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N-Heterocyclic Carbene Palladium Catalyzed Regioselective Oxidative Trifluoroacetoxylation of Unactivated Methylene sp^3 C−H Bonds in Linear Alkyl Esters

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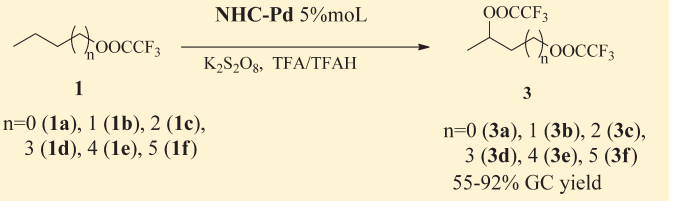
ABSTRACT: Several N-heterocyclic carbene palladium catalyzed oxidation of nonactivated sp^3 C−H bonds in linear primary and secondary trifluoroacetic acid esters have been developed. A high selectivity for the oxidation of the omega-1 carbon atom in trifluoroacetic acid *n*-propyl to *n*-octyl esters was realized by an appropriate choice of N-heterocyclic carbene palladium complexes.



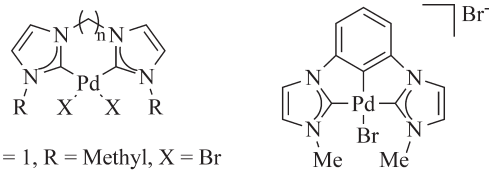
INTRODUCTION

The functionalization of unactivated C−H bonds remains a significant challenge in organic chemistry, owing to reactivity and selectivity problems. In principle, complementary selectivities are accessible by using radical,[1] carben(e)oid,[2] or nitren(e)oid[3] reactivities, which favor the functionalization of tertiary and secondary carbon atoms, or by using C−H activation in the coordination sphere of a transition metal, which on the basis of fundamental mechanistic studies favors the functionalization of primary (olefinic) and aromatic carbon atoms.[4] While an increasing number of transition metal catalyzed functionalizations of aromatic sp^2 C−H bonds provides efficient and more atom economic strategies in organic syntheses,[5] transition metal catalyzed functionalizations of unactivated sp^3 C−H bonds are much less common, and the inhibition of the catalytically active site by stronger donors than sp^3 C−H bonds usually poses a serious problem.[6−10]

In accordance with the aforementioned mechanistic results, exclusive selectivity for the functionalization of methyl vs methylene carbon atoms in the coordination sphere of transition metals was experimentally observed in the rhodium/iridium catalyzed borylation,[7] the platinum catalyzed silylation,[8] and the iridium catalyzed dehydrogenation[9c] of alkane C−H bonds. The chelate assisted alkane C−H functionalizations so far known, i.e., the palladium catalyzed arylation of alkyl side chains,[10] the palladium catalyzed oxidative acetoxylation of O-methyl oximes,[11] or related electrophilic C−H functionalizations of α-amino[12] or carboxylic acids[13] under platinum catalysis, yield highly selective (or exclusive) methyl vs methylene functionalized products. Here, we report the palladium catalyzed oxidative trifluoroacetoxylation of trifluoroacetic acid esters, which proceed with both chelate assistance and with so far unprecedented selectivity for methylene vs methyl functionalization.

RESULTS AND DISCUSSION

High thermal stability and resistance under acidic conditions of palladium N-heterocyclic carbene (NHC) complexes **A**−**F**



A: n = 1, R = Methyl, X = Br
B: n = 1, R = Methyl, X = Cl
C: n = 2, R = Methyl, X = Br
D: n = 3, R = Methyl, X = Br
E: n = 1, R = n-Butyl, X = Br
F

Figure 1. Palladium NHC complexes under investigation.

were chosen as precatalysts, which were prepared using slightly modified literature procedures (Figure 1).[14] The catalytic system under investigation consists of palladium NHC complexes **A**−**F**, trifluoroacetic- acid/-anhydride (TFAH/TFA), and potassium peroxodisulphate.

