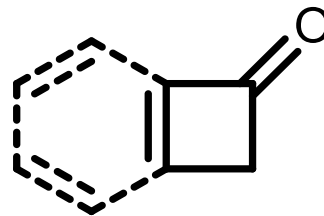
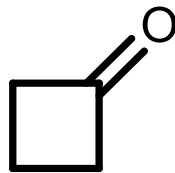


Synthesis of Cyclobutanone and Cyclobutenone



Penghao Chen

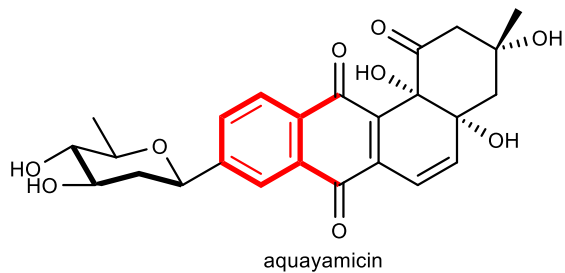
Dong Group Seminar

Aug, 22nd, 2013

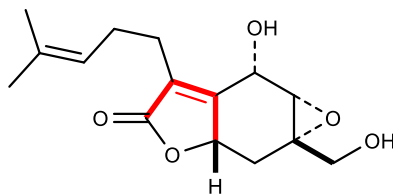
Salan, J., in *Science of Synthesis*, **26** (2004), p.557

Ruben Martin, *Synthesis*, **2013**, *45*, 563

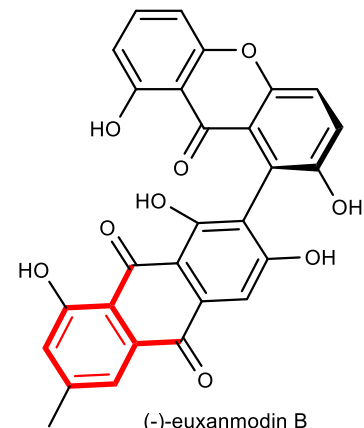
Synthetic Application



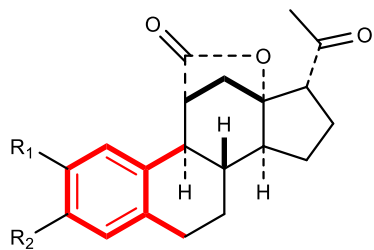
aquayamicin



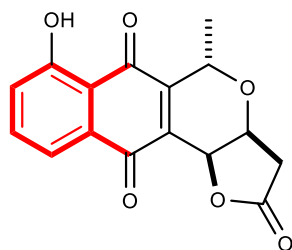
paniculide B



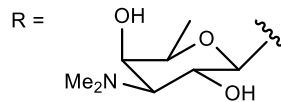
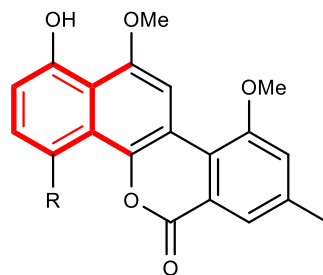
(-)-euxanmodin B



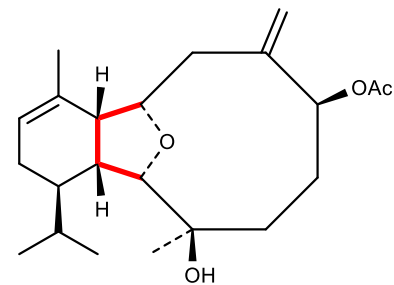
$R_1 = R_2 = \text{MeO}$
 $R_1 = \text{F}, R_2 = \text{H}$
 $R_1 = \text{OH}, R_2 = \text{H}$



nanaomycin D



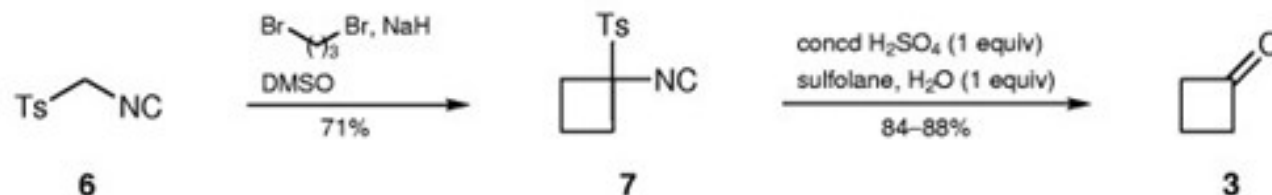
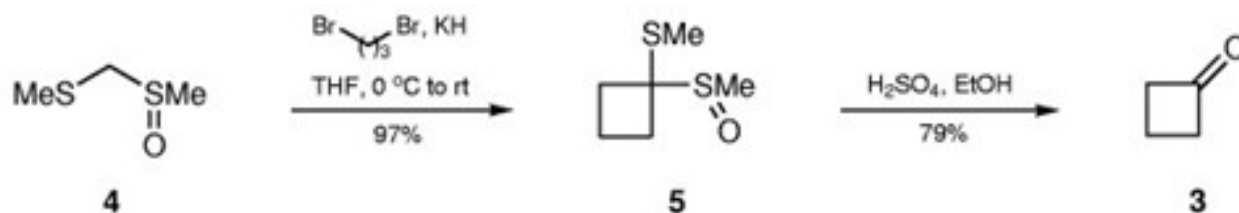
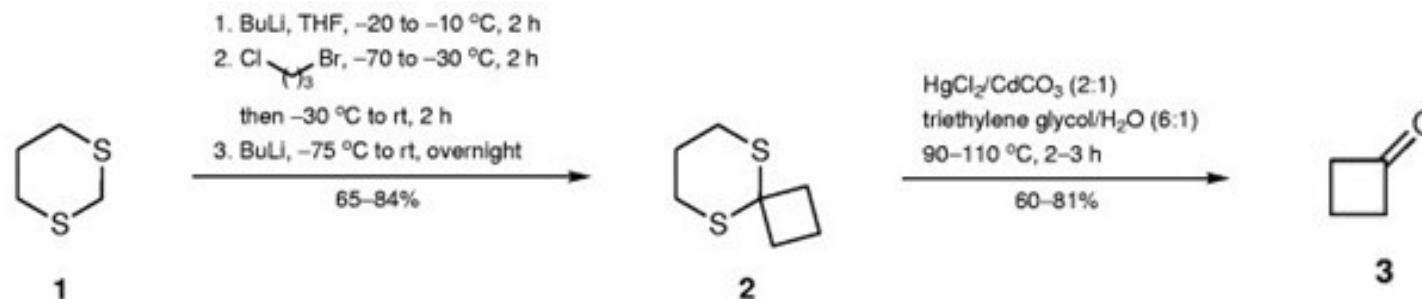
deacetylraivodomycin M
 $R = \text{H}; \text{defucogilvocarcin M}$



(-)-deacetoxyalcyonin acetate

Cyclobutanone Synthesis

Cyclodialkylation by 1,3-Dihalopropanes



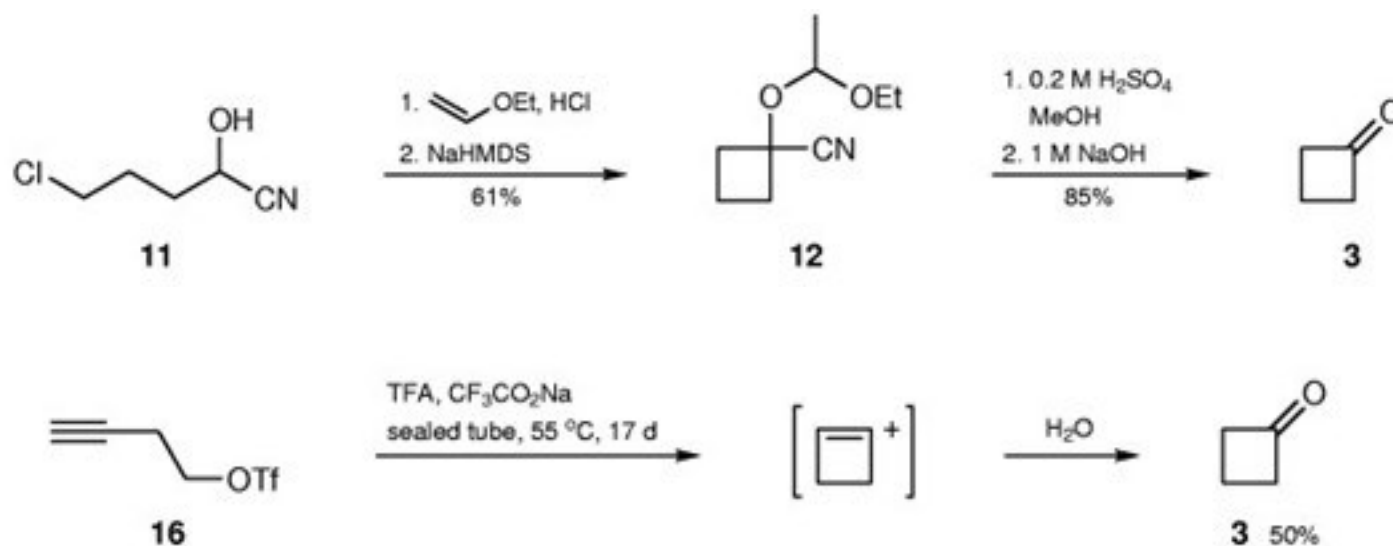
Seebach, D.; Jones, N. R.; Corey, E. J., *J. Org. Chem.*, **1968**, *33*, 300.

Ogura, K.; Yamashita, M.; Suzuki, M.; Tsuchihashi, G., *Tetrahedron Lett.*, **1974**, 3653.

Possel, O.; van Leusen, A. M., *Tetrahedron Lett.*, **1977**, 4229.

