DOI: 10.1002/adsc.201000517

Catalytic Asymmetric Bromine-Lithium Exchange: A New Tool to Build Axial Chirality

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Received: July 1, 2010; Published online: October 12, 2010

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201000517.

Abstract: We present here the first *catalytic* desymmetrization of the 2,2′,6,6′-tetrabromobiphenyl **1** and analogues, by a bromine-lithium exchange catalyzed by either diamines or diether derivatives (0.5 equiv.), yielding axially chiral compounds in high yield (up to 89%) and high enantioselectivity (up to 82%).

Keywords: asymmetric catalysis; atropoisomerism; biaryls; diphosphines; metal-halogen exchange

Introduction

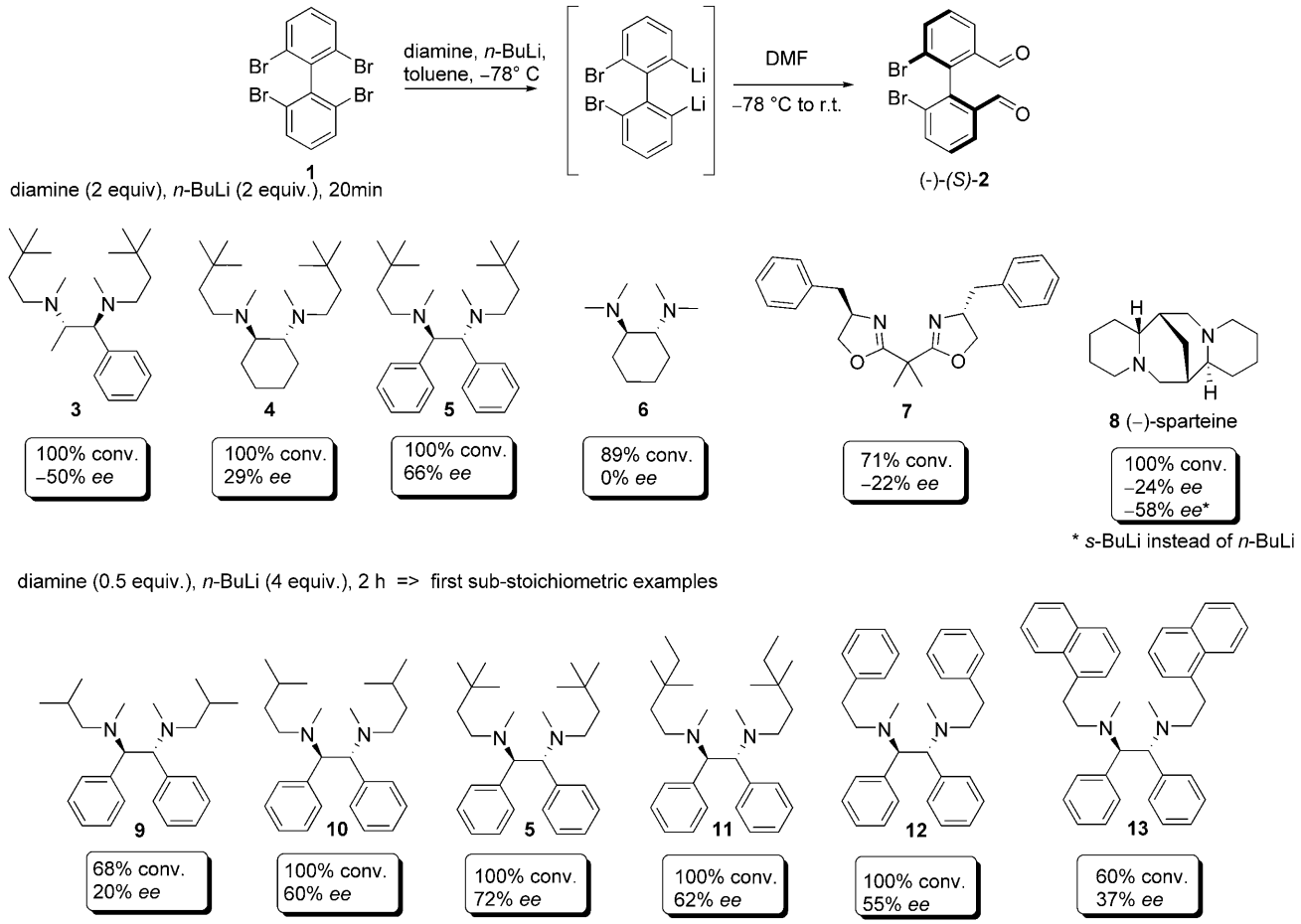
Halide-lithium exchange is a powerful tool, well known by organic chemists, "*functionalisation by lithiation and electrophilic quench is among the most fundamental of synthetic transformation*".[1] The first halogen-lithium exchange reported in the literature was published by Marvel in 1927 without understanding the role of organolithium reagent.[2] Wittig, followed by Gilman started in 1938 to study independently this reaction and were really the first to apply this chemistry in organic synthesis.[3] Since then, only new applications of this reaction or mechanistic studies were reported.[1,4] In all these reports iodine-lithium exchange appeared to be very reactive in many different solvents, even at low temperature and with different alkyllithium reagents. In contrast, bromine-lithium exchange is much less employed because it seems more difficult to proceed: polar solvents, higher temperature and strong alkyllithium bases (*s*-BuLi or *t*-BuLi) need to be used in order to achieve complete conversion.

In our laboratory we discovered that diamines can catalyze the bromine-lithium exchange in an apolar solvent such as toluene or even hexane at low temperature (−78 °C) using *n*-BuLi. With these observations we envisaged the application of this reaction in an asymmetric version using chiral diamines. This new methodology appeared to be efficient and we published one of the first desymmetrizations of different classes of prochiral polybrominated compounds by an asymmetric bromine-lithium exchange in the presence of a stoichiometric amount of different diamines with enantiomeric excess up to 63%.[5] At the same time, Kagan et al. also reported this new concept, where they presented the desymmetrization of prochiral aromatic or vinylic dihalide substrates in the presence of a stoichiomeric amount of diamines, with enantiomeric excess up to 26%.[6] Then, using Mg instead Li, the group of Brückner described the kinetic resolution of symmetrical alcohols in the presence of stoichiomeric amounts of enantiomerically pure lithium alkoxides.[7] To the best of our knowledge, high levels of enantiomeric excess and the use of a catalytic amount of catalyst have never been reported so far.

