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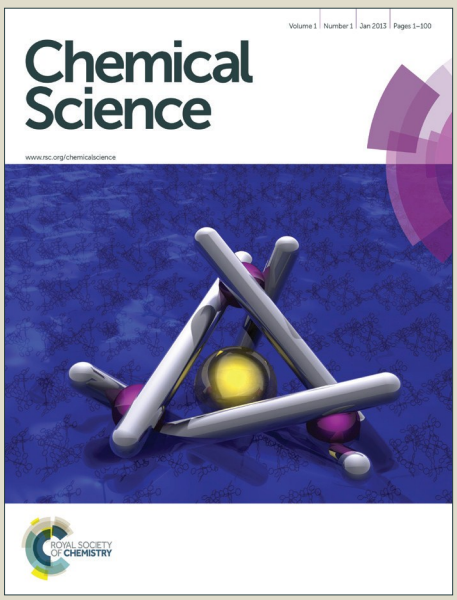

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ARTICLE

Ferrocenyl chiral bisphosphorus ligands for highly enantioselective asymmetric hydrogenation *via* the noncovalent ion pair interaction

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A new class of ferrocenyl chiral bisphosphorus ligands, Wudaphos, was developed, which exhibits excellent *ee* and activity (*ee* up to 99%, TON up to 20, 000) for the asymmetric hydrogenation of both 2-aryl and 2-alkyl acrylic acids through the ion pair noncovalent interaction under base free and mild reaction conditions. Well-known anti-inflammatory drugs such as Naproxen and Ibuprofen together with the intermediate for the preparation of Roche ester and some bioactive compounds were also efficiently obtained with excellent *ee*. Control experiments were conducted that revealed the ion pair noncovalent interaction and chain length played important roles.

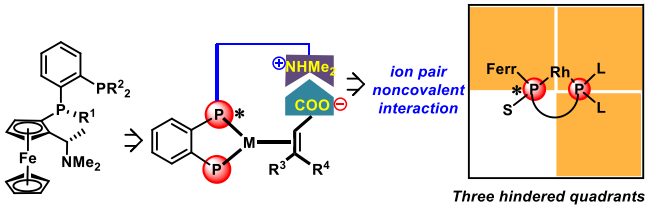
Introduction

Since 1960s, exploration of new efficient chiral phosphine ligands remains a continuous work for transition-metal catalyzed asymmetric reactions.[1] Development of new asymmetric reactions largely relies on the exploration of new efficient chiral phosphine ligands.[2] As a result, the research of developing more efficient and practical phosphine ligands in terms of excellent enantioselectivity and activity, good air stability, ease of preparation, remains highly desirable in asymmetric catalysis.

Table 1 Distance dependencies of the representative noncovalent interactions.

Entry	Noncovalent interaction	Energy dependence on distance
1	**Steric repulsion**	$1/r^{12}$
2	**H-bond**	Complicated ~ $1/r^2$
3	**Ion pair**	$1/r$

Attractive noncovalent interactions play a key role in the design of catalysis. Similar to the enzymatic catalysis, attractive noncovalent interactions are responsible for many of the remarkable rate accelerations and stereoselectivity improvements by lowering the kinetic barrows through the stabilization of the transition state and suppressing the degree of the freedom in the transition state.[3] Consequently, intensive research efforts have been directed toward the development of new efficient catalytic system utilizing attractive noncovalent interactions.[4] As summarized by Jacobson *et al.* (Table 1),[3] among the three representative noncovalent interactions, the steric repulsion is highly distance dependent ($1/r^{12}$) wherein weak interaction was observed with long distance. H-bond interaction ($1/r^2$) and ion pair interaction ($1/r$) are relatively less distance dependent and the ion pair interaction showed the strongest interaction. We anticipated that the strong ion pair noncovalent interaction can be utilized in the development of new efficient catalytic system for asymmetric hydrogenation (AH), wherein the substrates can interact with the catalyst strongly, accelerating the reaction rate to a large extent. However, few examples have been reported concerning of the strong ion pair noncovalent interaction and the substrate scope was limited.[5]



Scheme 1. The new ferrocenyl ligands and the corresponding model of the three hindered quadrants. L = large substitutent, S = small substitutent, Ferr = ferrocene.

