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Electrocatalytic Formal [2+2] Cycloaddition Reactions between Anodically Activated Enyloxy Benzene and Alkenes

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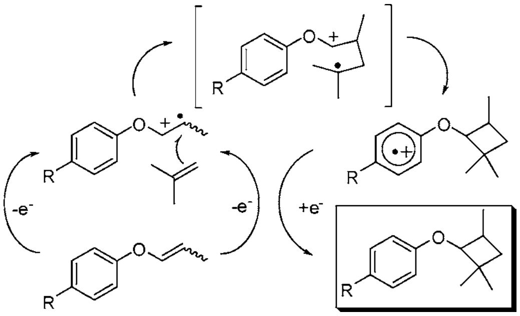
ABSTRACT



Electrocatalytic formal [2+2] cycloadditions between anodically activated enyloxy benzene and alkenes have been accomplished in a lithium perchlorate/nitromethane electrolyte solution. The enyloxy benzene moiety of these electrolytic substrates played an important role in the formation of a radical cation that could accept nucleophilic alkenes, followed by intramolecular electron transfer between the cyclobutane and phenyl ether moieties of the intermediates.

Electrochemical reactions have proven valuable for reversing the polarity of alkenes and triggering radical anion-based or radical cation-based cyclization reactions.[1] Anodic olefin coupling initiated by oxidation of electron-rich olefins can provide powerful tools for achieving intra- and intermolecular cyclization reactions and for building new ring systems. In these cases, several combinations of olefins can be introduced, thereby securing diverse functional groups in the newly cyclized skeletons.[2]

Previously, we established a novel pathway for intermolecular olefin cross-coupling that is useful for constructing [2+2] cycloadducts between in situ generated electron-deficient olefins and nonactivated olefins.[3] The reaction was uniquely regulated by both the oxidation potentials and intra- and intermolecular electron transfers.

In these reactions, for example, anodic oxidation of 1-methoxy-4-(4-methoxybut-3-enyl)benzene in the presence of aliphatic alkenes in lithium perchlorate/nitromethane

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[1] (a) Moeller, K. D. *Tetrahedron* **2000**, *56*, 9527. (b) Sperry, J. B.; Whitehead, C. R.; Ghiviriga, I.; Walczak, R. M.; Wright, D. L. *J. Org. Chem.* **2004**, *69*, 3726. (c) Mihelcic, J.; Moeller, K. D. *J. Am. Chem. Soc.* **2004**, *126*, 9106. (d) For a review of electrolytic reductive couplings, see: Nielsen, M. F.; Utley, J. H. P. In *Organic Electrochemistry*, 4th ed.; Lund, H., Hammerich, O., Eds.; Marcel Dekker: New York, 2001; p 795. (e) Little, D. R. *Electrochem. Soc. Interface* **2002**, *11*, 36. (f) Little, D. R. In *Electrochemistry VI: Electroorganic Synthesis: Bond Formation at Anode and Cathode*; Topics in Current Chemistry 185; Steckhan, E., Ed.; Springer: Berlin, 1997; p 1. (g) Anderson, J. D.; Baizer, M. M.; Petrovich, J. P. *J. Org. Chem.* **1966**, *31*, 3890.

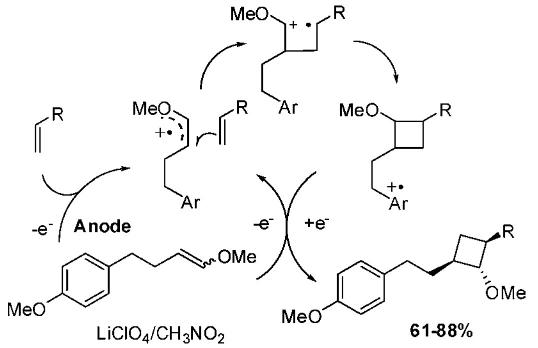
[2] (a) Moeller, K. D.; Marzabadi, M. R.; New, D. G.; Chiang, M. Y.; Keith, S. *J. Am. Chem. Soc.* **1990**, *112*, 6123. (b) Moeller, K. D.; Tinao, L. V. *J. Am. Chem. Soc.* **1992**, *114*, 1033. (c) Hudson, C. M.; Moeller, K. D. *J. Am. Chem. Soc.* **1994**, *116*, 3347. (d) Little, D. R. *Chem. Rev.* **1996**, *96*, 93. (e) Ledwith, A. *Acc. Chem. Res.* **1972**, *5*, 133. (f) Delaunay, J.; Mabon, G.; Orliac, A.; Simonet, J. *Tetrahedron Lett.* **1990**, *31*, 667. (g) Delaunary, J.; Orliac, A.; Simonet, J. *Tetrahedron Lett.* **1995**, *36*, 2083. (h) Fourets, O.; Cauliez, P.; Simonet, J. *Tetrahedron Lett.* **1998**, *39*, 565. (i) Janssen, G. R.; Motevalli, M.; Utley, J. H. P. *Chem. Commun.* **1998**, 539.

