Asymmetric Construction of a Ferrocenyl Phosphapalladacycle from Achiral Enones and a Demonstration of its Catalytic Potential

Kennard Gan, Abdul Sadeer, Chang Xu, Yongxin Li, Sumod A. Pullarkat

Division of Chemistry and Biological Chemistry, School of Physical and Mathematical Sciences, Nanyang Technological University, 21 Nanyang Link, Singapore 637371

Supporting Information Placeholder

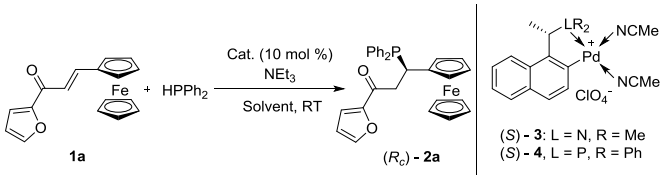
ABSTRACT: A new approach toward ferrocenyl phosphapalladacycle construction from achiral enones *via* asymmetric hydrophosphination and subsequent diastereoselective C-H activation is described. Its catalytic efficacy toward C-C bond formation is subsequently illustrated.

Ferrocenyl phosphines incorporating central and planar chirality elements have a proven track record as powerful auxiliaries in asymmetric synthesis.[1] As a result, extensive efforts have been invested in their challenging synthesis.[2] These pursuits focused on the development of ferrocenyl diphosphine and phosphapalladacyclic systems, which contain both the aforementioned stereogenic components on the same molecule. The synthesis of ferrocenyl phosphapalladacycles generally comprises of two steps, i.e, i) the formation of a *C*-chiral monophosphine and ii) subsequent palladation via C-H / C-Br activation. There are a couple of traditional approaches by which the former may be achieved, either through enantioselective[3] / diastereoselective[4] lithiation controlled by pre-existing chiral element(s), or secondary phosphine substitution of an enantiopure Ugi amine derivative.[5] Both these methods although highly selective and synthetically relevant are however, limited by the necessity of employing an enantiopure substrate. The desired ferrocenyl phosphapalladacycle may then be secured by either diastereotopic C-H activation[6], or oxidative addition of palladium(0).[7]

A hitherto unexplored route for the enantioselective formation of mono-ferrocenyl phosphines is the palladium-catalyzed asymmetric hydrophosphination (AHP) reaction. The emergence of AHP of activated alkenes affording high yields, short reaction times and excellent selectivities offers an atom - economical yet efficient approach to achieve this goal.[8] However, ferrocenyl appended substrates have been conspicuously absent from this library. Furthermore, the use of these chiral monophosphine adducts towards the preparation of viable catalysts has rarely been explored. Herein, we report the first AHP based enantioselective construction of a series of *C*-chiral tertiary ferrocenyl phosphines and the subsequent diastereoselective cyclopalladation of one of the congeners.

We began our investigation by screening an array of conditions for the asymmetric addition of diphenylphosphine to **1a** catalyzed by (*S*) - **3** (Table 1).

Table 1. Palladacycle catalyzed AHP of 1a.



Entry	Solvent	t (hrs)	Yield[b] (%)	*ee*[c] (%)
1	DCM	12	> 99	60
2	MeOH	2	> 99	60
3[d]	MeOH	2	> 99	> 99
4[e]	MeOH	168	49	n.d

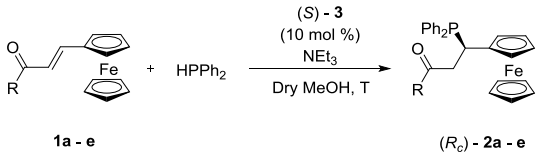
[a] All reactions were performed in the presence of 0.27 mmol $HPPh_2$, 0.27 mmol **1a**, 10 mol % (*S*) - **3** and 0.27 mmol NEt_3 in 5 ml solvent at RT. [b] Isolated yield. [c] *ee* determined from $^{31}P\{^1H\}$ NMR integration *via* use of chiral derivatizing agent. Absolute stereochemistry determined *via* single X - ray crystallography. [d] Dry MeOH. [e] Dry MeOH, Cat. (*S*) - **4**.

