

Catalytic asymmetric reactions using environmentally friendly reagents and catalyst: Asymmetric synthesis versus kinetic resolution*

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Abstract: Kinetic resolution of racemic compounds is a familiar method for the preparation of optically active compounds. However, an inevitable and critical drawback from the point of view of green chemistry is the consequent wastage of half of the starting compound. A catalytic asymmetric synthesis of 5-arylcyclohex-2-enones was developed starting from racemic 5-(trimethylsilyl)cyclohex-2-enone, which overcomes the drawback of kinetic resolution. A chiral amidophosphane- or BINAP–Rh(I)-catalyzed asymmetric conjugate arylation of racemic 5-(trimethylsilyl)cyclohex-2-enone with arylboronic acids in dioxane-water (10:1) afforded *trans*- and *cis*-3-aryl-5-(trimethylsilyl)cyclohexanones in reasonably high enantioselectivity. Dehydrosilylation of the product mixture with Cu(II) chloride in dimethylformamide (DMF) gave 5-arylcyclohex-2-enones with up to 93 % ee in high yield. Enantiofacial selectivity with chiral phosphane–Rh(I) overrides the *trans*-diastereoselectivity that is maintained in the achiral or racemic phosphane–Rh(I)-catalyzed conjugate arylation of 5-(trimethylsilyl)cyclohex-2-enone.

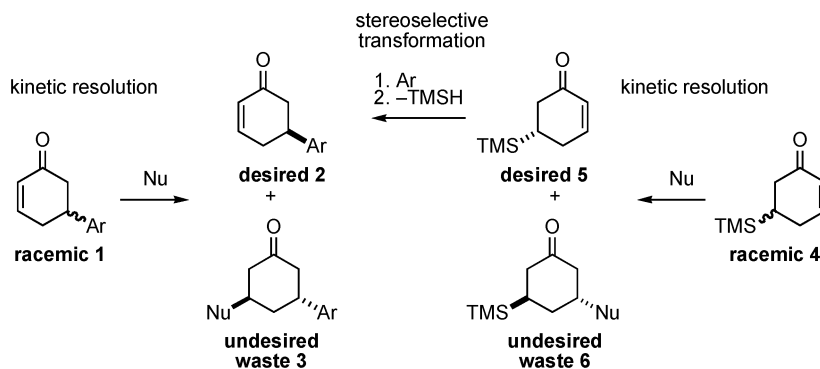
Keywords: asymmetric synthesis; kinetic resolution; catalysts; arylation; cyclohexenones.

INTRODUCTION

Chiral substituted cyclohexenones have been utilized as versatile building blocks for the synthesis of biologically potent compounds [1]. Although the derivation of naturally occurring compounds [2] and asymmetric synthesis of their precursors [3] have been developed for the synthesis of these chiral cyclohexenones, kinetic resolution of racemic substituted cyclohexenones, for example, racemic **1** to **2**, by the catalytic asymmetric reactions [4] including enzymatic reactions [5] has been the most reliable method, resulting in the recovery of a nearly pure enantiomer (Scheme 1). By the criteria of green chemistry, however, kinetic resolution involves an inevitable and potentially fatal disadvantage, arising from wastage of half of the starting material **3**. Furthermore, careful control of the reaction progress is necessary to maximize the recovery of the desired starting material **2**. Since the enantioenriched 5-(trimethylsilyl)cyclohex-2-enone **5** itself has been the choice of chiral starting material for the stereoselective transformation to 5-substituted cyclohex-2-enones **2**, **5** has been the target of kinetic resolution [4a,f,5a]. We describe herein the straightforward asymmetric synthesis of 5-arylcyclohex-2-enones

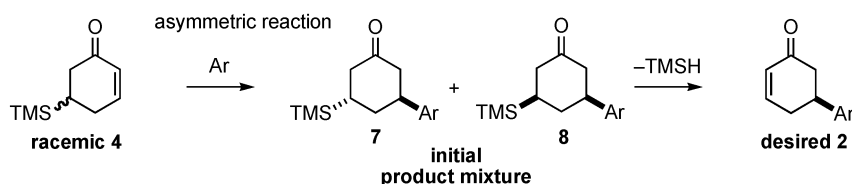
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2 with high ee from racemic 5-(trimethylsilyl)cyclohex-2-enone **4** via chiral phosphane–Rh(I)-catalyzed conjugate arylation [6,7] and subsequent oxidative dehydrosilylation of the product mixture (Scheme 2) [8].



