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[8+2] and [8+3] Cyclization Reactions of Alkenyl Carbenes and 8-Azaheptafulvenes: Direct Access to Tetrahydro-1-azaazulene and Cyclohepta[*b*]pyridinone Derivatives

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Dedicated to Professor José Gimeno on the occasion of his 60th birthday

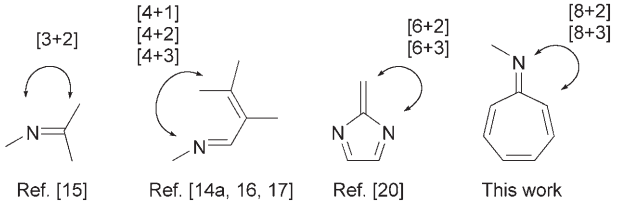
Abstract: The reactivity of Fischer alkenyl carbenes toward 8-azaheptafulvenes is examined. Alkenyl carbenes react with 8-azaheptafulvenes with complete regio- and stereoselectivity through formal [8+3] and [8+2] heterocyclization reactions, which show an unprecedented dependence on the C_β substituent at the alkenyl carbene complex. Thus, the formal [8+3] heterocyclization reaction is completely favored in carbene complexes that bear a coordinating moiety to give tetrahydrocyclohepta[*b*]pyridin-2-ones. Otherwise, alkenyl carbenes that lack appropriate coordinating groups undergo a formal [8+2] cyclization with 8-azaheptafulvenes to give compounds that bear a tetrahydroazaazulene structure. A likely mechanism for these reactions would follow well-established models and would involve a 1,4-addition/cyclization in the case of the [8+2] cyclization or a 1,2-addition/[1,2] shift–metal-promoted cyclization for the [8+3] reaction. The presence of a coordinating moiety in the carbene would favor the [1,2] metal shift through transition-state stabilization to lead to the [8+3] product. All these processes provide an entry into the tetrahydroazaazulene and cycloheptapyridone frameworks present in the structure of biologically active molecules.

Keywords: azaazulenes · azafulvenes · carbenes · chromium · cyclization

Introduction

Over the last few years, the ability of α,β-unsaturated carbene complexes to participate in cyclization reactions and thus allow the construction of a great number of cyclic compounds has been demonstrated.[1] The strong activation of carbon–carbon double and triple bonds by metal carbenes has permitted [4+2][2] and [3+2][3] cycloadditions to proceed with very high selectivity. More importantly, when a metal–carbon bond is involved, these α,β-unsaturated complexes can behave as one-, three-, or even five-carbon synthetic equivalents. In this context, two-component carbocyclization reactions—[2+1],[4] [3+2],[5] [3+3],[6] [4+3],[5b,7] [5+1],[8] [5+2],[9] [6+3][10]—have been reported, as well as multicomponent processes such as [3+2+1],[11] [3+2+2],[12] and [5+2+1][13] cyclization.

Conversely, the reaction of α,β-unsaturated Fischer carbenes with substrates that contain heteroatoms has been less intensively studied. Apart from the known [4+2], [2+2], and 1,3-dipolar heterocycloaddition reactions that occur through the activated carbon–carbon bond,[14] some reactions involving the metal–carbene functionality have been described; imines and unsaturated imines are the substrates in most of these reactions (Scheme 1). Thus, Akiyama and



Scheme 1. Cyclization reactions of imine derivatives with unsaturated Fischer carbene complexes.

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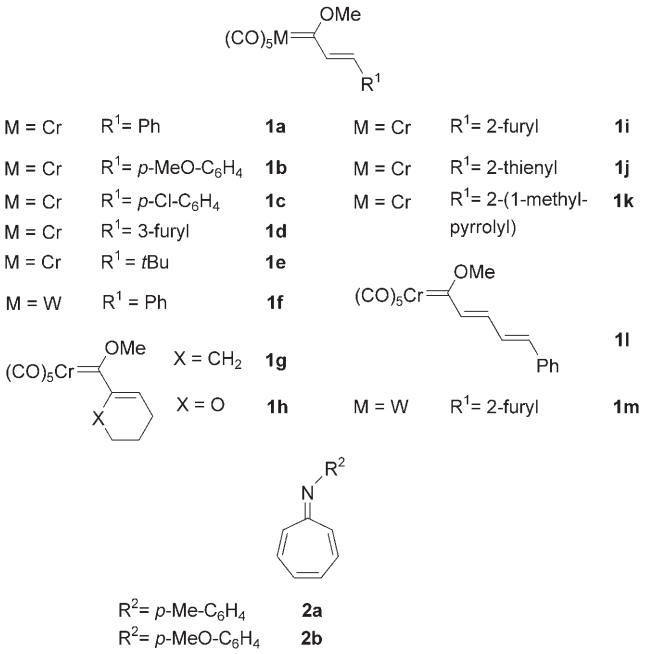
co-workers reported that simple imines undergo diastereo- and enantioselective [3+2] cyclization with enantiopure alkenyl carbene complexes to provide pyrrolidinone derivatives.[15] Moreover, the reaction of α,β-unsaturated imines with simple carbenes and alkynyl carbenes takes place through the terminal N1 and C4 atoms to afford the [4+1][16] and [4+2][14a]/[4+3][17] cycloadducts, respectively (Scheme 1). Convinced of the potential of Fischer metal carbene complexes and imines in heterocyclic synthesis,[18] we were intrigued by new pathways for these reactions. Specifically, we focused our attention on the 8-azaheptafulvene framework, a particular eight-π-electron cross-conjugated imine, which seems to be a suitable system for higher-order cycloaddition reactions.[19] The feasibility of this goal is supported by the precedent of the [6+2] and [6+3] cycloaddition reactions of unsaturated carbene complexes with pentafulvenes and 2,5-diazapentafulvenes (Scheme 1).[20]

Herein we describe the first cycloaddition reactions of Fischer carbene complexes with the 8-azaheptafulvene system. Specifically, we show that alkenyl carbene complexes **1** react with azaheptafulvenes **2** (Scheme 2) to produce the [8+2] and [8+3] cycloadducts **3**–**6** in a selective way (Scheme 1).

Abstract in Spanish: Se ha estudiado la reactividad de alquenilcarbenos de Fischer con 8-azaheptafulvenos. Los alquenilcarbenos reaccionan con 8-azaheptafulvenos a través de reacciones de heterociclación formales [8+3] y [8+2] con completa regioselectividad y estereoselectividad, mostrando una dependencia del sustituyente C_β del complejo alquenilcarbeno sin precedentes. Así, en los complejos carbeno que contienen un resto coordinante la reacción de heterociclación formal [8+3] se favorece completamente para dar tetrahidrociclohepta[*b*]piridin-2-onas. Por otra parte, los alquenilcarbenos que carecen de grupos coordinantes apropiados, experimentan una ciclación formal [8+2] con los 8-azaheptafulvenos para dar compuestos con estructura de tetrahidroazuleno. Un mecanismo probable para estas reacciones se fundamenta en modelos bien establecidos e implica una adición 1,4/ciclación en el caso de la ciclación [8+2] o una adición 1,2/ciclación promovida por una migración 1,2 del metal en el caso de la reacción [8+3]. La presencia de un resto coordinante en el carbeno favorece la migración 1,2 del metal a través de una estabilización del estado de transición, conduciendo al producto [8+3]. Todos estos procesos representan una vía de acceso a los esqueletos de tetrahidroazuleno y ciclohepatapiridona presentes en la estructura de moléculas biológicamente activas.

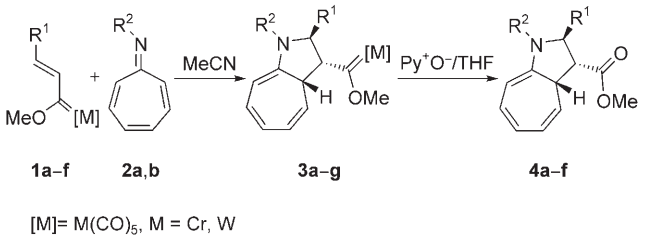


Scheme 2. Carbene complexes **1** and azaheptafulvenes **2** used.

