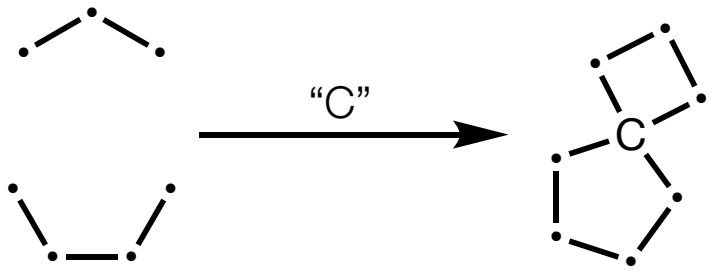
Single-Carbon Atom Doping via Atomic Carbon Equivalents

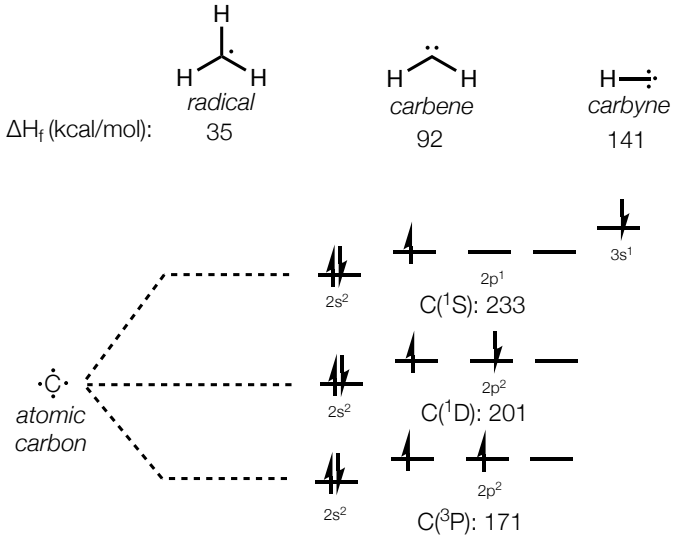


Sebastian Fernandez - Shenvi Lab

2024/03/29

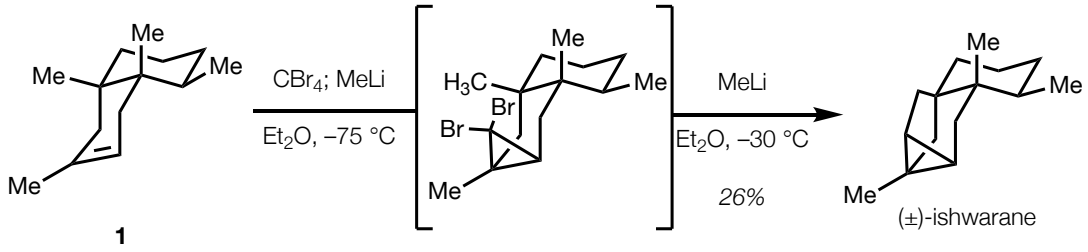
What is Atomic Carbon?

Comparison of neutral, electrically unsaturated carbon species:[1]



Example:

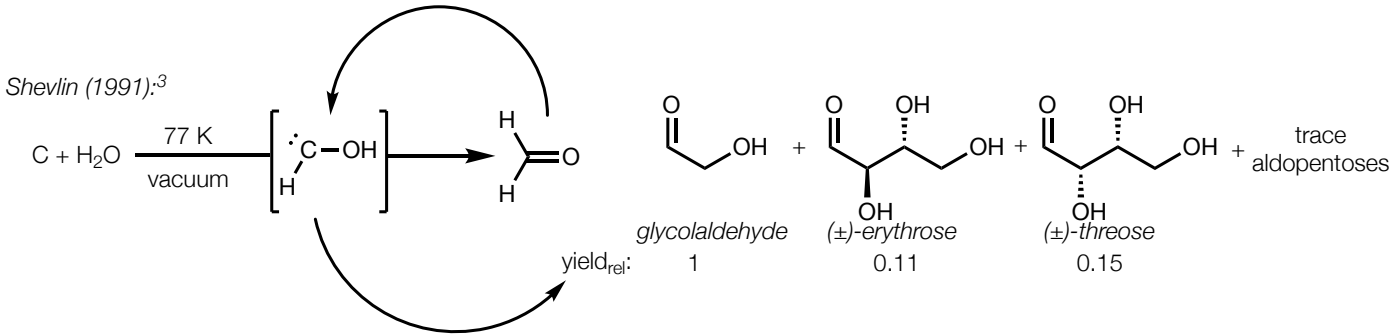
Cory (1977):[2]



- See Seyfirth-Gilbert, Corey-Fuchs, Doering-LaFlamme

Atomic Carbon in Nature

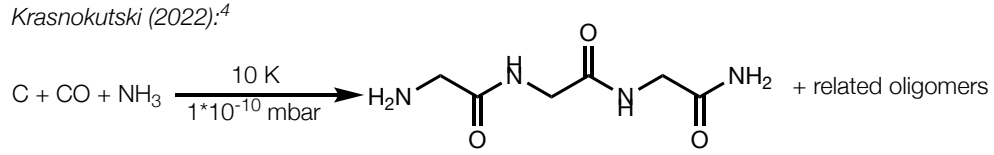
Shevlin (1991):[3]



Why should we care?

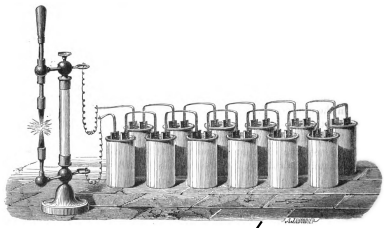
- Ideal atom economy
- Enables potentially simplifying disconnections

Krasnokutski (2022):[4]



1.) *Reactive Intermediate Chemistry*; Moss, R. A., Platz, M., Jones, M., Eds.; Wiley-Interscience: Hoboken, N.J, 2004.
2.) Cory, R. M.; Burton, L. P. J.; Chan, D. M. T.; McLaren, F. R.; Rastall, M. H.; Renneboog, R. M. ***Can. J. Chem.*** **1984**, *62*, 1908.
3.) Flanagan, G.; Ahmed, S. N.; Shevlin, P. B. ***J. Am. Chem. Soc.*** **1992**, *114*, 3892.
4.) Krasnokutski, S. A.; Chuang, K.-J.; Jäger, C.; Ueberschaar, N.; Henning, T. ***Nat Astron*** **2022**, *6*, 381.

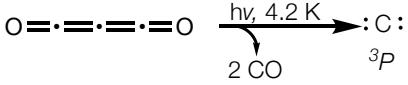
Generation of Atomic Carbon: A Brief Timeline



1800-1810

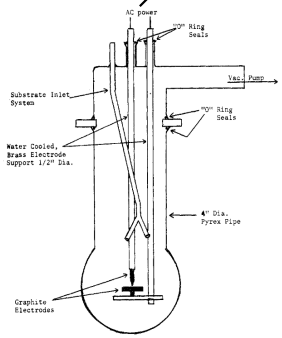
Carbon arc lamp invented by Sir Humphry Davy

Thompson (1966):[5]



Photolysis of carbon suboxide reported to generate C(³P)

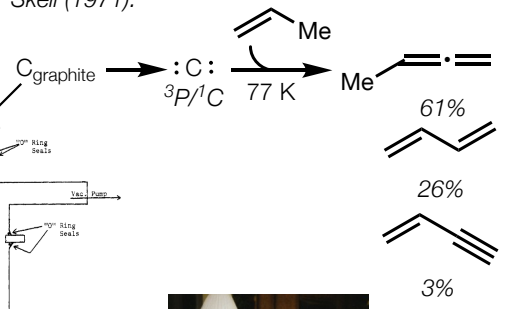
1966



1964

Carbon arc reactor first described by Skell

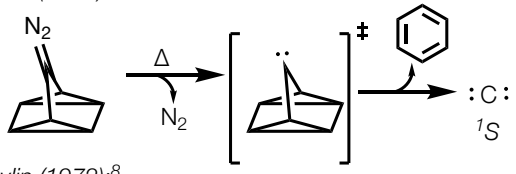
Skell (1971):[6]



