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The interrupted Pummerer reaction in a sulfoxide-catalyzed oxidative coupling of 2-naphthols

Zhen He, Alexander P. Pulis, and David J. Procter*

Abstract: A benzothiophene S-oxide catalyst, generated *in situ* by sulfur oxidation with H_2O_2 , mediates the oxidative coupling of 2-naphthols. Key to the catalytic process is the capture and inversion of reactivity of a 2-naphthol partner, using an interrupted Pummerer reaction of an unusual benzothiophene S-oxide, followed by subsequent coupling with a second partner. The new catalytic manifold has been showcased in the synthesis of the bioactive natural products, ($\pm$)-nigerone and ($\pm$)-isonigerone. Although Pummerer reactions are used widely, their application in catalysis is rare, and our approach represents a new catalytic manifold for metal-free C–C bond formation.

Carbon-carbon bond formation underpins almost every synthetic undertaking¹ and oxidative processes that unite two nucleophilic partners,² at the expense of a C–H bond in each partner, are at the forefront of synthetic technology. Such couplings are typically achieved using stoichiometric metals, or metal catalysts,² however, metal-free processes that do not rely on expensive metal catalysts, and do not generate metallic waste, are desirable.^{3,4}

The Pummerer reaction,⁵ including its so-called interrupted variant,⁶ involves the activation of sulfoxides and the subsequent transformation of the resultant sulfonium salts. As tools for synthesis, the family of Pummerer processes continues to find widespread application en route to important targets, including natural products, bioactive molecules and advanced materials.⁵ It is therefore surprising that the use of Pummerer reactions to drive catalysis is rare,⁷ and the use of sulfoxides to catalyze carbon-carbon bond formation via Pummerer processes has not been described. We postulated that sulfoxides could serve as catalysts for oxidative union of two carbon nucleophiles through the operation of an interrupted Pummerer process (Scheme 1A). In such a process, activated sulfoxide derivatives **A** would engage nucleophile partners in an interrupted Pummerer reaction to form sulfonium salts **B**. A reversal of natural reactivity is made possible through the formation of **B**: the first nucleophile becomes electrophilic and is now activated for coupling with a second, liberating the coupled product and a sulfide leaving group. Selective oxidation of the sulfide would render the process catalytic in the sulfur species. Although interrupted Pummerer reactions generally operate under mild conditions in which sulfonium species must be regenerated presents acute challenges. For example, selective oxidation and electrophilic activation of sulfur must be possible in the presence of other nucleophiles,⁸ and interrupted Pummerer reactivity must out-run

side reactions (e.g. classical Pummerer chemistry)⁹ and rearrangements of sulfonium intermediates **A** and **B**.^{5b-5c,6a-6t,10}

Here we describe the realization of an interrupted Pummerer catalytic manifold in a carbon-carbon bond-forming, oxidative coupling of 2-naphthols that delivers important 1,1'-bi-2-naphthols (BINOLs) (Scheme 1B). The BINOL motif is one of the most recognizable and well-established ligand architectures in catalysis,¹¹ in addition to being found in bioactive molecules, natural products¹² and functional materials.¹³ BINOLs are most efficiently formed by oxidative coupling of 2-naphthols and various stoichiometric and catalytic processes, including excellent catalytic enantioselective variants, have been employed.^{11h,14} To our knowledge no metal-free, organocatalytic synthesis of BINOLs has been reported. The process constitutes a rare example of a catalytic Pummerer process, uses synthetically under-explored benzothiophene S-oxides,^{6r,6t,15} and employs inexpensive H_2O_2 as the terminal oxidant. The high functional group compatibility of the process has been exploited in the synthesis of ($\pm$)-nigerone and related natural products.

