Copper–ClickFerrophos-Complex-Catalyzed Enantioselective Reductive Aldol Reaction

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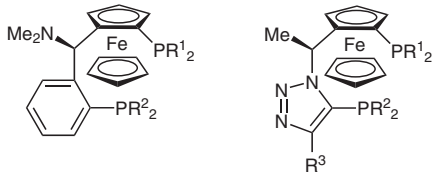
Abstract: We have prepared several ClickFerrophos families and tested for the Cu(I)-catalyzed asymmetric reductive aldol reaction of ketones and aldehydes with an acrylic ester in the presence of phenylsilane. The Cu(I)–ClickFerrophos complex is efficient for the reaction of ketones with methyl acrylate to afford the *erythro* adducts both highly diastereo- and enantioselectively; the diastereomeric ratio of *erythro*/*threo* is improved when compared to the analogous Taniaphos.

Key words: aldol reactions, asymmetric catalysis, metallocenes, phosphorus, copper

The reductive aldol reaction, which is a sequence of conjugate reductions of an α,β-unsaturated ester with a metal-hydride species and trapping by an acceptor such as ketone and aldehyde, is of current interest because it is an efficient synthetic tactic in organic synthesis.[1] The initial reduction step generates intermediate enolate species, which attack carbonyl groups to give the corresponding aldol products. It should be a powerful tool for alternative aldol reactions, offering the advantage of the in situ generation of enolates as nucleophilic condensation counterparts without stoichiometric amounts of strong bases. In these processes, transition metals are typically utilized as catalysts with silane or borane reductants. Shibasaki's[2] and Riant's[3] groups independently developed the asymmetric version of the reaction using copper–chiral diphosphine complexes in the presence of hydrosilane or borane. Nishiyama's group reported the rhodium–phebox-catalyzed asymmetric reductive aldol reactions.[4] Each reaction is successful in giving products with high enantioselection. Lam's group reported the intramolecular version of the reaction of ω-carbonyl-α,β-unsaturated esters giving β-hydroxylactones with good enantiomeric excess using a chiral copper–diphosphine catalyst.[5a] They also reported the cobalt-catalyzed diastereoselective intra- and intermolecular reactions with α,β-unsaturated amides.[5b] The reductive aldol reactions are nevertheless still developing and have room for improvement regarding substrate scope, yields, and enantioselectivity.

In a previous study, we developed a new chiral ferrocenyl ligand, the ClickFerrophos, using click chemistry methodology, and reported its metal-complex-catalyzed asymmetric hydrogenation and 1,3-dipolar addition of the azomethine ylide in excellent enantioselectivities (up to 99.7% ee).[6] The ClickFerrophos ligand was found to be a useful ligand for asymmetric synthesis and some times works more effectively than Taniaphos (Figure 1), which has analogous 1,5-diphos structures. We are interested in the successful use of the Cu–Taniaphos complex in the reductive aldol reaction, where it catalyzes the reaction with a high enantioselectivity compared to other phosphine ligands. The efficiency of the Taniaphos ligand may due to the 1,5-diphos unit which is a capable eight-membered-ring chelate to the metal. ClickFerrophos also contains a 1,5-diphos unit and it could effectively work in the reaction. We have prepared several ClickFerrophos families[9] and tested them for Cu(I)-catalyzed asymmetric reductive aldol reaction of ketones and aldehydes with acrylic esters.



Taniaphos

T1: $R^1 = R^2 = Ph$
T2: $R^1 = R^2 = Cy$

ClickFerrophos

CF1: $R^1 = R^2 = R^3 = Ph$
CF2: $R^1 = R^2 = Ph$, $R^3 = H$
CF3: $R^1 = R^2 = Cy$, $R^3 = Ph$
CF4: $R^1 = R^2 = Cy$, $R^3 = H$
CF5: $R^1 = R^2 = c\text{-}C_5H_9$, $R^3 = Ph$
CF6: $R^1 = R^3 = Ph$, $R^2 = Cy$

