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Dynamic Kinetic Resolution of Flavonoids via Asymmetric Allylic Alkylation: Construction of Two Contiguous Stereogenic Centers on Nucleophiles

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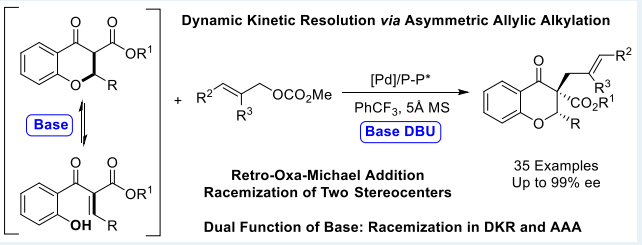
ABSTRACT: The extension of racemization strategies of dynamic kinetic resolution in organic synthesis is a longstanding challenge, especially racemizing two or more stereogenic centers simultaneously. Through the combination of a palladium-catalyzed asymmetric allylic alkylation and a base-promoted retro-oxa-Michael addition, a dynamic kinetic resolution of 2,3-disubstituted flavonoids was achieved with up to 99% enantioselectivities, and two contiguous stereocenters (including a quaternary stereogenic center) were constructed simultaneously on the nucleophile flavonoids. The key feature of the reaction was a base-promoted retro-oxa-Michael addition for fast racemization of two stereogenic centers on the nucleophiles, which can pave the way to developing asymmetric reactions of flavonoids through dynamic kinetic resolution.



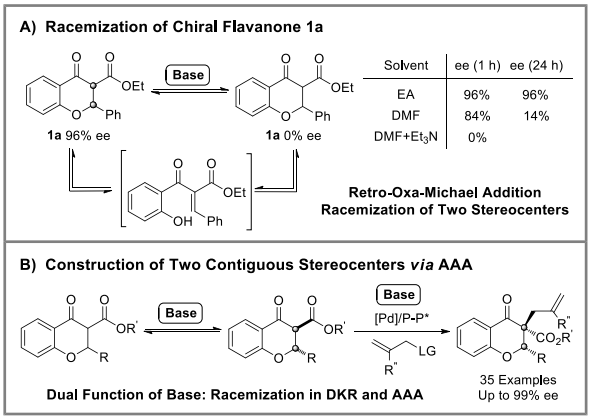
KEYWORDS: *retro-oxa-Michael addition, DKR, asymmetric allylic alkylation, palladium catalysis, flavonoids*

During the past few decades, dynamic kinetic resolution (DKR)[1] has been demonstrated as a powerful tool in asymmetric synthesis, allowing full conversion of the racemic starting materials to the target chiral products, which overcomes the limitation of classical kinetic resolution. To achieve an efficient and selective DKR, requirements have to be fulfilled, including (i) the rapid racemization of the reactant, which is independent of the catalyst and mutually compatible, and (ii) a subtle balance of relative rates in the synchronized catalytic cycles. Although great success has been achieved in the racemization of one chiral center during dynamic kinetic resolution processes, a strategy for rapidly racemizing two or more stereocenters simultaneously remains an unmet synthetic challenge.

Due to their special structural properties, the chiral flavonoid family is receiving wide attention.[2] Flavonoids are prone to transformation from the cyclic form to the linear form under basic conditions through a retro-oxa-Michael addition,[3] leading to fast racemization of the stereocenters (Scheme 1A).[4] As 2,3-disubstituted flavonoids have four stereoisomers, the enantiocontrol of their asymmetric transformations is extremely difficult. One example was discovered by Sherer's group,[3c] who reported a Ru-catalyzed asymmetric transfer hydrogenation of tricyclic chromanones, utilizing retro-oxa-Michael addition to simultaneously racemize two stereocenters.

Although the dynamic kinetic resolution of nucleophiles in asymmetric allylic alkylation (AAA)[5] with one chiral center has been well established,[6] to the best of our knowledge, there has been no report of DKR of nucleophiles with two or more stereogenic centers. In contrast, there are only some examples of kinetic resolution via AAA to construct two stereocenters on nucleophiles.[7] Considering that the asymmetric allylic

Scheme 1. Dynamic Kinetic Resolution of Flavonoids via Asymmetric Allylic Alkylation



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alkylation mostly proceeded under the basic conditions, we envisioned whether 2,3-disubstituted flavonoids could be used as the nucleophiles in asymmetric allylic alkylation, allowing the construction of two stereocenters in the nucleophile flavonoids. However, there are some challenges remaining: first, the compatibility of the base in the two reaction processes, and second, the enantio- and diastereoselective control of the reaction. Herein, we report a dynamic kinetic resolution of flavonoids based on a retro-oxa-Michael addition via a palladium-catalyzed asymmetric allylic alkylation to enantio- and diastereoselectively construct two contiguous stereogenic centers (including a quaternary carbon stereogenic center) on the nucleophiles simultaneously (Scheme 1B).

