Recent Developments in Enantioselective Radical Reactions Employing SOMO-catalysis

Literature presentation
31.01.12

Jacqueline Habegger

Organo-SOMO catalysis

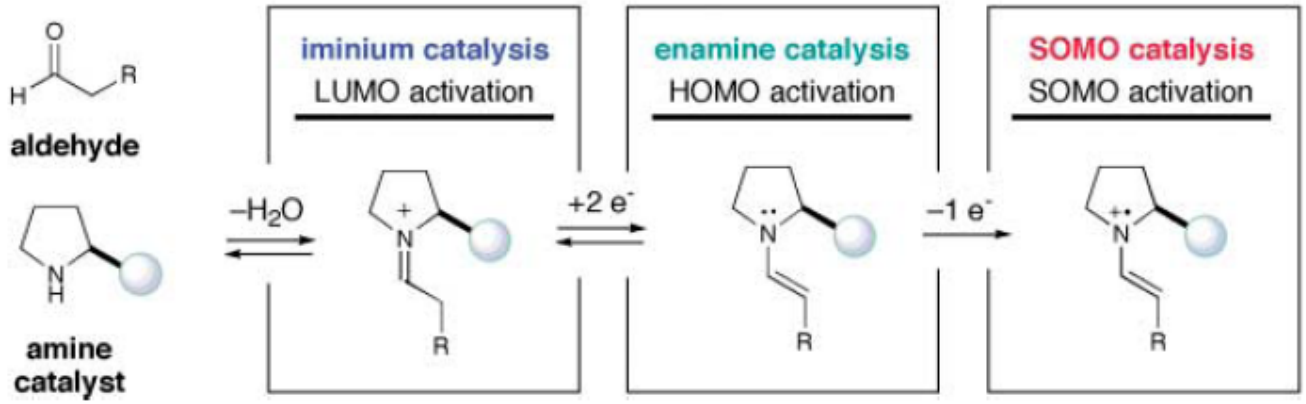


Fig. 1. SOMO catalysis via single-electron oxidation of a transiently formed enamine. LUMO, lowest unoccupied molecular orbital; R, an arbitrary organic substituent.

MacMillan, *Science* **2007**, 316, p. 582-585

Iminium catalysis: Lowers energy of enone/enal substrate LUMO; activation towards conjugate additions , Friedel-Crafts alkylation, etc.

Enamine catalysis: Raises energy of substrate HOMO; activation towards attack by electrophiles

SOMO catalysis: A radical cation with an activated singly occupied molecular orbital

