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Communication

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

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Benzoisothiazolone (BIT) Organo-/Copper Cocatalyzed Redox Dehydrative Construction of Amides and Peptides from Carboxylic Acids using $(EtO)_3P$ as Reductant and O_2 in Air as the Terminal Oxidant.

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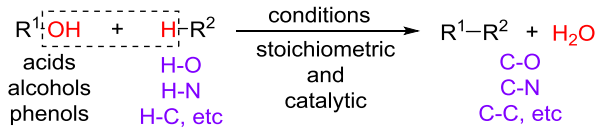
Supporting Information Placeholder

ABSTRACT: Carboxylic acids and amine/amino acid reactants convert 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 O_2 as the terminal oxidant and a slight excess of triethylphosphite as the reductant. Triethylphosphate 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). Historically these transformations were carried out with minimal attention to environmental issues or to atom-economies using processes that stoichiometrically activate the hydroxylic partner.

Scheme 1. Dehydrative Bond Construction



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 H_2O 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) [11,16,17] and to alkylations using alcohols (the Mitsunobu Reaction),[12-14] oxidation-reduction condensation is a broadly general protocol, but it suffers from significant atom-in-economies 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]

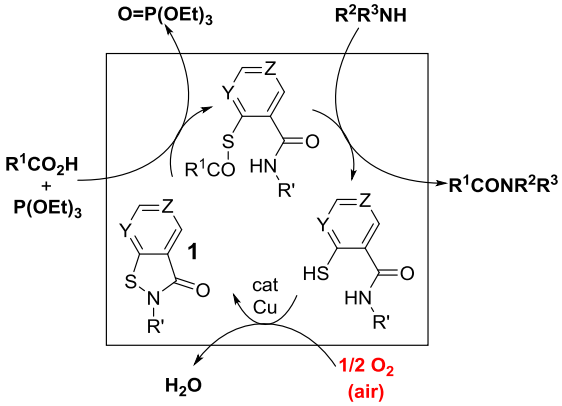
The substrate generality and gentle reaction conditions of oxidation-reduction condensation have stimulated interest in the development of reaction variants that can operate in the catalytic mode. To accomplish this task a sub-stoichiometric loading of simple and stable organocatalytic oxidants or reductants 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 % of DEAD as a catalytic oxidant, with 2 equivalents of $PhI(OAc)_2$ as the terminal oxidant and 2 equivalents of Ph_3P as the reductant.[22] Taniguchi improved upon Toy's observations in his use of 10 mol % of an azo compound, which was regenerated under the reaction conditions using 10 mol % of an Fe-phthalocyanine catalyst and O_2 in air as the terminal oxidant.[23] In Taniguchi's chemistry 2 equivalents of Ph_3P were required. O'Brien has approached catalytic oxidation-reduction condensation reactions from the perspective of the reductant. One example of a triorganophosphine-catalyzed Mitsunobu reaction where $PhSiH_3$ is the terminal reductant appears at the end of an O'Brien patent[24] in which triorganophosphine-catalyzed Wittig reactions are the principle focus of the document.[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: non-toxic 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 be both inexpensive and its reaction byproducts should be easy to remove from the resulting reaction mixture.

In pursuit of these goals, we disclose within a new aerobic, catalytic oxidation-reduction condensation system for efficient *acylative* bond formations. It is based upon the use of benzoisothiazolones (BITs) as easily prepared and modified S—N bond-derived organocatalytic oxidants (Scheme 2). Furthermore, for these acylative condensation reactions we avoid problematic stoichiometric triorganophosphine reductants by their replacement with inexpensive, low molecular weight triethylphosphite as the terminal reducing agent, which transforms into easily removed triethylphosphate as the byproduct. This contrasts with most other oxidation-reduction condensation reactions where aliphatic phosphites are avoided as reducing agents because of significant interference from adverse dealkylation events.[21,27]

