Asymmetric Guerbet Reaction to Access Chiral Alcohols

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Abstract: The first example of asymmetric Guerbet reaction has been developed. Using commercially available, classic Noyori Ru(II)-diamine-diphosphine catalysts, well-known in asymmetric hydrogenation, racemic secondary alcohols are shown to couple with primary alcohols in the presence of a base, affording new chiral alcohols with enantiomeric ratios of up to 99:1. Requiring no reducing agents, the protocol provides an easy, alternative route for the synthesis of chiral alcohols. Mechanistic studies reveal that the reaction proceeds via a Ru-catalyzed asymmetric hydrogen-autotransfer process in concert with a base-promoted allylic alcohol isomerization.

Introduction

Guerbet reaction, i.e. the coupling of two primary alcohols to give a new alcohol product, was discovered more than 100 years ago by Marcel Guerbet (Figure 1a).[1] Since its discovery, the reaction has been extensively studied and found broad applications in the production of plasticizers, lubricants, fuels, fuel additives, and personal care products.[2] The alcohols so formed are chiral, but racemic. If the Guerbet reaction could be made enantioselective, it would provide an appealing new approach to accessing chiral alcohols that deviates from the most-widely practiced asymmetric hydrogenation[3] or asymmetric transfer hydrogenation[4] of ketones, necessitating no reducing agents and producing water as the only byproduct. Optically active chiral alcohols serve as versatile chiral synthons for the production of numerous pharmaceuticals, agrochemicals and fine chemicals. However, to the best of our knowledge, an asymmetric variant of the Guerbet reaction remains unknown.

Mechanistically, the cross coupling of racemic secondary alcohols with primary alcohols shares the same mechanism as the typical Guerbet reactions, with all proceeding via a "borrowing hydrogen" or hydrogen autotransfer process.[5] A large number of catalysts have been reported to catalyze this transformation to give *racemic alcohol products* (Figure 1b).[6] In related studies, Nishibayashi,[7] Adolfsson,[8] Donohoe[9] and their co-workers showed that enantioenriched alcohol[7,8] or ketone[9] products could be obtained in the cross coupling of ketones with

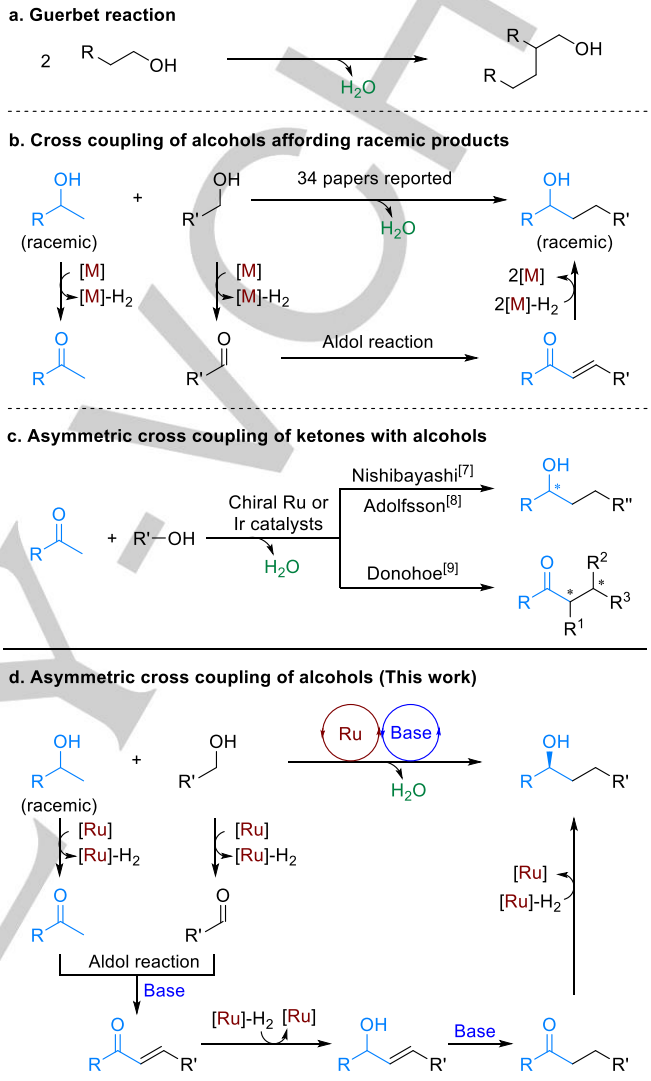

Figure 1. Guerbet reaction, cross coupling of ketones with alcohols and cross coupling of alcohols via hydrogen autotransfer.

