Halogen-Halogen Interaction

2024.11.22. Literature Seminar

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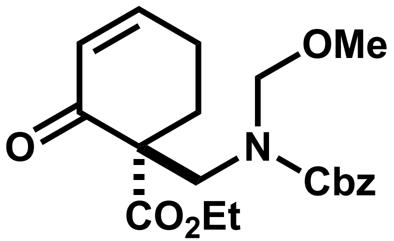
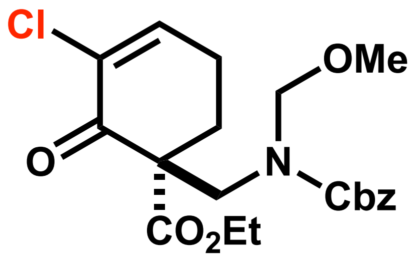
1. **Introduction (Halogen-Halogen Interaction)**

2. **Activation of a Metal-Halogen Bond by Halogen Bonding (Main paper)**

Dose Halogen-Halogen Interaction Exist?

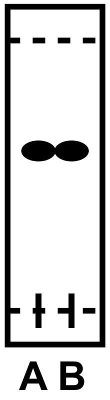


A

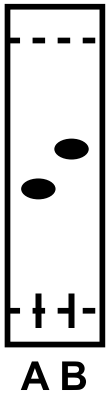


B

hexane/EtOAc = 1/1



CH_2Cl_2/EtOAc = 20/1



Halogen atom seems to interact with halogen-containing solvent.
-> How dose halogen atom interact with halogen atom?

Suggestion of Halogen-Halogen Interaction

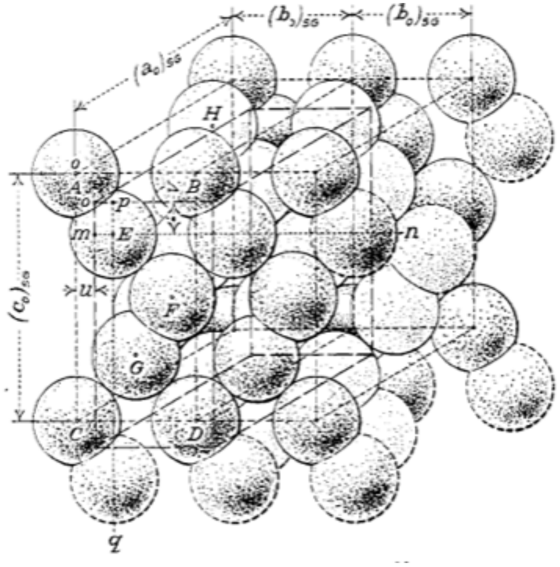
in 1819[1)]

$$I_2 + I^{\ominus} \rightleftharpoons I_3^{\ominus} \equiv I{-}I\cdots I^{\ominus}$$

Halogen-Halide interation?

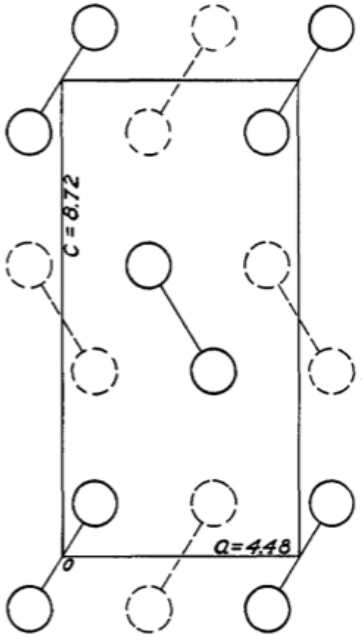
in 1928[2)]

Orthorhombic ("直方晶系") crystal of I_2



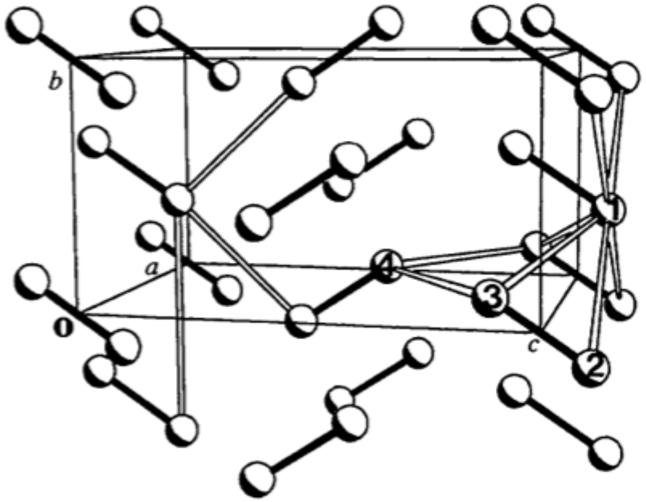
in 1936[3)]

Orthorhombic crystal Br_2 at −150 ºC



in 1952[4)]

Orthorhombic crystal Cl_2 at −160 ºC



Other diatomic molecules (H_2[5)], N_2[6)], etc.): hexagonal ("六方晶系")

-> There is the interation between halogen molecules?

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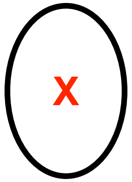
1) Pelletier, P. *Ann. Chim. Phys.* **1819**, *10*, 142. 2) Harris, P. M.; Mack, E.; Blake, F. C. *J. Am. Chem. Soc.* **1928**, *50*, 1583. 3) Vonnegut, B.; Warren, B. E. *J. Am. Chem. Soc.* **1936**, *58*, 2459. 4) a) Collin, R. L. *Acta Crystallogr.* **1952**, *5*, 431. b) Tsirelson, V. G.; Zhou, P. F.; Tang, T. H.; Bader, R. F. W. *Acta Crystallogr. Sect. A. Found. Crystallogr.* **1995**, *51*, 143. 5) Barrett, C. S.; Meyer, L.; Wasserman, J. *J. Chem. Phys.* **1966**, *45*, 834. 6) a) Bleak, J.; Lesar, R.; Etters, R. D. *J. Chem. Phys.* **1990**, *92*, 5430. b) Press, W.; Huller, A. *J. Chem. Phys.* **1978**, *68*, 4465.

Model for Closely Packed Halogen Molecular

Nyburg's model

	F	Cl	Br	I
van der Waals radius[1]	1.47	1.76	1.85	1.98
Major axis[2]	1.38	1.78	1.84	2.13
Minor axis[2]	1.30	1.58	1.64	1.76
Δaxis	0.08	0.20	0.20	0.37

[Å]



oblate shape

Oblate shape enables close packing?

Williams's model[3]

lattice energy ("格子エネルギー") of Cl_2

empirical force model (no partial bond energy)	ovserved energy
−17.2 kcal/mol	−31.9 kcal/mol

-> Δenergy = −14.7 kcal/mol

Attractive non-bonding interaction exists?

*lattice energy: the energy charge upon formation of one mole of a crystalline ionic compound from its constituent ions, which are assumed to initially be in the gaseous state (WIkipedia).

$$Cl_2\ (\text{gas}) \xrightarrow[\text{−lattice energy}]{} Cl_2\ (\text{crystal})$$

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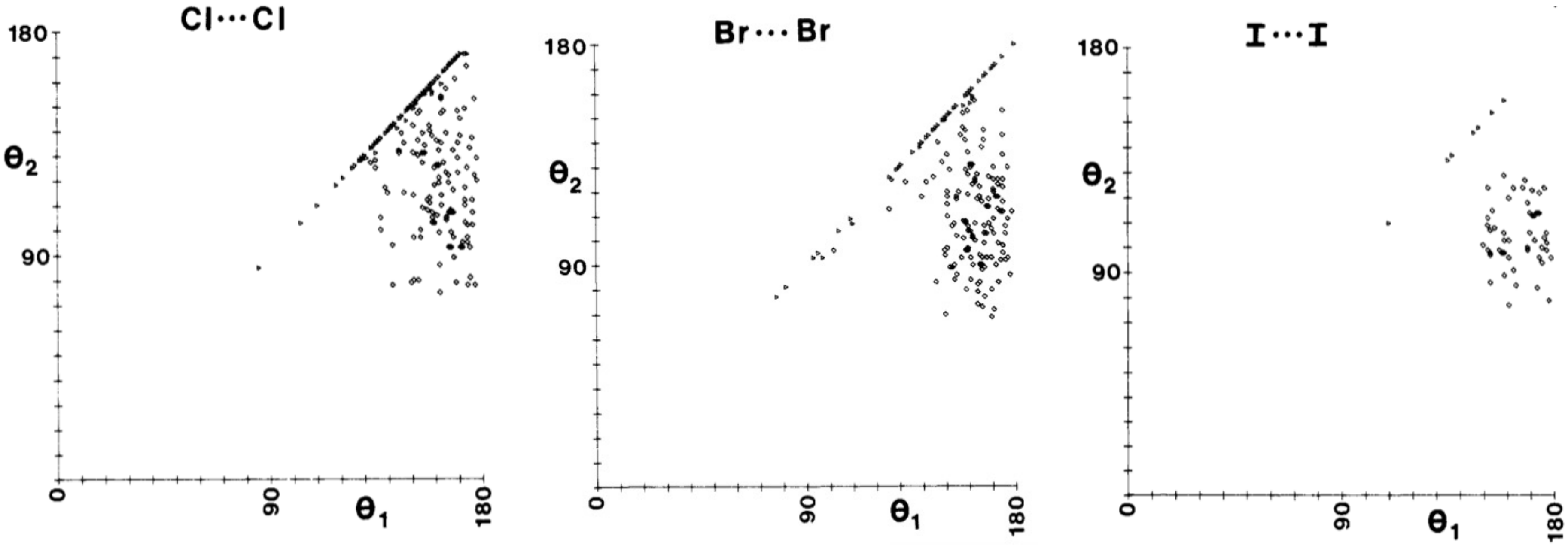
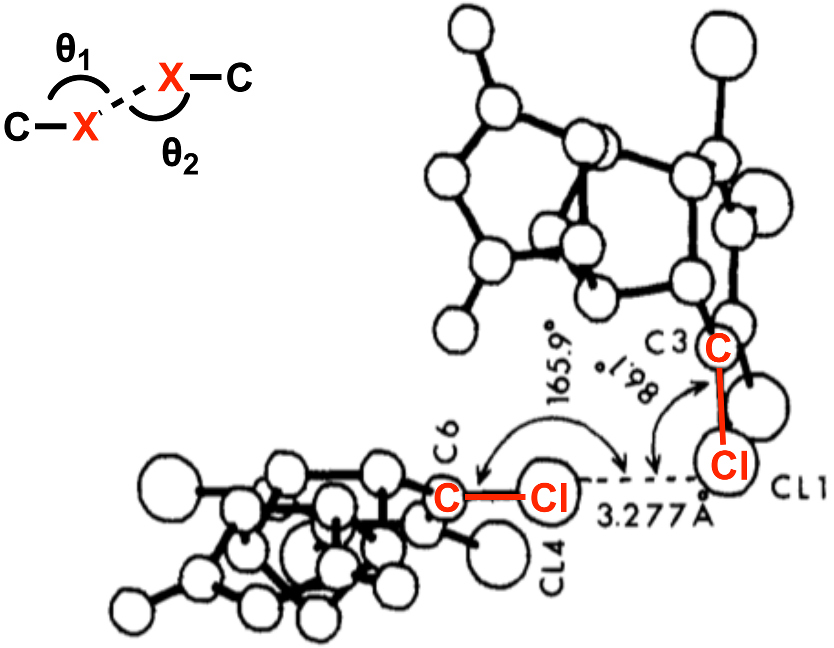
1) Bondi, A. *J. Phys. Chem.* **1964**, *68*, 441. 2) Nyburg, S. C.; Faerman, C. H. *Crystallogr. Sect.B* **1985**, *41*, 274. 3) Williams, D. E.; Hsu, L. Y.; *Acta Crystallogr. Sect. A Found. Crystallogr.* **1985**, *41*, 296.

Interaction Angle of C-X•••X-C

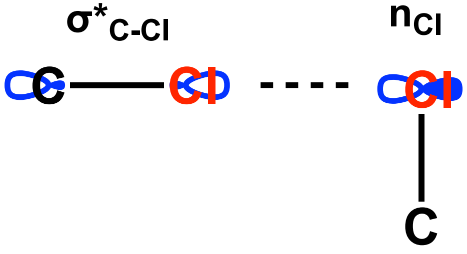
Williams's model





Type I: $\theta_1 \sim \theta_2 \sim 150$ °

Type II: $\theta_1 \sim 180$ °, $\theta_2 \sim 90$ °



In Type II, there is n-σ* interaction?

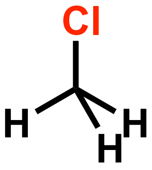
Ramasubbu, N.; Parthasarathy, R.; Murray-Rust, P. *J. Am. Chem. Soc.* **1986**, *108*, 4308.