Herewith we present the first catalytic asymmetric bromine-lithium exchange catalyzed by either diamine or diether derivatives (0.5 equiv.), for the preparation of new atropoisomers with quantitative yield and enantiomeric excesses up to 82%.

Results and Discussion

Compared to our preliminary communication,[5] we wished to improve first the selectivity and, second, the amount of catalyst, since the use of a catalytic amount of ligand in such reaction remains very challenging. Towards this end, we prepared different new diamines and tried them in our test reaction, where, after the Li-Br exchange, the new dilithiated species is quenched with DMF, to provide dialdehyde **2**. (Scheme 1).



Scheme 1.

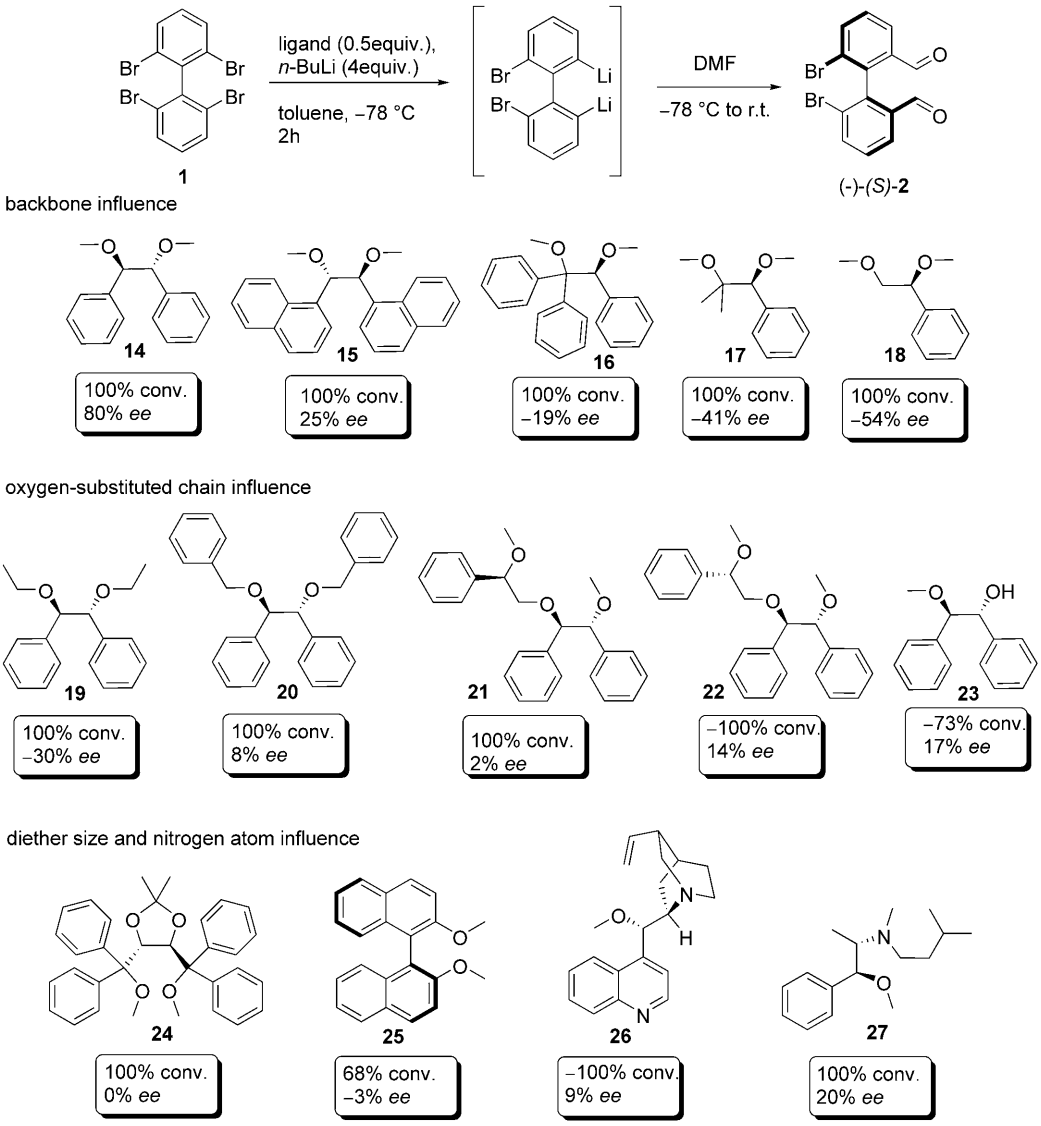
At the beginning we investigated the influence of the backbone of the diamines. Three different diamines have been tested. The one derived from the pseudo-ephedrine **3**, the one derived from the cyclohexanediamine **4** and finally the one derived from the 1,2-diphenylethanediamine **5**. We clearly observed that the backbone had a great influence and the phenyl moiety appeared to be the best substituent in order to have a good transfer of the chiral information. Thus, with two equivalents of diamine **5** (per brominated substrate) a good selectivity (up to 66% *ee*) could be obtained, with full conversion. We then tested other diamine ligands, such as tetramethylcyclohexanediamine **6**, which induces no selectivity. The bis-oxazoline family of ligands has also been examined, the best selectivity being observed with **7** (22% *ee*). (−)-Sparteine **8**, the most well known chiral diamine, has been tried as well, but with 5 equivalents of *s*-BuLi in order to get full conversion. In this case, 58% enantioselectivity was measured. As described in our first communication, the results with *n*-BuLi and *t*-BuLi were worse, as was the case with only 2 equivalents of BuLi.

Finally, with the best ligand **5** in hand, we turned our attention to the development of a catalytic version of this reaction (Table 1). For this purpose we reduced the amount of the diamine from 2 to 0.15 equivalents (entry 1 to 6, Table 1) and observed that 50 mol% of catalyst was the ratio of choice (entry 3). This amount corresponds to 25% catalyst per Li-Br exchange. Although with smaller amounts of catalysts the reaction still proceeds, it becomes

Table 1. Evaluation of ligand **5**.

Entry	Ligand **5** (equiv.)	*n*-BuLi (equiv.)	Time	Conv. [%]	*ee* [%]
1	2	2	20 min	100	66 (*R*)
2	1	4	2.5 h	100	72
3	0.5	4	2.5 h	100	72
4	0.25	4	4 h	100	58
5	0.2	4	4 h	100	55
6	0.15	4	4 h	100	50
7	0.2	3	4 h	84	37
8[a]	0.5	4	2.5 h	100	53

[a] 2 equiv. of 2-(dimethylamino)ethanol were added.



