Multicomponent Approach for the Synthesis of Phenanthridine and Acridine Ring Systems via the Coupling of Fischer Carbene Complexes with Heteroaromatic *o*-Alkynyl Carbonyl Derivatives

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Abstract: A one-pot multicomponent synthesis of phenanthridine and acridine derivatives is described. This method includes the in situ generation of furo[3,4-*c*]isoquinoline and furo[3,4-*b*]quinoline intermediates by the coupling of heteroaromatic *o*-alkynyl carbonyl derivatives with Fischer carbene complexes and subsequent trapping of these intermediates by suitable dienophiles.

Key words: azaisobenzofuran, heterocycles, Diels–Alder reaction, chromium, carbene complexes

Fused azaheterocycles are a family of biological agents with particularly interesting pharmacological properties related to the planarity of the system. Substituted phenanthridines and acridines are important classes of heterocyclic compounds in medicinal chemistry and are attractive synthetic targets due to their widespread occurrence in nature and broad range of biological activity including antitumor and antiviral activity.[1] A large number of acridine drugs, natural alkaloids or synthetic molecules, have been tested as antibacterial and antimalarial agents.[2] Classical synthetic methods for these heterocyclic molecules involve multistep condensation reactions resulting in the desired azaheterocycles;[3,4] however, many synthetic routes require harsh conditions and thus appear to be unsuitable for the synthesis of functionalized heterocycles incorporating sensitive functional groups. In multistep reactions, the limited substrate scope and the frequent requirement of harsh reaction conditions, with extremely high temperatures, limit the usefulness and generality of these methods. This has led to the search for new synthetic methods that would facilitate the preparation of an appropriate series of compounds. Thus, a synthesis suitable for both of these heterocyclic compounds and also their analogues is required. As a contrast to this multistep strategy, a new concept for the synthesis of a target compound with a higher chemical efficiency is emerging. Multicomponent reactions (MCRs) are responsible for this higher efficiency.[5] MCRs provide a complementary approach to a number of structures and should find applications in library generation. In a preliminary communication, we described the synthesis of phenanthridine ring systems using the MCR approach.[6] In this paper, we wish to report full details of the multicomponent coupling approach for the synthesis of phenanthridine derivatives, along with the synthesis of acridine derivatives, using Fischer carbene chemistry. This process involves the first-time generation of furo[3,4-*c*]isoquinoline and furo[3,4-*b*]quinoline intermediates by the coupling of Fischer carbene complexes[7] with heteroaromatic *o*-alkynyl carbonyl derivatives. These intermediates can actively participate in inter- and intramolecular cycloaddition reactions. Hence, our synthetic strategy includes the generation of the furo[3,4-*c*]isoquinoline intermediates **3** formed by the coupling of *o*-alkynylisoquinolinecarbonyl derivatives **1** with Fischer carbene complex **2** and of the furo[3,4-*b*]quinoline intermediates **7** formed by the coupling of *o*-alkynylquinolinecarbonyl derivatives **5** with Fischer carbene complex **6**, and trapping of these intermediates using suitable dienophiles for the synthesis of phenanthridine and acridine derivatives (Scheme 1).

The requisite 3-alkynylisoquinoline-4-carbonyl derivatives necessary for our study were readily prepared using the series of reactions depicted in Scheme 2. 3-Chloro-1-phenylisoquinoline-4-carbaldehyde (**10**) was prepared from dihydroisoquinolinone **9**[8] by a two-step procedure involving a Vilsmeier–Haack reaction followed by oxidation with potassium permanganate under acidic conditions.[9] The Sonogashira coupling of chloride **10** with (trimethylsilyl)acetylene afforded 1-phenyl-3-(trimethylsilylethynyl)isoquinoline-4-carbaldehyde (**11**), which on treatment with the appropriate Grignard reagent and subsequent oxidation with pyridinium dichromate resulted in the ketones **12**–**14**.

Similarly, the corresponding quinoline derivative **16**[10] was prepared by the palladium-catalyzed Sonogashira reaction of 3-formyl-2-iodoquinoline (**15**)[11] with (trimethylsilyl)acetylene (Scheme 3). Exposure of aldehyde **16** to an aryl or alkyl Grignard reagent in diethyl ether followed by pyridinium dichromate oxidation resulted in the alkynyl carbonyl derivatives **17**–**19**.

In the first phase of these studies, a three-component coupling reaction of carbene complex **2**, 3-alkynylisoquinoline-4-carbaldehyde **11** and dimethyl maleate in refluxing tetrahydrofuran was carried out, which on exposure to silica gel led to the synthesis of the phenanthridine derivative **21** (Scheme 4). Formation of compound **21** occurs through the generation of the transient furo[3,4-*c*]isoquinoline intermediate **20**, followed by Diels–Alder reaction

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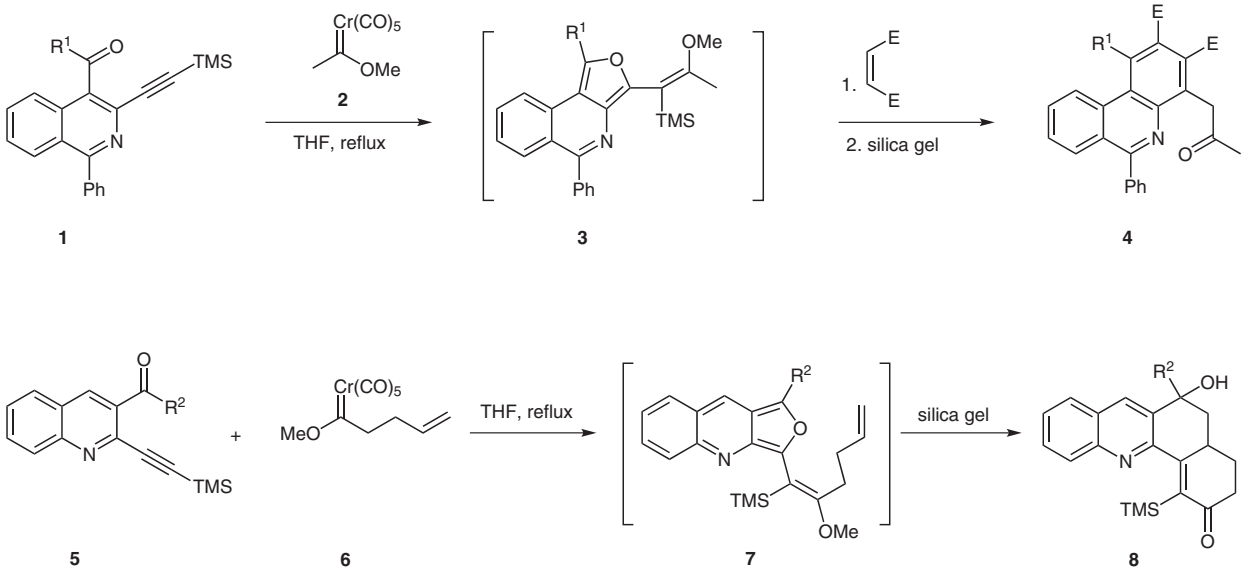
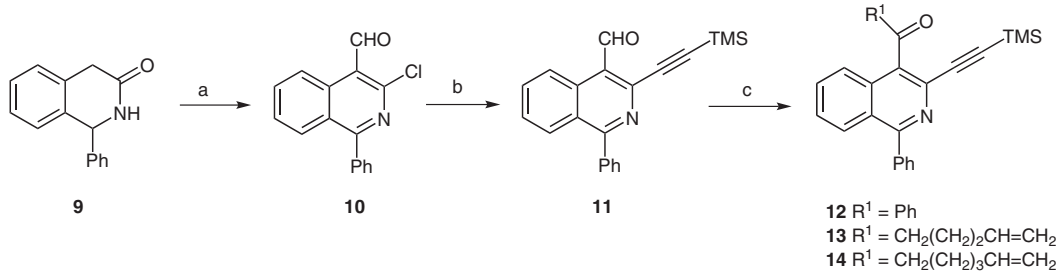
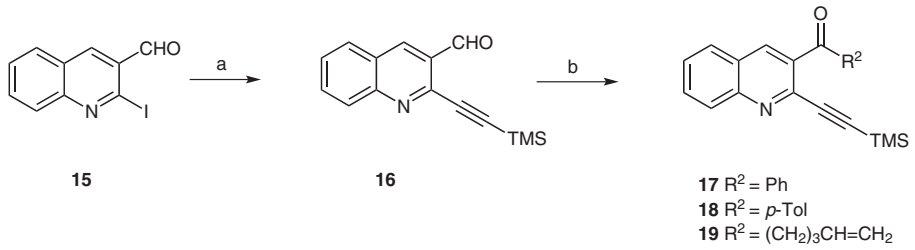


