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[7] Since the ligand adopts a rigid envelope conformation,[4] the η^3-allyl complexes exist in *exo* and *endo* forms. In the mechanistic discussion involving **2**, we depicted only the *exo* form; similar but not identical considerations also apply to the *endo* isomer. Selected NMR data for [Pd(**B**)(η^3-dimethylpropenyl)]$^+$: $^{31}P\{^1H\}$ NMR (121.5 MHz, CD_2Cl_2, 298 K): major isomer (85 %): $\delta = 32.3$ (d, $^2J_{P,P} = 35.6$ Hz), 36.9 (br d, $^2J_{P,P} = 35.6$ Hz); minor isomer (15 %): $\delta = 29.9$ (br), δ 34.2 (br); 2D ^1H NOESY spectrum (400 MHz, CD_2Cl_2, 243 K): η^3-dimethylpropenyl ligand (a = *anti*, s = *syn*, c = central): major isomer: $\delta = 5.41$ (m, H_s), 4.41 (dd, $^3J_{Hc\text{-}Ha} = 12.9$ Hz, $^3J_{Hs,Hc} = 7.5$ Hz, H_c), 4.34 (m, H_a); minor isomer**:** $\delta = 5.97$ (br m, H_s), 5.12 (dd, $^3J_{Hc,Ha} = 13.0$, $^3J_{Hs,Hc} = 8.0$ Hz, H_c), 4.20 (m, H_a)**.** Details of the *endo*/*exo* isomerization and the effects of chloride ions will be reported elsewhere.

[8] The X-ray structure of the *exo* isomer of [Pd(**A**)(η^3-cyclohexenyl)]$^+$ shows one methyl group of the ligand **A** in close proximity to the organic substrate.[4] This corresponds to barrrier **a** in Scheme 1. The methyl group barrier **b** is somewhat more distant and not related to **a** by a C_2 axis.

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[12] When large quantities of malonate anion are present (i.e., with the $NaH/CH_2(COOR)_2$ method), the overall rate of the reaction is faster, and the enantioselectivity of the product greatly reduced (*ee* = 33 % (S)). We believe that the malonate anion possibly increases the rate of the oxidative addition step by coordination[11] of the carbanion to Pd^0 and thus accelerates the product-forming step. Under these conditions the rate of isomerization of the intermediate Pd allyl cations is not sufficient to obtain high enantioselectivity.

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Catalytic Enantioselective Aza Diels – Alder Reactions of Imino Dienophiles

Sulan Yao, Mogens Johannsen,* Rita G. Hazell, and Karl Anker Jørgensen*

The asymmetric catalytic hetero Diels – Alder class of reactions has attracted considerable interest due to the importance of the products formed.[1] The asymmetric oxa Diels – Alder reactions of aldehydes[2] and ketones[3] catalyzed by chiral Lewis acid catalysts can be performed with a high degree of stereoselectivity, whereas methods are still lacking for the corresponding catalytic enantioselective aza Diels – Alder reaction.[4–6] The asymmetric aza Diels – Alder reaction provides an effective route to optically active piperidine and tetrahydroquinoline heterocycles, as well as other compounds of fundamental importance.[1]

Yamamoto et al. have recently developed an enantioselective aza Diels – Alder reaction of aldimines with Danishefsky's diene using a stoichiometric amount of a chiral boron complex.[4] To our knowledge, the first catalytic enantioselective aza Diels – Alder reaction with a chiral zirconium complex as the catalyst was elegantly achieved by Kobayashi et al. for reactions of aldimines derived from 1-naphthaldehyde and 2-aminophenol, for example.[5] The highest enantiomeric excess (*ee*) obtained was 93 % with 20 mol % of the chiral zirconium catalyst.

Here we present a catalytic enantioselective aza Diels – Alder reaction of imines derived from ethyl glyoxylate with activated dienes. The optically active aza Diels – Alder adducts formed contain an ester functionality in the α-position to the nitrogen atom in the ring and an α,β-unsaturated ketone fragment. These adducts make attractive precursors for a variety of synthetic targets, such as a straightforward and very efficient route to optically active, nonnatural α-amino acids of the piperidine type.

