# Iridium(I) Complexes Bearing NHC/Phosphine Ligands

## Synthesis and Application in HIE Processes

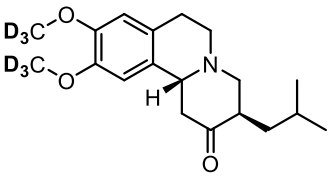
Renan Zorzatto

Professor William J. Kerr

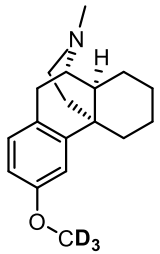
# Hydrogen Isotope Exchange

Hydrogen isotopes find several applications

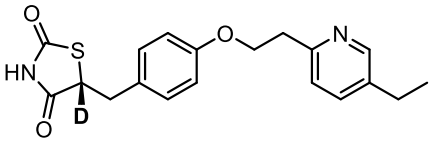
*Increased metabolic stability*[1]



Deutetrabenazine
(SD-809)
VMAT2 inhibitor



$d_3$-dextromethorphan
(AVP-786)
NMDA receptor antagonist



$d_1$-(*R*)-pioglitazone
(DRX-065)
PPAR-γ activator

1 Mullard, A., *Nat. Rev. Drug. Discov.*, **2016**, *15*, 219.
2 *a)* Pleiss, U., *J. Label Compd. Radiopharm.*, **2011**, *54*, 283; *b)* Elmore, C. S.; Powell, M. E.; Heys, J. R., *J. Label Compd. Radiopharm.*, **2008**, *51*, 343.
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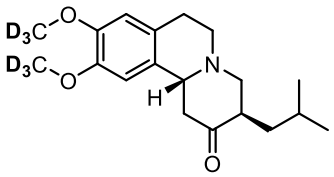

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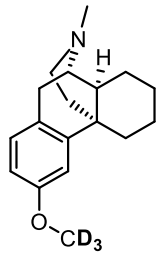

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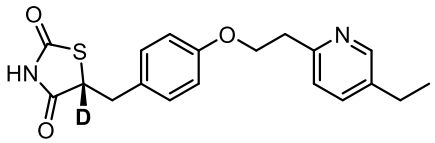

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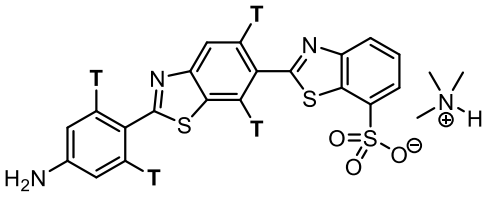
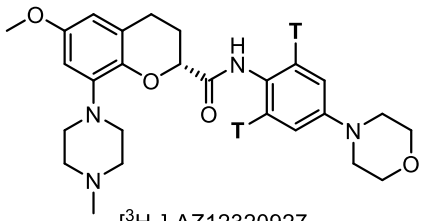
*ADMET Studies*[2]



[$^3H_4$]-Primuline



[$^3H_2$]-AZ12320927

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2 *a)* Pleiss, U., *J. Label Compd. Radiopharm.*, **2011**, *54*, 283; *b)* Elmore, C. S.; Powell, M. E.; Heys, J. R., *J. Label Compd. Radiopharm.*, **2008**, *51*, 343.
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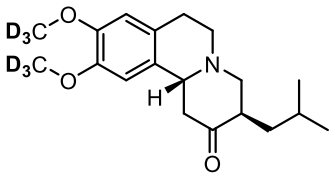

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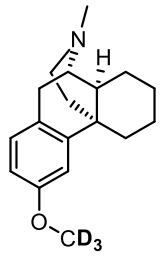

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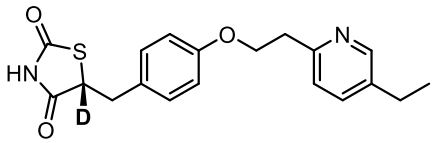

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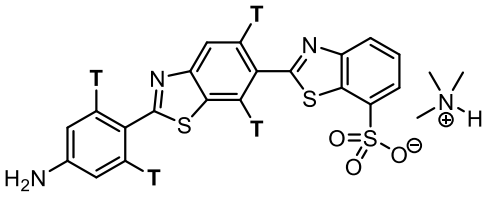

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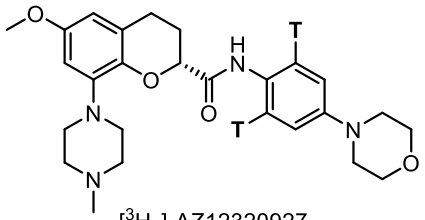
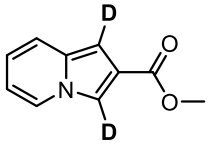
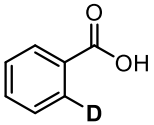
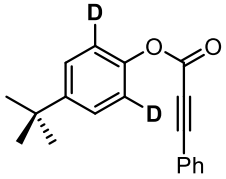


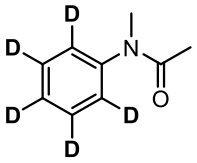
[$^3$H$_2$]-AZ12320927

*KIE / Mechanistic Studies*[3]









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2 *a)* Pleiss, U., *J. Label Compd. Radiopharm.*, **2011**, *54*, 283; *b)* Elmore, C. S.; Powell, M. E.; Heys, J. R., *J. Label Compd. Radiopharm.*, **2008**, *51*, 343.
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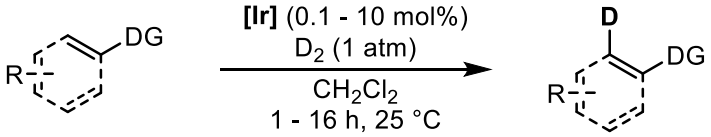
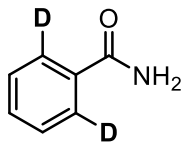
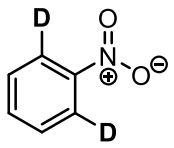
Development of Ir(I) catalysts in the Kerr group and their application in HIE[4]

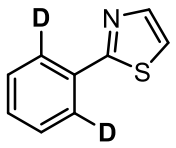


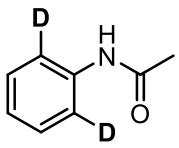

**1** (5 mol%) **97%**
**4** (110 mol%) **65%**



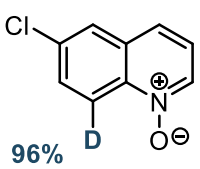

**1** (5 mol%) **98%**
**4** (100 mol%) **0%**



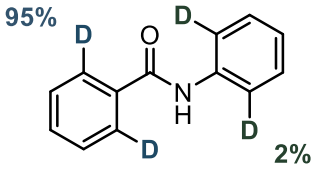

**1** (5 mol%) **82%**
**4** (100 mol%) **80%**



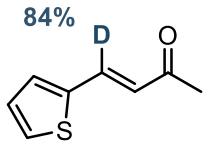

**2** (5 mol%) **95%**
**4** (140 mol%) **40%**




**1** (0.25 mol%)

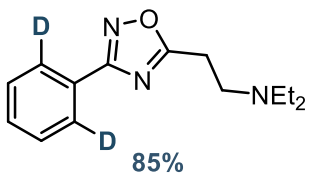



**3** (0.5 mol%)



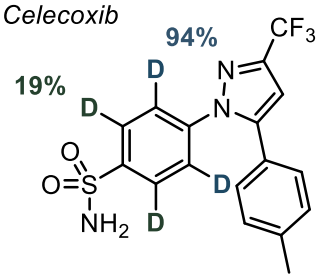

**1** (0.1 mol%)

*Perebron*

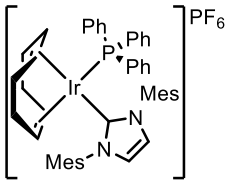



**2** (5 mol%)

*Celecoxib*




**2** (10 mol%)

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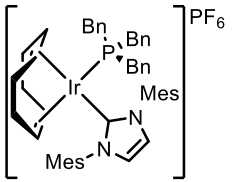
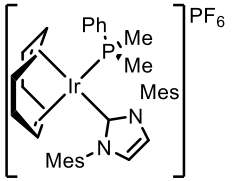
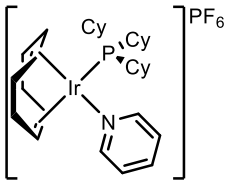



**2**




**3**

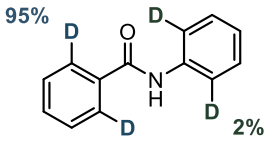


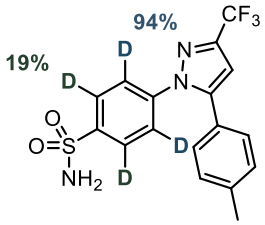

**4**

4 *a*) Brown, J. A. *et al.*, *Chem. Commun.*, **2008**, 1115; *b)* Brown, J. A. *et al.*, *Adv. Synth. Catal.*, **2014**, *356*, 3551; *c*) Kerr, W. J. *et al.*, *Chem. Eur. J.*, **2014**, *20*, 14604; *d)* Atzrodt, J. *et al.*, *Tetrahedron*, **2015**, *71*, 1924; *e)* Kerr, W. J. *et al.*, *ACS Catal.*, **2015**, *5*, 402; *f*) Ellames, G. J. *et al.*, *Tetrahedron*, **2001**, *57*, 9487.

