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Atropisomeric Scaffolds

Synthesis of Atropisomerically Defined, Highly Substituted Biaryl Scaffolds through Catalytic Enantioselective Bromination and Regioselective Cross-Coupling**

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The challenge of atropisomer-selective syntheses is often manifested in drug discovery projects,[1] and also in the synthesis of materials with interesting optical properties.[2] With respect to the former, numerous small-molecule ligands for proteins and enzyme inhibitors exist as conformational racemates, with low barriers to atropisomerization (Figure 1).

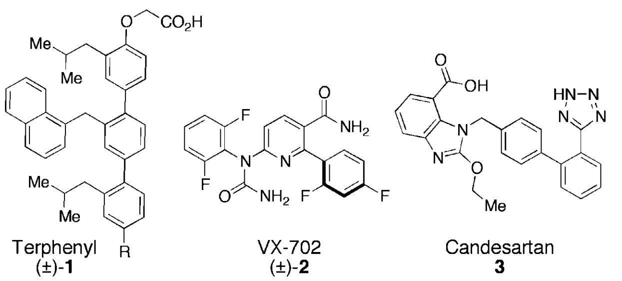
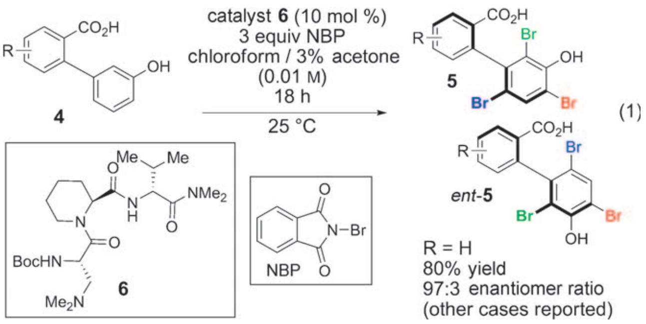


Figure 1. Representative bioactive polyaryl compounds.

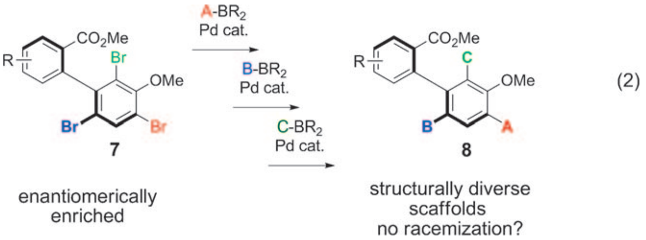
For example, terphenyl compounds (**1**; disruptors of protein–protein interactions),[3] heteroarene- and heteroatom-substituted biphenyls (**2**; kinase inhibitors),[4] and other biologically active scaffolds (**3**; biphenyl tetrazole)[5] all exhibit the possibility for stereochemically unique atropisomeric conformations. Nonetheless, binding of the small molecule to the biological target often occurs with enantiospecificity, as the inherent chirality of the receptor effects in situ dynamic kinetic resolution of the ligand, provided the barrier to atropisomerization is low enough. Thus, the preparation of single atropisomer scaffolds could lead to increases in potency for small molecules, through an increase in the effective concentration of the biologically active atropisomer, with the exclusion of a less active, or alternatively active form.

We recently reported an approach to the catalytic enantioselective synthesis of atropisomerically enriched biaryl compounds.[6] Our strategy is predicated on a peptide-catalyzed electrophilic aromatic substitution reaction, wherein compounds such as **4** are converted into tribrominated compounds (**5**), through the action of the catalyst **6** [Eq. (1)]. The utility of this process may be expanded through a variety of strategies, including the expansion of the types of catalysts and substrates that may be employed. As important, if compounds such as **5** may be differentially, and sequentially functionalized, then the scaffold diversity of atropisomerically pure compounds ultimately derived from catalyst **6** is similarly expanded.



(1)

Thus, a goal in our laboratory has been the development of sequential, regioselective cross-coupling reactions of the tribromides delivered through the dynamic kinetic resolution of substrates like **4**. For example, the ability to convert **7** into **8** [Eq. (2)], in a general sense, would greatly increase the number of easily accessible atropisomerically pure biaryl compounds.[7] While much study has been directed toward the development of enantiomer- and atropisomer-selective[8] cross-coupling reactions, regioselective couplings have received less attention, with most efforts directed toward polyhalogenated heterocycles and dihalogenated benzene derivatives.[9] Thus, our ambition was to develop sequential cross-couplings at each Br position, such that one could essentially fashion "A–B–C" differentially functionalized scaffolds with total control [Eq. (2)].