Figure 1 ClickFerrophos and Taniaphos Families

In our initial experiment, we screened the (*S*,*Rp*)-ClickFerrophos ligand family (**CF1**–**CF6**) for the reaction of acetophenone **1a** (Ar = Ph) with methyl acrylate **2a** (1.2 equiv) using a catalytic amount of $[CuF(PPh_3)_3]\cdot 2MeOH$ and a stoichiometric quantity of phenylsilane at –50 °C in toluene.[7] The results are summarized in Table 1. In the presence of the Cu(I) complex of (*S*,*Rp*)-**CF1** (1.0 mol%), the reaction proceeded smoothly and was complete in one hour affording the aldol adduct as a mixture of diastereomers; the *erythro*-**3a** (Ar = Ph) and *threo*-**4a** (Ar = Ph) were obtained in the ratio of *erythro*/*threo* = 71:29. The *erythro*-**3a** was the major diastereomer and its enantiomeric excess and absolute configuration were determined using a chiral GC column and compared to the reported result;[3a] (2*S*,3*R*)-**3a** was produced in –73% ee (entry 1).

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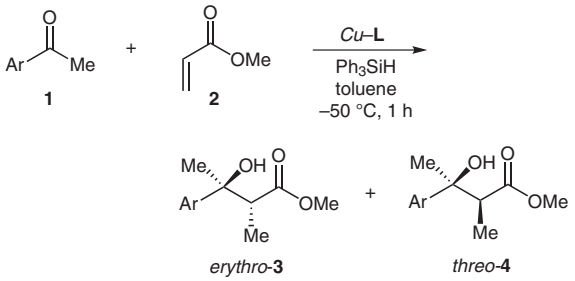
The disubstituted triazole derivative of the ClickFerrophos **CF2** similarly gave the (2*S*,3*R*)-**3a** as the major diastereomer in the ratio of *erythro*/*threo* = 69:31 with a higher enantioselectivity (–84% ee, entry 2). The use of dicyclohexyl derivative **CF3** successfully improved diastereoselectivity up to *erythro*/*threo* = 96:4, and (2*R*,3*S*)-**3a** was obtained in up to 83% ee as the enantiomer of those which were obtained using **CF1** (entries 3 and 4). The disubstituted triazole **CF4** and the dicyclopentyl derivative **CF5** also gave (2*R*,3*S*)-**3a** in a good diastereoselectivity with a moderate enantioselectivity (69% ee and 76% ee, respectively; entries 5 and 6). The use of the monocyclohexyl derivatives **CF6** was not successful for the reaction producing (2*S*,3*R*)-**3a** with low diastereoselectivity and enantioselectivity (entry 7). The results of the reaction using the Taniaphos ligands (**T1** and **T2**) are also shown for comparison (entries 8–10). The results may suggest that **CF1** and **CF3** tend to give slightly higher diastereoselectivities than the Taniaphos in each case, although the enantioselectivity was not as high as that with the Taniaphos.



Scheme 1 The Cu–ClickFerrophos-catalyzed reductive aldol reaction of ketones **1** with methyl acrylate **2a**

Thus, the dicyclohexyl derivative **CF3** was revealed to be the most effective for the reaction, and we next examined the scope of the reaction with respect to the ketone substrate using **CF3** under similar conditions.[10] The results for the representative substituted acetophenones and thienyl methyl ketones are shown in Table 2. The reaction of these ketones with **2** successfully proceeded to give the corresponding aldol adducts in high diastereoselectivities and enantioselectivities. The reaction with the *p*- and *m*-haloacetophenones gave the corresponding *erythro* aldol adducts **3** in as high diastereo- (ratio of *erythro*/*threo*) and enantioselectivities as the acetophenone (entries 2–4). The introduction of the CF_3 substituent at the *para* position may affect the stereoselectivity, thus decreasing the enantioselectivity and diastereoselectivity (entries 5 and 6). The rate of the reaction decreased and extending the reaction time to three hours was necessary for a satisfactory yield. The 4-methoxy substituent increased both the diastereomeric ratio and enantiomeric excess of the *erythro*-**3**, but in low yield (entry 7). The reaction with the 2- and 3-thienyl methyl ketones gave the *erythro* aldol adduct in high diastereomeric ratio and enantiomeric excess (entries 8 and 9). Based on the results in Table 2, the **CF3** ligand was revealed to be superior with respect to the diastereoselectivity affording higher diastereomeric ratios than the Taniaphos ligand although it bears improving the ee values.