# Hydrogen Isotope Exchange

Sterically demanding directing groups remained underexplored



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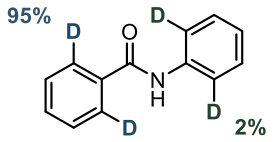
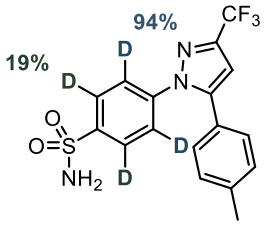
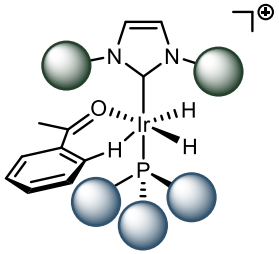
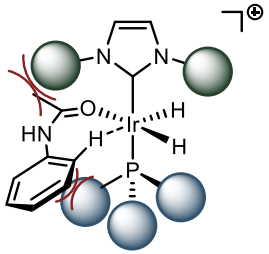



*5-mmi*
↓ ring strain
↓ steric interactions




*6-mmi*
↑ ring strain
↑ steric interactions

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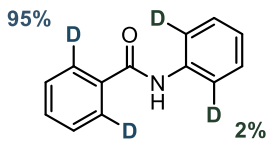


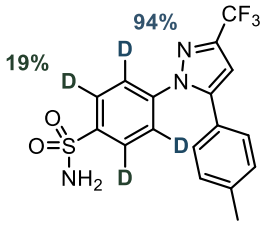


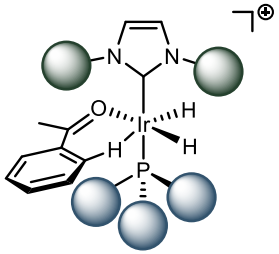


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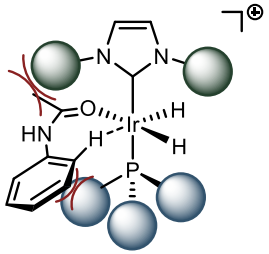
↓ steric interactions




*6-mmi*
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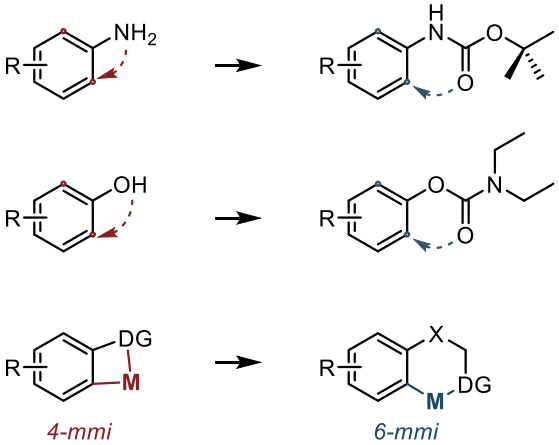
↑ steric interactions



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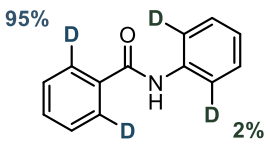
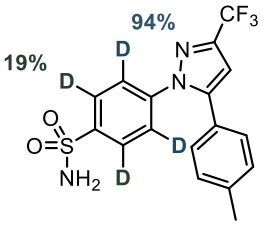
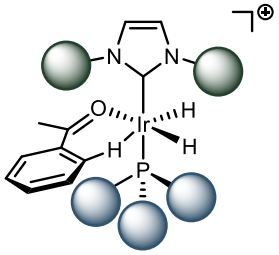
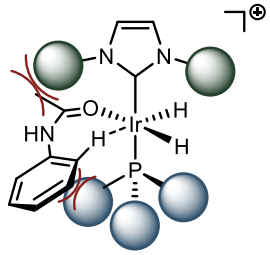


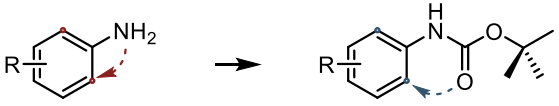



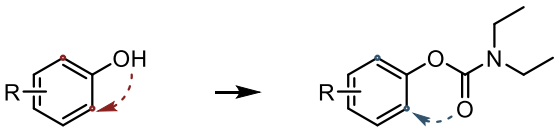



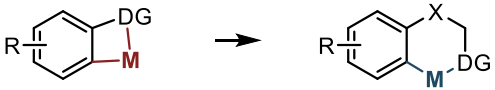

*5-mmi*
↓ ring strain
↓ steric interactions



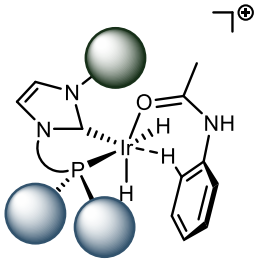

*6-mmi*
↑ ring strain
↑ steric interactions




*4-mmi* *6-mmi*




*Bidentate Ligand*
accomodates ring strain
↓ steric interactions

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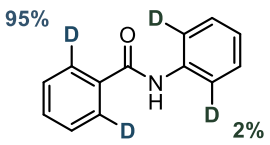
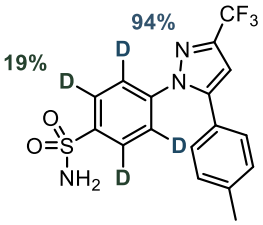
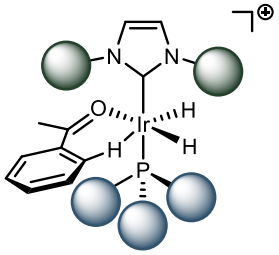
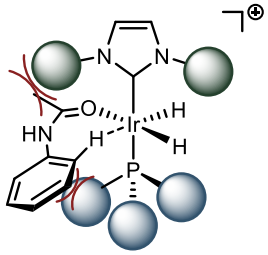


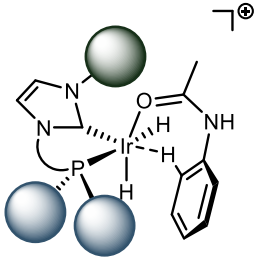



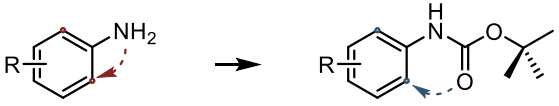

*5-mmi*
↓ ring strain
↓ steric interactions

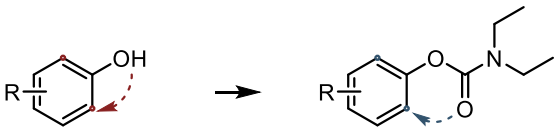


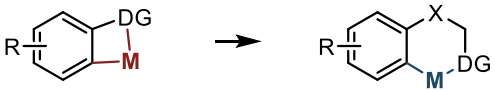

*6-mmi*
↑ ring strain
↑ steric interactions



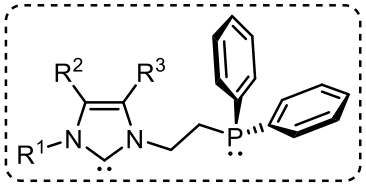

*Bidentate Ligand*
accomodates ring strain
↓ steric interactions



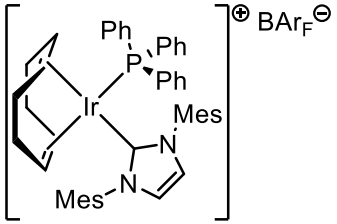




*4-mmi* *6-mmi*

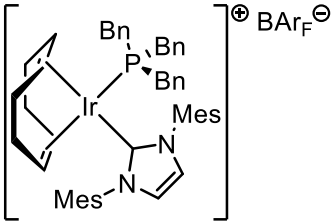


# Applications in HIE of Carbamates

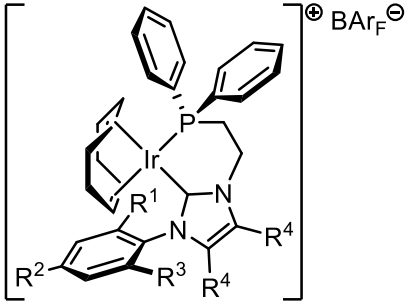
Synthetically valuable carbamates remained unsuitable substrates for HIE