Recently highly enantioselective hetero Diels – Alder and ene reactions of α-carbonyl esters and α-dicarbonyl compounds have been developed.[2, 3] These results prompted us to investigate whether the corresponding α-imino carbonyl compounds could be substrates in an enantioselective aza Diels – Alder reaction. We anticipated that the imino nitrogen atom and the oxygen atom would coordinate to the chiral Lewis acid complex to form a fixed chiral environment around the aldimino group.

The potential of the α-imino carbonyl compounds **1a – d** as possible substrates for the aza Diels – Alder reaction with Danishefsky's diene (**2a**) [Eq. (1); Tos = $H_3CC_6H_4SO_2$; TMS = Me_3Si] was investigated. Different chiral ligands, such as the 2,2′-bis(diphenylphosphanyl)-1,1′-binaphthyl (BINAP) ligands **3a**, **b** and the bisoxazoline ligands **4a – c**, have, in combination with various Lewis acid complexes and under

[*] Prof. K. A. Jørgensen, M. Johannsen, S. Yao, R. G. Hazell
Center for Metal Catalyzed Reactions
Department of Chemistry, Aarhus University
DK-8000 Aarhus C (Denmark)
Fax: (+45) 861-961-99
E-mail: kaj@kemi.aau.dk

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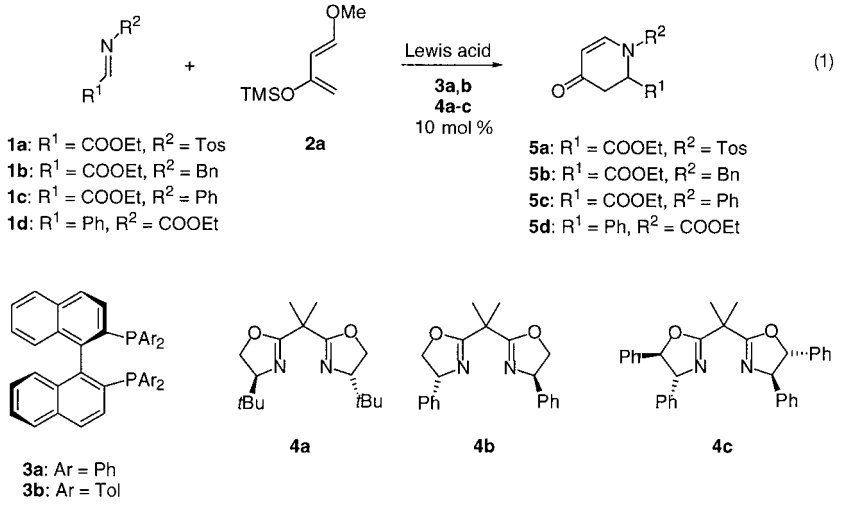
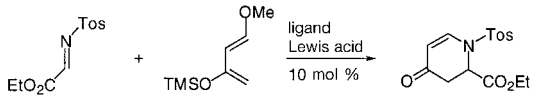


different reaction conditions, been tested as catalysts for the aza Diels–Alder reaction.

The α-imino carbonyl compounds **1a–d** all react smoothly with **2a** to generate the aza Diels–Alder adducts **5a–d** in good yield in the presence of various complexes derived from the chiral ligands **3a**, **b**, **4a–c** and Lewis acids such as $Zn(OTf)_2$, $Cu(OTf)_2$, CuOTf, $CuClO_4$, $AgSbF_6$, AgOTf, $AgClO_4$, $Pd(SbF_6)_2$, $Pd(ClO_4)_2$, $Pd(OTf)_2$, and $RuSbF_6$ (Tf = F_3CSO_2). However, under the present reaction conditions, only the α-imino ester **1a** reacted enantioselectively with **2a** to yield the product **5a**, when copper(I)–BINAP complexes were used as catalyst. Table 1 contains some representative results for the aza Diels–Alder reaction of **1a** with **2a** in the presence of **3a**, **b**, **4a–c** in combination with different metal salts. The combination of BINAP **3a** as the chiral ligand with $CuClO_4 \cdot 4MeCN$ or $2CuOTf \cdot C_6H_6$ as the metal salt results in a reasonable yield of the aza Diels–Alder adduct **5a** with an *ee* value of 64 or 61%, respectively (entries 1 and 2). Slow addition of **2a** improves the yield and the *ee* value of **5a** slightly (entry 3). Use of the 2,2′-bis(ditolylphosphanyl)-1,1′-binaphthyl (tol-BINAP) ligand **3b** with $CuClO_4 \cdot 4MeCN$ gives an even higher enantioselectivity of 80% *ee* (entry 4). $Cu(OTf)_2$ with **3b** in THF also results in a good *ee* value (entry 5). When CH_2Cl_2 is used as the solvent for the same reaction, however, the enantioselectivity is reduced to 40% (entry 6). If silver(I) and palladium(II) salts are used instead of copper(I), reasonable yields of **5a** are obtained but with low *ee* values (entries 9–14), while the use of ruthenium(I) leads to a racemic product (entry 15). The various combinations of bisoxazoline ligands **4a–c** with copper(I), copper(II), and zinc(II) salts as Lewis acid catalysts result in reasonable yields of **5a** but with very low *ee* values (entries 7, 8, 16, 17). In relation to the present aza Diels–Alder reaction, it should be noted that the combination of BINAP and late transition metals has recently been shown to be an effective catalyst for the enantioselective alkylation of imines by enol silanes and allyl stannane.[7]