[3] Chiba, K.; Miura, T.; Kim, S.; Kitano, Y.; Tada, M. *J. Am. Chem. Soc.* **2001**, *123*, 11314.

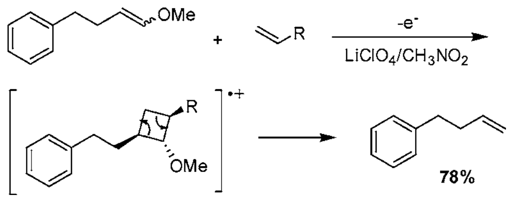
10.1021/ol7019845 CCC: $37.00

electrolyte solution[4] gave the corresponding [2+2] cycloadducts in good yield (Scheme 1). In this electrochemical system, anodic activation of enol ethers possessing the methoxy phenyl group gave various cyclobutane rings in their reactions with alkenes. However, in the absence of the methoxy phenyl group in the enol ether, olefin metathesis occurred instead between the aliphatic alkenes and the anodically activated enol ethers (Scheme 2).[5]

Scheme 1



Scheme 2

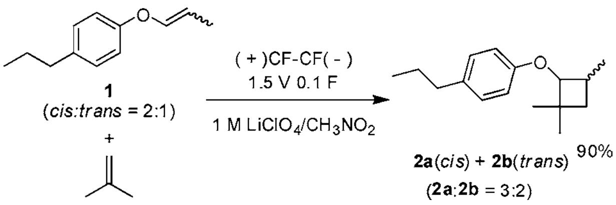


These results suggest that an electron-rich aromatic ring is involved in completing the formation of the cyclobutane ring through the use of an intramolecular electron transfer between the cation radical of the cyclobutane and the methoxyphenyl group.

On the basis of this plausible reaction mechanism, we investigated numerous substrates for electrocatalytic [2+2] cycloadditions possessing both the enol ether and phenyl ether moieties in the same molecule. Herein we report our efforts to develop a unique pathway for the electrocatalytic intermolecular formal [2+2] cross-coupling of enyloxy benzene derivatives with carbon nucleophiles possessing unsaturated C−C bonds, thereby providing various cyclobutyl phenyl ethers.

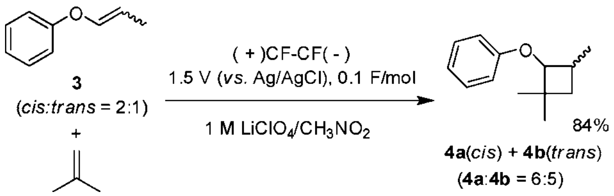
Initially, anodic oxidation of 1-(prop-1-enyloxy)-4-propylbenzene **1** (a 2:1 mixture of *cis*/*trans* isomers) was attempted in the presence of an excess (20 mol equiv) of *iso*-butene in 1 M lithium perchlorate/nitromethane electrolyte solution using a carbon felt anode and cathode. After applying 0.1 F/mol at 1.5 V (vs Ag/AgCl), the desired cycloadduct **2** was obtained in 90% yield as a mixture of **2a** (*cis*) and **2b** (*trans*) (**2a**/**2b** 3:2) (Scheme 3).

Scheme 3



Similarly, anodic oxidation (0.1 F/mol at a constant potential) of (prop-1-enyloxy)benzene **3a**,**b** (a 2:1 mixture of *cis*/*trans* isomers) in the presence of excess *iso*-butene (20 mol equiv) in 1 M lithium perchlorate/nitromethane electrolyte solution gave cycloadduct **4** in 84% yield as a mixture of **4a** (*cis*) and **4b** (*trans*) (**4a**/**4b** 6:5) (Scheme 4).

