Methanol Activation in Organic Synthesis

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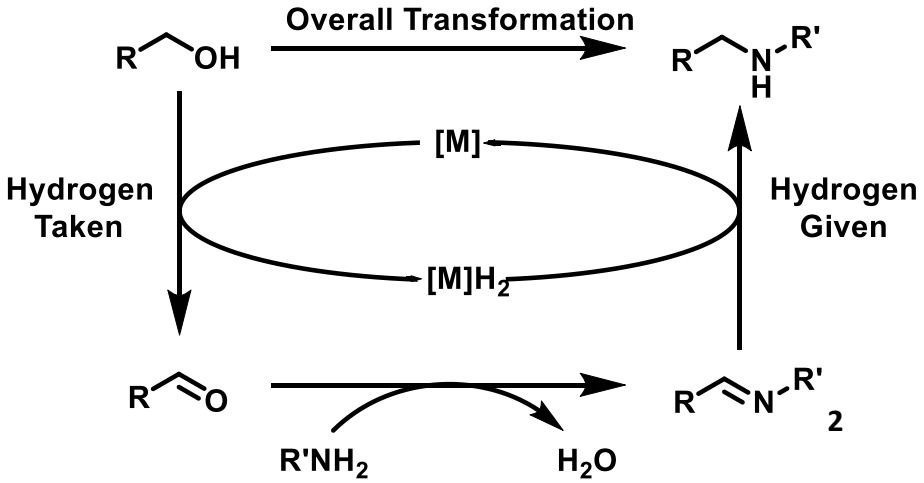
TJD Group Meeting

140513

Activation of alcohols:

- Activation of alcohols well known in synthesis:
  - Classical methods tend to involve either protonation or conversion into a leaving group.
  - Protonation can fail as it may also protonate the incoming nucleophile, especially if it is an amine, and these conditions are not tolerated by acid-sensitive functionality.
  - Conversion to alkyl halides or sulfonates can lead to inherent toxicity problems, many are mutagenic.
- "Borrowing hydrogen":
  - Oxidise alcohol to aldehyde, convert into another functional group, then reduce intermediate to final product. E.g. Alcohol → Aldehyde → Imine → Amine
  - Only waste product is water.
  - Variety of catalysts based on ruthenium and iridium with varying levels of complexity.

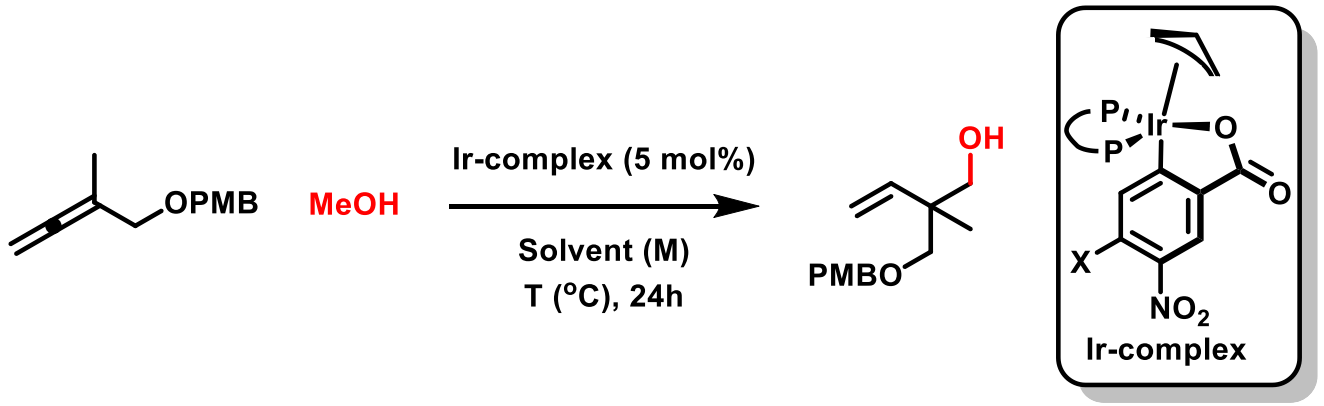


Activation of methanol:

