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Transforming Racemic Compounds into Two New Enantioenriched Chiral Products via Intermediate Kinetic Resolution

Jian Zhang, Mingyang Song, Weijun Tang, Dong Xue, Jianliang Xiao, Huaming Sun, and Chao Wang*

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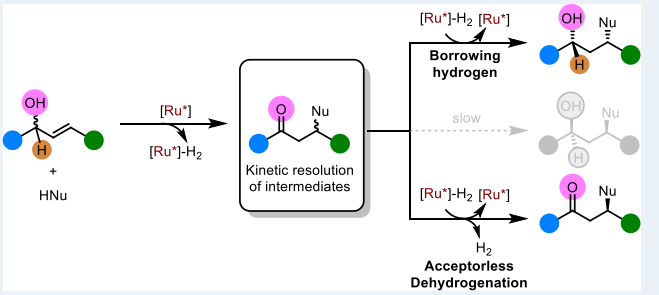
ABSTRACT: Converting racemic compounds to enantioenriched products is an important and economic approach for accessing enantioenriched chiral molecules. A common method is kinetic resolution. Herein, we present a mode of kinetic resolution that transforms racemic compounds into enantioenriched products, in which the kinetic resolution of reaction intermediates is the key. Catalyzed by a single Ru complex, racemic allylic alcohols are shown to react with a glycine-derived Schiff base to afford two chiral compounds, a δ-carbonyl product and a δ-hydroxy variant, with good yields and stereoselectivities (up to >20:1 dr, 99% ee, 920 s factor). Mechanistic studies suggest that multiple hydrogen transfer events exist in the reaction: a dehydrogenative coupling process, which leads to a pair of racemic intermediates, and a transfer hydrogenation-enabled kinetic resolution process that resolves the intermediates, alongside H_2 release at the catalyst.



KEYWORDS: *allylic alcohol, kinetic resolution, hydrogen transfer, amino alcohol, asymmetric catalysis*

INTRODUCTION

Enantioenriched chiral compounds are of great importance to the pharmaceutical and fine chemical industries. The kinetic resolution[1] (KR) of cheap and readily available racemic chiral compounds via chemical transformation is one of the most used methods for obtaining enantioenriched chiral compounds. KR explores the difference in the reaction rates of two enantiomers in a racemic sample, converting one of the enantiomers into a product with the other one unchanged (Figure 1a(1)). The theoretical maximum yield of the product for KR is only 50% if the maximum enantioselectivity is pursued, where half of the starting material is generally wasted. Due to this limitation, new modes for the resolution of racemic chiral compounds have been actively pursued. There are, however, only two other well-established methods available for resolving racemic compounds beyond KR, i.e., dynamic KR (DKR) and parallel KR[2] (PKR). DKR couples KR with in situ racemization of enantiomers, allowing for transforming the enantiomers into a single enantioenriched product with a maximum theoretical yield of 100% (Figure 1a(2)).[1a,3] A precondition for DKR is that the substrate must be able to racemize much faster than its conversion to the desired product. The more recent PKR, developed by Vedejs in 1997, can also achieve a total combined yield of 100% for the desired products. In PKR, two chiral reagents or catalysts react independently with two enantiomers to give two different enantioenriched chiral products (Figure 1a(3)). Although the theoretical yield of PKR is 100%, the requirement of similar formation rates for the two products is not easy to achieve, making it hard to establish a successful PKR reaction. Hence, the development of new modes of transforming racemic compounds into enantioenriched products with a 100% theoretical yield is still highly desirable.

Herein, we present a new mode for resolving racemic chiral compounds. In this mode, the racemic substrates are first converted into a new pair of reactive racemic intermediates, which are then kinetically resolved, affording two different enantioenriched new chiral products with a maximum theoretical yield of 100% (Figure 1a(4)). In contrast to the other modes of resolution, this new mode rests on the kinetic difference of the reacting intermediates rather than that of the substrates. It could thus turn racemates that are conventionally challenging to resolve into valuable products and expand the scope of competent catalysts, providing a complementary strategy to DKR and PKR for transforming racemic compounds into enantioenriched products. We tentatively dub this mode the intermediate KR (IKR) of racemic substrates. Very recently, Feng and co-workers reported an elegant example of the KR of racemic intermediates generated from pro-chiral substrates,[4] which also involves an IKR process. Ideally, the IKR of racemic substrates would see

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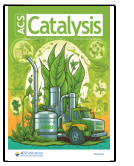