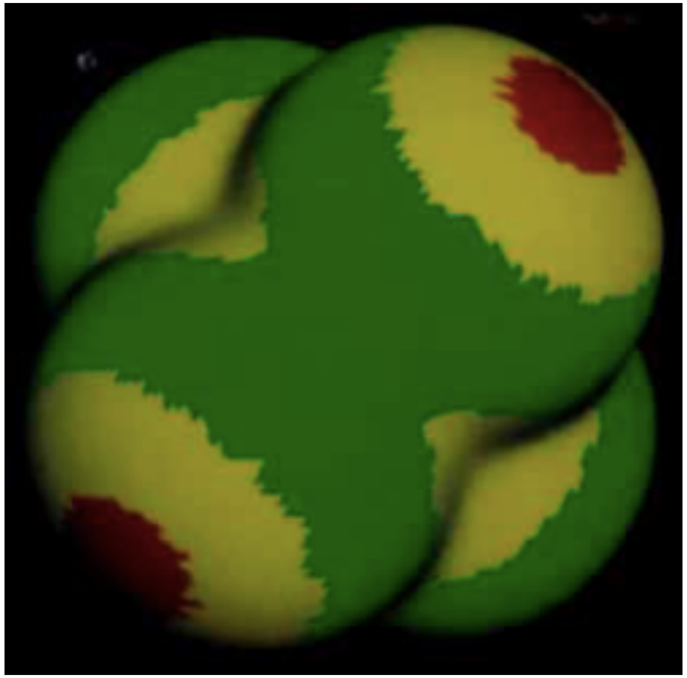
Calculation of Electrostatic Potential

Williams's model

hole of positive potential

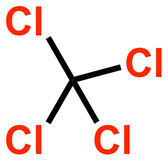
ring of negative potential



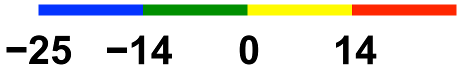


hole of positive potential

ring of negative potential



hf/6-31g(d)

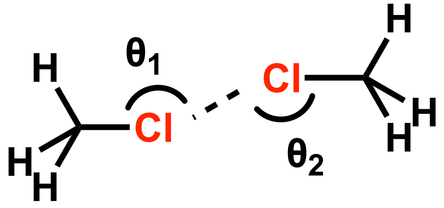


Hole of positive potential is called as "σ-hole"

Brinck, T.; Murray, J. S.; Politzer, P. *Int. J. Quantum Chem.* **1992**, *44*, 57.

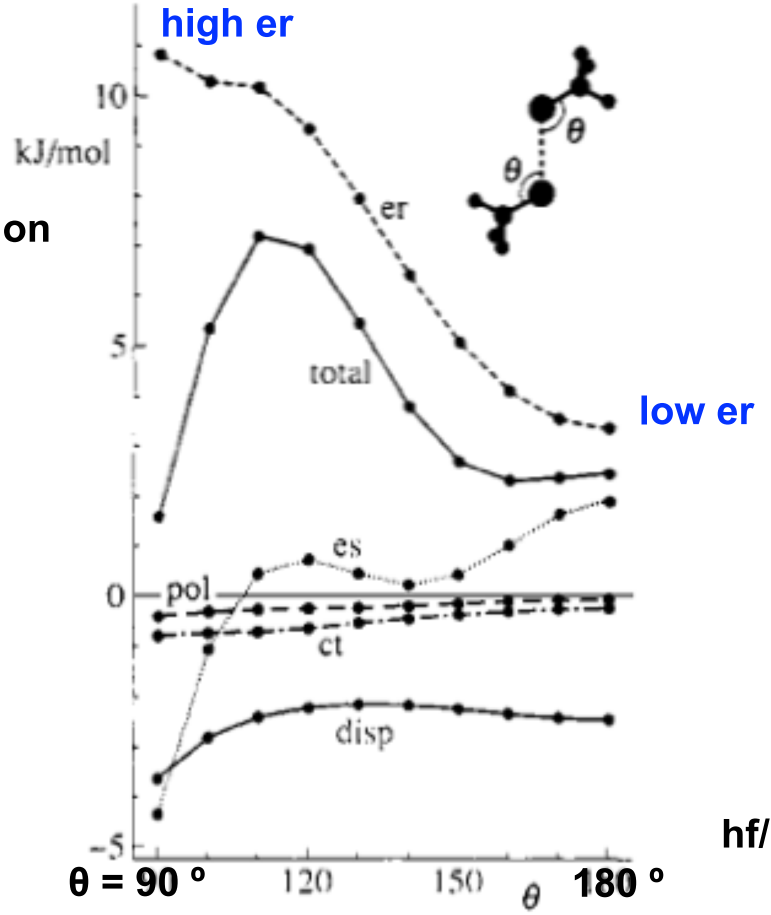
Calculation of Electrostatic Potential

Nyburg's model

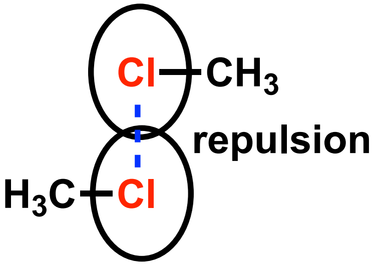


er: exchange-repulsion
pol: polarization
ct: charge-transfer
disp: dispersion
es: electrostatic

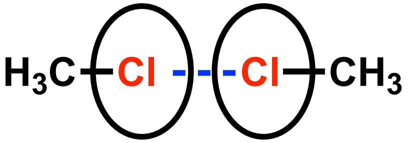
in case of $\theta_1 = \theta_2$, Cl-Cl: 3.5 Å



hf/6-31g(d)



θ = 90 º



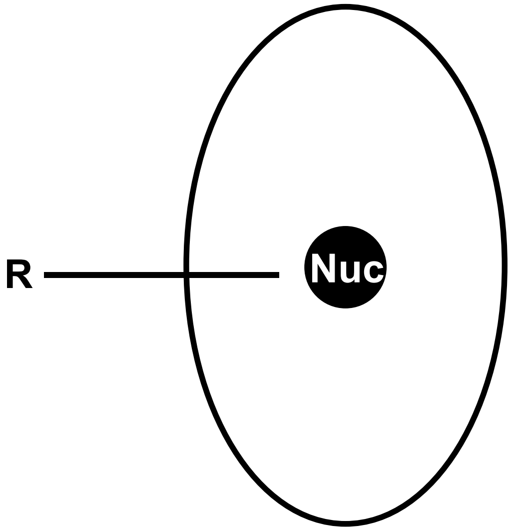
θ = 180 º

Exchange-repulsion energy is anisotropic.
->Clorine atom is oblate shape?

Price, S. L.; Stone, A. J.; Lucas, J.; Rowland, R. S.; Thornley, A. E. *J. Am. Chem. Soc.* **1994**, *116*, 4910.

Coupling two Models

far from nucleus
-> negative charge

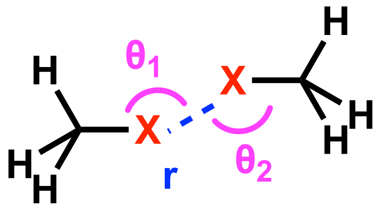


close to nucleus
-> positive charge

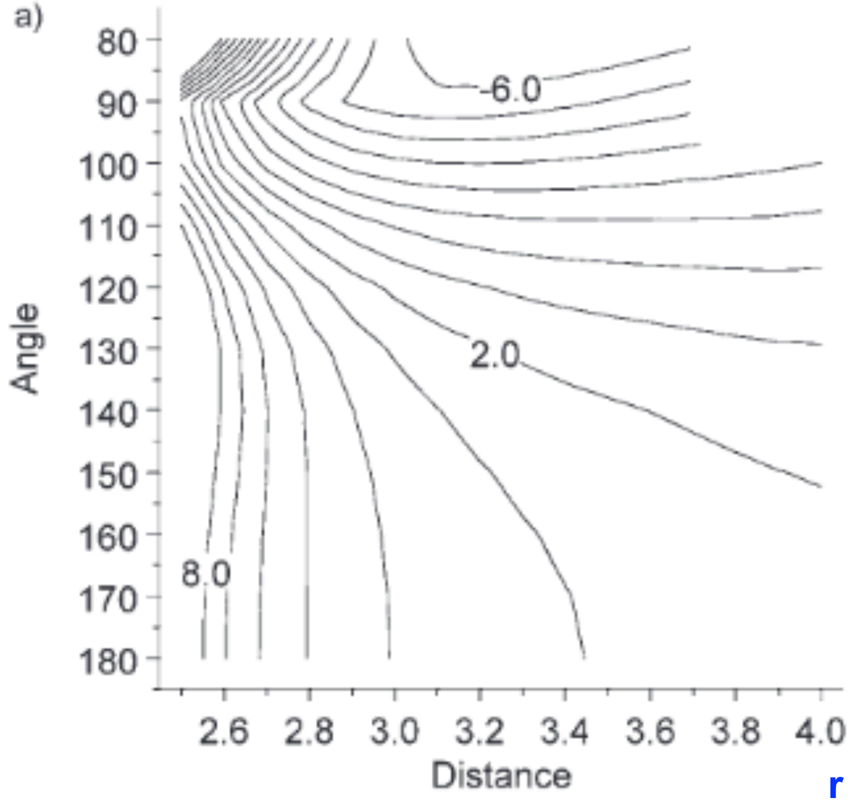
halogen atom

Nyburg's model and Williams's model should be treated as the same concept

Calculation of Electrostatic Interaction (I)



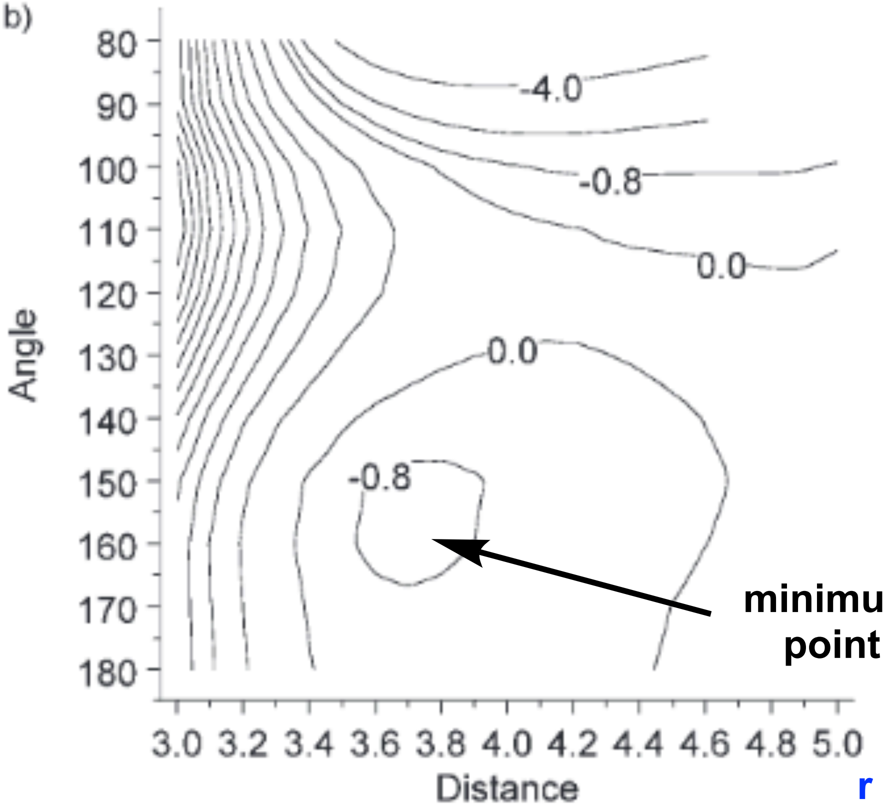
θ ($\theta_1 = \theta_2$)



r

H_3CF

θ ($\theta_1 = \theta_2$)



minimum point

r

H_3CCl

(H_3CBr and H_3CI are similar to H_3CCl.)

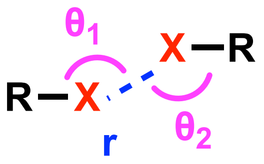
mp2/dz

Awwadi, F. F.; Willett, R. D.; Peterson, K. A.; Twamley, B. *Chem. Eur. J.* **2006**, *12*, 8952.

