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Enantioselective palladium-catalyzed addition of malonates to 3,3-difluoropropenes

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ABSTRACT

Monofluoroalkenes bearing a malonate unit at the β position can be synthesized by the enantioselective addition of diesters to 3,3-difluoropropenes. The difference in reactivity regarding the geometry and the substituents of the alkene of the 3,3-difluoropropenes, as well as the alkyl groups of the malonates, was studied and limitations were identified. The reaction was also performed with different 3,3-difluoropropenes. Further synthetic transformations of a newly functionalized monofluoroalkene were also accomplished.

1. Introduction

The fluorine atom presents unique and interesting properties [1], which explains the importance of its incorporation in organic molecules for applications in medicinal chemistry, agrochemistry and material sciences [2–4]. Of all the fluorinated motifs, monofluoroalkenes are useful as non-hydrolyzable amide bonds or enol ethers isosteres [5,6]. Numerous synthetic strategies towards monofluoroalkenes have been developed over the years [7]. Our group has been particularly interested in using 3,3-difluoropropenes as starting materials to access monofluoroalkenes using catalyzed or metal-free process (Fig. 1a) [8–10]. In this context, we recently reported the palladium-catalyzed addition of dimethylmalonate and its derivatives to different 3,3-difluoropropenes (Fig. 1b) [11]. Many monofluoroalkenes bearing a malonate at the β position were obtained in up to 78% yield. As a preliminary result, we also disclosed that the reaction of trisubstituted alkene (*E*)-**1** provided the chiral monofluoroalkene **2** in 56% yield and 55% ee using (*R*)-BINAP as the chiral ligand (Fig. 1c), a rare example of enantioselective reaction involving the activation of a C–F bond [12]. Herein, we report our progress based on this initial result (Fig. 1d). Specifically, optimization of the chiral ligand and a study of the reactivity depending on the geometry of the alkene, on its substituents and on the alkyl groups of the malonate was performed, as well as the extension of the reaction on different 3,3-difluoropropenes. This study allowed the identification of some limitations. Synthetic transformations were also accomplished on a monofluoroalkene.

2. Results and discussion

The enantioselective palladium-catalyzed addition of dimethylmalonate was first studied on 3,3-difluoropropene (*E*)-**1** and the initial screening of chiral ligands is summarized in Table 1. As reported previously [11], (*R*)-BINAP provided the higher ee at this point (55% ee) [13], compared to (*R*)-DM-BINAP (<1% ee) and (*R,S*)-JOSIPHOS (17% ee). Further screening revealed that (*R*)-SEGPHOS (78% ee) was superior that its more hindered analogs: (*R*)-DM-SEGPHOS (59% ee) and (*R*)-DTBM-SEGPHOS (29% ee). While (*S*)-MeO-BIPHEP also gave interesting results (−74% ee), it was decided to pursue the study with (*R*)-SEGPHOS.

Further optimization of the reaction conditions was then undertaken (Table 2). A screening of solvents (Table 2, entries 1–9) showed that when the reaction was run in toluene, Et_2O or CH_2Cl_2, low yields and similar enantiomeric excess were observed compared to THF. Using of CH_3CN, dioxane or 2-methyl(tetrahydrofuran) provided similar results to THF. Interestingly, performing the transformation in CH_2Cl_2 afforded **2** with a

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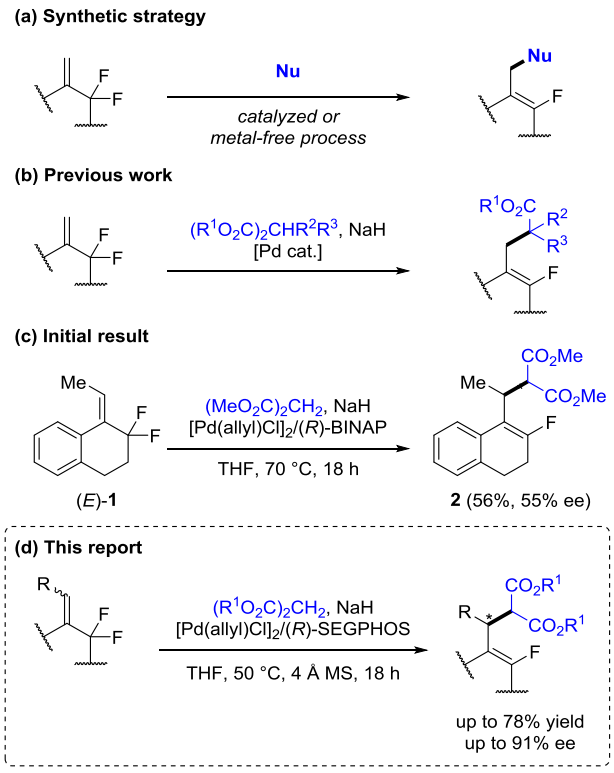


