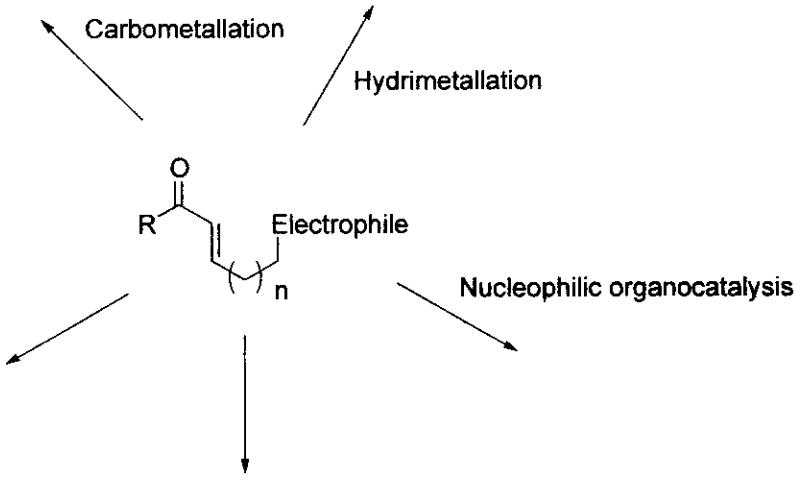
Copper-Catalyzed Tandem Conjugate Addition-Electrophilic Trapping: Ketones, Esters, and Nitriles as Terminal Electrophiles

Kyriacos Agapiou, David F. Cauble, and Michael J. Krische*

J. AM. CHEM. SOC. **2004,** *126*, 4528-4529

1. Catalytic nucleophilic activation of the enone is achieved through (1) hydrometallation (i.e. 1,4-reduction), (2) electron transfer (i.e. anion radical/homo-enolate formation), (3) carbometallation (i.e. 1,4-addition), and (4) nucleophilic catalysis (i.e. reversible 1,4-addition).

2. Intramolecular reaction.



Diastereoselective Cobalt-Catalyzed Aldol and Michael Cycloreductions

Baik, T. et al. *J. Am. Chem. Soc.* **2001**, *123*, 5112-5113

1. Catalytic enone hydrometallation for enolate generation.
2. Phenylsilane as terminal reductant.
3. syn:anti = >99:1 for aldol cycloreduction.
4. only anti for Michael cycloreduction.
5. Some chemoselectivity in unsymmetrical bisenone.

