SYNTHESIS IN DRUG DESIGN

TARGET IDENTIFICATION

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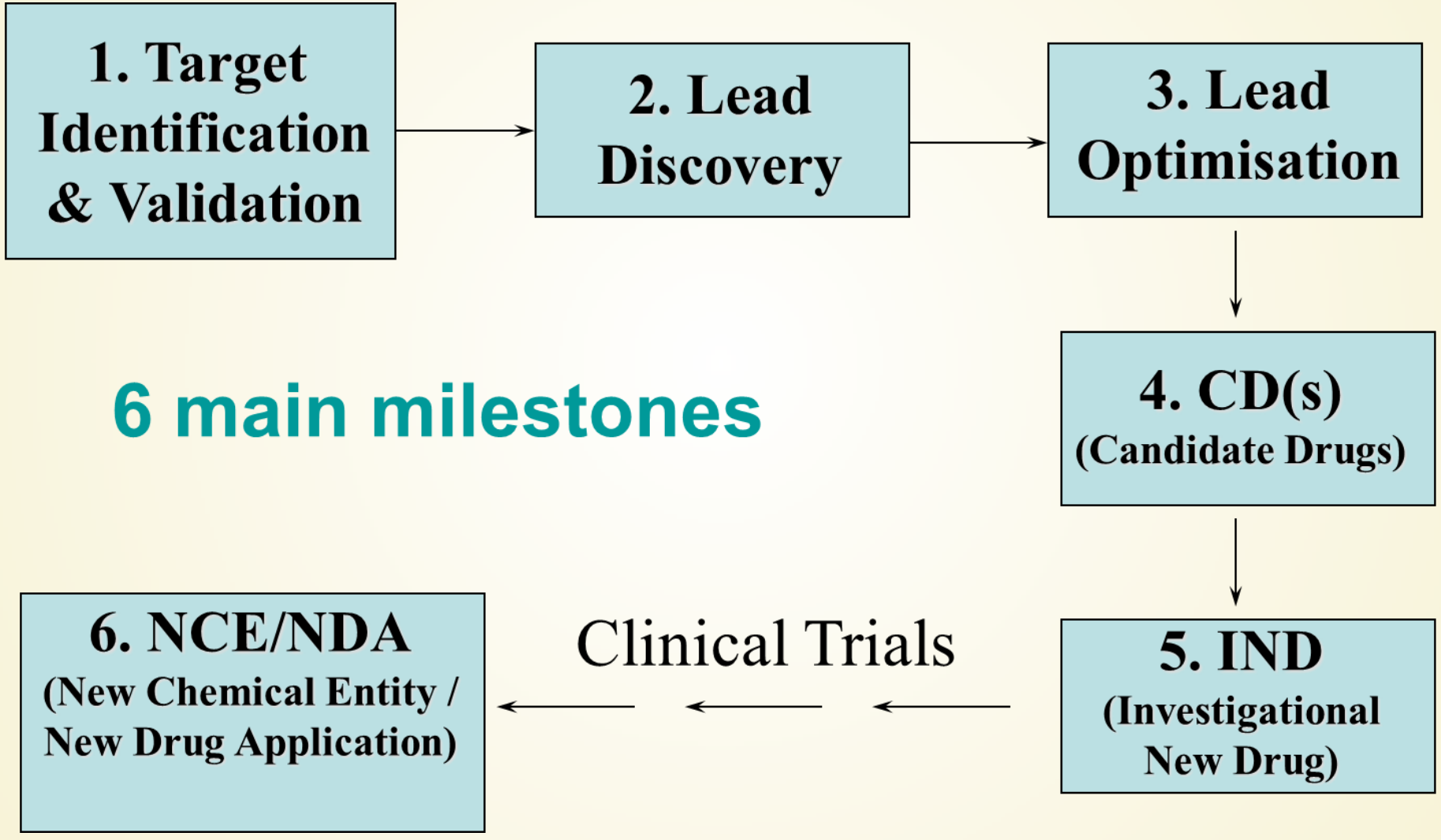
Drug Design - Course Hub

