Communication

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Pd-Catalyzed Asymmetric Allylic Alkylation of Pyrazol-5-ones with Allylic Alcohols: the Role of Chiral Phosphoric Acid in C-O Bond Cleavage and the Stereocontrol

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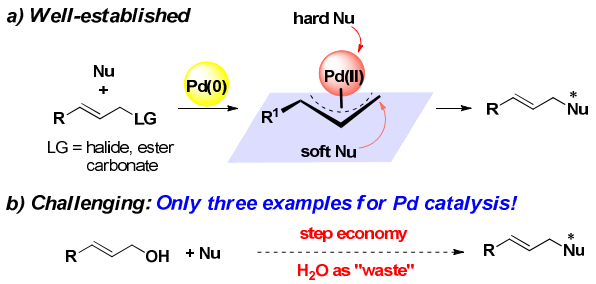
Supporting Information

ABSTRACT: A combination of palladium complex of chiral phosphoramidite and chiral phosphoric acid enables allylic alcohols to undergo a highly efficient asymmetric allylic alkylation of pyrazol-5-ones for the first time, affording multiply functionalized heterocyclic products in high yields and with excellent enantioselectivities that would be of great potential in the synthesis of pharmaceutically interesting molecules.

Asymmetric catalytic reactions involving C-C bond formation have allowed synthetic access to biologically important molecules, among which, the asymmetric allylic alkylation (AAA)[1] has long been intensely studied for its diversity of bond-forming types and extensive applications in total synthesis. For most of the history of Pd-catalyzed AAA reactions, activated precursors of π-allyl fragments, such as allylic halides, esters and carbonates, have dominantly been employed to accept the nucleophilic attack of soft or hard nucleophilies (Figure 1, a). Nowadays, the environmental issues have drawn much attention that alternative sustainable processes are becoming more and more privileged, especially in the field of synthetic chemistry.[2] For this reason, allylic alcohols are considered as promising allylic component in AAA reaction because of their wide synthetic reliability and step economy.[3] However, the hydroxy is known to be a poor leaving group to presumably obstruct the practical use of allylic alcohols in allylic alkylation, particularly the enantioselective variants (Figure 1, b). The external activators, including Lewis acids[1c, 4] and Brønsted acids[1c,5,7] have been explored to circumvent this formidable challenge. Trost first introduced triethylborane to assist the palladium to break C-O bond, resulting in the AAA reactions of soft nucleophiles with allylic alcohols.[4a] Recently, List established an AAA reaction of α-enolizable aldehydes with allyl alcohols using ACDC strategy,[7] in which a catalytic amount of chiral phosphoric acid was able to facilitate the oxidative addition of palladium to allylic alcohols and to solely control the stereochemistry as well (Scheme 1, eq 1). Despite of these important advances, the rejuvenation of AAA reaction can still be anticipated by creating new strategy capable of overcoming is-

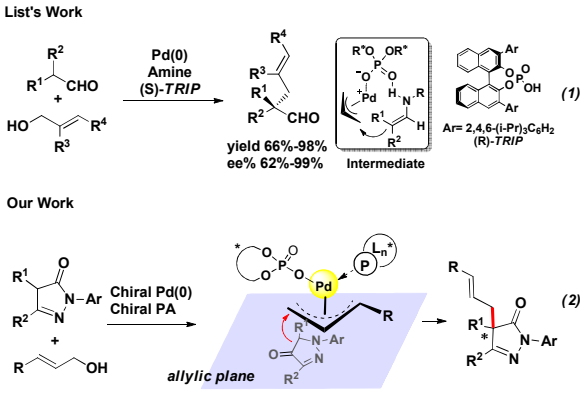
Figure 1. The profile of AAA reaction



sues associated with limited nucleophile/allyl alcohol pairs in current processes.

Efficient assembly of optically pure multi-functionalized heterocyclic compounds, especially those with quaternary stereocenters,[8] is challenging but would be of great importance. Recently, pyrazol-5-one-derived enantiomers have drawn much attention because they appear prevalently in a collection of non-steroidal anti-inflammatory drugs,[9] such as Analgin, Nifenazone, and Feprazone, leading to an increasing demand for the efficient syn-

