Palladium-Catalyzed Enantioselective Arylation of Racemic Ketones to Form Bridged Bicycles via Dynamic Kinetic Resolution

Xiaolei Huang, William Ray Jun Jie Oh and Jianrong Steve Zhou*

Abstract: Enantioselective α-arylation of racemic ketones containing existing α'-stereocenters is reported for the first time under conditions of base-induced dynamic kinetic resolution. Bridged bicyclic rings are formed in good ee values, which are difficult to obtain otherwise. Furthermore, reactions in DMSO-d6 resulted in extensive deuteration of both α and α' positions in the products, supporting a pathway involving rapid, reversible deprotonation of ketones under the catalytic conditions.

Bridged bicycles are important structural motifs in pharmaceuticals, bioactive molecules and natural products, for example, dezocine[1] is a marked opioid analgesic and (*S*)-pentazocine[2] is mainly used as a painkiller. Huperzine A is an alkaloid from Chinese herb that has potential use in treatment of Alzheimer's disease and it is currently being used as a cognitive enhancer.[3] Therefore, developing stereoselective synthesis of this class of ringed compounds from simple starting material is an important endeavor.[4]

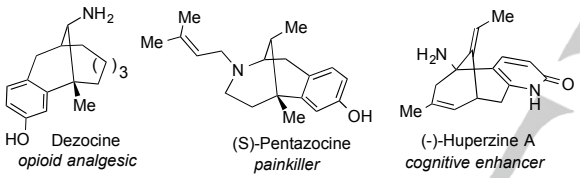
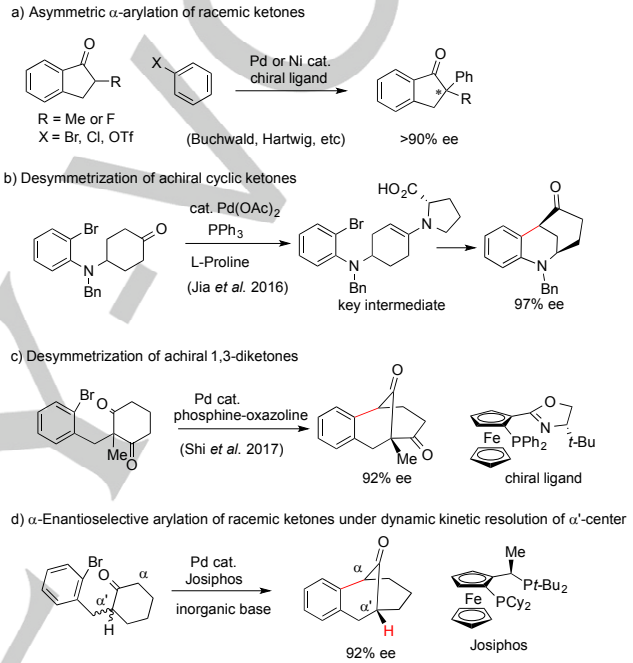


Figure 1. Drugs and natural products containing bridged bicyclic cores

Pd- and Ni-catalyzed asymmetric *α*-arylation of carbonyl compounds add aryl rings to cyclic ketones, lactones and amides and they form an important class of C-C bond forming reactions.[5] For example, Buchwald, Hartwig and others have reported intermolecular *α*-arylation of cyclic ketones (Scheme 1a), lactones, alkylnitriles and oxindoles to form quaternary stereocenters with good enantioselectivity.[6] Meanwhile, catalytic intramolecular versions of *α*-arylation have also been achieved for both aldehydes and amides, which resulted in monocyclic rings.[7] Our group in recent years also disclosed arylation conditions that established tertiary α-stereocenters, which are sensitive to strong bases.[8]

For construction of bridged bicycles, in 2016 Jia and co-workers reported arylative desymmetrization of achiral 4-substituted cyclohexanones to afford [3.3.1]-bicyclic rings with good to excellent ee values, which proceeded via a key intermediate of a proline-derived enamine (Scheme 1b).[9] Very recently, Shi *et al.* also applied a similar strategy of desymmetrization to achiral cyclic 1,3-diketones (Scheme 1c).[10]



Scheme 1. Asymmetric α-arylation of ketones

In this work, we report an intramolecular arylation of racemic ketones bearing *α'*-substituents that afforded bridged bicycles in good enantiomeric excess (Scheme 1d).[11] As a key feature of our reaction design, a moderately strong base was used to promote rapid racemization at *α'* position of the ketone via reversible enolization, while a chiral Pd catalyst was able to differentiate the two enantiomers by arylating one of them at *α* position selectively. Without fast equilibration of the *α'*-stereocenter, only racemic products are to be expected.