Scheme 2.

more sluggish and the enantioselectivity drops. Moreover, it is important to notice that *n*-BuLi was used in excess for achieving full conversion and high selectivity, since **1** does not undergo tri- and tetra-exchange under these experimental conditions (entry 5 *vs.* 7).[4i,j,k,l] Finally, as described by O'Brien, we tried to add 2-(dimethylamino)ethanol to block the first aryllithium species, in order to allow the diamine to proceed to another Br-Li exchange and, perhaps, increase the selectivity.[8] The reaction worked well but induced lower selectivity (entry 3 *vs.* 8).

With these best conditions in hands (entry 3) we tried to improve the design of our catalyst by modifications of the large substituent of the nitrogen. We observed that with a decrease or an increase of the bulkiness the selectivity was lowered (**5** *vs.* **10** and **5** *vs.* **11**). The same trend was observed when we moved to planar hindrance, from a γ-*tert*-butyl group to a phenyl and 1-naphthyl group (**5** *vs.* **12** and **13**). Reduction of the carbon chain by one carbon (**9**) was again detrimental for the selectivity and even for the conversion, probably because the steric bulk was too close to the reactive center.[9]

After having studied the diamines, we wished to examine the influence of other catalysts exhibiting similar properties towards organilithium reagents. We consequently turned our attention to diether derivatives, since they have proven their efficiency in this field.[10] We directly tried the diether **14** , described by Tomioka, and surprisingly we obtained full conversion and a good selectivity (80% *ee*). Moreover the catalyst could be recovered at the end of the reaction with 80% yield, by column chromatography. Therefore, we prepared different classes of diethers and tested them in our standard reaction (Scheme 2). We first checked the influence of the backbone on these

diethers, but unfortunately all attempts to increase the selectivity failed. Indeed when we moved to 1-naphthyl derivative **15** we observed not only a huge drop of enantioselectivity but also an inversion of it! We also prepared three catalysts derived from the (*S*)-mandelic acid (**16**, **17** and **18**). Interestingly, by decreasing the hindrance of the backbone an increase of enantioselectivity was observed up to 54% *ee*. Then, as for the diamines we studied the influence of the substituents on the oxygen atom. By moving from methyl **14**, to ethyl **19** and benzyl **20**, a drop of enantioselectivity was noted as well as an inversion (only with **19**).

These effects could be explained by the fact that diethers may proceed through either a five-membered chelate (or closed transition state) or through an open system. As explained by Tomioka,[10] only the chelate is able to efficiently transfer the chiral information to the organometallic reagent (Figure 1). In such a case, the substituent on the oxygen adopts a conformation where it is *anti* to the substituent of the backbone. This situation occurs with OMe groups (**14**), but not with OEt (**19**) or OBn (**20**), which are more bulky. The reaction then occurs under the open TS with lower, and different, enantioselectivity. The same probably happens with a too bulky backbone (see **15**). Such a situation does not occur with diamines which coordinate lithium more strongly than diethers.

An ether-alcohol catalyst **23** has been tried as well, without any success, proving the importance of the diether function. Two tridentate ligands (**21** and **22**) already developed by Tomioka[10c] have been also prepared and, unfortunately, showed a low selectivity. A small match/mismatch effect could be observed. The nature of the backbone was examined with diethers **24** and **25**. However, they both afforded racemates. This clearly shows the real importance of being in the presence of a 1,2-diether and not a 1,4, certainly due to the formation of the crucial 5-membered chelate ring in order to get a good chirality transfer.

Finally we tested two amino-ether catalysts, one derived from the cinchonidine alkaloid **26** and the other derived from the (1*S*,2*S*)-(+)-pseudoephedrine **27**. In spite of its great efficiency already observed in numerous reactions, **26** appeared to be a really poor catalyst in our system. The poor selectivity observed with **27** shows the difficulties of tuning the catalyst. With our best catalyst in hand (**14**) we investigated somewhat more its properties (catalyst loading or alkyllithium reagent) under these standard conditions (Table 2).

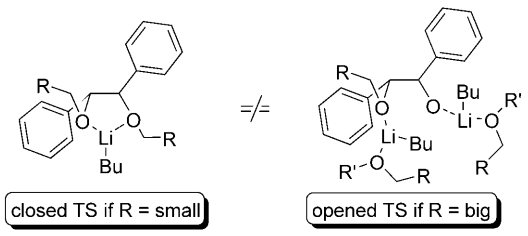


Figure 1.

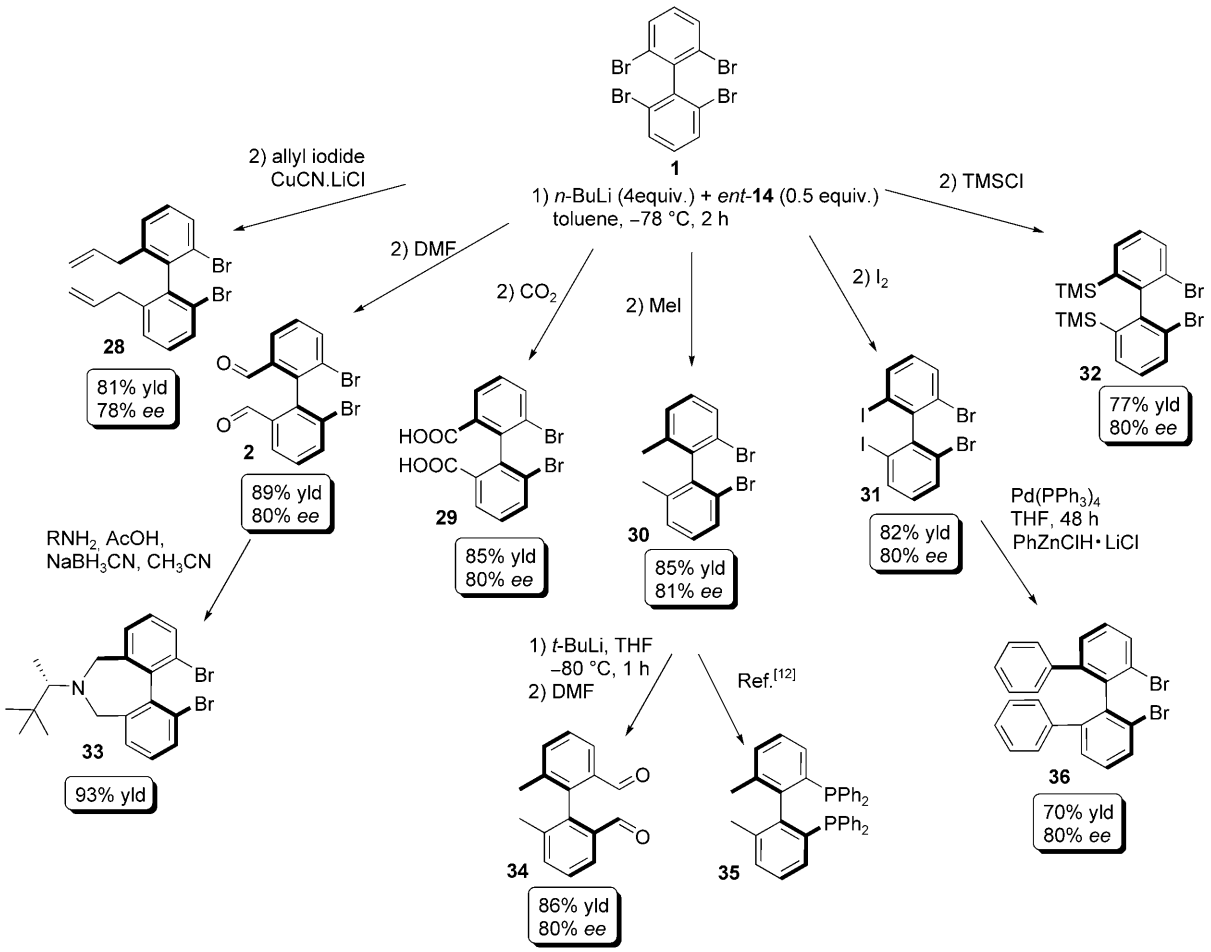
Table 2. Evaluation of ligand **14**.

