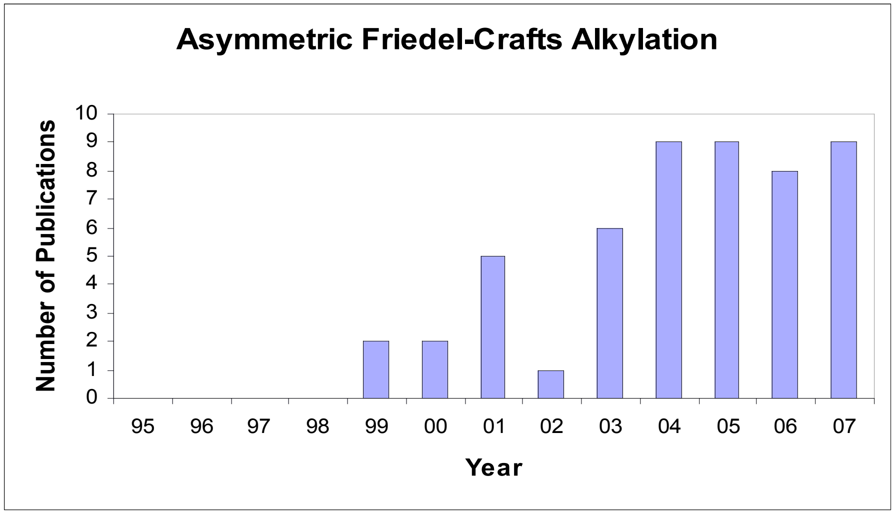
Enantioselective Friedel-Crafts Alkylations Catalyzed by Bis(oxazolinyl)pyridine – Scandium(III) Triflate Complexes

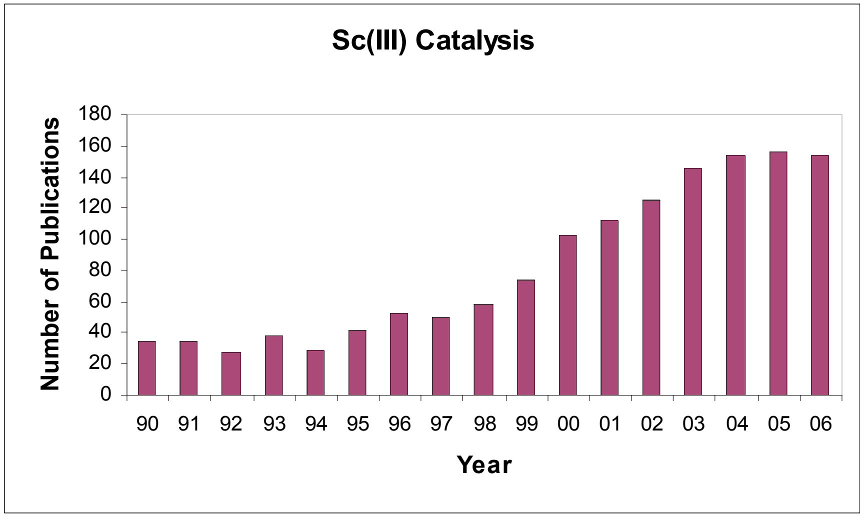
by David A. Evans, Keith R. Fandrick, Hyun-Ji Song, Karl A. Scheidt, and Risheng Xu.

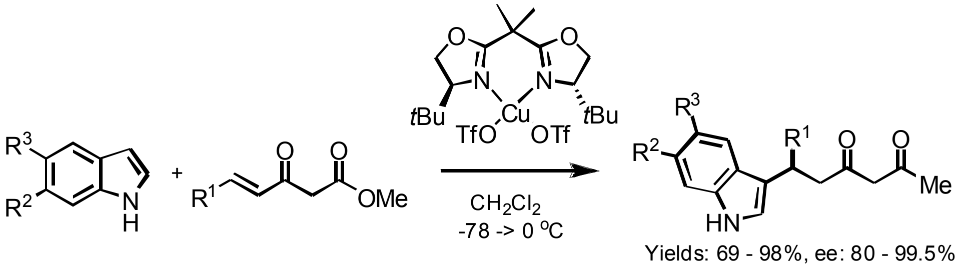
JACS ASAP Article, 2007.

Current Literature: 7/28/07: David Arnold

Background: Asymmetric Friedel-Crafts Alkylation and Scandium Catalysis

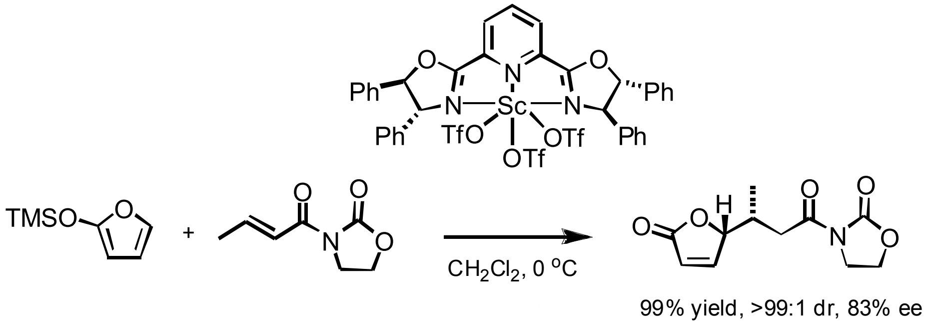


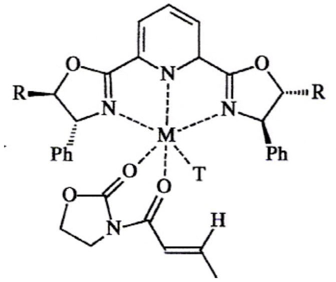




- R^1: alkyl or aryl
- R^2 and R^3: alkyl, aryl, ester and methoxy

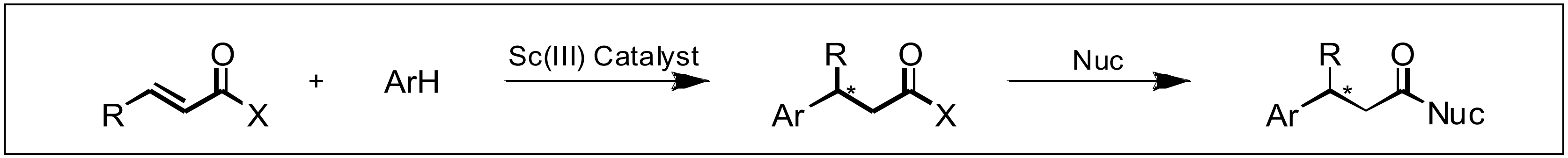
Angew. Chem. Int. Ed. **2001**, *40*, 160-163.





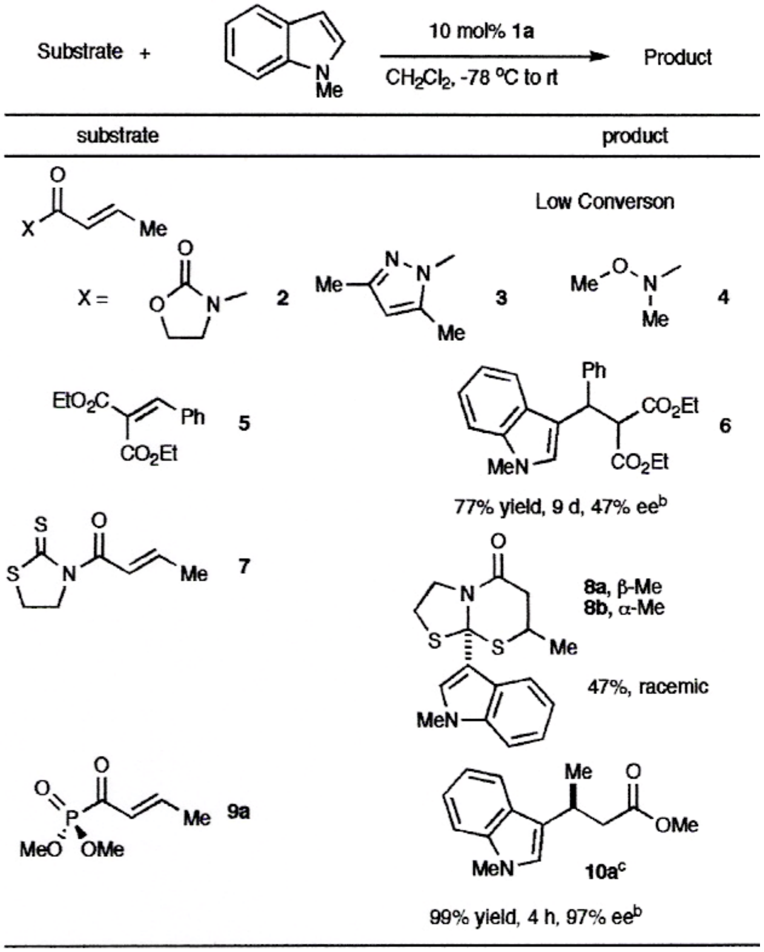
- Tetrahedron **2001**, *57*, 10203.

