DOI: 10.1002/adsc.200505126

Palladium-Catalysed Enantioselective Conjugate Addition of Aromatic Amines to α,β-Unsaturated *N*-Imides. Effect of the Chelating Moiety

Pim Huat Phua,[a] Johannes G. de Vries,[b] King Kuok (Mimi) Hii[a,*]

[a] Department of Chemistry, Imperial College London, Exhibition Road, South Kensington, London SW7 2AZ, U. K.
E-mail: mimi.hii@imperial.ac.uk
[b] DSM Research-Life Sciences, Advanced Synthesis, Catalysis and Development, P. O. Box 18, 6160 MD Geleen, The Netherlands
E-mail: Hans-JG.Vries-de@dsm.com

Received: March 24, 2005; Accepted: May 3, 2005; Published online: September 26, 2005

Dedicated to John M. Brown, FRS on the occasion of his 65th birthday.

Supporting Information for this article is available on the WWW under http://asc.wiley-vch.de/home/.

Abstract: Palladium-catalysed enantioselective additions of aromatic amines to α,β-unsaturated *N*-imides **4**–**6** are reported. The *N*-substituent of the Michael acceptor appears to have an unusual modulating effect on the amine activity. The effects of introducing different substituents are examined. Overall, the yield and selectivity of the system appear to be less sensitive to environmental effects than previous systems. The importance of the counteranion is revealed.

Keywords: asymmetric catalysis; conjugate addition; hydroamination; palladium; substituent effects

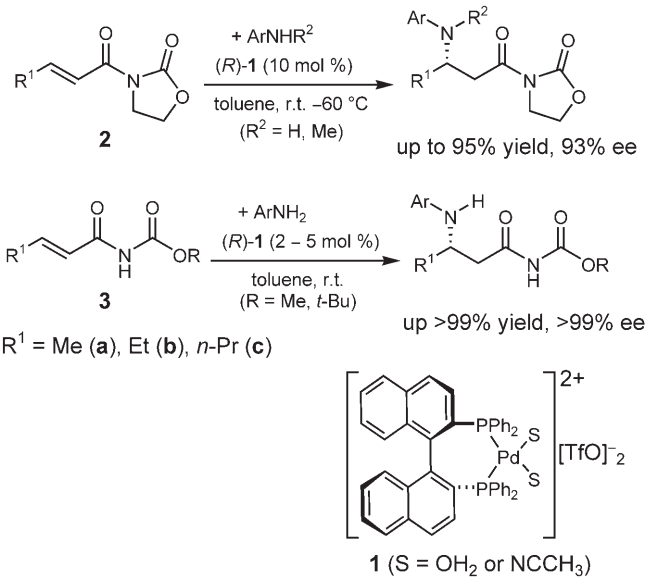
Introduction

Previously, we reported the dicationic diphosphinepalladium(II) bis(trifluoromethanesulfonate) $[(BINAP)Pd(solvate)_2]^{2+}[TfO]^-_2$ (**1**) as an efficient catalyst for the conjugate addition of aromatic amines to alkenoyl-*N*-oxazolidinones **2** and *N*-carbamate esters **3** with high enantioselectivity (Scheme 1).[1]

Both substrates **2** and **3** contain 1,3-dicarbonyl groups. We postulated that they are able to form templates with the Lewis-acidic palladium metal centre, predisposing the attack of the nucleophile stereoselectively at the β-position (Fig. 1). In the absence of these chelating moieties, the addition of aniline to methyl crotonate proceeded in just 24% ee under the same reaction conditions.[1d]

Given that the reaction conditions are identical, the disparity between the reactivity of the two substrates is striking, and appears to be dependent on the nature of the chelating moiety. For example, the addition of aromatic amines to alkenoyl-*N*-oxazolidinones **2a** requires a relatively high catalytic loading (10 mol %) to achieve 93% yield in 18 h (93% ee). In contrast, amine addition to the analogous substrate **3a** is much more facile, only 2–5 mol % of the catalyst was required to afford comparable yields.

Intrigued by this dramatic change in reactivity between the cyclic and acyclic Michael acceptors, we initiated a study to examine other olefin substrates contain-



Scheme 1. Enantioselective addition of aromatic amines to α,β-unsaturated *N*-oxazolidinones **2** and *N*-carbamates **3** catalysed by **1**.

