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Copper Hydride-Catalyzed Conjugate Reduction-Aldol Addition Domino Reaction of α,β-Unsaturated Carboxylates with Ketones

Zengchang Li,[a] Lan Jiang,[b] Zhengning Li,*[,a,b] and Huiying Chen[c]

[a] *College of Environmental and Chemical Engineering*, *Dalian University*, *Dalian*, *Liaoning 116622*, *China*
[b] *Liaoning Key Laboratory of Bioorganic Chemistry*, *Dalian University*, *Dalian*, *Liaoning 116622*, *China*
[c] *College of Life Science*, *Dalian Nationalities University*, *Dalian*, *Liaoning 116600*, *China*

Copper hydride-catalyzed conjugate reduction-intermolecular aldol addition domino reactions were realized using *α*,*β*-unsaturated carboxylates as hydride acceptors and a silane as the reducing reagent. High diastereoselectivities were achieved with 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene as the ligand and *tert*-butyl acrylate as the hydride acceptor.

Keywords reduction, aldol addition, domino reaction, copper hydride, catalysis

Introduction

The hydrides of group IIIA and IVA metals have been widely used as reducing reagents, whereas those of transition metals have been employed as catalysts in reduction reactions. Organocopper compounds are generally associated with conjugate addition to *α*,*β*-unsaturated substrates. Copper hydride has been regarded as the reagent of choice for conjugate reduction of *α*,*β*-unsaturated carbonyl compounds including ketones, esters and amides.[1,2] It has also been utilized as the catalyst in chemoselective 1,4-reduction of *α*,*β*-unsaturated carbonyls as well as in the reduction of ketones.[3] Even though 1,4-reductions can proceed in the presence of other transition metal hydrides (*e.g.* rhodium, cobalt and palladium),[4-6] the use of copper hydride has its inherent advantages of lower price and higher selectivity.[7] Reactions of copper hydrides with *α*,*β*-unsaturated carbonyl compounds generate enolates, which are potential nucleophiles towards carbonyl groups. Performing the reduction and nucleophilic addition to unsaturated carbon atom in a one-pot manner results in reductive-aldol addition domino reactions,[8] making the process more efficient. Additionally, the formation of enolates via the addition of copper hydride to *α*,*β*-unsaturated carbonyls is regioselective under mild conditions, whereas the alternative formation of enolates via deprotonation of ketones is not as regioselective or requires careful control of reaction conditions. Furthermore, the domino process avoids the possible side aldol reaction/Claisen ester condensation reaction generally associated with the deprotonation of ketones or esters, making the reaction more chemoselective. Because of this, copper hydride-catalyzed conjugate reductive aldol addition reactions under mild conditions offer a powerful tool in the synthesis of *β*-hydroxy carbonyls and related molecules. This has been well documented in the last decade, especially about reductive intramolecular aldol addition reactions yielding five- and six-membered rings.[1a] Chiu has found that five- and six-membered carbocyclic *β*-hydroxyketones can be produced in high diastereoselectivity using Stryker's reagent at low temperatures.[9] Formation of five- and six-membered *β*-hydroxylactones and 4-hydroxypiperidon-2-ones has also been achieved in high diastereoselectivity from *α*,*β*-unsaturated esters and amides respectively.[10,11] Additionally, the asymmetric versions of this type of reaction have also been reported using optically pure chiral ligand.[7,12]

Compared to the fact that there are abundant examples of copper hydride-catalyzed conjugate reductive intra-molecular aldol addition,[13] there are a few reports about conjugate reductive intermolecular aldol addition.[14] In 2000, Lipshutz *et al*. showed that CuH-catalyzed 1,4-reduction-Mukaiyama aldol reactions can be carried out in one bottle.[15] Reactions of silanes with enones in the presence of catalytic amounts of $[CuH(PPh_3)]_6$ gave enol silyl ethers, which were trapped by adding aldehydes at −78 ℃ under the activation of Lewis acids (BF_3•OEt_2 or $TiCl_4$). This yielded the desired aldol products (82%—89%) as a diastereomeric mixture. In 2006, Shibasaki *et al.* reported the first example of a copper-catalyzed intermolecular reductive

