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# Harnessing sulfur and nitrogen in the cobalt(III)-catalyzed unsymmetrical double annulation of thioamides: probing the origin of chemo- and regio-selectivity†

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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 a more conventional 'N' coordination of thioamides to the 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, the late-stage annulation of biologically relevant motifs and drug candidates is disclosed (17 examples). The 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 has drawn significant attention, as this method is largely applicable for the construction of complex molecular scaffolds.[1–4] 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.[5,6] 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).[7–20] Meanwhile, the more abundant, relatively inexpensive and less toxic 3d-TM cobalt complexes, such as Cp*Co(III)-type species,[21,22] 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).[23–30] In contrast, the use of such Co-catalysts for the direct unsymmetrical di-functionalization of inert C–H bonds, which requires two DGs, is unknown and more challenging. Along these lines, the heteroatom-guided double annulation of arene C–H bonds with alkynes has been realized by the coordination of 'N' to Ru, Rh, and Ir.[14–20,31,32] In that respect, the coordination of amide 'N' over 'O' has granted access to polycyclic amides, wherein a metalated isoquinolone species plays a crucial role.[33–37] With thioamides, such complexation of 'N' to TM over 'S' provides isoquinolones, as metalated-thioisoquinolone is prone to hydrolysis under such oxidative conditions (Fig. 1B, **B-I**).[38] Perhaps the propensity of 'S' to undergo 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. 1B).[39] A worthwhile endeavor would thus be to develop a double annulation method linked to the construction of S-enabled heterocycles through C–H activation of thioamides.[40–43] Envisaging a complete coordination switch-over from 'N' to 'S' to TM would result in a metalated isothiochromenimine species **B-II** from mono-annulation of the thioamide's S-moiety with an alkyne (Fig. 1B). The second

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† Electronic supplementary information (ESI) available: 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, and $^1$H, $^{13}$C and $^{19}$F NMR spectra of the compounds (PDF). CCDC 2045975–2045977. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/d1sc00765c

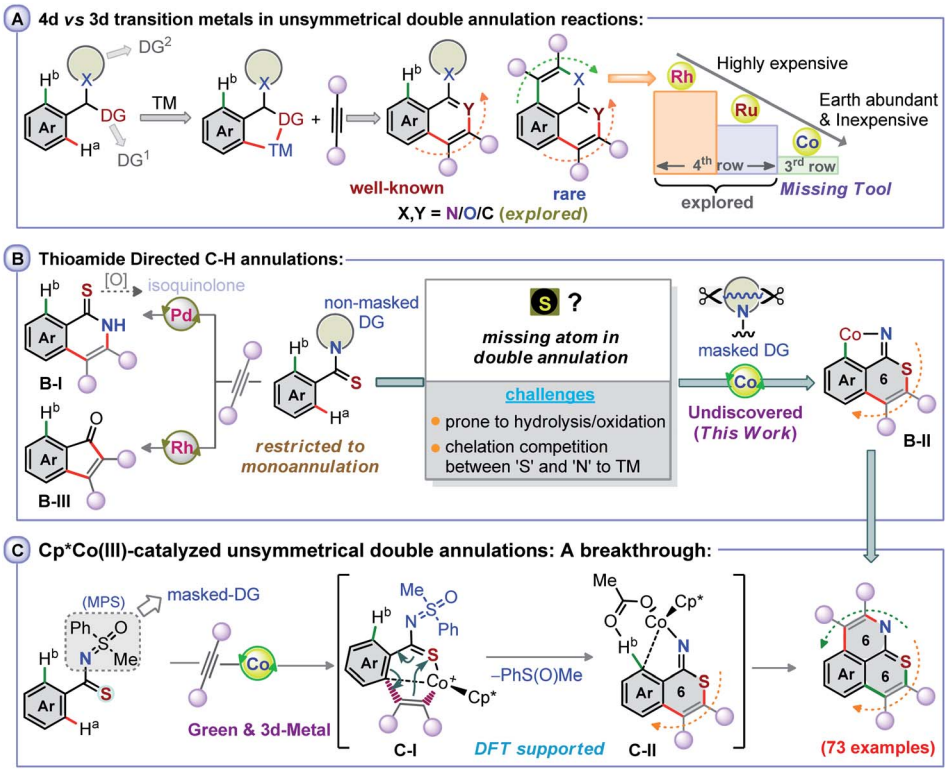



Fig. 1 Concept of Co(III)-catalyzed double annulation of thioamides.

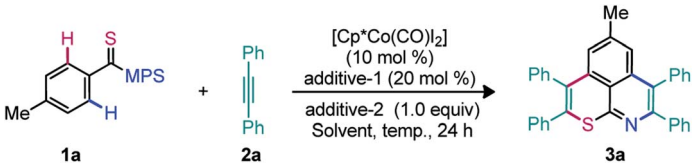
annulation of **B-II** could then possibly form a hitherto unknown S,N-bearing double annulation product. To make this objective feasible, a thioamide with an N-masked DG is inevitable since Rh-catalyzed annulation of benzothioamides with alkynes explicitly delivers indenones (Fig. 1B, **B-III**);[44] the transformation possibly involves C–N bond cleavage and a subsequent desulfurization.[44]

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),[37] to allow the double annulation of arylthioamides with alkynes using a Co(III) catalyst, which is unprecedented (Fig. 1C). The salient features of the transformation are: the coordination preference of 'S' to the Co-catalyst over 'N' in the mono-annulation of MPS-enabled thioamides; a 6π-electrocyclization of a 7-membered S-chelated cobaltacycle **C-I**; *in situ* cleavage of the sulfoximine N=S bond to form an isothiochromenimine–Co intermediate **C-II**; the 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. 1C, 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).[45] The catalytic system [Cp*Co(CO)$I_2$] (10 mol%), $AgSbF_6$ (20 mol%), and $Cu(OAc)_2 \cdot H_2O$ (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 a trace of **3a** was not detected 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).[3] 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). 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, and 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). The reaction has been independently performed with Ru(II) and Rh(III) catalysts and the desired product **3a** was obtained in 55% and 49% yields, respectively