Scheme 1 Kinetic resolution of racemic **1** or **4** to 5-arylcyclohex-2-enones **2**.

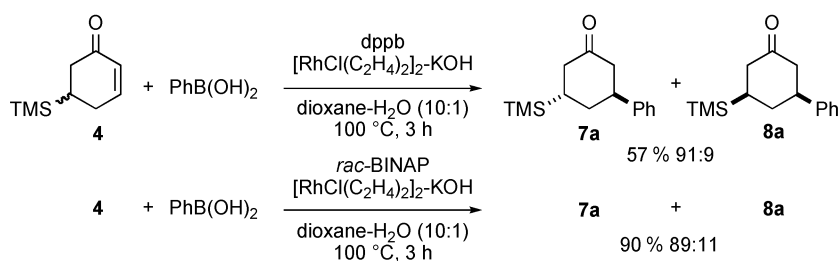
If the enantiofacial control of a chiral catalyst, favoring *re*-face addition, is operative in the reaction of racemic **4**, undesired **6** is produced and desired **5** is recoverable unchanged because *re*-face attack to **5** gives *cis*-diastereomer [4,5]. This principle of kinetic resolution relies on the substrate-controlled *trans*-selective conjugate addition [9] to 5-substituted cyclohex-2-enones [2a,10]. On the other hand, if the enantiofacial control by a chiral catalyst overrides the substrate-controlled *trans*-selective conjugate addition, *trans*-**7** and *cis*-**8** are the products that have the same absolute configuration at the newly created chiral centers (Scheme 2). Subsequent dehydrosilylation [4f,5a] thereof gives 5-substituted cyclohex-2-enones **2** with high ee in ideally quantitative yield, completing an asymmetric synthesis of **2** from racemic **4**. This two-step asymmetric synthesis protocol is apparently superior to kinetic resolution.



Scheme 2 Asymmetric synthesis of **2** starting from racemic **4**.

SUBSTRATE-CONTROLLED *TRANS*-SELECTIVITY BY ACHIRAL OR RACEMIC PHOSPHANE–Rh(I) CATALYST

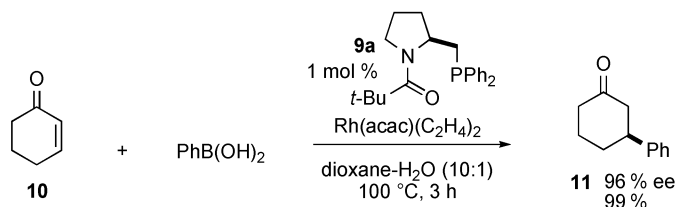
The *trans*-diastereoselectivity by the substrate control was confirmed by the dppb- [RhCl(C₂H₄)₂]₂-KOH catalyzed Miyaura arylation [11] of racemic **4** [4f] with phenylboronic acid in dioxane-water at 100 °C, giving a racemic mixture of *trans*-**7a** (Ar = Ph) and *cis*-**8a** (Ar = Ph) in 57 % yield, favoring **7a** (91:9), and thereby indicating that *trans*-diastereoselectivity is operative in the Rh(I)-catalyzed phenylation of **4** (Scheme 3). With *rac*-BINAP in place of dppb, the same substrate control was observed to give mixture in 90 % yield, favoring *trans*-addition (89:11).



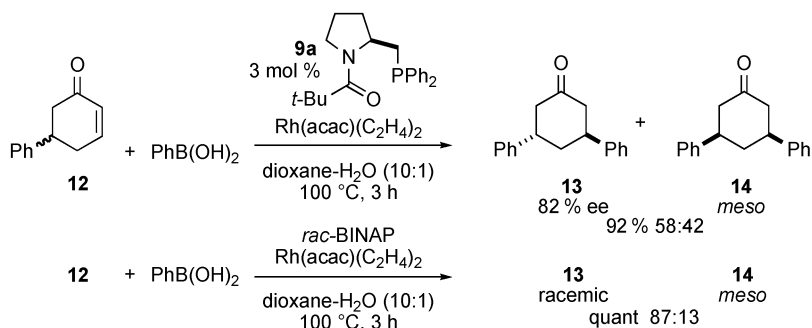
Scheme 3 *trans*-Selective phenylation of **4**.

