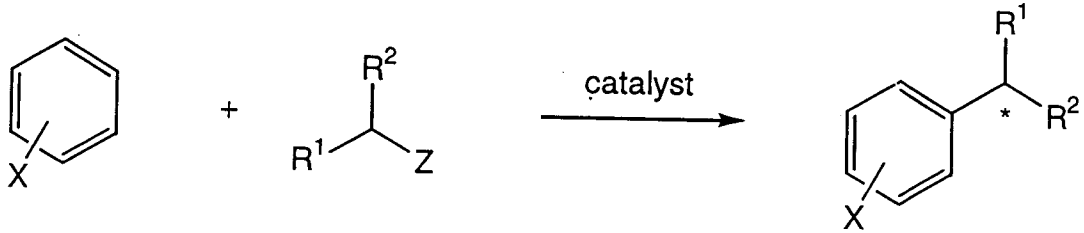
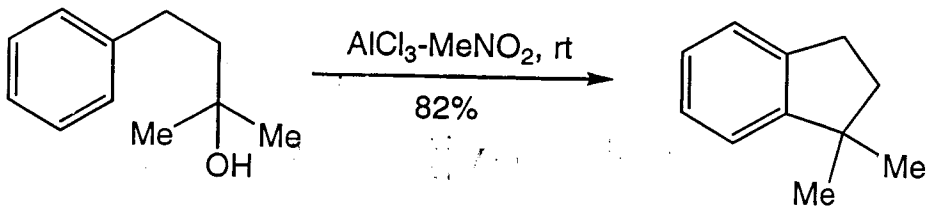
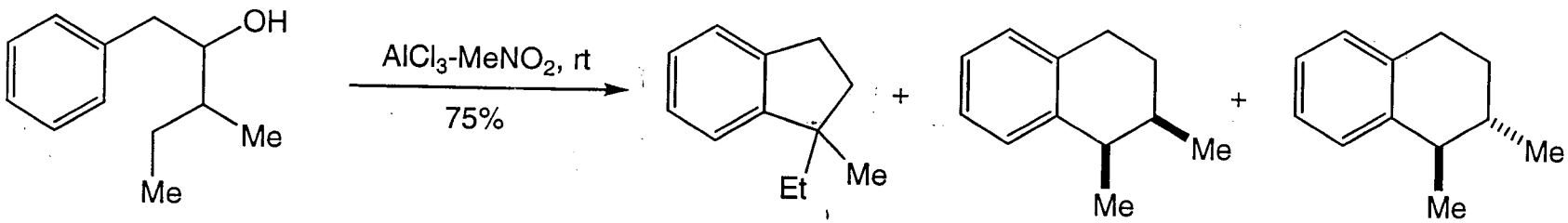
Advances in Stereoselective Friedel-Crafts Alkylation



Background Bit...

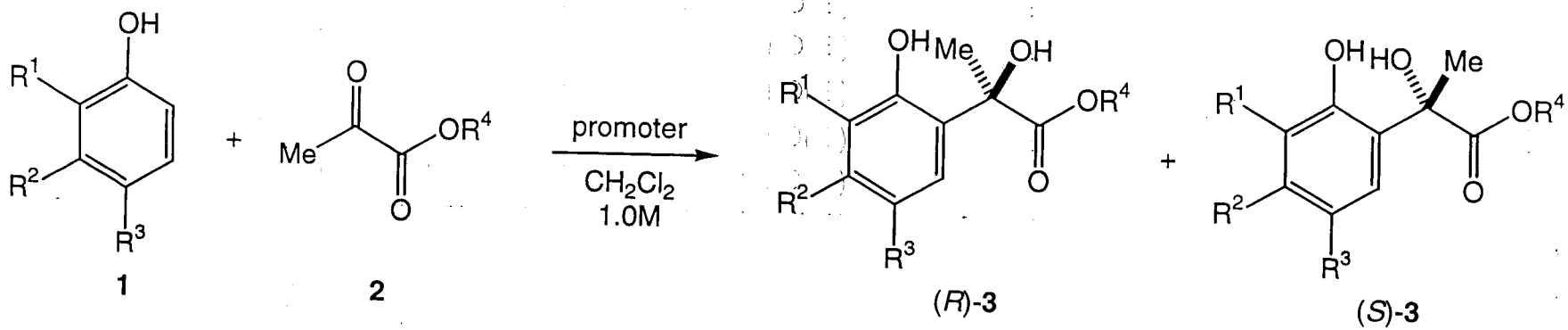
- First reported in May 1877 by Charles Friedel and James Crafts to the Chemical Society of France.
- Initially, aluminum chloride was the catalyst of choice. Now a variety of "acidic" catalysts are available including acidic halides, modified zeolites, cation exchange resins, superacids, solid super acids, and of course proton acids.
- Common alkylating agents are alkyl halides, alkenes, alkynes, alcohols, esters, ethers, carbonyl compounds, mercaptans and thiocyanates.
- The scope of the Friedel-Crafts reaction is very wide, yet until recently, little advance has been made in the field of catalytic enantioselective alkylation.





2:1:7

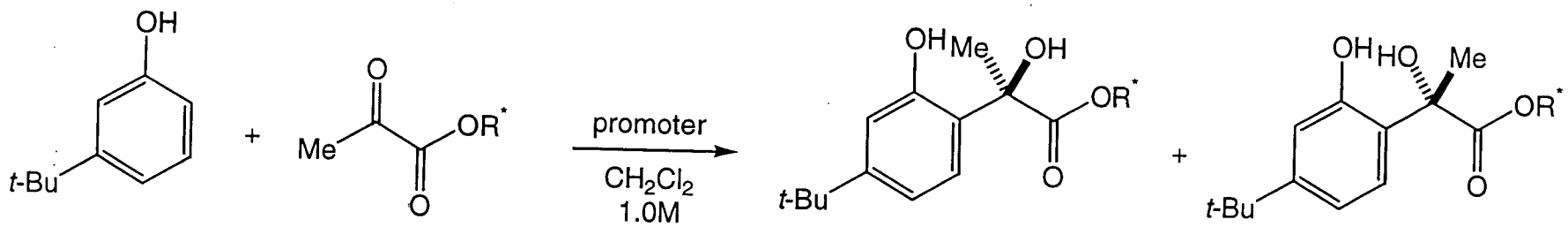
Early Studies with Chiral Lewis Acids



conditions: phenol:alkoxide:pyruvic ester, 1:1:1; 17 °C, 5 h, enantiomeric excesses determined by ^{1}H NMR

entry	1	R^1	R^2	R^3	2	R^4	promoter	product	yield, %	ee, % (config)
1	**1a**	H	*t*-Bu	H	**2a**	Et	(-)-menthyl-O(Et)AlCl	**3aa**	59	39 (*R*)
2	**1a**	H	*t*-Bu	H	**2a**	Et	(-)-borneyl-O(Et)AlCl	**3aa**	11	3 (*R*)
3	**1a**	H	*t*-Bu	H	**2a**	Et	(+)-neomenthyl-O(Et)AlCl	**3aa**	48	8 (*S*)
4	**1a**	H	*t*-Bu	H	**2a**	Et	(-)-cinchonidinyl-O(Et)AlCl	**3aa**	16	4 (*R*)
5	**1a**	H	*t*-Bu	H	**2a**	Et	(+)-menthyl-$OTiCl_3$	**3aa**	62	2 (*R*)
6	**1a**	H	*t*-Bu	H	**2b**	*t*-Bu	(-)-menthyl-O(Et)AlCl	**3ab**	20	4 (*R*)
7	**1a**	H	*t*-Bu	H	**2c**	C_6H_{11}	(-)-menthyl-O(Et)AlCl	**3ac**	40	46 (*R*)
8	**1b**	H	H	H	**2a**	Et	(-)-menthyl-O(Et)AlCl	**3ba**	12	19 (*R*)
9	**1c**	H	Me	H	**2a**	Et	(-)-menthyl-O(Et)AlCl	**3ca**	39	23 (*R*)
10	**1d**	H	OMe	H	**2a**	Et	(-)-menthyl-O(Et)AlCl	**3da**	77	22 (*R*)
11	**1e**	H	H	Me	**2a**	Et	(-)-menthyl-O(Et)AlCl	**3ea**	20	21 (*R*)
12	**1f**	H	OCH_2O		**2a**	Et	(-)-menthyl-O(Et)AlCl	**3fa**	84	13 (*R*)
13	**1g**	$(CH{=}CH)_2$	H		**2a**	Et	(-)-menthyl-O(Et)AlCl	**3ga**	89	13 (*R*)

