

Transmetalation

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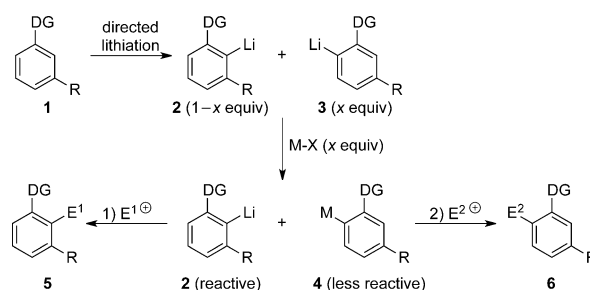
Functionalizations of Mixtures of Regioisomeric Aryllithium Compounds by Selective Trapping with Dichlorozirconocene

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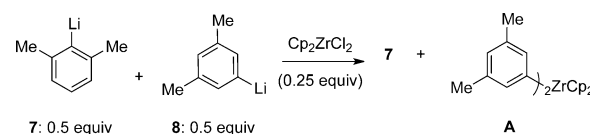
Abstract: The reaction of mixtures of aryllithium regioisomers obtained either by directed lithiation or by Br/Li exchange with substoichiometric amounts of Cp_2ZrCl_2 proceeds with high regioselectivity. The least sterically hindered regioisomeric aryllithium is selectively transmetalated to the corresponding arylzirconium species leaving the more hindered aryllithium ready for various reactions with electrophiles. As an application, these regioselective transmetalations from Li to Zr were used to prepare all three lithiated regioisomers of 1,3-bis(trifluoromethyl)benzene.

Organolithium compounds are important organometallic intermediates in organic synthesis.^[1] The most convenient preparation of aryllithiums involves a halogen–lithium exchange or a directed metalation.^[2] The presence of a directing group usually ensures lithiation at the *ortho*-position; however, in cases where unsymmetrical substrates of type **1** are used, a mixture of regioisomeric aryllithiums **2** and **3** may be produced.^[3] The formation of such mixtures hampers synthetic applications. This lack of regioselectivity could potentially be solved by a preferential transmetalation of one of two regioisomers **2** and **3**. Therefore, we envisioned that a selective transmetalation of the less sterically hindered aryllithium **3** with an appropriate metal salt (M–X) may selectively produce the new metalated arene **4** leaving the more sterically hindered aryllithium (**2**) untouched and therefore available for a reaction with an electrophile (E^{1+}) leading to the 1,2,3-trisubstituted arenes of type **5**. On the other hand, in the organometallic species (**4**), produced after the transmetalation step, the carbon–metal bond should be significantly less reactive than the carbon–lithium bond in **2** and may thus be trapped by a second and different electrophile (E^{2+}) producing the regioisomeric 1,3,6-trisubstituted arene of type **6** (Scheme 1).

Herein, we report a successful method for solving the regioselectivity problem in such arene lithiations. Preliminary experiments for identifying an appropriate metal salt (M–X) to perform selective transmetalations were performed on 1:1 mixtures of 2,6-dimethylphenyllithium (**7**) and 3,5-dimethylphenyllithium (**8**) and showed that reactions with various Zn, Mg, Cu, Ti, and Sn salts gave no selective transmetalation. However, Cp_2ZrCl_2 ^[4] reacted preferentially with 3,5-dime-



Scheme 1. Nonselective metalation of unsymmetrical arenes followed by selective transmetalation.



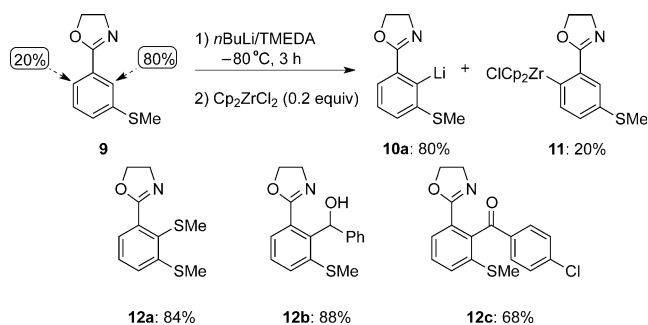
Scheme 2. Chemoselective transmetalation using Cp_2ZrCl_2 .

