Dehydrogenative Cross-Coupling

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Cobalt-Catalyzed C–H Thiolation through Dehydrogenative Cross-Coupling

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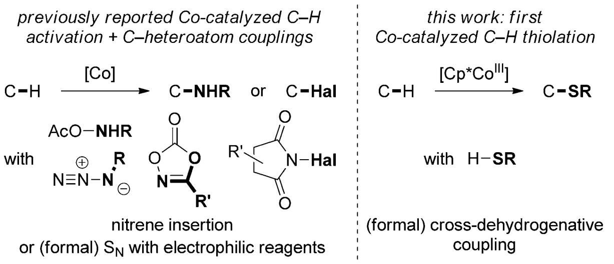
Dedicated to Professor Gerhard Erker on the occasion of his 70th birthday

Abstract: *A cobalt-catalyzed dehydrogenative cross-coupling of thiols and indoles is reported. Using a cooperative reaction system, a new mode of action for the cobalt-catalyzed C–heteroatom bond formation was found. The directed C–H activation catalysis overrides an undirected thiolation of indole in the 3-position that occurs in the absence of cobalt. Mechanistic studies indicate a sequence of C–H activation, thiolate transfer, and reductive elimination.*

The direct functionalization of C–H bonds is one of the most expedient ways of introducing and expanding molecular complexity[1] and research is currently focused on developing applicable transformations using abundant metals such as cobalt as catalysts.[2] Several distinct catalyst systems featuring cobalt in various oxidation states and employing unique precursors and ligands have been found.[3] On the one hand, modular systems typically consisting of a Co^{II} precursor, ligands, and catalyst modifiers such as Grignard reagents or oxidants are powerful catalysts for the directed C–H activation followed by C–C coupling with organometallic reagents, electrophiles, or unsaturated moieties.[4] On the other hand, well-defined Cp^*Co^{III} complexes ($Cp^* = C_5Me_5$) proved to be C–H activation catalysts that can compete with the performance of their noble metal congeners in the synthesis of functionalized products and in some cases offer distinct reactivity.[5] Introduced by the group of Matsunaga and Kanai[6] and taken up by Ackermann,[7] Chang,[8] Ellman,[9] Glorius,[10] and others,[11] Cp^*Co^{III} complexes have been used in directed C–C and, less commonly, C–N and C–Hal coupling reactions.[12] The general mechanistic patterns of metallacycle functionalization in these examples tend to be limited to addition/insertion with unsaturated reaction partners and formal nucleophilic substitution reactions where the organocobalt intermediate generated by C–H activation is the nucleophile (Scheme 1).

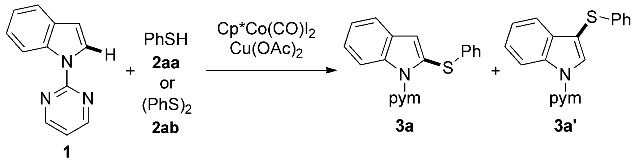


Scheme 1. Cobalt-catalyzed formation of a C–heteroatom bond by C–H activation.

We envisioned a dehydrogenative C–H thiolation based on C–H activation catalyzed by the Cp^*Co^{III} catalyst.[13] This process involves two main challenges. Firstly, sulfur compounds can cause catalyst deactivation. We reasoned that the "hard" nature of the Cp^*Co^{III} moiety might alleviate this problem. Secondly, the transformation requires a finely tuned oxidant system to achieve catalyst turnover and prevent overoxidation.

The thioether moiety is common in bioactive compounds and intermediates in the synthesis of organic materials.[14] The direct thiolation of C–H bonds presents an attractive strategy for the introduction of this valuable motif. Nevertheless, despite recent advances in this direction[15] there is still need for complementary methods in order to attain a broader utility of this transformation. Herein we report the unique reactivity of the Cp^*Co^{III} catalyst to promote the first cobalt-catalyzed C–H thiolation. C2-Thiolated indoles are obtained selectively in good to excellent yields with a high degree of functional-group tolerance employing a cooperative system with Cu^{II} as well as Lewis acid additives.

Initially, we explored the thiolation of *N*-pyrimidyl indole (**1**) in 1,2-dichloroethane (DCE) at 80 °C in the presence of various oxidants (Scheme 2). $Cu(OAc)_2$ selectively mediates the thiolation in the 3-position of the indole in the absence of Cp^*Co^{III} (**3a'**).[16] However, a switch in regioselectivity was observed in the presence of Cp^*Co^{III}: with thiophenol, the desired 2-phenylthioindole **3a** is formed nearly exclusively in 29 % yield. Optimization of the reaction conditions led to



Scheme 2. Initial studies on the regioselective C–H thiolation of **1**.