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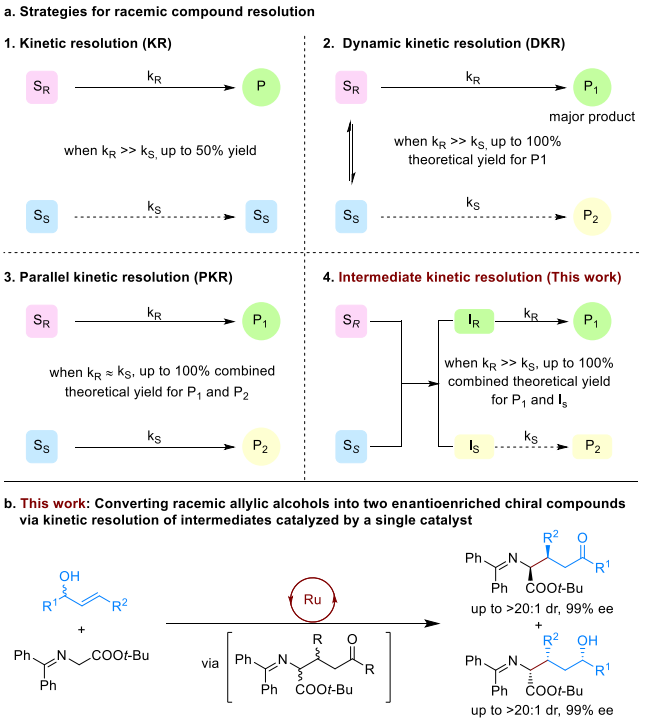


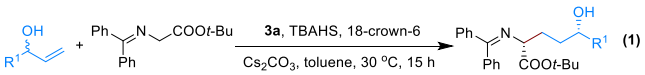
Figure 1. Strategies for resolving racemic chiral compounds.

racemic enantiomers being rapidly converted to racemic intermediates, which are then transformed to enantioenriched products in a one-pot fashion. In this article, we describe such a process.

IKR is demonstrated with the hydroalkylation of racemic allylic alcohols. Specifically, racemic allylic alcohols are shown to react with a glycine-derived Schiff base to give two different amino acid derivates with excellent stereoselectivities catalyzed by a single Ru complex, in which the KR of a pair of racemic ketone intermediates occurs (Figure 1b). The overall IKR process affords two chiral products with multiple chiral centers that are valuable but difficult to access;[5] the δ-functionalized amino acid derivatives could be used as intermediates for the synthesis of enantioenriched biologically active amino acids and heterocyclic compounds.[6] A notable feature of the transformation is that only one chiral catalyst is required to afford two different chiral products with a combined maximum theoretical yield of 100%. The catalyst plays dual roles: activating the relatively stable racemic substrates into reactive intermediates and catalyzing the KR of the resulting racemic intermediates.

RESULTS AND DISCUSSION

Recently, we developed a catalytic system for the asymmetric hydroalkylation[7] of racemic allylic alcohols, which affords chiral amino acid derivatives with two remote chiral centers via borrowing hydrogen catalysis.[8] The stereoselectivities of the transformation are controlled by a chiral Ru catalyst via a dynamic kinetic asymmetric transformation process and a diastereoselectivity amplification process of the product [eq 1]. However, the substrate scope for the catalytic system



☐ Dynamic kinetic asymmetric transformation and diastereoselectivity amplification
☐ Limited to allylic alcohols with a terminal olefin group

was limited to allylic alcohols with a terminal olefin group. For allylic alcohols with an internal olefin group, such as **2a** (Table 1), three chiral centers in the borrowing hydrogen product could be generated; hence, a new strategy to control the stereoselectivity is needed (e.g., **5a** in Table 1). Our initial thoughts were to use a chiral dehydrogenation/hydrogenation catalyst to control the enantioselectivity of the alcohol group and a chiral phase transfer catalyst[9] (PTC) to control the stereoselectivity of the Michael addition step. It was found that the reaction of the model substrates **1a** and **2a** in the presence of a chiral PTC (**PTC-1** or **PTC-2**) and a chiral Ru catalyst (**3a**) could afford the desired product **5a** with excellent diastereo- and enantioselectivities in yields close to 50% (Table 1, entries 1 and 2, **2a** was used in excess based on our previous work[8,10]). Interestingly, a ketone product **4a** was also formed in 25% (with **PTC-1**) and 41% (with **PTC-2**) yields, respectively, with >20:1 diastereoselectivities and good enantioselectivities. Surprisingly, the control experiment showed that similar results could also be obtained in the absence of a PTC (Table 1, entry 3). Note that the reaction produces two new enantioenriched compounds with the common α and β positions of opposite configuration using a single chiral catalyst; hence, an IKR process is likely to be involved.

The Ru catalyst **3a** was proven to be crucial for the reaction. The diamine diphosphine Ru complexes (**3b**−**3d**) without cyclometalation gave poor activities or selectivities (Table 1, entries 4−6), and the Ru complex **3e** without a diamine ligand was inactive for the reaction (Table 1, entry 7). By lowering the reaction temperature to 10 °C and increasing the amount of **2a**, the enantioselectivity of **4a** increased to 80% (Table 1, entry 8). Solvent screening revealed that mesitylene could further improve the enantioselectivity of **4a** to 86%, albeit with a relatively lower yield of **4a** (Table 1, entry 9). The best overall selectivity for both **4a** and **5a** was achieved by using 1.5 mol % of the Ru catalyst **3a** and mesitylene as solvent at 10 °C for 36 h (Table 1, entry 10). It is worth noting that moderate yields and good stereoselectivities were obtained using a 1:1 ratio of **1a** and **2a** (Table 1, entry 11) in a shorter time of 12 h, with 50% of **2a** unreacted. The unreacted **2a** isolated from the reaction mixture is essentially racemic, suggesting that both enantiomers of **2a** could be converted to products at an equal rate. Delightfully, the products (**4a′** and **5a′**) with opposite chiral configurations could be obtained by simply switching the Ru catalyst **3a** to its enantiomer **3a′** (Table 1, entry 12), both of which are commercially available. It is worth noting that the s factors for the KR of **4a** are excellent (Table 1).