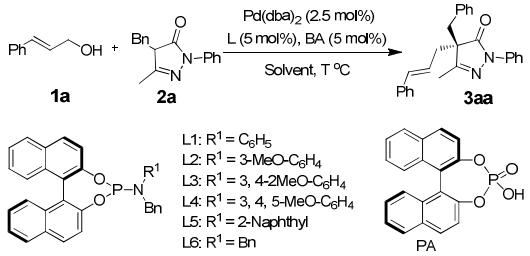
Scheme 1. The combination of Pd(0)/chiral ligand complex and chiral Brønsted acid



thetic methods. As a result, enantioselective functionalization of

pyrazol-5-ones has already been investigated.[10] However, no asymmetric alkylation of pyrazol-5-ones has been available, yet. Herein, we report the first asymmetric allylic alkylation of pyrazol-5-ones using allylic alcohol directly as a reaction component, which was achieved by the combination of palladium complex of chiral phosphoramidite[11] and chiral phosphoric acid.[12] In this protocol, the chiral phosphoric acid facilitates the formation of π-allylic-Pd complex by activation of C-O bond. Moreover, a remarkable synergistic effect between ligand and counteranion was observed (Scheme 1, b).

Table 1. Investigation of Ligands and Brønsted acid[a]

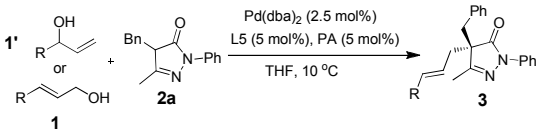


entry	L	BA	Solvent	T(°C)	yield (%)[b]	ee (%)[c]
1	L1	PA	toluene	25	72	49
2	L2	PA	toluene	25	86	77
3	L3	PA	toluene	25	88	88
4	L4	PA	toluene	25	78	78
5	L5	PA	toluene	25	85	90
6	L6	PA	toluene	25	25	84
7	L5	(S)-PA	toluene	25	80	81
8	L5	PA	Et_2O	25	91	90
9	L5	PA	CH_2Cl_2	25	17	76
10	L5	PA	THF	25	89	91
11	**L5**	**PA**	**THF**	**10[d]**	**86**	**94**
12	L5	PA	THF	0[e]	50	92
13	L5	TFA	THF	10[d]	58	84
14	L5	*p*-TSA	THF	10[d]	18	84
15	L5	-	THF	10[d]	-	-

[a]Unless indicated otherwise, reactions of **1a** (0.12 mmol), **2a** (0.10 mmol), $Pd(dba)_2$ (0.0025 mmol), **BA** (0.005 mmol) and **L** (0.005 mmol) were carried out in 2 mL solvent for 16h. [b]Isolated yield. [c]Determined by HPLC analysis. [d]The reaction was carried out for 36 h. [e]The reaction was carried out for 48h.

We initially endeavored to develop a chiral counteranion-directed AAA reaction using cinnamic alcohol **1a**[7] and pyrazol-5-one **2a** as substrates, but the results were disappointing.[13] We then turned our attention to a combination of chiral phosphoric acid (PA) and easily available binol-derived chiral phosphoramidite ligands that possess axial chirality only (Table 1, entries 1 - 6). To our delight, the use of PA and L1 allowed the formation of the alkylation product **3a** in 72% yield, with a promising 49% ee (entry 1). Afterwards, various different electronic effect-related substituents on the aniline moiety of ligands were investigated and the enantioselectivity was substantially enhanced to 90% ee, in 85% yield (entry 5). Notably, the (*S*)-PA was tested to give lower enantioselectivity than its enantiomer, suggesting that the (*R*)-PA acted as the matched co-catalyst (entry 7). The examination of solvents proved that THF fitted the reaction best (entries 8 - 10). As one of the determining factors, appropriate lower temperature (10 °C) was beneficial to the stereochemical control (94% ee) with no significant erosion of yield (86%) (entries 11 and 12). Moreover, two typical achiral Brønsted acids, TFA (trifluoroacetic acid) and p-TSA (p-toluenesulfonic acid), were employed as activators to replace chiral phosphoric acid, but they gave much worse results in terms of yield and enantioselectivity under otherwise identical conditions (entries 13 and 14 vs 11), which suggested the indeed existence of the cooperative effect between the chiral ligand and counteranion.[14] Finally, the decisive role of Brønsted acid in C-O bond cleavage would be convinced by the fact that no starting materials were consumed when Pd(0) complex was used alone (entry 15).

