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Te(II)-Catalyzed Cross-Dehydrogenative Phenothiazination of Anilines

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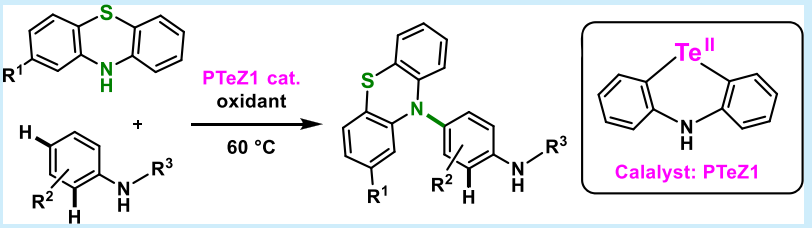
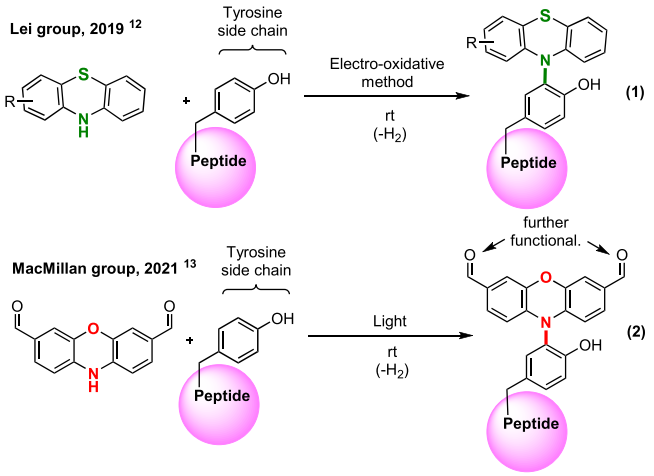


ABSTRACT: Oxidative clicklike reactions are useful for the late-stage functionalization of pharmaceuticals and organic materials. Hence, novel methodologies that enable such transformations are in high demand. Herein we describe a tellurium(II)-catalyzed cross-dehydrogenative phenothiazination (CDP) of aromatic amines. A key feature of this method is a cooperative effect between the phenotellurazine catalyst and the silver salt, which serves as a chemical oxidant for the reaction. This novel catalysis concept therefore enables a considerably broader scope compared with previous chemical oxidation methods.

Cross-dehydrogenative coupling (CDC) reactions have become a promising pathway for C−H functionalization because of their step- and atom-efficient nature.[1−8] In particular, the concepts of cross-dehydrogenative phenochalcogenazination (CDP) and phenothiazination are becoming increasingly popular because of their "oxidative click" character.[9−11] Indeed, these enable the late-stage functionalization and modification of peptides at their tyrosine units. In 2019, Lei and coauthors clicked some phenothiazines onto tyrosine derivatives and peptides by means of electro-oxidation (Scheme 1, eq 1).[12] More recently, MacMillan and co-workers utilized this concept to click new functionality onto the tyrosine positions of peptides with a photochemical method (Scheme 1, eq 2).[13]

Scheme 1. CDP Oxidative Click Concept



This methodology is very effective at selectively modifying tyrosine units in the presence of large and sensitive peptide scaffolds because of the high specificity of the CDP reaction toward electron-rich phenols.[14] Moreover, such oxidative click concepts are operationally minimal, typically containing only an oxidant, and are effective at very mild temperatures.[10] Nevertheless, the oxidative CDP click reaction becomes more challenging in terms of scope and functional group tolerance when applied to anilines. In the past few years, chemical oxidative[15] and in particular electro-oxidative[16−18] methods have been developed (Scheme 2). In the former case, however, only a limited number of five- and six-membered cyclic anilines could be utilized,[15] indicating a demand for novel, efficient methodologies.

Because of the large atomic size, unique chalcogen bonding ability, and activation properties of tellurium, the field of tellurium catalysis has considerably expanded over the last few months.[19−24] Recently, our group reported an unusual tellurium(II)-catalyzed CDP reaction in the presence of O_2, associated with a considerably expanded substrate scope

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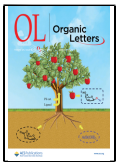

