# Enantioselective desymmetrizing palladium catalyzed carbonylation reactions: the catalytic asymmetric synthesis of quaternary carbon center containing 1,3-dienes†

Simon J. Byrne,[b] Anthony J. Fletcher,[a] Paul Hebeisen[c] and Michael C. Willis*[a]

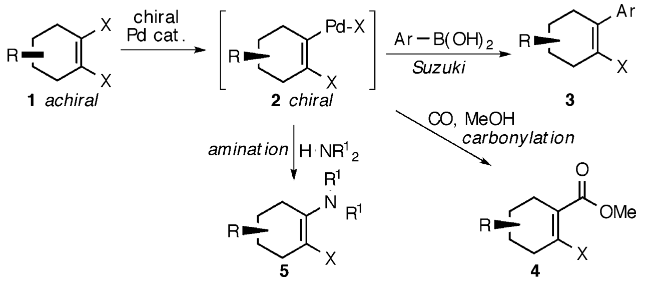
*Received 5th November 2009, Accepted 3rd December 2009*
*First published as an Advance Article on the web 21st December 2009*
**DOI: 10.1039/b923186b**

**A desymmetrization protocol has been used to develop a palladium catalyzed enantioselective carbonylation process. Achiral cyclic bis-alkenyltriflates are converted to their corresponding monoester derivatives with selectivities of up to 96% ee.**

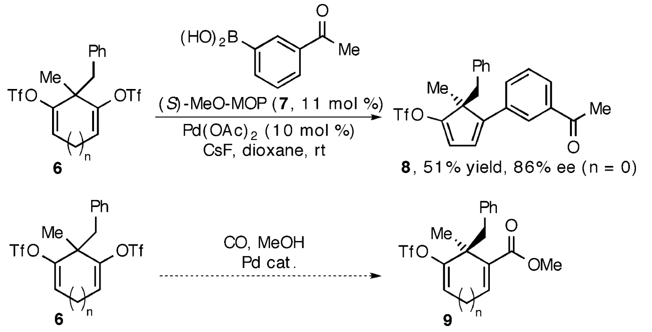
The catalytic asymmetric synthesis of all carbon quaternary centers remains a challenge to synthetic chemists.[1] Despite some notable successes,[2] a general, single strategy that allows access to a varied range of functional groups has not been described. One approach to developing such a strategy is to target a key class of catalytic intermediates that are capable of being transformed into a number of distinct functionalities; if these intermediates can be accessed in an enantioselective fashion, then the asymmetric synthesis of a diverse range of products should be possible. Palladium(0) complexes are known to catalyze a host of synthetically useful transformations, including cross-couplings, Heck-type processes, carbonylations, reductions, and many more.[3] Importantly, the majority of these transformations involve a notional common intermediate; the oxidative addition product of the palladium(0) catalyst to an aryl- or vinyl halide (or pseudohalide). It follows that if the subsequently formed aryl- or vinyl palladium species could be obtained with high enantioselectivities, then asymmetric versions of these important catalytic processes should be possible.[4] Scheme 1 presents a version of this concept based on enantioselective desymmetrization.[5,6]

Achiral substrate **1** contains two enantiotopic groups X, each capable of undergoing oxidative addition with a Pd(0) catalyst. Selective oxidative addition to **1** would generate key vinyl palladium intermediate **2** in an enantiomerically enriched form. The chiral vinyl palladium intermediate **2** could then be advanced through a number of different processes, for example, Suzuki coupling (**2** → **3**), carbonylation (**2** → **4**) or amination (**2** → **5**). To adapt this process to the enantioselective synthesis of an all carbon quaternary center would simply require that the substrate **1** contains a suitable achiral quaternary center.

We have previously reported a version of the process described in Scheme 1 in the context of developing an enantioselective Suzuki coupling.[7] For example, the coupling of an achiral ditriflate **6** with 3-acetyl benzene boronic acid, employing a catalyst featuring the chiral phosphine ligand MeO-MOP (**7**), delivered the Suzuki product **8** with 86% ee (Scheme 2). In this Communication we demonstrate how the same class of ditriflate precursors can be employed successfully in a second palladium catalyzed enantioselective transformation; enantioselective carbonylation (**6** → **9**, Scheme 2).



