Article

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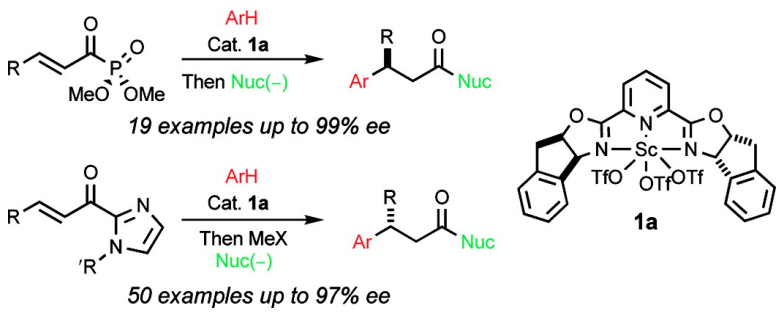

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Enantioselective Friedel−Crafts Alkylations Catalyzed by Bis(oxazolinyl)pyridine−Scandium(III) Triflate Complexes

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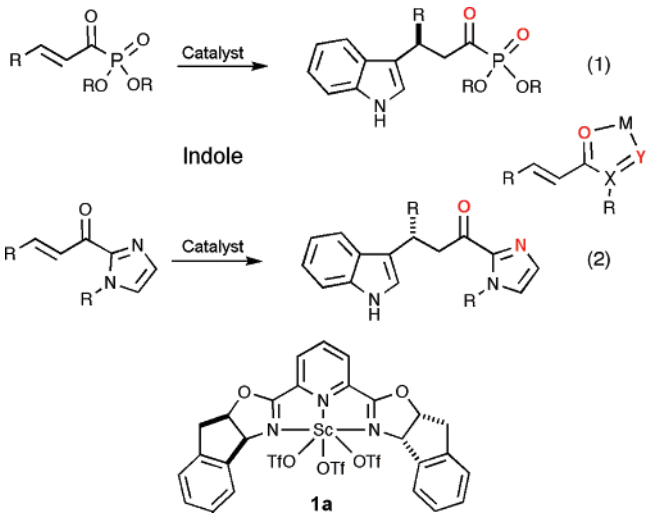
Abstract: The enantioselective Friedel−Crafts addition of a variety of indoles catalyzed by bis(oxazolinyl)-pyridine−scandium(III) triflate complexes (Sc(III)−pybox) was accomplished utilizing a series of β-substituted α,β-unsaturated phosphonates and α,β-unsaturated 2-acyl imidazoles. The acyl phosphonate products were efficiently transformed into esters and amides, whereas the acyl imidazole adducts were converted to a broader spectrum of functionalities such as esters, amides, carboxylic acids, ketones, and aldehydes. The sense of stereoinduction and level of enantioselectivity were found to be functions of the size of the substrate employed, the substitution on the ligand, and the catalyst loading. Molecular modeling of the catalyst with the bound substrates was performed based on the crystal structures of the catalyst complexes and the sense of stereoinduction observed in the addition reaction. Nonlinear effects over a range of catalyst concentrations implicate a mononuclear complex as the active catalyst.

Introduction

The Friedel−Crafts reaction and its enantioselective variants are powerful carbon−carbon bond forming transformations in organic chemistry.[1] Due to the prevalence of the indole nucleus in both natural products[2] and potential medicinal agents,[3] considerable effort has been extended in the development of enantioselective alkylation reactions between this important heterocycle and α,β-unsaturated carbonyl compounds.[4] This investigation documents our studies directed toward the development of the chiral scandium(III)−pybox complex **1a** for the enantioselective alkylation of the indole and pyrrole nuclei, and related electron-rich heteroaromatic substrates, with compatible α,β-unsaturated carbonyl derivatives.

This investigation has focused on the evaluation of both substrate structure, its chelating potential (eqs 1, 2), and catalyst architecture for the development of an effective enantioselective alkylation process.

Jørgensen was the first to extrapolate the Cu(II) chelation motif in exploring this reaction utilizing our Cu(II)−bis-(oxazoline) catalyst with α-keto esters and alkylidene malonates (eqs 3, 4).[5] Tang later improved on the use of arylidene malonates in the Friedel−Crafts reaction by utilizing trisoxazoline Cu(II) complexes.[6] Concurrently, Umani−Ronchi reported the addition reaction on two fronts: first, with the use of α,β-unsaturated thioesters with a Pd(II)−(Tol-binap) catalyst, and second, by designing a single-point binding catalyst for this important transformation.[7] During this present investigation, Palomo demonstrated that α′-hydroxy enones are also competent



(1) For a review of the Friedel−Crafts reaction, see: Olah, G. A.; Krishnamurti, R.; Prakash, G. K. S. Friedel−Crafts Alkylations. In *Comprehensive Organic Synthesis;* Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 3, pp 293−339.
(2) For examples of natural products which are relevant to the formed stereocenter, see: cycloaplysinopsin (a) Mancini, I.; Guella, G.; Zibrowius, H.; Pietra, F. *Tetrahedron* **2003**, *59*, 8757−8762. 10,11-Dimethoxynareline: (b) Kam, T.; Choo, Y. *J. Nat. Prod.* **2004**, *67*, 547−552. Hapalindoles: (c) Kinsman, A. C; Kerr, M. A. *J. Am. Chem. Soc.* **2003**, *125*, 14120−14125. (d) Huber, U.; Moore, R. E.; Patterson, G. M. L. *J. Nat. Prod.* **1998**, *61*, 1304−1306.
(3) For examples of potential medicinal agents relevant to the formed stereocenter, see: (a) Rawson, D. J.; Dack, K. N.; Dickinson, R. P.; James, K. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 125−128. (b) Dillard, R. D., et al. *J. Med. Chem.* **1996**, *39*, 5119−5136. (c) Chang-Fong, J.; Rangisetty, J. B.; Dukat, M.; Setola, V.; Raffay, T.; Roth, B.; Glennon, R. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 1961−1964.
(4) For a review of the asymmetric Friedel−Crafts reaction, see: Bandini, M.; Melloni, A.; Umani-Ronchi, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 550−556.
(5) (a) Jensen, K. B.; Thorhauge, J.; Hazell, R. G.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2004**, *40*, 160−163. (b) Zhuang, W.; Hansen, T.; Jørgensen, K. A. *Chem. Commun.* **2001**, 347−348. For a review on the use of Cu-(II)−bis(oxazoline) catalysts, see: (c) Johnson, J. S.; Evans, D. A. *Acc. Chem. Res.* **2000**, *33*, 325−335.
(6) (a) Zhou, J.; Tang, Y. *Chem. Commun.* **2004**, 432−433. (b) Zhou, J.; Ye, M.-C.; Huang, Z.-Z.; Tang, Y. *J. Org. Chem.* **2004**, *69*, 1309−1320.

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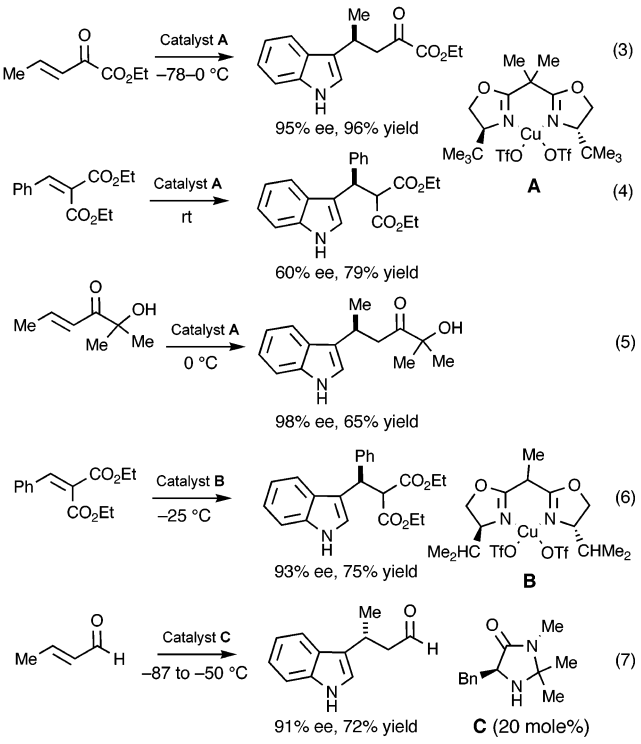
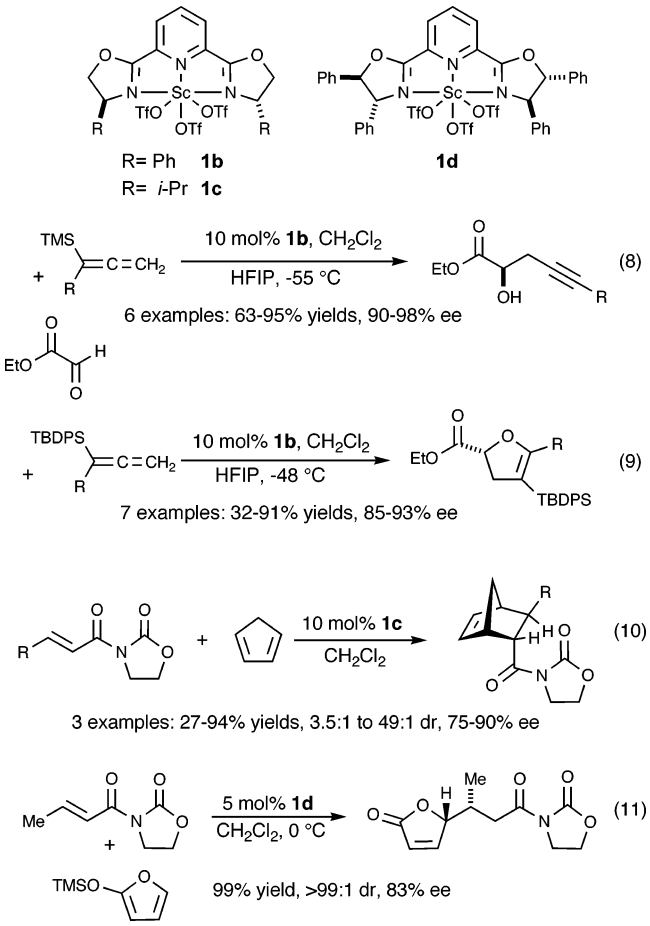
electrophiles for indole and pyrrole alkylations at ambient temperatures with the same catalyst (eq 5).[8] Organocatalytic processes have also been recently reported (eq 7).[9] Despite the advances in the development of this reaction, there remains a need for a general catalyst that functions under mild reaction conditions.

Enantioselective Friedel Crafts Reactions with the Indole Nucleus



While Cu(II) complexes have proven to be effective chelating chiral Lewis acids in this and related transformations (eqs 3−6),[10] we have continued to expand the list of Lewis acids that might be employed for these reactions. Our previous studies identified bis(oxazolinyl)pyridine−scandium(III) (Sc(III)−pybox) complexes as potential catalyst candidates for this process.[11−15] The present investigation presents a full account of our studies in this area.

Chiral Sc(III) Complexes. The potential utility of pybox−$Sc(OTf)_3$ complexes as chelating chiral Lewis acids surfaced in 2001 in independent publications from our laboratory (eqs 8, 9)[11] and those of Fukuzawa (eq 10)[16] and Desimoni (eq 11).[17] Subsequently, this catalyst complex has been used in enantioselective Nazarov cyclizations[18] and carbonyl ylide dipole cycloadditions.[19] In each of these examples, the substrates are designed for chelate organization; accordingly, one might conclude that chelate control is probably operating in these reactions.



