Unexpected effect of the fluorine atom on the optimal ligand-to-palladium ratio in the enantioselective Pd-catalyzed allylation reaction of fluorinated enol carbonates†

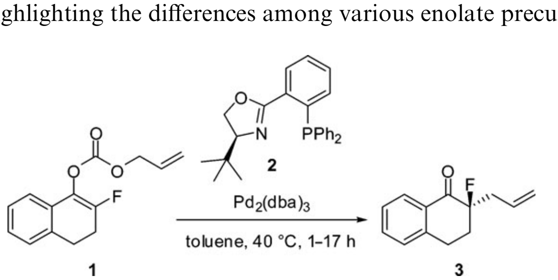
Étienne Bélanger, Clément Houzé, Nicolas Guimond, Katy Cantin and Jean-François Paquin*

Received (in College Park, MD, USA) 25th February 2008, Accepted 15th April 2008
First published as an Advance Article on the web 15th May 2008
DOI: 10.1039/b803097a

The enantioselective Pd-catalyzed allylation reaction of fluorinated allyl enol carbonates is presented; a key feature of this transformation is the important effect of the ligand-to-palladium ratio on the enantioselectivity of the α-fluoroketones, since using a ligand excess (L/Pd ratio = 1.25 : 1) led to moderate results (30–76% ee), while using a L/Pd ratio <1 : 1.67 (to as low as 1 : 4) allowed the desired products to be obtained with high enantiopurity (up to 94% ee).

The development of novel methods to synthesize fluorinated molecules is an active field of research due to the importance of these compounds in medicinal chemistry and other related fields.[1] A practical method to generate complex fluorinated compounds is to functionalize simple and readily available fluorinated substrates. However, this approach is not always trivial, since fluorinated substrates often show different and sometimes unexpected reactivities compared to their non-fluorinated analogues.[2] As a result, reaction conditions developed for non-fluorinated substrates are not always optimal for fluorinated examples.

Our group is interested in using fluorinated enolates as nucleophiles in allylic alkylation reactions[3,4] for the synthesis of chiral organofluorine compounds. We have recently reported the first enantioselective Pd-catalyzed allylation of fluorinated silyl enol ethers.[5,6] A variety of cyclic tertiary α-fluoroketones[1c,7] were prepared in good yields and with excellent enantioselectivities (up to 95% ee). Following this work, we became interested in exploring an alternative approach to similar products by using fluorinated enol carbonates, such as **1**, as fluorinated enolate precursors. Carbonates would have a number of added benefits over the silyl enol ethers, including increased stability and simplified reaction conditions. Herein, we report an enantioselective Pd-catalyzed allylation reaction of fluorinated allyl enol carbonates (eqn (1)). We also report the discovery of an unusual metal-catalyzed reaction where only a low ligand-to-metal ratio (L/M <1 : 1.67) is necessary in order to obtain high enantioselectivities. The importance of the L/M ratio for fluorinated carbonates drastically contrasts with non-fluorinated carbonates, where the L/M ratio has no influence on enantioselectivity. Furthermore, this phenomenon is only observed with fluorinated allyl enol carbonates and not with other fluorinated substrates (silyl enol ethers or β-keto allyl esters), thus highlighting the differences among various enolate precursors.



(1)

We initially examined the reaction of allyl enol carbonate **1** catalyzed by $Pd_2(dba)_3$ (2.5 mol%) and ligand **2**[8] (eqn (1)). Using excess ligand (6.25 mol%, L/Pd = 1.25 : 1), the desired product, **3**, was obtained in 85% yield and low enantiomeric excess (59% ee). Efforts to optimize the enantiopurity by varying classic factors were unsuccessful.[9] This was surprising, since the successful allylation of non-fluorinated allyl enol carbonates has been reported under similar conditions.[6,10]

A significant advance was made when probing the effect of the ligand-to-palladium ratio (L/Pd, Fig. 1). While excess (*i.e.* L/Pd >1 : 1) or equimolar (*i.e.* L/Pd = 1 : 1) amounts of chiral ligand were detrimental to the enantioselectivity (60–64% ee), using less than 1 equiv. of chiral ligand relative to the metal (*i.e.* L/Pd = 1 : 1.33 or 1 : 1.1) resulted in an improved enantiomeric excess (80–83% ee). High enantioselectivities (92–93% ee) were obtained by further decreasing the L/Pd ratio.[11,12] Interestingly, a L/Pd ratio as low as 1 : 4

