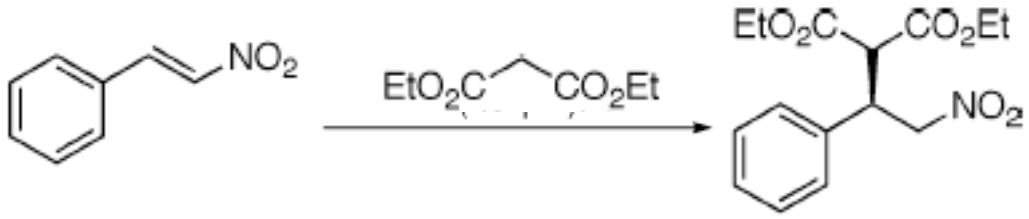
Asymmetric organocatalytic Michael addition to nitro-olefins

Literature presentation 4/06

The michael addition to nitro-olefins



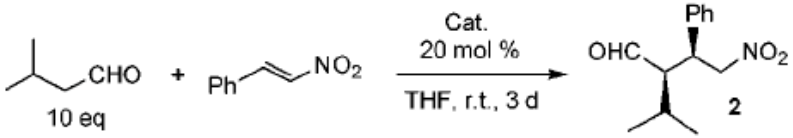
Chiral nitro-alkanes:
Useful building blocks

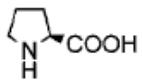
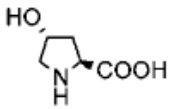
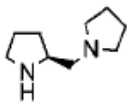
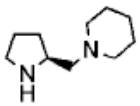
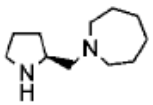
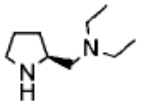
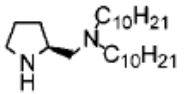
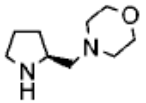
ORGANOCATALYSTS USED:

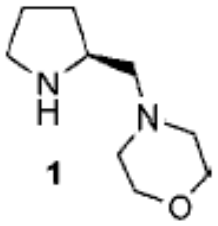
1) Chiral diamines
2) Cinchona alkaloids
3) Biunctional thioureas

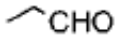
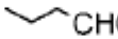
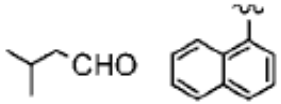
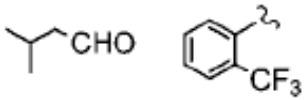
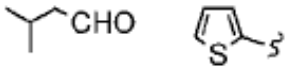
The first example:diamines as promising catalysts

Table 1. Catalyst Screening for the Michael Reaction



entry	cat	yield[a] (%)	dr[b] (*syn/anti*)	ee[c] (*syn*)
1		< 5	93 : 7	25
2		< 5	--	--
3		80	80 : 20	75
4		89	83 : 17	73
5		80	82 : 18	64
7		70	82 : 18	70
8		88	80 : 20	47
9		78	92 : 8	72



aldehyde	R'	time	yield[a] (%)	dr[b] (*syn/anti*)	ee[c] (*syn*)
	Ph	3 h	85	90/10	56[d]
	Ph	27 h	94	86/14	65
		3 d	67	96/4	75[e]
		3 d	77	98/2	78[e]
		2 d	82	86/14	71

