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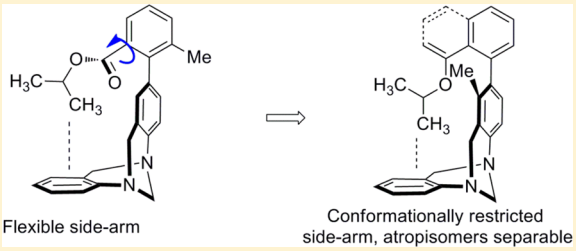
Wilcox Molecular Torsion Balance with Rigid Side Arm and Separable Atropisomers for Investigating CH−π Interactions

Brijesh Bhayana*

Wellman Center for Photomedicine, Massachusetts General Hospital, 40 Blossom Street, Boston, Massachusetts 02114, United States

Supporting Information

ABSTRACT: A new variant of the Wilcox molecular torsion balance featuring a naphthyl-alkyl side arm was synthesized. The energy barrier for axial isomerization in the new balance was sufficiently high to allow for separation of the two rotamers and to observe their isomerization kinetics. The CH−π interaction energies in derivatives of the new and the original ester balance were in close agreement, suggesting that the motion in ester linkage is not an important factor in folding in the ester balance.



The molecular torsion balance developed by Wilcox and co-workers has been used in a number of studies for quantification of various weak noncovalent interactions.[1−9] Within the torsion balance, the folding energy is easily determined via NMR spectroscopy; however, the rapid exchange between balance's folded and unfolded states on the NMR time scale has hindered the ability to isolate its two rotamers and study their folding kinetics.[10] Such studies are important for extending the utility of the torsion balance strategy. For example, with a separable torsion balance, factors affecting energy barrier for atropisomerization in hindered biaryl systems can be studied.[11−15] Alternatively, high rotational barriers could allow separate characterization of the folded and unfolded conformers by X-ray crystallographic analysis. Such potential applications provided the impetus for developing a torsion balance with separable atropisomers.

In the design of the new balance, various alternatives were available for increasing the rotational barrier. However, the substitution of the ester side arm with a naphthyl-alkyl ether side arm was particularly appealing. Unlike the ester linker, the naphthyl ether linker imposed a much more restricted geometry on the interacting fragment while presenting it to the bottom arene. A comparison of folding ratios of the new and the original balance then also allowed for elucidation of effects of motion in the ester linker on CH−π interactions in the original balance. A balance with a naphthyl-alkyl ether side arm was thus chosen as the target candidate for synthesis.

The synthesis of the derivatives of the new balance (Scheme 1) were accomplished via Suzuki coupling between pinacol boronate ester of Troger's base derived from 4-bromo-2,5-dimethylaniline and the triflates of the monoalkyl ethers of naphthalene-1,8-diol.[16−18] The folded and unfolded conformers were separable via silica gel chromatography and were quite stable toward atropisomerization at room temperature. With the exception of the methyl ether balance, the new balances showed no trace of axial isomerization even after several days in solution at room temperature. While the axial stability was advantageous for separation purposes, it also hindered the ability to measure the folding energy (ΔG°_{fold}) at room temperature as it slowed the equilibration process to inconveniently long times. It was therefore necessary to equilibrate the balances at elevated temperatures prior to their NMR analysis at 298 K. In DMSO-d_6 as solvent, the equilibration temperature had negligible effect on the folding ratios in the temperature range of 70−140 °C,[19] which validated the use of the equilibration method for determination of room temperature ΔG°_{fold} values. In addition to the effect of temperature, the effect solvent on folding energy was also investigated. The ΔG°_{fold} values were nearly identical in chloroform, 1,2-dichloroethane, and DMSO.[20] The folding ratios of Wilcox's ester balances were also found to be unaffected by solvent (e.g., DMSO, chloroform, acetone, CH_2Cl_2, nitromethane) or temperature.[1,2] The conformational equilibrium in the new and the original balance is thus driven by similar factors.