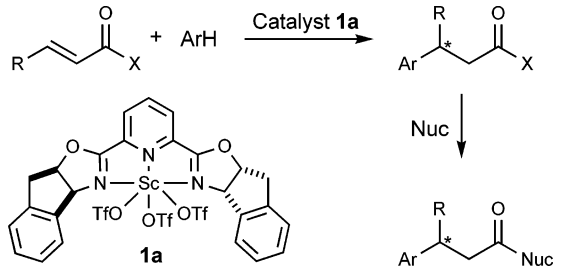
In addition to the illustrated allenylsilane additions (eqs 8, 9),[11] we have also explored the utility of pybox−$Sc(OTf)_3$ complexes in aldol additions to ethyl glyoxylate,[12] in ene reactions with ethyl glyoxylate and *N*-phenyl glyoxamide,[13] and in the addition of allylsilanes to *N*-phenylglyoxamide.[14] This report provides a full account of the development of the Friedel−Crafts reaction utilizing scandium triflate complex **1a** focusing on reaction generality and the subsequent product elaborations (Scheme 1).[15] In order to access the full potential of this catalyst, we explored the nature of the binding of α,β-unsaturated acyl phosphonate and α,β-unsaturated 2-acyl imidazole substrates to the catalyst with an emphasis on the geometry of the Sc(III)−PyBox catalyst−substrate complexes.

Results and Discussion

We initiated our investigation in the indole Friedel−Crafts reaction with scandium(III)−pybox complex **1a** by focusing on

(7) (a) Bandini, M.; Melloni, A.; Tommasi, S.; Umani-Ronchi, A. *Helv. Chem. Acta* **2003**, *86*, 3753−3763. (b) Bandini, M.; Fagioli, M.; Melchiorre, A. M.; Umani-Ronchi, A. *Tetrahedron Lett.* **2003**, *44*, 5843−5846. (c) Bandini, M.; Fagioli, M.; Garavelli, M.; Melloni, A.; Trigari, V.; Umani-Ronchi, A. *J. Org. Chem.* **2004**, *69*, 7511−7518.
(8) Palomo, C.; Oiarbide, M.; Kardak, B. G.; García, J. M.; Linden, A. *J. Am. Chem. Soc.* **2005**, *127*, 4154−4155.
(9) (a) Paras, N. A.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2001**, *123*, 4370−4371. (b) Austin, J. F.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 1172−1173.
(10) For selected reviews of bis(oxazoline) Cu(II) catalysis, see: (a) Evans, D. A.; Rovis, T.; Johnson, J. S. *Pure Appl. Chem.* **1999**, *71*, 1407−1415. (b) See also ref 5c.
(11) Evans, D. A.; Sweeney, Z. K.; Rovis, T.; Tedrow, J. S. *J. Am. Chem. Soc.* **2001**, *123*, 12095−12096.
(12) Evans, D. A.; Masse, C. E.; Wu, J. *Org. Lett.* **2002**, *4*, 3375−3378.
(13) Evans, D. A.; Wu, J. *J. Am. Chem. Soc.* **2005**, *127*, 8006−8007.
(14) Evans, D. A.; Aye, Y.; Wu, J. *Org. Lett.* **2006**, *8*, 2071−2073.
(15) Preliminary accounts of this work have been communicated: (a) Evans, D. A.; Scheidt, K. A.; Fandrick, K. R.; Lam, H. W.; Wu, J. *J. Am. Chem. Soc.* **2003**, *125*, 10780−10781. (b) Evans, D. A.; Fandrick, K. R.; Song, H.-J. *J. Am. Chem. Soc.* **2005**, *127*, 8942−8943. (c) Evans, D. A.; Fandrick, K. R. *Org. Lett.* **2006**, *8*, 2249−2252.
(16) Fukuzawa, S.; Matsuzawa, H.; Metoki, K. *Synlett* **2001**, *5*, 709−711.
(17) Desimoni, G.; Faita, G.; Filippone, S.; Mella, M.; Zampori, M. G.; Zema, M. *Tetrahedron* **2001**, *57*, 10293−10212.
(18) (a) Liang, G.; Gradl, S. N.; Trauner, D. *Org. Lett.* **2003**, *5*, 4931−4934. (b) Liang, G.; Trauner, D. *J. Am. Chem. Soc.* **2004**, *126*, 9544−9545.
(19) Suga, H.; Inoue, K.; Inoue, S.; Kakehi, A. *J. Am. Chem. Soc.* **2002**, *124*, 14836−14837.

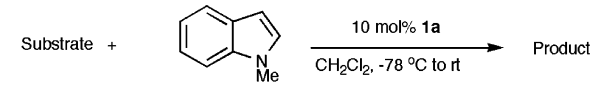
Scheme 1. Asymmetric Friedel–Crafts Alkylations Catalyzed by Bis(oxazolinyl)pyridine–Scandium(III) Triflate Complex **1a**

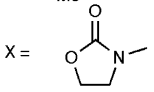
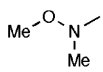
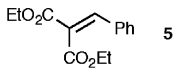
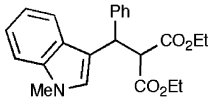
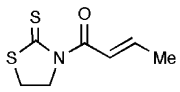
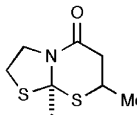
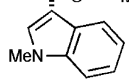
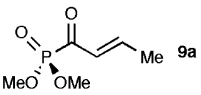
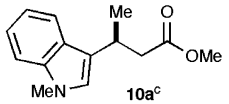


previously reported bidentate conjugate acceptors. Attempts at the addition employing α,β-unsaturated acyl oxazolidinone **2**[20] were disappointing as the reaction proceeded sluggishly (Table 1). We next considered the more reactive α,β-unsaturated thiazolidine-2-thione **7**[21] for the illustrated reaction. Instead of the desired Michael adduct, we observed the formation of bicyclic products **8a** and **8b** as racemates. We speculate that the formation of product **8** arises from the initial intramolecular attack of the thione to the unsaturated enone followed by the Friedel–Crafts reaction with the nucleophilic indole.[22] The α,β-unsaturated acyl pyrazole **3** and the α,β-unsaturated Weinreb amide **4** also provided trace amounts of product. The Friedel–Crafts reaction with the previously employed aryl alkylidene malonate **5**[5,23] was sluggish and provided the desired product in modest enantioselectivity (47% ee). Considering the previous success our group has had with α,β-unsaturated acyl phosphonates in the hetero Diels–Alder reaction,[24] we thought that these substrates might provide the needed increase in reactivity. We were pleased to see that the illustrated transformation with acyl phosphonate **9a** proceeded in quantitative yield and excellent enantioselectivity (97% ee, Table 1). With the success of the reaction with the acyl phosphonate **9a** we next explored the attributes of the addition reaction focusing on this substrate. It should be noted that the intermediate β-indolyl acyl phosphonates were converted to the corresponding methyl esters (**10a**) by direct addition of MeOH and DBU to the reaction mixture[25] for the purpose of product characterization and analysis.

α,β-Unsaturated Acyl Phosphonate Substrates. With the high stereoselectivity obtained in the indole alkylation utilizing α,β-unsaturated acyl phosphonate **9a**, we turned our attention to optimizing ligand and reaction parameters. A pybox ligand survey was conducted to determine the optimal ligand for the illustrated transformation (Table 2). All of the pybox ligands evaluated proved to be inferior to the Inda-pybox ligand **1a**. Interestingly, the Ph-pybox ligand **1b** provided the opposite sense of stereoinduction (−77% ee) as the structurally similar

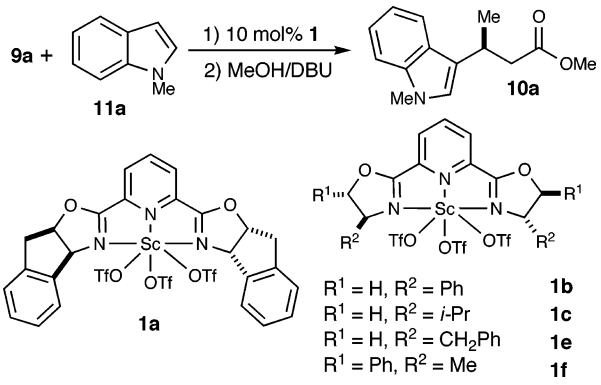
Table 1. Survey of Bidentate Enones in the Friedel–Crafts Reaction with *N*-Methyl Indole Catalyzed by Complex **1a**[a]



substrate	product
X =  **2**	Low Converson
 **3**	 **4**
 **5**	 **6** 77% yield, 9 d, 47% ee[b]
 **7**	 **8a**, β-Me **8b**, α-Me  47%, racemic
 **9a**	 **10a**[c] 99% yield, 4 h, 97% ee[b]

[a] Reactions were performed at 0.1–0.4 M in substrate. [b] Enantiomeric excess was determined by chiral HPLC (ODH, ADH, or OJH). [c] Initial acyl phosphonate product was treated with MeOH and DBU to acquire the corresponding methyl ester product **10a**.

Table 2. Pybox Ligand Survey for the Reaction with Acyl Phosphonate **9a**[a]



catalyst	conversion (%)	% ee[b]
1a	99	98
1b	99	−77
1c	99	72
1e	99	69
1f	99	−77

[a] All reactions were performed in CH_2Cl_2 at −78 °C and 0.13 M in substrate. [b] Enantiomeric excess was determined by chiral HPLC analysis.

Inda-pybox **1a** complex (98% ee). A subsequent solvent survey revealed that dichloromethane was optimal with regards to both enantioselectivities and yields (Table 3). THF provided the product in comparable enantioselectivity, but the reaction is less efficient than when it is conducted with dichloromethane. Diethyl ether and toluene were not effective solvents probably

(20) For some examples of the use of α,β-unsaturated acyl oxazolidinones from our group, see: (a) Evans, D. A.; Scheidt, K. A.; Johnson, J. N.; Willis, M. C. *J. Am. Chem. Soc.* **2001**, *123*, 4480–4491. (b) Evans, D. A.; Barnes, D. M.; Johnson, J. S.; Lectka, T.; von Matt, P.; Miller, S. J.; Murry, J. A.; Norcross, R. D.; Shaughnessy, E. A.; Campos, K. R. *J. Am. Chem. Soc.* **1999**, *121*, 7582–7594.

(21) Evans, D. A.; Miller, S. J.; Lectka, T.; von Matt, P. *J. Am. Chem. Soc.* **1999**, *121*, 7559–7573.

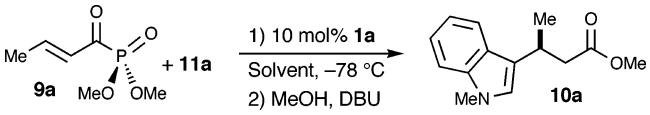
(22) A similar mechanism was proposed by Palomo in the sulfur transfer in *N*-enoyl oxazolidine-2-thiones. Palomo, C.; Oiarbide, M.; Dias, F.; Ortiz, A.; Linden, A. *J. Am. Chem. Soc.* **2001**, *123*, 5602–5603.

(23) For use of alkylidene malonates from our group, see: Evans, D. A.; Rovis, T.; Kozlowski, M. C.; Downey, C. W.; Tedrow, J. S. *J. Am. Chem. Soc.* **2000**, *122*, 9134–9142.