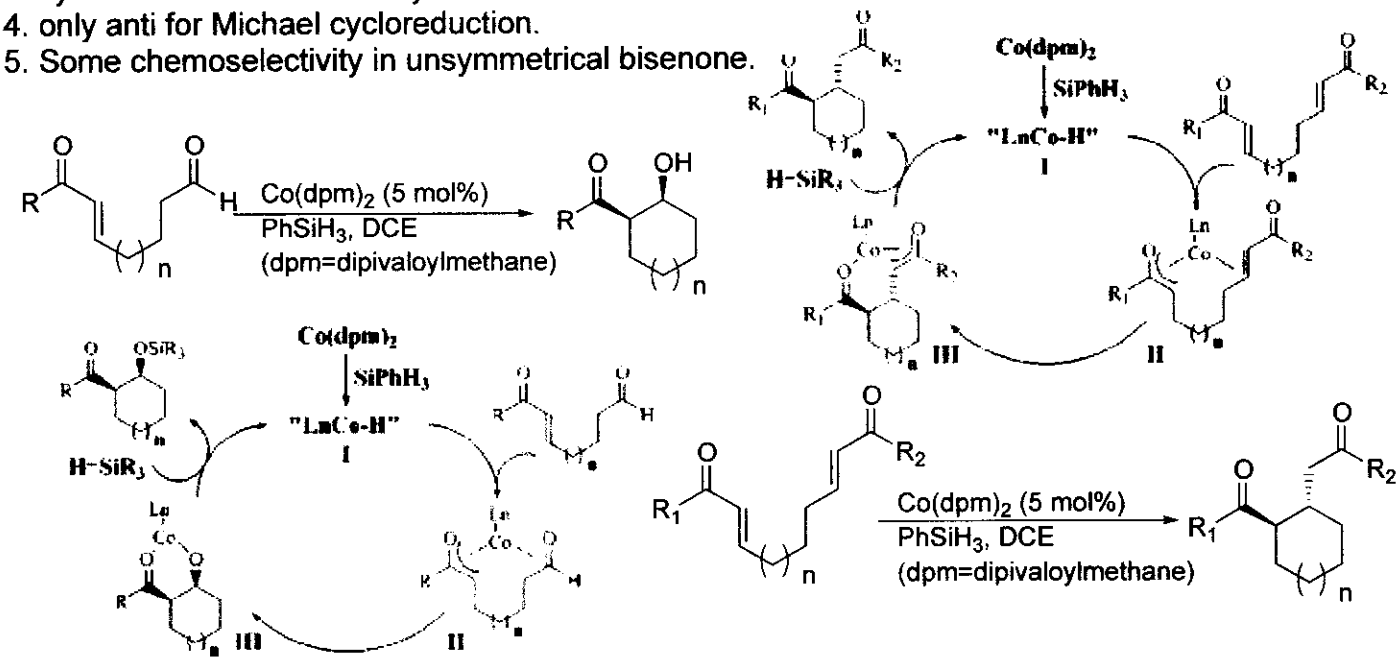
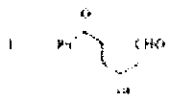
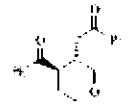
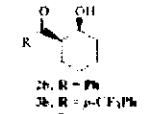
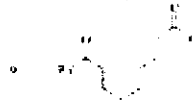
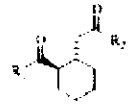
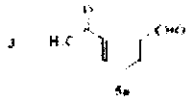
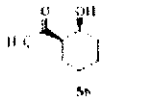
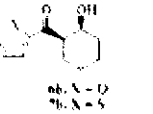
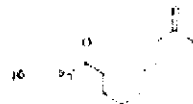
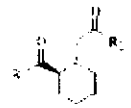
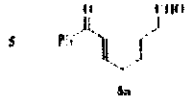
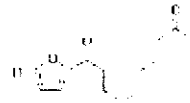
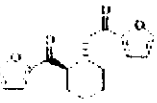
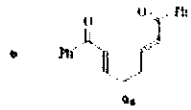
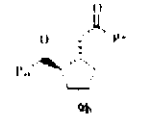
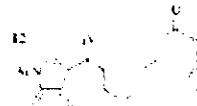
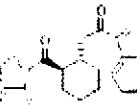
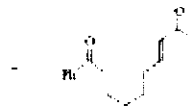
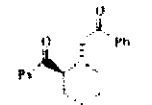


Table 1. Cobalt-Catalyzed Aldol and Michael Cycloreductions

substrate	product	yield(%)	substrate	product	yield(%)
		70			63
		87 72 68			62
		38			
		75 73			54
		35			52
		62			68
		73			

1 ~ 5 ; 25 ~ 35 °C, 1.2 eq of $PhSiH_3$

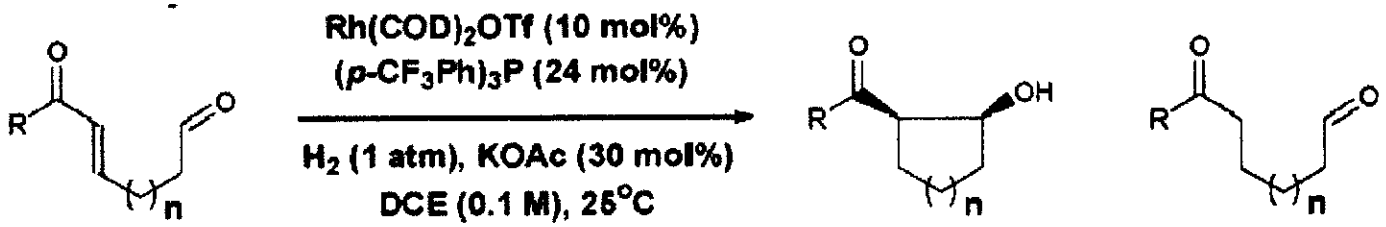
6 ~ 12 ; 50 ~ 75 °C, 2.4 eq of $PhSiH_3$