Juan M. Betancort and Carlos F. Barbas III*

Org. Lett., Vol. 3, No. 23, **2001**

Proposed transition state

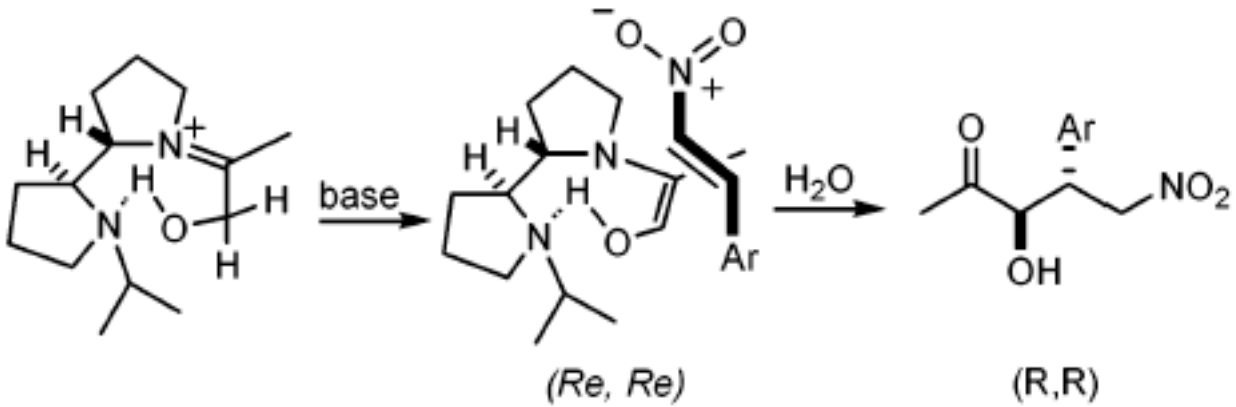
Scheme 1. Proposed Transition State

Juan M. Betancort and Carlos F. Barbas III*

Org. Lett., Vol. 3, No. 23, **2001**

a-hydoxy ketones:control of selectivity via H-bondng

Scheme 1. Proposed Mechanism for Diamine-Catalyzed Michael Addition

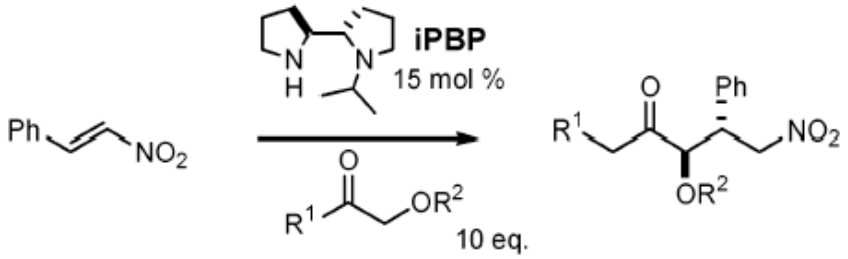


Olivier Andrey, Alexandre Alexakis,* and Gérald Bernardinelli

Org. Lett., Vol. 5, No. 14, **2003**

Michael addition of a-hydroxy ketone

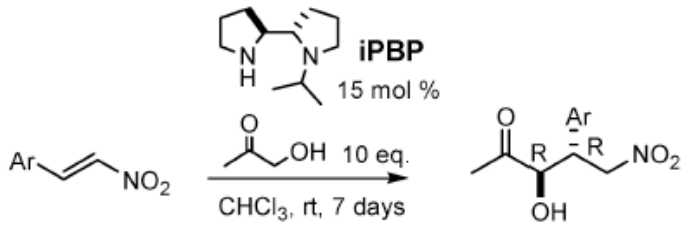
Table 1. Asymmetric Addition of α-alkoxycarbonyl Compounds to Nitrostyrene, Catalyzed by Diamine **iPBP**



entry	R^1	R^2	solvent	reaction conditions	dr[a] *anti*/*syn*	yield[b] (%)	ee[c] (%)
1	Me	Me	$CHCl_3$	rt, 2 days	17:83	75	69
2	Me	H	$CHCl_3$	rt, 7 days	83:17	79	97.6
3	*n*-Pr	H	$CHCl_3$	60 °C, 7 d	92:8	21	98.4
4	Me	H	CH_2Cl_2	rt, 7 days	82:18	68	98.3
5	Me	H	Et_2O	rt, 7 days	70:30	60	81
6	Me	H	THF	rt, 7 days	60:40	37	73
7	Me	H	MeOH	rt, 2 days	75:25	53	93
8	Me	H	*i*PrOH	rt, 4 days	68:32	48	75
9	Me	H	DMF	rt, 7 days		0[d]	
10[e]	Me	H	MeOH	rt, 4 days	30:70	67	11

[a] Determined by ^{1}H NMR or SFC of the crude product. [b] Isolated yield after column chromatography. [c] Determined by chiral GC or SFC of the purified product (major diastereomer). [d] Decomposition of the starting marterial. [e] With L-proline as chiral catalyst.

Table 2. Asymmetric Addition of α-Hydroxyacetone to Nitroolefins, Catalyzed by Diamine **iPBP**, in Chloroform



1-10a **1-10b**

entry/product	Ar	dr[a] *anti*/*syn*	yield[b] (%)	ee[c] (%)
1	Ph	83:17	79	97.6
2	4-MePh	84:16	68	97.6
3	4-MeOPh	81:19	65	97.3
4	4-Cl-Ph	87:13	81	97.8
5	2-CF_3Ph	95:5	84	98.5
6	2,6-Cl_2Ph	84:16	83	98.1
7	3,4-Cl_2Ph	88:12	66	98.1
8	2,4-Cl_2Ph	91:9	85	98.6
9	1-naphthyl	78:22	68	98.3
10	2-thienyl	78:22	66	96.3

[a] Determined by ^{1}H NMR or SFC of the crude product. [b] Isolated yield after column chromatography. [c] Determined by chiral SFC of the purified product.

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Org. Lett., Vol. 5, No. 14, **2003**

Protonated pyrrolidine-pyridine catalysts

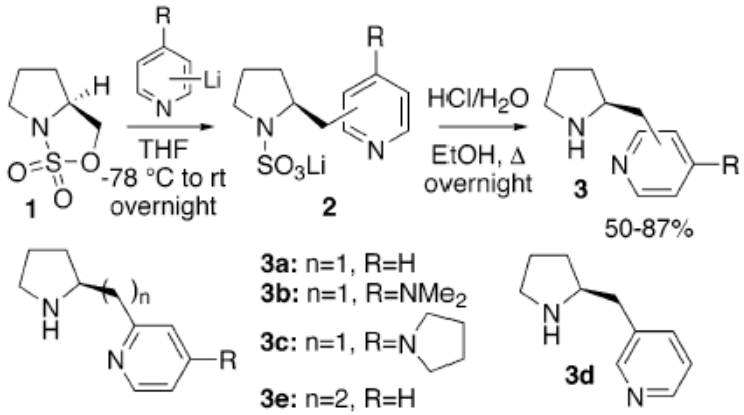
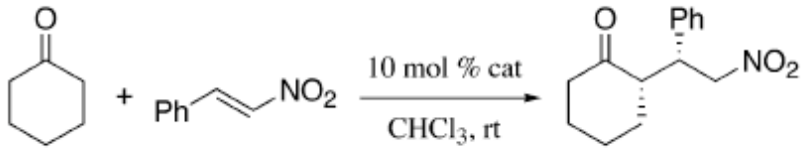


