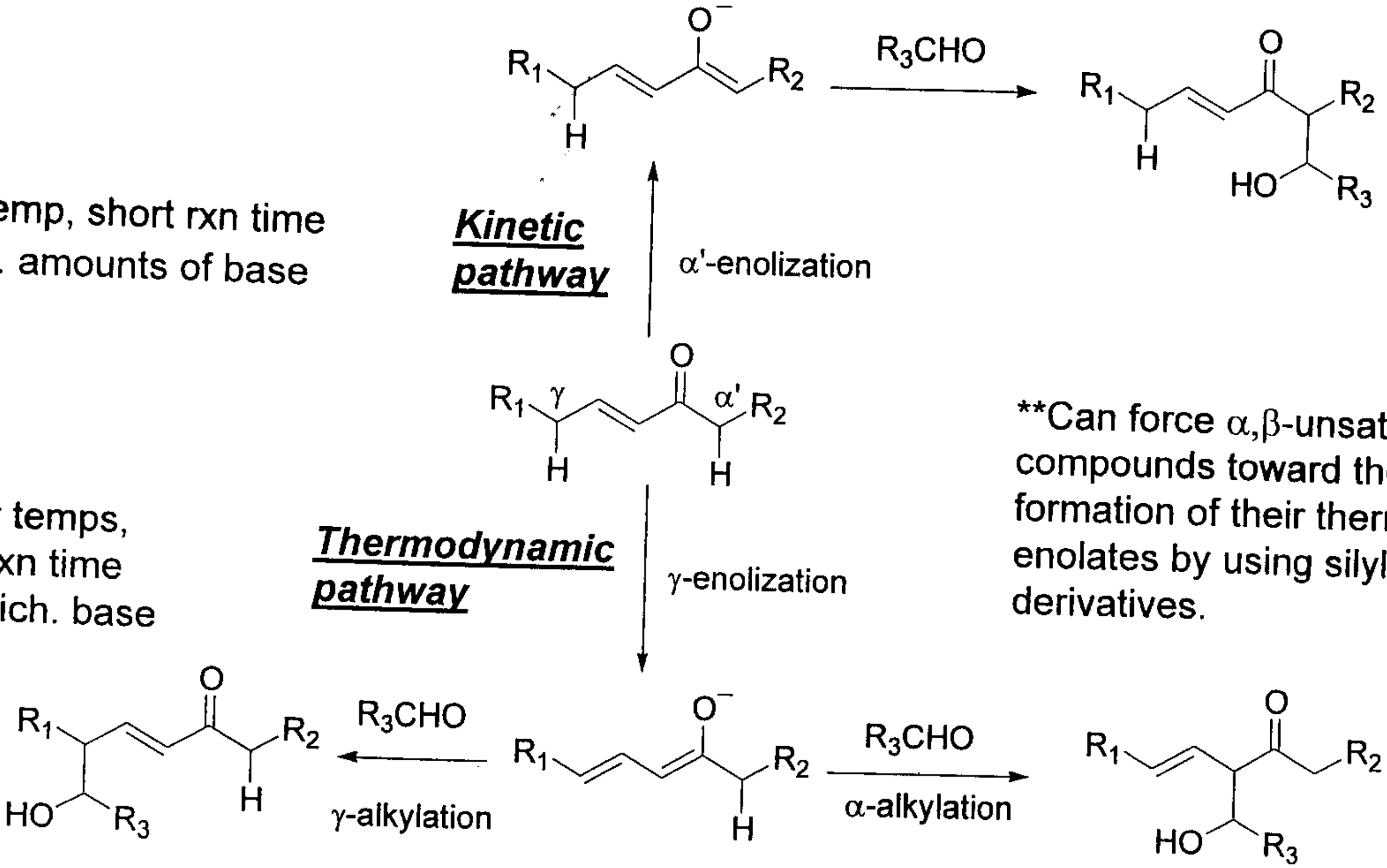
Lewis Base Activation of Lewis Acids: Vinylogous Aldol Reactions

