

Bioinspired organometallic chemistry*

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Abstract: Given the stability of the bond between a mercaptide ligand and various redox-active metals, it is of interest that Nature has evolved significant metalloenzymatic processes that involve key interactions of sulfur-containing functionalities with metals such as Ni, Co, Cu, and Fe. From a chemical perspective, it is striking that these metals can function as robust biocatalysts *in vivo*, even though they are often “poisoned” as catalysts *in vitro* through formation of refractory metal thiolates. Insight into the nature of this chemical discrepancy is under study in order to open new procedures in synthetic organic and organometallic chemistry.

INTRODUCTION AND BACKGROUND

The highly discriminating activation of a stable carbon–sulfur moiety in the presence of a vast sea of oxygen and nitrogen heteroatoms plays a key role in a number of biochemical transformations [1–5]. To accomplish this task, Nature relies on the use of thiophilic metals such as Ni to achieve the selective activation of a soft, polarizable C–S substrate in a hard environment [6]. It is also significant that, although a thiolate ligand shows a high affinity toward essential trace metals such as Ni, Cu, Zn, and Fe, this affinity does not interfere with the ability of these metals to function in a catalytic mode in biological systems [1,7].

Can Nature be mimicked and highly efficient metal-mediated catalysis of thioorganics be achieved at ambient temperature under mild conditions in the laboratory? The key step in this endeavor is labilization under mild conditions of the often stable bond that forms between a catalytically active metal (such as Ni, Pd, and Rh) and the soft thiolate ligand. Insight into mild activation of the metal thiolate bond can be gleaned from Nature where three biologically relevant means of releasing the metal from a strong metal–thiolate bond are found.

1. Zinc(II), a ubiquitous, non-redox-active metal is found throughout biological systems and has an affinity for thiolate second only to copper(II) [8]. In fact, the affinity of zinc(II) for thiolate is sufficiently high that it can displace copper(II) from sulfhydryl binding sites, *in vivo*, and even remove thiolate from Pt(II), *in vitro* [9,10].
2. A metal–thiolate linkage can be broken upon *S*-alkylation, the derived thioether being a considerably weaker ligand than the thiolate. Zinc thiolate *S*-alkylation by a phosphate methyl ester is a key step in the DNA methyl phosphotriester repair center of *Escherichia coli* ADA [11].
3. In contrast to the metal–thiolate bond, the metal–disulfide bond possesses an extremely small sta-

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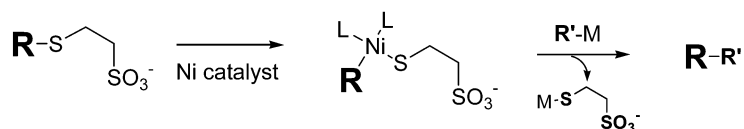
bility constant [12]. Under very mild oxidative conditions (i.e., disulfide exchange), metal thiolates can be transformed to disulfides with liberation of the metal [13]. This principle underlies a growing number of examples where metal ions are mobilized in biological systems by oxidation of the thiolate ligand to a disulfide [14–17].

By addressing these three means for labilizing a metal–thiolate bond, new laboratory-based synthetic processes that involve carbon–sulfur bond scission and lead to new carbon–carbon and carbon–heteroatom bond formation under very mild conditions should be feasible. This article describes progress toward achieving that goal.

