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Reprint of Papers

Sustainable Chemistry

Ethyl lactate: An Efficient Green Mediator for Transition Metal Free Synthesis of Symmetric and Unsymmetric Azobenzenes

Gyan Chandra Pariyar,[a] Tandra Kundu,[b] Bijeta Mitra,[b] Suvodip Mukherjee,[b] and Pranab Ghosh*[b]

Ethyl lactate, a bio-based completely degradable green solvent has been explored as an efficient reaction medium for the synthesis of symmetric as well as unsymmetric azobenzenes using various amines. As an environment friendly solvent, ethyl lactate has been found to have an interesting effect in this methodology for the formation of azobenzenes without the use of any transitional metal catalysts at room temperature.

Introduction

With the growing concern regarding environmental health, green methodologies have received special weightage in the recent past. During organic synthesis, the reaction medium offers a fundamental role by not only facilitating the contact between the reactants but sometimes also varying the course of the reaction. Therefore, a reaction medium which is not only environmentally benign but also possesses exceptional functions and properties has always been welcomed with open hands in the field of green organic synthesis. Lately, ethyl lactate (EL), a biodegradable environment friendly biomass-derived solvent has received considerable interest over traditional solvents as an economically feasible green solvent. The motive behind is due to its distinctive properties such as fully bio-degradable, non-toxic, non-corrosive, non-ozone depleting, high stability and solubility with water and majority of organic compounds.[1]

EL can be effortlessly produced by fermentation of biomass raw materials.[2] Due to non-toxicity, it has been approved by European Food Safety Authorities and Food and Drug Administration for the use as food additives and pharmaceutical additives.[3] It also has been fruitfully engaged in the extraction of various bioactive compounds and diverse food such as carotenoids,[4] polyphenols,[5] amino acids[6] and caffeine.[7] Besides, it has successfully being employed as a green solvent in a number of effective organic reactions[8] for the preparation of significant compounds such as spirooxindole-pyran derivatives,[9] 1,4-benzothiazines,[10] bis(Indolyl)methanes,[11] polyfunctionalized alkenes,[12] quinoxalines,[13] 4(3*H*)-quinazolinones,[14] 2-pyrazoline derivatives[15] and enaminones.[16]

For a long period, aromatic azo-compound has received considerable amount of interest among the chemists. The main reason behind this is the tremendous collection of application of these compound promises in the field of food additives, indicators, organic dyes and therapeutic agents (Figure 1).[17] Further, due to their exceptional photochemical response, these compounds have been extensively used as liquid crystals,[18] smart polymers,[19] photo switches in biological systems[20] and photo chromic ligands in optochemical genetics.[21] By C–H activation/functionalization, azo-derivatives have been recently reported to be used for synthesis of valuable compounds like *o*-alkoxyazobenzenes,[22] *o*-acylazobenzenes[23] and indole derivatives.[24] They are also used in the construction of filters and proactive glass.

From literature survey, it has been recognized that a number of methods have been reported so far for the synthesis of azo-compounds. Among the few are Mills reaction, Wallach reaction, oxidation of amines, reduction of azobenzenes, thermolysis of azides, opening of quinine acetals, reaction of quinine acetals with arylhydrazines, dehydrogenation of arylhydrazines, metal catalyzed coupling of arylhydrazines, triazene rearrangements, oxidation of amines, diamerization of diazonium salts and opening of benzotriazoles.[25] Comparing all these methods, the easiest methodology is the one step route in the synthesis of azo-compounds by oxidation of amines. Literature survey shows that the synthesis of azo-compounds by oxidation of amines have been achieved by a number of catalysts, which are gold nanoparticles immobilized on TiO_2, silver nanoparticles, nickel peroxide, MnO_2, $NaBO_3$, $BaMnO_4$, $AgMnO_4$, $Pb(OAc)_4$, Ag_2CO_3, $Ce(OH)_3O_2H$, $RuCl_3/H_2O_2$, *t*-BuOI, *t*-BuOCl, galvinoxyl/$K_3Fe(CN)_6$, KO_2, platinum and palladium nanowires and Cu(I)-diaziridinone.[26] A generalize scheme for the different processes so far reported in literature are drawn in Scheme 1.