Denmark, S; Beutner, G.L. *J.Am. Chem Soc.* **2003**, 125, 7800

James Mignone
July 5, 2003

Regiochemical Issues



Low temp, short rxn time
stoich. amounts of base

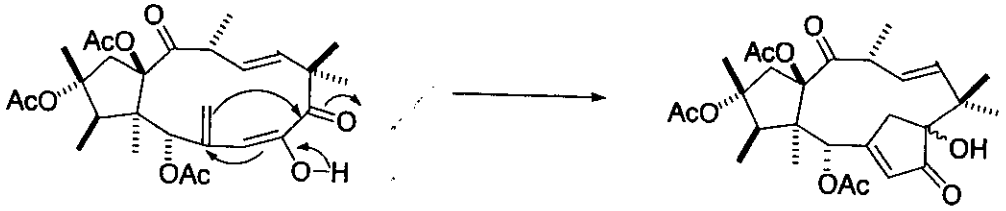
Higher temps,
Long rxn time
substoich. base

**Can force α,β-unsaturated compounds toward the formation of their thermo. enolates by using silyl derivatives.

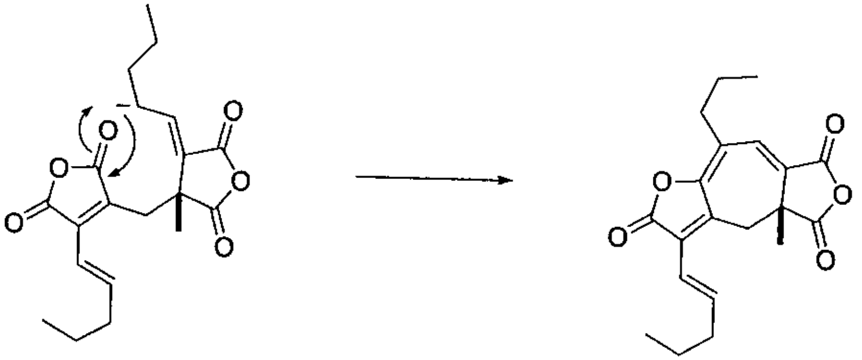
Casiraghi, G.; Appendino, G.; Rassu, G. *Chem Rev.* **2000**, 100, 1929.

Relevance of Vinylogous Aldol Additions in Natural Product Chemistry

A



B



An intramolecular vinylogous aldol reaction has been postulated to rationalize the carbon-carbon connectivity of euphoperfoliane **(A)** and the cycloheptadiene derivative of isoglaucanic acid **(B)**.

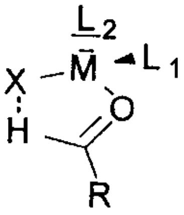
Casiraghi, G.; Appendino, G.; Rassu, G. *Chem Rev.* **2000**, 100, 1929.

Catalytic Enantioselective Aldol Addition

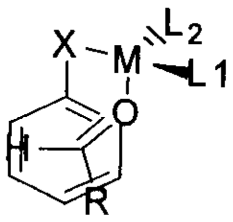
- High enantioselectivity for the catalyzed aldol reaction relies on effective channeling of the reactants through a transition state that is substantially lower in energy than competing diastereomeric transition-states.

- A high level of transition-state organizatioin is required, which can be achieved by:

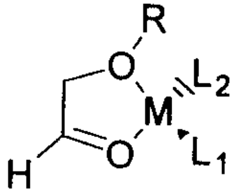
a) mode of binding ($\eta 1$ vs $\eta 2$) of the carbonyl group to the Lewis acid
b) the regiochemistry of complexation to the two available C=O lone pairs
c) establishment of a fixed diastereofacial bias.
d) the incorporation of stabilizing interactions



