Electronic Supporting Information

for

Highly enantioselective Mannich reaction of aldehydes with cyclic N-acyliminium ions by synergistic catalysis

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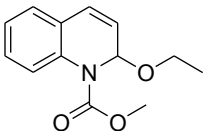
General Methods

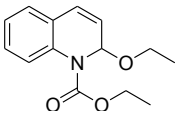
All reagents were purchased from commercially available sources. Anhydrous CH_2Cl_2 on molecular sieves, MeOH (HPLC grade) were used the reaction as solvents without any further purification. THF and toluene were distilled on sodium/benzophenone ketyl. Solvents for extraction and chromatography were distilled before use. Analytical TLC were performed on silica gel sheets with detection by exposure to ultraviolet light (254 nm) and/or by immersion in an acidic staining solution of *p*-anisaldehyde in EtOH. Silica gel 60 was used for flash chromatography. ^{1}H NMR spectra were recorded at 250 MHz. Chemical shifts are reported in ppm downfield from tetramethylsilane with the solvent resonance as the internal standard (deuterochloroform: δ 7.26). Signal patterns are indicated as follows: br s, broad singlet; s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. Coupling constants (*J*) are given in hertz (Hz). ^{13}C NMR spectra were recorded at 62.5 MHz, with complete proton decoupling. Chemical shifts are reported in ppm downfield from tetramethylsilane with the solvent resonance as the internal standard (deuterochloroform: δ 77.16). Melting points were determined on a Kofler apparatus and are uncorrected. HRESIMS were acquired in positive ion mode on a Q-TOF premier spectrometer equipped with a nanoelectrospray ion source. Analytical high performance liquid chromatography (HPLC) were performed on a Waters 600E equipped with Varian Prostar 325 detector using a Daicel chiralpak AD-H column or a Phenomenex® Lux 5u-Cellulose-1 column, with detection at 220 nm. Optical rotations were measured on Perkin-Elmer 241 Polarimeter at 20 °C and 589 nm.

Syntheses and characterization of *N*-acyliminium ion precursors



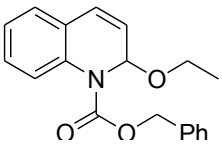
_N_-Methoxycarbonyl-2-ethoxy-1,2-dihydroquinoline (1a)

Following a modification of a previously described procedure,[1,3] a 250 mL round – bottomed flask was loaded with quinoline (97% purity, 2.66 g, 19.2 mmol), water (2.0 mL), dichloromethane (20 mL), ethanol (20 mL) and $NaHCO_3$ (2.52 g, 30 mmol). Freshly distilled methyl chloroformate (3.40 g, 2.8 mL, 36 mmol) was added dropwise over 20 minutes at 0 °C and the resulting suspension was stirred for 2 hours. The reaction was quenched by adding water (15 mL) and the aqueous phase was extracted with dichloromethane (3x25 mL). The combined organic layers was dried over Na_2SO_4 and concentrated in vacuum to afford an amorphous solid which was recrystallized (hexanes) to give a white solid (1.7 g, 71%).



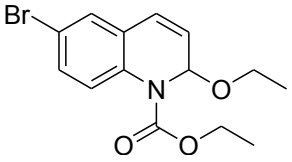
_N_-Ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline (1b)

Following a modification of a previously described procedure,[1,3] a 100 mL round-bottomed flask was charged with quinoline (97% purity, 1.26 g, 9.5 mmol), ethanol (3.2 mL, 47 mmol), water (0.4 mL, 21 mmol) and $NaHCO_3$ (1.1 g, 13 mmol) and the resulting yellowish solution was cooled at 0 °C. Freshly distilled ethyl chloroformate (1.08 g, 10 mmol) was added dropwise over 20 minutes and the reaction mixture was allowed to stir one hour and then quenched with water (10 mL). The aqueous layer was extracted with ethyl acetate (3x15 mL) and the combined organic phases were dried over Na_2SO_4. Removal of solvents under vacuum gave a semisolid which was recrystallized in hexanes to afford the title compound (1.63 g, 69%). The spectral properties are consistent with a previous report.[2]



_N_-Benzyloxycarbonyl-2-ethoxy-1,2-dihydroquinoline (1c)

