Chapter 5

SOMO Catalysis: A New Mode of Organocatalytic Activation*†

Introduction

Over the last four decades, the capacity to induce asymmetric transformations using enantioselective catalysts has remained a focal point for extensive research efforts in both industrial and academic settings. During this time, thousands of new asymmetric catalytic reactions have been invented, yet most are derived from a small number of long-established activation modes. Activation methods such as Lewis acid catalysis[1], metal-insertions[2], and hydrogen-bonding catalysis[3] have spawned countless reactions within each class, dramatically expanding the synthetic toolbox available to practitioners of chemical synthesis. Therefore, the design and implementation of novel catalytic activation modes that enable the invention of previously unknown transformations is a necessary objective for the continued advancement of the field of organic chemistry.

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* A report of this work has been published. Portions taken in part from: Beeson, T. D.; Mastracchio, A.; Hong, J.-B.; Ashton, K.; MacMillan, D. W. C. *Science* **2007**, *316*, 582.

† The work reported in this chapter was conducted by T. D. Beeson, with the exception of the aldehyde α-allylation substrate scope, which was conducted in cooperation with A. Mastracchio.

1 Yamamoto, H., Ed. *Lewis Acids in Organic Synthesis*; Wiley-VCH; New York, 2000.

2 (a) Crabtree, R. H. *The Organometallic Chemistry of the Transition Metals*, 4th edition; Wiley-Interscience; Hoboken, NJ, 2005. (b) Noyori, R. in *Asymmetric Catalysis in Organic Synthesis*; Wiley-VCH; New York, 1994, pp 123–173. (c) Ojima, I., Ed. *Catalytic Asymmetric Synthesis*, 2nd edition; Wiley-VCH; New York, 2000.

3 Taylor, M. S.; Jacobsen, E. N. *Angew. Chem. Int. Ed.* **2006**, *45*, 1520.

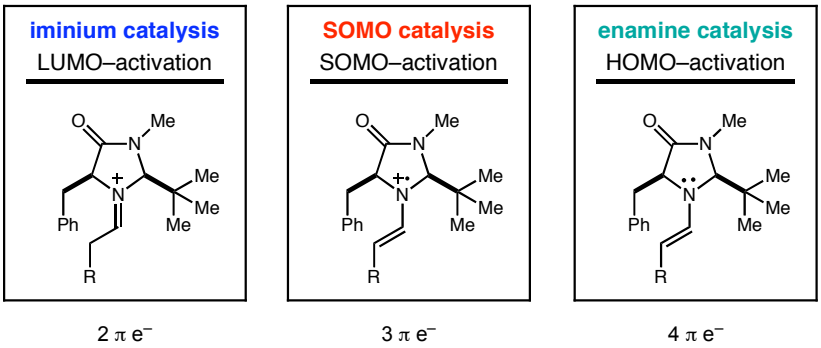
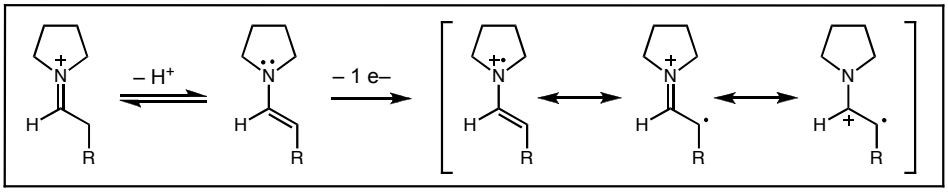


Figure 1. Singly occupied molecular orbital (SOMO) catalysis, a new activation mode that electronically bisects iminium and enamine catalysis.

The previous chapters have discussed both iminium and enamine catalysis, two activation modes that have enabled the discovery of more than sixty new asymmetric chemical reactions to date.[4] Although both have proved to be broadly useful strategies for the enantioselective functionalization of aldehydes and ketones, their expansion to include alkylations,[5] alkenylations, and arylations has been scarce or not yet come to fruition. Given that the π-systems of an iminium and an enamine differ by two electrons, we questioned whether it might be possible to access a new mode of catalytic activation by chemically intercepting the three-electron species that electronically bisects

Scheme 1. Formation of a reactive radical cation by enamine single-electron oxidation



enamine and iminium formation (Figure 1). Whereas enamines react specifically with electrophiles, we hypothesized that a one-electron oxidation of a transient enamine

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[4] (a) Lelais, G.; MacMillan, D. W. C. *Aldrichim. Acta* **2006**, *39*, 79. (b) Erkkilä, A.; Majander, I.; Pihko, P. *Chem. Rev.* **2007**, *107*, 5416. (c) Mukerjee, S.; Yang, J. W.; Hoffmann, S.; List, B. *Chem. Rev.* **2007**, *107*, 5471.

[5] The intramolecular enamine-catalyzed α-alkylation of aldehydes has been accomplished: Vignola, N.; List, B. *J. Am. Chem. Soc.* **2004**, *126*, 450.

species should generate a three-π-electron radical cation that is activated toward a range of nucleophiles, thereby enabling a diverse range of previously unknown asymmetric transformations (Scheme 1).

Proof of Concept Validation

From the outset we recognized that the viability of this concept relied upon the meeting of two key requirements. First, the oxidation potential of the enamine would need to be sufficiently lower than its aldehyde and amine precursors such that a single-electron oxidant could chemoselectively oxidize the enamine in preference to the other species present. The first ionization potential of 1-(but-1-enyl)pyrrolidine[6] has been measured to be 1.56 eV lower than pyrrolidine[7] and 2.6 eV lower than butanal[7] (Figure 2). This data reveals the transient enamine component to be sufficiently more susceptible to oxidation than the accompanying reaction partners.

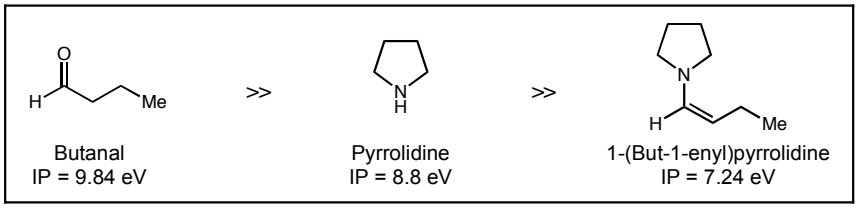

Figure 2. First ionization potentials of an enamine and its precursor aldehyde and amine.

Second, an amine catalyst class was needed that would enforce high levels of facial selectivity to the radical cation. We recognized that like enamines, the radical cation's 3-π-electron system is delocalized with the p-orbital of the nitrogen lone pair

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[6] The second ionization potential of 1-(but-1-enyl)pyrrolidine is 10.04 eV. Müller, K.; Previdoli, F.; Desilvesro, H. *Helv. Chim. Acta* **1981**, *64*, 2497.

[7] Lide, D. R., Ed., *Handbook of Chemistry and Physics*; 76th edition; CRC Press; New York, 1995; p 220.

(Scheme 1) and therefore, the orbitals should maintain a geometry nearly identical to that of its parent enamine. We were able to confirm this on the basis of density functional theory (DFT) calculations performed on the enamine and its radical cation formed between proprionaldehyde and imidazolidinone catalyst **1**. As shown in Figure 3,

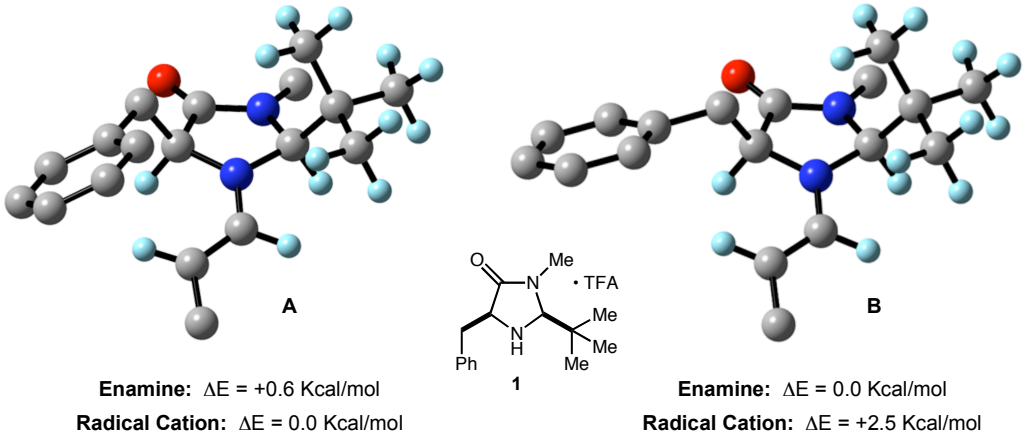

Figure 3. 3-D representations depicting the two lowest energy conformations for both the enantio-differentiated enamine and its radical cation formed between imidazolidinone catalyst **1** and propionaldehyde. Relative energies calculated using density functional theory (DFT).[8]

the two lowest energy conformations, **A** and **B**, display significant facial bias towards one face of the π-system. In conformation **B**, the benzene ring rests directly over the π-system and generates a highly effective facial bias, while in conformation **A**, it is rotated away from the π-system and the facial bias is slightly diminished. Interestingly, while the enamine has a slight preference for conformation **B** (ΔE = 0.6 Kcal/mol), the radical cation highly favors conformation **A** (ΔE = 2.5 Kcal/mol), presumably due to a type of "cation-π" interaction between the benzene ring and the delocalized radical cation of the π-system.

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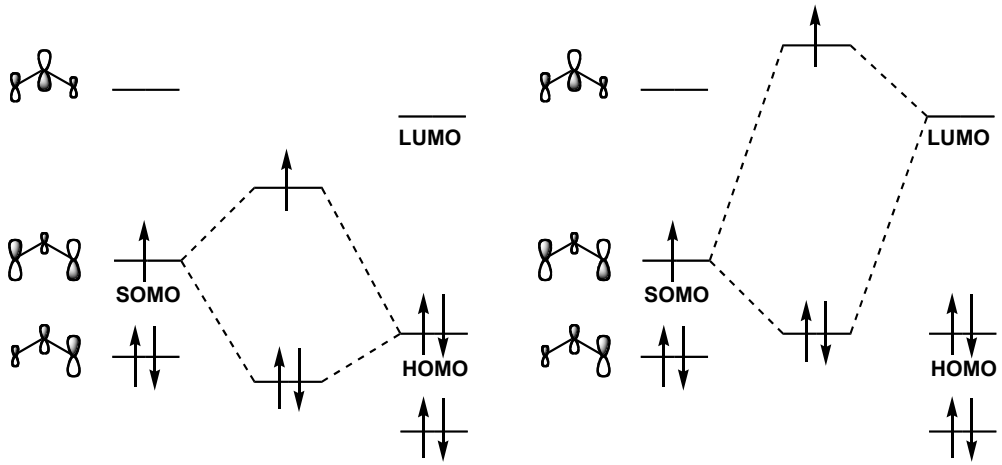
[8] Gaussian DFT calculations performed by Prof. Robert Pascal, Department of Chemistry, Princeton University. Calculations performed using B3LYP/6-311+G(2d,p)//B3LYP/6-31G(d).

