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Scaffold-Divergent Synthesis of Ring-Fused Indoles, Quinolines, and Quinolones via Iodonium-Induced Reaction Cascades

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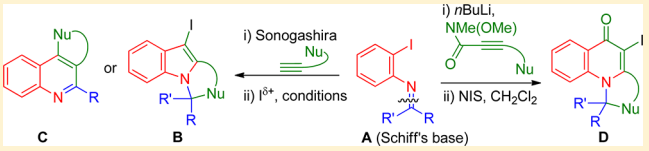
Supporting Information

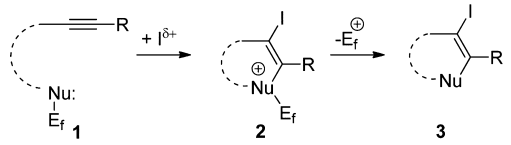
ABSTRACT: *N*-(2-Iodophenyl)imines **A** are readily formed from Schiff's base condensation of 2-iodoanilines with carbonyls and ketals. These imines provide useful substrates in scaffold-divergent synthesis through the attachment of an alkyne (Songashira coupling or acyl substitution of a Weinreb amide) followed by an iodonium-induced reaction cascade to give ring-fused indoles **B**, quinolines **C**, or quinolones **D** depending on the reaction conditions employed.



INTRODUCTION

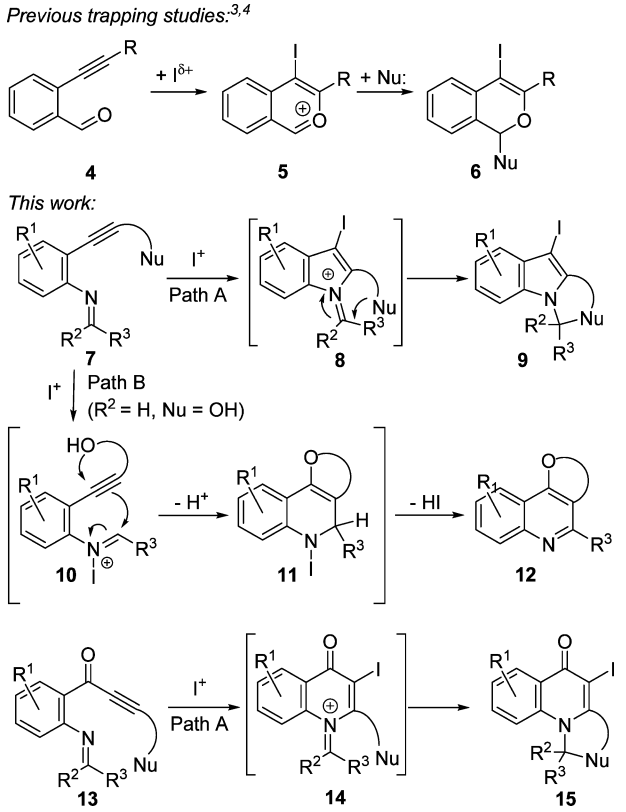
Electrophilic activation of alkynes toward intramolecular nucleophilic attack has emerged as a highly effective means of forming a variety of carbocyclic and heterocyclic ring systems.[1,2] A particularly useful reaction is the 5- and 6-endo-digonal iodocyclization of a tethered heteroatomic nucleophile Nu upon an alkyne using an iodonium source **1** → **2** → **3** (Scheme 1).

Scheme 1. Iodocyclization with Electrofugal (E_f) Displacement



The electrofuge (E_f) may either be a proton or an alkyl group that is removed using either a base or nucleophile (usually I^-), respectively. An interesting variation on the use of an electrofuge is the trapping of the initially formed cyclic cation by another nucleophile in a reaction cascade. For example, Barluenga and Larock have demonstrated that iodocyclization of *o*-alkynylbenzaldehydes **4** gives a benzopyranium ion **5** that undergoes subsequent nucleophilic attack to give a highly substituted 4-iodobenzopyran **6** (Scheme 2).[3,4] We rationalized that a similar cascade could be used in a cocyclization strategy to form ring-fused indoles **9** where readily accessible *N*-(2-alkynylphenyl)-imines **7** undergo iodocylization to an imminum ion **8** that can then be trapped by a nucleophile tethered to the alkynyl group giving **9** (Path A, Scheme 2). Herein, we report our investigations into this approach to ring-fused indoles **9**.[5,6] We also describe an equivalent cocylization process for the formation of ring-fused quinolones **13** → **14** → **15**. Interestingly, during our evaluation of different reaction conditions to effect cocyclizations to give indoles **9**, we have identified an alternative pathway (Path B) involving iodonium activation of the imine **7** (R^2 = H, Nu = OH) such that it becomes an electrophile and

Scheme 2. Iodocyclization with Nucleophilic Trapping



undergoes a concerted cocyclization with the tethered alkynol to give a ring-fused quinolines **7** → **10** → **11** → **12** (Path B). The ring structures made available through these cocyclization strategies may provide useful scaffolds exhibiting interesting

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biological activities. Examples of related structures that have exhibited biological activity include the HCV NSB5 polymerase inhibitor **16**,[7] the steroid dehydrogenase inhibitor **17**,[8] the acetylcholinesterase (AChE) inhibitor **18**,[9] and the topoisomerase inhibitor **19** (Figure 1).[10]

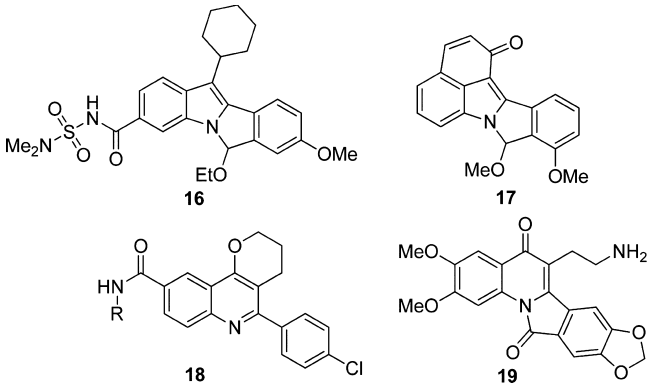
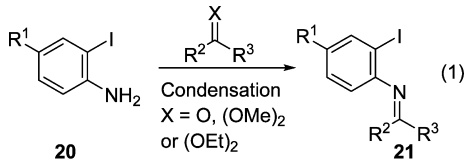


Figure 1. Bioactive ring-fused indoles, quinolines, and quinolones.

RESULTS AND DISCUSSION

For the purpose of our investigation, we first prepared a series of different *N*-(2-iodophenyl)imines **21** (eq 1). These could be



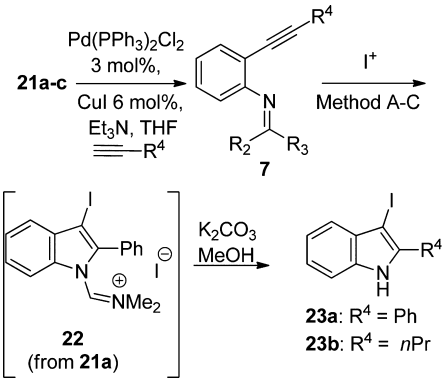
21a $R^1 = R^2 = H$, $R^3 = NMe_2$, 99%
21b $R^1 = R^2 = H$, $R^3 = Ph$, 85%
21c $R^1 = H$, $R^2 = R^3 = Ph$, 92%
21d $R^1 = H$, $R^2 = OMe$, $R^3 = Ph$, 91%
21e $R^1 = H$, $R^2 = R^3 = PMP$,[a] 69%
21f $R^1 = R^2 = H$, $R^3 = PMP$,[a] NI[b]
21g $R^1 = R^2 = H$, $R^3 = Tol$,[c] 88%
21h $R^1 = H$, $R^2 = H$, $R^3 = OEt$, NI[b]
21i $R^1 = Me$, $R^2 = R^3 = Ph$, 79%

[a]PMP = 4-methoxyphenyl
[b]NI = not isolated
[c]Tol = 4-methylphenyl

accessed from the corresponding 2-iodoaniline **20** via condensation reactions and were generally formed in good yields (69–99%). However, two of these imines, **21f** and **21h**, were not isolated because of stability issues but used directly in the subsequent coupling and iodocyclization steps (vide infra).

Our initial studies focused on the use of imines to act as labile activating groups for promoting iodocyclization to give simple NH-indoles (Table 1). The iodocyclization of simple 2-alkynylanilines to NH-3-iodoindoles has been previously achieved using a strong base and a gold salt (KOH, $NaAuCl_4$, I_2) or the use of a very powerful iodonium source ($Pyr_2I{\cdot}BF_4$).[2d,j] Knight demonstrated that 2-alkynylanilines bearing electron-withdrawing groups (Boc and Tosyl) on the nitrogen could be iodocyclized under mildly basic conditions (K_2CO_3, I_2).[2e] These activating groups can then be readily cleaved under acidic (Boc) or basic (Tosyl) conditions to give the NH-3-iodoindole. Finally, *N*,*N*-dialkyl-2-alkynylanilines can be iodocyclized to *N*-alkyl-3-iodoindoles under relatively mild conditions.[2a,l,k] We have briefly explored the use of imines as

Table 1. Synthesis of NH-3-Iodoindoles 23



	7					
entry		R^2	R^3	R^4	method[a]	**23** (%, from **21**)
1	**7a**	H	NMe_2	Ph	**A**	**23a** (78)
2	**7b**	Ph	Ph	Ph	**B**	**23a** (70)
3	**7b**	Ph	Ph	Ph	**C**	**23a** (87)
4	**7c**	Ph	Ph	*n*Pr	**B**	**23b** (94)
5	**7d**	H	Ph	*n*Pr	**B**/**C**	**23b** (0)

[a]Method **A**: I_2, CH_2Cl_2, then K_2CO_3, MeOH (aq); **B**: NIS, CH_2Cl_2; **C** I_2, K_2CO_3, CH_3CN.

alternative activating group to complement these other methods to NH-3-iodoindoles (Table 1). Sonogashira coupling of **21** with terminal alkynes gives efficient access to the desired *N*-(2-alkynylphenyl)imines **7**. Since compounds **7** are prone to protocyclization on silica gel, the crude material was not chromatographed but subjected directly iodocyclization (Table 1). The dimethylcarboximidate group in **7a** (R^2 = H, R^3 = NMe_2) was effective in promoting iodocyclization using I_2 in CH_2Cl_2 to give the imminium intermediate **22**, which was readily cleaved upon treatment with K_2CO_3 in MeOH (methanolysis) to afford the NH-3-iodoindole **23a** (78%, from **21a**) (Method A, entry 1, Table 1). The diphenylimine (R^2 = R^3 = Ph) also undergoes facile iodocyclization using either NIS in CH_2Cl_2 (Method B) or I_2 and K_2CO_3 in CH_3CN (Method C) (entries 2–4, Table 1). These reactions occur with in situ cleavage of the imminium intermediate to give direct access to NH-3-iodoindoles **23a** and **23b** in good yields (70–94%, from **21a**). Aldimines (R^2 = H, R^3 = Ph) failed in the iodocyclization step, with hydrolysis to form the 2-alkynylaniline and benzaldehyde being the major byproducts (entry 5, Table 1). Thus, diphenylimine and dimethylcarboximidate are useful activating groups for achieving access to NH-3-iodoindoles under neutral or slightly basic conditions, complementing the earlier approaches described above.

