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Chiral bromine–lithium exchange catalyzed by diamines

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ABSTRACT

Different classes of prochiral polyhalide compounds have been tested in a chiral bromine–lithium exchange in the presence of different diamines with enantiomeric excesses of up to 63%.

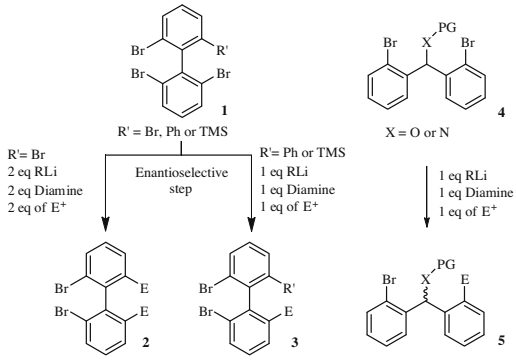
1. Introduction

The first halogen–lithium exchange was published by Marvel in 1927 where he noted the formation of toluene when *n*-BuLi was mixed with *o*- or *m*-bromotoluene.[1] In 1938 Wittig and Gilman started to independently study this reaction and obtained the same conclusions concerning orthometallation or halogen–lithium exchange with *p*-bromoanisole or *o*-bromoanisole, respectively, in the presence of lithium base in ether.[2] Since then, only new applications of this reaction or mechanistic studies have been reported.[3]

In our laboratory we studied organolithium compounds in presence of chiral diamines,[4] and in order to prepare aromatic lithium reagents starting from the corresponding aromatic halide we noted that the exchange between an aromatic bromide and *n*-BuLi did not occur at low temperature without the presence of a diamine in toluene,[4] in contrast to aromatic iodides, where a diamine is not required. To the best of our knowledge, since Wittig and Gilman, no chiral version of this reaction has been reported. Hence we started a program in applying our diamines in a chiral version of this bromine–lithium exchange. However, during our investigations, Kagan et al. published a new concept where they present the desymmetrization of prochiral aromatic or vinylic dihalide substrates in presence of diamines.[5] Herein, we report our results in the state they were.

2. Results and discussion

Two classes of substrates were studied. The first allows for an axial chirality by the desymmetrization of prochiral aromatic halide compounds such as **1**, by selectively exchanging only one of two enantiotopic bromines (Scheme 1). Of particular interest was **1** (R = Br), because its halogen–lithium exchange has already been studied by Leroux et al., but not in a chiral version.[6] The second class of substrates concerns more the 'classical' central chirality. This could be obtained in the case of the protected diaryl alcohol or amine **4** (Scheme 1).



Scheme 1.

The starting material 2,2′,6,6′-tetrabromobiphenyl **8** was prepared in two steps, according to the procedure described by Leroux,[6c] and was obtained with an overall yield of 47% thanks to an Ullman coupling starting from the 1,3-dibromobenzene **6** (Scheme 2). In order to optimize this reaction and to prevent the use of nitrobenzene, which is very difficult to separate from the product, we decided to perform a one-pot procedure using benzoquinone or chloranil as a coupling agent.[7]

Thus, after the aromatic deprotonation of **6**, and transmetallation to the Cu reagent, we added either benzoquinone or chloranil to afford, after recrystallization in acetonitrile, the expected compound in 42% and 47% isolated yields, respectively (Scheme 2). This method gave similar overall yields but was more convenient on a large scale.

For alcohol **9** we performed a one-pot procedure using an α-bromo phenyl Grignard, prepared according to Knochel,[8] yielding 67% of the expected compound. The alcohol was then protected with different groups in order to examine the influence of the steric and coordination effects on the Br–Li exchange step (Scheme 3).

For the synthesis of the Boc-protected amine, the α-bromo phenyl Grignard was reacted with imine **17** as the electrophile, to provide the expected compound **18** in 60% overall yield.