Reductive Generation of Enolates from Enones Using Elemental Hydrogen: Catalytic C-C Bond Formation under Hydrogenative Conditions

Jang H-Y. et al. *J. AM. CHEM. SOC.* **2002**, *124*, 15156-15157

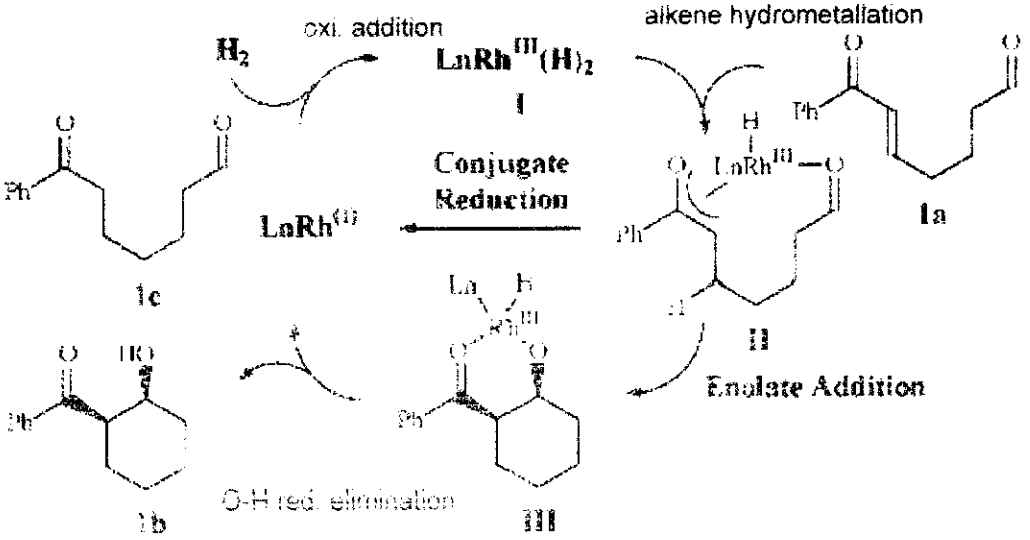
1. Use of elemental hydrogen as terminal reductant..
2. the reductive generationof enolates from enones under hydrogenative conditions.
3. Exposure of conjugate reduction product **1c** to identical conditions does not produce **1b**. Additionally, enone **1a** is unreactive toward triarylphosphine addition, thus excluding tandem Baylis-Hillman cyclization-conjugate reduction pathways.

Table 2. Rh-Catalyzed Hydrogenative Aldol Cycloreduction of Monoenone Monoaldehydes **1a-7a**



substrate	product (syn:anti)	1,4-reduction
1a, $n = 2$, R = Ph	**1b**, 89% (10:1)	**1c**, 0.1%
2a, $n = 2$, R = *p*-MeOPh	**2b**, 74% (5:1)	**2c**, 3%
3a, $n = 2$, R = 2-naphthyl	**3b**, 90% (10:1)	**3c**, 1%
4a, $n = 2$, R = 2-thiophenyl	**4b**, 76% (19:1)	**4c**, 2%
5a, $n = 2$, R = 2-furyl	**5b**, 70% (6:1)	**5c**, 10%
6a, $n = 1$, R = Ph	**6b**, 71% (24:1)	**6c**, 1%
7a, $n = 2$, R = CH_3	**7b**, 65% (1:5)	

Scheme 1. Proposed Catalytic Cycle: Conjugate Reduction versus Electrophilic Trapping

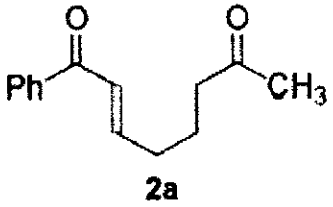


Diastereo- and Enantioselective Catalytic Carbometallative Aldol Cycloreduction: Tandem Conjugate Addition-Aldol Cyclization

Cauble, D. F. et al. *J. AM. CHEM. SOC.* **2003**, *125*, 1110-1111.