Scheme 1 Tandem generation and trapping of furo[3,4-*c*]isoquinoline and furo[3,4-*b*]quinoline intermediates



Scheme 2 Synthesis of isoquinolines substituted with an aldehyde or a ketone group. *Reagents and conditions*: (a) $POCl_3$, DMF, THF, 0 °C; then $KMnO_4$, H_2SO_4, r.t., 42%; (b) (trimethylsilyl)acetylene, $(Ph_3P)_2PdCl_2$, Ph_3P, CuI, Et_3N, THF, r.t., 67%; (c) (i) R^1MgBr; (ii) CrO_3·2py, **12** (72%), **13** (52%), **14** (47%).



Scheme 3 Synthesis of functionalized quinolines. *Reagents and conditions*: (a) (trimethylsilyl)acetylene, $(Ph_3P)_2PdCl_2$, CuI, Et_3N, THF, r.t., 86%; (b) (i) R^2MgBr; (ii) CrO_3·2py, **17** (70%), **18** (69%), **19** (45%).

with the dimethyl maleate present in the reaction mixture. When *N*-methylmaleimide was used as the dienophile, however, the [4+2] oxa-bridged adduct **22** could be isolated together with the phenanthridine derivative **23**. The chemical shift values of the H_B and H_C protons (<4 ppm), the 0-Hz coupling between H_A and H_B, and the N–Me signal (~3.0 ppm)[7a,12] confirm the *exo* stereochemistry of the oxa-bridged adduct **22**. This oxa-bridged adduct **22** was converted into the phenanthridine derivative **23** on treatment with 1,8-diazabicyclo[5.4.0]undec-7-ene in refluxing toluene.[13] In contrast, in the analogous coupling of **11** with carbene complex **2** in the presence of *N*-phenylmaleimide as dienophile, the phenanthridine derivative **24** was isolated as the only product (Scheme 4).

The tandem generation and intramolecular trapping of furo[3,4-*c*]isoquinoline and furo[3,4-*b*]quinoline intermediates was studied using unactivated alkenyl tethers of various length. The reaction of carbene complex **2** with ketone **13** bearing an unactivated alkenyl tether afforded a mixture of the oxa-bridged adduct **27** and the [1,7]-hydrogen-shift product **29** (Scheme 5). Interestingly, under similar reaction conditions, no intramolecular cycloaddition leading to the oxa-bridged adduct **28** was obtained when the dienophile tether to the ketone was increased by one

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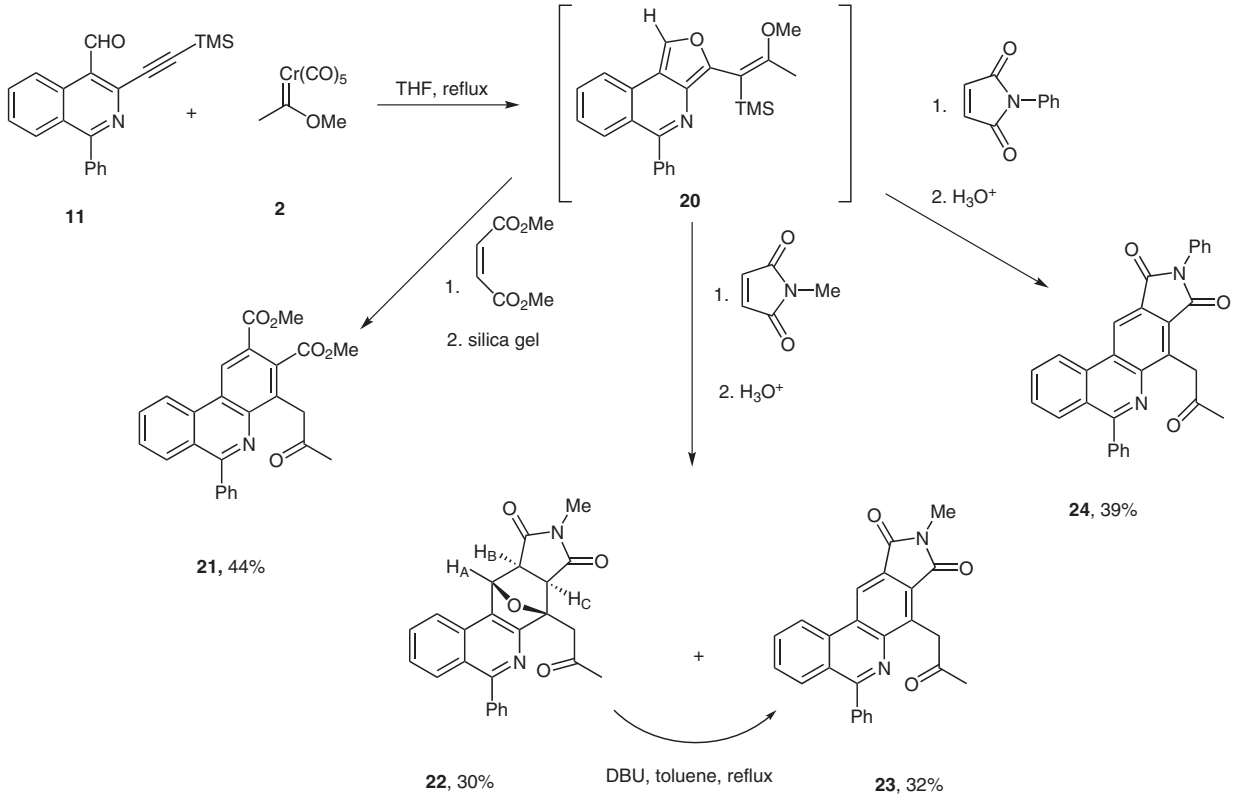
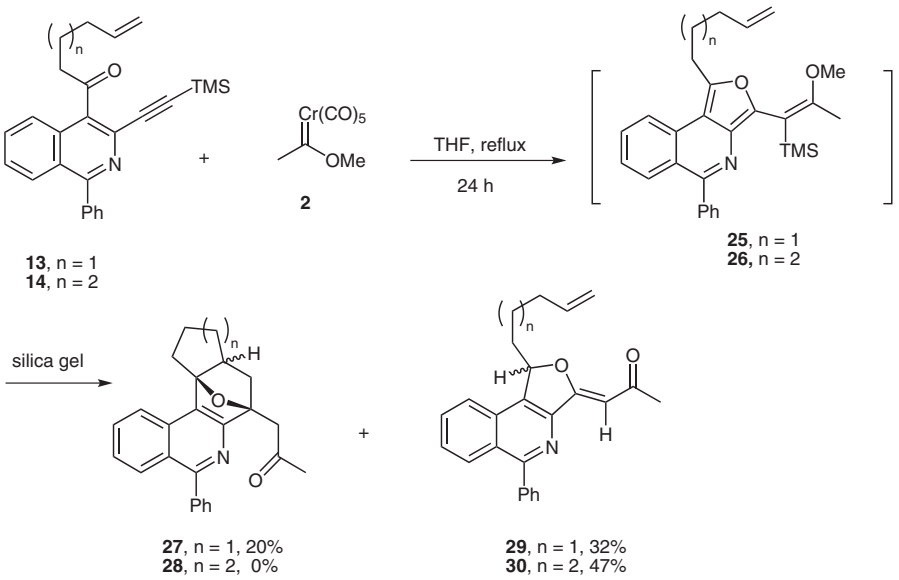