- Few catalysts show activation of MeOH:
  - Alkylation of amines:
    - $IrCl(cod)_2/Py_2NP(iPr)_2$ (*Adv. Synth. Catal.*, **2009**, p2903)
  - Alkylation of nitriles:
    - $RhCl_3.3H_2O/PPh_3$ (*Tet. Lett.*, **1981**, p4107)
    - Ru/Hydrotalcite (*J. Am. Chem. Soc.,* **2004**, p5662)
- Suggested by Krische (*Nat. Chem.*, **2011**, p287) that the reason for the more difficult activation of methanol is due to the higher energetic demand for methanol dehydrogenation:
  - $\Delta H(MeOH) = +84\ kJ\ mol^{-1}$
  - $\Delta H(EtOH) = +68\ kJ\ mol^{-1}$
- However, more recently, other examples have appeared in the literature, suggesting that this is not such a difficult process.

Ir-catalysed coupling with allenes:

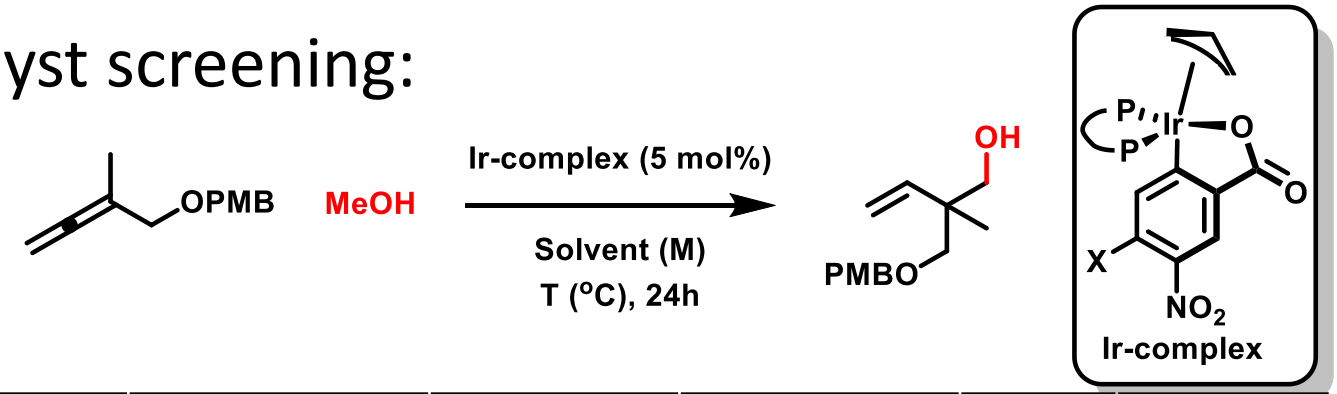
- Krische and coworkers have developed a method for oxidising methanol and the *in situ* capture of formaldehyde with allenes.



Krische, *Nature Chemistry*, **2011**, p287

Ir-catalysed coupling with allenes:

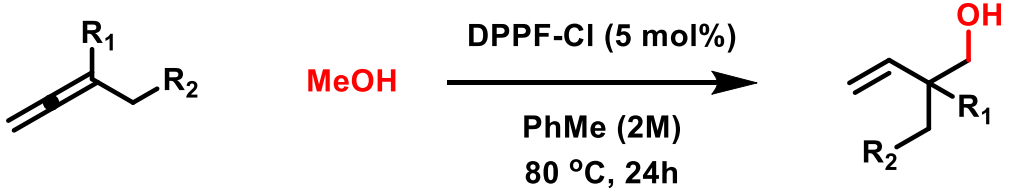
- Catalyst screening:

