Cobalt-catalyzed oxidative esterification of allylic/benzylic C(sp^3)–H bonds

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ABSTRACT

A protocol for the cobalt-catalyzed oxidative esterification of allylic/benzylic C(sp^3)–H bonds with carboxylic acids was developed in this work. Mechanistic studies revealed that C(sp^3)–H bond activation in the hydrocarbon was the turnover-limiting step and the in-situ formed [Co(III)]Ot-Bu did not engage in hydrogen atom abstraction (HAA) of a C–H bond. This protocol was successfully incorporated into a synthetic pathway to β-damascenone that avoided the use of NBS.

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1. Introduction

As a result of its wide applications, esterification is one of the most fundamental and important reactions in organic chemistry and in the synthesis of many natural products, pharmaceutical molecules and fine chemicals.[1] Consequently, considerable attention has been directed towards the development of practical and efficient strategies for ester synthesis.[2] One highly efficient approach is direct C(sp^3)–H oxidative functionalization, thereby converting alkanes into esters, either as the carboxylic or alkoxy unit.[3–5] However, the development of direct and selective methods for alkane functionalization remains in its infancy due to the low reactivity of C(sp^3)–H bonds.[6]

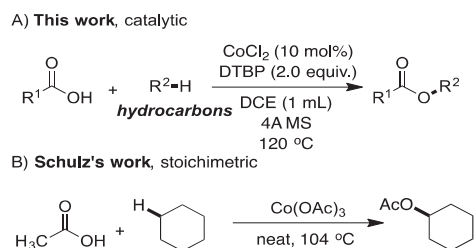Various types of peroxides have been employed as stoichiometric oxidants and often as the sources of oxygen functionality in transition-metal[3,4,7] or metal-free-catalyzed[5,8] oxidative esterification through a radical mechanism. Until now, copper catalysis using peroxides as oxidants has been developed into a well-defined methodology for C(sp^3)–H bond esterification.[3] In principle, they are related to the classic Kharasch-Sosnovsky reaction.[9] In contrast, no study has been focused on cobalt, the other reported Kharasch-Sosnovsky catalyst.[9a] The ability of Co(II) complexes to dissociate peroxides, together with much other experimental, mainly kinetic, evidence, has led to the widely accepted opinion that their function is primarily to generate free radicals.[10] However, direct attack on the C(sp^3)–H σ bond by Co(III) species formed in situ may also be operative (Scheme 1B).[11,12] Most importantly, the behavior of Co(III) complexes may be significantly different from that of Cu(II)

Scheme 1. Cobalt-mediated direct esterification of C(sp^3)–H bonds.

complexes in the oxidation of alkyl radicals. As previously reported by Kochi,[11b] the former favors oxidative substitution over oxidative elimination. Therefore, we considered to explore the limits and scope of the cobalt-catalyzed oxidative esterification of hydrocarbons with carboxylic acids in the presence of a peroxide as the oxidant (Scheme 1A).

2. Results and discussion

First, we identified effective precatalysts and conditions for the intermolecular esterification of unactivated C–H bonds by evaluating the reactivity of benzoic acid (**1a**, 0.5 mmol) and cyclohexene (**2a**, 10.0 equiv.) with various cobaltous salts (0–30 mol%) and t-BuOOt-Bu (DTBP). As shown in Table 1, the desired allylic ester cyclohex-2-en-1-yl benzoate (**3aa**) was produced, accompanied by a significant amount of [1,1'-bi(cyclohexane)]-2,2'-diene (**5a**). In

Table 1
Development of the intermolecular oxidative esterification of benzoic acid (**2a**) with cyclohexene (**1a**).[a]

Entry	Cat.	Solvent	Yield (%)[b]			
			3aa[h]	**4a**[h]	**5a**[i]	**6a**[i]
1	CoCl$_2$	–	19	3	13	6
2	CoCl$_2$	EAC	10	2	6	7
3	CoCl$_2$	DCE	29	2	13	6
4	CoCl$_2$	CH$_3$CN	28	1	4	6
5	CoCl$_2$	PhCF$_3$	37	2	17	4
6	CoI$_2$	DCE	27	1	10	5
7	Co(OH)$_2$	DCE	7	1	14	6
8	Co(OAc)$_2$	DCE	9	1	13	7
9	Co(acac)$_2$	DCE	9	1	13	6
10[c]	CoCl$_2$	DCE	46	4	10	6
11[c,d]	CoCl$_2$	DCE	21	3	8	5
12[c,e]	CoCl$_2$	DCE	17	2	6	3
13[c,f]	CoCl$_2$	DCE	74	1	8	4
14[c,f,g]	CoCl$_2$	DCE	82	1	6	5