→ α-functionalisation of aldehydes with weak nucleophiles via radical trapping

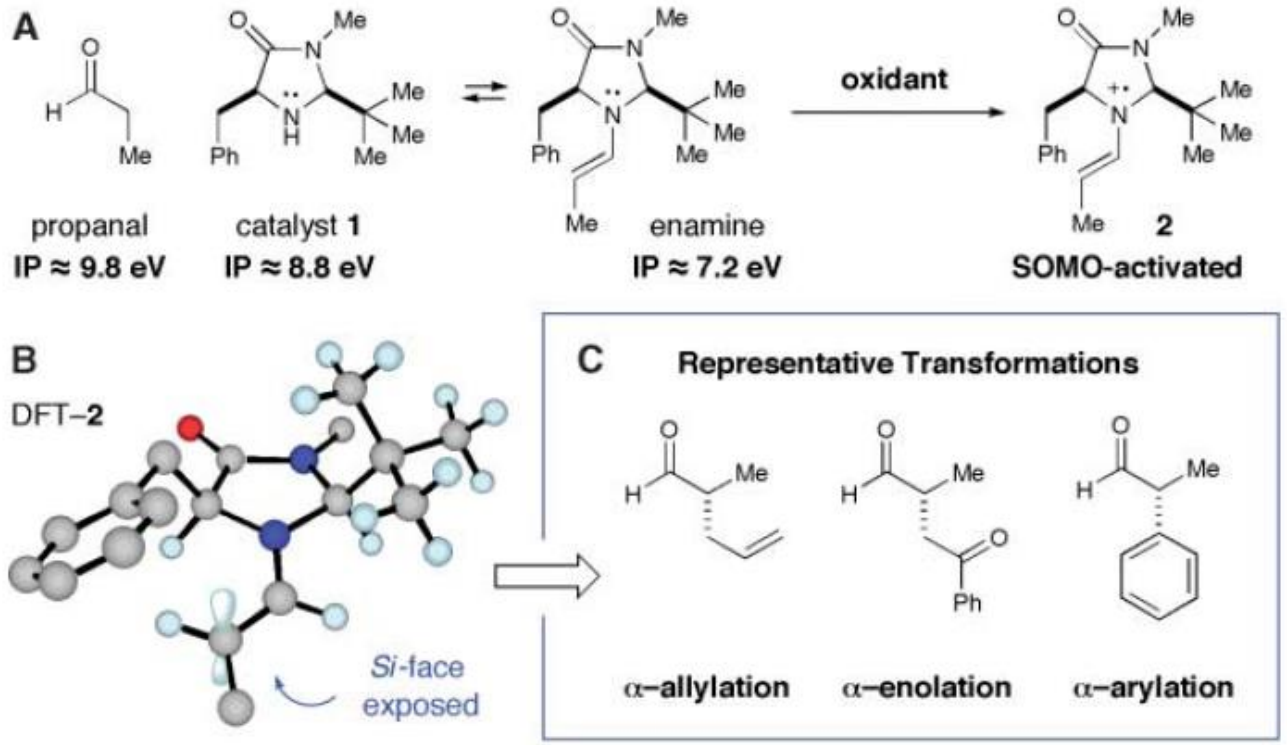
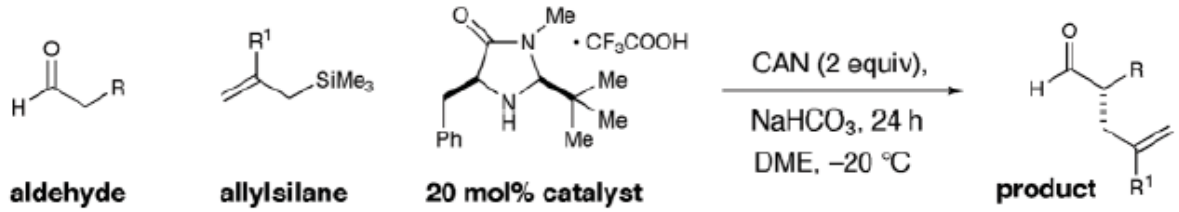


Fig. 2. (**A**) Catalytic chemical steps leading to formation of the SOMO-activated intermediate. Me, methyl; Ph, phenyl. (**B**) DFT—calculated three-dimensional structure of the enantio-differentiated radical cation. (**C**) Possible transformations arising from enantioselective organocatalytic SOMO catalysis.

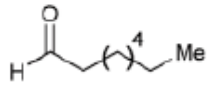
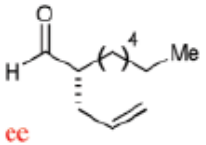
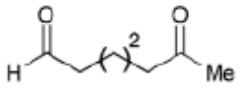
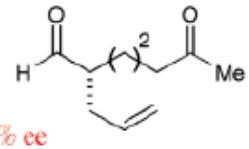
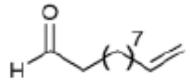
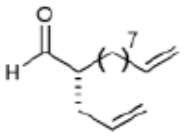
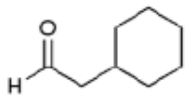
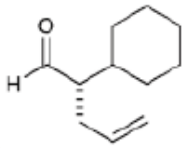
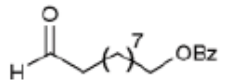
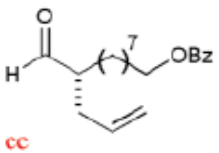
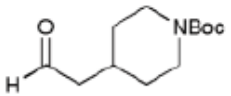
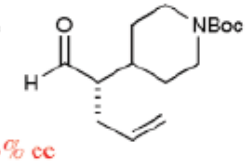
MacMillan, *Science* **2007**, 316, p. 582-585

- Formation of a 3π e^- radical cation with a singly occupied molecular orbital via 1 e^- oxidation of the enamine
- 3π e^- system projected away from bulky *tert*-butyl goup
- Selective population of *E* configuration to minimize non-bonding interactions with the imidazolidinone ring

Table 1. Representative SOMO catalysis. Enantioselective aldehyde α-allylation is shown. Bz, benzoyl; Boc, *tert*-butyl carbamoyl; Et, ethyl.