With the optimal conditions in hand, we then explored the substrate scope for the reaction of **1a** with different allylic alcohols (Table 2). First, different aryl groups on the alkene carbon of allylic alcohols were examined (Table 2, entries 1−15). Both electron-donating and electron-withdrawing substituents on the *ortho*-, *meta*-, and *para*-positions of the phenyl ring of allylic alcohols could be well tolerated. Excellent yields, diastereoselectivities (>20:1), and enantioselectivities (mostly >95% ee) were obtained for the alcohol product (**5a**−**5o**). Notably, >20:1 dr and 99% ee were obtained for products **5d**, **5j**, and **5l**. The absolute configuration of product **5m** was

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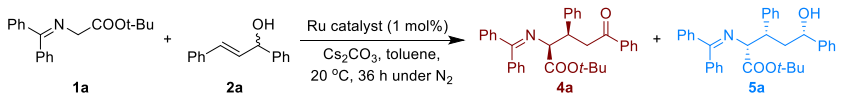
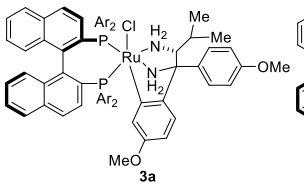
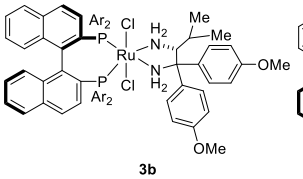
Table 1. Optimization of Reaction Conditions



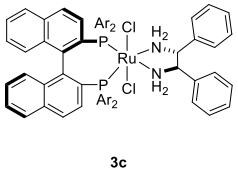
Entry[a]	Ru catalyst	PTC	Yield of **4a** (%)[b]	dr[c]	ee (%)[d]	Yield of **5a** (%)[b]	dr[c]	ee (%)[d]	s[e]
1	**3a**	**PTC-1**	25	>20:1	88	48	>20:1	98	290
2	**3a**	**PTC-2**	41	>20:1	76	44	>20:1	98	228
3	**3a**	-	34	>20:1	74	46	>20:1	97	146
4	**3b**	-	44	>20:1	55	42	>20:1	30	3
5	**3c**	-	6	>20:1	20	4	>20:1	98	120
6	**3d**	-	46	>20:1	40	32	>20:1	98	147
7	**3e**	-	0	-	-	0	-	-	-
8[f]	**3a**	-	42	>20:1	80	49	>20:1	98	244
9[g]	**3a**	-	33	>20:1	86	48	>20:1	97	183
10[h]	**3a**	-	35	>20:1	90	50	>20:1	97	203
11[i]	**3a**	-	21	>20:1	70	22	>20:1	97	138
12[i]	**3a'**	-	34 (**4a'**)[j]	>20:1	88	48 (**5a'**)[k]	>20:1	94	94



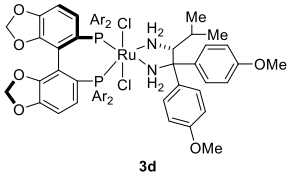
3a
Ar = 3,5-dimethyl phenyl



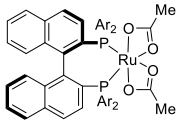
3b
Ar = 3,5-dimethyl phenyl



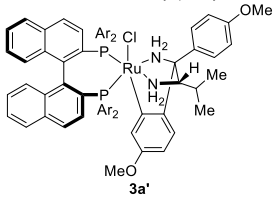
3c
Ar = 3,5-dimethyl phenyl



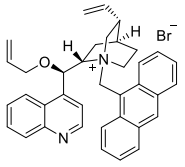
3d
Ar = 3,5-dimethyl phenyl



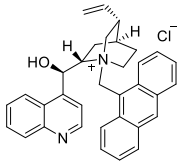
3e
Ar = *p*-methylphenyl



3a'
Ar = 3,5-dimethyl phenyl



PTC-1



PTC-2

[a]Unless otherwise indicated, reaction conditions were carried out with **1a** (0.20 mmol), **2a** (0.30 mmol), catalyst (1 mol %), Cs_2CO_3 (0.20 mmol), toluene (1 mL), 20 °C, under N_2, 36 h. The absolute configuration of **5a** was assigned by analogy to the X-ray structure of product **5m** in Table 2, and the absolute configuration of **4a** was deduced from the structure of **5a**. [b]Determined by ^{1}H NMR analysis with 1,3,5-trimethoxybenzene as an internal standard. [c]The dr value was determined by NMR spectroscopy of the crude reaction mixture. [d]The ee value was determined by HPLC analysis of the pure isolated product. [e]s refers to the selectivity factor for the KR of **4a** and C refers to the concentration of **4a**. Calculated according to $C = (ee^{4a})/(ee^{4a} + ee^{5a})$, $s = \ln[(1 - C)(1 - ee^{4a})]/\ln[(1 - C)(1 + ee^{4a})]$. [f]**2a** (0.40 mmol), 10 °C, 30 h. [g]**2a** (0.40 mmol), 10 °C, mesitylene as a solvent, 30 h. [h]**2a** (0.40 mmol), 1.5 mol % [Ru catalyst], 10 °C, mesitylene as a solvent, 36 h. [i]**2a** (0.20 mmol), 10 °C, mesitylene as a solvent, 12 h. [j]**4a**′ is the enantiomer of **4a**. [k]**5a**′ is the enantiomer of **5a**.

