PROTON BASED CATALYSIS: IMINES AS ELECTROPHILES

Bronsted Acid-Catalyzed Direct Aza-Darzens Synthesis of N-Alkyl cis-Aziridines

Amie L. Williams and Jeffrey N. Johnston *J. Am. Chem. Soc.* **2004**, *126*, 1612-1613.

Enantioselective Mannich-Type Reaction Catalyzed by a Chiral Brønsted Acid

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

Chiral Proton Catalysis: A Catalytic Enantioselective Direct Aza-Henry Reaction

Benjamin M. Nugent, Ryan A. Yoder, and Jeffrey N. Johnston *J. Am. Chem. Soc*. **2004**, *126*, 3418-3419

Activation of Carbonyl Compounds by Double Hydrogen Bonding:
An Emerging Tool in Asymmetric Catalysis

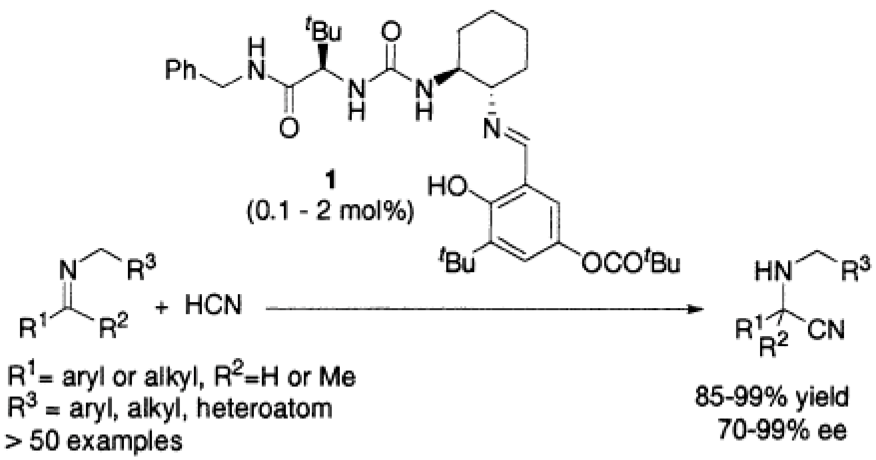
Petri N. Pihko *Angew. Chem. Int. Ed.* **2004**, *43*, 2062-2064.

