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Synthesis of a Sterically Crowded Atropisomeric 1,8-Diacridylnaphthalene for Dual-Mode Enantioselective Fluorosensing

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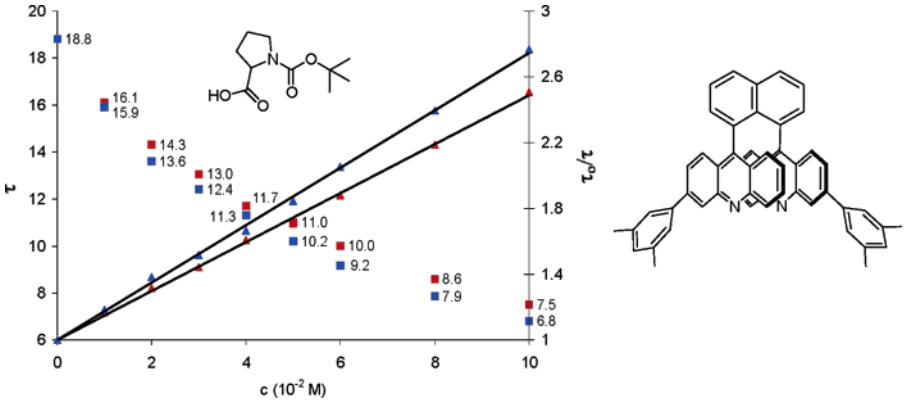

An efficient synthetic route to a sterically crowded 1,8-diheteroarylnaphthalene-derived enantioselective fluorosensor that operates in two different detection modes utilizing fluorescence lifetime and intensity has been developed. Screening of palladium-catalyzed Negishi, Kumada, Suzuki, Hiyama, and Stille coupling methods showed that the latter affords highly congested 1,8-diarylnaphthalenes in superior yields. Despite severe steric hindrance, axially chiral 1,8-bis(3-(3′,5′-dimethylphenyl)-9-acridyl)naphthalene, **1**, was obtained in 68% yield from 1,8-dibromonaphthalene, **14**, and 3-(3′,5′-dimethylphenyl)-9-tributylstannylacridine, **13**, via two consecutive Stille cross-coupling steps using tetrakis(triphenylphosphine)-palladium(0) as catalyst in the presence of copper(II) oxide. The preparation of **1** involved formation of 4-(3′,5′-dimethylphenyl)-2-chlorobenzoic acid, **7**, through microwave-assisted Suzuki coupling of 4-bromo-2-chlorobenzoic acid, **10**, and 3,5-dimethylphenylboronic acid, **11**, followed by regioselective amination with aniline and acridine ring construction in phosphorus oxybromide. Lithiation, subsequent treatment with trimethylstannyl chloride, and Stille cross-coupling then completed the five-reaction sequence providing **1** in 57% overall yield. The enantiomers of **1** were separated by semipreparative HPLC on a (*R*,*R*)-Whelk-O 1 column and successfully employed in enantioselective fluorosensing of *N*-*t*-Boc-protected serine, **20**, glutamine, **22**, proline, **23**, and 2-hydoxy-2-methylsuccinic acid, **21**. Fluorescence titration experiments with **23** revealed that both static and dynamic quenching occur with distinctive enantioselectivity. Addition of (*R*)-**23** to a solution of (+)-**1** in acetonitrile resulted in stronger fluorescence quenching than titration with the (*S*)-enantiomer of **23**. The fluorescence lifetime, τ, of **1** was determined as 18.8 ns and steadily decreased to 7.5 and 6.8 ns in the presence of 0.1 M of (*S*)-**23** and (*R*)-**23**, respectively.

Introduction

The development of sensitive essays for fast determination of the enantiomeric composition of chiral compounds has attracted increasing attention due to potential applications in high-throughput screening of asymmetric reactions.[1] Enantioselective fluorescence spectroscopy with chiral sensors offers a variety of advantages over traditional chromatographic and NMR spectroscopic techniques including different detection modes (fluorescence quenching, enhancement, and lifetime), high sensitivity, low cost of instrumentation, waste reduction, time efficiency, and the possibility of real-time analysis. To date, few enantioselective fluorosensors[2] including binaphthyl-derived

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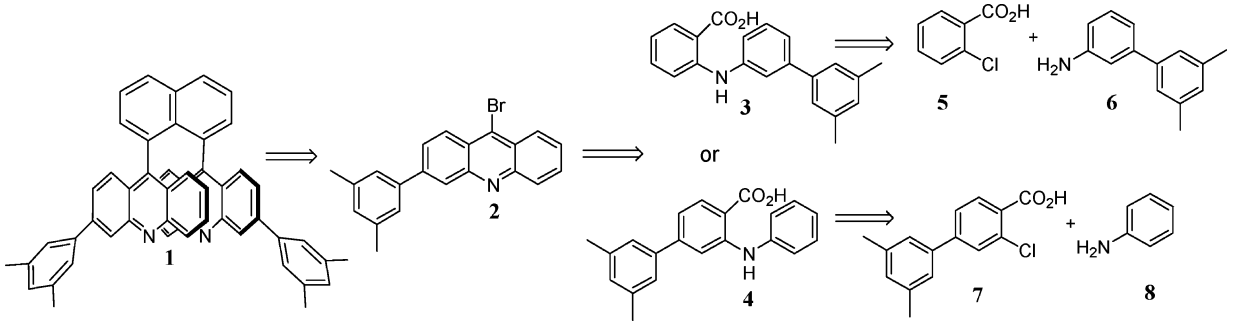
SCHEME 1. Retrosynthesis of 1,8-Bis(3-(3′,5′-dimethylphenyl)-9-acridyl)naphthalene, 1