(2)

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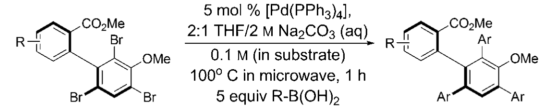
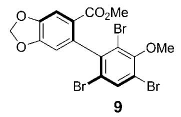
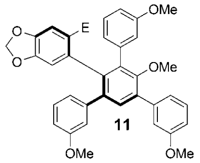
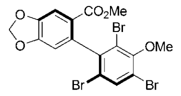
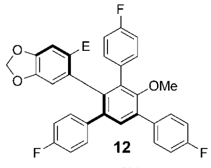
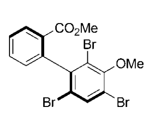
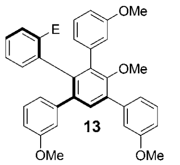
As noted in Equation (2), a critical aspect of the study involves the assurance that there is no racemization of the starting materials during any of the cross-coupling steps. While the barriers to atropisomerization of trisubstituted biaryls are known to be quite high ($>30\ \mathrm{kcal\,mol^{-1}}$),[10] one could imagine that racemization might occur under the elevated temperatures associated with many Pd-catalyzed cross-coupling protocols. Moreover, the processes of oxidative addition, transmetalation, and reductive elimination would all involve the formation of and cleavage of rather long arene–Pd bonds, that in principle, could lead to lower barriers to atropisomerization or racemization. There are indeed pioneering examples in the literature that demonstrate that such cross-couplings may occur without racemization.[11] Yet, the earliest of the reports considered aryl triflates, which undergo cross-coupling under different conditions and are highly substituted with bulky groups. Such compounds could present higher intrinsic barriers to atropisomerization than the tribromides we projected to explore. Moreover, subsequent reports focus mostly on binaphthyl-based systems, which also generally possess intrinsically high barriers.[12] Thus, for the cases we wished to study, close literature precedent seemed scant. Thus, our initial experiments sought to verify that all three Br atoms of **7** could be substituted to form enantiomerically pure pentaaryls.

As shown in Table 1, we subjected atropisomerically enriched tribromide **9** to standard Suzuki cross-coupling reaction conditions (5 mol% $[\mathrm{Pd(PPh_3)_4}]$, 5 equiv arylboronic acid, refluxing THF/2 M aq. Na_2CO_3),[13] which delivered pentaarene **11** in excellent yield upon isolation (Table 1, entry 1a). Critically, no degradation of enantiomeric ratio (e.r.) was observed, as determined by HPLC analysis. We also determined that implementing analogous conditions under microwave irradiation[14] for 1 hour at 100 °C yielded the desired product; once again no racemization had occurred under these conditions. Thus, compound **11** was once again obtained in 95% yield, with no loss in the e.r. value (Table 1, entry 1b). The pentaarene **12** was similarly obtained in 95% yield upon isolation with total preservation of e.r. value (Table 1, entry 2). Tribromide **10** was also converted into its corresponding pentaarene **13** with no racemization (Table 1, entry 3).

Table 1: Homofunctionalization of tribromobiaryls.



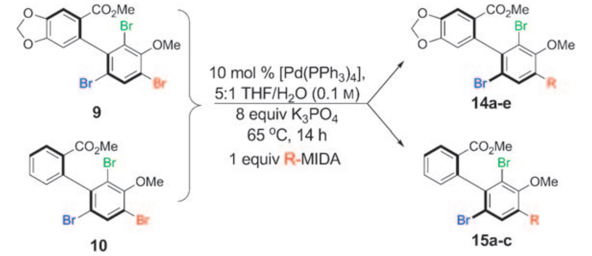
Entry	Substrate	Product	Sub. e.r. Prod. e.r.[a]	Yield [%][b]
1a 1b	 **9**	 **11**	95.0:5.0 95.0:5.0	95[c] 95[d]
2	 **9**	 **12**	95.0:5:0 96.0:4.0	95[d]
3	 **10**	 **13**	97.0:3.0 97.0:3.0	67[d]

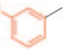
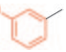
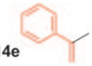
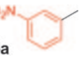
[a] Enantiomer ratios as determined by HPLC using a chiral stationary phase. [b] Average yield of the isolated product from three experimental runs. [c] Reaction conducted in refluxing THF/H_2O. [d] Reaction conducted at 100 °C under microwave conditions. See the Supporting Information for tables.