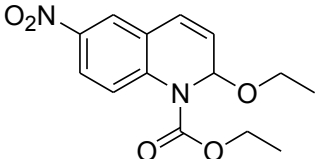
Following a modification of a previous described procedure,[1,3] a 250mL round – bottomed flask was loaded with quinoline (97% purity, 19.2 mmol, 2.66 g), water (2.0 mL), dichloromethane (20 mL), ethanol (20 mL) and $NaHCO_3$ (2.52 g, 30 mmol). Freshly distilled benzyl chloroformate (6.14 g, 5.13 mL , 36 mmol) was added dropwise over 20 minutes at 0 °C and the resulting suspension was stirred for 2 hours. The reaction was quenched by adding water (15 mL) and the aqueous phase was extracted with dichloromethane (3x25 mL). The combined organic layers ware dried over Na_2SO_4, filtered and concentrated to give an oil which was subjected to flash chromatography (7 hexanes/ 3 Et_2O/ 1 Et_3N) to afford a colourless oil (4.4 g, 75%). The spectral properties are consistent with a previous report.[2]



***N*-Ethoxycarbonyl-6-bromo-2-ethoxy-1,2-dihydroquinoline (1d)**

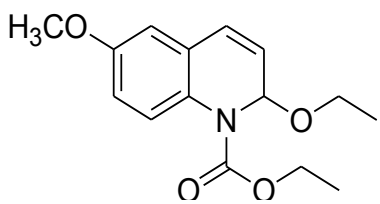
Following a modification of a previously described procedure,[1,3] a 10 mL round-bottomed flask was charged with 6-bromoquinoline (97%, 375 mg, 1.75 mmol), dichloromethane (1.50 mL), ethanol (1.50 mL), water (0.15 mL) and $NaHCO_3$ (220 mg, 2.62 mmol) and the resulting heterogeneous solution was cooled at 0 °C. Freshly distilled ethylchloroformate (0.21 mL, 2.10 mmol) was added dropwise over 5 minutes and the reaction was allowed to react for 16 hours while allowing the ice bath to expire. The reaction mixture was added of water (5 mL), extracted with dichloromethane (3x5 mL), dried over Na_2SO_4, filtered and concentrated to give a yellow oil. Subsequent flash chromatography (7 hexanes/ 3 Et_2O/ 1 Et_3N) afforded compound **1c** as colourless oil (435 mg, 84%).

^{1}H NMR (250 MHz, $CDCl_3$) δ 7.58 (d, 1H, *J* = 8.4 Hz), 7.39 (d, 1H, *J* = 2.3 Hz), 7.37-7.37 (m, 1H), 6.66 (d, 1H, *J* = 9.2 Hz), 6.20 (dd, 1H, *J* = 9.2, 5.5 Hz), 6.12 (d, 1H, *J* = 5.5 Hz), 4.43 – 4.22 (m, 2H), 3.72 – 3.50 (m, 2H), 1.35 (t, 3H, *J* = 7.1 Hz), 1.13 (t, 3H, *J* = 7.0 Hz). ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 154.6, 132.9, 130.6, 129.5, 127.7, 126.7, 126.0, 125.2, 117.0, 78.1, 62.9, 62.7, 15.2, 14.5. HRMS (ESI) m/z [M + Na^+] Calcd for $C_{14}H_{16}BrNO_3Na$ 348,0206, found 348.2001.



***N*-Ethoxycarbonyl-6-nitro-2-ethoxy-1,2-dihydroquinoline (1e)**

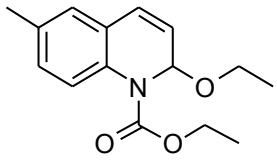
Following a modification of a previously described procedure,[1,3] 6-nitroquinoline (98%, 812 mg, 10.0 mmol) and freshly distilled ethylchloroformiate (2.4 mL, 30 mmol) were added to 50 mL round-bottomed flask and cooled in an ice bath. To that suspension, a solution of Et_3N (5.0 mL) and ethanol (5.0 mL) was added dropwise over 10 minutes and the resulting reaction mixture was allowed to react 1 hour at 0 °C and 16 hours at room temperature. Water (10 mL) was carefully added and the aqueous layer was extracted with dichloromethane (3x10 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated. The reaction crude was subjected to a flash chromatography (9 hexanes/1 Et_3N/ 0.5 DCM) to afford a yellow solid (1.3 g, 43%). The spectral properties are consistent with a previous report.[3]