Scheme 4 Synthesis of phenanthridine derivatives



Scheme 5 Generation and Diels–Alder trapping of furo[3,4-*c*]isoquinoline intermediates using an intramolecular approach

methylene unit (i.e., ketone **14**). In this reaction, the [1,7]-hydrogen-shift product **30** was the only product isolated from the reaction mixture. Formation of the [1,7]-hydrogen-shift products **29/30** suggests either (i) that unactivated dienophile lowers the rate of the Diels–Alder step of the tandem reaction process, or (ii) that the furo[3,4-*c*]isoquinoline intermediates **25/26** can directly hydrolyze to form the [1,7]-hydrogen-shift products **29/30**, respectively.[7a,14] In contrast, the reaction of carbene complex **2** with alkynylquinolinyl ketone **19** bearing an unactivated alkenyl tether, under the same reaction conditions, gave exclusively the alcohol **32** with no [1,7]-hydrogen-shift product (Scheme 6).

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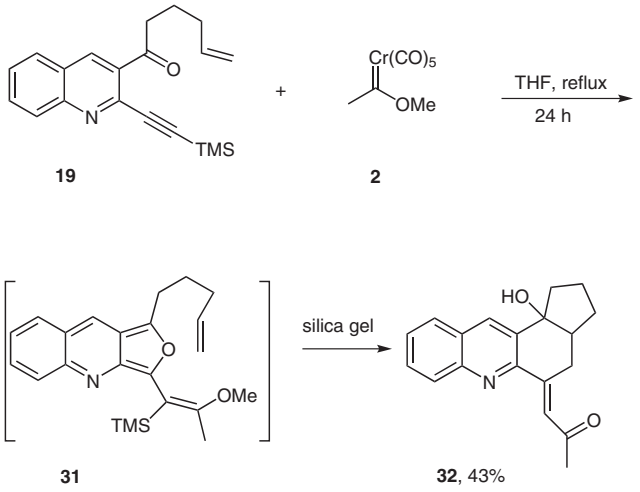


Scheme 6 Generation and intramolecular Diels–Alder trapping of a furo[3,4-*b*]quinoline intermediate

The reaction process was also tested using a γ,δ-unsaturated Fischer carbene complex. The coupling of monoprenylated carbene complex **6** with alkynyl carbonyl derivatives **11/12** under the same conditions as previously described underwent intramolecular Diels–Alder reaction through the generation of the furo[3,4-*c*]isoquinoline intermediates **33/34** leading to the tetracyclic skeletons **37/38**, respectively (Scheme 7). The initial Diels–Alder adducts **35/36**, resulting from **33/34**, appear to be unstable with respect to the ring-opening process.[15] Compounds **37** and **38**, bearing the tetracyclic skeleton, are aza analogues of tetracyclic triterpenes. Thus, the reaction may be useful for the synthesis of analogues of natural products.

The intramolecular trapping of transient furo[3,4-*b*]quinoline intermediates was also studied by using carbene complex **6** and its bisprenylated species **39**.[16] The *o*-alkynylquinolinecarbonyl derivatives **16/17/18**[10] underwent similar reaction with carbene complexes **6/39** which led to acridine derivatives **41**–**44** through the generation of the furo[3,4-*b*]quinoline intermediates **40** (Scheme 8).

In summary, we have developed a convenient one-pot synthesis of phenanthridine and acridine ring systems by the coupling of Fischer carbene complexes with heteroaromatic *o*-alkynyl carbonyl derivatives, with the generation of reactive furo[3,4-*c*]isoquinoline and furo[3,4-*b*]quinoline intermediates.

Melting points were determined on a Sunbim melting point apparatus and are uncorrected. IR spectra were recorded neat or as KBr discs on a Jasco FT/IR-460 Plus spectrometer. ^{1}H and ^{13}C NMR spectra were recorded using tetramethylsilane as internal reference on Bruker AC 400, DRX 500, DPX 300, Avance 600 and UltraShield™ 500 spectrometers (chemical shift values in δ, *J* in Hz). Mass spectra were obtained using an Agilent 6120 mass spectrometer.

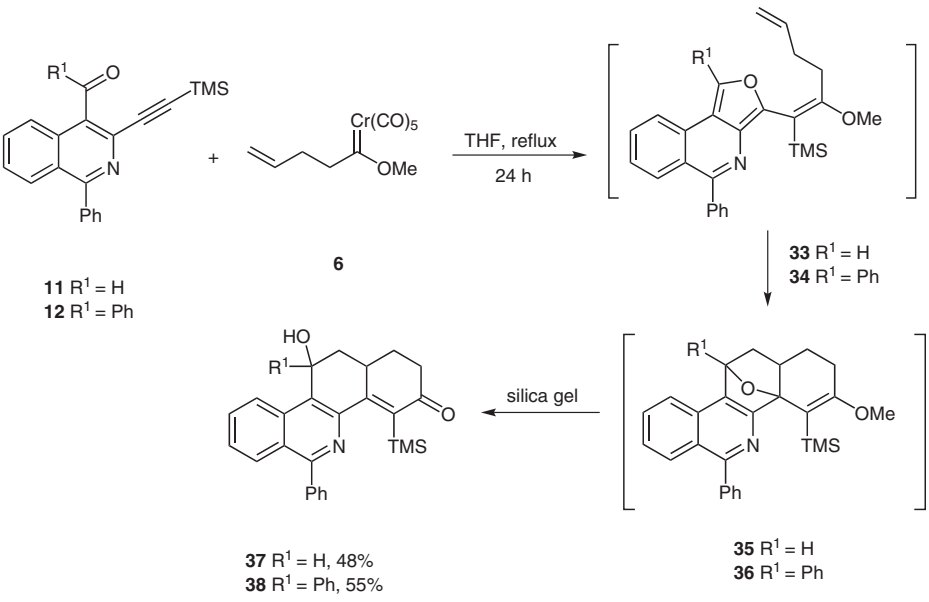
1-Phenyl-3-(trimethylsilylethynyl)isoquinoline-4-carbaldehyde (11)

A mixture of 3-chloro-1-phenylisoquinoline-4-carbaldehyde (**10**; 1.34 g, 5.0 mmol), $(Ph_3P)_2PdCl_2$ (0.176 g, 0.25 mmol), Ph_3P (33 mg, 0.125 mmol), (trimethylsilyl)acetylene (736 mg, 7.5 mmol) and Et_3N (759 mg, 7.5 mmol) in THF (20 mL) was stirred at r.t. for 20 min, and then CuI (10 mg, 0.05 mmol) was added. The reaction mixture was stirred at r.t. for 16 h, then the solvent was removed on a rotary evaporator. The residue was treated with CH_2Cl_2 (10 mL) and the mixture was filtered through Celite®. The filtrate was concentrated and the residue was purified by silica gel column chromatography (EtOAc–petroleum ether, 1:9) to afford alkyne **11**.

