Cascade Reactions in Organic Chemistry

Born: Eocene to Holocene era

Education: c.a. 40 MM years of evolution

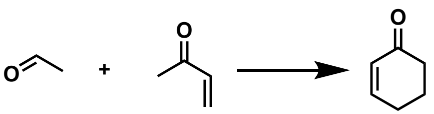
Positions: Diverse appointments held in CA, OR, and WA

Research interests: Extremely broad, including enzyme-mediated synthesis, reactivity of molten carbon, and CO_2 fixation.

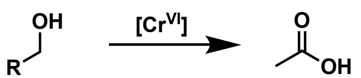
Cascade reaction: A rigorous definition

A cascade (also called tandem, also called domino) reaction must satisfy three criteria:

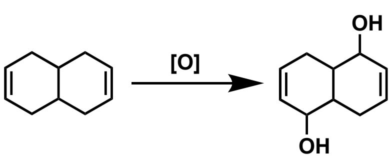
1. *Multiple transformations are acheived in a single pot*
2. *In this single pot, a single set of reaction conditions is maintained*
3. *Each transformation is dependent on the preceding transformation*



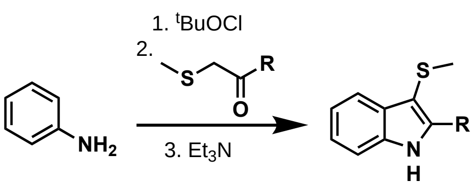
formally, a cascade



formally, a cascade



polyfunctionalizations are not cascades



One-pot telescoping is not a cascade

Take-home learnings from this group meeting

1. *The purported motivation of cascades is to increase synthetic efficiency, but rarely is this goal acheived.*

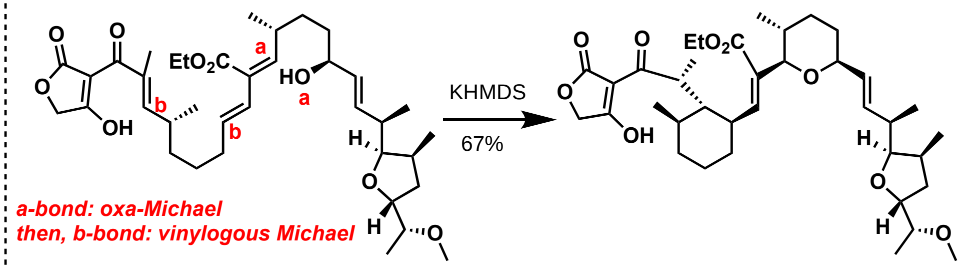
2. *Cascade reactions are generally extremely substrate-dependent, and rarely lead to the discovery of novel broad-scope reactivity.*

3. *The use of cascade reactions in industry (at bench- or process-scale) is minimal.*

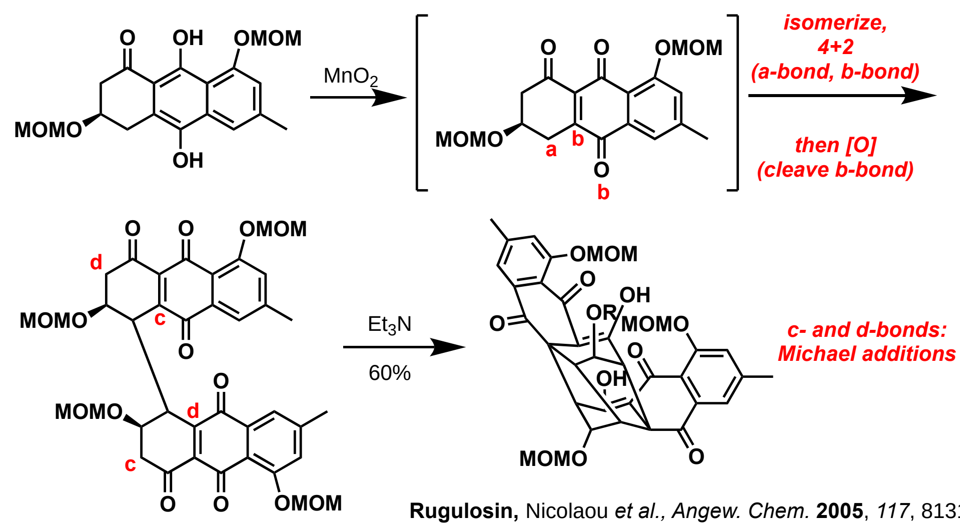
4. *Cascade reactions can be binned into a small number of reactivity paradigms, and quickly understood on that basis.*

Bin 1: Anionic cascades

Common theme: Michael / Oxa-Michael / Aldol reactivity



Tetronasin, Ley *et al.*, *J. Chem Soc., Perkin Trans.*, **1998**, *1*, 2259.

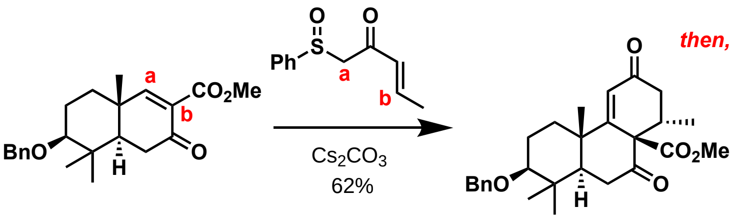


Rugulosin, Nicolaou *et al.*, *Angew. Chem.* **2005**, *117*, 8131.

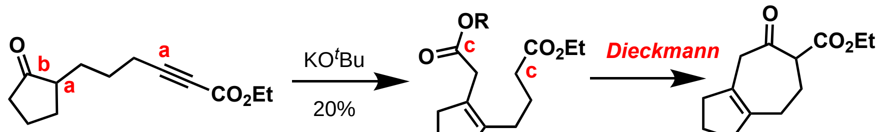
Bin 1: Anionic cascades (cont.)