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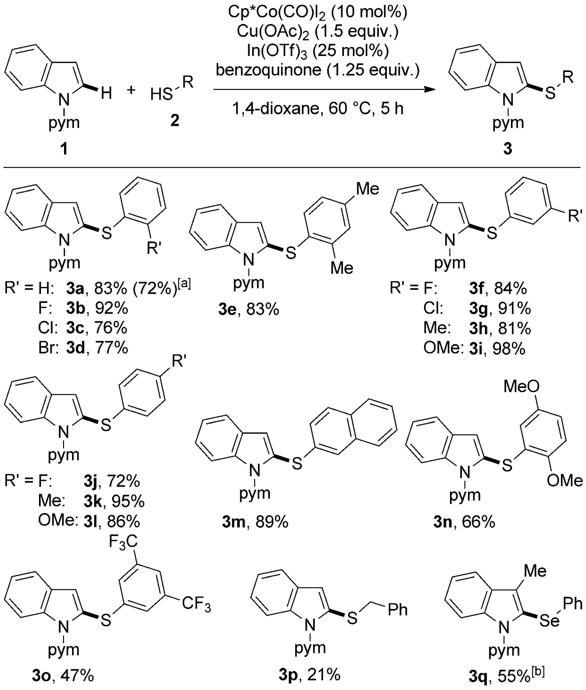
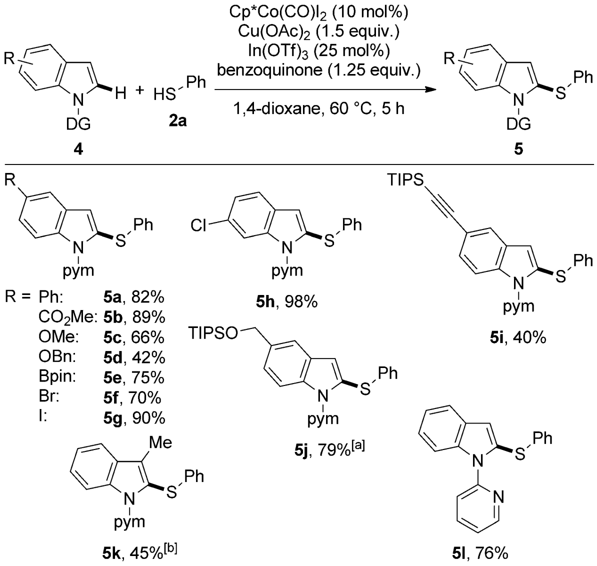
83% yield of **3a**; the reaction was conducted with a co-oxidant system of Cu(OAc)$_2$ and benzoquinone[6c] as well as In(OTf)$_3$ as an additive in 1,4-dioxane at 60°C after 5 h (for more information on the optimization, see the Supporting Information (SI)). The desired regioselectivity was confirmed by crystal structure analysis of **3a**.[17] A gram-scale reaction with 5 mol% of [Cp*CoI$_2$]$_2$ gave 72% yield of **3a**.

The reaction tolerates a wide range of substituents on both the thiol and the indole reaction partners (Scheme 3). We found no systematic influence of substituents in the *ortho*-, *meta*-, or *para*-positions or slight modifications of the electronic properties at the thiol. Thus, halide- (**3b–d**, **3f**, **3g**, **3j**), methyl- (**3e**, **3h**, **3k**), and methoxy-substituted (**3i**, **3l**) 2-arylthioindoles as well as a naphthylthioindole (**3m**) were obtained in 72–95% yield. Notably, both of the electronically most varied thiols afforded the corresponding dimethoxy- (**3n**) and bis(trifluoromethyl)- (**3o**) substituted products in slightly decreased yields of 66% and 47%, respectively. Gratifyingly, the thiolation could be extended to benzyl mercaptan, providing benzylthio indole **3p** in 21% yield. Using our protocol, we furthermore achieved the directed selenation in 55% yield (**3q**) using diphenyl diselenide as reaction partner. No desired product was obtained from heteroaryl or saturated alkyl thiols.



Scheme 3. Scope of thiols. Reactions performed on 0.5 mmol scale with 2.0 equiv of **2** in 1.25 mL solvent, yields of isolated product are given. [a] 5 mmol scale, 5 mol% [Cp*CoI$_2$]$_2$ as catalyst, 11 h. [b] With 3-methyl-1-pyrimidylindole and (PhSe)$_2$ (1 equiv), 22 h.

