

Cobalt-Catalyzed Multi-Substituted Alkene Synthesis from 1,3-Dithiolanes and Grignard Reagents

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Dedicated to Professor Keiji Maruoka on the occasion of his 70th birthday.

Abstract: The cobalt-catalyzed reaction between 1,3-dithiolanes and Grignard reagents, for the efficient synthesis of multi-substituted alkene products, is described. The method was applicable to a variety of benzylic dithiolane substrates, affording di-, tri-, and tetra-substituted 1,1-diaryl alkene products in good to excellent yields. The use of benzylic

Grignard reagents with aryl aldehyde-derived 1,3-dithiolanes enabled access to natural product-derived stilbene architectures with exquisite *E* selectivity. The operational simplicity, low catalyst loadings, and scalability demonstrate the general utility of the method.

Introduction

Since the discovery of a cobalt-catalyzed Kumada-type cross-coupling by Kharasch in the 1940s,^[1] the development of cobalt-based alternatives to conventional cross-coupling methodologies has become an area of persistent interest in catalytic methodology expansion.^[2] This is primarily due to the cobalt catalyst systems not only enjoying relatively good natural abundance, low cost, and low toxicity in comparison to the commonly employed palladium and nickel salts, but also in achieving unique reactivity (such as suppressed β -hydride elimination)^[3] with respect to platinum group counterparts. The cobalt-catalyzed activation of C–S bonds^[4] for productive downstream coupling has remained a significant challenge, and has been achieved in only a few reports. A notable contribution from Gosmini and co-workers^[5] demonstrated the Negishi-type cross-coupling of thioether-substituted benzothiazoles with aromatic organozinc reagents, generated via a cobalt-catalyzed zincation protocol, as highlighted in Scheme 1A.

In parallel, through the Takeda olefination (first reported in 1997, Scheme 1B),^[6] thioacetals and thioacetals have been showcased as valuable precursors to multi-substituted alkene products. Despite this advance, this well-established protocol requires superstoichiometric titanium reagents and generally gives rise to poor *E/Z* selectivity in the products. Cyclic thioacetals are particularly attractive as substrates for cross-

coupling owing to their ease of synthesis and ability to tolerate harsh reaction conditions. Moreover, aldehyde-derived thioacetals are amenable to downstream functionalization – for example, lithiation of the α -S C–H bond can facilitate umpolung functionalization of the parent carbonyl compound via the Corey-Seebach reaction.^[7] Thus, cyclic thioacetals and thioacetals have enjoyed widespread use as both protecting groups^[8] and functional handles in complex molecule synthesis.^[9] Based on this precedent, we reasoned that a synthetic protocol which could selectively convert the robust 1,3-dithiolane to a variety of alkene structures would be of high synthetic value.

To this end, we were intrigued to explore whether cobalt catalysis could be employed to facilitate a Kumada-type coupling reaction between readily available 1,3-dithiolanes and Grignard reagents (Scheme 1C). In analogy to previous endeavors employing ligated nickel catalysts,^[10] we hypothesized that a suitable cobalt-derived catalyst system could activate a C–S bond in the 1,3-dithiolane moiety, enabling C–C bond formation with the organometallic reagent. Following a second catalyzed C–S activation event and subsequent β -hydride elimination, the multi-substituted alkene product would be formed, and the catalyst system would be regenerated (Scheme 1D). Alternatively, and in accordance with the mechanism proposed for the cobalt- and iron-mediated olefination of geminal dihalides, an arylated cobaltate complex could be formed *in situ*, from which C–C bond formation could occur via 1,2-shift of the aryl group from cobalt to carbon.^[11,21] Given the rich chemistry of Grignard reagents and 1,3-dithiolanes, a synthetic protocol combining these two entities using a simple and inexpensive cobalt catalyst would provide a powerful transformation, applicable to industry and academia alike. Herein, we wish to report our findings.