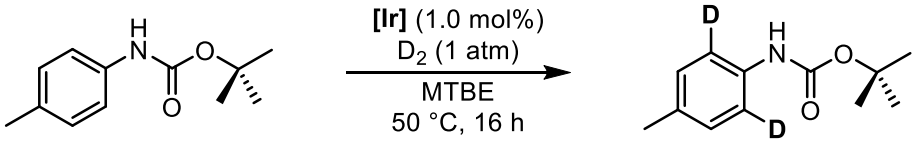

**5a**




**5b**




| Catalyst | $R^1$ | $R^2$ | $R^3$ | $R^4$ |
|---|---|---|---|---|
| **6a** | H | H | H | H |
| **6b** | H | H | $CH_3$ | H |
| **6c** | $CH_3$ | $CH_3$ | $CH_3$ | H |
| **6d** | H | H | H | $CH_3$ |
| **6e** | H | H | $CH_3$ | $CH_3$ |
| **6f** | $CH_3$ | $CH_3$ | $CH_3$ | $CH_3$ |

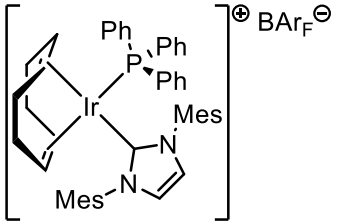



| Entry | Catalyst | %D† | Entry | Catalyst | %D† |
|---|---|---|---|---|---|
| 1 | **5a** | 12 | 5 | **6c** | 94 |
| 2 | **5b** | 11 | 6 | **6d** | 77 |
| 3 | **6a** | 77 | 7 | **6e** | 88 |
| 4 | **6b** | 92 | 8 | **6f** | 87 |

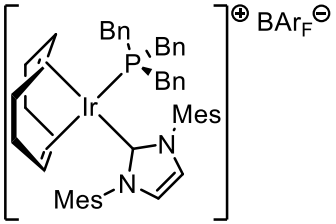
†Average of 3 runs. Determined by $^1$H NMR spectroscopy.

# Applications in HIE of Carbamates

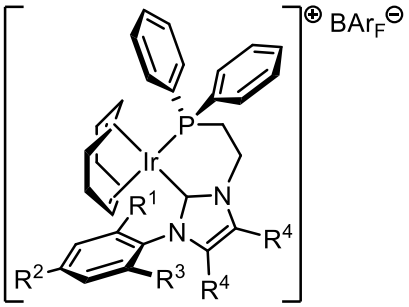
Synthetically valuable carbamates remained unsuitable substrates for HIE



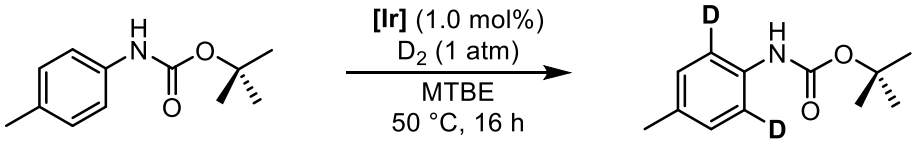

**5a**




**5b**




| Catalyst | $R^1$ | $R^2$ | $R^3$ | $R^4$ |
|---|---|---|---|---|
| **6a** | H | H | H | H |
| **6b** | H | H | $CH_3$ | H |
| **6c** | $CH_3$ | $CH_3$ | $CH_3$ | H |
| **6d** | H | H | H | $CH_3$ |
| **6e** | H | H | $CH_3$ | $CH_3$ |
| **6f** | $CH_3$ | $CH_3$ | $CH_3$ | $CH_3$ |

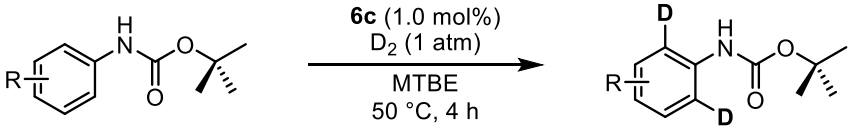


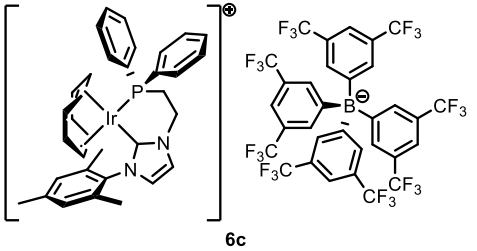

| Entry | Catalyst | %D† | Entry | Catalyst | %D† |
|---|---|---|---|---|---|
| 1 | **5a** | 12 | 5 | **6c** | 94 |
| 2 | **5b** | 11 | 6 | **6d** | 77 |
| 3 | **6a** | 77 | 7 | **6e** | 88 |
| 4 | **6b** | 92 | 8 | **6f** | 87 |

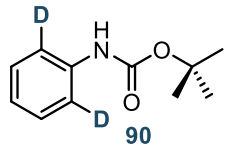
†Average of 3 runs. Determined by $^1$H NMR spectroscopy.

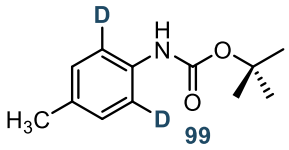
# Applications in HIE of Carbamates

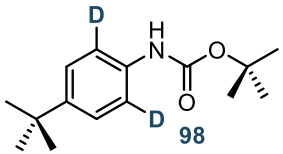
Scope of *O*-*tert*-butyl-*N*-phenyl carbamates

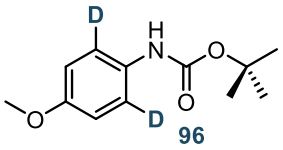


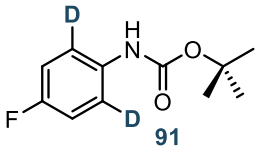



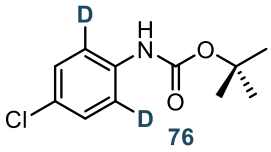



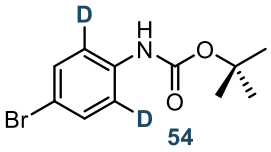



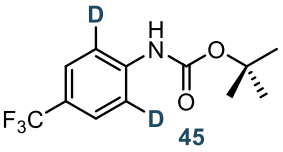



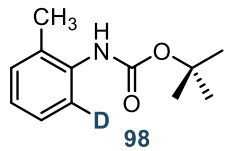



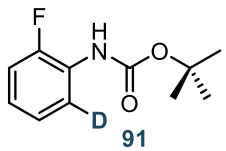



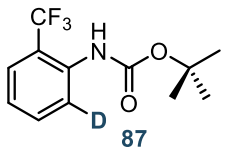



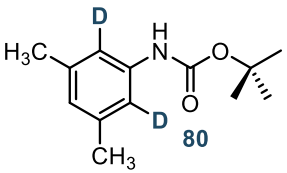



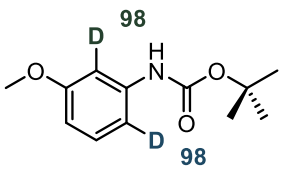



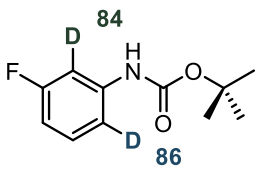



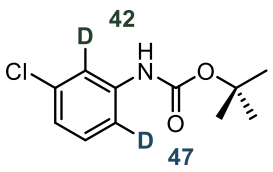



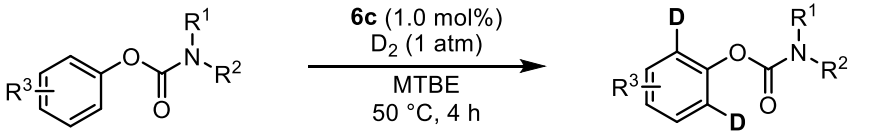



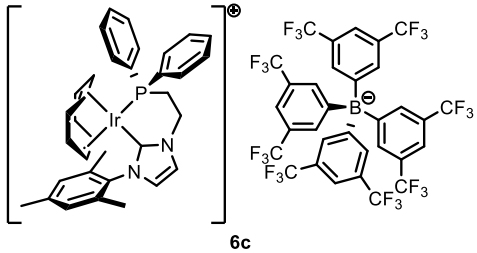



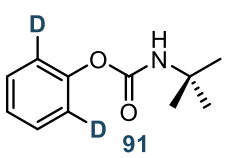

† All results indicate the average of 3 runs. Deuterium incorporation was determined by $^1$H NMR spectroscopy.