Entry	Ligand **14** (equiv.)	RLi (equiv.)	Conv. [%]	*ee* [%]
1	0.25	*n*-BuLi (4)	100	57
2	0.5	*n*-BuLi (4)	100	80
3	0.5	*n*-BuLi (2)	58	50
4	0.5	*n*-BuLi (10)	100	50
5	1	*n*-BuLi (4)	100	80
6	1	*n*-BuLi (2)	84	65
7	2	*n*-BuLi (2)	100	55
8	2	*s*-BuLi (5)	100	−50
9	2	*t*-BuLi (5)	100	−32

As was observed with diamines the amount of *n*-BuLi is really important in order to reach a good level of selectivity (entries 2, 3 and 4). Again, 0.5 equivalent of catalyst appeared to be the optimum quantity (entries 1, 2 and 5). The reaction with *s*- and *t*-BuLi gave, strangely, an inversion of the selectivity. This may be explained either by a difference in aggregation state, or, as shown before (Figure 1), by an open transition state due to the higher steric requirements. It is also important to notice that with *s*- and *t*-BuLi no substoichiometric quantity of catalyst can be envisaged. Indeed, *s*- and *t*-BuLi perform the Br-Li exchange even without the ligand at a significant rate; the background reaction becomes really competitive. In summary, the diether catalyst **14** (0.5 equiv.) seems to be the best, in combination with *n*-BuLi (4 equiv.). In addition, it is commercially available or easy to prepare in large scale, in both enantiomeric forms.

After these optimization studies, we turned our attention to the reactivity of the dilithiated species and the synthetic utility of this new methodology, by quenching the reaction with various electrophiles (Scheme 3). Besides the formylation with DMF, used as the standard quench, the carboxylation with CO_2 gave the diacid **29**, with the same *ee* (80%). The *ee* could not be improved by additional recrystallizations. Iodination, by simple addition of molecular iodine, performed very well to afford 2,2′-diiodo-6,6′-dibromobiphenyl **31**. Direct silylation with TMSCl gave the disilylated compound **32**, in high yield (77%) and *ee* (80%). Reactions with Ph_2PCl or $Ph_2P(O)Cl$ failed to produce clean reactions products.

The direct alkylation reaction with methyl iodide proceeded very well, provided THF is added as cosolvent. Fortunately, we were able to determine the absolute configuration of **30** by comparison of its optical activity with the one already described in the literature.[12] The direct allylation, with allyl bromide, did

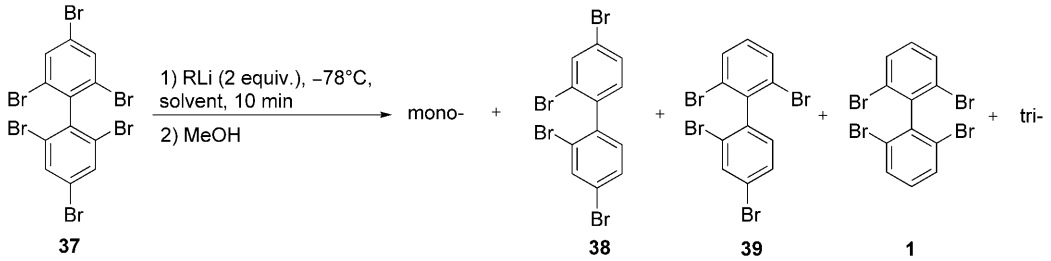


Scheme 3.

not proceed as well. Reaction with allyl iodide, provided the iodinated product, through I-Li exchange. However, if the dilithiated reagent is first transmetallated to the copper reagent, the desired diallylated product **28** could be obtained cleanly and in high yield (and *ee* 78%). The arylation reaction was attempted through a Negishi cross-coupling, through transmetallation with $ZnCl_2$ and further reaction with phenyl iodide and various Pd catalysts. Unfortunately only the product resulting from the mono-arylation was detected and fragmentation of the intermediate was observed under forcing conditions (microwave or thermal heating).

These primary products could be elaborated into even more complex structures. For example, reaction of dialdehyde **2** with a chiral amine provided azepine **33**, with a diastereomeric ratio identical to the initial enantiomeric ratio. Similar azepines have been used as catalysts in asymmetric epoxidation reactions.[11] Moreover, we noticed that the second bromine-lithium exchange worked very well at low temperature in presence of *t*-BuLi, and no racemization was observed. Thus, compound **30** could be submitted to a second Br-Li exchange and the new dilithiated species was quenched with DMF to afford the new dialdehyde **34**, in 86% yield. Attempted kinetic resolution by running this second dilithiation in the presence of chiral diamines only gave marginal improvements (see below). Although we did not repeat it, the diphosphine **35** could also be prepared according to the procedure described by Roche.[12] This new dilithiated species has already been shown, by the team of Cereghetti, to afford numerous diphosphine ligands.[13]

Since the direct arylation did not work (see above), the reverse arylation was attempted. Phenylzinc chloride could react, under Pd catalysis, with **31**, selectively with the iodides and not at all with the bromides. For the first time, on this type of chiral compound, a Negishi cross-coupling could thus be performed without any racemization at room temperature (**36**), opening the door on a large number of possible transformations. It is important to notice that we present here some possible reactions, but, actually, numerous electrophiles can be introduced in the first and second steps, allowing an infinity of combinations, since tran-



Scheme 4.

sition metals are compatible with our chemistry (**28** or **36**).

