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Oxazaborolidinone-Catalyzed Enantioselective Friedel−Crafts Alkylation of Furans and Indoles with α,*β*-Unsaturated Ketones

Shinya Adachi, Fumi Tanaka, Kazuya Watanabe, and Toshiro Harada*

Department of Chemistry and Materials Technology, Kyoto Institute of Technology, Matsugasaki, Sakyo-ku, Kyoto, Japan 606-8585

harada@chem.kit.ac.jp

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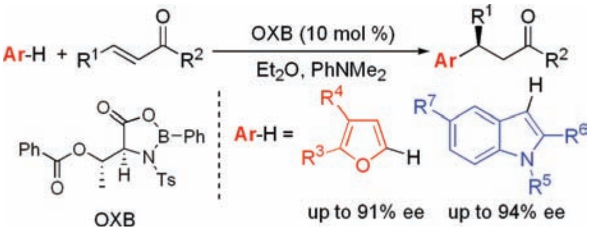
ABSTRACT



***allo*-Threonine-derived oxazaborolidinone (10 mol %) catalyzes the Friedel−Crafts alkylation of furans and indoles with simple acyclic α,*β*-unsaturated ketones to give products with high yield and high enantioselectivity. The use of *N,N*-dimethylaniline (2.5−10 mol %) as an additive is essential for enantioselectivity.**

Recently, much attention has focused on the catalytic enantioselective Friedel−Crafts (F−C) alkylation reaction as an atom-economical method for forming a carbon−carbon bond between electron-rich aromatics and electron-deficient alkenes in a stereodefined manner.[1] Major efforts have been made to develop the F−C alkylation of indoles and pyrroles because of a wide interest in these frameworks as ubiquitous constituents in pharmacologically important molecules. A number of highly enantioselective metal-catalyzed reactions have been developed for bidentate chelating substrates since the first report of the Cu(box)(OTf)$_2$-catalyzed reaction for β,γ-unsaturated-α-ketoesters by Jørgensen and co-workers.[2,3] More recently, efficient catalysts have been reported for a simple nonchelating α,β-unsaturated ketone as an electron-deficient alkene.[4,5]

Furans also represent an important class of electron-rich five-membered heterocycles that are broadly found as structural motifs of many natural products and pharmaceutically important substances.[6] Moreover, they can be employed as useful intermediates in synthetic chemistry.[7] Therefore, the synthesis and transformation of furans have attracted significant attention.[8] While furans are generally less nu-

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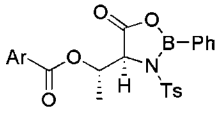
cleophilic than indoles and pyrroles,[9] they do undergo the F−C alkylation with α,β-unsaturated ketones by the catalysis of either Brønstead acids or Lewis acids to give racemic products.[10] However, the catalytic enantioselective version of the reaction of furans is much less developed than that of indoles and pyrroles.

In their study on the copper-catalyzed enantioselective F−C alkylation, Jørgensen and co-workers reported several examples of the reaction of 2-methylfuran with β,γ-unsaturated-α-ketoesters.[2,11] The enantioselective reaction of highly nucleophilic 2-methoxyfuran with α,β-unsaturated 2-acyl imidazoles[12] and nitroalkenes[13] has been reported. To date, however, the scope of the reaction with respect to both furan derivatives and electron-deficient alkenes remains to be expanded.



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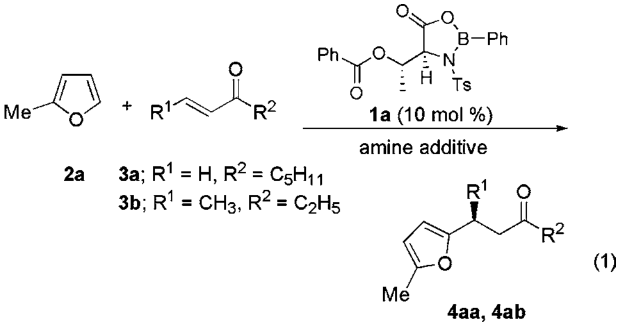
We have recently developed *allo*-threonine derived oxazaborolidinones (OXB) **1** as efficient chiral Lewis acid catalysts for the enantioselective activation of a ketone carbonyl group.[14,15] In addition to the high enantioselectivity, OXB **1** exhibits high activity to the less reactive substrates as demonstrated by the successful application to the Mukaiyama-type aldol addition to nonactivated ketones.[15d] These characteristics prompted us to employ **1** in the F−C reaction between less reactive heteroaromatics and α,β-unsaturated ketones.

