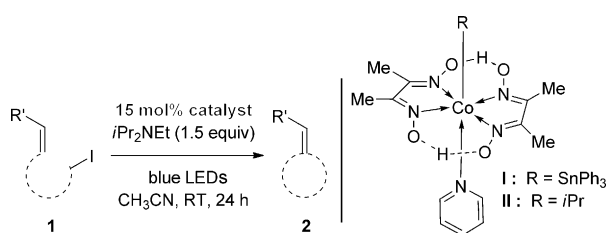


Cobalt-Catalyzed Coupling of Alkyl Iodides with Alkenes: Deprotonation of Hydridocobalt Enables Turnover**

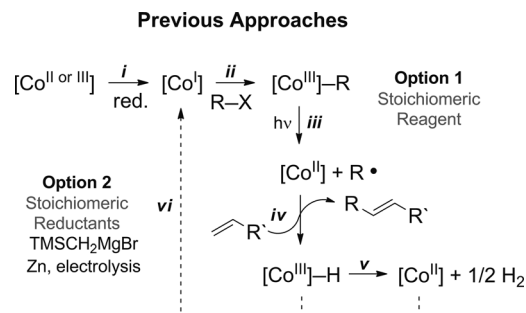
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The use of radical reactions to assemble complex molecular architectures is acknowledged as a very powerful tool in organic synthesis.^[1] The fact that transition metals can influence the reaction outcome has added further value to this field.^[2] Among the various metals used in radical additions, cobalt has a unique position.^[3] A particularly useful application formally corresponds to a Heck-type coupling, in which an alkyl group derived from an alkyl halide undergoes addition to an olefin followed by unsaturation to return a substituted olefin.^[4] Herein, we report an intramolecular, cobalt-catalyzed alkyl Heck-type reaction of alkyl iodides to olefins (Scheme 1, **1**→**2**). The transformation proceeds under exceptionally mild reaction conditions upon irradiation of the reaction vessel with visible light in the presence of an amine base. Significantly, catalysis is enabled by the presence of a base that deprotonates a putative hydridocobalt intermediate.



Scheme 1. Cobalt-catalyzed Heck-type cyclization.

Alkyl- or stannyl cobaloximes (bis(dimethylglyoximate)-cobalt), such as **I** and **II** and structurally related complexes, have emerged as useful radical precursors^[3,5b] and have been intensively investigated as model systems for coenzyme B₁₂.^[6] They are traditionally obtained in moderate yields by the reaction of a preformed cobalt(I) complex with an electrophile (Scheme 2, step *ii*).^[7,8] Once formed, these cobaloximes are air-stable and can be stored for months on the bench if kept in the dark.^[9] The light emitted by an incandescent lamp is usually sufficient to induce homolytic Co–R bond cleavage (step *iii*) and generate a Co^{II} complex along with intermedi-



Scheme 2. Previous use of organocobalt reagents/catalysts in alkyl Heck-type couplings.

ates (i.e. radicals), which are known to participate in a host of reactions.^[10] In synthetic applications employing stoichiometric organocobalt reagents the reactive intermediates most typically undergo addition to an olefin to give a new organocobalt species. These then undergo disproportionation (or formal β -hydride elimination) to give a new olefin and an hydridocobalt(III) (step *iv*). The latter subsequently decompose to H₂ and ill-defined Co^{II} complexes (step *v*).^[11b]

A number of groups have recognized that the regeneration of a cobalt(I) species (step *vi*) would enable catalysis (steps *ii*–*vi*). This has been most notably effected under reductive conditions, namely electrolytically, by Zn or by the stoichiometric use of Grignard reagents.^[12]

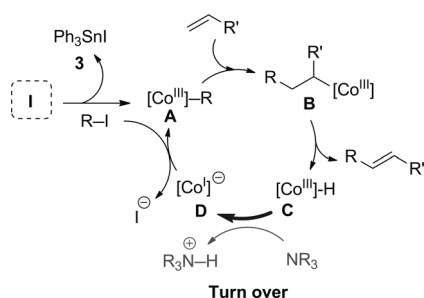
Careful analysis of these methods reveals potential complications with respect to functional group compatibility (e.g. aldehydes and ketones); indeed, it has been noted that enoates are unsuitable substrates in such Heck-type couplings.^[12a] We became intrigued with the possibility of generating a catalytic cycle under nonreductive conditions. Consequently, we envisioned the conversion of the hydridocobalt intermediate to the desired Co^I species by the action of base (Co^{III}–H + R₃N→Co^I + R₃NH⁺). In this respect, Schrauzer et al. have shown that hydridocobaloximes possess pK_a values of approximately 10 and are readily deprotonated under alkaline conditions.^[11]