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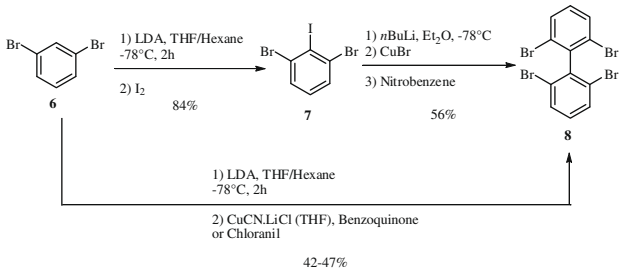
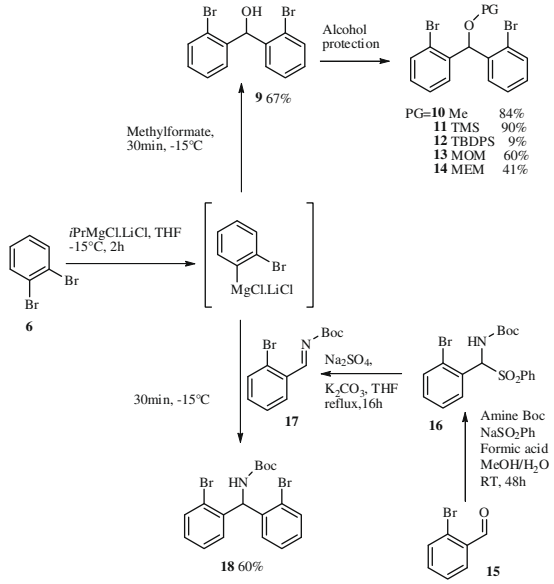
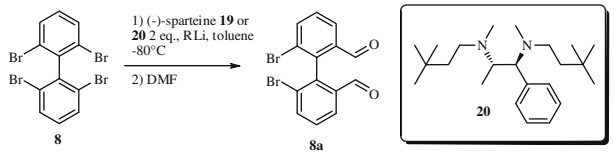


Scheme 2.



Scheme 3.

The chiral halogen–lithium exchange was first tested in the presence of 2 equiv of *n*-BuLi and 2 equiv of (−)-sparteine **19** in toluene at −80 °C, on substrate **8** (Scheme 4). We were surprised to find that even with more than 2 equiv of *n*-BuLi, only two bromines were substituted and each one on a different aryl portion. The last observation was already noted by Leroux, but in THF.[6] After 20 min, the reaction was over and DMF was added to trap the diorganolithium species. An enantiomeric excess of 24% was determined by SFC analysis (Table 1, entry 1). In addition to toluene, several other solvents were tested, but either the enantioselectivity was lower (THF), or compound **8** was insoluble (Et_2O). The Br–Li exchange was also tested with other organolithium reagents. MeLi and PhLi (entries 2 and 3) did not show any trace of the desired lithium reagent, whereas *s*-BuLi and *t*-BuLi (entries 4 and 5) did promote the exchange, albeit at a much slower rate. Interestingly, the observed enantioselectivity was higher (63% and 50%, respectively). However, even after prolonged times, the reaction did not proceed further, probably due to the insolubility of **8** at low temperature.



Scheme 4.

Table 1
Screening of organolithium reagents for the Br–Li exchange

Entry	Ligand	RLi	Time	Conv[a] (%)	ee (%)
1	**19**	*n*-BuLi	20 min	100	24
2	**19**	MeLi	20 min	0	—
3	**19**	PhLi	20 min	0	—
4	**19**	*s*-BuLi	2 h	32	63
5	**19**	*t*-BuLi	2 h	53	50
6	**20**	*n*-BuLi	20 min	100 (90)	50
7	**20**	*s*-BuLi	2 h	32	44
8	**20**	*t*-BuLi	2 h	100	55

Conditions: see general procedure A (Ref. 10).
[a] In parentheses, yield of the isolated product.

In addition to (−)-sparteine **19**, we also tested our recently described diamine **20**.[9] Under the same conditions as aforementioned, full conversion was observed with *n*-BuLi, and, after quenching with DMF, a 90% isolated yield of adduct **8a** was obtained with 50% ee (Table 1, entry 6). No improvement was observed with *s*-BuLi or *t*-BuLi (entries 7 and 8). An in situ quench with DMF was also attempted, but the reaction of *n*-BuLi on DMF was faster than the Br–Li exchange.

Catalytic versions of this reaction were tested and the results are summarized in Table 2.

Table 2
Screening of catalyst loading

Entry	Ligand (equiv)	RLi (2 equiv)	Time	Conv (%)	ee (%)
1	**20** (0.05)	*n*-BuLi	2 h	27	16
2	**20** (0.1)	*n*-BuLi	2 h	20	21
3	**20** (0.2)	*n*-BuLi	1 h	28	22
4	**20** (2)	*n*-BuLi	20 min	100	50
5	**19** (0.2)	*n*-BuLi	30 min	10	8
6	**19** (1)	*n*-BuLi	30 min	80	18
7	**19** (2)	*n*-BuLi	20 min	100	24
8	**19** (4)	*n*-BuLi	20 min	100	26

Conditions: see general procedure A (Ref. 10).