Herein, we wish to report the enantioselective F−C reactions of furans with simple α,β-unsaturated ketones catalyzed by OXB **1a** (Ar = Ph). Also reported is an application of the same catalyst system to the F−C alkylation of indoles, which significantly expands the scope of alkene partners of the reaction.

We recently reported that OXB **1a** (10 mol %) catalyzes the Diels−Alder reaction of furan with alkyl vinyl ketones ($CH_2{=}CHCOR$) at −78 °C in toluene to give the corresponding *endo* adducts in high enantioselectivity up to 98% ee.[15c] During this study, the formation of F−C product **4aa** (8%) was observed in the reaction of 2-methylfuran (**2a**) with vinyl ketone **3a** under similar conditions (eq 1).[16] The possibility of asymmetric induction at the β position was then examined in the reaction with crotyl ketone **3b** (Table 1).



(1)

Table 1. Enantioselective F−C Reaction of 2-Methylfuran (**2a**) with 4-Hexen-3-one (**3b**) Catalyzed by OXB **1a**[a]

entry	solvent	additive (mol %)	yield (%)	ee (%)
1[b,c]	toluene		69	1
2[b]	EtCN		48	4
3	Et_2O		97	2
4	toluene	$PhNMe_2$ (5)	97	44
5	EtCN	$PhNMe_2$ (5)	84	55
6	Et_2O	$PhNMe_2$ (5)	96	69
7	Et_2O	$PhNMe_2$ (10)	92	80
8	Et_2O	$PhNMe_2$ (20)	23	82
9	Et_2O	2,6-lutidine (10)	7	22
10	Et_2O	DTBP (10)	12	22

[a] Unless otherwise noted, reactions were carried out by using **3b** (1.0 mmol, 0.3 M), **2a** (5.0 equiv), and OXB **1a** (10 mol %) at −40 °C for 20 h. [b] The reaction was carried out for 2 h. [c] The reaction was carried out at 0 °C.

Initial examination of the reaction of **2a** with **3b** resulted in the nonenantioselective formation of the corresponding F−C product **4ab** irrespective of the solvents employed (entries 1−3). Further examination revealed the remarkable effect of amine additives. Thus, in the presence of *N*,*N*-dimethylaniline (5 mol %), **4ab** was obtained in an enan-

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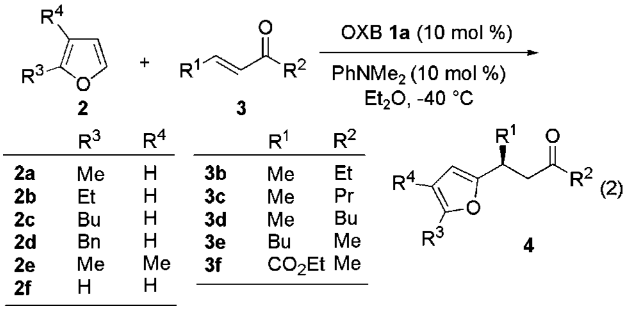
(16) The corresponding Diels−Alder adduct was not obtained in this reaction.

tiomerically enriched form in high yield (entries 4−6). Increasing the amount of the additive to 10 mol % in Et$_2$O brought about an improved enantioselectivity of 80% ee (entry 7), while a further increase (20 mol %) resulted in a decrease in the product yield (entry 8). Other amine additives also exerted a positive effect on enantioselectivity while being inferior to *N*,*N*-dimethylaniline (entries 9 and 10).

