



The Phenol-Phenothiazine Coupling: an Oxidative Click Concept

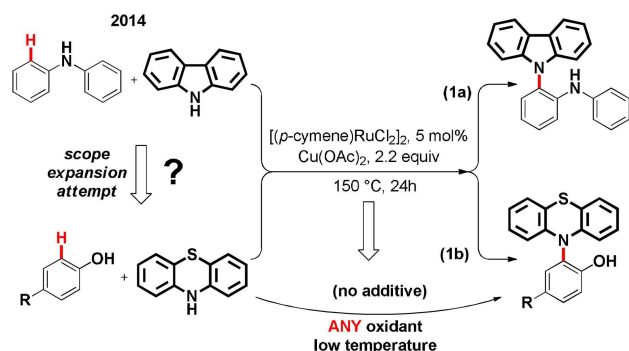
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The phenol-phenothiazine coupling reaction is attracting increasing attention, in part due to its enabling character of innovative radical, photochemical, and electrochemical concepts. Indeed, this C–N bond forming cross dehydrogenative

coupling accommodates almost any oxidizing strategy, often with mild reaction conditions. This concept paper analyses the particularity of this simple, cheap, and reliable coupling reaction, and discusses some of its probable future applications.

A Serendipitous Discovery

Not many organic scaffolds, which are as ancient, as cheap, and as available as phenols^[1] and phenothiazines^[2–4] enjoy so important and yet so diverse fields of applications such as essential bio-active compounds,^[3] or organic materials.^[4] Wouldn't it be wonderful to have a straightforward method to couple them together? In early 2014, my first PhD student, Marie-Laure Louillat-Habermeyer and I, were trying to transpose an odd Ru(II)-Cu(II) catalyzed C–N bond forming dehydrogenative coupling reaction between carbazoles and diarylamines that we had recently developed,^[5] towards these broader and arguably more important classes of substrates (phenols and phenothiazines, Scheme 1). Through naïve acidity and structural analogies, we imagined replacing carbazoles with phenols, and diarylamines with phenothiazines into our previously developed



Scheme 1. A serendipitous discovery.

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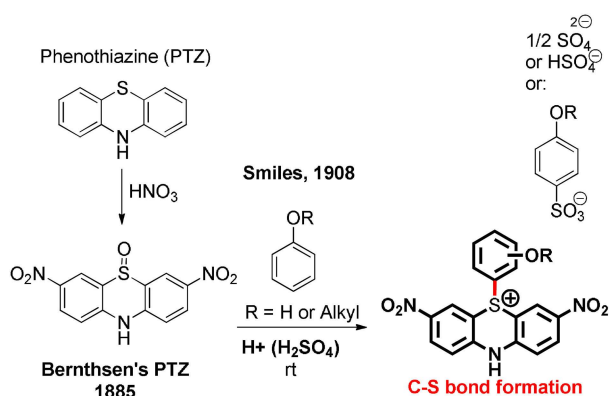
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Ruthenium catalyzed C–N dehydrogenative bond formation concept. To our pleasant surprise, this worked immediately (Scheme 1b). Indeed, a new cross C–N dehydrogenative coupling product was detected between phenols (C–H substrate) and phenothiazines (N–H substrate). We therefore excitedly re-optimized the Ru(II)/Cu(II) system in this novel reaction. Eventually came the time to re-verify the necessity of every additive of the reaction, notably the Ru(II) and Cu(II) salts, *before* engaging into the substrate scope of the reaction. And indeed, how many times has the key question: “Wait, have we verified that we really need this or that additive?” led to a full change of paradigm in the project? Sure enough, omission of the Ru(II) catalyst, it quickly transpired, still delivered the phenothiazinated phenol coupling product. That was interesting as ruthenium salts are quite onerous additives. There then remained only the much cheaper Cu(II) salt, a metal with a pronounced history of mediating C–N bond forming reactions.^[6] But this was not the end of it. I still remember this Friday afternoon of July 2014 (the 25th) as if it was yesterday, when we realized, shocked, that omission of the Cu(II) salt had not suppressed the reaction either.^[7] Thus, the C–N dehydrogenative coupling reaction seemed to run without any metal catalyst. What could have gone wrong? This may seem trivial today, but this went against most known aromatic amination concepts at the time (with or without pre-activation, one could think of Ullmann-Goldberg and Buchwald-Hartwig reactions,^[8] and of all the recent C–H bond oxidative amination methods).^[9] Thus, this could simply not be true, and for several days thereafter, we seriously doubted our results. Control experiments with brand new (free of metal traces) reactors and stirring bars however, and different substrate batches, implacably confirmed this verdict. Latter studies from us and other research groups demonstrated the high specificity of this click-like phenol-phenothiazine coupling reaction, under almost any oxidizing conditions, at sometimes room temperature.