In order to verify the hypothesis, we first conducted racemization experiments of chiral flavanone **1a** with a 96% ee value (Scheme 1A). When **1a** was stirred in a solution of ethyl acetate (EA), the ee value was maintained over 24 h. An apparently partial racemization was observed when the polar aprotic *N*,*N*-dimethylformamide (DMF) was used as the solvent. In the presence of the base triethylamine (Et_3N), full racemization of **1a** was obtained in 1 h. The results of the above experiments showed that the chiral 2,3-disubstituted flavanone **1a** was able to rapidly racemize under the basic conditions through a retro-oxa-Michael addition pathway and that the racemization of two stereocenters happened simultaneously.

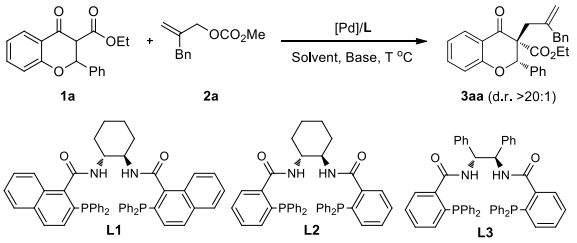
After racemization experiments, racemic flavanone **1a** and 2-benzylallyl methyl carbonate **2a** were selected as the model substrates to investigate suitable reaction parameters. The effect of bases was first screened (Table 1, entries 1−3). The reaction occurred smoothly with Et_3N and cesium carbonate (Cs_2CO_3), offering similar enantioselectivities. Notably, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as the base could slightly improve the ee value (entry 3). The solvent was then evaluated, and it was revealed that benzotrifluoride ($PhCF_3$) was essential (entry 4). Other solvents, such as DMF, 1,2-dichloroethane (DCE) or 1,4-dioxane, led to lower ee values (entries 3, 5, and 6). Different catalyst precursors were also examined, including $Pd(OAc)_2$, $Pd(dba)_2$, and $Pd_2(dba)_3$, which all resulted in moderate to good yields and high enantioselectivities (entries 7−9). On consideration of the yield and enantioselectivity, $Pd_2(dba)_3$ was chosen as the optimal catalyst precursor.

The amount of base was then screened (Table 1, entries 10−12), and it was found that 1 equiv of DBU was the best choice. With ligands **L2** and **L3**, the yields and enantioselectivities were both slightly lower (entries 13 and 14). When the $Pd_2(dba)_3$ catalyst loading was reduced to 1.0 mol %, a 62% yield was obtained (entry 15). To further improve the enantioselectivity, the effect of temperature was tested (entries 16−18). When the reaction temperature was decreased to 0 °C, a slightly higher enantioselectivity was achieved and the yield could be maintained. Of note, the enantioselectivity of the reaction was significantly affected by a trace amount of water (entry 17). To this end, 5 Å molecular sieves (MS) were added for repeatability. Finally, the optimized conditions were established (entry 18).

With the optimized conditions in hand, we set out to explore the substrate scope. First, the ester substituents on the flavanones **1** were examined (Scheme 2). Flavanones **1** with various alkyl substituents on the ester, including ethyl (**1a**), methyl (**1b**), isopropyl (**1c**), *tert*-butyl (**1d**), and benzyl (**1f**), were all suitable substrates, providing the desired products with good to excellent ee values and yields. The reaction was slightly sensitive to the steric bulk of the R group; when cyclohexyl (**1e**) was introduced, a moderate 83% ee was obtained.