aldehyde **allylsilane** **20 mol% catalyst** **product**

entry	aldehyde	product*	entry	aldehyde	product*
1		 81% yield, 91% ee	4		 72% yield, 87% ee
2		 75% yield, 92% ee	5		 75% yield†, 94% ee
3		 72% yield, 95% ee	6		 70% yield, 93% ee

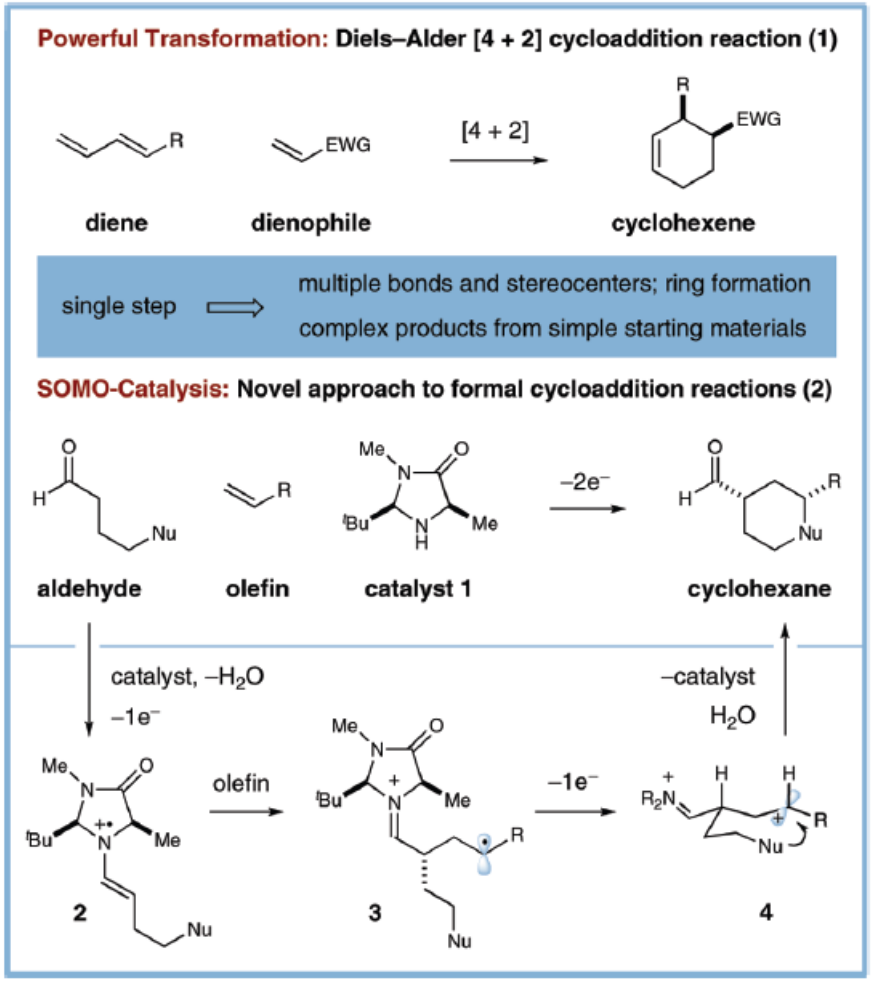
- Good functional group tolerance (olefins, ketones, esters, carbamates…)

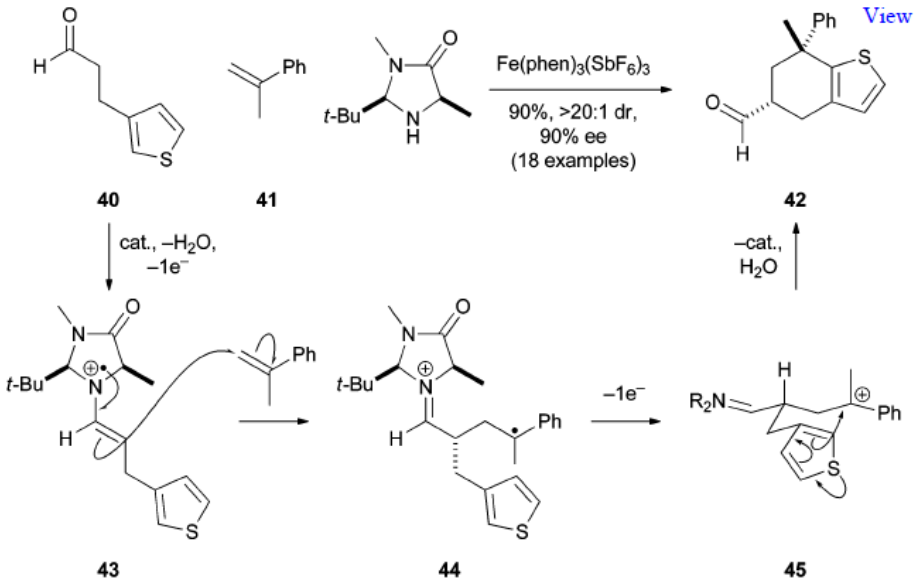
- A diverse array of allyl-silanes can be used