determined to be (2*R*, 3*S*, 5*S*) by X-ray crystallography analysis.[11] The yields for product **4** are relatively lower and the enantioselectivities vary; nevertheless, the diastereoselectivities are excellent (**4a**−**4o**). Substrates with heterocyclic groups are viable, as demonstrated with 2-thienyl and 2-furyl groups (Table 2, entries 14 and 15). Allylic alcohols with different aryl groups adjacent to the hydroxy group were also investigated as substrates (Table 1, entries 16−28). Again, excellent diastereoselectivities and enantioselectivities were obtained, with >20:1 dr and 99% ee for products **5p**, **5r**, **5s**, **5t**, and **5ab**. The yields and stereoselectivities vary for product **4** (**4p**−**4ab**), with the best results observed for product **4q** (42% yield, >20:1 dr, 99% ee). The steric hindrance of the aryl group adjacent to the hydroxy group affects the activity more significantly than that from the aryl group on the alkene carbon. While good results were given for the ortho-substituted phenyl groups on the alkene carbon (Table 2, entries 13 and 14), no reaction was observed for allylic alcohols with ortho-substituted phenyl groups adjacent to the hydroxy group. This is likely because the steric hindrance around the hydroxy group makes it difficult for the dehydrogenation of the group to initiate the reaction. For all of the viable substrates, the s factors are greater than 60, with the highest reaching 920 (Table 2, entry 16).

The usefulness of the protocol was demonstrated by a gram-scale reaction and the derivatization of enantioenriched chiral products. The model reaction of **1a** with **2a** catalyzed by **3a** could be performed at a gram-scale, affording **4a** in 31% yield (0.78 g) and **5a** in 48% yield (1.21 g), with selectivities similar to the small-scale reaction (Figure 2a). Product **4a** could be utilized to synthesize a proline derivative **6** with 3 stereogenic centers by simple hydrolysis and intramolecular reductive amination in just 2 steps with an overall yield of 81% (Figure 2b). Hydrolysis of product **5a** gave δ-hydroxy amino ester product 7, which might have biologic applications[5] (Figure 2c). The product **5m** could undergo Pd-catalyzed intra-

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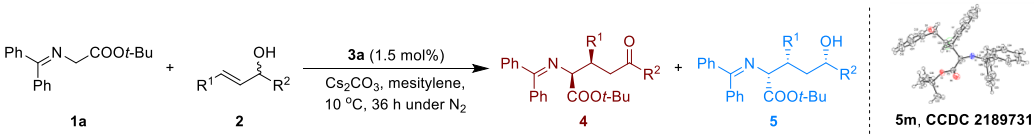
Table 2. Substrate Scope for the Reaction of 1a with Different Allylic Alcohols



5m, CCDC 2189731

Entry[a]	R^1	R^2	Product	Yield of 4 (%)[b]	dr[c]	ee (%)[d]	Product	Yield of 5 (%)[b]	dr[c]	ee (%)[d]	s[e]
1	Ph	Ph	4a	34	>20:1	90	5a	49	>20:1	97	203
2	4-$CH_3C_6H_4$	Ph	4b	31	>20:1	91	5b	45	>20:1	97	210
3	4-*t*-BuC_6H_4	Ph	4c	26	>20:1	90	5c	50	>20:1	96	152
4	4-$OCH_3C_6H_4$	Ph	4d	31	>20:1	73	5d	45	>20:1	99	438
5	4-FC_6H_4	Ph	4e	22	>20:1	71	5e	39	>20:1	95	83
6	4-ClC_6H_4	Ph	4f	39	>20:1	82	5f	49	>20:1	98	254
7	4-BrC_6H_4	Ph	4g	30	>20:1	96	5g	49	>20:1	97	260
8	4-IC_6H_4	Ph	4h	26	>20:1	95	5h	49	>20:1	98	371
9	4-$CF_3C_6H_4$	Ph	4i	39	>20:1	86	5i	48	>20:1	99	556
10	3-$CH_3C_6H_4$	Ph	4j	34	>20:1	74	5j	50	>20:1	99	444
11	3-ClC_6H_4	Ph	4k	35	>20:1	95	5k	49	>20:1	96	183
12	2-$CH_3C_6H_4$	Ph	4l	33	>20:1	92	5l	50	>20:1	99	659
13	2-BrC_6H_4	Ph	4m	39	>20:1	85	5m	48	>20:1	98	270
14	2-thienyl	Ph	4n	23	>20:1	52	5n	45	>20:1	99	335
15	2-furyl	Ph	4o	30	>20:1	51	5o	50	>20:1	98	165
16	Ph	4-$CH_3C_6H_4$	4p	30	>20:1	98	5p	45	>20:1	99	922
17	Ph	4-$OCH_3C_6H_4$	4q	42	>20:1	99	5q	40	>20:1	98	525
18	Ph	4-FC_6H_4	4r	30	>20:1	89	5r	50	>20:1	99	600
19	Ph	4-ClC_6H_4	4s	37	>20:1	71	5s	33	>20:1	99	425
20	Ph	4-BrC_6H_4	4t	40	>20:1	94	5t	36	>20:1	99	713
21	Ph	3-$CH_3C_6H_4$	4u	25	>20:1	73	5u	45	>20:1	98	218
22	Ph	3-$OCH_3C_6H_4$	4v	41	>20:1	93	5v	47	>20:1	95	133
23	Ph	3-FC_6H_4	4w	35	>20:1	87	5w	49	>20:1	93	78
24	Ph	3-ClC_6H_4	4x	40	>20:1	95	5x	40	>20:1	97	246
25	Ph	3-BrC_6H_4	4y	40	>20:1	90	5y	42	>20:1	98	307
26	Ph	2-Naphthyl	4z	30	>20:1	92	5z	45	>20:1	97	217
27	Ph	Piperonyl	4aa	30	>20:1	71	5aa	32	>20:1	94	69
28	Ph	2-thienyl	4ab	32	>20:1	82	5ab	40	>20:1	99	511