The aza Diels–Alder reactions of the α-imino ester **1a** with the activated dienes **2a**, **b** catalyzed by different BINAP-$CuClO_4 \cdot 4MeCN$ catalysts under various reaction conditions are presented in Table 2. The reaction of α-imino ester **1a** with diene **2a** catalyzed by **3a**-$CuClO_4 \cdot 4MeCN$ (10 mol%) gives the aza Diels–Alder adduct **5a** in 78% yield with an *ee* value of 67% (Table 2, entry 1), while under similar reaction conditions **3b** gives a yield of only 68% but an improvement of the *ee* value to 80% (entry 2). The absolute stereochemistry of **5a** was assigned to be (*S*) at C1 on the basis of an X-ray structure analysis (Figure 1a). Use of the diene **2b** leads to a

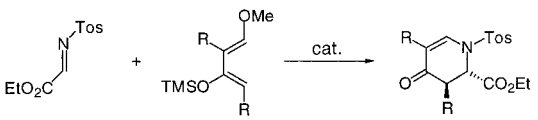
Table 1. The results for the aza Diels–Alder reaction of **1a** with **2a** in the presence of **3a**, **b**, and **4a–c** in combination with different Lewis acids (10 mol%) at −78 °C in THF, unless otherwise indicated.



Entry	Ligand	Lewis acid	Yield (**5a**)[a] [%]	*ee*[b] [%]
1	**3a**	$CuClO_4 \cdot 4MeCN$	65	64
2	**3a**	$2CuOTf \cdot C_6H_6$	60	61
3[c]	**3a**	$CuClO_4 \cdot 4MeCN$	78	67
4	**3b**	$CuClO_4 \cdot 4MeCN$	68	80
5	**3b**	$Cu(OTf)_2$	42	77
6[d]	**3b**	$Cu(OTf)_2$	72	40
7	**4a**	$2CuOTf \cdot C_6H_6$	74	12
8	**4a**	$Cu(OTf)_2$	60	10
9	**3a**	$AgSbF_6$	75	33
10	**3b**	AgOTf	85	30
11	**3b**	$AgClO_4$	90	34
12	**3b**	$Pd(SbF_6)_2$	76	30
13	**3b**	$Pd(ClO_4)_2$	68	11
14	**3b**	$Pd(OTf)_2$	88	11
15	**3b**	$RuSbF_6$	70	0
16	**4b**	$Zn(OTf)_2$	74	17
17	**4c**	$Zn(OTf)_2$	70	8

[a] Yield of isolated product. [b] Determined by HPLC with a Chiralpak-AD column. [c] Slow addition of **2a**. [d] Solvent: CH_2Cl_2.

Table 2. Results for the aza Diels–Alder reaction of **1a** with **2a**, **b** catalyzed by different $CuClO_4 \cdot 4MeCN$ complexes with the ligands **3a** and **b** at −78 °C in THF.



Entry	Catalyst	Load [mol%]	Alkene	Yield[a] [%]	*ee*[b] [%]
1	**3a**/$CuClO_4 \cdot 4MeCN$	10	**2a**	78	67
2	**3b**/$CuClO_4 \cdot 4MeCN$	10	**2a**	68	80
3	**3b**/$CuClO_4 \cdot 4MeCN$	10	**2b**	67	94
4	**3b**/$CuClO_4 \cdot 4MeCN$	5	**2b**	70[c]	94
5	**3b**/$CuClO_4 \cdot 4MeCN$	1	**2b**	70[c]	96
6[d]	**3b**/$CuClO_4 \cdot 4MeCN$	10	**2b**	70	81

[a] Total yield of isolated product. [b] Determined by HPLC with a Chiralpak-AD column. [c] Diastereoselective ratio = 10:1; [d] T = 20 °C.