Table 1 Optimization of the reaction conditions[a]



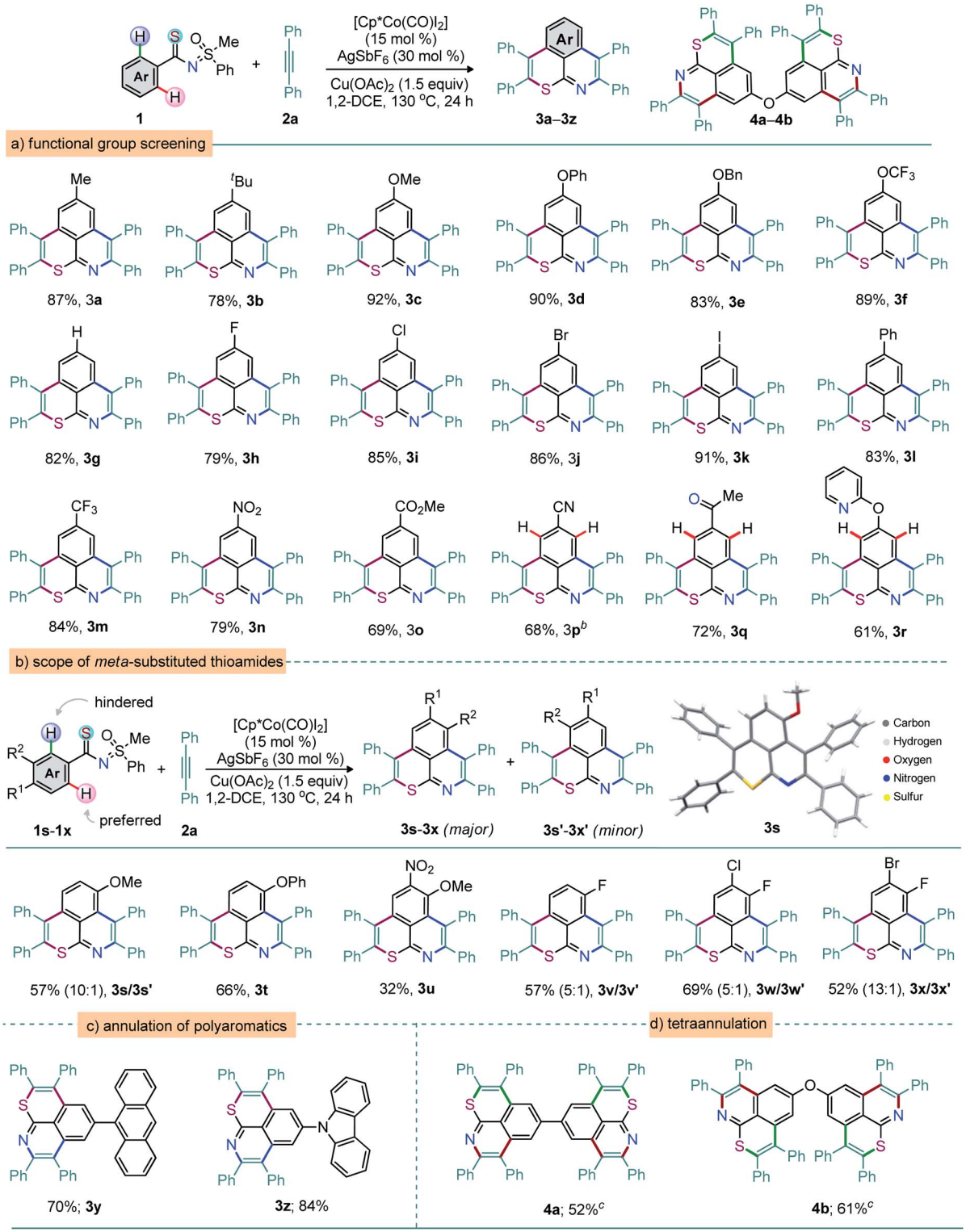

| Entry | Additive 1 (20 mol%) | Additive 2 (1.0 equiv.) | Solvent | Yield of **3a**[b] (%) |
|---|---|---|---|---|
| 1 | $AgSbF_6$ | $Cu(OAc)_2 \cdot H_2O$ | $ClCH_2CH_2Cl$ | 59 |
| 2 | $AgSbF_6$ | — | $ClCH_2CH_2Cl$ | Trace |
| 3 | $AgSbF_6$ | NaOAc | $ClCH_2CH_2Cl$ | 9 |
| 4 | $AgSbF_6$ | KOAc | $ClCH_2CH_2Cl$ | 5 |
| 5 | $AgSbF_6$ | CsOAc | $ClCH_2CH_2Cl$ | Trace |
| 6 | $AgSbF_6$ | $Zn(OAc)_2 \cdot 2H_2O$ | $ClCH_2CH_2Cl$ | 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[g] |
| 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 |
| 17[c,d,e] | $AgSbF_6$ | $Cu(OAc)_2$ | $ClCH_2CH_2Cl$ | 55 |
| 18[c,d,f] | $AgSbF_6$ | $Cu(OAc)_2$ | $ClCH_2CH_2Cl$ | 49 |


[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), and 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. [e] [$RuCl_2$(*p*-cymene)]$_2$ (10 mol%). [f] [Cp*$RhCl_2$]$_2$ (5.0 mol%). [g] NR = no reaction. ND = not determined.

(entries 17–18). To validate the role of the DGs in this study, the annulation of thioamides (**I–IV**, see the 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. Thus, the MPS-DG is essential to access the thiopyrano-isoquinoline skeleton.

