Communication

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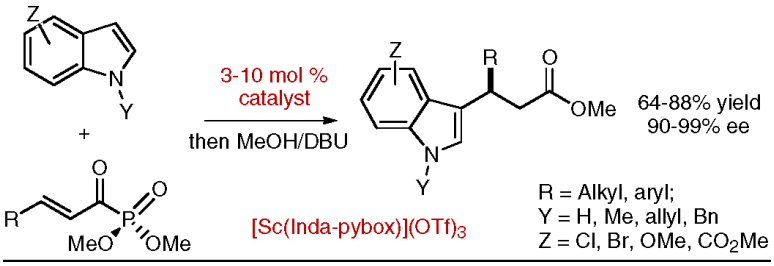

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Enantioselective Indole Friedel−Crafts Alkylations Catalyzed by Bis(oxazolinyl)pyridine−Scandium(III) Triflate Complexes

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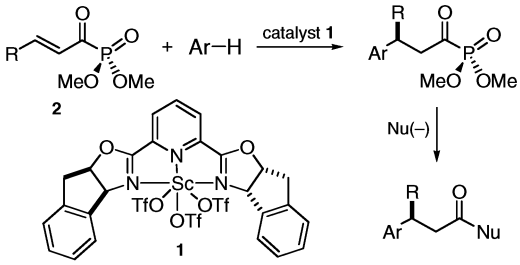
The Lewis acid-promoted addition of aromatic nucleophiles to electron-deficient alkenes is a powerful bond-forming reaction in organic chemistry.[1] While the development of asymmetric catalytic versions of this reaction provides access to important enantioenriched aryl-substituted products, only a few examples of this process have been reported.[2] Previous reports from this laboratory have demonstrated that bis(oxazolinyl)pyridine (pybox)−scandium(III) triflate complexes are effective chiral Lewis acid catalysts exhibiting good chelating potential.[3,4] In this Communication, we describe the utility of the chiral scandium complex **1**[5] in the catalyzed additions of electron-rich aromatic substrates to α,β-unsaturated acyl phosphonates[6] **2** (eq 1). These intermediate acyl phosphonates are effective active esters that may be employed in subsequent acyl-transfer reactions. Accordingly, these intermediates may be further transformed without isolation into product esters or amides.[7]



(1)

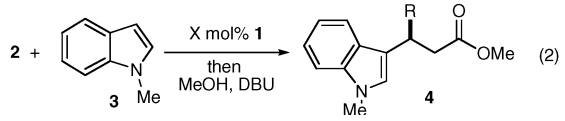
Since the indole skeleton is an important substructure in both natural products and therapeutic agents,[8] *N*-methylindole (**3**) was selected for this study. A series of $Sc(OTf)_3$−pybox complexes were evaluated in the illustrated reaction, and pybox complex **1** emerged as the most promising Lewis acid catalyst. For the purpose of product analysis and characterization, the intermediate β-indolyl acyl phosphonates were converted to the corresponding methyl esters by direct addition of MeOH and an amine to the reaction mixture (DBU, room temperature, 30 min).[7]

The Friedel−Crafts alkylation of *N*-methylindole (**3**) with representative acyl phosphonates **2** is provided in Table 1.[9] Entry 1 indicates that the reaction may be conducted at temperatures up to −20 °C without deleterious effect on selectivity. High enantioselectivities may be maintained at catalyst loadings as low as 3 mol % (95% ee, 72% yield, entry 4). The reaction is also tolerant of a selection of β-alkyl substitutents on the unsaturated acyl phosphonate (**2**) (entries 5−8). Even the encumbering isopropyl substituent does not adversely affect the yield or enantioselectivity (entry 6, 99% ee, 82% yield).

A representative selection of indole derivatives was next evaluated in the Friedel−Crafts alkylation with acyl phosphonate **2a** (Table 2). Although the parent indole reacted with diminished selectivity (entry 1, 83% ee), the other *N*-alkyl-substituted indoles (methyl, allyl, and benzyl) afford alkylated products with higher selectivity (90−99% ee, entries 2−8).