H-bonding



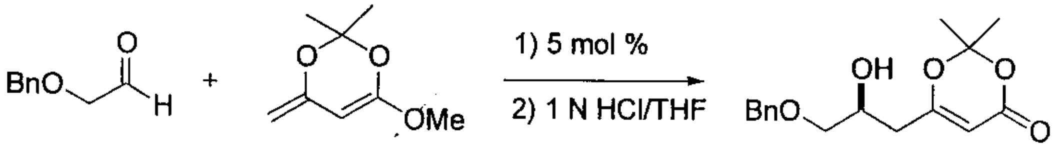
π-stacking



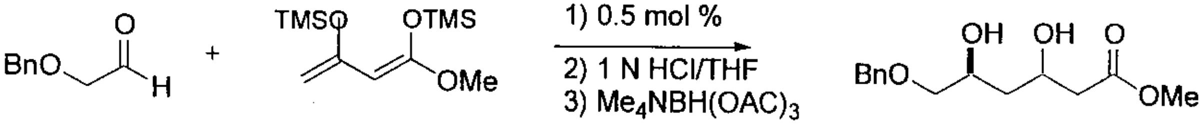
chelation

Evans, D.A.; Kozlowski, M.C. *J. Am. Chem. Soc.* **1999**, *121*, 669.

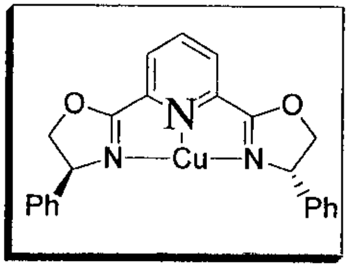
Catalytic Enantioselective Aldol Additions of Enolsilanes to (Benzoloxy)acetaldehyde using C_2-Symmetric Copper(II) Complexes.



92% ee, 94% yield



15:1 anti:syn, 97% anti ee
91 % yield diol

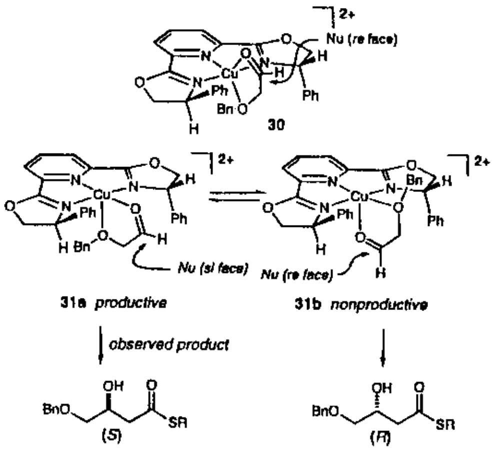


tridentate bis(oxazolinyl)-
pyridine (pybox)

Evans, D.A.; Kozlowski, M.C. *J. Am. Chem. Soc.* **1999**, *121*, 669.

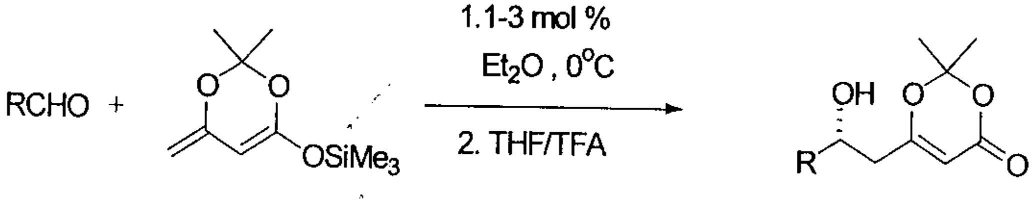
Catalyst Characterization and Stereochemical Models

The proposed requirement for chelation in the Cu(II) mediated acetaldehyde aldol reaction requires the formation of a five-coordinate Cu(II) catalyst-substrate complex.

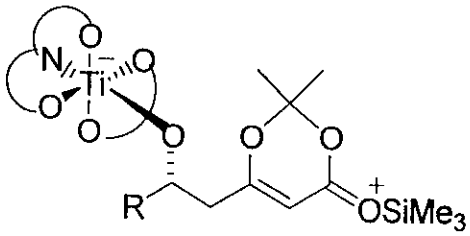


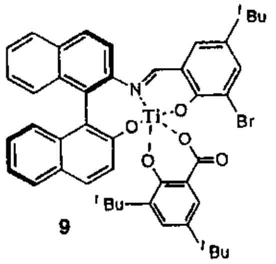
Evans, D.A.; Kozlowski, M.C. *J. Am. Chem. Soc.* **1999**, *121*, 669.

Catalytic, Enantioselective Dienolate Additions to Aldehydes: Preparation of Optically Active Acetoacetate Aldol Adducts.