* E-mail: znli@dl.cn; Tel.: 0086-0411-87403576; Fax: 0086-0411-87402449
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aldol domino reactions using catalysts generated from $CuF(PPh_3)_3$•2MeOH or CuOBu-*t*, (*R*)-tol-BINAP and silanes,[16] yielding the product in moderate diastereoselectivity. In the same year, Riant's group demonstrated highly diastereo- and enantioselective copper-catalyzed reductive aldol reactions of ketones with methyl acrylate at −50 ℃ in the presence of $CuF(PPh_3)_3$•2MeOH-taniaphos and $PhSiH_3$.[17] In 2009, Fukuzawa applied (S,R_p)-5-(diphenylphosphino)-1-{1-[2-(diphenylphosphino)ferrocenyl]ethyl}-1*H*-1,2,3-triazole (clickFerrophos), which have similar structures to taniaphos, in Cu(I)-catalyzed asymmetric reductive aldol reactions of ketones and aldehydes with an acrylic ester in the presence of phenylsilane and obtained both high diastereo- and enantioselectivities.[18] A recent development of Cu-catalyzed conjugation-aldol reaction involves borylation-aldol reaction.[19]

The copper catalysis has been one of the research subjects of our group.[20] Very recently, we reported that copper hydride ligated with bis[(1,2-diphenylphosphino)-phenyl] ether (DPEphos, Figure 1) could catalyze the reductive-intramolecular aldol addition of β'-oxoalkyl α,β-unsaturated carboxylates efficiently.[21] It is of great importance to perform more challenging reductive-intermolecular aldol addition domino reaction. Herein, we report that the intermolecular domino reaction of α,β-unsaturated carboxylates with ketones and a silane can be accomplished in the presence of CuH-DPEphos or CuH ligated with 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (Xantphos), and that high diastereoselectivity can be achieved.

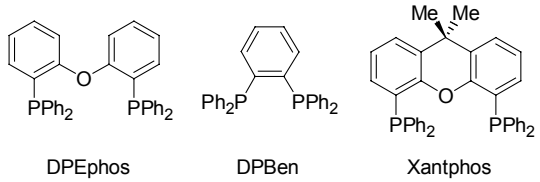

Figure 1 Structures of DPEphos, DPBen and Xantphos

Experimental

A typical procedure for reductive aldol reactions of phenylethanone, acrylate and poly(methylhydrosiloxane) (PMHS) is as follows (mode 4): under a nitrogen atmosphere and at room temperature, a solution of $CuF(PPh_3)_3$•2MeOH (5.6 mg, 0.0060 mmol), DPEphos (3.1 mg, 0.0058 mmol) in THF (2.0 mL) in a dried Schlenk tube was stirred for 30 min before PMHS (0.15 mL, 2.5 mmol) was added. After the mixture was stirred for 15 min, a solution of ketone **1A** (72 mg, 0.60 mmol) and **2** (70 μL, 0.78 mmol) was added, and the mixture was continually stirred until complete or nearly complete consumption of **1A** was reached, as monitored with GC. Quenching of the reaction and hydrolysis of the formed silyl ether were conducted by the addition of ammonium fluoride solution in methanol-water (3/1) (10 mL, 0.3 mol/L) and stirring for a certain period. The mixture was analyzed with GC. General workup and column chromatographic separation gave the reductive-aldol addition product as colorless liquid (102 mg, 81% yield).

Structures of the reductive aldol addition products were confirmed by MS and NMR data, which were in agreement to those reported in the literature. Stereochemistry of the products which have been reported in literature was referred to literature data of chemical shifts and coupling constants.[17,18] For those diastereomers unreported in literature, their stereochemistry was deduced by comparing the proton coupling constants in ^{1}H NMR with their structural analogues. Structures of carbonyl reduction products were deduced from mass spectra and retention time in GC with the samples prepared by reduction of ketones with sodium borohydride.

