A Metalloradical Approach to *2H*-Chromenes

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Abstract

Cobalt(III)–carbene radicals, generated through metalloradical activation of salicyl *N*-tosylhydrazones by cobalt(II) complexes of porphyrins, readily undergo radical addition to terminal alkynes to produce salicyl-vinyl radical intermediates. Subsequent hydrogen atom transfer (HAT) from the hydroxy group of the salicyl-moiety to the vinyl-radical leads to the formation of 2*H*-chromenes. The Co(II)-catalyzed process can tolerate various substitution patterns and produces the corresponding 2*H*-chromene products in good isolated yields. EPR spectroscopy and radical-trapping experiments with TEMPO are in agreement with the proposed radical mechanism. DFT calculations reveal the formation of the salicyl-vinyl radical intermediate by a metalloradical mediated process. Unexpectedly, subsequent HAT from the hydroxy moiety to the vinyl radical leads to formation of an *o*-quinone methide intermediate, which dissociates spontaneously from the cobalt center and easily undergoes an endo-cyclic, sigmatropic ring-closing reaction to form the final 2*H*-chromene product.

Introduction

2*H*-Chromenes (2*H*-1-benzopyran derivates)[1] are important structural motifs that exist in numerous natural products (e.g. tannins and polyphenols found in teas, fruits, and vegetables) and medicines possessing interesting biological activities (Figure 1). For example, the 2*H*-chromene is a crucial substructure of a wide variety of known pharmaceutical agents and drug candidates with antitumor, antibacterial, antiviral, antioxidative, antide-pressant, antihypertensive, antidiabetic, fungicidal, insecticidal and antiviral activities.[2] Furthermore, 2*H*-chromenes find interesting applications as photochromic materials and in the synthesis of dyes.[3] As a result, considerable efforts have been made for their synthesis over the past decades.[4, 5] Synthetic methods developed so far include Pd-catalyzed ring-closure of 2-isoprenyl phenols,[5a] Claisen-rearrangement of propargyl phenol ethers,[5b] Ru-catalyzed ring-closing methathesis protocols,[5c–f] nucleophilic substitution of chromene acetals (e.g. with allylsilanes, trialkyl-tin compounds[5f] and Grignard reagents[5g,h]) and Petasis-like reactions using vinylic boronate esters, boronic acids and trifluorborates.[5i–k] All of these routes involve multistep reaction sequences and many of them require the use of complicated prefunctionalized fragments, show a limited degree of functional group tolerance and lead to formation of regioisomeric product mixtures.[5l]

Therefore, the development of shorter, more efficient and broadly applicable synthetic routes towards 2*H*-chromenes is certainly in demand. Herein we describe a novel metallo-radical approach.

As stable metalloradicals with well-defined open-shell doublet d^7-electronic configuration, cobalt(II) complexes of porphyrins, [Co^{II}(Por)], have emerged as a new class of catalysts capable of carbene transfer[6] reactions proceeding *via* radical mechanisms involving discrete Co^{III}-carbene radical intermediates (species **C** in Scheme 1 is a relevant example for the reactions described in this study).[7] In comparison with classical electrophilic Fischer-type carbenes, these carbene radical intermediates have a reduced tendency to undergo undesirable carbene dimerisation reactions. Furthermore, they reveal discrete catalytic radical-type reactions. For example, cyclopropanation reactions mediated by [Co(Por)] catalysts proceed via 'carbene radical' addition to the olefinic substrate, thus allowing conversion of electron-deficient olefins.[6,7] In addition, the metalloradical-catalyzed approach was successfully applied for highly enantioselective alkyne cyclopropenation[8] as well as regioselective synthesis of furans.[9]

Recently, we developed a metalloradical-catalyzed carbene carbonylation protocol to synthesize ketenes, using *N*-tosylhydrazones as 'carbene precursors'.[10] The use of *N*-tosylhydrazones[11] as diazo precursors in [Co(Por)]-based metalloradical catalysis was thus far unprecedented, which may open up a new area to bring about new chemical transformations using *in-situ* generated unstable diazo-precursors that are otherwise difficult to handle.[11]

To explore the use of metalloradical catalysis in other radical-induced cyclization reactions, we envisioned the possibility of a new catalytic pathway for the construction of 2*H*-chromenes from salicyl tosylhydrazones and alkynes (Scheme 1). In this process, we anticipated formation of vinyl radical intermediates **D** through radical addition of Co(III)–carbene radical **C** to the alkyne substrate.[8,9] Subsequent hydrogen atom transfer (HAT) from the *ortho*-hydroxy group to the vinyl radical moiety of **D** is then expected to generate the 2*H*-chromene product. In addition to its fundamental importance, such catalytic tandem radical addition processes are synthetically attractive, as they enable the direct synthesis of multi-substituted chromenes from *N*-tosylhydrazones and acetylenes.

Herein, we report a general and regioselective protocol for the one-pot synthesis of 2*H*-chromenes involving intermolecular radical-induced 6π-electrocyclization of acetylenes with salicyl tosylhydrazones using cobalt(II)-based metalloradical catalysis. This unprecedented tandem addition pathway of Co(III)–carbene radicals has a broad substrate scope and can be applied to various combinations of tosylhydrazones and terminal acetylenes, including challenging and electron-deficient alkynes. Furthermore, we disclose a plausible reaction mechanism for these reactions based on a combination of experimental observations, control experiments, labelling experiments, EPR spectroscopy and computational studies (DFT).

Results and Discussion

Initial studies focused on the reaction between tosyl hydrazone **1a** and phenyl acetylene **2a** to produce 2*H*-chromene **3a** (Table 1). Various reaction conditions were screened to optimize the catalytic process and to explore the potential of asymmetric induction. Three different [Co^{II}(Por)] catalysts (Figure 2) were employed: [Co^{II}(**P1**)], [Co^{II}(**P2**)], and the chiral catalyst [Co^{II}(**P3**)] (see Supporting Information for experimental details). The catalysts [Co^{II}(**P2**)] and [Co^{II}(**P3**)] were previously reported,[6] being excellent cyclopropanation catalysts due to the cooperative effect of the H-bond donor motifs in the

second co-ordination sphere.[7,13] Initial experiments were focused on the evaluation of ligand and solvent effects on the possibility of catalytic 2*H*-chromene formation from salicyl tosylhydrazone **1a** and phenylacetylene (**2a**), using the above-mentioned [Co^{II}(Por)] catalysts at 90 °C (Table 1).

Optimization of the reaction conditions revealed that the reaction proceeded most efficiently in nonpolar solvents such as toluene, chlorobenzene or 1,2-dichlorobenzene, whereas reactions in solvents of high polarities such as THF, dioxane, MeCN, and DMF afforded poor yields (Table 1, entries 1–8). Among the series of bases examined such as K$_3$PO$_4$, K$_2$CO$_3$, Cs$_2$CO$_3$, LiO^{t}Bu, NaO^{t}Bu, KO^{t}Bu and NaOMe, the best results were obtained with KO^{t}Bu (Table 1, entries 7–15). Lowering the reaction temperature decreased the yield of **3a** slightly (Table 1, entry 20).

