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► **To cite this version:**

Ophélie Montiège, Marion Siccardi, Morgane Sanselme, Cédric Schneider, Jean-François Brière, et al. Regio- and Stereoselective Electro-Mediated Carboalkoxylation of 1,3-Dienes. *Organic Letters*, 2024, 26 (51), pp.11105-11110. <10.1021/acs.orglett.4c03922>. <hal-04877605>

HAL Id: hal-04877605

<https://normandie-univ.hal.science/hal-04877605v1>

Submitted on 9 Jan 2025

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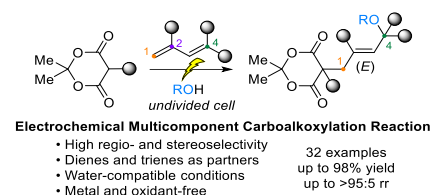
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Regio- and Stereoselective Electro-Mediated Carboalkoxylation of 1,3-Dienes

Ophélie Montiège, Marion Siccardi, Morgane Sanselme, Cédric Schneider*, Jean-François Brière* and Hélène Beucher*



ABSTRACT: 1,3-dienes are versatile raw materials to build molecular complexity. We report herein mild conditions for the regio- and stereoselective (only *E* isomer obtained) 1,4-carboalkoxylation of 1,3-dienes. This electrochemical multicomponent reaction provides an eco-efficient and straightforward access to a diverse range of (*E*)-polyfunctionalized allyl ether products, without the requirement of any metal catalyst.

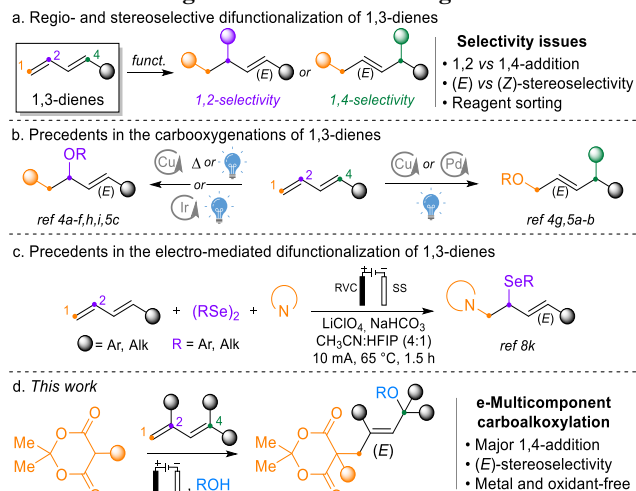
Conjugated dienes are abundant and readily available feedstocks.¹ The intermolecular difunctionalization of 1,3-dienes has attracted considerable research interest from the synthetic community, as it enables to create molecular complexity, by simultaneously forging two C-C/C-heteroatom bonds thanks to straightforward multicomponent reactions (MCR). Although attractive, this process remains challenging mostly due to stereo- (*E* vs *Z* isomer) and regioselective (1,2- vs 1,4-addition) issues (Scheme 1.a). Over the past decades, the transition metal catalysis through two-electron-based mechanisms has paved the way for transformation of dienes with excellent regio- and stereoselectivity.² More recently, the powerful radical-based strategies promoted by organometallic complexes under thermal or photocatalyzed conditions have become complementary approaches for the rapid installation of various functionalities in an orthogonal fashion.³ In that field, the three-components radical carboxygenations of 1,3-dienes has furnished highly represented motifs in organic molecules alongside the C-C/C-O bonds construction. Yet, the vast majority of achievements have been focused so far on carboesterification processes⁴ with only limited examples of carboalkoxylation reactions (Scheme 1.b).⁵ Moreover, 1,4-regioselective carboxygenations remain scarce and restricted to specific coupling partners, as well as limited dienes substitution pattern.^{4g,5a-b}