Indole derivatives with either electron-withdrawing or electron-donating substituents at C(5) are competent substrates (entries 4−7).[10] While a C(4) chlorine substituent lowers conversion (51% yield), a good level of enantioselectivity is still observed (90% ee) (entry 8).

Table 1. Scandium-Catalyzed Alkylations of *N*-Methylindole with Representative α,β-Unsaturated Acyl Phosphonates **2**[a]

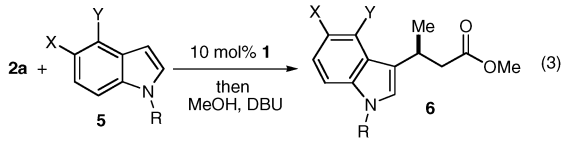


(2)

entry	phosphonate	R	mol % **1**	time (h)	ee (%)[b]	yield (%)
1[c]	**2a**	Me	10	4	93	79 (**4a**)
2	**2a**	Me	10	4	97	75 (**4a**)
3	**2a**	Me	5	20	98	88 (**4a**)
4	**2a**	Me	3	48	95	72 (**4a**)
5[d]	**2b**	Et	10	17	97	65 (**4b**)
6	**2c**	*i*-Pr	10	20	99	82 (**4c**)
7[e]	**2d**	$CH_2OTBDPS$	10	17	94	57 (**4d**)
8	**2e**	Ph	20	48	80	85 (**4e**)

[a] All reactions were carried out in CH_2Cl_2 at −78 °C (0.2 M), except where noted. [b] Enantiomeric excess determined by chiral HPLC using Chiracel OD-H columns. [c] Reaction carried out at −20 °C. [d] Reaction carried out at −50 °C. [e] Morpholine quench: 94% ee, 73% yield.

Table 2. Scandium-Catalyzed Alkylation of Substituted Indoles with Crotonyl Acyl Phosphonate (**2a**)[a]



(3)

entry	indole	R	X	Y	time (h)	ee (%)[b]	yield (%)
1	**5a**	H	H	H	3	83	83 (**6a**)
2	**5b**	allyl	H	H	5	98	76 (**6b**)
3	**5c**	Bn	H	H	20	99	85 (**6c**)
4	**5d**	Bn	Br	H	19	>99	64 (**6d**)
5	**5e**	Bn	Cl	H	19	>99	66 (**6e**)
6	**5f**	Bn	CO_2Me	H	16	97	68 (**6f**)
7	**5g**	Bn	OMe	H	19	97	67 (**6g**)
8[c]	**5h**	Bn	H	Cl	48	90	51 (**6h**)

[a] All reactions carried out in CH_2Cl_2 at −78 °C (0.2 M in substrate). [b] Enantiomeric excess determined by chiral HPLC using Chiracel OD-H columns. [c] 20 mol % catalyst.