Cyclobutanone Synthesis

Cyclization by Intramolecular Substitution



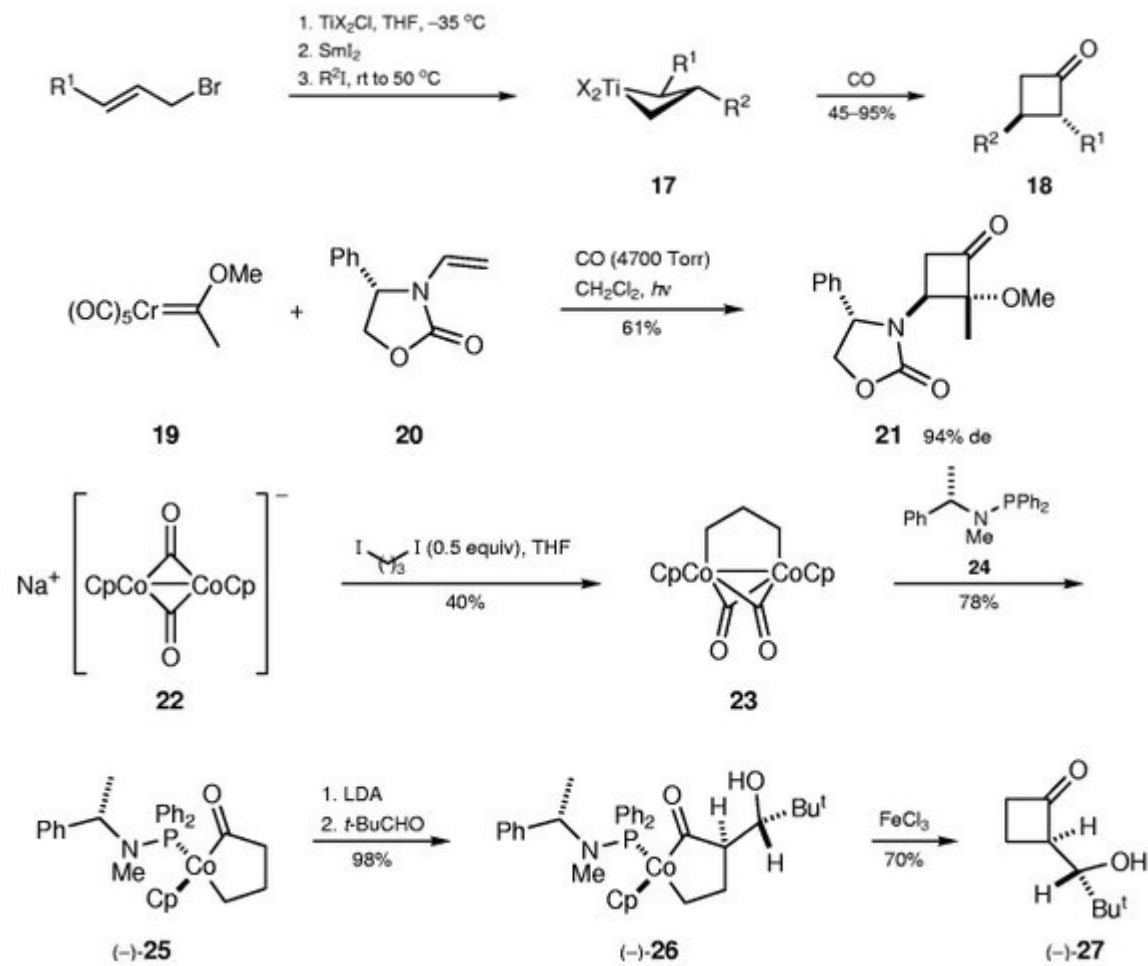
Stork, G.; Depezay, J. C.; d'Angelo, J., *Tetrahedron Lett.*, **1975**, 389.

Klinkmüller, K. D.; Marschall, H.; Weyersthal, P., *Chem. Ber.*, **1975**, 108, 191.

Hummel, K.; Hanack, M., *Justus Liebigs Ann. Chem.*, **1971**, 746, 211.

Cyclobutanone Synthesis

Ring Formation by Carbonylation



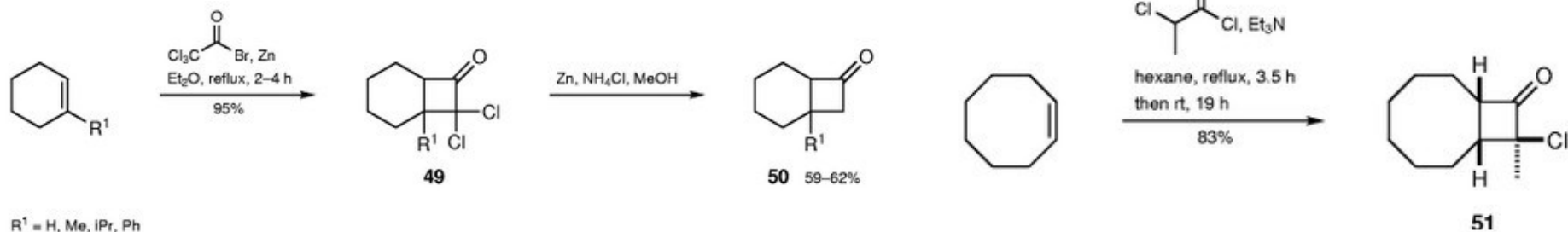
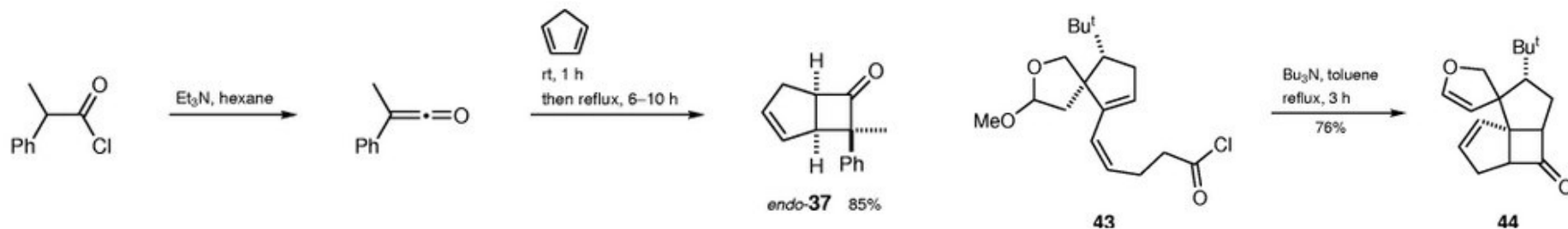
Carter, C. A. G.; Greidanus, G.; Chen, J.-X.; Stryker, J. M., *J. Am. Chem. Soc.*, **2001**, *123*, 8872.

Hegedus, L. S.; Bates, R. W.; Söderberg, B. C., *J. Am. Chem. Soc.*, **1991**, *113*, 923.

Theopold, K. H.; Becker, R. N.; Bergman, R. G., *J. Am. Chem. Soc.*, **1982**, *104*, 5250.

Cyclobutanone Synthesis

[2 + 2] Cycloaddition



Brady, W. T.; Parry, F. H.; Stockton, J. D., *J. Org. Chem.*, **1971**, *36*, 1486.

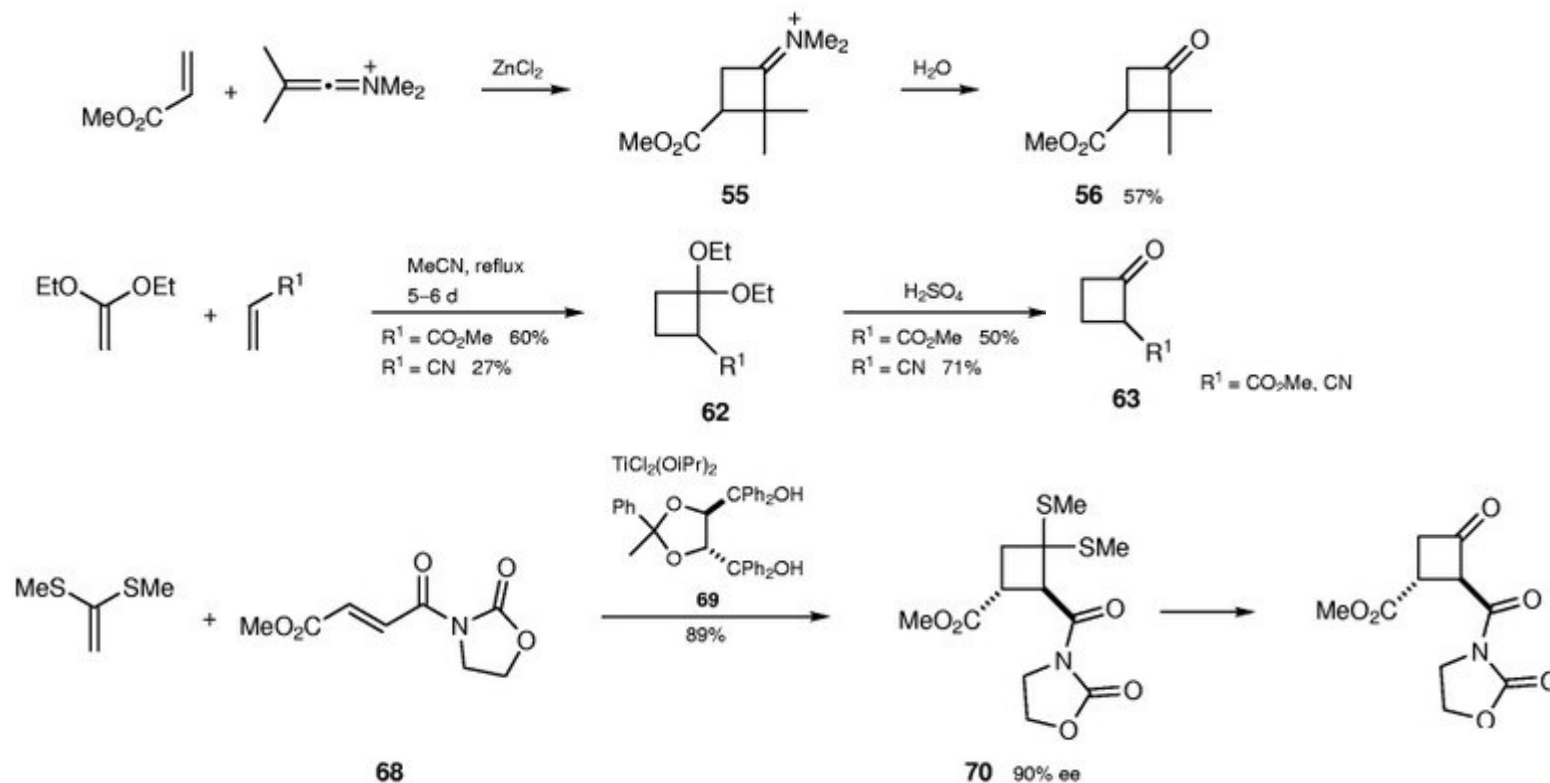
Lee, S. Y.; Kulkarni, Y. S.; Burbaum, B. W.; Johnston, M. I.; Snider, B. B., *J. Org. Chem.*, **1988**, *53*, 1848.

Jefferies, P. W.; Molina, G.; Cass, M. W.; Cortese, N. A., *J. Org. Chem.*, **1982**, *47*, 3871.

Hassner, A.; Pinnick, H. W.; Ansell, J. M., *J. Org. Chem.*, **1978**, *43*, 1774.

Cyclobutanone Synthesis

[2 + 2] Cycloaddition



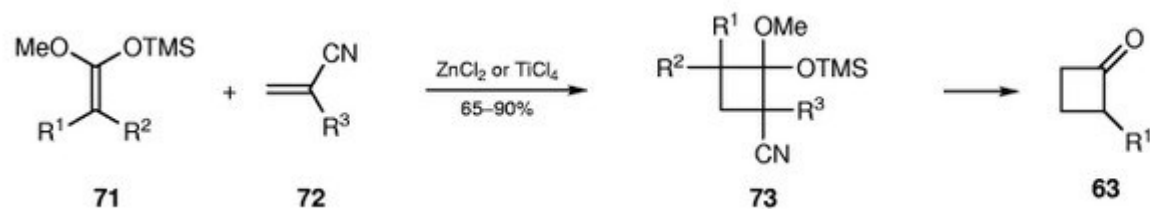
Sidani, A.; Marchand-Brynaert, J.; Ghosez, L., *Angew. Chem. Int. Ed. Engl.*, **1974**, *13*, 267.

Amice, P.; Conia, J. M., *Tetrahedron Lett.*, **1974**, 479.

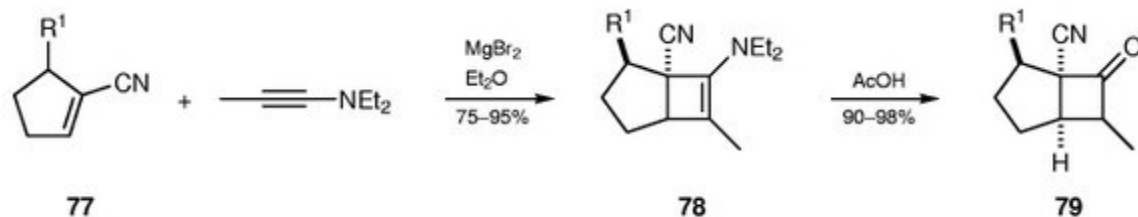
Narasaka, K.; Hayashi, Y.; Shimadzu, H.; Niihata, S., *J. Am. Chem. Soc.*, **1992**, *114*, 8869.