Early Studies using Chiral Pyruvic Esters

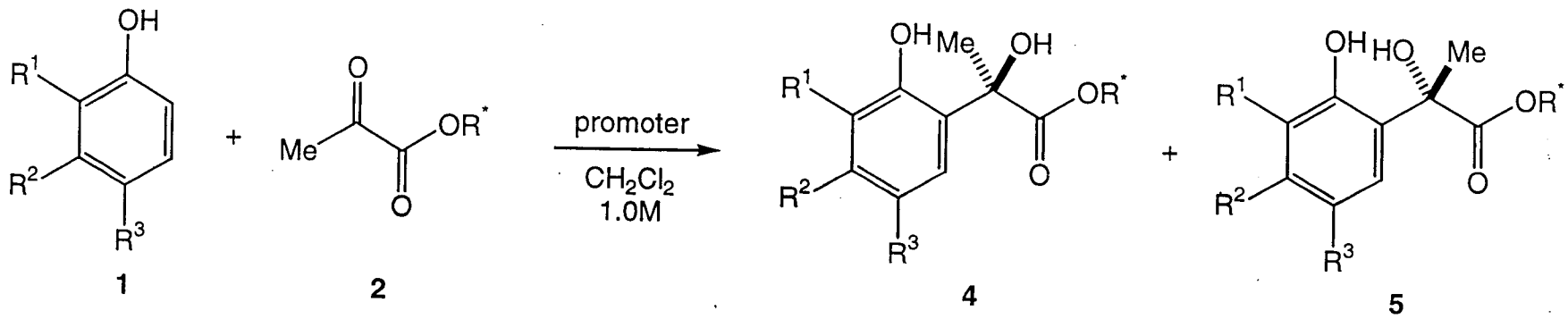


1a **2** **4a** **5a**

conditions: phenol:alkoxide:pyruvic ester, 1:1:1; 17 °C, 5 h, ratios determined by r.p. HPLC

entry	**2**	R*	promoter	temp, °C	products	yield, %	ratio, **4:5**	config
1	**2d**	(-)-menthyl	EtO(Et)AlCl	-20	**4ad** + **5ad**	60	27:73	*S*
2	**2e**	(+)-menthyl	EtO(Et)AlCl	-20	**4ae** + **5ae**	59	73:27	*R*
3	**2d**	(-)-menthyl	EtO(Et)AlCl	17	**4ad** + **5ad**	63	36:64	*S*
4	**2d**	(-)-menthyl	$EtOTiCl_3$	-60	**4ad** + **5ad**	64	24:76	*S*
5	**2e**	(+)-menthyl	$EtOTiCl_3$	-60	**4ae** + **5ae**	65	75:35	*R*

Employing Double Diastereoselection

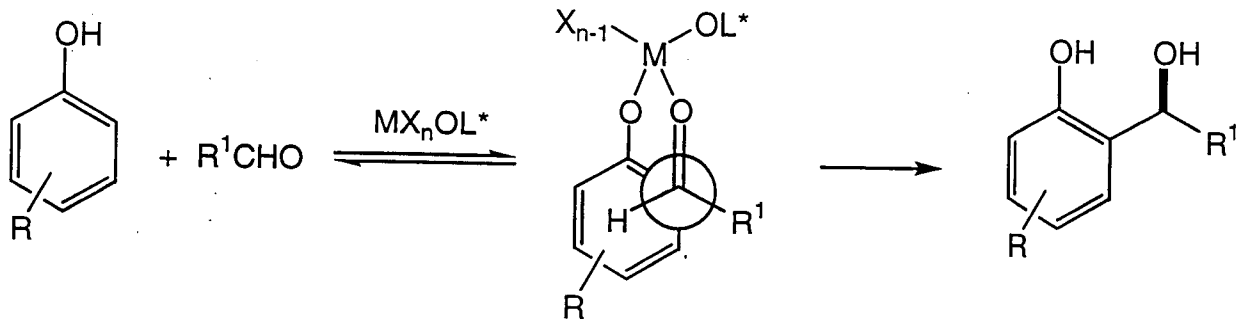


conditions: phenol:alkoxide:pyruvic ester, 1:1:1; Al-based: -20 °C, 24 h; Ti-based: -60 °C, 3 h; ratios determined by HPLC

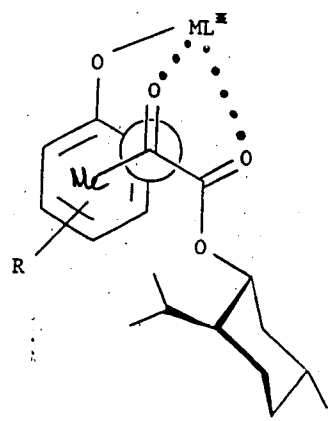
entry	1	R^1	R^2	R^3	2	R^*	promoter	products	yield, %	ratio, 4:5	config
1	**1a**	H	*t*-Bu	H	**2d**	(-)-mentyl	(+)-menthyl-O(Et)AlCl	**4ad** + **5ad**	58	22:78	*S*
2	**1a**	H	*t*-Bu	H	**2d**	(-)-mentyl	(-)-menthyl-O(Et)AlCl	**4ad** + **5ad**	56	40:60	*S*
3	**1a**	H	*t*-Bu	H	**2d**	(-)-mentyl	(-)-menthyl-$OTiCl_3$	**4ad** + **5ad**	65	12:88	*S*
4	**1a**	H	*t*-Bu	H	**2d**	(-)-mentyl	(+)-menthyl-$OTiCl_3$	**4ad** + **5ad**	64	27:73	*S*
5	**1a**	H	*t*-Bu	H	**2e**	(+)-mentyl	(+)-menthyl-$OTiCl_3$	**4ae** + **5ae**	66	87:13	*R*
6	**1g**	$(CH{=}CH)_2$		H	**2e**	(+)-mentyl	(+)-menthyl-$OTiCl_3$	**4ge** + **5ge**	86	93:7	*R*
7	**1g**	$(CH{=}CH)_2$		H	**2d**	(-)-mentyl	(-)-menthyl-$OTiCl_3$	**4gd** + **5gd**	85	6:94	*S*
8	**1f**	H	OCH_2O		**2e**	(+)-mentyl	(+)-menthyl-$OTiCl_3$	**4fe** + **5fe**	78	86:14	*R*
9[a]	**1b**	H	H	H	**2d**	(-)-mentyl	(-)-menthyl-$OTiCl_3$	**4bd** + **5bd**	41	27:73	*S*
10[b]	**1h**	H	OMe	H	**2d**	(-)-mentyl	(-)-menthyl-$OTiCl_3$	**4hd** + **5hd**	47	32:68	*S*

[a] T = 20 °C. [b] T = -20 °C.

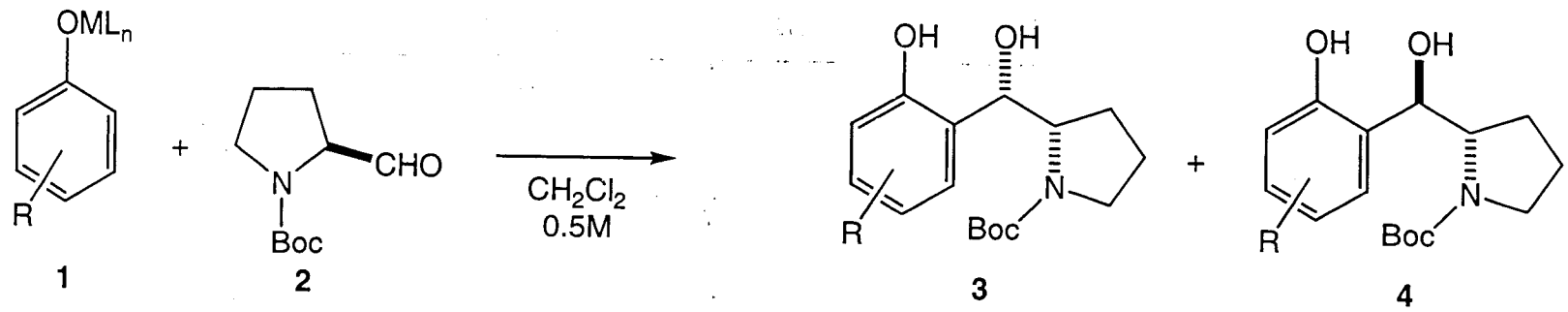
Transition State Analysis of Bigi's Pyruvate Alkylation



Staggered T.S. for the chelation-controlled metal-mediated alkylation of (-)-menthyl pyruvate to a phenolate. The proximate phenolic ortho-carbon approaches the carbonyl carbon along the *si* face.



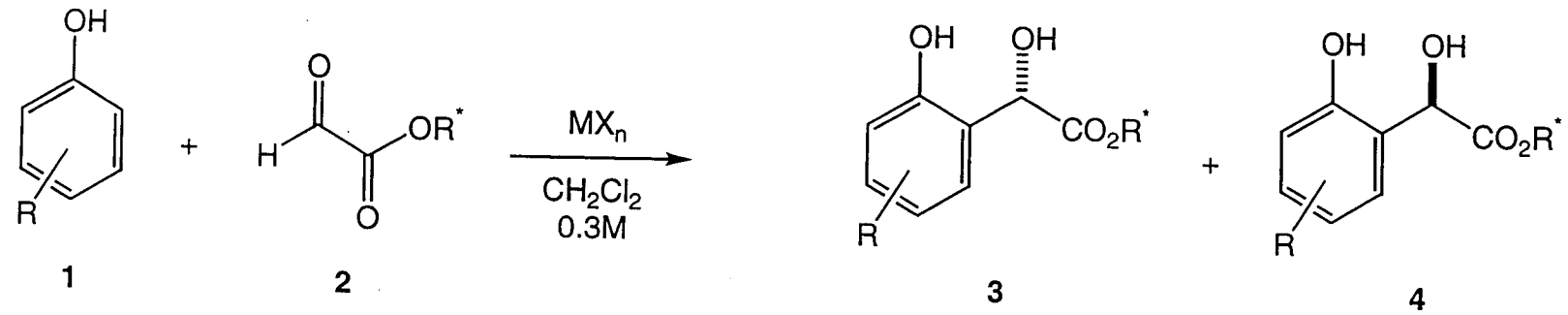
Alkylation using Chiral α-Amino Aldehydes



conditions: alkoxide:aldehyde, 1:1; room temperature; 3 h (EtMgBr-based); 48 h (Ti(O-*i*-Pr)$_4$-based)

entry	**1**	R	ML$_n$	major product	overall yield, %	ratio, **3**:**4**	configuration
1	**1a**	2-*t*-Bu	MgBr	**3a**	65	>99:1	*syn*-(*S*,*S*)
2	**1b**	4-MeO	MgBr	**3b**	50	99:1	*syn*-(*S*,*S*)
3	**1c**	H	MgBr	**3c**	65	>99:1	*syn*-(*S*,*S*)
4	**1d**	3-MeO	MgBr	**3d**	70	99:1	*syn*-(*S*,*S*)
5	**1e**	3,4-OCH$_2$O	MgBr	**3e**	75	97:3	*syn*-(*S*,*S*)
6	**1e**	3,4-OCH$_2$O	Ti(OCH(CH$_3$)$_2$)$_3$	**4e**	72	8:92	*anti*-(*R*,*S*)
7	**1d**	3-MeO	Ti(OCH(CH$_3$)$_2$)$_3$	**4d**	51	12:88	*anti*-(*R*,*S*)

