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Zinc-mediated enantioselective addition of terminal 3-en-1-ynes to cyclic trifluoromethyl ketimines

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ABSTRACT

A facile enantioselective addition of terminal 3-en-1-ynes to cyclic *N*-acyl trifluoromethyl ketimines is reported. In the presence of Zinc/BINOL complexes, a series of enynylated tertiary carbinamines were readily obtained in 90–97% yield with 70–97% enantiomeric excess in a single chemical operation under mild reaction conditions.

1. Introduction

The incorporation of CF_3 group into organic molecules can substantially alter their physical properties, such as metabolic stability, lipophilicity and conformational behavior [1]. In particular, the presence of the strong electron-withdrawing CF_3 group adjacent to the C—N bond makes α-(trifluoromethyl)-amines function as an effective peptide bond replacement by generating a metabolically stable, poorly basic amine [2]. Owing to these promising properties, α-(trifluoromethyl)-amines have been found wide applications in pharmaceuticals and chemical biology [3]. For the enantioselective preparation of α-(trifluoromethyl)-amines, a variety of efficient methods has been established which include catalytic hydrogenation [4], nucleophilic addition to trifluoromethylated imines [5], and trifluoromethylation of imines [6]. Among these, the nucleophilic addition of terminal alkynes to fluorinated imines represents a convergent and efficient approach to the synthesis of optically active propargylic amines [7]. In this context, a great effort has been devoted the development of highly selective metal-promoted systems for these enantioselective alkynylation reactions [8]. However, despite significant progress in this area, previous studies are mainly focused on simple terminal alkynes as nucleophilic species [9]. In particular, the terminal 3-en-1-ynes as nucleophiles could rapidly provide enyne carbinamines which are present in some biologically important natural products and medicinally relevant synthetic compounds [10]. Recently, our group has disclosed that terminal 3-en-1-ynes could act as a suitable nucleophilic species for the enynylation of *N*-sufonyl aldimines and ketones catalyzed by chiral metal complexes, which provide enynylated amine and alcohol adducts in a single chemical operation with excellent chiral induction [11]. Thus, encouraged by these results and as a part of our continuous interests in the synthesis of new class of chiral trifluoromethylated amines [12], herein, we report the results of our investigations on asymmetric enynylation of cyclic *N*-acyl trifluoromethyl ketimines. With this method, a range of chiral tertiary trifluoromethylated carbinamines were obtained with up to 97% yield and 97% *ee* in the presence of chiral Zinc-BIONL complexes. Notably, this study represents the first catalytic enantioselective enynylation of ketimines to access chiral trifluoromethylated tertiary carbinamines in a single chemical operation. Moreover, the obtained dihydroquinazolinones bearing the trifluoromethyl moiety at the quaternary stereogenic carbon center are the core units present in many anti-HIV agents, such as DPC 961, DPC 963, and DPC 083 (Fig. 1) [13].

2. Results and discussion

On the basis of our precedent enantioselective diynylation of cyclic trifluoromethyl ketimines [9d], we first examined the model reaction of ketimine **1a** with enyne **2a** under otherwise identical reaction conditions. However, the use of chloramphenicol-amine derivatives as ligands together with dimethylzinc could only give up to 50% enantiomeric excess. Inspired by the success of enynylation of *N*-sufonyl aldimines catalyzed by chiral Zn-BINOL complexes [11b], we subsequently investigated the use of (1,1-binaphthalene)-2,2-diol (BINOL) derivatives as chiral inductor. As illustrated in Table 1, the 4-phenyl-

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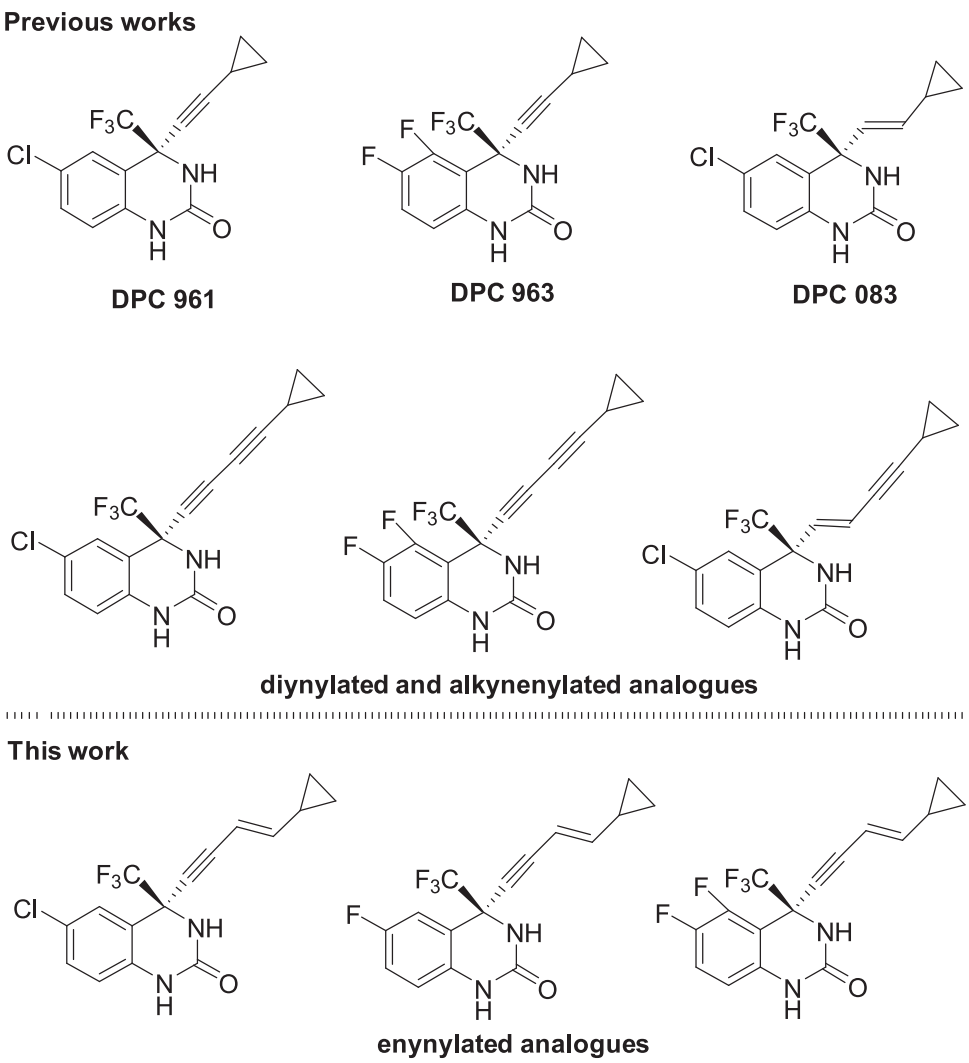