Scheme 2. An Aerobic, Benzoisothiazolone-Catalyzed Amidation

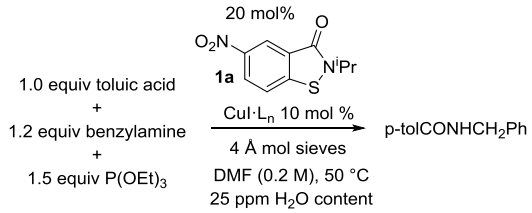


1a: Z = CNO_2, Y = H, R = ^{i}Pr
1b: Z = CNO_2, Y = H, R = 2,6-xylyl
1c: Z = N, Y = Y, R = ^{i}Pr
1d, Z = Y = H, R = Ph
1e, Z = H, Y = N, R = Ph
1f, Z = Y = H, R = 2-pyridyl
1g, Z = CNO_2, Y = H, R = C(Me_2)-2-pyridyl

Mukaiyama demonstrated the value of sulfenamides as stoichiometric oxidants (when paired with triorganophosphine reductants) in acylative oxidation-reduction condensation reactions for the dehydrative generation or amides and peptides.[28] The benzoisothiazolones 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. And, significantly, in the presence of catalytic Cu salts, sulfenamides in general,[29] and BITs more specifically,[30,31] are easily regenerated under mild oxidative conditions (air or O_2 atmosphere) from their reduced partners. Thus, as depicted in Scheme 2, by proceeding through S-acyl-2-mercaptobenzoic acid amides benzoisothiazolones should function as aerobically recyclable *organocatalytic* oxidants in acylative oxidation-reduction-condensation reactions. In support of the proposed catalytic cycle, *S*-acyl thiosalicylamides form directly from a carboxylic acid, a benzoisothiazolone and a stoichiometric *triorganophosphine*.[30,32]

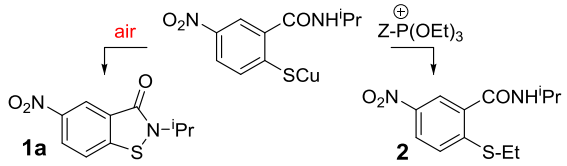
To begin the study, 1.0 equiv *p*-toluic acid, 1.2 equiv benzylamine, and 1.5 equiv triethylphosphite under dry air were exposed at 50 °C in DMF to 20 mol % of 5-nitro-*N*-isopropyl-benzoisothiazolone **1a**[30,32] in the presence of a variety of 10% CuI-N-ligand catalysts (Scheme 3). Activated 4 Å molecular sieves were used to keep 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*-tolylCONHBn in only 45% yield. Lower amide yields were noted when CuI was replaced with other Cu(I) sources (CuCl, CuBr, $Cu(MeCN)_4PF_6$, CuMeSal[35]). Control experiments with *p*-toluic acid, benzyl amine, $(EtO)_3P$ and molecular sieves showed only trace levels of amide formed after 24 h at 50 °C.