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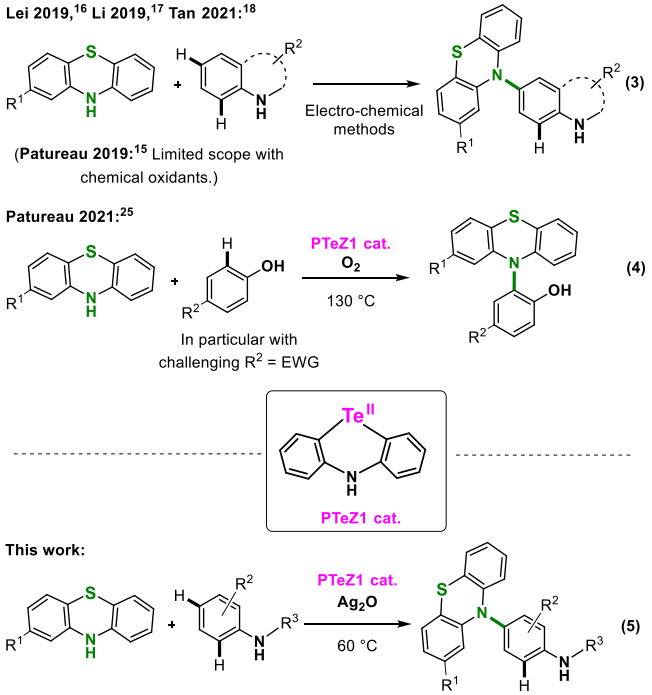
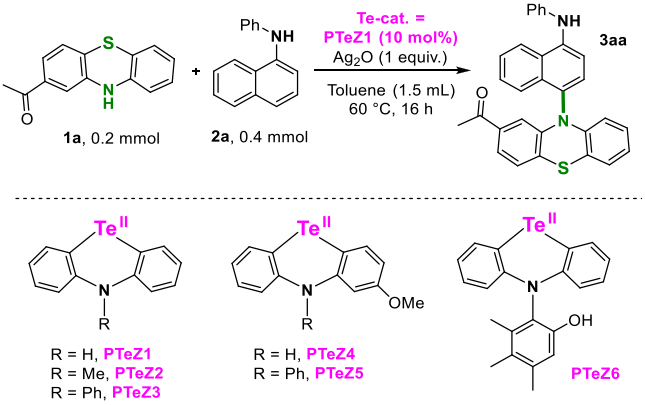
Scheme 2. CDP Reaction with Anilines



(Scheme 2, eq 4).[25] Given the exceptional redox properties of Te(II) catalysts,[25] we envisioned that these could also be used to perform the oxidative CDP click reaction on some other challenging substrate classes, such as anilines and secondary amines, while avoiding an electrochemical setup.[16−18]

Our study commenced with 2-acetylphenothiazine (**1a**) and *N*-phenyl-1-naphthylamine (**2a**) in the presence of our previously developed Te(II) catalyst **PTeZ1** (Table 1). Through a series of optimization experiments, we identified Ag_2O as the optimal chemical oxidant, toluene as the best solvent, and 60 °C as the optimal temperature. This allowed the access to CDP product **3aa** in 93% isolated yield (Table 1, entries 1−3). Importantly, the omission of the Te(II) catalyst resulted in a significantly decreased yield (64%; entry 4). A higher reaction temperature (110 °C; entry 5) or longer reaction time (44 h; entry 6) did not improve this result, highlighting the importance of the Te catalyst for obtaining a high yield of the desired product. None of the other phenotellurazine candidates that we explored (**PTeZ2** to **PTeZ6**) performed any better (entries 7−11). Nevertheless, it is interesting to note that the N−H functional group of the catalyst is not a requirement to promote the reaction, as **PTeZ3** gave **3aa** in 93% yield (entry 8). Furthermore, O_2 did not perform well as an oxidant in this reaction (entries 12 and 13),[26,27] in contrast to a previous method.[25] Moreover, it operates at much lower temperatures. This therefore demonstrates that the concept is not limited to an O_2−Te interaction but can also accommodate other oxidants. This oxidant tolerance of the Te(II) redox catalyst could therefore prove highly important for the development of future CDC reactions.[1−8] No other tested oxidants performed well in this reaction, such as DTBP (entries 14 and 15). Moreover, although the addition of TEMPO (entry 16) or BHT (entry 17) did not shut down the reaction, the desired product was delivered in reduced yields, which might have been caused by radical or redox interference of those additives with the

Table 1. Screening of the Reaction Conditions[a]



entry	variations from the optimal conditions[a]	yield of **3aa** (%)[b]
1	***none***	**93**
2	CH_3CN instead of toluene	79
3	RT instead of 60 °C	69
4	no Te cat.	64
5	no Te cat. at 110 °C	56
6	no Te cat. for 44 h	65
7	Te cat. = **PTeZ2**	83
8	Te cat. = **PTeZ3**	**93**
9	Te cat. = **PTeZ4**	88
10	Te cat. = **PTeZ5**	91
11	Te cat. = **PTeZ6**	81
12	O_2 (1 atm) instead of Ag_2O	n.r.
13	O_2 instead of Ag_2O at 110 °C	11
14	DTBP instead of Ag_2O	n.r.
15	DTBP instead of Ag_2O at 110 °C	41
16	addition of TEMPO (1.5 equiv)	79
17	addition of BHT (1.5 equiv)	44

[a]Reaction conditions: **1a** (0.2 mmol), **2a** (0.4 mmol), **PTeZ1** (0.02 mmol), Ag_2O (0.2 mmol), toluene (1.5 mL), 60 °C, 16 h. [b]Isolated yields.

oxidizing system. In any case, no TEMPO nor BHT adducts could be detected in the reaction mixtures.