MacMillan, *Science* **2007**, *316*, p. 582-585

Enolation: MacMillan, *J. Am. Chem. Soc.* **2007**, *129*, 7004
Vinylation: MacMillan, *J. Am. Chem. Soc.* **2008**, *130*, 398
Arylation: MacMillan, *J. Am. Chem. Soc.* **2009**, *131*, 11640
Carbo-oxidation: MacMillan, *J. Am. Chem. Soc.* **2008**, *130*, 16494

Enantioselective cascade cycloadditions

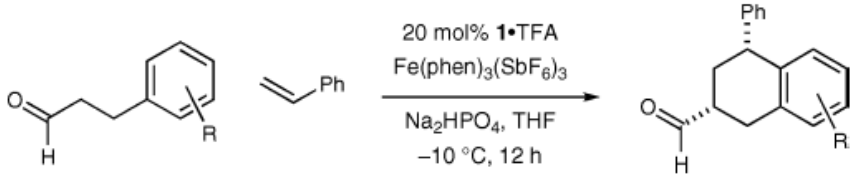


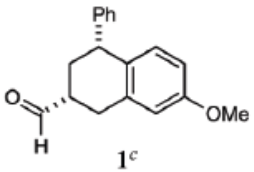


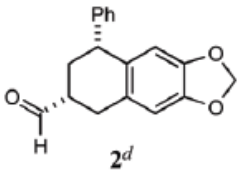
- Direct and selective access to complex cyclohexyl motifs
- Simple aldehyde and olefin substrates
- Catalyst mediated
- Highly predictable with respect to regio-, diastereo-, and enantiocontrol

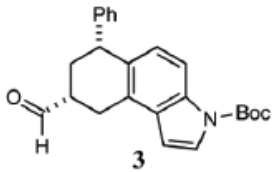
MacMillan, *J. Am. Chem. Soc.*, **2010**, 132, 10015

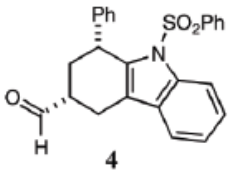
Table 2. Enantioselective SOMO-Cycloaddition: Arene Scope[a,b]

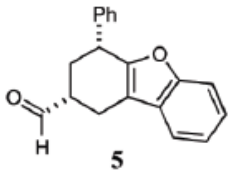


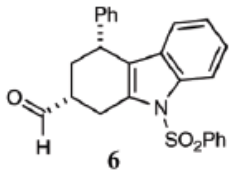

1[c]
76%, >20:1 dr, 94% ee


2[d]
85%, 8:1 dr, 93% ee


3
83%, >20:1 dr, 94% ee


4
70%, 10:1 dr, 92% ee


5
85%, 8:1 dr, 93% ee


6
77%, 6:1 dr, 92% ee

(3 + 2) and (4 + 2) Cascade Cycloadditions Via Allyl Silanes (eqs 3 & 4)