Scheme 2. The interaction of the SOMO of a radical with (a) HOMO and (b) LUMO orbitals[9]



(a) SOMO-HOMO (b) SOMO-LUMO

Since radical cations generated from the oxidation of enamines are stabilized due to delocalization of the radical with the π-system (Scheme 1), the singly occupied molecular orbital (SOMO) is relatively low in energy and prefers to interact with the highest occupied molecular orbital (HOMO) of nucleophiles rather than the lowest unoccupied molecular orbital (LUMO) of electrophiles (Scheme 2). Radical cations generated from pre-formed enamines have been shown to react with both unactivated olefins[10] and electron-rich olefins such as silylenolethers.[11] Therefore, as a first attempt at our proposed SOMO-catalyzed reaction, the intramolecular cyclization of cis-6-nonenal was studied using our second-generation imidazolidinone catalyst[12] **1** in the presence of a variety of oxidants. Both organic and metal-based oxidants were analyzed

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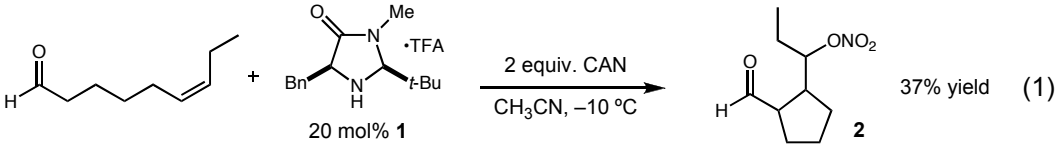
[9] Figure adapted from: Fleming, I. *Frontier Orbitals and Organic Chemical Reactions*; John Wiley & Sons, Ltd.; Chichester, 2000; p 183.

[10] Cossy, J.; Bouzide, A. *J. Chem. Soc., Chem. Commun.* **1993**, 1218.

[11] Narasaka, K.; Okauchi, T.; Tanaka, K.; Murakami, M. *Chem. Lett.* **1992**, 2099.

[12] Austin, J. F.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 1172.

and, to our delight, reactions performed with ceric ammonium nitrate (CAN) generated the 5-exo cyclized product **2** with subsequent trapping by a nitrate ligand (equation 1).



α-Allylation of Aldehydes

With this proof of concept in hand, we recognized the potential of this new activation mode to enable the invention of many new and useful enantioselective reactions. Radical cations have been shown to participate in many non-catalytic C–C, C–O, C–N, C–S and C–X (where X is a halogen) bond formations,[13] leading us to believe that SOMO catalysis might provide access to a diverse and powerful collection of previously unknown asymmetric reactions. One such reaction of intense interest within our group and others was the direct and enantioselective α-allylation of aldehydes, due to the established importance of allylation products as chiral synthons in chemical synthesis. While advancements in the α-allylation of other carbonyl species had been accomplished,[14] at the time of this work, there were no aldehyde α-allylation methods in existence.[15,16] In fact, direct allylic alkylations of dicarbonyl species had been established

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[13] Also see references 8 and 9. (a) Kirchgessner, M.; Sreenath, K.; Gopidas, K. R. *J. Org. Chem.* **2006**, *71*, 9849. (b) Sutterer, A.; Moeller, K. D. *J. Am. Chem. Soc.* **2000**, *122*, 5636. (c) Lee, H. B.; Sung, M. J.; Blackstock, S. C.; Cha, J. K. *J. Am. Chem. Soc.* **2001**, *123*, 11322. (d) Renaud, P.; Sibi, M. P., Eds.; *Radicals in Organic Synthesis*; Wiley-VHC; Weinheim, 2001; Vol. 2, pp 144–205.

[14] Trost, B. M.; Crawley, M. L. *Chem. Rev.* **2003**, *103* 2921.

[15] Before publication of this work, a non-enantioselective α-allylation of aldehydes appeared in the literature: Ibrahem, I.; Córdova, J. A. *Angew. Chem. Int. Ed.* **2006**, *45*, 1952.

[16] After completion of this work, the following enantioselective α-allylation of aldehydes appeared in the literature: Mukerjee, S.; List, B. *J. Am. Chem. Soc.* **2007**, *129*, 11336.

but methods for the allylic alkylation of ketones have required covalent attachment of the allylating species for intramolecular alkylation[17] or preforming of the silylenol ether[18a] or metal enolate[18] to act as the reactive species.[19]

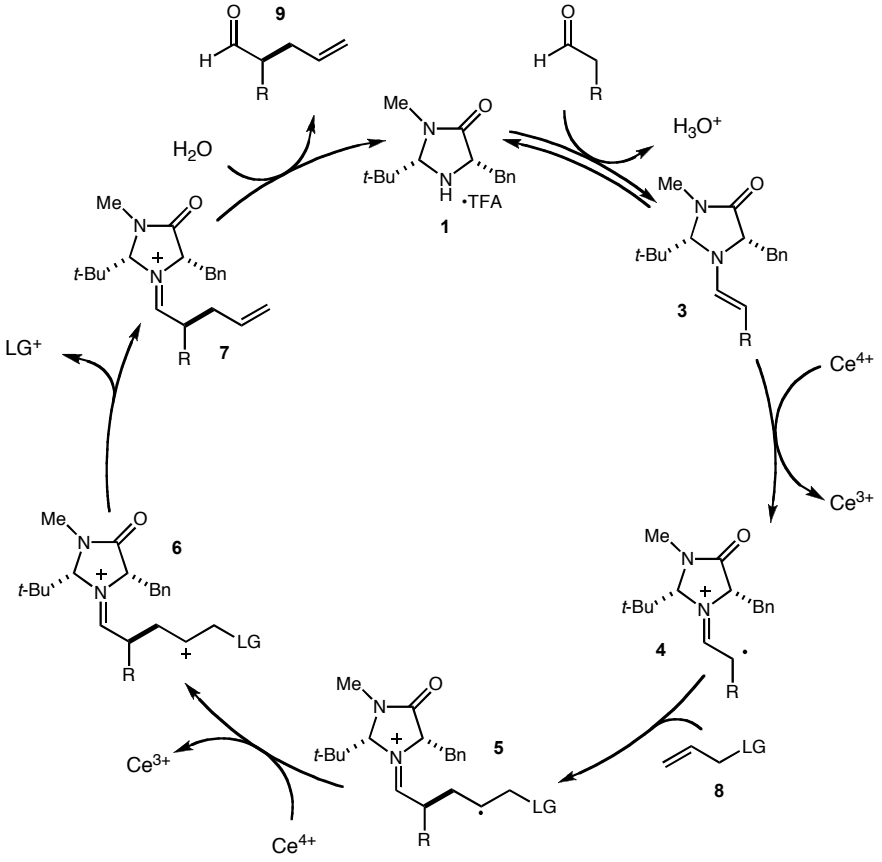

Figure 4. Proposed catalytic cycle of the SOMO-catalyzed aldehyde α-allylation reaction.

Mechanistically, we speculated that a transiently formed radical cation **4** could combine with an allyl π-nucleophile **8** with a facile leaving group to generate a secondary radical **5** (Figure 4). Upon further oxidation to the secondary carbocation **6**, the leaving

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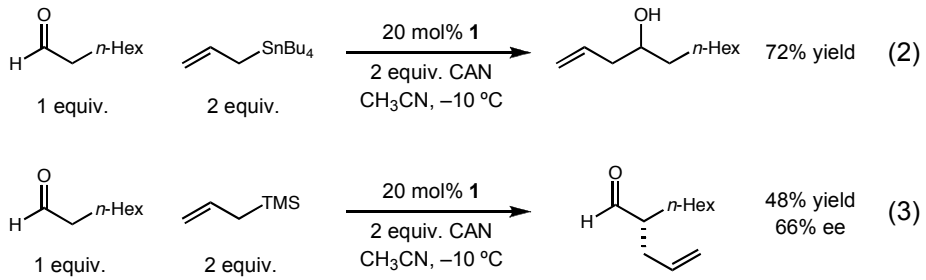
[17] (a) Behenna, D. C.; Stoltz, B. M. *J. Am. Chem. Soc.* **2004**, *126*, 15044. (b) Trost, B. M.; Xu, J. *J. Am. Chem. Soc.* **2005**, *127*, 2846. (c) Trost, B. M.; Xu, J. *J. Am. Chem. Soc.* **2005**, *127*, 17180.

[18] Doyle, A. G.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2005**, *127*, 62.

[19] Direct ketone allylic alkylation via in situ formation of lithium enolates has now been accomplished: (a) Braun, M.; Meier, T. *Synlett*, 2968. (b) Zheng, W.-H.; Zheng, B.-H.; Zhang, Y.; Hou, X.-L. *J. Am. Chem. Soc.* **2007**, *129*, 7718.

group could eliminate to generate the α-allylated iminium species **7**, which upon hydrolysis would provide the desired α-allylated aldehyde **9** and regenerate the catalyst.

With this in mind, we first examined a variety of allylating reagents with the capacity to generate stabilized intermediates and/or leaving groups. Of the reagents studied, only allyltributylstannane and allyltrimethylsilane afforded the desired α-allylated aldehyde, however, allyltributylstannane predominantly reacted with the carbonyl of the starting material (equation 2). On the other hand, allyltrimethylsilane reacted solely with the transient enamine radical cation, and to our delight, generated the desired product in 66% ee and 48% yield (equation 3).



A broad survey of potential single–electron oxidants was conducted to ascertain whether CAN was the optimal oxidant for the SOMO-catalyzed α-allylation reaction, including hypervalent idodides, quinones and an assortment of transition metals. Since oxidation potentials can vary widely with the choice of solvent, oxidants were studied in both CH_3CN and methylene chloride (CH_2Cl_2). While certain iron and copper oxidants were shown to generate product in CH_3CN,[20] the reactions progressed with much lower efficiency than CAN and therefore, we chose to pursue further optimization of the CAN-mediated reaction.

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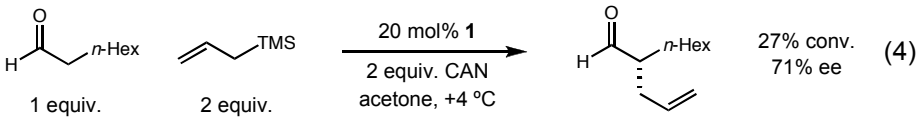
[20] Approximately 5% conversion was obtained with $Fe(NO_3)_3$, $Cu(NO_3)_2$, and $Cu(OTFA)_2$. 11% conversion was obtained with $Fe(Phen)_3(PF_6)_3$.

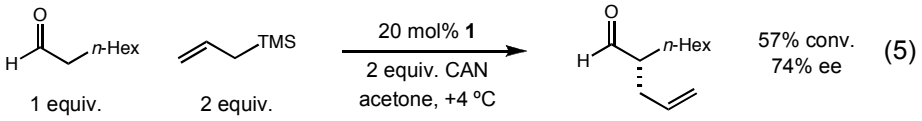
The first major achievement came after literature analysis suggested that the radical cation might be able to react with oxygen in the atmosphere,[21] competing with the allylsilane for product formation. Degassing the reaction mixture prior to addition of the starting aldehyde dramatically improved the conversion and at +4 ºC in CH_3CN, the conversion more than doubled from 23% to 53%. Reactions subsequently performed in acetone achieved higher enantioselectivities and also saw a dramatic increase in conversion upon oxygen exclusion (equations 4 and 5).

Reaction without degassing:



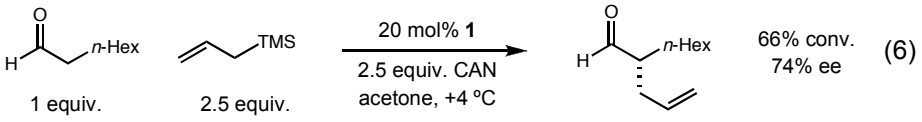
1 equiv. 2 equiv. (4)

Degassed reaction conditions:



1 equiv. 2 equiv. (5)

Additionally, as our understanding of the reaction mechanism dictated that a minimum of 2 moles of CAN were required per mole of aldehyde, we increased the relative stoichiometry of the reaction and determined that 2.5 equivalents of oxidant and allylsilane were optimal (equation 6). Additional amounts of oxidant prohibited efficient stirring of the reaction and provided lower overall yields.



