

Benzoisothiazolone Organo/Copper-Cocatalyzed Redox Dehydrative Construction of Amides and Peptides from Carboxylic Acids using (EtO)₃P as the Reductant and O₂ in Air as the Terminal Oxidant

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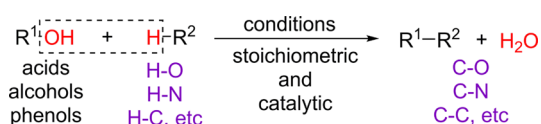
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S Supporting Information

ABSTRACT: Carboxylic acids and amine/amino acid reactants can be converted to amides and peptides at neutral pH within 5–36 h at 50 °C using catalytic quantities of a redox-active benzoisothiazolone and a copper complex. These catalytic “oxidation–reduction condensation” reactions are carried out open to dry air using O₂ as the terminal oxidant and a slight excess of triethyl phosphite as the reductant. Triethyl phosphate is the easily removed byproduct. These simple-to-run catalytic reactions provide practical and economical procedures for the acylative construction of C–N bonds.

Condensative bond constructions that join a hydroxylic reactant to an N, O, or C partner and eliminate the elements of water constitute one of the foundational transformations of organic synthesis, broadly writ (Scheme 1).

Scheme 1. Dehydrative Bond Construction



Historically these transformations were carried out with minimal attention to environmental issues or to atom economies using processes that stoichiometrically activate the hydroxylic partner.

In recent years, attention to environmental issues and sustainability have stimulated a shift to the development of new condensative bond-forming processes that take advantage of catalytic protocols that can eliminate the elements of water directly from hydroxylic reactants and their bond-forming partners without recourse to expensive and wasteful stoichiometric activators.^{1–10} It is a common corollary, however, that catalytic protocols often sacrifice substrate generality in the pursuit of atom efficiency.

Of the many stoichiometric activation methods that enable dehydrative bond formation, “oxidation–reduction condensation” reactions are uniquely mild.^{11–15} These transformations remove the elements of H₂O from two reaction partners through the combined use of a gentle organic oxidant to accept [2H] and a gentle organic reductant to accept [O]. Applied to acylations using carboxylic acids (Mukaiyama reaction)^{11,16,17} and to alkylations using alcohols (Mitsunobu reaction),^{12–14}

oxidation–reduction condensation is a broadly general protocol, but it suffers from significant atom *ineconomies* in its requirement for stoichiometric quantities of both an organic oxidant and reductant. In most cases, the organic oxidants used for the alkylative processes are azo reagents such as diethyl azodicarboxylate, which is toxic and potentially hazardous;^{18,19} disulfides and sulfenamides are typical oxidants for the acylative transformations.¹¹ In all but a few cases^{20,21} the organic reductants are triorganophosphines, which leave behind tedious-to-remove stoichiometric quantities of triorganophosphine oxides.¹⁸

The substrate generality and gentle reaction conditions of oxidation–reduction condensation have stimulated interest in the development of reaction variants that can operate in the catalytic mode. To accomplish this task, a substoichiometric loading of simple and stable organocatalytic oxidants or reductants is linked, in efficient catalytic regeneration cycles, to (preferably) earth-abundant, inexpensive terminal oxidants and reductants. *To date, no examples of organocatalytic oxidation–reduction condensations that carry out acylations have been described;* rather, the literature reveals an initial focus on catalytic protocols for the *alkylative* variant of oxidation–reduction condensation. Toy demonstrated that Mitsunobu reactions could be achieved using 10 mol % DEAD as a catalytic oxidant, with 2 equiv of PhI(OAc)₂ as the terminal oxidant and 2 equiv of Ph₃P as the reductant.²² Taniguchi improved upon Toy’s observations in his use of a 10 mol % loading of an azo compound, which was regenerated under the reaction conditions using 10 mol % Fe–phthalocyanine catalyst and O₂ in air as the terminal oxidant.²³ In Taniguchi’s chemistry, 2 equiv of Ph₃P is required. O’Brien has approached catalytic oxidation–reduction condensation reactions from the perspective of the reductant. One example of a triorganophosphine-catalyzed Mitsunobu reaction in which PhSiH₃ is the terminal reductant appears at the end of an O’Brien patent²⁴ in which triorganophosphine-catalyzed Wittig reactions are the principal focus.^{25,26} Thus, the recent literature reveals modest success in achieving catalytic protocols for oxidation–reduction condensation reactions.