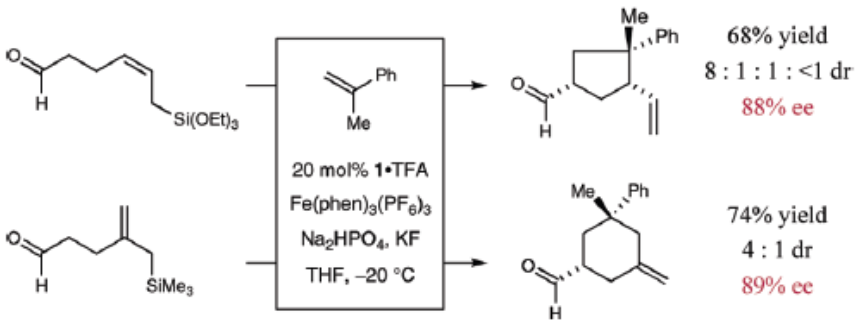
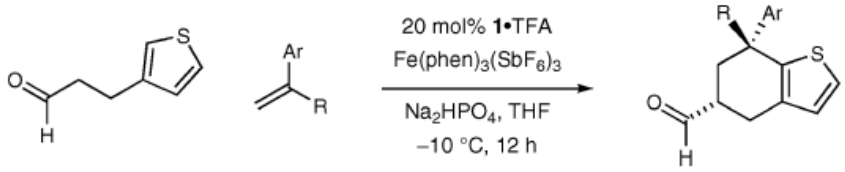
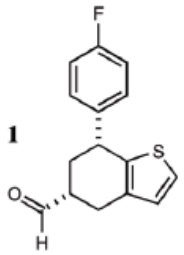
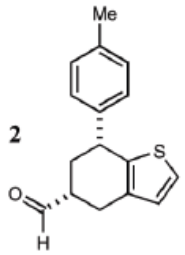
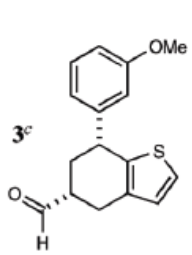


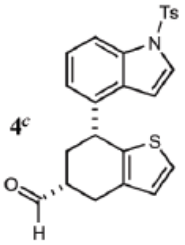
Table 3. Enantioselective Cascade Cycloaddition: Olefin Scope[a,b]