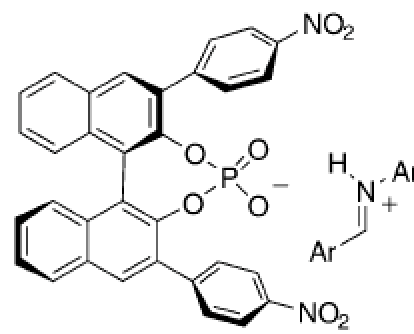
PROTON BASED CATALYSIS: IMINES AS ELECTROPHILES

Proton Assisted Catalysis

Hydrogen Bonding

Ion Pair catalysis





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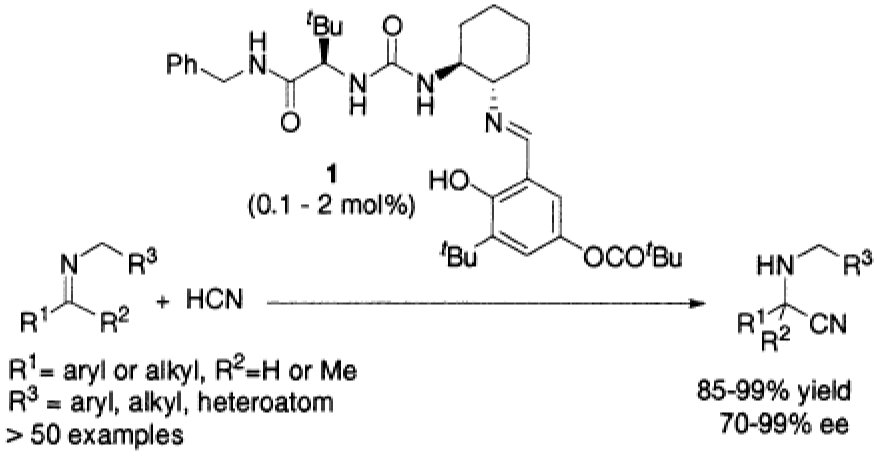
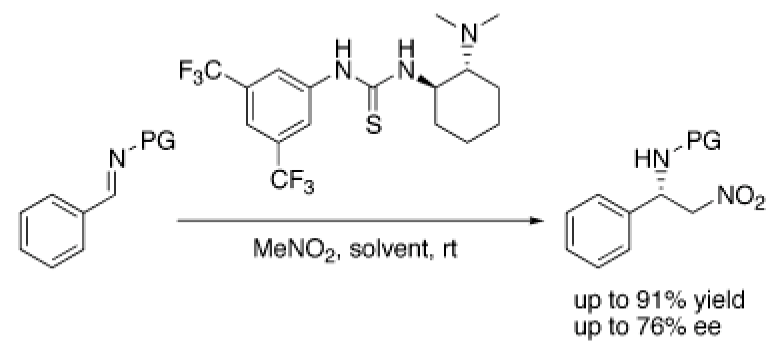
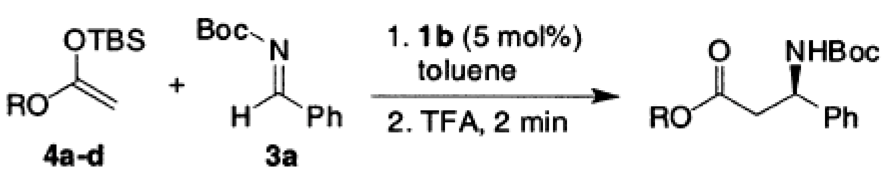
Hydrogen bonding and Bronsted Acid catalyzed asymmetric reactions of Imines



Jacobsen et. al. *JACS* **2002**, *124*, 10012

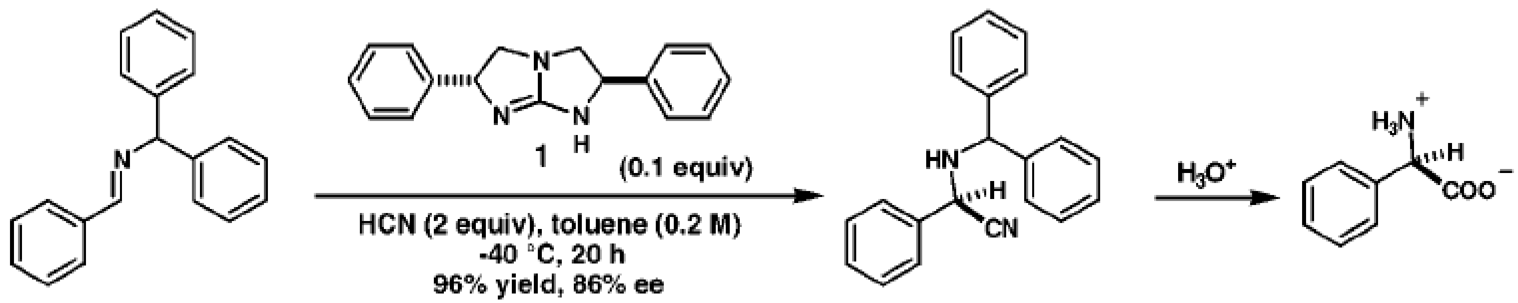


Takemoto *Org. Lett.* **2004**, *6*, 625.

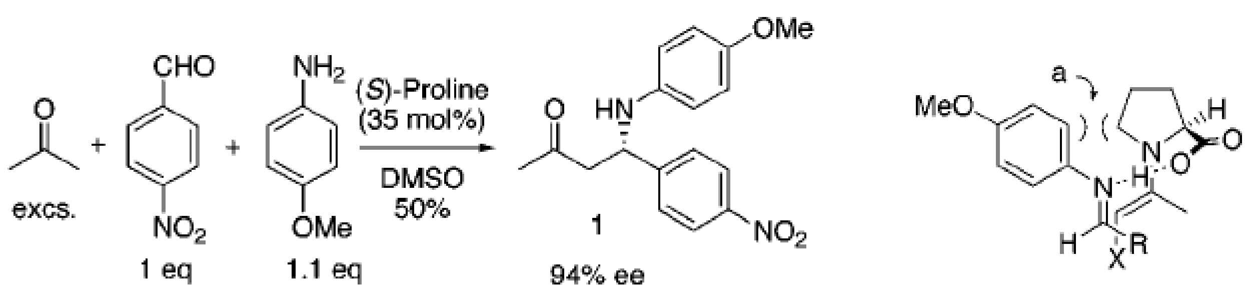


Jacobsen et. al. *JACS* **2002**, *124*, 12964.