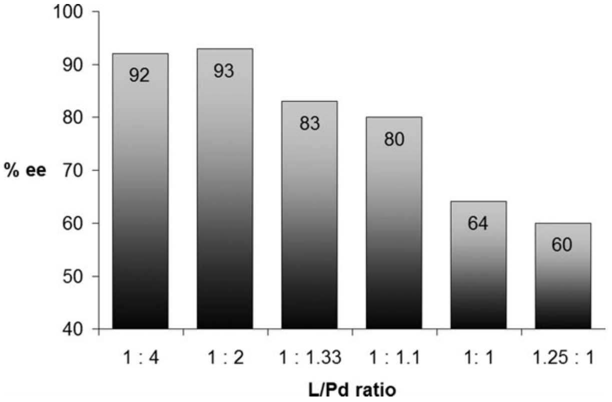


Fig. 1 Effect of L/Pd ratio on the enantioselectivity in the allylation of allyl enol carbonate **1** (*cf.* eqn (1)).

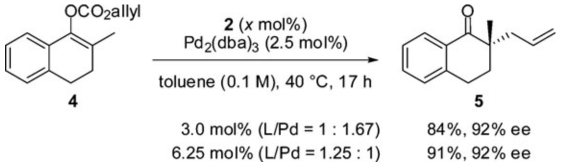
Canada Research Chair in Organic and Medicinal Chemistry, Département de chimie, Université Laval, 1045 avenue de la Médecine, Québec, QC, Canada G1V 0A6. E-mail: jean-francois.paquin@chm.ulaval.ca

† Electronic supplementary information (ESI) available: General experimental procedures, specific details of representative reactions, and the isolation and spectroscopic information of the new compounds prepared. See DOI: 10.1039/b803097a

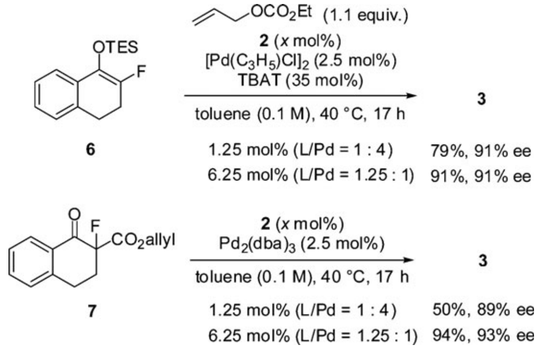
(*i.e.* 1.25 mol% ligand) could be used without affecting the yield or enantioselectivity.[13]

Using these conditions, we next explored the scope of the reaction. A variety of cyclic allyl enol carbonates were examined, including tetralone derivatives (Table 1, entries 1–7), thiochromanone (entries 8–9), indanone (entries 10–11), and benzosuberone (entries 12–13). It is interesting to note that, in all cases, the yields of α-fluoroketones were similar, regardless of the L/Pd ratio, whereas a substantial improvement in the enantiomeric excess was observed with an L/Pd ratio <1 : 1.67. For example, reducing the amount of chiral ligand from 6.25 to 1.25 mol% for the reaction of a thiochromanone carbonate (entries 8–9) resulted in an enantiomeric excess improvement from 42 to 92% ee! Finally, the reaction of an acyclic substrate (entries 14–15) resulted in a moderate enantioselectivity regardless of the L/Pd ratio. This may be related to the fact that the initially generated *Z* palladium enolate rapidly equilibrates to an *E*/*Z* mixture prior to allylation.

While this reaction is quite general for a variety of cyclic fluorinated allyl enol carbonates, we were intrigued to verify whether the drastic effect of the L/Pd ratio on the enantioselectivity was specific to fluorinated substrates. We therefore subjected methyl-substituted carbonate **4** to the reaction conditions and varied the amount of chiral ligand (Scheme 1).[14] Regardless of the L/Pd ratio, the desired ketone, **5**, was isolated in similar yields and with an identical enantiomeric excess (92% ee), suggesting that the fluorine is playing a critical role in the allylation of fluorinated allyl enol carbonates.[15]

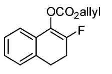
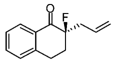
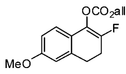
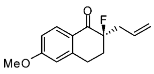
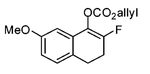
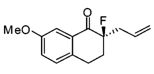
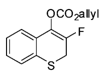
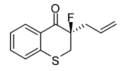
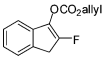
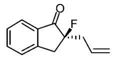
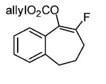
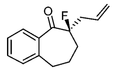
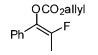
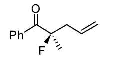


Scheme 1 Allylation of a non-fluorinated allyl enol carbonate.



