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Synthesis of isoquinolines through the coupling of Fischer carbene complexes with *o*-alkynylpyridine carbonyl derivatives

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ABSTRACT

The reaction of Fischer carbene complex with *o*-alkynylpyridine carbonyl derivatives has been investigated. This involves the generation of furo[3,4-*c*]pyridine as transient intermediates through the coupling of *o*-alkynylpyridine carbonyl derivatives with carbene complex and subsequent Diels–Alder trapping with suitable dienophiles resulted in the formation of isoquinoline derivatives and the entire sequence can be run in one pot. When an olefinic tether was present, intramolecular Diels–Alder cycloaddition occurred followed by ring opening to yield tricyclic alcohols.

1. Introduction

Isoquinoline is an important heterocyclic template which possesses diverse biological activities owing to its presence in variety of natural products [1] and pharmaceuticals [2–5]. Isoquinoline species are also utilized as chiral ligands for transition metal catalysts [6–9], and their iridium complexes are used in organic light-emitting diodes [10–13]. Numerous elegant synthesis have been developed for isoquinolines [14–34], however the exploration of diversity-oriented synthetic routes for this class of compounds still remains a challenge. One of the important pathways for synthesis of these compounds involves the use of Diels–Alder reaction [27–34]. The method depends critically on the availability of the appropriate dienes. Heterocyclic *o*-quinodimethanes and their stable analogs have been utilized in this regard [32–36]. On the other hand, the use of heteroaromatic isobenzofurans [37–39] as dienes is emerging as a powerful alternative to the above method. Furo[3,4-*c*]pyridine intermediate is one of the interesting member of the heteroaromatic isobenzofurans and important building block for the synthesis of isoquinoline derivatives such as heterocyclic analogues of 1-arylnaphthalene lignans [32]. The generation of this intermediate include (i) thermal retro Diels–Alder reaction of 1,4-epoxides [40], (ii) lithiation and subsequent *o*-silylation of pyridine–phthalides [41], (iii) the Hamaguchi–Ibata reaction of *o*-aminodiazocarbonyl precursors [33,39], and (iv) sequential Pummerer–Diels–Alder route [32]. Multicomponent coupling reactions offer an incredible level of diversity for the production of diverse structural entities from a few simple components. As part of our continuing interest in the chemistry of azaisobenzofurans [42], we wish to describe a multicomponent coupling approach to the synthesis of isoquinoline derivatives by using Fischer carbene chemistry. Our strategy towards isoquinoline synthesis is based on the pioneering work of Herndon and coworkers [43–48] as outlined in Scheme 1. This involves the generation of furo[3,4-*c*]pyridine as transient intermediates through the coupling of *o*-alkynylpyridine carbonyl derivatives **1** with Fischer carbene complex **2**, and subsequent Diels–Alder trapping with suitable dienophiles resulted in the formation of isoquinoline derivatives **5**. The full details of our efforts in this area are described herein.

2. Results and discussion

Requisite alkynyl carbonyl derivatives **1** required for the synthesis of isoquinolines were readily prepared from the commercially available 3-bromo-4-pyridine carboxaldehyde (**6**) [49] (Scheme 2). The Sonogashira coupling of **6** with trimethylsilylacetylene afforded alkyne aldehyde **1a** in 80% yield, which on treatment with a phenyl-Grignard reagent in diethyl ether and subsequent oxidation with PDC gave the corresponding alkyne carbonyl derivative **1b** in 60% yield.

In the first phase of the studies, tandem carbene–alkyne coupling – furo[3,4-*c*]pyridine intermediate formation – intermolecular Diels–Alder reactions were examined using *N*-methylmaleimide/*N*-phenylmaleimide as dienophile. Coupling of carbene complex **2** with alkyne **1** in refluxing THF in presence of electron