macrocycles,[3] dendrimers,[4] oligomers,[5] or chiral bisboronic acids[6] and C_2-symmetric diacridylnaphthalenes[7] have been developed. We have recently reported a synthetic route to highly congested axially chiral 1,8-diarylnaphthalenes[8] including fluorescent diacridylnaphthalenes that do not show any sign of *syn*/*anti*-isomerization and subsequent racemization even at high temperatures.[9] The incorporation of bulky aryl rings into the *peri* positions of naphthalene via two consecutive cross-coupling steps is synthetically challenging due to severe steric hindrance to carbon−carbon bond formation. As a consequence, attempts to prepare conformationally stable 1,8-diarylnaphthalenes have often been unsuccessful or resulted in very low yields, which has limited the use of this class of compounds as asymmetric sensors and catalysts.[10] Herein, we wish to report a significantly improved procedure that provides efficient access to a highly congested 1,8-diacridylnaphthalene fluorosensor. The sensor has been applied in sensing studies of chiral amino and hydroxy acids showing both enantioselective fluorescence quenching and enantioselective fluorescence lifetime changes. To the best of our knowledge, this is the first example of a chiral fluorosensor that operates in two different detection modes.

Results and Discussion

Our initial retrosynthetic analysis of 1,8-bis(3-(3′,5′-dimethylphenyl)-9-acridyl)naphthalene, **1**, suggested cross-coupling of 1,8-dibromonaphthalene with 9-acridylstannanes which can be prepared via ring construction of the corresponding 9-bromoacridine **2** from readily available anthranilic acid, **3**, followed by lithiation and subsequent treatment with trimethylstannyl chloride (Scheme 1). This approach involves Cu/Cu_2O-catalyzed amination of 2-chlorobenzoic acid, **5**, with 3-(3′,5′-dimethylphenyl)aniline, **6**, and ring construction in the presence of phosphorus oxybromide.[11] The formation of **2** from *N*-3-(3′,5′-dimethylbiphenyl)anthranilic acid, **3**, turned out to be very inefficient due to low regioselectivity, and we obtained equal amounts of 9-bromoacridyl derivatives **2** and **9** (Scheme 2). Apparently, ring closure proceeds with similar rates at both *ortho*-positions of the aniline moiety of **3**. We envisioned that construction of **2** from anthranilic acid **4** would avoid this issue and provide much more effective access to acridyl bromide **2** (Scheme 1). A synthetically much more challenging problem was to improve the yield of the final cross-coupling step. Because of severe steric hindrance, Stille cross-coupling of 1,8-dibromo- or 1,8-diiodonaphthalene and 3-(3′,5′-dimethylphenyl)-9-tri-*n*-methylstannylacridine, **12**, affords **1** in only 30%. We therefore decided to reevaluate the feasibility of 1,8-diarylnaphthalene formation through screening of a range of reaction conditions and explored the use of other palladium-catalyzed cross-coupling methods.

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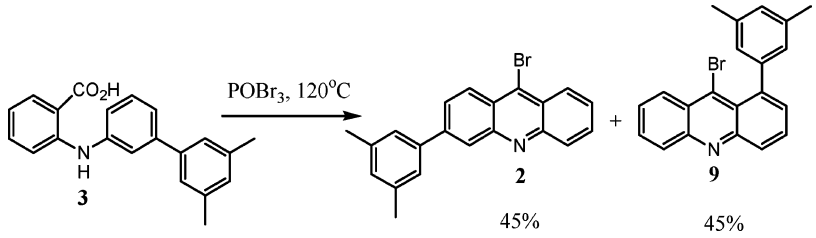
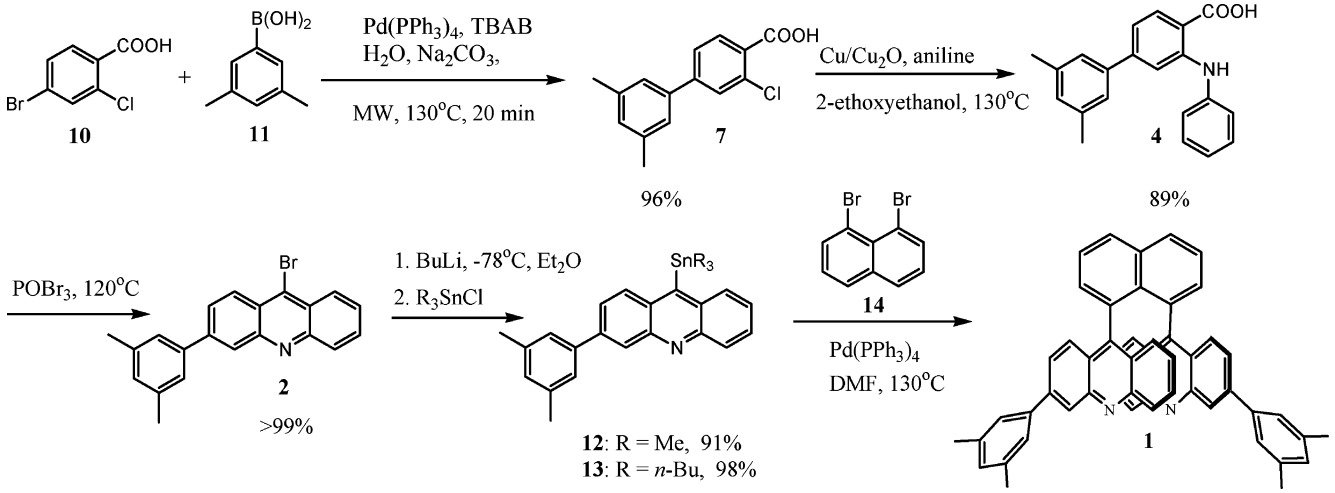
SCHEME 2. Ring Construction of 9-Bromoacridine 2 Using Anthranilic Acid 3



SCHEME 3. Synthesis of 1,8-Diacridylnaphthalene 1



Microwave-assisted Suzuki cross-coupling of 4-bromo-2-chlorobenzoic acid, **10**, and 3,5-dimethylphenylboronic acid, **11**, gave 4-(3′,5′-dimethylphenyl)-2-chlorobenzoic acid, **7**, in 96%. Regioselective Cu/Cu_2O-catalyzed amination of **7** with aniline yielded anthranilic acid **4** in 89%, which was then quantitatively converted to 9-bromoacridyl derivative **2** using phosphorus oxybromide as solvent. Noteworthy, all reaction products are easily purified by crystallization eliminating the need for cumbersome chromatographic workup. Since cyclization of **4** occurs with an unsubstituted aniline moiety, this route exclusively forms acridyl bromide **2**, thus significantly enhancing overall yields while chromatographic separation of **2** from **9** becomes unnecessary. Treatment of **2** with butyllithium followed by addition of trialkylstannyl chlorides was found to afford 9-acridylstannanes **12** and **13** in high yields (Scheme 3). The stannanes were then employed in Stille cross-couplings with 1,8-dibromonaphthalene, **14**, vide infra.