Scheme 2 Allylation of alternative fluorinated enolate precursors.

Table 1 Reactions of various fluorinated allyl carbonates[a]

Entry	Substrate	Product	L/Pd ratio	Result	
				Yield (%)[b]	ee (%)[c]
1	 1	 3	1 : 4	93	92
2			1 : 1.67	97	93
3			1.25 : 1	85	59
4			1 : 4	87	92
5			1.25 : 1	98	57
6			1 : 4	92	94
7			1.25 : 1	86	54
8			1 : 4	90	92
9			1.25 : 1	93	42
10			1 : 1.67	91	82
11			1.25 : 1	90	30
12			1 : 4	83	88
13			1.25 : 1	87	76
14			1 : 1.67	58	34
15			1.25 : 1	75	36

[a] 5 mol% Pd (2.5 mol% of $Pd_2(dba)_3$) was used in all the reactions, along with the appropriate amount of ligand (see ESI for details). [b] Isolated yield. [c] Determined by chiral HPLC.

Having established the importance of both the fluorine atom and the L/Pd ratio in this reaction, we next examined the effect of the L/Pd ratios in reactions with other fluorinated enolate precursors (which had previously employed a L/Pd >1 : 1 to achieve high enantiomeric excesses) (Scheme 2). We first revisited the allylation of fluorinated silyl enol ethers.[5] The reaction of **6** using a L/Pd of 1 : 4 afforded α-fluoroketone **3** with a similar result (79%, 91% ee) compared to the reaction with an excess of ligand (L/Pd = 1.25 : 1). We then examined the reaction of α-fluoro-β-keto ester **7**, which is an isomeric equivalent of fluorinated allyl enol carbonate **1**.[16] Using a L/Pd ratio of 1 : 4 gave a lower yield of **3** compared to a L/Pd ratio of 1.25 : 1, but a similarly high enantiomeric excess. These results clearly highlight the fact that, unlike non-fluorinated enolate precursors, different fluorinated enolate precursors have different reactivity patterns and should not be considered equivalent.[6,10,16a]

In conclusion, we have detailed the first enantioselective Pd-catalyzed allylation reaction of fluorinated allyl enol carbonates. In addition, we have discovered an important and uncommon effect of the L/Pd ratio on the enantioselectivity, whereby a L/Pd ratio <1 : 1.67 (and as low as 1 : 4) is necessary in order to obtain the α-fluoroketones in high enantiopurity (up to 94% ee). Although these conditions are presently limited to cyclic fluorinated allyl enol carbonates, the use of a L/Pd ratio <1 : 1 in other catalytic asymmetric reactions would have tremendous benefits. Notably, chiral ligands are often more expensive and less accessible than metal catalysts, and therefore reducing the amount of ligand in any given reaction may result in lower costs.[17] Detailed mechanistic studies are currently under way to explain this unusual finding.

This work was supported by the Canada Research Chair Program, the Natural Sciences and Engineering Research Council of Canada, the Canada Foundation for Innovation, Merck Frosst Centre for Therapeutic Research and the Université Laval. OmegaChem Inc. is thanked for a generous gift of L-*tert*-leucine.