alcohols using chiral Ru or Ir catalysts (Figure 1c). *However, asymmetric cross coupling of two alcohols remains elusive*. We hypothesized that if a chiral catalyst capable of both dehydrogenation and hydrogenation reactions could be found, it might be possible to make the borrowing hydrogen or Guerbet reaction enantioselective. Although dehydrogenation and hence racemization of the product by the same catalyst are also likely, the increased steric bulkiness in the product would hinder this reaction. Herein, we disclose that by employing a Noyori Ru-diamine-diphosphine catalyst, well-known in asymmetric hydrogenation, *enantiomerically enriched chiral alcohols could be produced from the cross coupling of racemic secondary alcohols with primary benzylic alcohols, providing the first examples of asymmetric Guerbet reaction.* The catalysis disclosed also adds a new transformation to the asymmetric "borrowing hydrogen" reactions[10] reported by Nishibayashi,[7] Williams,[11] Oe,[12] Adolfsson,[8] Zhao,[13] Beller,[14] Rodriguez,[15]

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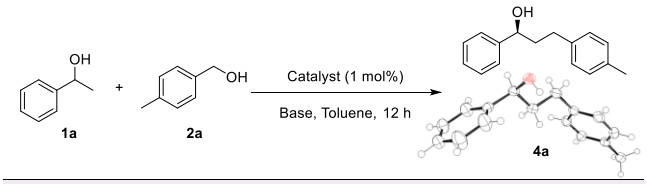
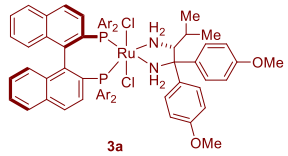
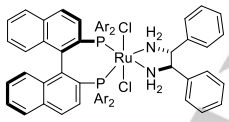
Table 1. Optimization of the reaction conditions for *β*-alkylation of 1-phenylethanol with 4-tolylmethanol.



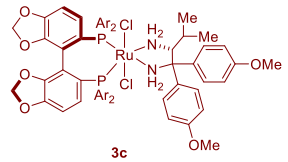
Entry	Temperature (°C)	Base (equiv.)	Catalyst	Yield (%)	er[b]
1	80	NaOH (0.25)	**3a**	48	68:32
2	60	NaOH (0.25)	**3a**	12	93:7
3	50	NaOH (0.25)	**3a**	4	96:4
4	60	*t*BuOK (0.25)	**3a**	13	95:5
5	60	*t*BuOK (0.25)	**3b**	3	93:7
6	60	*t*BuOK (0.25)	**3c**	12	95:5
7	60	*t*BuOK (0.25)	**3d**	4	80:20
8[c]	60	*t*BuOK (0.25)	**3e**	21	51:49
9[c]	60	*t*BuOK (0.25)	**3f**	92	51:49
10	60	*t*BuOK (1)	**3a**	47	92:8
11[d]	60	*t*BuOK (1)	**3a**	64	93:7
12[e]	60	*t*BuOK (1)	**3a**	35	96:4



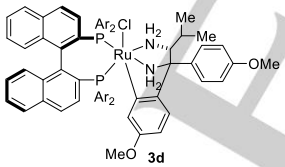
3a
Ar = 3, 5-dimethyl phenyl



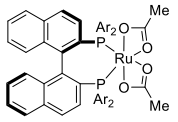
3b
Ar = 3, 5-dimethyl phenyl



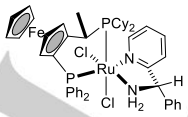
3c
Ar = 3, 5-dimethyl phenyl



3d
Ar = 3, 5-dimethyl phenyl



3e
Ar = *p*-methylphenyl



3f

[a] Reaction conditions: **1a** (1 mmol), **2a** (1 mmol), catalyst (1 mol%), toluene (2 mL) under Ar, 12 h, isolated yield. [b] The enantiomeric ratio (er) was determined by HPLC analysis of pure isolated product, and the absolute configuration was determined by X-ray crystallography. [c] *R*-**4a** was the major product. [d] **1a** : **2a** = 3 : 1. [e] **1a** : **2a** = 3 : 1, with 0.5 mol% catalyst.