thylphenyllithium **8** leaving **7** untouched and ready for a selective reaction with an electrophile (Scheme 2). Only the less sterically hindered aryllithium **8** reacts with Cp_2ZrCl_2 leading to a less reactive diarylzirconium species (**A**). These encouraging results led us to examine the lithiation of various substrates of type **1**. Since oxazolines are important directing groups for *ortho*-lithiations, we first examined the lithiation of the 3-thiomethylaryloxazoline (**9**).^[5] Thus, the lithiation of **9** with *n*BuLi–TMEDA (1.1 equiv, -80°C , 3 h) produces a 4:1 mixture of the regioisomeric 2- and 6-lithio derivatives as shown by iodolysis. Addition of Cp_2ZrCl_2 (0.2 equiv, -80°C , 1 h) achieved a completely selective transmetalation of the sterically less hindered 6-lithio derivative of **9**, providing the zirconium species (**11**) and leaving the lithiated arene (**10a**) untouched. Thus, treatment of a mixture of **10a** and **11** with MeSSMe (0.8 equiv, -80°C , 1 h) produces only the trisubstituted arene (**12a**) in 84% yield.^[6,7] Similarly, the addition of PhCHO (0.8 equiv, -80°C , 1 h) affords alcohol (**12b**) in 88% yield and quenching with 4-chlorobenzoyl chloride provides ketone **12c** in 68% yield (Scheme 3).

We then extended our study to unsymmetrical arenes **13–16** (Table 1). Thus, the methoxy-substituted oxazoline **13** produces after lithiation with *n*BuLi–TMEDA (1.1 equiv, -80°C , 3 h) a 93:7 mixture. 1,3-Dicyanobenzene (**14**) affords, after metalation with TMPLi (TMP = 2,2,6,6-tetramethylpiperidyl; 1.05 equiv, -80°C , 0.5 h), an 85:15 mixture; the reaction of benzonitrile **15** with TMPLi (1.0 equiv, -80°C , 20 min) gives a 60:40 mixture. Alkynylbenzene **16** also

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Scheme 3. Regioselective functionalization of oxazoline (**9**). Conditions: 1) *n*BuLi (1.1 equiv), TMEDA (1.1 equiv); 2) Cp_2ZrCl_2 (0.2 equiv); 3) E^1 (0.8 equiv); 4) H_2O .

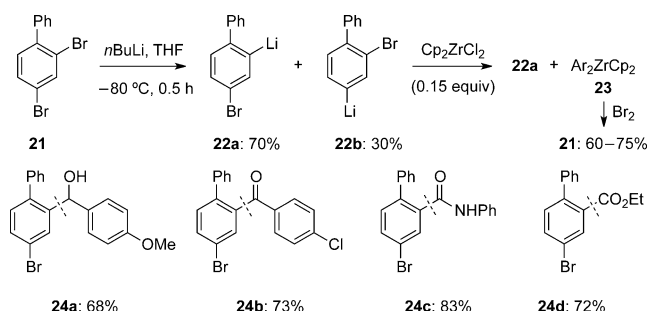
Table 1: Regioselective functionalization of unsymmetric arenes.