Table 1. Catalytic Asymmetric Michael Addition of Cyclohexanone (**4**) to Nitrostyrene **5** under Various Conditions[a]



4 + **5** → **6**

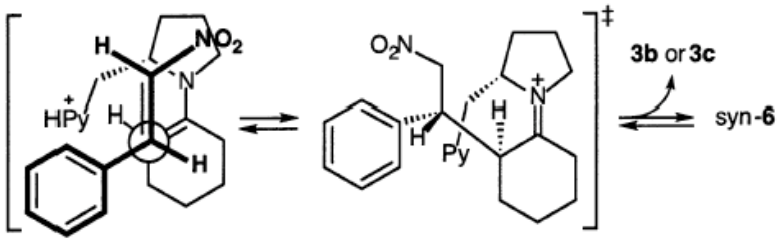
entry	cat.	solvent	time (h)	yield[b] (%)	dr[c] (*syn*/*anti*)	ee (%)[d] (*syn*)
1	**3a**	$CHCl_3$	24	82	95/5	63
2[e]	**3a**	$CHCl_3$	36	76	97/3	86
3	**3b**	$CHCl_3$	36	78	95/5	88
4[e]	**3b**	$CHCl_3$ (+ acid[f])	36	99	97/3	94
5[e]	**3b**	**$CHCl_3$ (+acid[g])**	**20**	**98**	**98/2**	**95**
6[e]	**3c**	$CHCl_3$ (+acid[f])	24	97	97/3	95
7[e]	**3c**	**$CHCl_3$ (+acid[g])**	**24**	**95**	**98/2**	**99**
8	**3d**[h]	$CHCl_3$	48	66	91/9	56
9	**3e**[h]	$CHCl_3$	48	55	92/8	55

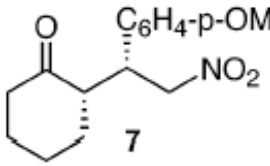
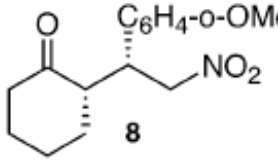
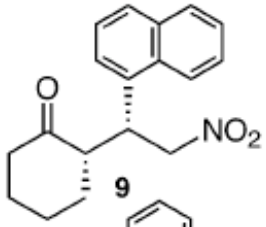
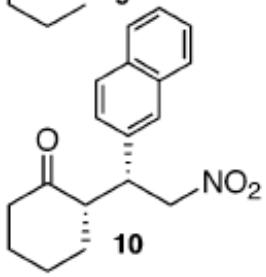
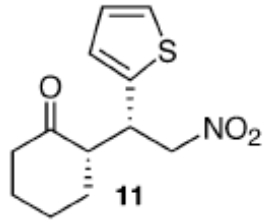
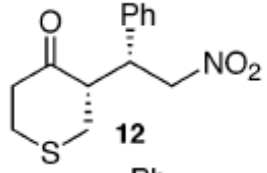
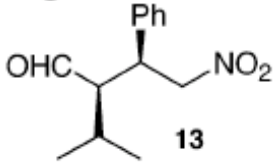
[a] Unless otherwise noted, all reactions were conducted in $CHCl_3$ (2 mL) using **4** (0.5 mL, 20 equiv) and **5** (0.25 mmol) in the presence of 10 mol % of the catalyst. [b] Isolated yield. [c] Determined by ^1H NMR of the crude mixture. [d] Determined by chiral HPLC analysis (Chiralpak AD, hexane/2-propanol = 90:10). [e] At 0 °C. [f] 2,4-Dinitrobenzenesulfonic acid (10 mol %) was added. [g] 2,4-Dinitrobenzenesulfonic acid (5 mol %) was added.

Takaaki Ishii, Shingo Fujioka, Yusuke Sekiguchi, and Hiyoshizo Kotsuki*

J. AM. CHEM. SOC. 2004, *126*, 9558−9559

Scheme 2



entry	time	product	yield (%)	dr (*syn*/*anti*)	ee (%) (*syn*)
1[b]	46 h	 **7**	97	97 / 3	93
2[c]	24 h		100	97 / 3	96
3[b]	21 h	 **8**	100	98 / 2	92
4[c]	24 h		99	98 / 2	93
5[b]	50 h	 **9**	92	97 / 3	98
6[c]	36 h		100	97 / 3	93
7[b]	24 h	 **10**	99	99 / 1	94
8[c]	8 h		99	98 / 2	93
9[b]	29 h	 **11**	92	94 / 6	88
10[c]	48 h		98	93 / 7	90
11[b]	68 h	 **12**	95	99 / 1	96
12[c]	24 h		98	98 / 2	92
13[b]	6 d	 **13**	45	97 / 3	7
14[c]	6 d		42	96 / 4	9
15[d]	48 h		93	98 / 2	22

[a] All reactions were performed in $CHCl_3$ (2 mL) at 0 °C using ketone (20% vol) and nitroolefin (0.25 mmol) in the presence of 10 mol % of **3** and 5 mol % of 2,4-dinitrobenzenesulfonic acid. [b] **3b** was used. [c] **3c** was used. [d] **3a** was used.