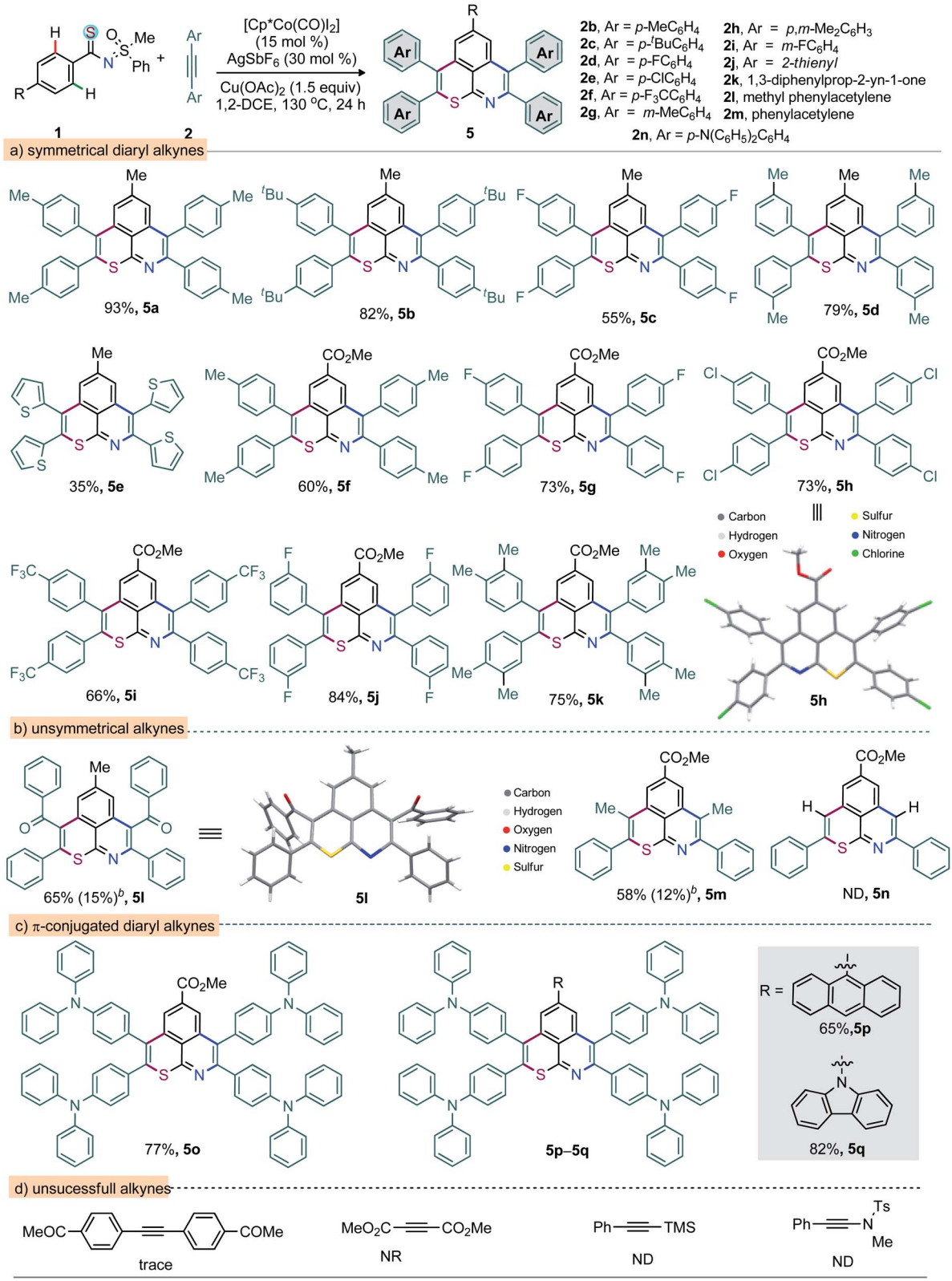
To probe the reaction generality, the double annulation of MPS-enabled thioamides **1a–s** (prepared *via* EDC coupling of aryl carboxylic acids with MPS followed by the Lawesson reaction; see the ESI†) with alkynes was explored under the optimized conditions shown in Table 1, entry 16, and the results are detailed in Schemes 1–3.[45] At first, the 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 78–92% 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) also proved 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*-$CO_2$Me groups at the aryl moiety also reacted efficiently with **2a** to furnish **3m–o** in 69–84% yield (Scheme 1a). Thus, the electronic bias of thioamides did not virtually affect the reaction outcome. Of note, the weakly coordinating functionalities such as keto and pyridyl groups did not affect the reaction outcome. Efforts towards the synthesis of MPS-enabled thioamides showed that strongly directing groups like the 2-pyridyl or the 2-pyrazole moiety were unsuccessful. 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, the MPS-DG is highly precise for site selective C–H metalation and annulation sequence of thioamides in the presence of other coordinating groups.[46,47] 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 bonds imposed by the *meta*




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)$I_2$] (15 mol%), $AgSbF_6$ (30 mol%), and $Cu(OAc)_2$ (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)$I_2$] (20 mol%), $AgSbF_6$ (40 mol%), $Cu(OAc)_2$ (0.6 mmol), and 1,2-DCE (3.0 mL) at 130 °C for 36 h.

$R^2$ group, it is likely that the first annulation takes place at the less hindered one.[48]

The structure of the major product would therefore indicate whether 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