1 equiv. 2.5 equiv. (6)

Next we studied the effect of temperature and concentration, hoping to obtain the needed improvement in enantiocontrol. As shown in Table 1, a slight increase in

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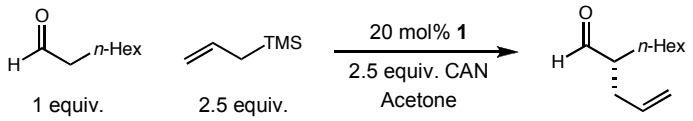
[21] Nair, V.; Rajan, R.; Mohana, K.; Sheeba, V. *Tetrahedron Lett.* **2003**, *44*, 4585.

selectivity was achieved at –20 ºC, with maximum conversions obtained at more dilute concentrations. At the same time, a variety of imidazolidinone catalyst architectures were studied, including geminally disubstituted and *trans*-oriented catalysts, however, catalyst **1** consistently yielded the best results. Acid co-catalysts of varying pKa values were also studied, and while a few of the acids achieved comparable conversions and enantioselectivities, they did not improve on the results already obtained with the trifluoroacetic acid (TFA) salt of catalyst **1**. Likewise, the electronic requirement of the trialkylsilane component was investigated with a variety of alkyl- and aryl-substituted allylsilanes, and allyltrimethylsilane was shown to be the preferable allylating reagent. Full details of these experiments can be found in Appendix A on page 115.

Table 1. Effect of Temperature and Concentration



1 equiv. 2.5 equiv.

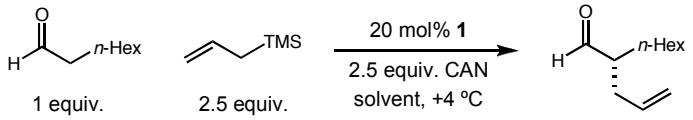
entry	Conc. (M)	Temp (ºC)	time (h)	% conversion[a]	% ee[b]
1	0.0625	+4	3	64	75
2	0.0625	–10	6	72	77
3	0.0625	–20	18	75	80
4	0.0833	–20	18	75	80
5	0.125	–20	18	67	80
6	0.167	–20	18	44	80
7	0.250	–20	18	48	80

(a) Conversion determined by GLC analysis relative to an internal standard (methyl cyclohexanecarboxylate). (b) Enantiomeric excess determined by GLC analysis (Varian Chirasil-Dex-CB).

Since we had achieved such a dramatic improvement in enantioselectivity when the reaction medium was changed from CH_3CN to acetone (66% ee versus 74% ee), additional solvents were studied to ascertain whether further improvements in selectivity could be attained. As shown in Table 2, reactions performed in ethyl acetate (EtOAc)

were similar to those in acetone while chloroform provided no desired product. Surprisingly, reactions performed in the etherial solvents tetrahydrofuran (THF) and dimethoxyethane (DME) attained significantly higher levels of enantioselectivity; however, the reaction efficiencies were much lower than those in other solvents.

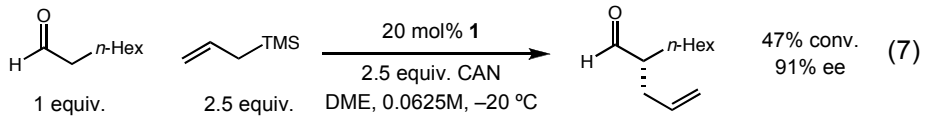
Table 2. Effect of Solvent on the α-Allylation Reaction



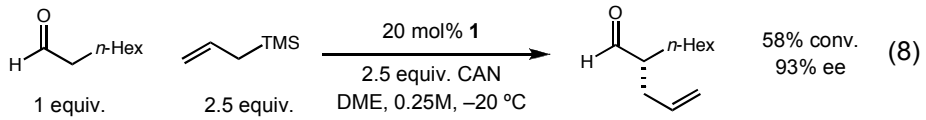
entry	solvent	time (h)	% conversion[a]	% ee[b]
1	CH_3CN	2	53	66
2	Acetone	3	66	74
3	EtOAc	13	44	73
4	$CHCl_3$	13	0	–
5	THF	6	19	82
6	DME	6	31	85

(a) Conversion determined by GLC analysis relative to an internal standard (methyl cyclohexanecarboxylate). (b) Enantiomeric excess determined by GLC analysis (Varian Chirasil-Dex-CB).

Nevertheless, further optimization of the reaction performed in DME demonstrated that excellent enantioselectivity and improved reaction efficiency could be achieved with lower reaction temperatures and higher concentrations (equations 7 and 8), a surprising result considering that lower concentrations were optimal for reactions performed in acetone. Although excellent enantioselectivities for the α-allylation reaction had been realized, reaction efficiencies remained inadequate and needed further optimization.

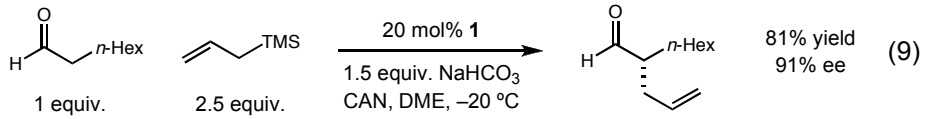


(7)



(8)

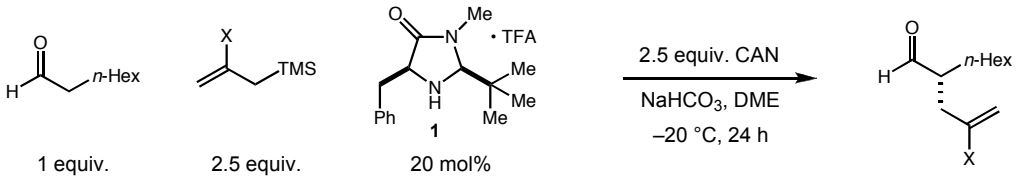
At this point in time, we began to question whether the large excess of allylsilane required in the reaction was possibly the result of acidic degradation induced by the silane cation or nitric acid formed during the reaction. For this reason, we studied a variety of base additives that could act as scavengers of these acidic byproducts. Of the bases studied, sodium bicarbonate ($NaHCO_3$), potassium bicarbonate ($KHCO_3$), and di-*tert*-buylpyridine (DTBP) provided the most improvement, with 1.5 equivalents of $NaHCO_3$ consistently achieving the best results. Gratifyingly, the α-allylation of octanal could now be accomplished in 81% yield and 91% ee (equation 9).



(9)

Furthermore, we explored the generality of the α-allylation reaction by investigating a variety of substituted allylsilanes and aldehydes containing common functionalities. As demonstrated in Table 3, an assortment of π-rich substituted allylsilanes readily participate as allylic alkylating reagents in this new catalytic protocol. Both methyl and phenyl 2-substituted allylsilanes reacted without loss in reaction efficiency or enantiocontrol (entries 1–2). Perhaps most striking is the electron-deficient acrylate substrate (entry 4), which reacted as effectively as the more π-rich substrates, likely due to its capacity to stabilize the subsequently formed radical through the captodative effect. The ester appendage acts effectively as an electron-withdrawing "captor," while the β-silicon serves in a "dative" capacity to donate electrons from the silicon-carbon σ-bond to the radical p-orbital.

Table 3. SOMO-Catalyzed Reactions with Substituted Allylsilanes



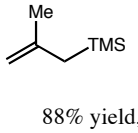
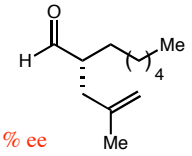
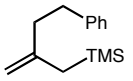
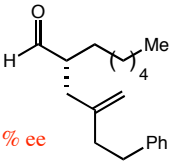
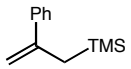
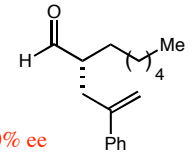
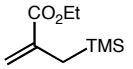
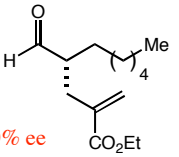
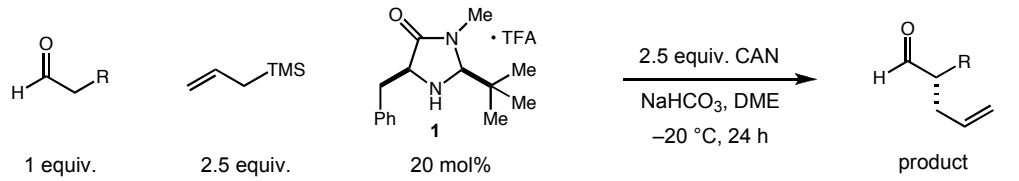
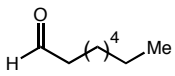
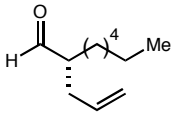
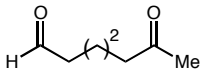
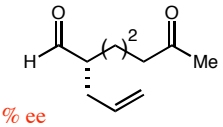
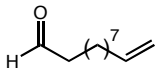
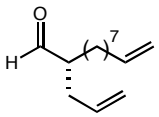
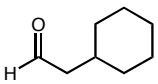
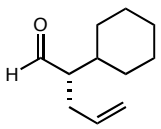
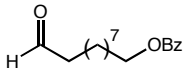
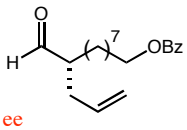
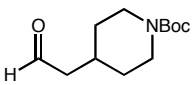
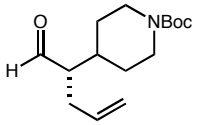
entry	allylsilane	product	entry	allylsilane	product
1			3		
	88% yield, 91% ee			77% yield, 88% ee	
2			4		
	87% yield, 90% ee			81% yield, 90% ee	

Table 4. SOMO-Catalyzed α-Allylation of Various Aldehydes



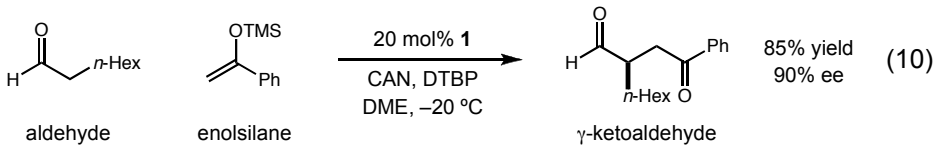
entry	aldehyde	product	entry	aldehyde	product
1			4		
	81% yield, 91% ee			72% yield, 87% ee	
2			5		
	75% yield, 92% ee			75% yield[a], 94% ee	
3			6		
	72% yield, 95% ee			70% yield, 93% ee	

(a) Yield determined by GLC analysis relative to an internal standard (methyl cyclohexanecarboxylate).

Additionally, aldehyde substrates with various functionalities including olefins, ketones, and esters, as well as protected alcohols and amines were well tolerated in the α-allylation reaction (Table 4, entries 1–4). We were very pleased to find that the more sterically demanding cyclohexyl and piperidine substrates reacted just as effectively, achieving good yields and excellent enantioselectivities (Table 4, entries 5–6).