Scheme 3. BIT Catalyzed Amidation Exploratory Study



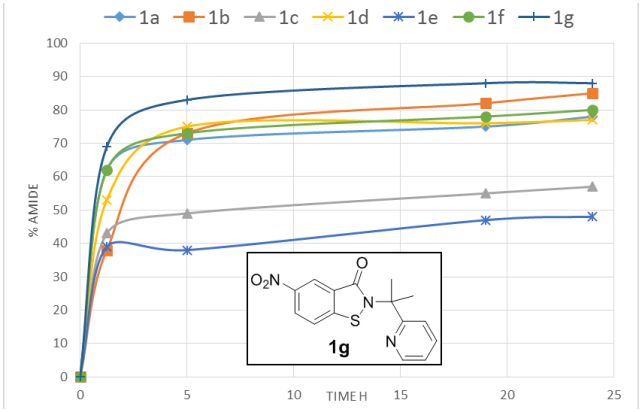
Since Cu(I) will oxidize under the aerobic reaction conditions used, $CuI_2(NMI)_4$ was prepared[36] and used subsequently as a discrete aerobic reoxidation catalyst. The exploratory study was then continued using 1.0 equiv *p*-toluic acid, 1.2 equiv benzylamine, 1.5 equiv triethylphosphite, and 10 mol % $CuI_2(NMI)_4$ at 50 °C under a dry-air atmosphere with activated 4 Å molecular sieves. A survey of reaction solvents (DMF, MeCN, THF, EtOAc, toluene) revealed optimum performance of the organocatalytic oxidant 5-nitro-N-isopropyl-benzoisothiazolone **1a** (20%) in MeCN (>70% amide in 10 h at 50 °C). Wide variability in the performance the 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 vs 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] **1g**[41]) was carried out. The formation of *p*-tolylCONHBn from1.0 equiv p-toluic acid, 1.2 equiv benzylamine, and 1.5 equiv $(EtO)_3P$ was investigated using 10 mol % $CuI_2(NMI)_4$ and 20 mol % BIT in MeCN at 50 °C (dry-air atmosphere and activated 4 Å molecular sieves).

Figure 1. Benzoisothiazolone Screening[a]



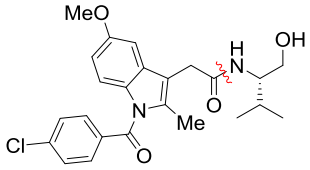
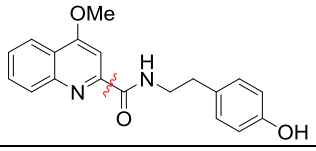
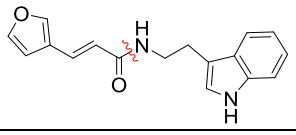
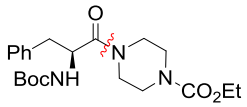
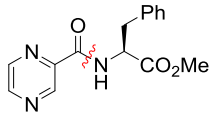
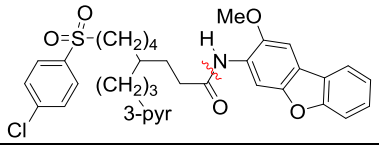
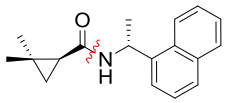
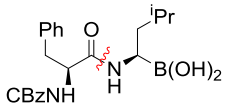
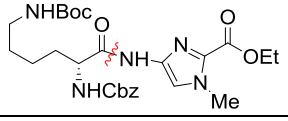
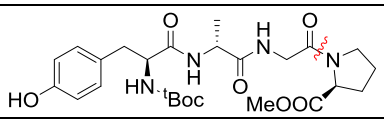
[a] Refer to Scheme 2 for the structures of BIT's **1a-1f**.

These experiments revealed modest differences in 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 analogs of **2** (Scheme 4) before full conversion of reactants to product was achieved. Among the BITs studied thus far, BIT **1g** was the best performer providing the fastest reaction rate and the highest conversion to amide (Figure 1).

Using a catalytic redox system comprised of 20 mol % organocatalyst **1g**, 10 mol % $CuI_2(NMI)_4$) in MeCN under dry air (4 Å mol 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 triethylphosphite (Table 1).

Table 1. BIT Catalyzed Aerobic Amidations[a,b]

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

[a] For those substrates examined (**3a**, **3b**, **3f**) no epimerization was observed. Similarly, no diastereomers were noted for **3i**, **3j**, and **3l**. [b] Reaction Conditions: 10% $CuI_2(NMI)_4$, 20% BIT **1g**, 1 equiv acid, 1.2 equiv amine or amine·HCl/DIEA, 1.5 equiv $(EtO)_3P$, 0.2 M in MeCN, 50 °C, dry air, 4 Å mol sieves (1.6-2.2 x wt % of acid). [c] 5 g scale. [d] 0.1 M [e] 0.15 M, 30 mol % BIT used. [e] The 2,2-dimethylpropane-1,3-diol boronate ester was the substrate. Hydrolysis occurred concurrent with reaction/workup.