In that context, we tackled an alternative carboalkoxylation sequence by means of an electrochemical and metal-free MCR as a sustainable approach.⁶ In sharp contrast with the well-developed electro-mediated difunctionalization of alkenes,⁷ its application to 1,3-diene precursors remains in its infancy.⁸ Pioneering investigations have been devoted to di-component reactions involving mono- and di-carboxylation in the presence of carbon dioxide,^{8a-f} alkylation or arylation processes from iodinated precursors with a limited scope.^{8i,j} Recently, Terent'ev, Pan and Meng reported an unique electro-mediated three-components difunctionalization reaction of 1,3-dienes, giving access to selenium-containing allylazoles (C-Se/C-N bonds

formation) with an excellent regioselectivity towards the formation of the 1,2-addition products (Scheme 1.c).^{8k}

Herein, we report a novel electro-mediated 1,4-carboalkoxylation of 1,3-dienes under metal and oxidant free conditions with high regio- and stereoselectivity. Based on a hypothetical radical-polar cross-over mechanism under a double anodic oxidation approach, this electrochemical multicomponent reaction (e-MCR) provides an eco-efficient and straightforward access to a diverse range of 1,4-(*E*)-polyfunctionalized allyl ether products. Importantly, this achievement highlights Meldrum's acid (MA) derivatives as key partners of our e-MCR, whose previous used in radical based processes required excesses of manganese, silver or iron-complexes as oxidants.⁹

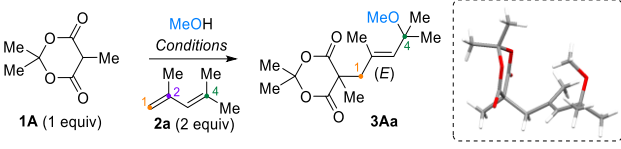
Scheme 1. Origin of the Reaction Design



We first investigated the reaction conditions using methylated MA **1A** and 2,4-dimethylpenta-1,3-diene **2a** (see Supporting Information (SI) for more details). We conducted the electrochemical reaction in an undivided cell, using ⁿBu₄NBF₄ as

the electrolyte (0.5 equiv) and methanol (MeOH) as solvent with 2.5 F/mol and 5 mA at room temperature (rt) under nitrogen atmosphere. As preliminary investigations showed that a platinum cathode allowed a promising outcome, we screened the anode materials in these conditions (Table 1). Carbon graphite anode yielded the desired product **3Aa** in a promising 33% NMR yield as a single 1,4-regio- and stereo-(*E*)-isomer (entry 1 vs entries 2-5). The structure of product **3Aa** was ascertained by X-ray crystallography analysis (see SI). Among various solvent combinations, a mixture of MeOH and DMF (1:1) afforded **3Aa** in an improved 63% NMR yield (entry 6). Trying to decrease the amount of MeOH (40 and 80 equiv of MeOH in DMF) was deleterious to the process (entries 7-8). Yet, decreasing the electron density to 3 mA and increasing the charge to 3 F/mol delivered **3Aa** in an excellent 80% NMR yield (entries 9-10). ⁿBu₄NBF₄ turned out to be the best electrolyte (entries 11-12), while being required to secure an acceptable conversion into **3Aa** (58% NMR yield, entry 13). The efficiency of the reaction dropped when performed under air (entry 14) and the need of electricity was confirmed to be essential for the reaction to proceed (entry 15).

Table 1. Optimization of the Reaction



Conditions: A (+) | Pt (-), electrolyte (0.5 equiv), Solvent, X F/mol, Y mA, rt, N₂

