DOI: 10.1002/adsc.201000721

Iridium-Catalyzed Asymmetric Allylic Amination with Polar Amines: Access to Building Blocks with Lead-Like Molecular Properties

Paolo Tosatti,[a] Joachim Horn,[a] Amanda J. Campbell,[b] David House,[b] Adam Nelson,[a,*] and Stephen P. Marsden[a,*]

[a] School of Chemistry, University of Leeds, Leeds LS2 9JT, U.K.
Fax: (+44)-0113-343-6565; e-mail: s.p.marsden@leeds.ac.uk or a.s.nelson@leeds.ac.uk
[b] GlaxoSmithKline, Medicines Research Centre, Gunnels Wood Road, Stevenage SG1 2NY, U.K.

Received: September 21, 2010; Published online: December 5, 2010

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201000721.

Abstract: The combination of an air-stable iridium catalyst and the dipolar aprotic solvent dimethyl sulfoxide (DMSO) allowed, for the first time, the systematic exploitation of highly polar, functionalized amines in asymmetric allylic substitutions: low molecular weight, sp^3-rich chiral building blocks were obtained with physicochemical properties that will be valuable in the synthesis of lead-like small molecules.

Keywords: allylic compounds; allylic substitution; asymmetric catalysis; iridium; lead-like compounds

Controlling the molecular properties of lead compounds is essential to reduce attrition rates in drug discovery.[1] High lipophilicity and molecular weight are both associated with high attrition rates, and are almost inevitably further inflated during lead optimization.[1a–d] Low numbers of aromatic rings[1e] and high fractions of sp^3-hybridized carbons[1f] are favourable lead-like properties, and polar, chiral, low molecular weight compounds are consequently attractive starting points for drug discovery.[1] Huge progress has been made in asymmetric synthesis over the past 30 years, but procedures appropriate for parallel synthesis have rarely been developed and validated for polar, highly functionalized substrates.[2]

Iridium-catalyzed allylic amination is a valuable reaction for the enantioselective synthesis of allylic amines,[3] and has been widely exploited in target synthesis.[4] A wide range of nitrogen nucleophiles has been exploited in the reaction including amines, ammonia (and its equivalents), heteroarylamines, sulfonamides and carbamates (including their activated derivatives).[4–9] Extensive studies have led to the optimization of the reaction, and the elucidation of its mechanism.[8b,10] The most active catalyst can be generated *in situ* from $[Ir(cod)Cl]_2$ (cod = 1,5-cyclooctadiene), a chiral phosphoramidite[11] and a base[10n] (typically DABCO, TBU or *n*-$PrNH_2$), but the formation of the catalytically competent iridacycle is very sensitive to the presence of either water or oxygen.[3b,10d] High enantioselectivity has been observed in low-polarity solvents (typically THF) and, although rapid reactions have been observed in more polar solvents (e.g., DMF, EtOH, MeCN), the enantioselectivity of the re-

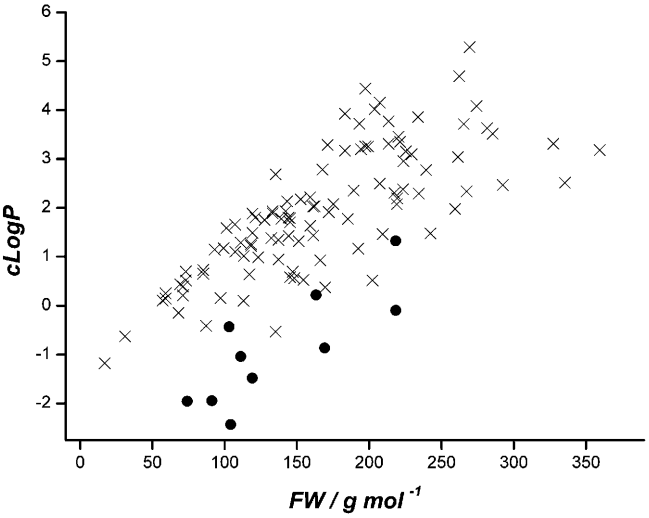


Figure 1. Physicochemical properties of nucleophiles in iridium-catalyzed allylic amination reactions: data is provided for all nucleophiles that have been previously used (×) and the nucleophiles exploited in this study (●).[13]