For work up and isolation, the MeCN was filtered and the solids washed with CH_2Cl_2. The solvents were evaporated and the products 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, with electron deficient heterocycles and benzene derivatives, and it works well for amines with a significant range of pKa(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 5 g scale delivering 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**, **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 alluded to in Scheme 2, above, the catalytic cycle assumes the intermediacy an S-acylthiosalicylamide.[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** plus 1.05 equiv of $P(OEt)_3$ 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. In the presence of 1.15 equiv of L-H_2N-Phe-OMe (free based from its HCl salt with diisopropylethylamine), 10 mol % of the Cu catalyst $CuI_2(NMI)_4$ and air, the thioester converted completely to Cbz-L-Trp-L-Phe-OMe within a few minutes at 50 °C as judged by TLC. It took 6 h at 50 °C for the BIT **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).

A number of additional observations are relevant to the mechanism of the BIT catalyzed aerobic redox dehydration reactions. (1) ^{31}P NMR experiments demonstrated only a slow background oxidation of phosphite to phosphate. (2) Neither triphenylphosphine nor triphenylphosphite performed well as stoichiometric reductants. (3) The use of an O_2 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 (BITs) as organocatalytic oxidants (coupled to O_2 in air as the terminal oxidant) using triethylphosphite as a 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 towards 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

Full experimental details and characterization data are provided. This material is available free of charge via the Internet at http://pubs.acs.org."

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Notes LSL, PG, and MGL are listed as inventors on a PCT Filing: "Heterocyclic Coupling Catalysts and Methods Related Thereto". PCT/US2014/059606 on October 8, 2014.

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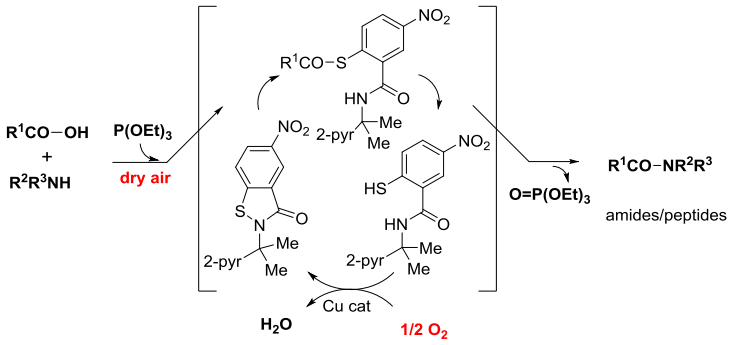
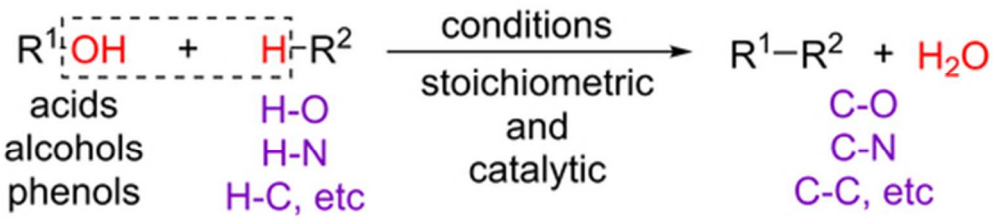
(41) Chen, F. J.; Liao, G.; Li, X.; Wu, J.; Shi, B. F. *Org. Lett.* **2014**, *16*, 5644-5647.

(42) A dependence of the reaction pathway on the nature of the BIT and the reaction solvent was noticed. Thus, N-alkyl substituted BITs rapidly produce the anticipated S-acylthiosalicylamide thioesters, while N-aryl substituted BITs were problematic, particularly in polar solvents like DMF. ^{31}P NMR spectroscopy traced the difference to a very rapid, direct deoxygenation of the N-aryl BITs by triethylphosphite, particularly in polar solvents. Full details of the direct deoxygenation of BITs by triethylphosphite will be disclosed separately.

