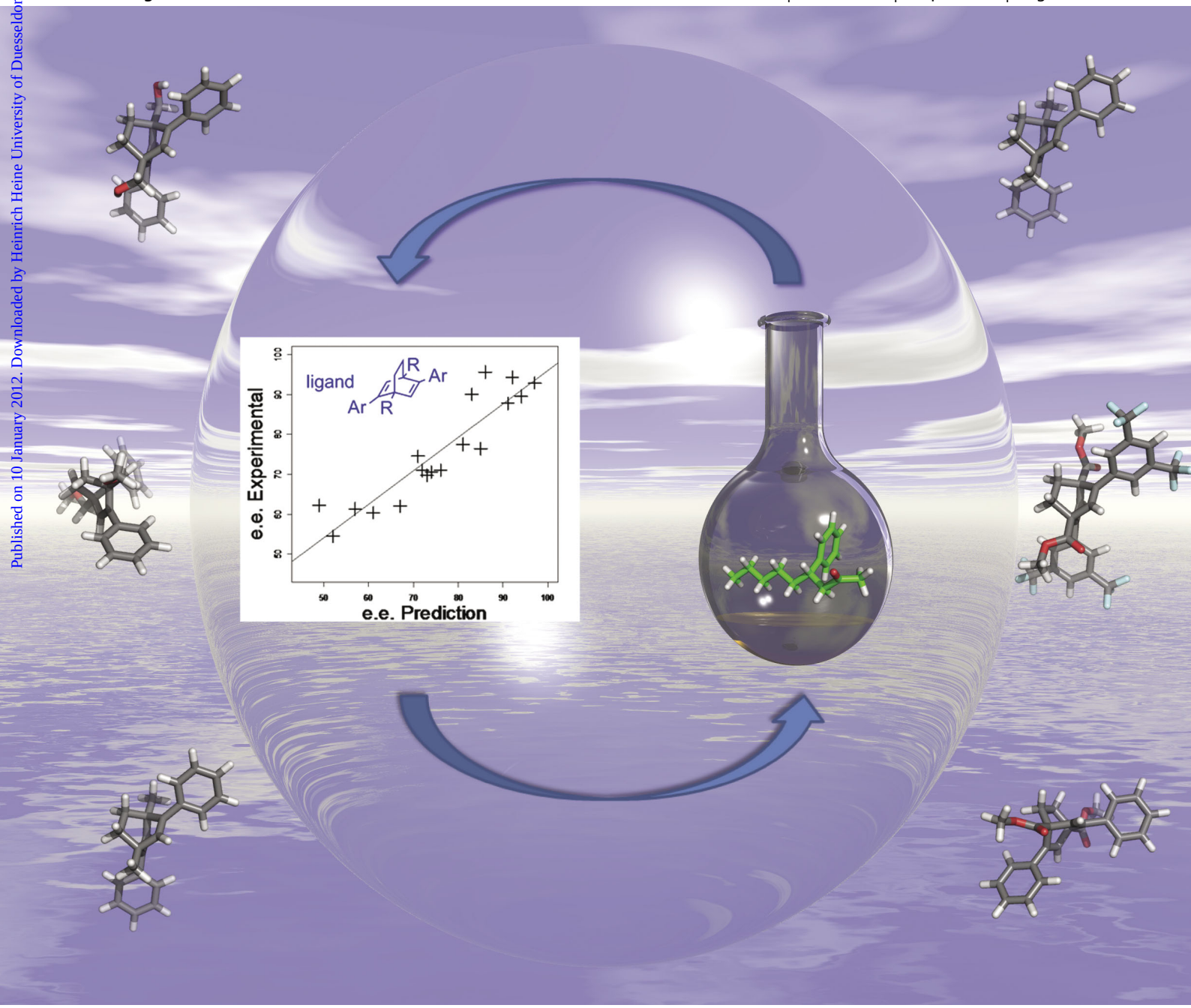
ChemComm

Chemical Communications

www.rsc.org/chemcomm

Volume 48 | Number 27 | 4 April 2012 | Pages 3249–3364



ISSN 1359-7345

COMMUNICATION

Andrew J. Carnell *et al.*

Chiral bicyclic [2.2.2] octadiene ligands for Rh-catalysed catalytic asymmetric conjugate additions to acyclic enones: a quantitative structure–property relationship