Control experiments showed that no product was obtained in the absence of a [Co^{II}(Por)] catalyst (Table 1, entry 24). While other cobalt(II) sources like CoCl$_2$ and Co(OAc)$_2$ (Table 1, entries 21 and 22) only afforded the 2*H*-chromene product in trace amounts (<5%), other typical carbene transfer catalysts such as Rh$_2$(AcO)$_4$ proved to be essentially ineffective (Table 1, entry 23). Interestingly, CuBr$_2$ produced benzofurans in high yield instead of chromenes, as was recently reported by Wang and co- workers.[12] Notably, these CuBr$_2$ catalyzed benzofuran formation reactions were proposed to proceed *via* completely different, non-radical allene intermediates (Scheme 2).

The catalysts [Co^{II}(**P1**)], [Co^{II}(**P2**)], and [Co^{II}(**P3**)] showed similar activities (Table 1; entries 15–20). However, for salicyl tosylhydrazone substrates containing electron withdrawing groups, the catalysts [Co^{II}(**P2**)] and [Co^{II}(**P3**)] performed better than [Co^{II}(**P1**)] (for example see Table 3, entry 6). Unexpectedly, reactions with the chiral catalyst [Co^{II}(**P3**)] did not result in any significant enantioselectivity (chiral HPLC) under the various reaction conditions applied. In all further catalytic studies, we therefore focussed on reactions with [Co^{II}(**P2**)] in 1,2-dichlorobenzene at 90 °C. To explore the versatility of the metalloradical-catalyzed tandem vinylation-cyclization coupling protocol, several reactions employing a variety of terminal alkynes and *N*-tosylhydrazones were performed using the above optimized reaction conditions. The reaction proved to be tolerant of alkynes **2** containing various functional groups, including aryl, alkyl, naphthyl, and heterocyclic functionalities (Table 2). The reaction was not significantly affected by the substituents on the aromatic ring of the terminal alkyne; both electron-rich (Table 2, entries 2–5) and electron-deficient arylalkynes (Table 2, entries 6–8) were effective. Reactions of naphthyl alkyne and 3-thienylacetylene with *N*-tosylhydrazone **1a** furnished the corresponding 2*H*-chromenes in moderate yields (Table 2, entries 9–10). Alkyl alkynes such as 4-phenyl-1-butyne proved also suitable reaction partners, generating the corresponding 2*H*-chromene in moderate yield (Table 2, entry 11). Reactions with 1,2-disubstituted alkynes did not lead to chromene formation (Table 2, entry 12). Instead, carbene dimerization was observed, along with some other unidentified products, while most of the 1,2-disubstituted alkyne could be recovered from reaction mixture. Carbene dimerization was also observed for reactions of **1a** in absence of alkynes.

To further expand the scope of the reaction, various substituted salicyl *N*-tosylhydrazones were employed as substrates to test the catalytic formation of 2*H*-chromenes using phenylacetylene as a reaction partner.

As shown in Table 3, hydrazones with electron-donating groups at the *meta-*, *para-* or disubstituted at both *meta-*and *para-*positions were all effective, affording the corresponding 2*H*-chromenes **3m**, **3n** and **3o** in good yields (Table 3, entries 1–3). Reactions also proceeded with electron-withdrawing groups on the hydrazone moiety, albeit leading to

lower yields (Table 3, entries 4–7). For example, the use of the salicyl hydrazone **1e** having an electron-withdrawing fluoro atom at the *ortho*-position led to the corresponding chromene in a moderate yield (Table 3, entry 4). Similarly, salicyl hydrazones substituted with bromo atoms are also tolerated in the chromene formation reaction (Table 3, entries 5 and 6).

It is noteworthy that substrate **1h**, having a strong electron-withdrawing *nitro* group at its *para*-position, produced the corresponding chromene **3s** in moderate yield (Table 3, entry 7). However, the presence of strong electron-withdrawing groups on the aromatic ring of the hydrazones made the reactions sluggish and hence longer reaction times were needed. The naphalene-based to-sylhydrazone **1i** gave access to 2*H*-chromene **3t** (Table 3, entry 8), which is of interest in the field of photochromic materials (see also Figure 1).[3]

To shed more light on the catalytic reaction mechanism, we performed a set of control experiments, labelling studies and EPR spectroscopic investigations. Additionally, we explored the mechanism computationally.

EPR spectroscopic analysis of the reaction mixture using salicyl tosylhydrazone (**1a**), phenylacetylene (**2a**) and [Co^{II}(**P1**)] (sample taken from a solution under the applied catalytic reaction conditions, EPR spectrum recorded at RT) reveals a strong EPR signal indicating the formation of an organic radical or ligand radical species (see Figure 3). An identical EPR signal was detected in absence of phenyl acetylene. Some hyperfine structure is visible, but the pattern is poorly resolved (spectral simulations show a maximum isotropic proton hyperfine splitting $A^{iso}_H < 12$ MHz; in case of cobalt hyperfine splitting, $A^{iso}_{Co} < 8$ MHz). The species detected may stem from carbene radical **C** (see Scheme 1), but detection of a stable free organic radical or a ligand radical species formed from **C** as a side-product cannot be excluded. The detection of an identical signal, of roughly the same intensity, in the presence and absence of excess phenyl acetylene makes it actually rather unlikely that the signal detected stems directly from species **C** (DFT calculations shown in Scheme 3 suggest that species **C** should rapidly react with phenyl acetylene to form the more stable species **D** or **H**). However, irrespective of the exact interpretation of the EPR signal detected, these data are clearly indicative for formation of radicals upon reacting [Co(Por)] catalyst with diazo compounds.[7] In good agreement, no 2*H*-chromene formation was observed when the catalytic reaction was performed in the presence of an excess of the radical scavenger TEMPO (~10 equivalents with respect to the catalyst; TEMPO = 2,2,6,6-tetramethyl-piperidinoxyl). These data clearly support a radical-type mechanism (for the proposed mechanism, see Scheme 3). Furthermore, isotope-labelling experiments using *N*-tosylhydrazone **1a–D**, containing a deuterium-substituted phenoxyl moiety (70% ArO-*D* based on ^{1}H NMR spectrocopy), produces the corresponding 2*H*-chromenes with a deuterium atom at the expected 2-position (60% based on ^{1}H NMR). This is suggestive for direct hydrogen atom transfer (HAT) from the phenoxyl moiety to the vinyl-radical in intermediate **D** (Scheme 3).

