DOI: 10.1002/hlca.201900192

FULL PAPER

HELVETICA chimica acta

A Phosphorus(III)-Mediated (4+1)-Cycloaddition of 1,2-Dicarbonyls and Aza-*o*-Quinone Methides to Access 2,3-Dihydroindoles

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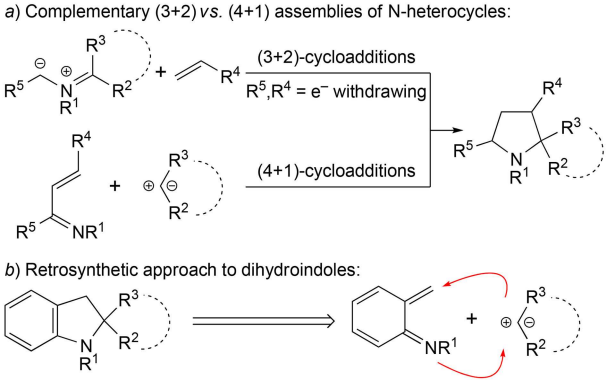
A (4+1)-cycloaddition is reported between 1,2-dicarbonyls and aza-*o*-quinone methide precursors to access 2,3-dihydroindoles bearing a tetra-substituted carbon center. The utilization of dioxyphospholenes as carbene surrogates provided dihydroindoles in 20–90% yield, wherein the electronic nature of the dioxyphospholene impacts its role in the reaction.

Keywords: cycloaddition, aza-*o*-quinone methides, dihydroindoles, *Kukhtin–Ramirez* reaction, 1,2-dicarbonyls.

Introduction

Despite the number of elegant approaches for the construction of heterocyclic frameworks, the selective and convergent assembly of highly substituted nitrogen-containing ring scaffolds remains a significant challenge in pharmaceutical drug development.[1–5] The prevalence of these subunits in designed small molecules and natural products exhibiting promising anticancer and anti-bacterial properties further illustrates the need for efficient, convergent approaches to these motifs.[6–8] Dipolar cycloadditions, specifically the (3+2) assembly of an azomethine ylide and an electron deficient alkene, constitutes a powerful tool in the construction of pyrrolidine derivatives (*Scheme 1,a*). However, the potential complications due to the inherent reactivity and lack of chemoselectivity associated with 1,3-dipoles, combined with the structural requirements (i.e., electron withdrawing substituents) for both components, led us to consider alternative disconnects.[9–16] One complementary approach involves the (4+1)-cycloaddition between a 1,3-heterodiene and a disubstituted, biphilic C_1 subunit to construct the pyrrolidine core. Given our previous success in the (4+1) assembly of heterocyclic scaffolds, we were motivated to evaluate this strategy toward C_2-disubstituted dihydroindoles (*Scheme 1,b*).

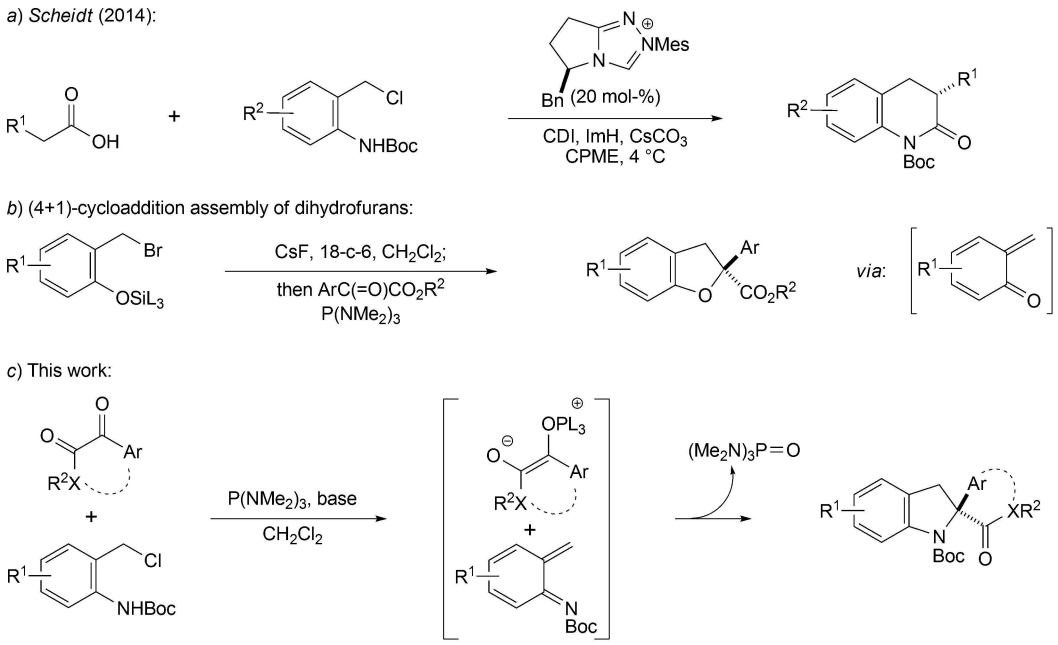


Scheme 1. Cycloaddition construction of *N*-heterocycles.

While the transition metal-catalyzed decomposition of diazo compounds can serve as a versatile source of C_1 synthons, we sought a metal-free alternative to our previously reported Rh-catalyzed (4+1)-cycloadditions.[17,18] For this study, we chose to utilize a *Kukhtin–Ramirez*-like redox neutral condensation to exploit the biphilic nature of oxyphosphonium enolates as C_1 subunits.[19–24] Recent work by *Radosevich*, *He*, and our own group have demonstrated the versatility of this approach in providing direct access to C–C and C–X bonds.[25–29]

Inspired by *Scheidt* and coworkers elegant enantioselective assembly of benzopiperidinones employing

Supporting information for this article is available on the WWW under https://doi.org/10.1002/hlca.201900192



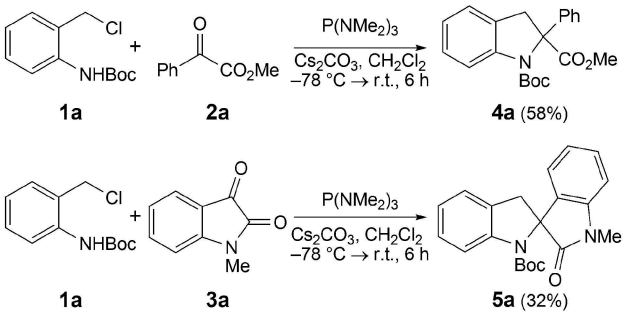
Scheme 2. Selected quinone methides in (4 + *n*)-cycloadditions.

an NHC-catalyzed [4 + 2]-cycloaddition of *in situ* generated aza-*o*-quinone methides (aza-*o*-QM) and aliphatic carboxylic acids (*Scheme 2,a*), and building on our previous work toward dihydrobenzofurans (*Scheme 2,b*), we speculated that aza-*o*-QMs could serve as 1,3-heterodienes in the construction of 2,3-dihydroindoles employing readily accessible oxyphosphonium enolates as C_1 synthons.[25,27,30–38] Herein, we report the successful development of a phosphorus(III)-mediated redox construction of 2,3-dihydroindoles resulting from the addition of 2-amino benzyl halides to 1,2-dicarbonyls (*Scheme 2,c*). The resulting (4 + 1)-cycloaddition represents a complementary method for heterocycle assembly and adds to the growing ensemble of synthetic methods based on *Kukhtin–Ramirez*-like reactivity.