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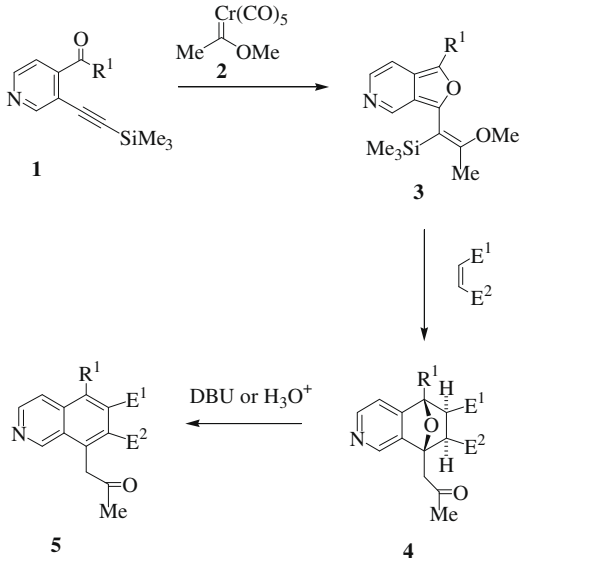
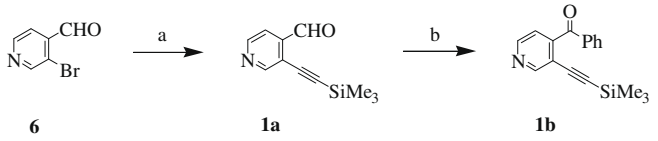
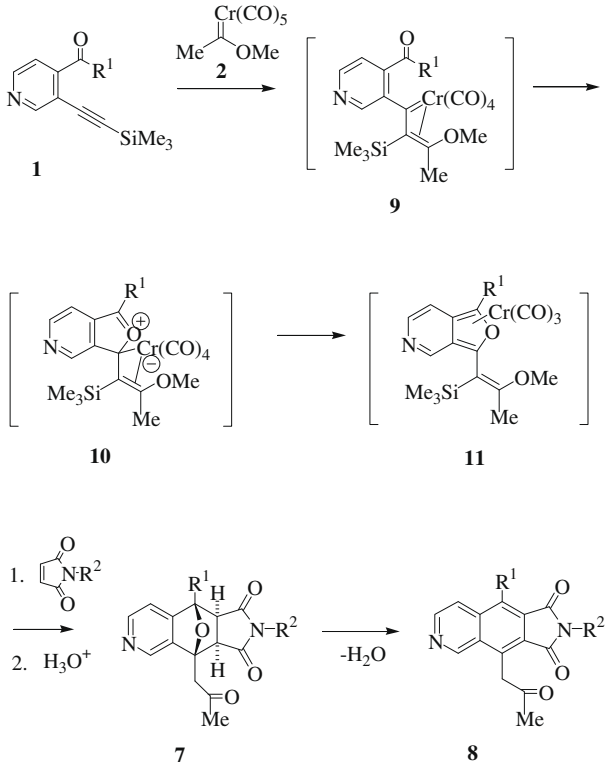


Scheme 1.



Scheme 2. Reagents and conditions: (a) trimethylsilylacetylene, $(Ph_3P)_2PdCl_2$, PPh_3, CuI, THF, Et_3N, rt, 80%; (b) (i) PhMgBr; (ii) CrO_3, 2Py, 60%.



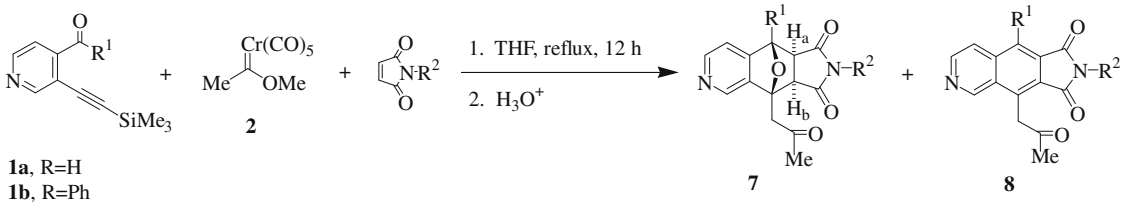
Scheme 3.

deficient dienophiles led to the synthesis of isoquinoline derivatives (see Table 1). This reaction pathway was general, and in all cases this type of coupling led to the synthesis of isoquinoline derivatives **8** through the tandem generation of azaisobenzofuran intermediate and subsequent trapping with Diels–Alder dienophile followed by acid/base catalyzed aromatization. In case of alkynyl ketones **1b** (entry C), in addition to isoquinoline derivative **8C**, an oxa-bridged adduct **7C** was also isolated. The stereochemistry of the oxa-bridge adduct is *exo* which can be anticipated from the chemical shifts of H_a and H_b (<4 ppm) [43,50,51]. This oxa-bridged adduct **7C** can be readily converted to the corresponding isoquinoline derivative **8C** on treatment with DBU in refluxing toluene [42,52].

Formation of the products in Table 1 most likely occurs via the reaction pathway in Scheme 3. Initial coupling affords the vinylcarbene complex **9**, which undergoes ylide formation to afford the azaisobenzofuran intermediate **11**. The Diels–Alder reaction should initially provide the bridged structure **7**; however in most of the examples tested this intermediate rapidly undergoes dehydration to afford the isoquinoline ring systems **8** except the example (entry C, Table 1). Compounds **8C** and **8D** may be viewed as heterocyclic analogues of 1-arylnaphthalene lignans [32].