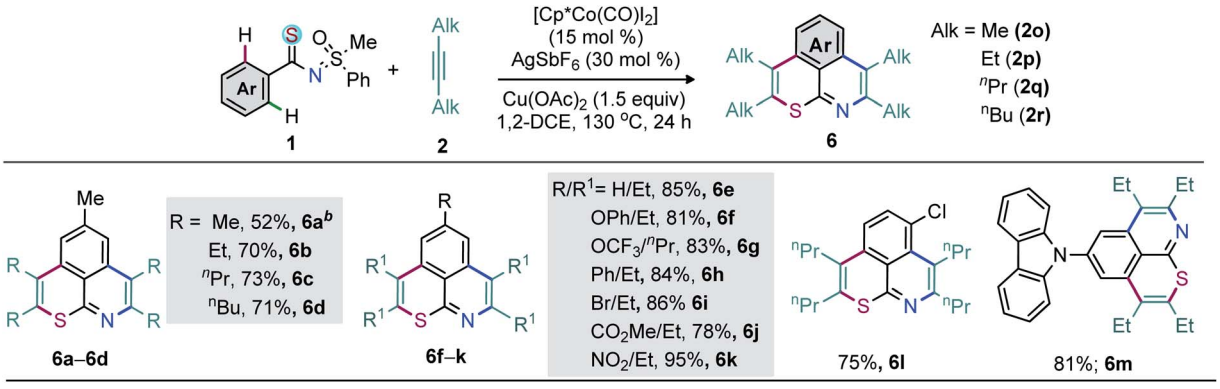



Scheme 2 Double annulation of **1** with 1,2-diarylacetylenes[a]. [a]Reactions were carried out with **1** (0.3 mmol), **2** (0.9 mmol), [Cp*Co(CO)$I_2$] (15 mol%), $AgSbF_6$ (30 mol%), $Cu(OAc)_2$ (0.45 mmol), and 1,2-DCE (2.0 mL) at 130 °C for 24 h. [b]Other isomers. NR = no reaction. ND = not determined.

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**.[49] 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. The mixtures of regioisomers also originated 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 the photophysical properties of the molecular skeleton.[50] Thus, anthracene- and carbazole-anchored thiopyrano-isoquinolines **3y** (70%) and **3z** (84%) were successfully prepared (Scheme 1c). Meanwhile, the *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* the 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-diarylalkynes (**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, the 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*-$CO_2$Me 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**.[49] Thus, alkynes with electronic bias have no detrimental effect on the double annulation sequence. Next, unsymmetrical alkynes were tested. The reactions of **1a** with **2k** and **1o** with **2l**, respectively, delivered **5l** (65%) and **5m** (58%) as the major products along with other minor regioisomers (Scheme 2b). The structure of **5l** was confirmed by X-ray analysis.[49] Thus, the oxidative annulations follow a 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.[7,8,51] However, phenyl acetylene (**2m**) provides a 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. On the other hand, the reaction was unsuccessful with electron deficient alkynes such as 1-[4-(4-acetyl-phenylethynyl)-phenyl]-ethanone and dimethyl acetylene dicarboxylate, silylated alkynes and ynamides.

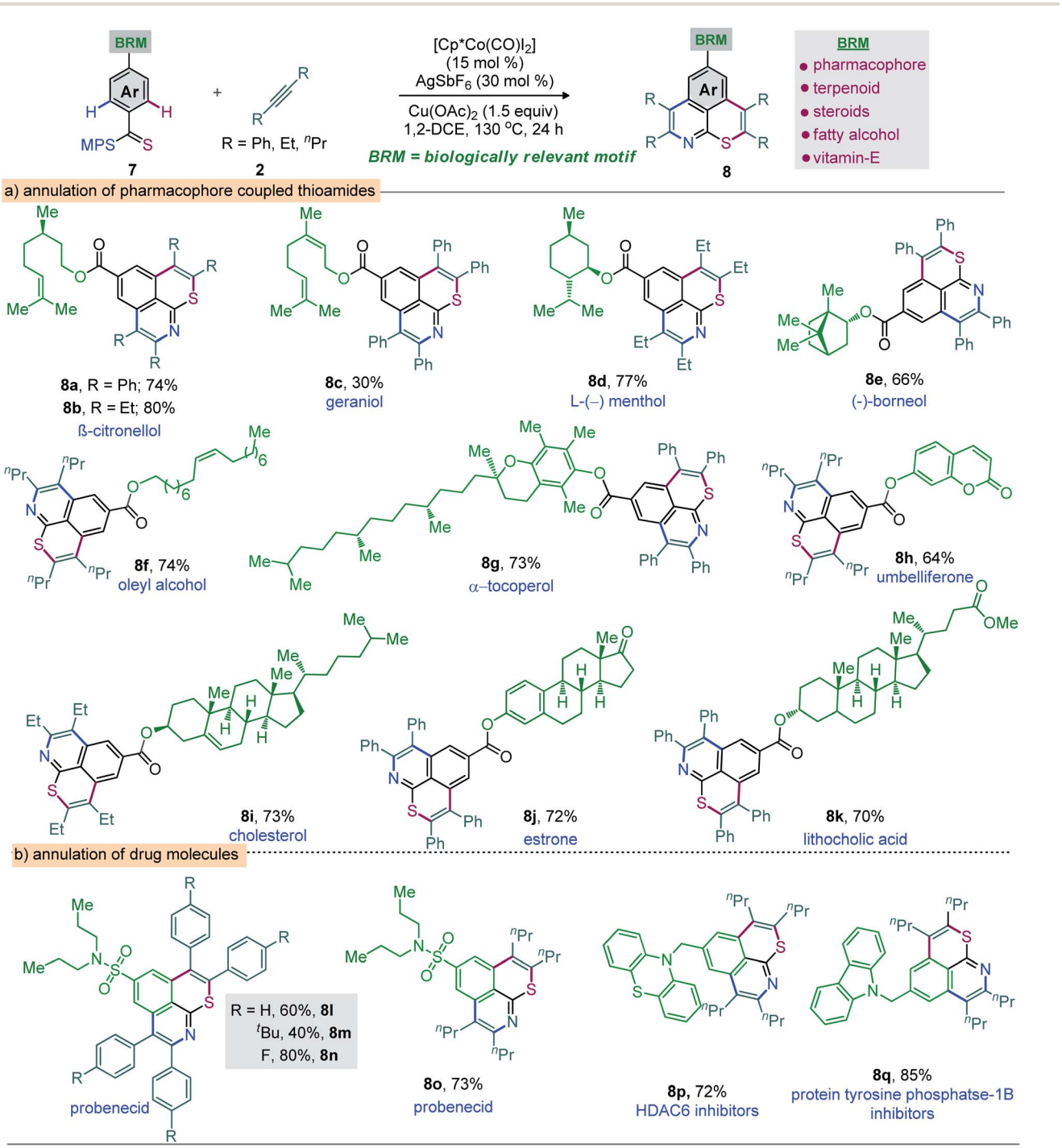
Not only 1,2-diarylalkynes but also 1,2-dialkylalkynes (**2o–r**) are relevant partners in this cascade double annulation (Scheme 3). In this context, 2-butyne (**2o**), 3-hexyne (**2p**), 4-octyne (**2q**), and 5-decyne (**2r**) were independently reacted with **1a** to furnish a range of peripheral decorated thiopyrano-isoquinolines **6a–d** (52–73%). Analogously, **6e** was synthesized in 85% yield. The annulation of thioamides bearing either electron-donating (OPh and $OCF_3$), arene (Ph), halo (Br), and electron-withdrawing ($NO_2$ and $CO_2$Me) substituents in the *para* position of the phenyl ring with **2p**/**2q** was also accomplished, providing **6f–k** in good yields (Scheme 3).