Cyclobutanone Synthesis

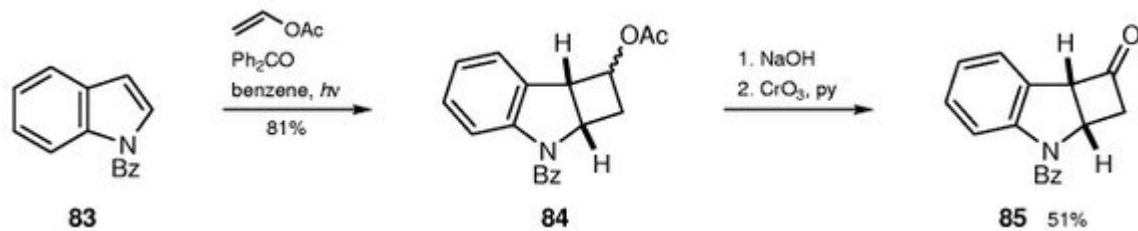
[2 + 2] Cycloaddition



R¹ = H, Me; R² = (CH₂)₄Me, Cy; R³ = H, Cl



R¹ = H, Me



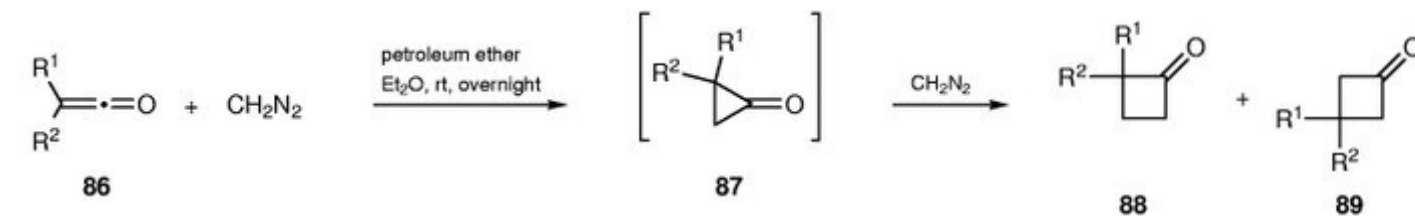
Quendo, A.; Rousseau, G., *Synth. Commun.*, **1989**, *19*, 1551.

Ficini, J.; d'Angelo, J.; Eman, A.; Touzin, A. M., *Tetrahedron Lett.*, **1976**, 683.

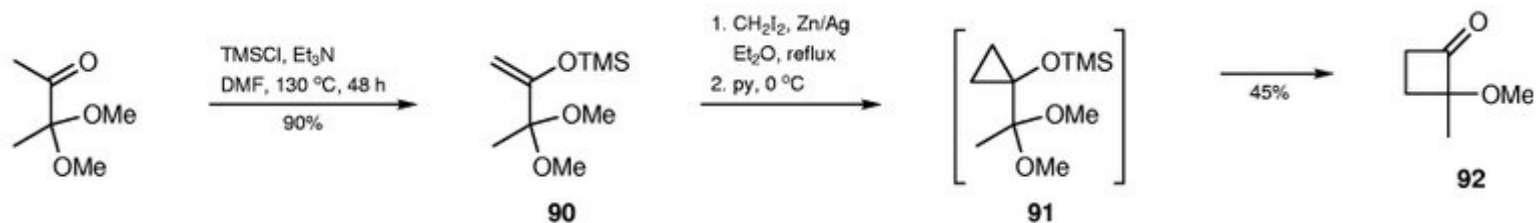
Ikeda, M.; Uno, T.; Hamma, K.; Ohno, K.; Tamura, Y., *Synth. Commun.*, **1980**, *10*, 437.

Cyclobutanone Synthesis

Ring Enlargement of Three-Membered Ring



R¹ = Me, *t*-Bu; R² = H, Me

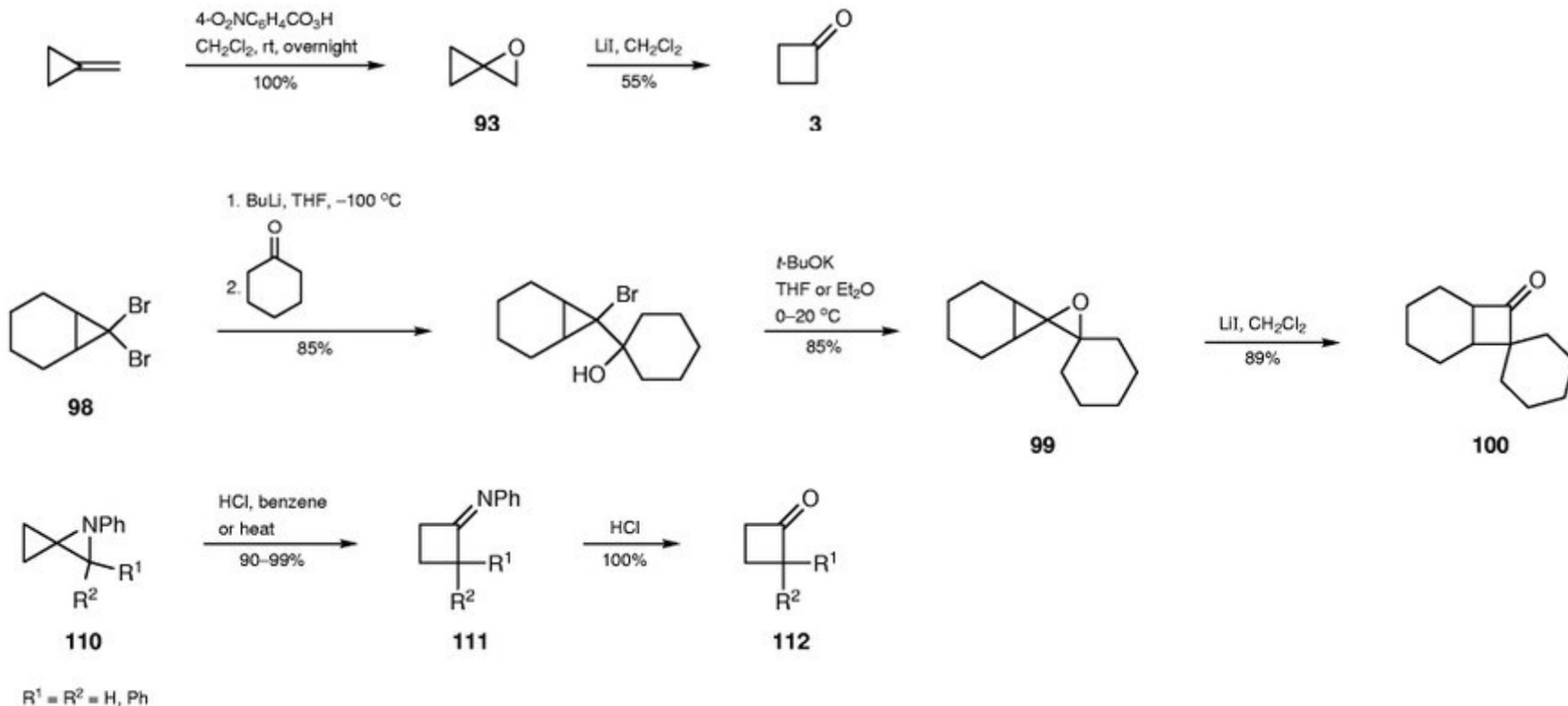


Conia, J. M.; Salaün, J., *Bull. Soc. Chim. Fr.*, **1964**, 1957.

Barnier, J. P.; Garnier, B.; Girard, C.; Denis, J. M.; Salaün, J.; Conia, J. M., *Tetrahedron Lett.*, **1973**, 1747.

Cyclobutanone Synthesis

Rearrangement of Spiro[2,2]pentanes



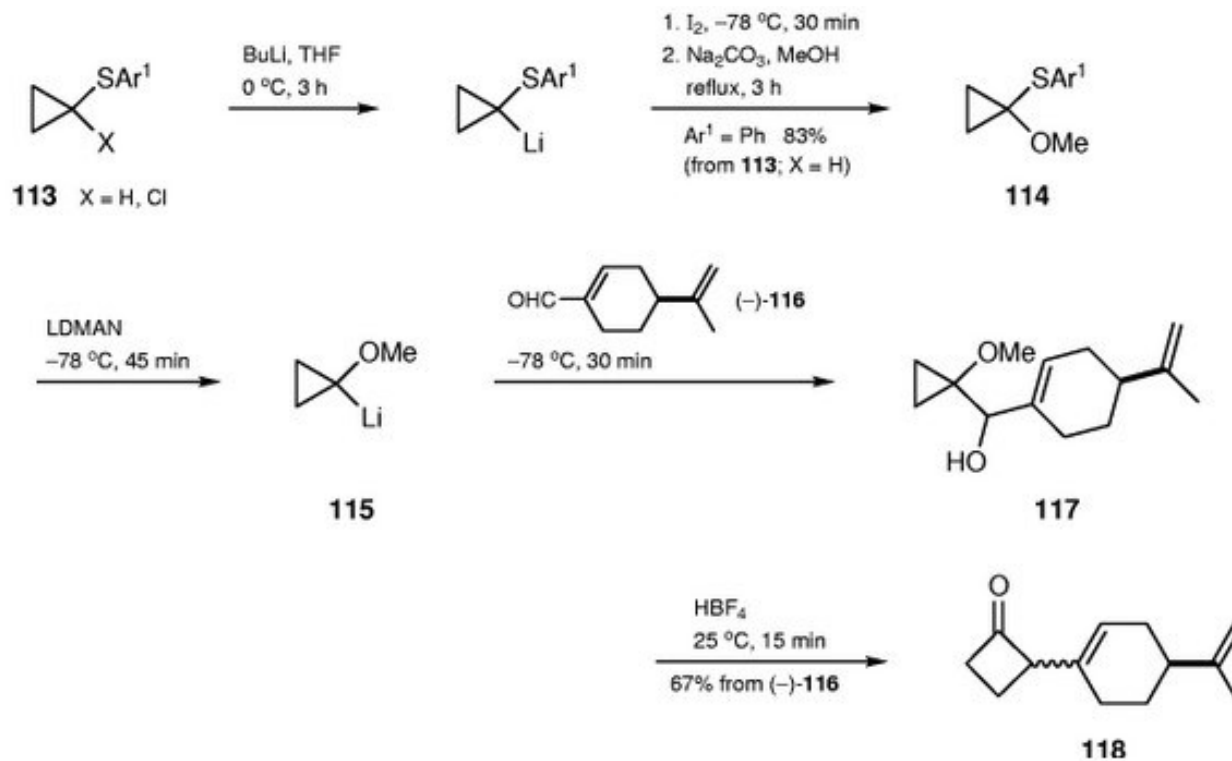
Salaün, J.; Garnier, B.; Conia, J. M., *Tetrahedron*, **1974**, *30*, 1413.

Braun, M.; Dammann, R.; Seebach, D., *Chem. Ber.*, **1975**, *108*, 2368.

Crandall, J. K.; Conower, W. W., *J. Org. Chem.*, **1974**, *39*, 63.

