Expanding the Strained Alkyne Toolbox: Generation and Utility of Oxygen-Containing Strained Alkynes

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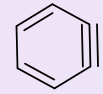
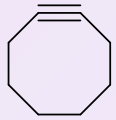
Joseph Salamoun
Current Literature 04/09/16
Wipf Group

Examples of Strained Alkynes

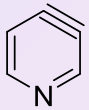


benzyne

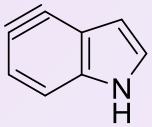
2,3-thiophyne



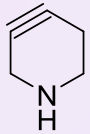
cyclooctyne



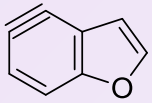
3,4-pyridyne



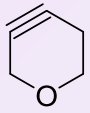
4,5-Indolyne



3,4-piperidyne

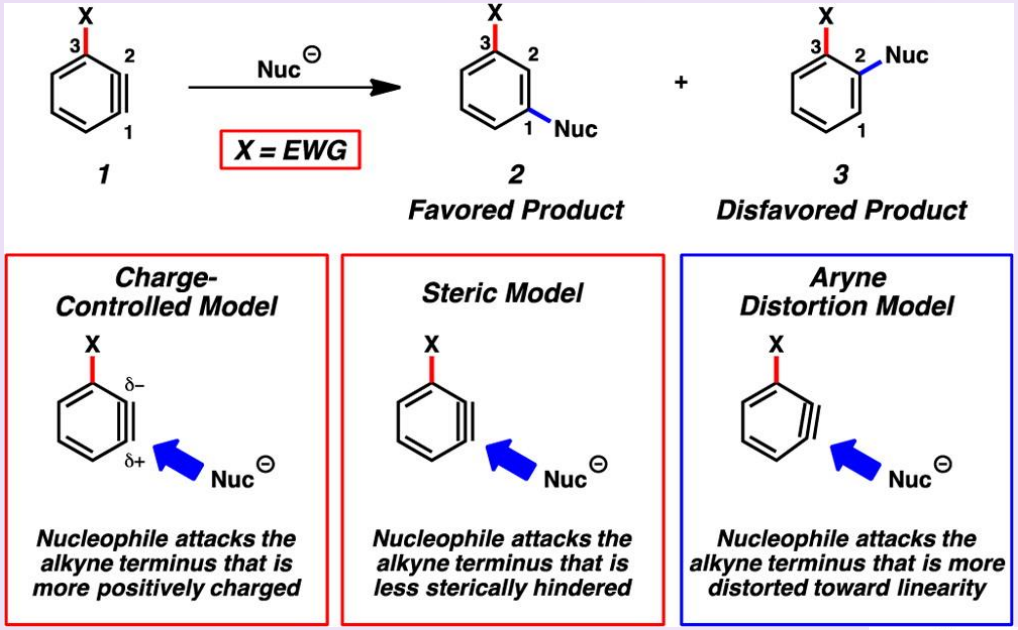


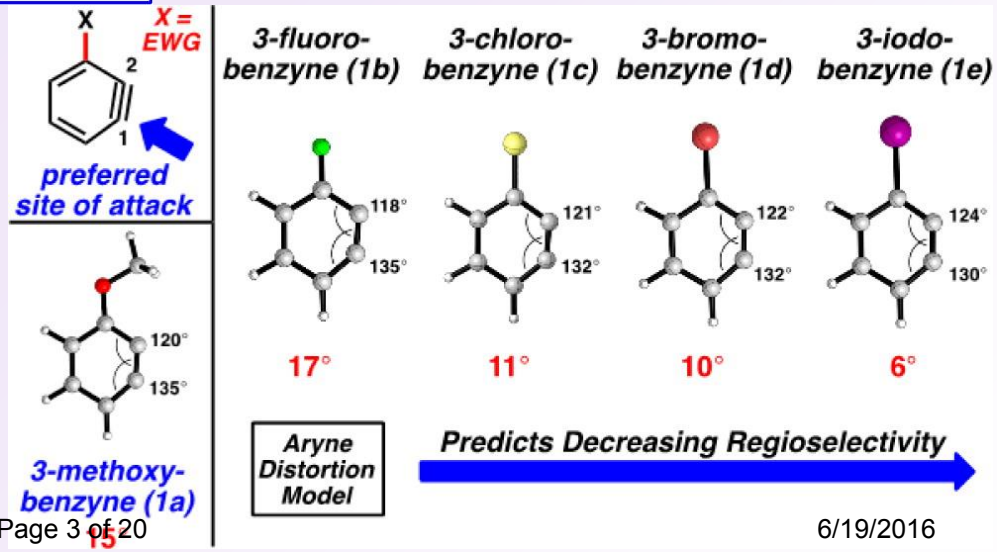
4,5-benzofuranyne



3,4-oxacyclohexyne

Distortion/Interaction Model to Predict Regioselectivity





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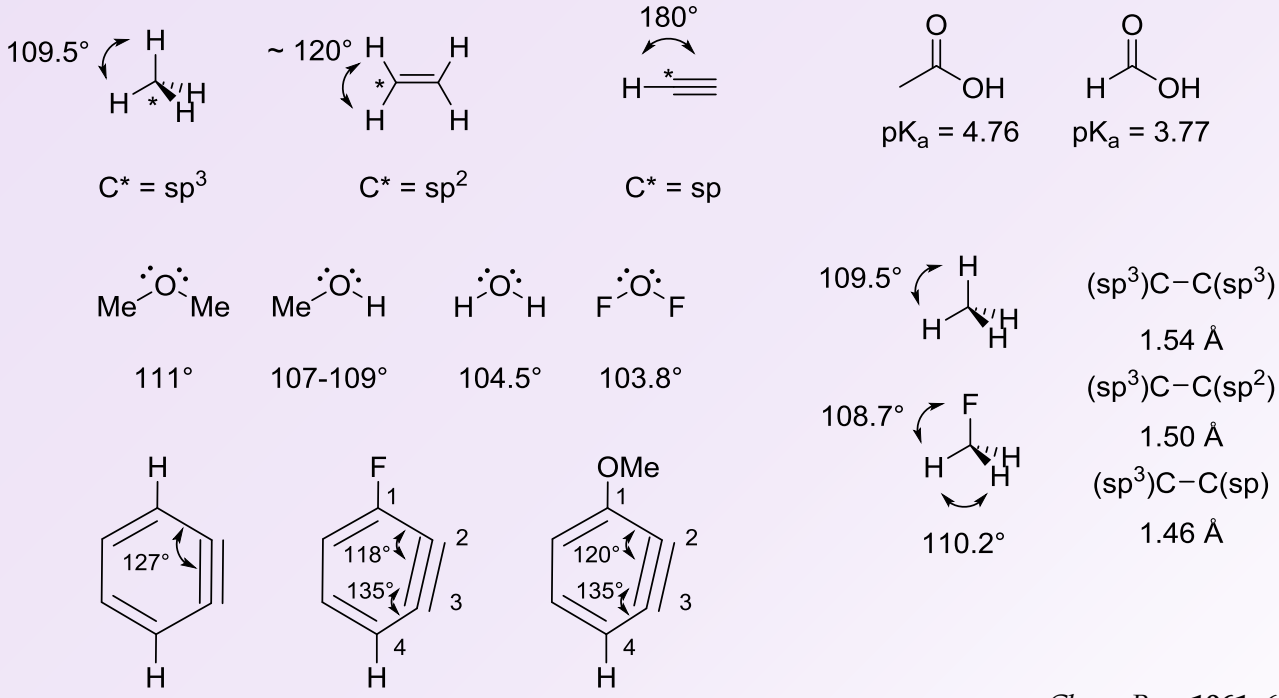
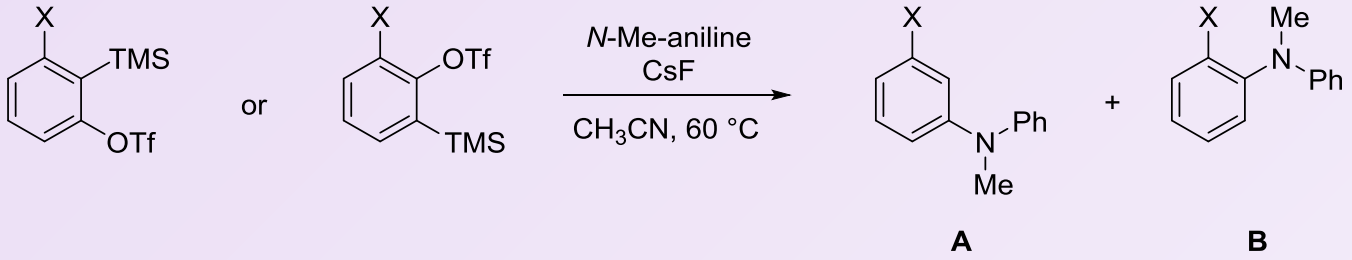
Bent's Rule

- sp^n orbitals; n does not have to be an integer.
