A new class of oxazolidinone- and phthalimide-based oxidation dye couplers and their effect on azomethine dye color

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ARTICLE INFO
Article history:
Received 20 August 2017
Received in revised form 20 September 2017
Accepted 21 September 2017
Available online 22 September 2017

Keywords:
Azomethine
Haircolor
Oxidation dye
Oxazolidinone
Phthalimide
Coupler

ABSTRACT
In the study of the effects of auxochromes on azomethine dye color, an oxazolidinone ring in the acceptor portion of the dye was useful both as a masking group for preparation of the electron-donating hydroxyethyl group, and as an electron-withdrawing auxochrome. In the case of m-aminophenol derivatives coupled with p-phenylenediamine, there was a 15 nm bathochromic shift relative to the parent azomethine of the series (PPD-MAP)3 and a 30 nm bathochromic shift relative to the azomethine formed from PPD and AHT, which contains an electron-donating group. However, unlike many electron-withdrawing groups, the oxazolidinone group does not significantly slow the rate of oxidative coupling of the MAP derivative with the primary intermediate to form the azomethine dye; it was about 70% of that for PPD with AHT, making the oxazolidinone-containing MAP a potentially effective oxidation dye intermediate. The effect on color of an oxazolidinone moiety in the acceptor portion of an azomethine formed with a 4,5-diaminopyrazole as the primary intermediate was similar in the magnitude of the bathochromic shift. Finally, including an auxochrome (phthalimide) that is electron-withdrawing in the acceptor portion of the azomethine, but which has decreased overlap with the p-system of the chromophore due to twisting out of plane caused by steric interactions, results in a significant hypsochromic shift.

1. Introduction

1.1. Oxidation dye chemistry – formation of vibrant dimers

Azomethine dyes (also called indo dyes) are a mainstay of the oxidation hair dye category. Although there are recent examples in the patent literature in which they are used as the pre-formed dye [1,2], the current accepted practice is for the component parts to be applied to hair with an oxidant to allow them to form inside the fiber. Azomethine dyes are formed oxidatively from primary intermediates such as p-phenylenediamine (1; PPD) (via p-benzoquinonediiminium ion 2) and couplers such as 4-amino-2-hydroxytoluene (3; AHT) and resorcinol (5). When blocked couplers like 3 are used, the reaction stops at the dimer stage giving brilliant, pure colors as in Scheme 1 [3,4].

1.2. Oxidation dye chemistry – formation of oligomeric base colors

When oligomerization is allowed to occur, as with coupling of p-phenylenediamine and resorcinol [5–7], muted base colors such as 8–10, described by Brody and Burns [5], Corbett [6], and Bailey et al. [7], are formed (Scheme 2) [7].

1.3. Oxidation dye chemistry – effects of auxochromes on color and rate of formation

The color of a dye can be modified by addition of electron-donating or -withdrawing groups at specific positions in either the donor or acceptor portions of a dye molecule [8]. For azomethine dyes, the orientation of the electron-donating and electron-withdrawing substituents relative to one another, their degree of...
withdrawal or donation, and the effect on the planarity of the conjugated system are all important factors in the color and intensity produced [4]. For example, the color of the azomethine dye formed from a \( m \)-phenylenediamine (MPD) or a \( m \)-aminophenol (MAP) and a PPD derivative shifts bathochromically as one of the PPD nitrogens is substituted and electron density is increased. Substitution of the aromatic rings of the primary intermediate also can shift the color relative to the parent compounds, but these substitutions also can affect the coupling kinetics dramatically [9]. A strong electron-withdrawing group like cyano or nitro in the primary intermediate can drastically reduce or prevent oxidation to the benzoquinonediiminium ion, but if oxidation does occur, they increase the rate of coupling. Strong electron donating groups can increase the oxidation rate, but significantly decrease the coupling rate. The reverse effect on coupling rates is seen when the coupler is modified. Therefore, a balance is always sought.

Ureido derivatives of MPDs give attractive colors [10], but couple more slowly than materials without electron-withdrawing groups. Because the auxochromes (groups that affect color) can be used to fine-tune color and to create previously inaccessible colors, we were interested in preparing a series of \( m \)-aminophenols in which the parent was substituted separately with electron-donating and electron-withdrawing groups, and particularly in determining whether newly accessible shades could be generated by inclusion of electron-donating or withdrawing substituents in the acceptor portion of the azomethine dye.

1.4. Oxidation dye chemistry — synthesis of couplers with varied electron densities

There is an inherent challenge with inclusion of a third electron-donating group in the acceptor portion of the azomethine when that group is an amine or hydroxyl group if 1,2,4-substitution is the goal, as it was in this case. As will be described in the Results and Discussion section, assembly of the azomethine either via \( \text{SNAr} \) reactions or oxidative coupling has drawbacks. It seemed that one approach to overcome these issues would be to incorporate groups that were protected or masked, and that could be removed or cleaved easily as the final step of the azomethine synthesis. Both phthalimide and oxazolidinone groups seemed to be appropriate to

![Scheme 1](image1.png)

Scheme 1. Reaction of \( p \)-phenylenediamine (1) and the phenolate form (3a) of 4-amino-2-hydroxytoluene (3) stops at the dimer (azomethine dye) giving a bright violet color.

