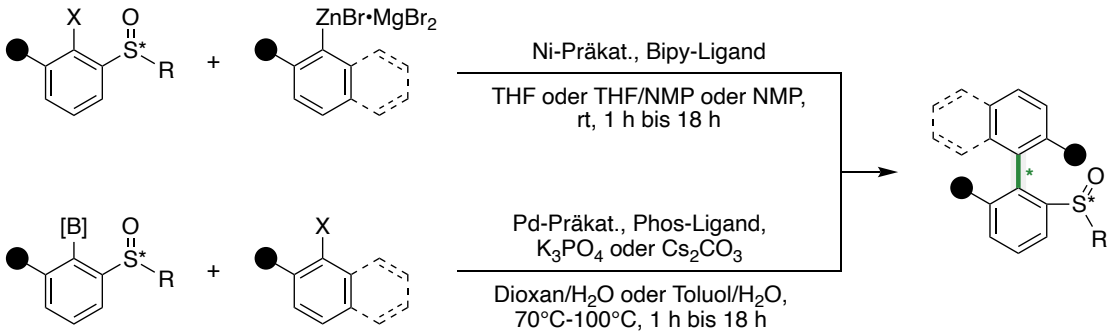


[9] W. Zhong, X. Liu, *Tetrahedron Letters*, **2014**, 55, 4909–4911.

Ausblick und zukünftige Ambitionen

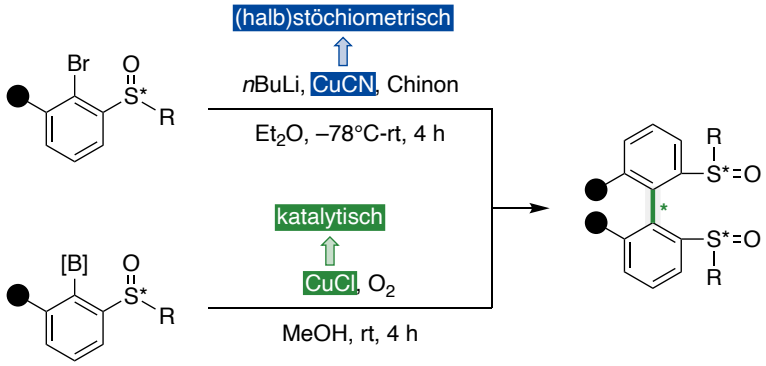
Kupplungsreaktionen

Kreuzkupplungen:



X = Br, I, OTs, OMs, etc.
[B] = Bpin, $B(OH)_2$
R = *p*Tol, CF_3

Homokupplungen:[10]

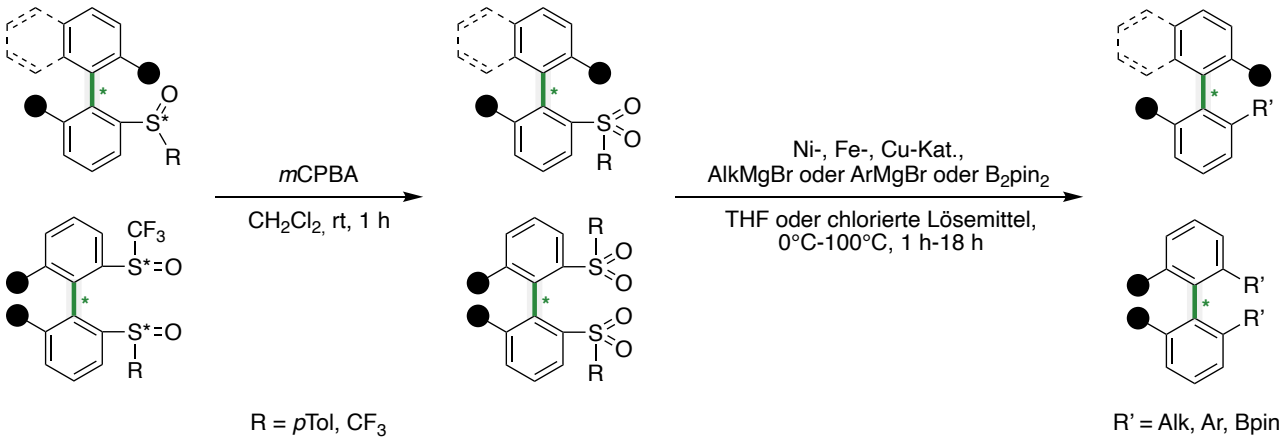


[B] = Bpin, $B(OH)_2$
R = *p*Tol, CF_3

[10] S. N. S. Vasconcelos, J. S. Reis, I. M. de Oliveira, M. N. Balfour, H. A. Stefani, *Tetrahedron*, **2019**, 75(13), 1865–1959.

Ausblick und zukünftige Ambitionen

Funktionalisierungsreaktionen



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