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Metalloradical Approach to 2*H*-Chromenes

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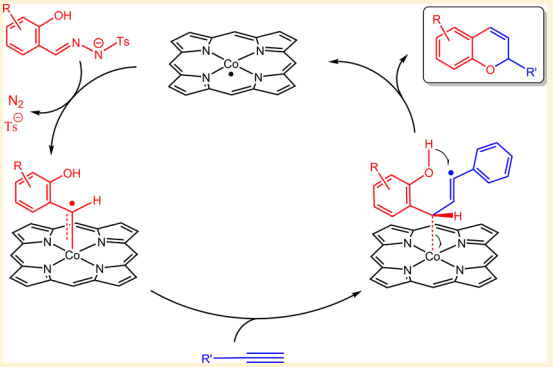
Supporting Information

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 endocyclic, 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).

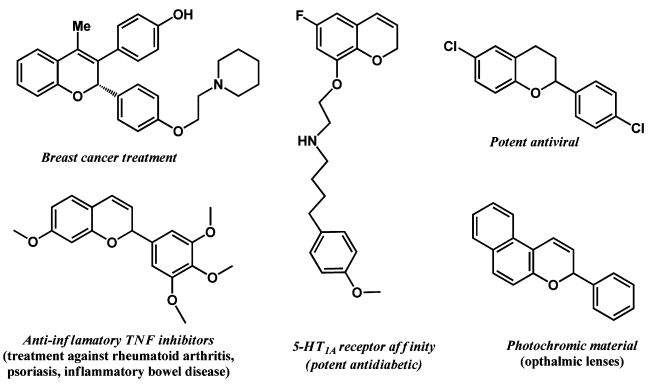


Figure 1. Selected examples of pharmacologically active and photochromic compounds based on 2*H*-chromene and related scaffolds.

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, antidepressant, 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 trifluoroborates.[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 toward 2*H*-chromenes is certainly in demand. Herein we describe a novel metalloradical 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 dimerization reactions. Furthermore, they reveal discrete catalytic radical-type reactions. For example, cyclopropanation reactions mediated by [Co^{II}(Por)] catalysts proceed via "carbene radical" addition to

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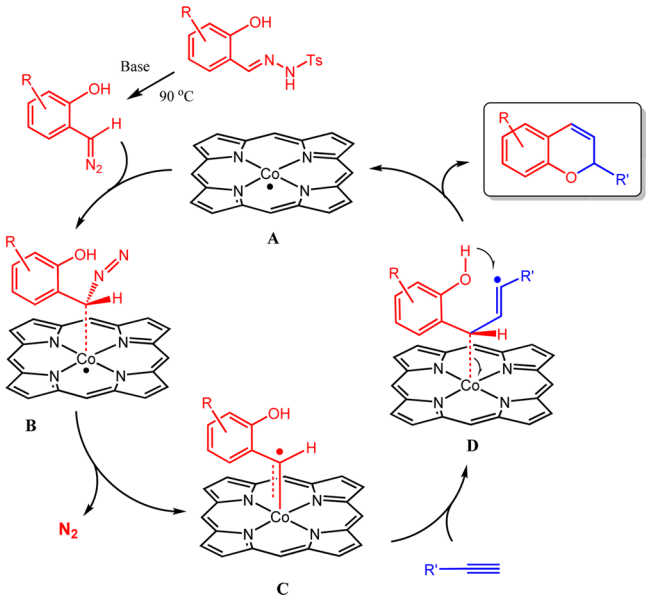
Scheme 1. Simplified Representation of the [Co^{II}(Por)]-Catalyzed Metalloradical Coupling−Cyclization Protocol Using Alkynes and Salicyl Tosylhydrazones To Produce 2*H*-Chromenes



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^{II}(Por)]-based metalloradical catalysis was thus far unprecedented, and 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]

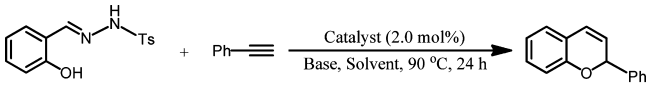
To explore the use of metalloradical catalysis in other radical-induced cyclization reactions, we envisioned the possibility of a new catalytic pathway for the construction of 2*H*-chromenes from salicyl tosylhydrazones and alkynes (Scheme 1). In this process, we anticipated formation of vinyl radical 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-cyclization 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-cyclization 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, labeling experiments, EPR spectroscopy, and computational studies (DFT).

RESULTS AND DISCUSSION

Initial studies focused on the reaction between tosylhydrazone **1a** and phenylacetylene **2a** to produce 2*H*-chromene **3a** (Table 1).