Table 1 Asymmetric Reductive Aldol Reaction of Acetophenone **1a** with Methyl Acrylate **2a** Catalyzed by Cu(I)–ClickFerrophos Complexes[a]

Entry	L	Yield (%)	**3a**/**4a**	ee (%) of **3a** [ee (%) of **4a**][b]
1	**CF1**	91	71:29	–73 (–53)
2	**CF2**	83	69:31	–84 (–56)
3	**CF3**	90	96:4	83 (55)
4[c]	**CF3**	65	91:9	81 (29)
5	**CF4**	93	95:5	69 (31)
6	**CF5**	51	95:5	76 (53)
7	**CF6**	54	89:11	–37 (–1)
8	**T1**	92	64:36	–83 (–94)
9[d]	**T1**	99	76:24	–85 (–94)
10[d]	**T2**	99	92:8	95 (72)

[a] Compound **1a** (1.0 mmol), **2** (1.2 mmol), $[CuF(PPh_3)_3]\cdot 2MeOH$ (0.01 mmol), ligand (0.01 mmol), $PhSiH_3$ (1.4 mmol), toluene (5.0 mL), –50 °C, 1 h.
[b] Determined by chiral GC column (CP CHIRASIL DEX CB, 25 m).
[c] The reaction was carried out in THF.
[d] The reported result, see ref. 3a.

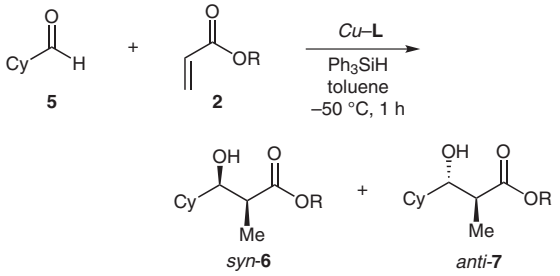
Table 2 Cu(I)–**CF3**-Complex-Catalyzed Asymmetric Reductive Aldol Reaction of **1** with **2a**[a]

Entry	Ar	Yield (%)[b]	**3**/**4**	ee (%) of **3**[b]
1	Ph	90	96:4	83
2	4-FC_6H_4	93	95:5	84
3	4-ClC_6H_4	83	95:5	85
4	3-ClC_6H_4	68	96:4	80
5	4-$F_3CC_6H_4$	49	91:9	73
6[c]	4-$F_3CC_6H_4$	83	90:10	74
7[c]	4-$MeOC_6H_4$	36	99:1	87
8[d]	2-thienyl	65	98:2	84
9[d]	3-thienyl	82	97:3	84

[a] Compound **1** (1.0 mmol), **2** (1.2 mmol), $[CuF(PPh_3)_3]\cdot 2MeOH$ (0.01 mmol), **CF3** (0.01 mmol), $PhSiH_3$ (1.4 mmol), toluene (5.0 mL), –50 °C, 1 h.
[b] Determined by GC (CP CHIRASIL DEX CB).
[c] Reaction time 3 h.
[d] Reaction time 24 h.

We further examined the copper-catalyzed reductive aldol reaction of aldehydes using the ClickFerrophos families **CF1**–**CF4** under the same conditions as the reaction with

