Asymmetric Catalysis

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Palladium-Catalyzed Decarboxylative Asymmetric Allylic Alkylation of β-ketoesters: An Unusual Counterion Effect**

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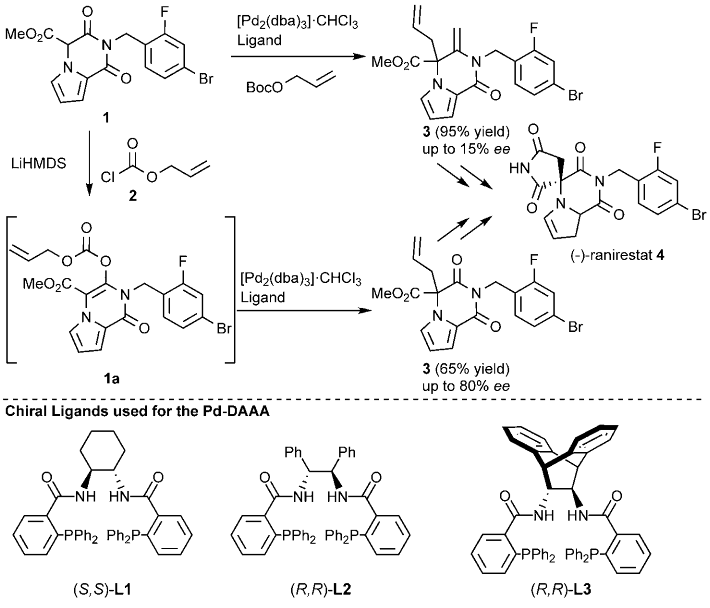
The formation of quaternary stereogenic centers in an enantioselective fashion remains a significant challenge in the synthesis of complex organic molecules.[1] The palladium-catalyzed asymmetric allylic alkylation (Pd-AAA) has proven to be a highly effective method for the construction of stereogenic quaternary centers.[2] Recently, the palladium-catalyzed decarboxylative asymmetric allylic alkylation (Pd-DAAA) has been developed into a powerful method for the chemo-, regio-, and enantioselective formation of C–C bonds.[3] In many cases, the intramolecular Pd-DAAA reaction has been shown to deliver the desired product in an increased yield and enantiomeric excess, relative to the intermolecular Pd-AAA.[4] The improvement in reactivity and enantioselectivity is particularly noticeable in examples where the new stereogenic center is formed on the nucleophile, which is typically a challenging system for the Pd-AAA.



Scheme 1. Pd-AAA and Pd-DAAA in the total synthesis of (−)-ranirestat (**4**) using chiral diphenylphosphinobenzoic acid derived ligands. Boc = *tert*-butoxycarbonyl, dba = dibenzylideneacetone, HMDS = hexamethyldisilazane.

Additionally, the Pd-DAAA has been shown to function on a variety of substrates that contain either an allyl ester or an allyl enol carbonate. Besides non-functionalized ketones, α-hydroxyketones, α-hydroxyaldehydes and vinylogous (thio)esters, and 2-acylimidazoles have been used to construct new stereogenic centers with high levels of enantioselectivity.[5] The scarcity of methods to construct stereogenic centers on β-ketoesters[6] led us to explore the Pd-DAAA as a viable strategy. Herein, we report the success of these efforts and the unusual influence of the cations on the sense of chirality for the Pd-DAAA when using the same enantiomer of the ligand.

During our studies towards the total synthesis of (−)-ranirestat (**4**; Scheme 1),[7] we were faced with the challenge of forming a tetrasubstituted stereogenic center by a Pd-AAA.[8] The intermolecular reaction between imidomalonate **1** and allyl *tert*-butyl carbonate was disappointing, and afforded the alkylated product **3** in a 95 % yield but with a mere 15 % *ee* (Scheme 1).[9] In exploring a Pd-DAAA strategy, the starting imidomalonate **1** was treated with LiHMDS and allyl chloroformate (**2**), thus leading to the presumed enol carbonate **1a**, which could not be isolated because of its instability. However, subsequent treatment of the putative intermediate **1a** with $[Pd_2(dba)_3]\cdot CHCl_3$ and **L3** in a one-pot operation, afforded the desired product in a 65 % yield and a much improved 80 % *ee.*