In our working hypothesis for the Heck-type coupling of alkyl iodides and olefins, bench-stable cobaloxime complexes **I** and **II** were expected to provide convenient entry into a catalytic cycle. For example the reaction of **I**^[5b] and an alkyl iodide under irradiation would produce Ph₃SnI (**3**) and **A** (Scheme 3), which in turn should add to an olefin to afford adduct **B**. Following disproportionation, **B** would furnish a new olefin and hydridocobalt **C**. If the deprotonation of **C** could be effected under reaction conditions compatible with the overall process then a Co^I species **D** would be generated. A subsequent reaction with the starting alkyl iodide would

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Scheme 3. Working hypothesis for base-mediated catalytic alkyl Heck-type couplings.

regenerate **A** and thereby complete the catalytic cycle. Despite the simplicity of the proposed turnover step there is no literature report of its application to enable catalysis.

The hypothesis delineated above was investigated with substrate **4** using the readily prepared, air- and moisture-stable catalyst **I**.^[5] Irradiation (500 W sunlamp) of a 0.05 M solution of **4** (1 equiv), **I** (0.2 equiv), and *i*Pr₂NEt (1.5 equiv) in degassed^[13] MeCN for 16 h resulted in nearly full consumption (95 %) of **4** and produced a 5:1 mixture of the cyclization product **5** and the elimination product **6** (Table 1, entry 1).^[14] With the proof of concept validated, the effect of varying the reaction parameters was investigated for the purposes of optimization.^[15] Using the initial reaction conditions but with a lower catalyst loading (0.1 equiv) led to incomplete conversion (48 %; Table 1, entry 2). At higher concentrations of the reactants (0.1 M in **4**) a significant drop in reactivity (< 30 % conversion) was observed. The use of benzene as solvent^[5b] did not prove advantageous. The substitution of *i*Pr₂NEt for Et₃N or 1,8-bis(dimethylamino)-naphthalene did not significantly affect the conversion (see the Supporting Information). The importance of the cobalt catalyst (Table 1, entry 3) and irradiation (Table 1, entry 4) was established by conducting the corresponding control

experiments. As irradiation with light proved to be crucial, the use of another light source was investigated. Commercial blue-light-emitting diodes^[16] (LEDs; λ_{max} 465 nm) were selected on the basis of the absorption spectra of **I** and **II**.^[3f,5a] We were pleased to find that the reaction proceeded smoothly upon irradiation with blue LEDs, and full conversion was achieved after 16 h using only 10 mol % catalyst (Table 1, entry 5). When using blue LEDs, base was also necessary (Table 1, entry 6). The reaction rate depends strongly on the light density, and the best results were obtained if the flask was placed at a 5 mm distance from the LEDs.^[17] Tin-free catalyst **II** proved to be equally as efficient^[18] as **I** but afforded significantly higher amounts of elimination product **6** for this specific substrate (Table 1, entry 7). This is rather an unexpected outcome, which suggests that the stannane coproduct **3** is not an innocent bystander. Interestingly, temperature had no effect on the reaction outcome and identical conversion and selectivity was observed at 0 °C, 25 °C, and 65 °C.

With the optimized reaction conditions in hand, we investigated the functional group tolerance and the scope of the method (Table 2). The cobalt-catalyzed cyclization follows the same trend observed for free radical cyclizations, that is, the formation of 5-membered rings is highly preferred and products arising from 6-*endo* addition were not observed. In contrast to the model substrate **4**, elimination to furnish dienes was not observed to be in competition with the formation of 5-membered-ring products when either **I** or **II** were examined as catalysts. Addition to terminal, di- and trisubstituted olefins proceeds with high efficiency, and the last of these olefins is particularly noteworthy as it leads to a cyclization product incorporating a quaternary center (Table 2, entry 4).

