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ARTICLE TYPE

Palladium-Catalyzed Intramolecular Cp-H Bond Functionalization/Arylation: An Enantioselective Approach to Planar Chiral Quinilinoferrocenes

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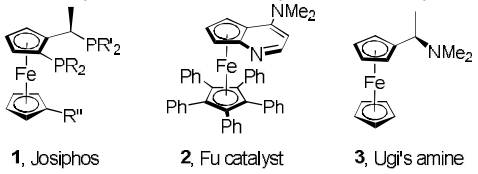
A palladium-catalyzed intramolecular asymmetric Cp-H functionalization/cyclization reaction to construct planar chiral quinilinoferrocenes was reported. The current investigation indicated that Carriera's *O*-PINAP ligands gave the best enantiomeric induction. The palladium-catalyzed reaction allowed a variety of chiral quinilinoferrocenes to be synthesized with broad functional group tolerance.

Ferrocenes, as well as other planar chiral molecules have recently attracted significant attention in the field of both synthetic chemistry, material science and bioorganometallic chemistry.[1] Ferrocene and its relative structures represent an important and privileged scaffold for some chiral ligands or catalysts, such as Josiphos[2] and Fu's catalysts (Figure 1, **1** and **2**).[3]

Since the first preparation of an optically active planar chiral ferrocene,[4] specially the development of diastereoselective synthesis of planar chiral ferrocenes from Ugi's amine (Figure 1, **3**),[5] numerous planar chiral based ligands and catalysts were developed. Nowadays ferrocene, as well as binaphthalene, spirobiindane have become three most successful scaffolds for ligands and catalysts in the area of asymmetric catalysis.

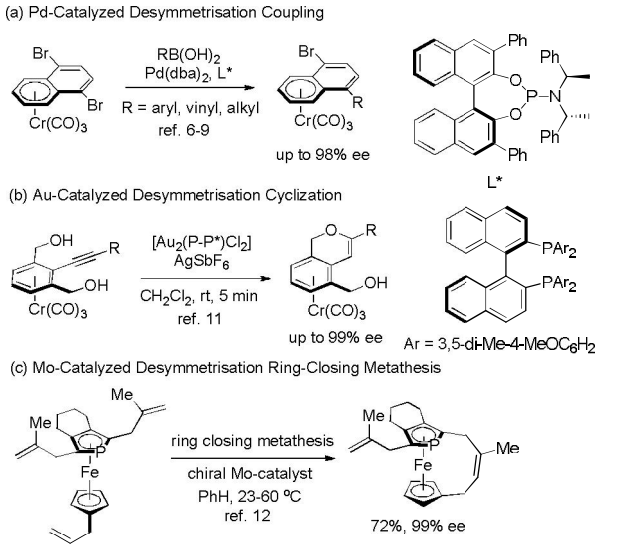


1, Josiphos **2**, Fu catalyst **3**, Ugi's amine

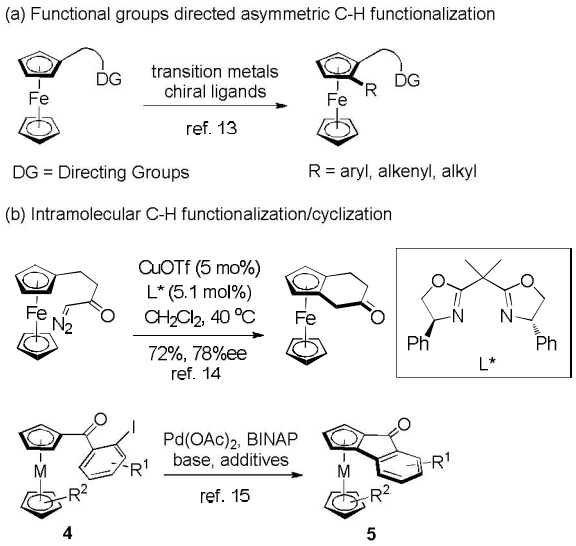
Figure 1. Representative Ferrocene-Based Planar Chiral Ligand, Catalyst, and the structure of Ugi's amine