Zhou,[16] Popowycz,[17] Donohoe[9] and Dydio.[18] It proceeds via an interesting cooperative Ru-catalyzed hydrogen autotransfer and base-catalyzed isomerization process (Figure 1d).

Results and Discussion

1. Reaction development. We commenced our studies by screening of a variety of known asymmetric hydrogenation catalysts, in the hope to find a catalyst that would enable the asymmetric coupling of 1-phenylethanol **1a** with 4-tolylmethanol **2a** (Table 1). Pleasingly, we found that amongst the catalysts screened, the Ru(II)-diamine-diphosphine complex **3a**, which was developed by Noyori, Ohkuma and co-workers for asymmetric hydrogenation of ketones,[19] could catalyze the coupling of **1a** with **2a**, affording **4a** with 48% yield and 68:32 er in the presence of 0.25 equivalent of NaOH at 80 °C for 12 h (Table 1, entry 1). The observation is somewhat surprising, as such Ru complexes have rarely been used in asymmetric hydrogen transfer reactions.[20] Decreasing the reaction temperature led to much higher enantioselectivities, albeit with lower yields (Table 1, entries 2-3). A slightly better enantioselectivity and similar yield was obtained by replacing NaOH with *t*BuOK as base (Table 1, entry 4). In comparison, the other commercially available hydrogenation/transfer hydrogenation catalysts afforded inferior asymmetric induction, except catalyst **3c** which showed a similar activity and enantioselectivity to **3a** (Table 1, entries 5-9, see more examples in Table S3 in the SI). Notably, the more electron-rich **3f** displayed a much higher activity, with the product being almost racemic though (Table 1, entry 9). Further optimization of reaction conditions, including solvent, the amount of base, substrate ratio, and time (see SI for details), led to the alcohol **4a** being isolated in a good yield of 64% with a high enantiomeric ratio of 93:7, using 1 mol% of **3a**, 1 equivalent of *t*BuOK, and 3 equivalents of **1a** (relative to **2a**) at 60 °C for 12 h (Table 1, entry 11). Although the yield of **4a** could be further increased by prolonging the reaction time, the enantioselectivity was found to decrease (*vide infra*). The reaction was shown to be feasible at a higher S/C of 200, affording 35% yield and 96:4 er in 12 h (Table 1, entry 12). The configuration of the major enantiomer **4a** was determined to be *S* by single-crystal X-ray diffraction, as shown in Table 1.

2. Substrate scope, gram-scale reaction and synthetic application. We went on to explore the substrate scope of the reaction using the conditions shown in entry 11 of Table 1 with **3a** or **3c** as catalysts (Figure 2, see section 4 in the SI for detailed conditions). The reaction of various racemic secondary alcohols with primary benzylic alcohols was first examined (Figure 2, **4a**-**4u**). As can be seen, the alcohols were obtained in good to excellent enantioselectivities. However, this is achieved at the expense of yield to some degree. In particular, in order to obtain acceptable enantioselectivities for *para* and *meta*-substituted secondary alcohols (**4b**-**4j**), the product yields need to be controlled to be moderate, as the er would erode at higher conversions (*vide infra*). Interestingly, we noted that substrates with an *ortho*-methyl group on the phenyl ring of 1-phenylethanols generally afforded better results in terms of both yields and enantioselectivities, e.g. **4k**-**4o** vs **4a**-**4e**. Notably, **4l** was obtained in 75% NMR yield and 99:1 er. This *ortho*-methyl effect presumable stems from the increased steric hindrance in the product that inhibits dehydrogenation-triggered racemization. Aliphatic secondary alcohols could also react, as exemplified with **4p**, albeit with a low enantioselectivity, which could be improved via recrystallization. A furan heterocycle could be tolerated (**4u**). Realizing the *ortho*-methyl effect, the coupling of (2,4-dimethylphenyl)ethan-1-ol (**1m**) with various primary alcohols was next investigated (Figure 2, **5a**-**5ad**). High enantioselectivities were observed for these couplings with

