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Facile Rearrangement of the 6,11-Diphenyldibenzo[*b*,*f*][1,4]diazocine Skeleton into a Substituted 2-(2-Aminophenyl)-1,3-diphenylisoindole via Anomalous Carbolithiation or Hydrolithiation: Corroboration of Operative SET Processes[‡]

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In memory of our late colleague and friend, Wei Liu (1982–2014)

Keywords: Rearrangement / Carbolithiation / Hydrolithiation / SET addition / Nitrogen heterocycles / Lithiation

The starting 6,11-diphenyldibenzo[*b*,*f*][1,4]diazocine has been individually treated with R–Li reagents in THF, where R = AlH_4, $PhCH_2$, Ph_2CH, Ph_3C, CH_3, $CH_3(CH_2)_3$, C_6H_5 or Ph–C≡C, to learn whether an expected 1,2- or 1,4-addition would cleanly occur. Contrary to such an assumption based on nucleophilic attack, this [1,4]diazocine with $PhCH_2Li$ yielded only the enantiomers of (4b,11*R*)-11-benzyl-4b,11-diphenyl-4b,11-dihydro-5*H*-benzo[4,5]imidazo[2,1-*a*]isoindole; with Ph_2CHLi yielded 2-[1-(4-benzhydrylphenyl)-phenyl-2*H*-isoindol-2-yl]analine; and with $LiAlH_4$ 2-(2-aminophenyl)-1,3-diphenylisoindole. Finally, individual reactions of the [1,4]diazocine with CH_3Li, *n*BuLi or PhLi gave 4–5 inseparable products, instead of any simple 1,2 or 1,4 adduct. The anomalous carbolithiations and hydrolithiation observed are irreconcilable with a nucleophilic mechanism but in excellent accord with a SET radical-anion pathway.

Introduction

Known Diphenyldibenzodiazocine Isomers

Our interest in nitrogen analogs of cyclooctatetraene (**1**) has stemmed from the rigid, tub-shape of **1** itself and all other nitrogen analogs of **1**.[2] In our reinvestigation of the purported 3,4,7,8-tetraphenyl-1,2,5,6-tetraazocine,[3] we determined that no such structure was isolated but that the putative substance is actually the well-known 2,4,5-triphenylimidazole.[4] Further literature search ascertained that the three isomers depicted in **2**, **3** and **4** have all been prepared and characterized by spectral, elemental and molecular mass analyses.[5–7] A single-crystal X-ray diffraction study on **2** had already been performed,[8] as shown in Figure 1. In addition, Rheingold's and our group have carried out X-ray diffraction and supplemental spectral measurements on **3** and **4**, as depicted in Figures 2 and 3.[1,9]

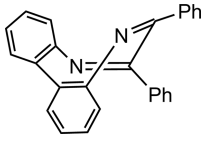

Figure 1. 6,7-Diphenyldibenzo[*e*,*g*][1,4]diazocine (**2**).

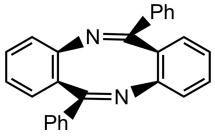

Figure 2. 6,12-Diphenyldibenzo[*b*,*f*][1,5]diazocine (**3**).

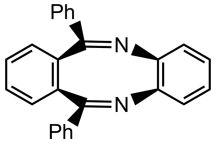

Figure 3. 6,11-Diphenyldibenzo[*b*,*f*][1,4]diazocine (**4**).

The three-dimensional structures of diazocines **2**, **3** and **4** all have a tub-shaped configuration of the eight-membered

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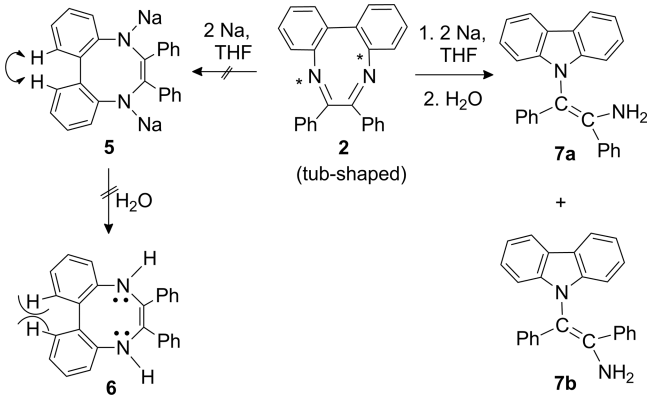
central ring. This brings the transannular C=N groups into closer proximity.

Tub-Shaped Diazocines as Effective Probes of Possible Aromatic Structures Involved in SET Reactions

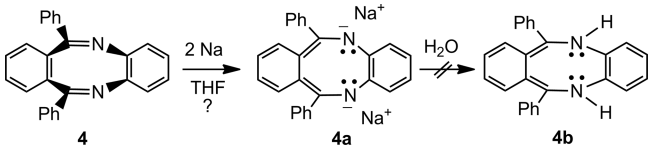
Our initial goal in synthesizing efficiently such diazocines as **2**, **3** and **4** was to learn whether these heterocycles would be capable of adding two electrons to form planar Hückel aromatic ten *pi*-electron eight-membered dianions or protonated dihydrodiazocenes and/or undergoing transannular reactions typical of the parent cyclooctatetraene (**1**). To that end, tub-shaped **2** in THF was treated with an excess of a suspension of sodium or lithium metal at 25 °C, with the expectation of generating the salt **5** or upon hydrolysis, neutral **6**. However, hydrolytic workup and fractional recrystallizations provided none of **6** but separate crystals of the *Z*- and *E*-isomers of enamines **7a** and **7b**, each of which separated isomers was examined by X-ray crystallography and was found to have the assigned structure.[8] Clearly, the profound rearrangement of diazocine **2** upon reduction with sodium must have involved transannular bonding in the transition state between the asterisked N and C sites in **2** (Scheme 1). Because of the tub-shape of **2**, reaching such a transition state apparently requires less energy than attaining the necessary planarity for Hückel aromaticity.[10]



Scheme 1.

In order to avoid the destabilizing *ortho*-H repulsions in **5** (bracketed by arrows), we then examined the analogous electron-transfer reduction of isomers of **2** namely, 6,12-diphenyldibenzo[*b*,*f*][1,5]diazocine (**3**) (Figure 2) and 6,11-diphenyldibenzo[*b*,*f*][1,4]diazocine (**4**) (Figure 3).

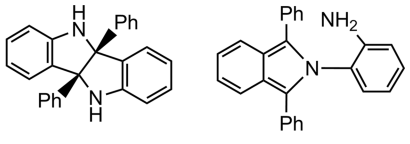
Of the two diazocines **3** and **4**, the latter structure **4** appeared more promising because the intermediate sodium salt **4a** puts the negative charge on both N-centers (Scheme 2). Despite this seemingly favorable structural feature for **4**, neither diazocine **3** or **4** yielded the desired dihydro derivative of a planar ten-π-electron Hückel aromatic system upon reduction with sodium or lithium metal in THF and subsequently hydrolysis. For example, in Scheme 2 the expected aromatic dihydro product **4b** anticipated from **4** was not found. Instead, such reduction of **3** or **4** yielded the interesting transannular dihydro isomer **8**, or the highly unusual rearranged isomer **9**, respectively (actually akin to the rearranged dihydro isomers **7a** and **7b** obtained in the reduction of **2**, Scheme 1). Likewise, the reduction of either **3**[8] or **4**[1] with alternative one-electron SET reductants such as Ti(O*i*Pr)$_2$ also yielded such unexpected products.



Scheme 2.

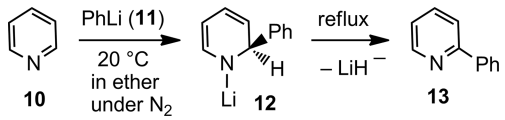
Thus no experimental evidence has been found for the intermediacy of any planar ten-*pi*-electron dianion or dihydro derivative in such SET reductions. Apparently, the X-ray crystal structures of tub-shaped **3** and **4** hold the *trans*-imino groups in such close proximity that the electron density of the radical anion of the one imino (–C=N–) group can readily delocalize over the other –C=N– group.

