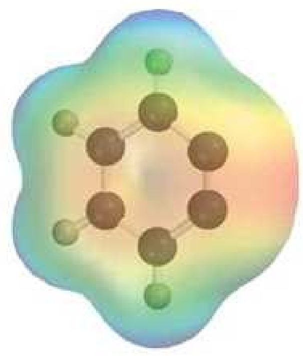
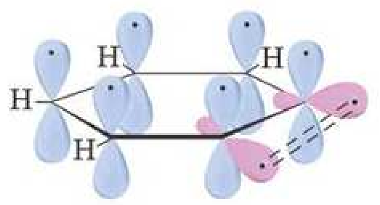


Chemistry of Dehydro-Diels-Alder Reaction

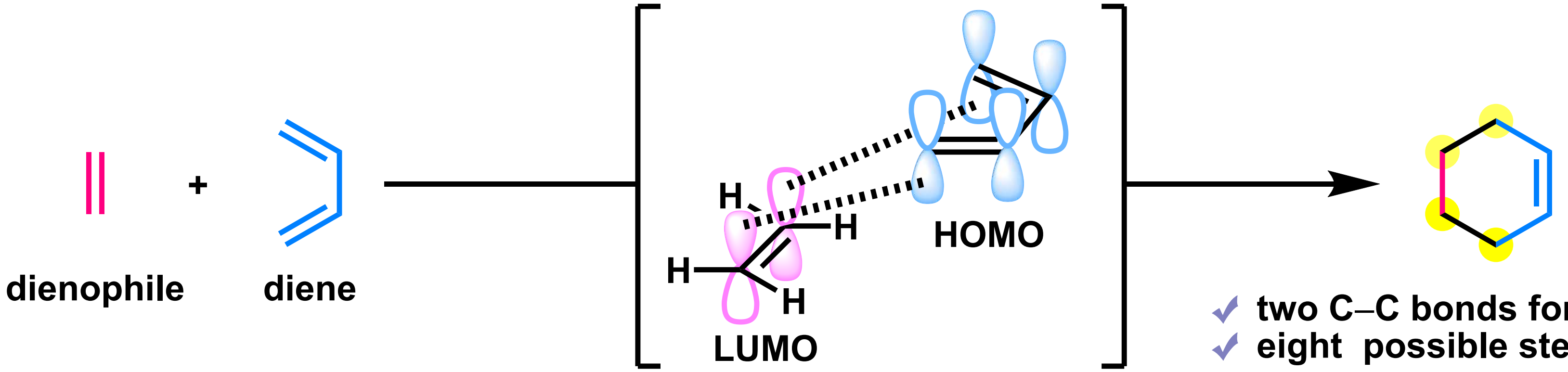


LS 2016.10.24

Takahiro Kawamata

Contents

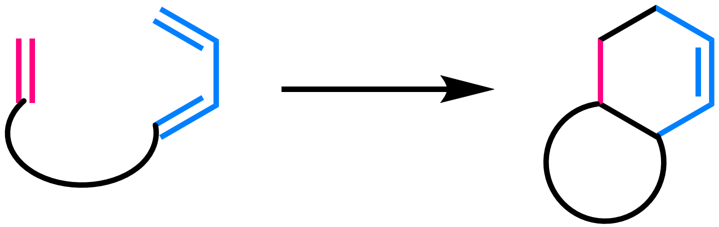
Diels-Alder Reaction



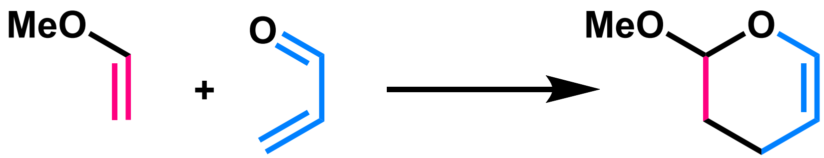
✓ two C–C bonds formation
✓ eight possible stereoisomers

Specific types or variants of Diels-Alder reactions

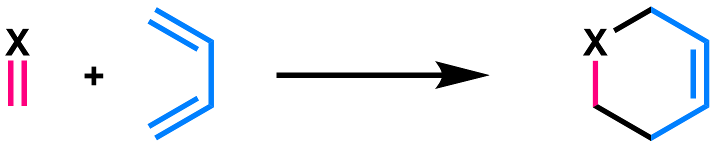
- **intramolecular (IMDA) reaction**



- **inverse electron demand HDA reaction**

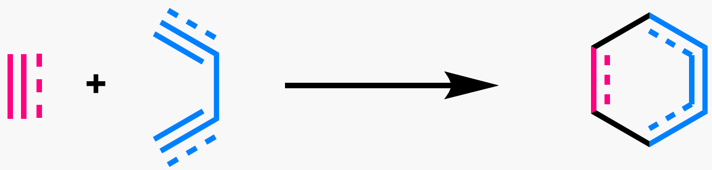


- **hetero-Diels-Alder (HDA) reaction**



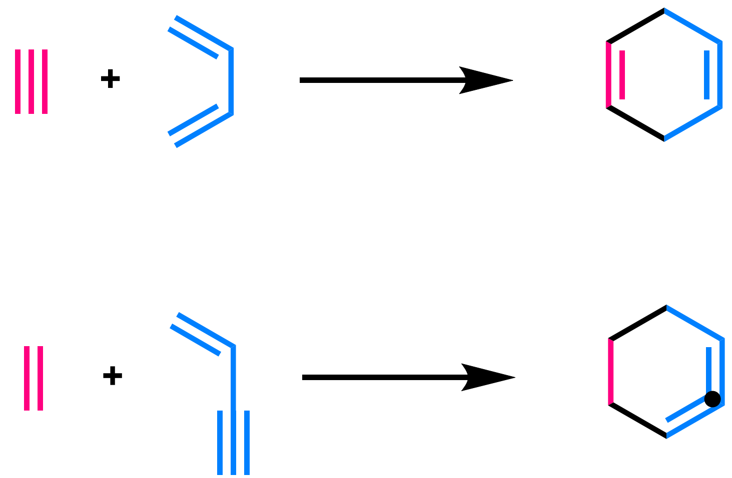
X = O, N, S

- **dehydro-Diels-Alder (DDA) reaction**

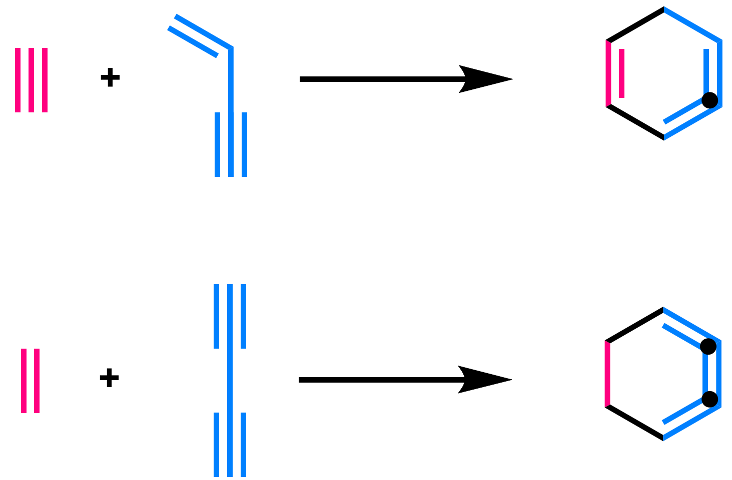


Dehydro-Diels-Alder Reaction

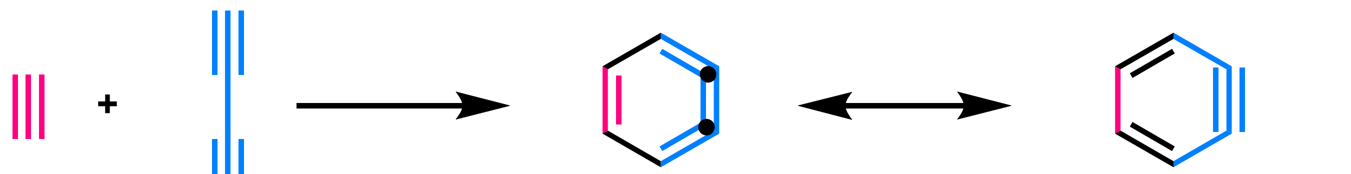
Didehydro-Diels-Alder (DDDA) reaction



Tetradehydro-Diels-Alder (TDDA) reaction



Hexadehydro-Diels-Alder (HDDA) reaction



Wessig, P.; Müller, G. *Chem. Rev.* **2008**, *108*, 2051.

Landmark Events

Benzyne/aryne chemistry

1902
First evidence for intermediacy of a benzyne

1953-1963
Definitive support for the intermediacy of benzyne

1967
~1000 publications of benzyne-related studies

1983
Kobayashi method (o-TMSC$_6$H$_4$OTf + F$^-$); the most widely used protocol

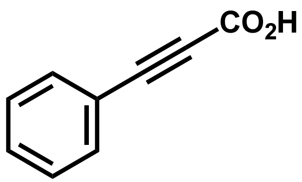
1900 — 1920 — 1940 — 1960 — 1980 — 2000

1898
Michael describes the dimerization of phenylpropynoic acid

1928
Diels and Alder report the first diene + dienophlie cycloaddition reaction

1997
First examples of triyne cyclizations to generate benzynes by Ueda and Johnson

2012
Hexadehydro Diels-Alder (HDDA) reaction shown to have broad scope by Hoye

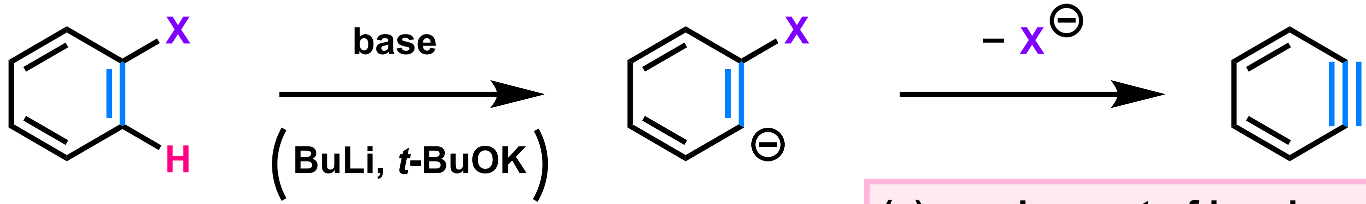


Diels-Alder chemistry

Baire, B.; Niu, D.; Willoughby, P. H.; Woods, B. P.; Hoye, T. R. *Nature Protocols* **2013**, *8*, 501.

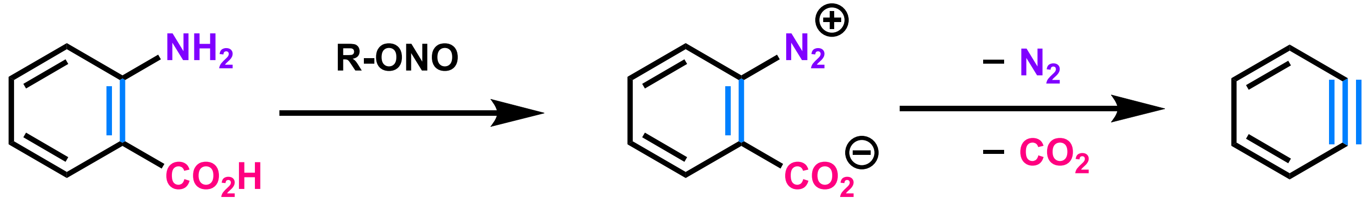
Methods for the Generation of *o-Benzyne*

Conventional method of benzyne generation



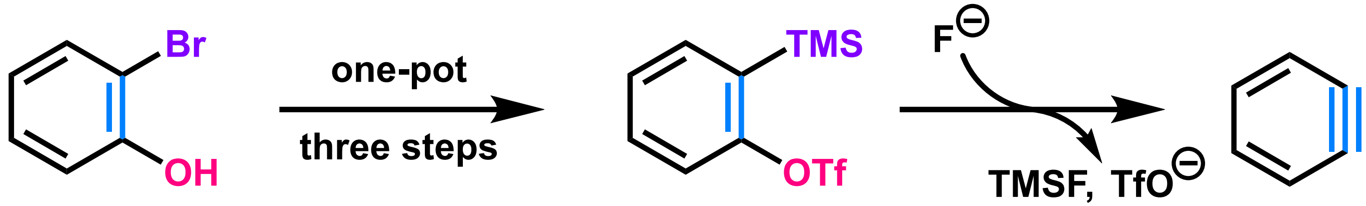
(–) requirement of harsh conditions
(–) base sensitive substrate not tolerable

Benzyne from benzenediazonium 2-carboxylate



(–) explosive nature of diazonium compounds

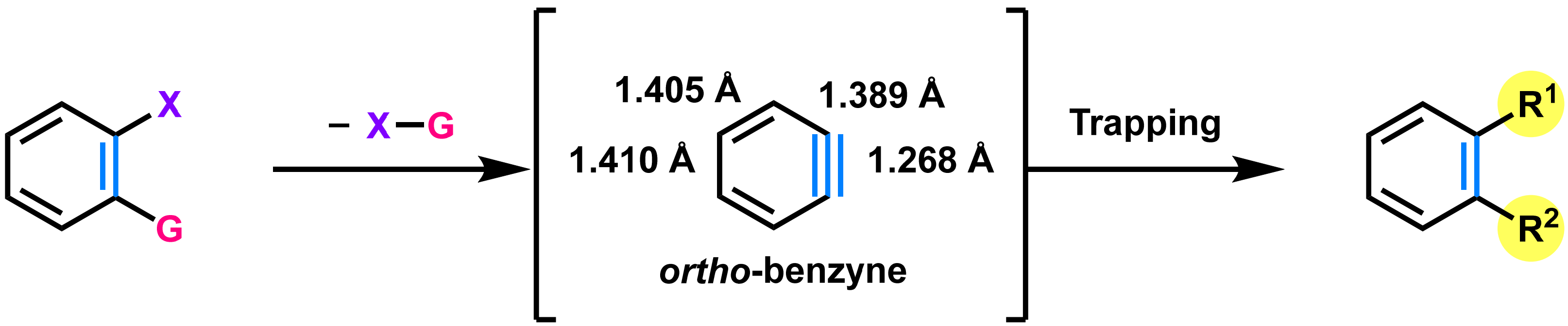
Benzyne generation from 2-(trimethylsilyl)aryl triflate (widely used Kobayashi method)



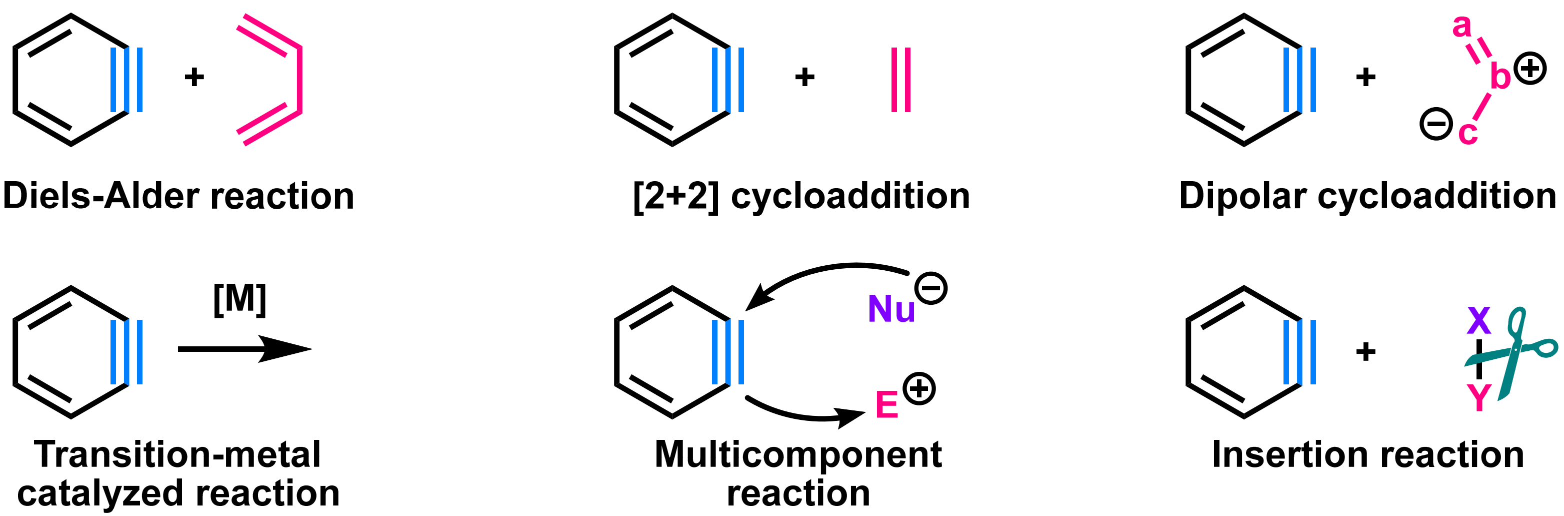
(+) mild and base-free protocol
(+) compatibility with various substrates

Bhojgude, S. S.; Bhunia, A.; Biju, A. T. *Acc. Chem. Res.* **2016**, *49*, 1658.

o-Benzyne Generation and Trapping



Possible modes of action of benzyne



Bhunia, A.; Yetra, S. R.; Biju, A. T. *Chem. Soc. Rev.* **2012**, *41*, 3140.