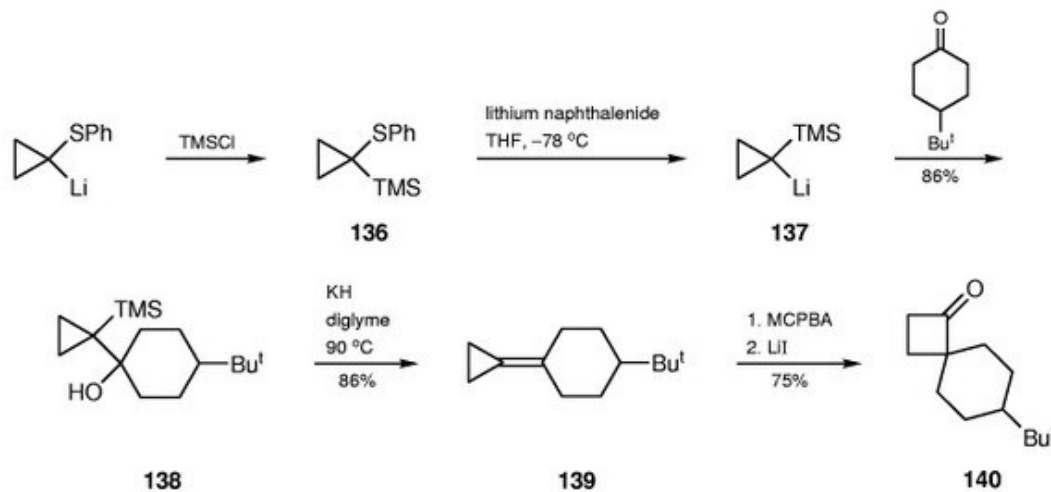
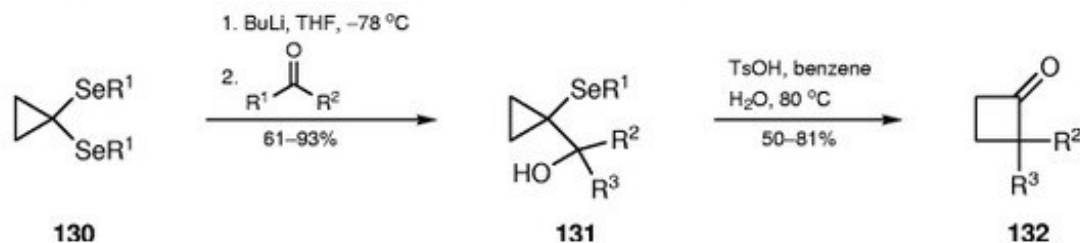
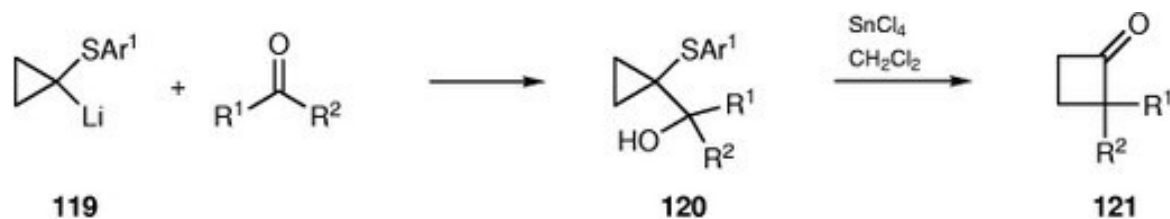
Cyclobutanone Synthesis

Rearrangement of (1-hydroxyalkyl)cyclopropane



Cyclobutanone Synthesis

Rearrangement of (1-hydroxyalkyl)cyclopropane



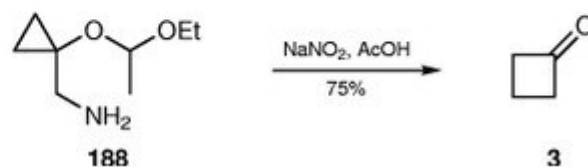
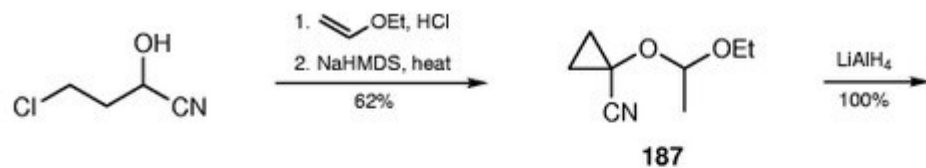
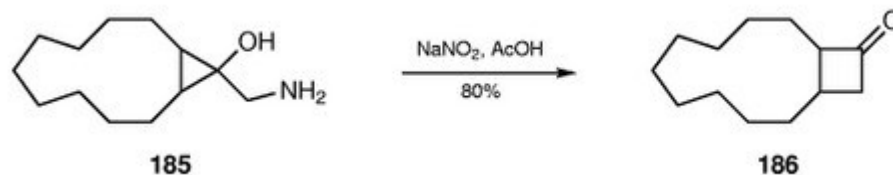
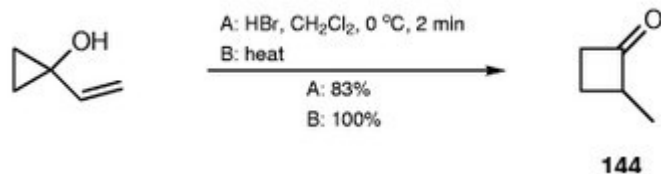
Trost, B. M.; Keeley, D. E., *J. Am. Chem. Soc.*, **1974**, *96*, 1252.

Krief, A., *Top. Curr. Chem.*, **1987**, *135*, 1.

Cohen, T.; Sherbine, T. P.; Matz, J. R.; Hutchins, R. R.; Mc Herty, B. M.; Willey, P. R., *J. Am. Chem. Soc.*, **1984**, *106*, 3245.

Cyclobutanone Synthesis

Rearrangement of Cyclopropanol Derivatives



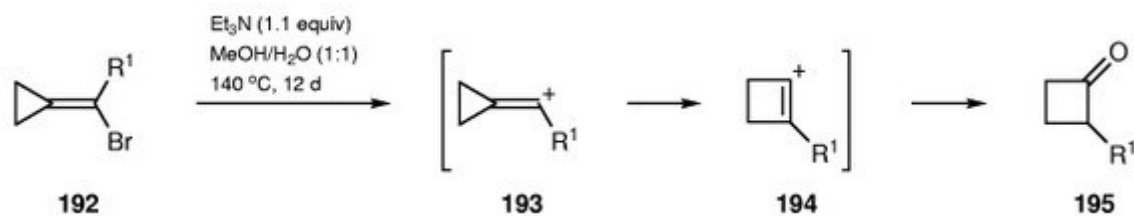
Salaün, J.; Conia, J. M., *Tetrahedron Lett.*, **1972**, 2849.

Wasserman, H. H.; Hearn, M. J.; Haveaux, B.; Thyges, M., *J. Org. Chem.*, **1976**, 41, 153.

Stork, G.; Depezay, J. C.; d'Angelo, J., *Tetrahedron Lett.*, **1975**, 389.

Cyclobutanone Synthesis

Rearrangement of (1-Bromoalkylidene)cyclopropanes



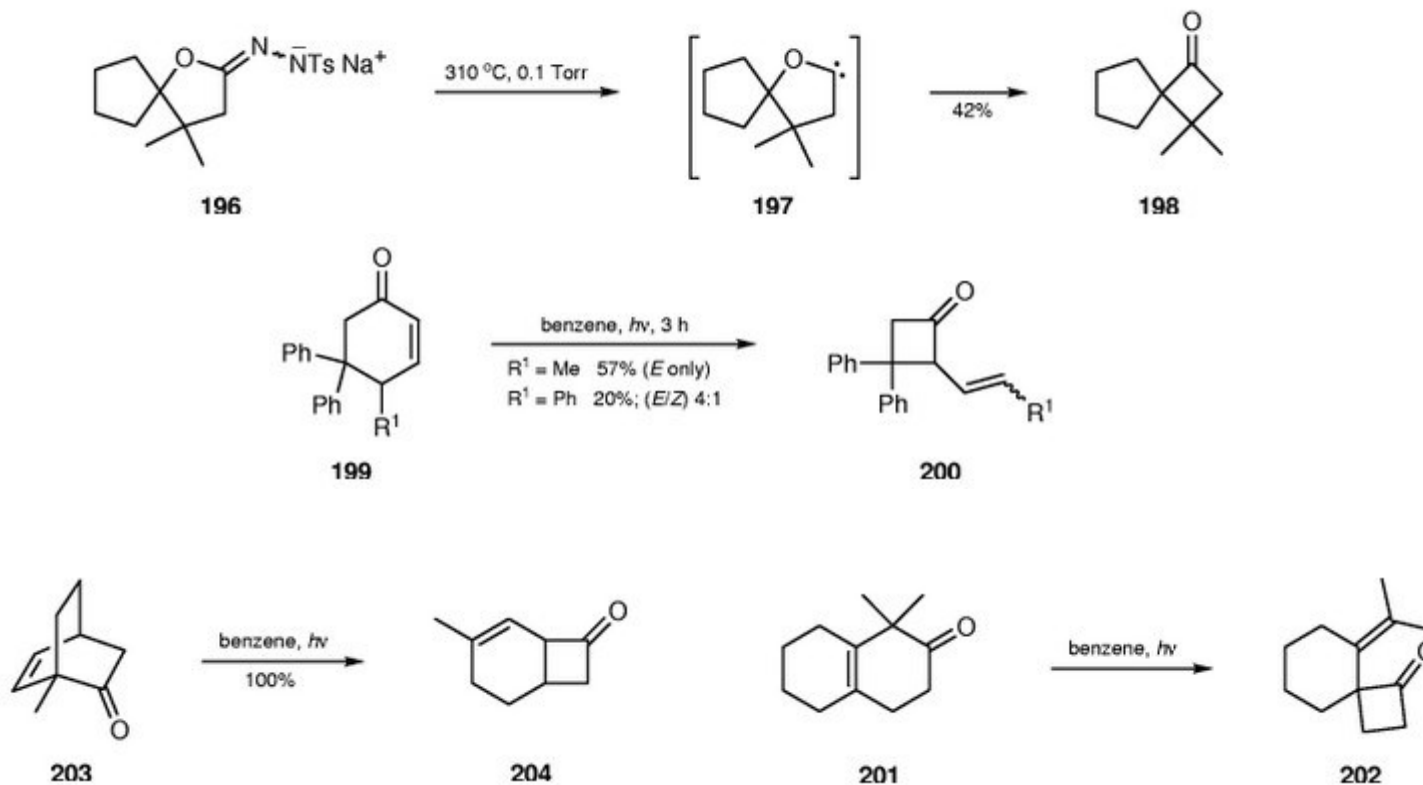
Caubere, P.; Coudert, G., *Bull. Soc. Chim. Fr.*, **1971**, 2234.

Bässler, T.; Hanack, M., *Tetrahedron Lett.*, **1971**, 2171.

Salaün, J.; Hanack, M., *J. Org. Chem.*, **1975**, 40, 1994.

Cyclobutanone Synthesis

Ring Contraction



Smith, A. B., III; Foster, A. M.; Agosta, W. C., *J. Am. Chem. Soc.*, **1972**, *94*, 5100.

