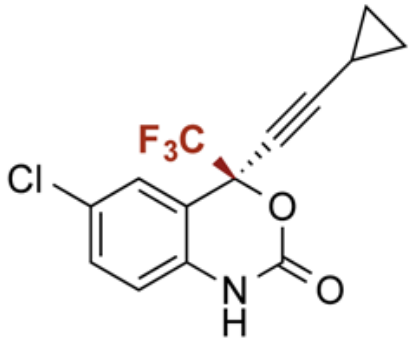
Catalytic Enantioselective Trifluoromethylation

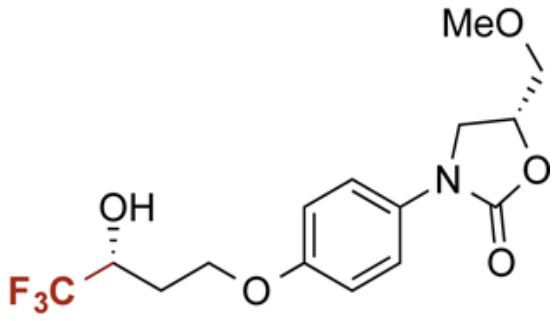
Reporter: Leming Wang

Supervisor: Prof. Yong Huang

2018.06.25



Efavirenz



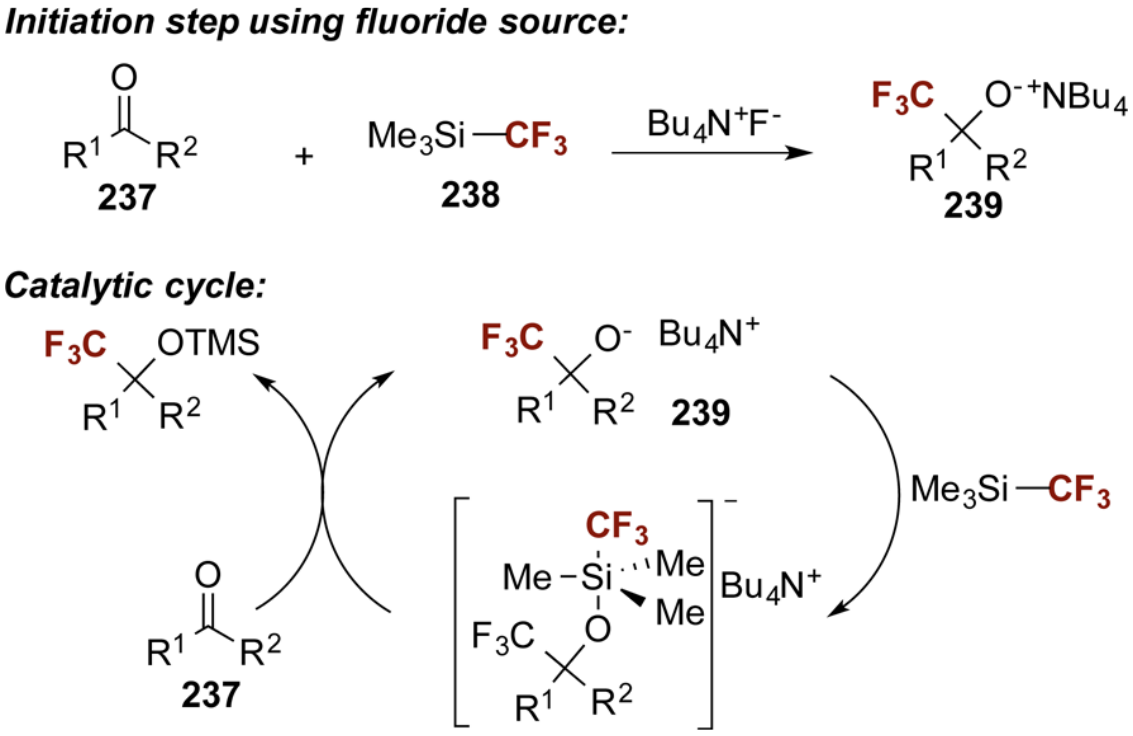
Befloxatone

(a) Wouters, J.; Moureau, F.; Evrard, G.; Koenig, J. J.; Jegham, S.; George, P.; Durant, F. Bioorg. Med. Chem. 1999, 7, 1683.
(b) Pedersen, O. S.; Pedersen, E. B. Synthesis 2000, 479.
(c) Ren, J.; Milton, J.; Weaver, K. L.; Short, S. A.; Stuart, D. I.;Stammers, D. K. Structure 2000, 8, 1089.

Outline

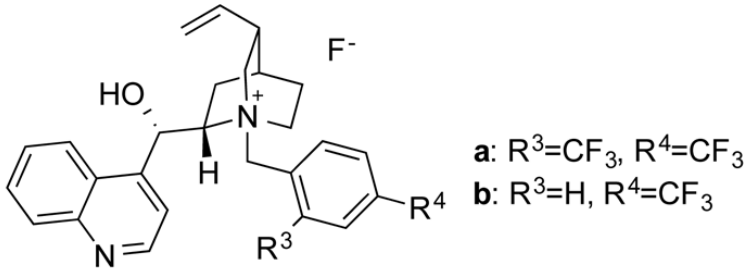
- Asymmetric Nucleophilic Trifluoromethylation
- Electrophilic Trifluoromethylation
- Radical Trifluoromethylation

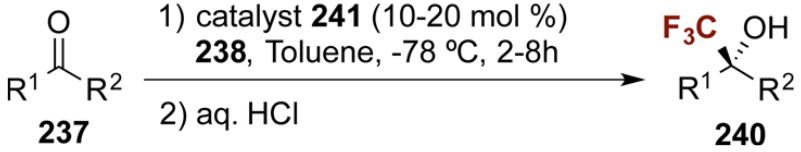
Nucleophilic Trifluoromethylation



Prakash, G. K. S.; Krishnamurti, R.; Olah, G. A. *J. Am. Chem. Soc.* **1989**, *111*, 393.

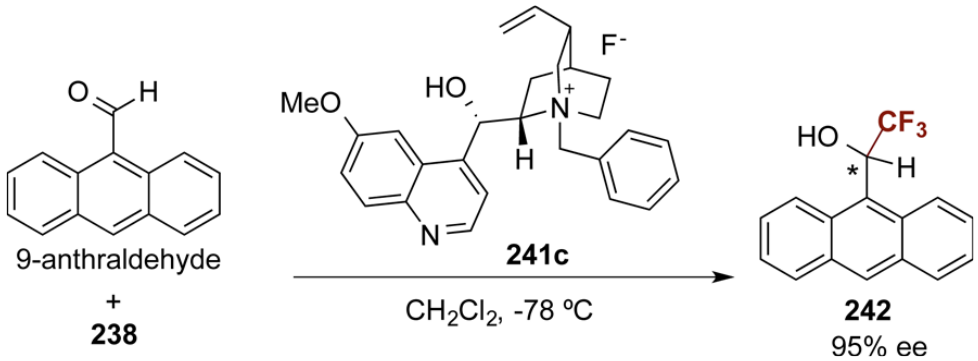
Asymmetric Trifluoromethylation of Aldehydes and Ketones Using Chiral Ammonium Fluoride Catalysts





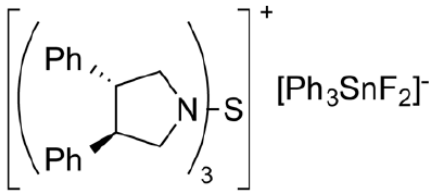
entry	R^1	R^2	cat. (mol %)	yield (%)	ee
1	Ph	H	**241a** (20)	>99	46 (*R*)
2	nC_7H_{15}	H	**241b** (20)	>99	15
3	9-anthraldehyde		**241b** (10)	98	45 (*R*)
4	Ph	Me	**241b** (20)	91	48
5	Ph	*i*Pr	**241b** (20)	87	51

Iseki, K.; Nagai, T.; Kobayashi, Y. *Tetrahedron Lett.* **1994**, *35*, 3137.

