Sulfur versus Nitrogen Chelation in C–H Activation: Cobalt(III)-Catalyzed Unsymmetrical Double Annulation of Thioamides

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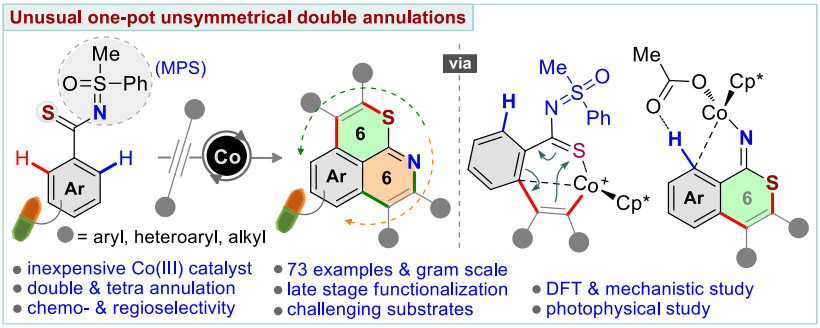


ABSTRACT: An unconventional cobalt(III)-catalyzed one-pot domino double annulation of aryl thioamides with unactivated alkynes is presented. Sulfur (S), nitrogen (N), and *o,o′*-C–H bonds of aryl thioamides are involved in this reaction, enabling access to rare 6,6-fused thiopyrano-isoquinoline derivatives. A reverse 'S' coordination over more conventional 'N' coordination of thioamides to Co-catalyst specifically regulates the formation of four [C–C and C–S at first and then C–N and C–C] bonds in a single operation, a concept which is uncovered for the first time. The power of the N-masked methyl phenyl sulfoximine (MPS) directing group in this annulation sequence is established. The transformation is successfully developed, building a novel chemical space of structural diversity (56 examples). In addition, late-stage annulation of biologically relevant motifs and drug candidates are disclosed (17 examples). Preliminary photophysical properties of thiopyrano-isoquinoline derivatives are discussed. Density functional theory (DFT) studies authenticate the participation of a unique 6π-electrocyclization of a 7-membered S-chelated cobaltacycle in the annulation process.

Introduction

Transition metal (TM)-catalyzed heteroatom-aided oxidative C–H annulation of arenes have drawn significant attention, as these methods are largely applicable for the construction of complex molecular scaffolds.[1] Such proximity-driven atom- and step-efficient annulation strategies are synthetically valuable for the construction of natural and non-natural products, biologically important candidates, and molecules relevant to materials.[2] In spite of a broad synthetic versatility, these annulation methods forming C–C, C–N, and C–O bonds are typically based on the use of precious 4d- and 5d-late transition metal-based catalysts (Rh, Ru, Pd, and Ir).[3-4] Meanwhile, the more abundant, relatively inexpensive and less toxic 3d–TM cobalt complexes, such as Cp*Co(III)-type species,[5] have emerged as attractive alternatives to the expensive Rh and Ir catalysts and have allowed to uncover mono-functionalization/cyclization processes involving unactivated arene C–H bonds guided by a directing group (DG) (Fig. 1A, right).[6-7] In contrast, the use of such Co-catalyst for the direct unsymmetrical di-

functionalization of inert C–H bonds, which requires two DGs, is unknown and more challenging (Fig. 1A, left). Along these lines, the heteroatom-guided double annulation of arenes C–H bonds with alkynes has been realized by the coordination of 'N' to Ru, Rh, and Ir.[4,8] In that respect, the coordination of amide 'N' over 'O' has granted access to polycyclic amides, wherein a metalated isoquinolone B-I species plays a crucial role (Fig. 1B).[9] With thioamides, such complexation of 'N' to TM over 'S' provides isoquinolones,[10a] as metalated-thioisoquinolone B-II is prone to hydrolysis under such oxidative conditions (Fig. 1B).[10a]

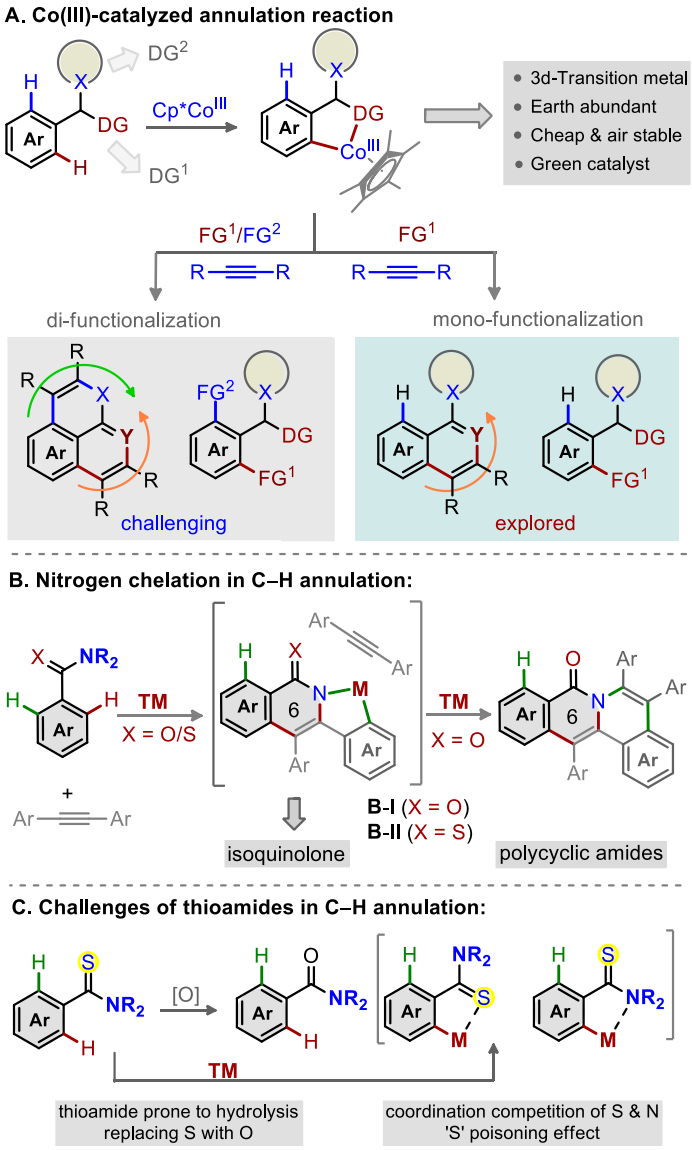


Figure 1. Directing group assisted double annulations of arenes and challenges

Perhaps the propensity of 'S' to oxidation, the coordination competition between 'S' and 'N' to the TM catalyst, or the 'S' poisoning effect on the TM catalyst makes the second C–H functionalization difficult (Fig. 1C).[10] A worthwhile endeavor would thus be to develop an annulation method linked to the construction of S-enabled heterocycles through C–H activation of thioamides.[11] Envisaging a complete coordination switch-over from 'N' to 'S' to TM would result in a metalated isothiochromenimine species **D-I** from mono–annulation of thioamide's S–moiety with an alkyne (Fig. 2A). Second annulation of **D-I** could then possibly form a hitherto unknown S,N-bearing double annulation product (Fig. 2B).

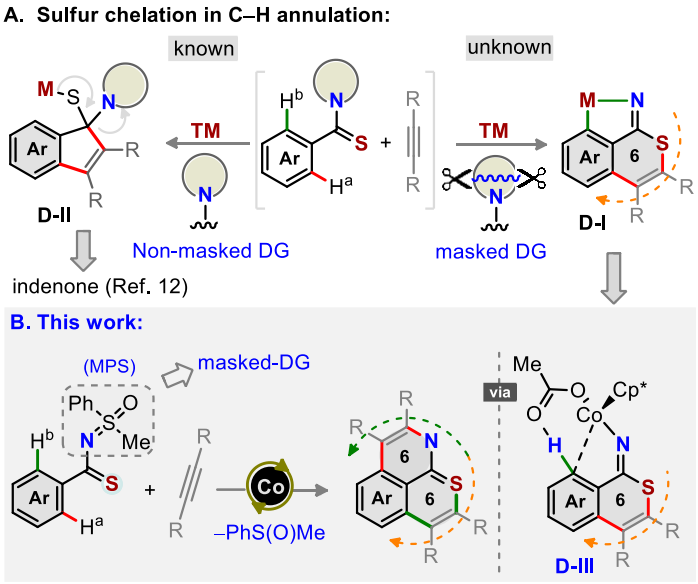


Figure 2. Concept of double annulation of thioamides

To make this objective feasible, a thioamide with N-masked DG is inevitable since Rh-catalyzed annulation of benzothioamides with alkynes explicitly delivers indenones;[12] the transformation possibly involves C–N bond cleavage of intermediate **D-II** and a subsequent desulfurization (Fig. 2A).[12] We therefore considered using a transformable masked-imine equivalent N-methylphenyl sulfoximine (MPS) DG, which cleaves in a redox-neutral pathway to form a sulfoxide (see the mechanistic part),[9e] to allow the double annulation of arylthioamides with alkynes using a Co(III) catalyst, which is unprecedented (Fig. 2B). Salient features of the transformation are: coordination preference of 'S' to Co-catalyst over 'N' in the mono-