Hydrogen bonding and Bronsted Acid catalyzed asymmetric reactions of Imines

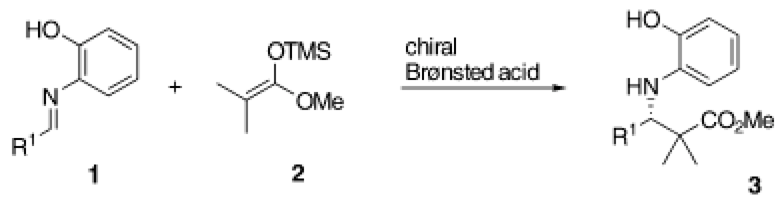


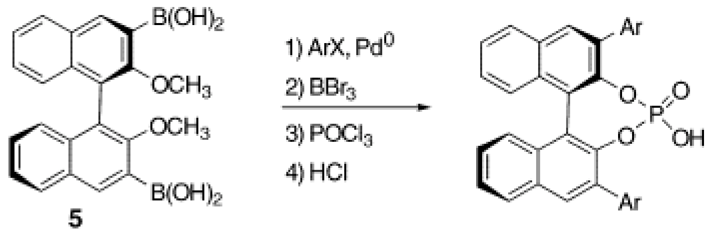
Corey et. al. Org. Lett. **1999**, *1*, 157



List et. al. *JACS* **2002**, 827.
Barbas (2002), Hayashi (2003)

Enantioselective Mannich-Type Reaction Catalyzed by a Chiral Brønsted Acid





4a: Ar=H
4b: Ar=C_6H_5
4c: Ar=2,4,6-$Me_3C_6H_2$
4d: Ar=4-$MeOC_6H_4$
4e: Ar=4-$NO_2C_6H_4$

Table 1: Effect of the aromatic substituents of **4**.[a]

Entry	Ar	*t* [h]	Yield [%]	*ee* [%]
1	H	22	57	0
2	Ph	20	100	27
3	2,4,6-$Me_3C_6H_2$	27	100	60
4	4-$MeOC_6H_4$	46	99	52
5	4-$NO_2C_6H_4$	4	96	87

[a] Aldimine **1a** (R^1 = Ph) (1.0 equiv) and **2** (3.0 equiv) were treated with Brønsted acid **4** (30 mol%) in toluene at −78 °C.

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

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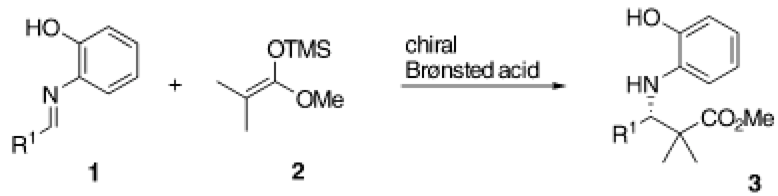

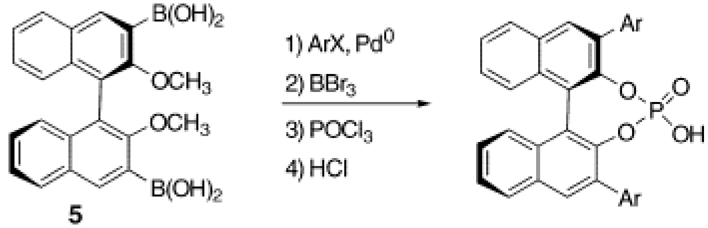

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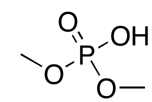


dimethylphosphoric acid

pKa 1.26

Table 2: Catalytic enantioselective Mannich-type reactions.[a]