Notes and references

1. (*a*) T. Hiyama, in *Organofluorine Compounds: Chemistry and Applications*, ed. H Yamamoto, Springer-Verlag, Berlin, Heidelberg, New York, 2000, pp. 1–23 and pp. 137–182; (*b*) A. M. Thayer, *Chem. Eng. News*, 2006, **84**, 15; (*c*) J.-A. Ma and D. Cahard, *Chem. Rev.*, 2004, **104**, 6119; (*d*) C. Bobbio and V. Gouverneur, *Org. Biomol. Chem.*, 2006, **4**, 2065; (*e*) K. L. J. Kirk, *J. Fluorine Chem.*, 2006, **127**, 1013; (*f*) J.-P. Bégué and D. J. Bonnet-Delpon, *J. Fluorine Chem.*, 2006, **127**, 992; (*g*) S. Purser, P. R. Moore, S. Swallow and V. Gouverneur, *Chem. Soc. Rev.*, 2008, **37**, 320.
2. For example, see: (*a*) M. Marhold, A. Buer, H. Hiemstra, J. H. van Maarseveen and G. Haufe, *Tetrahedron Lett.*, 2004, **45**, 57; (*b*) F. Grein, A. C. Chen, D. Edwards and C. M. Crudden, *J. Org. Chem.*, 2006, **71**, 861; (*c*) S. Kobayashi, H. Tanaka, H. Amii and K. Uneyama, *Tetrahedron*, 2003, **59**, 1547; (*d*) C. M. Crudden, A. C. Chen and L. A. Calhoun, *Angew. Chem., Int. Ed.*, 2000, **39**, 2851; (*e*) T. Ernet, A. H. Maulitz, E.-U. Würthwein and G. J. Haufe, *J. Chem. Soc., Perkin Trans. 1*, 2001, 1929; (*f*) W. Heitz and A. Knebelkamp, *Macromol. Rapid Commun.*, 1991, **12**, 69; (*g*) S. J. Getty and W. T. J. Borden, *J. Am. Chem. Soc.*, 1991, **113**, 4334; (*h*) J. Banus, H. J. Emeléus and R. N. J. Haszeldine, *J. Chem. Soc.*, 1951, 60.
3. For reviews on asymmetric allylic alkylation reactions, see: (*a*) J.-F. Paquin and M. Lautens, in *Comprehensive Asymmetric Catalysis: Supplement 2*, ed. E. N. Jacobsen, A Pfaltz and H Yamamoto, Springer-Verlag, Berlin, 2004, pp. 73–95; (*b*) A. Pfaltz and M. Lautens, in *Comprehensive Asymmetric Catalysis*, ed. E. N. Jacobsen, A Pfaltz, H Yamamoto, Springer, New York, 1999, vol. 2, pp. 833–884; (*c*) B. M. J. Trost, *J. Org. Chem.*, 2004, **69**, 5813; (*d*) B. M. Trost and C. Lee, in *Catalytic Asymmetric Synthesis*, ed. I Ojima, Wiley-VCH, New York, 2nd edn, 2000, pp. 593–649; (*e*) G. J. Helmchen, *J. Organomet. Chem.*, 1999, **576**, 203; (*f*) B. M. Trost, *Chem. Pharm. Bull.*, 2002, **50**, 1; (*g*) B. M. Trost and D. L. Van Vranken, *Chem. Rev.*, 1996, **96**, 395; (*h*) B. M. Trost, *Acc. Chem. Res.*, 1996, **29**, 355.
4. For a recent review on the use of pre-formed enolates in Pd-catalyzed allylic alkylation reactions, see: M. Braun and T. Meier, *Synlett*, 2006, 661.
5. É. Bélanger, K. Cantin, O. Messe, M. Tremblay and J.-F. Paquin, *J. Am. Chem. Soc.*, 2007, **129**, 1034.
6. For a related reaction of non-fluorinated substrates using similar conditions, see: (*a*) D. C. Behenna and B. M. Stoltz, *J. Am. Chem. Soc.*, 2004, **126**, 15044; (*b*) J. A. Keith, D. C. Behenna, J. T. Mohr, S. Ma, S. C. Marinescu, J. Oxgaard, B. M. Stoltz and W. A. Goddard III, *J. Am. Chem. Soc.*, 2007, **129**, 11876.
7. (*a*) V. A. Brunet and D. O'Hagan, *Angew. Chem., Int. Ed.*, 2008, **47**, 1179; (*b*) G. K. S. Prakash and P. Beier, *Angew. Chem., Int. Ed.*, 2006, **45**, 2172; (*c*) P. M. Pihko, *Angew. Chem., Int. Ed.*, 2006, **45**, 544.
8. (*a*) G. Helmchen and A. Pfaltz, *Acc. Chem. Res.*, 2000, **33**, 336; (*b*) J. M. Williams, *Synlett*, 1996, 705.