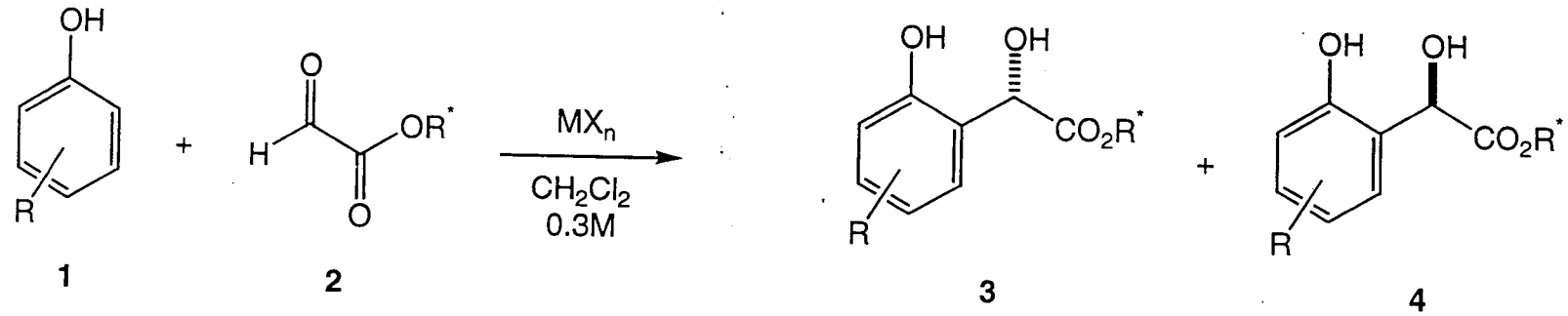
Stereoselective Alkylation using Chiral Glyoxylates



conditions: phenol:glyoxylate, 1:1; 6 h; R^* = (-)-menthyl

entry	1	R	MX_n	major product	temp, °C	overall yield, %	ratio, **3**:**4**	configuration
1	**1a**	3-*t*-Bu	Et_2AlCl	**3ia**	0	28	60:40	*S*
2	**1a**	3-*t*-Bu	Et_2AlCl	**3ia**	0	34	56:44	*S*
3	**1a**	3-*t*-Bu	EtMgBr	**3ia**	0	40	56:44	*S*
4	**1a**	3-*t*-Bu	EtMgBr	**3ia**	-30	28	70:30	*S*
5	**1a**	3-*t*-Bu	$InCl_3$	**3ia**	-30	18	70:30	*S*
6	**1a**	3-*t*-Bu	1/2 $SnCl_4$	**3ia**	0	50	71:29	*S*
7	**1a**	3-*t*-Bu	1/2 $TiCl_4$	**3ia**	20	65	70:30	*S*
8	**1a**	3-*t*-Bu	1/2 $TiCl_4$	**3ia**	0	60	71:29	*S*
9	**1a**	3-*t*-Bu	1/2 $TiCl_4$	**3ia**	-30	53	75:25	*S*
10	**1a**	3-*t*-Bu	1/2 $TiCl_4$	**3ia**	-60	28	79:21	*S*
11	**1a**	3-*t*-Bu	$TiCl_4$	**3ia**	0	63	74:26	*S*
12	**1a**	3-*t*-Bu	$TiCl_4$	**3ia**	-30	58	75:25	*S*
13	**1b**	4-OMe	1/2 $TiCl_4$	**3ib**	-30	50	76:24	*S*
14	**1c**	H	1/2 $TiCl_4$	**3ic**	-30	43	73:27	*S*

Stereoselective Alkylation using Chiral Glyoxylates: 2nd Gen.

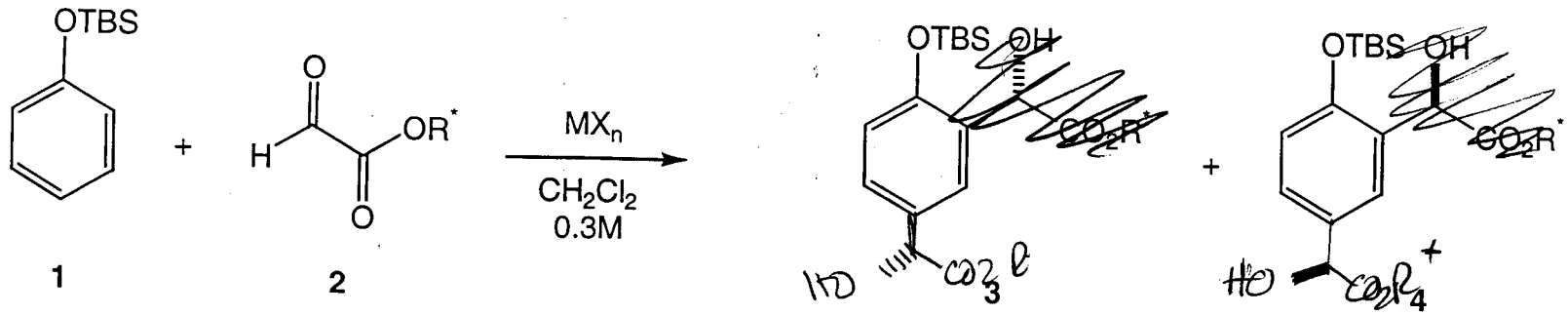


conditions: phenol:glyoxylate, 1:1; 6 h; R^* = (-)-8-phenylmenthyl

entry	1	R	MX_n	major product	temp, °C	overall yield, %	ratio, **3**:**4**	configuration
1	**1a**	3-*t*-Bu	$EtAlCl_2$	**3ja**	20	40	93:7	*S*
2	**1a**	3-*t*-Bu	BCl_3	**3ja**	20	41	79:21	*S*
3[a]	**1a**	3-*t*-Bu	$Ti(O\text{-}i\text{-}Pr)_4$	**3ja**	20	23	65:35	*S*
4	**1a**	3-*t*-Bu	1/2 $SnCl_4$	**3ja**	20	60	96:4	*S*
5	**1a**	3-*t*-Bu	$TiCl_4$	**3ja**	20	95	97:3	*S*
6	**1a**	3-*t*-Bu	1/2 $TiCl_4$	**3ja**	20	90	97:3	*S*
7	**1a**	3-*t*-Bu	1/2 $TiCl_4$	**3ja**	0	68	97:3	*S*
8	**1a**	3-*t*-Bu	$TiCl_4$	**3ja**	-30	65	98:2	*S*
9	**1a**	3-*t*-Bu	1/2 $TiCl_4$	**3ja**	-30	57	98:2	*S*
10	**1a**	3-*t*-Bu	1/2 $TiCl_4$	**3ja**	-60	35	98:2	*S*
11	**1b**	4-MeO	$TiCl_4$	**3jb**	20	97	97:3	*S*
12	**1d**	4-Cl	$TiCl_4$	**3jd**	20	62	97:3	*S*

[a] Reaction time = 48 h

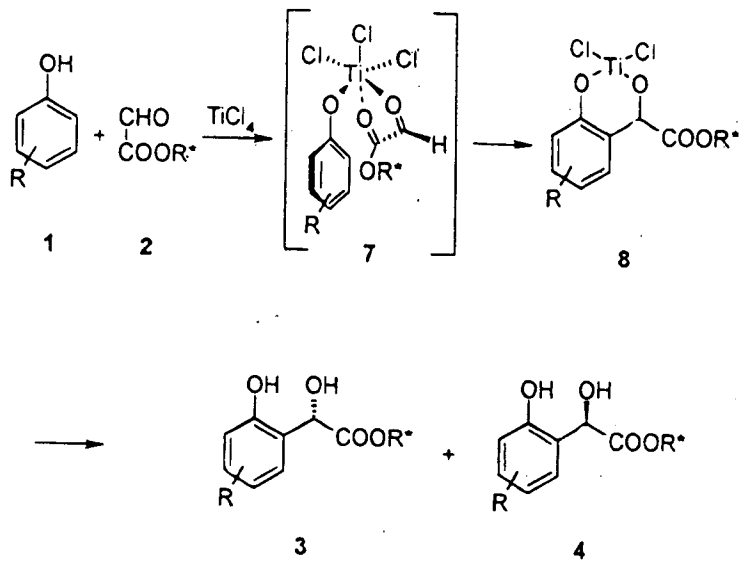
Para Alkylation Using a Bulky Silyl Phenol



conditions: phenol:glyoxylate, 1:1; 6 h

entry	R*	MX_n	major product	overall yield, %	ortho/para+ortho, %	ratio, **3**:**4**
1	(-)-menthyl	$SnCl_4$	**3i**	78	3	78:22
2	(-)-menthyl	$TiCl_4$	**3i**	46	13	75:25
3	(-)-menthyl	$FeCl_3$	**3i**	23	5	54:46
4	(-)-menthyl	$AlCl_3$	traces	-	-	-
5	(-)-menthyl	$C_6H_{11}OAlCl_2$	no reaction	-	-	-
6	(-)-menthyl	$MgCl_2$	no reaction	-	-	-
7	(-)-menthyl	$ZnCl_2$	no reaction	-	-	-
8	(-)-menthyl	$Ti(O\text{-}i\text{-}Pr)_3Cl$	no reaction	-	-	-
9	(-)-8-phenyl menthyl	$SnCl_4$	**3j**	70	-	>98:2
10	(-)-trans-2-phenylcyclohexyl	$SnCl_4$	**4k**	62	-	6:94