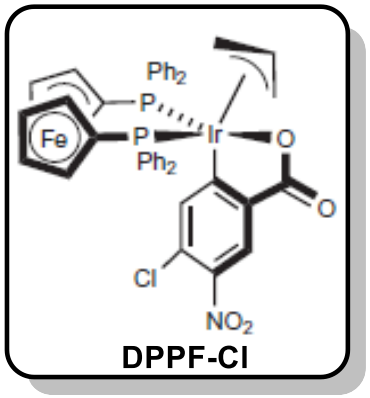


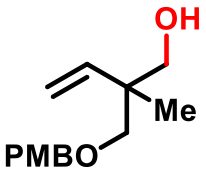
Entry	Ligand, X	Eq. MeOH	Solvent (M)	T (°C)	Yield (%)
1	BIPHEP, H	10	PhMe (1)	80	29
2	BIPHEP, H	15	PhMe (1)	80	39
3	BIPHEP, H	20	PhMe (1)	80	36
4	BIPHEP, OMe	15	PhMe (1)	80	37
5	BIPHEP, CN	15	PhMe (1)	80	39
6	BIPHEP, Cl	15	PhMe (1)	80	44
7	DPPF, Cl	15	PhMe (1)	80	63
8	**DPPF, Cl**	**15**	**PhMe (2)**	**80**	**67**

Ir-catalysed coupling with allenes:

- Substrate scope:







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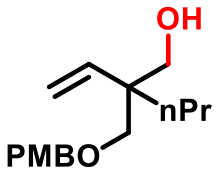

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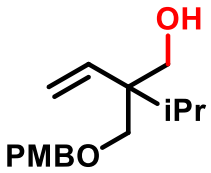

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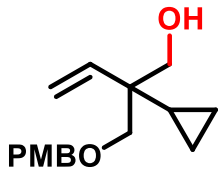

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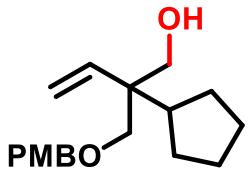

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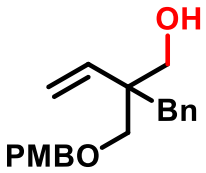

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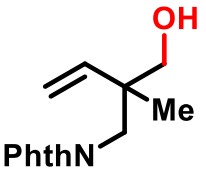

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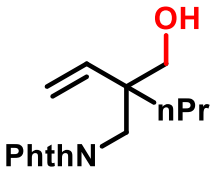

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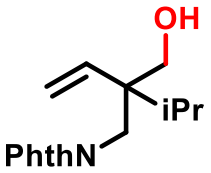

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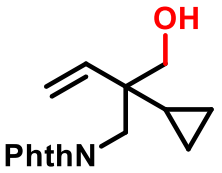

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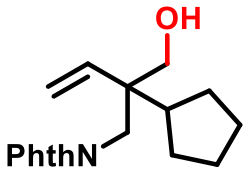

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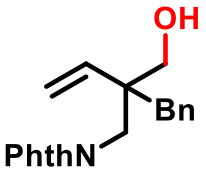

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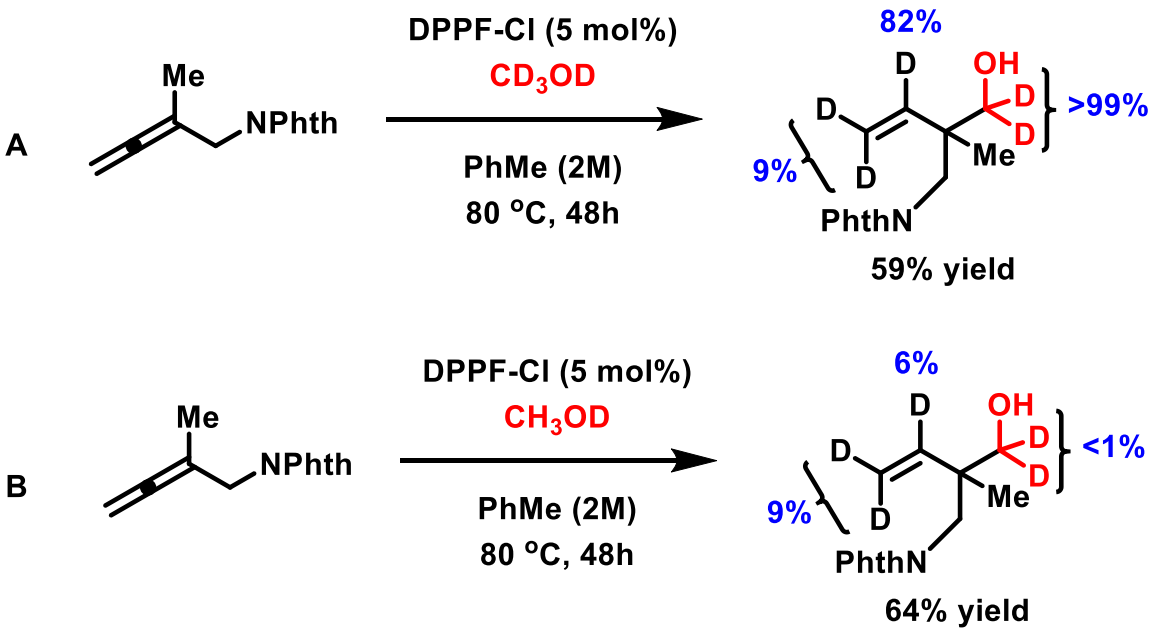
Ir-catalysed coupling with allenes:

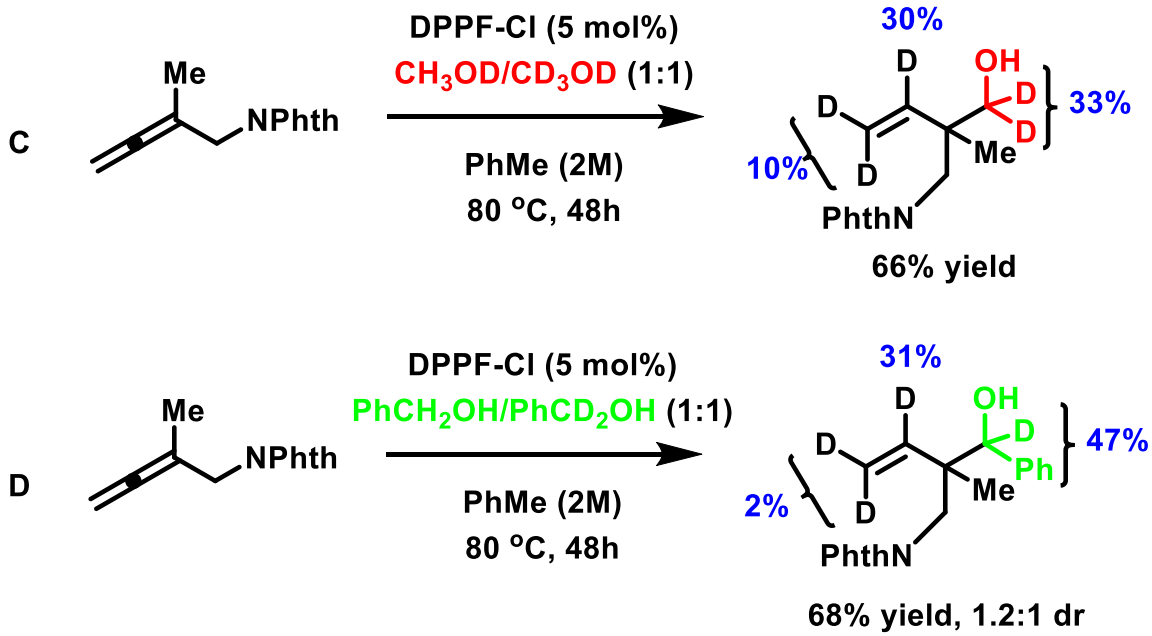
- Mechanistic studies:



  - These results suggest that allene hydrometallation is reversible, forming a transient vinyliridium species.

