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A highly efficient kinetic resolution of Morita–Baylis–Hillman adducts achieved by N–Ar axially chiral Pd-complexes catalyzed asymmetric allylation†

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Palladium complexes with an axially chiral N–Ar framework have been developed. These complexes showed high stereoselectivities in asymmetric allylic arylation to achieve the kinetic resolution of Morita–Baylis–Hillman adducts, affording up to 99% ee of (*E*)-allylation products and 92% ee of recovered Morita–Baylis–Hillman adducts.

Design and synthesis of axially chiral ligands have played a significant role in the development of asymmetric catalysis, and have attracted a great deal of attention from both academia and industry.[1] Although many successful examples using axially chiral ligands with a biaryl framework[2] have been disclosed, there are still a considerable amount of reactions in which these ligands are not efficient. The search for new well-designed axially chiral ligands is therefore still a remarkably challenging subject in the field of asymmetric catalysis.

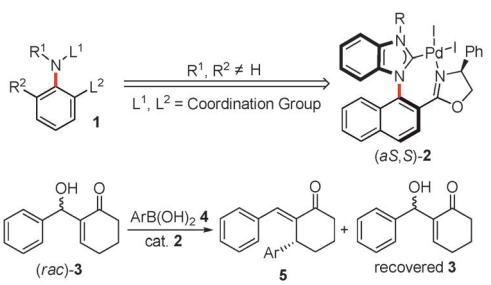
Like the atropisomerism resulting from restricted rotation around the biaryl axis produced by *ortho*-substituents,[3] certain properly substituted *N*-aryl compounds also showed this similar isomerism.[4] Since this atropisomeric framework was firstly introduced into the design of axially chiral ligands,[5] a variety of axially chiral ligands has been disclosed by several groups.[6] However, the development of axially chiral bidentate ligands **1** with sterically bulky groups (R^1 and R^2) along with coordination groups (L^1 and L^2) on the *ortho*-site of the N–Ar axis has received less attention.[7] The development of ligands **1** will undoubtedly enrich the design strategy of axially chiral ligands.

On the other hand, compared with the well-established catalytic asymmetric allylation (AA) using allylic derivatives such as halides and carboxylates,[8] the successful examples with the direct use of allylic alcohols as the ideal allylation agents are rare because the hydroxyl group is a poor leaving group.[9] It is a challenging task to develop highly active catalysts for this transformation.[10]

During our ongoing studies on the development of axially chiral bis(*N*-heterocyclic carbene)–metal complexes (metal = Pd, Ir, Cu, Au, Pt, *etc.*) with a biaryl framework as well as their applications in asymmetric catalysis,[11] we found that complex **6a** can promote asymmetric 1,4-conjugate addition of arylboronic acids to cyclic enones, affording the corresponding addition products in up to 99% yield and 97% ee.[11] Considering the formation of palladium enolate or π-palladium complex in the 1,4-conjugate addition[12] and the feasibility of elimination of β-OH–Pd to generate a C=C moiety,[13] we envisioned that Morita–Baylis–Hillman (MBH) adducts **3** with an allylic alcohol motif could be directly used as allylation agents in AA. More importantly, kinetic resolution (KR)[14] of racemic **3** by Pd-catalyzed AA could be also envisioned to furnish enriched **3** which are valuable chiral reagents in organic synthesis.[15] Herein, we wish to report Pd-complexes (*aS*,*S*)-**2** with an axially chiral N–Ar framework catalyzed highly enantioselective allylic arylation to achieve the kinetic resolution of MBH adducts **3** (Scheme 1).

Using methyl 1-hydroxy-2-naphthoate as the starting material, stable axially chiral Pd-complexes, (*aS*,*S*)-**2**, were synthesized in eight steps and easily isolated by silica gel column chromatography (see the ESI†). The structure of complex (*aS*,*S*)-**2a** was further confirmed by single-crystal X-ray diffraction (see the ESI†). Due to the steric repulsion between the substituents on the oxazoline ring and Pd salt, the Pd(II)-complex with *R*-geometry of the chiral *N*-naphthyl axis failed to be prepared.[16]

With complexes (*aS*,*S*)-**2** in hand, the Pd-catalyzed AA of arylboronic acids with MBH adducts was examined. Racemic



Scheme 1 Design of N–Ar axially chiral Pd-complexes and their applications in asymmetric catalysis.