Of particular interest to us was to explore the use of *N*-(2-alkynylphenyl)imines **7** bearing tethered nucleophiles in reaction cascades, where iodocyclization of **7** gives an imminium ion **8** that undergoes intramolecular attack by the pendant nucleophile to give a cocyclized product **9** (Scheme 2). To evaluate this we coupled a series *N*-(2-iodophenyl)imines **21** to several terminal alkynes containing nucleophilic substituents (R^4 = alcohol or electron-rich arene) under Sonogashira conditions to give *N*-(2-alkynylphenyl)-imines **7** (Table 2). Again, imines **7** were not able to be purified by chromatography and so were subjected directly to iodocyclization (Method B/C, Table 2). Using Method B (NIS in CH_2Cl_2) most imines **7** were successfully cyclized to the ring-fused indoles **9** in moderate to good yields over the two steps from **21** 43–94% (Method B, Table 2). An exception to this was the iodocyclization of phenylaldimine **7** (R^2 = H, R^3 = Ph, R^4 = CH_2OH), which failed

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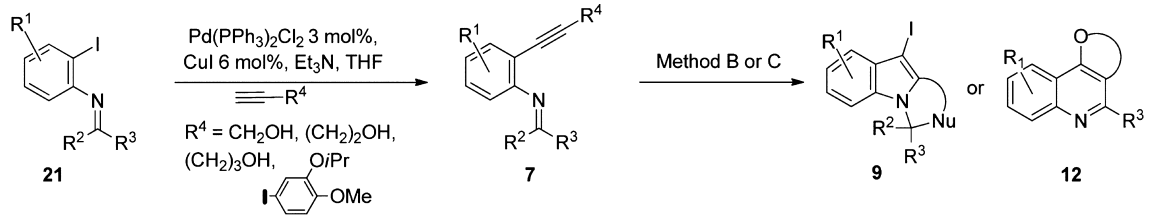
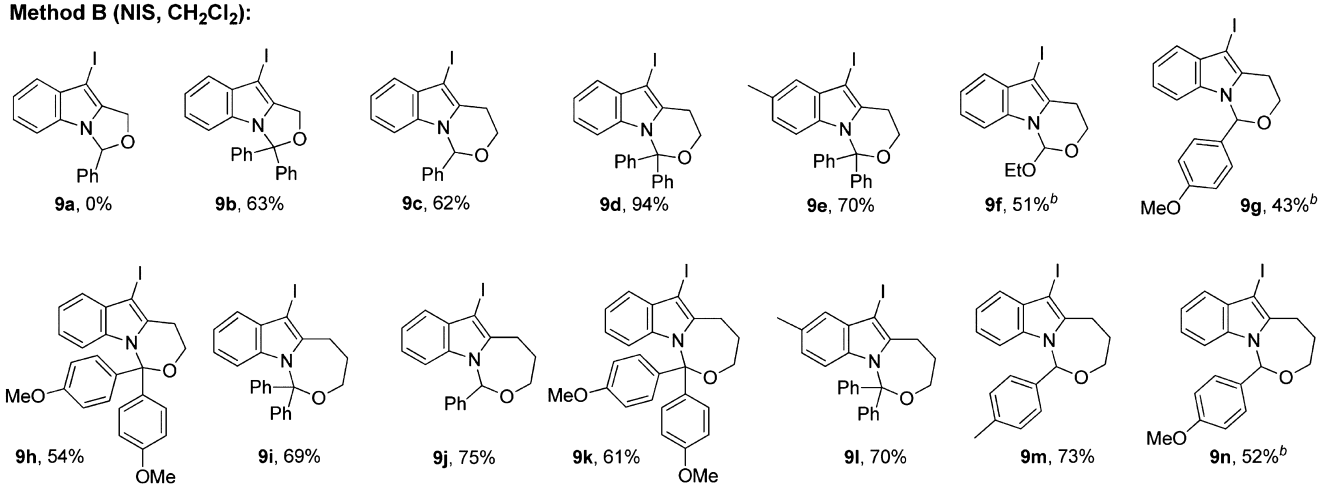
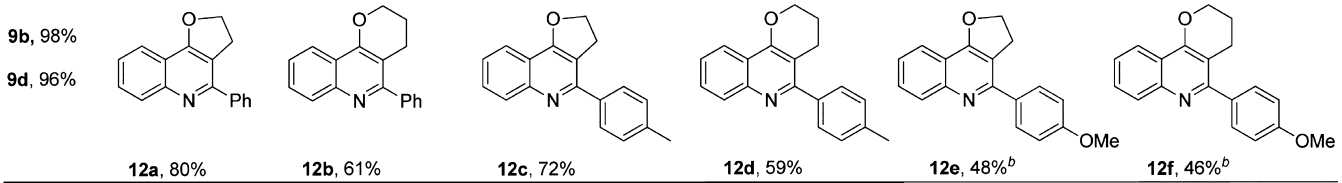
Table 2. Synthesis of Ring-Fused Indoles 9 and Quinolines 12[a]



Method B (NIS, CH_2Cl_2):



Method C (I_2, K_2CO_3, CH_3CN):

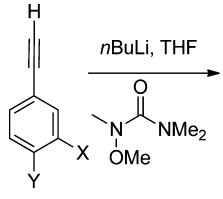


[a]Unless otherwise stated, the isolated yield of **9** and **12** is calculated from the relevant imine **21**. [b]Isolated yield calculated from 2-iodoaniline **20**.

to yield cocyclized product **9a**, returning the imine hydrolysis products 2-(propynol)aniline and benzaldehyde (not shown). By contrast, the related aldimine substrates bearing OH groups on longer tethers [$R^4 = (CH_2)_2OH$ or $(CH_2)_3OH$] were successfully iodocyclized to the ring-fused 3-iodoindoles: **9c** (62%), **9g** (41%), **9j** (75%), **9m** (73%) and **9n** (52%). These results suggest that suitably distal nucleophiles (OH) can promote iodocyclization avoiding the competing aldimine hydrolysis seen when either a shorter tether is used ($R^4 = CH_2OH$) or where no nucleophile is present ($R^4 = n$Pr). In addition to R^4 = alcohol, cocyclization was also achieved where R^4 = electron-rich arene, **9p** (52%) (see also below).

For diphenylimines cocyclization of **7** gave the same product **9** under Method C (I_2, K_2CO_3, CH_3CN) as Method B (NIS, CH_3Cl_2) in, for example, **9b** (98%) and **9d** (96%). However, cocyclization of arylaldimines bearing tethered alcohols **7** [R^2 = H, R^3 = aryl, $R^4 = (CH_2)_2OH$, $(CH_2)_3OH$] using Method C gave an alternative product in the form of the furano and pyrano fused quinolones **12a–f** in reasonable yields (**12a–d** 59–80% over two steps from iodoimine **21** and **12e,f** 46–48% over three steps from iodoaniline **20**).

The iodocyclization used to form indoles **21** and **9** was also extended to quinolones **25** and **15** (Table 3). Lithiation of the iodoimines **21** (iodide for lithium exchange) followed by acyl substitution of the Weinreb amides **24** gave alkynones **13**, which were not isolated but subject directly to iodocyclization to afford iodoquinolones **15** and/or **25** (see below). Weinreb amides **24** were readily formed from the corresponding terminal alkynes by deprotonation and acyl substitution of 1-methoxy-1,3,3-trimethylurea (eq 2).[11]



24a: X = Y = H, 68%
24b: X = H, Y = OMe, 87%
24c: X = OMe, Y = H, 40%
24d: X = O*i*Pr, Y = OMe, 58%

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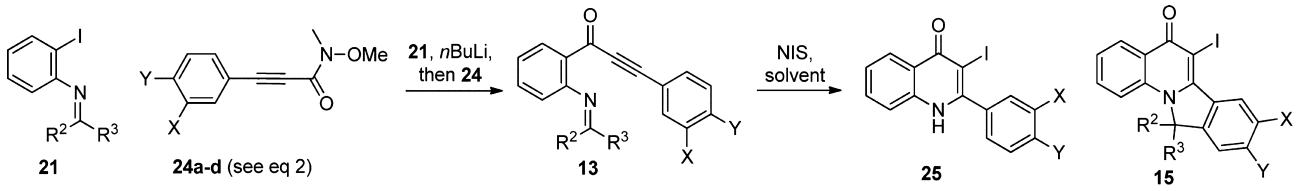
Table 3. Synthesis of 3-Iodoquinolones 25 and 15



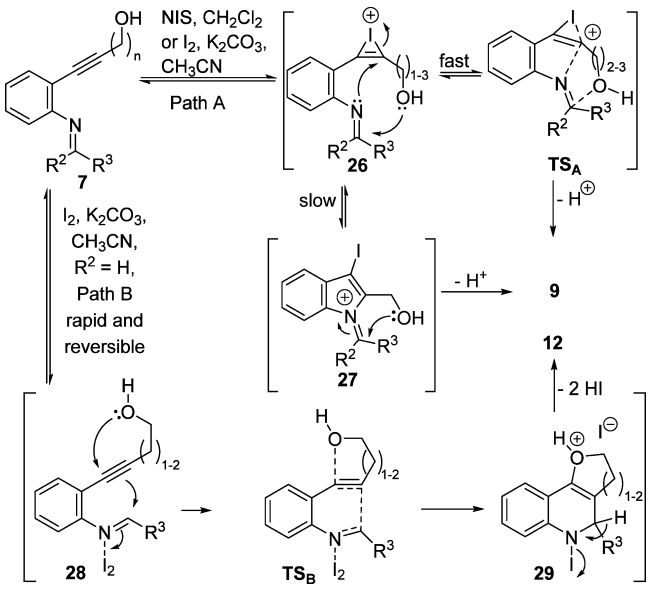
	13[a]						
entry		R^2	R^3	X	Y	iodocyc. solvent	product (%, from **21**)
1	**13a**	Ph	Ph	H	H	CH_3CN	**25a** (36), **15a** (47)
2	**13b**	OMe	Ph	H	H	CH_3CN	**25a** (58)
3	**13c**	OMe	Ph	H	OMe	CH_3CN	**25b** (61)
4	**13d**	OMe	Ph	OMe	H	CH_2Cl_2	**15d** (85)[b]
5	**13e**	OMe	Ph	O*i*Pr	OMe	CH_2Cl_2	**15e** (90)
6	**13f**	Ph	Ph	OMe	H	CH_2Cl_2	**15f** (59)
7	**13g**	Ph	Ph	O*i*Pr	OMe	CH_2Cl_2	**15g** (95)

[a]This material was not isolated but subject directly to the iodocyclization step to give **15** or **25**. [b]Isolated as a 1:1 mixture of regiosiomers (X = OMe, *ortho* and *para* to CR^2R^3).

We initially investigated the use of imines **13** to promote iodocyclization to give an NH-3-iodoquinolones **25**. The diphenylimine group was not as effective in the cyclization of **13** ($R^1 = R^2 =$ Ph) to give NH-3-iodoquinolones **25** as it had been in the cyclization of **7** ($R^1 = R^2 =$ Ph) to give NH-3-iodoindoles **23** because of an increased propensity of unactivated arenes (X = Y = H) to undergo trapping to give **15**. Thus, iodocyclization of **13a** using NIS in CH_3CN gave a mixture of NH-3-iodoquinolone **25a** and cocyclized material **15a** (entry 1, Table 3). However, the use of the methylbenzimidate group overcame this issue, allowing alkynones **13b** and **13c** to be iodocyclized to NH-3-iodoquinolones **25a** and **25b** in reasonable yield, 58 and 61%, respectively, from **21** (entry 2 and 3, Table 3). When the nucleophilic arene was activated by the presence of suitable donors (X = electron donor) and the iodocyclization was performed in anhydrous CH_2Cl_2, the cocyclization product **15** dominated and was isolated in moderated to good yields 59–90% (entries 4–7, Table 3).

On the basis of observations made during this study, we have made a number of tentative mechanistic proposals (Scheme 3).