Recent advances in Pd-catalyzed C−C bond-forming reactions[12] and the development of practicable Negishi,[13] Kumada,[14] Suzuki,[15] Stille,[16] and Hiyama coupling procedures[17] encouraged us to improve the final step in the synthesis of 1,8-diacridylnaphthalene **1**. Based on our previous studies, we knew that the unsatisfactory yields of **1** obtained by Stille coupling of **12** and **14** are mostly due to homocoupling of aryl stannanes, transfer of a methyl group instead of an acridyl ring during transmetalation, and dehalogenation. To limit synthetic efforts, we chose to study formation of 1,8-diphenylnaphthalene, **19**, somewhat resembling the crowded structure of **1**. Since we observed that the synthesis of 1,8-diarylnaphthhalenes **1** and **19** via palladium-catalyzed cross-coupling suffers from the same side reactions, formation of the latter was considered an ideal reaction for screening and optimization studies. We envisioned that a procedure that affords **19** in excellent yields could also

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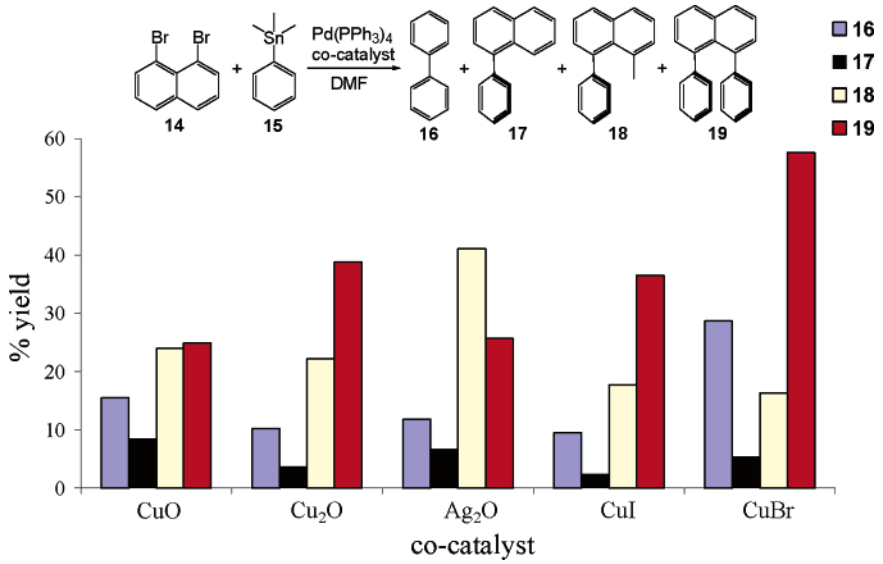

FIGURE 1. Comparison of cocatalysts employed in the $Pd(PPh_3)_4$-catalyzed Stille coupling of 1,8-dibromonaphthalene and phenyltrimethylstannane. Reaction conditions: A mixture of 1,8-dibromonaphthalene (0.17 mmol), phenyltrimethylstannane (0.51 mmol), $Pd(PPh_3)_4$ (0.05 mmol), and cocatalyst (0.25 mmol) in anhydrous DMF (3 mL) was stirred at 130 °C for 20 h under inert atmosphere. Yields were determined by GC using individual response factors and anthracene as internal standard.

be successfully applied in the synthesis of other sterically crowded 1,8-diarylnaphthalenes such as **1**. We found that **19** and the corresponding cross-coupling byproducts **16**−**18** can be quantitatively analyzed by GC using anthracene as internal standard, which proved invaluable for time-efficient screening of coupling methods and reaction conditions. Initially, we examined Kumada, Negishi, Suzuki, and Hiyama coupling of 1,8-dibromonaphthalene and phenyl- or pyridylmagnesium, zinc, boronic acid, and siloxane derivatives employing $Pd(PPh_3)_4$, $PdCl_2$dppf, or $Pd_2(dba)_3$/*t*-Bu_3P as catalyst as well as *t*-BuOK, K_3PO_4, or Cs_2CO_3 as base in THF, DME, and DMF, respectively. Unfortunately, **19** was obtained in only moderate yields by Hiyama or Suzuki cross-coupling reactions, and no sign of formation of **1** was observed when arylmagnesium and zinc analogues were employed.

By contrast, Stille coupling of 1,8-dibromonaphthalene and phenyltrimethylstannane proved to be superior over the above methods, and we therefore decided to optimize reaction conditions through screening of various catalyst sources, solvents, and cocatalysts. The formation of considerable amounts of 1-methyl-8-phenylnaphthalene, **18**, during cross-coupling of 1,8-dibromonaphthalene, **14**, and phenyltrimethylstannane, **15**, indicated that steric hindrance to transmetalation results in undesirable methyl rather than acridyl transfer. Liebeskind et al. reported that copper(I) salts facilitate Stille cross-couplings through formation of intermediate organocopper species that undergo transmetalation at a higher rate than arylstannanes.[18] Although the exact mechanism of the copper-mediated transmetalation remains elusive, various additives have successfully been employed as cocatalysts in Stille coupling reactions.[19] Employment of five different metal salts in the $Ph(PPh_3)_4$-catalyzed coupling of **14** and **15** showed that **19** is produced in 35−60% in the presence of CuI, Cu_2O, and CuBr, while lower yields were obtained with CuO and Ag_2O (Figure 1). Methyl transfer resulting in the formation of **18** was found to become the dominant reaction outcome when Ag_2O was used. As expected, considerable amounts of homocoupling product **16** were produced due to the use of excess of stannane **15**, but more importantly, less than 10% of dehalogenation product **17** was observed in all cases.