***N*-Ethoxycarbonyl-6-methoxy-2-ethoxy-1,2-dihydroquinoline (1f)**

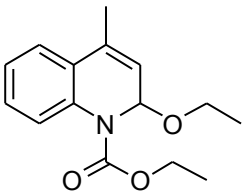
Following a modification of a previously described procedure,[1,3] 6-methoxyquinoline (98%, 812 mg, 5.0 mmol) and freshly distilled ethylchloroformiate (2.4 mL, 25 mmol) were added to 25 mL round-bottom flask and cooled in an ice bath. To that suspension, a solution of Et_3N (2.5 mL) and ethanol

(2.5 mL) was added dropwise over 10 minutes and the resulting reaction mixture was allowed to react 1 hour at 0 °C and 2 hours at room temperature. Water (10 mL) was carefully added and the aqueous layer was extracted with dichloromethane (3x10 mL). Removal of the solvents afforded a sticky semisolid that was suspended in ethyl acetate and filtered. The solution was dried over Na_2SO_4 and concentrated to provide compound **1e** (3.9 g, 70%) as a yellowish oil. The spectral properties are consistent with literature data.[3]



Ethyl 2-ethoxy-6-methylquinoline-1(2*H*)-carboxylate (1g)

The title compound was synthesized following a previously described procedure.[3]



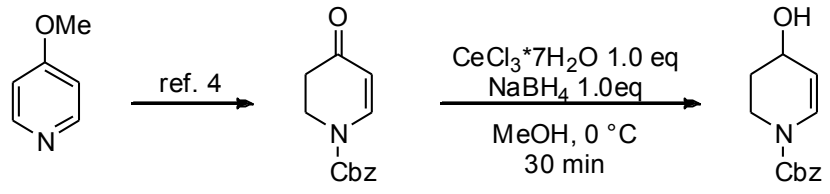
Ethyl 2-ethoxy-4-methylquinoline-1(2*H*)-carboxylate (1h)

A 100 mL round –bottomed flask was loaded with 4-methylquinoline (97% purity, 2.58 g, 17.5 mmol), water (1.5 mL), dichloromethane (15 mL), ethanol (15 mL) and $NaHCO_3$ (2.2 g, 26.2 mmol). Freshly distilled ethyl chloroformate (2.28 g, 2.0 mL, 21 mmol) was added dropwise over 20 minutes at 0 °C and the resulting suspension was stirred for 2 hours. The reaction was quenched by adding water (8 mL) and the aqueous phase was extracted with dichloromethane (3x15 mL). The combined organic layers was dried over Na_2SO_4 and concentrated in vacuum to afford an orange oil which was subjected to flash chromatography (7 hexanes/3 Et_2O/1 Et_3N, R_f= 0.45) to give the title compound (913 mg, 20%).

^{1}H NMR (250 MHz, $CDCl_3$) δ 7.66 (dd, 1H, *J* = 8.1, 1.0 Hz), 7.38 (dd, 1H, *J* = 7.7, 1.6 Hz), 7.34 – 7.24 (m, 1H), 7.22 – 7.12 (m, 1H), 6.06 (dd, 1H, *J* = 5.7, 0.5 Hz), 5.99 (dd, 1H, *J* = 5.7, 1.3 Hz), 4.42 – 4.19 (m, 2H), 3.80 – 3.52 (m, 2H), 2.22 – 2.14 (m, 3H), 1.40 – 1.30 (m, 3H), 1.12 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 154.9, 133.7, 133.5, 127.5, 126.0, 124.5, 124.1, 123.9, 121.3, 78.3, 62.6, 62.5, 18.7, 15.2, 14.5.

HRMS (ESI) m/z [M + Na^+] Calcd for $C_{15}H_{19}NO_3Na$ 284.1263, found 284.1265.

