Organocatalysts

Highly Enantioselective Organocatalytic Hydroxyalkylation of Indoles with Ethyl Trifluoropyruvate**

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Dedicated to Professor George A. Olah

Over the years, the application of organofluorine compounds has received extensive attention in the pharmaceutical industry and in materials science owing to the unique properties of fluorinated compounds.[1] Trifluoromethylated compounds are particularly interesting as the strong electron-withdrawing effect of the CF_3 group leads to exceptional properties. These molecules are frequently applied as drugs or chiral resolution agents as examples.[1,2] Despite the numerous methodologies, the synthesis of trifluoromethylated compounds are still in great demand.[3] The Friedel–Crafts alkylation of aromatic compounds with activated carbonyl compounds is one of the most important C–C bond-forming reactions.[4] Despite its importance, the number of asymmetric Friedel–Crafts reactions is limited and mostly based on the use of chiral Lewis acids.[5] A recently developed organocatalytic Friedel–Crafts alkylation reaction represents an important addition to this field.[6]

Herein, we describe the first highly enantioselective organocatalytic Friedel–Crafts hydroxyalkylation reaction. We demonstrate that with the application of pseudoenantiomeric cinchona alkaloids as catalysts in the reaction of substituted indoles and ethyl 3,3,3-trifluoropyruvate, the synthesis of both enantiomeric products is possible (Scheme 1).

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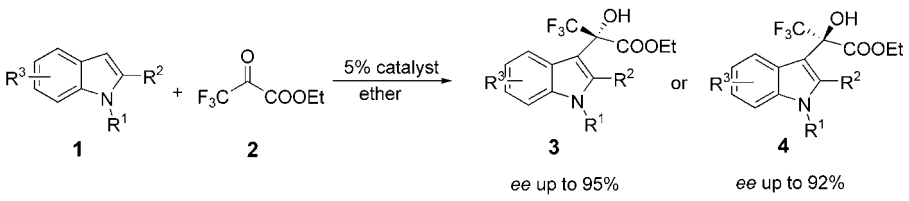
[**] Dedicated to Professor George A. Olah on the occasion of the 10th anniversary of his Nobel Prize. Financial support by the NSF (CHE-9512445) at Michigan Technological University and by the Loker Hydrocarbon Research Institute at USC is gratefully acknowledged. Professor Tse Lok Ho of National Chiao Tung University, Taiwan, is thanked for useful discussions.

Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.

  DOI: 10.1002/ange.200462877



1 2 3 4

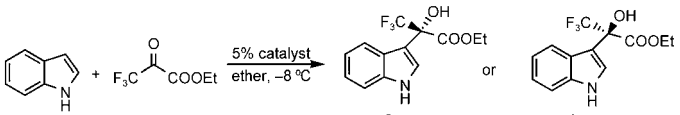
Scheme 1. Synthesis of chiral 3,3,3-trifluoro-2-(indol-3-yl)-2-hydroxylpropionic acid esters through catalysis by cinchona alkaloids. R^1 = H, Me; R^2 = H, Me, Ph; R^3 = H, Me, F, Cl, Br, I.

The target compounds are related to the well-known Mosher's acid,[2] and many of them have recently been synthesized as racemic mixtures by a superacid-catalyzed process.[7] In another recent attempt, a chiral copper(II)–bisoxazoline complex was used as a catalyst in the reaction of activated aromatics and ethyl 3,3,3-trifluoropyruvate and yielded the *S* enantiomer of the products.[8] Our present approach is based on the interaction between **2** and chiral alcohols including cinchona alkaloids.[9] By using these auxiliaries, a chiral intermediate can be obtained which can induce effective enantiodifferentiation in an organocatalytic process that is free of Lewis acids.[10] Cinchona alkaloids are very effective catalysts in many areas of asymmetric synthesis, such as chiral-base or phase-transfer catalysis, and organometallic reactions.[11] However, there are no data available concerning their use as chiral auxiliaries in Friedel–Crafts-type reactions. Our above hypothesis was tested in the reaction of indole (**1a**) and **2** with several optically active alcohols (e.g. menthol, α-methyl and α-trifluoromethyl benzyl alcohols) and aminoalcohols (e.g. prolinols, hydroxyprolines), including cinchona alkaloids and some of their derivatives (see Table 1), as chiral auxiliaries.