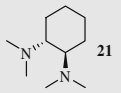
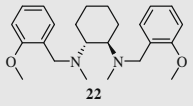
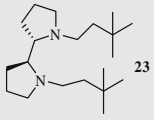
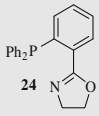
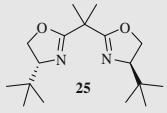
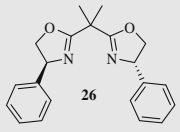
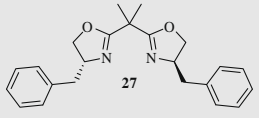
These results show a partial conversion when the reaction is performed under catalytic conditions even with an extension of the reaction time. This is due to the low solubility of the substrate in toluene at −80 °C. It appears that the reaction proceeds at the 'hot point' during the addition of the substrate on the diamine and *n*-BuLi. With 2 equiv of diamine the reaction is so fast that at the end of the addition all starting material is consumed. In contrast, the rate of the Br–Li exchange is much slower with a catalytic amount of ligand, and, at the end of the addition, the reaction is not complete and the starting material freezes in the Schlenk, thus stopping the reaction.

In addition to diamines **19** and **20**, the screening of other ligands has been performed and the results are summarized in Table 3.

Due to the high cost of these ligands, only the catalytic version was undertaken (except entries 1 and 8). Nevertheless, some interesting trends could be observed. Inexpensive diamine **21**, did not afford any enantioselectivity, even in stoichiometric amount. In all other cases the conversion and selectivity were low, certainly due to a catalytic use of ligand. However, ligand **25** appeared to be the most reactive one providing the expected compound in 85% conversion and 20% ee. Nevertheless, the only attempt with stoichiometric amount of bis-oxazoline **27** did improve the conversion, but the enantioselectivity remained poor.

Since many problems were related to the solubility of 2,2′,6,6′-tetrabromobiphenyl **8**, we decided to replace one bromine by a

Table 3
Screening of other ligands

Entry	Ligand	Equiv	Conv (%)	ee (%)
1	 **21**	2	89	0
2	 **22**	0.2	29	2
3	 **23**	0.2	39	15
4	 **24**	0.2	19	—
5	 **25**	0.2	85	20
6	 **26**	0.2	6	4
7	 **27**	0.2	22	18
8		2	71	22

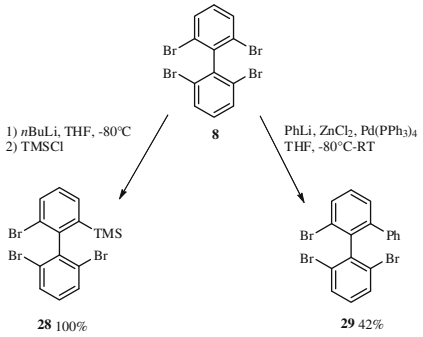
Conditions: see general procedure A (Ref. 10).

more lipophilic group such as phenyl or trimethylsilyl. To prepare such substrates we performed a monolithiation of **8** in presence of 1 equiv of *n*-BuLi in THF at −80 °C.[6] Trapping with TMSCl allowed us to obtain **28** in 100% yield. Alternatively, after transmetallation to zinc, a Negishi coupling afforded **29** in 42% yield (Scheme 5).

These new substrates were tested in the chiral Br–Li exchange under our standard conditions. The results are summarized in Table 4.

Unfortunately, at −80 °C, these new substrates did not appear more soluble in toluene than 2,2′,6,6′-tetrabromobiphenyl **8**, hence both the conversion and the enantioselectivity were not better. This means that during the enantiodetermining step the discrimination between a bromine atom and a phenyl or a TMS is not better than that between a bromine atom and a lithium, which is the case during the second bromine–lithium exchange with **8**.

In addition to atropoisomeric substrates, we then turned our attention to the protected alcohols and amine **4** (Table 5). In contrast to 2,2′,6,6′-tetrabromobiphenyl **8**, the use of an excess of base led to a double Br–Li exchange, hence only 1 equiv of



Scheme 5.