Quartenary carbon formation

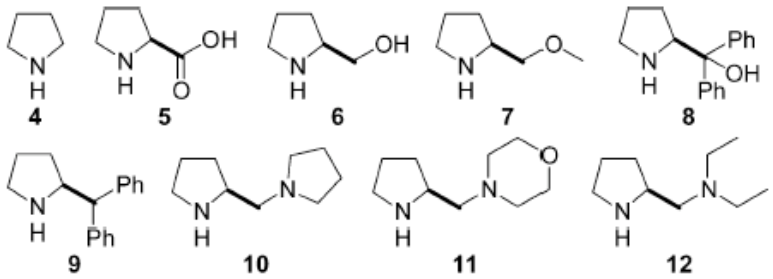


Figure 1. Various amine catalysts.

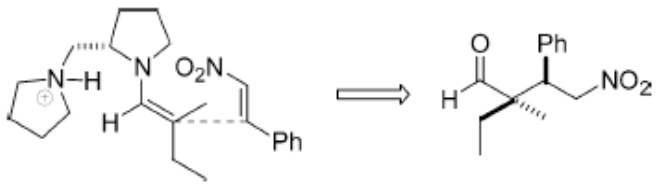
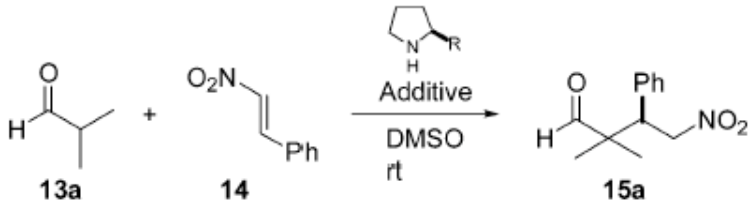


Figure 2. Proposed transition state.

Table 1. Organocatalyzed Direct Michael Reactions for the Synthesis of Quaternary Carbon



entry	catalyst[a]	additive (equiv)	time (h)	yield (%)	ee[b] (%)
1[c]	**4**	AcOH (1.5)	12	84	
2	**5**		48	87	23
3	**6**		48	79	63
4	**7**		48	72	17
5	**8**	AcOH (0.3)	96	<1	65
6	**9**	AcOH (0.3)	96	82	21
7	**10**		0.5	90	50
8	**10**	TFA (0.3)	24	96	61
9	**11**	TFA (0.3)	96	19	73
10	**12**	TFA (0.3)	96	4	75

[a] Catalyst structures are shown in Figure 1. [b] Determined by chiral HPLC using a CHIRALPAK AS-H column. [c] Isobutylaldehyde (1.2 equiv) was used.

Nobuyuki Mase,† Rajeswari Thayumanavan, Fujie Tanaka,* and Carlos F. Barbas III*

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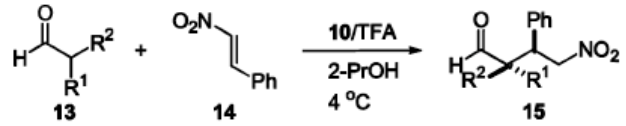
Table 3. Diamine **10**/TFA-Catalyzed Direct Michael Reactions for the Synthesis of Quaternary Carbon



entry	donor **13**	R^1	R^2	time (h)	product **15**	yield (%)	dr[a] (syn/anti)	ee (%)[b] (syn/anti)
1	**13a**	Me	Me	48	**15a**	87	-	80
2	**13b**		$-(CH_2)_4-$	24	**15b**	93	-	91
3	**13c**		$-(CH_2)_5-$	96	**15c**	90	-	59
4	**13d**	Me	Et	96	**15d**	94	74/26	81/75
5	**13e**	Me	Pr	96	**15e**	95	74/26	86/67
6	**13f**	Me	nonyl	96	**15f**	96	70/30	85/58
7	**13g**	Me		96	**15g**	93	84/16	75/45
8	**13h**	Me	Ph	96	**15h**	87[c]	89/11	18/79
9	**13i**	Me		96	**15i**	75[c]	55/45	65/65
10	**13j**	Me		96	**15j**	64[c]	54/46	70/64
11	**13k**	Me		96	**15k**	75[c]	67/33	74/43

[a] Determined by ^1H NMR. [b] Determined by chiral HPLC analysis using CHIRALCEL OD-H, OJ-H, and/or CHIRALPAK AS-H columns. [c] Starting material was recovered in 9% (entry 8), 25% (entry 9), 30% (entry 10), and 16% (entry 11) yields.