1. Ketone as aldolpartner to avoid Rh-cat. addition of arylboronic acid to aldehyde.
2. a single diastereomer.
3. X-ray crystal of 1b and 2b.

Scheme 1. Optimization of the Diastereoselective Carbometallative Aldol Cycloreduction of **2a**



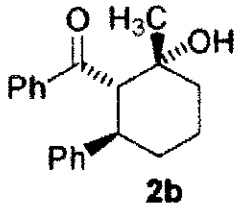
2a

$[Rh(COD)Cl]_2$ (2.5 mol%)
Ligand (7.5 mol%)

$PhB(OH)_2$ (200 mol%)

H_2O (500 mol%)

Dioxane (0.1 M), 95 °C

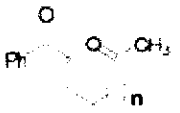
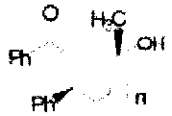
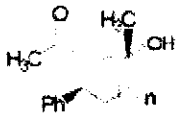
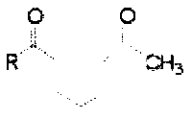
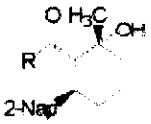
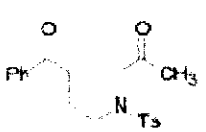
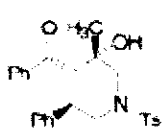


2b

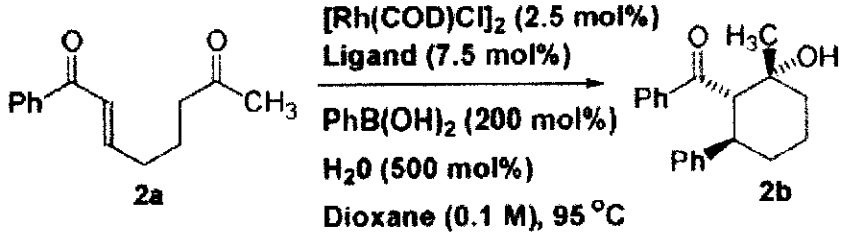
Ligand	Yield
PPh_3	trace
biphep	24%
dppf	33%
dppe	44%
dppb	72%
dppb[c]	87%
dppb[d]	87%

a (a) All reactions were performed on a 0.5 mmol scale. (b) Reactions were stopped after 18 h or upon complete consumption of 2a. (c) Addition of TEA (1000 mol %). (d) Addition of KOH (10 mol %).

Table 1. Catalytic Diastereoselective Carbometallative Aldol Cycloreduction

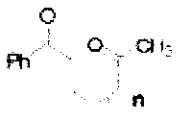
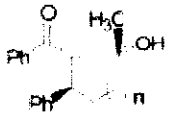
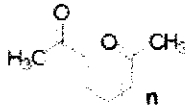
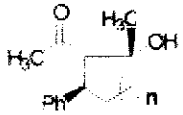
Entry	Substrate	Product	Isolated Yield
1			
	1a, n = 1 2a, n = 2	1b 2b	73% 87%
2			
	3a, n = 1 4a, n = 2	3b 4b	75% 45%
3			
	4a, R = CH_3 2a, R = Ph	4c 2c	40% 70%
4			
	5a	5b	84%

Scheme 2. Optimization of the Enantioselective Carbometallative Cycloreduction of **2a**