NEW DRUG DEVELOPMENT



6 main milestones

THE ROLES OF SYNTHESIS

Several roles for synthesis in drug development:

1. Target Identification – *eg. 'tag' a bioactive drug to find its biological target*
2. Lead discovery – *eg. synthetic libraries*
3. Lead optimisation – *medicinal chemistry*
4. Investigational New Drug → Clinical Trials → Clinical Use – *process chemistry*

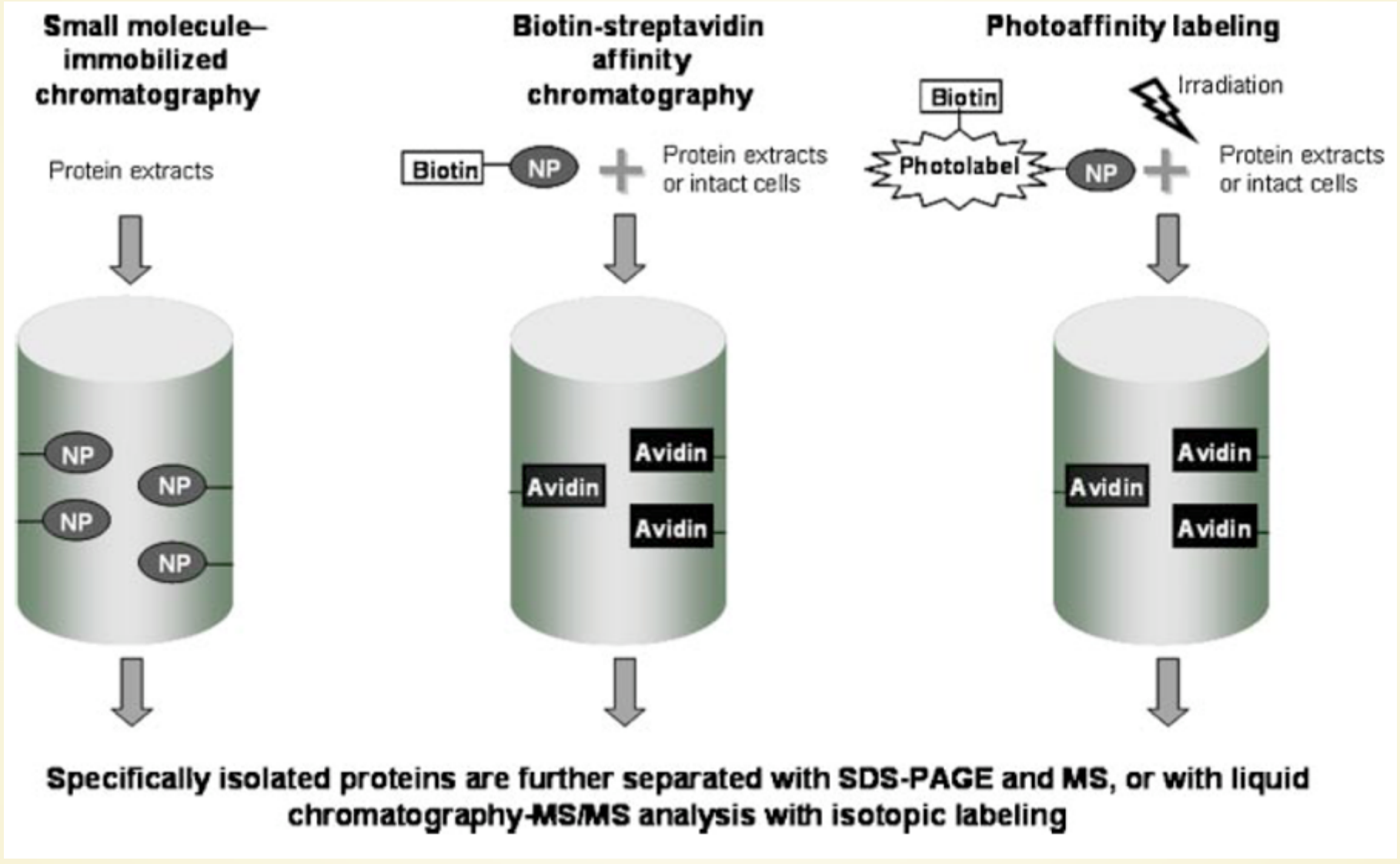
1. TARGET IDENTIFICATION

Identify regions of molecule that can be altered without destroying bioactivity, then:

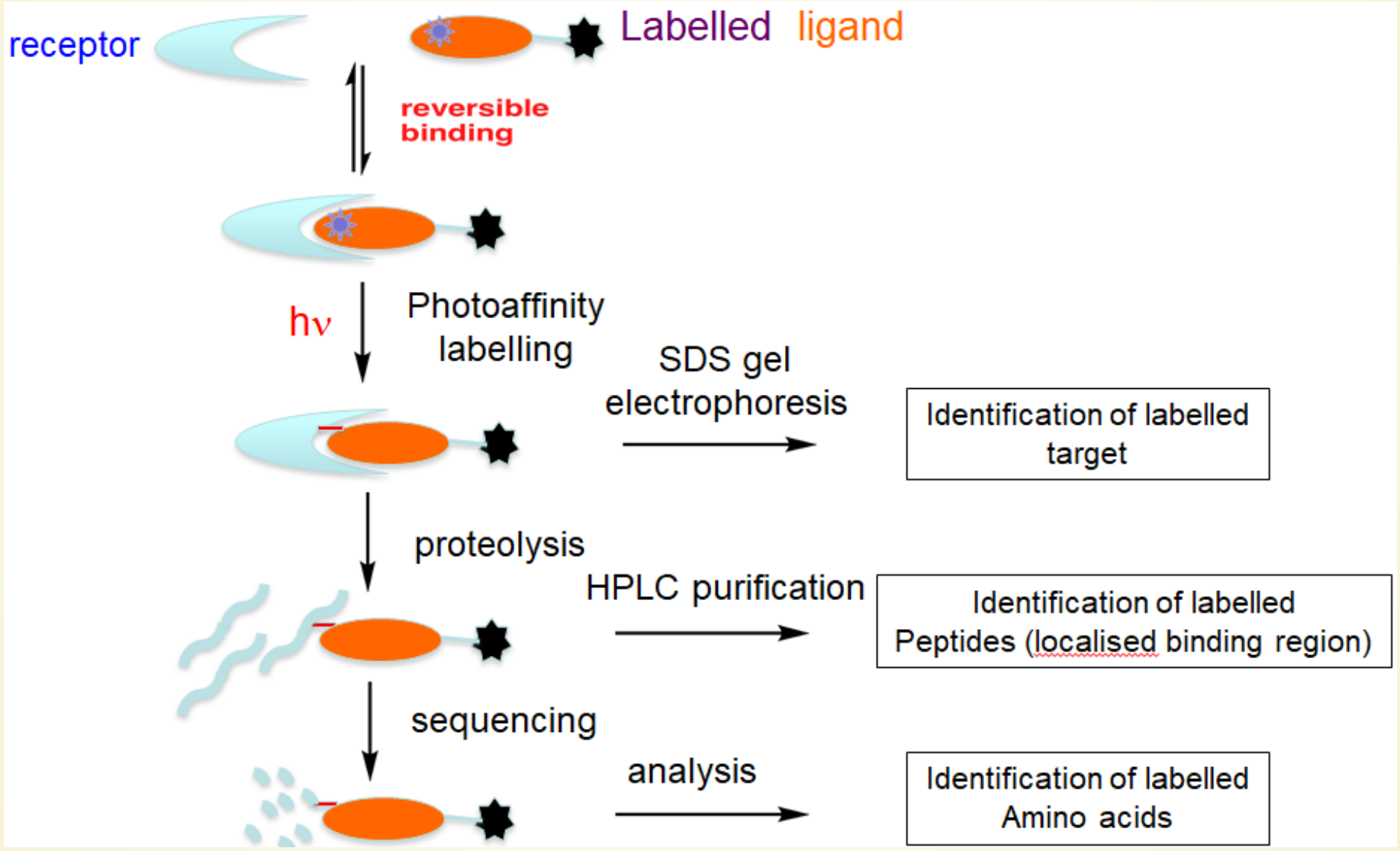
- A) immobilise on solid support, capture biological target then elute and identify, *or*
- B) incorporate a photoaffinity tag, expose to cells or lysate, irradiate, then identify 'tagged' biological target