Next, we explored the scope of the reaction (Scheme 3). A large selection of functional groups were well-tolerated, such as halides (F, Cl, Br), methoxy, thioether, trifluoromethyl, trifluoromethoxy, cyano, acetyl, and tosyl moieties. Both 1- and 2-naphthylamines performed best (**3aa** to **3ao**), with several CDP yields above 90%. Nevertheless, promising yields were also obtained with some simple diarylamines (**3ap** to **3ar**, 44−48%).

In order to further characterize the Te-catalyzed nature of this method, we then inspected the yields of a few selected entries in Scheme 3 in the absence of any Te catalyst under otherwise identical conditions (Scheme 4). Importantly, for each examined example (**3aa**, **3ba**, **3ga**, **3al**, **3an**, **3ao**, **3ac**, and **3aq**), the yield of the CDP product was always superior in the presence of the Te(II) catalyst. In some cases, such as **3ba**, **3an**, and **3aq**, the yield even doubles in the presence of the Te(II) catalyst at the given reaction time. In other cases, such as **3al**, there is only a minor difference (Scheme 4). Thus, the benefit of utilizing Te(II) catalysis is mostly observed for CDP products with a weaker uncatalyzed background reaction pathway. The Te(II) catalyst therefore increases the scope of the reaction. Finally, it should be noted that an alternative Te(II)-catalyzed system with O_2 (1 atm) as the terminal

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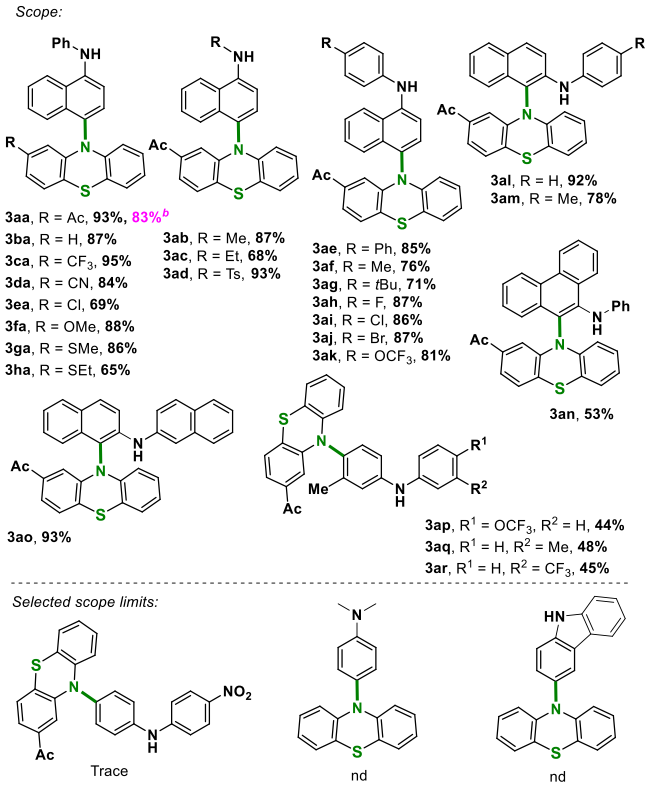
Scheme 3. Reaction Scope[a]

