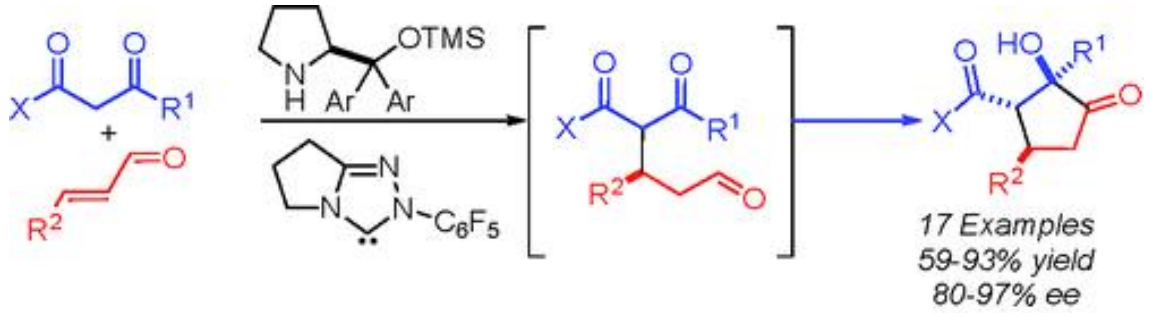
Asymmetric Synthesis of Functionalized Cyclopentanones Via a Multicatalytic Secondary Amine/*N*-Heterocyclic Carbene Catalyzed Cascade Sequence



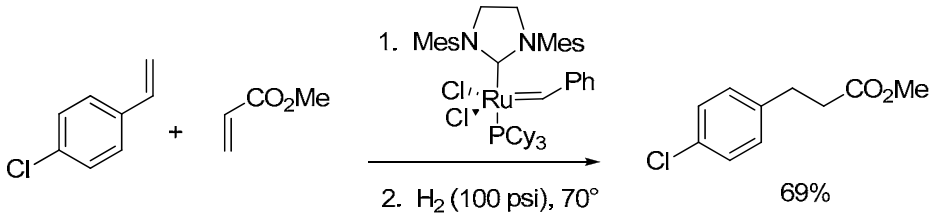
Stephen P. Lathrop and Tomislav Rovis
J. Am. Chem. Soc. 2009, 131 (38) 13628-13630

Previously in the Field of Cascade Catalysis

Single catalyst

J. L. Gleason and A. Ajamian
Angew. Chem. Int. Ed, 2004, 43, 3754

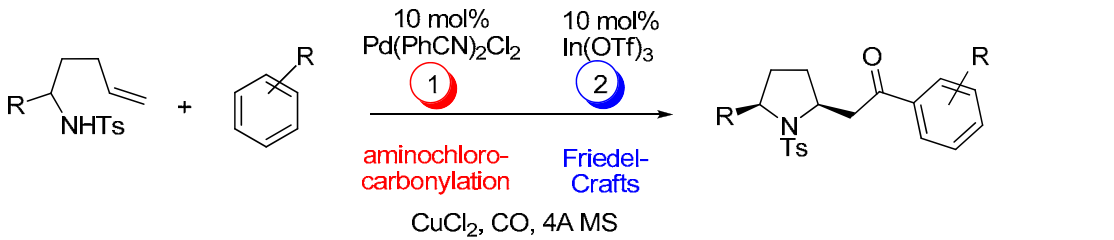
Two Birds with One Metallic Stone



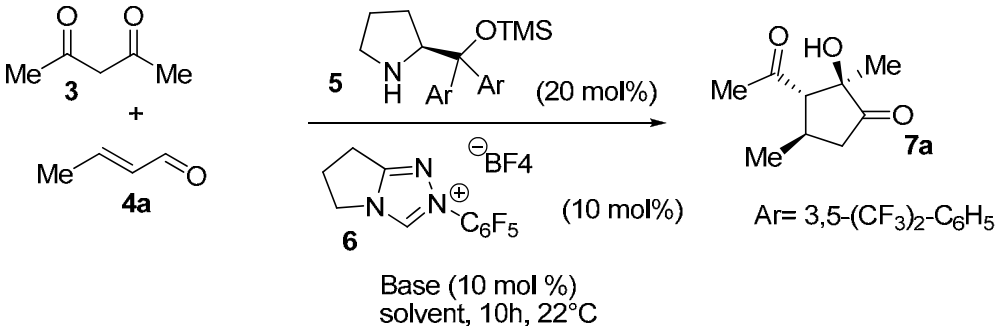
Multiple catalyst

Tim A. Cernak and Tristan H. Lambert
J. Am. Chem. Soc. 2009, 131, 3124

Tandem Palladium(II)/Indium(III)-Catalyzed Aminochlorocarbonylation/Friedel-Crafts Acylation