(24) Evans, D. A.; Johnson, J. S.; Olhave, E. J. *J. Am. Chem. Soc.* **2000**, *122*, 1635–1649.

(25) Dialkyl acyl phosphonates are highly effective acylating agents. Sekine, M.; Kume, A.; Hata, T. *Tetrahedron Lett.* **1981**, *22*, 3617–3620.

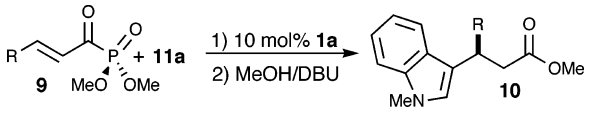
Table 3. Solvent Survey for the Reaction with Acyl Phosphonate **9a**[a]



solvent	time (h)	ee (%)[b]	yield (%)
CH_2Cl_2	4.3	97	94
THF	40	96	50
Et_2O	40	NA	1
toluene	46	NA	3

[a] Reactions were performed at 0.13 M in substrate. [b] Enantiomeric excess was determined by chiral HPLC analysis.

Table 4. Alkylations of *N*-Methylindole **11a** with Representative Acyl Phosphonates **9**[a]



R	mol % **1a**	temp (°C)	time (h)	% ee[b]	yield (%)
Me (**9a**)	10	−78	4	97	75 (**10a**)
Me (**9a**)	10	−56	20	96	99[c] (**10a**)
Me (**9a**)	10	−24	20	74	99[c] (**10a**)
Me (**9a**)	5	−78	20	98	88 (**10a**)
Me (**9a**)	3	−78	48	95	72 (**10a**)
Et (**9b**)	10	−50	17	97	65 (**10b**)
i-Pr (**9c**)	10	−78	20	99	82 (**10c**)
CH_2OTBDPS (**9d**)[d]	10	−78	17	94	57 (**10d**)
Ph (**9e**)	20	−78	48	80	85 (**10e**)

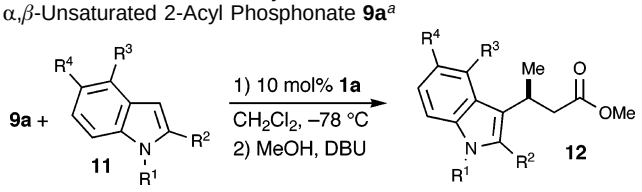
[a] All reactions were performed in CH_2Cl_2 at −78 °C (0.2 M). [b] Enantiomeric excess was determined by chiral HPLC analysis. [c] Reported as conversion based on ^{1}H NMR spectroscopy. [d] Morpholine quench to acquire the corresponding morpholine amide product: 94% ee, 73% yield.

due to catalyst insolubility. The effects of reaction temperature were also evaluated, and it was demonstrated that the reaction must be maintained ≤−50 °C to provide good enantioselectivity (Table 4). In addition, the illustrated reaction could be performed with as little as 3 mol % **1a** without loss of enantioselectivity. Our survey of the reaction variables reassured us that our initial reaction parameters were optimal, and such were employed for the rest of the study.

With the desired catalyst system in hand, the electrophile scope was evaluated. The reaction is tolerant of alkyl β-substitution on the enone **9** (>95% ee, Table 4). However, the corresponding reaction with the cinnamate derivative **9e** requires longer reaction times at higher catalyst loadings and displays a moderate decrease in stereoinduction (80% ee).

We next turned our attention to the effects of substitution of the indole ring in the illustrated transformation (Table 5). An increase in the steric requirements of the nitrogen substituent was shown to have a beneficial effect on stereoselectivity (indole **11b**, 83% ee; *N*-methylindole **11a**, 96% ee; *N*-benzylindole **11d**, 99% ee, Table 5). However, an increase the steric requirements at the 2-position of the indole nucleus leads to lower levels of stereoinduction (1,2-dimethylindole **11f**, 86% ee; 1-methyl 2-phenylindole **11g**, 65% ee). Strong electron-withdrawing groups on the indole nitrogen were shown to deactivate the substrate (1-tosylindole **11e**, and 4-nitroindole **11l**). Besides these limitations, the reaction is well tolerant of alkyl, methoxy, and carboxyl-4 and -5 substitution on the indole ring providing the products with excellent levels of selectivity (85−99% ee) and in good yields (62−85% yield, Table 5).

Table 5. Friedel−Crafts Alkylations of Substituted Indoles with α,β-Unsaturated 2-Acyl Phosphonate **9a**[a]

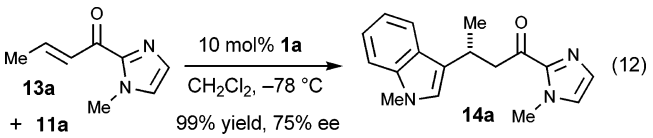


indole	R^1	R^2	R^3	R^4	time (h)	ee (%)[b]	yield (%)
11b	H	H	H	H	3	83	83 (**12b**)
11a	Me	H	H	H	21	96	78 (**10a**)
11c	Allyl	H	H	H	5	98	76 (**12c**)
11d	Bn	H	H	H	20	99	85 (**12d**)
11e	Ts	H	H	H		no reaction	
11f	Me	Me	H	H	2	86	94 (**12f**)
11g	Me	Ph	H	H	20	65	62 (**12g**)
11h	Bn	H	H	Br	19	>99	64 (**12h**)
11i	Bn	H	H	Cl	19	>99	66 (**12i**)
11j	Bn	H	H	OMe	19	96	67 (**12j**)
11k	Bn	H	H	CO_2Me	17	96	68 (**12k**)
11l	Bn	H	NO_2	H	6 d	NA	trace
11m[c]	Bn	H	Cl	H	20	99	85 (**12m**)
11n[c]	Bn	H	CO_2Me	H	47	85	68 (**12n**)

[a] All reactions were performed at 0.2 M in substrate. [b] Enantiomeric excess was determined by chiral HPLC analysis. [c] Reactions performed with 20 mol % **1a**.

α,β-Unsaturated 2-Acyl Imidazole Substrates. Although the acyl phosphonates **9** were found to be effective in the Friedel−Crafts reaction with indoles there are drawbacks to this substrate. First, the requisite α,β-unsaturated acyl phosphonates **9** were prepared in modest yields (20−47% yields), and the parent acyl phosphonate itself is a sensitive "active ester" functional group. Second, the reaction suffers from low substrate tolerance (only β-alkyl substituted enones provided >90% ee), and the reaction must be performed at ≤−50 °C to maintain high enantioselectivities (>90% ee). In consideration of the marginal stability of these active esters, we sought a new reactive bidentate enone that would exhibit an increased level of stability and comparable reactivity.

The 2-acyl imidazole group has been known as a latent acyl-transfer reagent.[26] Since α,β-unsaturated 1-acyl pyrazoles **3** have been successfully used as bidentate conjugate acceptors in asymmetric transformations,[27] we felt that 2-acyl imidazoles **13** could be employed in the same capacity. We surmised that the α,β-unsaturated 2-acyl imidazoles **13** would be more reactive due to the decrease in electron donation into the carbonyl group of the enone compared to the amide, ester, and imidate counterparts. It was therefore not surprising that substrate **13a** performed well in the conjugate addition (eq 12).

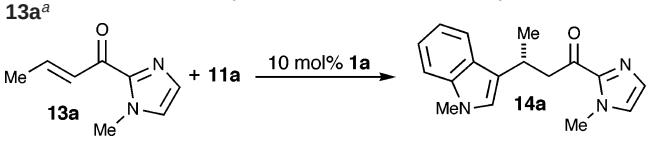


(12)

Interestingly, the catalyst system with acyl imidazole **13a** produced the opposite enantiomer of the formed stereocenter

(26) For the transformation of 2-acyl benzimidazoles to esters, amides, β-diketones, and β-ketoesters, see: (a) Miyashita, A.; Suzuki, Y.; Nagasaki, I.; Ishiguro, C.; Iwamoto, K.-I.; Higashino, T. *Chem. Pharm. Bull.* **1997**, *45*, 1254−1258. (b) For the transformation of 2-acyl imidazoles to ketones, β-diketones, β-ketoesters, and aldehydes, see: Ohta, S.; Hayakawa, S.; Nishimura, K.; Okamoto, M. *Chem. Pharm. Bull.* **1987**, *35*, 1058−1069.
(27) Itoh, K.; Kanemasa, S. *J. Am. Chem. Soc.* **2002**, *124*, 13394−13395.

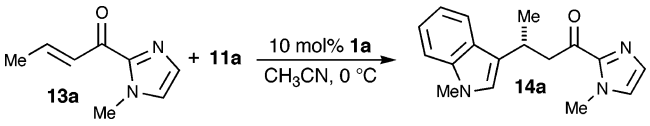
Table 6. Solvent Survey for the Reaction with 2-Acyl Imidazole **13a**[a]



solvent[b]	temp (°C)	conv (%)[c]	time (h)	% ee[d]
CH_2Cl_2	−78	99	5	75
THF	−78 to −27	17	48	79
toluene	−78 to −27	17	48	33
CH_3CN	−38	99	17	89
CH_2Cl_2/THF	−78	81	48	30
CH_2Cl_2/toluene	−78	89	48	60
CH_2Cl_2/CH_2CN	−78 to −27	99	48	79

[a] Reactions were performed at 0.26 M in substrate. [b] Mixed solvent systems refer to a 1:1 mixture of the corresponding solvents. [c] Conversion based on ^{1}H NMR spectroscopy. [d] Enantiomeric excess was determined by chiral HPLC analysis.

Table 7. Effects of Water on the Friedel−Crafts Reaction with α,β-Unsaturated 2-Acyl Imidazole **13a**[a]



additive	conv. (%)[b]	% ee[c]
none	99	87
15 mg 4 Å MS	99	90
0.05 equiv of H_2O	99	84
0.5 equiv of H_2O	80	53

[a] Reactions were performed at 0.26 M in substrate. [b] Conversion based on ^{1}H NMR spectroscopy. [c] Enantiomeric excess was determined by HPLC analysis.

as was seen in the corresponding reaction with acyl phosphonates **9a** while proceeding with a decrease in enantioselection (75% ee).

In order to improve the enantioselectivity of the addition reaction, we turned our attention to the optimization of reaction variables. A survey of solvents revealed acetonitrile as the choice solvent, offering an increase in enantioselectivity to 89% ee (Table 6). Water was found to be deleterious to the reaction (Table 7), as the addition of 4 Å sieves to the reaction increased the enantioselectivty of the transformation (90% ee) and afforded more reproducible results. Conversely, the addition of 0.5 equiv of water led to an erosion of selectivity (53% ee) and conversion (80%) in the illustrated transformation.

Upon examination of the effects of catalyst loading, we observed an inverse relationship between the amount of catalyst **1a** employed and the enantioselectivity of the process (Figure 1) when α,β-unsaturated 2-acyl imidazole **13a** was used as the electrophile: 1 mol % (98% ee), 10 mol % (90% ee), 20 mol % (78% ee), 50 mol % (11% ee). This rather dramatic trend was most evident when a stoichiometric amount of catalyst **1a** was used, resulting in a turnover in asymmetric induction (−31% ee). In contrast, when the reaction is performed with acyl phosphonate **9a**, we observed a rather flat catalyst loading profile as usually seen with related catalytic systems: 1 mol % (81% ee), 5 mol % (98% ee), 10 mol % (98% ee), 25 mol % (95% ee), 100 mol % (93% ee).

