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Eosin Y-catalyzed photo-induced direct C(sp^2)-H bond azo coupling of imidazo-heteroarenes and anilines with aryl diazonium salts

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Abstract: Herein, we describe a greener approach to the eosin-Y Na_2 catalyzed, C(sp^2)-H bond azo coupling of imidazo-heteroarene with aryl diazonium salts, under acid free conditions. This direct photoredox process resulted in the corresponding azo products in good to excellent yields. Besides, this new approach could also be applicable to anilines, which is a poorly reactive substrate by other methods. The main features of this reaction are that it provides high yields and is gram-scalable and applicable to biologically relevant imidazo-heteroarenes and anilines.

Imidazo-heteroarenes are ubiquitous heterocycles that represent an important “privileged scaffold”.[1,2] Their structure is present in many pharmaceuticals and also has applications in material sciences.[3-7] Therefore, it is not surprising that the synthesis and functionalization of imidazo-heteroarenes have received considerable attention in different areas of scientific research.[1,2,8-14] Analogously, aryl-azo compounds are widely used in several areas, including the chemical industry, pharmaceuticals, chemo-sensors, electronics and liquid crystals (**1a-d**, Figure 1).[15-16] In this way, very recently, Feringa described the photoisomerization and biological evaluation of a diazo based privileged series of novel photoswitchable quorum-sensing agonists and antagonists.[16a]

The development of new synthetic procedures to obtain multi-targeted hybrids of these skeletons (aryl-azo imidazo-heteroarenes) in a single structure would be useful, due to their diverse applications (**1e-f**, Figure 1).[17a] Although, there are several reports on the preparation of aryl-azo compounds,[17b-h] most of the protocols often suffer from acidic condition, long reaction time, low temperature, inert atmosphere, low yields and reduced stability of diazonium salts at room temperature.[17h] The majority of these methods proceed through strong acidic conditions which limits their use in complex synthesis, specially, when the substrate contain an acid-labile group. Only few studies on the reaction of biologically relevant heteroarenes, imidazo-heterocycles as well as *N*,*N*-disubstituted anilines are found in the literature, mainly involving mild and clean transformations or a lack thereof (Scheme 1A-B).[18-21]

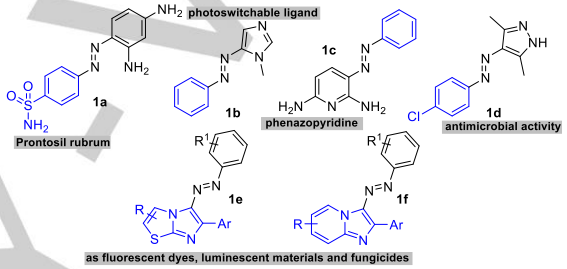
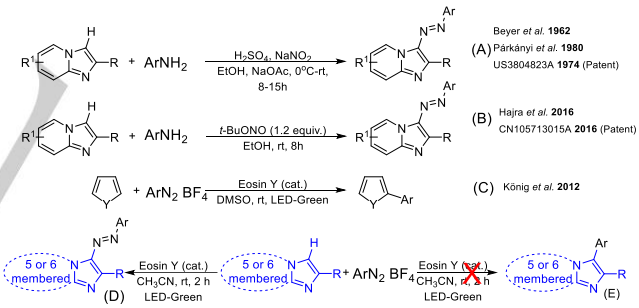


Figure 1. Examples of important azole-heterocyclic azo derivatives.



Scheme 1. Reaction of biologically relevant heterocyclic with diazonium salts

In recent years, there has been a surge of interest in the development of new organic transformations via photo-redox catalysis by the synthetic community, resulting in several interesting publications.[22-28] In this regard, organic dyes such as eosin-Y Na_2, fluorescein and rose bengal have emerged as versatile photo-catalysts in the cross-coupling reaction for C-C and C-X bond formation.[29-34]

As part of our research interest in designing and developing sustainable processes as well as in the C(sp^2)-H functionalization of biologically relevant heteroarenes,[35-40] herein, we disclose for the first time a photo-induced eosin-Y Na_2 catalyzed azo coupling of imidazo-heteroarene. Using this scalable approach, aryl-azo imidazo-heteroarenes were obtained in good to excellent yields from the corresponding biologically relevant imidazo-heteroarenes and aryl diazonium tetrafluoroborate via C(sp^2)-H functionalization.