The mechanism was further investigated computationally using DFT methods (see experimental section and Supporting Information for details). Plausible radical-type pathways were investigated at the BP86, def2-TZVP level, using the non-functionalized [Co(Por)] system as a simplified catalyst model (Scheme 3). The choice of the computational method is in line with our previous computational studies, dealing with closely related catalytic group-transfer reactions mediated by [Co(Por)] systems proceeding via similar carbene-[7, 10] and nitrene-radical intermediates.[13] We evaluated the mechanism both at the uncorrected DFT level and with DFT-D3 to include Grimme's dispersion corrections.

As expected, dispersion corrections have a profound influence on the substrate binding affinity of the cobalt centre, making formation of diazo adduct **B** exergonic rather than endergonic. However, the corrections have little influence on the relative transition state barriers of the subsequent steps, and overall the DFT-D3 and DFT reaction profiles are very similar. Further discussion is focussed on the calculated DFT-D3 relative free energies (ΔG°_{298K}).

Elimination of N_2 from **B** via **TS1** (barrier: $\Delta G^{\ddagger} = +8.47$ kcal mol^{-1}) is exergonic ($\Delta G^{\circ} = -14.75$ kcal mol^{-1}), producing the key cobalt(III)-carbene radical intermediate **C** (Scheme 3) similar to 'carbene radical' formation in the previously reported cyclopropanation mechanism with [Co(Por)] species.[7] Species **C** formed should be in rapid equilibrium with 'bridging carbene' **C'** according to these calculations. Related species were previously detected with EPR spectroscopy in frozen solutions.[7a]

Radical addition of **C** to the phenylacetylene substrate produces 'vinyl radical' species **D** in an exergonic process ($\Delta G^{\circ} = -22.99$ kcal mol^{-1}) via a low barrier ($\Delta G^{\ddagger} = +5.04$ kcal mol^{-1}) transition state **TS2**. Spin density plots reveal that both **C** and **D** are substrate-centred radicals (Figure 4). The unpaired electron in 'carbene radical' **C** has a high spin density at the 'carbene carbon' and is further delocalised over the adjacent hydroxyl-phenyl moiety. The unpaired electron of 'vinyl-radical' species **D** has a high spin density at the expected vinyl position and is further delocalized over the adjacent phenyl moiety (Figure 4).

Two conceivable reaction pathways from species **D** were considered in the DFT calculations (Scheme 3): Productive formation of 2*H*-chromene **G** and non-productive formation of cyclopropene **I** (Scheme 3). Overall 2*H*-chromene formation is much more exergonic ($\Delta G^{\circ} = -73.56$ kcal mol^{-1}) than cyclopropene formation ($\Delta G^{\circ} = -38.94$ kcal mol^{-1}). The productive 2*H*-chromene formation pathway involves hydrogen atom transfer (HAT) from the hydroxyl-moiety of **D** to its vinyl-radical moiety.

The rate limiting transition state barrier for HAT via **TS3** ($\Delta G^{\ddagger} = +17.47$ kcal mol^{-1}) is easily accessible under the applied reaction conditions. In agreement with these DFT calculations, experimental data reveal a small but significant KIE of 1.3 ± 0.1. This value was determined from the **3a**/**3a–D** product ratio obtained in an internal competition experiment using **1a** and **1a–D** in a 1:1 ratio. Note that the absolute value of the KIE determined in this manner should be treated with some care. It is based on deuterium labeling of a rather acidic C-H bond of product **3a** in a reaction performed under basic conditions at elevated temperatures. Under these conditions, H/D-scrambling between **3a** and unreacted **1a–D** cannot be excluded and is even likely. Hence, the measured KIE value puts a lower limit to the intrinsic KIE for HAT.

Unexpectedly, the HAT process does not produce a stable phenoxyl-radical species according to DFT. Instead, spontaneous dissociation of the substituted *trans*-configured *o*-quinone methide **E** is observed, as a result of simultaneous Co-C bond homolysis during HAT via **TS3**.

Formation of **E** is exergonic ($\Delta G^{\circ} = -20.32$ kcal mol^{-1}). Rotation about the C-C single bond in **E** produces the *cis*-configured *o*-quinone methide **F**, which easily undergoes endo-cyclic ring-closure via **TS4** ($\Delta G^{\ddagger} = +6.09$ kcal mol^{-1}) to form the final 2*H*-chromene product **G**. Related thermal (non-catalyzed) sigmatropic rearrangements of other (proposed) *o*-quinone methide intermediates, prepared via entirely different routes, have previously been reported to produce 2*H*-chromenes.[4a,14] Hence, according to DFT, the final ring-closing steps required for 2*H*-chromene formation occur outside the coordination sphere of cobalt, far away from the chiral influence of the catalyst. Considering that these ring-closing

steps determine the enantioselectivity of the reaction, the computational results are in line with the experimental observations showing 2*H*-chromene formation without asymmetric induction, despite using the chiral [Co^{II}(**P3**)] catalyst (Figure 2) known to be a highly enantioselective carbene-transfer catalyst in other reactions.[6–9]

Besides 2*H*-chromene formation, intermediate **D** is also expected to undergo easy formation of a cyclopropene ring (Scheme 3). Considering that the same catalysts as used in the present study were previously shown to be active for alkyne cyclopropenation,[8] these reactions should proceed via similar intermediates. However, aryl cyclopropenes similar to **I** tend to be (very) unstable,[15] and thus far only acceptor-type carbenes have been reported as suitable reactions partners in [Co^{II}(Por)]-catalyzed cyclopropenation reactions of aryl acetylenes.[8] In agreement with the reported cyclopropenation activity, formation of **I** is feasible. In fact, the **TS5** barrier for ring-closure towards **I** is even lower than the rate limiting **TS3** barrier for HAT in the productive pathway for 2*H*-chromene formation. However, cyclopropenation is much less exergonic, and is calculated to be reversible under the applied reaction conditions. The same transition state **TS5** allows for regeneration of intermediate **D** to re-enter into the productive, much more exergonic pathway leading to 2*H*-chromenes. Hence, 2*H*-chromene formation rather than cyclopropene formation is a thermodynamically controlled feature, made kinetically possible by the catalyst. The calculations are in excellent agreement with the experimental observations, showing only 2*H*-chromene formation without cyclopropene side-products.

Conclusions

In summary, we have developed a new one-pot protocol for the regioselective synthesis of 2*H*-chromenes. These reactions proceed via radical-induced addition-cyclization of terminal alkynes with carbene radicals. Salicyl *N*-tosylhydrazones are used as convenient carbene-radical precursors in these new cobalt(II)-metalloradical mediated reactions. This straightforward methodology has a broad substrate scope and can be applied for various salicyl *N*-tosylhydrazones compounds with different substitutents and terminal alkynes. The cobalt(II)-mediated process provides a direct method for diastereoselective synthesis of 2*H*-chromenes from simple and readily available organic building blocks. To the best of our knowledge, the reactions described in this paper are the first examples of cobalt(II)-based metalloradical transformations leading to formation of six-membered heterocyclic ring structures. The catalytic process proceeds via remarkably selective tandem radical addition-cyclization reactions, involving radical addition of unusual carbene-radical intermediates to alkynes, followed by HAT and subsequent ring-closure. The successful development of this new catalytic reaction is expected to open a heretofore unexplored research avenue, which hopefully triggers the further development of catalytic radical-induced (6π-electro)cyclization processes for selective syntheses of diverse and unusual heterocycles that are difficult to prepare otherwise.