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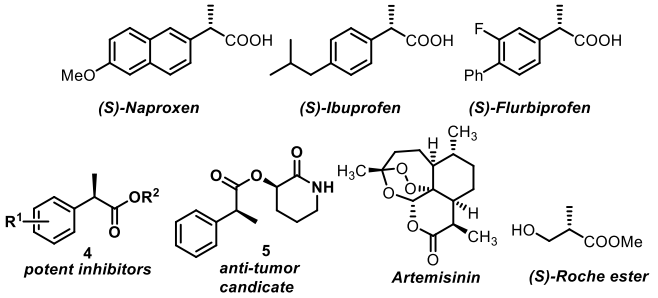
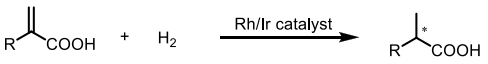
With regard to the utilization of the strong ion pair noncovalent interaction in the development of new chiral catalysts for AH, we found the Ugi's amine is a privileged motif in which the dimethyl amine moiety can play as a proton acceptor which can interact with the acid substrates strongly through the noncovalent ion pair interaction (Scheme 1). Moreover, the Ugi's amine motif can conveniently incorporate planar chirality, C-chirality and P-chirality into the catalytic system as exemplified by many efficient chiral ligands such as Josiphos,[6] Walphos,[7] Taniaphos,[8] Bophoz,[9] Mandyphos,[10] TRAP,[11] Trifer[5a] and Chenphos[5b]. Herein, we report a new class of bisphosphorus ligands incorporating the Ugi's amine motif (Scheme 1). *This type of bisphosphorus ligands possesses one chiral phosphine and the chiral Ugi's amine moiety. Two large substituents of the non-chiral phosphine together with the ferrocene backbone block three quadrants and the small substituent of the chiral phosphine makes the remaining quadrant open. This three blocked quadrant model is believed to have good chiral induction.*[12] Furthermore, *the dimethyl amine unit in the ligand can be a proton acceptor thus can interact with the acid substrates through the noncovalent ion pair interaction.* According to the above hypothesis, this catalytic system is believed to exhibit excellent enantioselectivity and activity in the AH of unsaturated acid substrates.



Scheme 2. Representative drugs and chemicals featuring the α-substituted propanoic acid moiety.

AH of 2-substituted acrylic acids will generate chiral α-substituted propanoic acids which are important units that widely exist in pharmaceuticals and fine chemicals (Scheme 2). Good examples are the well-known non-steroid anti-inflammatory and analgesic drugs such as naproxen, ibuprofen and flurbiprofen,[13] the esterification potent inhibitors **4** against the inflammatory phenotype of the cystic fibrosis (CF) lung disease,[14] the bioactive natural product **5** isolated from the Fusarium oxysporum which shows cytotoxicity against three human cancer cell lines PC-3, PANC-1 and A549,[15] and artemisnin[16] which is a famous drug against Plasmodium falciparum malaria that won the 2015 Nobel Prize in medicine. Furthermore, α-substituted propanoic acid can also be used to prepare the synthetically important Roche ester, a well-known synthon in total synthesis.[17] Although AH of 2-substituted acrylic acids was previously realized by chiral Ru catalysts,[18] the reactions were limited by the generally required high pressure. Chiral Rh and Ir catalysts have also recently been reported to realize this valuable transformation.[19] However, most of these catalytic systems need an equivalent base to neutralize the free acid.[19] This method is non-direct and needs additional procedure to remove the base. Herein we report a ferrocenyl catalytic system that can finely utilize the free acid *via* the attractive noncovalent ion pair interaction to realize this valuable transformation in a direct and concise way without any base with *ee* (enantiomeric excess) up to 99% and TON up to 20, 000 (Scheme 3).