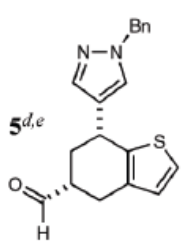


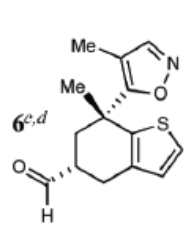

1
79%, 11:1 dr, 93% ee

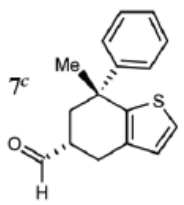

2
82%, 15:1 dr, 91% ee

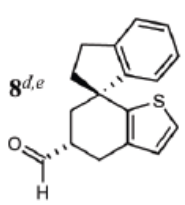

3[c]
90%, 19:1 dr, 94% ee

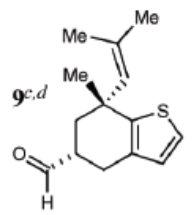

4[c]
87%, >20:1 dr, 92% ee


5[d,e]
69%, 4:1 dr, 90% ee


6[c,d]
72%, >20:1 dr, 88% ee

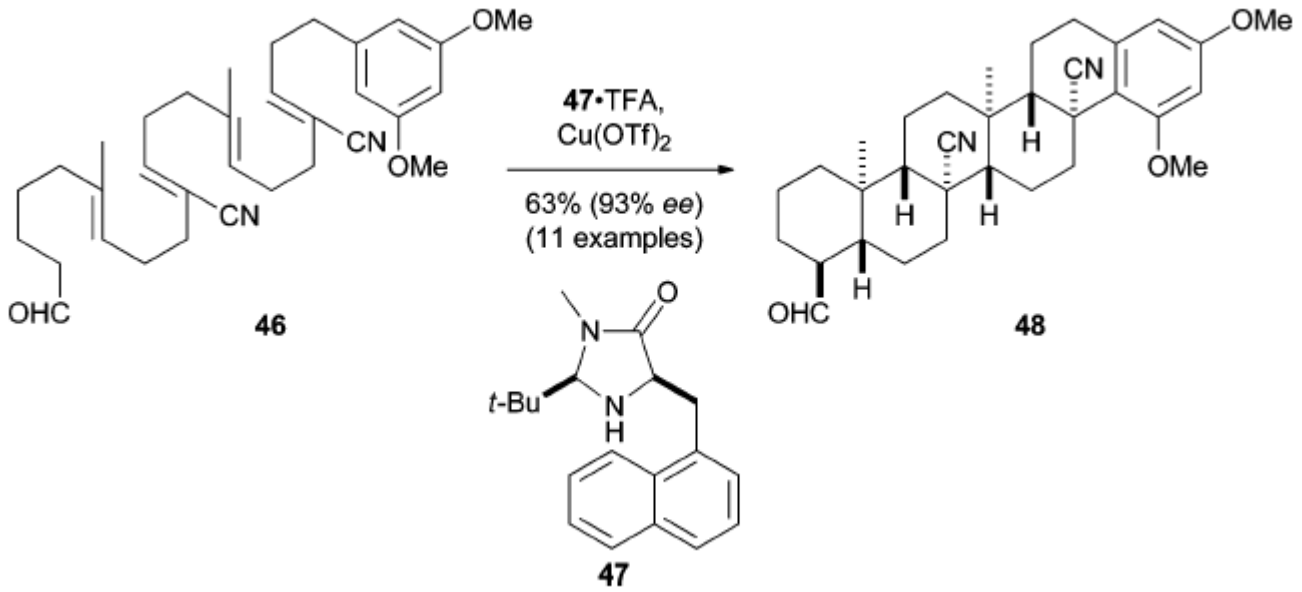

7[c]
90%, >20:1 dr, 90% ee


8[d,e]
72%, 13:1 dr, 88% ee


9[c,d]
86%, 6:1 dr, 70% ee

[a] Results listed as product, yield, diastereomeric ratio (dr), enantiomeric excess (% ee). [b] Diastereomeric ratio, % ee determined as in Table 1. [c] Reaction conducted at −20 °C. [d] Reaction performed with $Fe(phen)_3(PF_6)_3$ as oxidant. [e] Reaction conducted at −40 °C.

Polyene Cyclization



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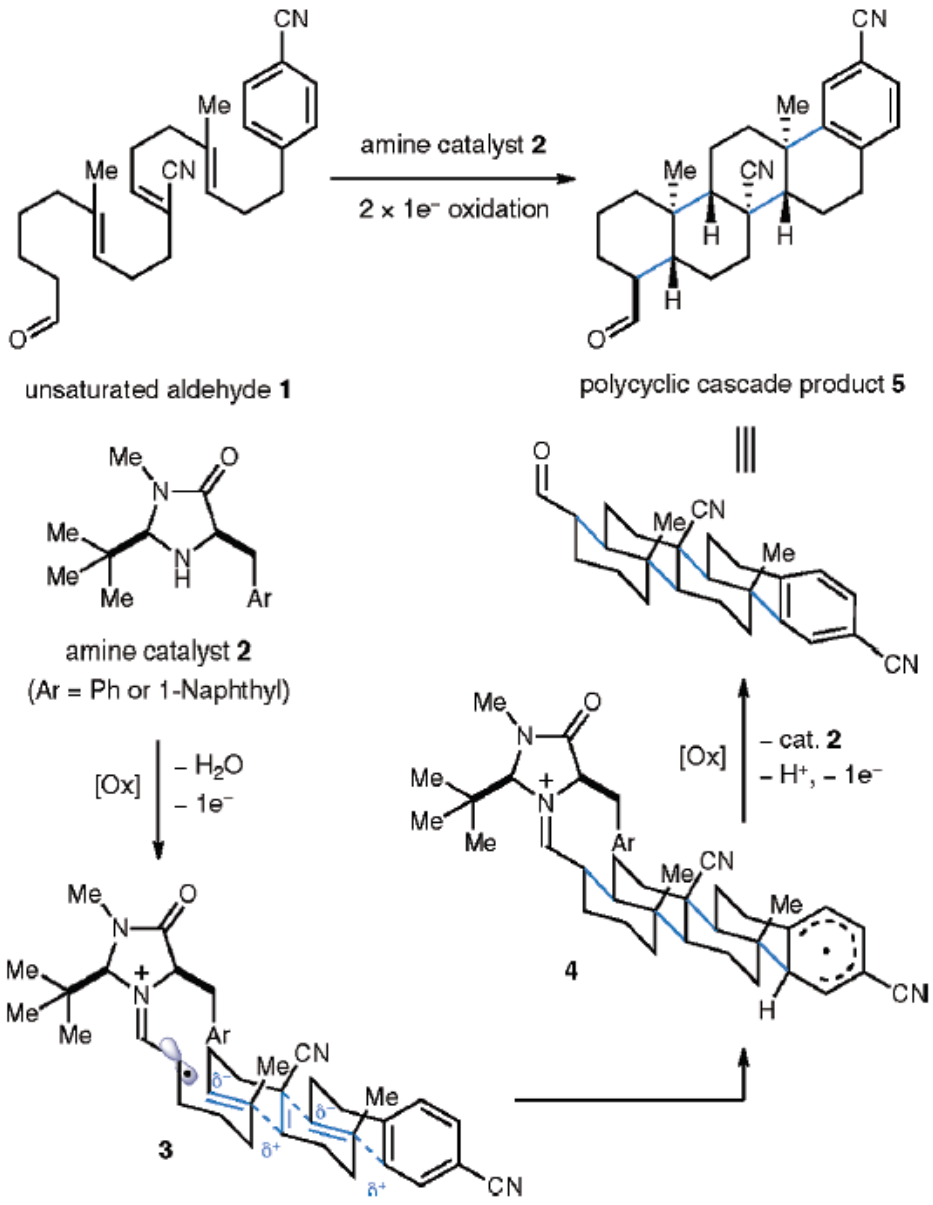
A new application of SOMO catalysis to the enantioselective construction of multiple C-C bonds and contiguous stereocentres in the context of steroidal and terpenoidal architecture

