Systematic Mechanistic Investigation on Cerium Catalyzed Alkane Functionalization

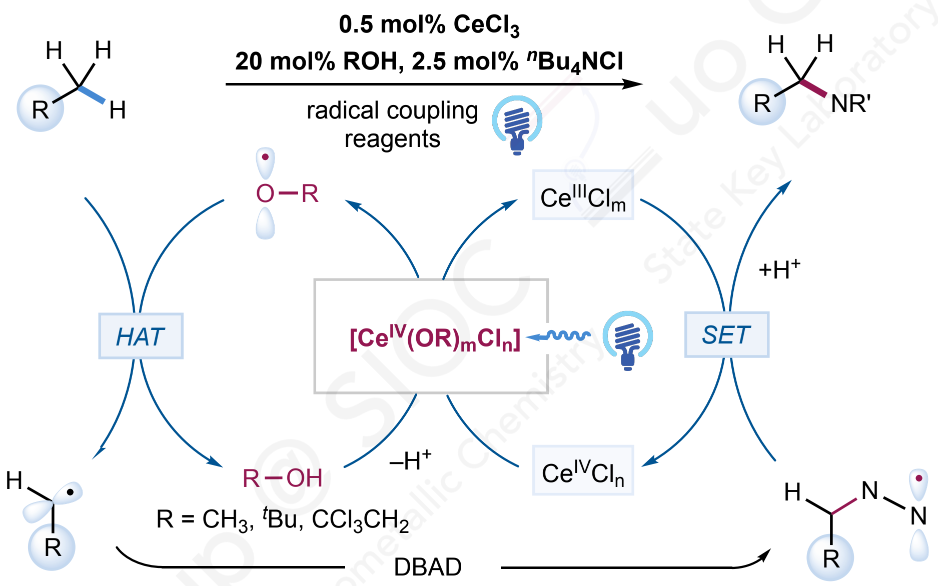
——Who got it wrong, Cl or RO radical？

Qing An

20231026 || Zuo Group || SIOC

Mechanistic investigation on cerium catalyzed alkane functionalization

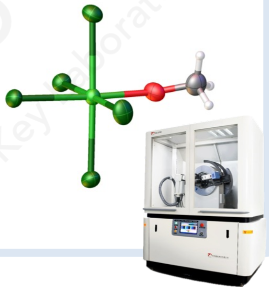
■ Proposed catalytic cycle



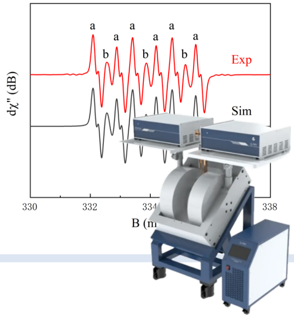
In this proposed catalytic cycle:

- $[Ce(OR)Cl_5]^{2-}$ as the catalytically relevant photoactive species
- $[Ce(OR)Cl_5]^{2-}$ generated RO· under LMCT excitation
- RO· mediated HAT as rate- & selectivity determining step

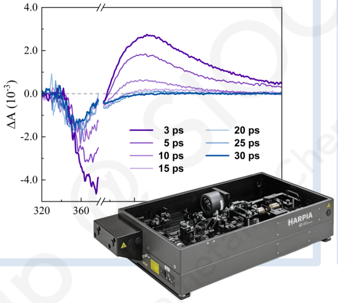
✓ XRD



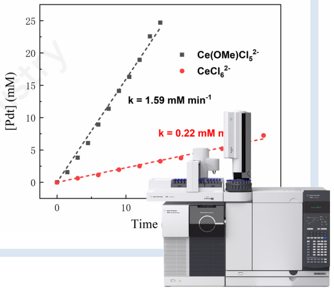
✓ EPR



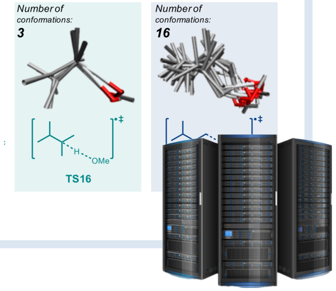
✓ TA



✓ Kinetic analysis

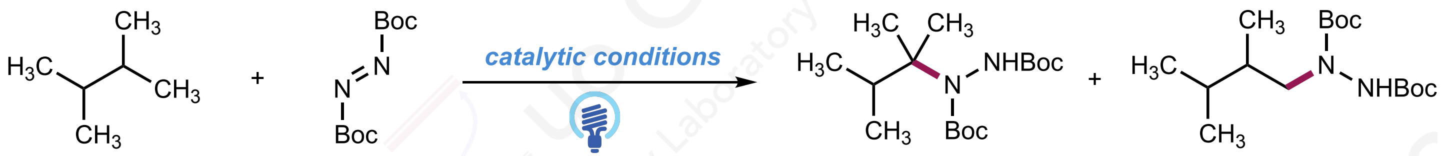


✓ DFT calculation



The possibility of chlorine radical and related complexes as HAT agents

■ Regioselectivity investigations: original condition & metal-free condition



original conditions

0.5 mol% $CeCl_3$

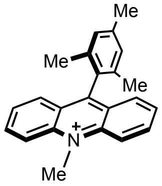
2.5 mol% TABCl

20 mol% alcohol

➡ R–O or Cl or [Cl···ROH] •

metal-free conditions

5 mol% Mes-Acr$^+$



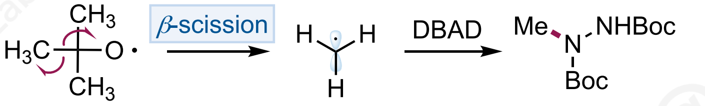
50 mol% TABCl

20 mol% alcohol

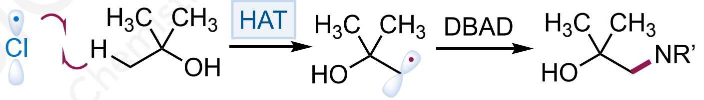
➡ Cl or [Cl···ROH] •

entry	ROH	intrinsic selectivity 3º : 1º (DMB)	yield
1	**MeOH**	**194:1**	76%
2	**CCl_3CH_2OH**	**5:1**	87%
3	***t*BuOH**	**11:1**	48%[a]
4	**none**	**6:1**	11%

entry	ROH	intrinsic selectivity 3º : 1º (DMB)	yield
5	**MeOH**	**6:1**	27%
6	**CCl_3CH_2OH**	**6:1**	23%
7	***t*BuOH**	**6:1**	25%[b]
8	**none**	**6:1**	26%



observed in entry 3

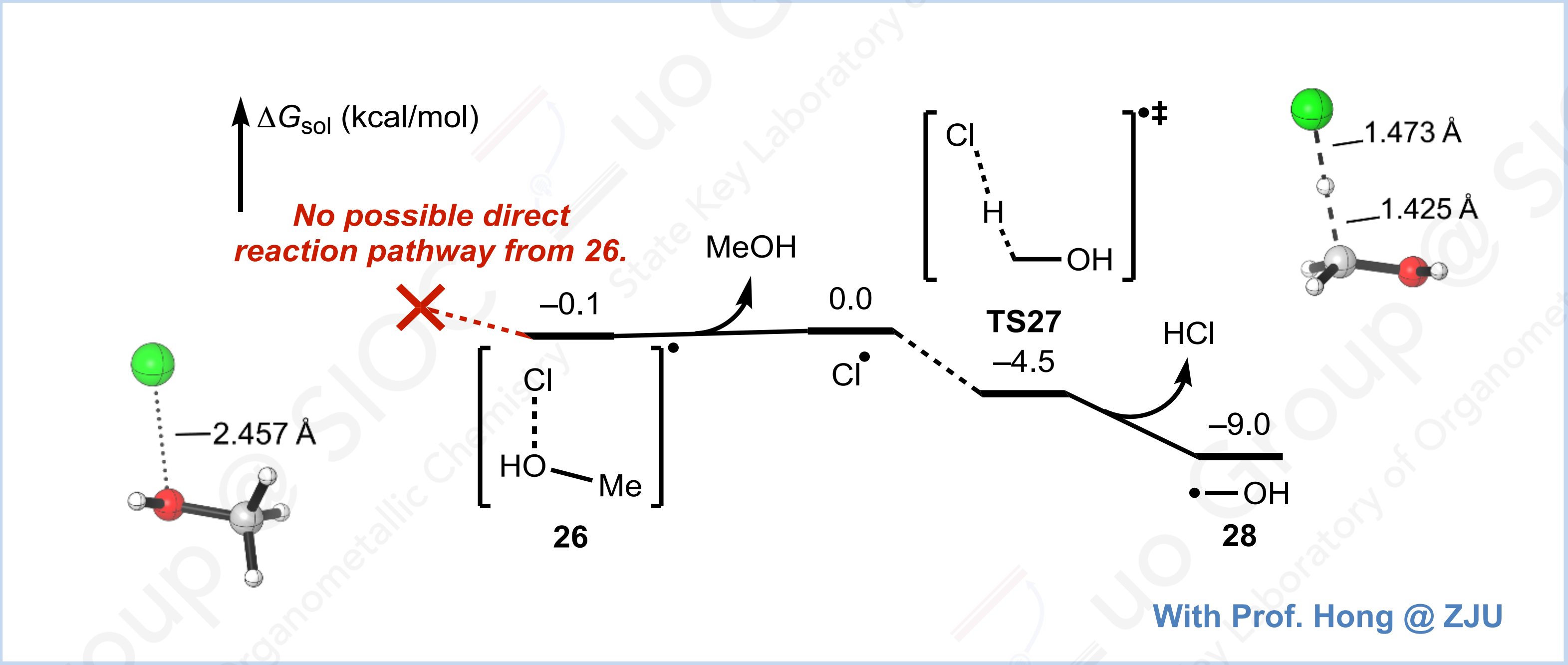


observed in entry 7

➢ **Chlorine radical and related complexes were not responsible for selectivity control**

