Efficient Synthesis of Highly Functionalized Indazoles and 2,3-Dihydro-1,2-benzisoxazoles by Reaction of Stable Fischer Dienyl Carbenes and Isocyanides

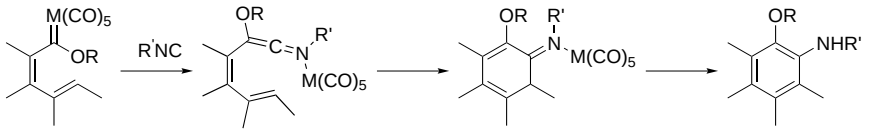
José Barluenga,* Fernando Aznar, and M. Angel Palomero[a]

Abstract: A range of stable chromium and tungsten Fischer dienyl carbenes have been prepared by [3+2] cycloaddition of alkenylethynyl carbene complexes with nitrones or diazoalkanes. Treatment of these systems with isocyanides gives entry to highly functionalized 2,3-dihydro-1,2-benzisoxazoles and indazoles in a completely regioselective fashion, under mild conditions, and with high yields. This methodology can be also applied to the preparation of analogous naphthoisoxazoles starting from arylethynyl Fischer complexes. Reductive cleavage of the isoxazole moiety in the prepared heterocycles also enables the efficient synthesis of highly substituted *p*-aminophenols.

Keywords: benzisoxazoles · carbenes · cycloaddition · indazoles · isocyanides

Introduction

Fischer carbene complexes have been extensively used in synthetic organic chemistry, since they enable high-yielding transformations under mild conditions and in a regioselective fashion.[1] Alkenyl Fischer carbenes are particularly interesting in their synthetic applications due to their tendency to undergo cyclization and co-cyclization with unsaturated substrates. Dötz benzannulation products,[2] and many other different scaffolds, arise from their reaction with acetylenes.[3]



Scheme 1. Reaction of isocyanides and Fischer dienyl carbene complexes.

Isocyanides also react with carbene complexes, giving rise to ketenimine intermediates that evolve to form various types of organic products depending on the substitution pattern of the starting carbenes.[4] More specifically, when an alkoxy alkenyl complex bearing an additional double bond is used, *o*-alkoxyanilines are obtained from the electrocyclic ring-closure of the initially formed ketenimine intermediate (Scheme 1).[5] It is noteworthy that the double bond involved in the cyclization belongs to an aromatic ring in most cases reported to date. This reaction has been successfully applied to the preparation of analogues of indolocarbazole natural products[6] and to the total synthesis of calphostins.[7]

One of the current interests of our research group focuses on the preparation of novel Fischer dienyl carbene complexes through cycloaddition reactions of alkynyl carbenes bearing a vinyl substituent and suitable substrates. The reaction of alkynyl complexes **1** with 2-amino-1,3-butadienes[8] or enol ethers[9] gave the desired 1,3,5-metallahexatrienes **2** and **3**, respectively (Scheme 2). While the [4+2] cycloadducts **2** were reactive at room temperature and evolved directly to form organic products, dienyl carbenes **3** arising from the [2+2] cycloaddition to enol ethers could be isolated, and further studies of their reactivity were carried out.[10]

The next step of our study consisted of the preparation of 1,3,5-metallahexatrienes, which contain a heterocyclic five-membered ring, by application of the well-known [3+2] cycloaddition of alkynyl Fischer carbenes and nitrones[11] or diazoalkanes.[12] Both types of dipole systems underwent cycloaddition with alkynyl carbenes **1** to afford the expected 1,3,5-metallahexatrienes. We envisaged that annulation of these new dienyl carbenes, by reaction with isocyanides, would provide access to highly substituted 2,3-dihydro-1,2-benzisoxazoles or indazoles.

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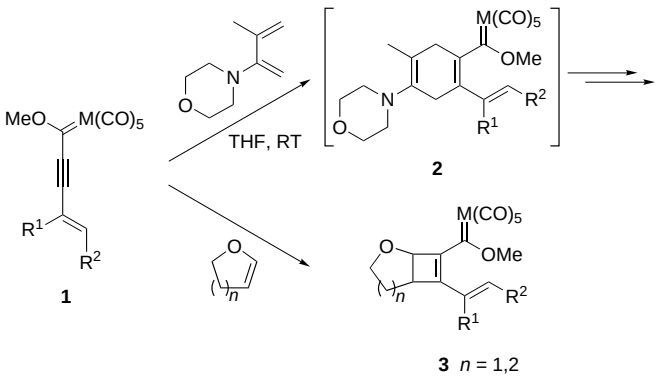


Scheme 2. Cycloaddition reactions of alkenylethynyl alkoxy Fischer complexes and 2-amino-1,3-butadienes or enol ethers.

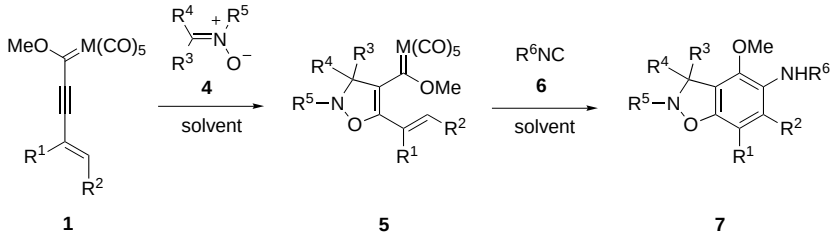
As far as we know, all the reported approaches to these kinds of systems are based on the preparation of the heterocyclic moiety starting from preformed benzene derivatives,[13, 14] which imposes a limitation when hexasubstituted aromatic rings are required as starting materials. However, our methodology would overcome this problem, since the aromatic ring would be generated in the final step by means of a completely regioselective benzannulation reaction. Therefore, the use of three successive processes, [3+2] cycloaddition, isonitrile-insertion, and ring-closure, would provide a good synthetic method for the preparation of the cited benzene fused heterocycles.