Michael / Oxa-Michael / Aldol reactivity (cont.)

a-bond: Michael then, b-bond: Michael then, eliminate

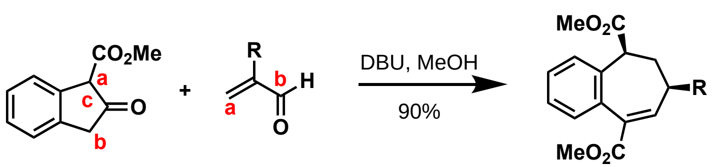


Cassaine, Deslongchamps and coworkers, *Org. Lett.* **2013,** 15, 6271.



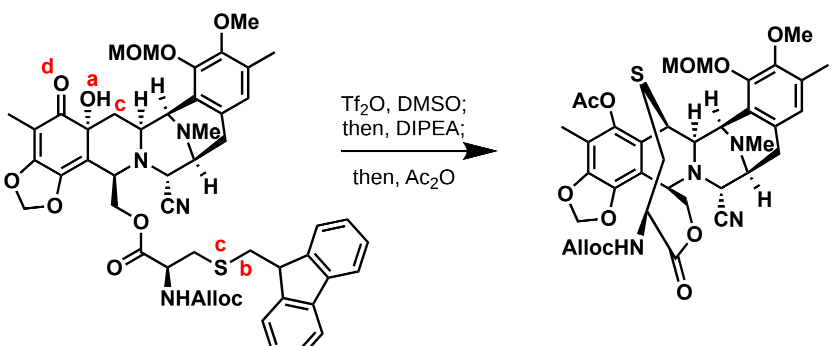
Michael (a-bond), then vinylogous retro-Dieckmann (cleave b-bond)

Miesch and coworkers, *Eur. J. Org. Chem.* **2010,** 6944.



Michael (a-bond), then aldol (b-bond), then retro-Dieckmann (cleave c-bond)

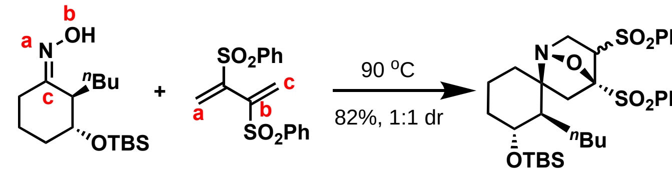
Rodriguez and coworkers, *J. Org. Chem.* **1997,** *62,* 3034.



Eliminate a, then eliminate b, then aromative Michael (c-bond), then acetylate d

Ecteinascidin 743, Corey *et al., J. Am. Chem. Soc.,* **1996,** *118,* 9202.

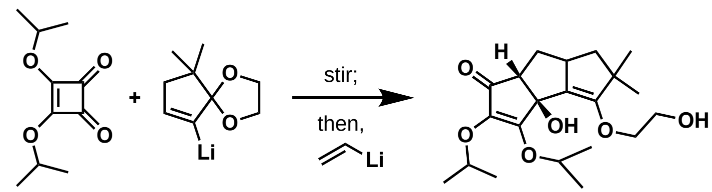
Michael / Oxa-Michael / Aldol reactivity (cont.)



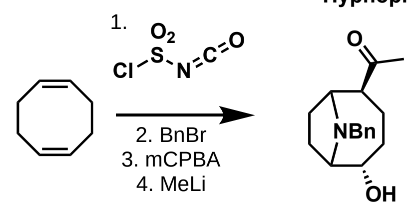
a-bond: Michael addition then, nitrone 3+2 (b-, c-bonds)

Perhydrohistrionicotoxin, Padwa and coworkers, *J. Org. Chem.,* **2008,** *73,* 9601.

Anionic cascades initiated by carbonyl additions

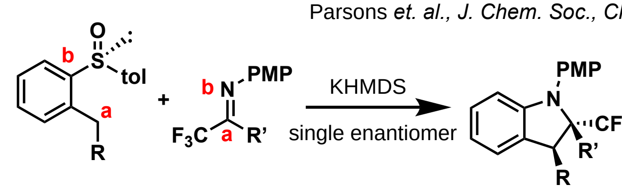


Hypnophilin, Paquette and coworkers, *Org. Lett.,* **2002**, *4*, 71.



1. beta-lactam formation
2. amide benzylation
3. epoxidation
4. lactam ring-opening, epoxide opening cascade

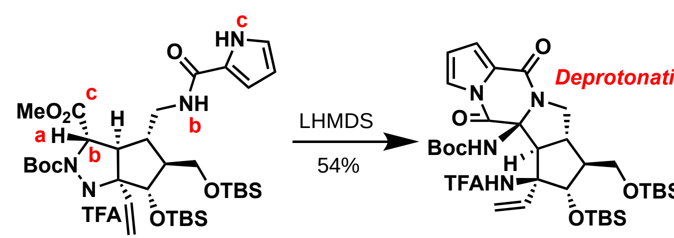
Parsons *et. al., J. Chem. Soc., Chem. Commun.,* **1995,** 1461.



a-bond: Benzylic anion addition; b-bond: SNAr

Fustero and coworkers, *ACIE,* **2008,** *47,* 7941.

Nitrogen anion cascades

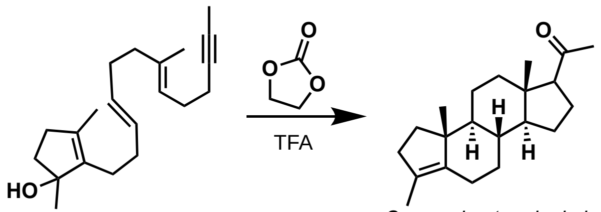


Deprotonation (a) / hydrazine opening aminal formation (b-bond) lactam formation (c-bond)

Palau'amine, Namba *et al., Nature Comm.,* **2015,** *6,* 8731.