Results and Discussion

We selected 2-(3',5'-dimethoxyphenyl)-2-methyl-1,3-dithiolane (**1a**) as a model substrate to begin investigating the cobalt-catalyzed olefination reaction with phenylmagnesium bromide

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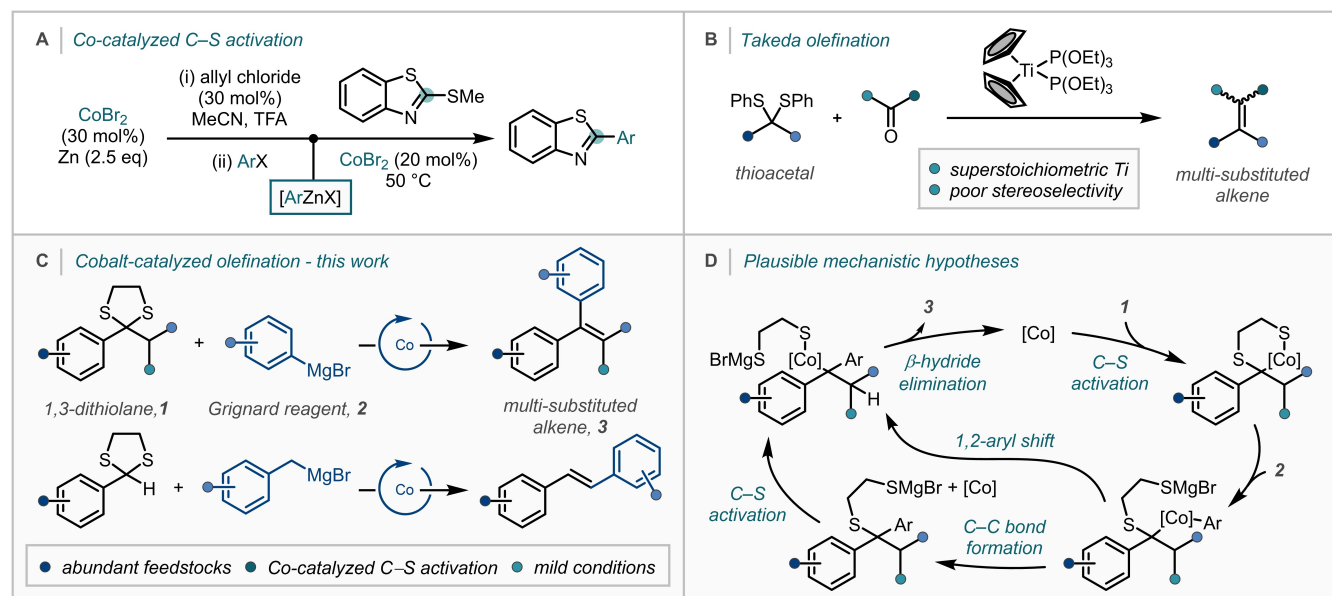
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This manuscript is part of a special collection on the occasion of Keiji Maruoka's 70th Birthday.



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Scheme 1. Cobalt catalysis in the activation of C–S bonds for cross-coupling and olefination reactions.

(**2a**, Scheme 2). Pleasingly, an early success was enjoyed when **1a** was reacted with 3 equivalents of **2a** in the presence of 5 mol% CoBr_2 in 1,4-dioxane at 60 °C for 1 hour, whereby the desired 1,1-diaryl alkene structure (**3a**) was obtained in 34% NMR yield, as measured against an internal standard (entry 1). Pleasingly, switching 1,4-dioxane to 1,2-dimethoxyethane (DME) had a dramatic effect on reactivity, and the desired product **3a**