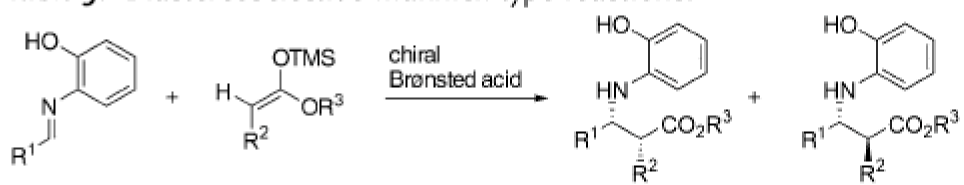
Entry	R^1	Product	Yield [%]	*ee* [%]
1	Ph	**3a**	98	89
2	*p*-MeC_6H_4	**3b**	100	89
3	*p*-FC_6H_4	**3c**	100	85
4	*p*-ClC_6H_4	**3d**	100	80

[a] Aldimine **1** (1.0 equiv) and **2** (1.5 equiv) were treated with **4e** (10 mol%) in toluene at −78°C for 24 h.

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

Enantioselective Mannich-Type Reaction Catalyzed by a Chiral Brønsted Acid

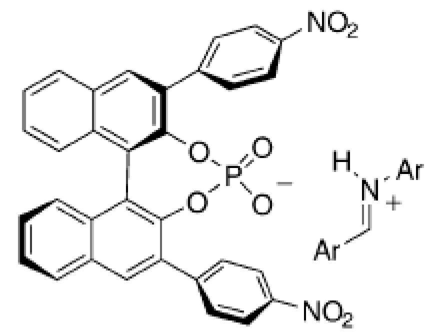
Table 3: Diastereoselective Mannich-type reactions.[a]



1 **6** **7**

Entry	R1	R2	R3	Yield [%]	*syn/anti*	*ee* [%][b]
1	Ph	Me[c]	Et	100	87:13	96
2	*p*-MeOC_6H_4	Me[c]	Et	100	92:8	88
3	*p*-FC_6H_4	Me[c]	Et	100	91:9	84
4	*p*-ClC_6H_4	Me[c]	Et	100	86:14	83
5	*p*-MeC_6H_4	Me[c]	Et	100	94:6	81
6	2-Thienyl	Me[c]	Et	81	94:6	88
7	PhCH=CH	Me[c]	Et	91	95:5	90
8	Ph	PhCH_2[d]	Et	100	93:7	91
9	*p*-MeOC_6H_4	PhCH_2[d]	Et	92	93:7	87
10	PhCH=CH	PhCH_2[d]	Et	65	95:5	90
11	Ph	Ph_3SiO[e]	Me	79	100:0	91

[a] Aldimine **1** (1.0 equiv) and ketene silyl acetal **6** (1.5 equiv) were treated with **4e** (10 mol%) in toluene at −78 °C for 24 h. [b] *ee* value of *syn* isomer. [c] *E/Z* = 87:13. [d] *E/Z* = 87:13. [e] *E/Z* = 91:9.



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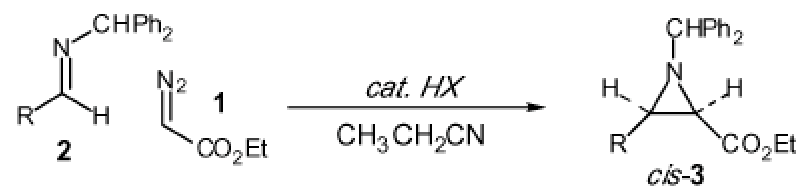
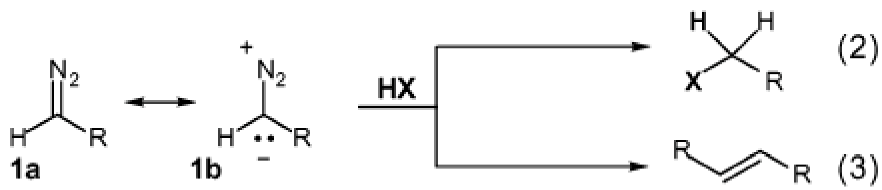
Bronsted Acid-Catalyzed Direct Aza-Darzens: Synthesis of N-Alkyl cis-Aziridines

Aza-Darzens Reaction





- Alkylation (**eq 1**) and Homocoupling (**eq 2**) decomposition pathway are slow relative to aziridine ring formation.
- Stochiometric amount of base generated during the reaction has little effect on the turnover of the reaction.