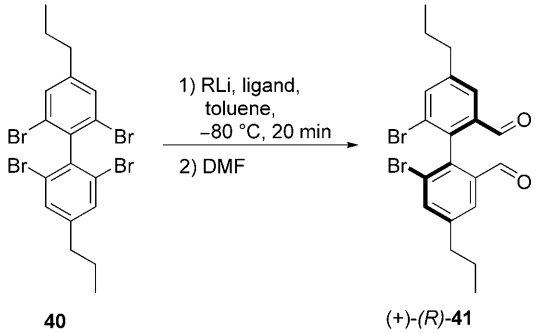
In a desire to extend our methodology, two different substrates were prepared (**37** and **40**). We studied the behaviour of the 2,2′,4,4′,6,6′-hexabromobiphenyl **37** in the presence of different alkyllithium reagents in different solvents (Scheme 4). The lithiated intermediate has been hydrolyzed after 10 min with methanol in order to measure the ratio between the different species by GC-MS. The results are summarized in Table 3.

Unfortunately, whatever the solvent used, the bromine-lithium exchange was not regioselective at all. In all cases a mixture between, starting material, mono-, bis-, and tri-exchange was observed. In the presence of a large excess of *n*-BuLi with TMEDA a complex mixture was obtained (tri- and tetra-exchange was observed).

Table 3. Lithiation of **37**.

Entry	RLi	Starting product **37** [%]	Mono [%]	**38** [%]	**39** [%]	**1** [%]
1[a]	*n*-BuLi	0	0	30	63	6
2[b]	*n*-BuLi	20	14	24	37	6
3[b]	*s*-BuLi	6	44	4	10	18
4[b]	*t*-BuLi	51	35	2	3	7
5[c]	*n*-BuLi	0	0	68	22	10
6[c]	*s*-BuLi	0	0	14	57	18
7[c]	*t*-BuLi	0	0	35	53	11

[a] THF as solvent.
[b] Toluene as solvent and 2 equiv. of TMEDA were added.
[c] Ether as solvent (hydrolysis after 30 min).



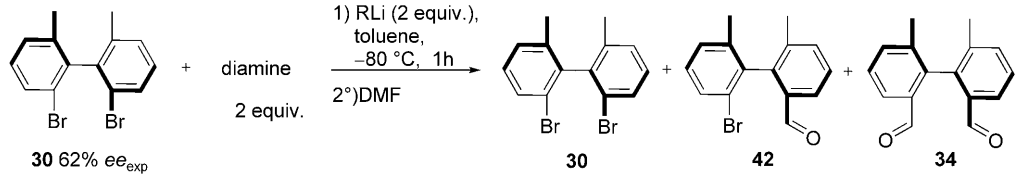
Scheme 5.

After such problems of regioselectivity we decided to study the influence of a substituted chain on the starting material. Since **1** was poorly soluble in solvent, we thought that an alkyl chain could improve its solubility and maybe the selectivity of the reaction. Toward this end, we prepared **40**, in a three-step sequence (see Experimental Section for details).

Table 4. Lithiation of **40**.

Entry	Ligand (equiv.)	RLi (equiv.)	Conv. [%]	ee [%]
1	**8** (2)	*n*-BuLi (2)	100	-34
2	**8** (2)	*s*-BuLi (5)	100	-56
3[a]	**5** (2)	*n*-BuLi (2)	75	52
4[b]	*ent*-**14** (0.5)	*n*-BuLi (4)	100	-55

[a] Absolute configuration assigned by analogy with **2**.
[b] Reaction time: 2 h.



ee_{Th}	diamine	RLi	SM/ee_{SM}	Mono/ee_{mono}	Bis/ee_{bis}
62%	(–)-sparteine	*s*-BuLi	0%/nd	66%/54%	34%/80%
58%	**5**	*n*-BuLi	47%/41%	53%/74%	0%/nd

Scheme 6.

In the presence of a stoichiometric amount of (−)-sparteine **8** (Scheme 5 and Table 4, entries 1 and 2) the same results were obtained with *s*-BuLi compared to **1**, or a slight increase in terms of selectivity with *n*-BuLi (34% *vs.* 24% with **1**). In contrast, our sparteine surrogate **5** (entry 3) gave 48% *ee*, but only partial conversion (66% *ee* with **1**). This may be explained by the geometry of the active complex during the 2nd Br-Li exchange which does not match with the 4,4′-disubstituted position. The diether **14** (entry 4) has been tried as well and again a drop in terms of selectivity was observed (55% *ee vs.* 80% *ee* with **1**).

In the previous example with the formation of **34**, the second double bromine-lithium exchange did not require any ligand. However, the presence of a chiral ligand could induce a kinetic resolution. To that end, we tried different sets of conditions on the dilithiation of **30** of 62% *ee* (Scheme 6). Using the best conditions with (−)-sparteine (2 equivalents of *s*-BuLi), all the starting material was consumed and we observed a decrease of enantiomeric exces of the mono-substituted product and an increase of the bis-substitued one. This shows that (−)-sparteine is matching with the major enantiomer of the mono-lithiated intermediate, producing **34** in 34% conversion and with a selectivity up to 80%. In contrast, under the best conditions with diamine **5** (2 *n*-BuLi,), the bis-subtituted product **34** was not observed and almost half of the starting material was recovered. The enantiomeric exces of the starting material was slightly diminished and the mono-substituted **42** one was increased to 74%. In order to check our results we calculated the theoretical enantiomeric excess of the starting material and in the both cases around 60% *ee* was obtained. In conclusion, no efficient kinetic resolution was observed, preventing any utilization for improving our results.

Finally, we were interested in better understanding the mechanism of this reaction. The first Br-Li exchange is not enantiodiscriminating, whereas the second one is. Therefore we wondered if during the Br-Li exchange of the 2nd bromine, the reactive complex (**14**+*n*-BuLi) was a monomeric or dimeric one.