***Syn*-3A**: Colorless solid, m.p. 56－59 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.43 (d, J=7.8 Hz, 2H), 7.34 (t, J=7.6 Hz, 2H), 7.24 (t, J=7.5 Hz, 1H), 3.84 (s, 1H), 3.75 (s, 3H), 2.86 (q, J=7.1 Hz, 1H), 1.55 (s, 3H), 0.96 (d, J=7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 177.75, 145.11, 128.21, 126.77, 124.95, 74.40, 52.01, 49.38, 30.03, 12.87. LRMS (EI, 70 eV) *m*/*z* (%): 208 (4, M^+), 193 (36), 191 (2), 177 (4), 161 (22), 149 (1) 133 (5), 121 (100)), 105 (88), 91 (21), 77 (57), 57 (17), 43 (85), 28 (6); IR (CH_2Cl_2) *v*: 3493, 3033, 2982, 1704, 1497, 1447, 1434, 1371, 1352, 1296, 1197, 1171, 1125, 1091, 1068, 1039, 1027, 1004, 975, 928, 878, 764, 697 cm^{-1}. The NMR data are in agreement to those reported in literature.[17,18]

***Anti*-3A**: Colorless liqud; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.42 (d, J=7.8 Hz, 2H), 7.31 (t, J=7.5 Hz, 2H), 7.21 (t, J=7.0 Hz, 1H), 4.03 (s, 1H), 3.45 (s, 3H), 3.02 (q, J=7.0 Hz, 1H), 1.46 (s, 3H), 1.32 (d, J=7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 177.20, 147.60, 128.20, 126.89, 124.74, 74.75, 51.73, 48.64, 26.71, 12.58; LRMS (EI, 70 eV) *m*/*z* (%): 208 (4, M^+), 193 (0.5), 177 (1), 161 (1), 147 (0.2) 131 (3), 121 (100), 105 (21), 88 (10), 77 (13), 57 (4), 43 (38), 28 (2); IR (CH_2Cl_2) *v*: 3493, 2984, 2950, 1712, 1601, 1494, 1446, 1435, 1379, 1349, 1270, 1228, 1198, 1174, 1125, 1092, 1068, 1028, 1002, 976, 934, 911, 875, 765, 700 cm^{-1}. The NMR data are in agreement to those reported in literature.[17,18]

Spectral data of other reductive aldol addition products can be found in the additional file.

Results and Discussion

Our experiment started from the reaction of phenylethanone (**1A**), methyl acrylate (**2**) and PMHS, which has been reported using other ligands and other silanes as the reducing reagent in the literature. Previously, Shibasaki *et al.* obtained the reductive aldol reaction products with moderate diastereoselectivity (diastereomer ratio from 44/56 to 57/43) using $(EtO)_3SiH$ as the reducing agent and BINAP as the ligand.[16] It is also known from the literature that high yield could be ob-

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tained by very slow addition of the silane. When the silane was added in one portion, 1-phenylethanol was the major product, and the yields of the reductive-aldol addition product were only 37% and 47% with *in situ* prepared CuOBu-*t* and $CuF(PPh_3)_3$•2EtOH, respectively, as the copper source.

Four reaction modes were used in our experiments in recognizing the competitive reduction of the ketone by copper hydride.

Mode 1: solutions of **1A**, **2** and PMHS in toluene (0.5 mL×2) were transferred into a stirred solution of $CuF(PPh_3)_3$•2MeOH (2 mol%) and a ligand in 1.0 mL of toluene. After the completion of the reaction, the mixture was quenched, hydrolyzed, and analyzed with GC.

