ORGANIC LETTERS

2010
Vol. 12, No. 5
1136−1138

Enantioselective Friedel−Crafts Reaction of β-Trifluoromethylated Acrylates with Pyrroles and Its Application to the Synthesis of Trifluorinated Heliotridane

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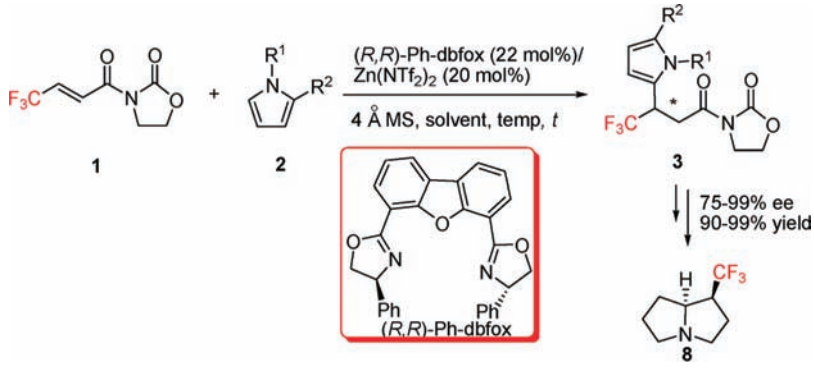
Received January 23, 2010

ABSTRACT



The first chiral Lewis acid catalyzed enantioselective Friedel−Crafts alkylation of pyrroles with β-CF_3 acrylates has been investigated, which afforded various types of chiral trifluoromethylated compounds in excellent yields (90−99%) with high ee's (up to 99% ee). With the aid of the Friedel−Crafts reaction adduct, optically active trifluorinated heliotridane was successfully constructed.

Incorporation of fluorine(s) into pharmaceuticals often enhances their pharmacological properties.[1] Among organofluorine molecules, chiral trifluoromethylated compounds, especially trifluoromethylated heterocyclic systems, play a unique and significant role in agricultural and medicinal chemistry.[2] As a consequence, exploitation of an efficient method for the synthesis of these compounds is highly desirable. Two strategies are often utilized to synthesize compounds bearing a trifluoromethyl (CF_3) group at the chiral center: The first strategy is the transfer of a CF_3 group from a reagent. This strategy seems to be straightforward and practical, but direct enantioselective trifluoromethylation remains a challenge, and high ee's are rarely reached.[3] An

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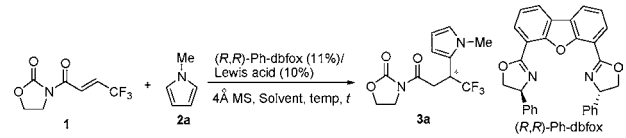
10.1021/ol100171z
Published on Web 02/09/2010

alternative strategy is the use of trifluoromethylated compounds as building blocks, and CF_3 sources are mainly from trifluoromethyl ketones and trifluoropyruvates.[4] We envisaged that β-trifluoromethyl acrylates would be an excellent candidate as an acceptor in the Friedel−Crafts reaction,[5] which provides a potential chiral CF_3 group and can be transformed into β-trifluoromethylated carboxylic acids.

Asymmetric Friedel−Crafts (FC) reactions have witnessed rapid development in recent years.[6] Indoles have usually served as nucleophiles in FC reactions, and the use of pyrroles, especially unprotected pyrroles, in FC reactions is rarely reported,[7] despite their usefulness in pharmaceuticals.[8] In 2001, MacMillan and co-workers pioneered the work of catalytic asymmetric FC alkylation with pyrroles.[9a] Recently, the Sibi group described the first protocol of highly enantioselective Friedel−Crafts alkylations/enolate protonation using various pyrrole nucleophiles.[9b] As part of a program that focuses on the construction of chiral trifluoromethylated products,[10] we herein report the first chiral Lewis acid catalyzed enantioselective FC reactions of protected and unprotected pyrroles with β-CF_3 acrylates.

