Bimetallic Catalysis

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Enantioselective Bimetallic Catalysis of Michael Additions Forming Quaternary Stereocenters**

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Direct conjugate additions of α-carbonyl-stabilized nucleophiles to activated olefins are among the most attractive reactions for C–C bond constructions owing to their ideal atom economy and the versatility of the activating functional groups involved. For catalytic asymmetric versions, a high level of efficiency has been demonstrated with 1,3-dicarbonyl-based nucleophiles.[1] In contrast, the realization of a general, practical, highly active, and highly enantioselective catalyst for the conjugate addition of α-cyanoacetates to enones remains elusive. This might be explained by the fact that α-cyanoacetates are incapable of two-point binding to a Lewis acid. In this study we were particularly interested in the direct Michael addition of trisubstituted α-cyanoacetates to enones, in light of the demand for efficient catalytic asymmetric C–C bond-forming methods that create substituted quaternary stereocenters[2] and thus provide access to broadly useful multifunctional chiral building blocks.[3]

Enolate formation by deprotonation of trisubstituted α-cyanoacetates with a Brønsted base such as a tertiary amine can trigger the conjugate addition to enones,[4] but the basic conditions might also induce various side reactions with base-sensitive functionalities. To obtain synthetically useful enantioselectivities and yields, low-temperature reaction techniques, high catalyst loadings, and extended reaction times are usually required. In their seminal study in 1992, Ito and co-workers reported that a Rh^{I} complex bearing a *trans*-chelating diphosphine ligand is able to catalyze the addition of α-cyanopropionate to vinyl ketones with high enantioselectivity in the absence of a base.[5] Unfortunately, α substituents bulkier than Me impeded valuable enantioselectivities. Subsequently, Richards et al. found that Pd^{II}–pincer complexes also promote the same reaction utilizing iPr$_2$NEt as cocatalyst,[6] but with low enantioselectivity. With a sterically demanding Pd^{II}–pincer complex, Uozumi et al. later achieved good enantioselectivity under similar reaction conditions yet found the same limitation with α-Me substituents.[7] A conceptually different approach was developed by Jacobsen et al., who employed a dimeric O-bridged Al–salen complex.[8] In contrast to the soft Lewis acid catalysts, this catalyst tolerated an α-phenyl-substituted α-cyanoacetate. The application of a variety of α-aryl- and α-amino-substituted α-cyanoacetates was described for the addition to α,β-unsaturated imides without the necessity of an additional base.[9] The use of unsubstituted vinyl acceptors was not mentioned in this study.

Herein we report the application of the bispalladacycle complex **FBIP-Cl** which exploits the principal advantages of soft Lewis acids like high catalytic activity as a consequence of low oxophilicity, resulting in negligible product inhibition,[10] and overcomes the narrow structural restrictions for the previously reported late-transition-metal catalysts. The rationale behind this development was that a soft bimetallic complex capable of simultaneously activating both substrates would not only lead to superior catalytic activity, but also to an enhanced level of stereocontrol as a result of the highly organized transition state: the α-cyanoacetate should be activated by enolization promoted by coordination of the nitrile moiety to one Pd^{II} center, while the enone should be activated as an electrophile by coordination of the olefinic double bond to the carbophilic Lewis acid. Cooperative reactivity between two metal centers has been suggested for enzymatic systems[11] and is emerging as an intriguing design principle for artificial catalysts.[12]

Bispalladacycle **FBIP-OTs**, which was generated in situ from **FBIP-Cl** by treatment with AgOTs,[13] was indeed able to smoothly catalyze the addition of α-phenyl-substituted cyanoacetate **1Aa** (R = Me) to methyl vinyl ketone (MVK) (precatalyst loading 0.5 mol%), albeit with poor enantioselectivity (Table 1, entry 1).[14,15] The enantioselectivity was considerably increased by use of bulky ester groups, though at the expense the reaction rate (Table 1, entries 2 and 4; initial reaction rates at $c = 0.20\ \mathrm{mol\,L^{-1}}$: **1Ab**: $40.6\ \mathrm{mmol\,L^{-1}\,h^{-1}}$; **1Ad**: $18.4\ \mathrm{mmol\,L^{-1}\,h^{-1}}$). To increase the reactivity of the *tert*-butyl ester **1Ad**, various solvents were screened. The reaction medium was found to have a strong influence: the enantioselectivity decreased in all solvents tested relative to the selectivity in CH_2Cl_2, while a significantly enhanced reaction rate was noticed in cyclohexane, Et_2O, diglyme, and EtOH (Table 1, entries 7, 8, 11, and 13). Whereas in the protic solvent EtOH, nearly racemic product was formed, the reaction in in diglyme showed promising selectivity, which