We next explored the effects of reaction temperature (Figure 2) and ligand substitution (Table 8). As illustrated in Table 8, the Inda-pybox complex **1a** again proved to be optimal for the

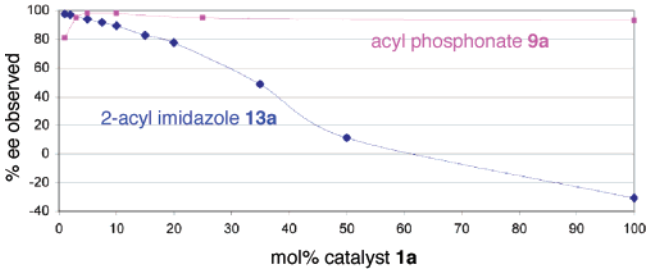


Figure 1. Catalyst loading profile for the Friedel−Crafts reaction with α,β-unsaturated 2-acyl imidazole **13a** (0.26 M in substrate, CH_3CN, 4 Å MS, −40 °C) and α,β-unsaturated acyl phosphonate **9a** (0.13 M in substrate, CH_2Cl_2, −78 °C) with *N*-methylindole (**11a**) catalyzed by Sc(III)−Inda-pybox **1a**.

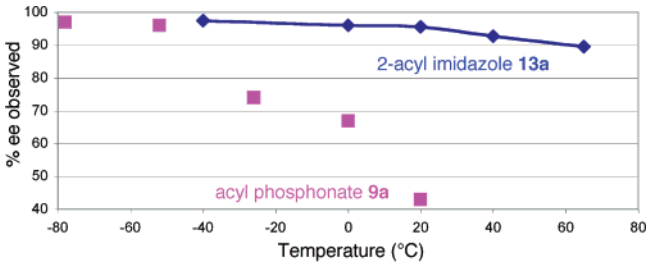
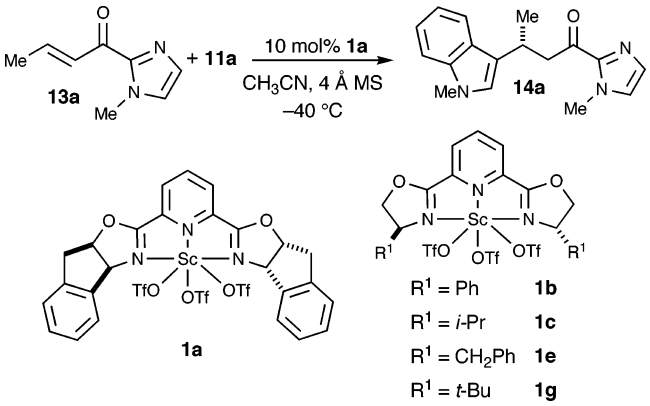


Figure 2. Temperature profile for the alkylation of *N*-methylindole (**11a**) with 2-acyl imidazole **13a** (1 mol % **1a**, 0.26 M in substrate, CH_3CN, 4 Å MS) and acyl phosphonate **9a** (10 mol % **1a**, 0.13 M in substrate, CH_3Cl_2).

Table 8. Ligand Survey for the Reaction between 2-Acyl Imidazole **13a** and *N*-Methylindole (**11a**)[a]



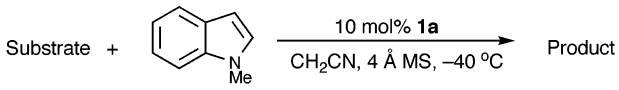
catalyst	conversion (%)[b]	% ee[c]
1a	91	98
1b	78	93
1c	55	96
1e	39	92
1g	19	36

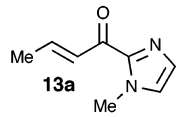
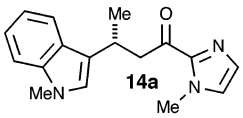
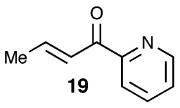
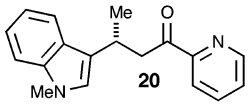
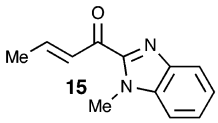
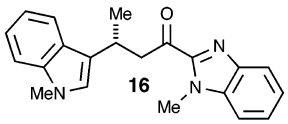
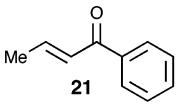
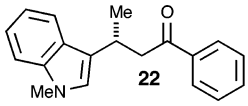
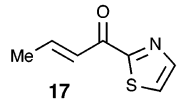
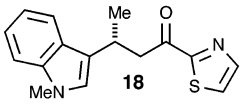
[a] All reactions were performed at 0.26 M in substrate. [b]Conversion based on ^{1}H NMR spectroscopy. [c]Enantiomeric excess was determined by chiral HPLC analysis.

transformation with regards to both enantiofacial control and reaction conversion. In contrast to the case with the acyl phosphonates (Table 2), we did not observe a reversal in selectivity when we employed the structurally similar Ph-pybox catalyst **1b**.

After determining the optimal ligand for the transformation, the impact of reaction temperature was evaluated. The reaction with imidazole **13a** showed an excellent temperature profile (Figure 2): the reaction could be performed at temperatures up to 65 °C while maintaining excellent enantiofacial control (90%

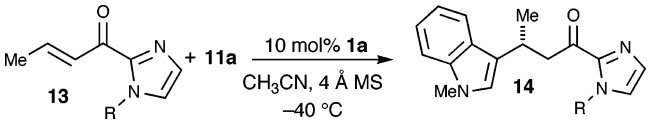
Table 9. Survey of α,β-Unsaturated 2-Acyl Heterocyclic Substrates in the Indole Friedel−Crafts Reaction Catalyzed by Sc(III)−Inda-pybox Complex **1a**[a]



substrate	product	substrate	product
 **13a**	 **14a** 99% yield, 20 h, 92% ee[b]	 **19**	 **20** 68% yield, 20 h, 31% ee[b]
 **15**	 **16** 92% yield, 20 h, 85% ee[b]	 **21**	 **22** 14% yield, 74 h, 30% ee[b]
 **17**	 **18** 97% yield, 20 h, 94% ee[b]		

[a] Reactions were performed at 0.26 M in substrate. [b] Enantiomeric excess was determined by chiral HPLC analysis.

Table 10. Survey of *N*-Substitution on the 2-Acyl Imidazole **13** in the Indole Friedel−Crafts Reaction[a]



R	time (h)	yield (%)	% ee[b]
Me (**13a**)	20	99	92 (**14a**)
i-Pr (**13b**)	20	99	95 (**14b**)
t-Bu (**13c**)	18	17	NA (**14c**)
Ph (**13d**)	18	99	91 (**14d**)
Bn (**13e**)	18	95	94 (**14e**)

[a] Reactions were performed at 0.26 M in substrate. [b] Enantiomeric excess was determined by chiral HPLC analysis.

Table 11. Survey of β-Substitution on the α,β-Unsaturated 2-Acyl Imidazole **13** in Reaction Catalyzed by Sc(III) Complex **1a**[a]

R	time (h)	yield (%)	% ee[b]
Me (**13a**)	3	93	93 (**14a**)
Et (**13f**)	12	97	92 (**14f**)
n-Bu (**13g**)	8	95	93 (**14g**)
i-Pr (**13h**)	12	78	94 (**14h**)
CO_2Et (**13i**)	12	95	96 (**14i**)
Ph (**13j**)	8	94	91 (**14j**)
$CH_2OTBDPS$ (**13k**)	8	71	91 (**14k**)
2-furan (**13l**)	8	86	83 (**14l**)

[a] Reactions were performed at 0.26 M in substrate for 20 h. [b] Enantiomeric excess was determined by chiral HPLC analysis.

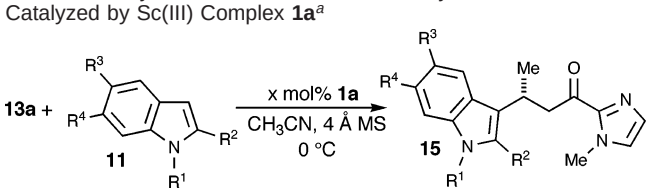
ee). This is a notable contrast to the temperature profile observed with acyl phosphonate **9a** wherein low temperatures are required for high levels of stereoinduction (≤−50 °C, Figure 2).

Other heterocyclic α,β-unsaturated ketones were examined to determine whether other candidate enone substrates might also be viable for these indole alkylations (Table 9). When benzimidazole **15** was employed, a modest decrease in enantioselectivity was observed. We were pleased to see thiazole **17** performed well in the conjugate addition (97% yield, 94% ee). Even though the thiazole **17** offered a marginal increase in selectivity relative to the imidazole **13a**, we decided to pursue the imidazoles on the basis of practical considerations. In order to ascertain the importance of the second nitrogen or sulfur atom in the heterocycle, we evaluated the 2-pyridyl **19** and phenyl **21** substrates in the addition reaction. As suspected, these substrates proved to display inferior selectivities (<32% ee). We speculate that substrates **19** and **21** do not participate as bidentate substrates for the reaction, and thus the second heteroatom in the heterocycles (**13**, **15**, and **17**) must be vital for chelate organization.

Considering the nonbonding interactions in the binding pocket of catalyst **1a** we anticipated that the size of the imidazole *N*-substituent could influence catalyst performance. As can be seen in Table 10, an increase in the steric requirements of the *N*-substituent on the substrate generally leads to an improvement in reaction selectivity; however, this effect cannot be taken to the extreme as the *tert*-butyl analogue **13c** performed sluggishly in the conjugate addition. Even though the isopropyl *N*-substituted imidazole **13b** was marginally better in overall yields (99%) and selectivity (95%), we focused on the evaluation of the more economical *N*-methylimidazoles **13a**.

Attention was then directed toward an evaluation of the effects of enone β-substitution (Table 11). The survey demonstrated that the reaction is tolerant of alkyl, aryl, and even carboxylate substitution at 0 °C.[28] This is in contrast to observations with acyl phosphonate **7**, which only provided high selectivities (>90% ee) at low temperatures (−78 °C) and only with β-alkyl substituents.

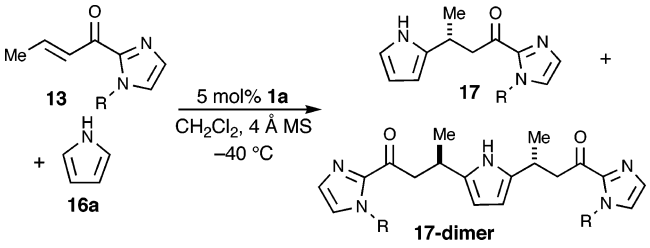
Table 12. Alkylations of Indoles **11** with 2-Acyl Imidazole **13a** Catalyzed by Sc(III) Complex **1a**[a]



indole	R^1	R^2	R^3	R^4	mol % **1a**	time (h)	ee (%)[b]	yield (%)
11b	H	H	H	H	2.5	20	65	80 (**15a**)
11a	Me	H	H	H	2.5	3	93	93 (**14a**)
11c	allyl	H	H	H	2.5	24	88	80 (**15c**)
11d	Bn	H	H	H	2.5	8	98	90 (**15d**)
11f	Me	Me	H	H	2.5	2	91	88 (**15f**)
11g	Me	Ph	H	H	5	90	66	43 (**15g**)
11j	Bn	H	OMe	H	2.5	20	97	99 (**15j**)
11h	Bn	H	Br	H	5	20	92	55 (**15h**)
11i	Bn	H	Cl	H	5	20	95	70 (**15i**)
11o	Bn	H	Me	H	5	20	93	91 (**15o**)
11p	Bn	H	H	OMe	5	20	95	99 (**15p**)

[a] All reactions were performed at 0.26 M in substrate. [b] Enantiomeric excess was determined by chiral HPLC analysis.