We then employed various palladium catalysts in the coupling reaction of **14** and **15** using CuBr as cocatalyst and DMF as solvent (Figure 2). While Stille coupling with tris(dibenzylideneacetone)dipalladium(0), $Pd_2(dba)_3$, in the presence of 1,1′-bis(diphenylphosphino)ferrocene, dppf, proved unsuccessful, 1,8-diphenylnaphthalene **19** was obtained in 40% yield when $Pd(OAc)_2$ was used, but this catalyst also produced 32% of 1-methyl-8-phenylnaphthalene **18**. Fortunately, the undesirable methyl transmetalation could be suppressed with other catalysts such as Pd(*t*-$Bu_3P)_2$ or combinations of $Pd_2(dba)_3$ and 2-di(*tert*-butyl)phosphinobiphenyl, 2-dicyclohexylphosphinobiphenyl, or triphenylarsine providing **19** with 34−47% yield.[20] The best results were obtained with tetrakis(triphenylphosphine)palladium-(0), $Pd(PPh_3)_4$, which gave the desired cross-coupling product **19** in 58% yield in the presence of copper(I) bromide. Again, dehalogenation played only a minor role in the palladium-catalyzed Stille coupling of **14** and **15**, and 1-phenylnaphthalene

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(20) We did not observe any formation of coupling products **17**−**19** from **14** and **15** using $Pd(OAc)_2$, Pd(1,5-cyclooctadiene)Cl_2, and $Pd_2(dba)_3$ in the presence of 2-dicyclohexylphosphino-2′,6′-diisopropoxy-1,1′-biphenyl in refluxing DMF after 20 h.

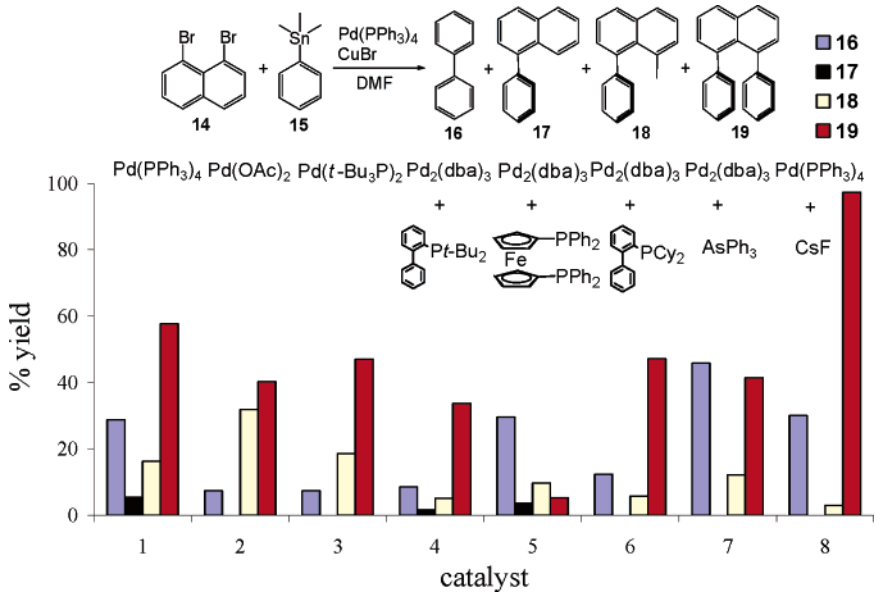


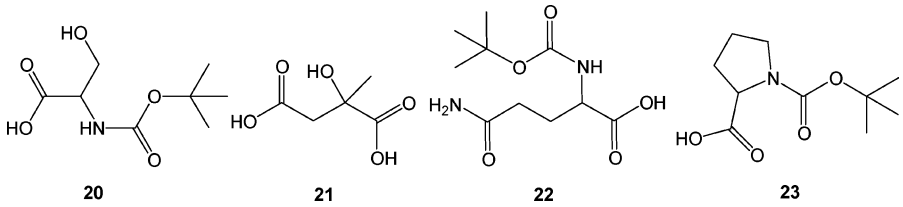
FIGURE 2. Stille cross-coupling of 1,8-dibromonaphthalene and phenyltrimethylstannane using various Pd catalysts. Reaction conditions: A mixture of 1,8-dibromonaphthalene (0.17 mmol), phenyltrimethylstannane (0.51 mmol), Pd catalyst (0.05 mmol), and CuBr (0.25 mmol) in anhydrous DMF (3 mL) was stirred at 130 °C for 20 h under nitrogen. Yields were determined by GC using individual response factors and anthracene as internal standard.