Outline

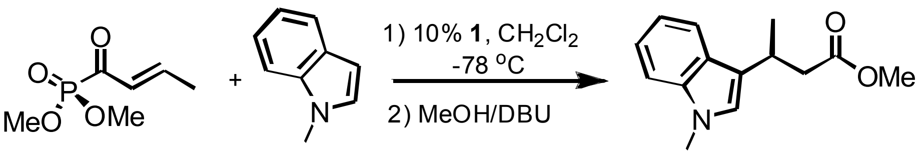


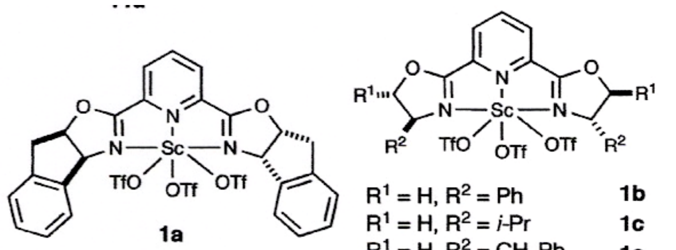
- Initial Substrate Study
- Optimization and Reaction Scope
- Product Elaboration
- Crystal Structures
- Mechanistic Considerations
- Conclusion

Initial Substrate Screen and Optimization of the Friedel-Crafts Reaction using α,β-Unsaturated Acyl Phosphonates


Substrate + [N-methylindole] $\xrightarrow[\text{CH}_2\text{Cl}_2\text{, -78 °C to rt}]{\text{10 mol\% 1a}}$ Product

substrate	product
X = (oxazolidinone) **2**; (pyrazole) **3**; MeO–N(Me) **4**	Low Converson
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]





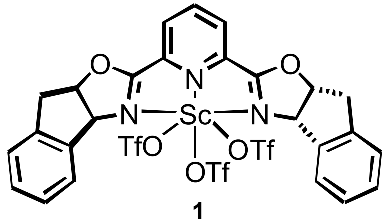
1a

R^1 = H, R^2 = Ph **1b**
R^1 = H, R^2 = *i*-Pr **1c**
R^1 = H, R^2 = CH_2Ph **1e**
R^1 = Ph, R^2 = Me **1f**

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

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

Investigation of Reaction Scope for the Reactions Between Substituted α,β-Unsaturated Acyl Phosphonates and Indoles



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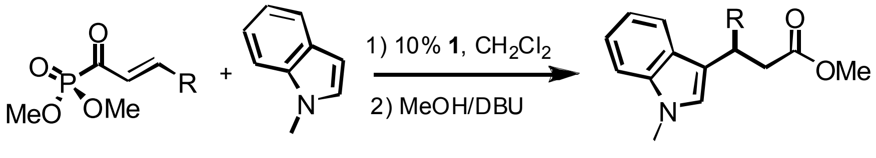
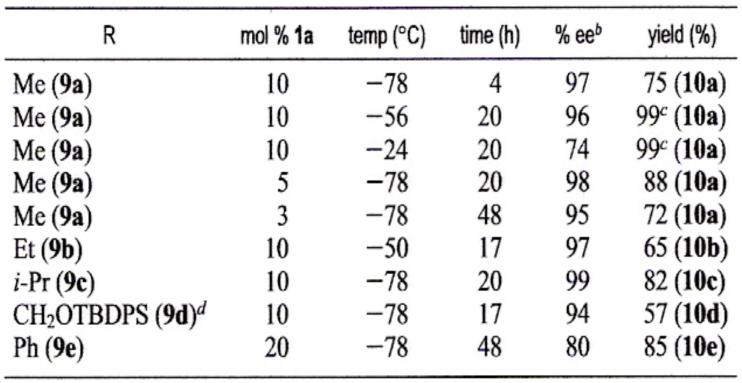
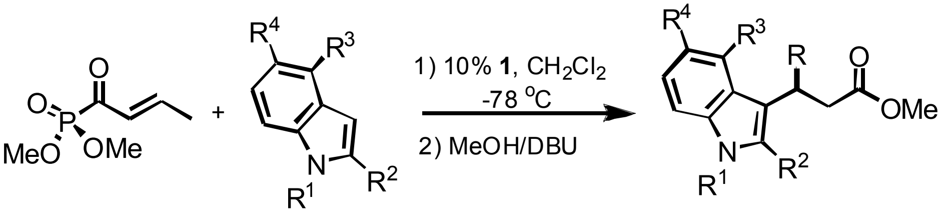
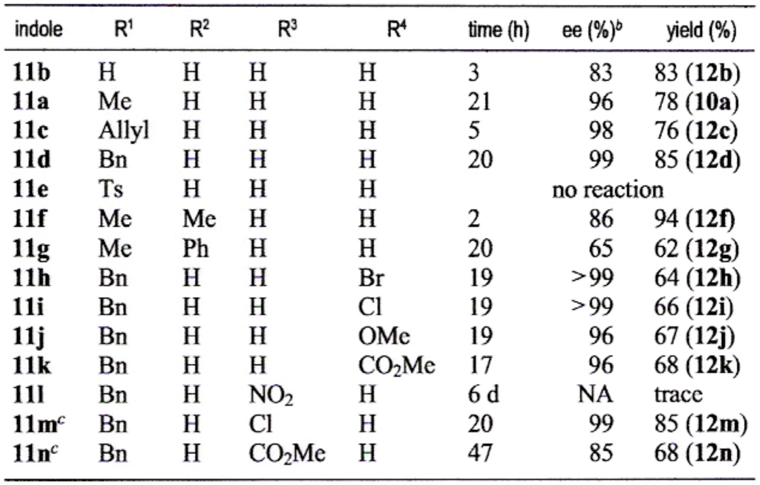




R	mol % 1a	temp (°C)	time (h)	% ee[b]	yield (%)
Me (**9a**)	10	−78	4	97	75 (**10a**)
Me (**9a**)	10	−56	20	96	99[c] (**10a**)
Me (**9a**)	10	−24	20	74	99[c] (**10a**)
Me (**9a**)	5	−78	20	98	88 (**10a**)
Me (**9a**)	3	−78	48	95	72 (**10a**)
Et (**9b**)	10	−50	17	97	65 (**10b**)
i-Pr (**9c**)	10	−78	20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

- Good tolerance for alkyl substitution at temperatures below -50 °C and with low catalyst loadings.

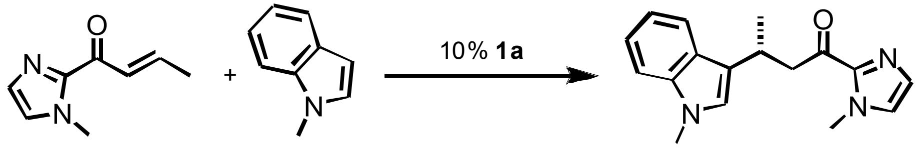




indole	R¹	R²	R³	R⁴	time (h)	ee (%)[b]	yield (%)
11b	H	H	H	H	3	83	83 (**12b**)
11a	Me	H	H	H	21	96	78 (**10a**)
11c	Allyl	H	H	H	5	98	76 (**12c**)
11d	Bn	H	H	H	20	99	85 (**12d**)
11e	Ts	H	H	H		no reaction	
11f	Me	Me	H	H	2	86	94 (**12f**)
11g	Me	Ph	H	H	20	65	62 (**12g**)
11h	Bn	H	H	Br	19	>99	64 (**12h**)
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**)

- Electron-withdrawing groups deactivate the indole substrate.
- Overall good tolerance for methoxy, halogen and ester functionality.