Calculation of Electrostatic Interaction (II)

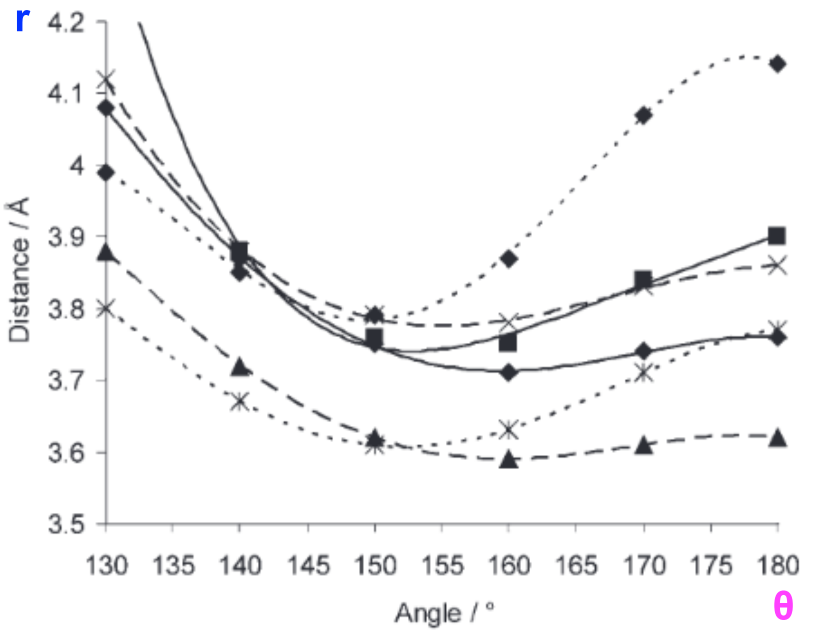
at energy minima…

		θ	r	mp2/cbs energy
Cl—CH_3	◆	156 °	3.43 Å	−0.66 kcal/mol
Br—CH_3	■	153 °	3.58 Å	−1.24 kcal/mol
I—CH_3		147 °	3.86 Å	−1.81 kcal/mol
Cl—Ph	▲	152 °	3.38 Å	−1.25 kcal/mol
Br—Ph	×	150 °	3.65 Å	−2.09 kcal/mol
I—Ph		148 °	3.81 Å	−2.16 kcal/mol
Cl—≡	*	142 °	3.46 Å	−0.99 kcal/mol
Br—≡	◆	140 °	3.65 Å	−1.30 kcal/mol
I—≡		144 °	4.04 Å	−1.45 kcal/mol



θ ($\theta_1 = \theta_2$)

van der Waals radius
Cl: 1.76 Å, Br: 1.85 Å, I: 1.98 Å



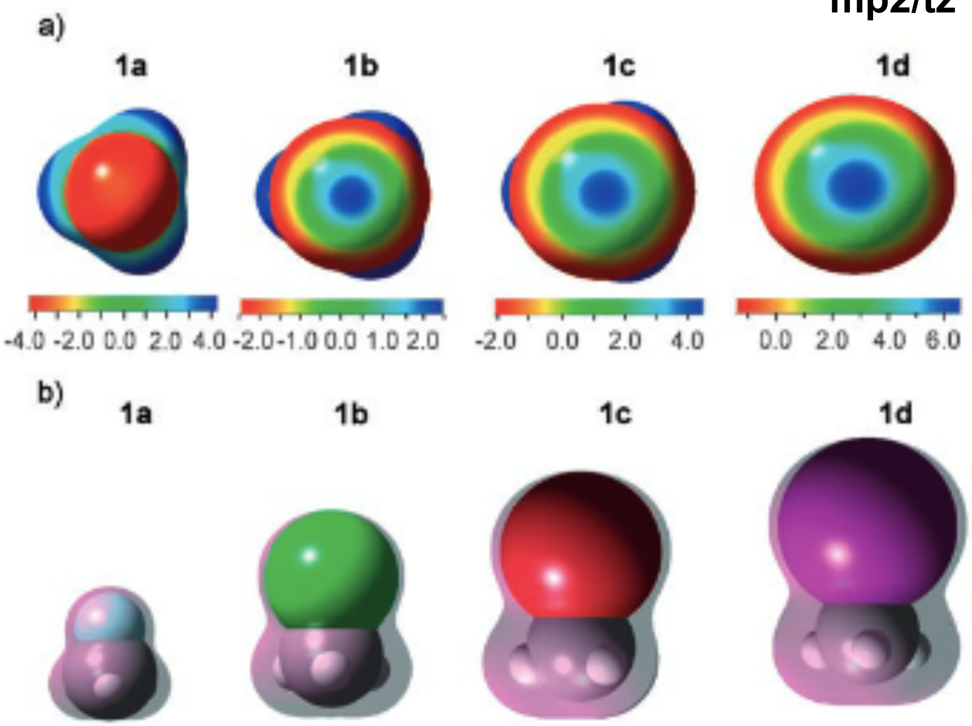
plot of r, at minimum energy about certain θ

halogen interaction seems
I > Br > Cl, sp^2 > sp > sp^3 (*ipso* carbon)

Awwadi, F. F.; Willett, R. D.; Peterson, K. A.; Twamley, B. *Chem. Eur. J.* **2006**, *12*, 8952.

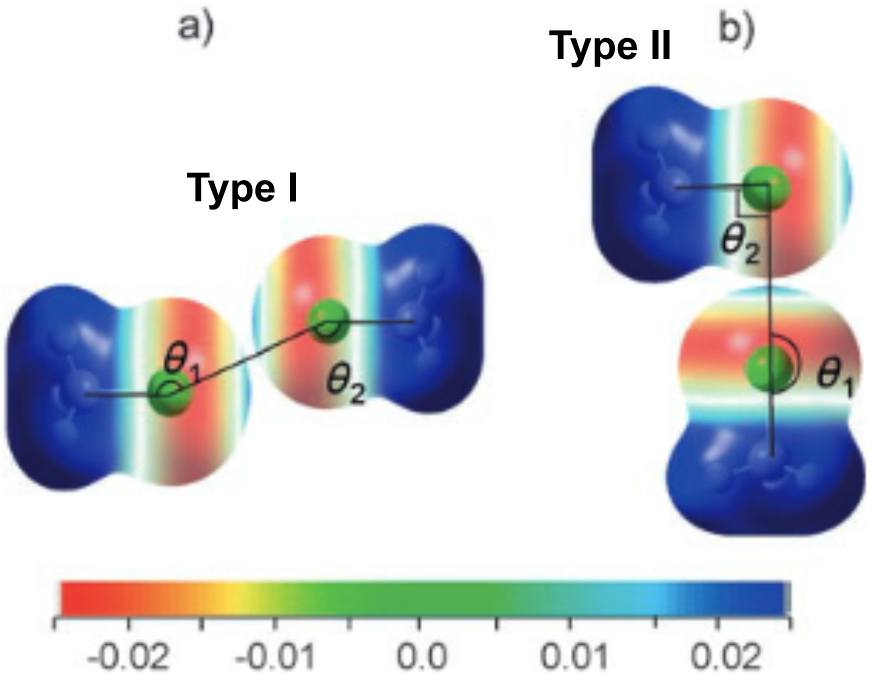
Calculation of Electrostatic Potential (I)

mp2/tz



Note!: Color represents different electron density dependenting on molecules.

$F-CH_3$ $Cl-CH_3$ $Br-CH_3$ $I-CH_3$

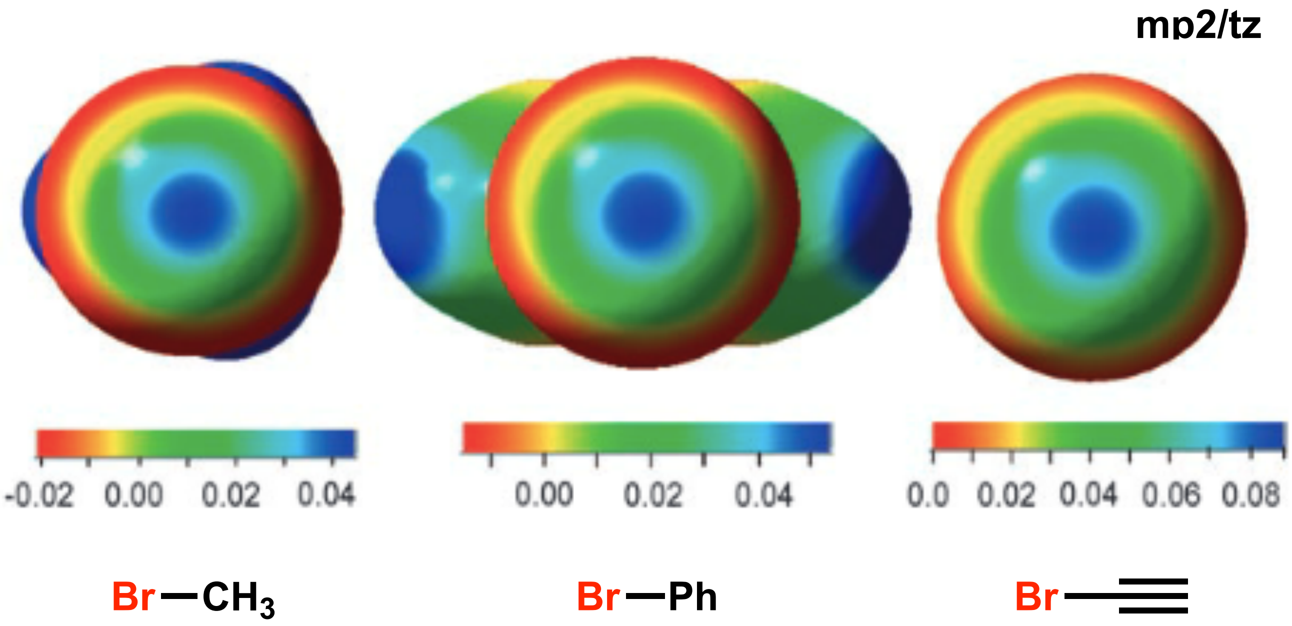


Heavier halogen
-> more distorted sphere
-> higher difference between major axis and minor axis.
-> more polarized surface
-> stronger interaction

Interaction between negative surface and positive surface

Awwadi, F. F.; Willett, R. D.; Peterson, K. A.; Twamley, B. *Chem. Eur. J.* **2006**, *12*, 8952.

Calculation of Electrostatic Potential (II)



Note!: Color represents different electron density dependenting on molecules.

more s charactor of *ipso*-carbon
-> more electrodefient halogen
-> increase positive potential at end cap, whereas decrease negative potential at ring

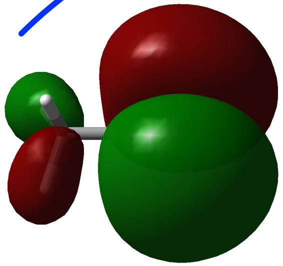
For strong interaction, more positive potential at end cap and more negative potential at ring are necessary. Therefore, s charactor of *ipso*-carbon should be moderate to interact strongly, which causes the the order of interaction strength as $sp^2 > sp > sp^3$.

Awwadi, F. F.; Willett, R. D.; Peterson, K. A.; Twamley, B. *Chem. Eur. J.* **2006**, *12*, 8952.

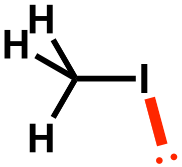
Anisotropy caused by sp I atom?

negative ring

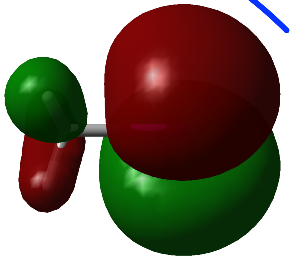
σ-hole



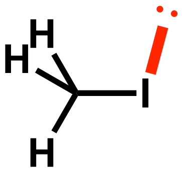
HOMO
−0.30303 eV



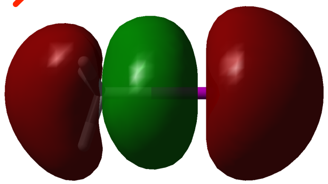
100% Ip



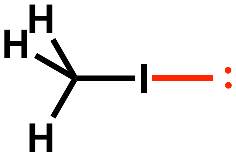
HOMO−1
−0.30303 eV



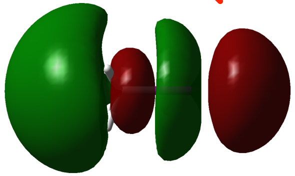
100% Ip



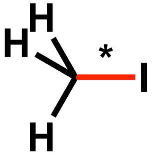
HOMO−2
−0.40664 eV



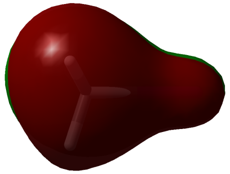
50% Ip, 4% Is, 35% Cp, 4% Hs



LUMO
−0.00685 eV



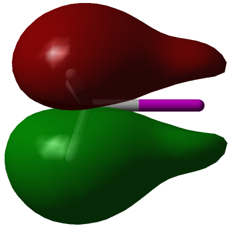
88% Ip, 9% Id 1)



HOMO−3
−0.51015 eV

one of C-H?

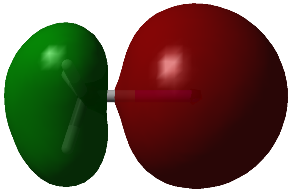
51% Cp, 44% Hs



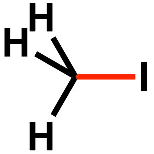
HOMO−4
−0.51017 eV

one of C-H?