Yield: 1.1 g (67%); white solid; mp 126 °C; R_f = 0.69 (EtOAc–petroleum ether, 1:9).

IR (KBr): 2155, 1686 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 11.04 (s, 1 H), 9.33 (d, *J* = 8.5 Hz, 1 H), 8.08 (d, *J* = 8.4 Hz, 1 H), 7.86 (td, *J* = 7.8, 1.0 Hz, 1 H), 7.73–7.66 (m, 2 H), 7.60 (t, *J* = 7.7 Hz, 1 H), 7.57–7.50 (m, 3 H), 0.30 (s, 9 H).



Scheme 7 Synthesis of phenanthridines using a monoprenylated Fischer carbene complex

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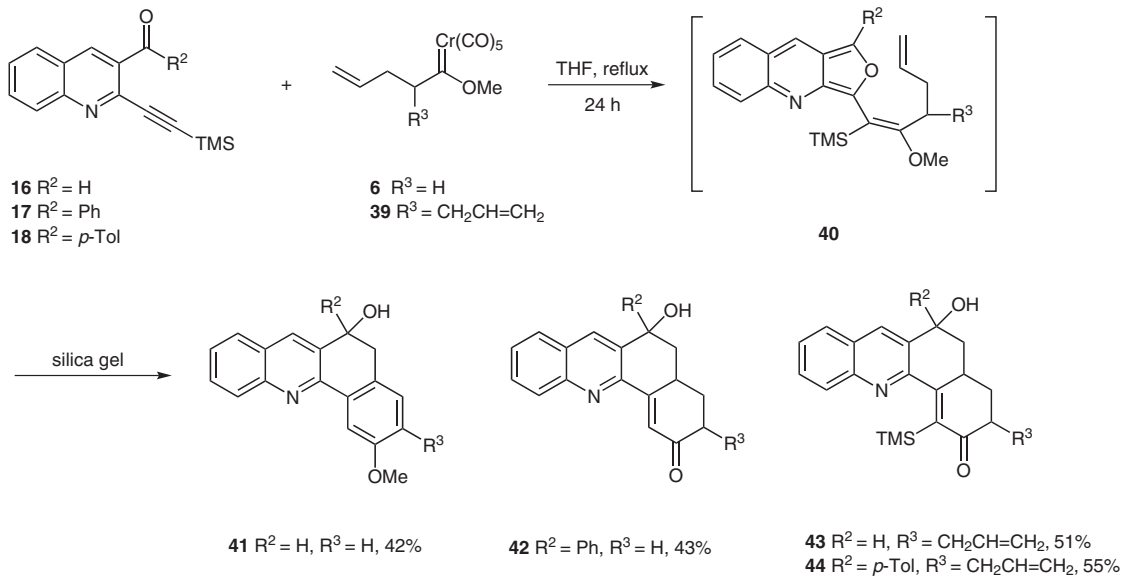

Scheme 8 Synthesis of acridines using mono-/bisprenylated Fischer carbene complexes

^{13}C NMR (125 MHz, $CDCl_3$): δ = 194.3, 166.2, 143.3, 138.3, 133.6, 133.1, 130.0 (2 C), 129.5, 128.4 (3 C), 128.3, 126.1, 125.0, 124.9, 103.6, 100.8, –0.3 (3 C).

MS: *m*/*z* (%) = 330 (100) $[M + H]^+$, 258 (10).

Anal. Calcd for $C_{21}H_{19}NOSi$: C, 76.56; H, 5.81; N, 4.25. Found: C, 76.21; H, 5.72; N, 4.02.

Alkynyl(iso)quinolinecarbonyl Derivatives; General Procedure

To a stirred soln of aldehyde (2 mmol) in anhyd Et_2O (10 mL) was added dropwise a soln of aryl-/alkylmagnesium bromide (2.2 mmol) in anhyd Et_2O [prepared from aryl/alkyl bromide (3 mmol) and magnesium (4 mmol) in anhyd Et_2O (10 mL)] over a period of 20 min at 0 °C. After being stirred for 3 h, the mixture was allowed to warm to r.t. and the reaction was then quenched with sat. aq NH_4Cl (5 mL). The organic layer was separated and the aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic layer was washed with brine (5 mL) and dried (Na_2SO_4). The solvent was removed under reduced pressure and the crude alcohol was used in the next step.

A soln of the crude alcohol in anhyd CH_2Cl_2 (2 mL) was added to a red soln of CrO_3·2py [prepared from a vigorously stirred suspension of CrO_3 (6 mmol) and pyridine (12 mmol) in anhyd CH_2Cl_2 (12 mL) at r.t. for 1.5 h] and the mixture was stirred at r.t. for 4 h. The mixture was then diluted with Et_2O (10 mL) and passed through a bed of silica gel (5 g). The solution was then concentrated under reduced pressure and purified by silica gel column chromatography (EtOAc–petroleum ether, 2:8).

Phenyl[1-phenyl-3-(trimethylsilylethynyl)isoquinolin-4-yl]methanone (12)

Yield: 0.583 g (72%); white solid; mp 117–119 °C; R_f = 0.43 (EtOAc–petroleum ether, 1:9).

IR (KBr): 2160, 1666 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.13 (d, *J* = 8.5 Hz, 1 H), 7.97 (d, *J* = 8.0 Hz, 2 H), 7.74 (d, *J* = 8.5 Hz, 1 H), 7.72 (d, *J* = 8.0 Hz, 2 H), 7.67 (t, *J* = 7.5 Hz, 1 H), 7.63 (t, *J* = 7.5 Hz, 1 H), 7.60–7.52 (m, 4 H), 7.49 (t, *J* = 7.5 Hz, 2 H), –0.06 (s, 9 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 196.2, 162.3, 138.6, 137.1, 134.4, 133.9, 133.9, 132.4, 131.3, 130.0 (4 C), 129.0, 128.7 (2 C), 128.3 (2 C), 128.2, 128.1, 125.8, 124.6, 102.4, 101.3, –0.77 (3 C).

MS: *m*/*z* (%) = 406 (100) $[M + H]^+$.

Anal. Calcd for $C_{27}H_{23}NOSi$: C, 79.96; H, 5.72; N, 3.45. Found: C, 79.73; H, 5.59; N, 3.57.

1-[1-Phenyl-3-(trimethylsilylethynyl)isoquinolin-4-yl]hex-5-en-1-one (13)

Yield: 0.412 g (52%); thick liquid; R_f = 0.78 (EtOAc–petroleum ether, 1:4).

IR (neat): 2157, 1702 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.05 (d, *J* = 8.4 Hz, 1 H), 7.71 (d, *J* = 3.6 Hz, 2 H), 7.67–7.61 (m, 2 H), 7.59–7.47 (m, 4 H), 5.83 (m, 1 H), 5.06 (d, *J* = 17.2 Hz, 1 H), 5.01 (d, *J* = 10.0 Hz, 1 H), 3.15 (t, *J* = 7.5 Hz, 2 H), 2.21 (q, *J* = 6.8 Hz, 2 H), 1.94 (pentet, *J* = 7.5 Hz, 2 H), 0.25 (s, 9 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 206.2, 162.1, 138.5, 137.7, 136.1, 132.9, 131.3 (2 C), 130.9, 129.9 (2 C), 129.0, 128.3, 128.2, 128.1, 125.8, 124.0, 115.4, 102.3, 100.2, 43.9, 33.2, 22.9, –0.36 (3 C).

MS: *m*/*z* (%) = 399 (35) $[MH^+ + 1]$, 398 (100) $[M + H]^+$.

