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Cinchona alkaloid/TMAF combination: Enantioselective trifluoromethylation of aryl aldehydes

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ABSTRACT

The catalytic enantioselective trifluoromethylation reaction of aromatic aldehydes using the Ruppert–Prakash reagent (Me_3SiCF_3) has been disclosed, with an operationally simple procedure, based on the combination of sterically demanding cinchona alkaloid-derived phase-transfer catalyst **3b** with tetramethylammonium fluoride (TMAF). Our methodology provides medicinally important α-trifluoromethyl alcohols with high chemical yields and moderate to good enantioselectivities (50–70% ee).

1. Introduction

Asymmetric nucleophilic trifluoromethylation of carbonyl compounds using the Ruppert–Prakash reagent, (trifluoromethyl)-trimethylsilane, Me_3SiCF_3 represents one of the most fundamental approaches for the synthesis of optically active trifluoromethylated alcohols, which are important synthons for the preparation of drugs [1] such as Befloxatone [2] and Efavirenz [3]. Chiral trifluoromethylated alcohols are also attracting much attention in the field of material sciences, especially the development of novel liquid crystals [4]. Enantioselective trifluoromethylation was initially examined by Iseki and Kobayashi et al. in 1994. Chiral ammonium fluorides derived from cinchona alkaloids catalyzed the trifluoromethylation of aryl ketones to furnish the corresponding trifluoromethylated alcohols with low to moderate enantioselectivities, up to 48% ee [5]. After the initial report, considerable effort was devoted to the development of an efficient catalytic system for the nucleophilic enantioselective trifluoromethylation reaction [6]. In 2007, we disclosed a novel protocol for the first highly enantioselective nucleophilic trifluoromethylation reaction of aromatic ketones based on the combination of ammonium bromide of cinchona alkaloid **3a** with tetramethylammonium fluoride (TMAF), furnishing tetrasubstituted aryl trifluoromethyl alcohols in high yield with high enantioselectivity up to 94% ee [7]. This cinchona alkaloid **3a**/TMAF combination was also found to be effective for the enantioselective trifluoromethylation of alkynyl ketones with up to 98% ee [8] and it was applied to the first catalytic asymmetric synthesis of Efavirenz [9]. However, this catalytic system involving the **3a**/TMAF combination was not effective for the enantioselective trifluoromethylation of aryl aldehydes. We then reported the chiral crown ether-catalyzed enantioselective trifluoromethylation reaction of aldehydes, but observed that enantioselectivities were not satisfactory (up to 44% ee) [10]. Very recently, Chen et al. reported catalytic enantioselective trifluoromethylation of aromatic aldehydes using (IPr)CuF and quinidine-derived quaternary ammonium salt as the cooperative catalyst, however ee values are still improvable (up to 81% ee) [11]. As part of our ongoing research programs directed at the development of efficient methodologies for the asymmetric trifluoromethylation using Me_3SiCF_3 [7–10,12], we herein report the enantioselective trifluoromethylation of aromatic aldehydes by employing our catalytic combination system consisting of sterically demanding cinchona alkaloid **3b** and TMAF (Scheme 1).

2. Results and discussion

Although our previous attempts were unsuccessful for the enantioselective trifluoromethylation of aryl aldehydes by the **3a**/TMAF combination (0% ee by catalyst **3a**, Scheme 2), the advantage of this cinchona alkaloids/TMAF combination catalysis is the ease with which chiral catalysts as a partner of TMAF for enantioselective trifluoromethylation of target substrates can be screened. Thus, we started our investigation with the trifluoromethylation of 2-naphthaldehyde **1a** in the presence of a catalytic amount of