TABLE 1. Pd-Catalyzed Formation of 1,8-Diacridylnaphthalene 1[a]

entry	stannane	solvent	catalyst (mol %)	additives	*T* (°C)	**1** (% yield)[d]
1	**12**	dioxane	$Pd(PPh_3)_4$ (36)	CuBr, CsF	100	0
2	**12**	DMF	$Pd(PPh_3)_4$ (36)	CuBr, CsF	130	0
3	**12**	DMF	$Pd(PPh_3)_4$ (36)	CuBr	130	31
4	**12**	DMF	$Pd(PPh_3)_4$ (36)	CuO	130	32
5	**12**	DMF	$Pd_2(dba)_3$ (36) + DHPP[b] (52)	CuBr	130	20
6	**13**	DMF	$Pd(PPh_3)_4$ (36)	CuO	130	66[c]
7	**13**	DMF	$Pd(PPh_3)_4$ (36)	CuBr	130	35
8	**13**	DMF	$Pd(PPh_3)_4$ (36)	Cu_2O	130	5
9	**13**	DMF	$Pd_2(dba)_3$ (36) + P(*n*-Bu)$_3$ (52)	CuO	130	0
10	**13**	DMF	$Pd[P(t\text{-}Bu)_3]_2$ (36)	CuO	130	10
11	**13**	DMF	$Pd(PPh_3)_4$ (36)	CuO	100	68[c]
12	**13**	dioxane	$Pd(PPh_3)_4$ (36)	CuO	100	48[c]
13	**13**	DMF	$Pd(PPh_3)_4$ (15)	CuO	100	53[c]
14	**13**	DMF	$Pd(PPh_3)_4$ (5)	CuO	100	24

[a] Reactions were conducted with 1,8-dibromonaphthalene (0.25 mmol), acridyl stannane **12** or **13** (1.0 mmol), Pd catalyst, cocatalyst, and additive (0.5 mmol) in DMF or dioxane (3 mL) for 48 h under nitrogen. [b] DHPP is 2-dicyclohexylphosphinobiphenyl. [c] Reaction was performed for 20 h under nitrogen. [d] Isolated yields.

CHART 1. Structures of Carboxylic Acids 20−23 Used in Enantioselective Sensing Studies



17 was observed in less than 5% in all cases. Employing $Pd(PPh_3)_4$ and CuBr in refluxing THF, DMA, and dioxane for 20 h yielded **19** in 41, 51, and 57% yield, respectively. To our delight, the yield of **19** further increased to 97% through addition of cesium fluoride, which may be attributed to activation of fluorophilic stannane **15**.[21]

The most promising reaction conditions were then applied in the synthesis of 1,8-diacridylnaphthalene **1**. Stille coupling of **12** and **14** using $Pd(PPh_3)_4$ in the presence of CuBr and CuO gave **1** in 31−32% yield, while addition of cesium fluoride for activation of the stannane for the transmetalation step did not result in the formation of the desired cross-coupling product (Table 1, entries 1−4). The striking difference in the results obtained by cesium fluoride-promoted Stille coupling with phenyl- and acridylstannanes can probably be attributed to the low stability of the latter. We have observed that acridylstannanes easily decompose when stored in solution at room temperature and therefore assume that this occurs even more

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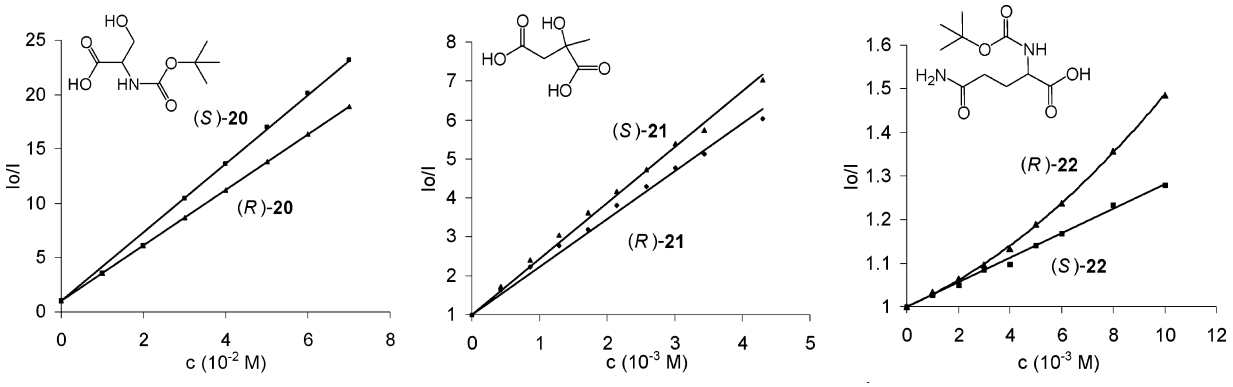

FIGURE 3. Stern−Volmer plots showing enantioselective fluorescence quenching of (+)-**1** in the presence of the enantiomers of carboxylic acids **20**, **21,** and **22**. The concentration of (+)-**1** in acetonitrile was 2.6 × 10^{-6} M. Excitation (emission) wavelength was 360 nm (550 nm).

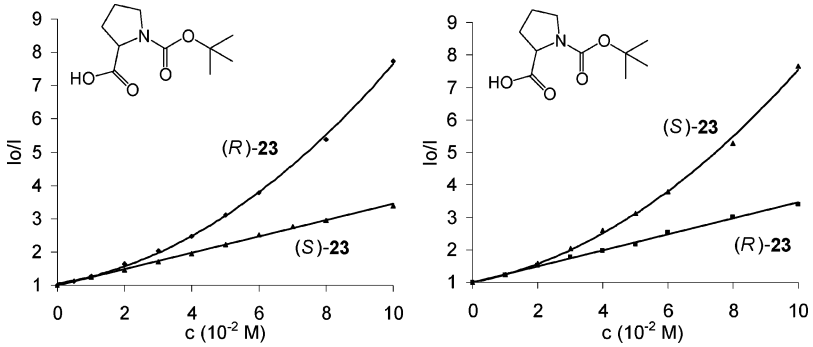

FIGURE 4. Stern−Volmer plots showing enantioselective fluorescence quenching of (+)-**1** (left) and (−)-**1** (right) in the presence of (*R*)- and (*S*)-**23**. The concentration of **1** in acetonitrile was 2.6 × 10^{-6} M. Excitation (emission) wavelength was 360 nm (550 nm).