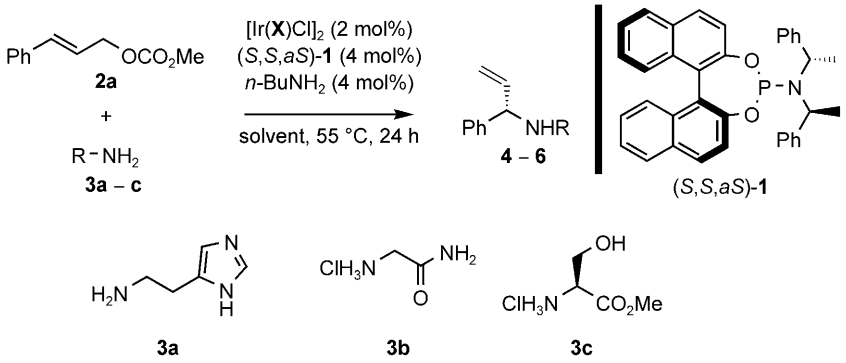
action is generally compromised.[3b,10d] Thus, although a wide range of nitrogen nucleophiles have been exploited, emphasis has been placed on rather lipophilic substrates (Figure 1).

We sought to develop a procedure for iridium-catalyzed allylic substitution reactions to allow polar, highly functionalized amines to be exploited as nucleophiles. Crucially, it was important to avoid the requirement for an inert atmosphere to allow the procedure to be conducted in parallel format. Therefore, a recently developed air-stable metallacycle catalyst, formed from $[Ir(dbcot)Cl]_2$[12] (dbcot = dibenzo-[*a*,*e*]cyclooctatraene), a chiral phosphoramidite and a base, that avoids the need for Schlenk techniques, was of great interest to our study.[10d]

Initial studies focused on reactions involving cinnamyl methyl carbonate **2a** and the polar amines **3a–c** (Table 1). In THF, the reaction gave poor results, with moderate yields for methyl serinate **3c** and very low or no conversion for histamine **3a** and glycinamide **3b**. Speculating that this may be due to the limited solubility of these nucleophiles in THF, we investigated the use of DMSO as solvent but, with $[Ir(cod)Cl]_2$ as the precatalyst, $<5\%$ conversion was observed in all cases (entries 7, 9 and 11). These results are consistent with previous attempts at Ir-catalysed allylic substitution in this solvent.[6a] Remarkably, however, the specific combination of $[Ir(dbcot)Cl]_2$ and DMSO was effective with all of the amines **3a–c**, and the required products **4**, **5** and **6A** were obtained as single regioisomers in good yield and with excellent enantio- or diastereoselectivity (entries 8, 10 and 12).

Interestingly, the reaction was significantly faster in DMSO than in THF: with the amine **3c**, the product **6A** was obtained in 81% yield after just 3.5 h in DMSO (entry 12) compared with 66% yield after 24 h in THF (entry 6). We also tested other polar solvents[14] in combination with $[Ir(dbcot)Cl]_2$, but DMSO proved to be the most effective and, in addition, is inexpensive, non-toxic, readily available and compatible with highly polar substrates that are valuable in medicinal chemisry. With $[Ir(dbcot)Cl]_2$, results were broadly comparable in the presence and absence of inert atmosphere, and thus subsequent reactions were performed without recourse to a protective atmosphere.

Table 1. Solvent and pre-catalyst comparison using polar amines.



