Highly Enantioselective Friedel-Crafts Reaction of Indoles with Imines by a Chiral Phosphoric Acid

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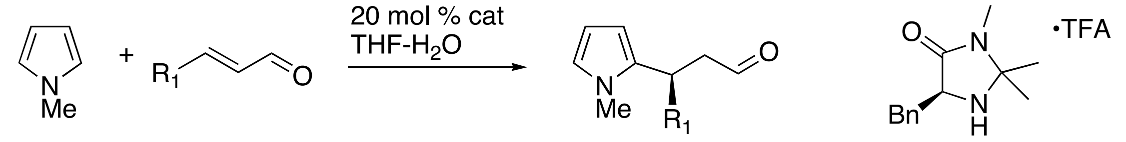
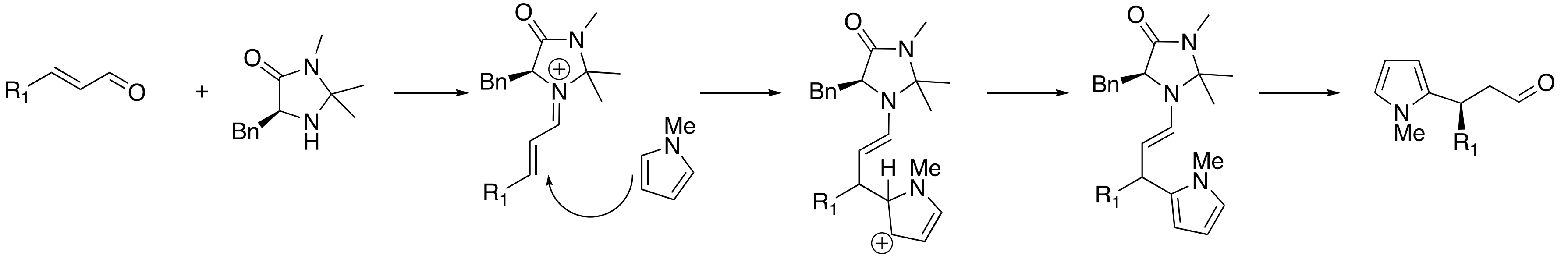
Current Literature Presention

Bryan Wakefield

Organocatalytic Friedel-Crafts Reaction

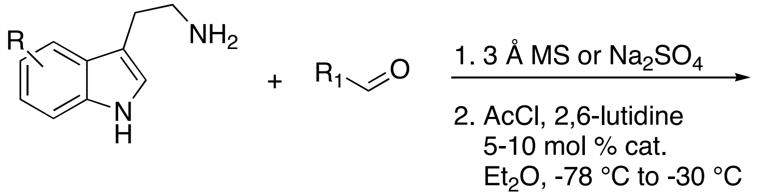


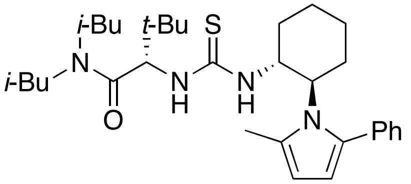
Entry	R_1	Yield (%)	*ee* (%)
1	Me	83	91
2	Pr	81	90
3	*i*-Pr	80	91
4	Ph	87	93
5	*p*-$MeOC_6H_4$	79	91
6	$BnOCH_2$	90	87
7	MeO_2C	72	90



Paras, N. A.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2001**, *123*, 4370
More examples:
Austin, J. F.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *123*, 1172
Paras, N. A.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 7894

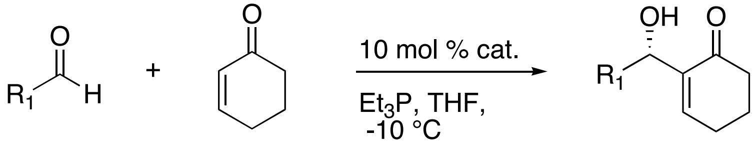
Chiral Hydrogen-Bond Donors

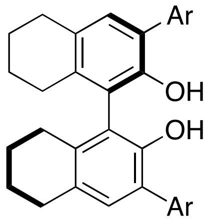




Entry	R	R_1	Yield (%)	*ee* (%)
1	H	$CH(CH_2CH_3)_2$	65	93
2	H	$CH(CH_3)_2$	67	85
3	H	*n*-C_5H_{11}	65	95
4	H	$CH_2CH(CH_3)_2$	75	93
5	H	$CH_2CH_2OTBDPS$	77	90
6	5-MeO	$CH(CH_2CH_3)_2$	81	93
7	6-MeO	$CH(CH_2CH_3)_2$	76	85