- more s character is directed towards electropositive groups.
- more p character is directed towards electronegative groups.
- more s character = more electronegative.



Chem. Rev. **1961**, 61, 275.
J. Am. Chem. Soc. **2014**, *136*, 15798.

Computed vs. Experimental



entry	X	computed $\Delta\Delta G^{\ddagger}$ (ratio **A**:**B**)	experimental yield (ratio **A**:**B**)
1	OMe	5.2 kcal/mol (>500:1)	94% (**A** only)
2	F	4.1 kcal/mol (>500:1)	80% (**A** only)
3	Cl	2.4 kcal/mol (>57:1)	66% (>20:1)
4	Br	1.4 kcal/mol (>11:1)	67% (13:1)
5	I	1.7 kcal/mol (>19:1)	57% (9:1)

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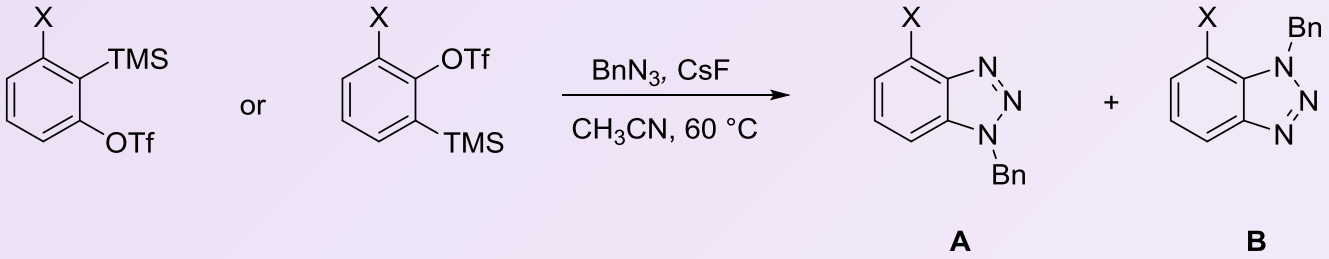
Computed vs. Experimental



entry	X	computed $\Delta\Delta G^{\ddagger}$ (ratio **A**:**B**)	experimental yield (ratio **A**:**B**)
1	OMe	3.4 kcal/mol (>292:1)	94% (**A** only)
2	F	2.5 kcal/mol (>71:1)	68% (**A** only)
3	Cl	1.4 kcal/mol (>10:1)	53% (>16:1)
4	Br	1.2 kcal/mol (>8:1)	45% (12:1)
5	I	0.9 kcal/mol (>5:1)	43% (6:1)

