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Enantioselective palladium-catalyzed C–H functionalization of pyrroles using an axially chiral 2,2′-bipyridine ligand†

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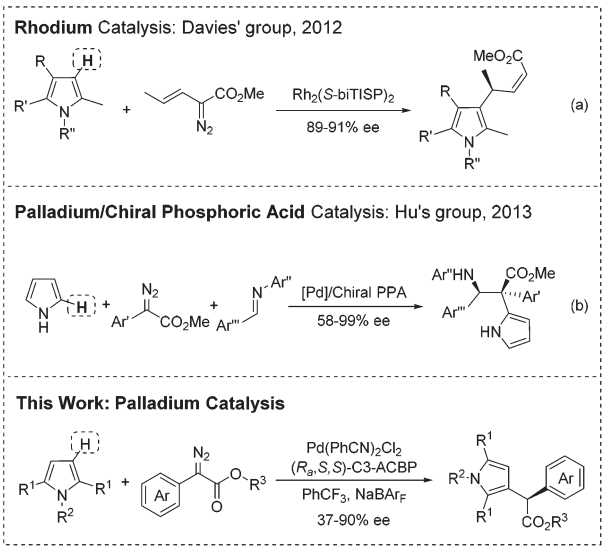
An enantioselective C–H functionalization of pyrrole derivatives with diazo compounds has been successfully realized with up to 90% ee by employing dichlorobis(benzonitrile)palladium with an axially chiral bipyridine ligand C3-ACBP as the catalyst. Asymmetric C–H functionalization at the gram scale was also conducted smoothly with good reactivity and enantioselectivity.

Chiral pyrrole derivatives are widely distributed in natural products and biologically active molecules, such as heme, chlorophyll and pyrrole alkaloids.[1] To construct the chiral pyrrole skeletons, direct functionalization of simple and commercially available pyrroles is considered to be the most convenient approach. However, compared to the advances in asymmetric functionalization of indoles,[2,3] such an approach with pyrrole is rather difficult, mainly for the following reasons. Firstly, the pyrrole derivatives are relatively unstable under acidic reaction conditions.[4] In addition, the stereoselective control of pyrrole functionalization is also challenging because of weak steric interactions with chiral catalysts owing to its inherent smaller size.

So far, the most widely used approach is enantioselective Friedel–Crafts reactions of pyrrole using chiral transition-metal catalysts or organocatalysts.[5] An alternative approach is the asymmetric functionalization of pyrrole with metal carbenoid intermediates generated by metal-catalyzed decomposition of diazo compounds which have played a crucial role in organic chemistry as versatile synthetic intermediates.[6,7] Some catalytic systems of asymmetric cyclopropanation of pyrroles with metal carbenoids have been successfully realized for the construction of chiral pyrrole derivatives.[8] Compared to the cyclopropanation of pyrrole derivatives, only a few examples of asymmetric C–H insertion of pyrroles with carbenoids have been reported (Scheme 1). In 2012, the rhodium-catalyzed asymmetric vinylogous alkylation between pyrrole and methyl (*Z*)-2-diazo-3-pentenate has been reported by Davies group,



Scheme 1 Asymmetric C–H functionalization of pyrroles catalyzed by chiral metal complexes.

providing an effective method for C-3 functionalization of pyrroles with good levels of enantioselectivity.[9] In addition, Hu and co-workers have discovered three-component reactions of pyrrole, diazoesters, and imines using palladium/chiral phosphoric acid as the catalyst, providing a facile access to chiral pyrrole derivatives in moderate yields with high control of diastereo- and enantioselectivities.[10] Despite the progress made recently, developing novel and compatible catalytic systems for the asymmetric functionalization of pyrroles by metal carbenoids is still highly desirable.

