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Highly enantioselective zinc/BINOL-catalyzed alkynylation of α-ketoimine ester: a new entry to optically active quaternary α-CF_3 α-amino acids†

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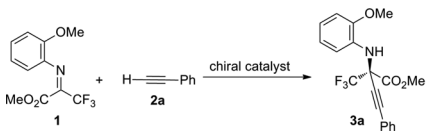
An effective method for highly enantioselective alkynylation of ketoimine (α-trifluoromethyl ketoimine ester) has been developed *via* a zinc/BINOL catalyzed process. This protocol provides a useful and facile access to optically active quaternary α-trifluoromethyl α-amino acids and related derivatives of interest in life sciences.

The potential of peptides as drug candidates is limited by their poor bioavailability and low stability in physiological conditions.[1] To circumvent these problems and improve the therapeutic profile of peptides, one of the important strategies is to use peptidomimetics.[2] Among the peptidomimetic approaches, introducing α-trifluoromethyl α-amino acids (α-Tfm-AAs)[3] into peptides is significantly promising. Due to the unique properties of the CF_3 group, such a special class of fluorinated amino acids could greatly influence the bioavailability of peptides by improving enzymatic stability and enhancing *in vivo* absorption as well as drug permeability through certain body barriers.[4] To date, however, only one example on the catalytic asymmetric synthesis of such valuable quaternary fluorinated amino acids has been reported, during our manuscript preparation.[5,6] Therefore, new methods for their widespread synthetic application are highly desirable.

As a part of our research,[7] we envisioned that the catalytic enantioselective alkynylation of α-CF_3 ketoimine ester might provide an attractive route to optically active quaternary α-Tfm-AAs. Through simple manipulations, the triple carbon–carbon bond offers a unique and highly valuable opportunity for further synthetic elaboration on the β,γ-positions of α-Tfm-AAs. In addition, the enantioselective alkynylation of ketoimines is a key step in the manufacturing of anti-HIV agent DPC961, which contains a CF_3 group at the tetra-substituted chiral center at a propargyl position.[8] However, from a synthetic standpoint, the catalytic enantioselective alkynylation of ketoimines is a great challenge, which has not been realized so far.[9–11] The main reason is that ketoimines are less reactive than aldimines, and it is difficult to discriminate the enantiofacial selectivity.[12] As a result, it significantly impeded the access of optically active tertiary propargyl amines to synthesize biologically active molecules. Herein, we describe the first example of catalytic enantioselective alkynylation of ketoimine (α-CF_3 ketoimine ester) in high yields with up to 99% ee. The low catalyst loading (5 mol% of BINOL), mild reaction conditions and high reaction efficiency and enantioselectivity of the zinc/BINOL catalyzed process provide a facile access to optically active quaternary α-Tfm-AAs and related derivatives.

We began our studies by choosing α-CF_3 ketoimine ester **1** and phenylacetylene **2a** as model substrates (eqn (1)).



(1)

Initially, a common chiral catalyst, Cu(I) salts together with 1,3-bis(oxazolin-2-yl)pyridine ligands (PyBox),[11a,c] was examined; however, undesired products instead of **3a** were obtained (see Table S1 in the Supporting Information). Other transition metal catalysts, such as $Sc(OTf)_3$ and $Zn(OTf)_2$, gave similar results. These negative results are presumably because the catalysts used above can also serve as Lewis acids which may destabilize the α-CF_3 ketoimine ester **1** and lead to the formation of side products. Thus, we assumed that using a pre-generated metal alkynilide in conjunction with a chiral ligand catalyst might avoid the decomposition of **1** and furnish the reaction in a catalytic enantioselective manner. To our delight, when the reaction was carried out with **1** (1.0 equiv.), **2a** (2.4 equiv.), Me_2Zn[13] (1.5 equiv.), and 10 mol% (*R*)-3,3′-Ph_2-BINOL **4a** in toluene at room temperature, the resulting Zn(II)/BINOL[14] catalytic system provided desired product **3a** in good yield (78%) with 87% ee. Encouraged by this preliminary result, we further investigated a series of reaction parameters (such as solvent effect and the ratio of **2a**/Me_2Zn), and found that the nature of solvent

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† Electronic supplementary information (ESI) available: Detailed experimental procedures, and analytical data for all new compounds and crystallographic for **6** (CIF). CCDC 816912. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c1cc10403a