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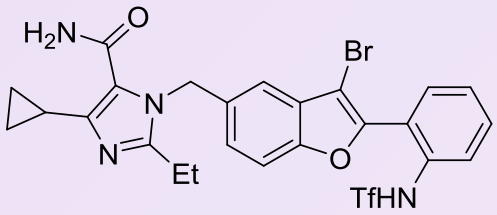
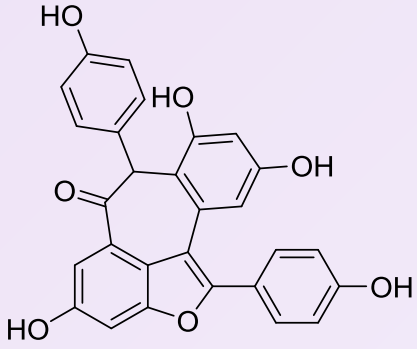
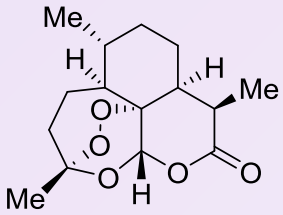
Benzofuran- and Pyran-Containing Natural Products and Pharmaceuticals



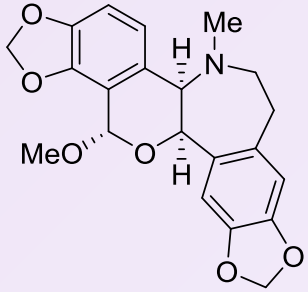
Saprisartan
(hypertension & heart failure)



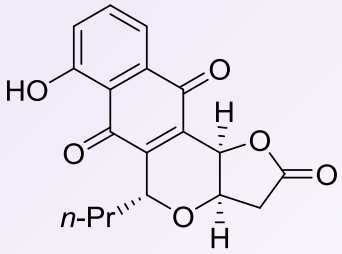
Hopeafuran/Shoreaphenol
(antimicrobial)



Artemisinin
(antimalarial)

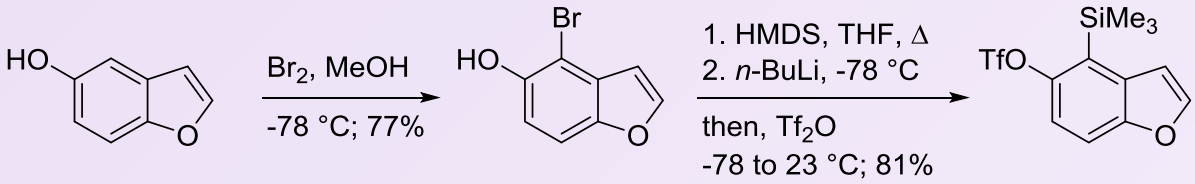


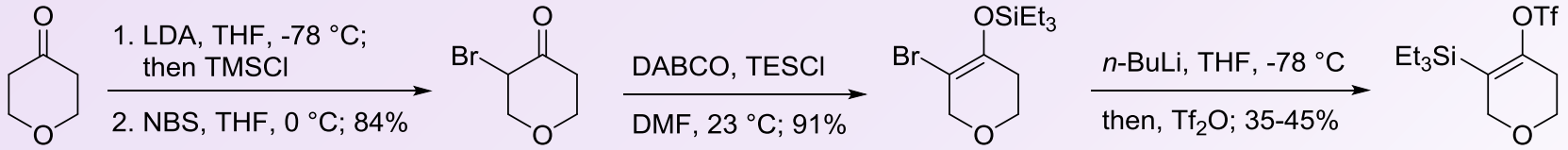
Rhoeadine
(sedative & antitussive)



Frenolicin B
(AKT1 kinase inhibitor)

Synthesis of Silyl Triflates





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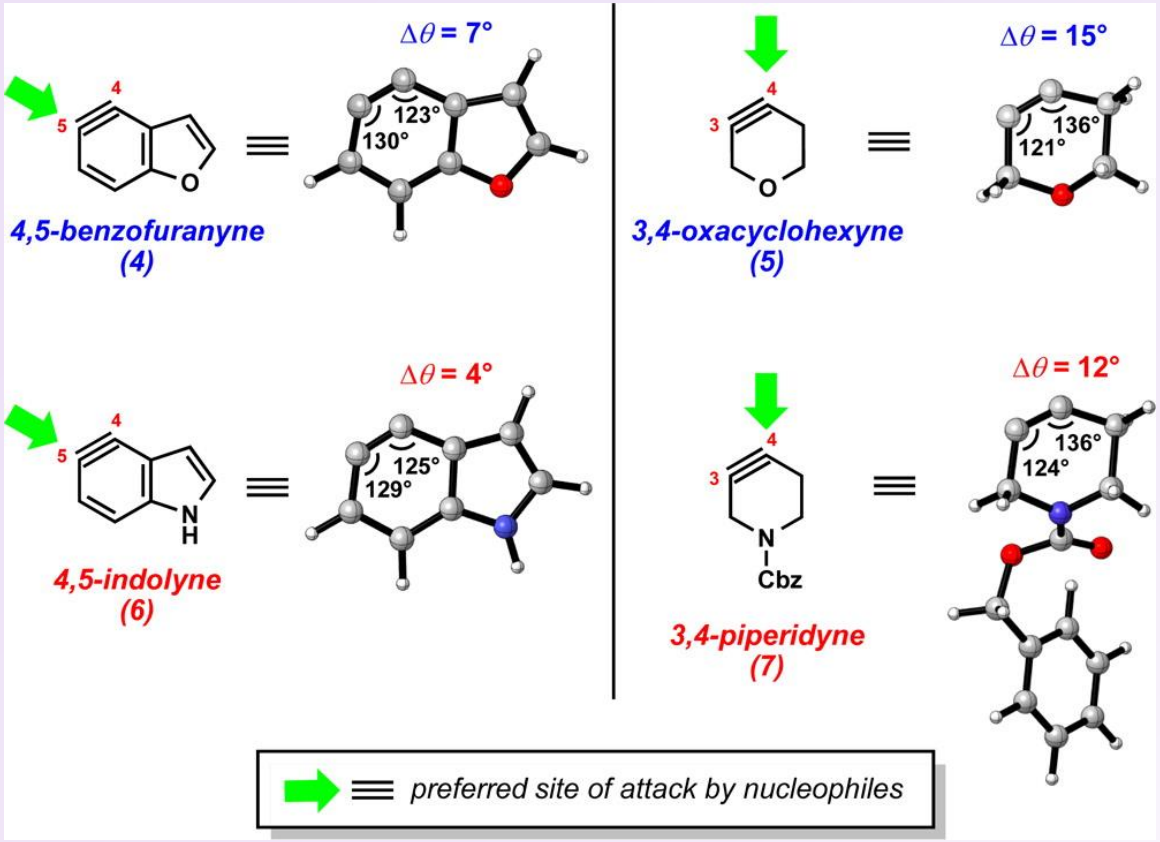
Predicated Regioselectivity Based on Distortion/Interaction Model