**Scheme 1** Palladium catalyzed enantioselective desymmetrization as a route to enantioenriched compounds.



**Scheme 2** Enantioselective desymmetrization based Suzuki coupling and carbonylation reaction.

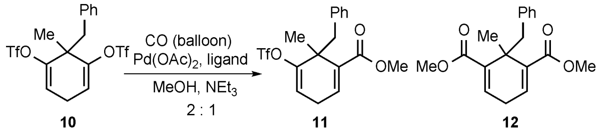
Palladium catalyzed carbonylation reactions of aryl and vinyl halides (and pseudohalides) are well established,[8] and a number of enantioselective reactions have been developed,[9] including examples based on enantioselective desymmetrization.[10] However, as far as we are aware no examples of processes distinguishing between two enantiotopic vinyl halides (or pseudohalides) leading to an asymmetric quaternary center have been reported. To validate our proposed reaction we elected to study the carbonylation chemistry of 6-membered ditriflate **10** (Table 1).[11] Our initial reaction conditions were based on those successfully employed by Schmalz in the palladium catalyzed desymmetrization of dihaloaryl tricarbonylchromium complexes.[10b] Treatment of ditriflate **10** with a

---

[a]*Department of Chemistry, Chemistry Research Laboratory, University of Oxford, Mansfield Road, Oxford, UK, OX1 3TA. E-mail: michael.willis@chem.ox.ac.uk; Fax: +44 1865 285002; Tel: +44 1865 285126*
[b]*Department of Chemistry, University of Bath, Bath, UK, BA2 7AY*
[c]*Discovery Chemistry, F. Hoffmann-La Roche Ltd, Pharmaceutical Research Basel, CH-4070, Basel, Switzerland*

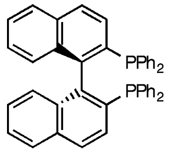
† Electronic supplementary information (ESI) available: Experimental procedures and analytical data for new compounds. See DOI: 10.1039/b923186b

**Table 1** The development of reaction conditions for the desymmetrization of ditriflate **10**[a]

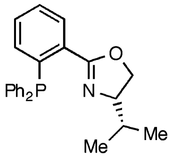


| entry | ligand | temp./°C | time/h | yield **11** [b](ee)[c] | yield **12**[b] |
|---|---|---|---|---|---|
| 1[d] | $P^tBu_3 \cdot HBF_4$ | 60 | 2 | 34% (—) | 46% |
| 2 | **13** | 60 | 2 | <5% (—) | 0% |
| 3 | **14** | 60 | 2 | 21% (21%) | 0% |
| 4 | **7** | 60 | 2 | 41% (65%) | 13% |
| 5 | **7** | 45 | 2 | 34% (74%) | 9% |
| 6 | **15** | 45 | 1 | 38% (89%) | 45% |
| 7 | **15** | 45 | 2 | 40% (95%) | 55% |
| 8 | **15** | 45 | 4 | 34% (95%) | 57% |
| 9 | **15** | 20 | 17 | 33% (78%) | 8% |
| 10 | **16** | 45 | 2 | 27% (96%) | 57% |

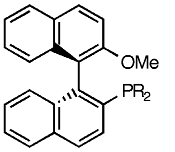
[a] Reaction conditions; ditriflate **10** in 2 : 1 MeOH : $NEt_3$ (0.1 M), $Pd(OAc)_2$ (10 mol%), ligand (10 mol%). [b] Isolated yields. [c] Determined by chiral HPLC. [d] $PdCl_2$ used.