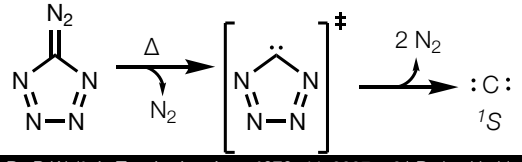
1970s

First C(¹S) synthetic equivalents reported by Shevlin

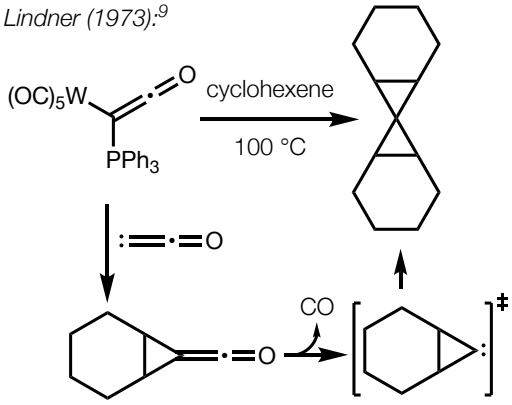
Shevlin (1970):[7]



Shevlin (1972):[8]



Lindner (1973):[9]

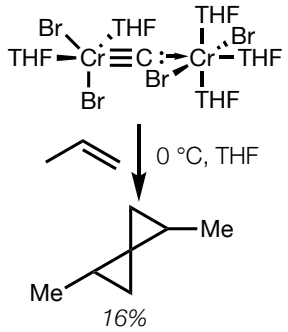


First organometallic C equivalent reported by Lindner

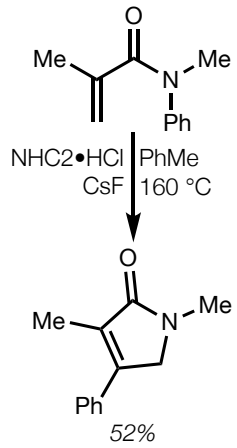
1973

2021

Takai (2021):[10]



Tobisu (2023):[11]



2023

Use of NHC as C atom donor

5.) Moll, N. G.; Thompson, W. E. *J. Chem. Phys.* **1966**, *44*, 2684.
6.) Skell, P. S.; Havel, J. J.; McGlinchey, M. J. *Acc. Chem. Res.* **1973**, *6*, 97.
7.) Shevlin, P. B.; P. Wolf, A. *Tetrahedron Lett.* **1970**, *11*, 3987.
8.) Shevlin, P. B. *J. Am. Chem. Soc.* **1972**, *94*, 1379.
9.) Berke, H.; Lindner, E. Angew. Chem. Int. Ed. 1973, 12, 667.
10.) Kurogi, T.; Irifune, K.; Takai, K. *Chem. Sci.* **2021**, *12*, 14281.
11.) Kamitani, M.; Nakayasu, B.; Fujimoto, H.; Yasui, K.; Kodama, T.; Tobisu, M. *Science* **2023**, *379*, 484.

Generation of Stereocenters via Single Carbon-Atom Doping Using *N*-Isocyanides

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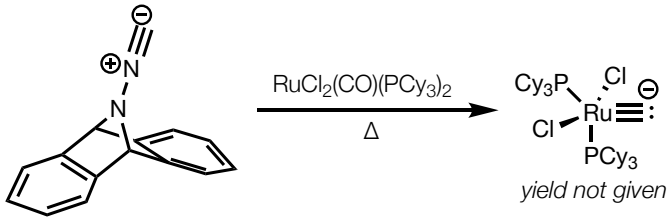
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

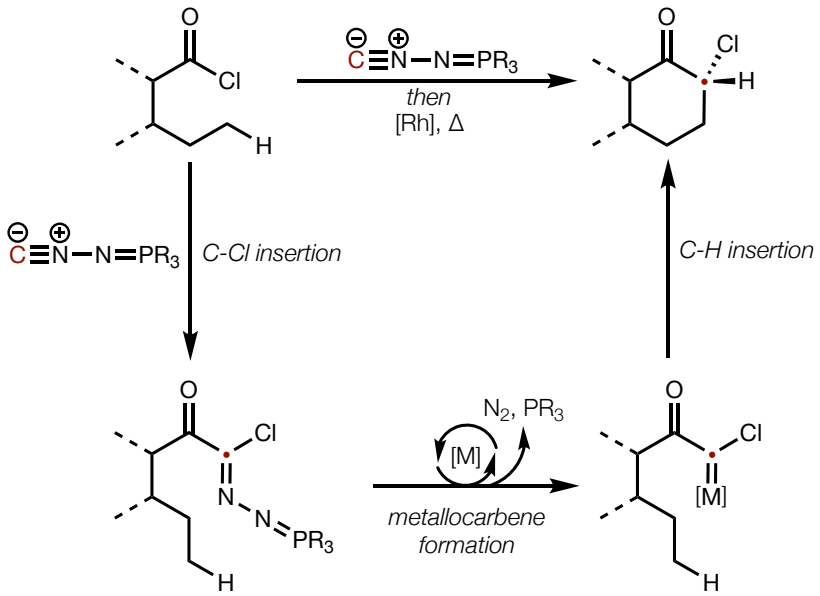
Cummins (2017):[12]



yield not given

- Explosively decomposes to carbide complex
- Can isonitriles serve as carbon atom equivalents in organic reactions?

Desired Transformation:



Prof. Mamoru Tobisu

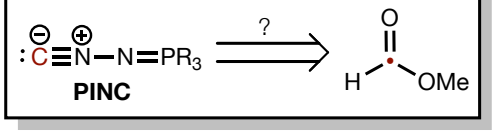
Career

- 2001 — PhD under Shinji Murai
- 2001-2005 — Takeda, Scientist
- 2005-2011 — Assistant prof. with Naoto Chatani
- 2011-2017 — Associate prof.
- 2017 — Tenured prof.

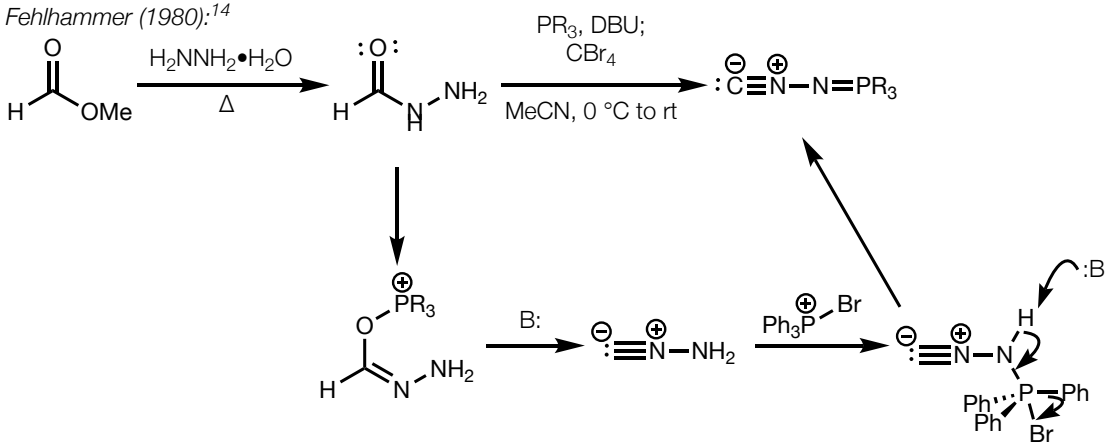
12.) Joost, M.; Nava, M.; Transue, W. J.; Cummins, C. C. *Chem. Commun.* **2017**, *53*, 11500.
13.) Fujimoto, H.; Nishioka, T.; Imachi, K.; Ogawa, S.; Nishimura, R.; Tobisu, M. *J. Am. Chem. Soc.* **2025**.