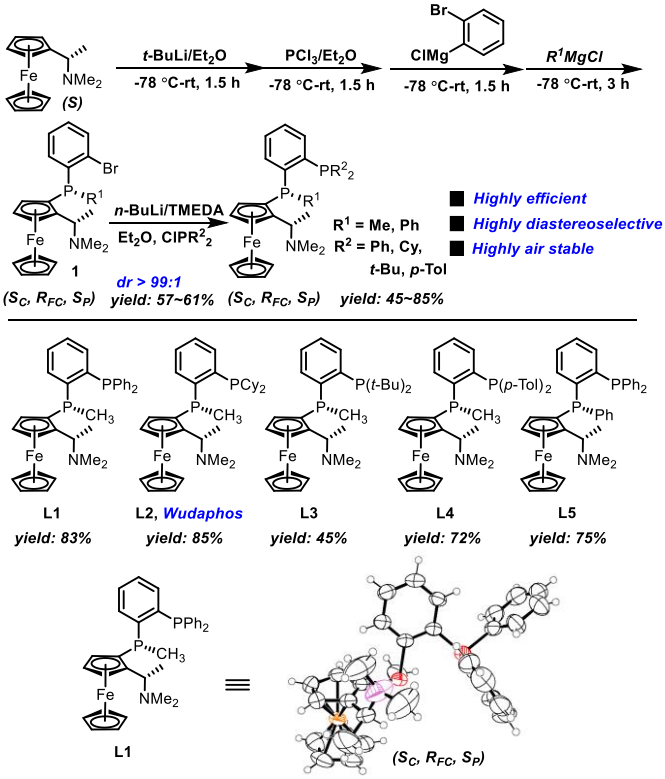


a) Previous work: equivalent base was essential

b) This work: direct hydrogenation through secondary interaction without any base

Scheme 3. AH of 2-substituted acrylic acids.

Results and discussion



Scheme 4. Synthesis of the ferrocenyl new bisphosphorus ligands.

The new ferrocenyl bisphosphorus ligands we report herein can be easily synthesized in two-pot with very high diastereoselectivity (dr > 99:1) (Scheme 4). Starting from (*S*)-Ugi's amine, one pot sequential reaction gave **1** efficiently. Importantly, compound **1** was obtained as a single diastereomer as determined by NMR which makes the synthesis to be very simple and practical. The subsequent lithiation followed by treating with different chlorophosphines afforded the desired ligands **L1**-**L5** in good yields. Moreover, the absolute configuration of **L1** was determined by X-ray spectrum analysis as (S_C, R_{FC}, S_p).[20] Importantly, ligands **L1-L5**

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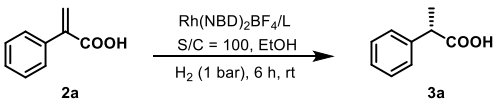
are all highly air stable even storing under air for more than one year.

With ligands **L1**-**L5** in hand, AH of 2-substituted acrylic acids was initiated by evaluating ligand effects using 2-phenyl acrylic acid **2a** as a model substrate (Table 2). We are pleased to find that the substrate was all smoothly converted except when using **L5** as the ligand (Table 2, entry 5) in the absence of any base. The hydrogenation results highly depended on the ligand structure. With **L1**, good *ee* was obtained (Table 2, entry 1). Changing the phenyl group in **L1** into cyclohexyl group (**L2**, Table 2, entry 2), the *ee* significantly increased to 98%. However, to our surprise, further changing the phenyl group into the steric bulky *t*-butyl group resulted in a very low *ee* and the product configuration was changed from (*S*) to (*R*) (**L3**, Table 2, entry 3). This is probably due to the much too big steric hindrance of the *t*-butyl group which influences the noncovalent ion pair interaction between the ligand and substrate. Further changing the phenyl group into the *p*-tolyl group resulted in decreased *ee* (**L4**, Table 2, entry 4). Using **L5** as ligand with a phenyl group instead of a methyl group attached to the chiral phosphine, the *ee* dropped significantly (**L5**, Table 2, entry 5). This result corresponds to the hypothesis we made that the ligand should have three blocked quadrants and make the remaining quadrant open in order to get good enatioselectivities (Scheme 1). In terms of the reactivity and enantioselectivity, **L2** was selected as the optimum ligand for the further investigation. Due to the remarkable performance, herein we name **L2** as Wudaphos.