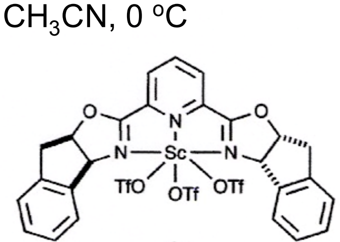
Investigation of α,β-Unsaturated 2-Acyl Imidazole Substrates for use in the Friedle-Crafts Alkylations of *N*-Methylindole



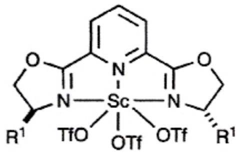
solvent[b]	temp (°C)	conv (%)[c]	time (h)	% ee[d]
CH_2Cl_2	−78	99	5	75
THF	−78 to −27	17	48	79
toluene	−78 to −27	17	48	33
CH_3CN	−38	99	17	89
CH_2Cl_2/THF	−78	81	48	30
CH_2Cl_2/toluene	−78	89	48	60
CH_2Cl_2/CH_2CN	−78 to −27	99	48	79

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

- CH_3CN, 0 °C



1a



R1 = Ph **1b**
R1 = *i*-Pr **1c**
R1 = CH_2Ph **1e**
R1 = *t*-Bu **1g**

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

- CH_3CN, 4 Å MS, -40 °C

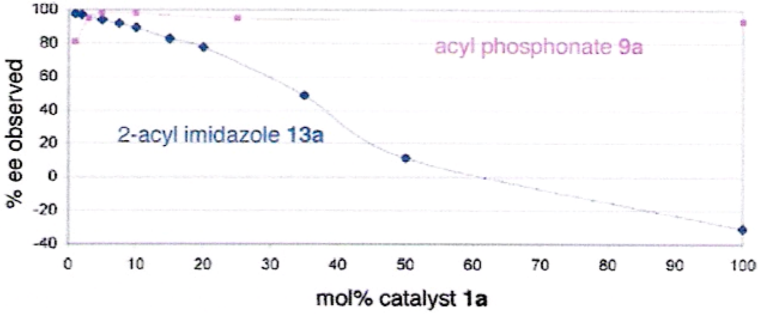


Figure 1. Catalyst loading profile for the Friedel−Crafts reaction with α,β-unsaturated 2-acyl imidazole **13a** (0.26 M in substrate, CH_3CN, 4 Å MS, −40 °C) and α,β-unsaturated acyl phosphonate **9a** (0.13 M in substrate, CH_2Cl_2, −78 °C) with *N*-methylindole (**11a**) catalyzed by Sc(III)−Inda-pybox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

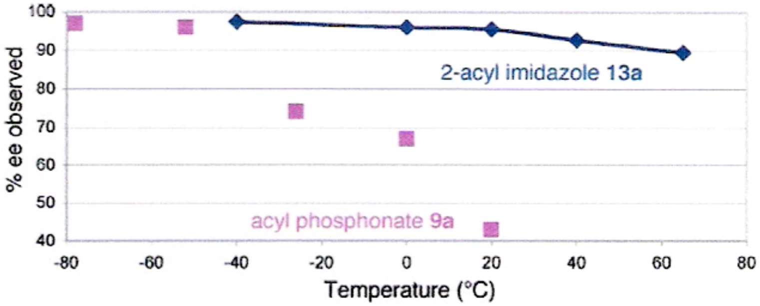
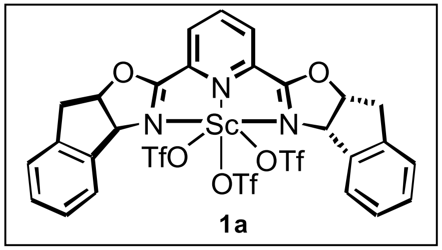


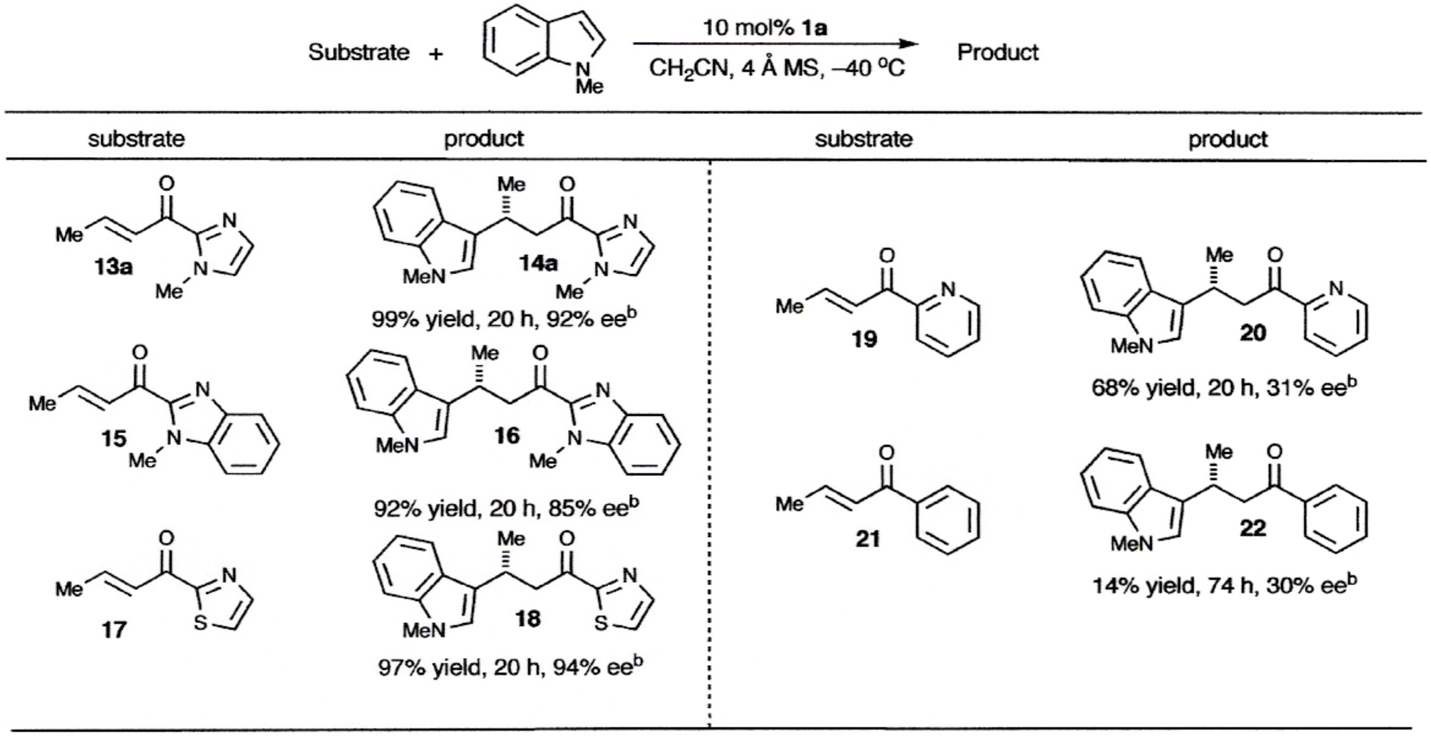
Figure 2. Temperature profile for the alkylation of *N*-methylindole (**11a**) with 2-acyl imidazole **13a** (1 mol % **1a**, 0.26 M in substrate, CH_3CN, 4 Å MS) and acyl phosphonate **9a** (10 mol % **1a**, 0.13 M in substrate, CH_3Cl_2).

- The 2-acyl imidazole substrate offers comparable %ee over a more robust temperature range than the corresponding acyl phosphonate.
- Opposite enantiomer is observed.

Comparison of α,β-Unsaturated 2-Acyl Heterocyclic Substrates in the Sc(III) Catalyzed Friedel-Crafts Reaction with *N*-Methylindole: Importance of Tight Substrate/Catalyst Chelation



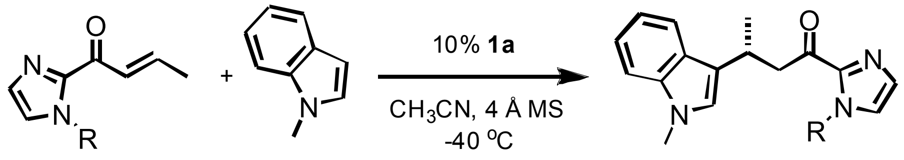
1a

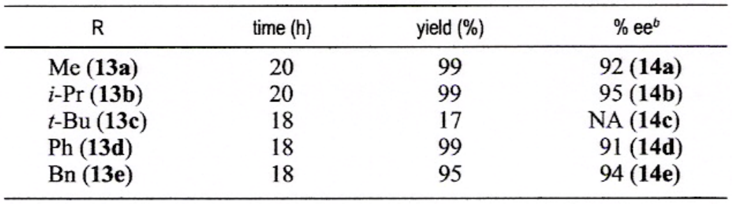


substrate	product	
13a	14a	99% yield, 20 h, 92% ee^b
15	16	92% yield, 20 h, 85% ee^b
17	18	97% yield, 20 h, 94% ee^b
19	20	68% yield, 20 h, 31% ee^b
21	22	14% yield, 74 h, 30% ee^b

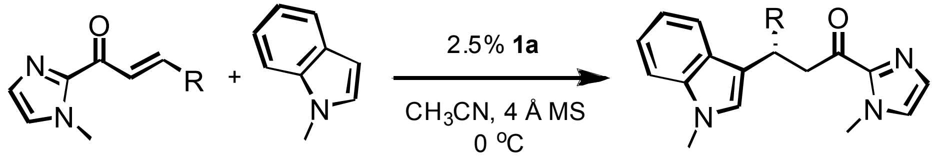
- α,β-Unsaturated 2-acyl heterocyclic substrates containing five membered heterocyclic rings chelate optimally to the Sc(III) catalyst and afford the best reaction enantioselectivities.