Results and Discussion

Our initial foray into dihydroindole construction began by examining the net (4 + 1)-cycloaddition employing a biphilic oxyphosphonium enolate as a C_1 synthon and a 1,4-dipole aza-*o*-QM. Employing conditions comparable to those forged by *Scheidt* and coworkers, presumptive aza-*o*-QM generation by treatment of benzyl chloride **1a** with Cs_2CO_3 followed by exposure to the oxyphosphonium enolate derived from methyl benzoyl formate (**2a**) and $P(NMe_2)_3$ led to formation of dihydroindole **4a** in 58% yield (*Scheme 3*). Likewise, the (4 + 1)-cycloaddition between *N*-methyl isatin (**3a**) and **1a** under comparable reaction conditions provided spirooxindole **5a** in 32% yield. Encouraged by these initial results, we turned our attention toward optimizing formation of dihydroindole cycloadducts **4** and **5** and gaining mechanistic insight into the phosphorus(III)-mediated (4 + 1)-cycloaddition.

Although an initial survey of solvent effects employing either polar or non-polar aprotic solvents (*e.g.*, PhMe, THF, DMF, *etc.*) on the cycloaddition of **1a** and **2a** revealed only minor variations in yield and conversion, we noted that conducting the reaction in CH_2Cl_2 provided reproducible results with superior yields of **4a**. In general, a survey of amine and inorganic bases (*e.g.*, $^{i}Pr_2NEt$, Li_2CO_3, Cs_2CO_3) resulted



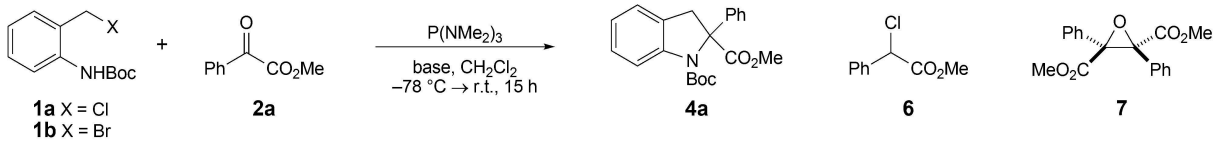
Scheme 3. Initial findings.

in only modest changes to 40–44% of the yield of **4a** (*Table 1, Entries 1* and *2*). Likewise, employing benzyl bromide **1b** as the aza-*o*-QM precursor under conditions comparable to that illustrated in *Scheme 3* failed to improve the yield of **4a** in comparison to benzyl chloride **1a** (*Table 1, Entry 3*). A similar outcome was observed when the corresponding sulfonates (*e.g.*, X = $MeSO_3$, $TsSO_3$) were employed. Interestingly, treatment of benzyl chloride **1a** and **2a** with $P(NMe_2)_3$ in the absence of an exogenous base provided **4a** in 50% yield (*Table 1, Entry 4*). Speculating that the intermediate oxyphosphonium enolate derived from the addition of $P(NMe_2)_3$ to **2a** acts as an effective, soluble organic base for aza-*o*-QM generation, we anticipated that increasing the equivalents of α-keto ester **2a** and $P(NMe_2)_3$ relative to **1a** should improve the yield of **4a**. Gratifyingly, the addition of two equivalents of **2a** and $P(NMe_2)_3$ to **1a** provided **4a** in 90% yield by NMR in which the intermediate oxyphosphonium enolate was distributed unequally between **4a**, α-chloro ester **6**, and epoxide **7** in a 10:10:1 ratio (*Table 1, Entry 5*).[39,40]

While epoxide **7** is a common self-condensation product in *Kukhtin–Ramirez*-like functionalizations, the formation of α-chloro ester **6** presumably arises from the addition of HCl across the oxyphosphonium enolate intermediate in a fashion commensurate with *Radosevich*'s 2015 study.[25] The formation of **4a** and **6** in a 1:1 ratio supports a mechanism wherein the presumptive aza-*o*-QM intermediate arises from a 1,4-elimination of the benzyl chloride in **1a** by a sacrificial equivalent of oxyphosphonium enolate that is then converted to the α-chloro ester through phosphine oxide displacement. Based on this mechanistic hypothesis, we surmised that by employing a strong, exogenous base in a polar, aprotic solvent, we could reduce the formation of α-chloro ester **6** and epoxide **7**. To that end, pre-treatment of **1a** with NaH followed by 1.2 equiv. each of **2a** and $P(NMe_2)_3$ provided **4a** in 57% yield and chloroester **6** in a 19:1 ratio favoring the desired cycloadduct (*Table 1, Entry 6*). Increasing the amount of **2a** and $P(NMe_2)_3$ to 2.0 equiv. each subsequently increased the yield of **4a** to 95% and effectively eliminated formation of **6** (*Table 1, Entry 7*). The byproduct distribution observed in *Entries 5–7* would seem to suggest that the oxyphosphonium enolate can act as an effective base or nucleophile in initiating the (4+1)-cycloaddition. While the yield of **4a** in *Entry 7* when employing NaH was modestly improved compared to the absence of base, the 2.0 equiv. of **1a** required led us to proceed with the operationally simpler conditions depicted in *Entry 5*.