Results and Discussion

[8+2] Cycloaddition of Alkenyl Carbene Complexes 1 with 8-Aryl-8-azaheptafulvenes 2

First, chromium alkenylcarbene **1a** (R^1 = Ph) was mixed with 8-azaheptafulvene **2a** (R^2 = *p*-Me-C_6H_4) (1:1 molar ratio) in MeCN, and the mixture was stirred for 12 h at room temperature. Removal of the solvent and analysis of the crude reaction mixture by ^1H and ^{13}C NMR spectroscopy revealed the formation of a new carbene complex **3a** (Scheme 3). As all attempts at purification resulted in partial oxidation, compound **3a** was subjected to oxidation with pyridine oxide (THF, 25 °C, 1 h) to furnish, after extraction with diethyl ether and filtration through celite, pure 1,2,3,3*a*-tetrahydro-1-azaazulene **4a** (91% overall yield from **1a**) as a single diastereomer (Scheme 3 and Table 1, entry 1). When this [8+2] cycloaddition/oxidation sequence was extended to alkenyl carbenes **1b**–**e** and 8-azaheptafulvene **2a**, the expected tetrahydro-1-azaazulenes **4b**–**e** were obtained in high yields (79–86%) and always with complete



[M]= M(CO)5, M = Cr, W

Scheme 3. [8+2] Cycloaddition of Fischer carbene complexes **1a**–**f** and 8-azaheptafulvenes **2**. Py = pyridine.

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Table 1. Cycloadducts **4** from carbene complexes **1a–f** and azaheptafulvenes **2**.

Entry	1	2	M	R^1	R^2	Product	Yield [%][a]
1	**1a**	**2a**	Cr	Ph	*p*-Me-C_6H_4	**4a**	91
2	**1b**	**2a**	Cr	*p*-MeO-C_6H_4	*p*-Me-C_6H_4	**4b**	86
3	**1c**	**2a**	Cr	*p*-Cl-C_6H_4	*p*-Me-C_6H_4	**4c**	84
4	**1d**	**2a**	Cr	3-furyl	*p*-Me-C_6H_4	**4d**	79
5	**1e**	**2a**	Cr	*t*Bu	*p*-Me-C_6H_4	**4e**	84
6	**1a**	**2b**	Cr	Ph	*p*-MeO-C_6H_4	**4f**	80
7	**1f**	**2a**	W	Ph	*p*-Me-C_6H_4	**4a**	84

[a] Overall yields after celite filtration (hexanes/EtOAc = 2:1).

stereoselectivity (Table 1, entries 2–5). Moreover, we found that the N-deprotectable azaheptafulvene **2b** (R^2 = *p*-MeO-C_6H_4)[21] underwent cycloaddition efficiently with carbene **1a** (80% yield; Table 1, entry 6). On the other hand, the [8+2] cycloaddition can also be carried out with tungsten carbene complexes. Thus, the cycloadduct **4a** was also formed from the tungsten carbene **1f** in yields slightly lower than that reached with the chromium carbene **1a** (84 vs. 91% yield; Table 1, entries 7 and 1).

The structural arrangement and stereochemistry of compounds **4** were in accordance with the spectroscopic data (^{1}H and ^{13}C NMR, HRMS), and the full structure was unambiguously determined for **4d** (R^1 = 3-furyl, R^2 = *p*-Me-C_6H_4) by an X-ray analysis of crystals grown from hexanes/chloroform (Figure 1).

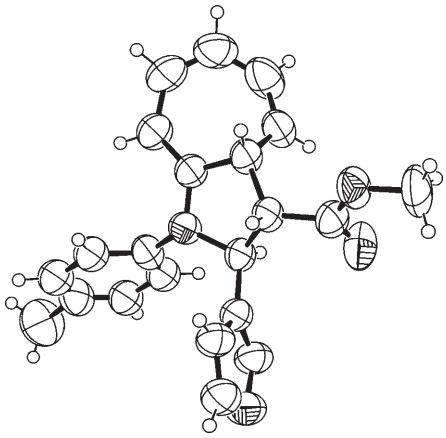
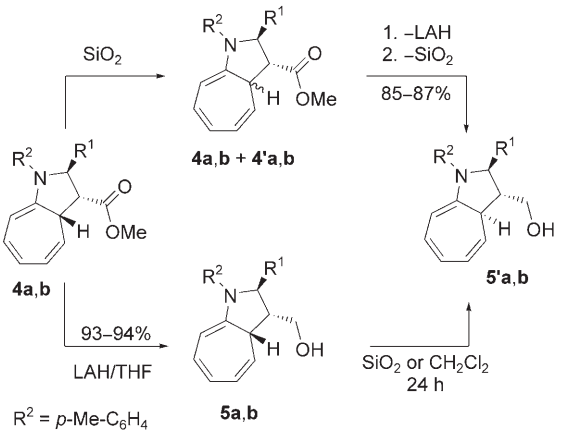


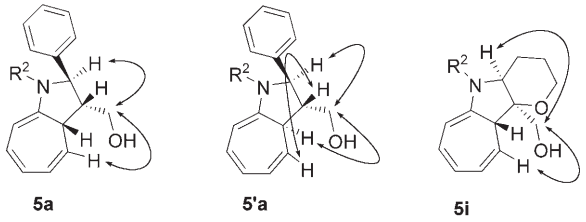
Figure 1. X-ray crystal structure of compound **4d**.

Owing to the presence of a cycloheptatriene unit and an enolizable ester function, compounds **4** might easily undergo epimerization, either thermally or under acidic/basic conditions (Scheme 4). For instance, compounds **4a** and **4b** afforded various mixtures of epimers **4a**,**b** and **4′a**,**b** when subjected to column chromatography (SiO_2, hexanes/EtOAc = 10:1) as a consequence of [1,5] hydrogen sigmatropic shifts. Gratifyingly, the resulting epimeric mixture could be transformed into the stereochemically pure alcohols **5′a**,**b** by LAH reduction (THF, 25 °C, 1 h) and column



Scheme 4. Reduction and epimerization of ester cycloadducts **4a** and **4b**. LAH = lithium aluminum hydride.

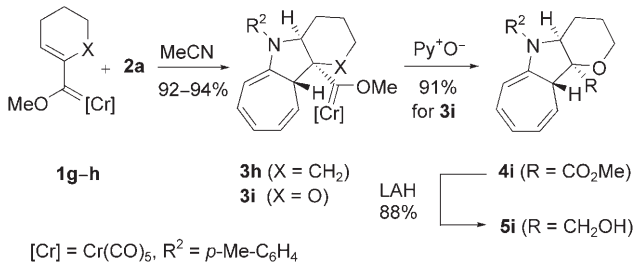
chromatography (85–87% yield). In accordance with this finding, the treatment of **4a**,**b** with LAH (THF, 25 °C, 1 h) resulted in clean ester reduction to alcohols **5a**,**b** (93–94% yield) without detectable epimerization. Furthermore, these cycloadducts completely epimerized to **5′a**,**b** either by column chromatography or upon standing in dichloromethane. The relative stereochemistry of **5a**,**b** and **5′a**,**b** was confirmed by NOESY experiments on compounds **5a** and **5′a** (Scheme 5). The *trans* arrangement of the R^1 and ester



Scheme 5. Selected NOESY correlations for compounds **5a**, **5′a**, and **5i**.

groups probably makes this portion thermodynamically stable, whereas the epimerization of the C-bridged atom to the more stable *trans*,*trans* isomer by consecutive [1,5] hydrogen rearrangements seems favorable.

