Access to enantioenriched 2,3- and 2,5-dihydrofurans with a fully substituted C2 stereocenter by Pd-catalyzed asymmetric intermolecular Heck reaction†

Gustavo M. Borrajo-Calleja,a Vincent Bizet,a Thomas Bürgib and Clément Mazet*a

A palladium-catalyzed intermolecular asymmetric Heck reaction with dihydrofurans with a trisubstituted double bond is reported. The use of two different chiral ligands provides access to valuable 2,3- and 2,5-dihydrofurans with a fully substituted C2 stereocenter with high levels of regio- and enantiocontrol.

Introduction

During the past decades, building on the seminal contributions of Overman and Shibasaki, the asymmetric intramolecular Heck reaction has been successfully applied in natural product synthesis to install tertiary and quaternary stereocenters.1,2 In stark contrast, the intermolecular version of this asymmetric transformation has not reached the same level of development and its synthetic utility remains limited (Fig. 1).3 A survey of the literature following Hayashi’s pioneering contribution indicates that this transformation has been used essentially as a benchmark reaction to validate the design of novel homotopic and heterotopic chiral ligands.4,5 While variations of the electronic and steric nature of the aryl halides and pseudo-halides has been investigated in detail, most of these studies have been focused on the use of dihydrofurans or N-protected dihydropyrroles to afford the corresponding coupling products with a C2 tertiary center. Systematic studies where emphasis has been placed on exploring the diversity of the olefinic coupling partner are scarce, in particular for the construction of congested quaternary centers or related fully saturated centers. Very recently, Sigman has reported a series of elegant contributions for the redox-relay Heck arylation of acyclic alkenyl alcohols enabling the installation of remote tertiary and quaternary stereogenic centers.6,7 Despite these recent breakthroughs, it is apparent that the development of an intermolecular asymmetric Heck reaction to enable the construction of fully saturated stereocenters in cyclic systems constitutes an important synthetic challenge.*

Fig. 1 Access to quaternary and related fully saturated stereocenters by asymmetric Heck reactions.

In this report, we disclose a methodology that gives access to chiral 2,3- and 2,5-dihydrofurans (dhfs) with a fully substituted C2 stereocenter. Our study highlights the complementarity in product selectivity between two distinct chiral ligands while it also delineates the scope of trisubstituted dihydrofurans compatible with the catalytic systems.

Results and discussion

The choice of our model reaction was inspired by a report from Pregosin and co-workers where 5-methyl-2,3-dihydrofuran 1a was cross-coupled with phenyl triflate 2a using (R)-DTB-MeO-BIPHEP (i.e. (R)-(+)-2,2′-bis[di(3,5-di-tert-butylphenyl)phosphino]-6,6′-dimethoxy-1,1′-biphenyl).9 To the best of our knowledge this represents the only precedent of an asymmetric intermolecular Heck reaction employing a cyclic substrate with a trisubstituted olefinic moiety. Despite an excellent enantioselectivity (4aa: 98% ee), the low yield (38%), the moderate...
regioselectivity (1.0 : 6.0) and the impractical reaction time (7 days) certainly precluded further developments. We began our investigations by evaluating an array of chiral (P,N) and (P,P) ligands as to their complementarity in providing access to the product of direct cross-coupling 3 and the product of further isomerization 4, respectively, as is well documented for unsubstituted cyclic substrates.  

With an initial set of reaction conditions (Pd(OAc)_2, toluene, i-Pr_2NEt, 110 °C, 62 h), only traces of products 3aa and 4aa were observed in the coupling between 1a and 2a using L1 (Table 1, entry 1). Evaluation of two of our home-made chiral (P,N) ligands did not significantly enhance the reactivity, even though 3aa was the only detectable product of cross-coupling.  

