Scalable Synthesis of Strained Cyclooctyne Derivatives

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Received: 28.10.2013; Accepted after revision: 09.12.2013

Abstract: Modifications to the Popik synthesis of aza-dibenzocyclooctyne (DIBAC) derivatives are described, which avoids tedious purifications and dramatically improves the yield. A new and analogous route to biarylazacyclooctynone (BARAC) through an amide disconnection was also attempted. The BARAC derivatives prepared were found to be unstable under the conditions employed, undergoing a known rearrangement. Finally, the synthesis of a difluoro-DIBAC derivative with a second-order rate constant intermediate between DIBAC and BARAC derivatives (0.50 M–1) is described. While more difficult to synthesize, this molecule was found to be considerably more stable than any BARAC derivatives that were prepared.

Key words: cycloaddition, alkynes, azides, click coupling, dibenzocyclooctyne

The reactivity of cyclooctynes toward azides in 1,3-dipolar cycloadditions was first discovered by Blomquist and Liu in 1953,[2] and later confirmed by Wittig and Krebs in 1961.[3] Cyclooctynes are the smallest all-carbon cyclic alkynes that are isolable and stable under ambient conditions. Larger cyclooctynes have minimal ring strain and are much less reactive.[4] Smaller cyclic alkynes can be made in situ, and some are isolable, but, in most cases they quickly decompose.[5] Only a handful of stable, smaller, heteroatom-containing derivatives are known, such as the thiepin derivatives explored by Krebs and colleagues in the 1970s.[6,7] The increased stability of these molecules results from the addition of a sulfur atom within the seven-membered ring to relieve the ring strain. These 'angle-strained' cyclooctynes attracted a great deal of attention in the 1970s and 1980s, and the literature was exhaustively reviewed by Krebs and Wilke in 1983.[5]

The notion of using cyclooctynes for rapid bioconjugation or as 'click' reagents[8] did not appear in the literature until 2004 when Bertozzi introduced the idea of using cyclooctynes instead of terminal alkynes in the 1,3-dipolar Huisgen cycloaddition reaction.[9] This reaction, now referred to as the strain-promoted alkyne–azide cycloaddition (SPAAC) reaction, does not require a copper catalyst, eliminating the dependency of this reaction on a toxic metal, and thereby allowing its use in vivo.[9] Cyclooctynes are also subject to fewer side reactions with nucleophiles relative to other active alkynes, such as acetylene esters, which react with a variety of nucleophiles, hampering their chemical compatibility and rendering them generally unsuitable for biological work.[10]

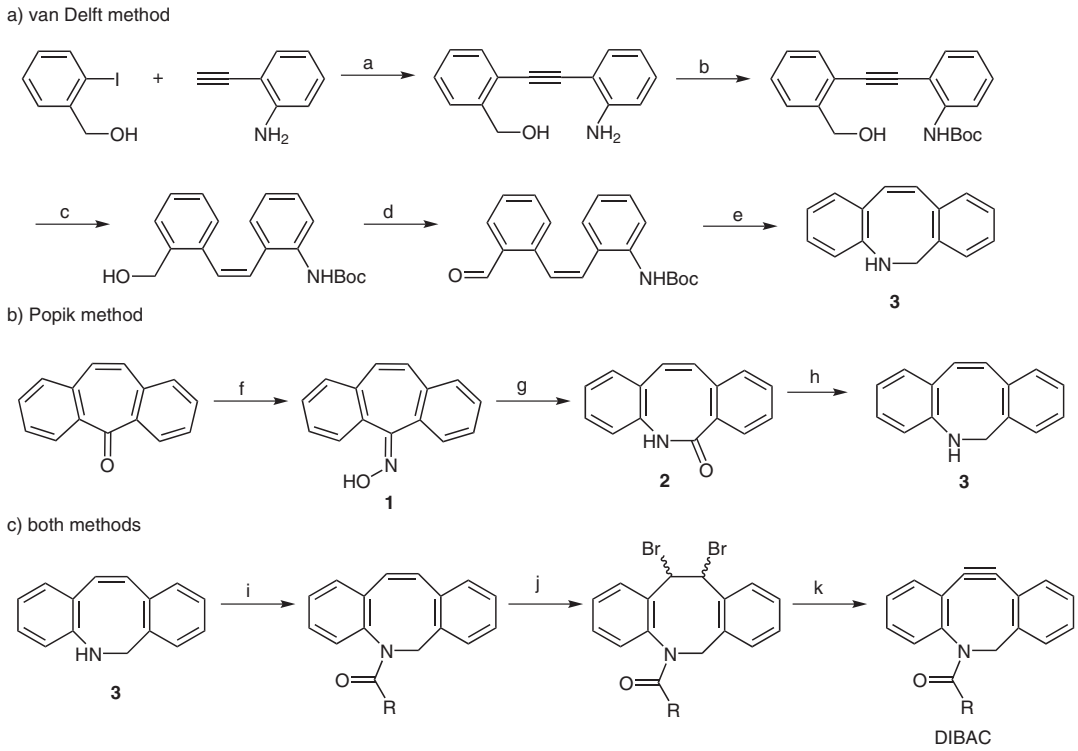
The parent compound, cyclooctyne, is not sufficiently strained to be reactive at low concentrations and temperatures.[5,11] Thus, in most cases where SPAAC is used, a modified or substituted cyclooctyne is needed.[12] The second-order rate constants of several different cyclooctyne derivatives have been measured, including those functionalized with fluorine atoms, amides, and aryl rings.[12] Typically, this rate constant is measured for the reaction between the cyclooctyne in question and benzyl azide in a polar solvent (typically acetonitrile or methanol), and is used to compare the relative reactivities of various cyclooctynes.[12] In general, it has been found that substituents with greater electron-withdrawing character, or ones that introduce additional ring strain via sp^2 centers on the cyclooctyne, increase the reactivity of the alkyne. These effects and their consequences have recently been explored using DFT calculations.[13]

SPAAC has required the development of a new series of cyclooctynes with reactivities, stabilities, and chemical handles suited to their use in larger bio- or macromolecules.[4,12] The most reactive of the stable cyclooctynes are azadibenzocyclooctynes (DIBACs)[14,15] and biarylazacyclooctynones (BARACs).[12,16] In particular, reactions of difluorinated BARAC derivatives with azides exhibit the largest rate constants.[17] The orthogonality of SPAAC reactions to acid, base, and biological conditions[18] has enabled their use in biological applications, such as drug delivery,[19] live cell labeling,[9] bioconjugation of proteins, nucleic acids and polysaccharides,[20] and the synthesis of hydrogels for 3D cell cultures.[21]

Outside of chemical biology, cyclooctynes have had limited application, presumably a result of the synthetic difficulty in their production. The two most commonly used synthetic methods toward DIBACs rely on the synthesis of a common intermediate **3**, followed by bromination and elimination to generate the product (Scheme 1, c). The first method, developed by van Delft and co-workers (Scheme 1, a),[14] utilizes a Sonogashira cross-coupling, followed by a Dess–Martin oxidation and reductive amination to generate intermediate **3**. The Popik method[15] (Scheme 1, b) instead starts with a commercially available tricyclic compound (dibenzosuberenone); the central 7-membered ring is expanded using a Beckmann rearrangement, followed by a lithium aluminum hydride reduction to generate **3**.