Palladium is an indispensable and versatile metal in modern organic synthesis.[11] The palladium-catalyzed carbene transfer reactions based on migratory insertion provide an efficient and straightforward access to desired molecules.[12]

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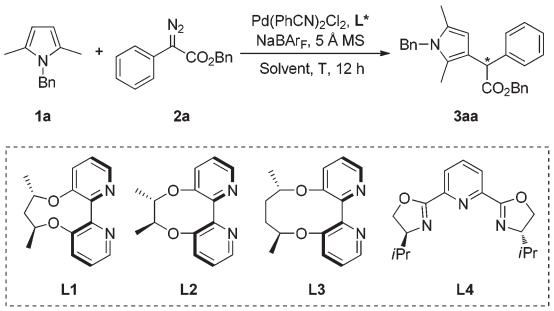
Some efficient catalytic systems have been developed and applied in palladium-catalyzed asymmetric carbene transfer reactions by several groups.[10,13] Recently, a series of axially chiral 2,2′-bipyridine ligands developed by our group have been applied in transition metal-catalyzed asymmetric carbene transfer reactions including enantioselective C–H functionalization of indoles, insertion of O–H.[14] As an extension to our efforts in application of chiral 2,2′-bipyridine ligands,[15] we report herein a palladium-catalzyed asymmetric C–H functionalization of pyrroles with α-aryl-α-diazoacetates, the reaction occurs at the C3 position of pyrrole derivatives with up to 90% of enantioselctivity.

At the outset of this study, 1-benzyl-2,5-dimethyl-1*H*-pyrrole **1a** and benzyl α-phenyl-α-diazoacetates **2a** were employed as model substrate to study the asymmetric C–H functionalization of pyrrole as shown in Table 1. Initial examinations began with solvents, under the catalysis of $Pd(PhCN)_2Cl_2$/(*R*$_{ax}$,*S*,*S*)-C3-ACBP in dichloromethane at 30 °C, the reaction occurred in 68% ee and 88% yield in 12 h (entry 1). However, the reaction conducted in THF with poor reactivity (entry 2). A slightly better enantioselectivity was observed in toluene, benzene, and $CHCl_3$ (entries 3–5). Solvent screening revealed that $PhCF_3$ was optimal (entry 6). Subsequently, to further improved the reactivity and enantioselectivity, the effect of temperature was examined. Fortunately, elevation of the reaction temperature to 40 °C, the ee increased to 86% (entry 7). When temperature increased to 50 °C, the yield and ee value obviously decreased to 77% and 62%, respectively (entry 8). Therefore, we selected 40 °C as the optimal temperature.

Table 1 The evaluation of reaction parameters[a]



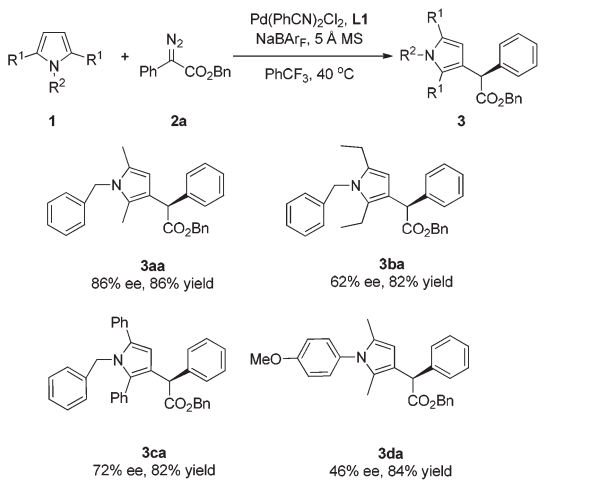
Entry	Solvent	*T* (°C)	L*	Yield[b] (%)	ee[c] (%)
1	DCM	30	**L1**	88	68
2	THF	30	**L1**	<5	—
3	Toluene	30	**L1**	83	79
4	Benzene	30	**L1**	84	72
5	$CHCl_3$	30	**L1**	62	77
6	$PhCF_3$	30	**L1**	84	85
7	$PhCF_3$	40	**L1**	86	86
8	$PhCF_3$	50	**L1**	77	62
9	$PhCF_3$	40	**L2**	85	85
10	$PhCF_3$	40	**L3**	90	83
11	$PhCF_3$	40	**L4**	83	20

[a] Conditions: **1a** (0.3 mmol), **2a** (0.2 mmol), $Pd(PhCN)_2Cl_2$ (5 mol%), **L** (6 mol%), $NaBAr_F$ (12 mol%), solvent (2 mL), 5 Å MS (200 mg), 12 h. [b] Isolated yields. [c] Determined by chiral HPLC.