Entry	Substrate	Electrophile	Product ^[a]
1	13	ClCO_2Et	17a : $\text{E}^1 = \text{CO}_2\text{Et}$, 85 %
2	13	BuSSBu	17b : $\text{E}^1 = \text{SBu}$, 83 %
3	14	$(p\text{TolS})_2$	18a : $\text{E}^1 = Sp\text{Tol}$, 73 %
4	14	$(\text{BrCCl}_2)_2$	18b : $\text{E}^1 = \text{Br}$, 75 %
5	14	TMSCl	18c : $\text{E}^1 = \text{TMS}$, 66 %
6	15	furfural	19a : $\text{E}^1 = \text{CH(OH)2-furyl}$, 75 %
7	15	$(\text{ICH}_2)_2$	19b : $\text{E}^1 = \text{I}$, 78 %
8	15	$\text{cyclopropanecarbonyl chloride}$	19c : $\text{E}^1 = \text{COcPr}$, 61 % ^[b]
9	16	$c\text{HexNCO}$	20a : $\text{E}^1 = \text{CONHcHex}$, 85 %
10	16	<i>i</i> PrOBpin	20b : $\text{E}^1 = \text{Bpin}$, 90 %
11	16	$4\text{-ClC}_6\text{H}_4\text{CHO}$	20c : $\text{E}^1 = \text{CH(OH)4-ClC}_6\text{H}_4$, 79 %
12	16	furfural	20d : $\text{E}^1 = \text{CH(OH)2-furyl}$, 95 %
13	16	$(\text{ICH}_2)_2$	20e : $\text{E}^1 = \text{I}$, 74 %
14	16	$(\text{BrCCl}_2)_2$	20f : $\text{E}^1 = \text{Br}$, 72 %
15	16	MeSSMe	20g : $\text{E}^1 = \text{SMe}$, 87 %
16	16	$\text{cyclohexyl isocyanate}$	20h : 77 %

[a] Yield of analytically pure product (> 99%). [b] $\text{Sc}(\text{OTf})_3$ was added.

furnishes an 80:20 mixture after lithiation with TMPLi (1.0–1.1 equiv, -80°C , 0.5 h). Treatment of these aryllithium mixtures with the appropriate amount of Cp_2ZrCl_2 allows selective transmetalation of the less sterically hindered aryllithium providing a less reactive arylzirconium species and leaving the major aryllithium reagent ready to react with various electrophiles producing > 97% regioisomerically pure products of type **17–20**. In a typical experiment, the lithiated arylloxazoles derived from **13** were treated with Cp_2ZrCl_2 (0.1 equiv, -80°C , 1 h) followed by the addition of ethyl chloroformate (0.9 equiv, -80°C , 1 h) providing the 2-carbomethoxy arene (**17a**) in 85% yield free of any regioisomeric by-product. Similarly addition of BuSSBu led to the production of thioether **17b** in 83% yield. The 85:15 mixture of lithiated **14** was similarly treated with Cp_2ZrCl_2 (0.15 equiv, -80°C , 0.5 h) followed by various electrophiles ($(p\text{TolS})_2$, $(\text{BrCCl}_2)_2$, TMSCl), furnishing regioisomerically pure 1,2,3-trisubstituted dinitriles **18a–c** in 66–75% yield (entries 3–5). The same strategy was applied to arene **15**. After the addition of Cp_2ZrCl_2 (0.35–0.4 equiv, -80°C , 0.5 h), the more sterically hindered 3-lithio isomer reacted with various electrophiles (furfural, $(\text{ICH}_2)_2$, or cyclopropanecarbonyl chloride in the presence of 10% $\text{Sc}(\text{OTf})_3$ ^[8]) producing the regioisomerically pure products (crude ratio 97:3) **19a–c** in 61–78% yield (entries 6–8). Also, the unselective lithiation of **16** leads, after the addition of Cp_2ZrCl_2 (0.25 equiv, -80°C , 0.5 h) and various electrophiles (cyclohexyl isocyanate, *i*PrOBpin, 4-chlorobenzaldehyde, furfural, $(\text{ICH}_2)_2$, $(\text{BrCCl}_2)_2$, MeSSMe, 2,4-dichlorobenzoyl chloride), to isomerically pure products (**20a–h**) in 72–95% yield (entries 9–16).

This methodology was also successfully applied to regioisomeric mixtures of aryllithiums obtained by Br/Li exchange (Scheme 4). Indeed, dibromobiphenyl **21** undergoes a non-