Historical Perspective (Smiles Almost Had It)

One is often surprised upon the discovery of very simple reaction concepts that those had not been stumbled upon before. In retrospect, it is probably quite misleading to assume

that most essential reaction concepts have been already discovered, and as a corollary, that there remains only to combine those essential reactivity concepts into more complex ones. Although increasing complexity is an essential and necessary approach for the development of innovative synthetic methods, some of the latest extremely simple reactivity breakthroughs suggest that there remains much to explore in terms of essential reactivity.^[10] We have looked back thoroughly to the oldest reactions involving phenols and phenothiazines. As far we know today, no one before us has ever mixed phenols and phenothiazines under mildly oxidizing conditions (the phenothiazinated phenol cross coupling product would have been arguably unmissable, even with the more limited 19th century analytical techniques). But it came pretty close. Indeed, more than a century ago, in 1908, a young British chemist named Samuel Smiles, a sulfur chemistry expert later known for the “Smiles rearrangement,”^[11] tried to condensate phenol onto the so-called Bernthsen phenothiazine,^[2b] under strongly acidic conditions (Scheme 2).^[12] The thereby obtained condensation



Scheme 2. The work of Smiles in 1908.

product *is not* the C–N coupling product however, which we discovered, but rather an unusual ionic C–S condensation product^[12] (which can nowadays be confirmed by NOESY NMR). In fact, Bernthsen's phenothiazine is one of the rare phenothiazines that *does not* operate in the (C–N) phenol-phenothiazine



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coupling reaction, due to the strong unfavorable electronic influence of the two nitro groups. It is remarkable that Smiles briefly considered a C–N condensation product hypothesis,^[12b] but (rightfully) discarded it as unlikely! If Smiles had thought to try the phenothiazine precursor instead (absence of nitro groups) under any mildly oxidizing conditions, there is little doubt that he would have found the general (C–N) phenol-phenothiazine coupling reaction. It waited another century for us.