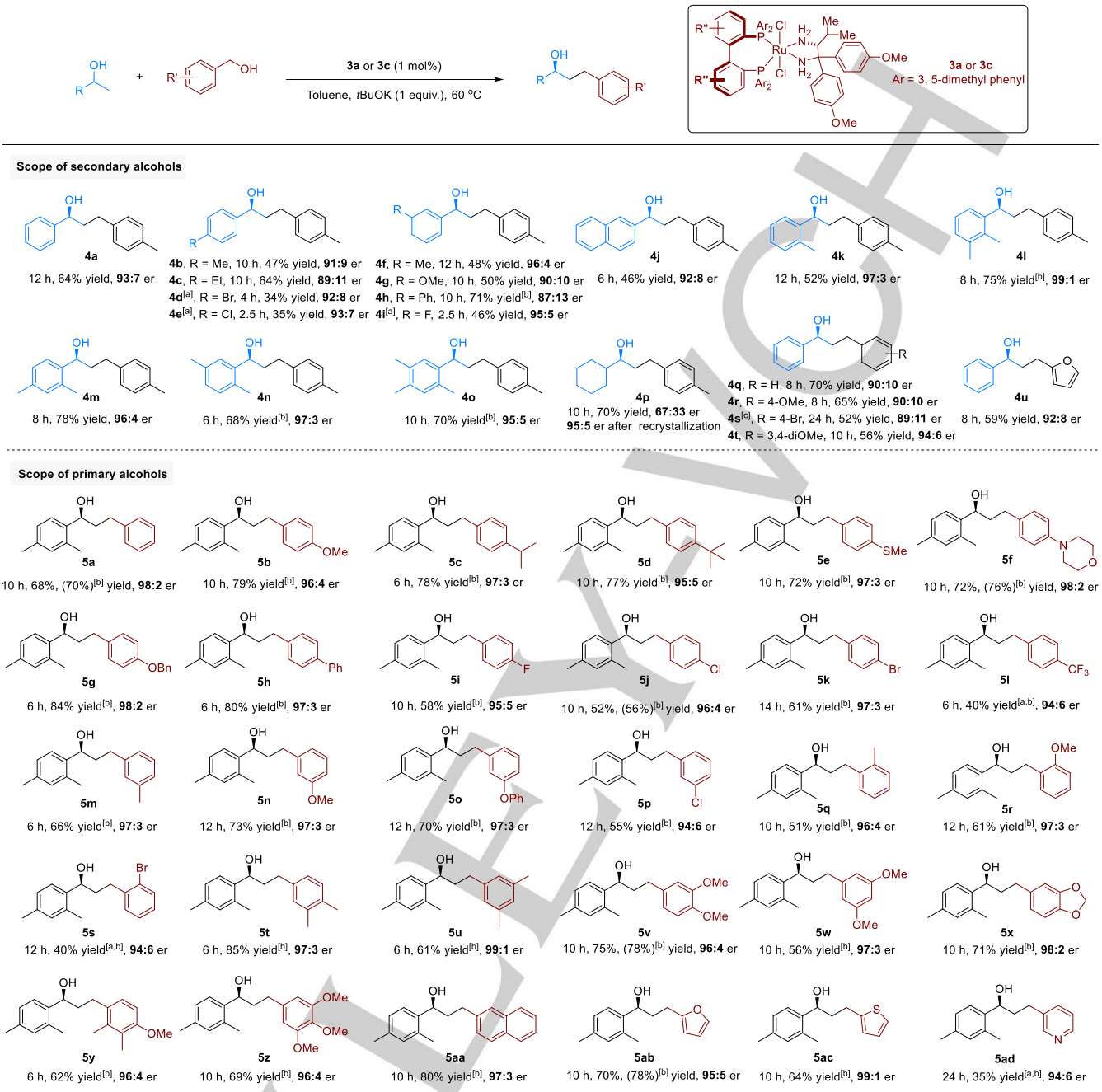


Figure 2. Substrate scope for asymmetric *β*-alkylation of secondary alcohols with primary alcohols. Reaction conditions: secondary alcohol (3 mmol), primary alcohol (1 mmol), *t*BuOK (1 mmol), catalyst (1 mol%), toluene (2 mL), under Ar, Isolated yield. The products could not be totally separated from unreacted substrates via silica chromatography for examples with only ^{1}H NMR yields. The enantiomeric ratio (er) was determined by HPLC analysis of pure isolated product for all the examples. See SI for detailed reaction conditions. [a] **3c** was used as catalyst. [b] ^{1}H NMR yield with 1,3,5-trimethoxybenzene as an internal standard. [c] 2mol% of **3a** was used.