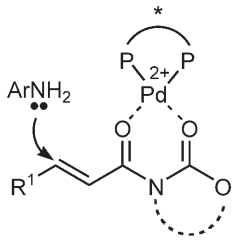
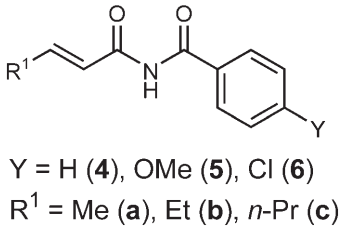


Figure 1. Chelation-assisted stereoselectivity.



Y = H (**4**), OMe (**5**), Cl (**6**)
R^1 = Me (**a**), Et (**b**), *n*-Pr (**c**)

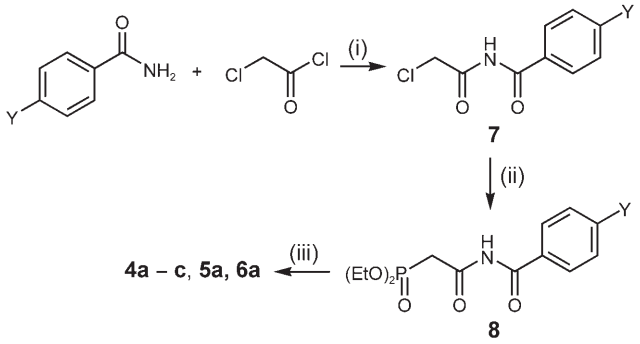
Figure 2. α,β-Unsaturated *N*-imides.

ing a structural motif containing non-cyclic 1,3-chelating carbonyls. Previously, α,β-unsaturated *N*-imides have been employed as Michael acceptors in enantioselective addition of a remarkable range of nucleophiles, including hydrazoic acid,[2] as well as cyanide,[3] stabilised carbanions[4] and oximes,[5] catalysed by Salen-Al complexes. In this paper, the palladium-catalysed conjugate addition of aromatic amines to alkenoyl *N*-imide substrates, **4**–**6** (Fig. 2), will be examined. The result will be compared with those obtained in the previous studies (Scheme 1). Additionally, substituent (Y) at the *para*-position of the benzoyl group was introduced, to probe the electronic effects exerted by the terminal carbonyl group.

Results and Discussion

Synthesis of *N*-Imide Substrates

The *N*-imide substrates may be prepared in multigram quantities in three steps by adopting published procedures (Scheme 2).[6] Following acyl substitution of chloroacetyl chloride with the corresponding benzamides, Arbuzov, and Horner–Wadsworth–Emmons (HWE) reactions were performed to furnish imides **4a**–**c**, and **5a**. Due to the low nucleophilicity of 4-chlorobenzamide, a different procedure was adopted for the synthesis of **6a**, obtained from the reaction between crotonyl chloride and deprotonated 4-chlorobenzamide.



Scheme 2. Preparation of *N*-alkenoyl *N*-imides **4a** – **c** and **5a**: (i) heat; (ii) $P(OEt)_3$, heat; (iii) R^1CHO, DBU, THF.

Catalytic Conjugate Addition Reactions

Effect of Solvents (Table 1)

The reaction between aniline and crotonyl *N*-imide **4a** was performed initially in five different reaction media (Table 1).[7] As was observed in previous systems, the non-coordinating toluene offered the highest yield of the product with the best stereoselectivity (Table 1, entry 1), whereas polar, more coordinating, solvents such as acetonitrile and methanol were detrimental to yield and selectivity (entries 4 and 5). However, unlike previous systems,[1c–d] dichloromethane and THF were well-tolerated (entries 2 and 3), thus suggesting that the chelate ring obtained with the *N*-imide (Fig. 1) is more stable towards solvents of weak coordinating ability.

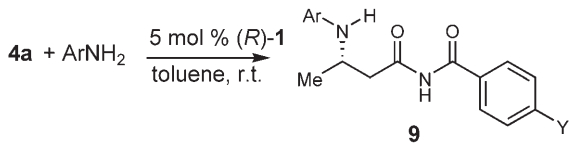
Rates of Addition of Different Aromatic Amines (Table 2)

Previously, the relative rates of amine addition to the *N*-Boc substrate **3a** were found to be in the order: 4-chloroaniline > aniline > 4-anisidine (unusually decreasing in the order of increasing nucleophilicity).[1c] The same experiments were replicated for the addition

Table 1. Effect of solvents in the addition of aniline to **4a** (Scheme 3).[a]

Entry	Solvent	Conversion[b] [%]	ee[c] [%]
1	toluene	84	89
2	dichloromethane	82	81
3	tetrahydrofuran	86	84
4	acetonitrile	49	39
5	methanol	47	28

[a] Reaction conditions: catalyst/amine/*N*-imide **4a** in a ratio of 0.05/1.0/1.1, in the chosen solvent, at room temperature, 18 h.
[b] Calculated by ^{1}H NMR integration.
[c] Determined by chiral HPLC.