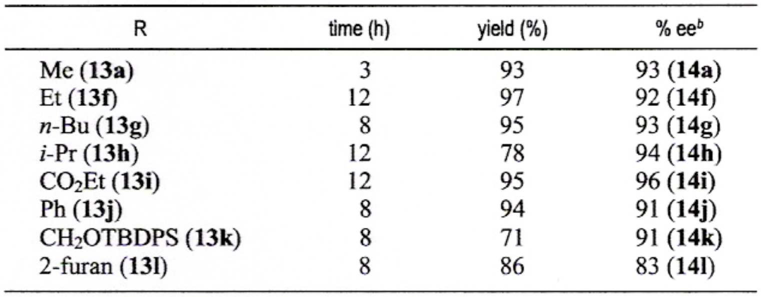
Investigation of Reaction Scope for the Reactions Between Substituted α,β-Unsaturated 2-Acyl Imidazoles and Indoles





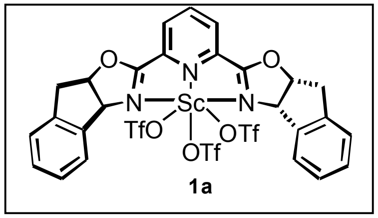
R	time (h)	yield (%)	% ee[b]
Me (**13a**)	20	99	92 (**14a**)
i-Pr (**13b**)	20	99	95 (**14b**)
t-Bu (**13c**)	18	17	NA (**14c**)
Ph (**13d**)	18	99	91 (**14d**)
Bn (**13e**)	18	95	94 (**14e**)





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**)

- Good tolerance for alkyl, aryl and carboxylate β-substitution at 0 °C



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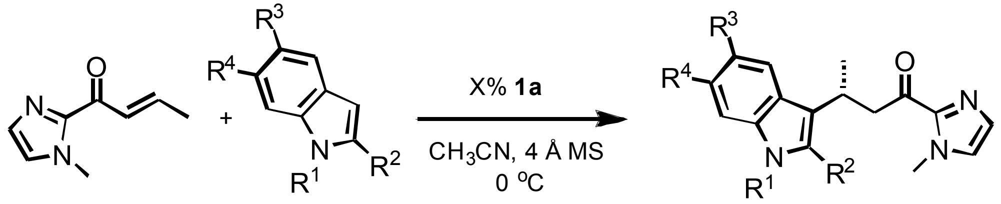
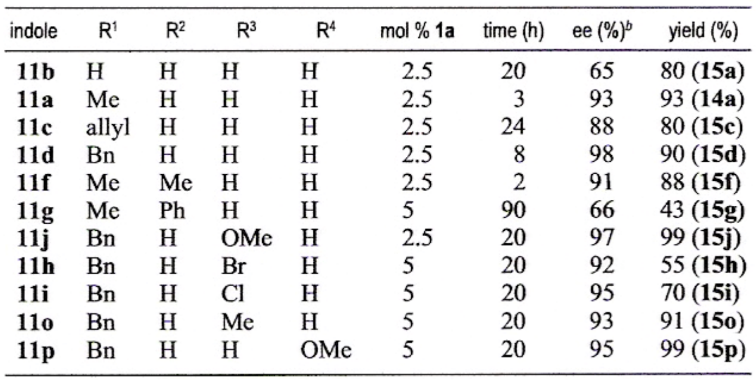
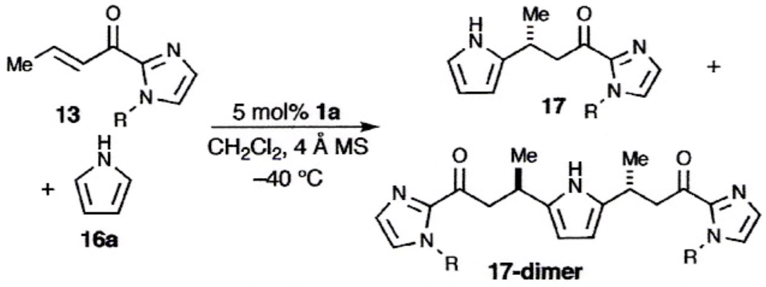




indole	R^1	R^2	R^3	R^4	mol % **1a**	time (h)	ee (%)[b]	yield (%)
11b	H	H	H	H	2.5	20	65	80 (**15a**)
11a	Me	H	H	H	2.5	3	93	93 (**14a**)
11c	allyl	H	H	H	2.5	24	88	80 (**15c**)
11d	Bn	H	H	H	2.5	8	98	90 (**15d**)
11f	Me	Me	H	H	2.5	2	91	88 (**15f**)
11g	Me	Ph	H	H	5	90	66	43 (**15g**)
11j	Bn	H	OMe	H	2.5	20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

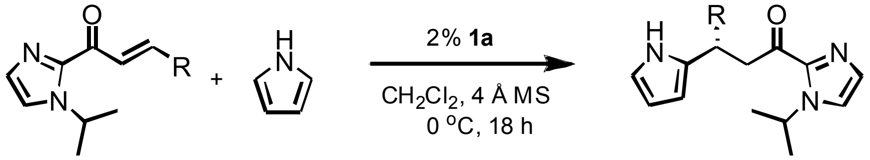
- Low tolerance for bulky substituents in the R^2 position.
- Good tolerance for alkyl, methoxy and halogen substituents in the R^3 and R^4 position.

Friedel-Crafts Reactions with α,β-Unsaturated 2-Acyl Imidazoles and Substituted Pyrroles



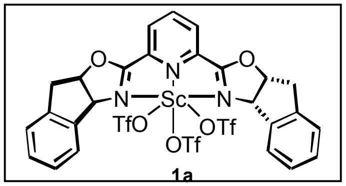
R	monomer/dimer[b]	yield (%)	% ee[c]
Me (**13a**)	2.2:1[d]	69	87 (**17a**)
i-Pr (**13b**)	>10:1	91	94 (**17b**)
Ph (**13d**)	>20:1	98	94 (**17d**)
Bn (**13e**)	>10:1	84	91 (**17e**)

- Increasing the steric bulk of R increases enantioselectivity and suppresses dimer formation.

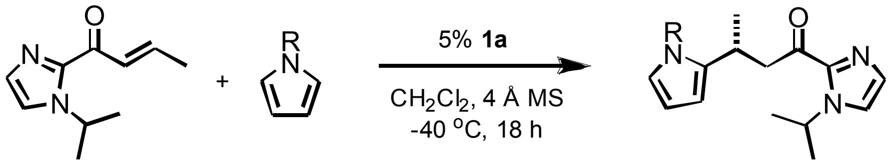


R	yield (%)	% ee[b]
Me (**13b**)	90	93 (**17b**)
Et (**13m**)	91	86 (**17m**)
i-Pr (**13n**)	90	91 (**17n**)
CO_2Et (**13o**)	99	84 (**17o**)
Ph (**13p**)	99	96 (**17p**)
4-MeOPh (**13q**)	98	92 (**17q**)
4-MeO_2CPh (**13r**)	99	96 (**17r**)
2-furan (**13s**)	95	91 (**17s**)

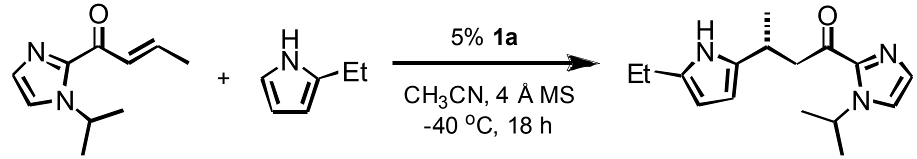
- Good tolerance for alkyl, aryl and carboxylate β-substitution.



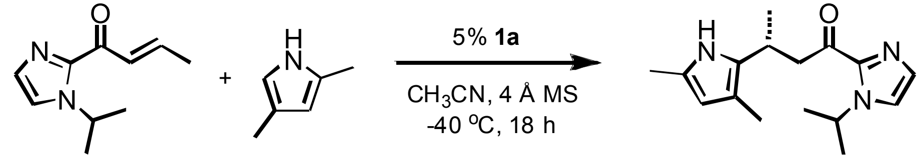
1a



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



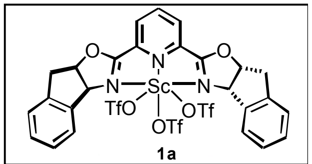
99% yield, 93% ee



99% yield, 69% ee

- Enantioselectivity is decreased with increasing steric demand of the N-alkylpyrrole substituents and substituents in the pyrrole 3-position.

