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Catalytic enantioselective synthesis of 2-aryl-chromenes†

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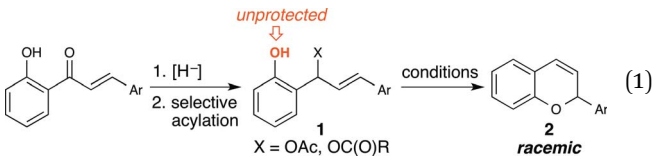
An enantioselective Pd-catalyzed 6-*endo*-trig reaction for the synthesis of 2-aryl-chromenes has been developed. A systematic optimization of a TADDOL-derived ligand set resulted in the identification of a novel monodentate phosphoramidite–palladium catalyst that accesses 2-aryl-2*H*-chromenes with high yield and enantioselectivity under mild conditions. The products obtained from this method can be transformed into biologically active compounds through functionalization of the chromene alkene.

Introduction

Chromenes constitute a privileged class of structural motifs present in a myriad of natural products and medicinally important agents.[1] Given the prevalence of this structural unit, there has been considerable interest in developing methods for the generation of the chromene skeleton. While procedures to access racemic 2-aryl-2*H*-chromenes are readily available,[2] the difficulty in generating enantioselective variants is underscored by the scarcity of documented strategies to produce these bioactive structures. The construction of enantioenriched 2-aryl-2*H*-chromenes has been recently reported by You through a Ru-catalyzed ring-closing metathesis reaction of chiral allyl ethers[3] and also by Schaus *via* the chiral Brønsted acid (CBA)/Lewis acid-catalyzed addition of aryl boronates to *in situ* formed pyrylium ions.[4] In addition, Rueping has recently reported a CBA-catalyzed closure of allylic cations, but this innovative approach requires substitution at C4.[5] Based on our platform developing new approaches to construct pyran and related motifs,[6] we began investigating substrate/catalyst activation combinations to access chromenes *via* an asymmetric catalytic process. After extensive exploration with substrates such as **1** (not shown), easily accessed from chalcone precursors, the use of either organocatalysis or transition metal catalysis led to an invariable observation: compounds with unprotected *ortho*-substituted phenols were typically unstable and often underwent uncatalyzed cyclizations to racemic chromenes rapidly (eqn (1)).



(1)

With this crucial data in hand and the background reaction a major hurdle, our reaction design criteria became clear: (a) promote phenol formation during the course of the reaction, (b) avoid any background reactions by activating an allylic system through a chiral metal complex or organocatalytic mechanism, and (c) promote a 6-*endo*-trig type closure of the phenol/phenoxide with control of the absolute stereochemistry. Based on this logic, we envisaged that 2-aryl-2*H*-chromenes could be constructed through a 6-*endo*-trig Pd-catalyzed asymmetric allylic substitution (Fig. 1).[7] While Pd-catalyzed allylic alkylation is a prominent strategy for C–C and C–heteroatom bond formation,[8] to the best of our knowledge there are no reports of a general asymmetric 6-*endo*-trig variant.[9]

Results and discussion

We began our investigation by combining bis-acetate **1a** with potassium carbonate, $Pd_2(dba)_3$ and a variety of phosphoramidite ligands. Initial survey of bidentate ligands, such as PHOX or Trost ligand, afforded low reaction conversion and enantioselection. Although monodentate phosphoramidites are efficient chiral ligands in promoting various Pd-catalyzed reactions,[10] their application in asymmetric allylic substitutions remains underdeveloped. Motivated by a recent report from van Leeuwen and coworkers involving the use of BINOL- and TADDOL-derived phosphoramidites for Pd-catalyzed intermolecular allylic alkylations,[11] our initial ligand screen included BINOL-, SIPHOS-, and TADDOL-derived phosphoramidites.[12] Our preliminary experiments with BINOL-derived ligand **L1a** provided chromene **2a** in quantitative yield with an encouraging 69 : 31 enantiomeric ratio