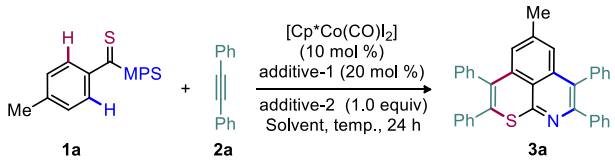
annulation of MPS-enabled thioamides; in-situ cleavage of sulfoximine N=S bond to make isothiochromenimine–Co intermediate **D-III**; construction of a wide array of rare 6,6-fused thiopyrano–isoquinoline skeletons; late stage double annulation of pharmaceutically active compounds and drug molecules; mechanistic insights through complete DFT studies.

Results and Discussion

To assess the cascade unsymmetrical double annulation shown in Fig. 2B, a reaction between N-[4-methylbenzothioyl]-S-methyl-S-phenylsulfoximine (**1a**; 1.0 equiv) and 1,2-diphenyl acetylene (**2a**; 3.0 equiv) was examined using an air stable Co-precatalyst (Table 1).[13] The catalytic system [{Cp*Co(CO)I_2} (10 mol%), $AgSbF_6$ (20 mol%), $Cu(OAc)_2 \cdot H_2O$ (1.0 equiv)] in 1,2-dichloroethane (DCE) at 120 °C for 24 h was at first tested (entry 1). The desired sulfur and nitrogen enabled 6,6-fused thiopyrano-isoquinoline **3a** was gratifyingly obtained in 59% yield. The reaction was found clean by TLC and crude ^{1}H NMR, despite the usual instability of thioamides towards oxidative catalytic systems. The metal acetate seems crucial since **3a** was not detected as trace in the absence of $Cu(OAc)_2 \cdot H_2O$ (entry 2). In addition to the putative oxidative role of the additive in the regeneration of the active cobalt(III) species, it is likely that its acetate ligands are part of the concerted-metalation-deprotonation (CMD) process (see the mechanistic part below).[1e] Accordingly, different acetate sources [NaOAc, KOAc, CsOAc, $Zn(OAc)_2 \cdot 2H_2O$, and AgOAc] were screened, but they proved to be less efficient than $Cu(OAc)_2 \cdot H_2O$ (entries 3–7). Interestingly, the use of anhydrous $Cu(OAc)_2$ improved the yield to 68% (entry 8).[11] The additives $AgBF_4$, $NaSbF_6$, and KPF_6 were evaluated under the conditions of entry 8 (entries 9–11), but only $AgBF_4$ effectively led to **3a** in 55% yield (entry 9). Among the solvents tested DCE, PhMe, DMF, HFIP, CH_3CN, 1,4-dioxane, or TCE (entries 8, 12–14), DCE was clearly the most efficient one (entry 8). The yield of **3a** was increased to 76% when the reaction was performed using the Cp*Co(CO)I_2 complex (15 mol%), $AgSbF_6$ (30

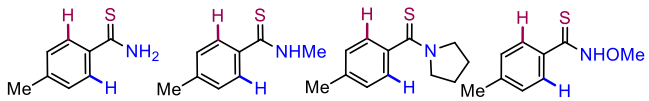
mol%), and $Cu(OAc)_2$ (1.5 equiv) (entry 15). Rising the temperature to 130 °C further improved the yield of **3a** to 87% (entry 16).[15]

Table 1. Optimization of the Reaction Conditions[a]



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

entry	additive 1 (20 mol%)	additive 2 (1.0 equiv)	solvent	yield of **3a** (%)[b]
1	$AgSbF_6$	$Cu(OAc)_2·H_2O$	$ClCH_2CH_2Cl$	59
2	$AgSbF_6$	–	$ClCH_2CH_2Cl$	trace
3	$AgSbF_6$	NaOAc	$ClCH_2CH_2Cl$	9
4	$AgSbF_6$	KOAc	$ClCH_2CH_2Cl$	5
5	$AgSbF_6$	CsOAc	$ClCH_2CH_2Cl$	trace
6	$AgSbF_6$	$Zn(OAc)_2·2H_2O$	$ClCH_2CH_2Cl$	12
7	$AgSbF_6$	AgOAc	$ClCH_2CH_2Cl$	40
8	$AgSbF_6$	$Cu(OAc)_2$	$ClCH_2CH_2Cl$	68
9	$AgBF_4$	$Cu(OAc)_2$	$ClCH_2CH_2Cl$	55
10	$NaSbF_6$	$Cu(OAc)_2$	$ClCH_2CH_2Cl$	trace
11	KPF_6	$Cu(OAc)_2$	$ClCH_2CH_2Cl$	trace
12	$AgSbF_6$	$Cu(OAc)_2$	PhMe/DME	25/39
13	$AgSbF_6$	$Cu(OAc)_2$	HFIP/CH_3CN	30/NR
14	$AgSbF_6$	$Cu(OAc)_2$	dioxane/TCE	60/41
15[c]	$AgSbF_6$	$Cu(OAc)_2$	$ClCH_2CH_2Cl$	76
16[c,d]	**$AgSbF_6$**	**$Cu(OAc)_2$**	**$ClCH_2CH_2Cl$**	**87**



I, ND **II**, ND **III**, ND **IV**, ND

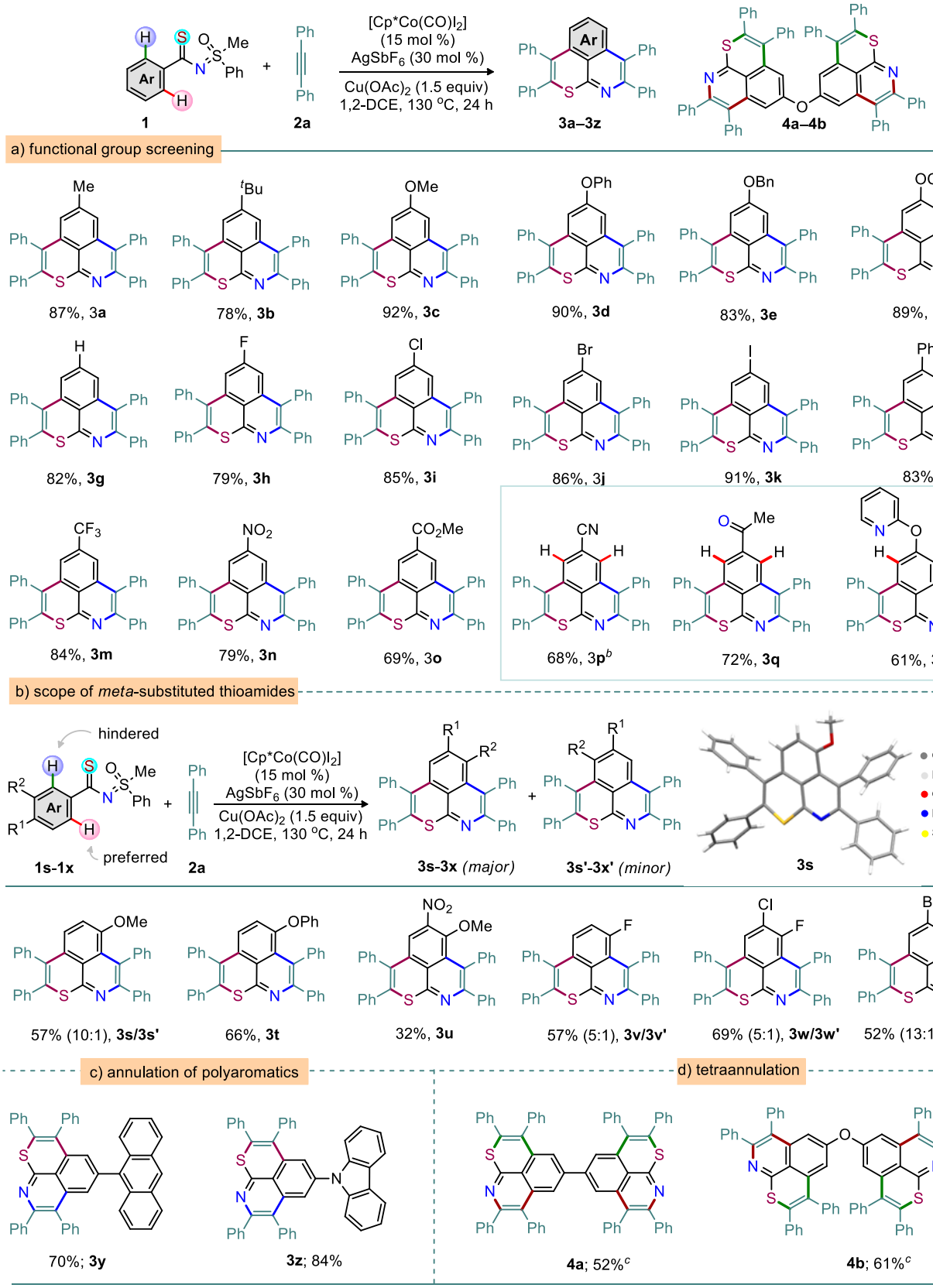
[a]Reaction conditions: **1a** (0.3 mmol), **2a** (0.9 mmol), [Cp*Co(CO)I_2] (10 mol%), additive-1 (20 mol%), additive-2 (0.3 mmol), solvent (2.0 mL) at 120 °C. [b]Isolated yield. [c][Cp*Co(CO)I_2] (15 mol%), $AgSbF_6$ (30 mol%), and $Cu(OAc)_2$ (1.5 equiv). [d]Reactions were carried at 130 °C. NR = no reaction. ND = not determined.