Benzyl 4-hydroxy-3,4-dihydropyridine-1(2*H*)-carboxylate (7)



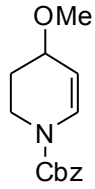
7

In a round-bottomed flask a solution of 1-*N*-(benzyloxycarbonyl)-1,4,5,6-tetrahydro-4-pyridone (463 mg, 2.0 mmol) in methanol (5.0 mL) was cooled at 0 °C and added with $CeCl_3 7H_2O$ (746 mg, 2.0 mmol) to give a milky solution. Sodium borohydride (76 mg, 2.0 mmol) was added portionwise over 15 minutes. The reaction was allowed to react for 30 minutes, quenched with water (4 mL) and the aqueous phase was extracted with dichloromethane (3x10 mL). The combined organic phases were dried over Na_2SO_4 and concentrated under vacuum to give a sticky oil which was subjected to flash chromatography (2 hexanes/ 3 Et_2O). The title compound was recovered as colourless oil (424 mg, 91%). It can be stored at -20 °C for weeks.

^{1}H NMR (250 MHz, $CDCl_3$) δ 7.48 – 7.28 (m, 5H), 7.05 (d, 1H, *J* = 8.2 Hz, minor rotamer), 6.94 (d, 1H, *J* = 8.2 Hz, major rotamer), 5.23 – 4.91 (m, 3H), 4.28-4.17 (m, 1H), 4.07 – 3.84 (m, 1H), 3.52 – 3.34 (m, 1H), 1.98-1.72 (s, 2H), 1.51 (bs, 1H).

^{13}C NMR (62.5 MHz, $CDCl_3$) δ (153.3, 152.7, rotamers), 135.6, 128.3, 128.0, 127.8, 126.9, 126.4, (108.4, 108.0, rotamers), 67.5, (60.2, 60.1, rotamers), (37.8, 37.7, rotamers), 30.1.

HRMS (ESI) m/z [M + Na^+] Calcd for $C_{13}H_{15}NO_3Na$ 256.0950, found 256.0950.



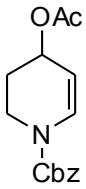
Benzyl 4-methoxy-3,4-dihydropyridine-1(2*H*)-carboxylate (12)

A freshly prepared benzyl 4-hydroxy-3,4-dihydropyridine-1(2H)-carboxylate **7** (500 mg, 2.15 mmol) and pyridinium *p*-toluenesulfonate (99%; 109 mg; 0.43 mmol) were dissolved in methanol (5.4 mL) and the resulting colourless solution was allowed to react 30 minutes at room temperature. Addition of water (5 mL) and extraction of the aqueous phase (3x 10 mL, dichloromethane) gave a solution which was dried over Na_2SO_4, filtered and concentrated. Subsequent flash chromatography (7 hexanes/ 3 AcOEt) afforded a colourless oil (457 mg, 86%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.20 (m, 5H), 6.99 (d, 1H, *J* = 8.6 Hz, minor rotamer), 6.88 (d, 1H , *J* = 8.6 Hz, major rotamer), 5.13 – 4.92 (m, 3H), 3.91 – 3.75 (m, 1H), 3.67 (q, 1H, *J* = 4.1 Hz), 3.34 (d, 1H, *J* = 12.1 Hz), 3.28 (s, 3H), 1.96 – 1.84 (m, 1H), 1.77 – 1.63 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 153.0, 136.1, 128.6, 128.3, 128.2, 127.6, 105.2, (69.4, 69.2, rotamers), 67.9, 55.5, (38.4, 38.2, rotamers), 26.9.

HRMS (ESI) m/z [M + Na^+] Calcd for $C_{14}H_{17}NO_3Na$ 270.1106, found 270.1105.