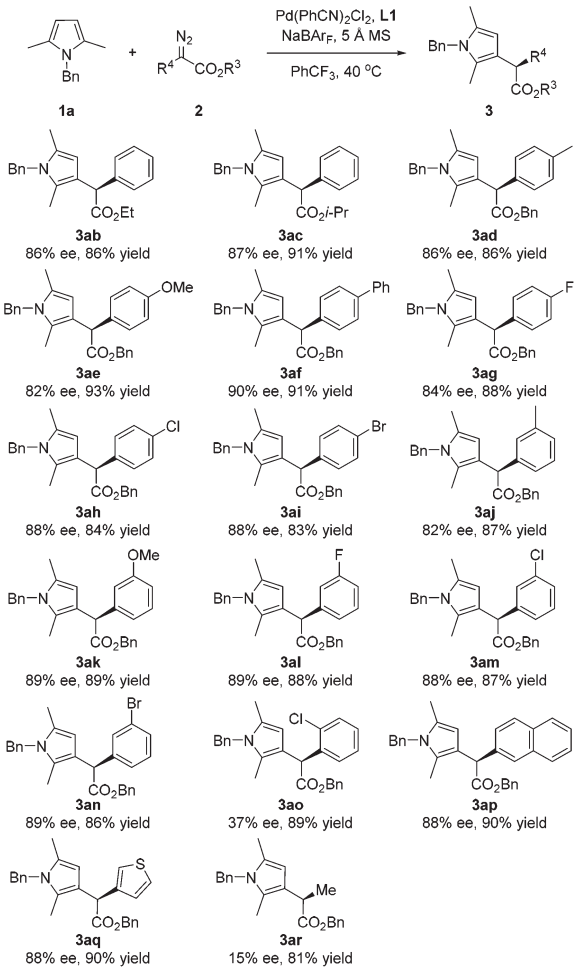
Intrigued by the above results, some chiral ligands including bipyridines ligand designed by our group and pyridine-oxazoline were explored (Table 1). (*R*$_{ax}$,*S*,*S*)-C2-ACBP **L2** gave the desired product **3aa** with slightly lower ee value and yield (entry 9). The (*R*$_{ax}$,*S*,*S*)-C4-ACBP **L3** was proved to be beneficial for the reactivity, albeit comparatively low enantioselectivity was observed (entry 10). A commercially available pyridine-oxazoline ligand **L4** was also tested (entry 11), furnishing the desired product with poor 20% ee. Given the reactivity and enantioselectivity of this reaction, we selected (*R*$_{ax}$,*S*,*S*)-C3-ACBP **L1** as the optimal ligand.

To further improve the enantioselectivity, we investigated the influence of the structure of the pyrrole derivatives (Scheme 2). Initially, selecting more steric 1-benzyl-2,5-diethyl-1*H*-pyrrole as the substrate, the ee value decreased to 62% (**3ba**). This result indicated that the carbon number of alkyl chain of R_1 has conspicuous influence on the enantioselectivity of this reaction. Subsequently, replacing the alkyl group with phenyl group, disappointedly, the ee value also decreased to 72% (**3ca**). In addition, the 4-methoxyphenyl protected pyrrole proceeded smoothly with good yield, but the ee value sharply dropped to 46% (**3da**). Considering the above results, we still selected the 1-benzyl-2,5-dimethyl-1*H*-pyrrole **1a** as the optimal substrate to test reaction generality.

With the optimal conditions in hand, we turned our attention to explore C–H functionalization of a wide array of diazo substrates (Scheme 3). As expected, various diazo substrates performed very well under the standard reaction conditions. Firstly, the reaction conducted smoothly for diazoacetates bearing different ester groups, providing the corresponding products in 86–87% ees and 86–91% yields (**3aa–3ac**). Subsequently, the diazoesters bearing a variety of substituted aromatic groups were examined. The influence of the steric groups and electronic properties of substituents on the phenyl rings was exploited. The results indicated that this protocol



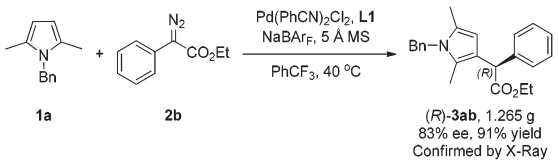
Scheme 2 The evaluation of pyrrole derivatives. Conditions: **1** (0.3 mmol), **2a** (0.2 mmol), $Pd(PhCN)_2Cl_2$ (5 mol%), **L1** (6 mol%), $NaBAr_F$ (12 mol%), $PhCF_3$ (2 mL), 5 Å MS (200 mg), 40 °C, 12 h.