The biggest advantage to the van Delft method is the high yield obtained at each step. An overall 70% yield was ob-

SYNTHESIS 2014, 46, 0669–0677
Advanced online publication: 10.01.2014
DOI: 10.1055/s-0033-1340509; Art ID: SS-2013-M0714-OP



Scheme 1 Literature syntheses of DIBAC. *Reagents and conditions*: (a) $PdCl_2(PPh_3)_2$, CuI, Et_3N, THF, N_2/H_2, r.t.; (b) Boc_2O, THF, 70 °C, 2 d; (c) 10% $Pd/BaSO_4$, quinoline, H_2, MeOH, r.t. 1.5 h; (d) Dess–Martin periodinane, $NaHCO_3$, CH_2Cl_2, r.t., 40 min; (e) (1) 2 M HCl in EtOAc, r.t. 1 h, (2) $NaBH_4$, H_2O, r.t., overnight; (f) $NH_2OH{\cdot}HCl$, pyridine, EtOH, reflux, 12 h; (g) polyphosphoric acid, 125 °C, 1 h; (h) $LiAlH_4$, Et_2O, reflux, 15 h; (i) various conditions; (j) Br_2, CH_2Cl_2, 0 °C, 2 h; (k) *t*-BuOK, THF, –40 °C, 2 h.

tained over five steps to synthesize **3**. The Popik method, although having fewer steps, has a much lower overall yield of ca. 40% for the three steps leading to **3**. Nonetheless, the Popik method uses less expensive reagents, is simpler to perform, and displays excellent atom economy. We chose to adapt and further develop the Popik method for synthesizing DIBACs with the aim of producing an easily scalable synthetic route.

Here, we describe our development of a streamlined synthesis of DIBAC derivatives with a focus on scale and simplicity of purification for materials chemists. It also discusses attempts to synthesize BARAC by an analogous route and outlines the synthesis of a difluorinated DIBAC derivative with reactivity intermediate to those of DIBAC and BARAC.

En route to synthesize DIBACs using the Popik method, substantial improvements were made on the original synthesis. In particular, the ring-expanding Beckmann rearrangement, discovered in 1886,[22] which converts an oxime into an amide using an acid catalyst, was the focus of our attention. For the reaction shown in Scheme 2 (a), Popik and co-workers used polyphosphoric acid at 125 °C, affording a 73% yield; Kim and co-workers recently obtained an 89% under the same conditions,[23] and Feringa and colleagues completed the same reaction, but with trichlorotriazine, which resulted in a yield of 67%.[24] The subsequent $LiAlH_4$ reduction has been shown to be equally problematic.[23] Our experience suggests that the root of these problems with inconsistent yield is the poor solubility of the compounds during reaction and workup. Accordingly, we attempted the Beckmann rearrangement with Eaton's reagent, developed in 1973, consisting of a 1:10 solution by weight of phosphorus pentoxide and methanesulfonic acid.[25] Eaton's reagent has been shown to be much more effective in dissolving poorly soluble, nonpolar organic molecules, as well as being more active and amenable to easy workup. The reaction was done in undiluted Eaton's reagent at 100 °C, and, after 30 minutes, showed complete conversion to the product in quantitative yield. When the reaction was scaled up to 50 grams, the same quantitative yields were observed. Furthermore, with this improvement in yield, purification (aside from washing the precipitate with a small volume of ethyl acetate) was not required for either of the first two synthetic steps. The reduction of the amide with $LiAlH_4$, followed by acylation with an acyl chloride was facile. By improving the efficacy of the earlier reactions, we were able to avoid a chromatographic purification until after introduction of the solubilizing side-chain, greatly enhancing the overall yield. This allowed us to generate compound **3** in three steps from the commercially available dibenzosuberenone with greater than 90% yield, on a multi-gram scale.

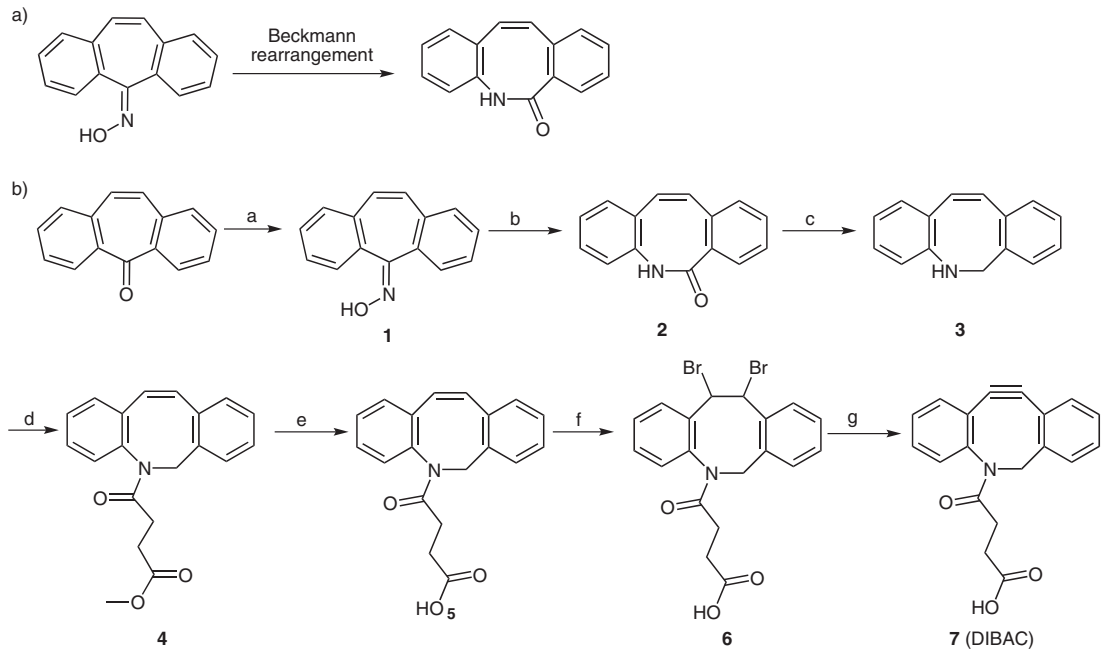
Acylation, bromination, and elimination of the olefin was straightforward (Scheme 2, b), and performed as described in the literature.[14] It should be noted that elimina-

tion with potassium *tert*-butoxide can be problematic if an ester functionality is used as a side-chain protecting group. Yields are highest when ~2.5 equivalents are added slowly, portionwise, as per van Delft and co-workers.[14] However, if the methyl protecting group is removed prior to elimination, this side-reaction is suppressed, and yields are in excess of 90%.

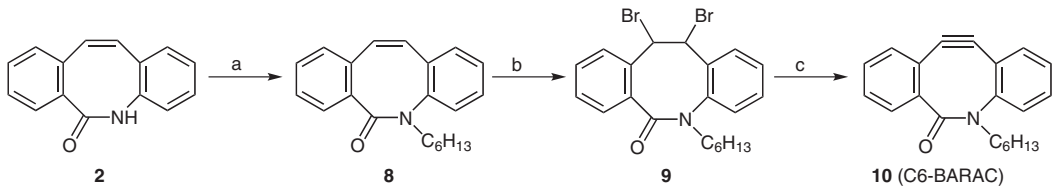
Using this improved synthetic scheme, we were able to substantially increase the yield of the desired DIBAC derivative **7** to 71% over six steps, and reduce purification to only one chromatographic step. It is quite reasonable to complete this procedure in two to three laboratory days – even on a multi-gram scale (Scheme 2).