To probe the viability of a mechanism that proceeds through an acyl aniline deprotonation by the oxyphosphonium enolate derived from **2a**, we subjected deuterium labeled **1a** and α-keto ester **2a** to the optimized reaction conditions in *Table 1*, *Entry 5*, and evaluated the amount of deuterium incorporation in the resulting α-chloro ester **6** (*Scheme 4*). Exposure of **1a–d** to two equivalents of **2a** and $P(NMe_2)_3$ resulted in an 85% yield of cycloadduct **4a** and 82% yield of α-chloro ester **6d** with 50% *d*-incorporation. While the relative acidity of the α-proton in **6** likely contributed to the modest level of *d*-incorporation,

Table 1. Optimized Formation of Dihydroindole **4a**[a]

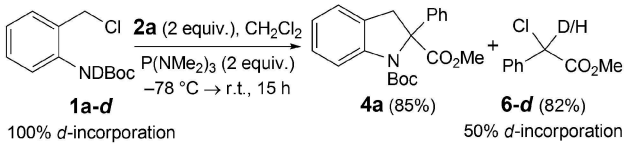


1a X = Cl
1b X = Br

2a **4a** **6** **7**

Entry	**1**	Base	Equivalents of **2a**	NMR Yield of **4a** [%][b]	**4a/6/7**
1	**1a**	$^{i}Pr_2NEt$	1.2	40	1:0:0
2	**1a**	Li_2CO_3	1.2	44	1:0:0
3	**1b**	Cs_2CO_3	1.2	40	1:0:0
3	**1b**	Cs_2CO_3	1.2	40	1:0:0
4	**1a**	–	1.2	50	1:0:0
5	**1a**	–	2.0	90	10:10:1
6[c]	**1a**	NaH	1.2	57	19:1:11
7[c]	**1a**	NaH	2.0	95	1:0:1

[a] Conditions: **1** (0.2 mmol), **2a** and $P(NMe_2)_3$ employed in equimolar amounts, base (0.4 mmol), in CH_2Cl_2 (0.3 M). [b] Employing 10 mol-% trimethoxybenzene as an internal standard at 500 MHz. [c] Modified standard conditions included NaH (0.22 mmol) and 1,2-$F_2C_6H_4$ (0.3 M) as solvent.

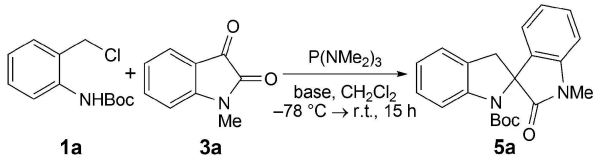


Scheme 4. Deuterium incorporation in **6-*d***.

this would seem to support the viability of a mechanism involving an initial oxyphosphonium enolate deprotonation of the *N*-acyl aniline derivative.

We next turned our attention toward evaluating the (4 + 1)-cycloaddition employing isatin derivatives as C_1 synthons. Interestingly, employing isatin **3a** under the optimized reaction conditions employed in our optimization study for α-keto ester **2a**, failed to provide the corresponding spirooxindole **5a** (*Table 2*, *Entry 1*). Likewise, the addition of either NEt_3 or KO^{t}Bu yielded solely the epoxide resulting from self-condensation of **3a** and decomposition of the aza-*o*-QM precursor **1a**. However, upon addition of 10 mol-% Cs_2CO_3 gave **5a** in 37% yield (*Table 2*, *Entry 2*). Increasing the amount of Cs_2CO_3 to a full equivalent did not significantly impact the yield of **5a**, and comparable results were obtained with K_2CO_3 (*Table 2*, *Entries 3* and *4*). Given that an exogenous base is required when employing isatin **3a**, whereas the oxyphosphonium enolate derived from formate **2a** is sufficient to provide the corresponding cycloadduct **4a** in good yield illustrates the impact subtle structural changes in the starting materials can have on the reaction outcome. Additionally, this observation is consistent with the higher pK_a of α-aryl formyl enolates in comparison to the corresponding enolate derived from *N*-alkyl oxindoles and the intermediary acidity of the *N*-acyl aniline **1**.[41]

Table 2. Employing *N*-Me Isatin as a C_1 Synthon.[a]



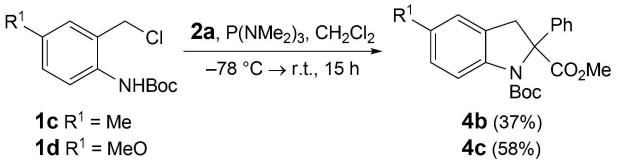
1a 3a 5a

Entry	Base	Equivalents of Base	Ratio **3a/1a**	Yield [%]
1	–	–	2.0	0
2	Cs_2CO_3	0.1	1.2	37
3	Cs_2CO_3	1.2	1.2	30
4	K_2CO_3	1.2	1.2	28
5[b]	Cs_2CO_3	1.2	1.2	54
6[b]	Cs_2CO_3	2.0	2.0	77

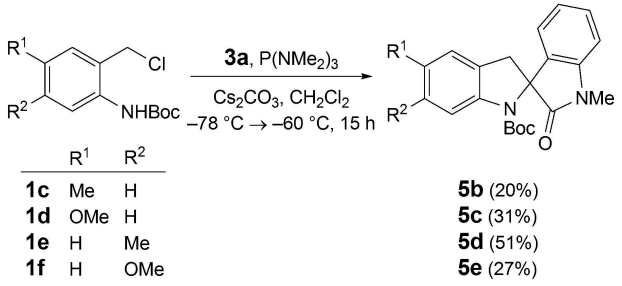
[a] Conditions: **1a** (0.2 mmol), **3a** (0.24 mmol), $P(NMe_2)_3$ (0.24 mmol), base (0.24 mmol), in CH_2Cl_2 (0.2 M). [b] Reaction temperature: −78 °C to −60 °C.

During these initial experiments we determined that self-condensation of **3a** occurred prior to consumption of **1a** as the reaction warmed to room temperature, and at a seemingly faster rate than what we observed with **2a**. However, when the reaction was allowed to warm from −78 °C to −60 °C, and maintained at this temperature for 15 h, a 54% yield of **5a** was obtained (*Table 2*, *Entry 5*). This finding is consistent with previous studies on *Kukhtin-Ramirez*-like reactivity wherein self-condensation of the 1,2-dicarbonyl is retarded at lower temperatures.[39] Increasing the amount of Cs_2CO_3, $P(NMe_2)_3$, and **3a** from 1.2 to 2.0 further improved the yield of dihydroindole **5a** to 77% (*Table 2*, *Entry 6*). Having identified an optimal set of conditions for the (4 + 1)-cycloadditions employing 1,2-dicarbonyls **2a** and **3a**, we turned our attention toward ascertaining the architectural limitations in the assembly of dihydroindoles **4** and **5**.