A wide range of indoles with protecting groups and functionalities commonly used in synthesis can be thiolated under the optimized reaction conditions (Scheme 4). For example, ester (**5b**), methyl ether (**5c**), and silyl ether (**5j**) are well tolerated, providing protected 2-phenylthioindoles in 66–89% yield. The presence of a benzylether resulted in a lower yield (**5d**, 42%). Products containing pinacol boronate (**5e**, 75%), halides (**5f–h**, 70–98%), or a silyl alkyne (**5i**, 40%) can be used for further derivatization. The product of a sterically hindered 3-methyl indole (**5k**) was obtained in 45% yield even after a prolonged reaction time. The *N*-pyridyl moiety can be employed as a directing group in the thiolation (**5l**, 76%), yet other directing groups were found to be inefficient.



Scheme 4. Scope of indoles. Reactions performed on 0.5 mmol scale with 2.0 equiv of **2a** in 1.25 mL solvent, yields of isolated product are given. [a] 0.2 mmol scale. [b] 20 h reaction time.

A robustness screen[18] was carried out to expediently characterize further functional-group and heterocycle tolerance of the protocol (for details see the Supporting Information). The pyrimidyl directing group can be removed under basic conditions from the products to generate thiolated free *N*-H indoles, as exemplified with product **3a** in 90% yield.

Intrigued by the novelty of the reactivity underlying this transformation, we wanted to gain insight into its mechanism and the role of each reaction component. Firstly, control experiments confirmed the unique role of Cp*Co^{III} as the catalyst in this transformation. Only traces of **3a** were detected when [Cp*RhCl$_2$]$_2$, other cobalt salts, or Sc(OTf)$_3$ (a Lewis acid substitute) were used. Both Cu(OAc)$_2$ and In(OTf)$_3$ are essential for product formation as well, while the absence of benzoquinone lowers the yield of **3a** to 41%. Under the optimized reaction conditions, a mixture of the 3- and 2-thiolated indoles **3a′** and **3a** (8% and 12%, respectively) is obtained when Cp*Co is omitted.[19]

While the reaction can be performed using AgSbF$_6$, In(OTf)$_3$ provided better yields than those obtained with the silver salt commonly used for abstracting halides from the cobalt precatalyst. To probe the role as a halide abstractor, we employed a precatalyst featuring very weakly coordinating B(C$_6$F$_5$)$_4$ anions that does not require halide abstractors.[9] Under the standard conditions, 59% yield of **3a** was formed using this precatalyst, along with an increased amount of **3a′**. Without In(OTf)$_3$, only 10% yield of **3a** was formed. Thus, we assume this additive has a secondary role besides halide abstraction from the precatalyst. As most other Lewis and carboxylic acid additives did not improve the yield, we assume In^{III} has a beneficial effect on the coordination chemistry of thiolates, which are known to form polynuclear complexes with copper and other metals.

Thiophenol can be oxidized to thiolate radicals by Cu^{II}. From radical trapping studies and the selectivity of thiolation of *N*-methyl indole at the 3-position, we conclude that the occurrence of radical species in the reaction cannot be ruled out but a mechanism involving radicals for the formation of the desired product seems unlikely (for details see the Supporting Information).

In a competition experiment, the electron-rich 5-OMe indole **4c** is favored over the electron-poorer 5-CO_2Me indole **4b** (23 % vs. 10 % yield after 10 min). This can either reflect properties of an electrophilic C–H activation mechanism, a higher stability of a C–H metalated intermediate of more electron-rich indoles, or a beneficial influence of the increased nucleophilicity on a functionalization step. Likewise, the electron-rich 4-methoxythiophenol (**2l**) was favored over 3,5-bis(trifluoromethyl)thiophenol (**2o**) (17 % vs. 13 % yield after 10 min), yet the small effect precludes an interpretation.

Mass spectrometric analysis of the reaction mixture after 5 min revealed the presence of the cobaltacycle generated by C–H activation of **1** as well as the complex of this cobaltacycle with a phenyl thiolate. Other detected species include $[Cp^*Co(OAc)]^+$, cobalt thiolates, and coordination complexes of copper(I) and copper(II) with **1** and/or **3a**.