The possibility of chlorine radical and related complexes as HAT agents

■ TD-DFT calculation for HAT process between chlorine radical and CH_3OH



With Prof. Hong @ ZJU

DLNPO-CCSD(T)/cc-pVTZ-SMD(MeCN)//B3LYP-D3(BJ)/def2-SVP level

- ➢ **Chlorine radical-alcohol complex was precluded by unreasonable HAT transition and barrierless HAT between chlorine radical and CH_3OH**

■ Walsh & Schelter, *Science 2021, 372, 847*

TD-DFT: [Cl···ROH]• as HAT agent was supported by a low-energy transition state

Cerium alkoxide pentachloride complexes as photoactive species

Preparation and characterization for cerium alkoxide complexes

Preparation and Isolation

$$CeCl_6^{2-} + ROH \xrightarrow[\text{dark, anhydrous}]{\text{NaHCO}_3\text{, NaOR or BocNHNBoc}^-} Ce(OR)Cl_5^{2-}$$

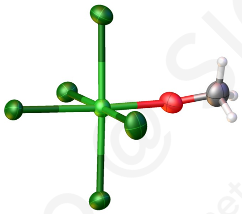
cation: Et_4N^+ or $^nBu_4N^+$

R = CH_3, ^{t}Bu, ^{i}Pr or CH_2CCl_3

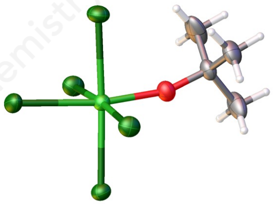
R = CH_3, ^{t}Bu, ^{i}Pr
XRD characterized

- ***moisture sensitive***
- ***photoactive species***
- ***catalytically relevant***
- ***in situ* generated**

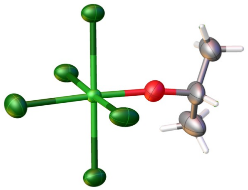
XRD



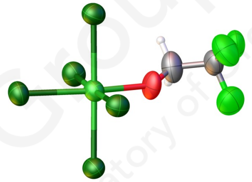
$[Ce(OCH_3)Cl_5]^{2-}$



$[Ce(O^tBu)Cl_5]^{2-}$



$[Ce(O^iPr)Cl_5]^{2-}$



$[Ce(OCH_2CF_3)Cl_5]^{2-}$

^{1}H NMR

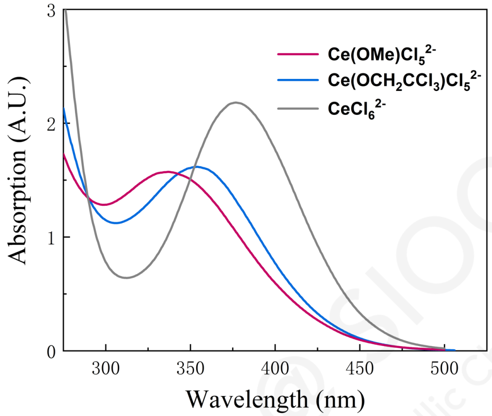
compound	characteristic signal in ^{1}H NMR: chemical shift (δ ppm), multiplicity			
	$–OCH_3$	$–OCH(CH_3)_2$	$–OC(CH_3)_3$	$–OCH_2CCl_3$
ROH	3.23, s	3.82, m	1.16, s	4.10, d
$[Ce(OR)Cl_5]^{2-}$	4.98, s	5.32, m	1.27, s	5.63, s

[a] chemical shift were determined relative to the residual peak of CH_3CN (1.94 ppm).

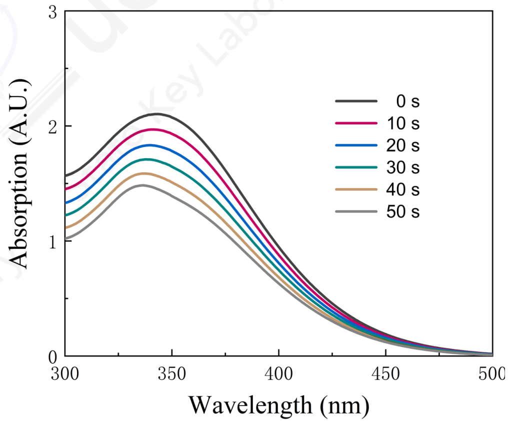
Cerium alkoxide pentachloride complexes as photoactive species

■ Preparation and characterization for cerium alkoxide complexes

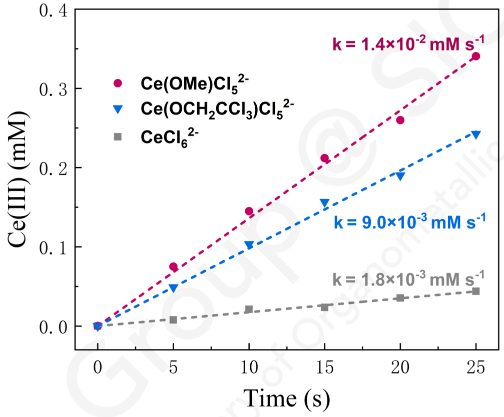
- **UV-vis spectroscopy and steady-state photolysis (375 nm laser irradiation)**



Coordination rendering blue-shifted LMCT band (300–500 nm)

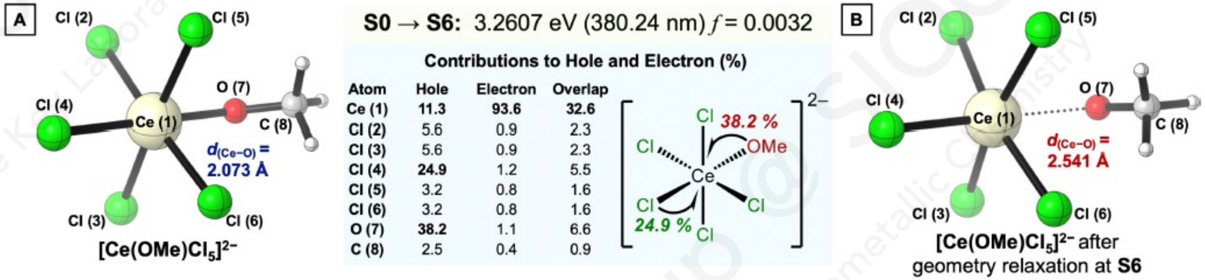


$[Ce(OR)Cl_5]^{2-}$ exhibits superior LMCT homolysis efficiency



Different photolysis rate observed based on the decay of Ce(IV) LMCT band

- **DFT-calculation: Hole-electron analysis of S0 → S6 excitation of $[Ce(OMe)Cl_5]^{2-}$**



$[Ce(OMe)Cl_5]^{2-}$

S0 → S6: 3.2607 eV (380.24 nm) *f* = 0.0032

Contributions to Hole and Electron (%)

Atom	Hole	Electron	Overlap
Ce (1)	11.3	93.6	32.6
Cl (2)	5.6	0.9	2.3
Cl (3)	5.6	0.9	2.3
Cl (4)	24.9	1.2	5.5
Cl (5)	3.2	0.8	1.6
Cl (6)	3.2	0.8	1.6
O (7)	38.2	1.1	6.6
C (8)	2.5	0.4	0.9

$[Ce(OMe)Cl_5]^{2-}$ after geometry relaxation at **S6**

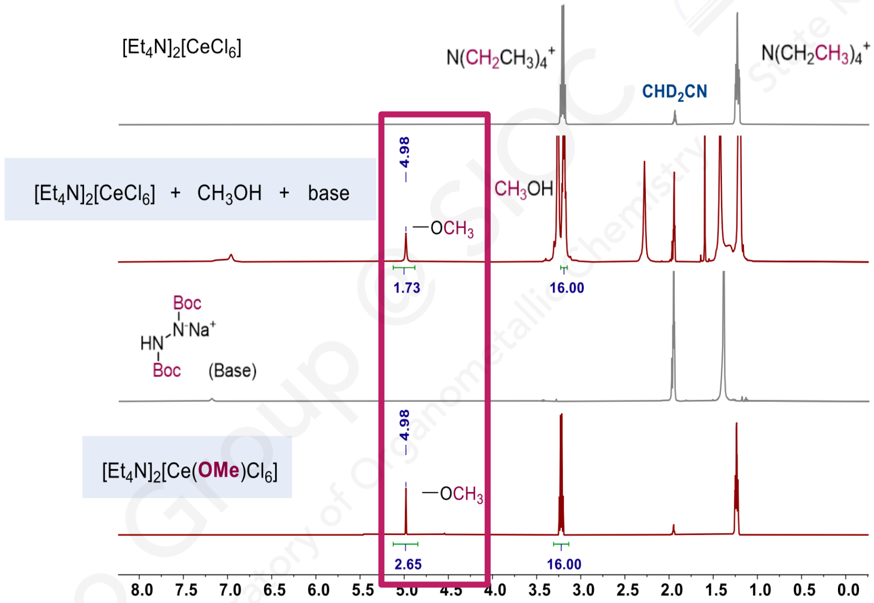
- ➢ **Only the Ce–O bond was significantly elongated during the relaxation**