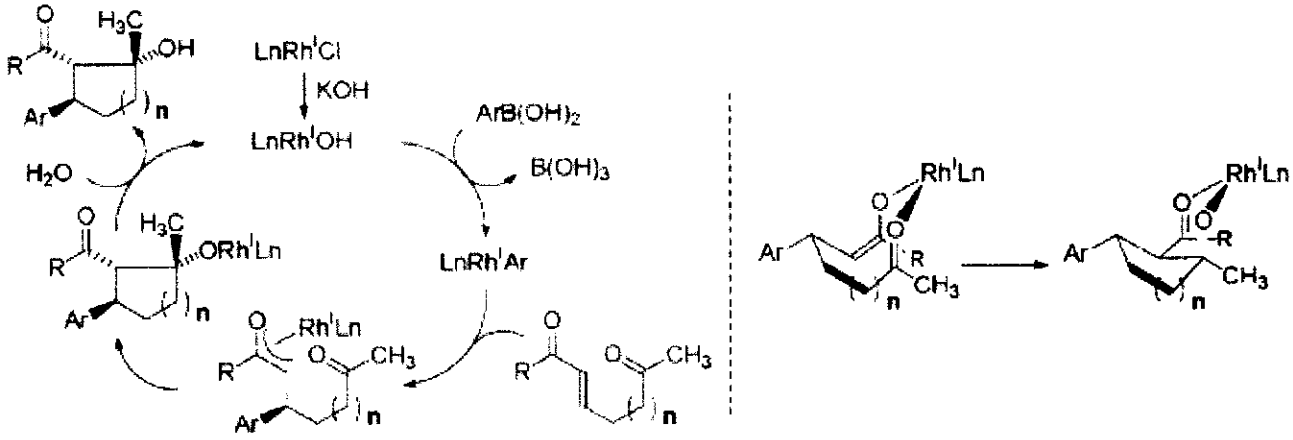


Ligand	Yield (ee %)
(*R,S*)-Josiphos	57% (0)
(*R,R*)-MeDuphos	67% (0)
(*R*)-Phanephos	79% (5)
(*R*)-Tol-BINAP	94% (62)
(*R*)-BINAP	90% (77)
(*R*)-BINAP[c]	80% (87)
(*R*)-BINAP[d,e]	88% (88)

Table 2. Catalytic Enantioselective Carbometallative Aldol Cycloreduction[a]

Entry	Substrate	Product	Isolated Yield (ee%)
1			
	1a, n = 1 2a, n = 2	1b 2b	78% (77) 88% (88)
2			
	3a, n = 1 4a, n = 2	3b 4b	88% (94) 69% (95)

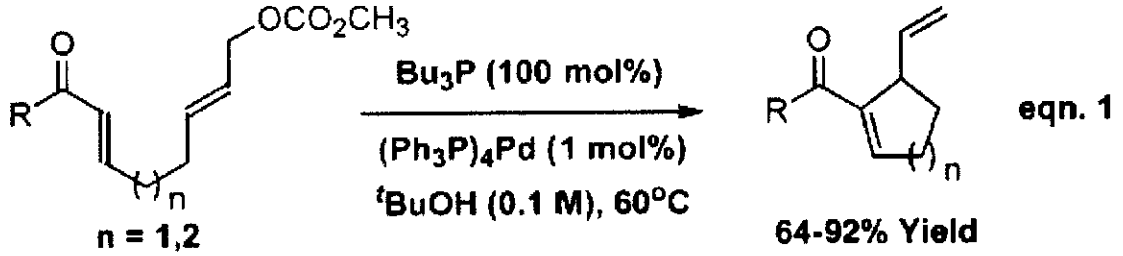
Scheme 3. Proposed Catalytic Cycle and Stereochemical Model