Although most of the methodologies reported gave a good yield of the product, but still there are few disadvantages

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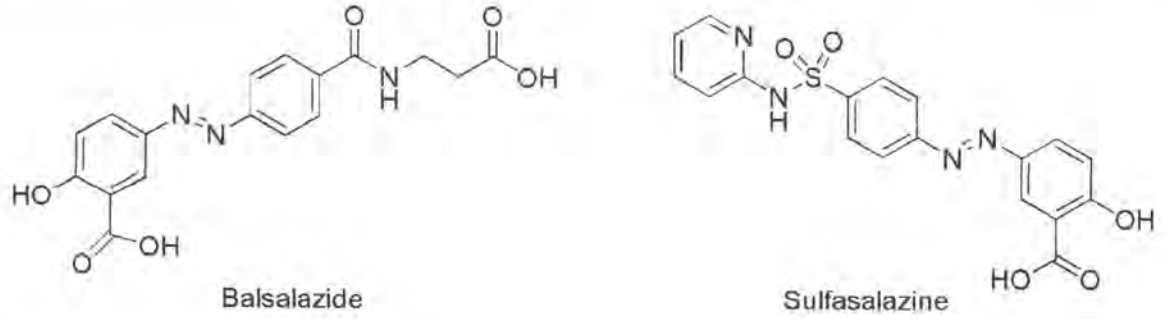
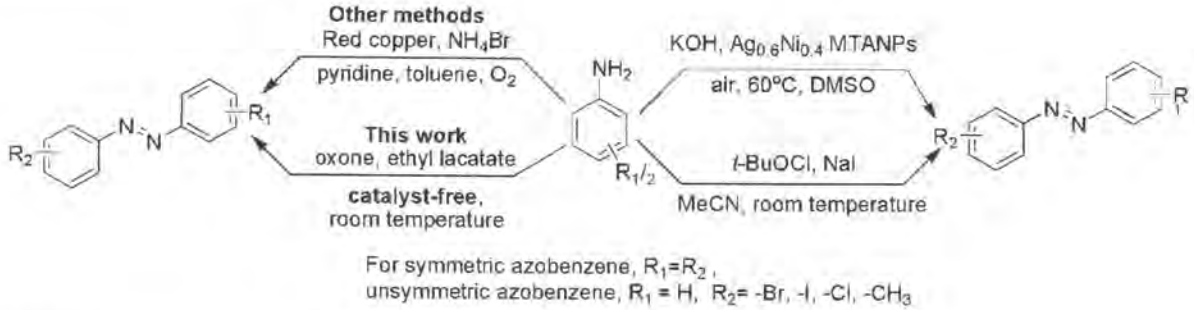


Figure 1. Biologically active molecules having azo-moiety



Scheme 1. Different processes of azobenzene synthesis

associated with them which includes use of environmental hazardous solvents, high temperature, use of expensive catalysts which may eventually led to metal contamination, use of transition metal catalysts, extended reaction time and tedious purification process. The formation of the by-products such as nitroso, nitro-, and azoxy-compounds depending on the catalysts and reaction conditions, is also one if the major concerns of these protocols during the oxidation of amines.[27]

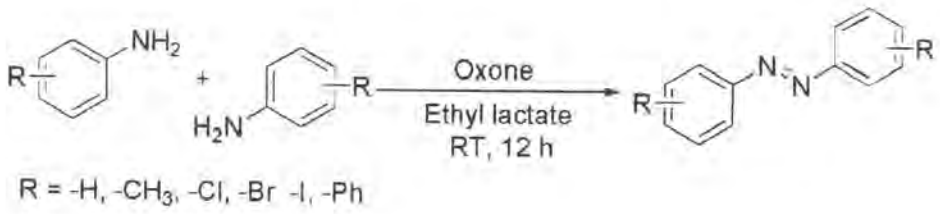
Hence, selection of methodology that will not only give a good yield of the product but also will minimize the formation of the by-products has been a challenge in the synthesis of azobenzenes by oxidation of amines. During the course of our research work, with an aim to develop a new methodology for our synthesis, we found that easily accessible, environmental benign and economical solvent ethyl lactate can be explored as an effective mediator in the synthesis of azobenzenes from amines without any additional catalyst.

Thus, in our work, we report ethyl lactate as an efficient, green solvent for the synthesis of both symmetric and unsymmetric azobenzenes at room temperature (Scheme 1, 2). During the synthesis of symmetric azobenzenes, oxone performed the role of an oxidant.