RESULTS

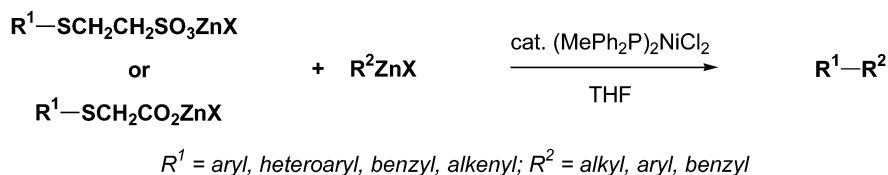
Biomimetic cross-coupling

We have previously demonstrated a new synthetic process that has its conceptual basis in a bioorganometallic transformation with presumed primordial origins; namely, the putative final steps in methanogenesis, the production of methane from methyl coenzyme M [$\text{CH}_3\text{S}(\text{CH}_2)_2\text{SO}_3^-$] mediated by methyl coenzyme M reductase [3,7]. In this remarkably efficient process, a nickel hydrocorphinoid cofactor (F_{430}) ruptures the $\text{CH}_3\text{-S-}$ bond of $\text{CH}_3\text{SCH}_2\text{CH}_2\text{SO}_3^-$ generating a $\text{CH}_3\text{-Ni}$ intermediate, which subsequently suffers protonation to methane. We sought to generalize the C–S oxidative addition to *S*-substituted coenzyme M derivatives (and inhibit the biologically relevant protonation) in order to intercept the organonickel intermediate for alternative processes, such as the formation of carbon–carbon bonds by way of a cross-coupling protocol (Scheme 1).



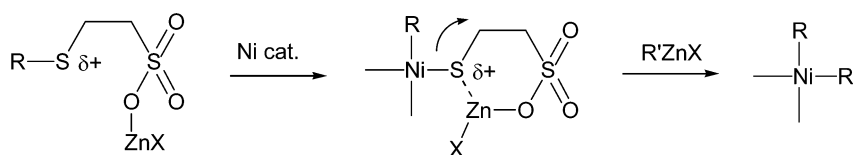
Scheme 1 Coenzyme M-derived cross-coupling.

In order to study this possibility, zinc salts of *S*-(substituted)thioethanesulfonate, (*S*-derivatized coenzyme M), and *S*-(substituted)thioglycolic acid were prepared and exposed to organozinc reagents in the presence of a nickel precatalyst between room temperature and 50 °C. An efficient and general coupling ensued (Scheme 2); examples can be found in the published manuscript [18].



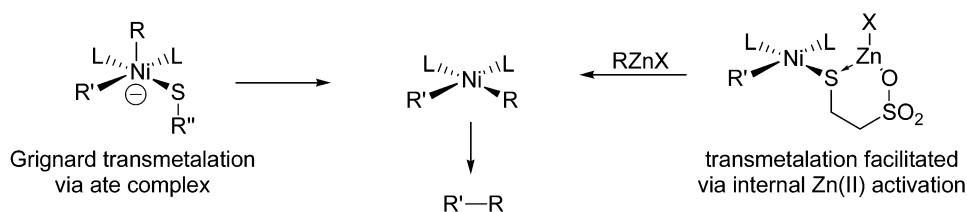
Scheme 2 Organozinc cross-coupling of thioethylsulfonates and thioglycolates.

Control experiments established that *Zn(II)* was a critical cofactor for the reaction; the cross-coupling failed in the presence of other sulfonate and carboxylate counterions (Na, K, Mg, Al, Cu). The control experiments also revealed the importance of the pendant ionizable sulfonate and carboxylate moieties; simple aryl thioethers and carboxylic esters were unreactive under the experimental conditions. These studies suggested a significant acceleration of the rate of cross-coupling by an *internal, ligand-bound* zinc ion, which presumably activated the Ni-thiolate ligand (formed after oxidative addition of the C–S bond to low-valent Ni) and thus facilitated transmetallation (Scheme 3).



Scheme 3 Internal Zn(II)-mediated activation of nickel thiolate.

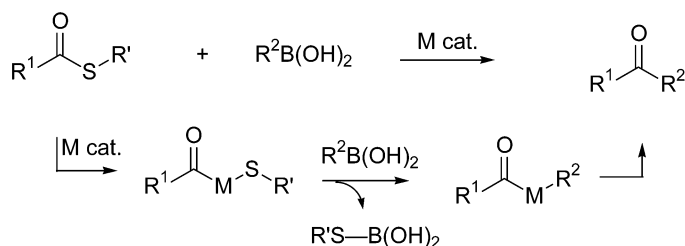
Prior to our work, Wenkert and Luh had disclosed a variety of nickel-catalyzed couplings of thioorganics with Grignard reagents [19]. How do the Wenkert/Luh reactions differ from those described in this manuscript? Since Grignard reagents easily participate in a nickel-catalyzed coupling with aryl thioethers, but organozinc reagents do not, the ease of transmetalation to the nickel thiolate appears to be the critical difference. From this reactivity difference, we infer that Grignard reagents are sufficiently reactive to affect transmetalation at a nickel thiolate bond, possibly through an anionic nickelate intermediate (Scheme 4). The less-reactive zinc reagents, which probably do not generate “ate” intermediates, require prior labilization of the nickel thiolate bond, in this case through an internally ligated Zn(II).