Transition State Analysis of Bigi's Glyoxylate Alkylation



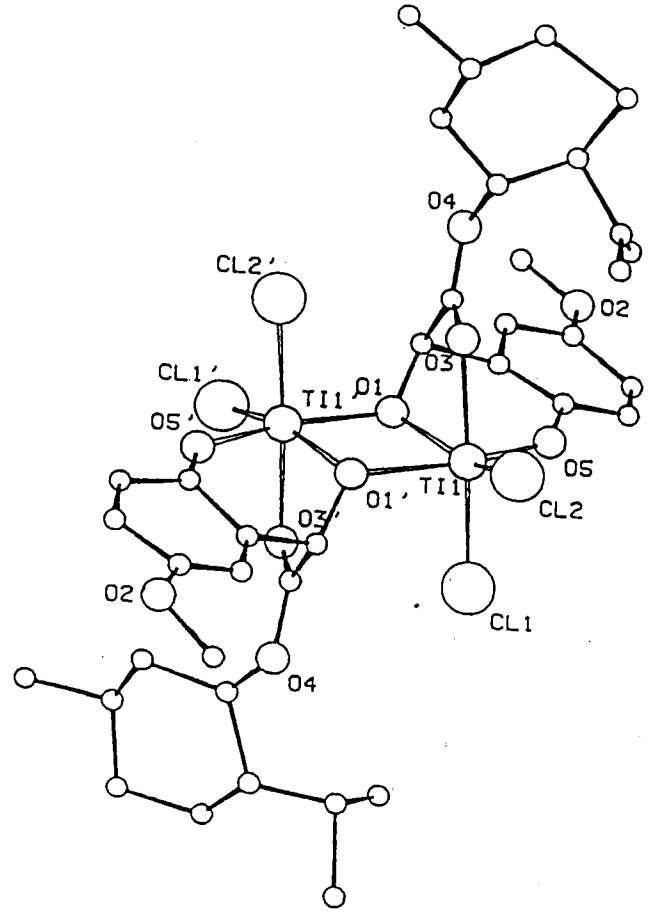
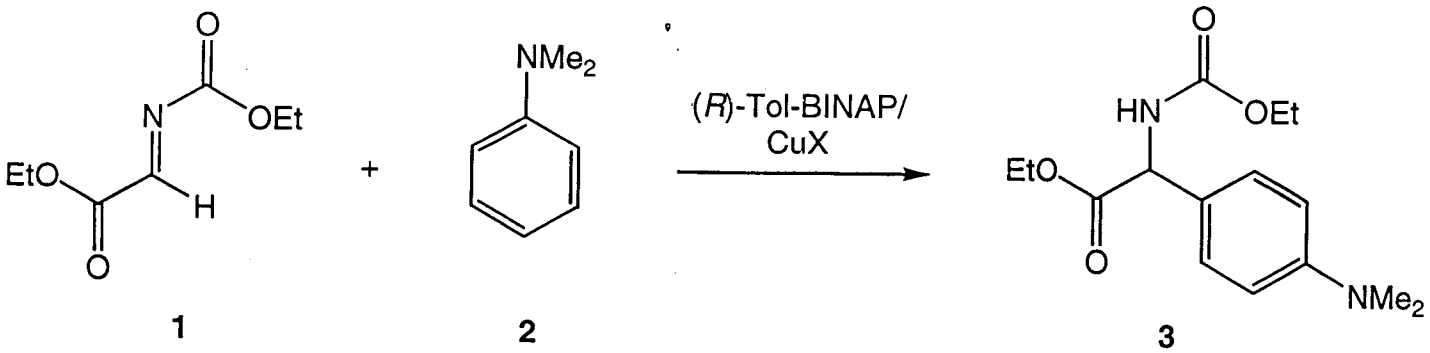


Figure 1. View of complex 8.

Catalytic Alkylation of Aniline Using Imines

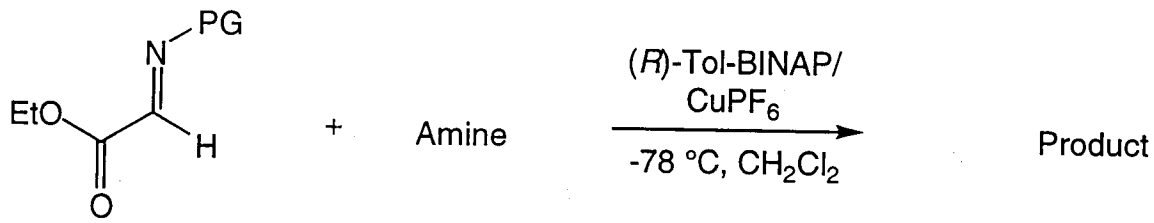


entry	CuX	catalyst conc, mol %	solvent	temp, °C	yield, %	ee, %
1	$CuClO_4$	10	THF	rt	81	14
2	$CuClO_4$	10	THF	-78	81	87
3	$CuClO_4$	10	CH_2Cl_2	-78	82	85
4	$CuClO_4$	5	THF	-78	78	93
5	$CuPF_6$	5	THF	-78	75	96
6	$CuPF_6$	1	THF	-78	79	81
7	$CuPF_6$	5	THF	-78	76	93

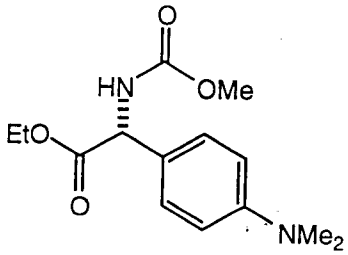
Alkylation affords exclusively the para-product

catalytically speaking!

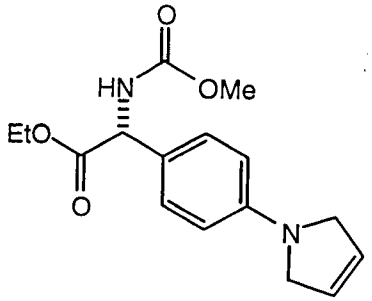
Catalytic Alkylation of Various Amines



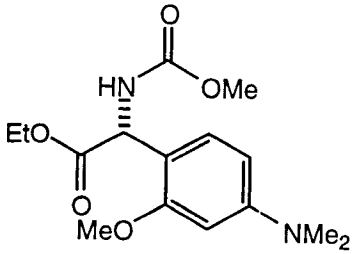
1 **2** **3**



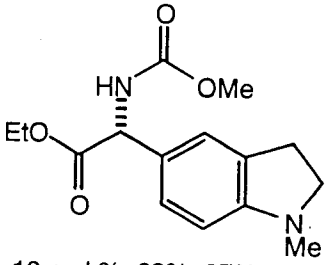
5 mol %, 75%, 93% ee



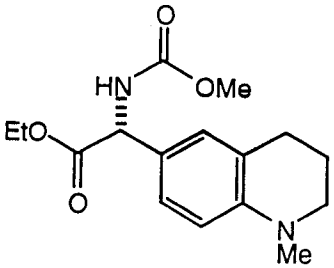
5 mol %, 88%, 86% ee



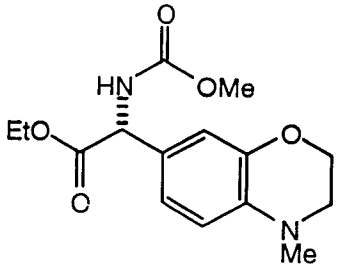
5 mol %, 68%, 72% ee
10 mol %, 79%, 76% ee
5 mol %, 56%, 79% ee (THF)



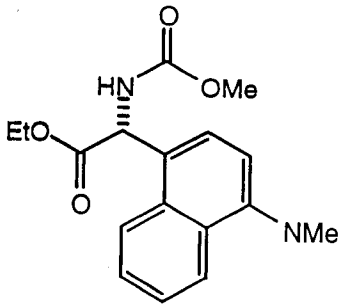
10 mol %, 63%, 97% ee
20 mol %, 79%, 98% ee