Can also label with fluorescent or radioactive tag to study cellular or whole body distribution

A) IMMOBILISE LEAD COMPOUND



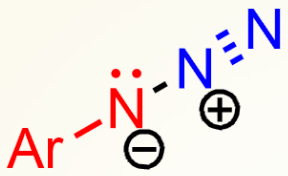
B) PHOTOAFFINITY LABELING



PHOTOACTIVATABLE GROUPS

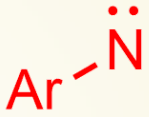
Photoactivatable groups **Reactive species**

azides



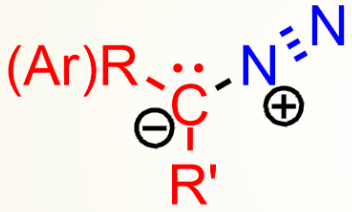
hν

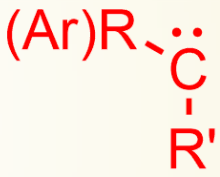
$-N_2$



nitrenes

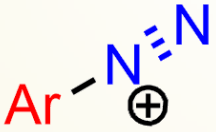
diazo compounds





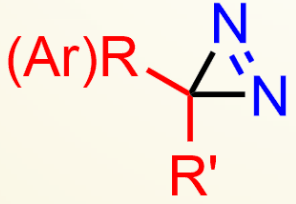
carbenes

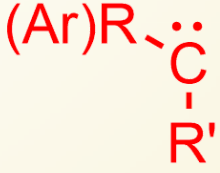
diazonium salts



carbocations

diazirines

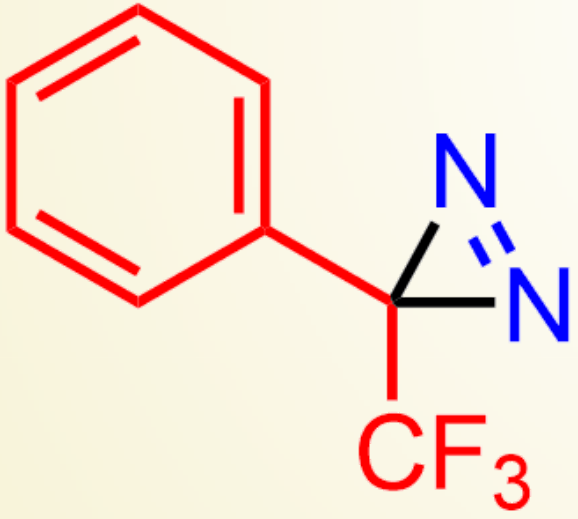




carbenes

ARYL TRIFLUOROMETHYL DIAZIRINES

- trifluoromethyl group suppresses diazo isomerisation
- *advantage* of excellent chemical stability prior to photolysis
- *disadvantage* – synthetic challenges