Anal. Calcd for $C_{26}H_{27}NOSi$: C, 78.54; H, 6.84; N, 3.52. Found: C, 78.71; H, 6.65; N, 3.68.

1-[1-Phenyl-3-(trimethylsilylethynyl)isoquinolin-4-yl]hept-6-en-1-one (14)

Yield: 0.386 g (47%); thick liquid; R_f = 0.47 (EtOAc–petroleum ether, 1:9).

IR (neat): 2158, 1701, 1640 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.07 (d, *J* = 8.5 Hz, 1 H), 7.73–7.67 (m, 2 H), 7.66–7.61 (m, 2 H), 7.63–7.42 (m, 4 H), 5.82 (m, 1 H), 5.03 (dd, *J* = 17.0, 1.0 Hz, 1 H), 4.97 (d, *J* = 10.0 Hz, 1 H), 3.16 (t, *J* = 7.5 Hz, 2 H), 2.13 (q, *J* = 7.0 Hz, 2 H), 1.86 (pentet, *J* = 7.5 Hz, 2 H), 1.55 (pentet, *J* = 7.5 Hz, 2 H), 0.26 (s, 9 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 206.3, 162.1, 138.5, 138.3, 136.1, 132.9, 131.3, 130.9, 129.9 (2 C), 129.0, 128.3 (2 C), 128.2, 128.1, 125.8, 124.0, 114.8, 102.3, 100.2, 44.5, 33.6, 28.6, 23.2, –0.36 (3 C).

MS: *m*/*z* (%) = 413 (30) $[MH^+ + 1]$, 412 (100) $[M + H]^+$.

Anal. Calcd for $C_{27}H_{29}NOSi$: C, 78.79; H, 7.10; N, 3.40. Found: C, 78.57; H, 6.83; N, 3.54.

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Phenyl[2-(trimethylsilylethynyl)quinolin-3-yl]methanone (17)
Yield: 0.460 g (70%); thick yellow liquid; R_f = 0.60 (EtOAc–petroleum ether, 1:9).

IR (neat): 2180, 1668 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 8.36 (s, 1 H), 8.19 (d, *J* = 8.5 Hz, 1 H), 7.91–7.81 (m, 4 H), 7.68–7.61 (m, 2 H), 7.49 (t, *J* = 7.5 Hz, 2 H), 0.01 (s, 9 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 195.3, 148.4, 138.4, 136.6, 133.5, 131.4, 130.2 (2 C), 129.4, 128.8, 128.5 (2 C), 128.1 (2 C), 127.9, 126.3, 102.2, 101.8, –0.7 (3 C).

MS: *m*/*z* (%) = 331 (30) $[MH^+ + 1]$, 330 (100) $[M + H]^+$, 268 (20).

Anal. Calcd for $C_{21}H_{19}NOSi$: C, 76.56; H, 5.81; N, 4.25. Found: C, 76.31; H, 5.92; N, 4.10.

1-[2-(Trimethylsilylethynyl)quinolin-3-yl]hex-5-en-1-one (19)
Yield: 0.288 g (45%); thick yellow liquid; R_f = 0.35 (EtOAc–petroleum ether, 1:9).

IR (neat): 2158, 1703 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 8.35 (s, 1 H), 8.13 (d, *J* = 8.5 Hz, 1 H), 7.86 (d, *J* = 8.5 Hz, 1 H), 7.79 (td, *J* = 8.5, 1.0 Hz, 1 H), 7.59 (td, *J* = 8.5, 1.0 Hz, 1 H), 5.81 (m, 1 H), 5.04 (dd, *J* = 17.0, 1.2 Hz, 1 H), 4.99 (dd, *J* = 10.5, 1.2 Hz, 1 H), 3.23 (t, *J* = 7.0 Hz, 2 H), 2.17 (q, *J* = 7.0 Hz, 2 H), 1.88 (pentet, *J* = 7.0 Hz, 2 H), 0.31 (s, 9 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 202.5, 148.5, 139.4, 137.8, 136.5, 135.6, 131.7, 129.2, 128.4, 128.1, 126.3, 115.4, 103.0, 100.4, 41.7, 33.1, 23.6, –0.3 (3 C).

MS: *m*/*z* (%) = 323 (20) $[MH^+ + 1]$, 322 (70) $[M + H]^+$, 279 (28), 261 (15), 260 (100).

Anal. Calcd for $C_{20}H_{23}NOSi$: C, 74.72; H, 7.21; N, 4.36. Found: C, 74.51; H, 7.09; N, 4.49.

Coupling of Carbene Complex 2 with Alkynylisoquinolinecarbaldehyde 11 and Maleimides/Dimethyl Maleate; General Procedure
To a refluxing soln of alkynyl aldehyde **11** (1 mmol) and a maleimide or dimethyl maleate (1 mmol) in THF (5 mL) was added a soln of carbene complex **2** (1.1 mmol) in THF (10 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 r.t. and was concentrated on a rotary evaporator. EtOAc (20 mL) was added and the mixture was filtered through Celite® (1.0 g). The solvent was removed on a rotary evaporator, and the crude product was dissolved in Et_2O (20 mL).

To this solution of crude product in Et_2O was added aq HCl (1:1, 0.5 mL) and the mixture was stirred at r.t. for 6 h. The organic layer was separated. The aqueous layer was neutralized with sat. $NaHCO_3$ soln (3 mL) and extracted with EtOAc (3 × 10 mL). The combined organic layer (Et_2O layer and EtOAc extracts) was washed with H_2O (3 mL) and brine (3 mL), and dried (Na_2SO_4). Evaporation of solvent and purification of the residue by chromatography gave the pure products.

Compound 21 by the Coupling of Carbene Complex 2 with 1-Phenyl-3-(trimethylsilylethynyl)isoquinoline-4-carbaldehyde (11) and Dimethyl Maleate
The general procedure above was followed using alkynyl aldehyde **11** (165 mg, 0.50 mmol), dimethyl maleate (72 mg, 0.50 mmol) and carbene complex **2** (138 mg, 0.55 mmol). The only exception was that, instead of HCl treatment, the crude product was dissolved in $CHCl_3$ (20 mL) and stirred with silica gel (2 g) for 6 h. The solvent was evaporated and the residue was purified by silica gel column chromatography.

Yield: 0.093 g (44%); white solid; mp 122 °C (dec); R_f = 0.30 (EtOAc–petroleum ether, 3:7).

IR (KBr): 1736, 1712 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 9.24 (s, 1 H), 8.79 (d, *J* = 8.0 Hz, 1 H), 8.25 (d, *J* = 8.0 Hz, 1 H), 7.94 (t, *J* = 8.0 Hz, 1 H), 7.77–7.73 (m, 2 H), 7.72 (t, *J* = 8.0 Hz, 1 H), 7.60–7.53 (m, 3 H), 4.44 (s, 2 H), 4.02 (s, 3 H), 3.99 (s, 3 H), 2.22 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 205.6, 169.3, 166.3, 162.9, 143.8, 139.2, 134.5, 134.0, 133.5, 131.3, 130.1 (2 C), 129.2, 129.1, 128.3 (3 C), 125.7, 125.3, 124.6, 123.5, 122.8, 52.8 (2 C), 43.7, 30.0.

MS: *m*/*z* (%) = 450 (11) $[M + Na]^+$, 428 (100) $[M + H]^+$, 396 (58).

HRMS: *m*/*z* $[M + Na]^+$ calcd for $C_{26}H_{21}NNaO_5$: 450.1317; found: 450.1311.