Scheme 4



These results indicated that the reaction is driven by an electrocatalytic process and that the alk-1-enyloxybenzene is also one of the essential moieties for electrocatalytic [2+2] cycloaddition reactions with aliphatic alkenes. Furthermore, the isolated *cis* isomer of 1-(prop-1-enyloxy)-4-propylbenzene **1** provided products in the ratio *cis*/*trans* 2:1, and the *trans* isomer of **1** gave products in the ratio *cis*/*trans* 2:7. The configurations of these cycloadducts were confirmed by NOE spectra (Figure 1). The formation of mixed stereoisomers of the cyclobutane ring from each stereochemically purified enyloxy benzene indicated that electrocatalytic cycloaddition proceeded by stepwise C−C bond formation and subsequent ring closure. Table 1 shows the electrochemical reactions of **1** in the presence of 10 mol equiv of methylenecyclohexane. The desired spiro-products **5a** (*cis*) and **5b** (*trans*) were obtained (yield 64%, *cis*/*trans* ratio 1:1) together with noncyclized byproduct **6** (yield 15%). In this reaction, a sterically hindered cyclohexyl ring possibly reduces the yield of the desired [2+2] cycloaddition products. Noncyclized products are presumably formed via an intramolecular hydride rearrangement (Figure 2). The above results provided further evidence that anodically triggered cyclobutane ring formation proceeds in a stepwise fashion.

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[4] (a) Chiba, K.; Tada, M. *J. Chem. Soc., Chem. Commun.* **1994**, 2485. (b) Ayerbe, M.; Cossio, F. P.; Kim, F.; Euskal, H. U.; San, S.-D. *Tetrahedron Lett.* **1995**, *36*, 4447. (c) Chapuis, C.; Kucharska, A.; Rzepecki, P.; Jurczak, J. *Helv. Chim. Acta* **1998**, *81*, 2314. (d) Kumareswaran, R.; Vankar, P. S.; Reddy, M. V. R.; Pitre, S. V.; Roy, R.; Vankar, Y. D. *Tetrahedron* **1999**, *55*, 1099. (e) Sankararaman, S.; Sudha, R. *J. Org. Chem.* **1999**, *64*, 2155.

[5] Miura, T.; Kim, S.; Kitano, Y.; Tada, M.; Chiba, K. *Angew. Chem., Int. Ed.* **2006**, *45*, 1461.

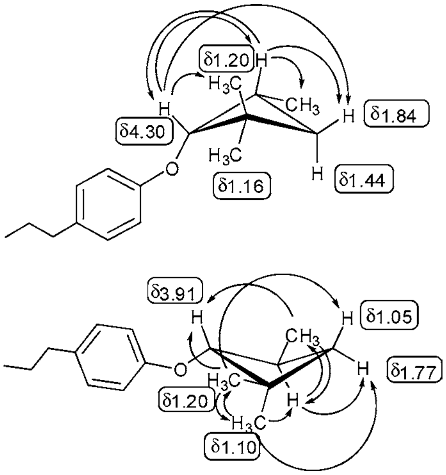


Figure 1. Interpretation of NOE difference spectra of the cyclobutane ring.

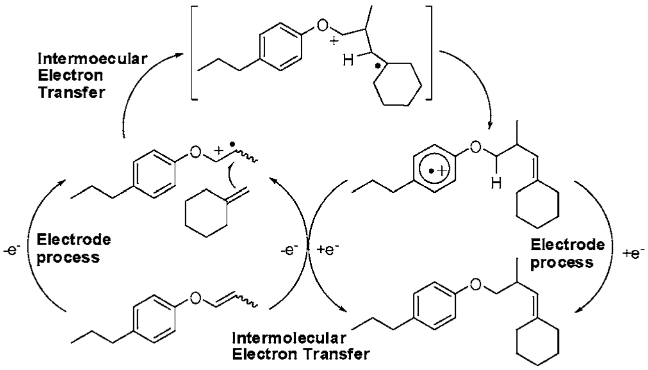
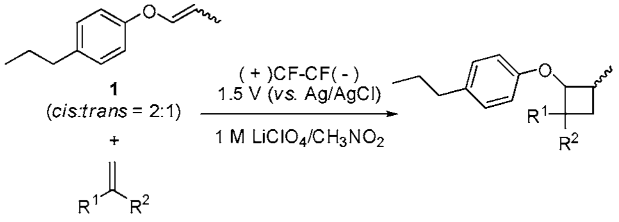