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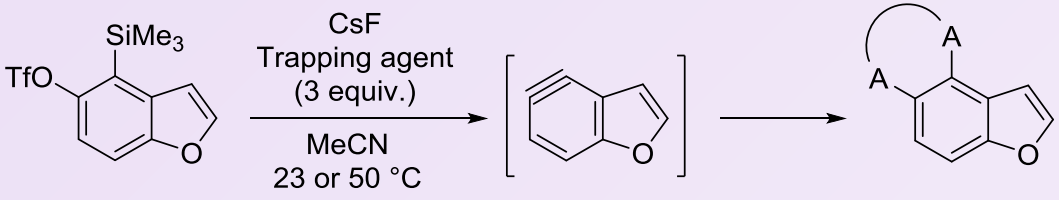
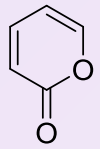
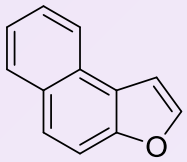
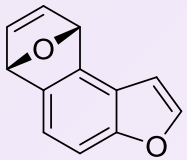
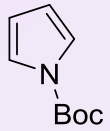
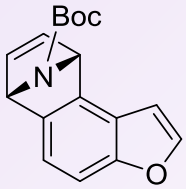
Diels-Alder Cycloadditions of 4,5-Benzofuranyne



entry	trapping agent	product	yield
1			68%
2			96%
3			75%

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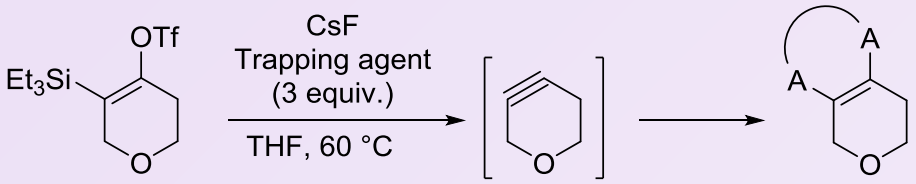
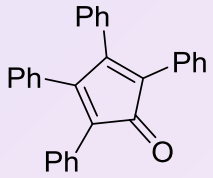
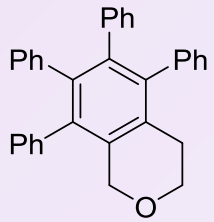
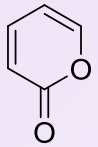
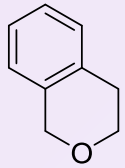
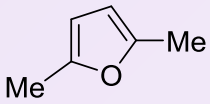
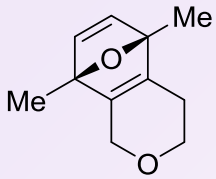
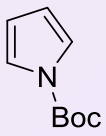
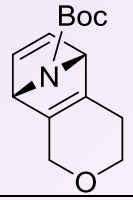
Diels-Alder Cycloadditions of 3,4-Oxacyclohexyne



entry	trapping agent	product	yield
1			100%
2			49%
3			50%
4			48%

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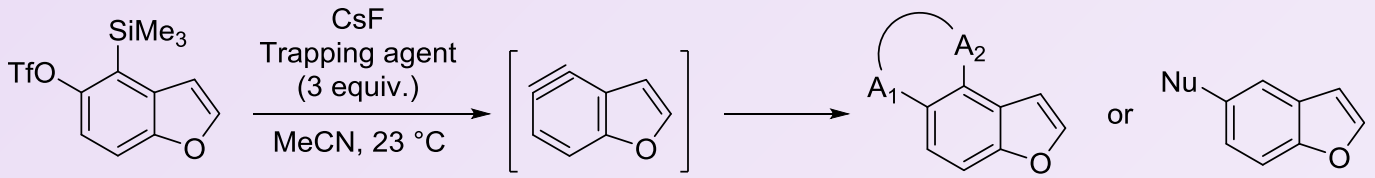
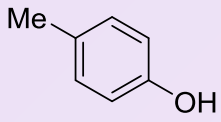
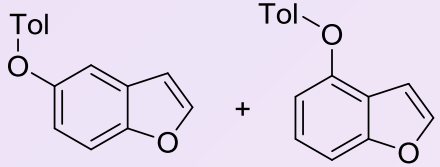
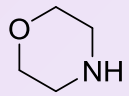
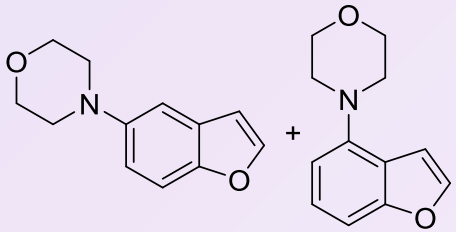
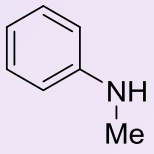
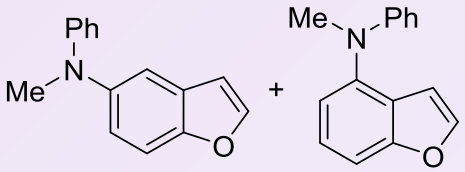
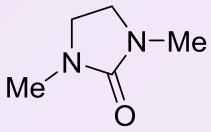
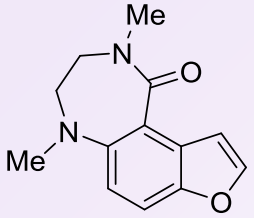
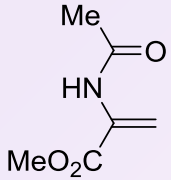
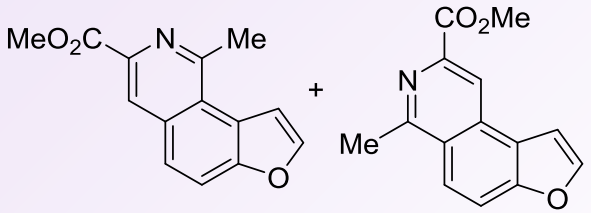
Benzofuranyne with Nucleophiles and Cycloaddition Partners