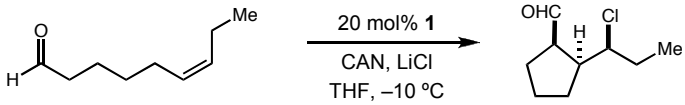
SOMO-Catalysis Applications

Over the last few years, the advent of SOMO-catalysis as a new activation mode has allowed our lab to rapidly invent many previously unknown catalytic and enantioselective transformations. For example, Drs. Jang and Hong showed that silylenol ethers were able to act efficiently as SOMO nucleophiles to produce enantiopure 1,4-dicarbonyls (equation 10), presumably through a similar mechanism as the α-allylation reaction in which a β-silyl radical intermediate at the carbonyl carbon undergoes oxidation to the carbocation, and subsequent silyl cation elimination.[22] Similarly, postdoctoral fellow Dr. Hahn Kim realized the potential of vinyl boronates to act as π-nucleophiles that could undergo radical combination alpha to the boronate (equation 11),



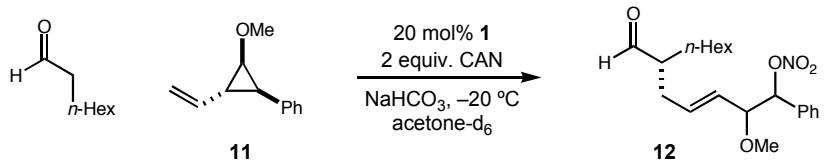
[22] Jang, H.-Y.; Hong, J.-B.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2007**, *129*, 7004.

generating a beta-stabilized radical intermediate similar to that produced in the α-allylation reaction.[23] Interestingly, postdoctoral fellow Dr. Kate Ashton discovered that the intramolecular 5-exo-cyclization reaction of cis-6-nonenal could be terminated with a halogen nucleophile, out-competing the nitrate ligand, and generating three contiguous stereocenters (equation 12).[24] In addition, SOMO-catalyzed α-arylations[24] and α-carbo-oxidations[25] have also been accomplished, and to date, a total of fourteen new transformations have been invented in our lab using the SOMO-catalysis protocol.



(12)

Finally, a demonstration of the radical-based mechanism of SOMO-catalysis has been carried out using the radical clock **11** developed by Newcomb and coworkers to distinguish between radical and cationic pathways.[26] Exposing **11** to our SOMO-catalysis reaction conditions resulted in scission of the benzylic cyclopropyl bond followed by nitrate trapping to form **12**, which is in complete accord with a radical-based pathway (equation 13).



(13)

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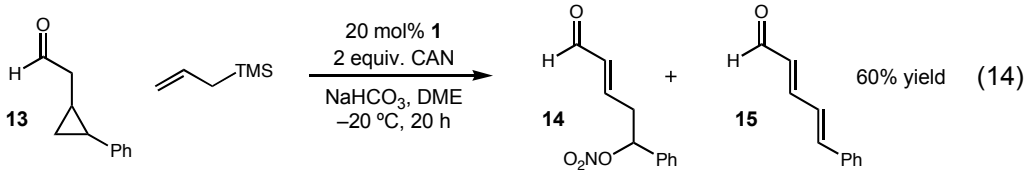
[23] Kim, H.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2008**, *130*, 398.

[24] Beeson, T. D.; Mastracchio, A.; Hong, J.-B.; Ashton, K.; MacMillan, D. W. C. *Science* **2007**, *316*, 582.

[25] Jones, C. M.; Graham, T. H.; MacMillan, D. W. C. in press.

[26] (a) Newcomb M.; Chestney, D. L. *J. Am. Chem. Soc.* **1994**, *116*, 9753. (b) Le Tadic-Biadatti, M.-H.; Newcomb, M. *J. Chem. Soc. Perkin Trans.* **1996**, *2*, 1467.

In addition, graduate student Robert Knowles has shown that the cyclopropyl aldehyde **13** undergoes facile ring opening to generate the α,β-unsaturated aldehyde **14** with subsequent nitrate trapping (equation 14). The nitrated product rapidly eliminates nitric acid while standing at ambient temperature to form the fully conjugated diene **15**. Notably, there was no detection of any α-allylated cyclopropyl aldehyde in these experiments.



(14)

Conclusion

In summary, we have described a new mode of chemical activation based on the catalytic formation of chiral radical cations. While enamines react only with electrophiles, single-electron oxidation to the radical cation allows reactions with SOMO nucleophiles at the same reacting center and enabling a diverse range of previously unknown asymmetric transformations. This technology, termed SOMO-catalysis, has enabled the first enantioselective α-allylation of aldehydes through a radical mechanism with simple allylsilanes. Using this new platform of reactivity, several previously unknown asymmetric methodologies have been developed, demonstrating the value of SOMO-catalysis as a new activation mode for the field of organic chemistry.

Supporting Information

General Information. Commercial reagents were distilled prior to use following the guidelines of Perrin and Armarego.[27] Organic solutions were concentrated under reduced pressure on a Büchi rotary evaporator. Chromatographic purification of products was accomplished using forced-flow chromatography on Iatrobeads 6RS–8060 according to the method of Still.[28] Filtration of reactions was performed using EMD Silica Gel 60 230-400 mesh. Thin-layer chromatography (TLC) was performed on EM Reagents 0.25 mm silica gel 60-F plates. Visualization of the developed chromatogram was performed by fluorescence quenching using anisaldehyde, ceric ammonium molybdenate, potassium permanganate or iodine stain. Supercritical fluid chromatography (SFC) and gas liquid chromatography (GLC) assays to determine enantiomeric excess were developed using racemic samples.

^{1}H and ^{13}C NMR spectra were recorded on Varian Mercury 300 (300 MHz and 75 MHz respectively) unless otherwise noted, and are internally referenced to residual protio solvent signals. Data for ^{1}H and ^{13}C NMR are reported as follows: chemical shift (δ ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), integration, coupling constant (Hz), and assignment. IR spectra were recorded on a Perkin Elmer Spectrum BX FT-IR spectrometer and are reported in terms of frequency of absorption (cm^{-1}). Mass spectra were obtained from the California Institute of

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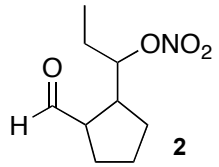
[27] Perrin, D. D.; Armarego, W. L. F. *Purification of Laboratory Chemicals*, 3rd edition; Pergamon Press; Oxford, 1988.
[28] Still, W. C.; Kahn, M.; Mitra, A. J. *J. Org. Chem.* **1978**, *43*, 2923.

Technology Mass Spectral Facility unless otherwise noted. Gas liquid chromatography (GLC) was performed on a Hewlett-Packard 6850 Series gas chromatograph equipped with a split-mode capillary injection system and flame ionization detectors using a Varian Chirasil-Dex-CB (25 m x 0.25 mm) column or Hewlett Packard HP-1 (30m x 0.32mm) column. Supercritical fluid chromatography (SFC) was performed on a Berger Minigram equipped with a variable-wavelength UV detector using a Chiralcel® OJH, ODH and Chiralpak®ADH column (25 cm) as noted (4.0 mL/min.). Optical rotations were recorded on a Jasco P-1010 Polarimeter.



2

1-(2-formylcyclopentyl)propyl nitrate 2 (equation 1): To an oven-dried 50 mL round-bottom flask equipped with a magnetic stir bar and charged with (2*R*,5*R*)-5-benzyl-2-*tert*-butyl-3-methyl-imidazolidin-4-one trifluoroacetic acid salt **1** (72 mg, 0.20 mmol) and ceric ammonium nitrate (CAN) (1.10g, 2.0 mmol) was added acetonitrile (CH_3CN) (16 mL) and the mixture cooled to –10 ºC. *Cis*-6-nonenal (167 μL, 1.00 mmol) was added and the reaction stirred vigorously 24 h at –10 ºC, and then filtered through a pad of silica gel, eluting with ether (Et_2O). Purification on silica gel (5–50% Et_2O/Pentanes) afforded 1-(2-formylcyclopentyl)propyl nitrate as a mixture of two diastereomers. (75 mg, 37% yield). IR (film) 2962, 2876, 2815, 2719, 1719, 1616, 1459, 1386, 1269, 912.9, 852.2, 784.0, 753.7, 695.5 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) for the major diastereomer δ 9.64 (d, J = 2.4 Hz, 1H, C**H**O), 4.99–5.05 (m, 1H, C**H**NO_3), 2.57–2.72 (m, 2H, C**H**C**H**CHO), 1.20–1.97 (m, 8H, CH(C$\mathbf{H_2})_3$, C$\mathbf{H_2}CH_3$), 0.99 (t, J = 7.5 Hz, 3H, C$\mathbf{H_3}$); ^{13}C NMR (75 MHz, acetone-d_6) major diastereomer: δ 202.4, 88.1, 55.3, 41.9, 30.1, 27.4,

25.5, 25.3, 9.3. Minor diastereomer: δ 202.4, 87.1, 54.0, 41.6, 27.9, 27.6, 25.2, 25.0, 9.9. HRMS (ES) exact mass calculated for $[M+H]^+$ ($C_9H_{16}NO_4$) requires *m/z* 201.1001, found *m/z* 201.1002.

General Procedure for the α-Allylation of Aldehydes:

To an oven-dried 25 mL round-bottom flask equipped with a magnetic stir bar and charged with (2*S*,5*S*)-5-benzyl-2-*tert*-butyl-3-methyl-imidazolidin-4-one trifluoroacetic acid salt **1** (72 mg, 0.20 mmol), ceric ammonium nitrate (CAN) (1.37g, 2.5 mmol), and oven-dried sodium bicarbonate (126 mg, 1.5 mmol) was added dimethoxyethane[29] (DME) (4.0 mL). The suspension was cooled to –50 ºC and deoxygenated by stirring vigorously under vacuum for 3–5 min.[30] The mixture was back-filled with argon and degassed twice more. The allyltrimethylsilane substrate (2.5 mmol) was added followed by the aldehyde substrate (1.0 mmol). The reaction was warmed to -20 ºC and stirred for 24 h under an argon atmosphere. The reaction was then cooled to -50 ºC and quickly filtered through a pad of silica gel, eluting with Et_2O. The flask was washed with a minimal amount of DME to transfer any remaining yellow solid to the silica pad. The filtrate was concentrated *in vacuo* and purified by forced flow chromatography to afford the title compounds. The enantioselectivity was determined either by chiral GLC analysis or chiral SFC analysis after reduction to the primary alcohol and acylation with 2-naphthoylchloride.

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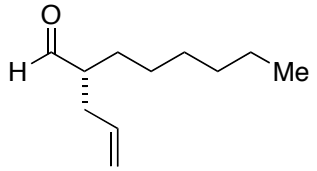
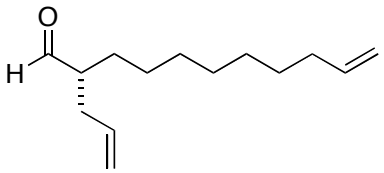
[29] Wet, non-distilled DME. Alternatively, 0.3 equiv. H_2O can be added to dry DME.

[30] The method of freeze-pump thaw, when used to deoxygenate the reaction mixture, showed less consistent results and lower yields, possibly due to the heterogeneity of the reactions.

α-Allyl Aldehydes

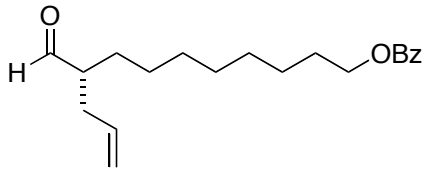


(*R*)-2-Allyloctanal (Table 4, entry 1): Prepared according to the general procedure from octanal (156 μL, 1.00 mmol) to afford a yellow oil. Purification on Iatrobeads (2–10% Et_2O/Pentanes) afforded (*R*)-2-allyloctanal as a colorless oil (137 mg, 81% yield, 91% ee). IR (film) 3075, 2928, 2858, 2703, 1728, 1708, 1641, 1458, 992.6, 915.5, 724.0 cm^{-1}; ^1H NMR (300 MHz, acetone-d_6) δ 9.59 (d, *J* = 2.4 Hz, 1H, C**H**O), 5.69–5.84 (m, 1H, C**H**=CH_2), 4.97–5.10 (m, 2H, CH=C**H**$_2$), 2.30–2.46 (m, 2H, CHC**H**$_2$CH, C**H**CHO), 2.17–2.28 (m, 1H, CHC**H**$_2$CH), δ 1.38–1.72 (dm, 2H, C**H**$_2$(CH_2)$_4$), 1.20–1.38 (m, 8H, CH_2(C**H**$_2$)$_4$), 0.87 (t, *J* = 6.9 Hz, 3H, C**H**$_3$); ^{13}C NMR (75 MHz, acetone-d_6) δ 204.7, 136.4, 116.9, 51.7, 33.5, 32.2, 29.9, 28.8, 27.4, 23.1, 14.2. HRMS (EI+) exact mass calculated for $[M-H]^+$ ($C_{11}H_{20}O$) requires *m/z* 168.1514, found *m/z* 168.1508. $[\alpha]_D$ = +12.7 (c = 1.0, $CHCl_3$). Enantiopurity was determined by GLC using a Varian Chirasil-Dex-CB (25 m x 0.25 mm) column (100 °C isotherm); (*S*) isomer t_r = 23.2 min and (*R*) isomer t_r = 23.8 min.