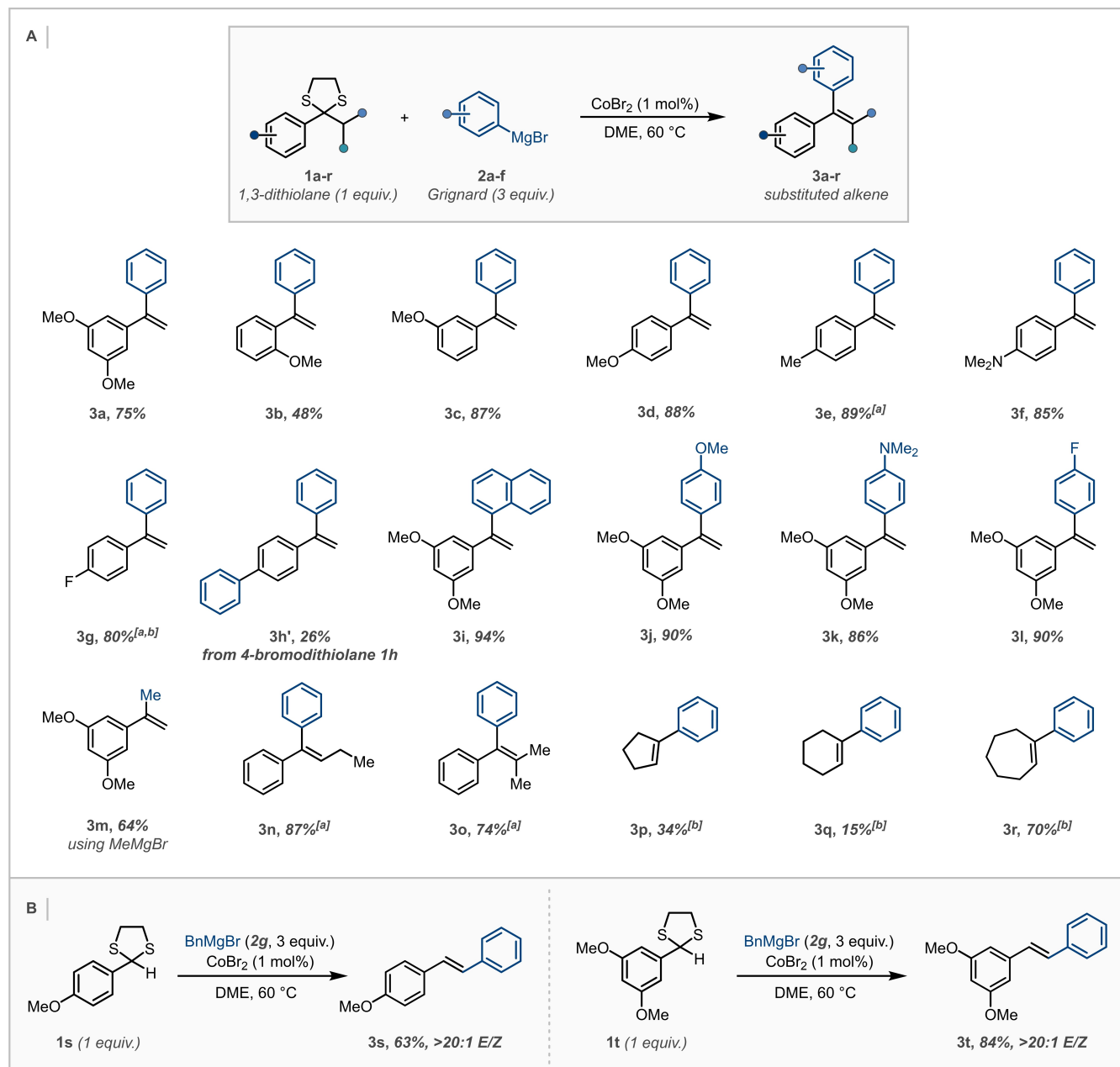
| entry | 2a equiv. | CoBr_2 / mol% | solvent | temperature | 3a yield / % |
|------------------|---------------------|---------------------------|-------------|---------------------|-------------------------|
| 1 | 3 | 5 | 1,4-dioxane | 60 °C | 34 |
| 2 | 3 | 5 | DME | 60 °C | 90 |
| 3 | 3 | 1 | DME | 60 °C | 87 |
| 4 | 3 | 0.1 | DME | 60 °C | 30 |
| 5 | 2 | 1 | DME | 60 °C | 75 |
| 6 | 3 | 1 | DME | r.t. ^[a] | 71 |
| 7 ^[b] | 3 | 1 | DME | 60 °C | 85 (75 ^[c]) |

