Catalytic Enantioselective Construction of All-Carbon Quaternary Stereocenters: Synthetic and Mechanistic Studies of the C-Acylation of Silyl Ketene Acetals

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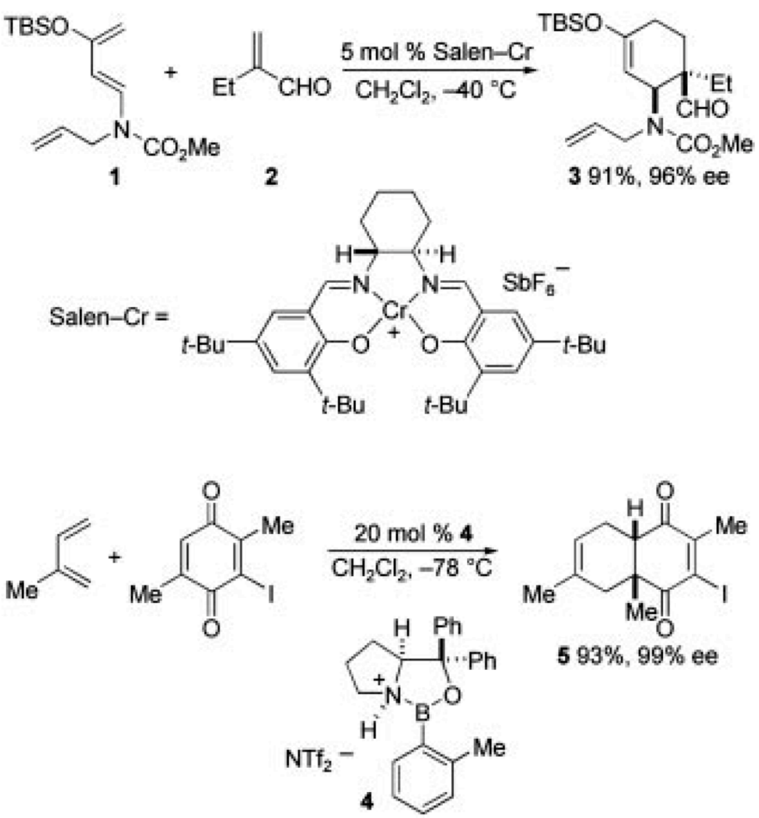
JACS, **2005**, *127*, 5604

Catalytic Asymmetric Synthesis of All-Carbon Quaternary Stereocenters

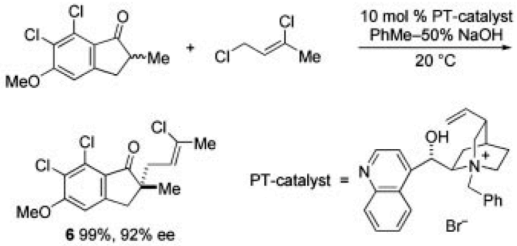
- While the development of asymmetric oxidation and reduction has become well developed, the same can not be said for the synthesis of all-carbon quaternary stereocenters.
- Some general methods for constructing these centers are Diels-Alder reactions, combinations of chiral carbon nucleophiles with carbon electrophiles or chiral allylmetal electrophiles with carbon nucleophiles, intramolecular Heck reactions and cyclopropanations

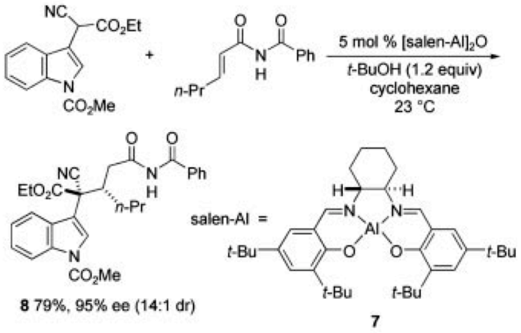


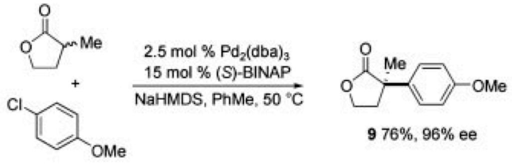
Proc. Natl. Acad. Sci. U.S.A., **2004,** 5363
JACS, **124**, 4628
JACS, **125,** 6388