Experimental Section

General Considerations

All manipulations were performed under a nitrogen atmosphere using standard Schlenk techniques. All solvents used for catalysis were dried over and distilled from sodium (toluene) or CaH$_2$ (dichloromethane, hexane, ethyl acetate, methanol). All the cobalt-porphyrin catalysts [Co^{II}(**P1**)], [Co^{II}(**P2**)] [Co^{II}(**P3**)], and N tosylhydrazone sodium salts were synthesized according to published procedures.[7a,8,11] All the alkynes were used as purchased from Aldrich. All other chemicals were purchased from commercial suppliers and used without further purification. NMR spectra (^1H and ^{13}C) were measured on a Varian

INOVA 500 MHz (125 MHZ for ^{13}C), a Bruker AV400 (100 MHZ for ^{13}C) or a Varian MERCURY 300 MHz (75 MHZ for ^{13}C) spectrometer. Mass spectra of the newly synthesised compounds were recorded in Agilent-5973 GC-MS spectrometer the corresponding HRMS data were recorded on JEOL AccuTOF 4G *via* direct injection probe. Elemental analysis of the newly synthesized complexes were performed by the Mikroanalytisches Laboratorium Kolbe, Germany. EPR spectra were recorded on a Bruker EMXplus spectrometer.

General Procedure for Cyclization of Salicyl Tosylhydrazones and Terminal Alkynes

Under a nitrogen atmosphere, the respective ([Co^{II}(Por)] catalyst (2 mol %) and salicyl tosylhydrazone (**1a–i**) (0.3 mmol) were added to a flame-dried Schlenk tube. The tube was capped with a Teflon screw cap, evacuated, and backfilled with nitrogen. The screw cap was replaced with a rubber septum. Base KO^{t}Bu (3 equiv.; 0.9 mmol) and the terminal alkyne (**2a–l**) (3 equiv.; 1 mmol) dissolved in 4 ml 1,2-dichlorobenzene (anhydrous) were added at once *via* a syringe. The Schlenk tube was then placed in an oil bath and heated to the desired temperature for a set period. After the reaction finished, the resulting mixture was concentrated and the residue was purified by flash chromatography (silica gel) or preparative TLC to give the products (**3a–t**). Up to 40% of the starting alkyne could be recovered from the reaction mixture.

Deuterium-Labelling Experiment and KIE measurement

Deuterium-labelled salicyl tosylhydrazone (**1b**) was synthesised by stirring the corresponding non-labelled tosylhydrazone in d$_6$-DMSO-D$_2$O mixture for 24 h. 70% of deuterium incorporation, as determined by ^{1}H-NMR spectroscopy, was found in the resulting deuterated-*N*-tosylhydrazone. The catalytic reaction with the deuterium-labelled (70%) tosylhydrazone (**1a**) and phenylacetelene (**2a**) was performed in absolutely inert atmosphere using deuterated bromobenzene as the solvent. ^{1}H NMR spectroscopy revealed 60% deuterium incorporation (85% w.r.t starting deuterium labelled *N*-tosylhydrazone) at the C2-position of the 2*H*-chromene product in the crude reaction mixture. The KIE was calculated from the **3a**/**3a–D** product ratio (deuterated 2*D*-chromene *vs* non-deuterated 2*H*-chromene product, as determined by ^{1}H NMR integration) obtained in an internal competition experiment using non-deuterated salicyl tosylhydrazone 1**a** and deuterated **1a–D** in a 1:1 ratio (one equivalent of alkyne) under the optimized reaction conditions described above.

EPR Spectra of Catalytic Reaction Mixtures

A reaction mixture consisting of salicyl tosylhydrazone **1a** (0.5 mmol), phenylacetylene (1.5 mmol), KO^{t}Bu (1 mmol) and cobalt catalyst [Co^{II}(**P1**)] (Co(TPP)) (15 mol%) in 5 ml toluene was heated to 90 °C for a short while before recording an EPR spectrum at RT. The spectrum (Figure 3) revealed an intense signal at $g = 2.0044$.

Computational Details

Geometry optimizations were carried out with the Turbomole program package[16] coupled to the PQS Baker optimizer[17] via the BOpt package,[18] at the spin unrestricted ri-DFT level using the BP86[19] functional and the resolution-of-identity (ri) method.[20] We optimized the geometries of all stationary points at the def2-TZVP basis set level,[21] both with and without Grimme's dispersion corrections (disp3 version).[22] The identity of the transition states was confirmed by following the imaginary frequency in both directions (IRC). All minima (no imaginary frequencies) and transition states (one imaginary frequency) were characterized by calculating the Hessian matrix. ZPE and gas-phase thermal corrections (entropy and enthalpy, 298 K, 1 bar) from these analyses were calculated. The relative (free) energies