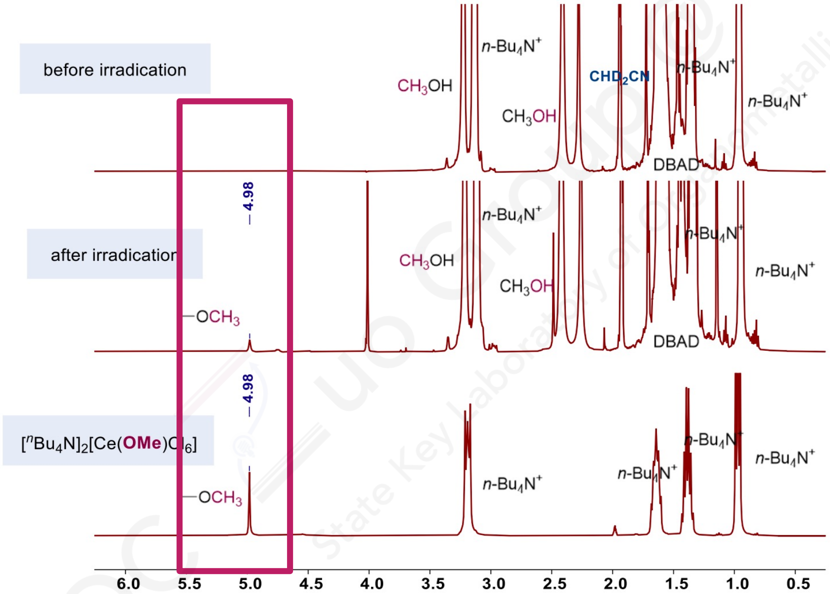
Cerium alkoxide pentachloride complexes as photoactive species

In situ generation of cerium alkoxide complexes under catalytic conditions

$$[CeCl_6]^{2-} + CH_3OH \xrightarrow[\text{dark}]{[BocNNHBoc]^-} [Ce(OCH_3)Cl_5]^{2-}$$

$$CeCl_3 + CH_3OH \xrightarrow[\lambda = 450\ \text{nm}]{\text{DBAD, CyH, TBACl}} [Ce(OCH_3)Cl_5]^{2-}$$





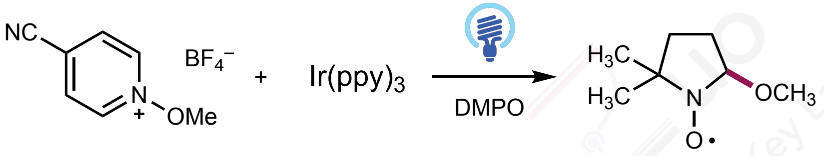
- **$[Ce(OR)Cl_5]^{2-}$ can be generated in the induction period of catalytic reaction**

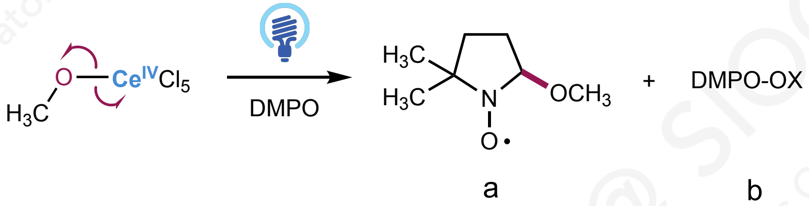
- Walsh & Schelter, *Science 2021, 372, 847*

^{1}H NMR, UV-vis, luminesence: $[Ce(OR)Cl_5]^{2-}$ cannot be generated in catalytic condition (no base)

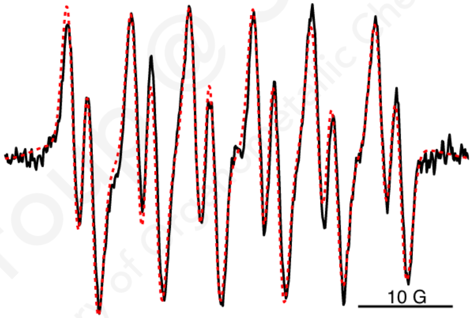
Operando EPR experiments to investigate the identity of ligand-centered radicals

- **Spin-trapping experiments with DMPO as trapping reagent: $[Ce(OCH_3)Cl_5]^{2-}$**



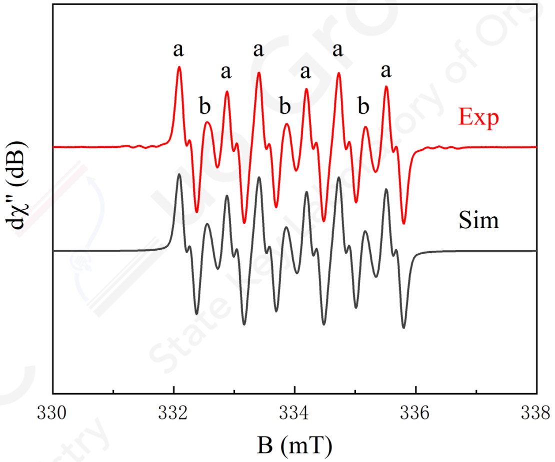


DMPO-OMe: A_N = 13.1 G, A_H = 6.9 G, A_H = 1.9 G



Dagousset, G., *et al.*
Angew. Chem. Int. Ed. **2018**, *57* , 13790.

a. A_N = 13.2 G, A_H = 7.8 G, A_H = 1.6 G
b. A_N = 12.9 G



in accordance with data reported by Dagousset

- **$[Ce(OCH_3)Cl_5]^{2-}$ would generate methoxy radical under LMCT excitation**

Operando EPR experiments to investigate the identity of ligand-centered radicals

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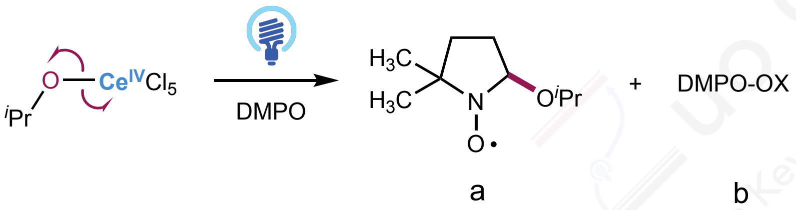
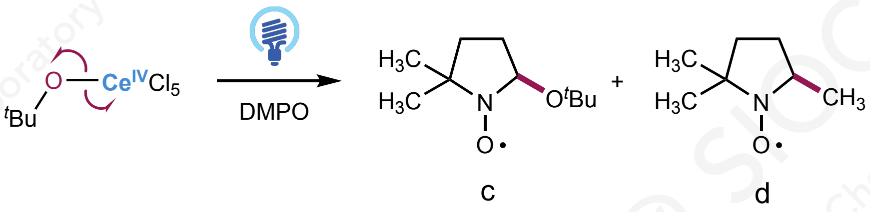


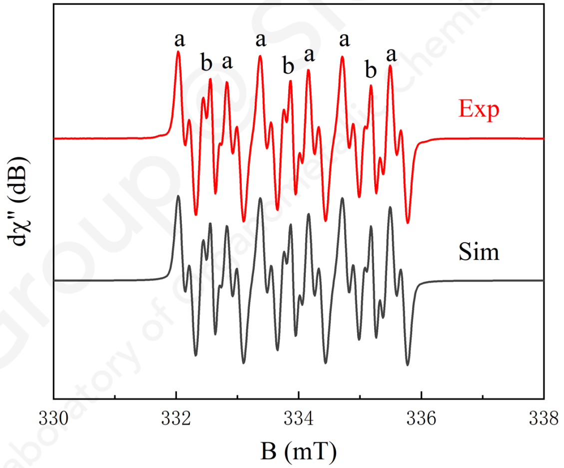


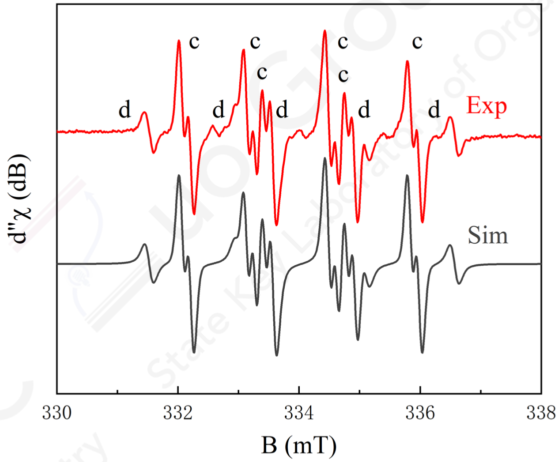
a. A_N = 13.4 G, $A_{H\beta}$ = 7.8 G, $A_{H\gamma}$ = 1.6 G

b. A_N = 12.9 G

c. A_N = 13.5 G, $A_{H\beta}$ = 10.6 G, $A_{H\gamma}$ = 1.3 G, g = 2.0054

d. A_N = 14.2 G, $A_{H\beta}$ = 21.3 G, g = 2.0053





in accordance with data reported by

Hartung, J., et al. *Org. Biomol. Chem.* **2006**, *4* , 2313.

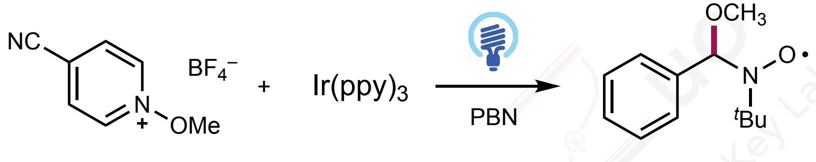
in accordance with data reported by

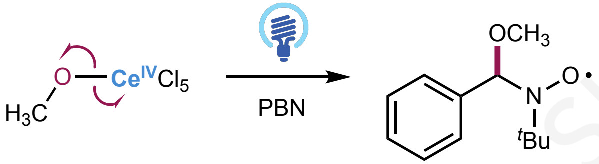
Dagousset, G., *et al. Angew. Chem. Int. Ed.* **2018**, *57* , 13790.