Scheme 3. Conjugate addition of aromatic amines to **4a**.

Table 2. Relative rates of addition of substituted anilines to **4a** (Scheme 3).[a]

Entry	Time [h]	Conversion[b] [%]		
		4-$ClC_6H_4NH_2$	$PhNH_2$	4-$MeOC_6H_4NH_2$
1	0.5	71	74	39
2	1	74	76	52
3	4	81	80	73
4	8	83	84	77
5	24	86	87	80

[a] Reaction monitored by ^{1}H NMR. Catalyst/amine/*N*-imide **4a** in a ratio of 0.05/1.0/1.1, in toluene-d_8 at room temperature.
[b] Calculated by relative integrals of resonance signals of substrate and product.

of the amines to **4a** in toluene-d_8, using ^{1}H NMR spectroscopy to monitor the progress of the reaction (Table 2). Interestingly, a different trend was obtained. Although the addition of the most electron-rich anisidine remained sluggish, the relative rates of addition of the other two were found to be virtually the same! The nature of the *N*-substituent evidently has a modulating effect on the reactivity of the amines, although the origin of this is not clear at this stage.

Substituent Effects (Table 3)

The homologation of the β-substituent was examined in the next part of our investigation. In the analogous addition to substrate **3a**–**3c**, ee values varied considerably between 16 to > 99% ee.[1c] In contrast, the enantioselectivity of the present system appeared to be relatively insensitive to the electronic structure of the amine, ranging between 73–89% for the addition to **4a** (Table 3, entries 1–4), 51–63% to **4b** (entries 5–8) and 55–70% to **4c** (entries 9–12). Also noticeable are the comparatively low ees obtained from the addition of the electron-deficient 4-chloroaniline. In each case, it is substantially inferior compared to the addition of the electronically 'neutral' aniline and 4-toluidine (entries 1 *vs.* 2/3, 5 *vs.* 6/7 and 9 *vs.* 10/11). Nonetheless, the present system offers an improvement for the addition of electron-rich aromatic amines. In the previous system, the addition of 4-anisidine to substrates **3** was particularly non-selective; when R^1 = Me (**a**), Et (**b**) and *n*-Pr (**c**), ee values of 73, 16 and 17% were obtained, respectively. In comparison, the addition to **4a**–**c** proceeded with ees of 80, 51 and 55%, respectively (entries 4, 8 and 12).

As expected, the R^1 substituent has a dramatic effect on the rate of catalytic turnover. Additions to pentenoyl (**4b**) and hexenoyl (**4c**) substrates were slower, requiring a longer reaction time than the equivalent addition to the **4a**. Once again, the yields of these additions are far less sensitive to the electronic nature of the amine for a given Michael acceptor (entries 1–4, 5–8 and 9–12).

Next, the electronic effect exerted by the terminal carbonyl group was examined by studying the addition to butenoyl *N*-imides **5a** and **6a**, where electron-donating (OMe) or withdrawing (Cl) groups were introduced at the *para*-position of the benzoyl unit (Table 4).

Remarkably, neither the yield nor enantioselectivity of the reactions are much affected by the *para*-substituent of the benzoyl group. For the addition of 4-chloroaniline, decreasing the electron-density of the *N*-benzoyl moiety led to a slight enhancement of the enantiomeric excess (entries 1–3). Apart from this, other additions of aniline, *p*-toluidine and *p*-anisidine appeared to be in-

Table 3. Addition of $ArNH_2$ to **4a**–**c** (Scheme 3).[a]