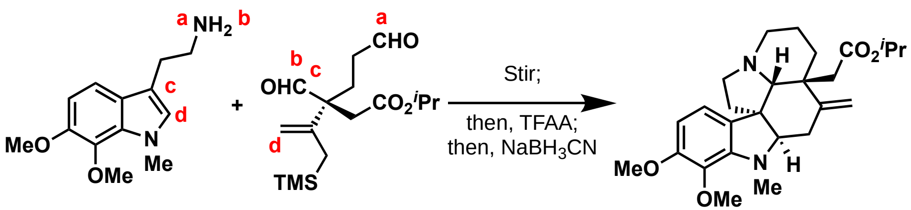
Bin 2: Cationic cascades

Polyene / olefin-cation-pi cascades



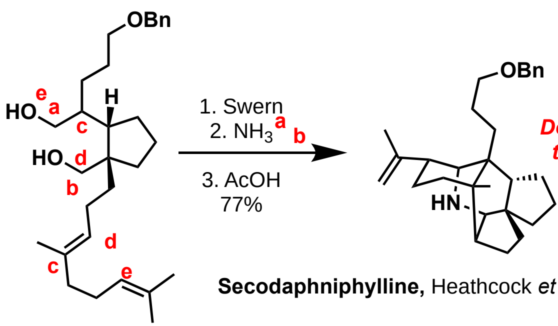
Covered extensively in other Baran group meetings; See Polyene Cyclizations (Harwood, 2018)

Cationic cascades driven by reactive nitrogen electrophiles



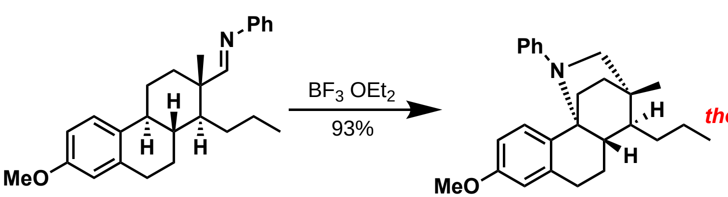
Double condensation (a-, b-bonds), then aza-Mannich (c-bond), then aza-Sakurai (d-bond), then imine reduction

Aspidophytine, Corey and coworkers, *J. Am. Chem. Soc.*, **1999**, *121,* 6771.



Double condensation (a-, b-bonds), then aza-Diels-Alder (c-, d-bonds), then aza-Prins (e-bond)

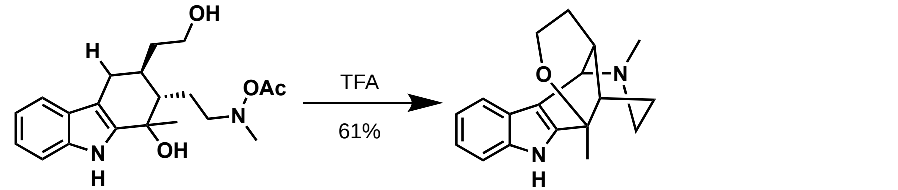
Secodaphniphylline, Heathcock *et al., J. Org. Chem.*, **1992**, *57,* 2566.



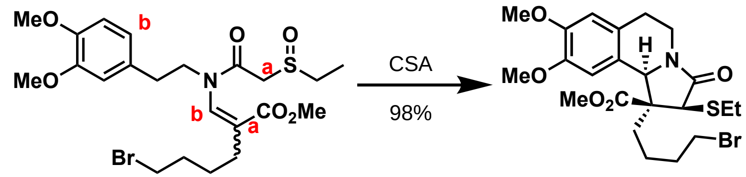
1,5-hydride shift, then, amine capture

Tietze and coworkers, *Angew. Chem. Int. Ed.*, **1999**, *38,* 200.

Cationic cascades driven by reactive nitrogen electrophiles (cont.)



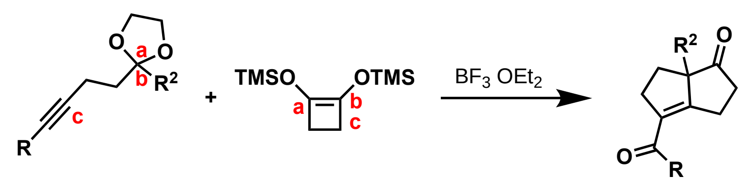
Gilbertine, Blechert and coworkers, *J. Am. Chem. Soc.*, **2004**, *126,* 3534.



a-bond: enamine-Pummerer, then, b-bond: Pictet-Spengler

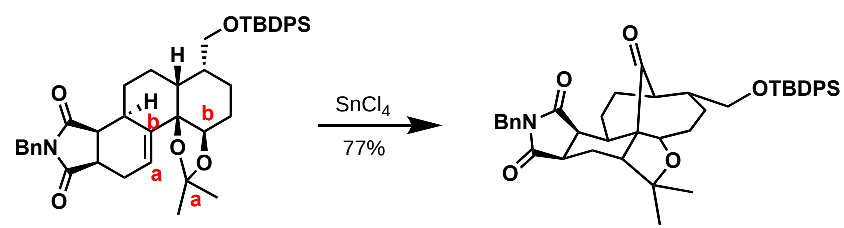
Jamtine, Padwa *et. al., Org. Lett.*, **2002**, *4,* 715.

Pinacol-type cascades



Aldol (a-bond), then pinacol rearrangement (b-bond), then 5-exo-dig (c bond), then trapping by water

Curran and coworkers, *J. Org. Chem.*, **1995**, *60,* 337.