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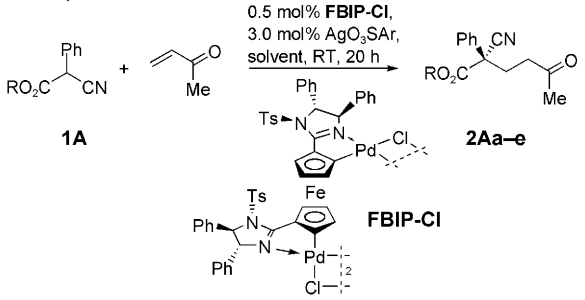
Table 1: Optimization of the model reaction.[a]



Entry	1 A	R	Solv.	Ar	Additive (mol%)	Yield [%][b]	*ee* [%][c]
1	**1 Aa**	Me	CH_2Cl_2	*p*-Tol	–	95	11
2	**1 Ab**	Et	CH_2Cl_2	*p*-Tol	–	93	33
3	**1 Ac**	Bn	CH_2Cl_2	*p*-Tol	–	>99	41
4	**1 Ad**	***t*Bu**	CH_2Cl_2	*p*-Tol	–	**81**	**81**
5	**1 Ad**	*t*Bu	$CHCl_3$	*p*-Tol	–	60	69
6	**1 Ad**	*t*Bu	toluene	*p*-Tol	–	71	56
7	**1 Ad**	*t*Bu	*c*-C_6H_{12}	*p*-Tol	–	96	62
8	**1 Ad**	*t*Bu	Et_2O	*p*-Tol	–	94	54
9	**1 Ad**	*t*Bu	THF	*p*-Tol	–	69	46
10	**1 Ad**	*t*Bu	DME	*p*-Tol	–	49	38
11	**1 Ad**	*t*Bu	**diglyme**	*p*-Tol	–	**97**	**75**
12	**1 Ad**	*t*Bu	MeCN	*p*-Tol	–	13	11
13	**1 Ad**	*t*Bu	EtOH	*p*-Tol	–	>99	4
14	**1 Ad**	*t*Bu	diglyme	Mes	–	99	84
15	**1 Ad**	*t*Bu	diglyme	**Tipp**	–	**>99**	**86**
16	**1 Ad**	*t*Bu	diglyme	Tipp	HOAc (10)	99	90
17	**1 Ad**	*t*Bu	diglyme	Tipp	HOAc (1)	99	90
18[d]	**1 Ad**	*t*Bu	diglyme	Tipp	**HOAc (20)**	**>99**	**90**
19[e]	**1 Ad**	*t*Bu	diglyme	Tipp	HOAc (20)	94	88
20[e]	**1 Ad**	*t*Bu	diglyme	Tipp	HOAc (10)	93	86
21	**1 Ae**	**R**[f]	diglyme	Tipp	HOAc (20)	**>99**	**95**

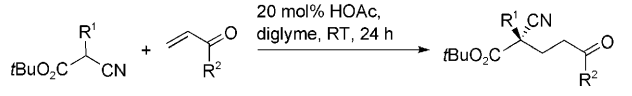
[a] 25 mg **1 A**, 2.0 equiv MVK, 0.5 mL solvent if not mentioned otherwise. [b] Determined by ^{1}H NMR spectroscopy. [c] Determined by HPLC methods. [d] 0.2 mol% **FBIP-Cl**, 1.2 mol% Ag salt, 110 μL diglyme. [e] 0.1% **FBIP-Cl**, 0.6% Ag salt, 110 μL diglyme. [f] R = CH(*i*Pr)$_2$, 250 mg **1 Ae**,1.4 mL diglyme. Mes = 2,4,6-Me_3-C_6H_2; Tipp = 2,4,6-*i*Pr_3-C_6H_2.

could be further enhanced by increasing the steric demand of the sulfonate counteranion without diminishing the catalytic activity (Table 1, entries 14 and 15).