Herein we report an easy and efficient preparation of highly functionalized 2,3-dihydro-1,2-benzisoxazoles or indazoles by reaction of isocyanides with stable 1,3,5-metallahexatrienes, which were in turn obtained by dipolar cycloaddition of alkenyl ethynyl Fischer carbene complexes with nitrones or diazoalkanes. Both processes took place under mild conditions, in a completely regioselective fashion, and in high yields.

Abstract in Spanish: *Se han preparado varios ejemplos de complejos dienil carbeno de Fischer estables, de cromo y de volframio, por reacción de cicloadición [3+2] entre alqueniletinil complejos carbeno y nitronas o diazoalcanos. El tratamiento de estos sistemas con dos equivalentes de un isocianuro permite obtener 2,3-dihidro-1,2-benzisoxazoles e indazoles altamente funcionalizados de forma completamente regioselectiva, en condiciones suaves y con altos rendimentos. La misma metodología puede aplicarse a la preparación de naftoisoxazoles a partir de ariletinil carbenos de Fischer. La ruptura en condiciones reductoras del enlace nitrógeno-oxígeno del anillo de isoxazol previamente obtenido conduce a p-aminofenoles sustituidos con excelentes rendimientos.*

Results and Discussion

Preparation of 2,3-dihydro-1,2-benzisoxazoles 7: Treatment of chromium or tungsten alkynyl complexes **1** with equimolar amounts of nitrones **4** at room temperature afforded the expected dienyl carbenes **5** in very good yields (Scheme 3, Table 1). Cycloaddition reactions were completely chemo- and regioselective, since only the isomer shown in Scheme 3 was obtained. This adduct results from the addition of the oxygen atom of the nitrone to the most electrophilic β-position of the Fischer alkynyl carbene. No products derived from the cycloaddition to the double bond of the carbene complex were observed. Reaction times were typically short, both for chromium and tungsten complexes, and the starting materials were consumed in less than half an hour in all cases.



Scheme 3. Preparation of 1,3,5-metallahexatrienes **5** and their cyclization to afford 2,3-dihydro-1,2-benzisoxazoles **7**.

Table 1. Preparation of 1,3,5-metallahexatrienes **5**.[a]

Entry	1	M	R^1	R^2	4	R^3	R^4	R^5	5	Yield [%][b]
1	**1a**	Cr		$(CH_2)_3$	**4a**	Ph	H	*t*Bu	**5a**	97
2	**1b**	W		$(CH_2)_3$	**4a**	Ph	H	*t*Bu	**5b**	98
3	**1c**	Cr		$O(CH_2)_3$	**4a**	Ph	H	*t*Bu	**5c**	95
4	**1d**	Cr		$(CH_2)_4$	**4a**	Ph	H	*t*Bu	**5d**	89
5	**1e**	W		$(CH_2)_4$	**4a**	Ph	H	*t*Bu	**5e**	97
6	**1f**	W	Me	Ph	**4a**	Ph	H	*t*Bu	**5f**	88
7	**1g**	Cr		$CH_2OC(CH_3)_2OCH_2$	**4a**	Ph	H	*t*Bu	**5g**	82
8	**1a**	Cr		$(CH_2)_3$	**4b**	Me	H	*t*Bu	**5h**	98
9	**1c**	Cr		$O(CH_2)_3$	**4b**	Me	H	*t*Bu	**5i**	81
10	**1a**	Cr		$(CH_2)_3$	**4c**	Ph	H	Bn	**5j**	[c]
11	**1a**	Cr		$(CH_2)_3$	**4d**	Me	Me	*i*Pr	**5k**	[c]

[a] *t*Bu = *tert*-butyl, Bn = benzyl, *i*Pr = isopropyl. [b] Reaction conditions: THF, room temperature, 0.5 h. Yields refer to isolated products after flash chromatography. [c] Complex not isolated.

Results displayed in Table 1 are for reactions carried out in tetrahydrofuran (THF), although the [3+2] cycloadditions proceeded with comparable yields and rates when dichloromethane or toluene were used as solvents. This observation, as well as the high regioselectivity of the process, is in agreement with the concerted mechanism proposed for the dipolar cycloaddition of nitrones with alkynyl Fischer carbene complexes.[11]

Most of the dienyl carbenes **5** were stable and could be isolated by flash chromatography. In only one of the cases studied, when nitrone **4c** was used, did the cycloadduct **5j** decompose under the workup conditions, and, therefore, had to be stored in solution (Table 1, entry 10).

2,3-Dihydro-1,2-benzisoxazoles **7** were obtained in very good yields upon treatment of dienyl complexes **5** with two

equivalents of *tert*-butyl- or benzylisocyanide (**6a**,**b**) at room temperature (Scheme 3, Table 2). Based on reported mechanistic studies,[5] the annulation process can be assumed to occur through the insertion of one molecule of isocyanide into the metal–carbon bond of the starting carbene to afford a pentacarbonylmetal-complexed dienyl ketenimine intermediate, followed by a six-electron electrocyclic ring-closure and tautomerism of the resulting imine, to produce the final aniline derivative.[15] The second equivalent of isocyanide is required to demetalate the intermediate formed during the metathesis process. The ketenimine complex has not been detected since the electrocyclization is very fast at room temperature, but its existence is supported by the previous characterization of an analogous species.[16]

Table 2. Preparation of 2,3-dihydro-1,2-benzisoxazoles **7**.[a]

Entry	5	6	R^6	7	Yield [%][b]	
					Stepwise	One-pot
1	**5a**	**6a**	*t*Bu	**7a**	89	77
2	**5b**	**6a**	*t*Bu	**7a**	90	72
3	**5c**	**6a**	*t*Bu	**7b**	78	–
4	**5d**	**6a**	*t*Bu	**7c**	91	–
5	**5e**	**6a**	*t*Bu	**7c**	87	–
6	**5f**	**6a**	*t*Bu	**7d**	72	61
7	**5g**	**6a**	*t*Bu	**7e**	82	79
8	**5h**	**6a**	*t*Bu	**7f**	88	–
9	**5i**	**6a**	*t*Bu	**7g**	94	–
10	**5j**	**6a**	*t*Bu	**7h**	–	83
11	**5k**	**6a**	*t*Bu	**7i**	–	45
12	**5a**	**6b**	Bn	**7j**	92	75