Within the new balance, the methyl ether showed a small preference for the unfolded state (ΔG°_{fold} = +0.27 kcal/mol). The larger alkyl groups preferred the folded state, indicating the presence of attractive CH−π interactions (Table 1). The new balance was therefore suitable for quantifying such interactions. The folding energies (ΔG°_{fold}) of various ethers at 298 K were in the range of 0.4−0.5 kcal/mol,[21] which were close to the ΔG°_{fold} values reported by Wilcox (0.3−0.5 kcal/mol) for analogous esters (Table 1).[1−3,7] The close similarity in folding energies of the new and the original derivatives was interesting given that they had different side arms. The ester side arm has a greater conformational flexibility since the dihedral angle between the top aromatic ring and the ester C(O)O plane is adjustable. Ab initio calculations suggest that, in the ester balance, the C(O)O plane of the ester should be significantly twisted out of plane with respect to the top aromatic ring in the minimum energy configuration.[22] Solid-state structures of the ester balances available in literature also support this view.[1,6] In contrast, the side arm in the new balance is essentially planar. The similarity in the folding energies therefore suggests that *the motion in the ester linkage is not*

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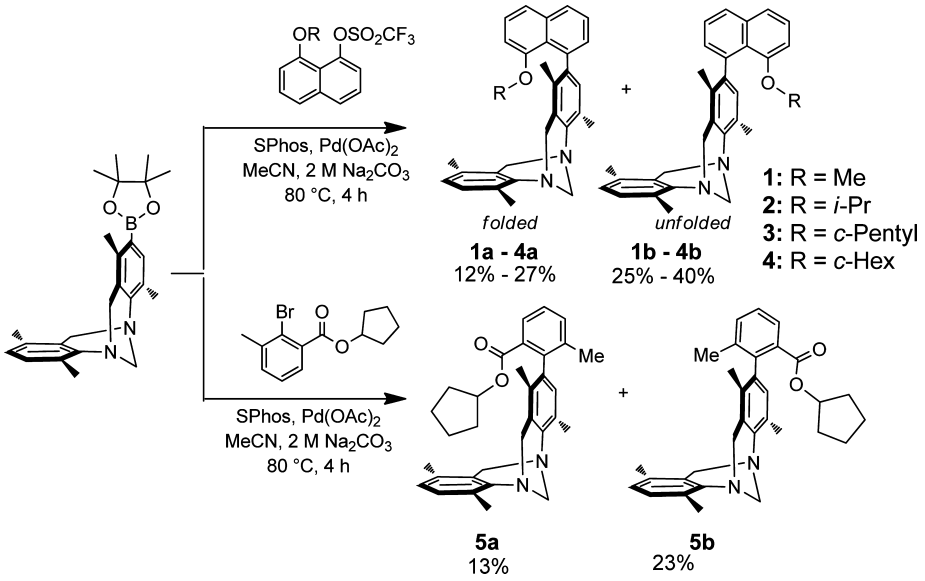
Scheme 1. Synthesis of the New Torsion Balances



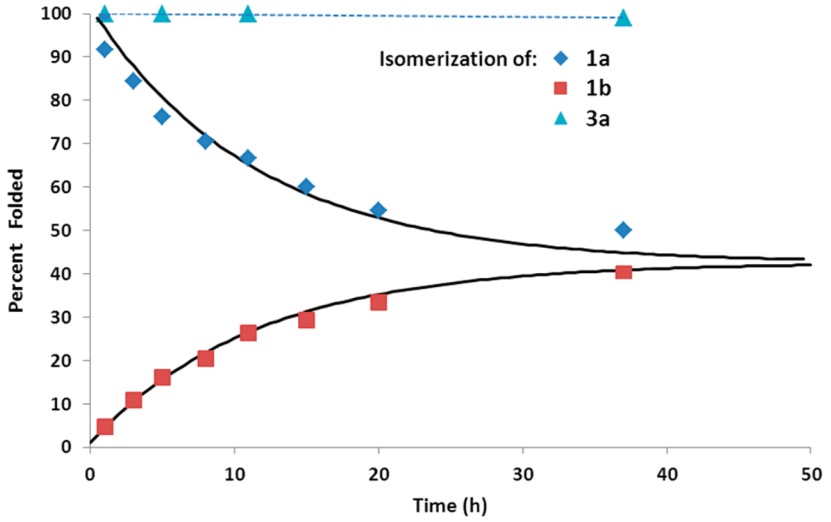


Figure 1. Isomerization kinetics (T = 47 °C) of conformers **1a**, **1b**, and **3a**. Solid lines show the simulated equilibration curves with rate constant values of $k_{fold\rightarrow unfold}$ = 0.05 h^{-1} and $k_{unfold\rightarrow fold}$ = 0.035 h^{-1}.

an important factor in folding in the ester balance, and that the torsion balance CH−π interaction energies are general rather than reflecting the specifics of a particular structural framework.