In summary then, despite our failure to achieve the primary goal of generating ten-*pi* electron Hückel aromatic systems such as **6** or **4b**, this research has uncovered novel reductive rearrangements leading to most interesting and versatile heterocycles, widely useful in synthesis,[6] **7a**, **7b**, **8** and **9**.

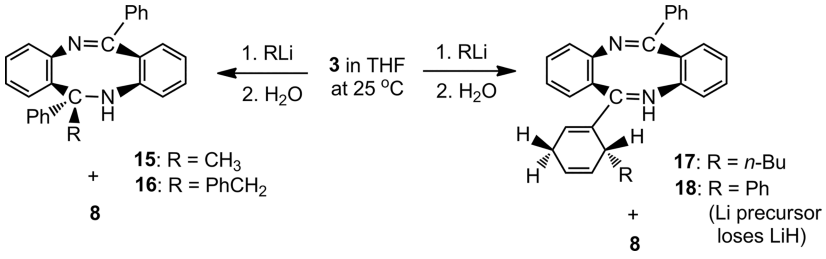


Nature of the Carbolithiation Mechanism with Diazocines

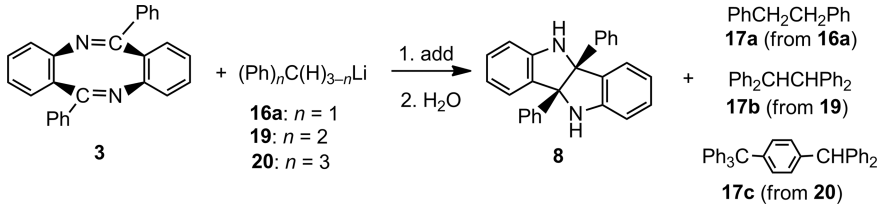
Perhaps the most interesting reaction of azaaromatic nuclei is their ready carbolithiation by organolithium reagents, which reaction was discovered accidentally by Karl Ziegler and co-workers, when they were evaluating pyridine (**10**) as a solvent for the polar phenyllithium oligomer (**11**) (Scheme 3).[11] Addition of **11** to yield soluble adduct **12** at 20 °C is followed by elimination of LiH in refluxing ether to produce 2-phenylpyridine (**13**). Alternatively, direct hydrolysis of **12** yields the 1,2-dihydro derivative of **13**. An analogous 1,2-carbolithiation of quinoline, isoquinoline and phenanthridine and a 1,4-addition to the central ring of acridine have been achieved.[12] Because of the high polarity of the C–Li bond (in the extreme, a C$^-$···Li$^+$ ion pair), it has been proposed that such carbolithiations be considered as nucleophilic additions.[13]



Scheme 3.



Scheme 4.



Scheme 5.

Therefore, to define the mechanistic nature of such carbolithiations experimentally, we had set out in the previous publications[9] to examine the nature and scope of the reactions of diazocine **3** with a variety of alkyl-, aryl-, 1-alkynyl- and benzyl-lithium reagents. All of these reagents except the 1-alkynyllithium, Ph–C≡C–Li (**14**) underwent 1,2-carbolithiation or 1,4-carbolithiation when allowed to react in a molar ratio of **3**/RLi = 1.0:1.1 at 25 °C in THF (Scheme 4).

The observed 1,2- and 1,4-carbolithiations summarized in Scheme 4 can readily be rationalized as taking place via 1,2- or 1,4-nucleophilic addition, but the formation of indoloindole **8** cannot be the result of any such process. A further compelling observation was made when diazocine **3** was treated individually with benzyllithium (**16a**), benzhydryllithium (**19**) and tritylithium (**20**) in a molar ration of **3**/RLi = 1.0:2.2 in refluxing THF for 24 h. Under such conditions and after final hydrolysis, all of **3** was converted into **8** quantitatively and the benzyl, benzhydryl and trityl groups were converted in high yield into the expected dimers, bibenzyl (**17a**) 1,1,2,2-tetraphenylethane (**17b**) and (4-benzhydrylphenyl)triphenylmethane (**17c**), known to be the coupling product of trityl radicals (Scheme 5).[9a] The yields of such dimers (**17a**–**17c**) ranged from 90–99% of the theoretical amount. Clearly, processes other than simple nucleophilic additions must be operative in these transformations.

In order to discern the operative reaction mechanism more clearly in the present study, we then scrutinized the reactions of diazocine **4** with the same three benzylic lithium reagents **16a**, **19** and **20**. Surprisingly, we found that although all three lithium reagents readily reacted, in no case did any simple 1,2- or 1,4-addition result but rather SET reactions involving free radicals predominated in the product formation.

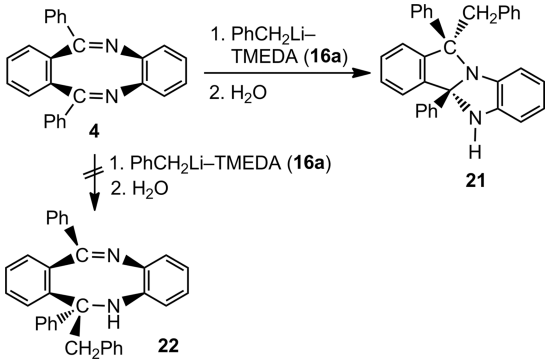
Results

Overall Reactions of 6,11-Diphenyldibenzo[*b*,*f*][1,4]diazocine (4) with Various Lithium Reagents

These reactions of diazocine **4**, with the same lithium reagents as chosen for diazocine **3**, were performed on the same scale and under the same reaction conditions: a 2.2:1.0 molar equivalent ratio of RLi/**4** on a millimolar scale in THF for 24 h at 25 °C before hydrolysis. The total array of organolithium reagents evaluated were the following: benzyllithium·TMEDA (**16a**), benzylhydryllithium (**19**), tritylithium (**20**), methyllithium (**16b**) *n*-butyllithium (**16c**) phenyllithium (**11**) and phenylethynyllithium (**14**). Under these conditions all these organolithiums, except **14**, reacted with diazocine **4** completely. Neither at 25 °C for 24 h nor at reflux for 8 h additionally did **14** show any reaction.

Reaction of Diazocine 4 with Benzyllithium (16a)

Diazocine **4** (1 equiv.) was allowed to react with 2.2 equiv. of benzyllithium–TMEDA complex **16a** in THF at room temperature for 24 h (Scheme 6). Upon hydrolytic workup, (4b*S*,11*R*)-11-benzyl-4b,11-diphenyl-4b,11-dihydro-



Scheme 6.

5*H*-benzo[4,5]imidazo[2,1-*a*]isoindole (**21**) was formed exclusively by a kinetically controlled and *exo*,*syn* addition of **16a** transannularily across the eight-membered ring of **4**. Compound **21** was recrystallized from absolute ethanol as colorless crystals, m.p. 174–175 °C (Scheme 6). Bibenzyl (**17a**) was also found in 6% yield, apparently by the dimerization of **16a**. The expected product from a 1,2-*exo*,*syn*-addition of benzyllithium (**16a**) to **4** (cf. ref.[9]), namely **22**, was not found.

The ^{1}H-NMR spectrum of (4b*S*,11*R*)-11-benzyl-4b,11-diphenyl-4b,11-dihydro-5*H*-benzo[4,5]imidazo[2,1-*a*]isoindole (**21**) has 26 protons, including a N–H at δ = 2.20 ppm and CH_2 doublets at δ = 3.11 and 3.52 ppm; the ^{13}C-NMR spectrum has the appropriate number of ^{13}C signals of 28, including Ph–CH_2 at δ = 30.90 ppm, N–CAr^2 at δ = 44.73 ppm and N–C–N at δ = 76.58 ppm; the infrared spectrum has a N–H stretch at 3408 cm^{-1}. The 3-D X-ray crystal structure has been determined as **21**, which structure shows that the two phenyl groups are *syn* to each other (**21** in Scheme 6).

