Tetrahedron Letters 54 (2013) 4613–4616

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

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

Organocatalytic enantioselective *aza*-Friedel–Crafts reaction of sesamols with *N*-sulfonylimines catalyzed by 6′-OH *Cinchona* alkaloids

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ARTICLE INFO

Article history:
Received 8 March 2013
Revised 4 June 2013
Accepted 8 June 2013
Available online 22 June 2013

Keywords:
Friedel–Crafts reaction
Cinchona alkaloids
Imines
Sesamol
Organocatalysis

ABSTRACT

An unprecedented asymmetric *aza*-Friedel–Crafts reaction of sesamol with *N*-sulfonylimines has been reported. A variety of *N*-sulfonylimines reacts with sesamol derivatives in the presence of 6′-OH *Cinchona* alkaloids to provide a new series of chiral aminophenol adducts in good yield and good to high level of enantioselectivity.

Asymmetric organocatalytic Friedel–Crafts (F–C) reaction has emerged as a powerful tool for the synthesis of highly functionalized chiral arene and heteroarene derivatives.[1,2] One of the important parts of this reaction is stereoselective *aza*-Friedel–Crafts reaction, which involves 1,2-addition of aromatic and hetero-aromatic compounds to the imines to provide chiral amines bearing arene/heteroarene substituents.[3–7] In 2004, Terada and co-workers developed the first organocatalytic asymmetric *aza*-Friedel–Crafts reaction, employing chiral phosphoric acid as catalyst for 1,2-addition of furan derivatives to aldimines.[4] Since then, asymmetric organocatalytic *aza*-Friedel–Crafts reaction of indole and pyrrole derivatives[3] has been at the center stage for obtaining bioactive molecules, but organocatalytic enantioselective *aza*-Friedel–Crafts reactions of other arene derivatives have scarcely been investigated. In 2011, our group[5] and Wang's group[6] independently reported the enantioselective *aza*-Friedel–Crafts reaction of naphthols with *N*-sulfonylimines catalyzed by 6′-OH *Cinchona* alkaloids. Recently, Qu's group has published an enantioselective *aza*-Friedel–Crafts reaction of phenols with *N*-tosylaldimines.[7]

An electron rich phenol, sesamol is a very useful molecule which can be functionalized by asymmetric as well as nonasymmetric F–C reaction.[8,9,11–13] Sesamol has a 1,3-benzodioxol moiety, which is found in many synthetic bioactive and natural molecules such as (+)-bicuculline, paroxetine, tadalafil, and 5,6-methylenedioxy-2-aminoindane (MDAI) (Fig 1).[10] The reactivity of sesamol derivatives was exploited independently by Zhang's[11] and Nagasawa's[12] groups for enantioselective Michael-type Friedel–Crafts reaction with nitro-olefins catalyzed by cinchonidine derived thiourea-tertiary amine and C3-linked guanidine/bis-thiourea organocatalyst, respectively. Very recently, Feng and co-workers published an enantioselective 1,4-addition of activated phenols including sesamol to (*E*)-4-oxo-4-arylbutenoates promoted by *N*,*N*′-dioxide-scandium (III) complex as the catalyst.[13] The use of sesamol derivatives in catalytic enantioselective Friedel–Crafts reaction is limited to 1,4-addition on unsaturated acceptors and 1,2-addition remains elusive. To the best of our knowledge, the enantioselective *aza*-Friedel–Crafts reaction of sesamol derivatives is not known.

Among various organocatalysts, the C6'-OH *Cinchona* alkaloids have emerged as powerful bifunctional catalysts for various asymmetric transformations.[14] Owing to the biological importance of 1,3-benzodioxol moiety and synthetic importance of the enantioselective *aza*-Friedel–Crafts reaction, we have explored the catalytic ability of C6′-OH *Cinchona* alkaloids to develop the enantioselective *aza*-Friedel–Crafts reaction of sesamol derivatives with *N*-sulfonylimines.