A. Catalytic Nu–Nu coupling by Interrupted Pummerer reaction

B. This work: Benzothiophene S-oxide-catalyzed, metal-free C–C coupling

Scheme 1. The Interrupted Pummerer reaction in sulfoxide-catalyzed oxidative couplings. (A) A new approach to nucleophile-nucleophile coupling that uses a sulfoxide catalyst to reverse the natural reactivity of one partner. (B) The realization of an interrupted Pummerer catalytic manifold in a carbon-carbon bond-forming, oxidative coupling of 2-naphthols that delivers important 1,1'-bi-2-naphthols.

As a prelude to our studies in catalysis, we first investigated the ability of sulfoxides to mediate the homocoupling of 2-naphthols in a stoichiometric process. In particular, the studies were designed to ascertain whether; (i) 2-naphthols would undergo *nucleophilic* addition to the activated sulfoxide (*cf.* **A**) through oxygen or through carbon in an S_EAr fashion;¹⁶ (ii) if the reaction occurred through oxygen, would the resultant aryloxysulfonium salts **I** now act as *electrophiles* and couple with

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a second equivalent of 2-naphthol. Thus, 2-naphthol (**1a**) and a variety of sulfoxides **3** were combined in the presence of the electrophilic activator TFAA (Figure 1). Pleasingly, when 3-methyl benzothiophene S-oxide (**3a**) was employed in CH₂Cl₂, the desired coupling product **2a** was formed in high isolated yield (87%). Dibenzothiophene S-oxide (**3b**) also produced **2a** but in slightly lower yield. The use of DMSO (**3c**), phenyl methyl sulfoxide (**3d**), and diphenyl sulfoxide (**3e**) produced complex mixtures thus highlighting the importance of the thieno moiety in **3a** and **3b** for efficient coupling (*vide infra*). Finally, benzothiophene S-oxides **3f** and **3g** bearing bulky substrates at C3 proved less effective in the coupling than **3a**. The C3 substituent is likely to play a role in disfavoring the competing rearrangement of aryloxysulfonium salts **1**.^{6r,6t}

Figure 1. Preliminary studies: stoichiometric sulfoxide mediated oxidative coupling. Reaction conditions: **1a** (0.20 mmol), **3** (0.11 mmol), CH₂Cl₂ (1.0 mL), at –40 °C; TFAA (0.17 mmol) then added and stirred for 15 min; warmed to rt. Yield determined by ¹H NMR analysis of the crude reaction mixture. Isolated yield in parentheses. [a] Complex mixture formed.

Table 1. Optimization of the sulfoxide-catalyzed oxidative homocoupling.^[a]

Entry	Changes to conditions	Yield 2a (%)
1	H ₂ O ₂ and TFAA added in one portion	45
2	none	90 (84)
3	no 3a '	trace
4	no TFA	trace
5	no TFAA	0
6	UHP was used instead of H ₂ O ₂	85
7	^t BuOOH (5.5 M) was used instead of H ₂ O ₂	45

[a] Reaction condition: **1a** (0.2 mmol), **3a**' (0.02 mmol), CH₂Cl₂/TFA (0.5/0.5 mL), 0 °C; 30% aqueous H₂O₂ (0.25 mmol) and TFAA (0.25 mmol) added in five portions over 2 h; warmed to rt. Yield determined by ¹H NMR analysis of the crude reaction mixture. Isolated yield in parentheses.

For a catalytic process, chemoselective oxidation of the sulfide byproduct, to the sulfoxide and not the sulfone, by a convenient terminal oxidant in the presence of the other nucleophilic reaction components is crucial. H₂O₂ and TFAA^{6r,6t} were added in one portion to a solution of 2-naphthol (**1a**) and 10 mol% of sulfide **3a**'. Pleasingly, **2a** was obtained in 45% yield (Table 1, entry 1). However, significant quantities of sulfone **3a**' were formed thus limiting catalytic turnover. Adding the oxidant and activator in portions greatly improved reaction efficiency and product **2a** was isolated in 84% yield (entry 2). Control experiments revealed that **3a**', TFA, and TFAA were all essential for the reaction to proceed (entry 3–5). Other terminal oxidants (e.g. UHP and ^tBuOOH) were less effective (entry 6–7).