With the aim of expanding the synthetic utility of this reaction, α,β-disubstituted carbene complexes were used with the expectation that complex cycloadducts with a quaternary carbon center would be accessible (Scheme 6). Thus, carbocyclic and heterocyclic carbenes **1g** and **1h** were treated with 8-azaheptafulvene **2a** under the same reaction conditions to furnish the polycyclic chromium carbenes **3h** and **3i** as a single diastereomer, according to the ^{1}H NMR spectrum of the crude reaction mixture. Further purification by column chromatography (SiO_2, hexanes/ethyl acetate = 10:1) afforded the pure cycloadducts in 92–94% yield. In turn, the cycloadduct **3i** was subjected to oxidative demetalation (pyridine oxide/THF, room temperature, 1 h) to afford the corresponding ester **4i** (91% yield). Finally, LAH reduction of



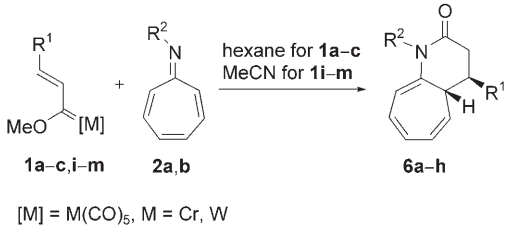
Scheme 6. [8+2] Cycloaddition reaction of cyclic carbene complexes **1g–h** and 8-azaheptafulvene **2a**.

the latter gave rise to alcohol **5i** (88% yield). NOESY experiments on compound **5i** (Scheme 5) allowed us to ascertain the relative stereochemistry of adducts **3i–5i**. Unlike the bicyclic adducts **4a–f** (Scheme 3), the tricyclic adducts **3h**, **3i**, **4i**, **and 5i** are configurationally stable and do not suffer epimerization under the purification conditions.

Therefore, this first regio- and diastereoselective [8+2] cycloaddition of Fischer carbenes represents a facile access to the interesting tetrahydroazaazulene structure[22] in which three stereogenic centers are created in a stereoselective manner. Notably, the sole precedent of [8+2] cycloaddition of 8-azaheptafulvenes to olefins found in the literature is limited to doubly activated styrenes.[19d] Accordingly, this new reaction demonstrates once again the superiority of alkenyl carbenes over classical metal-free electrophilic alkenes in the participation of selective cycloaddition reactions.

[8+3] Cycloaddition of Alkenyl Carbene Complexes 1 with 8-Aryl-8-azaheptafulvenes 2

During the study into the optimization of the [8+2] cycloaddition reaction described above, we found that when the reaction of carbene **1a** and 8-azaheptafulvene **2a** was carried out in hexane instead of MeCN, a minor compound was formed along with the known cycloadduct **3a** in a 1:2 ratio. After column chromatography of the crude mixture (SiO_2, hexanes/EtOAc = 10:1), the new compound was isolated and identified as the 1,2,4,4*a*-tetrahydrocyclohepta[*b*]pyridin-2-one **6a** as a single diastereomer (Scheme 7 and Table 2, entry 1). Therefore, a new [8+3] cycloaddition between **1a** and **2a** was found to compete by performing the reaction in



Scheme 7. [8+3] Cycloaddition reaction of alkenyl Fischer carbene complexes **1a–c**,**i–m** and 8-azaheptafulvenes **2**.

Table 2. Cyclohepta[*b*]pyridin-2-ones **6** from alkenyl carbenes **1** and 8-azaheptafulvenes **2**.

Entry	**1**	R^1	**2**	R^2	Product	Yield [%][a]
1	**1a**	Ph	**2a**	*p*-Me-C_6H_4	**6a**	27[b]
2	**1b**	*p*-MeO-C_6H_4	**2a**	*p*-Me-C_6H_4	**6b**	21[b]
3	**1c**	*p*-Cl-C_6H_4	**2a**	*p*-Me-C_6H_4	**6c**	25[b]
4	**1i**	2-furyl	**2a**	*p*-Me-C_6H_4	**6d**	87
5	**1j**	2-thienyl	**2a**	*p*-Me-C_6H_4	**6e**	85
6	**1k**	2-(*N*-methylpyrrolyl)	**2a**	*p*-Me-C_6H_4	**6f**	70
7	**1l**	(*E*)-C_6H_5CH=CH	**2a**	*p*-Me-C_6H_4	**6g**	78
8	**1i**	2-furyl	**2b**	*p*-MeO-C_6H_4	**6h**	83
9	**1m**	2-furyl	**2a**	*p*-Me-C_6H_4	**6d**	51

[a] Yields after purification by column chromatography (silica gel, hexanes/EtOAc = 10:1). [b] Obtained along with the corresponding [8+2] cycloadduct (**6a–c**/**4a–c** = 1:2).

hexane. In the same way, the use of β-aryl alkenyl carbenes **1b** and **1c** led to separable mixtures of cycloadducts **6b**,**c** and **3b**,**c** (Table 2, entries 2 and 3). Surprisingly, it was observed that carbene **1i** (R^1 = 2-furyl) and azaheptafulvene **2a** underwent the [8+3] cycloaddition exclusively and independently of the solvent used—either hexane or MeCN—to give **6d** in high yield (Table 2, entry 4).[23] This particular reaction pathway for carbene **1i** was successfully extended to other alkenyl carbenes bearing similar heterocyclic substituents, such as **1j** (R^1 = 2-thienyl) and **1k** (R^1 = 2-(*N*-methylpyrrolyl)), as well as dienyl carbene **1l** (R^1 = *trans*-styryl), to lead exclusively to adducts **6e–g** (Table 2, entries 5–7). Moreover, the chromium furyl alkenyl carbene **1i** reacted efficiently with the *N*-*p*-methoxyphenyl azaheptafulvene **2b** to afford the *N*-*p*-methoxyphenyl-protected adduct **6h** (83% yield; Table 2, entry 8),[21] whereas its tungsten analogue **1m** reacted with **2a** to provide the adduct **6d** in rather low yield (51% yield; Table 2, entry 9). Significantly, the reaction of 3-furyl alkenyl carbene **1d** with **2a** did not follow this [8+3] cycloaddition model but led cleanly to the [8+2] cycloadduct **4d** (see above; Table 1, entry 4).

The structures of cycloadducts **6** were ascertained on the basis of their NMR spectroscopic and HRMS data. An X-ray analysis allowed us to confirm unambiguously the structure of compound **6e** (Figure 2).

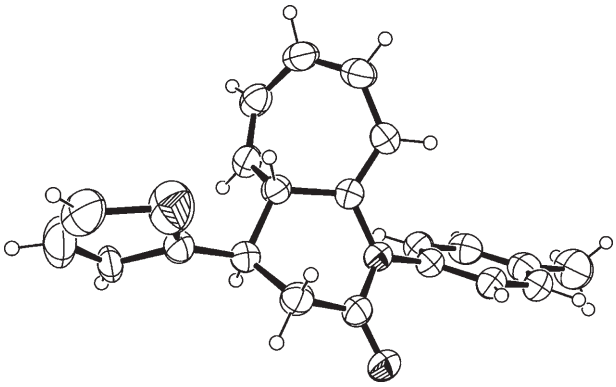


Figure 2. X-ray crystal structure of compound **6e**.

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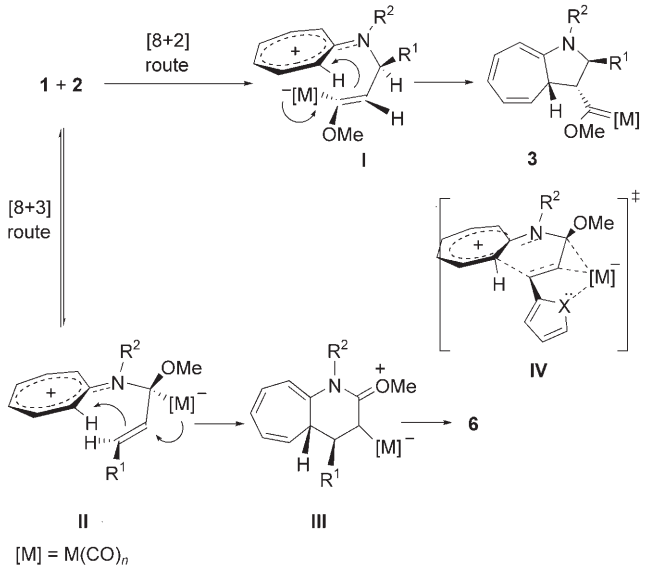
Finally, this new [8+3] cyclization of alkenyl carbenes makes accessible the cyclohepta[*b*]pyridine structure, which is present in the skeleton of some biologically active compounds[24] and natural products, such as the homoaporphine family of alkaloids.[25]

Mechanistic Proposal

A tentative mechanism that might explain the [8+2] and [8+3] cycloaddition models as well as the observed preference for one over the other, depending on the substituent at the C_β carbon atom of the alkene, is displayed in Scheme 8.