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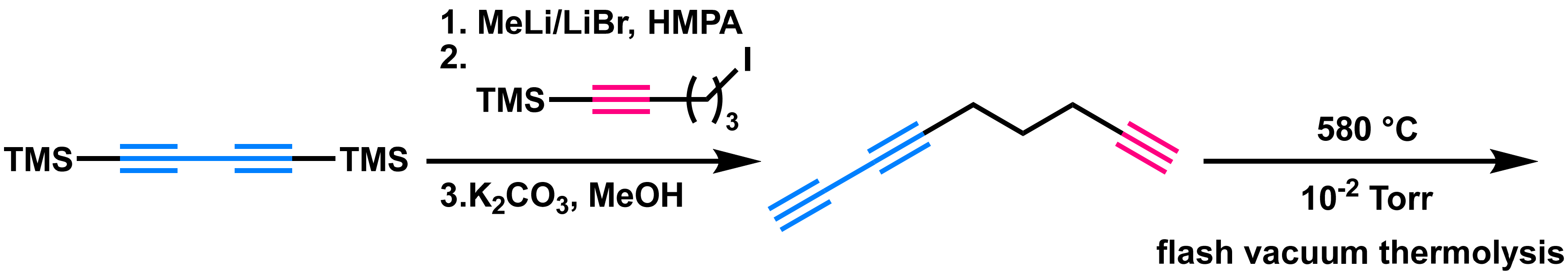
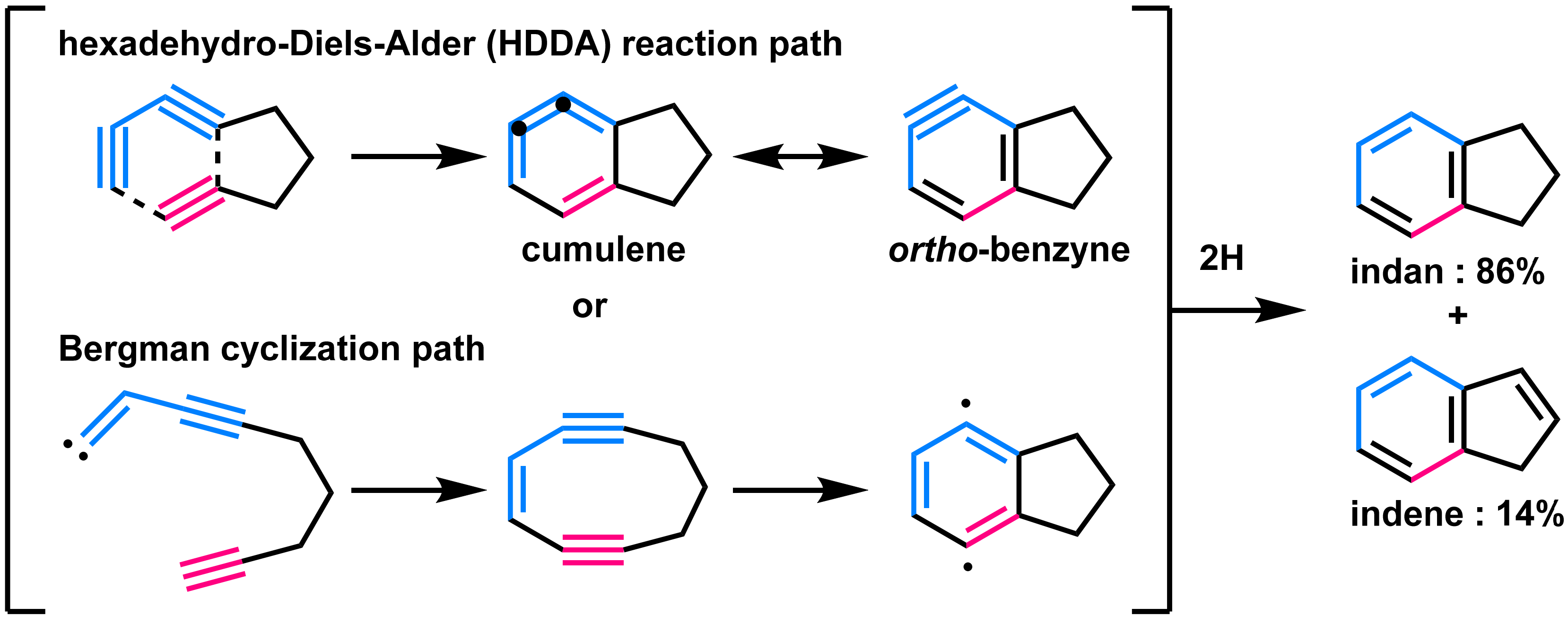
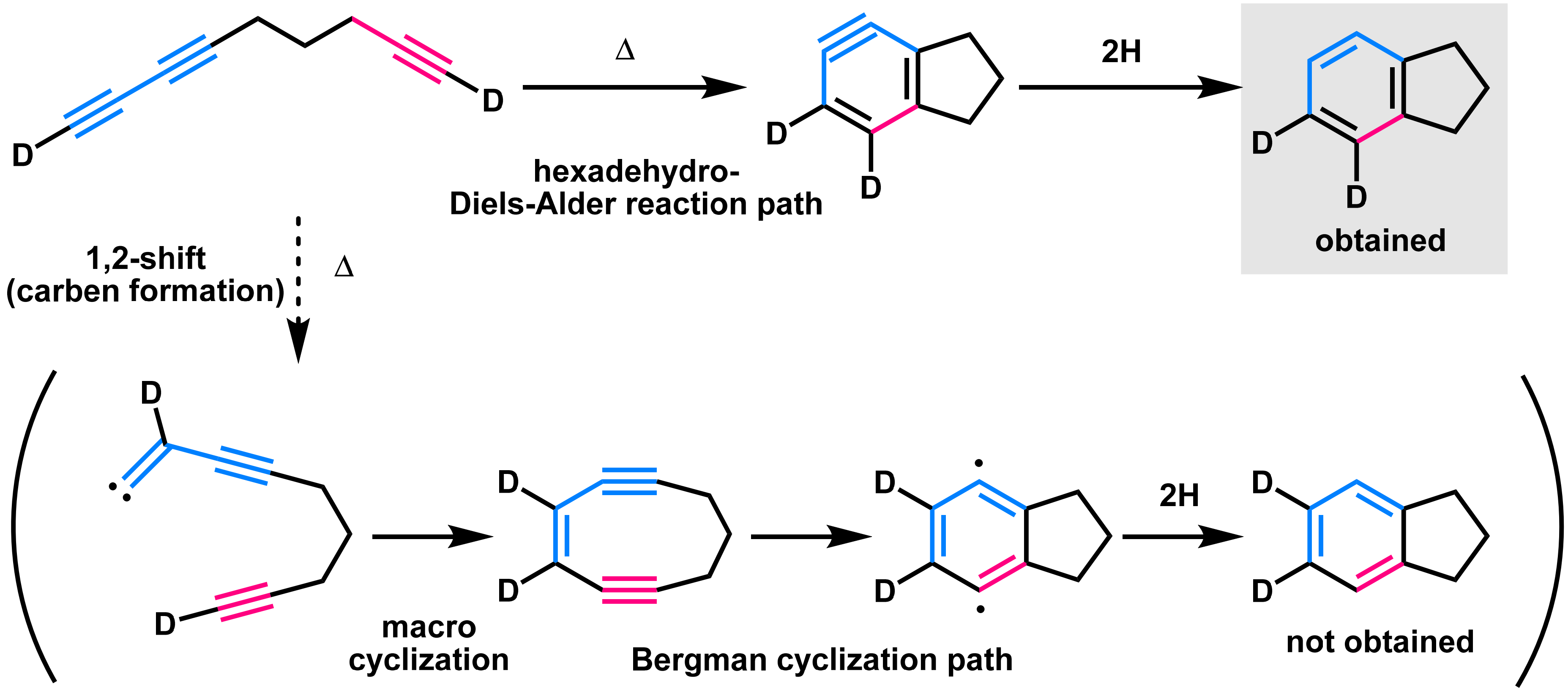
Johnson's Discovery





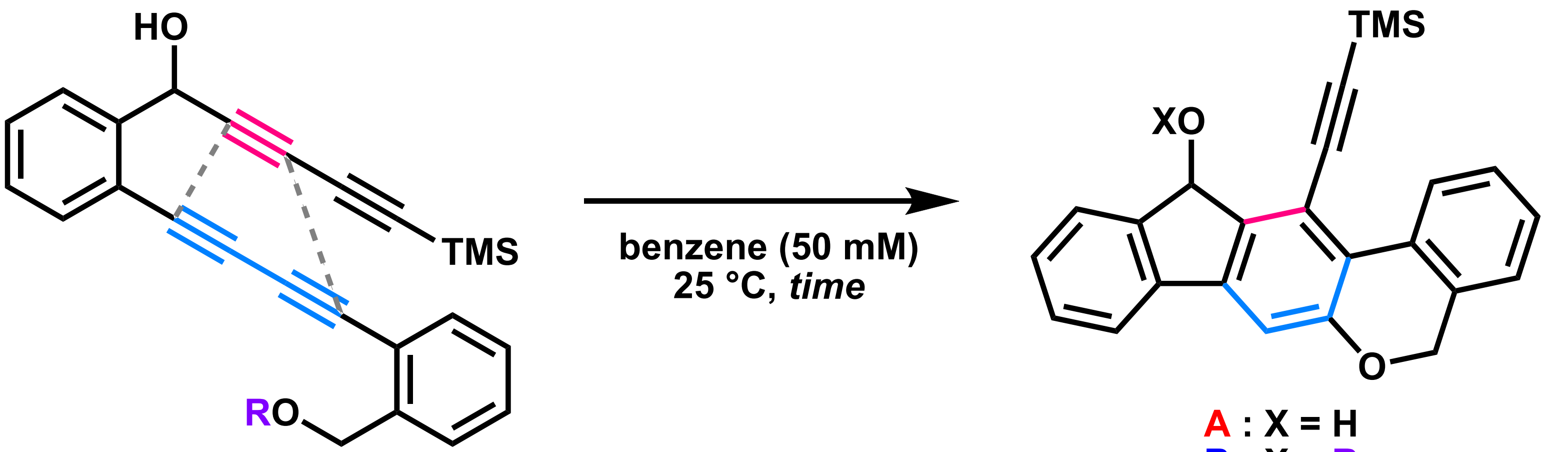
Bradley, A. Z.; Johnson, R. P. *J. Am. Chem. Soc.* **1997**, *119*, 9917.

Deuterium Labeling Study

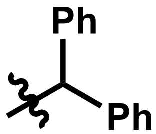
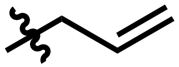
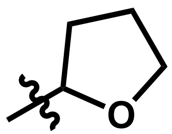


Bradley, A. Z.; Johnson, R. P. *J. Am. Chem. Soc.* **1997**, *119*, 9917.

Studies by Ueda Group

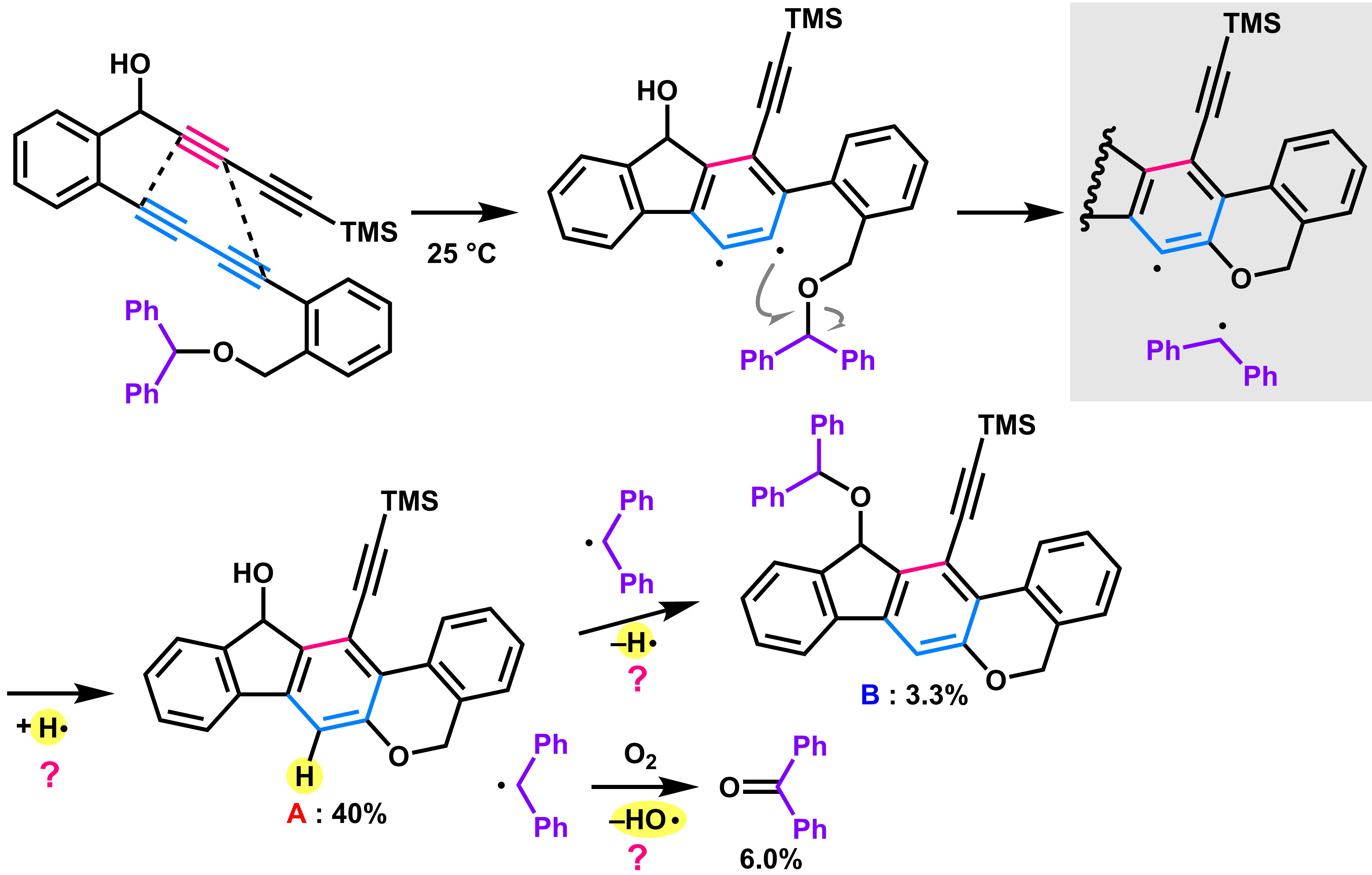


A : X = H
B : X = R

R	*time*	results	R	*time*	results
Me	48	A : 45%, B : 38%		72	A : 40%, B : 3.3% benzophenone : 6.0%
	72	A : 66%, B : 6.3%		48	A : 52%, B : not detected
	72	A : 53%, B : 14%			

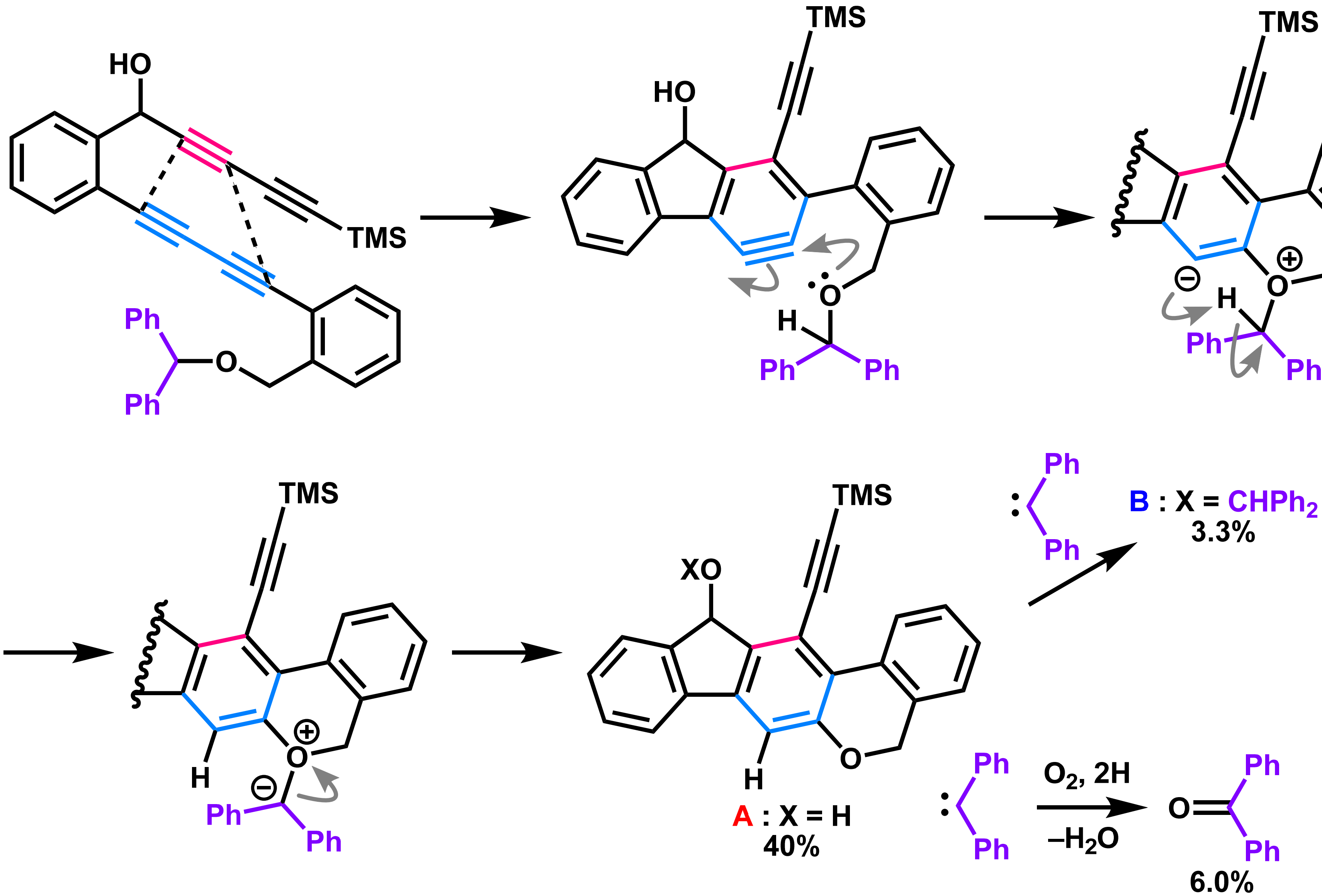
Miyawaki, K.; Suzuki, R.; Kawano, T.; Ueda, I. *Tetrahedron Lett.* **1997**, *38*, 3943.