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† Electronic supplementary information (ESI) available: Experimental procedures and spectroscopic data for all new compounds. CCDC 984483 and 969569. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c4sc00423j

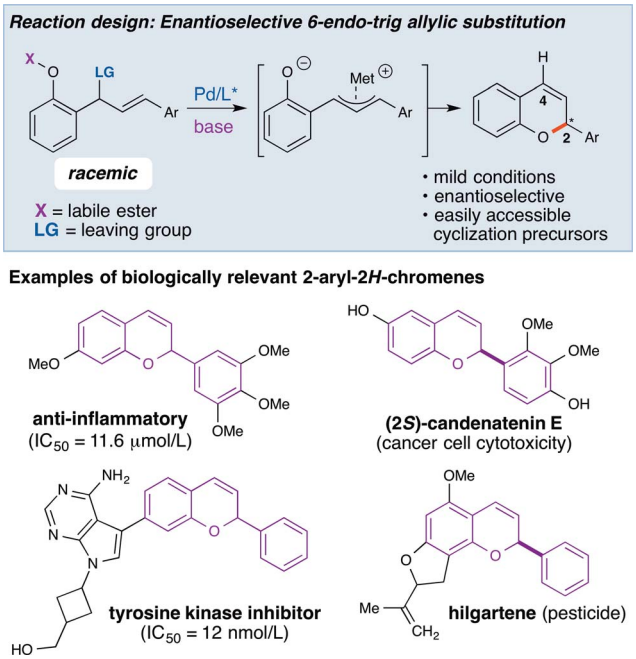


Fig. 1 Reaction design for 2*H*-chromenes.

(Table 1, entry 1). Unfortunately, modification of the amine constituent to piperidine, dimethylamine, 1-phenylethylamine (results not shown) or bis[(*S*)-1-phenethyl]amine (entry 2), was detrimental to both the conversion and enantioselectivity. The modification of the ligand backbone to SIPHOS-derived ligand (R_a,*R*,*R*)-**L2** and TADDOL-derived ligand **L3a** resulted in significantly improved levels of enantioselectivity (entries 3 and 5, respectively). Interestingly, the diastereomer (S_a,*R*,*R*)-**L2** (entry 4) afforded racemic chromene product, suggesting a mismatch of stereogenic elements.

Due to the shortened reaction time with ligand **L3a** compared to **L2** and the opportunity to rapidly evaluate a wide range of TADDOL-derived ligands, we focused our efforts on the optimization of this ligand backbone. We began by evaluating a variety of *N*-substituents, including achiral and sterically less demanding amine moieties (entry 6–8). In comparison to ligand **L3a**, other acyclic amines such as dimethylamine (entry 6) and diisopropyl amine (entry 7) resulted in decreased enantioselectivity, while replacement with the more rigid piperidinyl substituent afforded chromene **2a** with improved selectivity (82 : 18 er, entry 8).[12d] To understand the effects of ligand rigidity on engendering enantioselection, the isopropylidene acetal of **L3** was substituted with an acyclic dimethyl ether motif. With the less rigid **L4** as the ligand, chromene **2a** was furnished with low enantioselectivity (entry 9).

The last point of variation of the TADDOL-derived ligands lies in the substitution about the arene rings. The examination of various aryl-substituted TADDOL ligands (entry 10–12) revealed that enantioselectivity can be enhanced through the placement and positioning of methyl groups on the aryl ring, culminating in a 93 : 7 er attained for ligand **L3g** (entry 12). A full investigation of this distal effect and the balance between electronic and steric parameters on this ligand is currently ongoing. We then revisited the effects of the nitrogen substituent. Interestingly, the replacement of the piperidine with a pyrrolidine resulted in a significant decrease in enantioselectivity (entry 13), while incorporation of a 7-membered azepane maintained the previously observed 93 : 7 er (entry 14). Efforts to increase enantioselectivity by utilizing acyclic amines were ineffective (entry 15). Finally, the incorporation of ethyl groups at the 3- and 5-position of the aryl ring was explored. We were pleased to find that with this ligand (**L3k**), chromene **2a** was obtained in 71% isolated yield with 95 : 5 er (entry 16).