RSC Publishing

1359-7345(2012)48:27;1-7

ChemComm

Dynamic Article Links
View Article Online

Cite this: *Chem. Commun.*, 2012, **48**, 3279–3281

www.rsc.org/chemcomm

COMMUNICATION

Chiral bicyclic [2.2.2] octadiene ligands for Rh-catalysed catalytic asymmetric conjugate additions to acyclic enones: a quantitative structure–property relationship†

Yunfei Luo,‡ Neil G. Berry and Andrew J. Carnell*

Received 16th November 2011, Accepted 24th December 2011
DOI: 10.1039/c2cc17120a

A series of chiral bicyclic [2.2.2]diene ligands gave variable ee values for Rh-catalysed asymmetric conjugate addition to an acyclic enone. The interplay between electronic and steric effects was captured in a robust predictive quantitative structure–property relationship (QSPR) model for enantioselectivity.

Chiral diene ligands, developed independently by Hayashi, Carreira and others have attracted a great deal of interest in asymmetric catalysis for reactions catalysed by rhodium and iridium.[1] A range of synthetically useful reactions, most notably asymmetric conjugate addition of aryl boronates to enones, can be achieved in high yields and enantiomeric excess using both C_1- and C_2-symmetric diene ligands.[2] Previous structural modifications of bicyclic ligands,[4a–e] appeared to suggest that steric factors dominate selectivity, with an empirical model devised to explain stereochemical outcomes based on binding orientation of the enone with respect to the alkene substituents on the C_2-symmetric diene ligands.[4b,e] We recently described a chemoenzymatic approach that gave ready and flexible access to a new series of 1,4-disubstituted C_2-symmetric bicyclic [2.2.2]diene ligands.[3] The inclusion of bridgehead 1,4-methyl groups in the ligands enabled us for the first time to note a significant electronic effect, which improved catalytic performance and allowed us in some cases to lower the equivalents of aryl boronic acid required. Catalysts with electron rich ligands gave excellent activity for both cyclic and linear enone substrates whereas enantioselectivity for linear enones was lower. However, use of several electron deficient ligands resulted in improved enantioselectivity.

Du[2b,c] and Trost[2f] have recently reported the use of readily accessible chiral linear chain dienes that exhibit promising performance in conjugate addition reactions. However, structurally similar ligands show diverse results both in enantioselectivity and reactivity. These are difficult to predict and a library of ligands often needs to be synthesized and tested in order to select the best for a given transformation. A similar situation exists in the sulfino-olefin hybrid ligand-catalyzed conjugate addition reactions.[5]

The kinetic profile of the Rh-catalyzed conjugate addition is well established both with phosphine and diene ligands, where the transmetallation is the rate limiting step.[6] While detailed theoretical studies have been published on asymmetric induction by phosphine and nitrogen based ligand complexes,[7,8] studies on chiral dienes have only recently appeared. DFT calculations by Kantchev[9] for the chiral diene-Rh(I)-catalysed conjugate addition to cyclohexanone suggest that the enantioselection step is the carborhodation and not enone coordination and Brown[10] has shown that distortions in the transition state for carborhodation dictate enantioselectivity. These studies strongly suggest that transfer of chiral information from the ligand to the product is under stereoelectronic rather than purely steric control.

Intrigued by the subtle and often difficult to interpret effects at play, we examined a series of 18 bicyclic ligands for the asymmetric conjugate addition of phenyl boronic acid **2** to the acyclic substrate non-3-en-2-one **1** to afford (*S*)-ketone-**3** (Table 1). Experimentally determined enantioselectivity (ee) was used to generate a predictive quantitative structure–property relationship (QSPR) computational model (Fig. 1). This showed a remarkably consistent relationship between the properties of the ligand and the enantioselectivity outcome that appears to be applicable to acyclic but not cyclic enone substrates.