Table 2 Ligand effects in the asymmetric hydrogenation of 2-phenyl acrylic acids.[a]



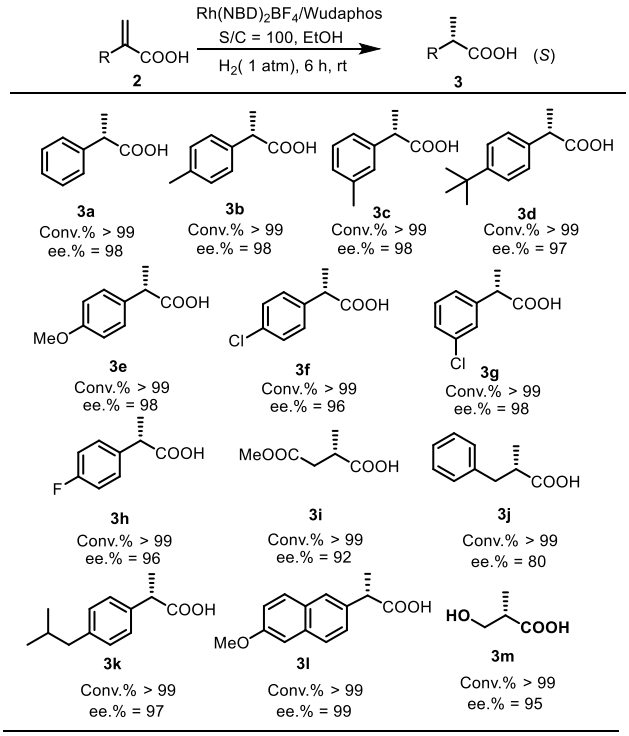
2a 3a

Entry	Ligand	Conv.%[b]	Ee%[c]	Configuration[d]
1	**L1**	> 99	84	(*S*)
2	**Wudaphos**	> 99	98	(*S*)
3	**L3**	> 99	33	(*R*)
4	**L4**	> 99	74	(*S*)
5	**L5**	67	57	(*S*)

[a] The reaction was conducted in 0.1 mmol scale in 1 mL of EtOH, $[Rh(NBD)_2]BF_4$ (NBD = norbornadiene) was used as metal precursor, S/C = 100, L/Rh = 1.1:1, temperature = rt, H_2 pressure = 1 bar, reaction time = 6 h. [b] Substrate conversion, determined by ^1H NMR. [c] enantiomeric excess of **3a**, determined by chiral HPLC after treating **3a** with CH_2N_2. [d] Configuration of **3a**, determined by comparing the optical rotation data with those reported by the literature.

Subsequently, substrate scope of the AH of 2-substituted acrylic acids was investigated using the optimum ligand Wudaphos under the best reaction conditions (For the screening of the reaction conditions and the discussion of the solvent effects, see supporting information). As listed in Table 3, 2-aryl acrylic acids were efficiently hydrogenated with excellent enantioselectivities under mild reaction conditions in the absence of any base regardless of whether the substituents on the phenyl ring were electron donating (Table 3, **3a**-**3e**), electron withdrawing (Table 3, **3h**), or halogen (Table 3, **3f**-**3h**). 2-Alkyl acrylic acids were also smoothly hydrogenated with high *ee* (Table 3, **3i**, **3j**, **3m**). Thus, the intermediate for the preparation of Roche ester was conveniently obtained in high *ee* (Table 3, **3m**). Furthermore, the well-known *anti*-inflammatory drugs ibuprofen and naproxen were also easily obtained in excellent *ee* under mild conditions (Table 3, **3k**, **3l**). Our catalyst system shows clear advance compared with the previous systems owing to its high enantioselectivity and base free conditions.