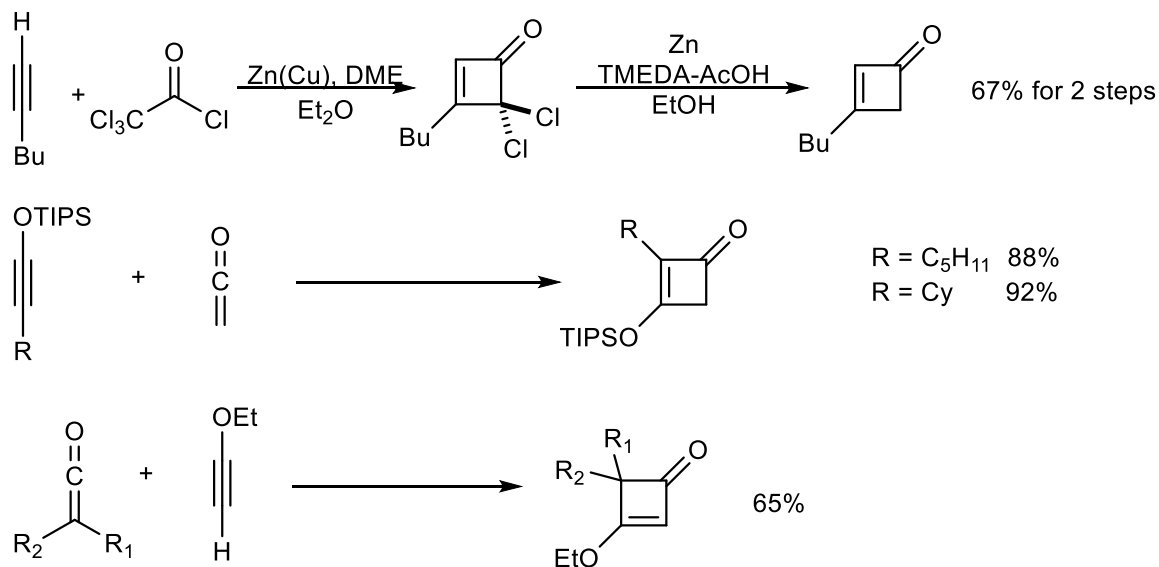
Zimmerman, H. E.; Solomon, R. D., *J. Am. Chem. Soc.*, **1986**, *108*, 6276.

Engel, P. S.; Schexnayder, M. A.; Ziffer, H.; Seeman, J. I., *J. Am. Chem. Soc.*, **1974**, *96*, 924.

Demuth, M.; Raghavan, P. R.; Carter, C.; Nakano, K.; Schaffner, K., *Helv. Chim. Acta*, **1980**, *63*, 2434.

Cyclobutenone Synthesis

[2 + 2] Cycloaddition by ketene and alkyne



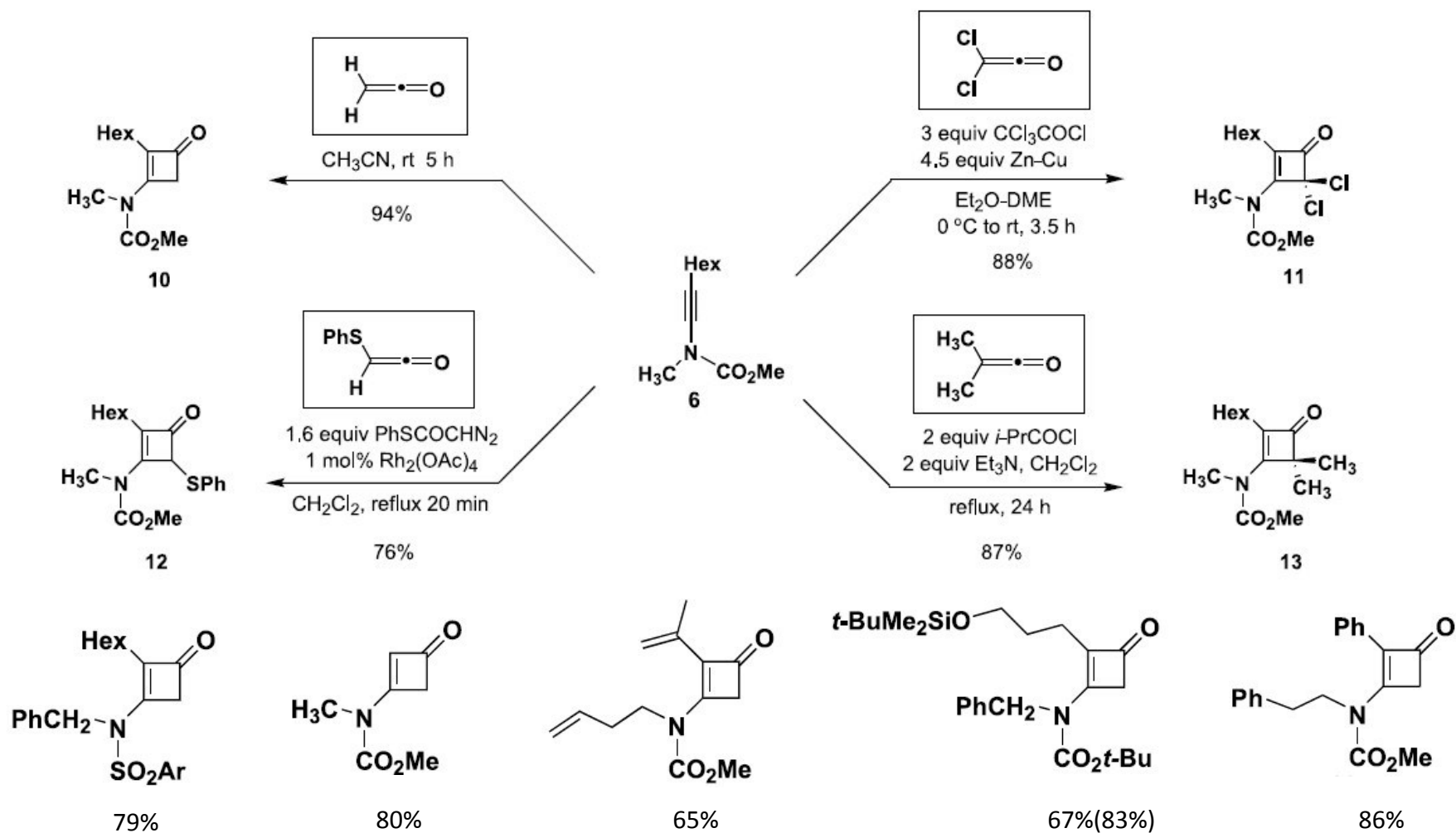
Danheiser R. L.; Savariar S.; Cha D. D. *Organic Syntheses, Coll.* **1993**, 8, 82; **1990**, 68, 32.

Wasserman H. H.; Dehmlow E. *Tetrahedron Lett.* **1962**, 3, 1031.

Kowalski C. J.; Lal G. S. *J. Am. Chem. Soc.* **1988**, 110, 3693.

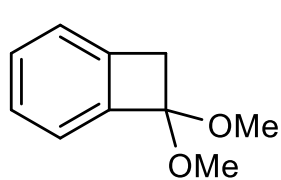
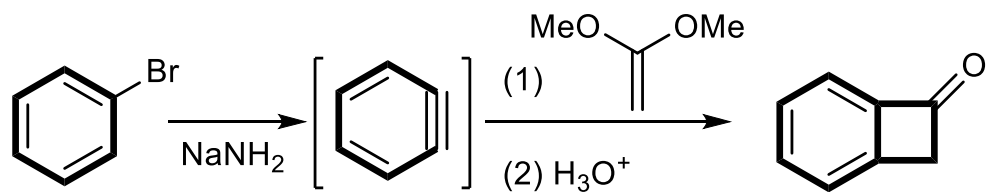
Cyclobutenone Synthesis

[2 + 2] Cycloaddition by ketene and alkyne

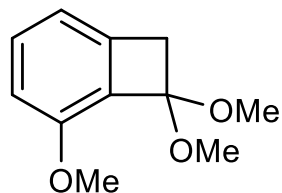


Cyclobutenone Synthesis

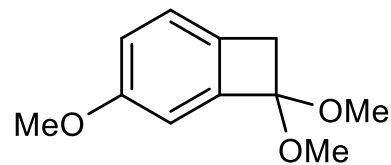
[2 + 2] Cycloaddition by ketene and benzyne



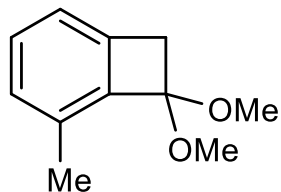
63%



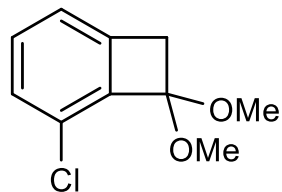
o: 70%
m: 76%



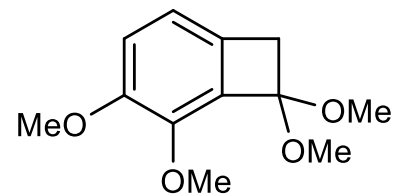
64% (7:1)



38%(3:1)