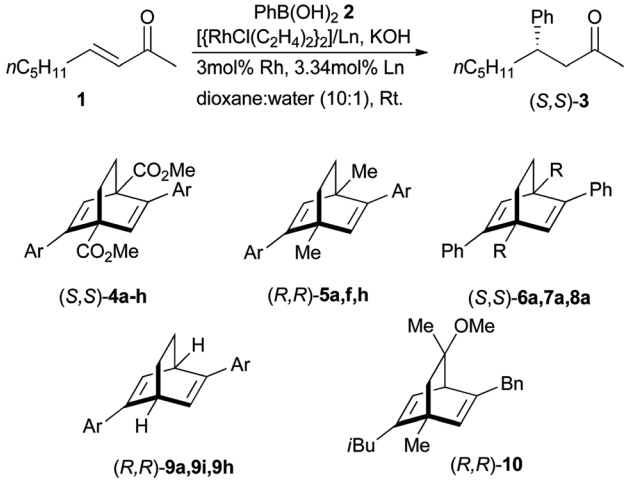
Ligands were prepared according to previously reported methods (details in ESI).[3,4b] Almost all ligands tested gave consistently high yields, however ee's were more variable. Ligands **4a–h** (entries 1–8), containing the 1,4-diester groups, show an increase in ee with electron withdrawing substituents on the aryl rings. These ligands gave lower ee's than those reported for Hayashi's diene ligand **9a** (entry15).[4b] This may have been expected based on the larger steric requirement of the 1,4-diester groups; indeed for the *cyclic* substrate 2-cyclohexenone, ligand **4a** gave diminished selectivity when compared to ligand **9a** or our 1,4-dimethyl ligand **5a**.[3] However, for the *acyclic* substrate **1**, the 1,4-diester ligand **4a** out-performs the 1,4-dimethyl ligand **5a** significantly (74% ee *vs.* 52% ee; entries 1 and 9), suggesting that electronic factors may be more important for acyclic than for cyclic substrates. Introduction of 3,5-$(CF_3)_2C_6H_3$- aryl groups in the ligand **5f** (entry 10) gave much improved selectivity (97% ee), supporting this idea.

Department of Chemistry, University of Liverpool, Crown Street, Liverpool, L69 7ZD, UK. E-mail: acarnell@liv.ac.uk; Fax: +44 151 7943587; Tel: +44 151 794 3531

† Electronic supplementary information (ESI) available: ^{1}H-NMR, ^{13}C-NMR, IR, HRMS, HPLC; QSPR modelling. See DOI: 10.1039/c2cc17120a

‡ Current address: School of Chemistry, University of Edinburgh, West Mains Road, Edinburgh, UK.

Table 1 Yields and ee's for conjugate addition to enone **1**[a]



Entry	Ln	1,4-R	2,5-Aryl	Yield	Ee of (*S*)-**3**
1	**4a**	CO_2Me	Ph	95	74
2	**4b**	CO_2Me	3-$CF_3C_6H_4$	92	85
3	**4c**	CO_2Me	3-$CH_3C_6H_4$	98	73
4	**4d**	CO_2Me	4-$CF_3C_6H_4$	95	81
5	**4e**	CO_2Me	4-$MeOC_6H_4$	99	76
6	**4f**	CO_2Me	3,5-$(CF_3)_2C_6H_3$	95	86
7	**4g**	CO_2Me	3,5-$(CH_3)_2C_6H_3$	96	71
8	**4h**	CO_2Me	3,4,5-$(MeO)_3C_6H_2$	98	72
9	**5a**	Me	Ph	99	52
10	**5f**	Me	3,5-$(CF_3)_2C_6H_3$	99	97
11	**5h**	Me	3,4,5-$(MeO)_3C_6H_2$	99	49
12	**6a**	CH_2OH	Ph	98	67
13	**7a**	CH_2OMe	Ph	98	57
14	**8a**	CH_2F	Ph	95	61
15	**9a**	H	Ph	95	94
16	**9i**	H	4-(MeOCO)C_6H_4	99	92
17	**9h**	H	3,4,5-$(MeO)_3C_6H_2$	98	83
18	**10**	H, Me	*i*-Pr, Bn	99	91

[a] See ESI for reaction conditions and method for ee determinations.

