ChemComm

Cite this: *Chem. Commun.*, 2011, **47**, 3739–3741

www.rsc.org/chemcomm

COMMUNICATION

Highly efficient desymmetrisation of a tricarbonylchromium 1,4-dibromonaphthalene complex by asymmetric Suzuki–Miyaura coupling†‡

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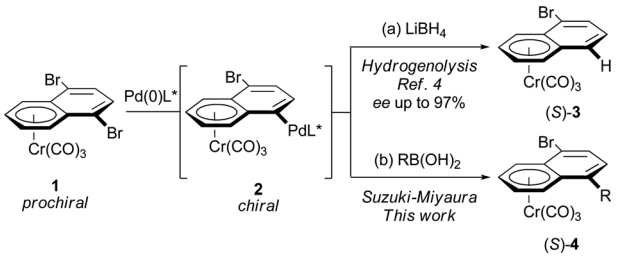
Received 18th January 2011, Accepted 10th February 2011
DOI: 10.1039/c1cc10347d

Access to planar chiral complexes has been sought by catalytic desymmetrisation of a prochiral complex *via* asymmetric Suzuki–Miyaura cross-coupling. High selectivities of up to 98% *ee* were achieved using a bulky chiral palladium catalyst.

Optically pure arene tricarbonylchromium complexes have found wide applications in asymmetric synthesis, natural product synthesis and as chiral ligands in asymmetric catalysis.[1] Most of the methods for their preparation involve the resolution of racemic mixtures or stereoselective transformations. The inherent limitation of these methodologies is the use of a stoichiometric amount of chiral reagents or auxiliaries. Asymmetric catalysis would provide a powerful alternative to circumvent these issues, but surprisingly few examples of catalytic asymmetric induction of planar chirality have been reported.[2] An attractive possibility is the desymmetrisation of prochiral complexes by a chiral catalyst that discriminates between two enantiotopic groups. This strategy was first investigated by Uemura and Hayashi,[3a–c] and subsequently by Schmalz,[3d,e] using Pd-catalysed asymmetric cross-coupling reactions. However, moderate enantioselectivities and yields were achieved. More recently, Uemura *et al.* successfully developed an asymmetric gold(I)-catalysed process for the synthesis of highly enantioenriched planar chiral isochromene chromium complexes.[2e]

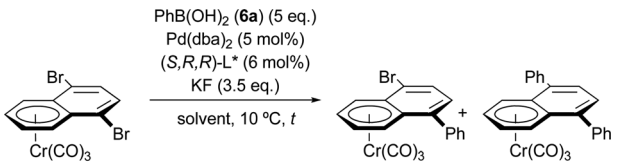
Based on the efficient Pd-catalysed enantioselective hydrogenolysis of [Cr(CO)$_3$(5,8-dibromonaphthalene)] (**1**) developed in our laboratory (Scheme 1, path (a)),[4] the challenging desymmetrisation *via* asymmetric C–C bond formation was investigated with the objective of accessing a larger array of planar chiral complexes than those obtainable by asymmetric hydrogenolysis. Similar levels of asymmetric induction may be expected considering that oxidative addition of the Pd(0) catalyst to **1** would generate the common chiral palladium intermediate **2**.[5] This pivotal precursor could then be advanced through various processes. We here report the realization of this endeavour by the development of an efficient enantioselective desymmetrisation of [Cr(CO)$_3$(5,8-dibromonaphthalene)] (**1**) using a Suzuki–Miyaura cross-coupling reaction (Scheme 1, path (b)).



Scheme 1 Palladium-catalysed enantioselective desymmetrisation as a route to enantioenriched planar chiral complexes.

We started this project by examining the coupling of complex **1** and PhB(OH)$_2$ **6a** in toluene using KF as a base (Table 1). These reaction conditions were based on those previously employed in the efficient Suzuki–Miyaura coupling of [Cr(5-bromonaphthalene)(CO)$_3$] ((*S*)-**3**).[6,7] Preliminary experiments revealed that the bulky phosphoramidite ligand L* (Fig. 1), that was successfully used in the enantioselective hydrogenolysis reaction,[4] was also well suited for this transformation. The axial chirality as well as the central chirality on the amine part

Table 1 Optimisation of the asymmetric Suzuki–Miyaura coupling of **1** with PhB(OH)$_2$ (**6a**)



Entry	Solvent	*t*/h	**1**[a] (%)	**4a**[a] (%)	**5a**[a] (%)	*ee* **4a**[b] (%)
1	Toluene	7	12	66	22	91
2	Tol/H_2O[c]	4	87	12	1	91
3	Toluene[d]	4	5	62	33	93
4[e]	Toluene[d]	20	13	66	21	90
5[f]	Toluene[d]	18	5	66	29	98

[a] Determined by ^{1}H NMR. [b] Determined by chiral HPLC. [c] 9 : 1 mixture. [d] Reagent grade toluene. [e] 2 mol% of PdL*. [f] Reaction carried out at 0 °C.