The X-ray data were obtained from the racemic mixture **21** and are presented for the enantiomer drawn in Figure 4.

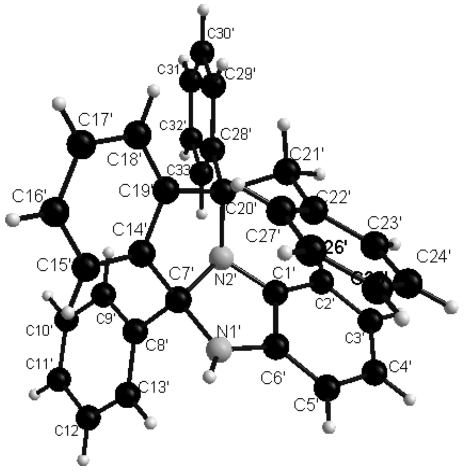
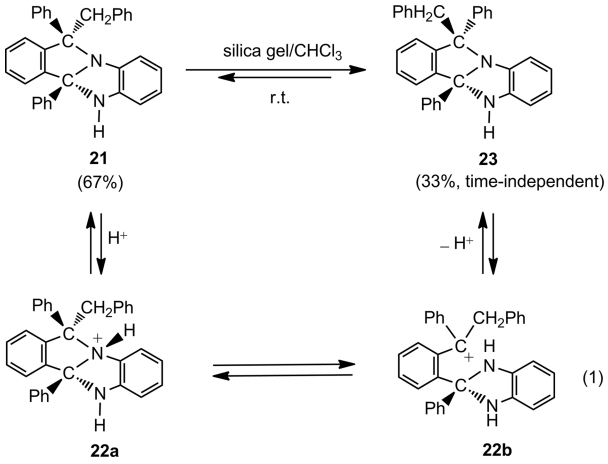


Figure 4. Thermal ellipsoid (30%) diagrams for (4b*S*,11*R*)-11-benzyl-4b,11-diphenyl-4b,11-dihydro-5*H*-benzo[4,5]imidazo[2,1-*a*]-isoindole (**21**). Selected bond lengths (atom separations) [Å] and bond angles of (4b*S*,11*R*)-11-benzyl-4b,11-diphenyl-4b,11-dihydro-5*H*-benzo-[4,5]imidazo[2,1-*a*]isoindole (**21**) are shown as the following: N(1)–C(6) 1.406(2), N(1)–C(7) 1.479(2), N(2)–C(1) 1.413(2), N(2)–C(20) 1.492(2), N(2)–C(7) 1.494(2), C(7)–C(14) 1.501(2), C(7)–C(8) 1.533(2), C(14)–C(19) 1.385(2), C(20)–C(28) 1.540(2), C(20)–C(21) 1.563(2), C(21)–C(22) 1.516(2), C(6)–N(1)–C(7) 106.64(13), C(1)–N(2)–C(20) 122.05(13), C(1)–N(2)–C(7) 105.97(13), C(20)–N(2)–C(7) 112.45(12), N(2)–C(7)–C(14) 103.20(13), N(1)–C(7)–C(8) 110.95(13), N(2)–C(7)–C(8) 109.18(13), C(14)–C(7)–C(8) 113.94(14), N(2)–C(20)–C(19) 101.58(13), N(2)–C(20)–C(21) 113.58(13), C(28)–C(20)–C(21) 108.91(13), C(22)–C(21)–C(20) 118.18(14).

Isomerization of Benzyllitlhium-Diazocine-4 Adduct (21) in Silica Gel-Chloroform Slurry under an Air Atmosphere

Attempted column chromatographic purification of **21** led to the equilibration of racemic **21** to its diastereomeric racemate **23**. Thus (4b*S*,11*R*)-11-benzyl-4b,11-diphenyl-4b,11-dihydro-5*H*-benzo[4,5]imidazo[2,1-*a*]isoindole (**21**) (1.0 mmol) was mixed with undried chloroform (acidic to litmus) and silica gel and stirred in open air for 48 h [Equation (1)]. Upon workup, (4b*S*,11*S*)-11-benzyl-4b,11-diphenyl-4b,11-dihydro-5*H*-benzo[4,5]imidazo[2,1-*a*]isoindole (**23**), (cf. preceding paragraph for X-ray data obtained from one enantiomer of the racemic mixture) was produced in 33% yield, along with starting material, **21**. Compound **23** was purified by column chromatography and recrystallized from absolute ethanol as colorless crystals, m.p. 164–165 °C. The acid-catalyzed equilibration of **21** with **23** can be viewed as occurring via **22a** and **22b** [Equation (1)]. Isomer **21** is thermodynamically more stable than **23** by about 600 kcal/mol.



The ^{1}H-NMR spectrum of **23** has 26 protons, including the N–H at δ = 3.76 ppm and CH_2 doublets at δ = 3.93 and 4.81 ppm; the ^{13}C-NMR spectrum has the appropriate

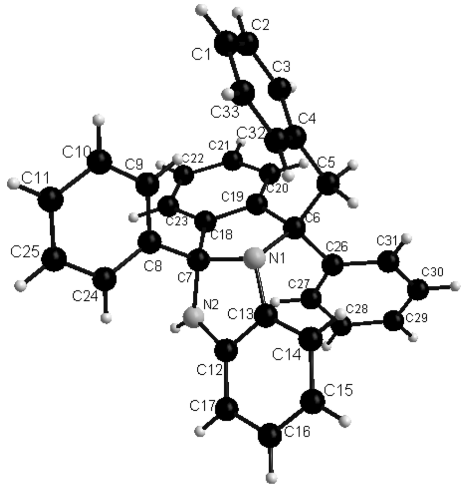
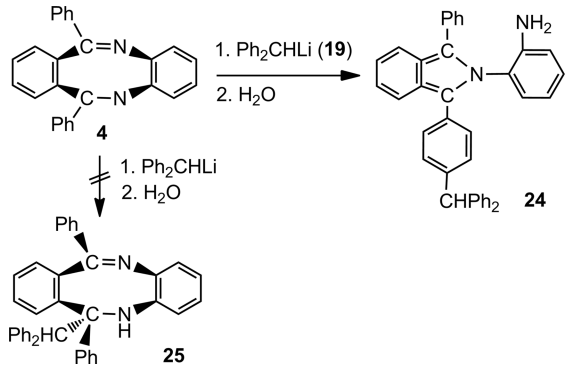


Figure 5. Thermal ellipsoid (30%) diagrams for (4b*S*,11*S*)-11-benzyl-4b,11-diphenyl-4b,11-dihydro-5*H*-benzo[4,5]imidazo[2,1-*a*]-isoindole (**23**). Selected bond lengths (atom separations) [Å] and bond angles of (4b*S*,11*S*)-11-benzyl-4b,11-diphenyl-4b,11-dihydro-5*H*-benzo[4,5]imidazo[2,1-*a*]isoindole (**23**) are shown as the following: N(1)–C(13) 1.414(1), N(1)–C(7) 1.495(1), N(1)–C(6) 1.505(1), N(2)–C(12) 1.401(2), N(2)–C(7) 1.480(1), C(5)–C(6) 1.549(2), C(6)–C(19) 1.517(2), C(6)–C(26) 1.539(2), C(12)–C(17) 1.383(2), C(12)–C(13) 1.403(2), C(18)–C(19) 1.382(2), C(19)–C(20) 1.393(2), C(13)–N(1)–C(7) 105.30(8), C(13)–N(1)–C(6) 119.75(9), C(7)–N(1)–C(6) 111.96(8), C(12)–N(2)–C(7) 106.03(9), N(1)–C(6)–C(19) 101.28(8), N(1)–C(6)–C(26) 114.21(9), N(1)–C(6)–C(5) 109.54(8), N(2)–C(7)–N(1) 103.10(8), N(2)–C(7)–C(18) 113.38(9), N(1)–C(7)–C(18) 102.79(8), N(1)–C(7)–C(8) 112.37(9), C(12)–C(13)–N(1) 109.63(10), C(18)–C(19)–C(6) 111.99(9), C(20)–C(19)–C(6) 127.68(10).

number of ^{13}C signals of 26, including the Ph–CH_2 at δ = 45.20 ppm, the N–CAr_2 at δ = 79.01 ppm and the N-C–N at δ = 93.92 ppm; and the infrared spectrum has an N–H stretch at 3393 cm^{-1}. The 3-D structure has been determined by X-ray diffraction, which showing that the two phenyl groups are *anti* to each other (Figure 5).