In this study, we firstly attempted the C-C coupling of activated heteroarenes and aryl diazonium salt, based on the

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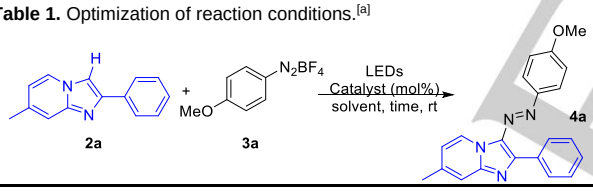
report by König (Scheme 1E).[34] However, in the case of imidazo-heteroarenes, we observed the formation of C-N in the azo-compound, exclusively (Scheme 1D).

For the optimization of this azo-coupling via C(sp^2)-H bond functionalization, we used 7-methyl-2-phenylimidazo[1,2-*a*]pyridine **2a** and 4-methoxybenzene diazonium tetrafluoroborate **3a** as model substrates (Table 1). Initial screening was performed for the catalyst, in the presence of blue LEDs, using CH_3CN as the solvent (entries 1-6). The desired azo product **4a** was obtained in very low yield when the reaction was performed in the absence of a photo-catalyst (entry 1). Subsequently, different photo-catalysts (5 mol%) were tested for this coupling reaction and eosin-Y Na_2 was found to be the most efficient, affording the C(sp^2)-H bond azo product **4a** in 96% yield (entry 4 *vs* 2,3,5,6).

In the next step, the loading of the catalyst was screened for this transformation (entries 7-8) and 5 mol% was found to be ideal. With regard to the influence of the solvent on this coupling reaction (entries 9-15), CH_3CN provided an excellent result in terms of promoting the formation of **4a** (entry 4 *vs* 9-15).

Subsequently, the influence of the reaction time was monitored for this transformation (entries 4,16,17) and the optimized reaction time was found to be 2 h (entry 4). Lastly, the effect of light on this transformation was examined (entries 18-20). The coupled azo product **4a** was obtained in low yield when the reaction was performed in the dark. In the presence of white LEDs, **4a** was obtained in 77% yield (entry 19). In the case of green LEDs, **4a** was obtained quantitatively, showing the superiority of green LEDs for this transformation.

Table 1. Optimization of reaction conditions.[a]



Entry	catalyst [mol %]	Solvent	LEDs	*t* [h]	Yield [%][b]
1	--	CH_3CN	Blue	2	31
2	Rose Bengal (5)	CH_3CN	Blue	2	50
3	Fluorescein (5)	CH_3CN	Blue	2	66
4	Eosin-Y Na_2(5)	CH_3CN	Blue	2	96
5	Alizarin (5)	CH_3CN	Blue	2	69
6	*p*-Terphenyl (5)	CH_3CN	Blue	2	78
7	Eosin-Y Na_2 (6)	CH_3CN	Blue	2	97
8	Eosin-Y Na_2 (4)	CH_3CN	Blue	2	81
9	Eosin-Y Na_2 (5)	1,4-Dioxane	Blue	2	39
10	Eosin-Y Na_2 (5)	DCM	Blue	2	60
11	Eosin-Y Na_2 (5)	DMF	Blue	2	75
12	Eosin-Y Na_2 (5)	DMC	Blue	2	60
13	Eosin-Y Na_2 (5)	MeOH	Blue	2	50
14	Eosin-Y Na_2 (5)	H_2O	Blue	2	19
15	Eosin-Y Na_2 (5)	THF	Blue	2	27
16	Eosin-Y Na_2 (5)	CH_3CN	Blue	1	75
17	Eosin-Y Na_2 (5)	CH_3CN	Blue	3	97
18[c]	Eosin-Y Na_2 (5)	CH_3CN	Dark	2	30
19[d]	Eosin-Y Na_2 (5)	CH_3CN	White	2	77
20[e]	Eosin-Y Na_2 (5)	CH_3CN	Green	2	Quantitative

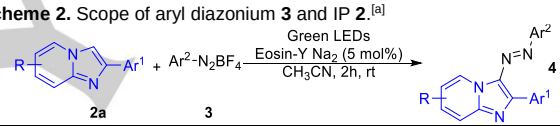
[a] Reaction conditions: **2a** (0.25 mmol), **3** (0.26 mmol), catalyst (5 mol%), solvent (2 mL). [b] Isolated yields.