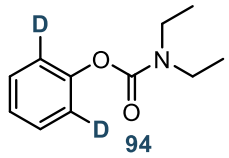
# Applications in HIE of Carbamates

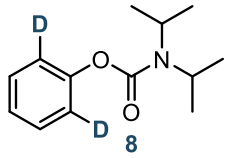
Scope of *O*-phenyl carbamates

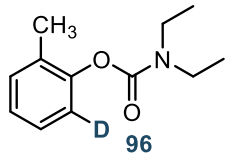


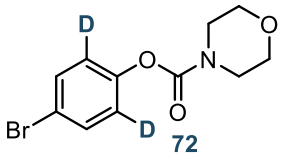



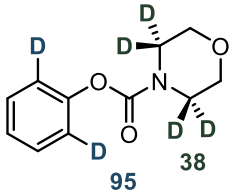



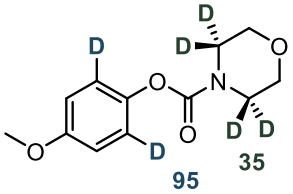



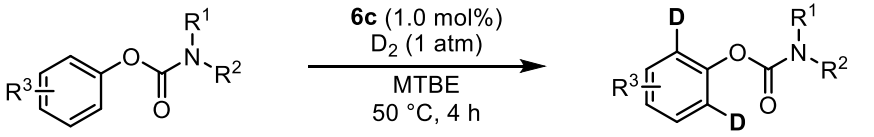



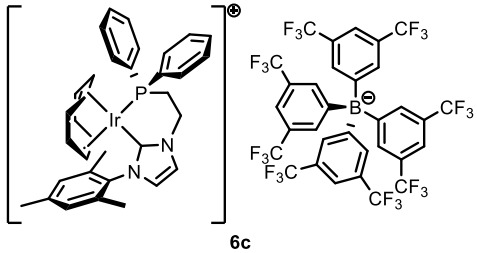



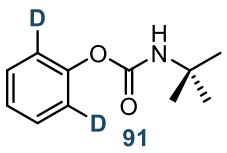

† All results indicate the average of 3 runs. Deuterium incorporation was determined by $^1$H NMR spectroscopy. *5.0 mol% **6c** was employed.

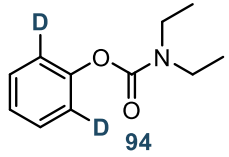
# Applications in HIE of Carbamates

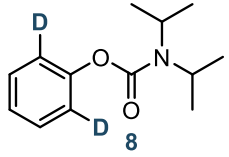
Scope of *O*-phenyl carbamates

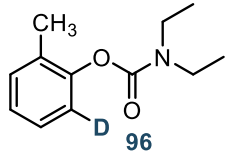


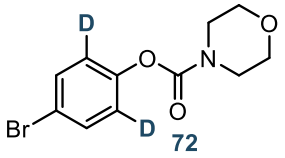



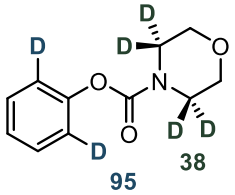



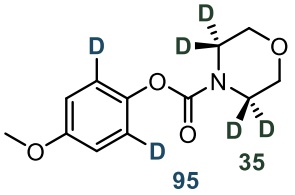



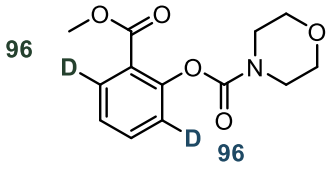



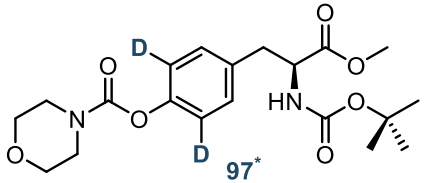



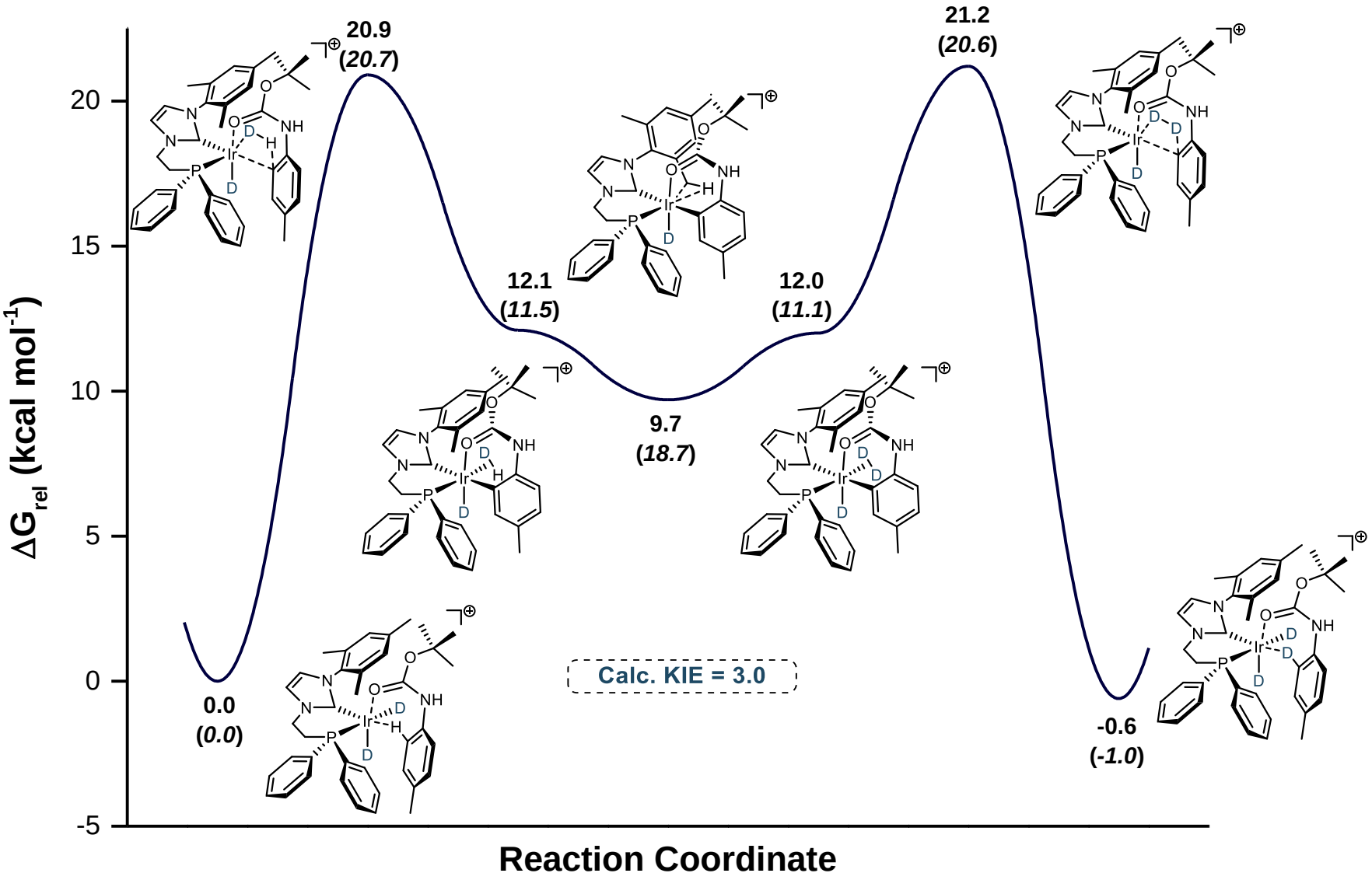




† All results indicate the average of 3 runs. Deuterium incorporation was determined by $^1$H NMR spectroscopy. *5.0 mol% **6c** was employed.