The study of folding kinetics is essential for deciphering the effects of dynamic solvent influences on solute's conformational changes and estimation of activation parameters. The folding kinetics of the folded and unfolded conformers was studied by NMR spectroscopy, and their activation energies for atropisomerization were determined. Upon warming, both conformers reached the same equilibrium state. The rate of atropisomerization was found to decrease with the increase in the size of the alkoxy group. As seen in Figure 1, while the folded and the unfolded conformers of methyl ether balance reached the equilibrium state in approximately 50 h at 47 °C, almost no atropisomerization was observed for the bulkier cyclopentyl ether balance under the same conditions. The rate constants for unfolding ($k_{fold\rightarrow unfold}$) and folding ($k_{unfold\rightarrow fold}$) processes were estimated by comparing the experimental data with the results of the numerical simulation of the rate equations.[23] At equilibrium, these rate constants satisfy the rate constants with

Table 1. Folding Ratios and Folding Energies of the Derivatives of the New Balance

balance (R)	% folded at equilibrium	ΔG°_{fold} (kcal/mol)
CH_3	38	+0.27[a] [0.0][b]
$CH(CH_3)_2$	62	−0.55[c] [−0.44][b]
c-Pent	59	−0.48[c] [−0.35][b]
c-Hex	59	−0.48[c] [−0.37][b]

[a]Calculated at 298 K after equilibrating the balance at 80 °C followed by NMR analysis at 298 K. $\Delta G^{\circ}_{fold,methyl\ ether} = -RT\ln([folded]/[unfolded])$. [b]Folding energy of the analogous ester balance. [c]Calculated as $\Delta G^{\circ} = -RT\ln([folded]/[unfolded]) - \Delta G^{\circ}_{fold,methyl\ ether}$.

the Eyring equation furnishing the energy barrier for atropisomerization. $\Delta G^{\ddagger}$ values of ≈26 kcal/mol (T = 47 °C) and ≈27 kcal/mol (T = 80 °C) were estimated for the methyl (Figure 1) and the isopropyl ether (Figure 2), respectively.

In addition to the ether balance, an ester balance (**5a**,**b**; Scheme 1) containing three *ortho* substituents along the biaryl

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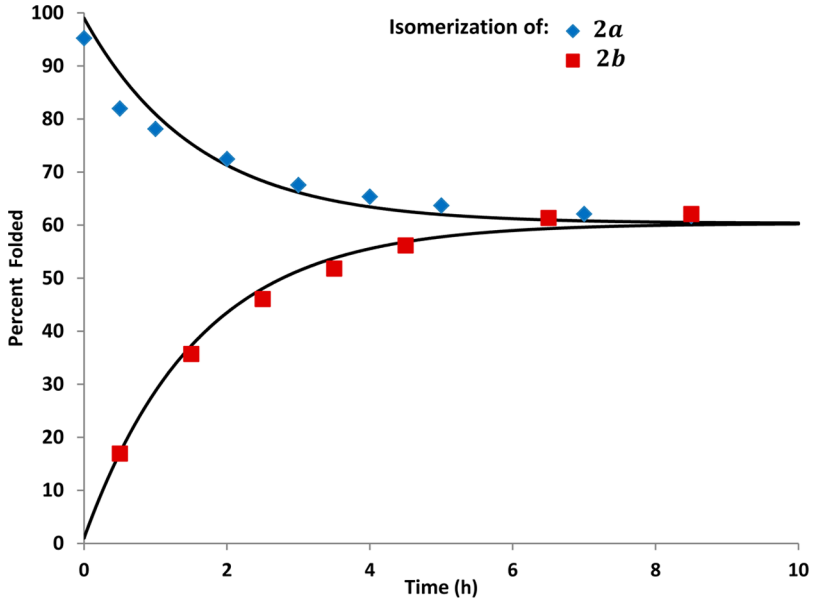