Albeit the very success in preparation of chiral ferrocenes by the use of Ugi' amine or by introducing auxiliaries, catalytic asymmetric construction of planar chiral compounds has been continuously attracted by synthetic chemists recent years, since it provides a versatile, effective and economic strategy for the synthesis of these chiral molecules. Initial studies of palladium-catalyzed reactions focused on the desymmetrization of dihalogenated prochiral metallocenes by the groups of Uemura,[6] Schmalz,[7] Kündig,[8] and Richards (Scheme 1a).[9] Kündig and co-workers also described an organo-catalyzed desymmetrization acylation reaction of a chromium diol.[10] Asymmetric Au(I)-catalyzed alcohol-alkyne cyclization of chromium complexes was studied by Uemura and co-workers (Scheme 1b).[11] Ogasawara and Takahashi group synthesized a class of bridged planar chiral phosphaferrocenes by asymmetric alkene ring-closing metathesis,

Scheme 1. Construction of Planar Chiral Compounds by Transition Metal-Catalyzed Desymmetrization Reactions



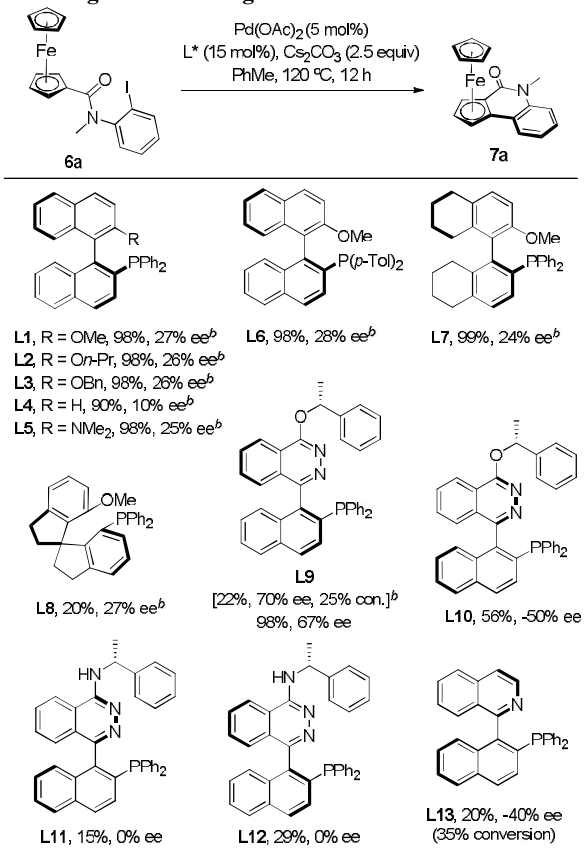
Scheme 2. Construction of Planar Chiral Compounds via Transition Metal-Catalyzed Asymmetric C-H Functionalization Strategy



where the phosphorus atom is essential for the achievement of high enantioselectivities (Scheme 1c).[12] Very recently, You, Wu and Shibata groups developed transition metal-catalyzed functional group directed Cp-H bond activation/C-C bond formation reactions to efficiently synthesize chiral ferrocenes (Scheme 2a).[13] Intramolecular carbenoids insertion reaction catalyzed by chiral copper complexes was successfully used to construct planar chiral ferrocenes, however the products were sensitive to oxidation upon exposure to air (Scheme 2b).[14] You and our groups successfully realized a palladium-catalyzed intramolecular Cp-H bond functionalization/arylation reaction, which delivered chiral ferrocenes and ruthenocenes **5** with high yields and excellent enantioselectivities (Scheme 2b).[15] Albeit these successful examples, development of new methods for catalytic asymmetric synthesis of planar chiral molecules with diverse skeletons, which are potentially applied in asymmetric catalysis is still urgent and necessary.