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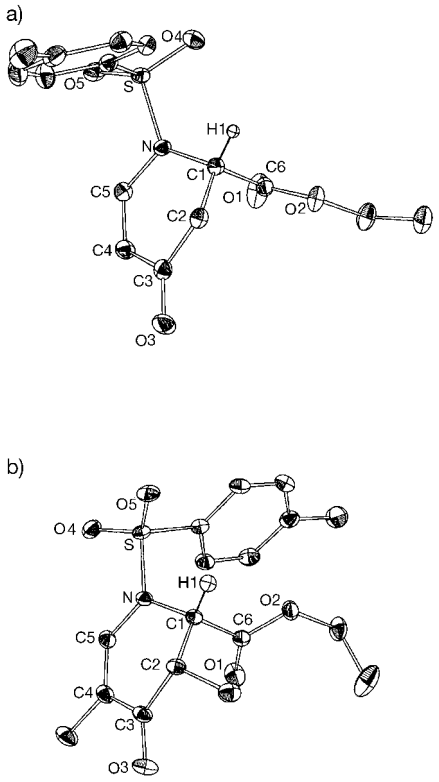

Figure 1. The X-ray crystal structure of **5a** shows the (*S*) configuration at C1 (a), while the X-ray crystal structure of *cis*-**6** shows the *cis* configuration at C1 and C2 (b).

significant improvement in the *ee* value of the major diastereomer *trans*-**6** of the aza Diels–Alder adduct (94% *ee*, diastereoselectivity ratio of 10:1; entry 3); while an *ee* value of 81% is obtained at room temperature (entry 6). The relative configuration of the minor diastereomer, *cis*-**6**, which corresponds to an *endo* approach of the diene, was also assigned by means of X-ray crystallography (Figure 1b). The major diastereomer, *trans*-**6**, is probably formed by *exo* attack of the diene. The aza Diels–Alder reaction can proceed with 5 mol% and, most importantly, 1 mol% of the catalyst **3b**-$CuClO_4 \cdot 4MeCN$ without adversely affecting the yield or the enantioselectivity (entries 4, 5). With a catalyst loading of 1 mol%, an *ee* value of 96% is obtained at $-78\,^{\circ}C$ (entry 5). The advantage of this aza Diels–Alder reaction is that it can be performed on the gram scale with a catalyst loading of only 1 mol% of **3b**-$CuClO_4 \cdot 4MeCN$. Under these conditions, the diastereomer *trans*-**6** can be isolated from the reaction of **1a** with **2b** in a yield of 90% with a diastereoselectivity ratio of 4:1 and an *ee* value of 93%, compared with 70% total yield of isolated product and stereoselectivity of 96% on a 0.2 mmol scale.

As evident from Table 1, the aza Diels–Alder reaction is almost independent of the counterion in the metal salt; the influence of metal, solvent, imine, and catalyst loading is, however, more pronounced. Generally, the diastereoselectivity decreased when the catalyst loading was reduced. The enantioselectivity of the minor diastereomer, the *endo* adduct *cis*-**6**, however, remained less than 30% even at low loading. An examination of the solvent effects in the reaction of **1a** with **2b** catalyzed by **3b**-$CuClO_4 \cdot 4MeCN$ at $-78\,^{\circ}C$ led to the conclusion that THF is the optimal solvent. In all other solvents not only did the diastereoselectivity decrease, but also the enantioselectivity of *trans*-**6** (Et_2O: 79% *ee*, CH_2Cl_2: 80% *ee*, toluene: 65% *ee*, DMF: 0% *ee*).

The potential of this new enantioselective aza Diels–Alder reaction of the α-imino ester **1a** with activated dienes is evident from the results in Table 2: highly valuable products in organic chemistry can be obtained with *ee* values of up to 96%. Furthermore, such enantiomeric excess is obtained in the presence of only 1 mol% of **3b**-$CuClO_4 \cdot 4MeCN$ catalyst, and the reaction can be performed on the gram scale with higher yields and the same high enantioselectivity.