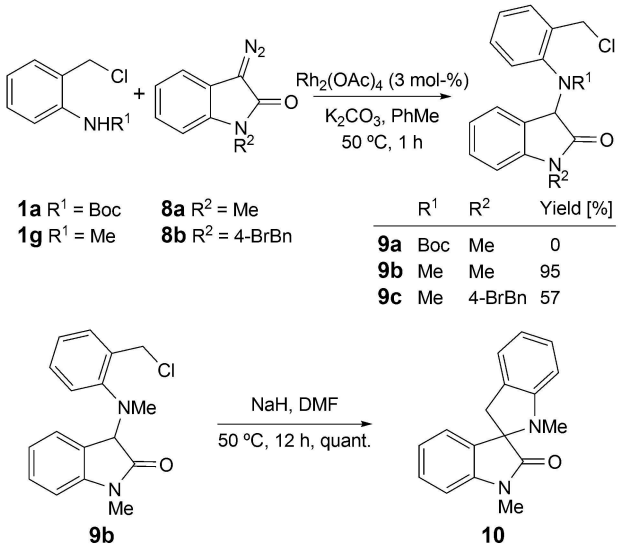
In general, and quite distinct from our findings related to the corresponding (4 + 1)-cycloadditions through *o*-quinone methides, the adducts derived from various aniline derivatives were obtained in consistently modest yields. Additionally, the incorporation of specific functional groups ultimately inhibited product formation. For example, treatment of *N*-acyl anilines bearing halogen substituents at C(4) or C(5) with either **2a** or **3a** under those optimal conditions identified in *Table 1* resulted in either exclusive epoxide formation or an intractable mixture of products. However, the presence of a methyl or methoxy substituent at C(5) in anilines **1c** and **1d** enabled formation of the corresponding cycloadducts **4b** and **4c** respectively, albeit in modest yields (*Scheme 5*). Employing *N*-methyl isatin **3a** led to dihydroindoles **5b** and **5c** in significantly decreased yields (*Scheme 6*). While methyl substitution at C(6) of **1a** provided dihydroindole **5d** in 51% yield, the presence of a C(6)-methoxy group decreased the yield of the cyclo-



Scheme 5. Dihydroindole construction.



Scheme 6. Spiropyrrolidine oxindole assembly.

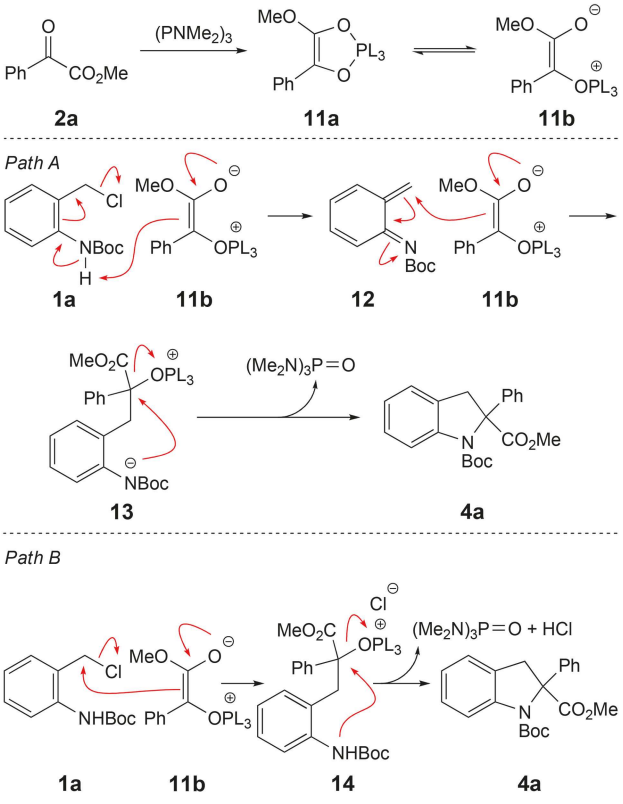


Scheme 7. Rh-Catalyzed C(3)-amino oxindole synthesis.

adduct. Interestingly, the *N*-Boc group on aniline **1a** proved critical as we observed no cycloadduct formation from the corresponding *N*-Ts, -Bn, -Ac, or -Cbz derivatives. Additionally, stereoelectronic variations of formate **2** or isatin **3** through the presence of aryl electron-withdrawing or electron-donating substituents resulted in trace product formation with self-condensation of the corresponding oxyphosphonium enolates as the major reaction pathway.

Based on our recent efforts in the C(3)-functionalization of oxindoles employing diazooxindoles in a (4+1)-cycloaddition, we sought to evaluate the comparative efficacy of a Rh(II)-metallocarbene as the C_1 synthon with 2-amino benzyl chlorides.[42–44] Interestingly, treatment of aza-*o*-QM precursor **1a** with diazooxindole **8** in the presence of $Rh_2(OAc)_4$ and K_2CO_3 yielded only recovered starting material. However, employing *N*-methyl aniline **1g** resulted in formation of C(3)-amino oxindole **9b** in 95% yield (*Scheme 7*)[1]. Likewise, the addition of *N*-bromobenzyl diazooxindole **8b** to aniline **1g** provided oxindole **9c** in 57% yield. While aniline addition to the electrophilic metallocarbene sets the stage for an intramolecular benzylation, the combination of a slow rhodium enolate C-alkylation and facile protonation precluded spirooxindole formation. The importance of the metal counterion was further illustrated by the quantitative yield achieved in the formation of spirooxindole **10** upon treatment of amino oxindole **9b** with NaH at 50 °C for 12 h.

Based on our current and previous findings, as well as those reported by *Ramirez*,[19–22] *Scheidt*,[32] *Radosevich*,[25,27,31,34–38] and *Xiao*,[33] our working mechanistic hypothesis addresses two possible competing pathways *en route* to dihydroindole formation (*Scheme 8*). Addition of $P(NMe_2)_3$ to formate **1a** leads to an equilibrium between dioxaphospholene **11a** and oxyphosphonium enolate **11b**, of which the enolate is



Scheme 8. Potential competing reaction mechanisms.

[1]This structure was verified using single X-ray crystallography on the *N*-4-bromobenzyl diazooxindole derivative. See *Supporting Information* for details.

the presumptive reactive constitutional isomer. Whether facilitated by an exogenous base or oxyphosphonium enolate **11b** as shown, subsequent deprotonation of the aniline N–H initiates an elimination of the benzyl chloride to provide aza-*o*-QM **12** (*path A*). The *Michael* addition of a second equivalent of **11b** followed by an intramolecular displacement of $(Me_2N)_3P{=}O$ provides the corresponding dihydroindole **4a**. Alternatively, formation of the crucial C(2)–C(3) bond in dihydroindoles **4** and **5** could arise from a direct displacement of the benzyl chloride in **1** by oxyphosphonium enolate **11b** to yield the phosphonium chloride **14** (*path B*). Subsequent ring closure yields the cycloadduct in a fashion comparable to that illustrated by *path A*. While a mechanism proceeding through an aza-*o*-QM intermediate is consistent with our previous work toward the construction of dihydrobenzofurans,[30] a direct benzyl chloride substitution mechanism cannot be ruled out.