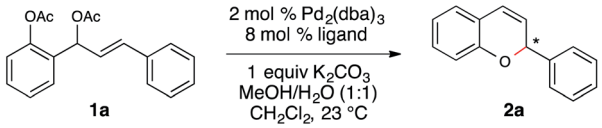
With selective conditions developed, several bis-acetate substrates were evaluated (Table 2). The high levels of enantio selectivity observed for **2a** were maintained with extended aromatic substrates (**2b** and **2c**). Electron-donating groups on the styrenyl component were also well tolerated, with methyl substitution in the *ortho*- or *para*-positions (**2d** and **2e**, respectively) affording the chromene products in good yield and excellent enantioselectivity. The electron-rich 3-methoxy substituted cyclization precursor also performed well in this reaction, generating chromene **2f** (78%, 94 : 6 er).

The incorporation of electron-withdrawing (**2g–2l**) substituents around the aromatic ring was also accommodated. Furthermore, we found that the electronegative fluorine substituent can occupy various positions while maintaining high er. The erosion of enantioselectivity was observed with substrates possessing a trifluoromethyl, dichloro, or the strongly electronegative nitro group (**2j–2l**), but a fluorine substituent was tolerated at various positions (**2m** and **2n**). The electron-donating methoxy group was also accommodated, albeit with a slight decrease in enantioselectivity (**2o**). Additionally, the preparation of chromene **2p** indicates that this system tolerates moderate substitution adjacent to the phenoxide.

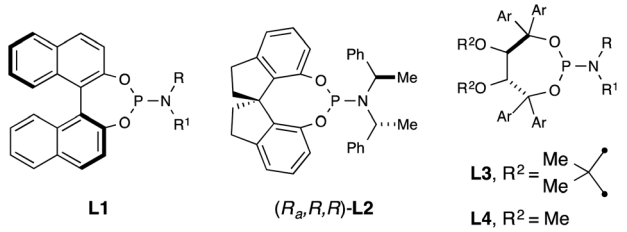
The complete conversion of racemic substrates **1** to the enantioenriched chromenes indicates that a dynamic kinetic asymmetric transformation (DYKAT) might be operative.[13] Since both enantiomers of the starting material must go through a common intermediate, and the *unsymmetrical* 1,3-disubstituted allyl substrate precludes racemization through a palladium π–σ–π allyl rearrangement, the generation of an achiral *ortho*-quinone methide intermediate (**4**) is proposed to account for the high levels of enantioselectivity observed for the chromene products (Scheme 1).

Our current understanding of the reaction starts with the subjection of either enantiomer of **1a** to potassium carbonate and methanol, which rapidly produces the nucleophilic phenoxide *in situ* (±**3**, Path A). This deacylation promotes ejection of the secondary acetate to form the achiral *trans*-*o*-quinone methide (*o*-QM, **4a**).[14] A subsequent coordination and addition of the chiral palladium complex generates the π allyl intermediate (**5**) which undergoes intramolecular attack of the proximal phenoxide after bond rotation to achieve the proper conformation (**6**). For this pathway, the rate of *o*-QM formation is faster than addition of the palladium–ligand complex to ±**3** (or ±**1**). If this is not the case, then an alternative potential pathway could be operative (Path B). This process involves the generation of diasteromeric π allyl