To validate the role of the DGs in this study, the annulation of thioamides (I-IV, see bottom of Table 1) with **2a** was attempted under the optimized conditions. However, no desired product was formed when N-unprotected (**I**), N-methyl (**II**), and N-pyrrolidinyl (**III**) thioamides were independently exposed to the catalytic system; complex reaction mixtures were observed in most cases with complete degradation of the thioamides. The reaction of the N-methoxy protected thioamide **IV** with **2a** was also unsuccessful. [11] Thus, the MPS-DG is essential to access the thiopyrano-isoquinoline skeleton.

To probe the reaction generality, the double annulation of MPS-enabled thioamides **1a**–**s** (prepared *via* EDC coupling of aryl carboxylic acids with MPS followed by Lawesson reaction; see the SI) with alkynes was explored under the optimized conditions shown in Table 1, entry 16, and the results are detailed in Schemes 1–3. [13] At first, annulation of various MPS-thioamides with **2a** was surveyed (Scheme 1). The electron-donating groups [*p*-Me, *p*-^{t}Bu, and *p*-OMe; *p*-OPh, *p*-OBn, and *p*-OCF_3 (protecting unit)] at the aryl motif of thioamides **1a**–**f** were perfectly tolerated, leading to the desired double annulation products **3a**–**f** in 79–92% yield (Scheme 1a). Likewise, electron-neutral phenyl-group enabled **3g** was constructed in high yield (82%). Readily transformable halo groups (F, Cl, Br, or I) proved also compatible, leading to the respective thiopyrano-isoquinolines **3h**–**k** in good yields (Scheme 1a). The π-conjugated **3l** was isolated in 83% yield. Thioamides **1m**–**o** exhibiting electron-withdrawing *p*-CF_3, *p*-NO_2, and *p*-CO_2Me groups at the aryl moiety also reacted efficiently with **2a** to furnish **3m**–**o** in 69–84% yield (Scheme 1a). Thus, electron-bias of thioamides did virtually not affect the reaction outcome. Of note, the Lewis basic CN, keto and pyridyl groups did not compete with the MPS-thioamide as potential DGs. The MPS-guided selectivity was indeed still observed with **1p**–**r**, furnishing the thiopyrano-isoquinolines **3p** (68%), **3q** (72%), and **3r** (61%) (Scheme 1a). Thus, MPS–DG is highly precise for site selective C–H metalation and annulation sequence of thioamides in presence of other coordinating groups.[14] In general, the DG–modulated annulation

of *meta*−substituted arenes provides inseparable mixtures of cyclized manifolds (Scheme 1b). In our case, due to the steric demand around one of the *ortho* C–H arene bond imposed by the *meta* R^2 group, it is likely that the first annulation takes place at the less hindered one.[15] The structure of the major product would therefore inform if the first annulation on the R^1 side involves the S or the N atom. In other words, the study of this regioselectivity issue could validate the hypothesis of 'S' vs 'N' coordination preference. Unsymmetrical double annulations of *meta*-substituted thioamides with **2a** were thus accomplished. An inseparable mixture of thiopyrano-isoquinolines **3s** and **3s'** was isolated when *m*-methoxy thioamide **1s** was exposed to **2a** (10:1; 57%). X-ray crystallographic analysis indisputably elucidated the molecular topology of the major isomer **3s**.[16]

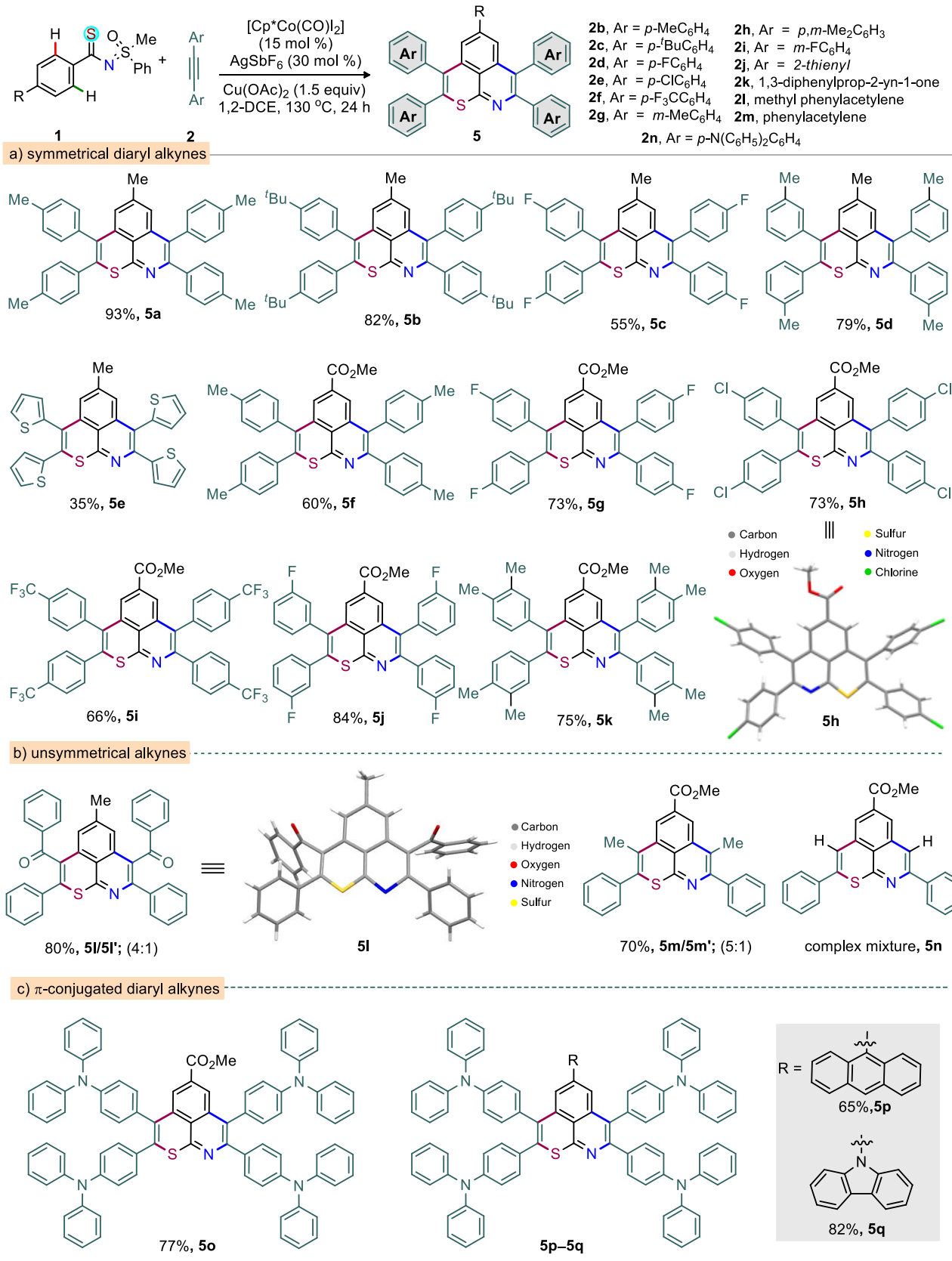
Scheme 1. Synthesis of 6,6-fused thiopyrano-isoquinolines