Scheme 8. Proposed mechanisms for the cyclization of **1** and **2**.

First, we anticipate that models for both individual pathways have already been well-established. Thus, the [8+2] cycloaddition would involve the 1,4-addition of the heptafulvene nitrogen atom to the activated carbon–carbon double bond of the carbene to form the intermediate **I**. Further cyclization from the *endo* metal conformation, which would be favored by charge interaction between the ionic metal and cycloheptatrienyl-ring moieties, would provide the kinetic carbene cycloadduct **3**. On the other hand, the formation of the [8+3] cycloadduct would be initiated by 1,2-nucleophilic attack of the nitrogen atom on the metal–carbene bond to generate the zwitterionic species **II**. At this point, if we assume this step to be reversible under the reaction conditions, the following steps would control the overall process. Thus, the cyclization is known to be induced by [1,2] metal migration to generate the intermediate **III**, a species that would lead to the final cycloadduct **6** upon reductive metal elimination and enol ether hydrolysis. According to this scenario, the rate of cyclization of **II** to **III** seems to control the type of cycloaddition. Thus, the presence of substituents (2-furyl, 2-thienyl, 2-pyrrolyl, styryl, but not 3-furyl) capable of coordinating to the metal would stabilize the transition state **IV** (Scheme 8) and drive the reaction according to the [8+3] model.[26] To the best of our knowledge, there is no precedent for this dependence of the substituent on the reaction course.

Conclusions

New higher-order heterocyclization reactions have been described for alkenyl Fischer carbenes with fulvenoid substrates. Alkenyl carbene complexes react with 8-azaheptafulvenes with complete regio- and stereoselectivity through [8+2] and [8+3] heterocyclization reactions. The progress of the reaction is highly dependent on the C_β substituent of the alkenyl carbene complex. The presence of a coordinating moiety favors the reaction to proceed completely by the [8+3] cyclization route, whereas formal [8+2] cycloaddition takes place when the carbene complex lacks appropriate coordinating groups. This work can be regarded as a selective and straightforward entry into the tetrahydroazaazulene and cycloheptapyridone frameworks. The presence of this skeleton in the structures of biologically active molecules enhances the interest of the cycloadducts described herein and makes them promising for bioactivity screening.

Experimental Section

General

All reactions involving air-sensitive compounds were carried out under nitrogen atmosphere (99.99%). All glassware were oven-dried (120°C), evacuated, and purged with nitrogen. All common reagents and solvents were obtained from commercial suppliers and used without further purification unless otherwise indicated. Fischer carbene complexes **1**[27] and 8-azaheptafulvenes **2**[28] were prepared by following described procedures. Solvents were dried by standard methods and distilled prior to use. Flash column chromatography was carried out on silica gel 60, 230–240 mesh. NMR spectra were recorded on Bruker AC-200, AC-300, or DPX-300 spectrometers. ^{1}H NMR spectra were recorded in $CDCl_3$ (unless otherwise noted) at 300.08 MHz at 20°C with tetramethylsilane ($\delta = 0.0$ ppm) as the internal standard. ^{13}C NMR spectra were recorded in $CDCl_3$ (unless otherwise noted) at 75.46 MHz at 20°C. ^{1}H NMR signal multiplicities are abbreviated as: s = singlet, d = doublet, m = multiplet. ^{13}C NMR signal multiplicities were determined by DEPT (distortionless enhancement by polarization transfer) and are abbreviated as: q = CH_3, t = CH_2, d = CH, s = quaternary carbon atoms; some ^{13}C NMR signals overlapped. COSY, HMSQC (heteronuclear multiple/single quantum coherence), HMBC, and NOESY experiments were carried out on a Bruker AMX-400 spectrometer. Standard pulse sequences were employed for the DEPT experiments. High-resolution mass spectrometry (HRMS) was performed on a Finnigan Mat95 mass spectrometer, and electron-impact (EI) techniques (70 eV) were employed. Elemental analysis was carried out with a Perkin–Elmer 240 B microanalyzer.

Syntheses

General procedure for the synthesis of **3** and **4**: A solution of **1a–h** (0.5 mmol) and **2** (0.5 mmol) in MeCN (3 mL) was stirred under nitrogen at room temperature for 12 h, and the solvent was removed in vacuo. The crude adducts **3a–g** and **3i** were oxidized to the corresponding esters **4a–f** and **4i** by treatment in THF with pyridine oxide (3 equiv) followed by extraction, workup, and filtration through celite (hexanes/EtOAc = 2:1). The crude carbenes **3h** and **3i** were purified by column chromatography (silica gel, hexanes/EtOAc = 10:1).

3h: Yield = 94%. ^{1}H NMR: δ = 7.03 (d, 7.9 Hz, 2H), 6.84 (d, J = 7.9 Hz, 2H), 6.47 (dd, J = 10.2, 7.4 Hz, 1H), 6.15–6.04 (m, 2H), 5.13 (d, J = 6.7 Hz, 1H), 4.93 (s, 3H), 4.37 (dd, J = 7.8, 5.8 Hz, 1H), 3.68 (s, 1H), 2.96–2.86 (m, 1H), 2.21 (s, 3H), 2.14–2.06 (m, 2H), 1.66–1.43 (m, 4H), 0.85–0.71 ppm (m, 2H); ^{13}C NMR (C_6D_6): δ = 372.4 (s), 222.1 (s), 216.2 (s, 4C), 141.6 (s), 140.0 (s), 136.0 (s), 131.0 (d), 129.8 (s, 2C), 126.9 (d), 126.5 (s, 2C), 120.1 (d), 107.6 (d), 94.3 (d), 71.0 (s), 68.7 (d), 63.6 (q), 53.6 (d), 35.1 (t), 24.2 (t), 23.9 (t), 21.1 (q), 20.6 ppm (t); HRMS: m/z calcd for $C_{27}H_{25}CrNO_6$: 511.1087 $[M]^+$; found: 511.1089.

3i: Yield = 92%. ^{1}H NMR: δ = 7.18 (d, J = 8.5 Hz, 2H), 7.04 (d, J = 8.5 Hz, 2H), 6.58 (dd, J = 10.4, 6.7 Hz, 1H), 6.27–6.13 (m, 2H), 5.37 (d, J = 7.0 Hz, 1H), 5.08 (s, 3H), 4.48 (dd, J = 9,5, 6.1 Hz, 1H), 4.12–4.03 (m, 1H), 3.87 (s, 1H), 3.50–3.41 (m, 1H), 2.62 (d, J = 5.2 Hz, 1H), 2.08–1.93 (m, 1H), 1.90–1.77 (m, 1H), 1.55–1.42 (m, 1H), 1.39–1.25 ppm (m, 1H); ^{13}C NMR: δ = 368.5 (s), 223.2 (s), 216.2 (s, 4C), 141.2 (s), 139.7 (s), 135.8 (s), 131.4 (d), 130.0 (d, 2C), 127.7 (d), 125.7 (d, 2C), 120.3 (d), 107.0 (d), 94.5 (s), 94.2 (d), 68.4 (q), 66.0 (t), 61.3 (d), 53.7 (d), 22.4 (t), 21.5 (q), 19.6 ppm (t); HRMS: m/z calcd for $C_{25}H_{23}CrNO_6$: 485.0925 $[M-CO]^+$; found: 485.0923.