Scheme 3. Mechanistic Proposal for Formation of 9 and 12



First, we were struck by the capacity of the pendant alcohols [$R^4 = (CH_2)_2OH$, $(CH_2)_3OH$] in **7** to promote cocyclization of aldimines to give a ring-fused 3-iodoindoles, despite the fact that iodocyclization of the aldimines **7** ($R^2 =$ H) where the OH is absent (e.g., $R^4 = n$Pr) or attached to shorter tether ($R^4 = CH_2OH$) failed to iodocyclize and underwent competitive imine hydrolysis. This prompted us to propose a mechanism where the tethered OH group promotes iodocyclization (cocyclization), possibly by stabilizing the emerging positive charge on the imine nitrogen during nucleophilic attack on the alkyne, as in transition state $\mathbf{TS_A}$.[5] The shorter tether in **7** ($R^4 = CH_2OH$) may prevent access to $\mathbf{TS_A}$ because of geometric constraints, preventing overlap between the OH electron lone pair and π^* of the imine (a disfavored 5-*endo-trig*).[12]

To get a better understanding of the nature of the alkyne substituents on cyclization rates, we undertook a reaction rate study of the diphenylimine systems **7** ($R^2 = R^3 =$ Ph), and unlike the aldimines system **7** ($R^2 =$ H, $R^3 =$ Ph), in these cases all the iodocyclization products were successfully formed irrespective of the alkyne substituent (Figure 2). Tracking the extent of conversion as a function of time, we found that the propynol group ($R^4 = CH_2OH$) iodocyclized much more slowly than the other systems **7** [$R^4 = n$Pr, $(CH_2)_2OH$, $(CH_2)_3OH$]; that is, **9b** is formed much more slowly than **21b**, **9d**, and **9i**. Since **7** ($R^4 = CH_2OH$) cyclizes slower than all other substrates, including **7** ($R^4 = n$Pr), it is not necessary to evoke a disfavored 5-*endo-trig* in $\mathbf{TS_A}$ to explain the inability to form **9a**. Instead, we attribute the slow cyclization of **7** ($R^4 = CH_2OH$) to **9b** to an electron-withdrawing inductive effect of OH upon the alkyne. This inductive effect may significantly reduce the rate of iodonium attack upon the alkyne and/or impede the nucleophilic attack of the imine upon iodonium/alkyne complex **26**, which requires the development of a transient positive charge on the alkyne-carbon proximal to the electron withdrawing CH_2OH group. Presumably, this inductive effect impedes the rate of formation of **9a** to a sufficient degree that competing hydrolysis of the aldimine becomes the prevailing pathway. However, this does not explain why the phenylaldimine **7d** ($R^2 =$ H, $R^3 =$ Ph, $R^4 = n$Pr) failed to iodocyclize (entry 5, Table 1) despite the efficient iodo-cocyclization of many other aldimine substrates bearing pendant OH groups **7** [$R^2 =$ H, $R^3 =$ aryl, $R^4 = (CH_2)_{2/3}OH$] (Method B, Table 3). One possibility is that diphenylimines do not require the nucleophilic assistance because of the increased stabilization given to the

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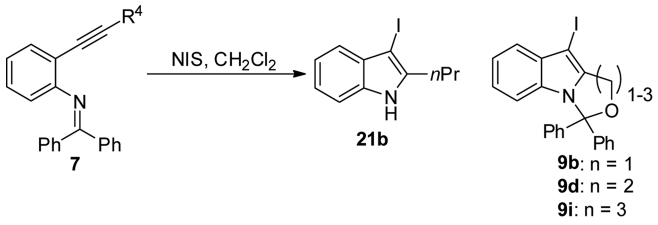


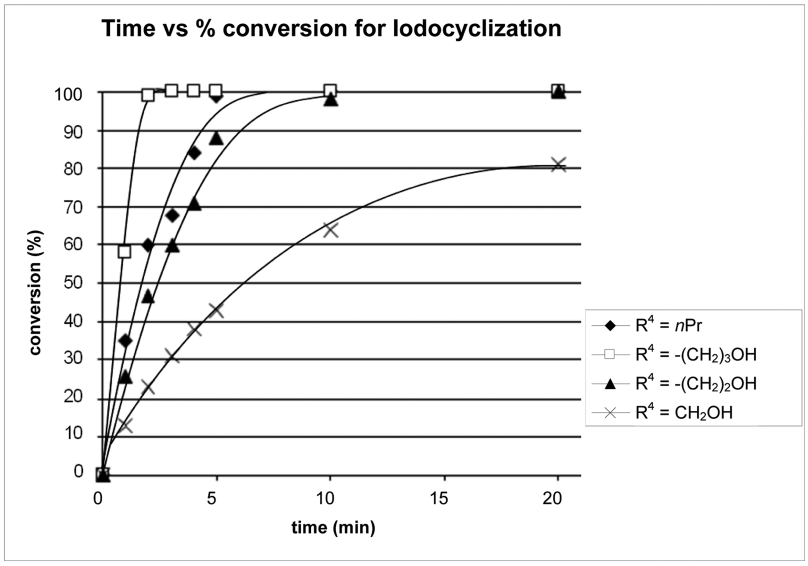
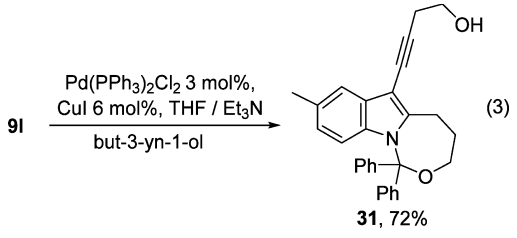


Figure 2. Conversion 7 → **21**/**9** vs time.

imminium ion by the two phenyl groups, favoring a stepwise mechanism through **27**, whereas aldimines do benefit from the presence of pendant nucleophiles ($\mathbf{TS_A}$).

Another interesting feature of the reaction profile of the aldimine systems **7** (R^2 = H) is the capacity to redirect the cocyclization path from fused indoles **9** toward ring-fused quinolones **12** (Scheme 2). Reaction of **22** with NIS in CH_2Cl_2 (Method B) gives indoles **9** (Path A) and with I_2 and K_2CO_3 in CH_3CN (Method C) gives **12** (Path B). The alternation between these two pathways is effectively complete, with only a specific cocyclization product **9**/**12** being observed under each method. It is proposed that, relative to iodine, NIS in CH_2Cl_2 acts more effectively as an electrophilic π-acid complexing the alkyne favoring reaction through $\mathbf{TS_A}$ to give **9** (Path A). On the other hand, I_2 is well-known to activate both alkynes and imines to electrophilic attack, enabling access to both $\mathbf{TS_A}$ (or **27**) and $\mathbf{TS_B}$. Presumably $\mathbf{TS_B}$ is lower in energy for **7** (R^2 = H) than is $\mathbf{TS_A}$, favoring formation of **12**.[13] For substrates **7** where $R^2 \neq$ H, conformer **28** and $\mathbf{TS_B}$ are sterically encumbered, favoring cyclization through **26** → **27** → **9** under either conditions method B or C (Path B).

The use of iodonium ions as activating agents in these reaction cascades has the added advantage of enabling subsequent elaboration of the product using Pd-mediated coupling techniques;



(3)

for example, Songashira coupling of **91** gives **31** 72% (eq 3). Thus providing efficient acess to highly substituted polycycles through functional group tolerant chemistry.

■ CONCLUSIONS

The reactions described in this study enable ready access to a range of different polycyclic scaffolds, ring-fused indoles **9**, quinolines **12**, and quinolones **15**, through minor alterations in the reaction conditions and/or substrate substitution patterns. While some imine substrates **21** and intermediates **7** and **13** have proven to be unstable to chromatography, this has not impeded access to the target products since subsequent coupling and/or iodocyclization steps can be conducted without purification of the respective intermediate. Moreover, the overall yields obtained over the three step process leading to the target products **23**, **9**, **12**, **25**, and **15** have been quite reasonable, 40−90%. The presence of the iodide functionality in polycycles **9** and **12** affords excellent opportunity for the further elaboration of these valuable structural classes.

■ EXPERIMENTAL SECTION

General Methods. All reactions were performed under an inert atmosphere of anhydrous N_2(g) using glassware that was first heated (heat gun) under reduced pressure, backfilled with N_2(g), and allowed to cool to ambient temperature prior to use (vacuum-gas manifold). Toluene, tetrahydrofuran (THF), acetonitrile (CH_3CN) and dichloromethane (CH_2Cl_2) were dried using a commercial solvent purification system. Reagents were used as supplied by commercial vendors without further purifications or drying. Column (flash) chromatography was performed on either 40−60 μm silica gel or neutral alumina (activation grade III), as indicated. IR spectra were obtained on an FT-IR spectrometer and are reported in terms of frequency of absorption (cm^{-1}). ^{1}H NMR spectra were recorded at 300 MHz and are reported

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as follows: chemical shift (δ_H) (integration, multiplicity and coupling constant (Hz)). The following abbreviations were used to explain multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad, dd = doublet of doublets, dt = doublet of triplets. ^{13}C NMR spectra were recorded at 75 MHz and reported in terms of chemical shift (δ_C). All chemical shifts were calibrated using residual nondeuterated solvent as an internal reference and are reported in parts per million relative to trimethylsilane. High-resolution mass spectra (HRMS) were recorded on a time-of-flight mass spectrometer fitted with either an electrospray (ESI) or atmospheric pressure ionization (APCI) ion source.

***N*-(Dimethylaminomethylene)-2-iodoaniline (21a).** A mixture of 2-iodoaniline (2.19 g, 10.0 mmol) and *N*,*N*-dimethylformamide dimethylacetal (1.46 mL, 11.0 mmol) in anhydrous DMF (20 mL) was heated at 80 °C overnight. More *N*,*N*-dimethylformamide dimethylacetal (0.66 mL, 5.0 mmol) was added, and the mixture was heated for another 8 h. After cooling to room temperature, water (30 mL) was added, and the mixture was extracted with ethyl acetate (3 × 50 mL). The combined organic phase was washed with water and dried over $MgSO_4$. Removal of solvent afforded the title compound (2.73 g, 99%) as a yellow oil: δ_H (300 MHz, $CDCl_3$) 3.09 (3H, br s), 3.16 (3 H, br s), 6.75 (1H, dt, *J* 3.0, 7.0 Hz), 6.93 (1H, m_c), 7.24 (1H, dd, *J* 2.0, 6.0 Hz), 7.41 (1H, s), 7.81 (3H, dd, *J* 2.0, 6.0 Hz); δ_H (300 MHz, $CDCl_3$) 34.5, 40.0, 96.9, 118.8, 123.7, 129.0, 138.6, 152.5, 152.9; HRMS (APCI) calculated for $[C_9H_{12}IN_2]^+$ (MH^+) *m*/*z* 275.0045 found 275.0054.

***N*-Benzylidene-2-iodoaniline (21b).** This material was prepared according to a previously described procedure and yielded the title compound in an 85% yield (^1H NMR identical to that previously reported).[14]

***N*-(Diphenylmethylene)-2-iodoaniline (21c).** A mixture of 2-iodoaniline (2.19 g, 10.0 mmol), benzophenone (1.82 g, 10.0 mmol) and *p*-toluenesulfonic acid (cat.) in toluene (50 mL) was heated under reflux overnight with the aid of a Dean−Stark apparatus. The mixture was filtered, and the filtrate was concentrated under reduced pressure. The residue was redissolved in diethyl ether (50 mL), washed with a saturated solution of sodium bicarbonate (20 mL), brine (20 mL) and dried over $MgSO_4$. The resulting dark brown residue was purified by flash chromatography using petroleum spirit/ethyl acetate (25:1) as eluent to give the title compound (3.52 g, 92%) as yellow solid: mp 79−82 °C; δ_H (300 MHz, $CDCl_3$) 6.49 (1H, dd, *J* 1.2, 7.8 Hz), 6.32 (1H, d, *J* 7.8 Hz), 7.06 (1H, t, *J* 7.9 Hz), 7.17−7.29 (4H, m), 7.43−7.51 (3H, m), 7.74 (1H, d, *J* 7.9 Hz), 7.85 (2H, d, *J* 7.2 Hz); δ_C (75 MHz, $CDCl_3$) 91.6, 120.2, 124.4, 127.9, 128.2, 128.3, 128.6, 128.8, 129.5, 131.0, 135.8, 138.4, 138.7, 152.8, 168.6; HRMS (ESI) calculated for $[C_{19}H_{14}IN]^+$ (MH^+) *m*/*z* 384.0249 found 384.0262.