Conclusions

In conclusion, we have developed a convergent, (4+1)-cycloaddition for the synthesis of C(2)-disubstituted dihydroindoles employing 2-amino benzyl chlorides with 1,2-dicarbonyls in a phosphoramide-mediated redox annulation. This method provides the corresponding 5-membered *N*-heterocycles and highlights the delicate balance of basicity and nucleophilicity of the versatile, intermediary oxyphosphonium enolates. Studies focused on resolving the curious influence of various benzyl chloride and 1,2-dicarbonyl substitution on the outcome of this cycloaddition and the competing mechanistic scenarios *en route* to dihydroindole assembly are currently underway and will be reported in due course.

Experimental Section

General Experimental Procedures

Solvents and reagents were reagent grade and used without further purification unless noted otherwise. 1,2-Difluorobenzene and 1,4-dioxane were passed through a column of activated alumina stored over molecular sieves under argon. All reactions were carried out in flame-dried glassware under an argon or nitrogen atmosphere unless otherwise specified. ^{1}H-NMR spectra were obtained at either 400, or 500 MHz. ^{13}C-NMR were obtained at 125 or 150 MHz. Chemical shifts are reported in parts per million ([ppm], δ), and referenced from tetramethylsilane (TMS). Coupling constants are reported in Hertz [Hz]. Spectral splitting patterns are designated as *s*, *singlet*; *d*, *doublet*; *t*, *triplet*; *q*, *quartet*; *m*, *multiplet*; comp *m*, complex *multiplet*; app, apparent; and br. *s*, broad singlet. IR Spectra were obtained using a *Thermo Electron Nicolet 380* FT-IR using a silica (Si) crystal in an attenuated total resonance (ATR) tower and reported as wavenumber [cm^{-1}]. High- and Low-resolution electrospray ionization (ESI) measurements were made with a *Bruker MicroTOF II* mass spectrometer. Analytical thin layer chromatography (TLC) was performed using *EMD 250 micron 60 F_{254}* silica gel plates, visualized with UV light and stained with *p*-anisaldehyde. Flash column chromatography was performed according to *Still*'s procedure[45] using EMD 40–63 μm 60 Å silica gel. Known compounds **1** were synthesized according to literature procedures.[32]

General Procedure for the Synthesis of 2,3-Dihydroindoles (**4**)

$P(NMe_2)_3$ (0.4 mmol) was added dropwise to a solution of **2** (0.4 mmol) in CH_2Cl_2 (2 mL) at −78 °C. The resulting solution was stirred for 10 min followed by the addition of **1** (0.2 mmol). The *reaction* mixture was allowed to warm to room temperature over 15 h then concentrated under reduced pressure. The residue was purified by flash column chromatography eluting with a solvent gradient of hexanes/AcOEt (20:1 to 10:1) to afford the title compound **4**.

1-*tert*-Butyl 2-Methyl 2-Phenyl-2,3-dihydro-1*H*-indole-1,2-dicarboxylate (**4a**). Dihydroindole **4a** was synthesized on a 0.2 mmol scale to provide 46 mg (90%) of the title compound as a colorless oil: IR (neat): 2978, 2953, 2929, 1751, 1705, 1371. ^{1}H-NMR (500 MHz, $CDCl_3$): 7.47 (*d*, *J*=7.6, 2 H); 7.31 (*t*, *J*=7.0, 2 H); 7.27–7.24 (*m*, 2 H); 7.04 (*d*, *J*=6.7, 1 H); 6.97 (*t*, *J*=6.8, 1 H); 3.86 (*d*, *J*=16.2, 1 H); 3.80 (*s*, 3 H) 3.39 (*d*, *J*=16.2, 1 H); 1.56 (br., 2 H); 1.27 (br., 7 H). ^{13}C-NMR (125 MHz): 172.6; 129.1; 129.0; 128.4; 128.2; 128.0; 127.6; 127.5; 126.7; 124.4; 123.2; 115.2; 77.4; 76.0; 52.9; 29.9; 28.2. HR-ESI-TOF-MS: 254.1194 ($[M+H]^+$, $C_{16}H_{15}NO_2^+$; calc. 254.1176).

1-*tert*-Butyl 2-Methyl 5-Methyl-2-phenyl-2,3-dihydro-1*H*-indole-1,2-dicarboxylate (**4b**). Dihydroindole **4b** was synthesized on a 0.3 mmol scale to provide 41 mg (37%) of the title compound as a colorless oil: IR (neat): 2978, 2927, 2850, 1750, 1704, 1492, 1367, 1228, 1147. ^{1}H-NMR (500 MHz, $CDCl_3$): 7.92 (br., 1 H); 7.46 (*d*, *J*=6.6, 2 H); 7.31 (*t*, *J*=7.1, 2 H); 7.26 (*t*, *J*=8.1, 1 H); 7.05 (*d*, *J*=7.8, 1 H); 6.86 (*s*, 1 H); 3.84 (*d*, *J*=16.2, 1 H); 3.79 (*s*,

3 H); 3.35 (*d*, *J* = 16.0, 1 H); 2.27 (*s*, 3 H); 1.60 (br., 2 H); 1.26 (br., 7 H). ^{13}C-NMR (100 MHz): 172.2 (2 C); 132.3; 129.2; 128.7; 128.3; 127.8; 127.6; 127.0; 126.3; 124.7; 114.5; 81.5; 73.0; 52.5; 46.2; 27.8; 20.7. HR-ESI-TOF-MS: 368.1871 ([*M* + H]$^+$, $C_{22}H_{26}NO_4^+$; calc. 368.1856).

1-*tert*-Butyl 2-Methyl 5-Methoxy-2-phenyl-2,3-dihydro-1*H*-indole-1,2-dicarboxylate (**4c**). Dihydroindole **4c** was synthesized on a 0.3 mmol scale to provide 31 mg (58%) of the title compound as a colorless oil: IR (neat): 3064, 2922, 2850, 1751, 1702, 1490, 1377, 1256, 1136. ^{1}H-NMR (500 MHz, $CDCl_3$): 7.95 (*d*, *J* = 6.2, 1 H); 7.46 (br., 2 H); 7.31 (*t*, *J* = 6.5, 2 H); 7.26 (*t*, *J* = 4.8, 1 H); 6.78 (*d*, *J* = 8.0, 1 H); 6.62 (*d*, *J* = 2.5, 1 H); 3.84 (*d*, *J* = 16.1, 1 H); 3.80 (*s*, 3 H); 3.75 (*s*, 3 H); 3.36 (*d*, *J* = 16.0, 1 H); 1.60 (br., 2 H); 1.26 (br., 7 H). ^{13}C-NMR (100 MHz): 172.3; 160.3; 156.0; 141.4; 136.3; 127.8; 127.3; 126.5 (2 C); 115.5; 112.7; 110.6; 81.4; 73.2; 55.7; 52.7; 46.4; 28.0. HR-ESI-TOF-MS: 384.1783 ([*M* + H]$^+$, $C_{22}H_{26}NO_5^+$; calc. 384.1805).