Fig. 1. Dihydroquinazolinone-based anti-HIV agents and analogues.

substituted ligand **L1** could deliver the desired product **3a** in 97% yield at room temperature in toluene, albeit with low enantioselectivity (28% *ee*, Table 1, entry 1). Subsequently, a series of BINOL-type ligands containing various groups at the 3,3′-positions of the binaphthol backbone were evaluated for the model reaction (Table 1, entries 2–12). To our delight, when the subsitituted group at the 3,3′-position of BINOL was a strong electron-withdrawing group such as trifluoromethyl group, nitrogroup, trifluoromethylsulfonyl group and multiple-fluorine atoms on the phenyl group, high enantiomeric excess up to 86% together with excellent yield was obtained (Table 1, entries 2–3, 9–10). On the contrary, low enantioselectivity was observed when electron-donating or electron-neutral subsititued groups was placed on the BINOL backbone (Table 1, entries 1, 4–5, 8). Moderate outcome was obtained for halogen-substituted BINOL at it's 3,3′-positions (entries 6–7). Finally, to further increase steric hindrance of strong electron-withdrawing groups on the substituted phenyl group of BINOL derivative, ligand **L11** and **L12** were prepared and employed in the reaction. Gradually, the *ee* of afforded product could be improved to 92%. Optimized reaction conditions regarding chemical yield and enantioselectivity was established with ligand **L12** by screening different solvents, lowering the reaction temperature, and the amount of ligand (entries 13–17). Overall, the addition reaction of terminal 3-en-1-yne **2a** to cyclic trifluoromethyl ketimines **1a** could be efficiently performed in toluene at 10 °C to afford the trifluoromethylated product **3a** in 97% yield and 94% *ee* with 10 mol% ligand **L12**.

With the optimized reaction conditions in hand, we then set out to investigate the substrate scope of this transformation. Representative results are summarized in Table 2. A series of phenylbuta-3-en-1-ynes substituted by different groups including electron-rich and electron-withdrawing groups or at different positions on the phenyl ring are all tolerated in the reaction and provided constantly excellent yields (90% to 97%) with *ee* values ranging from 69% to 97% (Table 2, entries 1–11). Generally, electron-donating substituted enynes deliver desired product with higher enantioselectivity than that of electron-withdrawing ones (for example, entry 2 *vs* 8, entry 3 *vs* 4, entry 4 *vs* 10). 2-Thiophenyl- and 2-naphthyl-substituted enynes were also feasible substrates, providing the corresponding products **3f** and **3g** both with 86% *ee*. Then, other cyclic *N*-acyl trifluoromethyl ketimines bearing electron-withdrawing, electron-donating, or electron-neutral groups on the phenyl ring were also probed under identical reaction conditions with enyne **2a**. Pleasingly, these substrates could undergo the enantioselective addition smoothly with excellent yield and high *ee* (entries 12–18). It is worth noting that di-substituted dihydroquinazolinones were also viable substrates, thus delivering **3n** with 95% *ee* (entry 14). Furthermore, chiral trifluoromethylated tertiary carbinamines **3s–3u,** which are the analogues of anti-HIV agents, were also obtained by employing but-1-en-3-yn-1-ylcyclopropane as nucleophile, albeit with decreasing enantioselectivity. However, notably, an improvement of the enantiopurity of adducts could be achieved by simple recrystallization (entries 3, 5, 8–11 and 17–21). Additionally, another alkyl-substituted enyne was also examined in this reaction, affording adduct **3v** with high yield and moderate enantioselectivity which is one limitation of current method (entry