Scheme 1. Enantioselective Polycyclization via SOMO Catalysis



- Formation of α-imino radical **3**
- Series of 6-*endo-trig* cyclizations
- Termination by a suitable arene
  → cyclohexadienyl radical **4**
- Second oxidation step
  → cyclohexadienyl cation
- Rearomatization
- Liberation of catalyst
  → Pentacycle **5**

Electronic properties of tethered polyene: alternating sequence of polarity-inverted C=C bonds (acrylonitrile and isobutene moieties)

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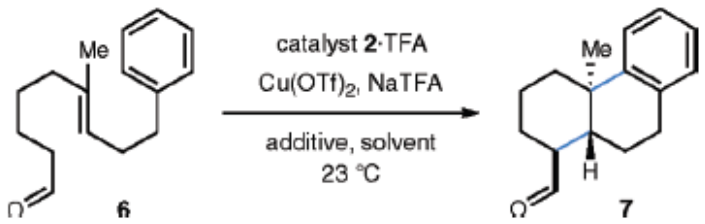
Bi-and Tricyclization

Table 1. Reaction Optimization for Enantioselective Bicyclization[a]



entry	catalyst	additive[b]	solvent	yield (%)[c]	ee (%)[d]
1	**2a**, Ar = Ph (20 mol%)	none	MeCN	11	34
2	**2a**, Ar = Ph (20 mol%)	TFA	MeCN	16	35
3[e]	**2a**, Ar = Ph (20 mol%)	TFA	MeCN	42	42
4[e]	**2b**, Ar = 1-Np (20 mol%)	TFA	MeCN	56	74
5[e]	**2b**, Ar = 1-Np (20 mol%)	TFA	*i*-PrCN/DME[f]	54	87
6[e]	**2b**, Ar = 1-Np (30 mol%)	TFA	*i*-PrCN/DME[f]	70	87

[a] Reactions were peformed on a 0.20 mmol scale using 2.5 equiv of $Cu(OTf)_2$ and 2.0 equiv of NaTFA. [b] Using 3.0 equiv of TFA. [c] Isolated yield. [d] Determined by chiral HPLC analysis. [e] With slow addition of oxidant and base as a solution in MeCN or *i*-PrCN. [f] A 3:2 *i*-PrCN/DME mixture (0.08 M).

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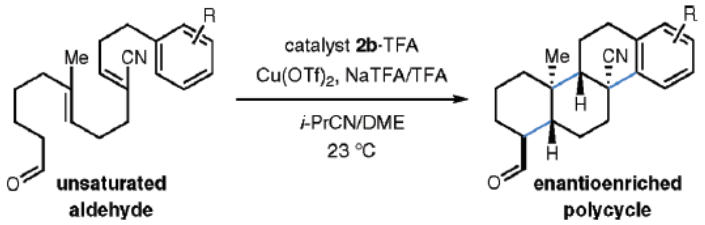
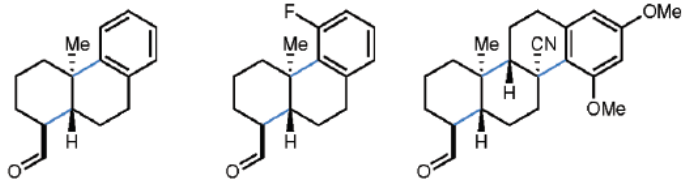
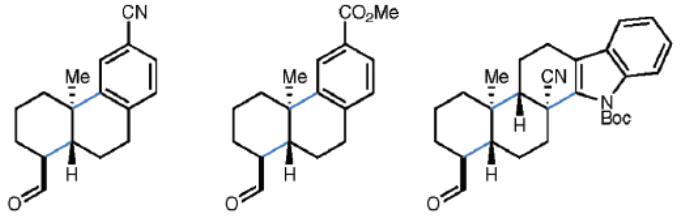
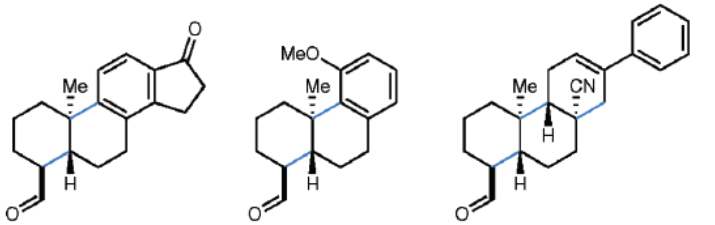
Table 2. Scope Studies in Enantioselective Bi- and Tricyclization[a,b,c]