entry	trapping agent	product(s)
1		 73% (8.5:1)
2		 78% (4.2:1)
3		 83% (10:1)
5[b]		 90%
6		 51% (2.9:1)

[b] Neat with 10 equiv. of imidazolidinone at 50 °C.

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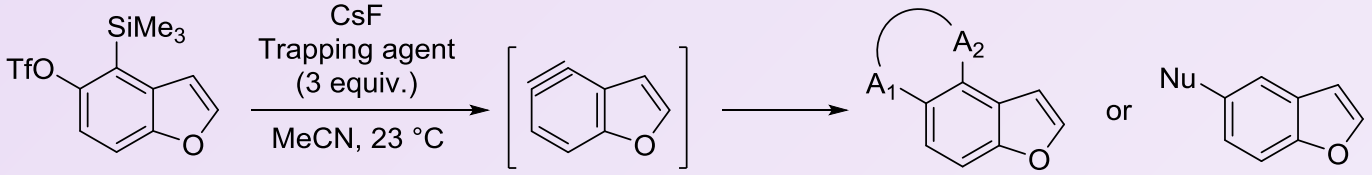
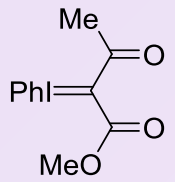
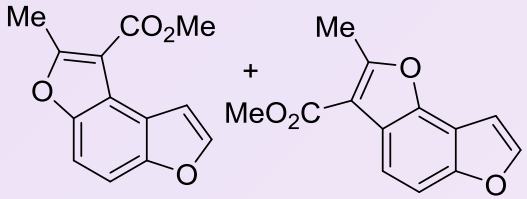
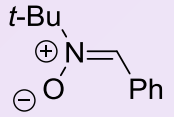
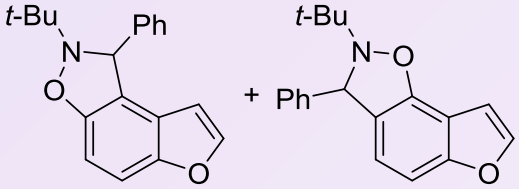
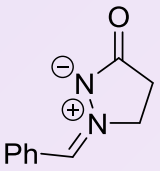
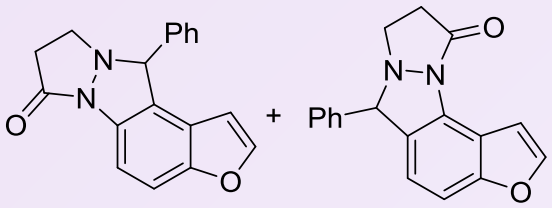
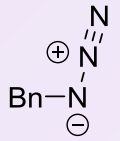
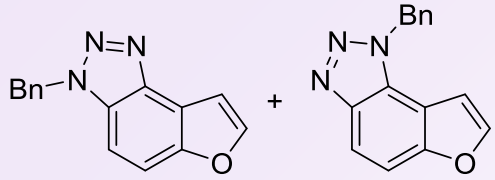
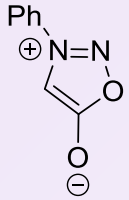
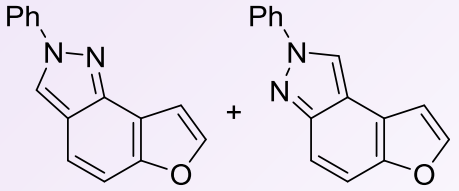
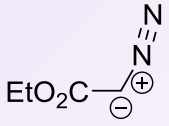
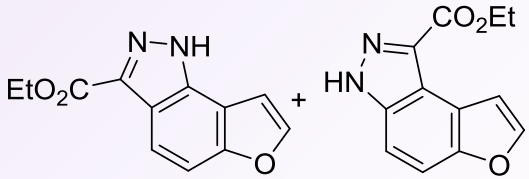
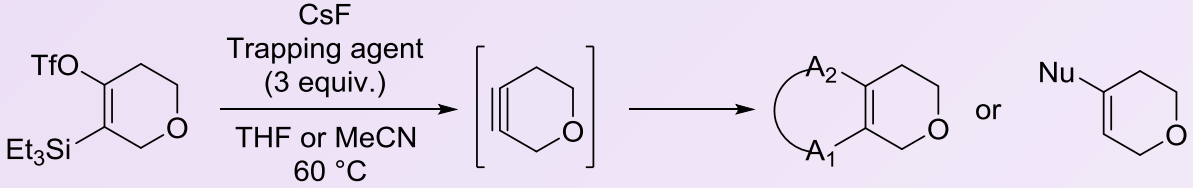
Benzofuranyne with Nucleophiles and Cycloaddition Partners