Inspired by the significant improvement in both the reactivity and enantioselectivity of the in situ Pd-DAAA, we sought to determine the generality of this reaction, which has not been studied with dicarbonyl compounds. To extend the existing reaction with imidomalonate (**1**), we focused on β-ketoesters, which are important chiral building blocks for the synthesis of biologically active molecules.[6a,10] Recently, Jacobsen and co-workers reported a guanidinium-catalyzed Claisen rearrangement of *O*-allyl β-ketoesters to afford *C*-allyl β-ketoester products with quaternary stereogenic centers.[11]

To optimize the reaction conditions for β-ketoesters, we investigated the reaction between tetralones **5a**–**5c** and allyl chloroformate (**2**; Table 1). Treatment of tetralone **5a** under the reaction conditions employed with imidomalonate **1** afforded the product **6a** in a 90 % yield and 41 % *ee* (Table 1, entry 1). The reaction conditions were screened systematically by changing the solvent, base, and chiral ligand

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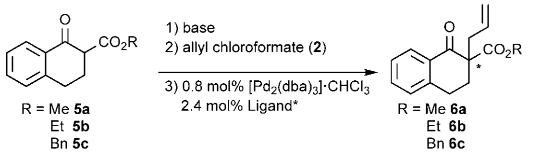
Table 1: Select optimizations for the Pd-DAAA of β-ketoester **5a**.[a]



Entry	Solvent	Base[b]	Ligand	Yield [%][c]	*ee* [%][d]
1	DME	LiHMDS	**L3**	90	41 (*S*)
2	THF	LiHMDS	**L3**	93	63 (*S*)
3	CH_2Cl_2	LiHMDS	**L3**	90	84 (*R*)
4	1,2-DCE	LiHMDS	**L3**	99	88 (*R*)
5	THF	NaHMDS	**L3**	53	37 (*S*)
6	1,2-DCE	K_2CO_3	**L2**	20	88 (*S*)
7	1,2-DCE	Cs_2CO_3	**L3**	36	66 (*S*)
8	THF	Cs_2CO_3	**L3**	90	75 (*S*)
9	1,2-DCE	Cs_2CO_3	**L1**	36	72 (*R*)
10	DME	Cs_2CO_3	**L2**	86	86 (*S*)
11	1,4-dioxane	Cs_2CO_3	**L2**	29	85 (*S*)
12	THF	Cs_2CO_3	**L2**	99	89 (*S*)
Lit.[e]	toluene	TMG	**L1**	97	77 (*S*)

[a] All the reactions were performed with 0.125 mmol of **5a** using 1.6 equiv of base and 1.0 equiv of **2**. [b] Reactions run with LiHMDS and NaHMDS were run at −78 to 4 °C and reactions run with Cs_2CO_3 and K_2CO_3 were run at RT. [c] Yield is of the isolated product. [d] The *ee* values were determined by HPLC analysis using a chiral stationary phase. [e] Ref. [6a]. Bn = benzyl, 1,2-DCE = 1,2-dichloroethane, DME = 1,2-dimethoxyethane, THF = tetrahydrofuran, TMG = *N*,*N*,*N*′,*N*′-tetramethylguanidine.