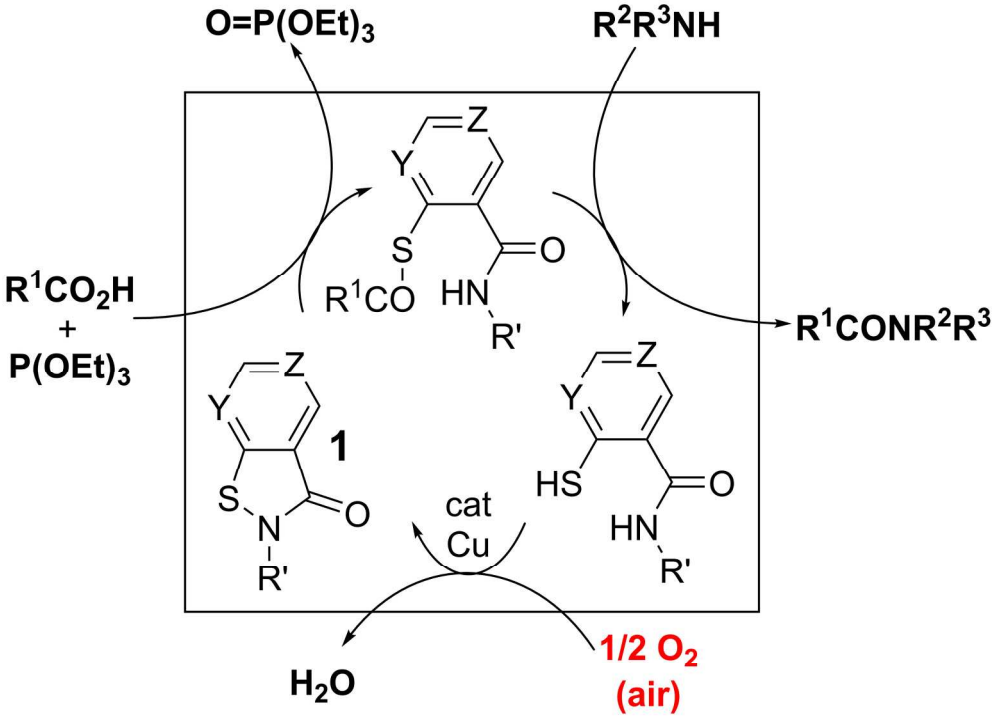
(43) Denton and Lambert describe the catalytic nucleophilic substitution of alcohols in reference #2.

SYNOPSIS TOC





Scheme 1
21x4mm (600 x 600 DPI)



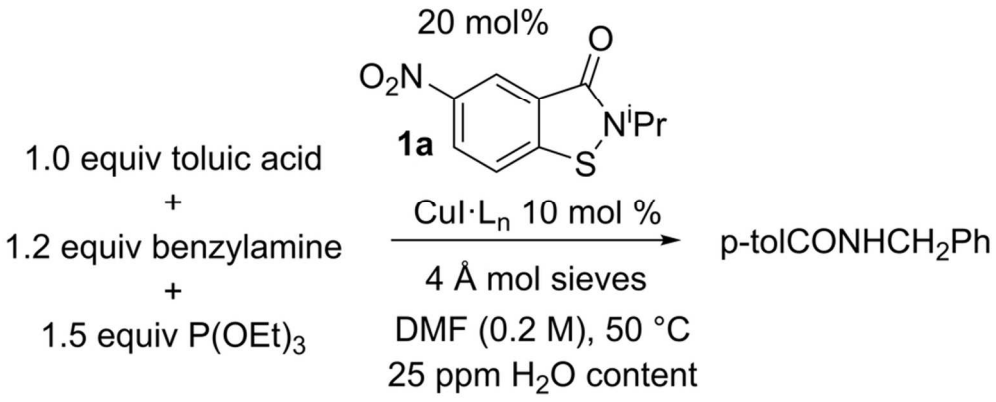
1a: Z = CNO_2, Y = H, R = ^{i}Pr **1d**, Z = Y = H, R = Ph