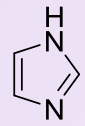
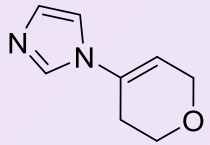
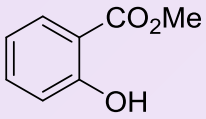
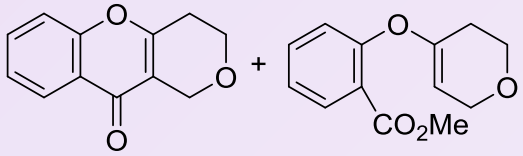
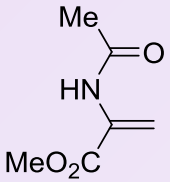
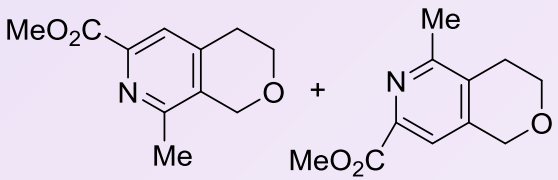
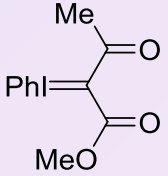
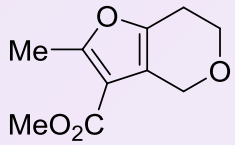
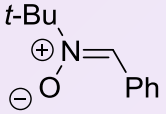
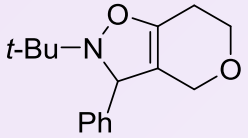
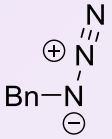
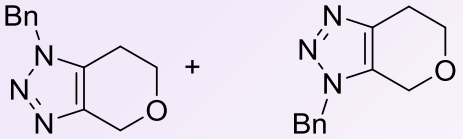
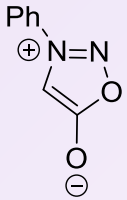
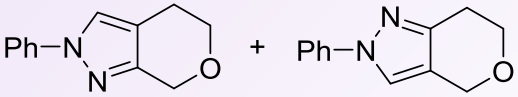
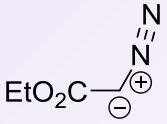
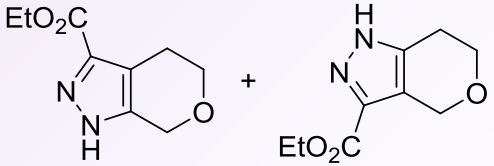


entry	trapping agent	product(s)
6		 66% (12:1)
7		 82% (5.4:1)
8		 64% (4.5:1)
9		 71% (6.2:1)
10		 85% (1.3:1)
11		 65% (2.5:1)

J. Am. Chem. Soc. DOI: 10.1021/jacs.6b01986

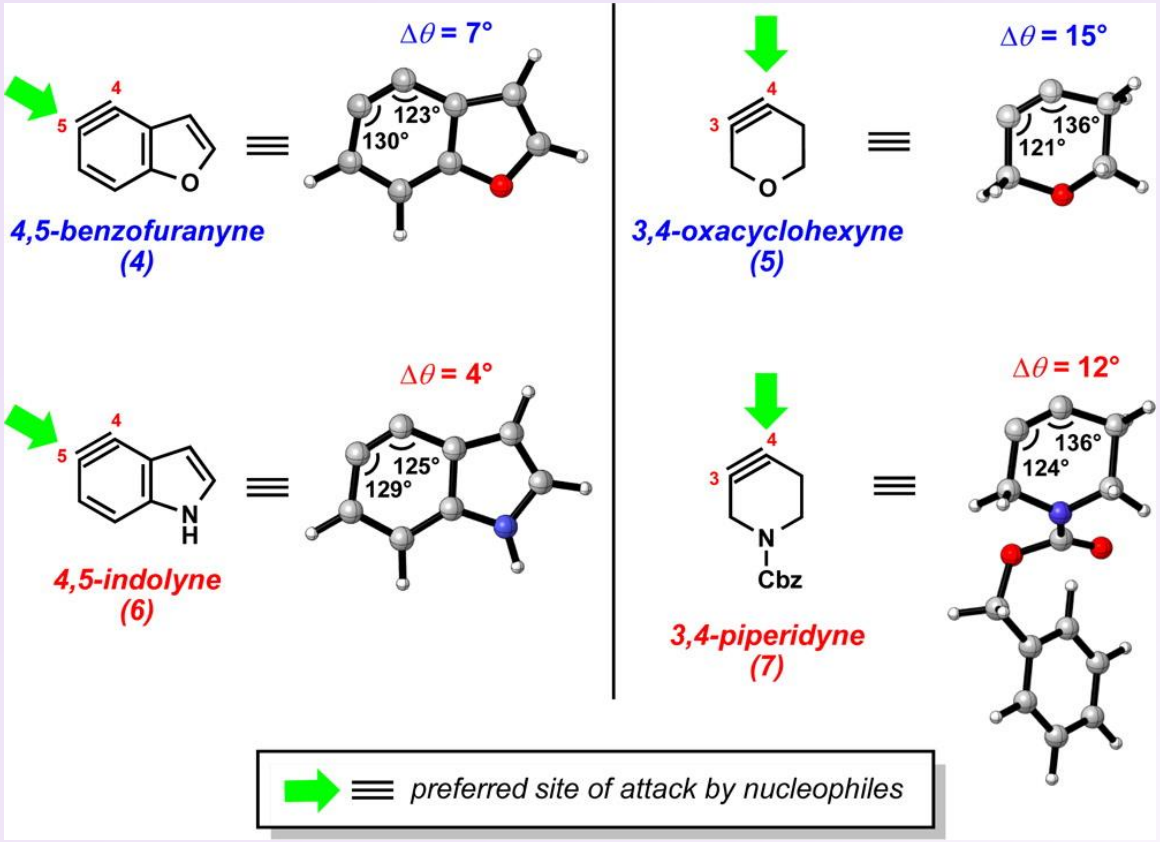
3,4-Oxacyclohexyne with Nucleophiles and Cycloaddition Partners



entry	trapping agent	product(s)
1		 59% (>20:1)
2		 79% (>20:1)
3		 71% (2.6:1)
4		 70% (>20:1)
5		 73% (>20:1)
6		 69% (7.2:1)
7		 88% (1.5:1)
8		 64% (6.1:1)