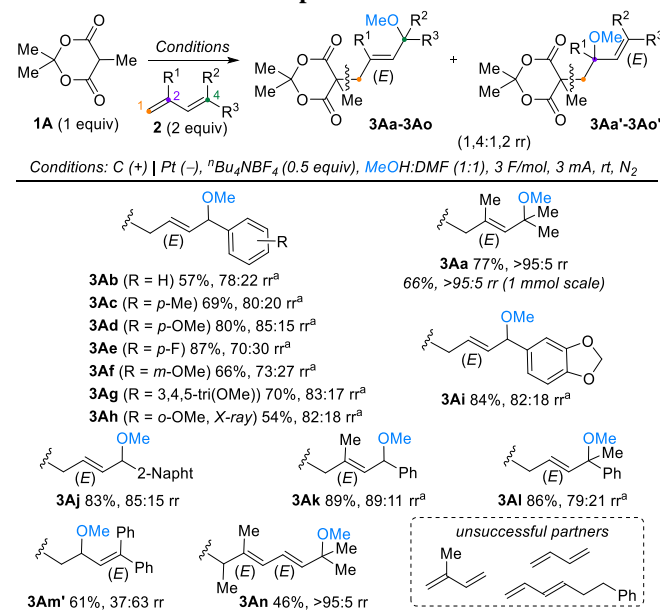
Entry	A (+)	Solvent	X, Y	Electrolyte	Yield ^a (%)
1	C	MeOH	5, 2.5	ⁿ Bu ₄ NBF ₄	33
2	Pt	MeOH	5, 2.5	ⁿ Bu ₄ NBF ₄	traces
3	Au	MeOH	5, 2.5	ⁿ Bu ₄ NBF ₄	15
4	SS	MeOH	5, 2.5	ⁿ Bu ₄ NBF ₄	<10
5	RVC	MeOH	5, 2.5	ⁿ Bu ₄ NBF ₄	30
6	C	DMF:MeOH ^b	5, 2.5	ⁿ Bu ₄ NBF ₄	63
7	C	DMF:MeOH ^c	5, 2.5	ⁿ Bu ₄ NBF ₄	60
8	C	DMF:MeOH ^d	5, 2.5	ⁿ Bu ₄ NBF ₄	66
9	C	DMF:MeOH ^b	3, 2.5	ⁿ Bu ₄ NBF ₄	73
10	C	DMF:MeOH ^b	3, 3	ⁿ Bu ₄ NBF ₄	80
11	C	DMF:MeOH ^b	3, 3	Et ₄ NBF ₄	66
12	C	DMF:MeOH ^b	3, 3	ⁿ Bu ₄ NPF ₆	62
13	C	DMF:MeOH ^b	3, 3	/	58
14 ^e	C	DMF:MeOH ^b	3, 3	ⁿ Bu ₄ NBF ₄	56
15 ^f	C	DMF:MeOH ^b	/	ⁿ Bu ₄ NBF ₄	0

Reaction performed at 0.08 M (*versus* **1A**) on 0.2 mmol scale. ^aNMR yield determined using Bn₂O as an internal standard. ^bRatio MeOH:DMF 1:1. ^c40 equiv of MeOH in DMF. ^d80 equiv of MeOH in DMF. ^eReaction performed under air. ^fReaction performed without electricity.

With the optimized conditions in hand, we moved to the scope of the reaction with C5-methyl MA derivative **1A**. The model reaction with the 2,4-dimethylpenta-1,3-diene **2a** led to the corresponding product **3Aa** in 77% isolated yield (Scheme 2), even at 1 mmol scale (72% isolated yield). To our delight, under similar electrochemical conditions, the carboalkoxylation was extended to a variety of arylated dienes **2b-m** to afford the