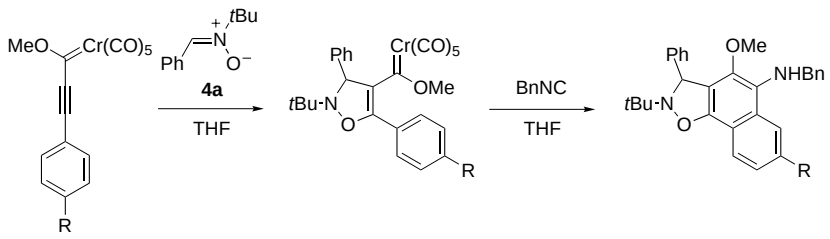
[a] *t*Bu = *tert*-butyl, Bn = benzyl. [b] Yields refer to reactions carried out in THF.

Reactions were monitored by TLC analyses, and total consumption of the starting carbenes **5** was observed in less than three hours in all the cases. The benzannulation process was neither metal nor solvent dependent, and similar yields and reaction times were observed with both chromium and tungsten starting complexes (Table 2, entries 1, 2, 4, and 5), and when THF, diethyl ether, dichloromethane, or toluene were used. Yields shown in Table 2 refer to the reactions carried out in THF. 2,3-Dihydro-1,2-benzisoxazoles **7** can also be obtained in a one-pot process from alkynyl carbenes **1**: once the [3+2] cycloadduct was formed, isocyanide was added to the crude reaction mixture to afford compounds **7** without noticeable loss in the yields (Table 2, entries 1, 2, 6, 7, and 12). This fact enabled us to directly synthesize product **7h**, for which metallahexatriene precursor **5j** could not be isolated (Table 2, entry 10).

The benzannulation process, however, appeared to be sensitive to the substrate. Thus, when the dienyl carbene arising from the reaction of **1a** with the sterically hindered nitrone, *N*-(1-methylethylidene)-1-methylethylamine-*N*-oxide (**4d**) was treated with *tert*-butylisocyanide in THF, only a 45% yield of the corresponding aniline derivative **7i** was isolated (Table 2, entry 11). On the other hand, trimethylsilylcyanide, which is known to react through its isomeric form with Fischer dienyl carbenes,[6] did not allow us to efficiently prepare the desired benzisoxazole derivatives. Although small amounts of the final product were detected in the ^{1}H NMR spectrum of the crude mixture, the major product of the reaction of **5a** with trimethylsilylcyanide was the amide derived from the hydrolysis of the ketenimine intermediate (see Experimental Section). The electrocyclization only took place to a small extent, even after heating in THF at reflux for several days.

Since this protocol provided entry into highly substituted 2,3-dihydro-1,2-benzisoxazoles, we decided to extend this methodology to the preparation of analogous naphthoisoxazoles. The starting Fischer complexes **9** were prepared as described in the literature,[11] by reaction of aryl-substituted alkynyl carbenes **8** with nitrone **4a**. Further treatment with benzylisocyanide in THF gave rise to naphtalene derivatives **10** in moderate yields (Scheme 4). These annulation reactions were slower than those of dienyl complexes **5** and proceeded in lower yields. This is probably due to the higher energetic cost required to break the aromaticity of the ring present in the structure of **9** during the electrocyclization. It is noteworthy that the best results were obtained when complex **9a**, bearing a non-substituted phenyl moiety, was used. The influence of the substituents in the aromatic ring can be explained by assuming that the electron-withdrawing group facilitates the first step of the process, the isonitrile insertion, but makes the intermediate more stable towards the electrocyclization. The opposite behavior could be proposed for a system containing an electron-donating group. Therefore, it seemed reasonable that the global transformation proceeded in lower yields when substituted aromatic rings were used.

Preparation of indazoles 13: Trimethylsilyl diazomethane was chosen as the most suitable dipole for the preparation of 1,3,5-metallahexatrienes from complexes **1**, since it is known that [3+2] cycloadditions of this system with alkynyl Fischer carbenes are more chemoselective for the carbon–carbon triple bond than those of diazomethane.[12] According to literature procedures, a 2 M solution of trimethylsilyl diazomethane in hexanes was slowly added to chromium or tungsten alkynyl complexes **1** in THF at 0 °C. The reaction mixture immediately changed from red to dark orange, and



8a R = H **9a** 95% **10a** 82 %

8b R = OMe **9b** 83% **10b** 68 %

8c R = Cl **9c** 84% **10c** 63 %

Scheme 4. Preparation of 1,3,5-metallahexatrienes **9** and their cyclization to afford naphthoisoxazole derivatives **10**.

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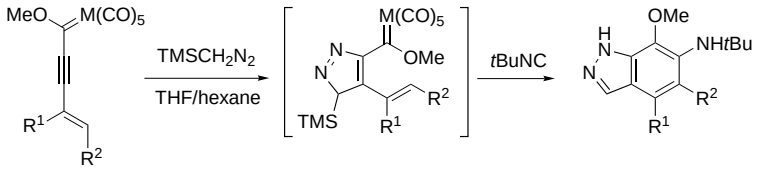


1 **12** **13**

Scheme 5. Preparation of indazoles **13**.

TLC analysis revealed the formation of a new material, presumably metallahexatriene **12** (Scheme 5). These dienyl carbenes decomposed very rapidly when solvents were removed, which prevented their isolation and characterization, but were stable enough to be handled in solution. This behavior is similar to that of metallahexatriene **5j** (Scheme 3, Table 2) and this encouraged us to attempt the tandem isocyanide insertion–electrocyclization. Addition of two equivalents of *tert*-butylisocyanide to the reaction mixture at 0 °C indeed gave indazole derivatives **13**, isolated as single regioisomers, in good yields (Scheme 5, Table 3), and no

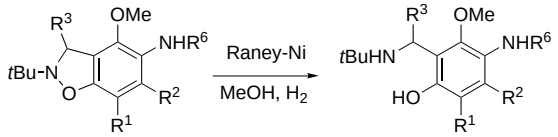
Table 3. Preparation of indazoles **13**.