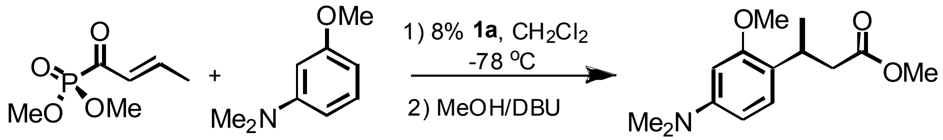
Extension of the Reaction Scope to the Synthesis of 2-Substituted Indoles, Intermolecular Friedel-Crafts Alkylations and Alkylation of 3-Dimethylaminoanisole and 2-Methoxyfuran



1a

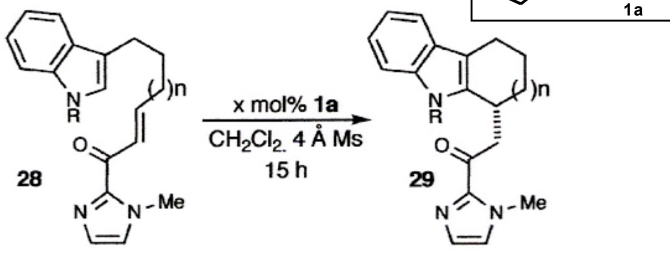
R	yield (%)	% ee[b]
Me (**13b**)	99	95 (**23b**)
Et (**13m**)	97	77 (**23m**)
i-Pr (**13n**)	62	72 (**23n**)
Ph (**13o**)	98	96 (**23o**)
4-MeOPh (**13p**)	97	90 (**23p**)
4-CO_2MePh (**13q**)	85	97 (**23q**)
4-ClPh (**13r**)	98	96 (**23r**)
2-ClPh (**13s**)	90	93 (**23s**)
4-BrPh (**13t**)	85	95 (**23t**)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

- Good yields and enantioselectivities for both alkyl and aryl substrates.



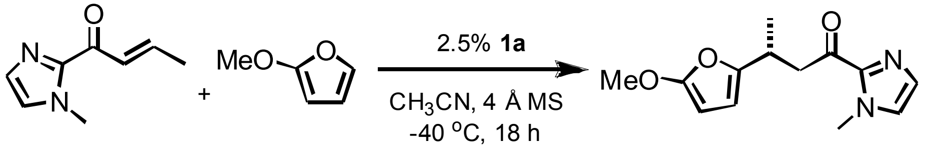
76% yield, 87% ee

- The corresponding reaction using the α,β-unsaturated 2-acyl *N*-methylimidazole afforded low conversion and poor enantioselectivity (<20% yield, 22% ee)



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	

- Good yields and enantioselectivities for the formation of 6-membered rings. Reaction was unsuccessful for 5- and 7-membered rings.

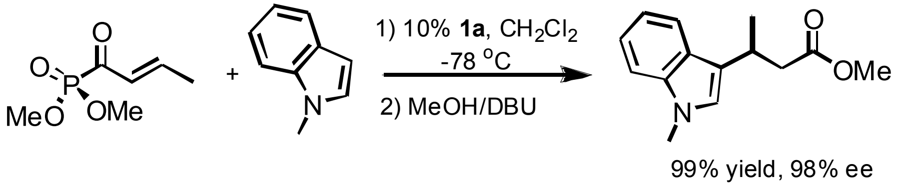


65% yield, 98% ee

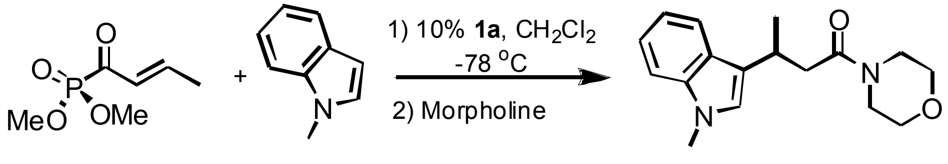
- The corresponding reaction using the α,β-unsaturated acyl phosphonate provided a complex mixture of products.

Elaboration of Friedel-Crafts Alkylation Products

- Efficient conversion of acyl phosphonates to esters and amides.



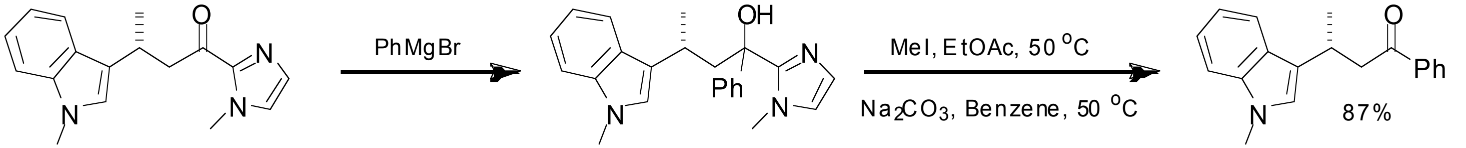
99% yield, 98% ee



88% yield, 96%ee

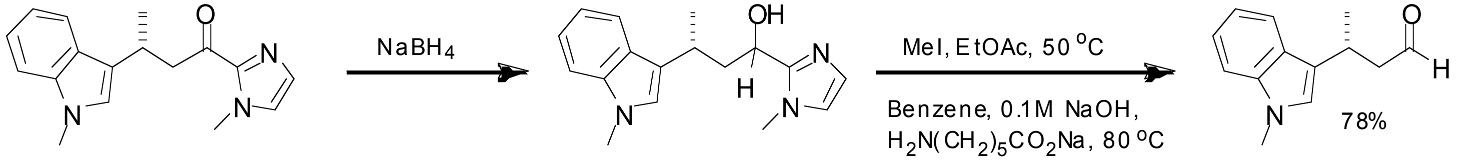
- Conversion of 2-Acyl imidazoles to ketones, aldehydes, esters, carboxylic acids, amides and cyclic products.

- Ketones

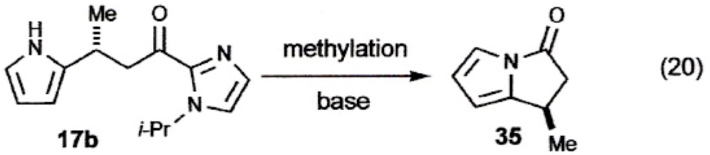


87%

- Aldehydes

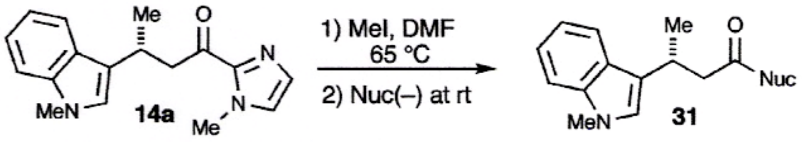


78%



17b **35** (20)

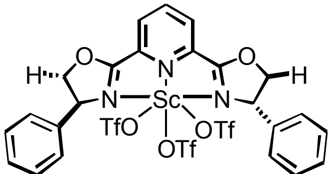
conditions	yield (%)
1.1 equiv MeOTf, CH_3CN, rt, then 3 equiv DMAP	99
1.1 equiv MeOTf, CH_3CN, rt, then 3 equiv Hünig's Base	99



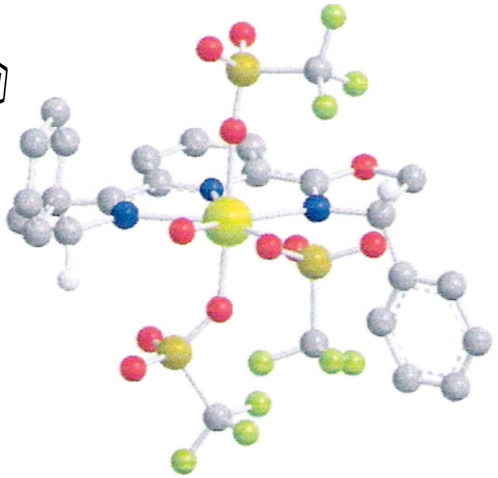
14a **31**

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**)

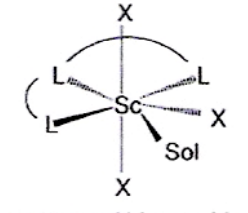
Crystal Structures for the Sc(III)Triflate Hydrates of the Ph-pybox and Inda-pybox Complexes: Analysis of Possible Bidentate Substrate Binding