Why Now

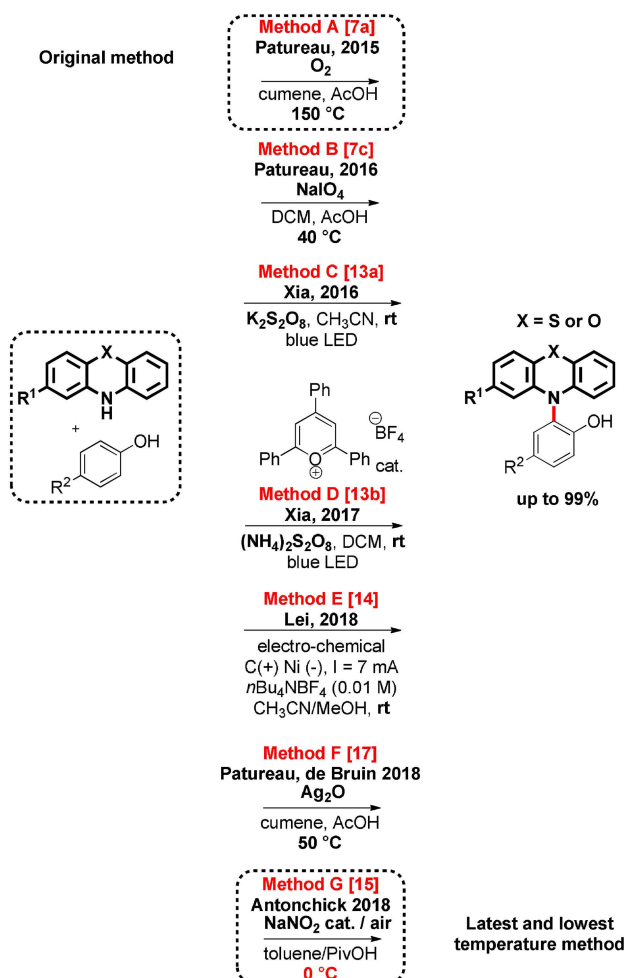
The phenol-phenothiazine coupling reaction has recently enabled unprecedented reactivity concepts to emerge. In the 2015 original publication, it was our concept of (at the time unprecedented) metal-free oxygen mediated cross dehydrogenative amination reaction.^[7] In 2016–17, W. Xia et al. used it as a model reaction for their metal free photo-catalyzed amination concept at moderate temperature.^[13] Similarly, in 2018, the group of A. Lei used it as model reaction for their electrochemical dehydrogenative amination concept, at room temperature.^[14] Most recently in 2018, Antonchick et al. used it as a model reaction for their low temperature (0 °C!) nitrosonium catalyzed dehydrogenative amination concept.^[15] It is clear that the exploration of all these new innovative reactivity concepts is (initially at least) enabled by the high specificity of the phenol-phenothiazine coupling reaction. This is not to mean that the above mentioned innovative reactivity concepts will not / have not evolved beyond the phenol-phenothiazine coupling reaction concept, on the contrary. However, the phenol-phenothiazine coupling reaction clearly offers a reliable platform, from which to invent new reactivity concepts and applications. It is this realization that stimulated this concept paper on the topic.

Scope

The general phenol-phenothiazine coupling reaction concept can be defined by the reaction in which an unprotected phenol and an unprotected phenothiazine are united under any type of oxidizing conditions to form a C–N bond *hetero-coupling* product, wherein the only by-product is formally H₂ or a derivative of it. Much like a “click reaction” (i.e. the azide-alkyne cycloaddition),^[16] this reaction may be catalyzed or non-catalyzed. In view of the high specificity and robustness of this reaction, one could arguably qualify this concept as “oxidative click reaction.” It should be noted that almost any oxidizing conditions are applicable (Scheme 3).^[7,13–15] Moreover, anilines,^[14c] indoles (C–H substrate) and phenoxazines (N–H substrate) are also competent building blocks in this coupling reaction.^[7a]

All Oxidants Work!

In our first report of this coupling reaction, we went directly for the cheapest oxidant: O₂. This was the first variant of this coupling reaction ever reported (Scheme 3).^[7a] The original method however, although very simple, comes to the cost of very high reaction temperatures, up to 150 °C. Our recent mechanistic investigations with the de Bruin research group demonstrated that this was not due to some high energy transition state however, thus causing us to assume that O₂ diffusion/concentration factors could be limiting.^[17] As a matter of fact, all non-gaseous oxidants that have been reported since consistently allow lower reaction temperatures. These are summarized in Scheme 3, in chronological order.^[7,13–15] Clearly, very diverse oxidizing strategies have been successfully engaged in this coupling reaction, from aerobic oxidation^[7,15] to photocatalytic oxidation,^[13] to radical or non-radical oxidation, all the way to electro-chemical oxidation.^[14] A catalytic approach was most recently proposed by Antonchick, allowing to lower the reaction temperature to an impressive 0 °C.^[15] There is every reason to believe that more catalytic approaches