General Procedure for the Synthesis of Spiropyrrolidine Oxindoles (**5**)

$P(NMe_2)_3$ (0.4 mmol) was added dropwise to a mixture of **1** (0.2 mmol) and Cs_2CO_3 (0.4 mmol) in CH_2Cl_2 (0.5 mL). The mixture was cooled to −78 °C and a solution of **3** (0.4 mmol) in CH_2Cl_2 (0.5 mL) was added dropwise. The reaction was allowed to warm slowly to −60 °C by removal of the dry ice/acetone bath, stirred for 15 h at −60 °C, then filtered through a pad of *Celite* and concentrated under reduced pressure. The resulting residue was purified by flash chromatography eluting with CH_2Cl_2/hexanes/AcOEt (12:7:1) to afford the title compound **5**.

***tert*-Butyl 1′-Methyl-2′-oxo-1′,2′-dihydro-2,3′-spirobi[indole]-1(3*H*)-carboxylate** (**5a**). Spiropyrrolidine oxindole **5a** was synthesized on a 0.2 mmol scale to provide 54 mg (77%) of the title compound as a yellow oil: IR (neat): 3054, 2978, 2934, 1708, 1613, 1482, 1470, 1375, 1351, 1315, 1240. ^{1}H-NMR (500 MHz, $CDCl_3$): 7.98 (*d*, *J* = 8.1, 1 H); 7.31 (*t*, *J* = 7.7, 1 H); 7.25 (*t*, *J* = 7.7, 1 H); 7.14 (*d*, *J* = 7.3, 1 H); 7.10 (*d*, *J* = 7.3, 1 H); 7.01–6.98 (*m*, 2 H); 6.84 (*d*, *J* = 7.8, 1 H); 3.64 (*d*, *J* = 16.1, 1 H); 3.25 (*s*, 3 H); 3.20 (*d*, *J* = 16.1, 1 H) 1.12 (*s*, 9 H). ^{13}C-NMR (125 MHz): 176.8; 151.2; 143.5; 142.9; 132.7; 129.3; 128.2; 124.6; 123.3; 123.1; 121.9; 115.2; 110.1; 108.2; 81.6; 68.9; 41.7; 28.0; 26.7. HR-ESI-TOF-MS: 373.1505 ([*M* + Na]$^+$, $C_{21}H_{22}N_2NaO_3^+$; calc. 373.1523).

***tert*-Butyl 1′,5-Dimethyl-2′-oxo-1′,2′-dihydro-2,3′-spirobi[indole]-1(3*H*)-carboxylate** (**5b**). Spiropyrrolidine oxindole **5b** was synthesized on a 0.2 mmol scale to provide 14 mg (20%) of the title compound as a yellow oil: IR (neat): 2957, 2921, 2851, 1724, 1709, 1614, 1491, 1470, 1366, 1149, 1086, 752, 734. ^{1}H-NMR (400 MHz, $CDCl_3$): 7.84 (*d*, *J* = 8.2, 1 H); 7.31 (*t*, *J* = 7.6, 1 H); 7.10 (*d*, *J* = 7.6, 1 H); 7.06 (*d*, *J* = 7.9, 1 H); 6.99 (*t*, *J* = 7.6, 1 H); 6.96 (*s*, 1 H); 6.83 (*d*, *J* = 7.6, 1 H); 3.60 (*d*, *J* = 16.1, 1 H); 3.24 (*s*, 3 H); 3.16 (*d*, *J* = 16.1, 1 H); 2.32 (*s*, 3 H); 1.11 (*s*, 9 H). ^{13}C-NMR (100 MHz): 176.6; 151.0; 142.7; 141.0; 132.6; 132.4; 129.0; 128.4; 127.0; 125.0; 123.1; 121.7; 114.6; 107.9; 81.2; 68.7; 41.4; 27.8; 26.5; 20.9. HR-ESI-TOF-MS: 387.1685 ([*M* + Na]$^+$, $C_{22}H_{24}N_2NaO_3^+$; calc. 387.1679).

***tert*-Butyl 5-Methoxy-1′-methyl-2′-oxo-1′,2′-dihydro-2,3′-spirobi[indole]-1(3*H*)-carboxylate** (**5c**). Spiropyrrolidine oxindole **5c** was synthesized on a 0.06 mmol scale to provide 7 mg (31%) of the title compound as a yellow oil: IR (neat): 3055, 2927, 1726, 1704, 1612, 1490, 1470, 1374, 1323, 1256, 1141, 1125, 1088, 1013. ^{1}H-NMR (500 MHz, $CDCl_3$): 7.87 (*d*, *J* = 8.9, 1 H); 7.31 (*t*, *J* = 7.6, 1 H); 7.10 (*d*, *J* = 7.5, 1 H); 7.00 (*t*, *J* = 7.5, 1 H); 6.83 (*d*, *J* = 7.9, 1 H); 6.78 (*dd*, *J* = 6.6, 2.3, 1 H); 6.73 (*s*, 1 H); 3.79 (*s*, 3 H); 3.62 (*d*, *J* = 16.2, 1 H); 3.24 (*s*, 3 H); 3.16 (*d*, *J* = 16.2, 1 H); 1.11 (*s*, 9 H). ^{13}C-NMR (125 MHz): 176.8; 156.2; 132.8; 129.3; 129.0; 128.5; 125.5; 124.0; 123.3; 121.9; 115.6; 112.9; 111.1; 108.2; 81.3; 69.0; 56.0; 41.8; 28.0; 26.7. HR-ESI-TOF-MS: 403.1621 ([*M* + Na]$^+$, $C_{22}H_{24}N_2NaO_4^+$; calc. 407.1628).

***tert*-Butyl 1′,6-Dimethyl-2′-oxo-1′,2′-dihydro-2,3′-spirobi[indole]-1(3*H*)-carboxylate** (**5d**). Spiropyrrolidine oxindole **5d** was synthesized on a 0.14 mmol scale to provide 26 mg (51%) of the title compound as a yellow oil: IR (neat): 2978, 2926, 1706, 1612, 1498, 1471, 1427, 1366, 1313, 1249, 1147, 1128, 1084. ^{1}H-NMR (500 MHz, $CDCl_3$): 7.84 (*s*, 1 H); 7.30 (*t*, *J* = 7.5, 1 H); 7.10 (*d*, *J* = 7.5, 1 H); 7.00–6.98 (*m*, 2 H); 6.84–6.82 (*m*, 2 H); 3.59 (*d*, *J* = 15.9, 1 H); 3.24 (*s*, 3 H); 3.15 (*d*, *J* = 15.9, 1 H); 2.36 (*s*, 3 H); 1.12 (*s*, 9 H). ^{13}C-NMR (125 MHz): 176.8; 151.3; 143.6; 142.9; 138.2; 132.8; 129.3; 124.2; 123.8; 123.3; 121.9; 115.9; 110.1; 108.2; 81.6; 69.2; 41.4; 28.0; 26.7; 21.9. HR-ESI-TOF-MS: 387.1684 ([*M* + Na]$^+$, $C_{22}H_{24}N_2NaO_3^+$; calc. 387.1679).