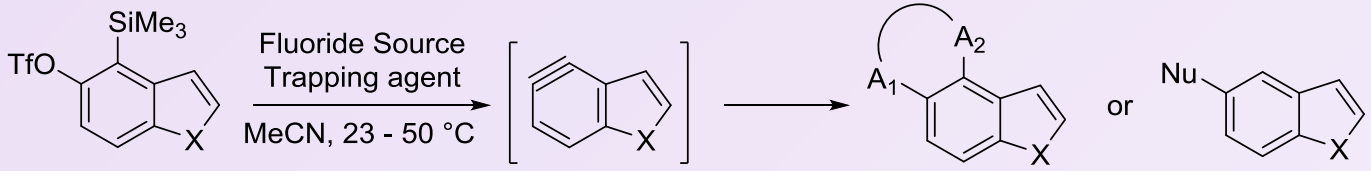
J. Am. Chem. Soc. DOI: 10.1021/jacs.6b01986

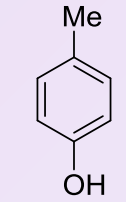
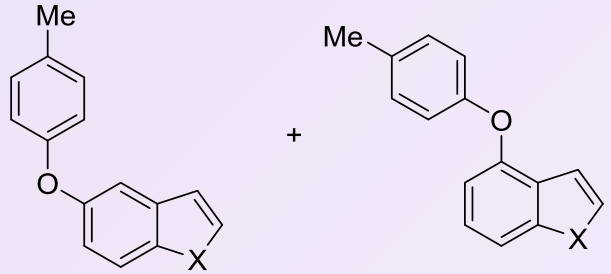
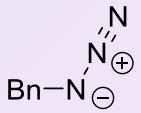
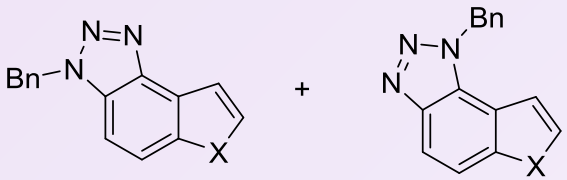
N vs. O: Predicated Regioselectivity Based on Distortion/Interaction Model



J. Am. Chem. Soc. DOI: 10.1021/jacs.6b01986

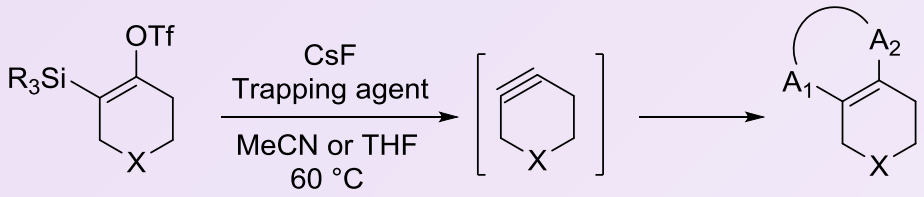
N vs. O

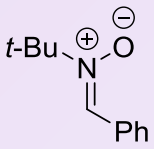
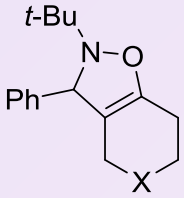
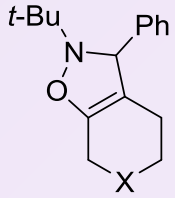
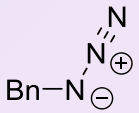
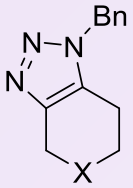


entry	trapping agent	product(s)	yield (X = NMe)	yield (X = O)
1			3.0:1 (80%)	8.5:1 (73%)
2			2.4:1 (86%)	6.2:1 (71%)

J. Am. Chem. Soc. DOI: 10.1021/jacs.6b01986

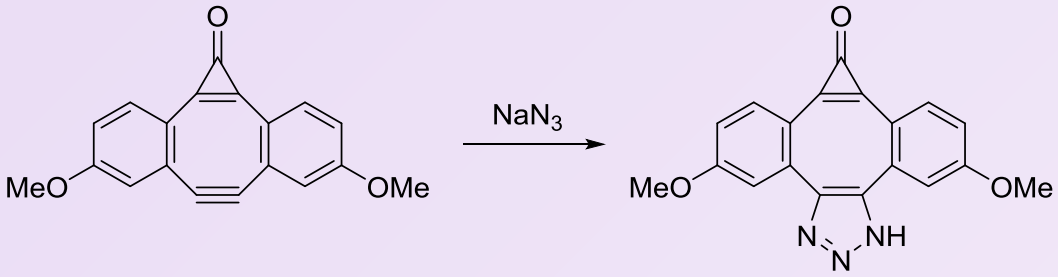
N vs. O



entry	trapping agent	product(s)			yield (X = NCbz; R = Me)	yield (X = O; R = Et)
1			+		12.7:1 (84%)	>20:1 (73%)
2			+		5.3:1 (81%)	7.2:1 (69%)

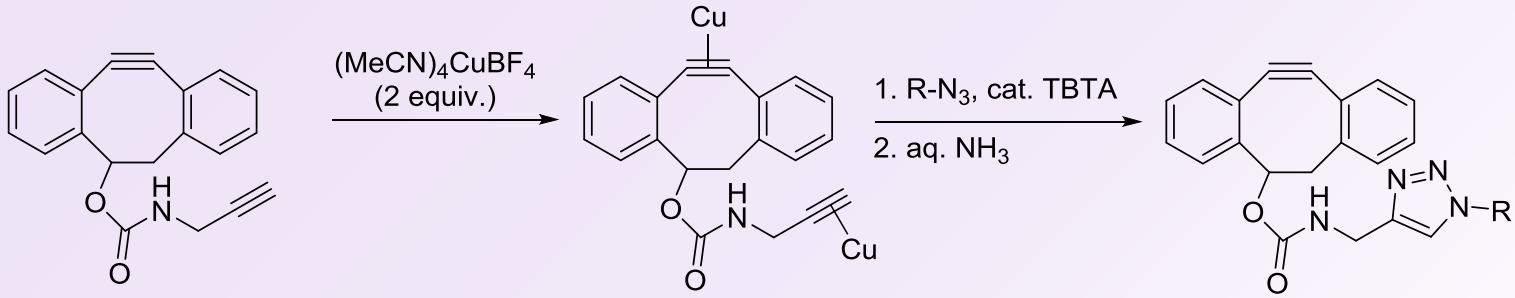
J. Am. Chem. Soc. DOI: 10.1021/jacs.6b01986