Catalytic Asymmetric Synthesis of All-Carbon Quaternary Stereocenters continued

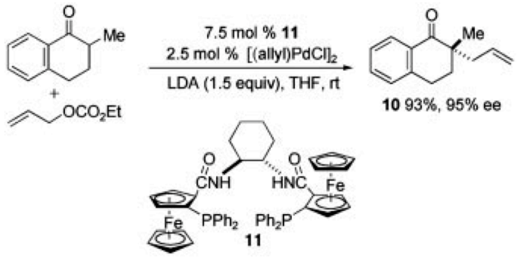
Reactions of Chiral Carbon Nucleophiles with Carbon Electrophiles

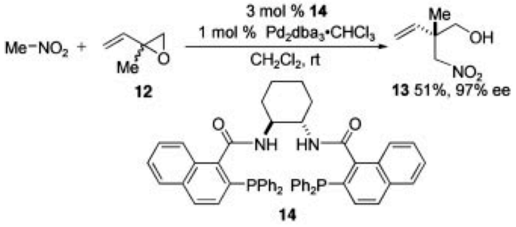






Reactions of Chiral Allylmetal Electrophiles with Carbon Nucleophiles

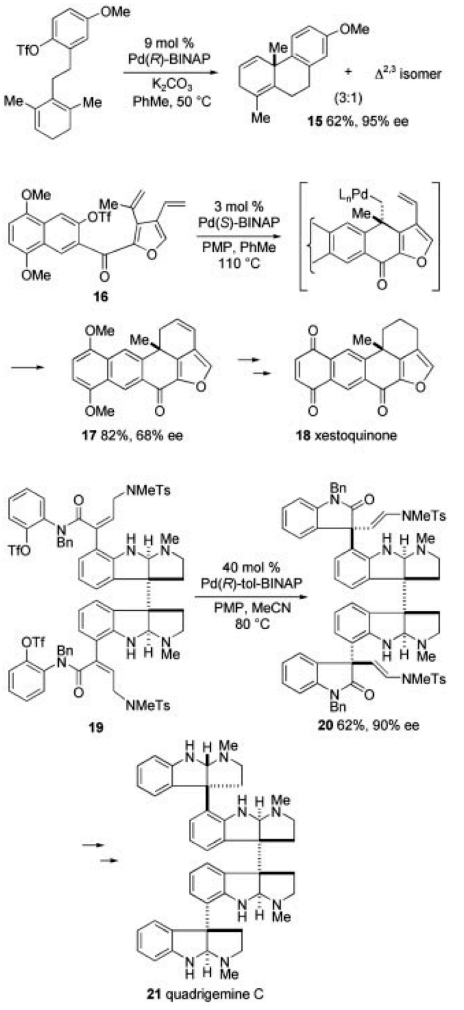




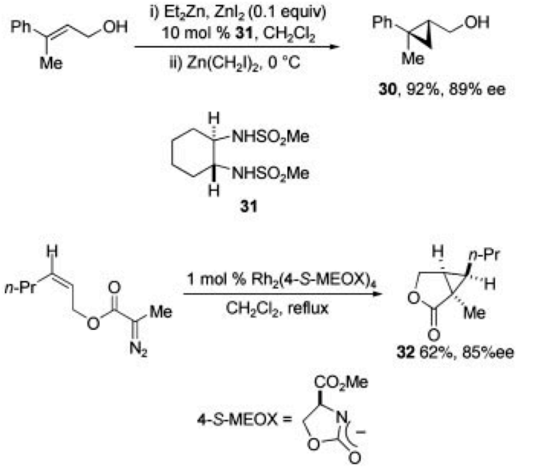
*Angew. Chem. Int. Ed.,***25,** 476
JACS, **125**, 11204
Acc. Chem. Res. **36,** 234
Org. Lett. **3**, 149
JACS **123,** 12907