employed. LiHMDS and Cs_2CO_3 proved optimal for this reaction, whereas other bases like NaHMDS and K_2CO_3 provided the product **6a** in diminished yields (entries 5 and 6, respectively). Based on these results, two sets of reaction conditions were developed, one employing LiHMDS as the base (entry 4), and another using Cs_2CO_3 as the base (entry 12). Both sets of reaction conditions provided β-ketoester **6a** in a 99 % yield and with a high *ee* value (88 and 89 %, respectively; entries 4 and 12). In contrast, when the intermolecular Pd-AAA was used the desired product **6a** was afforded with only a 77 % *ee*. Other halogenated or ether-like solvents were less efficient at promoting the transformation, and provided the product **6a** in lower yield and enantiopurity (see the Supporting Information). In previous cases that employed the intermolecular Pd-AAA reaction, enantioselectivity could be improved by switching the ester moiety from a methyl to a bulky benzyl group. In contrast, exchanging the methyl ester (**5a**) for either an ethyl (**5b**) or benzyl ester (**5c**) in the Pd-DAAA afforded the desired products **6b** and **6c**, respectively, in good yields (84 % and 96 %, respectively), but with lower enantioselectivities (87 % *ee* and 81 % *ee*, respectively). Also, the use of chloroformate surrogates like imidazole carboxylates or their imidazolium salts did not improve the enantioselectivity of the reaction (see the Supporting Information).

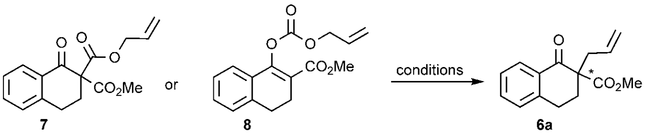
During our optimization studies, a remarkable reversal in the stereoselectivity (from *R* to *S*) was observed and was dependent on the solvent and base used. For example, the use of LiHMDS with 1,2-DCE as the solvent provided the *R* enantiomer of the desired product in an 88 % *ee* (Table 1, entry 4). However, when THF was employed, under otherwise identical reaction conditions, the *S* enantiomer of the product was obtained in 63 % *ee* (entry 2). In contrast, the use of Cs_2CO_3 in either 1,2-DCE or THF gave the same enantiomer of product **6a** and this matched the result that was obtained when LiHMDS was used in THF (compare entries 2, 4, 7, and 8).

We sought to determine the origin for the reversal in enantioselectivity. We hypothesized that changing the cation could determine the intermediate formed or which prochiral face of the nucleophile would attack the π-allyl/Pd intermediate. Previously, our group has observed that C versus O carbonylation with allyl carbonate can be reversed, and is dependent on the base employed; small cations, such as Li, tend to afford the C-carbonylated product while larger cations, such as Na, K, and Cs, tend to carbonylate at the oxygen atom.[4a] Potentially, the reversal in enantioselectivity is caused by the differential reactivity between the allyl ester and the allyl enol carbonate. Furthermore, the bases might deprotonate the amide N–H on the ligand, and change the chiral environment to reverse the enantioselectivity. An alternative possibility is that the various coordination spheres and aggregation states of the cations employed might effect which face of the prochiral nucleophile attacks the chiral π-allyl/Pd intermediate.

To determine the origin of the reversal in the enantiomer formed, we sought to isolate the intermediate allyl enol carbonate and allyl ester and subject them to the reaction conditions independently, in the absence of base. The treatment of β-ketoester **5a** sequentially with Cs_2CO_3 and allyl chloroformate (**2**) provided enol carbonate **8** which showed limited stability under ambient conditions. Alternatively, a known protocol was used to obtain the allyl ester **7** (4:1 mixture of **7**/**8**).[12] The yield and absolute configuration of the product **6a** was investigated under a range of different reaction conditions from the intermediates **7** or **8** (Table 2).

Product **6a** was obtained as the *S* enantiomer when no exogenous base was added, and was independent of the intermediate (**7** or **8**), solvent, and ligand (**L2** or **L3**) employed

Table 2: Effect on absolute stereochemistry in the Pd-DAAA.[a]



Entry	Solvent	Substrate	Ligand	Conv. [%][b]	*ee* [%][c]
1	1,2-DCE	**7**[d]	**L3**	70	76 (*S*)
2	1,2-DCE	**8**	**L3**	99	68 (*S*)
3	THF	**8**	**L3**	99	73 (*S*)
4	THF	**8**	**L2**	99	88 (*S*)
5	1,2-DCE	**8**[e]	**L3**	92	70 (*R*)
6	1,2-DCE	**8**	**L3**[f]	99	60 (*S*)

[a] For reaction conditions see Table 1. [b] Determined by ^1H NMR spectroscopy. [c] Determined by HPLC analysis using a chiral stationary phase. [d] Used 0.023 mmol of substrate in 0.5 mL of solvent (4:1 mixture of **7**/**8**). [e] Reaction mixture was cooled to −78 °C and 0.6 equiv of LiHMDS were added with subsequent addition of the palladium(0) catalyst. [f] The catalyst was pre-treated with 2 equiv LiHMDS.