➢ **$[Ce(OR)Cl_5]^{2-}$ would generate alkoxy radical under LMCT excitation**

Operando EPR experiments to investigate the identity of ligand-centered radicals

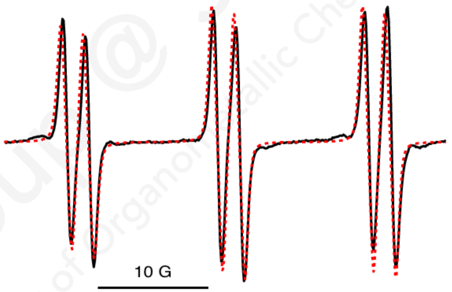
■ Spin-trapping experiments with PBN as trapping reagent: $[Ce(OCH_3)Cl_5]^{2-}$

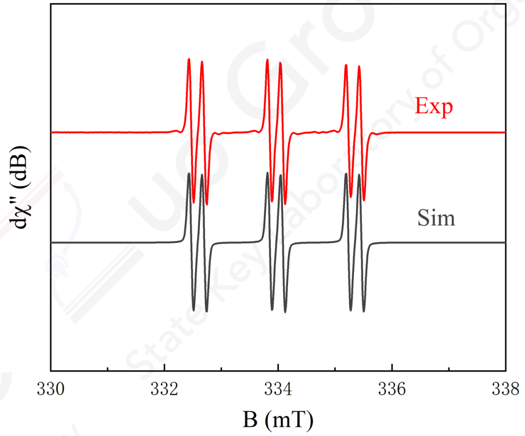




PBN-OMe: $A_N = 13.6$ G, $A_H = 2.0$ G

$A_N = 13.8$ G, $A_H = 2.3$ G





Dagousset, G., *et al.*
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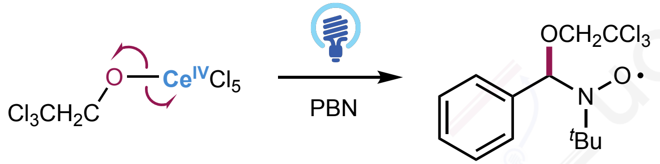
in accordance with data reported by Dagousset

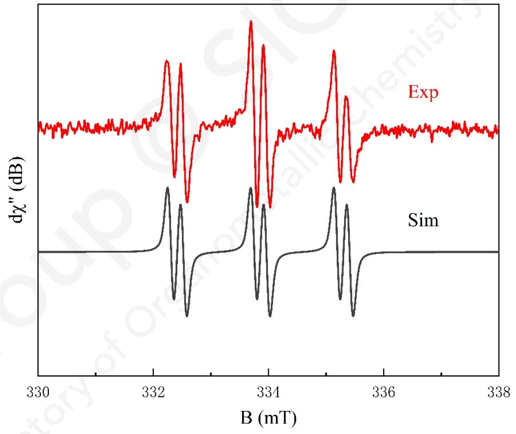
➢ **$[Ce(OCH_3)Cl_5]^{2-}$ would generate methoxy radical under LMCT excitation**

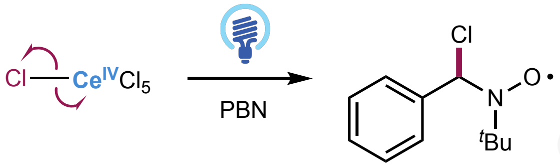
Operando EPR experiments to investigate the identity of ligand-centered radicals

- **Spin-trapping experiments with PBN as trapping reagent: $[Ce(OCH_2CCl_3)Cl_5]^{2-}$, $[CeCl_6]^{2-}$**

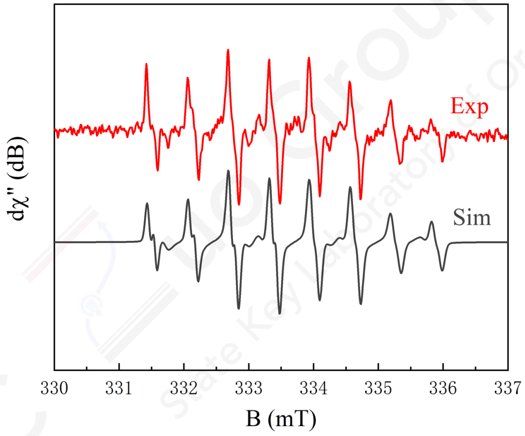


$A_N = 14.4$ G, $A_H = 2.2$ G





$A_N = 12.6$ G, $A_H = 0.8$ G, $A_{Cl\text{-}35} = 6.3$ G, $A_{Cl\text{-}37} = 5.1$ G,



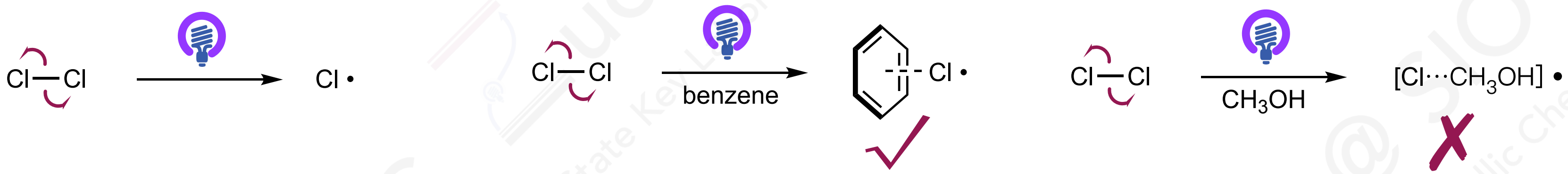
in accordance with data reported by
Janzen, E.G.S., *et al. Inorg. Chim. Acta*
1984, *83,L7–L8.*

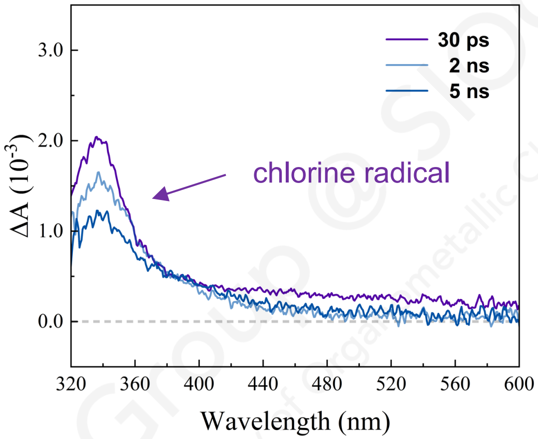
- **Walsh & Schelter, *Science 2021, 372, 847***

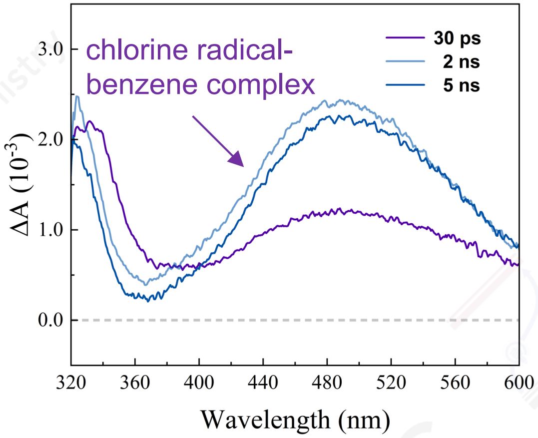
TD-DFT: $[Ce(OR)Cl_5]^{2-}$ would generate chlorine radical, not alkoxy radical under LMCT excitation

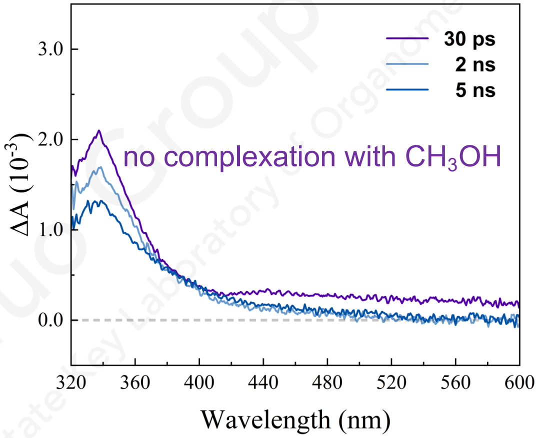
TA spectroscopy experiments to probe the LMCT process at fs timeframe

■ Detection of the signal of chlorine radical and related complexes







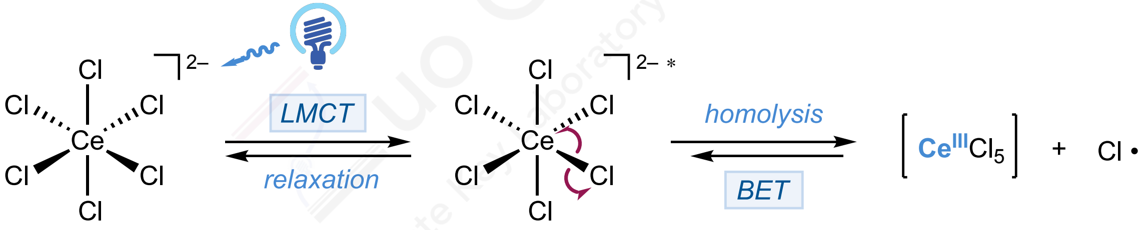


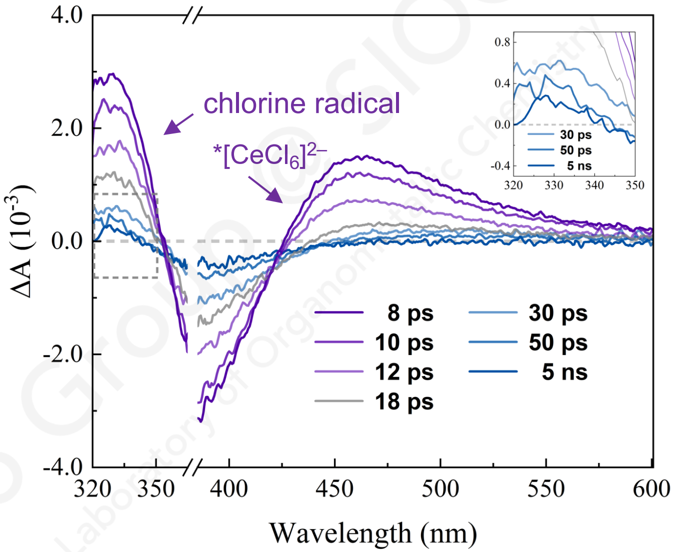
in accordance with data reported by
Ingold, K. U. et al., *J. Am. Chem. Soc.* **1985**, *107*, 5464.