The results from entries 1–15 in Table 1 were obtained with technical-grade MVK. Surprisingly, purification of MVK by distillation led to a sharp decrease in enantioselectivity (74% *ee*, 0.2% mol% **FBIP-Cl**, 1.2% mol% Ag-O_3S-Tipp, 2 equiv MVK, diglyme, RT). Since commercial MVK is stabilized by acetic acid and hydroquinone, the impact of these two additives was studied. While hydroquinone slightly retarded the reaction, the presence of catalytic amounts of acetic acid proved beneficial in terms of enantioselectivity. Almost identical results were obtained with 1, 10, and 20 mol% HOAc (Table 1, entries 16–20). Reducing the precatalyst loading to 0.2 mol% led to identical results (Table 1, entry 18), and even with as little as 0.1 mol% precatalyst, the reaction was still relatively efficient after a reaction time of 20 h (Table 1, entries 19 and 20). Although substrate **1 Ae** bearing the especially bulky (diisopropyl)-methyl ester unit led to even higher selectivity under the optimized reaction conditions (Table 1, entry 21), for practical reasons *t*Bu esters were chosen for the investigation of the reaction scope.

Significantly, reactions of a range of α-aryl-α-cyanoacetate donors with various vinyl ketone acceptors proceeded with excellent yield and high enantioselectivity (Table 2). The

Table 2: Scope and limitations of the reaction.[a]



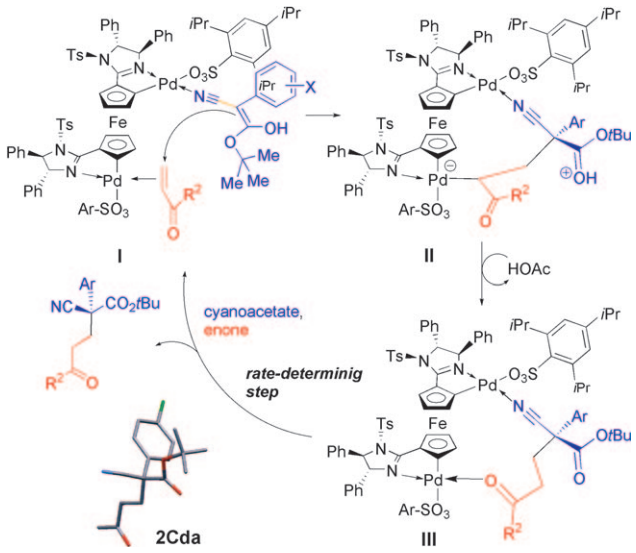
Entry	1	R^1	R^2	2	FBIP-Cl [mol%]	Yield [%][b]	*ee* [%][c]
1	**1 Ad**	Ph	Me	**2 Ada**	0.2	>99	90
2[d]	**1 Ad**	Ph	Me	**2 Ada**	0.2	99	89
3	**1 Ad**	Ph	Et	**2 Adb**	0.75	>99	88
4	**1 Ad**	Ph	*n*-Pr	**2 Adc**	1.0	90	86
5	**1 Ad**	Ph	*n*-Pent	**2 Add**	1.0	98	89
6	**1 Ad**	Ph	Ph	**2 Ade**	1.0	95	77
7	**1 Ad**	Ph	*p*-MeO-C_6H_4	**2 Adf**	1.0	80	76
8	**1 Bd**	*p*-Br-C_6H_4	Me	**2 Bda**	0.1	>99	94
9[e]	**1 Bd**	*p*-Br-C_6H_4	Me	**2 Bda**	0.05	>99	89
10	**1 Cd**	*p*-Cl-C_6H_4	Me	**2 Cda**	0.1	>99	95
11[f]	**1 Cd**	*p*-Cl-C_6H_4	Me	**2 Cda**	0.05	99	91
12[e,f]	**1 Cd**	*p*-Cl-C_6H_4	Me	**2 Cda**	0.02	98	85
13	**1 Cd**	*p*-Cl-C_6H_4	Et	**2 Cdb**	0.5	>99	94
14	**1 Dd**	*p*-F-C_6H_4	Me	**2 Dda**	0.5	>99	95
15	**1 Dd**	*p*-F-C_6H_4	Me	**2 Dda**	0.2	>99	93
16	**1 Ed**	*p*-Me-C_6H_4	Me	**2 Eda**	0.25	>99	91
17	**1 Fd**	*m*-Br-C_6H_4	Me	**2 Fda**	0.5	>99	91
18	**1 Gd**	*m*-Cl-C_6H_4	Me	**2 Gda**	0.5	>99	91
19	**1 Hd**	*m*-CF_3-C_6H_4	Me	**2 Hda**	0.5	>99	91
20	**1 Id**	*m*-MeO-C_6H_4	Me	**2 Ida**	1.0	>99	80
21	**1 Jd**	*m*-Me-C_6H_4	Me	**2 Jda**	0.5	>99	90