Proposed Transition State

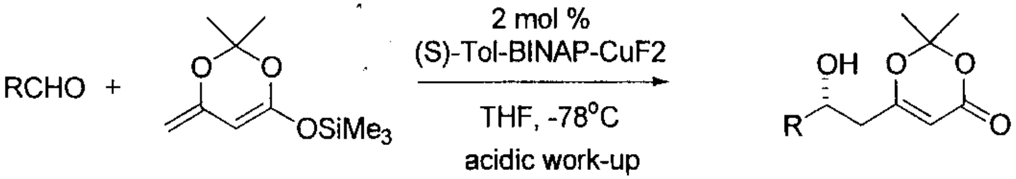




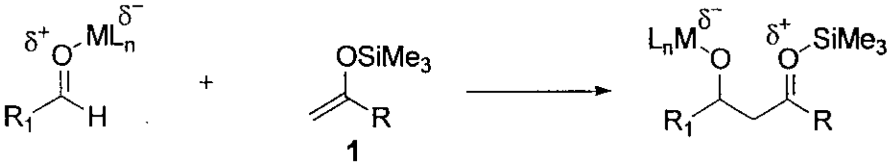
9 (1)

Catalytic, enantioselective aldehyde addition which employs O-SiMe$_3$ dienolates and as little as 1-3 mol % of the Ti(IV) complex.

This process proceeds by catalytic generation of a chiral metal dienolate initiated by as little as 2 mol % of the transition metal fluoride complex.

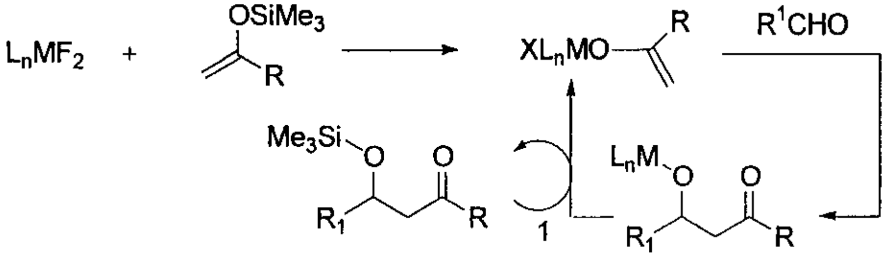


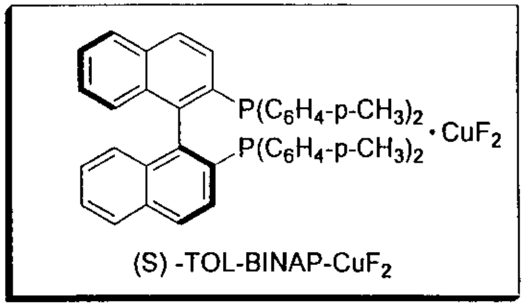
Common mechanism for catalytic enantioselective aldol addition reaction



versus

Carreira's mechanism





(S) -TOL-BINAP-CuF$_2$

Carreira, E.M.; Kruger, J. *J. Am. Chem. Soc.* **1998**, *120*, 837.

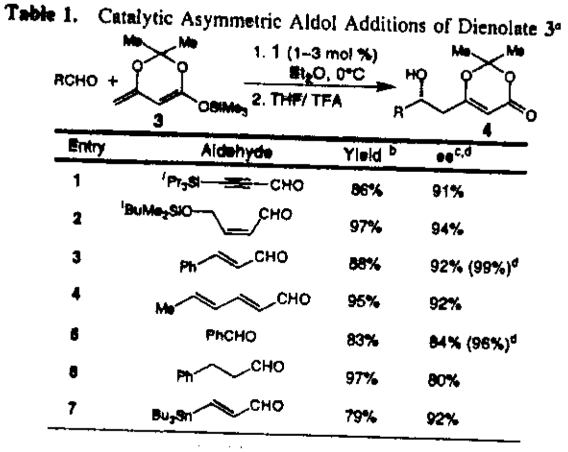
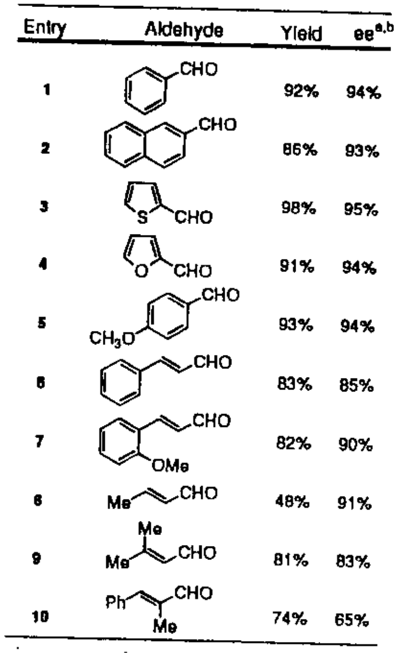
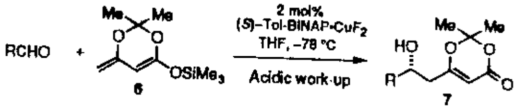