Entry	**1**	M	R^1	R^2	**13**	Yield [%]
1	**1a**	Cr	$(CH_2)_3$		**13a**	73
2	**1b**	W	$(CH_2)_3$		**13a**	76
3	**1c**	Cr	$O(CH_2)_3$		**13b**	78
4	**1d**	Cr	$(CH_2)_4$		**13c**	79
5	**1h**	Cr	Me	Ph	**13d**	81

products derived from the decomposition of either the starting complex **1**, or the precursor dienyl carbene **12**, were detected. Thus, we can deduce that the dipolar cycloaddition of the alkynyl complex **1** and trimethylsilyl diazomethane proceeded regioselectively to afford the intermediate complexes **12**, which underwent benzannulation, again in a regioselective manner. The trimethylsilyl group was probably removed during the workup, upon exposure to air and sunlight, to cleave the pentacarbonylmetal isocyanide complex formed in the metathesis process.

Regioselective preparation of highly substituted *p*-aminophenols 14 by reductive cleavage of 2,3-dihydro-1,2-benzisoxazoles 7: The synthetic utility of the reaction sequence that leads to 2,3-dihydro-1,2-benzisoxazoles **7** could be enhanced by subsequent transformations which gave entry to new organic structures. It is well known that isoxazole rings are reductively cleaved to give 1,3-enaminoketones, and that their dihydro, tetrahydro, and benzo derivatives also undergo ring-opening to furnish different types of compounds depending on the reduction conditions and the substitution pattern of the starting heterocycles.[17] We decided to take advantage of this behavior to prepare benzene derivatives with three or four electron-donating groups, which appeared to be very interesting compounds, from the 2,3-dihydro-1,2-benzisoxazoles we had just obtained.

Our first attempts to reduce the nitrogen–oxygen bond of compounds **7**, which included treatment with zinc in refluxing acetic acid and palladium-catalyzed hydrogenation, did not give satisfactory results. The former conditions led to complex mixtures of products, and catalytic hydrogenation with 10% Pd/C under 20 bars of hydrogen pressure only resulted in a small conversion of the starting material. The reductive cleavage was finally accomplished by reaction of **7** with Raney nickel in methanol, under a hydrogen atmosphere, to give aminoalcohols **14** in almost quantitative yields (Scheme 6, Table 4). When dihydrobenzisoxazole **7j**, arising from metathesis with benzyl isocyanide, was used, not only was the ring cleaved, but the *N*-benzyl group was also removed to directly afford aniline derivative **14h**. The lower yield observed in this case may be due to the instability of the unprotected aniline towards oxidation (Table 4, entry 8).



7a-e R^6 = *t*Bu **14a-e** R^6 = *t*Bu
7j R^6 = Bn **14f** R^6 = H

Scheme 6. Reductive cleavage of the isoxazole moiety of **7** to afford *p*-aminophenols **14**.

Table 4. Reduction of isoxazole N–O bond to prepare **14**.

Entry	**7**	*t* [h]	**14**	Yield [%]
1	**7a**	12	**14a**	97
2	**7b**	24	**14b**	98
3	**7c**	12	**14c**	95
4	**7d**	12	**14d**	89
5	**7f**	24	**14e**	98
6	**7g**	24	**14f**	94
7	**7e**	48	**14g**	97
8	**7j**	48	**14h**[a]	58

[a] Benzyl moiety was cleaved in the reduction process.

Conclusion

In summary, we have developed an efficient method for the synthesis of highly substituted 2,3-dihydro-1,2-benzisoxazoles **7** or indazoles **13**. [3+2] Cycloaddition of alkynyl Fischer carbene complexes **1**, bearing an alkenyl substituent, with nitrones or trimethylsilyl diazomethane gave rise to novel 1,3,5-metallahexatrienes, which were stable and sometimes isolable compounds. It was also possible to carry out their benzannulation reaction with isocyanides. Both processes proceeded under mild conditions, in a completely regioselective fashion, and with high yields. The final benzene-fused heterocycles could be obtained by two successive reactions or, more conveniently, by a one-pot process starting from alkynyl complexes **1**.

Our protocol provides a good alternative to the reported methods for the synthesis of compounds **7** and **13**, since it does not require highly substituted aromatic rings as starting materials. Instead, the benzene moiety is prepared in the last step by means of a regioselective annulation reaction.

Further transformation of 2,3-dihydro-1,2-benzisoxazoles **7** was carried out to give hexasubstituted aromatic rings **14**, which have at least three electron-donating groups.

Experimental Section

General methods: All reactions were performed under N_2 atmosphere. Tetrahydrofuran (THF), diethyl ether, dichloromethane, and toluene were dried and distilled by standard procedures before use. Column chromatography eluents were distilled prior to use. All other reagents used in the reactions were of the best commercial grade available. Column chromatography was carried out on silica gel 60 (230–400 mesh). R_f data refer to the solvent system in which column chromatography was performed. All melting points are uncorrected. NMR spectra were recorded at 300 or 200 MHz for ^{1}H, and 75 or 50.3 MHz for ^{13}C, with tetramethylsilane as internal standard for ^{1}H and the residual solvent signals as standard for ^{13}C. Chemical shifts are given in ppm. Mass spectra were obtained by EI (70 eV) or MALDI-tof. IR spectra are given in cm^{-1}. General procedures for the preparation and characterization of new compounds are given here with selected specific examples. Analytical and spectroscopic data for all new compounds prepared are available as Supporting Information.