Gleaned from these examples, the challenges to the development of environmentally sustainable catalytic oxidation–reduction condensation reactions, whether for alkylative or acylative dehydrative bond formation, are clear: Nontoxic

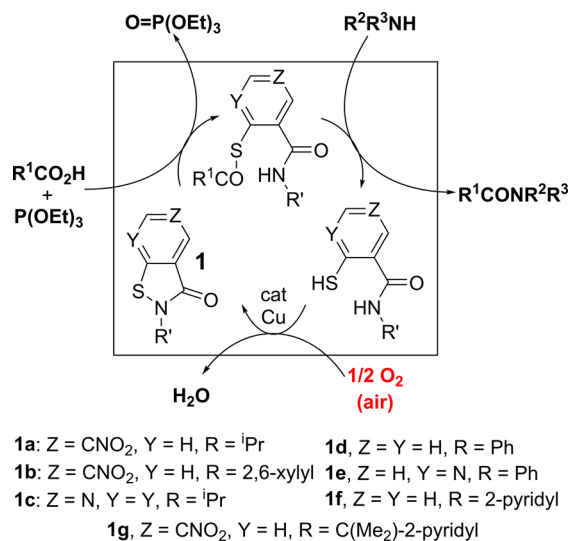
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and safe organic oxidants and reductants are required to drive the redox dehydration chemistry. They are best used at low organocatalytic loadings by pairing with inexpensive and practical earth-abundant terminal oxidants and reductants for recycling. If either the organic oxidant or reductant is used stoichiometrically, then it should both be inexpensive and result in reaction byproducts that are easy to remove from the resulting reaction mixture.

In pursuit of these goals, we disclose herein a new aerobic, catalytic oxidation–reduction condensation system for efficient acylative bond formations. It is based upon the use of benzothiazolones (BITs) as easily prepared and modified S–N bond-derived organocatalytic oxidants (Scheme 2).

Scheme 2. Aerobic Benzothiazolone-Catalyzed Amidation

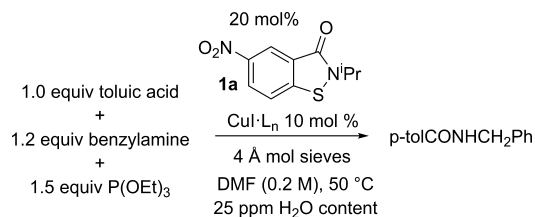


Furthermore, for these acylative condensation reactions, we avoid problematic stoichiometric triorganophosphine reductants by replacing them with inexpensive, low-molecular-weight triethyl phosphite as the terminal reducing agent, which is transformed into easily removed triethyl phosphate as the byproduct. This contrasts with most other oxidation–reduction condensation reactions, in which aliphatic phosphites are avoided as reducing agents because of significant interference from adverse dealkylation events.^{21,27}

Mukaiyama demonstrated the value of sulfenamides as stoichiometric oxidants (when paired with triorganophosphine reductants) in acylative oxidation–reduction condensation reactions for the dehydrative generation of amides and peptides.²⁸ The BITs used in the present study represent a specific heterocyclic subset of sulfenamides, those whose S–N bond reactivity can be easily tuned through simple modification of the aromatic ring as well as the N substituent. Significantly, in the presence of catalytic Cu salts, sulfenamides in general²⁹ and BITs more specifically^{30,31} are easily regenerated under mild oxidative conditions (air or O₂ atmosphere) from their reduced partners. Thus, as depicted in Scheme 2, by proceeding through S-acyl-2-mercaptobenzoic acid amides, BITs should function as aerobically recyclable organocatalytic oxidants in acylative oxidation–reduction condensation reactions. In support of the proposed catalytic cycle, S-acylthiosalicylamides are formed directly from a carboxylic acid, a benzothiazolone, and a stoichiometric triorganophosphine.^{30,32}

To begin the study, 1.0 equiv of *p*-toluic acid, 1.2 equiv of benzylamine, and 1.5 equiv of triethyl phosphite under dry air were exposed at 50 °C in DMF to 20 mol % 5-nitro-*N*-isopropylbenzothiazolone (**1a**)^{30,32} in the presence of a variety of 10% CuI–N-ligand catalysts (Scheme 3). Activated 4

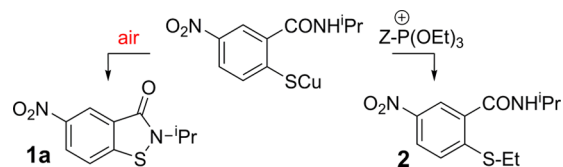
Scheme 3. BIT-Catalyzed Amidation Exploratory Study



Å molecular sieves were used to keep the moisture content within the reaction medium at low levels.³³ From among the N-ligands bipyridine, 4,5-diazafluorenone,³⁴ and *N*-methylimidazole (NMI), NMI performed best, although it delivered (*p*-tolyl)CONHBn in only 45% yield. Lower amide yields were noted when CuI was replaced with another Cu(I) source (CuCl, CuBr, Cu(MeCN)₄PF₆, or CuMeSal³⁵). Control experiments with *p*-toluic acid, benzylamine, (EtO)₃P, and molecular sieves showed the formation of only trace levels of amide after 24 h at 50 °C.