CHIRAL PHOSPHANE–Rh(I) CATALYST-CONTROLLED ENANTIOFACIAL SELECTIVITY OVERRIDING SUBSTRATE CONTROL

We anticipated that the high enantioselectivity of up to 97 % ee observed with an amidophosphane **9a**-Rh(I) catalyst in the conjugate arylation of cyclohex-2-enone **10** (Scheme 4) [12] would override the *trans*-diastereoselectivity, providing a mixture of **7** and **8**, both with high ee. It was very pleasing to find that the reaction of racemic 5-phenylcyclohex-2-enone **12** with phenylboronic acid under catalysis by chiral **9a**-Rh(I) gave a 58:42 mixture of *trans*-**13** with 82 % ee and *meso*-**14** in 92 % yield, indicating that chiral catalyst-controlled enantiofacial selection overrides the substrate-controlled *trans*-diastereoselectivity (Scheme 5). It is also important to note that the *rac*-BINAP-Rh(I) catalyst gave a racemic mixture of **13** and **14**, favoring *trans*-addition (87:13), and thereby indicating that substrate-controlled *trans*-selectivity is still operative.



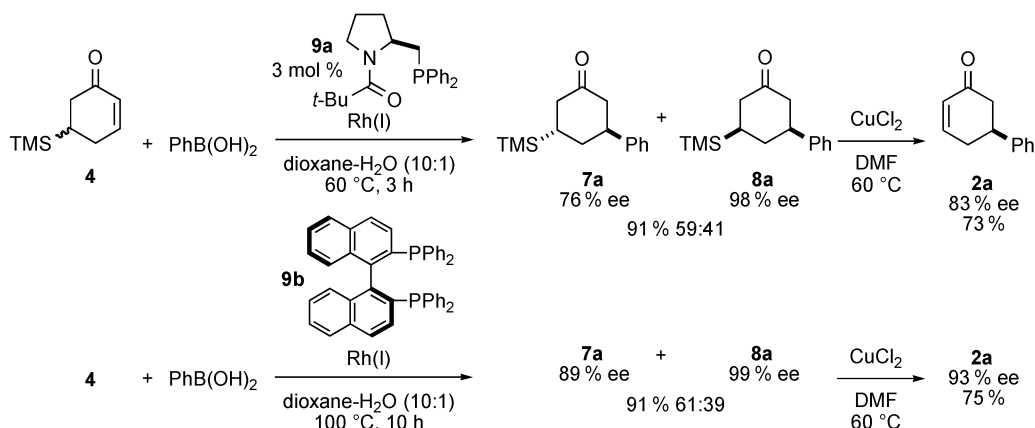
Scheme 4 Catalytic asymmetric phenylation of cyclohex-2-enone **10**.



Scheme 5 Asymmetric phenylation of racemic **12**.

ASYMMETRIC SYNTHESIS OF 5-ARYLCYCLOHEX-2-ENONES BY CHIRAL PHOSPHANE-Rh(I)-CATALYZED ARYLATION OF RACEMIC 5-(TRIMETHYLSILYL)-CYCLOHEX-2-ENONE AND SUBSEQUENT DEHYDROSILYLATION

The reaction of racemic **4** with phenylboronic acid was catalyzed by 3 mol % of **9a**-[RhCl(C₂H₄)₂]₂ and 1 equiv of KOH in dioxane-water (10:1) at 60 °C to afford successfully a 59:41 mixture of **7a** and **8a** in 91 % yield (Scheme 6). The enantioselectivity was determined by chiral stationary-phase high-performance liquid chromatography (HPLC) to be 76 and 98 % ee, respectively. Treatment of the above mixture of **7a** and **8a** with Cu(II) chloride in dimethylformamide (DMF) [13] at 60 °C for 5 h gave (*S*)-**2a** (Ar = Ph) with 83 % ee in 66 % two-step yield from racemic **4**. (*S*)-BINAP **9b** was much more effective to give a 61:39 mixture of **7a** with 89 % ee and **8a** with 99 % ee in 91 % combined yield. Subsequent dehydrosilylation to (*S*)-**2a** with 93 % ee was carried out in 68 % overall yield.



Scheme 6 Catalytic asymmetric synthesis of **2a** starting from racemic **4**.

Other aryl groups having electron-donating and -withdrawing substituents were successfully introduced into racemic **4** by the reaction with corresponding arylboronic acids, and subsequent dehydrosilylation gave **2** with reasonably high ee as shown in Fig. 1.