Reaction of Diazocine 4 with Benzhydryllithium (19)

Diazocine **4** (1 equiv.) was allowed to react with 2.2 equiv. of **19** in THF at room temperature for 24 h (Scheme 7).



Scheme 7.

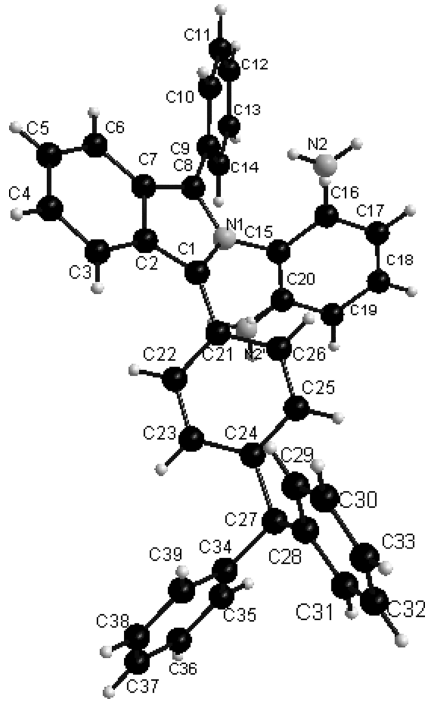


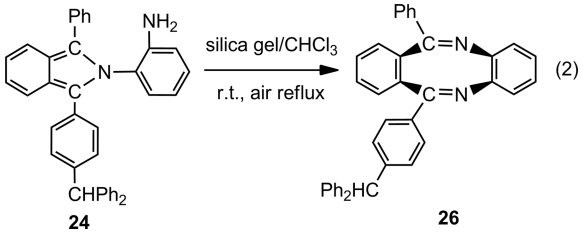
Figure 6. Thermal ellipsoid (30%) diagrams for 2-[1-(4-benzhydrylphenyl)-2-phenyl-2*H*-isoindol-2-yl]aniline (**24**). Selected bond lengths (atom separations) [Å] and bond angles of 2-[1-(4-benzhydrylphenyl)-3-phenyl-2*H*-isoindol-2-yl]aniline (**24**) are shown in the following: N(1)–C(8) 1.381(2), N(1)–C(1) 1.389(2), N(1)–C(15) 1.442(2), N(2)–C(16) 1.335(2), C(1)–C(2) 1.403(2), C(1)–C(21) 1.469(2), C(2)–C(3) 1.425(2), C(2)–C(7) 1.437(2),C(3)–C(4) 1.370(2), C(4)–C(5) 1.427(2), C(7)–C(8) 1.395(2), C(24)–C(27) 1.525(2), C(27)–C(28) 1.524(2), N(1)–N(2) 2.833(3), N(2)–C(1) 3.823(3), N(2)–C(8) 3.092(3), C(8)–N(1)–C(1) 110.84(11), C(8)–N(1)–C(15) 124.04(11), C(1)–N(1)–C(15) 124.93(11), N(1)–C(1)–C(2) 106.58(11), N(1)–C(1)–C(21) 124.75(12), N(1)–C(8)–C(7) 107.50(11), N(1)–C(8)–C(9) 124.41(12).

Upon hydrolytic workup, 2-[1-(4-benzhydrylphenyl)-3-phenyl-2*H*-isoindol-2-yl]aniline (**24**) formed in quantitative yield. Compound **24** was recrystallized from absolute ethanol as yellow crystals, m.p. 236–238 °C. None of possible adduct **25** was found. Also 7% of **19** was dimerized to 1,1,2,2-tetraphenylethane. The crystal structure of compound **24** is shown in Figure 6.

Oxidation of the Hydrolyzed Benzhydryllithium–Diazocine 4 Adduct 24 by Stirring in Silica Gel/Chloroform under an Air Atmosphere

This oxidative method for converting the unsubstituted diazocine **4** directly into the corresponding isoindole **9** was first discovered and described in ref.[1] Here this method was found useful in producing **26** from **24** in excellent yield.

The 2-[1-(4-benzhydrylphenyl)-3-phenyl-2*H*-isoindol-2-yl] aniline (**24**) was mixed in undried chloroform with siliga gel and stirred under reflux in open air for 48 h [Equation (2)]. Upon workup, (5*Z*,11*Z*)-6-(4-benzhydrylphenyl)-11-phenyldibenzo[*b*,*f*][1,4]diazocine (**26**) was produced in 96% yield. Compound **26** was recrystallized from absolute ethanol as colorless crystals, m.p. 204–205 °C.



The ^1H-NMR spectrum of **26** has 28 protons, including a C–H singlet at δ = 5.53 ppm; the ^{13}C-NMR spectrum has the appropriate number of ^{13}C signals of 27, including two

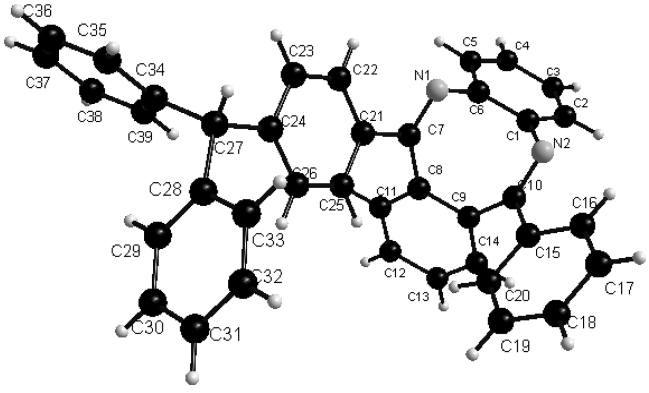
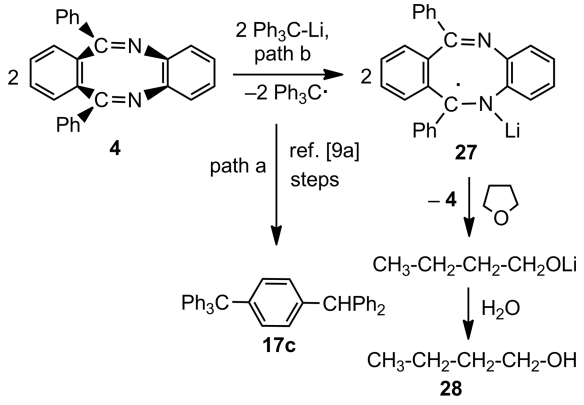


Figure 7. Thermal ellipsoid (30%) diagrams for (5*Z*,11*Z*)-6-(4-benzhydrylphenyl)-11-phenyldibenzo [*b*,*f*][1,4]diazocine (**26**). Selected bond lengths (atom separations) [Å] and bond angles of (5*Z*,11Z)-6-(4-benzhydrylphenyl)-11-phenyldibenzo[*b*,*f*][1,4]diazocine (**26**) are shown in the following: N(1)–C(7) 1.280(2), N(1)–C(6) 1.420(2), N(2)–C(10) 1.281(2), N(2)–C(1) 1.424(2), C(7)–C(21) 1.483(2), C(7)–C(8) 1.502(2), C(8)–C(9) 1.400(2), C(10)–C(15) 1.490(2), C(22)–C(23) 1.383(2), C(24)–C(27) 1.533(2), C(27)–C(28) 1.528(2), N(1)–N(2) 2.911(1), N(1)–C(10) 3.162(1), N(2)–C(7) 3.185(2), C(7)–C(10) 2.896(2), C(7)–N(1)–C(6) 120.10(10), C(10)–N(2)–C(1) 118.77(10), N(1)–C(7)–C(21) 118.42(10), N(1)–C(7)–C(8) 122.80(10), N(2)–C(10)–C(15) 119.51(10), N(2)–C(10)–C(9) 122.98(10), C(28)–C(27)–C(24) 110.49(9).