Method Development

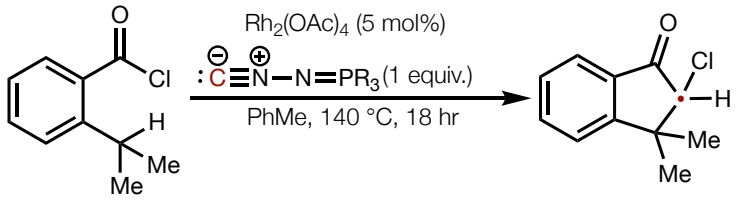
Isonitrile Synthesis:



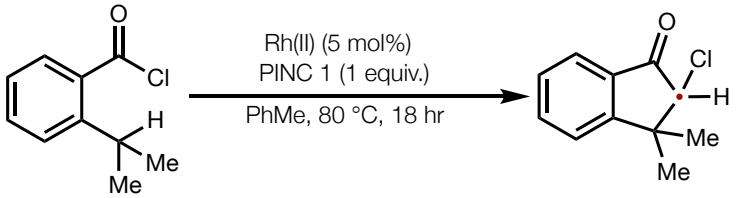
Fehlhammer (1980):[14]



Isonitrile Screen:



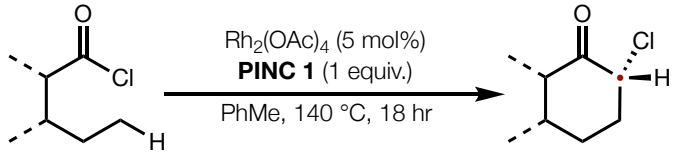
Entry	R	Yield (%)
1	**Ph**	**74**
2	p-ClPh	60
3	p-OMePh	37
4	Cy	20

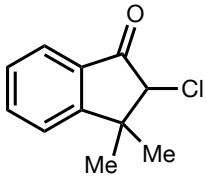


Entry	Rh(II)	Yield (%)
1	**$Rh_2(OAc)_4$**	**29**
2	$Rh_2(TPA)_4$	1
3	$Rh_2(TFA)_4$	4
4	$Rh_2(esp)_2$	10
5	none	0

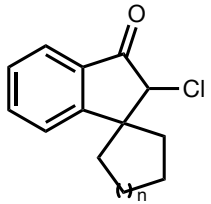
13.) Fujimoto, H.; Nishioka, T.; Imachi, K.; Ogawa, S.; Nishimura, R.; Tobisu, M. *J. Am. Chem. Soc.* **2025**.
14.) Weinberger, B.; Fehlhammer, W. P. *Angew. Chem. Int. Edi.* **1980**, *19*, 480.

Abbreviated Scope

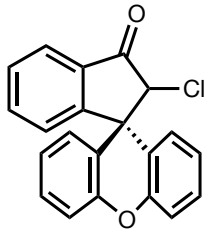




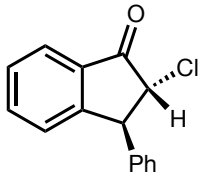
2a: 74%



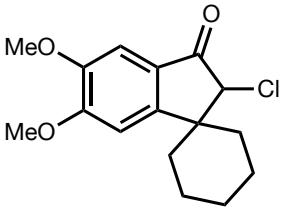
2b (n=1): 59%
2c (n=2): 56%
2d (n=1): 59%



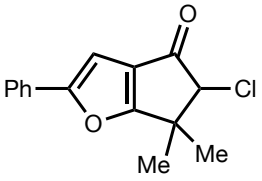
2e: 45%



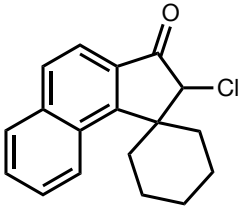
2f: 45%
>20:1 dr



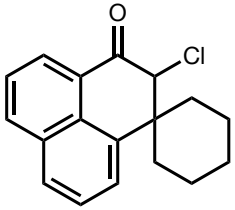
2g: 52%



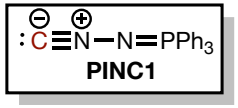
2h: 46%



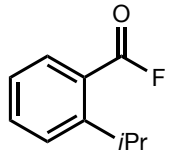
2i: 41%



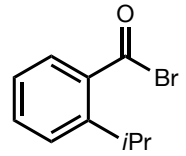
2j: 29%



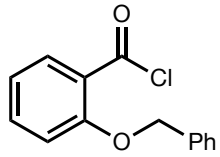
Problematic Substrates:



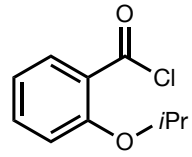
no conversion



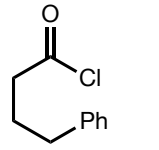
8%



trace



trace



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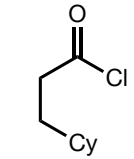
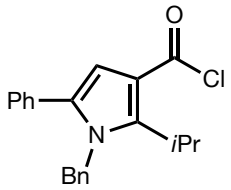


12%



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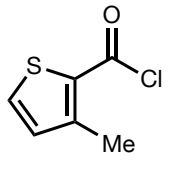
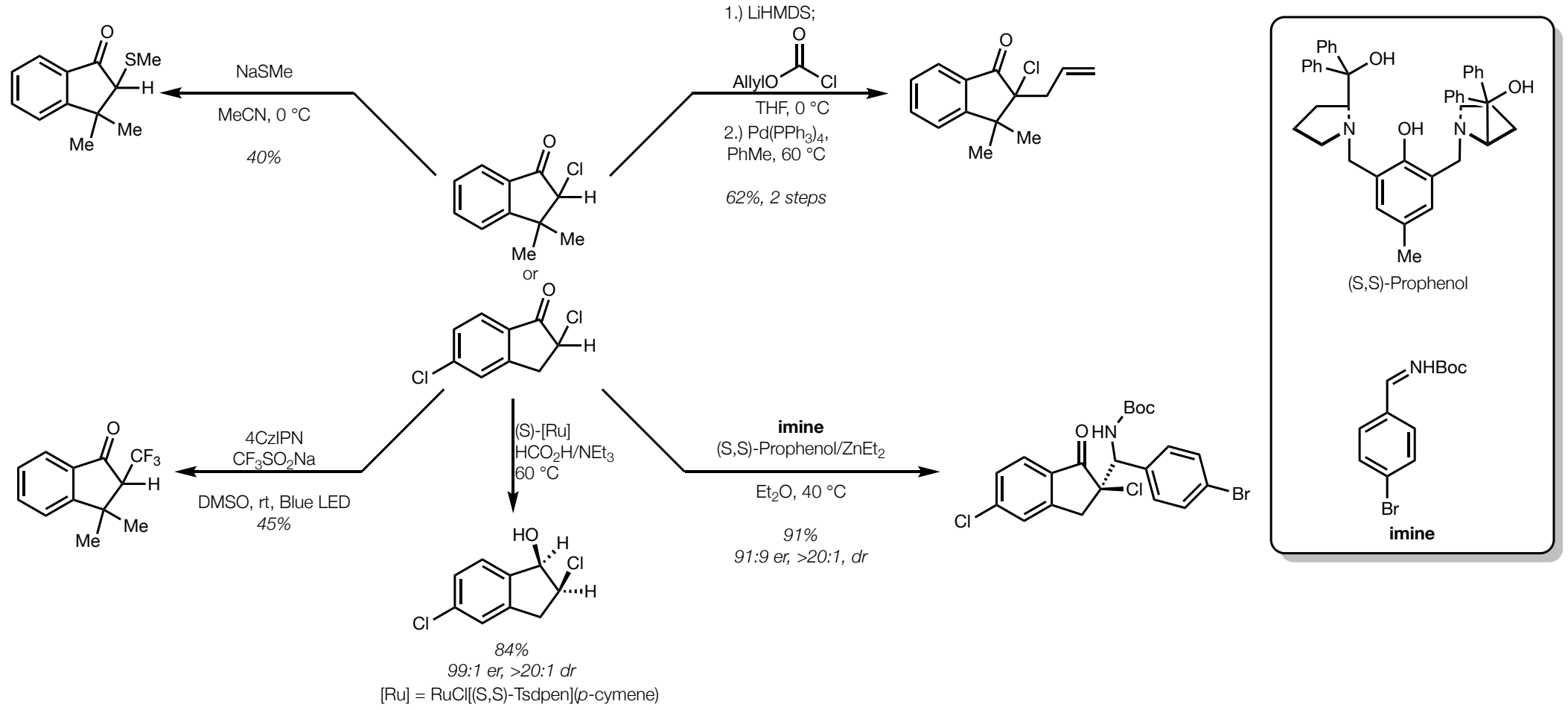


trace

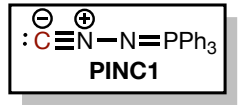
13.) Fujimoto, H.; Nishioka, T.; Imachi, K.; Ogawa, S.; Nishimura, R.; Tobisu, M. *J. Am. Chem. Soc.* **2025**.