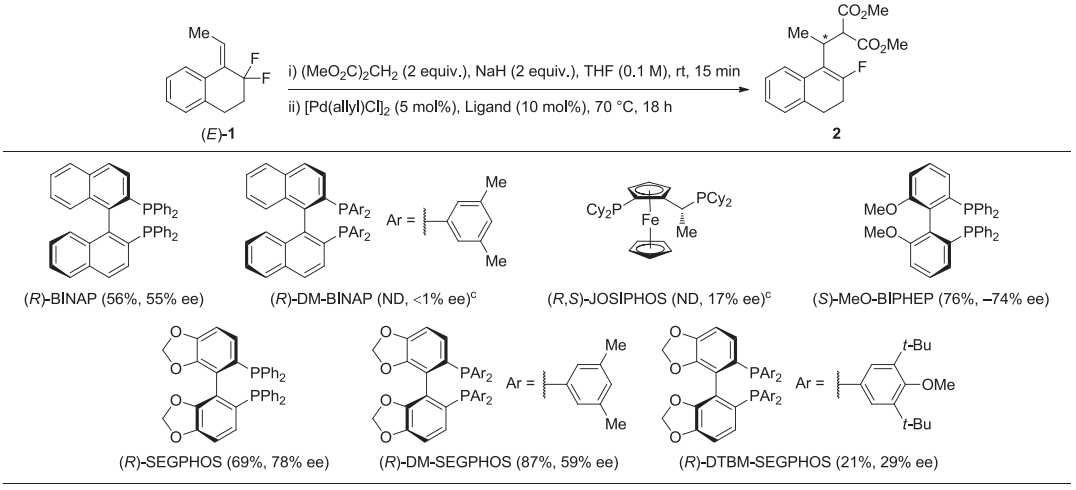
Fig. 1. Previous work, initial result and current work.

higher enantiomeric excess (Table 2, entry 7), however, in low yield due to an incomplete conversion. A mixture of CH_2Cl_2 and THF was explored, but no improvement was observed (Table 2, entries 8–9). To counter the formation of unidentified side products, lower temperatures (Table 2, entries 10–11) were tested, and 50 °C was found to be the most efficient. It was noted that using 20 mol% of (*R*)-SEGPHOS (Table 2, entry 12) provided a small increase of the enantiomeric excess, but at the expense of the yield due to purification issues. Other bases were screened (Table 2, entries 13–17), but no formation of the final product was observed. Finally, using 15 mol% of (*R*)-SEGPHOS and adding 4 Å molecular sieves in the reaction mixture provided a good compromise between yield and enantioselectivity as **2** was isolated in 75% yield with 80% ee (Table 2, entry 19).

In parallel, a few additional ligands structurally-related to SEGPHOS were screened (Table 3) using the conditions reported in entry 12 of Table 2. No reaction was observed at 50 °C when using (*R*)-DIFLUORPHOS. However, at 70 °C, the product was obtained in 45% yield and 30% ee. In the case of (*R*)-SYNPHOS, a good yield was obtained (79%), but with lower enantioselectivity (33% ee) compared to (*R*)-SEGPHOS. Finally, (*R*)-C_3-TunePhos gave the monofluoroalkene with a better yield, but with a lower enantiomeric excess than with (*R*)-SEGPHOS (70%, 62% ee). In the end, (*R*)-SEGPHOS provided the highest enantioselectivity and the conditions used in entry 19 of Table 2 were used for the rest of the study.

As the synthesis of the 3,3-difluoropropenes allowed, in some cases (vide infra), the separation of the (*E*) and (*Z*) isomers, the effect of the alkene geometry on the reaction was studied (Table 4). Higher yield and enantiomeric excess were observed starting from (*E*)-**1** (75%, 80% ee) compared to (*Z*)-**1** (66%, 55% ee) [14]. Furthermore, when a 29:71 E/*Z* mixture of **1** was used, the reactivity was found to be closer to that of (*Z*)-**1** (68%, 58% ee). The difference may be due to the nature of the diastereomeric π-allyl complex formed [15]. Indeed, in the case of the (*E*) isomer, the most stable syn π-allyl complex is initially produced while with the (Z) isomer, the less stable anti π-allyl complex would be generated. The latter could isomerize via a σ-π-σ mechanism producing a mixture of diastereomeric π-allyl complexes, with different (and lower) enantioselectivity. Afterwards, the influence of the alkene substituent was evaluated. The replacement of the methyl group by an ethyl moiety resulted in a considerable decrease in the yields for both (*E*)-**3** (15%) and (*Z*)-**3** (32%), probably due to an increase in the steric hindrance. Interestingly, the reaction showed a similar enantioselectivity with

Table 1
Initial screening of ligands[a,b].



[a]Isolated yield of **2**.

[b]The ee's were determined by chiral HPLC.

[c]The yield could not be determined. Numerous side products were present in the crude mixture and purification only provided a small pure sample for HPLC analysis.