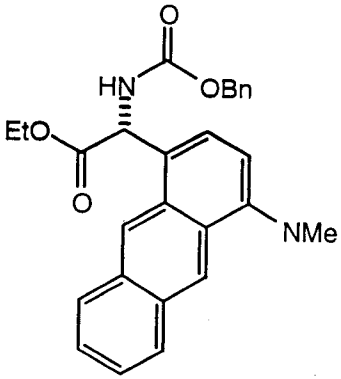
5 mol %, 82%, 87% ee



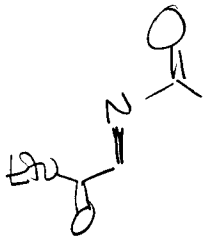
10 mol %, 44%, 52% ee

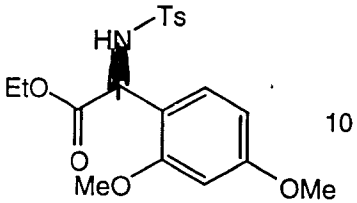


5 mol %, 75%, 92% ee



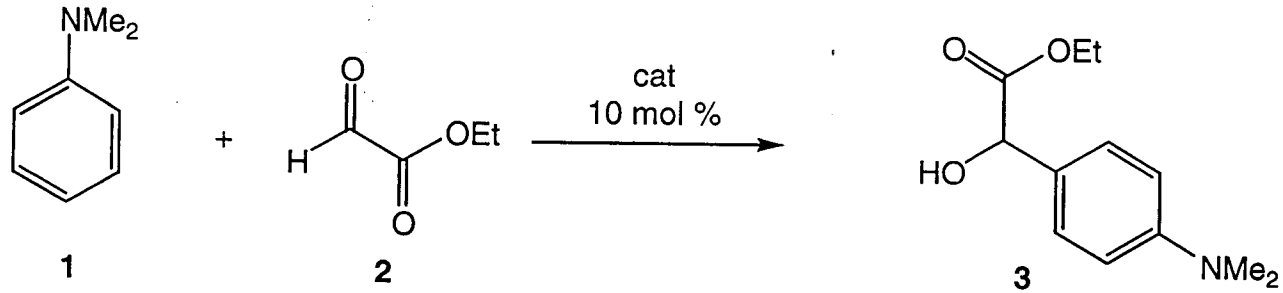
5 mol %, 65%, 89% ee



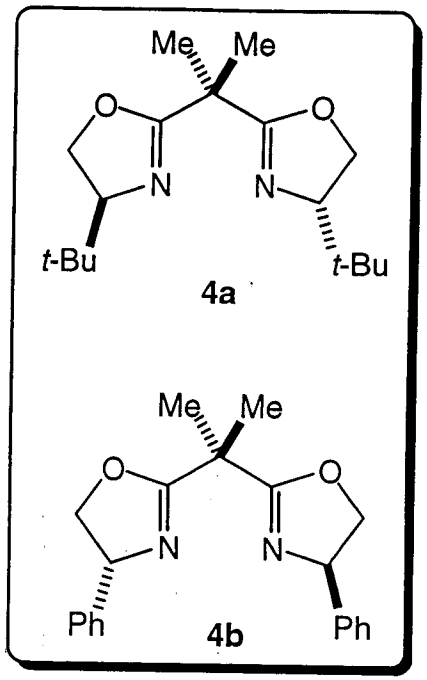


10 mol %, 83%, 79% ee

Catalytic Alkylation of Aniline Using Glyoxylates

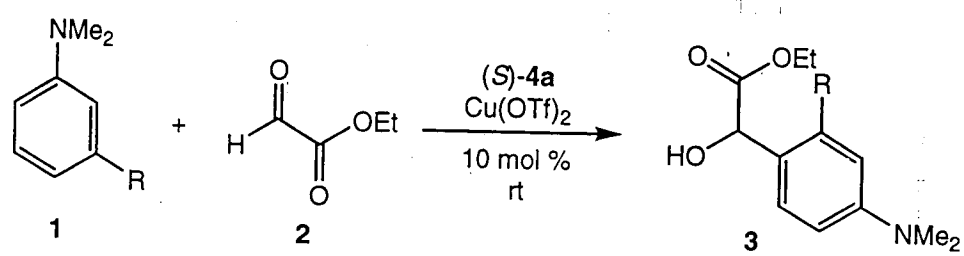


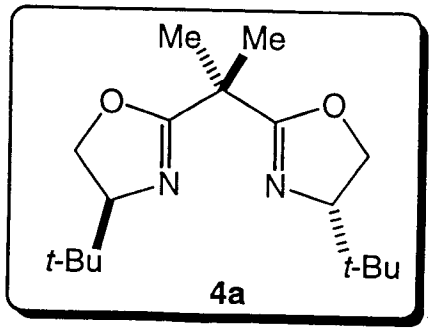
entry	glyoxylate, equiv.	catalyst	solvent	temp, °C	yield, %	ee, % (conf.)
1	1.5	(*S*)-**4a**-Cu(OTf)$_2$	CH_2Cl_2	rt	81	80
2	1.5	(*S*)-**4a**-Cu(OTf)$_2$	Et_2O	rt	78	89
3	1.5	(*S*)-**4a**-Cu(OTf)$_2$	THF	rt	72	90
4	10	(*S*)-**4a**-Cu(OTf)$_2$	CH_2Cl_2	rt	90	82
5	5	(*S*)-**4a**-Cu(OTf)$_2$	THF	-30	71	74
6	5	(*S*)-**4a**-Cu(OTf)$_2$	$MeNO_2$	0	32	18
7	5	(*S*)-**4a**-Cu(SbF$_6$)$_2$	THF	rt	36	0
8	1.5	(*R*)-**4b**-Cu(OTf)$_2$	CH_2Cl_2	rt	70	54
9	1.5	(*R*)-**4b**-Cu(OTf)$_2$	Et_2O	rt	76	42
10	1.5	(*R*)-**4b**-Cu(OTf)$_2$	THF	rt	81	22
11	1.5	(*R*)-**4b**-Zn(OTf)$_2$	CH_2Cl_2	0	41	12
12	1.5	(*S*)-**4a**-Cu(OTf)$_2$	CH_2Cl_2	0	85	61
13	1.5	(*S*)-**4a**-Cu(OTf)$_2$	Et_2O	0	92	90
14	1.5	(*S*)-**4a**-Cu(OTf)$_2$	THF	0	82	94
15	5	(*S*)-**4a**-Cu(OTf)$_2$	Et_2O	0	94	86
16	5	(*S*)-**4a**-Cu(OTf)$_2$	THF	rt	91	82
17[a]	5	(*S*)-**4a**-Cu(OTf)$_2$	THF	rt	74	88
18[b]	5	(*S*)-**4a**-Cu(OTf)$_2$	THF	rt	45	87



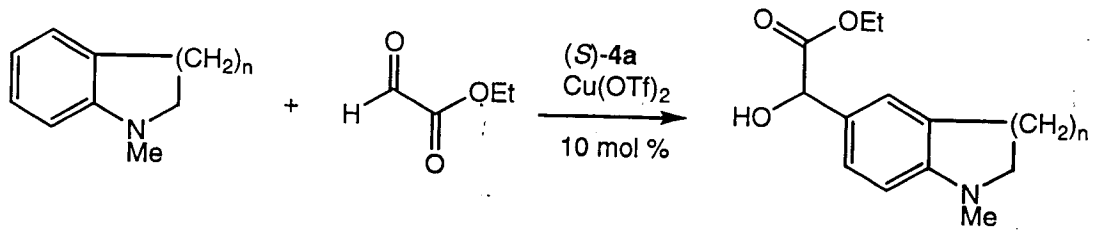
[a] using 5 mol % catalyst
[b] using 1 mol % catalyst

Catalytic Alkylation of Various Amines Using Glyoxylates



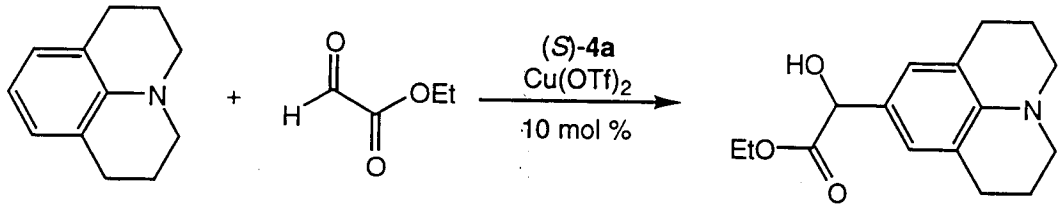


entry	glyoxylate, equiv.	R	time, d	yield, % CH_2Cl_2/THF	ee, % CH_2Cl_2/THF
1	1.5	H	1	81/72	80/90
2	5	F	1	80/58	85/81
3	5	Cl	2	84/41	93/95
4	5	Br	4	68/36	88/89
5	5	Me	1	77/76	80/92
6	5	OMe	1	21/19	77/86

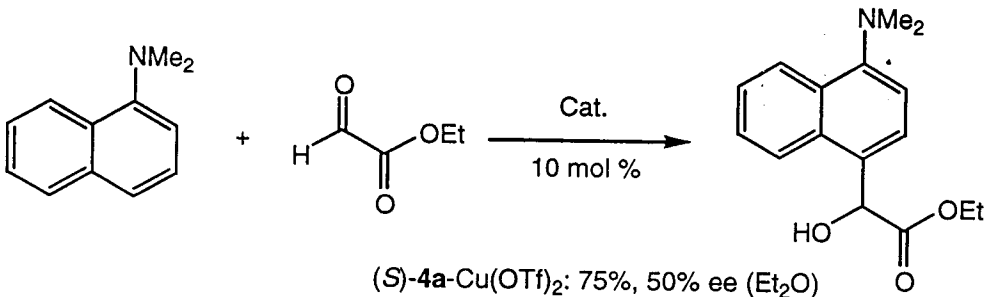


n=1: 76%, 83% ee (0 °C)
n=2: 76%, 90% ee (rt)
n=2: 56%, 93% ee (0 °C)

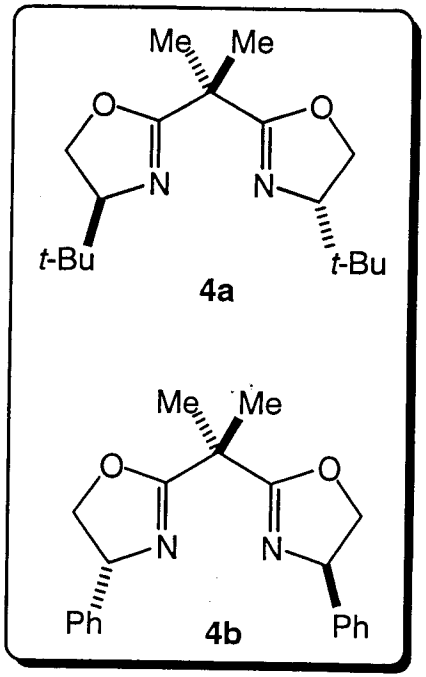
Catalytic Alkylation of Various Amines Using Glyoxylates