synthetically sensible yields in general (> 90:10 er for all, and notably 99:1 er for **5u**). The electronic properties of substituents on the phenyl rings of the primary benzylic alcohols appear to affect their activities slightly, with electron-donating groups performing better than electron-withdrawing ones (**5b**-**5d**, **5g** vs **5i**-**5l**). Again, *para*, *meta* and *ortho*-substituents on the phenyl rings of these alcohols are all tolerated. Worth noting are substrates with *N*, *O* and *S*-containing heterocycles, which are viable for the reaction (**5f**, **5ab**-**5ad**). However, aliphatic primary alcohols failed to give the desired product, probably due to the complex reactivity of the aliphatic aldehyde intermediates.

The utility of the protocol is further demonstrated by a gram-scale reaction and synthetic application of one of the alcohol products (Figure 3). Thus, coupling of 1-(2,4-dimethylphenyl) ethan-1-ol (**1m**) with (4-morpholinophenyl)methanol (**2g**) afforded 1.22 g of **5f** with 95:5 er (Figure 3a, section 5 in the SI), and the alcohol **5s** underwent cyclization via Pd-catalyzed intramolecular C-O bond coupling to form a chiral chroman

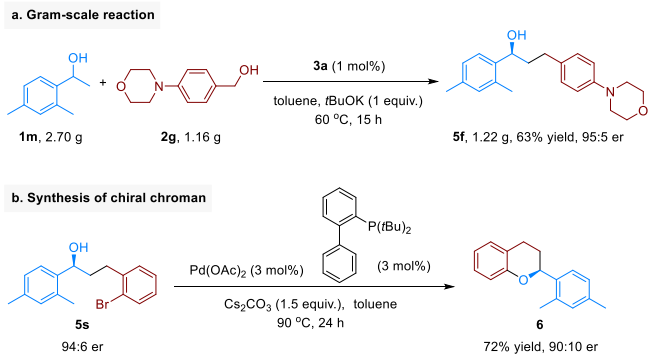
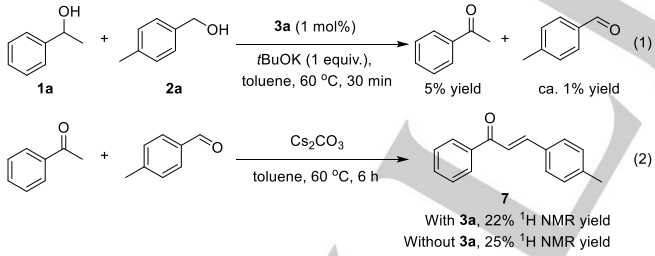


Figure 3. Gram-scale reaction and synthetic application.

compound **6** with only slight erosion of the enantiomeric ratio (Figure 3b, section 6 in the SI). This latter reaction provides a convenient route for accessing chiral chromans, which exist as the core skeleton of many natural products with biological activities.[21]

3. Mechanistic studies. To gain mechanistic insight into this new transformation, a series of probing experiments were then carried out. Previous studies on achiral cross coupling of alcohols with transition metal catalysts[6] suggest that the asymmetric Guerbet reaction under question might proceed via dehydrogenation of both alcohols to a ketone and an aldehyde, followed by aldol condensation and reduction (Figure 1d). Analysis by ^{1}H NMR of the crude reaction mixture resulting from the coupling **1a** with **2a** in 30 minutes with **3a** as catalyst revealed indeed the formation of acetophenone (5% yield) and 4-methylbenzaldehyde (ca 1% yield) (Eq. 1, also see section 7.1 in the SI for details). It is conceivable that acetophenone would condense with 4-methylbenzaldehyde to afford an *α,β*-unsaturated ketone **7** under the basic conditions employed, with or without **3a** (Eq. 2, also see section 7.2 in the SI for details).[22]