Rapid racemization of α' center in a model ketone **1a** is the key to achieving asymmetric arylation under conditions of dynamic kinetic resolution. We reasoned that rapid, reversible enolization of **1a** can be monitored by H/D exchange between the ketone and a deuteriated solvent containing weakly acidic deuterons (Table 1). After many trials, we found that around 95% deuterium was incorporated into both *α'*- and *α*-positions of **1a** when it was heated with 3 equiv of Cs_2CO_3 in DMSO-d_6 at 80 ºC for 30 min (entry 1); at room temperature only 2% deuterium was incorporated. The use of K_3PO_4 also led to >90% deuterium incorporation (entry 2), while the use of PhOK and PhONa resulted in 86% and 74% deuterium at *α'*-position, respectively (entries 3-4). **1a** did not undergo reversible racemization when K_2CO_3 was used as base (entry 5). However, a strong base KO*t*-Bu led to decomposition of **1a** to many byproducts containing a

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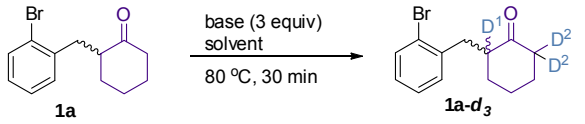
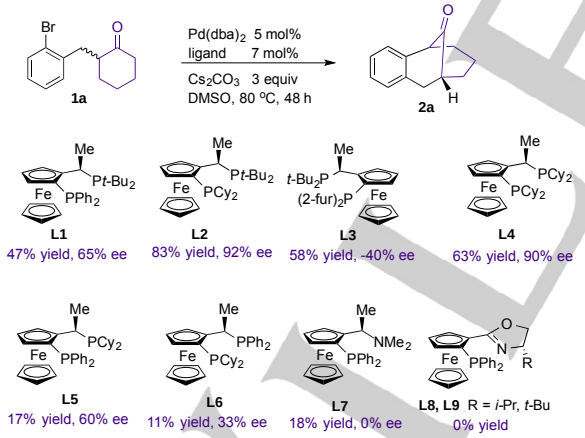
trace amount of hydrodebrominated byproduct, 2-benzylcyclohexanone, presumably via a pathway of electron transfer from potassium enolate to the aryl bromide (entry 6).[12] Next, we investigated the use of other solvents in the presence of Cs_2CO_3 (entries 7-8). In MeCN-d_3 solvent, the incorporation of deuterium into **1a** was much slower (61% D), while in CD_3OD, 97% deuterium was detected. Thus, we identified a few inorganic bases such as Cs_2CO_3, K_3PO_4, KOPh, and NaOPh in highly polar DMSO for effective reversible deprotonation of ketones.

