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Copper-Catalyzed Regioselective 1,2-Alkylesterification of Dienes to Allylic Esters

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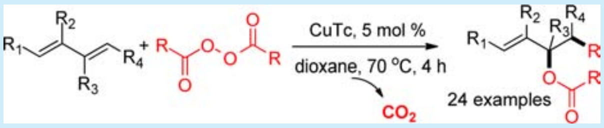
Ⓢ *Supporting Information*

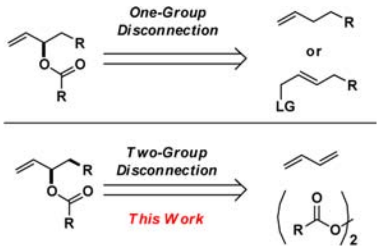
ABSTRACT: Copper catalyzed 1,2-alkylesterification of 1,3-dienes with diacyl peroxides affords branched allylic esters in excellent regioselectivity, including products with a newly generated fully substituted carbon center. The only byproduct is CO_2. The reaction proceeds by a radical mechanism as suggested by spin trap and crossover experiments.



Branched allylic esters are useful synthetic intermediates and can be generated by some elegant methods, including metal-catalyzed allylic substitution,[1] oxidative C−H esterification,[2] and copper-catalyzed Kharasch−Sosnovsky reactions.[3] Most existing methods use an olefin to generate allylic radicals or allyl-metal complexes as key intermediates. Despite the many merits of this strategy, the main drawback is that the structure of the product is limited by the structure of the olefin substrates. More often, the generation of a specific olefin substrate is more difficult than the allylic oxidation step. Retrosynthetically, the synthesis of allylic esters from olefin substrates represents a one-group disconnection, in which the substrate and product have similar molecular complexity.[4] A more efficient strategy would involve a two-group disconnection in which the desired allylic esters are assembled from readily available substrates with low molecular complexity that can incorporate multiple functional groups in a single chemical step (Scheme 1).[4]

We hypothesized that 1,3-butadiene would be the ideal starting material for the development of a more efficient two-group disconnection to allylic esters (Scheme 1). This four-carbon feedstock, which is a product of petroleum cracking, is inexpensive and abundant. Efficient methods for double functionalization of 1,3-butadiene with different functional groups have been developed.[5−11]

Scheme 1. Strategies for Generation of Allylic Esters



Although the catalyzed alkylesterification (oxyalkylation) of styrenes has been done by Wang's group,[12] the efficient catalyzed alkylesterification of dienes is not known. We envisioned that 1,3-butadiene would react with a radical to generate a new allylic radical species, which then could couple with other reagents in the presence of metal catalysts. In many cases, such allylic radical species are difficult to obtain from olefins. It is well-known that, upon heating or in the presence of metal ions, alkyl diacyl peroxides decompose to acyloxy radicals, alkyl radicals, and CO_2.[13] The rate of addition of alkyl radicals into butadiene to generate allyl radicals is fast.[5] We envisioned that, with a suitable catalyst, the newly generated allyl radical can couple with the acyloxy radicals already present in the reaction mixture. Herein, we describe a general method for the synthesis of branched allylic esters, including such containing a newly generated fully substituted carbon, by a copper-catalyzed, regioselective 1,2-alkylesterification of 1,3-dienes with diacyl peroxides. It is noteworthy that this reaction is an environmentally benign process and the only byproduct of this reaction is CO_2. Moreover, no other chemicals than solvent and catalyst are needed in this reaction. Gratifyingly, when the reaction between 1,3-butadiene (**1**) and lauroyl peroxide (**2a**, LPO) was attempted by bubbling **1** into a solution of LPO and CuCl (10 mol %) as the catalyst in $CH_3CN/H_2O/HOAc$, 15% of the desired product **3a** was obtained (Table 1, entry 1). Additionally, 20% of 1-undecene and n-docosane ($C_{22}H_{46}$; most likely arising from alkyl radical homodimerization) were isolated.[13] An examination of a number of copper catalysts (entries 3−7, 10) revealed that CuTc (Tc = thiophene-2-carboxylate) was the most effective. Under optimized conditions, **3a** was obtained in 66% yield of

