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Zinc promoted asymmetric propargylation of *N*-(2-chlorotetrafluoroethanesulfin)imines

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ABSTRACT

Zinc promoted asymmetric Barbier-type homopropargylation of aldimines is demonstrated. 2-Chlorotetrafluoroethanesulfinamide was used as the chiral auxiliary and the corresponding homopropargylamines were obtained in good yields with up to 98% diastereoselectivity under mild conditions.

1. Introduction

Homopropargylic amines represent the core of many pharmaceuticals [1] and constitute versatile precursors of nitrogen-containing building blocks [2]. Their racemic synthesis through the attack of nucleophiles to imines has been well developed [3]. However, only a few methods were reported for the efficient preparation of enantiomerically enriched homopropargylic amines [4,5], and their synthesis still remains a challenge. In 2008, the reaction of enantiomerically pure *N*-sulfinylimines with Grignard reagents was reported in the enantioselective synthesis of dihydroisoindol-4-ols [6]. However, only one example was given for the propargylic reaction, the addition of 1-propynylmagnesium bromide to (*S*)-*tert*-butanesulfinimine derived from 5-methyl furfural at −50 °C, which afforded the corresponding adduct in 70% yield with 95% *de*. Very recently, Yus and coworkers reported the Barbier-type reaction of chiral *tert*-butanesulfinimines with silylated propargyl bromides promoted by indium under sonication [7]. Good yields and diastereoselectivities were achieved, but the diastereoselectivities were poor when zinc was used instead of indium. It is well known that the Barbier-type synthesis involving the attack of propargyl zinc to imines is appealing for cheap materials and mild reaction conditions [2(b),8]. Up to now, however, direct asymmetric addition of propargyl zinc to imines with both good diastereoselectivities and yields has not been reported.

Herein, we report for the first time the Ti(O*i*-Pr)$_4$ and CuCl catalyzed diastereoselective homopropargylation of 2-chlorotetrafluoroethanesulfinimines with propargyl zinc.

2. Results and discussion

Recently, a kind of practical fluorinated chiral auxiliary, polyfluoroalkanesulfinamide, was developed in our laboratory [9]. Like the *tert*-butanesulfinyl induced aminoallylation [10], zinc mediated one-pot aminoallylation of aldehyde was achieved successfully using (*S*)-2-chlorotetrafluoroethanesulfinamide (**1**) as the auxiliary (Scheme 1) [11]. The corresponding allylic amines **4** with a configuration of *Ss, Sc* were obtained in good yields with high diastereoselectivities. Due to the strong electron-withdrawing effect of fluoroalkanesulfinyl group, the reaction could take place at lower temperature. In addition, the presence of fluorine facilitated the detection of the reaction process and the diastereoselectivity by ^{19}F NMR spectrum without working-up of the reaction mixture.

Inspired by this result, we further tried the aminopropargylation of aldehydes following the procedure depicted in Scheme 1. In an initial trial, compound **1** was treated with 1.1 equiv of 4-chlorobenzaldehyde (**2a**) in the presence of zinc powder (2.0 equiv) and Ti(O*i*-Pr)$_4$ (1.5 equiv) in THF at room temperature.

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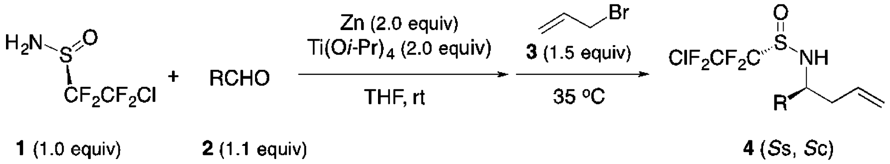
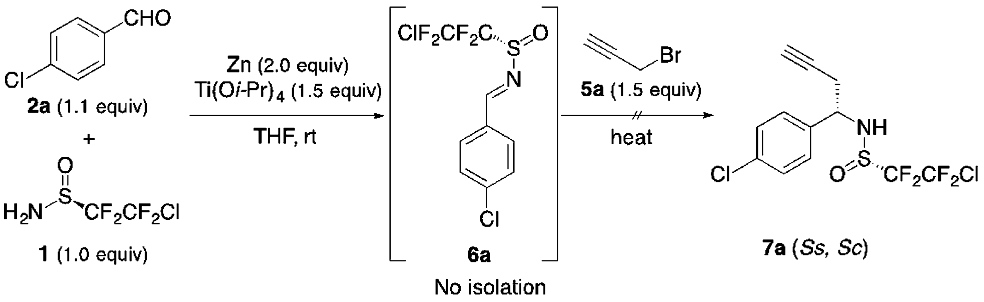


Scheme 1. One-pot aminoallylation of aldehydes.