Scheme 4 Contrasting modes of nickel thiolate activation.

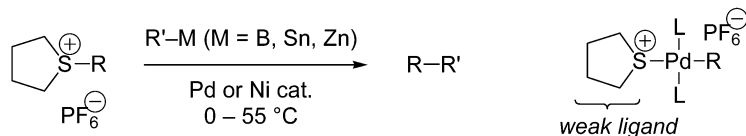
Thiol ester–boronic acid cross-coupling. Catalysis using alkylative activation of the palladium thiolate intermediate

From a synthetic perspective, the coupling of stable organosulfur compounds with boronic acids would be a boon to the synthetic chemist, since both reaction partners are readily available and are stable molecules of low toxicity. Their coupling would provide a uniquely mild method for the synthesis of highly functionalized organics, one example being the coupling of thiol esters and boronic acids to ketones (Scheme 5). Given the precedent for oxidative addition of thioorganics to low-valent nickel and palladium [20–25], the conceptual key to this proposed coupling reaction will be transmetalation of the boronic acid to the metal thiolate intermediate, with concomitant replacement of the thiolate ligand. Unfortunately, the low thiophilicity of boron combined with the low nucleophilic reactivity of organoboron derivatives render this transmetalation problematic.



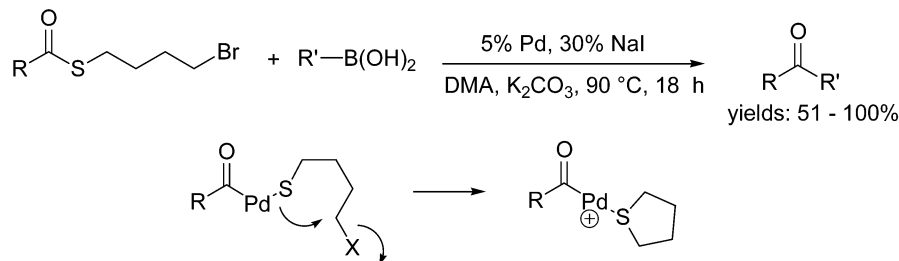
Scheme 5 Thiol ester–boronic acid cross-coupling.

One solution to this problem was found in the unusual efficacy of tetrahydrothiophene-based sulfonium salts as partners in nickel and palladium-catalyzed cross-coupling with organozinc, -tin, and -boron reagents, where it was convincingly demonstrated that tetrahydrothiophene does not interfere with palladium or nickel catalysis (Scheme 6) [26,27].



Scheme 6 Sulfonium salts as cross-coupling reactants.

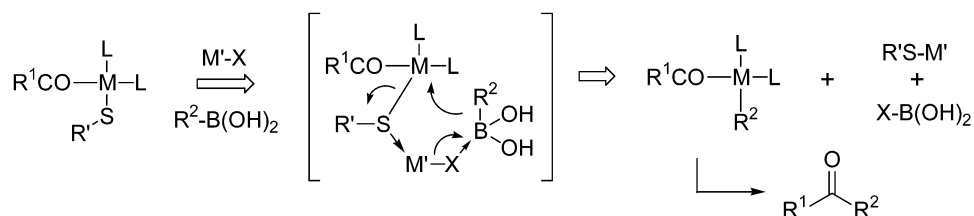
This led to the notion of “alkylative activation” of refractory metal thiolate intermediates, as a way to weaken the metal–sulfur bond [28] and overcome the low thiophilicity of boron. Although simple thiol esters and boronic acids do not participate in cross-coupling in the presence of palladium catalysts (Fukuyama [29] and Terfort [30] have reported low yields of ketone from the palladium-catalyzed coupling of a thiol ester with a boronic acid), efficient thiol ester–boronic acid cross-coupling catalyzed by palladium is observed for 4-halo-*n*-butyl thiol esters (Scheme 7) [31]. In the presence of 5–10% *trans*-di(μ -acetato)-bis[*o*-(di-*o*-tolylphosphino)benzyl]-dipalladium(II) [32,33], 20–45% NaI, 4–6 equiv K_2CO_3 , in dimethylacetamide (DMA) at 90–95 °C for 12–24 h various boronic acids underwent cross-coupling with thiol esters **1a–c** to give the desired ketones, which were isolated in good to excellent yields; examples can be found in the published manuscript [31]. Alkylative conversion of the stable palladium–thiolate bond to a labile palladium–thioether bond is presumed to be crucial to the catalysis.