Considering that our optimized production of the precursor amide **2** is straightforward and scalable, we decided to attempt the synthesis of the more reactive BARAC derivatives using an analogous approach (Scheme 3). Through the use of a toluene/water phase-transfer system (to minimize ring opening), we were able to rapidly alkylate **2** with a number of alkyl bromides in near quantitative yield. This alkylation chemistry was found to be compatible with silyl ether, methyl ester, and tetrahydropyran (THP) protecting groups. This was followed by clean bromination of the double bond in excellent yield.

Unfortunately, elimination of the dibromide precursor using either potassium *tert*-butoxide or KHMDS was ineffective, unpredictable, and low-yielding. We attempted this route on several N-alkylated derivatives. Our side chains included methyl, hexyl, and hexadecyl alkyl chains; THP and TIPS protected propanols; and a 4-carbon methyl ester (Figure 1). We were able to produce two BARAC derivatives in very low yield (hexyl, and TIPS-propanol). The synthesis of these products was confirmed by in situ reaction with benzyl azide and TLC-M/S, as well as ^{1}H NMR analysis (hexyl derivative). Product yields were less than 10%, and both products partially decomposed during flash chromatography on silica gel. Eliminations on the other derivatives showed no evidence of product, but rather yielded highly fluorescent products that failed to react with benzyl azide, yet had the correct mass (determined by electrospray mass spectrometry). We attribute these results to formation of rearrangement products as observed by Chigrinova et al.[18]



Scheme 2 Optimization of DIBAC synthesis. *Reagents and conditions*: (a) $NH_2OH{\cdot}HCl$, pyridine, EtOH, reflux, overnight (98%); (b) Eaton's Reagent, 100 °C, 30 min (97%); (c) $LiAlH_4$, Et_2O, 35 °C, overnight (91%); (d) methyl 4-chloro-4-oxobutyrate, CH_2Cl_2, Et_3N, 0 °C, 2 h (87%); (e) LiOH, MeOH–H_2O, reflux, 16 h, 95%; (f) Br_2, CH_2Cl_2, 0 °C, 2 h, 99%; (g) *t*-BuOK, THF, –40 °C, 2 h, 95%.



Scheme 3 Attempted synthesis of a BARAC. *Reagents and conditions*: (a) 1-bromohexane, sat. aq NaOH, toluene, Bu_4NBr (5 mol%), 60 °C (85%); (b) Br_2, CH_2Cl_2, 0 °C (88%); (c) *t*-BuOK, THF, –40 °C (<10%).

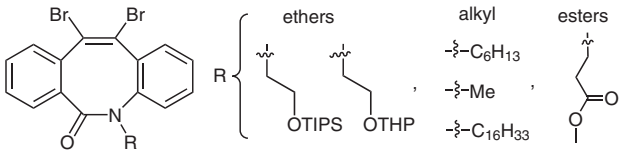


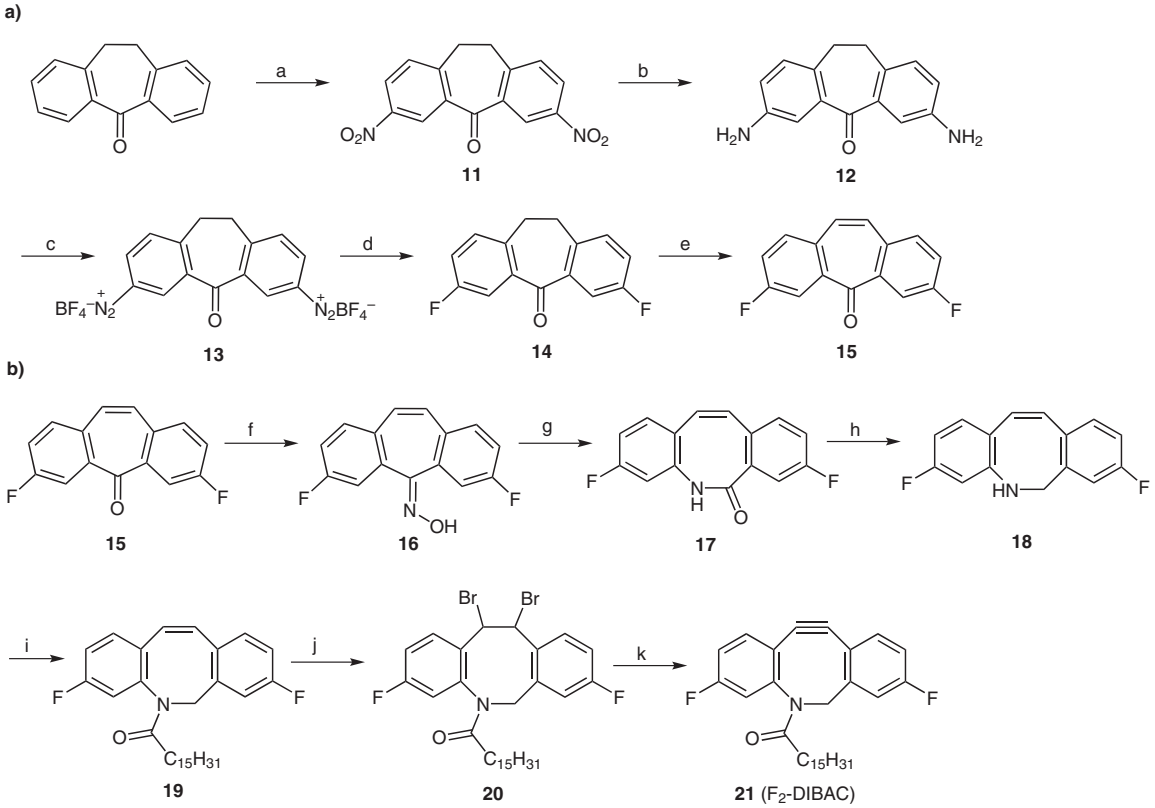
Figure 1 BARAC precursors for elimination attempts

As mentioned, in the rare cases where cyclooctyne compounds were accessible, the yields were low, and the compounds showed only modest stability under ambient conditions. While we have only attempted the synthesis of a relatively small number of the possible derivatives, we do not believe that this is a viable route to BARAC compounds on the scale required for materials chemistry, nor do we believe that BARAC derivatives are sufficiently stable for these uses.

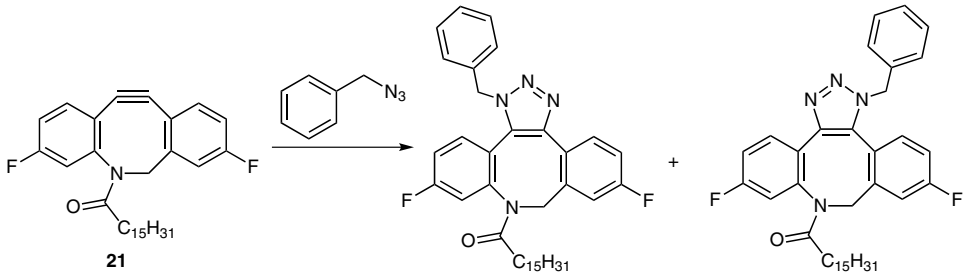
van Delft and co-workers[14] have calculated the second-order rate constant (k) of the parent DIBAC to be 0.31 $M^{-1}s^{-1}$. To date, this is the most reactive DIBAC reported in the literature. In order to produce a DIBAC compound with a reactivity similar to BARAC, a DIBAC derivative was synthesized that was disubstituted in the 2 and 7 positions with fluorine atoms. The synthetic route to difluoro-DIBAC (F_2-DIBAC, **21**) is outlined in Scheme 4 (a).