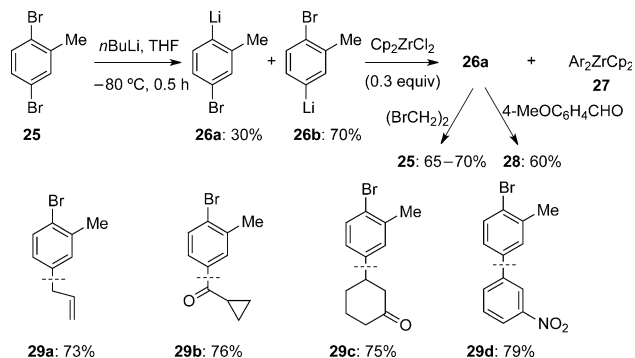


Scheme 4. Regioselective functionalization of dibromobiphenyl (**21**). Conditions: i) *n*BuLi (1.05 equiv), ii) Cp_2ZrCl_2 (0.15 equiv), iii) E^1 (0.70–0.75 equiv), iv) Br_2 (excess). All products obtained in > 97:3 regioisomeric ratio.

regioselective Br/Li exchange with *n*BuLi (THF, 1.05 equiv, -80°C , 0.5 h) producing a 70:30 mixture of isomers **22a** and **22b**. The addition of Cp_2ZrCl_2 (0.15 equiv, -80°C , 1.5–2 h) led to a selective transmetalation (> 97:3) of the less sterically hindered aryllithium (**22b**), providing the bis-aryl zirconocene (**23**) and unreacted **22a**. Functionalization of **22a** with a range of electrophiles (4-methoxybenzaldehyde, 4-chlorobenzoyl chloride, phenyl isocyanate, ethyl cyanoformate) produces the corresponding products (**24a–d**) in 68–83%

yield. The remaining diarylzirconocene (**23**) was converted back to the starting dibromide **21** in 60–75% yield by adding bromine.^[9]

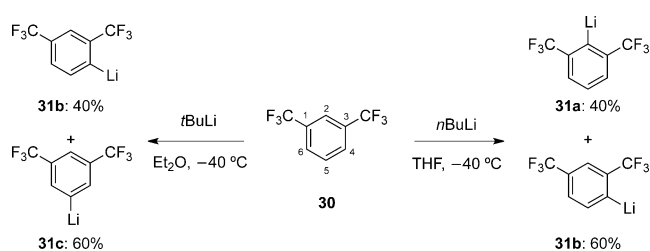
Interestingly, the related 2,5-dibromotoluene (**25**) also undergoes an unselective Br/Li exchange with *n*BuLi (THF, 1 equiv, –80 °C, 0.5 h) producing a 30:70 mixture of the two regioisomeric lithium species **26a** and **26b** (Scheme 5). The major regioisomer (**26b**) is converted into the corresponding



Scheme 5. Regioselective functionalization of 2,5-dibromotoluene (**25**). Conditions: i) *n*BuLi (1.0 equiv), ii) Cp_2ZrCl_2 (0.3 equiv), iii) $(\text{BrCH}_2)_2$ or ArCHO (0.40–0.45 equiv), iv) E^2 (0.45–0.55 equiv). All products obtained in > 97:3 regioisomeric ratio.

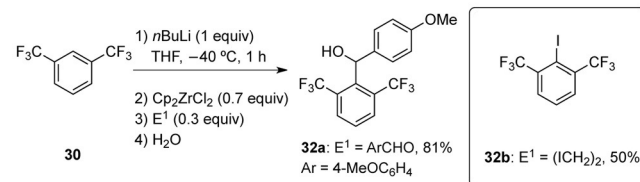
diarylzirconocene (**27**) upon addition of Cp_2ZrCl_2 (0.3 equiv, –80 °C, 1.5 h). Quenching of the aryllithium **26a** with $(\text{BrCH}_2)_2$ or 4-MeOC₆H₄CHO (0.4–0.45 equiv, –80 °C, 0.5–1 h) generates the starting material (**25**) or the corresponding alcohol **28**, leaving the zirconocene species **27** untouched. Further allylation, acylation, 1,4-addition, and cross-coupling allows functionalization of the zirconocene **27** providing the expected products (**29a–d**) in 73–79% yield.