[a] 100–250 mg **1**, 2.0 equiv MVK, 0.2–1.4 mL diglyme. [b] Yield of isolated product. [c] Determined by HPLC. [d] 1.2 equiv MVK. [e] Reaction time 48 h. [f] 40 °C.

class of targeted products was recently shown to be highly useful for the synthesis of enantioenriched esters of $\beta^{2,2}$-amino acids.[4b] As shown in entry 2 of Table 2, a large excess of MVK was not required. The reaction rate slowed with increasing size of the alkyl substituent R^2 on the vinyl ketone, and precatalyst loadings of up to 1.0 mol% were required to attain quantitative yields (Table 2, entries 2–4), though the enantioselectivity was not considerably influenced. In contrast, the reactions of aryl vinyl ketones were less enantioselective (76–77% *ee*, Table 2, entries 5 and 6). On the α-aryl substituent R^1, both electron-withdrawing and -donating substituents were well tolerated (Table 2, entries 8–21). Acceptor substituents in *para* position (Table 2, entries 8–15) slightly increased the reactivity and asymmetric induction and made it possible to further decrease the precatalyst loading to 0.02% (Table 2, entry 12, turnover number: 2450 (monomeric catalyst)), while alkyl donors decelerated the process only a little. Substituents in *meta* position generally retarded the addition, necessitating higher precatalyst loadings, but they had no negative impact on the enantiomer ratio

irrespective of their electronic nature.[16] The developed process is operationally simple and does not require the use of inert gas; the described experiments were conducted in air. In most cases chromatographic purification was not necessary to obtain analytically pure products as no side products were formed. Excess enone was removed by evaporation, and the catalyst was removed by filtration over a short pad of silica gel.

In the development of the described methodology, we assumed that both nucleophile and electrophile are activated by a cooperative bimetallic mechanism (Scheme 1). Coordination of the nitrile group to the Pd^{II} center would facilitate enolization, while the enone would be activated by coordination of the C=C bond to the carbophilic Pd^{II}. The configurational outcome would depend upon the face selectivity of the enol approaching the Michael acceptor. To differentiate between the enantiotopic faces, the catalyst must thus control the conformation with regard to the C–CN σ bond and also direct the enone. Control of the reactive conformation is achieved by the use of a bulky ester moiety and an especially large sulfonate counteranion, which should point away from each other to minimize unfavorable steric interactions. The direction of the enone is accomplished by the cooperative mechanism, which is in accordance with the absolute configuration (*Si*-face attack on **1**) determined for **2Cda** by X-ray crystal structure analysis (Scheme 1).[17]



Scheme 1. Proposed cooperative intramolecular bimetallic mechanism and X-ray crystal structure of **2Cda**.

Kinetic, spectroscopic, and enantioselectivity data provide strong evidence for a mechanism involving bimetallic catalysis. In previous studies on the aza-Claisen rearrangement, we showed that the Cl-bridged dimer **FBIP-Cl** forms a monomeric catalyst species by activation with silver tosylate, in which one MeCN ligand reversibly and diastereoselectively adopts one of two possible coordination sites on the Pd^{II} center, while the other coordination site remains blocked by the sulfonate anion.[13b] The latter ligand is not replaced by an excess of MeCN. It was therefore likely that substrate coordination proceeds selectively by MeCN substitution. Activation of **FBIP-Cl** with Ag-O_3S-Tipp provided a similar monomeric species as indicated by ^{1}H NMR analysis. For **FBIP-O_3S-Tipp**, NOESY/ROESY experiments revealed that the active catalyst sites are, as expected, *trans* to the imidazoline N donor (see the Supporting Information). Treatment of the activated catalyst with α-cyanoacetate **1Ad** (2.5 equiv/Pd) in $CDCl_3$ effected rapid partial MeCN–substrate exchange as revealed by ^{1}H NMR spectroscopy (see the Supporting Information). Based on the hard–soft acid–base (HSAB) concept it is expected that the softer N rather than the harder O atoms would bind to the soft Lewis acid to promote enolization. This is further supported by the fact that no Michael addition product was formed when **1Ad** was replaced with diethyl α-phenyl malonate.[18]