Ir-catalysed coupling with allenes

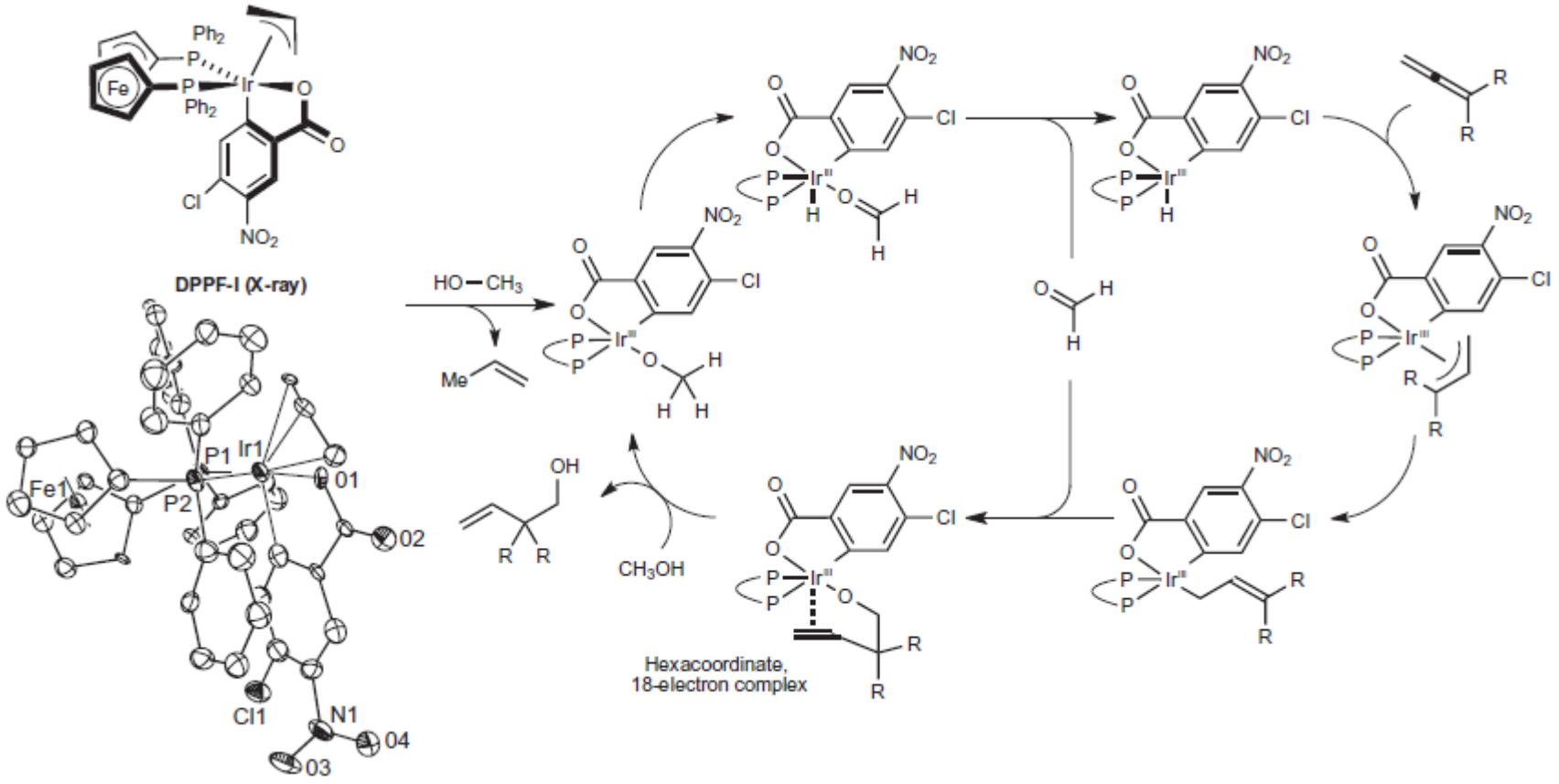
- Mechanistic studies cont:



  - For methanol addition, k_H/k_D = 2.0, whereas for benzyl alcohol, k_H/k_D = 1.1, suggesting that:
    - Dehydrogenation turnover-limiting for MeOH
    - Carbonyl addition turnover-limiting for BnOH
  - Noteworthy that higher temperatures needed for methanol.
  - Relative energies of dehydrogenation and electrophilicities of carbonyl.