Compounds 22 and 23 by the Coupling of Carbene Complex 2 with 1-Phenyl-3-(trimethylsilylethynyl)isoquinoline-4-carbaldehyde (11) and *N*-Methylmaleimide

Compound 22
Yield: 0.124 g (30%); white solid; mp 171 °C (dec); R_f = 0.25 (EtOAc–petroleum ether, 3:7).

IR (KBr): 1703 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 8.18 (d, *J* = 8.5 Hz, 1 H), 7.97 (d, *J* = 8.5 Hz, 1 H), 7.79 (t, *J* = 7.5 Hz, 1 H), 7.66 (d, *J* = 6.5 Hz, 2 H), 7.60–7.49 (m, 4 H), 6.18 (s, 1 H), 3.85 (d, *J* = 17.2 Hz, 1 H), 3.49 (d, *J* = 17.2 Hz, 1 H), 3.30 (d, *J* = 6.5 Hz, 1 H), 3.14 (d, *J* = 6.5 Hz, 1 H), 3.07 (s, 3 H), 2.30 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 203.2, 175.6, 174.6, 160.8, 158.1, 139.1, 131.1, 130.6, 130.3 (2 C), 130.2, 128.9 (2 C), 128.3 (2 C), 127.2, 125.7, 122.8, 87.9, 78.7, 51.1, 50.2, 41.3, 31.4, 25.2.

MS: *m*/*z* (%) = 435 (10) $[M + Na]^+$, 413 (100) $[M + H]^+$, 302 (90), 260 (9).

HRMS: *m*/*z* $[M + H]^+$ calcd for $C_{25}H_{21}N_2O_4$: 413.1501; found: 413.1492.

Compound 23
Yield: 0.126 g (32%); white solid; mp 203 °C (dec); R_f = 0.55 (EtOAc–petroleum ether, 3:7).

IR (KBr): 1759, 1713 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 9.03 (s, 1 H), 8.80 (d, *J* = 8.5 Hz, 1 H), 8.20 (d, *J* = 8.5 Hz, 1 H), 7.97 (t, *J* = 8.0 Hz, 1 H), 7.80–7.70 (m, 3 H), 7.62–7.50 (m, 3 H), 4.99 (s, 2 H), 3.25 (s, 3 H), 2.42 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 205.6, 168.7, 168.1, 162.4, 145.2, 139.1, 135.7, 134.0, 131.5, 130.1 (2 C), 129.3, 129.1, 128.9, 128.6, 128.3 (2 C), 128.2, 127.1, 125.5, 123.2, 117.2, 41.0, 30.8, 24.2.

MS: *m*/*z* (%) = 395 (100) $[M + H]^+$.

Anal. Calcd for $C_{25}H_{18}N_2O_3$: C, 76.13; H, 4.60; N, 7.10. Found: C, 76.01; H, 4.79; N, 6.94.

9-Methyl-7-(2-oxopropyl)-5-phenyl-6,9-diaza-8*H*-cyclopenta[*b*]phenanthrene-8,10(9*H*)-dione (23)
To a stirred soln of oxa-bridged compound **22** (21 mg, 0.05 mmol) in toluene (3 mL), DBU (76 mg, 0.5 mmol) was added dropwise at r.t. The mixture was heated to reflux for 1.5 h. After being cooled to r.t., the mixture was washed with 10% aq HCl (1.0 mL) and dried (Na_2SO_4). After evaporation of the solvent, the crude product was purified by preparative thin-layer silica gel chromatography (EtOAc–petroleum ether, 1:1) to give aromatized product **23** as a yellow solid; yield: 8 mg (42%).

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Compound 24 by the Coupling of Carbene Complex 2 with 1-Phenyl-3-(trimethylsilylethynyl)isoquinoline-4-carbaldehyde (11) and *N*-Phenylmaleimide

Yield: 0.178 g (39%); white solid; mp 216 °C; R_f = 0.38 (EtOAc–petroleum ether, 3:7).

IR (KBr): 1767, 1712 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 9.14 (s, 1 H), 8.82 (d, *J* = 8.0 Hz, 1 H), 8.28 (d, *J* = 8.0 Hz, 1 H), 7.97 (td, *J* = 7.5, 1.0 Hz, 1 H), 7.81–7.74 (m, 3 H), 7.63–7.57 (m, 3 H), 7.56–7.49 (m, 4 H), 7.43 (t, *J* = 7.5 Hz, 1 H), 5.05 (s, 2 H), 2.43 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 205.4, 167.6, 166.9, 162.7, 145.5, 139.1, 136.4, 134.0, 131.8, 131.6, 130.1 (2 C), 129.4, 129.2, 129.1 (2 C), 129.0, 128.4 (2 C), 128.2, 128.1, 127.7, 127.6, 126.7 (2 C), 125.6, 123.3, 117.9, 41.1, 30.8.

MS: *m*/*z* (%) = 458 (33) [MH^+ + 1], 457 (100) [M + H]$^+$.

Anal. Calcd for $C_{30}H_{20}N_2O_3$: C, 78.93; H, 4.42; N, 6.14. Found: C, 78.71; H, 4.67; N, 6.31.

Coupling of Carbene Complex 2 with Alkynyl(iso)quinolinecarbonyl Derivatives; General Procedure

To a refluxing soln of an alkynyl carbonyl derivative **13/14/19** (1 mmol) in THF (10 mL) was added a soln of carbene complex **2** (1.1 mmol) in THF (10 mL) over a period of 1 h. After the addition was complete, the mixture was heated to reflux for a period of 24 h. The mixture was allowed to cool to r.t. and was concentrated on a rotary evaporator. EtOAc (20 mL) was added and the mixture was filtered through Celite® (1.0 g). The solvent was removed on a rotary evaporator, and the crude product was dissolved in $CHCl_3$ (20 mL) and stirred with silica gel (2 g) at r.t. for 6 h. Evaporation of solvent and purification of the residue by chromatography gave the pure products.

Compounds 27 and 29 by the Coupling of Carbene Complex 2 with 1-[1-Phenyl-3-(trimethylsilylethynyl)isoquinolin-4-yl]hex-5-en-1-one (13)

Compound 27

Yield: 0.074 g (20%); gummy solid; R_f = 0.55 (EtOAc–petroleum ether, 1:4).

IR (neat): 1707 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.14 (d, *J* = 8.4 Hz, 1 H), 8.08 (d, *J* = 8.4 Hz, 1 H), 7.72–7.62 (m, 3 H), 7.57–7.40 (m, 4 H), 3.59 (d, *J* = 14.8 Hz, 1 H), 3.35 (d, *J* = 14.8 Hz, 1 H), 2.97 (m, 1 H), 2.43 (m, 1 H), 2.26 (s, 3 H), 2.20–2.02 (m, 4 H), 1.98–1.80 (m, 2 H), 1.69 (m, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 206.3, 160.0, 159.2, 139.8, 131.1, 130.6, 130.3 (2 C), 130.1, 128.9, 128.5, 128.3 (2 C), 125.9, 125.7, 122.3, 97.6, 86.2, 48.8, 44.9, 39.9, 31.9, 31.6, 29.6, 27.1.

MS: *m*/*z* (%) = 370 (100) [M + H]$^+$, 352 (40) [$MH^+ - H_2O$], 312 (20).

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{25}H_{24}NO_2$: 370.1807; found: 370.1801.

Compound 29

Yield: 0.118 g (32%); yellow solid; mp 135–136 °C; R_f = 0.25 (EtOAc–petroleum ether, 1:4).