(*R*)-2-Allyl-undec-10-enal (Table 4, entry 2): Prepared according to the general procedure from undecylenic aldehyde (200 μL, 1.00 mmol) to afford a yellow oil.

Purification on Iatrobeads (2–10% Et_2O/Pentanes) afforded (*R*)-2-allyl-undec-10-enal as a colorless oil (156 mg, 75% yield, 92% ee). IR (film) 3077, 2927, 2855, 2704, 1728, 1641, 1441, 993.1, 912.1, 721.4 cm^{-1}; ^1H NMR (300 MHz, acetone-d_6) δ 9.59 (d, *J* = 2.2 Hz, 1H, C**H**O), 5.69–5.86 (m, 2H, $CHCH_2C\mathbf{H}{=}CH_\mathbf{2}$, $CH_2CH_2C\mathbf{H}{=}CH_2$), 4.86–5.10 (m, 4H, $CHCH_2CH{=}C\mathbf{H_2}$, $CH_2CH_2CH{=}C\mathbf{H_2}$), 2.30–2.46 (m, 2H, $CHC\mathbf{H}_2CH$, C**H**CHO), 2.17–2.28 (m, 1H, $CHC\mathbf{H}_2CH$), 1.98–2.06 (m, 2H, $CH_2C\mathbf{H_2}CH{=}CH_2$), 1.20–1.72 (m, 12H, $CH(C\mathbf{H_2})_\mathbf{6}$); ^{13}C NMR (75 MHz, acetone-d_6) δ 204.7, 139.7, 136.5, 116.9, 114.6, 51.7, 34.4, 33.5, 29.9, 29.6, 29.5, 28.8, 27.5. HRMS (FAB+) exact mass calculated for $[M+\bullet]^+$ ($C_{14}H_{24}O$) requires *m/z* 208.1827, found *m/z* 208.1822. $[\alpha]_D$ = +12.1 (c = 1.0, $CHCl_3$). Enantiopurity was determined by SFC analysis after reduction to the primary alcohol and acylation with 2-naphthoylchloride. (Chiralcel®OJH 5% Isocratic MeCN). t_S(minor) = 3.9 min. t_R(major) = 4.4 min.



(*R*)-9-Formyldodec-11-enyl benzoate (Table 4, entry 3): Prepared according to the general procedure from 9-formylnonyl benzoate (138 mg, 0.5 mmol) to afford a yellow oil. Purification on Iatrobeads (10–50% Et_2O/Pentanes) afforded (*R*)-9-formyldodec-11-enyl benzoate as a colorless oil (114 mg, 72% yield, 95% ee). IR (film) 3077, 2927, 2855, 2704, 1728, 1641, 1441, 993.1, 912.1, 721.4 cm^{-1}; ^1H NMR (300 MHz, acetone-d_6) δ 9.59 (d, *J* = 2.1 Hz, 1H, C**H**O), 7.99–8.04 (m, 2H, Ph), 7.59–7.66 (m, 1H, Ph), 7.47–7.54 (m, 2H, Ph), 5.69–5.84 (m, 1H, $C\mathbf{H}{=}CH_\mathbf{2}$), 4.97–5.10 (m, 2H, $CH{=}C\mathbf{H_2}$),

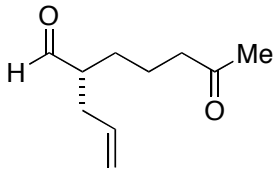
4.30 (t, J = 6.5 Hz, 2H, C**H**$_2$OBz), 2.30–2.46 (m, 2H, CHC**H**$_2$CH, C**H**CHO), 2.17–2.28 (m, 1H, CHC**H**$_2$CH), 1.20–1.82 (m, 14H, (C**H**$_2$)$_7$CH$_2$OBz); ^{13}C NMR (75 MHz, acetone-d_6) δ 204.7, 166.6, 136.5, 133.7, 131.4, 130.0, 129.3, 116.9, 65.4, 51.7, 33.5, 30.2, 29.9, 29.8, 29.3, 28.8, 27.4, 26.6. HRMS (EI+) exact mass calculated for $[M+\bullet]^+$ ($C_{20}H_{28}O_3$) requires m/z 316.2039, found m/z 316.2041. $[\alpha]_D$ = +5.8 (c = 1.0, $CHCl_3$). Enantiopurity was determined by SFC analysis after acetal formation with (*R,R)*-pentadiol of both (*R*)-9-formyldodec-11-enyl benzoate and (*S*)-9-formyldodec-11-enyl benzoate, separately. (Chiralcel®ODH 5–10% MeCN). (*R,R,S*) isomer t_r = 6.2 min and (*R,R,R*) isomer t_r = 6.9 min.

9-Formylnonyl Benzoate: A solution of 10-hydroxydecyl benzoate (2.9 g, 10.4 mmol) in dichloromethane (DCM) (40 mL) was cooled to 0 ºC and pyridinium chlorochromate (PCC) was added (3.4 g, 15.6 mmol). The reaction was warmed to ambient temperature and stirred for 4 h. The reaction was filtered through Florisil®, washed with Et_2O, and concentrated in vacuo. Purification by forced flow chromatography (30% Et_2O/Pentanes) afforded the title compound (1.58 g, 55% yield). IR (film) 2922, 2851, 1714, 1451, 1386, 1309, 1269, 1173, 1105, 1070, 1024, 708 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.77 (t, J = 1.83 Hz, 1H, C**H**O), 8.04–8.06 (m, 2H, *ortho*-phenyl), 7.54–7.58 (m, 1H, *para*-phenyl), 7.43–7.46 (m, 2H, *meta*-phenyl), 4.32 (t, J = 6.78 Hz, 2H, C**H**$_2$OC(O)Ph), 2.34–2.44 (m, 2H, C**H**$_2$CHO), 1.75–1.79 (m, 2H, C**H**$_2$CH$_2$OC(O)Ph), 1.62–1.65 (m, 2H, C**H**$_2$CH$_2$CHO), 1.33–1.47 (m, 10H, CH$_2$(C**H**$_2$)$_5$CH$_2$); ^{13}C NMR (125 MHz, acetone-d_6) δ 202.9, 166.7, 133.8, 131.5, 130.1,

129.4, 64.6, 44.3, 34.2, 30.1, 30.0, 29.9, 26.8, 25.7, 22.7. HRMS (EI+) exact mass calculated for $[M+H]^+$ ($C_{17}H_{25}O_3$) requires *m/z* 277.1804, found *m/z* 277.1795.

10-Hydroxydecyl benzoate: To a solution of 1,10-decanediol (5.0 g, 28.7 mmol) in 100 mL of tetrahydrofuran (THF) was added triethylamine (TEA) (4.8 mL, 34.4 mmol) and the reaction mixture was cooled to 0 ºC. Benzoyl chloride (1.7 mL, 14.3 mmol) was slowly added and the reaction mixture was stirred at 0 ºC for 45 min, then at ambient temperature overnight. The reaction was concentrated in vacuo until 15 mL of solvent remained, then filtered and washed with Et_2O. The filtrate was concentrated in vacuo and filtered a second time, and the filtrate purified by forced flow chromatography (30–100% Et_2O/Pentanes) (2.91 g, 73% yield). IR (film) 3362, 2922, 2851, 1717, 1451, 1383, 1312, 1269, 1173, 1110, 1067, 1024, 706 cm^{-1}; ^1H NMR (400 MHz, acetone-d_6) δ 8.04 (dd, *J* = 8.4 Hz, 1.2 Hz, 2H, *ortho*-phenyl), 7.62–7.66 (m, 1H, *para*-phenyl), 7.50–7.55 (m, 2H, *meta*-phenyl), 4.32 (t, *J* = 6.8 Hz, 2H, C**H**$_2$OC(O)Ph), 3.51–3.55 (m, 2H, C**H**$_2$OH), 3.38–3.44 (m, 1H, O**H**), 1.75–1.82 (m, 2H, C**H**$_2$CH$_2$OC(O)Ph), 1.31–1.54 (m, 14H, (C**H**$_2$)$_7$CH$_2$OH; ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.9, 133.0, 130.7, 129.7, 128.5, 65.3, 63.3, 33.0, 29.7, 29.6, 29.6, 29.4, 28.9 26.2, 25.9. HRMS (EI+) exact mass calculated for $[M+\bullet]^+$ ($C_{17}H_{26}O_3$) requires *m/z* 278.1882, found *m/z* 278.1879.[31]

[31] Mass spectra obtained from the Princeton University Mass Spectral Facility.



(*R*)-2-Allyl-6-oxoheptanal (Table 4, entry 4): Prepared according to the general procedure from 6-oxoheptanal[32] (128 mg, 1.0 mmol) to afford a yellow oil. Purification on Iatrobeads (20–60% Et_2O/Pentanes) afforded (*R*)-2-allyl-6-oxoheptanal as a colorless oil (121 mg, 72% yield, 87% ee). IR (film) 3418, 3079, 2931, 2862, 2720, 1718, 1642, 1416, 1361, 1164, 996.4, 919.5, 725.7 cm^{-1}; ^1H NMR (300 MHz, acetone-d_6) δ 9.60 (d, *J* = 2.1 Hz, 1H, C**H**O), 5.69–5.84 (m, 1H, C**H**=CH_2), 4.97–5.11 (m, 2H, CH=C$\mathbf{H_2}$), 2.46 (t, *J* = 6.9 Hz, 2H, C$\mathbf{H_2}$OCH_3), 2.32–2.44 (m, 2H, CHC$\mathbf{H_2}$CH, C**H**CHO), 2.18–2.28 (m, 1H, CHC$\mathbf{H_2}$CH), 2.06 (s, 3H, C$\mathbf{H_3}$), 1.39–1.68 (m, 4H, CH(C$\mathbf{H_2}$)$_\mathbf{2}$); ^{13}C NMR (75 MHz, acetone-d_6) δ 207.6, 204.6, 136.3, 117.0, 51.6, 43.4, 33.4, 29.6, 28.1, 21.6. HRMS (EI+) exact mass calculated for $[M+\bullet]^+$ ($C_{10}H_{16}O_2$) requires *m/z* 168.1150, found *m/z* 168.1149. $[\alpha]_D$ = –8.0 (c = 1.0, $CHCl_3$). Enantiopurity was determined by GLC analysis after acetal formation with (*R,R)*-pentadiol of both (*R*)-2-allyl-6-oxoheptanal and (*S*)-2-allyl-6-oxoheptanal, separately. Varian Chirasil-Dex-CB (25M x 0.25mm) column (115 ^{0}C isotherm); (*R,R,R*) isomer t_r = 93.5 min and (*R,R,S*) isomer t_r = 96.6 min.

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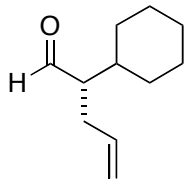
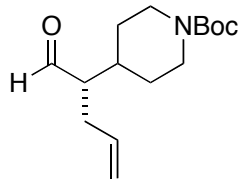
[32] Hong, B.-C.; Chen, F.-L.; Chen, S.-H.; Liao, J.-H.; Lee, G.-H. *Org. Lett.* **2005**, *7*, 557.