We started our investigation by screening different bifunctional *Cinchona*-derived organocatalysts (Fig. 2) (10 mol %) for the *aza*-Friedel–Crafts reaction of sesamol (**1a**) with *N*-tosylimine **2a** in toluene as solvent and 4 Å molecular sieves as an additive at rt (Ta-

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http://dx.doi.org/10.1016/j.tetlet.2013.06.032

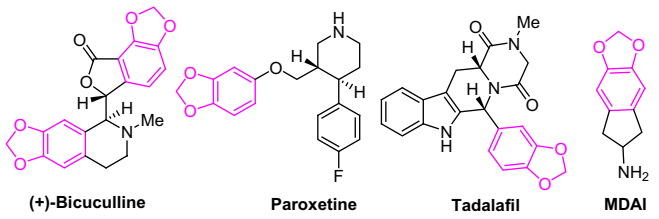


Figure 1. Medicinally important compounds containing 1,3-benzodioxol framework.

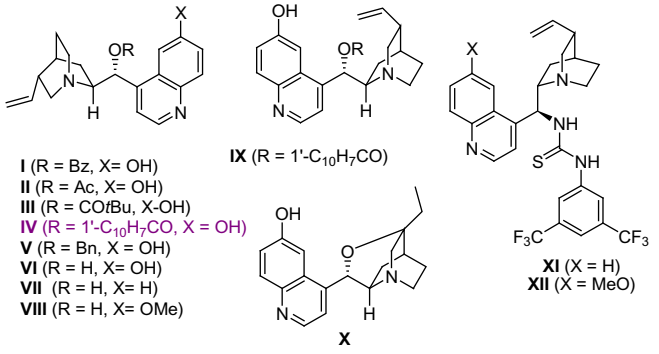


Figure 2. Structure of the catalyst used.

ble 1). As observed in the enantioselective addition of naphthol to imines,[5] the 6′-OH *Cinchona* alkaloids bearing ester moiety at C-9 position provide better enantioselectivity (Table 1, entries, 1–4) of **3a** than the catalyst bearing the ether (**V**, Table 1, entry 5) or hydroxyl (**VI**, Table 1, entry 6) group at this position. Among different ester bearing cupreine derivatives the catalyst bearing the 1′-naphthoyl group provides highest enantioselectivity of *aza*-F–C adduct with good level of enantioselectivity (Table 1, entry 4). The natural *Cinchona* alkaloids (**VII** and **VIII**) resulted in no enantioinduction in **3a** (Table 1, entries 7–8). The pseudoenantiomer of **IV** that is, **IX** provides opposite enantiomer of **3a** in 86% yield and 60% ee (Table 1, entry 9). Other *Cinchona*-derived bifunctional organocatalysts such as β-isocupreidine (**X**) and thioureas (**XI** and **XII**), however provide high yield, but the enantioselectivity was moderate (Table 1, entries 10–12).

Further, different solvents were screened by using 10 mol % of **IV** as catalyst (Table 1, entries, 13–20). After screening, chloroform was identified as the best solvent in terms of asymmetric induction (Table 1, entry 15).

After optimizing the conditions, the substrate scope was evaluated by screening different *N*-sulfonylimines with sesamol. Different *N*-tosyl- and *N*-benzenesulfonylimines bearing electron withdrawing groups at different positions of the phenyl ring provide high yield and very good level of enantioselectivity (Table 2, entry 1–8). The *N*-sulfonylimines derived from benzaldehyde and 1-naphthaldehyde react efficiently with sesamol to provide good yield and good enantioselectivity of corresponding *aza*-F–C adducts (entries Table 2, 8–11). The reaction of sesamol with imines bearing electron releasing groups provides the desired adduct in good yield and very good enantioselectivity (Table 2, entries 12 and 13). The imine bearing the heteroaromatic group was also tolerated under the optimized reaction condition, which reacts with sesamol to provide *aza*-F–C adduct in 80% yield and good enantioselectivity (Table 2, entry 14).