Table 1. H/D exchange of a model ketone **1a**

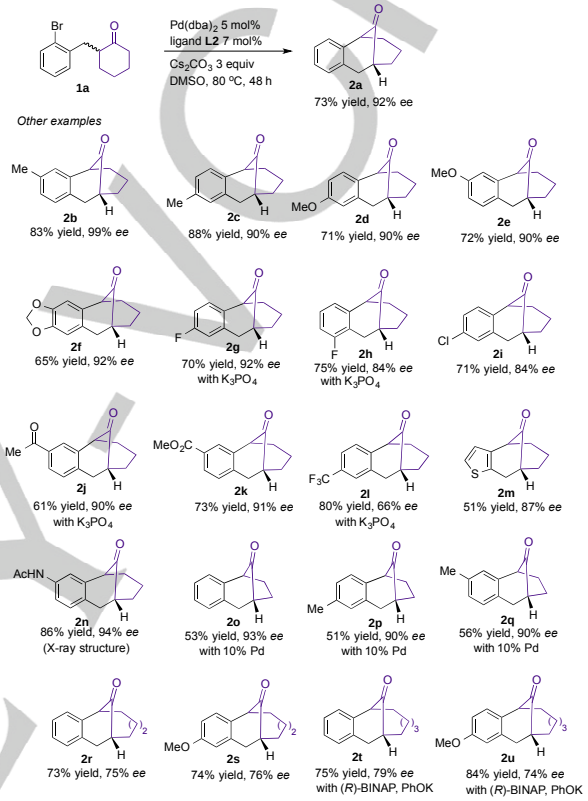


Entry	Base	Solvent	Yield (%)	D^1 (%)	D^2 (%)
1	Cs_2CO_3	DMSO-d_6	94	95	94
2	K_3PO_4	DMSO-d_6	96	90	92
3	NaOPh	DMSO-d_6	94	86	81
4	KOPh	DMSO-d_6	96	74	71
5	K_2CO_3	DMSO-d_6	97	0	0
6	KO*t*-Bu	DMSO-d_6	0	-	-
7	Cs_2CO_3	MeCN-d_3	97	61	31
8	Cs_2CO_3	MeOH-d_4	96	97	97



Scheme 2. The effect of chiral phosphines on model arylation

With the optimal conditions in hand, we searched for chiral ancillary phosphines that can offer a good level of stereoinduction in the model reaction of **1a**. Unfortunately, common chelating diphosphines such as (*R*)-binap, (*R*)-difluorphos, (*R*)-segphos and (*R*)-MeO-biphep led to merely <30% ee. After further screening, we were gratified to discover that a Josiphos ligand[13] **L1** improved the ee value to 65% (Scheme 2). Further fine-tuning of the structures of Josiphos family of bisphosphines (**L2-L6**) revealed that a bulky, strongly donating ligand **L2**, which has a PCy_2 group on the ferrocene ring and P(*t*-Bu)$_2$ group on the side chain, offered the desired product **2a** in good yield and ee value (92% ee). Similarly, a closely related bis(dicyclohexylphosphine) **L4** also provided satisfactory result (63% yield and 90% ee). In comparison, **L5** and **L6** containing one less-donating diphenylphosphine group on either arm led to catalysts of much lower activity (<20% yield) and stereoselectivity. Moreover, ferrocene-derived phosphine-oxazolines **L8**-**L9** did not form active palladium catalyst at all.



Scheme 3. Examples of intramolecular arylation of racemic *o*-bromobenzyl cyclohexanones (**2a**-**n**), cyclopentanones (**2o**-**q**), cyclooctanones (**2r**-**s**) and cyclononanones (**2t**-**u**)

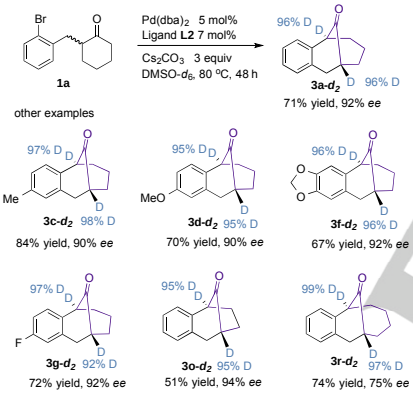
In the course of condition optimization, we found that various Pd(0) and Pd(II) salts gave very similar results, while different bases, Cs_2CO_3, K_3PO_4, $K_3PO_4{\cdot}H_2O$, KOPh and NaOPh were all effective and gave excellent stereo-induction in the model reaction. Among them, Cs_2CO_3 gave the best chemical yield of **2a**. The use of strong bases such as KO*t*-Bu and KOH, however, led to decomposition of **1a** to a complex mixture containing a trace amount of a hydrodebromination byproduct. Among various solvents, polar aprotic solvents such as DMSO, DMF, DMA and NMP, which can effectively solvate alkaline metal ions of the bases, were crucial to achieving high levels of enantiomeric induction. In alcoholic solvents, hydrodebromination was much more significant and no desired product **2a** was formed. Increasing the reaction temperature to 100 °C decreased the ee, while at room temperature the arylation reaction did not proceed.