Since Cu(I) is oxidized under the aerobic reaction conditions used, CuI₂(NMI)₄ was prepared³⁶ and used subsequently as a discrete aerobic reoxidation catalyst. The exploratory study was then continued using 1.0 equiv of *p*-toluic acid, 1.2 equiv of benzylamine, 1.5 equiv of triethyl phosphite, and 10 mol % CuI₂(NMI)₄ at 50 °C under a dry-air atmosphere with activated 4 Å molecular sieves. A survey of reaction solvents (DMF, MeCN, THF, EtOAc, and toluene) revealed optimum performance of the organocatalytic oxidant **1a** (20%) in MeCN (>70% amide in 10 h at 50 °C). The wide variability in the performance of organocatalyst **1a** in the different solvents studied was traced to its unproductive conversion to the catalytically inactive S-ethylation product, **2**, in the presence of electrophilic ethoxyphosphonium intermediates (Scheme 4).

Scheme 4. Organocatalyst Aerobic Recycle versus Degradation



Finally, a brief comparative survey of the different redox organocatalytic BITs listed at the bottom of Scheme 2 (**1a**,^{30,32} **1b**,^{30,32} **1c**,³⁰ **1d**,^{37,38} **1e**,³⁹ **1f**,⁴⁰ and **1g**⁴¹) was carried out. The formation of (*p*-tolyl)CONHBn from 1.0 equiv of *p*-toluic acid, 1.2 equiv of benzylamine, and 1.5 equiv of (EtO)₃P was investigated using 10 mol % CuI₂(NMI)₄ and 20 mol % BIT in MeCN at 50 °C (dry-air atmosphere and activated 4 Å molecular sieves). These experiments revealed modest differences in the initial reaction rates as the nature of the aromatic ring and the N substituent were varied. The most noticeable factor was the ability of the BIT to sustain catalytic turnover after ca. 2 h and not convert to the catalytically inactive S-ethylation analogues of **2** (Scheme 4) before full conversion of

reactants to product was achieved. Among the BITs studied to date, BIT **1g** was the best performer, providing the highest reaction rate and the highest conversion to amide (Figure 1).

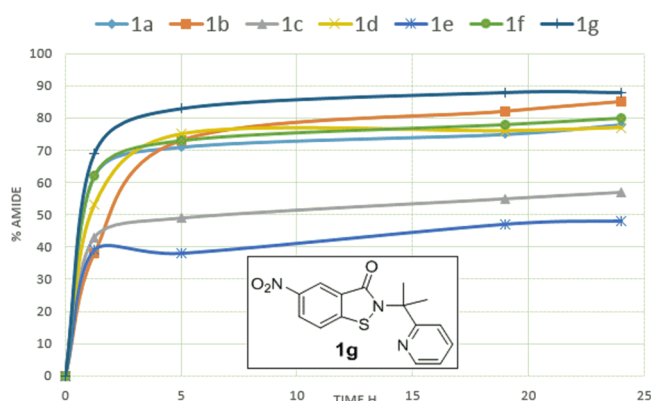


Figure 1. Benzoisothiazolone screening (see Scheme 2 for the structures of BITs 1a–f).

By the use of a catalytic redox system comprising 20 mol % organocatalyst **1g** and 10 mol % $\text{CuI}_2(\text{NMI})_4$ in MeCN under dry air (4 Å molecular sieves) at 50 °C, a variety of amides were constructed from 1.0 equiv of a carboxylic acid, 1.2 equiv of an amine, and 1.5 equiv of triethyl phosphite (Table 1). For workup and isolation, the MeCN was filtered, and the solids were washed with CH_2Cl_2 . The solvents were evaporated, and the products were obtained by SiO_2 chromatography. The entries in Table 1 span 1° and 2° amines, aliphatic and aromatic amines, amino acids and amino alcohols/phenols. The method is compatible with oxidation-prone substrates such as alkenes, boron derivatives, and furans and indoles as well as with electron-deficient heterocycles and benzene derivatives, and it works well for amines with a significant range of $\text{p}K_a(\text{H})$, chiral amine partners, chiral acid partners, and others. No racemization of stereocenters was observed for those substrates studied. The synthesis of peptide **3a** shown in Table 1 was carried out on a 5 g scale and delivered the product in 91% yield after 24 h at 50 °C. Neither phenols nor alcohols appear to interfere with the amidation sequence (i.e., amides **3c** and **3d**). Finally, while CH_3CN performed well as a solvent for many reactant pairs, the poor solubility of some amine/carboxylic acid pairs in CH_3CN can compromise performance in the current rendition of the catalytic reaction system.