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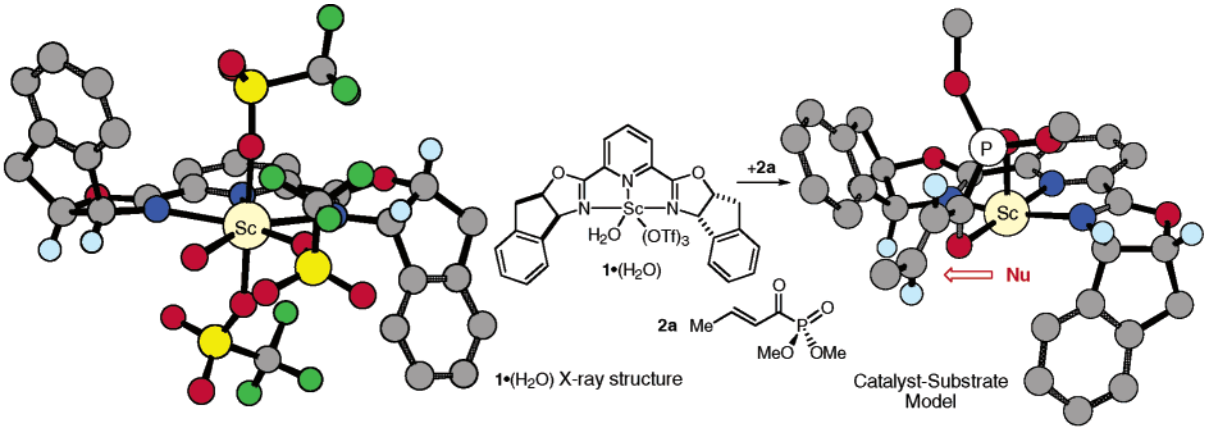
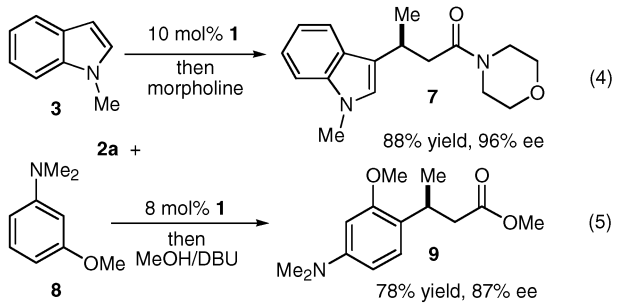


Figure 1. Crystal structure of the complex **1**·hydrate. Model of the [Sc((*S*,*S*,*S*,*S*)-Inda-pybox)(OTf)(crotonyl-acyl phosphonate **2a**)]$^{2+}$ complex.

The procedure may be altered to afford amide reaction products directly (eq 4). In this instance, the reaction is carried out as reported in Table 1 (entry 1) and quenched with morpholine (room temperature) to afford **7** (96% ee, 88% yield).[11] In addition, these reactions are not limited to indole alkylations. For example, the electron-rich 3-dimethylaminoanisole (**8**) is also an effective nucleophile (eq 5).



The structure of the scandium−pybox complex **1**, as its derived monohydrate **1**·(H_2O), was determined by X-ray crystallography (Figure 1). The pentagonal bipyramidal geometry of this complex is remarkably similar to that of a closely related X-ray structure, Sc[(*S*,*S*)-Ph-pybox(H_2O)]($OTf)_3$, recently reported by us.[3a] A model that rationalizes the observed sense of asymmetric induction (eq 1) is provided in Figure 1.[12] All extraneous ligands in this model have been removed for clarity. Placement of the sterically demanding coordinating phosphonate oxygen in the more accessible apical position orients the carbonyl oxygen toward the ligand plane. The addition of nucleophiles from the indicated s-cis enoate diastereoface should be favored on the basis of resident nonbonding interactions. At the present time, the issue of the coordination number (6 or 7) of the catalyst−substrate complex remains unresolved.

In summary, scandium−pybox complexes are efficient catalysts for the Friedel−Crafts additions of electron-rich aromatic nucleophiles to α,β-unsaturated acyl phosphonates. Further studies of the utility of these scandium complexes as chiral Lewis acids are in progress.

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Supporting Information Available: Experimental procedures, spectral data for all new compounds, crystallographic data, and stereochemical proof (PDF, CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) Only alkylation at the 3-position of the indole structure was observed.

(10) Substitution at the 2-position only slightly affects enantioselectivity, e.g., for 1,2-dimethylindole addition to **2a**, 86% ee, 94% yield.

(11) For examples of additions to morpholine amides, see: Douat, C.; Heitz, A.; Martinez, J.; Fehrentz, J.-A. *Tetrahedron Lett.* **2000**, *41*, 37−40 and references therein.

(12) The stereochemical model was created from the crystal structure of **1**·H_2O as follows. The coordinates of **1**·H_2O were accessed with ChemBats3D Pro (version 7.0). The two vicinal triflates and water molecule were replaced by the acyl phosphonate, and the molecular energy was minimized (MM2) with the ligand−metal bonds held constant.

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