***N*-(Methoxyphenylmethylene)-2-iodoaniline (21d).** A mixture of 2-iodoaniline (2.19 g, 10.0 mmol), trimethylorthobenzoate (1.9 mL, 11.0 mmol) and *p*-toluenesulfonic acid (cat.) in toluene (50 mL) was heated under reflux overnight with the aid of a Dean−Stark apparatus. The mixture was filtered, and the filtrate was concentrated under reduced pressure. The residue was redissolved in diethyl ether (50 mL), washed with a saturated solution of sodium bicarbonate (20 mL), brine (20 mL) and dried over $MgSO_4$. Flash chromatography using petroleum spirit/ethyl acetate (25:1) as eluent afforded the title compound (3.07 g, 91%) as yellow oil and mainly single double bond isomer (ratio of isomers = 10:1): δ_H (300 MHz, $CDCl_3$, * denotes resonances associated with the minor isomer) 3.99* (3H, s), 4.11 (3H, s), 6.59 (1H, d, *J* 7.9 Hz), 6.73 (1H, t, *J* 7.6 Hz), 7.15 (1H, t, *J* 7.6 Hz), 7.26−7.40 (5H, m), 7.50−7.59 (2H, m), 7.84 (1H, d, *J* 7.9 Hz), 8.10* (1H, d, *J* 8.4 Hz); δ_C (75 MHz, $CDCl_3$) 54.5, 93.0, 121.2, 124.0, 128.0, 128.3, 128.78, 128.8, 130.1, 131.1, 138.8, 150.0, 159.6; HRMS (ESI) calculated for $[C_{14}H_{12}INO]^+$ (MH^+) *m*/*z* 338.0042 found 338.0049.

***N*-[Bis(4-methoxyphenyl)methylene]-2-iodoaniline (21e).** A mixture of 2-iodoaniline (1.09 g, 5.0 mmol), *bis*-(4-methoxyphenyl)-methanone (1.21 g, 5.0 mmol) and *p*-toluenesulfonic acid (cat.) in toluene was heated under reflux for two days with the aid of a Dean−Stark apparatus. The mixture was concentrated under reduced pressure, and the residue was redissolved in dichloromethane and passed through a pad of Celite. The crude mixture was purified by flash chromatography using petroleum spirit/ethyl acetate (10:1) as eluent to afford the title compound (1.52 g, 69%) as yellow solid: mp 119−120 °C; δ_H (300 MHz, $CDCl_3$) 3.82 (3H, s), 3.92 (3H, s), 6.54 (1H, dd, *J* 1.3, 7.9 Hz), 6.66 (1H, dd, *J* 1.3, 7.8 Hz), 6.83 (2H, d, *J* 8.6 Hz), 6.99 (2H, d, *J* 8.8 Hz), 7.12 (1H, dd, *J* 1.0, 7.4 Hz), 7.18 (2H, d, *J* 8.6 Hz), 7.79 (1H, dd, *J* 1.0, 7.8 Hz), 7.87 (2H, d, *J* 8.8 Hz); δ_C (75 MHz, $CDCl_3$) 55.1, 55.4, 92.1, 113.2, 113.5, 120.5, 124.0, 128.2, 128.3, 130.5, 131.4, 131.9, 138.3, 153.2, 159.7, 162.0, 167.6; HRMS (ESI) calculated for $[C_{21}H_{18}INO_2]^+$ (MH^+) *m*/*z* 444.0461 found 444.0463.

***N*-(4-Methylbenzylidene)-2-iodoaniline (21g).** A mixture of 2-iodoaniline (2.19 g, 10.0 mmol) and *p*-tolualdehyde (1.18 mL, 10.0 mmol), *p*-toluenesulfonic acid (cat.) and powdered 5 Å molecular sieves (10 g) in benzene (50 mL) was stirred at room temperature for 7 days. The mixture was filtered, and the filtrate was concentrated under reduced pressure. The crude material was suspended in minimum amount of absolute ethanol (ca. 5 mL), filtered and dried to afford the title compound (2.81 g, 88%) as pale yellow solid: mp 47−49 °C (lit. mp[15] 33−35 °C). The ^1H NMR of this material is identical to that previously reported.[15]

***N*-(Diphenylmethylene)-4-methyl-2-iodoaniline (21i).** A mixture of 4-methyl-2-iodoaniline[16] (2.33 g, 10.0 mmol), benzophenone (1.82 g, 10.0 mmol) and *p*-toluenesulfonic acid (cat.) in toluene (100 mL) was heated under reflux with the aid of a Dean−Stark apparatus for 2 days. The mixture was concentrated under reduced pressure, and the crude residue was taken up in diethyl ether (50 mL), washed with a saturated solution of sodium bicarbonate (20 mL) and brine. The organic phase was separated and dried over $MgSO_4$. The crude mixture was purified by flash chromatography using petroleum spirit/ethyl acetate (20:1) as eluent to give the title compound (3.14 g, 79%) as yellow solid: mp 78−80 °C; δ_H (300 MHz, $CDCl_3$) 2.25 (3H, s, Me), 6.41 (1H, d, J 8.0 Hz), 6.90 (1H, dd, J 1.0, 8.0 Hz), 7.22−7.27 (2H, m), 7.31−7.36 (3H, m), 7.47−7.56 (3H, m), 7.64 (1H, s), 7.89 (2H, m); δ_C (75 MHz, $CDCl_3$) 20.1, 91.7, 120.0, 127.9, 128.2, 128.7, 129.1, 129.5, 131.0, 134.2, 136.0, 138.7, 150.0, 168.7; HRMS (ESI) calculated for $[C_{20}H_{16}IN]^+$ (MH^+) *m*/*z* 398.0406 found 398.0418.

General Procedure for Sonogashira Coupling to Give *N*-(2-Alkynylphenyl)imines 7 (0.5 mmol scale). The *N*-(2-iodophenyl)-imine **21** (0.5 mmol) was dissolved in a mixture of THF (4 mL) and triethylamine (2 mL). To this solution was added the relevant terminal alkyne (1.2 mmol) and $Pd(PPh_3)Cl_2$ (10.5 mg, 15 μmol), and the solution was deoxygenated by bubbling nitrogen gas through the solution for 1 min prior to the addition of CuI (7.6 mg, 40 μmol). The resultant reaction mixture was stirred overnight under nitrogen at room temperature and then diluted with diethyl ether (25 mL) and transferred to a separatory funnel. This mixture was washed with saturated NH_4Cl aq (30 mL) and brine (30 mL) and then dried over $MgSO_4$ and concentrated under a vacuum. The resulting residue, containing mostly *N*-(2-alkynylphenyl)imines **7**, was used in the subsequent cyclization step without further purification.

General Procedures for Iodocyclization (0.5 mmol scale). *Method A (I_2, CH_2Cl_2).* I_2 (190 mg, 0.75 mmol) was added to a solution of the crude *N*-(2-alkynylphenyl)imine **7** (~0.5 mmol, obtained from the general procedure for Sonogashira coupling, described above) in dry CH_2Cl_2 (5 mL) and stirred at room temperature until the complete disappearance of starting material was observed by TLC analysis (up to 1 h). The reaction mixture was then transferred to a separatory funnel and diluted with CH_2Cl_2 (7 mL). This solution was then washed with $Na_2S_2O_3$ 10% w/v aq (10 mL), dried over $MgSO_4$, and then concentrated under reduced pressure. The residue was then diluted with MeOH (3.0 mL), and K_2CO_3 (276 mg, 2.0 mmol) was added. The resultant suspension was then stirred at room temperature for 24 h. After this time the mixture was diluted with diethyl ether (15 mL), filtered and concentrated under reduced pressure. The residue was then subjected by flash chromatography on silica gel or deactivated alumina (as indicated) to afford the pure product.

Method B (NIS, CH_2Cl_2). *N*-Iodosuccinimide (135 mg, 0.6 mmol) was added to a solution of the crude *N*-(2-alkynylphenyl)imine **7** (~0.5 mmol, obtained from the general procedure for Sonogashira coupling, described above) in dry CH_2Cl_2 (2.5 mL), and the mixture was stirred at room temperature for 1 h. The reaction mixture was

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then transferred to a separatory funnel and diluted with CH_2Cl_2 (7 mL). This solution was then washed with $Na_2S_2O_3$ 10% w/v aq (10 mL), dried over $MgSO_4$, and then concentrated under reduced pressure. The residue was then subjected to flash chromatography on silica gel or deactivated alumina (as indicated) to afford the pure product.

Method C (I_2, K_2CO_3, CH_3CN). I_2 (190 mg, 0.75 mmol) was added to a suspension of K_2CO_3 (104 mg, 0.75 mmol) and *N*-(2-alkynylphenyl)imine **7** (~0.5 mmol, obtained from the general procedure for Sonogashira coupling, described above) in dry CH_3CN (5 mL). The resultant solution was stirred at room temperature for 2 h (TLC analysis indicated complete consumption of starting material). After this time, $Na_2S_2O_3$ 10% w/v aq (10 mL) was added, and the mixture was transferred to a separatory funnel and extracted with diethyl ether (2 × 10 mL). The organic phases were combined, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was then subjected to flash chromatography on silica gel or deactivated alumina (as indicated) to afford the pure product.

3-Iodo-2-phenyl-1*H*-indole (23a). *N*-(Dimethylaminomethylene)-2-iodoaniline (**21a**) (137 mg, 0.5 mmol) was coupled to phenylacetylene (55 μL, 0.7 mmol) using the general method for Sonogashira coupling described above, and the resultant product **7a** was subjected to iodocyclization using Method A (above). The product was purified using flash chromatography on deactivated alumina(III) using petroleum spirit and ethyl acetate (10:1) as eluent giving **23a** as pale yellow solid (123 mg, 78%): mp 79−81 °C (lit.[17] mp 71−80 °C); δ_H (300 MHz, $(CD_3)_2CO$) 7.20−7.25 (2H, m), 7.42−7.53 (5H, m), 7.88−7.91 (2H, m), 10.95 (1H, br); δ_C (75 MHz, $(CD_3)_2CO$) 57.3, 112.6, 121.5, 121.9, 124.0, 129.3, 129.5, 132.8, 133.4, 138.1, 139.2; HRMS (ESI) calculated for $[C_{14}H_9IN]^+$ (M-H$^+$) *m*/*z* 317.9780 found 317.9782.

The same product (**23a**) was formed when **21a** was substituted for **21b**, and the crude product resulting from Songashara Coupling (**7b**) was subjected to iodocyclization using either Method B or C, giving **23a** in 70 and 87% yield, respectively (see Table 1).

3-Iodo-2-propy-1*H*-indole (23b). Iodoimine **21b** (191 mg, 0.5 mmol) was coupled to 1-pentyne (58 μL, 0.6 mmol) using the general method for Sonogashira coupling described above, and the resultant product **7c** was subjected to iodocyclization using Method B (above). The product was purified using flash chromatography on deactivated alumina(III) using petroleum spirit and ethyl acetate (10:1) as eluent, giving **23b** as a tan oil (133 mg, 94%): δ_H (300 MHz, $(CD_3)_2CO$) 0.98 (3H, t, *J* 7.4 Hz), 1.78 (2H, sextet, *J* 7.4 Hz), 2.82 (2H, t, *J* 7.4 Hz), 7.08−7.13 (2H, m), 7.27−7.34 (2H, m), 10.5 (1H, br); δ_C (75 MHz, $(CD_3)_2CO$) 13.6, 22.9, 30.6, 57.6, 111.6, 120.2, 120.4, 122.4, 131.2, 137.1, 141.3; HRMS (APCI) calculated for $[C_{11}H_{12}IN]^+$ (MH$^+$) *m*/*z* 285.0014 found 285.0018.