Catalytic Asymmetric Synthesis of All-Carbon Quaternary Stereocenters continued

Intramolecular Heck Reactions



Cyclopropanation



J. Org. Chem. **60**, 4322
JACS, **118**, 10766
JACS, **124,** 9008
J. Org. Chem. **62**, 584
Tet. Asym. **6**, 2157

Earlier Work in this Area in the Fu Group

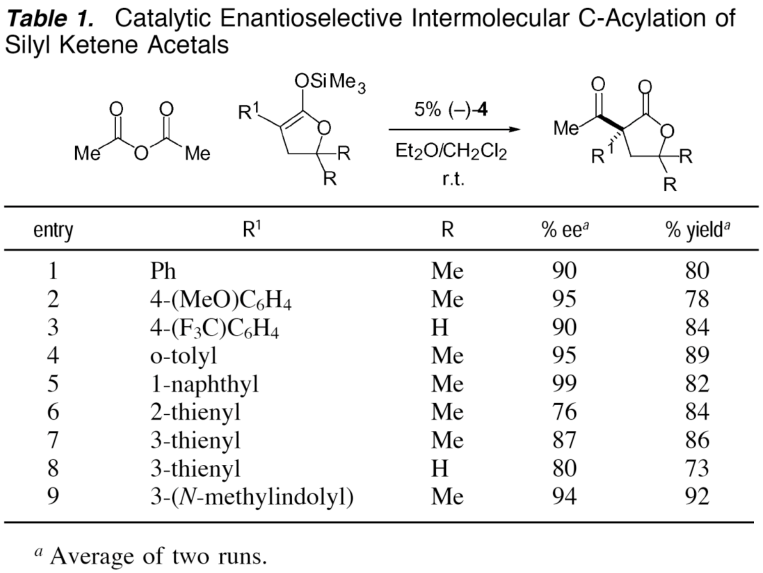
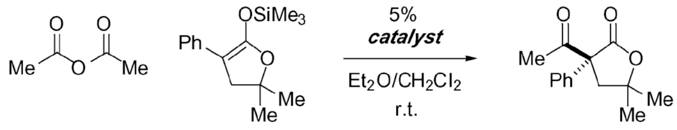


Table 1. Catalytic Enantioselective Intermolecular C-Acylation of Silyl Ketene Acetals

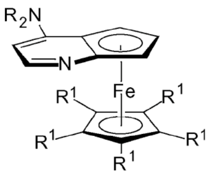
entry	R^1	R	% ee[a]	% yield[a]
1	Ph	Me	90	80
2	4-(MeO)C_6H_4	Me	95	78
3	4-(F_3C)C_6H_4	H	90	84
4	o-tolyl	Me	95	89
5	1-naphthyl	Me	99	82
6	2-thienyl	Me	76	84
7	3-thienyl	Me	87	86
8	3-thienyl	H	80	73
9	3-(*N*-methylindolyl)	Me	94	92

[a] Average of two runs.



(2)

catalyst:	(–)-**1**	40% ee
	(–)-**2**	33% ee
	(–)-**3**	87% ee
	(–)-**4**	90% ee



NR_2 = dimethylamino	R^1 = Me	(–)-**1**
pyrrolidino	Me	(–)-**2**
dimethylamino	Ph	(–)-**3**
pyrrolidino	Ph	(–)-**4**

