Tetrahedron 67 (2011) 6340–6346

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Direct asymmetric aldol reactions in brine with recyclable fluorous β-aminosulfonamide organocatalysts

Tsuyoshi Miura [a,*], Kie Imai [a], Hikaru Kasuga [a], Mariko Ina [a], Norihiro Tada [a], Nobuyuki Imai [b], Akichika Itoh [a]

[a] Gifu Pharmaceutical University 1-25-4, Daigaku-nishi, Gifu 501-1196, Japan
[b] Faculty of Pharmacy, Chiba Institute of Science, 15-8 Shiomi-cho, Choshi, Chiba 288-0025, Japan

ARTICLE INFO

Article history:
Received 28 April 2011
Received in revised form 2 June 2011
Accepted 3 June 2011
Available online 16 June 2011

Keywords:
Fluorous
Organocatalyst
Aldol
Water
Recycle

ABSTRACT

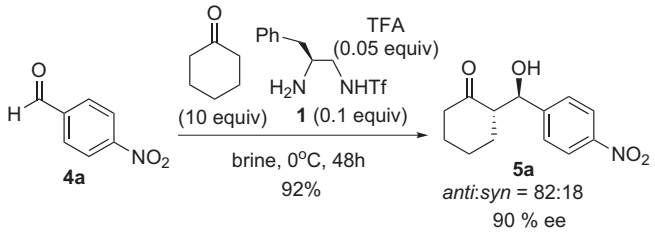
Fluorous organocatalyst **3** promotes direct asymmetric aldol reactions of ketones with aldehydes in brine, leading to the synthesis of the corresponding *anti*-aldol products in high yields with up to 96% ee. Fluorous organocatalyst **3** is easily recovered by solid-phase extraction using fluorous silica gel and can be reused up to five times without purification.

1. Introduction

The development of an organocatalytic enantioselective aldol reaction has become a major area of research during the past decade as a result of its ability to yield stereoselective carbon–carbon bonds, generating chiral β-hydroxycarbonyl compounds as synthetic building blocks.[1] In addition, the properties of organocatalysts, such as low toxicity, high stability, and convenient handling, make them appealing candidates for synthetic chemistry. Since List et al. reported the first direct asymmetric aldol reaction catalyzed by proline in 2000,[2] many other aldol reactions using proline analogues as the main organocatalyst have been reported.[1] As an alternative approach to asymmetric aldol reactions, several groups have worked with primary amine catalysts, exchanging the cyclic secondary amine of proline derivatives.[3,4] Moreover, the use of water as a reaction medium that replaces organic solvents has attracted a great deal of attention because of its affordability, safety, and environmentally benign nature, all of which are important requirements of sustainable green chemistry.[4–6] Because type I aldolases, which are natural enzymes, employ the primary amino group of a lysine residue to catalyze aldol reactions via the enamine intermediate under aqueous conditions,[7] it was suggested that an organocatalyst with a primary amino group may be suitable for the direct asymmetric aldol reaction in water. Several excellent primary amine organocatalysts for the aldol reactions under aqueous conditions have been reported.[4] In this context, we have recently reported direct asymmetric aldol reactions in brine catalyzed by chiral β-aminosulfonamide **1** derived from L-phenylalanine (Scheme 1);[8] unfortunately the organocatalyst was discarded after the reaction because of the difficulty in recovering and reusing it. Ultimately, the ability to recover and recycle expensive organocatalysts from the reaction mixture after completion of the reaction is highly desirable. Fluorous chemistry can be used as a recycling method to overcome this problem.[9] Fluorous chemistry has been developed extensively since Horváth and Rábai first reported the concept of the fluorous biphasic system in 1994.[10] Further, Curran et al. elaborated on its use as a recycling technique by the fluorous solid-phase extraction (FSPE) methodology using fluorous silica gel.[9,11] Subsequently, fluorous recycling techniques have been applied in organocatalytic chemistry.[12] Fluorous organocatalysts were applied to asymmetric Diels–Alder reactions,[13] aldol reactions,[6n,14] Michael reactions,[15] reductions,[16] epoxidations,[17] and α-chlorinations of aldehydes[18] and could be recovered and reused by their fluorous characteristics. To recover and reuse valuable organocatalyst **1**,[8] we developed a recyclable organocatalyst **3** with a fluorous tag that promotes asymmetric direct aldol reactions in brine, as discussed in our preliminary communication.[4i] Herein, we describe in detail asymmetric direct aldol reactions in brine using fluorous organocatalysts **3** (Fig. 1).

* Corresponding author. E-mail address: miura@gifu-pu.ac.jp (T. Miura).

0040-4020/$ – see front matter © 2011 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2011.06.004



Scheme 1. Our previous work.

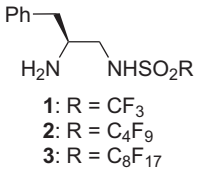
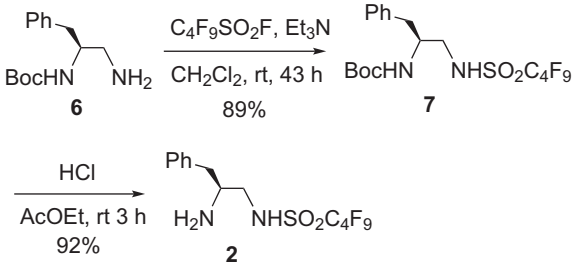


Fig. 1. Structure of organocatalysts.