Table 1. Catalytic Asymmetric Aldol Additions of Dienolate 3[a]

Entry	Aldehyde	Yield [b]	ee[c,d]
1	$^{i}Pr_3Si$—≡—CHO	86%	91%
2	$^{t}BuMe_2SiO$ CHO	97%	94%
3	Ph CHO	88%	92% (99%)[d]
4	Me CHO	95%	92%
5	PhCHO	83%	84% (96%)[d]
6	Ph CHO	97%	80%
7	Bu_3Sn CHO	79%	92%

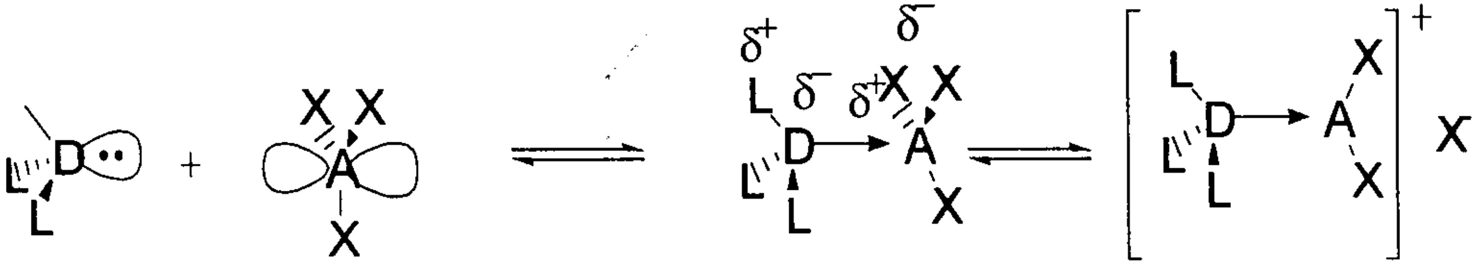


Entry	Aldehyde	Yield	ee[a,b]
1	CHO	92%	94%
2	CHO	86%	93%
3	S CHO	98%	95%
4	O CHO	91%	94%
5	CH_3O CHO	93%	94%
6	CHO	83%	85%
7	CHO OMe	82%	90%
8	Me CHO	48%	91%
9	Me Me CHO	81%	83%
10	Ph CHO Me	74%	65%



Carreira, E.M.; Kruger, J. *J. Am. Chem. Soc.* **1998**, *120*, 837.

Lewis Base Activation of Lewis Acids: Catalytic Enantioselective Allylation and Propargylation of Aldehydes



Lewis Base

Lewis Acid

increased negative charge

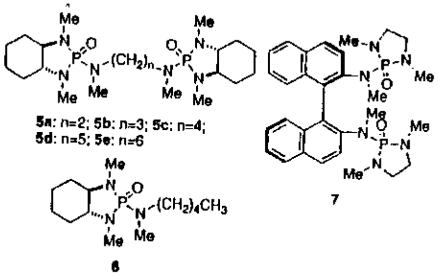
increased positive charge

By the use of a chiral Lewis base, a highly active and chirally modified Lewis acid is generated.

Denmark investigated the use of chiral phosphoramide as the Lewis base and $SiCl_4$ as the achiral Lewis acid.