JACS, **2003,** *125,* 4050

Earlier Work in this Area in the Fu Group continued

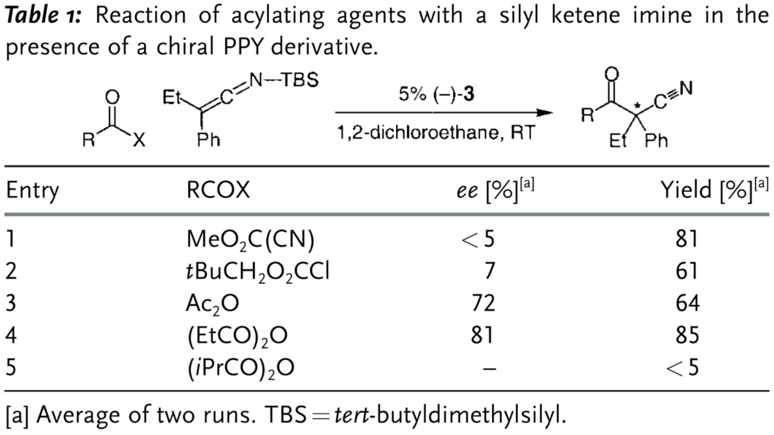


Table 1: Reaction of acylating agents with a silyl ketene imine in the presence of a chiral PPY derivative.

Entry	RCOX	*ee* [%][a]	Yield [%][a]
1	MeO$_2$C(CN)	< 5	81
2	*t*BuCH$_2$O$_2$CCl	7	61
3	Ac$_2$O	72	64
4	(EtCO)$_2$O	81	85
5	(*i*PrCO)$_2$O	–	< 5

[a] Average of two runs. TBS = *tert*-butyldimethylsilyl.

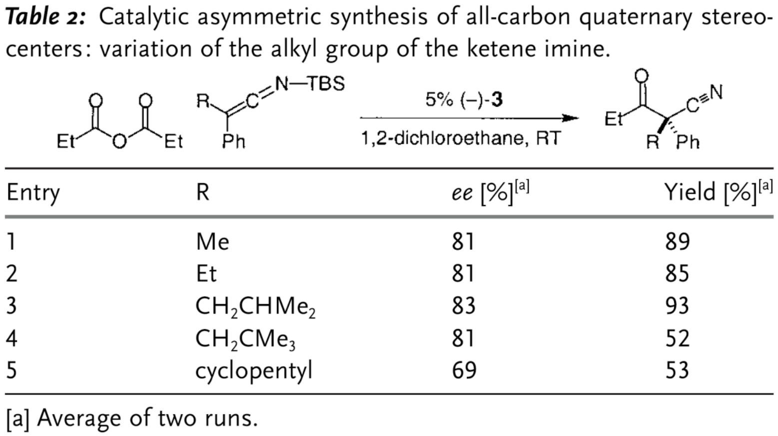


Table 2: Catalytic asymmetric synthesis of all-carbon quaternary stereocenters: variation of the alkyl group of the ketene imine.

Entry	R	*ee* [%][a]	Yield [%][a]
1	Me	81	89
2	Et	81	85
3	CH$_2$CHMe$_2$	83	93
4	CH$_2$CMe$_3$	81	52
5	cyclopentyl	69	53

[a] Average of two runs.

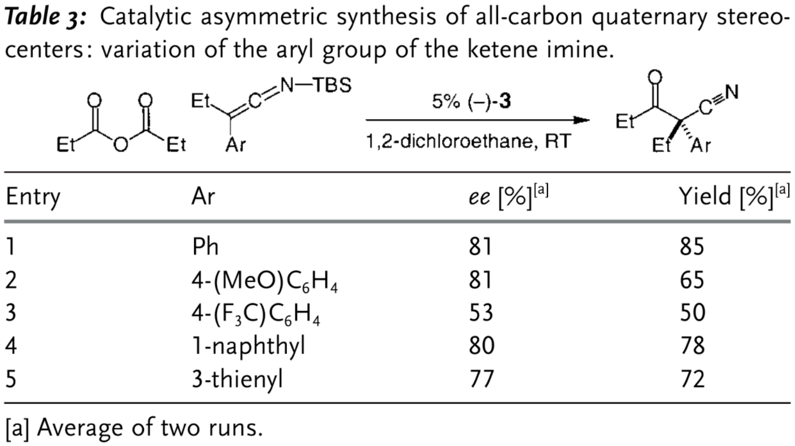
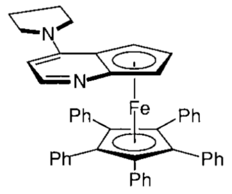


Table 3: Catalytic asymmetric synthesis of all-carbon quaternary stereocenters: variation of the aryl group of the ketene imine.