(Table 2 , entries 1–4). This trend indicates that the change in enantioselectivity is dependent on the base, and independent of whether intermediate **7** or **8** is formed in situ. Furthermore, when LiHMDS was utilized as an additive with 1,2-DCE as the solvent, a reversal in absolute stereochemistry was observed from 68% *ee* (*S*)-**6a** (entry 2) to 70% *ee* (*R*)-**6a** (entry 5). This result further supports our hypothesis that the cation was determining the stereochemistry in the reaction. To address whether a dilithiated ligand species was being generated during the reaction, the catalyst was pretreated with 2.0 equivalents of LiHMDS relative to the ligand. Although this catalyst system retained high reactivity, product **6a** was again isolated as the *S* enantiomer, albeit in a diminished 60% *ee* (entry 6).

To investigate a possible counterion effect, lithium scavengers such as 12-crown-4[13] and *N,N,N′,N′*-tetramethylethylenediamine (TMEDA) were added to the reaction medium (using reaction conditions from entry 4 of Table 1; Figure 1). The graph shows that the enantioselectivity varies with the amount of TMEDA added. A similar but stronger trend was observed when 12-crown-4 was added to the reaction mixture. The enantiopurity dropped significantly from 89% (*R*) to 38% (*S*) with 3.0 equivalents of 12-crown-4. Neither TMEDA nor 12-crown-4 affected the enantioselectivity in reactions that used Cs_2CO_3 as the base, thus further supporting the observed "lithium effect". Finally, when THF was used as the solvent, the enantiopurity of product **6a** was not affected by the addition of 12-crown-4 to LiHMDS (98% yield, 66% *ee* (*S*), compared with 63% *ee* (*S*) in entry 2, Table 1). This strongly coordinating solvent itself acts as a lithium scavenger and therefore addition of 12-crown-4 did not affect the enantioselectivity.

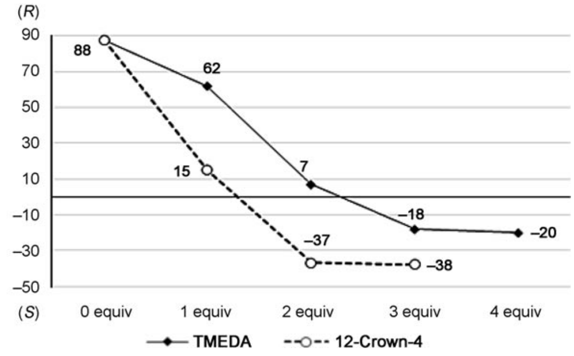


Figure 1. TMEDA and 12-crown-4 as lithium scavengers in the Pd-DAAA reaction of β-ketoester **5a** in 1,2-DCE using LiHMDS as the base.

We propose that lithium aggregates are responsible for the switch in the enantiomer obtained. During our studies, 1.6 equivalents of LiHMDS in 1,2-DCE were found to be optimal; when only 1.0 equivalent of LiHMDS was utilized, the levels of enantioselectivity diminished. Such an observation could be explained by a situation in which more than one lithium ion is involved in the aggregate. In comparison to other bases, a bulky LiHMDS aggregate might approach the π-allyl/Pd complex from the opposite face (**A**; Figure 2).[14] This argument is additionally supported by experiments which demonstrated that increasing the amount of Cs_2CO_3 had no effect on the enantioselectivity of the transformation (**B**; Figure 2).