Figure 2. Isomerization kinetics (T = 80 °C) of conformers **2a** and **2b**. Solid lines show the simulated equilibration curves with rate constant values of $k_{fold\rightarrow unfold}$ = 0.25 h^{-1} and $k_{unfold\rightarrow fold}$ = 0.38 h^{-1}.

axis was also synthesized using the standard Suzuki coupling strategy. The conformers of this balance showed no axial isomerization even after heating at 100 °C for 20 h, indicating a much higher rotational barrier. Conformational stability and well-defined architecture could make this kind of balance potentially useful for newer applications.

In conclusion, incorporation of a naphthyl-alkyl ether side arm in the torsion balance allowed for the separation of the folded and unfolded conformers and recording of their folding kinetics for the first time. The ability to separate the two atropisomers and study their conformational dynamics will greatly increase the scope of application of the Wilcox balance.

EXPERIMENTAL SECTION

^{1}H NMR spectra were recorded on a 300 MHz spectrometer, and resonances are given in parts per million relative to the residual solvent resonance ($CHCl_3$ δ 7.26, $(CH_3)_2SO$ δ 2.54). ^{13}C NMR spectra were recorded at 75 MHz and are referenced to the residual solvent ($CDCl_3$ δ 77.0 ppm). High-resolution mass spectra (HRMS) were recorded in the electrospray ionization (ESI) mode on a TOF mass analyzer. IR resonances are given in cm^{-1}.

Representative Procedure for Kinetic Isomerization and Determination of Rate Constants. A NMR tube containing a sample of a pure compound dissolved in DMSO-d_6 was placed in a heated aluminum block maintained at a fixed temperature. The sample tube was withdrawn at different intervals of time and cooled to the room temperature in a water bath, and the NMR spectra were recorded. The equilibrium folding ratio was determined by keeping the sample in the heat bath for a prolonged period of time (several days at 70 °C or 4 h at 140 °C) and checking for constancy in the isomer ratio. The plots for the experimental data were generated in the MS Excel program. In the COPASI program, irreversible first-order rate law equations for folding and unfolding processes, initial concentration values ($[C_{folded}]_0$, $[C_{unfolded}]_0$), and the guess values for the rate constants $k_{fold\rightarrow unfold}$ and $k_{unfold\rightarrow fold}$ were entered according to the software's input format. The values of rate constants were chosen such that the equilibrium condition $k_{fold\rightarrow unfold}[C_{folded}]_{eq} = k_{unfold\rightarrow fold}[C_{unfolded}]_{eq}$ was satisfied with good precision. For given $k_{fold\rightarrow unfold}$ and $k_{unfold\rightarrow fold}$ values, simulation curves were generated for both folding and unfolding processes. These curves were copied and stacked over the experimental data plots in the Excel spreadsheet. The rate constant values in COPASI were varied until the simulation curves matched the experimental data as judged by visual inspection. The energy barriers for atropisomerization ($\Delta G^{\ddagger}$) were calculated using the rate constant values of the best fits in the Eyring equation: $k = (k_B T/h) \times \exp[-\Delta G^{\ddagger}/RT]$.

Representative Procedure for the Suzuki Coupling Reaction. A 6 mL glass vial equipped with a magnetic stir bar and a Teflon screw cap was charged with 8-methoxynaphthalen-1-yl trifluoromethanesulfonate (61 mg, 0.2 mmol), 1,4,7,10-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-6,12-dihydro-5,11-methanodibenzo[*b*,*f*][1,5]diazocine (101 mg, 0.25 mmol), $Pd(OAc)_2$ (1.1 mg, 0.005 mmol), and dicyclohexyl(2′,6′-dimethoxy-[1,1′-biphenyl]-2-yl)phosphine (SPhos, 4.1 mg, 0.01 mmol). After these additions, the vial was purged with argon and 0.5 mL of acetonitrile (HPLC grade), followed by 0.5 mL of 2.0 M Na_2CO_3, was added to it with a syringe. The reaction mixture was then stirred at 80 °C for 4 h in an aluminum block, cooled to room temperature, and then purified using silica gel chromatography (ethyl acetate−hexanes gradient) to yield **1a** and **1b** as amorphous solids.