During the optimization process, it was evident that while the AHP proceeded smoothly in DCM and MeOH, poor conversions were obtained with THF, acetone and acetonitrile. Results show a pronounced difference between the performances of the 2 catalysts (Entry 3 *vs.* 4). While the N-C palladacycle (*S*) - **3** catalyzed the reaction within 2 hours at RT, its P-C analogue (*S*) - **4** failed to deliver full conversion even after 1 week. It was also noted that MeOH was a superior solvent as compared to DCM, yielding the product within 2 hours whilst offering the same selectivity (Entry 1 *vs.* 2). Further examination with dry MeOH revealed a significant increase in selectivity of up to > 99 % (Entry 2 *vs.* 3). Interestingly, when the AHP was conducted in MeOH, the tertiary phosphine adduct precipitated upon formation, thus enabling a facile procedure in which the enantio-enriched tertiary phosphine product can be isolated by mere filtration. Encouraged by these results, we proceeded to substrate screening (Table 2).

Although good conversions were attained with most substrates, both the 2-pyrrole and $(p\text{-}NO_2)C_6H_4$ conjoined enones failed to reach full conversion even after 1 week. This can be attributed to the ability of these substrates to form chelates on Pd, thus disrupting the catalyst regeneration process.[8c] The results attained with ferrocenyl enone **1a** showed unparalled selectivity in comparison with other substrates (**1b** - **e**) when the AHP was conducted at RT. In an effort to achieve im-

proved selectivities, we conducted a series of low temperature experiments. (Table 2, Entries 2-5) Furthermore, it is observed that the AHP with aromatic substituents generally resulted in higher selectivities as compared to their aliphatic counterpart. (Table 2, Entries 1-4 *vs.* 5)

Table 2. Asymmetric Hydrophosphination of Ferrocenyl Enones[a]

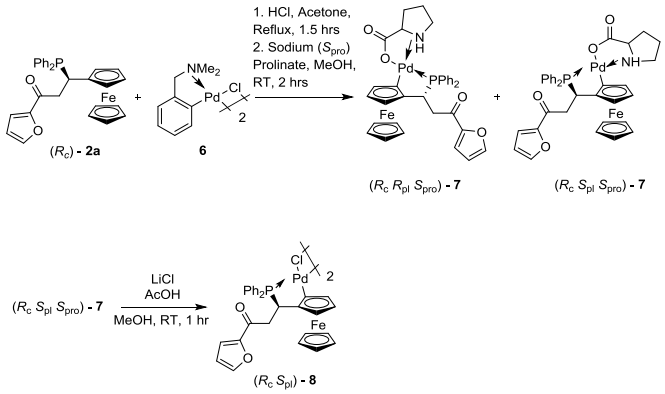


Entry	R (Product)	t (hrs)	Yield[b] (%)	*ee*[c] (%)
1	2-furyl (**2a**)	2	> 99	> 99
2[d]	3-thienyl (**2b**)	72	> 99	66
3[d]	Ph (**2c**)	96	> 99	84
4[d]	(*p*-OMe)C_6H_4 (**2d**)	168	> 99	> 99
5	Me (**2e**)	216	> 99	42

[a] All reactions were performed in the presence of 0.27 mmol of $HPPh_2$, 0.27 mmol of **1a - e**, 10 mol % (*S*) - **3** and 0.27 mmol NEt_3 in 5 ml of dry MeOH at RT. [b] Isolated yield. [c] *ee* determined from $^{31}P\{^1H\}$ integrated *via* use of chiral derivatizing agent. Absolute stereochemistry determined *via* X - ray crystallography. [d] AHP conducted at - 80 °C.