Table 13. Effects of *N*-Substitution of 2-Acyl Imidazole in the Pyrrole Friedel−Crafts Reaction[a]



R	monomer/dimer[b]	yield (%)	% ee[c]
Me (**13a**)	2.2:1[d]	69	87 (**17a**)
i-Pr (**13b**)	>10:1	91	94 (**17b**)
Ph (**13d**)	>20:1	98	94 (**17d**)
Bn (**13e**)	>10:1	84	91 (**17e**)

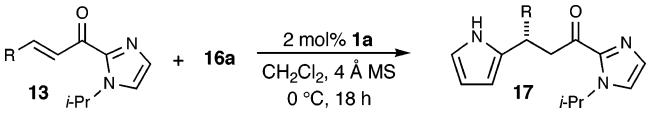
[a] Reactions were performed at 0.13 M in substrate for 20 h. [b] Monomer/dimer ratio was determined by either ^{1}H NMR spectroscopy or chiral HPLC. [c] Enantiomeric excess was determined by chiral HPLC analysis. [d] Dimer consisted of a 20:1 mixture of C_2-symmetric (99% ee): *meso*-dimer (achiral, not shown).

As was seen with acyl phosphonates **9** (Table 5), the reaction with the α,β-unsaturated 2-acyl imidazoles **13** displays improved enantiofacial control with *N*-benzyl substituted indoles (Table 12).[15b] Concurrent to that observed with the acyl phosphonates, an increase in the steric requirements of the 2-substituent is not well tolerated. However, slightly improved selectivity was seen for 1,2-dimethylindole (91% ee) as compared to acyl phosphonate **9a** (86% ee, Table 5). Halogen, alkyl, and methoxy 5- and 6-substituted *N*-benzylindoles were competent nucleophiles for the addition reaction (92−97% ee, Table 12).

Pyrrole Alkylations. Due to our success in the indole Friedel−Crafts reactions with α,β-unsaturated 2-acyl imidazoles **13**, our attention was then directed toward the analogous pyrrole alkylations. Initial attempts with 2-acyl imidazole **13a** and pyrrole (8 equiv) were encouraging, as the reaction displayed good levels of selectivity (87% ee, Table 13). From the modest improvement in reaction selectivity in the indole Friedel−Crafts reaction by increasing the steric demand of the *N*-substituent on the 2-acyl imidazoles, we felt that this might also be in effect for the corresponding pyrrole reactions. We were pleased to see that this was true: as the *N*-*i*-Pr imidazole substrate **13b** provided the alkylation product in an improved enantiomeric excess of 94%. In addition, the increased steric bulk of the *N*-substituent on the imidazole had a beneficial effect on the suppression of dimer formation (**17-dimer**, Table 13). Although the phenyl *N*-substituted imidazole **13d** was superior in overall yield (98%) and selectivity (94% ee), we focused on the more readily prepared *N*-*i*-Pr imidazole substrates with a small sacrifice in yield for this study. As with the indole Friedel−Crafts reaction with the 2-acyl imidazoles **13** (Figure 1), there was an inverse relationship between catalyst loading (**1a**) and enantioselectivity observed for the pyrrole counterpart. However, due to the decreased concentration (0.13 M in substrate) used for the pyrrole reactions, this effect was attenuated: 2 mol % **1a**, 95% ee; 5 mol % **1a**, 94% ee; 10 mol % **1a**, 93% ee; 20 mol % **1a**, 86% ee; 30 mol % **1a**, 78% ee; 50 mol % **1a**, 62% ee.

We were pleased to see that the pyrrole Friedel−Crafts reaction can be conducted at 0 °C with minimal effects on stereoinduction, and at this temperature, the reaction was amenable to a wide range of β-substituted α,β-unsaturated 2-acyl imidazoles **13** (Table 14). Alkyl-, aryl-, and carboxylate-substituted enones were well tolerated (84−96% ee). Unlike the examples in the indole study, the cinnamate-derived

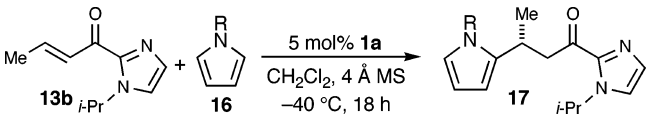
Table 14. Survey of β-Substitution on the Imidazole **13** in the Pyrrole Alkylation[a]



R	yield (%)	% ee[b]
Me (**13b**)	90	93 (**17b**)
Et (**13m**)	91	86 (**17m**)
i-Pr (**13n**)	90	91 (**17n**)
CO_2Et (**13o**)	99	84 (**17o**)
Ph (**13p**)	99	96 (**17p**)
4-MeOPh (**13q**)	98	92 (**17q**)
4-MeO_2CPh (**13r**)	99	96 (**17r**)
2-furan (**13s**)	95	91 (**17s**)

[a] Reactions were performed at 0.13 M in substrate. [b] Enantiomeric excess was determined by chiral HPLC analysis.

Table 15. Effects of Pyrrole *N*-Substitution with 2-Acyl Imidazole **13b**[a]

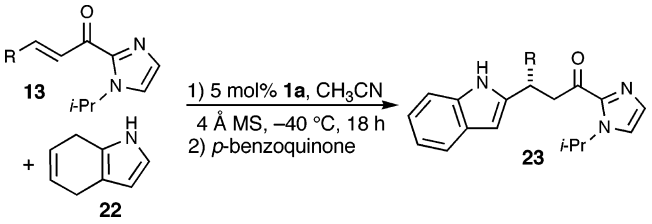


R	% ee[b]	yield (%)
H (**16a**)	94	96 (**17b**)
Me (**16b**)	78	89 (**17t**)
Bn (**16c**)	11	67 (**17u**)

[a] All reactions were performed at 0.13 M in substrate with 8 equiv of pyrrole. [b] Enantiomeric excess was determined by chiral HPLC analysis.

(28) Improved selectivities were obtained when the reaction was performed at −40 °C: R = Me (1 mol% **1**a) 97% yield, 97% ee; R = Et (5 mol% **1**a) 73% yield, 94% ee; R = *n*-Bu (5 mol% **1**a) 88% yield, 94% ee; R = CO_2-Et (1 mol% **1**a) 99% yield, 99% ee; R = Ph (1 mol% **1**a) 80% yield, 97% ee; R = CH_2OTBDPS (2.5 mol% **1**a) 83% yield, 96% ee; R = 2-furan (5 mol% **1**a) 99% yield, 86% ee.

Table 16. Enantoselective Syntheses of 2-Substituted Indoles: 4,7-Dihydroindole Alkylation of 2-Acyl Imidazoles **13**[a]

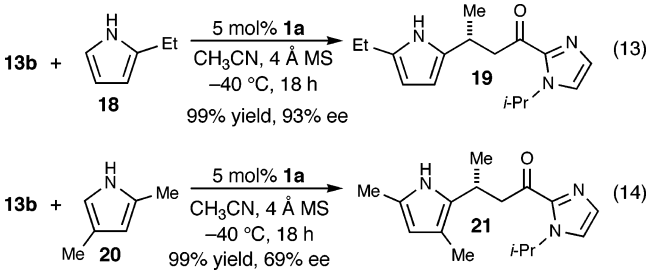


R	yield (%)	% ee[b]
Me (**13b**)	99	95 (**23b**)
Et (**13m**)	97	77 (**23m**)
i-Pr (**13n**)	62	72 (**23n**)
Ph (**13o**)	98	96 (**23o**)
4-MeOPh (**13p**)	97	90 (**23p**)
4-CO_2MePh (**13q**)	85	97 (**23q**)
4-ClPh (**13r**)	98	96 (**23r**)
2-ClPh (**13s**)	90	93 (**23s**)
4-BrPh (**13t**)	85	95 (**23t**)
2-furyl (**13u**)	92	80 (**23u**)

[a] Reactions were performed at 0.13 M in substrate. [b] Enantiomeric excess was determined by chiral HPLC analysis.

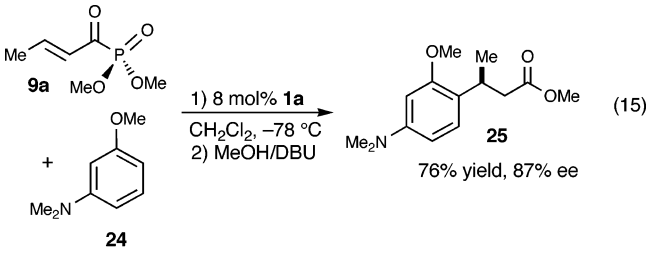
substrates are optimal (92−96% ee), whereas the fumarate **13o** was only moderately tolerated (84% ee).

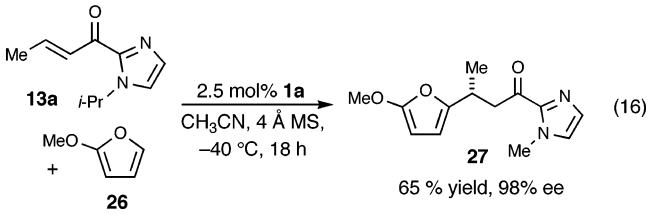
While *N*-substitution in the indole alkylations improves enantioselection, the opposite trend was noted with the analogous pyrrole alkylations with optimal results being obtained with no *N*-substituent on the heterocycle (Table 15). Concurrent to these results, substitution adjacent to the reaction center (3-position) is deleterious to reaction as can be seen in the comparison illustrated in eqs 13 and 14.



With the success of the pyrrole alkylations, we felt that dihydroindole (**22**, Table 16) would be a suitable nucleophile for the conjugate addition, thus enabling the synthesis of enantiomerically enriched 2-substituted indoles. This strategy was first reported by Saraçoglu in the synthesis of 2-substituted indoles via an oxidation of the intermediate dihydroindole addition product.[29] We were pleased to observe that the corresponding reaction with 2-acyl imidazole **13b** proceeded well with this nucleophile (90% ee, 99% yield). The syntheses of the enantiomerically enriched 2-substituted indole products were accomplished in one-pot operations by the addition of excess *p*-benzoquinone at the end of the conjugate addition providing a range of 2-substituted indoles in good yields and selectivities (Table 16).

3-Dimethylaminoanisole and 2-Methoxyfuran Alkylations. Other aromatic nucleophiles were next evaluated in this transformation. The Friedel−Crafts reaction utilizing 3-dimethylaminoanisole **24** with α,β-unsaturated acyl phosphonate **9a** proceeded cleanly to produce the methyl ester addition product (with acyl phosphonate cleavage, methanol, and DBU) in good yield and good selectivity (76% yield, 87% ee, eq 15). However, the corresponding reaction with this nucleophile using α,β-unsaturated 2-acyl imidazole **13a** proceeded in poor yields (<20%) and selectivity (22% ee). Contrary to that observed with 3-dimethylaminoanisole **24**, the conjugate addition reaction with 2-methoxyfuran[30] proved viable with the use of α,β-unsaturated 2-acyl imidazole **13a** (65% yield, 98% ee, eq 16), yet the corresponding addition reaction with α,β-unsaturated acyl phosphonate **9a** produced a complex mixture of products.