Derivatization

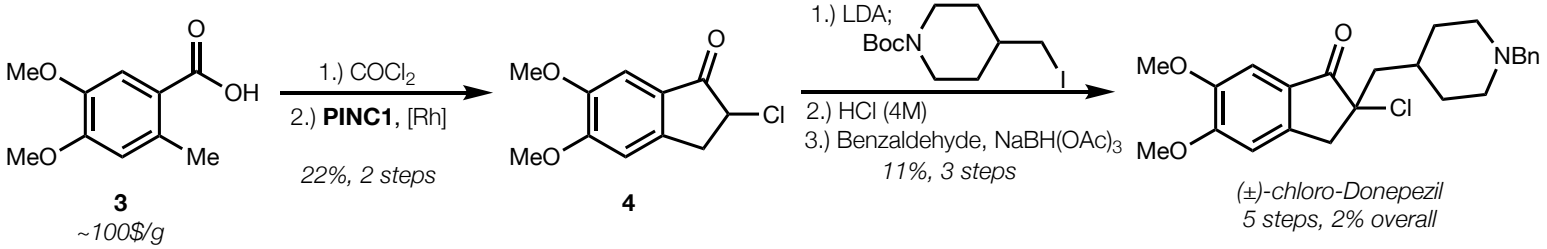


13.) Fujimoto, H.; Nishioka, T.; Imachi, K.; Ogawa, S.; Nishimura, R.; Tobisu, M. *J. Am. Chem. Soc.* **2025**.

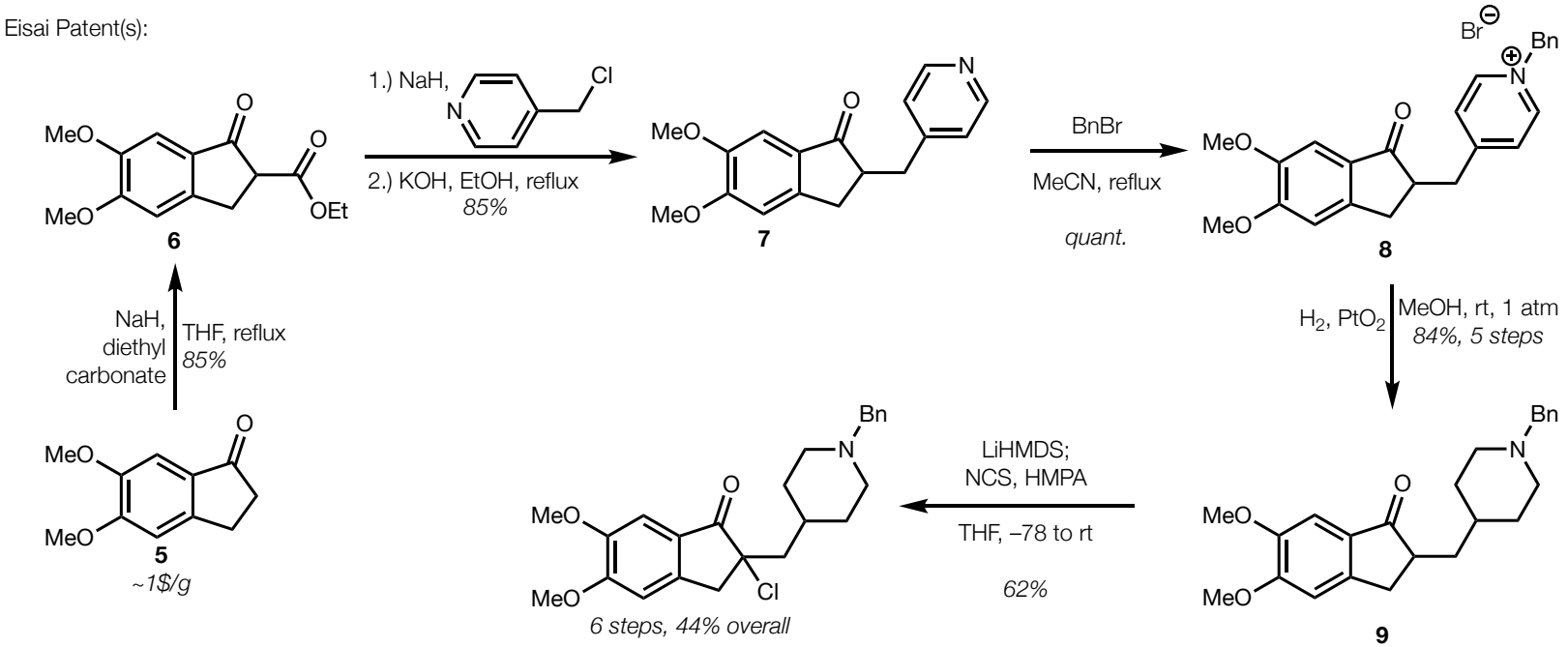
Derivatization - Synthesis of chloro-Donepezil



Tobisu's Synthesis:

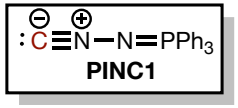


Eisai Patent(s):

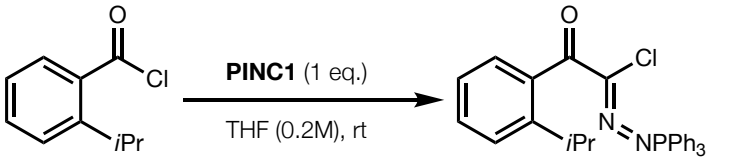


13.) Fujimoto, H.; Nishioka, T.; Imachi, K.; Ogawa, S.; Nishimura, R.; Tobisu, M. *J. Am. Chem. Soc.* **2025**.
15a.) EISAI - US6252081, 2001, B1; 15b.) EISAI - EP1209151, 2002, A1

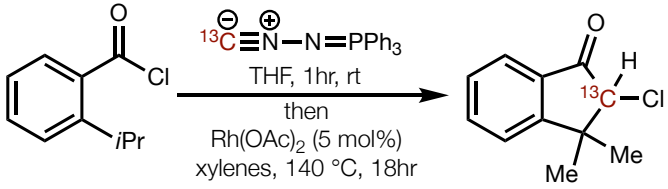
Mechanistic Studies



Characterization of Phosphazine Intermediate:

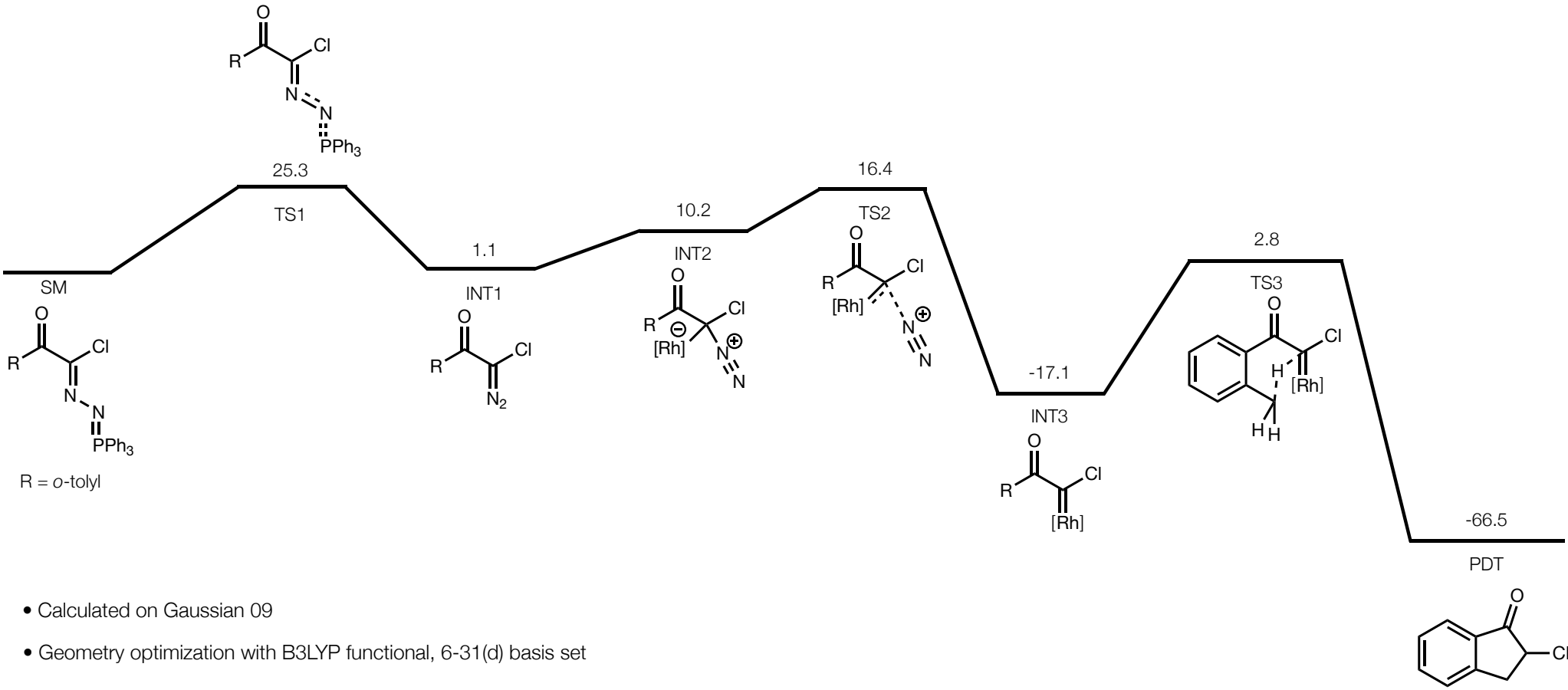


Isotopic Labeling:



13.) Fujimoto, H.; Nishioka, T.; Imachi, K.; Ogawa, S.; Nishimura, R.; Tobisu, M. *J. Am. Chem. Soc.* **2025**.

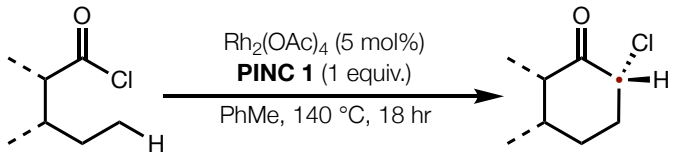
Computational Studies



- Calculated on Gaussian 09
- Geometry optimization with B3LYP functional, 6-31(d) basis set

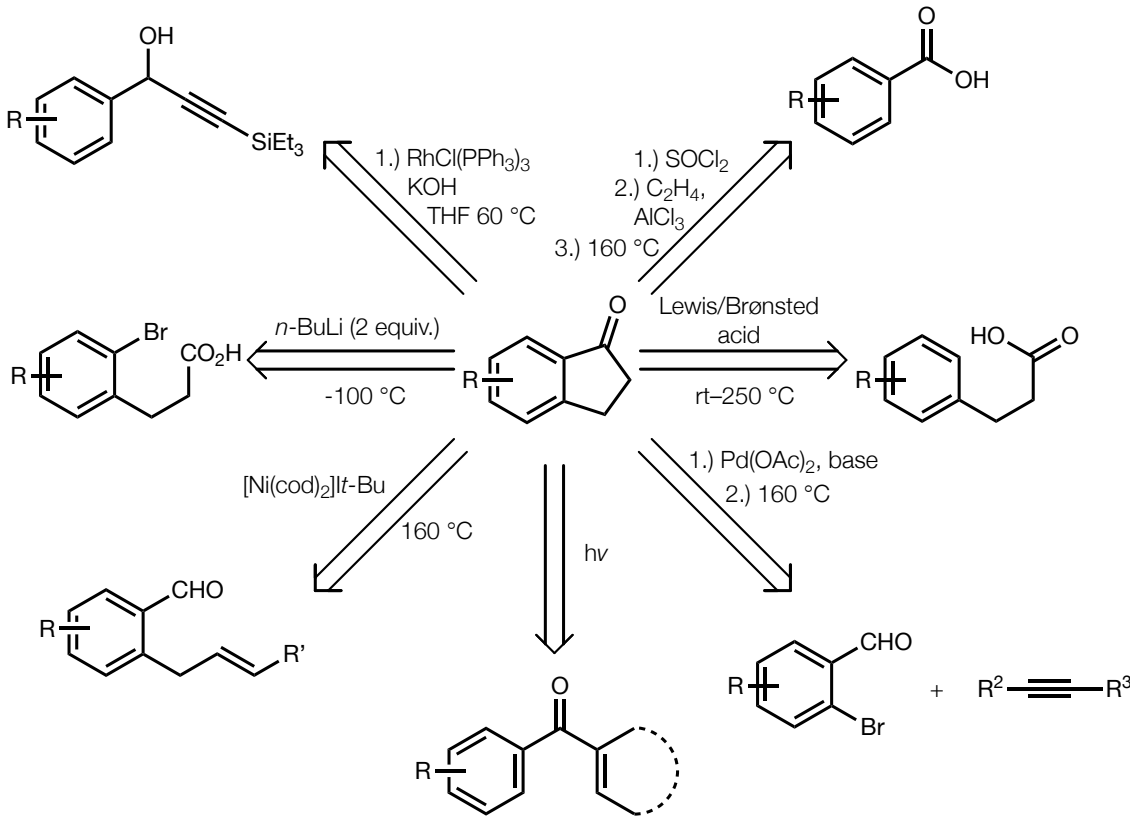
13.) Fujimoto, H.; Nishioka, T.; Imachi, K.; Ogawa, S.; Nishimura, R.; Tobisu, M. *J. Am. Chem. Soc.* **2025**.

Summary



- Development of (N-isocyanoimino)phosphoranes as atomic carbon equivalents
- Novel synthesis of substituted indanones from acyl chlorides
  - Tolerant of benzylic substitution, varied aryl groups
  - Comparatively mild addition to repertoire for synthesizing indanones

Abridged syntheses of indanones:[16]



13.) Fujimoto, H.; Nishioka, T.; Imachi, K.; Ogawa, S.; Nishimura, R.; Tobisu, M. ***J. Am. Chem. Soc.*** **2025**.
16.) Turek, M.; Szczęsna, D.; Koprowski, M.; Bałczewski, P. ***Beilstein J. Org. Chem.*** **2017**, *13*, 451.