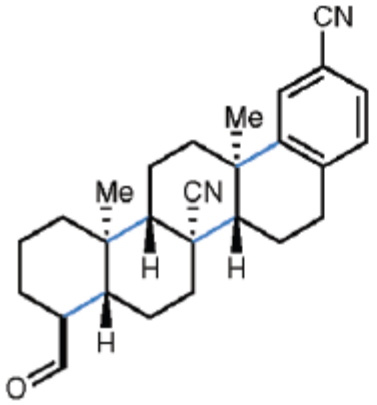




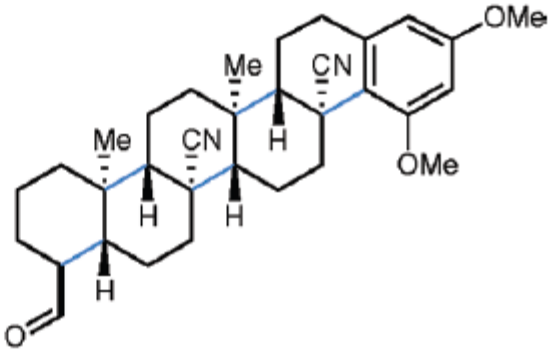


[a] Conditions: Slow addition (7 h) of $Cu(OTf)_2$ (2.5 equiv), NaTFA (2.0 equiv), and TFA (3.0 equiv) in *i*-PrCN (2 parts) to aldehyde and catalyst (30 mol %) in 1:2 *i*-PrCN/DME to give a 0.08 M solution with subsequent stirring for 17 h at room temperature. [b] Isolated yield. [c] ee was determined by chiral HPLC analysis. [d] Ortho/para mixture (4:1 for **10**; 2:1 for **12**). [e] ee of the ortho product; 91% ee for the para regioisomer of **12**.

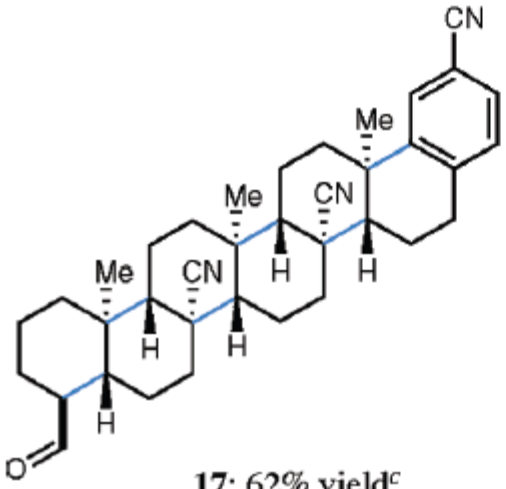
Scheme 2. Extended Ring Systems by Organo-SOMO Catalysis[a]



5: 56% yield, 92% ee[b]



16: 63% yield, 93% ee[b]



17: 62% yield[c]

6 new C–C bonds

11 contiguous stereocenters

5 all-carbon quaternary stereocenters

92% yield per bond formation

[a] Conditions: See Table 2, footnotes *a*–*c*. [b] Determined by chiral supercritical fluid chromatography (SFC). [c] Determination of enantiomeric excess in this case was not possible because of the sparing solubility of the polycycle in HPLC or SFC solvents: $[\alpha]_D = -25.3$ ($c = 0.68$, $CHCl_3$); also see ref 22.

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