Using literature procedures,[26,27] 3,7-difluorosuberone was generated in modest yield (Scheme 4, a). The bridging double-bond was introduced using $POCl_3/PCl_5$ according to literature procedures for other suberone derivatives.[28,29] Once the fluorine atoms were in place, the synthesis was carried out in the same manner as the parent DIBAC, with similar yield (Scheme 4, b). A 16-carbon side chain was used to provide solubility to the final alkyne. Following bromination and elimination, *p*-difluoro-DIBAC (**21**) was successfully isolated and its synthesis was confirmed by ^1H and ^{13}C NMR spectroscopy, as well as mass spectrometry.

The reactivity of **21** was compared to the parent DIBAC compound. We measured the second-order rate constant (k) by reacting **21** with benzyl azide (Scheme 5) in acetonitrile-d_6 and monitoring the disappearance of the starting material by ^1H NMR spectroscopy, using hexamethyldisilane (HMDS) as an internal standard. The reciprocal of the concentration of *p*-difluoro-DIBAC was plotted against time to give $k = 0.50$ $M^{-1}s^{-1}$. The same procedure was performed on the parent DIBAC, and the observed rate constant was consistent with that reported in the literature ($k = 0.31$ $M^{-1}s^{-1}$).[14] The kinetic plot for **21** is shown in Figure 2. Thus, a 60% increase in reactivity was achieved with *p*-difluoro-DIBAC, as compared to the parent molecule. This increase in reactivity was almost identical to what has been observed for the 2,7-difluorinated BARAC relative to the nonfluorinated parent compound. As expected, *p*-difluoro-DIBAC is substantially more sta-



Scheme 4 Synthesis of *p*-difluoro-DIBAC (**21**). *Reagents and conditions*: (a) HNO_3, H_2SO_4, 85 °C, 2 h (49%); (b) $SnCl_2$, HCl–AcOH, reflux, 2 h (73%); (c) $NaNO_2$, HBF_4, H_2O, 0 °C to r.t., 2 h (89%); (d) xylene, 125 °C, 3 h (48%); (e) $POCl_3/PCl_5$, 90 °C, 3 h (55%); (f) $NH_2OH{\cdot}HCl$, pyridine, 110 °C, overnight (87%); (g) Eaton's reagent, 100 °C, 30 min (99%); (h) $LiAlH_4$, Et_2O, 35 °C, overnight (94%); (i) palmitoyl chloride, pyridine, CH_2Cl_2, r.t., 4 h (80%); (j) Br_2, CH_2Cl_2, 0 °C, 1.5 h (99%); (k) *t*-BuOK, THF, –40 °C, 2 h (83%).



Scheme 5 Reaction of *p*-difluoro-DIBAC (**21**) with benzyl azide

ble than BARAC; it is stable when stored at room temperature over the course of months, and has no proclivity to react with acetonitrile, even when heated to reflux, unlike BARAC.[18] To our knowledge, difluoro-DIBAC is the most reactive cyclooctyne that remains fully stable under ambient conditions.

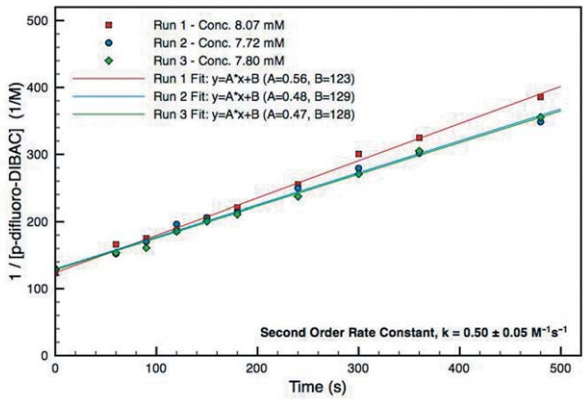


Figure 2 Second order rate constants of **21**; measured from the reaction with benzyl azide in acetonitrile at 25 °C[14]

Dibenzocyclooctynes have many potential uses as orthogonal, reactive functional groups in polymer and materials chemistry. Until now, their use has been limited by the tedious and low-yielding synthetic procedures reported for their preparation. In order to facilitate their adoption in materials chemistry, we have optimized the synthetic route to DIBAC. A key to this improved synthesis was the use of Eaton's reagent to carry out the ring-expanding Beckman rearrangement, which allowed for a substantial increase in reaction scale and a dramatic improvement in yield. While we were unable to develop a similar route to BARAC, it was possible to produce the more stable, yet highly reactive cyclooctyne, *p*-difluoro-DIBAC. We have found this derivative to exhibit the highest reactivity toward azides of any DIBAC derivative that has been reported thus far.

LRMS was performed using electrospray ionization with quadrupole mass analysis (Micromass Quattro Ultima) and HRMS was performed using electrospray ionization with quadrupole/TOF mass analysis. All mass spectra were recorded in positive ion mode (ESI+). ^{1}H and ^{13}C NMR spectra were performed in DMSO-d_6 or $CDCl_3$ and all spectra referenced to the residual solvent peaks. ^{13}C NMR spectra were recorded using the DEPTq or uDEFT pulse sequences.

Kinetic Experiments: Kinetic experiments were performed according to a literature procedure.[16] The C16 derivatives of DIBAC and F_2-DIBAC were reacted with benzyl azide in $CDCl_3$ at a 1:1 ratio and at concentrations of 7.7–8.1 mM. Hexamethyldisilane was used as an internal standard. The conversion was calculated by ^{1}H NMR integration ratios relative to the internal standard. All experiments were performed in triplicate. The second order rate constant was calculated by plotting the reciprocal of substrate concentration versus time and fitting the plot to a linear regression.

5*H*-Dibenzo[*a*,*d*]cyclohepten-5-one oxime (1)[15]

A mixture of absolute EtOH (600 mL) and pyridine (130 mL) was added to a 1 L round-bottomed flask containing hydroxylamine hydrochloride (84.2 g, 1.2 mol), and dibenzosuberenone (50.0 g, 240 mmol). The mixture was stirred and heated to reflux with a heating mantle for 15 h. At this point, TLC showed the complete consumption of starting material (TLC: 5% MeOH in CH_2Cl_2). Once cooled to ca. 35 °C, the reaction mixture was diluted with CH_2Cl_2 (500 mL) and the organic layer was washed with aq 1 M HCl (3 × 200 mL), followed by brine (200 mL). The organic layer was dried (Na_2SO_4), filtered, and evaporated to afford a light brown solid; yield: 52.9 g (98%).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.68–7.67 (m, 1 H), 7.60–7.59 (m, 1 H), 7.45–7.35 (m, 6 H), 6.92 (q, *J* = 12, 18.6 Hz, 2 H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 156.6, 135.5, 134.7, 133.9, 130.9, 130.8, 129.6, 129.3, 129.2, 129.1, 128.9, 127.9, 127.8.

Dibenzo[*b*,*f*]azocin-6(5*H*)-one (2)[15]

A flask was charged with the oxime **1** (50.0 g, 225 mmol) and flushed with dry argon. Eaton's reagent[25] (P_2O_5/$MeSO_3H$, 300 mL) was added in a single portion. The reaction mixture immediately turned dark red. The reaction vessel was placed in an oil bath and stirred at 100 °C. After 30 min, TLC (5% MeOH in CH_2Cl_2) showed complete conversion. The reaction was quenched by the addition of H_2O (1 L) and the product was collected by extraction with multiple volumes of hot EtOAc. The EtOAc fractions were combined and concentrated to ca. 100 mL, and allowed to cool to r.t. The product was collected by filtration, then washed with an additional EtOAc (100 mL) to afford **2** as a light brown powder; yield: 48.4 g (97%); mp >260 °C.