An interesting question then is how **7** would be reduced to the product **4a**. The Noyori Ru-diamine-diphosphine catalysts are well-known to be selective for the reduction of C=O, instead of C=C, double bonds in substrates such as *α,β*-unsaturated ketones.[19b, 19c] Monitoring the reduction of **7** with **1a** as reductant and **3a** as catalyst showed that only the carbonyl reduction product **8**, an allylic alcohol, was formed in the initial stage of the reaction in the presence of Cs_2CO_3 (Figure 4).[22] This is in line with what would be expected of the Noyori catalyst. The quantity of **8** decreased after 0.5 h followed by the appearance of a ketone intermediate **9** and the final product **4a** (Figure 4). The intermediate **8** was then synthesized and examined. In the presence of **1a** (1 equiv.), *t*BuOK (1 equiv.), and **3a** (1 mol%) in toluene, the allylic alcohol **8** was primarily converted to **9** (14% yield) and **4a** (46% yield) (see section 7.3 in

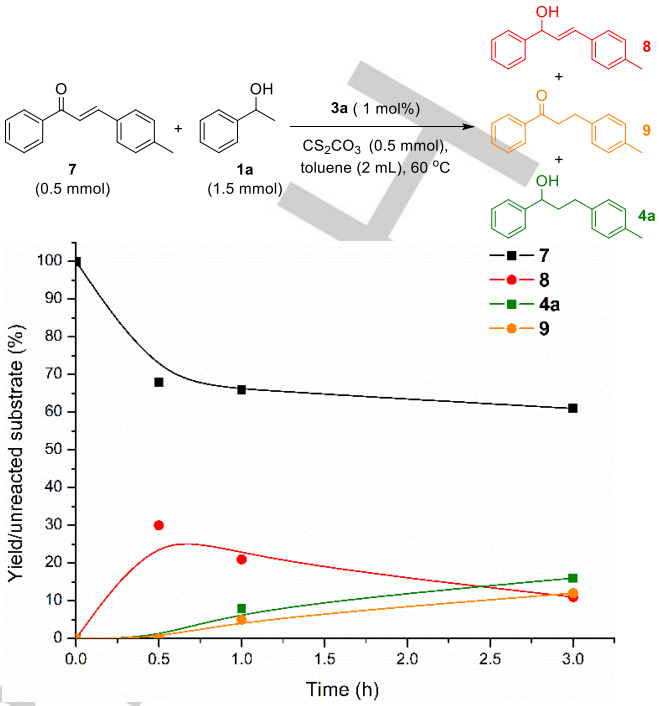
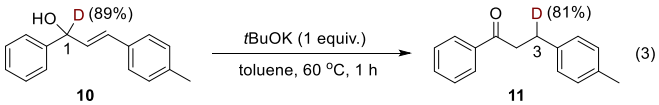


Figure 4. Time-dependent distribution of substrate, intermediates and product for **3a** catalyzed reduction of **7** with **1a** as hydrogen source. Yields and the quantity of unreacted substrate were determined by ^{1}H NMR with 1,3,5-trimethoxybenzene as an internal standard.

the SI for details). These observations suggest that **7** could be first reduced to **8**. The allylic alcohol could then be transformed into the ketone product **9**, reduction of which would afford **4a** under the reaction conditions.

If this is the case, another question arises, that is, how the allylic alcohol **8** could be transformed into the ketone **9**. Ohkuma and co-workers have showed that the **3a** type catalyst is unable to isomerize allylic alcohols,[23] which is also confirmed by our experiments (see section 7.4.1 in the SI for details). However, it has been reported that allylic alcohols can be isomerized into ketones under the catalysis of a base.[24] Indeed, we found that **8** could be isomerized to **9** requiring only a base (section 7.4.1 in the SI). The cation of the bases appears to be critical for the isomerization, with *t*BuOK being the best base (section 7.4.2 in the SI). When the C^1-deuterated allylic alcohol **10** was used, the majority of the deuterium atoms were transferred from C^1 to C^3 position of **10**, affording **11** (Eq. 3). Moreover, the isomerization



proceeded equally well in the presence of 1 equivalent of a radical scavenger, TEMPO (2,2,6,6-tetramethylpiperidinyloxy) or 1,1-diphenylethylene. These results suggest that the isomerization does not involve a radical mechanism[24a] and may proceed via an intramolecular 1,3-hydrogen transfer process proposed by Martín-Matute and co-workers.[24b] Comparing the isomerization rate of **8** with that of the C^1-deuterium labelled **10** revealed an approximate kinetic isotope effect of k_H/k_D ~ 5 (section 7.4.3 in the SI), suggesting a rate-determining C^1-H