Scheme 7 Thiol ester cross-coupling using alkylative activation.

General thiol ester–boronic acid coupling using dual thiophilic/borophilic activation

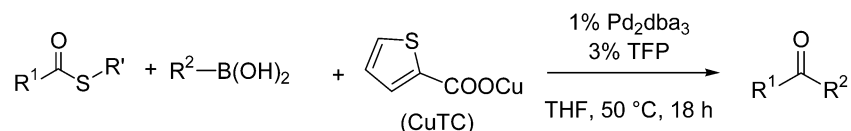
How else can transmetalation from $RB(OH)_2$ to $M-SR'$ be facilitated when the $M-SR'$ bond is kinetically difficult to break and the transformation is thermodynamically unfavorable? A dual thiophilic/borophilic activation of the $R^1COML_2SR'/R^2B(OH)_2$ dyad was conceived using an additive $M'-X$, where M' has high affinity for thiolate and does not interfere with catalysis by Ni or Pd, and X of $M'-X$ has high affinity for boron (Scheme 8). Together, these attributes could facilitate transmetalla-



Scheme 8 Dual thiophilic/borophilic activation.

tion of a relatively strong metal–thiolate bond and overcome the thermodynamic deficit of the weak boron–sulfur bond.

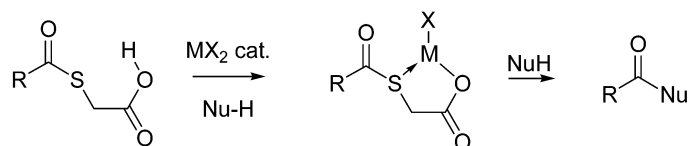
Pursuing this tactic, a mild and general method for the palladium-catalyzed coupling of thiol esters and boronic acids under nonbasic conditions was developed using Cu(I) carboxylates as additives (Scheme 9) [34]. The wide availability of both reaction partners and the nonbasic reaction conditions suggested new possibilities for the synthesis of highly functionalized and base-sensitive compounds under these cross-coupling conditions. For example, trifluoromethyl ketones were easily prepared via the cross-coupling of boronic acids with trifluoroacetyl thiol esters; additional examples can be found in the published manuscript [34]. The use of a Cu(I) carboxylate was critical to the reaction; both the Cu(I) and the carboxylate play key roles in the process.



Scheme 9 Thiol ester–boronic acid cross-coupling mediated by CuTC.

Zinc-mediated alcoholysis of *S*-acyl thioglycolic acids

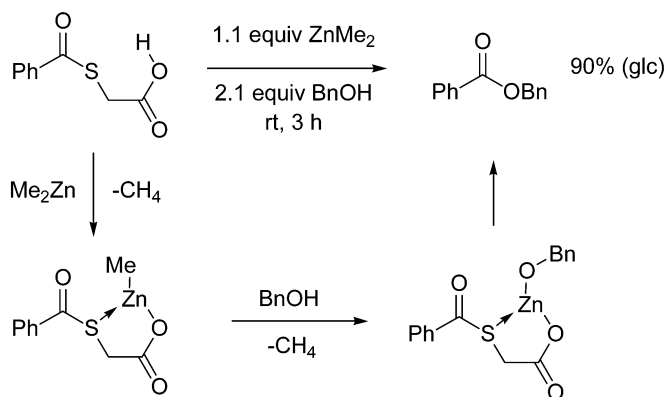
Thiol esters such as acetyl coenzyme A have evolved as important acyl building blocks in biological systems, because they are stable under protic conditions, and yet can be selectively activated for reaction in the presence of oxygen- and nitrogen-based functionality [35]. Although thiol esters are not commonly used for normal esterifications in the laboratory, they have found application in various macrolactonizations [36–38]. For laboratory-based applications, *S*-acyl thioglycolic acids appeared to offer interesting possibilities for selective, metal-mediated activation of acyl transfer processes functioning through internal activation of the thiol ester by the pendant metal carboxylate (Scheme 10). Depending on the nature of the nucleophile, esters, amides or peptides could be obtained.