Taylor, M. S.; jacobsen, E. N. *J. Am. Chem. Soc.* **2004**, *126*, 10558





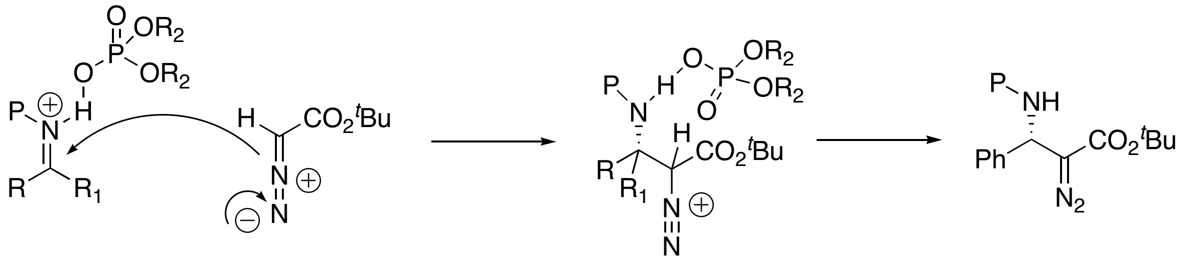
Ar= 3,5-CF_3-phenyl
or 3,5-Me-phenyl

Entry	R_1	Yield (%)	*ee* (%)
1	CH_2CH_2Ph	88	90
2	CH_2CH_2OBn	74	82
3	Cy	71	96
4	*i*-Pr	82	95
5	Ph	40	67

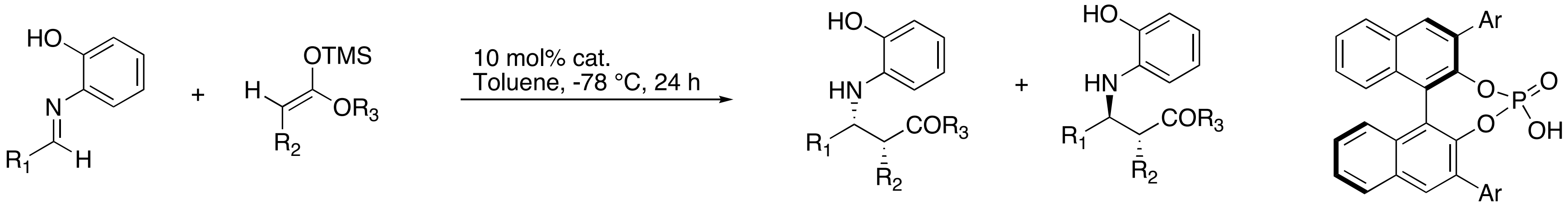
McDouglas, M. T.; Schaus, S. E. *J. Am. Chem. Soc.* **2003,** *125*, 12094

Advantages of Phosphoric Acids

-Tetradentate structure affords a conformationally stable structure
    -Can be used to eliminate rotation by constraining the phosphorus in a ring
    -Other acids such as sulfonic and carboxylic freely rotate.
-Acidity is great enough to activate imines.
    -pKa of diethyl phosphate is 1.39.
-The phosphoryl oxygen should function as a Lewis basic site.
    -This could allow phosphoric acids to act as bifunctional catalysts.



Chiral Phosphoric Acids as Organocatalysts

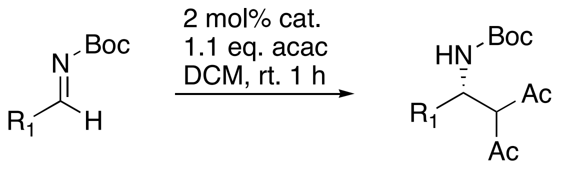


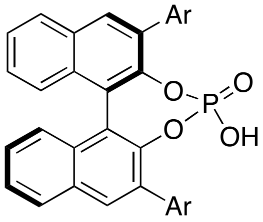
Ar= 4-$NO_2C_6H_4$

Entry	R_1	R_2	R_3	Yield (%)	*syn/anti*	*ee* (%)
1	Ph	Me	Et	100	87:13	96
2	*p*-$MeOC_6H_4$	Me	Et	100	92:8	88
3	*p*-FC_6H_4	Me	Et	100	91:9	84
4	*p*-ClC_6H_4	Me	Et	100	86:14	83
5	*p*-MeC_6H_4	Me	Et	100	94:6	81
6	2-Thienyl	Me	Et	81	94:6	88
7	PhCH=CH	Me	Et	91	95:5	90
8	Ph	Bn	Et	100	93:7	91
9	*p*-$MeOC_6H_4$	Bn	Et	92	93:7	87
10	PhCH=CH	Bn	Et	65	95:5	90
11	Ph	Ph_3SiO	Me	79	100:0	91