Table 1 Optimization of reaction conditions

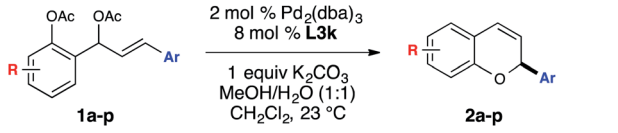


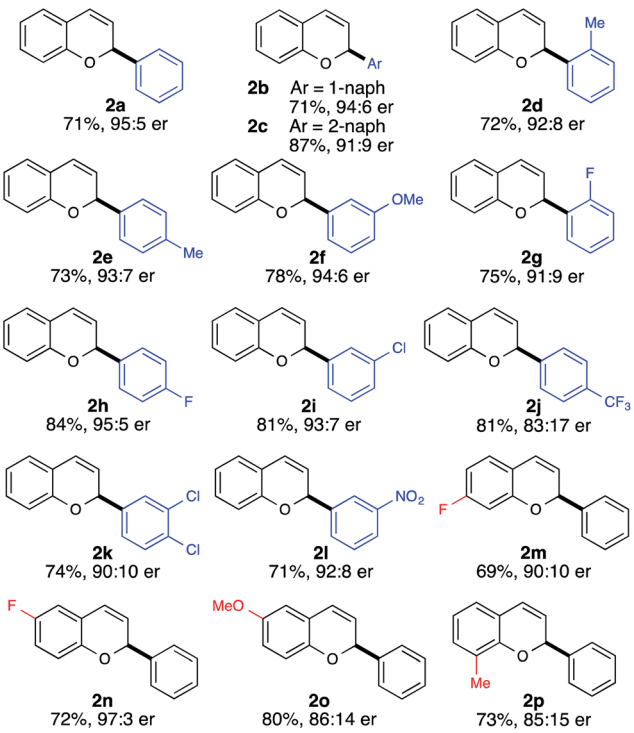
Entry	Ligand	Ar	NRR[1]	Time[a]	er[b]
1	**L1a**	—	$N(i\text{-}Pr)_2$	2 h	69 : 31
2	**L1b**	—	$N((S)\text{-}CH(Me)(Ph))_2$	21 h	57 : 43
3	(R_a,*R*,*R*)-**L2**	—	—	1 day	79 : 21
4	(S_a,*R*,*R*)-**L2**	—	—	1 day	50 : 50
5	**L3a**	Ph	$N((S)\text{-}CH(Me)(Ph))_2$	12 h	74 : 26
6	**L3b**	Ph	$N(Me)_2$	2 h	60 : 40
7	**L3c**	Ph	$N(i\text{-}Pr)_2$	4 h	65 : 35
8	**L3d**	Ph	$N(CH_2)_5$	2 h	82 : 18
9	**L4**	Ph	$N(CH_2)_5$	3 h	53 : 47
10	**L3e**	2-Me-C_6H_4	$N(CH_2)_5$	12 h	85 : 15
11	**L3f**	3-Me-C_6H_4	$N(CH_2)_5$	19 h	90 : 10
12	**L3g**	3,5-Me-C_6H_3	$N(CH_2)_5$	38 h	93 : 7
13	**L3h**	3,5-Me-C_6H_3	$N(CH_2)_4$	2 day	71 : 29
14	**L3i**	3,5-Me-C_6H_3	$N(CH_2)_6$	2 day	93 : 7
15	**L3j**	3,5-Me-C_6H_3	N(Me)(Cy)	19 h	93 : 7
16	**L3k**	3,5-Et-C_6H_3	$N(CH_2)_5$	19 h	95 : 5



[a] Time to reach 100% conversion as measured by ^{1}H NMR (500 MHz). Longer reactions did not provide side products. [b] Enantiomeric ratio determined by HPLC.

Table 2 Substrate scope[a]