More Examples of Strained Alkynes: CuAAC vs. SPAAC

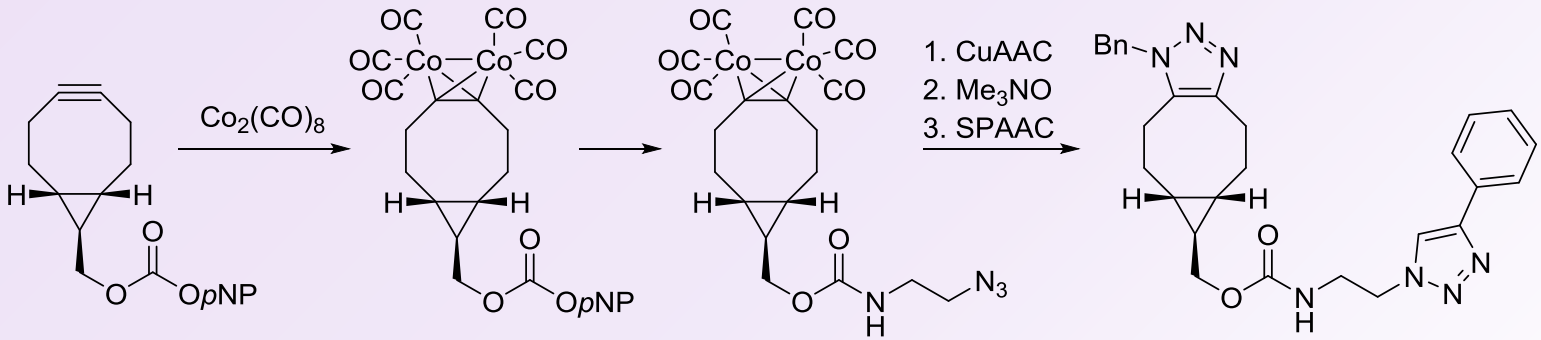


non-fluorescent highly-fluorescent

Bioorg. Med. Chem. Lett. **2016**, 26, 1651.

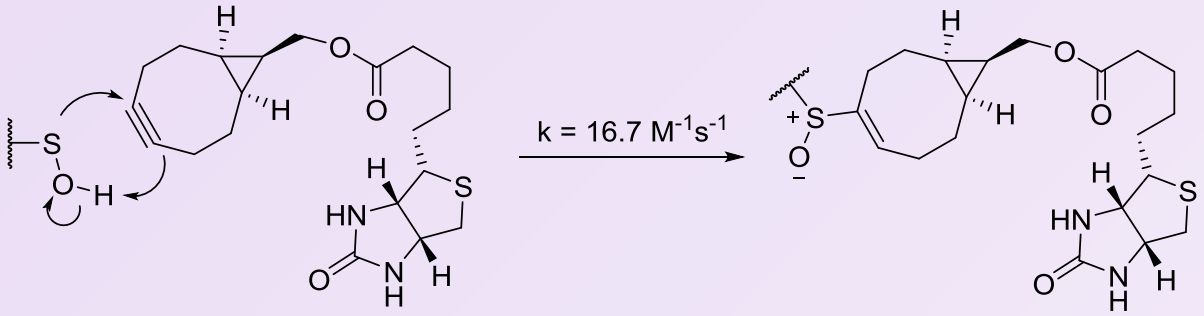


J. Am. Chem. Soc. **2014**, 136, 13590.

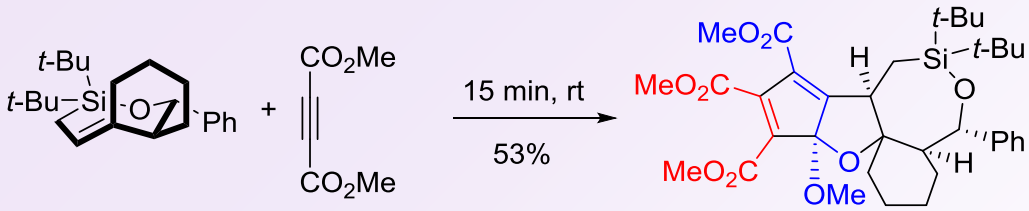


Chem. Commun. **2015**, 51, 6647.

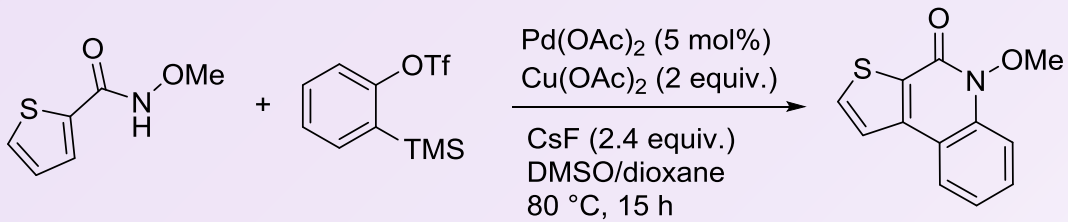
Recent Examples of Strained Alkynes and Alkenes



J. Am. Chem. Soc. **2014**, 136, 6167.



Agnew. Chem. Int. Ed. **2016**, 55, 790.



87%

Org. Lett. **2014**, 16, 5354.

Conclusions

- Reactivity of strained alkynes removes the need for harsh conditions and additional reagents.
- Rapid/convergent construction of highly functionalized scaffolds.
- Understanding (and then improving) regioselectivity allows for better predictability/design.
- Preparation of strained alkynes requires multiple steps which may not be appealing in a linear sequence.
- Future application in synthesis of complex molecules will further highlight the methodologies' utility.