C=N at 169.74 and 169.56 ppm, and an H–CAr_3 group at δ = 56.71 ppm; and the infrared spectrum has two C=N stretches at 1631 and 1620 cm^{-1}. The 3-D structure has been determined by X-ray diffraction (Figure 7).

Reaction of Diazocene 4 with Tritylithium (20)

Diazocine **4** (1 equiv.) was allowed to react with tritylithium (**20**) in THF under 3 sets of conditions: 1) 10 h at –78 °C; 2) room temp. for 48 h; and 3) refluxing THF for 10 h. Upon hydrolysis, the resulting product compositions were very similar: the diazocine **4** was partially recovered unchanged and the Ullmann–Borsum hydrocarbon (**17c**) was formed in 15% yield, as was 1-butanol (5%). But no isoindole **8** whatsoever was detected, as was corroborated by the absence of ^{1}H and ^{13}C-NMR peaks characteristic of **8**. These results can be interpreted in terms of **4** accepting electrons to give **27** from two equivalents of Ph_3–Li and then forming **17c** from the known coupling trityl radicals (path a) and the lithium salt of **27** transferring electrons to THF with rupture of the ring (path b) to yield **28** upon hydrolysis (Scheme 8).[14]



Scheme 8.

Reactions of Diazocine 4 with Phenylethynyllithium (14)

Phenylethynyllithium (**14**) (2 equiv.) was allowed to react with diazocine **4** (1 equiv.) in THF at –78 °C for 2 h and at room temperature for 24 h. Upon hydrolytic workup, definitely no isoindole **9** and no diphenyldiacetylene were produced and no new signals in the ^{1}H and ^{13}C-NMR spectra were found. When the reaction was carried out under reflux for 8 h, the same result was obtained.

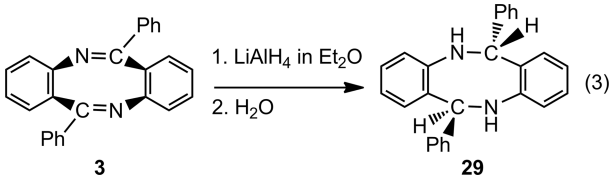
To try to enhance the dissociation of the C–Li bond of **14**, hexamethylphosphoramide (2 equiv.) was mixed with phenylethynyllithium (**14**) (2 equiv.). Then diazocine **4** (1 equiv.) was added and the reaction mixture was refluxed for 8 h. Upon workup again, neither isoindole **8** nor diphenyldiacetylene were produced. In addition, no new signals in the ^{1}H- and ^{13}C-NMR spectra were found.

Attempted Reactions of Diazocine 4 with Organolithium Reagents

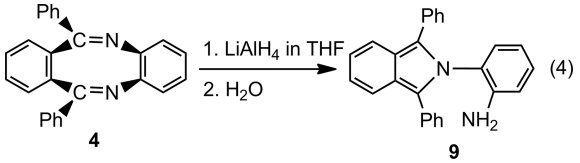
Two equivalents of methyllithium (**28**) was allowed to react with diazocine **4** (1 equiv.) in THF at –78 °C for 2 h and at room temperature for 24 h. Upon hydrolytic workup, definitely no signals of remaining diazocine **4** or generated isoindole **9** were found in the ^{1}H- and ^{13}C-NMR spectra. No pure products could be separated from the intractable crude mixture, either by fractional crystallizations or column chromatography. The TLC analysis on silica gel revealed about 4 to 5 components as closely spaced spots. These spots were assumed to be adducts of **4** and CH_3Li but no adduct was formed with any high selectivity. When *n*-butyllithium (**16c**) and phenyllithium (**11**) were employed under similar reaction conditions, a very similar outcome was obtained. Apparent reasons for the complexity of these reactions are considered in the Discussion section.

Reductive Rearrangement of Diazocine 4 into Isoindole 9 via Treatment with $LiAlH_4$ (29) in THF and Subsequent Hydrolysis

Preliminary to our attempts to hydrometallate the iminolinkages of diazocine **3**, we took notice of prior work with $LiAlH_4$ in ether achieving the *bis*-hydrometallation of **4** into a 3:1 mixture of the 6,12-diphenyl-*trans*(**29**)/*cis* isomers [Equation (3)].[15]



Accordingly, diazocine **4** (150 mg, 0.42 mmol, 1.0 molar equiv.) dissolved in 10.0 mL of dry THF under anhydrous argon was mixed with 0.50 mL of 2 M $LiAlH_4$ in THF (0.92 mmol, 1.0 molar equiv.) at –78 °C for 10 min. After being warmed to room temp. the brown mixture was stirred for 18 h. Hydrolytic workup (gas evolution) gave an organic residue of almost pure isoindole **9** by TLC and NMR criteria [Equation (4)].

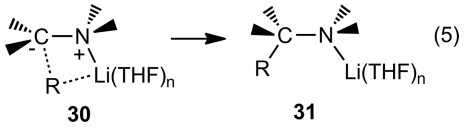


Discussion

Extreme Mechanistic Pathways under Discussion for the 1,2-Carbolithiation of Diazocines 3 and 4

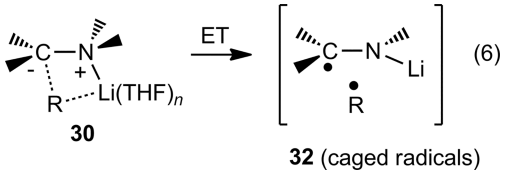
1,2-Nucleophilic carbolithiation of an imino linkage in diazocine **3** and **4** could be depicted as in Equation (3), where the complex of the imino group with R–Li (**30** solvated with THF) rearranges via a bridging transition state into the *exo*,

syn-carbolithiation adduct **31** [Equation (5)]. No electrons become unpaired and the R and Li groupings never become separated during the process.

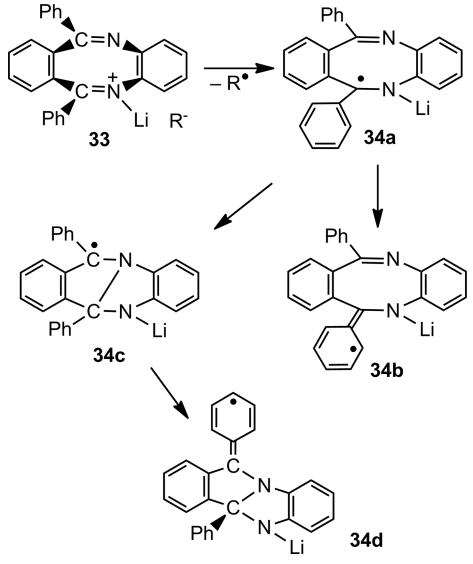


With diazocine **4** and the benzylic lithiums, $PhCH_2Li$ (**16a**), Ph_2CHLi (**19**) and Ph_3CLi, no 1,2-carbolithiation of an imino group whatsoever was observed. Hence, no 1,2- or 1,4-nucleophilic carbolithiation could be involved in the observed reactions (Scheme 6, Schemes 7 and 8). Finally, neither diazocine **3** nor **4** reacts at all with 1-phenylethynyllithium (**14**). Now in reactions with a wide variety of carbonyl substrates, reagent **14** behaves as an efficient addend, producing the Grignard-like adducts.[16] Thus simple nucleophilic addition is unlikely operative in the carbolithiation of either diazocine **3** or diazocine **4**.

