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

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Keywords

Atropisomer; Regioselective; Cross-Coupling; Peptide; Bromination

The challenge of atropisomer-selective synthesis is often manifest 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). For example, terphenyl compounds (e.g., **1**, disruptors of protein-protein interactions,)[3] heteroarene- and heteroatom-substituted biphenyls (e.g., kinase inhibitors; **2**),[4] and other biologically active scaffolds (e.g., biphenyl tetrazole **3**)[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 to tribrominated compounds (e.g. **5**), through the action of 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.

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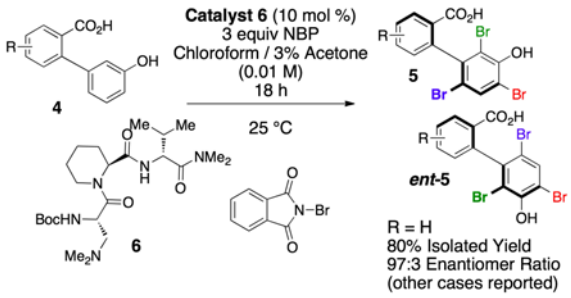
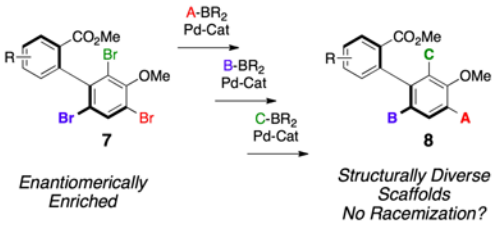
Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.



(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 resolutions of substrates like **4**. For example, the ability to convert **7** to **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 torward the development of enantio- and atropisomer selective[8] cross-coupling reactions, regioselective couplings have received less attention, with most efforts directed toward poly-halogenated 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)

As noted in eq 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 kcal/mol),[10] one could imagine that racemization might occur under the often-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/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 that undergo cross-coupling under different conditions, and several of these 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 penta-aryls.

As shown in Table 1, we subjected atropisomerically enriched tribromide **9** to standard Suzuki cross-coupling conditions (5 mol % $Pd(PPh_3)_4$, 5 equiv aryl boronic acid; refluxing THF: 2M Na_2CO_3(aq),[13] which delivered penta-arene **11** in excellent isolated yield (95%; entry 1a). Critically, no degradation of enantiomeric ratio (er) was observed, as determined by chiral HPLC analysis. We also determined that implementing analogous conditions under microwave irradiation[14] for 1 h 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 of er (entry 1b). So too, penta-arene **12** was obtained in 95% isolated yield with total preservation of er (entry 2). Tribromide **10** was also converted to its derived penta-arene **13** with no racemization (67% yield; entry 3).

With these encouraging observations in hand, we then 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] On the other hand, application of the MIDA (*N*-methyliminodiacetic acid) boronates developed by Burke and coworkers led to improved results.[16] Notably, this approach resulted in good yields, and high regioselectivities, as determined by NMR, 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 due to anisotropy; see 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, with **14a** isolated in 70% yield (entry 1). The reactions tend to be quite clean, and in cases of incomplete conversion, unreacted tribromide can be recovered (e.g., 20% of **9** recovered, as noted in Table 2). Similarly, the *m*-methoxy-phenyl moiety may be introduced at the A-position to give **14b** with 17:1:1 regioselectivity, allowing isolation of 48% of pure product (entry 2). Heterocyclic coupling partners are also successfully employed in these reactions. The *N*-tosyl-pyrrolo moiety may be introduced to deliver **14c** in 55% isolated yield (entry 3). A 3-pyridyl substituent may be introduced at the A-position to give **14d** in 52% yield (entry 4). Formal Heck couplings are also possible, as the α-styryl substituent is introduced to give **14e** in 49% yield (entry 5). Comparable results are achieved when tribromide **10** is employed as the starting material, as noted in entries 6–8 (to give **15a**–**c**), reflecting the diversity of atropisomerically pure “A-coupled” products that may be formed. Any undesired regioisomers could be separated using semi-preparative HPLC. 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 regioselectivity (>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 (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, employing $NaBH_4$ as the hydride source.[20] While selectivity for the formation of **14h** was somewhat lower (4:1), purification was straightforward allowing isolation of **14h** in 56% yield (entry 3). Substitution of the “A-position” with an amine, ether or H-atom functionality 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 tetra-aryl 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) resulted in modest improvements (~3:1 regioselectivity), as did Pd_2dba_3/(*R*)-BINAP system (~3:1). Of particular note, the enantiomeric Pd_2dba_3/(*S*)-BINAP system resulted in higher yields and selectivity (~5.5:1 regioselectivity). Regioselectivity was further improved to 10.0:1 with a 52% isolated yield 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 us to observe a modest kinetic resolution with a k_{rel} of approximately 4, 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% isolated yield (entry 2). Heteroarene-substituted compounds such as **15c** perform comparably, with **18** and **19** each formed with 6-7:1 regioselectivity (entries 3 and 4). Isolated yields for these compounds are somewhat lower (41%–52%), but the reactions are clean, with products readily purified, and **15c** may be recovered to varying extents. Moreover, even the H-substituted biphenyl **14h** is converted to **20** with 2.5:1 regisolectivity (37% yield; 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," targeting differentially substituted, enantiomerically enriched penta-aryl 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 aryl boronic acid, refluxing 2:1 THF/2M Na_2CO_3(aq)) resulted in incomplete conversions after 18 h, we found that the microwave-based conditions described in Table 1 resulted in full conversion, and good isolated yields (Table 5). Thus, Table 5 presents a series of atropisomerically defined, optically active penta-arenes. Entry 1 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% isolated yield to give **21** with no detectable racemization (entry 1). Entry 2 shows the synthesis of an atropisomerically defined "pseudo-enantiomer" of compound **21**,[25] wherein the order of cross-coupling has been swapped. Thus, penta-arene **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 (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, Table 5 presents compounds that were prepared with verified preservation of the enantiomeric ratios.