1b: Z = CNO_2, Y = H, R = 2,6-xylyl **1e**, Z = H, Y = N, R = Ph

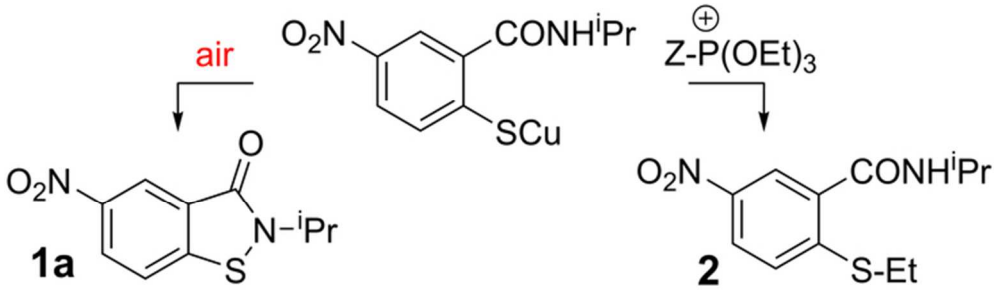
1c: Z = N, Y = Y, R = ^{i}Pr **1f**, Z = Y = H, R = 2-pyridyl

1g, Z = CNO_2, Y = H, R = $C(Me_2)$-2-pyridyl

Scheme 2
98x95mm (600 x 600 DPI)



Scheme 3
42x17mm (600 x 600 DPI)



31x9mm (600 x 600 DPI)