Intramolecular Friedel−Crafts Alkylations. Although the intermolecular Friedel−Crafts reaction has received attention, the corresponding intramolecular examples are not common.[31] We initially focused on the tethered *N*-benzyl indole **28b** due to the fact that *N*-benzyl indoles performed with the highest stereoinduction in the intermolecular examples (Tables 5 and 12). However, this reaction was practically void of any enantioselectivity (9% ee, Table 17). Considering the effects of pyrrole *N*-alkyl substitution in the intermolecular reactions (Table 15), we felt that an improvement in enantioselectivity might be realized with an unalkylated indole substrate as the ring is being formed at the 2-position of the indole nucleus in the intramolecular reaction. Indeed, this was the case as the reaction to form the six-membered ring with indole substrate **28c** proceeded in excellent selectivity and yield (97% ee, 99% yield). As seen with the pyrrole and indole examples, there was an inverse relationship between enantioselectivity and mol % **1a** employed (Table 17). We were surprised to observe that the corresponding reactions to form the five- or seven-membered rings were unsuccessful (**28a** and **28d**).

Product Elaboration. Acyl phosphonates are well suited for subsequent elaboration due to the inherent lability of the acyl phosphoryl moiety. Thus, esters and amides are efficiently accessed by treating the reaction product either with an alcohol

(29) Çavdar, H.; Saraçoglu, N. *Tetrahedron* **2005**, *61*, 2401−2405.

(30) For the use of 2-methoxyfuran in a conjugate addition reaction see: Itoh, K.; Kitoh, K.; Sera, A. *Heterocycles* **1999**, *51*, 243−248.

(31) (a) For nonasymmetric examples of intramolecular Friedel−Crafts alkylations, see: Bandini, M.; Melloni, A.; Tommasi, S.; Umani-Ronchi, A. *Synlett* **2005**, *8*, 1199−1222. (b) For the asymmetric intramolecular Friedel−Crafts alkylations with a tethered pyrrole to α,β-unsaturated carbonyl substrates, see: Banwell, M. G.; Beck, D. A.; Smith, J. A. *Org. Biomol. Chem.* **2004**, *2*, 157−159.

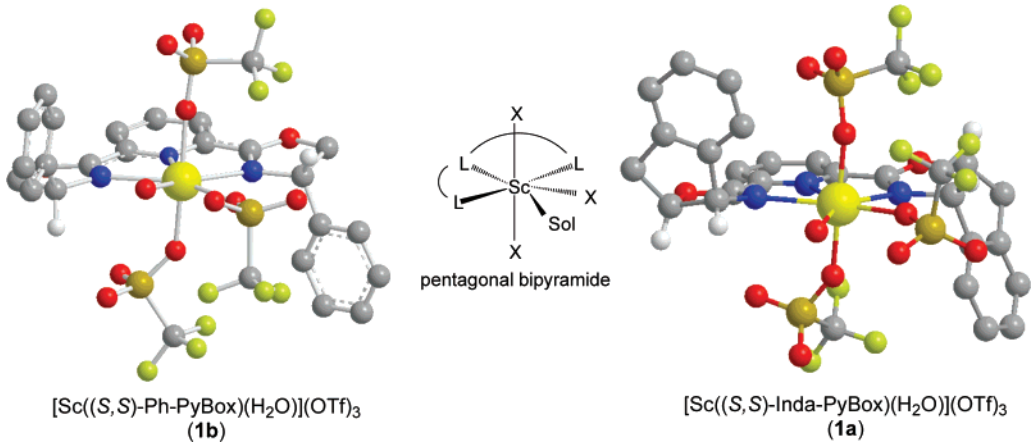


Figure 3. X-ray structures of scandium(III) triflate−pybox(aquo) complexes **1a** and **1b**.

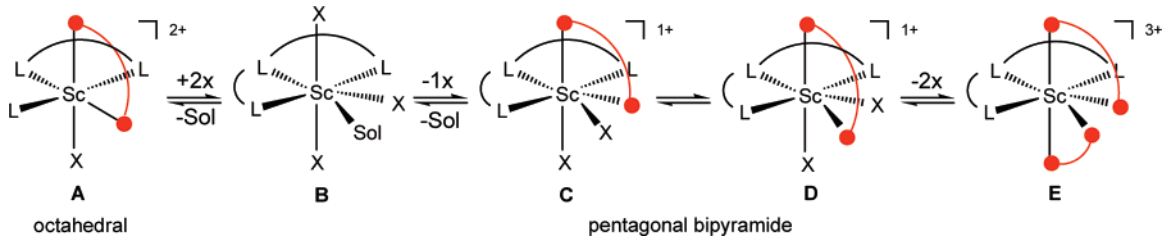
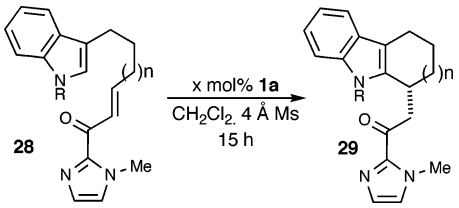


Figure 4. Coordination geometries for bidentate binding to Sc(III)−pybox complexes.

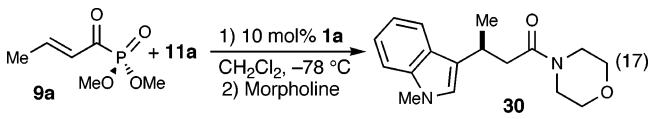
Table 17. Intramolecular Alkylations of Tethered Indoles[a]



imidazole	*n*	R	mol % **1a**	temp (°C)	yield (%)	% ee[b]
28a	0	H	5	0−rt	no conversion	
28b	1	Bn	5	0	99	9 (**29b**)
28c	1	H	2	−40	99	97 (**29c**)
28c	1	H	5	−40	99	96 (**29c**)
28c	1	H	20	−40	99[c]	88 (**29c**)
28c	1	H	50	−40	99[c]	79 (**29c**)
28d	2	H	10	0−rt	decomposition	

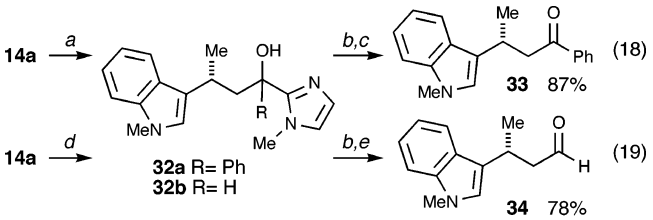
[a] Reactions were performed at 0.07 M in substrate. [b] Enantiomeric excess was determined by chiral HPLC analysis. [c] Conversion based on ^{1}H NMR spectroscopy.

and an amine base (DBU) or with morpholine under mild conditions (eq 17).



88% yield, 96% ee

On the other hand, the imidazoyl moiety of the 2-acyl imidazoles may be transformed into an excellent leaving group upon *N*-alkylation.[26] The 2-H acidities of these imidazolium salts are in the range 19−24 (pK_a, DMSO) making them comparable in acidity to an oxazolidinone.[32] As such, aldehydes, ketones, esters, amides, β-diketones, and β-ketoesters are readily acquired from the corresponding *N*-methylated 2-acyl imidazoles.[26] Iodomethane alkylation in DMF at moderately elevated temperatures proved to be successful as the methylated 2-acyl imidazole salts were isolated in good yields. Excess alkylating agent was removed with a stream of nitrogen, and the addition of a variety of nucleophiles completed the one-pot cleavage operation (Table 18). Esters (86−95% yield), amides (77−88% yields), and the carboxylic acids (87%) were accessed using this procedure. In addition, the 2-acyl imidazole **14a** could be transformed into a ketone or an aldehyde[33−34] by initially treating **14a** with a Grignard reagent to acquire the tertiary alcohol **32a** or alternatively reduced to the secondary alcohol **32b** with sodium borohydride (eqs 18 and 19).

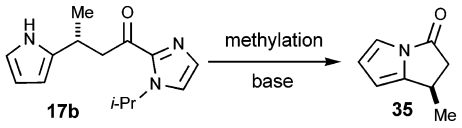


[a] PhMgBr, THF, –78 °C to 0 °C. [b] MeI, EtOAc, 50 °C. [c] Benzene, 10 wt% Na_2CO_3, 50 °C. [d] $NaBH_4$, MeOH, rt, [e] Benzene, 0.1 M NaOH, $H_2N(CH_2)_5CO_2Na$, 80 °C.

The resulting imidazole group was then methylated with iodomethane in ethyl acetate and eliminated under basic conditions to reveal the ketone **33** (87%) or aldehyde **34** (78%), respectively.

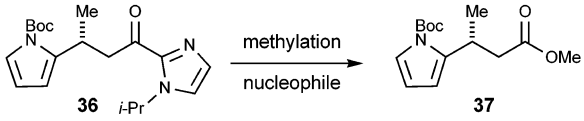
Related transformations are illustrated in eqs 20−22. In the first instance, the cleavage and cyclization of 2-acyl imidazole

17b to form the 2,3-dihydro-1*H*-pyrrolizine **35** was achieved (eq 20). Methylation of **17b** with methyl triflate (1.1 equiv, MeCN, 25 °C, 2 h) was followed by the addition of a base (3 equiv DMAP or Hünig's base) to initiate the intramolecular acylation in quantitative yield.



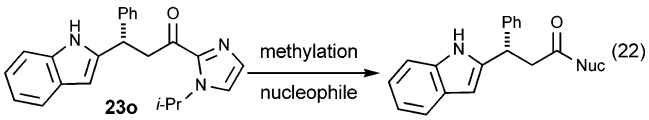
(20)

conditions	yield (%)
1.1 equiv MeOTf, CH_3CN, rt, then 3 equiv DMAP	99
1.1 equiv MeOTf, CH_3CN, rt, then 3 equiv Hünig's Base	99



(21)

conditions	yield (%)
14 equiv MeI, DMF, 65 °C, 18 h then MeOH and DBU	89
1.1 equiv MeOTf, CH_3CN, rt, 2 h then MeOH and DBU	92



(22)

conditions	yield (%)
1.1 equiv MeOTf, CH_3CN, rt then MeOH and DBU	99 (**38**)
1.1 equiv MeOTf, CH_3CN, rt then H_2O and DBU	71 (**39**)

The cleavage of 2-acyl imidazoles **36** and **23o** (eqs 21, 22) may be achieved under the same conditions. Again, methyl triflate (1.1 equiv, MeCN, 25 °C, 2 h) proved to be the most reliable alkylation reagent. The subsequent addition of MeOH and DBU to the reaction vessel provided the methyl ester **37** in 92% yield in a one-pot procedure. Indole **23o** may also be transformed into its methyl ester **38** in quantitative yield or the corresponding carboxylic acid **39** in good yield. It should be noted that the addition of 4 Å molecular sieves to scavenge any residual moisture is necessary for reproducible results.