Entry	Ar	*ee* [%][a]	Yield [%][a]
1	Ph	81	85
2	4-(MeO)C$_6$H$_4$	81	65
3	4-(F$_3$C)C$_6$H$_4$	53	50
4	1-naphthyl	80	78
5	3-thienyl	77	72

[a] Average of two runs.



(–)-**3**

Angew. Chem. Int. Ed. **2005,** *44*, 949

Current Paper: Catalytic Enantioselective Construction of All-Carbon Quaternary Centers using Acyclic Silyl Ketene Acetals

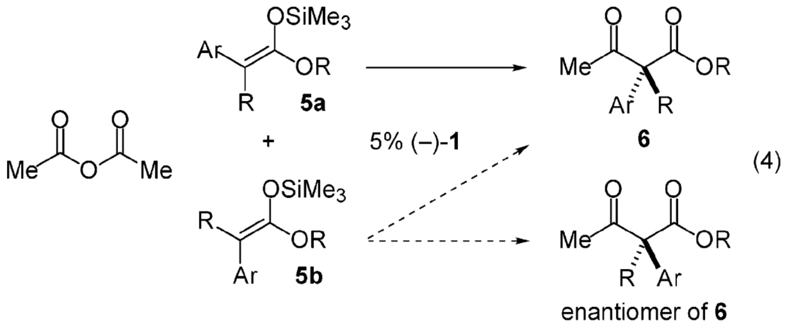
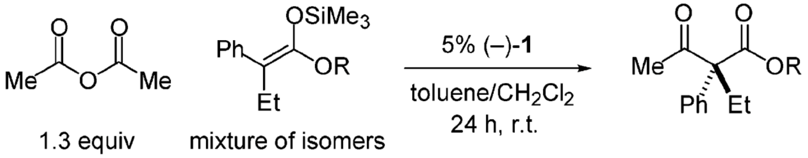
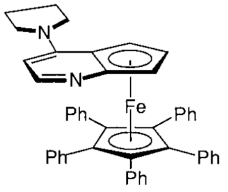


Table 1. Catalytic Asymmetric C-Acylations of Acyclic Silyl Ketene Acetals: Effect of the R Group of the Ester on Enantioselectivity[a]



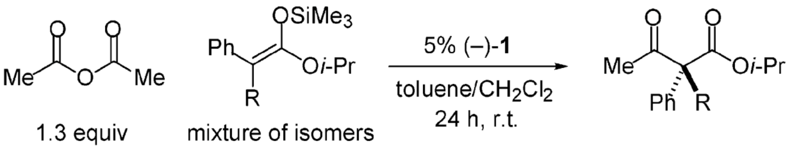
entry	R	isomer ratio	% ee	% yield
1	Me	1.5/1	70	87
2	CH_2CMe_3	1.1/1	79	75
3	*i*-Pr	1.8/1	85	92
4	*i*-Bu	1.5/1	93	47

[a] All data are the average of two runs.



(–)-**3**

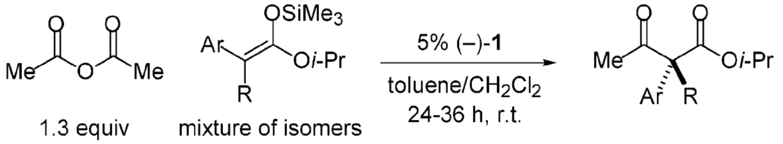
Table 2. Catalytic Asymmetric C-Acylations of Acyclic Silyl Ketene Acetals: Scope with Respect to the Alkyl Substituent[a]

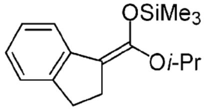


entry	R	isomer ratio	% ee	% yield
1	Me	1.8/1	69	54
2	Et	1.8/1	85	92
3	*i*-Bu	3.3/1	85	82
4	*i*-Pr	1.7/1	97	45

[a] All data are the average of two runs.