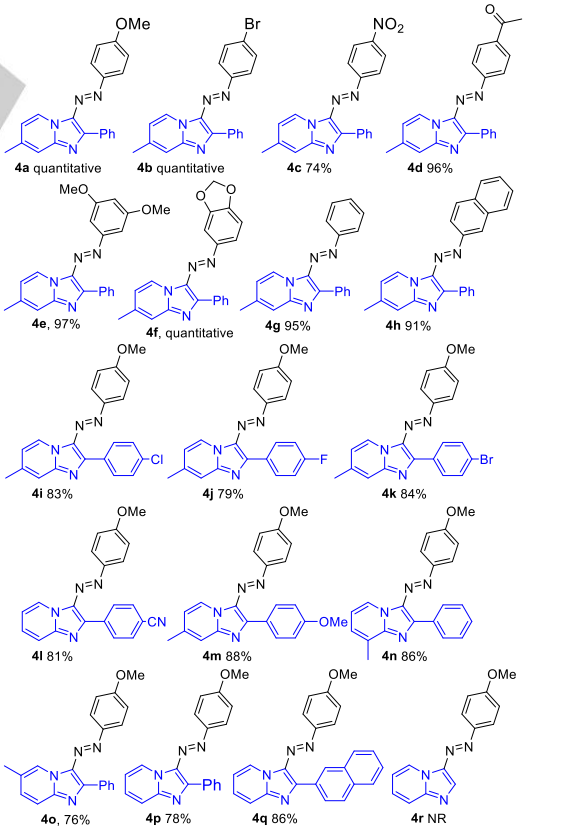
LCMS analysis of **2a** (ESI S2S19) demonstrated the presence of a single product. With the best reaction parameters in hand (Table 1, entry 4), the generality and scope of the C(sp^2)-H bond azo coupling of other imidazo[1,2-*a*]pyridine (IPs) **2** with various aryldiazonium tetrafluoroborates **3** were investigated (Scheme 2).

The reaction worked effectively for structurally diverse aryldiazonium tetrafluoroborates **3**. A variety of diazonium salts having both electron withdrawing groups (-Br, -NO_2, -COMe) and electron donating groups (-OMe, -OCH_2O-) as well as unsubstituted phenyl ring were tested, affording the corresponding azo coupled **4a-g** product in good to excellent yields. There was a slight negative effect on the yield when 4-nitrobenzenediazonium tetrafluoroborate was used as the substrate. The system also tolerated bulky group, i.e., 2-naphthyl, resulting in **4h** in yield of 91%. Similarly to the previous report,[21] only E isomers were formed in this transformation.

To check the synthetic versatility of this protocol, the reaction scope was also tested using different IP cores **2** with diazonium salt **3a** (Scheme 2), under the optimized conditions. The reaction afforded the corresponding azo coupled products **4a,i-q** in 76% to 99% yields. In general, the electronic effect of the substituents on the phenyl group, attached at the C-2 position of IP **2**, had no major effect on the yields of the azo products **4a,i-m**. Similarly, a bulky substrate (R = 2-naphthyl) resulted in the desired product **4q** in 86% yield.

Scheme 2. Scope of aryl diazonium **3** and IP **2**.[a]