Scheme 10 Internal metal-mediated activation of thiol esters.

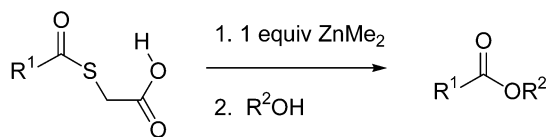
As an initial probe of this possibility, metal-mediated alcoholysis of *S*-acyl thioglycolic acids was investigated (Scheme 11). Gas evolution was observed upon treatment of a solution of *S*-benzoyl thioglycolic acid in THF at room temperature with 1 equiv of ZnMe_2 . After 15 min, 1 equiv of benzyl alcohol was added, and again evolution of gas was observed. Upon stirring this reaction mixture at room temperature for 3 h, conversion to benzyl benzoate was achieved (90% by glc monitoring). That internal activation of the thiol ester by the zinc carboxylate was indeed important as suggested by the lack of reaction of *p*-methylthiobenzoic acid *S*-ethyl ester with benzyl alcohol in the presence of ZnMe_2 in THF after 3 h at room temperature.

Benzoylation and acetylation of different alcohols were explored using this new procedure (Table 1) [39]. Primary alcohols such as benzyl, allyl, and alkyl alcohols (entries 1–4) reacted well between room temperature and 55 °C. For secondary alcohols good yields were obtained at 55 °C (entries 5–8). A phenol was also benzoylated using these conditions (entry 9). Both benzoylation and acetylation of (*S*)-ethyl lactate were carried out in good yield at 55 °C (entries 10 and 11). When enantiomerically pure alcohols were used (entries 6, 7, 10, and 11), the corresponding esters were obtained without racemization (HPLC assays and measure of the $[\alpha]_D$).



Scheme 11 Selective Zn(II)-mediated alcoholysis of *S*-benzoylglycolic acid.

Table 1 Zn(II)-mediated alcoholysis of *S*-acylglycolic acids.



Run	R ¹	R ²	Temp.	Yield ^a
1	Ph	Bn	rt	94%
2	CH ₃	neryl	55 °C	89%
3	Ph	Ph(CH ₂) ₂ -	rt	85%
4	CH ₃	Ph(CH ₂) ₂ -	rt	87%
5	CH ₃	1-methoxy-2-indanol	55 °C	81%
6	CH ₃	(1 <i>R</i> ,2 <i>S</i> ,5 <i>R</i>)-menthol	55 °C	79%
7	Ph	(1 <i>R</i> ,2 <i>S</i> ,5 <i>R</i>)-menthol	55 °C	83%
8	CH ₃	dihydrocholesterol	55 °C	67%
9	Ph	Ph	rt	50%
10	CH ₃	(<i>S</i>)-Ethyl lactate	55 °C	81%
11	Ph	(<i>S</i>)-Ethyl lactate	55 °C	89%

^aYield for pure compounds after distillation or flash chromatography.

CONCLUSIONS

Using the biochemically relevant principles of transition metal-thiolate activation, four different metal-mediated transformations of thioorganic molecules have been described. Zinc(II) salts of *S*-(substituted)thioethanesulfonates (*S*-derivatized coenzyme M) and *S*-(substituted)thioglycolic acids were shown to undergo efficient nickel-catalyzed cross-coupling with organozinc reagents between room temperature and 50 °C. Intramolecular thiolate alkylation was used to render a thiol ester–boronic acid cross-coupling catalytic in palladium. A more general thiol ester–boronic acid coupling was accomplished by way of a dual thiophilic/borophilic activation using a copper(I) carboxylate. Finally, the synthetic potential of *S*-acylthioglycolic acids as metal-induced active ester equivalents was studied using Zn(II) to activate the thiol ester. With this procedure, a variety of esters (primary and secondary) have been prepared in good yields under mild conditions

