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A Novel Thermomorphic System for Electrocatalytic Diels-Alder Reactions

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ummary of main observation and conclusion The discovery that lithium bis(trifluoromethane)sulfonamide (LiTFSI)/1-nitropropane (PrNO₂) solution functions as a less polar alternative to lithium perchlorate (LiClO₄)/nitromethane (MeNO₂) solution has led to the development of a novel thermomorphic cystem for electrocatalytic Diels-Alder reactions. Methyl cyclohexane (Me-c-Hex) can form a monophasic condition with LiTFSI/PrNO₂ solution at room temperature, enabling the use of hydrophobic dienophiles. After the electrochemical reaction, a biphasic condition can be formed at -50 °C, where the cycloadducts are selectively recovered from the upper Me-c-Hex phase and the remaining lower LiTFSI/PrNO₂ solution can be reused.

Background and Originality Content

Electrochemical approaches have proven to be powerful edox options in the field of synthetic organic chemistry.¹ Cathodes and anodes can induce reductive and oxidative single electron transfer (SET) even under mild conditions by employing electrons as reagents or catalysts.² Both reducing and oxidizing powers can simply be controlled by the potentials applied, with the equivalents (amount of electricity) used for the reactions monitored in real time. The choice of cooperative ² dditives/catalysts³ and electrode materials⁴ can also be unique variables that can have a significant impact on the synthetic outcomes. The only factor that must be considered is that the olution used for the reaction must have sufficient electrical conductivity. For this reason, polar organic solvents such as MeOH, MeCN, or DMF are typically used in combination with a large amount of supporting electrolyte, which subsequently requires separation and disposal. Furthermore, substrates must Le soluble in highly polar electrolyte solutions and therefore, the

of hydrophobic compounds is restricted. Although several electrochemical reaction systems have been devised that enable recycling and/or decreasing supporting electrolyte,⁵ the use of ydrophobic substrates remains an intrinsic challenge.

Previously, we found that cyclohexane (*c*-Hex) can form hermomorphic systems with typical polar organic solvents, ncluding MeOH, MeCN, or DMF, where biphasic and monophasic conditions were reversibly switched over a moderate temperature range.⁶ While the monophasic condition serves as an effective homogeneous reaction environment for both hydrophobic and hydrophilic substrates and/or reagents, selective eparation can be possible in the biphasic condition. We applied this system to some electrochemical reactions, where the monophasic condition could be recognized as a less polar electrolyte solution, enabling the use of hydrophobic substrates (Figure 1).⁷ Since hydrophobic products were selectively recovered in the upper *c*-Hex phase under biphasic conditions, the lower electrolyte solution could be reused for further reactions.

We have been developing reactions triggered by anodic oxidative SET⁸ in highly concentrated lithium perchlorate (LiClO₄)/nitromethane (MeNO₂) solution.⁹ Since the use of this solution is crucial for most cases, recycling and/or reducing the amount of LiClO₄ are in high demand. Although the *c*-Hex-based biphasic systems have found some promising applications in combination with $LiClO_4/MeNO_2$ solution,¹⁰ thermomorphic properties were not exhibited, presumably due to the salting-out effect. Therefore, the use of hydrophobic substrates in LiClO₄/MeNO₂ solution is still restricted. In this context, we recently demonstrated that nitroethane (EtNO₂) could be a superior alternative to MeNO₂ for some reactions.¹¹ Furthermore, we also found that lithium bis(trifluoromethane)sulfonamide (LiTFSI) could also be used as a supporting electrolyte instead of LiClO₄ in MeNO₂.⁹ We questioned whether LiTFSI/EtNO₂ solution could be a less polar alternative to LiClO₄/MeNO₂ solution, which can form a thermomorphic system with c-Hex. Described herein is the discovery of a novel thermomorphic system that enables the recycling of the supporting electrolyte and allows the use of hydrophobic substrates.

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Figure 1. Schematic illustration of electrochemical reactions in mermomorphic systems.

esults and Discussion

The present work began with the investigation of the LIFSI/EtNO₂ solution using an electrocatalytic Diels-Alder reaction of trans-anethole (1) with isoprene (2) as a model (Table 1). Previously, we found that the reaction was completed with a catalytic amount of electricity in LiClO₄/MeNO₂ or LiTFSI/MeNO₂ solutions to afford the cycloadduct (3) in excellent yields (Entries 1 and 2). When the reaction was carried out in 0.5 M LiTFSI/EtNO2 solution, the cycloadduct (3) was also obtained in excellent yield ithout any difficulty (Entry 3). Furthermore, c-Hex was found to form a thermomorphic system with the same volume of LiTFSI/EtNO₂ solution, causing a monophasic condition at room temperature and a biphasic condition at around -7 °C. In order to test the feasibility of this system for a hydrophobic substrate, the dienophile (4) was prepared and used instead of trans-anethole ...). Unfortunately, the dienophile (4) was barely soluble in a 1:1 (v) mixture of c-Hex and 0.5 M LiTFSI/EtNO₂ solution and no significant oxidation peak was observed in cyclic voltammetry (CV) measurements (Figure 2).

 Table 1. Electrocatalytic Diels-Alder reaction of trans-anethole (1).