Table 4
Enantioselective Br–Li exchange on substrates **28** and **29**

Entry	Substrate	Ligand	Equiv	Time (min)	Conv (%)	ee (%)
1	**28**	**20**	0.2	20	33	22
2	**28**	**20**	2	20	56	28
3	**28**	**19**	2	20	97	3
4	**29**	**20**	0.2	5	48	18

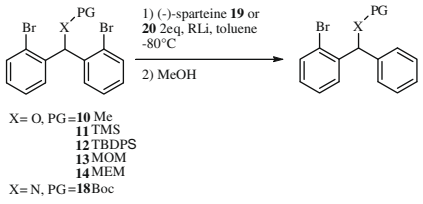
Conditions: see general procedure A (Ref. 10).

Table 5
Alcohol or ethers screening in chiral Br–Li exchange

Entry	Substrate	Ligand	RLi	Time	Conv (%)	ee (%)
1	**9**	TMEDA	*n*-BuLi	1 h 30 min	4	—
2	**10**	**19**	*n*-BuLi	45 min	73	16
3	**10**	**19**	*s*-BuLi	3 h	53	8
4	**10**	**19**	*t*-BuLi	3 h 30 min	16	13
5	**11**	**19**	*n*-BuLi	2 h 30 min	15	10
6	**12**	**19**	*n*-BuLi	2 h	nd	6
7	**12**	**20**	*n*-BuLi	2 h	nd	7
8	**12**	**21**	*n*-BuLi	2 h	nd	2
9	**13**	**19**	*n*-BuLi	1 h 30 min	45	29
10	**13**	**20**	*n*-BuLi	2 h	55	4
11	**14**	**19**	*n*-BuLi	2 h	65	6
12	**14**	**20**	*n*-BuLi	2 h	58	9
13	**18**	**19**	*n*-BuLi	2 h	50	14

Conditions: see general procedure B (Ref. 10).
TMEDA = *N*,*N*,*N*′,*N*′-tetramethylethylenediamine.

organolithium could be introduced in the reaction. The chiral exchange has been tested in our classical conditions, and the lithiated intermediate was quenched by methanol (Scheme 6).



Scheme 6.

For the free alcohol **9**, only 4% conversion was observed with TMEDA, hence the chiral version was not attempted. In the case of silyl ethers **11** and **12**, a Brook rearrangement was observed; these reactions are not clean due to the presence of monolithiated, bislithiated, Brook species and starting materials, even with a large protecting group such as **12**. In the other cases the conversions were moderate, again due to the bislithiated compound or the remaining starting material. It is interesting to note, again, that

the Br–Li exchange proceeds more slowly with *s*-BuLi and *t*-BuLi (entries 3 and 4). The best enantiomeric excess was obtained with the MOM protecting group in the presence of (−)-sparteine **19** (entry 7). Our ligand **20** appeared, in these cases, to be less efficient than **19**. The Boc-protected amine **18** was also desymmetrized with 14% enantiomeric excess. Other types of protecting groups and diamines need to be tested to improve this result.

3. Conclusion

The enantioselective Br–Li exchange is a promising new way to introduce chirality. Although the enantioselectivity is still moderate (63% at best) a better choice of substrates and ligands should soon improve these results.

Acknowledgment

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10. *General procedure*: (A) To a clean and dry Schlenk tube were added diamine (0.2 mmol) and 1.5 ml of toluene. Then the whole was cooled to −80 °C and *n*-BuLi (0.2 mmol) was added dropwise to the mixture. The substrate (0.1 mmol) diluted in toluene (0.5 ml) at rt was added dropwise to the previous mixture. At the end of the reaction, DMF was added (0.4 mmol) and the mixture was allowed to warm until rt. At rt, HCl 1 M was added and the organic phase was separated. The aqueous one was extracted three times with dichloromethane. The organic phases were mixed and dried over sodium sulfate and concentrated on a rotatory evaporator. The diamine can be recovered after a basic workup of the aqueous phase. The product was purified on column chromatography on silica gel, and was eluted with ethyl acetate and cyclohexane 1/9.
(B) To a clean and dry Schlenk tube were added diamine (0.1 mmol), substrate (0.1 mmol), and 2 ml of toluene. Then, the solution was cooled to −80 °C and *n*-BuLi (0.1 mmol) was added dropwise to the mixture. At the end of the reaction, drops of methanol were added. At rt the product was extracted with ether in the presence of HCl 1 M. The organic phases were mixed and dried over sodium sulfate and concentrated in a rotatory evaporator. The diamine can be recovered after a basic workup of the aqueous phase.