^{1}H NMR (600 MHz, DMSO-d_6): δ = 9.87 (s, 1 H), 7.33–7.31 (m, 2 H), 7.27–7.21 (m, 2 H), 7.17–7.09 (m, 4 H), 7.01 (d, *J* = 11.6 Hz, 1 H), 6.90 (d, *J* = 11.6 Hz, 1 H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 171.7, 136.3, 136.1, 134.4, 133.4, 132.6, 130.1, 128.9, 128.8, 128.0, 127.8, 127.7, 127.4, 126.4, 126.2.

5,6-Dihydrodibenzo[*b*,*f*]azocine (3)[14,15]

Dibenzo[*b*,*f*]azocin-6(5*H*)-one (**2**; 3.00 g, 13.6 mmol) and $LiAlH_4$ (10.3 g, 271 mmol) were added to a 200 mL flame-dried, argon-purged round-bottomed flask. Anhydrous Et_2O (35 mL) was slowly added to the reaction mixture via syringe. The mixture was stirred and heated to reflux for 15 h. TLC (2:1, hexanes–EtOAc) showed

complete disappearance of the starting material. The mixture was cooled in an ice/water bath at 0 °C, and CH_2Cl_2 (150 mL) was added to the flask, followed by the dropwise addition of H_2O until all the $LiAlH_4$ was quenched. An additional amount of H_2O (50 mL) was added, and the inorganic precipitate was removed by filtration. The organic layer was separated, dried (Na_2SO_4), filtered, and the solvent removed by rotary evaporation to give **3** as a yellow solid; yield: 2.54 g (91%); mp 102–104 °C.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.28–7.25 (m, 1 H), 7.21–7.17 (m, 3 H), 6.98 (dd, *J* = 7.8 Hz, 1 H), 6.89 (td, *J* = 7.2 Hz, 1 H), 6.61 (t, *J* = 7.8 Hz, 1 H), 6.55 (d, *J* = 13.2 Hz, 1 H), 6.48 (d, *J* = 7.8 Hz, 1 H), 6.37 (d, *J* = 13.2 Hz, 1 H), 4.59 (s, 2 H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 147.2, 139.4, 138.3, 134.9, 132.9, 130.3, 129.1, 128.2, 127.9, 127.6, 127.6, 122.0, 118.2, 117.9.

MS (ESI-Quad.): *m*/*z* calcd for $C_{15}H_{14}N$ $[M + H]^+$: 208.10; found: 208.2.

Methyl 4-Dibenzo[*b*,*f*]azoncin-5(6*H*)-yl-4-oxobutanoate (4)[30]
Under an argon atmosphere, amine **3** (3.00 g, 14.5 mmol) was dissolved in CH_2Cl_2 (100 mL) and Et_3N (4 mL, ca. 2 equiv) was added, and the mixture was cooled to 0 °C in an ice bath. Methyl 4-chloro-4-oxobutyrate (3.27 g, 2.67 mL, 21.7 mmol) was added dropwise via syringe. The reaction mixture was stirred for 2 h at r.t., at which time TLC (2:1, hexanes–EtOAc) showed complete conversion. The solution was washed with aq 2 M NaOH (3 × 50 mL), aq 2 M (3 × 50 mL), and brine (1 × 100 mL), dried (Na_2SO_4), and filtered. The solvent was evaporated and the product purified by column chromatography (3:1 hexanes–EtOAc). The product **4** was obtained as a white amorphous solid; yield: 4.05 g (87%).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.26–7.24 (m, 5 H), 7.17–7.11 (m, 3 H), 6.79 (d, *J* = 13.2 Hz, 1 H), 6.61 (d, *J* = 13.2 Hz, 1 H), 5.51 (d, *J* = 15 Hz, 1 H), 4.25 (d, *J* = 15 Hz, 1 H), 3.61 (s, 3 H), 2.62–2.57 (m, 1 H), 2.49–2.39 (m, 2 H), 2.04–1.91 (m, 1 H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 173.6, 171.0, 140.7, 136.7, 136.0, 134.8, 132.8, 131.9, 131.0, 130.3, 128.7, 128.4, 128.1, 127.5, 127.1, 54.7, 51.8, 29.7, 29.2.

4-Dibenzo[*b*,*f*]azoncin-5(6*H*)-yl-4-oxobutanoic Acid (5)
A round-bottomed flask equipped with a stir bar was charged with **4** (4.86 g, 15.1 mmol) and MeOH (100 mL). A solution of LiOH (2.17 g, 90.8 mmol) in H_2O (50 mL) was added to the flask. A condenser was attached to the round-bottomed flask and the reaction mixture was stirred and heated to reflux for 16 h. The mixture was quenched with aq 1 M $NaHSO_4$ (100 mL), and then extracted with CH_2Cl_2 (3 × 100 mL). The organic layers were combined and washed with H_2O (100 mL) and brine (100 mL), and then dried (Na_2SO_4), and filtered. The solvent was removed under reduced pressure to afford compound **5** as a white solid, which was used without further purification; yield: 4.45 g (95%).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.30–7.26 (m, 3 H), 7.25–7.22 (m, 2 H), 7.19–7.11 (m, 3 H), 6.81 (d, *J* = 12.6 Hz, 1 H), 6.61 (d, *J* = 12.6 Hz, 1 H), 5.53 (d, *J* = 15.6 Hz, 1 H), 4.30 (d, *J* = 15 Hz, 1 H), 2.63–2.58 (m, 1 H), 2.53–2.49 (m, 1 H), 2.44–2.39 (m, 1 H), 2.08–2.03 (m, 1 H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 176.3, 172.1, 140.2, 136.7, 136.0, 134.3, 133.1, 132.0, 131.0, 130.3, 128.9, 128.6, 128.2, 127.6, 127.4, 127.3, 54.8, 29.9, 29.7.

5-[11,12-Didehydrodibenzo[*b*,*f*]azocin-5(6*H*)-yl]-4-oxobutanoic Acid (7, DIBAC)
A round-bottomed flask was charged with **5** (0.910 g, 2.96 mmol) and CH_2Cl_2 (40 mL). The flask was flushed with argon and the solution was stirred and cooled to 0 °C in an ice/water bath. Br_2 (1.42 g, 0.46 mL, 8.89 mmol) was added dropwise to the mixture in the flask via syringe. According to TLC (10% MeOH in CH_2Cl_2), the reaction was complete after 2 h, at which point the flask was removed from the ice/water bath and CH_2Cl_2 (50 mL) was added to the mixture. The organic layer was washed with sat. aq Na_2SO_3 (3 × 50 mL), H_2O (1 × 50 mL), and brine (1 × 50 mL). The organic layer was dried (Na_2SO_4) and filtered. Finally, the solvent was removed under reduced pressure to give **6** as an off-white solid; yield: 1.38 g (99%, two regioisomers, identity confirmed by TLC-MS and ^{1}H NMR). The product was used immediately in the next reaction.