The scope of the OXB-catalyzed F−C reaction of furans was examined in Et$_2$O at −40 °C in the presence of *N*,*N*-dimethylaniline (eq 2, Table 2). In addition to methyl derivative **2a**, the reaction worked well with other 2-substituted furans **2b**−**d** (entries 1−4). The reactions of the 2-ethyl, -butyl, and -benzyl derivatives with **3b** afforded the corresponding F−C products of 77−84% ee in high yields. Of these, benzyl derivative **2d** was somewhat less reactive and 20 mol % of the catalyst was required. 2,3-Dimethylfuran (**2e**) exhibited high enantioselectivity (91% ee) in the reaction with **3b** (entry 5). On the other hand, parent furan (**2f**) hardly reacted with **3b** (entry 6). Other aliphatic enones, such as crotyl alkyl ketones **3c**,**d** and 1-hexenyl methyl ketone (**3e**), also serve as an acceptor of the F−C alkylation (entries 7 and 8), while the attempted reactions with benzalacetone (**3g**; R^1 = Ph, R^2 = Me) resulted in the recovery of the enone. Enone **3f** bearing an ethoxy carbonyl group at the β-position was also a good substrate (entries 9 and 10). The reaction of **2a** and **2e** gave the corresponding product **4af** and **4ef** in 85% ee and 89% ee, respectively, in high yield.

Table 2. OXB-Catalyzed Enantioselective Friedel−Crafts Reaction of Furans **2** with Enones **3**[a]



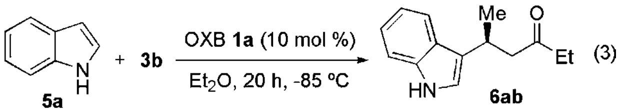
	R^3	R^4
2a	Me	H
2b	Et	H
2c	Bu	H
2d	Bn	H
2e	Me	Me
2f	H	H

	R^1	R^2
3b	Me	Et
3c	Me	Pr
3d	Me	Bu
3e	Bu	Me
3f	CO$_2$Et	Me

entry	furan	enone	product	yield (%)	ee (%)[b]
1	**2a**	**3b**	**4ab**	92	80
2	**2b**	**3b**	**4bb**	95	77
3	**2c**	**3b**	**4cb**	96	79
4[c]	**2d**	**3b**	**4db**	62	85
5	**2e**	**3b**	**4eb**	98	91
6	**2f**	**3b**	**4fb**	trace	
7	**2a**	**3c**	**4ac**	79	81
8	**2a**	**3d**	**4ad**	92	86
9[c]	**2e**	**3e**	**4ee**	87	85
10	**2a**	**3f**	**4af**	81	85
11[d]	**2e**	**3f**	**4ef**	99	89

[a] Unless otherwise noted, reactions were carried out by using **3** (1.0 mmol), **2** (5.0 equiv), PhNMe$_2$ (10 mol %), and OXB **1a** (10 mol %) in Et$_2$O (3.1 mL) at −40 °C for 20 h. [b] Determined by chiral HPLC analysis. The *S* configuration of **4ac** was assigned by converting it into (*S*)-2-methyl-4-oxo-heptanoic acid. See Supporting Information for details. [c] The reaction was carried out with 20 mol % of OXB and PhNMe$_2$. [d] The reaction was carried out for 44 h.

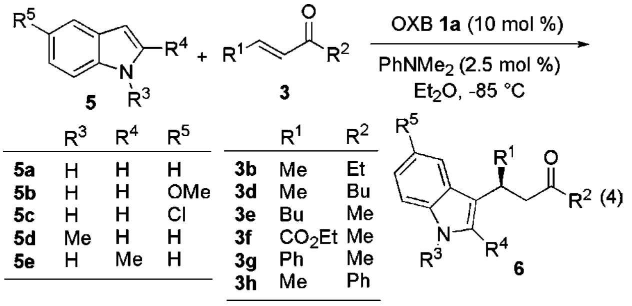
Catalysis by OXB was examined also for the F−C alkylation of indoles because of the synthetic importance of the transformation. Unlike furans **2**, indole (**5a**) underwent the enantioselective F−C alkylation with **3b** in the absence of *N*,*N*-dimethylaniline at lower temperature (−85 °C) to give **6ab** in 78% ee and in 90% yield (eq 3). The addition of 2.5 mol % of the amine improved the selectivity to 87% ee, while further increase (5 mol %) resulted in a decrease in yield.