Mechanistic Studies

Crystal Structures. Although we have previously presented octahedral models for the scandium(III)−pybox complex to account for the sense of stereoinduction in addition reactions involving glyoxylates[11] and α,β-unsaturated acyl phosphonates,[15a] we have been able to obtain crystal structures of the hydrates

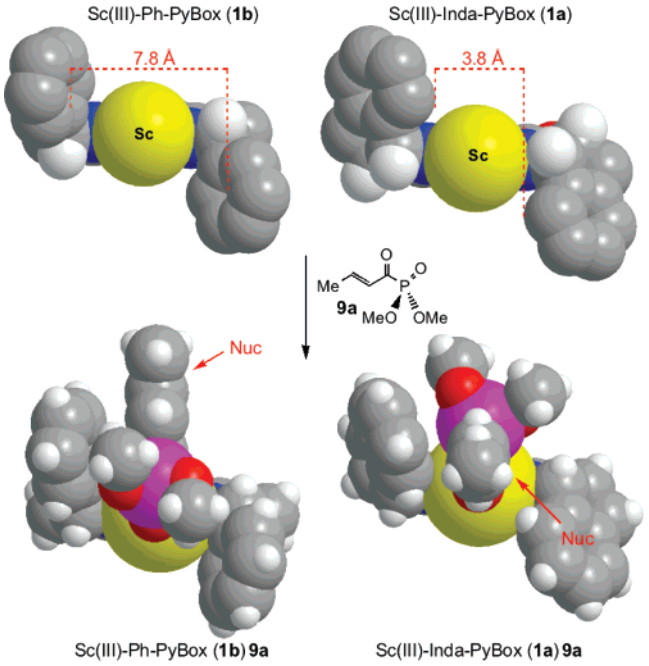


Figure 5. Crystal structures of catalyst complex **1a** and **1b** and stereochemical models for complexes **1a** and **1b** with a bound α,β-unsaturated acyl phosphonate substrate **9a** (triflates and water molecules omitted for clarity).

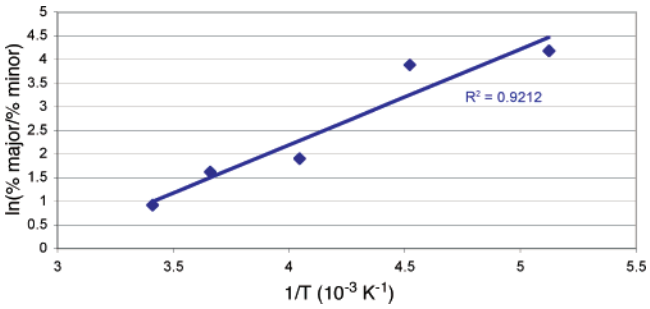
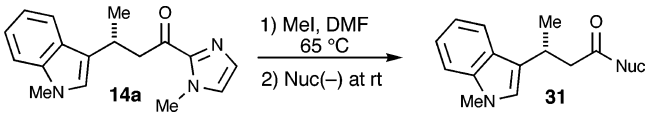


Figure 6. Eyring plot for the indole Friedel−Crafts reaction between α,β-unsaturated acyl phosphonate **9a** and Sc(III) complex **1a.**

Table 18. Cleavage of 2-Acyl Imidazole **14a**



Nuc(−) conditions	Nuc	time	yield (%)
MeOH/DBU	−OMe	30 min	93 (**31a**)
EtOH/DBU	−OEt	30 min	86 (**31b**)
i-PrOH/DBU	$-OCH(CH_3)_2$	30 min	95 (**31c**)
H_2O/DBU	−OH	30 min	87 (**31d**)
i-$PrNH_2$	$-NHCH(CH_3)_2$	20 min	77 (**31e**)
morpholine	morpholine	1 h	88 (**31f**)
aniline	−NHPh	12 h	84 (**31g**)

of both the Ph-pybox complex **1b**[11] and Inda-pybox complex **1a**[15a] (Figure 3) that show a seven-coordinate pentagonal bipyramidal geometry. We utilized this fact by employing the seven-coordinate cationic Sc(III)−pybox ($ScCl_2(SbF_6)$−PyBox) complexes with bidentate glyoxylates for asymmetric enolsilane additons.[12] However, with four available coordination sites on the Sc(III)−pybox complexes, there is an ambiguity concerning the binding of bidentate substrates to these complexes (Figure 4). We speculate that coordination complexes **C**−**E** might be

(32) (a) For the pK_a in DMSO of the 2-proton of the *N*,*N*-dimethyl benzimidazolium ion, see: Bordwell, F. G. *Acc. Chem. Res.* **1988**, *21*, 456−463. (b) For the pK_a in DMSO of the 2-proton of the *N*,*N*-dimethyl imidazolium ion, see: Alder, R. W.; Allen, P. R.; Williams, S. J. *J. Chem. Soc., Chem. Commun.* **1995**, 1267−1268. (c) For the pK_a in water of the 2-protons of the *N*,*N*-dialkyl imidazolium ions, see: Amyes, T. L.; Diver, S. T.; Richard, J. P.; Rivas, F. M.; Toth, K. *J. Am. Chem. Soc.* **2004**, *126*, 4336−4374.

(33) For the methylation and cleavage of β-hydroxyl 2-acyl imidazoles, see: Davies, D. H.; Hall, J.; Smith, E. H. *J. Chem. Soc., Perkin Trans.* **1991**, *1*, 2691−2698.

(34) Davies, H. W.; Matasi, J. J.; Ahmed, G. *J. Org. Chem.* **1996**, *61*, 2305−2313.

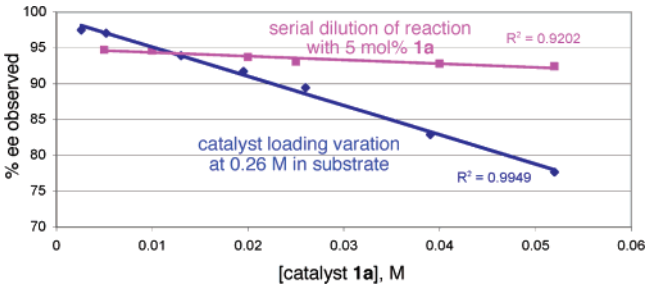


Figure 7. Effects of catalyst concentration on enantioselectivity in the indole Friedel−Crafts reaction of α,β-unsaturated 2-acyl imidazole **13a** catalyzed by Sc(III) complex **1a**.

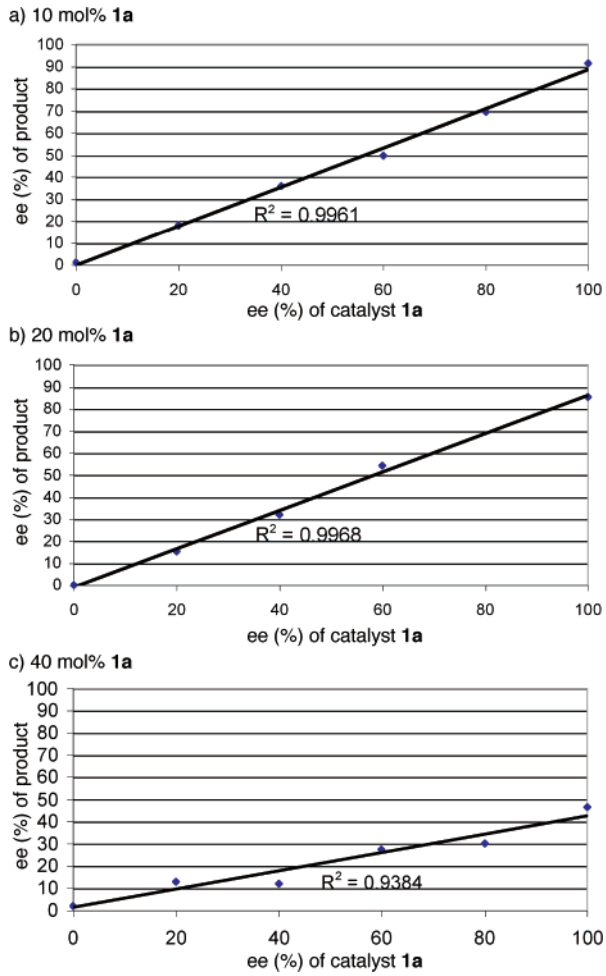


Figure 8. Nonlinear effects for the addition reaction of α,β-unsaturated 2-acyl imidazole **13a** catalyzed by Sc(III) complex **1a**: (a) 10 mol % **1a**, (b) 20 mol % **1a**, (c) 40 mol % **1a**.

sterically disfavored in preference to the octahedral complex **A**. However, if smaller substrates are employed one might imagine that complexes **C**−**E** could contribute to the addition reactions.

Acyl Phosphonate 9a. The indole addition reaction of α,β-unsaturated acyl phosphonate **9a** catalyzed by scandium complexes **1a** (Inda-pybox) displays the opposite sense of stereoinduction to that observed in the reaction with the structurally similar complex **1b** (Ph-pybox). Considering the steric requirements of the bulky acyl phosphonate moiety, we speculate the complexes are octahedral with the bound substrate **9a** as depicted in Figure 5 due to the limited space available for an

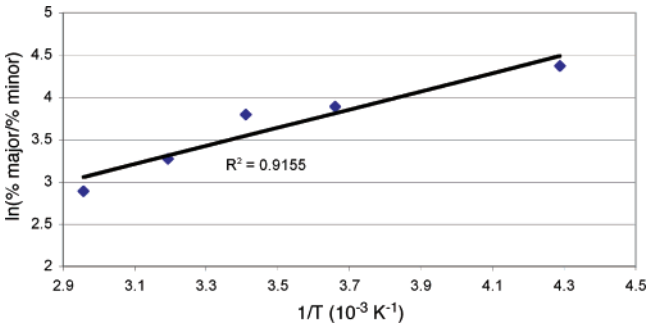


Figure 9. Eyring plot for the indole Friedel−Crafts reaction of α,β-unsaturated 2-acyl imidazole **13a** catalyzed by Sc(III) complex **1a**.

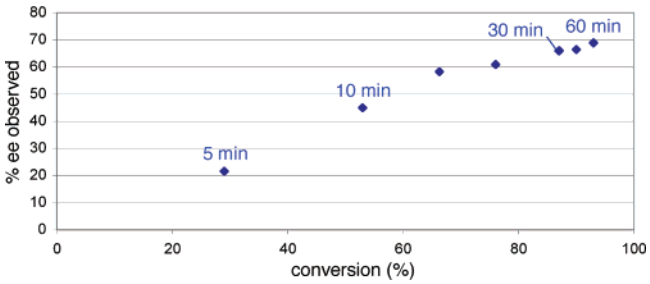


Figure 10. Effects of conversion on the enantioselectivity in the indole Friedel−Crafts reaction of α,β-unsaturated 2-acyl imidazole **13a** catalyzed by Sc(III) complex **1a** (reaction performed with 50 mol % **1a** at 0.026 M in substrate at −40 °C).

extra ligand to occupy the equatorial plane.[35] An examination of the crystal structures of catalyst **1b** (Sc(III)−Ph-pybox) and **1a** (Sc(III)−Inda-pybox) shows the available spaces in the equatorial planes of the two catalyst complexes are markedly different (Figure 5). The "slot" in the equatorial plane of the Ph-pybox complex **1b** is 7.8 Å, whereas the corresponding space in the Inda-pybox complex **1a** is only 3.8 Å. Thus, the equatorial position of the Sc(III)−Ph-pybox complex **1b** can accommodate the sterically demanding dimethyl phosphonate moiety of **9a**. This orientation positions the enone at the apical position, thus exposing the Re-face of the enone to nucleophilic attack. However, for the case of the Sc(III)−Inda-pybox complex **1a**, the space in the equatorial plane is reduced due to the inward rotation of the phenyl rings. This, in effect, excludes the sterically demanding dimethyl phosphonate from binding in the equatorial position and positions it in the apical site. With the enone bound at the equatorial position, the *Si*-face of the olefin is available for nucleophilic attack (Figure 5). These models are supported by the sense of stereoinduction observed in the corresponding reactions with these complexes. Although the apical position in complex **1b** is the most sterically accessible for the bulky phosphonate of **9a**, there appears to be a preference for the phosphonate residue in **9a** to occupy the equatorial position that overrides the inherent nonbonding interactions in this position.