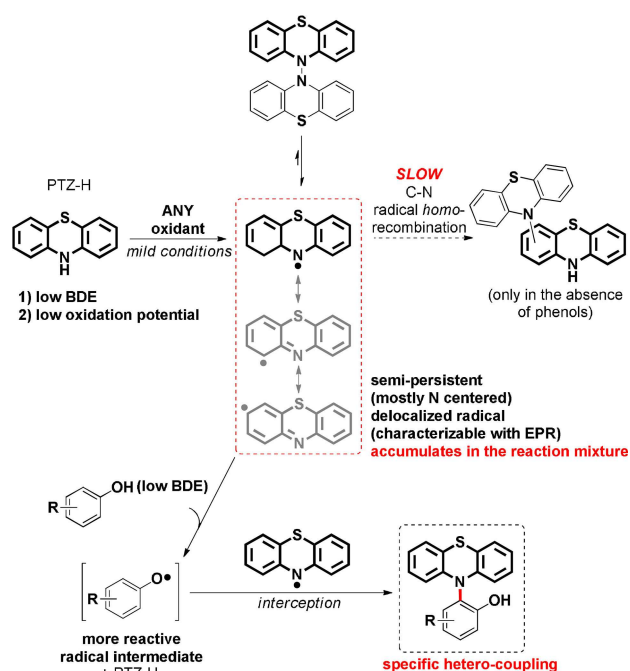


Scheme 3. Phenol-Phenothiazine coupling reaction, reported conditions.

will be developed in the near future, for example with transition metal salts.

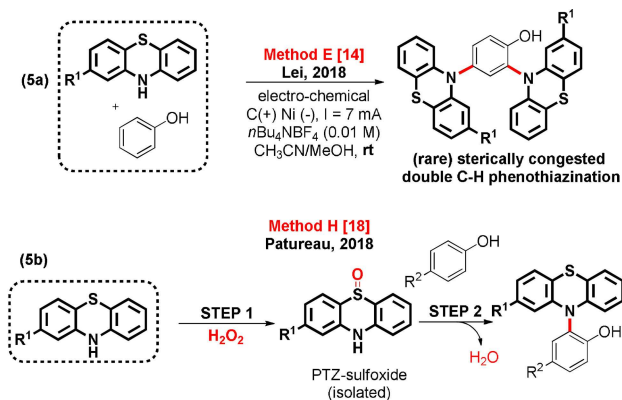
General Mechanistic Model

The secret of this highly specific coupling reaction lies in its mechanism. Recently, in collaboration with the de Bruin group, we presented a series of mechanistic experiments, and probed some of the most probable scenarios with DFT calculations, in order to give a rational interpretation to the high specificity of this coupling reaction.^[17] The conclusion of that study yielded the general mechanism depicted in Scheme 4. Here, it is



Scheme 4. General mechanism model (Patureau & de Bruin et al.).^[17]

important to note that this general mechanism applies to radical, mildly oxidizing conditions. In principle, one cannot exclude additional pathways and intermediates in the case of 1) extremely strong oxidants (for example, the phenothiazine's sulfur atom is susceptible to oxidation), 2) electro-chemical conditions, and 3) photo-activating conditions. Indeed, those concepts bring energy and the required oxidizing driving force in very different manners, which may afford somewhat different reactive intermediates. As an illustration, the A. Lei electro-chemical conditions (Scheme 3 and 5a), are the only ones, as far as I know, to be able to afford the double dehydrogenative C–N bond formation coupling product, in spite of the large steric bulk at the second C–H phenothiazination event.^[14] In all other methods, this bulk is sufficient to conveniently and exclusively stop at the first C–N bond forming coupling event. As a second example, it should be noted that phenothiazine-sulfoxide is a competent substrate, even in the absence of an external

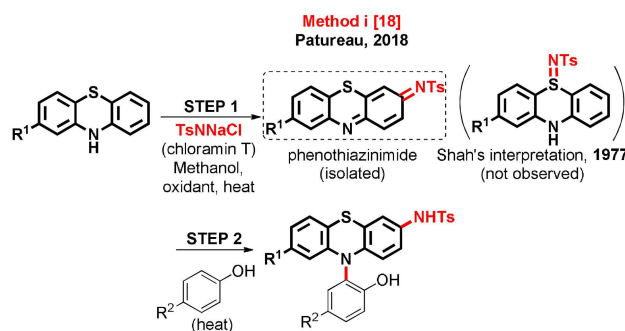


Scheme 5. There is maybe more than one mechanistic pathway.

oxidant (wherein the sulfoxide serves as internal oxidant, Scheme 5b).^[18] The precise mechanism with the phenothiazine-sulfoxide building block is not yet known however. In any case, what is remarkable is that in spite of probable condition dependent multiple pathways, one almost always obtains the very same oxidative C–H phenothiazinated phenol coupling product. This means that depending on the desired functional group tolerance, reaction temperature, scale, reactor requirements, and sustainable character of the oxidant, one can select an appropriate oxidative method (Scheme 3). This arguably makes the phenol-phenothiazine coupling reaction concept particularly reliable for future applications, for example in click-like systems.^[16] Because of the strong radical character of phenothiazines however, the general mechanistic model of Scheme 4 will probably remain in most cases the preferred scenario.