The model substrate **1a** can tolerate many substituents on the aryl rings in the cyclization and afforded high levels of ee values (Scheme 3), such as electron-donating methyl (**2b** and

2c), methoxy (**2d**-**2e**), acetamido groups (**2n**), electron-withdrawing fluorine (**2g** and **2h**), chlorine (**2i**), ketone (**2j**), and ester groups (**2k**). Moreover, the process tolerated acetal group (**2f**) and a thiophene ring (**2m**). The absolute configuration of product **2n** was determined to be (5*S*,9*R*) by single-crystal X-ray diffraction.[14] However, we noticed that the presence of an electron-withdrawing CF_3 group at *para* position of the aryl ring led to a drop of ee to 66% (**2l**). Unfortunately, when substituents were present next to the C-Br bond on the arene, the arylation still proceeded to deliver desired products in good yields, but only with <20% ee owing to steric effect.

Furthermore, Pd catalyst of **L2** was also successfully used in arylative cyclization of cyclopentanone derivatives with excellent ee (**2o-q**). The moderate yields can be attributed to the formation of many unidentified byproducts, each in small amounts. In cyclization of both cycloheptanone and cyclooctanone derivatives, we noticed that the Pd/Josiphos catalyst delivered only moderate ee of around 75% (**2r-u**).

Deuteration at strategic positions of drugs is an emerging strategy to achieve desirable pharmacokinetics of drugs such as extended half-lives, without affecting binding affinities and introducing unwanted toxicology. Deuterium drugs can allow a lower dosage to be used and thus, minimize the side effects.[15]

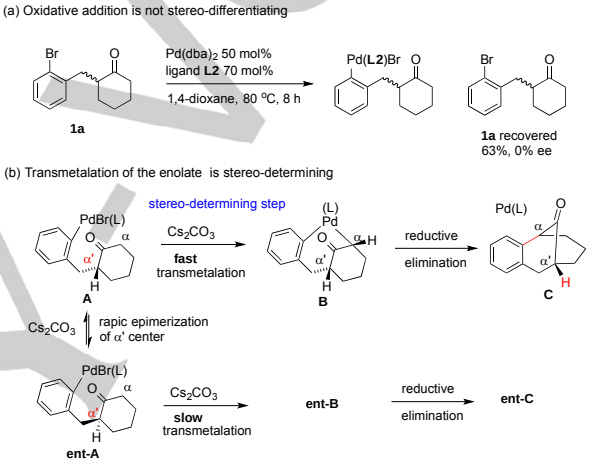


Scheme 4. Asymmetric intramolecular arylation and deuteration in DMSO-d_6

The base Cs_2CO_3 promoted rapid H/D exchange between ketone **1a** and DMSO-d_6 via reversible deprotonation. Thus, we envisioned that in DMSO-d_6, **1a** will be quickly deuteriated at both α and α' position under catalytic conditions. As a result, the bicyclic product **3a** will be dideuterated. To our gratification, indeed it occurred and both α and α' positions of **3a** were deuterated to 96% content (Scheme 4). Similarly, several substrates containing other cyclic ketones of different ring size also gave doubly labeled products in >90% deuterium content, and no significant change of yields and ee values were seen as compared to results in DMSO (Scheme 4).

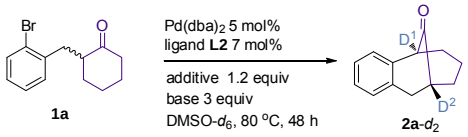
To gain insights into the reaction mechanism, We initially conducted oxidative addition of 50 mol% of a palladium(0) complex of ligand **L2** with a sample of racemic bromide **1a** (Scheme 5a). After 37% conversion, no resolution of **1a** by the chiral catalyst was seen in dioxane, judged from recovered starting material. In DMSO, the in situ generated palladium catalyst was barely soluble.

We then conducted catalytic arylation of **1a** in DMSO-d_6 in the presence of some additives (Table 2). For example, addition of 1.2 equiv of TMEDA to the reaction with Cs_2CO_3 led to a significant decrease of ee value of **3a-*d*$_2$** from 92% to 79% (entry 1 vs 2). Similarly, addition of either TEMDA or 18-crown-6 to the reaction with K_3PO_4 resulted in a drop of ee values from 90% to 82% (entry 3 vs 4-5). Notably, TMEDA alone could not function as a base in the catalytic reaction. Since the deuterium content in the coupling product changed little in each set of additive experiments, we concluded that deprotonation of the ketone was relatively fast and reversible under all conditions in Table 2. Therefore, these additives probably modified the structure of cesium and potassium enolates during transmetalation to the palladium center and transmetalation is probably the stereo-determining step in the catalytic cycle.