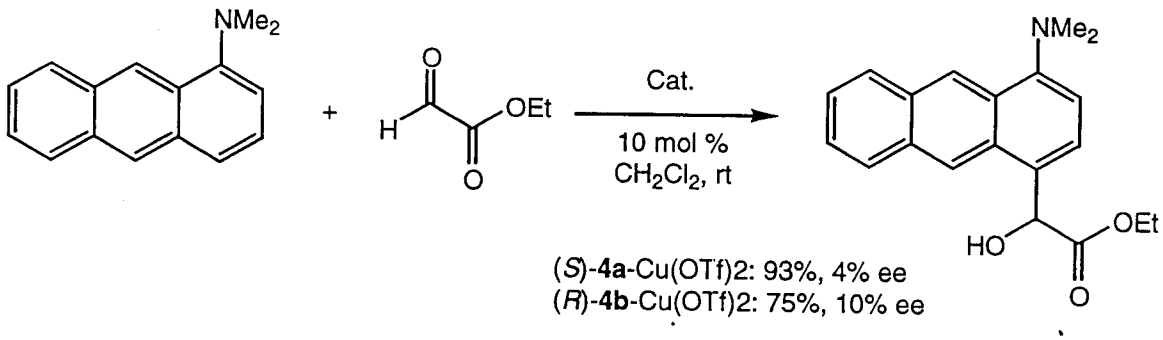


56%, 78% ee (-30 °C)



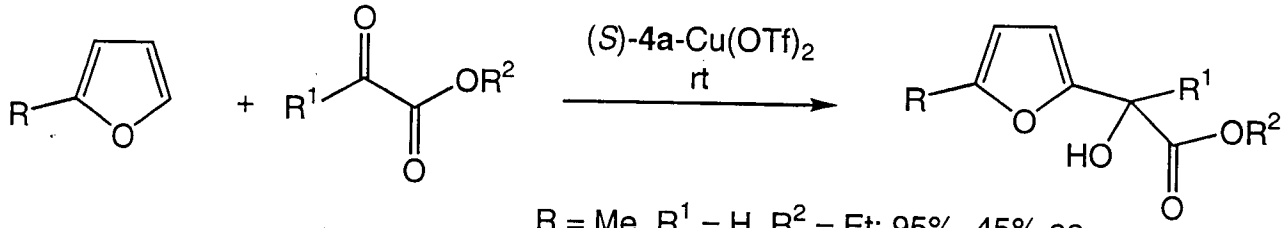
(*S*)-**4a**-Cu(OTf)$_2$: 75%, 50% ee (Et_2O)
(*S*)-**4a**-Cu(OTf)$_2$: 93%, 40% ee (CH_2Cl_2)
(*R*)-**4b**-Cu(OTf)$_2$: 97%, 38 % ee (CH_2Cl_2)



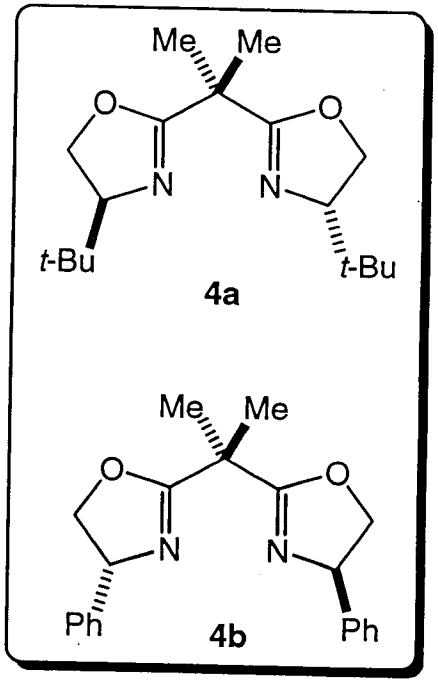


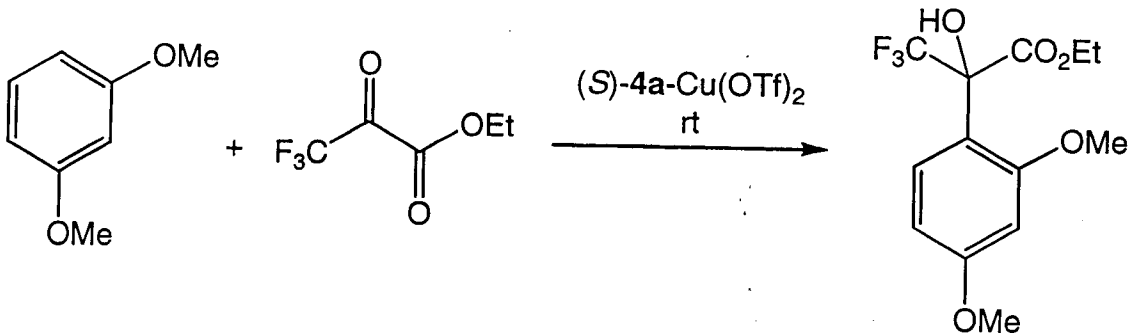
(*S*)-**4a**-Cu(OTf)2: 93%, 4% ee
(*R*)-**4b**-Cu(OTf)2: 75%, 10% ee

Catalytic Alkylation of Various Aromatics Using Glyoxylates



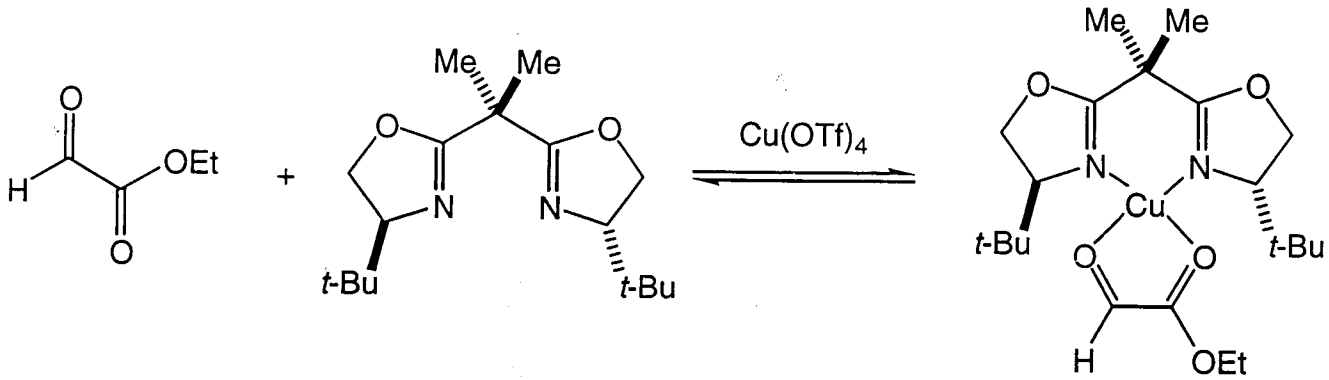
R = Me, R^1 = H, R^2 = Et: 95%, 45% ee
R = Me, R^1 = CF_3, R^2 = Me: 51%, 89% ee
R = TMS, R^1 = CF_3, R^2 = Et: 32%, 76% ee



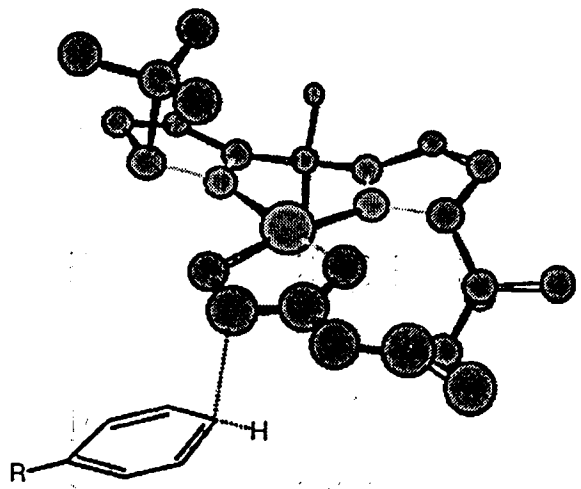


56%, 86% ee

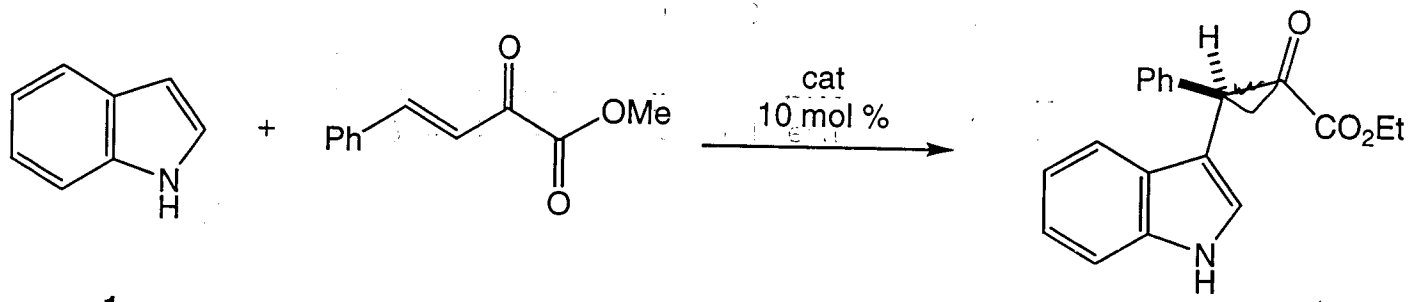
Transition State Rationale for Jørgensen's Glyoxylate Alkylation