Scheme 3 Substrate scope with respect to diazoacetates. Conditions: **1a** (0.3 mmol), **2** (0.2 mmol), $Pd(PhCN)_2Cl_2$ (5 mol%), **L1** (6 mol%), $NaBAr_F$ (12 mol%), $PhCF_3$ (2 mL), 5 Å MS (200 mg), 40 °C, 12 h.

was compatible with electron-donating as well as electron-withdrawing groups at the *para*-position of the phenyl ring of **2**, delivering the corresponding products in good yields and high enantioselectivities (**3ad–3ai**). It was noted that the best result of 91% yield with 90% ee was obtained when the 4-phenyl group was introduced (**3af**). The substituents at the *meta*-position of phenyl ring of **2** were tolerable (**3aj–3an**). Unfortunately, for the sterically hindered substrate **3ao** with an *ortho*-chloride group, the ee value sharply dropped to 37%. For the 2-naphthyl substituted diazoacetates, 88% ee was obtained (**3ap**). In addition, heteroaromatic thienyl substituted diazoacetates could perform smoothly, giving the corresponding product (**3aq**) with 88% ee. To our disappointment, when the alfa-alkyl substituted benzyl 2-diazopropanoate **2r** was used, the ee value sharply dropped to 15% (**3ar**).

Moreover, to further demonstrate the practicality of this methodology, the gram scale reaction was conducted, giving the desired product in 91% yield and slightly lower enantioselectivity (83% *vs.* 86%, Scheme 4). The absolute configuration of the product **3ab** was unambiguously assigned to be R



Scheme 4 Gram-scale experiment.

by X-ray crystallographic analysis after a simple recrystallization with ethyl acetate and *n*-hexane.

Conclusion

In summary, we have developed an efficient method for synthesis of optically active C-3 functionalization of pyrroles through palladium-catalyzed enantioselective C–H functionalization of pyrroles with an axially chiral bipyridine ligand C3-ACBP. A variety of chiral 2,3,5-trisubstituted pyrrole derivatives were readily obtained in good yields with up to 90% ee. This protocol further extended the application of Cn-ACBP bipyridine ligands. Further applications of the Cn-ACBP bipyridine ligands in other catalytic asymmetric reactions are undergoing in our laboratory and will be reported in due course.

Experimental

A typical procedure for enantioselective C–H functionalization

The powdered $Pd(PhCN)_2Cl_2$ (3.8 mg, 0.01 mmol), (R_a,*S*,*S*)-C3-ACBP **L1** (3.1 mg, 0.012 mmol), $NaBAr_F$ (21.3 mg, 0.024 mmol) and 5 Å molecular sieves (200 mg) were introduced into an oven-dried Schlenk tube under nitrogen. After benzotrifluoride (2.0 mL) was injected into the Schlenk tube, the solution was stirred at 40 °C under nitrogen for 2 h. Protected pyrroles **1a** (55.6 mg, 0.3 mmol) and α-phenyl-α-diazoactates **2a** (50.5 mg, 0.2 mmol) were then introduced in one portion. The resulting mixture was stirred at 40 °C until the full consumption of **2a**. After filtrating and removing solvent in vacuum, flash chromatography on silica gel using *n*-hexane/ethyl acetate (40/1) as the eluent gave the product **3aa** as yellow oil (71 mg, 86% yield, 86% ee). Enantiomeric excess was determined by HPLC (OD-H column, *n*-hexane/i-PrOH 80/20, 0.7 mL min^{-1}, 254 nm), 30 °C, t_1 = 9.7 min (maj), t_2 = 10.9 min.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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