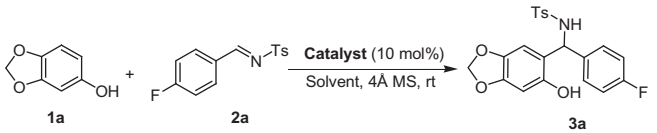
Sesamol substituted with methyl and iodo groups reacts efficiently with *N*-sulfonylimines to provide corresponding *aza*-F–C adducts in good yield and moderate to high enantioselectivity (Table 2, entries 15–17).

The *aza*-F–C reaction catalyzed by **IX** provides desired products with opposite configuration in high yield and slightly lower enantioselectivity than **IV** (entries 1, 3, 6, 9, and 10).

In order to demonstrate the practical and preparative utility of the present methodology, a gram-scale reaction was performed between sesamol **1a** (8 mmol) and imine **2a** (16 mmol) catalyzed by 10 mol % of **IV** (Scheme 1). The *aza*-F–C adduct **3a** was obtained in 85% yield after 72 h without any change of enantioselectivity (80%).

Further, we have tried to demonstrate the mechanism of the *aza*-F–C reaction catalyzed by C6′-OH *Cinchona* alkaloid by designing some new experiments. The model reaction catalyzed by **XIII** having no free hydroxyl group provided **3a** in low yield and poor enantioselectivity, which suggests the role of phenolic OH for high asymmetric induction in this reaction (Scheme 2, 1). The catalyst **XIV**, having no free amine moiety failed to catalyze the model reaction, highlighting the role of tertiary amine moiety for hydrogen bonding activation of sesamol. This fact was further proved by the failure of the reaction of OH protected sesamol (**1d**) with **2a** (Scheme 2, 2), due to the unavailability of free OH for hydrogen bonding within quinuclidine moiety of the catalyst. These results suggest that the simultaneous activation of both sesamol and imine is required in order to provide the *aza*-F–C product with high enantioselectivity. On the basis of these results a transition state (TS1) was proposed, in which catalyst **IV** behaves as bifunctional catalyst by providing favorable orientation and synergistic activation of both the substrate via hydrogen bonding activation of

Table 1
Catalyst screening and optimization of reaction conditions for the *aza*-Friedel–Crafts reaction of sesamol with imine[a]



Entry	Catalyst	Solvent	Time (h)	Yield[b] (%)	ee[c] (%)
1	**I**	Toluene	48	88	77
2	**II**	Toluene	50	90	73
3	**III**	Toluene	48	85	69
4	**IV**	Toluene	48	87	78
5	**V**	Toluene	50	92	61
6	**VI**	Toluene	50	93	40
7	**VII**	Toluene	48	81	0
8	**VIII**	Toluene	48	79	0
9	**IX**	Toluene	48	86	−60
10	**X**	Toluene	48	93	−45
11	**XI**	Toluene	48	93	−43
12	**XII**	Toluene	48	91	−40
13	**IV**	Xylene	48	89	66
14	**IV**	CH_2Cl_2	48	82	65
15	**IV**	$CHCl_3$	48	90	80
16	**IV**	MTBE	65	Traces	—
17	**IV**	1,4-dioxane	65	Traces	—
18	**IV**	MeOH	48	34	8
19	**IV**	DMF	65		0
20	**IV**	CH_3CN	48	21	43
21[d]	**IV**	$CHCl_3$	48	93	63
22[e]	**IV**	$CHCl_3$	72	88	81
23[f]	**IV**	$CHCl_3$	72	66	82

[a] Reaction condition: 0.1 mmol of **1a**, 0.2 mmol of **2a**, 10 mol % of catalyst, 50 mg of 4 Å molecular sieves. 0.5 mL of solvent.
[b] Yield after column chromatography.
[c] ee determined by chiral HPLC.
[d] 0.25 mL of $CHCl_3$ was used.
[e] 1 mL of $CHCl_3$ was used.
[f] 2 mL of $CHCl_3$ was used.