Benzyl 4-acetoxy-3,4-dihydropyridine-1(2*H*)-carboxylate (7-Ac)

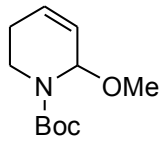
A freshly prepared benzyl 4-hydroxy-3,4-dihydropyridine-1(2*H*)-carboxylate **7** (466 mg, 2.0 mmol) were dissolved in pyridine (2.0 mL). The resulting solution was cooled at 0 °C and acetic anhydride (1.0 mL) was added dropwise. The reaction was allowed to react overnight and concentrated under vacuum to give a crude mixture which was subjected to flash

chromatography (4 pentane/ 1 Et_2O + 1% Et_3N). The title compound was recovered as sticky oil (413 mg, 75%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.29 (m, 5H), 7.12 (d, 1H, *J* = 8.2 Hz, minor rotamer), 7.02 (d, 1H, *J* = 8.3 Hz, major rotamer), 5.20 (s, 2H), 5.15-4.95 (m, 1H), 4.08 – 3.87 (m, 1H), 3.48 – 3.29 (m, 1H), 2.03 (ds, *J* = 0.9 Hz, 3H), 1.99 – 1.84 (m, 2H).

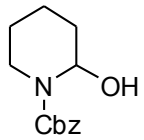
^{13}C NMR (100 MHz, $CDCl_3$) δ 170.6, (153.5, 152.1, rotamers), 136.0, 129.6, 129.1, 128.7, (128.5, 128.3, rotamers), (103.8, 103.4, rotamers), 68.1, 63.9, 38.1, 27.4, 25.8, 21.4.

HRMS (ESI) m/z [M + Na^+] Calcd for $C_{15}H_{17}NO_4Na$ 298.1055, found 298.1055.



***tert*-Butyl 2-methoxy-5,6-dihydropyridine-1(2*H*)-carboxylate (13)**

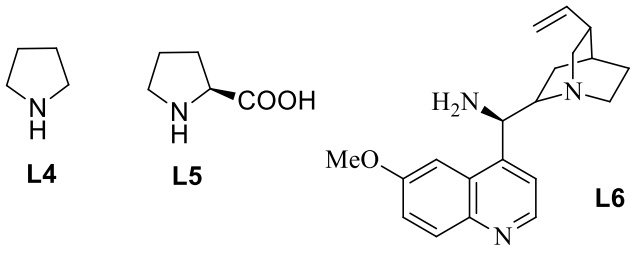
The title compound was synthesized following the literature procedure.[5]



Benzyl 2-hydroxypiperidine-1-carboxylate (14)

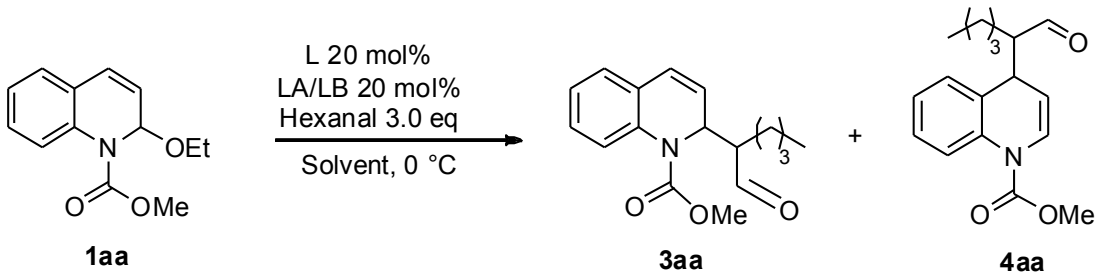
The title compound was synthesized following the literature procedure.[6]

Screening of reaction conditions



Scheme 1. Additional catalysts used in the screenings of reaction conditions

Table 1: Screening of solvents and catalysts for the addition of aldehydes on quinolinium ion