Scheme 2. One-pot aminopropargylation of **2a**.

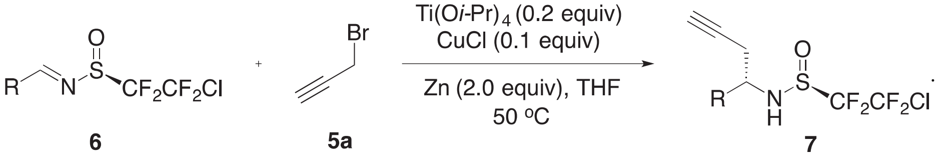
After **1** disappeared, propargyl bromide (**5a**) was added and the reaction temperature was raised to 35 °C. Unfortunately, only imine **6a** was obtained and no expected homopropargylic amine **7a** was observed in ^{19}F NMR spectrum (Scheme 2). Carrying out the reaction under reflux still failed to afford **7a**.

However, when imine **6a** was isolated and treated with **5a** (2.0 equiv) in the presence of 2.0 equiv of zinc and 0.2 equiv of Ti(O*i*-Pr)$_4$ at 35 °C in THF, a small amount of the desired product **7a** was observed in ^{19}F NMR spectrum. Raising the temperature to 50 °C, **7a** (*S*s, *S*c) was obtained in 80% yield with a *de* of 80% as shown in ^{19}F NMR spectrum (Table 1, entry 1). Further screening the reaction conditions showed that the addition of 0.1 equiv of CuCl could improve the yield of **7a** to 90% without any erosion in diastereoselectivity (entry 2). Additionally, when the reaction was carried out without Ti(O*i*-Pr)$_4$, **7a** was not detected and imine **6a** was recovered.

Under the optimized conditions, the scope of imines **6** was investigated and the results are summarized in Table 1. The reaction tolerated a broad range of functional groups and the electronic effect of substituents has little influence on the reactivity of imines **6**. Halide substituted imines **6c**–**6g** reacted well with **5a** to give the corresponding products **7c**–**7g** in good yields with high diastereoselectivities (Table 1, entries 4-8). The use of a bromo substitution allows further modification of products **7**. The reactions of electron-rich imines bearing methyl- (entry 9), phenyl- (entry 10), or methoxy-substitution (entry 12) proceeded well under the reaction conditions, although a slightly prolonged reaction time was required. Heteroaryl imines **6l** and **6m** (entries 13 and 14) reacted smoothly and afforded the corresponding products in good yields. Good yields were also achieved with imines derived from aliphatic aldedydes, although the diastereoselectivities were lower (entries 16–18). For imine **6q**, products **7q**

Table 1

2-Chlorotetrafluoroethanesulfinyl group induced homopropargylation of imines **6**



Entry	Imine	*R*	Time (*h*)	Product	Isolated yield (%)	*de* (%)[b]
1[a]	**6a**	*p*-ClC$_6$H$_4$	8	**7a**	(80)[b]	80
2	**6a**	*p*-ClC$_6$H$_4$	8	**7a**	79(90)[b]	80
3	**6b**	C$_6$H$_5$	10	**7b**	73	84
4	**6c**	*m*-ClC$_6$H$_4$	8	**7c**	66	76
5	**6d**	*o*-ClC$_6$H$_4$	10	**7d**	67	92
6	**6e**	*p*-FC$_6$H$_4$	9	**7e**	81	>96
7	**6f**	*o*-FC$_6$H$_4$	12	**7f**	58	>96
8	**6g**	*p*-BrC$_6$H$_4$	14	**7g**	61	88
9	**6h**	*p*-MeC$_6$H$_4$	10	**7h**	82	>98
10	**6i**	*p*-PhC$_6$H$_4$	13	**7i**	79	>98
11	**6j**	*p*-CF$_3$C$_6$H$_4$	7	**7j**	65	88
12	**6k**	*p*-MeOC$_6$H$_4$	11	**7k**	81	>98
13	**6l**	2-Furyl	11	**7l**	84	>98
14	**6m**	2-Thienyl	14	**7m**	65	72
15	**6n**	*t*-Bu	10	**6n**	–	–
16	**6o**	Cyclohexyl	9	**7o**	72	72
17	**6p**	(CH$_3$)$_2$CH	9	**7p**	74	64
18	**6q**	PhCH=CH(*E*)	10	**7q**/**7q′**	67/13	60

[a] The reaction was carried out without CuCl.

[b] Yields in brackets and *de* were determined by ^{19}F NMR spectra.