Cinchona alkaloids: bifunctional catalysis

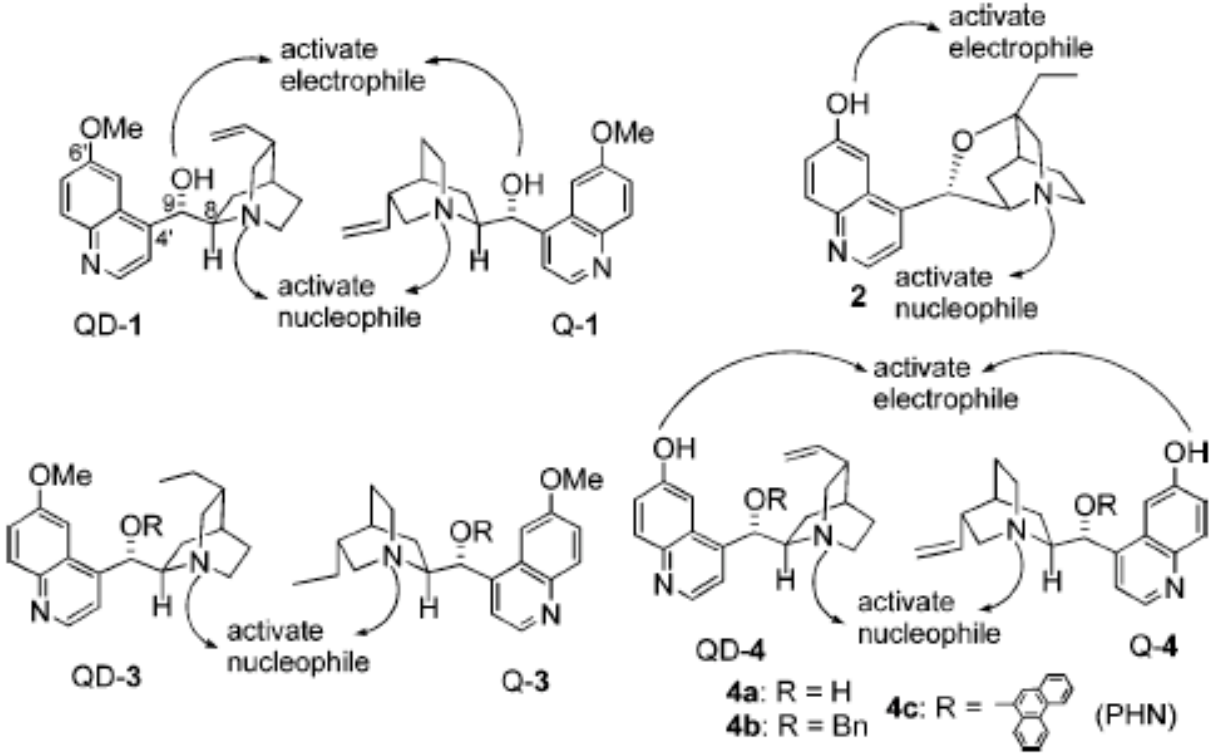
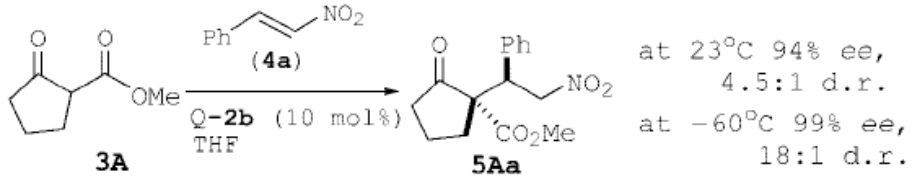


Figure 1. Mode of activation of nucleophile and electrophile by cinchona alkaloids.

Chiral quartenary carbon formation



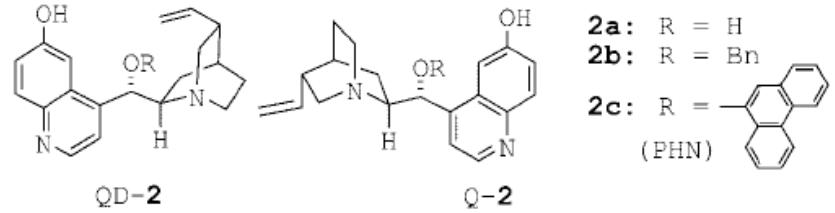
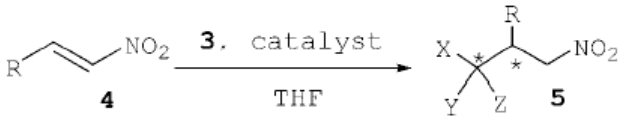


Table 1: Diastereoselective and enantioselective 1,4-addition catalyzed by Q-2.[a]