Denmark, S.E.; Wynn, T. *J. Am. Chem. Soc.* **2001**, *123*, 6199.

Denmark utilized bisphophoramides to increase the effective concentration of the second catalyst molecule.



5a: n=2; **5b**: n=3; **5c**: n=4; **5d**: n=5; **5e**: n=6

6

7

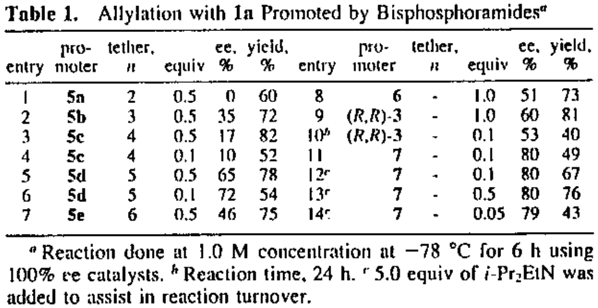
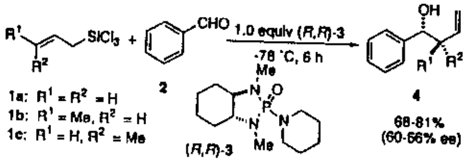


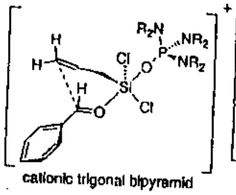
Table 1. Allylation with **1a** Promoted by Bisphosphoramides[a]

entry	promoter	tether, *n*	equiv	ee, %	yield, %	entry	promoter	tether, *n*	equiv	ee, %	yield, %
1	**5a**	2	0.5	0	60	8	**6**	-	1.0	51	73
2	**5b**	3	0.5	35	72	9	(*R*,*R*)-**3**	-	1.0	60	81
3	**5c**	4	0.5	17	82	10[b]	(*R*,*R*)-**3**	-	0.1	53	40
4	**5c**	4	0.1	10	52	11	**7**	-	0.1	80	49
5	**5d**	5	0.5	65	78	12[c]	**7**	-	0.1	80	67
6	**5d**	5	0.1	72	54	13[c]	**7**	-	0.5	80	76
7	**5e**	6	0.5	46	75	14[c]	**7**	-	0.05	79	43

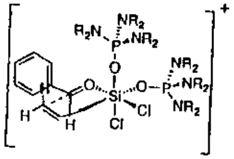
[a] Reaction done at 1.0 M concentration at −78 °C for 6 h using 100% ee catalysts. [b] Reaction time, 24 h. [c] 5.0 equiv of *i*-Pr_2EtN was added to assist in reaction turnover.

Denmark, S.E.; Fu, F. *J. Am. Chem. Soc.* **2000**, 122, 12021.





cationic trigonal bipyramid



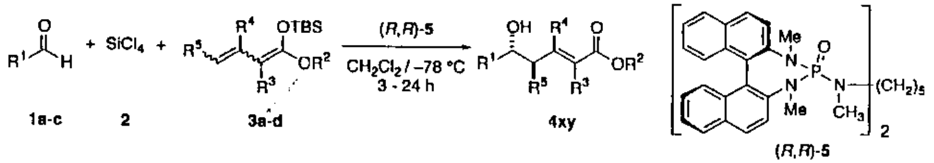
cationic octahedron

The trigonal bipyramidal TS is less enatioselective than the octahedral TS due to the diminished influence of the singular chiral promoter.

Denmark, S.E.; Fu, F. *J. Am. Chem. Soc.* **2000**, 122, 12021.

Lewis Base Activation of Lewis Acids. Vinylogous Aldol Reactions

Table 1. Vinylogous Aldol Reactions of Simple, Ester-Derived Dienolates **3a–d** with Aldehydes **1a–c**