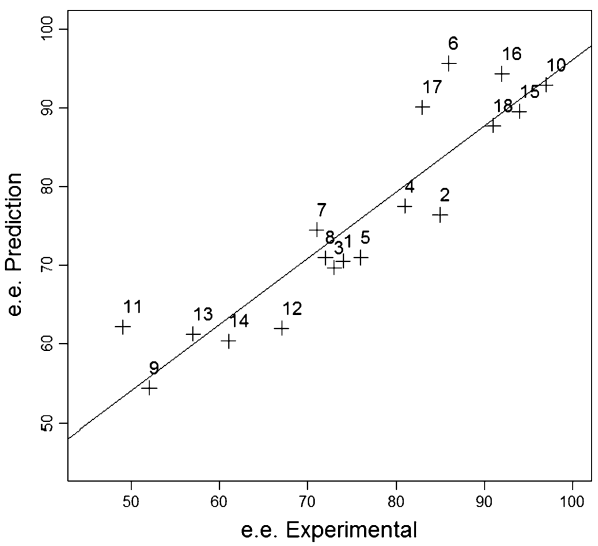


Fig. 1 QSPR model showing experimentally determined *versus* predicted ee's. Numbers correspond to entries in Table 1.

Here, we were surprised to find a more pronounced difference in enantioselectivity between 1,4-dimethyl ligands **5a** (52% ee) and **5f** (97% ee) (entries 9 and 10) than between 1,4-diester ligands **4a** (74% ee) and **4f** (86% ee) (entries 1 and 6). Clearly the introduction of the electron withdrawing 2,5-(3,5-$(CF_3)_2C_6H_3$) groups can offset the detrimental effect of the 1,4-dimethyl groups in these ligands for the transformation of acyclic substrates.

Interestingly the ee's obtained with ligands **4g,h** and **5h**, containing the more electron donating aryl groups, dropped, but only to levels similar to those obtained for the 2,5-phenyl ligands **4a** and **5a** respectively. For Hayashi's 1,4-unsubstituted diene **9a** (94% ee)[4b] a small reduction in ee occurred when introducing the electron withdrawing 4-methoxycarbonyl group in ligand **9i** (92% ee), where we would have expected an improved ee, and a 11% reduction in ee (below the parent **9a**) was observed for ligand **9h** (83% ee) containing the electron donating aryl groups.

Other changes at the 1,4-positions, whilst keeping the 2,5-phenyl groups constant, also resulted in differences in enantioselectivity for the acyclic substrate but not the cyclic substrate. For example for 2-cyclohexenone, the 1,4-diester ligand **4a** and 1,4-dimethoxymethyl ligand **7a** gave very similar ee's of 88–89%,[11] whereas for the acyclic substrate **1**, ligand **4a** gave 74% ee and ligand **7a** gave 57% ee. Of the three in the subgroup **6a**, **7a** and **8a**, the hydroxymethyl substituent in ligand **6a** gave the best enantioselectivity and all three were better than the 1,4-methyl substituted ligand **5a**. Carreira's ligand **10** was also tested and gave 91% ee. A direct comparison here is difficult since the 2- and 5-positions are not aryl.

Interest has grown recently in the development of predictive computational tools for asymmetric reactions[12] that do not require *a priori* knowledge of the reaction mechanism and can be used for high throughput screening of ligands. A QSPR model (Fig. 1) was developed to relate the experimental ee values with calculated properties of the 18 ligands shown in Table 1. Over 800 molecular properties (descriptors) were calculated[13,14] that were based entirely on the structure of the ligands (see ESI† for further details). Due to the uncertainty of the precise catalytic conformation of the ligands in the selectivity-determining step, the descriptors calculated were all independent of conformation. In our approach, only the ground state structure of the ligand is needed, with no requirement for inclusion of the metal or information about the transition state. This makes the calculations quick and considerably less demanding on computational resources than for *ab initio* or DFT calculations.

The multiple linear regression QSPR model was developed using a genetic function algorithm[15] with adjusted r^2 as the objective function. The genetic algorithm was used in order to search for a very good three-descriptor model out of the very large (>50 000) number of possible three-descriptor models that may be developed from all the calculated properties. We only sought models that contained a maximum of three descriptors in order to minimize chances of an erroneous good correlation.[16] A QSPR model was found that displayed extremely good statistical parameters. For example, for the training set the r^2_{adj} value of 0.80 indicates that 80% of the variance is explained by this model and the F value of 24.4 indicates a high level of

significance for the model.[17] The model was validated[17] and displayed excellent statistical parameters for leave-1-out cross validation (0.70), leave-10-out cross validation r^2 (0.70) and bootstrap r^2 (0.76). The same model was found consistently, running the genetic algorithm procedure many times. This convergence gives us confidence that this is an extremely good model with respect to this data set. As can be seen graphically in Fig. 1, this model is statistically robust. Other statistical measures and graphs corroborate this (supporting information).