In the second phase of the studies for the synthesis of isoquinoline derivatives, the coupling of 3-trimethylsilylethynylpyridine-

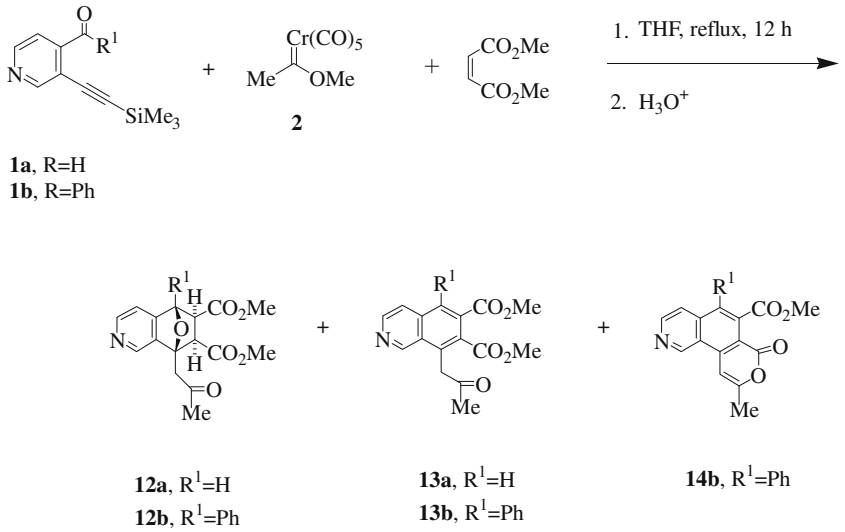
Table 1
Synthesis of isoquinoline through tandem furo[3,4-*c*]pyridine formation – Diels–Alder reaction.



1a, R=H
1b, R=Ph

Entry	R^1	R^2	Yield **7**[a]	Yield **8**[a]
A	H	Ph	–	44
B	H	Me	–	41
C	Ph	Ph	20	40
D	Ph	Me	–	52

[a] Isolated yield in %.



Scheme 4.

4-carboxaldehyde (**1a**), methyl-carbene complex **2** and dimethylmaleate was tested (Scheme 4). In this reaction, initially formed Diels–Alder adduct **12a** is not stable under reaction conditions and readily converted to the isoquinoline derivative **13a** in 24% yield. In the coupling of alkynyl ketones **1b** with **2** and dimethylmaleate, oxa-bridged adduct **12b** was isolated along with pyridine fused isocoumarin derivative **14b**. In this case, isoquinoline derivative **13b** was not isolated; it readily converted into **14b** under the reaction condition. Treatment of the oxa-bridged adduct **12b** with DBU in refluxing toluene afforded isocoumarin derivative **14b** in 45% yield, presumably via formation of isoquinoline derivative **13b**, followed by enolate generation at the more acidic benzylic position [53]. Partial conversion of **12b** to **14b** also took place on treatment with 10% aqueous hydrochloric acid.

In order to improve the yield of the products by the one-pot coupling reaction process, we have studied the coupling reaction of alkynyl aldehyde **1a**, carbene complex **2** and *N*-phenylmaleimide under two different conditions: (i) under refluxing dioxane and (ii) by separate and simultaneous addition of the carbene complex and dienophile to the refluxing solution of the alkynyl aldehyde **1a** in THF. In the first case the yield of the product was slightly improved from 44% to 49%. No improvement of yield was observed in the later case.

The final phase of these studies involve the use of γ,δ-unsaturated Fischer carbene complex **15** [54], in order to establish the feasibility of an intramolecular Diels–Alder cycloaddition in the furo[3,4-*c*]pyridines. The coupling of alkynyl carbonyl derivatives **1** with carbene complex **15** afforded tricyclic products **18** in one pot. In these cases, the only product was an oxanorbornene ring opening product **18** and not the initial Diels–Alder adduct **17**

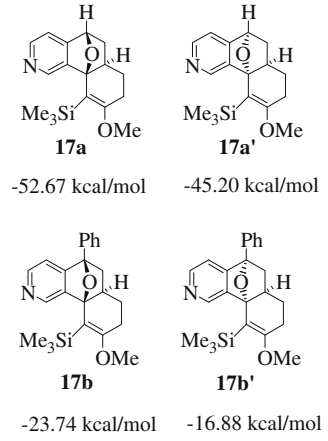
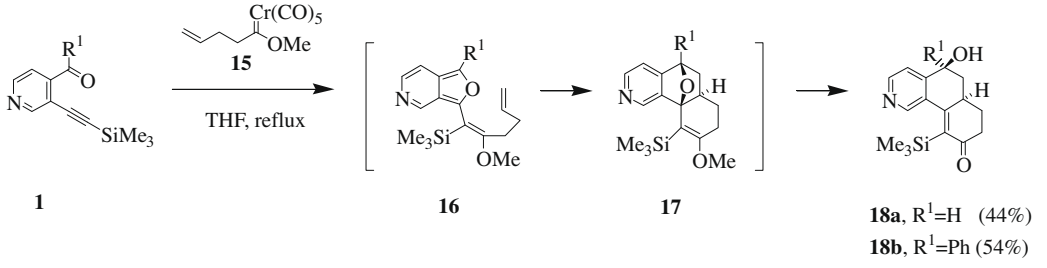


Fig. 1. Heats of formation for compounds **17a**, **17a′**, **17b**, **17b′**.