(*S*)-2-Cyclohexylpent-4-enal (Table 4, entry 5): Prepared according to the general procedure from 2-cyclohexylacetaldehyde (15.6 mg, 0.125 mmol) and methyl cyclohexanecarboxylate (19.9 mg, 0.140 mmol) as an internal standard (75% GC yield, 94% ee). Purification on Iatrobeads for characterization (10–50% Et_2O/Pentanes) afforded (*S*)-2-cyclohexylpent-4-enal as a volatile colorless oil containing Et_2O. IR (film) 3078, 2927, 2854, 2706, 1726, 1642, 1449, 994.1, 914.8, 851.6 cm^{-1}; ^1H NMR (300 MHz, acetone-d_6) δ 9.62 (d, *J* = 2.7 Hz, 1H, C**H**O), 5.68–5.81 (m, 1H, C**H**=CH_2), 4.94–5.08 (m, 2H, CH=C**H**$_2$), 2.36–2.47 (m, 1H, CHC**H**$_2$CH), 2.16–2.30 (m, 2H, CHC**H**$_2$CH, C**H**CHO), 1.60–1.78 and 1.02–1.33 (m, 11H, cyclohexyl); ^{13}C NMR (75 MHz, acetone-d_6) δ 205.0, 137.1, 116.5, 57.4, 38.4, 31.1, 30.8, 30.6, 27.0, 27.0, 26.8. HRMS (EI+) exact mass calculated for $[M+\bullet]^+$ ($C_{11}H_{18}O$) requires *m/z* 166.1358, found *m/z* 166.1361. $[\alpha]_D$ = +33.9 (c = 1.0, $CHCl_3$). Enantiopurity was determined by GLC using a Varian Chirasil-Dex-CB (25 m x 0.25 mm) column (100 °C isotherm); (*S*) isomer t_r = 36.3 min and (*R*) isomer t_r = 37.7 min.



***tert*-Butyl 4-((*S*)-1-formylbut-3-enyl)piperidine-1-carboxylate (Table 4, entry 6):** Prepared according to the general procedure from *tert*-butyl 4-(formylmethyl)piperidine-1-carboxylate[33] (114 mg, 0.5 mmol) to afford a yellow oil. Purification on Iatrobeads (25–50% Et_2O/Pentanes) afforded *tert*-butyl 4-((*S*)-1-formylbut-3-enyl)piperidine-1-carboxylate as a colorless oil (94 mg, 70% yield, 93% ee). IR (film) 2977, 2932, 2854, 2713, 1726, 1692, 1423, 1366, 1281, 1249, 1172, 918.0, 866.6, 769.3 cm^{-1}; ^1H NMR (300 MHz, acetone-d_6) δ 9.65 (d, *J* = 2.7 Hz, 1H, C**H**O), 5.69–5.84 (m, 1H, C**H**=CH_2), 4.98–5.10 (m, 2H, CH=C$\mathbf{H_2}$), 4.08 (bs, 2H, (C$\mathbf{H_a}H_b)_2$NBoc), 2.67 (bs, 2H, ($CH_a\mathbf{H_b}$)$_2$NBoc), 2.24–2.46 (m, 3H, CHC$\mathbf{H_2}$CH, C**H**CHO), 1.84–1.98 (m, 1H, C**H**CHCHO), 1.58–1.72 (m, 2H, (C$\mathbf{H_a}H_bCH_2)_2$NBoc), 1.41 (s, 9H, (C$\mathbf{H_3}$)$_3$), 1.13–1.31 (m, 2H, ($CH_a\mathbf{H_b}CH_2)_2$NBoc); ^{13}C NMR (75 MHz, acetone-d_6) δ 204.7, 154.8, 136.7, 116.9, 79.1, 56.5, 36.5, 30.8, 28.4. HRMS (EI+) exact mass calculated for $[M-H]^+$ ($C_{15}H_{24}NO_3$) requires *m/z* 266.1756, found *m/z* 266.1762. $[\alpha]_D$ = +7.8 (c = 1.0, $CHCl_3$). Enantiopurity was determined by SFC analysis after reduction to the primary alcohol and acylation with 2-naphthoylchloride. (Chiralcel®ODH 5–50% MeCN). t_R(major) = 5.9 min. t_S(minor) = 6.2 min.

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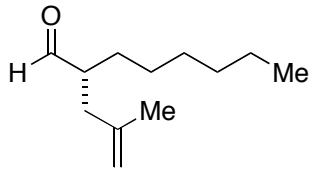
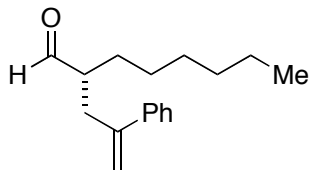
[33] Sato, T.; Okamoto, K.; Nakano, Y.; Uenishi, J.; Ikeda, M. *Heterocycles*, **2001**, *54*, 747.

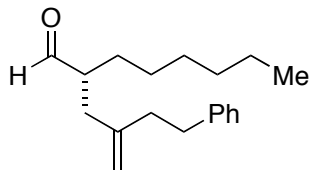


(*R*)-2-(2-Methylallyl)octanal (Table 3, entry 1): Prepared according to the general procedure from octanal (156 μL, 1.00 mmol) and methallyltrimethylsilane (440μL, 2.50 mmol) to afford a yellow oil. Purification on Iatrobeads (2–10% Et_2O/Pentanes) afforded (*R*)-2-(2-methylallyl)octanal as a colorless oil (160 mg, 88% yield, 91% ee). IR (film) 3075, 2929, 2857, 2703, 1729, 1651, 1456, 1377, 892.5, 724.0 cm^{-1}; ^{1}H NMR (300 MHz, acetone-d_6) δ 9.56 (d, *J* = 2.7 Hz, 1H, C**H**O), 4.74–4.77 (m, 1H, C=C**H**$_a$H$_b$), 4.70–4.72 (m, 1H, C=CH$_a$**H**$_b$), 2.35–2.52 (m, 2H, CHC**H**$_2$C=, C**H**CHO), 2.10–2.16 (m, 1H, CHC**H**$_2$C=), 1.70 (s, 3H, CC**H**$_3$), 1.40–1.66 (dm, 2H, C**H**$_2$(CH$_2$)$_4$), 1.22–1.34 (m, 8H, CH$_2$(C**H**$_2$)$_4$), 0.86 (t, *J* = 6.6 Hz, 3H, C**H**$_3$); ^{13}C NMR (75 MHz, acetone-d_6) δ 204.9, 143.7, 112.6, 50.1, 37.7, 32.3, 29.3, 27.5, 23.1, 22.3, 14.2. HRMS (EI+) exact mass calculated for $[M+\bullet]^+$ ($C_{12}H_{22}O$) requires *m/z* 182.1671, found *m/z* 182.1663. $[\alpha]_D$ = +14.5 (c = 1.0, $CHCl_3$). Enantiopurity was determined by GLC using a Varian Chirasil-Dex-CB (25 m x 0.25 mm) column (100 °C isotherm); (*S*) isomer t_r = 35.4 min and (*R*) isomer t_r = 36.1 min.



(*R*)-2-(2-Phenylallyl)octanal (Table 3, entry 2): Prepared according to the general procedure from octanal (156 μL, 1.00 mmol) and trimethyl(2-

phenylallyl)silane:[34] (476 mg, 2.50 mmol) to afford a yellow oil. Purification on Iatrobeads (3–30% Et_2O/Pentanes) afforded (*R*)-2-(2-phenylallyl)octanal as a colorless oil (213 mg, 87% yield, 90% ee). IR (film) 3082, 3057, 3025, 2955, 2929, 2857, 2710, 1727, 1628, 1600, 1574, 1495, 1456, 1378, 1303, 1076, 1028, 900.6, 778.7, 705.8 cm^{-1}; ^1H NMR (300 MHz, acetone-d_6) δ 9.58 (d, *J* = 2.7 Hz, 1H, C**H**O), 7.12–7.30 (m, 5H, **Ph**), 5.32 (d, *J* = 1.3 Hz, 1H, C=C**H**$_a$H$_b$), 5.13 (q, *J* = 1.3 Hz, 1H, C=CH$_a$**H**$_b$), 2.96 (ddd, *J* = 14.6 Hz, 7.4 Hz, 1.3 Hz, 1H, CHOCHC**H**$_a$H$_b$), 2.63 (ddd, *J* = 14.6 Hz, 6.9 Hz, 1.1 Hz, 1H, CHOCHCH$_a$**H**$_b$), 2.31–2.42 (m, 1H, C**H**CHO), 1.42–1.68 (m, 2H, CH_2(C**H**$_2$)$_4$), 1.18–1.34 (m, 8H, CH_2(C**H**$_2$)$_4$), 0.84 (t, *J* = 7.2 Hz, 3H, C**H**$_3$); ^{13}C NMR (75 MHz, acetone-d_6) δ 204.5, 147.0, 141.3, 129.2, 128.4, 127.0, 114.7, 50.4, 35.2, 32.2, 29.9, 29.0, 27.2, 23.1, 14.2. HRMS (EI+) exact mass calculated for $[M+\bullet]^+$ ($C_{17}H_{24}O$) requires *m/z* 244.1827, found *m/z* 244.1837. $[\alpha]_D$ = +13.4 (c = 1.0, $CHCl_3$). Enantiopurity was determined by SFC analysis after reduction to the primary alcohol. (Chiralcel®OJH 2–5% IPA). t_R(major) = 5.2 min. t_S(minor) = 6.1 min.



(*R*)-2-Hexyl-4-phenethyl-pent-4-enal (Table 3, entry 3): Prepared according to the general procedure from octanal (156 μL, 1.00 mmol) and trimethyl(2-methylene-4-phenylbutyl)silane[35] (546 mg, 2.50 mmol) to afford a yellow oil. Purification on

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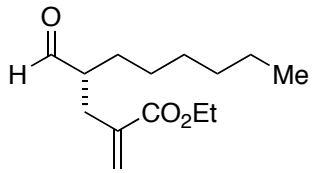
[34] Narayanan, B. A.; Bunnelle, W. H. *Tetrahedron Lett.* **1987**, *28*, 6261.

[35] Clark, J. S.; Dossetter, A. G.; Wong, Y. S.; Townsend, R. J.; Whittingham, W. G.; Russell, C. A. *J. Org. Chem*, **2004**, *69*, 3886.

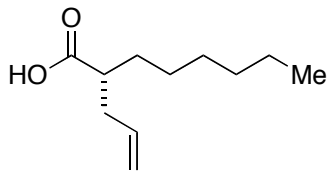
Iatrobeads (3–30% Et_2O/Pentanes) afforded (*R*)-2-hexyl-4-phenethyl-pent-4-enal as a colorless oil (209 mg, 77% yield, 88% ee). IR (film) 3085, 3027, 2955, 2929, 2857, 2708, 1727, 1645, 1604, 1496, 1454, 1077, 1031, 895.9, 747.2, 698.7 cm^{-1}; ^1H NMR (300 MHz, acetone-d_6) δ 9.57 (d, *J* = 2.9 Hz, 1H, C**H**O), 7.13–7.30 (m, 5H, **Ph**), 4.84 (app. d, *J* = 1.3 Hz, 1H, C=C**H**$_a$H$_b$), 4.79 (app. d, *J* = 1.1 Hz, 1H, C=CH$_a$**H**$_b$), 2.76 (dd, *J* = 8.2 Hz, 8.0 Hz, 2H, C**H**$_2$Ph), 2.14–2.57 (m, 5H, C**H**CHO, CHC**H**$_2$C=C, C**H**$_2$CH$_2$Ph), 1.38–1.68 (dm, 2H, C**H**$_2$(CH$_2$)$_4$), 1.20–1.38 (m, 8H, CH$_2$(C**H**$_2$)$_4$), 0.86 (t, *J* = 6.9 Hz, 3H, C**H**$_3$); ^{13}C NMR (75 MHz, acetone-d_6) δ 204.9, 147.2, 142.7, 129.1, 129.0, 126.5, 112.0, 50.2, 38.3, 36.1, 34.8, 32.3, 29.4, 27.5, 23.1, 14.2. HRMS (EI+) exact mass calculated for $[M+\bullet]^+$ ($C_{19}H_{28}O$) requires *m/z* 272.2140, found *m/z* 272.2129. $[\alpha]_D$ = +11.6 (c = 1.0, $CHCl_3$). Enantiopurity was determined by SFC analysis after reduction to the primary alcohol and acylation with 2-naphthoylchloride. (Chiralpak®ADH 2–25% IPA). t_S(minor) = 7.4 min. t_R(major) = 7.8 min.