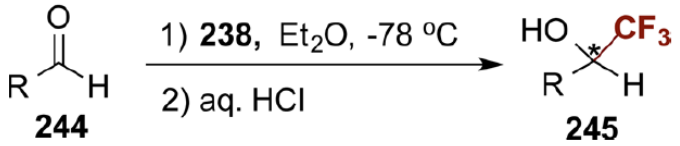


Ma, J.-A.; Cahard, D. *Chem. Rev*. **2008**, *108*, PR1.

Asymmetric Trifluoromethylation of Aldehydes Using Chiral Triaminosulfonium Catalysts



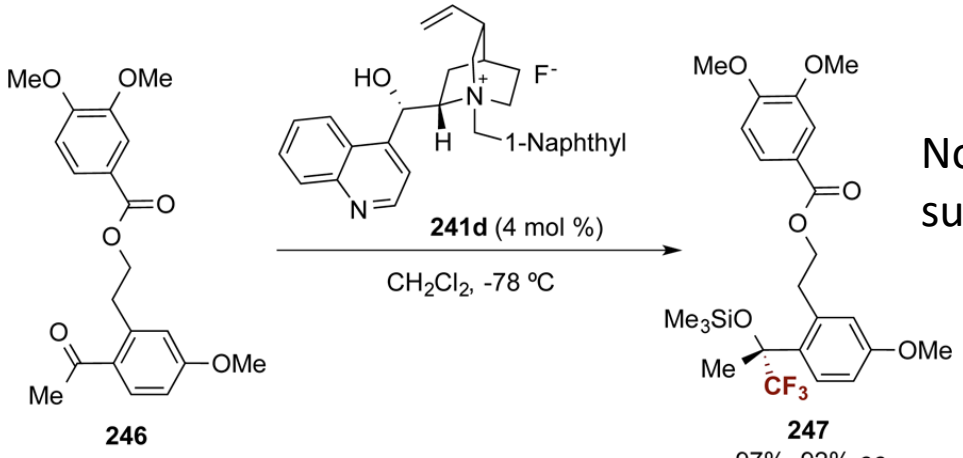
243 (10 mol %)



244 **245**

entry	RCHO	yield (%)	ee (%)
a	R = Ph	96	52 (*S*)
b	R = 4-$MeOC_6H_4$	97	37
c	R = 4-$CF_3C_6H_4$	90	24
d	R = 4-ClC_6H_4	93	30
e	R = (*E*)-PhCH=CH	99	18
f	R = C_6H_{11}	88	10

Kuroki, Y.; Iseki, K. *Tetrahedron Lett*. **1999**, *40*, 8231.



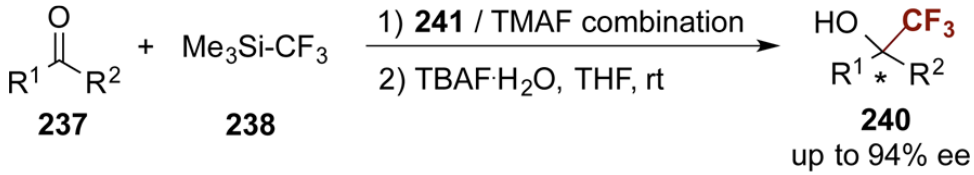
246 **247**

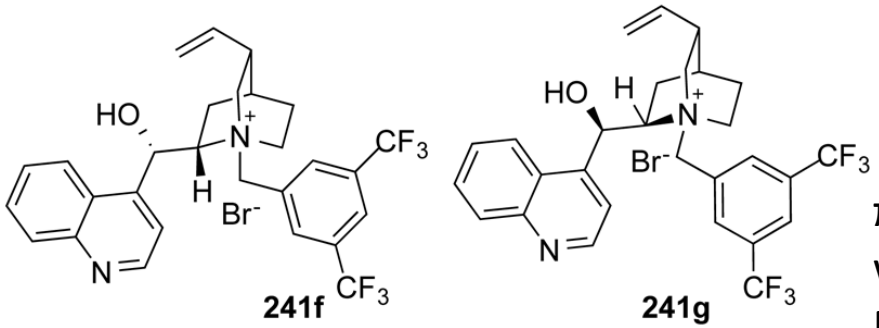
97%, 92% *ee*

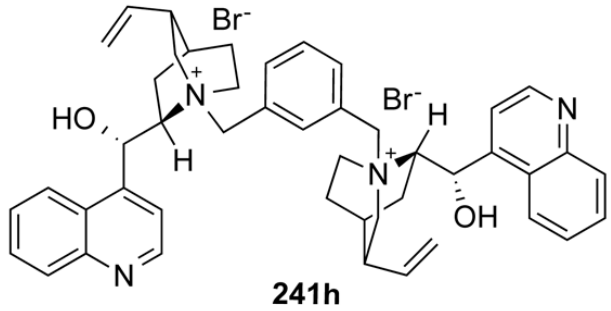
Not generally applicable; substrate dependent.

Caron, S.; Do, N. M.; Arpin, P.; Larivee, A. *Synthesis* **2003**, 1693.

Trifluoromethylation Catalyzed by Chiral Ammonium Bromides Combined with a Fluoride Source.

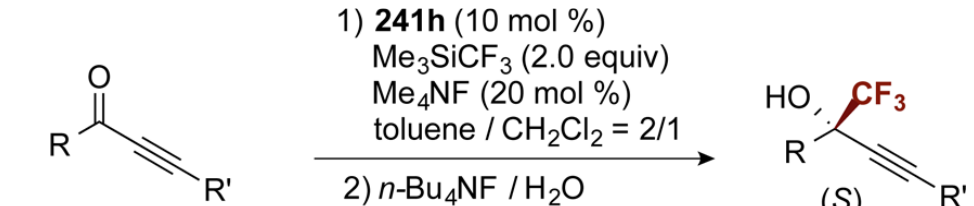






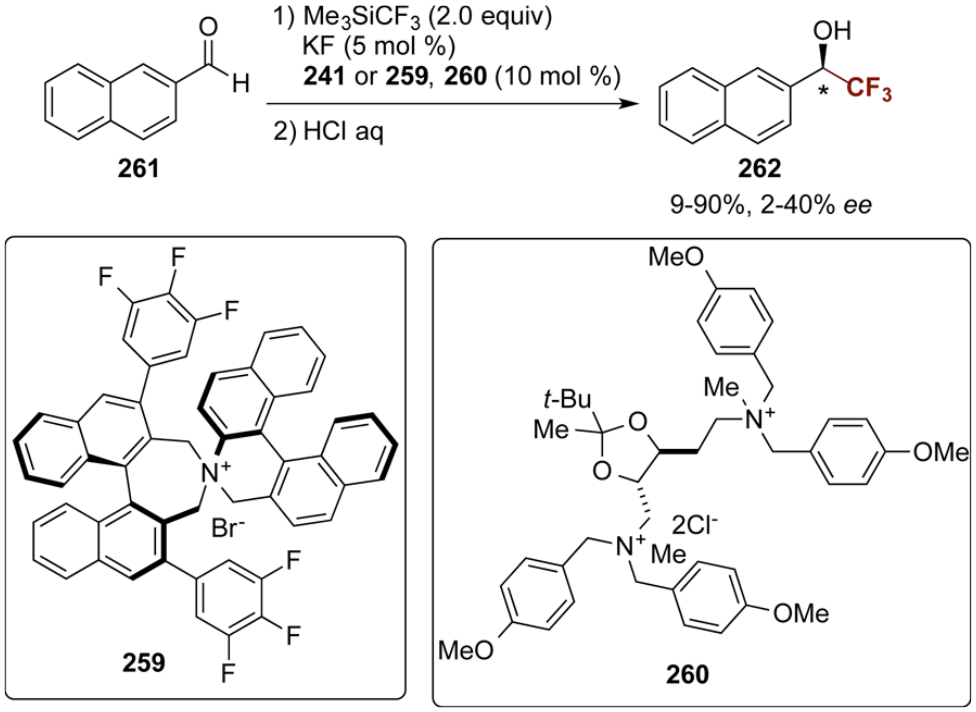
π-stacking interactions with aryl ketones;
Not for aryl aldehydes and aliphatic ketones.