Following our research interests on the catalytically asymmetric synthesis of planar chiral compounds, we report here our studies on the palladium-catalyzed intramolecular cyclization toward the synthesis of optically active quinilinometallocenes.

Table 1. Ligands Screening[a]



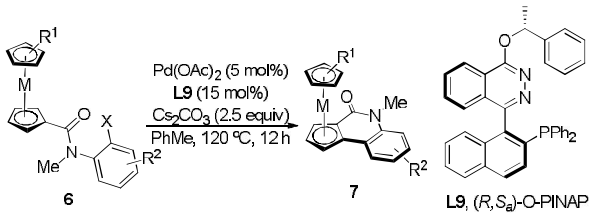
[a] The reaction was conducted on 0.10 mmol scale. The yields refer to the isolated yields, and the conversion was based on the crude ^{1}HNMR analysis. The absolute configuration of the product was not determined. [b] The reaction was conducted at 80 °C

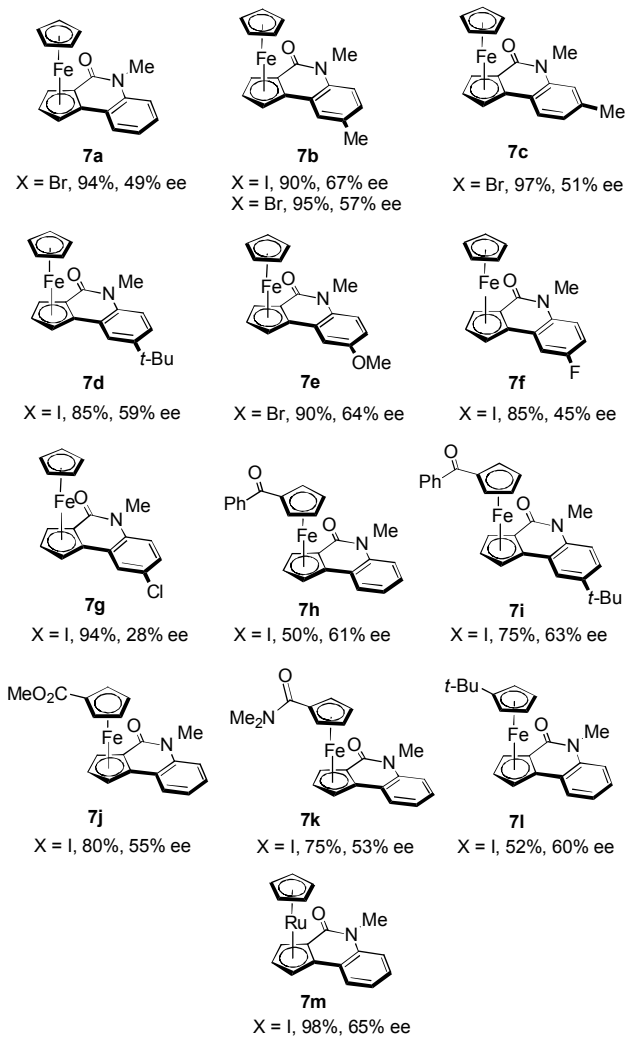
Initially we select **6a** as our modular substrate, which was readily obtained via the coupling of ferrocenecarboxylic acid chloride and the *N*-methyl-2-iodoaniline. To our surprise in sharp contrast the transformation from **4** to **5**, with all the screened bidentate phosphines or phosphine-oxazoline ligands including BINAP, Segphos, MeO-BIPHEP, Trost ligand, PHOX etc., only very trace amount of product could be detected and most of the starting material was recovered. With binaphthalene based monodentate ligands **L1**-**L5**, high yields were obtained while the enantioselectivities were only ranged from 10 to 27% at 80 °C. Increasing the steric size on the P-atom, such as **L6** did not affect either the yield or the enantioselectivity.. The cyclization reaction by utilizing the ligand (8H)-MOP **L7** afforded a slightly lower ee to **7a**, while the spiro ligand **L8** only gave a low conversion. Carreira's PINAP serial of ligands were also screened, it was found that the enantioselectivity was increasing to 70% when (*R,S*$_a$)-*O*-PINAP **L9** was used at 80 °C albeit with low conversion.[16] Increasing the reaction temperature to 120 °C led to significantly increasing the isolated yield while slightly affects the enantioselectivity. The addition of silver salt, such as $AgBF_4$, $AgSbF_6$, or pivalic acid as intramolecular proton abstraction species was found to be no beneficial for enantioselectivity. Reactions in toluene using the diastereomer **L10** [(*R,R*$_a$)-*O*-PINAP] led to the formation of **7a** in 56% yield and -50% ee. Upon further examination we found that toluene is the optimum solvent for this cyclization reaction.[17] We observed that (*R,R*$_a$)-*N*-PINAP **L11** and (*R,S*$_a$)-*N*-PINAP **L12** were not good ligands for this transformation. For comparison the reaction by the use of (*S*)-QUINAP (**L13**) as ligand was also investigated, and only 35% conversion and low enantioselectivity was observed.