Proposed Mechanism by Ueda Group

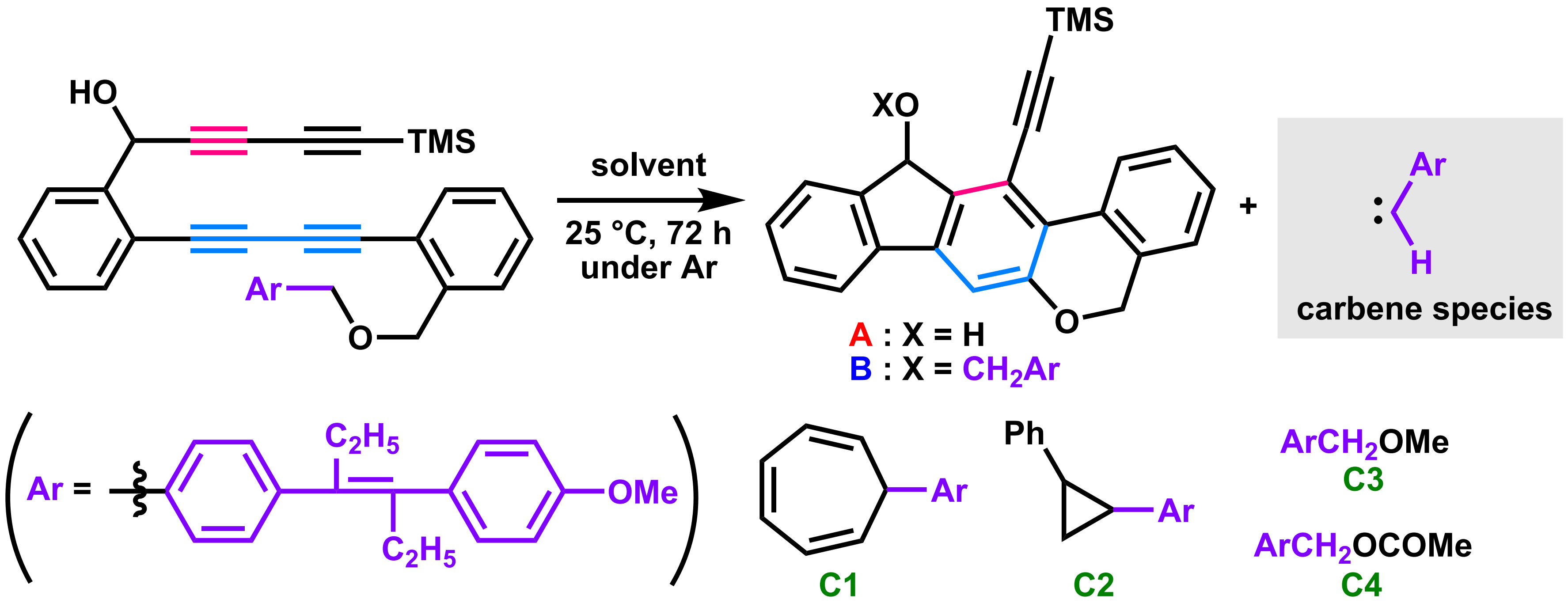


Miyawaki, K.; Suzuki, R.; Kawano, T.; Ueda, I. *Tetrahedron Lett.* **1997**, *38*, 3943.

My Proposal of the Mechanism



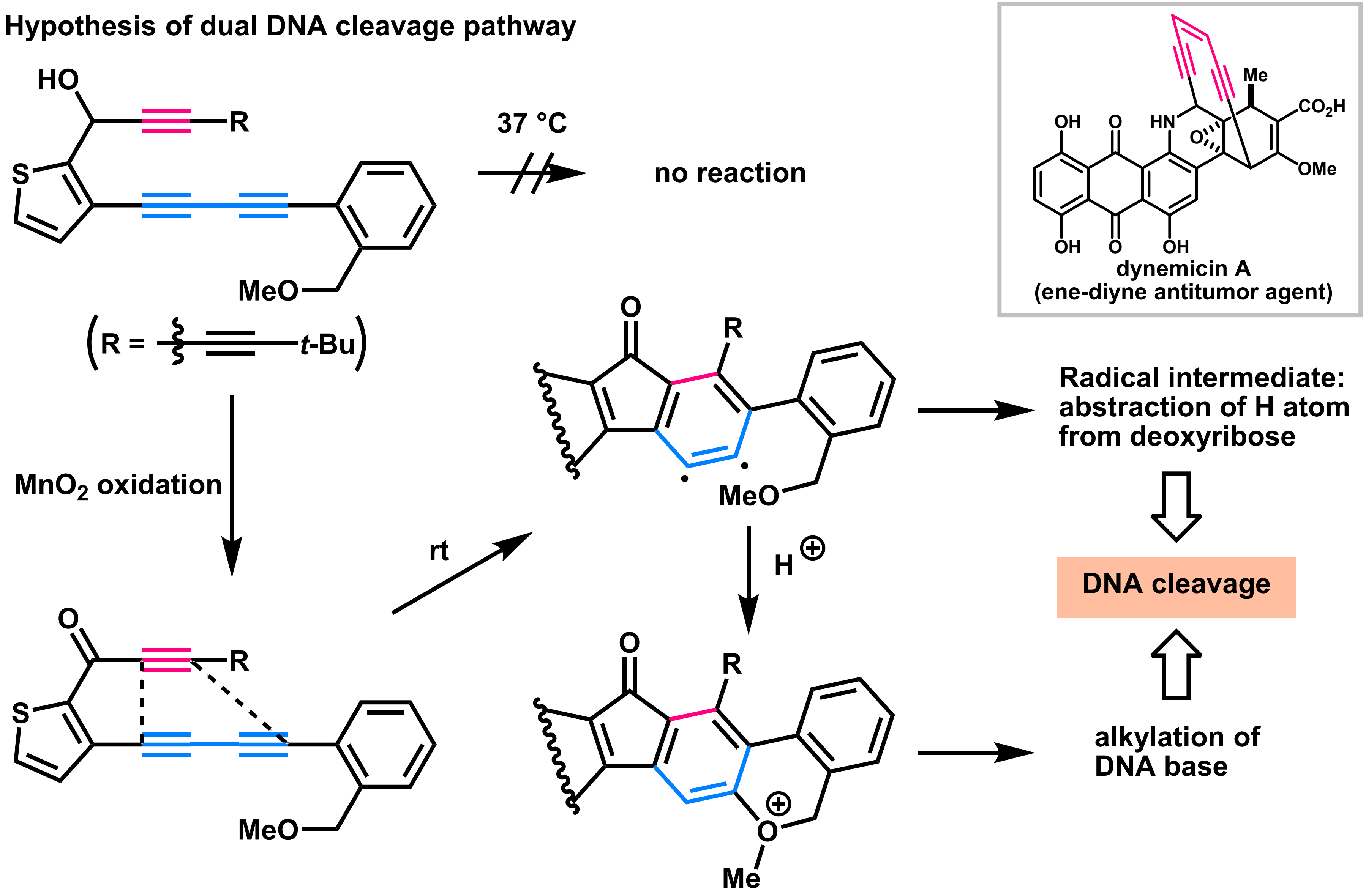
Evidence of Arylcarbene Formation



entry	solvent	concentration	A	B	C
1	benzene	30 mM	44%	13%	C1 : 16%
2	benzene	3.0 mM	47%	13%	C1 : 23%
3	benzene	0.3 mM	55%	4%	C1 : 37%
4	styrene	126 mM	33%	7%	C2 : 5%
5	MeOH	3.0 mM	62%	0%	C3 : 60%
6	$MeCO_2H$	3.0 mM	71%	0%	C4 : 66%

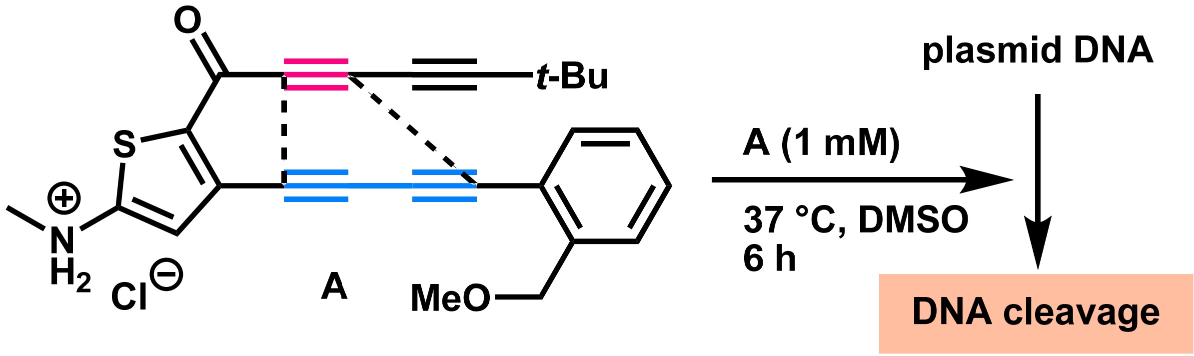
Ueda, I.; Sakurai, Y.; Kawano, T.; Wada, Y.; Futai, M. *Tetrahedron Lett.* **1999**, *40*, 319.

Application for DNA Cleavage

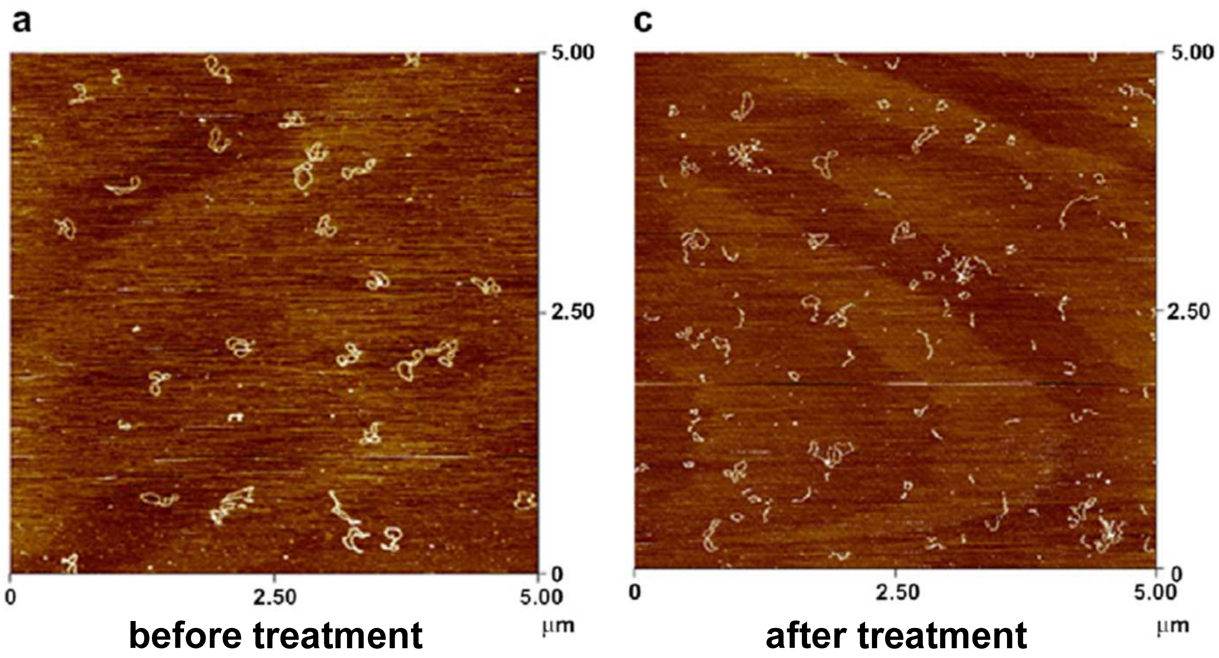


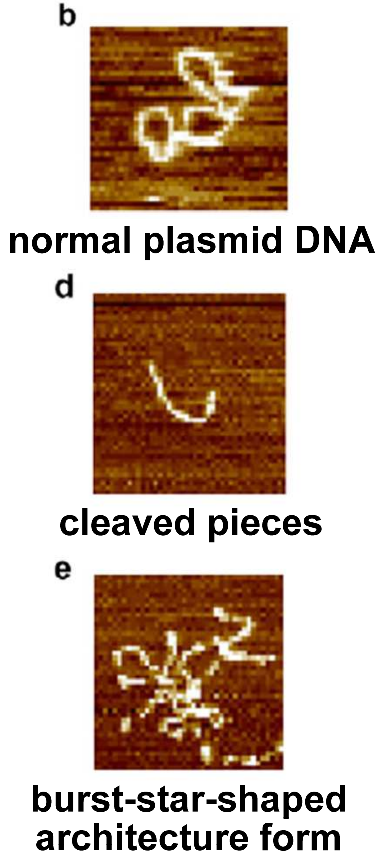
Torikai, K.; Otsuka, Y.; Nishimura, M.; Sumida, M.; Kawai, T.; Sekiguchi, K.; Ueda, I. *Bioorg. Med. Chem.* **2008**, *16*, 5441.

Direct Observation of Plasmid DNA by AFM



Visualization by atomic force microscopy (AFM)





Torikai, K.; Otsuka, Y.; Nishimura, M.; Sumida, M.; Kawai, T.; Sekiguchi, K.; Ueda, I. *Bioorg. Med. Chem.* **2008**, *16*, 5441.