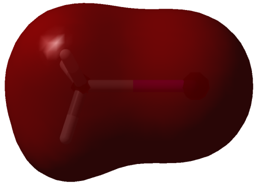
51% Cp, 44% Hs



HOMO−5
−0.70156 eV



70% Is, 6% Cp, 10% Cs, 11% Hs



HOMO−6
−0.84121 eV

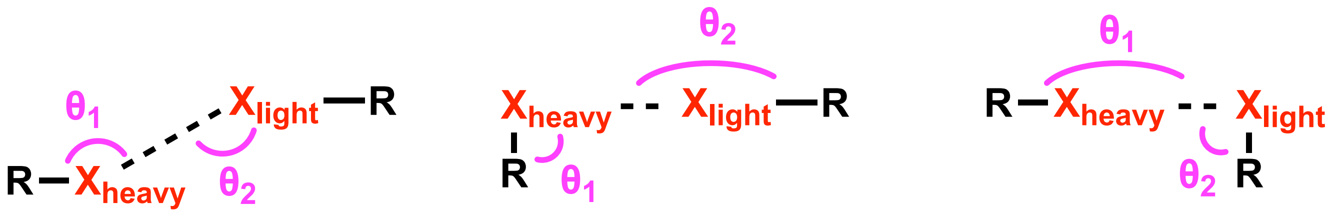
one of C-H?

C, H:m60-2x/6-31+g(d)
I: m06-2x/lanl2dz

Pernpointner, M.; Zobel, J. P.; Fasshauer, E.; Sil, A. N. *Chem. Phys.* **2012**, *407*, 39.

Hetero-Halogen Halogen Interaction (I)

X-ray data base analysis



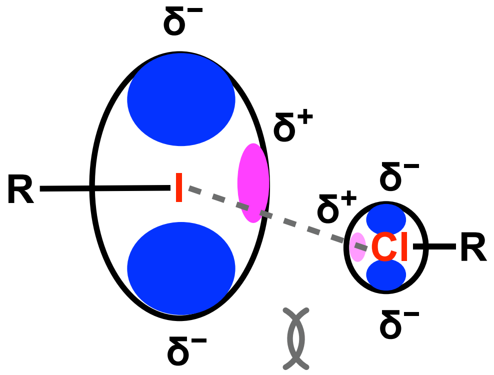
	Type I ($\theta_1 \sim \theta_2$)	Type II ($\theta_1 < \theta_2$)	Type II ($\theta_1 > \theta_2$)
Cl•••F	18	8	9
Br•••F	4	4	8
I•••F	2	0	6
Br•••Cl	4	13	23
I•••Cl	0	1	5
I•••Br	0	1	1

number of interactions

Type II ($\theta_1 > \theta_2$) becames favored as heavier halogen involes interaction.

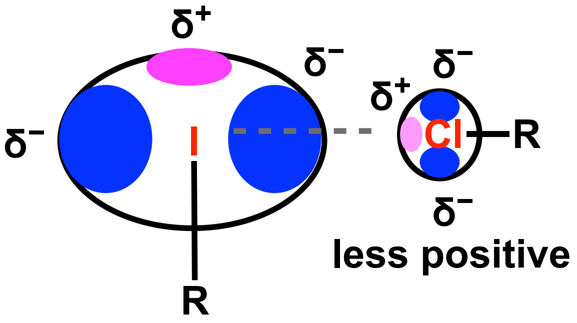
Edireddi, V. R.; Reddy, D. S.; Goud, B. S; Craig, D. C; Rae, A. D.; Desiraju, G. R. *J. Chem. Soc. –Perkin Trans.* **1994**, *2*, 2353.

Hetero-Halogen Halogen Interaction (II)



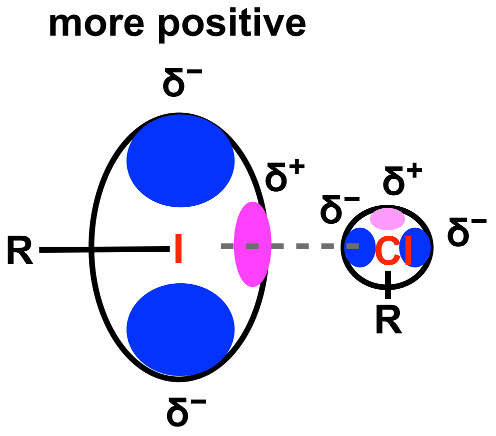
Type I (disfavored)

repulsion
between δ^- and δ^-



Type II ($\theta_1<\theta_2$, unfavored)

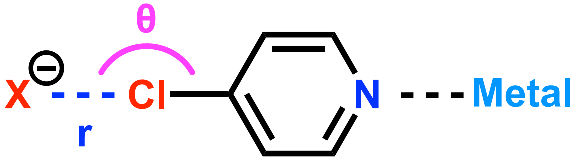
interaction between
less positive Cl and I



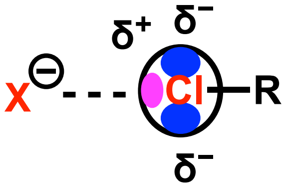
Type II ($\theta_1>\theta_2$, favored)

interaction between
more positive I and Cl

Halogen Halide Interaction



		r	θ	ΔE
no metal	$F^\ominus$	2.344 Å	179.7 °	−14.28 kcal/mol
	$Cl^\ominus$	3.093 Å	179.8 °	−6.28 kcal/mol
	$Br^\ominus$	3.309 Å	175.6 °	−5.22 kcal/mol
$Cu^\oplus$	$F^\ominus$	2.243 Å	180.0 °	−27.99 kcal/mol
	$Cl^\ominus$	2.930 Å	180.0 °	−16.87 kcal/mol
	$Br^\ominus$	3.119 Å	180.0 °	−15.12 kcal/mol



Halide intracts with σ-hole of halogen.

b97-1/lanl2dz(pp) (for Cu)
b97-1/aug-cc-pvdz (for others)

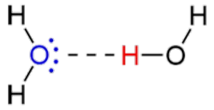
Xu, L.; Lv, J.; Sang, P.; Zou, J.-W.; Yu, Q.-S.; Xu, M.-B. *Chem. Phys.* **2011**, *379*, 66.

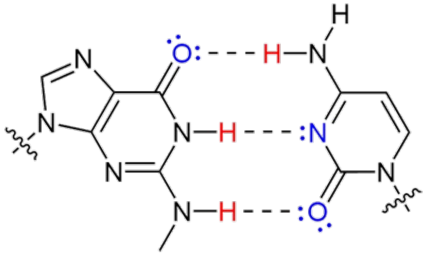
Contents

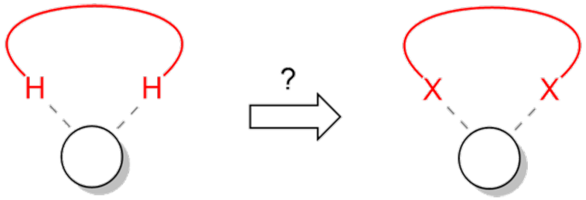
1. **Introduction (Halogen-Halogen Interaction)**

2. **Activation of a Metal-Halogen Bond by Halogen Bonding (Main paper)**

Introduction of Prof. Stefan M. Huber





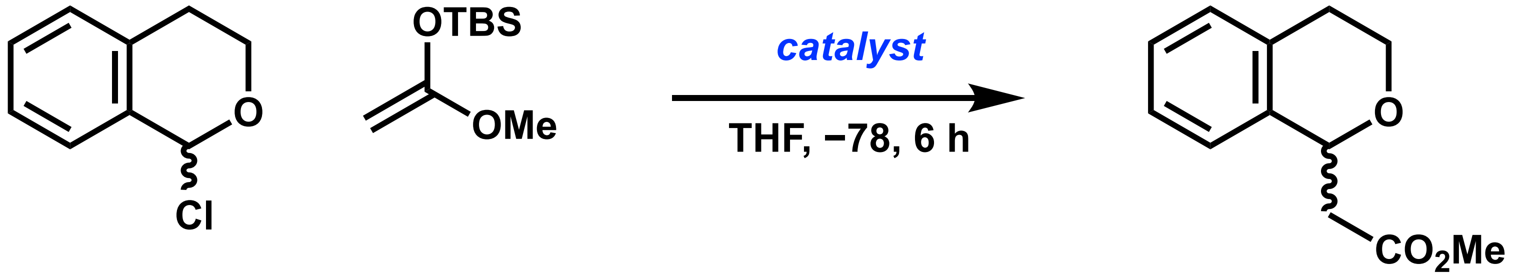


Prof. Stefan M. Huber
2003 B.S. @ Friedrich-Alexander Universität Erlangen-Nuremberg (Prof. Robert Weiss)
2007 Ph.D @ Friedrich-Alexander Universität Erlangen-Nuremberg (Prof. Robert Weiss)
2007~2008 postdoctoral research@ the University of Minnesota (Prof. Christopher J. Cramer, Prof. William B. Tolman)
2008 postdoctoral research @ the Université de Genève (Prof. Laura Gagliardi)
2009 postdoctoral research @ Friedrich-Alexander Universität Erlangen-Nuremberg (Prof. Harald Gröger)
2009~2013 independent research @ Technische Universität München
2014~2021 Associate Professor @ Ruhr-Universität Bochum
2022~ Full Professor @ Ruhr-Universität Bochum

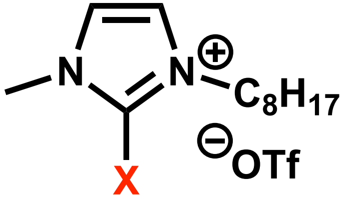
Research topic: Biomolecule, Organocatalysis (Hydrogen bond, Halogen bond, Chalcogen bond)

https://www.huberlab.ruhr-uni-bochum.de/hlab/index.html.en

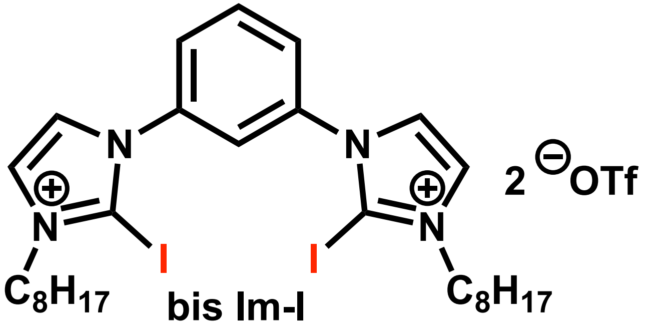
Previous Halogen Bond Catalyst



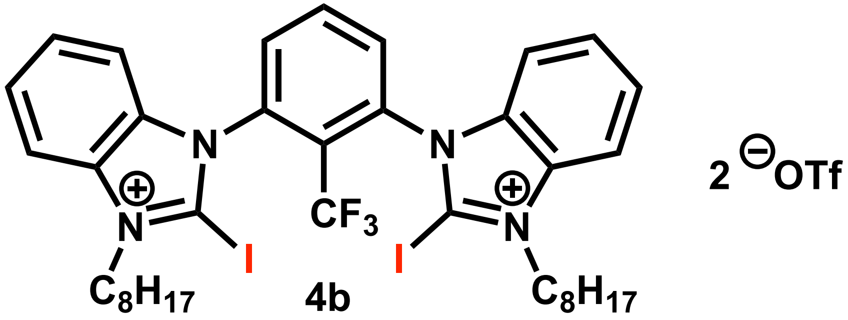
entry	*catalyst*	yields
1	none	<5%
2	I_2 (10 mol%)	<5%
3	$NaBPh_4$ (10 mol%)	17%
4	Im-Br (20 mol%)	<5%
5	Im-I (20 mol%)	67%
6	bis Im-I (10 mol%)	67%
7	4b (2.5 mol%)	85%
8	4b (0.5 mol%)	70%
9	4b’ (10 mol%)	73%