General procedure for the preparation of alkynyl carbene complexes 1: Fischer carbene complexes **1** were prepared by standard methodology from the corresponding acetylenes. 1-Ethynylcyclopentene and 1-ethynylcyclohexene were prepared by dehydratation of 1-ethynylcyclopentanol and of 1-ethynylcyclohexanol, respectively, with $POCl_3$ and pyridine.[18] 6-Ethynyl-3,4-dihydro-2*H*-pyrane was synthesized from 3-bromo-2-ethynyltetrahydropyran, which was in turn obtained by successive treatment of 3,4-dihydro-2*H*-pyran with bromine and ethynylmagnesium bromide.[19] 3-Methyl-4-phenylbut-2-en-1-yne, 4-methoxyphenylethyne, and 4-chlorophenylethyne were prepared by the Corey–Fuchs method starting from the corresponding aldehydes.[20] 5-Ethynyl-4,7-dihydro-2,2-dimethyl-1,3-dioxepine was prepared in our research group by a three-step reaction sequence.[21] Complexes **1a–f** have already been synthesized in our research group,[8, 9] and **1g** was obtained by the same experimental procedure: butyllithium (1.6 M in hexanes, 11 mmol) was added dropwise to a solution of chromium or tungsten hexacarbonyl (10 mmol) and the acetylene (11 mmol) in THF (20 mL) at $-80\,^\circ$C. The mixture was allowed to reach RT overnight and then treated with methyl triflate (20 mmol) at $-20\,^\circ$C. Hydrolysis with a saturated solution of Na_2CO_3 and extractive workup, followed by flash chromatography afforded Fischer carbenes **1**. When the complexes were solids they were further purified by recrystallization in hexanes at $-20\,^\circ$C.

{Pentacarbonyl[(4,7-dihydro-2,2-dimethyl-1,3-dioxepin-5-yl)ethynyl]methoxymethylene}chromium(0) (1g): Prepared from 5-ethynyl-4,7-dihydro-2,2-dimethyl-1,3-dioxepine according to the general procedure described above to afford, after flash chromatography (hexane/dichloromethane 1:1), **1g** in 52% yield as a red solid. $R_f = 0.36$; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta =$ 1.44 (s, 6H), 4.28 (s, 3H), 4.40 (s, 4H), 6.39 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 23.5$ (2 CH_3), 61.4 (CH_2), 62.9 (CH_2), 65.6 (CH_3), 92.2 (C), 102.5 (C), 123.8 (C), 133.8 (C), 144.4 (CH), 216.0 (C), 225.4 (C), 314.5 (C); IR (CH_2Cl_2): $\tilde{\nu} = 2059$, 1942 cm^{-1}; elemental analysis calcd (%) for $C_{16}H_{14}CrO_8$: C 49.75, H 3.65; found: C 49.99, H 3.57.

General procedure for the reaction of nitrones 4a or 4b with alkynyl carbene complexes 1: Dienyl carbene complexes **5a–i** were prepared by reaction of the corresponding complex **1** (1 mmol) and nitrone **4a** or **4b** (1 mmol) in dry THF (10 mL) at RT, under nitrogen atmosphere. The progress of the reaction was monitored by TLC. When the starting complex was consumed (typically after less than half an hour), solvents were removed under vacuum (0.1 mmHg), and the crude reaction mixture was directly purified by chromatography to afford the title compounds.

{[2-*tert*-Butyl-5-(1-cyclopentenyl)-2,3-dihydro-3-phenylisoxazol-4-yl]methoxymethylene}pentacarbonylchromium(0) (5a): Prepared from **1a** and **4a** according to the general procedure described above to afford, after flash chromatography (hexane/dichloromethane 5:1), **5a** in 97% yield as a dark orange solid. $R_f = 0.17$; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.28$ (s, 9H), 2.01 (dt, ^3J(H,H) = 7.8, 7.0 Hz, 2H), 2.53 (dd, ^3J(H,H) = 7.8, 7.0 Hz, 4H), 4.09 (s, 3H), 6.09 (s, 1H), 6.24–6.25 (m, 1H), 7.26–7.42 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 23.3$ (CH_2), 24.9 (3 CH_3), 32.7 (CH_2), 33.2 (CH_2), 61.1 (C), 65.1 (CH_3), 71.2 (CH), 127.5 (2 CH), 127.7 (CH), 128.5 (2 CH), 130.8 (C), 138.4 (CH), 143.0 (C), 143.1 (C), 146.5 (C), 216.6 (4 C), 223.2 (C), 337.9 (C); IR (CH_2Cl_2): $\tilde{\nu} = 2064$, 1939 cm^{-1}; elemental analysis calcd (%) for $C_{25}H_{25}CrNO_7$: C 59.64, H 5.01, N 2.78; found: C 59.41, H 4.87, N 2.90.

{[2-*tert*-Butyl-5-(1-cyclopentenyl)-2,3-dihydro-3-phenylisoxazol-4-yl]methoxymethylene}pentacarbonyltungsten(0) (5b): Prepared from **1b** and **4a** according to the general procedure described above to afford, after flash chromatography (hexane: dichloromethane 1:1), **5b** in 98% yield as a dark orange solid. $R_f = 0.57$; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.25$ (s, 9H), 2.07 (quint, ^3J(H,H) = 7.6 Hz, 2H), 2.55–2.64 (m, 2H), 2.67 (t, ^3J(H,H) = 7.6 Hz, 2H), 4.34 (s, 3H), 5.89 (s, 1H), 6.46–6.49 (m, 1H), 7.34–7.36 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 23.3$ (CH_2), 25.1 (3 CH_3), 33.5 (CH_2), 33.6 (CH_2), 61.5 (C), 67.5 (CH_3), 71.0 (CH), 127.5 (2 CH), 127.6 (CH), 128.5 (2 CH), 131.9 (C), 132.9 (C), 142.2 (CH), 143.0 (C), 157.8 (C), 197.6 (4 C), 202.1 (C), 300.6 (C); IR (CH_2Cl_2): $\tilde{\nu} = 2058$, 1942 cm^{-1}; elemental analysis calcd (%) for $C_{25}H_{25}NO_7W$: C 47.26, H 3.97, N 2.20; found: C 47.08, H 4.12, N 2.51.