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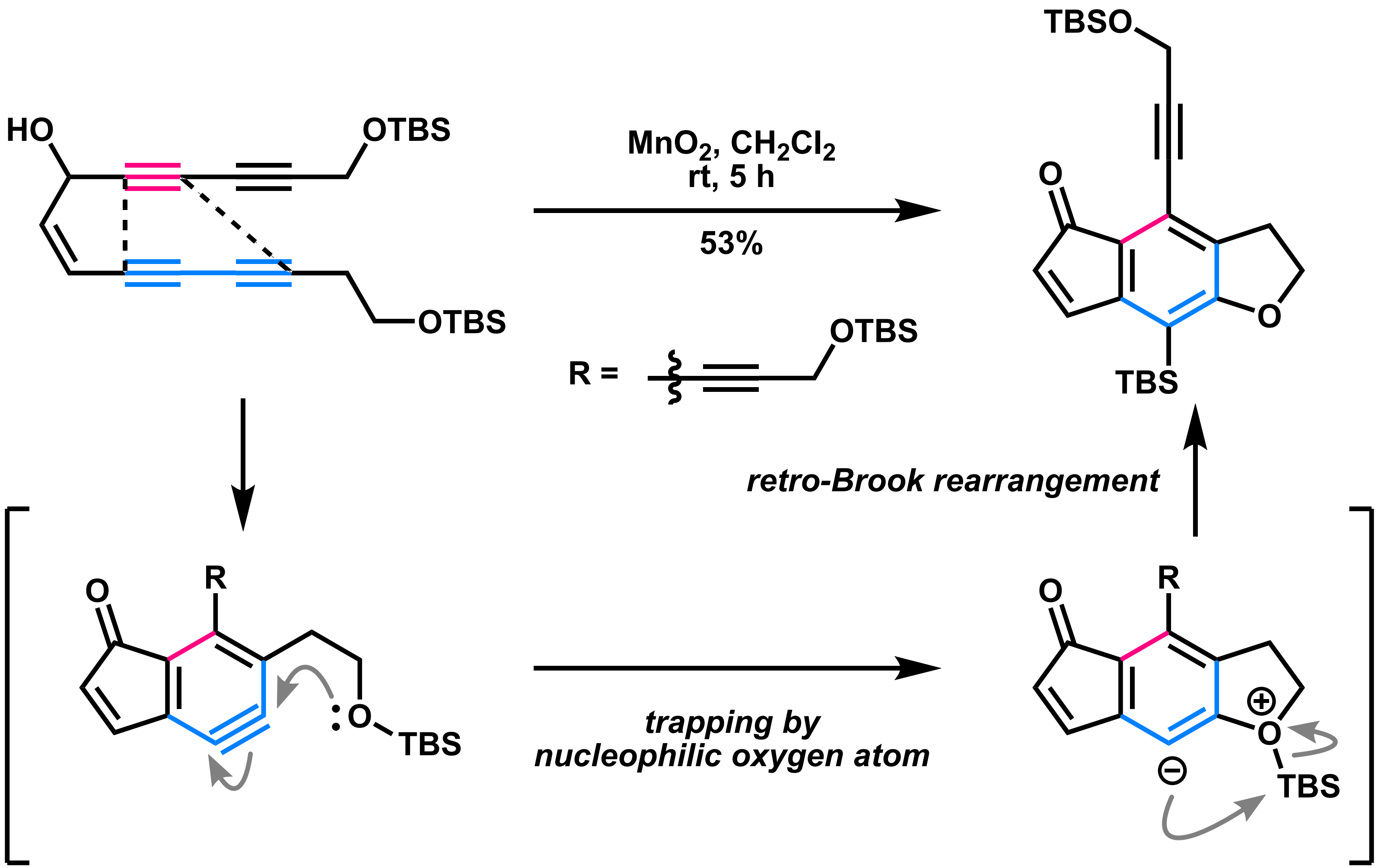
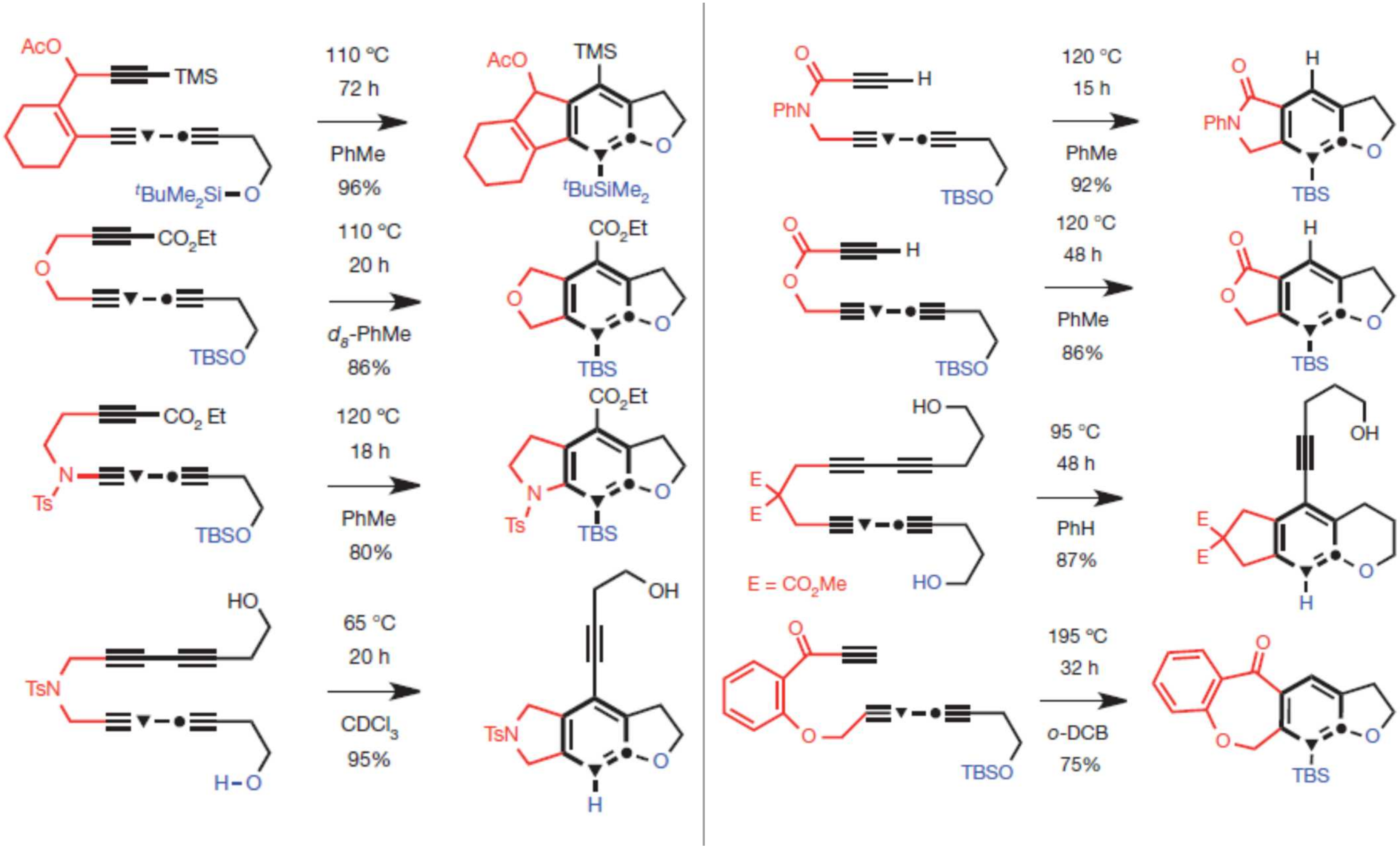
Revelation of HDDA reaction by Hoye Group



Hoye, T. R.; Baire, B.; Niu, D.; Willoughby, P. H.; Woods, B. P. *Nature*, **2012**, *490*, 208.

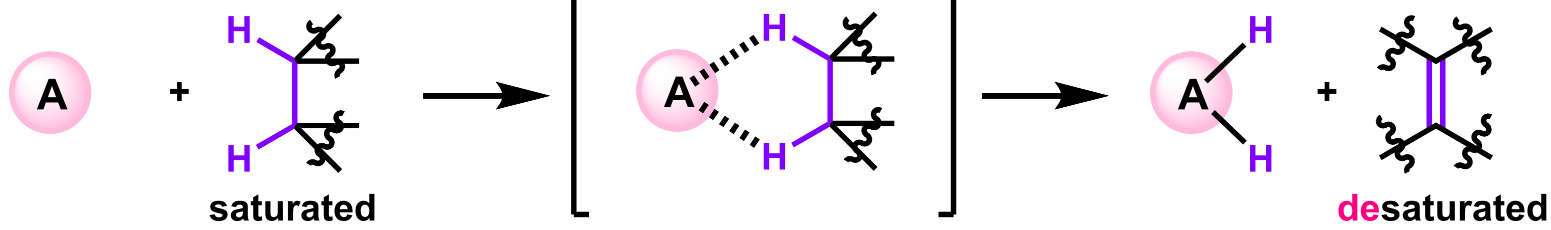
Substrate Scope of HDDA Reaction

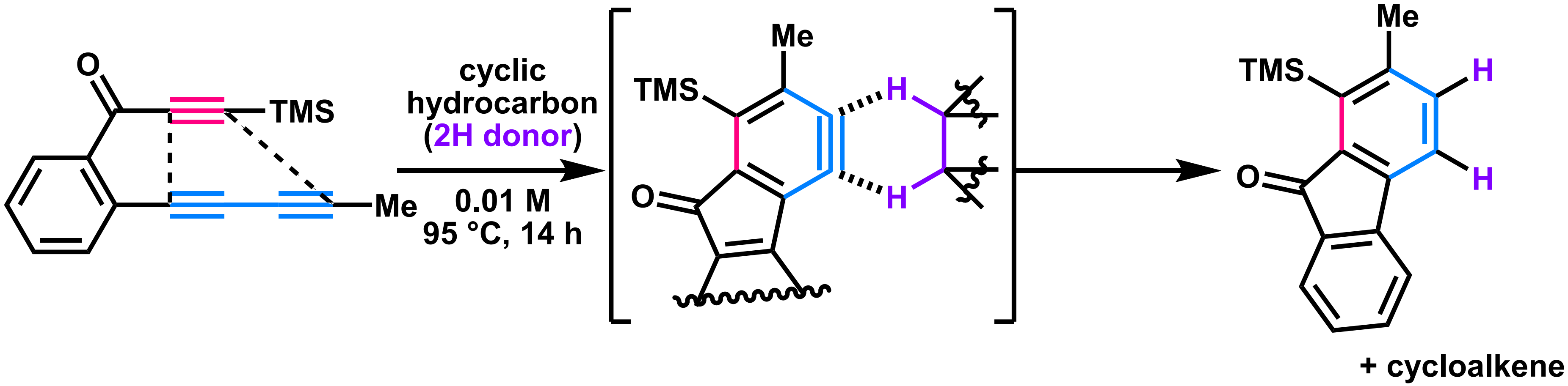


Hoye, T. R.; Baire, B.; Niu, D.; Willoughby, P. H.; Woods, B. P. *Nature*, **2012**, *490*, 208.

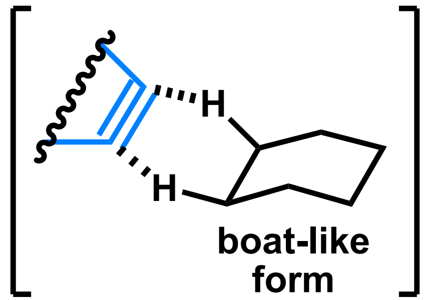
Application : Alkane Desaturation

Concept





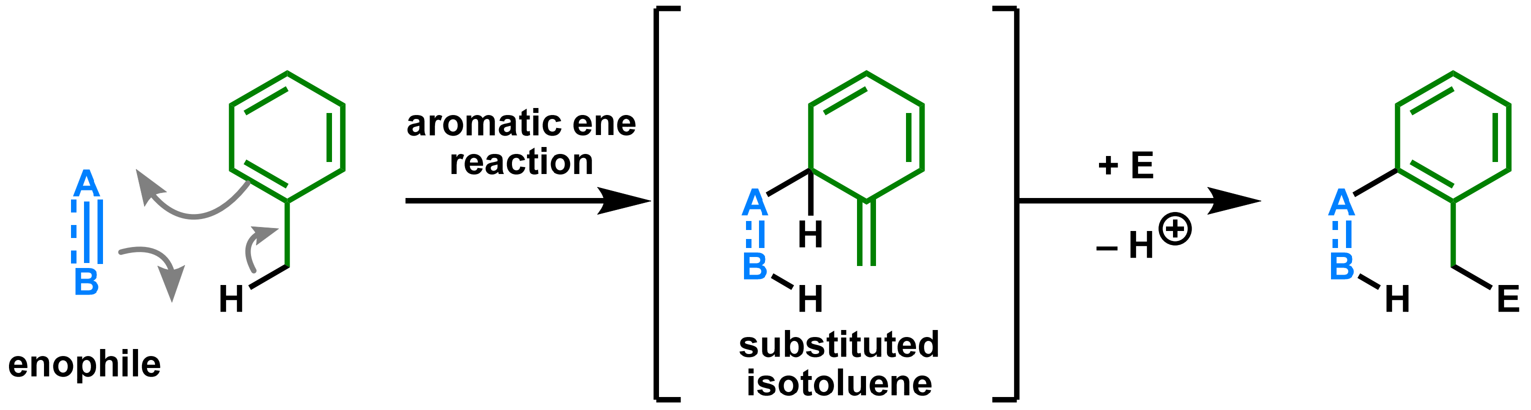
entry	2H donor	yield	k_{rel}	$\Delta G^{\ddagger}$ (kcal/mol)
1	cyclooctane	97%	2.6	17.6
2	cycloheptane	94%	2.3	17.7
3	cyclopentane	84%	1.0	18.7
4	cyclohexane	20%	0.01	24.1



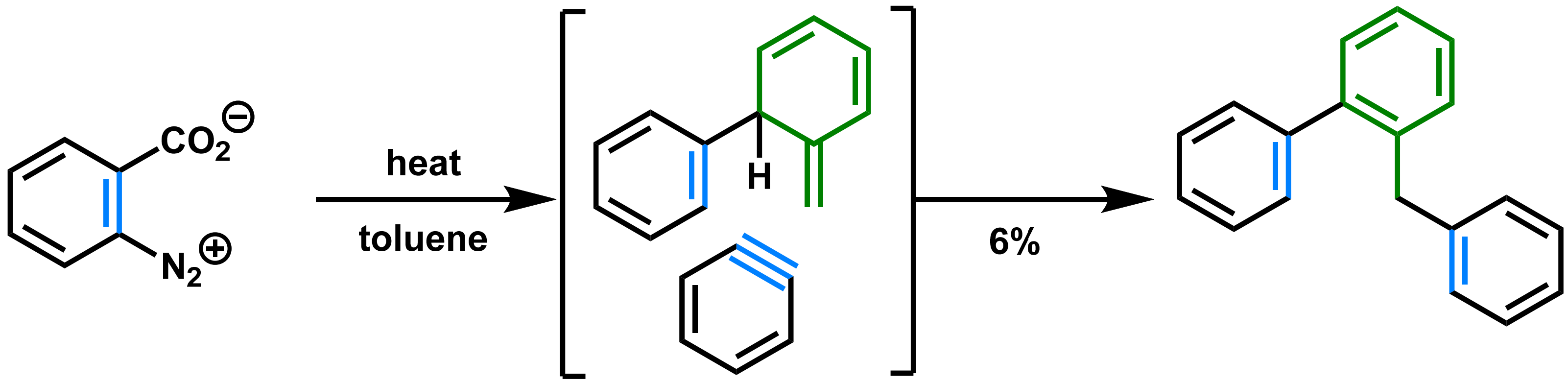
Niu, D.; Willoughby, P. H.; Woods, B. P.; Baire, B.; Hoye, T. R. *Nature*, **2013**, *501*, 531.

Application : Aromatic Ene Reaction (1)

Minimal structural elements for an aromatic ene reaction



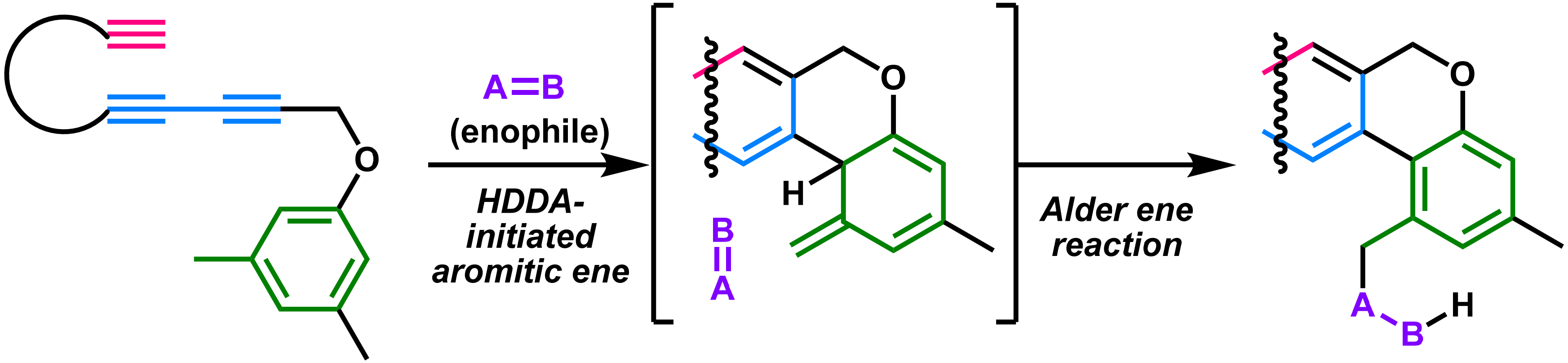
The only reported aromatic ene reaction

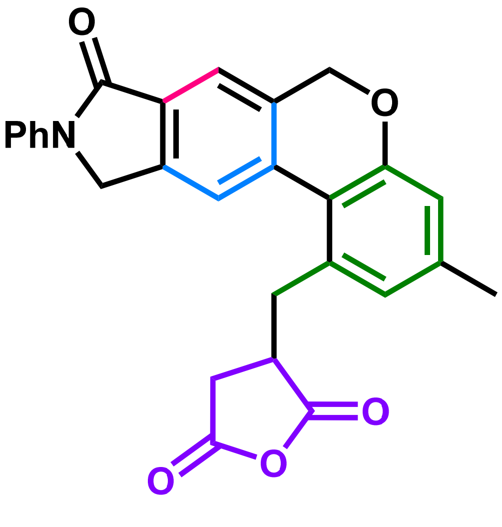


Brinkley, Y. J.; Friedman, L. *Tetrahedron Lett.* **1972**, *13*, 4141.