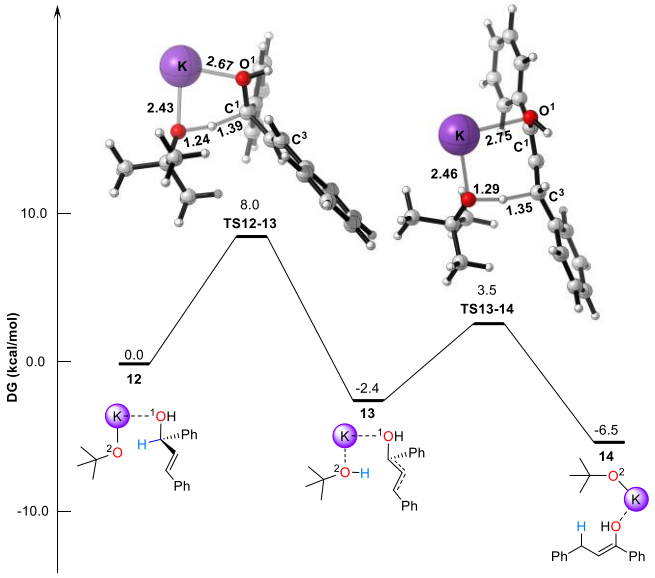
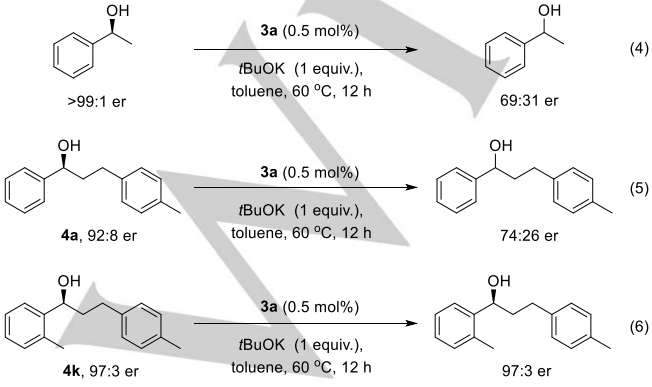


Figure 5. Free energy profile of the isomerization of a model allylic alcohol to the enolate intermediate assisted by *t*BuOK.

cleavage for the isomerization reaction.

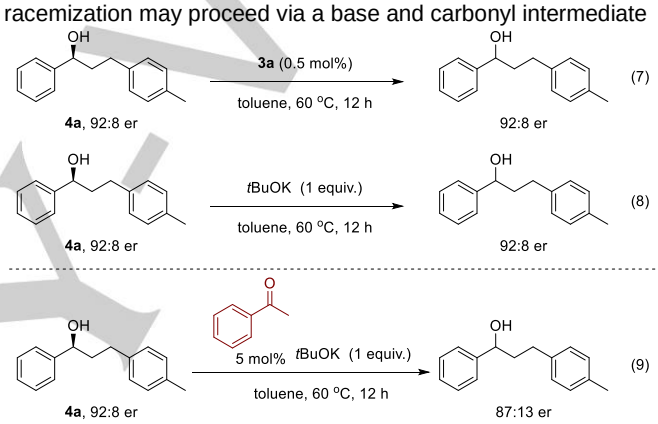
The isomerization was further studied with DFT calculations (section 7.4.4 in the SI). The base mediated 1,3-hydrogen shift mechanism gives a reasonable energy profile for the isomerization of a model allylic alcohol, with a rate-determining C^1-H cleavage step (**TS12-13**) involving the participation of K^+, which fits well with the experimental observations and is in line with the results of Martín-Matute and co-workers[24b] (Figure 5). Thus, we may conclude that the allylic alcohol **8** is transformed into the ketone **9** via a base-catalyzed isomerization process. The reduction of **9** to **4a** by **3a** should be facile. Indeed, isolated **9** was readily reduced to **4a** (90% yield, 94:6 er) with **1a** as hydrogen source (section 7.5 in the SI).