obtained from these calculations are reported in Scheme 3 and in Table S1 (Supporting Information).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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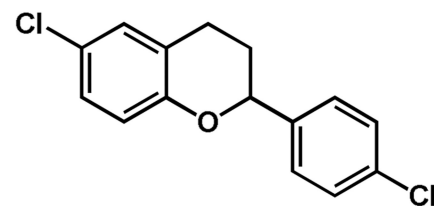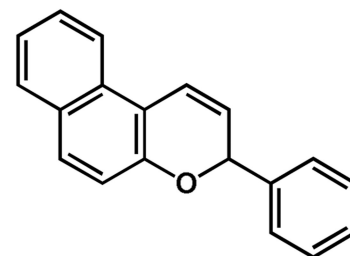22. Grimme S, Antony J, Ehrlich S, Krieg H. J. Chem. Phys. 2010; 132:154104. [PubMed: 20423165]
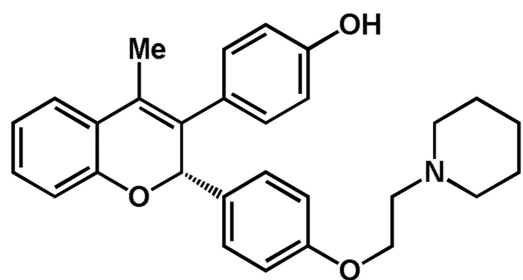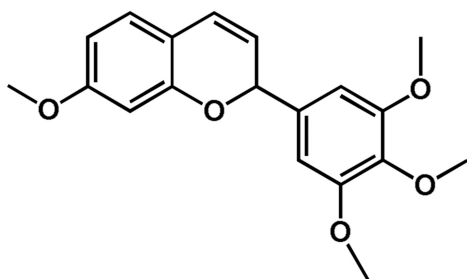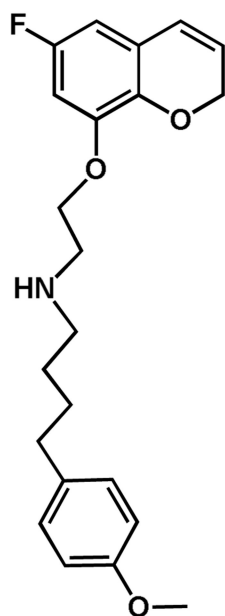
Figure 1.
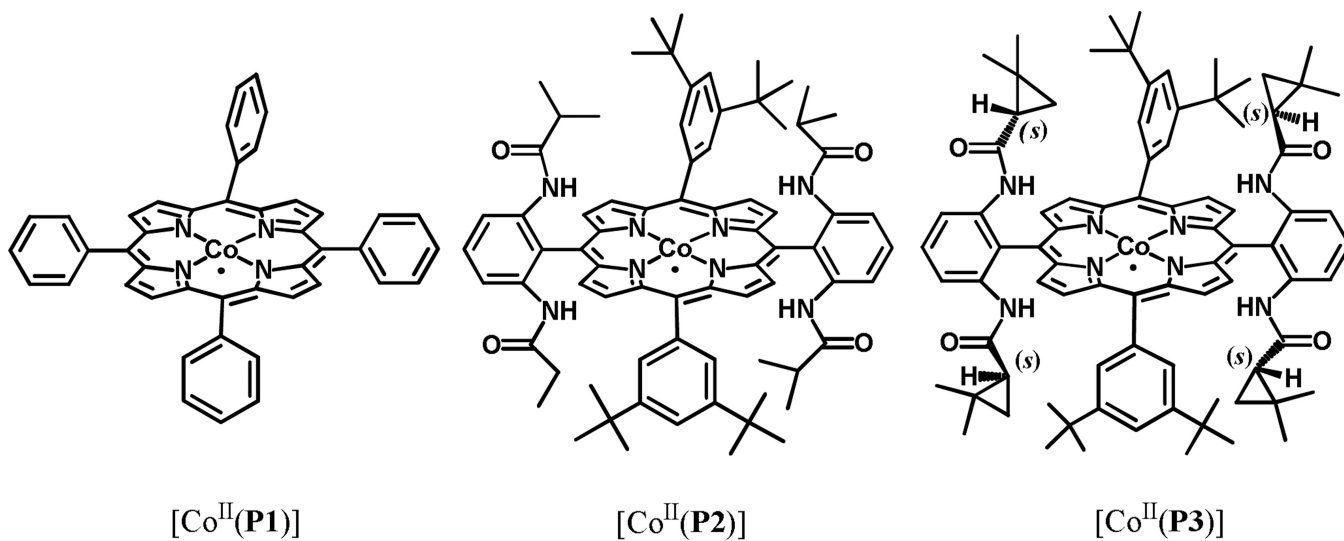Selected examples of pharmacologically active and photochromic compounds based on 2*H*-chromene and related scaffolds.