*[a]Reactions were carried out with 1 (0.3 mmol), 2 (0.9 mmol), [Cp*Co(CO)I₂] (15 mol%), AgSbF₆ (30 mol%), Cu(OAc)₂ (0.45 mmol) in 1,2-DCE (2.0 mL) at 130 °C for 24 h. [b]12 h. [c]1 (0.3 mmol), 2 (2.1 mmol), [Cp*Co(CO)I₂] (20 mol%), AgSbF₆ (40 mol%), Cu(OAc)₂ (0.6 mmol), 1,2-DCE (3.0 mL) at 130 °C for 36 h.*

This regioselectivity supports the fact that the first annulation is guided by the S- rather than the N-moiety of the thioamide functionality. Likewise, such annulations of *m*-phenoxy/*m*-OMe-*p*-NO_2 substituted thioamides **1t** and **1u** provided **3t** and **3u**, this time as single regioisomers, albeit in moderate yields. Mixtures of regioisomers also aroused from halide-bearing thioamides **1v** (57%, 5:1), **1w** (69%, 5:1), and **1x** (52%, 13:1). In general, the extended π-conjugation largely contributes to the tuning of photophysical properties of the molecular skeleton.[17] Thus, anthracene- and carbazole-anchored thiopyrano-isoquinolines **3y** (70%) and **3z** (84%) were successfully prepared (Scheme 1c). Meanwhile, tetra-annulation (*two consecutive double annulations*) of pre-functionalized 4,4′-aryldithioamides with **2a** led to structurally diverse linear (**4a**, 52%) and 'V-shaped' (**4b**, 61%) polyaromatics (Scheme 1d). *The construction of eight bonds (2 C−S, 2 C−N, and 4 C−C) via activation of four o-C−H bonds of arenes and annulation with four alkynes in a single operation is notable* (Scheme 1d). To further illustrate the reaction generality and synthetic diversity, a wide range of structurally and electronically distinct 1,2-diaryl alkynes (**2b**–**i**), 1,2-di(hetero)aryl alkyne (**2j**), 1,3-diphenylpro-2-yn-1-one (**2k**), methyl phenylacetylene (**2l**), phenylacetylene (**2m**), and N-bearing π-conjugated alkyne (**2n**) were surveyed (Scheme 2). The reaction between **1a** and 1,2−diaryl alkynes **2** [*p*-Me (**2b**), *p*-^{t}Bu (**2c**), *p*-F (**2d**), and *m*-Me (**2g**)] led to **5a** (93%), **5b** (82%), **5c** (55%), and **5d** (79%), respectively (Scheme 2a). Likewise, annulation of 2-thienyl bearing alkyne **2j** with **1a** provided **5e**, albeit in moderate yield (35%). Possibly the coordination of the thiophene sulfur to TM traps the catalyst in this case and affects the reaction productivity. The desired thiopyrano-isoquinolines **5f**–**i** were synthesized from **1o** (*p*-CO_2Me bearing aryl thioamide) when reacted independently with **2** [**2b→5f** (60%); **2d→5g** (73%); **2e→5h** (73%); **2f→5i** (66%); **2i→5j** (84%); **2h→5k** (75%); Scheme 2a]. X-ray crystallographic analysis ascertained the structure of **5h**.[16] Thus, alkynes with electron-bias have no detrimental effect on the double annulation sequence.

Scheme 2. Double annulation of 1 with 1,2-diarylacetylenes [a]

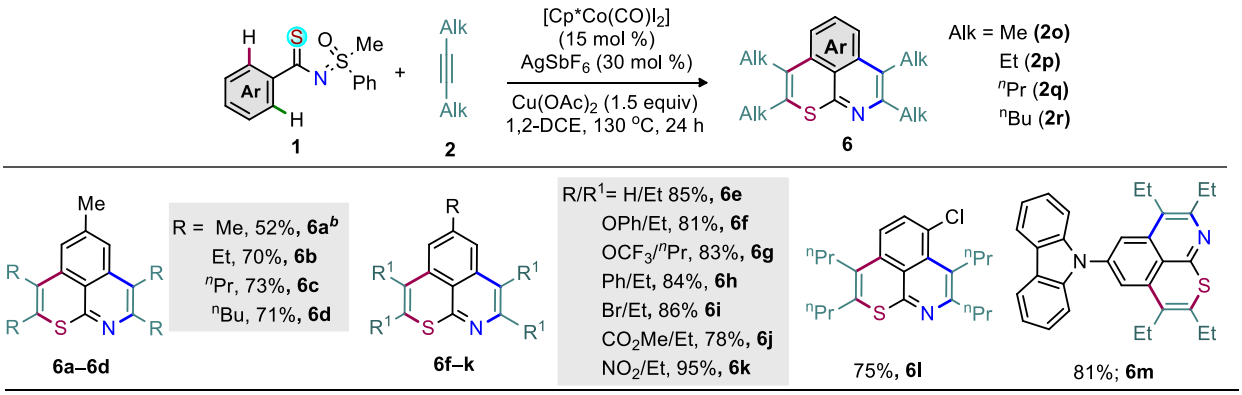


[a]*Reactions were carried out with* ***1*** *(0.3 mmol),* ***2*** *(0.9 mmol), [Cp*Co(CO)I$_2$] (15 mol%), AgSbF$_6$ (30 mol%), Cu(OAc)$_2$ (0.45 mmol), 1,2-DCE (2.0 mL) at 130 °C for 24 h.*

Next, unsymmetrical alkynes were tested. Reaction of **1a** with **2k** and **1o** with **2l** respectively delivered **5l** (4:1) and **5m** (5:1) as major products along with other minor regioisomers (Scheme 2b). The structure **5l** was confirmed by X-ray analysis.[16] Thus, the oxidative annulations follow conventional mechanistic path that involves metal-dπ interaction of organocobalt(III) species with phenyl ring; this might be a possible reason for this high regioselectivity.[3b–d,18] However, phenyl acetylene (**2m**) provides complex mixture due to dimerization under oxidative conditions (Scheme 2b). To access a π-extended molecular scaffold, the double annulation of **1o** with **2n** (*p*-diphenyl amine bearing sterically giant 1,2-diaryl alkyne) produced **5o** in 77% yield (Scheme 2c). Likewise, anthracene- and carbazole-bearing thiopyrano-isoquinolines **5p** (65%) and **5q** (82%) were fabricated from the annulation of MPS-thioamides **1z**/**1z′** with **2n**, respectively.

Not only 1,2-diarylalkynes, but also 1,2-dialkylalkynes (**2o**–**r**) are relevant partners in this cascade double annulation (Scheme 3). In this context, 2-butyne (**2o**), 3-hexyne (**2p**), 4-octyne (**2q**), and 5-decyne (**2r**) were independently reacted with **1a** to furnish a range of peripheral decorated thiopyrano-isoquinolines **6a**–**d** (52–73%). Analogously, **6e** was synthesized in 85% yield. The annulation of thioamides bearing either electron-donating (OPh, OCF_3), arene (Ph), halo (Br), and electron-withdrawing (NO_2, CO_2Me) substituents in the *para* position of the phenyl ring with **2p**/**2q** was also accomplished, providing **6f**–**k** in good yields (Scheme 3). Moreover, annulation of *m*-Cl bearing thioamide **1l** with **2q** led to **6l** with high regioselectivity. Thus, transformable groups (i.e. CO_2Me, NO_2, Br, Cl) can be easily introduced and could lead to further structural modifications. Lastly, the π-conjugated carbazole-molded thiopyrano-isoquinoline framework **6m** (81%) was synthesized (Scheme 3). In this context, the late-stage annulation of (hetero)arenes C–H bonds of biologically relevant motifs (BRM) is invaluable for the sustainable development of complex molecules with enhanced pharmacokinetic properties.