[a]Unless otherwise indicated, reaction conditions were carried out with **1a** (0.20 mmol), **2a** (0.40 mmol), **3a** (1.5 mol %), Cs_2CO_3 (0.20 mmol), mesitylene (1 mL), 10 °C, under N_2, 36 h. The absolute configuration of **5** was assigned by analogy to the X-ray structure of product **5m**, and the absolute configuration of **4** was deduced from the structure of **5**. [b]Yield of the isolated product. [c]The dr value was determined by NMR spectroscopy of the crude reaction mixture. [d]The ee value was determined by HPLC analysis of the pure isolated product. [e]*S* refers to the selectivity factor for the KR **4** and *C* refers to the concentration of **4**. Calculated according to $C = (ee^{4a})/(ee^{4a} + ee^{5a})$, $s = \ln[(1 - C)(1 - ee^{4a})]/\ln[(1 - C)(1 + ee^{4a})]$.

molecular C−O coupling to give substituted chiral chroman product **8** in a good yield and stereoselectivity (Figure 2d). Interestingly, product **5m** could also be selectively transformed into enantioenriched indoline derivative **9** via sequential hydrolysis and Cu-catalyzed selective intramolecular C−N coupling (Figure 2e). The enantioenriched heterocyclic products (**6**,[12] **8**,[6abc−d] and **9**[6efg−h]) with multiple chiral centers, which are difficult to obtain via other methods, could have potential biological applications or serve as intermediates for the synthesis of ligands and bioactive molecules.

The mechanism of the transformation was then considered. The yields and ee values for products **4a** and **5a** of the model reaction under standard reaction conditions were monitored (Figure 3). Both the yields of **4a** and **5a** increased gradually with time. Interestingly, the ee values of the ketone product **4a** increased from ca. 40% to ca. 90%, while the ee values of the alcohol product **5a** remained excellent and steady throughout (>95%). The increase in enantioselectivity for **4a** suggests that the two enantiomers of **4a** are kinetically resolved during the reaction.

Based on our previous work on the enantioselective transformation of allylic alcohols[8,10d] and the above time course of the reaction, the transformation may proceed via a dehydrogenation/Michael addition/reduction process. Our

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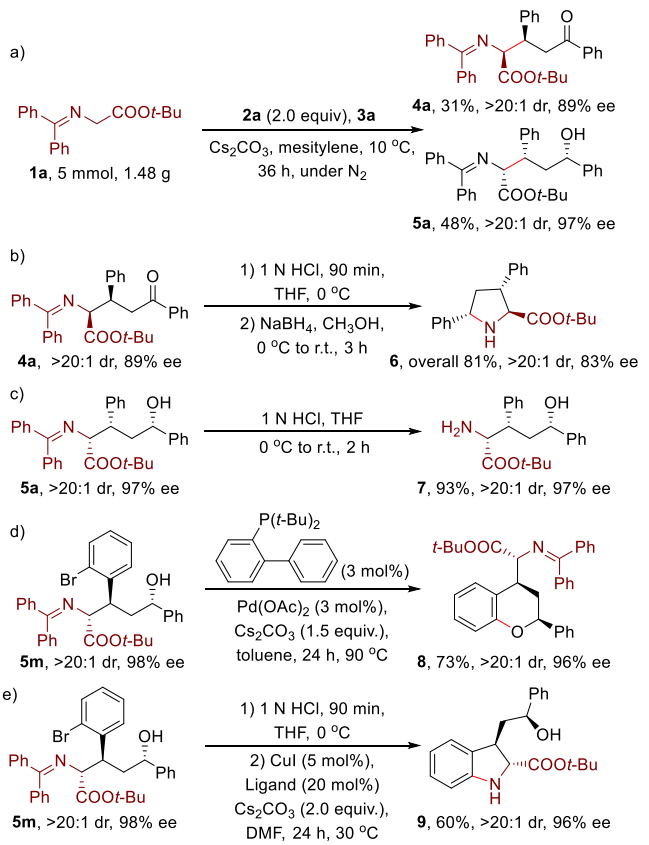