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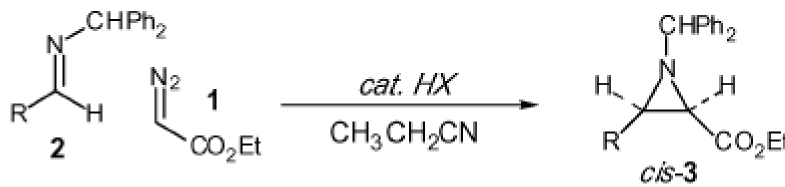
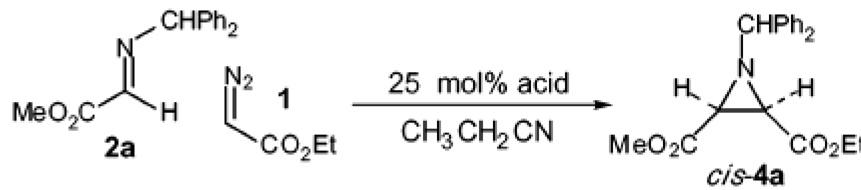
Aza-Darzens Reaction





Cis: trans 95:5

	pKa	entry	acid	T(°C)	t (h)[b]	yield (%)[c]
	-	1	none	25	24	< 5
	4.76	2	CH_3CO_2H	25	24	< 5
	0.23	3	CF_3CO_2H	25	18	63
(methane sulfonic acid)	-2.6	4	CSA	25	18	74
	-8.0	5	HCl	0	2.5	58
(trifloromethanesulfonic acid)	-14	6	TfOH	−78	5	67

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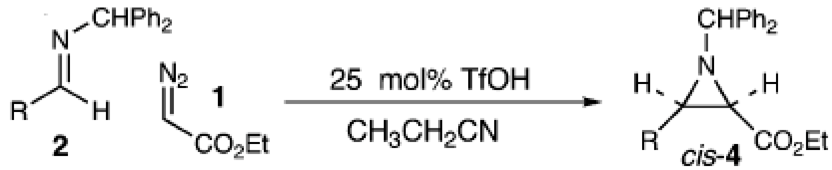
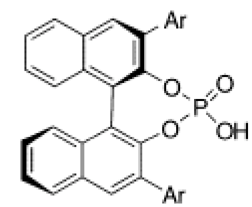
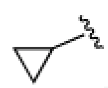
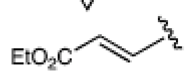
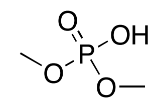




entry	R		T (°C)	*cis:trans*[d]	yield (%)[e]
1	MeO_2C	**a**	-78	>95:5	86
2	$^tBuO_2C$	**b**	-78	>95:5	89
3[b]	$^tBuO_2C$	**b**	-78	>95:5	75
4[c]	$^tBuO_2C$	**b**	25	>95:5	62
5	Cy	**c**	25	80:20	42
6	^tBu	**d**	25	60:40	45
7	Ph	**e**	0	82:18	42
8	2-py	**f**	-78	90:10	73
9		**g**	25	82:18	40
10		**h**	-78	>95:5	53

[a] All reactions were 0.3 M in substrate. [b] Five-gram scale reaction using 7 mol % TfOH; isolated yield after recrystallization from diethyl ether. [c] Solvent used: 1:1 THF:H_2O. [d] Measured by ^1H NMR (400 MHz). [e] Isolated yield after chromatography.