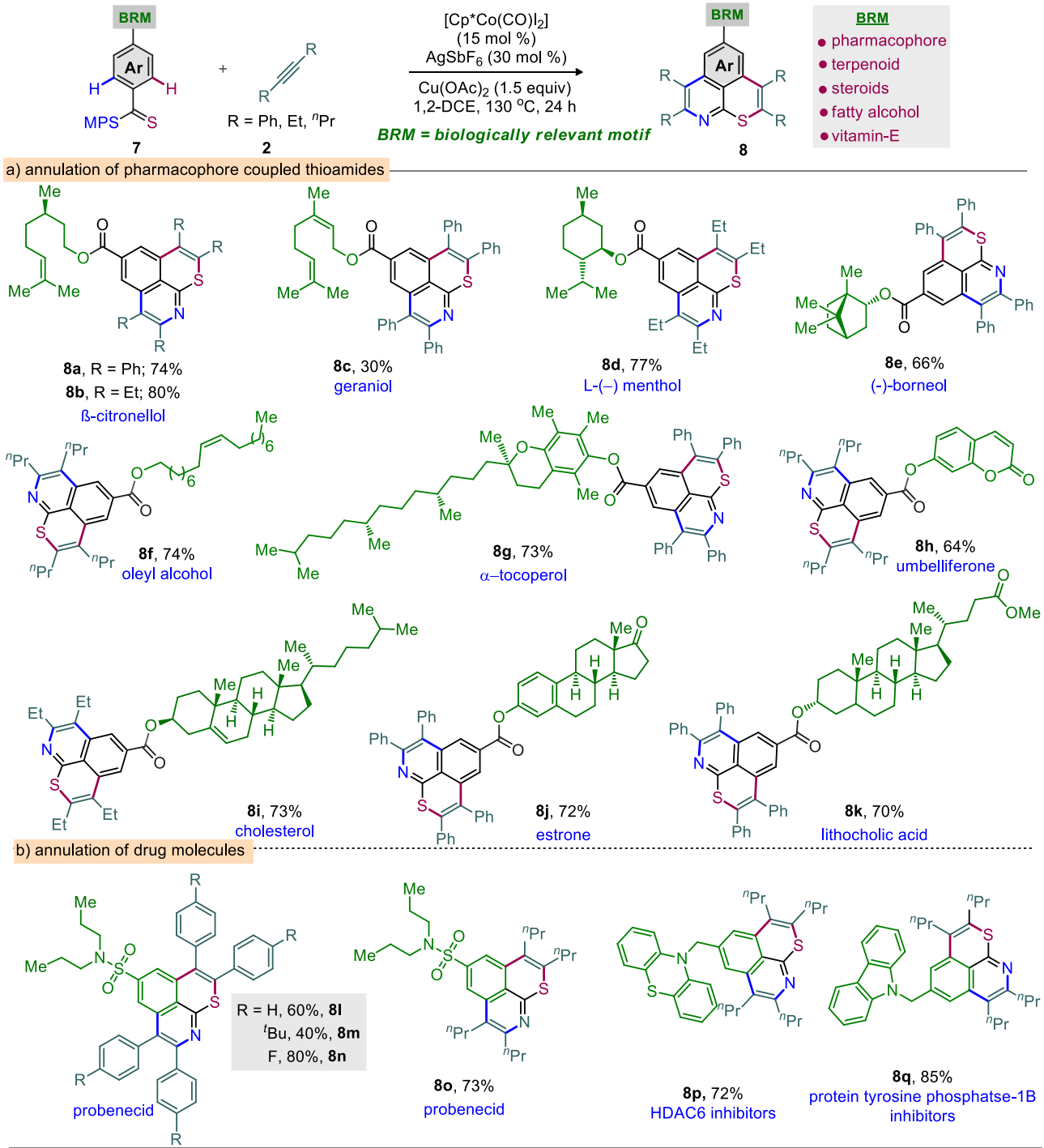
Scheme 3. Double annulation of 1 with 1,2-dialkyl alkynes 2[a]



[a]*Reactions were carried out with* ***1*** *(0.3 mmol),* ***2*** *(0.9 mmol), [Cp*Co(CO)I₂] (15 mol%), AgSbF₆ (30 mol%), Cu(OAc)₂ (0.45 mmol), 1,2-DCE (2.0 mL) at 130 °C for 24 h.* [b]***2o*** *(30 mmol).*

However, BRM exhibiting polar groups and unsaturated moieties invariably causes problems for site-selective C–H activation, as the TM binding competition between Lewis basic heteroatoms and the DG can lead to substrate decomposition and affect the C–H bond functionalization efficiency. We were therefore intrigued by the viability of the Co-catalyzed double C–H annulation of pharmacophore-coupled thioamides **7** (Scheme 4). However, the title reaction proved once again its reliability: thiopyrano–isoquinoline encapsulated terpenoids [*β*-citronellol (**8a** and **8b**), geraniol (**8c**)], natural products [menthol (**8d**), borneol (**8e**)], fatty alcohols [oleyl alcohol (**8f**), vitamin-E-tocopherol (**8g**)], coumarin [umbelliferone (**8h**)], and steroids [cholesterol (**8i**), estrone (**8j**), lithocholic acid (**8k**)] were made in 30–80% yields from the cascade annulations of respective pharmacophore-coupled MPS-thioamides with alkynes **2a/2p/2q** (Scheme 4a).[19] The olefin moieties of terpenoids, the molecular complexity of steroids, the ether linkage and other sensitive functional groups including carbonyl, lactone, and ester were tolerated. The structural and stereochemical integrity of the molecular skeletons were also preserved. To probe the efficacy of the method, the synthetic campaign was then directed towards marketed drug molecules (Scheme 4b).[20]

Scheme 4. Annulation of biological relevant motifs molded from MPS-enabled thioamides[a]



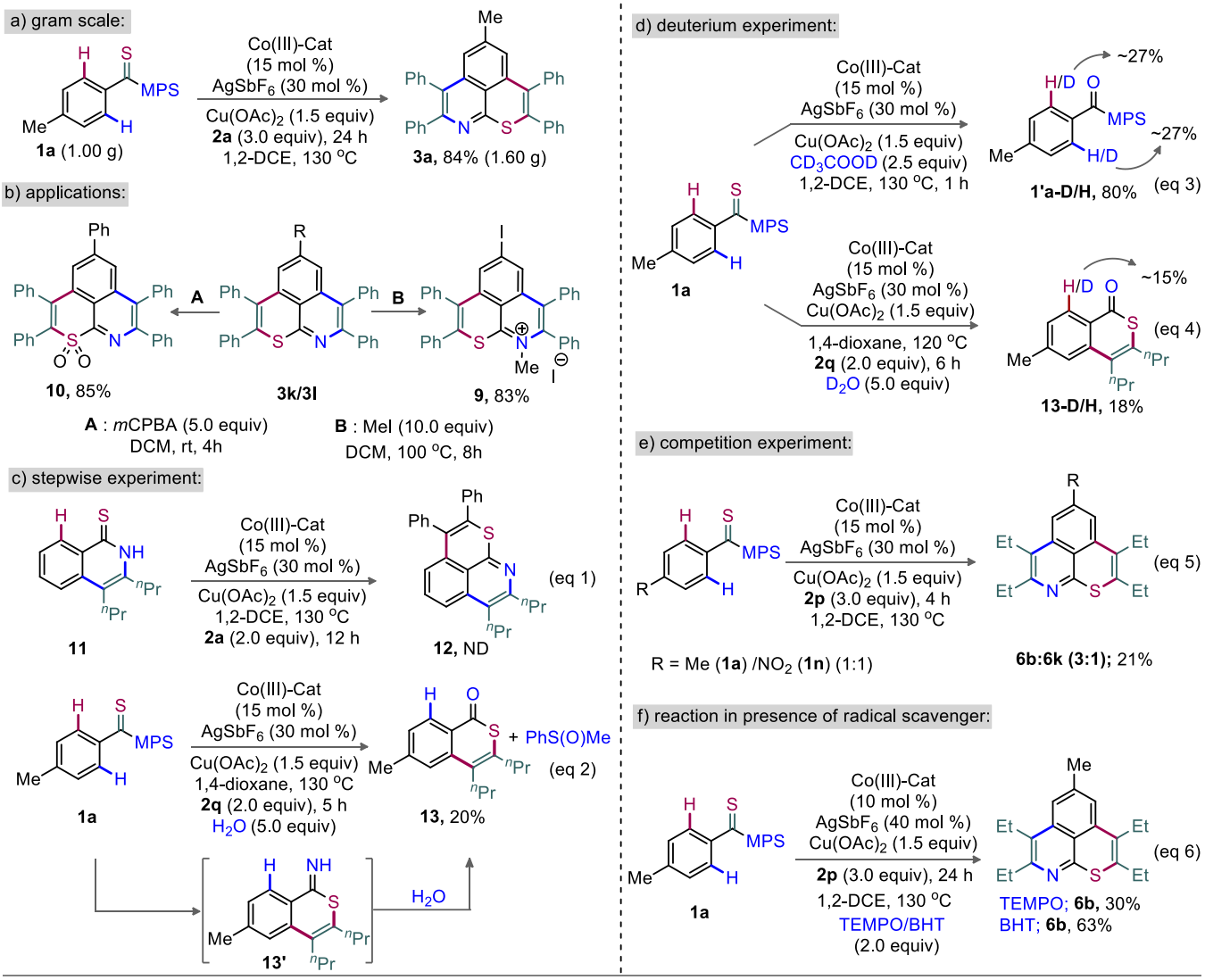
*[a]Reactions were carried out with **7** (0.3 mmol), **2** (0.9 mmol), [Cp*Co(CO)I$_2$] (15 mol%), AgSbF$_6$ (30 mol%), Cu(OAc)$_2$ (0.45 mmol),1,2-DCE (2.0 mL) at 130 °C for 24 h.*