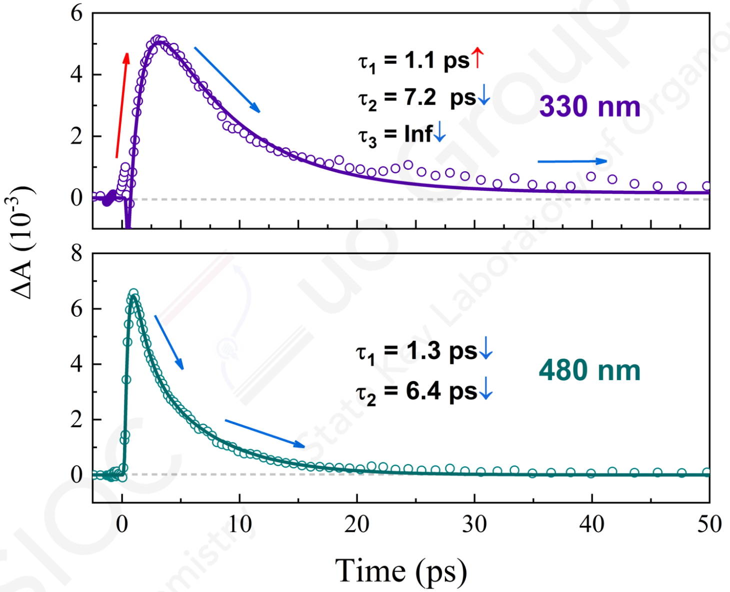
- ➢ **$[Cl\cdots ROH]\bullet$ would not form at catalytically relevant alcohol concentration**

TA spectroscopy experiments to probe the LMCT process at fs timeframe

■ Transient absorption experiments for $[CeCl_6]^{2-}$



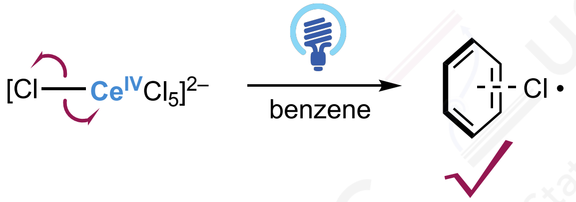


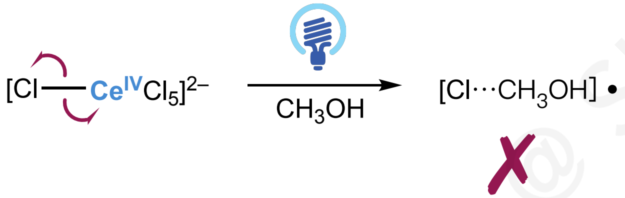


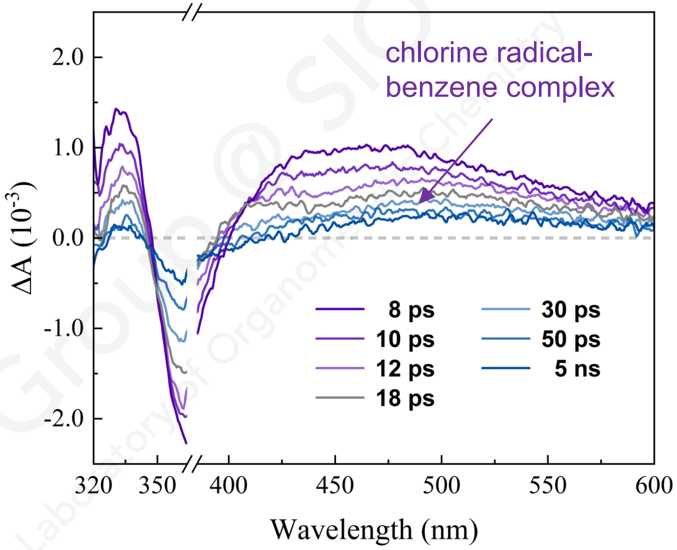
➢ **$[CeCl_6]^{2-}$ would generate chlorine radical under LMCT excitation**

TA spectroscopy experiments to probe the LMCT process at fs timeframe

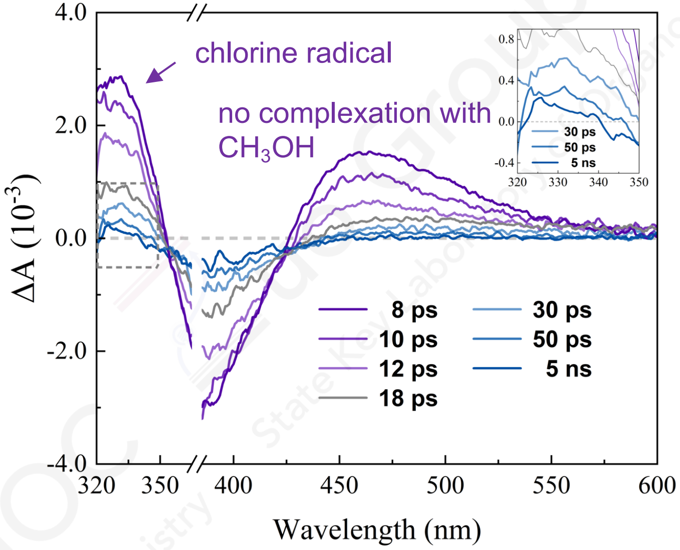
■ Transient absorption experiments for $[CeCl_6]^{2-}$ in the presence of benzene or alcohols







chlorine radical-benzene complex



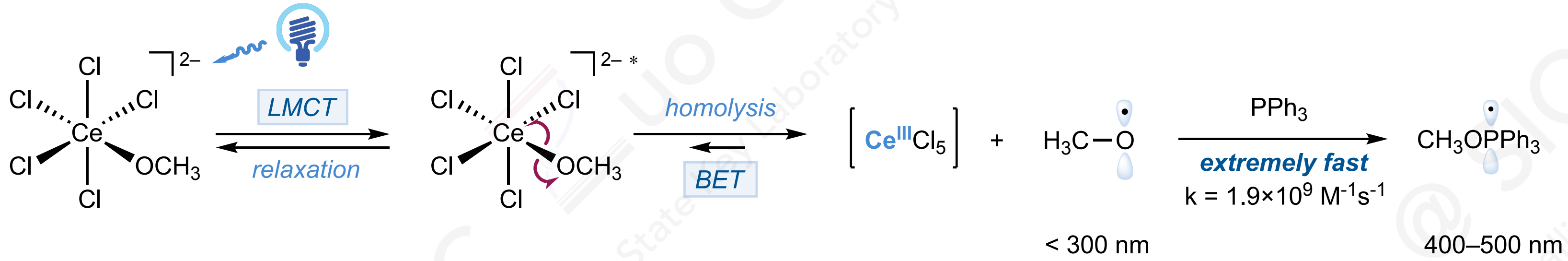
chlorine radical

no complexation with CH_3OH

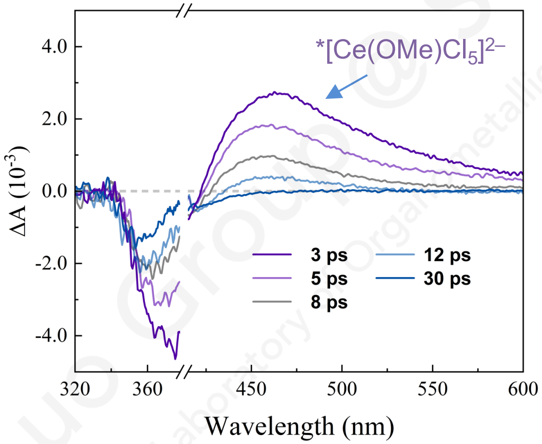
➢ **$[Cl\cdots ROH]$• would not form at catalytically relevant alcohol concentration**

TA spectroscopy experiments to probe the LMCT process at fs timeframe

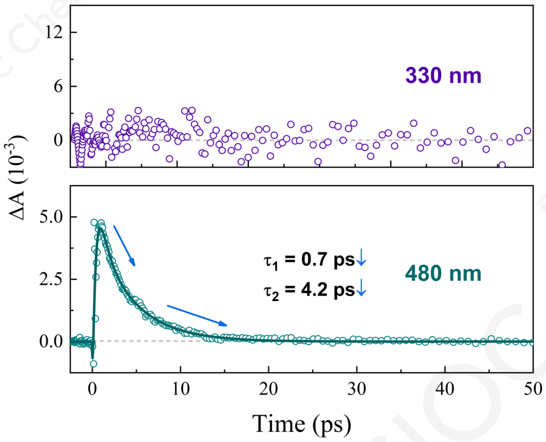
■ Transient absorption experiments for $[Ce(OCH)_3Cl_5]^{2-}$



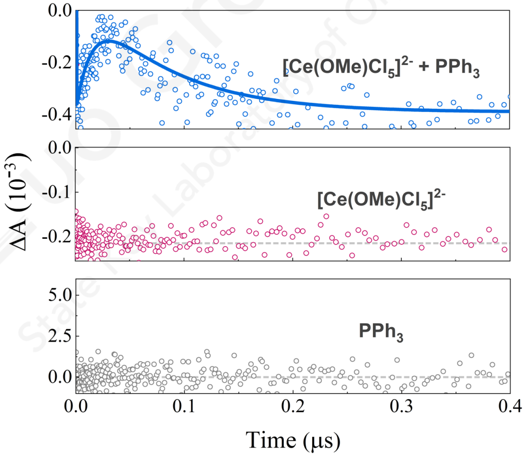
$[Ce(OMe)Cl_5]^{2-}$ in CD_3CN



Kinetic trace at 330 nm, 480 nm



$[Ce(OMe)Cl_5]^{2-}$ and PPh_3
Kinetic trace at 430 nm



no absorption in the range of 320–350 nm precluded the generation of Cl·

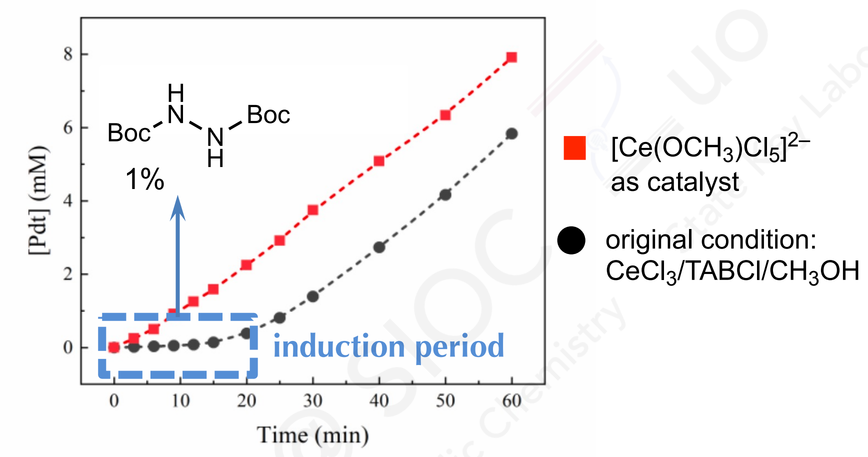
Small, R. D. et al.
J. Am. Chem. Soc. **1979**, *101*, 3780.