Moreover, the annulation of *m*-Cl bearing thioamide **1l** with **2q** led to **6l** with high regioselectivity. Thus, transformable groups (*i.e.* $CO_2$Me, $NO_2$, Br, and Cl) can be easily introduced and could lead to further structural modifications. Finally, the π-conjugated carbazole-molded thiopyrano-isoquinoline framework **6m** (81%) was synthesized (Scheme 3). The directed late-stage functionalization (LSF) of C–H bonds has been largely applied for the structural diversification of natural/non-natural products through site-specific introduction of




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)$I_2$] (15 mol%), $AgSbF_6$ (30 mol%), $Cu(OAc)_2$ (0.45 mmol), and 1,2-DCE (2.0 mL) at 130 °C for 24 h. [b]**2o** (30 mmol).

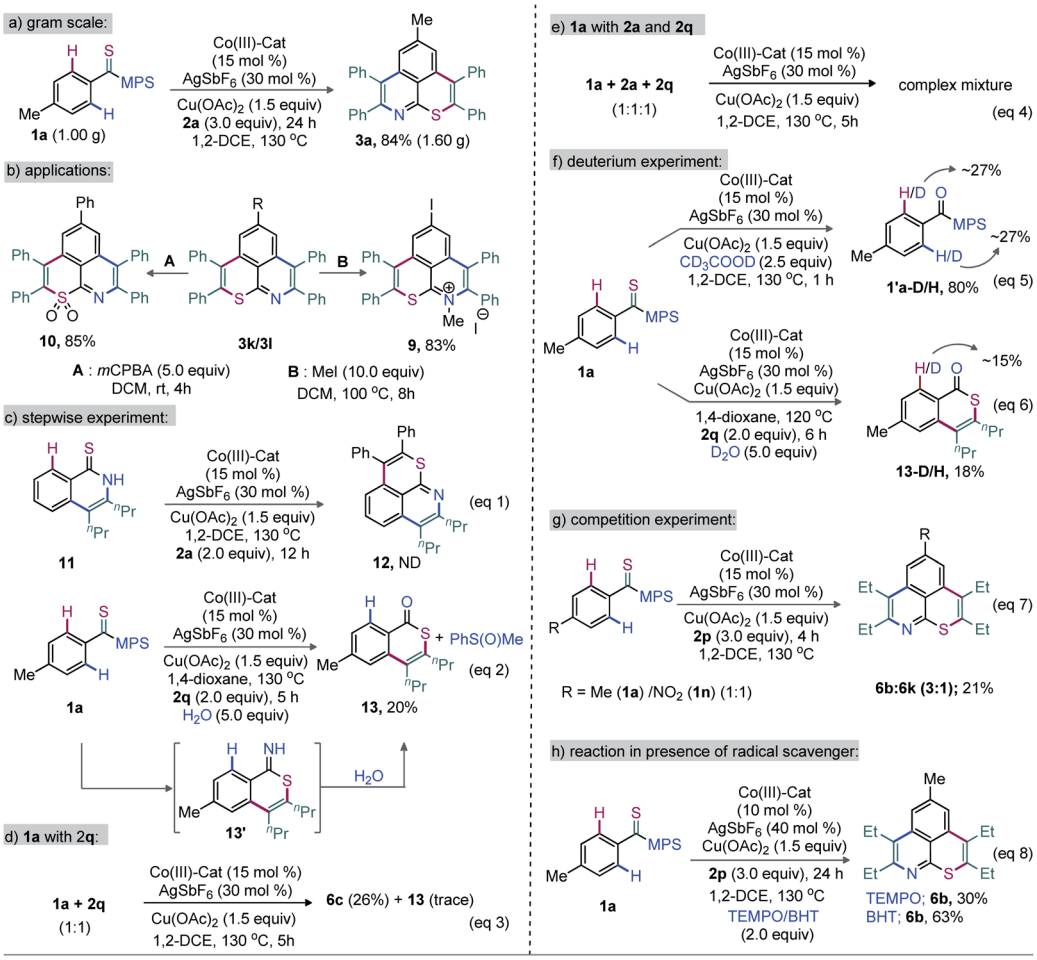
functional groups on the unactivated sites of complex molecules.[52–55] In this context, the late-stage annulation of (hetero) arene C–H bonds of biologically relevant motifs (BRMs) is invaluable for the sustainable development of complex molecules with enhanced pharmacokinetic properties. However, BRMs exhibiting polar groups and unsaturated moieties invariably cause 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**) and geraniol (**8c**)], natural products [menthol (**8d**) and borneol (**8e**)], fatty alcohols [oleyl alcohol (**8f**) and vitamin-E-tocopherol (**8g**)], coumarin [umbelliferone (**8h**)], and steroids [cholesterol (**8i**), estrone (**8j**), and lithocholic acid (**8k**)] were




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), and 1,2-DCE (2.0 mL) at 130 °C for 24 h.