4a: Yield = 91%. ^{1}H NMR: δ = 7.42 (d, J = 7.7 Hz, 2H), 7.32–7.22 (m, 5H), 7.01 (d, J = 7.7 Hz, 2H), 6.60 (dd, J = 10.5, 6.8 Hz, 1H), 6.38–6.19 (m, 2H), 5.48 (d, J = 6.8 Hz, 1H), 5.20 (dd, J = 8.5, 4.9 Hz, 1H), 5.02 (d, J = 9.4 Hz, 1H), 3.75 (s, 3H), 3.53 (t, J = 9.4 Hz, 1H), 2.69–2.50 (m 1H,), 2.21 ppm (s, 3H); ^{13}C NMR: δ = 171.2 (s), 141.5 (s), 140.2 (s), 139.5 (s), 134.7 (s), 131.1 (d), 129.4 (d, 2C), 128.4 (d, 2C), 127.9 (d), 127.7 (d, 2C), 127.6 (d), 124.8 (d, 2C), 120.9 (d), 111.1 (d), 93.5 (d), 69.9 (d), 53.6 (q), 51.8 (d), 43.6 (d), 20.7 ppm (q); HRMS: m/z calcd for $C_{24}H_{23}NO_2$: 357.1729 $[M]^+$; found: 357.1732.

4b: Yield = 86%. ^{1}H NMR: δ = 7.34 (d, J = 7.8 Hz, 2H), 7.00 (d, J = 8.0 Hz, 2H), 6.90 (d, J = 7.8 Hz, 2H), 6.81 (d, J = 8.0, Hz, 2H), 6.62 (t, J = 6.8 Hz, 1H), 6.38–6.21 (m, 2H), 5.46 (d, J = 6.2 Hz, 1H), 5.22–5.20 (m, 1H), 4.96 (d, J = 9.2 Hz, 1H), 3.85 (s, 3H), 3.81 (s, 3H,), 3.47 (t, J = 8.7 Hz, 1H), 2.66–2.64 (m, 1H), 2.29 ppm (s, 3H); ^{13}C NMR (C_6D_6): δ = 171.1 (s), 159.5 (s), 141.7 (s), 140.9 (s), 134.8 (s), 131.7 (d), 131.4 (s), 129.6 (d, 2C), 129.2 (d, 2C), 128.5 (d), 125.7 (d, 2C), 121.4 (d), 114.0 (d, 2C), 110.9 (d), 94.3 (d), 70.1 (d), 54.3 (q), 53.9 (q), 51.2 (d), 44.0 (d), 20.5 ppm (q); HRMS: m/z calcd for $C_{25}H_{25}NO_3$: 387.1834 $[M]^+$, found: 387.1836; elemental analysis: calcd (%) for $C_{25}H_{25}NO_3$: C 77.49, H 6.50, N 3.61; found: C 77.67, H 6.39, N 3.77.

4c: Yield = 84%. ^{1}H NMR: δ = 7.38 (d, J = 8.3 Hz, 2H), 7.31 (d, J = 7.8 Hz, 2H), 7.07 (d, J = 7.8 Hz, 2H), 6.90 (d, J = 8.3 Hz, 2H), 6.62 (dd, J = 10.2, 6.6 Hz, 1H), 6.35–6.20 (m, 2H), 5.48 (d, J = 6.7 Hz), 5.20 (dd, J = 8.8, 5.0 Hz, 1H), 4.97 (d, J = 9.6 Hz, 1H), 3.73 (s, 3H), 3.48–3.40 (m, 1H), 2.69–2.60 (m, 1H), 2.21 ppm (s, 3H); ^{13}C NMR: δ = 171.2 (s), 141.4 (s), 140.2 (s), 138.1 (s), 135.5 (s), 133.6 (s), 129.7 (d, 2C), 129.3 (d, 2C), 128.8 (d, 2C), 127.8 (d), 125.1 (d, 2C), 124.9 (d), 121.4 (d), 111.1 (d), 93.9 (d), 69.3 (d), 53.8 (q), 52.1 (d), 43.7 (d), 20.9 ppm (q); HRMS: m/z calcd for $C_{24}H_{20}ClNO_2$: 389.1177 $[M-2H]^+$; found: 389.1173.

4d: Yield = 79%. ^{1}H NMR: δ = 7.38 (d, J = 8.0 Hz, 2H), 7.37–7.23 (m, 1H), 7.13–7.06 (m, 2H), 6.97 (d, J = 8.0 Hz, 2H), 6.62 (t, J = 10.2 Hz, 1H), 6.50–6.48 (m, 1H), 6.34–6.28 (m, 1H), 6.29–6.15 (m, 1H), 5.41 (d, J = 6.5 Hz, 1H), 5.29–5.17 (m, 1H), 4.98 (d, J = 9.7 Hz, 1H), 3.81 (s, 3H,), 3.51 (t, J = 9.2 Hz, 1H), 2.69–2.61 (m, 1H), 2.25 ppm (s, 3H); ^{13}C NMR: δ = 171.3 (s), 155.3 (d), 141.5 (s), 140.2 (s), 135.4 (s), 131.3 (d), 127.8 (d, 2C), 126.7 (d), 124.9 (d, 2C), 124.5 (d), 124.0 (s), 116.4 (d), 110.7 (d), 107.4 (d), 93.9 (d), 61.8 (d), 52.0 (q), 51.5 (d), 43.5 (d), 20.9 ppm (q); HRMS: m/z calcd for $C_{22}H_{21}NO_3$: 347.1521 $[M]^+$; found: 347.1524; elemental analysis: calcd (%) for $C_{22}H_{21}NO_3$: C 76.06, H 6.09, N 4.03; found: C 75.89, H 6.13, N 4.24.

4e: Yield = 84%. ^{1}H NMR: δ = 7.13–7.09 (m, 4H), 6.58–6.50 (m, 1H), 6.26–6.18 (m, 1H), 6.15–6.08 (m, 1H), 5.27 (d, J = 6.9 Hz, 1H), 4.97 (dd, J = 9.0, 4.8 Hz, 1H), 4.23 (d, J = 7.6 Hz, 1H), 3.86 (s, 3H), 3.48 (dd, J = 9.7, 7.6 Hz, 1H), 2.67–2.55 (m, 1H), 2.32 (s, 3H), 0.93 ppm (s, 9H); ^{13}C NMR (C_6D_6): δ = 173.3 (s), 144.4 (s), 143.6 (s), 136.6 (s), 131.01 (d), 129.8 (d, 2C), 127.3 (d), 126.4 (d, 2C), 119.5 (d), 111.8 (d), 93.1 (d), 75.3 (d), 51.9 (q), 46.4 (d), 44.3 (d), 29.5 (s), 26.9 (q), 22.5 ppm (q, 3C); HRMS: m/z calcd for $C_{22}H_{27}NO_2$: 337.2042 $[M]^+$, found: 337.2046.

4f: Yield = 80%. ^{1}H NMR: δ = 7.48–7.21 (m, 5H), 6.98 (d, J = 7.7 Hz, 2H), 6.76 (d, J = 7.7 Hz, 2H), 6.69–6.50 (m, 1H), 6.39–6.30 (m, 1H), 6.28–6.20 (m, 1H), 5.41 (d, J = 6.1 Hz, 1H), 5.29–5.20 (m, 1H), 4.98 (d, J = 9.3 Hz, 1H), 3.81 (s, 3H), 3.78 (s, 3H), 3.57 (t, J = 9.0 Hz, 1H), 2.75–2.65 ppm (m, 1H); ^{13}C NMR: δ = 171.1 (s), 157.0 (s), 142.2 (s), 139.2 (s), 135.7 (s), 128.7 (d), 128.3 (d, 2C), 127.9 (d, 2C), 127.8 (d), 127.6 (d), 126.8 (d, 2C), 120.7 (d), 114.0 (d, 2C), 110.6 (d), 93.5 (d), 70.3 (d), 55.0 (q), 53.0 (q), 51.8 (d), 43.5 ppm (d); HRMS: m/z calcd for $C_{24}H_{23}NO_3$: 373.1672; found 373.1676; elemental analysis: calcd (%) for $C_{24}H_{23}NO_3$: C 77.19, H 6.21, N 3.75; found: C 77.46, H 6.34, N 3.89.