Scheme 2. Optimization of the cobalt-catalyzed olefination reaction between 1,3-dithiolane **1a** and phenylmagnesium bromide **2a**. Reaction conditions: **1a** (0.1 mmol), **2a** (0.3 mmol), CoBr_2 (5 μmol), solvent (0.05 M), 60 °C, 1 h. Yields obtained by ^1H NMR spectroscopic analysis using 1,3,5-trimethoxybenzene as an internal standard. [a] Reaction was stirred at room temperature for 18 h. [b] Reaction conducted on 0.5 mmol scale. [c] Isolated yield.

was obtained in 90% yield (entry 2). Furthermore, we were delighted to observe that the catalyst loading could be reduced to 1 mol% without a considerable drop in reaction efficiency (entry 3), however reducing the loading further to 0.1 mol% resulted in lower yields (entry 4). Productive coupling was observed using 2 equivalents of **2a**, but this was accompanied by a drop in yield (entry 5). A similar result was obtained when the reaction was conducted at room temperature for a significantly extended period of time (entry 6). On increased scale, with 3 equivalents of **2a** and 1 mol% CoBr_2 in DME at 60 °C, alkene **3a** was obtained in 75% isolated yield (entry 7).

With the optimized reaction conditions in hand, the scope of the methodology with respect to the 1,3-dithiolane fragment was first investigated (Scheme 3A). Using phenylmagnesium bromide **2a** as a model nucleophilic partner, we were pleased to observe that good reaction efficiency was maintained when installing a variety of functionality on the aromatic ring – ethers (**3a–d**), alkyl groups (**3e**), amines (**3f**), and halogens (**3g**) were all tolerated. Interestingly, 4-bromo-substituted dithiolane **1h** underwent sequential olefination and Kumada cross-coupling reactions to afford biphenyl **3h'** as the major product in 26% yield. Both *para*- (**3d**) and *meta*- (**3c**) substituted substrates performed well in the reaction, whereas *ortho* (**3b**) substitution impeded the reaction, resulting in decreased yields. Notably, in this case a significant amount of unreacted starting material was also recovered.

Variation of the organometallic nucleophile was also possible. Performing the reaction with freshly-prepared solutions of 4-methoxy- and 4-dimethylamino-aryl Grignard reagents afforded the desired products in excellent yields with no modification to the reaction conditions (**3j–k**). Electron-deficient arylmagnesium species also performed well in the reaction (**3l**). Moreover, a naphthyl (**3i**) and a methyl (**3m**)



Scheme 3. Scope of the cobalt-catalyzed olefination reaction between 1,3-dithiolanes and Grignard reagents. Reaction conditions: 1,3-dithiolane **1** (0.5 mmol), Grignard reagent **2** (1.5 mmol), CoBr_2 (5 μmol), 1,2-dimethoxyethane (0.05 M), 60 °C. Yields quoted are isolated. [a] The product was inseparable from the Grignard-derived homodimer. The reported yield is adjusted for the presence of this impurity. [b] The reaction was conducted at room temperature.

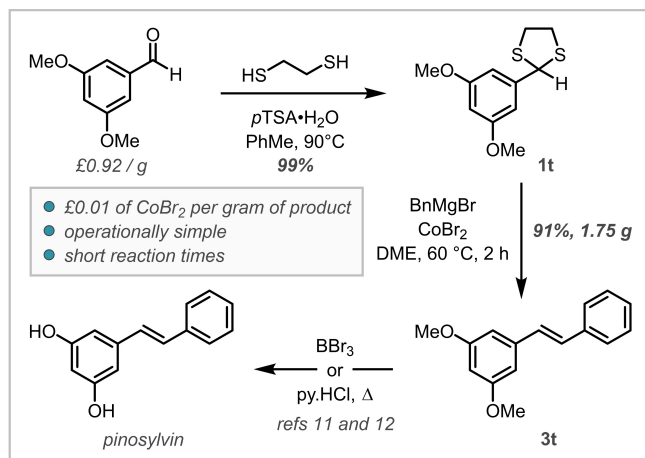
group could be incorporated in this manner, affording the corresponding alkenes in good to excellent yields.