9-Iodo-3,3-diphenyl-1,3-dihydrooxazolo[3,4-*a*]indole (9b). Iodoimine **21c** (161 mg, 0.42 mmol) and 2-propyn-1-ol (35 μL, 0.6 mmol) were coupled using the general method for Sonogashira coupling described above, and the resultant product was subjected to iodocyclization using Method B (above). The reaction mixture was purified by column chromatography on silica gel using petroleum spirit/ethyl acetate (10:1) as eluent afforded **9b** as yellow-orange solid (116.0 mg, 63%): mp 139.5−140.5 °C; δ_H (300 MHz, $CDCl_3$) 5.18 (2H, s), 6.87 (1H, d, *J* 8.2 Hz), 7.11 (1H, t, *J* 7.9 Hz), 7.23 (1H, t, *J* 7.9 Hz), 7.41−7.51 (11H, m); δ_C (75 MHz, $CDCl_3$) 45.2, 65.6, 99.4, 110.6, 120.6, 121.0, 122.5, 127.8, 128.3, 129.3, 132.4, 135.0, 139.2, 142.5; HRMS (APCI) calculated for $[C_{22}H_{16}INO]^+$ (MH$^+$) *m*/*z* 438.0355 found 438.0358.

Iodocyclization using Method C gave the same product in 98% yield.

5-Iodo-1-phenyl-3,4-dihydro-1*H*-[1,3]oxazino[3,4-*a*]indole (9c). Iodoimine **21b** (147 mg, 0.48 mmol) and 3-butyn-1-ol (46 μL, 0.6 mmol) were coupled using the general method for Sonogashira coupling described above, and the resultant product was subjected to iodocyclization using Method B (above). Column chromatography on deactivated alumina(III) using petroleum spirit/ethyl acetate (20:1) afforded **9c** as pale yellow oil (112.0 mg, 62%): δ_H (300 MHz, $(CD_3)_2SO$) 3.00−3.07 (2H, m), 3.95−4.12 (2H, m), 6.53 (1H, d, *J* 8.2 Hz), 6.77 (1H, s), 6.91 (1H, t, *J* 7.4 Hz), 7.07 (1H, t, *J* 7.3 Hz), 7.23−7.31 (3H, m), 7.38−7.43 (3H, m); δ_C (75 MHz, $(CD_3)_2SO$) 24.8, 57.4, 60.9, 86.1, 111.0, 119.4, 120.5, 121.5, 127.5, 128.6, 129.5, 134.3, 136.2, 137.7; HRMS (APCI) calculated for $[C_{17}H_{14}INO]^+$ (MH$^+$) *m*/*z* 376.0198 found 376.0202.

5-Iodo-1,1-diphenyl-3,4-dihydro-1*H*-[1,3]oxazino[3,4-*a*]-indole (9d). Iodoimine **21c** (195 mg, 0.51 mmol) and 3-butyn-1-ol (46 μL, 0.6 mmol) were coupled using the general method for Sonogashira coupling described above, and the resultant product was subjected to iodocyclization using Method B (above). Column chromatography on silica gel using petroleum spirit/ethyl acetate (10:1) afforded **9d** as pale yellow solid (216 mg, 94%): mp 176.5−177 °C; IR (cm^{-1}) 2953, 1544, 1489, 1445; δ_H (300 MHz, $CDCl_3$) 3.21 (2H, t, *J* 6.1 Hz), 4.03 (2H, t, *J* 6.1 Hz), 6.34 (1H, d, *J* 8.4 Hz), 6.89 (1H, t, *J* 8.3 Hz), 7.14 (1H, t, *J* 8.3 Hz), 7.27−7.50 (11H, m); δ_C (75 MHz, $CDCl_3$) 25.5, 58.6, 59.6, 94.7, 113.0, 120.1, 120.5, 122.0, 128.3, 128.8, 129.2, 129.7, 135.8, 136.4, 140.3; HRMS (APCI) calculated for $[C_{23}H_{18}INO]^+$ (MH$^+$) *m*/*z* 452.0511 found 452.0513.

Iodocyclization using Method C gave the same product in 98% yield.

5-Iodo-7-methyl-1,1-diphenyl-3,4-dihydro-1*H*-[1,3]oxazino-[3,4-*a*]indole (9e). Iodoimine **21i** (100 mg, 0.25 mmol) and 3-butyn-1-ol (23 μL, 0.3 mmol) were coupled using the general method for Sonogashira coupling described above, and the resultant product was subjected to iodocyclization using Method B (above). The reaction mixture was purified by column chromatography on deactivated alumina(III) using petroleum spirit/ethyl acetate (25:1 then 10:1) afforded **9e** as pale yellow solid (81 mg, 70%): mp 167−167.5 °C; δ_H (300 MHz, $(CD_3)_2SO$) 2.30 (3H, s), 3.08 (2H, t, *J* 6.0 Hz), 3.85 (2H, t, *J* 6.0 Hz), 6.09 (1H, d, *J* 8.5 Hz), 6.61 (1H, d, *J* 8.5 Hz), 7.06−7.13 (5H, m), 7.35−7.45 (6H, m); δ_C (75 MHz, $(CD_3)_2SO$) 20.7, 24.7, 58.2, 59.0, 93.9, 112.2, 119.1, 123.3. 128.3, 129.2, 129.3, 134.1, 136.1, 139.9; HRMS (APCI) calculated for $[C_{24}H_{20}INO]^+$ (MH$^+$) *m*/*z* 466.0668 found 466.0663.

1-Ethoxy-5-iodo-3,4-dihydro-1*H*-[1,3]oxazino[3,4-*a*]indole (9f). A solution of 2-iodoaniline (101.0 mg, 0.5 mmol) and *p*-toluenesulfonic acid (2 mg) in triethylorthoformate (2 mL) was heated under reflux overnight. After the solvent was removed, the crude mixture was taken up in diethyl ether (10 mL) and washed with $NaHCO_3$ aq 5% w/v (10 mL), water (10 mL) and brine (10 mL). The organic phase was dried over $MgSO_4$ and concentrated under reduced pressure to afford **21h**, which was unstable and used in the next step without further purification. This crude form of **21h** and 4-butyn-1-ol (46 μL, 0.6 mmol) were coupled using the general method for Sonogashira coupling described above, and the resultant product was subjected to iodocyclization using Method B (above). Column chromatography on deactivated alumina(III) using petroleum spirit/ethyl acetate (50:1) afforded **9f** as pale yellow solid (87.5 mg, 51%): mp 71−72 °C; IR (cm^{-1}) 2979, 1706, 1454, 1336; δ_H (300 MHz, $(CD_3)_2CO$) 1.26 (3H, t, *J* 7.1 Hz), 2.90−3.01 (2H, m), 3.80−3.90 (2H, m), 4.08 (1H, m, ddd, *J* 2.9, 5.9, 11.0 Hz), 4.34 (1H, dt, *J* 4.4, 11.0 Hz), 6.52 (1H, s), 7.17−7.22 (2H, m), 7.32−7.36 (1H, m), 7.38−7.42 (1H, m); δ_C (75 MHz, $(CD_3)_2CO$) 15.4, 25.6, 57.2, 58.0, 62.4, 99.8, 111.5, 120.5, 122.0, 123.2, 130.8, 135.7; HRMS (APCI) calculated for $[C_{13}H_{14}INO_2]^+$ (MH$^+$) *m*/*z* 344.0148 found 344.0155.

5-Iodo-1-(4-methoxyphenyl)-3,4-dihydro-1*H*-[1,3]oxazino-[3,4-*a*]indole (9g). A mixture of 2-iodoaniline **20** (R^1 = H) (359.1 mg, 1.64 mmol), 4-methoxybenzaldehyde (0.2 mL, 1.64 mmol), *p*-toluenesulfonic acid (cat.) and powdered 5 Å molecular sieves (1.64 g) in benzene (10 mL) was stirred at room temperature for 3 days. The mixture was filtered, and the filtrate was concentrated under reduced pressure to afford **21f** (crude product). This crude product and 3-butyn-1-ol (0.13 mL, 2.0 mmol) were coupled using the general method for Sonogashira coupling described above, and the resultant product was subjected to iodocyclization using Method B (above). Column chromatography on deactivated alumina(III) using petroleum spirit/ethyl acetate (20:1) afforded **9g** as yellow oil (286.0 mg, 43%): δ_H (300 MHz, $(CD_3)_2SO$) 2.98−3.07 (2H, m), 3.76 (3H, s), 3.93−4.01 (1H, m), 4.08−4.15 (1H, m), 6.52 (1H, d, *J* 8.2 Hz), 6.69 (1H, s),

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6.92−6.97 (3H, m), 7.06 (1H, t, *J* 7.2 Hz), 7.19 (2H, d, *J* 8.7 Hz), 7.27 (1H, d, *J* 7.8 Hz); δ_C (75 MHz, $(CD_3)_2SO$) 24.8, 55.1, 57.3, 60.9, 86.0, 111.1, 113.9, 119.3, 120.4, 121.5, 128.9, 129.5, 129.8, 134.3, 136.4, 160.0; HRMS (APCI) calculated for $[C_{18}H_{16}INO_2]^+$ (MH^+) *m*/*z* 406.0304 found 406.0288.

5-Iodo-1,1-bis(4-methoxyphenyl)-3,4-dihydro-1*H*-[1,3]-oxazino[3,4-*a*]indole (9h). Iodoimine **21e** (211.8 mg, 0.48 mmol) and 3-butyn-1-ol (46 μL, 0.6 mmol) were coupled using the general method for Sonogashira coupling described above, and the resultant product was subjected to iodocyclization using Method B (above). Column chromatography on silica gel using petroleum spirit/ethyl acetate (20:1) afforded **9h** as colorless oil (132.1 mg, 54%): δ_H (300 MHz, $(CD_3)_2CO$) 3.12 (2H, t, *J* 6.1 Hz), 3.81 (6H, s), 3.93 (2H, t, *J* 6.1 Hz), 6.37 (1H, d, *J* 8.4 Hz), 6.80 (1H, dt, *J* 1.0, 7.8 Hz), 6.89−6.94 (4H, m), 7.02−7.12 (5H, m), 7.34 (1H, d, *J* 7.8 Hz); δ_C (75 MHz, $(CD_3)_2CO$) 24.9, 54.4, 57.1, 58.5, 94.0, 112.7, 113.0, 119.3, 120.0, 121.4, 129.3, 129.7, 132.4, 136.1, 159.9, 204.8; HRMS (APCI) calculated for $[C_{25}H_{22}INO_3]^+$ (MH^+) *m*/*z* 512.0723 found 512.0727.

6-Iodo-1,1-diphenyl-1,3,4,5-tetrahydro-[1,3]oxazepino[3,4-*a*]-indole (9i). Iodoimine **21c** (190.1 mg, 0.5 mmol) and 4-pentyn-1-ol (56 μL, 0.6 mmol) were coupled using the general method for Sonogashira coupling described above, and the resultant product was subjected to iodocyclization using Method B (above). Column chromatography on deactivated alumina(III) using petroleum spirit/ethyl acetate (20:1) afforded **9i** as colorless solid (160.0 mg, 69%): mp 127−128 °C; δ_H (300 MHz, $(CD_3)_2CO$) 1.87−1.91 (2H, m), 3.26−3.31 (2H, m), 3.89 (2H, t, *J* 6.6 Hz), 6.17 (1H, d, *J* 8.5 Hz), 6.70 (1H, t, *J* 8.2 Hz), 6.97 (1H, t, *J* 7.3 Hz), 7.24−7.29 (5H, m), 7.36−7.42 (6H, m); δ_C (75 MHz, $CDCl_3$) 26.7, 27.4, 62.9, 65.3, 98.0, 114.4, 120.2, 120.7, 121.7, 128.0, 128.2, 128.7, 130.0, 130.8, 137.9, 140.2, 142.9; HRMS (APCI) calculated for $[C_{24}H_{20}INO]^+$ (MH^+) *m*/*z* 466.0668 found 466.0662.