Approach of aniline from underside, as drawn



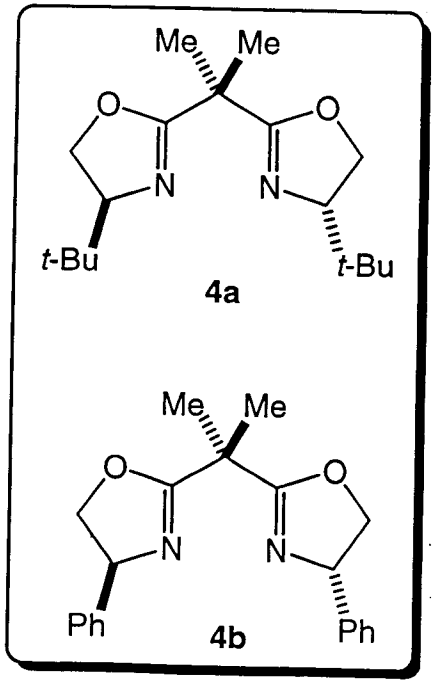
Catalytic Alkylation of Amines Using Keto Esters



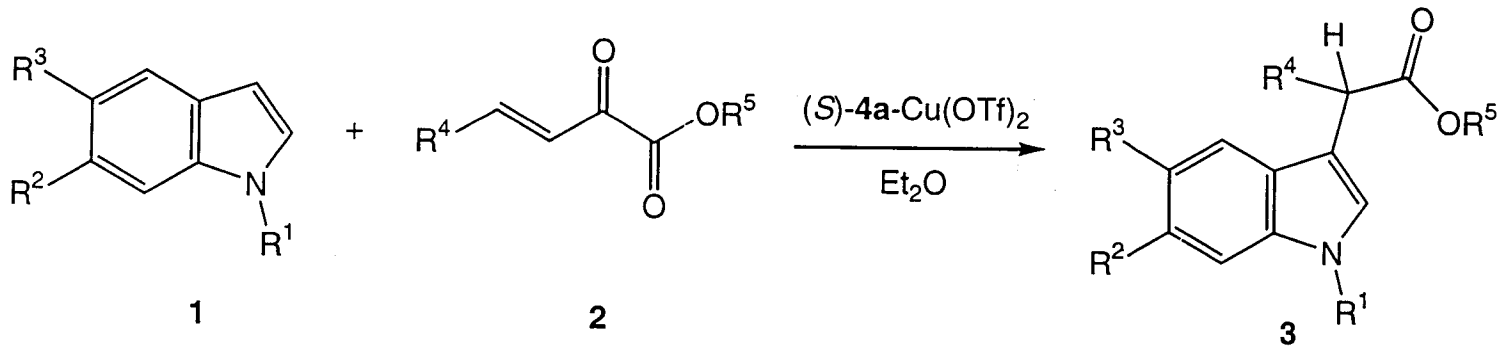
1 2 3

entry	catalyst	solvent	temp, °C	time, h	conv. %	ee, %
1	-	CH_2Cl_2	20	24	27	0
2	(*S*)-**4a**-Cu(OTf)$_2$	CH_2Cl_2	0	0.5	100	36
3	(*S*)-**4a**-Cu(OTf)$_2$	CH_2Cl_2	-78	3	100	88
4	(*S*)-**4a**-Cu(OTf)$_2$	Et_2O	rt	0.5	100	88
5	(*S*)-**4a**-Cu(OTf)$_2$	Et_2O	-78	16	100	97
6	(*S*)-**4a**-Cu(OTf)$_2$	THF	-78	1	100	74
7	(*S*)-**4a**-Cu(SbF$_6$)$_2$	CH_2Cl_2/pentane (1:2)	-78	16	99	89
8[a]	(*S*)-**4a**-Cu(SbF$_6$)$_2$	Et_2O	-78 to -30	64	100	99.5
9	(*S*)-**4b**-Zn(OTf)$_2$	Et_2O	0 to 20	18	100	87
10	(*S*)-**4b**-Cu(OTf)$_2$	Et_2O	-78	16	100	42[b]

[a] 2 mmol scale using 2 mol % catalyst. [b] obtained the opposite enantiomer to **4a**.

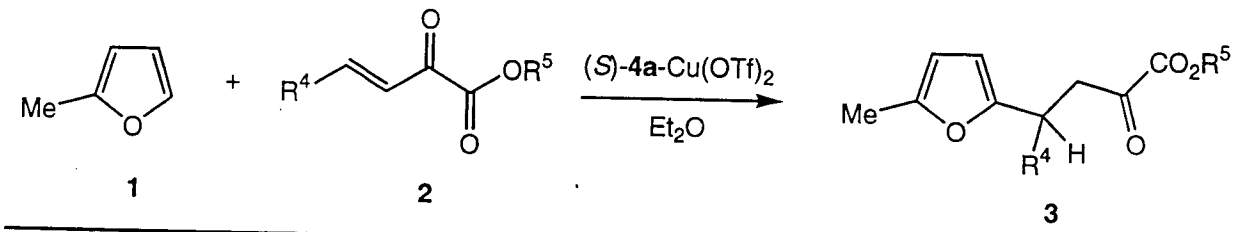


Catalytic Alkylation of Various Amines Using Keto Esters

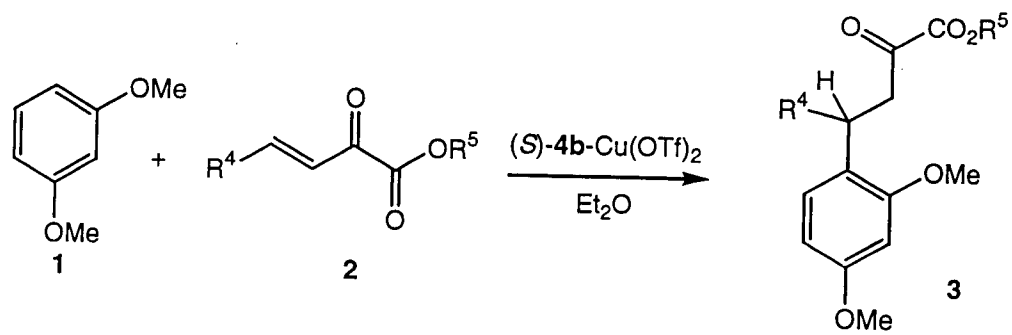


entry	R^1	R^2	R^3	R^4	R^5	cat. conc. mol %	temp, °C	time, h	yield, %	ee, %
1	H	H	H	Ph	Me	2	-78 to -30	64	77	99.5
2	Me	H	H	Ph	Me	5	-78 to -30	48	98	96
3	H	OMe	H	Ph	Me	5	-78	1	95	>99.5
4	H	H	Cl	Ph	Me	10	-20 to 0	16	69	97
5	H	H	CO_2Me	Ph	Me	10	-20 to 0	16	82	94
6	H	H	H	Me	Et	5	-78	16	96	95
7	H	OMe	H	Me	Et	5	-78	1	95	>99.5
8	H	H	Cl	CH_2OBn	Et	10	-20 to 0	16	70	80
9	H	OMe	H	CH_2OBn	Et	5	-78	1	98	95

Catalytic Alkylation of Various Aromatics Using Keto Esters

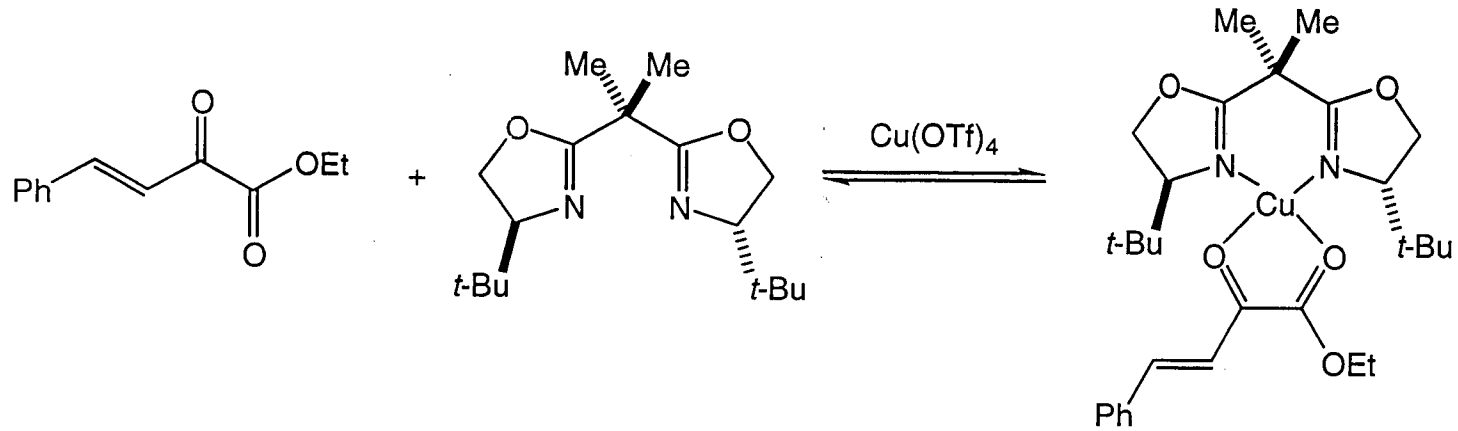


entry	R^4	R^5	cat. conc. mol %	temp, °C	time, h	yield, %	ee, %
1	Ph	Me	10	0	48	99	88
2	Me	Et	10	0	24	93	88
3	CH_2OBn	Et	10	8	24	90	80
4	*p*-Cl-Ph	Me	10	0	18	90	79



entry	R^4	R^5	cat. conc. mol %	temp, °C	time, h	yield, %	ee, %
1	Ph	Me	10	0	48	99	88
2	Me	Et	10	0	24	93	88