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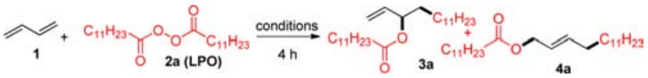
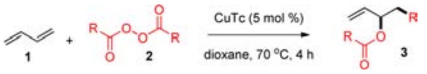
Table 1. Reaction Conditions Optimization[a]

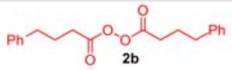
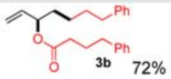
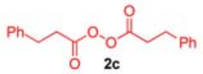
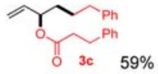
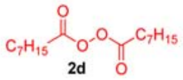
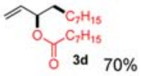
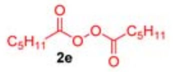
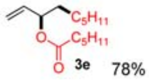
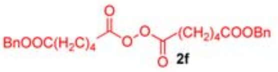
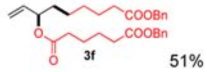
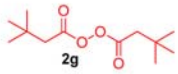
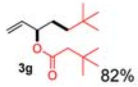
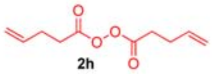
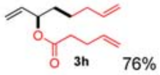
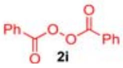


entry	catalyst (mol %)	solvent	temp (°C)	yield of **3a** (%)[b]
1	CuCl (10)	$CH_3CN/H_2O/$ HOAc	90	15
2	CuCl (20)	$CH_3CN/H_2O/$ HOAc	90	34
3	CuCl (10)	1,4-dioxane	80	58
4	$Cu(OAc)_2$ (10)	1,4-dioxane	80	29
5	CuBr (10)	1,4-dioxane	80	56
6	CuI (10)	1,4-dioxane	80	47
7	$CuCl_2$ (10)	1,4-dioxane	80	63
8	CuCl (10)	1,4-dioxane	70	67
9	CuCl (10)	1,4-dioxane	60	29
10	CuTc (10)	1,4-dioxane	70	69
11	CuTc (5)	1,4-dioxane	70	66
12	none	1,4-dioxane	70	0

[a] 1,3-Butadiene was bubbled into a solution of **2a** (1 mmol) in solvent (2 mL). [b] Yields of isolated products.

Table 2. Scope of the Diacyl Peroxides[a]



entry	diacyl peroxide	products (yield)[b]
1	 **2b**	 **3b** 72%
2	 **2c**	 **3c** 59%
3	 **2d**	 **3d** 70%
4	 **2e**	 **3e** 78%
5	 **2f**	 **3f** 51%
6	 **2g**	 **3g** 82%
7	 **2h**	 **3h** 76%
8	 **2i**	trace

[a] 1,3-Butadiene was bubbled into a solution of **2** (2 mmol) in dioxane (4 mL). [b] Yields of isolated products.

isolated product with CuTc (5 mol %) at 70 °C in dioxane. Decomposition of LPO leading to lauric acid, 1-undecene, and n-docosane was the main competing reaction. The above-mentioned three compounds were observed by GCMS and ^1H NMR. Product **3a** was not detected in the absence of Cu catalyst (entry 12). Notably, the corresponding linear product **4a** was not isolated in any of the reaction optimization runs.

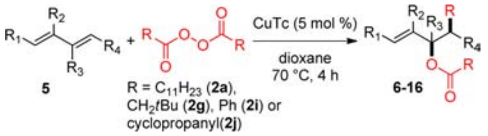
Next, other diacyl peroxides were synthesized from corresponding carboxylic acids (two steps) or acyl chlorides (one step) in moderate to high yields. Then these diacyl peroxides were evaluated as substrates (Table 2). Besides unfunctionalized alkyl diacyl peroxides, ester or olefin-functionalized analogues also reacted with 1,3-butadiene smoothly to produce 1,2-difunctionalization products in good to moderate yields. However, benzoyl peroxide failed to give the anticipated product.