^{1}H NMR (600 MHz, $CDCl_3$): δ (both regioisomers) = 7.74 (d, *J* = 7.8 Hz, 1 H), 7.66 (d, *J* = 7.2 Hz, 0.5 H), 7.29–7.27 (m, 1 H), 7.23–7.04 (m, 7.5 H), 6.94–6.90 (m, 2 H), 5.88 (d, *J* = 10.2 Hz, 1 H), 5.83 (d, *J* = 15 Hz, 1 H), 5.81 (d, *J* = 7.8 Hz, 0.5 H), 5.25 (d, *J* = 9.6 Hz, 0.5 H), 5.16 (d, *J* = 10.2 Hz, 1 H), 5.15 (d, *J* = 14.4 Hz, 0.5 H), 5.05 (d, *J* = 14.4 Hz, 0.5 H), 4.22 (d, *J* = 15 Hz, 1 H), 2.92–2.87 (m, 1 H), 2.80–2.62 (m, 2.5 H), 2.59–2.51 (m, 2 H), 2.29–2.24 (m, 0.5 H).

Compound **6** (1.34 g, 2.88 mmol), was dissolved in anhydrous THF (50 mL), under argon atmosphere. The reaction mixture was stirred and cooled to –40 °C in an MeCN/dry ice bath. A 1 M solution of *t*-BuOK in THF (10.0 mL, 10 mmol) was added dropwise to the reaction mixture via syringe. After 1.5 h, an additional amount of *t*-BuOK in THF (3 mL) was added to the reaction mixture. According to TLC (10% MeOH in CH_2Cl_2), the reaction was complete after another 30 min of stirring. The flask was removed from the MeCN/dry ice bath and warmed to r.t. The reaction was quenched with aq 1 M $NaHSO_4$ until the pH reached 1. The aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL), the organic layers were combined and washed with H_2O and brine (50 mL each), followed by drying (Na_2SO_4). The solvent was removed under reduced pressure to yield **7** as an off-white solid; yield: 0.85 g (95%); mp 170 °C (dec.).

^{1}H NMR (600 MHz, DMSO-d_6): δ = 11.98 (s, 1 H), 7.66 (d, *J* = 8.4 Hz, 1 H), 7.62 (d, *J* = 7.2 Hz, 1 H), 7.52–7.45 (m, 3 H), 7.39–7.33 (m, 2 H), 7.29 (d, *J* = 7.2 Hz, 1 H), 5.03 (d, *J* = 14.4 Hz, 1 H), 3.63 (d, *J* = 14.4 Hz, 1 H), 2.61–2.56 (m, 1 H), 2.32–2.27 (m, 1 H), 2.21–2.16 (m, 1 H), 1.80–1.76 (m, 1 H).

^{13}C NMR (151 MHz, DMSO-d_6): δ = 173.5, 170.7, 151.4, 148.4, 132.4, 129.6, 128.9, 128.2, 127.9, 127.6, 126.8, 125.1, 122.5, 121.5, 144.3, 108.0, 54.9, 29.2, 28.9.

HRMS (ESI-TOF): *m*/*z* $[M + H]^+$ calcd for $C_{19}H_{15}NO_3$: 306.1130; found: 306.1119.

Anal. Calcd for $C_{19}H_{15}NO_3$: C, 74.74; H, 4.95; N, 4.59. Found: C, 74.27; H, 4.97; N, 4.57.

3,7-Difluorodibenzosuberenone (15)[27]
Adapting a literature procedure,[28,29] 3,7-difluorodibenzosuberone (**14**; 4.6 g, 18.7 mmol) was dissolved in $POCl_3$ (12 mL) under N_2 atmosphere, and PCl_5 (8.5 g, 41 mmol) was added in one portion. The mixture was heated for 5 h at 90 °C. CH_2Cl_2 (10 mL), MeOH (5 mL), and H_2O (5 mL) were added to quench the reaction. This mixture spontaneously refluxed, and was stirred for 4 h. The mixture was extracted with $CHCl_3$ (100 mL) and the organic layer was washed with H_2O (100 mL). After drying (Na_2SO_4), filtration, and evaporation, the residue was recrystallized from EtOH to afford the product **15** as colorless crystals; yield: 2.5 g (55%); mp 162–164 °C, bp 252 °C.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.96 (dd, *J* = 9.9, 2.8 Hz, 2 H), 7.57 (dd, *J* = 8.6, 5.3 Hz, 2 H), 7.37 (ddd, *J* = 8.6, 7.4, 2.8 Hz, 2 H), 7.02 (s, 2 H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 133.75, 133.70, 130.1, 120.39, 120.24, 116.86, 116.70.

HRMS (ESI-TOF): *m*/*z* $[M + H]^+$ calcd for $C_{15}H_9F_2O$: 243.0633; found: 243.0632.

3,7-Difluoro-5*H*-dibenzo[7]annulen-5-one Oxime (16)
Compound **15** (1.5 g, 6.2 mmol) and $NH_2OH{\cdot}HCl$ (1.7 g, 24.3 mmol) were added to a flask followed by pyridine (6 mL) and EtOH (12 mL). The reaction mixture was heated to reflux for 15 h until TLC (20% Et_2O in hexanes) showed full conversion. The mixture

was diluted with EtOAc (200 mL), and washed with aq 1 M HCl (3 × 50 mL). The organic layer was washed with brine (40 mL), and then dried ($MgSO_4$), followed by filtration. The solvent was removed under reduced pressure to obtain compound **16** as off-white crystals; yield: 1.42 g (87%).

^{1}H NMR (600 MHz, DMSO-d_6): δ = 11.72 (s, 1 H), 7.56 (dd, *J* = 9, 6 Hz, 1 H), 7.51 (dd, *J* = 8.4, 6 Hz, 1 H), 7.35–7.28 (m, 4 H), 6.94 (dd, *J* = 12, 1.2 Hz, 2 H).

^{13}C NMR (151 MHz, DMSO-d_6): δ = 163.1, 162.2, 161.4, 160.5, 151.5, 137.2, 137.1, 132.2, 132.1, 131.6, 131.5, 131.3, 131.2, 130.9, 129.9, 129.0, 128.8, 116.1, 116.0, 115.9, 115.8, 115.7, 114.5, 114.4.

HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{10}F_2NO$: 258.0730; found: 258.0723.

3,8-Difluorodibenzo[*b*,*f*]azocin-6(5*H*)-one (17)

Compound **16** (1.4 g, 5.4 mmol) and Eaton's reagent (P_2O_5/$MeSO_3H$, 20 mL) were added to a flask under argon atmosphere. The mixture was stirred and heated to 100 °C. After 30 min, the mixture was cooled, quenched with H_2O (100 mL), then extracted with hot EtOAc (3 × 100 mL). While still warm, the organic layer was washed with H_2O (100 mL) and brine (100 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated in vacuo to obtain compound **17** as a light brown powder; yield: 1.4 g (99%); mp >260 °C; R_f = 0.6 (CH_2Cl_2–MeOH, 95:5).

^{1}H NMR (600 MHz, DMSO-d_6): δ = 10.05 (s, 1 H), 7.22–7.13 (m, 4 H), 7.06 (td, *J* = 8.4, 2.4 Hz, 1 H), 6.98 (d, *J* = 10.8 Hz, 2 H), 6.86 (d, *J* = 11.4 Hz, 1 H).

^{13}C NMR (151 MHz, DMSO-d_6): δ = 170.0, 161.8, 160.2, 137.8, 137.7, 137.6, 137.5, 131.9, 130.7, 130.6, 130.3, 130.2, 129.7, 129.6, 129.5, 116.6, 116.4, 114.3, 114.1, 113.7, 113.6, 113.1, 112.9.