Entry	3	4	Cat.	*T* [°C]	*t*	Yield [%][b]	d.r.[c]	*ee* [%][d]
1	**3A**	**4a**	Q-**2b**	−60	48 h	94	95:5	99
2	**3A**	**4e**	Q-**2b**	−60	4 d	87	>98:2	99
3	**3B**	**4a**	Q-**2a**	−20	72 h	93	>98:2	99
4	**3B**	**4b**	Q-**2a**	−20	74 h	91	>98:2	99
5	**3B**	**4c**	Q-**2a**	−20	74 h	95	>98:2	>99
6	**3B**	**4e**	Q-**2c**	23	4 d	83	>98:2	99
7	**3C**	**4a**	Q-**2c**[e]	−20	63 h	73[g]	91:9	>99
8	**3D**	**4d**	Q-**2b**	−60	44 h	87	98:2	99
9	**3D**	**4e**	Q-**2c**	−60	48 h	82	98:2	99
10	**3E**	**4a**	Q-**2b**	−60	48 h	76[g]	86:14	99
11	**3F**	**4a**	Q-**2a**	−20	60 h	78[g]	92:8	92
12	**3F**	**4f**	Q-**2a**	−20	84 h	78[g]	93:7	92
13	**3G**	**4a**	Q-**2a**[f]	−50	6 d	77	95:5	96
14	**3H**	**4a**	Q-**2b**[f]	−50	6 d	77[g]	>98:2	>99
15	**3H**	**4f**	Q-**2a**	−20	84 h	75	93:7	98

[a] Unless noted, reactions were conducted on a 0.2-mmol scale in 0.2 mL THF with 10 mol% Q-**2**. [b] Yield of isolated product. [c] Determined by ^{1}H NMR analysis of crude product. [d] Determined by HPLC analysis. [e] Here 15 mol% catalyst was used. [f] Here 20 mol% catalyst was used. [g] Yield of the pure major diastereomer.

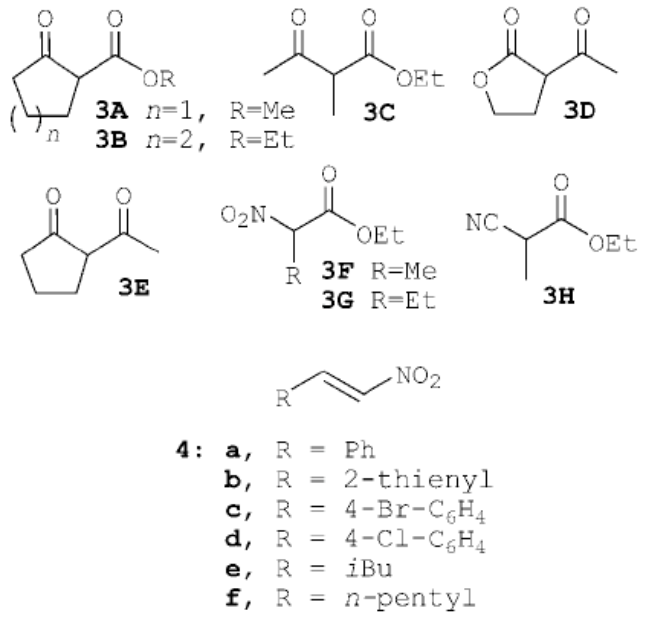


Figure 1. Carbon nucleophiles **3** and Michael acceptors **4** from Table 1.

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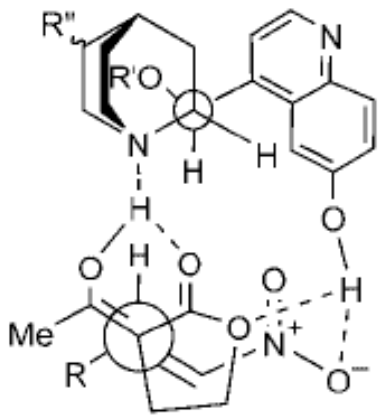

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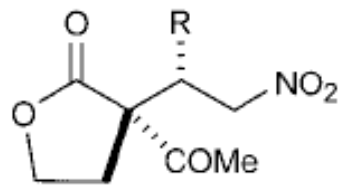
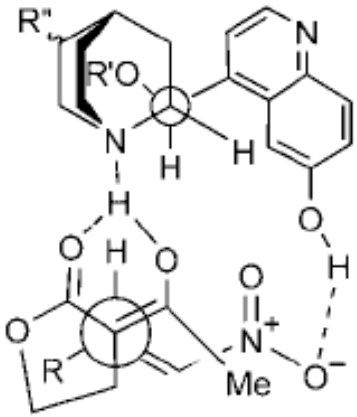