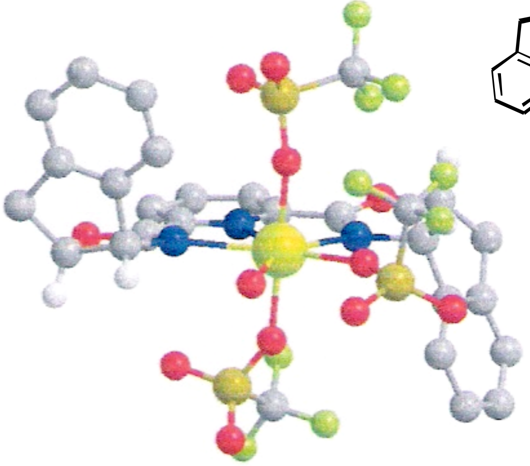
1b



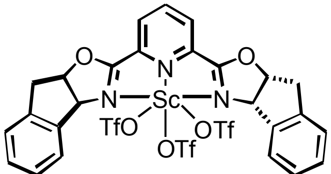
[Sc((*S*,*S*)-Ph-PyBox)(H_2O)]($OTf)_3$
(**1b**)



pentagonal bipyramide

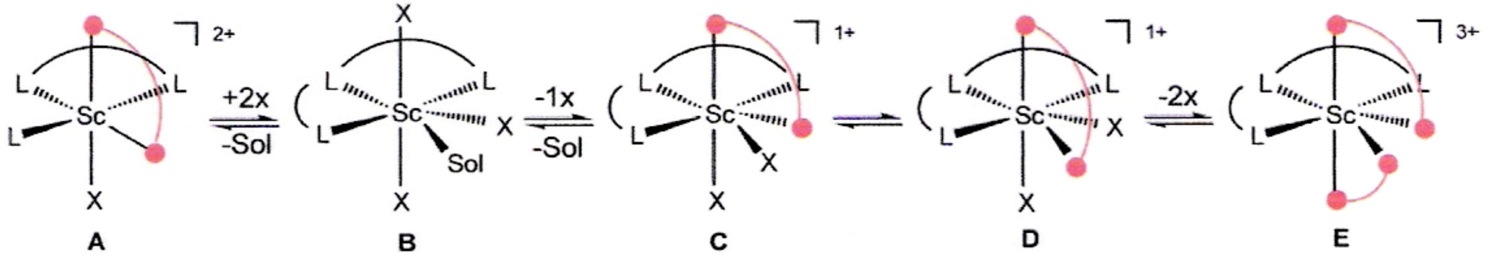


[Sc((*S*,*S*)-Inda-PyBox)(H_2O)]($OTf)_3$
(**1a**)



1a

- Crystal structures show seven-coordinate pentagonal bipyramidal geometry



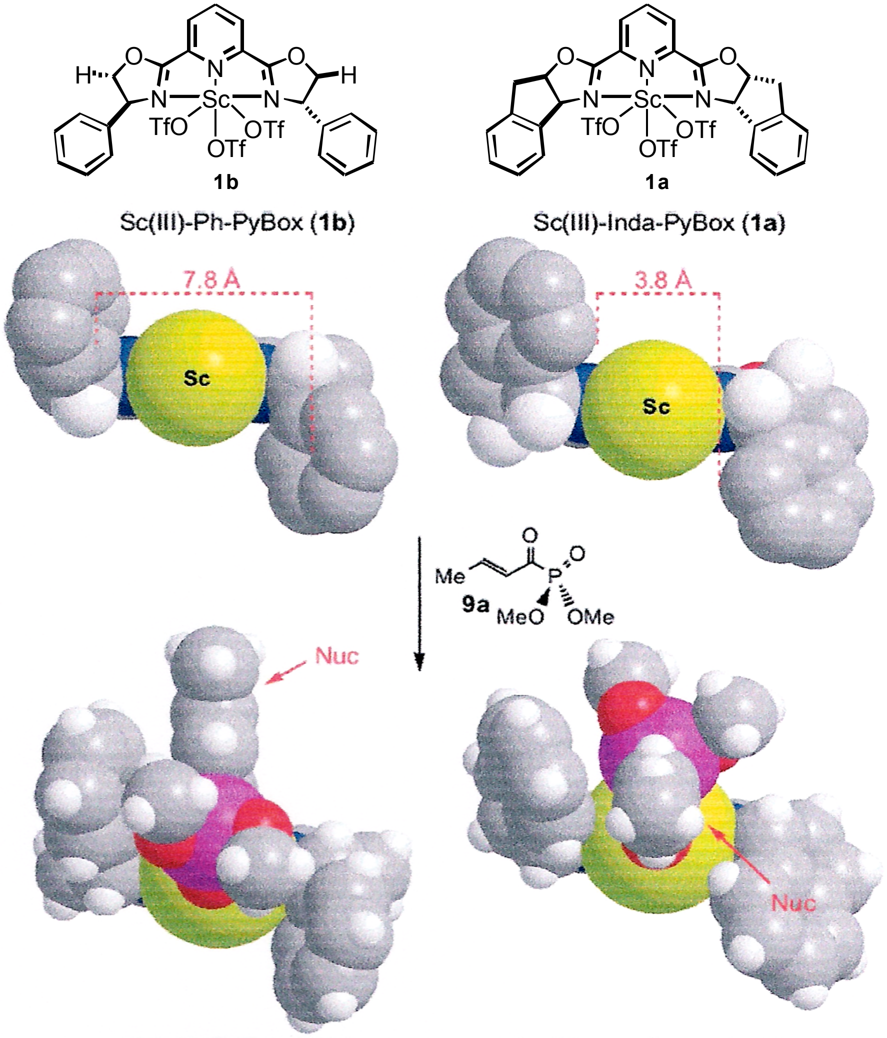
octahedral

pentagonal bipyramide

- Sterically favored when binding bulky substrates.

- Possibly active when sterically less demanding substrates are used.

Mode of Binding for the Acyl Phosphonate Substrates with both the Sc(III)-Ph-PyBox and Sc(III)-Inda-PyBox Complexes



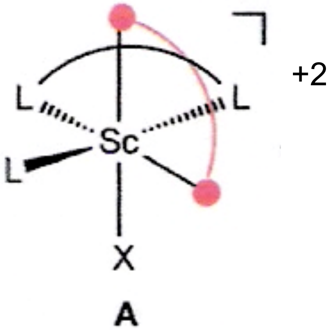
Sc(III)-Ph-PyBox (**1b**)

Sc(III)-Inda-PyBox (**1a**)

Sc(III)-Ph-PyBox (**1b**) **9a**

Sc(III)-Inda-PyBox (**1a**) **9a**

- Cavity size in the equatorial plane influences the acyl phosphonate binding orientation and accounts for the different stereochemistry observed in the products.



A

octahedral

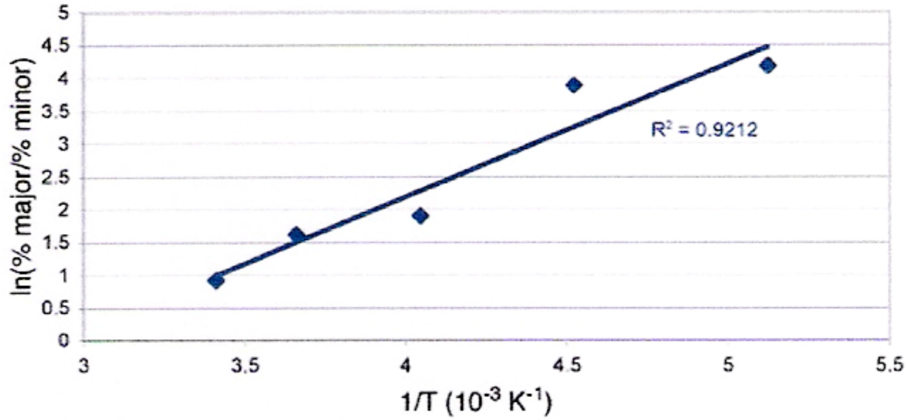
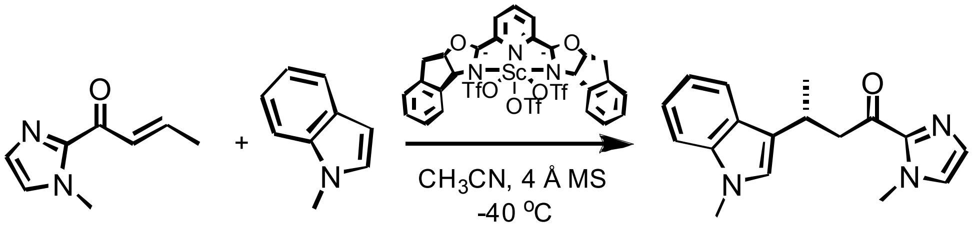