![Scheme 2](image2.png)

Scheme 2. Representative scheme showing oligomerization of \( p \)-phenylenediamine and resorcinol anion (5a) under oxidative conditions to form a muted greenish-brown color [7].
mask amino groups if the azomethines could not be prepared directly. For example, since the oxazolidinone group potentially could be converted to the electron-donating 2-hydroxyethylamino group, this could be an efficient way to provide azomethine dyes with either electron-withdrawing (oxazolidinone) or electron-donating (2-hydroxyethylamino) groups via the same synthetic route. We also envisioned that judicious assembly of the donor and acceptor portions of the azomethine dye could lead us to a useful new class of oxidation dye couplers.

2. Results and discussion

2.1. Synthetic approaches to azomethines

The electron-donating 2-hydroxyethylamino group is well-known in oxidation dye chemistry. It is generally easy to introduce, the final dyes usually are not prone to side reactions such as hydrolysis, and it aids in solubility in typical aqueous dyeing systems. There are two main ways by which azomethine dyes containing this, or other electron-donating groups might be prepared. The first approach is modeled after Corbett’s work on aminoidamines [11] and the work of Bailey et al. on PPD-resorcinol oligomerization [7]. By this approach, the desired azomethine dye is assembled via a series of SNAr reactions and reductions to form the penultimate diphenylamine, which is then oxidized to the desired compound. However, when the desired compound is a m-aminophenol derivative, SNAr substitution, particularly the second substitution, is predicted to be sluggish at best (Scheme 3).

The second way is to oxidatively couple the precursor primary intermediate and m-coupler (Scheme 4), and then to do a series of purifications to obtain the desired compound. This approach also has several issues that would need to be addressed. Both 1 and 13 are readily oxidized and can act as primary intermediates, and in fact, 13 can form two oxidized species: a p-benzoquinonedimine and an o-benzoquinonemonoimine. This should lead to a very complex reaction mixture. However, the oxidative coupling approach still seemed a better choice if this issue could be overcome.

2.2. Synthetic design of new azomethines via oxidative coupling of couplers with reduced electron density and masked functional groups

The oxazolidinone ring was an efficient synthon for preparation of azomethines that had an electron-withdrawing (acceptor) group in the acceptor portion of the dye. It is well-known [12–15] that the oxazolidinone ring can be used as a masked 2-hydroxyethylamino group. The ring also would be stable under the normal oxidative hair dyeing conditions (pH 8.5–11; H₂O₂). This would allow a single synthetic route to generate the azomethine dyes with either electron-donating or electron-withdrawing substituents in the acceptor portion of the molecule, and avoid the problems inherent in normal oxidative coupling of 1 and 13. In fact, if not for the use of the oxazolidinone, preparation or isolation of dye 12 would have been difficult.

Although an oxazolidinone attached to the aromatic ring satisfies the criteria of electron-withdrawal and stability, how it would affect the ability of a compound containing it to undergo oxidative coupling, and what the effect would be on the color of the azomethine dye formed was unknown. It was possible to prepare and convert oxazolidinone derivative 16 to azomethine 17 by reaction with PPD and to convert 16 to the azomethine dye containing the electron-donating hydroxyethylamino group (Scheme 5), thus producing two of the desired compounds via one synthetic pathway.

Introducing the oxazolidinone by direct substitution of the fluorine atom of 14, mediated by the non-nucleophilic base NaH, was cleanest and most straightforward. Reaction in DMF was generally complete in 2 h, and 15 was purified easily on a CombiFlash (hexanes–EtOAc linear gradient on silica). Reduction of the nitro group and hydrogenolysis of the benzyl ether were accomplished simultaneously in ethanol over Pd/C at 75 psig. Although the next step (oxidative coupling) can be mediated by bubbling air through an alkaline solution of 1 and 16, the reaction was slow and by-products formed. However, potassium ferricyanide oxidation gave a cleaner product. Although 17 needed to be separated from the resultant ferrocyanide salt, this was accomplished easily by filtration through Celite® followed by column chromatography. Stirring 17 with LiOH in ethanol at 20 °C gave 2-hydroxyethylamino derivative 12, and these new dyes (12 and 17) now could be compared to known PPD-based azomethine dyes.

It was clear visually that both the 2-hydroxyethylamino group and the oxazolidinone groups shifted the color significantly, and in opposite directions relative to the parent dye (PPD-MAP). Compound 20, in which a phthalimide group replaced the oxazolidinone group, was prepared (Scheme 6) by the same approach as was used for oxazolidinone compound 17 as the final novel example in the series. The phthalimide group is electron-withdrawing, but also would have steric interactions that are unfavorable for complete overlap with the π-system of the chromophore.