General procedure for the preparation of 2,3-dihydro-1,2-benzisoxazoles 7 (procedure A): A solution of complex **5** (0.5 mmol) and isocyanide **6** (1 mmol) in dry THF (10 mL) was stirred under nitrogen atmosphere until TLC analysis revealed the complete consumption of the starting material and the formation of a new compound. For reactions arising from chromium complexes, removal of THF under vacuum, addition of hexane (50 mL), and exposure to sunlight and air for 12 h, followed by flash chromatography afforded the title compounds. For tungsten complexes, the residue was loaded directly onto a silica gel column without previous exposure to light and air.

General procedure for the preparation of 2,3-dihydro-1,2-benzisoxazoles 7 by a one-pot process from carbene complexes 1 (Procedure B): A solution of complex **1** (1 mmol) and nitrone **4a** or **4b** (1 mmol) in dry THF (10 mL) was stirred at RT, under nitrogen atmosphere, until TLC analysis revealed the formation of the corresponding cycloadduct. At that point, isocyanide **6** (2 equiv) was added and the mixture was stirred until the dienyl complex was totally consumed. The same reaction workup described above (sunlight- and air-induced decomplexation, and flash chromatography in the case of chromium complexes, and flash chromatography only for tungsten complexes) led to compounds **7**.

2-*tert*-Butyl-5-*tert*-butylamino-3,6,7,8-tetrahydro-4-methoxy-3-phenyl-2*H*-indeno[5,4:*d*]isoxazole (7a): Prepared according to general procedures A and B described above, both from chromium and tungsten complexes, to afford, after flash chromatography (hexane/ethyl acetate 5:1), **7a** as a light yellow solid. $R_f = 0.33$; m.p. 134–136 °C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta =$ 1.16 (s, 9H), 1.21 (s, 9H), 2.08 (tt, ^3J(H,H) = 7.4, 7.0 Hz, 2H), 2.68 (br s, 1H), 2.87 (t, ^3J(H,H) = 7.4 Hz, 2H), 2.87 (t, ^3J(H,H) = 7.0 Hz, 2H), 3.40 (s, 3H), 5.68 (s, 1H), 7.22–7.37 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 25.4$ (3 CH_3), 25.8 (CH_2), 29.1 (CH_2), 30.3 (3 CH_3), 32.5 (CH_2), 54.7 (C), 58.3 (CH_3), 60.9 (C), 65.6 (CH), 116.4 (C), 118.9 (C), 127.0 (CH), 127.5 (2 CH), 128.2 (2 CH), 143.5 (C), 143.6 (C), 149.3 (C), 149.3 (C), 150.2 (C); HRMS: *m*/*z* calcd for $C_{25}H_{34}N_2O_2$: 394.2620; found: 394.2615; MS (70 eV): *m*/*z* (%): 394 (27), 338 (40), 281 (100), 266 (50), 105 (25), 83 (54); elemental analysis calcd (%) for $C_{25}H_{34}N_2O_2$: C 76.10, H 8.69, N 7.10; found: C 75.91, H 8.35, N 6.89.

2-*tert*-Butyl-5-*tert*-butylamino-3,6,7,8-tetrahydro-4-methoxy-3-methyl-2*H*-indeno[5,4:*d*]isoxazole (7f): Prepared according to general procedure A to afford, after flash chromatography (hexane/ethyl acetate 5:1), **7f** as a light yellow solid. $R_f = 0.28$; m.p. 93–95 °C (decomp); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.12$ (s, 9H), 1.14 (s, 9H), 1.42 (d, ^3J(H,H) = 6.1 Hz, 3H), 2.01 (quint, ^3J(H,H) = 7.0 Hz, 2H), 2.73 (t, ^3J(H,H) = 7.0 Hz, 2H), 2.80 (t, ^3J(H,H) = 7.0 Hz, 2H), 3.82 (s, 3H), 4.69 (q, ^3J(H,H) = 6.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 23.3$ (CH_3), 25.1 (3 CH_3), 25.9 (CH_2), 29.0 (CH_2), 30.3 (3 CH_3), 32.6 (CH_2), 54.8 (C), 57.5 (CH_3), 58.8 (CH), 60.3 (C), 116.5 (C), 119.5 (C), 127.8 (C), 143.1 (C), 149.1 (C), 149.9 (C); HRMS:

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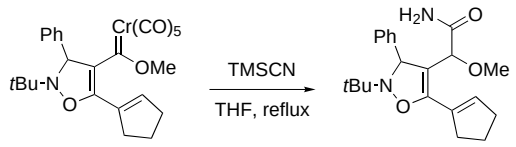
m/z calcd for $C_{20}H_{32}N_2O_2$: 332.2464; found: 332.2464; MS (70 eV): *m/z* (%): 332 (35), 276 (46), 261 (37), 219 (100), 205 (60), 193 (18); elemental analysis calcd (%) for $C_{20}H_{32}N_2O_2$: C 72.25, H 9.70, N 8.43; found C 72.08, H 9.99, N 8.05.

4-(Aminocarbonylmethoxymethyl)-2-*tert*-butyl-5-cyclopent-1-enyl-3-phenyl-2,3-dihydroisoxazole (15): This compound was obtained from the reaction **5a** and trimethylsilyl cyanide (Scheme 7). The protocol was analogous to procedure A, but in this case, the reacting mixture was heated at reflux in THF for 48 h. Flash chromatography (hexane/ethyl acetate 5:1) gave **15** in 43% yield as a light yellow solid. $R_f = 0.30$; m.p. 102–104 °C; ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 1.17$ (s, 9H), 1.98–2.02 (m, 2H), 2.48–2.67 (m, 4H), 3.42 (s, 3H), 4.90 (s, 1H), 5.26 (s, 1H), 6.21–6.22 (m, 1H), 7.34–7.44 (m, 5H); ^{13}C NMR (50.3 MHz, $CDCl_3$): $\delta = 23.1$ (CH_2), 24.8 (3CH_3), 32.8 (CH_2), 33.0 (CH_2), 57.3 (CH), 61.0 (C), 64.5 (CH_3), 68.1 (CH_3), 103.8 (C), 115.2 (C), 127.9 (2CH), 127.9 (CH), 128.4 (2CH), 129.9 (C), 136.4 (CH), 141.8 (C), 150.6 (C); elemental analysis calcd (%) for $C_{21}H_{28}N_2O_3$: C 72.46, H 9.35, N 8.19; found: C 72.79, H 9.12, N 8.28.