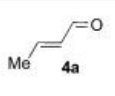
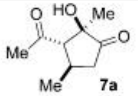
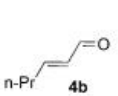
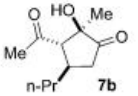
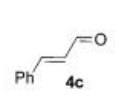
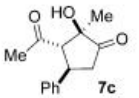
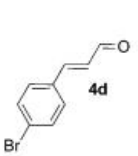
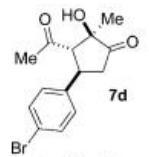
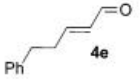
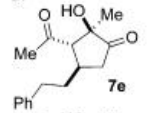
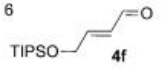
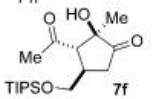
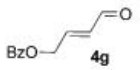
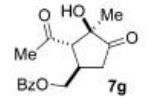
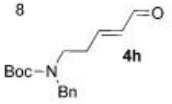
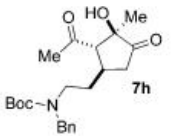
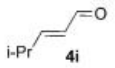
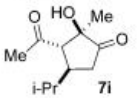


Catalyst and Solvent Screen

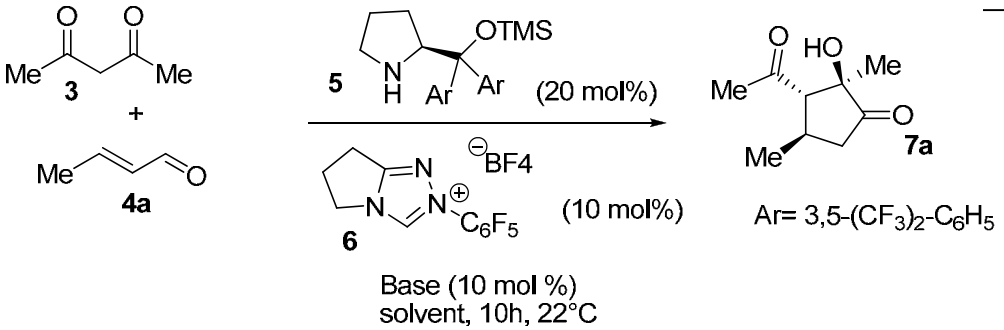


entry[a]	solvent	base	yield (%)	dr[b]	ee (%)[c,d]
1	CH_2Cl_2	none	trace	nd	nd
2	CH_2Cl_2	Et_3N	31	80:20:<1:<1	84
3	CH_2Cl_2	NaOAc	55	80:20:<1:<1	86
4	EtOH	NaOAc	<20	80:20:<1:<1	70
5	PhMe	NaOAc	53	80:20:<1:<1	84
6	$CHCl_3$	NaOAc	60	85:15:<1:<1	86
7[e]	$CHCl_3$	NaOAc	93	85:15:<1:<1	86

α,β-insaturated aldehyde scope

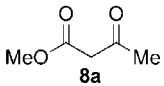
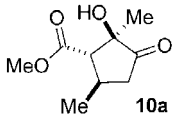
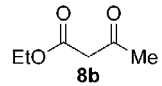
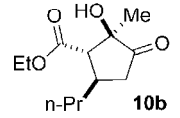
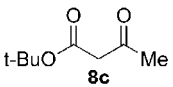
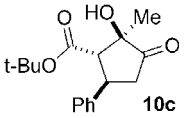
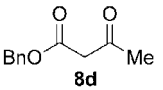
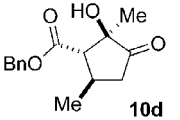
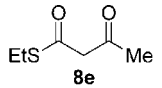
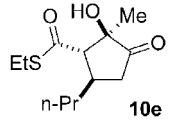
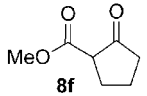
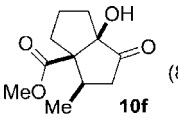
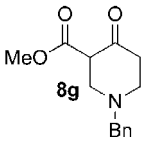
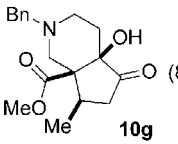
entry[a]	aldehyde (4)	product	yield (%) (dr[b])	ee[c,d]
1			93 (85:15:<1<1)	86
2			77 (85:15:<1<1)	93
3			60 (80:20:<1:<1)	85
4			70 (85:15:<1<1)	80
5			59 (80:20:<1:<1)	95
6			71 (75:25:<1:<1)	92
7			72 (80:20:<1:<1)	95
8			60 (85:15:<1:<1)	90
9			32 (67:33:<1:<1)	82