Cinchona alkaloids were found to be excellent catalysts for the test reaction, while the other chiral auxiliaries resulted in both poor yields and enantioselectivities of the products. As such, cinchona alkaloids were selected for further studies. After optimizing the reaction conditions (solvent, temperature, cinchona/trifluoropyruvate/indole ratios), the activity and selectivity of cinchona derivatives were compared. The optimized conditions and summarized results are shown in Table 2.

Table 2 shows that cinchonidine (CD) was the best catalyst towards the formation of **3a**, while cinchonine (CN) gave the highest yield and *ee* value for **4a**. Both catalysts provided excellent yields and enantioselectivities (up to 99% yield, 95% *ee*) in providing the opposite enantiomers. The initial reaction rates indicate that the application of cinchona alkaloids as catalysts significantly increases the reaction rates; in the case of CD the hydroxyalkylation takes place with rates that are more than two orders of magnitude higher than in the absence of catalyst. This observation unambiguously indicates that the enantiodifferentiation is a kinetic phenomenon in this reaction. Furthermore, the data obtained with *O*- and *N*-substituted cinchona derivatives clearly demonstrate that both the nitrogen atom of the quinuclidine ring and the 9-hydroxyl group play a vital role in the enantiodifferentiation. Blocking any of these two moieties results in very low enantioselectivities. On

Table 2: Enantioselective hydroxyalkylation of indole with ethyl 3,3,3-trifluoropyruvate in ether at −8 °C catalyzed by different cinchona alkaloids.

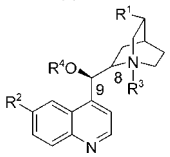


1a 2 3a 4a

Catalyst	*t* [h][a]	Major product	Reaction rate [mmol h^{-1}][b]	Yield [%][c]	*ee* [%][d]
–	90	**3a**+**4a** (racemic)	5.2×10^{-3}	95	0
CD	2	**3a**	8.2×10^{-1}	99	95
CN	2	**4a**	6.5×10^{-1}	98	90
QN	2.5	**3a**	3.4×10^{-1}	98	92
QD	3	**4a**	1.4×10^{-1}	98	87
DHQD	3	**3b**	1.2×10^{-1}	98	83
NBnCD	8	**3a**	8.3×10^{-2}	98	4
NBnCN	24	**4a**	2.1×10^{-2}	98	6
AcOCD	16	**3a**	4.2×10^{-2}	97	7
AcOCN	17	**4a**	3.9×10^{-2}	97	3

[a] Time needed to complete the reaction; [b] Initial rates; [c] Isolated yields; [d] Average of five parallel reactions.

Table 1: Structures of cinchona alkaloids and their derivatives, used as catalysts for enanatioselective hydroxylations of indole with ethyl-3,3,3-trifluoropyruvate.

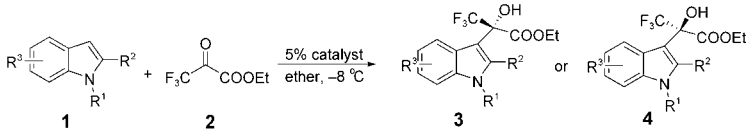


R^1	R^2	R^3	R^4	C8	C9	Catalyst	
vinyl	H	–	H	*R*	*S*	cinchonidine	CD
vinyl	H	–	H	*S*	*R*	cinchonine	CN
vinyl	OCH_3	–	H	*R*	*S*	quinine	QN
vinyl	OCH_3	–	H	*S*	*R*	quinidine	QD
Et	OCH_3	–	H	*S*	*R*	dihydroquinidine	DHQD
vinyl	H	Bn	H	*R*	*S*	*N*-benzylcinchonidine	NBnCD
vinyl	H	Bn	H	*S*	*R*	*N*-benzylcinchonine	NBnCN
vinyl	H	–	Ac	*R*	*S*	9-*O*-acetylcinchonidine	AcOCD
vinyl	H	–	Ac	*S*	*R*	9-*O*-acetylcinchonine	AcOCN

Bn = benzyl.

the basis of these results CD and CN were selected for the synthesis of *S* and *R* isomeric products, respectively. A wide range of substituted indoles were studied, and representative results are tabulated in Table 3.