6-Iodo-1-phenyl-1,3,4,5-tetrahydro-[1,3]oxazepino[3,4-*a*]-indole (9j). Iodoimine **21b** (80.0 mg, 0.26 mmol) and 4-pentyn-1-ol (28 μL, 0.3 mmol) were coupled using the general method for Sonogashira coupling described above, and the resultant product was subjected to iodocyclization using Method B (above). Column chromatography on deactivated alumina(III) using petroleum spirit/ethyl acetate (20:1) afforded **9j** as pale yellow solid (76.1 mg, 75%): mp 96−100 °C; δ_H (300 MHz, $(CD_3)_2SO$) 1.78−1.86 (2H, m), 2.78−2.86 (1H, m), 3.19−3.27 (1H, m), 3.99−4.13 (2H, m), 7.03−7.13 (5H, m), 7.26−744 (5H, m); δ_C (75 MHz, $(CD_3)_2SO$) 26.7, 28.1, 61.1, 63.3, 66.3, 86.1, 110.3, 120.3, 120.4, 122.3, 126.8, 128.7, 128.8, 129.5, 136.68, 136.72, 142.0; HRMS (APCI) calculated for $[C_{18}H_{16}INO]^+$ (MH^+) *m*/*z* 390.0355 found 390.0357.

6-Iodo-1,1-bis(4-methoxyphenyl)-1,3,4,5-tetrahydro-[1,3]-oxazepino[3,4-*a*]indole (9k). Iodoimine **21e** (207.8 mg, 0.47 mmol) and 4-pentyn-1-ol (56 μL, 0.6 mmol) were coupled using the general method for Sonogashira coupling described above, and the resultant product was subjected to iodocyclization using Method B (above). Column chromatography on deactivated alumina using petroleum spirit/ethyl acetate (10:1 then 3:2) afforded **9k** as colorless solid (151.1 mg, 61%): mp 113−114 °C; δ_H (300 MHz, $(CD_3)_2CO$) 1.84−1.88 (2H, m), 3.24−3.29 (2H, m), 3.79 (6H, s), 3.84 (2H, t, *J* 6.6 Hz), 6.24 (1H, d, *J* 8.5 Hz), 6.71 (1H, t, *J* 7.8 Hz), 6.88−6.99 (5H, m), 7.13−7.18 (4H, m), 7.25 (1H, d, *J* 7.8 Hz); δ_C (75 MHz, $(CD_3)_2CO$) 27.5, 28.3, 55.7, 62.8, 65.5, 98.9, 114.1, 115.6, 121.0, 121.3, 122.5, 131.0, 131.9, 133.7, 138.9, 144.1, 160.9; HRMS (APCI) calculated for $[C_{26}H_{24}INO_3]^+$ (MH^+) *m*/*z* 526.0879 found 526.0868.

6-Iodo-8-methyl-1,1-diphenyl-1,3,4,5-tetrahydro-[1,3]-oxazepino[3,4-*a*]indole (9l). Iodoimine **21i** (100.5 mg, 0.25 mmol) and 4-pentyn-1-ol (28 μL, 0.3 mmol) were coupled using the general method for Sonogashira coupling described above, and the resultant product was subjected to iodocyclization using Method B (above). Column chromatography on deactivated alumina(III) using petroleum spirit/ethyl acetate (25:1 then 10:1) afforded **9l** as colorless solid (83.7 mg, 70%): mp 172−173 °C; IR (cm^{-1}) 2945, 1445, 1300; δ_H (300 MHz, $(CD_3)_2CO$) 1.85−1.90 (2H, m), 2.29 (3H, s), 3.23−3.27 (2H, m), 3.88 (2H, t, *J* 6.5 Hz), 6.02 (1H, d, *J* 8.6 Hz), 6.52 (1H, dd, *J* 1.1, 8.6 Hz), 7.04 (1H, s), 7.23−7.40 (10H, m); δ_C (75 MHz, $CDCl_3$) 21.1, 26.9, 27.6, 61.2, 62.5, 98.0, 114.2, 120.5, 123.4, 128.1, 128.3, 128.6, 128.8, 128.9, 129.7, 130.1, 131.0, 136.4, 140.5, 143.0; HRMS (APCI) calculated for $[C_{25}H_{22}INO]^+$ (MH^+) *m*/*z* 480.0824 found 480.0822.

6-Iodo-1-(*p*-tolyl)-1,3,4,5-tetrahydro-[1,3]oxazepino[3,4-*a*]-indole (9m). Iodoimine **21g** (83.1 mg, 0.26 mmol) and 4-pentyn-1-ol (28 μL, 0.3 mmol) were coupled using the general method for Sonogashira coupling described above, and the resultant product was subjected to iodocyclization using Method B (above). Column chromatography on deactivated alumina(III) using petroleum spirit/ethyl acetate (100:0 then 20:1) afforded **9m** as colorless oil (76.0 mg, 73%): δ_H (300 MHz, $(CD_3)_2SO$) 1.74−1.90 (2H, m), 2.30 (3H, s), 2.75−2.87 (1H, m), 3.17−3.25 (1H, m), 3.89−3.96 (2H, m), 6.93 (2H, d, *J* 8.0 Hz), 7.02−7.14 (3H, m), 7.21 (2H, d. *J* 8.0 Hz), 7.25−7.28 (2H, m); δ_C (75 MHz, $(CD_3)_2SO$) 20.3, 26.7, 28.0, 60.9, 66.1, 86.0, 110.3, 120.2, 120.4, 122.2, 126.7, 129.3, 129.5, 133.7, 136.7, 138.1, 141.9; HRMS (APCI) calculated for $[C_{19}H_{18}INO]^+$ (MH^+) *m*/*z* 404.0511 found 404.0512.

6-Iodo-1-(4-methoxyphenyl)-1,3,4,5-tetrahydro-[1,3]-oxazepino[3,4-*a*]indole (9n). This material was prepared from 2-iodoaniline (180.1 mg, 0.83 mmol), 4-methoxybenzaldehyde (0.1 mL, 0.83 mmol) and 4-pentyn-1-ol (0.1 mL, 1.07 mmol) using an identical reaction sequence and purification procedure as that described for **9g**. This afforded the product **9n** as yellow oil (181.3 mg, 52%): δ_H (300 MHz, $CDCl_3$) 1.61−2.00 (2H, m), 2.89−3.00 (1H, m), 3.31−3.40 (1H, dt, *J* 4.2, 15.2 Hz), 3.86 (3H, s), 3.96−4.03 (1H, m), 4.08−4.15 (1H, m), 6.92−6.96 (2H, m), 7.02−7.08 (3H, m), 7.21−7.27 (3H, m), 7.49 (1H, d, *J* 7.2 Hz); δ_C (75 MHz, $CDCl_3$) 21.2, 28.5, 55.3, 60.9, 66.2, 86.6, 109.6, 114.3, 120.7, 121.1, 122.6, 128.4, 128.6, 130.2, 137.1, 141.7, 160.0; HRMS (APCI) calculated for $[C_{19}H_{18}INO_2]^+$ (MH^+) *m*/*z* 420.0461 found 420.0460.

1-Ethoxy-6-iodo-1,3,4,5-tetrahydro-[1,3]oxazepino[3,4-*a*]-indole (9o). This product was prepared using an identical method to that described for **9f** (above) except that 4-pentyn-1-ol was used in place of 3-butyn-1-ol. Column chromatography on deactivated alumina(III) using petroleum spirit/ethyl acetate (50:1) afforded **9o** as pale yellow oil (110.0 mg, 62%): δ_H (300 MHz, $CDCl_3$) 1.37 (3H, t, *J* 7.1 Hz), 2.03−2.09 (2H, m), 3.21−3.35 (2H, m), 3.65−3.87 (2H, m), 4.00 (1H, td, *J* 4.3, 12.0 Hz), 4.34−4.43 (1H, m), 6.64 (1H, s), 7.27−7.39 (3H, m), 7.47 (1H, dd, *J* 2.0, 7.0 Hz); δ_C (75 MHz, $CDCl_3$) 14.7, 27.2, 28.3, 61.8, 62.7, 63.7, 100.2, 109.0, 120.8, 121.1, 122.7, 130.1, 136.6, 140.7; HRMS (APCI) calculated for $[C_{14}H_{16}INO_2]^+$ (MH^+) *m*/*z* 358.0304 found 358.0302.

11-Iodo-9-isopropoxy-8-methoxy-6,6-diphenyl-6*H*-isoindolo[2,1-*a*]indole (9p). Iodoimine **21c** (186.9 mg, 0.49 mmol) and 5-ethynyl-1-isopropoxy-2-methoxybenzene[18] (115 mg, 0.6 mmol) were coupled using the general method for Sonogashira coupling described above, and the resultant product was subjected to iodocyclization using Method B (above). Column chromatography on silica gel using petroleum spirit/ethyl acetate (20:1) afforded **9p** as light green solid (145.5 mg, 52% over two steps): mp 152−153 °C; δ_H (300 MHz, $(CD_3)_2CO$) 1.39 (6H, d, *J* 6.1 Hz), 3.79 (3H, s), 4.69 (1H, setptet, *J* 6.1 Hz), 7.01−7.02 (2H, m), 7.07−7.13 (1H, m), 7.19 (1H, s), 7.25−7.42 (11H, m), 7.79 (1H, s); δ_C (75 MHz, $(CD_3)_2CO$) 21.2, 44.2, 55.5, 71.4, 76.2, 107.4, 108.6, 110.7, 120.0, 120.6, 122.1, 122.6, 127.7, 127.9, 128.2, 133.7, 134.7, 140.6, 145.3, 147.8, 151.8; HRMS (APCI) calculated for $[C_{31}H_{26}INO_2]^+$ (MH^+) *m*/*z* 572.1087 found 572.1091.

4-Phenyl-2,3-dihydrofurano[3,2-*c*]quinoline (12a). Iodoimine **21c** (192.0 mg, 0.5 mmol) and 3-butyn-1-ol (46 μL, 0.6 mmol) were coupled using the general method for Sonogashira coupling described above, and the resultant product was subjected to iodocyclization using Method C (above). Column chromatography on silica gel using petroleum spirit/ethyl acetate (10:1) afforded the **12a** as pale yellow solid (99.1 mg, 80%): mp 60.5−61 °C; δ_H (300 MHz, $CDCl_3$) 3.61 (2H, t, *J* 8.9 Hz), 4.91 (2H, t, *J* 8.9 Hz), 7.48−7.59 (4H, m), 7.69−7.75 (1H, m), 7.95−8.03 (3H, m), 8.18 (1H, d, *J* 8.6 Hz); δ_C (75 MHz, $CDCl_3$) 30.0, 73.0, 115.0, 115.9, 121.3, 125.2, 128.2, 128.4, 128.7, 129.2, 129.5, 139.8, 149.1, 155.4, 164.2; HRMS (ESI) calculated for $[C_{17}H_{13}NO]^+$ (MH^+) *m*/*z* 248.1075 found 248.1072.

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5-Phenyl-3,4-dihydro-2*H*-pyrano[3,2-*c*]quinoline (12b). Iodoimine **21c** (183.0 mg, 0.48 mmol) and 4-pentyn-1-ol (56 μL, 0.6 mmol) were coupled using the general method for Sonogashira coupling described above, and the resultant product was subjected to iodocyclization using Method C (above). Column chromatography on silica gel using petroleum spirit/ethyl acetate (10:1) afforded the **12b** as pale yellow oil (76.3 mg, 61%): IR (cm^{-1}) 2933, 1618, 1578, 1491; δ_H (300 MHz, $CDCl_3$) 2.08 (2H, m), 2.82 (2H, t, *J* 6.3 Hz), 4.51 (2H, t, *J* 5.2 Hz), 7.47−7.74 (6H, m), 8.11 (1H, d, *J* 8.2 Hz), 8.20 (1H, d, *J* 8.2 Hz); δ_C (75 MHz, $CDCl_3$) 21.9, 23.7, 67.0, 110.5, 121.1, 125.2, 128.1, 128.2, 128.7, 129.0, 129.1, 140.5, 147.3, 157.3, 160.9; HRMS (ESI) calculated for $[C_{18}H_{15}NO]^+$ (MH^+) *m*/*z* 262.1232 found 262.1229.