rapidly in the presence of fluoride. We also noticed that other phosphine ligands such as 2-dicyclohexylphosphinobiphenyl, DHPP, tri-*tert*-butyl phosphine, and tri-*n*-butyl phosphine do not improve coupling yields (entries 5, 9, and 10). However, $Pd(PPh_3)_4$-catalyzed cross-coupling of 3-(3′,5′-dimethylphenyl)-9-tributylstannylacridine, **13**, and dibromide **14** in DMF at 100 or 130 °C gave 1,8-diacridylnaphthalene **1** in 66−68% yield after 20 h, which corresponds to remarkable 82% for each individual coupling step (entries 6 and 11). As expected, decreased yields of **1** were obtained at lower catalyst loadings (entries 13 and 14). The excellent results obtained with tributylstannylacridine **13** can be attributed to limited formation of byproducts since we did not observe any traces of dehalogenation and butyl transmetalation products. Apparently, transmetalation of the butyl groups of stannane **13** is significantly less favored than methyl transfer from acridylstannane **12**. The revised synthetic strategy toward 1,8-diacridylnaphthalene **1** and the significantly improved Stille coupling procedure thus increased the overall yield from 12% to 57%.

Having developed a practicable synthetic route to axially chiral 1,8-diacridylnaphthalene **1**, we decided to study its use for enantioselective fluorosensing of *N*-*t*-Boc-protected serine **20**, glutamine **22**, proline **23**, and 2-hydoxy-2-methylsuccinic acid, **21** (Chart 1). The enantiomers of **1** were separated on a (*R*,*R*)-Whelk-O 1 column, and the dextrorotatory enantiomer was employed in fluorescence titration experiments using acetonitrile as solvent. We were delighted to observe enantioselective fluoresence quenching in all cases (Figures 3 and 4). Both enantiomers of amino acids **20** and **21** gave linear Stern−Volmer plots, which can be attributed to static quenching due to formation of diastereomeric 1:1 hydrogen bond adducts with (+)-**1**.[7] By contrast, the (*R*)-enantiomer of both **22** and **23**

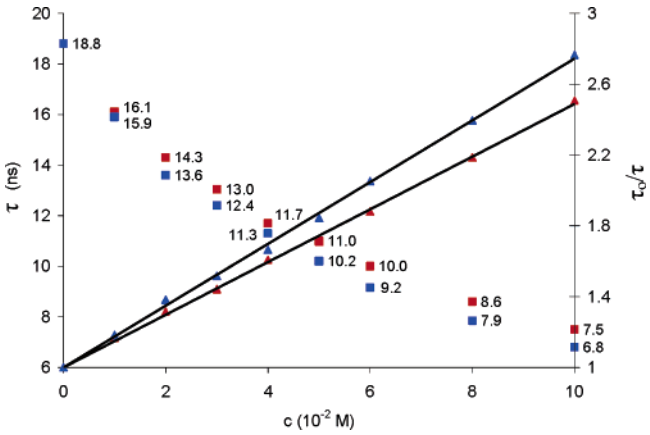

FIGURE 5. Fluorescence lifetime titration of (+)-**1** in the presence of the enantiomers of **23** in acetonitrile. Fluorescence lifetime, τ, of (+)-**1** in the presence of various amounts of (*R*)-**23** (blue box) and (*S*)-**23** (red box); ratio of the fluorescence lifetime of (+)-**1** in the absence and in the presence of (*R*)-**23** (blue triangle) and (*S*)-**23** (red triangle). Sensor **1** exhibits a single-componential decay that was fitted at 550 nm. The sample was excited at 370 nm.

showed nonlinear quenching indicating either formation of 1:2 adducts or significant dynamic quenching contributions. As expected, opposite behavior was observed when (−)-**1** was used for enantioselective sensing of the enantiomers of **23** (Figure 4). In this case, addition of (*R*)-**23** to a solution of the levorotatory sensor resulted in linear quenching, whereas (*S*)-**23** gave an exponential Stern−Volmer curve.

Static and dynamic quenching exhibit two different fluorescence sensing modes. While static quenching results from formation of a complex between the fluorosensor and the

quencher, dynamic quenching refers to collisional encounters between the analyte and the sensor during the lifetime of the excited state of the fluorophore. Fluorescence lifetime measurements of (+)-**1** in the absence and presence of various amounts of the enantiomers of **23** revealed enantioselective dynamic quenching. The fluorescence lifetime, τ, of **1** was determined as 18.8 ns and steadily decreased upon addition of either enantiomer of **23**. Interestingly, (*R*)-**23** was found to more effectively reduce the fluorescence lifetime of (+)-**1** than the (*S*)-enantiomer of **23**. Fluorescence lifetimes of (+)-**1** were determined as 7.5 and 6.8 ns in the presence of 0.1 M of (*S*)-**23** and (*R*)-**23**, respectively (Figure 5). To the best of our knowledge, this is the first example of enantioselective fluorosensing based on lifetime measurements.

Conclusion

Screening of the usefulness of palladium-catalyzed Negishi, Kumada, Suzuki, Hiyama, and Stille coupling procedures for the construction of highly congested 1,8-diarylnaphthalenes showed that superior results are obtained with arylstannanes, in particular when undesirable alkyl transfer during transmetalation and dehalogenation can be controlled. Despite severe steric hindrance, 1,8-bis(3-(3′,5′-dimethylphenyl)-9-acridyl)-naphthalene, **1**, was obtained in 68% yield from 1,8-dibromonaphthalene, **14**, and 3-(3′,5′-dimethylphenyl)-9-tributylstannylacridine, **13**, using $Pd(PPh_3)_4$ as catalyst in the presence of copper(II) oxide. We believe that our Stille coupling procedure will also be useful for the synthesis of other sterically crowded biaryls. Fluorescence titration experiments with enantiopure **1** and *N*-*t*-Boc-protected serine, **20**, glutamine, **22**, proline, **23**, and 2-hydroxy-2-methylsuccinic acid, **21**, showed enantioselective static and enantioselective collisional quenching, demonstrating the versatility of both fluorescence spectroscopy and our diacridylnaphthalene-derived sensor, which operates in two different fluorescence detection modes. Further studies of new sensing applications and the underlying chiral recognition mechanism of **1** are currently underway in our laboratories.