***tert*-Butyl 6-Methoxy-1′-methyl-2′-oxo-1′,2′-dihydro-2,3′-spirobi[indole]-1(3*H*)-carboxylate** (**5e**). Spiropyrrolidine oxindole **5e** was synthesized on a 0.06 mmol scale to provide 7 mg (27%) of the title compound as a yellow oil: IR (neat): 3057, 2931, 1707, 1612, 1497, 1470, 1448, 1376, 1321, 1249, 1162, 1086. ^{1}H-NMR (500 MHz, $CDCl_3$): 7.66 (*d*, *J* = 2.0, 1 H); 7.31 (*t*, *J* = 7.9, 1 H); 7.12 (*d*, *J* = 7.2, 1 H); 7.00 (*d*, *J* = 8.2, 1 H); 7.00 (*t*, *J* = 7.2, 1 H); 6.83

(*d*, *J*=7.8, 1 H); 6.57 (*dd*, *J*=8.2, 2.3, 1 H); 3.84 (*s*, 3 H); 3.56 (*d*, *J*=16.0, 1 H); 3.24 (*s*, 3 H); 3.13 (*d*, *J*=16.0, 1 H); 1.11 (*s*, 9 H). ^{13}C-NMR (125 MHz): 176.5; 160.1; 151.0; 144.5; 142.6; 132.5; 129.1; 124.6; 123.1; 121.6; 118.6; 109.5; 108.0; 101.0; 81.4; 69.5; 55.6; 40.8; 27.7; 26.5. HR-ESI-TOF-MS: 407.1625 ($[M+Na]^+$, $C_{22}H_{24}N_2NaO_4^+$; calc. 407.1628).

***tert*-Butyl [2-(Chloromethyl)phenyl](^{2}H)carbamate (1a-*d*)**. A mixture of **1a** (100 mg, 0.4 mmol) and Cs_2CO_3 (269 mg, 0.8 mmol) in CH_2Cl_2 (2 mL) was stirred for 5 min, followed then by the addition of D_2O (2 mL) and stirred for an additional 20 min. The mixture was transferred to a separatory funnel and extracted with CH_2Cl_2 (3×5 mL). The resulting organic fractions were dried (Na_2SO_4) and concentrated under reduced pressure to afford 68 mg (68%) of **1a**–**d** as a white solid: IR (neat): 2979, 2933, 2534, 1809, 1724, 1496, 1377, 1368, 1249, 1166, 1118, 1055, 735. ^{1}H-NMR (400 MHz, $CDCl_3$): 7.85 (*d*, *J*=8.0, 1 H); 7.35 (*td*, *J*=7.6, 1.6, 1 H); 7.26 (*dd*, *J*=7.6, 1.5, 1 H); 7.06 (*td*, *J*=7.5, 1.0, 1 H); 4.61 (*s*, 2 H); 1.54 (*s*, 9 H). ^{13}C-NMR (125 MHz): 153.2; 147.0; 137.2; 130.3; 130.2; 124.2; 122.8; 81.1; 44.4; 28.5; 27.6. HR-ESI-TOF-MS: 241.0857 ($[M+H]^+$, $C_{12}H_{16}NO_2Cl^+$; calc. 241.0870).

Methyl Chloro(phenyl)(^{2}H)acetate (6-*d*). $P(NMe_2)_3$ (41 mg, 0.24 mmol) was added dropwise to a solution of **2a** (41 mg, 0.24 mmol) in CH_2Cl_2 (2 mL) at −78 °C. The resulting solution was stirred for 10 min followed by the addition of **1a**–**d** (30 mg, 0.12 mmol). The mixture was allowed to warm to room temperature over 15 h, then concentrated under reduced pressure. The residue was purified by flash column chromatography eluting with a solvent gradient of hexanes/AcOEt (20:1 to 10:1) to provide 18 mg (83%) of **6**–**d** as a clear oil and 36 mg (85%) of **4a** as a clear oil. Spectral data for **6**–**d** agree with literature sources:[46] IR (neat): 3031, 2954, 2924, 2853, 1754, 1455, 1436, 1281, 1162, 1006, 728, 695. ^{1}H-NMR (500 MHz, $CDCl_3$): 7.51–7.48 (*m*, 2 H); 7.40–7.37 (*m*, 3 H); 5.37 (*s*, 0.5 H); 3.78 (*s*, 3 H). ^{13}C-NMR (100 MHz): 168.9; 135.7; 129.3; 128.9; 127.9; 59.0; 53.4.

3-{[2-(Chloromethyl)phenyl](methyl)amino}-1-methyl-1,3-dihydro-2*H*-indol-2-one (9b). Compound **1g** (15.6 mg, 0.1 mmol), K_2CO_3 (13.8 mg, 0.1 mmol), and $Rh_2(OAc)_4$ (1.4 mg, 0.003 mmol) were added sequentially to a flame-dried vial and constituted in PhMe (0.5 mL). A solution of **8** (20.8 mg, 0.12 mmol) in PhMe (0.5 mL) was added to the mixture through slow addition with a syringe pump over 1 h at 50 °C. The mixture was then cooled to room temperature and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with a solvent gradient of hexanes/AcOEt (3:1) to afford 25 mg (95%) of **9b** as an orange oil: IR (neat): 2925, 2855, 2652, 1739, 1610, 1470, 1368, 1328, 1092, 756. ^{1}H-NMR (500 MHz, $CDCl_3$): 7.59 (*dd*, *J*=8.1, 1.1, 1 H); 7.47 (*dd*, *J*=7.6, 1.6, 1 H); 7.38 (*d*, *J*=7.4, 1 H); 7.36–7.30 (*m*, 2 H); 7.15 (*t*, *J*=7.5, 1.2, 1 H); 7.08 (*tt*, *J*=7.6, 0.9, 1 H); 6.84 (*d*, *J*=7.8, 1 H); 5.04 (*d*, *J*=11.1, 1 H); 5.02 (*s*, 1 H); 4.95 (*d*, *J*=11.1, 1 H); 3.23 (*s*, 3 H); 2.57 (*s*, 3 H). ^{13}C-NMR (125 MHz): 175.0; 150.7; 143.8; 132.1; 131.4; 129.3; 129.0; 125.4; 124.8; 124.4; 123.7; 122.6; 108.0; 66.0; 42.9; 36.3; 26.0. HR-ESI-TOF-MS: 265.1321 ($[M+H-HCl]^+$, $C_{17}H_{17}N_2O^+$; calc. 265.1335).