$[Co^{II}(\mathbf{P1})]$ $[Co^{II}(\mathbf{P2})]$ $[Co^{II}(\mathbf{P3})]$

Figure 2.
Structures of cobalt(II) complexes of porphyrins: **P1** = Tetraphenylporphyrin; **P2** = 3,5-Di^{t}Bu-IbuPhyrin; **P3** = 3,5-Di^{t}Bu-ChenPhyrin.
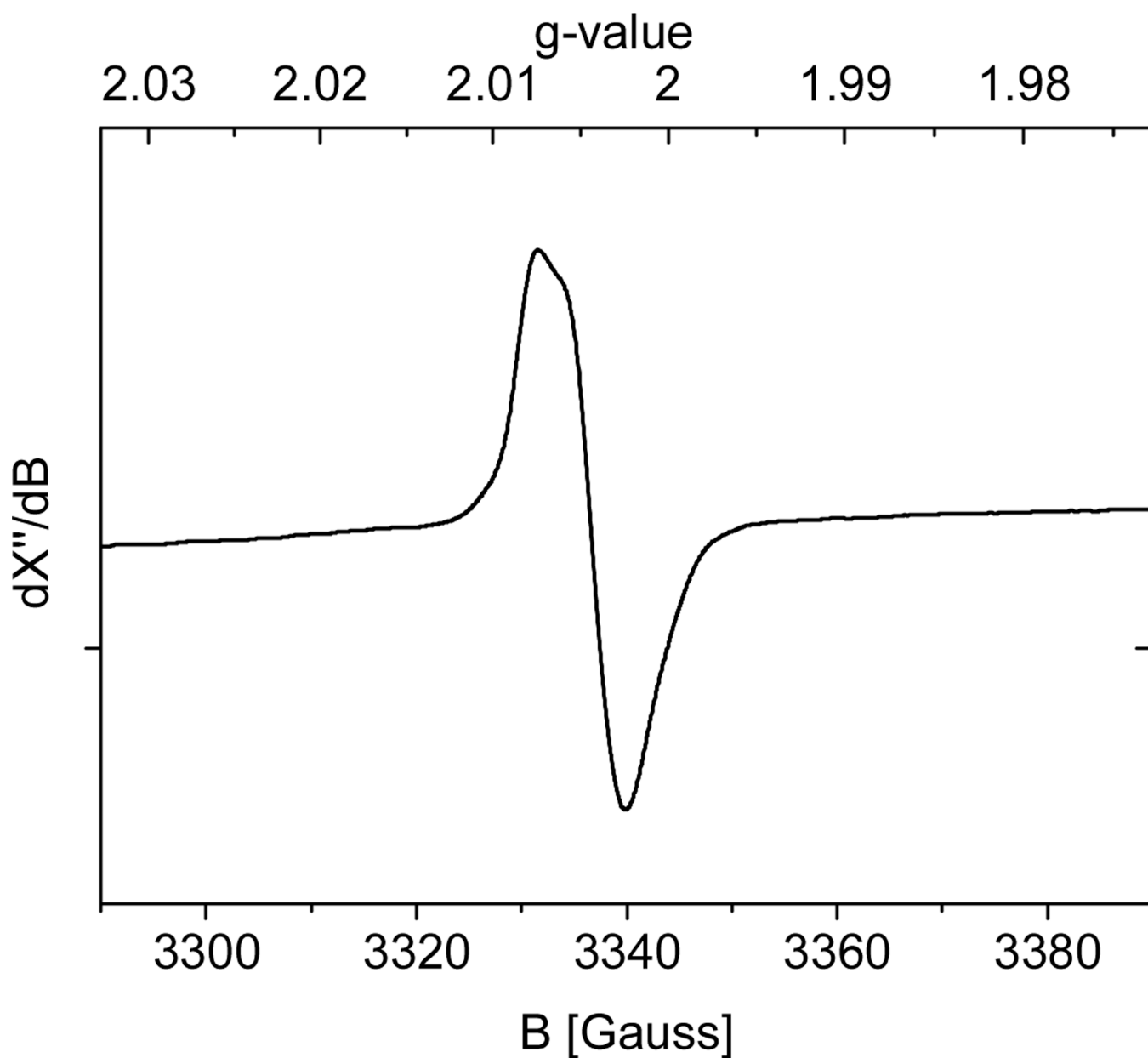
Figure 3.
X-band EPR spectrum recorded from a reaction mixture of salicyl tosylhydrazone **1a**, phenyl acetylene, KO^{t}Bu and cobalt catalyst [Co^{II}(**P1**)] in toluene solution. Spectrum recorded at RT. Frequency = 9.360420 GHz, modulation amplitude 2 gauss, microwave power 20 mW.
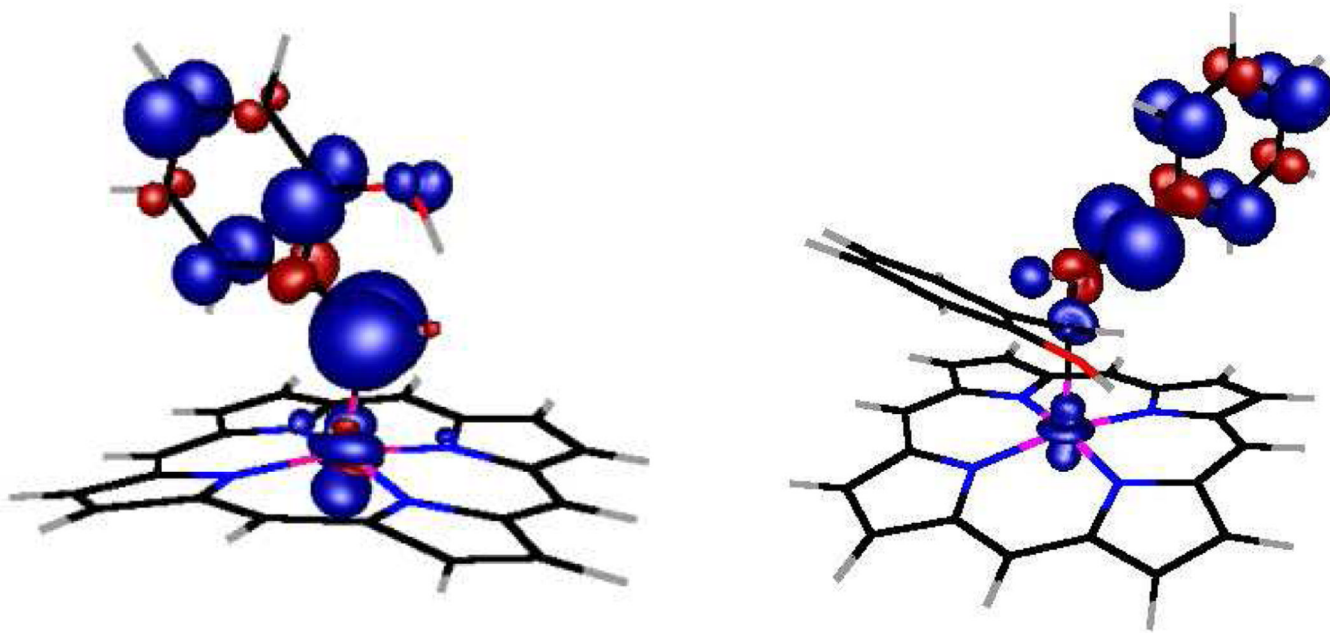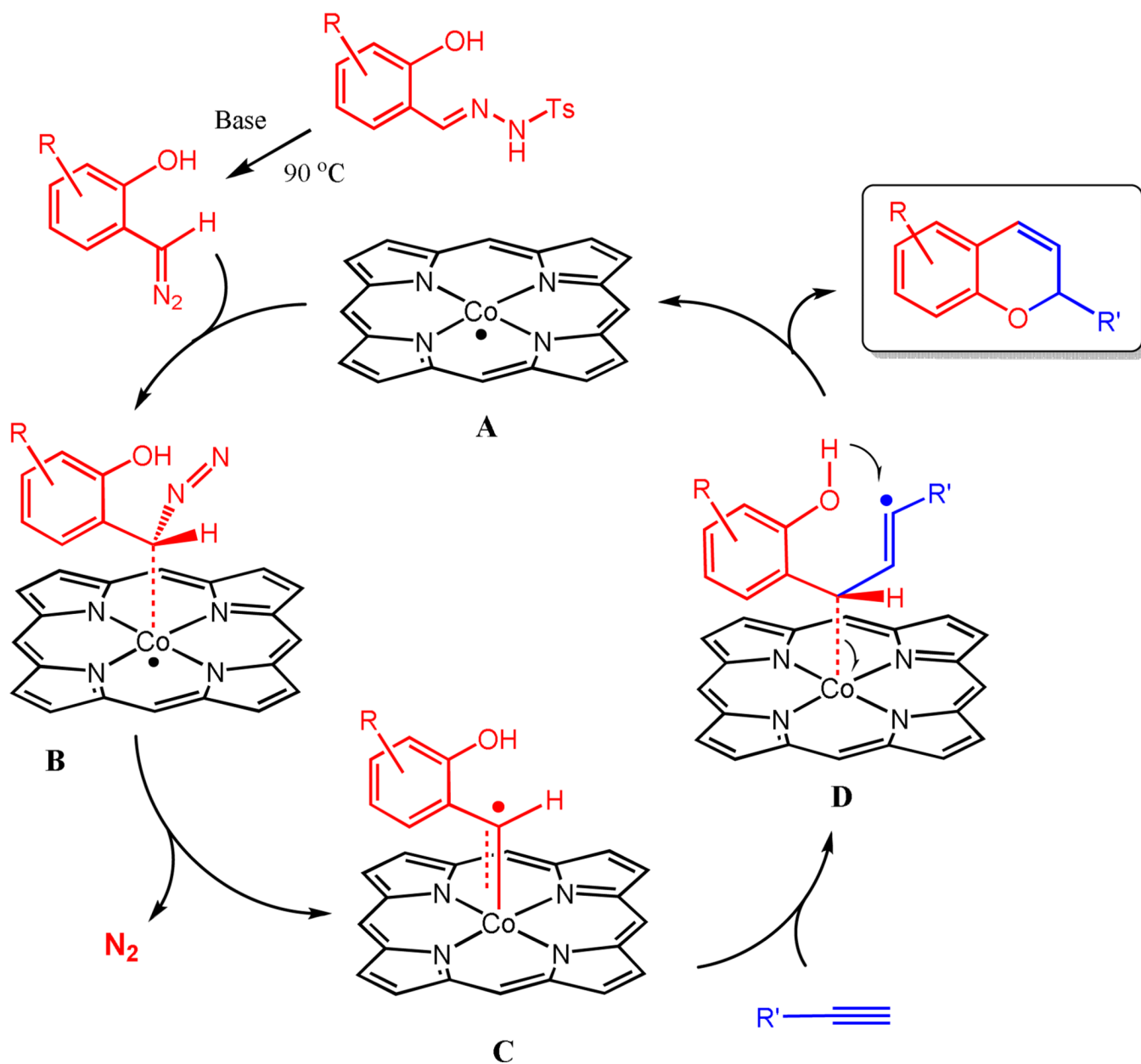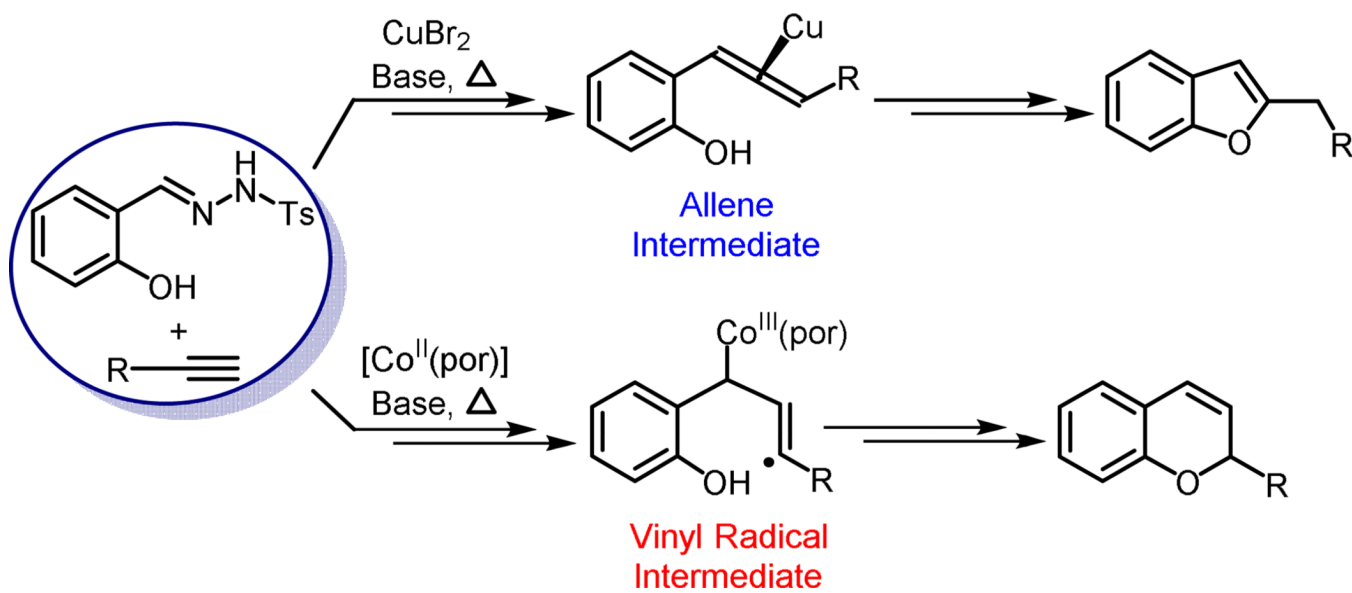
Figure 4.
(**a**) Spin density plots of the DFT-optimized "carbene radical" species **C** (left) and "vinyl radical" species **D** (right).