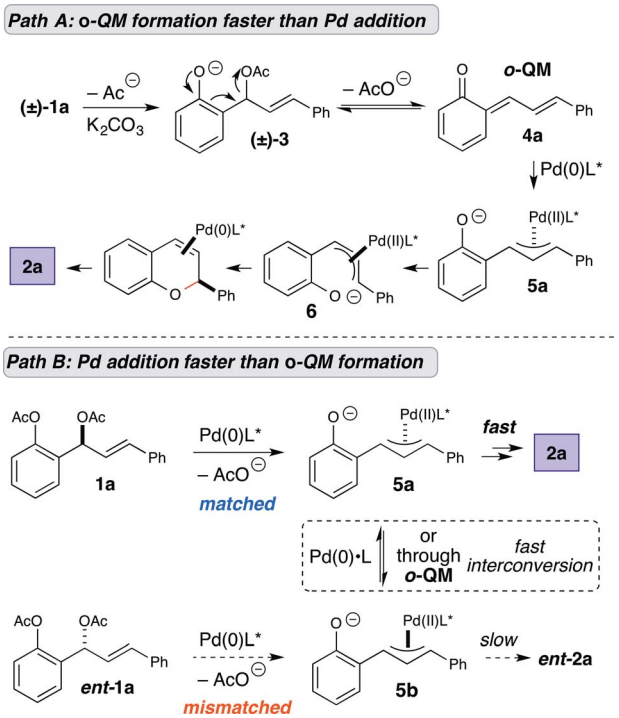


[a] See ESI for details. Yield of isolated product after chromatography. Enantiomeric ratio determined by HPLC analysis.

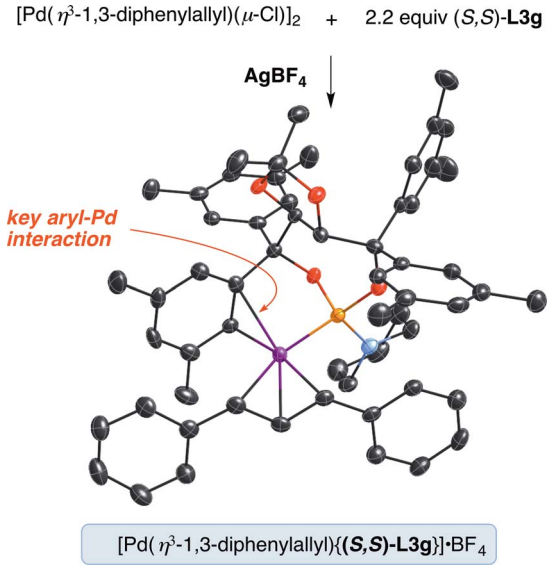
palladium complexes (**5a** or **5b**) from each enantiomer of **3**. While one of these additions would be the "matched" case, a rapid interconversion between the diasteromeric intermediates is required so the "mismatched" complex undergoes smooth conversion to the observed enantiomer (**2a**) *vs.* the undesired isomer (***ent*-2a**). Possible mechanisms for this involve generation of the achiral *o*-QM or direct addition of the palladium complex. For a related system, the possibility for racemization of the π-allylpalladium complex (such as **5b**) by an intermolecular nucleophilic attack (or *anti*-addition) of a Pd(0) has been investigated.[15] We currently favor Path A due to the lack of observed correlation between enantioselectivity and catalyst concentration, which disfavors Path B. Additionally, the use of bis-benzoylated substrates (*vs.* acetates) proceeds at the approximately the same rate with the similar levels of er and yield (see ESI† for details). More extensive investigations of this process are currently underway.

We wished to further elucidate the structure of the Pd(II)–**L3k** complex and its interaction with the bis-acetate substrate **1a**, but to date have been unable to obtain suitable crystals. However, X-ray quality crystals of the related Pd(II) complex has been solved using ligand **L3g** in conjunction with 1,3-diphenyl allyl acetate as a substrate surrogate incapable of closure (Scheme 2). The structure shows that the phosphoramidite ligand **L3g** is coordinated to the Pd(II) center through its phosphorus center and a single aryl ring.[16] This η^2-arene stabilization results in the observed 1 : 1 phosphoramidite–Pd(II) complex and supports mono-coordination of a bulky ligand to the palladium.[17]

To highlight the potential of this new approach, we pursued the synthesis of catechin **8**, which has demonstrated anti-staphylococcal activity due to their ability to reverse methicillin resistance in strains of drug resistant *S. aureus*.[18] Interestingly, this catechin analog has increased activity compared to the parent (−)-epicatechin gallate, which bears additional hydroxyl groups on the catechin core (**7**). The regioselective hydroboration of **2a** delivered chromanol **7** with 9 : 1 dr favoring the desired *anti* relationship. The esterification of chromanol **7** with tri-*O*Bn gallic acid chloride followed by hydrogenolysis afforded **8** in 65% yield over the two steps. In a second vignette, the synthesis of hydroxyflavanone **10** was accomplished. The racemate of this compound exhibited promising levels of inhibition of *M. tuberculosis H37Rv*.[19] The application of our methodology allows access to enantioenriched **10** and could facilitate