produced in 30–80% yields from the cascade annulations of respective pharmacophore-coupled MPS-thioamides with alkynes **2a**/**2p**/**2q** (Scheme 4a).[52,53] 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).[54,55] The targeted uricosuric renal tubular blocking agent probenecid-fused-thiopyranoisoquinolines **8l–o** were prepared in good yields. No site selective functionalization of the arene C–H bond proximal to the sulfonamide group took place. Likewise, HDAC6 inhibitor *N*-benzylphenothiazine **8p** and protein tyrosine phosphate-1B inhibitor *N*-benzylcarbazole **8q** fused thiopyranoisoquinolines were constructed in 72% and 85% yields, 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 on a gram scale: **3a** (1.60 g, 84%) was prepared from the reaction of **1a** (1.0 g, 3.45 mmol) with **2a** (1.85 g, 10.36 mmol) in the presence of the Co(III) catalyst (Scheme 5a). The 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-(2*H*)-thione (**11**) and **2a** was carried out under the optimized conditions at 130 °C for 12 h (Scheme 5c, eqn (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 **2q** 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, eqn (2)). This information clearly suggests that the first annulation involves the thioamide 'S' moiety over 'N' to form imine intermediates such as **13'** (Scheme 5c, eqn (2)). Eventually, the hydrolysis of **13'** furnishes **13**. Under dry conditions, a second




Scheme 5 Gram scale, applications, and controlled experiments.

annulation of **13'** with the alkyne could produce the thiopyrano-isoquinoline scaffold. A reaction between **1a** and **2q** (1.0 equivalent each) under the standard conditions led to **6c** in 26% yield with a trace of **13** (see eqn (3), Scheme 5d). On the other hand, the reaction of **1a** with an equimolar mixture of **2a** and **2q** provided a complex mixture of four annulation products, leading to a tedious and unsuccessful purification (Scheme 5e, eqn (4)). We next ran various D/H exchange experiments of **1a** (Scheme 5f, eqn (5) and (6)). Exposing **1a** to the standard conditions in the presence of $CD_3CO_2D$ (2.5 equiv.) at 130 °C resulted in D-incorporation at the C2 (27%) and C6 (27%) positions of **1'a-D/H** (80%) (eqn (5)). Similarly, 15% deuterium incorporation occurred at the proximal C(arene)–H of iso-thiochromenone **13-D/H** (18%) when the reaction of **1a** with **2q** was performed in the presence of $D_2O$ (eqn (6)). Therefore, the 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 5g, eqn (7)). Moreover, the reaction was still possible in the presence of radical scavengers (TEMPO and BHT); the possible involvement of a radical pathway is therefore discarded (Scheme 5h, eqn (8)).

DFT computations were carried out to validate the proposed mechanism. The Gaussian 09 software package was used[56] with its implemented M06 functional,[57] the 6-31G(d,p) basis set[58,59] for all main group elements, and the LANL2DZ (ECP) basis set for Co.[60–62] Single point calculations were conducted at the M06/6-311++G(d,p)-SDD(ECP)[63] level of theory. Solvation energies were obtained at the single point level using the SMD approach for 1,2-dichloroethane.[64] The discussed values are solvent-corrected Gibbs free energies at 393.15 K in kcal $mol^{-1}$ ($\Delta G_{393}$). A 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. 2). In general, the Cp cobalt(III) complexes can adopt singlet (S), triplet (T), and quintet (*Q*) spin states.

In agreement with our previous studies,[65,66] 16-electron complexes are more stable in the triplet state. For instance, complex **D** shows $\Delta E_{S-T} = -3.8$ kcal $mol^{-1}$ and $\Delta E_{S-Q} = 20.0$ kcal $mol^{-1}$. On the other hand, 18-electron complexes are usually more stable in the singlet state; complex **E** for instance exhibits $\Delta E_{S-T} = 7.8$ kcal $mol^{-1}$ and $\Delta E_{S-Q} = 25.9$ kcal $mol^{-1}$. 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 (MECPs) 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 $mol^{-1}$ (−12.1 kcal $mol^{-1}$ without the solvent effect). The hydrogen bond with the acetate ligand and an $\eta^1$-coordination between Co and the ipso-carbon make the concerted-metalation-deprotonation (CMD) process viable. The C–H metalation then occurs through $TS_{BC}$, lying 12.8 kcal $mol^{-1}$ above the reference system. The resulting metallacycle **C** is only 0.2 kcal $mol^{-1}$ more stable than **A**. Importantly, the coordination of the 'N' atom of the MPS instead of thioamide 'S' led to a complex located at 16.3 kcal $mol^{-1}$ and the corresponding C–H metalation transition state was found at 26.6 kcal $mol^{-1}$ instead of 12.8 kcal $mol^{-1}$ 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

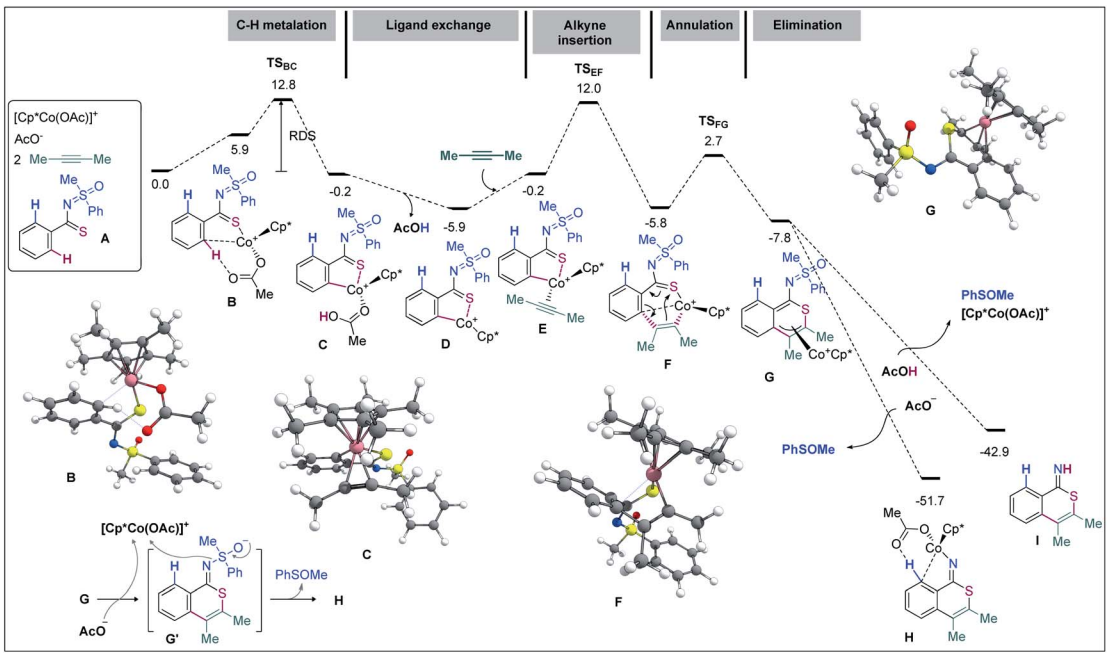



Fig. 2 Free energy profile ($\Delta G_{393}$, kcal $mol^{-1}$): part 1 (first annulation).