Mizuta, S.; Shibata, N.; Akiti, S.; Fujimoto, H.; Nakamura, S.; Toru, T. *Org. Lett*. **2007**, *9*, 3707.



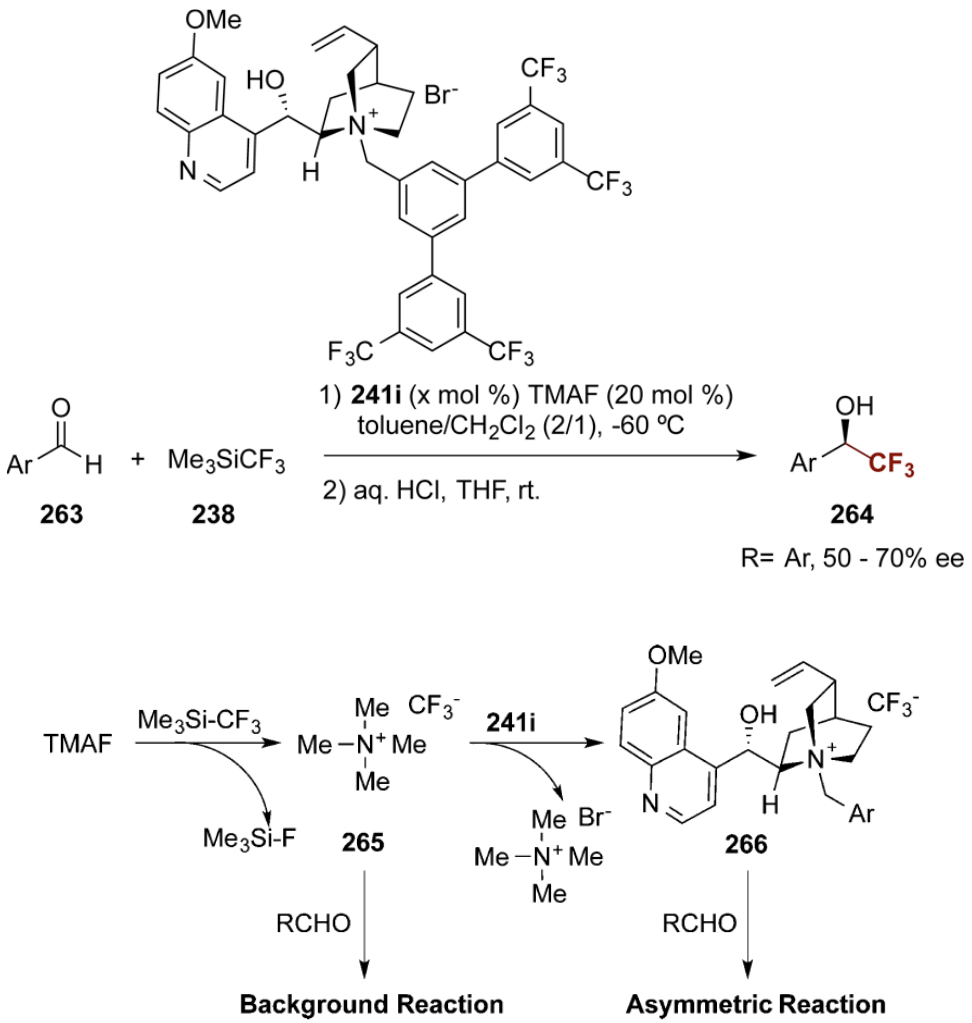
Kawai, H.; Tachi, K.; Tokunaga, E.; Shiro, M.; Shibata, N. *Org. Lett*. **2010**, *12*, 5104.

Trifluoromethylation Catalyzed by Chiral Ammonium Bromides Combined with a Fluoride Source.



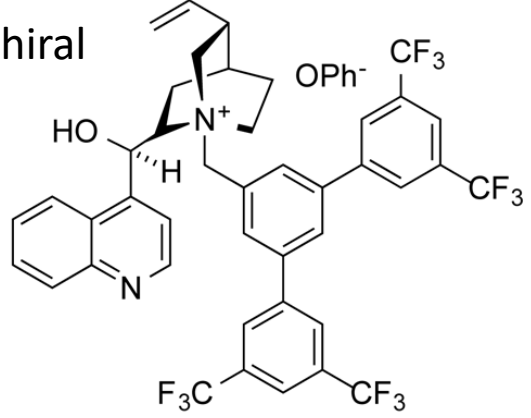
Mizuta, S.; Shibata, N.; Hibino, M.; Nagano, S.; Nakamura, S.; Toru, T. *Tetrahedron* **2007**, *63*, 8521.

Trifluoromethylation Catalyzed by Chiral Ammonium Bromides Combined with a Fluoride Source.

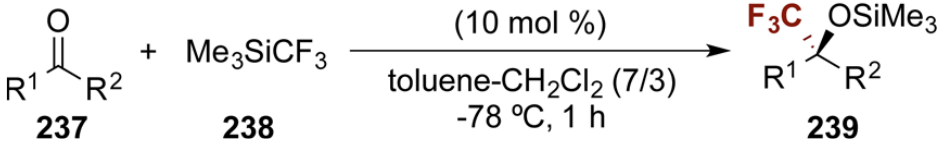


Kawai, H.; Mizuta, S.; Tokunaga, E.; Shibata, N. *J. Fluorine Chem*. **2013**, *152*, 46.

Trifluoromethylation Catalyzed by Chiral Ammonium Phenoxides



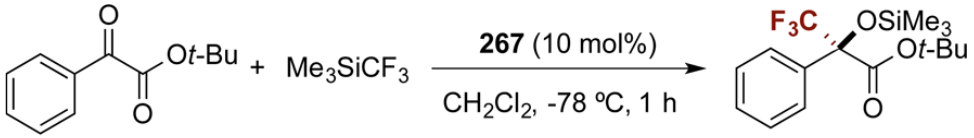
cat. **267**



237 **238** **239**

entry	R^1	R^2	yield (%)	ee (%)
1	2-$(NO_2)C_6H_4$	Me	93	71
2	4-$(NO_2)C_6H_4$	Me	97	73
3	3-$(CN)C_6H_4$	Me	96	71
4	3-BrC_6H_4	Me	97	61
5	3-$(MeO)C_6H_4$	Me	90	59
6	1-naphthyl	Me	91	51
7	2-naphthyl	Me	95	77
8	3-pyridyl	Me	90	46
9	4-pyridyl	Me	93	60
10	3-$(NO_2)C_6H_4$	Et	99	64

Nagao, H.; Yamane, Y.; Mukaiyama, T. *Chem. Lett.* **2007**, *36*, 666.

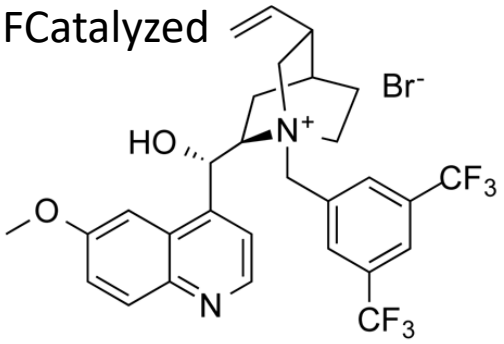


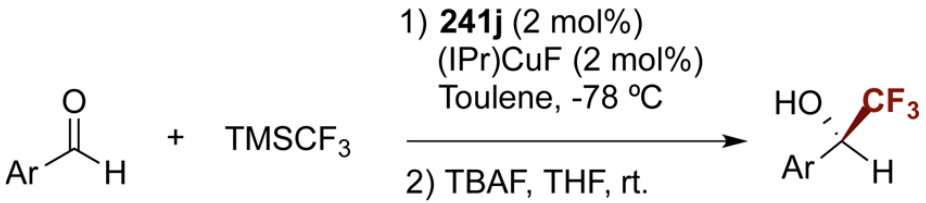
268 **269**

90%, 60% *ee*

Nagao, H.; Kawano, Y.; Mukaiyama, T. Bull. *Chem. Soc. Jpn.* **2007**, *80*, 2406