Entry	Y	Ar	Product	*t* [h]	Conversion[b] [%]	ee[c] [%]
1	Me	4-ClC_6H_4	**9a**	18	88 (82)	73
2	Me	Ph	**9b**	18	84 (76)	89
3	Me	4-MeC_6H_4	**9c**	18	81 (80)	83
4	Me	4-$MeOC_6H_4$	**9d**	18	70 (64)	80
5	Et	4-ClC_6H_4	**9e**	72	70 (68)	54
6	Et	Ph	**9f**	72	75 (74)	63
7	Et	4-MeC_6H_4	**9 g**	72	70 (54)	59
8	Et	4-$MeOC_6H_4$	**9 h**	72	76 (70)	51
9	Pr	4-ClC_6H_4	**9i**	72	78 (75)	58
10	Pr	Ph	**9j**	72	69 (65)	67
11	Pr	4-MeC_6H_4	**9k**	72	71 (69)	70
12	Pr	4-$MeOC_6H_4$	**9 l**	72	69 (62)	55

[a] Reaction conditions: catalyst/amine/*N*-imide **4a** in a ratio of 0.05/1.0/1.1, in toluene at room temperature (25 ^{0}C).
[b] Calculated by ^{1}H NMR integration. Value in parenthesis denotes isolated yield after column chromatography.
[c] Determined by chiral HPLC.

Table 4. Addition of $ArNH_2$ to **4a**, **5a** and **6a** (Scheme 3).[a]

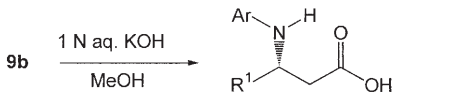
Entry	Y	Ar	Product	Conversion[b] [%]	ee[c] [%]
1	H (**4a**)	4-ClC_6H_4	**9a**	88 (82)	73
2	OMe (**5a**)	4-ClC_6H_4	**9 m**	89 (83)	67
3	Cl (**6a**)	4-ClC_6H_4	**9n**	85 (80)	78
4	H (**4a**)	Ph	**9b**	81 (76)	89
5	OMe (**5a**)	Ph	**9o**	89 (85)	89
6	Cl (**6a**)	Ph	**9p**	83 (75)	89
7	H (**4a**)	4-MeC_6H_4	**9c**	81 (80)	83
8	OMe (**5a**)	4-MeC_6H_4	**9q**	86 (85)	78
9	Cl (**6a**)	4-MeC_6H_4	**9r**	87 (85)	83
10	H (**4a**)	4-$MeOC_6H_4$	**9d**	70 (64)	80
11	OMe (**5a**)	4-$MeOC_6H_4$	**9 s**	82 (77)	83
12	Cl (**6a**)	4-$MeOC_6H_4$	**9 t**	85 (82)	80

[a] As described in footnote[a] to Table 3.
[b] Calculated by ^1H NMR integration. Value in parenthesis denotes isolated yield after purification by column chromatography.
[c] Determined by chiral HPLC.

sensitive to the *N*-benzoyl substituent (entries 4–6, 7–9 and 10–12). Previously, we also observed little difference between the addition of aniline to *tert*-butyl carbamate **3a** (where R = *t*-Bu, Scheme 1) and its methyl analogue (R = Me).[1c] Thus, the enantioselectivity appears to be more dependent on the electronic nature of the amine substrate and the homology of the olefin substituent (R^1), with the *N*-substituent exerting a more global effect.

Assignment of Absolute Configuration

The product **9a** was converted to the corresponding *N*-phenyl-substituted β-alanine **10** by hydrolysis with aqueous potassium hydroxide (Scheme 4). The (*S*)-(+)-configuration was thus established by comparison of the optical rotation with previously established values.[1c] In this instance, the sense of stereoinduction is unchanged by a change in the *N*-substituent.

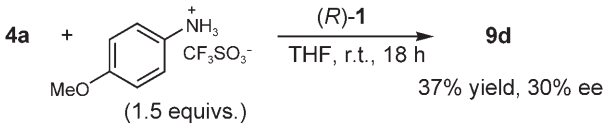


(*S*)-(+)-**10**
$[\alpha]_D$ (*c* 1.0, $CHCl_3$) +14.6° (89% ee)

Scheme 4. Establishing the absolute configuration of **10**.