5Dd: R=4-Cl-C_6H_4
5De: R=*i*Bu



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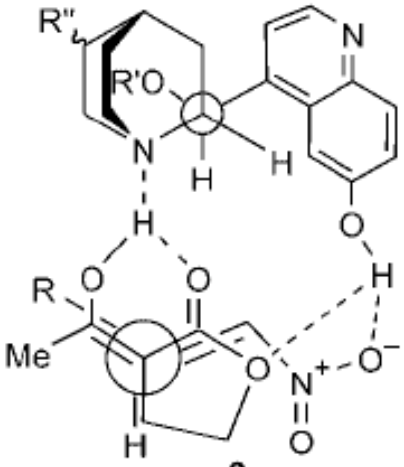
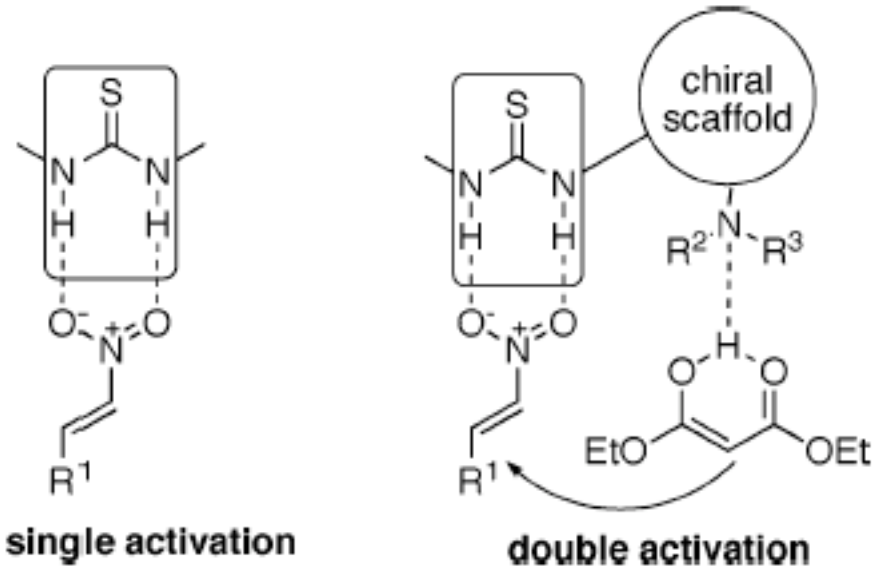


9

Thiourea bifunctional catalysis



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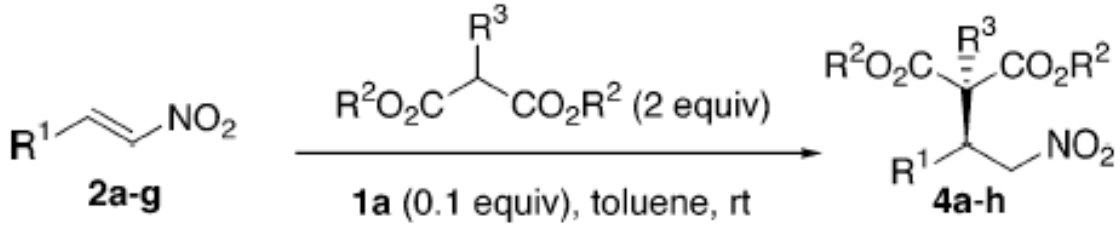
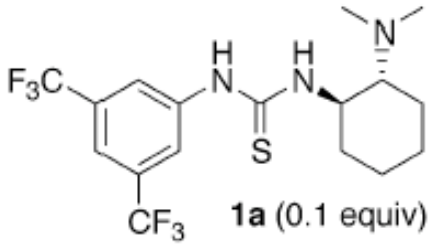
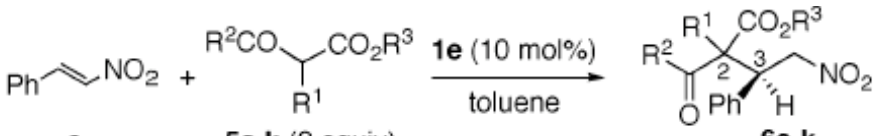


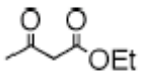
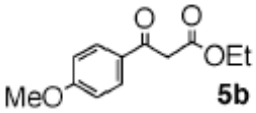
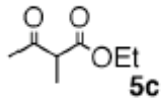
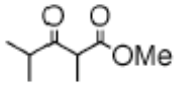
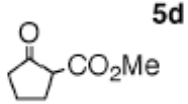
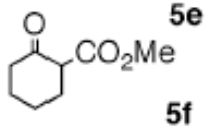
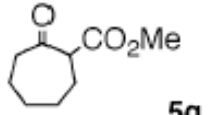
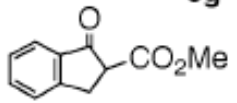
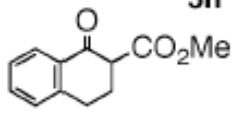
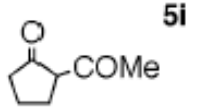


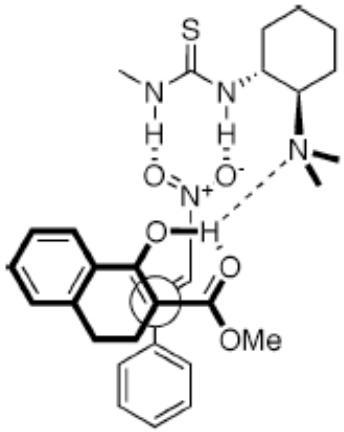
entry	R^1	R^2	R^3	adduct	time (h)	% yield[b]	% ee[c] (config.)[d]
1	Ph	Et	H	**4a**	24	86	93 (*S*)
2	2,6-$(MeO)_2$Ph	Et	H	**4b**	72	87	93 (*S*)
3	4-F−Ph	Et	H	**4c**	12	87	92 (*S*)
4	1-naphthyl	Et	H	**4d**	24	95	92 (−)[e]
5	2-thienyl	Et	H	**4e**	48	74	90 (−)[e]
6	pentyl	Et	H	**4f**	48	78	81 (*S*)
7	^{i}Bu	Et	H	**4g**	48	88	81 (*S*)
8	Ph	Me	Me	**4h**	36	82	93 (−)[e]

[a] The reaction was conducted with nitroolefins (1 equiv), nucleophiles (2 equiv), and toluene at room temperature. [b] Isolated yield. [c] Enantiomeric excess was determined by HPLC analysis of **4** using a chiral column. [d] Absolute configuration was determined by comparing the specific rotation of **4** with that of literature data.[6] [e] Not determined.