Table 3. Catalytic Asymmetric C-Acylations of Acyclic Silyl Ketene Acetals: Scope with Respect to the Aryl Substituent[a]



entry	Ar	R	isomer ratio	% ee	% yield
1	Ph	Et	1.8/1	85	92
2	6-(MeO)-2-naphthyl	Me	1.5/1	90	92
3	4-(MeO)C_6H_4	Et	1.4/1	90	83
4	4-(F_3C)C_6H_4	Et	2.1/1	92	96
5[b]	2-thienyl	Et	10/1	73	68
6[c]			1.4/1	81	82

[a] All data are the average of two runs. [b] The TBS-substituted silyl ketene acetal was employed. [c] CH_2Cl_2 was employed as the solvent.

Current Paper: Catalytic Cycle and Mechanistic Considerations

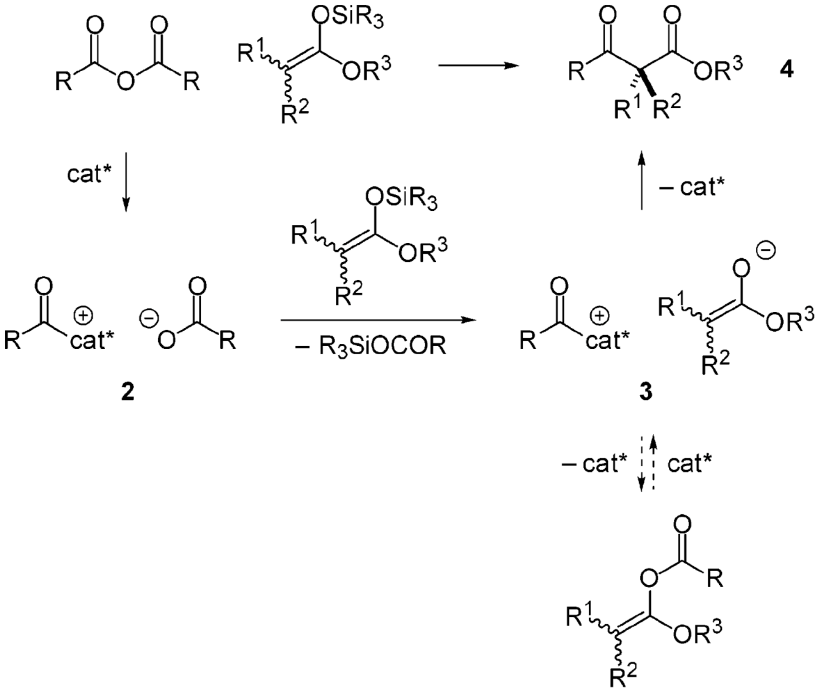


Figure 1. Possible Pathway for the Catalytic Asymmetric C−Acylation of Silyl Ketene Acetals: Dual Activation of the Nucleophile and the Electrophile.

Current Paper: Catalytic Cycle and Mechanistic Considerations

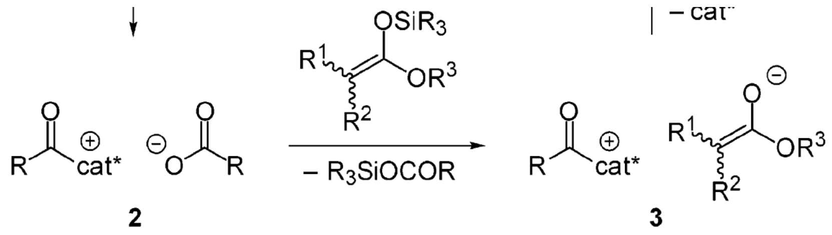
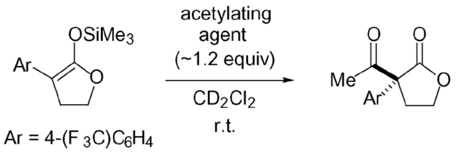
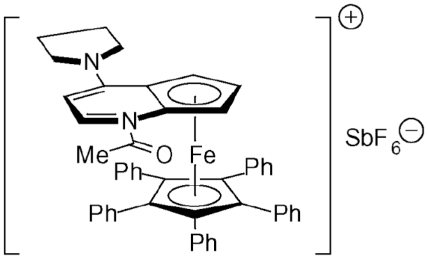