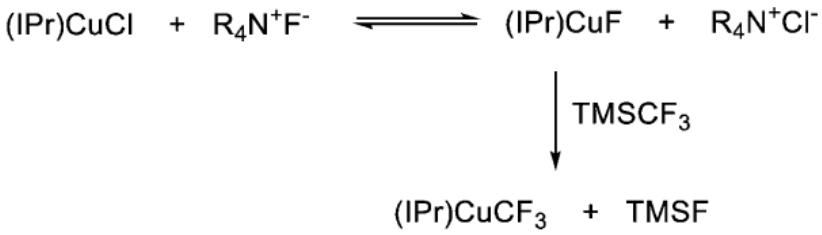
Chiral Ammonium Bromide and (IPr)CuFCatalyzed Trifluoromethylation





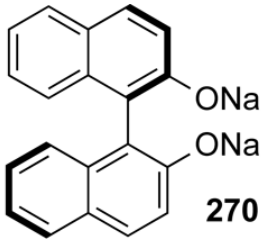
263 **238** **264**

Ar	yield (ee)
2-naphthyl	90%, 75%
1-naphthyl	88%, 60%
Ph	80%, 60%
4-BrC_6H_4	81%, 57%
3-BrC_6H_4	82%, 51%
4-MeC_6H_4	88%, 68%
4-PhC_6H_4	90%, 66%
3-$MeOC_6H_4$	89%, 74%
3,4-$O(CH_2)C_6H_3$	92%, 81%
3,4-$O(CH_2)_2C_6H_3$	92%, 79%
4-$EtSC_6H_4$	85%, 74%

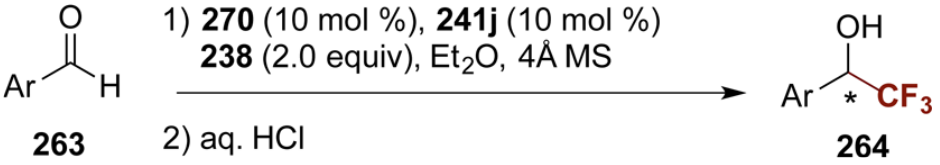


Wu, S. X.; Zeng, W.; Wang, Q.; Chen, F. X. *Org. Biomol. Chem*. **2012**, *10*, 9334.

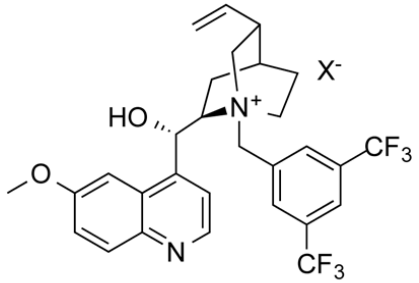
Trifluoromethylation Catalyzed by Chiral Ammonium Bromide and Sodium Phenoxide.



270

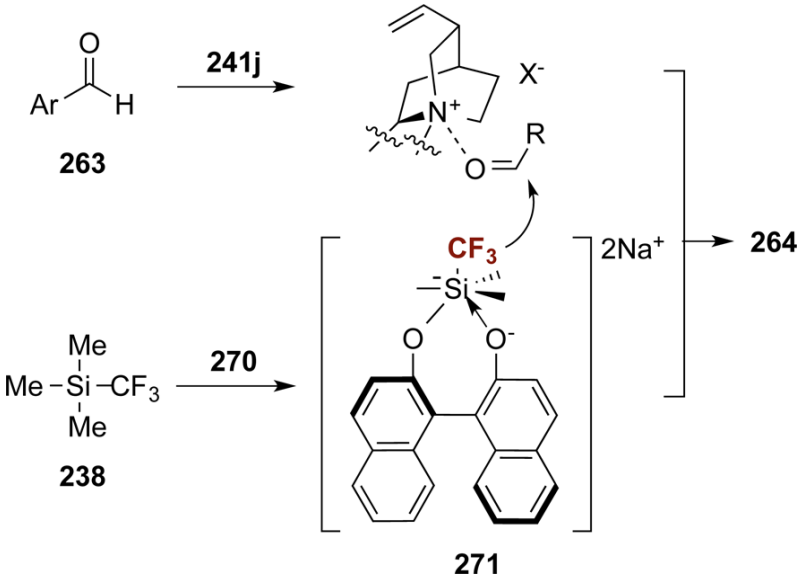


263 **264**



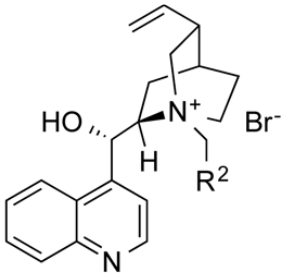
X = F, **241c**
= Br, **241j**

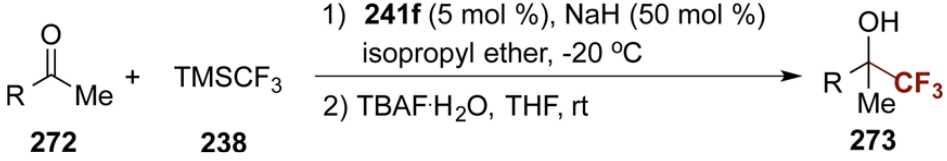
entry	aldehyde	yield (%)	ee (%)
1	2-naphthaldehyde	85	71
2	benzaldehyde	72	56
3	4-methylbenzaldehyde	87	60
4	3-methylbenzaldehyde	88	58
5	4-chlorobenzaldehyde	72	50
6	3-chlorobenzaldehyde	95	56
7	4-phenylbenzaldehyde	73	56
8	4-methoxybenzaldehyde	87	41
9	piperonal	95	46
10	4-fluorobenzaldehyde	86	57
11	3-thiophenecarboxaldehyde	68	45



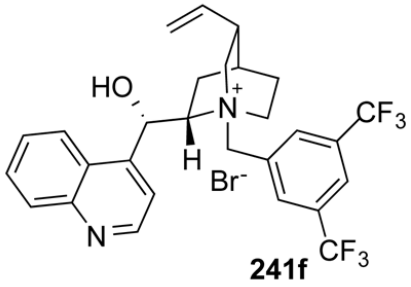
Zhao, H. T.; Qin, B.; Liu, X. H.; Feng, X. M. *Tetrahedron* **2007**, *63*, 6822.

Asymmetric Trifluoromethylation Using Chiral Quaternary Ammonium Salt 241f with NaH



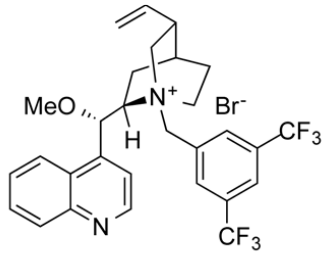


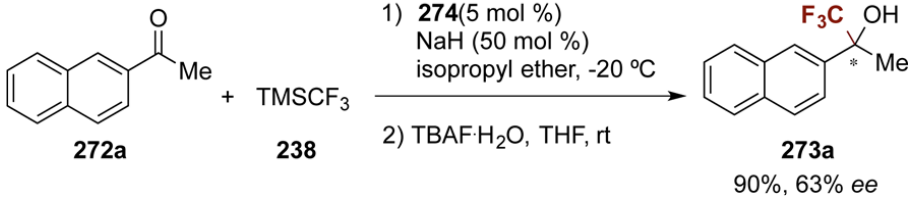
272 238 273



241f

entry	R	time (h)	yield (%)	ee (%)
1	2-naphthyl	6	96	81 (*R*)
2	1-naphthyl	6	98	82
3	2-FC_6H_4	19	47	68
4	3-ClC_6H_4	19	96	68
5	4-ClC_6H_4	19	83	61
6	4-BrC_6H_4	48	43	60
7	3-$NO_2C_6H_4$	48	30	68 (*R*)
8	4-$NO_2C_6H_4$	24	64	50
9	3-$MeOC_6H_4$	96	38	58
10	4-MeC_6H_4	3	70	67
11	(*E*)PhCH=CH	22	31	59