the acetophenone. The results are shown in Table 3. For the reaction of the cyclohexanecarbaldehyde with methyl acrylate **2a**, the use of **CF1** afforded a mixture of the *syn*-(2*S*,3*R*)-**6a** (R = Me) and *anti*-(2*S*,3*S*)-**7a** (R = Me) adducts in the ratio of *syn*/*anti* = 67:33 with 52% ee (*syn*) and 58% ee (*anti*), respectively (entry 1); the enantiomeric excess and absolute configuration were determined using a chiral GC column comparing to the reported result (Scheme 2).[3b,4] The reaction at a lower temperature (–78 °C) hardly affected the enantioselectivity for both **6** and **7** (entry 2).[8] The reaction with the *tert*-butyl **2b** and cyclohexyl esters **2c** increased the enantioselectivity for **6** up to 89% ee in the ratio of **6**/**7** being almost 50:50 (entries 3–5). The reaction with the **CF2**–**CF4** ligands was unsuccessful, giving low diastereo- and enantioselectivities although the smooth reaction proceeded to give the aldol adduct in a moderate to good yield (entries 6–8). The reaction of benzaldehyde with *tert*-butyl acrylate using **CF1** under the same conditions gave the *anti* adduct with 72% ee in the ratio of *syn*/*anti* = 22:78.



Scheme 2 The Cu–ClickFerrophos-catalyzed reductive aldol reaction of cyclohexanecarbaldehyde **5** with acrylates **2**

Table 3 Asymmetric Reductive Aldol Reaction of Cyclohexanecarbaldehyde **5** with Acrylate **2a**–**c** Catalyzed by Cu(I)–ClickFerrophos Complexes[a]

Entry	L	R	Conversion (%)	**6**/**7**[b]	ee (%) of **6**[b] [ee (%) of **7**]
1	**CF1**	Me	99	67:33	52 (58)
2[c]	**CF1**	Me	99	50:50	55 (54)
3	**CF1**	*t*-Bu	99	46:54	89 (54)
4[c]	**CF1**	*t*-Bu	99	52:48	80 (38)
5	**CF1**	Cy	99	41:59	74 (73)
6	**CF2**	Me	99	60:40	19 (25)
7	**CF3**	Me	99	26:74	–30 (–25)
8	**CF4**	Me	89	22:78	7 (7)
9	**T1**	Me	99	51:49	78 (59)

[a] Compound **1** (1.0 mmol), **2** (1.2 mmol), $[CuF(PPh_3)_3]\cdot 2MeOH$ (0.01 mmol), **CF3** (0.01 mmol), $PhSiH_3$ (1.4 mmol), toluene (5 mL), –50 °C, 1 h.
[b] Determined by chiral GC column (CP CHIRASIL DEX CB, 25 m).
[c] The reaction was carried out at –78 °C.

In conclusion, the copper–ClickFerrophos (**CF3**) complex very effectively worked in the reductive aldol reaction of ketones with methyl acrylate to give the corresponding *erythro* adduct in both high diastereo- and enantioselectivities. The **CF1** was effective for the reaction of aldehydes with *tert*-butyl and cyclohexyl acrylate to give the *syn* adduct with a high enantioselectivity, but without any diastereoselectivity.

References and Notes

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(7) The use of other silanes such as dimethylphenylsilane, diethylmethylsilane, and triethoxysilane resulted in poor yields and selectivities under the same conditions.
(8) Additives such as the triethylamine and tricyclohexyl phosphine did not affect the stereoselectivity.
(9) **Preparation of (*S*,*Rp*)-5-(Diphenylphosphino)-1-{1-[2-(diphenylphosphino)ferrocenyl]ethyl}-1*H*-1,2,3-triazole (CF2)**
A 100 mL round-bottom flask containing a magnetic stirring bar was charged with 1-(1-azidoethyl)-2-bromoferrocene (400 mg, 1.20 mmol), trimethylsilylacetylene (180 μL, 1.32 mmol), *t*-BuOH (3.0 mL), and H_2O (3.0 mL). Sodium ascorbate (257 mg, 1.32 mmol) was added to the flask followed by $CuSO_4\cdot 7H_2O$ (162 mg, 0.65 mmol), and the resulting mixture was magnetically stirred for 24 h. The mixture was then extracted with CH_2Cl_2 (10 × 3 mL). The combined extracts were washed(brine), dried ($MgSO_4$), and the solvent was removed on a rotary evaporator to leave a yellow residue. The residue was treated overnight with a THF (5.0 mL) solution of TBAF (1.5 mmol) in THF at 50 °C. THF was removed by using a rotary evaporator and diluted with CH_2Cl_2 (20 mL) The solution was washed with H_2O, dried ($MgSO_4$), and the solvent was removed using a rotary evaporator. The residue was subjected to column chromatography on SiO_2 (hexane–EtOAc = 2:1 as eluent) to give the pure (*S*,*Rp*)-1-[1-(2-bromoferrocenyl)ethyl]-1*H*-1,2,3-triazole. Yellow solid; yield 140 mg, 0.40 mmol, 33%; mp 120–121 °C; $[\alpha]_D^{25}$ +81 (*c* 0.36, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 2.04 (d, 3 H, *J* = 6.4 Hz), 4.26 (s, 5 H), 4.42 (s, 1 H), 4.53 (s, 1 H), 5.88 (q, 1 H, *J* = 6.9 Hz), 7.30 (s, 1 H), 7.56 (s, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.0, 54.9, 64.9, 66.9, 71.1, 71.5, 79.1, 84.6, 121.7, 132.9.