As shown in Scheme 2 above, the catalytic cycle assumes the intermediacy of an *S*-acylthioisacylamide.^{30,32} The viability of this proposed thioester pathway is supported by control experiments: 1.0 equiv of Cbz-L-Trp-OH reacted with 1.0 equiv of BIT **1g** and 1.05 equiv of $\text{P}(\text{OEt})_3$ in MeCN to generate the thioester Cbz-L-Trp-S(CO) C_6H_3 -4- NO_2 -2-CONHC(Me) $_2$ -2-pyridyl in 81% yield within 5 min at 50 °C. Then, in the presence of 1.15 equiv of L-H $_2$ N-Phe-OMe (free-based from its HCl salt with diisopropylethylamine), a 10 mol % loading of the Cu catalyst $\text{CuI}_2(\text{NMI})_4$, and air, the thioester was completely converted to Cbz-L-Trp-L-Phe-OMe within a few minutes at 50 °C as judged by thin-layer chromatography. It took 6 h at 50 °C for **1g** to quantitatively regenerate, after which time the amide was isolated in 96% yield. In the absence of the Cu catalyst, the thioester reacted more slowly with the amine in MeCN at 50 °C to generate the amide (61% yield in 15 min).

Table 1. BIT-Catalyzed Aerobic Amidations^{a,b}

	product	#	% (t, h)
1	Cbz-L-Trp-Phe-OMe	3a	89 (18) 91 (24)^c
2	Cbz-L-Phe-NHcyclopropyl	3b	79 (10)
3		3c	68 (18)
4		3d	71 (36) ^d
5		3e	72 (18)
6		3f	83 (18)
7		3g	78 (36) ^e
8		3h	82 (36)
9		3i	78 (24)
10		3j	77 (24) ^f
11		3k	79 (24)
12		3l	61 (36)

^aFor those substrates examined (**3a**, **3b**, and **3f**), no epimerization was observed. Similarly, no diastereomers were noted for **3i**, **3j**, and **3l**.

^bReaction conditions: 10% $\text{CuI}_2(\text{NMI})_4$, 20% BIT **1g**, 1 equiv of acid, 1.2 equiv of amine or amine-HCl/DIEA, 1.5 equiv of $(\text{EtO})_3\text{P}$, 0.2 M in MeCN, 50 °C, dry air, 4 Å molecular sieves (1.6–2.2 × wt % of acid). ^c5 g scale. ^d0.1 M. ^e0.15 M, 30 mol % BIT were used. ^fThe 2,2-dimethylpropane-1,3-diol boronate ester was the substrate. Hydrolysis occurred concurrent with reaction/workup.

A number of additional observations are relevant to the mechanism of the BIT-catalyzed aerobic redox dehydration reactions: (1) ³¹P NMR experiments demonstrated only slow background oxidation of phosphite to phosphate; (2) neither triphenylphosphine nor triphenyl phosphite performed well as

stoichiometric reductants; (3) the use of an O₂ atmosphere in place of dry air was deleterious; and (4) the viability of the thioester catalytic pathway depicted in Scheme 2 depends on both the choice of the specific BIT organocatalyst and the reaction solvent used.⁴²

In conclusion, we have demonstrated the versatility of benzoisothiazolones as organocatalytic oxidants (coupled to O₂ in air as the terminal oxidant) using triethyl phosphite as the terminal reductant for effective catalytic oxidation–reduction condensation reactions that directly generate amides and peptides from carboxylic acids. Although not yet optimized, the current reaction system represents a first step toward an economical and environmentally suitable redox catalytic dehydrative bond formation.⁴³ Improvements in the current acylative system as well as extensions of the concept are under active study. Mechanistic details of the current acylative catalytic process will be reported shortly.

■ ASSOCIATED CONTENT

● Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b03168.

Experimental details and characterization data (PDF)

Crystallographic data for Cu₂(NMI)₄ (CIF)

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Notes

The authors declare the following competing financial interest(s): L.S.L., P.G., and M.G.L. are listed as inventors on a PCT filing: Heterocyclic Coupling Catalysts and Methods Related Thereto. PCT/US2014/059606, October 8, 2014.

■ ACKNOWLEDGMENTS

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