4i: Yield = 91%. ^{1}H NMR: δ = 7.19 (d, J = 8.1 Hz, 2H), 7.05 (d, J = 8.1 Hz, 2H), 6.57 (dd, J = 10.8, 6.6 Hz, 1H), 6.27–6.15 (m, 2H), 5.31 (d, J = 6.6 1H), 5.02 (dd, J = 9.1, 8.4 Hz, 1H), 4.05 (s, 1H), 4.03–3.96 (m, 1H), 3.92 (s, 3H), 3.56–3.40 (m, 2H), 2.35 (s, 3H), 2.09–1.97 (m, 1H), 1.95–1.87 (m, 1H), 1.68–1.60 (m, 1H), 1.40–1.27 ppm (m, 1H); ^{13}C NMR: δ = 171.1 (s), 141.6 (s), 139.4 (s), 136.0 (s), 131.6 (d), 129.9 (d, 2C), 127.6 (d), 126.4 (d, 2C), 120.5 (d), 107.5 (d), 93.8 (d), 83.2 (s), 65.5 (t), 62.1 (q), 52.6 (d), 51.8 (d), 21.1 (t), 21.0 (q), 19.4 ppm (t); HRMS: m/z calcd for $C_{21}H_{23}NO_3$: 337.1673 $[M]^+$; found: 337.1674; elemental analysis: calcd (%) for $C_{21}H_{23}NO_3$: C 74.75, H 6.87, N 4.15; found: C 74.87, H 6.70, N 4.01.

Synthesis of **5a**,**b**,**i** and **5′a**,**b**: The ester adducts **4a**,**b**,**i** (0.4 mmol) were treated with LAH (0.8 mmol) in toluene (1.5 mmol) under nitrogen, and the mixture was stirred for 1 h. Next, the reaction was quenched with the addition of a few drops of NaOH (2 M), and the mixture was filtered through Na_2SO_4 and celite. The filtrate was concentrated under vacuum to give alcohols **5a**,**b**,**i**. Additionally, if the resulting crude mixture was purified by column chromatography (silica gel, hexanes/EtOAc = 5:1) alcohols **5′a**,**b** and **5i** were obtained.

5a: Yield = 94%. ^{1}H NMR (C_6D_6): δ = 7.37 (d, J = 8.1 Hz, 2H), 7.23–7.11 (m, 5H), 7.09 (d, J = 8.1 Hz, 2H), 6.88–6.78 (m, 1H), 6.59–6.41 (m, 2H), 5.96 (d, J = 6.5 Hz, 1H), 5.55–5.48 (m, 1H), 4.51 (d, J = 9.1 Hz, 1H), 3.83–3.75 (m, 1H), 3.62–3.50 (m, 1H), 2.85–2.78 (m, 1H), 2.60–2.51 (m, 1H), 2.04 ppm (s, 3H); ^{13}C NMR (C_6D_6): δ = 143.0 (s), 142.4 (s), 141.6 (s), 134.0 (s), 132.0 (d), 130.0 (d, 2C), 129.1 (d, 2C), 128.5 (d), 127.8 (d), 127.6 (d, 2C), 124.1 (d, 2C), 122.5 (d), 112.2 (d), 96.1 (d), 71.5 (d), 60.1 (t), 50.3 (d), 43.8 (d), 20.9 ppm (q).

5b: Yield = 93%. ^{1}H NMR (C_6D_6): δ = 7.26 (d, J = 7.8 Hz, 1H), 7.11 (d, J = 7.6 Hz, 2H), 6.89 (d, J = 7.6 Hz, 2H), 6.89 (d, J = 7.8 Hz, 2H), 6.67–6.53 (m, 1H), 6.51–6.47 (m, 1H), 5.95 (d, J = 6.7 Hz, 1H), 5.61–5.53 (m, 1H), 4.49 (d, J = 8.9 Hz, 1H), 4.01–3.90 (m, 1H), 3.72–3.60 (m, 1H), 3.47 (s, 3H), 2.92–2.84 (m, 1H), 2.73–2.61 (m, 1H), 2.11 ppm (s, 3H); ^{13}C NMR: δ = 169.3 (s), 142.7 (s), 141.3 (s), 133.9 (s), 133.3 (s), 130,5 (d), 129.7 (d, 2C), 128.6 (d, 2C), 127.3 (d), 124.3 (d, 2C), 122.2 (d), 114.3 (d), 111.3 (d), 95,3 (d), 70.8 (d), 60.3 (t), 54.5 (q), 50.0 (d), 43.4 (d), 20.6 ppm (q).

5′a: Yield = 85%. ^{1}H NMR (CD_2Cl_2): δ = 7.30–7.27 (m, 5H), 7.15 (d, J = 8.6 Hz, 2H), 7.10 (d, J = 8.6 Hz, 2H), 6.46 (dd, J = 10.7, 7.1 Hz, 1H), 6.27–6.15 (m, 1H), 6.05 (dd, J = 10.7, 5.6 Hz, 1H), 5.41 (d, J = 7,1 Hz, 1H), 5.10 (d, J = 7.2 Hz, 1H), 5.03 (dd, J = 11.0, 4.7 Hz, 1H), 3.91 (dd, J = 11.1, 6.5 Hz, 1H), 3.84 (dd, J = 11.1, 5.5 Hz, 1H), 2.77–2.74 (m, 1H), 2.59–2.50 (m, 1H), 2.21 ppm (s, 3H); ^{13}C NMR (C_6D_6): δ = 146.5 (s), 141.9 (s), 139.0 (s), 133.0 (s), 131.3 (d), 129.6 (d, 2C), 128.7 (d, 2C), 128.5 (d), 127.2 (d, 2C), 127.0 (d), 123.7 (d, 2C), 123.1 (d), 121.1 (d), 94.1 (d), 69.3 (d), 62.3 (t), 56.3 (d), 45.2 (d), 20.5 ppm (q); HRMS: m/z calcd for $C_{23}H_{23}NO$: 329.1780 $[M]^+$; found: 329.1779; elemental analysis: calcd (%) for $C_{23}H_{23}NO$: C 83.85, H 7.04, N 4.25; found: C 83.70, H 7.35, N 4.36.

5′b: Yield = 87%. ^{1}H NMR (C_6D_6): δ = 7.19 (d, J = 7.7 Hz, 2H), 7.13 (d, J = 7.4 Hz, 2H), 6.89 (d, J = 7.4 Hz, 2H), 6.71 (d, J = 7.7 Hz, 2H), 6.70–6.61 (m, 1H), 6.50–6.46 (m, 1H), 6.42–6.33 (m, 1H), 5.89 (d, J = 6.9 Hz, 1H), 5.19–5.11 (m, 1H), 5.09 (d, J = 7.0 Hz, 1H), 3.62–3.51 (m, 2H), 3.23 (s, 3H), 3.08–3.00 (m, 1H), 2.51–2.45 (m, 1H), 2.09 ppm (s, 3H); ^{13}C NMR (C_6D_6): δ = 159.8 (s), 147.8 (s), 139.1 (s), 133.3 (s), 133.1 (s), 131.8 (d), 129.7 (d, 2C), 128.5 (d, 2C), 128.1 (d), 124.4 (d, 2C), 123.8 (d), 120.8 (d), 114.1 (d, 2C), 94.2 (d), 69.0 (d), 62.3 (t), 56.1 (d), 54.5 (q), 45.1 (d), 20.5 ppm (q); HRMS: m/z calcd for $C_{24}H_{25}NO_2$: 359.1885 $[M]^+$;

found: 359.1880; elemental analysis: calcd (%) for $C_{24}H_{25}NO_2$: C 80.19, H 7.01, N 3.90; found: C 80.31, H 6.90, N 4.03.