A remaining, intriguing question is *why the alcohol product does not appear to be racemized via dehydrogenation, given the similarity of the product to the substrate*. Monitoring the reaction of **1a** with **2a** catalyzed by **3a** showed that whilst the yield of **4a** increased with time, the enantioselectivity decreased considerably from >90% ee to <40% ee over a period of 36 h (Figure S3 in section 7.6 of the SI), showing that the product **4a** could be racemized under the reaction conditions. Control experiments further showed indeed that both the starting



secondary alcohol substrate and the product **4a** could undergo racemization under the catalytic conditions (Eqs. 4 and 5). However, the racemization rate is slower for the product **4a** than for the starting secondary alcohol (Eqs. 4 and 5), which might be due to the increased steric hindrance in **4a**. More significantly, no racemization was observed for the sterically bulkier product **4k** under the same conditions (eq. 6), further corroborating the argument for steric effect. These observations suggest that both the substrate and product undergo racemization. However, the racemization process is sensitive to steric hindrance, with the bulkier product racemizing slower than the substrate. This inference may not be surprising, considering the steric hindrance imposed by the two bulky ligands at the equatorial plane of **3a**.

Additional control experiments showed that the racemization is not catalyzed by **3a** (Eq. 7) or promoted by the base alone (Eq. 8). Instead, racemization was observed in the presence of a ketone and base without **3a** (eq. 9), suggesting that the racemization may proceed via a base and carbonyl intermediate



through a MPV-type mechanism.[25] As this MPV-type hydrogen transfer is sensitive to steric hindrance,[25] the racemization of sterically bulky products would be slow, which fits well with the experimental results.

The above mechanistic studies support the mechanistic picture shown in Figure 1d. The two alcohol starting materials are both first dehydrogenated to give Ru hydride intermediates and two carbonyl compounds, which condense to afford to an *α,β*-unsaturated ketone intermediate in the presence of a base. The unsaturated ketone intermediate is then reduced by a Ru hydride to produce an allylic alcohol intermediate, which undergoes a base-catalyzed isomerization to form a ketone. Finally, the ketone is reduced by a Ru hydride to afford the chiral alcohol product. As the chiral center is generated in this step, the enantioselectivity of the overall reaction should be determined by the chiral Ru catalyst, in a manner resembling the related Noyori asymmetric hydrogenation. Whist both the secondary alcohol substrate and the product could be racemized via a MPV process, the racemization rate is significantly lower for the product, due to enhanced steric effects.

Conclusion

In summary, we have developed a chiral version for the century-old Guerbet reaction, which allows for the asymmetric coupling of second alcohols with primary alcohols to afford new, chiral alcohols. Catalyzed by commercially available Ru asymmetric

hydrogenation catalysts but requiring neither H_2 nor any other reducing agents, this asymmetric Guerbet reaction is highly enantioselective in general and can be performed at a gram-scale, providing a convenient new route for the synthesis of chiral alcohols. Mechanistic studies suggest that the reaction proceeds via a metal-base cooperative process, with the former enabling the hydrogen autotransfer reaction while the latter promoting the isomerization of intermediary allylic alcohols.

Acknowledgements

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Keywords: chiral alcohol • alkylation • hydrogen autotransfer • ruthenium • asymmetric catalysis

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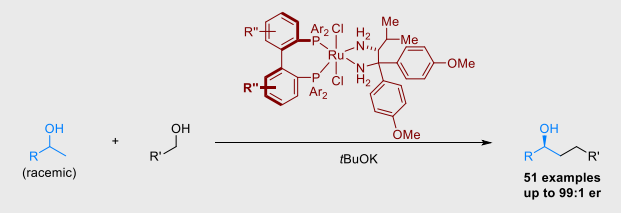
RESEARCH ARTICLE



Commercially available, classic Noyori Ru(II)-diamine-diphosphine catalysts catalyze the cross coupling of racemic secondary alcohols with primary alcohols in the presence of a base, affording new chiral alcohols with enantiomeric ratios of up to 99:1.

*K. Wang, L. Zhang, W. J. Tang, H. M. Sun, D. Xue, M. Lei, J. L. Xiao, C. Wang**

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Asymmetric Guerbet Reaction to Access Chiral Alcohols