2. Results and discussion

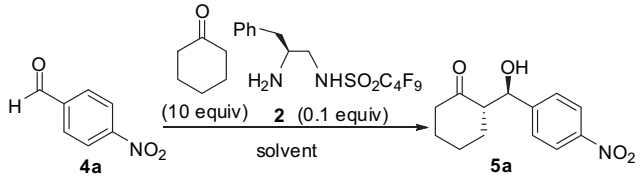
To recover and reuse valuable organocatalyst **1**, we initially attempted the preparation of fluorous organocatalyst **2**, which attached a perfluorobutyl group as a fluorous tag to **1** instead of trifluoromethyl group (Scheme 2). Treatment of compound **6**,[19] which is an intermediate in the preparation of organocatalyst **1**, with perfluorobutanesulfonyl fluoride in the presence of triethylamine in CH_2Cl_2 resulted in sulfonamide **7** with 89% yield. The Boc group of **7** was removed by treatment with HCl in ethyl acetate to afford the desired fluorous β-aminosulfonamide **2** with 92% yield.



Scheme 2. Preparation of fluorous organocatalyst **2**.

The reaction conditions were optimized for enantioselective direct aldol reactions using fluorous organocatalyst **2**, as shown in Table 1. Aldol reactions were carried out with *p*-nitrobenzaldehyde (**4a**) and cyclohexanone (10 equiv) as test reactants in the presence of a catalytic amount of **2** (0.1 equiv). Methanol, 2-propanol, and acetonitrile are poor solvents for aldol reactions and provided low enantioselectivities (entries 1–3). Moderate enantioselectivities were observed when THF, 1,4-dioxane, DMF, DMSO, and NMP were used as the other polar solvents (entries 4–8). The neat conditions without reaction solvent caused lowering of stereoselectivity to yield the *anti*-aldol product with 56% ee (entry 9). The aldol reaction in water, an environmentally benign solvent, enhances the enantioselectivity up to 85% ee. This demonstrated that water is a more suitable solvent for the aldol reactions than commonly used organic solvents (entry 10). Furthermore, although longer reaction times (120 h) were needed in water, performing the reaction at 0 °C enhanced enantioselectivity. Moreover, brine proved to be the best solvent for direct aldol reaction catalyzed by organocatalyst **2** (entry 12). Overall, organocatalyst **2** is an excellent catalyst and shows higher stereoselectivity at room temperature for shorter reaction time compared to the original organocatalyst **1** (entry 13). Unfortunately, despite our attempts to recover the catalyst by FSPE using fluorous silica gel, oraganocatalyst **2** could not be adsorbed by fluorous silica gel even at 40 wt % of fluorine content and was eluted with 70% methanol.

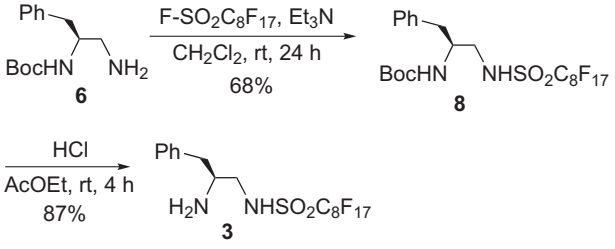
Table 1
Optimization of reaction solvents



Entry	Solvent	Temp	Time (h)	Yield[a] (%)	*anti*/*syn*[b]	ee[c] (%)
1	MeOH	rt	48	78	57:43	39
2	*i*-PrOH	rt	96	77	51:49	42
3	CH_3CN	rt	100	83	55:45	39
4	THF	rt	120	81	57:43	64
5	1,4-Dioxane	rt	120	79	56:44	61
6	DMF	rt	120	75	57:43	54
7	DMSO	rt	23	65	67:33	71
8	NMP	rt	45	81	73:27	75
9	Neat	rt	48	81	54:46	56
10	H_2O	rt	24	84	73:27	85
11	H_2O	0 °C	120	78	79:21	89
12	Brine	0 °C	168	81	79:21	91
13	**Brine**	**rt**	**20**	**82**	**80:20**	**92**

[a] Isolated yield.
[b] Determined by ^1H NMR.
[c] Determined by HPLC analysis using Chiralcel OD-H.

We next attempted to prepare fluorous organocatalyst **3** containing 51 wt % of fluorine, hoping to improve its recoverability with the FSPE technique (Scheme 3). Compound **6** reacts with perfluorooctanesulfonyl fluoride in the presence of triethylamine in CH_2Cl_2 to give fluorous compound **8** with 68% yield. Treatment of **8** with HCl in ethyl acetate results in the desired fluorous β-aminosulfonamide **3** with 87% yield.



Scheme 3. Preparation of fluorous organocatalyst **3**.

Based on the optimal conditions for aldol reactions using organocatalyst **2**, the reaction conditions were optimized for the enantioselective direct aldol reactions using fluorous organocatalyst **3**, as shown in Table 2. Aldol reactions were carried out with *p*-nitrobenzaldehyde (**4a**) and cyclohexanone (10 equiv) as test reactants in the presence of a catalytic amount of **3** (0.1 equiv) in brine. A lowering of stereoselectivity was observed when the aldol reaction using organocatalyst **3** was performed under the optimal conditions with **2** (Table 2, entry 1 vs Table 1, entry 13). Although the reaction at 0 °C enhanced stereoselectivity, a long reaction time (163 h) was necessary for completion of the reaction (entry 2). The addition of trifluoroacetic acid (TFA, 0.05 equiv) improved the enantioselectivity under both room temperature and 0 °C conditions (entries 3 and 4). The enantioselectivities reduced