−0.2 kcal mol$^{-1}$ on the free energy surface). The migratory alkyne insertion of **E** produces the seven-membered complex **F** (−5.8 kcal mol$^{-1}$), where the metal receives electron density from the aryl moiety. This step passes through $TS_{EF}$, lying at 12.0 kcal mol$^{-1}$, and is exergonic by 5.6 kcal mol$^{-1}$. Next, the 6π-electrocyclization of **F** gives the π-allyl intermediate **G** at −7.8 kcal mol$^{-1}$. The corresponding transition state, $TS_{FG}$, was found as low as 2.7 kcal mol$^{-1}$ on the surface. The $AcO^-$ mediated removal of PhSOMe of **G** affords **H** (−51.7 kcal mol$^{-1}$) *via* **G′** (Fig. 2), which is useful for the second CMD process. Alternatively, the protonation of **G** with AcOH provides the otherwise stable compound **I** at −42.9 kcal mol$^{-1}$.[67] The second annulation pathway is shown in Fig. 3. 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 a free energy of activation of 12.5 kcal mol$^{-1}$ and is exergonic by 7.5 kcal mol$^{-1}$ to provide **M**. The reductive elimination of **M** passes through $TS_{MN}$ requiring 7.7 kcal mol$^{-1}$ to produce **N** (found at −95.8 kcal mol$^{-1}$). This irreversible step leads to the experimentally observed tricyclic product with a release of 36.8 kcal mol$^{-1}$. The ligand exchange of **N** with **A** further lowers the free energy by 3.0 kcal mol$^{-1}$ to produce the final product **O** (at −98.8 kcal mol$^{-1}$) along with **P**. The $Cu(OAc)_2$ mediated oxidation of complex **P** provides **B** for a new cycle.[68,69]

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 Fig. 4.[1,3] At the outset, iodide abstraction and ligand exchange among $Cp^*Co(CO)I_2$, $AgSbF_6$, and $Cu(OAc)_2$ at first

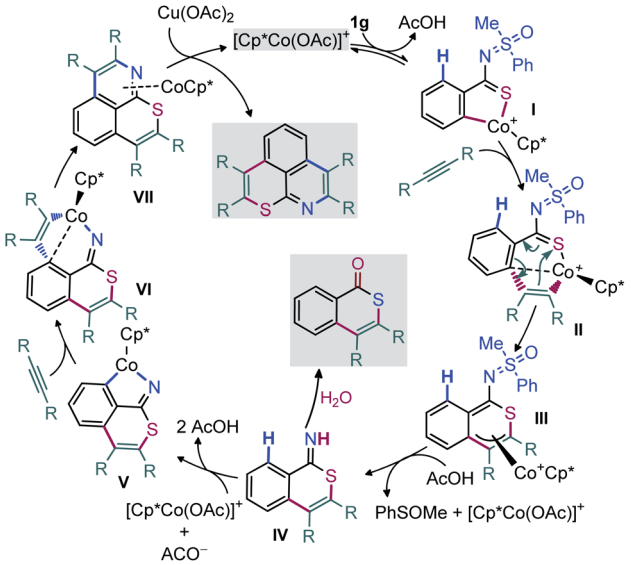



Fig. 4 Plausible catalytic cycle.

provide the active cationic $[Cp^*Co(OAc)]^+$ catalyst. Thereafter, the coordination of 'S' in thioamide with the active species, followed by the activation of the proximal *o*-C(arene)–H bond, forms the five membered cyclocobalated species **I**; this C–H dissociation follows a CMD process (see eqn (5) and (6) in Scheme 5).

Next, the migratory insertion of an alkyne into **I** affords a cyclic seven-membered Co-intermediate **II**. The 6π-electrocyclization of **II** then provides the π-allyl intermediate **III**.