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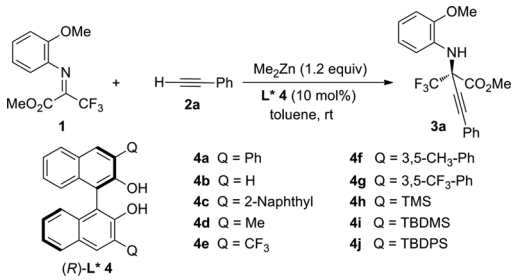
Table 1 Optimization of enantioselective addition of phenylacetylene **2a** to α-CF_3 ketoimine ester **1**[a]

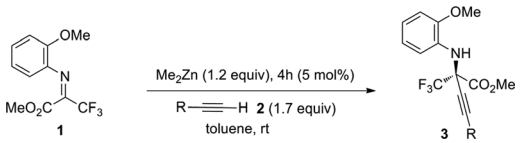


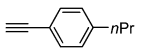
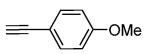
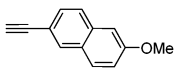
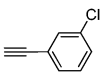
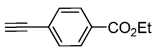
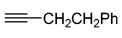
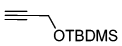
Entry	Chiral ligand	**3a** yield (%)[b]	ee (%)[c]
1	**4a**	90	85
2	**4b**	51	10
3	**4c**	86	74
4	**4d**	92	74
5	**4e**	91	84
6	**4f**	90	70
7	**4g**	85	88
8	**4h**	91	97
9	**4i**	93	91
10	**4j**	83	61
11[d]	**4h**	90	97.3 (98.3)
12[e]	**4h**	90	95.7 (96.1)

[a] Reaction conditions (unless otherwise specified): **1** (0.3 mmol), **2a** (2.0 equiv.), Me_2Zn (1.2 equiv.), **L* 4** (10 mol%), toluene (1.2 mL), 8 h rt. [b] Isolated yield. [c] Determined by chiral HPLC analysis after column chromatography and number in parentheses was obtained before column chromatography. [d] **2a** (1.7 equiv.), **4h** (5 mol%), 19 h, rt. [e] PMP instead of OMP was used for protecting α-ketoimine ester **1**.

is critical for the reaction efficiency (see Table S2 in the Supporting Information). Non-polar solvent toluene was the optimum reaction medium, and a higher reaction yield (90%) with a comparable enantioselectivity (85% ee) of **3a** was afforded, when 2.0 equiv. of **2a** and 1.2 equiv. of Me_2Zn in toluene were used. Other solvents, such as hexane, CH_2Cl_2, or $CHCl_3$, resulted in less effective results, either in yield or in enantiomeric excess. With these reaction conditions, different BINOL type ligands **4** modified at positions 3, 3′ were evaluated (Table 1). The results in entries 1–7 showed that both steric and electronic effects of the substituents at positions 3, 3′ of BINOL are critical to the reaction enantioselectivity. Moderately bulky and/or electron-deficient substituents led to good ee values (entries 1, 5 and 7), for example, the CF_3 group containing ligands **4e** and **4g** provided higher ee than their nonfluorinated counterparts. With this finding in mind, we then investigated the ligands with silyl groups, since the steric and electronic effects of the silyl group can be easily controlled by tuning the substituents on the Si atom (entries 8–10). When (*R*)-3,3′-TMS_2-BINOL **4h** was examined, the highest ee (97%) was observed (entry 8), while more bulky group, *tert*-butyldimethylsilyl (TBDMS) or *tert*-butyldiphenylsilyl (TBDPS), led to lower enantioselectivity (entries 9 and 10). Worthy of note is that even decreasing the loading of chiral ligand **4h** to 5 mol% with utilization of 1.7 equiv. of phenylacetylene **2a**, a compatible enantiomeric excess value (97% ee) with 90% yield of **3a** was still achieved (entry 11). Furthermore, we found that the protecting group *o*-methoxyphenyl (OMP) on the α-ketoimine ester **1** is not essential for the enantioselectivity of the reaction, since the replacement of OMP with *p*-methoxyphenyl group (PMP) resulted in a comparable enantiomeric excess (entry 12).

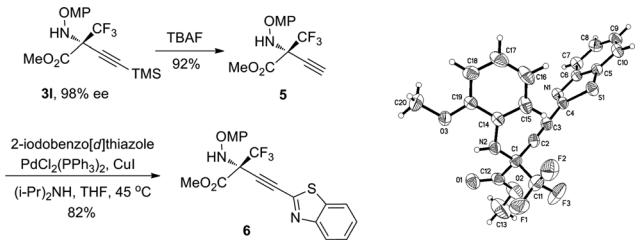
Table 2 Enantioselective addition of terminal alkynes **2** to α-CF_3 ketoimine ester **1**[a]