Catalyst and Solvent Screen

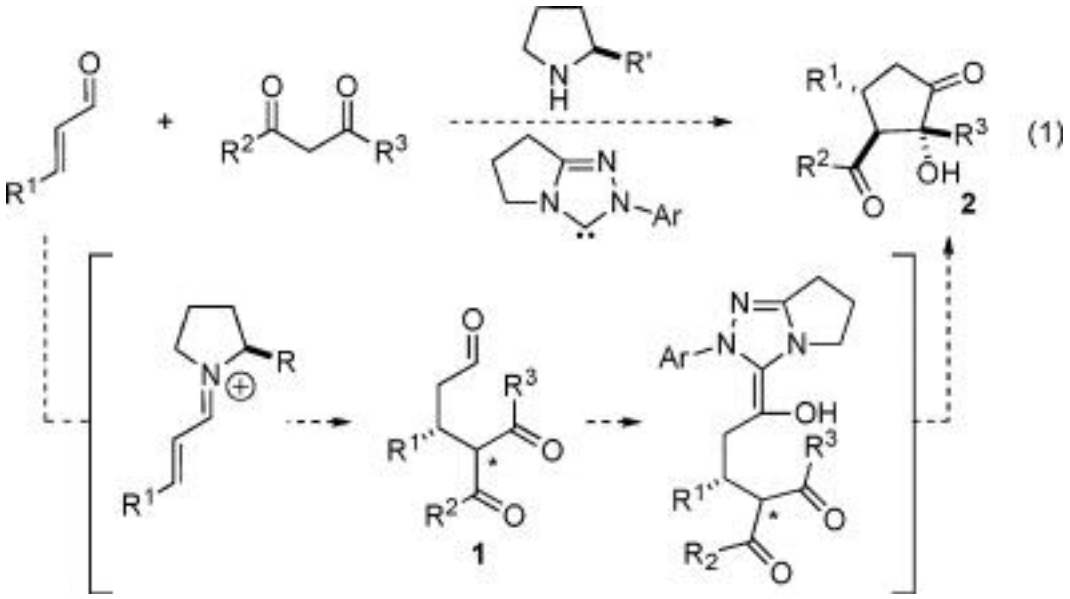


entry[a]	solvent	base	yield (%)	dr[b]	ee (%)[c,d]
1	CH_2Cl_2	none	trace	nd	nd
2	CH_2Cl_2	Et_3N	31	80:20:<1:<1	84
3	CH_2Cl_2	NaOAc	55	80:20:<1:<1	86
4	EtOH	NaOAc	<20	80:20:<1:<1	70
5	PhMe	NaOAc	53	80:20:<1:<1	84
6	$CHCl_3$	NaOAc	60	85:15:<1:<1	86
7[e]	$CHCl_3$	NaOAc	93	85:15:<1:<1	86

β-ketoester scope

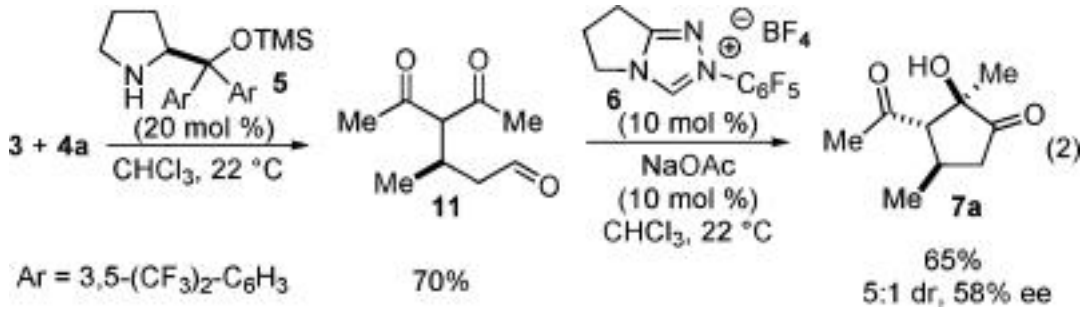
entry[a]	R^2	β-ketoester	product	yield (%) (dr[b])	ee[c,d]
1	Me **4a**	 **8a**	 **10a**	90 (64:33:3:<1)	91
2	*n*-Pr **4b**	 **8b**	 **10b**	80 (60:30:8:2)	93
3	Ph **4c**	 **8c**	 **10c**	86 (60:35:5:<1)	97
4	Me **4a**	 **8d**	 **10d**	90 (58:39:2:<1)	82
5	*n*-Pr **4b**	 **8e**	 **10e**	56 (69:22:6:3)	81
6	Me **4a**	 **8f**	 **10f**	79 (80:20:<1:<1)	94
7	Me **4a**	 **8g**	 **10g**	76 (85:15:<1:<1)	90

Mechanistic proposal



1) Michael addition
2) Intramolecular crossed benzoin reaction

Stepwise process:
Lower yield
Lower ee



Thank you for your attention

Any question?