Table 1. Conditions of [Co^{II}(Por)]-Catalyzed 2*H*-Chromene Synthesis Using Salicyl *N*-Tosylhydrazone and Phenylacetylene[a]



1a **2a** **3a**

entry	catalyst	base	solvent	yield[b] (%)
1	[Co^{II}(**P1**)]	Cs_2CO_3	PhMe	45
2[c]	[Co^{II}(**P1**)]	Cs_2CO_3	THF	35
3	[Co^{II}(**P1**)]	Cs_2CO_3	dioxane	25
4[c]	[Co^{II}(**P1**)]	Cs_2CO_3	DCE	40
5[c]	[Co^{II}(**P1**)]	Cs_2CO_3	MeCN	<5
6	[Co^{II}(**P1**)]	Cs_2CO_3	DMF	0
7	[Co^{II}(**P1**)]	Cs_2CO_3	PhCl	70
8	[Co^{II}(**P1**)]	Cs_2CO_3	1,2-$PhCl_2$	70
9	[Co^{II}(**P1**)]	K_2CO_3	PhCl	20
10	[Co^{II}(**P1**)]	$KHCO_3$	PhCl	<10
11	[Co^{II}(**P1**)]	K_3PO_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.

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

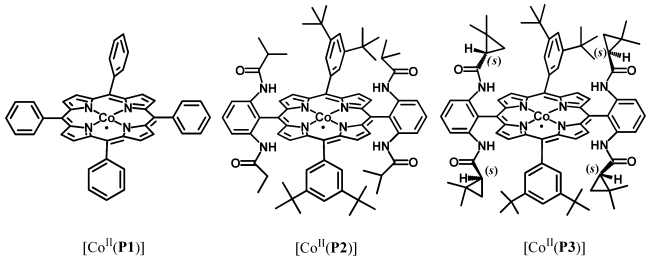


Figure 2. Structures of cobalt(II) complexes of porphyrins: **P1** = tetraphenylporphyrin; **P2** = 3,5-Di^{t}Bu-IbuPhyrin; **P3** = 3,5-Di^{t}Bu-ChenPhyrin.

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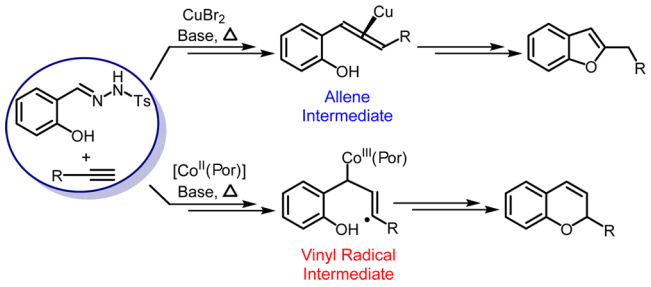
[Co^{II}(**P3**)]. The catalysts [Co^{II}(**P2**)] and [Co^{II}(**P3**)] were previously reported,[6] being excellent cyclopropanation catalysts due to the cooperative effect of the H-bond donor motifs in the second coordination sphere.[7,13] Initial experiments were focused on the evaluation of ligand 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_3PO_4, K_2CO_3, Cs_2CO_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).

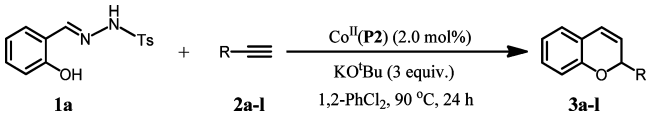
Control experiments showed that no product was obtained in the absence of a [Co^{II}(Por)] catalyst (Table 1, entry 24). While other cobalt(II) sources like $CoCl_2$ and $Co(OAc)_2$ (Table 1, entries 21 and 22) only afforded the 2*H*-chromene product in trace amounts (<5%), other typical carbene-transfer catalysts such as $Rh_2(OAc)_4$ 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, nonradical allene intermediates (Scheme 2).

Scheme 2. Proposed Nonradical $CuBr_2$-Catalyzed Cyclizations (Top) versus Radical-Type [Co^{II}(Por)]-Catalyzed Cyclizations (Bottom) of Terminal Alkynes with Salicyl Carbenes Generated from the Corresponding Tosylhydrazones



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 focused 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

Table 2. Reaction of *N*-Tosylhydrazone 1a with Various Terminal Alkynes Catalyzed by [Co^{II}(P2)]^{a,b}



1a **2a-l** **3a-l**

Entry	Alkyne		Product		Yield (%)
1	Ph—	(**2a**)		(**3a**)	75
2		(**2b**)		(**3b**)	71
3		(**2c**)		(**3c**)	73
4	MeO—	(**2d**)		(**3d**)	69
5	N—	(**2h**)		(**3e**)	62
6	F—	(**2e**)		(**3f**)	80
7	Br—	(**2f**)		(**3g**)	73
8	F$_3$C—	(**2g**)		(**3h**)	81
9	MeO	(**2i**)		(**3i**)	58
10	S	(**2j**)		(**3j**)	71
11	Ph	(**2k**)		(**3k**)	51
12	Ph—	(**2l**)		(**3l**)	--

[a]Stoichiometry: *N*-tosylhydrazone (**1a**) (0.3 mmol; 1.0 equiv) and alkyne (**2a−j**) (1.0 mmol; 3.0 equiv). [b]Isolated yields after chromatography.