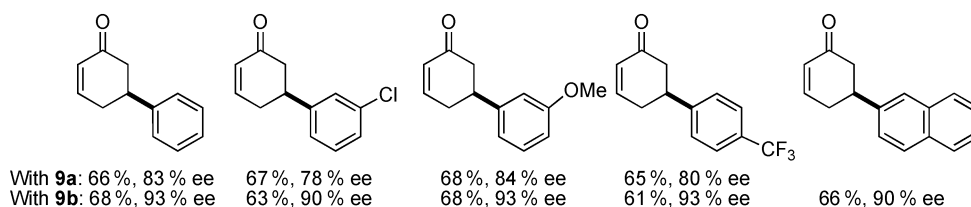
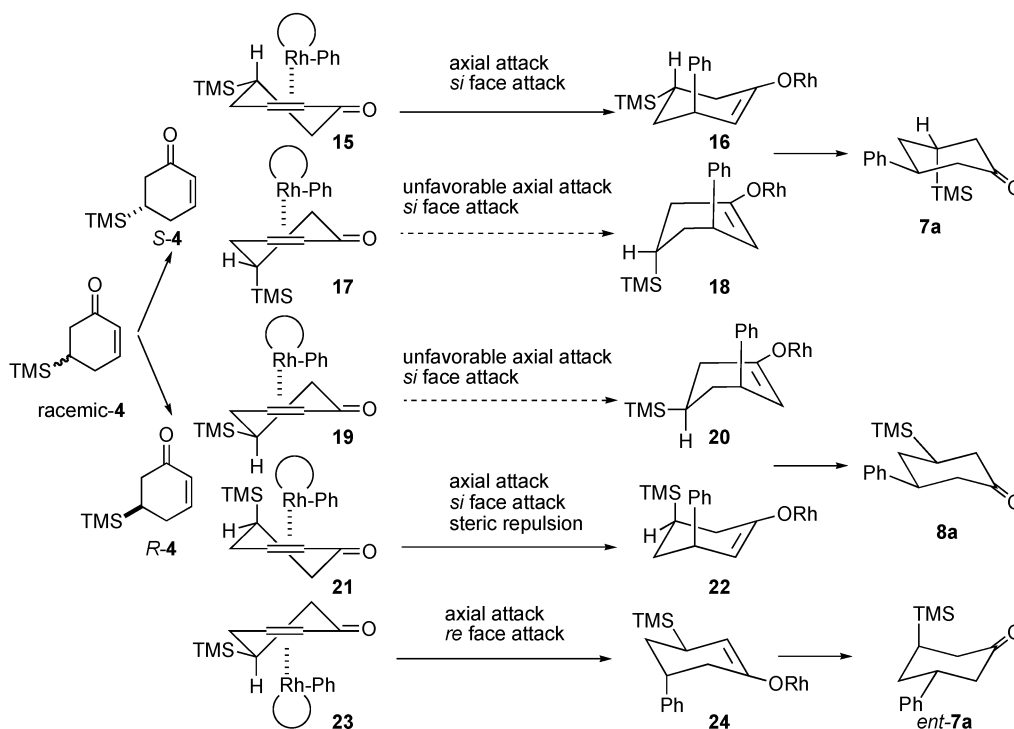


Fig. 1 5-Arylcyclohex-2-enones **2** synthesized from racemic **4**.

STEREOSELECTIVE PATHWAYS OF ASYMMETRIC CONJUGATE ARYLATION

Two controlling factors are operative in the asymmetric arylation of racemic **4** with phenylboronic acid (Scheme 7). Chiral catalyst-controlled *si*-face attack and cyclohex-2-enone-controlled axial attack both are favorable in the reaction model shown as **15** to give **7a** via **16** from (*S*)-**4**, and the model **17** is not preferred due to unfavorable axial attack. The reaction of (*R*)-**4** giving **8a** is problematic due to the unfavorable transformation of **19** to **20**, and **21** to **22**, giving lower chemical yield of **8a** as has been ob-

served. Favorable axial and unfavorable *re*-face attack may be operative as shown in **23** to give *ent*-**7a** via **24**, resulting in the lower enantioselectivity and higher yield of **7a** as has been observed. These models explain well the present asymmetric transformation of racemic **4** to **7a** and **8a**.



Scheme 7 Stereoselective pathways to **7a** and **8a**.

CONCLUSION

The two-step asymmetric synthesis of 5-arylcyclohex-2-enones is now the powerful and environmentally friendly tool for organic synthesis. The present asymmetric reaction protocol overcomes the drawback involved in the catalytic kinetic resolution. Enantiofacial selectivity with chiral phosphane–Rh(I) exceeds the *trans*-diastereoselectivity that is maintained in achiral or racemic phosphane–Rh-catalyzed conjugate arylation of 5-(trimethylsilyl)cyclohex-2-enone. Application of this concept to the synthesis of other cycloalkenones is in progress in our laboratory [14].

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