The initial reaction rate using the corresponding S_p-configured ferrocenyl monoimidazoline monopalladacycle **FIP-Cl**[19] activated by Ag-O_3S-Tipp was only 2.1 times slower than that with the bispalladacycle under identical reaction conditions (0.5 mol% precatalyst, 25 mg **1Ad**, 2 equiv MVK, 0.2 equiv HOAc, 0.5 mL diglyme, RT), but the product was formed with low and inversed enantioface-selectivity (−45% *ee*, preferential attack of MVK on the *Re* face of **1**).[20]

The initial rate of the model reaction catalyzed by **FBIP-O_3S-Tipp** follows a first-order dependence for the activated catalyst, the Michael donor and the Michael acceptor (see the Supporting Information, Plots S1–S6). However, the rate-determining step is not the formation of the C–C bond (i.e. the enantioselectivity-determining step) but the decomplexation of the bidentate product which is able to form a chelate complex with the bimetallic system (chelate effect) thus stabilizing complex **III** against ligand exchange. This was evidenced by the relationship between the initial conversion monitored by HPLC methods (sample quenching by hexane/diglyme/*i*PrOH leads to the release of product **2** from **III**) and the reaction time (Figure 1). Extrapolation of the straight line to $t_0 = 0$ h provides a positive *y* intercept. In other words: upon addition of the reagents, C–C bond formation occurs

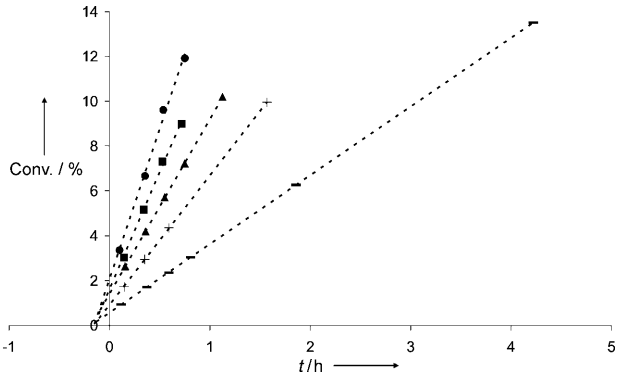


Figure 1. Relationship between the initial conversion (determined by HPLC) and reaction time (25 mg **1Ad**, 2.0 equiv MVK, cat. Ag-O_3S-Tipp, 0.5 mL diglyme) for different loadings of the **FBIP-Cl** precatalyst; ●: 1.0 mol% ($y = 13.3x + 2.06$), ■: 0.8 mol% ($y = 10.4x + 1.61$), ▲: 0.6 mol% ($y = 7.78x + 1.42$), +: 0.4 mol% ($y = 5.80x + 0.92$), –: 0.25 mol% ($3.10x + 0.57$); $R^2 \geq 0.995$ in all cases.

almost instantaneously. The amount of product correlates within the experimental error to twice the amount of precatalyst loading since the dimeric precatalyst forms two active monomeric catalyst species. In contrast, for the corresponding monopalladacycle catalyst **FIP-Cl**, for which we also found a first-order dependence for the activated catalyst excluding a bimetallic intermolecular double activation mechanism, the plots start at the zero point (see the Supporting Information, Plot S9) showing that the C–C bond formation does not proceed instantaneously in this case. *Re*-face attack of the enone to complex **I** (monometallic mechanism) is therefore significantly slower than the intramolecular C–C bond formation. This explains why the monometallic activation pathway does not destroy the enantioselectivity for **FBIP-Cl** despite the similar overall activity of monometallic **FIP-Cl**. The fact that there is no large difference in the overall rate is consequently just because of the slow decomplexation in **III**, whereas for the monopalladacycle there is no chelate effect which explains in that case decomplexation is considerably faster.

The decomplexation of **2** is a reversible step for the bispalladacycle since a slight product inhibition was determined (see the Supporting Information, Plots S7–S8). Larger R^2 residues retard the decomplexation and turnover, since initial attack of substrate **1** on **III** is likely to occur by an associative mechanism at the Pd center, which coordinates to the more labile ketone donor.