A. Homocoupling^a

B. Cross-coupling^h

Figure 2. Substrate scope for the sulfoxide-catalyzed oxidative coupling of 2-naphthols. [a] Reaction conditions: **1** (0.2 mmol), **3a**' (0.02 mmol) in CH₂Cl₂/TFA (0.5/0.5 mL), at 0 °C; then 30% H₂O₂ aqueous (0.25 mmol) and TFAA (0.25 mmol) were added separately in five portions over 2 h; warmed to rt. [b] 20 mol% catalyst **3a**' was used. [c] Dibenzothiophene **3b**' was used as the precatalyst and Tf₂O was used instead of TFAA. [d] without **3a**'. [e] Used CH₂Cl₂/TFA (1.0/1.0 mL) and heated to 50 °C. [f] 1.6 g of **1v** used. [g] H₂O₂

and TFAA were added in five portions over 10 min. [h] Reaction conditions: **1** (0.1 mmol), **4** (0.1 mmol) and **3a'** (0.02 mmol) in CH₂Cl₂/TFA (0.5/0.5 mL), at 0 °C; then 30% H₂O₂ aqueous (0.25 mmol) and TFAA (0.25 mmol) were added separately in five portions over 2 h and then warmed to rt.

Using 10 mol% of **3a'**, a range of 2-naphthols **1**, bearing electron neutral, electron rich and electron poor substituents at a variety of positions on the ring system, underwent smooth coupling to give BINOLs **2** in moderate to good yield (Figure 2A). Ester (**2e**, **2v**), methoxy (**2c**, **2j**, **2m**, **2r**, **2z**), cyano (**2f**), bromo (**2d**, **2o**, **2u**), trifluoromethyl (**2k**), and additional free hydroxyl (**2n**, **2w**, **2z**, **2aa**) functional groups were well tolerated. Interestingly, the coupling of 2-naphthols **1** containing a benzothiophene substituent (formation of **2l** and **2t**) did not require addition of an external benzothiophene as a benzothiophene S-oxide catalyst is likely formed *in situ* from the substrates. Crucially, products bearing 3,3' disubstitution, a key motif for the function of the most powerful BINOL based ligands,¹¹ were successfully formed (**2u–x**). The catalytic coupling worked well on gram scale: 1.6 g of **1v** produced **2v** (0.93 g) with similar efficiency as to that achieved on a smaller scale. We also achieved the coupling of highly oxygenated 2-naphthols **1z** and **1aa** to give BINOLs **2z** and **2aa** in high yield. A previously reported attempt to oxidatively couple **1z**, to give **2z**, using a copper catalyst was unsuccessful.^{14s} Notably, the results from reactions using 10 mol% of **3a'** were highly consistent with those obtained from reactions using stoichiometric **3a**.¹⁷ This underscores the remarkable selectivity achieved in the stages of the catalytic process. Our sulfoxide-catalysis approach can also be used in C–H/C–H-type cross-coupling between 2-naphthols and arene partners; the combination of 2-naphthols with various electron-rich arene partners gave the desired cross-coupled products (**5a–5f**) in moderate yield (Figure 2B). 2-Naphthol homocoupling products were also observed (See Supporting Information).

A. Proposed mechanism for the sulfoxide-catalyzed oxidative coupling of 2-naphthols

B. Mechanistic probe for the formation of intermediate I

Scheme 2. (A) Proposed catalytic cycle. (B) Probing the intermediacy of an aryloxysulfonium salt.