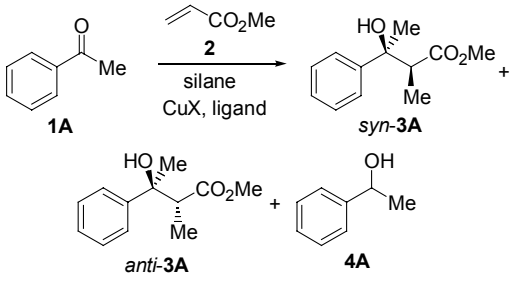
Mode 2: the same procedure as in mode 1 was used except that 2.0 mL of THF replaced 1.0 mL of toluene as the solvent.

Mode 3: silane was added to a stirred solution of $CuF(PPh_3)_3$•2MeOH (1 mol%) and a ligand in 1.0 mL of THF, followed by the addition of solutions of **1A** and **2** in THF. The product mixture was treated in the same way as that used in mode 1.

Mode 4: everything is the same as that in mode 3 except that 2.0 mL instead of 1.0 mL of THF was used.

As shown in Table 1, mode 1 presented that a 38% yield of **3A** was formed as a mixture of diastereomers (Entry 1). The direct reduction of **1A** was a major competitive side reaction, which was also indicated by Shibasaki's result using the ligand BINAP. However, the reaction was more selective with DPEphos as the ligand. Diastereomeric ratio between *anti*-**3A** and *syn*-**3A** reached 59/41, whereas in Shibasaki's case, the ratio is below 55/45. Switching the solvent from toluene to THF resulted in higher conversion of **1A** and higher yield of **3A** (Entry 2). It is obvious that mode 4 is better than mode 1, 2 and 3 using DPEphos as the ligand, in terms of the conversion of **1A** and the yield of **3A** (Entry 4 vs. Entries 1—3). The diastereoselectivity of **3A** was not sensitive to the addition sequence of the reagents. Other diphosphine ligands linked with $(CH_2)_n$ were also employed to assess their influence on the diastereoselectivities. Lower diastereoselectivities were obtained using 1,2-bis(diphenylphosphino)ethane (dppe) and 1,3-bis(diphenylphosphino)propane (dppp) (Entries 5, 6); comparable diastereoselectivity but with lower yield of **3A** was observed when 1,4-bis(diphenylphosphino)butane (dppb) was used (Entries 7 and 8). With 1,2-bis(diphenylphosphino)benzene (DPBen, Figure 1), the ligand in efficient copper catalyst for conjugate reduction of challenging unsaturated carbonyls,[22,23] lower yield and diastereoselectivity of the aldol product were obtained (Entry 9). There were no differences of the yields and the diastereomeric distribution when the reaction was also carried out with 2 equiv. of PPh_3 and no additional PPh_3 (based on copper complex) (Entries 10 and 11). However, the diastereoselectivity is lower than that using DPEphos as the additional ligand (Entries 9, 10 vs. Entry 4).

Table 1 Reductive aldol reaction using different ligands[a]



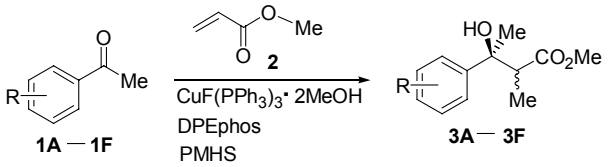
Entry	Ligand	Mode[a]	Time/h	Component[b]//%		
				1	**3A** (*anti*-/*syn*-)	**4A**
1	DPEphos	1	3.6	27.3	38 (59/41)	16.5
2	DPEphos	2	1.0	7.7	75 (60/40)	1.4
3	DPEphos	3	3.3	12.7	65 (59/41)	8.3
4	DPEphos	4	1.0	6.9	81 (59/41)	0.7
5	dppe	4	1.0	4.9	69 (48/52)	0.3
6	dppp	4	1.0	3.2	80 (51/49)	1.0
7	dppb	3	3.0	13.9	76 (59/41)	0.9
8	dppb	4	1.0	5.5	67 (59/41)	0.2
9	DPBen	4	1.0	3.2	96.8 (43/57)	0.0
10	PPh_3	4	1.0	8.6	91.4 (52/48)	0.0
11	—	4	1.0	10.3	89.4 (53/47)	0.2