February Surprise

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Communication

Generation of Stereocenters via Single-Carbon-Atom Doping Using *N*-Isocyanides

Hayato Fujimoto,* Teruki Nishioka, Kazuya Imachi, Satoshi Ogawa, Rio Nishimura, and Mamoru Tobisu*

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ORGANIC CHEMISTRY

Spiro-C(sp^3)-atom transfer: Creating rigid three-dimensional structures with Ph_2SCN_2

Qiu Sun[1], Jan-Niklas Belting[1], Julian Hauda[1], David Tymann[1], Patrick W. Antoni[1], Richard Goddard[2], Max M. Hansmann[1]*

Sun *et al.*, *Science* **387**, 885–892 (2025) 21 February 2025

13.) Fujimoto, H.; Nishioka, T.; Imachi, K.; Ogawa, S.; Nishimura, R.; Tobisu, M. *J. Am. Chem. Soc.* **2025**.
17.) Sun, Q.; Belting, J.-N.; Hauda, J.; Tymann, D.; Antoni, P. W.; Goddard, R.; Hansmann, M. M. *Science* **2025**, *387*, 885.

Spiro-C(sp³)-atom transfer: Creating Rigid 3D Structures with Ph_2SCN_2

Career

Visiting researcher with Mark Lautens, UToronto

Alexander von Humboldt postdoctoral fellow with Guy Betrand, UCSD

technische universität dortmund

Junior professor

2009-2011 MsC, Chemistry

2012-2013

2012-2015 PhD under Stephen Hashimi

2015-2017

2018-2019 Group leader, Georg August Universität Göttingen

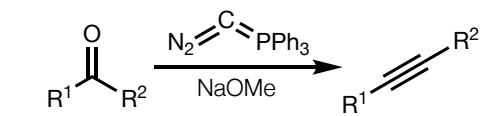
2019-2023

2023 Tenured professor

Prof. Max Hansmann

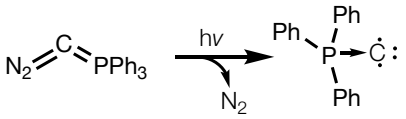
Development of Atomic Carbon Equivalents:

Ph_3PCN_2 - A stable reagent for carbon-atom transfer (2024):[18]



R = alkyl, aryl, H

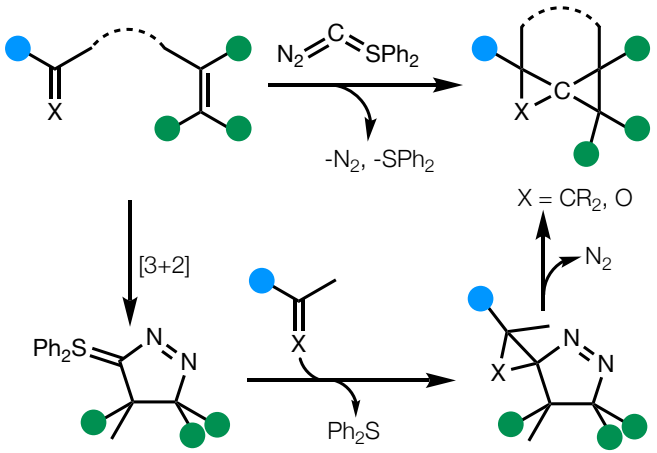
Ph_3PC – A Monosubstituted C(0) Atom in Its Triplet State (2025):[19]



observed in situ

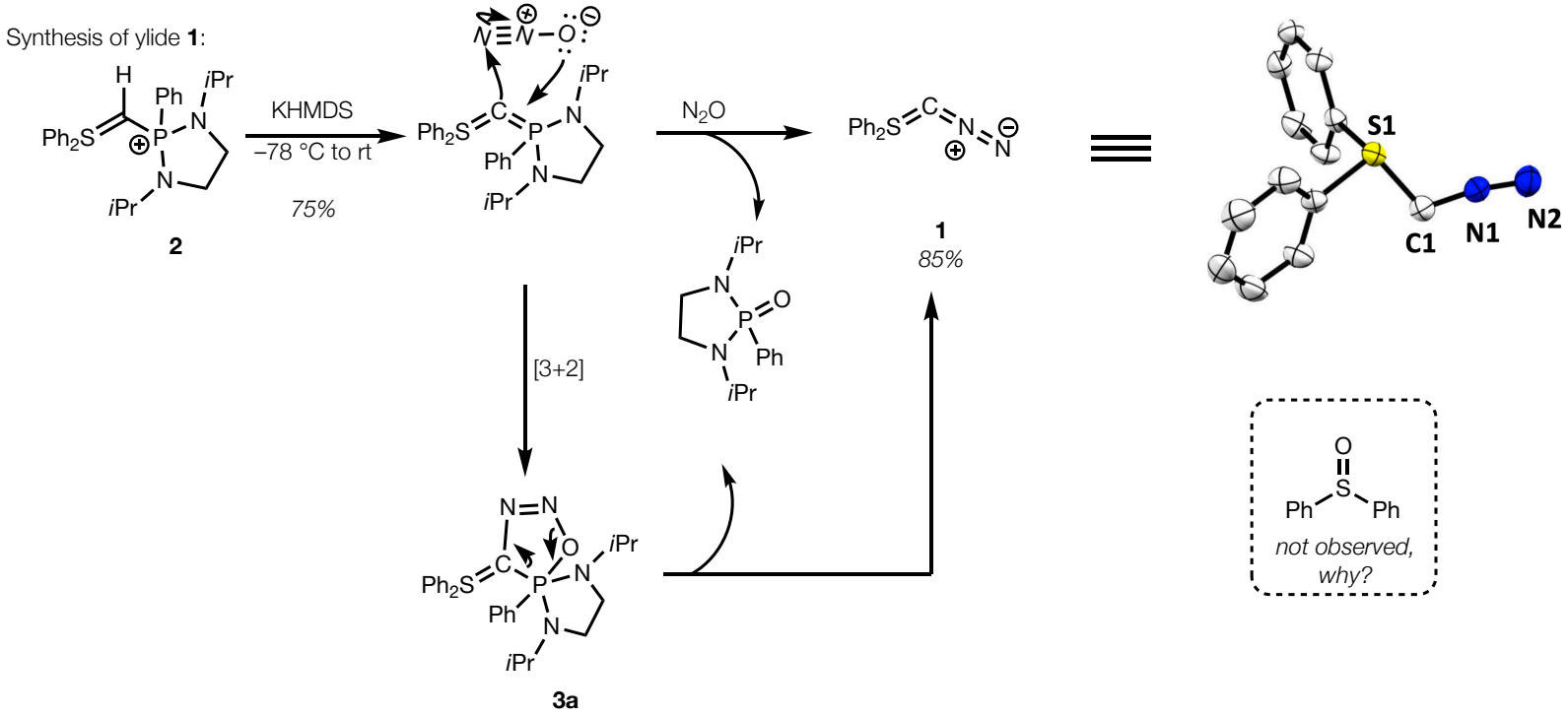
Can atomic carbon equivalents reliably generate spirocyclic systems?

Desired Transformation:



17.) Sun, Q.; Belting, J.-N.; Hauda, J.; Tymann, D.; Antoni, P. W.; Goddard, R.; Hansmann, M. M. *Science* **2025**, *387*, 885.