(Scheme 5). Formation of **18** likely occurs via the desired reaction pathway involving formation of furo[3,4-*c*]pyridines **16**, followed by intramolecular Diels–Alder reaction and subsequent ring opening of the strained oxanorbornene system.

Six-membered-ring-forming intramolecular Diels–Alder reactions of isobenzofurans normally proceed with *exo* stereochemistry [50,55–58]. Comparison of energies calculated using the PM3 semi-empirical single point molecular orbital method with 10×10 configuration space for the most stable conformations (MM+ optimize followed by PM3 optimizations) of *exo* and *endo* Diels–Alder adducts reveals that the *exo* products are the most sta-



Scheme 5.

ble products in both cases (Fig. 1). Calculation shows that **17a** is more stable than **17a′** by 7.47 kcal/mol and **17b** is more stable than **17b′** by 6.86 kcal/mol.

3. Conclusion

The results presented herein demonstrate the potential of the tandem carbene–alkyne coupling – furo[3,4-*c*]pyridine intermediate formation – inter/intramolecular Diels–Alder sequence leading to the synthesis of isoquinoline derivatives in one pot. Our results clearly indicate that the tandem-cascade process provides a rapid entry into heteroaromatic azaisobenzofurans. This area of research is currently being pursued in more detail in our laboratory.

4. Experimental

4.1. General

All melting points are uncorrected. Unless otherwise noted, all reactions were carried out under an inert atmosphere in flame dried flasks. Solvents and reagents were dried and purified by distillation before use as follows: tetrahydrofuran, diethyl ether from sodium benzophenone ketyl; dichloromethane and chloroform from P_2O_5; DMF and diisopropylamine from CaH_2; triethylamine and pyridine from solid KOH. After drying, organic extracts were evaporated under reduced pressure and the residue was column chromatographed on silica gel (Spectrochem, particle size 100–200 mesh), using an ethyl acetate–petroleum ether (60–80 °C) mixture as eluent unless specified otherwise.

4.2. 3-Trimethylsilylethynylpyridine-4-carboxaldehyde (**1a**) [49]

A mixture of 3-bromo-4-carboxaldehyde (**6**) (600 mg, 3.2 mmol), $Pd(PPh_3)_2Cl_2$ (115 mg, 0.16 mmol), PPh_3 (21 mg, 0.08 mmol), trimethylsilylacetylene (475 mg, 4.8 mmol) and triethylamine (490 mg, 4.8 mmol) in THF (15 mL) was stirred for 20 min at room temperature, and then CuI (10 mg, 0.05 mmol) was added. The reaction mixture was stirred for 14 h at room temperature. After removal of the solvent, the residue was treated with dichloromethane and filtered through a bed of Celite (2.0 g). After evaporation of the solvent, the crude product was purified by column chromatography (silica gel, ethyl acetate/petroleum ether, 1:9) to yield aldehyde **1a** (525 mg, 80%) as low melting solid. IR (neat, cm^{-1}): 2853, 2156, 1710; ^1H NMR (500 MHz, $CDCl_3$): δ 10.50 (s, 1H), 8.86 (s, 1H), 8.69 (d, 1H, J = 5.0 Hz), 7.65 (d, 1H, J = 5.0 Hz), 0.28 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 190.7, 154.8, 149.4, 140.8, 121.1, 118.8, 105.9, 96.8, −0.60 (3C); MS: *m*/*e* (relative intensity): 204 (MH^+, 100), 176 (7).

4.3. Phenyl-(3-trimethylsilylethynylpyridine-4-yl)methanone (**1b**)

A solution of phenylmagnesium bromide (0.6 M, 5 mL, 3 mmol) in diethyl ether [prepared from bromobenzene (650 mg, 4.2 mmol) and magnesium (120 mg, 5 mmol) in 15 mL diethyl ether] was added dropwise to a stirred solution of aldehyde **1a** (550 mg, 2.7 mmol) in diethyl ether (10 mL) over a period of 20 min at 0 °C. After 3 h stirring the mixture was allowed to come at room temperature and then quenched with saturated aqueous NH_4Cl (5 mL). The organic layer was separated and the aqueous layer was extracted with diethyl ether (3 × 10 mL). The combined organic layer was washed with brine (5 mL) and dried over anhydrous Na_2SO_4. After removal of the solvent, the crude alcohol was dissolved in dry CH_2Cl_2 (5 mL) and added to a red solution of CrO_3·2Py [prepared from vigorously stirred suspension of CrO_3 (800 mg, 8 mmol) and pyridine (1.26 g, 16 mmol) in CH_2Cl_2 (15 mL) for 1.5 h at room temperature] and stirred at room temperature for 4 h. The mixture was then diluted with Et_2O (15 mL) and passed through a bed of silica gel (10 g). After evaporation of the solvent, the crude product was purified by column chromatography (silica gel, ethyl acetate/petroleum ether, 1:9) to give ketone **1b** (450 mg, 60%) as colourless thick liquid. R_f (10% EtOAc/petroleum ether) 0.42; IR ($CHCl_3$, cm^{-1}): 2162, 1672; ^1H NMR (500 MHz, $CDCl_3$): δ 8.77 (s, 1H), 8.67 (d, 1H, J = 4.80 Hz), 7.79 (d, 2H, J = 7.5 Hz), 7.61 (t, 1H, J = 7.5 Hz), 7.47 (t, 2H, J = 7.5 Hz), 7.34 (d, 1H, J = 4.80 Hz), -0.05 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 194.8, 153.1, 148.9, 148.8, 135.8, 133.8, 130.0 (2C), 128.5 (2C), 121.2, 117.4, 104.4, 98.92, -0.75 (3C); MS: *m*/*e* (relative intensity): 281(MH^++1, 28), 280 (MH^+, 100); Anal. Calc. for $C_{17}H_{17}NOSi$: C, 73.08; H, 6.13; N, 5.01. Found: C, 72.85; H, 6.31; N, 4.83%.