Figure 2. Gram-scale reaction and synthetic applications. (a) Gram-scale synthesis. (b) Synthesis of pyrrolidine **6** by hydrolysis and intramolecular reductive amination. (c) Synthesis of δ-hydroxy amino ester **7** by hydrolysis. (d) Synthesis of chiral chroman product **8** via Pd-catalyzed intramolecular C−O coupling. (e) Synthesis of indoline derivative **9** via sequential hydrolysis and Cu-catalyzed selective intramolecular C−N coupling.

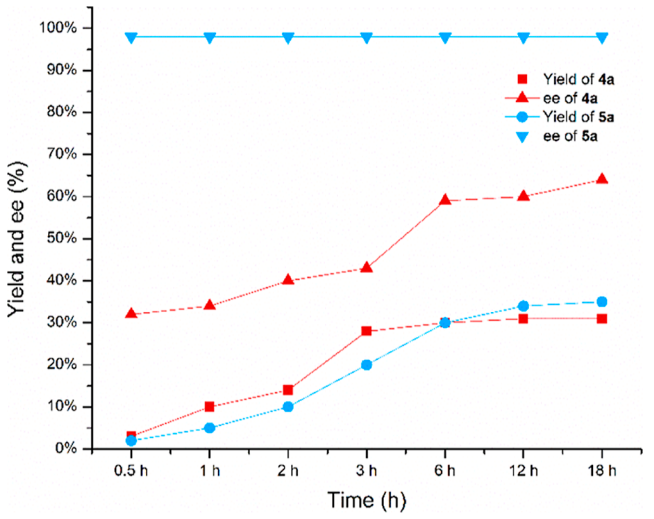

Figure 3. Variation of yields and ee values versus time for products **4a** and **5a** under the standard reaction conditions.

previous studies showed that catalyst **3a** could dehydrogenate alcohols to initiate hydrogen transfer processes.[8,10a,d,e] The dehydrogenation of allylic alcohol **2a** would produce chalcone as an intermediate. With this in mind, the reaction of **1a** with chalcone under the standard reaction conditions in the absence of **2a** was carried out. Product **10** with ca. 67% yield, >20:1 dr, and 0% ee was obtained, possibly via a Michael addition process. The reaction of **1a** with chalcone could also take place without Ru catalyst **3a** (Figure 4a); however, the base Cs_2CO_3 is indispensable. It is worth noting that excellent diastereoselectivity (20:1 dr) was obtained for **10** without the chiral catalyst. These results suggest that the reaction starts with the dehydrogenation of **2a** by **3a** to form chalcone, which