Akiyama, T.; Itoh, J.; Yokota, K.; fuchibe, K. *Angew. Chem. Int. Ed.* **2004,** *43,* 1566

Chiral Phosphoric Acids as Organocatalysts



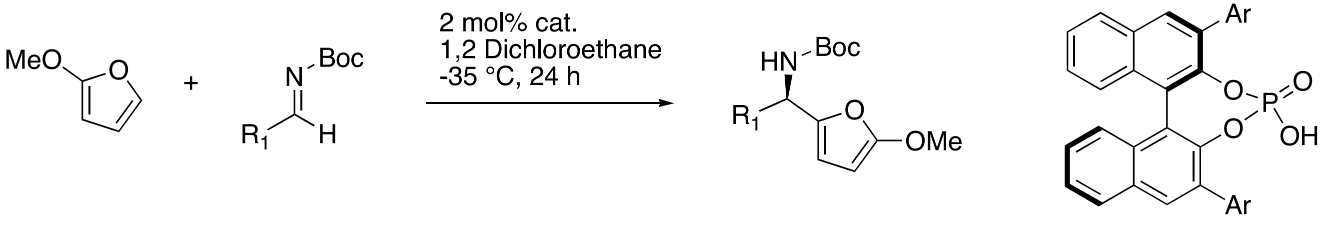


Ar= 4-(ß-Naph)-C_6H_4

Entry	R_1	Yield (%)	*ee* (%)
1	*p*-$MeOC_6H_4$	93	90
2	*p*-MeC_6H_4	98	94
3	*p*-BrC_6H_4	96	98
4	*p*-FC_6H_4	94	96
5	*o*-MeC_6H_4	94	93
6	1-Naph	99	92

Uraguchi, D.; Terada, M. *J. Am. Chem. Soc.* **2004,** *126,* 5356

Chiral Phosphoric Acids as Organocatalysts

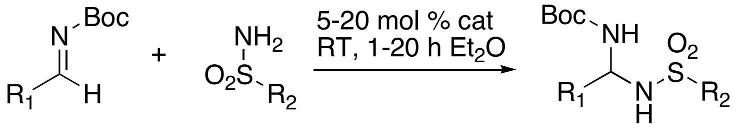


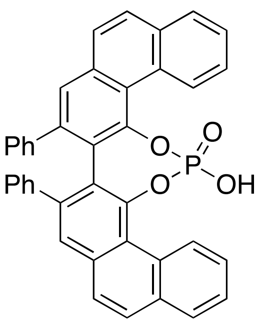
Ar= 3,5-dimesitylphenyl

Entry	R_1	Yield (%)	*ee* (%)
1	p-$MeOC_6H_4$	95	96
2	o-MeC_6H_4	84	94
3	m-MeC_6H_4	80	94
4	p-MeC_6H_4	96	97
5	o-BrC_6H_4	85	91
6	m-BrC_6H_4	89	96
7	p-BrC_6H_4	86	96
8	p-ClC_6H_4	88	97
9	p-FC_6H_4	82	97
10	1-naphthyl	84	86
11	2-naphthyl	93	96
12	2-furyl	94	86
13	Ph	95	97

Uraguchi, D.;Sorimachi, K.; Terada, M. *J. Am. Chem. Soc.* **2004,** *126,* 11804