# Mechanistic Investigations

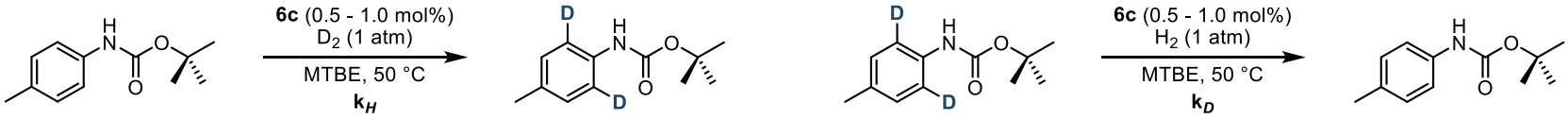
Mechanism was investigated by DFT calculations†

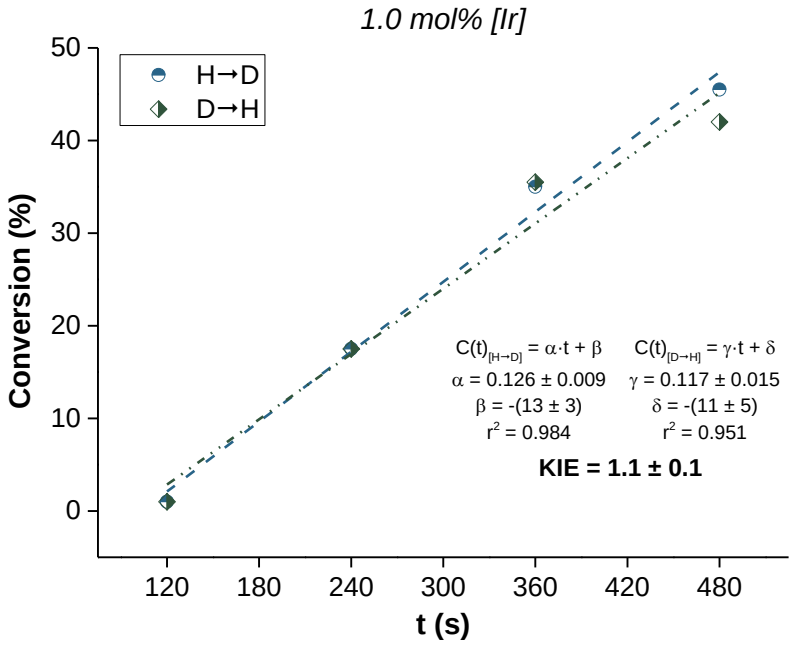


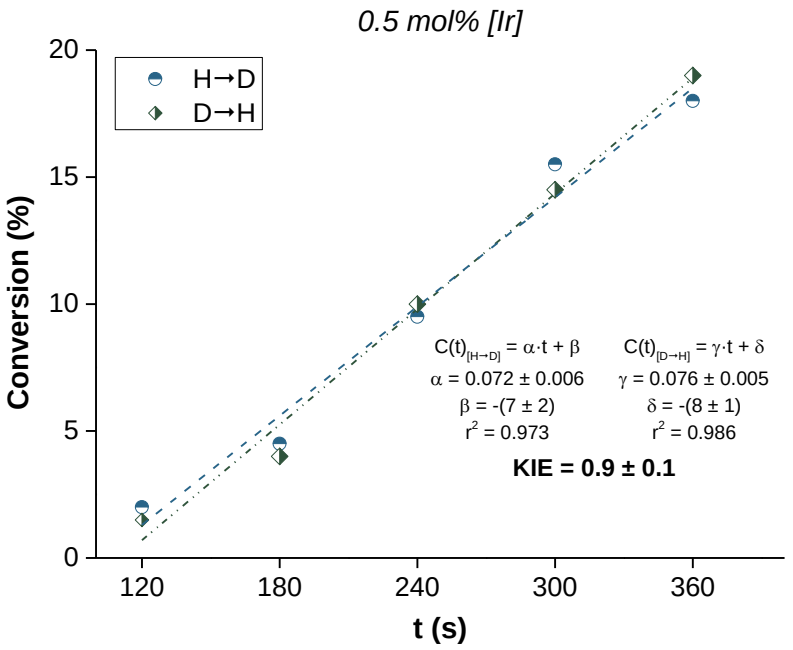

† Reported values correspond to $\Delta G_{rel}$. $\Delta H_{rel}$ are shown in parentheses.
PES calculated at the M06L level of theory employing 6-31G(d) basis set for light atoms and Stuttgart ECP with its associated basis set for Ir in Gaussian 09W, Revision A.02.

# Mechanistic Investigations

Rate studies and KIE measurements were performed



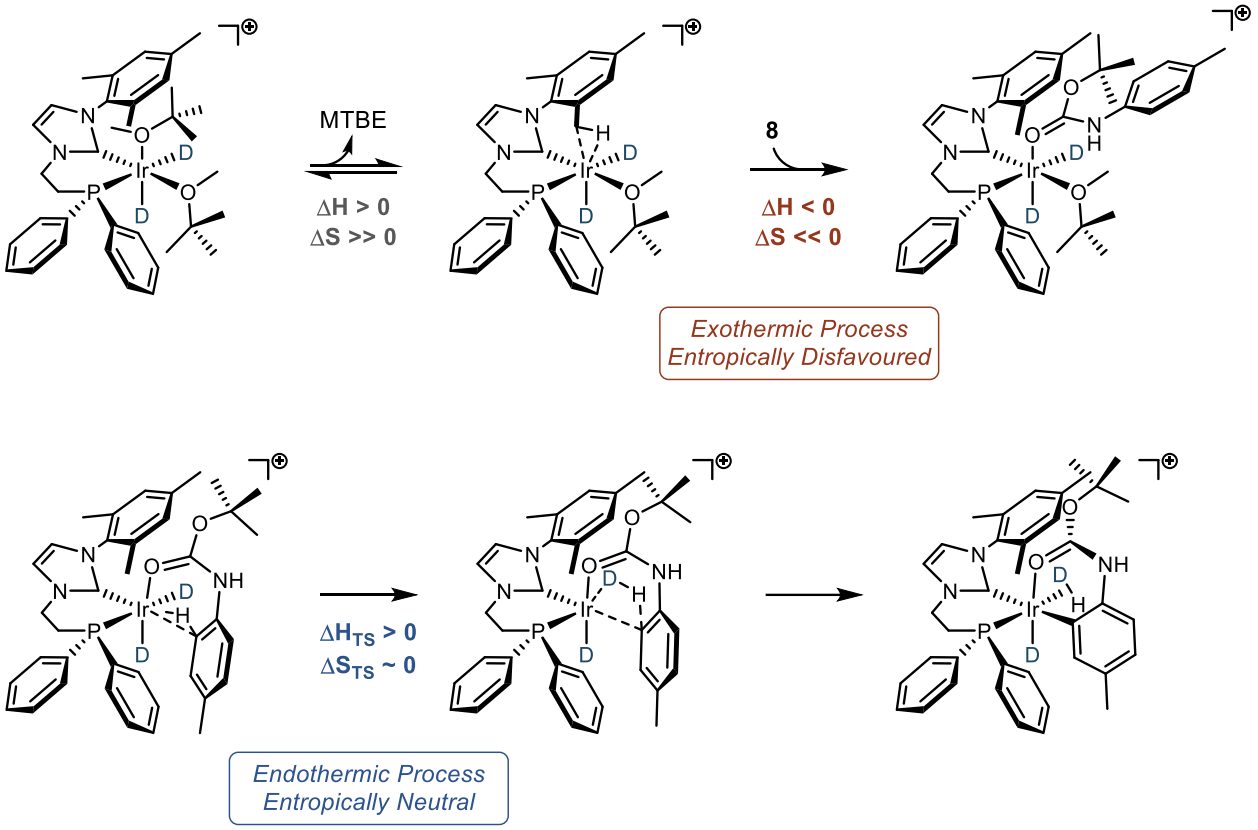




- KIE **inconsistent** with C—H activation being the rate limiting step.
- Coordination of substrate is a likely competing process.
- *O*-methyl carbamate was considered as a mechanistic probe.