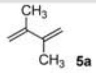
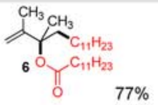
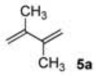
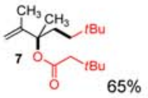
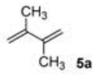
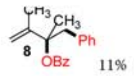
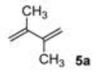
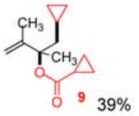
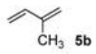
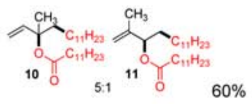
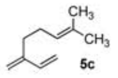
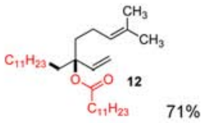
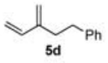
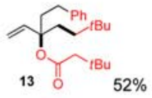
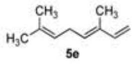
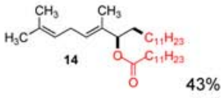
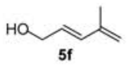
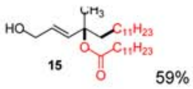
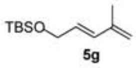
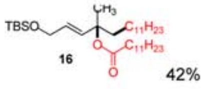
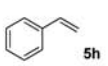
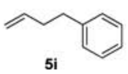
Substituted 1,3-dienes were also suitable as substrates (Table 3). 2,3-Dimethyl-1,3-butadiene (**5a**) reacted with LPO (**2a**), **2g**, and **2j** to afford 1,2-alkylesterification products (**6**, **7**, **9**) having a newly generated fully substituted carbon in good to moderate yield (77%, 65%, and 39%, entries 1, 2, 4). No 1,4-alkylesterification product was observed. This time, benzoyl peroxide gave the anticipated product in low yield when 2,3-dimethyl-1,3-butadiene (**5a**) was applied (11%, entry 3). Similarly, C-2 monosubstituted dienes (**5b**−**d**) and disubstituted diene **5e** gave 1,2-alkylesterification products (**10**, **12**, **13**, **14**) with LPO or bis(*tert*-butylacetyl) peroxide. In these cases (entries 5−8), 1,2-alkylesterification products having a newly generated fully substituted carbon center were the only (**12**, **13**, **14**) or the major (**10**) isomers. The latter was formed as a 5:1 mixture with the regioisomer (**11**) containing a secondary carbon. A free hydroxyl group (diene **5f**, entry 9) or TBS (*tert*-butyldimethylsilyl) ether group (diene **5g**, entry 10) were well tolerated, and the 1,2-alkylesterification products (**15**, **16**) were obtained in 59% and 42% yield, respectively. To further understand the reaction, 4-phenyl-1-butene and styrene were examined with LPO under the best reaction conditions. Styrene led to a complex mixture from which no product could be isolated (entry 11) when 4-phenyl-1-butene showed no reactivity at all (entry 12). These two experiments suggest that this is the copper catalyzed difunctionalization process of dienes rather than the copper catalyzed difunctionalization of olefins.[14]

To explore the reaction mechanism, several experiments were conducted. First, when TEMPO was added into the standard reaction, no alkylesterification product was observed and only the radical coupling product **17** was isolated in 58% yield (Scheme 2). Second, with NHPI (*N*-hydroxyphthalimide), the anticipated product **6** and an NHPI adduct **18** were isolated in 18% and 30% yield, respectively. Compound **18** presumably arises from the formation of a nitroxyl radical from NHPI under the reaction conditions.

To further understand the behavior of alkyl and acyloxy radicals in the reaction, crossover experiments between two different diacyl peroxides were performed (Scheme 3). When equimolar amounts of efficient diacyl peroxides **2c** and **2g** (Scheme 3a) were used, four products were obtained. This result is consistent with the alkylation and esterification being separate, intermolecular events. On the other hand, the crossover reaction between an effective (**2g**) and a noneffective (**2i**) diacyl peroxide with 2,3-dimethyl-1,3-butadiene (Scheme 3b) resulted in products **7** and **21** in a 7:10 ratio. Interestingly, when the hybrid diacyl peroxide **2k** was treated with 2,3-dimethyl-1,3-butadiene, an additional 1,4-alkylesterification product (**22**) was observed (Scheme 3c). The ratio of **7**:**21**:**22** was 6:10:6. We attribute this result to the different decomposition rate of the diacyl peroxides and different dicarboxylation rate of the acyloxy radicals.