**13**



**14**



**7**, R = Ph [(*S*)-MeO-MOP]
**15**, R = Cy
**16**, R = $^i$Pr

balloon pressure of CO in a 2 : 1 MeOH : $NEt_3$ solvent mix, using a simple achiral catalyst, delivered a mixture of the mono- and diesters **11** and **12** in reasonable yield (Entry 1). Disappointingly, exchanging the achiral ligand for BINAP (**13**) resulted in a poorly active catalyst (Entry 2). The P–N chelating phosphine oxazoline **14** fared slightly better, delivering 21% of the monoester with 21% ee (Entry 3). A significant increase in reactivity and selectivity was achieved when MeO-MOP (**7**) was employed as ligand; a 2 h reaction at 60 °C delivered 41% of the monoester in 65% ee, along with 13% of the diester (Entry 4). Lowering the reaction temperature to 45 °C allowed the monoester to be obtained in 34% yield with an ee of 74% (Entry 5). Further improvements were achieved with the modified MOP-ligand **15**, which features a bulky, electron-rich $PCy_2$ substituent;[12] optimum conditions with this ligand system involved a reaction of 2 h at 45 °C, to deliver the monoester in 40% yield with an ee of 95% (Entries 6–9). The final entry in the Table shows that the diisopropylphosphine-variant of MOP (**16**) is also an effective ligand (Entry 10). It is interesting to note that the optimal ligands for the palladium catalyzed desymmetrizing-carbonylation of ditriflate **10** feature the same general structure as the optimum ligand for the corresponding desymmetrizing Suzuki couplings. In particular, the requirement for a P–O ligand seems important to achieve good levels of reactivity and selectivity in both reactions.

Inspection of the relationship between monoester **11** yield and ee, and the yield of diester **12**, for the reactions given in Table 1, suggested that the excellent ees obtained in these reactions were the result of an *in situ* kinetic resolution. To confirm this we recorded the conversion to monoester **11** and diester **12**, as well as the ee of monoester **11**, as a function of time (Fig. 1). Although the absolute values shown in Fig. 1 do not match exactly with those in Table 1,[13] the same trends, *i.e.*, an increase in the ee of the monoester as the amount of the diester increases, are apparent.

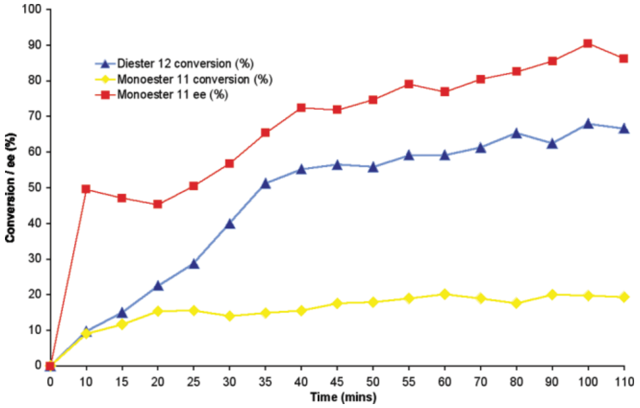


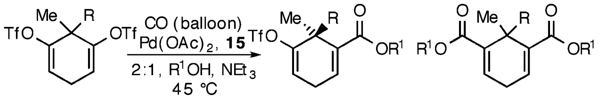
**Fig. 1** The enantioselective carbonylation of ditriflate **10** to generate monoester **11** and diester **12** using a $Pd(OAc)_2$/ligand **15** catalyst. Conversions determined by $^1H$ NMR spectroscopy and ees determined by chiral HPLC.

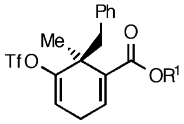
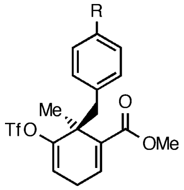
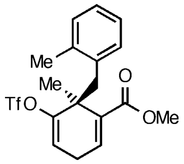
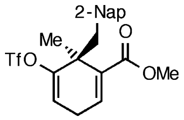
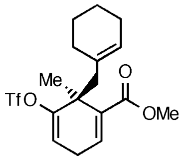
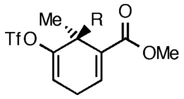
With conditions established to deliver monoester **11** with high ee, albeit with only moderate yield, we next explored the scope of the enantioselective carbonylation process (Table 2). Using the methyl/benzyl-substituted substrate (**10**) we established that both ethyl and isopropyl esters could be efficiently and selectively generated, however, the use of *tert*-butanol as a nucleophile was unsuccessful (Entries 1–3). We next explored a variety of substituents on the benzyl group of the quaternary center; entries 4–7 demonstrate that substitution of the 4-position is well tolerated, with the required monoesters being generated in excellent ee. The use of a 2-Me-substituent was less successful, resulting in reduced selectivity (Entry 8). The 2-naphthyl example, shown in Entry 9, underwent highly selective carbonylation. Exchange of the aryl portion of the benzyl substituent for a cyclohexenyl group also resulted in reduced reactivity and selectivity (Entry 10). The final two Entries examine substrates featuring methyl/*n*-propyl and methyl/ethyl quaternary centers; the methyl/*n*-propyl example is desymmetrized to deliver the monoester with an impressive 87% ee (Entry 11). Although the methyl/ethyl example is not as selective, the monoester is still obtained in 61% ee.