Entry	**3**	X	Solvent	**4–6**	Yield [%]	*ee*[a] or *dr*[b]
1	**3a**	cod	THF	**4**	<5[c]	n.d.[f]
2	**3a**	dbcot	THF	**4**	<5[c]	n.d.
3[d]	**3b**	cod	THF	**5**	<5[c]	n.d.
4[d]	**3b**	dbcot	THF	**5**	27	*ee* 80%
5[d]	**3c**	cod	THF	**6A**	<5[c]	n.d.
6[d]	**3c**	dbcot	THF	**6A**	66	*dr* 93:7
7	**3a**	cod	DMSO	**4**	<5[c]	n.d.
8	**3a**	dbcot	DMSO	**4**	66	*ee* 97%
9[d]	**3b**	cod	DMSO	**5**	<5[c]	n.d.
10[d]	**3b**	dbcot	DMSO	**5**	83	*ee* 91%
11[d]	**3c**	cod	DMSO	**6A**	<5[c]	n.d.
12[d,e]	**3c**	dbcot	DMSO	**6A**	81	*dr* 93:7

[a] Determined by chiral HPLC.
[b] Diastereoisomeric ratio of the isolated product (determined by 500 MHz ^{1}H NMR spectroscopy).
[c] Conversion after 24 h determined by 500 MHz ^{1}H NMR analysis of the crude mixture.
[d] K_3PO_4 (1.3 equiv.) was used as additive.
[e] Reaction time 3.5 h.
[f] n.d. = not determined.

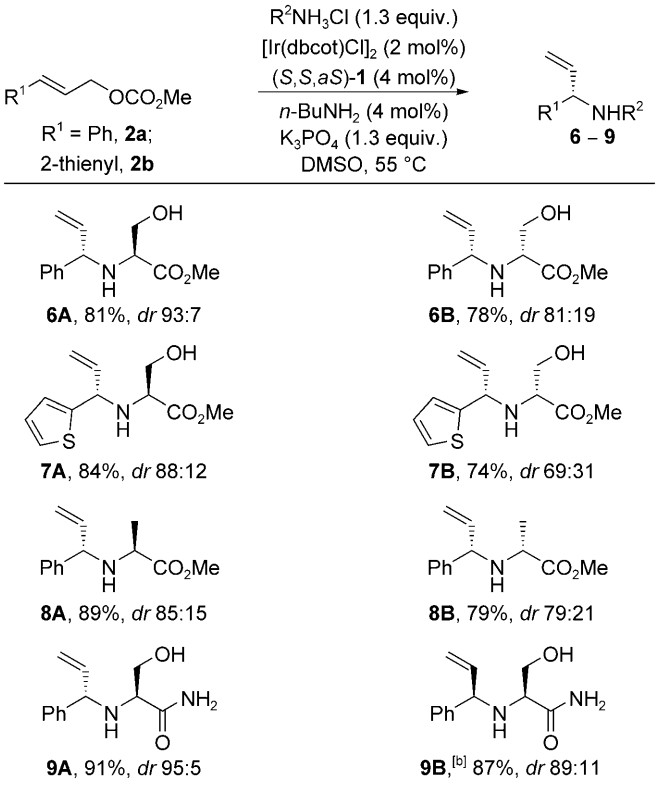
Using these optimized conditions, we determined the effect of the relative configurations of the catalyst and the amino acid-derived nucleophile on the outcome of the substitution. Accordingly, the Ir-catalyzed reactions between an allylic carbonate (**2a** or **2b**) and L- or D-configured amino acid derivatives were investigated (Table 2). With an L-configured amino acid and (*S,S,aS*)-**1**, the products **6–9A** were obtained in good to excellent yield and stereoselectivity. In contrast, in the other diastereomeric series, increased reaction times were required, and slightly lower, though still synthetically useful, yields and diastereoselectivities were observed. Although a significant matched/mismatched effect was observed, the stereochemical outcome of the reaction was largely controlled by the configuration of the chiral ligand. Again, no trace of linear regioisomers was observed. The approach allowed both diastereomeric series of products to be prepared with complementary stereoselectivity, demonstrating that significant epimerisation of nucleophile or the product did not occur under the reaction conditions.