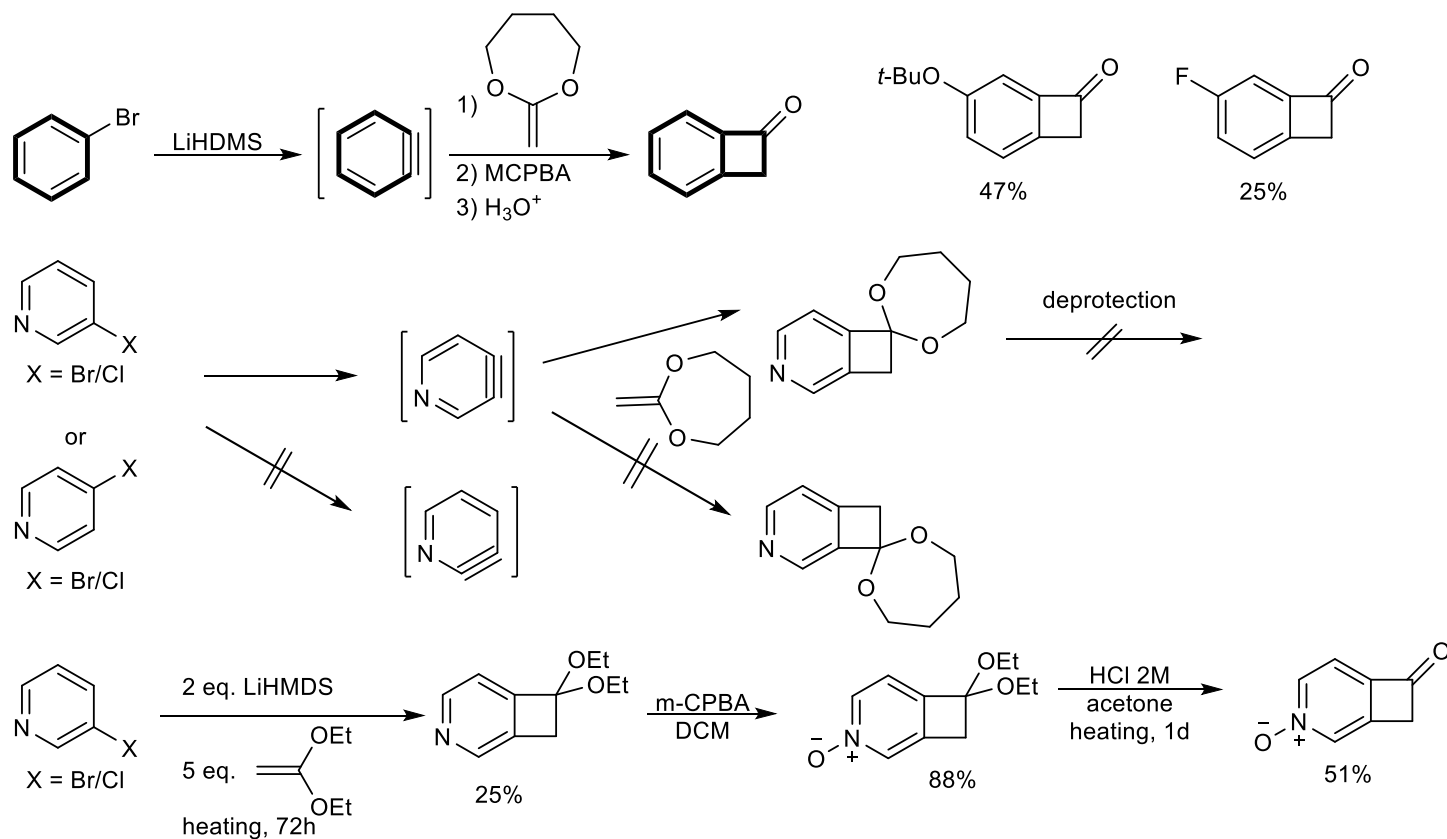
m: 76%



o: 73%
m: 69%

Cyclobutenone Synthesis

[2 + 2] Cycloaddition by ketene and benzyne



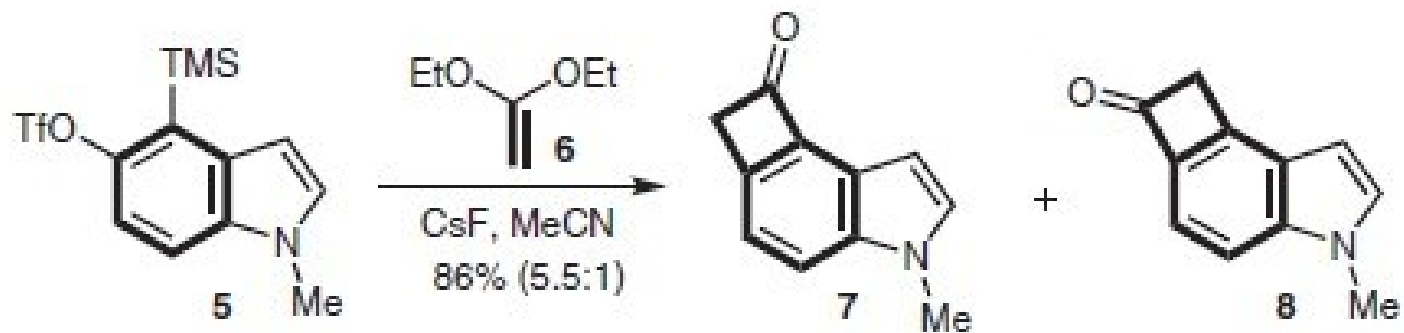
Maurin, P.; Ibrahim-Ouali, M.; Santelli, M. *Eur. J. Org. Chem.* **2002**, 151.

Maurin, P.; Ibrahim-Ouali, M.; Santelli, M. *Tetrahedron Lett.* **2001**, 42, 8147.

Mariet, N.; Ibrahim-Ouali, M.; Santelli, M. *Tetrahedron Lett.* **2002**, 43, 5789.

Cyclobutenone Synthesis

[2 + 2] Cycloaddition by ketene and benzyne

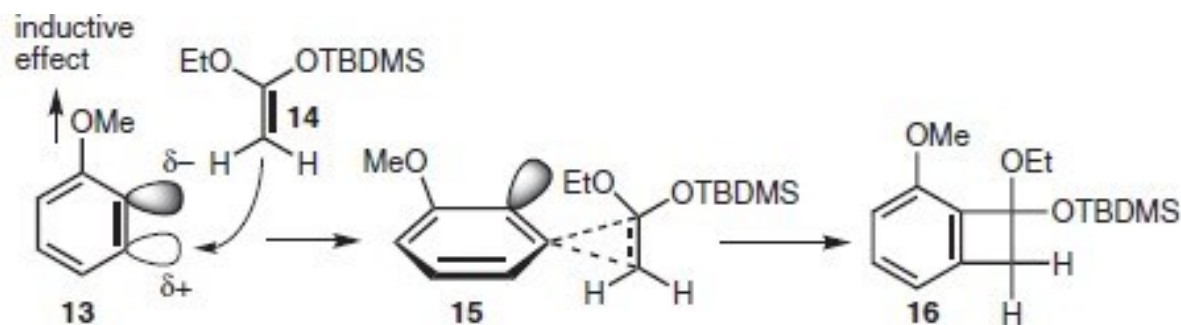
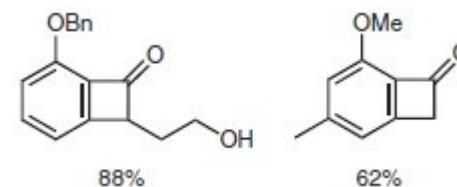
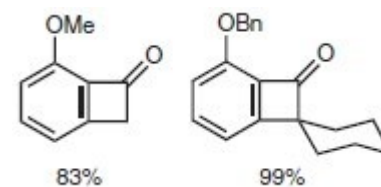
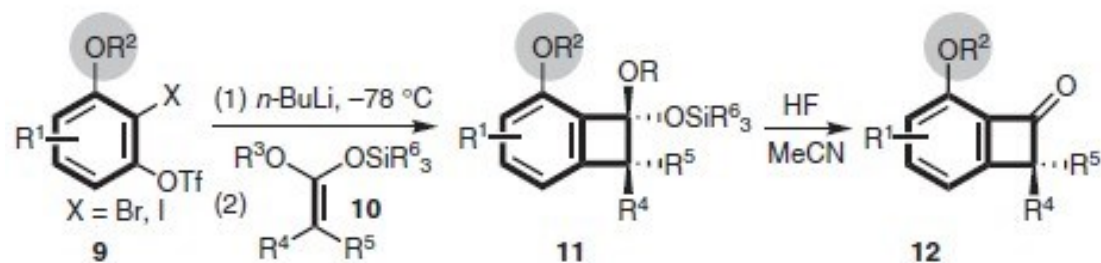


Im, G. Y. J.; Bronner, S. M. Paton, R. S.; Cheong, P. H. Y.; Houk, K. N.; Garg, N. K. *J. Am. Chem. Soc.* **2010**, *132*, 17933.

Bronner, S. M.; Bahnck, K. B.; Garg, N. K. *Org. Lett.* **2009**, *11*, 1007.

Cyclobutenone Synthesis

[2 + 2] Cycloaddition by ketene and benzyne

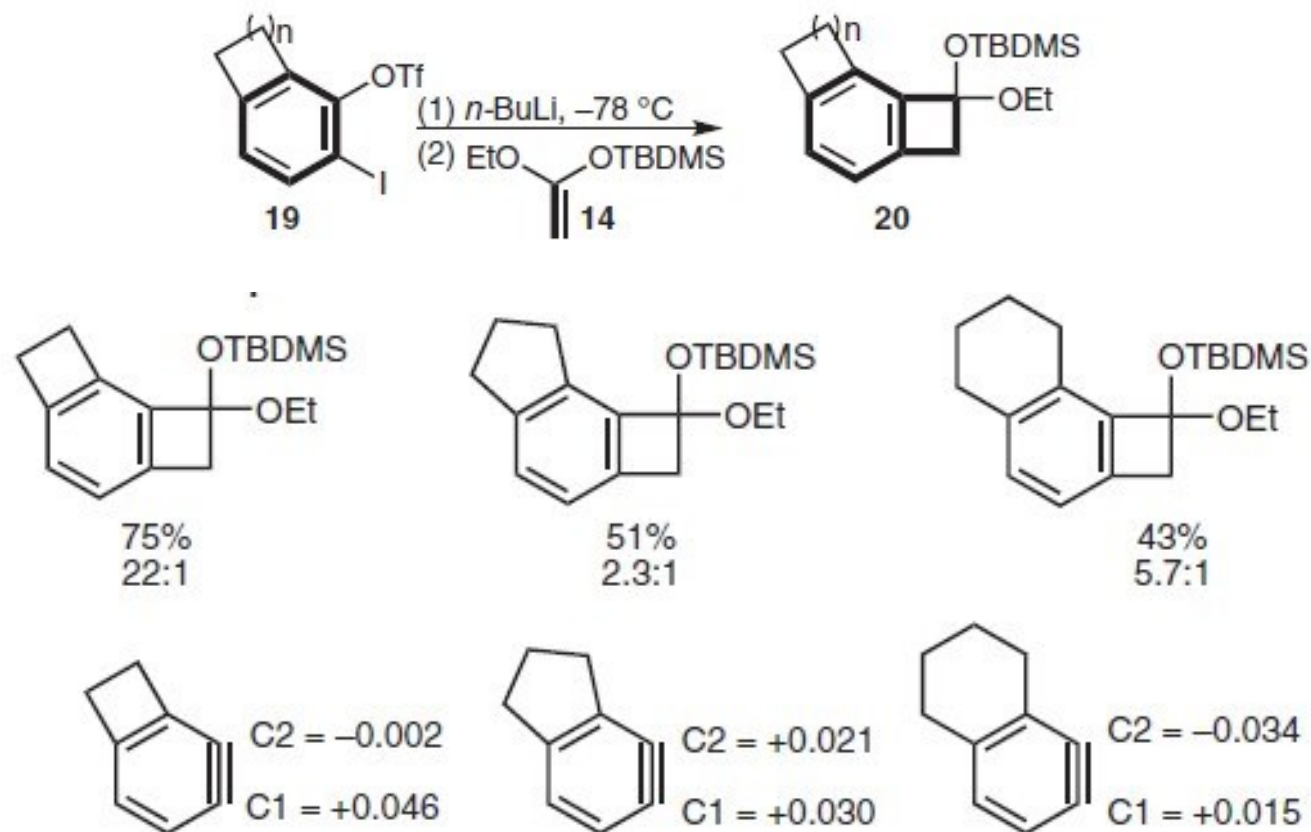


Hosoya, T.; Kuriyama, Y.; Suzuki, K. *Synlett*, **1995**, 177.

Hamura, T.; Hosoya, T.; Kuriyama, Y.; Miyamoto, M.; Yasui, Y.; Matsumoto, T.; Suzuki, K. *Helv. Chim. Acta* **2002**, *85*, 3589.