Scheme 5. A proposed reaction pathway

Table 2. The effect of additives on asymmetric arylation

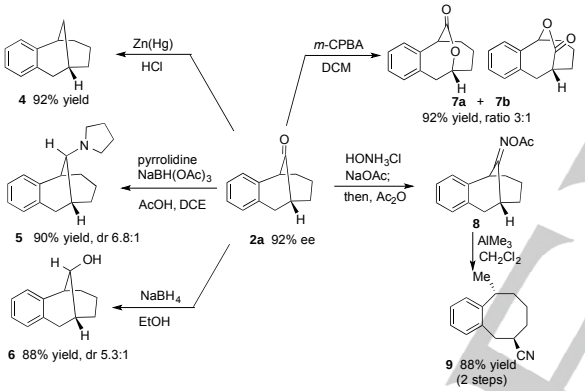


Entry	Base	Additive	**2a**-d_2(%)	Ee(%)	D^2 (%)
1	Cs_2CO_3	none	84	92	96
2	Cs_2CO_3	TMEDA	64	79	94
3	K_3PO_4	none	72	90	92
4	K_3PO_4	TMEDA	75	82	93
5	K_3PO_4	18-crown-6	82	82	91

Putting all the data together, we suggest the following reaction sequence involving a stereo-determining transmetalation step (Scheme 5b). Oxidative addition of racemic **1a** to (Josiphos)Pd(0) results in two diastereomeric complexes **A** and **ent-A**, which are under rapid equilibrium in the presence of the base. Then, after deprotonation, transmetalation of **A** from the resulting cesium enolate to arylpalladium bromide was much

faster than that of **ent-A**. The final step of reductive elimination from Josiphos-ligated palladium complexes to form the C-C bond is a relatively fast process.

The arylation products can be easily transformed to other useful chiral building blocks (Scheme 6). For example, Zn(Hg)-mediated deoxygenation of ketone **2a** gave **4** in an excellent yield without any erosion of the ee value. Under reductive amination conditions with $NaBH(OAc)_3$ and pyrrolidine, **2a** was converted to amine **5** with an anti/syn ratio of 6.8/1.[16] The anti-isomer of **5** is an analogue of a bicyclic amine with analgesic activity.[17] $NaBH_4$ reduction of **2a** resulted in alcohol **6** with anti/syn ratio of 5.3:1. **2a** was also converted into lactones **7a** and **7b** via Baeyer-Villiger oxidation with a ratio of 3:1. In addition, the oxime ester of **2a** underwent Beckmann fragmentation when treated with $AlMe_3$, leading to a medium-ringed benzocyclooctane **9** as a single isomer.[18] The *Si* face of the benzylic cation was blocked by the newly formed CN group in the benzofused intermediate, thus $AlMe_3$ attacked from its opposite face. It should be pointed out that stereoselective synthesis of medium-sized rings with more than one stereocenter remains a challenging task.[19]



Scheme 6. Derivatization of product **2a**

In conclusion, we have reported an asymmetric intramolecular arylation of ketones that afforded the bicyclic bridged-rings and it established two tertiary stereocenters centers with high ee values under conditions of dynamic kinetic resolution. Furthermore, the use of DMSO-d_6 resulted in doubly deuterated bridged bicyclic ketones with >95% deuterium content, which may have potentially use in development of deuterium drugs.

Acknowledgements

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Keywords: palladium catalysis • arylation • ketones • enolates • dynamic kinetic resolution

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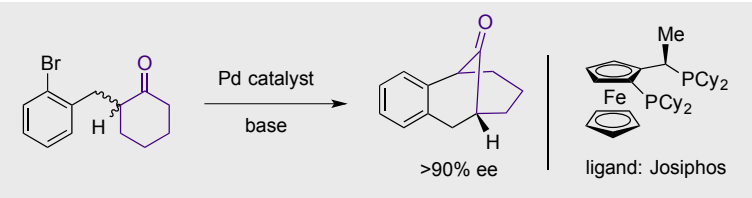

Enantioselective α-arylation of racemic ketones containing existing α'-stereocenters proceeds to give bridged bicycles in high ee via base-assisted dynamic kinetic resolution. The reactions in DMSO-d_6 result in doubly deuterated bridged bicyclic ketones with >95% deuterium, owing to fast reversible H/D exchange at both α and α' positions of ketones.

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