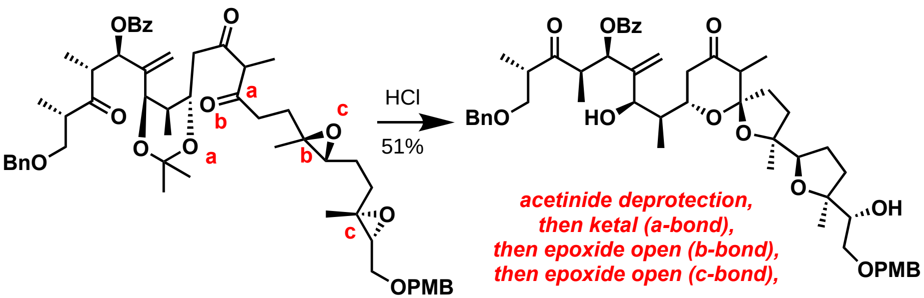


Prins (a-bond), then, pinacol rearrangement (b-bond)

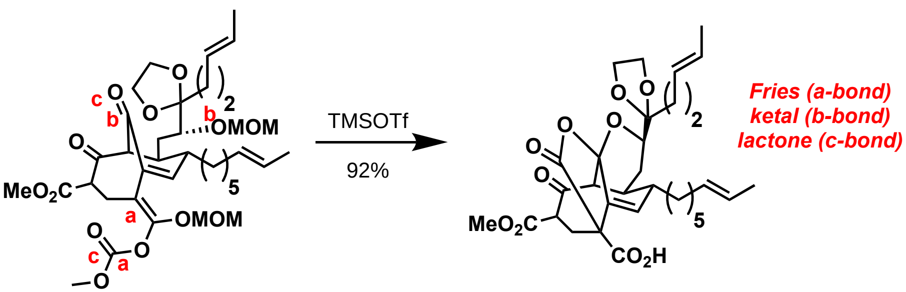
Barriault and coworkers., *Org. Lett*, **2005**, *7,* 5921.

Bin 2: Cationic cascades (cont.)

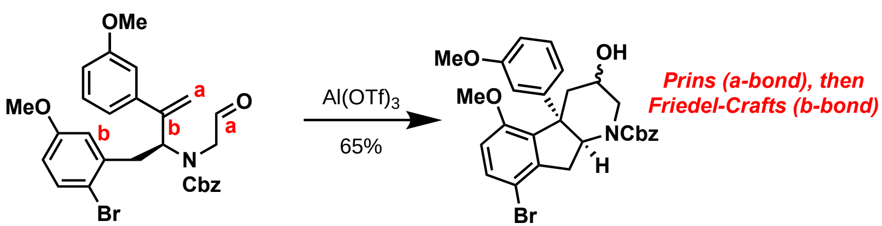
Cationic cascades driven by protonated oxygen electrophiles



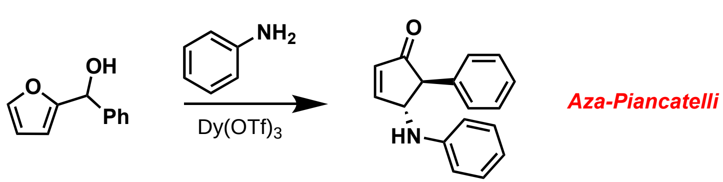
Etheromycin, Paterson *et al., Tetrahedron Lett.*, **1993,** *34*, 7137.



CP molecules, Shair and coworkers, *J. Am. Chem. Soc.*, **2000,** *122,* 7424.



Haouamine A, Aubé and coworkers, *Org. Lett.*, **2011**, *13,* 2614.

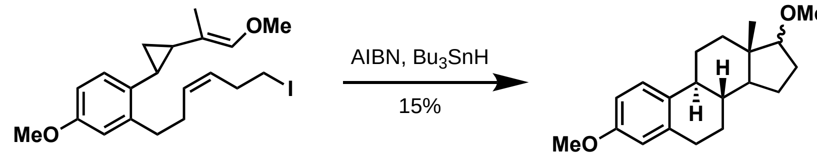


Read de Alaniz and coworkers, *Angew. Chem. Int. Ed.*, **2010,** *49,* 9484.

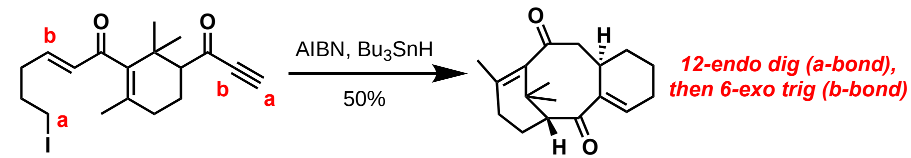
Bin 3: Radical cascades

Radical chains (AIBN / R_3SnH or equivalent)

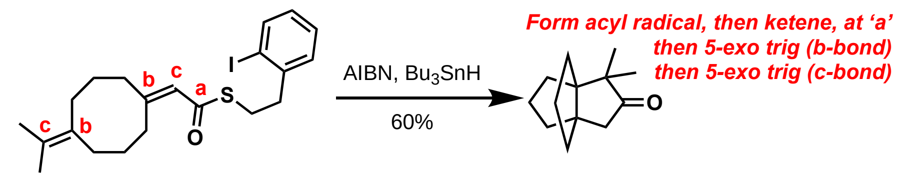
For a classic, see **Hirsutene**, Curran and coworkers, *J. Am. Chem. Soc.* **1985,** *107,* 1448.



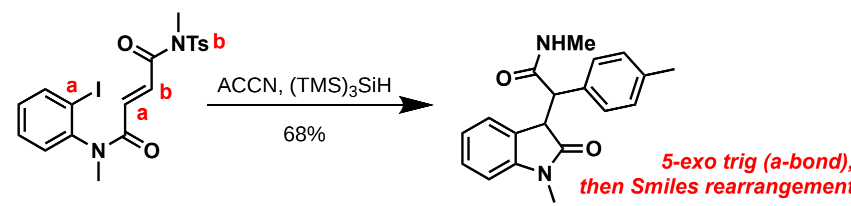
Oestrone, Pattenden *et al., Tetrahedron Lett.*, **2004,** *45,* 4027.