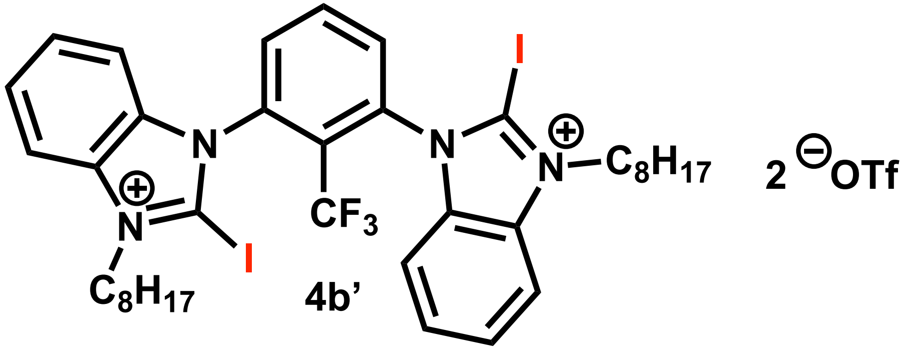
Im-X



bis Im-I



4b

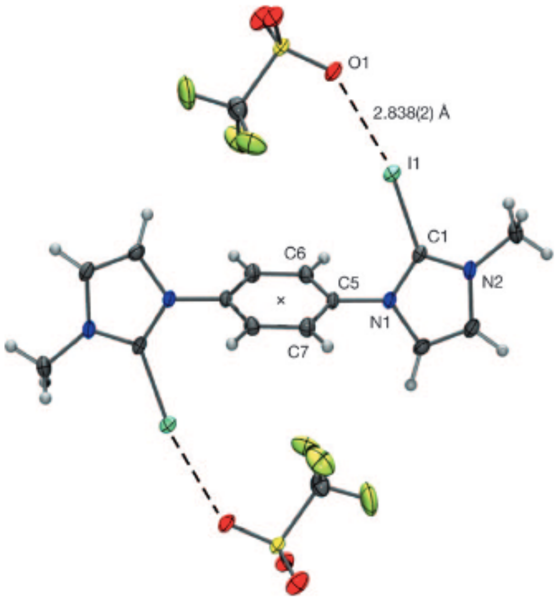


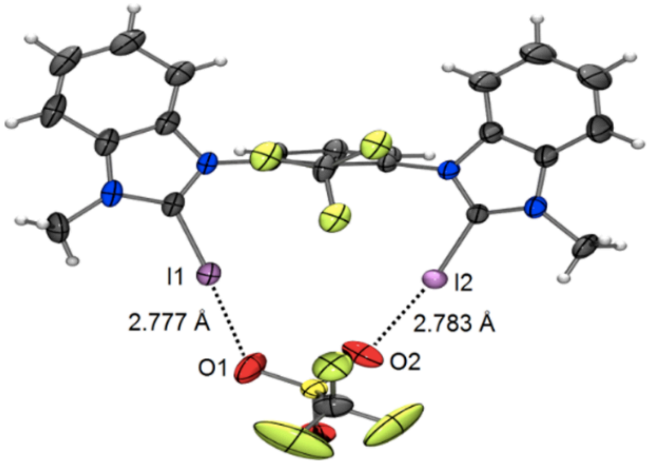
4b’

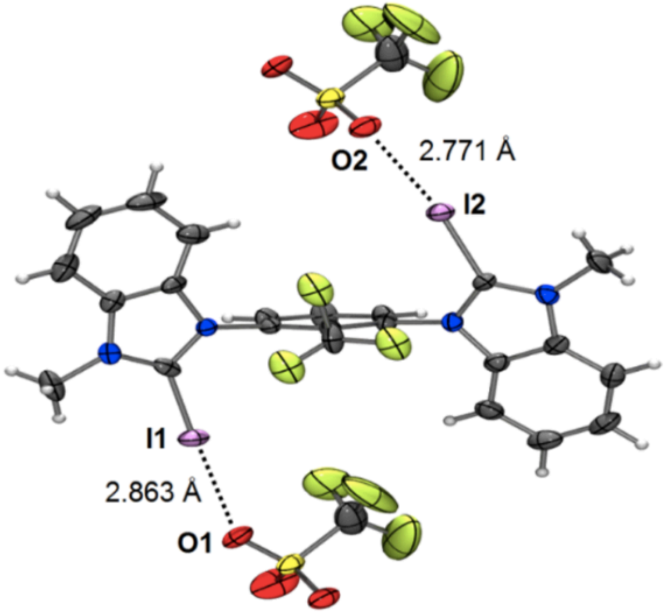
Preorganized bidentate catalyst gave better results.

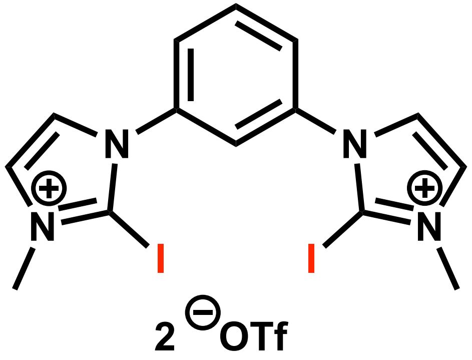
Jungbauer, S. H.; Huber. S. M. *J. Am. Chem. Soc.* **2015**, *137*, 12110.

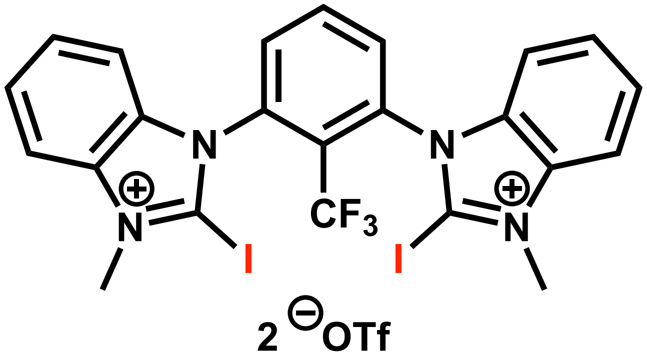
X-Ray Structural Analysis of Catalyst

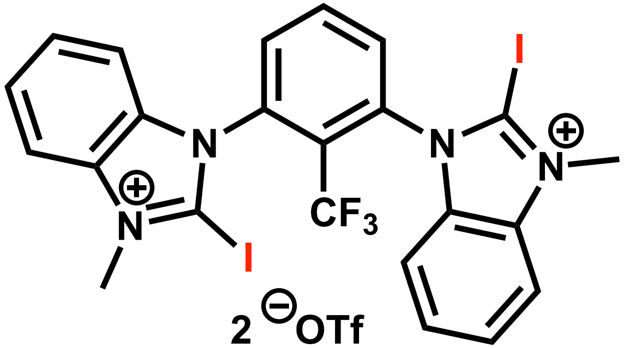












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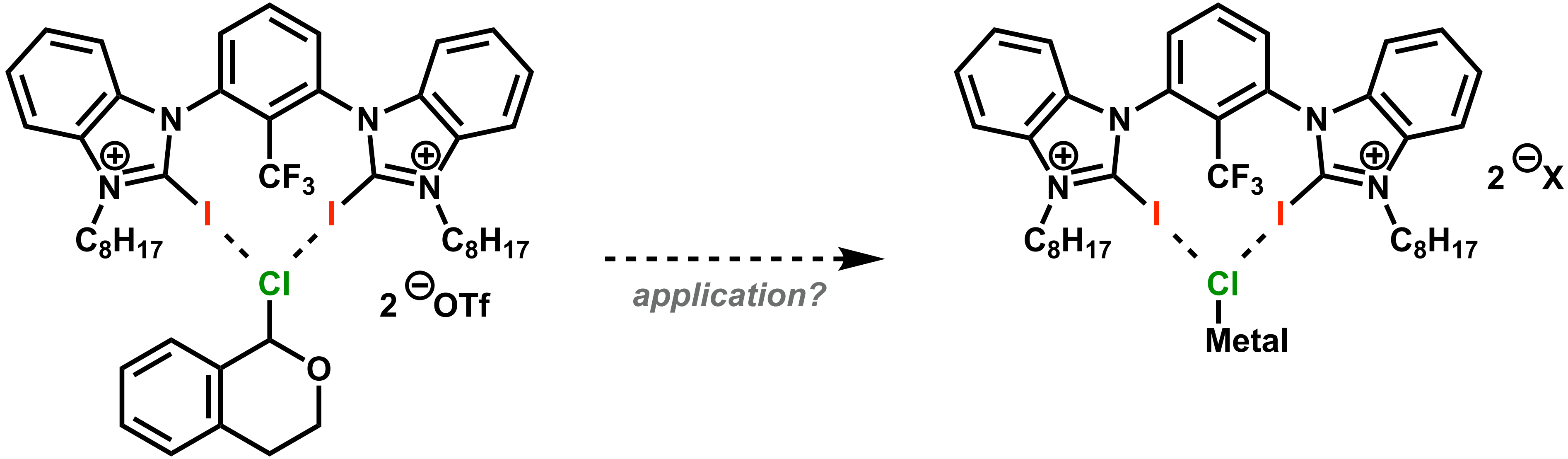
1) Walter, S. M.; Kniep, F.; Herdtweck, E.; Huber, S. M. *Angew. Chem. Int. Ed.* **2011**, 50, 7187. 2) Jungbauer, S. H.; Huber. S. M. *J. Am. Chem. Soc.* **2015**, *137*, 12110.

X-Ray Structural Analysis of Catalyst

previous study

new application



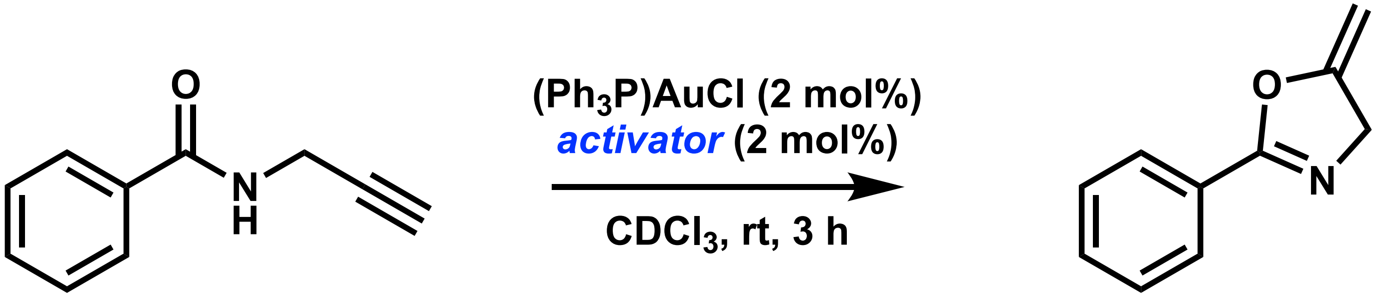
Halogen-halogen interaction can activate C-Cl bond.

Can Metal-Cl bond be activated?

---

1) Jungbauer, S. H.; Huber. S. M. *J. Am. Chem. Soc*. **2015**, *137*, 12110. 2) Wolf, J.; Huber, F.; Erochok, N.; Heinen, F.; Guerin, V.; Legault, C. Y.; Kirsch, S. F.; Huber, S. M. *Angew. Chem. Int. Ed.* **2020**, *59*, 16496.

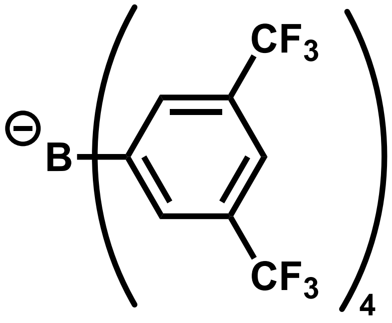
Au^I-Catalyzed Cyclization of Amide (1)



A **B**

entry	*activator*	conversion of A	k_{rel}*
1	none	<5%	-
2	AgOTf	5%	100
3	$AgBF_4$	14%	180
4	$AgPF_6$	44%	740
5	$NaBAr^F{}_4$	95%	3500
6	$Me_4NBAr^F{}_4$	<5%	15

*relative initial rates after 70 min, referenced to 3

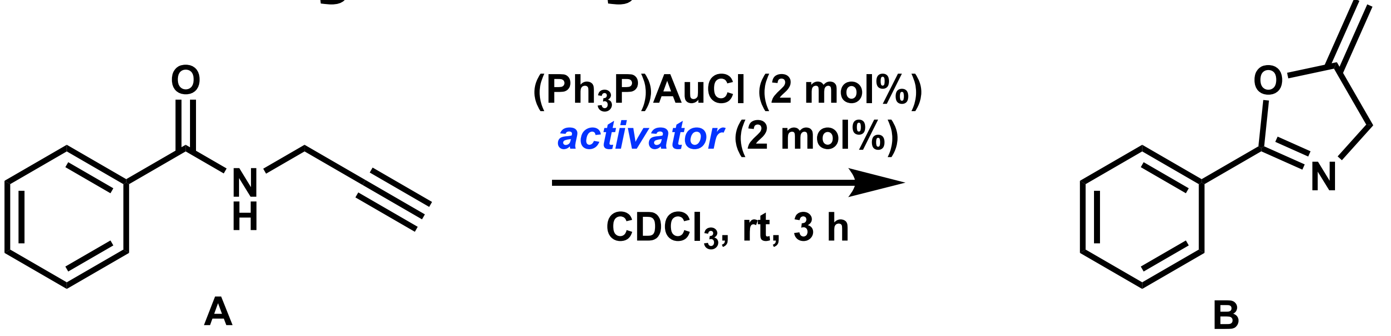


$^{\ominus}BAr^F{}_4$

Bulkiness of counteranion was important.

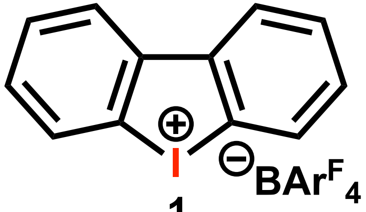
Wolf, J.; Huber, F.; Erochok, N.; Heinen, F.; Guerin, V.; Legault, C. Y.; Kirsch, S. F.; Huber, S. M. *Angew. Chem. Int. Ed.* **2020**, *59*, 16496.