[a] In modes 1 and 2, molar ratio of **1**∶**2**∶ligand∶$CuF(PPh_3)_3$•2MeOH∶PMHS=1∶1.2∶2%∶2%∶6.0 (molar ratio), room temperature; in modes 3 and 4, **1**∶**2**∶ligand∶$CuF(PPh_3)_3$•2MeOH∶PMHS=1∶1.3∶1%∶1%∶4.0, room temperature; [b] determined by GC.Table 2 summarizes selected results of the reactions of the substituted phenylethanones carried out with Mode 4. With a substituent attached to the *para*-position of phenyl, comparable or higher yields were obtained. In regarding to the diastereoselectivity, those with electron-donating substituents gave higher selectivities (Entries 6, 7 vs. 1), whereas those with electron-withdrawing ones afforded lower selectivities (Entries 2—5 vs. 1).

The results of the domino reactions of replacing methyl acrylate with methyl crotonate (**5**) were shown in Table 3. The reactions were slower than those using acrylate, and lower yields of the aldol products **6A**—**6D**, **6F** and **6G**, in the range of 57%—70%, were also observed. The diastereoselectivities did not improve with the introduction of a methyl group to the *β*-C in the acrylate. Like the reaction of acrylate, diastereomeric aldol products were slightly favored when using the substituted phenylethanones.

Unable to improve the diastereoselectivity by changing the acid moiety of the unsaturated esters, we envisioned that decreasing the reaction temperature and the employment of bulky alkyl ester may help. The diastereoselectivity in the aldol addition is controlled by the orientation of the enolate generated from the unsaturated ester and groups attached to carbonyl in the

Table 2 Reductive aldol reaction of methyl acrylate with substituted phenylethanones[a]

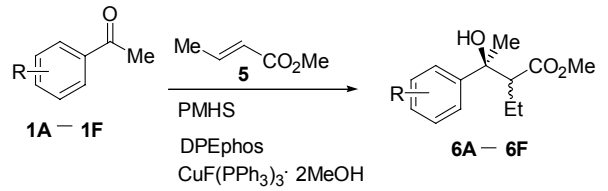


1A: R = *p*-H; **1B**: R = *p*-Cl;
1C: R = *p*-Br; **1D**: R = *p*-NO_2;
1E: R = *m*-NO_2; **1F**: R = *p*-CH_3;
1G: R = *p*-CH_3O

Entry	1	Component[b]/%			Yield of 3[c]/%
		1	3 (*anti*-/*syn*-)	4	
1	**1A**	6.9	92.4 (59/41)	0.7	81
2	**1B**	5.3	93.5 (51/49)	1.2	80
3	**1C**	0.0	94.0 (50/50)	5.5	82
4	**1D**	0.0	100.0 (43/57)	0.0	95
5	**1E**	1.4	97.0 (48/52)	1.5	97
6	**1F**	0.0	95.2 (62/38)	4.8	89
7	**1G**	8.5	91.5 (61/39)	0.0	86

[a] **1** ∶ **2** ∶ DPEphos ∶ $CuF(PPh_3)_3$•2MeOH: PMHS = 1 ∶ 1.3 ∶ 1% ∶ 1% ∶ 4.0 (molar ratio), room temperature, 1 h, mode 4; [b] determined by GC; [c] isolated yield.