Chiral Lewis acids prepared from Ph-dbfox (Ph-dbfox = (*R*,*R*)-4,6-dibenzofurandiyl-2,2-bis(4-phenyloxazoline)) and different metal salts were screened in CH_2Cl_2 at rt for the asymmetric FC reaction of **1** with **2a** (entries 1−6). Lewis acids such as $Cu(OTf)_2$, $Cu(NTf_2)_2$, and $Zn(OAc)_2$ in combination with ligand Ph-dbfox led to disappointing results (Table 1, entries 1−3). Moderate enantioselectivity was

Table 1. Optimization of the Asymmetric FC Reaction[a]



entry	Lewis acid	solvent	temp (°C)	t (h)	yield (%)[b]	ee (%)[c]
1	$Cu(OTf)_2$	CH_2Cl_2	20	24	trace	ND
2	$Cu(NTf_2)_2$	CH_2Cl_2	20	24	trace	ND
3	$Zn(OAc)_2$	CH_2Cl_2	20	24	trace	ND
4	$Zn(OTf)_2$	CH_2Cl_2	20	24	40	38
5	$Zn(ClO_4)_2$	CH_2Cl_2	20	4	86	75
6	$Zn(NTf_2)_2$	CH_2Cl_2	20	2	96	75
7	$Zn(NTf_2)_2$	toluene	20	6	93	60
8	$Zn(NTf_2)_2$	Et_2O	20	6	91	72
9	$Zn(NTf_2)_2$	$CHCl_3$	20	2	90	70
10	$Zn(NTf_2)_2$	CH_2Cl_2	−40	12	98	89
11	$Zn(NTf_2)_2$	CH_2Cl_2	−60	24	96	96
12[d]	$Zn(NTf_2)_2$	CH_2Cl_2	−75	24	96	98

[a] Unless noted, all reactions performed at 0.10 M in substrate **1** and 0.50 M in substrate **2a**, with 10 mol % catalyst loading in 0.5 mL of solvent. [b] Isolated yields. [c] Determined by chiral HPLC; ND = not determined. [d] Reaction performed at 0.20 M in substrate **1**, with 0.25 mL of solvent and 20 mol % catalyst used.

obtained in the presence of $Zn(OTf)_2$ (entry 4). Gratifyingly, $Zn(NTf_2)_2$/Ph-dbfox gave the adduct **3a** in good ee and excellent yield (entry 6). Notably, the use of $Zn(ClO_4)_2$/Ph-dbfox as a chiral Lewis acid provided **3a** in comparable enantioselectivity, but less efficiently than $Zn(NTf_2)_2$ (entry 5). Therefore, $Zn(NTf_2)_2$/Ph-dbfox was chosen as a catalyst system in the following reactions. A subsequent solvent survey revealed that CH_2Cl_2 was the solvent of choice with regards to both enantioselectivity and yield. In addition, the effects of reaction temperature were also evaluated. It was demonstrated that ee's obtained and the reaction time required were dependent on the reaction temperature. Lowering the reaction temperature resulted in increased enantioselectivity from 75% to 89% ee (entry 6 vs 10) with 98% yield. The enantioselectivity was further increased at −60 °C, generating **3a** in up to 96% ee with 96% yield (entry 11). The best ee (98%) was observed at −75 °C under higher catalyst loading with a higher concentration (entry 12).

Under the optimized reaction conditions, a variety of pyrroles were screened using **1** as the nucleophile acceptor. The results are presented in Table 2. The reaction of unprotected pyrrole **2b** gave the product **3b** in 97% yield with 99% ee (entry 1). The absolute configuration of **3b** was assigned as *S*.[11] It should be noted that high enantioselectivities were observed independent of the substitutions on the pyrrole nitrogen as well as the 2-position (92−97% ee, entries 2−7). In addition, pyrroles containing electron-withdrawing and sterically bulky groups such as Bn and Ph displayed inferior reactivity and selectivity (<90% ee, entries

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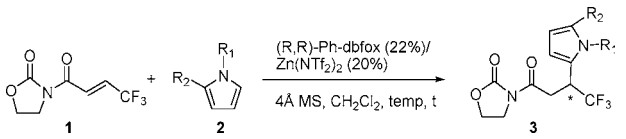
(11) The absolute configuration of **3b** was assigned as *S* after derivatization to **4** and comparison of optical rotation to a sample of (*R*)-**4** synthesized differently. See Supporting Information for details.