2a **5a-k** (2 equiv) **6a-k**

entry	5	temp. (°C)	time (h)	yield[a] (%)	dr[b] (2*R*/2*S*)[c]	ee (%)[d] major
1	 **5a**	rt	0.5	91	-[d]	89[e]
2	 **5b**	rt	2	99	-[d]	89
3	 **5c**	rt	6	89	22/78	91
4	 **5d**	rt	48	87	36/64	95
5	 **5e**	-50	24	96	93/7	93
6	 **5f**	-20	36	93	96/4	85
7	 **5g**	-40	24	76	83/17	89
8	 **5h**	-50	3	96	57/43	93
9	 **5i**	rt	2	97	95/5	90
10	 **5j**	-60	24	94	7/93	81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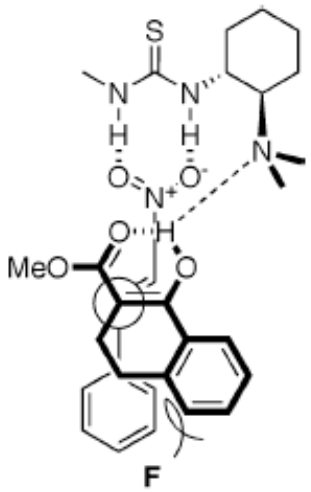
N+
O-
O
H
O
OMe

E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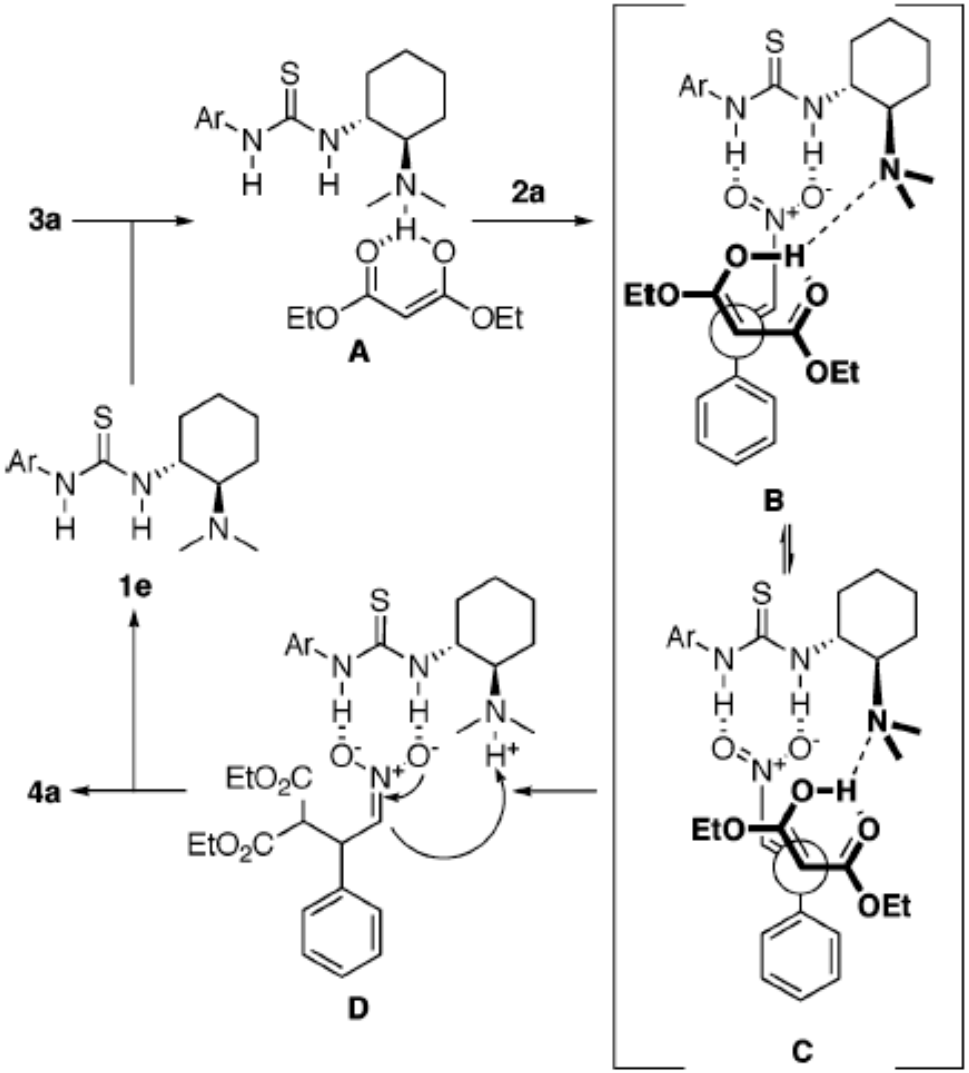
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