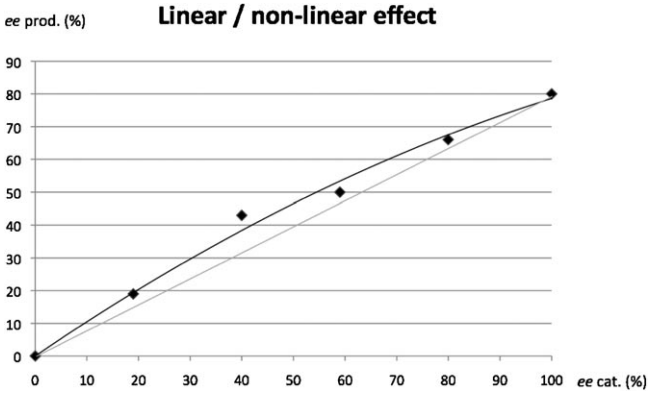
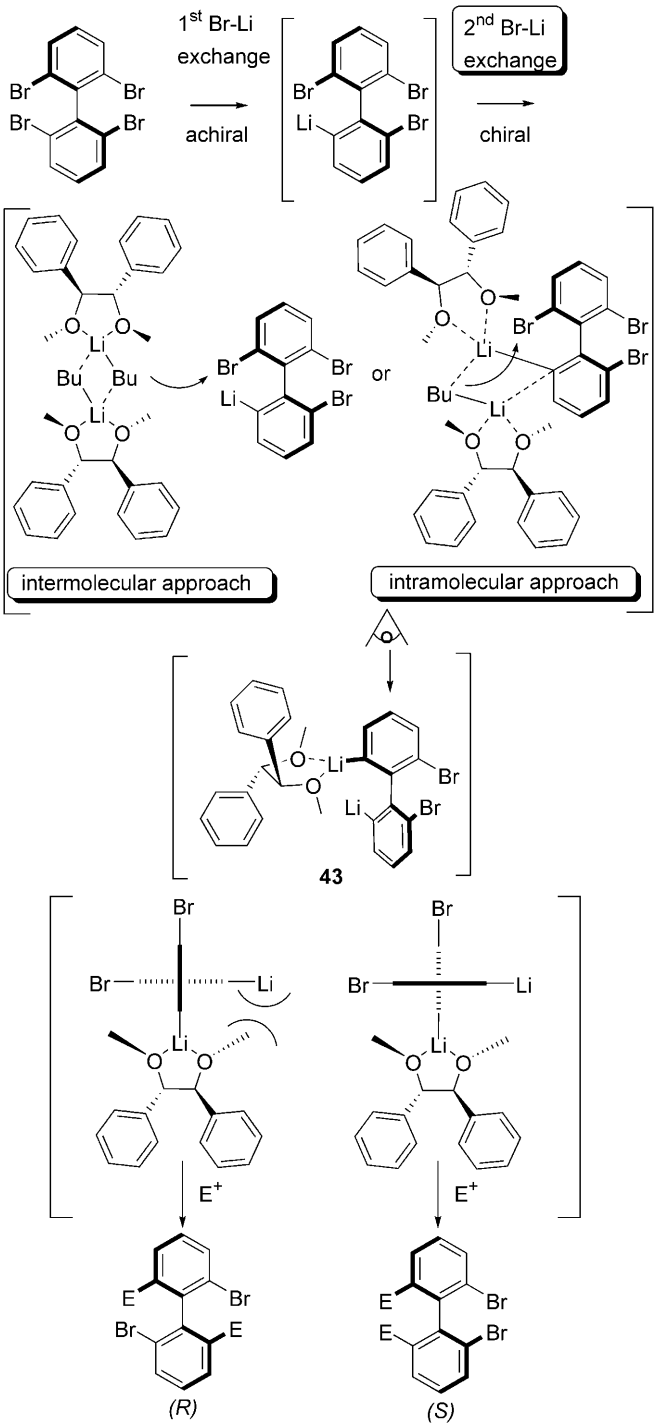


Figure 2.



Scheme 7.

To this end we studied the eventual non-linear effect of our system, using diethers **14** and *ent*-**14** as catalyst (Figure 2). A very small positive non-linear effect could be observed. Unfortunately it is not possible to draw any conclusion with such results.

Concerning the relative rates of the first and second lithiation, we observed that if only one equivalent of *n*-BuLi is added to the mixture of **1** and ligand

14, only mono-substituted adduct was obtained (< 2% di-substituted + 20% starting material). Therefore, it is clear that the second lithiation is slower than the first one.

Nevertheless, two alternative pathways can be postulated (Scheme 7). The second Br-Li exchange could follow either an intermolecular approach or an intramolecular one. In the intermolecular approach, the dimeric [BuLi·**14**] complex chooses one of the two enantiotopic Br atoms for the Br-Li exchange. In the intramolecular approach, a mixed dimer [ArLi/BuLi·**14**] is involved, which undergoes the Br-Li exchange within the mixed dimer. At this point, it is not possible to favour one or the other pathways, without extensive theoretical calculations. However, if one considers the final dilithiated complex [**43**·diether] we may postulate that the lithium species (aggregate) is much bigger than a simple bromine. Then, when one OMe group is located towards the Li atom (on the left), a strong steric destabilizing interaction occurs, whereas, when the OMe group looks towards the Br atom, this interaction is decreased. If this hypothesis is correct, it would yield the (*S*) enantiomer, as observed experimentally.

Conclusions

To conclude, we have presented herein a simple method to build axial chirality using a cheap catalyst **14**, prepared in one step from a commercially available starting material. We also developed a one-step procedure to prepare the 2,2′,6,6′-tetrabromobiphenyl **1** in decent yield (up to 60%), inspired by the work of Iyoda,[14] instead of the two-step previous procedure (45% overall yield).[15] To the best of our knowledge this work is the first to perform a bromine-lithium exchange with high selectivity (up to 82% *ee*) and with a ***catalytic*** amount of ligand (0.5 equiv, 25% per Br-Li exchange). Moreover, the synthesis of numerous optically active diphosphine ligands can be achieved starting with the same starting material (**1**) in a versatile three-step procedure, compared to the five steps and resoluion already described in the literature.[12] Finally, we proved the efficiency of diether derivatives in this chemistry and tried to understand more about this new reaction. New catalysts and substrates are under investigation in our laboratory.