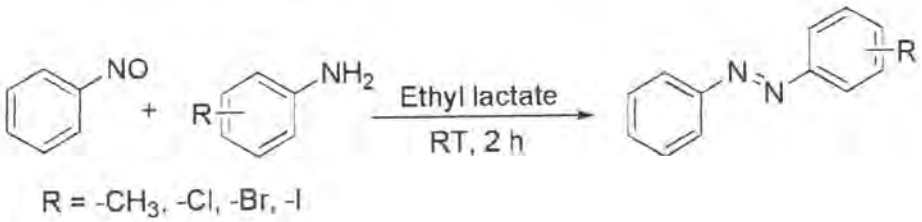
Result and discussion

i) Synthesis of symmetric azobenzenes

To standardize the reaction protocol, aniline was taken as the starting material and the progress of the reaction was monitored by TLC. The reaction was first carried out by taking 1 mmol of aniline and 0.5 mmol of oxone under neat condition for 12 hours when only trace amount of the product was obtained (Table 1, Entry 1). Now with the same reaction conditions, different solvents were used to monitor the reaction. Water only furnished trace amount of the product (Table 1, Entry 2). However, with chloro-

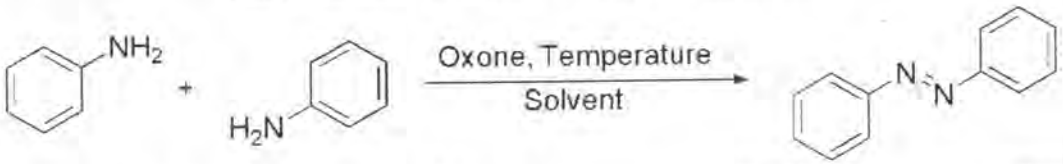


Scheme 2. Synthesis of symmetric azobenzene from amines



Scheme 3. Synthesis of unsymmetric azobenzene from amines

Table 1. Optimization of reaction condition for symmetric azobenzene[a]



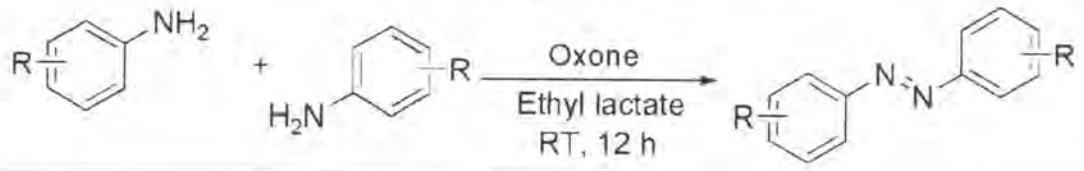
Entry	Oxone (mmol)	Solvent	Time (h)	Yield (%)[b]
1	0.5	Neat	12	Trace
2	0.5	Water	12	trace
3	0.5	$CHCl_3$	12	50
4	0.5	PEG 400	12	74
5	0.5	Toluene	12	55
6	0.5	EtOH	12	59
7	0.5	MeOH	12	40
8	0.5	EL/H_2O (2:1)	12	76
9	0.5	EL/H_2O (1:1)	12	75
10	0.5	EL/H_2O (1:2)	12	73
11	**0.5**	**EL**	**12**	**78**
12	1.0	EL	12	62
13	0.25	EL	12	38
14	0.5	EL	24	78
15	0.5	EL	06	60
16	0.5	EL	12	35[c]