Au^{I}-Catalyzed Cyclization of Amide (2)



entry	*activator*	conversion of A	k_{rel}*
7	1	60%	1100
8	2	38%	660
9	3	<5%	1
10	4a	92%	3100
11	4b	<5%	18
12	4c	25%	330

*relative initial rates after 70 min, referenced to 3



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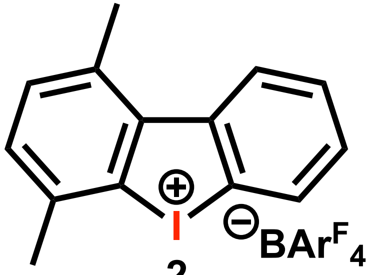

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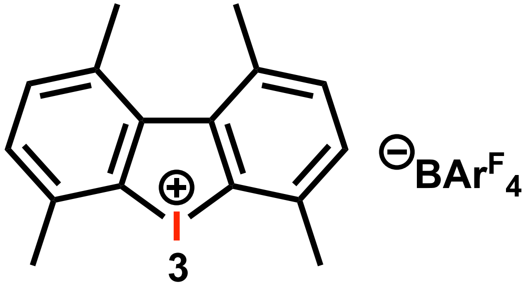

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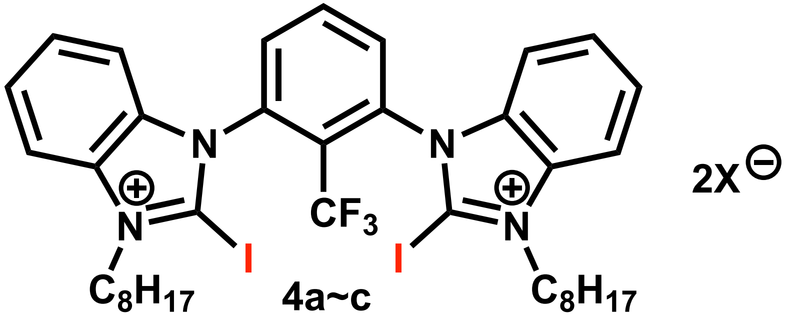


4a~c

4a: X = BAr^F_4
4b: X = OTf
4c: X = PF_6

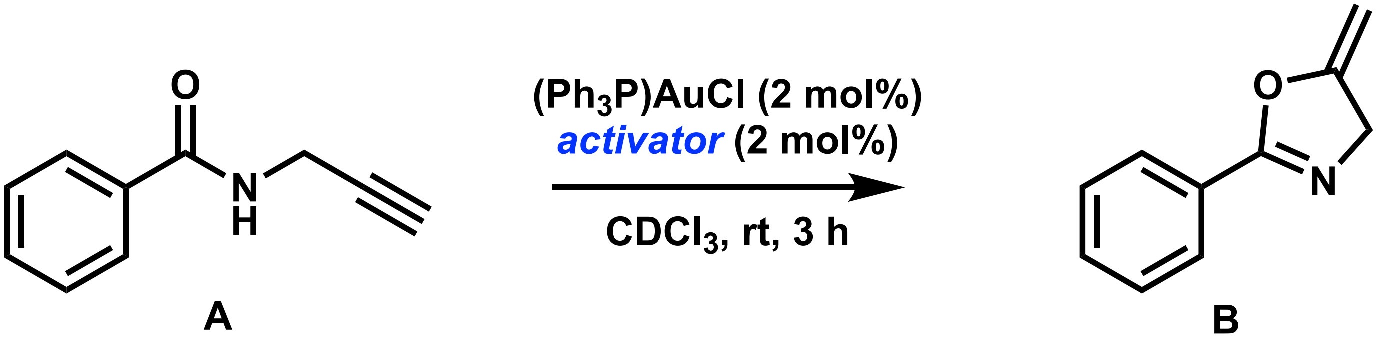
Hindered iodine atom didn't have reactivity.

Bidentate catalyst 4 highly accelerated the reaction.

---

1) Huber. S. M. et al. *Angew. Chem. Int. Ed.* **2020**, *59*, 16496. 2) Huber. S. M. et al. *J. Am. Chem. Soc.* **2015**, *137*, 12110.

Au^I-Catalyzed Cyclization of Amide (3)

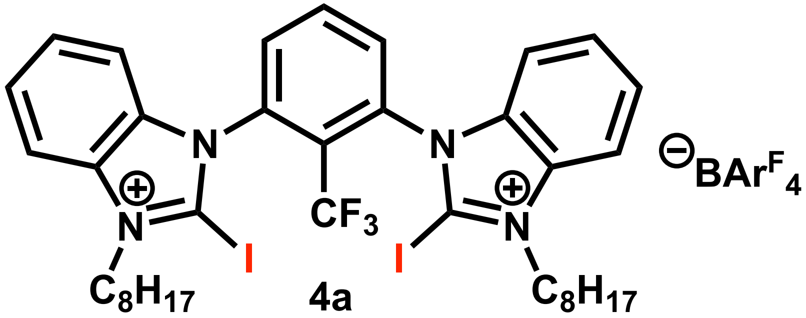


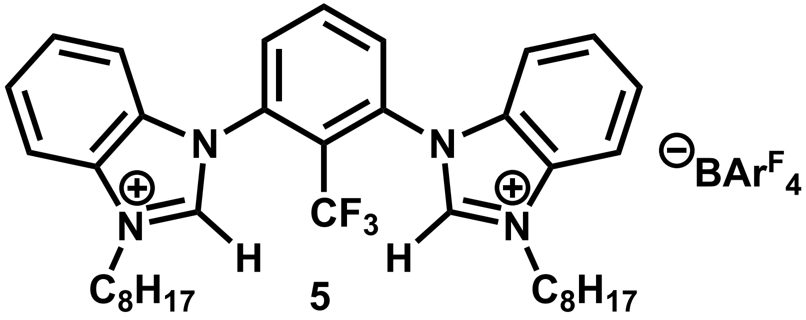
$(Ph_3P)AuCl$ (2 mol%)
activator (2 mol%)
$CDCl_3$, rt, 3 h

entry	*activator*	conversion of A	k_{rel}*
10	4a	92%	3100
13	5	<5%	15
14	I_2 (1 mol%)	<5%	-

*relative initial rates after 70 min, referenced to 3

Cationic iodine atom was essential for the reaction.


4a


5

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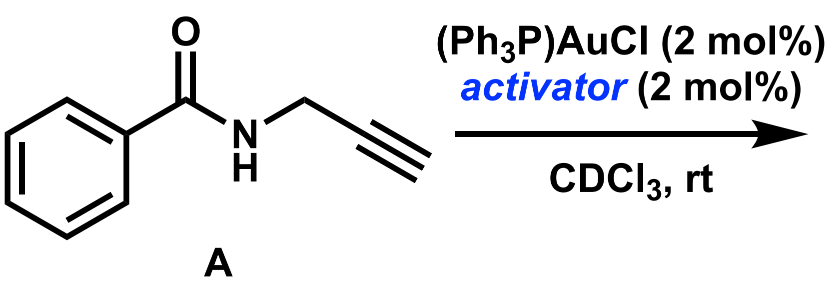
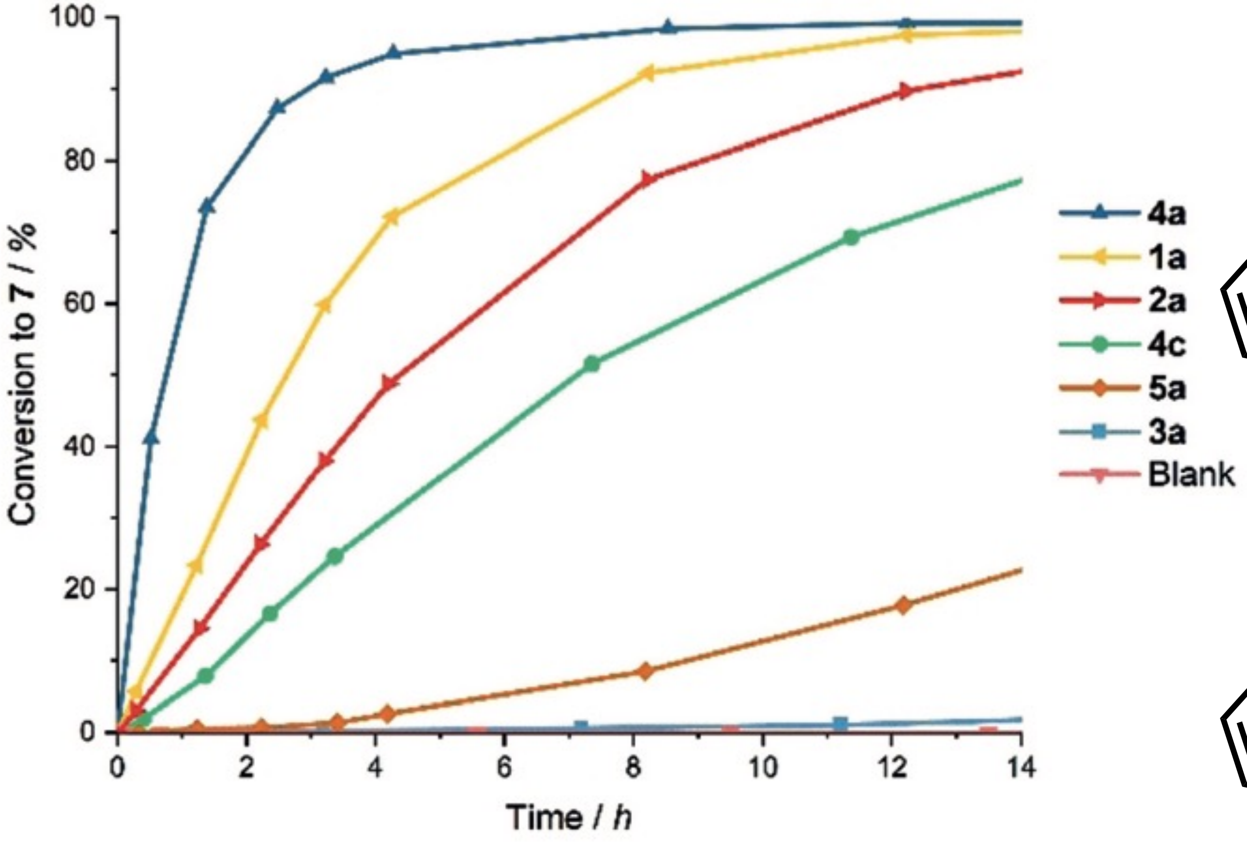
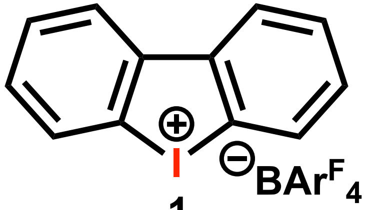
1) Jungbauer, S. H.; Huber. S. M. *J. Am. Chem. Soc.* **2015**, *137*, 12110. 2) Wolf, J.; Huber, F.; Erochok, N.; Heinen, F.; Guerin, V.; Legault, C. Y.; Kirsch, S. F.; Huber, S. M. *Angew. Chem. Int. Ed.* **2020**, *59*, 16496.