corresponding major 1,4-addition products **3Ab-Am** in good to excellent regioselectivity (regioisomeric ratio “rr” = 1,4:1,2) and a perfect stereoselectivity towards a single (*E*)-isomer (>95:5 E/Z, as only one stereoisomer is observed by ¹H NMR). Neither the position of the substituent on the phenyl ring nor its nature (EDG vs EWG) had a significant impact on the course of the reaction, except a slight decrease in regioselectivity (70:30 rr) observed with the *para*-fluoro derivative **3Ae** as an inductive electron-withdrawing group. We further probed the steric hindrance on the different positions of the dienes. We were pleased to observe that a methyl group at R¹ (**3Ak**) and R³ (**3Al**) gave the corresponding products in excellent 89% and 86% yields, respectively, and affected only slightly the regioselectivity of the reaction, with a slight increase in favour of the 1,4-addition product in the former case (**3Ak**, 89:11 rr vs **3Al**, 79:21 rr). However, increasing the size of the R³ substituent had a significant impact, with an inversion of the regioselectivity and the major 1,2-addition product **3Am'** obtained in 61% yield and 37:63 rr. We were pleased to see that our methodology could be extended to the use of trienes as coupling partners, giving the desired product **3An** in 46% yield, with an excellent regioselectivity (1,6 addition only observed) and stereoselectivity (only *E* isomer). Unfortunately, although 2,4-dimethylpenta-1,3-diene **3Aa** appeared to be an ideal partner of this e-MCR, other alkylated dienes were not compatible under our optimized conditions.

Scheme 2. Substrate Scope for Dienes

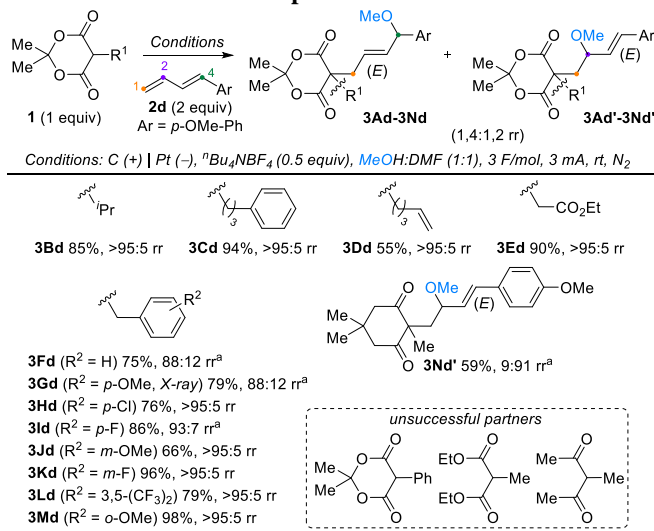


Reaction performed at 0.08 M (*versus* **1A**) on 0.2 mmol scale. Isolated yields (%) after column chromatography. 1,4:1,2 regioisomeric ratios (rr) were determined on the crude product by ¹H NMR. ^aIsolated as a mixture of regioisomers.

We then turned our attention towards the influence of the substitution at the C5-position of the MA component. Once again, an excellent stereoselectivity towards the formation of the (*E*)-isomer was observed (>95:5 E/Z) (Scheme 3). Increasing the steric hindrance (**3Bd**) or the length of the alkyl chain (**3Cd**) gave the desired 1,4-addition products in high yields (85% and 94%, respectively) and regioselectivity (>95:5 rr). Worthy of note, an alkene pendant at C5 is compatible with this method, without obvious competitive cyclization event, as **3Dd** was obtained in 55% yield with >95:5 rr. Moreover, an ester functional

group was well tolerated delivering **3Ed** in 90% yield (>95:5 rr). C5-benzylated-MA derivatives were also prominent substrates for this e-MCR, as compound **3Fd** could be obtained in 75% yield with a regioselectivity of 88:12 rr. Once again, the position of the substituents or its electronic properties did not impact the course of the reaction (**3Gd-3Md**), it appears that essentially steric hindrance matters. Interestingly, the methylated-dimedone **1N** delivered **3Nd'** in 59% yield with the opposite regioselectivity as the 1,2-addition product was obtained as major regioisomer (9:91 rr), but still with excellent *E*-stereoselectivity, highlighting the uniqueness of MA component in this e-MCR. While a MA with a C5-phenyl substituent did not lead to any product, likely due to the higher stability of the putative radical species, other 1,3-dicarbonyl radical precursors such as methylated 1,3-diketone or malonate derivatives were incompetent precursors of this e-MCR, showing the singularity of cyclic dicarbonyl derivatives.