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 and 10). Alkyl alkynes such as 4-phenyl-1-butyne proved also to be suitable reaction partners, generating the corresponding 2*H*-chromene in moderate yield (Table 2, entry 11). Reactions with 1,2-disubstituted alkynes did

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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 the reaction mixture. Carbene dimerization was also observed for reactions of **1a** in the 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.

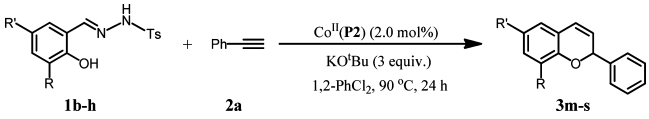
As shown in Table 3, hydrazones with electron-donating groups at the meta-, para-, or disubstituted at both meta- and para-positions were all effective, affording the corresponding 2*H*-chromenes **3m**, **3n**, and **3o** in good yields (Table 3, entries 1−3). Reactions also proceeded with electron-withdrawing 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 naphthalene-based tosylhydrazone **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]

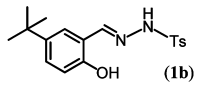
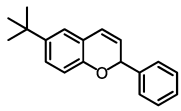
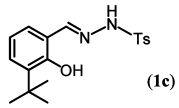
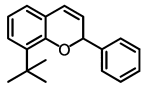
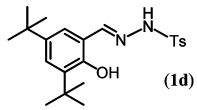
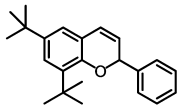
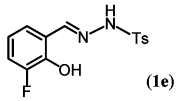
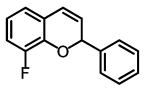
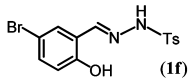
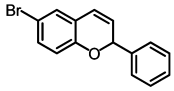
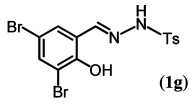
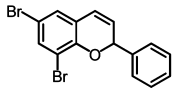
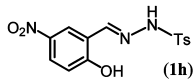
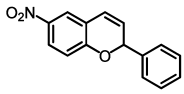
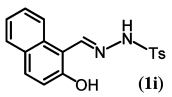
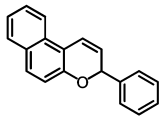
To shed more light on the catalytic reaction mechanism, we performed a set of control experiments, labeling studies, and EPR spectroscopic investigations. Additionally, we explored the mechanism computationally.

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

Table 3. [Co^{II}(P2)]-Catalyzed Reaction of *N*-Tosylhydrazones 1b−i with Phenylacetylene[a,b]



1b-h 2a 3m-s

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) and alkyne (**2a**) (1.0 mmol; 3.0 equiv). [b]Isolated yields after chromatography. [c]Reaction time 40 h. [d]Yield with [Co^{II}(**P1**)].

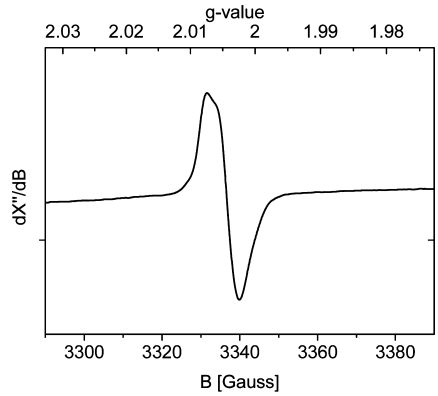


Figure 3. X-band EPR spectrum recorded from a reaction mixture of salicyl tosylhydrazone **1a**, phenylacetylene, KO^{t}Bu, and cobalt catalyst [Co^{II}(**P1**)] in toluene solution. Spectrum recorded at RT. Frequency = 9.360420 GHz, modulation amplitude = 2 Gauss, microwave power = 20 mW.

was detected in absence of phenylacetylene. Some hyperfine structure is visible, but the pattern is poorly resolved (spectral simulations show a maximum isotropic proton hyperfine splitting A_H^{iso} < 12 MHz; in the case of cobalt hyperfine splitting, A_{Co}^{iso} < 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 phenylacetylene 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 phenylacetylene 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^{II}(Por)] catalyst with diazo compounds.[7] In good agreement, no 2*H*-chromene formation was observed when the catalytic reaction was performed in the