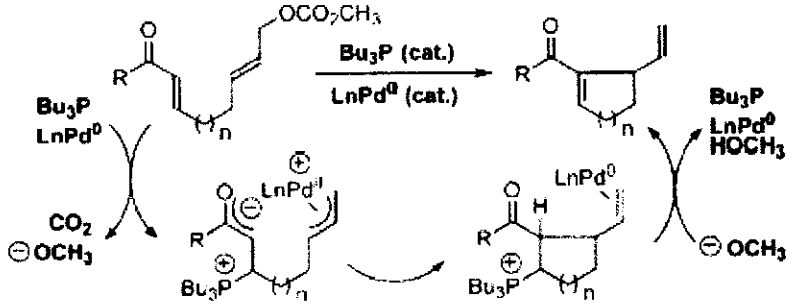
Catalytic Enone Cycloallylation via Concomitant Activation of Latent Nucleophilic and Electrophilic Partners: Merging Organic and Transition Metal Catalysis

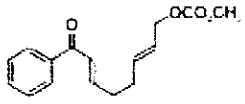
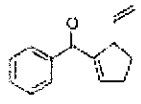
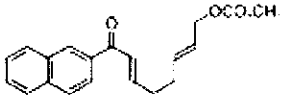
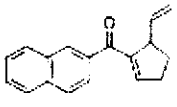
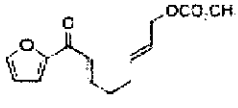
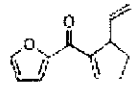
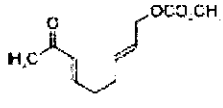
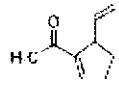
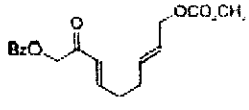
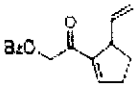
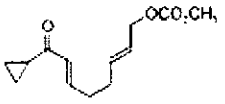
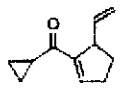
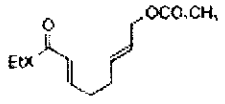
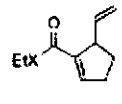
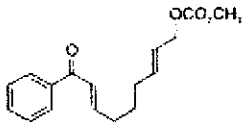
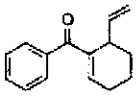
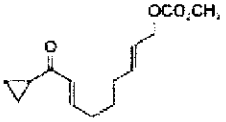
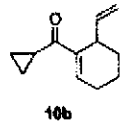
Jellerichs, B. G. et al. *J. AM CHEM. SOC.* **2003**, *125*, 7758-7759

1. two-component catalyst systems; activation of latent nucleophilic (enone) and electrophilic (allyl carbonate) partners is achieved through phosphine addition and π-allyl formation.



Scheme 1. Proposal: Catalytic Cycloallylation via Concommitant Activation of Latent Nucleophilic and Electrophilic Partners



Entry	Substrate	Product	Yield (%)[a]
1	 1a	 1b	92
2	 2a	 2b	82
3	 3a	 3b	83
4	 4a	 4b	71
5	 5a	 5b	81
6	 6a	 6b	76
7	 7a, X = O 8a, X = S	 7b, X = O 8b, X = S	>5 73
8	 9a	 9b	64
9	 10a	 10b	66

Copper-Catalyzed Tandem Conjugate Addition-Electrophilic Trapping: Ketones, Esters, and Nitriles as Terminal Electrophiles