Experimental Section

4-(3′,5′-Dimethylphenyl)-2-chlorobenzoic Acid, 7. Into a glass vessel (capacity 10 mL) were placed 4-bromo-2-chlorobenzoic acid, **10** (235 mg, 1.0 mmol), 3,5-dimethylphenylboronic acid, **11** (150 mg, 1.0 mmol), tetrabutylammonium bromide (332 mg, 1.0 mmol), $Pd(PPh_3)_4$ (10 mg, 0.01 mmol), Na_2CO_3 (403 mg, 3.8 mmol), and deionized water (2 mL). The mixture was heated to 130 °C (100 W) for 20 min using a continuous focused microwave power delivery system. The cooled reaction mixture was poured into water and extracted with Et_2O. The combined organic layers were dried over $MgSO_4$ and removed in vacuo. Recrystallization of the residue from EtOAc gave **7** (250 mg, 96%) as white crystals: ^{1}H NMR (300 MHz, $CDCl_3$) δ = 2.40 (s, 6H), 7.07 (s, 1H), 7.22 (s, 2H), 7.57 (dd, J = 2.0 Hz, 8.3 Hz, 1H), 7.71 (d, J = 2.0 Hz, 1H), 8.10 (d, J = 8.3 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 11.1, 114.8, 115.0, 116.0, 119.6, 120.1, 122.7, 124.9, 128.0, 128.4, 136.7, 159.5. Anal. Calcd for $C_{15}H_{13}ClO_2$: C, 69.10; H, 5.03. Found: C, 69.31; H, 4.95.

4-(3′,5′-Dimethylphenyl)-2-(*N*-phenylamino)benzoic Acid, 4. Chlorobenzoic acid **7** (520 mg, 2.0 mmol) was mixed with aniline (205 mg, 2.2 mmol), Cu (12 mg, 0.18 mmol), Cu_2O (13 mg, 0.09 mmol), K_2CO_3 (276 mg, 2 mmol), and 2-ethoxyethanol (1 mL) in a three-neck round-bottom flask equipped with a reflux condenser. The reaction mixture was heated to 130 °C for 24 h under inert atmosphere. The cooled reaction mixture was poured into water, treated with charcoal, and filtrated through Celite. The crude product was obtained by precipitation upon acidification with dilute HCl. The desired product was re-crystallized from EtOAc to afford **4** (561 mg, 89%) as white crystals: ^{1}H NMR (300 MHz, $CDCl_3$) δ = 2.35 (s, 6H), 6.90 (dd, J = 1.5 Hz, 8.5 Hz, 1H), 7.00 (s, 1H), 7.13 (s, 2H), 7.30−7.44 (m, 6H), 8.07 (d, J = 8.6 Hz, 1H), 9.40 (bs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 22.1, 110.0, 113.1, 117.4, 123.5, 124.6, 125.8, 130.2, 130.6, 133.7, 139.0, 141.0, 141.2, 149.0, 149.6, 173.6. Anal. Calcd for $C_{20}H_{18}NO_2$: C, 79.47; H, 6.03; N, 4.41. Found: C, 79.07; H, 6.47; N, 4.09.

9-Bromo-3-(3′,5′-dimethylphenyl)acridine, 2. Anthranilic acid **4** (140 mg, 0.44 mmol) was added to phosphorus oxybromide (1.4 g, 4.9 mmol) in a three-neck round-bottom flask equipped with a reflux condenser. The mixture was heated to 120 °C for 2 h. Excess of phosphorus oxybromide was removed by distillation and the residual solution was poured into aqueous ammonium hydroxide and extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and dried in vacuo to give **5** (160 mg, >99%) as a yellow powder: ^{1}H NMR δ = 2.44 (s, 6H), 7.09 (s, 1H), 7.46 (s, 2H), 7.63 (ddd, J = 1.1 Hz, 6.6 Hz, 8.8 Hz, 1H), 7.82 (dd, J = 6.9 Hz, 8.5 Hz, 1H), 7.94 (dd, J = 1.6 Hz, 9.1 Hz, 1H), 8.27 (d, J = 8.8 Hz, 1H) 8.39−8.47 (m, 3H); ^{13}C NMR δ = 22.0, 125.3, 125.5, 126.0, 126.7, 127.0, 127.2, 127.5, 127.8, 129.9, 130.2, 130.4, 135.4, 138.6, 139.3, 142.8, 149.2, 149.2. Anal. Calcd for $C_{21}H_{16}NBr$: C, 69.61; H, 4.42; N, 3.87. Found: C, 70.03; H, 4.30; N, 3.40.

3-(3′,5′-Dimethylphenyl)-9-trimethylstannylacridine, 12. A solution of 9-bromo-3-(3′,5′-dimethylphenyl)acridine **2** (0.6 g, 1.6 mmol) in 10 mL of anhydrous diethyl ether/THF (1:1) was cooled to −78 °C under nitrogen. To the solution was added dropwise 1.6 M of *n*-BuLi in hexanes (1.5 mL, 2.4 mmol) over a period of 15 min, and the reaction mixture was stirred for 1 h. A 1.0 M solution of Me_3SnCl in hexanes (3 mL, 3 mmol) was then added in one portion. The reaction mixture was allowed to warm to room temperature, stirred for 18 h, and concentrated under vacuum. Purification of the orange residue by flash chromatography (100:30:1 hexanes/ethyl acetate/triethylamine) afforded **12** (0.65 g, 91%) as yellow crystals. GC−MS analysis revealed the presence of 5−10% of 3-(3′,5′-dimethylphenyl)acridine that could not be separated by chromatography. The stannane was therefore employed in the Stille coupling with 1,8-dibromonaphthalene without further purification: ^{1}H NMR δ = 0.70 (s, 9H), 2.44 (s, 6H), 7.08−7.10 (m, 1H), 7.49−7.56 (m, 3H), 7.76 (ddd, J = 1.4 Hz, 6.6 Hz, 8.8 Hz, 1H), 7.88 (dd, J = 1.9 Hz, 9.1 Hz, 1H), 8.13 (d, J = 8.5 Hz, 1H), 8.22 (d, J = 9.1 Hz, 1H), 8.27 (d, J = 8.5 Hz, 1H), 8.49 (m, 1H); ^{13}C NMR δ = −4.2, 21.8, 125.3, 125.4, 125.5, 127.7, 129.6, 129.8, 130.1, 130.4, 130.8, 132.8, 133.5, 138.4, 139.8, 142.0, 148.2, 148.2, 156.4.