Towards Taxanes, Pattenden and coworkers, *J. Chem. Soc., Perkin. Trans. 1,* **1998,** 3181.

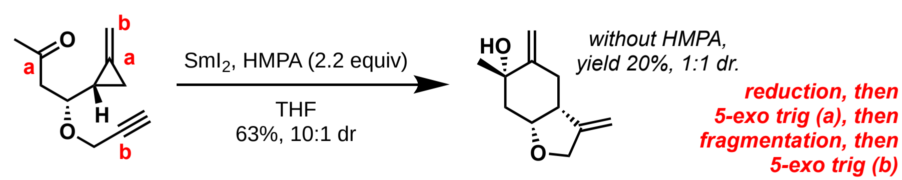


Pattenden and coworkers, *Org. Biomol. Chem.*, **2005,** *3,* 340.



Sapi and coworkers, *Chem. Commun.* **2012,** *48,* 2442.

Radical cascades driven by reductions

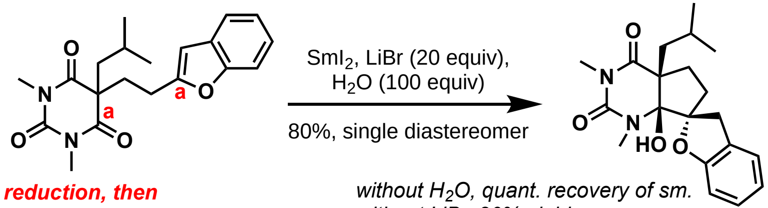


Killburn and coworkers, *Chem. Commun.*, **1998**, 1875.

For more coverage of Sm-mediated cascades, see Baran group meeting, "Samarium (II) Iodide" (Lewis, 2010)

Bin 3: Radical cascades (cont.)

Radical cascades driven by reductions (cont.)



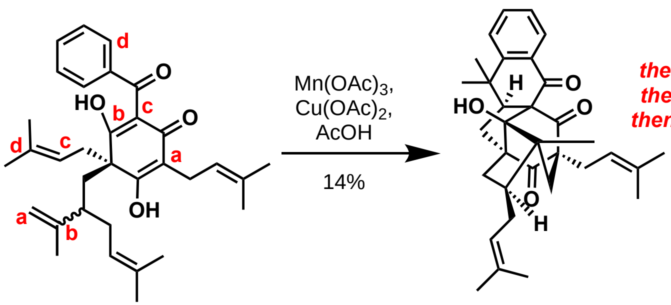
reduction, then 5-exo trig (a-bond)

without H_2O, quant. recovery of sm.
without LiBr, 20% yield.

Procter and coworkers, *J. Am. Chem. Soc.*, **2017**, *139*, 1661.

Ti(III) also common initiating reductant. See Baran group meeting "Organotitanium Chemistry" (Merchant, 2017)

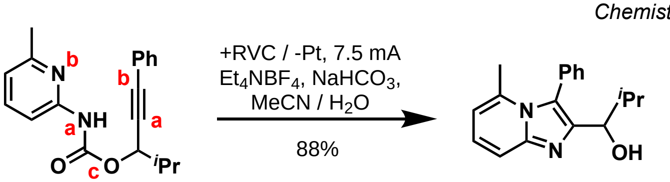
Radical cascades driven by oxidations



oxidation at a, then 7-endo trig (a-bond), then 5-exo trig (b-bond), then 5-exo trig (c-bond), then 6-endo trig (d-bond)

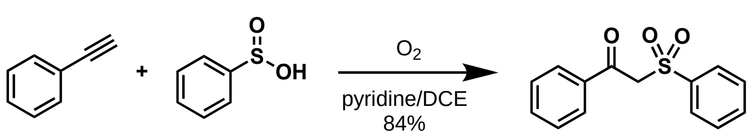
Garcibracteatone, George and coworkers, *Org. Lett.*, **2012**, *14*, 5162.

Extensive coverage of this pathway in Baran group meeting "Manganese (III) in Organic Chemistry" (Voica, 2010)



5-exo dig (a-bond), then 5-endo trig (b-bond), then radical cleavage of c-bond

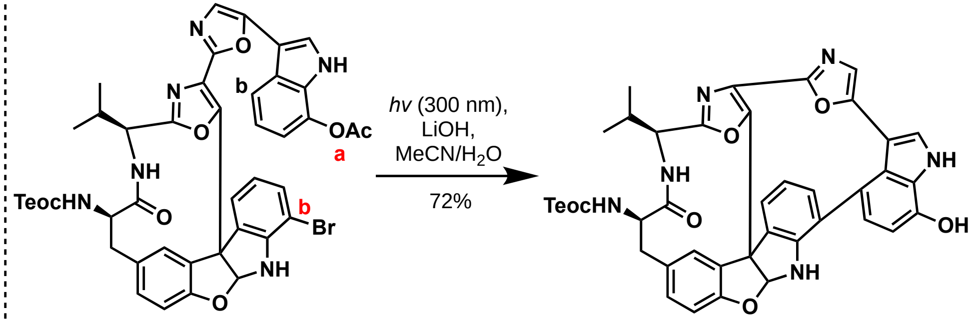
Xu and coworkers, *Angew. Chem.*, **2018**, *130*, 1652.



oxidation of sulfinate, then addition into alkyne, then trapping with dioxygen, then reduction of peroxide with sulfinate

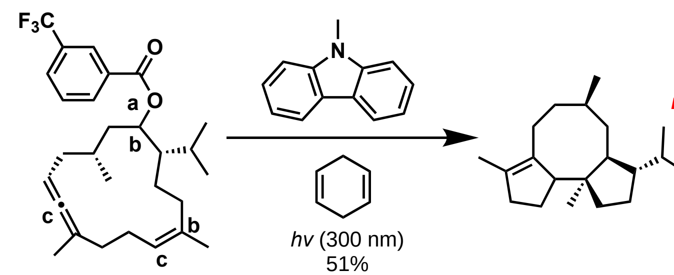
Lei and coworkers, *J. Am. Chem. Soc.* **2013**, *135*, 11481.