In further support of the stereochemical model, an Eyring plot (Figure 6) of the addition reaction with α,β-unsaturated

(35) Modeling was performed by locking the ligand, metal, and one apical ligand in place in the crystal structure utilizing Spartan '04 (Windows XP, 3.0 GHz, 1.0 GB). The acyl phosphonate was then docked onto the apical position and equatorial position (while locking the Sc−O distance to be the same as to what is observed in the crystal structure for the corresponding Sc−OTf bonds). A single-point energy minimization was performed utilizing MMFF subjected to the constraints as stated above.

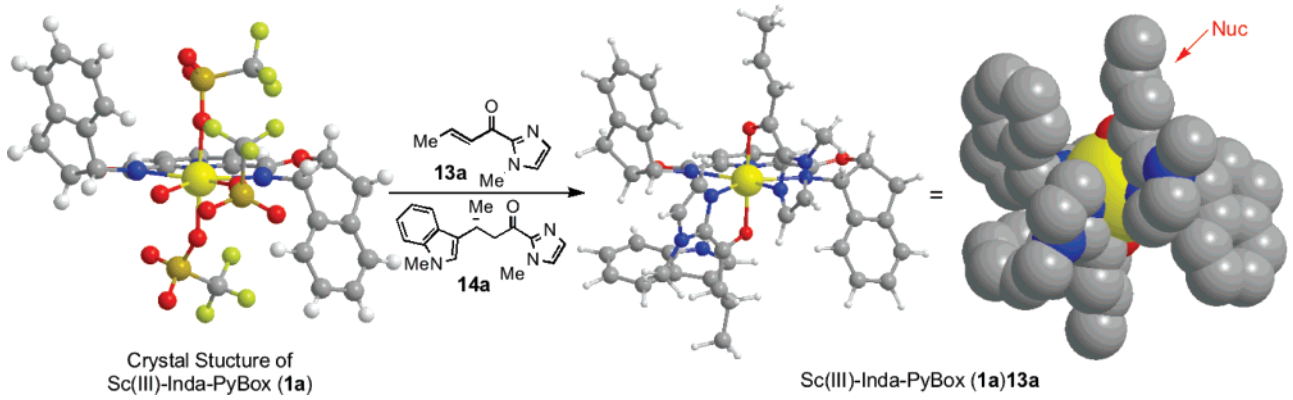


Figure 11. Cylindrical−ball and space-filling models of catalyst complex **1b** with bound α,β-unsaturated 2-acyl imidazole **13a** and product molecule **14a**.

acyl phosphonate **9a** and catalyst **1a** shows a linear relationship between ln (% major enantiomer/% minor enantiomer) and the reciprocal of the temperature ($\times 10^{-3}$ K^{-1}), indicating that only a single set of diastereomeric transition states are operating in the reaction.[36] We can interpret this result as indicating that a single binding geometry is operating in the illustrated addition reaction.

Acyl Imidazole 13a. The addition reaction with α,β-unsaturated 2-acyl imidazoles **13a** and Sc(III)−Inda-pybox complex **1a** shows the opposite sense of stereoinduction as compared to the corresponding reaction with the acyl phosphonate **9a**. In addition, this reaction displays an inverse correlation between catalyst loading (mol % **1a**) and enantioselectivity (Figure 1), which is absent in the corresponding reaction with the acyl phosphonate **9a**. In order to ascertain the cause of the catalyst loading profile we explored the effects of catalyst concentration on enantioselectivity. As can be seen in Figure 7, diluting the reaction does lead to a small improvement in enantioselectivity; however, this effect is more evident when the catalyst concentration is decreased by lowering the catalyst loading. This suggests that the observed catalyst loading profile is not directly related to the catalyst concentration.

To gain further insight into the nature of the catalyst−substrate complex, we explored the effects of catalyst enantiomeric excess versus reaction enantioselectivity (Figure 8). We observed a linear relationship between the ligand enantiomeric excess and the enantioselectivity of the addition reaction when the analysis was performed with 10 mol % **1a**. Because different forms of the active catalyst complex could be more prevalent at higher catalyst loadings, we conducted the same analysis at 20 and 40 mol % **1a**. As seen in Figure 8, there are linear relationships between catalyst ee and the enantioselectivity of the addition reaction at these higher catalyst loadings as well. Based on these results, we conclude the active catalyst is mononuclear.

The Eyring plot (Figure 9) of the addition reaction with α,β-unsaturated 2-acyl imidazoles **9a** and catalyst **1a** displays a linear relationship between ln (% major enantiomer/% minor enantiomer) and the reciprocal of the temperature ($\times 10^{-3}$ K^{-1}), indicating that only a single set of diastereomeric transition states are operating in this temperature range.[36] We speculate that this result is due to a single set of coordination geometries operating in the addition reaction.

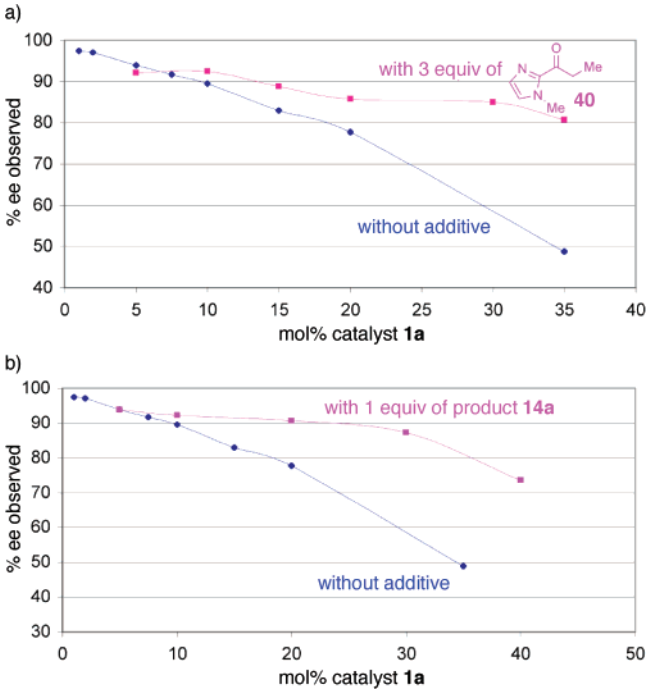


Figure 12. Effects of enantioselectivity on the indole addition reaction of α,β-unsaturated 2-acyl imidazole **13a** with (a) 3 equiv of propionyl 2-acyl imidazole **40** and (b) 1 equiv of product **14a**.

We next turned our attention to the effect of reaction conversion on the enantioselectivity of the addition reaction. This experiment was conducted with 50 mol % **1a** to augment this effect and at one-tenth the concentration in order to decrease the reaction rate so that samples could conveniently be collected at various reaction conversions. As seen in Figure 10, there is an increase in enantioselectivity with higher reaction conversion, thus indicating a possible beneficial effect of product formation in the illustrated transformation.

Considering that the crystal structure of the hydrate of catalyst complex **1a** shows a pentagonal bipyramidal geometry and the fact that the reaction displays an increase in enantioselectivities with reaction conversion, we speculate that the reaction proceeds through a seven-coordinate 1:1:1 product/substrate/catalyst complex (Figure 11)[37] that is favored at lower catalyst loading and is more enantioselective than the corresponding 1:1 substrate/catalyst complex that would be favored at higher

(36) Buschmann, H.; Scharf, H.-D.; Hoffman, N.; Esser, P. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 477−515.

catalyst loadings. The imidazole group is planar and less sterically demanding than the dimethyl phosphonate moiety, and thus two of these units can occupy the equatorial positions of the catalyst, with one being the substrate and the other being the product molecule. This would place the carbonyl groups at the apical positions with the enone of the substrate oriented for nucleophilic attack on the *Re*-face, in accord with a sense of stereoinduction observed in the reaction. Inversion of the binding of the substrate would be excluded as this would lead to a severe steric interaction between the enone and the imidazole ring of the bound product. We cannot help but notice the proximity of the indole ring of the product to the pyridine ring of the bound pybox ligand. Considering the electron-rich nature of the indole ring and the electron deficient nature of the metal-bound pyridine of the pybox ligand, we speculate there might be a beneficial electrostatic interaction between these heterocycles that contributes to the binding of a product molecule versus another substrate in the seven-coordinate model.

To further validate this hypothesis a series of experiments were conducted where the catalyst loading of the reaction was varied but included in the reaction a series of 2-acyl imidazole additives, first with 3 equiv of the achiral saturated 2-acyl imidazole **40** and second with 1 equiv of product **14a**. (Figure 12).[38] For the cases of low catalyst loading (<10 mol % **1a**), we did not notice a significant improvement on reaction facial selectivities compared to the original catalyst loading profile. However, when we raised the catalyst loading from 20 to 50 mol % **1a** we observed a significant improvement in enantioselectivity when the additives were present. To disprove any stereoinduction from the product **14a**, a control experiment was performed with no catalyst and 1 equiv of product, and no reaction was detected in this experiment. Also, the corresponding reaction with 1 equiv of product and no ligand with 10 mol % $Sc(OTf)_3$ produced no noticeable enantioselectivity.

(37) Modeling performed by locking the positions of the ligand, metal, triflates, and water molecule in the crystal structure utilizing Spartan '04 (Windows XP, 3.0 GHz, 1.0 GB). The 2-acyl imidazole was then docked onto the apical position and one of the available equatorial positions. A product molecule was then docked onto one of the apical positions and the remaining equatorial position. A single-point energy minimization was performed utilizing MMFF subjected to the constraints as stated above.

(38) Reactions were performed with 92% ee product as an additive (1 equiv) and were allowed to proceed to 100% conversion. Conversion and enantioselectivity were determined by chiral HPLC analysis. Enantioselectivity of the reaction was determined by: $ee_{rxn} = 2ee_{obsd} - 92$.

Conclusions

A highly enantioselective Michael-type indole Friedel−Crafts reaction with a variety of β-substituted α,β-unsaturated acyl phosphonates and β-substituted α,β-unsaturated 2-acyl imidazoles catalyzed by bis(oxazolinyl)pyridine−scandium(III) triflate complexes have been developed. The addition reaction was found to be more versatile with the α,β-unsaturated 2-acyl imidazoles as pyrrole, indole, and intramolecular Friedel−Crafts reactions were found to be highly stereoselective. The acyl phosphonate products were efficiently transformed into esters and amides, whereas the acyl imidazole products were converted to more diverse functionalities such as esters, amides, a carboxylic acid, a ketone, and an aldehyde. We also developed a mild and efficient cleavage protocol for the diversification of the 2-acyl imidazole products utilizing a slight excess of MeOTf in acetonitrile as the key methylating condition. The binding coordination of the bis(oxazolinyl)pyridine−scandium(III) triflate complexes was probed by the series of experiments performed with both the α,β-unsaturated acyl phosphonate and the α,β-unsaturated 2-acyl imidazoles. The complexes appear to adopt coordination geometries that are sterically favorable, with the more bulky bidentate acyl phosphonate substrates invoking octahedral geometries. Whereas, the less sterically demanding 2-acyl imidazole substrates were able to adopt the seven-coordinate pentagonal bipyramidal coordination geometry seen in the crystal structures of the hydrate of scandium(III) Ph-pybox **1b** and Inda-pybox **1a** complexes by invoking an active catalyst that has a bound product molecule.

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

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