Table 3 Substrate scope using Wudaphos as the ligand. [a]



[a] The reaction was conducted in 0.1 mmol scale in 1 mL of EtOH, $[Rh(NBD)_2]BF_4$ (NBD = norbornadiene) was used as metal precursor, wudaphos was used as ligand, S/C = 100, L/Rh = 1.1:1, temperature = rt, H_2 pressure = 1 bar, reaction time = 6 h, the configuration of all the product was determined as (*S*) by comparing the optical rotation data with those reported by the literature, *ee* was determined by chiral HPLC after esterification with CH_2N_2, conversion of the substrates was determined by ^1H NMR.

Asymmetric hydrogenation of 2-substituted acrylic acids was also conducted with low catalyst loading using **2a** as a model substrate under 50 bar H_2 atmosphere. Satisfyingly, our catalyst system showed excellent activity under very mild condition in the absence of any base when the catalyst loading was 0.02 mol% (S/C = 5, 000) without any decrease of *ee* (Table 4, entry 1). Moreover, the hydrogenation also proceeded smoothly with full conversion and high *ee* when lowering the catalyst loading to 0.01 mol% (S/C = 10, 000, Table 4, entry 2) or 0.005 mol% (S/C = 20, 000, Table 4, entry 3) *albeit* with slight drop of *ee*. As shown in scheme 5, the potent inhibitors **4**[18] and the bioactive natural product **5**[19] can be readily synthesized following literature procedures starting from the hydrogenation product **3a**.

In order to gain more insights into this catalyst system, several

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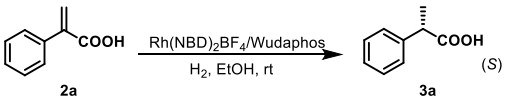
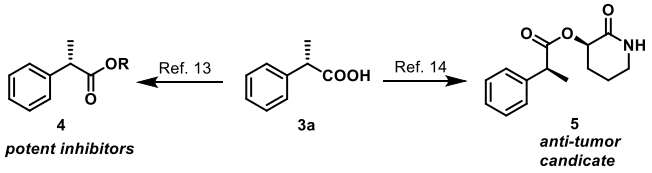
Table 4 TON experiment with Wudaphos as the ligand. [a]



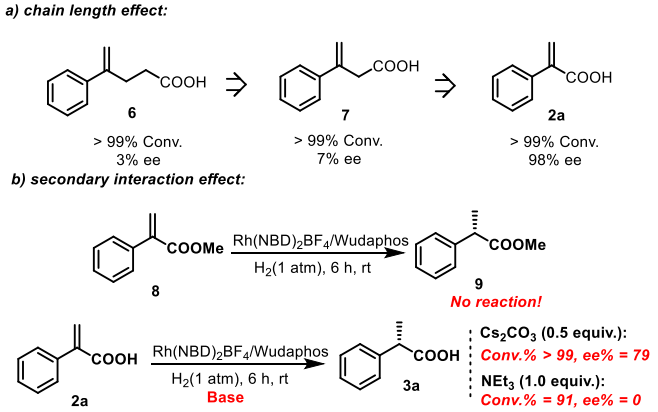
Entry	S/C	Time (h)	Conv.% [b]	Ee% [c]
1	5, 000	6	> 99	98
2	10, 000	12	> 99	97
3	***20, 000***	***24***	***> 99***	***96***

[a] The reaction was conducted in EtOH, $[Rh(NBD)_2]BF_4$ (NBD = norbornadiene) was used as metal precursor, wudaphos was used as ligand L/Rh = 1.1:1, temperature = rt, H_2 pressure = 50 bar. [b] Substrate conversion, determined by ^1H NMR. [c] enantiomeric excess of **3a**, determined by chiral HPLC after esterification with CH_2N_2.