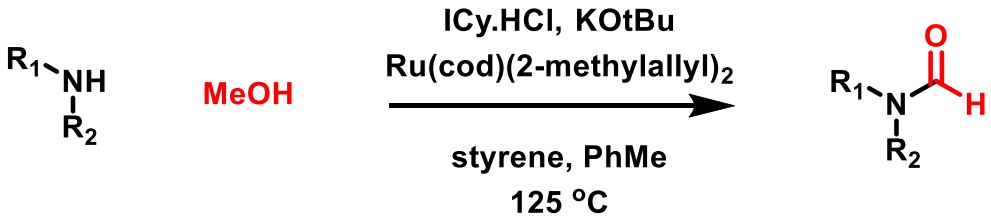
Ir-catalysed coupling with allenes

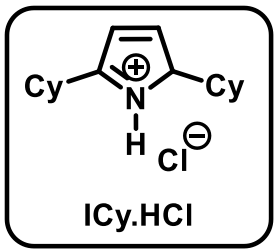
- Proposed mechanism

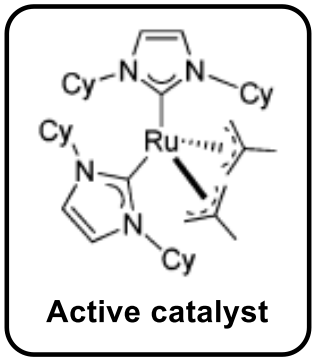


N-formylation of amines with MeOH

- Recently, Glorius and coworkers have developed a relatively mild formylation of amines utilising MeOH as a formyl source.



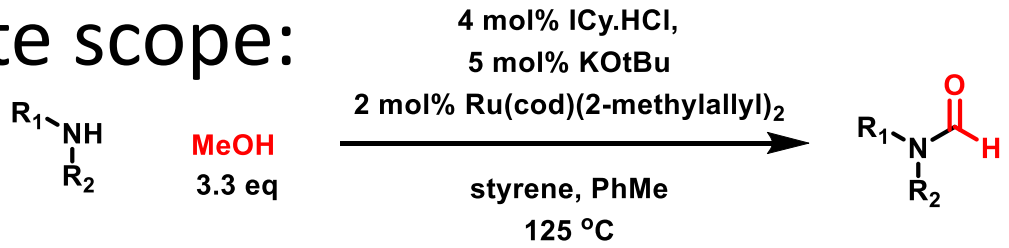


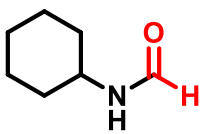


Glorius, *Org. Lett.*, **2013**, p1776

N-formylation of amines with MeOH

- Substrate scope:





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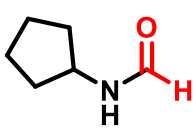

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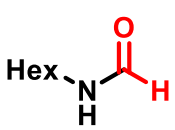

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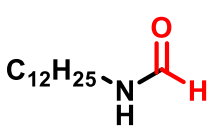

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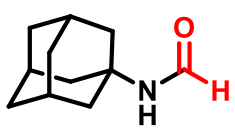

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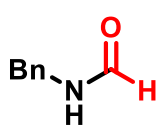

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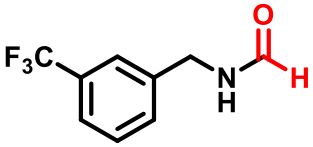

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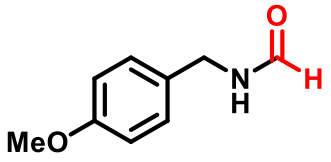

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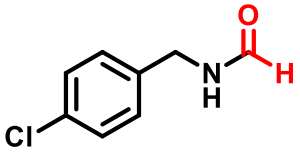

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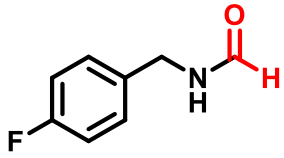