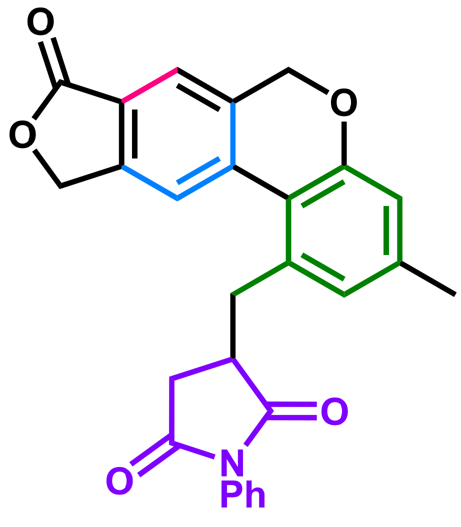
Niu, D.; Hoye, T. R. *Nat. Chem.* **2014**, *6*, 34.

Application : Aromatic Ene Reaction (2)

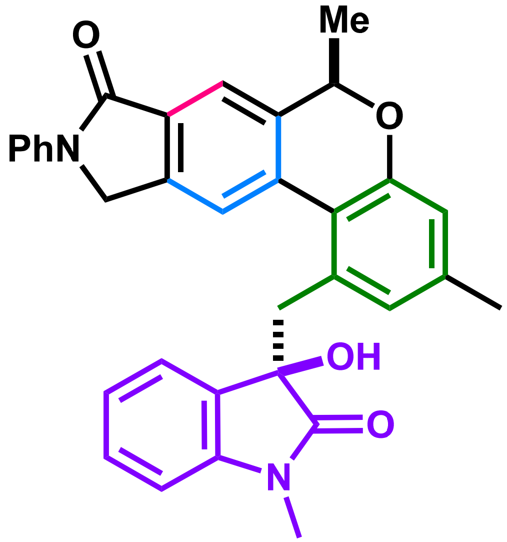




dichloroethane, 120 °C, 18 h
63%



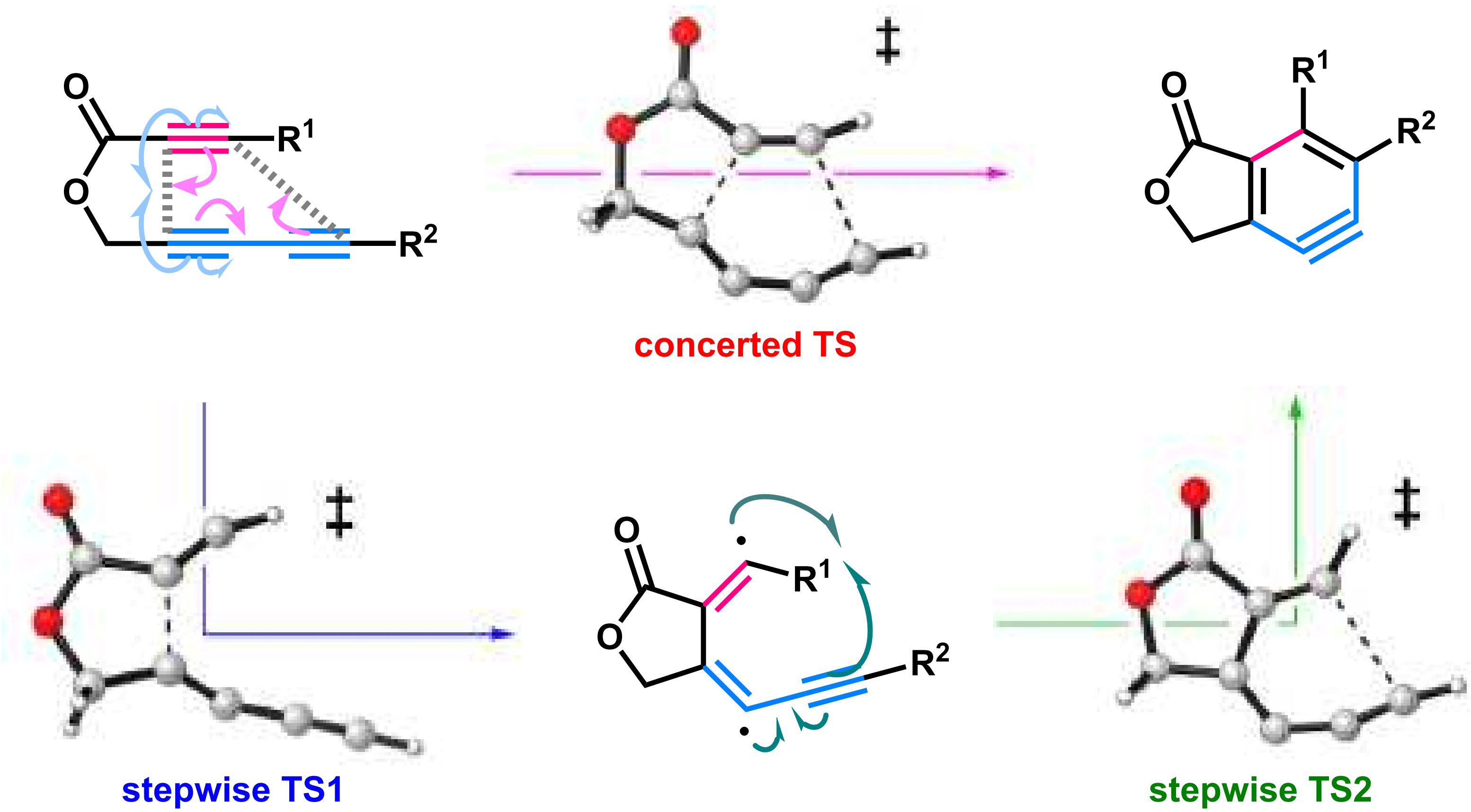
dichlorobenzene, 165 °C, 3.5 h
72%



dichloroethane, 120 °C, 18 h
76% (dr = 4:1)

Niu, D.; Hoye, T. R. *Nat. Chem.* **2014**, *6*, 34.

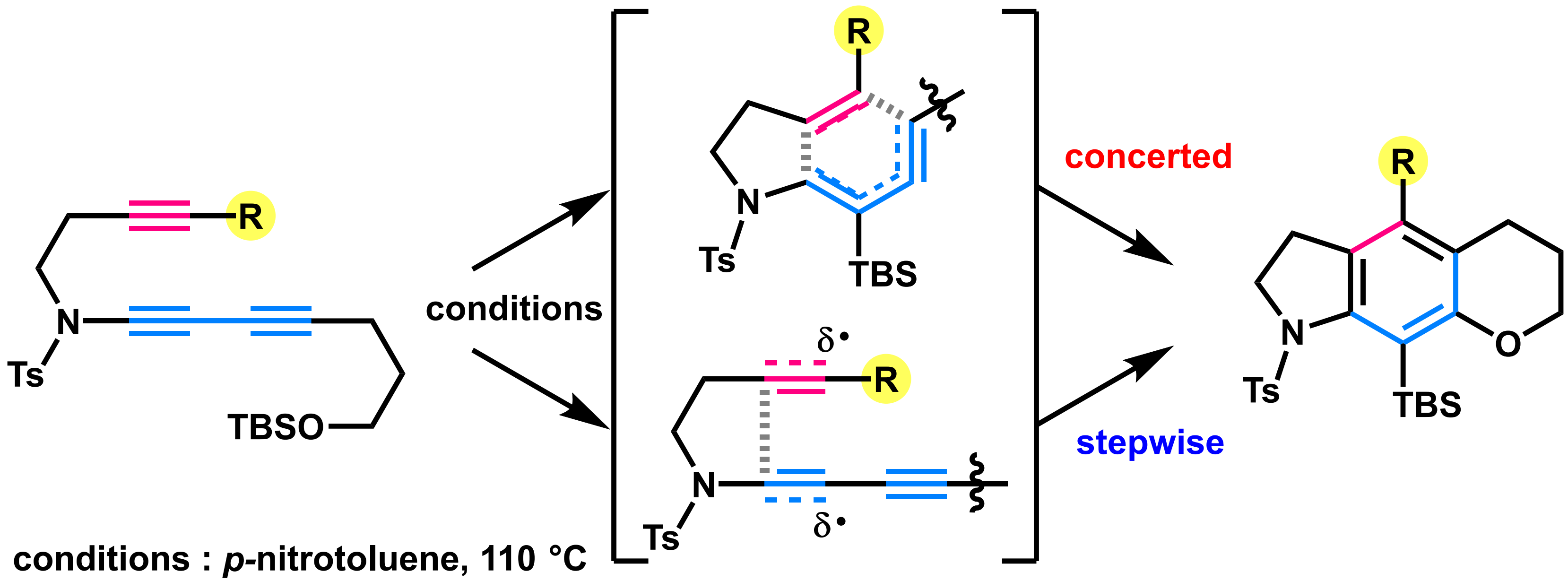
Mechanistic Study of HDDA Reaction



concerted or stepwise ?

Wang, T.; Niu, D. Hoye, T. R. *J. Am. Chem. Soc.* **2016**, *138*, 7832.

Relative Rates of the HDDA Reactions



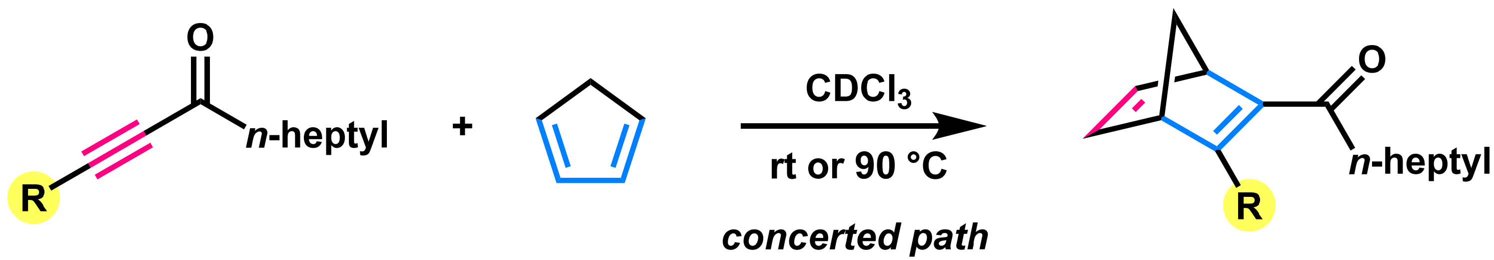
conditions : *p*-nitrotoluene, 110 °C

entry	R	k_{rel}	σ_p	RSE (kcal/mol)
1	≡—Me	320	0.03	–12.1
2	CHO	100	0.42	–7.7
3	COMe	16	0.34	–6.7
4	CO_2Me	9.1	0.34	–4.9
5	$CONEt_2$	1	0.26	–4.9
6	H	<<1	0	0
7	CF_3	<<1	0.54	+1.9

σ_p : Hammet constant, RSE : radical-stabilizing energy

Wang, T.; Niu, D. Hoye, T. R. *J. Am. Chem. Soc.* **2016**, *138*, 7832.

Relative Rates of Diels-Alder Cycloadditions

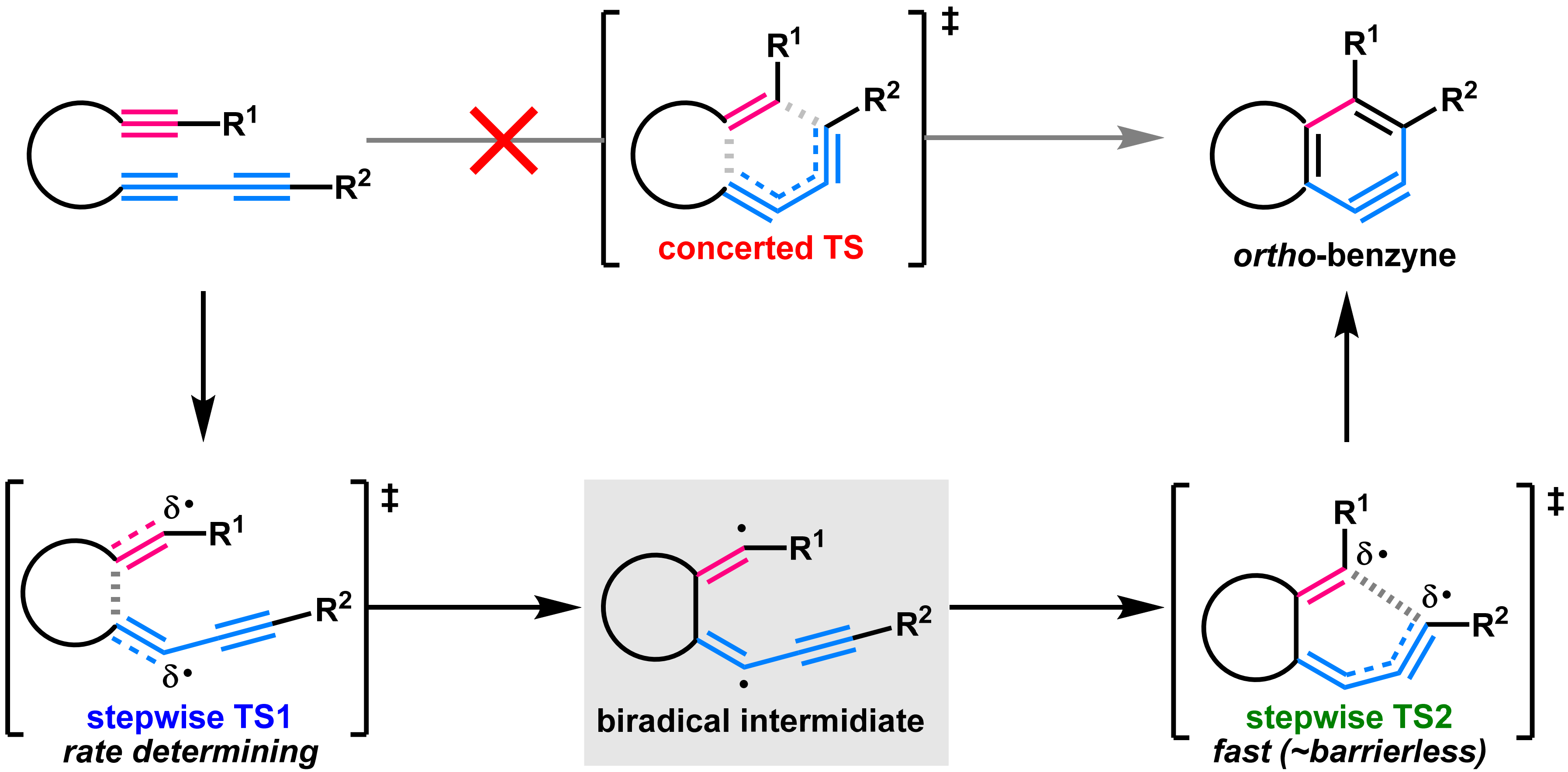


entry	R	k_{rel}	σ_p	RSE (kcal/mol)
1	CHO	47,000	0.42	–7.7
2	CF_3	16,800	0.54	+1.9
3	COEt	2,100	0.34	–6.7
4	CO_2Me	840	0.34	–4.9
5	$CONEt_2$	50	0.26	–4.9
6	H	10	0	0
7	≡—Me	1	0.03	–12.1

σ_p : Hammet constant, RSE : radical-stabilizing energy

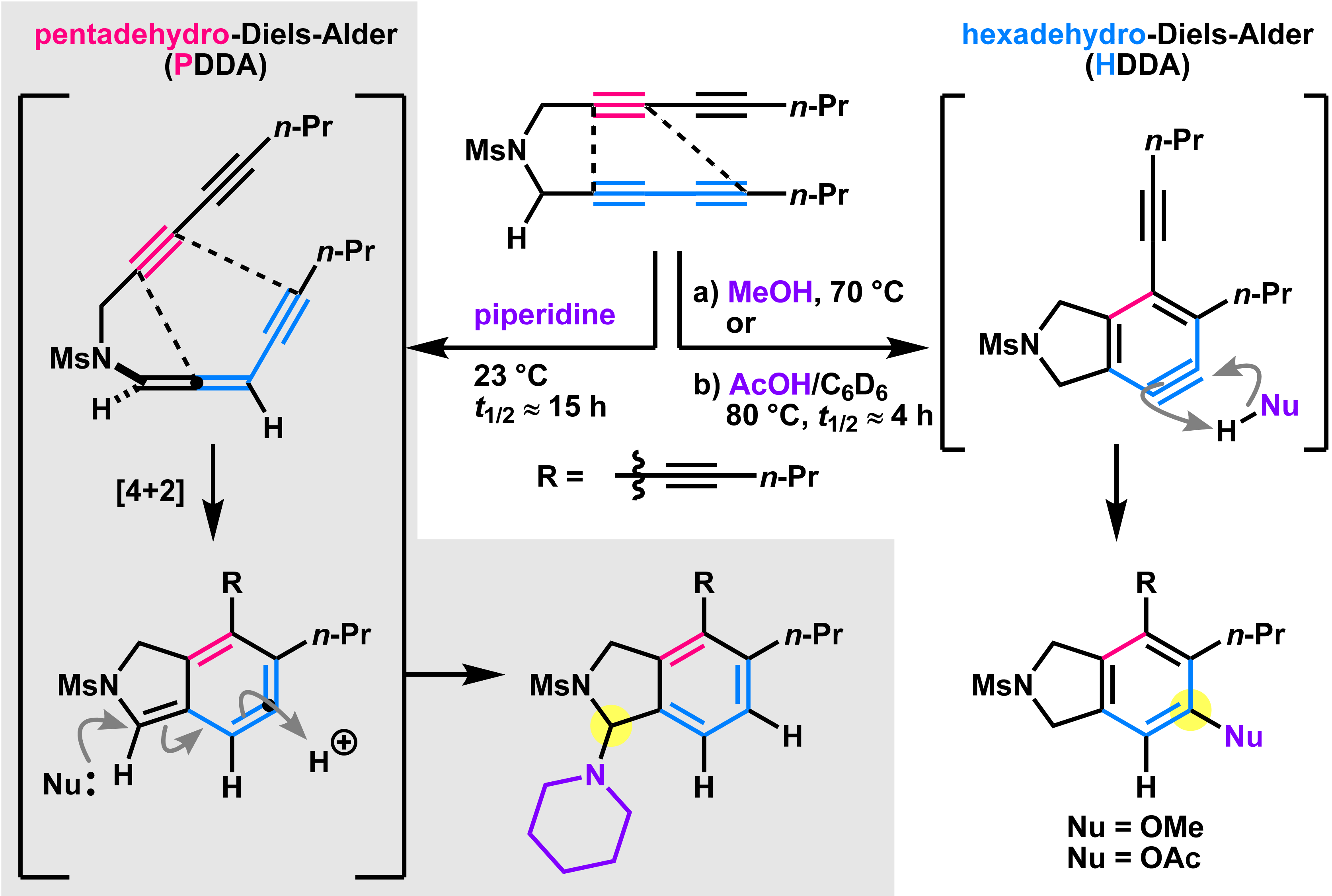
Wang, T.; Niu, D. Hoye, T. R. *J. Am. Chem. Soc.* **2016**, *138*, 7832.