5a **15**

Scheme 7. Preparation of amide **15** by reaction of metallahexatriene **5a** and trimethylsilylcyanide.

General procedure for the reaction of nitrone 4a with alkynyl carbene complexes 8: Dienyl carbene complexes **9a–c** were prepared by reaction of the corresponding complex **8** (1 mmol) with nitrone **4a** (1 mmol) in dry THF (10 mL), at RT, under nitrogen atmosphere. The progress of the reaction was monitored by TLC. When the starting complex was consumed, solvents were removed under vacuum (0.1 mmHg), and the crude reaction mixture was purified by chromatography to afford the title compounds.

{[2-*tert*-Butyl-2,3-dihydro-3,5-diphenylisoxazol-4-yl]methoxymethylene}-pentacarbonylchromium(0) (9a): Prepared from **8a** and **4a** according to the general procedure described above. This carbene complex has already been reported in the literature.[11]

{[2-*tert*-Butyl-2,3-dihydro-5-(4-methoxyphenyl)-3-phenylisoxazol-4-yl]-methoxymethylene}pentacarbonylchromium(0) (9b): Prepared from **8b** and **4a** according to the general procedure described above to afford, after flash chromatography (hexane/dichloromethane 5:1), **9b** in 83% yield, as a dark orange oil. $R_f = 0.34$; ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 1.34$ (s, 9H), 3.88 (s, 3H), 4.08 (s, 3H), 6.19 (s, 1H), 7.00 (d, ^3J(H,H) = 8.7 Hz, 2H), 7.30–7.51 (m, 7H); ^{13}C NMR (50.3 MHz, $CDCl_3$): $\delta = 25.1$ (3CH_3), 55.2 (CH_3), 61.3 (C), 65.2 (CH), 71.7 (CH_3), 114.0 (2CH), 120.4 (C), 127.2 (2CH), 127.2 (C), 127.6 (CH), 128.6 (2CH), 129.8 (2CH), 143.1 (C), 151.0 (C), 161.4 (C), 216.5 (4C), 223.0 (C), 335.3(C); IR (CH_2Cl_2): $\tilde{\nu} = 2058$, 1943 cm^{-1}; elemental analysis calcd (%) for $C_{27}H_{25}CrNO_8$: C 59.67, H 4.64, N 2.58; found: C 59.47, H 4.86, N 2.91.

General procedure for the preparation of naphthoisoxazoles 10: A solution of complex **9** (0.5 mmol) and benzylisocyanide **6b** (1 mmol) in dry THF (10 mL) was stirred under nitrogen atmosphere, until TLC analysis revealed the consumption of the starting material and the formation of a new compound. Removal of THF under vacuum, addition of hexane (50 mL) and exposure to sunlight and air for 12 h, followed by flash chromatography, afforded compounds **10**.

2-*tert*-Butyl-5-*tert*-butylamino-2,3-dihydro-4-methoxy-3-phenylnaphtho-[2,1:*d*]isoxazole (10a): Prepared from **9a** and **4b** according to the general procedure described above to afford, after flash chromatography (hexane: ethyl acetate 5:1), **10a** in 82% yield as a light yellow oil. $R_f = 0.32$; ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 1.38$ (s, 9H), 2.51 (d, ^2J(H,H) = 14.2 Hz, 1H), 3.09 (s, 3H), 3.11 (d, ^2J(H,H) = 14.2 Hz, 1H), 5.54 (s, 1H), 7.10–7.15 (m, 2H), 7.31–7.58 (m, 12H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 24.8$ (3CH_3), 46.8 (CH_2), 53.4 (CH), 60.9 (C), 71.8 (CH_3), 78.2 (C), 104.8 (C), 116.3 (C), 126.2 (CH), 127.2 (CH), 127.8 (2CH), 127.8 (2CH), 127.9 (2CH), 128.0 (C), 128.5 (CH), 128.7 (2CH), 128.9 (2CH), 129.0 (CH), 129.0 (C), 134.0 (C), 143.1 (C), 151.2 (C); HRMS: *m/z* calcd for $C_{29}H_{30}N_2O_2$: 438.2307; found: 438.2296; MS (70 eV): *m/z* (%): 438 (7), 361 (46), 305 (100), 291 (22), 105 (92), 77 (30); elemental analysis calcd (%) for $C_{29}H_{30}N_2O_2$: C 79.42, H 6.89, N 6.39; found: C 79.09, H 7.02, N 6.53.

General procedure for the preparation of indazoles 13: Trimethylsilyldiazomethane (1.1 mmol, 2.0 M in hexanes) was added dropwise over 10 min to a solution of complex **1** (1 mmol) in dry THF (10 mL) under a nitrogen atmosphere at 0 °C. The resulting mixture was stirred at the same temperature until TLC analysis revealed the formation of the corresponding cycloadduct. At that point, isocyanide **6a** (2 equiv) was added by syringe and stirring was continued, at RT, until the dienyl complex was totally consumed. For reactions arising from chromium complexes, removal of THF under vacuum, addition of hexane (50 mL) and exposure to sunlight and air for 12 h, followed by flash chromatography, afforded compounds **13**. For tungsten complexes, the residue was loaded directly onto a silica gel column without exposure to light and air.