With these encouraging observations in hand, we set out to assess the possibility of regioselective cross-couplings, presumably at the "A position" first. Our initial attempts of Suzuki coupling with boronic acids resulted in low yields and selectivities.[15] In contrast, the application of the *N*-methyliminodiacetic acid (MIDA) boronates developed by Burke and co-workers led to improved results.[16] Notably, this approach resulted in good yields, and high regioselectivities, as determined by NMR spectroscopy, for the cross-coupling of aryl groups, heterocyclic functions, and alkenes to the tribromides. In no case was a significant degree of racemization observed. Moreover, regioselectivity, as assigned by HMBC NMR anaylsis (and further supported by changes in ^{1}H NMR shifts resulting from anisotropy; see the Supporting Information), was apparent. For example, as shown in Table 2, the *m*-nitrophenyl substituent could be introduced into the A position with 11:1:1 regioselectivity, and **14a** was isolated in 70% yield (Table 2, entry 1). The reactions tend to be quite clean, and in cases of incomplete conversion, the unreacted tribromide can be recovered (e.g., 20% of **9** recovered, as noted in Table 2). Similarly, the *m*-methoxyphenyl moiety may be introduced at the A-position to give **14b** with 17:1:1 regioselectivity, thus allowing isolation of 48% of the pure product (Table 2, entry 2). Heterocyclic coupling partners are also successfully employed in these reactions. The *N*-tosylpyrrolo moiety may be introduced to deliver **14c** in 55% yield upon isolation (Table 2, entry 3). A 3-pyridyl substituent may be introduced at the A-position to give **14d** in 52% yield (Table 2, entry 4). Formal Heck couplings are also possible, as the α-styryl substituent is introduced to give **14e** in 49% yield (Table 2, entry 5). Comparable results are achieved when tribromide **10** is employed as the starting material (Table 2, entries 6–8) to give products **15a–c**, thus reflecting the diversity of atropisomerically pure "A-coupled" products that may be formed. Any undesired regioisomers could be separated using semi-preparative HPLC methods. The demonstrated ability to substitute the A-position of **9** and **10** may represent one of the first examples of a general asymmetric synthesis of axially chiral *p*-terphenyls, often studied as mimetics of α helices.[3]

We also wished to establish whether or not regioselectivity could be achieved in heteroatom-based cross-couplings of enantiomerically enriched tribromides.[17] Indeed, these too were found to be regioselective processes. For example, **9** may be subjected to Pd-catalyzed amination[18] to give highly substituted aniline **14f** in 60% yield, with high regioselectiv-

Table 2: Regioselective cross-couplings of tribrominated biaryls.



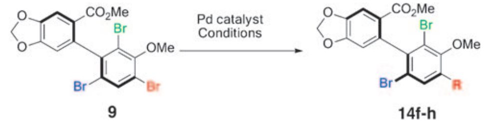
Entry	Product R	Sub.	Yield [%][a] (Rec. sub. [%])	Regiosel. (A/B/C)[b,c,d]	Sub. e.r. Prod. e.r.[e,f]
1	 **14a**	**9**	70 (20)	11.0:1.0:1.0	95.0:5.0 97.0:3.0
2	 **14b**	**9**	48 (20)	17.0:1.0:1.0	95.0:5.0 98.0:2.0
3	**14c** 	**9**	55 (20)	> 30.0:1.0:1.0	95.0:5.0 97.5:2.5
4	**14d** 	**9**	52 (23)	24.0:2.0:1.0	95.0:5.0 94.5:4.5
5	 **14e**	**9**	49 (–)	5.0:1.0:1.0	95.0:5.0 95.0:5.0
6	 **15a**	**10**	45 (19)	10.0:1.0:1.0	95.0:5.0 97.0:3.0
7	**15b** 	**10**	45 (30)	10.0:1.0:–	95.0:5.0 95.5:4.5
8	**15c** 	**10**	52 (23)	14.0:1.0:1.0	95.0:5.0 96.0:4.0

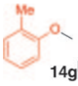
[a] Average yields of isolated product of three experimental runs. [b] Assigned by NMR analysis. [c] Ratio determined by ^1H NMR spectroscopy. [d] Averaged over three experimental runs. [e] Enantiomer ratios as determined by HPLC analysis. [f] Averaged over three runs.

ity (> 20:1:1) and with no detectable racemization (Table 3, entry 1). Pd-catalyzed etherification[19] proceeds with similarly high regioselectivity to give biaryl ether **14g** in 55% yield, once again without perceptible loss of optical activity (Table 3, entry 2). Quite strikingly, we were also able to replace the remote Br atom of **9** (i.e., the A position) with an H atom by employing $NaBH_4$ as the hydride source.[20] While selectivity for the formation of **14h** was somewhat lower (4:1), purification was straightforward thus allowing isolation of **14h** in 56% yield (Table 3, entry 3). Substitution of the A-position with an amine, ether, or H significantly expands the scope of accessible atropisomerically enriched biaryl compounds that may be obtained under this protocol.