Scheme 1.
Simplified representation of the [Co^{II}(Por)]-catalyzed metalloradical coupling-cyclization protocol using alkynes and salicyl tosylhydrazones to produce 2*H*-chromenes.

Scheme 2.
Proposed non-radical CuBr$_2$-catalyzed cyclizations (top) *versus* radical-type [Co^{II}(Por)]-catalyzed cyclizations (bottom) of terminal alkynes with salicyl carbenes generated from the corresponding tosylhydrazones.
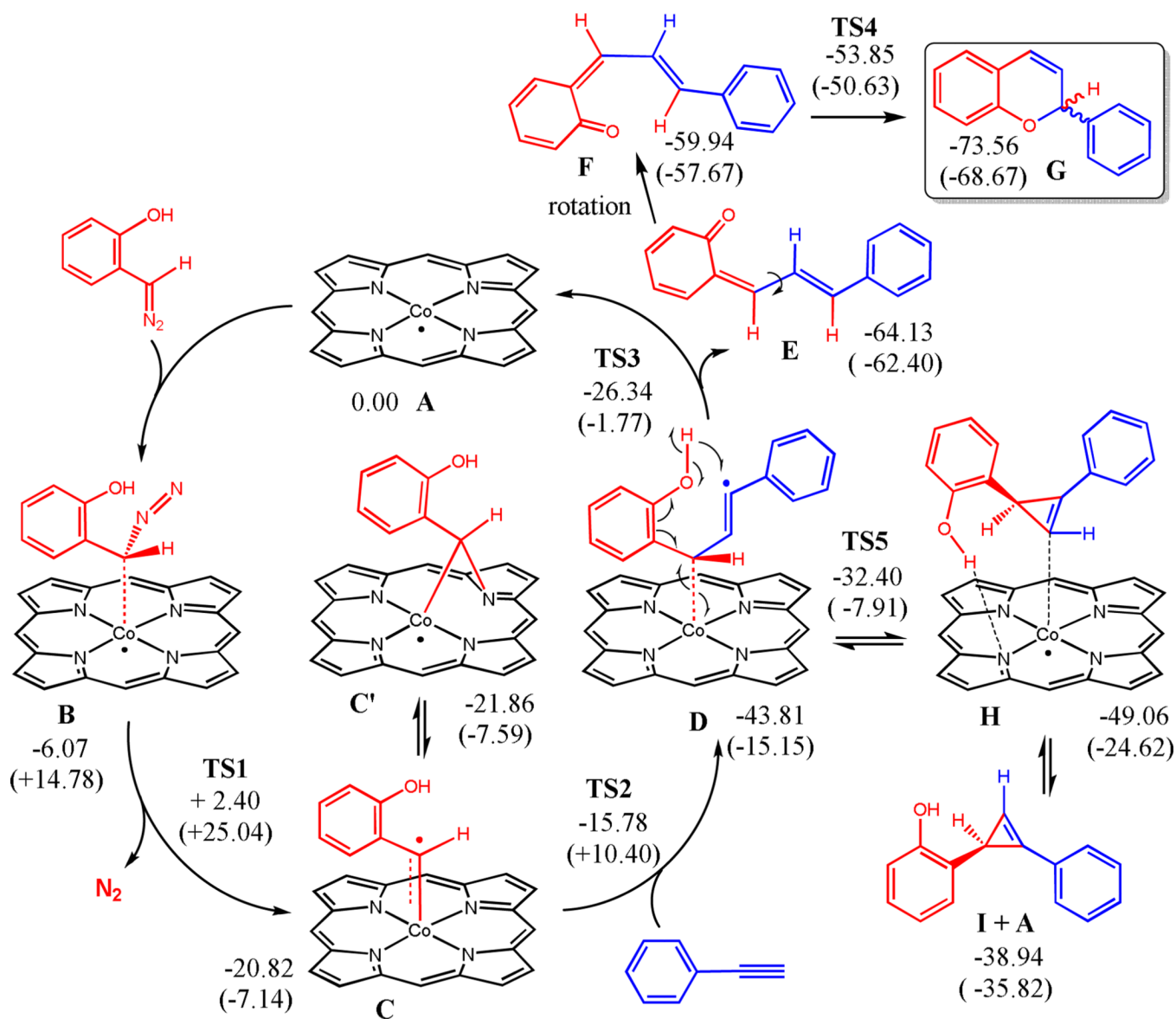
Scheme 3.
[Co(Por)]-catalysed metalloradical coupling-cyclization of alkynes and salicyl tosylhydrazones. DFT-D3 calculated (Turbomole BP86, def2-TZVP) free energies (ΔG^o_{298K}) in kcal mol^{-1} (DFT free energies without dispersion corrections between brackets). All energies, including the transition states, are reported with respect to species **A** as the reference point.

