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Asymmetric Bromine–Lithium Exchange: Application toward the Synthesis of Natural Product

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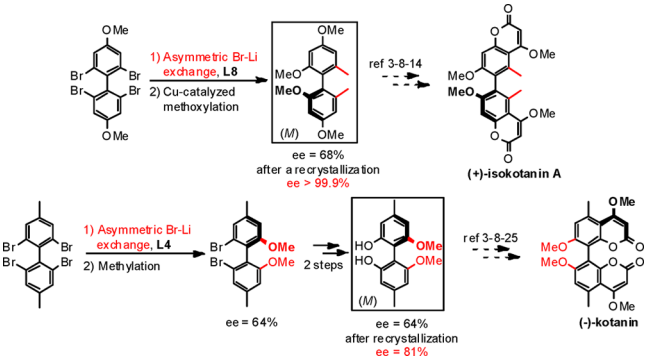
ABSTRACT



Asymmetric bromine–lithium exchange has been successfully employed to synthesize bicoumarin chiral building blocks of (+)-isokotanin A and (−)-kotanin in good yields and with an excellent level of enantioselectivity. This is the first reported example of formal syntheses, using this direct methodology, leading to the single (*M*)-atropoisomer of (+)-isokotanin A and (−)-kotanin building blocks, without any resolution step.

The formation of axially chiral compounds is still a topic of interest, particularly when a chiral stoichiometric auxiliary should be avoided.[1] The asymmetric lithium–halogen exchange provides a highly valuable and innovative synthetic method for building axial chirality.[2] These first reports deal with the improvement of the methodology, but none of which report on a direct application toward natural product synthesis. In fact, axial chirality is present in a wide range of biologically active natural products.[3] One of the most famous examples of this is glycopeptide vancomycin isolated for the first time in 1953 by the pharmaceutical company Eli Lilly, from a soil bacterium *Amycolatopsis orientalis*[4] that possesses important antibiotic activities. Axial chirality is also present in several other natural product families:[3] phenylanthraquinones ((+)-knipholone[3−5]), perylenequinones (pleichrome[3−6]), lignans ((+)-schizandrin[3−7]), and bicoumarins (desertorin C, isokotanin A, and kotanin)[3−8] to name a few. However, there are scarcely any strategies in natural product synthesis that report the successful introduction of axial chirality:[3−9] for example, intermolecular atropodiastereoselective biaryl

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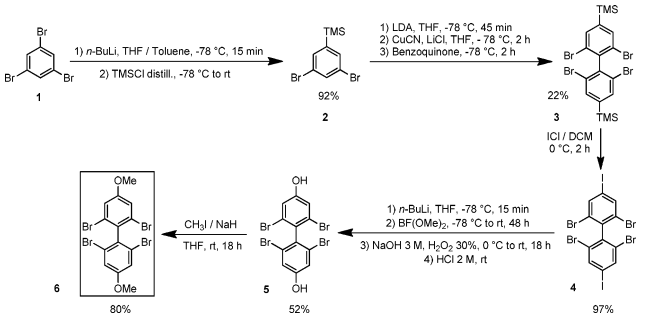
10.1021/ol4021157

coupling with a chiral auxiliary (e.g., oxazoline by Meyers[3−10]), intramolecular atropodiastereoselective oxidative coupling (e.g., with copper, by Lipshutz[11]), dynamic kinetic resolution of nonconfigurationally stable biaryls by atroposelective lactone cleavage,[3−8a] and atropoenantioselective oxidative homocoupling (e.g., with copper by Kozlowski[3,9−12]). In our study, we selected the bicoumarin scaffold to apply our direct asymmetric bromine−lithium exchange strategy following the formal synthesis of (+)-isokotanin A and (−)-kotanin chiral building blocks.

Optically pure isokotanin A, isolated from *Aspergillus alliaceus*,[13] was synthesized for the first time by Lin and Zhong[14] via an intermolecular atropodiastereoselective biaryl coupling.[10a] Considering the synthetic pathway toward isokotanin A, we identified 2,2′,6,6′-tetrabromo-4,4′-dimethoxy-1,1′-biphenyl **6** as the starting point for the preparation of key-intermediate **13** (see Scheme 3). The easier way to **6** was to apply the standard coupling conditions[2b,c] to 1,3-dibromo-5-methoxybenzene. However, no desired product was isolated, probably due to the *ortho*-directional character of the methoxy group during the metalation step.[15] Therefore, we explored two other chemical pathways to synthesize 2,2′,6,6′-tetrabromo-4,4′-dimethoxy-1,1′-biphenyl **6**. Path A (Scheme 1) started with the commercially available 1,3,5-tribromobenzene **1**, with which a Br−Li exchange, in a mixture of THF/toluene at −78 °C, was performed, to introduce the TMS functionality of compound[16] **2**, in 92% yield. Then, we carried out an oxidative coupling, of the intermediate cyanocuprate, to generate biaryls. This step, already well studied in our laboratory,[2b,c,17] was employed to give the desired compound **3** in 22% yield. Next, we treated compound **3** with iodine monochloride in dichloromethane at 0 °C to generate the desired 2,2′,6,6′-tetrabromo-4,4′-diiodo-1,1′-biphenyl **4** in 97% yield. Then, in a one-pot three-step sequence, Br−Li exchange was performed in THF, at −78 °C, and then quenched with fluorodimethoxyborane diethyl ether, followed by an *in situ* oxidation with hydrogen peroxide/NaOH 2 M solution, which led to the desired product **5** in 52% yield. Finally a methylation reaction in THF at rt gave the key intermediate 2,2′,6,6′-tetrabromo-4,4′-dimethoxy-1,1′-biphenyl **6** in 80% yield.