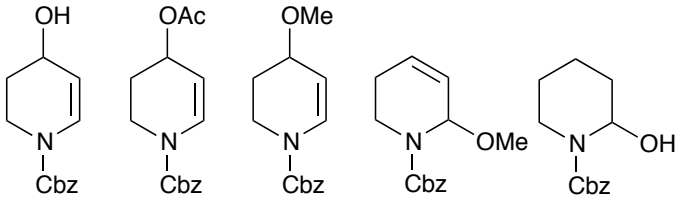
1aa **3aa** **4aa**

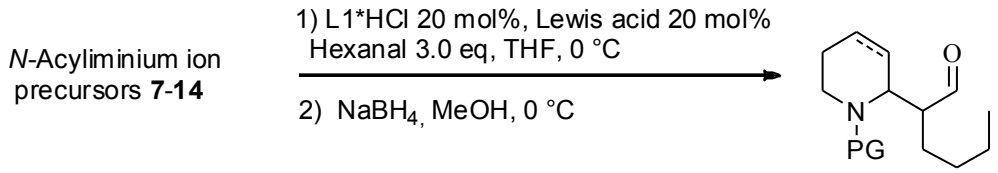
Entry	L	Solvent	LA	Conv. % (Yield %)	3aa/ 4aa	*Syn*-3aa/ *anti*-3aa	Ee% *Syn*-3aa
1	**L4**	Tol	$In(OTf)_3$	88(81)	84/16	82/18	Na
2	**L5**	Tol	$In(OTf)_3$	>5	-	-	-
3	**L5**	DMF	$In(OTf)_3$	47	36/11	82/18	Nd
4	**L1**	Hex	$In(OTf)_3$	52(42)	86/14	67/33	83
5	**L3a**	Hex	$In(OTf)_3$	60 (51)	90/10	75/25	74
6	**L1**	DCM	$In(OTf)_3$	79 (52)	90/10	58/48	43
7	**L2**	DCM	$In(OTf)_3$	81	78/22	60/10	Nd
8	**L3a**	DCM	$In(OTf)_3$	78 (63)	84/16	74/26	92
9	**L1**	DMF	$In(OTf)_3$	52(45)	87/13	65/35	29
10	**L2**	DMF	$In(OTf)_3$	63(51)	83/17	63/37	Nd
11	**L3a**	DMF	$In(OTf)_3$	63 (55)	90/10	60/40	58
12	**L1**	THF	$In(OTf)_3$	100 (90)	90/10	58/42	6
13	**L2**	Et_2O	$In(OTf)_3$	93 (84)	63/37	61/39	78
14	**L2**	TBE	$In(OTf)_3$	91 (81)	75/25	58/42	84
15	**L2**	Dioxane	$In(OTf)_3$	93 (84)	86/14	46/54	92

Representative reaction conditions reported in Table 1

An oven-dried 10 mL pyrex vial was charged with **1a** (47 mg, 0.20 mmol) followed by the specified solvent (0.25 M), catalyst (20 mol%) and hexanal (74 μL, 0.60 mmol). The resulting solution was cooled to 0 °C and added with $In(OTf)_3$ (22.5 mg, 0.04 mmol). The mixture was allowed to react until no *N,O*-acetal **1a** was detected by TLC (pre-treated with 10% triethylamine in hexanes), quenched with water (5 ml), extracted three times with Et_2O (8 mL) and the combined organic phases were dried over $MgSO_4$. Removal of solvents afforded a crude which was purified by flash chromatography (8 hexanes /2 Et_2O). R_f=0.46 for compound **4aa;** R_f=0.29 for compound **3aa**.

Table 2: Screening of *N*-acyliminium precursors for the alkylation of piperidine compounds.



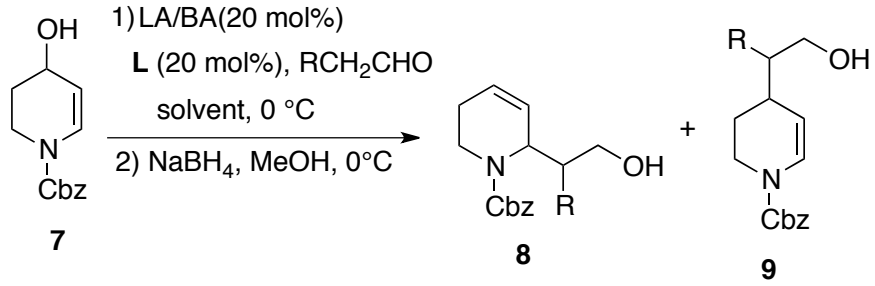


Entry	N-Acyliminium ion Precursor	Lewis acid	Reaction Time	Conv.	Yield %
1	**7-Ac**	$In(OTf)_3$	20 h	100%	0 %
2	**12**	$In(OTf)_3$	20 h	0 %	0 %
3	**12**	BF_3*OEt_2 2.0 eq	1 h	100%	0 %
4	**13**	$In(OTf)_3$	2 h	100%	0 %
5	**14**	$In(OTf)_3$	3 h	100%	0 %
6	**7**	$In(OTf)_3$	20 h	100%	35% (**8a**)