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† This article is part of a ChemComm web-based themed issue on new advances in catalytic C–C bond formation *via* late transition metals.

‡ Electronic supplementary information (ESI) available: Experimental procedures and analytical data for the reported compounds. CCDC 806187. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c1cc10347d

(*S,R,R*)-L*:

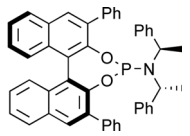


Fig. 1 Chiral phosphoramidite ligand used in this project.

and the steric bulk in the 3,3′-positions were all essential elements to achieve high levels of asymmetric induction.

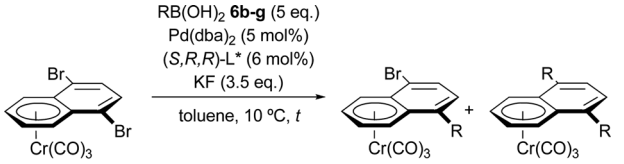
The reaction in toluene at 10 °C resulted in high conversion of **1** after 7 h and delivered 66% of the coupled product (*S*)-**4a** in 91% *ee*, along with 22% of the bisphenylated complex (entry 1).[8,9] Several other solvents (*e.g.*, DME, CH_2Cl_2, trifluorotoluene) were examined but none of them outperformed the results shown in entry 1. The use of water as a co-solvent was then envisaged to aid in the solubilisation of the inorganic base and therefore enhance the reaction rate. It was found, however, that this significantly lowered the rate of reaction (entry 2). In sharp contrast, the use of commercial reagent grade (non-dried) toluene allowed high conversion in only 4 h (entry 3). Such water traces in toluene provide a good compromise between solubilising KF in the medium and avoiding KF to remain exclusively in the aqueous phase,[10] which would be detrimental to the reaction.[11] Lowering the catalyst loading to 2 mol% gave rise to a slightly less efficient process and required longer reaction time (entry 4). Finally, the reaction carried out at 0 °C afforded (*S*)-**4a** in similar yield (66%) and greatly enhanced enantioselectivity of 98% after 18 h (entry 5). Further decrease of the reaction temperature did not improve this result (not shown).

Control experiments involving longer reaction times indicated an increase in the enantiomeric purity of **4a** during the course of the reaction. A similar observation was made for the parent hydrogenolysis reaction and thorough investigation had revealed the presence of an *in situ* kinetic resolution.[4b,12] Similarly, monitoring experiments were conducted by means of ^{1}H NMR analysis and chiral HPLC for the asymmetric Suzuki–Miyaura coupling (see ESI‡). These experimental data clearly showed that the minor enantiomer (*R*)-**4a** is converted faster into **5a** resulting in enrichment in (*S*)-**4a**, thereby supporting the presence of substantial kinetic resolution in this process as well.

The effect of the tricarbonylchromium fragment was next studied. A competition experiment between [$Cr(CO)_3$(5,8-dibromonaphthalene)] (**1**) and free 1,4-dibromonaphthalene showed that their respective relative reactivities were about 8 : 1, indicating significant rate enhancement by $Cr(CO)_3$ complexation.[13]

With optimised conditions established, the generality of the process was explored with a range of boronic acids (Table 2). The temperature was adjusted to 10 °C to avoid long reaction times with the sensitive chromium complexes. Electron-rich aromatic boronic acids, such as *p*-$MePhB(OH)_2$ and *p*-$MeOPhB(OH)_2$, performed well, affording the coupled products **4b,c** in 92 and 93% *ee*, respectively (entries 1 and 2). However, their electron-deficient counterpart displayed reduced reactivity although high enantioselectivity was maintained (entry 3). (*E*)- and (*Z*)-Vinylboronic acids were also tolerated, delivering compounds **4e,f** in satisfactory yields and with enantioselectivities of 91 and 98%, respectively (entries 4 and 5). Finally, the introduction of an alkyl unit was evaluated. Butylboronic acid was efficiently coupled to give **4g** in good yield and 92% *ee* (entry 6).