Additives and Counteranion

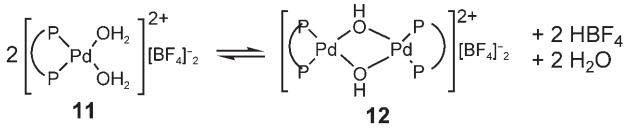
Following our initial work on the conjugate addition of aromatic amines to *N*-oxazolidinones,[1b] Sodeoka et al. reported that the enantioselectivity of these additions may be enhanced by employing the trifluoromethanesulfonate salt of the amine as the Michael donor.[8] The authors reasoned that this suppresses uncatalysed addition of the aromatic amine, and prevents catalyst deactivation by amine coordination. Thus, the reaction between **4a** and the trifluoromethanesulfonate salt of *p*-anisidine was carried out. In our case, the use of the amine salt led to a decrease in the yield and selectivity (Scheme 5).[9]



Scheme 5. Addition of trifluoromethanesulfonate salts.

In the concluding part of this investigation, we examined the effect of the counteranion. We attempted to prepare the tetrafluoroborate salt of complex **1** *via* the commonly adopted halide abstraction route. The addition of silver(I) tetrafluoroborate to a solution of [*R*-(BINAP)$PdCl_2$] led to the formation of a mixture of compounds (^{31}P NMR), including the expected monomeric complex **11**, and a μ-hydroxy dimeric palladium(II) complex **12** (Scheme 6), characterised by a distinct singlet ^1H resonance at *ca.* −3 ppm (corresponding to the bridging OH groups). Treating the mixture of compounds with molecular sieve 4 Å in dichloromethane for 3 days shifts the equilibrium to the dimeric compound **12**.[10] Conversely, by employing acetone/water during the halide abstraction reaction, the monomeric palladium species **11** may be isolated.[11]

When the isolated complexes were used as catalysts in the addition of aniline to **4a**, lower yields and ee values were obtained: 86% (75% ee) and 31% (36% ee) for **11** and **12**, respectively. The dimeric species appears to be much less catalytically active than the monomeric



Scheme 6. Equilibrium mixture between monomeric and dimeric palladium(II) complexes.

complex. We speculate that the tetrafluoroborate salt of monomeric complex **11** undergoes dynamic exchange with the dimeric structure in solution – the small amount of HBF_4 released during this interchange catalyses a competitive racemic process, which leads to the erosion of the enantioselectivity. Thus, the trifluoromethanesulfonate counteranion plays an important role by stabilising the monomeric structure (possibly through hydrogen bonding), which leads to enhanced catalyst performance.

Conclusion

The enantioselective addition of primary aromatic amines to α,β-unsaturated *N*-imides, catalysed by the dicationic palladium trifluoromethanesulfonate complex **1**, has been examined under a number of reaction conditions. In certain cases, significant improvements were reported. These studies reveal important factors governing reactivity and selectivity in these reactions. The important role of the counteranion was also revealed. The reaction mechanisms of these reactions will be further elucidated by kinetic and spectroscopic techniques, and reported in due course.

Experimental Section

General Remarks

All manipulations involving air- and moisture-sensitive organometallic reagents were performed under a dry nitrogen atmosphere using standard Schlenk techniques. Column chromatography was performed on silica gel (Kieselgel 60, 63–200 μm). ^1H, ^{13}C and ^{31}P NMR spectra were obtained on a Jeol EX-270 instrument (^1H at 270 MHz, ^{31}P at 109.3 MHz and ^{13}C at 67.5 MHz). The chemical shifts are reported in δ (ppm), reference to residual protons and ^{13}C signals of $CDCl_3$. ^{31}P spectra were referenced to H_3PO_4. The coupling constants are in Hertz (*J* Hz). Infrared spectra were recorded on a Mattson Instrument Satellite FTIR spectrometer; the samples were prepared either in Nujol mull or as liquid film between NaCl plates, or pressed into KBr discs. Optical rotation values were measured on a Perkin Elmer 343 polarimeter using a 10 cm solution cell. Concentration of the samples is given in g/mL. Melting points (uncorrected) were determined on an Electrothermal Gallenkamp apparatus. Chiral HPLC analyses were performed on a Gilson HPLC system equipped with an autoinjector with a 20 μL loop); detection was effected by UV absorption at 254 nm. Elemental analyses were carried out by Elemental Analysis Service, University of North London. Mass spectra (MS) were recorded on a Micromass Autospec-Q Mass Spectrometer using EI techniques. All dried solvents were purchased from Sigma Aldrich and stored under a nitrogen atmosphere. All commercial reagents were used as received without further purification.

Preparations of catalyst **1**,[1a] **4a–c**,[6] **11** and **12**[10] have been previously described.