2.3. Effect of electron-donating and electron-withdrawing auxochromes on solution color

Table 1 compares the unsubstituted parent dye (PPD-MAP azomethine 21) of the series to azomethine dyes that are substituted in the acceptor portion of the molecule with either electron-donating (–Me and –NHCH₂CH₂OH) or electron-withdrawing (oxazolidinone or phthalimide) groups. It is clear from the table that as electron-donating groups are bonded to the ring of the acceptor portion, color can be shifted more toward orange (hypsochromically). Relative to the parent azomethine, the color of the unprotected amine substituted derivative was shifted nearly 50 nm. However, azomethine 17, which contained the electron-withdrawing oxazolidinone group, was bluer than the parent azomethine, with the λmax shifted bathochromically by

![Scheme 3](image-url)

Scheme 3. Example preparation of azomethine (indoline) dye 12 containing an electron-donating aminoalkyl group in the donor portion of the molecule via multiple SNAr reactions.
15 nm relative to 21. Compound 17 also was shifted bathochromically about 30 nm compared to compound 4, which contained the electron-donating methyl group on the acceptor ring. In addition, including electron-donating vs. electron-withdrawing groups resulted in an effect on extinction coefficient. Table 1 shows that there is a small (ca. 20%) increase in $\varepsilon$ for 17 over 4.

2.4. Effect on color of orbital overlap of the auxochrome and the chromophore

For compound 17, the color was shifted bathochromically by about 15 nm, making it bluer than the parent PPD-MAP. For phthalimide dye 20, although there are two electron-withdrawing carbonyl groups attached to the amine, the color was similar to the PPD-AHT analog, which has a weakly electron-donating methyl group. This is not very surprising since steric interactions twist the molecule and decrease electron overlap with the $\pi$-system of the chromophore (Fig. 1).

2.5. Effect of electron-withdrawing group on competition kinetics

Azomethine dye 17 was particularly interesting because unlike the ureido group, the oxazolidinone moiety did not appear to significantly decrease coupling rate, and it was stable both at pH 10 and to the strongly nucleophilic peroxy anion (HOO$^-$). This indicated that 16 might be useful as an oxidation dye coupler.

Although 16 and 19 gave intense colors on hair when reacted with PPD, it was still important to determine whether the rate of coupling was competitive with current commercial couplers. Because 20 can be hydrolyzed slowly in pH 10 buffer, but 16 and 17 were stable under those conditions, 16 was used for the competition kinetics to make the interpretation more straightforward. PPD, 16, AHT, and K$_3$Fe(CN)$_6$ were combined in a ratio of 1:1:1:4, and the reaction was monitored by UPLC. It is known that electron-withdrawing groups in the coupler decrease the rate of color formation [9], and the rate of color formation from PPD and 16 was somewhat slower than for PPD and AHT, as would be expected. At the completion of the reaction, the product mixture was 40% of 17 and 60% of PPD-AHT azomethine dye 4, showing that the rate of coupling was ca. 67% that of PPD and AHT, indicating that 16 can compete effectively with standard current couplers used in hair-color shades.

2.6. Azomethines based on 4,5-diaminopyrazoles

In haircolor products it is important that a coupler can be used with multiple primary intermediates to develop shades. 4,5-Diaminopyrazoles are another key class of primary intermediates, particularly in vibrant shades. If the trend established with PPDs is
Table 1

<table>
<thead>
<tr>
<th>Dye</th>
<th>$\lambda_{\text{max}}$ (nm)</th>
<th>$\varepsilon$ (M$^{-1}$·cm$^{-1}$)</th>
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<tr>
<td>17</td>
<td>516</td>
<td></td>
</tr>
<tr>
<td>21</td>
<td>504</td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>502</td>
<td>10,500</td>
</tr>
<tr>
<td>23</td>
<td>468</td>
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</table>

Fig. 1. MM2 energy minimized 3D structure of phthalimide azomethine 20, showing the decreased overlap of the phthalimide nitrogen with the chromophore $\pi$-system. The phthalimide ring is in the left foreground.

followed, the color of the azomethine from a 4,5-diaminopyrazole and 16 should be shifted bathochromically relative to the parent azomethine. In fact, this is observed when 1-N-hexyl-4,5-diaminopyrazole (22) is coupled with 16 under oxidative conditions (Scheme 7).

Compounds 26a–26d were prepared by the same procedure to give a complete series that included the parent compounds (26a and 26b), the azomethine dye with the electron-withdrawing oxazolidinone (23), and the electron-donating methyl groups (26c and 26d; Scheme 8).

Relative to azomethine dyes 26c and 26d formed form 2,6-dimethyl-3-aminophenol, which contained two weakly electron-donating substituents, the absorbance maximum for azomethine dye 23 was shifted bathochromically by 20 nm. Also interesting, although perhaps not unexpected, was the fact that there was no effect on color whether the pyrazole nitrogen was substituted with 2-hydroxyethyl or hexyl. As with the azomethines based on PPD, the addition of the electron-withdrawing oxazolidinone ring (as in 23) to the acceptor portion of the dyes based on 4,5-diaminopyrazoles caused an increase in extinction coefficient over the dye containing the electron-donating methyl groups (26d; Table 2).

2.7. Hair dyeing under oxidative conditions

Both PPD and the 4,5-diaminopyrazoles gave colors in solution with both the oxazolidinone- and phthalimide-modified MAPs that could be desirable. Virgin natural white tresses were dyed with the subject couplers and primary intermediates to determine whether they could be useful in oxidation dyeing products. The comparison was limited to the intermediates that would act solely as couplers. Under normal oxidative dyeing conditions coupler 13 would also act as a primary intermediate, just as the well-known o-amino-phenols, so it was excluded.