Experimental Section

Ethyl 1-tosyl-3,5-dimethyl-4-oxo-1,2,3,4-tetrahydropyridine-2-carboxylate (*trans*-**6** and *cis*-**6**): (*R*)-tol-BINAP (30 mg, 0.044 mmol) and $CuClO_4 \cdot 4MeCN$ (13 mg, 0.04 mmol) were added to a flame-dried Schlenk tube under N_2. The mixture was dried under vacuum for 30 min, anhydrous THF (1 mL) was added and the resulting suspension was stirred for 1–2 h. The clear yellow catalyst solution was then cooled to $-78\,^{\circ}C$, and **1a** (105 mg, 0.4 mmol) was added, followed by **2b** (115 μL, 0.5 mmol). The reaction solution was stirred overnight, then trifluoroacetic acid (0.1 mL in 20 mL CH_2Cl_2) was added and the mixture stirred for 30 min at $0\,^{\circ}C$. Evaporation of the solvent gave the crude product which was purified by flash chromatography (15/85 ethyl acetate/pentane) to give a total yield of 67% with a diastereoselectivity ratio of 10:1, *trans*-**6** (83 mg, 94% *ee*; Chiralpak-AD column, hexane/*i*PrOH 85/15, 1.0 mL min^{-1}) and *cis*-**6** (8 mg) as a light yellow oil; *trans*-**6**: $[\alpha]_D^{20} = -91.9$ ($c = 0.67$ in $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.76$ (d, $J = 8.3$ Hz, 2H; C_6H_4), 7.53 (t, $J = 1.1$ Hz, 1H; MeC=C*H*), 7.34 (d, $J = 7.6$ Hz, 2H; C_6H_4), 4.60 (m, 1H; COCHMeC*H*-CO_2Et), 3.98–4.10 (m, 2H; CO_2CH_2Me), 2.88 (dq, $J = 1.6$, 7.7 Hz, 1H; COC*H*MeCHCO$_2$Et), 2.45 (s, 3H; ArCH_3), 1.71 (d, $J = 1.1$ Hz, 3H; CH=CCH_3), 1.16 (t, $J = 7.1$ Hz, 3H; $CO_2CH_2CH_3$), 0.99 (d, $J = 7.7$ Hz, 3H; COCH_3CH); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 193.93$, 168.16, 145.12, 137.46, 135.07, 130.04, 127.47, 113.10, 62.26, 62.23, 42.35, 21.66, 17.06, 13.91, 12.95; *cis*-**6**: ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.72$ (d, $J = 8.8$ Hz, 2H; C_6H_4), 7.47 (t, $J = 1.1$ Hz, 1H; MeC=C*H*), 7.34 (d, $J = 7.7$ Hz, 2H; C_6H_4), 4.77 (m, 1H; COCHMeC*H*CO_2Et), 3.77–3.91 (m, 2H; $CO_2CH_2CH_3$), 2.85 (q, $J = 7.1$ Hz, 1H; CHMeC*H*CO$_2$Et), 2.43 (s, 3H; ArCH_3), 1.73 (d, $J = 1.1$ Hz, 3H; =CCH_3), 1.13–1.04 (m, 6H; COCHCH_3CO$_2$CH$_2$CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 192.59$, 167.08, 145.07, 136.79, 134.96, 130.04, 127.37, 114.51, 61.53, 61.31, 40.81, 21.64, 13.81, 12.95, 10.49.

Crystal structure analysis of **5a**: $C_{15}H_{17}NO_5S$, colorless platelets, $0.40 \times 0.34 \times 0.18$ mm^3, orthorhombic, space group $P2_12_12_1$, $a = 8.0821(3)$, $b = 11.8862(5)$, $c = 16.4544(7)$ Å, $V = 1580.7(1)$ Å^3, $Z = 4$, $\rho_{calcd} = 1.359$ Mg m^{-3}, $Mo_{K\alpha}$ radiation ($\lambda = 0.71073$ Å), $2\Theta_{max} = 58.6^{\circ}$, $T = 120$ K, $\mu = 0.227$ mm^{-1}, min./max. transmission 0.91/0.96. Area detector data collected on a Siemens SMART CCD diffractometer, nearly full sphere of reflections; data integration, correction for Lorentz, polarization, and absorption (by Gaussian integration) effects with SMART, SAINT, and XPREP software.[8] There were 21944 reflections measured, 3976 of which were independent, 3889 reflections with $I > \sigma(I)$ were used for refinement. Structure solved by direct methods (SIR97),[9] refined by full-matrix least-squares on $|F|^2$,[10] 269 parameters, hydrogen atoms refined with isotropic temperature parameters, all other atoms anisotropic, $R = 0.027$, w$R = 0.034$, max. residual electron density $\Delta\rho_{max} = 0.62(3)$ e Å^{-3}. The absolute configuration was determined by using the anomalous scattering from sulfur by refinement of the Rogers parameter.[11] The result was 0.93(9), which unambiguously established the chirality (Figure 1).[12] All hydrogen atoms, except the hydrogen atom at the chiral center, have been omitted for clarity.