➢ **Chlorine radical was precluded and alkoxy radical was confirmed**

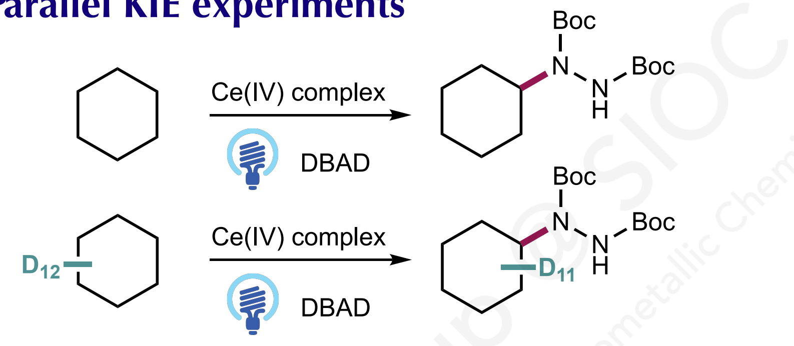
Kinetic investigations on the HAT process

Kinetic studies on cyclohexane amination

Kinetic profiles



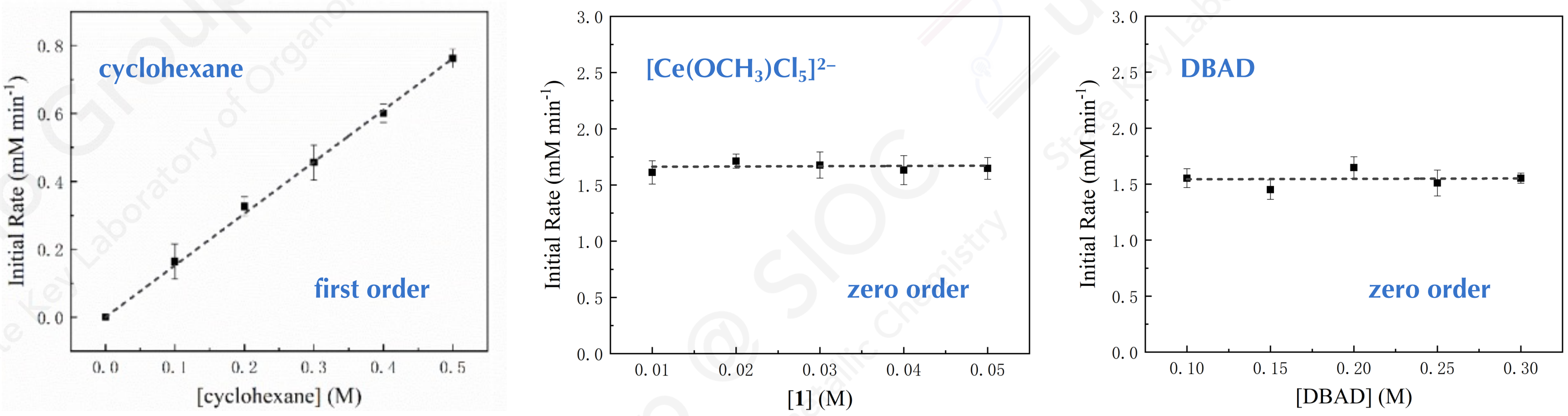
Parallel KIE experiments



$[Ce(OCH_3)Cl_5]^{2-}$ $k_H/k_D = 5.5$

$[CeCl_6]^{2-}$ $k_H/k_D = 1.1$

Reaction order: First order in alkane; zero order in DBAD and $[Ce(OCH_3)Cl_5]^{2-}$

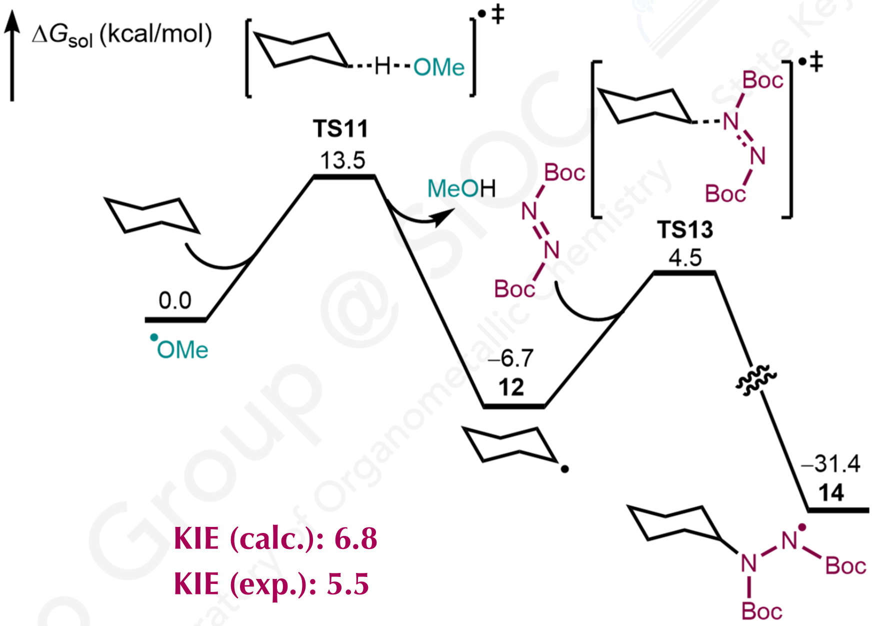


➢ $[Ce(OCH_3)Cl_5]^{2-}$ was catalytically relevant intermediate & CH_3O• mediated HAT was RDS

Kinetic investigations on the HAT process

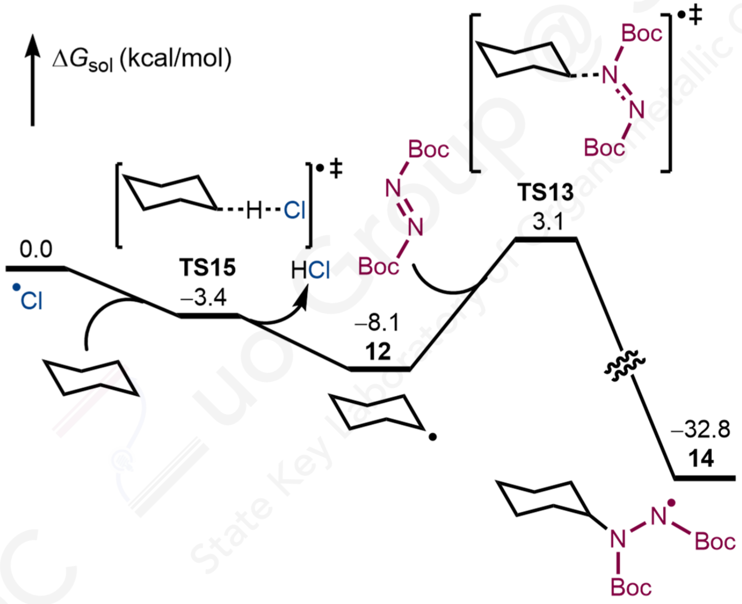
■ DFT calculations on the radical-mediated HAT process

Methoxy radical mediated HAT



KIE (calc.): 6.8
KIE (exp.): 5.5

chlorine radical mediated HAT



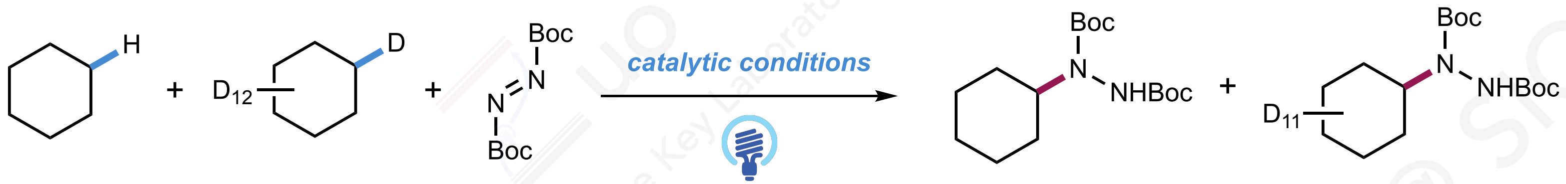
DLNPO-CCSD(T)/cc-pVTZ-SMD(MeCN)//B3LYP-D3(BJ)/def2-SVP level

With Prof. Hong @ ZJU

➢ **CH_3O• mediated HAT was the rate-determining step (RDS) for the overall amination**