2-(8-Methoxynaphthalen-1-yl)-1,4,7,10-tetramethyl-6,12-dihydro-5,11-methanodibenzo[*b*,*f*][1,5]diazocine (1a): Yield 21 mg (24%); ^{1}H NMR (300 MHz, $CDCl_3$) (folded) δ 7.76 (dd, J = 1.2 and 8.2 Hz, 1H), 7.5−7.4 (m, 2H), 7.35−7.2 (m, 2H), 7.0 (d, J = 8.2 Hz, 1H), 6.99 (m, 1H), 6.78 (d, J = 8.2 Hz, 1H), 6.6 (dd, J = 1.2 and 8.2 Hz, 1H), 4.5−4.3 (m, 4H), 4.1−4.0 (m, 2H), 2.89 (s, 3H), 2.46 (s, 3H), 2.43 (s, 3H), 2.1 (s, 3H), 1.65 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.6, 146.3, 144.4, 140.5, 138.2, 135.4, 132.6, 130.7, 129.9, 129.0, 128.4, 128.2, 128.0, 127.3, 126.5, 125.7, 125.6, 124.9, 124.8, 124.3, 121.2, 105.8, 66.5, 54.8, 54.3, 54.2, 17.8, 17.1, 14.9; IR 2941, 1506, 1474, 1462, 1373, 1307, 1258, 1219, 1071, 963, 946, 885; HRMS-ESI $[M + H]^+$ calcd for $C_{30}H_{31}N_2O^+$ 435.2431, found 435.2430.

2-(8-Methoxynaphthalen-1-yl)-1,4,7,10-tetramethyl-6,12-dihydro-5,11-methanodibenzo[*b*,*f*][1,5]diazocine (1b): Yield 35 mg (40%); ^{1}H NMR (300 MHz, $CDCl_3$) (unfolded) δ 7.76 (dd, J = 1.1 and 8.2 Hz, 1H), 7.5−7.3 (m, 3H), 7.07 (dd, J = 1.2 and 7.1 Hz, 1H), 7.02−6.99 (m, 1H), 6.88 (s, br, 1H), 6.81 (d, J = 7.5 Hz, 1H), 6.75 (d, J = 7.5 Hz, 1H), 4.47 (dd, J = 8.8 and 16.8 Hz, 2H), 4.35 (s, br, 2H), 4.01 (t, J = 16.3 Hz, 2H), 3.48 (s, 3H), 2.42 (s, 6H), 2.12 (s, 3H), 1.65 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.9, 146.5, 144.1, 140.6, 138.3, 135.4, 132.8, 130.4, 130.3, 129.2, 128.5, 128.4, 127.9, 127.1, 126.8, 125.7, 125.5, 125.0, 124.5, 124.3, 121.2, 106.0, 66.5, 55.7, 54.1, 53.6, 17.8, 17.0, 16.9, 14.8; IR 2939, 1506, 1474, 1460, 1374, 1304, 1257, 1219, 1071, 963, 946, 878; HRMS-ESI $[M + H]^+$ calcd for $C_{30}H_{31}N_2O^+$ 435.2431, found 435.2430.