Chiral Phosphoric Acids as Organocatalysts



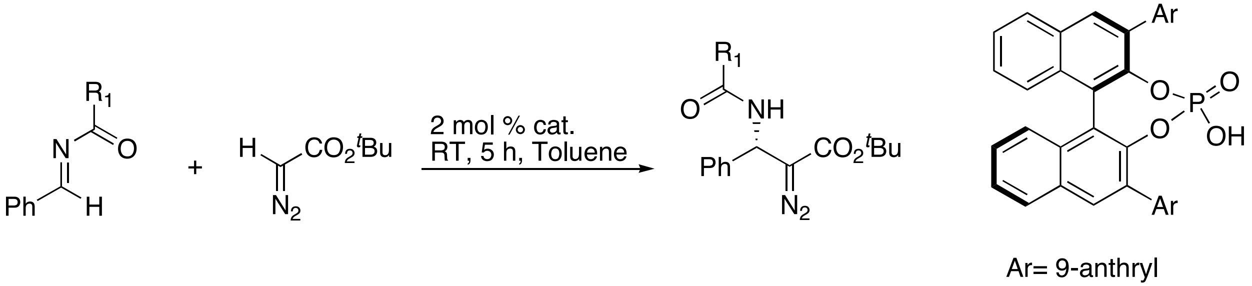


S-VAPOL derivied

Entry	R_1	R_2	Yield (%)	*ee* (%)
1	Ph	*p*-MeC_6H_4	95	94
2	Ph	Me	86	93
3	Ph	*p*-$MeOC_6H_4$	89	91
4	Ph	*o*-MeC_6H_4	80	73
5	Ph	*p*-ClC_6H_4	98	95
6	*p*-ClC_6H_4	*p*-MeC_6H_4	88	94
7	*p*-BrC_6H_4	*p*-MeC_6H_4	96	92
8	*p*-$CF_3C_6H_4$	*p*-MeC_6H_4	99	99
9	*p*-$MeOC_6H_4$	*p*-MeC_6H_4	92	90
10	2-thienyl	*p*-MeC_6H_4	94	87

Rowland, G. B.; Zhang, H.; Rowland, E. B.; Chennamadhavuni, S.; Wang, Y.; Antilla, J. C. *J. Am. Chem. Soc.* **2005**, 15696

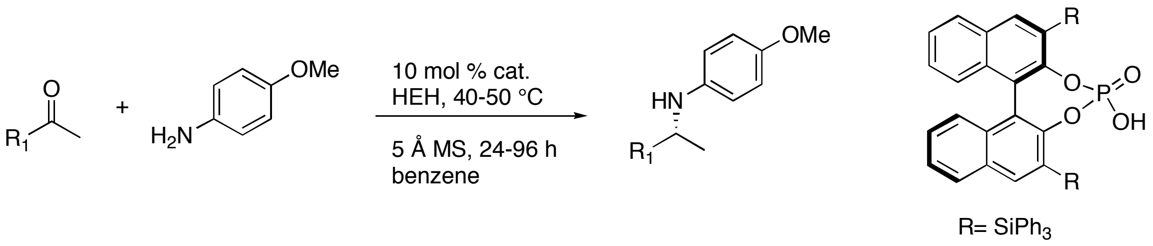
Chiral Phosphoric Acids as Organocatalysts



Entry	R_1	Yield (%)	*ee* (%)
1	Ph	59	90
2	*o*-BrC_6H_4	80	90
3	*o*-MeC_6H_4	84	90
4	*o*-$MeOC_6H_4$	77	92
5	*m*-$MeOC_6H_4$	76	91
6	1-naphthyl	82	90
7	*p*-BrC_6H_4	68	86
8	*p*-MeC_6H_4	72	91
9	*p*-$MeOC_6H_4$	73	93
10	*p*-$Me_2NC_6H_4$	81	97

Uraguchi, D.; Sorimachi, K.; Terada, M. *J. Am. Chem. Soc.* **2005**, *127*, 9360

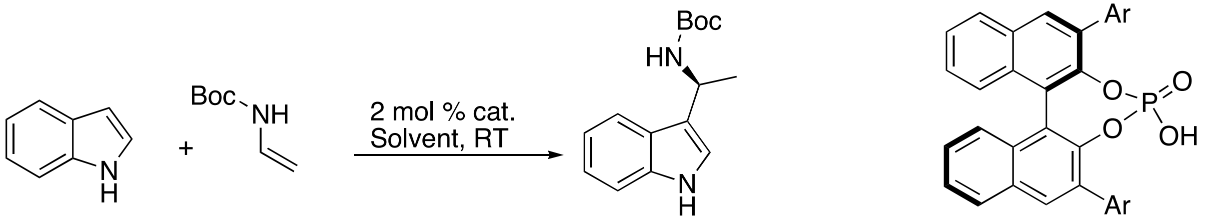
Chiral Phosphoric Acids as Organocatalysts



Entry	R_1	Yield (%)	*ee* (%)
1	Ph	87	94
2	*p*-MeC_6H_4	79	91
3	*p*-$MeOC_6H_4$	77	90
4	*p*-$NO_2C_6H_4$	71	95
5	*p*-ClC_6H_4	75	95
6	*p*-FC_6H_4	75	94
7	*m*-FC_6H_4	81	95
8	*o*-FC_6H_4	60	83
9	2-naphthyl	73	96