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39. The compounds 2-acetylsulfanyl acetic acid and 2-acetylsulfanyl benzoic acid were prepared by modifications of procedures reported in the literature. **2-Acetylsulfanyl acetic acid.** Thioacetic acid (7.60 g, 10.00 mmol) was added to a mixture of *tert*-butyl chloroacetate (15.05 g, 10.00 mmol) and triethylamine (15.3 mL, 11.00 mmol) in THF (175 mL). The reaction mixture was stirred under nitrogen at room temperature overnight. Et₂O/hexane (2:1, 300 mL) was added and the solid was removed by filtration. After evaporation of the solvent under reduced pressure, 19.00 g of a pale orange liquid was obtained (100%). This product was used in the next step without further purification. The former product (9.5 g, 5.00 mmol) was dissolved in TFA (11.60 mL, 15.06 mmol) and the mixture was stirred at room temperature with a CaCl₂-tube until the starting material disappeared (TLC analysis, ca. 24 h). After evaporation of the solvent under vacuum, a red liquid was obtained. Purification of the crude product by flash chromatography gave 5.34 g (91%) of 2-acetylsulfanyl acetic acid as a colorless oil. bp 93–95 °C, 0.9 mmHg, short-path distillation; lit. [Benary, *Chem. Ber.* **46**, 2104 (1913), Beilstein registry number 1753984; M. Rimper, *Chem. Ber.* **99**, 1528–1531 (1966)] bp 106–108 °C, 1.2 Torr; IR (CH₂Cl₂, NaCl, cm⁻¹): 3600 (br, m), 1714 (s), 1610 (shoulder, m). ¹H NMR (CDCl₃, 400 MHz): δ10.60–10.70 (br s, 1 H), 3.72 (s, 2 H), 2.39 (s, 3 H). **2-Acetylsulfanyl benzoic acid.** To a solution of 2-mercaptoacetic acid (7.71 g, 50.00 mmol) in THF (30 ml) was added portionwise Na₂CO₃ (11.66 g, 110.00 mmol). Then, benzoyl chloride (4.32 g, 55.00 mmol) was added dropwise under nitrogen at 0 °C, and resulting mixture was stirred overnight at room temperature. The reaction mixture was diluted with Et₂O (60 mL), and the solid was filtered. The solid was dissolved in water, and the solution was acidified until a precipitate appeared. The solid was filtered, and recrystallized from Et₂O to yield 8.96 g (91%) of 2-acetylsulfanyl benzoic acid as a white solid: mp 124–125 °C (Et₂O; lit. [Hinsberg, *Chem. Ber.* **43**, 654 (1910); P. Kumar, A. T. Rao, B. Pande, *J. Chem. Soc., Chem. Commun.* **21**, 1580–1581 (1992); F. G. Bordwell and P. J. Bouton, *J. Am. Chem. Soc.* **20**, 854–860 (1956) mp 125 °C (benzene)]; IR (CH₂Cl₂, KBr, cm⁻¹): 1743 (w), 1711 (s). ¹H NMR (CDCl₃, 400 MHz): δ8.10 (d, *J* = 7.6 Hz, 1 H), 7.60–7.58 (m, 2 H), 7.52–7.26 (m, 2 H), 2.46 (s, 2 H). **Zn-Mediated alcoholysis.** To a solution of the corresponding *S*-acyl thioglycolic acid (2.2 mmol) in anhyd THF (3 mL) under nitrogen was added 1.20 mL of Me₂Zn (2.4 mmol). The reaction mixture was stirred at room temperature until no further evolution of gas was observed (approx 15 min). To this mixture was added via syringe a solution of the corresponding alcohol (2.0 mmol) in anhyd THF (3 mL) (evolution of gas). The reaction mixture was stirred at room temperature or 55 °C until TLC analysis indicated completion of the reaction (a white precipitate appeared). The reaction mixture was then diluted with Et₂O (15 mL), washed with NH₄Cl (15 mL), NaHCO₃ (15 mL), and brine (10 mL) and then dried over MgSO₄. The solvent was evaporated under reduced pressure and the resulting pale yellow oil was purified by distillation or flash chromatography.