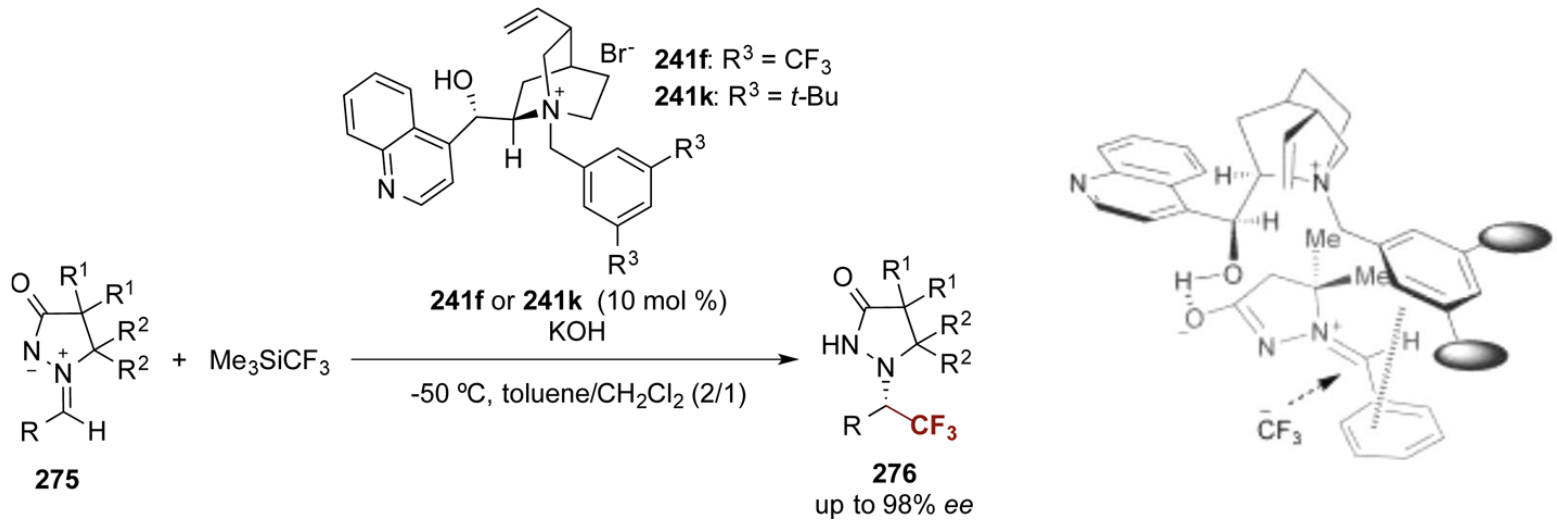


272a 238 273a

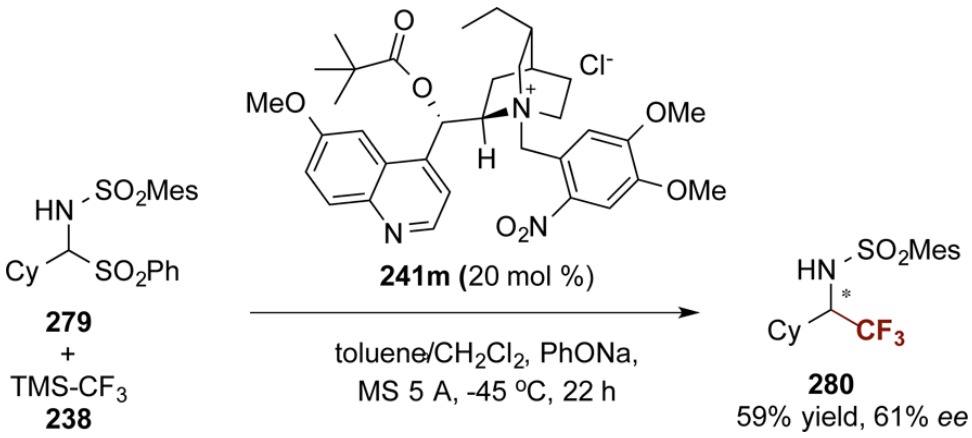
90%, 63% *ee*

Hu, X. L.; Wang, J.; Li, W.; Lin, L. L.; Liu, X. H.; Feng, X. M. *Tetrahedron Lett*. **2009**, *50*, 4378.

Asymmetric Trifluoromethylation Using Phase-Transfer Catalysis.

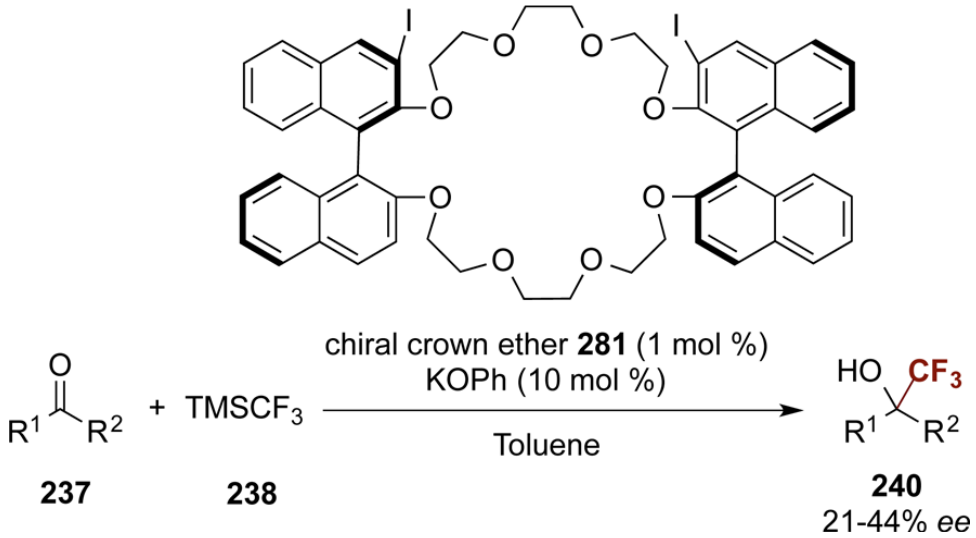


Kawai, H.; Kusuda, A.; Nakamura, S.; Shiro, M.; Shibata, N. *Angew. Chem., Int. Ed.* **2009**, *48*, 6324.

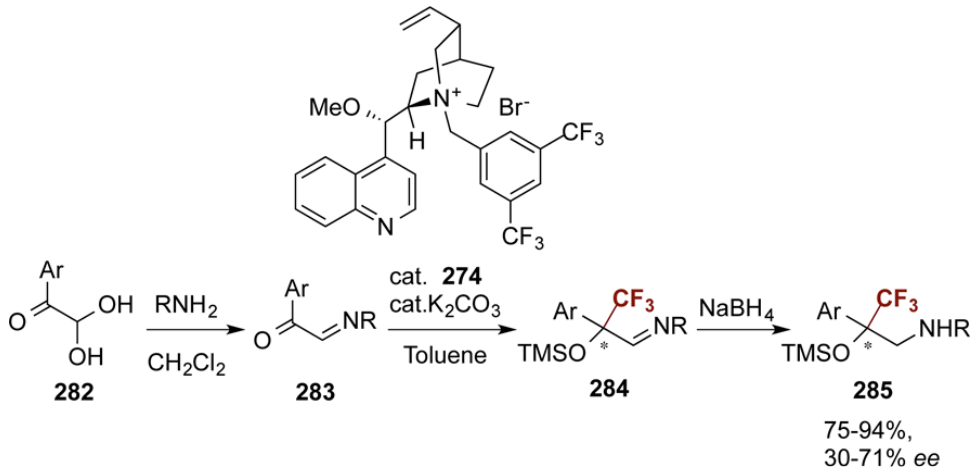


Bernardi, L.; Indrigo, E.; Pollicino, S.; Ricci, A. *Chem. Commun.* **2012**, *48*, 1428.

Asymmetric Trifluoromethylation Using Phase-Transfer Catalysis.