The alternative mechanism for the carbolithiation of the imino linkage in these diazocines **3** and **4** would involve electron transfer in the imino complex of the R–Li(THF)$_n$ (**30**) [Equation (6)].



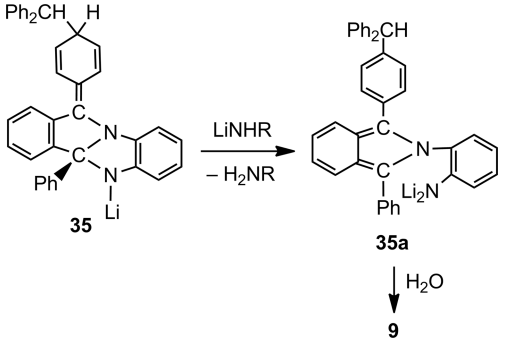
In this event the two radicals are held in proximity by dynamic radical caging in the solvent and hence could recombine with each other at radical sites on other carbon centers not adjacent to the imino N (**32**, solvent omitted). For example, an R–Li complex with diazocine **4** can undergo electron transfer to form **34a** with radical character delocalized on asterisked carbon centers (Scheme 9). Depending both on the lifetime and steric demands of R$^{\cdot}$, radical coupling could occur at carbon in **34a**, **34b** and with rearrangement, in **34c** and **34d**. These radicals might well be interrelated as high-energy isomers, rather than resonance structures.



Scheme 9.

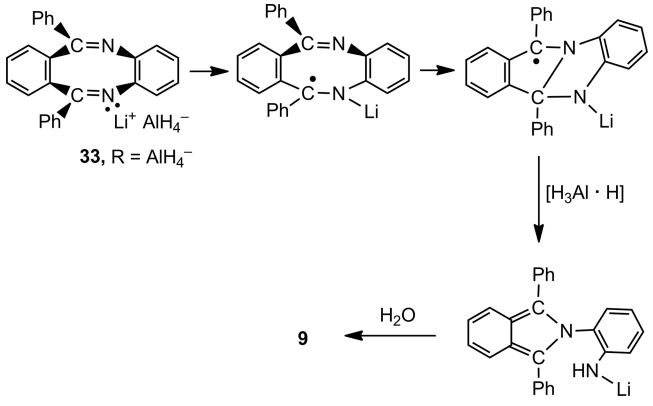
In our carbolithiations of diazocine **4** with benzylic lithium reagents, we have found that $PhCH_2Li$ adds to the N center and radical **34c** (**21** in Scheme 6), *trans* to the 11-phenyl group. The Ph_2CHLi adds to the N center and radical **34d** with unknown stereochemistry (**24** in Scheme 7). Furthermore, we assume that Ph_3CLi also carbolithiates as with **34d**, but such a labile adduct redissociates again to yield **17c** and **4**.

In the case of the reaction of benzhydryllithium with diazocine **4**, the initial coupling product **35** would then undergoe a base-promoted elimination reaction with further RLi to produce **35a** and then the observed hydrolysis product **9** (Scheme 10).



Scheme 10.

With the foregoing results in mind, it is reasonable to suggest that the several (4–5) unknown components formed from **4** and CH_3Li, $CH_3CH_2CH_2CH_2Li$ or PhLi in individual reactions could result from the coupling of radicals **34a**–**34d** with the group furnished by the R–Li reagent.[18] Furthermore, such coupling could result in some cases with the formation of *cis*- and *trans*-isomers and/or isomeric nuclear skeletons (e.g., with **34c** and **34d**). Proof that attempted hydrometalation of **4** can induce skeletal isomerization has been demonstrated by the outcome shown in Scheme 11, where an SET pathway for this transformation can readily be depicted.



Scheme 11.

Conclusions

(1) An investigation of a range of organolithium reagents in THF, containing sp^2- and sp^3-hybridized carbon atoms bonded to lithium, namely methyllithium, *n*-butyllithium, phenyllithium, benzyllithium, benzhydryllithium and trityllithium indeed do effect the carbometallation of diazocine **4** but in every case yielding a result incompatible with the operation of simple nucleophilic addition. In a straightforward nucleophilic addition, such reactions should occur in a selective 1,2 or 1,4 manner without skeletal change.

(2) In a comparative study of the reactions of diazocine **4** individually with benzyllithium, benzhydryllithium and tritylithium, it was found that none of the three benzylic lithium reagents underwent a normal 1,2- or 1,4-carbolithiation to the C=N or C=C–C=N functional groups. Instead benzyllithium and benzhydryllithium underwent totally abnormal carbolithiation of the rearranged skeleton of the diazocine **4** system. Tritylithium executed electron-transfers with both diazocine **4** and THF to produce the dimer of two trityl groups, **17c**, and the lithium salt of 1-butanol.

(3) The individual reactions of diazocine **4** with methyllithium, *n*-butyllithium and phenyllithium in THF did not produce selectively the 1,2 or 1,4 adducts expected from simple nucleophilic addition. Instead, each organolithium generated four to five hydrolyzed adducts of unknown structure unattainable through normal carbolithiation.

(4) Phenylethynyllithium in THF, which performs successful nucleophilic additions to a wide variety of carbonyl substrates, is completely unreactive toward diazocine **4** between –78 °C to +80 °C or in the presence of HMPA. An electronic rationale for the inertness of this lithium reagent is presented in ref.[9b] in Table 3. In a proposed SET pathway the necessary radical cluster, **32** in Equation (6), would be too high in energy with an alkynyl radical (R–C≡C˙) to participate.

(5) The observations made concerning the reactions of diazocine-4 and organolithiums above under points (2)–(4) are completely incompatible with the operation of a nucleophilic carbolithiation. In contrast, all such reaction traits can be readily accommodated by the stepwise electron-transfer and radical-coupling process depicted and discussed at Equation (6) (cf. supra).

Experimental Section

General Experimental Procedures

General Reaction and Hydrolytic Workup Procedures: All reactions were carried out under a positive pressure of anhydrous, oxygen-free argon. All solvents employed with organometallic compounds were dried and distilled from a sodium metal-benzophenone ketyl mixture prior to use.[18]

Routinely, the organometallic reaction mixtures were hydrolyzed with deoxygenated water. Ether was added to the hydrolysate, the organic layer was separated and the organic layer then dried with anhydrous Na_2SO_4. The volatile solvent was removed and ^1H- and ^{13}C-NMR spectra and TLC were recorded on the crude organic products. Where preparative yields were to be corroborated, column chromatographic separation of products on silica gel with a hexane/ethyl acetate eluent was carried out.

Analytical Methods: The IR spectra were recorded with a Perkin–Elmer instrument, model 457, and samples were measured either as mineral oil mulls or as KBr films. The NMR spectra (^1H and ^{13}C) were recorded with a Bruker spectrometer, model Avance III 600, and tetramethylsilane Me_4Si was used as the internal standard. The chemical shifts reported are expressed on the scale in parts per million (ppm) from the Me_4Si reference signal. Melting points were determined on a Thomas-Hoover Unimelt capillary melting point apparatus and are uncorrected.

Authentic ^1H- and ^{13}C-NMR spectra for comparison with those of all known compounds listed in Supplemental Information and are accessible from AIST: Integrated Spectral Database System of Organic Compounds.[19]

Preparation of Known Starting Materials and Products

6,12-Diphenyldibenzo[*b*,*f*][1,4]diazocine (4): The requisite *o*-dibenzoylbenzene was prepared in strict adherence to a published procedure[20] from phthaloyl chloride and phenylmagnesium bromide in diethyl ether, in 27% yield and recrystallized from 95% ethanol, m.p. 146–147 °C.