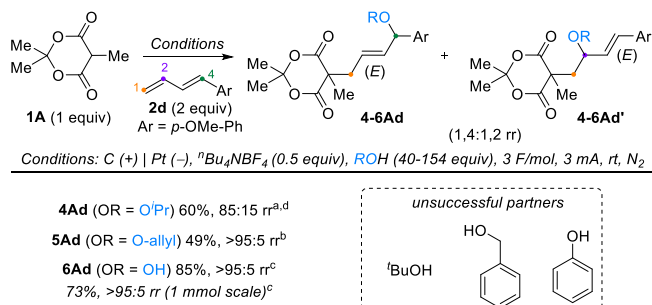
Scheme 3. Substrate Scope for Meldrum's Acids



Reaction performed at 0.08 M (versus **1**) on 0.2 mmol scale. Isolated yields (%) after column chromatography. 1,4:1,2 rr were determined on the crude product by ¹H NMR. ^aIsolated as a mixture of regioisomers.

We further evaluated the scope of alcohols (Scheme 4). Isopropanol could be used as a co-solvent in the reaction, delivering the corresponding product **4aD** in 60% yield with 85:15 rr. We managed to reduce the amount of alcohol to 40 equivalents to obtain the *O*-allylated desired compound **5Ad** in a good 49% yield with an excellent regioselectivity towards the 1,4-addition product. Unfortunately, *tert*-butanol, phenol and benzylic alcohol gave low yields. Yet, very interestingly, water could be engaged as a nucleophile in our e-MCR delivering the free allylic alcohol derivative **6Ad** in 85% yield and with an excellent regioselectivity of >95:5 rr, even at 1 mmol scale (73% yield).^{5c}

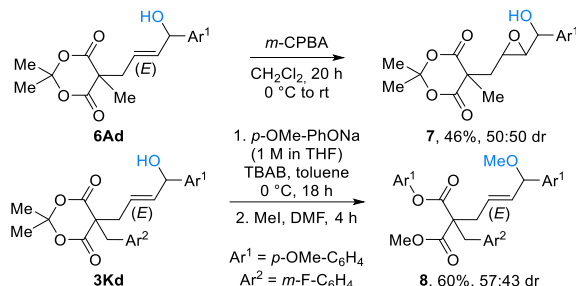
Scheme 4. Substrate Scope for Alcohols



Reaction performed at 0.08 M (versus **1A**) on 0.2 mmol scale. Isolated yields (%) after column chromatography. 1,4:1,2 rr were determined on the crude product by ¹H NMR. ^aA mixture of ROH:DMF (1:1) was used (meaning 154 equiv of ROH). ^b40 equiv of alcohol were used. ^c80 equiv of alcohol were used. ^dIsolated as a mixture of regioisomers.

To further illustrate the synthetic utility of our protocol and the versatility of the products, transformations were conducted (Scheme 5). Epoxidation of the allylic alcohol **6Ad** was successfully performed to afford the corresponding product **7** in 46% isolated yield (50:50 dr). The opening of the MA moiety of **3Kd** following our previously described protocol,¹⁰ gave product **8** in 60% isolated yield (57:43 dr), thus demonstrating the efficient access to allyl ethers containing an all-carbon quaternary stereocenter.

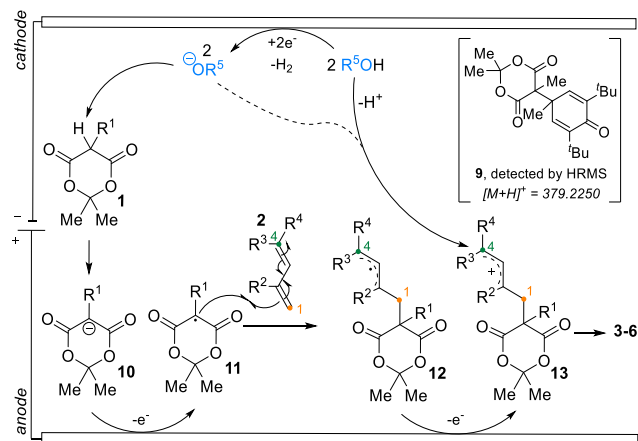
Scheme 5. Post-functionalization Reactions



Diastereoisomeric ratios (dr) were determined on the crude product by ¹H NMR. Products have been isolated as a mixture of diastereoisomers.