4-Methoxyl-*N*-(but-2-enoyl)benzamide (5a)

Prepared by the procedure described previously.[6] White solid; yield: 1.53 g (70%); anal. found: C 65.66, H 5.95, N 6.26; $C_{12}H_{13}NO_3$ requires: C 65.74, H 5.98, N 6.39%; $R_f = 0.45$ (EtOAc/hexanes, 4/1); mp 168.0–168.3 °C; IR (KBr): $\nu_{max} =$ 3290 (NH), 1708 and 1673 cm^{-1} (C=O); ^1H NMR (270 MHz, $CDCl_3$): δ = 8.88 (1H, s, NH), 7.88 (2H, d, *J* = 6.9 Hz, Ar), 7.25 (1H, dq, *J* = 15.3 and 6.9 Hz, CH_3CH), 7.15 (2H, d, *J* = 6.9 Hz, Ar), 6.95 (1H, d, *J* = 15.3 Hz, CH=C*H*), 3.86 (3H, s, OCH_3), 1.97 (3H, d, *J* = 6.9 Hz, CH_3); ^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 167.7 (N*C*=O), 165.2 (Ar*C*=O), 163.6 (Ar), 146.5 (CH_3CH=CH), 130.0 (Ar), 125.1 (Ar), 124.4 (CH_3CH=*C*H), 114.1 (Ar), 55.5 (OCH_3), 18.5 (CH_3); MS (EI): *m/z* = 220/219 (M^+, 5/36%), 135 (100), 107 (8), 77 (15), 69 (28).

N-(But-2-enoyl)-4-chlorobenzamide (6a)

To a stirred solution of 4-chlorobenzamide (1.5 g, 10 mmol) in dry THF (10 mL) at −20 °C was added EtMgBr (1 M in THF solution, 10 mL, 10 mmol) slowly. After stirring for 1 h, *trans*-crotonyl chloride (1.4 mL, 14 mmol) was added. The resulting mixture was stirred for 2 h, then warmed up to room temperature. Stirring was continued for 1 h, before the reaction was quenched by the addition of saturated aqueous NH_4Cl (10 mL). The layers were separated, and the aqueous layer was extracted with ethyl acetate (3 × 10 mL). The combined organic layers were washed with water and brine, dried over Na_2SO_4, and evaporated. The crude product was subject to column chromatography, then recrystallised from $CHCl_3$-hexane to give **6a** as an analytically pure white solid; yield: 0.6 g (27%); mp 129.8–130.0 °C ($CHCl_3$-hexane); Anal. found: C 59.05, H 4.50, N 6.26; $C_{11}H_{10}ClNO_2$ requires: C 59.07, H 4.51, N 6.26%; $R_f = 0.55$ (EtOAc/hexanes, 1/1); IR (KBr): $\nu_{max} = 3272$ (NH), 1708 and 1670 cm^{-1} (C=O); ^1H NMR (270 MHz, $CDCl_3$): δ = 9.17 (1H, s, NH), 7.87 (2H, d, *J* = 6.7 Hz, Ar), 7.46 (2H, d, *J* = 6.7 Hz, Ar), 7.39 (1H, dq, *J* = 8.6 and 5.2 Hz, CH_3CH), 7.23 (1H, d, *J* = 8.6 Hz, CH=C*H*), 1.99 (3H, d, *J* = 5.2 Hz, CH_3); ^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 167.7 (N*C*=O), 165.1 (Ph*C*=O), 147.4 (CH_3CH=CH), 139.6 (Ar), 131.4 (Ar), 129.4 (Ar), 124.1 (Ar), 18.6 (CH_3); MS (EI): *m/z* = 225/223 (M^+, 13/36), 141 (34), 139 (100), 111 (35), 75 (25), 69 (100).

Catalytic Reactions Conducted in Parallel using a Radley's 12-Position Reaction Carousel

For the typical catalytic experiment, each reaction tube was loaded with the catalyst, a stirrer bar and fitted with a screw

cap (with a nitrogen inlet and rubber septum). The reaction tubes were placed in the carousel and purged and filled with nitrogen. The solvent, *N*-imide and amine were then added successively to each tube. The reaction mixtures were magnetically stirred, while the temperature of the heating block was maintained at 25 ^{0}C by means of a thermostat. The progress of the reaction was monitored by extracting the aliquots of reaction mixture periodically *via* the rubber septum and recording the corresponding ^{1}H NMR spectra. All reactions were duplicated to within $\pm 3\%$ accuracy. After the prescribed period of time, the solvent was evaporated and the residue subjected to column chromatography.