Transition State Rationale for Jørgensen's Glyoxylate Alkylation



Approach of aniline from underside, as drawn

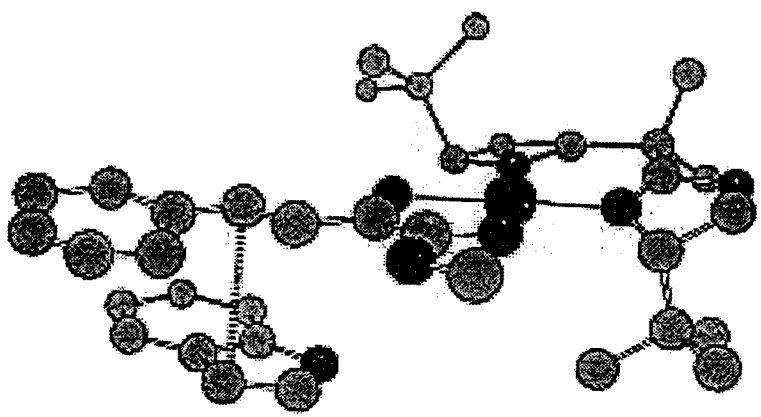
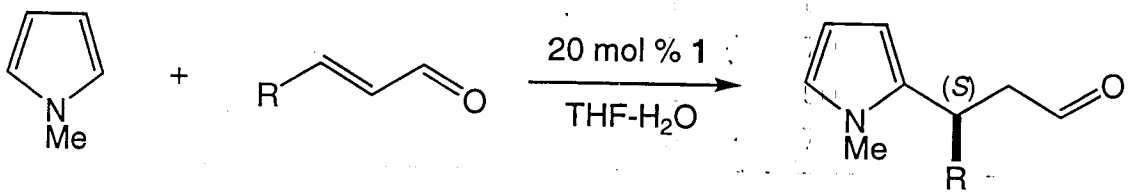
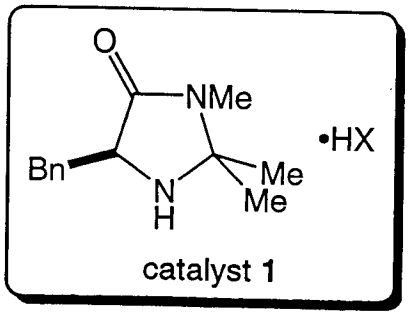


Figure 2. A model for the approach of indole to the β,γ-unsaturated α-ketoester **2a** coordinated to (*S*)-**4a** in a square-planar fashion. This model can account for the absolute configuration of the formed Friedel–Crafts product **3d**. Color scheme: gray = carbon, red = oxygen, green = copper, blue = nitrogen.

Alkylation of Pyrroles Using Catalytic Imidazolines





R = Ph

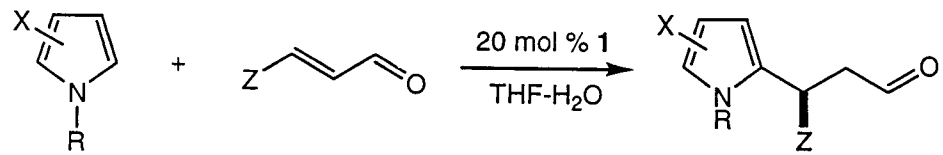
entry	H-X cocatalyst	temp, °C	time, h	yield, %	ee, %
1	$NCCH_2CO_2H$	23	32	10	80
2	Cl_2CHCO_2H	23	32	62	80
3	Cl_3CCO_2H	23	3	64	81
4	TFA	23	3	78	81
5	TFA	-30	42	87	93

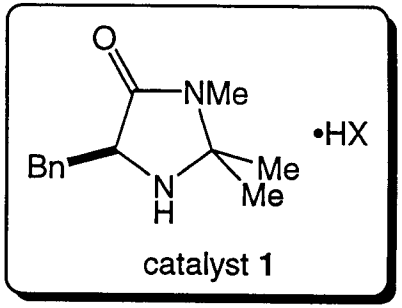
catalyst = **1**•TFA

entry	R	temp, °C	time, h	yield, %	ee, %
1	Me	-60	72	83	91[a]
2	Pr	-50	72	81	90
3	*i*-Pr	-50	72	80	91
4	4-MeOPh	-30	104	79	91
5	CH_2OBn	-60	72	90	87[a]
6	CO_2Me	-50	104	72	90[b]

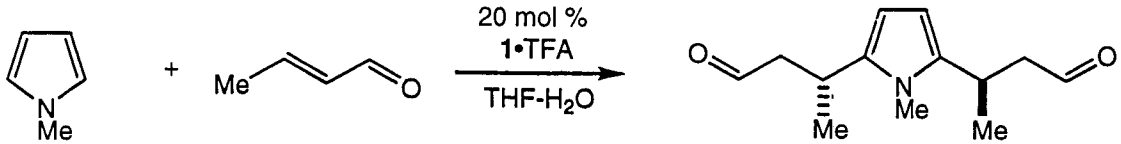
[a] using 10 mol % catalyst. [b] using **1**•$NCCH_2CO_2H$.

Alkylation of Various Pyrroles Using Catalytic Imidazolines

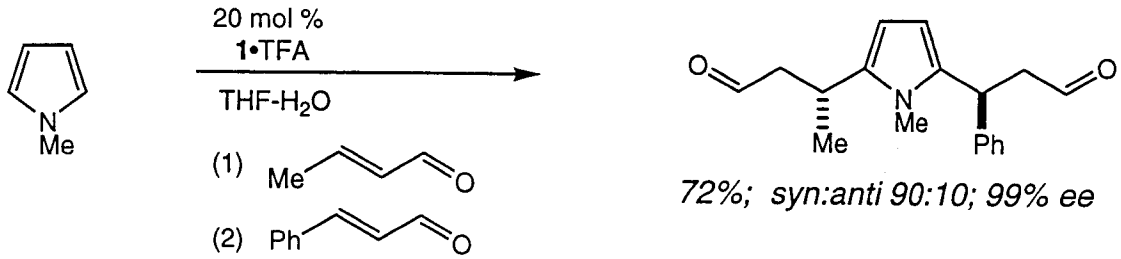




entry	H-X cocatalyst	R	X	Z	yield, %	ee, %
1	TFA	Me	H	Ph	87	93
2	Cl_3CCO_2H	Bn	H	Ph	80	89
3	Cl_3CCO_2H	Allyl	H	Ph	83	91
4	$NCCH_2CO_2H$	H	H	CO_2Me	74	90
5	Cl_3CCO_2H	Me	2-Bu	Ph	87	90
6	Cl_3CCO_2H	Me	3-*i*-Pr	Ph	68	97

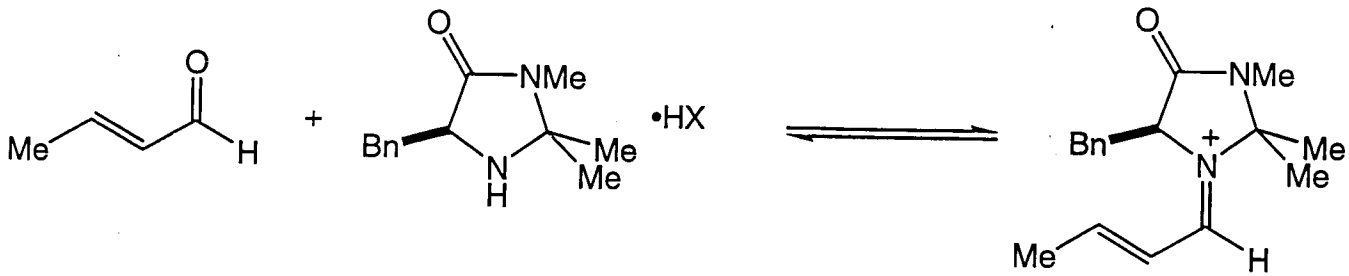


83%; C_2:meso 90:10; 98% ee

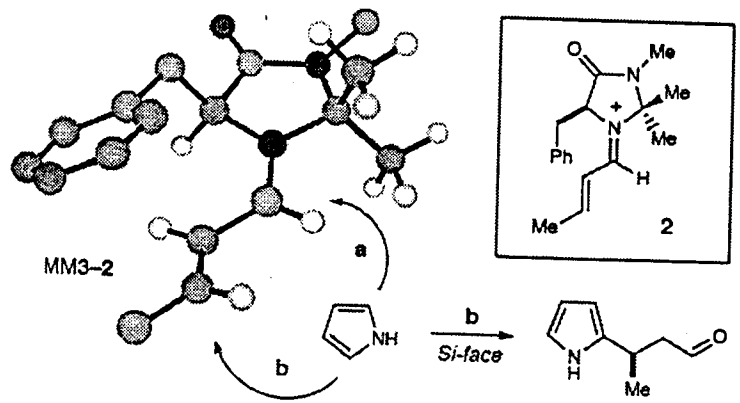


72%; syn:anti 90:10; 99% ee

Mechanism for MacMillan's Imidazoline Catalyzed Alkylation



Then 1,4-addition occurs preferentially over "conventional" 1,2-addition.



a = conventional acid catalyzed pathway

b = non-conventional 1,4-addition

Conclusions

- Although much is known about the Friedel-Crafts reaction, there is still only limited reports of catalytic enantioselective process.
- Initial reports by Jorgensen and MacMillan should pave the road for more profound advances in this field.
- Substrate generality, for both the arene and electrophile, will be necessary for the enantioselective process to be a viable tool in organic chemistry.

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