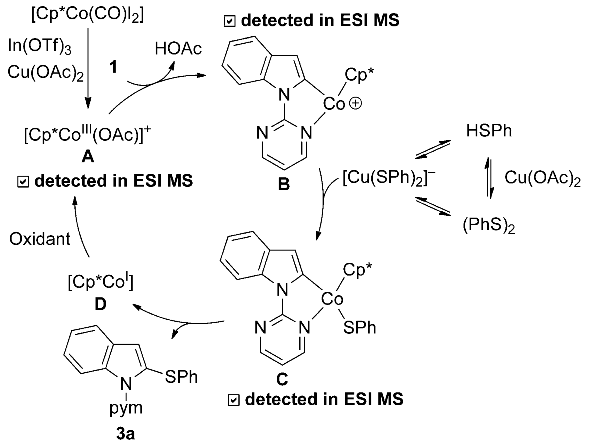
Copper plays an essential role in the formation of an active thiolation agent. Also, the original sulfur source influences the reaction outcome (Table 1). While the thiolation reaction occurs with both thiophenol and diphenyl disulfide, lower regioselectivity is observed with the disulfide. The thiolation also proceeds readily with CuSPh, providing 75% yield of **3a** with, and 27% without $Cu(OAc)_2$. The nature of the ultimate thiol source in the reaction was probed by a reactivity analysis of these sulfur compounds. After only 15 min, the reaction is almost complete with both PhSH and CuSPh, yet only traces of **3a** are present with $(PhS)_2$. Clearly, more time is required for the formation of an active thiolating agent from the disulfide. For additional insight on the interchange of the sulfur species in the reaction, we performed a pretreatment test, adding the indole substrate only after stirring the rest of the reaction mixture at 60 °C for 30 min. After another 15 min, 22 % yield of **3a** had formed in the reaction with the disulfide. Conversely, the yield with CuSPh was decreased to 33 % and no significant difference in yield was observed with PhSH (Table 1). Evidently, PhSH is transformed into an active thiolating agent much faster than the disulfide. PhSCu is converted into a less reactive species under the reaction conditions, likely to the disulfide. Anionic Cu^I complexes like $[Cu(SPh)_2]^-$ have been suggested as the active species in copper-catalyzed C–S cross-coupling.[20] Our results are indicative of similar species as intermediates for the transmetalation of thiolates to cobalt.

Table 1: Reactivity study with different sulfur reagents in the reaction with **1**.[a]

Entry	[S]	**3a**; **3a′** 5 h	**3a**; **3a′** 15 min	**3a**; **3a′**, delayed addition of **1**[b]
1	PhSH (2 equiv)	95 %; –	79 %; –	82: –
2	$(PhS)_2$ (1 equiv)	63 %; 5 %	trace; trace	22 %; trace
3	PhSCu (2 equiv)	75 %; –	69 %; –	33 %; trace

[a] 10 mol% $Cp^*Co(CO)I_2$, 1.5 equiv $Cu(OAc)_2$, 1.25 equiv benzoquinone, 25 mol% $In(OTf)_3$, 1,4-dioxane, 60 °C. Yields determined by GC-FID with mesitylene as internal standard. [b] 30 min at 60 °C before addition of **1**, then 15 min at 60 °C.

On the basis of the evidence and literature precedent, we tentatively propose the mechanism shown in Scheme 5. The active catalyst **A** is formed from the precursor by iodide abstraction with $In(OTf)_3$ and acetate transfer. Directed C–H activation generates cobaltacycle **B**. Several copper and sulfur compounds can be present in varying oxidation states and degrees of association. Presumably, anionic Cu^I species transfer thiolate to **B**, forming cobalt thiolate **C**. Reductive elimination releases the product and a cobalt(I) species that is reoxidized by copper or benzoquinone to the active catalyst **A**. Alternative mechanisms include nucleophilic attack of **B** to an electrophilic Cu^{II} or Cu^{III} thiol species or transmetalation of the indole from **B** onto a copper species with subsequent reductive elimination of the product at copper.



Scheme 5. Proposed mechanism.

We have developed a cobalt-catalyzed dehydrogenative cross-coupling of thiols and indoles. A cooperative reaction system is employed to achieve a regioselective and robust transformation. This reaction represents a new mode of action for the cobalt-catalyzed formation of C–heteroatom bonds. The directed C–H activation catalysis overrides an undirected thiolation of indole in the 3-position that occurs in the absence of cobalt. Evidence is provided to support a mechanism including C–H activation, thiolate transfer, and subsequent reductive elimination.

Acknowledgements

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Keywords: C–H activation · C–heteroatom coupling · cobalt · cross-coupling · thiolation

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Communications

Dehydrogenative Cross-Coupling

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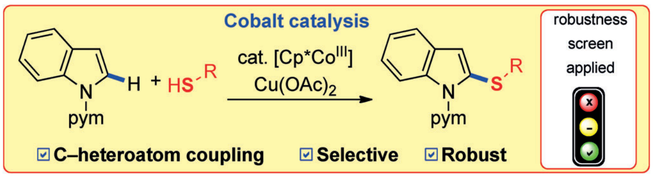
Cobalt-Catalyzed C−H Thiolation through Dehydrogenative Cross-Coupling



Co-laboration! A new method for the dehydrogenative cross-coupling of thiols and indoles features a novel mode of action for the cobalt-catalyzed formation of a C−heteroatom bond. Mechanistic studies indicate a sequence of C−H activation, thiolate transfer, and reductive elimination.