Kinetic Plot of Cyclization of Amide







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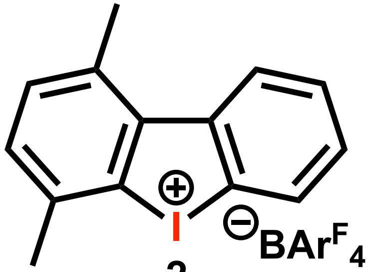

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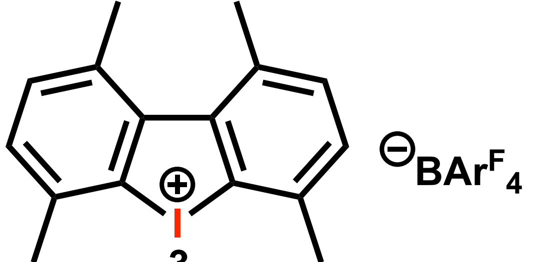

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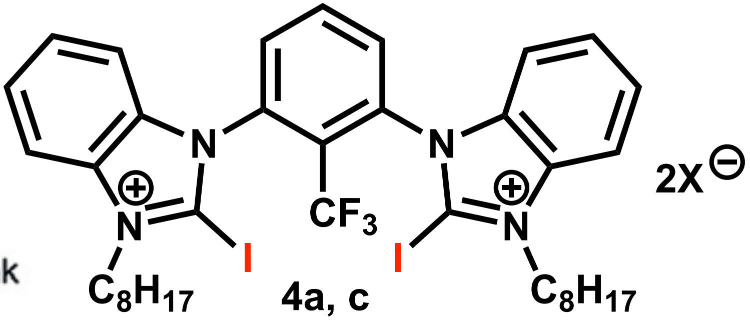
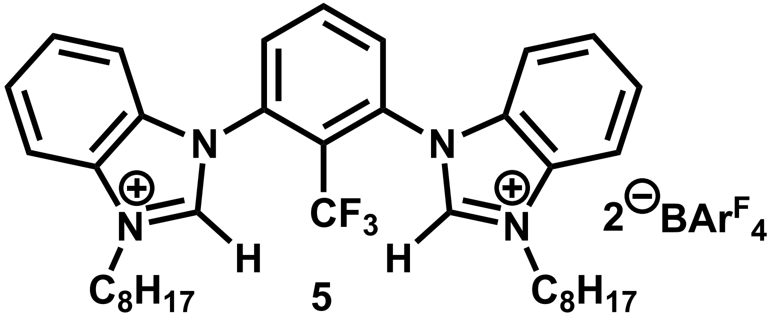


4a, c

4a: X = BAr$^F_4$

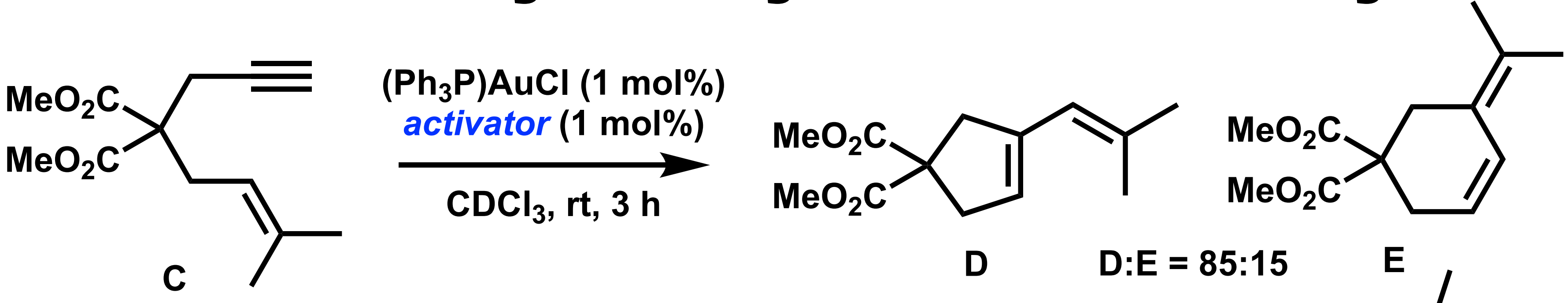
4c: X = PF$_6$



5

Wolf, J.; Huber, F.; Erochok, N.; Heinen, F.; Guerin, V.; Legault, C. Y.; Kirsch, S. F.; Huber, S. M. *Angew. Chem. Int. Ed.* **2020**, *59*, 16496.

Au^I-Catalyzed Cyclization of Enyne

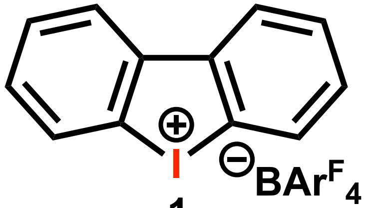


$(Ph_3P)AuCl$ (1 mol%)
activator (1 mol%)
$CDCl_3$, rt, 3 h

D:E = 85:15

entry	*activator*	conversion of A	k_{rel}*
0	none	<5%	-
1	1	76%	740
2	2	43%	420
3	3	<5%	1
4	4a	83%	830
5	5	<5%	41
6	$NaBAr^F{}_4$	84%	850
7	$Me_4NBAr^F{}_4$	<5%	5

*relative initial rates after 70 min, referenced to 3



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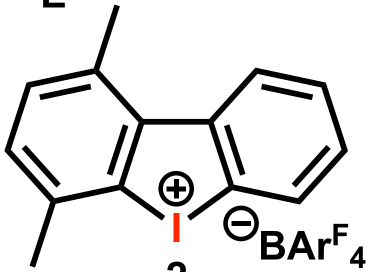

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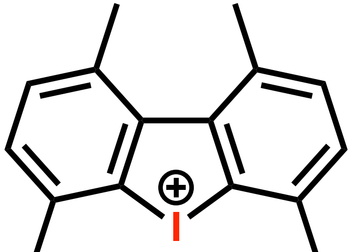

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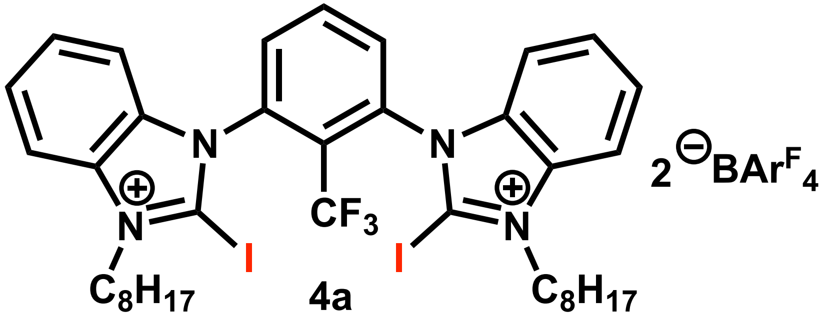
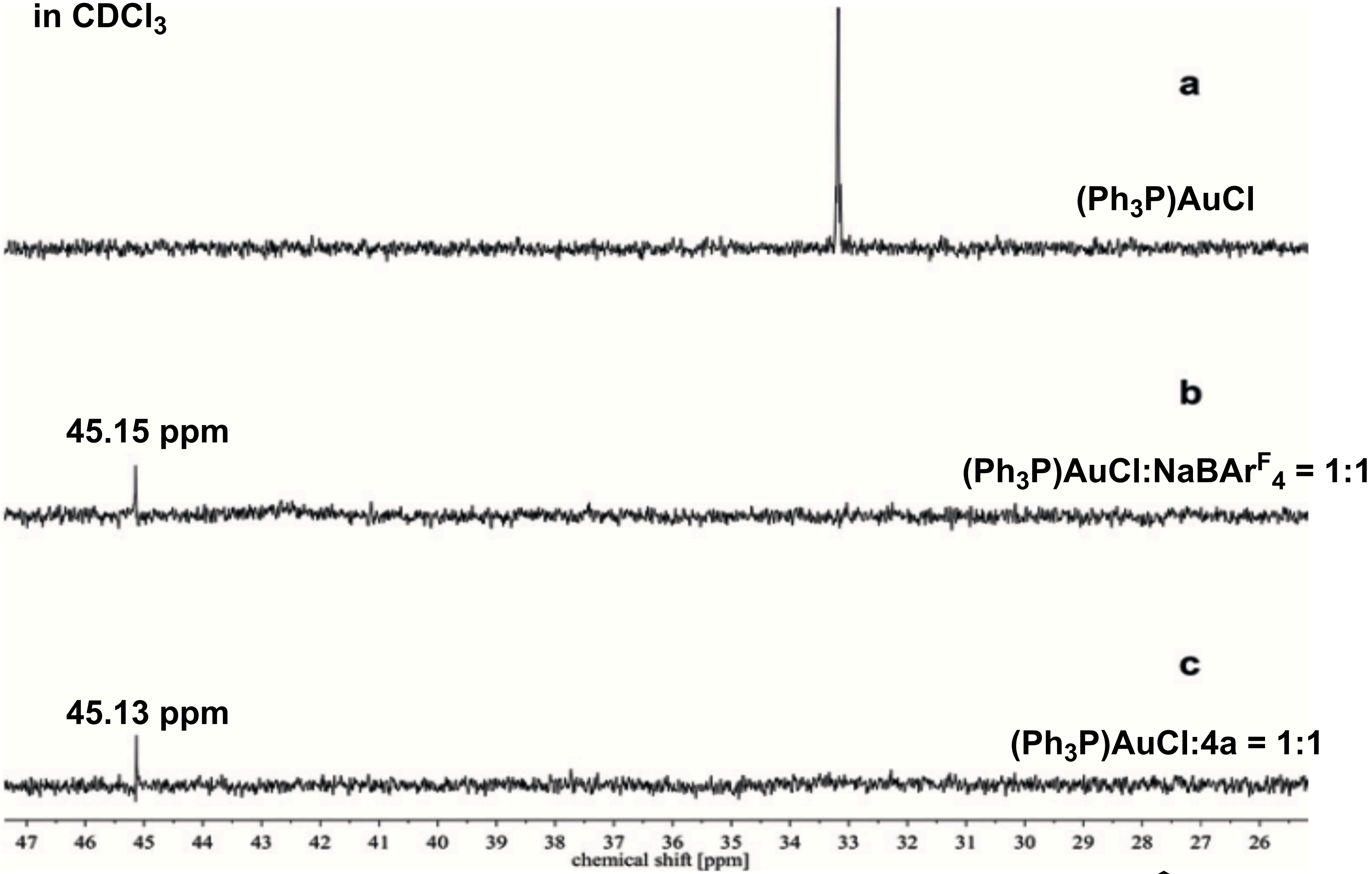


4a

Similar results were observed about cyclization of enyne C.

Wolf, J.; Huber, F.; Erochok, N.; Heinen, F.; Guerin, V.; Legault, C. Y.; Kirsch, S. F.; Huber, S. M. *Angew. Chem. Int. Ed.* **2020**, *59*, 16496.

31P NMR Shift



in $CDCl_3$

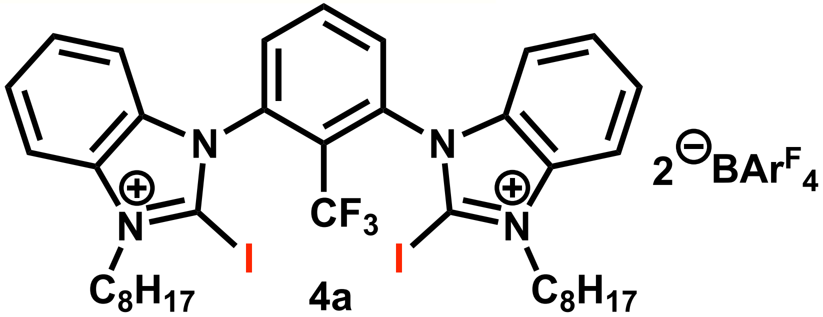
$(Ph_3P)AuCl$

45.15 ppm

$(Ph_3P)AuCl:NaBAr^F{}_4 = 1:1$

45.13 ppm

$(Ph_3P)AuCl:4a = 1:1$



4a

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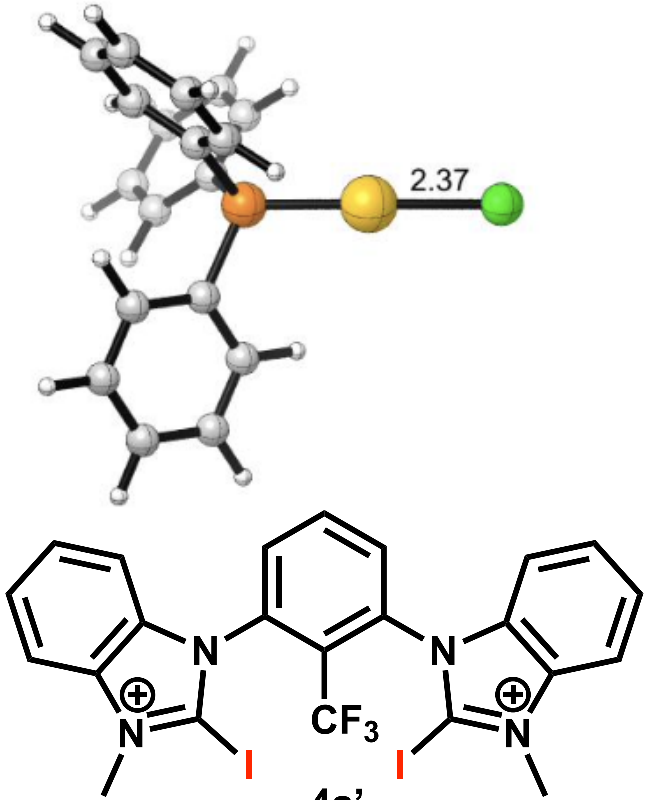
1) Huber. S. M. et al. *Angew. Chem. Int. Ed.* **2020**, *59*, 16496. 2) Maier, M. E. et. al. *Chem. Eur. J.* **2012**, *18*, 14732.