In summary, we have reported an iterative atropisomer selective, asymmetric bromination/cross-coupling strategy for the preparation of enantiomerically enriched, complex poly-aryl compounds. Thus far, arenes, heterocycles, and heteroatoms have been introduced with regioselectivity into a tribrominated biaryl scaffold, employing readily available catalysts

and straightforward 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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16. Knapp DM, Gillis EP, Burke MD. J Am Chem Soc. 2009; 131:6961–6963. [PubMed: 19405470]
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18. Schlummer B, Scholz U. Adv Synth Cat. 2004; 346:1599–1626.
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20. Chae J, Buchwald SL. J Org Chem. 2004; 69:3336–3339. [PubMed: 15132539]
21. The reactions perform equally well on a variety of reaction scales. Typical runs were performed with several hundred mg of substrate (1–2 mmol). Reactions on the gram-scale proceed with minimal variation in results.
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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 SI).

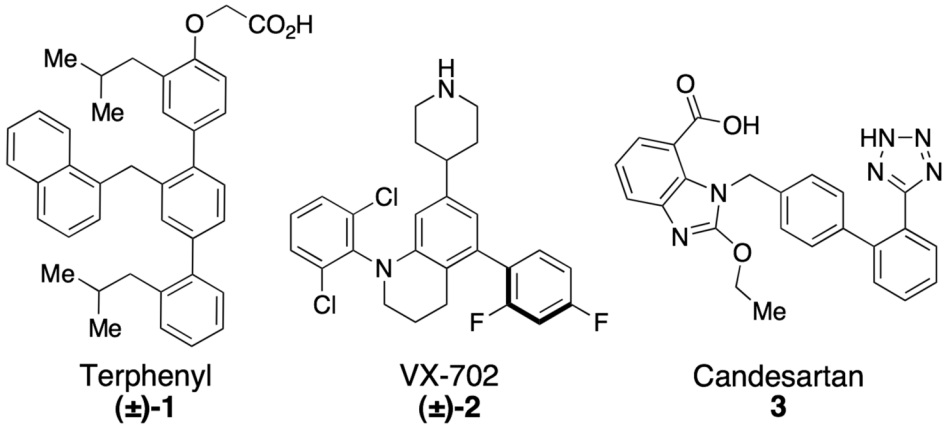
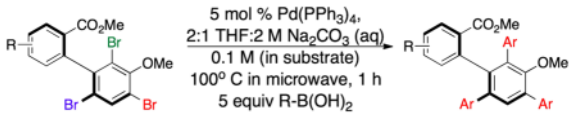
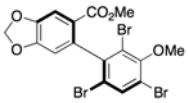
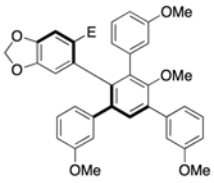
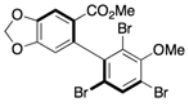
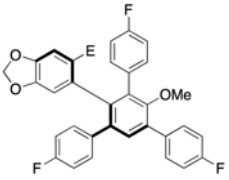
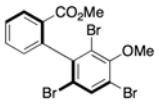
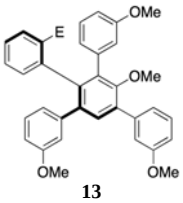


Figure 1.
Representative bioactive polyaryl compounds.

Table 1

Homo-functionalization of tribromobiaryls.



entry	substrate	product	SM er Pdt er[a]	% yield[b]
1a	 **9**	 **11**	95.0:5.0	95[c]
1b			95.0:5.0	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 were determined by chiral HPLC.

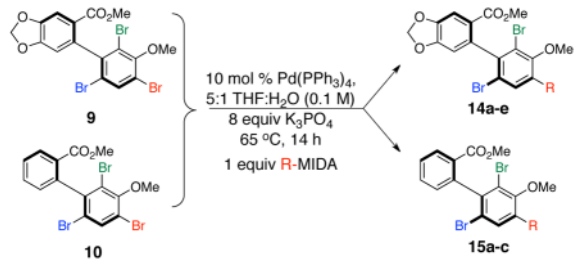
[b] Average isolated yield of three experimental runs.