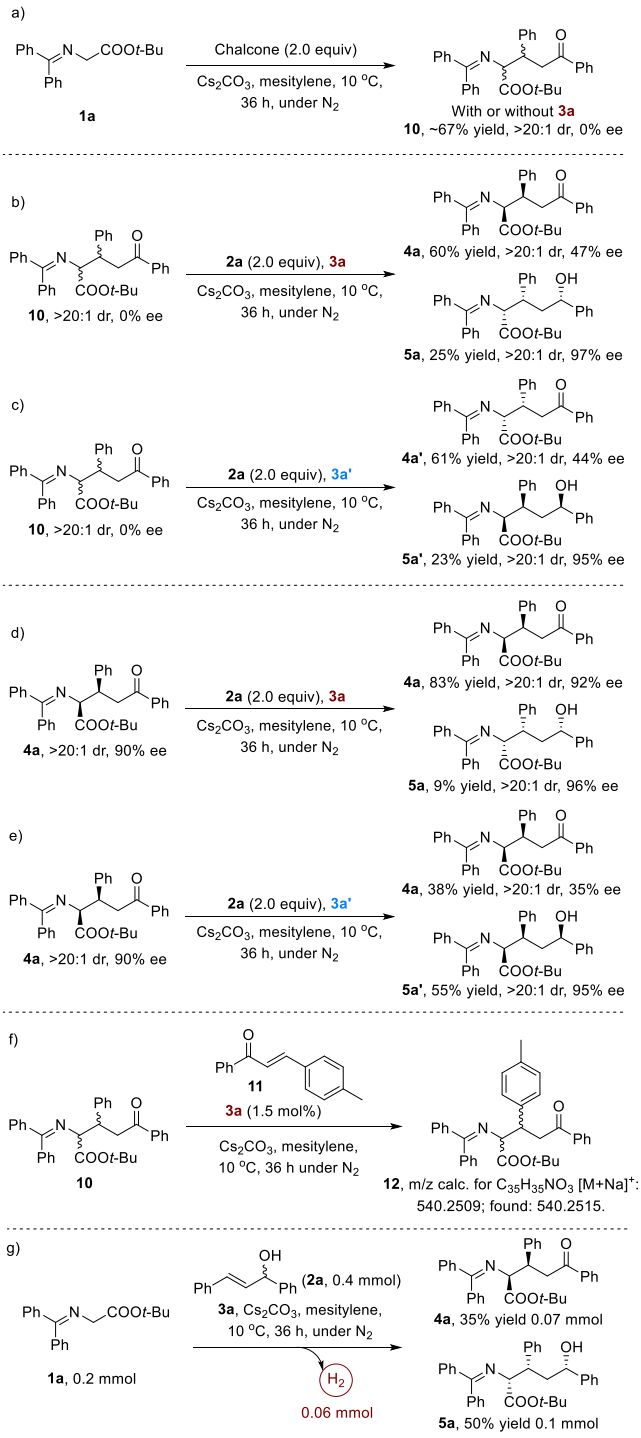

Figure 4. Reactions aimed to peer into the reaction mechanism. (a) Conjugation addition of **1** to chalcone. (b−e) Control experiments for the reduction of ketone intermediates. (f) Evidence for the *retro*-Michael addition reaction. (g) Detection of hydrogen gas.

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undergoes a diastereoselective Michael addition with **1a** to give racemic intermediate **10**.

Subjecting the racemic ketone **10** (>20:1 dr) to the standard reaction conditions in the absence of substrate **1a** afforded **4a** with 60% yield, >20:1 dr, and 47% ee, and **5a** with 25% yield, >20:1 dr, and 97% ee (Figure 4b). The low yield of **5a** might be due to the competition for reduction by chalcone resulting from the dehydrogenation of **2a**. In addition, by switching catalyst **3a** to **3a′**, **10** was converted into products **4a′** (61% yield, >20:1 dr, and 44% ee) and **5a′** (23% yield, >20:1 dr, and 95% ee), which are enantiomers of **4a** and **5a**, respectively (Figure 4c). These results suggest that the ketone group of **10** could be reduced using **2a** as a hydrogen source and there is a match/mismatch effect between the chirality of **10** and the Ru catalyst, resulting in different reduction rates for the two enantiomers of **10**. Furthermore, the reduction of **4a** (>20:1 dr, 90% ee) with **2a** catalyzed by **3a** gave only 9% of product **5a** with the majority of **4a** left (Figure 4d); however, a 55% yield of **5a′** was obtained by switching the catalyst from **3a** to **3a′** (Figure 4e). The above results all corroborate that racemic intermediate **10** is formed in the model reaction, which is then kinetically resolved via a Ru-catalyzed hydrogen transfer process, thus pointing to an IKR process in operation.

If products **5** are formed from the KR of racemic intermediates, it is expected that the yields and enantioselectivities of product **4** should be high when the yields of **5** are close to 50% and the enantioselectivities of **5** are very high. However, the yields and enantioselectivities of **4** are generally inferior to **5**, particularly in cases of **4d**, **4n**, **4o**, and **4u**. A plausible explanation for this phenomenon is that the racemic intermediate could undergo a *retro*-Michael addition, resulting in the partial decomposition of **4** and the erosion of the enantioselectivities of **4**. The existence of a *retro*-Michael addition process for the racemic intermediate is demonstrated with **10** (Figure 4f). When **10** is stirred with an *α,β*-unsaturated ketone **11** under standard reaction conditions, product **12** is observed in HRMS (see Section 7.1 in the Supporting Information for details). The formation of **12** could be due to a *retro*-Michael addition of **10** to give **1a**, followed by a Michael addition of **1a** with **11**. The amount of crossover product formed was determined by ^{19}F NMR studies (see Section 7.1 in the Supporting Information for details).

A remaining concern is the mass balance of the reaction as the stoichiometry of IKR in question demands the release of hydrogen. For instance, in the model reaction under the optimized reaction conditions, 0.2 mmol of **1a** was transformed into 0.07 mmol (35% yield) of **4a** and 0.1 mmol (50% yield) of **5a** (Table 1, entry 11), with 0.14 mmol of hydrogen atom missing. The formation of **5a** from **1a** and **2a** should proceed via a borrowing hydrogen pathway,[13] which is a redox-neutral process. However, the reaction of **1a** with **2a** to form **4a** should be a dehydrogenative coupling process. Thus, there should be an oxidant to accept the hydrogen produced or a stoichiometric amount of hydrogen gas being released. A possible oxidant is excess substrate **2a**, whose C=C bond could be reduced. However, no C=C bond-reduced product from **2a** was observed in the crude ^{1}H NMR spectrum of the model reaction under the standard reaction conditions (see Section 7.2 in the Supporting Information for details). Interestingly, 0.06 mmol of hydrogen gas (Figure 4g), almost the quantity needed to produce 0.07 mmol of **4a**, was detected in the headspace of the model reaction under standard reaction conditions (see Sections 7.3 and 7.4 in the Supporting Information for details). The formation of a stoichiometric amount of hydrogen gas supports the notion that **4a** is formed via an acceptorless dehydrogenative coupling process.[14] It is worth noting that both hydrogen-borrowing and acceptorless dehydrogenative coupling processes exist in our reaction, which is unprecedented in hydrogen transfer reactions.