Conclusion of Mechanistic Study



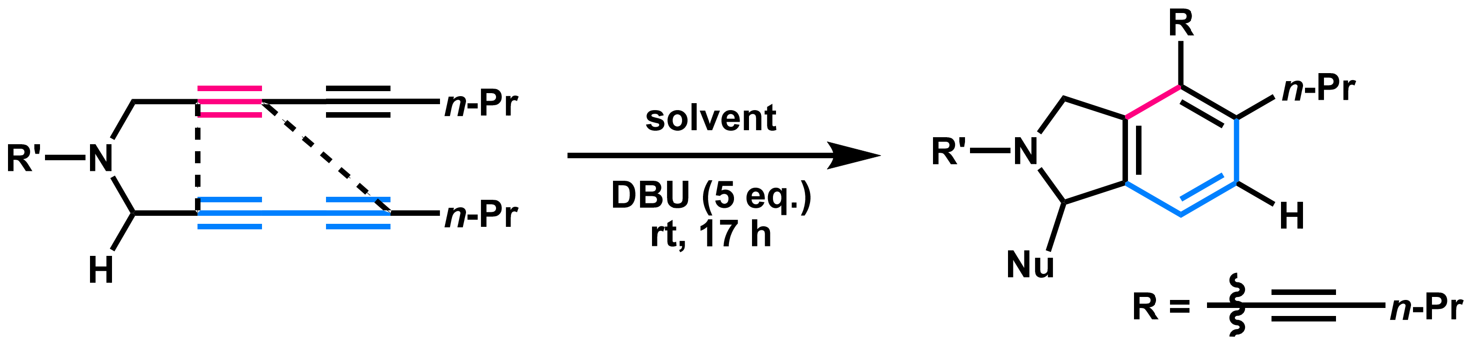
Wang, T.; Niu, D. Hoye, T. R. *J. Am. Chem. Soc.* **2016**, *138*, 7832.

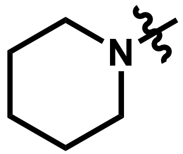
Pentadehydro-Diels-Alder Reaction



Wang, T.; Naredla, R. R.; Thompson, S. K.; Hoye, T. R. *Nature*, **2016**, *532*, 484.

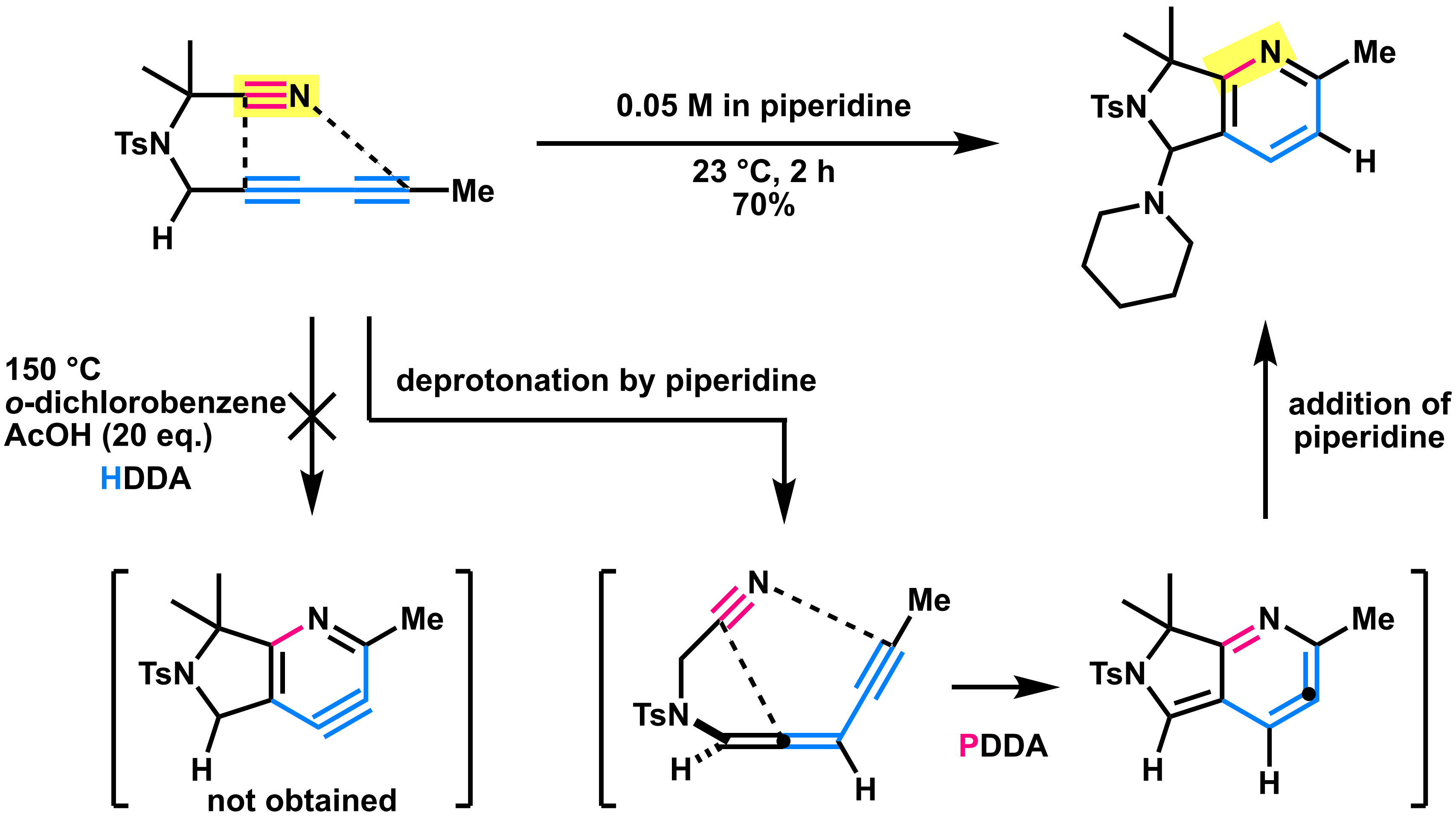
Scope of the PDDA Cascades of Substrates



entry	R'	solvent	Nu	yield
1	Ms	piperidine		81%
2	Ts	piperidine		52%
3	Bz	piperidine		25%
4	Ms	*n*-butylamine	*n*-BuN	86%
5	Ms	methanol	MeO	80%
6	Ms	MeCN/H_2O	HO	15%

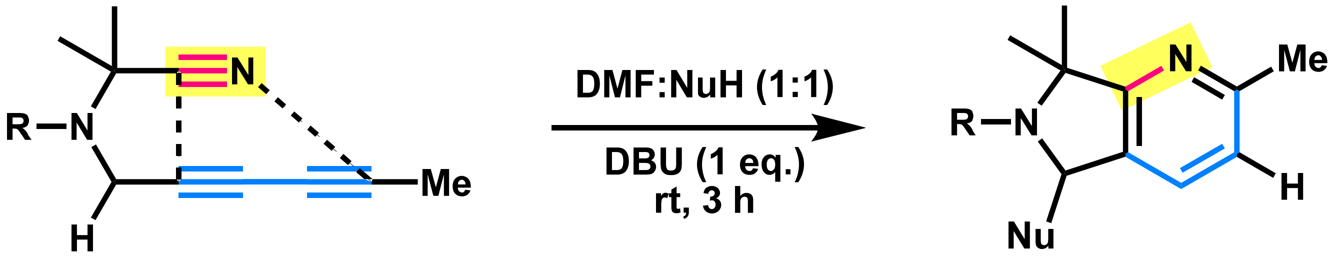
Wang, T.; Naredla, R. R.; Thompson, S. K.; Hoye, T. R. *Nature*, **2016**, *532*, 484.

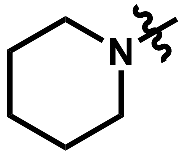
Aza-PDDA Reactions



Wang, T.; Naredla, R. R.; Thompson, S. K.; Hoye, T. R. *Nature*, **2016**, *532*, 484.

Scope of the Aza-PDDA Cascades of Substrates

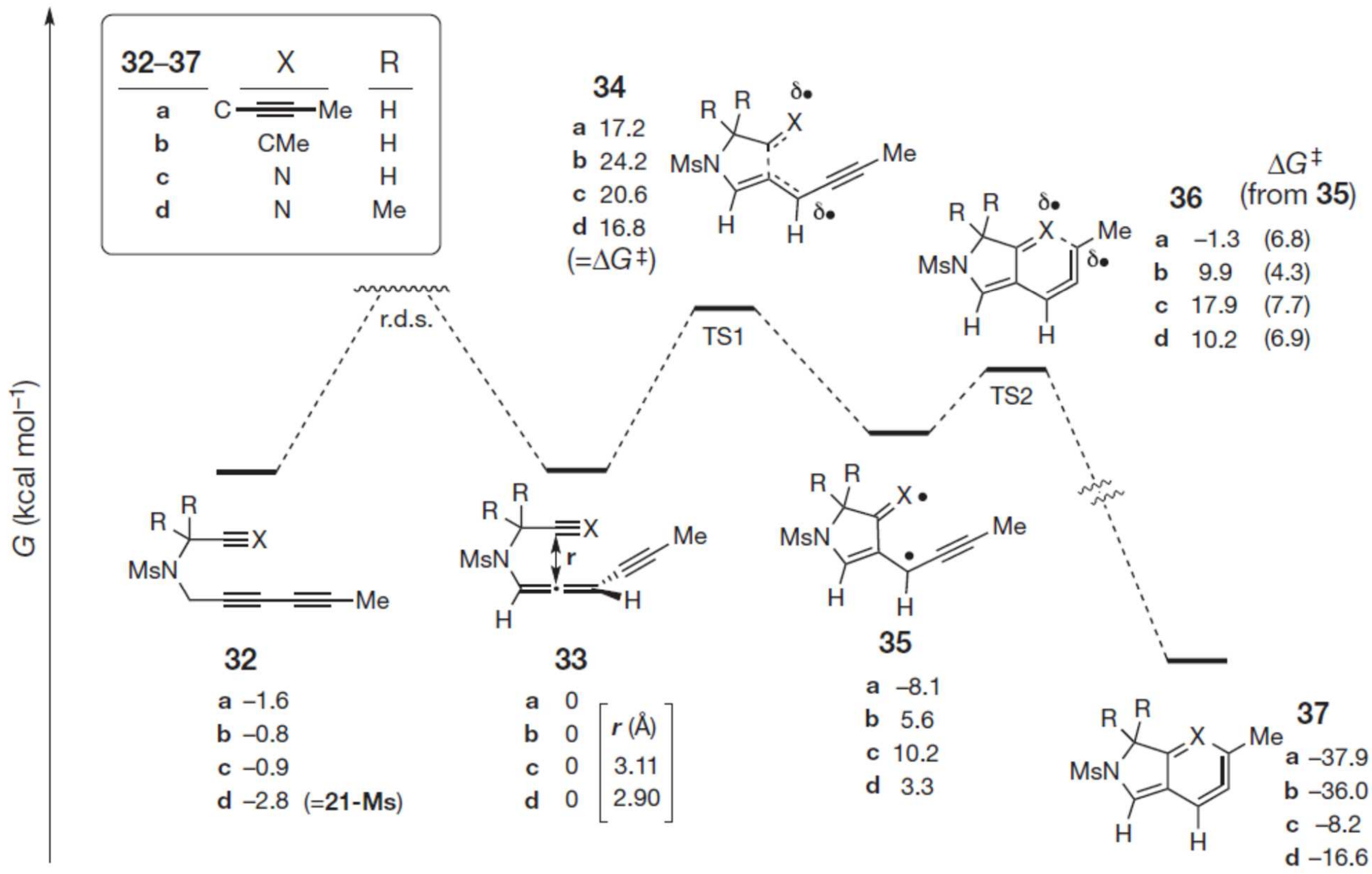


entry	R	NuH	Nu	yield
1	Ts	piperidine		71%
2	Ms	piperidine		69%
3	Ts	*n*-butylamine	*n*-BuN–	46%
4	Ts	methanol	MeO–	72%
5	Ts	MeCN/H_2O* (3:1)	HO–	57%

* MeCN was used instead of DMF.

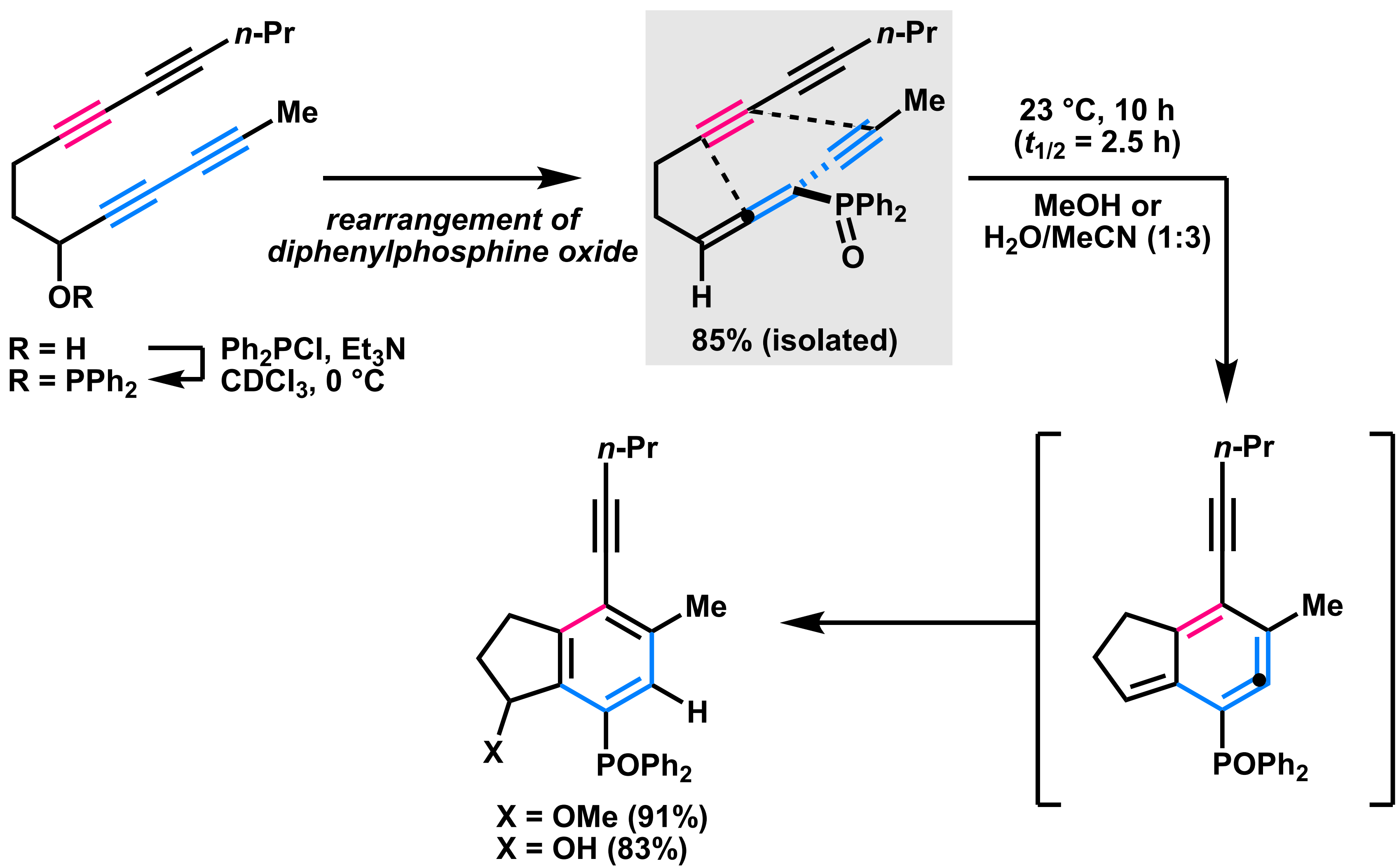
Wang, T.; Naredla, R. R.; Thompson, S. K.; Hoye, T. R. *Nature*, **2016**, *532*, 484.