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2-(8-Isopropoxynaphthalen-1-yl)-1,4,7,10-tetramethyl-6,12-dihydro-5,11-methanodibenzo[*b*,*f*][1,5]diazocine (2a): Yield 20 mg (22%); ^{1}H NMR (300 MHz, $CDCl_3$) (folded) δ 7.75 (dd, J = 1.1 and 8.2 Hz, 1H), 7.5−7.32 (m, 2H), 7.3 (d, J = 7.7 Hz, 1H), 7.18 (dd, J = 1.2 and 7.0 Hz, 1H), 6.98 (d, J = 7.6 Hz, 1H), 6.92 (s, br, 1H), 6.78 (d, J = 7.5 Hz, 1H), 6.55 (d, J = 7.5 Hz, 1H), 4.5−4.36 (m, 4H), 4.11 (m, 1H), 4.03 (d, J = 16.9 Hz, 2H), 2.45 (s, 3H), 2.42 (s, 3H), 2.07 (s, 3H), 1.65 (s, 3H), 0.24 (d, J = 6 Hz, 3H), 0.21 (d, J = 6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.3, 146.4, 144.3, 141.4, 138.4, 135.7, 132.6, 130.2, 129.8, 129.1, 128.5, 127.9, 127.8, 127.2, 126.6, 125.7, 125.4, 125.1, 124.8, 124.7, 120.1, 106.1, 67.7, 66.5, 54.4, 54.2, 20.0, 19.6, 17.7, 17.0, 16.9, 14.8; IR 2972, 1578, 1474, 1374, 1257, 1219, 1114, 1097, 768, 735; HRMS-ESI $[M + H]^+$ calcd for $C_{32}H_{35}N_2O^+$ 463.2744, found 463.2742.

2-(8-Isopropoxynaphthalen-1-yl)-1,4,7,10-tetramethyl-6,12-dihydro-5,11-methanodibenzo[*b*,*f*][1,5]diazocine (2b): Yield 24 mg (26%); ^{1}H NMR (300 MHz, $CDCl_3$) (unfolded) δ 7.75 (dd, J = 1.1 and 8.2 Hz, 1H), 7.5−7.3 (m, 3H), 7.03 (dd, J = 1.2 and 7.5 Hz, 1H), 7.03−6.9 (m, 1H), 6.85 (m, 1H), 6.82 (d, J = 7.5 Hz, 1H), 6.70 (d, J = 7.5 Hz, 1H), 4.5−4.2 (m, 5H), 4.01 (t, J = 18 Hz, 2H), 2.42 (s, 3H), 2.41 (s, 3H), 2.12 (s, 3H), 1.66 (s, 3H), 0.91 (d, J = 6 Hz, 3H), 0.82 (d, J = 6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.3, 146.6, 144.2, 141.4, 138.6, 135.7, 132.8, 130.4, 130.2, 129.2, 128.1, 127.9, 127.2, 126.8, 125.7, 125.4, 125.0, 124.8, 124.6, 120.2, 106.3, 67.9, 66.5, 54.2, 53.7, 20.9, 20.8, 19.6, 17.8, 17.0, 16.8, 14.9; IR 2973, 1579, 1474, 1374, 1258, 1219, 1114, 1097, 768, 731; HRMS-ESI $[M + H]^+$ calcd for $C_{32}H_{35}N_2O^+$ 463.2744, found 463.2744.

2-(8-(Cyclopentyloxy)naphthalen-1-yl)-1,4,7,10-tetramethyl-6,12-dihydro-5,11-methanodibenzo[*b*,*f*][1,5]diazocine (3a): Yield 12 mg (12%); ^{1}H NMR (300 MHz, $CDCl_3$) (folded) δ 7.75 (dd, J = 1.1 and 8.2 Hz, 1H), 7.5−7.3 (m, 3H), 7.11 (dd, J = 1.1 and 8.2 Hz, 1H), 7.02−6.97 (m, 1H), 6.84 (s, br, 1H), 6.78 (d, J = 7.5 Hz, 1H), 6.58 (d, J = 7.5 Hz, 1H), 4.46 (dd, J = 6.3 and 17 Hz, 2H), 4.33 (m, 2H), 4.2−4.4 (m, 1H), 4.0 (m, 2H), 2.43 (s, 3H), 2.41 (s, 3H), 2.1 (s, 3H), 1.6 (s, 3H), 1.4−0.6 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.7, 146.6, 144.3, 141.5, 138.4, 135.5, 132.6, 130.1, 130.0, 129.0, 128.44, 128.42, 128.3, 127.2, 126.6, 125.7, 125.3, 125.0, 124.9, 120.0, 106.3, 78.3, 66.3, 54.2, 53.9, 31.7, 31.4, 30.9, 23.6, 23.1, 17.8, 17.1, 16.9, 14.7; IR 2943, 1577, 1378, 1257, 1097, 824, 769, 735; HRMS-ESI $[M + H]^+$ calcd for $C_{34}H_{37}N_2O^+$ 489.2900, found 489.2900.