We further determined the scope of the reaction using a range of allylic carbonates and polar amino acid derivatives (Table 3). The expected products were obtained as single regioisomers, with generally high enantio- or diastereoselectivity. The highly polar and functionalised nucleophile serinol afforded the product **10** in high yield and with excellent enantioselectivity. The reaction was notably successful with both regioisomers of mono-*N*-Boc protected 2,3-diaminopropionic acid methyl ester (**11–14**) as well as otherwise unprotected amino esters (**15–23**). In addition, the structure of the allylic carbonate **2** could be widely varied, and good yields were obtained employing carbonates with aryl (**2a**), heteroaryl (**2b**), *n*-alkyl (**2c**) and substituted alkyl (**2g–i**) R^1 substituents. The reaction was, however, significantly slower with a *sec*-alkyl R^1 group (as in **2d** and **2e**) such that completion was not reached even after 20 h; with $R^1 = t$-Bu (as in **2f**), the starting materials were recovered. The scope of the reactions was broad: free alcohols (**6, 7**, **9**, **10** and **18–23**), indoles (**15**) and imidazoles (**16**), as well as protected alcohols (as in **22** and **23**) or amines (as in **11–14** and **21**) were tolerated.

The relative and absolute configurations of the products **9A** and **22** were assigned by X-ray crystallographic analysis,[15] confirming that the sense of stereochemical control exerted by the chiral ligand was the same as has been observed in other Ir-catalysed allylic aminations using ligand **1**.[4]

In summary, we have developed a simple and reliable method for the asymmetric amination of allylic carbonates using a wide range of polar amine nucleophiles which is amenable to operation in parallel format, and does not require an inert atmosphere. The unique combination of DMSO as solvent and $[Ir(dbcot)Cl]_2$ as precatalyst was essential to the success and generality of the reaction. The range of highly functionalised amines validated included amino acid derivatives with free hydroxy, carbamate, amide and unprotected *N*-heterocyclic functionalities. Crucially, the method allows a wide range of polar amines to be exploited as nucleophiles, systematically expanding the physicochemical properties of the products into useful drug-like space for the first time, whilst still allowing the introduction of small lipophilic groups (Figure 1). The method allows the direct construction of highly-functionalised products valuable in the synthesis of diverse chiral scaffolds with lead-like molecular properties, which will be reported in due course.

Table 2. Matched and mismatched effects using chiral amino acid derivatives.[a]



[a] Diastereoisomeric ratio of the isolated products determined by 500 MHz ^{1}H NMR spectroscopy.

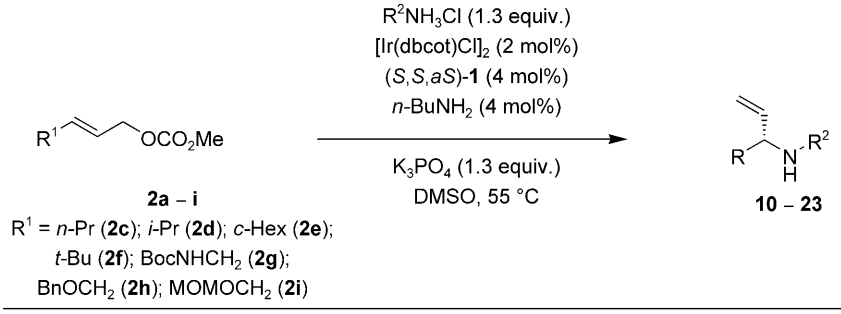
[b] (*R,R,aR*)-**1** was used as chiral ligand.