(*R*)-Ethyl 4-formyl-2-methylenedecanoate (Table 3, entry 4): Prepared according to the general procedure from octanal (156 μL, 1.00 mmol) to afford a yellow oil. Purification on Iatrobeads (10–50% Et_2O/Pentanes) afforded (*R*)-ethyl 4-formyl-2-methylenedecanoate as a colorless oil (194 mg, 81% yield, 90% ee). IR (film) 2930, 2858, 2712, 1720, 1630, 1466, 1370, 1302, 1185, 1153, 1027, 948.7, 854.3, 818.8, 724.7 cm^{-1}; ^1H NMR (300 MHz, acetone-d_6) δ 9.58 (d, *J* = 2.7 Hz, 1H, C**H**O), 6.16 (d, *J* = 1.3

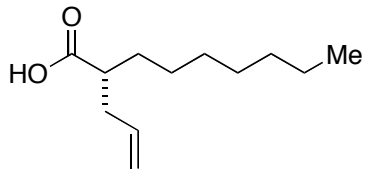
Hz, 1H, C=C**H**$_a$H$_b$), 5.66 (d, *J* = 1.3 Hz, 1H, C=CH$_a$**H**$_b$), 4.16 (q, *J* = 7.2 Hz, 2H, OCH$_2$CH$_3$), 2.64–2.73 (m, 1H, C**H**$_a$H$_b$C=CH$_2$), 2.47–2.58 (m, 1H, C**H**CHO), 2.37–2.45 (m, 1H, CH$_a$**H**$_b$C=CH$_2$), 1.38–1.72 (dm, 2H, C**H**$_2$(CH$_2$)$_4$), 1.26 (t, *J* = 7.2 Hz, 3H, OCH$_2$C**H**$_3$), 1.22–1.36 (m, 8H, CH$_2$(C**H**$_2$)$_4$), 0.86 (t, *J* = 6.6 Hz, 3H, C**H**$_3$); ^{13}C NMR (75 MHz, acetone-d$_6$) δ 204.3, 166.9, 139.2, 126.9, 61.1, 51.2, 32.2, 31.8, 29.9, 29.2, 27.4, 23.1, 14.3, 14.2. HRMS (EI+) exact mass calculated for [M-H]$^+$ (C$_{14}$H$_{23}$O$_3$) requires *m/z* 239.1647, found *m/z* 239.1659. $[\alpha]_D$ = +13.0 (c = 1.0, CHCl$_3$). Enantiopurity was determined by achiral GLC after acetal formation with (*R,R*)-pentanediol and (*S,S*)-pentanediol, separately. Hewlett Packard HP-1 (30 m x 0.32 mm) column (140 °C isotherm); (*R,R,R*) and (*S,S,S)* isomer t_r = 91.5 min and (*R,R,S*) and (*S,S,R)* isomer t_r = 93.7 min.

Determination of Absolute Stereochemistry



(*R*)-2-Allyloctanoic acid: To a flask containing (*R*)-2-allyloctanal (45 mg, 0.267 mmol, 91% ee) and dissolved in *tert*-butanol (800 μL) and water (300 μL) at 0 ºC was added sodium dihydrogenphosphate hydrate (9.2 mg, 0.067 mmol) followed by 2-methyl-2-butene (124 μL, 1.17 mmol). Separately, sodium chlorite (42 mg, 0.374 mmol) was dissolved in water (500 μL) and cooled to 0 ºC, and the solution added to the aldehyde solution. The reaction was allowed to warm to ambient temperature over 4 h. Saturated sodium sulfite (1.00 mL) was added and stirred vigorously 5 min. The reaction was

acidified to pH~2, extracted with Et_2O (3 x 25 mL), and dried over Na_2SO_4. Purification by forced flow chromatography on Iatrobeads (5–50% Et_2O/Pentanes) afforded a colorless oil (31 mg, 63% yield), which corresponded to the reported literature compound.[36] $[\alpha]_D$ = +12.7 (c = 1.0, EtOH), Lit. (*S*)-2-allyloctanoic acid $[\alpha]_D$ = –11.1 (c = 1.0, EtOH).



(*R*)-2-Allylnonanoic acid: Prepared according to the oxidation procedure for (*R*)-2-allyloctanoic acid from (*R*)-2-allylnonanal[37] (45 mg, 0.250 mmol, 91% ee). Purification by forced flow chromatography on Iatrobeads (5–50% Et_2O/Pentanes) afforded a colorless oil (37 mg, 76% yield). Spectral data for the title compound matched the reported literature compound.[38] $[\alpha]_D$ = +5.99 (c = 1.0, $CHCl_3$), Lit. (*S*)-2-allylnonanoic acid $[\alpha]_D$ = –8.1 (c = 2.78, $CHCl_3$).

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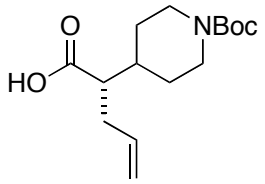
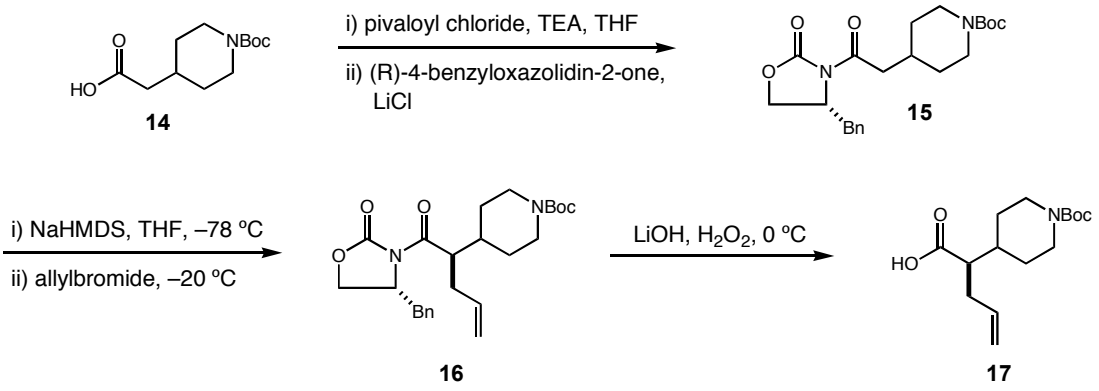
[36] Hasegawa, T.; Yamamoto, H. *Bull. Chem. Soc. Jpn.* **2000**, *73*, 423.

[37] (*R*)-2-Allylnonanal was prepared according to the general procedure from nonanal (132 mg, 73% yield, 91% ee).

[38] Expósito, A.; Fernández-Suárez, M.; Iglesias, T.; Muñoz, L.; Riguera, R. *J. Org. Chem.* **2001**, *66*, 4206.



(*S*)-2-(1-*tert*-Butoxycarbonyl)piperidin-4-yl)pent-4-enoic acid: Prepared according to the oxidation procedure for (*R*)-2-allyloctanoic acid from *tert*-butyl 4-((*S*)-1-formylbut-3-enyl)piperidine-1-carboxylate (52 mg, 0.194 mmol, 93% ee). The reaction was extracted with EtOAc (3 x 25 mL) in place of Et_2O (40 mg, 73% yield). IR (film) 3073, 2977, 2934, 2861, 1733, 1659, 1428, 1367, 1282, 1249, 1167, 1138, 993.8, 916.7, 866.4, 766.3 cm^{-1}; ^1H NMR (400 MHz, acetone-d_6) δ 5.74–5.85 (m, 1H, C**H**=CH_2), 4.96–5.10 (m, 2H, CH=C$\mathbf{H_2}$), 4.08 (bs, 2H, (C$\mathbf{H_a}H_b)_2$NBoc), 2.67 (bs, 2H, ($CH_a\mathbf{H_b}$)$_2$NBoc), 2.24–2.38 (m, 3H, CHC$\mathbf{H_2}$CH, C**H**CHO), 1.58–1.80 (m, 3H, (C$\mathbf{H_a}H_bCH_2)_2$NBoc, C**H**CHCHO), 1.41 (s, 9H, (C$\mathbf{H_3}$)$_3$), 1.10–1.32 (m, 2H, ($CH_a\mathbf{H_b}CH_2)_2$NBoc); ^{13}C NMR (Bruker Avance II 500, APT experiment, 125 MHz, acetone-d_6) δ 176.2, 155.8, 137.8, 117.6, 80.1, 52.1, 39.6, 35.1, 31.4, 29.4. HRMS (FAB+) exact mass calculated for $[M+H]^+$ ($C_{15}H_{26}NO_4$) requires *m/z* 284.1862, found *m/z* 284.1872. $[\alpha]_D$ = +12.23 (c = 1.0, EtOH).



(*R*)-2-(1-*tert*-Butoxycarbonyl)piperidin-4-yl)pent-4-enoic acid: *tert*-Butyl 4-(formylmethyl)piperidine-1-carboxylate[31] (500 mg, 2.2 mmol) was converted to the corresponding carboxylic acid **14** using the procedure described for (*R)*-2-allyloctanoic acid (473 mg, 88% yield).

The carboxylic acid **14** was converted to the 4-[2-((*R*)-4-benzyl-2-oxo-oxazolidin-3-yl)-2-oxo-ethyl]-piperidine-1-carboxylic acid *tert*-butyl ester **15** in like manner as described by Fuwa et al.[39] The carboxylic acid **14** (217 mg, 0.89 mmol) was dissolved in dry THF (7.0 mL) and TEA (248 μL, 1.78 mmol) and cooled to –78 ºC. Pivaloyl chloride (132 μL, 1.07 mmol) was added and the reaction was gradually warmed to 0 ºC over 90 min. (*R*)-4-benzyloxazolidin-2-one (158 mg, 0.89 mmol) was added followed by lithium chloride (113 mg, 2.67 mmol) and the reaction was warmed to ambient temperature and stirred overnight. The reaction was diluted with ethyl acetate (EtOAc) (25 mL) and washed with water (10 mL), brine (10 mL), dried over Na_2SO_4, filtered and concentrated in vacuo. Purification by forced flow chromatography (silica gel, 10–50% EtOAc/Hexanes) afforded **15** (215 mg, 60% yield).

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[39] Fuwa, H.; Okamura, Y.; Natsugari, H. *Tetrahedron* **2004**, *60*, 5341.