Table 3 Reductive aldol reaction of methyl crotonate with substituted phenylethanone[a]

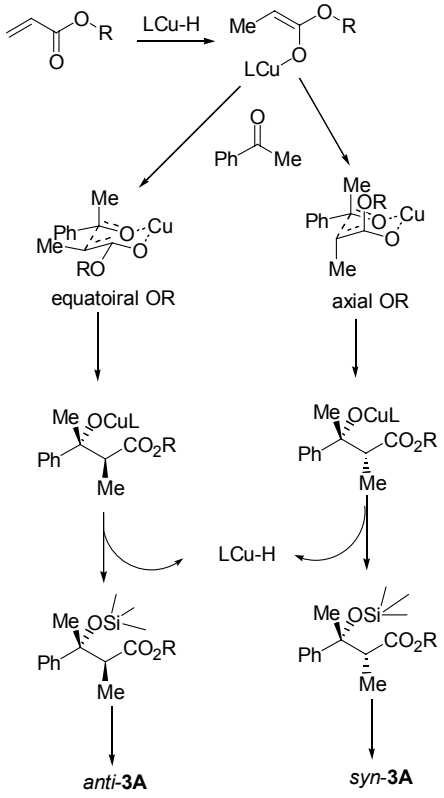


Entry	1	Time/h	Component[b]/%			Yield of 6[c]/%
			1	6 (*anti*-/*syn*-)	4	
1	**1A**	1.6	11.4	85.8 (60/40)	2.7	70
2	**1B**	1	6.6	85.7 (49/51)	5.3	62
3	**1C**	1	5.7	86.8 (48/52)	7.5	57
4	**1D**	1	0	45.6 (40/60)	54.4	54
5	**1F**	2	6.4	92.5 (66/34)	1.0	63
6	**1G**[d]	1	22.2	77.7 (58/42)	0	75
7	**1G**[d,e]	1	3.7	96.3 (59/41)	0	70

[a] Molar ratio of **1** ∶ **5** ∶ DPEphos ∶ $CuF(PPh_3)_3$•2MeOH ∶ PMHS = 1 ∶ 1.3 ∶ 1% ∶ 1% ∶ 4.0, THF, room temperature, mode 4; [b] determined by GC; [c] isolated yield; [d] 0.65 equiv. **5** was added after the first addition of 1.3 equiv. **5** in 30 min. Total reaction time 2 h since the first addition of **1** and 1.3 equiv. **5**; [e] 5 mol% of $CuF(PPh_3)_3$•2MeOH and 5 mol% of DPEphos.

proposed 6-membered ring transition state as described in Scheme 1. Early experiments have shown that deprotonation of ester yielded lithium enolate in favor of (*Z*) isomer, addition of this isomer produced *anti*-isomer of aldol product.[24] We presume that the same configuration of copper enolate was generated from the addition of copper hydride to acrylate. For an ester with a small alkoxy group, there is little energy difference when the alkoxy is at either in an axial position or an equatorial position in the transition states of the aldol addition. However, a bulky alkyl group in the ester would differentiate the axial and equatorial orientation of the alkoxy group in the transition ring, and therefore, might favor the formation of *anti*-isomer of aldol products.

Scheme 1 A possible reaction mechanism of CuH-catalyzed reduction of acrylate with a silane, and the followed aldol reaction with phenylethanone



In order to test the assumption, *tert*-butyl ester was used and the domino reaction generated the aldol product in 78% isolated yield for reductive aldol product **8A** (Table 4, Entry 1). The diastereomer ratio was improved to 76/24 (Table 4, Entry 1) from 59/41 using the methyl ester (Table 2, Entry 1). For other substituted phenylethanones, the ratios for products **8B**—**8G** also increased when methyl ester was replaced by *tert*-butyl ester.

Decreasing the temperature also favored the more stable equatorial rather than the less stable axial group orientation in transitional state, and therefore improved the diastereoselectivity of the aldol products. As shown in Table 4, with phenylethanone as the substrate and THF as the solvent, the aldol products ratio increased with lowering the temperature; the *anti*-/*syn*- ratio changed from 76/24 at room temperature to 80/20 and 84/16 at 0 ℃ and −20 ℃, respectively (Entries 1, 3, 5). These ratios are much higher than the 57/43 obtained by