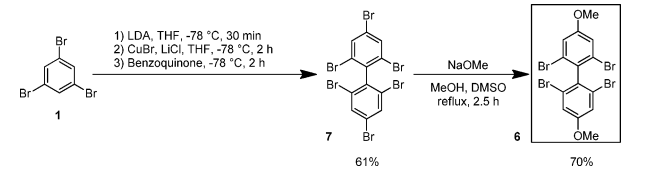
According to the modest overall yield obtained with path A (8.2% after 5 steps), we redesigned a much more

Scheme 1. Path A of 2,2′,6,6′-Tetrabromo-4,4′-dimethoxy-1,1′-biphenyl **6** Synthesis



straightforward synthesis of the key intermediate 2,2′,6,6′-tetrabromo-4,4′-dimethoxy-1,1′-biphenyl **6** according to Scheme 2. An aromatic nucleophilic disubstitution[18] on the 2,2′,4,4′,6,6′-hexabromo-1,1′-biphenyl[2c] **7** was performed, in the presence of anhydrous sodium methoxide powder in a mixture of DMSO/MeOH at reflux, affording the compound of interest **6** in 70% yield. It is noteworthy that only the 4 and 4′ bromides were substituted. With path B in hand (Scheme 2, overall yield of 43% after 2 steps), we were now able to run the synthesis on a gram scale and optimize the last two steps.

Scheme 2. Path B of 2,2′,6,6′-Tetrabromo-4,4′-dimethoxy-1,1′-biphenyl **6** Synthesis



Next, we needed to achieve the introduction of axial chirality by asymmetric Br−Li exchange (Table 1). Therefore, we screened diamine ligands **L1** to **L4**[19] and diether ligands **L5** to **L8** (synthesized according to the procedure described by Hall et al.[20]), under standard conditions[2c] as previously developed in our laboratory.

The best result was obtained with Tomioka's diether ligand **L8** (entry 8, Table 1) which has already demonstrated its efficiency[2c,21] with organolithium reagents. It allowed us to generate a promising enantiomeric excess of

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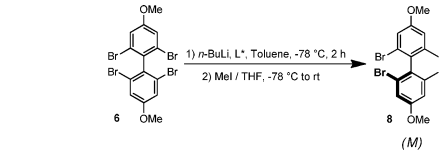
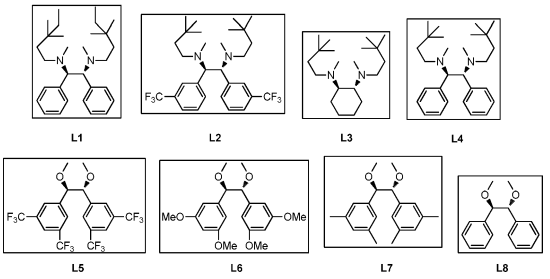
Table 1. Screening of Chiral Ligands for the Asymmetric Br−Li Exchange





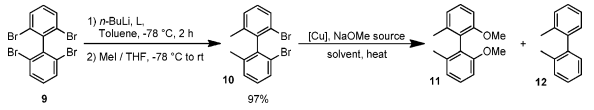
entry[a]	L* (0.5 equiv)	conv [%]	yield [%]	*ee* [%][b]
1	**L1**	100	88	44
2	**L2**	100	60	50
3	**L3**	100	82	54
4	**L4**	100	84	64
5	**L5**	100	82	22
6	**L6**	100	84	40
7	**L7**	100	93	33
8	**L8**	**100**	**84**	**68**

[a] Reaction conditions: At −78 °C, the (*R*,*R*) ligand L* (0.5 equiv) was dissolved in 2 mL of dry toluene. Then, the organolithium reagent (*n*-BuLi 1.6 M in hexanes, 4 equiv) was added at −78 °C before the substrate (0.11 mmol, 1 equiv) previously dissolved in 1 mL of dry toluene. The reaction mixture was then stirred at −78 °C for 2 h. It was finally quenched by methyl iodide (5 equiv) previously mixed in 1 mL of dry THF and warmed-up to rt for 1 h. Full conversion and the desired product were confirmed by ^{1}H NMR. [b] Determined by SFC analysis using a chiral stationary phase.