In a 20 mL Schlenk tube containing a magnetic stirring bar were charged the triazole bromoferrocene prepared above (100 mg, 0.28 mmol) and dry THF (3.0 mL) under a slight pressure of nitrogen. The flask was cooled at –78 °C, and a hexane solution of *n*-BuLi (0.44 mL, 0.70 mmol, 1.6 M) was then added using a syringe through the septum with magnetic stirring. After 10 min, Ph_2PCl (130 μL, 0.70 mmol) was injected into the mixture at –78 °C and stirred for 1 h. When the addition was completed, the mixture was allowed to warm to r.t. and then stirred for an additional 2 h. The reaction was quenched with sat. NH_4Cl, and the solution was then extracted with Et_2O (3 × 20 mL). The combined extracts were washed(brine), dried (Na_2SO_4), filtered, and the solvent was removed on a rotary evaporator to leave a yellow solid. The crude **CF2** was purified by recrystallization from hexane–CH_2Cl_2. Yellow solid; yield, 130 mg, 0.20 mmol, 73%; mp 167–168 °C; $[\alpha]_D^{25}$ +95 (*c* 0.34, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.61 (d, 3 H, *J* = 6.8 Hz), 3.81 (s, 1 H), 4.10 (s, 5 H), 4.45 (t, 1 H, *J* = 2.6 Hz), 4.90 (s, 1 H), 6.30 (m, 1 H), 6.60–7.60 (m, 21 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.6, 53.9 (dd, *J* = 9.2, 11.7), 69.8, 70.2, 70.8 (d, *J* = 3.7 Hz), 71.8 (d, *J* = 4.9 Hz), 75.3 (d, *J* = 10.2 Hz), 92.4 (d, *J* = 26.0 Hz), 127.0, 127.7 (d, *J* = 5.5 Hz), 127.9 (d, *J* = 8.1 Hz), 128.1 (d, *J* = 6.8 Hz), 128.3 (d, *J* = 7.2 Hz), 128.7, 128.8, 129.2, 129.8, 130.9 (d, *J* = 16.9 Hz), 132.4 (d, *J* = 18.6 Hz), 133.1 (d, *J* = 7.2 Hz), 133.3, 133.4, 133.5 (d, *J* = 7.9 Hz), 134.0, 134.1 (d, *J* = 21.5 Hz), 135.4 (d, *J* = 21.1 Hz), 137.1 (d, *J* = 8.5 Hz), 138.6, 139.1 (d, *J* = 9.6 Hz). ^{31}P NMR (121 MHz, $CDCl_3$): δ = –40.4 (d, *J* = 37.0 Hz), –24.5 (d, *J* = 37.0 Hz). HRMS: *m/z* calcd for $C_{38}H_{33}FeN_3P_2$ [M + H$^+$]: 650.1577; found: 650.1573. The crystallographic data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. CCDC-717051.