Table 2. Scope for allylic alcohols[a]



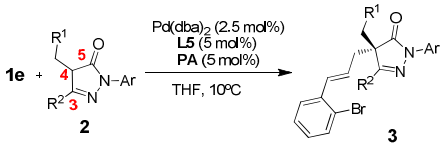
entry	1/1'	R	3	Yield(%)[b]	ee(%)[c]
1	**1b**	2-$MeOC_6H_4$	**3ba**	98	91
2	**1c**	3-$MeOC_6H_4$	**3ca**	95	93
3	**1d**	4-$MeOC_6H_4$	**3da**	97	90
4	**1e**	2-BrC_6H_4	**3ea**	86	96
5	**1f**	3-BrC_6H_4	**3fa**	99	95
6	**1g**	4-BrC_6H_4	**3ga**	95	95
7	**1h**	4-FC_6H_4	**3ha**	95	95
8	**1i**	2-$NO_2C_6H_4$	**3ia**	99	96
9	**1j**	$(CH_2)_8CH_3$	**3ja**	81	90
10	**1k**	Me	**3ka**	81	91
11	**1l**	n-Pr	**3la**	77	85
12	**1′**	4-MeC_6H_4	**3a′**	94	91

[a]Unless indicated otherwise, reactions of **1** (0.12 mmol), **2a** (0.10 mmol), $Pd(dba)_2$ (0.0025 mmol), **L5** (0.005 mmol) and **PA** (0.005 mmol) were carried out in 2 mL THF for 36 h. [b]Isolated yield. [c]Determined by HPLC analysis.

This combined strategy for AAA reaction was then subject to a rigorous test of substrates scope (Table 2). First of all, a series of functionalized allylic alcohols were examined when **2a** was used as the nucleophile, furnishing the corresponding products **3ba** - **3ka** in 81% - 98% yield and 90% - 96% ee (entries 1-10). This

protocol tolerated a range of substituents on the phenyl moiety of allylic alcohols **1**, including those bearing either of electronically donating, neutral or withdrawing substituents. Basically, the relatively electron-deficient cinnamic alcohols (**1e-1i**, entries 4 - 8) always performed better in stereochemical control than the relatively electronically neutral or rich ones (**1b - 1d**, **1′**, entries 1-3, 10). Notably, the bromide was surprisingly well tolerated under this Pd(0) catalysis (entries 4-6). Besides, under the optimized conditions, aliphatic allylic alcohol **1j** – **1l** and a branched substrate **1′** could also be able to afford the allylic adducts **3ja** – **3la** and **3a′** with excellent outcomes (entries 9 -12). The configuration of **3fa** was determined by X-ray analysis of its crystal (see Supporting Information).

Table 3. Scope for Pyrazol-5-ones[a]



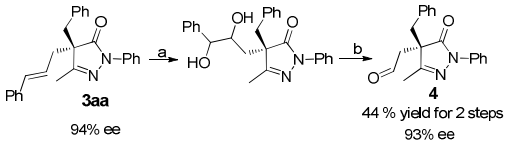
Entry	**2**[b]	R^1	R^2	**3**	Yield (%)[c]	ee (%)[d]
1	**2b**	Ph	Ph	**3eb**	81	66
2	**2c**	Ph	*n*-Pr	**3ec**	97	95
3	**2d**	Ph	*i*-Pr	**3ed**	96	88
4	**2e**	Ph	Et	**3ee**	85	95
5	**2f**[e]	Ph	Me	**3ef**	99	97
6	**2g**	2-FC_6H_4	Me	**3eg**	98	96
7	**2h**	3-FC_6H_4	Me	**3eh**	93	95
8	**2i**	4-FC_6H_4	Me	**3ei**	92	96
9	**2j**	2-$MeOC_6H_4$	Me	**3ej**	99	96
10	**2k**	4-$MeOC_6H_4$	Me	**3ek**	96	95
11	**2l**	α-Naph	Me	**3el**	89	94
12	**2m**	2-thienyl	Me	**3em**	99	97
13	**2n**	Me	Me	**3en**	74	94
14	**2o**	H	Me	**3eo**	90	97
15	**2p**	Ph	H	**3ep**	60	92

[a]Unless indicated otherwise, reactions of **1e** (0.12 mmol), **2** (0.10 mmol), $Pd(dba)_2$ (0.0025 mmol), L5 (0.005 mmol) and PA (0.005 mmol) were carried out in 2 mL THF for 36h. [b]Unless indicated otherwise, Ar = Ph. [c]Isolated yield. [d]Determined by HPLC analysis. [e]Ar = 4-Cl-C_6H_4.

The following test for the generality of pyrazol-5-ones **2** was then conducted (Table 3). The excellent stereocontrol was keenly awake to the change of substituents at C3-position of pyrazol-5-ones. As a consequence, the replacement of methyl with phenyl or hindered i-propyl led to lower levels of enantioselectivity, while n-propyl, ethyl and H could keep the enantioselectivity at similar or even higher levels (entries 1-4, 15). One of the best results was obtained by introducing a Cl on the benzene ring of aniline moiety (99% yield, 97% ee; entry 5). Notably, this chiral ligand/conteranion combined strategy allowed a diverse spectrum of substituents at C4-position of pyrazol-5-ones to afford the corresponding products in high yields and with excellent enantioselectivities (74%-99% yield, 94%-97% ee; entries 6 – 14).