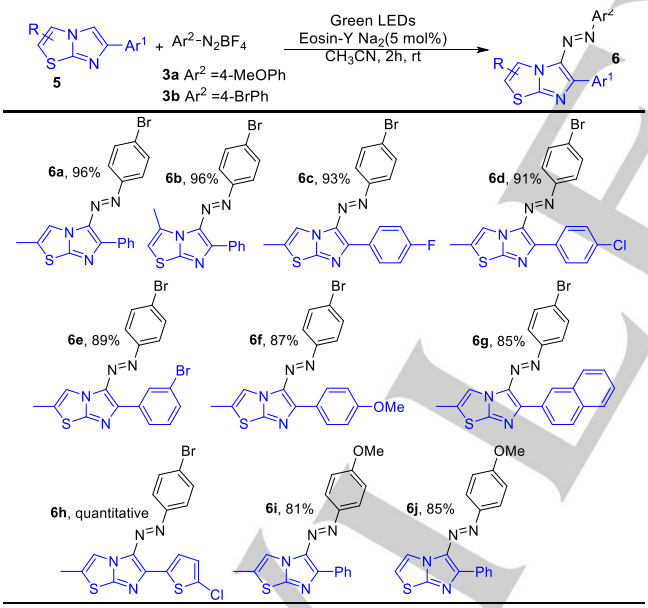


[a] Isolated yields.

Furthermore, there was a mild effect on the yields due to the position of the substituent attached to the pyridine moiety of the IP **2**, affording **4a,n,o** in 99%, 86% and 76% yields, respectively. Lastly, when C-2(H) IP **2** was used as a substrate, no reaction was observed.

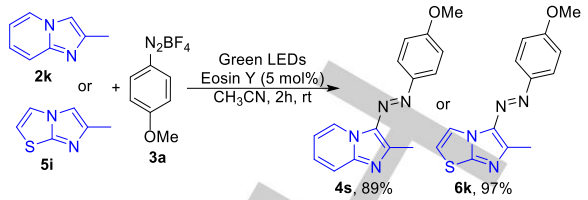
Following the success obtained in the eosin-Y Na_2-catalyzed C(sp^2)–H bond azo coupling of IP nucleus **2**, the reaction scope was further extended to structurally different imidazo[2,1-*b*]thiazole (IT) cores **5** and diazonium salts **3a** and **3b** as the coupling partner, under the optimized reaction conditions (Scheme 3). To our delight, the reaction worked effectively with the IT **5** as substrates. In comparison with IP **2**, there was no effect of the substituent and its position on the thiazole ring, resulting in **6a-b** in excellent yields. Furthermore, the electronic effect of the substituents on the phenyl group at the C-6 position, with electron withdrawing groups (-F, -Cl, Br) as well as an electron donating group (-OMe), had no major influence on the yields of **6c-f**. Similarly, a bulky substrate (R = 2-naphthyl) resulted in the desired product **6g** in 85% yield. We were also encouraged to find that 5-chlorothiophen-2-yl substituted IT **5h** afforded the desired product **6h** quantitatively. Lastly, the diazonium salt with a 4-methoxy group **3a** resulted in the coupled products (**6i,j**) in slightly lower yields compared to those with the 4-bromo group **3b** (**6a** *vs* **6i**). There was no product formation when other *N*-heterocyclic arenes (benzothiazole, indole, 1,3,4-oxadiaozle) were tested.

Scheme 3. Scope of aryl diazonium **3** and IT **5**.[a]



[a] Isolated yields.

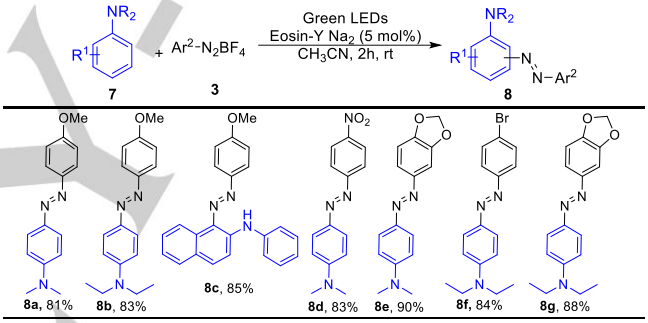
The preparation of diazo product of IP and IT with alkyl moiety at C-2 and C-6 position, respectively, is difficult.[21] To our delight, using this photoinduced diazotization reaction allowed us to access this kind of compounds in good yields (Scheme 4).



Scheme 4. Reaction of biologically relevant azole-heterocyclics with diazonium salts.