With PPD, the trend on hair was the same as in solution; the oxazolidinone-containing coupler (16) had the bluest color, i.e. the $b^\prime$ value was the lowest, and the hue angle ($h$) was shifted furthest toward the blue (Table 3). To judge practical utility in oxidation dye systems, it was worthwhile to include the common coupler MAP, although it should be noted MAP is not a blocked coupler and can form trimeric materials [16,17], unlike AHT, 16, and 19, so a direct comparison to the color of the dimers from AHT, 16, and 19 cannot be made. This is in contrast to the reported absorbance spectra earlier, which were of the individual purified dimers after separation by UPLC, so comparison of the absorbance maxima of the azomethine dimers within the series was possible.

4,5-Diaminopyrazoles are used in oxidative dye products to give brilliant orange to reddish-violet colors on hair. In solution studies dimer 23 had the highest absorbance wavelength in the series, and it seemed that this could give a purer red on hair, i.e. a higher $a^\prime$ value and a $b^\prime$ value closer to zero, also represented as a hue angle close to 0°. Again, the parent coupler of the series (MAP) can form a trimer, and it did give a reddish color on hair, although the $a^\prime$ value for 26a was significantly lower than for 23. This was offset by less of a yellow contribution (lower $b^\prime$). It also should be noted that for these tresses dyed at equimolar concentrations, the tress for 26a was significantly more intense, so at equal intensity (to 23) the color may not have appeared as red. The difference in hue angle for tresses dyed with 23 and 26a were similar, with the tress dyed with 26a being only 0.7° more red. Consistent with the solution experiments, 26c was significantly less red that the others, due to the two electron-donating groups in the acceptor portion (Table 4).

3. Experimental

3.1. Materials

p-Phenylenediamine and m-aminophenol were purchased from Jos. H. Lowenstein and Sons, NY, NY, USA. 2-(Benzyloxy)-1-fluoro-4-nitrobenzene and 2-oxazolidinone were purchased from Sigma-Aldrich, St. Louis, MO, USA. 2-(2-Hydroxy-4-nitrophenyl)isoindoline-1,3-dione (18) was purchased from Aurum Pharmatech,
Franklin Park, NJ, USA. All commercial chemicals were used as received. Water refers to deionized water. Compressed O2 and H2 were purchased from Wright Brothers, Inc, Montgomery, OH, USA. Dr. John M. Gardlik of Procter & Gamble, Cincinnati, OH, USA generously provided 3-amino-2,6-dimethylphenol (24b), 1-hexyl-1H-pyrazole-4,5-diamine sulfate, and 2-(4,5-diamino-1H-pyrazol-1-yl)ethan-1-ol hemisulfate.

3.2. Instruments

1H NMR were recorded on a Varian Unity-Inova 300 MHz NMR spectrometer (Agilent Technologies, Santa Clara, CA, USA). Spectra were referenced internally to solvent residual peaks. MS was carried out on a Waters Micromass ZQ spectrometer and HRMS was done on a ThermoScientific Orbitrap Elite (Waters Corporation, Milford, MA, USA). Thin-layer chromatography (TLC) was performed using Analytech silica gel plates with fluorescent indicator (Mitsubishi Chemical Analytech CO, Tokyo, Japan). Flash chromatography was performed using a Teledyne Isco CombiFlash EZ Prep chromatography system equipped with a UV detector (Teledyne Technologies, Inc., Lincoln, NE, USA). UPLC was performed on a Waters Acuity™ system with a PDA e) Detector (Waters Corporation, Milford, MA, USA). Color readings were taken on a Konica Minolta CM-3700 A spectrophotometer (Konica Minolta Business Solutions, Ramsey, NJ, USA), using a 1 cm aperture width, with D65 illumination and characterized by the L* value. An L* of 100 is considered white and L* of 0 is considered black, therefore the higher the L* value the lower the color intensity. Absorbance spectra to calculate extinction coefficients were obtained on a Cary 100 UV/visible spectrophotometer (Agilent Technologies, Santa Clara, CA, USA).

3.3. Methods

3.3.1. Synthesis of 3-(2-(benzyloxy)-4-nitrophenyl)oxazolidin-2-one (15)

To a dry, 50 mL round bottom flask was added 2-(benzyloxy)-1-fluoro-4-nitrobenzene (2.65 g, 10.7 mmol) and DMF (15 mL). To another dry, 50 mL round bottom flask was added 2-oxazolidinone (1.00 g, 11.5 mmol) as a white solid and DMF (20 mL). To the solution was added 60% NaH in mineral oil (0.440 g, 11.0 mmol). The suspension was sonicated at room temperature for 10 min, then stirred magnetically for 40 min until the evolution of hydrogen ceased. The DMF solution of 1-fluoro-2,4-dinitrobenzene was then transferred to the flask containing 2-oxazolidinone sodium salt. After complete addition, the reaction was allowed to stir at room temperature and monitored by UPLC. The color of the solution changed from pale yellow to near black. Once the reaction was complete, DMF was removed under vacuum and the reaction mixture was purified by flash chromatography (SiO2, hexane/EtOAc gradient) to afford 3.13 g pale yellow crystalline solid (93% yield). 1H NMR (300 MHz, CDCl3): δ 4.10 (dd, 2 H, J1 = 6.9 Hz, J2 = 8.7 Hz), 4.48, (dd, 2 H, J1 = 6.9 Hz, J2 = 8.7 Hz), 5.23 (s, 2 H), 7.43 e 7.48 (m, 5 H), 7.70 (d, 1 H, J = 9.3 Hz), 7.94 e 7.96 (m, 2 H). HRMS Found: [M+H]-315.0975; molecular formula C16H14N2O5 requires [M+H]315.0975.