Table 1

Conditions of [Co^{II}(Por)]-catalysed 2*H*-chromene synthesis using salicyl *N*-tosylhydrazone and phenyl acetylene.[a–c]
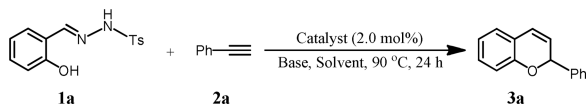
| Entry	Catalyst	Base	Solvent	Yield(%)
1	[Co^{II}(**P1**)]	Cs$_2$CO$_3$	PhMe	45
2[c]	[Co^{II}(**P1**)]	Cs$_2$CO$_3$	THF	35
3	[Co^{II}(**P1**)]	Cs$_2$CO$_3$	Dioxane	25
4[c]	[Co^{II}(**P1**)]	Cs$_2$CO$_3$	DCE	40
5[c]	[Co^{II}(**P1**)]	Cs$_2$CO$_3$	MeCN	<5
6	[Co^{II}(**P1**)]	Cs$_2$CO$_3$	DMF	0
7	[Co^{II}(**P1**)]	Cs$_2$CO$_3$	PhCl	70
8	[Co^{II}(**P1**)]	Cs$_2$CO$_3$	1,2-PhCl$_2$	70
9	[Co^{II}(**P1**)]	K$_2$CO$_3$	PhCl	20
10	[Co^{II}(**P1**)]	KHCO$_3$	PhCl	<10
11	[Co^{II}(**P1**)]	K$_3$PO$_4$	PhCl	20–25
12	[Co^{II}(**P1**)]	NaOMe	PhCl	75
13	[Co^{II}(**P1**)]	LiO^{t}Bu	PhCl	20
14	[Co^{II}(**P1**)]	NaO^{t}Bu	PhCl	60–65
15	[Co^{II}(**P1**)]	KO^{t}Bu	PhCl	77
16	[Co^{II}(**P2**)]	KO^{t}Bu	PhCl	75
17	[Co^{II}(**P3**)]	KO^{t}Bu	PhCl	77
18	[Co^{II}(**P2**)]	KO^{t}Bu	1,2-PhCl$_2$	77
19	[Co^{II}(**P3**)]	KO^{t}Bu	1,2-PhCl$_2$	78
20[d]	[Co^{II}(**P2**)]	KO^{t}Bu	1,2-PhCl$_2$	70
21	Co^{II}Cl$_2$	KO^{t}Bu	1,2-PhCl$_2$	<5
22	Co^{II}(OAc)$_2$	KO^{t}Bu	1,2-PhCl$_2$	<5
23	Rh$^{II}_2$(OAc)$_4$	KO^{t}Bu	1,2-PhCl$_2$	0
24	None	KO^{t}Bu	1,2-PhCl$_2$	0

[a]Stoichiometry: *N*-tosylhydrazone (**1a**) (0.3 mmol; 1.0 equiv.) and alkyne (**2a**) (1.0 mmol; 3.0 equiv.).

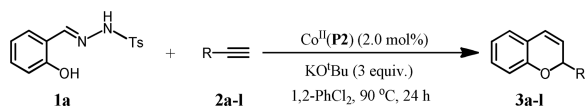[b]*Isolated* yields after column chromatography.

[c]Reaction temperature: 60 °C.

[d]Reaction temperature: 55 °C.

Table 2

Reaction of *N*-tosylhydrazone **1a** with various terminal alkynes catalyzed by [Co^{II}(**P2**)].[a,b]
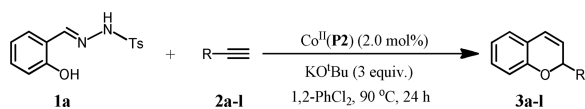
Entry	Alkyne	Product	Yield (%)
1	Ph—≡ (2a)	(3a)	75
2	(2b)	(3b)	71
3	(2c)	(3c)	73
4	MeO— (2d)	(3d)	69
5	(2h)	(3e)	62
6	F— (2e)	(3f)	80
7	Br— (2f)	(3g)	73
8	F$_3$C— (2g)	(3h)	81
9	(2i)	(3i)	58
10	(2j)	(3j)	71

Table 3

[Co^{II}(**P2**)]-catalyzed reaction of *N*-tosyl-hydrazones **1b–i** with phenyl acetylene.[a–d]
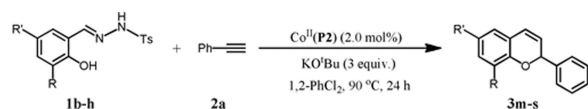
Entry	Hydrazone	Product	Yield (%)
1	(1b)	(3m)	79
2	(1c)	(3n)	73
3	(1d)	(3o)	75
4[c]	(1e)	(3p)	57
5[c]	(1f)	(3q)	45
6[c]	(1g)	(3r)	25 (14)[d]
7[c]	(1h)	(3s)	35
8[c]	(1i)	(3t)	44

[a]Stoichiometry *N*-tosylhydrazone (**1a–i**) (0.3 mmol; 1.0 equiv.) : alkyne (**2a**) (1.0 mmol; 3.0 equiv.).

[b]*Isolated* yields after chromatography.

[c]Reaction time 40h.

[d]Yield with [Co^{II}(**P1**)].