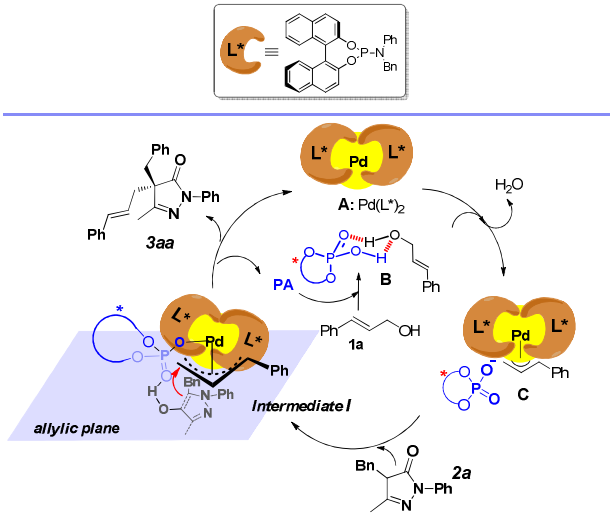
The allylic alkylation products obtained from the AAA reaction can be applied to the synthesis of optically pure and multiply functionalized pyrazol-5-one derivatives. The exposure of pyrazol-5-one derivative **3aa** to a combined dihydroxylation reagent of ruthenium trichloride, sodium periodate and sulphuric acid in a solvent mixture of ethyl acetate, acetonitrile and water, followed by oxidation with sodium periodate in a mixture of THF, ether and water to furnish a chiral aldehyde **4** in over all 40% yield and with a maintained enantioselectivity (Scheme 2).[15]

Scheme 2. Synthetic application of allylic adducts of pyrazol-5-one



Conditions: a) 0.5 mol% $RuCl_3$, 1.5 eq $NaIO_4$, 20 mol% H_2SO_4 EtOAc/CH_3CN/H_2O (3:3:1), 0 °C, overnight; b) 1.5 eq $NaIO_4$, THF/Et_2O/H_2O, rt, 2h.

Scheme 3. Proposed catalytic cycle for combination of chiral ligand and chiral counteranion



To gain insight into palladium species in the catalysis, HRMS analysis of a reaction mixture of the palladium complex with **1a** and phosphoric acid (PA) was conducted and identified that two molecules of the chiral ligand (L5) favorably coordinated to palladium.[16] On the basis of these fact and experimental observations, a plausible catalytic cycle was proposed (Scheme 3). The $Pd(L^*)_2$ **A** innitially reacted with phosphoric acid-activated cinnamic alcohol **B** by hydrogen bonding[7] to expelled the hydroxy group to give the crucial cationic π-allyl palladium(II) complex **C**, accompanying with generation of a molecule of water owing to the participation of the chiral phosphoric acid. Subsequently, the

AAA reaction presumably proceeded with the enolizable pyrazol-5-one **2a** via the intermediate **I** and the chiral phosphate counteranion was inclined to have a hydrogen-bonding interaction with incoming nucleophile **2a**, which was stereoselectively activated for the nucleophilic substitution of π-allyl complex **C**. In this stereochemistry-determining step, the chiral palladium complex and chiral phosphate counteranion worked cooperatively to activate the substrates and to control the stereochemistry of the AAA reaction, affording the product **3aa** with high enantioselectivity, and simultaneously the parent chiral palladium(0) complex **A** and phosphoric acid were regenerated for the next catalytic cycles.

In summary, we have demonstrated that the combined use of a palladium complex of chiral phosphoramidite and chiral phosphoric acid enables allylic alcohols to participate in a highly enantioselective allylic alkylation of pyrazol-5-ones for the first time. This protocol have tolerated a diverse scope of functional groups in either allylic alcohols or pyrazo-5-ones, furnishing multiply functionalized heterocyclic products in high yields and with excellent enantioselectivities that would be of great potential in the synthesis of pharmaceutically interesting molecules. More importantly, the combination of two different simple chiral sources is robust in the creation of a diverse library of chiral elements for the control of stereoselectivity in asymmetric catalysis. Moreover, such a strategy essentially avoided the fussy turning of structurally complicated chiral ligands, which was always encountered in traditional metal-based asymmetric catalysis.

ASSOCIATED CONTENT

Supporting Information.
Complete experimental procedures and characterization data for the prepared compounds. This material is available free of charge via the internet at http://pubs.acs.org

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Author Contributions

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(16) For HRMS analysis of the intermediate, please see Supporting Information.

Table of Contents