HRMS (ESI-TOF): *m*/z [M + H]$^+$calcd for $C_{15}H_{10}F_2NO$: 258.0730; found: 258.0736.

3,8-Difluoro-5,6-dihydrodibenzo[*b*,*f*]azocine (18)

Compound **17** (0.20 g, 0.78 mmol) and $LiAlH_4$ (0.542 g, 14.28 mmol) were added to an argon-purged flask along with anhydrous Et_2O (8 mL). The reaction mixture was heated to 35 °C for 16 h, whereupon the TLC (2:1 hexanes–EtOAc) showed complete conversion. The mixture was diluted with Et_2O (50 mL) and then slowly poured into a beaker of ice water to quench the $LiAlH_4$. The mixture was filtered and extracted with Et_2O (2 × 50 mL). The combined organic layers were washed with H_2O (50 mL) and brine (50 mL). The organic layer was dried (Na_2SO_4), filtered, and concentrated in vacuo to obtain compound **18** as a yellow solid; yield: 0.18 g (94%); mp >260 °C; R_f = 0.7 (hexanes–EtOAc, 2:1).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.14 (dd, *J* = 8.4, 5.4 Hz, 1 H), 6.97 (td, *J* = 8.4, 2.4 Hz, 1 H), 6.93–6.89 (m, 2 H), 6.48 (d, *J* = 13.2 Hz, 1 H), 6.32 (td, *J* = 7.8, 2.4 Hz, 1 H), 6.27 (d, *J* = 12.6 Hz, 1 H), 6.16 (dd, *J* = 10.8, 2.4 Hz, 1 H), 4.54 (s, 2 H).

^{13}C NMR (151 MHz, DMSO-d_6): δ = 163.2, 162.3, 140.1, 136.4, 136.3, 132.1, 131.9, 131.8, 126.3, 117.9, 115.8, 115.6, 115.0, 114.9, 105.3, 105.2, 104.0, 103.9, 48.9, 29.9.

HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{12}F_2N$: 244.0938; found: 244.0945.

1-[3,8-Difluorodibenzo[*b*,*f*]azocin-5(6*H*)-yl]hexadecan-1-one (19)

Compound **18** (0.15 g, 0.62 mmol) and pyridine (0.15 mL, 1.85 mmol) were added to an argon-purged flask along with CH_2Cl_2 (5 mL). Palmitoyl chloride (0.37 mL, 1.23 mmol) was added dropwise via syringe and the reaction was left to stir at r.t. Two hours later, the mixture was diluted with CH_2Cl_2 (20 mL) and washed with aq 1 M HCl (3 × 20 mL), H_2O (20 mL), and brine (20 mL). After drying (Na_2SO_4), filtering, and concentrating in vacuo, the crude product was purified by column chromatography (1:1, CH_2Cl_2–hexanes) to obtain **19** as a slow-to-solidify, white, amorphous solid; yield: 0.24 g (80%); mp 108–110 °C; R_f = 0.4 (CH_2Cl_2).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.28–7.25 (m, 1 H), 7.12–7.09 (m, 1 H), 7.03–6.99 (m, 2 H), 6.92–6.87 (m, 2 H), 6.69 (d, *J* = 13.2 Hz, 1 H), 6.49 (d, *J* = 13.2 Hz, 1 H), 5.45 (d, *J* = 15 Hz, 1 H), 4.14 (d, *J* = 15 Hz, 1 H), 2.06–2.01 (m, 1 H), 1.93–1.88 (m, 1 H), 1.49–1.44 (m, 2 H), 1.31–1.05 (m, 25 H), 0.88 (t, *J* = 6.6 Hz, 3 H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 195.3, 134.3, 134.2, 132.9, 132.8, 131.5, 126.1, 117.4, 117.3, 115.6, 115.5, 115.4, 114.5, 114.3, 54.5, 34.7, 29.9, 29.8, 29.7, 29.6, 29.5, 29.4, 29.2, 25.4, 22.9, 14.3.

HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{31}H_{42}F_2NO$: 482.3234; found: 482.3233.

1-[11,12-Dibromo-3,8-difluoro-11,12-dihydrodibenzo[*b*,*f*]azocin-5(6*H*)-yl]hexadecan-1-one (20)

Compound **19** (0.15 g, 0.31 mmol) was placed in an argon-purged flask along with CH_2Cl_2 (10 mL) and the solution was cooled to 0 °C. Br_2 (0.03 mL, 0.62 mmol) was added via syringe and the reaction was left to stir for 1.5 h at 0 °C until full conversion was observed by TLC (1:1, CH_2Cl_2–hexanes). The reaction was diluted with CH_2Cl_2 (50 mL), washed successively with sat. aq Na_2SO_3 (2 × 50 mL), H_2O (50 mL), and brine (50 mL). The organic layer was dried (Na_2SO_4), filtered, and concentrated in vacuo to obtain compound **20** as a light yellow solid; yield: 0.20 g (99%, 2 regioisomers). TLC/MS confirmed the presence of two regioisomers; R_f = 0.2 (1:1, CH_2Cl_2–hexanes).

^{1}H NMR (600 MHz, $CDCl_3$): δ (both regioisomers) = 7.72 (dd, *J* = 9, 5.4 Hz, 1 H), 7.04 (dd, *J* = 9, 6 Hz, 1 H), 6.91–6.88 (m, 2 H), 6.73 (dd, *J* = 8.4, 2.4 Hz, 1 H), 6.65 (dd, *J* = 9, 2.4 Hz, 1 H), 5.85 (d, *J* = 10.2 Hz, 1 H), 5.81 (d, *J* = 15 Hz, 1 H), 5.11 (d, *J* = 10.2 Hz, 1 H), 4.08 (d, *J* = 15 Hz, 1 H), 2.33–2.28 (m, 1 H), 2.13–2.07 (m, 1 H), 1.72–1.63 (m, 2 H), 1.30–1.22 (m, 33 H), 0.87 (t, *J* = 7.2 Hz, 4 H).

^{13}C NMR (151 MHz, $CDCl_3$): δ (both regioisomers) = 173.6, 163.9, 163.2, 162.3, 161.5, 139.1, 139.0, 135.3, 135.2, 134.7, 134.6, 133.2, 132.4, 132.3, 131.0, 130.9, 118.1, 117.9, 117.1, 116.9, 116.8, 116.7, 116.0, 115.9, 59.2, 54.8, 52.2, 36.2, 32.1, 29.9, 29.8, 29.7, 29.6, 29.5, 25.3, 22.9, 14.3.

HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{31}H_{42}Br_2F_2NO$: 640.1601; found: 640.1589.