In addition to the formation of 1,1-disubstituted alkenes, the present methodology proved efficacious in the formation of the more sterically-hindered tri- and tetra-substituted alkene motifs, furnishing **3n** and **3o** in 87% and 74% yields respectively.

Following a subtle change to the reaction conditions (performing the reaction at room temperature rather than 60 °C), cyclic dialkyl-substituted dithiolanes were also suitable substrates for this methodology, enabling the synthesis of tri-substituted alkenes within 5-, 6-, and 7-membered rings (**3p-r**).

In the case of the 5- and 6-membered rings, the reduced yield was indicative of poor conversion, as significant quantities of unreacted starting material were present in the crude reaction mixtures.

Given the requirement for β -hydride elimination to close the postulated catalytic cycle (Scheme 1D), we were interested in investigating the coupling of benzylic Grignard reagents with aldehyde-derived 1,3-dithiolanes (Scheme 3B), which could grant access to a variety of valuable stilbene architectures, a key motif in many bioactive natural products and marketed therapeutics.^[12] Pleasingly, when employing the standard reaction conditions, stilbene derivatives **3s** and **3t** were produced



Scheme 4. Gram-scale synthesis of stilbene **3t**, and application to the synthesis of bioactive stilbene natural products.

in good to excellent yields. In both cases, excellent *E* selectivity was observed (*E/Z* > 20:1).

To demonstrate the general utility and scalability of our cobalt-catalyzed protocol, the reaction of aldehyde-derived dithiolane **1t** with benzylmagnesium bromide **2g** was conducted on 8 mmol scale (Scheme 4). Without further optimization, and using only 18 mg of CoBr₂ (£0.02 – Sigma-Aldrich), the reaction afforded 1.75 g of stilbene **3t** as essentially a single *E*-stereoisomer in an improved yield of 91% after 2 h at 60 °C. From this intermediate, the natural product pinosylvin can be readily accessed, either by heating in the presence of pyridinium hydrochloride^[13] or by treatment with BBr₃.^[12] This illustrates the potential application of the present methodology to the large-scale synthesis of bioactive stilbene natural products from readily available and inexpensive starting materials.

Conclusions

In conclusion, the cobalt-catalyzed transformation of 1,3-dithiolanes into a variety of multi-substituted alkene frameworks has been developed. The ready availability of starting materials, low cost of the CoBr₂ catalyst, low catalyst loadings, and excellent scalability suggest that the reaction should be widely applicable in academic and industrial settings. Work to further scale-up and apply this olefination methodology in complex molecule synthesis is ongoing and will be reported in due course.

Experimental Section

Representative procedure for the cobalt-catalyzed olefination of 1,3-dithiolanes using Grignard reagents: to a solution of 1,3-dithiolane **1** (1 equiv.) and CoBr₂ (1 mol%) in anhydrous 1,2-dimethoxyethane (0.05 M) was added Grignard reagent **2** (as a solution in THF or Et₂O, 3 equiv.) at room temperature. The vessel was then immersed in a pre-heated water bath and stirred at 60 °C

for 1 h before the reaction mixture was quenched with 2 M aqueous KOH, and the layers were separated. The aqueous layer was extracted two times with Et₂O, and the combined organic extracts were dried over anhydrous MgSO₄, filtered, and concentrated *in vacuo*. The crude products were purified using flash column chromatography to afford the multi-substituted alkene products.

Supporting Information

The authors have cited additional references within the Supporting Information.^[10f,12a,14–29]

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Conflict of Interests

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: Alkene synthesis · Cobalt · C–S activation · 1,3-Dithiolane · Grignard reagent

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