MeO		
Entry ^a	Conditions ^b	Yield (%) ^c
1	1.0 M LiClO ₄ /MeNO ₂ , 0.1 F/mol	98
2	1.0 M LiTFSI/MeNO ₂ , 0.1 F/mol	98
3	0.5 M LiTFSI/EtNO ₂ , 0.2 F/mol	97
4	0.3 M LiTFSI/PrNO ₂ , 0.3 F/mol	98

^aReactions were carried out on a 1.00 mmol scale of *trans*-anethole (1) with 3 mol equiv. of isoprene (2) using carbon felt electrodes at rt. ^bElectrolysis was carried out at 1.0 V vs Ag/AgCl in 10 mL of nitroalkane.

^cDerermined by ¹H NMR analysis using benzaldehyde as an internal standard.



Figure 2. Cyclic voltammograms of the dienophile (**4**) in 0.5 M LiTFSI/EtNO₂ solution with c-Hex.

We then turned our attention to the use 1-nitropropane (PrNO₂) instead of EtNO₂. The reaction of *trans*-anethole (1) with isoprene (2) gave the cycloadduct (3) in excellent yield in 0.3 M LiTFSI/PrNO₂ solution (Table 1, Entry 4). Furthermore, c-Hex was found to form a monophasic condition with LiTFSI/PrNO₂ solution, however, a biphasic condition was not obtained even at the freezing point of c-Hex. We eventually found that methyl cyclohexane (Me-c-Hex) was able to form a thermomorphic system with LiTFSI/PrNO2 solution, causing a monophasic condition at room temperature and a biphasic condition at around -50 °C. Notably, the dienophile (4) was soluble in a 1:1 (v/v) mixture of Me-c-Hex and 0.3 M LiTFSI/PrNO₂ solution and a clear oxidation peak was observed in the CV measurement (Figure 3). To our delight, when the reaction of the dienophile (4) with isoprene was carried out in a 1:1 (v/v) mixture of Me-c-Hex and 0.3 M LiTFSI/PrNO₂ solution, the cycloadduct (5) was obtained in excellent yield with a catalytic amount of electricity. Oxidation potentials of isoprene (2) and the cycloadduct (5) were found to be significantly higher than that of the dienophile (4) (Figure S1). Therefore, the reaction was triggered by anodic oxidative SET of the dienophile (4), involving a radical cation chain mechanism (Figure S2). The product was selectively recovered from the upper Me-c-Hex phase under the biphasic condition at -50 °C (Scheme 1 and Figure 4). It should be noted that the remaining LiTFSI/PrNO₂ could be used at least 5 times (Figure 5).

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Figure 5. Reusability of LiTFSI/PrNO₂ solution.

Finally, the potential of the thermomorphic system was

demonstrated by the reaction of the dienophiles (4) with several dienes (6-11) (Table 2 and Figure S3). To our satisfaction, the electrocatalytic Diels-Alder reactions took place effectively in a 1:1 (v/v) mixture of Me-*c*-Hex and 0.3 M LiTFSI/PrNO₂ solution. The cycloadducts (12-17), except the cycloadduct (14), were obtained in high to excellent yields. In all cases, the reactions were completed with a catalytic amount of electricity and the cycloadducts were selectively recovered in the upper Me-*c*-Hex phase under the biphasic condition at -50 °C, realizing facile separation processes. It should be noted that not only the dienophile (4) but also the dienophile (18) was found to be a successful substrate for the reaction (Scheme 2).

Table 2. Scope of the dienophiles for electrocatalytic Diels-Alder reactions. a



^aReactions were carried out on a 0.10 mmol scale of the dienophile (4) with 3 mol equiv. of dienes (6-11) using carbon felt electrodes at rt.

Scheme 2. Electrocatalytic Diels-Alder reaction of the dienophile (18).



Conclusions

In conclusion, we have demonstrated that the LiTFSI/PrNO₂ solution can be a less polar alternative to the LiClO₄/MeNO₂ solution, and it can form a thermomorphic system with Me-*c*-Hex. The monophasic condition at room temperature serves as a less polar electrolyte solution, enabling the use of hydrophobic dienophiles for electrocatalytic Diels-Alder reactions. The

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cycloadducts could selectively be recovered in the upper Me-*c*-Hex phase under the biphasic condition at -50 $^{\circ}$ C, realizing facile separation processes and the recycling of the supporting electrolyte. We believe that the thermomorphic system described herein should find further applications for electrochemical reactions for hydrophobic substrates.

Experimental

General Procedure for Electrocatalytic Diels-Alder Reactions. T) a solution of LiTFSI/PrNO₂ (5 mL), the dienophile (0.10 mmol in mL Me-*c*-Hex) and the diene (3 mol equiv.) were added. Two pieces of carbon felt were inserted into the solution and electrolysis was performed using an undivided cell with stirring at a constant potential of 1.0 V vs. Ag/AgCl at room temperature. A c talytic amount of electric charge was passed through the solution (the reactions can also be monitored by TLC), followed by cooling to -50 °C to form a biphasic condition. The upper Nie-*c*-Hex phase was concentrated in vacuo to give the respective c cloadducts.

Supporting Information

The supporting information for this article is available on the WWW under https://doi.org/10.1002/cjoc.2018xxxxx.

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A Novel Thermomorphic System for Electrocatalytic Diels-Alder Reactions



Methyl cyclohexane can form a thermomorphic system with lithium bis(trifluoromethane)sulfonamide/1-nitropropane solution, where biphasic and monophasic conditions were reversibly switched over a practical temperature range. The monophasic condition serves as a less polar electrolyte solution, enabling the use of hydrophobic dienophiles for electrocatalytic Diels-Alder reactions.

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