4.4. General procedure 1 – coupling of carbene complex with alkynyl pyridine carbonyl derivatives and maleimides/dimethylmaleate

A solution of carbene complex **2** (1.1 mmol) in THF (10 mL) was added dropwise to a refluxing solution of alkynyl carbonyl derivatives **1** (1 mmol) and maleimide/dimethylmaleate (1.1 mmol) in THF (5 mL) over a period of 1 h. After the addition was complete, the mixture was heated to reflux for a period of 12 h. The mixture was allowed to cool to room temperature. After removal of the solvent, EtOAc (20 mL) was added and the residue was filtered through Celite (1.0 g). The solvent was removed, and the crude products were dissolved in ether (20 mL). To this solution of crude product in ether was added aqueous HCl (1:1) (0.5 mL) and the mixture was stirred for 6 h at room temperature. The organic layer was separated. The aqueous layer was neutralized with saturated $NaHCO_3$ solution (3 mL) and extracted with ethyl acetate (3 × 10 mL). The combined organic layer (diethyl ether layer and ethyl acetate layer) was washed with water (3 mL) and brine (3 mL), and dried over anhydrous Na_2SO_4. Evaporation of solvent and purification by column chromatography gave the pure products.

4.4.1. Coupling of carbene complex **2** with 3-trimethylsilylethynylpyridine-4-carboxaldehyde (**1a**) and N-phenylmaleimide (Table 1, entry A)

General procedure 1 was followed using alkynyl aldehyde **1a** (150 mg, 0.74 mmol), carbene complex **2** (202 mg, 0.81 mmol) and *N*-phenylmaleimide (141 mg, 0.81 mmol). The crude product was purified using column chromatography (silica gel, ethyl acetate/petroleum ether 2:3) to yield the isoquinoline derivative **8A** (107 mg, 44%) as white solids. Mp 210–212 °C (decomposed); R_f (50% EtOAc/petroleum ether) 0.24; IR (KBr, cm^{-1}): 1765, 1708; ^1H NMR (400 MHz, $CDCl_3$): δ 9.98 (s, 1H), 8.76 (d, 1H, J = 5.6 Hz), 8.59 (s, 1H), 8.44 (d, 1H, J = 5.6 Hz), 7.65–7.40 (m, 5H), 5.16 (s, 2H), 2.55 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 203.4, 167.1, 165.7, 150.5, 146.2, 138.7, 134.7, 131.3, 131.1, 129.8, 129.2 (2C), 128.5, 126.6 (2C), 125.6, 123.2, 122.6, 41.1, 30.4; MS: *m*/*e* (relative intensity): 331 (MH^+, 100), 289 (14); HRMS: Anal. Calc. for $C_{20}H_{15}N_2O_3$ (MH^+): 331.1083. Found: 331.1078.

4.4.2. Coupling of carbene complex **2** with 3-trimethylsilylethynylpyridine-4-carboxaldehyde (**1a**) and N-methylmaleimide (Table 1, entry B)

General procedure 1 was followed using alkynyl aldehyde **1a** (150 mg, 0.74 mmol), carbene complex **2** (202 mg, 0.81 mmol) and *N*-methylmaleimide (90 mg, 0.81 mmol). The crude product was purified using column chromatography (silica gel, ethyl acetate/petroleum ether 1:1) to yield the isoquinoline derivative **8B** (81 mg, 41%) as white solids. Mp 160–162 °C (decomposed); R_f (50% EtOAc/petroleum ether) 0.21; IR (KBr, cm^{-1}): 1762, 1705; ^1H NMR (500 MHz, $CDCl_3$): δ 9.46 (s, 1H), 8.75 (d, 1H, J = 5.5 Hz),

8.25 (s, 1H), 7.86 (d, 1H, J = 5.6 Hz), 4.92 (s, 2H), 3.24 (s, 3H), 2.45 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 203.4, 168.1, 166.8, 150.4, 146.0, 138.6, 133.8, 131.5, 129.5, 126.2, 122.7, 122.5, 41.1, 30.3, 24.3; MS: m/e (relative intensity): 269 (MH^+, 100), 242 (5); Anal. Calc. for $C_{15}H_{12}N_2O_3$: C, 67.16; H, 4.51; N, 10.44. Found: C, 66.96; H, 4.59; N, 10.39%.