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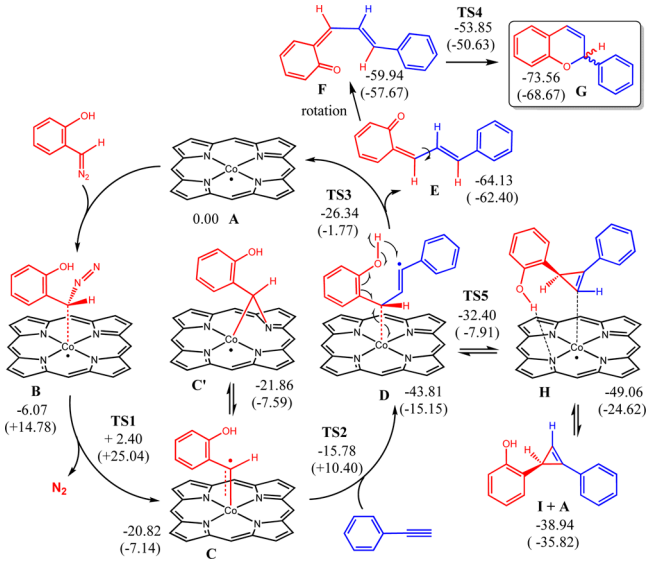
Scheme 3. [Co^{II}(Por)]-Catalyzed Metalloradical Coupling–Cyclization of Alkynes and Salicyl Tosylhydrazones[a]



[a]DFT-D3 calculated (Turbomole BP86, def2-TZVP) free energies (ΔG_{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.

presence of an excess of the radical scavenger TEMPO (~10 equiv 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-labeling experiments using *N*-tosylhydrazone **1a-D**, containing a deuterium-substituted phenoxyl moiety (70% ArO-D based on ^{1}H NMR spectrocopy), produce 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 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 and def2-TZVP level, using the nonfunctionalized [Co^{II}(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^{II}(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 center, 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 focused 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 (ΔG° = −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^{II}(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 (ΔG° = −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-centered radicals (Figure 4). The unpaired

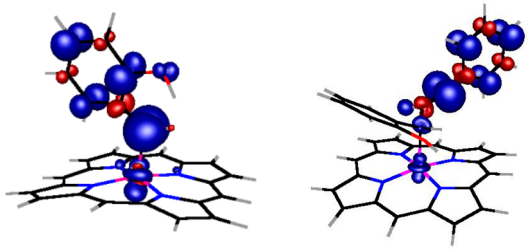


Figure 4. (a) Spin density plots of the DFT-optimized "carbene radical" species **C** (left) and vinyl radical species **D** (right).

electron in carbene radical **C** has a high spin density at the "carbene carbon" and is further delocalized 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 nonproductive formation of cyclopropene **I** (Scheme 3). Overall 2*H*-chromene formation is much more exergonic (ΔG° = −73.56 kcal mol^{-1}) than cyclopropene formation (ΔG° = −38.94 kcal mol^{-1}). The productive 2*H*-chromene formation pathway involves hydrogen atom transfer 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 (ΔG° = −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 endocyclic ring closure via **TS4** ($\Delta G^{\ddagger}$ = +6.09 kcal mol^{-1}) to form the final 2*H*-chromene product **G**. Related thermal (noncatalyzed) sigmatropic rearrangements of other (proposed) *o*-quinone methide intermediates, prepared via entirely different routes, have previously been reported to produce 2*H*-

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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 cyclopropanation,[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 reaction partners in [Co^{II}(Por)]-catalyzed cyclopropanation 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 toward **I** is even lower than the rate-limiting **TS3** barrier for HAT in the productive pathway for 2*H*-chromene formation. However, cyclopropanation 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*-tosylhydrazone compounds with different substituents 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 processes proceed 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**)], and [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 (^{1}H 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 synthesized compounds were recorded in Agilent-5973 GC-MS spectrometer, and the corresponding HRMS data were recorded on JEOL AccuTOF 4G via direct injection probe. Elemental analysis of the newly synthesized complexes was 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 of 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-Labeling Experiment and KIE Measurement. Deuterium-labeled salicyl tosylhydrazone (**1b**) was synthesized by stirring the corresponding nonlabeled tosylhydrazone in a DMSO-d_6−D_2O mixture for 24 h. Then, 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-labeled (70%) tosylhydrazone (**1a**) and phenylacetylene (**2a**) was performed in absolutely inert atmosphere using deuterated bromobenzene as the solvent. ^{1}H NMR spectroscopy revealed 60% deuterium incorporation (85% wrt starting deuterium-labeled *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 nondeuterated 2*H*-chromene product, as determined by ^{1}H NMR integration) obtained in an internal competition experiment using nondeuterated salicyl tosylhydrazone **1a** and deuterated **1a-D** in a 1:1 ratio (1 equiv 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 of 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).

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■ ASSOCIATED CONTENT

Supporting Information

NMR data, absolute energies (atomic units), and the coordinates of the DFT-optimized structures are provided. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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