Experimental Section

General Procedure for Allylic Amination with $[Ir(dbcot)Cl]_2$ and (*S,S,aS*)-1 in DMSO

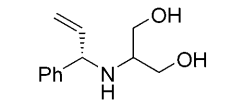
To a solution of $[Ir(dbcot)Cl]_2$ (4.3 mg, 0.005 mmol) and chiral phosphoramidite (*S,S,aS*)-**1** (5.4 mg, 0.010 mmol) in DMSO (0.5 mL) was added *n*-butylamine (1.0 μL,

Table 3. Scope of the reaction.[a]

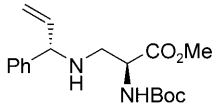


2a – i
R^1 = *n*-Pr (**2c**); *i*-Pr (**2d**); *c*-Hex (**2e**); *t*-Bu (**2f**); $BocNHCH_2$ (**2g**); $BnOCH_2$ (**2h**); $MOMOCH_2$ (**2i**)

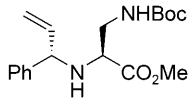
10 – 23



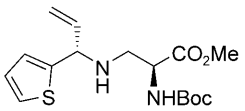
10,[b] 85%, *ee* 93%[c]



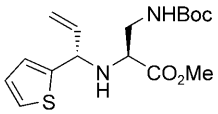
11,[b] 84%, *dr* 88:12



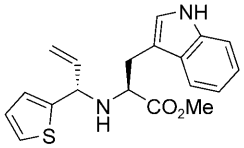
12,[b] 78%, *dr* 82:18



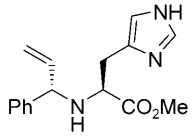
13,[b] 88%, *dr* 88:12



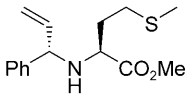
14,[b] 75%, *dr* 82:18



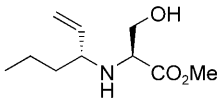
15, 78%, *dr* 88:12



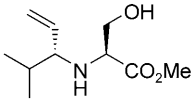
16,[d] 80%, *dr* 90:10



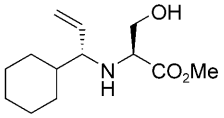
17, 89%, *dr* 94:6



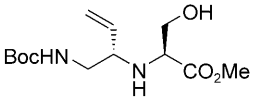
18, 89%, *dr* 87:13



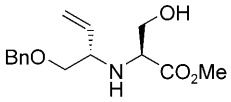
19,[e] 68%, *dr* 88:12



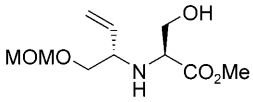
20,[e] 56%, *dr* 93:7



21, 82%, *dr* 95:5



22, 87%, *dr* 89.11



23, 85%, *dr* 88:12

[a] Diastereoisomeric ratio of the isolated products determined by 500 MHz ^{1}H NMR spectroscopy.
[b] No added K_3PO_4 (free amine was used).
[c] Determined by chiral HPLC.
[d] 2.6 equiv. of K_3PO_4 were used with L-His-OMe·2 HCl.
[e] Conversion after 24 h determined by ^{1}H NMR analysis of the crude mixture (**19** ≈ 75%; **20** ≈ 65%).

0.010 mmol) *via* microsyringe under air. The reaction vessel was sealed with a screw cap and the mixture heated at 50 °C for 30 min to allow the formation of the active catalyst species. After this time, the allylic carbonate (0.25 mmol), the nucleophile (0.33 mmol) and potassium phosphate (0.33 mmol, when necessary) were added and the resulting mixture was heated at 55 °C in a closed vessel. Upon completion, the mixture was allowed to reach room temperature and the solvent evaporated (by means of a GeneVac centrifugal evaporator) to give a crude product. The regioselectivity of the reaction was determined by ^{1}H NMR analysis of the crude product. The desired product was finally purified by flash chromatography.

Acknowledgements

EPSRC and GlaxoSmithKline are gratefully acknowledged for financial support to this study (EP/E020712/1). The au-

thors would like to thank Mr. Eric Hortense (GlaxoSmith-Kline) for chiral HPLC analyses and Mr. Colin Kilner (University of Leeds) for X-ray diffraction analyses.