With robust methods for synthesis of gram-scale[21] quantities of these A-coupled *p*-terphenyls, we then turned our attention to their further functionalization to yield A–B-coupled tetraaryl compounds. Initially, we observed that the standard conditions implemented in the A couplings gave moderate yields and little to no selectivity (low yields, 1.2:1 regioselectivities) in various attempted couplings (e.g., in the formation of **16**; Table 4). However, use of the sterically more-demanding Pd source [Pd^{II}(dppf)] (dppf = 1,1′-bis(diphenylphosphanyl)ferrocene) resulted in modest improvements (ca. 3:1 regioselectivity), as did [Pd_2dba_3]/(*R*)-binap system (ca. 3:1). Of particular note, the enantiomeric [Pd_2dba_3]/(*S*)-binap system resulted in higher yields and

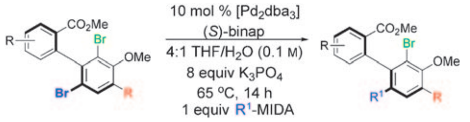
Table 3: Regioselective heteroatom cross-couplings.

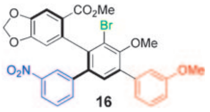
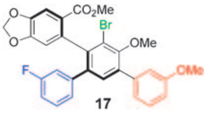
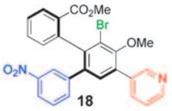
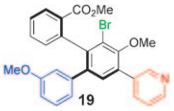
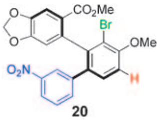


Entry	Product R	Sub.	Yield [%][a]	Regiosel. (A/B/C)[b,c,d]	Sub. e.r. Prod. e.r.[e,f]
1	 **14f**[g]	**9**	60	> 20.0:1.0:1.0	95.0:5.0 95.0:5.0
2	 **14g**[h]	**9**	55	> 20.0:1.0:1.0	95.0:5.0 95.0:5.0
3	H— **14h**[i]	**9**	56	4:1:–	95.0:5.0 97.0:3.0

[a] Average yields of isolated product of three experimental runs. [b] Assigned by NMR analysis. [c] Ratio determined by ^1H NMR spectroscopy. [d] Averaged over three experimental runs. [e] Enantiomer ratios were determined by HPLC analysis. [f] Averaged over three experimental runs. [g] 10% $Pd(OAc)_2$, 20% racemic binap, 100°C, 0.1 M in toluene. [h] 10% $Pd(OAc)_2$, 13% *t*Bu-XPhos, 2 equiv K_3PO_4, 100°C 0.3 M in toluene, [i] $NaBH_4$, 5 mol% $Pd(OAc)_2$, 5.5% binap, 1.5 equiv TMEDA, 50°C, 0.25 M in THF. The 56% yield shown in entry 3 refers to the isolated regioisomerically pure product. binap = 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl.

Table 4: Regioselective cross-couplings of dibrominated *p*-terphenyls.



Entry	Sub.	Product	Yield [%][b] (Rec. sub. [%])	Regiosel. (B/C)[c,d,e]	Sub. e.r. Prod. e.r.[a]
1	**14b**	 **16**	52 (20)	10.0:1.0	98.0:2.0 99.0:1.0
2	**14b**	 **17**	65 (10)	5.0:1.0	98.0:2.0 99.0:1.0
3	**15c**	 **18**	41 (24)	7.0:1.0	96.0:4.0 95.0:5.0
4	**15c**	 **19**	52 (18)	6.0:1.0	96.0:4.0 95.0:5.0
5	**14h**	 **20**	37 (36)	2.5:1.0[f]	96.0:4.0 95.0:5.0

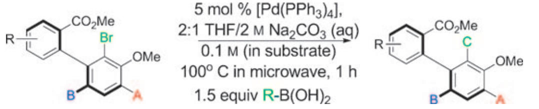
[a] Enantiomer ratios were determined by HPLC analysis using a chiral stationary phase. [b] Average yield of isolated product for three experimental runs. [c] Assigned by NMR analysis. [d] Ratio determined by ^1H NMR spectroscopy. [e] Averaged over three experimental runs. [f] Isolated as single regioisomer in 25% overall yield. dba = dibenzylideneacetone.