4.4.3. Coupling of carbene complex **2** with phenyl-(3-trimethylsilylethynylpyridine-4-yl)methanone (**1b**) and N-phenylmaleimide (Table 1, entry C)

General procedure 1 was followed using alkynyl ketone **1b** (150 mg, 0.54 mmol), carbene complex **2** (148 mg, 0.59 mmol) and *N*-phenylmaleimide (103 mg, 0.59 mmol). The crude product was purified using column chromatography (silica gel, ethyl acetate/petroleum ether 2:3) to yield the isoquinoline derivative **8C** (87 mg, 40%) as gummy solid and the oxa-bridged compound **7C** (45 mg, 20%) as yellowish thick liquid. Compound **8C**: R_f (50% EtOAc/petroleum ether) 0.58; IR (KBr, cm^{-1}): 1768, 1714; ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.57 (s, 1H), 8.70 (bs, 1H), 7.80–7.00 (m, 11H), 5.06 (s, 2H), 2.51 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 203.8, 167.0, 165.2, 139.1, 133.8, 132.9, 131.3, 129.8 (2C), 129.2, 129.0 (3C), 128.8, 128.6, 128.4 (3C), 126.8, 126.5 (2C), 126.4, 126.0, 125.9, 41.0, 28.4; FABMS: m/e (relative intensity): 407 (MH^+, 35), 107 (100); HRMS: Anal. Calc. for $C_{26}H_{19}N_2O_3$ (MH^+): 407.1396. Found: 407.1396. Compound **7C**: R_f (50% EtOAc/petroleum ether) 0.39; IR ($CHCl_3$, cm^{-1}): 1778, 1713; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.64 (s, 1H), 8.53 (bs, 1H), 7.60 (d, 2H, J = 7.6 Hz), 7.50 (t, 2H, J = 7.6 Hz), 7.46–7.30 (m, 4H), 7.16 (d, 1H, J = 4.4 Hz), 7.12 (d, 2H, J = 7.6 Hz), 3.77 (d, 1H, J = 6.8 Hz), 3.71 (d, 1H, J = 18.0 Hz), 3.50 (d, 1H, J = 18.0 Hz), 3.49 (d, 1H, J = 6.8 Hz), 2.45 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 204.9, 173.5, 171.7, 156.0, 149.3, 142.5, 132.3, 131.4, 129.2 (2C), 129.0, 128.7 (2C), 128.5 (2C), 126.4, 126.2 (2C), 125.7 (2C), 90.6, 86.0, 52.3, 50.8, 44.7, 30.6; FABMS: m/e (relative intensity): 425 (MH^+, 72), 252 (100), 208 (38); Anal. Calc. for $C_{26}H_{20}N_2O_4$: C, 73.57; H, 4.75; N, 6.60. Found: C, 73.23; H, 4.87; N, 6.42%.

4.4.4. Coupling of carbene complex **2** with phenyl-(3-trimethylsilylethynylpyridine-4-yl)methanone (**1b**) and N-methylmaleimide (Table 1, entry D)

General procedure 1 was followed using alkynyl ketone **1b** (150 mg, 0.54 mmol), carbene complex **2** (148 mg, 0.59 mmol) and *N*-methylmaleimide (65 mg, 0.59 mmol). The crude product was purified using column chromatography (silica gel, ethyl acetate/petroleum ether 2:3) to yield the isoquinoline derivative **8D** (96 mg, 52%) as yellowish thick liquid. R_f (50% EtOAc/petroleum ether) 0.50; IR ($CHCl_3$, cm^{-1}): 1762, 1704; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.48 (s, 1H), 8.65 (d, 1H, J = 5.0 Hz), 7.60 (d, 1H, J = 5.0 Hz), 7.59–7.50 (m, 3H), 7.40–7.30 (m, 2H), 4.99 (s, 2H), 3.13 (s, 3H), 2.49 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 203.8, 168.0, 166.3, 150.1, 146.1, 139.0, 138.3, 132.9, 132.8, 129.8 (3C), 128.9, 128.4 (3C), 127.1, 126.1, 41.0, 30.3, 24.1; MS: m/e (relative intensity): 346 (MH^++1, 20), 345 (MH^+, 100), 301 (20), 294 (25), 163 (30); HRMS: Anal. Calc. for $C_{21}H_{17}N_2O_3$ (MH^+): 345.1239. Found: 345.1232.