In summary, the catalytic enantioselective desymmetrization of cyclic bis-alkenyltriflates has been achieved by palladium catalyzed carbonylation. This provided the monoester products featuring all-carbon quaternary centers in excellent ee (up to 96%), and reasonable yield (approx. 40%). The reaction was also applicable to a range of alcohol coupling partners, showing little or no detriment to either yield or enantioselectivity. The high enantioselectivities seen in this reaction were partly due to the presence of a kinetic resolution, which preferentially removed the minor enantiomer of the monoester *via* a second coupling reaction to form an achiral diester. Variation of the substrate structure was also performed at the quaternary carbon center, with enantiotopic groups of different size and electronic nature explored.

In establishing this second enantioselective palladium catalyzed transformation using the same substrate class, we have begun to establish palladium catalyzed desymmetrization as a platform to develop a range of enantioselective coupling processes. The

**Table 2** Scope of the enantioselective carbonylation of cyclic 1,3-ditriflates[a]



| entry | product | monoester yield [b](ee)[c] | diester yield[b] |
|---|---|---|---|
| |  | | |
| 1 | $R^1 = Et$ | 34% (94%) | 47% |
| 2 | $R^1 = {}^iPr$ | 48% (90%) | 18% |
| 3 | $R^1 = {}^tBu$ | 14% (—) | <5% |
| |  | | |
| 4 | R = OMe | 34% (94%) | 47% |
| 5 | R = CN | 44% (89%) | 32% |
| 6 | $R = CF_3$ | 40% (85%) | 15% |
| 7 | R = F | 35% (95%) | 36% |
| 8 |  | 36% (80%) | 28% |
| 9 |  | 44% (93%) | 33% |
| 10 |  | 41% (74%) | 20% |
| |  | | |
| 11 | R = Pr | 32% (87%) | 38% |
| 12 | R = Et | 31% (61%) | 38% |

[a] Reaction conditions; ditriflate in 2 : 1 MeOH : $NEt_3$ (0.1 M), $Pd(OAc)_2$ (10 mol%), ligand **15** (10 mol%). The absolute configurations of the products have not been established, and are arbitrarily shown above. [b] Isolated yields. [c] Determined by chiral HPLC.

ability to selectively access a common vinyl palladium intermediate should allow further reactions to be developed, thus delivering an increasing range of functional groups and generating products useful in organic synthesis.

## Acknowledgements

This work was supported by the EPSRC and F. Hoffmann-La Roche Ltd.

## Notes and references

1 Reviews: (*a*) O. Riant and J. Hannedouche, *Org. Biomol. Chem.*, 2007, **5**, 873; (*b*) A. Steven and L. E. Overman, *Angew. Chem., Int. Ed.*, 2007, **46**, 5488; (*c*) P. G. Cozzi, R. Hilgraf and N. Zimmermann, *Eur. J. Org. Chem.*, 2007, 5969; (*d*) J. Chrsitoffers and A. Mann, *Angew. Chem., Int. Ed.*, 2001, **40**, 4591.

2 Selected recent examples of the catalytic enantioselective synthesis of quaternary all carbon centers, see: (*a*) T. Hashimoto, K. Sakata and K. Maruoka, *Angew. Chem., Int. Ed.*, 2009, **48**, 5014; (*b*) S. R. Levine, M. R. Krout and B. M. Stoltz, *Org. Lett.*, 2009, **11**, 289; (*c*) T. L. May, M. K. Brown and A. H. Hoveyda, *Angew. Chem., Int. Ed.*, 2008, **47**, 7358; (*d*) A. G. Doyle and E. N. Jacobsen, *Angew. Chem., Int. Ed.*, 2007, **46**, 3701; (*e*) S. Mukherjee and B. List, *J. Am. Chem. Soc.*, 2007, **129**, 11336.