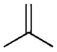
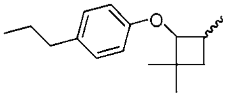
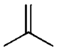
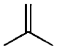
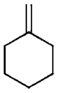
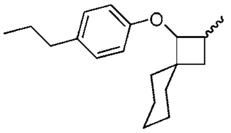
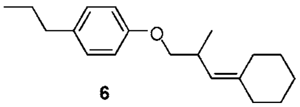
Figure 2. Reaction mechanism for methylenecyclohexane used as an alkene.

Table 2 shows examples of the anodically activated enyl phenyl ethers and alkenes. Anodic oxidation of sterically hindered 1-(2-methylprop-1-enyloxy)-4-propylbenzene **7** with excess *iso*-butene (20 mol equiv) gave the desired 1-propyl-4-(2,2,4,4-tetramethyl cyclobutoxy)benzene **8** in low yield (20%). The reaction of **7** with 20 mol equiv of methylenecyclohexane afforded the desired cycloadduct **9** and the noncyclized product **10** in very low yield. These low yields could be due to steric hindrance in the transition state leading to the four-membered ring during intermolecular C−C bond formation. However, electrocatalytic activation of **1** with ethyl vinyl ether (20 mol equiv) gave cyclized products of the cross-coupling reaction in good yield (yield 96%, obtained as a diastereomer mixture of 8:3:3:1) upon an electrical input of 0.1 F/mol (Scheme 5). Furthermore, anodic activation of enyloxy benzene **1** in the presence of an alkyne gave cycloadduct **12** (**12a** *cis*/**12b** *trans* 6:1) possessing a cyclobutene ring (Scheme 6). These products should be formed by the same reaction mechanism as with alkenes.

As shown above, enyloxy benzene is an effective substrate for electrocatalytic cyclobutane formation with aliphatic alkenes, alkynes, and enol ethers. In some cases, the reaction proceeded when a catalytic electrical input of less than 0.1

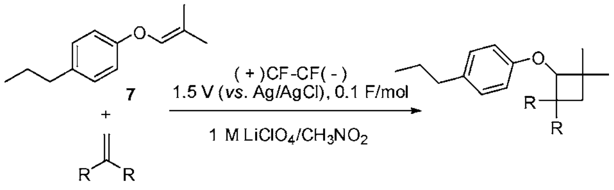
Table 1. Electrochemical Reactions of **1** with Alkene

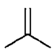
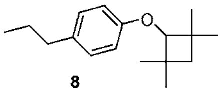
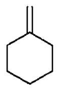
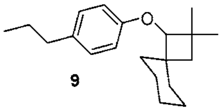
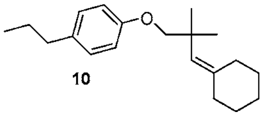


Enol Ether	Alkene	F/mol	Products	Yield (%)*
1 (*cis*:*trans* = 2:1)		0.10	 **2a**(*cis*) + **2b**(*trans*)	90 (**2a**:**2b** = 3:2)
1a (*cis*)		0.10		92 (**2a**:**2b** = 2:1)
1b (*trans*)		0.10		89 (**2a**:**2b** = 2:7)
1 (*cis*:*trans* = 2:1)		0.30	 **5a**(*cis*) + **5b**(*trans*) +  **6**	64 (**5a**:**5b** = 1:1) 15

*Isolated yield.