68% with an isolated yield of 84% for compound **8**. Finally, a dimethoxylation step catalyzed by copper[22] was required to yield the target molecule **13**. The optimization process was performed on a racemic mixture of 2,2′-dibromo-6,6′-dimethyl-1,1′-biphenyl **10**,[2c] obtained in high isolated yield (97%) from a racemic bromine−lithium exchange on 2,2′,6,6′-tetrabromo-1,1′-biphenyl **9**,[2b,c] followed by an electrophilic quench with methyl iodide.[2c] The copper and sodium methoxide sources, solvent, temperature, and reaction time were investigated (Table 2) to achieve full conversion and avoid formation of the side product **12**.

Using $CuCl_2$, CuI, and CuBr with sodium methoxide powder, in DMF, DMSO/MeOH, or DMF/MeOH, gave disappointing results. Full conversion was obtained, but almost only the side product **12** was detected (entries 1 to 3, Table 2). Switching to a 5.4 M sodium methoxide solution in MeOH and reducing the copper(I) bromide catalyst loading from 2 to 0.6 equiv in DMF (entry 7, Table 2)

Table 2. Optimization of the Dimethoxylation Reaction



entry[a]	CuX (equiv)	NaOMe source	solvent	*t* (°C)	conv [%]	**11:12** ratio[a]	yield [%]
1[c]	$CuCl_2$ (0.8)	solid	DMF	120	100	0:100	nd
2[d]	CuI (2)	solid	DMSO/ MeOH	190	100	12:88	nd
3[e]	CuBr (2)	solid	DMF/ MeOH	120	100	0:100	nd
4[f]	CuBr (2)	sol. in MeOH[b]	DMF	120	100	25:75	nd
5[f]	CuBr (0.2)	sol. in MeOH[b]	DMF	120	20	100:0	nd
6[f]	CuBr (1)	sol. in MeOH[b]	DMF	120	100	69:31	nd
7[f]	**CuBr (0.6)**	**sol. in MeOH**[b]	**DMF**	**120**	**>95**	**100:0**	**63**

[a] Reaction conditions: At rt, the substrate (0.1 mmol, 1 equiv) was dissolved in the appropriate reaction solvent (0.25 M). Then, sodium methoxide (1.4 mmol, 14 equiv) was added. The reaction mixture was heated to the corresponding temperature and the Cu salt was added. Conversion to the desired product was confirmed by ^{1}H NMR. [b] Sol. in MeOH for a 5.4 M solution of sodium methoxide in MeOH. [c] Reactions were carried for 5 h at 120 °C. [d] Reaction was carried for 192 h at 190 °C. [e] Reaction was carried for 17 h at 120 °C. [f] Reactions were carried for 120 h at 120 °C.

allowed, after 120 h at 120 °C, full conversion and isolation of 63% of the desired product **11**. By applying the conditions described in entry 7, Table 2 to the (*M*)-intermediate **8**, we reached, after a shorter reaction time (48 h instead of 120 h), full conversion, with a 42% yield and 72% ee for the target molecule **13** (Scheme 3). It is important to note that no erosion of the enantiomeric excess was observed during this transformation. Finally, a single recrystallization step in a 1:1 mixture of pentane/ether afforded enantiomerically pure **13** (ee > 99.9%, see X-ray in Supporting Information,[23]) in decent overall yield (6.4%).

One atroposelective synthesis of (−)-kotanin, isolated from *Aspergillus clavatus*,[24] has been reported so far by Lin and Zhong.[25] The authors reported an intramolecular atropodiastereoselective oxidative coupling[11] in order to build the biaryl skeleton. Considering this synthetic pathway to (−)-kotanin, we identified 2,2′,6,6′-tetrabromo-4,4′-dimethyl-1,1′-biphenyl **15** as a substrate of choice to apply the asymmetric Br−Li exchange to an early stage of

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(23) CCDC-953058 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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Scheme 3. Optimized Dimethoxylation Conditions

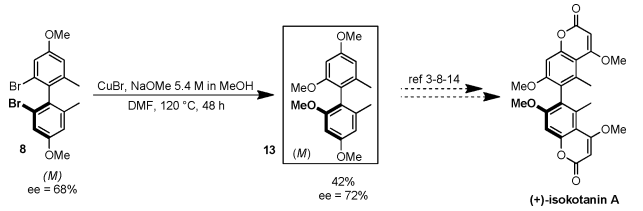
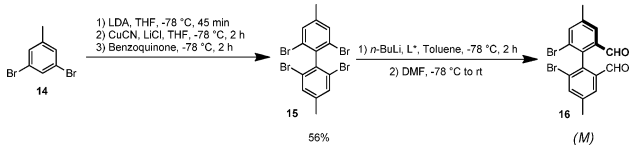