3 (*a*) J. Tsuji, *Palladium Reagents and Catalysts: New Perspectives for the 21st Century*, Wiley, Chichester, 2004; (*b*) *Handbook of Organopalladium Chemistry for Organic Synthesis*, (Eds, E. Negishi, A. de Meijere), Wiley, New York, 2002.

4 For an excellent review on enantioselective palladium-catalyzed transformations, see: L. F. Tietze, H. Ila and H. P. Bell, *Chem. Rev.*, 2004, **104**, 3453.

5 For reviews on enantioselective desymmetrization, see: (*a*) M. C. Willis, *J. Chem. Soc., Perkin Trans. 1*, 1999, 1765; (*b*) T. Rovis, in Recent Advances in Catalytic Asymmetric Desymmetrization Reactions, in *New Frontiers in Asymmetric Catalysis*, (Eds, K. Mikami, M. Lautens), Wiley, New York, 2007, pp. 275–312.

6 For alternative examples of palladium catalyzed enantioselective desymmetrizations, see: (*a*) E. P. Kündig, P. D. Chaudhuri, D. House and G. Bernardinelli, *Angew. Chem., Int. Ed.*, 2006, **45**, 1092; (*b*) A. B. Machotta, B. F. Straub and M. Oestreich, *J. Am. Chem. Soc.*, 2007, **129**, 13455; (*c*) B. M. Trost, J. Richardson and K. Yong, *J. Am. Chem. Soc.*, 2006, **128**, 2540; (*d*) E. A. Bercot and T. Rovis, *J. Am. Chem. Soc.*, 2004, **126**, 10248; (*e*) B. M. Trost and D. E. Patterson, *Chem.–Eur. J.*, 1999, **5**, 3279; (*f*) M. Shibasaki and E. M. Vogl, *J. Organomet. Chem.*, 1999, **576**, 1–15; (*g*) T. Hayashi, S. Niizuma, T. Kamikawa, N. Suzuki and Y. Uozumi, *J. Am. Chem. Soc.*, 1995, **117**, 9101.

7 M. C. Willis, L. H. W. Powell, C. K. Claverie and S. J. Watson, *Angew. Chem., Int. Ed.*, 2004, **43**, 1249.

8 A. Brennführer, H. Neumann and M. Beller, *Angew. Chem., Int. Ed.*, 2009, **48**, 4114.

9 (*a*) S. C. A. Nefkens, M. Sperrle and G. Consiglio, *Angew. Chem., Int. Ed. Engl.*, 1993, **32**, 1719; (*b*) T. Hayashi, J. Tang and K. Kato, *Org. Lett.*, 1999, **1**, 1487; (*c*) T. Aratani, K. Tahara, S. Takeuchi, Y. Ukaji and K. Inomata, *Chem. Lett.*, 2007, **36**, 1328; (*d*) T. Kusakabe, K. Kato, S. Takaishi, S. Yamamura, T. Mochida, H. Akita, T. A. Peganova, N. V. Vologdin and O. V. Gusev, *Tetrahedron*, 2008, **64**, 319.

10 (*a*) T. Suzuki, Y. Uozumi and M. Shibasaki, *J. Chem. Soc., Chem. Commun.*, 1991, 1593; (*b*) B. Gotov and H.-G. Schmalz, *Org. Lett.*, 2001, **3**, 1753.

11 The 5-membered ditriflates were unstable under the described carbonylation conditions and delivered dienone byproducts. The majority of the 6-membered ditriflates were prepared according to: M. C. Willis and C. K. Claverie, *Tetrahedron Lett.*, 2001, **42**, 5105.

12 Y. Uozumi and T. Hayashi, *J. Am. Chem. Soc.*, 1991, **113**, 9887.

13 The yield of monoester **11** recorded in Fig. 1 is less than the values shown in Table 1. This is attributed to sampling of the reaction needed for aliquot removal.