4.4.5. Coupling of carbene complex **2** with 3-trimethylsilylethynylpyridine-4-carboxaldehyde (**1a**) and dimethyl maleate (Scheme 4)

General procedure 1 was followed using alkynyl aldehyde **1a** (150 mg, 0.74 mmol) carbene complex **2**, (202 mg, 0.81 mmol) and dimethyl maleate (116 mg, 0.81 mmol). The crude product was purified using column chromatography (silica gel, ethyl acetate/petroleum ether 1:1) to yield the isoquinoline derivative **13a** (53 mg, 24%) as thick liquid. R_f (50% EtOAc/petroleum ether) 0.42; IR ($CHCl_3$, cm^{-1}): 1730; ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.39 (s, 1H), 8.70 (d, 1H, J = 5.5 Hz), 8.45 (s, 1H), 7.77 (d, 1H, J = 5.5 Hz), 4.31 (s, 2H), 3.97 (s, 6H), 2.32 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 203.6, 168.8, 165.8, 149.7, 144.9, 135.5, 131.4, 129.9, 129.8, 128.5, 128.2, 121.5, 53.0 (2C), 43.8, 29.7; MS: m/e (relative intensity): 303 (MH^++1, 18), 302 (MH^+, 100), 286 (25), 279 (15), 270 (15); Anal. Calc. for $C_{16}H_{15}NO_5$: C, 63.78; H, 5.02; N, 4.65. Found: C, 63.45; H, 5.19; N, 4.76%.

4.4.6. Coupling of carbene complex **2** with phenyl-(3-trimethylsilylethynylpyridine-4-yl)methanone (**1b**) and dimethyl maleate (Scheme 4)

General procedure 1 was followed using alkynyl ketone **1b** (178 mg, 0.64 mmol), carbene complex **2** (175 mg, 0.7 mmol) and dimethyl maleate (100 mg, 0.7 mmol). The crude product was purified using column chromatography (silica gel, ethyl acetate/petroleum ether 1:1) to yield the oxa-bridged compound **12b** (63 mg, 25%) as gummy yellow solids and isoquinoline–lactone **14b** (65 mg, 30%) as a yellow solid. Compound **12b**: R_f (50% EtOAc/petroleum ether) 0.31; IR (KBr, cm^{-1}): 1734; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.60 (s, 1H), 8.50 (d, 1H, J = 4.8 Hz), 7.69–7.62 (m, 2H), 7.50–7.40 (m, 3H), 7.06 (d, 1H, J = 4.8 Hz), 4.25 (d, 1H, J = 4.6 Hz), 3.75 (s, 3H); 3.55 (d, 1H, J = 17.6 Hz), 3.50 (d, 1H, J = 4.6 Hz), 3.49 (s, 3H), 3.33 (d, 1H, J = 17.6 Hz), 2.30 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 203.7, 172.6, 172.3, 162.5, 153.3, 145.5, 140.7, 128.5 (2C), 128.2, 126.5, 126.2 (2C), 121.2, 99.5, 77.2, 53.0, 52.4, 50.3, 47.6, 44.4, 20.3; MS: m/e (relative intensity): 396 (MH^+, 37), 378 (MH^+-H_2O, 7), 252 (100), 209 (14); Anal. Calc. for $C_{22}H_{21}NO_6$: C, 66.83; H, 5.35; N, 3.54. Found: C, 66.57; H, 5.51; N, 3.34%. Compound **14b**: Mp 112 °C; R_f (50% EtOAc/petroleum ether) 0.51; IR (KBr, cm^{-1}): 1744, 1643; ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.76 (s, 1H), 8.68 (d, 1H, J = 6.0 Hz), 7.53–7.45 (m, 3H), 7.42 (d, 1H, J = 6.0 Hz), 7.38–7.28 (m, 2H), 7.23 (s, 1H), 3.68 (s, 3H), 2.48 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 167.9, 160.6, 158.9, 148.6, 147.5, 138.5, 137.9, 136.3, 134.6, 134.5, 130.1, 129.0, 128.7, 128.4 (2C), 122.0, 119.9, 113.9, 98.1, 52.6, 20.3; MS: m/e (relative intensity): 346 (MH^+, 100), 320 (80), 252 (60); Anal. Calc. for $C_{21}H_{15}NO_4$: C, 73.03; H, 4.38; N, 4.06. Found: C, 73.36; H, 4.11; N, 4.23%.

4.4.7. Coupling of carbene complex **2** with 3-trimethylsilylethynylpyridine-4-carboxaldehyde (**1a**) and N-phenylmaleimide

General procedure 1 was followed using alkynyl aldehyde **1a** (100 mg, 0.49 mmol) carbene complex **2** (135 mg, 0.54 mmol) and *N*-phenylmaleimide (93 mg, 0.54 mmol) with the exception that the reaction was carried out in refluxing dioxane instead of THF. The crude product was purified using column chromatography (silica gel, ethyl acetate/petroleum ether 2:3) to give the isoquinoline derivative **8A** (78 mg, 49%).