Kinetic investigations on the HAT process

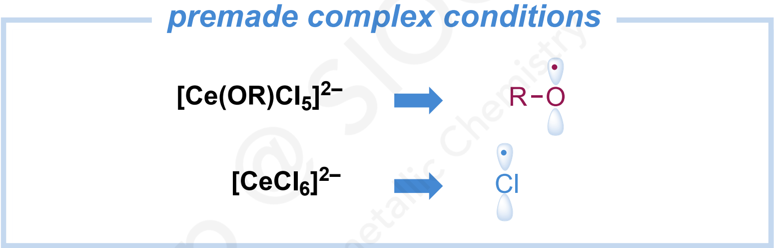
■ Competitive KIE experiments



cyclohexane:d_{12}-cyclohexane = 1:1

3-2a

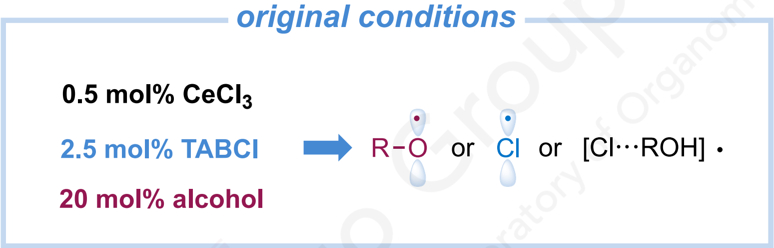
3-2b



premade complex conditions

$[Ce(OR)Cl_5]^{2-}$ ➡ R–O

$[CeCl_6]^{2-}$ ➡ Cl



original conditions

0.5 mol% $CeCl_3$

2.5 mol% TABCl

20 mol% alcohol

➡ R–O or Cl or [Cl···ROH] •

entry	**premade complex** 0.1 mmol Ce(IV) complex	KIE	yield
1	$[Ce(OMe)Cl_5]^{2-}$	5.1	26%
2	$[CeCl_6]^{2-}$	1.1	12%

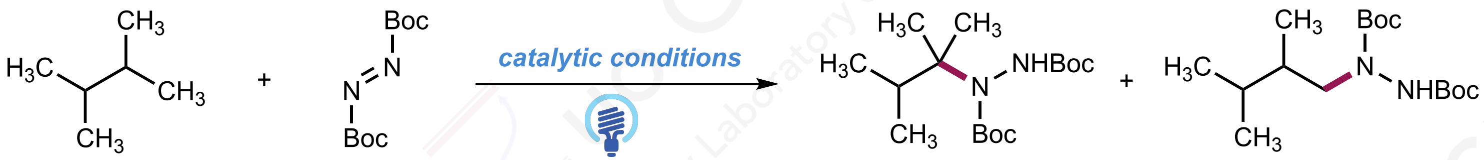
entry	**original conditions** 0.5 mol% $CeCl_3$, 2.5 mol% $n$$Bu_4NCl$	KIE	yield
3	with 20 mol% MeOH	5.1	19%
4	without alcohol	1.1	9%

[a] Yields and ratios were determined by GC-FID.

➢ **Alkoxy radicals were exclusive HAT species in the original conditions**

Regioselectivity investigations on the amination of feedstock alkanes

■ Regioselectivity investigations: premade complex conditions & chloride-free conditions



premade complex conditions

0.5 mol% $[Ce(OR)Cl_5]^{2-}$

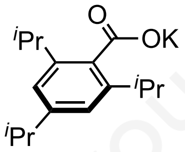
20 mol% alcohol

chloride-free conditions

0.5 mol% $(NH_4)_2Ce(NO_3)_6$

2.5 mol% ligand

20 mol% alcohol



entry	**ROH**	**intrinsic selectivity** 3° : 1° (DMB)	yield
1	**MeOH**	**194:1**	64%
2	**CCl_3CH_2OH**	**5:1**	74%
3	**none, with $CeCl_6^{2-}$**	**6:1**	70%

entry	**ROH**	**intrinsic selectivity** 3° : 1° (DMB)	yield
4	**MeOH**	**194:1**	41%
5	**CCl_3CH_2OH**	**5:1**	63%
6	**none**	**n.d.**	trace

[a] Yields and ratios were determined by GC-FID.

- ➢ **Alkoxy radicals were the exclusive HAT species and chloride only as supporting ligand**

■ Walsh & Schelter, *Science 2021, 372, 847*

^{1}H NMR: identical ratios were observed in the absence or presence of CCl_3CH_2OH

Regioselectivity investigations on the amination of feedstock alkanes

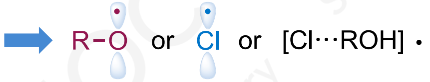
■ Regioselectivity investigations: premade complex conditions & chloride-free conditions

original conditions

0.5 mol% $CeCl_3$

2.5 mol% TABCl

20 mol% alcohol

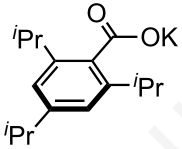


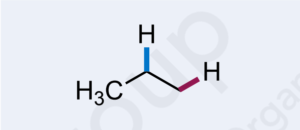
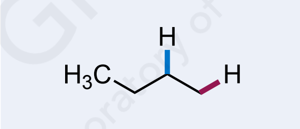
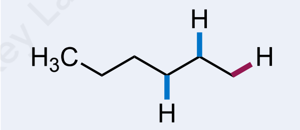
chloride-free conditions

0.5 mol% $(NH_4)_2Ce(NO_3)_6$

2.5 mol% ligand

20 mol% alcohol



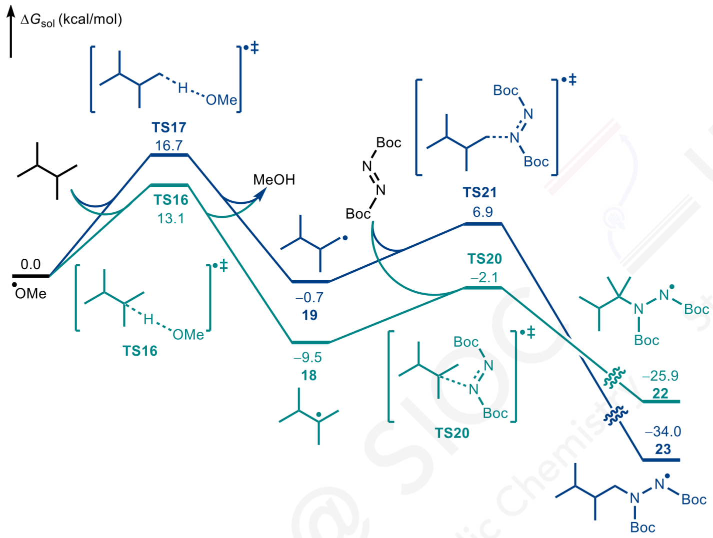
alkanes	original conditions	2º:1º	yield	chloride-free conditions	2º:1º	yield
	MeOH	11.7:1	39%	MeOH	12:1	39%
	TCE	3:1	70%	TCE	3:1	65%
	MeOH	12:1	72%	MeOH	12:1	52%
	TCE	2.5:1	76%	TCE	2.5:1	76%
	MeOH	15:18:1	70%	MeOH	16:18:1	51%
	TCE	2.5:2.5:1	72%	TCE	2.5:2.5:1	77%

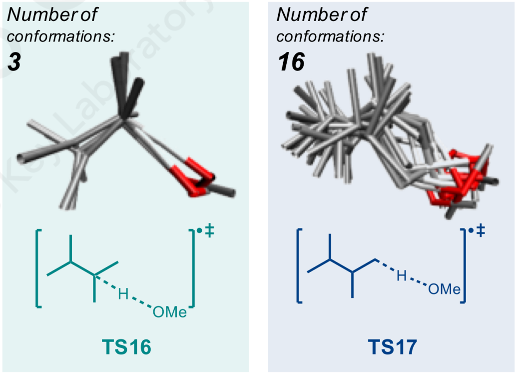
[a] Yields and ratios were determined by GC-FID.

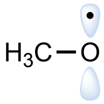
➢ **Alkoxy radicals were the exclusive HAT species and chloride only as supporting ligand**

DFT calculations on photoexcitation and radical-mediated HAT

■ The possibility of chlorine radical and related complexes as selective HAT agents