Crystal structure analysis of *cis*-**6**: $C_{17}H_{21}NO_5S$, colorless hexagons, $0.40 \times 0.30 \times 0.12$ mm^3, triclinic, space group $P\bar{1}$, $a = 8.6699(4)$, $b = 9.6790(4)$, $c = 10.6235(5)$ Å, $\alpha = 77.436(1)$, $\beta = 89.189(1)$, $\gamma = 89.652(1)^{\circ}$, $V = 870.04(5)$ Å^3, $Z = 2$, $\rho_{calcd} = 1.341$ Mg m^{-3}, $Mo_{K\alpha}$ radiation ($\lambda = 0.71073$ Å), $2\Theta_{max} = 60^{\circ}$, $T = 120$ K, $\mu = 0.212$ mm^{-1}, min./max. transmission 0.934/0.975. There were 7952 reflections measured, 4374 of which were independent, 3948

reflections with $I > \sigma(I)$ were used in the refinement of 302 parameters. The procedure was the same as for **5a**.

Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-102362 and CCDC-102363. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

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Mechanistic Insights into Cu-Catalyzed Asymmetric Aldol Reactions: Chemical and Spectroscopic Evidence for a Metalloenolate Intermediate**

Brian L. Pagenkopf, Jochen Krüger, Aleksandar Stojanovic, and Erick M. Carreira*

The aldol reaction ranks among the premier methods for carbon–carbon bond formation in chemical synthesis. Advances in both diastereoselective and enantioselective processes have produced remarkable achievements in the synthesis of stereochemically complex structures.[1] In contrast to the wealth of empirical and theoretical data available for diastereoselective aldol additions of metalloenolates to aldehydes,[2] mechanistic understanding of catalytic asymmetric processes with enol silanes is less advanced. Insight into the latter would be of considerable assistance in the design of newer, more efficient methods for asymmetric synthesis.[3]

We recently reported a catalytic aldol addition of the silyl dienolate **1** to a range of aldehydes in the presence of a bisphosphanyl-Cu^{II} fluoride complex which is generated in situ from (*S*)-Tol-BINAP,[4] $Cu(OTf)_2$, and $(Bu_4N)Ph_3SiF_2$ (Scheme 1).[5] Aromatic, heteroaromatic, and α,β-unsaturated

Scheme 1. Catalytic aldol addition of **1** to aldehydes.

aldehydes furnished aldol adducts with up to 95% *ee* and in 98% yield. Importantly, we postulated a metalloenolate as a key intermediate in the catalytic cycle.[6, 7] This role for a late transition metal catalyst contrasts the more conventional function of such metals as Lewis acids in related processes (Ag^{I},[8] Cu^{II},[9] Pd^{II},[6a–c] and Ni^{II}[10]). Here we report chemical and spectroscopic data that support the postulated catalytic cycle and the involvement of metalloenolate and metal aldolate intermediates.

In mechanistic studies of the Cu-mediated reaction we observed that 5 mol% of the corresponding $Cu^{I}F$ complex (prepared in situ from (*S*)-Tol-BINAP, $[CuOTf \cdot C_6H_6]$, and $(Bu_4N)Ph_3SiF_2$) served equally well in the catalytic aldol reaction of **1** and benzaldehyde (**7**; 94% *ee* and 97% yield).

[*] Prof. Dr. E. M. Carreira, Dr. B. L. Pagenkopf, Dr. J. Krüger, Dr. A. Stojanovic
Arnold and Mabel Beckman Laboratory for Chemical Synthesis, California Institute of Technology
Pasadena, CA 91125 (USA)
Fax: (+1) 626-564-9297
E-mail: carreira@cco.caltech.edu

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