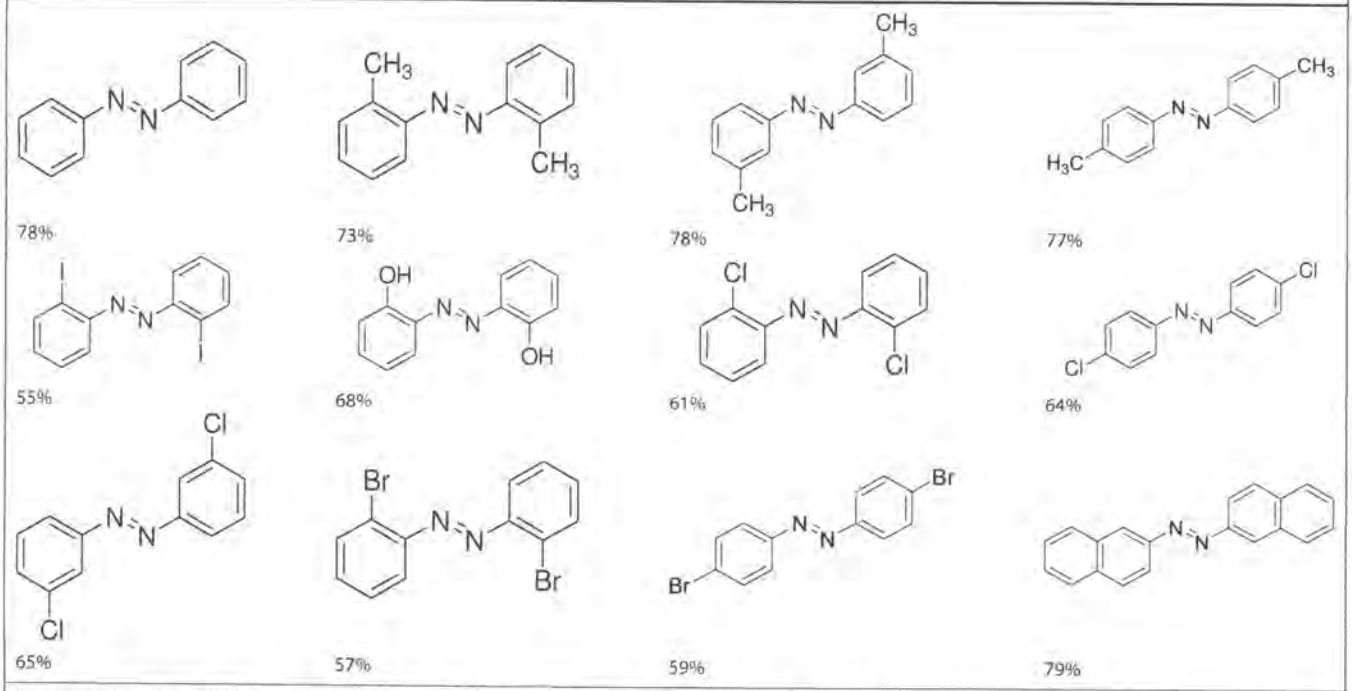
The bold significance represents the optimized protocol/conditions. [a]Reaction of aniline (1 mmol). [b]Isolated yield of product by column chromatography. [c]Reaction carried out at 90° C.

form the reaction gave encouraging yield of 50% (Table 1, Entry 3). PEG 400 further increased the yield to 74% (Table 1, Entry 4). Toluene and Ethanol gave 55% and 59% of the yield respectively (Table 1, Entry 5, 6). However slightly fewer yields of 40% was obtained with methanol (Table 1, Entry 7). We then decided to use ethyl lactate (EL) as the solvent and we were excited to find the yield increased to 78% (Table 1, Entry 11). We also used the solution of EL/H_2O at different ratios but yield remained almost the same (Table 1, Entry 10, 11, 12). Now with the solvent being optimized, we increased the amount of oxone to 1.0 mmol but here we were surprised to find that yield decreased considerably to 62% (Table 1, Entry 13). It may be due to the oxidation of aniline to nitrobenzene before undergoing coupling reaction. While reducing the amount of oxone to 0.25 mmol reduced the yield to 38% (Table 1, Entry 14). We further investigated the reaction by increasing the time to 24 hours which did not give any significant increase in the yield of the product (Table 1, Entry 15). However decreasing the time to 6 hours decreased the yield to 60%. Increasing the temperature of the reaction to 90° C also showed a large decrease in the yield (Table 1, Entry 16). The decrease of yield to 35% may be due to the oxidation of aniline to nitrobenzene at high temperature. Hence finally we report that the optimal reaction condition is 1 mmol of aniline and 0.5 mmol of oxone in ethyl lactate for 12 hours.

A number of amines have been employed in the synthesis of symmetric azobenzenes in our methodology. As evidence from table 2, good yield of different products has been obtained all at room temperature. The procedure has been generalized for a range of amines having electron-donating, electron-withdrawing groups on benzene ring as well as naphthyl rings. Better results were obtained for amines having electron-donating effect compare to those having electron-withdrawing effect. It may be due to the electron density on nitrogen atom making them more nucleophilic. It was also observed that ortho-product gave fewer yields than the other products. This may be due to steric factors at the ortho positions.