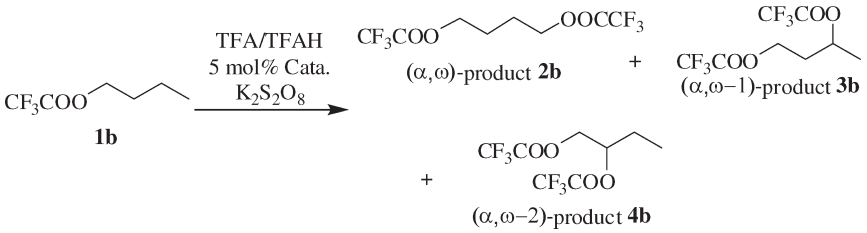
Initial experiments were conducted with trifluoroacetic acid butyl ester (**1b**) as a substrate in order to ascertain optimal reaction conditions by varying the catalyst, the reaction temperature, the amount of oxidant, and the reaction time (Table 1).

The yield of the combination of **2b** and **3b** was consistently above 90% after 36 h at 80 °C in the presence of 6 equiv of $K_2S_2O_8$ and 5 mol % of catalysts **A**−**E**, whereas complex **F** was somewhat less active (80%), indicating that the efficiency of bis(NHC)Pd complexes as catalysts was ascertained.

Figure 2 shows ^{13}C NMR spectra of the neat liquid reaction mixture (Table 1, entry 4) after 4, 18, and 36 h at 80 °C in the presence of 6 equiv of $K_2S_2O_8$ and 5 mol % of catalyst **D**. Significantly, independent of the conversion of **1b**, 1,4-di(c)butane (**2b**) and 1,3-di(trifluoroacetoxy)-butane (**3b**) in a ca. 1:7.3 ratio were formed, while no 1,2-di(trifluoroacetoxy)-butane (**4b**) and

Received: June 6, 2011
Published: October 11, 2011

Table 1. Optimization of the Reaction Conditions for Trifluoroacetoxylation of 1-Trifluoroacetoxybutane 1b[a]



entry	catalyst	1b/$K_2S_2O_8$ (mol/mol)	temperature (°C)	yield 2b (%) [b]	yield 3b (%)[b]
1	**A**	1:6	80	13	78
2	**B**	1:6	80	12	79
3	**C**	1:6	80	12	78
4	**D**	1:6	80	11	80
5	**E**	1:6	80	13	78
6	**F**	1:6	80	10	70
7	**D**	1:1.2	80	7	42
8	**D**	1:3	80	9	56
9	**D**	1:5	80	10	71
10	**D**	1:6	50	trace	10
11	**D**	1:6	60	6	33
12[c]	**D**	1:6	80	5	38
13[d]	**D**	1:6	80	0	0
14	**D**	1:6	70	7	42
15	**$Pd(OAc)_2$**	1:6	80	trace	trace
16		1:6	80	trace	trace

[a] Conditions: 5 mol % catalyst, 1 mmol of **1b** in 2 mL TFA/TFAH (6:1, v/v), 36 h. [b] The yield was determined by gas chromatography (perfluorononane as internal standard). [c] 18 h. [d] 4 h.

1,1-functionalized product were found. In addition, palladium acetate gave trace products and rapid formation of palladium black. Therefore, the NHC ligands in **A**−**F** are believed to stabilize the catalytically active species. Control experiments in the absence of the catalysts showed trace products, thus pointing to a palladium catalyzed reaction in presence of complexes **A**−**F**. As complex **D** proved to be most active, further studies were conducted in the presence of **D** as precatalysts.

With these optimized complementary reaction conditions in hand, we then explored the trifluoroacetoxylation of trifluoroacetic acid *n*-propyl to *n*-octyl esters (**1a**−**f**). First of all, methylene functionalization (α, ω-1) products were formed predominantly in these reactions, which were unequivocally identified by the high field methyl doublet (ca. δ 1.7−1.9 ppm) in the ^{1}H NMR spectra. While 1-(trifluoroacetoxy)propane (**1a**) gave higher amounts of the methyl functionalized (α,ω)-product as compared to **1b**, methylene functionalization still dominates by a 1.6:1 ratio. An even higher selectivity for the oxidation of methylene vs methyl carbon atoms was evident when C_5- to C_8-trifluoroacetic acid esters **1c**−**f** were subjected to identical reaction conditions. In these experiments, no methyl-functionalized (α,ω)-products could be detected by comparison to gas chromatography (GC) and NMR analyses of independently prepared samples. Moreover, a significant discrimination of different methylene groups was observed, placing the oxidated methylene groups only in the (α,ω-1)-position for C_5-ester **1c** and both (α,ω-1)-position and (α,ω-2)-position for C_6- to C_8-esters **1d**−**f** (Figure 3). It has to be noted, however, that with increasing chain lengths of **1**, increasing amounts of diastereomeric mixtures of higher oxidation products are formed and their conversions decreased.