Based on the above mechanistic studies, a possible reaction pathway and explanation for the stereoselectivity of the model reaction are proposed (Figure 5). Both enantiomers of **2a** are

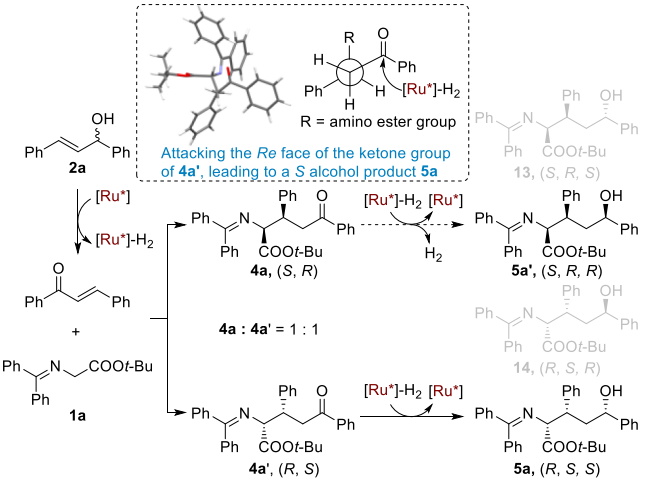

Figure 5. Proposed mechanism for the example of **2a** reacting with **1a**.

dehydrogenated to generate chalcone and a Ru hydride complex (Table 1, entry 10). Chalcone then reacts with **1a** via a base-promoted diastereoselective Michael addition pathway to produce a pair of new enantiomers **4a** (*S*, *R*) and **4a′** (*R*, *S*) in a racemic manner, whose ketone groups could be reduced by Ru hydrides. From the Newman projection of the stable confirmation of **4a′** (optimized with Spartan, Figure 5, top, see Section 7.5 in the Supporting Information for details), it is apparent that a Ru hydride will attack the less hindered Re face of the ketone group, leading to product **5a**. Similarly, the reduction of **4a** favors product **5a′**. Indeed, isomers **13** and **14** are not observed at all in the reaction. Also, the chirality of the Ru hydride derived from **3a** matches the chirality of **4a′**, leading to a much faster reduction rate than that of **4a** (>200 times according to the s factor). Thus, intermediates **4a** and **4a′** are kinetically resolved, affording **5a** as the major reduced product. The remaining hydride is released as hydrogen gas, presumably via protonation, to regenerate the Ru catalyst. The chirality of the final product alcohol **5a** is determined by the intermediate **4a′**, with the mechanism of reduction well studied in the literature.[15] It is worth noting that a DKR process is not involved in the reaction, which departs from our previous work.[8] The reason could be that the increased steric hindrance of **4a** and **4a′** makes it difficult to deprotonate the relative acidic hydrogen atom on the carbon adjacent to the ester group.

CONCLUSIONS

In conclusion, readily available racemic allylic alcohol could be converted to two new valuable enantioenriched chiral products with multiple chiral centers in a one-pot reaction catalyzed by a single Ru catalyst. The reaction involves both borrowing hydrogen and acceptorless dehydrogenative coupling pro-

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cesses, affording the two chiral products via the KR of racemic intermediates. This IKR protocol provides an alternative KR mode for racemic compounds and may inspire the development of new transformations for the synthesis of enantioenriched chiral compounds from racemates.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acscatal.3c04599.

Experimental procedures, spectroscopic traces for mechanistic studies, and characterization data for products (PDF)

Crystallographic information for 5m (CIF)

■ AUTHOR INFORMATION

Corresponding Author

Chao Wang − *Key Laboratory of Applied Surface and Colloid Chemistry, Ministry of Education, School of Chemistry and Chemical Engineering, Shaanxi Normal University, Xi'an 710062, China;* orcid.org/0000-0003-4812-6000; Email: c.wang@snnu.edu.cn

Authors

Jian Zhang − *Key Laboratory of Applied Surface and Colloid Chemistry, Ministry of Education, School of Chemistry and Chemical Engineering, Shaanxi Normal University, Xi'an 710062, China*

Mingyang Song − *Key Laboratory of Applied Surface and Colloid Chemistry, Ministry of Education, School of Chemistry and Chemical Engineering, Shaanxi Normal University, Xi'an 710062, China*

Weijun Tang − *Key Laboratory of Applied Surface and Colloid Chemistry, Ministry of Education, School of Chemistry and Chemical Engineering, Shaanxi Normal University, Xi'an 710062, China*

Dong Xue − *Key Laboratory of Applied Surface and Colloid Chemistry, Ministry of Education, School of Chemistry and Chemical Engineering, Shaanxi Normal University, Xi'an 710062, China;* orcid.org/0000-0002-7269-6356

Jianliang Xiao − *Department of Chemistry, University of Liverpool, Liverpool L69 7ZD, U.K.;* orcid.org/0000-0003-2010-247X

Huaming Sun − *Key Laboratory of Applied Surface and Colloid Chemistry, Ministry of Education, School of Chemistry and Chemical Engineering, Shaanxi Normal University, Xi'an 710062, China;* orcid.org/0000-0001-7133-1948

Complete contact information is available at: https://pubs.acs.org/10.1021/acscatal.3c04599

Notes

The authors declare no competing financial interest.

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