1. ketones, esters and nitriles as terminal electrophiles

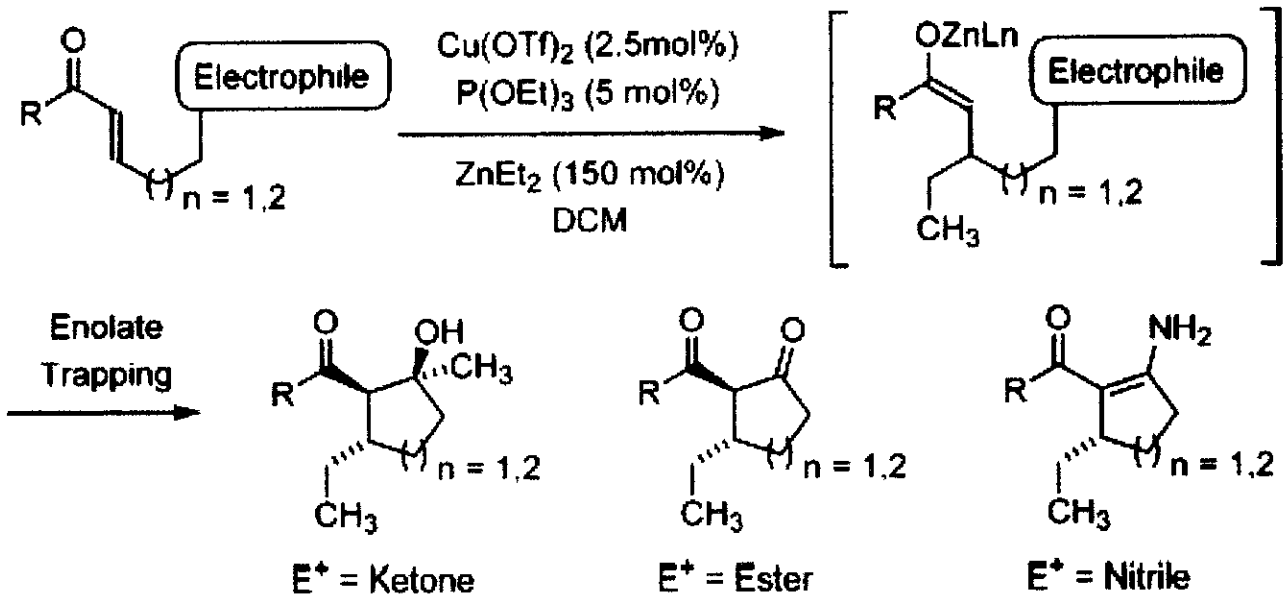
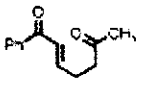
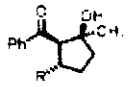
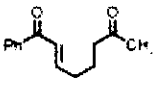
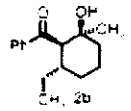
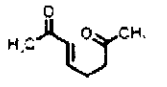
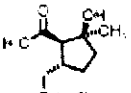
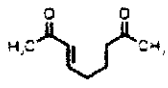
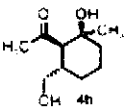
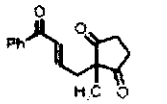
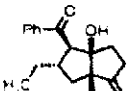
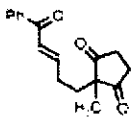
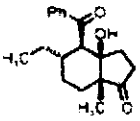
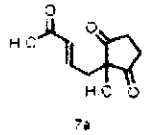
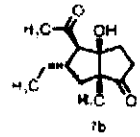
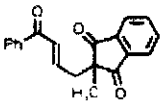
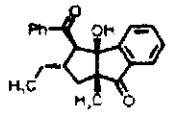
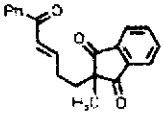
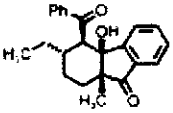
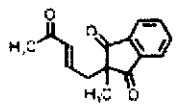
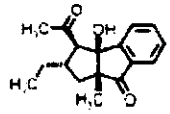


Table 1. Cu-Catalyzed Tandem Conjugate Addition-Aldol Cyclization a

Entry	Substrate	Product	Yield (%) (dr)
1	 1a	 1b, R = CH3, 1c, R = CH2CH3, 1d, R = CH(CH3)2, 1e, R = (CH2)3CH3	83 81 76 91 (>95:1)
2	 2a	 CH3 2b	98 (>95:1)
3	 3a	 CH3 3b	77 (3:1)
4	 4a	 OH 4b	96 (2.2:1)
5	 5a	 5b	99 (>95:1)
6	 6a	 6b	99 (10:1)
7	 7a	 7b	96 (2:1)
8	 8a	 8b	84 (8:1)
9	 9a	 9b	94 (>95:1)
10	 10a	 10b	78 (3:1)