9. Factors studied include: solvents (THF, dioxane, CH_2Cl_2, CH_3CN), chiral ligands ((*R*,*R*)-Trost ligand ((1*R*,2*R*)-(+)-1,2-diaminocyclohexane-*N*,*N*′-bis(2′-diphenylphosphinobenzoyl)), (*R*)-(*S*)-JOSIPHOS ((*R*)-(−)-1-[(*S*)-2-(diphenylphosphino)ferrocenyl]ethyldicyclohexylphosphine) (*R*)-BINAP), temperature (RT–40 °C) and concentration (0.033–0.1 M).
10. (*a*) B. M. Trost and J. Xu, *J. Am. Chem. Soc.*, 2005, **127**, 2846; (*b*) B. M. Trost and J. Xu, *J. Am. Chem. Soc.*, 2005, **127**, 17180.
11. For other examples showing the importance of the L/Pd ratio on the enantioselectivity in asymmetric allylic alkylation reactions, see: (*a*) X. Cheng and K. K. Hii, *Tetrahedron: Asymmetry*, 2003, **14**, 2045; (*b*) D.-R. Hou, J. H. Reibenspies and K. Burgess, *J. Org. Chem.*, 2001, **66**, 206; (*c*) A. M. Porte, J. Reibenspies and K. Burgess, *J. Am. Chem. Soc.*, 1998, **120**, 9180; (*d*) K. Burgess and A. M. Porte, *Tetrahedron: Asymmetry*, 1998, **9**, 2465.
12. For examples showing the importance of the L/M ratio on the enantioselectivity in other transformations, see: (*a*) R. Rasappan, M. Hager, A. Gissibl and O. Reiser, *Org. Lett.*, 2006, **8**, 6099; (*b*) G. C. Lloyd-Jones and C. P. Butts, *Tetrahedron*, 1998, **54**, 901.
13. All the reactions reported in Fig. 1 afforded **3** in good yield (>73%). Low conversion (<20%) was observed when a L/Pd ratio of <1 : 4 was used, whereas no product was detected without the chiral ligand being present.
14. The reaction of **4** using an excess of ligand under similar conditions ($Pd_2(dba)_3$ (2.5 mol%), ligand **2** (6.25 mol%), THF (0.033 M), 10 °C, 2 h) has been reported previously, and the desired product, **5**, was obtained with comparable results (87%, 91% ee). See ref. 6.
15. Other non-fluorinated substrates were also examined. The allyl enol carbonate derived from α-tetralone was reacted under our conditions (L/Pd = 1 : 4 and L/Pd = 1.25 : 1). However, none of the desired product was isolated in either case. Interestingly, when using a L/Pd ratio of 1 : 4, only starting material was recovered; when a L/Pd ratio of 1.25 : 1 was used, a mixture of various side-products were observed, with only traces of the desired product being detected. This transformation has been previously conducted using an excess of a chiral ligand (see ref. 10*a*). In addition, the allyl enol carbonate derived from 2-chloro-1-tetralone was also tested. In this case, a small increase in enantioselectivity was observed from L/Pd = 1.25 : 1 (34% ee) to L/Pd = 1 : 4 (49% ee).
16. (*a*) E. C. Burger, B. R. Barron and J. A. Tunge, *Synlett*, 2006, 2854; (*b*) J. T. Mohr, D. C. Behenna, A. M. Harned and B. M. Stoltz, *Angew. Chem., Int. Ed.*, 2005, **44**, 6924; (*c*) M. Nakamura, A. Hajra, K. Endo and E. Nakamura, *Angew. Chem., Int. Ed.*, 2005, **44**, 7248.
17. For example, in the PHOX ligand series (phosphinooxazolines), only *i*-Pr-PHOX is commercially available: (*S*)-*t*-Bu-PHOX has to be synthesized in four steps from L-*tert*-leucine (see ref. 8). For our system, and if we use *i*-Pr-PHOX for the sake of comparison, the ligand is seven times more expensive than the metal: (*S*)-*i*-Pr-PHOX (578 US\$ g^{-1} ≡ 216US\$ $mmol^{-1}$, 2007 Strem catalogue) *vs.* $Pd_2(dba)_3$ (162 US\$ g^{-1} ≡ 30 US\$ $mmol^{-1}$, 2007 Strem catalogue).