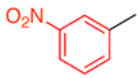
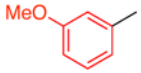
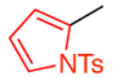
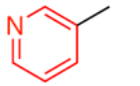
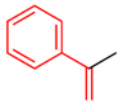
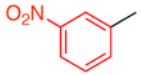
[c] Reaction conducted in refluxing THF/H_2O.

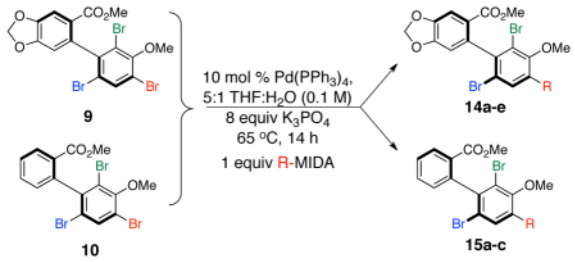
[d] Reaction conducted at 100 °C under microwave conditions, See supporting information for tables.

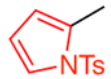
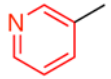
Table 2

Regioselective cross-couplings of tribrominated biaryls.



entry	product R=	substrate	% yield[a] (% rec. SM)	regioselectivity[b,c,d] (A:B:C)	SM er Pdt er[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



entry	product R=	substrate	% yield[a] (% rec. SM)	regioselectivity[b,c,d] (A:B:C)	SM er Pdt er[e,f]
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 isolated yields of three experimental runs.

[b] Assigned by NMR analysis.

[c] Ratio determined by ^{1}H NMR.

[d] Averaged over three experimental runs.

[e] Enantiomer ratios were determined by HPLC analysis.

[f] Averaged over three runs.

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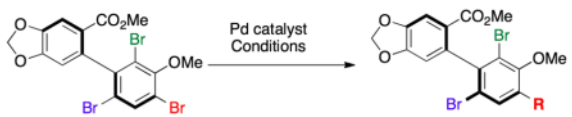
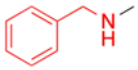
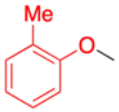
Table 3

Regioselective heteroatom cross-couplings.



9 **14f-h**

entry	R=	substrate	% yield[a]	regioselectivity[b,c,d]	SM er Pdt er[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[h]	>20.0:1.0:1.0	95.0:5.0 95.0:5.0
3	 **14h**[i]	**9**	56[i]	4:1:--	95.0:5.0 97.0:3.0

[a] Average Isolated yields of three experimental runs.

[b] Assigned by NMR analysis.

[c] Ratio determined by ^{1}H NMR.

[d] Averaged over three experimental runs.

[e] Enantiomer ratios were determined by HPLC analysis

[f] Averaged over three runs.

[g] 10% $Pd(OAc)_2$, 20% *rac* 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 refers to the isolated regioisomerically pure product.

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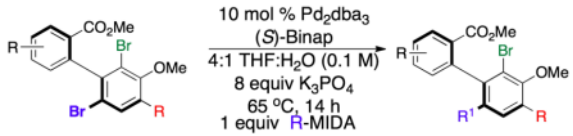
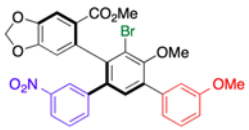
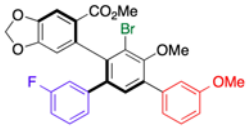
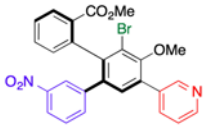
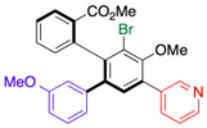
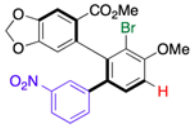
Table 4

Regioselective cross-couplings of dibrominated *p*-terphenyls.



entry	substrate	product	% yield (% rec. SM)[b]	regioselectivity[c,d,e]	SM er Pdt er[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 chiral HPLC.

[b] Average isolated yield of three experimental runs.

[c] Assigned by NMR analysis.

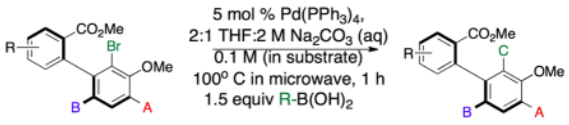
[d] Ratio determined by ^{1}H NMR.

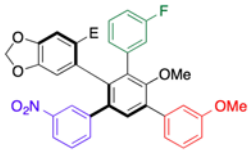
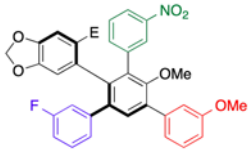
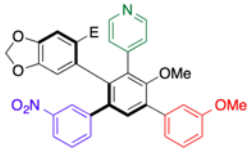
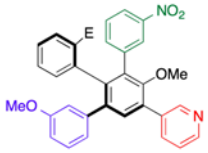
[e] Averaged over three experimental runs.

[f] Isolated as single regioisomer in 25 % overall yield

Table 5

Atropisomer enriched differentially trifunctionalized biaryls.



entry	substrate	product	% yield[b]	SM er Pdt er[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 chiral HPLC.

[b] Isolated yields, averaged over 2 experimental runs.

[c] Used 3 equiv of boronic acid.