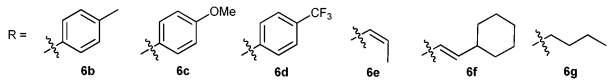
Table 2 Asymmetric Suzuki–Miyaura coupling of **1** with representative boronic acids



1 (*S*)-**4b-g** **5b-g**

Entry	$RB(OH)_2$	*t*/h	**1**[a] (%)	**4**[a] (%)	**5**[a] (%)	*ee* **4**[b] (%)
1	**6b**	10	5	63	32	92
2	**6c**	7	1	67	33	93
3	**6d**	23	6	55	39	95
4	**6e**	10	1	65	34	91
5	**6f**	17	9	62	29	98
6	**6g**	10	9	72	19	92

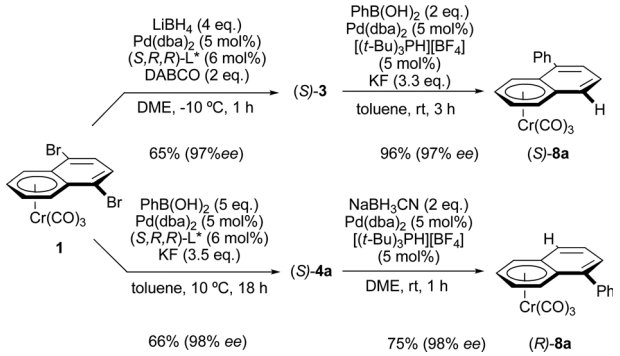
[a] Determined by ^{1}H NMR. [b] Determined by chiral HPLC.



Thus the asymmetric Suzuki–Miyaura coupling involving **1** appears to have a relatively wide scope and proceeds under mild reaction conditions since no decomplexation products were detected. Moreover, the relatively close *ee* values obtained in both hydrogenolysis and Suzuki–Miyaura based desymmetrisation processes are consistent with our assumption that the oxidative addition is the enantiodetermining step.

To gain more insight into the structure of the catalyst, the cationic [Pd(η^3-allyl)(*R,S,S*)-L*][SbF_6] (**7**) complex was prepared and fully characterised by NMR spectroscopy and X-ray diffraction. The ^{31}P NMR spectrum exhibited two singlets at δ 143.1 and 145 ppm in a very nearly 1 : 1 ratio, corresponding to two diastereoisomeric species.[14] Fig. 2 depicts the (*R,S,S,R*$_{Pd}$)-**7** diastereoisomer obtained upon crystallisation from CH_2Cl_2–cyclohexane.[15] The palladium center features a slightly distorted square planar geometry. Identification of a weak secondary η^2-interaction between the palladium and one of the benzyl substituents is in line with the work of Mezzetti and co-workers[16] and indicates that the phosphoramidite used in this study can function as a bidentate ligand. Evaluation of the buried volume of the phosphoramidite ligand L* revealed an exceptional high steric

Fig. 2 Molecular structure of [Pd(η^3-allyl)(1,2-η-Ph-L*-κP)-L*)]$^+$ ((*R,S,S,R*$_{Pd}$)-**7**), determined by X-ray crystallography, showing an 1,2-η-phenyl interaction.



Scheme 2 Access to both enantiomers of **8a** by using the same chiral ligand (*S,R,R*)-L*.

congestion in the first coordination sphere of the palladium center ($\%V_{Bur}$ = 55.4%).[17]

Finally, the potential complementarity of our two desymmetrising processes was illustrated with the synthesis of both enantiomers of [Cr((5-phenyl)naphthalene)$(CO)_3$] (**8a**) using the phosphoramidite ligand with identical absolute configuration (Scheme 2). Indeed, performing the asymmetric hydrogenolysis followed by a Suzuki–Miyaura cross-coupling reaction[6] using Fu's catalytic system[18] delivered enantiomer (*S*)-**8a** in 97% *ee* and 62% overall yield. Inverting the order of the sequence, namely the asymmetric Suzuki–Miyaura coupling followed by hydrogenolysis, afforded the opposite enantiomer (*R*)-**8a** with similar enantioselectivity. In both cases, the transformations were performed without erosion of enantioselectivity.

In conclusion, we have demonstrated that prochiral complex **1** could be successfully desymmetrised *via* asymmetric C–C bond formation. The enantioselective Suzuki–Miyaura coupling proved to be general, affording good yields and excellent enantioselectivities with an array of aryl-, vinyl- and even alkylboronic acids. These results are in close agreement with our assumption that the oxidative addition determines the stereochemical outcome of the reaction. Combining the two desymmetrisation processes would allow the access to a wide variety of planar chiral compounds with complete stereocontrol. Further studies will focus on the isolation and identification of a relevant reactive intermediate (*e.g.*, oxidative addition product) in order to get more insight into the origin of the asymmetric induction.

We thank the Swiss National Science Foundation and the University of Geneva for financial support. We are particularly grateful to P. Romanens for technical assistance and A. Pinto for NMR measurements.

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8 The absolute configuration of **4a**, and by analogy **4b–g**, was assigned based on X-ray diffraction analysis of compound **3** obtained by asymmetric hydrogenolysis, and corroborated by the further transformation of both compounds into **8a**.

9 Among all the inorganic bases surveyed,K_3PO_4 and Cs_2CO_3 showed similar efficiency in terms of reactivity and enantioselectivity. Nevertheless, KF was kept as the base of choice considering its lower price (3.65 USD mol^{-1}).

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