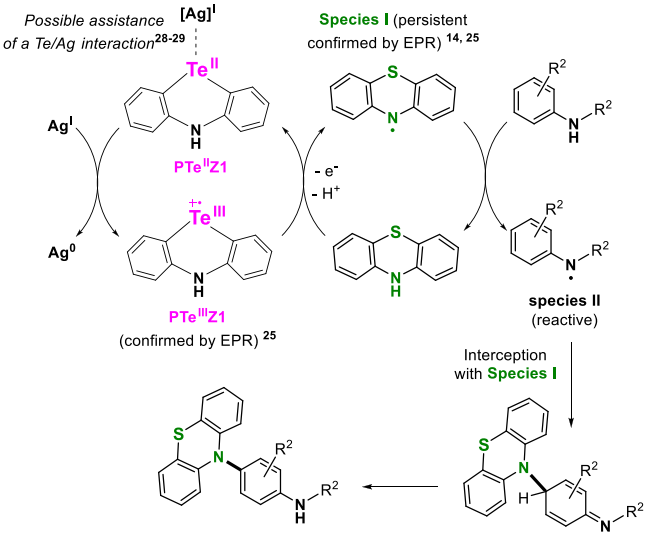


[a]Reaction conditions: **1** (0.2 mmol), **2** (0.4 mmol), **PTeZ1** (0.02 mmol), Ag_2O (0.2 mmol), toluene (1.5 mL), 60 °C, 16 h. Isolated yields are shown. [b]1 mmol scale (see the Supporting Information).

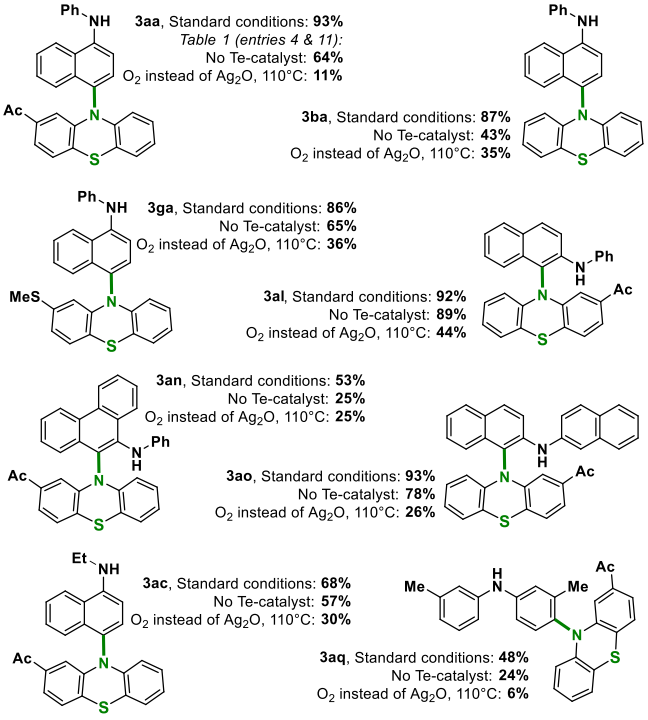
oxidant at 110 °C (Table 1, entry 11) systematically delivered much lower yields (Scheme 4). This again proves the superiority of the Te(II)/Ag(I) cooperative system in this method (Table 1, entry 1 and Schemes 3 and 4).

Mechanistically, phenotellurazine **PTeZ1** is known to possess a significantly lower oxidation potential ($E^{\circ}_{1/2,ox}$ = +0.08 V vs Fc^0/Fc^+) compared with the phenothiazine substrate (for phenothiazine **1b** with R = H, $E^{\circ}_{1/2,ox}$ = +0.22 V vs Fc^0/Fc^+).[25] It can therefore be assumed that the Te(II) catalyst **PTeZ1** will first be oxidized to the persistent Te(III) radical cation (Scheme 5). The latter species was previously

Scheme 5. Proposed Mechanism



Scheme 4. Control Experiments[a]



[a]Reaction conditions, unless otherwise specified: **1** (0.2 mmol), **2** (0.4 mmol), **PTeZ1** (0.02 mmol), Ag_2O (0.2 mmol), toluene (1.5 mL), 60 °C, 16 h. Isolated yields are shown.

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characterized by means of EPR spectroscopy.[25] The Te(II) to Te(III) oxidation process might be facilitated by a Te−Ag interaction, for which there are literature precedents.[28,29] The persistent Te(III) radical cation would then serve as a redox relay to oxidize the phenothiazine and aniline substrates. This likely takes place through the phenothiazine's N-centered persistent and neutral radical species **I**, a well-documented intermediate for the CDP reaction.[14,25] As soon as the more reactive N-centered neutral radical species **II** forms by hydrogen atom transfer (HAT), it is intercepted[30] by the accumulated persistent species **I** to generate the desired CDP product.

In conclusion, we developed an efficient Te(II)-catalyzed cross-dehydrogenative phenothiazination method for anilines. The reaction was found to possess a larger scope in the presence of the Te(II) catalyst, which also furnishes higher CDP yields. This method should therefore contribute to the development of Te(II) redox catalysis in the context of cross-dehydrogenative couplings as well as to the specific field of oxidative click CDP reactions.[31−37]

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.2c00125.

Synthetic methods; NMR, IR, and HRMS characterization of the products; and ^{1}H, ^{13}C, ^{19}F, and ^{125}Te NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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