Storer, R. I.; Carrera, D. E.; Ni, Y.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2006**, *128*, 84

Friedel-Crafts reaction with Aliphatic Imines

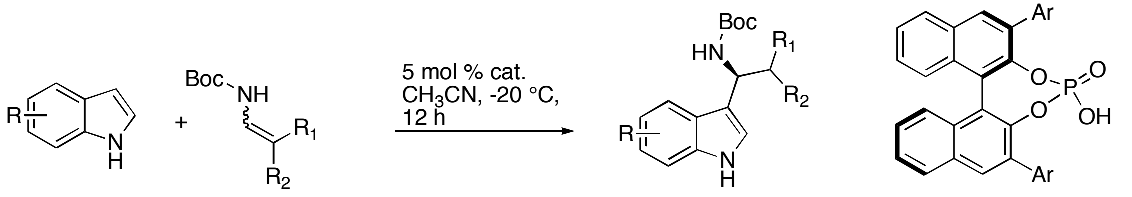


Ar= 2,4,6-Triisopropylphenyl

Entry	Solvent	Time (h)	Yield (%)	*ee* (%)
1	Toluene	3	26	80
2	$PhCF_3$	3	91	79
3	CH_2Cl_2	3	84	84
4	$(CH_2Cl)_2$	3	83	83
5	DMF	24	17	54
6	DMSO	24	22	10
7	CH_3NO_2	3	93	87
8	CH_3CN	3	84	88
9[a]	CH_3CN	6	85	91
10[b]	CH_3CN	12	95	93

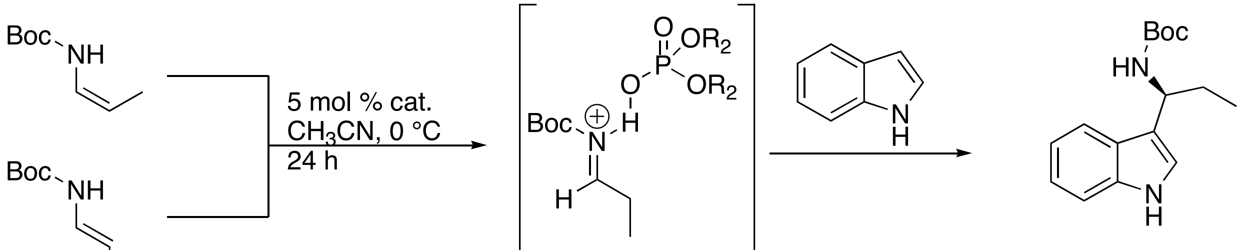
Terada, M.; Sorimachi, K. *J. Am. Chem. Soc.* **2007**, *129*, 292

Friedel-Crafts reaction with Aliphatic Imines



Ar= 2,4,6-Triisopropylphenyl

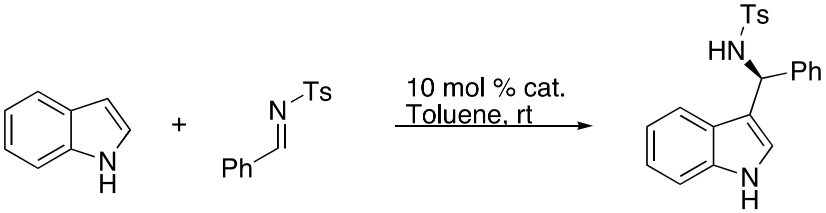
Entry	R	R_1	R_2	Enamine ratio (*E*/*Z*)	Yield (%)	*ee* (%)
1	H	H	Me	1:0	87	94
2	H	H	*n*-Bu	1:1	98	94
3	H	H	Bn	1:1	82	93
4	H	H	*i*-Pr	1:1	80	91
5	H	H	Ph	1:0	63	90
6	H	Me	Me	N/A	69	94
7	5-MeO	H	Me	1:0	90	90
8	5-Me	H	Me	1:0	84	93
9	5-Br	H	Me	1:0	91	93
10	6-Br	H	Me	1:0	78	96
11	5-CO_2Me	H	Me	1:0	86	93

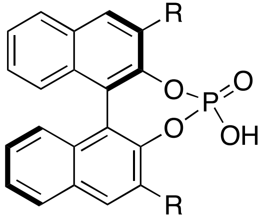


(*Z*)- 93% *ee* (93% yield)
(*E*)- 94% *ee* (69% yield)