# Mechanistic Investigations

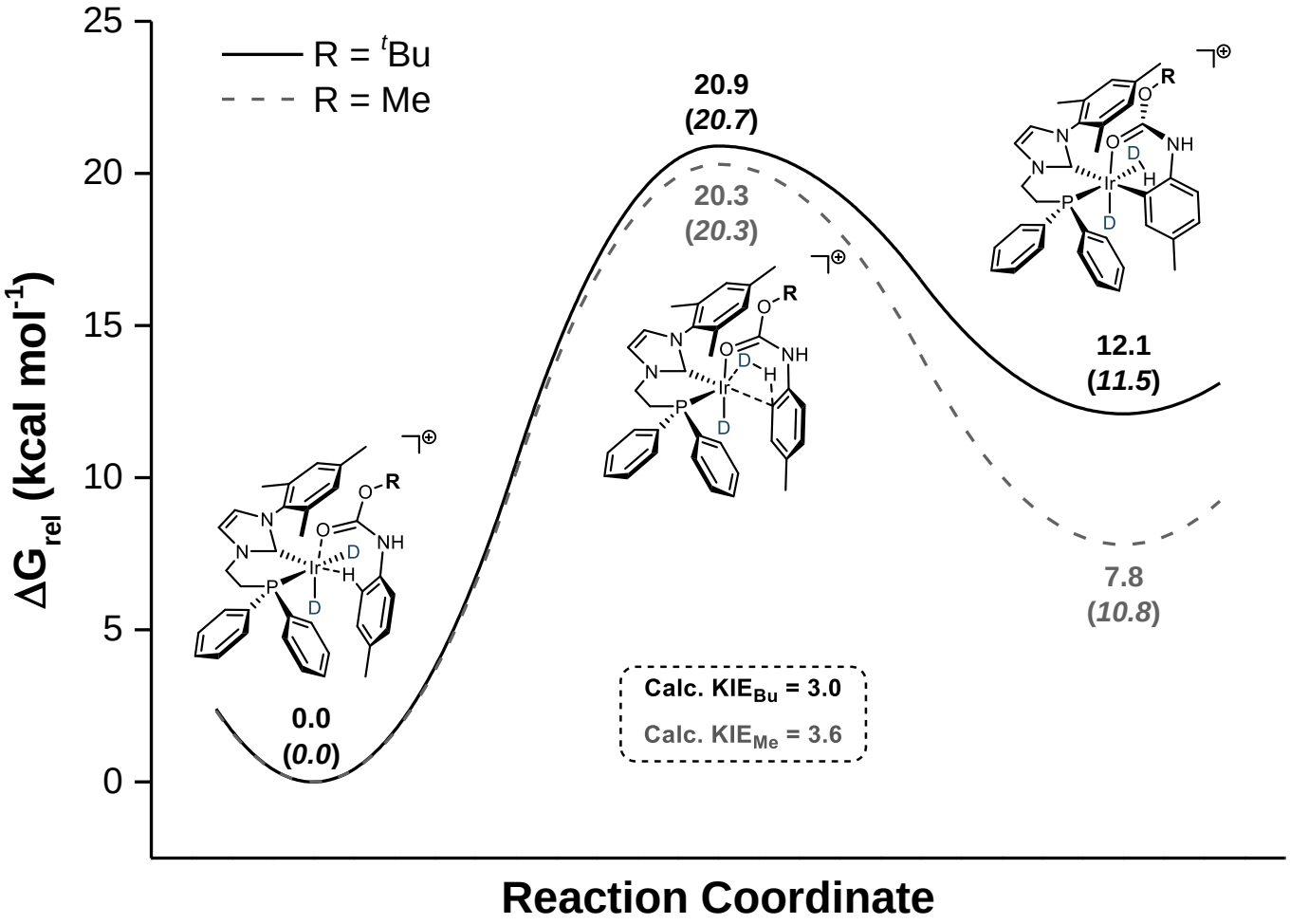
Rate studies and KIE measurements were performed




- KIE **inconsistent** with C—H activation being the rate limiting step.
- Coordination of substrate is a likely competing process.
- *O*-methyl carbamate was considered as a mechanistic probe.

# Mechanistic Investigations

Energetics of the C—H activation were evaluated†

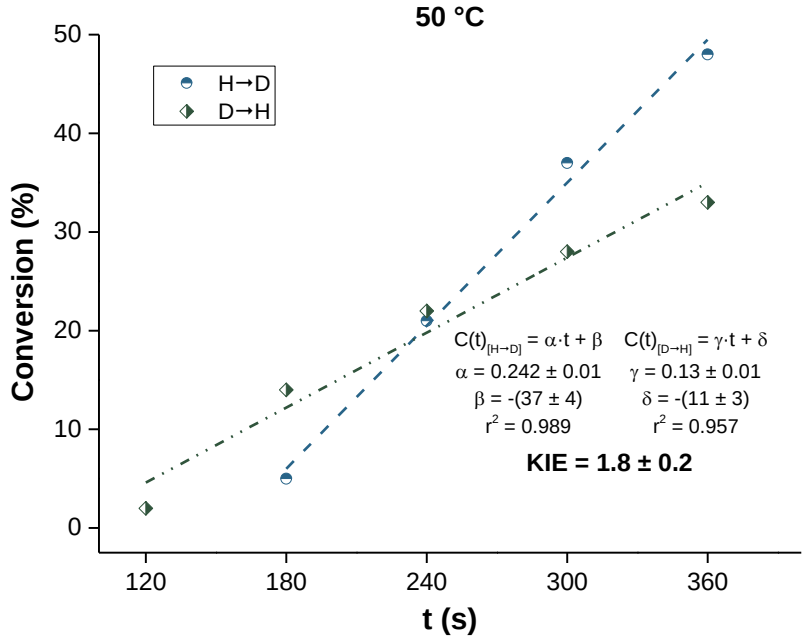


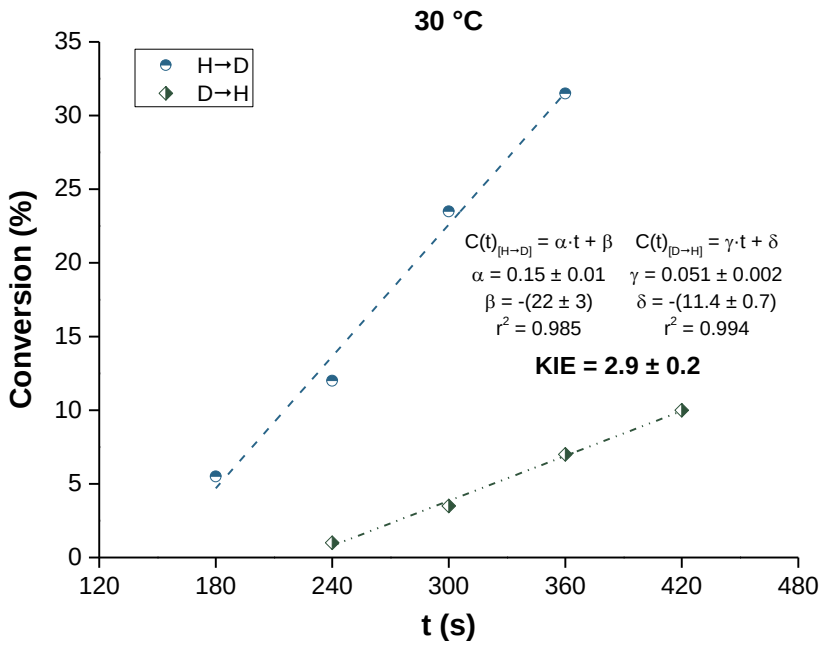

- Negligible steric effects during the C—H activation process.

† Reported values correspond to $\Delta G_{rel}$. $\Delta H_{rel}$ are shown in parentheses.
PES calculated at the M06L level of theory employing 6-31G(d) basis set for light atoms and Stuttgart ECP with its associated basis set for Ir in Gaussian 09W, Revision A.02.