Mechanistic Aspects of the PDDA Reaction



Wang, T.; Naredla, R. R.; Thompson, S. K.; Hoye, T. R. *Nature*, **2016**, *532*, 484.

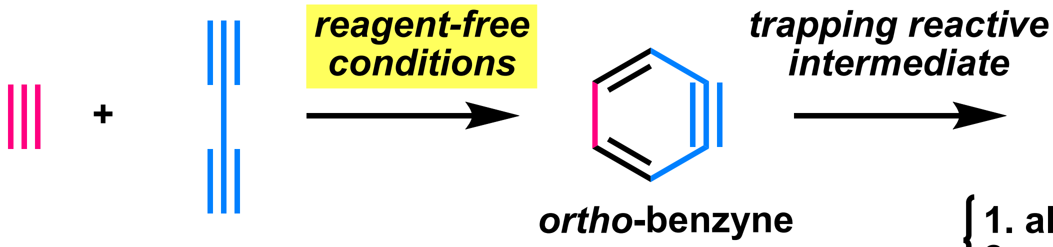
Evidence of Allenyne Intermediate



Wang, T.; Naredla, R. R.; Thompson, S. K.; Hoye, T. R. *Nature*, **2016**, *532*, 484.

Summary

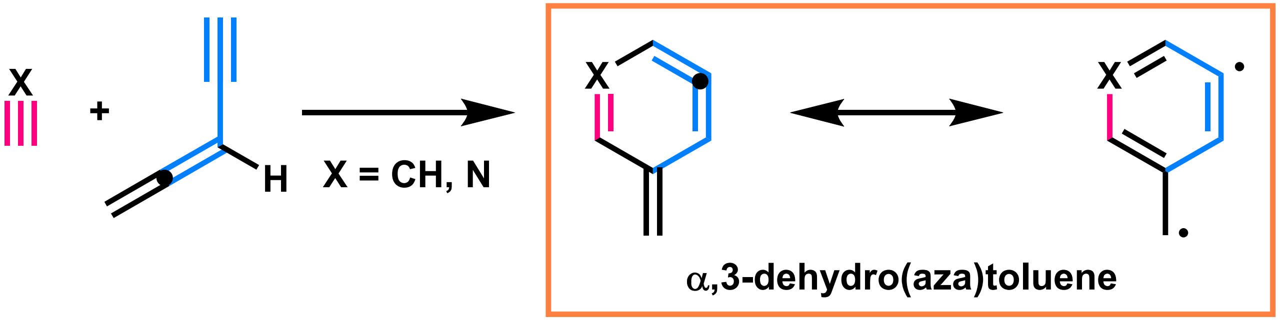
Hexadehydro-Diels-Alder (HDDA) reaction

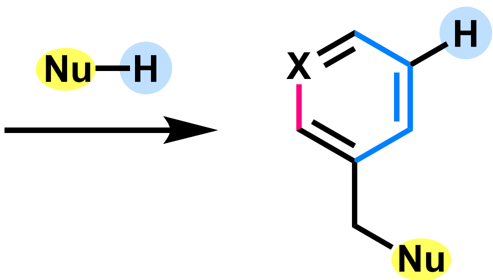


highly substituted benzenoid product

1. alkane desaturation
2. aromatic ene reaction

Pentadehydro-Diels-Alder (PDDA) reaction

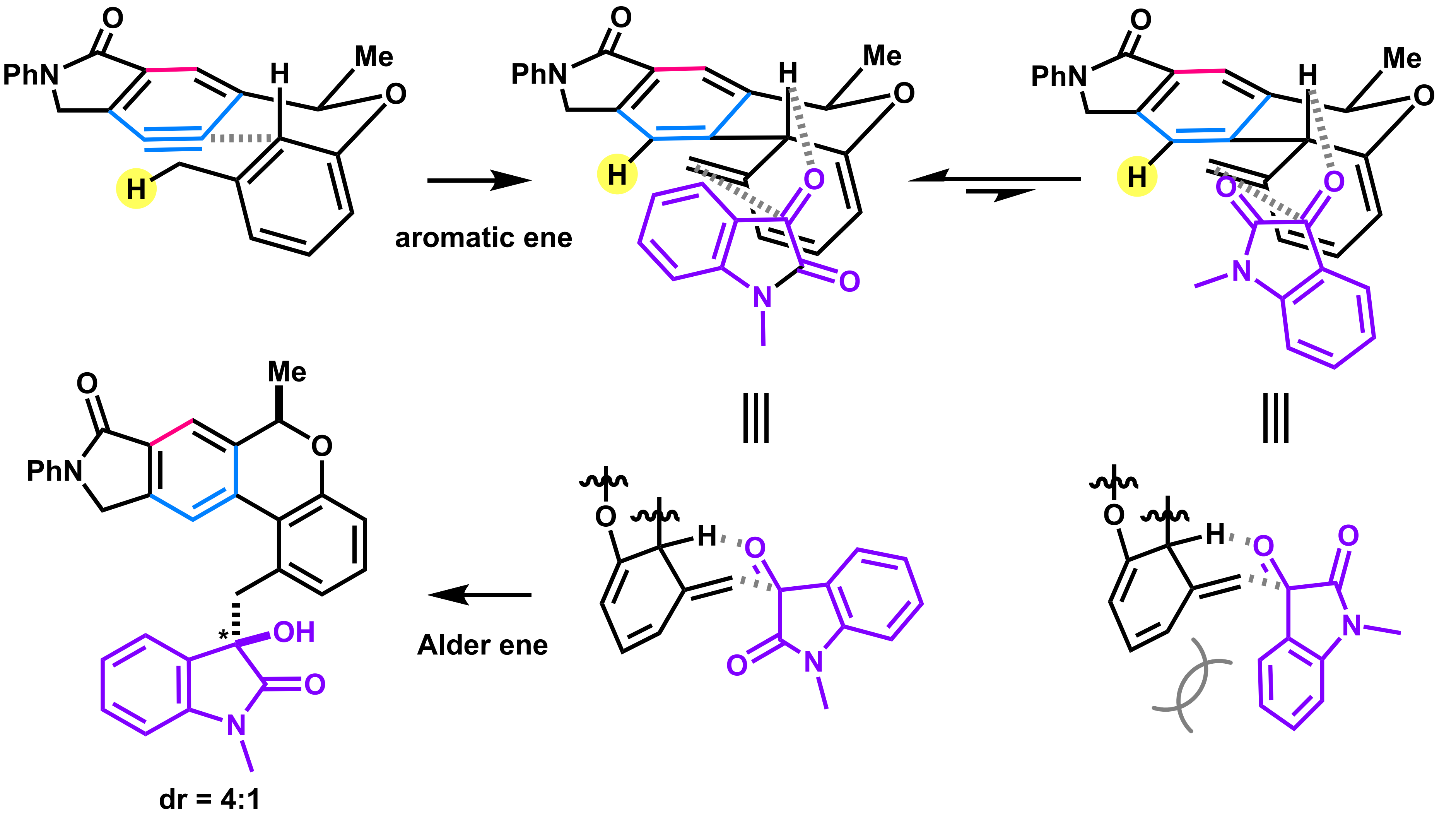




- The PDDA proceeds rapidly, much more quickly than the HDDA cyclization.
- The PDDA enables to synthesize pyridine-containing products which are impposible to obtain by the HDDA cyclization

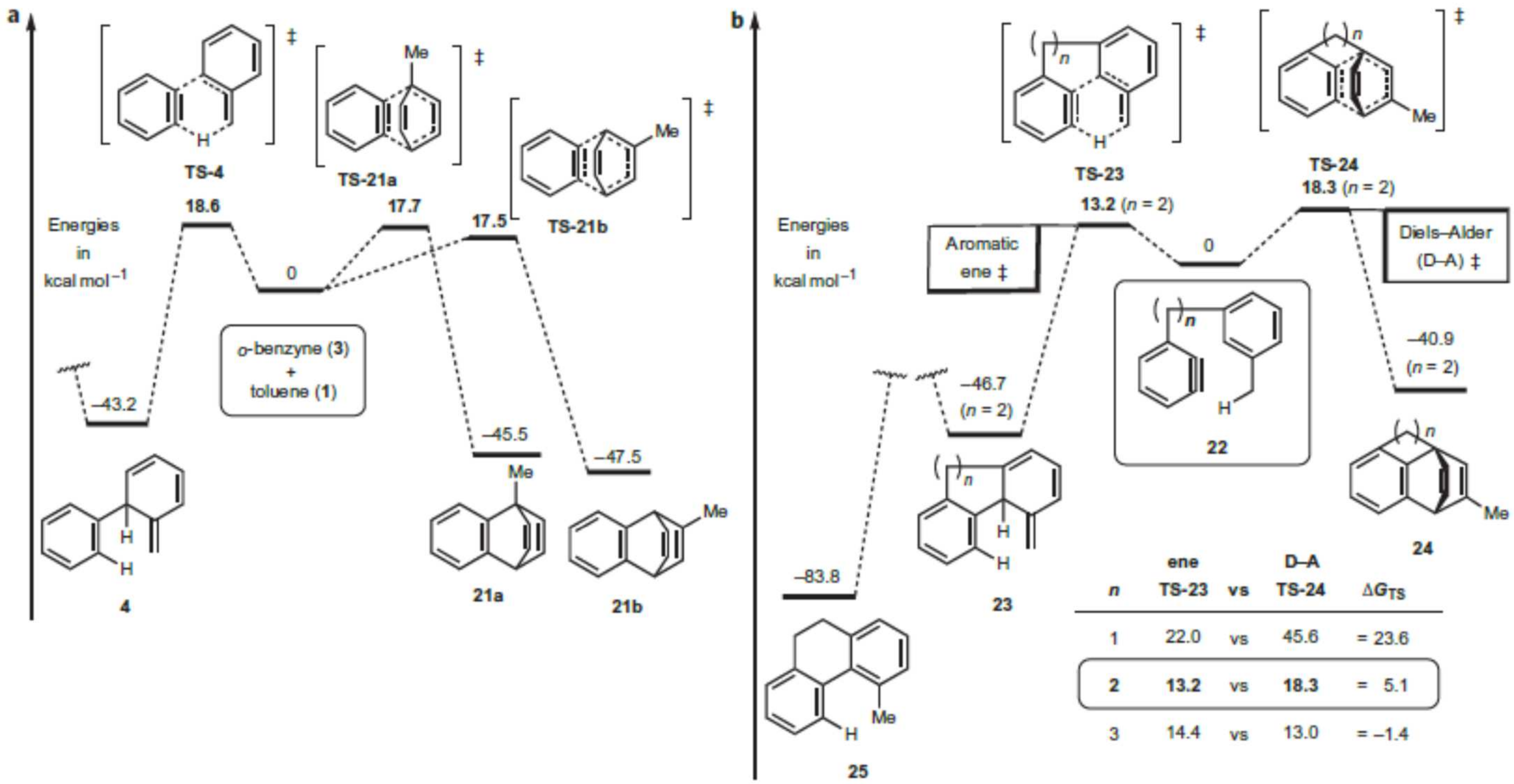
Appendix

Stereoselectivity of Aromatic Ene/Alder Ene Cascade



Niu, D.; Hoye, T. R. *Nat. Chem.* **2014**, *6*, 34.

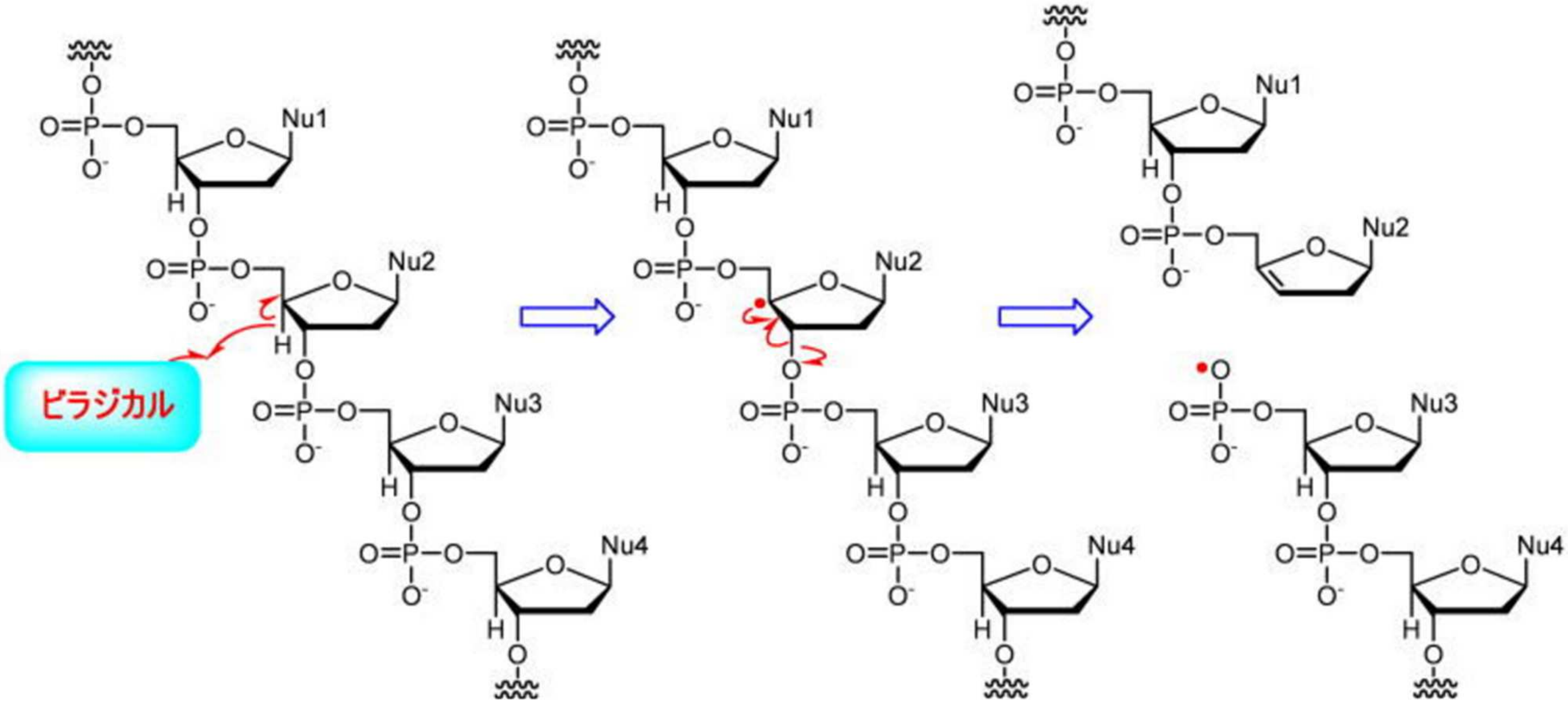
Competition between Aromatic ene and DA reaction



n	ene TS-23	vs	D–A TS-24	ΔG_{TS}
1	22.0	vs	45.6	= 23.6
2	**13.2**	vs	**18.3**	= 5.1
3	14.4	vs	13.0	= −1.4

Niu, D.; Hoye, T. R. *Nat. Chem.* **2014**, *6*, 34.