IR (KBr): 1635, 1623 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 8.23 (d, *J* = 8.4 Hz, 1 H), 7.88 (d, *J* = 8.4 Hz, 1 H), 7.83 (t, *J* = 7.5 Hz, 1 H), 7.75–7.68 (m, 2 H), 7.65 (t, *J* = 7.5 Hz, 1 H), 7.59–7.50 (m, 3 H), 6.32 (s, 1 H), 6.19 (dd, *J* = 7.5, 2.2 Hz, 1 H), 5.75 (m, 1 H), 5.01 (d, *J* = 17.2 Hz, 1 H), 4.98 (d, *J* = 14.4 Hz, 1 H), 2.46 (s, 3 H), 2.42 (m, 1 H), 2.20–2.10 (m, 2 H), 2.00 (m, 1 H), 1.75–1.48 (m, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 197.2, 164.9, 164.0, 144.7, 138.8, 137.9, 132.4, 131.6, 131.1, 130.3, 130.2 (2 C), 129.7, 129.3, 128.5 (2 C), 127.6, 123.4, 115.3, 97.7, 86.5, 34.4, 33.3, 31.2, 23.8.

MS: *m*/*z* (%) = 370 (100) [M + H]$^+$, 330 (35).

HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{25}H_{23}NNaO_2$: 392.1626; found: 392.1625.

Compound 30 by the Coupling of Carbene Complex 2 with 1-[1-Phenyl-3-(trimethylsilylethynyl)isoquinolin-4-yl]hept-6-en-1-one (14)

Yield: 0.180 g (47%); yellow solid; mp 144–145 °C; R_f = 0.24 (EtOAc–petroleum ether, 1:4).

IR (KBr): 1625, 1581 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 8.25 (d, *J* = 8.5 Hz, 1 H), 7.90 (d, *J* = 8.5 Hz, 1 H), 7.84 (t, *J* = 7.5 Hz, 1 H), 7.76–7.70 (m, 2 H), 7.66 (t, *J* = 7.5 Hz, 1 H), 7.60–7.50 (m, 3 H), 6.32 (s, 1 H), 6.19 (dd, *J* = 7.5, 2.5 Hz, 1 H), 5.76 (m, 1 H), 4.98 (d, *J* = 17.5 Hz, 1 H), 4.93 (d, *J* = 10.5 Hz, 1 H), 2.47 (s, 3 H), 2.46 (m, 1 H), 2.10–2.00 (m, 3 H), 1.55–1.41 (m, 4 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 197.1, 164.9, 163.9, 144.6, 138.7, 138.4, 132.4, 131.5, 131.0, 130.1 (2 C), 129.6, 129.2, 128.5, 128.4 (2 C), 127.5, 123.3, 114.7, 97.6, 86.6, 34.9, 33.4, 31.2, 28.6, 24.1.

MS: *m*/*z* (%) = 384 (100) [M + H]$^+$, 366 (7), 344 (8), 326 (9).

HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{26}H_{25}NNaO_2$: 406.1783; found: 406.1782.

Compound 32 by the Coupling of Carbene Complex 2 with 1-[2-(Trimethylsilylethynyl)quinolin-3-yl]hex-5-en-1-one (19)

Yield: 0.125 g (43%); gummy solid; R_f = 0.42 (EtOAc–petroleum ether, 1:3).

IR (neat): 3430, 1638 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 8.11 (d, *J* = 8.5 Hz, 1 H), 8.10 (s, 1 H), 7.83 (s, 1 H), 7.82 (d, *J* = 8.5 Hz, 1 H), 7.72 (td, *J* = 7.5, 1.3 Hz, 1 H), 7.55 (td, *J* = 7.5, 1.3 Hz, 1 H), 3.69 (m, 1 H), 3.06 (ddd, *J* = 19.0, 12.5, 3.0 Hz, 1 H), 2.43 (s, 3 H), 2.16–2.08 (m, 3 H), 2.09–1.90 (m, 4 H), 1.79 (m, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 199.6, 152.3, 149.7, 147.5, 136.4, 131.8, 129.8 (2 C), 128.1, 127.5, 127.3, 125.1, 78.3, 44.1, 35.9, 32.7, 28.4, 27.7, 21.5.

MS: *m*/*z* (%) = 295 (20) [MH^+ + 1], 294 (100) [M + H]$^+$, 276 (20).

Anal. Calcd for $C_{19}H_{19}NO_2$: C, 77.79; H, 6.53; N, 4.77. Found: C, 77.84; H, 6.62; N, 4.89.

Coupling of Mono-/Bisprenylated Carbene Complexes 6/39 with Alkynyl(iso)quinolinecarbonyl Derivatives; General Procedure

To a soln of an alkynyl carbonyl derivative **11/12/16/17/18** (1 mmol) in THF (5 mL) at reflux was added a soln of a γ,δ-unsaturated carbene complex **6/39** (1.1 mmol) in THF (10 mL) over a period of 1 h. After the addition was complete, the mixture was heated to reflux for 24 h. The mixture was cooled to r.t. The THF was removed under reduced pressure, EtOAc (10 mL) was added and the mixture was filtered through Celite® (1.0 g). After evaporation of the solvent, the crude product was purified by column chromatography.

Compound 37 by the Coupling of Carbene Complex 6 with 1-Phenyl-3-(trimethylsilylethynyl)isoquinoline-4-carbaldehyde (11)

Yield: 0.198 g (48%); white solid; mp 168–169 °C; R_f = 0.25 (EtOAc–petroleum ether, 3:7).

IR (KBr): 3374, 1630 cm^{-1}.

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^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.60 (d, *J* = 8.5 Hz, 1 H), 8.00 (d, *J* = 8.5 Hz, 1 H), 7.82 (t, *J* = 8.5 Hz, 1 H), 7.72–7.57 (m, 3 H), 7.57–7.50 (m, 3 H), 5.77 (t, *J* = 7.0 Hz, 1 H), 2.80 (m, 1 H), 2.70 (ddd, *J* = 15.0, 11.0, 4.5 Hz, 1 H), 2.56 (dt, *J* = 17.0, 3.5 Hz, 1 H), 2.38 (ddd, *J* = 17.0, 15.0, 4.5 Hz, 1 H), 2.24 (m, 1 H), 2.00 (s, 1 H, exchangeable with D_2O), 1.92 (m, 1 H), 1.87 (m, 1 H), 0.0 (s, 9 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 203.1, 165.8, 160.6, 146.1, 141.5, 138.6, 135.4, 130.5, 129.9 (2 C), 129.2, 128.6, 128.3, 128.1 (2 C), 127.8, 127.6, 125.2, 66.0, 41.5, 37.6, 36.8, 28.2, 2.01 (3 C).

MS: *m*/*z* (%) = 436 (100) $[M + Na]^+$, 414 (60) $[M + H]^+$, 398 (8).

Anal. Calcd for $C_{26}H_{27}NO_2Si$: C, 75.51; H, 6.58; N, 3.39. Found: C, 75.27; H, 6.32; N, 3.51.

Compound 38 by the Coupling of Carbene Complex 6 with Phenyl[1-phenyl-3-(trimethylsilylethynyl)isoquinolin-4-yl]methanone (12)

Yield: 0.270 g (55%); white solid; mp >220 °C (dec); R_f = 0.2 (EtOAc–petroleum ether, 1:9).

IR (KBr): 3447, 1636 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.11 (dd, *J* = 8.0, 2.0 Hz, 1 H), 7.85 (dd, *J* = 8.0, 2.0 Hz, 1 H), 7.58–7.50 (m, 5 H), 7.45–7.40 (m, 2 H), 7.33–7.27 (m, 5 H), 2.70 (m, 1 H), 2.67 (s, 1 H, exchangeable with D_2O), 2.51 (d, *J* = 12.0 Hz, 1 H), 2.43 (d, *J* = 17.5 Hz, 1 H), 2.34–2.20 (m, 2 H), 1.88 (m, 1 H), 1.68 (m, 1 H), –0.03 (s, 9 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 203.4, 165.4, 161.2, 146.4, 146.0, 142.5, 138.5, 134.9, 132.0, 129.8 (2 C), 129.7, 128.7, 128.6 (2 C), 128.3 (3 C), 128.0 (2 C), 127.5, 127.4, 126.1 (2 C), 76.2, 52.4, 36.7, 35.6, 27.7, 2.4 (3 C).