5i: Yield = 88%. ^{1}H NMR (C_6D_6): δ = 6.87 (s, 4H), 6.68 (dd, J = 10.7, 6.8 Hz, 1H), 6.40–6.37 (m, 1H), 6.32–6.28 (m, 1H), 5.58 (d, J = 6.8 Hz, 1H), 5.21 (dd, J = 9.2, 5.2 Hz, 1H), 3.87 (d, J = 12.1 Hz, 1H), 3.64 (d, J = 12.1 Hz, 1H), 3.44–3.36 (m, 1H), 3.28–3.26 (m, 1H), 2.92 (t, J = 2.6 Hz, 1H), 2.55 (d, J = 5.2 Hz, 1H), 2.04 (s, 3H), 1.79–1.71 (m, 1H), 1.62–1.45 (m, 1H), 1.09–1.05 (m, 1H), 0.78–0.72 ppm (m, 1H); ^{13}C NMR (C_6D_6): δ = 141.5 (s), 140.3 (s), 135.2 (s), 131.4 (d), 129.9 (d, 2C), 128.1 (d), 125.9 (d, 2C), 120.6 (d), 110.0 (d), 94.7 (d), 80.1 (s), 61.5 (d), 61.2 (t), 58.8 (t), 50.7 (d), 21.9 (t), 20.7 (q), 19.9 ppm (t); HRMS: m/z calcd for $C_{20}H_{23}NO_2$: 309.1723 $[M]^+$; found: 309.1729; elemental analysis: calcd (%) for $C_{20}H_{23}NO_2$: C 77.64, H 7.49, N 4.53; found: C 77.47, H 7.30, N 4.69.

General procedure for the synthesis of **6**: A solution of **1a–c**,**i–m** (0.5 mmol) and **2** (0.5 mmol) in hexane (3 mL; for **1a–c**) or MeCN (3 mL; for **1i–m**) was stirred under nitrogen at room temperature for 12 h. Next, the solvent was removed under vacuum, and the crude product was dissolved in hexanes/EtOAc (20:1) and air-oxidized in an open flask in sunlight (4–6 h). The solution was then filtered over celite, and the filtrate was concentrated under vacuum. The resulting crude product was purified by column chromatograhy (silica gel, hexanes/EtOAc = 10:1).

6a: Yield = 27%. ^{1}H NMR: δ = 7.41–7.31 (m, 2H), 7.31–7.22 (m, 3H), 7.20 (d, J = 8.3, 2H), 7.01 (d, J = 8.3 Hz, 2H), 6.50–6.45 (m, 2H), 6.29–6.20 (m, 1H), 5.49–5.44 (m, 1H), 5.25 (dd, J = 9.1, 5.4 Hz, 1H), 3.50–3.41 (m, 1H), 2.92 (d, J = 7.4 Hz, 2H), 2.39 (s, 3H), 2.22-2.16 ppm (m, 1H); ^{13}C NMR: δ = 170.9 (s), 141.1 (s), 137.2 (s), 137.0 (s), 134.7 (s), 129.9 (d, 2C), 128.8 (d, 2C), 128.7 (d), 127.8 (d, 2C), 127.4 (d), 127.2 (d, 2C), 127.1 (d), 122.8 (d), 111.4 (d), 44.7 (d), 43.1 (d), 40.3 (t), 21.0 ppm (q); HRMS: m/z calcd for $C_{23}H_{21}NO$: 327.1618 $[M]^+$; found 327.1614; elemental analysis: calcd (%) for $C_{23}H_{21}NO$: C 84.37, H 6.46, N 4.28; found: C 84.76, H 6.72, N 4.00.

6b: Yield = 21%. ^{1}H NMR: δ = 7.23–7.19 (m, 4H), 7.10 (d, J = 7.8 Hz, 2H), 6.90 (d, J = 8.3 Hz, 2H), 6.46–6.44 (m, 2H), 6.30–6.26 (m, 1H), 5.47–5.43 (m, 1H), 5.24 (dd, J = 8.3, 5.0 Hz, 1H), 3.81 (s, 3H), 3.45–3.40 (m, 1H), 2.99–2.89 (m, 2H), 2.36 (s, 3H), 2.20–2.13 ppm (m, 1H); ^{13}C NMR: δ = 171.0 (s), 158.7 (s), 137.2 (s), 137.1 (s), 134.9 (s), 133.2 (s), 129.9 (d, 2C), 128.8 (d), 128.2 (d, 2C), 127.8 (d, 2C), 127.4 (d), 127.1 (d), 122.5 (d), 114.2 (d, 2C), 111.4 (d), 55.2 (q), 44.9 (d), 42.4 (d), 40.6 (t), 21.1 ppm (q); HRMS: m/z calcd for $C_{24}H_{23}NO_2$: 357.1729 $[M]^+$; found: 357.1727.

6c: Yield = 25%. ^{1}H NMR: δ = 7.45 (d, J = 8.3 Hz, 2H), 7.30–7.20 (m, 4H), 7.00 (d, J = 8.3 Hz, 2H), 6.55–6.45 (m, 2H), 6.34–6.27 (m, 1H), 5.51–5.46 (m, 1H), 5.23 (dd, J = 9.1, 5.4 Hz, 1H), 3.51–3.41 (m, 1H), 2.95–2.88 (m, 2H), 2.37 (s, 3H), 2.19–2.12 ppm (m, 1H); ^{13}C NMR: δ = 170.6 (s), 139.8 (s), 137.4 (s), 137.0 (s), 134.5 (s), 133.1 (s), 130.1 (d, 2C), 129.1 (d, 2C), 129.0 (d), 128.6 (d, 2C), 127.8 (d, 2C), 127.7 (d), 127.2 (d), 122,4 (d), 111.6 (d), 44.7 (d), 42.7 (d), 40.2 (t), 21.1 ppm (q); HRMS: m/z calcd for $C_{23}H_{20}ClNO$: 361.1228 $[M]^+$; found: 361.1223.

6d: Yield = 87%. ^{1}H NMR: δ = 7.40–7.38 (m, 1H), 7.21 (d, J = 8.1 Hz, 2H) , 6.99 (d, J = 8.1 Hz, 2H), 6.50–6.48 (m, 2H), 6.41–6.36 (m, 2H), 6.19–6.17 (m, 1H), 5.40–5.32 (m, 2H), 3.64–3.57 (m, 1H), 3.06 (dd, J = 15.2, 3.4 Hz, 1H), 2.90 (dd, J = 15.2, 10.7 Hz, 1H), 2.36 (s, 3H), 2.35–2.29 ppm (m, 1H); ^{13}C NMR: δ = 169.6 (s), 154.4 (s), 141.9 (d), 137.2 (s), 136.6 (s), 133.7 (s), 129.9 (d, 2C), 129.0 (d), 127.8 (d, 2C), 127.3 (d), 127.0 (d), 122.3 (d), 110.8 (d), 110.1 (d), 105.5 (d), 41.8 (d), 37.0 (t), 36.4 (d), 20.9 ppm (q); HRMS: m/z calcd for $C_{21}H_{19}NO_2$: 317.1416 $[M]^+$; found 317.1411; elemental analysis: calcd (%) for $C_{21}H_{19}NO_2$: C 79.47, H 6.03, N 4.41; found: C 79.11, H 6.14, N 4.28.