Radical cascades driven by photoexcitation



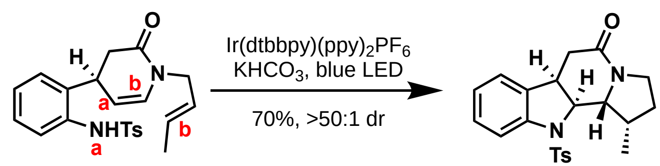
hydrolysis of phenol (a), then biradical formation, then combination (b-bond), then elimination of bromide

Diazonamide A, Harran and coworkers, *Angew. Chem.*, **2003**, *115*, 5111.



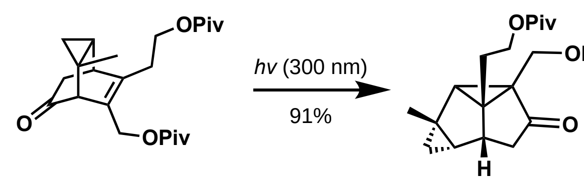
radical fragmentation at 'a', then 5-exo trig (b-bond), then 5-exo trig (c-bond)

Myers and coworkers, *J. Am. Chem. Soc.*, **1993**, *115*, 7926.



5-exo trig (a-bond), then 5-exo trig (b-bond)

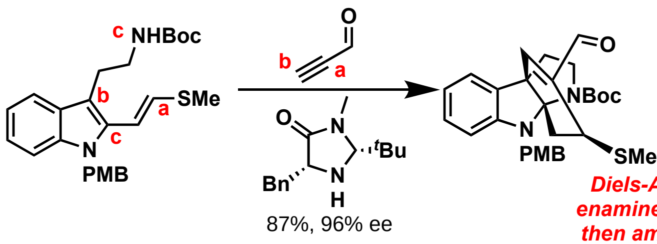
Qin and coworkers, *Chem.*, **2017**, *2*, 803.



Paquette and coworkers, *J. Am. Chem. Soc.*, **1991**, *113*, 9384.

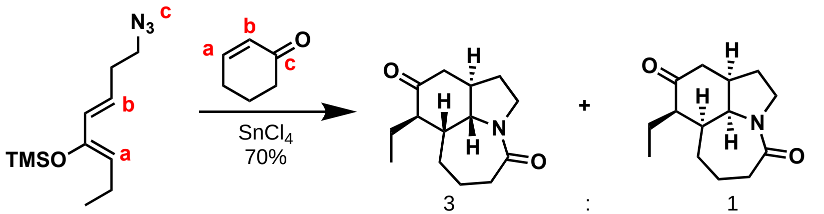
Bin 4: Pericyclic cascades

Pericyclic cascades driven by exergonic cycloadditions



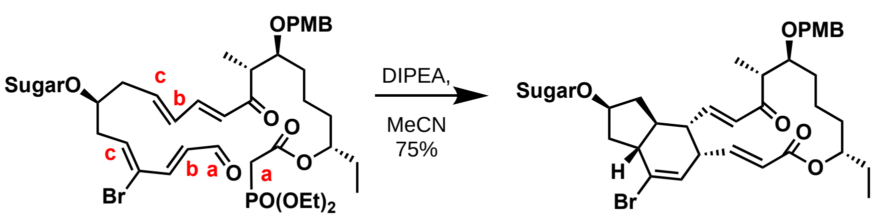
Diels-Alder (a-, b-bonds), then enamine/imine tautomerization, then aminal formation (c-bond)

Minfiensine, MacMillan and coworkers, *J. Am. Chem. Soc.*, **2009,** *131,* 13606.



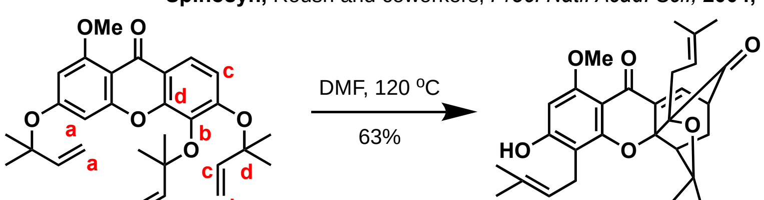
Diels-Alder (a-, b-bonds), then Schmidt (c-bond)

Stenine, Aubé and coworkers, *J. Am. Chem. Soc.*, **2005,** *127,* 15712.



HWE (a-bond), then Diels-Alder (b-, c-bonds)

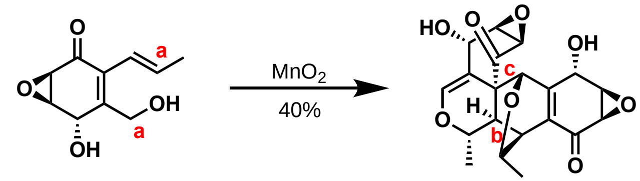
Spinosyn, Roush and coworkers, *Proc. Natl. Acad. Sci.*, **2004,** *101,* 11955.



Double Claisen rearrangement (a-, b- bonds), then Diels-Alder (c-, d-bonds)

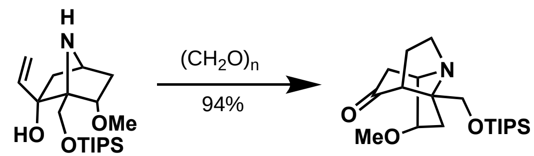
1-O-methylforbesione, Nicolaou *et al.*, *Angew. Chem. Int. Ed.*, **2001,** *40,* 4264.