[a] Reaction conditions: **1a** (0.5 mmol), **2a** (10.0 equiv.), cat. (5 mol%), DTBP (2.0 equiv.), solvent (1 mL), 100 °C, 24 h, under argon.
[b] Yields determined by GC with biphenyl as an internal standard.
[c] Cat. (10 mol%).
[d] DTBP (1.5 equiv.).
[e] DTBP (1.0 equiv.).
[f] MS (4A, 165 mg).
[g] 120 °C, 18 h.
[h] Yield calculated based on **1a**.
[i] Yield calculated based on DTBP; DCE = 1,2-dichloroethane, EAC = ethyl acetate.

addition, side products methyl benzoate (**4a**) and 3-methylcyclohex-1-ene (**6a**) were also detected, the proportion of which varied with the conditions used. The combination of CoCl$_2$ and DTBP was crucial for catalysis (entry 3), while other cobaltous salts provided reduced yields of **3aa** (entries 6–9). Independently investigating the reaction efficiency as a function of the catalyst amount indicated that a certain loading of catalyst was required for high selectivity towards the ester (entry 10 vs. 3 and Fig. S1). For example, introducing either less than 5 mol% or more than 15 mol% CoCl$_2$ resulted in markedly lower yields of the C–H esterification product. In addition, a higher dosage of oxidant (2.0 equiv.) than the theoretical amount (1.0 equiv.) was necessary to achieve an optimal result (entries 10–12). Moreover, a moderate amount of molecular sieves (MS, 4A, 165 mg) was found to be a requisite additive, probably functioning as a desiccant in the reaction (entry 13 vs. 10). Notably, a remarkably decreased yield of **3aa** was observed when the reaction time was extended from 18 h to 24 h (entry 14 vs. 13 and Fig. S2). Under the optimized conditions, **1a** smoothly reacted with **2a** (10.0 equiv.) in the presence of CoCl$_2$ (10 mol%) and DTBP (2.0 equiv.) in DCE (1 mL) at 120 °C to provide cyclohex-2-en-1-yl benzoate (**3aa**) in a high yield of 82% (entry 14).

We next examined the dependence of the C–H bond strength of the substrate on the selectivity for C–H esterification over C–C homocoupling when employing **2a** and DTBP with 10 mol% CoCl$_2$ at 120 °C (Table 2). Substrates **2g** (8%, entry 7), **2f** (1%, entry 6), **2e** (79%, entry 5) and **2a** (82%, entry 1) give the C–H esterification product in yields that generally increase with decreasing C–H bond strength. However, no ester was detected by either GC-MS or NMR measurements in the case of hydrocarbon R–H bonds of comparatively moderate strength, such as **2d** (entry 4), **2c** (entry 3) and **2b** (entry 2), under identical conditions. Instead, the respective C–C homocoupling product for **2d** and **2c** and 1,4-dihydronaphthalene/naphthalene for **2b** (formed upon the dehydrogenation of the

Table 2
Cobalt-catalyzed oxidative esterification of various C(sp^3)–H bonds with **2a**.[a]

Entry	R–H	C–H BDE [kcal mol^{-1}]	Yield (%)[b,c]
1	**2a**	82	**3aa** (82/80[d])
2	**2b**	83	**3ab** (N.D.)
3	**2c**	84	**3ac** (N.D.)
4	**2d**	86	**3ad** (N.D.)
5	**2e**	87	**3ae** (79/78[d])
6	**2f**	90	**3af** (1)
7	**2g**	97	**3ag** (8)
8[e]	**2g**	97	**3ag** (3)
9[f]	**2b**	83	**3ab** (33/32[d])
10[f]	**2d**	86	**3ad** (30/26[d])

[a] Reaction conditions: **1a** (0.5 mmol), **2** (10.0 equiv.), CoCl$_2$ (10 mol%), DTBP (2.0 equiv.), DCE (1 mL), MS (4A, 165 mg), 120 °C, 18 h, under argon.
[b] Yields determined by a combination of GC-MS (using the peak area normalization method) and ^{1}H NMR (with CH$_2$Br$_2$ as an internal standard).
[c] Yields calculated based on **1a**.
[d] Isolated yield.
[e] PhCF$_3$ (1 mL) used as a solvent.
[f] 12 h; N.D. = not detected.