Experimental Section

General Remarks

^{1}H (400 MHz or 300 MHz) and ^{13}C (100 MHz or 75 MHz) NMR spectra were recorded in $CDCl_3$ or MeOD and chemical shifts are given in ppm relative to residual $CDCl_3$ or MeOD. The evolution of the reactions was followed by GC-MS Hewlett Packard (EI mode) HP6890-5973. Optical rotations were measured at 20 °C in a 10 cm cell in the stated solvent; $[\alpha]_D$ values are given in 10^{-1} deg cm^2 g^{-1} (concentration c given as g/100 mL). Enantiomeric excesses were determined by chiral-GC (capillary column, 10 psi H_2) or chiral super fluid chromatography (SFC) with an appropriate program using a gradient of methanol. Flash chromatography was performed using silica gel 32–63 μm, 60 Å.

All reactions were carried out under an inert atmosphere. All solvents were dried on alumina columns. *n*-BuLi was purchased from Acros (1.6 M in hexanes) and used as received. The (*S*,*S*)-(−)-1,2-diphenyl-1,2-ethanediol was purchased from Aldrich and used as received. In case of a home-made batch, it is important to recrystallize it in dichloromethane, otherwise traces of osmium can be detrimental for the outcome of the Br-Li exchange. The ligands were flushed with nitrogen and stored in the refrigerator.

The preparation of the starting compounds and ligands is fully described in the Supplementary Information.

General Procedure for Asymmetric Br-Li Exchange

In a dry Schlenk tube was added the ligand (0.11 mmol, 0.5 equiv.) followed by toluene (2.8 mL), then the mixture was cooled to −78 °C for 10 min and *n*-BuLi (4 equiv.) was added dropwise to it. After 10 min the substrate (1 equiv, 0.213 mmol) dissolved in toluene (1.2 mL) was added dropwise and the whole was stirred during 2 h at −78 °C. Then the electrophile (6 equiv.) was added dropwise, in the appropriate solvent, and the whole was allowed to reach room temperature. The reaction was generally quenched with 1 M HCl and the product extracted with ether. The organic layers were dried over sodium sulfate and the solvents concentrated in a rotatory evaporator.

(*S*)-2,2′-Diallyl-6,6′-dibromobiphenyl (28)

Following the general procedure for asymmetric bromine-lithium exchange using *ent*-**14** as catalyst the *electrophile*, 5 equiv. of CuCN·LiCl, in 4 mL of THF was added and the reaction was warmed to −15 °C, then after 10 min at this temperature, allyl iodide (5 equiv.) was added and the whole was stirred for 2 h at this temperature. Chromatographic separation on silica gel with pentane/ether 9/1, gave a colourless oil; yield: 81%; *ee* = 78%; $[\alpha]_D^{20}$: 12.7° (*c* 0.985, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ = 3 (m, 4H), 4.9 (d, 2H, J = 16.9 Hz), 5 (d, 2H, J = 10.1 Hz), 7.2 (t, 2H, J = 7.8 Hz), 7.3 (d, 2H, J = 6.6 Hz), 7.55 (d, 2H, J = 7.8 Hz); ^{13}C NMR ($CDCl_3$): δ = 38.4, 116.9, 124.5, 128.1, 129.4, 130.6, 135.9, 139.9, 140.7; HR-MS: m/z = 389.9613, calcd. for $C_{18}H_{16}Br_2$: 389.9619.

(*S*)-6,6′-Dibromobiphenyl-2,2′-dicarbaldehyde (2)

Following the general procedure of asymmetric bromine-lithium exchange using *ent*-**14** as catalyst the *electrophile* pure dimethylformamide (DMF) was added. Chromatographic separation on silica gel with pentane/ether 9/1, gave a white solid; yield: 89%; *ee* = 80%; $[\alpha]_D^{20}$: −46.5° (*c* 1.015, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ = 7.6 (t, 2H, J = 7.8 Hz), 7.95 (dd, 2H, J = 8.1 and 1.3 Hz), 8.1 (dd, 2H, J = 7.8 and 1.3 Hz), 9.6 (s, 2H); ^{13}C NMR ($CDCl_3$): δ = 125.7, 128.6,

130.6, 136.3, 138.1, 140.3, 189.8; HR-MS: m/z = 365.8892, calcd. for $C_{14}H_8Br_2O_2$: 365.8891.

(*S*)-1,11-Dibromo-6-[(*S*)-3,3-dimethylbutan-2-yl]-6,7-dihydro-5*H*-dibenzo[*c*,*e*]azepine (33)[11]

To dialdehyde **2** (crop of 44% *ee*) (60 mg) in CH_3CN (3.6 mL) was added (*S*)-dimethylbutan-2-amine (2 equiv.). After 15 min of stirring, $NaBH_3CN$ (2 equiv.) was added and the reaction stirred for 20 h before the addition of AcOH (5 equiv.). Then the reaction was stirred for 1 h and the product was quenched with 1 M NaOH and extracted with DCM/MeOH (98/2). Chromatographic filtration on silica gel with DCM/MeOH (95/5), gave white solid with dr = 1/2.6 measured by NMR in accordance with *ee* of the starting material; yield: 93%. ^{1}H NMR ($CDCl_3$): δ = 0.8 (d, 2.13 H, J = 7.1 Hz), 0.9 (2 s, 9 H), 1.05 (d, 0.85 H, J = 7.1 Hz), 2.45 (q, 0.27 H, J = 7.1 Hz), 2.65 (q, 0.7 H, J = 7.1 Hz), 3.3–3.6 (m, 4 H), 7.2 (m, 4 H), 7.6 (m, 2 H).

(*S*)-6,6′-Dibromobiphenyl-2,2′-dicarboxylic Acid (29)

Following the general procedure of asymmetric bromine-lithium exchange using *ent*-**14** as catalyst, the *electrophile* CO_2 was bubbled into the Schlenk tube (dry ice in a syringe with a long needle) for 30 min at −78 °C, then the mixture was warmed up to rrom temperature. After quenching the reaction, the organic layer was made basic (10% NaOH) then extracted with ether. The aqueous phase was made acid (1 M HCl) then extracted EtOAc. Trituration with pentane, then trituration in a minimum of DCM gave a white powder with *ee* = 80% (measured after formation of the methyl diester); yield: 93%; $[\alpha]_D^{20}$: −2.5° (*c* 1.04, MeOH). ^{1}H NMR ($CDCl_3$): δ = 7.35 (t, 2 H, J = 8.1 Hz), 7.8 (dd, 2 H, J = 7.8 and 1.3 Hz), 8.1 (dd, 2 H, J = 7.8 and 1.3 Nz); ^{13}C NMR ($CDCl_3$): δ = 126.1, 130, 133.4, 137.4, 144.5, 168.6; HR-MS: m/z = 396.8713, calcd. for $C_{14}H_7O_4Br_2$: 396.8716.