References

[1] a) T. I. Oprea, A. M. Davis, S. J. Teague, P. D. Leeson, *J. Chem. Inf. Comput. Sci.* **2001**, *41*, 1308–1315; b) M. C. Wenlock, R. P. Austin, P. Barton, A. M. Davis, P. D. Leeson, *J. Med. Chem.* **2003**, *46*, 1250–1256; c) P. D. Leeson, B. Springthorpe, *Nat. Rev. Drug. Discov.* **2007**, *6*, 881–890; d) G. M. Keserü, G. M. Makara, *Nat. Rev. Drug. Discov.* **2009**, *8*, 203–214; e) F. Lovering, J. Bikker, C. Humblet, *J. Med. Chem.* **2009**, *52*, 6752–6756; f) T. J. Ritchie, S. J. F. Macdonald, *Drug Discovery Today* **2009**, *14*, 1011–1020.

[2] For recent comprehensive annual reviews of libraries for drug discovery and chemical biology, see: a) R. E. Dolle, B. E le Bourdonnec, A. J. Goodman, G. A. Morales, C. J. Thomas, W. Zhang, *J. Comb. Chem.* **2009**, *11*, 739–790; b) R. E. Dolle, B. E Bourdonnec, A. J. Goodman, G. A. Morales, C. J. Thomas, W. Zhang, *J. Comb. Chem.* **2008**, *10*, 753–802; c) T. W. J. Cooper, I. B. Campbell, S. J. F. Macdonald, *Angew. Chem.* **2010**, *122*, 8258–8267; *Angew. Chem. Int. Ed.* **2010**, *49*, 8082-8267.

[3] For reviews see: a) G. Helmchen, in: *Iridium Complexes in Organic Chemistry*, (Eds. L. A. Oro, C. Claver), Wiley-VCH, Weinheim, **2009**, pp 211–250; b) G. Helmchen, A. Dahnz, P. Dübon, M. Schelwies, R. Weihofen, *Chem. Commun.* **2007**, 675–691; c) R. Takeuchi, S. Kezuka, *Synthesis* **2006**, 3349–3366; d) R. Takeuchi, *Synlett* **2002**, 1954–1965.

[4] a) A. Farwick, G. Helmchen, *Org. Lett.* **2010**, *12*, 1108–1111; b) C. Gnamm, K. Brödner, C. M. Krauter, G. Helmchen, *Chem. Eur. J.* **2009**, *15*, 10514–10532; c) C. Gnamm, C. M. Krauter, K. Brödner, G. Helmchen, *Chem. Eur. J.* **2009**, *15*, 2050–2054; d) C. Förster, G. Helmchen, *Synlett* **2008**, 831–836; e) C. Gnamm, G. Franck, N. Miller, T. Stork, K. Brödner, G. Helmchen, *Synthesis* **2008**, 3331–3350; f) C. Welter, R. M. Moreno, S. Streiff, G. Helmchen, *Org. Biomol. Chem.* **2005**, *3*, 3266–3269.

[5] M. J. Pouy, L. M. Stanley, J. F. Hartwig, *J. Am. Chem. Soc.* **2009**, *131*, 11312–113113.

[6] a) C. Defieber, M. A. Ariger, P. Moriel, E. M. Carreira, *Angew. Chem.* **2007**, *119*, 3200–3204; *Angew. Chem. Int. Ed.* **2007**, *46*, 3139–3143; b) M. J. Pouy, A. Leitner, D. J. Weix, S. Ueno, J. F. Hartwig, *Org. Lett.* **2007**, *9*, 3949–3952.

[7] a) L. M. Stanley, J. F. Hartwig, *Angew. Chem.* **2009**, *121*, 7981–7984; *Angew. Chem. Int. Ed.* **2009**, *48*, 7841–7844; b) L. M. Stanley, J. F. Hartwig, *J. Am. Chem. Soc.* **2009**, *131*, 8971–8983.

[8] a) J.-B. Xia, W.-B. Liu, T.-M. Wang, S.-L. You, *Chem. Eur. J.* **2010**, *16*, 6442–6446; b) R. Weihofen, O. Tverskoy, G. Helmchen, *Angew. Chem.* **2006**, *118*, 5673–5676; *Angew. Chem. Int. Ed.* **2006**, *45*, 5546–5549; c) R. Weihofen, A. Dahnz, O. Tverskoy, G. Helmchen, *Chem. Commun.* **2005**, 3541–3543.