Examination of the QSPR model revealed that the descriptors were MATS6i (a 2D auto-correlation descriptor—Moran autocorrelation of lag 6 weighted by ionisation potential[14]), MATS3m (a 2D auto-correlation descriptor—Moran autocorrelation of lag 3 weighted by mass[14]) and nCt (number of total tertiary C(sp3)[14]). nCt is related to the steric properties of the ligand whereas MATS6i and MATS3m are related to the electronic properties of the ligands. However, precise interpretation of the descriptors for "manual" ligand design is challenging. Thus the design of future ligands can be performed *in silico*. Virtual screening using this QSPR of an *in silico* generated library of candidate ligands should identify potential ligands that will afford high ee values.

In the asymmetric rhodium-catalysed conjugate addition to acyclic enones there is a general trend in that more electron deficient diene ligands give better enantioselectivity and that electronic effects are more important than steric effects. This is corroborated by recent DFT calculations for cyclohexanone as the substrate.[9,10] However, for the acyclic substrates in particular the variation in ee is difficult to rationalize. We have developed a robust QSPR model that will be employed in the future for *in silico* ligand design of chiral diene lignds.

Notes and references

1 For selected reviews and highlights, see: (*a*) F. Glorius, *Angew. Chem., Int. Ed.*, 2004, **43**, 3364; (*b*) C. Defieber, H. Grutzmacher and E. M. Carreira, *Angew. Chem., Int. Ed.*, 2008, **47**, 4482; (*c*) R. Shintani and T. Hayashi, *Aldrichimica Acta*, 2009, **42**, 31.

2 (*a*) W. C. Boyd, M. R. Crimmin, L. E. Rosebrugh, J. M. Schomaker, R. G. Bergman and F. D. Toste, *J. Am. Chem. Soc.*, 2010, **132**, 16365; (*b*) X. Hu, M. Zhuang, Z. Cao and H. Du, *Org. Lett.*, 2009, **11**, 4744; (*c*) X. Hu, Z. Cao, Z. Liu, Y. Wang and H. Du, *Adv. Synth. Catal.*, 2010, **352**, 651; (*d*) Z. Cao and H. Du, *Org. Lett.*, 2010, **12**, 2602; (*e*) Q. Li, Z. Dong and Z.-X. Yu, *Org. Lett.*, 2011, **13**, 1122; (*f*) B. M. Trost, A. C. Burns and T. Tautz, *Org. Lett.*, 2011, **13**, 4566; (*g*) C.-G. Feng, Z.-Q. Wang, C. Shao, M.-H. Xu and G.-Q. Lin, *Org. Lett.*, 2008, **10**, 4101; (*h*) C.-G. Feng, Z.-Q. Wang, P. Tian, M.-H. Xu and G.-Q. Lin, *Chem.–Asian J.*, 2008, **3**, 1511; (*i*) C. Shao, H.-J. Yu, N.-Y. Wu, C.-Q. Feng and G.-Q. Lin, *Org. Lett.*, 2010, **12**, 3820; (*j*) Y. Luo and A. J. Carnell, *J. Org. Chem.*, 2010, **75**, 2057; (*k*) G. Pattison, G. Piraux and H. W. Lam, *J. Am. Chem. Soc.*, 2010, **132**, 14373; (*l*) A. Saxena and H. W. Lam, *Chem. Sci.*, 2011, **2**, 2326–2331.