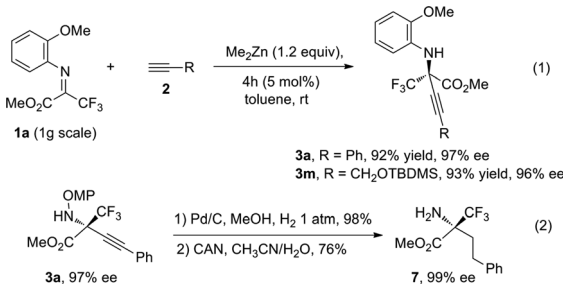
Entry	Alkyne **2**		**3** yield (%)[b]	ee (%)[c]
1	**2b**		**3b**, 92	97.5 (—)[d]
2	**2c**		**3c**, 87	95.9 (98.5)
3	**2d**		**3d**, 91	95.8 (96.0)
4	**2e**		**3e**, 90	93.9 (94.6)
5	**2f**		**3f**, 93	91.9 (91.9)
6[e]	**2g**		**3g**, 91	99.6 (99.5)
7	**2h**		**3h**, 91	98.2 (98.5)
8[f]	**2i**		**3i**, 91	97.6 (97.5)
9[e]	**2j**		**3j**, 86	95.6 (95.1)
10[e]	**2k**		**3k**, 95	95.9 (96.2)
11[f]	**2l**		**3l**, 84	97.7 (—)[d]
12[e]	**2m**		**3m**, 93	94.7 (—)[d]

[a] Reaction conditions (unless otherwise specified): **1** (0.3 mmol), **2** (1.7 equiv.), Me_2Zn (1.2 equiv.), **4h** (5 mol%), toluene (1.2 mL), 19–70 h RT. [b] Isolated yield. [c] Determined by chiral HPLC analysis after column chromatography and number in parentheses was obtained before column chromatography. [d] The ee can not be determined due to the impurity. [e] Using 2.5 equiv. of **2**. [f] Using 5.0 equiv. of **2**.

Under the optimum reaction conditions (Table 1, entry 11), the substrate scope of catalytic enantioselective alkynylation of α-ketoimine ester **1** was tested and representative results are illustrated in Table 2. A variety of terminal alkynes, including aryl-, alkyl-, and silyl-substituted terminal alkynes, are all suitable substrates for the reaction and provided good yields with excellent ee up to 99%. For all the aromatic terminal alkynes, the enantioselectivities depend on the electronic features of the substituents (entries 1–5). Electron-rich aryl alkynes (entries 1–3) provided slightly higher ee values than electron-deficient ones (entries 4–5). Conjugated alkyne **2g** also furnished reaction smoothly, affording **3g** in good yield with $>99\%$ ee (entry 6). It is noteworthy that terminal aliphatic alkynes, particularly the less studied and low steric 1-octyne **2k** (entry 10), provided the corresponding products in good yields with excellent ee values ranging from 96–98% (entries 7–10). Importantly, the successful highly enantioselective alkynylation of ketoimine by ethynylcyclopropane **2h** may offer a new strategy in the synthesis of anti-HIV drug DPC961[8] (entry 7). Functionalized terminal alkynes **2l–m** also tolerated the reaction conditions with excellent



Scheme 1 Determination of the absolute configuration of **3** by X-ray crystal structure of compound **6**.



Scheme 2 Gram-scale catalytic enantioselective synthesis of **3a** and **3m** and synthesis of **7**.

enantiomeric excesses up to 98%, providing feasibility for further functionalizations (entries 11–12).

It should be pointed out that for most of the reactions shown in Tables 1 and 2, we presented two ee values that were determined before and after column chromatography in view of the fact that trifluoromethyl group containing compounds are more prone to self-disproportionation of enantiomers (SDE) under the conditions of achiral chromatography reported by the Soloshonok group recently.[15,16] From the results illustrated in Tables 1 and 2, we can see the ee values obtained before column chromatography are similar to those obtained after (the sample used for determining ee is a mixture of all of the collected product after silica gel column chromatography), suggesting that the ee values obtained after purification are not influenced by the SDE effect.

The absolute configuration of **3** was determined to be *R* by the X-ray crystal structure of **6**, which was synthesized from **3l** in 2 steps (Scheme 1).

It is noteworthy that gram-scale reactions of catalytic asymmetric synthesis of **3a** and **3m** were also performed in compatible yields and ee values, indicating the good reliability of the process (Scheme 2, eqn (1)). From the viewpoint of synthetic application, a derivative of 2-amino-4-phenylbutanoic acid **7** with 99% ee was easily prepared *via* hydrogenation of **3a**, followed by treatment with cerium(IV) diammonium nitrate (Scheme 2, eqn (2)).

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16 The SDE tests of compounds **3a** and **3h** were also performed (please see Supporting Information Tables S3 and S4).