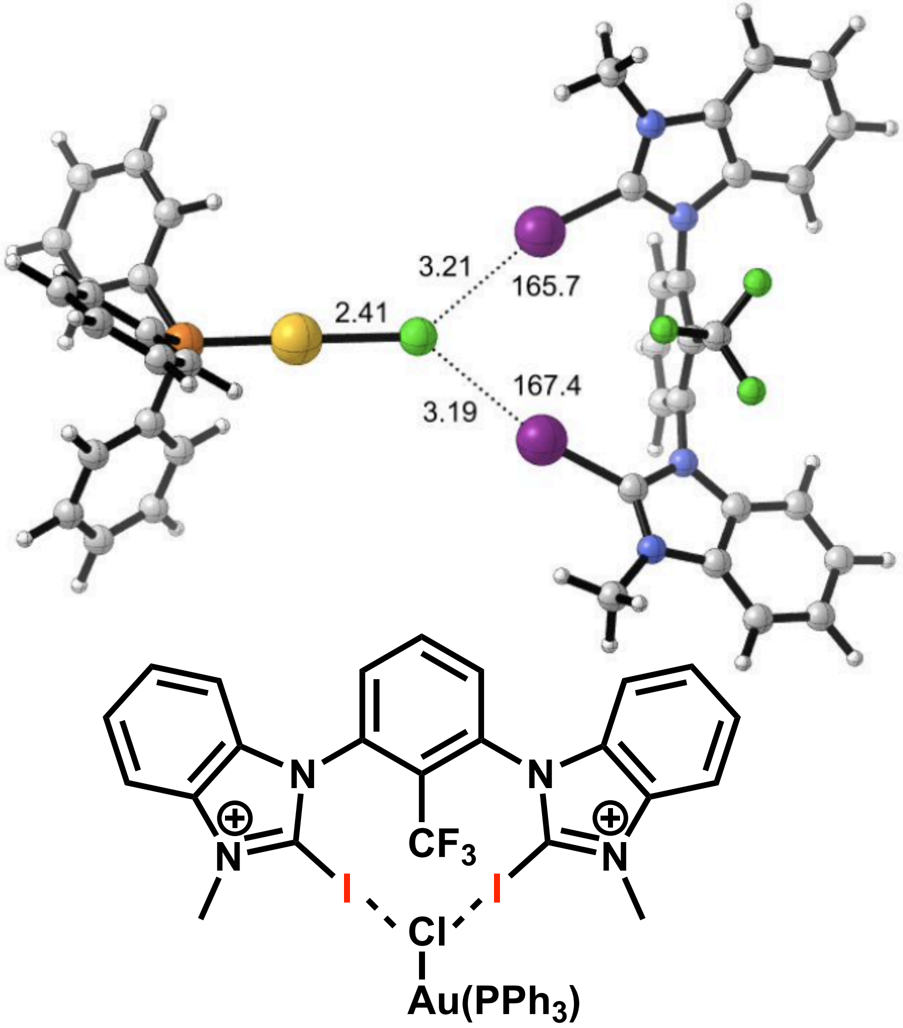
DFT Calculation

$(Ph_3P)AuCl$ +



4a’

0.0 kcal/mol

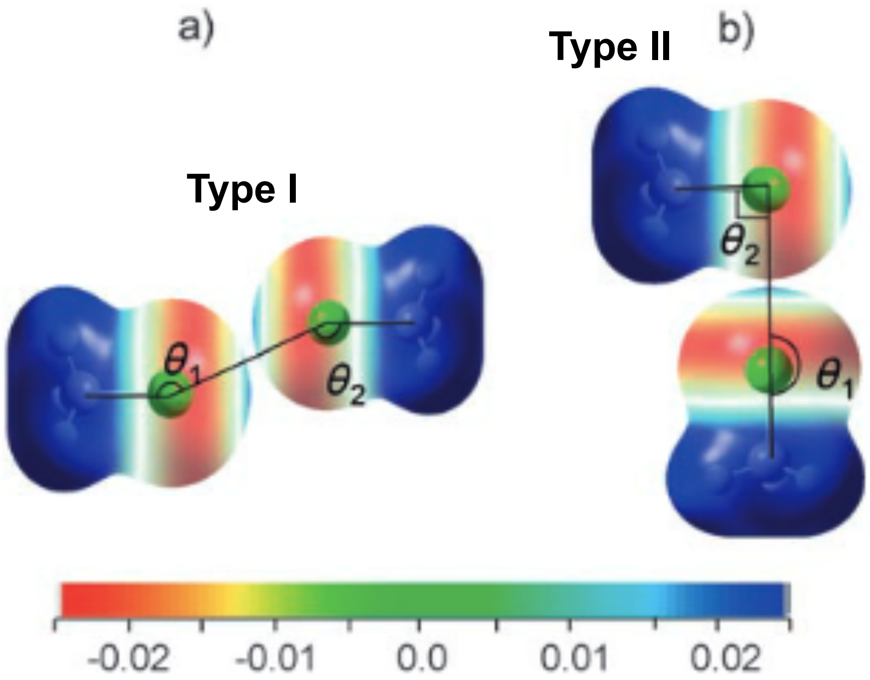


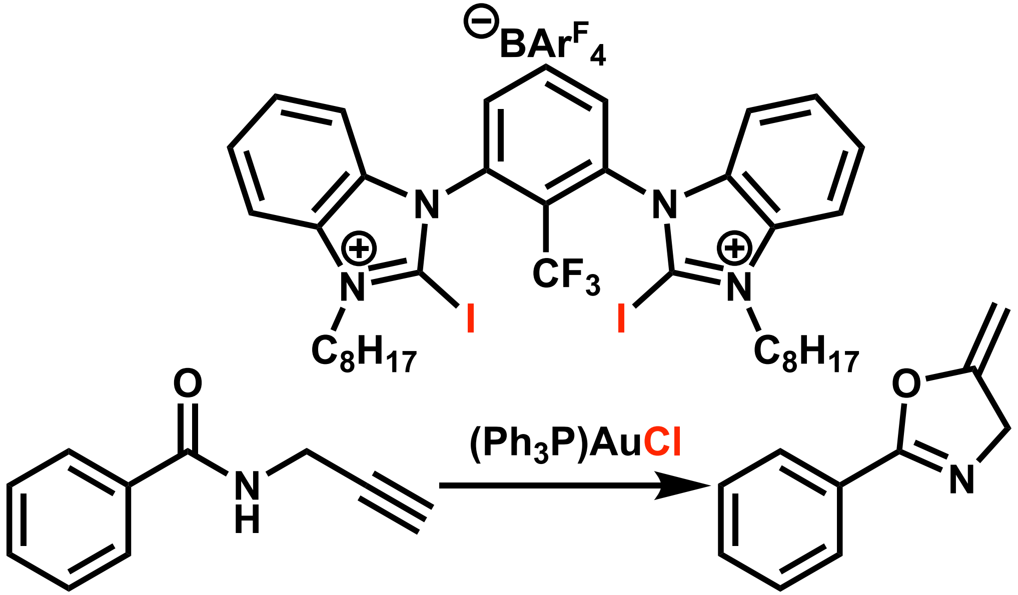
−5.4 kcal/mol

m06-2x-d3 def2-TZYP-(D), SMD18 ($CHCl_3$)

Wolf, J.; Huber, F.; Erochok, N.; Heinen, F.; Guerin, V.; Legault, C. Y.; Kirsch, S. F.; Huber, S. M. *Angew. Chem. Int. Ed.* **2020**, *59*, 16496.

Summary





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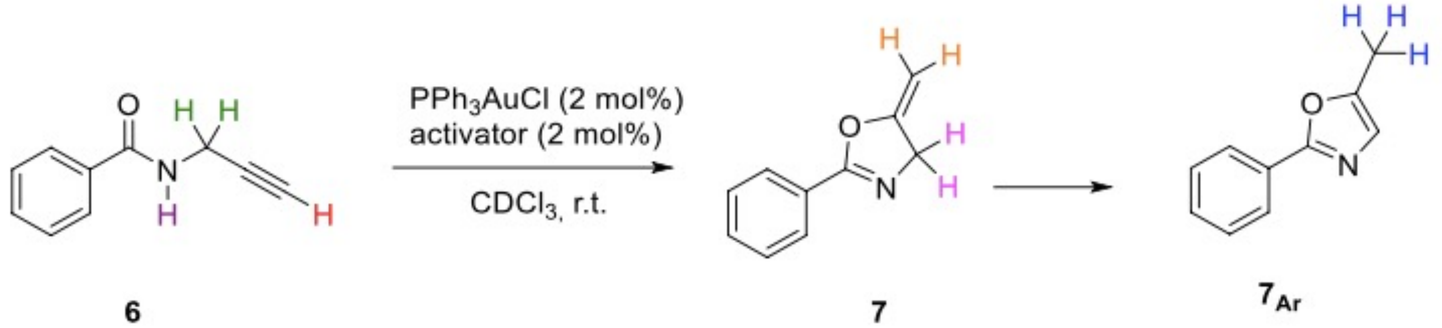
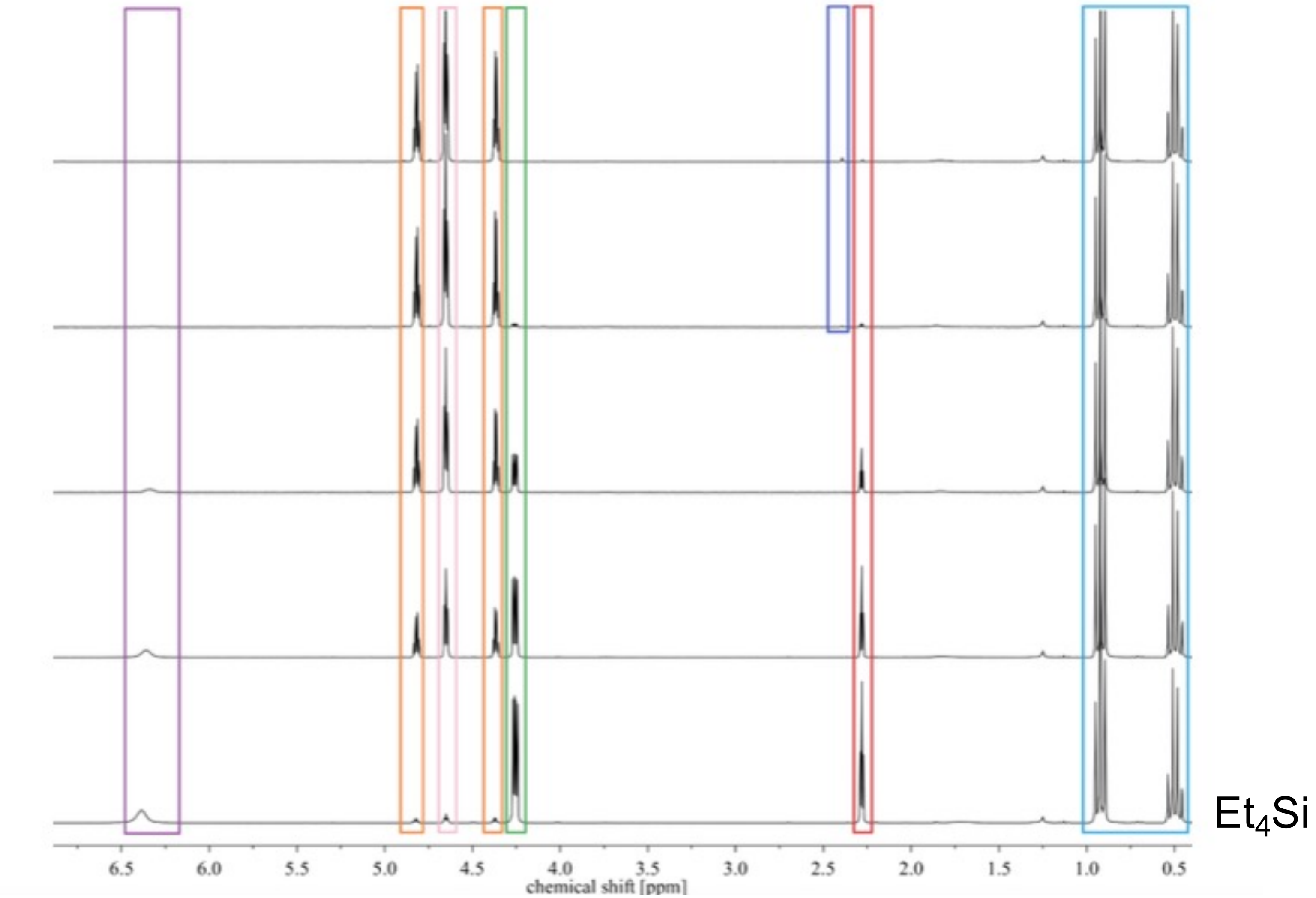
1) Awwadi, F. F.; Willett, R. D.; Peterson, K. A.; Twamley, B. *Chem. Eur. J.* **2006**, *12*, 8952. 2) Wolf, J.; Huber, F.; Erochok, N.; Heinen, F.; Guerin, V.; Legault, C. Y.; Kirsch, S. F.; Huber, S. M. *Angew. Chem. Int. Ed.* **2020**, *59*, 16496.

Apendix

1H NMR of 6, 7, and 7_{Ar}





Synthesis of 4