Feringa, B. L. *Acc. Chem. Res.* **2000**, *33*, 346-353

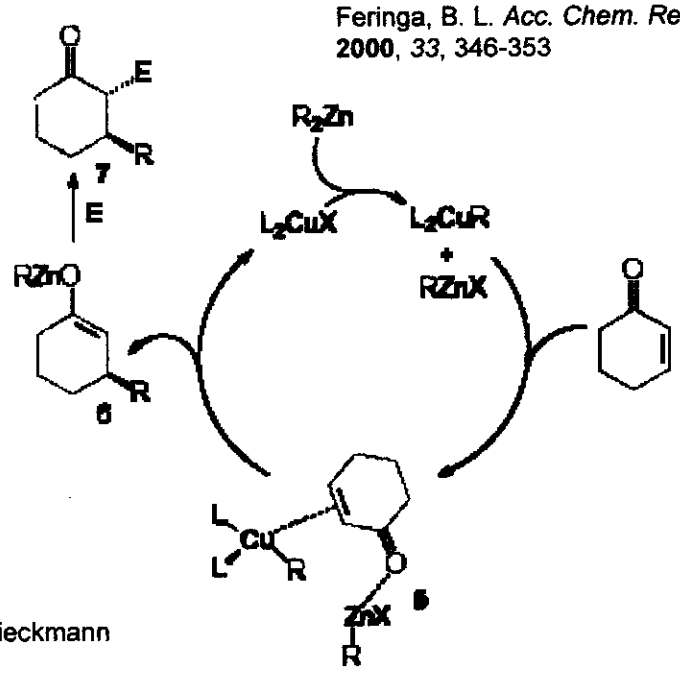
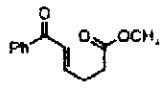
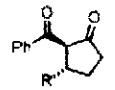
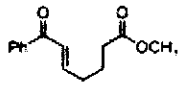
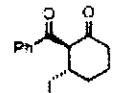
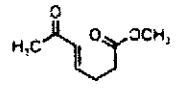
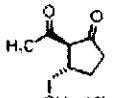
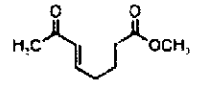
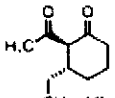
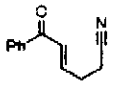
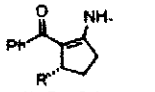
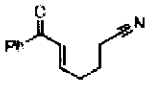
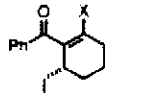
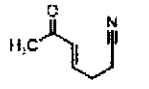
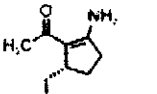
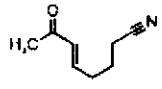
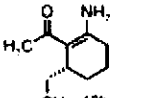
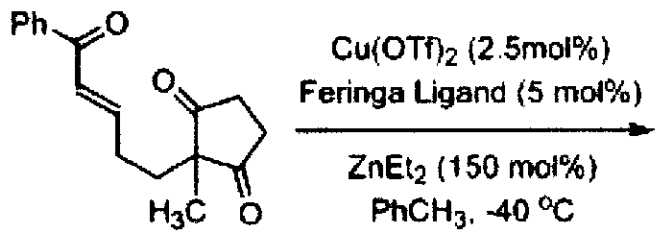
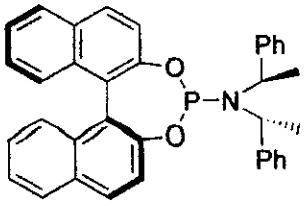


Table 2. Cu-Catalyzed Tandem Conjugate Addition-Dieckmann and Blaise Condensation

Entry	Substrate	Product[a]	Yield (%)
1	 11a	 11b, R = CH_3 11c, R = CH_2CH_3 11d, R = $(CH_2)_3CH_3$	93 88 88
2	 12a	 12b	87
3	 13a	 13b	90
4	 14a	 14b	93
5	 15a	 15b, R = CH_3 15c, R = CH_2CH_3 15d, R = $(CH_2)_3CH_3$	84 91 87
6	 16a	 16b X = NH_2 12b X = OH	73
7	 17a	 17b	98
8	 18a	 18b	85





In future,
study the substrates with diverse functionality.
dr or ee can be improved in some cases.
application toward the synthesis of total synthesis.