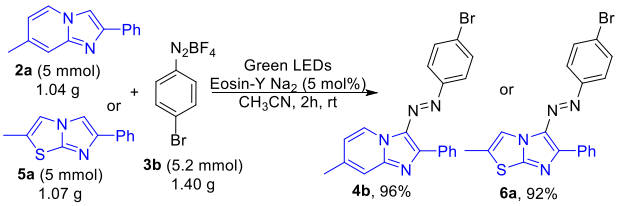
Furthermore, another main advantage of our method is that it is applicable to substituted-anilines. The use of aryl diazonium tetrafluoroborate in such type of coupling are rare and only limited number of literate is available.[17g-h] To our delight, when the optimized reaction conditions were tested for *N*,*N*-disubstituted anilines **7**, the resulted diazo products **8** were obtained in good yields (Scheme 5).

Scheme 5. Scope of aryl diazonium **3** and *N*,*N*-disubstituted anilines **7**.[a]



[a] Isolated yields.

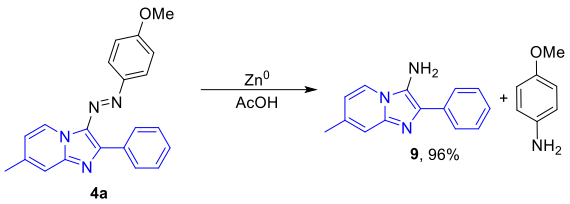
To further establish the synthetic utility of this protocol, scale-up reactions were carried out at the gram scale (Scheme 6). IP **2a**, IT **5a** and diazonium salt **3b** were selected as the reagents under the optimized conditions, affording **4b** and **6a**, respectively, with no major decrease in the yields. Thus, this protocol could be used as a robust methodology for the gram scale synthesis of azo-coupled IPs and ITs, which are precursors for important bioactive molecules.[1-7]



Scheme 6. Gram-scale reactions.

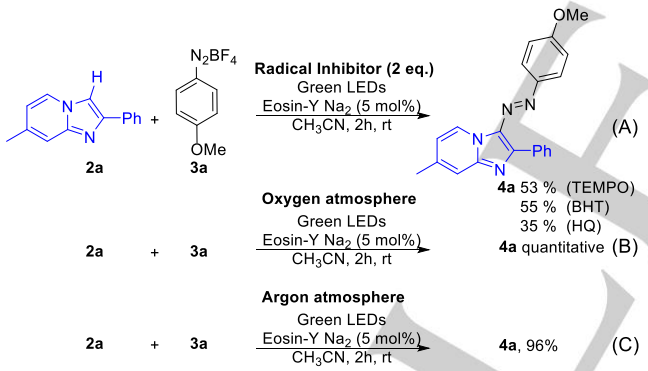
Additionally, an important feature of this new methodology is the access to C-3(NH_2) IP from the synthesized diazo-compounds **4**. For example, the diazo IP compound **4a** on

reduction with elemental zinc in acetic acid leads to the amino derivative **9**, in 96% isolated yield (Scheme 7), which is an important building block for other complex structures and biologically active compounds.[41-42]



Scheme 7. Access of amine containing IP from **4a**.

In order to gain an insight into the mechanism associated with this eosin-Y Na_2-catalyzed photo-induced azo coupling of azoles via C(sp^2)−H functionalization, control experiments were performed (Scheme 8). With the use of a 2 molar equiv. of radical inhibitors (TEMPO, BHT, hydroquinone), the reaction was not completely inhibited, resulting in the desired product **4a** in lower yields (Scheme 8A). This result may indicate that the transformation proceeds by both radical and ionic pathways. The standard reaction under an oxygen atmosphere and an inert atmosphere afforded the azo coupled products **4a** in 99% and 96% yields, respectively (Scheme 8B-C), indicating that the oxygen has no active role in this transformation.



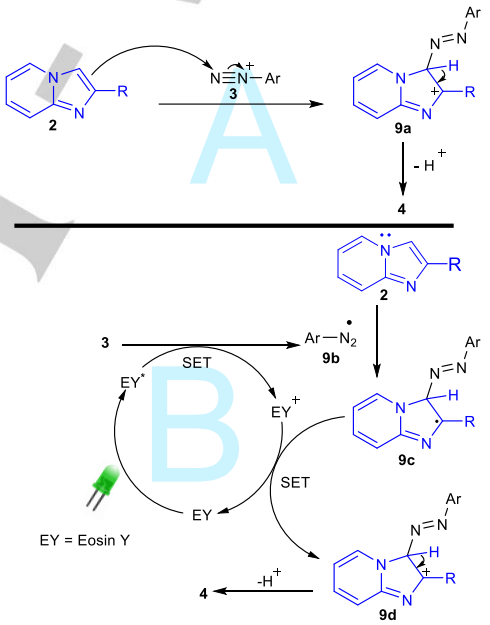
Scheme 8. Control Experiments.