(*S*)-2,2′-Dibromo-6,6′-dimethylbiphenyl (30)[12]

Following the general procedure of asymmetric bromine-lithium exchange using *ent*-**14** as catalyst and as *electrophile* MeI in 4 mL of THF. Chromatographic separation on silica gel with pure pentane, gave a white solid with *ee* = 81%; yield: 85%. For *ee* = 62% $[\alpha]_D^{20}$: −6.9° {*c* 0.62, EtOH) (lit.[12] $[\alpha]_D^{20}$: 11.6° (*c* 1, EtOH) for (*R*) enantio-pure}; ^{1}H NMR ($CDCl_3$): δ = 2.05 (s, 6 H), 7.2 (t, 2 H, J = 7.7 Hz), 7.3 (d, 2 H, J = 7.2 Hz), 7.6 (d, 2 H, J = 7.8 Hz); ^{13}C NMR ($CDCl_3$): δ = 20.6, 123.9, 129.06, 129.1, 130.2, 138.4, 140.8.

(*S*)-6,6′-Dimethylbiphenyl-2,2′-dicarbaldehyde (34)

In a dry Schlenk tube was added **30** (50 mg) followed by THF (2 mL). Then the mixture was cooled to −78 °C (dry ice in acetone) for 10 min and *t*-BuLi (4 equiv.) was added dropwise to it. After 1 h DMF (6 equiv.) was added and the whole was allowed to warm to room temperature. Then water was added (2 mL) and the product was extracted with ether (3 × 2 mL). The organic phases were filtered through a pad of Na_2SO_4 and solvents removed on a rotatory evaporator. Chromatographic separation on silica gel, with pure pentane, then pentane/ether (9/1), gave a white solid with *ee* = 80%; yield: 86%; $[\alpha]_D^{20}$: −53.9° (*c* 0.74, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ = 2 (s, 6 H), 7.55 (t, 2 H, J = 7.8 Hz), 7.65 (d, 2 H, J = 7.6 Hz), 8 (d, 2 H, J = 7.6 Hz), 9.65 (s, 2 H); ^{13}C NMR ($CDCl_3$): δ = 19.7, 126.4, 128.6, 134.5, 135.9, 137.5, 140, 191.5; HR-MS: m/z = 238.0994, calcd. for $C_{16}H_{14}O_2$: 238.0994.

(*S*)-2,2′-Dibromo-6,6′-diiodobiphenyl (31)

Following the general procedure of asymmetric bromine-lithium exchange using *ent*-**14** as catalyst and as *electrophile* I_2 in 4 mL of THF. Chromatographic separation on silica gel with pure pentane, gave a white solid with *ee* = 80%; yield: 82%; $[\alpha]_D^{20}$: 5.2° (*c* 0.955, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ = 7 (t, 2 H, J = 7.8 Hz), 7.7 (dd, 2 H, J = 8.1 and 1 Hz), 7.95 (dd, 2 H, J = 7.8 and 1 Hz); ^{13}C NMR ($CDCl_3$): δ = 100.1, 123.4, 131.3, 132.9, 138.5, 148.37; HR-MS: m/z = 561.6923, calcd. for $C_{12}H_{16}Br_2I_2$: 561.6926.

(*S*)-2,2′-Dibromo-6,6′-diphenylbiphenyl (36)

In a Schlenk tube, $Pd(PPh_3)_4$ (5 mol%), and **31** (70 mg) were mixed in THF (3 mL) and after 15 min PhZnCl·LiCl [addition of PhLi (5 equiv.) to $ZnCl_2$ (6 equiv.) in 1 mL of THF at room temperature] was added dropwise. The reaction was stirred at room temperature during 24 h. After quenching with 1 M HCl, the product was extracted with ether followed by evaporation of solvent. Chromatographic separation on silica gel with pure pentane, then pentane/ether (9/1) gave a white solid with *ee* = 80%; yield: 70%;$[\alpha]_D^{25}$: −75.0° (*c* 0.625, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ = 6.65 (d, 4 H, J = 8.3 Hz), 7–7.2 (m, 8 H), 7.25 (t, 2 H, J = 7.8 Hz), 7.7 (dd, 2 H, J = 7.8 and 1 Hz); ^{13}C NMR ($CDCl_3$): δ = 126.9, 127.1, 127.3, 129.1, 129.2, 129.3, 131.3, 139.4, 140.1, 143.4; HR-MS: m/z = 461.9618, calcd. for $C_{24}H_{16}Br_2$: 461.9619.

(*S*)-(6,6′-Dibromobiphenyl-2,2′-diyl)bis(trimethylsilane) (32)[16]

Following the general procedure of asymmetric bromine-lithium exchange using *ent*-**14** as catalyst with as *electrophile* TMSCl (5 equiv.) in 5 mL of THF. Chromatographic separation on silica gel with pure pentane, gave a colourless oil with *ee* = 80%; yield: 77%; $[\alpha]_D^{20}$: 2.9° (*c* 0.95, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ = 0 (s, 18 H), 7.25 (t, 2 H, J = 7.8 Hz), 7.6 (d, 2 H, J = 7.4 Hz), 7.7 (d, 2 H, J = 7.9 Hz); ^{13}C NMR ($CDCl_3$): δ = 0.3, 125.9, 128.8, 132.9, 133.7, 143, 147.5.

(*R*)-6,6′-Dibromo-4,4′-dipropylbiphenyl-2,2′-dicarbaldehyde (41)

Following the general procedure of asymmetric bromine-lithium exchange using **5** as catalyst, **40** as substrate and as e*lectrophile* DMF. Chromatographic separation on silica gel with pentane/ether (9/1), gave a white solid with *ee* = 52%; yield: 60% (absolute configuration was assigned by analogy with **2**); $[\alpha]_D^{20}$: +27.8° (*c* 0.795 in $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ = 0.95 (t, 6 H, J = 7.3 Hz), 1.75 (m, 4 H), 2.7 (t, 4 H, J = 7.6 Hz), 7.8 (s, 2 H), 7.85 (s, 2 H), 9.55 (s, 2 H); ^{13}C NMR ($CDCl_3$): δ = 13.8, 24, 37.3, 125.7, 128, 136.3, 137.8, 138, 145.9, 190.2; HR-MS: m/z = 472.97216, calcd. for $C_{20}H_{20}Br_2Na_1O_2$ $[M+Na]^+$: 472.97223.

Acknowledgements

The authors thank the Swiss National Science Foundation (No. 200020-126663) for financial support, and Chemetall GmbH fora generous gift of i-PrMgCl·LiCl.

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