4.4.8. Coupling of carbene complex **2** with 3-trimethylsilylethynylpyridine-4-carboxaldehyde (**1a**) and N-phenylmaleimide

General procedure 1 was followed using alkynyl aldehyde **1a** (100 mg, 0.49 mmol) carbene complex **2** (135 mg, 0.54 mmol) and *N*-phenylmaleimide (93 mg, 0.54 mmol), but in this case the carbene and dienophile were added separately and simultaneously to the aldehyde in refluxing THF. The crude product obtained after acid treatment was purified using column chromatography (silica gel, ethyl acetate/petroleum ether 2:3) which gave the isoquinoline derivative **8A** (72 mg, 45%).

4.5. Methyl 3-methyl-1-oxo-9-phenyl-1H-2-oxa-6-azaphenanthrene-10-carboxylate (**14b**)

To a stirred solution of oxa-bridged compound **12b** (50 mg, 0.13 mmol) in toluene (1 mL), DBU (198 mg, 1.3 mmol) was added

dropwise at room temperature. The mixture was heated at reflux for 1.5 h. After cooling to room temperature, the mixture was washed with 10% aqueous HCl (1 mL) and dried over anhydrous Na_2SO_4. After evaporation of the solvent, the crude product was purified by column chromatography (silica gel, ethyl acetate/petroleum ether, 1:1) to give lactone **14b** (20 mg, 45%) as yellow solid.

*4.6. 5-Hydroxy-10-trimethylsilyl-5,6,7,8-tetrahydro-6aH-benzo[h]isoquinoline-9-one (**18a**)*

To a solution of alkynyl aldehyde **1a** (162 mg, 0.8 mmol) in THF (4 mL) at reflux was added a solution of γ,δ-unsaturated carbene complex **15** [54] (255 mg, 0.88 mmol) in THF (10 mL) over a period of 1 h. After the addition was complete, the mixture was heated at reflux for 18 h. The reaction mixture was cooled to room temperature. The THF was removed under reduced pressure, ethyl acetate (10 mL) was added and the residue was filtered through Celite (1.0 g). After evaporation of the solvent, the crude product was purified by column chromatography (silica gel, ethyl acetate/petroleum ether, 1:1) to yield a white solid alcohol **18a** (100 mg, 44%). Mp 122 °C; R_f (50% EtOAc/petroleum ether) 0.26; IR (KBr, cm^{-1}): 3442, 1632; ^1H NMR (500 MHz, $CDCl_3$): δ 8.63 (d, 1H, J = 5.0 Hz), 8.55 (s, 1H), 7.46 (d, 1H, J = 5.0 Hz), 4.97 (dd, 1H, J = 8.5, 5.0 Hz), 2.69 (m, 1H), 2.50 (ddd, 1H, J = 17.1, 3.8, 3.0 Hz), 2.42 (dt, 1H, J = 13.2, 5.2 Hz), 2.32 (ddd, 1H, J = 17.1, 15.0, 5.0 Hz), 2.17 (m, 1H), 1.85–1.70 (m, 2H), 1.65 (bs, 1H), 0.10 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 202.7, 164.5, 151.4, 150.5, 149.1, 139.3, 131.2, 121.1, 68.1, 41.0, 38.3, 36.8, 28.7, 1.6 (3C); MS: m/e (relative intensity): 288 (MH^+, 17), 258 (20), 220 (16), 188 (100); HRMS: Anal. Calc. for $C_{16}H_{22}NO_2Si$ (MH^+): 288.1420. Found: 288.1416.

*4.7. 5-Hydroxy-5-phenyl-10-trimethylsilyl-5,6,7,8-tetrahydro-6aH-benzo[h]isoquinoline-9-one (**18b**)*

The procedure described for **18a** was employed using alkynyl ketone **1b** (140 mg, 0.5 mmol) and γ,δ-unsaturated carbene complex **15** (160 mg, 0.55 mmol). Purification was effected by column chromatography (silica gel, ethyl acetate/petroleum ether 4:6) to yield the alcohol **18b** (98 mg, 54%) as a white solid. Mp 168–169 °C; R_f (30% EtOAc/petroleum ether) 0.42; IR (KBr, cm^{-1}): 3426, 1659; ^1H NMR (400 MHz, $CDCl_3$): δ 8.64 (s, 1H), 8.59 (d, 1H, J = 5.2 Hz), 7.38–7.28 (m,3H), 7.20–7.13 (m, 2H), 7.11(d, 1H, J = 5.2 Hz), 2.63 (m, 1H), 2.5 (bs, 1H, exchangeable with D_2O), 2.52–2.40 (m, 2H), 2.28 (m, 1H), 2.11 (dd, 1H, J = 13.2, 9.6 Hz), 2.00 (m, 1H), 1.72 (m, 1H), 0.12 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 202.8, 164.6, 152.1, 151.4, 150.1, 145.1, 139.7, 131.9, 128.4 (2C), 127.9, 126.2 (2C), 121.5, 75.2, 48.0, 37.1, 37.0, 28.9, 1.6 (3C); MS: m/e (relative intensity): 364 (MH^+, 30), 284 (100); HRMS: Anal. Calc. for $C_{22}H_{26}NO_2Si$ (MH^+): 364.1733. Found: 364.1728.

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