To gain insights into the mechanism of the reaction, some control experiments were performed (see SI). First, the reaction was completely inhibited in the presence of free radical inhibitors, such as TEMPO and BHT. Moreover, the corresponding adduct **9** between MA and BHT was detected by HRMS only when electricity was turned on (with or without diene, Figure 1), and the presence of MeONa (without power supply) did not promote the MCR. These outcomes suggest the involvement of the corresponding radical species in the electrochemical-based mechanism. We also conducted cyclic voltammetry experiments, which showed the anodic oxidation of MA (likely after deprotonation) in basic conditions (E_{ox} (enolate-MA) = 0.44 V vs SCE in DMF),¹¹ while the anodic oxidation of dienes occurred at higher potentials (E_{ox} (diene **2a**) = 1.81 V¹² and E_{ox} (diene **2d**) = 1.16 V vs SCE in DMF).

Figure 1. Proposed Mechanism



With these results in hand and the reports from the literature,^{8k,13,14} we suggest the following radical-polar crossover mechanism (Figure 1). On one hand, the alkoxide is generated at the cathode upon reduction of the alcohol, and concomitant release of hydrogen. On the other hand, the enolate MA derivatives **10**, originated either from the deprotonation of **1** by methanolate or simply in equilibrium with **1** due to its high acidity ($pK_a = 4.8$ in water),¹⁵ will be oxidized at the anode to deliver radicals **11**.¹⁶ The addition of the electron-poor radical species **11** occurs to the less hindered position of dienes **2** driven by a match of polarity. The resulting and more-electron rich radical **12** will be further oxidized within the double layer of the anode to give cation **13**, which will be trapped by methanol or the alkoxide anion to deliver the desired products **3-6**. The regioselectivity in favour of the 1,4-adduct in our multicomponent carboalkoxylation reaction is worthy of note and in contrast to the vast majority of previous studies.^{4,5} Even though further mechanistic investigations are required, we assume at first, based on previous observation of Chen and colleagues,^{4b,5c} that an interplay between the electron-withdrawing character and the steric hinderance of the 1,3-dioxan-4,6-dione part may prevent the addition to the positive charge at C2. Furthermore, the unique boat conformation of MA may direct the addition of the alcohol at C4 of cation **11** thanks to a hydrogen bonding event.

In conclusion, we have developed an electro-mediated regio- and stereoselective 1,4-carboalkoxylation of 1,3-dienes providing (*E*)-polyfunctionalized allyl ethers. The substrate scope illustrates the impact of the electronic properties and the steric hinderance on the course of the reaction, and water could be directly engaged as a nucleophile in our e-MCR. Preliminary control experiments have demonstrated a radical-polar crossover mechanism likely starting with the anodic oxidation of the enolate-MA. Further studies are currently under investigation in our laboratory to fully assess the remarkable regioselectivity of this process and further expand the scope to other nucleophiles.

ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

Supporting Information Statement

The Supporting Information is available free of charge on the ACS Publications website. Full experimental details and optimization, spectral characterization and crystallographic data.

Accession Codes

CCDC 2383813 (**3Aa**), 2383811 (**3Ah**), 2383812 (**3Gd**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENT

This work was partially supported by Université Rouen Normandie, INSA Rouen Normandie, Centre National de la Recherche Scientifique (CNRS), European Regional Development Fund (ERDF), Région Normandie, Labex SynOrg (ANR-11-LABX-0029), Carnot Institute I2C, the graduate school for research XL-Chem (ANR-18-EUR-0020 XL CHEM). This project has been also funded with the support from the Région Normandie (Grant number: 00140561/23^E02626).

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