The targeted uricosuric renal tubular blocking agent probenecid-fused-thiopyranoisoquinolines **8l–o** were prepared in good yields. No site selective functionalization of arene C–H bond proximal to the sulfonamide group took place. Likewise, HDAC6 inihibitor *N*-

benzylphenothiazine **8p** and protein tyrosine phosphate-1B inihibitor *N*-benzylcarbazole **8q** fused thiopyranoisoquinolines were constructed in 72% and 85% yield, respectively (Scheme 4b). The N- and S- containing (hetero)arenes, for example, phenothiazine and carbazole, were unaffected by the electrophilic metal catalyst and harsh reaction conditions. The reaction was even successful at the gram scale: **3a** (1.61 g, 84%) was prepared from the reaction of **1a** (1.0 g, 3.45 mmol) with **2a** (1.85 g, 10.36 mmol) in presence of the Co(III) catalyst (Scheme 5a). Oxidation of the N- or S-heteroatom of thiopyrano-isoquinolines **3k**/**3l** provided access to N-methylated **9** in 83% yield and the respective sulfone **10** in 85% yield (Scheme 5b). [13]

To gain some mechanistic insight into this Co-catalyzed double annulation of thioamides with alkynes, a set of control experiments and deuterium labeling studies were planned. We believe that two sequential mono-annulations independently involving 'N' and 'S' heteroatoms of thioamides are responsible for the formation of the thiopyrano-isoquinolines. To validate this speculation, we intended to examine the coordination preference of thioamides 'N' and 'S' to TM. Thus, a reaction between isoquinoline-1(*2H*)-thione (**11**) and **2a** was carried out under the optimized conditions at 130 ºC for 13 h (Scheme 5c, eq 1). Interestingly, not even a trace of desired product **12** was formed, which rules out the participation of intermediate **11** in this transformation. The reaction of **1a** with **2p** under the standard catalytic conditions and in the presence of a controlled amount of H_2O (5.0 equiv) provided isothiochromenone **13** and methyl-phenyl sulfoxide (Scheme 5c, eq 2). This information clearly suggests that the first annulation involves thioamides 'S' moiety over 'N' to form imine intermediates such as **13'** (Scheme 5c, eq 2). Eventually, hydrolysis of **13'** furnishes **13**. Under dry conditions, a second annulation of **13'** with the alkyne could produce the thiopyrano-isoquinoline scaffold. We next ran various D/H exchange experiments of **1a** (Scheme 5d, eqs 3–4). Exposing **1a** to the standard conditions in presence of CD_3CO_2D (2.5 equiv) at 130 ºC resulted in D-incorporation at C2 (27%) and C6 (27%) positions of **1'a**–**D/H** (80%) (eq 3).

Scheme 5. Gram scale, applications, and controlled experiments



Similarly, 15% of deuterium incorporation happened at proximal C(arene)–H of isothiochromenone **13-D/H** (18%) when the reaction of **1a** with **2q** was performed in the presence of D_2O (eq 4). Therefore, activation of both the *o*- and *o*'-C(arene)–H bonds of MPS-bearing-1-thioamide with Cp*Co(III) seems reversible. Next, a competitive double annulation of an equimolar mixture of **1a** and **1n** with **2p** was probed, leading to **6b** and **6k** in a 3 : 1 ratio after 4 h; thus, an electron–rich arene reacts faster than an electron-poor one (Scheme 5e, eq 5). Moreover, the reaction was still possible in presence of radical scavengers (TEMPO and BHT); the possible involvement of a radical pathway is therefore discarded (Scheme 5f, eq 6).

DFT computations were carried out to validate the proposed mechanism. The Gaussian 09 software package was used[21] with its implemented M06 functional,[22] the 6-31G(d,p) basis set[23] for all main group elements, and the LANL2DZ (ECP) basis set for Co.[24] Single point calculations were conducted at the M06/6-311++G(d,p) -SDD(ECP)[25] level of theory. Solvation energies were obtained at the single point level using the SMD approach for 1,2-dichloroethane.[26] The discussed values are solvent–corrected Gibbs free energies at 393.15 K in kcal/mol (ΔG_{393}). The molecular system composed of substrate **A**, 2-butyne (2.0 equiv), $[Cp^*Co(OAc)]^+$, and an additional AcO^- (that ensures a second deprotonation of **A** from the Co complex) has been used as a reference for the free energies (Fig. 3). In general, the Cp cobalt(III) complexes can adopt singlet (S), triplet (T), and quintet (Q) spin states. In agreement with our previous studies,[27] 16-electron complexes are more stable in the triplet state. For instance, complex D displays $\Delta E_{S\text{-}T}$ = −3.8 kcal/mol and $\Delta E_{S\text{-}Q}$ = 20.0 kcal/mol. On the other hand, 18-electron complexes are usually more stable in the singlet state; complex E for instance exhibits $\Delta E_{S\text{-}T}$ = 7.8 kcal/mol and $\Delta E_{S\text{-}Q}$ = 25.9 kcal/mol. Since all major steps involve 18-electron complexes (16-electron species are only involved in dissociative ligand exchanges such as from **C** to **E**), we did not compute the minimum energy crossing points (MECP) of the singlet and triplet energy surfaces.

To start with, the coordination of **A** with $[Cp^*Co(OAc)]^+$ provides complex **B** at the expense of 5.9 kcal/mol (−12.1 kcal/mol without solvent effect). The hydrogen bond with the acetate ligand and a η^1-coordination between Co and the *ipso*-carbon makes the concerted-metalation-deprotonation (CMD) process viable. The C–H metalation then occurs through TS_{BC}, lying 12.8 kcal/mol above the reference system. The resulting metallacycle **C** is only 0.2 kcal/mol more stable than **A**.