Having identified ethyl as R, we investigated allyl substrates and found that the substituents have a strong effect on the

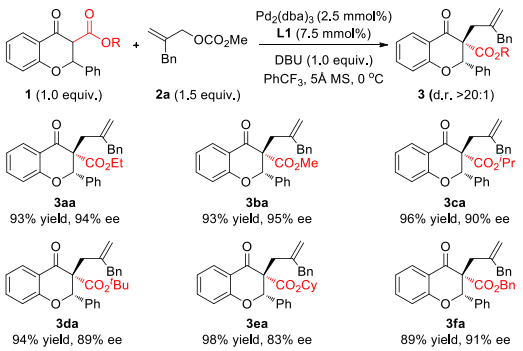
Table 1. Optimization of Conditions[a]



Entry	[Pd]	base (amt (equiv))	solvent/L	yield (%)[b]	ee (%)[c]
1	$[Pd(C_3H_5)Cl]_2$	Et_3N (1.2)	DMF/**L1**	88	84
2	$[Pd(C_3H_5)Cl]_2$	Cs_2CO_3 (1.2)	DMF/**L1**	77	86
3	$[Pd(C_3H_5)Cl]_2$	DBU (1.2)	DMF/**L1**	75	87
4	$[Pd(C_3H_5)Cl]_2$	DBU (1.2)	$PhCF_3$/**L1**	90	90
5	$[Pd(C_3H_5)Cl]_2$	DBU (1.2)	DCE/**L1**	81	88
6	$[Pd(C_3H_5)Cl]_2$	DBU (1.2)	dioxane/**L1**	91	86
7[d]	$Pd(OAc)_2$	DBU (1.2)	$PhCF_3$/**L1**	51	93
8[d]	$Pd(dba)_2$	DBU (1.2)	$PhCF_3$/**L1**	90	90
9	$Pd_2(dba)_3$	DBU (1.2)	$PhCF_3$/**L1**	85	92
10	$Pd_2(dba)_3$	DBU (0.2)	$PhCF_3$/**L1**	>95	79
11	$Pd_2(dba)_3$	DBU (1.0)	$PhCF_3$/**L1**	91	91
12	$Pd_2(dba)_3$	DBU (1.5)	$PhCF_3$/**L1**	80	93
13	$Pd_2(dba)_3$	DBU (1.0)	$PhCF_3$/**L2**	87	87
14	$Pd_2(dba)_3$	DBU (1.0)	$PhCF_3$/**L3**	57	81
15[e]	$Pd_2(dba)_3$	DBU (1.0)	$PhCF_3$/**L1**	62	93
16[f]	$Pd_2(dba)_3$	DBU (1.0)	$PhCF_3$/**L1**	92	92
17[g,h,i]	$Pd_2(dba)_3$	DBU (1.0)	$PhCF_3$/**L1**	>95	43
18[g]	$Pd_2(dba)_3$	DBU (1.0)	$PhCF_3$/**L1**	92 (93[h,j])	94

[a]Unless noted otherwise, reactions were carried out with **1a** (0.10 mmol), **2a** (0.15 mmol), [Pd] (2.5 mol %), **L** (7.5 mol %), base (*x* equiv), solvent (1.0 mL), 30 °C, 4−27 h. [b]The yield was measured by analyses of ^1H NMR spectra, using 1,3,5-trimethoxybenzene as the internal standard. [c]Determined by chiral HPLC. [d][Pd] (5.0 mol %). [e]$Pd_2(dba)_3$ (1.0 mol %). [f]10 °C instead of 30 °C. [g]0 °C instead of 30 °C. [h]Reaction on a 0.20 mmol scale, 24 h. [i]H_2O (1.0 equiv) was added. [j]5 Å MS (50.0 mg) was added. Isolated yield.

Scheme 2. Substrate Scope: Ester Group of Flavanones 1



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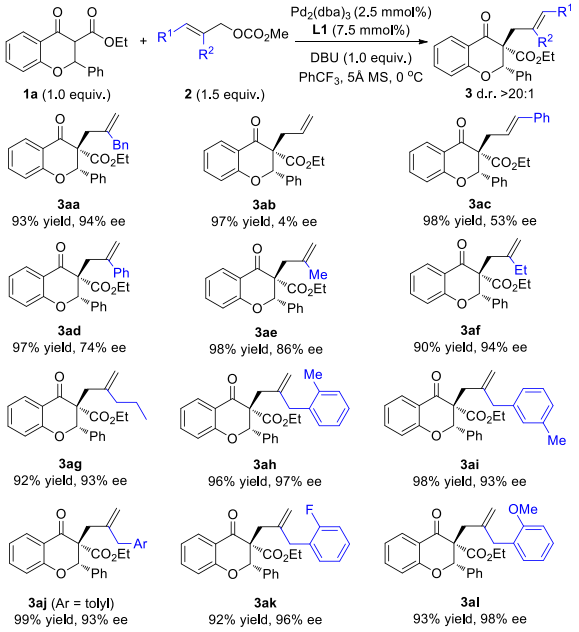
enantioselectivity. As shown in Scheme 3, simple allyl methyl carbonate (**2b**) underwent the alkylation reaction with **1a** to