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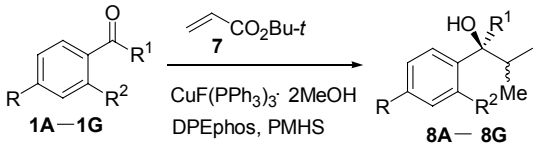
Shibasaki using (*R*)-tol-BINAP ligand.[16] Changing the solvent to toluene, an uncoordinated solvent, the same trend was observed. As expected, substrates **1B**—**1E** with electron-withdrawing groups are more reactive toward the enolate intermediate than **1A**, as shorter reaction time is needed for high conversion of ketone substrates. The diastereoselectivities for products **8B**—**8E** were improved by decreasing the reaction temperature and switching the alkyl group in the acrylate to a larger one (Entries 6—10), but they were lower than that of **8A** (Entry 5). It should be noted that **1E** was not very reactive at −30 ℃ (Entry 11). Enolate acceptors **1F** and **1G**, which contain electron-donating groups, were not as reactive but highly selective. *Anti*-/*syn* -ratio reached 84/16 for **8F**, and 87/13 for **8G** at −20 ℃ (Entries 12, 14). Lowering the temperature to −30 ℃ resulted in decreased conversion of **1F** and a little increase of the diastereomeric ratio of the aldol product **8F** (Entry 13 *vs.* 12). For **1G** which has a more electron-donating *para*-methoxyl group, longer reaction time and use of more acrylate were needed to improve the conversion of **1G** and the yield of **8G**. In this case, the *anti*-/*syn*- ratio did not change (Entry 16 *vs.* 15). It is worth noting that the sensitivity of the diastereoselectivities to reaction temperatures using the CuH-DPEphos catalyst is different from Riant's observation that varying the temperature from 0 ℃ to −50 ℃ did not influence the diastereoselectivity of the reaction.[17]

With a larger bite angle than DPEphos, 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (Xantphos, Figure 1) has demonstrated great selectivity in metal-catalyzed reactions such as hydroformylation.[25] Its copper complex exhibits excellent catalytic property in the reduction of *α*,*β*-unsaturated nitriles with PMHS.[26] Assuming that the orientation of the groups in the transition state is sensitive to the presence of bulky Xantphos ligand coordinating to copper, and thus improve the diastereoselectivities of the aldol products, we applied Xantphos ligand to the reductive aldol reactions among PMHS, *tert*-butyl acrylate and substituted phenylethanones. To our pleasure, higher diastereoselectivities were obtained with this ligand than those with DPEphos ligand. Some results are summarized in Table 5.

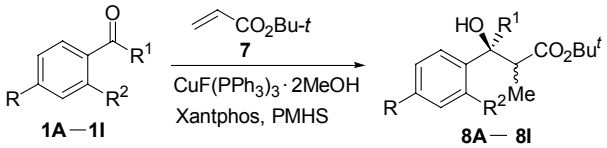
Table 4 Reductive aldol reaction of *tert*-butyl acrylate with substituted phenylethanones[a]



Entry	1	Temp./℃	Component[b]/%			Yield of 8[c]/%
			1	8 (*anti*-/*syn*-)	4	
1	**1A**	r.t.[d]	1.4	98.2 (76/24)	0.4	78
2	**1A**	5[e]	2.1	96.5 (80/20)	1.5	73
3	**1A**	0	2.5	97.0 (80/20)	0.5	81
4	**1A**	−15	8.3	91.7 (83/17)	0.0	73
5	**1A**	−20	2.6	97.4 (84/16)	0.0	68
6	**1B**	−30[d]	0.0	100.0 (70/30)	0.0	84
7	**1C**	−30[f]	0.0	77.3 (71/29)	0.0	90
8	**1D**	r.t.	0.0	97.6 (62/38)	2.4	73
9	**1D**	−30	0.0	91.6 (66/34)	8.4	83
10	**1E**	r.t.	0.0	97.6 (66/34)	6.1	80
11	**1E**	−30	86.3	8.3 (60/40)	5.4	—
12	**1F**	−20	2.6	97.4 (84/16)	0.0	68
13	**1F**	−30	7.2	91.2 (86/14)	1.5	83
14	**1G**	−20	16.8	83.2 (87/13)	0.0	73
15	**1G**	−30	20.8	79.1 (88/12)	0.0	66
16	**1G**	−30[d,g]	5.1	94.9 (87/13)	0.0	95