2-(8-(Cyclopentyloxy)naphthalen-1-yl)-1,4,7,10-tetramethyl-6,12-dihydro-5,11-methanodibenzo[*b*,*f*][1,5]diazocine (3b): Yield 35 mg (36%); ^{1}H NMR (300 MHz, $CDCl_3$) (unfolded) δ 7.75 (dd, J = 1.1 and 8.2 Hz, 1H), 7.5−7.3 (m, 3H), 7.02−6.97 (m, 2H), 6.84 (s, br, 1H), 6.81 (d, J = 7.5 Hz, 1H), 6.68 (d, J = 7.5 Hz, 1H), 4.58 (m, 1H), 4.46 (dd, J = 6.3 and 17 Hz, 2H), 4.33 (m, 2H), 4.01 (t, J = 17 Hz, 2H), 2.42 (s, 3H), 2.40 (s, 3H), 2.12 (s, 3H), 1.65 (s, 3H), 1.74−1.2 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.9, 146.6, 144.2, 141.3, 138.5, 135.6, 132.9, 130.4, 130.1, 129.1, 128.4, 128.1, 128.0, 127.2, 126.8, 125.7, 125.2, 125.0, 124.6, 124.4, 120.0, 106.0, 78.3, 66.4, 54.2, 53.7, 32.18, 32.14, 24.2, 24.1, 17.8, 17.0, 16.9, 14.8; IR 2942, 1577, 1377, 1257, 1097, 823, 769, 735; HRMS-ESI $[M + H]^+$ calcd for $C_{34}H_{37}N_2O^+$ 489.2900, found 489.2900.

2-(8-(Cyclohexyloxy)naphthalen-1-yl)-1,4,7,10-tetramethyl-6,12-dihydro-5,11-methanodibenzo[*b*,*f*][1,5]diazocine (4a): Yield 27 mg (27%); ^{1}H NMR (300 MHz, $CDCl_3$) (folded) δ 7.75 (dd, J = 1.1 and 8.2 Hz, 1H), 7.5−7.32 (m, 2H), 7.3 (d, J = 7.7 Hz, 1H), 7.11 (dd, J = 1.2 and 7.0 Hz, 1H), 6.98 (m, br, 1H), 6.89 (s, br, 1H), 6.77 (m, J = 7.5 Hz, 1H), 6.64 (d, J = 7.5 Hz, 1H), 4.48 (d, J = 16.9 Hz, 2H), 4.37 (m, 2H), 4.0 (dd, J = 8.8 and 16.9 Hz, 2H), 3.82 (m, 1H), 2.42 (s, 6H), 2.1 (s, 3H), 1.73 (s, 3H),1.5−0.11(m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.2, 141.7, 138.5, 135.7, 132.8, 132.5, 130.3, 130.2, 130.1, 129.2, 128.4, 128.3, 128.1, 127.3, 126.4, 125.6, 125.3, 125.1, 124.8, 120.2, 106.6, 74.6, 66.2, 54.2, 53.9, 53.6, 30.8, 30.6, 25.5, 23.8, 23.6, 17.8, 17.1, 16.9, 14.9; IR 2932, 1505, 1372, 1263, 1063, 823, 735; HRMS-ESI $[M + H]^+$ calcd for $C_{35}H_{39}N_2O^+$ 503.3057, found 503.3055.