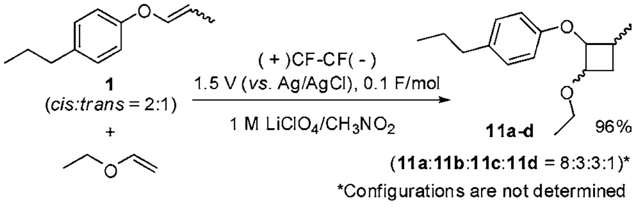
Table 2. Electrochemical Reactions of **7** with Alkene



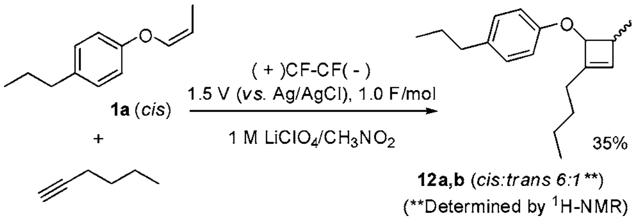
Alkene	F/mol	Products	Yield (%)*
	2.0	 **8**	20
	2.0	 **9** +  **10**	7 trace

*Isolated yield.

Scheme 5



Scheme 6



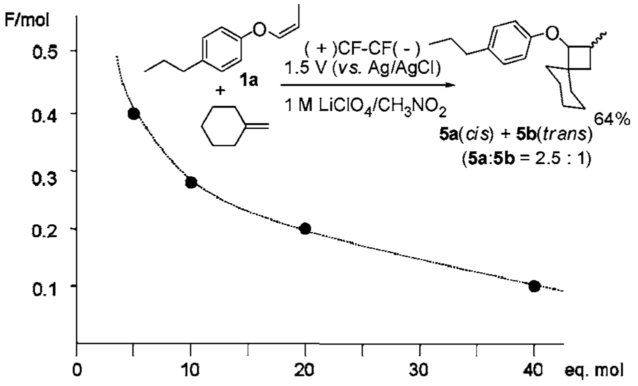


Figure 3. Relationship between reactivity and total electrical input required for completion of the cycloaddition reaction.

F/mol was applied. Generally, nucleophiles with low reactivity require much higher electrical input. We therefore attempted to clarify the relationship between reactivity and total electrical requirement for completion of the cycloaddition reaction. Figure 3 shows the relationship between the amount of excess methylenecyclohexane and total electrical input for complete cycloaddition of *cis*-1-(prop-1-enyloxy)-4-propylbenzene **1a**. In the presence of 40 mol equiv of methylenecyclohexane in 1.0 M lithium perchlorate/nitromethane electrolyte solution, applying just 0.1 F/mol gave product **5** in 64% yield (*cis*/*trans* 2.5:1) together with noncyclized product **6**. In contrast, in the presence of 10 mol equiv of methylenecyclohexane, about 0.3 F/mol was required to provide product **5** in 64% yield (*cis*/*trans* 2.5:1). Furthermore, in the presence of only 5 mol equiv of methylenecyclohexane, more than 0.4 F/mol was required to drive the reaction to completion (yield 64%, with no starting electrolytic substrate). These results suggest that carbon−carbon bond formation and reduction by an electrode-driven process should be competitive in electrocatalytic cyclobutane ring formation. In the presence of a large excess of methylenecyclohexane (a nucleophile), the radical cation intermediate generated by the anodic oxidation of the enyloxy benzene could be immediately trapped for participation in cyclobutane ring formation. However, in the presence of a lower concentration of the nucleophile, the radical cation of the enyloxy benzene should be mainly reduced at the anode by a reversible electron transfer because of the formation of the radical cation intermediate of higher potential. Results to date indicate that the total electrical input for this catalytic electrochemical process directly depends on the rate of carbon−carbon bond formation.

In conclusion, one of the essential functional groups has been identified for the electrocatalytic [2+2] cycloaddition of enol ethers. This was achieved using prop-1-enyloxy benzene, which formed the corresponding cyclobutane ring with alkenes in lithium perchlorate/nitromethane electrolyte solution. The enyloxy benzene moiety of these electrolytic substrates played an important role in the formation of a radical cation that could accept nucleophilic alkenes or alkynes, followed by intramolecular electron transfer between the cyclobutane and phenyl ether moieties of the intermediates. This efficient electrocatalytic process should find application in the synthesis of diverse cyclized skeletons which are generally difficult to obtain by conventional chemical processes. The development of a wide variety of these reactions is presently underway in our laboratory.

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Supporting Information Available: General procedure, characterization of products, and starting materials. This material is available free of charge via the Internet at http://pubs.acs.org.

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