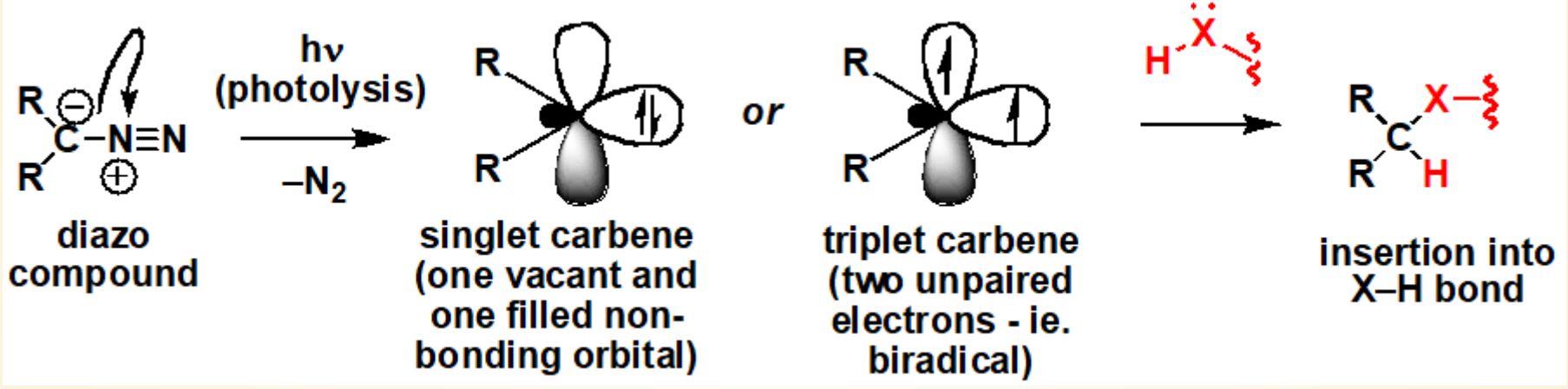


3-phenyl-3-(trifluoromethyl)diazirine

CARBENES AND NITRENES

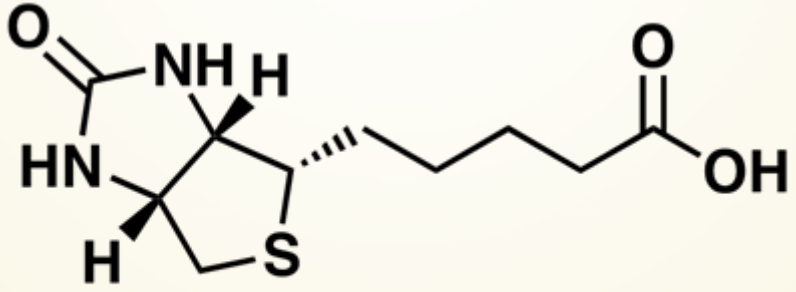
- Photoaffinity labelling relies on photochemical generation of highly reactive (short-lived) intermediates
- Carbenes and nitrenes are commonly employed as they are highly reactive:
  - Uncharged, yet electron deficient – only 6 valence electrons
  - Typical reactions include X–H, C–H and C=C insertion

CARBENE REACTIVITY



PHOTOAFFINITY LABEL OR TAG

- traditionally, radioactive labels have been used
- more recently biotin labelling has been favoured:



biotin

BIOTIN TAGGING

- detected via strong complex with tetrameric protein avidin ($K_D \approx 10^{-15}$ molL^{-1})
  - affinity purification - avidin-immobilised matrix
  - chemiluminescent detection – generated by peroxidase conjugated to avidin
  - detection limit less than 10^{-14} mol (comparable to radioisotopic methods)
- *Disadvantages:* biotin group is polar and large – affects biological activity?

SUMMARY

Chemical probes (natural products / lead compounds linked to fluorescent or photoaffinity/biotin groups) can be used to identify binding proteins / localisation of active molecules within cells of interest, eg. cancer cells.