Related Concepts

If one assumes that the above mentioned paradigm: “all oxidants work,” is true, then it should not matter if one would decide to work with say: chloramine T. Indeed why not? Moreover, the realization that phenothiazine-sulfoxides were still competent substrates with an internal oxidant model (Scheme 5b) comforted us (Rongwei Jin, Christina Bub, and I) in the idea of associating the chloramine T oxidant with phenothiazines and phenols.^[18] Indeed, chloramine T and related reagents are known to oxidize thioethers into the corresponding sulfon-imines and -imides. We were thus curious of the existence and reactivity of such scaffolds. Much to our surprise however, the allegedly known phenothiazine-sulfonimide scaffold originally reported by Shah in 1977, had been wrongly assigned.^[19] Indeed, the sulfonamido-nitrene precursor does not form the sulfonimide as reported in the literature. Instead, it inserts into one of the C–H bonds of the phenothiazine backbone to form, after straightforward oxidation, the phenothiazinimide structure depicted in Scheme 6.^[18,20] This represents a unique case of (metal-free) nitrene C–H insertion reaction that operates in spite of the presence of an



Scheme 6. Coupling concept variant with phenothiazinimides.

oxidizable thioether functional group in the substrate. Phenothiazinimides, it turned out, are also competent coupling partners for the C–H amination of phenols. This thus furnishes a two steps / three component coupling reaction, which is structurally and conceptually related to the topic of this concept paper. This three component coupling reaction clearly paves the way to future innovative synthetic approaches for the direct C–H functionalization of the phenothiazine's backbone.

Up-Coming Applications

There are a few arguably obvious next steps that are worth mentioning. First of all, some of the applications of the click reaction concept (i.e. alkyne-azide cycloaddition reaction)^[16] might soon appear with a phenol-phenothiazine “oxidative clicking approach,” especially now that the reaction is accessible even below room temperature (Scheme 3). A second obvious idea is to priorly link the phenol and the phenothiazine backbones with either a covalent or alternatively a supramolecular spacer, and engage those new scaffolds in the phenol-phenothiazine coupling reaction concept. This strategy will probably lead to interesting new materials. A final obvious idea is to develop an enantioselective variant of this reaction concept. Indeed, the *ortho*-phenothiazinated phenol coupling products possess a characteristic and robust C–N chirality axis (when the phenothiazine is unsymmetrically substituted), which is maintained by an intramolecular O–H...N Hydrogen bond. The largest diastereomeric excess that could be obtained so far however in this C–N bond forming concept with a chiral phenol (estrone) is almost negligible (*d.e.* = 15%).^[7c] However, the recent report of Antonchick (Method G, Scheme 3), which operates at an impressively low temperature of 0 °C, arguably re-opens that quest.^[15] I still hope we shall be the first to publish a catalytically induced 90% enantiomeric excess in the formation process of that C–N chiral axis, but it is going to be a tight race! Similarly to axially chiral (C–C) biaryls,^[21] this can be expected to remain an important research topic in the near future.^[22]

Conclusions

In conclusion, the very simple and highly specific phenol-phenothiazine coupling reaction concept has become a reliable platform for other, more elaborated (catalytic, photocatalytic, electrochemical) reactivity concepts to emerge, in particular in the field of cross dehydrogenative coupling reactions.^[23] Rapid expansion of the phenol-phenothiazine coupling concept is thus expected in the coming years, especially with those methods which allow low temperature reactions, such as under electrochemical,^[14] or catalytic oxidation conditions.^[15] The latter low temperature methods should very soon lead to: 1) click-like applications, and 2) new phenothiazine based materials through (enantioselective) C–H or N–H functionalization strategies.

Acknowledgements

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: Phenol-Phenothiazine coupling • cross dehydrogenative coupling • oxidative click concept • axial chirality • heterocyclic materials

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