Table 3. Asymmetric Br−Li Exchange Screening Conditions



entry[a]	L* (0.5 equiv)	conv [%]	yield [%]	*ee* [%][b]
1	**L1**	100	72	54
2	**L2**	100	84	38
3	**L3**	100	74	46
4	**L4**	**100**	**93**	**64**
5	**L5**	100	46	8
6	**L6**	100	63	36
7	**L7**	100	87	20
8	**L8**	100	76	50

[a] Reaction conditions: At −78 °C, the (*R*,*R*) ligand L* (0.5 equiv) was dissolved in 2 mL of dry toluene. Then, the organolithium reagent (*n*-BuLi 1.6 M in hexanes, 4 equiv) was added at −78 °C before the substrate (0.12 mmol, 1 equiv) previously dissolved in 1 mL of dry toluene. The reaction mixture was then stirred at −78 °C for 2 h. It was finally quenched by DMF (5 equiv) and warmed up to rt for 1 h. Full conversion to the desired product was confirmed by ^{1}H NMR. [b] Determined by SFC analysis using a chiral stationary phase.

the synthesis. Therefore, we screened the same diamine ligands **L1** to **L4**[19] and diether ligands **L5** to **L8**[20] as shown in Table 1, under standard conditions.[2c] For this task, we simply quenched the intermediate dilithium species with DMF to form the corresponding dialdehyde **16** (Table 3).

With the best ligand **L4** in hand, we proposed the chemical path detailed in Scheme 4. We began with an oxidative coupling of cyanocuprate[2b,c,17] of the commercially available starting material 1,3-dibromo-5-methylbenzene **14** to give the desired 2,2′,6,6′-tetrabromo-4,4′-dimethyl-1,1′-biphenyl **15** compound in 56% yield. We then proceeded with a one-pot three-step sequence, via the asymmetric Br−Li exchange in toluene at −78 °C, and subsequent quenching using fluorodimethoxyborane diethyl ether, by an *in situ* oxidation with hydrogen peroxide/NaOH 2 M solution. The crude product was then methylated in THF at rt to give compound **17** in 51%

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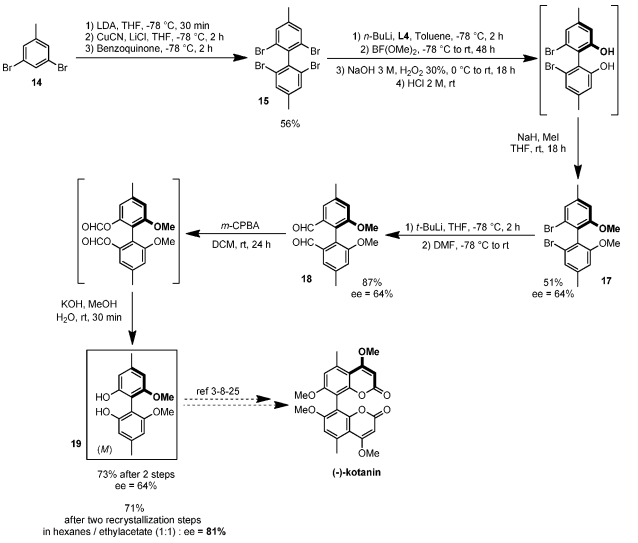
Scheme 4. (−)-Kotanin Chiral Building Block Proposed Chemical Pathway



overall yield and 64% ee. A second double Br−Li exchange in THF at −78 °C, with *t*-BuLi, afforded the corresponding bis-aldehyde **18** in 87% yield and 64% ee. It is important to note that no erosion of the enantiomeric excess was observed during the second double Br−Li exchange. That proves the optical stability of tetrasubstituted biaryls. Finally a Baeyer−Villiger/hydrolysis process[26] led to the target compound **19**, in 73% yield and 64% ee. After two recrystallizations, in a 1:1 mixture of hexane/ethylacetate, the (−)-kotanin chiral building block **19** was obtained in 81% ee and good overall yield (12.9%).

In conclusion, two key chiral building blocks for the synthesis of (+)-isokotanin A and (−)-kotanin have been successfully prepared in good yields. High levels of enantioselectivity were reached for these building blocks without any resolution step. The asymmetric Br−Li exchange methodology proved to be highly useful in natural product synthesis in order to install axial chirality. Further applications of this methodology are already ongoing in our laboratory.

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Supporting Information Available. Experimental procedures, NMR spectra, and chiral separations for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.