Allylation of **15** was performed in like manner to Evans et al.[40] **15** (172 mg, 0.427 mmol) was dissolved in THF (4 mL) and cooled to –78 ºC. $NaN(SiMe_3)_2$ (641 μL, 0.64 mmol) was added and the reaction was stirred for 1 h. Allylbromide (145 μL, 1.71 mmol) was then added and the reaction was warmed to –20 ºC over 6 h. A saturated NH_4Cl solution (5 mL) was added and the reaction stirred overnight. The reaction was diluted with EtOAc (25 mL) and washed with saturated aqueous NH4Cl (10 mL), and brine (10 mL), dried over Na_2SO_4, filtered and concentrated in vacuo. Purification by forced flow chromatography (silica gel, 5–50% EtOAc/hexanes) afforded 4-[(*R*)-1-((*R*)-4-benzyl-2-oxo-oxazolidine-3-carbonyl)-but-3-enyl]-piperidine-1-carboxylic acid *tert*-butyl ester **16** (60 mg, 32% yield).

The allylated oxazolidinone **16** was converted to the title compound **17** in like manner to the method of Stončius, et al.[41] **16** (40 mg, 0.09 mmol) was dissolved in THF (1 mL) and cooled to 0 ºC. H_2O_2 (30% aqueous, 44 μL, 0.39 mmol) was added dropwise followed by a solution of LiOH hydrate (8.4 mg, 0.20 mmol) in water (500 μL). Stirring was continued at 0 ºC for 3 h. Saturated Na_2SO_3 (500 μL) and saturated $NaHCO_3$ (500 μL) aqueous solutions were added and the mixture stirred vigorously allowing to warm to ambient temperature overnight. The reaction was acidified with 1N HCl to pH~2, and extracted with EtOAc (3 x 10 mL), dried over Na_2SO_4, filtered and concentrated in vacuo to afford the title compound **17** (20 mg, 80% yield). Spectral data was identical to the (*S*)-enantiomer synthesized above. $[\alpha]_D = -11.07$ (c = 1.0, EtOH).

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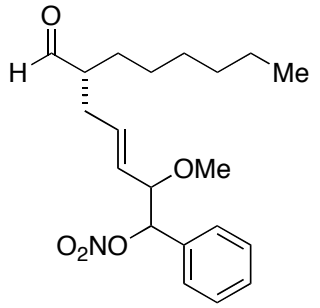
[40] Evans, D. A.; Ennis, M. D.; Mathre, D. J. *J. Am. Chem. Soc.* **1982**, *104*, 1737.

[41] Stončius, A.; Nahrwold, M.; Sewald N. *Synthesis* **2005**, *11*, 1829.

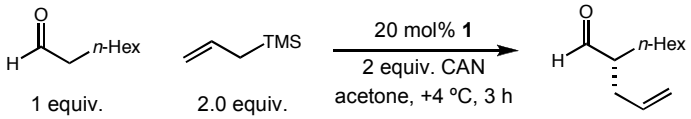


2-((*E*)-4-methoxy-5-nitrooxy-5-phenylpent-2-enyl)octanal: Prepared according to the general procedure, in acetone-d_6 with water (18mg, 1.0 mmol), from octanal (78 μl, 0.5 mmol) and (*trans, trans*-2-methoxy-3-phenylcyclopropyl)ethylene[26] to afford a yellow oil. Purification on Iatrobeads (5-50% Et_2O/Pentanes) afforded 2-((*E*)-4-methoxy-5-nitrooxy-5-phenylpent-2-enyl)octanal as a colorless oil. The product obtained is a 2:1:1:0.5 mixture of diastereomers. Data reported for the major diastereomer only. ^{1}H NMR (400 MHz, acetone-d_6) δ 9.59 (d, 1H, *J* = 2.4 Hz, C**H**O), 7.26–7.44 (m, 5H, Ph), 5.94 (d, 1H, *J* = 5.2, Hz, C**H**ONO_2), 5.66–5.73 (m, 1H, C**H**=CH), 5.35–5.42 (m, 1H, C**H**=CH), 4.04–4.09 (m, 1H, C**H**-OMe), 3.21 (s, 3H, OC**H**$_3$), 2.36–2.46 (m, 3H, C**H**CHO, C**H**$_2$CH=CH), 1.29–1.66 (m, 10H, (C**H**$_2$)$_5$CH$_3$) 0.87–0.89 (m, 3H, C**H**$_3$); ^{13}C NMR (150 MHz, acetone-d_6) δ 205.3, 135.9, 130.29, 130.0, 129.7, 129.4, 129.1, 87.5, 83.9, 57.2, 52.3, 34.7, 32.8, 32.5, 30.0, 28.0, 23.8, 14.9.

Appendix A

Additional Tables and Figures

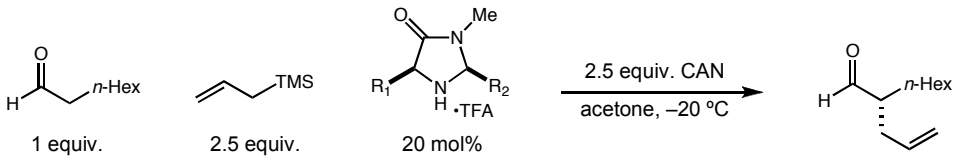
Table 5. Effect of Co-catalyst on the α-Allylation Reaction

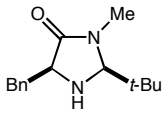
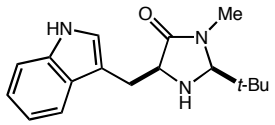
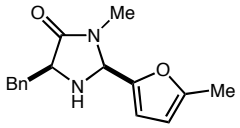
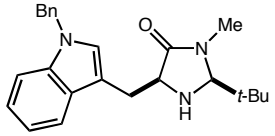
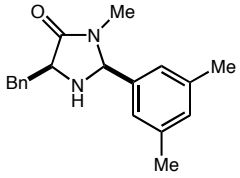
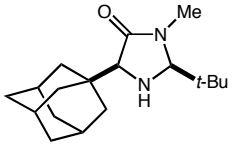


entry	Co-catalyst	pKa	% conversion[a]	% ee[b]
1	TfOH	–14	50	56
2	$HClO_4$	–10	49	75
3	HCl	–6.1	36	74
4	MsOH	–2.6	44	74
5	pTSA	–1.3	47	74
6	TFA	0.52	46	74
7	DCA	1.4	42	74
8	AcOH	4.8	40	74
9	4-NO_2-Phenol	7.1	40	75

(a) Conversion determined by GLC analysis relative to an internal standard (methyl cyclohexanecarboxylate). (b) Enantiomeric excess determined by GLC analysis (Varian Chirasil-Dex-CB).

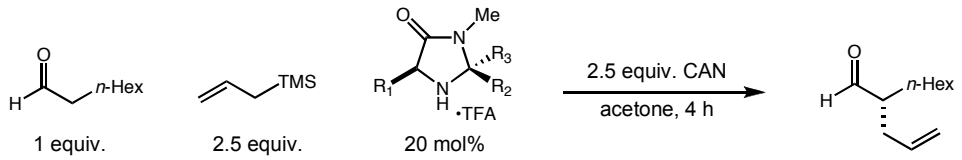
Table 6. Effect of Catalyst Architecture on the α-Allylation Reaction



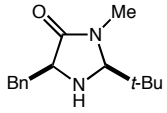
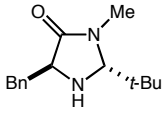
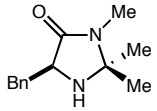
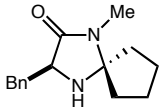
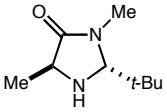
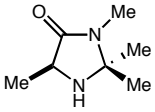
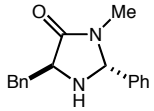
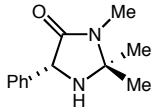
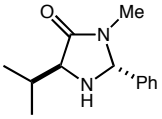
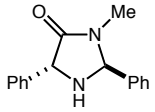
entry	catalyst	results[a]	entry	catalyst	results[a]
1		69% conv. 80% ee	6		26% conv. 38% ee
2		56% conv. 21% ee	7		23% conv. 46% ee
3		34% conv. 13% ee	8		54% conv. 78% ee

(a) After 18 h. Conversion determined by GLC analysis relative to an internal standard (methyl cyclohexanecarboxylate). Enantiomeric excess determined by GLC analysis (Varian Chirasil-Dex-CB).

Table 7. Effect of Catalyst Architecture on the α-Allylation Reaction

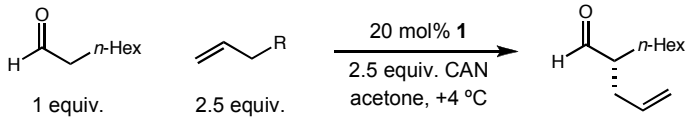


1 equiv. 2.5 equiv. 20 mol%

entry[a]	catalyst	+23 ºC	+4 ºC	entry[a]	catalyst	+23 ºC	+4 ºC
1		32% conv. 68% ee	58% conv. 74% ee	6		7% conv. 64% ee	6% conv. 81% ee
2		5% conv. 69% ee	6% conv. 84% ee	7		4% conv. 56% ee	3% conv. 81% ee
3		12% conv. 76% ee	13% conv. 82% ee	8		23% conv. 65% ee	17% conv. 71% ee
4			31% conv. 61% ee	9			10% conv. 44% ee
5			15% conv. 61% ee	10			10% conv. 43% ee

(a) Conversion determined by GLC analysis relative to an internal standard (methyl cyclohexanecarboxylate). Enantiomeric excess determined by GLC analysis (Varian Chirasil-Dex-CB). (b) After 4 h.

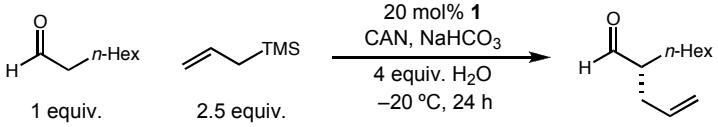
Table 8. Steric and Electronic Effects of the Allylsilane Component



entry	R	% conversion[a]	% ee[b]
1	$SiMe_3$	64	74
2	$SiMe_2Cl$	3	11
3	$SiMe_2CH_2Cl$	26	71
4	$SiMe_2$*p*-OMePh	58	71
5	Si(*i*-Pr)$_3$	trace	–
6	$SiPh_3$	12	37
7	$SiCl_3$	0	–
8	Si(OMe)$_3$	5	54
9	Si(OEt)$_3$	23	86

(a) After 2 h. Conversion determined by GLC analysis relative to an internal standard (methyl cyclohexanecarboxylate). (b) Enantiomeric excess determined by GLC analysis (Varian Chirasil-Dex-CB).

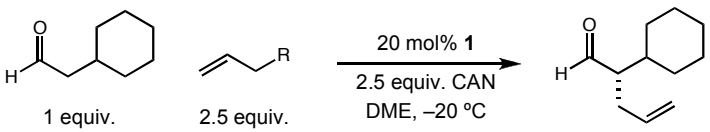
Table 9. Effect of Solvent with Water on the α-Allylation Reaction



entry	solvent (0.25M)	% conversion[a]	% ee[b]
1	DME	64	93
2	THF	80	83
3	Et_2O	23	86
4	EtOAc	53	82
5	DCM	32	66
6	$CHCl_3$	18	70
7	DMF	6	69

(a) Conversion determined by GLC analysis relative to an internal standard (methyl cyclohexanecarboxylate). (b) Enantiomeric excess determined by GLC analysis (Varian Chirasil-Dex-CB).

Table 10. Effect of Base Additive on the α-Allylation Reaction



1 equiv. 2.5 equiv.

entry	base	equiv.	% conversion[a]	% ee[b]
1	None	–	27	90
2	$NaHCO_3$	1.5	75	94
3	$NaHCO_3$	3.0	50	93
4	DTBP	1.5	36	92
5	DTBP	3.0	37	92

(a) After 24 h. Conversion determined by GLC analysis relative to an internal standard (methyl cyclohexanecarboxylate). (b) Enantiomeric excess determined by GLC analysis (Varian Chirasil-Dex-CB).