2-(8-(Cyclohexyloxy)naphthalen-1-yl)-1,4,7,10-tetramethyl-6,12-dihydro-5,11-methanodibenzo[*b*,*f*][1,5]diazocine (4b): Yield 25 mg (25%); ^{1}H NMR (300 MHz, $CDCl_3$) (unfolded) δ 7.72 (dd, J = 1.1 and 8.2 Hz, 1H), 7.5−7.2 (m, 3H), 7.02 (dd, J = 1.2 and 7.5 Hz, 1H), 7.01 (d, J = 7.5 Hz, 1H), 6.86 (s, br, 1H), 6.80 (d, J = 7.5 Hz, 1H), 6.72 (d, J = 7.5 Hz, 1H), 4.5−4.2 (m, 4H), 4.1−3.9 (m, 3H), 2.41 (s, 3H), 2.40 (s, 3H), 2.1 (s, 3H), 1.6 (s, 3H),1.5−0.5 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.4, 146.7, 144.3, 141.3, 135.8, 132.9, 130.3, 130.2, 129.3, 128.4, 128.3, 128.2, 128.1, 127.3, 126.8, 125.6, 125.2, 125.0, 124.8, 124.7, 120.2, 106.6, 74.1, 66.5, 54.2, 53.7, 31.0, 30.8, 25.8, 23.8, 23.6, 17.8, 17.1, 16.9, 14.9; IR 2939, 1575, 1505, 1371, 1253, 1069, 822, 727; HRMS-ESI $[M + H]^+$ calcd for $C_{35}H_{39}N_2O^+$ 503.3057, found 503.3053.

Cyclopentyl 3-Methyl-2-((2*S*,5*S*,11*S*)-1,4,7,10-tetramethyl-6,12-dihydro-5,11-methanodibenzo[*b*,*f*][1,5]diazocin-2-yl)-benzoate (5a): Yield 12 mg (13%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.62 (dd, J = 1.2 and 7.5 Hz, 1H), 7.31−7.24 (m, 2H), 6.97 (d, J = 7.5 Hz, 1H), 6.76 (d, J = 7.5 Hz, 1H), 6.69 (s, 1H), 4.81 (m 1H), 4.46 (dd, J = 6 and 17 Hz, 2H), 4.31 (m, 2H), 3.92 (dd, J = 4.5 and 17 Hz, 2H), 2.41 (s, 3H), 2.38 (s, 3H), 2.07 (s, 3H), 1.97 (s, 3H), 1.71 (s, 3H), 1.3−0.5 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.0, 146.4, 145.2, 140.5, 137.4, 135.5, 132.7, 132.6, 132.5, 130.2, 129.4, 129.0, 128.5, 127.1, 126.8, 126.4, 126.1, 125.0, 66.2, 54.0, 53.7, 32.0, 31.1, 23.0, 22.9, 20.3, 17.8, 17.06, 16.9, 14.4; IR 2946, 1701, 1436, 1394, 1379, 1335, 1287, 1178, 1096, 1066, 979; HRMS-ESI $[M + H]^+$ calcd for $C_{32}H_{37}N_2O_2^+$ 481.2850, found 481.2848.

Cyclopentyl 3-Methyl-2-((2*S*,5*S*,11*S*)-1,4,7,10-tetramethyl-6,12-dihydro-5,11-methanodibenzo[*b*,*f*][1,5]diazocin-2-yl)-benzoate (5b): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.65 (dd, J = 1.2 and 7.5 Hz, 1H), 7.33−7.24 (m, 2H), 7.02 (d, J = 7.5 Hz, 1H), 6.84 (d, J = 7.5 Hz, 1H), 6.70 (s, 1H), 5.07 (m, 1H), 4.46 (dd, J = 8.8 and 16.2 Hz, 2H), 4.23 (q, J = 12 Hz, 2H), 3.9 (d, J = 16.2 Hz, 2H), 2.43 (s, 3H), 2.37 (s, 3H), 2.12 (s, 3H), 1.92 (s, 3H), 1.7 (s, 3H), 1.6−0.8 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.9, 146.7, 145.4, 140.5, 137.5, 135.5, 132.9, 132.4, 130.6, 130.4, 129.6, 129.0, 128.3, 127.0, 126.87, 126.8, 125.8, 124.9, 66.1, 54.0, 53.5, 32.3, 32.1, 23.8, 23.7, 20.6, 17.8, 17.0, 16.9, 14.3; IR 2946, 1702, 1436, 1394, 1354, 1286, 1178, 1097, 1026, 979; HRMS-ESI $[M + H]^+$ calcd for $C_{32}H_{37}N_2O_2^+$ 481.2850, found 481.2848.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

^{1}H and ^{13}C NMR spectra are provided for the new balances. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: bbhayana@partners.org.

Notes

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