β-Amino *N*-Imides 9

The characterization data for **9a**–**9 t** can be found in the Supporting Information.

Hydrolysis of Compound 9b

Compound (−)-**9b** (0.10 g, 0.35 mmol, 89% ee) was dissolved in 1 N KOH in MeOH (2.5 equivs.) at room temperature for 1 h, after which the solvents were evaporated. The residue was dissolved in water, and washed with portions of Et_2O. The acidity of the aqueous phase was adjusted carefully to pH 4 by the addition of 1 N HCl, before extracting with EtOAc (4×10 mL). The combined organic layers were washed with brine, dried over $MgSO_4$ and evaporated to afford the β-amino acid **10**; yield: 64 mg (100%); $[\alpha]_D^{25}$: $+14.6^\circ$ (*c* 1, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$): $\delta = 7.21$ (2H, t, $J = 7.4$ Hz, Ph), 6.78 (1H, t, $J = 7.4$ Hz, Ph), 6.68 (2H, d, $J = 7.4$ Hz, Ph), 6.30 (2H, br s, N*H* and COO*H*), 3.89–3.98 (1H, m, CH), 2.66 (1H, dd, $J = 15.4$ and 5.9 Hz, CH_2), 2.51 (1H, dd, $J = 15.4$, 6.4 Hz, CH_2), 1.29 (3H, d, $J = 6.4$ Hz, CH_3); ^{13}C NMR (67.5 MHz, $CDCl_3$): $\delta = 176.6$ (*C*OOH), 146.1 (Ar), 129.4 (Ar), 118.7 (Ar), 114.5 (Ar), 46.5 (*C*H), 40.6 (*C*H$_2$), 20.1 (*C*H$_3$).

Acknowledgements

The authors are grateful to the Committee of Vice-Chancellors and Principals (CVCP) for an ORSA studentship (PHP), as well as Imperial College London and DSM for additional financial support. Palladium salts were provided by Johnson Matthey plc through a precious metal loan scheme. We thank Professor Paul Pregosin (ETH Zurich, Switzerland) for valuable discussions on counteranion effects.

References and Notes

[1] a) K. Li, P. N. Horton, M. B. Hursthouse, K. K. Hii, *J. Organometallic Chem.* **2003**, *65*, 250–258; b) K. Li, K. K. Hii, *Chem. Commun.* **2000**, 1132–1133; c) K. Li, X. Cheng, K. K. Hii, *Eur. J. Org. Chem*. **2004**, 959–964; d) P. H. Phua, K. Li, K. K. Hii, *Tetrahedron*, **2005**, in press.

[2] J. K. Myers, E. N. Jacobsen, *J. Am. Chem. Soc.* **1999**, *121*, 8959–8960.

[3] a) G. M. Sammis, E. N. Jacobsen, *J. Am. Chem. Soc*. **2003**, *125*, 4441–4443; b) G. M. Sammis, H. Danjo, E. N. Jacobsen, *J. Am. Chem. Soc*. **2004**, *126*, 9928–9929.

[4] M. S. Taylor, E. N. Jacobsen, *J. Am. Chem. Soc*. **2003**, *125*, 11204–11205.

[5] C. D. Vanderwall, E. N. Jacobsen, *J. Am. Chem. Soc*. **2004**, *126*, 14724–14725.

[6] S. N. Goodman, E. N. Jacobsen, *Adv. Synth. Catal.* **2002**, *344*, 953–956.

[7] Although the solubility of complex **1** in toluene is limited, the addition of aniline afforded a homogeneous yellow solution, which gradually turned a darker orange-red solution over the course of the reaction (18 h). The reaction mixtures in all of the other solvents were homogeneous from the onset.

[8] Y. Hamashima, H. Somei, Y. Shimura, T. Tamura, M. Sodeoka, *Org. Lett.* **2004**, *6*, 1861–1864.

[9] No product formation was observed in the absence of the catalyst.

[10] A. Fujii, E. Hagiwara, M. Sodeoka, *J. Am. Chem. Soc.* **1999**, *121*, 5450–5458.

[11] In the absence of acetonitrile, the product is plagued with the presence of the dimeric compound. The monomeric complex may also be obtained by the addition of HBF_4 to the equilibrating mixture. However, the complex prepared in this manner is not used in the catalytic reactions as residual acid could catalyse the Michael addition.