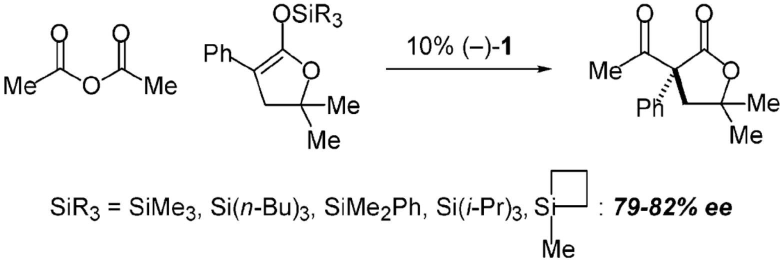
Table 2. Evidence for Dual Activation: Reactivity of a Silyl Ketene Acetal toward Several Potential Acetylating Agents



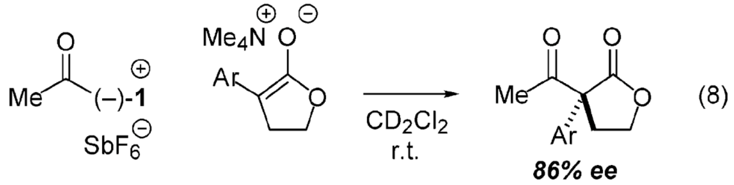
entry	acetylating agent	$t_{1/2}$ for reaction
1	Ac$_2$O	<2% conversion (60 h)
2	Ac$_2$O; 5% (−)-**4**	0.3 h
3	(+)-**9**	<2% conversion (60 h)
4	Ac$_2$O; 5% [Me$_4$N]OAc	<0.1 h



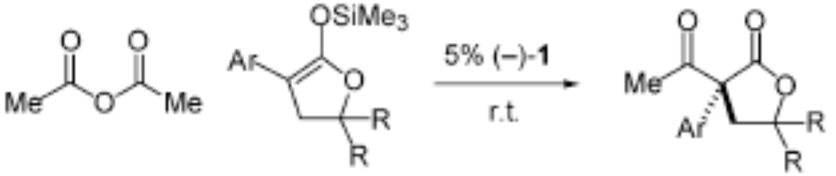
(–)-**9**



SiR$_3$ = SiMe$_3$, Si(n-Bu)$_3$, SiMe$_2$Ph, Si(i-Pr)$_3$, Si(Me) : ***79-82% ee***

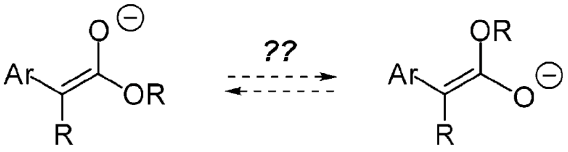


Current Paper: Catalytic Cycle and Mechanistic Considerations

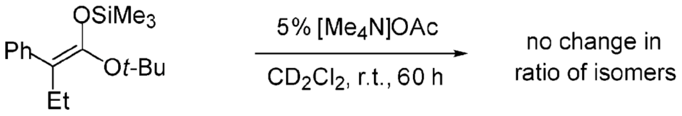


(3)

76-99% ee
(9 examples)



8a **8b**



Experiment 1: 1.6/1 mixture of isomers
Experiment 2: 2.6/1 mixture of isomers

-The minor isomer of the mixture was determined to be the more reactive isomer of the mixture.
-The %ee of the product remained constant with time throughout the reaction.
-These two points have lead to the conclusion that the reaction proceeds through an open transition state that uses the aryl and alkyl group for stereodifferentiation.

Conclusions

- The Fu group has developed an effective catalyst for the formation of all-carbon quaternary stereocenters through C-acylation of silyl ketene acetals.
- Furthermore, they have shed light on the mechanism and catalytic cycle of the reaction.
- Currently, the methodology is limited to silyl ketene acetals bearing an aryl group. The scope of this reaction should be expanded to remove the aryl requirement.