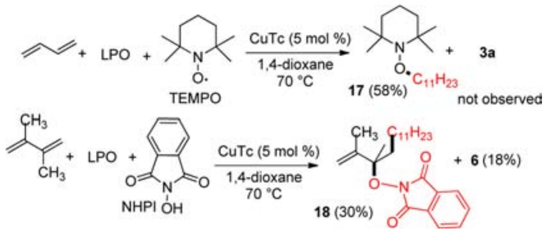
Table 3. Scope of Substituted 1,3-Dienes[a]



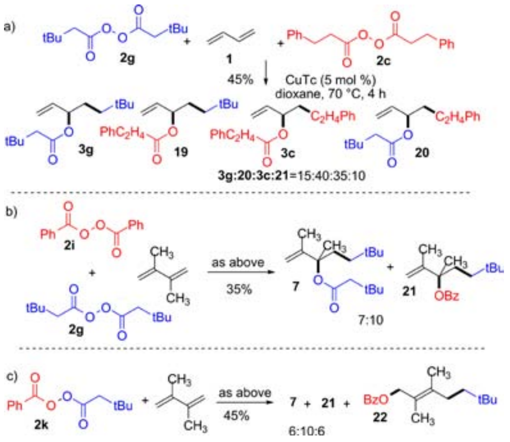
entry	dienes	products/yield[b]
1	 5a	 6 77%
2	 5a	 7 65%
3	 5a	 8 11%
4	 5a	 9 39%
5	 5b	 10 11 5:1 60%
6	 5c	 12 71%
7	 5d	 13 52%
8	 5e	 14 43%
9	 5f	 15 59%
10	 5g	 16 42%
11	 5h	Messy reaction
12	 5i	NR

[a] Diene (1.0 equiv) and diacyl peroxide (1.75 equiv) in dioxane (2 mL/mmol). [b] Yields of isolated products.

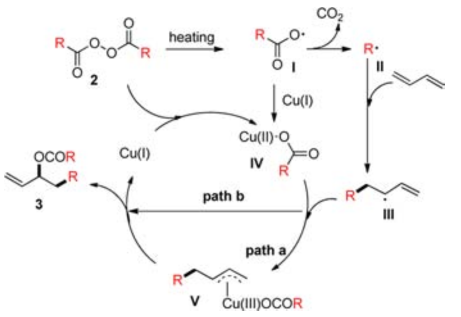
Scheme 2. Radical Trapping Experiments



Scheme 3. Crossover Reactions between Two Symmetrical (a,b) or One Unsymmetrical Diacyl Peroxides (c)



Scheme 4. Proposed Catalytic Cycle for Alkylesterification of Butadiene



Considering the results of the mechanistic experiments, a two-stage, radical mediated catalytic cycle is proposed (Scheme 4). Alkyl diacyl peroxides decompose under heating conditions (with or without the involvement of the copper catalyst) to afford alkyl radicals (II), CO_2, and copper(II) acyl species (IV). The alkyl radicals couple with 1,3-dienes to generate new allylic radicals (III). The regioselectivity pattern observed during the addition to substituted dienes implies that the alkyl radicals add to the least sterically hindered position in order to generate the allylic radical having the greatest degree of substitution, hence the highest stability. This alkyl radical reacts with the copper(II) acyl species forming a copper(III) species (V). And after reductive elimination preferentially at the most substituted carbon, the final products are formed, and the copper(I) catalyst is regenerated (path a).[14f−h,15] The alternative possible pathway is depicted in path b, with a copper(II) species (IV) transferring the acyl group to the allylic radicals and regenerating the copper(I) catalyst. Further studies to uncover the nature of active copper species are currently underway.

In summary, we have developed a new method that provides an efficient access to branched allylic esters from 1,3-dienes including products with a newly generated fully substituted carbon, which are difficult to access by other methods. The regioselectivity of the reaction is excellent, with only 1,2-alkylesterification products isolated. The reaction conditions are mild, and no extra reagent is needed in this reaction. A particular advantage of this reaction is using readily available difunctionalization reagents (diacyl peroxides) to simultaneously generate two different types of radicals, acyloxy and alkyl, after releasing one CO_2 molecule. The idea that 1,3-dienes combining diacyl peroxides could be a more versatile replacement for olefins is under investigation in other types of difunctionalizations.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03399.

Experimental details and NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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