PhNMe$_2$	yield	ee
0 mol %	90%	78%
2.5 mol %	92%	87%
5 mol %	56%	87%

A variety of indole derivatives **5a**−**e** underwent the F−C alkylation with enone **3b** by using OXB **1a** (10 mol %) with *N*,*N*-dimethylaniline (2.5 mol %) in Et$_2$O at −85 °C affording the corresponding product **6** of high ee (85−93%) (eq 4, entries 1−5 in Table 3). As shown in entries 6−9, the reaction was applicable to various 1-alkenyl alkyl ketones

Table 3. OXB-Catalyzed Enantioselective Friedel−Crafts Reaction of Indoles **5** with Enones **3**[a]



	R^3	R^4	R^5
5a	H	H	H
5b	H	H	OMe
5c	H	H	Cl
5d	Me	H	H
5e	H	Me	H

	R^1	R^2
3b	Me	Et
3d	Me	Bu
3e	Bu	Me
3f	CO$_2$Et	Me
3g	Ph	Me
3h	Me	Ph

entry	indole	enone	product	yield (%)	ee (%)[b]
1	**5a**	**3b**	**6ab**	92	87
2	**5b**	**3b**	**6bb**	85	89
3[c]	**5c**	**3b**	**6cb**	55	85
4	**5d**	**3b**	**6db**	93	93
5	**5e**	**3b**	**6eb**	91	87
6	**5a**	**3d**	**6ad**	81	92
7[c]	**5e**	**3e**	**6ee**	90	82
8[c]	**5a**	**3f**	**6af**	96	94
9[d]	**5e**	**3g**	**6eg**	87	84
10	**5e**	**3h**	**6eh**	52	37

[a] Unless otherwise noted, reactions were carried out by using **3** (1.0 mmol), **5** (1.0 equiv), PhNMe$_2$ (2.5 mol %), and OXB **1a** (10 mol %) in Et$_2$O (3.1 mL) at −85 °C for 20 h. [b] Determined by chiral HPLC analysis (see Supporting Information). The *S* configuration of **6ab**,[5a] **6af**,[5a] and **6ah**[4b] were assigned by comparison of the optical rotation signs with literature data. [c] The reaction was carried out for 96 h. [d] The reaction was carried out for 48 h.

3d−**g**. Unlike the reaction of furans, less reactive *β*-phenyl substituted enone **3g** afforded indole alkylation product **6eg** of 84% ee in high yield (entry 9). Catalysis by **1a** was not effective in the reaction with crotyl phenyl ketone **3g** (entry 10). Pedro and co-workers reported a highly enantioselective F−C alkylation of indoles catalyzed by a zirconium(IV)−BINOL complex (20 mol %).[4c,d] Their method is specifically effective for 1-alkenyl aryl ketones such as **3h**. Therefore, the present OXB-catalyzed reaction well complements the zirconium-catalyzed reaction for acyclic enones.

In summary, OXB catalysis is demonstrated to be effective in the enantioselective F−C alkylation of electron-rich heteroaromatics. The enantioselective F−C alkylation of furans with a monodentate α,*β*-unsaturated ketones is realized for the first time by OXB catalysis. In addition, the catalyst system is successfully applied to the alkylation of indoles, expanding the scope of substrates. The use of *N*,*N*-dimethylaniline as an additive is crucial to the enantioselectivity. Studies are underway to elucidate the role of the additive as well as to clarify the scope of the reactions.

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Supporting Information Available: Experimental procedures and characterization of products. This material is available free of charge via the Internet at http://pubs.acs.org.

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