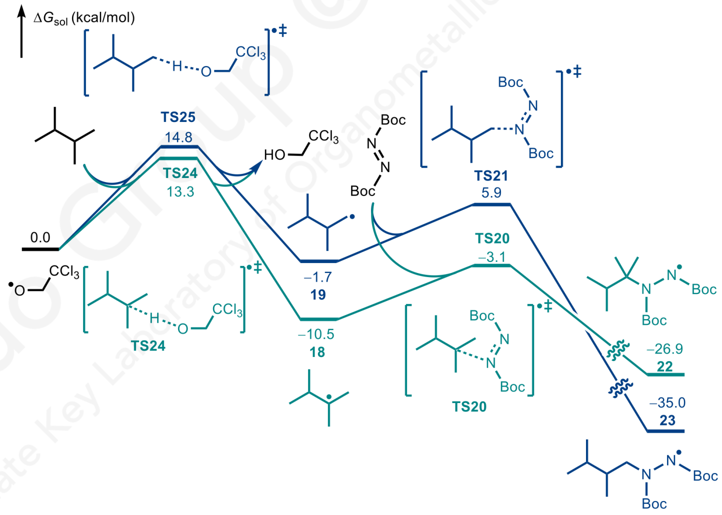


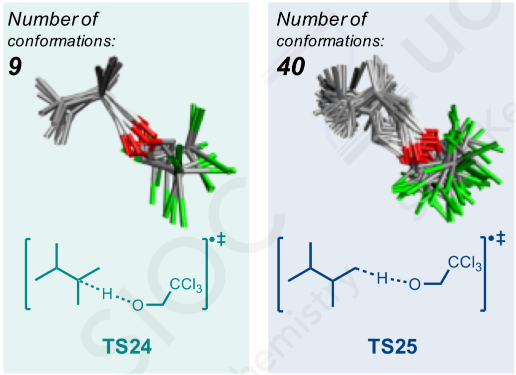


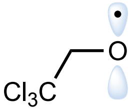
selectivity (calc.): 152:1

selectivity (exp.): 194:1

DLNPO-CCSD(T)/cc-pVTZ-SMD(MeCN)//B3LYP-D3(BJ)/def2-SVP level







selectivity (calc.): 12:1

selectivity (exp.): 5:1

With Prof. Hong @ ZJU

➢ **Alkoxy radical mediated HAT is rate- and selectivity-determining step**

Mechanistic investigation on cerium catalyzed alkane functionalization

Importance of Ce/ROH loading ratio

original conditions

0.5 mol% $CeCl_3$
2.5 mol% TABCl
20 mol% alcohol
→ Ce : ROH = 1 : 40

Walsh & Schelter, 2021

5 mol% $[Et_4N]_2[CeCl_6]$
20 mol% alcohol
→ Ce : ROH = 1 : 4

entry	catalytic conditions	CH_3OH loading	Ce:Cl:ROH	DMB regioselectivity (3° : 1°)	cyclohexane KIE (P_H : P_D)
1	0.5 mol% $Ce(OTf)_3$, 3 mol% $^n Bu_4NCl$	20 mol%	1:6:40	194:1	5.0
2	2 mol% $Ce(OTf)_3$, 12 mol% $^n Bu_4NCl$	20 mol%	1:6:10	27:1	3.0
3	5 mol% $Ce(OTf)_3$, 30 mol% $^n Bu_4NCl$	20 mol%	1:6:4	13:1	1.9

[a] Yields and ratios were determined by GC-FID.

- ➢ **High ratio of alcohol is necessary to ensure alkoxy radicals as predominant HAT agents**

Mechanistic investigation on cerium catalyzed alkane functionalization

■ Walsh & Schelter's work vs. this work

1. *in situ* formation of [$CeORCl_n$] (photoactive species)

Walsh and Schelter, Science 2021

- **Observations:** Mixing of $[NEt_4]_2[CeCl_6]$ with Cl_3CCH_2ONa generated $[Ce(OCH_2CCl_3)Cl_5]^{2-}$ However, mixing $[NEt_4]_2[CeCl_6]$ with Cl_3CCH_2OH does not generate $[Ce(OCH_2CCl_3)Cl_5]^{2-}$, as determined by ^1H NMR and UV-Vis.
- **Observation:** Irradiation of mixture of $[NEt_4]_2[CeCl_6]$ and Cl_3CCH_2OH does not generate $[Ce(OCH_2CCl_3)Cl_5]^{2-}$, as determined by UV-Vis.

➢ **Conclusion: Alcohol coordination to [Ce] does not occur.**

This work

- **Observations:** Mixing of $[CeCl_6]^{2-}$ with NaOR generated the corresponding $[Ce(OR)Cl_5]^{2-}$ complex. Mixing $[CeCl_6]^{2-}$ with ROH generated the corresponding $[Ce(OR)Cl_5]^{2-}$ complexes in the presence of base, such as $NaHCO_3$ or $[BocNNHBoc]^-$, as determined by XRD and ^1H NMR.
- **Observation:** Irradiation of mixture of $CeCl_3$, DBAD, and ROH generated the corresponding $[Ce(OR)Cl_5]^{2-}$ complexes, as determined by ^1H NMR.

➢ **Conclusion: Alcohol coordination to [Ce] does occur through generation of basic $[BocNNHBoc]^-$ through photoinduced reduction of DBAD by [Ce(III)] during induction period.**

Mechanistic investigation on cerium catalyzed alkane functionalization

■ Walsh & Schelter's work vs. this work

2. photoexcitation to release alkoxy radical (photo-generated radical species)

Walsh and Schelter, Science 2021

- **Observations:** TD-DFT calculation indicated the excited state of $[CeOCH_2CCl_3Cl_5]^{2-}$ leads to chlorine radical loss rather than RO• loss.

- **Observation:** No direct experimental study of heteroatom-centered radical generation from $[Ce(OR)Cl_5]^{2-}$ was described. Irradiation of $[NEt_4]_2[Ce(OCH_2Cl_3)Cl_5]$ in CD_3CN generated $ClCD_2CN$, $NCCD_2CD_2CN$, "$[NEt_4]_2[Ce^{III}Cl_5]$", and $DOCH_2Cl_3$ "presumably" through a "a quick acid-base reaction between DCl and" $[Ce]$-(OCH_2CCl_3) species after presumed Cl• HAT.

This work

- **Observations:** TD-DFT with more comprehensive analysis of MOs identified S0 to S6 featuring viable RO-to-Ce LMCT; structural relaxation indicated that Ce–OR bond was significantly elongated

- **Observation: 1. Operando EPR spin-trapping experiments** with $[Ce(OR)Cl_5]^{2-}$ confirmed RO• generation (R = Me, Cl_3CCH_2, ${}^tBu$), and precluded the generation of chlorine radical by comparison to EPR spin-trapping experiments with $CeCl_6^{2-}$. In the case of $[Ce(O^tBu)Cl_5]^{2-}$, methylated spin-trap products were observed, presumably stemming from scission of tert-butoxy radical to generate methyl radical.

  2. Transient absorption experiments with $[Ce(OCH_3)Cl_5]^{2-}$ precluded the generation of chlorine radical in contrast to TA experiments

Mechanistic investigation on cerium catalyzed alkane functionalization

■ Walsh & Schelter's work vs. this work

- ➢ **Conclusion: Alkoxy radical cannot be generated even if $[Ce(OCH_2CCl_3)Cl_5]^{2-}$ is relevant photoactive species**

with $CeCl_6^{2-}$ and Cl_2 photolysis, supported the generation of methoxy radical via the observation of CH_3OPPh_3 radical.

- ➢ **Conclusion: LMCT excitation of $[Ce(OR)Cl_5]^{2-}$ exclusively generates RO•.**

3. alkoxy radical-mediated HAT (C–H abstraction species)

Walsh and Schelter, Science 2021

- **Observations:** In DFT calculation, chlorine radical forms a stabilized complex with free alcohol, with substantial spin density on O. No computed pathway for HAT is presented, not a computed explanation of varying regioselectivities for different chlorine radical-alcohol complexes.
- **Observation:** Radical trapping experiments are provided in support of chlorine

This work

- **Observations:** Transient absorption experiments with Cl_2 photolysis in the absence and presence of alcohols indicated no complexation between chlorine radical and alcohols, whereas complexation between chlorine radical and benzene has been confirmed via the detection of the new absorption band.
- **Observation:** In high-level DFT calculations, chlorine radical-alcohol complex does not

Mechanistic investigation on cerium catalyzed alkane functionalization

Walsh & Schelter's work vs. this work

radical-alcohol complex, which require the assumption that alkoxide radical is not generated.

- **Observation:** Addition of ^{t}BuOH to $[CeCl_6]^{2-}$ catalyzed alkane amination resulted in altered regioselectivity cf. $[CeCl_6]^{2-}$ alone (2,3-dimethylbutane).
- **Observation:** Addition of Cl_3CH_2OH to $[CeCl_6]^{2-}$ catalyzed alkane amination resulted in identical regioselectivity cf. $[CeCl_6]^{2-}$ alone (n-hexane).

have a viable HAT pathway. The only feasible channel for this radical complex is to dissociate the alcohol and undergoes a classic, barrierless chlorine radical mediated HAT. The only productive pathway we can find for the reaction between chlorine radical and alcohol is a barrierless α-C-H abstraction of alcohol.

- **Observation**: Transient absorption experiments with $[CeCl_6]^{2-}$ show an identical kinetic trace of chlorine radical in the absence or presence of various alcohols, precludes the formation of radical complex
- **Observations**: Alkane HAT by chlorine radical generated through organophotoredox SET conditions shows no regioselectivity effect of added alcohols. When tBuOH is added, b-C–H of tBuOH is functionalized, presumably through chlorine radical HAT

Mechanistic investigation on cerium catalyzed alkane functionalization

Walsh & Schelter's work vs. this work

- **Observation**: Alcohol-controlled regioselectivities were observed in our original condition. The selectivity ratio in alkane amination enabled by $Cl_3CH_2O\bullet$ and $Cl\bullet$ are roughly identical, as revealed by chloride-free conditions and DFT calculations. As shown by Bietti and Houk, the polar effect renders highly e-deficient $Cl_3CH_2O\bullet$ the most reactive and least selective among $RO\bullet$.

- **Observations**: Methylated byproduct from b-scission of $^{t}BuO\bullet$ obtained with C–H aminations mediated by $[CeO^{t}BuCl_5]^{2-}$ or $CeCl_3$/TBACl/^{t}BuOH, supporting the intermediacy of tertbutoxy radical.

- **Observations**: Identical KIE and regioselectivity observed with $[Ce(OR)Cl_5]^{2-}$ and original catalytic conditions

Mechanistic investigation on cerium catalyzed alkane functionalization

Walsh & Schelter's work vs. this work

- **Conclusion: Chlorine radical, chlorine radical–alcohol complexes act as HAT agents, masking alkoxy radicals.**

- **Observation**: Observations: Identical regioselectivity observed with chloride-free conditions (Ce/benzoate/ROH) and original catalytic conditions. As the chloride-free conditions have precluded any involvement of chlorine radical or chlorine radical-alcohol complex, the identical selectivity in propane, butane and hexane amination, and the same large primary KIE in methane amination, indicate alkoxy radical-mediated HAT in our original report.

- **Conclusion: Chlorine radical-alcohol complexes, while thermodynamically possible, do not form in any relevant context.** Furthermore, identical alkoxy radical is the primary species responsible for C–H abstraction in original catalytic conditions, "chloride-free" conditions, and pre-formed heteroleptic Ce(IV) chloride alkoxide complexes, as indicated by kinetic and regioselectivity measures.