4-(4-Methylphenyl)-2,3-dihydrofurano[3,2-*c*]quinoline (12c). Iodoimine **21g** (157.1 mg, 0.49 mmol) and 3-butyn-1-ol (46 μL, 0.6 mmol) were coupled using the general method for Sonogashira coupling described above, and the resultant product was subjected to iodocyclization using Method C (above). Column chromatography deactivated alumina(III) using petroleum spirit/ethyl acetate (10:1) afforded **12c** as yellow solid (92.1 mg, 72%): mp 133−135 °C; δ_H (300 MHz, $CDCl_3$) 2.43 (3H, s), 3.58 (2H, t, *J* 8.9 Hz), 4.88 (2H, t, J 8.9 Hz), 7.31 (2H, d, *J* 7.9 Hz), 7.45 (1H, t, *J* 7.9 Hz), 7.66 (1H, t, J 8.5 Hz), 7.82 (2H, d, *J* 8.1 Hz), 7.94 (1H, d, *J* 8.2 Hz), 8.14 (1H, d, *J* 8.6 Hz); δ_C (75 MHz, $CDCl_3$) 21.4, 30.0, 73.5, 115.2, 115.7, 120.3, 121.4, 121.9, 125.6, 127.5, 128.2, 128.5, 129.3, 130.3, 135.6, 139.5, 147.9, 155.0, 165.1; HRMS (ESI) calculated for $[C_{18}H_{15}NO]^+$ (MH^+) *m*/*z* 262.1232 found 262.1227.

5-(4-Methylphenyl)-3,4-dihydro-2*H*-pyrano[3,2-*c*]quinoline (12d). Iodoimine **21g** (83.0 mg, 0.26 mmol) and 4-pentyn-1-ol (28 μL, 0.3 mmol) were coupled using the general method for Sonogashira coupling described above, and the resultant product was subjected to iodocyclization using Method C (above). Column chromatography on deactivated alumina(III) using petroleum spirit/ethyl acetate (9:1 then 5:1) afforded **12d** as colorless solid (42.0 mg, 59%): mp 97−99 °C; IR (cm^{-1}) 2921, 1616, 1588, 1491; δ_H (300 MHz, $CDCl_3$) 2.05−2.13 (2H, m), 2.48 (3H, s), 2.83 (2H, t, *J* 6.2 Hz), 4.51 (2H, t, *J* 5.1 Hz), 7.34 (2H, d, *J* 8.0 Hz), 7.49−7.57 (3H, m), 7.70 (1H, dt, *J* 1.2, 8.3 Hz), 8.12 (1H, d, *J* 8.4 Hz), 8.19 (1H, d, *J* 8.2 Hz); δ_C (75 MHz, $CDCl_3$) 21.2, 21.9, 23.8, 67.0, 110.6, 119.9, 121.1, 125.2, 128.7, 128.8, 129.0, 137.5, 138.0, 147.2, 157.3, 160.8; HRMS (ESI) calculated for $[C_{19}H_{17}NO]^+$ (MH^+) *m*/*z* 276.1388 found 276.1382.

4-(4-Methoxyphenyl)-2,3-dihydrofurano[3,2-*c*]quinoline (12e). This material was prepared from 2-iodoaniline (126.2 mg, 0.58 mmol), 4-methoxybenzaldehyde (0.07 mL, 0.6 mmol) and 3-butyn-1-ol (0.07 mL, 1.1 mmol) using as the same procedure as that described for **9g**, except that the iodocyclization was conducted using Method C. Column chromatography on deactivated alumina using petroleum spirit/ethyl acetate (9:1) afforded the **12e** as a colorless solid (77.1 mg, 48%): mp 136−136.5 °C; δ_H (300 MHz, $CDCl_3$) 3.62 (2H, t, *J* 8.9 Hz), 3.93 (3H, s), 4.91 (2H, t, *J* 8.9 Hz), 7.08 (2H, d, *J* 8.8 Hz), 7.49 (1H, dt, *J* 0.9, 8.0 Hz), 7.71 (1H, dt, *J* 1.2 Hz, 8.3 Hz,), 7.94−8.01 (3H, m), 8.15 (1H, d, *J* 8.6 Hz); δ_C (75 MHz, $CDCl_3$) 30.4, 55.4, 73.0, 114.0, 114.7, 115.9, 121.4, 125.1, 129.2, 129.6, 129.7, 132.7, 149.3, 155.1, 160.3, 164.2; HRMS (ESI) calculated for $[C_{18}H_{15}NO_2]^+$ (MH^+) *m*/*z* 278.1181 found 278.1177.

5-(4-Methoxyphenyl)-3,4-dihydro-2*H*-pyrano[3,2-*c*]-quinoline (12f). This material was prepared from 2-iodoaniline (138.1 mg, 0.64 mmol), 4-methoxybenzaldehyde (0.08 mL, 0.64 mmol) and 4-pentyn-1-ol (0.07 mL, 1.1 mmol) using as the same procedure as that described for **9g**, except that the iodocyclization was conducted using Method C. Column chromatography on deactivated alumina(III) using petroleum spirit/ethyl acetate (9:1) afforded **12f** as pale yellow solid (85.4 mg, 46%): mp 118−119 °C; IR (cm^{-1}) 2929, 1632, 1606, 1500; δ_H (300 MHz, $CDCl_3$) 2.06−2.14 (2H, m), 2.85 (2H, t, *J* 6.3 Hz), 3.93 (3H, s), 4.52 (2H, t, *J* 5.1 Hz), 7.04−7.08 (2H, m), 7.48−7.72 (5H, m), 8.08 (1H, d, *J* 8.4 Hz), 8.17 (1H, d, *J* 8.3 Hz); δ_C (75 MHz, $CDCl_3$) 22.0, 24.0, 55.4, 67.0, 110.6, 113.7, 120.0, 121.2, 125.1, 128.96, 129.0, 130.2, 133.1, 134.8, 147.3, 157.3, 159.7, 160.5; HRMS (ESI) calculated for $[C_{19}H_{17}NO_2]^+$ (MH^+) *m*/*z* 292.1338 found 292.1333.

General Procedure for the Preparation of Weinreb Amides 24a−d. This method has been adapted from that described by Whipple and Reich,[11] using 1-methoxy-1,3,3-trimethylurea in place of 1,3-dimethoxy-1,3-dimethylurea. *n*-BuLi (11 mmol, 2 M in hexanes) was added to a solution of arylethyne (10 mmol) in dry THF (15 mL) at −78 °C. The mixture was stirred at 0 °C for 1 h and then recooled to −78 °C. A solution of 1-methoxy-1,3,3-trimethylurea (13 mmol) in dry THF (6 mL) was added dropwise over 5 min. The mixture was then warmed to 0 °C and stirred for a further 1 h. A saturated solution of NH_4Cl aq (5 mL) was added, and the mixture was extracted with diethyl ether (3 × 20 mL). The combined organic phase was washed with water (10 mL), brine (10 mL) and dried over $MgSO_4$. The solvent was evaporated, and the residue was purified by flash chromatography using petroleum spirit and ethyl acetate (3:2) as eluent.

***N*-Methoxy-*N*-methyl-3-phenylpropiolamide (24a).** Prepared according to the general procedure for the preparation of Weinreb amides (above) using phenylacteylene (1.10 mL, 10 mmol), giving the product **24a** as a tan oil (1.285 g, 68%). The ^1H NMR of this material was identical to that previously reported.[11a]

***N*-Methoxy-3-(4-methoxyphenyl)-*N*-methylpropiolamide (24b).** Prepared according to the general procedure for the preparation of Weinreb amides (above) using 4-ethynyl-1-methoxybenzene (1.32 g, 10 mmol), giving the product **24b** as a tan oil (1.91 g, 87%): δ_H (300 MHz, $CDCl_3$) 3.31 (3H, br), 3.84 (6H, s), 6.88 (2H, d, *J* 8.7 Hz), 7.51 (2H, d, *J* 8.7 Hz); δ_C (75 MHz, $CDCl_3$) *32.4, 55.3, *61.9, 80.1, 90.9, *112.0, 114.1, 134.3, *154.8, 161.2 (* these peaks show broadening due to conformational effects); HRMS (APCI) calculated for $[C_{12}H_{14}NO_3]^+$ (MH^+) *m*/*z* 220.0974 found 220.0972.

***N*-Methoxy-3-(3-methoxyphenyl)-*N*-methylpropiolamide (24c).** Prepared according to the general procedure for the preparation of Weinreb amides (above) using 3-ethynyl-1-methoxybenzene (660 mg, 5.0 mmol), giving the product **24c** as a tan oil (438 mg, 40%): δ_H (300 MHz, $CDCl_3$) 3.32 (3H, br), 3.81 (3H, s), 3.84 (3H, s), 6.96−7.00 (1H, m), 7.09 (1H, s), 7.16 (1H, *J* 7.5 Hz), 7.25−7.30 (1H, m); δ_C (75 MHz, $CDCl_3$) *32.3, 55.2, *62.1, 80.4, *90.1, 116.7, 117.2, *121.2, 124.9, 129.6, *154.4, 159.2 (* these peaks show broadening due to conformational effects); HRMS (APCI) calculated for $[C_{12}H_{14}NO_3]^+$ (MH^+) *m*/*z* $[C_{12}H_{14}NO_3]^+$ (MH^+) *m*/*z* 220.0974 found 220.0972.

***N*-Methoxy-3-(4-isopropoxy-3-methoxyphenyl)-*N*-methyl-propiolamide (24d).** Prepared according to the general procedure for the preparation of Weinreb amides (above) using 5-ethynyl-1-isopropoxy-2-methoxybenzene (1.90 g, 10 mmol),[18] giving the product **24d** as a tan oil (1.61 g, 58%): IR (cm^{-1}) 2975, 2202, 1633, 1598, 1506; δ_H (300 MHz, $CDCl_3$) 1.43 (6H, d, *J* 6.1 Hz), 3.38 (3H, br), 3.90 (3H, s), 3.94 (3H, s), 4.58 (1H, quintet, *J* 6.1 Hz), 6.90 (1H, d, *J* 8.4 Hz), 7.14 (1H, d, *J* 1.7 Hz), 7.23 (1H, dd, *J* 1.8, 8.4 Hz); δ_C (75 MHz, $CDCl_3$) 21.9, *32.5, 55.9, *62.1, 71.6, 79.9, *91.3, 111.6, *112.1, 119.4, 126.8, 147.0, 152.5, *154.9 (* these peaks show broadening due to conformational effects); HRMS (APCI) calculated for $[C_{15}H_{20}NO_4]^+$ (MH^+) *m*/*z* 278.1392 found 278.1386.

General Procedure for the Formation of Ketones 13 and Their Iodocyclization to 25 or 15 (0.5 mmol scale). *n*-BuLi (0.55 mmol, 2 M in hexanes) was added to a solution of iodoimine **21** (0.5 mmol) in dry THF (2 mL) at −78 °C, and the reaction mixture was stirred for 10 min at this temperature. A solution of Weinreb amide **24** (0.6 mmol) in dry THF (2 mL) was then added dropwise over 5 min, followed by stirring at −78 °C for a further 1 h. A saturated solution of NH_4Cl aq (3 mL) was then added, and the mixture was warmed to room temperature, extracted with diethyl ether (3 × 10 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The resultant crude product **13** was dissolved in solvent (4 mL of either CH_3CN or CH_2Cl_2; see specific examples below). To this *N*-iodosuccinimide (0.6 mmol) was added, and the reaction mixture was stirred overnight. The reaction was quenched by addition of $Na_2S_2O_3$ 10% w/v (3 mL), and the mixture was extracted with diethyl ether (3 × 7 mL). The organic extracts were combined, washed with brine, and dried over $MgSO_4$. The solvent was evaporated, and the crude mixture was purified by flash chromatography.