An instructive formation of trifunctionalized oxidation products avoiding complicated diastereomeric mixtures was accomplished by reacting C_3- to C_7-α,ω-di(trifluoroacetoxy)alkanes (**2a**−**d**) as substrates. Notably, the main products (GC yields) are α,β,ω-trifunctionalized products for **2a** (23%) or **2b** (48%) and α,γ,ω-trifunctionalized products for **2c** (55%) or **2d** (76%) after 50 h, 80 °C, 6 equiv $K_2S_2O_8$, 5 mol % **D**. Moreover, 19% α,α,ω-trifunctionalized products were detected in the reaction mixture of **2b**, and 16% α,β,ω-tri(trifluoroacetoxy)alkane from **2c** (Figure 4).

These data are consistent with a chelate assisted oxidative alkane trifluoroacetoxylation, which, in contrast to already known chelate assisted alkane functionalizations catalyzed by palladium,[10,11] exhibits high selectivity for the functionalization of methylene vs methyl groups. While α,α-functionalization of **1a**−**f** is not observed because of unfavorable small chelate ring-sizes, appropriate chelate sizes for the α,ω-functionalization **2b** to form α,α,ω-trifunctionalized products are accessible. The noticeable drop in the conversion of **2a** is likely also due to slower α,β-functionalization and as compared to α,γ-functionalizations.

On the basis of our observation and previous literature,[15] a possible mechanism for this trifluoroacetoxylation reaction is proposed (Scheme 1). First, ligand-directed C−H activation

dx.doi.org/10.1021/om200484g |*Organometallics* 2011, 30, 6053–6056

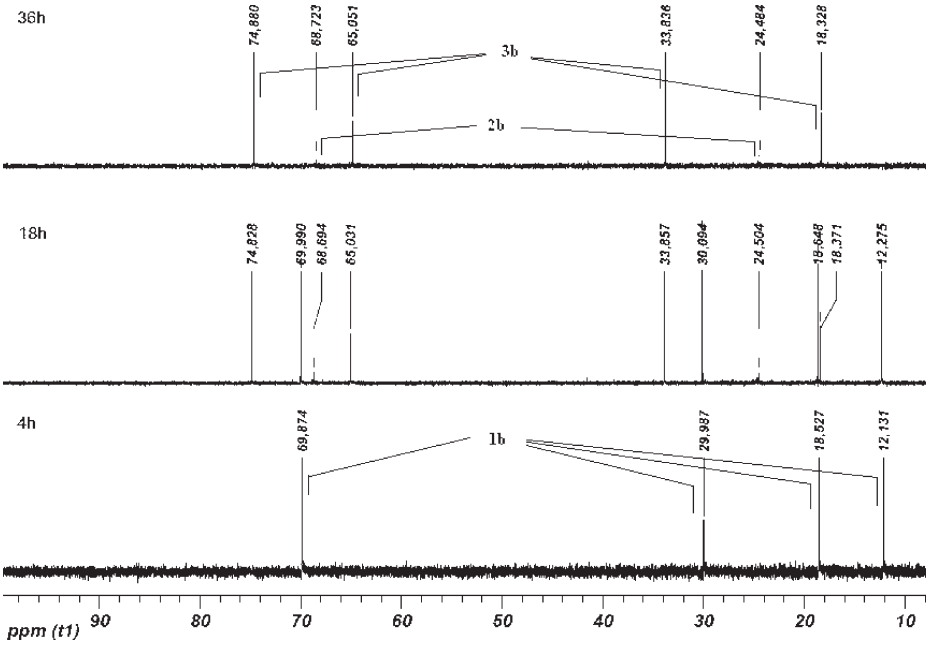


Figure 2. ^{13}C NMR spectra of the reaction mixtures of **1b** (Table 1, entry 4) after 4, 18, and 36 h. The signals for CF_3COO- have been omitted for clarity.