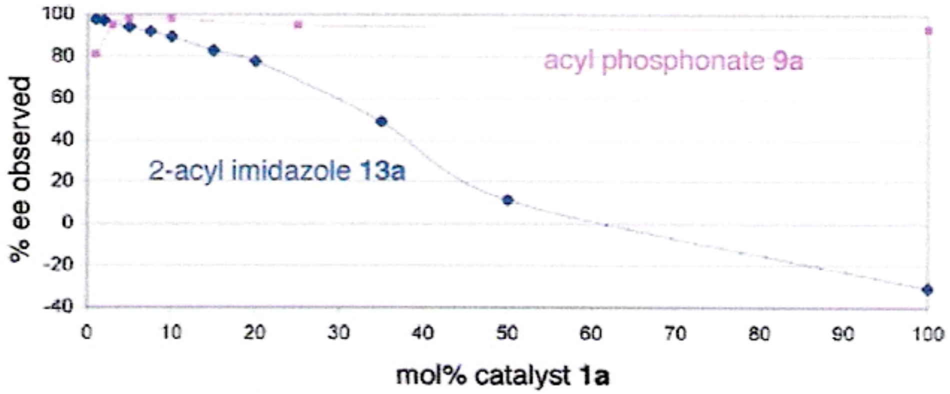
Figure 6. Eyring plot for the indole Friedel−Crafts reaction between α,β-unsaturated acyl phosphonate **9a** and Sc(III) complex **1a.**

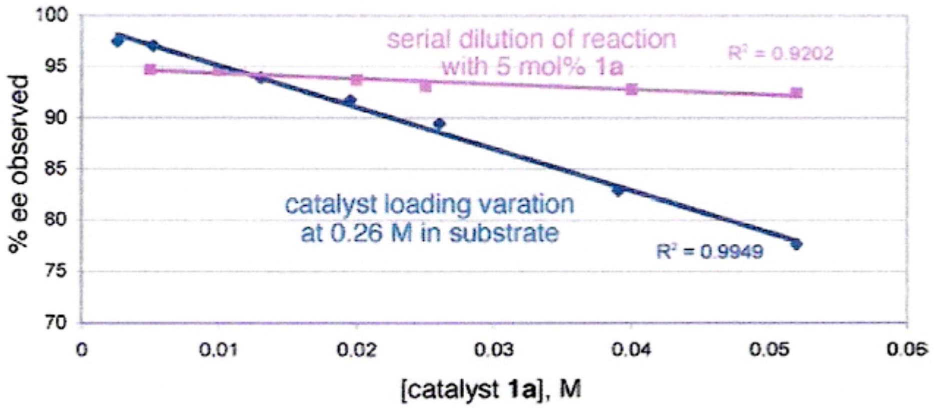
- The strong linear correlation for the Eyring plot suggest that a single set of diastereomeric transition states are operating over the measured temperature range.

Mechanistic Considerations for the 2-Acyl Imidazole Reactions with Indole: Effect of Catalyst Concentration on Enantioselectivity



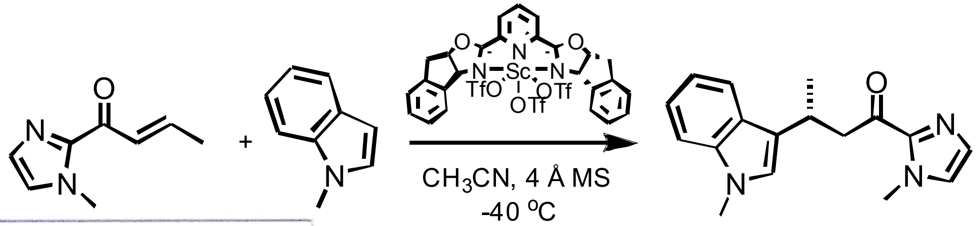
CH_3CN, 4 Å MS
-40 °C



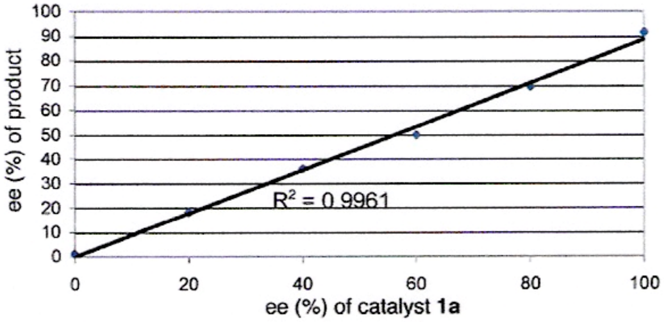


- Results indicate that the decrease in enantioselectivity with increasing mol% catalyst is not directly related to the catalyst concentration.

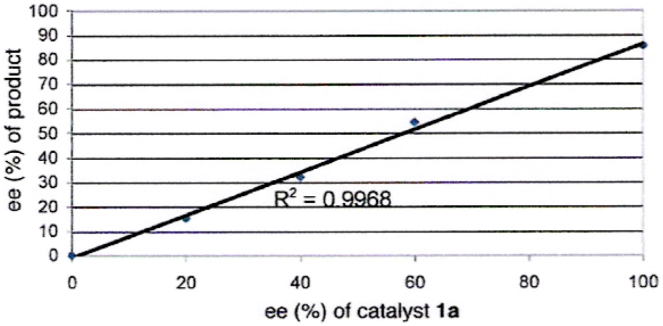
Mechanistic Considerations for the 2-Acyl Imidazole Reactions with Indole: Study of Nonlinear Effects and the Eyring Plot



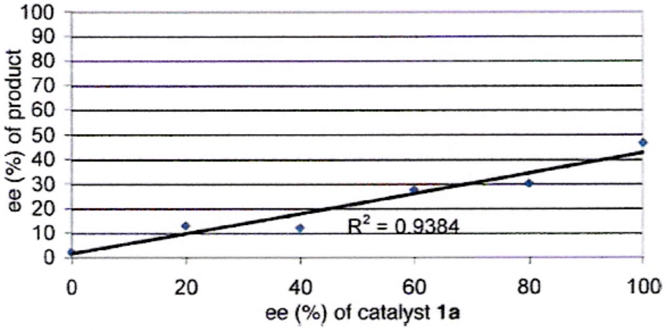
a) 10 mol% **1a**



b) 20 mol% **1a**



c) 40 mol% **1a**



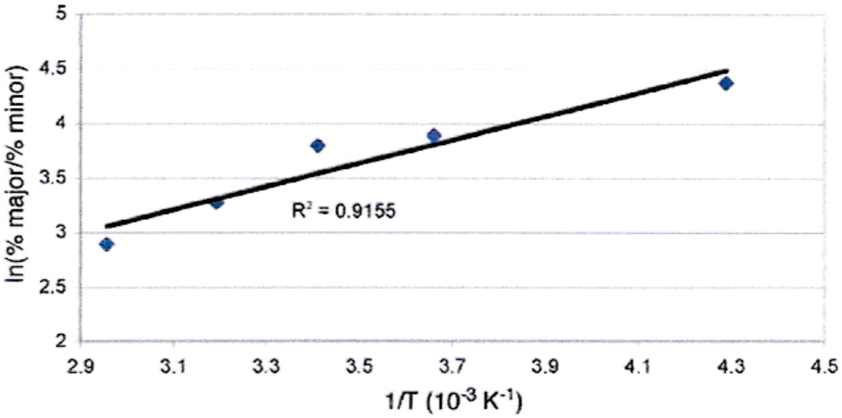


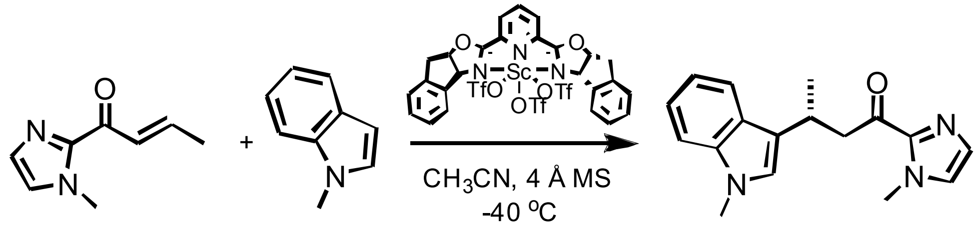
Figure 9. Eyring plot for the indole Friedel−Crafts reaction of α,β-unsaturated 2-acyl imidazole **13a** catalyzed by Sc(III) complex **1a**.