CF_3 -substituted aromatics are very important pharmaceutical targets and much recent work on the selective preparation of CF_3 -substituted molecules has been reported.^[10] The lithiation of 1,3-bis(trifluoromethyl)benzene (**30**) proceeds without any appreciable regiocontrol.^[11] Thus, metalation with *n*BuLi in THF produces a 40:60 mixture of the 2- and 4-lithio derivatives **31a** and **31b**. Alternatively, the use of *t*BuLi in ether leads to a 40:60 mixture of the 4- and 5-lithio derivatives **31b** and **31c** (Scheme 6). The production of regioisomeric mixtures makes these lithiations preparatively useless. However, using the zirconium transmetalation, it was possible to regioselectively functionalize the three positions of **30**. Selective lithiation at position 2 is reached by treating **30** with *n*BuLi (THF, 1 equiv, –40 °C, 1 h), followed by subsequent addition of Cp_2ZrCl_2 (0.7 equiv, –80 °C, 1.5 h); **31b** is converted into the corresponding zirconium species leaving **31a** as the sole remaining lithiated reagent. Its reaction with different electrophiles (4-MeOC₆H₄CHO, and $(\text{ICH}_2)_2$) furnishes the corresponding products **32a** and **32b** in 81 and 50% yield, respectively (Scheme 7). The selective functionalization at position 4 is possible using *t*BuLi (Et_2O , 1 equiv, –40 °C, 18 h) followed by the addition of Cp_2ZrCl_2 (0.3 equiv, –80 °C, 1–1.5 h) to the 40:60 mixture of **31b** and **31c**. In this case, **31c** is transmetalated into the corresponding

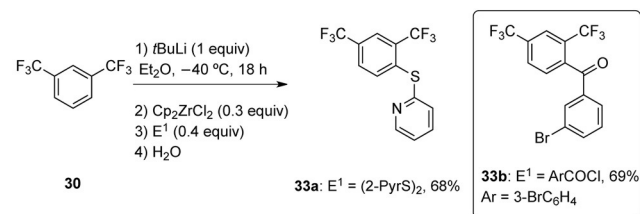


Scheme 6. Unselective 2-, 4-, or 5-lithiation of 1,3-bis(trifluoromethyl)benzene (**30**).

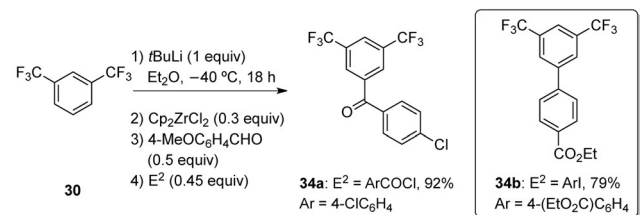
Functionalization at position 2:



Functionalization at position 4:



Functionalization at position 5:



Scheme 7. Selective 2-, 4-, or 5-functionalization of 1,3-bis(trifluoromethyl)benzene (**30**).

zirconium species and the lithium reagent (**31b**) is quenched with various electrophiles: (2-Pyr)₂, 3-bromobenzoyl chloride leading to **33a** and **33b** with 68 and 69% yield, respectively. On the other hand, lithiation with *t*BuLi in ether has been also used to functionalize the position 5, but in this case the mixture of **31b** and **31c** was treated with Cp_2ZrCl_2 (0.3 equiv, –80 °C, 1.5 h) followed by the addition of 4-MeOC₆H₄CHO (0.5 equiv, –80 °C, 1 h), which reacted exclusively with the lithio species (**31b**). The zirconium species reacted with subsequently introduced electrophiles (4-chlorobenzoyl chloride, ethyl 4-iodobenzoate) to produce the products **34a** and **34b** in 92 and 79% yield, respectively.

In conclusion, we have demonstrated that the regioselective transmetalation of isomeric mixtures of various aryllithiums can be readily achieved using a substoichiometric amount of Cp_2ZrCl_2 as the transmetalating agent. This selectivity is best explained by steric considerations. This method allows the selective differentiation of a mixture of regioisomeric aryllithiums.

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- [6] If Cp_2ZrCl_2 is not added, quenching the mixture of **10a** and **10b** with MeSSMe (0.8 equiv) produces a 4:1 mixture of the two regioisomeric bis-thioethers. Their isolation led to **12a** in 68% yield and the 6-thiomethyl isomer (**12a'**) in 14% yield.
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