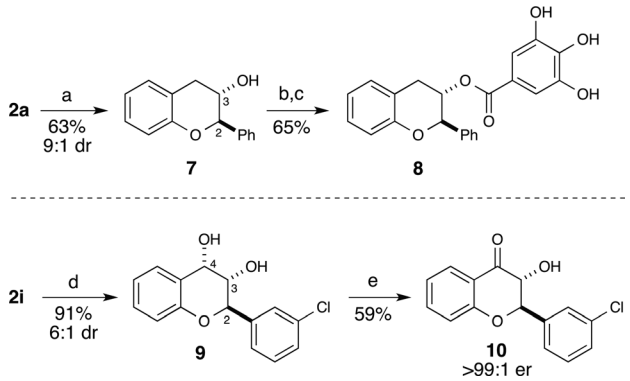


Scheme 1 Proposed reaction pathway.



Scheme 2 Molecular structure of [Pd(η^3-1,3-diphenylallyl){(*S*,*S*)-**L3g**}] BF_4. ORTEP at 80% probability with hydrogen atoms and BF_4^- omitted for clarity.

improved structure–activity relationship (SAR) studies. A *cis*-dihydroxylation of chromene **2i** (94 : 6 er) using 3 mol% OsO_4 and NMO provided 2,3-*trans*-3,4-phenylchromandiol (5.6 : 1 dr).[20] A recrystallization of the mixture provided a single diastereomer with >99 : 1 er. The exposure of diol **9** to MnO_2 resulted in the desired benzylic oxidation, without epimerization at C-3, to furnish **10** in 59% yield (Scheme 3).



Scheme 3 Transformation to bioactive flavonoids. Reagents and conditions: (a) (i) BH_3·THF, (ii) H_2O_2, NaOH; (b) tri-*O*Bn galloyl chloride, DMAP, Et_3N, CH_2Cl_2; (c) H_2, 10% Pd/C, EtOAc; (d) 3 mol% OsO_4, 4-methylmorpholine 4-oxide, *t*-BuOH, H_2O; (e) MnO_2, CH_2Cl_2.

Conclusions

We have developed a catalytic enantioselective method for the synthesis of 2-aryl-2*H*-chromenes. A ligand structure–selectivity relationship study resulted in the development of a novel monodentate phosphoramidite system that enabled the synthesis of these privileged heterocycles with high yield and enantioselectivity. Crystallographic analysis provides mechanistic support that aryl ligand–metal interactions provide unanticipated additional rigidity in competing diasteroemeric transition states which promotes the high levels of enantioselectivity for the newly formed C–O bond. Investigations involving the use of these chiral phosphoramidite ligands for the formation of other heterocycles and detailed mechanistic studies are underway.

Acknowledgements

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Notes and references

1 For selected examples, see: (*a*) K. Mukai, K. Okabe and H. Hosose, *J. Org. Chem.*, 1989, **54**, 557–560; (*b*) S. Cheenpracha, C. Karalai, C. Ponglimanont and A. Kanjana-Opas, *J. Nat. Prod.*, 2009, **72**, 1395–1398; (*c*) C. Tahtaoui, A. Demailly, C. Guidemann, C. Joyeux and P. Schneider, *J. Org. Chem.*, 2010, **75**, 3781–3785.