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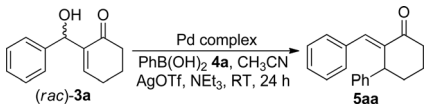
† Electronic supplementary information (ESI) available: Experimental procedures, characterization data of new compounds, and chiral HPLC analysis of allylation products and recovered MBH adducts. CCDC 798781 and 822886. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c1cc15543a

Table 1 Screening of chiral Pd-complexes[a]



			5aa			Recovered 3a		
Entry	Pd complex	Conv.[b] [%]	Yield[c] [%]	$E:Z$[b]	ee[d] [%]	Yield[c] [%]	ee[e] [%]	k_{rel}[f]
1	(*aS*,*S*)-**2a**, R = Me	23	22	90 : 10	98	76	13	2.9
2	(*aS*,*S*)-**2b**, R = Et	21	20	91 : 9	95	77	12	3.0
3	(*aS*,*S*)-**2c**, R = *i*-Pr	17	17	90 : 10	96	81	8	2.5
4[g]	(*aS*,*S*)-**2a**, R = Me	36	35	90 : 10	98	62	32	4.9
5[h]	(*aS*,*S*)-**2a**, R = Me	39	38	90 : 10	98	58	38	5.9

[a] Reaction conditions: 1.0 mL CH_3CN, 0.1 mmol **3a**, 0.2 mmol **4a**, 3 mol% Pd complex, 3 mol% AgOTf, 0.05 mmol NEt_3, RT, 24 h. [b] Determined by crude ^1H NMR spectra. [c] Isolated yields. [d] The enantioselectivity of (*E*)-**5aa** was determined by chiral HPLC analysis. [e] Determined by chiral HPLC analysis. [f] $k_{rel} = \ln[(1 - C)(1 - ee)]/\ln[(1 - C)(1 + ee)]/\ln[(1 - C)(1 + ee)]$, *C*: Conversion of **3a**, ee: % ee of recovered **3a**. [g] 10 mol% Pd complex, 10 mol% AgOTf. [h] 15 mol% Pd complex, 15 mol% AgOTf.

MBH adduct **3a** derived from the MBH reaction of cyclohexenone with benzaldehyde was used as a model substrate. The reaction of **3a** with phenylboronic acid **4a** was carried out in the presence of complex (*aS*,*S*)-**2a** (3 mol%), AgOTf (3 mol%), and NEt_3 (50 mol%), affording the trisubstituted alkene **5aa** in 22% yield along with a 90 : 10 *E*/*Z* ratio determined by crude ^1H NMR spectrum, in which the (*E*)-**5aa** was formed in 98% ee value (Table 1, entry 1). Moreover, to our delight, recovered **3a** was obtained in 13% ee with a k_{rel} value of 2.9. Complexes (*aS*,*S*)-**2b** and (*aS*,*S*)-**2c** were also tested in this reaction, giving similar results along with slightly lower ee-values of (*E*)-**5aa** and recovered **3a** (Table 1, entries 2 and 3). Increasing the employed amount of (*aS*,*S*)-**2a** to 10 mol% and 15 mol%, the ee-values of recovered alcohol **3a** could be significantly improved to 32% ee and 38% ee, respectively. While using other axially chiral Pd(II)-complexes in this KR (see ESI†), none of the allylation product **5aa** was formed.

In order to investigate the substrate scope of arylboronic acid in this interesting AA as well as further optimise this KR of MBH adduct **3a**, various arylboronic acids **4b–i** were next examined in the presence of 15 mol% (*aS*,*S*)-**2a**. It was found that the (*E*)-allylation products **5ab–ai** were obtained in excellent enantioselectivities with up to 99% ee (Table 2, entries 1–8). However, arylboronic acids **4** with different substitution patterns and electronic properties of substituents showed a significant influence on the reaction outcome. Arylboronic acids with *para*-substituted electron withdrawing groups were good resolution reagents for this AA of MBH adducts. Using **4f** gave recovered **3a** in 60% ee along with $k_{rel} = 10.5$ (Table 2, entry 5).

Subsequently, KR of various MBH adducts **4b–g** was also investigated under the standard conditions. All reactions proceeded smoothly to deliver the corresponding (*E*)-allylation products **5ba–ga** in 98–99% ee (Table 2, entries 9–14). Similarly, different substitution patterns and the electronic property of substituents on aromatic rings of **3b–g** also played a key role in this reaction. Substrate **3b** with a cyano group at the 4-position of the phenyl ring was an excellent substrate ($k_{rel} = 17.6$), giving product **5ba** in 45% yield and recovered **3b** in 52% yield with 70% ee (Table 2, entry 9). Combining the influence of arylboronic acid and MBH adducts on the reaction outcome of this catalytic reaction, the reaction of **3h** with **4f** was also carried out. It is noteworthy that up to 42.2 of the k_{rel} value along with 51% conv. was observed, giving **5hf** in 50% yield with 99% ee of (*E*)-**5hf** and recovered **3h** in 47% yield with 90% ee (Table 2, entry 15).

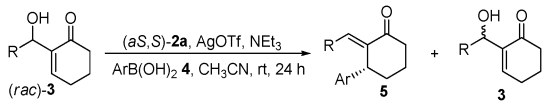
Compared to the sterically bulky aromatic moieties in alcohols **3b–g**, MBH adducts **3i** and **3j** derived from the corresponding aliphatic aldehydes were also tested in this catalytic reaction (Table 2, entries 16 and 17). To our delight, >50% yields of allylation products **5ia**[17] (57% yield and 99% ee for (*E*)-**5i**) and **5ja** (61% yield and 99% ee for (*E*)-**5j**) were obtained. Moreover, 91% ee of recovered **3i** and 92% ee of recovered **3j** were, respectively, obtained along with k_{rel} values of 14.9 and 11.1. The absolute configurations of allylation products **5** and MBH adducts **3** were determined by comparing the sign of optical rotation with that of (*R*)-**5hf** which is determined by X-ray diffraction (see the ESI†) and those of literature values,[18] respectively.