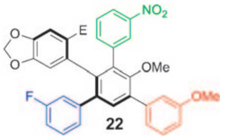
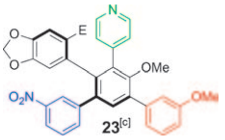
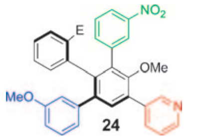
selectivity (ca. 5.5:1 regioselectivity). Regioselectivity was further improved to 10.0:1 with a 52 % yield (isolated) upon lowering the temperature from 100 °C to 65 °C (Table 4, entry 1). These results are striking as they suggest a moderate level of double diastereodiffentiation in the cross-coupling events.[22] Interestingly, application of these reaction conditions to racemic **14b** allowed observation of a modest kinetic resolution with a k_{rel} of approximately 4, thereby reflecting the differential behavior of the enantiomeric catalysts with homochiral **14b**. In any case, from a pragmatic perspective, these conditions and the [Pd_2dba_3]/(*S*)-binap catalyst system proved consistently effective when a range of aryl MIDA boronates were employed for coupling at the B position.[23]

Thus, we observed that in addition to formation of **16**, *m*-fluorophenyl substitution can be achieved such that **17** is obtained with 5:1 regioselectivity and 65 % yield upon isolation (Table 4, entry 2). Heteroarene-substituted compounds such as **15c** perform comparably, with **18** and **19** each formed with a 6:1 to 7:1 regioselectivity (Table 4, entries 3 and 4). Yields for these isolated compounds are somewhat lower (41–52 %), but the reactions are clean, the products are readily purified, and **15c** may be recovered to varying extents. Moreover, even the H-substituted biphenyl **14h** is converted into **20** with 2.5:1 regisolectivity (Table 4, entry 5). While the yield of **20** is modest, it is easily purified. Once again, no racemization is detected during any of the cross-coupling reactions of Table 4.

With efficient access to atropisomerically enriched A–B-coupled compounds, we then turned our attention to cross-couplings of the final C position to target differentially substituted, enantiomerically enriched pentaaryl compounds. While regioselectivity is no longer an issue, this process involves metal insertion into a hindered *ortho–ortho'* disubstituted bromide.[24] While standard Suzuki cross-coupling conditions (5 mol % [$Pd(PPh_3)_4$], excess arylboronic acid, refluxing 2:1 THF/2 M aq. Na_2CO_3) resulted in incomplete conversions after 18 hours, we found that the microwave-based conditions described in Table 1 resulted in full conversion, and good yields of isolated products (Table 5). Thus, Table 5 presents a series of atropisomerically defined, optically active pentaarenes. Entry 1 of Table 5 reveals a sequentially cross-coupled product in which three differentially substituted arene moieties have been introduced with control. The final arene is introduced in 77 % yield to give the isolated **21** with no detectable racemization (Table 5, entry 1). Entry 2 of Table 5 shows the synthesis of an atropisomerically defined "pseudoenantiomer" of compound **21**,[25] wherein the order of cross-coupling has been swapped. Thus, pentaarene **22** is produced with a final cross-coupling reaction that proceeds in 80 % yield. Heteroarenes may be introduced in the final cross-coupling event as well, as compound **23** is obtained in 80 % yield (Table 5, entry 3). A closely related, atropisomerically defined structure **24** may also be prepared, simply by choosing the order of the cross-coupling reactions, such that **24** may be isolated in 70 % yield. In all cases, the data in Table 5 shows compounds that were prepared with verified preservation of the enantiomeric ratios.

Table 5: Atropisomer enriched differentially trifunctionalized biaryls.



Entry	Sub.	Product (E=CO_2Me)	Yield [%][b]	Sub. e.r. Prod. e.r.[a]
1	16	 **21**	77	99.0:1.0 99.0:1.0
2	17	 **22**	80	99.0:1.0 99.0:1.0
3	16	 **23**[c]	80	99.0:1.0 99.0:1.0
4	19	 **24**	70	96.0:4.0 96.0:4.0

[a] Enantiomer ratios were determined by HPLC analysis using a chiral stationary phase. [b] Yields of isolated product averaged over two experimental runs. [c] Used 3 equiv of boronic acid.

In summary, we have reported an iterative atropisomer-selective, asymmetric bromination/cross-coupling strategy for the preparation of enantiomerically enriched, complex polyaryl compounds. Thus far, arenes, heterocycles, and heteroatoms have been introduced with regioselectivity into a tribrominated biaryl scaffold, employing readily available catalysts and straightforward reaction conditions. To the extent that enantiomerically enriched, atropisomerically defined compounds may be of interest in drug discovery or materials science, we are hopeful this work will be of broad interest.

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[25] We note that compounds **21** and **22** are nearly enantiomeric, differing as such by the position of the methoxy group. Yet, **21** and **22** exhibit the same sign of $[\alpha]_D$ (see the Supporting Information).