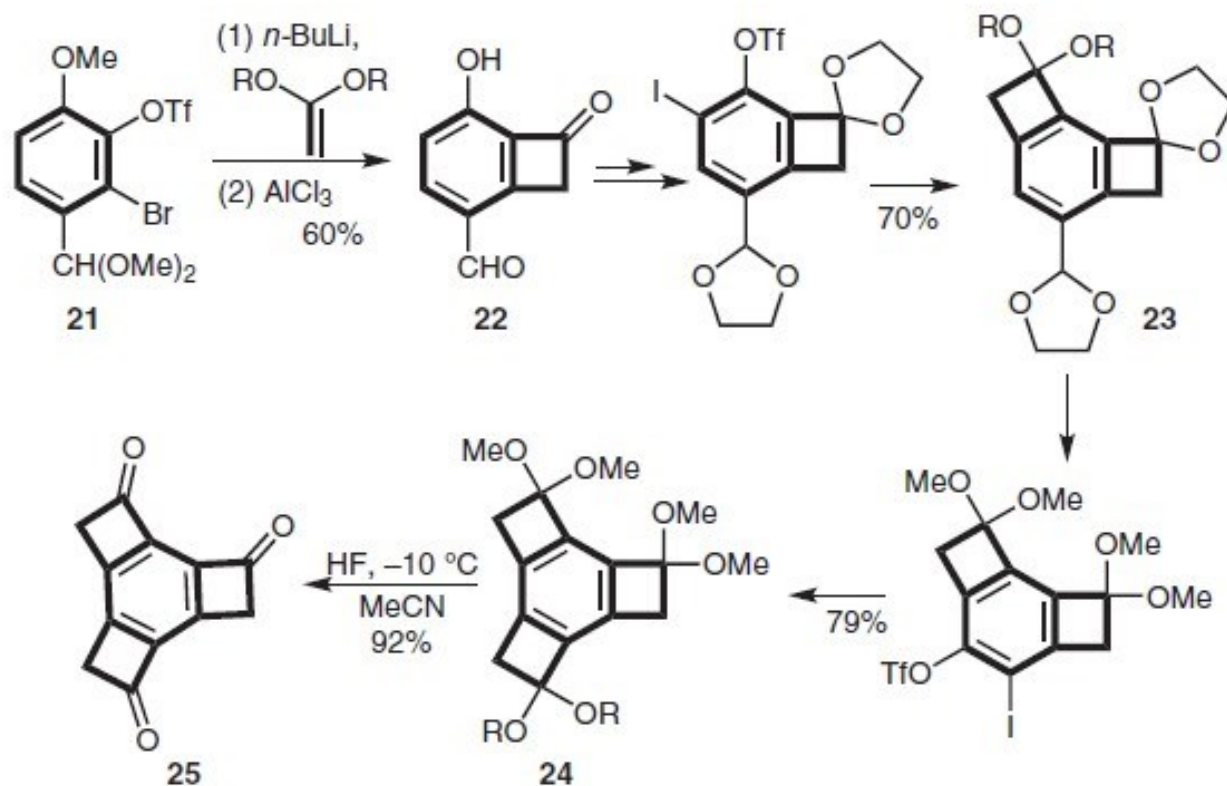
Cyclobutenone Synthesis

[2 + 2] Cycloaddition by ketene and benzyne



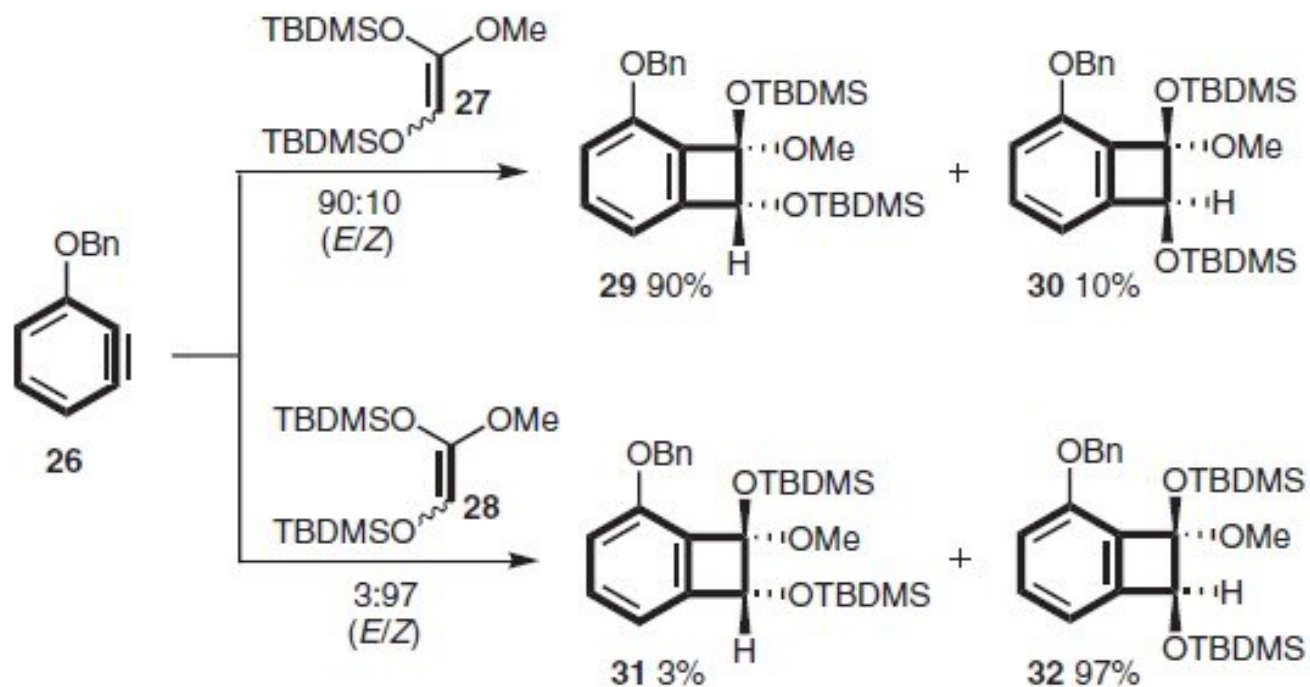
Cyclobutenone Synthesis

[2 + 2] Cycloaddition by ketene and benzyne



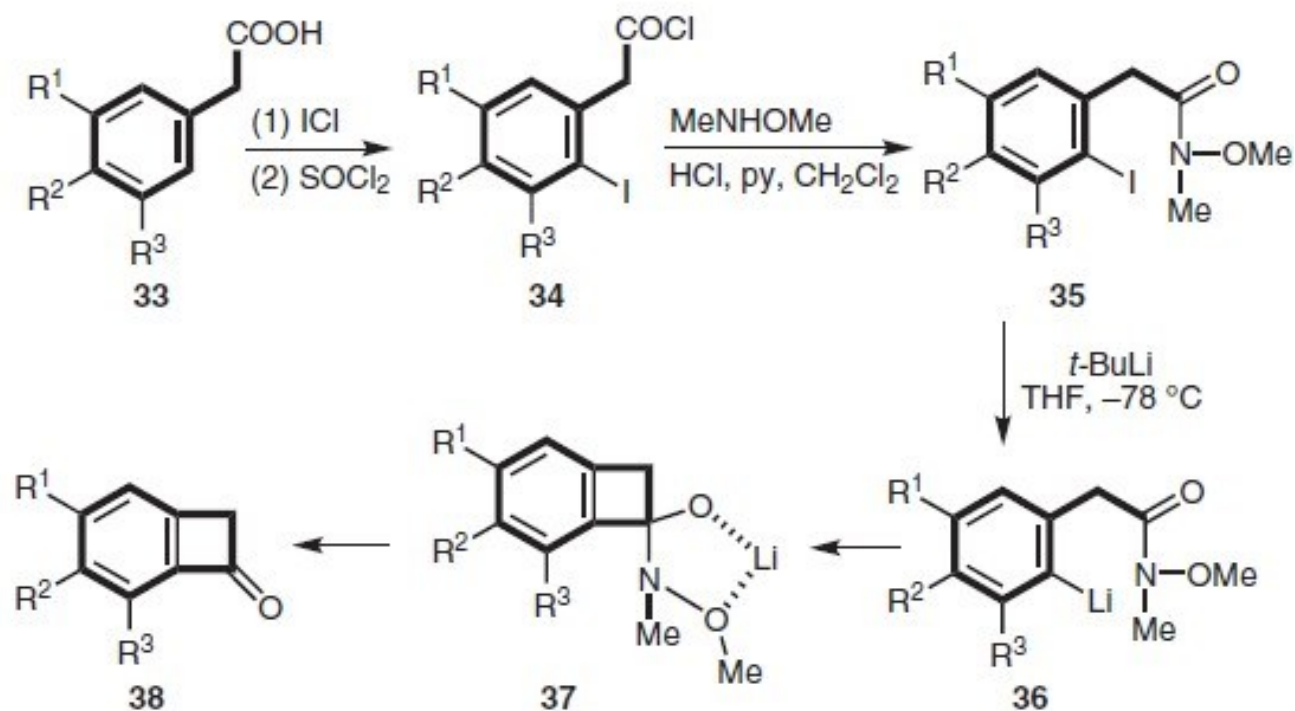
Cyclobutenone Synthesis

[2 + 2] Cycloaddition by ketene and benzyne



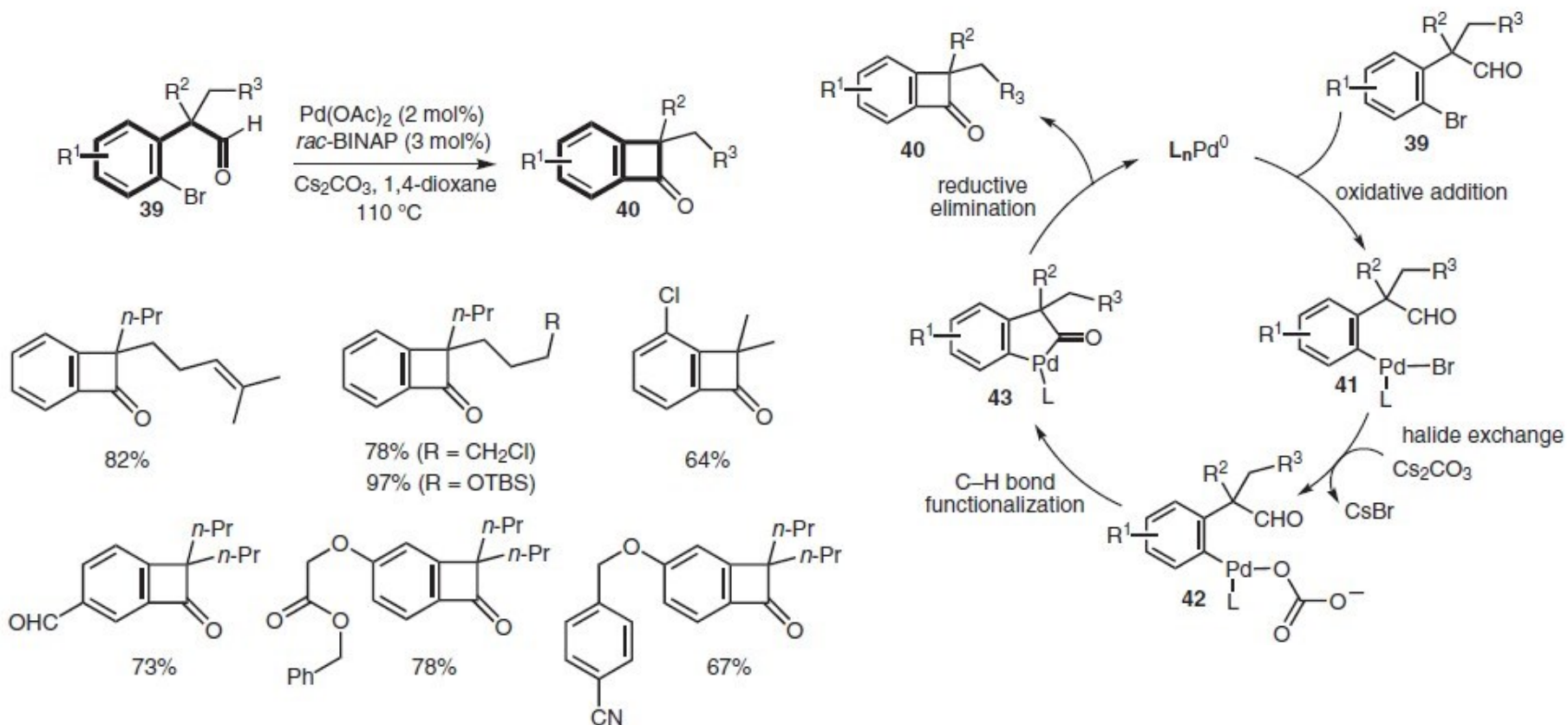
Cyclobutenone Synthesis

Metal-Mediated Intramolecular Reactions



Cyclobutenone Synthesis

Metal-Catalyzed Cross-Coupling Reactions



Martin, R.; Buchwald, S. L. *Org. Lett.* **2008**, *10*, 4561.

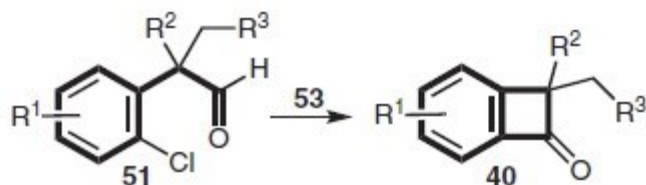
Vo, G. D.; Hartwig, J. F. *Angew. Chem. Int. Ed.* **2008**, *47*, 2127.