Method Development



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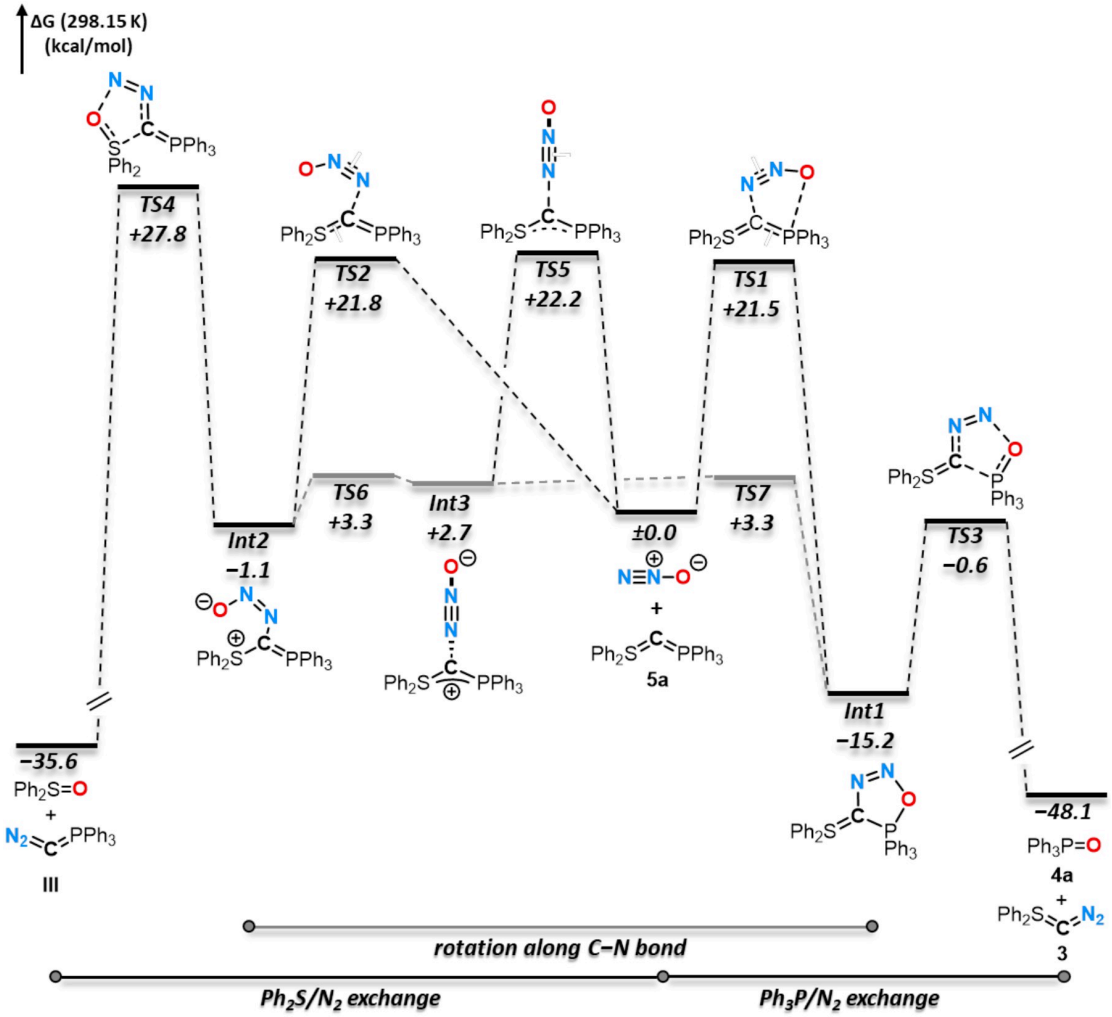
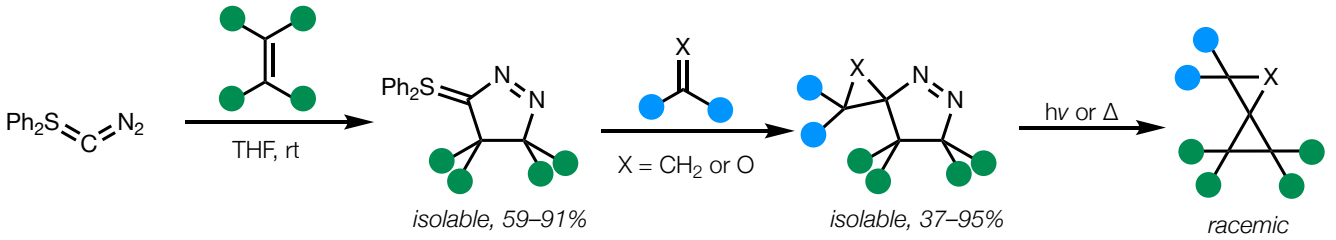
Method Development

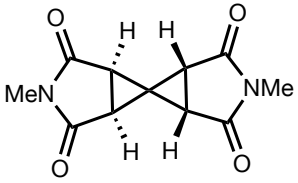


17.) Sun, Q.; Belting, J.-N.; Hauda, J.; Tymann, D.; Antoni, P. W.; Goddard, R.; Hansmann, M. M. *Science* **2025**, *387*, 885.

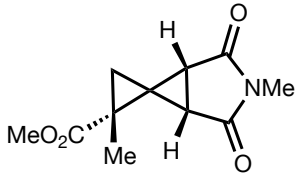
Abbreviated Scope

a.) Two-stage synthesis of biscyclopropanes:

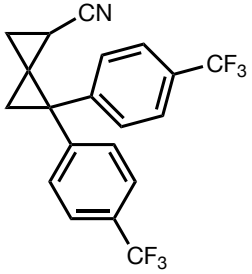




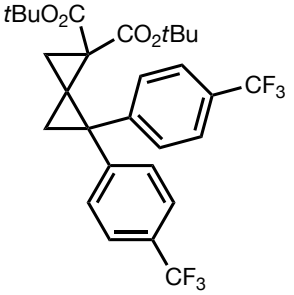
4a: *53%*



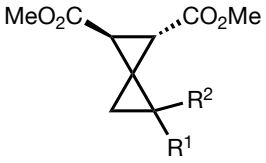
4b: *99%*



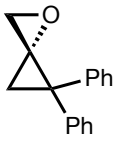
4c: *98%*



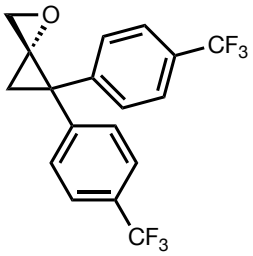
4d: *99%*



4e: R^1 = Me, R^2 = CO_2Me, *95%*
4f: R^1 = R^2 = Ph, *95%*
4g: R^1 = Me, R^2 = 2-py, *96%*
4h: R^1 = CF_3, R^2 = *p*-tol, *91%*



4i: *91%*



4j: *91%*

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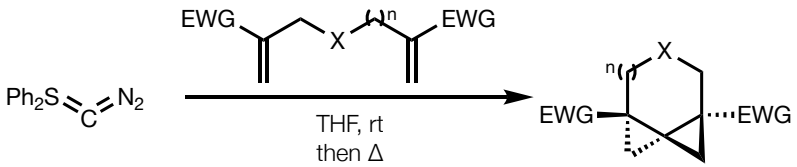
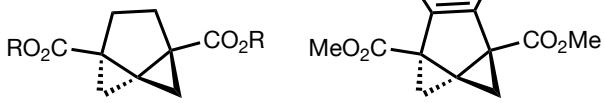
Abbreviated Scope

b.) Biscyclopropanation of tethered dienes



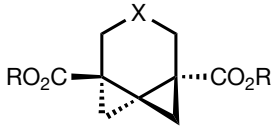
X = CH_2, S, O, N-Pg
racemic



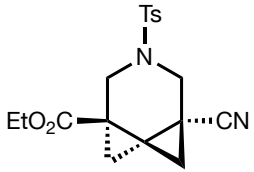
5a: R = Me, *72%*
5b: R = Et, *69%*

5c: *85%*

5d: *85%*

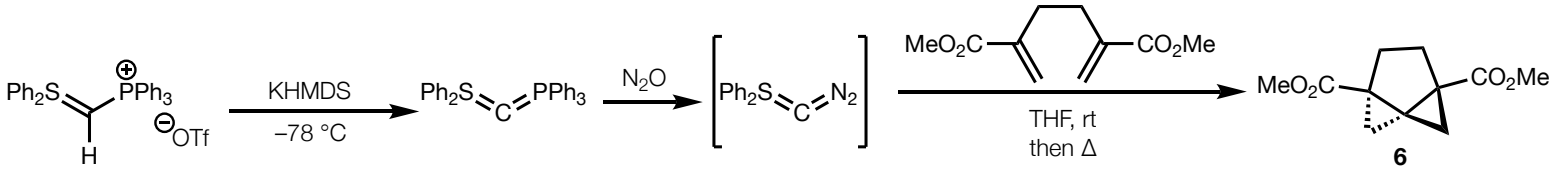


5e: X = CH_2, R = Et, *55%*[a]
5f: X = O, R = Me, *28%*
5g: X = S, R = Et, *53%*[a]