The procedure for preparing *o*-dibenzoylbenzene has been modified from that employed by Olliéro and Solladié,[7] namely by condensing this diketone and *o*-diaminobenzene in a 1:3 molar ratio in benzene and heating at reflux for 10 days with *p*-toluenesulfonic acid monohydrate in a ratio of 1:0.25. Instead, we have conducted the reaction in refluxing toluene with the condenser attached to a Dean–Stark trap. With this procedure the expected amount of water was collected after 12 h. The resulting solution was subjected to rotary evaporation. The dark residue was purified by column chromatography on silica gel employing a 3:1 by volume hexane/ethyl acetate eluent. From 5.73 g of the diketone and 6.50 g of the diamine, 6.32 g of **4** (100%) was obtained, yellow crystals, m.p. 197–198 °C (ref.[7] 184–189 °C). ^1H NMR ($CDCl_3$): δ = 7.82 (d, 4 H), 7.43 (t, 2 H), 7.40 (q, 2 H), 7.37 (t, 4 H), 7.16 (q, 2 H), 7.00 (m, 4 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 169.73, 141.91, 137.8, 136.43, 130.99, 128.97, 128.74, 128.25, 127.11, 124.05, 121.18 ppm.

2-(2-Aminophenyl)-1,3-diphenylisoindole (9): According to a published procedure,[7] an intimate mixture of 5.73 g (20 mmol) of *o*-dibenzoylbenzene, 2.16 g (20 mmol) of *o*-diaminobenzene and 1.0 g (5.3 mmol) of *p*-toluenesulfonic acid monohydrate was heated in an oil bath at 200 °C ± 5 °C for 2 h, whereupon it became a viscous melt. Although the authors claim they obtained a quantitative yield, the operative steps and criteria are not given. In our procedure the reaction mixture was stirred with a water/ethyl ether slurry and the organic layer was separated and dried with anhydrous Na_2SO_4. Filtration of the dried solution and evaporation of the solvent left a dark residue of crude **9** and other amino components. Column chromatography on silica gel with a 3:1 v/v hexane/ethyl acetate eluent yielded 4.18 g (85%) of **9**, 10% of phenazine (by ^1H NMR and TLC) and ≈ 5% of other amines: **9** from 95% ethanol, yellow crystals, m.p. 212–213 °C (ref.[7] 201–202 °C). ^1H NMR ($CDCl_3$): δ = 773 (q, 2 H), 7.30 (d, 3 H), 7.25 (m, 4 H), 7.17 (t, 2 H), 7.08 (t, 1 H), 7.04 (m, 2 H), 6.96 (d, 1 H), 6.62 (t, 1 H), 6.58 (d, 1 H), 3.47 (b, 2 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 143.17, 131.78, 130.16, 129.59, 129.54, 128.13, 126.45, 124.47, 124.41, 123.12, 122.5, 119.88, 118.29, 115.97 ppm.

Preparation and Analysis of Organolithium Reagents

n-Butyllithium (2.5 M in hexane) was used as received from the Aldrich Chemical Company, with all transfers being made under dry, oxygen-free argon with argon-flushed gastight syringes. Likewise, the benzylic lithium reagents were prepared, as described in the follow-

ing paragraphs, transferred and allowed to react under an argon atmosphere.[17]

Benzyllithium (16a), Prepared as Needed by Two Separate Procedures: (1) In THF by the cleavage of benzyl methyl ether by lithium metal pieces in THF at –10 °C and then analyzed by the Gilman double titration method.[17] (2) In toluene as the 1:1 complex with TMEDA by treatment of 1.0 equiv. of TMEDA in toluene with 1.0 equiv. of *n*-butyllithium in hexane and with subsequent analysis by adduction of an aliquot of **16a** with benzophenone.

Benzhydryllithium(diphenylmethyllithium) (19) was prepared by treating a solution of diphenylmethane (505 mg, 3.0 mmol, 1.0 equiv.) in THF (25 mL) with *n*-butyllithium in hexane (1.32 mL, 3.29 mmol, 1.1 equiv.) at room temperature. After 2 h the blood-red solution was analyzed by treating an aliquot with D_2O (100%), separating the organic layer after addition of ethyl ether, drying the organic layer, and removing volatiles and recording the ^{1}H-NMR spectrum of the organic residue. The relative integrated intensities of the phenyl protons to the methyl protons, which had been 10.0 to 2.0 in the starting diphenylmethane, were now 10.0 to 1.2, indicating 80% deuteriation at the CH_2 group and thus an 80% yield of **19**. The ^{1}H-NMR spectrum showed no trace of 5,5-diphenyl-1-pentanol, the product of the attack of **19** on THF at higher temperatures.

Trityllithium(triphenylmethyllithium) (20) was similarly prepared by treating a solution of triphenylmethane (180 mg, 0.75 mmol, 1.0 equiv.) in THF (20 mL) with *n*-butyllithium in hexane (0.32 mL, 0.80 mmol, 1.1 equiv.) at room temperature. After 2 h an aliquot of the resulting deep-red solution was worked up with D_2O and ethyl ether, as in the foregoing procedure. The original aryl to methyne proton ratio of 15:1.0 for the starting Ph_3CH was now 15:0.55, indicating a 45% yield of **20**. Neither in this preparation of **20** nor in the foregoing preparation of **19** was there any sign of remaining *n*-butyllithium. Were any such a lithium reagent still present in reactions with diazocine **4**, the known butylated adduct would have been formed. Thus, any *n*BuLi not consumed by lithiating Ph_2CH_2 or Ph_3CH must have been destroyed by the known attack of *n*BuLi on THF to produce ethylene and CH_2=CHOLi.

Phenylethenyllithium (14) was prepared by treating a solution of phenylacetylene (102 mg, 1.0 mmol, 1.0 equiv.) in 5 mL of THF with *n*-butyllithium in hexane (0.44 mL, 1.1 mmol, 1.1 equiv.) at –78 °C for 30 min and then at room temp. for 30 min to give a colorless solution of **14**, which was analyzed by treating an aliquot with D_2O (100%), separating the organic layer after addition of ethyl ether, drying the organic layer and removing volatiles and recording the ^{1}H-NMR spectrum of the organic residue. The relative integrated intensities of the phenyl protons to the methylidyne protons, which had been 5.0 to 1.0 in the starting phenylacetylene, were now 5.0 to 0, indicating 100% deuteriation at the CH group and thus a 100% yield of **14**.

Reactions of 6,11-Diphenyldibenzo[*b*,*f*][1,4]diazocine (4) with Organolithium Reagents

Reaction of Diazocine 4 with Benzyllithium and Reaction Variants: Diazocine **4** (360 mg, 1.0 mmol) was added to the benzyllithium-TMEDA complex (**16a**) (2.2 mmol) in 15 mL THF and stirred at room temperature for 24 h. After workup (4b*S*,11*R*)-11-benzyl-4b,11-diphenyl-4b,11-dihydro-5*H*-benzo[4,5]imidazo[2,1-*a*]isoindole (**21**) was obtained in quantitative yield by the usual hydrolytic workup. Bibenzyl was also found in this reaction in 6% yield. Crystals of **21** were obtained by recrystallization from absolute ethanol, m.p. 174–175 °C.

When keeping other conditions the same, but using only 1.1 mmol of benzyllithium–TMEDA complex **16a**, 57% of **21** was obtained.

^{1}H NMR ($CDCl_3$): δ = 8.01 (d, 2 H), 7.55 (d, 2 H), 7.51 (q, 3 H), 7.40 (t, 2 H), 7.33 (t, 1 H), 7.21 (t, 2 H), 7.16 (t, 1 H), 7.11 (d, 1 H), 7.01 (q, 2 H), 6.92 (m, 2 H), 6.80 (t, 2 H), 6.63 (d, 1 H), 5.96 (d, 2 H), 3.82 (d,1 H), 3.52 (d, 1 H), 3.11 (d, 1 H), 2.20 (s,1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 147.01, 146.86, 146.48, 145.76, 142.04, 140.78, 136.08, 130.67, 128.63, 128.50, 128.25, 127.72, 127.12, 127.09, 127.04, 126.92, 126.70, 125.91, 124.85, 123.71, 122.88, 122.49, 116.07, 114.78, 93.36, 76.58, 44.73, 30.90 ppm.