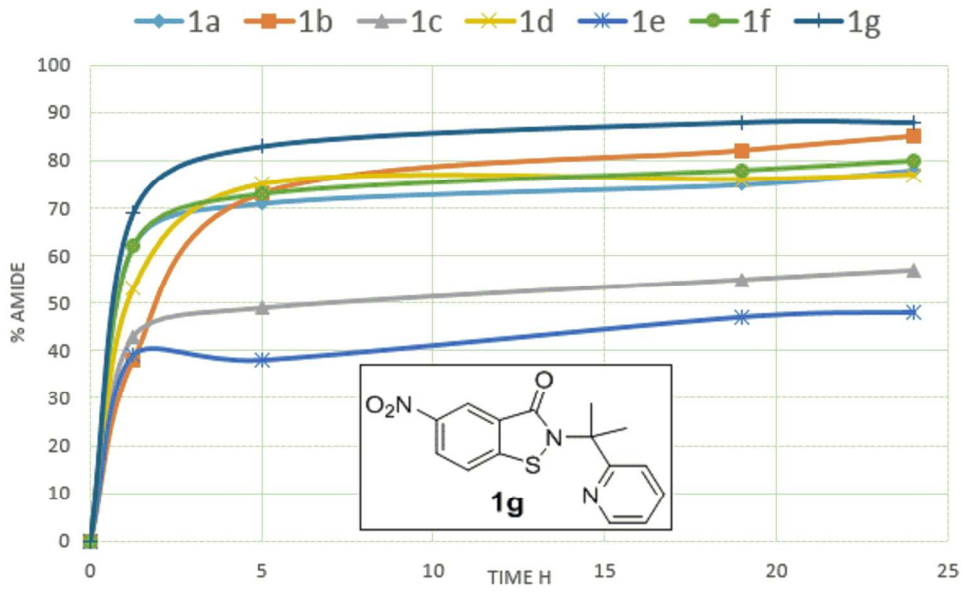
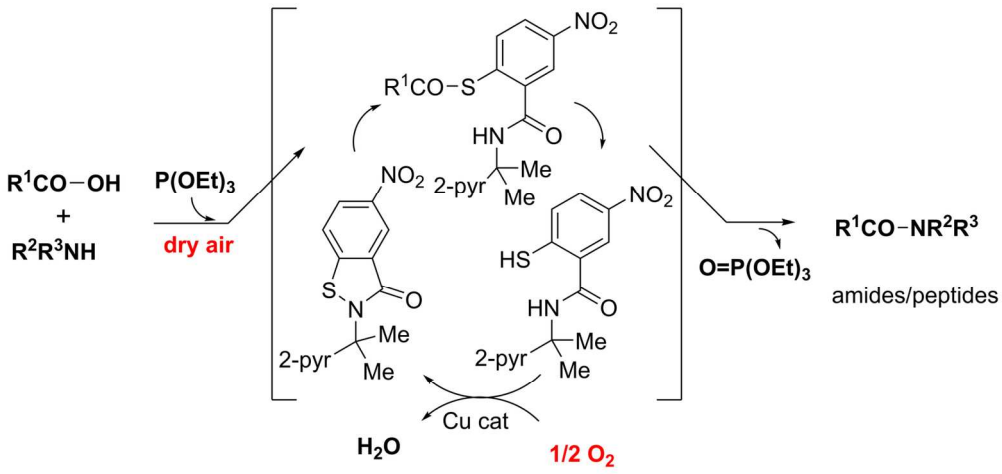
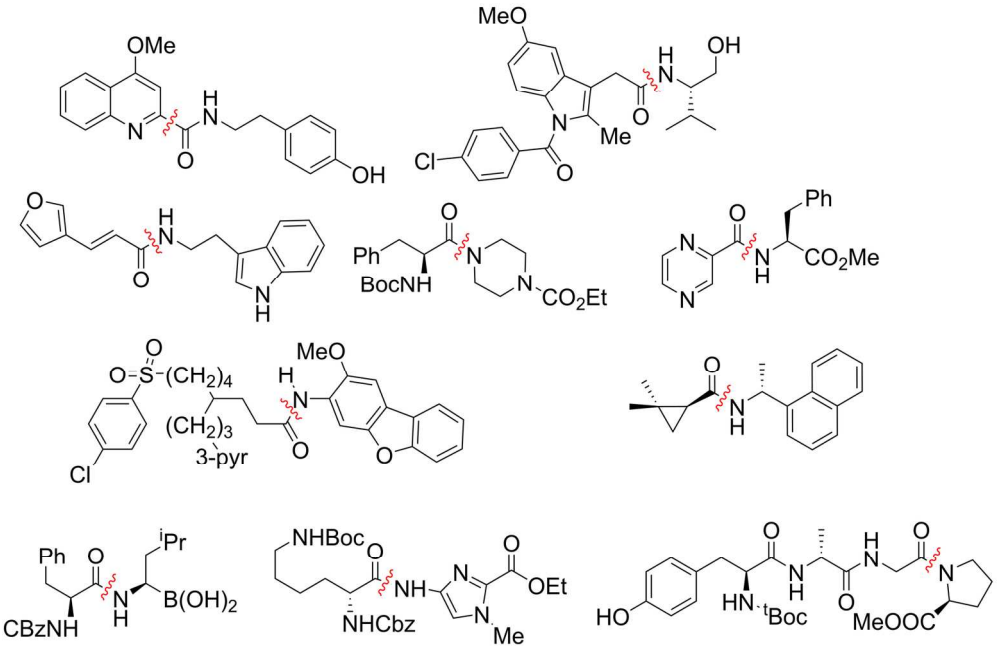


Figure 1
82x52mm (600 x 600 DPI)



TOC graphic
72x34mm (600 x 600 DPI)



Structures for Table 1
80x52mm (600 x 600 DPI)