Table 2. Ethyl lactate mediated synthesis of symmetric azobenzenes





Reaction conditions: Aniline (1 mmol), oxone (0.5 mmol) in ethyl lactate for 12 h at Room Temperature.

ii) Synthesis of asymmetric azobenzenes

Using the same procedure for the synthesis of symmetric azobenzenes, we tried the synthesis of unsymmetric azobenzenes using 1 mmol of aniline, 1 mmol of *p*-toluidine and 0.5 mmol of oxone for 12 hours. However a mixture of different products was detected giving only trace amount of the desired product. We also tried stepwise process where first 1 mmol of aniline was reacted with 0.5 mmol of oxone for 30 min followed by addition of 1 mmol of *p*-toluidine. However, here also nitrobenzene is formed as the major product which may be due to oxidation of intermediate nitrosobenzene formed by oxone.

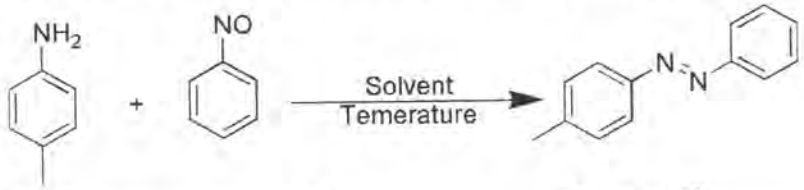
Therefore, we tried the reaction using *p*-toluidine and nitrosobenzene for 2 hours at room temperature. We were hopeful that the same solvent ethyl lactate that we used in the synthesis of symmetric azobenzenes might be applicable in this procedure and we were not surprised that it gave excellent yield of the desired product. We tried the reaction with a number of other solvents also but EL proved to be the best choice. No product was obtained when the reaction was carried out under neat condition (Table 3, Entry 1). As evident from Table 3, in water only trace amount of the product was obtained (Table 3, Entry 2). With ethanol, 47% of the yield was obtained (Table 3, Entry 3) and with DMF 32% was obtained (Table 3, Entry 4). As mentioned earlier, with EL, 83% of the product was isolated when carried out at room temperature for 2 hours (Table 3, Entry 5). With the increase of temperature to 80° C, the yield did not increase significantly (Table 3, Entry 6) which was also the case when the reaction was carried out for 6 hours (Table 3, Entry 7). However, decrease in the yield was observed when the reaction was carried for 1 hour (Table 3, Entry 8). So, finally we report the optimal reaction condition as 1 mmol of *p*-toluidine and 1 mmol of nitrosobenzene in 1 ml of ethyl lactate at room temperature for 2 h.

Amines having various substituents have been successfully converted into asymmetric azobenzene in good yields as depicted in Table 4. Various ortho- and para- substituted amines has been successfully converted into unsymmetric azobenzenes in good yield by our methodology. It is evident that ortho substituted amines gave fewer yields than the para substituted products. It may be due to the steric factor involved in ortho substituted products.

Mechanism

A plausible mechanism is given in Scheme 4. Oxone may have oxidized aniline either through radical mechanism or via electrophilic oxygen transfer with the subsequent generation of unstable nitrosobenzene. Electrophilic attack by the second molecule of aniline or other amines to nitrosobenzene,

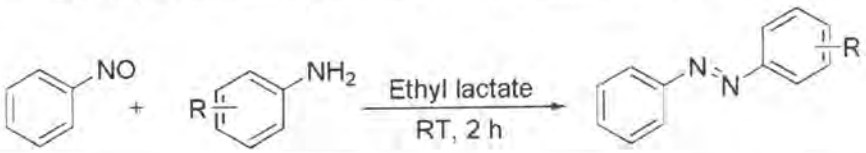
Table 3. Screening of the reaction conditions for synthesis of unsymmetric azobenzenes[a]