2 For selected examples, see: (*a*) R. C. Larock, L. Wei and T. R. Hightower, *Synlett*, 1998, 522–524; (*b*) Q. Wang and M. G. Finn, *Org. Lett.*, 2000, **2**, 4063–4065; (*c*) G. W. Kabalka, B. Venkataiah and B. C. Das, *Synlett*, 2004, 2194–2196; (*d*) A. Aponick, B. Biannic and M. R. Jong, *Chem. Commun.*, 2010, **46**, 6849–6851; (*e*) T. J. A. Graham and A. G. Doyle, *Org. Lett.*, 2012, **14**, 1616–1619.

3 (*a*) H. He, K. Y. Ye, Q. F. Wu, L. X. Dai and S. L. You, *Adv. Synth. Catal.*, 2012, **354**, 1084–1094; (*b*) C. Hardouin, L. Burgaud, A. Valleix and E. Doris, *Tetrahedron Lett.*, 2003, **44**, 435–437.

4 P. N. Moquist, T. Kodama and S. E. Schaus, *Angew. Chem., Int. Ed.*, 2010, **49**, 7096–7100.

5 M. Rueping, U. Uria, M. Y. Lin and I. Atodiresei, *J. Am. Chem. Soc.*, 2011, **133**, 3732–3735.

6 (*a*) W. J. Morris, D. W. Custar and K. A. Scheidt, *Org. Lett.*, 2005, **7**, 1113–1116; (*b*) M. M. Biddle, M. Lin and K. A. Scheidt, *J. Am. Chem. Soc.*, 2007, **129**, 3830–3831; (*c*) D. W. Custar, T. P. Zabawa and K. A. Scheidt, *J. Am. Chem. Soc.*, 2008, **130**, 804–805; (*d*) A. E. Nibbs, A. L. Baize, R. M. Herter and K. A. Scheidt, *Org. Lett.*, 2009, **11**, 4010–4013; (*e*) R. L. Farmer, M. M. Biddle, A. E. Nibbs, X. Huang, R. C. Bergan and K. A. Scheidt, *ACS Med. Chem. Lett.*, 2010, **1**, 400–405; (*f*) J. M. Tenenbaum, W. J. Morris, D. W. Custar and K. A. Scheidt, *Angew. Chem., Int. Ed.*, 2011, **50**, 5892–5895; (*g*) J. Wang, E. A. Crane and K. A. Scheidt, *Org. Lett.*, 2011, **13**, 3086–3089.

7 For a review of 6-*exo*-trig asymmetric allylic substitutions, see: (*a*) B. M. Trost, *J. Org. Chem.*, 2004, **69**, 5813–5837; For selected examples, see: (*b*) B. M. Trost, H. C. Shen and J. P. Surivet, *Angew. Chem., Int. Ed.*, 2003, **42**, 3943–3947; (*c*) B. M. Trost, H. C. Shen, L. Dong and J. P. Surivet, *J. Am. Chem. Soc.*, 2003, **125**, 9276–9277.

8 For leading reviews, see: (*a*) C. G. Frost, J. Howarth and J. M. J. Williams, *Tetrahedron: Asymmetry*, 1992, **3**, 1089–1122; (*b*) B. M. Trost and D. L. Van Vranken, *Chem. Rev.*, 1996, **96**, 395–422; (*c*) B. M. Trost and M. L. Crawley, *Chem. Rev.*, 2003, **103**, 2921–2943; (*d*) Z. Lu and S. Ma, *Angew. Chem., Int. Ed.*, 2008, **47**, 258–297.

9 J. Agarwal, C. Commandeur, M. Malacria and S. Thorimbert, *Tetrahedron*, 2013, **69**, 9398–9405.

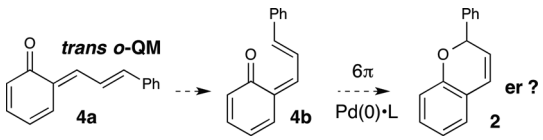
10 For a review highlighting TADDOL-derived phosphoramidites in asymmetric catalysis, see: H. W. Lam, *Synthesis*, 2011, 2011–2043.

11 M. D. K. Boele, P. C. J. Kamer, M. Lutz, A. L. Spek, J. G. de Vries, P. W. N. M. van Leeuwen and G. P. E. van Strijdonck, *Chem.–Eur. J.*, 2004, **10**, 6232–6246.