entry	dienolate	R¹	R²	R³	R⁴	R⁵	product	yield, %[a]	γ/α[b]	dr[b]	er[c]
1	**3a**[d]	Ph (**1a**)	Et	H	H	H	**4aa**	89[e]	>99:1		99:1
2	**3a**[d]	PhCH=CH (**1b**)	Et	H	H	H	**4ab**	84[e]	>99:1		98:2
3	**3a**[f]	$PhCH_2CH_2$ (**1c**)	Et	H	H	H	**4ac**	68[g]	>99:1		95:5
4	**3b**[d]	Ph (**1a**)	Me	Me	H	H	**4ba**	93[e]	>99:1		99.5:0.5
5	**3b**[d]	PhCH=CH (**1b**)	Me	Me	H	H	**4bb**	88	>99:1		99.5:0.5
6	**3b**[f]	$PhCH_2CH_2$ (**1c**)	Me	Me	H	H	**4bc**		ND		ND
7	**3c**[d]	Ph (**1a**)	Et	H	Me	H	**4ca**	91[e]	>99:1		96:4
8	**3c**[d]	PhCH=CH (**1b**)	Et	H	Me	H	**4cb**	97[h]	>99:1		94:6
9	**3c**[f]	$PhCH_2CH_2$ (**1c**)	Et	H	Me	H	**4cc**	73	>99:1		97.5:2.5
10	**3d**[d]	Ph (**1a**)	*t*-Bu	H	H	Me	**4da**	92[i]	99:1	>99:1	94.5:5.5
11	**3d**[d]	PhCH=CH (**1b**)	*t*-Bu	H	H	Me	**4db**	71	99:1	>99:1	91:9
12	**3d**[f]	$PhCH_2CH_2$ (**1c**)	*t*-Bu	H	H	Me	**4dc**		ND	ND	ND

- Reaction is favored at the less substituted γ-position
- The resulting enolate was exclusively E configuration

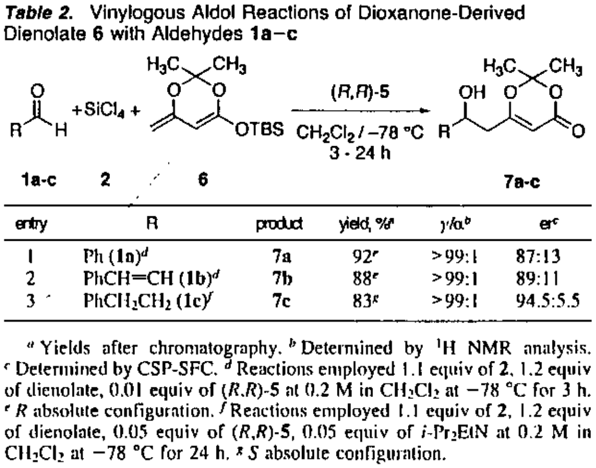


Table 2. Vinylogous Aldol Reactions of Dioxanone-Derived Dienolate **6** with Aldehydes **1a–c**

entry	R	product	yield, %^{a}	γ/α^b	er^c
1	Ph (**1a**)^d	**7a**	92^e	>99:1	87:13
2	PhCH=CH (**1b**)^d	**7b**	88^e	>99:1	89:11
3	$PhCH_2CH_2$ (**1c**)^f	**7c**	83^g	>99:1	94.5:5.5

[a] Yields after chromatography. [b] Determined by ^1H NMR analysis. [c] Determined by CSP-SFC. [d] Reactions employed 1.1 equiv of **2**, 1.2 equiv of dienolate, 0.01 equiv of (*R*,*R*)-**5** at 0.2 M in CH_2Cl_2 at −78 °C for 3 h. [e] *R* absolute configuration. [f] Reactions employed 1.1 equiv of **2**, 1.2 equiv of dienolate, 0.05 equiv of (*R*,*R*)-**5**, 0.05 equiv of *i*-Pr_2EtN at 0.2 M in CH_2Cl_2 at −78 °C for 24 h. [g] *S* absolute configuration.

The observed trend in enantioselectivity is opposite to that observed for ester derived dienolates.

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Conclusion

- Evans and Carreria used Ti(IV) and Cu(II) complexes to perform catalytic and highly regio-and enantioselective vinylogous aldol reactions.

-The generation of chirally modified and activated Lewis acids by Lewis base-promoted ionization of a weak Lewis acid is a highly enantioselective route to vinylogous aldol reactions.

-<u>Future work</u>

Extend this method to ketone and aldehyde-derived dienol ethers.

Apply this catalyst to other carbon-carbon bond forming reactions.