1-[(4-Bromophenyl)methyl]-3-diazo-1,3-dihydro-2*H*-indol-2-one (8b). Diazo oxindole (100 mg, 0.6 mmol), K_2CO_3 (104 mg, 0.8 mmol), and *p*-bromobenzyl bromide (173 mg, 0.7 mmol) were added sequentially to a flame-dried vial and dissolved in DMF (0.6 mL). After stirring for 15 h at room temperature, the mixture was diluted with Et_2O (20 mL) and washed with H_2O (3×60 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with hexanes/AcOEt (4:1) to afford 109 mg (53%) of **8b** as a red solid: M.p. 98–100 °C. IR (neat): 3057, 2927, 2857, 2087, 1676, 1608, 1467, 1397, 1377, 1338, 1167, 1011. ^{1}H-NMR (500 MHz, $CDCl_3$): 7.41 (*dt*, *J*=8.5, 2.5, 2 H); 7.19–7.18 (*m*, 1 H); 7.16 (*dt*, *J*=8.6, 2.4, 2 H); 7.09 (*dt*, *J*=7.6, 1.5, 1 H); 7.07 (*dt*, *J*=7.6, 1.5, 1 H); 6.78–6.76 (*m*, 1 H); 4.95 (*s*, 2 H). ^{13}C-NMR (125 MHz): 167.0; 135.3; 133.6; 132.1; 129.3; 125.7; 122.6; 121.9; 118.6; 117.0; 109.6; 43.9; 30.0. HR-ESI-TOF-MS: 328.0052 ($[M+H]^+$, $C_{15}H_{11}BrN_3O^+$; calc. 328.0080).

1-[(4-Bromophenyl)methyl]-3-{[2-(chloromethyl)phenyl](methyl)amino}-1,3-dihydro-2*H*-indol-2-one (9c). To a flame-dried 2-dram vial was added **1g** (15.6 mg, 0.1 mmol) and $Rh_2(OAc)_4$ (1.4 mg, 0.003 mmol) sequentially, and the mixture dissolved in PhMe (0.5 mL). A solution of **8b** (65.6 mg, 0.2 mmol) in PhMe (0.5 mL) was added through slow addition with a syringe pump over 1 h at room temperature. After stirring for an additional 1 h at room temperature, the mixture was concentrated under reduced pressure. The residue was purified by flash chromatography eluting with a solvent gradient of hexanes/AcOEt (3:1) to afford 24 mg (57%) of **9c** as an orange oil (CCDC #1895498). IR (neat): 3066, 3029, 2924, 2853, 1738, 1613, 1488, 1469, 1350, 1176, 1011, 754. ^{1}H-NMR (500 MHz, $CDCl_3$): 7.60 (*dd*, *J*=8.1, 1.1, 1 H); 7.48 (*dd*, *J*=7.6, 1.7, 1 H); 7.43–7.41 (*m*, 3 H); 7.34 (*ddd*, *J*=8.0, 7.4, 1.7, 1 H); 7.23 (*tt*, *J*=7.8, 1.2, 1 H); 7.20–7.15 (*m*, 3 H); 7.07 (*td*, *J*=7.6, 1.0, 1 H); 6.70 (*d*, *J*=7.8, 1 H); 5.09 (*s*, 1 H); 5.03 (*d*, *J*=11.1, 1 H); 4.97 (*d*, *J*=11.1, 1

H); 4.94 (*d*, *J* = 15.7, 1 H); 4.79 (*d*, *J* = 15.7, 1 H); 2.62 (*s*, 3 H). ^{13}C-NMR (125 MHz): 175.5; 150.9; 143.0; 135.1; 132.7; 132.2; 131.8; 129.7; 129.4; 125.9; 125.4; 125.1; 124.3; 123.2; 121.9; 109.3; 66.3; 43.4; 43.2; 37.0. HR-ESI-TOF-MS: 419.0759 ($[M+H-HCl]^+$, $C_{23}H_{20}BrN_2O^+$; calc. 419.0735).

1,1′-Dimethyl-1,3-dihydro-2,3′-spirobi[indol]-2′(1′*H*)-one (**10**). NaH (2.3 mg, 0.06 mmol) was added to a stirring solution of **9b** (16.5 mg, 0.05 mmol) in DMF (0.25 mL) at room temperature. After stirring at 50 °C for 12 h, water (ca. 0.5 mL) was added. The resulting mixture was extracted with AcOEt (3×5 mL), and the combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with hexanes/AcOEt (3:1) to give 13 mg (>99%) of **10** as an orange oil. IR (neat): 2923, 2852, 1719, 1608, 1485, 1468, 1370, 1345, 1091, 744. ^{1}H-NMR (500 MHz, $CDCl_3$): 7.33 (*td*, *J* = 7.8, 1.3, 1 H); 7.17–7.12 (*m*, 2 H); 7.07 (*dd*, *J* = 7.2, 0.7, 1 H); 7.00 (*td*, *J* = 7.6, 1.0, 1 H); 6.87 (*d*, *J* = 7.8, 1 H); 6.72 (*td*, *J* = 7.5, 0.9, 1 H); 6.47 (*d*, *J* = 7.8, 1 H); 3.53 (*d*, *J* = 15.6, 1 H); 3.25 (*s*, 3 H); 3.19 (*d*, *J* = 15.6, 1 H); 2.46 (*s*, 3 H). ^{13}C-NMR (150 MHz): 177.0; 151.9; 143.1; 129.5; 129.3; 127.9; 126.9; 124.1; 123.5; 123.0; 118.1; 108.4; 106.7; 73.9; 40.8; 30.7; 29.7; 24.6 (trace diazo dimer). HR-ESI-TOF-MS: 265.1352 ($[M+H]^+$, $C_{17}H_{17}N_2O^+$; calc. 265.1335).

Acknowledgements

This work was supported by the National Science Foundation (CAREER CHE-1056242 and 1665440).

Author Contribution Statement

K. Eckert and *A. Lepore* conducted the experiments and analyzed the data. Prof. *B. Ashfeld* conceived and designed the experiments. *K. Eckert* and Prof. *B. Ashfeld* prepared the manuscript.

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Received August 2, 2019
Accepted October 7, 2019