As shown in Table 2, catalyst **I** outperforms **II** in the cyclization reactions. Importantly, secondary and sterically shielded primary iodides are only efficiently transformed to the cyclized products by **I**. The stereochemical information of secondary iodides is lost during the reaction (Table 2, entry 5). The formation of 6-membered rings proceeds only in synthetically useful yields if the olefin is activated with an electron-withdrawing group. The reaction conditions proved to be compatible with a broad range of functional groups including aldehydes, ketones, aryl iodides and aryl bromides, olefins, acetals, carbamates, pyridines, thiophenes, and unprotected alcohols (Table 2; entries 9–15). We note that substrates including nitroarenes, α -bromo- and α -chloro esters are unsuitable for the reaction, as the starting material remained unreacted. Additionally, mixtures of isomeric olefin products are observed when there are multiple β -H elimination pathways for the intermediate organocobalt species, as previously noted by Giese et al.^[12b]

The utility of the method described is further highlighted by a concise synthesis of (\pm)-samin (Scheme 4). Compound **7** was subjected to iodoetherification with NIS/allyl alcohol and the product was then subjected to the optimal reaction conditions, to afford known intermediate **8**^[19] as a single diastereoisomer in excellent yield. Tetrahydrofuran **8** was converted into (\pm)-samin following the sequence previously described.

Table 1: Effect of reaction parameters on the cobalt-catalyzed alkyl Heck-type reaction.

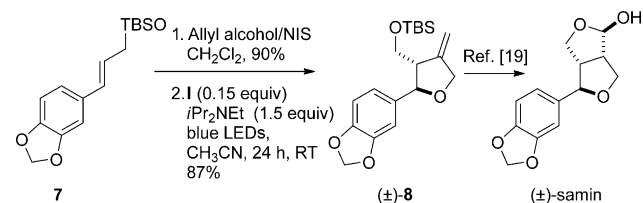
Entry	Cat. (equiv)	Light source	Conversion [%] (5/6) ^[a]
1	I (0.2)	sunlamp ^[b]	95 (5:1)
2	I (0.1)	sunlamp ^[b]	48 (5:1)
3	none	sunlamp	0
4	I (0.1)	no light ^[c]	< 5
5	I (0.1)	blue LEDs	> 95 (5:1)
6 ^[d]	I (0.1)	blue LEDs	10
7	II (0.1)	blue LEDs	> 95 (1.3:1)

Reaction conditions: **4** (0.05 M) in degassed MeCN. The sealed reaction vessel was placed in front of the light source (25 cm distance from sunlamp, 5 mm from LEDs) and irradiated for 16 h. [a] Conversion based on ¹H NMR analysis of crude reaction mixture. [b] 500 W tungsten halogen lamp. [c] Conducted at RT or 65 °C. [d] No *i*Pr₂NEt added. Bn = benzyl.

Table 2: Scope and functional group tolerance of the cobalt-catalyzed alkyl Heck-type cyclization.

Entry	Reactant	Product	Catalyst: yield [%]
1			I: 86 II: 91
2			I: 91 II: 85
3			I: 83 II: 47 ^[a]
4 ^[f]			I: 83 ^[b] II: 50 ^[a]
5 ^[f]			I: 82 II: < 5 ^[a]
6			I: 76 ^[c] II: 52 ^[c]
7			I: 89 II: 38 ^[a]
8			II: 91
9	X = 4-MeC ₆ H ₄		II: 81
10	X = 4-CNC ₆ H ₄		II: 84
11	X = 4-IC ₆ H ₄		II: 71 ^[d]
12	X = 2-BrC ₆ H ₄		II: 68 ^[e]
13	X = 4-(CH ₂ OH)C ₆ H ₄		II: 74
14	X = 4-(CHO)C ₆ H ₄		II: 78
15	X = thiophen-2-yl		II: 83 ^[e]

All experiments were run in degassed MeCN (0.05 M in substrate) in sealed Schlenk tubes. [a] Conversion based on ¹H NMR analysis of unpurified reaction mixture. [b] Yield after Jones oxidation of unpurified cyclization product. [c] Elimination accounts for the remaining material. [d] Catalyst II (0.3 equiv) used. [e] 48 h reaction time. [f] The relative configuration of the cyclized products was assigned in analogy to literature precedence for the reductive cyclization of these substrates. See Ref. [21]. BOC = *tert*-butoxycarbonyl.



Scheme 4. Synthesis of (±)-samin.

In summary, we have described a novel cobalt-catalyzed, intramolecular Heck-type coupling of alkyl iodides with olefins. The mild reaction conditions (*i*Pr₂NEt, cat. cobaloxime **I** and **II**, blue LEDs, RT) render the method compatible with a wide range of functional groups, such as amides, esters, ketones, and aldehydes. The development of the catalytic method follows from the key insight that a mild base can deprotonate a hydridocobalt intermediate and thereby regenerate a complex that is catalytically competent. In effect proton abstraction from an intermediate Co–H formally corresponds to reduction at the metal center.^[20] Future work will be dedicated to explore the effects of changing the catalyst structure, the axial ligand, and to expand this method to substrates beyond alkyl iodides and intramolecular couplings.

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