3 Y. Luo and A. J. Carnell, *Angew. Chem. Int. Ed.*, 2010, **49**, 2750.

4 (*a*) R. Shintani, K. Ueyama, I. Yamada and T. Hayashi, *Org. Lett.*, 2004, **6**, 3425; (*b*) Y. Otomaru, K. Okamoto, R. Shintani and T. Hayashi, *J. Org. Chem.*, 2005, **70**, 2503; (*c*) T. Gendrineau, O. Chuzel, H. Eijsberg, J.-P. Genet and S. Darses, *Angew. Chem., Int. Ed.*, 2008, **47**, 7669; (*d*) Z.-Q. Wang, C.-G. Feng, M.-H. Xu and G.-Q. Lin, *J. Am. Chem. Soc.*, 2007, **129**, 5336; (*e*) K. Okamoto, T. Hayashi and V. H. Rawal, *Chem. Commun.*, 2009, 4815.

5 For examples of sulfino/alkene hybrid ligands, see: (*a*) Y. Wang, X. Feng and H. Du, *Org. Lett.*, 2011, **13**, 4954; (*b*) X. Feng, Y. Wang, B. Wei, J. Yang and H. Du, *Org. Lett.*, 2011, **13**, 3300; (*c*) T. Thaler, L. N. Guo, A. K. Steib, M. Raducan, K. Karaghiosoff, P. Mayer and P. Knochel, *Org. Lett.*, 2011, **13**, 3182; (*d*) S.-S. Jin, H. Wang and M.-H. Xu, *Chem. Commun.*, 2011, **47**, 7230; (*e*) W.-Y. Qi, T.-S. Zhu and M.-H. Xu, *Org. Lett.*, 2011, **13**, 3410; (*f*) G. Chen, J. Gui, L. Li and J. Liao, *Angew. Chem., Int. Ed.*, 2011, **50**, 7681.

6 (*a*) T. Hayashi, M. Takahashi, Y. Takaya and M. Ogasawara, *J. Am. Chem. Soc.*, 2002, **124**, 5052; (*b*) A. Kina, H. Iwaamura and T. Hayashi, *J. Am. Chem. Soc.*, 2006, **128**, 3904; (*c*) A. Kina, Y. Yasuhara, T. Nishimura, H. Iwamura and T. Hayashi, *Chem.–Asian J.*, 2006, **1**, 707.

7 For DFT analysis on Rh-diphosphine-catalyzed conjugate addition see: (*a*) T. Itoh, T. Mase, T. Nishikata, T. Iyama, H. Tachikawa, Y. Kobayashi, Y. Yamamotod and N. Miyaurad, *Tetrahedron*, 2006, **62**, 9610; (*b*) T. Korenaga, K. Osaki, R. Maenishi and T. Sakai, *Org. Lett.*, 2009, **11**, 2325.

8 For DFT analysis on Pd-diphosphine-catalyzed conjugate addition see: (*a*) T. Nishikata, Y. Yamamoto, I. D. Gridnev and N. Miyaura, *Organometallics*, 2005, **24**, 5025; (*b*) Y. Lan and K. N. Houk, *J. Org. Chem.*, 2011, **76**, 4905–4909.

9 E. A. B. Kantchev, *Chem. Commun.*, 2011, **47**, 10969.

10 S. Gosiewska, J. A. Raskatov, R. Shintani, T. Hayashi and J. M. Brown, *Chem.–Eur. J.*, 2012, **18**, 80.

11 Y. Luo and A. J. Carnell, unpublished results.

12 (*a*) N. Weill, C. R. Corbeil, J. W. De Schutter and N. Moitessier, *J. Comput. Chem.*, 2011, **32**, 2878–2889; (*b*) S. E. Denmark, N. D. Gould and L. M. Wolf, *J. Org. Chem.*, 2011, **76**, 4337; (*c*) J. C. Ianni, V. Annamalai, P.-W. Phuan, M. Panda and M. C. Kozlowski, *Angew. Chem.*, 2006, **118**, 5628.

13 Talete srl, DRAGON (Software for Molecular Descriptor Calculation) Version 6.0 - 2010 - http://www.talete.mi.it/.

14 R. Todeschini and V. Consonni, *Molecular Descriptors*, Wiley-VCH, 2009.

15 http://www.phakiso.com/.

16 J. G. Topliss and R. P. Edwards, *J. Med. Chem.*, 1979, **22**, 1238.

17 A. Tropsha, P. Gramatica and V. K. Gombar, *QSAR Comb. Sci.*, 2003, **22**, 69.