The reaction scope of the Pd-DAAA of β-ketoesters with allyl chloroformate (**2**) was investigated using a variety of indanone and tetralone substrates (Scheme 2). A number of substitution patterns were tolerated on the aryl portion of the β-ketoester nucleophile. Slightly better results were obtained for the tetralone systems bearing electron-donating substituents on the aromatic ring (91% *ee* for **11**). Substrates containing heteroatoms (**12** and **13**) participated well in the reaction and afforded the desired products in high yield and *ee* value. Satisfactory results could also be obtained with the more challenging indanone systems, and products **16** and **17** were obtained in good yields and *ee* values. In contrast, low levels of enantioselectivity were obtained when the intermolecular Pd-AAA was employed with the corresponding benzyl ester of **17** and allyl acetate.[6b] In our case, indanones **16** and

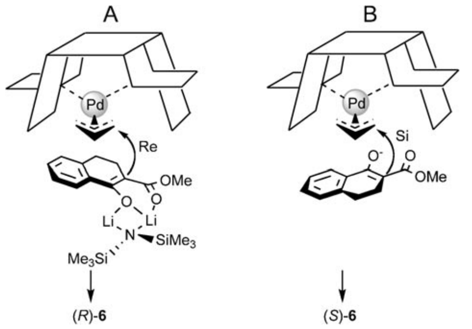
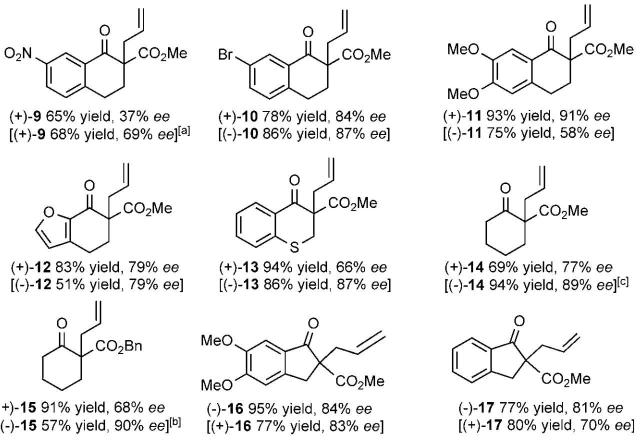


Figure 2. Proposed model for the observed reversal in enantioselectivity.



Scheme 2. Scope of the Pd-DAAA of β-ketoesters with allyl chloroformate. The results without square brackets are for reactions that used LiHMDS and 1,2-DCE and the results in square brackets are for reactions that used Cs_2CO_3 and THF. The yields are of isolated products and the *ee* values were determined by HPLC analysis using a chiral stationary phase. [a] (*S,S*)-**L2** instead of (*R,R*)-**L2** was used in this reaction. [b] The preformation time of the enol carbonate was 16 h.

17 could be obtained in good yields and improved enantioselectivity (81 % *ee* and 84 % *ee*, respectively). The switch in absolute stereochemistry between using LiHMDS and Cs_2CO_3 as base was observed with all the substrates examined.

In conclusion, we have developed a new Pd-DAAA using an imidomalonate, which was applied in the formal synthesis of (−)-ranirestat (**4**). This reaction was expanded to β-ketoesters, where allyl chloroformate was used to form the reactive allyl enol carbonates in situ. Two sets of reaction conditions were developed to allow fine-tuning of the reactivity and enantioselectivity. In all the cases examined, the levels of enantioselectivity exceeded those of the Pd-AAA for similar systems. For the first time, opposite product enantiomers were obtained when Li versus Cs enolates were employed. The origins for the change in absolute stereochemistry of the products were investigated by scavenging lithium cations with TMEDA or 12-crown-4 and the results suggested that lithium aggregates were responsible for the observed reversal. Tetralones bearing a variety of substitution patterns with both electron-donating and electron-withdrawing groups were used as nucleophiles and provided the allylated products in high yield and *ee* value.