# Mechanistic Investigations

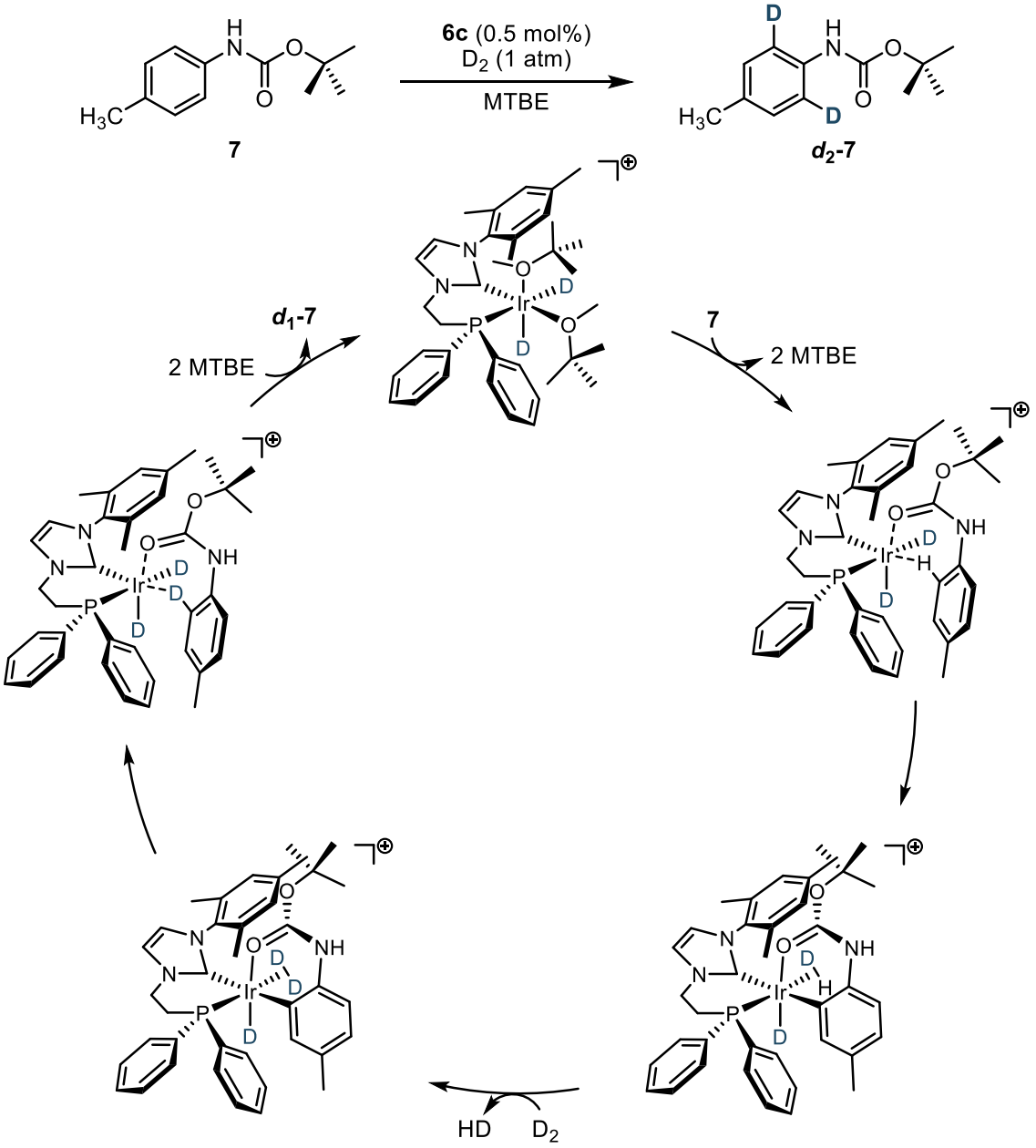
Rate studies and KIE measurements were performed


- KIE **consistent** with C—H activation being the rate limiting step.
- Strong temperature dependence suggests competition at 50 °C.

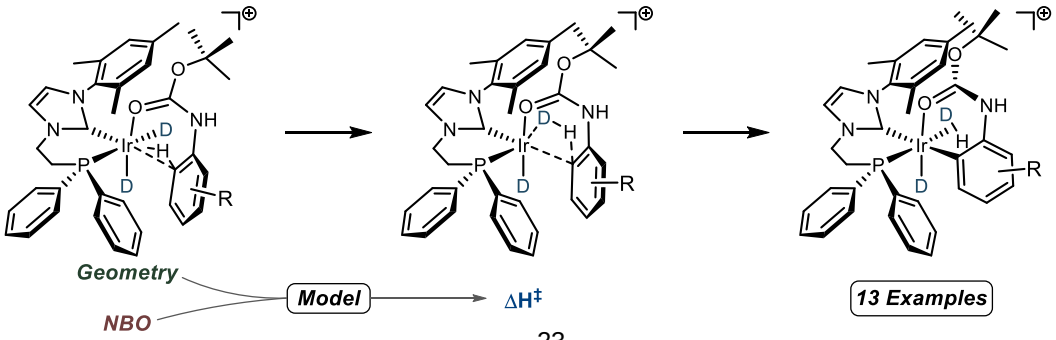
# Proposed Mechanism



# Modelling $\Delta H^{\ddagger}$

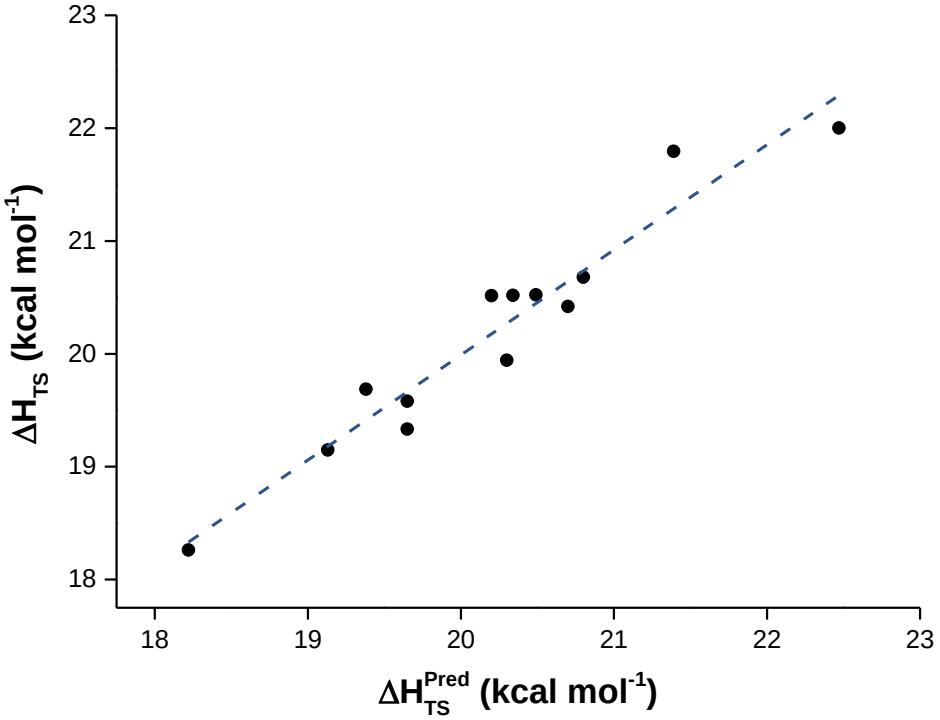
Analysis of predictors unveiled a method for prediction of $\Delta H^{\ddagger}$ for the C—H activation.

- Statistically significant model based on features of the Ir---C—H bond interaction:
  - **NBO Parameters:** $E^2[\sigma_{C-H} \rightarrow Ir]$ and $E^2[Ir \rightarrow \sigma^*_{C-H}]$
  - **Optimised Geometry:** $d_{Ir--H}$

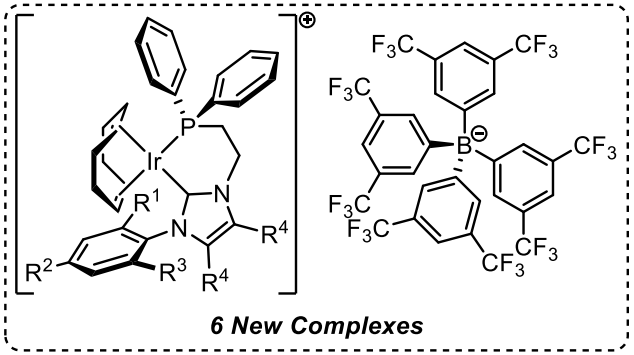



$\Delta H^{\ddagger} = a_0 + a_1 \cdot E^2[Ir \rightarrow \sigma^*_{C-H}] + a_2 \cdot E^2[\sigma_{C-H} \rightarrow Ir] + a_3 \cdot d_{Ir--H}$

| Parameter | Value | Descriptor | Value |
|---|---|---|---|
| $a_0$ | 128.9 | $r^2$ | 0.9318 |
| $a_1$ | -3.598 | $r^2_{adj}$ | 0.9090 |
| $a_2$ | 0.1472 | $r^2_{pred}$ | 0.8392 |
| $a_3$ | -40.91 | σ | 0.32 |