Representative reaction conditions of Table 2

An oven-dried 10 mL pyrex vial was charged with the *N*-acyliminium ion precursor **7, 7-Ac, 12-14** (0.20 mmol), dissolved in THF (0.40 mL) followed by hexanal (74 μL, 0.60 mmol) and **L1***HCl (10.2 mg, 0.04 mmol). The resulting solution was cooled to 0 °C and additioned with $In(OTf)_3$ (22.5 mg, 0.04 mmol). The mixture was allowed to react until no compounds **7, 7-Ac, 12-14** were detected by TLC. The solution was then cooled at 0 °C, diluted with methanol (0.20 mL) and additioned with sodium borohydride (15 mg, 0.4 mL). Upon disappearance of the corresponding aldehyde, the reaction mixture was quenched with water (4 mL) and the resulting aqueous layer was extracted with Et_2O four times. The combined organic layers were dried over $MgSO_4$, filtered and concentrated to afford a residue which was purified by flash chromatography or/and preparative TLC.

Table 3: Screening of reaction conditions using **7** as *N*-acyliminium precursor



Entry	R	L	LA/LB	Solvent	Temp	React. Time	8/9	*Syn*/*Anti* *8*	Yield	(Ee%)
1	C_4H_9	**L4**	$In(OTf)_3$	THF	rt	23 h	-	-	-	-
2	C_4H_9	**L4**	$Yb(OTf)_3$	THF	rt	16 h	-	-	-	-
3	C_4H_9	**L2**	$Yb(OTf)_3$	THF	rt	24 h	99/1	52/48	15%	Nd
4	C_4H_9	**L6**	$In(OTf)_3$	THF	rt	20 h	-	-	-	-
5	C_4H_9	**L6*TFA**	$In(OTf)_3$	THF	rt	1 h	-	-	-	-
6	C_4H_9	**L2**	-	THF	rt	60 h	-	-	-	-
7	C_4H_9	**L2**	$In(OTf)_3$	DCM	rt	1 h	-	-	-	-
8	C_4H_9	**L2**	$In(OTf)_3$	Tol	rt	1 h	99/1	Nd	<5%	Nd
9	C_4H_9	**L2**	$In(OTf)_3$	DMF	rt	24 h	99/1		<5%	
10	C_4H_9	**L2**	$In(OTf)_3$	DMSO	rt	56 h	-	-	-	-
11	C_4H_9	**L2**	$In(OTf)_3$	MTBE	rt	1 h	99/1	Nd	<5%	Nd
12	C_4H_9	**L2**	$In(OTf)_3$	Et_2O	rt	1 h	99/1	Nd	<5%	Nd
13	C_4H_9	**L2**	$In(OTf)_3$/	THF with 5 eq H_2O	rt	36 h	99/1	Nd	<5%	Nd
14	C_4H_9	**L3a**	$In(OTf)_3$/TsOH	Tol	rt	16 h	-	-	-	-
15	C_4H_9	**L2**	TsOH	THF	rt	24 h	-	-	-	-
16	$PhCH_2$	**L1**	$In(OTf)_3$	toluene	0 °C	3 h	95/5	Nd	<5%	Nd
17	$PhCH_2$	**L2**	$In(OTf)_3$	THF	0 °C	1 h	95/5	74/26	57%	63(*syn*)/ 6(*anti*)
18	$PhCH_2$	**L2**	$In(OTf)_3$	DCM	0 °C	1.5 h	-	-	-	-
19	$PhCH_2$	**L2**	$In(OTf)_3$	Hex	0 °C	1.5 h	95/5	53/47	41	84(*syn*)/ 70(*anti*)
20	$PhCH_2$	**L2**	$In(OTf)_3$	DMF	rt	27 h	95/5	57/43	44	88(*syn*)/ 56(*anti*)
21	$PhCH_2$	**L2**	$In(OTf)_3$	Acetone	0 °C	1 h	95/5	94/6	16	32(*syn*)/ 72(*anti*)