Experimental Section

General Procedure for the Pd-DAAA using LiHMDS as base: The substrate (0.125 mmol) was placed in a test tube under argon and was dissolved in the freshly distilled solvent (1.0 mL). The solution was cooled to −78 °C, and LiHMDS (0.2 mL, 1 M in THF) was added at once. The solution was stirred at −78 °C for 30 min and allyl chloroformate (13.3 μL, 0.125 mmol) was added. The resulting solution was stirred for 30 min at −78 °C at which point a premixed orange solution of $[Pd_2(dba)_3]\cdot CHCl_3$ (1.03 mg 0.001 mmol) and **L3** (2.4 mg, 0.003 mmol) was added to the reaction mixture. The resulting solution was stirred 16 hours at 4 °C and then filtered through a plug of Florisil, and washed with Et_2O (4 × 5 mL). The obtained yellow solution was adsorbed onto silica gel and purified by flash column chromatography (20:1–4:1 petroleum ether/Et_2O).

General Procedure for the Pd-DAAA using Cs_2CO_3 as base: The substrate (0.125 mmol) and cesium carbonate (65 mg, 0.2 mmol) were placed in a test tube under argon and the solvent (1 mL) was added to obtain a light yellow suspension which was stirred at RT. After 30 min allyl chloroformate (13.3 μL, 0.125 mmol) was added and a white precipitate was formed anytime between 30 min and 16 h. A premixed orange coloured solution of $[Pd_2(dba)_3]\cdot CHCl_3$ (1.03 mg, 0.001 mmol) and **L2** (2.3 mg, 0.003 mmol) was added by canula to the reaction mixture, and the resulting mixture was stirred for an additional 4–24 h at RT. The reaction mixture was then filtered through a plug of Florisil and washed through with Et_2O (4 × 5 mL). The obtained yellow solution was adsorbed onto silica gel and purified by flash column chromatography (20:1–4:1 petroleum ether/Et_2O).

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[1] a) E. J. Corey, A. Guzman-Perez, *Angew. Chem.* **1998**, *110*, 2092; *Angew. Chem. Int. Ed.* **1998**, *37*, 388; b) J. P. Das, H. Chechik, I. Marek, *Nat. Chem.* **2009**, *1*, 128; c) J. Christoffers, A. Mann, *Angew. Chem.* **2001**, *113*, 4725; *Angew. Chem. Int. Ed.* **2001**, *40*, 4591; d) K. Fuji, *Chem. Rev.* **1993**, *93*, 2037; e) D. Caine in *Comprehensive Organic Synthesis: Carbon-Carbon s-Bond Formation*, *Vol. 3* (Eds.: B. M. Trost, I. Fleming), Pergamon, New York, **1991**.

[2] a) *Topics in Organometallic Chemistry 14: Palladium in Organic Synthesis*, *Vol. 14* (Ed.: J. Tsuji) Springer, Berlin, **2005**; b) *Handbook of Organopalladium Chemistry for Organic Synthesis* (Ed.: E.-i. Negishi), Wiley, New York, **2002**.

[3] The first examples of Pd-DAAA: a) J. Tsuji, T. Yamada, I. Minami, M. Yuhara, M. Nisar, I. Shimizu, *J. Org. Chem.* **1987**, *52*, 2988; b) E. C. Burger, J. A. Tunge, *Org. Lett.* **2004**, *6*, 4113; for review see: c) J. A. Tunge, E. C. Burger, *Eur. J. Org. Chem.* **2005**, 15044; d) S.-L. You, L.-X. Dai *Angew. Chem.* **2006**, *118, 5372; Angew. Chem. Int. Ed.* **2006**, 45, 5246; *Angew. Chem. Int. Ed.* **2006**, *45*, 5246.

[4] For a comparison of the results of Pd-DAAA and Pd-AAA, compare the following references: a) B. M. Trost, J. Y. Xu, T. Schmidt, *J. Am. Chem. Soc.* **2009**, *131*, 18343; b) B. M. Trost, G. M. Schroeder, *Chem. Eur. J.* **2005**, *11*, 174.