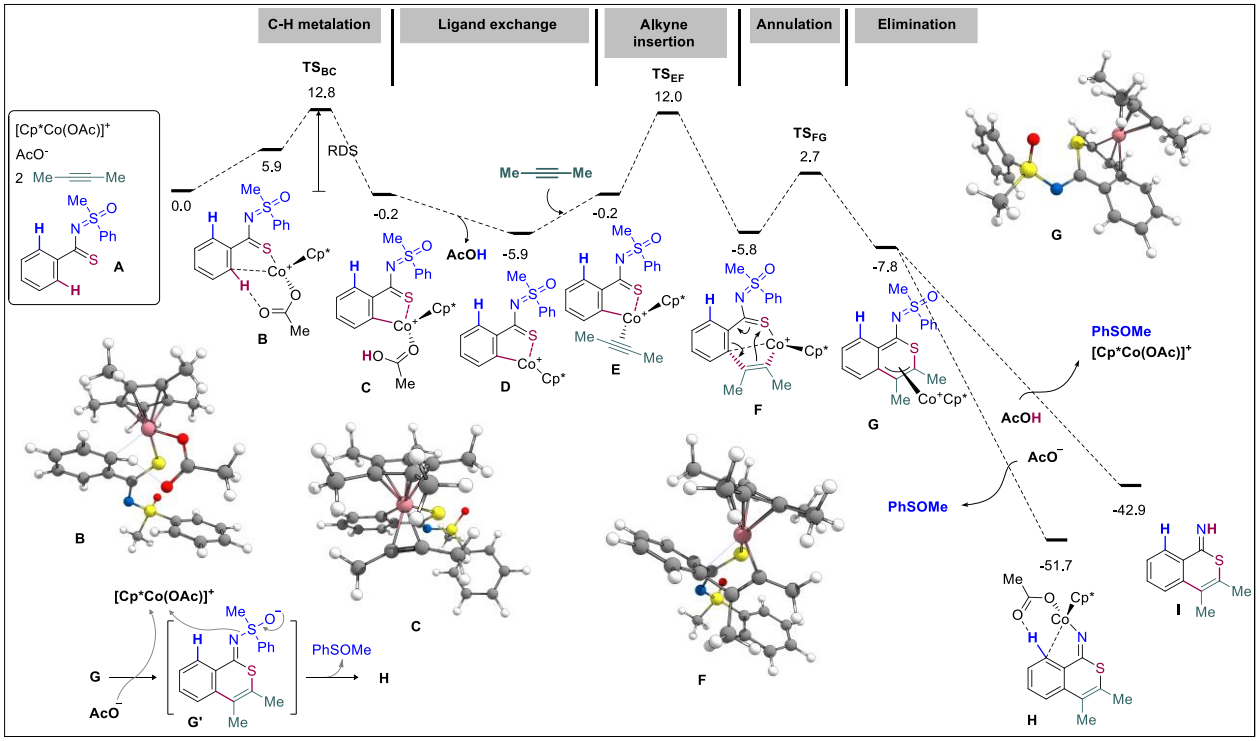


Figure 3. Free energy profile (ΔG_{393}, kcal/mol): Part 1 (first annulation)

Importantly, coordination of the 'N' atom of the MPS instead of thioamide 'S' led to a complex located at 16.3 kcal/mol and the corresponding C–H metalation transition state was found at 26.6 kcal/mol instead of 12.8 kcal/mol for the S-guided C–H metalation (not shown). It corroborates the above hypothesis of a preferred 'S' over 'N' coordination and rationalizes the selectivity observed. Going back to **B**, a stepwise ligand exchange between acetic acid and 2–butyne in **C** leads to the alkyne complex **E** (located at –0.2 kcal/mol on the free energy surface). The migratory alkyne insertion of **E** produces the seven-membered complex **F** (–5.8 kcal/mol), where the metal receives electron density from the aryl moiety. This step passes through $\mathbf{TS_{EF}}$, lying at 12.0 kcal/mol, and is exergonic by 5.6 kcal/mol. Next, the 6π-electrocyclization of **F** gives the π-allyl intermediate **G** at –7.8 kcal/mol. The corresponding transition state, $\mathbf{TS_{FG}}$, was found as low as 2.7 kcal/mol on the surface. The AcO^- mediated removal of PhSOMe of **G** affords **H** (–51.7 kcal/mol) via **G′** (Fig. 3), which is useful for the second CMD process. Alternatively, protonation of **G** with AcOH provides the otherwise stable compound **I** at –42.9 kcal/mol.[28]

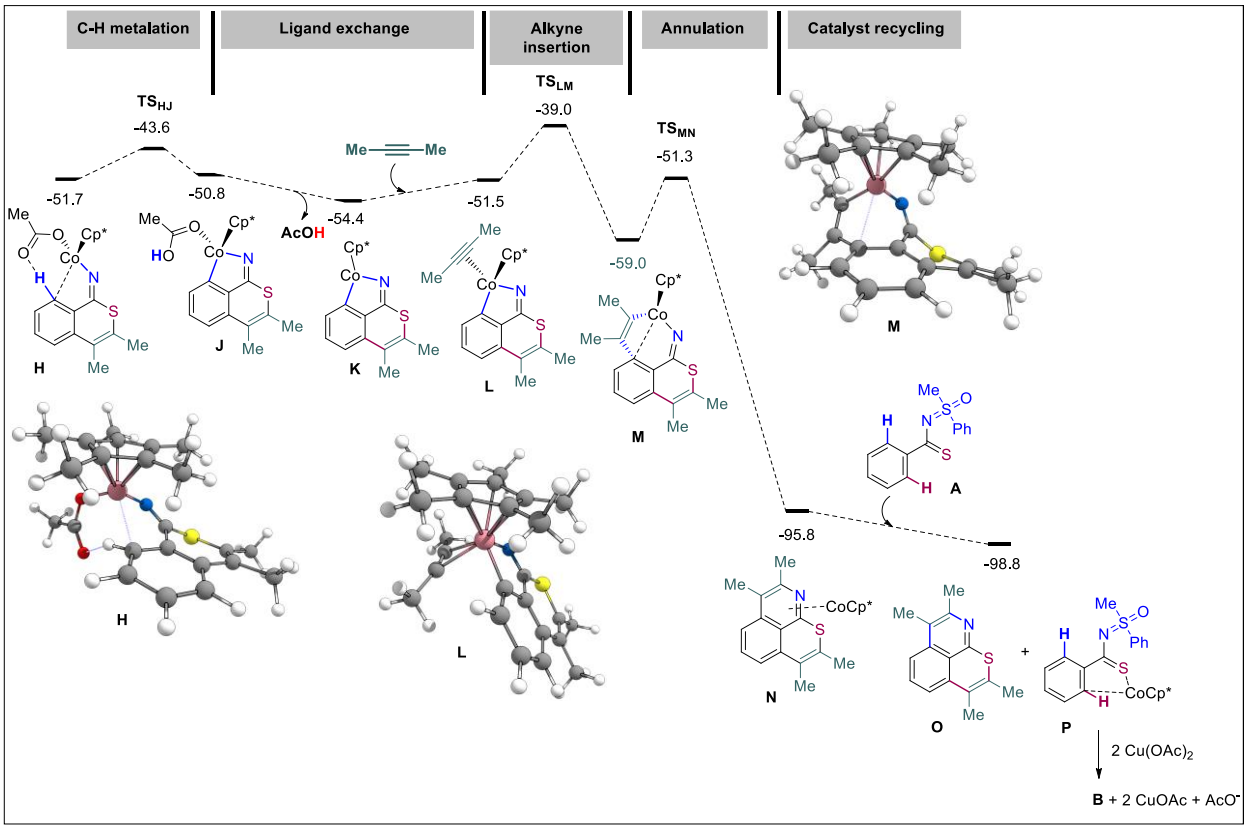


Figure 4. Free energy profile (ΔG_{393}, kcal/mol); Part 2 (second annulation)

The second annulation pathway is shown in Figure 4. It starts in a similar fashion, the computed profile between H and the alkyne complex L being rather flat. Next, the alkyne insertion in L requires 12.5 kcal/mol of free energy of activation and is exergonic by 7.5 kcal/mol to provide M. The reductive elimination of M passes through TS_{MN} requiring 7.7 kcal/mol to produce N (found at –95.8 kcal/mol). This irreversible step leads to the experimentally observed tricyclic product with a release of 36.8 kcal/mol. The ligand exchange of **N** with **A** further lowers the free energy by 3.0 kcal/mol to produce the final product **O** (at –98.8 kcal/mol) along with **P**. The $Cu(OAc)_2$ mediated oxidation of complex **P** provides **B** for new cycle.[29] In view of control experiments and DFT studies, a plausible mechanistic pathway for Cp*Co(III) catalyzed oxidative cascade double annulation of aryl thioamides with alkynes has been outlined in Figure 5.[1,3] At the outset, iodide abstraction and ligand exchange among $Cp^*Co(CO)I_2$, $AgSbF_6$, and $Cu(OAc)_2$ at first provide the active cationic $[Cp^*Co(OAc)]^+$ catalyst.