3.3.2. Synthesis of 3-hydroxy-4-(2-oxooxazolidin-3-yl)benzenaminium chloride (16)

To a Fisher Porter tube was added 10 wt% Pd/C (100 mg) and 3-(2-benzoxyl)-4-nitrophenyl)oxazolidin-2-one (10.0 g, 32 mmol) crystalline solid. EtOH (15 mL) and a stir bar were added to the Fisher Porter tube. To the suspension was added dry ice (0.5 g). The vessel was then coupled with the gauge while leaving the vent open until dry ice completely disappeared. The vessel was then
charged with H2 (75 psig) and vented to the air. The charge-vent cycle was repeated six times. The vessel was then charged with H2 (75 psig) and stirred magnetically at room temperature. After 24 h the stirring was stopped to allow the carbon to settle to the bottom. The reduction was considered complete when the clear solution on top showed no hint of yellow. The remaining pressure was then released. Concentrated aqueous HCl (0.5 mL, 6.1 mmol) and water (10 mL) were then added to the suspension. The suspension was then filtered through a 0.4 μm syringe filter to afford a clear and colorless solution. The solution was concentrated by vacuo to afford a grayish solid in quantitative yield. 1H NMR (300 MHz, CDCl3): δ 4.06 (t, 2 H, J = 8.0 Hz), 4.57 (t, 2 H, J = 8.0 Hz), 6.95 (dd, 1 H, J1 = 2.4 Hz, J2 = 8.4 Hz), 7.06 (d, 1 H, J = 2.4 Hz), 7.47 (d, 1 H, J = 8.4 Hz). HRMS Found: [M+H]+ 195.0766; molecular formula C9H11ClN2O3 requires [M+H]+ 195.0764.

### Table 2

<table>
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<th>Dye</th>
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<th>log ε (M⁻¹ cm⁻¹)</th>
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<td>487</td>
<td></td>
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<tr>
<td>26b</td>
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</tr>
<tr>
<td>36d</td>
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</tbody>
</table>

#### 3.3.3. Synthesis of 3-(4-amino-3-((4-amino phenyl)limino)-6-oxocyclohexa-1,4-dien-1-yl)oxazolidin-2-one (17)

To a 250 mL Erlenmeyer flask was added K3Fe(CN)6 (12.18 g, 37.0 mmol) and water (120 mL). The flask was then capped and sonicated to quickly dissolve all salt to produce a homogeneous yellow solution. To a 500 mL Erlenmeyer flask was added 1,4-diaminobenzene (1.00 g, 9.25 mmol) and 3-(4-amino-2-hydroxyphenyl)oxazolidin-2-one hydrochloride (2.00 g, 8.67 mmol). To the mixture was then added water (100 mL), ethanol (20.0 mL) and 28% ammonium hydroxide aq. solution (10.0 mL) to completely dissolve the dye precursors. The tinct solution turned light purple. The K3Fe(CN)6 solution was then transferred to the flask containing the dye precursors. The solution immediately turned purple black. The reaction mixture was then magnetically stirred for 30 min. After which solvents were removed by vacuo. The residual solid was dry loaded onto silica and purified with the CombiFlash automated flash chromatography system with CH2Cl2/MeOH as mobile phase. All purple fractions were collected, combined and purified again on the same system with a hexanes/EtOAc gradient as the mobile phase. 0.613 g of the final product was obtained as a purplish black tar-like solid (23.7% yield). 1H NMR (300 MHz, CD3OD): δ 3.62 (t, 2 H, J = 8.4 Hz), 4.46 (t, 2 H, J = 8.4 Hz), 5.69 (s, 1 H), 6.77 (d, 2 H, J = 8.7 Hz), 7.02 (d, 2 H, J = 8.7 Hz), 7.30 (s, 1 H). HRMS Found: [M+H]+ 299.1139; molecular formula C15H14N4O3 requires [M+H]+ 299.1139.