While 3aa was obtained in 76% ee with L3, L4 gave an excellent 94% ee value (entry 2 and 3). A slightly improved reactivity along with similar regio- and enantioselectivities were obtained with the electron-rich 4-methoxyphenyl trflate 2b (entry 4). An extensive optimization of all reaction parameters was then conducted. Multiple combinations of palladium sources, solvents and bases along with adjustment of the temperature, stoichiometry, concentration and reaction time led to the identification of a very efficient catalytic system (Pd_2(dba)_3, 2-Me-THF, i-Pr_2NEt, 100 °C, 48 h; see ESI† for details) affording 3ab in 64% and 93% ee with L4 (entry 5).

Of important note, while the catalyst loading, the relative stoichiometry between the coupling partners and the yields obtained (ca. 40–65%) are typical of intermolecular asymmetric Heck reactions, 48 h is unusually short for such a process involving cyclic olefins. Under classical thermal conditions, reaction times often range from 4 to 7 days.  

Unexpectedly, when the electron-deficient aryl trflate 2e was employed, no product of cross-coupling was observed.  

The prototypical (P,N) ligand L5 for intermolecular Heck reactions using unsubstituted dhf did not display better performances (entry 7 and 8). For sake of operational simplicity, the same protocol was used in the survey of several (P,P) ligands (entry 9–16). Consistent with literature precedents for the coupling of unsubstituted dhf, a marked regioselectivity switch in favor of the isomerized products 4 was observed with most ligands. Noticeably, while poor results were obtained in the coupling reactions with the electron-rich trflate 2b, the electron-deficient aryl trflate 2c permitted to reach excellent enantioselectivity levels with L2, and L8 (entry 10 and 16).  

This dichotomous situation was further confirmed when the scope or aryl trlates compatible with both L4 and L8 was delineated (Table 2). With the (P,N) ligand L4, a wide variety of electron-rich aryl trlates afforded quasi-exclusively 2,5-dihydrofuran (98 : 2 : 99 : 1) in consistently very high enantioselectivity (88–93% ee) and in practical yields. Remarkably, even the sterically demanding o-methoxyphenyl trflate 2k was cross-coupled efficiently (3ak : 53%, 99 : 1, 90% ee). Reduced yields were obtained with 2a and 2l, albeit the regio- and enantioslectivities remained excellent. Attempts to couple electron-deficient aryl trlates were unsuccessful. In contrast, with the (P,P) ligand L8, only electron-deficient aryl trlates 2c, 2m–r were found to be compatible electrophile coupling partners. This afforded 2,3-dihydrofuran with a saturated C2 stereocenter in excellent enantioselectivity and allowed functional groups such as cyano, nitro, trifluoromethyl, ester, aldehyde, ary1 and alkyl ketones to be introduced.

Seven different 5-substituted 2,3-dhfs were found to be suitable substrates with both methodologies (Table 3 and 4). These compounds proved particularly unstable and presented challenges for study because of the difficulty associated with their preparation and purification (see ESI†).

The C1-symmetric (P,N) ligand L4 and the C2-symmetric (P,P) ligand L8 gave access to 2,2-disubstituted 2,5-dhf and 2,2-disubstituted 2,3-dhf, respectively, in usually practical yields and with excellent regio- and enantioselectivity. Both catalytic