To support which reagent is the photoactive specie towards excitation of eosin-Y Na_2, a fluorescence emission intensity experiment was performed using different concentrations of imidazopyridine **2a** and aryl diazonium salt **3a**. (See Supporting Information section, ESI E20-21). The slope of the graph refers to the Stern-Volmer constant (K_{SV}), which shows a value of 6.025 10^3 M^{-1} for aryl diazonium salt **3a** only, which is clearly ascribed to interaction with eosin-Y Na_2 in the excited state leading to fluorescence quenching by electron transfer. Since absorption and emission bands for both compounds are in different areas of the spectra, this quenching suggests that the 4-methoxybenzenediazonium salt **3a** is activated by the photocatalyst, while 7-methyl-2-phenylimidazo[1,2-*a*]pyridine **2a** is inert under these conditions being the first responsible for initiating the photocatalytic cycle in the reaction.

Based on the control experiments reported in Scheme 8, ESI S20-21 (Figure SI-II, Table SI), and Table 1 (entry 18), as well as previous reports in the literature,[29-34,43] two possible mechanisms, *via* ionic and radical pathways, could be simultaneously operating in this transformation, as proposed in Scheme 9.

When the reaction follows the ionic pathway (Scheme 9A), the imidazole-heteroarene **2** reacts with the diazonium salt **3** to generate the azo species **9a**. This azo species **9a** undergoes deprotonation to furnish the desired azo product **4**.

In the radical pathway (Scheme 9B), the photo-catalyst (EY) would be excited by the light to give EY*, which generates EY^+ through a single electron transfer (SET) to **3**, generating **9b**•.[43] Radical species **9b**• on reaction with IP **2** generates **9c**•. These species suffer SET to EY^+ results **9c**$^+$, while regenerating the catalyst (EY). Lastly, the azo IP cation **9d**$^+$ on deprotonation would result in the desired product **4**.



Scheme 9. Plausible Mechanisms.

In conclusion, we have developed an acid free, eosin-Y Na_2-catalyzed procedure for the direct C(sp^2)-H bond azo coupling of imidazo-heteroarenes with aryl diazonium salts, at room temperature. Under the optimized reaction conditions, this alternative photo-redox approach worked efficiently to form the azo products in good to excellent yields from the corresponding imidazo-heteroarenes and anilines. This gram-scalable protocol utilizes economical catalyst and is applicable to biologically relevant imidazo-heteroarene and anilines. This is an important contribution considering the mildness of the reaction conditions as well as the potential therapeutic application of these compounds.

Conflicts of interest

The authors declare no conflict of interest

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NOTE: † SS and AASN contributed equally this work.

Keywords: Imidazo-heteroarenes • eosin-Y Na_2 • diazo • aniline • sustainable chemistry • aryl diazonium salts

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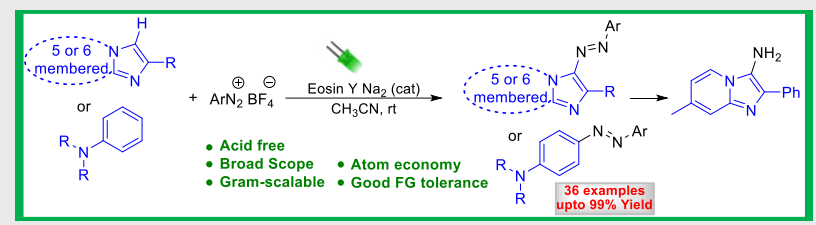

Highly efficient, clean and an acid free, eosin-Y Na_2-catalyzed method for the azo coupling of imidazo-heteroarenes/anilines were achieved through direct C(sp^2)-H functionalization using aryl diazonium via photo-redox approach.

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Eosin Y-catalyzed photo-induced direct c(sp^2)-H bond azo coupling of imidazo-heteroarenes and anilines with aryl diazonium salts