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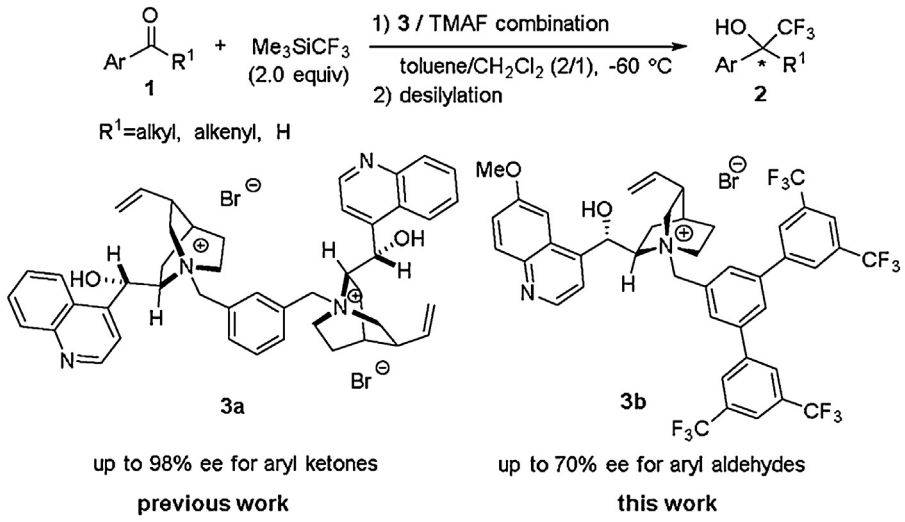
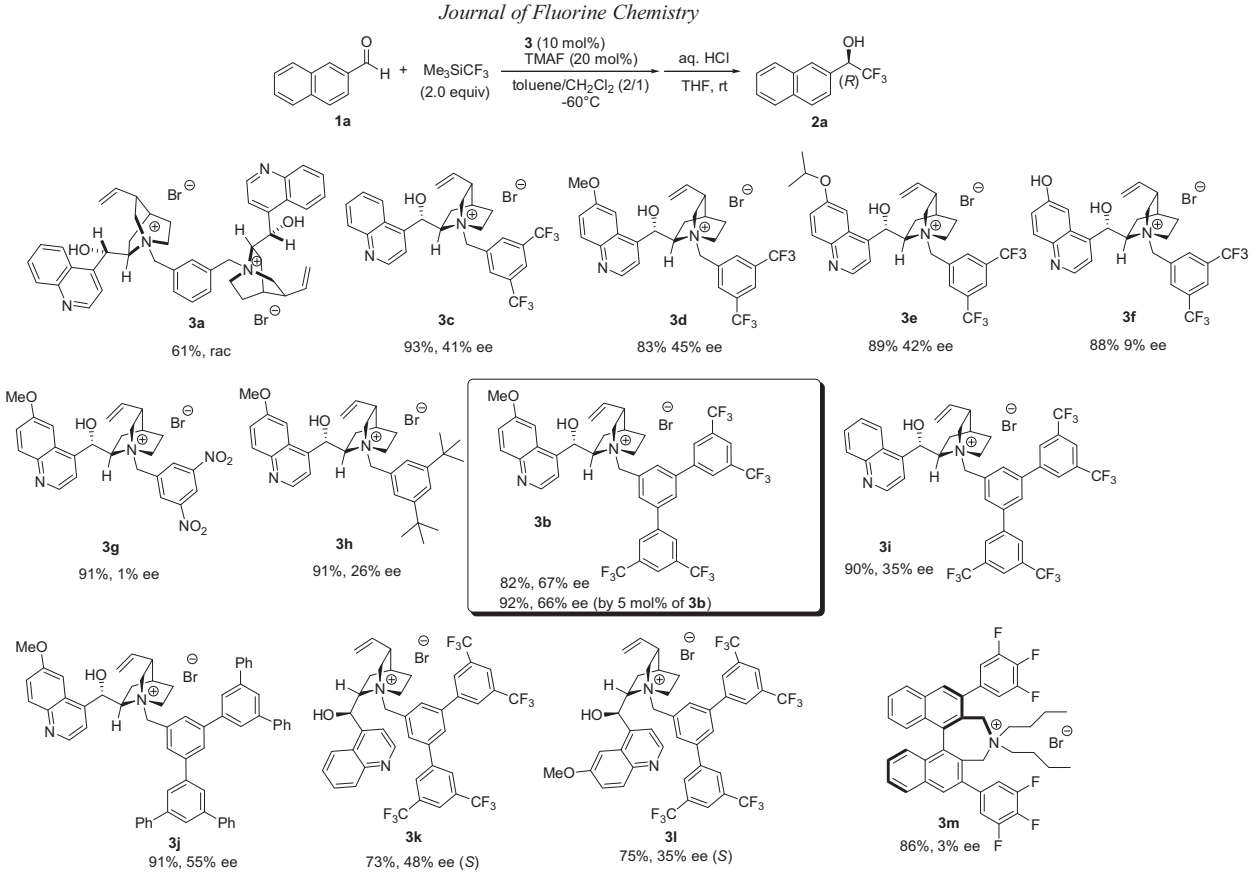


Scheme 1. Cinchona alkaloids/TMAF combination for enantioselective trifluoromethylation of aryl ketones and aryl aldehydes.

TMAF with Me_3SiCF_3 in toluene/CH_2Cl_2 (2/1) at −60 °C, and screened a broad range of ammonium bromides to find out a proper catalyst. The results are summarized in Scheme 2. The reaction catalyzed by **3c** produced (*R*)-**2a** in 93% yield with 41% ee. The enantioselectivity improved slightly to 45% ee using **3d**. The catalyst **3e**, which has isopropyl moiety on the quinoline ring, was found to be a little inferior to **3d** for this transformation (42% ee). Cupreidine-derived ammonium bromide **3f** gave **2a** in 88% with only 9% ee. Catalyst **3 g** having electron-withdrawing nitro groups was next investigated to furnish a disappointing result with no chiral induction (1% ee). N-3,5-Bis(*tert*-butyl)benzylqunidinium bromide (**3h**) was found to be less effective (26% ee). To our delight, when catalyst **3b** containing a sterically very demanding 3,5-bis(trifluoromethyl)phenyl benzyl group on the nitrogen was used, the enantioselectivity of **2a** improved effectively up to 67% ee. Catalyst loading of **3b** could be reduced to 5 mol% without any loss of enantioselectivity (66% ee). Other catalysts **3i** and **3j**, having a sterically demanding benzyl group, were less effective for this



Scheme 2. Screening of 3 as a partner of TMAF combination for enantioselective trifluoromethylation of naphthyl aldehyde **1a**.