Martin, R.; Buchwald, S. L. *Angew. Chem. Int. Ed.* **2007**, *46*, 7236.

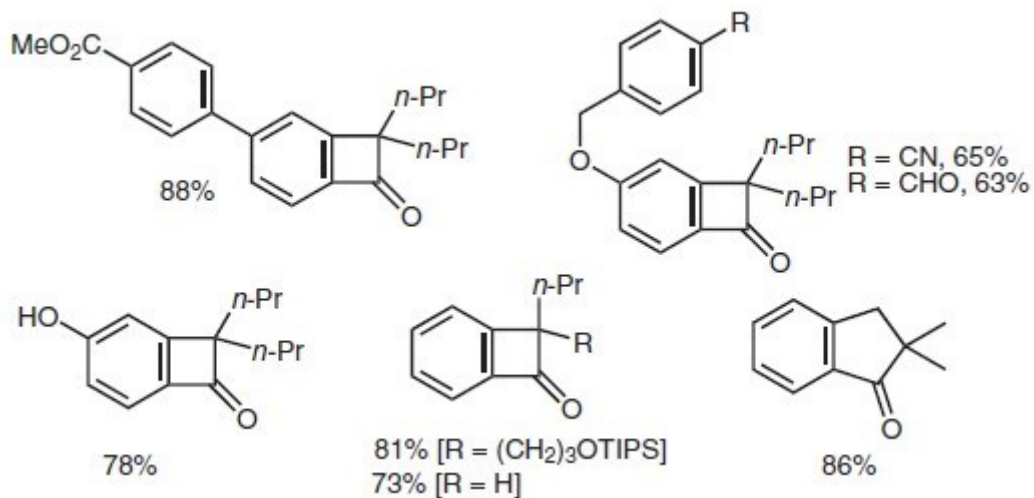
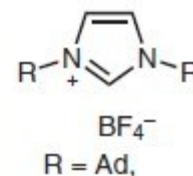
Álvarez-Bercedo, P.; Flores-Gaspar, A.; Correa, A.; Martin, R. *J. Am. Chem. Soc.* **2010**, *132*, 466.

Cyclobutenone Synthesis

Metal-Catalyzed Cross-Coupling Reactions

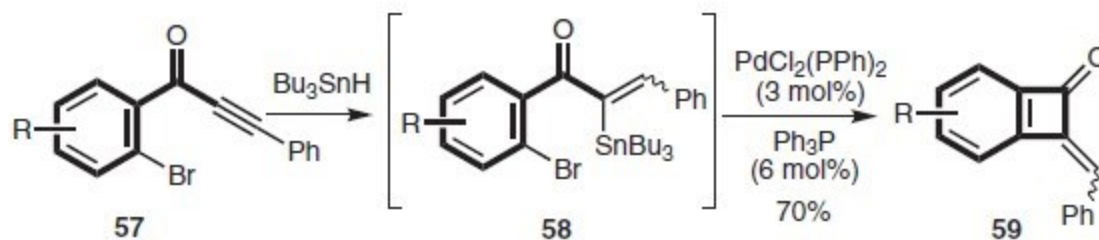
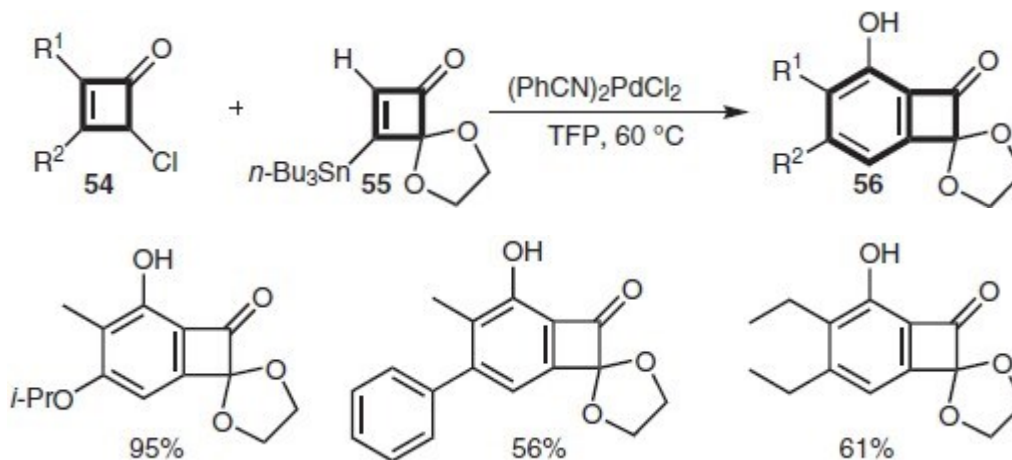


- high functional-group tolerance
- substitution patterns ($R^2 = H$)
- no decarbonylation
- site-selectivity



Cyclobutenone Synthesis

Stille Cross-Coupling Reactions

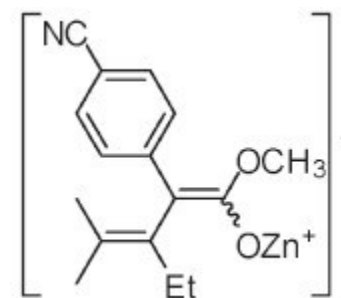
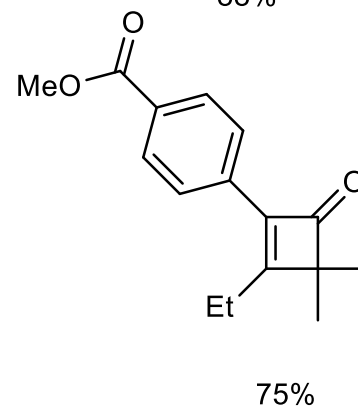
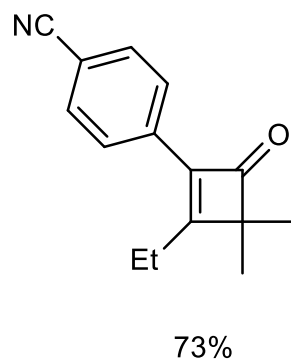
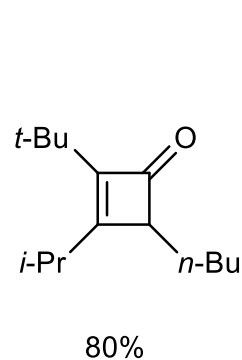
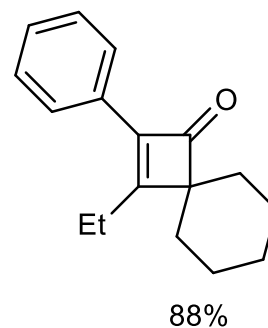
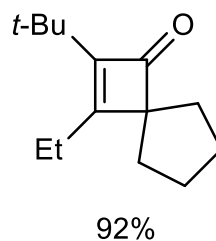
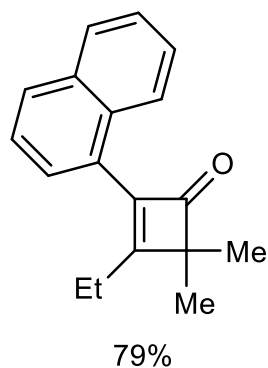
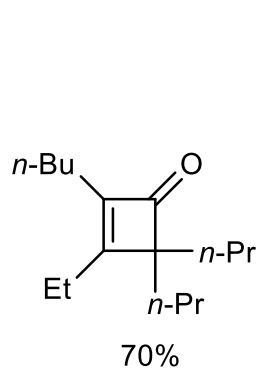
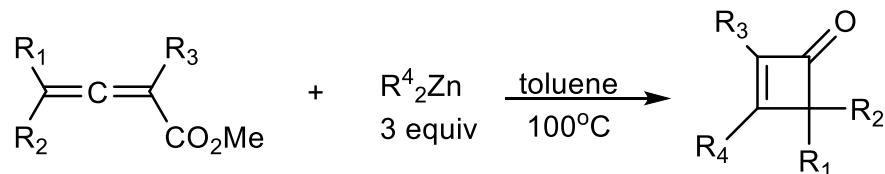


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Bradley, J. C.; Durst, T. *J. Org. Chem.* **1991**, *56*, 5459.

Cyclobutenone Synthesis

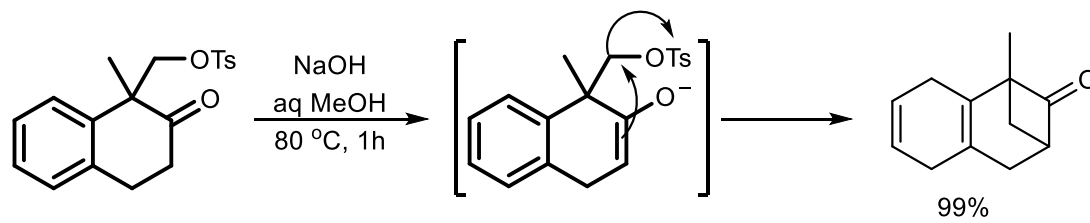
Tandem Michael Addition/Cyclization Reactions of 2,3-allenoate



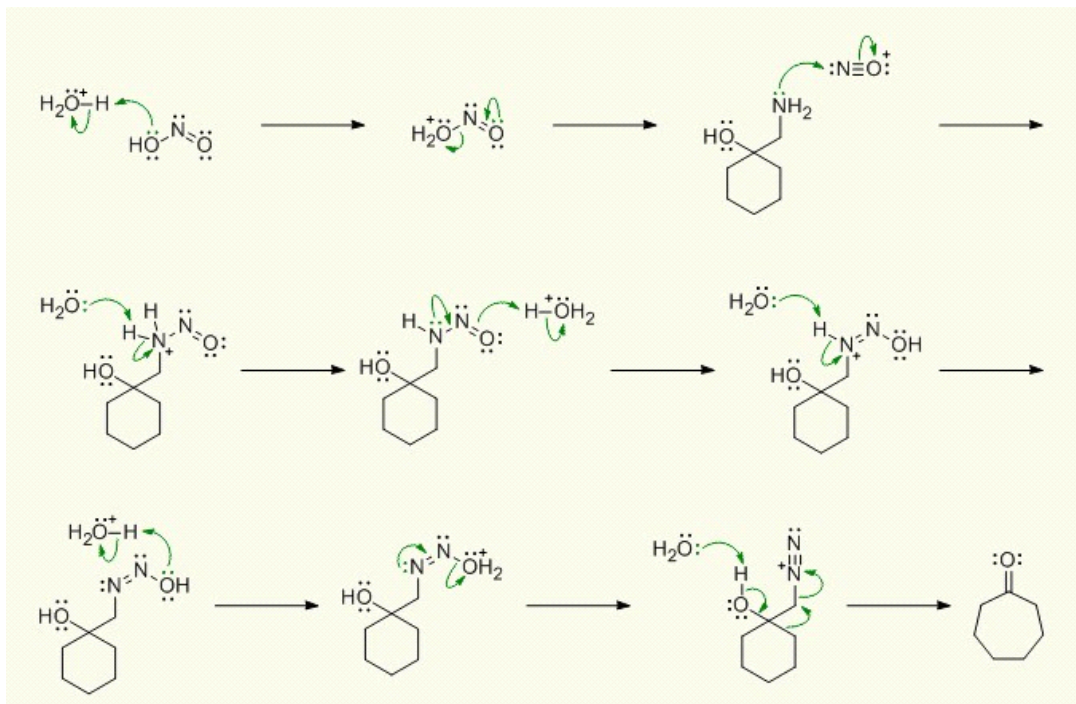
Thanks



Answers



Tiffeneau-Demjanov rearrangement



Answers