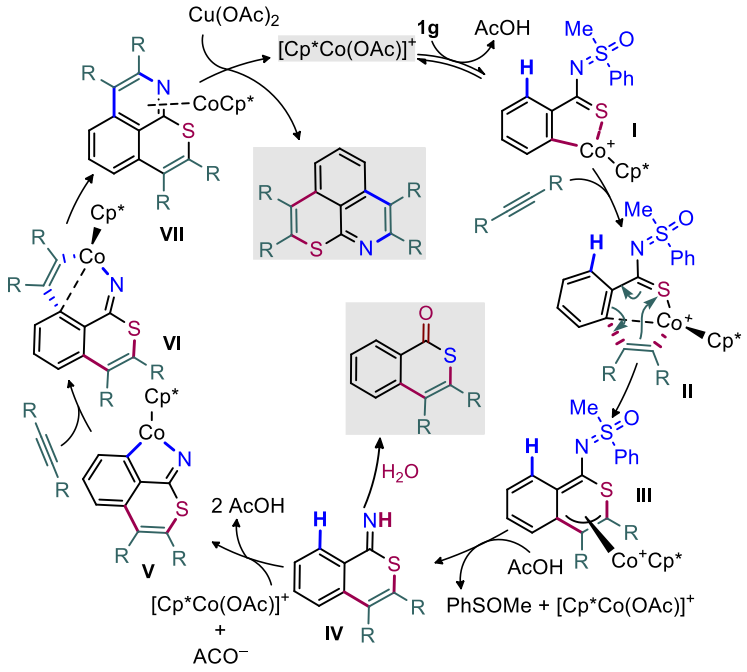


Figure 5. Plausible catalytic cycle

Thereafter, coordination of 'S' in thioamide with the active species, followed by activation of proximal *o*-C(arene)–H bond, forms the five membered cyclocobalated species **I**; this C–H dissociation follows a CMD process (see eq 3 in Scheme 5). Next, the migratory insertion of alkyne to **I** affords a cyclic seven-membered Co-intermediate **II**. The 6π-electrocyclization of **II** then provides the π-allyl intermediate **III**. Acetate mediated formal elimination of $[Cp^*Co(OAc)]^+$ and concurrent expulsion of sulfoxide provides the imine intermediate **IV**. Importantly, intermediate **IV** is prone to hydrolysis in presence of H_2O to form isothiochromenone. Afterwards, the imine assisted activation of *o*'-C(arene)–H bond of **IV** forms a five–membered cyclocobalated intermediate **V**. Subsequently, alkyne insertion to **V** provides the seven-membered metallacycle **VI**. Reductive elimination of the latter delivers the expected thiopyrano-isoquinoline product **3a** as ligand of the Co(I) complex **VII**. Finally, $Cu(OAc)_2$ regenerates the active Co(III) catalyst for next cycle. The intramolecular 6π–electrocyclization (that involves 4π-electrons of arylthioamide and 2π-electron of inserted alkyne) of seven-membered Co-species makes this Co-catalyzed annulation of thioamides

viable, a distinct feature for the TM-catalyzed annulation processes. In addition, the in-situ cleavage of transformable masked-imine MPS-DG under a redox-neutral pathway could be able to regenerate the active catalyst after 1st annulation (**III**→ **IV**) as well as to provide active imine intermediate **IV** for 'N' assisted 2nd annulation process (Fig. 5).

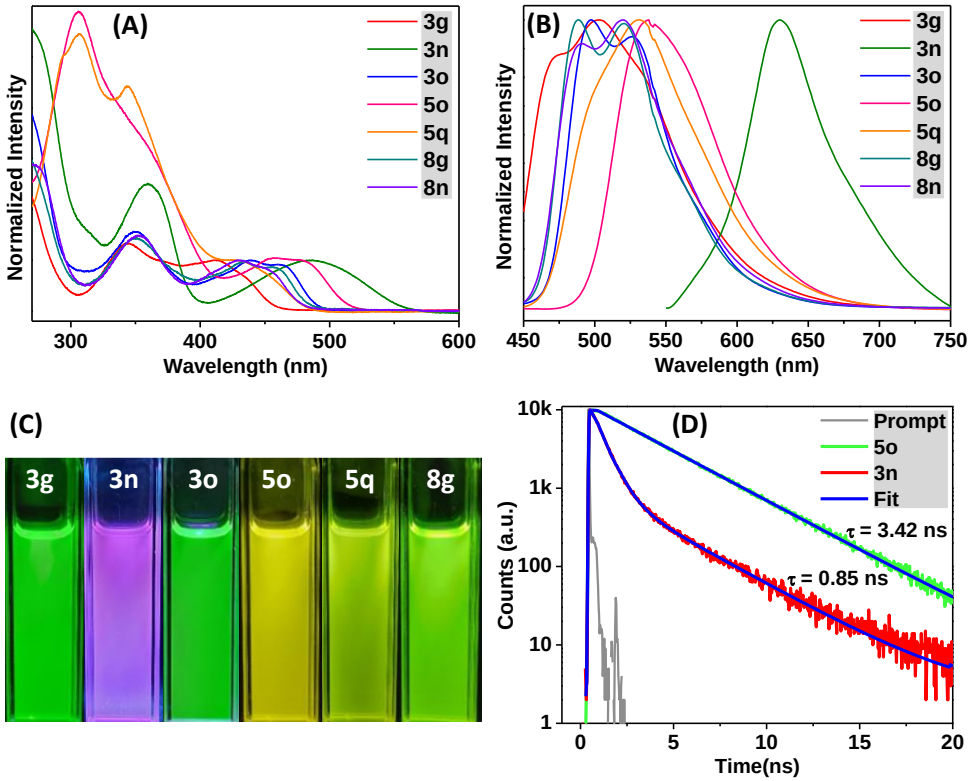


Figure 6. Normalized absorption (**A**) and fluorescence (**B**) spectra in DCM at RT (10^{-5} M); Observer fluorescence under UV excitation (365 nm) (**C**); Life time measurements (**D**).

Most of the synthesized thiopyrano-isoquinoline derivatives are brightly fluorescent. To probe the photophysical properties of the molecules, steady-state absorption (Fig. 6A) and emission (Fig. 6B) experiments were carried out. Most of the compounds exhibit strong absorption bands at 344–360 nm and 412–486 nm (Fig. 6A) while the emission maximum lies around 503–630 nm (Fig. 6B) with large Stokes shifts of 81–144 nm. Solvatochromic study did not show any intense colour change or fluorescence intensity variation. This phenomenon clearly reveals that the fluorescence is originating from the core structure of the compounds. Interestingly,

excitation of -NO_2 or -CO_2Me group bearing π-extended compounds **3n**–**o** provokes signification bathochromic shifts in emission. Likewise, the ester linked biologically relevant motifs **8g** and **8n** are also showing intense emission bands and could be useful as fluorescent drug carrier as well as fluorescent probe for cell imaging.[17] The enhanced fluorescence properties of π-extended scaffolds **5o** and **5q** with longer life time[30] (3.42 ns for **5o**; Scheme 3D) are notable and could be applicable for potential material applications.

Conclusion

A sulfoximine-directed Cp*Co(III)-catalyzed unsymmetrical double annulation of aryl thioamides with unactivated alkynes to obtain unusual 6,6-fused thiopyrano-isoquinolines has been uncovered. The major highlights of this transformation are: 1) the use of an earth-abundant 3d-transition-metal Co-catalyst for the double annulation of arenes *o,o′*-C–H bonds of thioamides through sequential coupling with alkynes; 2) reactivity preference of 'S' over 'N' in the annulation process of thioamides; 3) formation of four bonds [C–C, C–S and C–C, C–N] in a single operation; 4) it overcomes the previously encountered challenges, i.e. the 'S' poisoning effect on the transition-metal catalyst and the susceptibility of 'S' to oxidation. The transformation provides access to a wide range of novel thiopyrano-isoquinoline scaffolds, featuring broad scope with labile functional group tolerance and late-stage annulation of biologically-relevant molecules and drug candidates. DFT studies and deuterium scrambling experiments establish the importance of N-masked sulfoximine-directing group in this annulation and offer valuable inputs for understanding the mechanism. Importantly, a unique 6π-electrocyclization of a 7-membered S-chelated cobaltacycle makes the annulation process viable, which plays crucial for this double-annulation of thioamides. Preliminary photophysical studies of thiopyrano-isoquinoline are encouraging and attract further investigations. We believe that the present discovery could help to uncover synthetic handles for multiple annulations of unactivated C(sp^2/sp^3)–H bonds with unsaturated species that have so far remained unexplored.

ASSOCIATED CONTENT

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SUPPORTING INFORMATION

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1. Detailed experimental procedures, characterization (^{1}H, ^{13}C AND ^{19}F NMR, FTIR and HRMS) data, photophysical properties, X-ray crystallographic data (CIF), coordinates (x,y,z), energies (Hartree) and imaginary frequencies (cm^{-1}) of the computed species for DFT calculations, ^{1}H, ^{13}C and ^{19}F NMR spectra of the compounds (PDF)
2. HRMS copies (PDF)
3. X-ray crystallographic data for product 3s (Scheme 1) (CIF)
4. X-ray crystallographic data for product 5h (Scheme 2) (CIF)
5. X-ray crystallographic data for product 5l (Scheme 2) (CIF)

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Notes

The authors declare no competing financial interest.

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