dimethylphosphoric acid

pKa 1.26

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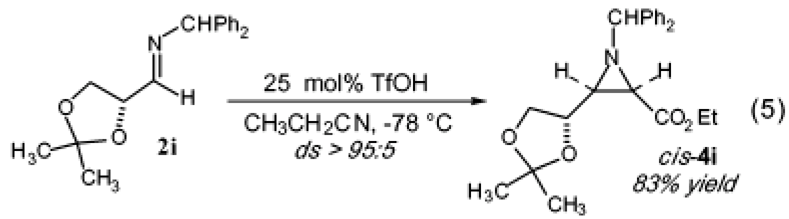
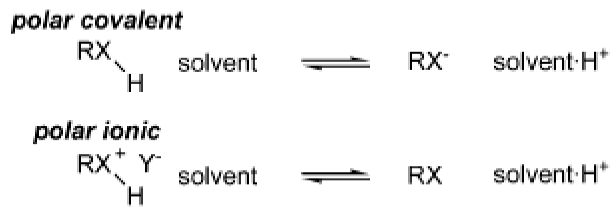
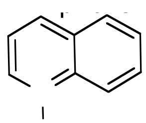
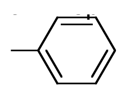


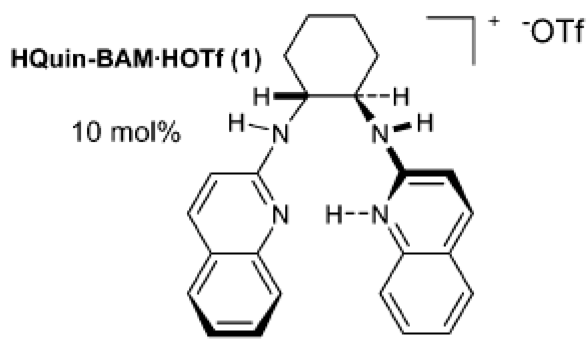
Chiral Proton Catalysis: A Catalytic Enantioselective Direct Aza-Henry Reaction

Proton (H^+) exists in two forms in nature classified by the type of hydrogen bonds as :
polar covalent and polar ionic.





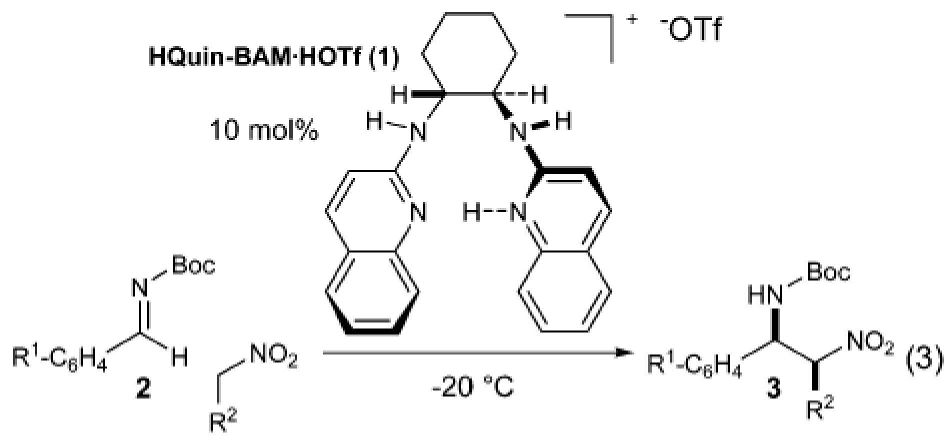




Bis-**AM**idine ligand (**Hquin-BAM**)

Steiner, T. *Angew. Chem., Int. Ed.* **2002**, *41*, 48.
Benjamin M. Nugent, Ryan A. Yoder, and Jeffrey N. Johnston *J. Am. Chem. Soc*. **2004**, *126*, 3418-3419

Chiral Proton Catalysis: A Catalytic Enantioselective Direct Aza-Henry Reaction



entry	R1	R2		% yield[c]	dr[b]	% ee[b]
1	H	H	**3a**	57	–	60
2	*p*-NO_2	H	**3b**	61	–	82
3	*m*-NO_2	H	**3c**	65	–	95
4	H	CH_3	**3d**	69	14:1	59
5	*p*-CF_3O	CH_3	**3e**	53	19:1	81
6	*p*-Cl	CH_3	**3f**	59	17:1	82
7	*m*-NO_2	CH_3	**3g**	51	11:1	89
8	*o*-NO_2	CH_3	**3h**	62	7:1	82
9	*p*-CF_3	CH_3	**3i**	50	19:1	84
10	*p*-NO_2	CH_3	**3j**	60	7:1	90