Pericyclic rearrangement cascades driven by net bond formation



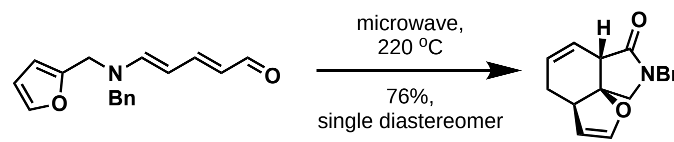
Oxidation, then 6-pi electrocyclization (a-bond), then Diels-Alder dimerization (b-, c-bonds)

Epoxyquinol A, Hayashi and coworkers, *Angew. Chem. Int. Ed.* **2002,** *41,* 3192.



Imine formation, then aza-Cope, then Mannich

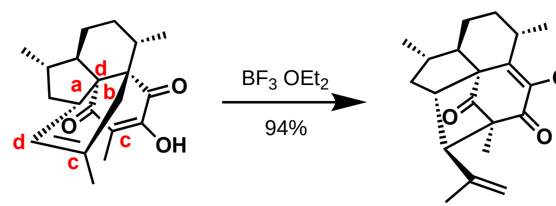
Asparagamine A, Overman and coworkers, *J. Am. Chem. Soc.*, **2003,** *125,* 15284.



Olefin isomerization, then six-pi, then [1,5] H-shift, then retro-six-pi, then Diels Alder

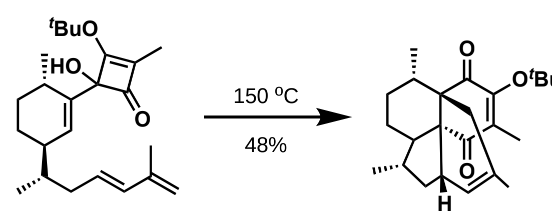
Vanderwal and coworkers, *J. Am. Chem. Soc.*, **2009,** *131,* 7546.

Pericyclic cascades driven by strain release



Retro-Diels-Alder (cleave a-, b-bonds), then 5+2 (form c- d-bonds)

Elisapterosin B, Jacobsen and coworkers, *Angew. Chem. Int. Ed.*, **2005,** *44,* 6046.

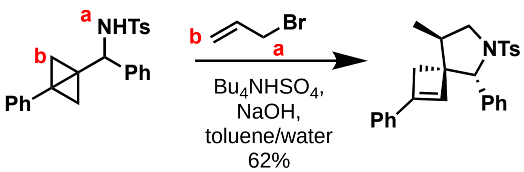


Retro-four-pi, then six-pi, then air oxidation to quinone, then Diels-Alder

Elisapterosin B, Harrowven *et al.*, *Angew. Chem. Int. Ed.* **2005,** *44,* 1221.

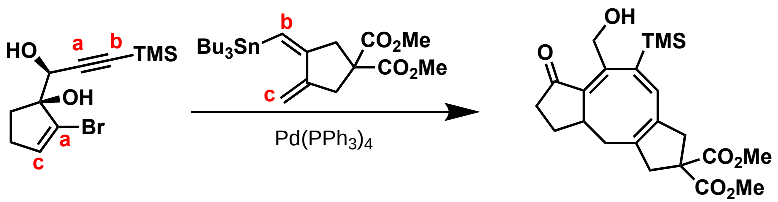
Bin 4: Pericyclic cascades (cont.)

Pericyclic cascades driven by strain release (cont.)



Allylation (a-bond), then formal Ene reaction (b-bond) (likely radical)

Wipf *et al.*, *Angew. Chem. Int. Ed.*, **2006,** *45,* 4172.

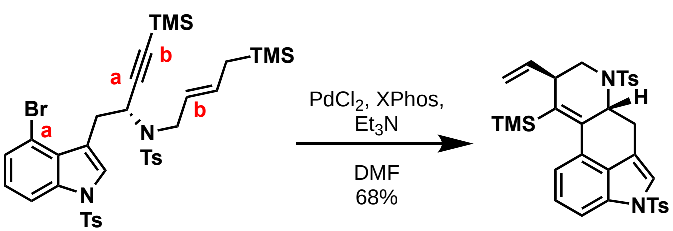


Carbopalladation (a-bond), then Stille (b-bond), then 10-pi (c-bond)

Towards Ophiobolin A, Suffert and coworkers, *Angew. Chem. Int. Ed.* **2004,** *43,* 2826.

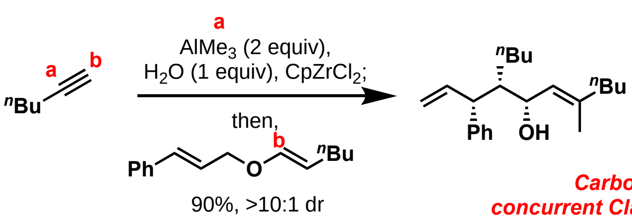
Bin 5: Transition metal-catalyzed cascades

Carbometallation cascades



Carbopalladation (a-bond), then Heck (b-bond)

Lysergol, Werz and coworkers, *Org. Lett.*, **2017,** *19,* 1914.

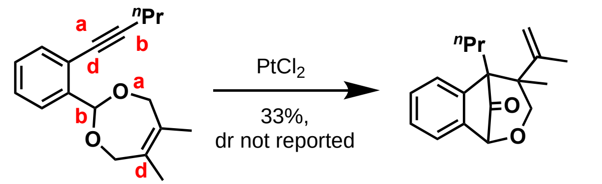


Carbometallation (a-bond), concurrent Claisen rearrangement, then, vinyl anion addition (b-bond)

Wipf *et al.*, *J. Org. Chem*, **2005,** *70,* 8096.

Bin 5: Transition metal-catalyzed cascades (cont.)