Terada, M.; Sorimachi, K. *J. Am. Chem. Soc.* **2007**, *129*, 292

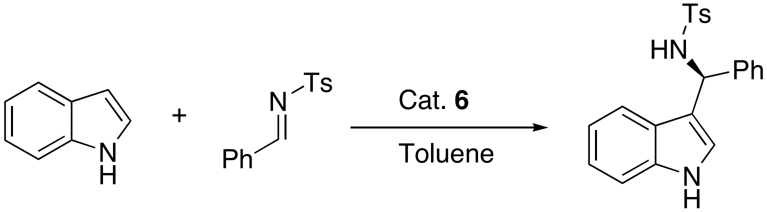
Friedel-Crafts reaction with Aromatic Imines





1- R = H
2- R = Ph
3- R = $SiPh_3$
4- R = 3,5-CF_3-Ph
5- R = 4-NO_2-Ph
6- R = 1-naphthyl

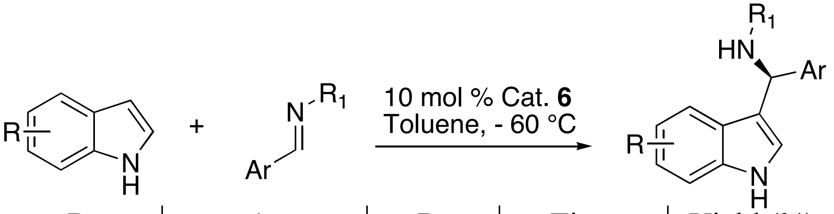
Entry	Cat.	Time	Yield (%)	*ee* (%)
1	1	4 h	85	0
2	2	14 h	60	73
3	3	4 h	69	73
4	4	30 min	80	83
5	5	10 min	66	92
6	6	10 min	78	93



Entry	Cat **6** (mol %)	Temp (° C)	Time	Yield (%)	*ee* (%)
1	10	Rt	10 min	78	93
2	10	0	10 min	80	95
3	10	-40	10 min	75	97
4	10	-60	30 min	83	98
5	10	-78	2 h	81	98
6	5	-60	1.5 h	83	96
7	2	-60	10 h	72	75

Kang, Q.; Zhao, Z.A.; You, S.L. *J. Am. Chem. Soc* **2007,** *129*, 1484.

Friedel-Crafts reaction with Aromatic Imines



Entry	R	Ar	R_1	Time	Yield (%)	*ee* (%)
1	H	C_6H_5	Ts	30 min	83	98
2	H	C_6H_5	Bs	15 min	88	99
3	5-OMe	C_6H_5	Bs	20 min	87	97
4	5-OMe	C_6H_5	Bs	15 min	84	99
5	5-Me	C_6H_5	Bs	15 min	89	99
6	5-Me	C_6H_5	Bs	15 min	83	99
7	5-Br	C_6H_5	Bs	40 min	82	98
8	5-Br	C_6H_5	Bs	40 min	89	99
9	5-Cl	C_6H_5	Bs	2 h	68	98
10	5-Cl	C_6H_5	Bs	1.5 h	87	99
11	H	*p*-MeC_6H_4	Ts	10 min	93	99
12	H	*m*-$NO_2C_6H_4$	Ts	15 min	85	89
13	H	*p*-ClC_6H_4	Ts	24 h	91	94
14	H	*p*-BrC_6H_4	Ts	24 h	71	82
15	H	*p*-$CF_3C_6H_4$	Ts	14 h	83	85
16	H	*m*-$MeOC_6H_4$	Ts	1 h	90	96
17	H	*m*-$MeOC_6H_4$	Ts	1 h	90	97
18	H	Cy	Ts	5 h	56	58
19	H	C_6H_5	Bs	40 min	94	99

Kang, Q.; Zhao, Z.A.; You, S.L. *J. Am. Chem. Soc* **2007,** *129*, 1484.

Conclusion

- Chiral phosphoric acids have been to catalyze a variety of asymmetric imine additions.
- Most recently, these acids have been used in a Friedel-Crafts reaction between both aliphatic and aromatic imines with excellent yields and *ee*.
- In the future, this chemistry could benefit from an expansion of its scope to include other aromatic rings such as aniline and pyrole derivatives.
- Also, the design of a new group of catalysts that could be used in additions to aldehydes and ketones would greatly increase the utility of chiral phosphoric acids