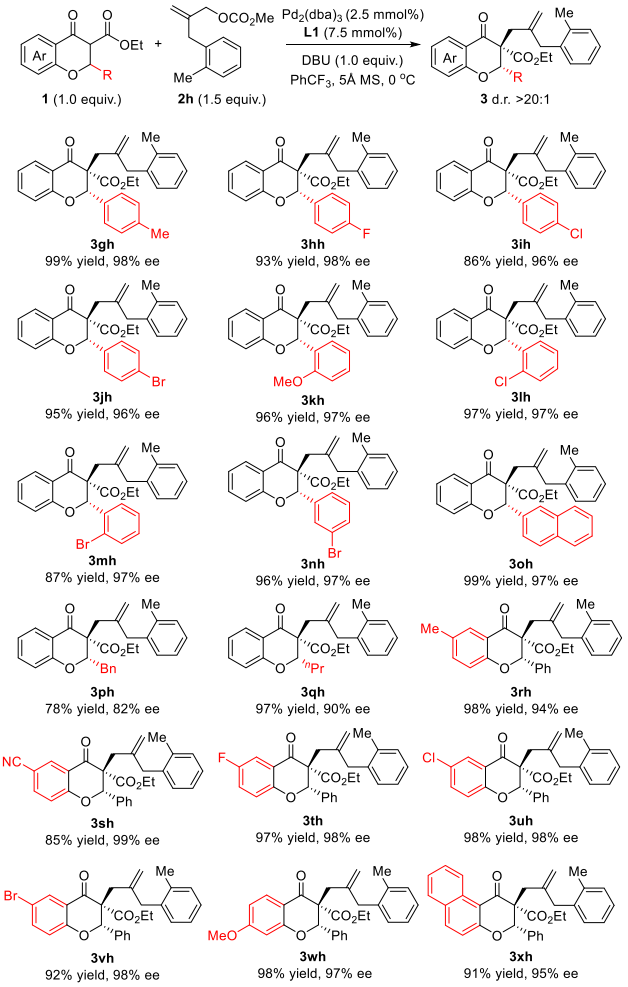
Scheme 3. Substrate Scope: Allyl Substrates 2



provide the corresponding product **3ab** in 97% yield with only a low 4% ee. An improved ee value was observed with cinnamyl methyl carbonate (**2c**). Then, our attention turned to the substituent on the 2-position of allyl methyl carbonate such as phenyl (**2d**), methyl (**2e**), ethyl (**2f**), and *n*-propyl (**2g**); the reaction proceeded smoothly to deliver **3ad**,**ae**,**af**,**ag** with satisfactory yields and moderate to excellent ee values. The bulkiness of the *ortho* substituent on the aryl group of allyl substrate (**2h**) had a positive effect on the enantioselectivity, and a negligible effect was observed with *meta* or *para* substituents on the substrates (**2i**,**j**). The electronic nature of the aryl groups on the allyl substrates had a marginal effect on enantioselectivity. For example, a substrate with an electron-withdrawing group (**2k**) at the *ortho* position reacted with **1a** to give the product **3ak** in 92% yield with 96% ee, and a substrate with an electron-donating methoxy group (**2l**) gave the product **3al** in similar yield and 98% ee value. To the best of our knowledge, the use of 2-substituted allyl electrophiles in asymmetric allylic alkylation has been scarcely reported.[8]

Subsequently, a study was initiated to further explore the substrate scope regarding flavonoids **1** with **2h** as the allyl reagent, and the results are summarized in Scheme 4. Fortunately, various aromatic substituted flavanones (**1g**−**o**) could react smoothly in this palladium-catalyzed asymmetric allylic alkylation to furnish the desirable products (**3gh**−**oh**) in good yields (86−99%), diastereoselectivities (>20:1), and enantioselectivities (96−98%) regardless of the presence of electron-donating or electron-withdrawing groups on the aromatic ring, which displayed valuable tolerance to functional groups, including methyl (**1g**), fluoro (**1h**), chloro (**1i**,**l**), bromo (**1j**,**m**,**n**) and methoxyl (**1k**). Thus, this offered ample opportunities for further product derivatization. Alkyl substituents displayed a negative effect on either the yield or enantioselectivity (**1p**,**q**). Substituents with methyl (**1r**), fluoro (**1t**), chloro (**1u**), or bromo (**1v**) on the carbocyclic ring of the flavanones **1** had a negligible effect on both the yields and

Scheme 4. Substrate Scope: Flavanones/Chromanones 1



enantioselectivities. A substrate with strong electron-withdrawing group (**1s**) or an electron-donating substituent (**1w**) significantly decreased the reactivity of this asymmetric allylic alkylation reaction, although almost perfect enantioselectivity could still be achieved. When naphthyl (**1x**) was introduced, the reaction became slow and a prolonged reaction time was necessary to get a satisfactory conversion.