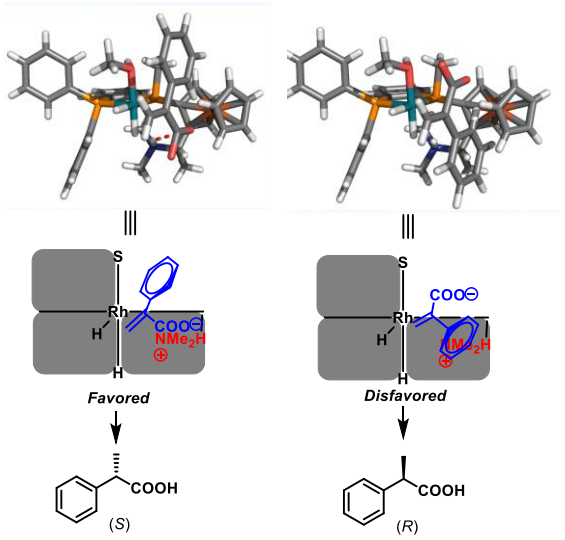
Scheme 5. Synthesis of the potent inhibitors **4** and the bioactive natural product **5**.

control experiments were also conducted. The effect of chain length between the olefin and the acid moiety was first investigated. It was found that chain length played an important role in determining the *ee*. Although hydrogenation of compounds **6**, **7** and **2a** all proceeded smoothly, the *ee* obtained in the hydrogenation of **6** and **7** was very low (Scheme 6), which indicated that excellent enantiomeric control was based on a matched chain length. Subsequently, the effect of the ion pair noncovalent interaction was also investigated. Hydrogenation of the ester substrate **8** didn't occur at all. The *ee* of the hydrogenation of **2a** also dropped evidently when adding 0.5 equivalent of Cs_2CO_3. Moreover, only racemic product was observed when one equivalent amount of triethylamine was added. It is probably due to the reason that the ion pair interaction between the ligand and substrate was interrupted by the additional base. These results suggested that the ion pair noncovalent interaction between ligand and acid substrates is critical (Scheme 6).



Scheme 6. Control experiments for the investigation of chain length effect and the ion pair noncovalent interaction effect.

On the basis of the observed (*S*)-enantioselectivity, the X-ray crystal structure of ligand **L1** (Scheme 1) and previous computational studies,[21] 3D models were built to account for the important roles of the ion pair interaction and the small substituent on the phosphine ligand (Scheme 7). The favorable ionic pair interaction is present and the phenyl group on the substrate experience a less repulsion with the phosphine ligand for the (*S*)-hydrogenation. Whereas, such ionic pair interaction cannot form and the phenyl group on the substrate has a larger repulsion with the ferrocenyl group for the (*R*)-hydrogenation. These 3D models also correspond to the hypothesis we made that the good enantiomeric control of the Wudaphos is based on the three hindered quadrant model.



Scheme 7. 3D models and the predicted enantiomeric control

Conclusions

In summary, a new class of ferrocenyl chiral bisphosphorus ligands, Wudaphos, was developed. The Wudaphos type ligands are highly air stable and exhibit excellent *ee* and activity (*ee* up to 99%, TON up to 20, 000) for the asymmetric hydrogenation of both 2-aryl and 2-alkyl acrylic acids. Importantly, the hydrogenation reaction was efficiently realized through the attractive ion pair noncovalent interaction in base free and mild reaction conditions, which shows clear advance compared with the previous catalytic system. Well-known anti-inflammatory drugs such as naproxen and ibuprofen together with the intermediate for the preparation of Roche ester and some bioactive compounds were efficiently obtained with excellent *ee*. Control experiments were conducted that revealed the ion pair noncovalent interaction played an important role and the excellent enantiomeric control was based on the matched chain length between the olefin and the acid moiety.

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20 The X-ray crystal data of **L1** has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 1456993. Copies of the data can be obtained, free of charge, on application to the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [Fax: +44 (1223)336033 or E-mail: deposit@ccdc.cam.ac.uk].

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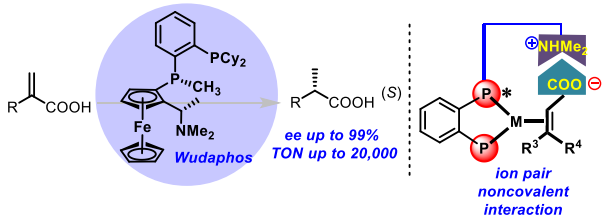

The new ferrocenyl bisphosphorus ligand, Wudaphos, was developed for highly enantioselective asymmetric hydrogenation based on the noncovalent ion pair interaction.