MS: *m*/*z* (%) = 491 (42) $[MH^+ + 1]$, 490 (100) $[M + H]^+$.

HRMS: *m*/*z* $[M + H]^+$ calcd for $C_{32}H_{32}NO_2Si$: 490.2202; found: 490.2194.

Compound 41 by the Coupling of Carbene Complex 6 with 2-(Trimethylsilylethynyl)quinoline-3-carbaldehyde (16)

Yield: 0.116 g (42%); gummy solid; R_f = 0.57 (EtOAc–petroleum ether, 3:7).

IR (neat): 3390, 1619 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.26 (s, 1 H), 8.16 (d, *J* = 3.0 Hz, 1 H), 8.15 (d, *J* = 3.0 Hz, 1 H), 7.83 (d, *J* = 8.0 Hz, 1 H), 7.70 (td, *J* = 8.0, 1.0 Hz, 1 H), 7.52 (td, *J* = 8.0, 1.0 Hz, 1 H), 7.23 (d, *J* = 8.0 Hz, 1 H), 6.98 (dd, *J* = 8.0, 3.0 Hz, 1 H), 5.14 (m, 1 H), 3.96 (s, 3 H), 3.22 (dd, *J* = 15.0, 4.8 Hz, 1 H), 3.12 (dd, *J* = 15.0, 8.5 Hz, 1 H), 2.09 (br s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.3, 151.7, 147.8, 134.8, 132.9, 132.2, 130.0, 129.4, 129.3, 127.7, 127.6, 127.3, 126.3, 117.4, 109.6, 77.2, 68.5, 36.9.

MS: *m*/*z* (%) = 279 (25) $[MH^+ + 1]$, 278 (100) $[M + H]^+$, 261 (10), 260 (60).

Anal. Calcd for $C_{18}H_{15}NO_2$: C, 77.96; H, 5.45; N, 5.05. Found: C, 77.85; H, 5.61; N, 4.96.

Compound 42 by the Coupling of Carbene Complex 6 with Phenyl[2-(trimethylsilylethynyl)quinolin-3-yl]methanone (17)

Yield: 0.146 g (43%); gummy solid; R_f = 0.33 (EtOAc–petroleum ether, 3:7).

IR (neat): 3407, 1660 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.43 (s, 1 H), 8.13 (d, *J* = 8.5 Hz, 1 H), 7.79 (d, *J* = 8.5 Hz, 1 H), 7.75 (td, *J* = 7.5, 1.0 Hz, 1 H), 7.64 (d, *J* = 2.0 Hz, 1 H), 7.55 (td, *J* = 7.5, 1.0 Hz, 1 H), 7.32–7.27 (m, 3 H), 7.13 (m, 2 H), 2.73 (s, 1 H), 2.60–2.49 (m, 3 H), 2.38 (ddd, *J* = 17.0, 15.0, 5.0 Hz, 1 H), 2.17 (t, *J* = 12.5 Hz, 1 H), 2.06 (m, 1 H), 1.90 (m, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 200.1, 155.8, 149.4, 147.8, 145.8, 137.1, 135.2, 130.3, 130.0, 128.7, 128.4 (2 C), 128.0, 127.8, 127.7, 126.8 (2 C), 125.0, 75.5, 46.6, 37.7, 33.4, 30.2.

MS: *m*/*z* (%) = 343 (30) $[MH^+ + 1]$, 342 (100) $[M + H]^+$, 322 (20).

Anal. Calcd for $C_{23}H_{19}NO_2$: C, 80.92; H, 5.61; N, 4.10. Found: C, 80.74; H, 5.73; N, 3.98.

Compound 43 by the Coupling of Carbene Complex 39 with 2-(Trimethylsilylethynyl)quinoline-3-carbaldehyde (16)

Yield: 0.192 g (51%); gummy solid; R_f = 0.51 (EtOAc–petroleum ether, 3:7).

IR (neat): 3437, 1640 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.39 (s, 1 H), 8.11 (d, *J* = 8.5 Hz, 1 H), 7.84 (d, *J* = 8.5 Hz, 1 H), 7.73 (t, *J* = 8.5 Hz, 1 H), 7.56 (t, *J* = 8.5 Hz, 1 H), 5.84 (m, 1 H), 5.15 (m, 1 H), 5.10 (d, *J* = 6.0 Hz, 1 H), 5.07 (s, 1 H), 2.86 (m, 1 H), 2.60–2.53 (m, 2 H), 2.45 (ddd, *J* = 12.5, 5.5, 4.0 Hz, 1 H), 2.21–2.14 (m, 2 H), 2.08–2.01 (m, 2 H), 1.91 (q, *J* = 12.5 Hz, 1 H), 0.16 (s, 9 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 205.9, 161.4, 152.4, 146.7, 143.1, 136.5, 134.5, 134.2, 130.0, 129.1, 128.3, 127.7, 127.4, 116.6, 68.5, 44.4, 41.2, 34.1, 33.4, 33.2, 2.37 (3 C).

MS: *m*/*z* (%) = 379 (30) $[MH^+ + 1]$, 378 (100) $[M + H]^+$, 363 (20), 362 (60).

Anal. Calcd for $C_{23}H_{27}NO_2Si$: C, 73.17; H, 7.21; N, 3.71. Found: C, 73.12; H, 7.11; N, 3.83.

Compound 44 by the Coupling of Carbene Complex 39 with *p*-Tolyl[2-(trimethylsilylethynyl)quinolin-3-yl]methanone (18)

Yield: 0.256 g (55%); gummy solid; R_f = 0.28 (EtOAc–petroleum ether, 1:9).

IR (neat): 3435, 1639 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.19 (s, 1 H), 8.17 (d, *J* = 8.0 Hz, 1 H), 7.76 (d, *J* = 8.0 Hz, 1 H), 7.75 (t, *J* = 7.5 Hz, 1 H), 7.55 (t, *J* = 7.5 Hz, 1 H), 7.11 (d, *J* = 8.0 Hz, 2 H), 7.05 (d, *J* = 8.0 Hz, 2 H), 5.73 (m, 1 H), 4.94 (d, *J* = 10.0 Hz, 1 H), 4.87 (d, *J* = 17.1 Hz, 1 H), 2.74 (m, 1 H), 2.53–2.45 (m, 4 H), 2.33 (s, 3 H), 2.31 (q, *J* = 12.5 Hz, 1 H), 2.07 (m, 1 H), 2.01–1.90 (m, 2 H), 0.18 (s, 9 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 206.1, 161.6, 152.7, 146.9, 143.5 (2 C), 137.6 (2 C), 136.4, 135.3, 130.3, 129.1, 129.0 (2 C), 128.4, 128.0, 127.4, 126.5 (2 C), 116.5, 75.7, 48.0, 44.6, 34.1, 33.3, 32.1, 21.0, 2.51 (3 C).

MS: *m*/*z* (%) = 469 (40) $[MH^+ + 1]$, 468 (100) $[M + H]^+$, 463 (25), 452 (75).

Anal. Calcd for $C_{30}H_{33}NO_2Si$: C, 77.05; H, 7.11; N, 2.99. Found: C, 77.31; H, 7.22; N, 2.81.

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