#### 3.3.4. Synthesis of 5-amino-4-((4-amino phenyl)limino)-2-((2-hydroxyethyl)amino)cyclohexa-2,5-dien-1-one (12)

To a scintillation vial was added the violet dye, 3-(4-amino-3-((4-amino phenyl)limino)-6-oxocyclohexa-1,4-dien-1-yl)oxazolidin-2-one (25.0 mg, 0.084 mmol), LiOH (20.0 mg, 0.84 mmol) and ethanol (6.0 mL) were then added to the vial. The scintillation vial was then capped and magnetically stirred at ambient temperature. The reaction was monitored by UPLC to make sure that all starting material was converted to product. After 2 h, the crude reaction mixture was loaded directly on a 40 g CombiFlash silica gel column and flushed with a CH2Cl2/MeOH gradient on automated CombiFlash chromatography system. The colored fractions were collected, concentrated, and purified again by the same method to afford a brownish red dye (20.0 mg, 87.6% yield). 1H NMR (300 MHz, CD3OD): δ 6.70 (t, 2 H, J = 8.6 Hz), 7.02 (d, 2 H, J = 8.6 Hz), 7.30 (s, 1 H), 6.69 (d, 2 H, J = 8.4 Hz), 6.74 (d, 1 H, J = 8.4 Hz), 6.78 (d, 2 H, J = 8.4 Hz). HRMS Found: [M+H]+ 273.1347; molecular formula C14H16N4O2 requires [M+H]+ 273.1346.

#### 3.3.5. Synthesis of 2-(4-amino-2-hydroxyphenyl)isoindoline-1,3-dionehydrochloride salt (19)

To a Fisher Porter tube was added 10 wt% Pd/C (50 mg) and 2-(2-hydroxy-4-nitrophenyl)isoazomethine-1,3-dione (0.60 g, 2.1 mmol) brown powder. EtOH (10 mL) and a stir bar were added to the Fisher Porter tube. To the suspension was added dry ice (0.5 g). The vessel was then coupled with the gauge while leaving the vent open until dry ice completely disappeared. The vessel was then charged with H2 (75 psig) and vented to the air. The charge-vent cycle was repeated six times. The vessel was then charged with H2 (75 psig) and stirred magnetically at room temperature. After 24 h the stirring was stopped to allow the carbon to settle to the bottom. The reduction was considered complete when the clear solution on top showed no hint of yellow. The remaining pressure was then released. Concentrated aqueous HCl (0.5 mL, 6.1 mmol) and water (10 mL) were then added to the suspension. The suspension was then filtered through a 0.4 μm syringe filter to afford a clear and colorless solution. The solution was concentrated by vacuo to afford a white powder in quantitative yield. 1H NMR (300 MHz, CD3OD): δ 3.08 (t, 2 H, J = 5.6 Hz), 3.67 (t, 2 H, J = 5.6 Hz), 5.60 (s, 1 H), 6.69 (d, 2 H, J = 8.4 Hz), 6.74 (d, 1 H, J = 8.4 Hz), 6.78 (d, 2 H, J = 8.4 Hz). HRMS Found: [M+H]+ 273.1347; molecular formula C14H16N4O2 requires [M+H]+ 273.1346.

#### 3.3.6. 2-(4-amino-3-((4-amino phenyl)limino)-6-oxocyclohexa-1,4-dien-1-yl)isoindoline-1,3-dione (20)

To a scintillation vial was added K3Fe(CN)6 (0.378 g, 1.15 mmol)
and water (12 mL). The vial was then capped and sonicated to quickly dissolve all salt to produce a homogeneous yellow solution. To a 100 mL pear shaped flask was added 1,4-diaminobenzene (31 mg, 0.29 mmol) and 2-(4-amino-2-hydroxyphenyl)isoindoline-1,3-dione hydrochloride (81 mg, 0.28 mmol). To the mixture was then added water (10 mL), ethanol (5.0 mL) and 28% ammonium hydroxide aq. solution (1.0 mL) to completely dissolve the dye precursors. The tint solution turned light purple. The K₃Fe(CN)₆ solution was then transferred to the flask containing the dye precursors. The solution immediately turned purple black. The reaction mixture was then magnetically stirred for 30 min. After which solvents were removed under vacuum. The residual solid was dry loaded onto silica and purified with the CombiFlash automated flash chromatography system with a CH₂Cl₂/MeOH gradient as mobile phase. All purple fractions were collected, combined and purified again on the same system with CH₂Cl₂/MeOH as mobile phase.

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Color readings taken with a Konica Minolta CM-3700 A spectrophotometer using a 1 cm aperture width for virgin natural white hair dyed with a combination of PPD and either 16, MAP, AHT, or 19 in a 75:20:5 water-ethanol-ammonium hydroxide solution at pH 10 in an incubator (30 °C) for 30 min.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dye</td>
<td>L*</td>
</tr>
<tr>
<td>17</td>
<td>24.09</td>
</tr>
<tr>
<td>21</td>
<td>18.85</td>
</tr>
<tr>
<td>4</td>
<td>17.9</td>
</tr>
<tr>
<td>20</td>
<td>18.33</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 4</th>
<th>Color readings taken with a Konica Minolta CM-3700 A spectrophotometer using a 1 cm aperture width for virgin natural white hair dyed with a combination of using 25a and either 16, MAP, or AHT in a 75:20:5 water-ethanol-ammonium hydroxide solution at pH 10 in an incubator (30 °C) for 30 min.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dye</td>
<td>L*</td>
</tr>
<tr>
<td>23</td>
<td>30.18</td>
</tr>
<tr>
<td>26a</td>
<td>21.09</td>
</tr>
<tr>
<td>26c</td>
<td>31.38</td>
</tr>
</tbody>
</table>
phase. Forty-seven mg of the final product was obtained as a purplish black tar-like solid (47% yield). 1H NMR (300 MHz, D2OD): δ 5.71 (s, 1 H), 6.81 (d, 2 H, J = 8.7 Hz), 6.93 (s, 1 H), 7.01 (d, 2 H, J = 8.7 Hz), 7.51–7.61 (m, 4 H). HRMS Found: [M+H]+: 359.1140; molecular formula C9H14N2O3 requires [M+H]+: 359.1139.