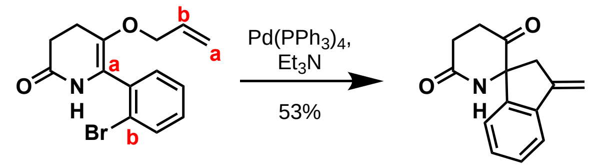
Nucleometallation cascades



Oxymetallation (a-bond), nucleophilic attack (b-bond), diatropic rearrangement, indene Claisen (d-bond)

Yamamoto and coworkers, *Chem. Lett.* **2005,** *34,* 174.

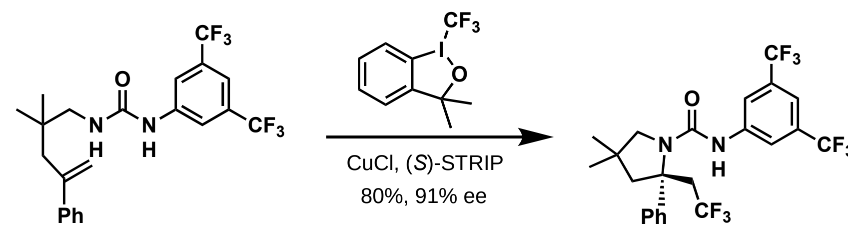
Isomerization cascades



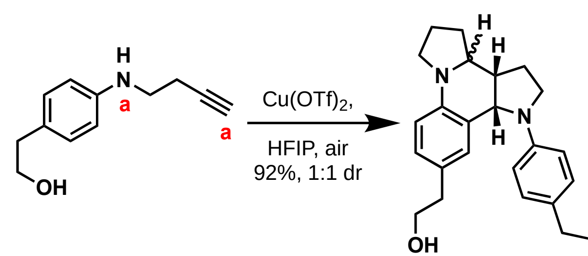
Claisen (a-bond), then Heck (b-bond)

Watson *et al.*, *Tetrahedron Lett.*, **1994,** *35,* 9763.

Metal-catalyzed radical/SET cascades



Liu and coworkers, *J. Am. Chem. Soc.*, **2016,** *138,* 9357.



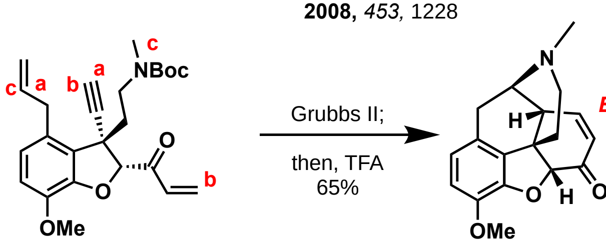
Oxidative 5-endo dig (a-bond), imine/enamine isomerization aza-Diels-Alder dimerization

Li and coworkers, *Eur. J. Org. Chem.*, **2016,** 3684.

Bin 5: Transition metal-catalyzed cascades (cont.)

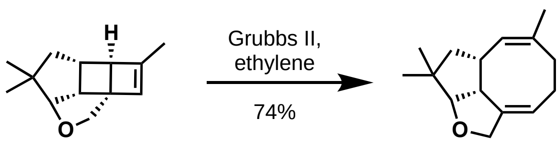
Metathesis cascades

For a classic example, see Cyanthiwigin F synthesis; Stoltz and coworkers, *Nature,* **2008,** *453,* 1228



Enyne metathesis (a-bond), then metathesis (b-bond), then 1,6-addition (c-bond)

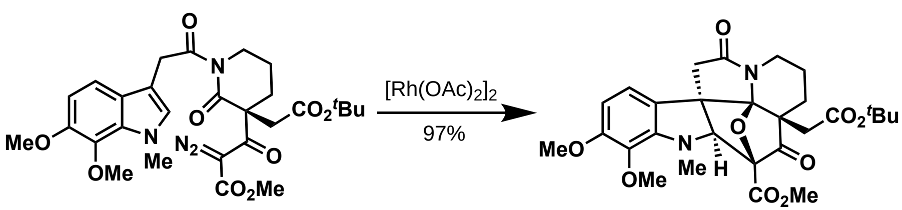
Morphine, Smith and coworkers, *Angew. Chem. Int. Ed.,* **2016**, *55,* 14306.



Ethylene metathesis, then Cope

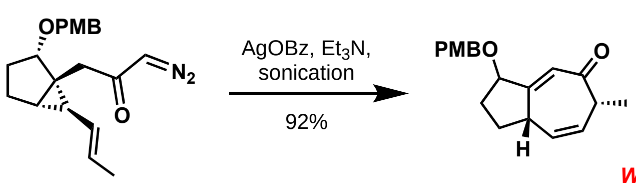
Asteriscanolide, Snapper and coworkers, *J. Am. Chem. Soc.*, **2000**, *122,* 8071.

Carbenoid cascades



Carbonyl ylide formation, then 3+2

Aspidophytine, Padwa and coworkers, *Org. Lett.*, **2006,** *8,* 3275.



Wolff, then ketene-Cope

Stoltz and coworkers, *J. Am. Chem. Soc.*, **2003,** *125,* 13624.

Cascade reaction utility: A cheminformatics approach**

Cascade efficiency as measured by yields

Average yield of a Michael reaction (random selection, n = 250): **84%**

Average yield of a Michael-Michael cascade (n = 26): **56%**

(75% "per step")

Cascade efficiency as measured by usage in process chemistry

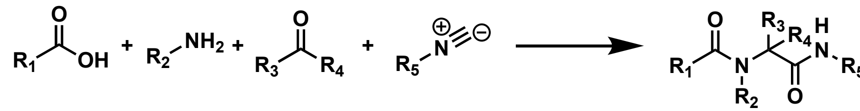
Percentage of 2017 *OPRD* syntheses that use cascade reactions: **7%**

Compare to Pd-catalyzed cross couplings: **81%**

Compare to amine acylations: **89%**

What were the cascades that *were* used in industry?

Almost exclusively Ugi reactions!



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****The following statistics were obtained using alpha-version cheminformatics data-mining software. Results are unvalidated and may be highly inaccurate.**