1-[3,8-Difluoro-11,12-didehydrodibenzo[*b*,*f*]azocin-5(6*H*)-yl]hexadecane-1-one (21, F_2-DIBAC)

Compound **20** (0.15 g, 0.23 mmol) was placed in an argon-purged flask along with anhydrous THF (5 mL) and the solution was stirred and cooled to –40 °C. A 1 M solution of *t*-BuOK in THF (0.47 mL, 0.47 mmol) was added dropwise and the reaction was stirred at –40 °C. After 1 h, another portion of 1 M *t*-BuOK in THF (0.23 mL, 0.23 mmol) was added dropwise. After 1 additional hour, the reaction was completed and the mixture was poured into H_2O (50 mL). The product was then extracted with CH_2Cl_2 (3 × 30 mL). The organic layers were combined and washed with H_2O (50 mL) and brine (50 mL). After drying (Na_2SO_4), filtering, and concentrating in vacuo, the crude product was purified by column chromatography (1:10, Et_2O–hexanes) to obtain **21** as a white solid; yield: 0.093 g (83%); mp 74–75 °C; R_f = 0.3 (1:5, Et_2O–hexanes).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.43 (dd, *J* = 9.6, 3 Hz, 1 H), 7.36 (dd, *J* = 8.4, 6 Hz, 1 H), 7.19 (dd, *J* = 8.4, 5.4 Hz, 1 H), 7.11 (td, *J* = 8.4, 2.4 Hz, 1 H), 7.07 (dd, *J* = 9, 2.4 Hz, 1 H), 7.00 (td, *J* = 8.4, 2.4 Hz, 1 H), 5.09 (d, *J* = 13.8 Hz, 1 H), 3.63 (d, *J* = 13.8 Hz, 1 H), 2.22–2.17 (m, 1 H), 1.98–1.93 (m, 1 H), 1.44–1.36 (m, 2 H), 1.30–0.98 (m, 25 H), 0.88 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 173.7, 163.3, 162.8, 161.7, 153.3, 153.2, 150.6, 150.5, 128.1, 128.0, 126.9, 126.8, 120.4, 120.2, 117.4, 117.2, 115.5, 115.4, 115.3, 115.1, 114.1, 106.9, 66.1, 55.1, 34.9, 32.1, 29.9, 29.8, 29.7, 29.6, 29.4, 29.0, 25.5, 22.9, 14.3.

HRMS (ESI-TOF): *m/z* [M + H]$^+$ calcd for $C_{31}H_{40}F_2NO$: 480.3078; found: 480.3060.

Anal. Calcd for $C_{31}H_{39}F_2NO$: C, 77.63; H, 8.20; N, 2.92. Found: C, 77.75; H, 8.20; N, 2.82.

***N*-Hexyldibenzo[*b*,*f*]azocin-6(5*H*)-one (8)**

Compound **2** (1.105 g, 5.00 mmol) was suspended in toluene (30 mL). Hexyl bromide (1.8 g, 10 mmol), and Bu_4NBr (200 mg, 0.6 mmol) were added, followed by sat. aq NaOH (30 mL). The mixture was stirred at 90 °C for 30 min until the reaction mixture turned completely clear and TLC (20% EtOAc in hexanes) showed complete conversion. The mixture was diluted with toluene (30 mL) and the NaOH layer separated. The organic layer was washed with H_2O (3 × 50 mL) and brine (1 × 50 mL), then dried ($MgSO_4$), and filtered. The residue was then adsorbed onto silica gel and the hexyl bromide was eluted with 100% hexanes, followed by the product with 100% CH_2Cl_2; yield: 1.30 g (85%); white amorphous solid.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.36 (s, 1 H), 7.19 (s, 4 H), 7.13 (td, *J* = 7.1, 2.1 Hz, 1 H), 7.08 (d, *J* = 7.7 Hz, 1 H), 6.98–6.96 (m, 1 H), 6.96 (d, *J* = 11.5 Hz, 1 H), 6.85 (d, *J* = 11.4 Hz, 1 H), 4.45 (ddd, *J* = 13.2, 9.2, 6.6 Hz, 1 H), 3.23 (ddd, *J* = 13.3, 9.3, 4.9 Hz, 1 H), 1.49 (m, 1 H), 1.39 (m, 1 H), 1.32 (m, 1 H), 1.25 (m, 5 H), 0.85 (t, *J* = 7.0 Hz, 3 H).

^{13}C NMR (151 MHz, $CDCl_3$, uDEFT): δ = 170.9, 141.5, 137.7, 136.3, 133.5, 133.3, 129.7, 128.6, 128.5, 127.6, 127.6, 127.3, 126.9, 126.9, 105.1, 50.7, 31.7, 28.0, 26.8, 22.7, 14.2.

***N*-Hexyl-11,12-didehydrodibenzo[*b*,*f*]azocin-6(5*H*)-one (10, C6-BARAC)**

Compound **8** (0.36 g, 1.2 mmol) was placed in an argon-purged flask along with CH_2Cl_2 (10 mL) and the solution was cooled to 0 °C. Br_2 (220 mg, 1.4 mmol) was added via syringe and the reaction mixture was left to stir for 2 h at 0 °C until full conversion was observed by TLC (product R_f = 0.6, CH_2Cl_2). The mixture was diluted with CH_2Cl_2 (50 mL), and the organic layer was successively washed with Na_2SO_3 (2 × 50 mL), H_2O (50 mL), and brine (50 mL). The organic layer was dried (Na_2SO_4) and concentrated. The yellow residue was filtered through silica gel (eluent: 100% CH_2Cl_2) to obtain compound **9**; yield: 0.490 g (88%, 2 regioisomers) as a white, amorphous solid. The presence of two regioisomers and the identity of **9** were confirmed by TLC/MS (ESI-Quad.). The product was used immediately in the next reaction. Compound **9** (490 mg, 1.05 mmol) was dissolved in anhydrous THF (50 mL) under argon atmosphere. A solution of 1 M *t*-BuOK THF (2.1 mL, 2.1 mmol) was added dropwise and the reaction was stirred at –40 °C. After 1 h, another portion of 1 M *t*-BuOK in THF (1.05 mL, 1.05 mmol) was also added dropwise. The solution turned bright purple. After one additional hour, the mixture was poured into H_2O (50 mL). The product was then extracted with CH_2Cl_2 (3 × 30 mL). The red/orange organic layers were combined and washed with H_2O (50 mL) and brine (50 mL), then dried ($MgSO_4$), filtered, and evaporated to dryness in vacuo. Purification of the product **10** by column chromatography was fruitless, as the product decomposed in solution and on the column. Nonetheless, after 2 columns (10% EtOAc in hexanes), ca. 50 mg of partially pure (ca. 80%) product was obtained. ^{1}H NMR, ESI + MS, and derivatization with benzyl azide confirmed the product identity.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.60–7.59 (m, 1 H), 7.56 (dd, *J* = 7.8, 1.0 Hz, 1 H), 7.47–7.43 (m, 4 H), 7.40–7.35 (m, 2 H), 3.08–3.03 (m, 1 H), 2.66 (m, *J* = 4.5 Hz, 1 H), 1.56–1.50 (m, 1 H), 1.43–1.31 (m, 3 H), 1.30–1.23 (m, 2 H), 1.23–1.16 (m, 2 H), 0.88–0.84 (m, 3 H).

^{13}C NMR (151 MHz, uDEFT, $CDCl_3$): δ = 176.8, 155.2, 149.8, 130.5, 129.40, 129.38, 128.8, 128.1, 127.88, 127.88, 126.5, 126.0, 122.8, 122.4, 110.1, 109.3, 51.7, 31.5, 29.2, 26.4, 22.7, 14.1.

MS (ESI-TOF): *m/z* [M + H]$^+$ calcd for $C_{21}H_{21}NO$: 304.17; found: 304.2.

Note: The product decomposed at r.t. on the timescale of days. Attempts with other side-chains, using the same procedure, were less successful.

Acknowledgment

Financial support for this work was provided by the National Science and Engineering Research Council of Canada (NSERC). R.C. is grateful for support through the Ontario Graduate Scholarships (OGS) program.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis.

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