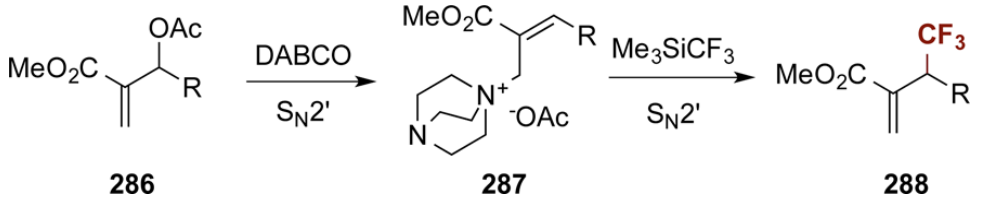


Kawai, H.; Kusuda, A.; Mizuta, S.; Nakamura, S.; Funahashi, Y.; Masuda, H.; Shibata, N. *J. Fluorine Chem.* **2009**, *130*, 762.

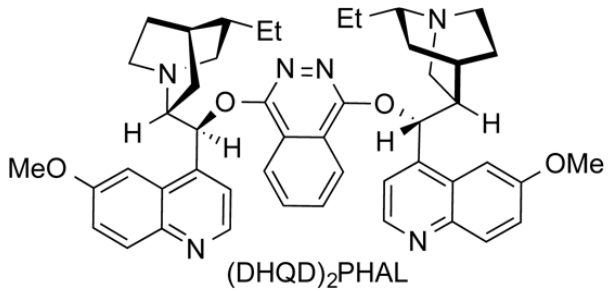


Obijalska, E.; Mlostoń, G.; Six, A. *Tetrahedron Lett*. **2013,** *54*, 2462.

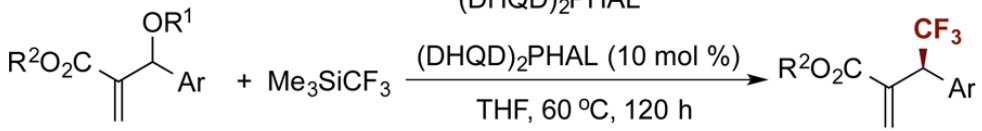
Allylic Trifluoromethylation of Morita−Baylis−Hillman Adducts



286 **287** **288**



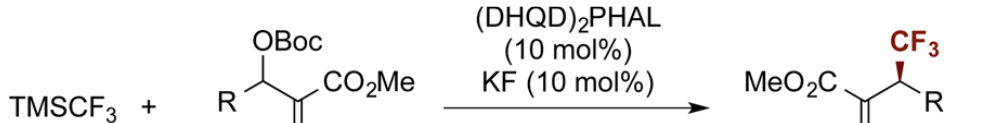
$(DHQD)_2PHAL$



289 **290**

entry	R^1	R^2	Ar	yield (%)	ee (%)
a	Ac	*t*Bu	C_6H_5	trace	nd
b	Boc	*t*Bu	C_6H_5	39	92
c	Boc	*t*Bu	2-BrC_6H_4	37	88
d	Boc	*t*Bu	4-BrC_6H_4	60	90
e	Boc	Me	C_6H_5	52	94

Furukawa, T.; Nishimine, T.; Tokunaga, E.; Hasegawa, K.; Shiro, M.; Shibata, N. *Org. Lett*. **2011**, *13*, 3972.

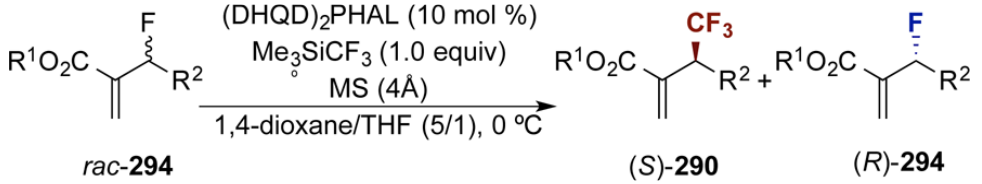


238 **292** **293**

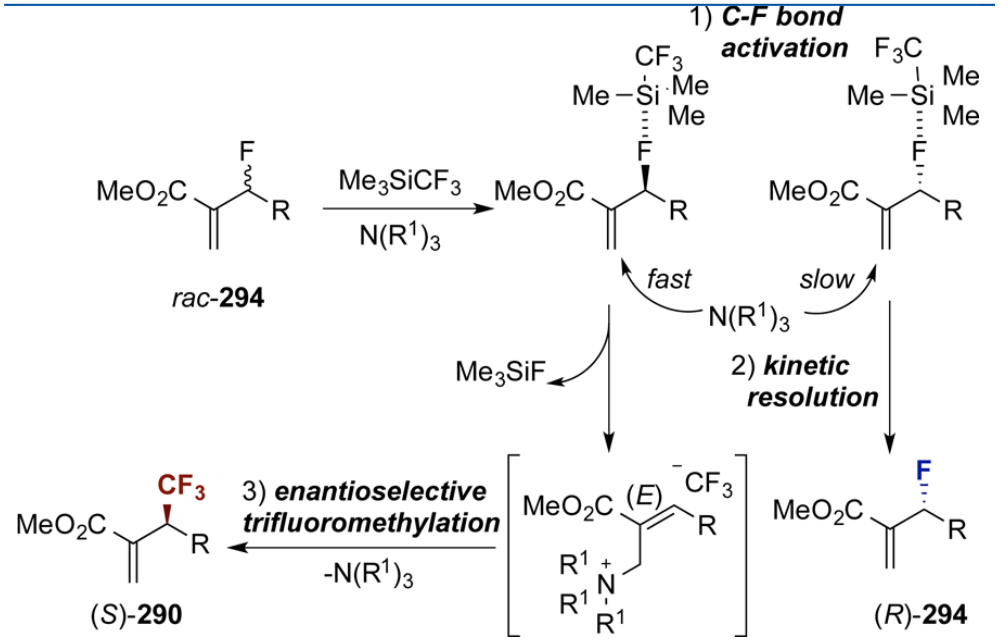
ee up to 95%
yield up to 86%

Li, Y.; Liang, F.; Li, Q.; Xu, Y. C.; Wang, Q. R.; Jiang, L. *Org. Lett.* **2011**, *13*, 6082.

Kinetic Resolution of Racemic Allyl Fluorides by Enantioselective C–F Bond Cleavage/Allylic Trifluoromethylation



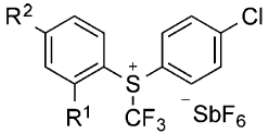
entry	R^1	R^2	conv. (%)	(*S*)-**290** ee (yield) (%)	recovered **294** ee (yield) (%)
1	Me	Ph	54	95 (51)	97 (41)
2	Me	4-MeC_6H_4	53	95 (48)	96 (40)
3	Me	3-$MeOC_6H_4$	55	94 (50)	97 (40)
4	*t*Bu	Ph	50	94 (48)	93 (42)



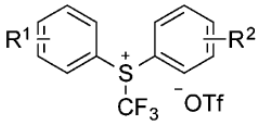
Nishimine, T.; Fukushi, K.; Shibata, N.; Taira, H.; Tokunaga, E.; Yamano, A.; Shiro, M.; Shibata, N. Angew. Chem., Int. Ed. 2014, 53, 517.