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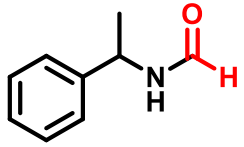

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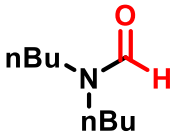

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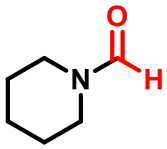

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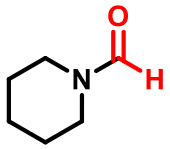

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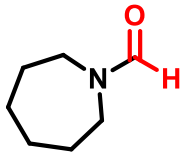

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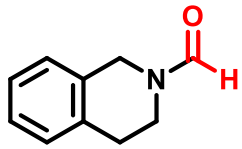

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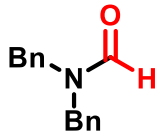

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[a] Reactions carried out with 4 mol% Ru(cod)(2-methylallyl)$_2$ and 8 mol% ICy.HCl

N-formylation of amines with MeOH

- Substrate scope cont:
  - Lower yields for substituted benzylamines due to “further reaction of formamide”
  - Reaction of enantiomerically pure amines yields products with no erosion of ee.
  - Reaction does not proceed for less nucleophilic amines, e.g. anilines
  - Reaction does not proceed in the presence of coordinating groups e.g. pyridines, carboxylic acids.

N-formylation of amines with MeOH

- Proposed mechanism:
  - Investigated by NMR.
  - No methylallyl ligands in active catalyst.

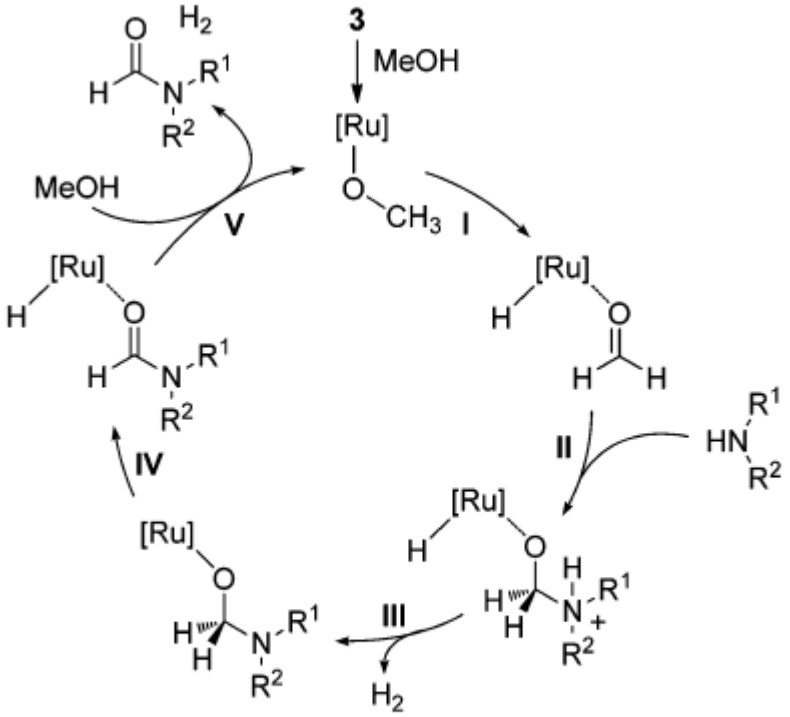
I. β-hydride elimination of methoxide ligand

II. Addition of amine to coordinated formaldehyde.

III. Extrusion of proton.

IV. Second β-hydride elimination of coordinated hemiaminal.

V. Ligand exchange.



[a] [Ru] = $ICy_2L^1L^2{}_nRu(II)$ complex; L^1 = anionic ligand (e.g., methoxide); L^2 = neutral ligand (e.g., MeOH, HNR_2); R^1,R^2 = alkyl, H.

Summary

- Activation of methanol is not as difficult as often stated.
- Krische and coworkers have developed a method for the hydroxymethylation of allenes using an Ir catalyst.
- Glorius and coworkers have also developed a formylation of amines using Ru-NHC catalysis.