Based on the above results, and our previous studies,^{6r,6t} we propose the catalytic cycle set out in Scheme 2A. Benzothiophene S-oxide **3a** reacts with TFAA to form activated sulfoxides **II**, which we have observed by NMR (See Supporting Information).¹⁸ Subsequently, 2-naphthols **1a** react through oxygen with **II** in an interrupted Pummerer process to form aryloxysulfonium salts **I**.^{6r,6t} The intermediacy of **I** is supported by the formation of cross-coupled product **7** from the stepwise addition of phenol **6** to one equivalent of activated benzothiophene S-oxide **3a**, and subsequent addition of 2-naphthol (Scheme 2B). Formation of the aryloxysulfonium salts **I**, bearing a benzothiophene leaving group on oxygen, allows the reversal, or umpolung, of the normal nucleophilic reactivity of C1 of 2-naphthols. Thus, the now electrophilic naphthol moiety in **I** engages with another equivalent of 2-naphthol **1** to form a new carbon-carbon bond in **III**, which undergoes rearomatization to form BINOLs **2**. The liberated benzothiophene is selectively re-oxidized with H₂O₂/TFA to complete the catalytic cycle. Key to the process is the lack of aromaticity in the five-membered ring in benzothiophenium salts **I**.¹⁹ Upon carbon-carbon bond formation and concurrent expulsion of benzothiophene, aromaticity is regained – a driving force that is absent when sulfoxides **3c–e** are used.

Scheme 3. Total synthesis of (±)-nigerone and (±)-isonigerone.

We have applied the sulfoxide-catalyzed method in a short synthesis of (±)-nigerone and (±)-isonigerone, bisnaphthopyrone natural products isolated from mold and exhibiting antitumor²⁰ and antibacterial²¹ activity (Scheme 3). Kozłowski employed 2-

naphthol **8** in the only reported total synthesis of nigerone.²² 2-Naphthol **8** underwent metal-free, sulfoxide-catalyzed oxidative coupling, delivering complex BINOL **9** in 50% isolated yield. Inspired by Kozlowski's route, **9** was transformed into bis-sulfoxide **10** which subsequently underwent piperidine mediated aldol reaction and cyclization to form a mixture of the natural products, isonigerone, bis-isonigerone and nigerone, in a combined 85% yield. Heating the mixture of isonigerone and bis-isonigerone in the presence of NaOH allowed equilibration and formation of the thermodynamic product, ($\pm$)-nigerone in 57% yield. The concise route to ($\pm$)-nigerone hinges on the high chemoselectivity of the sulfoxide-catalyzed oxidative coupling: the additional free hydroxyl group in **8** was incompatible with earlier catalytic couplings thus protection and later deprotection of the group was essential.²² Our approach constitutes the first synthesis of isonigerone, and also enabled us to characterize all three natural products by X-ray crystallographic analysis, thus lending further support to their structural assignment.²³

In summary, we have developed a metal-free, sulfoxide-catalyzed, oxidative coupling of 2-naphthols using inexpensive H₂O₂ as the terminal oxidant. Key to our approach is the use of a benzothiophene S-oxide catalyst that captures and inverts the reactivity of one partner by means of an interrupted Pummerer reaction. The resultant aryloxysulfonium salts undergo subsequent coupling with a second partner, driven by the regain of aromaticity upon expulsion of benzothiophene. The chemoselectivity of the new catalytic manifold has been showcased in a concise approach to the natural product ($\pm$)-nigerone and its congeners. As a new strategy for inducing carbon-carbon formation between nucleophilic partners, and a rare example of the use of a Pummerer process in catalysis, the method provides a blueprint for future metal-free, catalytic couplings.

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Entry for the Table of Contents

COMMUNICATION

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The interrupted Pummerer reaction in a sulfoxide-catalyzed oxidative coupling of 2-naphthols

A benzothiophene S-oxide catalyst, generated in situ using H_2O_2 , mediates the oxidative coupling of 2-naphthols, thus exemplifying a strategy for coupling nucleophilic partners. Key to the catalytic process is the capture and inversion of reactivity of one partner, using an interrupted Pummerer reaction, followed by subsequent coupling with a second partner. The new catalytic manifold has been showcased in the synthesis of bioactive natural products. Although Pummerer reactions are used widely, their application in catalysis is rare.