Table 2. Substrate Generality[a]



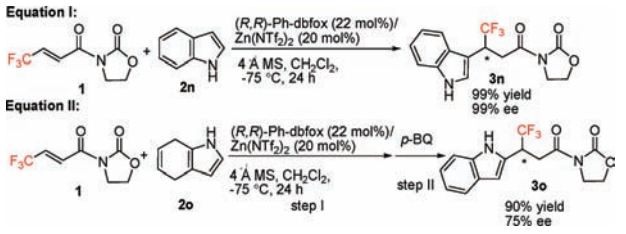
entry	R^1	R^2	**2**[b]	**3**	temp (°C)	t (h)	yield (%)[c]	ee (%)[d]
1	H	H	**2b**	**3b**	−75	24	97	99
2	H	Me	**2c**	**3c**	−75	24	96	97
3	H	Et	**2d**	**3d**	−75	24	98	92
4	Et	H	**2e**	**3e**	−75	24	96	96
5	*n*-Pr	H	**2f**	**3f**	−75	24	96	95
6	*n*-Bu	H	**2g**	**3g**	−75	36	95	93
7	allyl	H	**2h**	**3h**	−75	36	90	95
8	Bn	H	**2i**	**3i**	−60	48	93	85
9	Ph	H	**2j**	**3j**	−20	24	94	88
10	Me	Me	**2k**	**3k**	−75	24	97	94
11	Me	Et	**2l**	**3l**	−75	48	99	88
12	Me	Bn	**2m**	**3m**	−75	48	95	76

[a] Unless noted, all reactions performed at 0.20 M in substrate **1**, with 0.25 mL of solvent and 20 mol % catalyst used. [b] 5.0 equiv of pyrroles was used with the exception of *N*-methyl pyrroles having substituents at the 2-position (2.0 equiv). [c] Isolated yields. [d] Determined by chiral HPLC.

8 and 9), generally needing a higher reaction temperature for the reactions to reach completion. Disubstituted pyrroles **2k**−**m** also worked well under the same conditions to provide **3k**−**m** in up to 94% ee (entries 10−12).

We next focused on the asymmetric FC reaction of **1** with indole[5c] and 4,7-dihydroindole. Whereas the locus of nucleophilicity of pyrroles is at C-2, it resides at C-3 for the indoles. Initial examination of the indole **2n** (2 equiv) was encouraging, furnishing the 3-substituted indole with excellent levels of selectivity (99% ee) and in nearly quantitative yield (Scheme 1, eq I). Although C-2 substituted indoles were

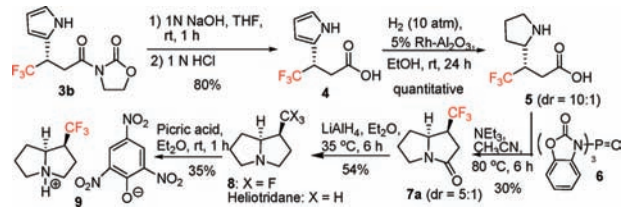
Scheme 1. Asymmetric FC Reaction between β-CF_3 Acrylates **1** and Indoles



rather difficult to be obtained in this FC reaction, we solved this problem by the use of pyrrole derivative **2o** as follows: the 4,7-dihydroindole **2o** was employed as a disubstituted pyrrole nucleophile and easily aromatized with *p*-benzoquinone (*p*-BQ) oxidation.[12] Taking advantage of this property, 2-substituted indole **3o** was successfully accessed with 75% ee in 90% yield (Scheme 1, eq II).[13]

To demonstrate the synthetic utility of the FC reaction, the synthesis of trifluorinated heliotridane[14] was carried out (Scheme 2). The FC reaction adduct **3b** (98% ee) was

Scheme 2. Synthesis of Trifluorinated Heliotridane



converted into the carboxylic acid **4** in 80% yield. Rhodium-catalyzed hydrogenation of **4** in the presence of H_2 (10 atm) at rt afforded 2-pyrrolidine carboxylic acid **5** in quantitative yield. Without further purification, **5** was successfully cyclized to the trifluoromethylated hexahydropyrrolizin-3-one **7a** in the presence of tris(1,3-dihydro-2-oxobenzoxazolin-3-yl) phosphine oxide **6** when heated under reflux in acetonitrile.[14b] A volatile trifluorinated heliotridane **8** was obtained by using $LiAlH_4$ reduction of **7a** in ether, which was finally isolated as a picrate **9**.

In summary, we have developed a simple asymmetric catalytic Friedel−Crafts reaction[15] to obtain various chiral trifluoromethylated pyrroles in good yields and with excellent enantioselectivities. The chiral product of the asymmetric FC reaction facilitated the preparation of unreported optically active trifluorinated heliotridane. The pharmacological property of **8** is currently being studied.

Acknowledgment. Support was provided by KAKENHI (21390030). We also thank Central Glass Co., Ltd. for support.

Supporting Information Available: Experimental procedures, spectra data for all new compounds, stereochemical proof of **3b** and **7a**, and HPLC charts. This material is available free of charge via the Internet at http://pubs.acs.org.

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