### Table 1 Reaction optimization

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<th>3 : 4&lt;sup&gt;c&lt;/sup&gt;</th>
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<sup>a</sup> Reaction conditions: 1a (1 mmol), 2a–e (0.2 mmol).  
<sup>b</sup> Entries 1–4: Pd(OAc)<sub>2</sub> (3 mol%), ligand (6 mol%), toluene, 110 °C, 62 h. Entries 5–16: Pd(dba)<sub>3</sub> (2.5 mol%), ligand (10 mol%), 2-Me-THF, 100 °C, 48 h.  
<sup>c</sup> Determined by 1H NMR of the crude reaction mixture.  
<sup>d</sup> Yield of pure compound after chromatography.  
<sup>e</sup> Determined by GC or HPLC with a chiral column.  
<sup>f</sup> Not determined.  
<sup>g</sup> No reaction.
systems behaved similarly and overall excellent results were obtained. The yield range obtained for these reactions are consistent with literature precedents. They do not only reflect the entropic cost inherent to an intermolecular cross-coupling reaction but also the difficulty associated with creating saturated stereocenters. In addition to primary alkyl substituents, a methyl ether, a free alcohol, a remote olefin and a benzyl substituent were compatible. Whereas the yields were slightly reduced in the reactions with 3e, it is remarkable that no competing Heck arylation was observed in the reactions with 1f which bears a remote olefinic moiety. Finally, a large-scale experiment (8.5 mmol) was conducted for the cross-coupling between 1a and 2c (Fig. 2). Using (R)-L2, the isomerized product (R)-4ac was isolated with excellent regioselectivity, good enantioselectivity and in 46% yield (0.725 g).
The absolute configuration of the cross-coupling products was established by vibrational circular dichroism (VCD). The most stable conformer of 3ab (obtained with (R,R,R)-L4) and 4ap (obtained with (R)-L8) were compared to the experimental IR absorption and VCD spectra recorded in CD3Cl2 solutions (see ES† for details). The good agreement between the predicted and measured data enabled the assignment of a (R) configuration to both compounds. The absolute configuration of all other cross-coupling products was assigned by analogy, on the basis of their optical activity.

Conclusions

In summary, we have developed an efficient protocol for the enantioselective intermolecular Heck reaction using a variety of 5-substituted 2,3-dihydrofurans. We found that electron-rich aryl triflates can be coupled with various trisubstituted olefinic substrates when a chiral (P,N) ligand is used. The corresponding 2,5-dihydrofurans with fully saturated C2 stereocenters were obtained in excellent regio- and enantioselectivities. Electron-deficient aryl triflates were compatible with the method when commercial chiral (P,P) ligands were employed, leading to 2,2-disubstituted 2,3-dihydrofurans with excellent stereocontrol. The diversity, functional group tolerance and scalability of the approach have been also demonstrated and provide access to disubstituted 2,3-dihydrofurans with excellent stereocontrol.

Disubstituted 2,3-dihydrofurans with excellent stereocontrol.

Notes and references

8 In the strict sense, the stereogenic centers generated in this study are not quaternary, even though they are very congested. We therefore use the term ‘fully saturated stereocenters’ to highlight this notion. A fully saturated center is defined by a tetrasubstituted C atom with at least one substituent different from H or C. For relevant reviews on the challenges associated with installing congested stereocenters, see: (a) J. Christoffers and A. Baro, Quaternary Stereocentres: Challenges and Solutions for Organic Synthesis, Wiley-VCH, Weinheim, 2005; (b) K. Fuji, Chem. Rev., 1993, 93, 2037; (c) M. Bella and T. Gasperi, Synthesis, 2009, 1583; (d) I. Marek and G. Sklute, Chem. Commun., 2007, 1683; (e) C. Hawner and A. Alexakis, Chem. Commun., 2010, 46, 7295.
Asymmetric intermolecular Heck reactions can be accelerated using microwave irradiation. However, in some cases a drop in enantioselectivity has been observed. When the reaction reported in Table 1 (entry 5) was conducted under microwave irradiation (150 °C, 2 h), 3ab was isolated in 38% yield and 87% ee. For relevant examples, see: (a) P. Nilsson, H. Gold, M. Larhed and A. Hallberg, *Synthesis*, 2002, 1611; (b) P. Kaukoranta, K. Källstrom and P. G. Andersson, *Adv. Synth. Catal.*, 2007, 349, 2595; (c) Y. Mata, O. Pámies and M. Diéguez, *Chem.–Eur. J.*, 2007, 13, 3296; (d) J. Mazuela, O. Pámies and M. Diéguez, *Chem.–Eur. J.*, 2010, 16, 3434.

Analysis of the crude reaction mixture by \(^{19}\text{F} \) NMR indicates detritiation of 2c, suggesting that oxidative addition into the C(sp\(^2\))–O bond of the aryl trflate is not problematic.

Ligand \( \text{L2} \) is ca. 8-fold less-expensive than \( \text{L8} \). This aspect and the relatively similar performances reported in Table 1 (entries 10 and 16) justify the use of \( \text{L2} \) for large-scale experiments.