Reaction of Diazocine 4 with Diphenylmethyllithium (19): Diazocine **4** (360 mg, 1 mmol.) was added to diphenylmethyllithium (**19**) (2 mmol) in 20 mL THF and stirred at room temperature for 24 h. After workup **4** was completely converted into the 2-[1-(4-benzhydrylphenyl)-3-phenyl-2*H*-isoindol-2-yl]aniline (**24**). 1,1,2,2-Tetraphenylethane was also generated by dimerization of **19** in 7% yield. Compound **24** was purified by column chromatography (eluent: hexanes/ethyl acetate, 3:1) in quantitative yield as yellow crystals, m.p. 236–238 °C. ^{1}H NMR ($CDCl_3$): δ = 7.74 (m, 2 H), 7.40–7.15 (m, 12 H), 7.15–6.90 (m, 10 H), 6.61 (m, 2 H), 5.50 (s, 1 H), 3.45 (br., 2 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 143.91, 143.222, 141.89, 131.82, 130.21, 129.84, 129.63, 129.50, 129.36, 129.18, 128.31, 128.13, 126.43 126.33, 124.55, 124.03, 123.11, 122.50, 122.38, 120.04, 119.88, 118.24, 115.91, 56.59 ppm.

Reactions of Diazocine 4 with Triphenylmethyllithium (20) and Reaction Variants: Diazocine **4** (360 mg, 1 mmol) was added to triphenylmethyllithium (**20**) (2 mmol) in 20 mL THF and stirred at room temperature for 24 h. After workup, triphenylmethane (84%), the Ullmann–Borsum hydrocarbon (**17c**) (14%), triphenylmethanol (1%) and 1-butanol (1%) were found in the crude hydrolysate.

When such a reaction was carried out in THF either at –78 °C or under reflux, the same products resulted.

Attempted Reactions of Diazocine 4 with Organolithium Reagents: Methyllitnium (**16b**) (0.4 mL, 3 M in diethoxymethane, 1.2 mmol) was added to diazocine **4** (180 mg, 0.5 mol) in 15 mL THF at –78 °C for 2 h and then at room temperature for 24 h. After workup definitely no signals of diazocine **4** or isoindole **24** was found in the ^{1}H- and ^{13}C-NMR spectra. But the complex crude product, which displayed by TLC analysis four to five closely spaced fluorescent spots, could not be separated either by crystallization or by column chromatography.

The same outcome resulted when the reaction was carried out with either *n*-butyllithium (**16c**) or phenyllithium (**11**) under similar reaction conditions.

Attempted Reactions of Diazocine 4 with Phenylethynyllithium (14) and Reaction Variants: Phenylethynyllithium (**14**) (1 mmol) was added to diazocine **4** (180 mg, 0.5 mmol) in 15 mL THF at –78 °C, then stirred at –78 °C for 2 h and at room temperature for 24 h. After workup only **4** was recovered. When such a reaction was heated at reflux for 8 h, the same outcome resulted.

Hexamethylphosphoramide (HMPA) (0.20 mL, 1 mmol) was admixed with phenylethynyllithium 101 (1 mmol) in 15 mL THF at –78 °C for 15 min and then [1,4]diazocine **4** (180 mg, 0.5 mmol) was added. Subsequent reflux for 8 h and usual workup yielded only **4**.

Isomerization of the Benzyllithium–Diazocine Adduct (16a) by Stirring in Silica Gel/Chloroform: The (4b*S*,11*R*)-11-benzyl-4b,11-diphenyl-4b,11-dihydro-5*H*-benzo[4,5]imidazo[2,1-*a*]isoindole (**21**) (0.45 g, 1.0 mmol) was mixed with 15 mL chloroform and silica gel

(5.0 g), and stirred in open in air for 48 h. After workup the product (4b*S*,11*S*)-11-benzyl-4b,11-diphenyl-4b,11-dihydro-5*H*-benzo[4,5]imidazo[2,1-*a*]isoindole (**23**) was determined as 33% yield from the ^{1}H-NMR spectrum of the reaction mixture, along with the unchanged starting material **21**. Compound **23** was purified by column chromatography (eluent: hexanes/ethyl acetate, 20:1) as colorless crystals, m.p. 164–165 °C. ^{1}H NMR ($CDCl_3$): δ = 7.36 (m, 2 H), 7.21 (d, 1 H), 7.18 (d, 3 H), 7.09 (m, 4 H), 6.99 (q, 5 H), 6.88 (t, 2 H), 6.75 (d, 2 H), 6.62 (t, 1 H), 6.56 (d, 1 H), 6.38 (t, 1 H), 6.26 (d, 1 H), 4.81 (s, 1 H), 3.93 (d, 1 H), 3.76 (d, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 148.15, 145.66, 144.22, 143.38, 142.49, 139.29, 137.18, 131.78, 128.41, 128.35, 127.91, 127.78, 127.37, 126.99, 126.85, 125.94, 125.60, 124.54, 123.70, 122.11, 119.50, 116.13, 108.59, 93.92, 79.01, 45.20 ppm.

Oxidation of the Diphenylmethyllithium–Diazocine Adduct 24 by Stirring in Silica Gel/Chloroform: 2-[1-(4-Benzhydrylphenyl)-3-phenyl-2*H*-isoindol-2-yl]aniline (**24**) (0.96 g, 1.8 mmol) was mixed in 25 mL chloroform and silica gel (10.0 g), then stirred for 48 h in open air. After workup, pure (5*Z*,11Z)-6-(4-benzhydrylphenyl)-11-phenyldibenzo[b,f] [1,4]diazocine (**26**) was obtained in quantitative yield by filtering off the silica gel and evaporating the volatile solvent. Compound **26** is a colorless solid, m.p. 204–205 °C. ^{1}H NMR ($CDCl_3$): δ = 7.69 (d, 2 H), 7.50 (d,1 H), 7.33 (m, 3 H), 7.26 (m, 2 H), 7.07 (m, 5 H), 6.94 (d, 1 H), 6.55 (m, 2 H), 6.34 (t, 1 H), 6.11 (d, 1 H), 6.06 (m, 1 H), 5.19 (d, 1 H), 5.09 (d, 1 H), 4.81 (s, 1 H), 3.39 (m, 1 H), 3.16 (m,1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 148.79, 146.43, 142.82, 142.25, 141.85, 139.25, 135.64, 128.93, 128.49, 128.27, 127.80, 127.63, 127.32, 126.86, 125.68, 124.30, 123.17, 121.67, 119.69, 118.13, 115.71, 109.38, 93.57, 77.23, 77.14, 65.78, 44.99, 15.24 ppm.

Reductive Isomerization of Diazocine 4 to Isoindole 9: A solution of diazocine **4** (150 mg, 0.42 mmol, 1.0 molar equivalent) formed in 10 mL of dry THF under an atmosphere of anhydrous, deoxygenatd argon was cooled to –78 °C in a Dry Ice-acetone bath and treated dropwise (via a gastight syringe) with a 2.0M solution of $LiAlH_4$ in THF (0.46 mL, 0.92 mmol, 2.2 M equivalents). After ten minutes at –78 °C the initially pale yellow solution had turned dark brown. The solution was then brought to room temp. for 12 h and worked up in the usual manner. The resulting crude product (160 mg) was shown to be almost pure isoindole **9** (> 98%) by NMR and TLC analysis, with traces of **4** and 1-butanol.

CCDC-956943 (for **21**), -956944 (for **23**), -956942 (for **24**) and -956945 (for **26**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Supporting Information (see footnote on the first page of this article): Copies of the ^{1}H- and ^{13}C-NMR spectra with fully displayed DEPT and IR spectra.

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