5h: *35%*

c.) One-pot carbon atom insertion sequence



6
81%

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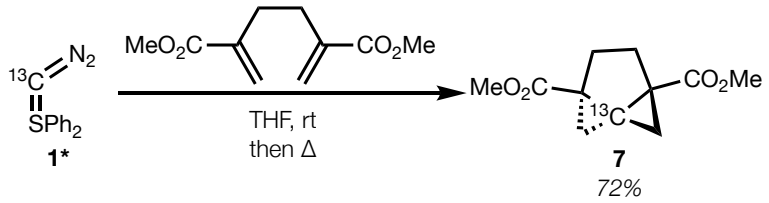
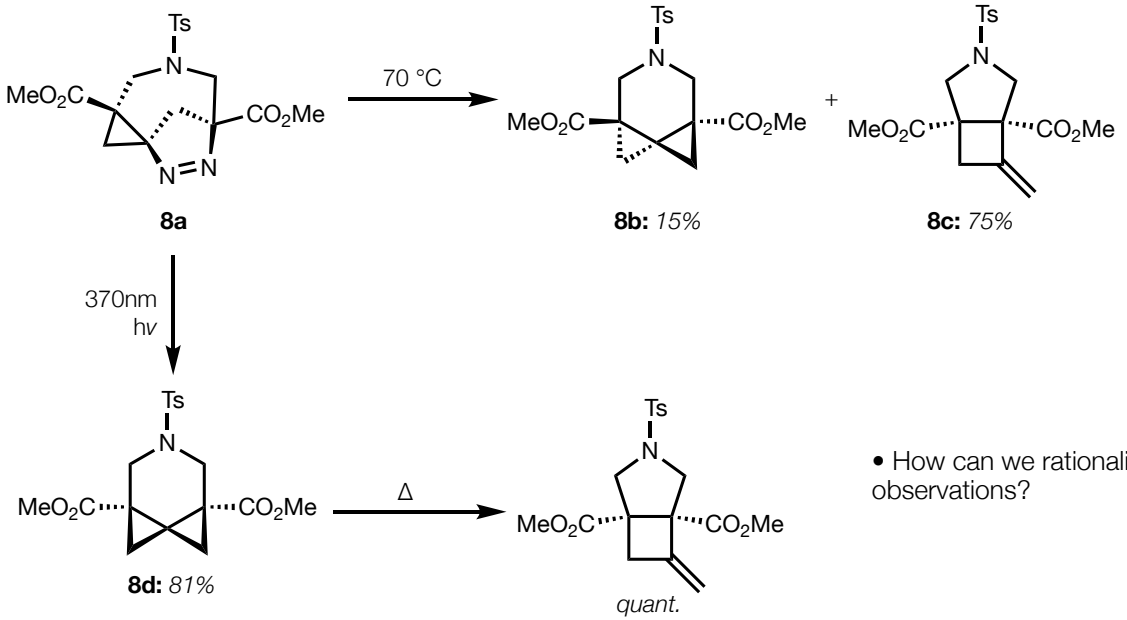
Mechanistic Studies

a.) Isotope labeling



b.) Nitrogen extrusion experiments

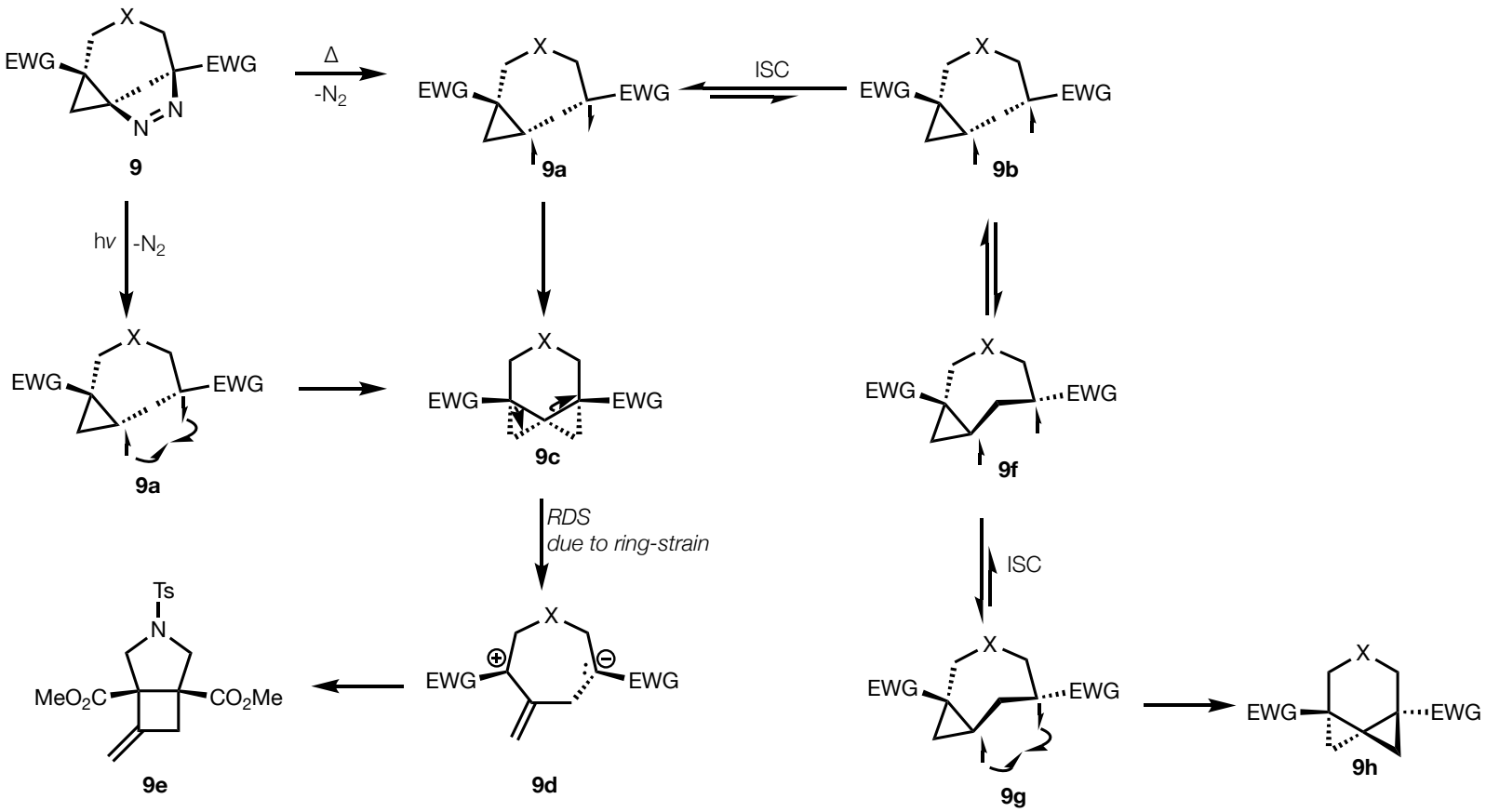


- How can we rationalize these observations?

17.) Sun, Q.; Belting, J.-N.; Hauda, J.; Tymann, D.; Antoni, P. W.; Goddard, R.; Hansmann, M. M. *Science* **2025**, *387*, 885.

Mechanistic Studies

c.) Proposed Mechanism



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Summary

- Development of diazosulfur ylides as general atomic carbon equivalents
- Controlled synthesis of biscyclopropanes via stepwise cyclopropanations
  - Tolerant of varying substitution, oxidation patterns
  - Low temperatures, high-yielding transformations
  - Proposed mechanism for formation of undesired azabicyclo[3.2.0]heptanes

17.) Sun, Q.; Belting, J.-N.; Hauda, J.; Tymann, D.; Antoni, P. W.; Goddard, R.; Hansmann, M. M. *Science* **2025**, *387*, 885.

Thanks for your time!
Questions?