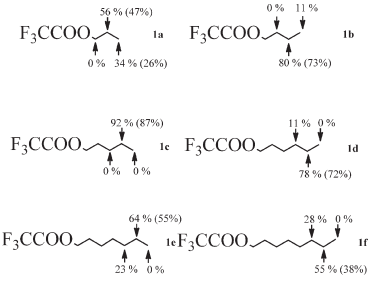


Figure 3. Bifunctionalized products obtained from linear (trifluoroacetoxy)-alkanes **1a**−**f** (the yield was determined by GC and the isolated yield is shown in parentheses).

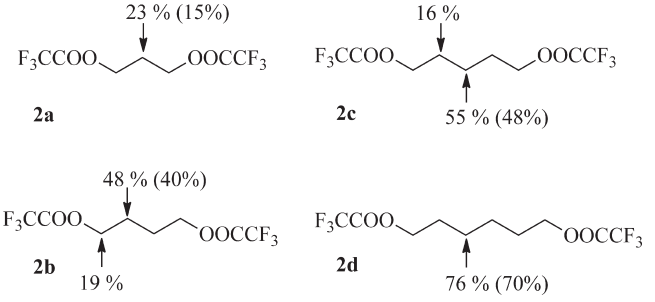


Figure 4. Trifunctionalized products obtained from α,ω-difunctionalized substrates **2a**−**d** (the yield was determined by GC and the isolated yield is shown in parentheses).

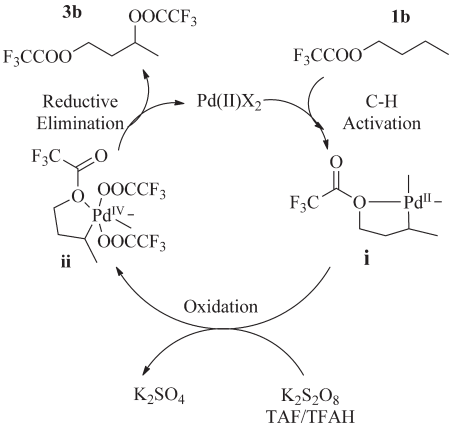
leads to the formation of a five-membered cyclopalladated intermediate (**i**), which is then oxidized to generate a Pd(IV) complex (**ii**). Subsequent reductive elimination releases the main product **3b**, and the catalyst is regenerated.

In conclusion, the oxidative trifluoroacetoxylation of aliphatic (trifluoroacetoxy)alkanes was presented. The combination of chelate assistance and selectivity for methylene groups allows for a moderate regiodiscrimination of aliphatic methylene groups in these substrates.

■ TYPICAL PROCEDURE

To a mixture of $K_2S_2O_8$ (6 mmol, 1.620 g) complex (0.05 mmol) in 2 mL TFA/TFAH (6:1) containing perfluorononane (120 μmol, 59 mg) was added 1 mmol of substrate in a gastight 8 mL screw top vial under air. The vial was closed, and the reaction mixture was heated under stirring in an aluminum block for 36 h at 80 °C. After cooling to room temperature, the vial was *carefully* opened to release oxygen overpressure. The solid was then separated by centrifugation, and the supernatant solution was subjected to NMR (neat reaction solution, benzene-d_6 capillary) and GC (perfluorononane as internal standard) analyses. Isolated yields were obtained from 20 mmol substrates after reaction and distillation.

Scheme 1. Plausible Mechanism for Trifluoroacetoxylation of 1-Trifluoroacetoxybutane 1b



dx.doi.org/10.1021/om200484g |*Organometallics* 2011, 30, 6053–6056

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ACKNOWLEDGMENT

Financial support from the National Science Foundation of China (Grant No. 20871032, 20971026) and Shanghai Leading Academic Discipline Project, Project Number: B108, is gratefully acknowledged.

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