6-Iodo-8-methoxy-11,11-diphenylisoindolo[2,1-*a*]quinolin-5(11*H*)-one (15a) and 3-Iodo-2-phenylquinolin-4(1*H*)-one (25a) (Table 3, entries 1 and 2). Iodoimine **21c** (187 mg, 0.5 mmol) and Weinreb amide **24a** (113 mg, 0.6 mmol) were coupled and iodocyclized using the general procedure for the formation of ketones **13** and their iodocyclization to **15** and **25** (above), using CH_3CN in

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the iodocyclization step (Table 3, entry 1). Flash chromatography on deactivated alumina(III) using petroleum spirit/ethyl acetate (4:1) yielded **15a** as a brown resin (120 mg, 47%) and **25a** as tan solid (63 mg, 36%). **15a**: δ_H (300 MHz, $(CD_3)_2SO$) 7.18 (1H, d, *J* 8.2 Hz), 7.31−7.40 (12H, m), 7.61−7.70 (3H, m), 8.25 (1H, d, *J* 7.7 Hz), 9.32 (1H, d, *J* 7.6 Hz); δ_C (75 MHz, $(CD_3)_2SO$) 80.5, 80.8, 119.4, 122.0, 124.5, 124.6, 126.4, 127.6, 128.5, 128.6, 128.8, 129.4, 131.3, 131.9, 133.2, 137.7, 138.1, 150.0, 152.7, 174.2; HRMS (APCI) calculated for $[C_{28}H_{19}INO]^+$ (MH^+) *m*/*z* 512.0506 found 512.0481. **25a**: The ^1H and ^{13}C NMR of this material were identical to those previously reported.[19]

Compound **25a** was selectively prepared by reacting iodoimine **21d** (169 mg, 0.5 mmol) with Weinreb amide **24a** (113 mg, 0.6 mmol) using the general procedure for the formation of ketones **13** and their iodocyclization to **15** and **25** (above), using CH_3CN in the iodocyclization step (Table 3, entry 2). Flash chromatography on deactivated alumina(III) using petroleum spirit/ethyl acetate gave **25a**[19] as tan solid (100 mg, 58%).

3-Iodo-2-(4-methoxyphenyl)quinolin-4-(1*H*)-one (25b) (Table 3, entry 3). Iodoimine **21d** (92.1 mg, 0.27 mmol) and Weinreb amide **24b** (66.0 mg, 0.30 mmol) were coupled and iodocyclized using the general procedure for the formation of ketones **13** and their iodocyclization to **15** and **25** (above), using CH_3CN in the iodocyclization step. Flash chromatography on deactivated alumina(III) using petroleum spirit/ethyl acetate (4:1) yielded **25b** as a tan solid (62 mg, 61%). The ^1H and ^{13}C NMR of this material were identical to those previously reported.[19]

6-Iodo-8,11(and 10,11)-dimethyoxy-11-phenylisoindolo-[2,1-*a*]quinolin-5(11*H*)-one (15d) (Table 3, entry 4). Iodoimine **21d** (57.0 mg, 0.17 mmol) and Weinreb amide **24c** (44.1 mg, 0.2 mmol) were coupled and iodocyclized using the general procedure for the formation of ketones **13** and their iodocyclization to **15** and **25** (above), using CH_2Cl_2 in the iodocyclization step. Flash chromatography on deactivated alumina(III) using petroleum spirit/ethyl acetate (4:1) yielded **15d** as a red solid (72.1 mg, 85%), comprising of a 1:1 mixture of 8/10-methoxy regioisomers. Spectra performed on regiosiomeric mixture: δ_H (300 MHz, $CDCl_3$) 3.03 (3H, s, OMe), 3.11 (3H, s), 3.81 (3H, s), 4.0 (3H, s), 7.06−7.45 (17H, m,), 7.58−7.67 (3H, m), 8.51 (2H, m), 8.94 (1H, s), 9.03 (1H, d, *J* 8.0 Hz); δ_C (75 MHz, $CDCl_3$) 51.0, 51.4, 55.9, 56.0, 80.8, 80.9, 100.4, 101.2, 110.8, 114.5, 117.6, 117.7, 119.0, 119.4, 121.9, 122.0, 124.4, 124.4, 124.5, 125.1, 126.4, 127.3, 127.4, 127.8, 127.9, 128.2, 128.5, 128.8, 128.9, 129.2, 129.9, 131.4, 132.2, 132.4, 134.1, 134.4, 136.0, 137.3, 137.5, 138.2, 139.7, 148.9, 154.8, 160.6, 175.5, 175.6; HRMS (APCI) calculated for $[C_{24}H_{19}INO_3]^+$ (MH^+) *m*/*z* 496.0404 found 496.0385. Subsequent chromatography of the isomeric mixture **15d** on silica gel provided a pure sample of the 8-methoxy regioisomer: δ_H (300 MHz, $(CD_3)_2CO$) 3.03 (3H, s), 3.97 (3H, s), 7.24 (1H, dd, *J* 8.5, 2.2 Hz), 7.30−7.37 (7H, m), 7.39 (1H, dt, *J* 8.5, 2.4 Hz), 7.50 (1H, dd, *J* 8.5, 2.4 Hz), 8.33 (1H, dd, *J* 6.7, 2.2 Hz), 8.91 (1H, d, *J* 2.2 Hz).

6-Iodo-8-isopropoxy-9,11-dimethoxy-11-phenylisoindolo-[2,1-*a*]quinolin-5(11*H*)-one (15e) (Table 3, entry 5). Iodoimine **21d** (41.0 mg, 0.12 mmol) and Weinreb amide **24d** (42.0 mg, 0.15 mmol) were coupled and iodocyclized using the general procedure for the formation of ketones **13** and their iodocyclization to **15** and **25** (above), using CH_2Cl_2 in the iodocyclization step. Flash chromatography on deactivated alumina(III) using petroleum spirit/ethyl acetate (4:1) yielded **15e** as a pale yellow oil (57 mg, 90%): δ_H (300 MHz, $(CD_3)_2CO$) 1.42 (6H, d, *J* 5.5 Hz), 3.05 (3H, s), 3.85 (3H, s), 4.72 (1H, quintet, *J* 6.0 Hz), 6.98 (1H, s,), 7.27−7.58 (9H, m), 8.32 (1H, dd, J 1.2, 8.0 Hz), 8.91 (1H, s); δ_C (75 MHz, $(CD_3)_2CO$) 21.8, 21.9, 51.0, 56.3, 72.2, 79.0, 100.7, 106.6, 112.4, 117.8, 121.9, 124.2, 125.1, 125.6, 127.7, 127.8, 128.7, 129.2, 129.5, 129.6, 132.4, 138.2, 138.3, 140.5, 148.8, 150.0, 155.1, 174.7; HRMS (APCI) calculated for $[C_{27}H_{25}INO_4]^+$ (MH^+) *m*/*z* 554.0823 found 554.0833.

6-Iodo-8-methoxy-11,11-diphenylisoindolo[2,1-*a*]quinolin-5(11*H*)-one (15f) (Table 3, entry 6). Iodoimine **21c** (80.2 mg, 0.21 mmol) and Weinreb amide **24c** (60.9 mg, 0.28 mmol) were coupled and iodocyclized using the general procedure for the formation of ketones **13** and their iodocyclization to **15** and **25** (above), using CH_2Cl_2 in the iodocyclization step. Flash chromatography on silica gel using petroleum spirit/ethyl acetate (10:1) yielded **15f** as a pink solid (67.0 mg, 59%): mp 281−284 °C; IR (cm^{-1}) 3063, 1686, 1591, 1536, 1482; δ_H (300 MHz, $(CD_3)_2SO$ + CH_2Cl_2) 3.88 (3H, s), 7.15−7.24 (2H, m), 7.28−7.39 (12H, m), 7.51 (1H, d, *J* 8.7 Hz), 8.25 (1H, d, *J* 7.6 Hz), 8.87 (1H, d, *J* 1.7 Hz); δ_C (75 MHz, $(CD_3)_2SO$ + CH_2Cl_2) 55.6, 79.7, 80.5, 110.4, 118.8, 119.2, 121.4, 124.1, 124.9, 127.1, 128.0, 128.1, 128.8, 131.4, 132.1, 137.2, 137.8, 144.7, 149.1, 158.5, 173.6; HRMS (APCI) calculated for $[C_{29}H_{21}INO_2]^+$ (MH^+) *m*/*z* 542.0612 found 542.0611.

6-Iodo-8-isopropoxy-9-methoxy-11,11-diphenylisoindolo-[2,1-a]quinolin-5(11*H*)-one (15g) (Table, entry 7). Iodoimine **21c** (69.0 mg, 0.18 mmol) and Weinreb amide **24d** (64.1 mg, 0.22 mmol) were coupled and iodocyclized using the general procedure for the formation of ketones **13** and their iodocyclization to **15** and **25** (above), using CH_2Cl_2 in the iodocyclization step. Flash chromatography on silica gel using petroleum spirit/ethyl acetate (4:1) yielded **15g** as a pale yellow solid (102.4 mg, 95%): mp 228−231 °C; δ_H (300 MHz, $(CD_3)_2SO$) 1.37 (6H, d, *J* 6.0 Hz), 3.72 (3H, s), 4.62 (1H, quintet, *J* 6.0 Hz), 7.06 (1H, s), 7.12 (1H, d, *J* 8.4 Hz), 7.26−7.44 (12H, m), 8.22 (1H, dd, *J* 1.4, 7.9 Hz), 8.86 (1H, s); δ_C (75 MHz, $(CD_3)_2SO$) 21.6, 55.3, 71.2, 79.7, 106.3, 110.7, 118.5, 121.1, 122.7, 123.7, 127.0, 128.1, 128.2, 131.1, 137.3, 137.7, 146.3, 149.8, 153.8, 173.4; HRMS (APCI) calculated for $[C_{32}H_{27}INO_3]^+$ (MH^+) *m*/*z* 600.1030 found 600.1034.

4-(8-Methyl-1,1-diphenyl-1,3,4,5-tetrahydro-[1,3]oxazepino-[3,4-*a*]indol-6-yl)but-3-yn-1-ol (31). A mixture of iodoindole **9l** (80 mg, 0.17 mmol), 3-butyn-1-ol (0.015 mL, 0.2 mmol) and $Pd(PPh_3)Cl_2$ (3.4 mg, 5.1 μmol) in a mixture of THF and triethylamine (3 mL, 2:1) was deoxygenated by bubbling nitrogen through for 10 min. Copper(I) iodide (2.6 mg, 14 μmol) was then added, and the mixture was stirred overnight at room temperature under a nitrogen atmosphere. After this time, NH_4Cl aq (sat.) (3 mL) was added to the reaction mixture, and the mixture was extracted with diethyl ether (3 × 5 mL). The combined organic extracts were washed with brine and dried over $MgSO_4$, and the solvent was removed under reduced pressure. Column chromatography on deactivated alumina(III) using petroleum spirit/ethyl acetate (2:1) afforded **31** as pale yellow solid (52 mg, 72%): mp 69−71 °C; IR (cm^{-1}) 2947, 1448, 1398, 1318; δ_H (300 MHz, $(CD_3)_2SO$) 1.80 (2H, m), 2.25 (3H, s), 2.67 (2H, t, *J* 6.8 Hz), 3.20−3.24 (2H, m), 3.66 (2H, q, *J* 6.5 Hz), 3.79 (2H, t, *J* 7.02 Hz), 4.88 (1H, t, J 5.7 Hz), 5.91 (1H, d, J 8.5 Hz), 6.49 (1H, d, J 9.2 Hz), 7.14−7.18 (5H, m), 7.39−7.42 (6H, m); δ_C (75 MHz, $(CD_3)_2CO$) 21.1, 25.0, 25.3, 28.5, 62.1, 62.2, 66.0, 75.6, 91.9, 98.5, 98.6, 114.9, 119.5, 123.7, 128.9, 129.1, 129.5, 129.7, 129.8, 130.7, 136.0, 141.5, 147.3; HRMS (APCI) calculated for $[C_{29}H_{28}NO_2]^+$ (MH^+) *m*/*z* 422.2120 found 422.2109.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Spectra (^1H and ^{13}C NMR) of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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