3.3.7. Synthesis of 3-(4-amino-3-(5-amino-1-hexyl-1H-pyrazol-4-yl)imino)-6-oxocyclohexa-1,4-dien-1-yl)oxazolidin-2-one (23)

To a 100 mL Erlenmeyer flask was added K2Fe(CN)6 (6.09 g, 18.5 mmol) and water (80 mL). The flask was then capped and sonicated to quickly dissolve all salt to produce a homogeneous yellow solution. To a 250 mL Erlenmeyer flask was added 4,5-diamino-1-hexyl-1H-pyrazole hemisulfate (1.04 g, 4.5 mmol) and 3-(4-amino-2-hydroxyphenyl)oxazolidin-2-one hydrochloride (1.0 g, 4.34 mmol). To the mixture was then added water (50 mL), ethanol (10.0 mL) and 28% ammonium hydroxideaq. solution (5.0 mL) to completely dissolve the dye precursors. The tint solution turned light red. The K2Fe(CN)6 solution was then transferred to the flask containing the dye precursors. The solution immediately turned dark red. The reaction mixture was then magnetically stirred for 30 min. After which solvents were removed by vacuo. The residual solid was dry loaded onto silica and purified with the combined solution on an automated flash chromatography system with CH2Cl2/MeOH as mobile phase. All red fractions were collected, combined and purified again on the same system with a hexanes/ETOAc gradient as mobile phase. 0.593 g of the final product was obtained as a dark red tar-like solid (36.7% yield). 1H NMR (300 MHz, CD3OD): δ 0.89 (br, 3 H), 1.31 (br, 6 H), 1.73 (br, 2 H), 3.86 (t, 2 H, J = 6.0 Hz), 4.20 (t, 2 H, J = 7.8 Hz), 4.44 (t, 2 H, J = 7.8 Hz), 5.54 (s, 1 H), 7.48 (s, 1 H), 7.57 (s, 1 H). HRMS Found: [M+H]+: 373.1983; molecular formula C18H24N5O3 requires [M+H]+: 373.1983.

3.3.8. 3-Amino-4-((5-amino-1-(2-hydroxyethyl)-1H-pyrazol-4-yl)imino)-2,6-dimethylcyclohexa-2,5-dien-1-one (26d)

To a 100 mL Erlenmeyer flask was added K2Fe(CN)6 (6.09 g, 18.5 mmol) and water (50 mL). The flask was then capped and sonicated to quickly dissolve all salt to produce a homogeneous yellow solution. To a 250 mL Erlenmeyer flask was added 2-(4,5-diamino-1H-pyrazol-1-y1)ethan-1-ol sulfate (1.08 g, 4.5 mmol) and 3-amino-2,6-dimethylphenol (0.617 g, 4.5 mmol). The mixture was then added water (50 mL), ethanol (10.0 mL) and 28% ammonium hydroxideaq. solution (5.0 mL) to completely dissolve the dye precursors. The tint solution turned light red. The K2Fe(CN)6 solution was then transferred to the flask containing the dye precursors. The solution immediately turned dark red. The reaction mixture was then magnetically stirred for 30 min. After which the reaction mixture was filtered, rinsed with water to yield 0.582 g of a dark red solid (47% yield). 1H NMR (300 MHz, DMSO-d6): δ 1.77 (s, 3 H), 1.94 (s, 3 H), 3.70 (q, 2 H, J = 5.4 Hz), 3.98 (t, 2 H, J = 5.7 Hz), 4.96 (t, 1 H, J = 5.1 Hz), 6.29 (br, 2 H), 6.58 (s, 2 H), 7.17 (s, 1 H), 7.73 (s, 1 H). HRMS Found: [M+H]+: 276.1458; molecular formula C13H17N5O2 requires [M+H]+: 276.1455.

3.3.9. Formation of azomethine dyes and measurement of absorbance maxima

For each primary intermediate-coupler pair, 0.0625 M of the primary intermediate and coupler were dissolved in 75:20:5 water:ethanol:28% ammonium hydroxide mixture. An equal volume of 0.25 M aqueous K2Fe(CN)6 was added to the solution of dye precursors, giving rapid color formation. The reaction mixture was purified on a Waters AcquityUPLC with a PDA e detector using a Waters AcquityUPLC C18 reverse phase column using an water-acetonitrile linear gradient with a 0.4 mL/min flow rate, and the absorbance maximum of the pure compound was determined.