[5] Enol carbonates can be easily formed by reactions of allyl imidazol carboxylates and the corresponding carbonyl compounds: a) B. M. Trost, J. Y. Xu, *J. Org. Chem.* **2007**, *72*, 9372; for Pd-DAAA for ketones, see: Ref. [4a] and b) B. M. Trost, J. Y. Xu, *J. Am. Chem. Soc.* **2005**, *127*, 17180; c) D. C. Behenna, B. M. Stoltz, *J. Am. Chem. Soc.* **2004**, *126*, 15044; for α-tertiary hydroxyaldehydes, see: d) B. M. Trost, J. Xu, M. Reichle, *J. Am. Chem. Soc.* **2007**, *129*, 282; for α-hydroxyketones, see: e) B. M. Trost, J. Xu, T. Schmidt, *J. Am. Chem. Soc.* **2008**, *130*, 11852; for vinylogous esters and thioesters, see: f) B. M. Trost, R. N. Bream, J. Xu, *Angew. Chem.* **2006**, *118*, 3181; *Angew. Chem. Int. Ed.* **2006**, *45*, 3109; for 2-acylimidazoles, see: g) B. M. Trost, K. Lehr, D. J. Michaelis, J. Xu, A. K. Buckl, *J. Am. Chem. Soc.* **2010**, *132*, 8915; for calculations on the mechanism of the DAAA on cyclic enol carbonates, see: h) J. A. Keith, D. C. Behenna, J. T. Mohr, S. Ma, S. C. Marinescu, J. Oxgaard, B. M. Stoltz, W. A. Goddard III, *J. Am. Chem. Soc.* **2007**, *129*, 11876; for Pd-DAAA in the synthesis of complex molecules, see: i) J. A. Enquist, Jr., B. M. Stoltz, *Nature* **2008**, *453*, 1228; j) D. E. White, I. C. Stewart, R. H. Grubbs, B. M. Stoltz, *J. Am. Chem. Soc.* **2008**, *130*, 810.

[6] a) B. M. Trost, R. Radinov, E. Grenzer, *J. Am. Chem. Soc.* **1997**, *119*, 7879; b) R. Radinov, unpublished results.

[7] V. Bril, R. A. Buchanan, *Diabetes Care* **2006**, *29*, 68.

[8] a) B. M. Trost, G. M. Schroeder, J. Kristensen, *Angew. Chem.* **2002**, *114*, 3642; *Angew. Chem. Int. Ed.* **2002**, *41*, 3492; examples for the use of Pd-AAA in complex synthesis: b) B. M. Trost, M. K. Brennan, *Org. Lett.* **2006**, *8*, 2027; c) B. M. Trost, M. U. Frederiksen, *Angew. Chem.* **2005**, *117*, 312; *Angew. Chem. Int. Ed.* **2005**, *44*, 308.

[9] B. M. Trost, M. Osipov, G. Dong, *Org. Lett.* **2010**, *12*, 1276.

[10] a) T. Hayashi, K. Kanehira, T. Hagihara, M. Kumada, *J. Org. Chem.* **1988**, *53*, 113; b) R. Kuwano, Y. Ito, *J. Am. Chem. Soc.* **1999**, *121*, 3236; c) R. Ooi, T. Miki, M. Taniguchi, M. Shiraishi, M. Takeuchi, K. Maruoka, *Angew. Chem.* **2003**, *115*, 3926; *Angew. Chem. Int. Ed.* **2003**, *42*, 3796.

[11] C. Uyeda, A. R. Rötheli, E. N. Jacobsen, *Angew. Chem.* **2010**, *122*, 9947; *Angew. Chem. Int. Ed.* **2010**, *49*, 9753.

[12] G. D. Johnson, W. B. Lindsey, B. R. Jones, *J. Am. Chem. Soc.* **1956**, *78*, 461.

[13] a) V. P. Y. Gadzekpo, G. J. Moody, J. D. R. Thomas, G. D. Christian, *Ion-Sel. Electrode Rev.* **1986**, *8*, 173; b) E. Angeletti, R. Baima, C. Canepa, I. Degani, G. Tonachini, P. Venturello, *Tetrahedron* **1989**, *45*, 7827.

[14] Detailed studies about π-allyl/Pd complexes and the graphics used can be found in the literature: B. M. Trost, F. D. Toste, *J. Am. Chem. Soc.* **1999**, *121*, 4545.