Electrophilic Trifluoromethylation

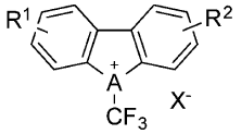
Scheme 112



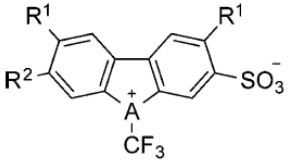
300



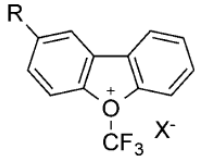
301



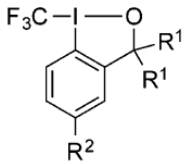
302 A = S, Se, Te
X = BF_4, OTf
302a, A=S, R^1=R^2= H, X= BF_4



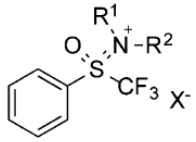
303
A = S, Se, Te
R^1 = H, Me
R^2 = H, NO_2



304
R = H, F, *t*-Bu
X = BF_4, PF_6, SbF_6, Sb_2F_{11}



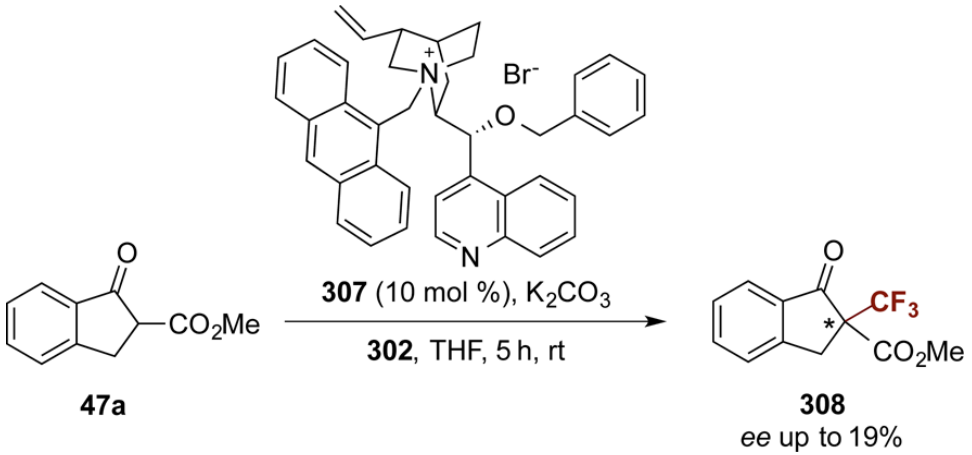
305
a, R^1 = Me, R^2 = H
b, R^1 = O, R^2 = H
c, R^1 = CF_3, R^2 = H
d, R^1 = CF_3, R^2 =Me



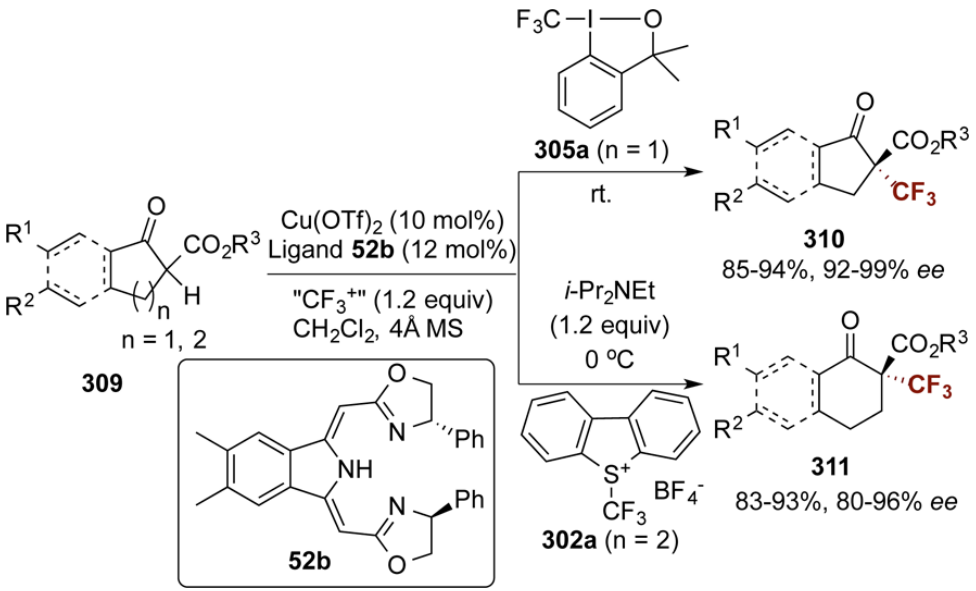
306
R^1 = Me, Et, *n*-Pr, *i*-Pr, Bn
R^2 = Me
X = OTf, BF_4

(a) Umemoto, T.; Ishihara, S. *Tetrahedron Lett*. **1990**, *31*, 3579. (b) Umemoto, T.; Ishihara, S. *J. Am. Chem. Soc.* **1993**, *115*, 2156. (c) Umemoto, T. *Chem. Rev*. **1996**, *96*, 1757. (d) Yang, J. J.; Kirchmeier, R. L.; Shreeve, J. M. *J. Org. Chem*. **1998**, *63*, 2656. (e) Eisenberger, P.; Gischig, S.; Togni, A. *Chem. Eur. J*. **2006**, *12*, 2579. (f) Kieltsch, I.; Eisenberger, P.; Togni, A. *Angew. Chem., Int. Ed*. **2007**, *46*, 754. (g) Umemoto, T.; Adachi, K.; Ishihara, S. *J. Org. Chem*. **2007**, *72*, 6905.

Electrophilic Trifluoromethylation

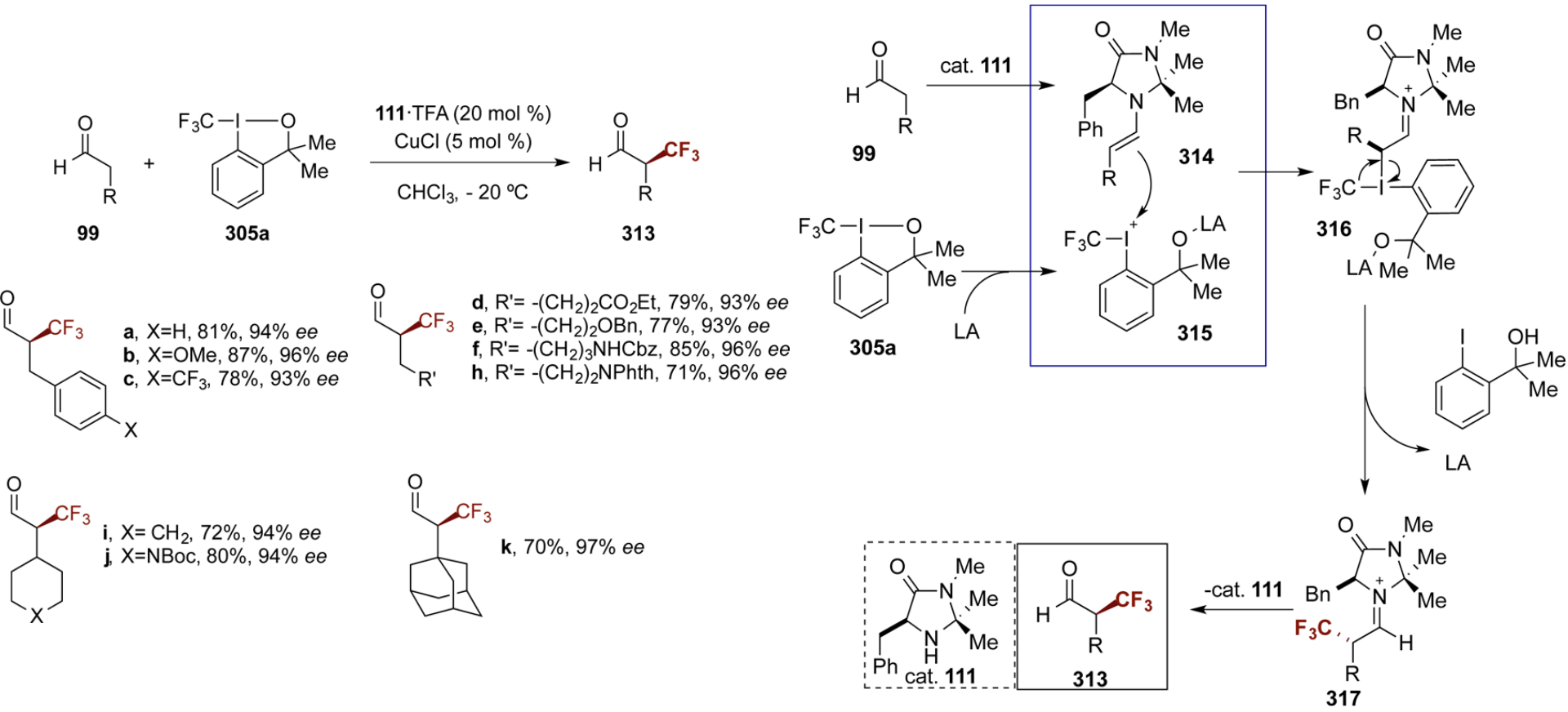


Ma, J.-A.; Cahard, D. *J. Fluorine Chem*. **2007**, *128*, 975.