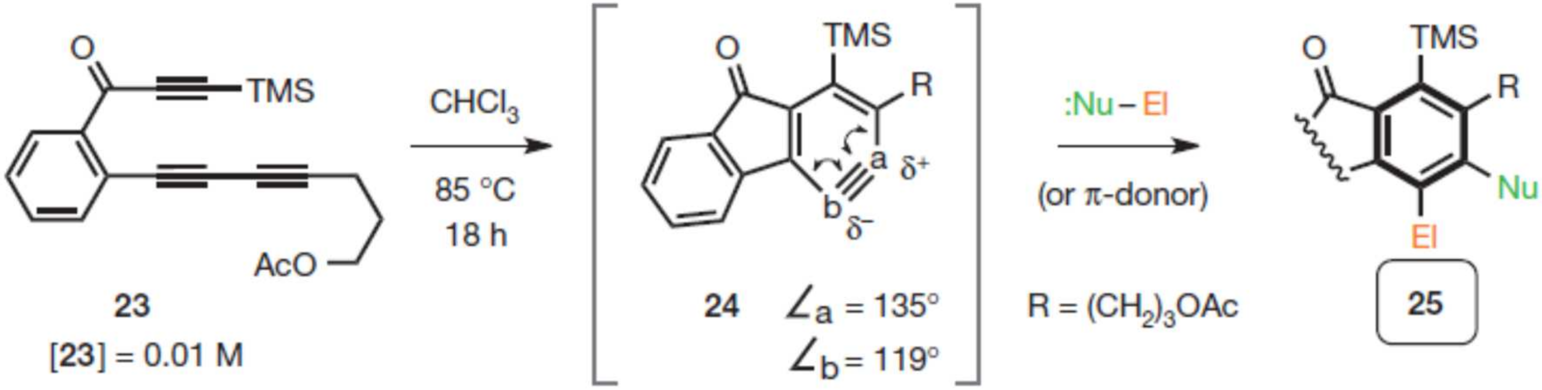
Mechanism of Radical Fragmentation



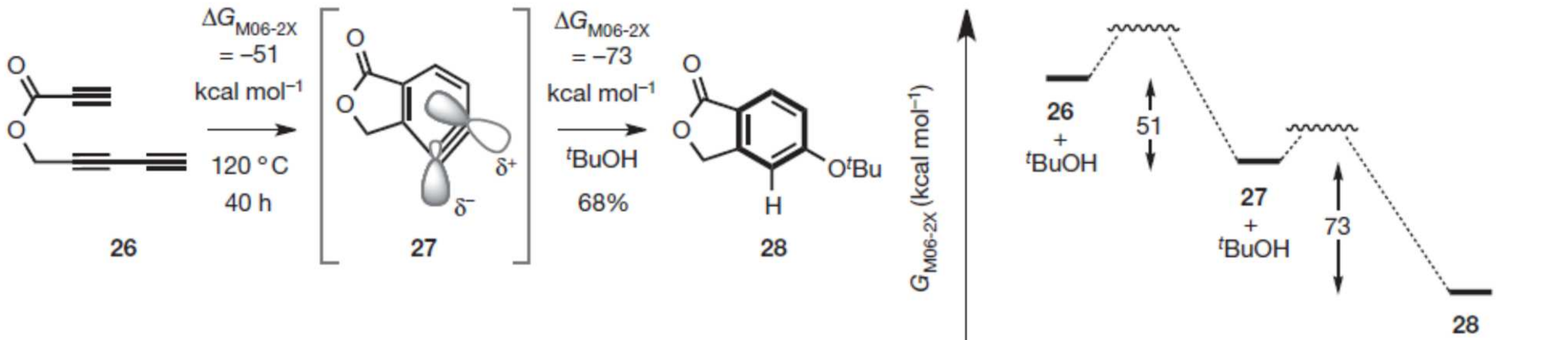
http://molecules.a.la9.jp/Anticancer.html

Geometry of Benzyne and Comparison of Energies

Geomety of benzyne

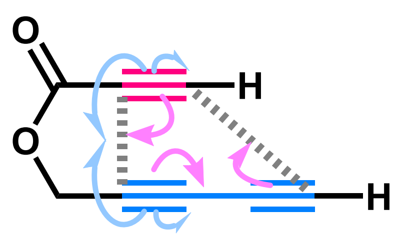


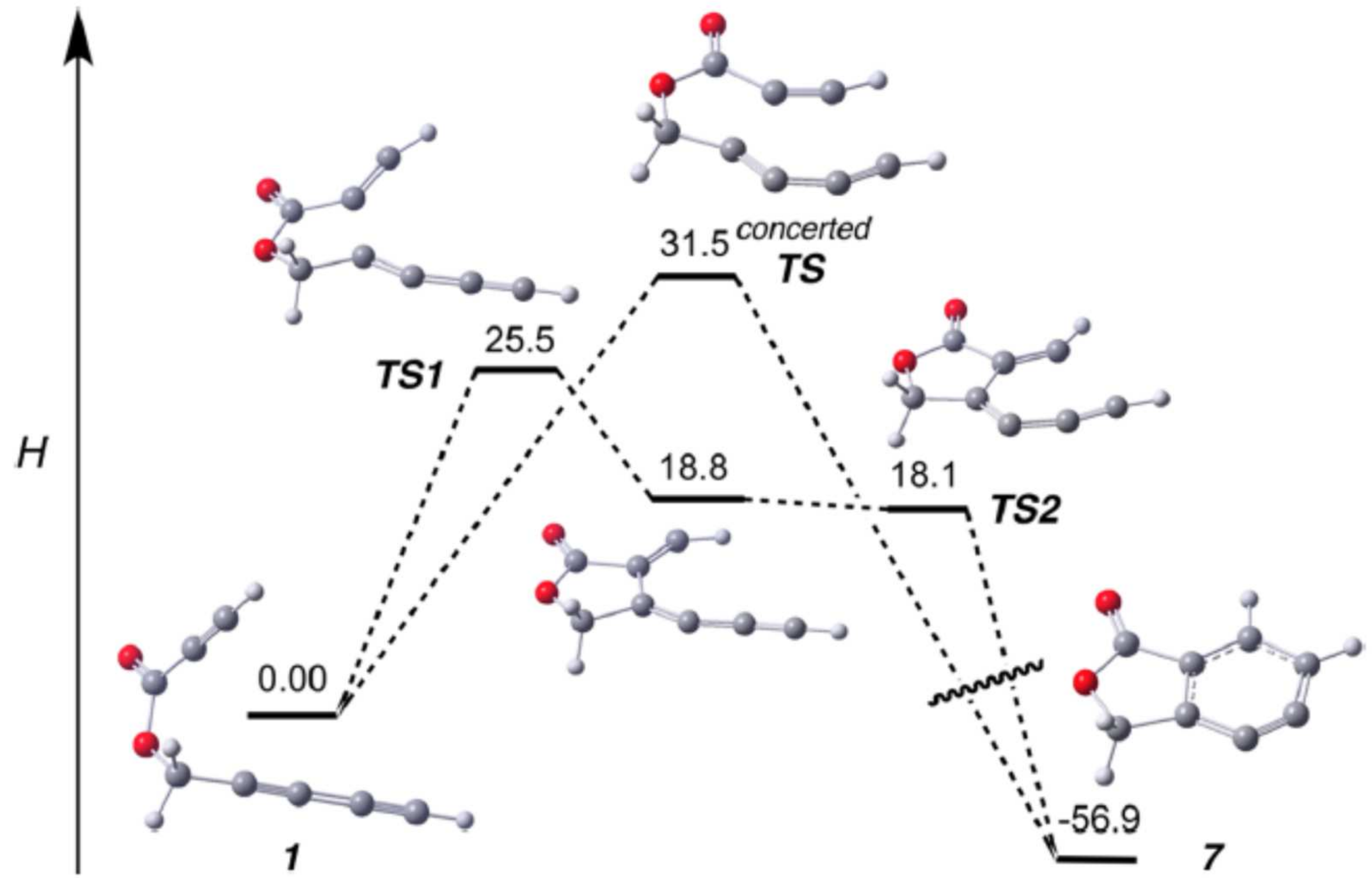
Comparison of computed free energy changes



Hoye, T. R.; Baire, B.; Niu, D.; Willoughby, P. H.; Woods, B. P. *Nature*, **2012**, *490*, 208.

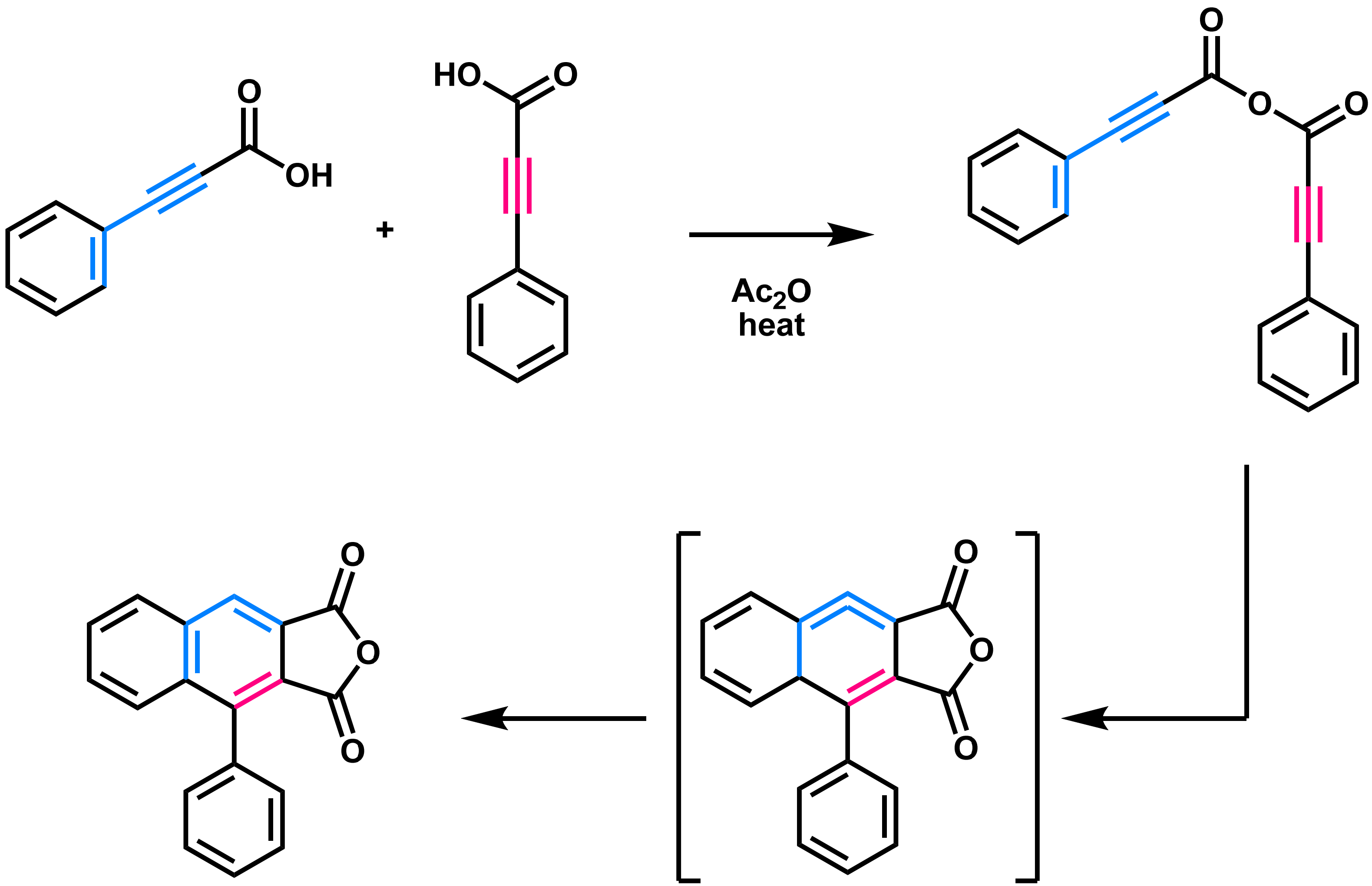
Comparison of Energies at B3LYP-D3BJ Level





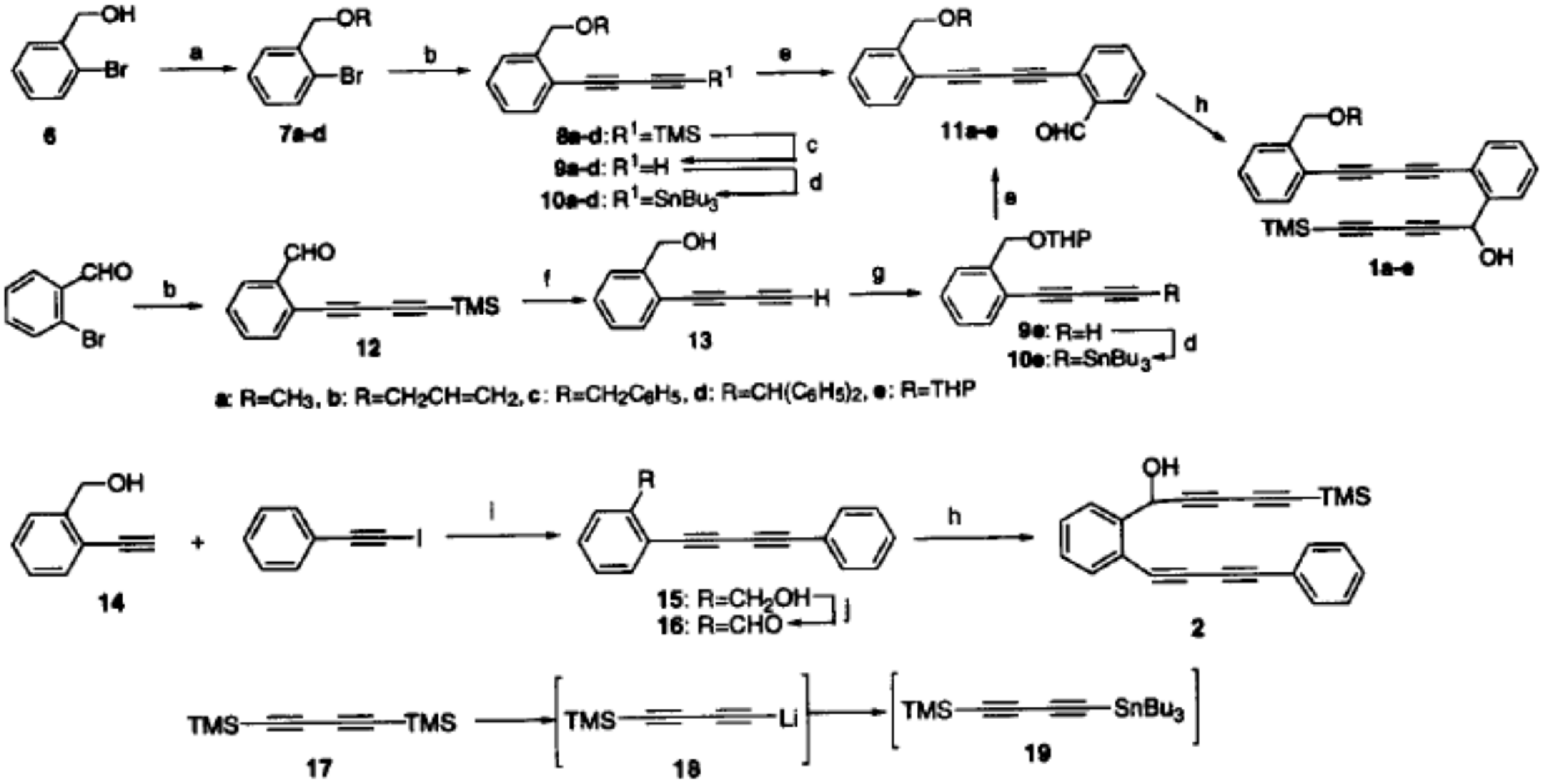
Marell, D. J.; Furan, L. R.; Woods, B. P.; Lei, X.; Bendelsmith, A. J.; Cramer, C. J.; Hoye, T. R.; Kuwata, K. T. *J. Org. Chem.* **2015**, *80*, 11744.

Dimerization of Phenylpropynoic Acid in 1898



Michael, A.; Bucher, J. E. *Chem. Zentrblt* **1898**, 731.

Substrate Synthesis by Ueda



Reaction conditions and Reagents: a) NaH or KO^tBu, RBr (or RI), Bu_4NI, C_6H_6 or THF, r.t., 0.5-1 h; b) **19**, $PdCl_2(PPh_3)_2$, Toluene, 80-110 °C; c) K_2CO_3, MeOH, 0 °C, 30 min; d) Bu_3SnCl, $[(CH_3)_2CH]_2NH$, 0 °C, 30 min, then added **9**, r.t., 24 h; e) 2-Bromobenzaldehyde, $PdCl_2(PPh_3)_2$, Toluene, 80-110 °C, 2h; f) $NaBH_4$, MeOH, 0 °C,10 min, then added K_2CO_3, 0 °C, 30 min; g) DHP, *p*-TosOH, CH_2Cl_2, r.t., 1 h; h) **18**, Ether, r.t 30 min; i) CuI, Pyrrolidine, -20 °C; j) IBX, DMSO, r.t.

Miyawaki, K.; Suzuki, R.; Kawano, T.; Ueda, I. *Tetrahedron Lett.* **1997**, *38*, 3943.