We proceeded to integrate planar chirality into the ferrocenyl skeleton *via* cyclopalladation. The fixing of planar chirality onto the ferrocene framework demands appropriate chiral control, either through an existing internal stereogenic centre or an external chiral auxiliary. Previous reports by Dunina adopted $Pd(OAc)_2$[9] and cyclopalladated ligand exchange (CLE)[10] as primary means to consummate a ferrocenyl P-C ligated palladium(II) complex. Although palladation attempts *via* $Pd(OAc)_2$ and CLE generated the targeted palladated product within 3 hours, poor yields of 20 % and 10 % were obtained respectively. Ensuing studies with $PdCl_2$, Na_2PdCl_4 and $PdCl_2(NCMe)_2$ all failed to stimulate effective C-H activation. These disappointing results could be attributed to insufficient steric promotion of the Cp - H bond by the - PPh_2 moiety, resulting in the formation of only coordination compounds.[9]

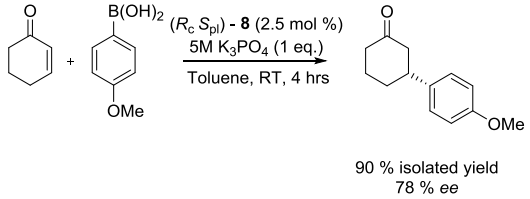
Scheme 1. Cyclopalladation



Thus, we resorted to a two-step process involving the coordination of (*R*) - **2a** to dimer **6** followed by subsequent cleavage of the N - C chelate with HCl under reflux. The crude $^{31}P\{^1H\}$ NMR spectra of **8** displayed 4 sets of singlets between δ 70 - 72, indicating complete conversion to the P - C chelate with an overall yield of 98%. Subsequent resolution with sodium prolinate (Scheme 3) gave 2 singlets at δ 68.1 and 68.8 with a ratio of 1:5.3, indicating an efficient cyclopalladation *de* of ca. 66 %. The diastereoselectivity achieved is controlled solely by the pre-existing *C*-chirality introduced during the AHP. Subsequent crystallization afforded enantiopure (R_c S_{pl} S_{pro}) - **7**.[11] Treatment of (R_c S_{pl} S_{pro}) - **7** with LiCl and AcOH in MeOH regenerated (R_c S_p) - **8** in quantitative yield with full chirality transfer. This protocol thus provides an efficient alternative for accessing ferrocenyl palladacycles from achiral activated alkenes *via* an efficient enantioselective hydrophosphination of achiral substrates followed by a diastereoselective *ortho*palladation.

With the newly synthesized ferrocenyl phosphapalladacycle in hand, we proceeded to conduct a prelimary illustration of its catalytic potential toward aryl boronic acid addition to 2-cyclohexenone.

Scheme 2. *p*-tolylphenylboronic acid addition to 2-cyclohexenone



This result compares favourably with those previously reported from Pd(II) catalyzed protocols and is evidence of the potential for this phosphapalladacycle.[7]

In conclusion, we have developed a highly enantioselective AHP based protocol for accessing ferrocenyl phosphine motifs from achiral substrates as well as a viable alternate protocol for achieving the subsequent diastereospecific *ortho*palladation of the ferrocenyl enone in order to generate cyclopalladated systems of interest incorporating both central and planar chiral elements. The catalytic demonstration indicated that such complexes are of relevance in asymmetric synthesis and this set of protocols can yield a tool set to generate more analogues of interest. Our current efforts are focused on the application of the catalyst to other organic transformations.

ASSOCIATED CONTENT

Supporting Information

Details of experiments and characterization data of products. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author

K. Gan, A. Sadeer, C. Xu, Y. Li, S. A. Pullarkat
Fax: (+) 6316-8906
E-mail: sumod@ntu.edu.sg
Homepage: http://www3.ntu.edu.sg/home/Sumod

Notes

The authors declare no competing financial interests.

ACKNOWLEDGMENT

We gratefully thank the Ministry of Education, Singapore for financial support and Nanyang Technological University for a research scholarship to Kennard.

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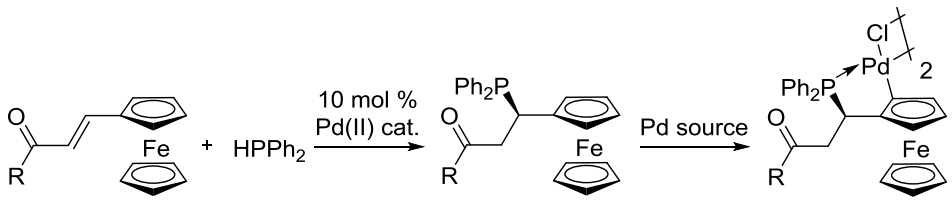
(11) Supporting Information Section 2.2. CCDC 991269.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