Deng, Q.-H.; Wadepohl, H.; Gade, L. H. *J. Am. Chem. Soc*. **2012**, *134,* 10769.

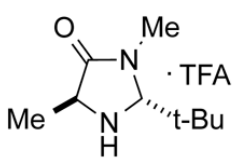
Electrophilic Trifluoromethylation



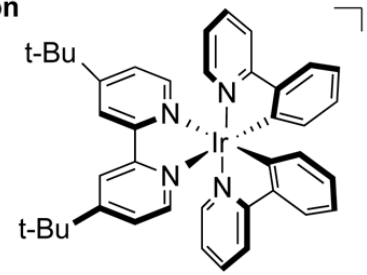
Allen, A. E.; MacMillan, D. W. C. *J. Am. Chem. Soc*. **2010**, *132*, 4986.

Radical Trifluoromethylation

Catalyst Combination



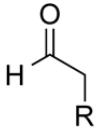
Organocatalyst. **328**



photocatalyst **321**
(0.5 mol %)

Photon Source

26 W fluoresent
light bulb

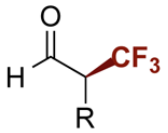


99

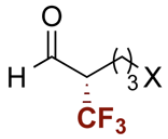
CF_3I

26 W
household light

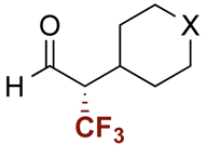
321·PF_6 (0.5 mol %)
328·TFA (20 mol %)
2,6-lutidine, DMF
- 20 °C



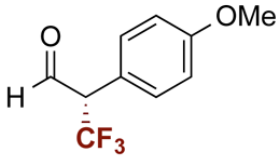
313



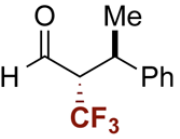
X = *n*-C_3H_7, 79%, 99% *ee*
OBn, 72%, 95% *ee*
CO_2Et, 86%, 97% *ee*
NPhth, 78%, 98% *ee*



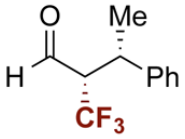
X = CH_2,
70%, 99% *ee*
=NBoc,
70%, 98% *ee*



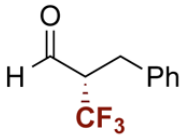
61%, 93% *ee*



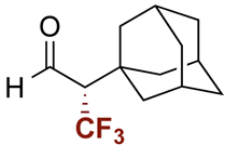
68%, > 20:1 dr
99%, *ee*



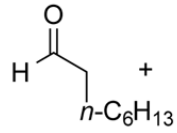
62%, > 20:1 dr
99%, *ee*



75%, 97% *ee*



73%, 90% *ee*

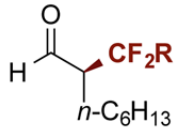


329

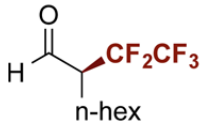
+ $R-CF_2I$

330

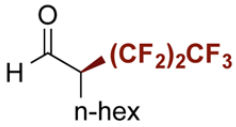
321·PF_6 (0.5 mol%)
328·TFA (20 mol%)
2,6-lutidine, DMF
Household Light
- 20 °C



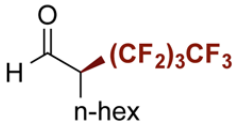
331



73%, 96% *ee*

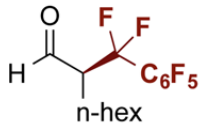


69%, 99% *ee*

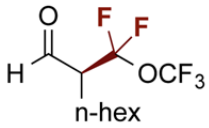


67%, 96% *ee*

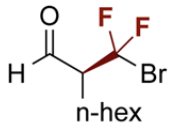
72%, 98% *ee*



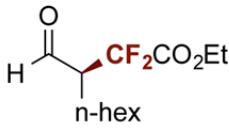
85%, 98% *ee*



71%, 99% *ee*



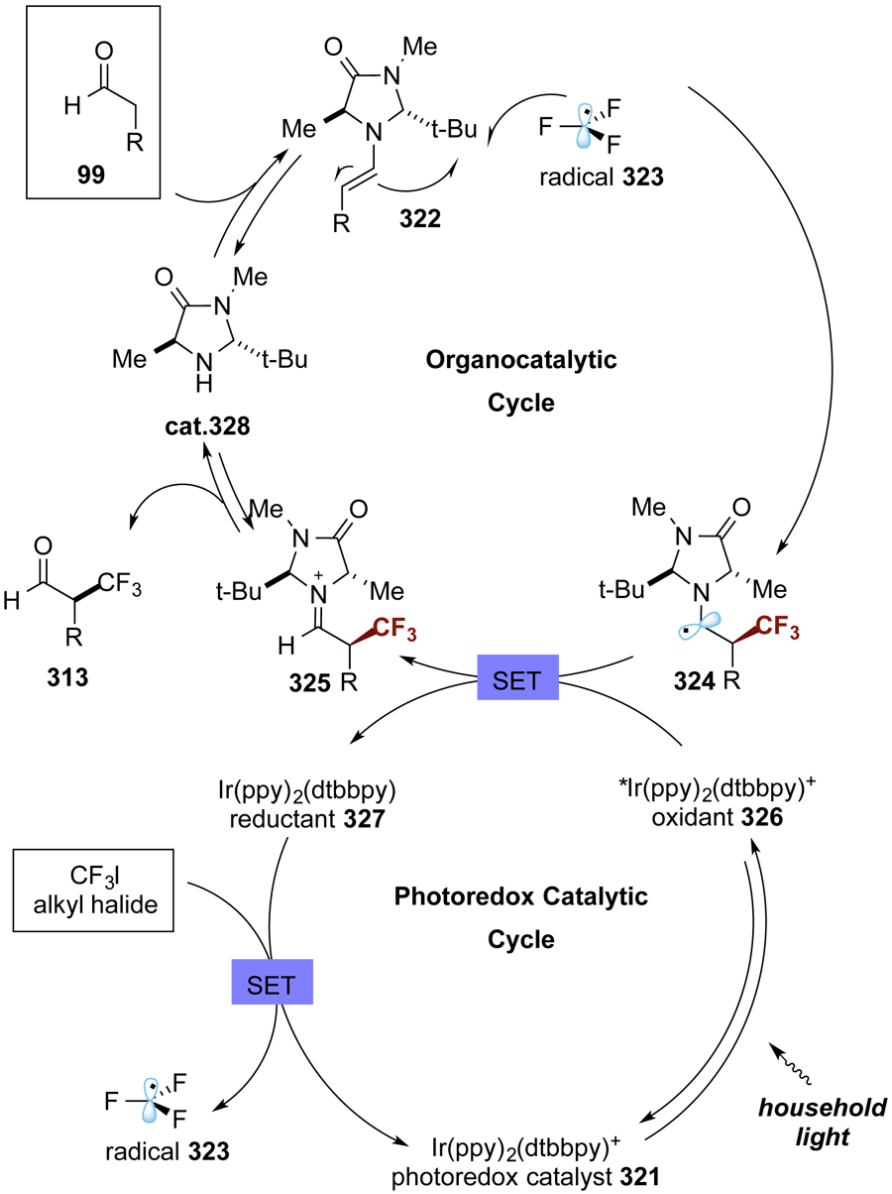
68%, 99% *ee*



89%, 99% *ee*

Nagib, D. A.; Scott, M. E.; MacMillan, D. W. C. *J. Am. Chem. Soc*. **2009**, *131*, 10875.

Radical Trifluoromethylation



Nagib, D. A.; Scott, M. E.; MacMillan, D. W. C. *J. Am. Chem. Soc*. **2009**, *131*, 10875.

Thank you for your attention