5-*tert*-Butylamino-3,6,7,8-tetrahydro-4-methoxycyclopenta[*e*]indazole (13a): Prepared from **1a** or **1b** according to the general procedure described above to afford, after flash chromatography (hexane/ethyl acetate 1:1), **13a** in 73% yield as a light yellow solid. $R_f = 0.40$; m.p. 132–134 °C; ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 1.30$ (s, 9H), 2.00 (quint, ^3J(H,H) = 7.4 Hz, 2H), 2.95 (t, ^3J(H,H) = 7.4 Hz, 2H), 3.12 (t, ^3J(H,H) = 7.4 Hz, 2H), 3.94 (s, 3H), 7.96 (br s, 1H); ^{13}C NMR (50.3 MHz, $CDCl_3$): $\delta = 25.3$ (CH_2), 30.6 (3CH_3), 31.9 (CH_2), 32.2 (CH_2), 55.1 (C), 59.1 (CH_3), 118.1 (C), 130.2 (C), 133.3 (CH), 133.8 (C), 134.2 (C), 135.2 (C), 135.9 (C); HRMS: *m/z* calcd for $C_{15}H_{21}N_3O$: 259.1685; found 259.1683; MS (70 eV): *m/z* (%): 171 (100), 158 (38), 149 (36), 143 (65), 131 (40), 116 (62); elemental analysis calcd (%) for $C_{15}H_{21}N_3O$: C 69.47, H 8.16, N 16.20; found: C 69.20, H 8.26, N 16.35.

5-*tert*-Butylamino-3,6,7,8-tetrahydro-4-methoxypyran[2,3:*e*]indazole (13b): Prepared from **1c** according to the general procedure described above to afford, after flash chromatography (hexane: ethyl acetate 1:1), **13b** in 78% yield as a light yellow solid. $R_f = 0.28$; m.p. 144–145 °C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.27$ (s, 9H), 2.05 (tt, ^3J(H,H) = 6.3, 5.1 Hz, 2H), 2.95 (t, ^3J(H,H) = 6.3 Hz, 2H), 3.85 (s, 3H), 3.12 (t, ^3J(H,H) = 5.1 Hz, 2H), 8.04 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 22.5$ (CH_2), 22.5 (CH_2), 30.7 (3CH_3), 55.0 (C), 59.1 (CH_3), 65.8 (CH_2), 109.2 (C), 112.9 (C), 131.6 (C), 132.4 (CH), 134.9 (C), 136.4 (C), 143.7 (C); LRMS (MALDI-tof): *m/z* calcd for $C_{15}H_{21}N_3O_2$: 275; found: 275; elemental analysis calcd (%) for $C_{15}H_{21}N_3O_2$: C 65.43, H 7.69, N 15.26; found: C 65.19, H 7.84, N 14.99.

General procedure for the reductive N–O bond cleavage of benzisoxazoles 7: An excess of Raney nickel (ca. 1 g of 50% slurry in water) was dried under vacuum (0.1 mmHg) and suspended in dry methanol (20 mL), under 1 atmosphere of hydrogen. Compound **7** (0.5 mmol) dissolved in methanol (5 mL) was added by syringe and the mixture was stirred at RT. The reactions were monitored by ^{1}H NMR analysis every 12 h, and stopped when all the starting material had been transformed into the product **14**. Filtration of the Raney nickel through a pad of Celite and flash chromatography afforded the corresponding amino alcohols.

5-*tert*-Butylamino-7-(*tert*-butylaminophenylmethyl)-6-methoxychroman-8-ol (14b): Prepared from **7b** according to the general procedure described above to afford, after flash chromatography (hexane/ethyl acetate 1:1), **14b** in 98% yield as a white solid. $R_f = 0.27$; m.p. 161–163 °C; ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 1.12$ (s, 9H), 1.21 (s, 9H), 1.96–2.02 (m, 2H), 2.67 (t, ^3J(H,H) = 6.4 Hz, 2H), 3.30 (s, 3H), 4.20–4.28 (m, 2H), 5.56 (s, 1H), 7.22–7.42 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 22.3$ (CH_2), 22.7 (CH_2), 28.5 (3CH_3), 30.5 (3CH_3), 52.6 (C), 54.6 (C), 56.5 (CH_3), 59.1 (CH), 65.9 (CH_2), 117.8 (C), 118.8 (C), 127.4 (CH), 127.8 (2CH), 128.2 (C), 128.9 (2CH), 139.9 (C), 143.8 (C), 143.9 (C), 145.6 (C); HRMS: *m/z* calcd for $C_{25}H_{36}N_2O_3$: 412.2726; found: 412.2720; MS (70 eV): *m/z* (%): 412 (5), 339 (27), 324 (20), 268 (100), 58 (30); elemental analysis calcd (%) for $C_{25}H_{36}N_2O_3$: C 72.78, H 8.80, N 6.79; found: C 72.94, H 8.45, N 6.92.

4-*tert*-Butylamino-2-(*tert*-butylaminophenylmethyl)-3-methoxy-5,6,7,8-tetrahydronaphtho-1-ol (14c): Prepared from **7c** according to the general procedure described above to afford, after flash chromatography (hexane/ethyl acetate 5:1), **14c** in 95% yield as a white solid. $R_K = 0.45$; m.p. 159–161 °C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.13$ (s, 9H), 1.20 (s, 9H), 1.76–1.78 (m, 4H), 2.60–2.61 (m, 2H), 2.71–2.73 (m, 2H), 3.35 (s, 3H), 5.59 (s, 1H), 7.19–7.32 (m, 3H), 7.38–7.41 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 22.5$ (CH_2), 23.1 (CH_2), 23.1 (CH_2), 26.4 (CH_2), 28.6 (3CH_3), 30.6

(3 CH_3), 52.4 (C), 54.3 (C), 56.3 (CH_3), 58.6 (CH), 116.3 (C), 120.6 (C), 127.2 (CH), 127.7 (2 CH), 128.5 (C), 128.8 (2 CH), 133.4 (C), 144.3 (C), 150.4 (C), 152.8 (C); HRMS: *m/z* calcd for $C_{26}H_{38}N_2O_2$: 410.2933; found: 410.2947; MS (70 eV): *m/z* (%): 410 (15), 337 (58), 281 (32), 266 (100), 238 (20), 83 (45); elemental analysis calcd (%) for $C_{26}H_{38}N_2O_2$: C 70.06, H 9.33, N 6.82; found: C 70.27, H 9.01, N 6.98.

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