Compound **CF4** was similarly prepared by replacing Ph_2Cl with Cy_2PCl. Yellow solid; yield, 58%; mp 100–102 °C; $[\alpha]_D^{25}$ +197 (*c* 0.24, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.90–2.10 (m, 47 H) including 2.04 (d, *J* = 7.0 Hz), 4.18 (s, 1 H), 4.26 (s, 5 H), 4.38 (s, 1 H), 6.12 (m, 1 H), 7.66 (s, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 23.2, 53.9 (dd, *J* = 9.6, 12.0 Hz), 26.0–36.0 (several cyclohexyl signals), 69.0, 69.3, 69.6, 71.3 (d, *J* = 4.3 Hz), 79.3 (d, *J* = 24.6 Hz), 93.8 (d, *J* = 25.8 Hz), 131.7 (d, *J* = 24.3 Hz), 137.8 (d, *J* = 4.7). ^{31}P NMR (121 MHz, $CDCl_3$): δ = –33.0 (s), –19.3 (s). HRMS: *m/z* calcd for $C_{38}H_{57}FeN_3P_2$ [M + H$^+$]: 674.3455; found: 674.3456.

Compound **CF3** was prepared by a similar preparative method for **CF1** by replacing Ph_2PCl with Cy_2PCl according to a previous study.[6a] Yellow solid; mp 100–101 °C; $[\alpha]_D^{25}$ +97 (*c* 0.31, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.90–2.30 (m, 47 H) including 2.04 (d, *J* = 6.9 Hz), 4.19 (s, 1 H), 4.29 (s, 5 H), 4.33 (s, 1 H), 6.17 (m, 1 H), 7.30–7.40 (m, 5 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 23.6 (dd, *J* = 3.2, 7.7 Hz), 26.0–36.0 (several cyclohexyl signals), 54.2, 68.5, 69.7, 71.2, 71.3, 78.4 (d, *J* = 25.3 Hz), 95.3 (d, *J* = 24.8), 127.9, 128.1, 128.4 (d, *J* = 30. 0 Hz), 129.3, 133.2, 151.6. ^{31}P NMR (121 MHz, $CDCl_3$): δ = –28.7 (s), –18.0 (s). HRMS: *m/z* calcd for $C_{44}H_{61}FeN_3P_2$ [M + H$^+$]: 750.3768; found: 750.3767.

(10) **General Procedure for Cu/CF3-Mediated Reductive Aldol Reaction of Ketones 1 with Methyl Acrylate (2)**

Under nitrogen, a 20 mL well-dried Schlenk tube equipped with a magnetic stirrer was charged with $CuF(PPh_3)_3$·2MeOH (9.0 mg, 0.01 mmol), **CF3** (7.5 mg, 0.01 mmol), and toluene (4.8 mL). The catalyst solution was stirred for 30 min at r.t., and phenylsilane (180 μL, 1.40 mmol) was then added at the same temperature. After cooling the solution at –50 °C, methyl acrylate (**2**, 110 μL, 1.20 mmol) and acetophenone (120 mg, 1.00 mmol) were simultaneously added to the solution. The mixture was stirred for 1 h at –50 °C, and then quenched by adding an aq NH_4F soln (5 mL). The aqueous layer was extracted by three portions of Et_2O (5 mL). The combined organic layers were then washed with brine (20 mL), dried over $MgSO_4$, filtered and concentrated by an evaporator. The residue was subjected to short SiO_2 column chromatography (hexane–EtOAc as the eluent) to give a diastereomeric mixture of the aldol adduct. The dr (*erythro*/*threo*) and ee values were determined by GC (CP CHIRASIL DEX CB 25 m) with reference to the literature.

***erythro*-Methyl 3-Hydroxy-2-methyl-3-phenylbutanoate (3a)**

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.32 (d, 3 H, *J* = 7.0 Hz), 1.46 (s, 3 H), 3.03 (q, 1 H, *J* = 7.0 Hz), 3.45 (s, 3 H), 4.02 (s, 1 H), 7.20–7.40 (m, 5 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 12.45, 26.6, 48.5, 51.6, 74.6, 124.6, 126.7, 128.1, 147.5, 177.1. GC Chirasil-Dex CB, 25 mm; isotherm 120 °C, t_R(major) = 18.5 min, t_R(minor) = 19.4 min. Other aldol products are fully characterized by spectroscopic analysis and the dr and ee values of products were determined by GC.