With the optimized reaction conditions in hand, the generality of this intramolecular cyclization reaction was investigated regarding both the electronic and steric properties of the substrates (Table 2). By the use of bromides in lieu of iodides, the reactions delivered the products with slight decreased ee values (Table 2, **7a** and **7b**). Substituents on the aniline moiety could be 4-methyl, 3-methyl, 4-*tert*-butyl and 4-methoxyl groups, and the reactions afforded the corresponding products in good yields and moderate enantioselectivities (**7b-e**). With 4-halo-2-iodoaniline derivatives, the ee of the products was significantly dropped (**7f-g**), for instance the reaction with 4-chloro-2-iodoaniline derivative as substrate afforded **7g** in only 28% ee. Both electron-withdrawing and electron-donating groups on the second Cp ring are well tolerated and generally moderate good yields and enantioselectivities could be achieved (**7h-l**). Bis(cyclopentadienyl) ruthenium derivative **6m** was also an effective substrate, and the corresponding reaction gave **7m** in excellent yield and 65% ee.

During the studies, we found that **6n** and **6o** are much less effective substrates for this transformation, and low conversions (<50%) were observed (Scheme 3). For instance, the reaction of **6n** gave **7n** in 42% isolated yields even though with an excellent enantioselectivity. Interestingly, the addition of PivOH could significantly increase the yield, while the ee was dropped dramatically. However, for compound **6o** there is no great benefit on conversion while the enantioselectivity was dropped to 16%.

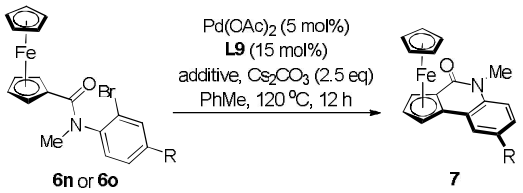
Table 2. Substrate Scope[a]





[a]The reactions were conducted on a 0.10 mmol scale of **6**; for details see the Supplementary Information.

Scheme 3. The effects by the addition of PivOH



Additive	R = CN (**7n**)	R = OCF_3 (**7o**)
no	42%, 88%ee [48% conversion]	33%, 48%ee [40% conversion]
PivOH (30 mol%)	98%, 4%ee	42%, 16%ee [45% conversion]

Conclusions

In summary we have studied a palladium-catalyzed asymmetric intramolecular Cp-H bonds functionalization/cyclization reaction of 2-halophenyl ferrocenecarboxylic amides. These substrates showed significant different reactivity in comparison with our previous results, and a new catalytic system, $Pd(OAc)_2/(R,S_a)$-*O*-PINAP, was developed to enantioselectively synthesize the planar chiral quinilinoferrocenes. The reaction provided an efficient way for the construction of planar chiral compounds with new skeletons.

Acknowledgment

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