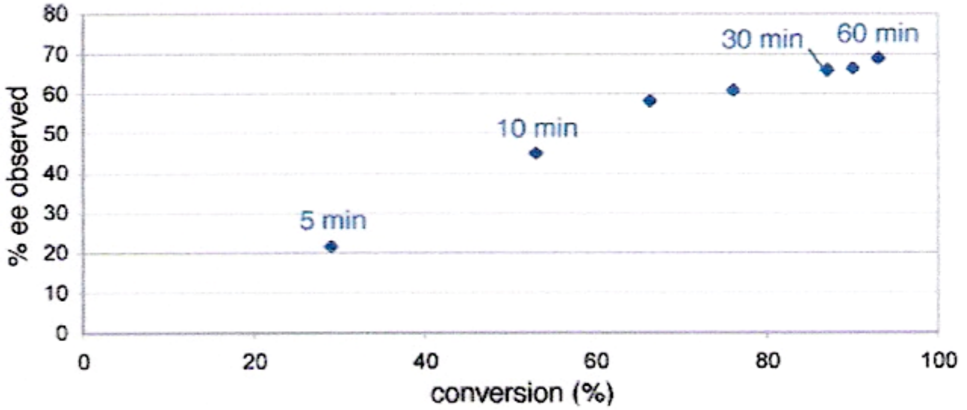
- Results:

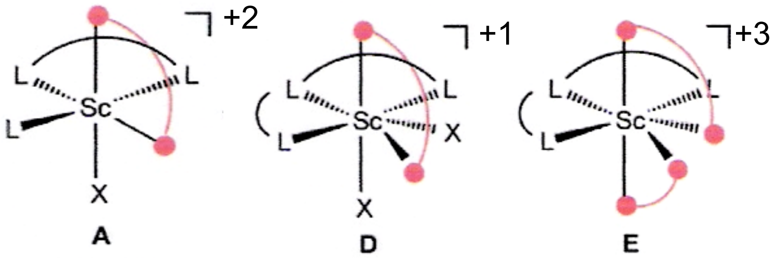
1) The study of nonlinear effects suggest that the active catalyst is mononuclear.

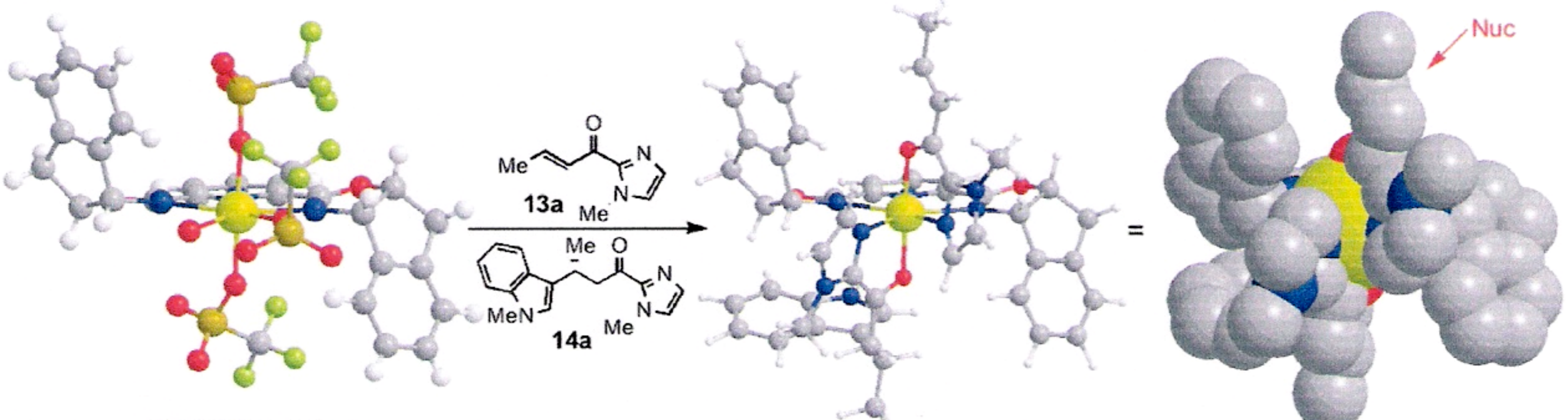
2) The Eyring plot suggest that a single set of diastereomeric transition states are operating over the measured temperature range.

Mechanistic Considerations for the 2-Acyl Imidazole Reactions with Indole: Product Enhancement of Enantioselectivity







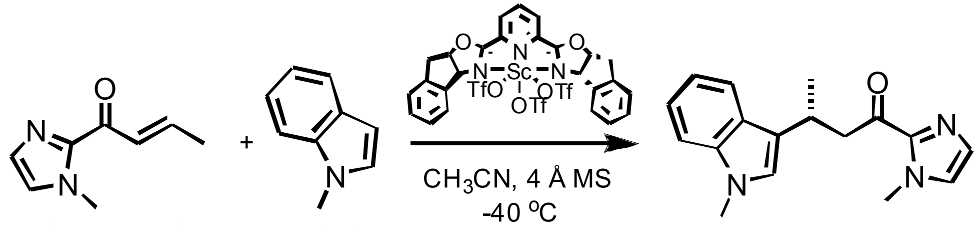


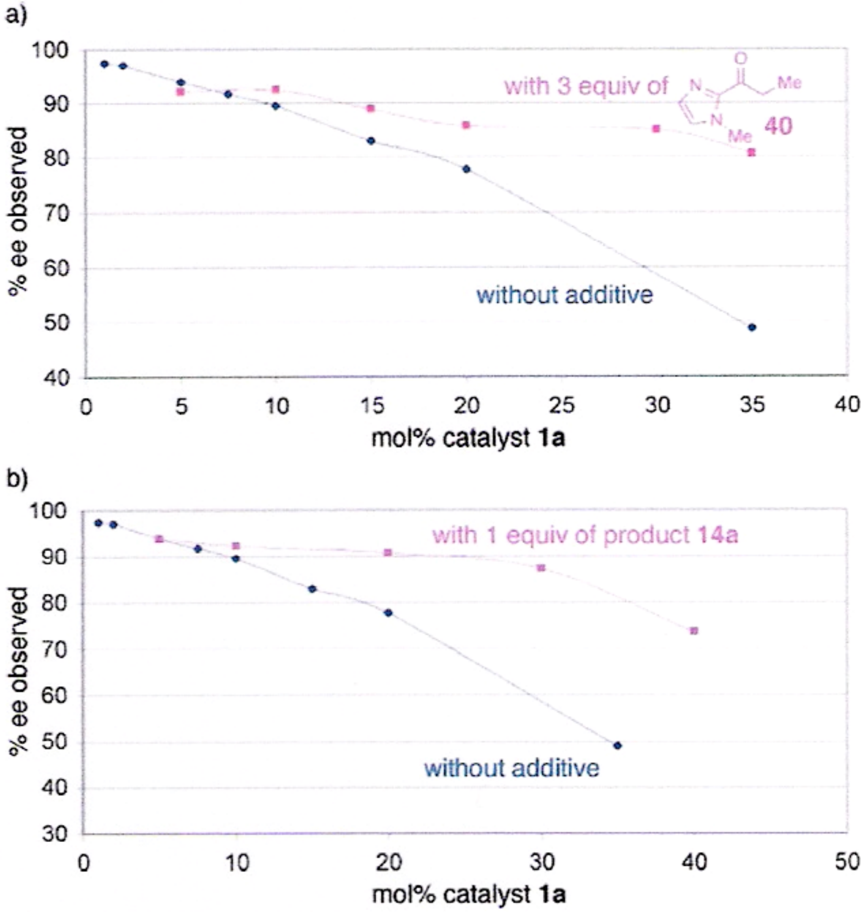
Crystal Stucture of
Sc(III)-Inda-PyBox (**1a**)

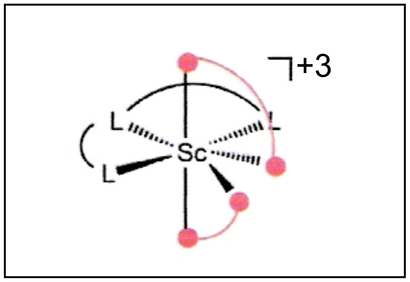
Sc(III)-Inda-PyBox (**1a**)**13a**

- Results suggest a seven –coordinate 1:1:1 product/substrate/catalyst complex.

Mechanistic Considerations for the 2-Acyl Imidazole Reactions with Indole: Product Enhancement of Enantioselectivity







- Results strongly support the formation of the seven –coordinate 1:1:1 product/substrate/catalyst complex.

Conclusion

- The authors have developed a highly efficient scandium(III) catalyzed Michael – Type indole Friedel – Crafts Alkylation Reaction based on α,β-unsaturated acyl phosphonate and 2-acyl imidazole substrates.

Good Yields
Overall Excellent Enantioselectivity
Good Product Elaboration

- The authors have also shed light on the mechanism of scandium(III) – pybox / bidentate substrate binding hence, elaborating on the origin of the observed product enantioselectivities and demonstrating the powerful utility of the scandium(III) – pybox catalyst.