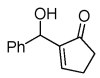
With up to 61% yields of enantiomerically pure allylation products **5** (up to 99% ee for (*E*)-**5**), this KR was not a standard KR which is limited to a maximum yield of 50% of the enriched product, and also was not a dynamic kinetic resolution as α-substituted allylation products were not found in all cases from the analysis of their crude ^1H NMR spectra. The KR method might proceed with the generation of new stereogenic centers with the same (*R*)-geometry under the control of chiral catalyst (*aS*,*S*)-**2** *via* a Pd-catalyzed 1,4-addition[19] and the subsequent elimination of the original chiral center *via* a Pd–OH elimination mechanism (see the ESI†).[20]

In summary, we have developed a novel type of palladium complexes (*aS*,*S*)-**2** with an axially chiral N–Ar framework. These Pd complexes are quite effective catalysts in the kinetic resolution of MBH adducts **3** by Pd-catalyzed asymmetric allylic alkylation between arylboronic acids and racemic MBH adducts **3** under mild reactions, affording allylation products **5** in 8–61% yields with 93–99% ee and the recovered **3** in 37–90% yields with 5–92% ee. Further studies focusing on the development of axially chiral metal catalysts with an N–Ar framework as well as their applications in asymmetric catalysis are undergoing.

Financial support from the National Natural Science Foundation of China (21072206, 20902019, 20472096, 20872162, 20672127, 20821002 and 20732008), the National Basic Research Program of China (973)-2010CB833302, and the Fundamental Research Funds for the Central Universities (WJ1014034 and WK1013004) is gratefully acknowledged.

Table 2 Substrate suitability for the Pd-catalyzed asymmetric allylic arylation[a]



				Alkylation product				Recovered alcohol			
Entry	R	Ar	Conv.[b] [%]	5	Yield[c] [%]	E/Z[b]	ee[d] [%]	3	Yield[c] [%]	ee[e] [%]	k_{rel}[f]
1	Ph	*o*-CH_3Ph	8	**5ab**	8	98 : 2	93	**3a**	90	5	3.9
2	Ph	*m*-CH_3Ph	24	**5ac**	23	94 : 6	95	**3a**	76	22	6.9
3	Ph	*p*-CH_3Ph	36	**5ad**	36	96 : 4	95	**3a**	63	38	7.4
4	Ph	*m*-ClPh	36	**5ae**	35	90 : 10	97	**3a**	63	26	3.5
5	Ph	*p*-ClPh	46	**5af**	45	90 : 10	98	**3a**	51	60	10.5
6	Ph	*o*-CH_3Oph	23	**5ag**	22	94 : 6	94	**3a**	74	15	4.3
7	Ph	2-Naph	36	**5ah**	34	90 : 10	98	**3a**	61	38	7.4
8	Ph	*p*-C_6H_5Ph	46	**5ai**	45	93 : 7	99	**3a**	50	61	9.9
9	*p*-CNPh	Ph	47	**5ba**	45	93 : 7	99	**3b**	52	70	17.6
10	*p*-CH_3Ph	Ph	35	**5ca**	34	90 : 10	99	**3c**	63	36	7.1
11	*p*-MeOPh	Ph	29	**5da**	28	99 : 1	98	**3d**	70	32	11.2
12	*m*-ClPh	Ph	44	**5ea**	44	94 : 6	99	**3e**	55	48	6.6
13	*o*-ClPh	Ph	34	**5fa**	33	99 : 1	98	**3f**	62	30	5.0
14	2,4-diClPh	Ph	42	**5ga**	40	95 : 5	99	**3g**	56	34	3.8
15	*p*-NO_2Ph	*p*-ClPh	51	**5hf**	50	98 : 2	99	**3h**	47	90	42.2
16	CH_3	Ph	58	**5ia**	57	99 : 1	99	**3i**	41	91	14.9
17	Cyclohexyl	Ph	62	**5ja**	61	94 : 6	99	**3j**	37	92	11.1
18		Ph	22	**5ka**	21	94 : 6	62	**3k**	76	13	3.1

[a] Reaction conditions: 1.0 mL CH_3CN, 0.1 mmol **3**, 0.2 mmol **4**, 15 mol% (*aS*,*S*)-**2a**, 15 mol% AgOTf, 0.05 mmol NEt_3. [b] Determined by crude ^{1}H NMR spectra. [c] Isolated yields. [d] The enantioselectivity of (*E*)-**5** was determined by chiral HPLC analysis. [e] Determined by chiral HPLC analysis. [f] $k_{rel} = \ln[(1 - C)(1 - ee)]/\ln[(1 - C)(1 + ee)]$, *C*: Conversion of **3**, ee: % ee of recovered **3**.

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