[a] **1**, 0.6 mmol, **1**∶**2**∶DPEphos∶$CuF(PPh_3)_3$•2MeOH∶PMHS =1∶1.3∶1%∶1%∶4.0 (molar ratio), THF, room temperature, mode 4, 1 h unless noted; [b] determined by GC; [c] isolated yield; [d] 1.5 h; [e] 3 h; [f] 1.3 h; [g] 0.65 equiv. **7** was added after the first addition of 1.3 equiv. **7** in 30 min. Total reaction time 2 h since the first addition of **1** and 1.3 equiv. **7**.

Table 5 Reductive aldol reaction of *tert*-butyl acrylate with substituted phenylethanones (**1**) using Xantphos ligand[a]



1H: R = H, R^1 = Me, R^2 = Me;
1I: R = Cl, R^1 = H, R^2 = H

Entry	1	Time/h	Component[b]/%			Yield of 8[c]/%
			1	8 (*anti*-/*syn*-)	4	
1	**1A**	1.0	6.2	88.8 (92/8)	5.0	72
2	**1B**	1.0	0.0	96.0 (81/18)	4.0	80
3	**1C**	1.0	0.0	97.0 (82/18)	3.0	79
4	**1D**	1.0	0.0	98.5 (72/28)	1.5	96
5	**1E**	1.0	18.5	81.5 (78/22)	0.0	70
6	**1F**	1.5[d]	0.0	93.3 (95/5)	6.7	61
7	**1G**	1.5	11.9	88.1 (96/4)	0.0	82
8	**1H**	2[d]	8.2	91.8/1 (75/25)	0.0	68
9	**1I**	3	0.0	72.0 (54/46)[e]	28.0	49

[a] **1**∶**7**∶Xantphos∶CuX∶silane=1∶1.3∶1%∶1%∶4, THF, −30 ℃; [b] determined by GC; [c] isolated yield; [d] 20 min after the addition of **1** and **7**, an additional 0.65 equiv. **7** was added; [e] determined by ^{1}H NMR.

For phenylethanone, the ratio rose to 92/8 (Entry 1). Impressively, the *anti*-/*syn*-isomer product ratio for the reaction of 4-methoxyphenylethanone reached 96/4 (Entry 7). High selectivities were also achieved for those with electron-withdrawing groups (Entries 2—5). The presence of a *meta*-nitro group in the ketone substrate gave much amount of substituted phenylethanol,

along with the aldol addition product (Entry 5). Effort to increase the diastereoselectivity by using an *ortho*-substituted phenylethanone **1H** is unsuccessful (Entry 8). The reaction was so slow that 5 h was needed to get a 57% conversion of **1H** at −30 ℃; increasing the reaction temperature to −15 ℃ led to high conversion of **1H**, but the diastereomeric ratio was not as high as that using its *para*-analogue **1F** (Entries 8 vs. 6). Aldehyde **1I** was also be utilized as enolate acceptor, but the diastereoselectivity is disappointing (Entry 9), which may be due to its higher reactivity than ketones, just as electron-deficient ketones are more reactive than electron-rich ketones, giving inferior diastereoselectivity.

Conclusions

In summary, copper hydride derived from $CuF(PPh_3)_3$•2MeOH, DPEphos or Xantphos, and PMHS can catalyze the intermolecular conjugate reductive aldol reactions of acrylate with ketones using PMHS as the reducing agent, generating *β*-hydroxycarboxylates in good yields. The diastereoselectivity can be improved remarkably by using *tert*-butyl esters, Xantphos ligand and low reaction temperatures.

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