6e: Yield = 85%. ^{1}H NMR: δ = 7.28–7.21 (m, 3H), 7.02–6.99 (m, 4H), 6.50–6.46 (m, 2H), 6.38–6.36 (m, 1H), 5.44 (d, J = 3.1 Hz, 1H), 5.36–5.31 (m, 1H), 3.83–3.77 (m, 1H), 3.10 (dd, J = 14.9, 3.5 Hz, 1H), 2.96 (dd, J = 14.9, 11.7 Hz, 1H), 2.37 (s, 3H), 2.26–2.23 ppm (m, 1H); ^{13}C NMR: δ = 169.9 (s), 144.9 (s), 137.3 (s), 136.7 (s), 134.0 (s), 130.0 (d, 2C), 128.9 (d), 127.7 (d, 2C), 127.5 (d), 127.2 (d), 126.9 (d), 124.1 (d), 124.0 (d), 122.5 (d), 111.2 (d), 45.4 (d), 40.7 (t), 38.4 (d), 21.1 ppm (q); HRMS: m/z calcd for $C_{21}H_{19}NOS$: 333.1187 $[M]^+$; found: 333.1185.

6f: Yield = 70%. ^{1}H NMR: δ = 7.22 (d, J = 5.5 Hz, 2H), 7.03 (d, J = 5.5 Hz, 2H), 6.63–6.62 (m, 1H), 6.49–6.45 (m, 2H), 6.32–6.31 (m, 1H), 6.11–6.09 (m, 1H), 5.95–5.93 (m, 1H), 5.40–5.38 (m, 1H), 5.26–5.23 (m, 1H), 3.68 (s, 3H), 3.54–3.49 (m, 1H), 2.96 (dd, J = 1H), 2.76 (dd, J = 1H), 2.37 (s, 3H), 2.34–2.20 ppm (m, 1H); ^{13}C NMR: δ = 169.8 (s), 137.3 (s), 136.6 (s), 134.2 (s), 132.0 (s), 130.0 (d, 2C), 129.1 (d), 127.9 (d, 2C), 127.4 (d), 127.1 (d), 122.7 (d), 122.6 (d), 110.0 (d), 107.1 (d), 105.6 (d), 42.3 (d), 39.3 (t), 34.8 (q), 33.8 (d), 21.1 ppm (q); HRMS: m/z calcd for $C_{22}H_{22}N_2O$: 330.1732 $[M]^+$; found 330.1732; elemental analysis: calcd (%) for $C_{22}H_{22}N_2O$: C 79.97, H 6.71, N 8.48; found: C 79.22, H 6.86, N 8.33.

6g: Yield = 78%. ^{1}H NMR: δ = 7.43–7.38 (m, 5H), 7.31 (d, J = 8.0 Hz, 2H), 7.06 (d, J = 8.0 Hz, 2H), 6.67 (d, J = 15.9 Hz, 1H), 6.54–6.52 (m, 2H), 6.40–6.32 (m, 1H), 6.23 (dd, J = 15.9, 7.1 Hz, 1H), 5.50–5.47 (m, 1H), 5.36–5.34 (m, 1H), 3.19–3.11 (m, 1H), 2.96 (dd, J = 14.6, 2.9 Hz, 1H), 2.77 (dd, J = 14.6, 12.0 Hz, 1H), 2.41 (s, 3H), 2.09–2.01 ppm (m, 1H); ^{13}C NMR: δ = 170.3 (s), 137.1 (s), 136.9 (s), 136.6 (s), 134.3 (s), 131.1 (d), 129.9 (d, 2C), 129.6 (d), 128.9 (d), 128.5 (d, 2C), 127.8 (d, 2C), 127.5 (d), 127.4 (d), 127.0 (d), 126.2 (d, 2C), 122.7 (d), 111.1 (d), 43.2 (d), 40.5 (d), 38.5 (t), 21.0 ppm (q); HRMS: m/z calcd for $C_{25}H_{23}NO$: 353.1780 $[M]^+$; found: 353.1777; elemental analysis: calcd (%) for $C_{25}H_{23}NO$: C 84.95, H 6.56, N 3.96; found: C 84.22, H 6.69, N 3.83.

6h: Yield = 83%. ^{1}H NMR: δ = 7.41–7.39 (m, 1H), 7.07 (d, J = 2.2 Hz, 2H), 6.93 (d, J = 2.20 Hz, 2H), 6.51–6.48 (m, 2H), 6.35–6.33 (m, 2H), 6.18–6.13 (m, 1H), 5.49–5.47 (m 1H), 5.34 (dd, J = 9.1, 5.6 Hz, 1H), 3.87 (s, 3H), 3.61–3.58 (m, 1H), 3.08 (dd, J = 15.5, 3.4 Hz, 1H), 2.93 (dd, J = 15.2, 10.7 Hz, 1H), 2.33–2.29 ppm (m, 1H); ^{13}C NMR: δ = 169.8 (s), 158.6 (s), 154.4 (s), 142.0 (d), 134.0 (s), 132.0 (s), 129.1 (d, 3C), 127.34 (d), 127.1 (d), 122.4 (d), 114.6 (d, 2C), 110.7 (d), 110.1 (d), 105.6 (d), 55.3 (q), 41.7 (d), 37.0 (t), 36.4 ppm (d); HRMS: m/z calcd for $C_{21}H_{19}NO_3$: 333.1365 $[M]^+$; found: 317.1316; elemental analysis: calcd (%) for $C_{21}H_{19}NO_3$: C 75.66, H 5.74, N 4.20; found: C 75.31, H 5.24, N 4.41.

X-ray Crystal-Structure Determination

The most relevant crystal and refinement data for **4d** and **6e** are as follows.

4d: $C_{22}H_{21}NO_3$, M_r = 347.40, T = 293(2) K, λ = 1.54178 Å, orthorhombic, $Pna2_1$, a = 17.6486(2), b = 18.2306(3), c = 5.7996(3) Å, V = 1865.99(12) Å^3, Z = 4, ρ_{calcd} = 1.237 Mg m^{-3}, μ = 0.660 mm^{-1}, $F(000)$ = 736, crystal size: 0.36 × 0.07 × 0.03 mm, θ range: 3.49–75.68°, index ranges: $-20 \le h \le 21$, $-22 \le k \le 21$, $-7 \le l \le 5$, reflections collected/unique = 7216/2896 (R_{int} = 0.0645), completeness to 2θ = 70.00 (97.6%), absorption correction: semi-empirical from equivalents, refinement method: full-matrix least squares on F^2, data/restraints/parameters = 2896/60/233, goodness-of-fit on F^2 = 0.917, final R indices ($I > 2\sigma(I)$): R_1 = 0.0733, wR_2 = 0.1765, R indices (all data): R_1 = 0.1314, wR_2 = 0.2167, extinction coefficient = 0.0097(12), largest difference peak and hole = 0.234 and −0.217 e Å^{-3}. The *ortho* and *meta* carbon atoms of the phenyl ring were disordered over two positions; refinement of the anisotropic displacement parameters was unstable for these atoms, therefore they were kept isotropic.

6e: $C_{21}H_{19}NOS$, M_r = 333.43, T = 293(2) K, λ = 1.54178 Å, triclinic, $P\bar{1}$, a = 7.0088(2), b = 11.8766(3), c = 12.3066(3) Å, α = 108.257(2), β = 105.501(2), γ = 103.853(2)°, V = 877.06 (4) Å^3, Z = 2, ρ_{calcd} = 1.263 Mg m^{-3}, μ = 1.675 mm^{-1}, $F(000)$ = 352, crystal size: 0.25 × 0.12 × 0.10 mm, θ range: 4.19–68.19°, index ranges: $0 \le h \le 8$, $-14 \le k \le 13$, $-14 \le l \le 13$, reflections collected/unique = 8575/3166 (R_{int} = 0.0506), completeness to 2θ = 68.19 (98.3%), absorption correction: semiempirical from equivalents, refinement method: full-matrix least squares on F^2, data/restraints/parameters = 3166/0/218, goodness-of-fit on F^2 = 1.128, final R indices ($I > 2\sigma(I)$): R_1 = 0.0811, wR_2 = 0.2585, R indices (all data): R_1 = 0.0929, wR_2 = 0.2773, extinction coefficient = 0.015(4), largest difference peak and hole = 0.817 and −0.667 e Å^{-3}.

CCDC-654648 (**4b**) and -654649 (**6e**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre at www.cam.ac.uk/data_request/cif.

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