This mechanism also explains why phenyl vinyl ketones (PVKs) reacted slower in this study than the less bulky MVK although they are intrinsically more electrophilic.[5] It is also in line with the reduced *ee* values obtained for PVKs (Table 2, entries 5 and 6), as the higher electrophilicity of the acceptor leads to increased product formation by the background reaction following the monometallic pathway (attack from the sterically better accessible *Re* face). Acceleration of the monometallic pathway is also observed with increasing amounts of MVK (see the Supporting Information, Plot S10). On the other hand, electron-withdrawing substituents on the α-aryl group of **1** decrease the inherent nucleophilicity of the generated enols and consequently minimize a monometallic background reaction, which explains the higher enantioselectivity.

The bimetallic mechanism involving coordination of the acceptor's C=C bond also points to the necessity for catalytic amounts of HOAc to obtain high enantioselectivity although it has no influence on the reaction rate. The conjugate addition should initially form complex **II** in which Pd^{II} is connected to the α-C atom. To form the targeted product, a proton transfer must take place from the protonated ester group to the nucleophilic enolate C atom. This event might compete with a β-hydride elimination to form a Pd^0 species if the proton transfer is not sufficiently fast.[21] Addition of HOAc could thus speed up the required proton transfer, while the generated acetate anion would liberate the neutral ester group.

In conclusion, we have developed a soft Lewis acid catalyst that is capable of promoting a highly enantioselective Michael addition of α-aryl-substituted α-cyanoacetates to vinyl ketones.[22] This challenge has previously not been met with success for soft Lewis acid complexes as a result of the difficulties encountered by remote enantiofacial discrimination of the cyano-substituted enol. To overcome the previous limitations, a catalytic system has been designed capable of a) controlling the conformation with regard to the C–CN σ bond of the Michael donor and b) directing the enone to differentiate the enantiotopic faces by a bimetallic cooperative mode of action. The proposed mechanism is supported by enantioselectivity data and by spectroscopic and kinetic investigations.[23] Remarkably the same precatalyst, which is readily prepared in diastereomerically pure form in four steps from ferrocene, has been found to be exceptionally efficient for aza-Claisen rearrangements and direct Michael additions despite the fundamental differences with regard to the involved transition-state geometries. The reaction has various operational advantageous as it proceeds at room temperature with low catalyst loadings and high concentrations, does not require inert gas, and typically provides excellent yields. Current efforts are directed towards an acceleration of the product decomplexation to further accelerate the catalytic turnover.

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[16] *ortho*-Substituted phenyl groups were not well tolerated and moderate enantioselectivity was obtained, e.g.: *o*-FC_6H_4: 57% *ee*, 1-naphthyl: 50% *ee*.

[17] CCDC 695750 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. HPLC analysis of the crystal used on a chiral stationary phase subsequently confirmed that the major enantiomer of **2Cda** was investigated.

[18] Complexation of MVK was not detected by ^{1}H NMR spectroscopy, indicating that such a complex is arguably too short-lived on the NMR timescale.

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[20] The corresponding ferrocenyl imidazoline monopalladacycle complex with a C_5Ph_5 spectator ligand resulted in ca. −50% *ee* under identical reaction conditions.

[21] A β-hydride elimination would result in the formation of Pd^0 species which are usually not stable as palladacycles and form "naked" Pd^0 (see Ref. [10]). The monopalladacycle formed by decomplexation of one Pd^0 would lead to a competing pathway providing preferentially the other enantiomer.

[22] The optimized conditions for α-aryl-substituted α-cyano acetates are not useful for α-alkyl-substituted substrates and result in poor enantioselectivity. Current studies are therefore directed toward the extension to this substrate class.

[23] One referee proposed a reversible Michael addition step as mechanistic alternative to explain the enantioselectivity. However, our data can almost rule out such a scenario. If the step **I** to **II** in Scheme 1 is reversible, lower *ee* values should be obtained with an increasing amount of acetic acid, since in that case the lifetime of **II** would be reduced. Before the equilibrium would be reached (in that scenario necessary for high *ee*), the intermediate would be trapped. For that reason we can also rule out that protonation would be the enantioselectivity-determining step. Cross experiments in which **2Ada** and **2Cdb** were treated with 2 mol% bispalladacycle catalyst at room temperature revealed overall irreversibility as the formation of **2Adb** and **2Cda** could not be detected by HPLC or NMR spectroscopy.