[9] D. J. Weix, D. Markowić, M. Ueda, J. F. Hartwig, *Org. Lett.* **2009**, *11*, 2944–2947.

[10] a) S. T. Madrahimov, D. Markowić, J. F. Hartwig, *J. Am. Chem. Soc.* **2009**, *131*, 7228–7229; b) S. Spiess, J. A. Raskatov, C. Gnamm, K. Brödner, G. Helmchen, *Chem. Eur. J.* **2009**, *15*, 11087–11090; c) J. A. Raskatov, S. Spiess, C. Gnamm, K. Brödner, F. Rominger, G. Helmchen, *Chem. Eur. J.* **2010**, *16*, 6601–6615; d) S. Spiess, C. Welter, G. Franck, J.-P. Taquet, G. Helmchen, *Angew. Chem.* **2008**, *120*, 7764–7767; *Angew. Chem. Int. Ed.* **2008**, *47*, 7652–7655; e) D. Markowić, J. F. Hartwig, *J. Am. Chem. Soc.* **2007**, *129*, 11680–11681; f) Y. Yamashita, A. Gopalarathnam, J. F. Hartwig, *J. Am. Chem. Soc.* **2007**, *129*, 7508–7509; g) D. Polet, A. Alexakis, K. Tissot-Croset, C. Corminboeuf, K. Ditrich, *Chem. Eur. J.* **2006**, *12*, 3596–3609; h) D. Polet, A. Alexakis, *Org. Lett.* **2005**, *7*, 1621–1624; i) C. Welter, A. Dahnz, B. Brunner, S. Streiff, P. Dübon, G. Helmchen, *Org. Lett.* **2005**, *7*, 1239–1242; j) A. Leitner, C. Shu, J. F. Hartwig, *Org. Lett.* **2005**, *7*, 1093–1096; k) A. Leitner, S. Shekhar, M. J. Pouy, J. F. Hartwig, *J. Am. Chem. Soc.* **2005**, *127*, 15506–15514; l) C. Shu, A. Leitner, J. F. Hartwig, *Angew. Chem.* **2004**, *116*, 4901–4904; *Angew. Chem. Int. Ed.* **2004**, *43*, 4797–4800; m) A. Leitner, C. Shu, J. F. Hartwig, *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 5830–5833; n) C. A. Kiener, C. Shu, C. Incarvito, J. F. Hartwig, *J. Am. Chem. Soc.* **2003**, *125*, 14272–14273; o) B. Bartels, C. García-Yebra, G. Helmchen, *Eur. J. Org. Chem.* **2003**, 1097–1103; p) T. Ohmura, J. F. Hartwig, *J. Am. Chem. Soc.* **2002**, *124*, 15164–15165; q) K. Tissot-Croset, D. Polet, A. Alexakis, *Angew. Chem.* **2004**, *116*, 2480–2482; *Angew. Chem. Int. Ed.* **2004**, *43*, 2426–2428; r) B. Bartels, C. García-Yebra, F. Rominger, G. Helmchen, *Eur. J. Inorg. Chem.* **2002**, 2569–2586.

[11] J. F. Teichert, B. L. Feringa, *Angew. Chem.* **2010**, *122*, 2538–2582; *Angew. Chem. Int. Ed.* **2010**, *49*, 2486–2528.

[12] D. R. Anton, R. H. Crabtree, *Organometallics* **1983**, *2*, 621–627.

[13] Instant JChem. was used for log P prediction (weighted method), Instant JChem. 5.3.6, 2010, ChemAxon (http://www.chemaxon.com).

[14] DMF, MeCN, 1,4-dioxane, HMPU and NMP were tested – see Supporting Information for details.

[15] CCDC 773163 (**9A**) and CCDC 787504 (**22**) contain 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. The absolute configurations of the products **9A** and **22** were assigned on the basis of the known configurations of L-serinamide and L-serine methyl ester, respectively.