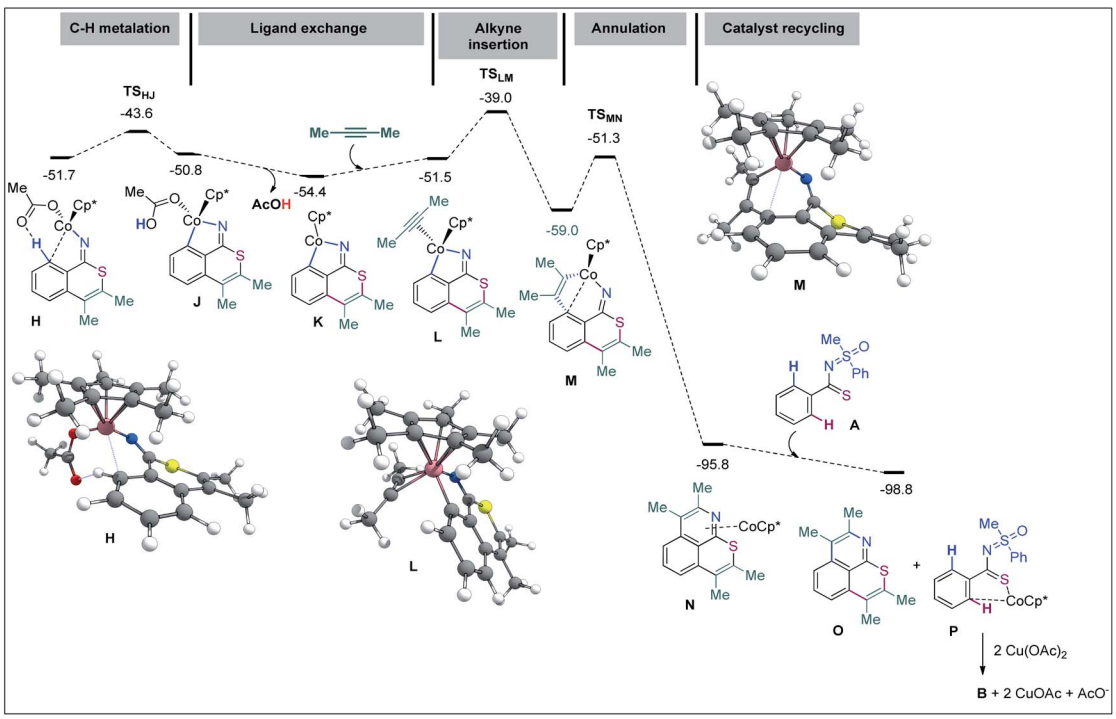



Fig. 3 Free energy profile ($\Delta G_{393}$, kcal mol$^{-1}$); part 2 (second annulation).

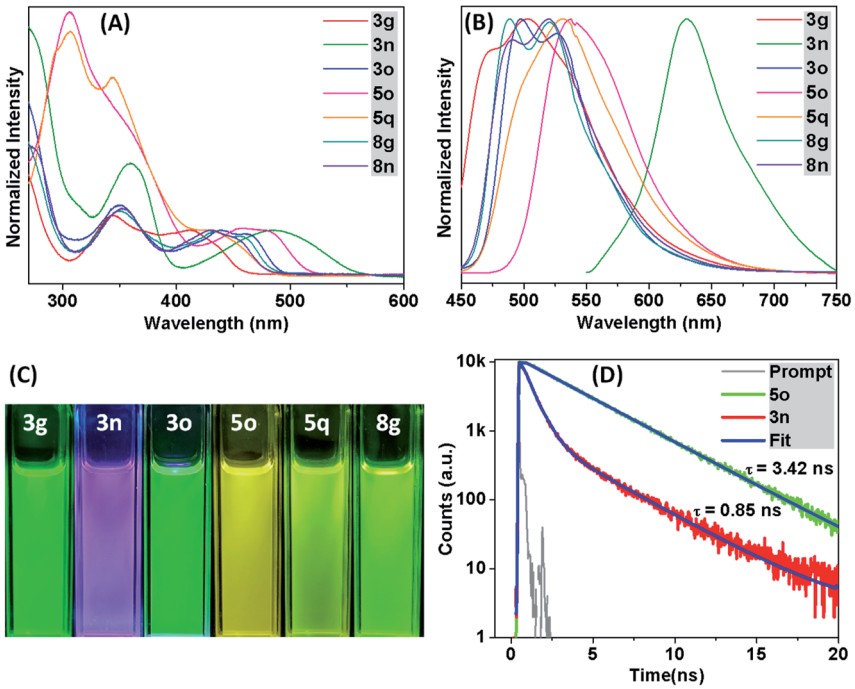



Fig. 5 Normalized absorption (A) and fluorescence (B) spectra in DCM at RT ($10^{-5}$ M); observed fluorescence under UV excitation (365 nm) (C); life time measurements (D).

Acetate mediated formal elimination of $[Cp^*Co(OAc)]^+$ and concurrent expulsion of sulfoxide provide the imine intermediate **IV**. Importantly, the intermediate **IV** is prone to hydrolysis in the presence of $H_2O$ to form an isothiochromenone. Afterwards, the imine assisted activation of the *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**. The reductive elimination of the latter delivers the expected thiopyrano-isoquinoline product **3a** as a ligand of the Co(I) complex **VII**. Finally, $Cu(OAc)_2$ regenerates the active Co(III) catalyst for the next cycle. The intramolecular 6π-electrocyclization (that involves 4π-electrons of arylthioamide and 2π-electrons 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 the 1st annulation (**III** → **IV**) as well as providing active imine intermediate **IV** for an 'N' assisted 2nd annulation process (Fig. 4). Most of the synthesized thiopyrano-isoquinoline derivatives are brightly fluorescent. To probe the photophysical properties of the molecules, steady-state absorption (Fig. 5A) and emission (Fig. 5B) experiments were carried out. Most of the compounds exhibit strong absorption bands at 344–360 nm and 412–486 nm (Fig. 5A), while the emission maximum lies around 503–630 nm (Fig. 5B) with large Stokes shifts of 81–144 nm. Solvatochromic study (Fig. 5C) did not show any intense colour change or fluorescence intensity variation. This phenomenon clearly reveals that the fluorescence originates from the core structure of the compounds. Interestingly, the excitation of $-NO_2$ or $-CO_2Me$ group bearing π-extended compounds **3n–o** induces signification bathochromic shifts in emission.

Likewise, the ester linked biologically relevant motifs **8g** and **8n** also show intense emission bands and could be useful as fluorescent drug carriers as well as fluorescent probes for cell imaging.[50] The enhanced fluorescence properties of π-extended scaffolds **5o** and **5q** with a longer life time[70] (3.42 ns for **5o**; Fig. 5D) 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 arene *o*,*o*′-C–H bonds of thioamides through sequential coupling with alkynes; (2) the reactivity preference of 'S' over 'N' in the annulation process of thioamides; (3) the formation of four bonds [C–C, C–S, C–C, and C–N] in a single operation; (4) the overcoming of 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 groups 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 a crucial role in this double annulation of thioamides. Preliminary photophysical studies of thiopyrano-isoquinolines are encouraging and they 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.

## Author contributions

M. S. and A. K. S. designed and investigated. M. S., A. S., S. S. and A. G. performed the experiments. DFT study done by V. G. UV and FL studies done by A. S., A. K. S. and V. G. wrote the paper. Review, editing & supervision done by A. K. S.

## Conflicts of interest

There are no conflicts to declare.

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