12 (*a*) A. H. M. de Vries, A. Meetsma and B. L. Feringa, *Angew. Chem., Int. Ed. Engl.*, 1996, **35**, 2374–2376; (*b*) A. Alexakis, J. Vastra, J. Burton, C. Benhaim and P. Mangeney, *Tetrahedron Lett.*, 1998, **39**, 7869–7872; (*c*) S. F. Zhu, Y. Fu, J. H. Xie, B. Liu, L. Xing and Q. L. Zhou, *Tetrahedron: Asymmetry*, 2003, **14**, 3219–3224; (*d*) H. Teller, M. Corbet, L. Mantilli, G. Gopakumar, R. Goddard, W. Thiel and A. Fürstner, *J. Am. Chem. Soc.*, 2012, **134**, 15331–15342; For a review of TADDOLs, see: (*e*) D. Seebach, A. K. Beck and A. Heckel, *Angew. Chem., Int. Ed.*, 2001, **40**, 92–138.

13 For examples of Pd-catalyzed DYKATs, see: (*a*) B. M. Trost and F. D. Toste, *J. Am. Chem. Soc.*, 1999, **121**, 3543–3544; (*b*) B. M. Trost, M. Osipov and G. Dong, *J. Am. Chem. Soc.*, 2010, **132**, 15800–15807; For examples of Pd-catalyzed stereoablative reactions, see: (*c*) T. Hamada, A. Chieffi, J. Ahman and S. L. Buchwald, *J. Am. Chem. Soc.*, 2002, **124**, 1261–1268; (*d*) J. T. Mohr, D. C. Behenna, A. M. Harned and B. M. Stoltz, *Angew. Chem., Int. Ed.*, 2005, **44**, 6924–6927.

14 For a review of *o*-QMs, see: R. W. Van de Water and T. R. R. Pettus, *Tetrahedron*, 2002, **58**, 5367–5405. It is also conceivable that the *trans-o*-QM (**4a**) could undergo conversion to the *cis* isomer (**4b**) to promote a 6π electrocyclization. However, the mode of stereoinduction for the high er observed would neccessitate a unlikely non-covalent interaction between **4b** and the Pd–ligand complex. Another possiblity for enantioselection involves the fast racemization of **3** through **4a** followed by the selective coordination and addition of palladium–ligand complex with one enantiomer of **3**.



15 K. L. Granberg and J. E. Bäckvall, *J. Am. Chem. Soc.*, 1992, **114**, 6858–6863.

16 T. E. Barder, S. D. Walker, J. R. Martinelli and S. L. Buchwald, *J. Am. Chem. Soc.*, 2005, **127**, 4685–4696.

17 The conversion and enantiomeric ratio of the chromene product, as well as reaction rate, remained unperturbed upon a reduction in ligand loading from 8 to 4 mol% (*i.e.*, 2 : 1 to 1 : 1 phsophoramidite : Pd). For selected examples of Pd-η^2-arene interaction, see: (*a*) C. H. Liu, C. S. Li and C. H. Cheng, *Organometallics*, 1994, **13**, 18–20; (*b*) M. Catellani, C. Mealli, E. Motti, P. Paoli, E. Perez-Carreno and P. S. Pregosin, *J. Am. Chem. Soc.*, 2002, **124**, 4336–4346.

18 J. C. Anderson, R. A. McCarthy, S. Paulin and P. W. Taylor, *Bioorg. Med. Chem. Lett.*, 2011, **21**, 6996–7000.

19 Y. M. Lin, Y. Zhou, M. T. Flavin, L. M. Zhou, W. Nie and F. C. Chen, *Bioorg. Med. Chem.*, 2002, **10**, 2795–2802.

20 D. Deffieux, S. Gaudrel-Grosay, A. Grelard, C. Chalumeau and S. Quideau, *Tetrahedron Lett.*, 2009, **50**, 6567–6571.