3.3.10. Quantitative NMR (qNMR)

Thymol (99.5%, Sigma-Aldrich) was used as the internal reference for all quantitative NMRs. In a typical experiment, thymol (15–18 mg) was added to a tared scintillation vial and weighed on an analytical balance to ten-thousandths decimal place. The dye molecule (equal molar to thymol or in slightly great amount, ~ molecular weight/10 mg) was then added to the same scintillation vial and also weighed to ten-thousandths decimal place. After the accurate masses of both the dye molecule and thymol were recorded, a deuterated solvent (DMSO-d6 or CD3OD, 3 mL) was then added to dissolve the mixture. 1H NMR was then taken with relaxation delay (d1) set to 30 s to allow proper integration of aromatic protons. The molar ratio of dye over thymol obtained from the 1H NMR and corresponding mass ratio obtained from weighing were used to calculate the absolute purity of the dye.

3.3.11. Determination of extinction coefficients

Compound 4, 17, 23, or 26d, the purity of which had been determined with qNMR with thymol as the internal reference, was dissolved in 5 w/w % aqueous ethanol to obtain a concentration of 10−4 M. The absorbance was measured at room temperature with a Cary 100 UV/visible spectrophotometer using a 1 cm path length cuvette, and was taken as the difference between the baseline and the absorbance at the λmax. Extinction coefficient was determined as:

\[ \varepsilon = \frac{A}{cl} \]

Where, \( \varepsilon \) is the extinction coefficient, \( A \) is the absorbance at \( \lambda_{max} \) and \( l \) is the cell path length.

3.3.12. Hair dyeing procedure

Primary intermediates and couplers for each experiment were dissolved in 75:20:5 water:ethanol:28% ammonium hydroxide prepare 100 mL of each primary intermediate-coupler pair at a concentration of 0.625 M each, as in Table 3. Ten mL of his solution was mixed with an equal volume of (commercial Wella™ color-charm 20 vol % H2O2 clear developer to give a solution at pH 10 ± 0.2. This was applied to 1.5 g virgin natural white hair tresses so the hair:dye bath weight ratio was 1:6. The tresses were covered to prevent evaporation of solvent and ammonia, and placed in a 30 °C oven for 30 min. The tresses were rinsed with water and shampooed once with Pantene® Clarifying Shampoo to remove surface dye deposits. The tresses were dried with a hairdryer on low heat, and then color readings on duplicate tresses were obtained.

4. Conclusions

There are two important perspectives to consider: the color of the final, synthesized azomethine dye, and whether a coupler containing these electron-donating or electron-withdrawing groups is useful as an oxidation dye intermediate. Preparation of azomethine dyes that contain three electron-donating auxochromes in the acceptor portion of the dye is fairly straightforward if the third group is an ether. There are multiple examples of these ether substituted m-phenylenediamines [18,19] and m-amino-phenolophenes [20] that are useful in oxidative coupling to form the acceptor portion of the azomethine. However, amino groups would more desirable than ether groups as auxochromes if larger shifts in color are desired [8]. Synthetic preparations of couplers with an additional amino substituent are not as straightforward, though. However, we have shown that groups such as oxazolidinone and phthalimidone significantly simplify preparations of azomethines with amines and substituted amines as the third electron-donating group.
group. Both the 2-hydroxyethylamino and amino groups, respectively, can be generated from them. The MAP derivatives with the electron-donating amines show the expected hypsochromic shift [4]. However, the oxazolidinone group causes a useful bathochromic shift in color for both PPD- and 4,5-diaminopyrazole-based azomethines. Additionally, it acts to increase the extinction coefficient for azomethines of both series. Because the phthalimide group is twisted out of the plane of the π-system of the chromophore, there is not a corresponding bathochromic shift for the phthalimide-containing azomethine dye. However, both the oxazolidinone- and phthalimide-containing dyes generate attractive colors in hair, and it is important to note that they have been stable under oxidative dyeing conditions. Finally, unlike other electron-withdrawing groups, the oxazolidinone group does not interfere with the coupling kinetics, and compound 16 competes effectively with the commercial coupler, AHT, with a rate that is about 70% as rapid, making it useful for developing hair dye shades. The exemplified compounds can be particularly useful for orange-red to violet colors in all oxidative hair dye products, but derivatives of these compounds have potential utility across the full color spectrum.

In terms of next steps, initial experiments have shown that the effects are the same when PTD is used as the primary intermediate, and as expected [16,17], NMR spectroscopy indicates the expected mixture of products resulting from coupling at both nitrogens of PTD. Although we have limited this work to MAP-based couplers, expansion to other common couplers is warranted, as is study of additional primary intermediates. Finally, the success of the oxazolidinone and phthalimide groups indicate that additional common electron-withdrawing protecting groups such as maleic acid, maleic acid, hydrazides, etc. are fertile ground for new auxochromes that provide beneficial color shifts without negatively affecting coupling rates.

Author contributions
The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes
The authors declare no competing financial interest.

Acknowledgments
The authors acknowledge Dr. Bob Strife of Procter & Gamble for acquiring the HRMS data, and Dr. Eric Hu of Aroz Tech for obtaining 1H NMR and MS data, and Dr. John Gardlik of Procter & Gamble for his generous gifts of 1-hexyl-1H-pyrazole-4,5-diamine sulfate, 2-(4,5-diamino-1H-pyrazol-1-yl)ethan-1-ol hemisulfate, and 3-amino-2,6-dimethylphenol.

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