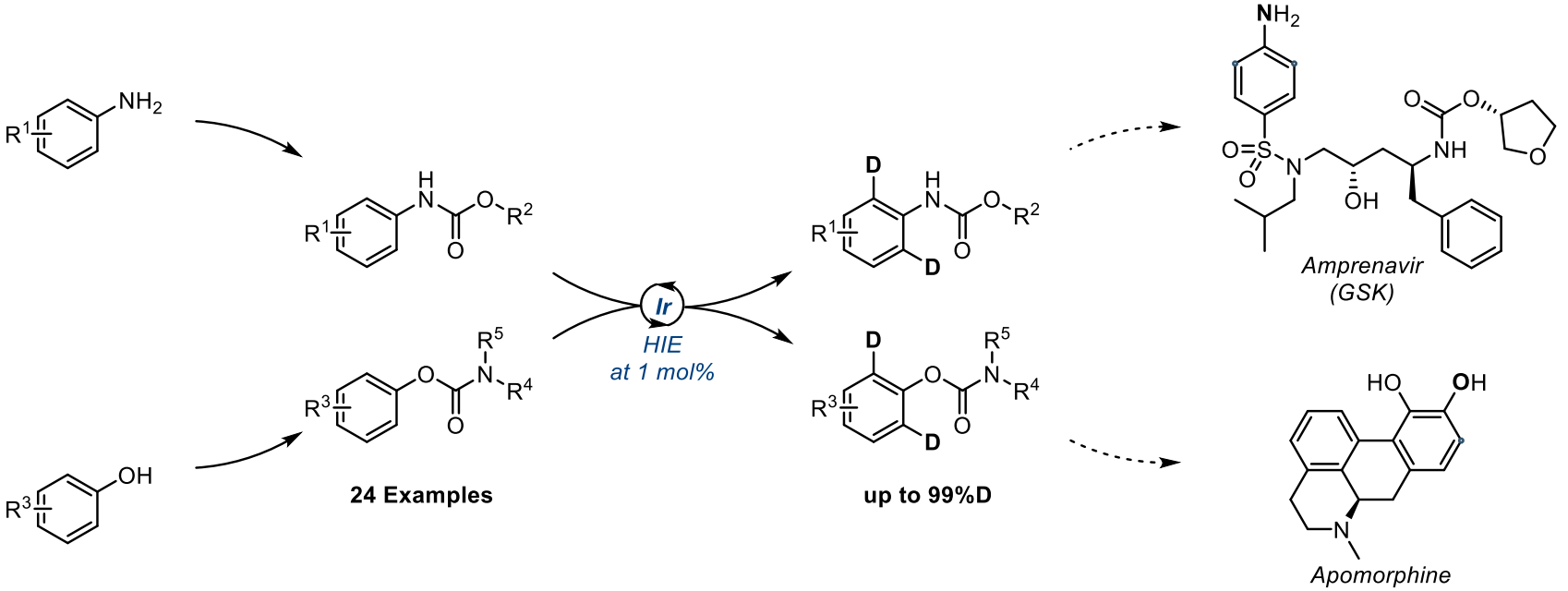


# Conclusion




*Novel chelating ligands*

*Modular synthesis*



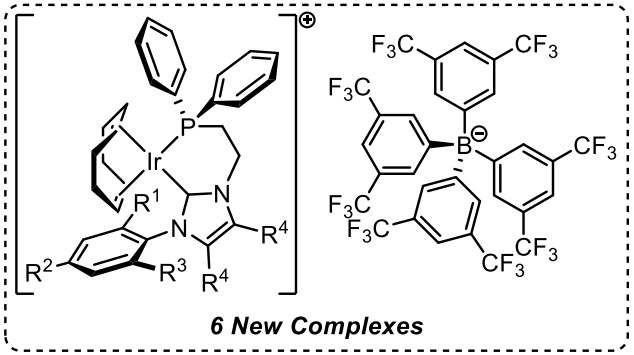

*Facile derivatisation*

*Efficient HIE*

*Low catalyst loadings*

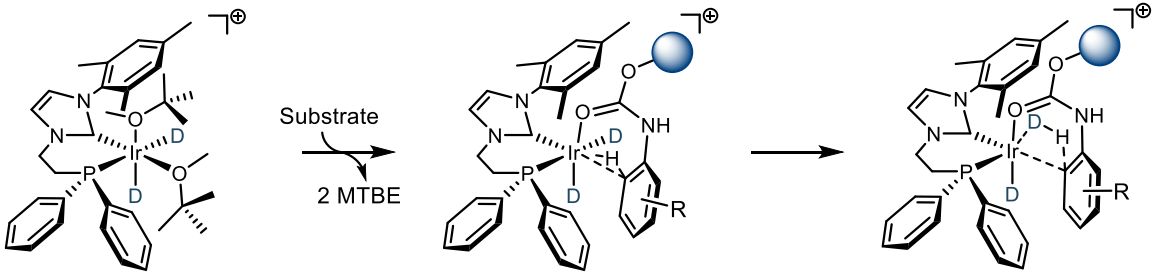
*Access to important class of molecules*

# Conclusion



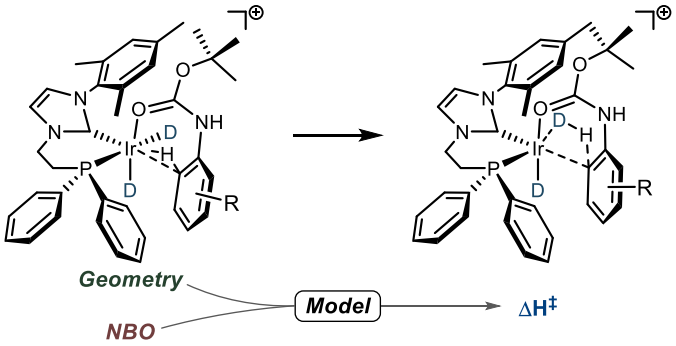

*Novel chelating ligands*

*Modular synthesis*




*Temperature-dependent mechanism*

*RLS defined by steric effects*




*Insights into the C—H activation process*

*Model expansion and application to other systems*

# Acknowledgements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**GSK**

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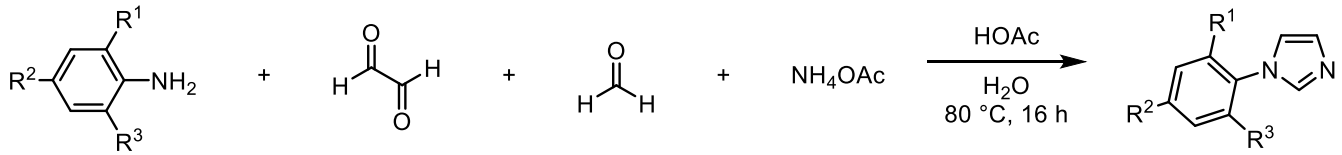
Dr Richard Mudd

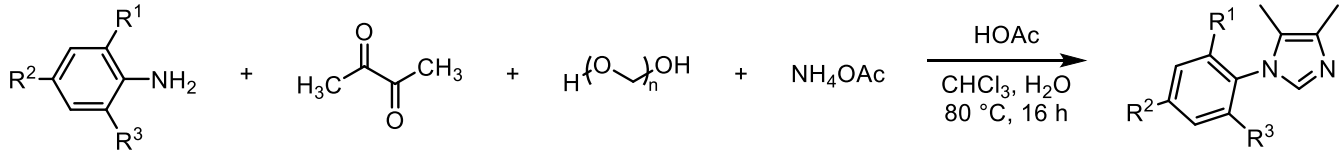
University of
Strathclyde
Glasgow

# Synthesis of Iridium(I) Complexes

Modular synthesis of bidentate NHC/phosphine ligands was uncovered




| $R^1$ | $R^2$ | $R^3$ | Yield |
|---|---|---|---|
| H | H | H | 52% |
| H | H | $CH_3$ | 50% |
| $CH_3$ | $CH_3$ | $CH_3$ | 49% |




| $R^1$ | $R^2$ | $R^3$ | Yield |
|---|---|---|---|
| H | H | H | 39% |
| H | H | $CH_3$ | 45% |
| $CH_3$ | $CH_3$ | $CH_3$ | 27% |