3-(3′,5′-Dimethylphenyl)-9-tri-*n*-butylstannylacridine, 13. A solution of 9-bromo-3-(3′,5′-dimethylphenyl)acridine, **2** (0.6 g, 1.6 mmol), in 10 mL of anhydrous diethyl ether/THF (1:1) was cooled to −78 °C under nitrogen. To the solution was added dropwise 1.6 M *n*-BuLi in hexanes (2.4 mmol, 1.5 mL) over a period of 15 min and the mixture stirred at the same temperature for 1 h. Then, $(n\text{-}Bu)_3SnCl$ (975 mg, 3 mmol) dissolved in 2 mL of diethyl ether was added in one portion. The reaction mixture was allowed to warm to room temperature, stirred for 18 h, and concentrated in vacuo. Purification of the orange residue by flash chromatography (95:5 methylene chloride/triethylamine) afforded **13** (0.9 g, 98%) as yellow crystals: ^{1}H NMR δ = 0.87 (t, J = 7.1 Hz, 7.3 Hz, 9H), 1.30−1.70 (m, 18H), 2.41 (s, 6H), 7.04 (s, 1H), 7.50−7.54 (m, 3H), 7.71−7.77 (m, 1H), 7.86 (dd, J = 2.0 Hz, 9.0 Hz, 1H), 8.09 (d, J = 8.5 Hz, 1H), 8.15 (d, J = 9.0 Hz, 1H), 8.26 (d, J = 8.5 Hz, 1H), 8.49 (d, J = 1.7 Hz, 1H); ^{13}C NMR δ = 14.1, 14.2, 22.1, 27.9, 29.7, 125.7, 125.9, 126.0, 128.1, 130.2, 130.3, 131.0, 131.1, 131.3, 133.9, 134.6. 139.1, 140.5, 142.6, 148.7, 148.8, 158.9.

1,8-Bis(3-(3′,5′-dimethylphenyl)-9-acridyl)naphthalene, 1. A three-neck round-bottom flask equipped with a reflux condenser was charged with 1,8-dibromonaphthalene (72 mg, 0.25 mmol), $Pd(PPh_3)_4$ (102 mg, 0.09 mmol), CuO (40 mg, 0.5 mmol), and 3

mL of DMF. The solution was stirred at 130 °C for 5 min, and a solution of 3-(3′,5′-dimethylphenyl)-9-tri-*n*-butylstannylacridine, **13** (600 mg, 1.0 mmol), in 2 mL of DMF was added in one portion. The reaction mixture was stirred at 130 °C for 20 h, quenched with 10% aqueous ammonium hydroxide, and extracted with methylene chloride. The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. Purification of the residue by flash chromatography (35:25:35:5 hexanes/ethyl acetate/methylene chloride/triethylamine) afforded equal amounts of the *syn*- and *anti*-diastereomers of **1** (118 mg, 68%) as yellow crystals.

anti-Isomer: ^{1}H NMR δ = 2.45 (s, 12H), 6.62−6.68 (m, 2H), 6.83−6.86 (m, 4H), 7.00−7.03 (m, 2H), 7.07 (s, 2H), 7.31−7.39 (m, 8H), 7.67 (d, J = 9.1 Hz, 2H), 7.73−7.78 (m, 2H), 7.91 (s, 2H). 8.31 (d, J = 8.2 Hz, 2H); ^{13}C NMR δ = 22.3, 124.8, 125.4, 125.5, 125.6, 125.9, 126.2, 126.3, 126.6, 127.0, 129.3, 129.8, 130.1, 130.5, 131.2, 134.2, 134.6, 135.5, 139.0, 140.8, 141.9, 146.1, 147.5, 147.6; mp >260 °C; LC/APCI/MS m/z = 691(M + H). Anal. Calcd for *anti*-$C_{52}H_{38}N_2$: C, 90.43; H, 5.55; N, 4.06. Found: C, 90.64; H, 5.30; N, 4.11.

syn-Isomer: ^{1}H NMR δ = 2.26 (s, 12H), 6.65−6.70 (m, 2H), 6.75−6.78 (m, 2H), 6.85−6.88 (m, 2H), 6.96−6.99 (m, 4H), 7.12 (s, 4H), 7.28−7.31 (m, 2H), 7.36−7.42 (m, 2H), 7.69−7.75 (m, 4H), 7.91 (d, J = 1.7 Hz, 2H), 8.27 (dd, J = 1.1 Hz, 8.4 Hz, 2H); ^{13}C NMR δ = 22.0, 124.8, 125.3, 125.4, 125.5, 125.8, 126.1, 126.3, 126.4, 126.9, 129.4, 129.7, 130.1, 130.4, 131.1, 134.2, 134.7, 135.5, 138.8, 140.7, 142.1, 146.1, 147.4, 147.5; mp 255 °C Anal. Calcd for *syn*-$C_{52}H_{38}N_2$: C, 90.43; H, 5.55; N, 4.06. Found: C, 90.70; H, 5.40; N, 4.36.

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Supporting Information Available: UV, CD, polarimetry, and fluorescence spectroscopy measurements of **1** and NMR spectra of all products. This material is available free of charge via the Internet at http://pubs.acs.org.

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