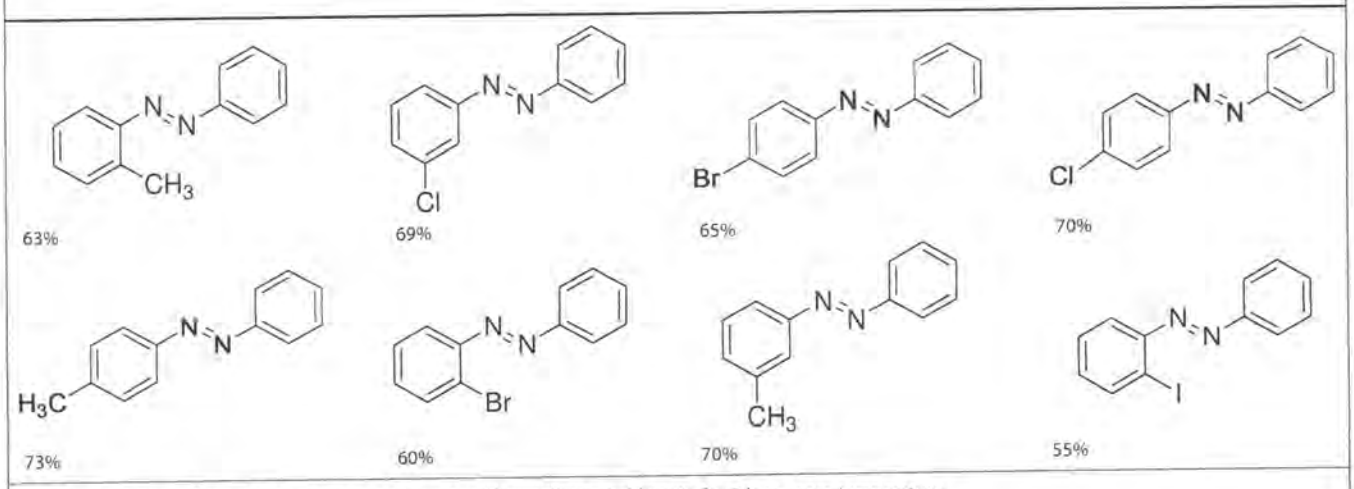


Entry	Solvent	Time (h)	Temperature (°C)	Yield (%)[b]
1	Neat	2	RT	Nil
2	Water	2	RT	Trace
3	Ethanol	2	RT	47
4	DMF	2	RT	32
5	**EL**	**2**	**RT**	**73**
6	EL	2	80	23
7	EL	6	RT	85
8	EL	1	RT	74

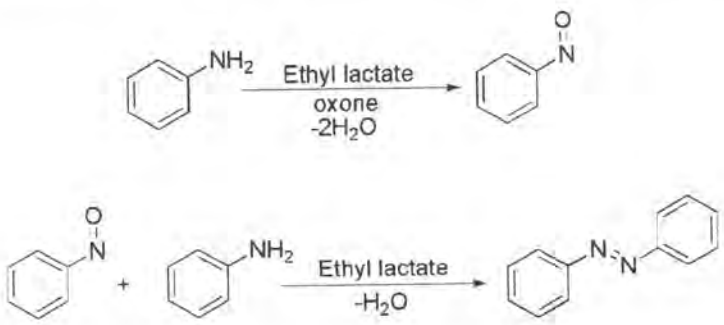
The bold significance represents the optimized protocol/conditions. [a]Reaction of amines(1 mmol) and nitrosobenzene (1 mmol). [b]Isolated yield of the products using column chromatography.

Table 4. Ethyl lactate mediated synthesis of unsymmetrical azobenzenes from nitrosobenzene





Reaction conditions: Nitrosobenzene (1 mmol), amines (1 mmol) in ethyl lactate for 2 h at room temperature.



Scheme 4. Plausible mechanism for azobenzene synthesis

followed by dehydration led to the formation of *trans*-azobenzenes.

Conclusion

In conclusion, we have developed an environmentally benign protocol for the single-step facile synthesis of symmetric and unsymmetric azobenzenes from amines by using ethyl lactate as a solvent without the use of any catalyst. The reaction protocol includes the use of an inexpensive and non-toxic green solvent and gives excellent yield of the desired products with simple and easy reaction conditions and workup process.

Supporting Information Summary

All the experimental details for the synthesis of symmetric and unsymmetric azobenzenes, 13 C-NMR, and 1 H-NMR spectra have been summarized in the supporting information data.

Acknowledgement

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: Amines · Ethyl lactate · Nitrosobenzene · Room temperature · Azobenzenes

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