Table 3: Enantioselective hydroxyalkylation of substituted indoles with ethyl 3,3,3-trifluoropyruvate in ether at −8 °C catalyzed by cinchona alkaloids.



1 **2** **3** **4**

Reactant	R^1	R^2	R^3	Catalyst	Product	Yield [%][a]	*ee* [%][b]
1a	H	H	H	CD	**3a**	99	95
	H	H	H	CN	**4a**	99	90
1b	H	H	5-Me	CD	**3b**	98	93
	H	H	5-Me	CN	**4b**	99	92
1c	H	H	6-Me	CD	**3c**	97	95
	H	H	6-Me	CN	**4c**	98	90
1d	H	H	5-F	CD	**3d**	97	92
	H	H	5-F	CN	**4d**	98	86
1e	H	H	5Cl	CD	**3e**	96	90
	H	H	5-Cl	CN	**4e**	98	86
1f	H	H	5-Br	CD	**3f**	97	87
	H	H	5-Br	CN	**4f**	96	85
1g	H	H	5-I	CD	**3g**	97	87
	H	H	5-I	CN	**4g**	97	85
1h	H	H	5-COOMe	CD	**3h**	96	88
	H	H	5-COOMe	CN	**4h**	97	85
1j	H	H	5-OMe	CD	**3j**	98	83
	H	H	5-OMe	CN	**4j**	96	83

[a] Isolated yields. [b] Average of five parallel reactions.

Results of Table 3 indicate that both enantiomers of the products can be synthesized with high yields and enantioselectivities by appropriate selection of the catalyst. As a limitation of the approach it is worth mentioning that 1-methyl-indole derivatives ($R^1 = Me$) always gave good yields, but only racemic mixtures of products. It was also observed that the substituent in the 2-position of indole also played a crucial role. When R^2 is a relatively small group (2-Me-indole), the *ee* value of the product decreases to 75% (from 95%) with CD and 64% (from 90%) with CN. When R^2 is bulkier (2-Ph-indole), enantiodifferentiation is not observed and a racemic mixture of products is obtained.

Although it is premature to provide a detailed mechanistic explanation at this level, the major observations regarding the mechanism are as follows: 1) The indole NH, cinchona 9-OH, and quinuclidine N groups cannot be blocked; 2) Substituents in the 2-position of aromatics hinder or block enantiodifferentiation; 3) ^{19}F NMR investigations, in agreement with the literature,[9] clearly showed that **2** forms hemiketals with cinchona alkaloids through the 9-hydroxyl group. Such intermediates, however, are not effective electrophiles. The reaction of the hemiketal (prepared from a 1:1 mixture of **2** and CD) and indole gave low *ee* values in an extremely slow reaction (64% yield after 20 h, 47% *ee*); 4) The enantiodifferentiation is a kinetic phenomenon in this system (see reaction rate data in Table 2). We propose that the alkaloid forms a weak hydrogen-bonded complex with indole and then anchors **2** to form an active hydrogen-bonded intermediate. Thus the alkaloid provides a chiral environment and also activates the electrophilic carbonyl group of **2**.

In conclusion, an unprecedented cinchona alkaloid catalyzed, highly enantioselective organocatalytic Friedel–Crafts hydroxyalkylation of indole derivatives has been developed. Besides the isolation of products in high yields and enantioselectivities, the major advantages of the process are that the reactions are clean and fast and that commercially available economic catalysts can provide both enantiomers of the products, as desired. The application of this new method carries the potential of also being extended to several other reactions.

Received: December 10, 2004
Revised: January 21, 2005
Published online: April 21, 2005

Keywords: alkylation · C–C coupling · cinchona alkaloids · enantioselectivity · nitrogen heterocycles

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