To further investigate the practical utility of this protocol, a gram-scale reaction was carried out under the standard conditions, and the asymmetric allylic alkylation reaction proceeded well to deliver the product with 95% yield and 92% ee (Scheme 5) without significant loss of enantioselectivity and reactivity. Moreover, the transformations of **3aa** were concentrated on functional groups, including carbonyl, ester, and alkenyl. A selective reduction of the carbonyl group of **3aa** with sodium borohydride ($NaBH_4$) proceeded smoothly, affording the chiral alcohol **4** in 88% yield with high diastereoselectivity (>20:1 dr). The protection of the hydroxyl group of the chiral alcohol **4** was successfully realized (93% yield) in the presence of acetic anhydride. Using lithium aluminum hydride ($LiAlH_4$) as the reductant, the chiral diol **6** could be effectively obtained in 90% yield without loss of optical purity. The relative configuration of the hydroxyl group in compound **4** was assigned as *cis*-**4** by an NOE spectrum of **5** (for details, please see the Supporting Information). Finally, oxidative cleavage of the terminal olefin by ozonolysis gave the chiral ketone **7** in 96% yield with >99% ee.

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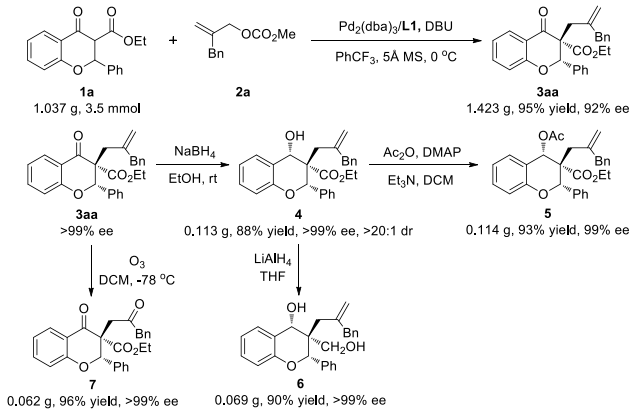
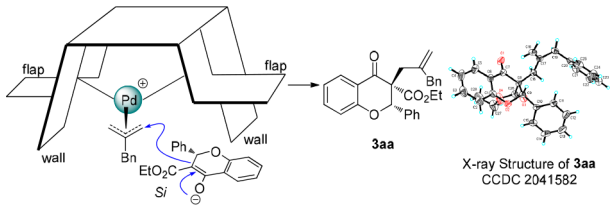
Scheme 5. Gram-Scale Experiment and Synthetic Transformations



The enantioselectivity of the palladium-catalyzed AAA could be illustrated using the model proposed by Trost et al.[5f,9a] As shown in Scheme 6, the enolate of the nucleophile approaches

Scheme 6. Proposed Stereochemical Pathway



the (π-allyl)palladium−**L1** complex by its *Si* face, which avoids the disfavored steric interaction between the "wall" of the ligand and the phenyl ring of the substrate. Furthermore, the absolute configuration of product (+)-**3aa** was unambiguously assigned as 2*S*,3*R* by an X-ray crystallographic analysis, and the absolute configurations of all other products were assigned by analogy.[9b]

In conclusion, utilizing a fast retro-oxa-Michael addition as the racemization step, we have first realized the dynamic kinetic resolution of 2,3-disubstituted flavonoids via palladium-catalyzed asymmetric allylic alkylation, and two contiguous stereogenic centers were constructed on the nucleophiles. A broad range of highly enantiomerically enriched flavonoids bearing a quaternary carbon was conveniently prepared with up to 99% yield and 99% ee. Such a racemization strategy may open a new avenue for the development of other metal-catalyzed asymmetric reactions of flavonoids via dynamic kinetic resolution. Further studies in this area are being actively pursued in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acscatal.1c03732.

Detailed experimental procedures, characterization of new compounds, spectra and X-ray data (PDF)

Crystallographic data (CIF)

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Notes

The authors declare no competing financial interest.

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