Kinetic Resolution via Rh-catalyzed C–C Activation of Cyclobutanones at Room Temperature

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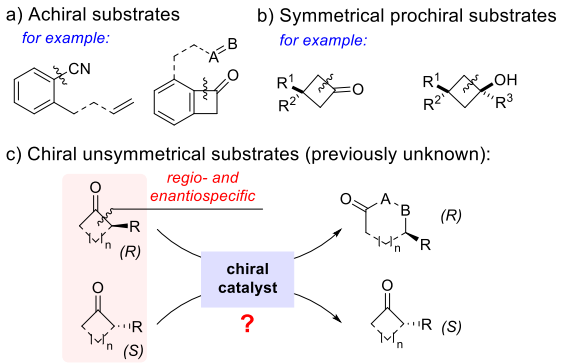
Supporting Information Placeholder

ABSTRACT: Herein we describe the development of a highly selective kinetic resolution of cyclobutanones via a Rh-catalyzed "cut-and-sew" reaction with selectivity factor up to 785. This reaction takes place at room temperature with excellent efficiency. Various *trans* 5,6-fused bicycles and C2-substituted cyclobutanones were obtained with excellent ee, which can be further used as chiral building blocks. DFT calculations reveal the crucial roles of the DTBM-segphos ligand in stabilizing the rate- and enantioselectivity-determining C–C oxidative addition transition state via favorable ligand-substrate dispersion interactions.

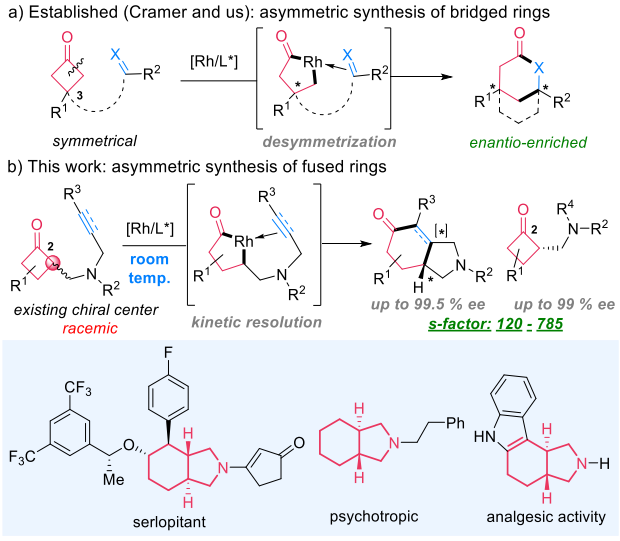
While highly desirable, controlling both reactivity and stereochemistry constitutes significant challenges during activation of inert chemical bonds. The recent advancement allows asymmetric C–H functionalization to emerge as a powerful tool for synthesis;[1] by contrast, the corresponding asymmetric C–C cleavage/functionalization, though attractive for preparing chiral complex ring systems, has been much less developed.[2] To date, the scope of transition metal-catalyzed asymmetric C–C activation[3] has been primarily restricted to either the cleavage of an achiral C–C bond, e.g. an aryl–CN bond[2b,c] or the C1-C8 bond in benzocyclobutenones[2d,e] or use of symmetrical substrates[2f-n] (Schemes 1a and 1b). Despite the fact that chiral unsymmetrical C–C bonds are common, the corresponding catalytic asymmetric transformation involving activation of these bonds remains elusive (Scheme 1c).

Scheme 1. Asymmetric C–C Activations



Our laboratory has an ongoing interest in developing a "cut-and-sew" approach for synthesis of various polycyclic structures widely found in bioactive compounds.[3r] This approach involves oxidative addition of a transition metal into the C–C bond of a cyclic ketone followed by migratory insertion of an unsaturated unit. In particular, the use of cyclobutanones as a common building block has been demonstrated in forming bridged and fused rings.[4] The enantioselective synthesis of bridged-ring systems via desymmetrization of cyclobutanones has been reported by Cramer[2f-h] and us[2i,j] through intramolecular carboacylation of olefins, carbonyls and allenes (Scheme 2a). However, enantioselective construction of fused rings, which would require substrates containing an existing C2-stereocenter, remained unknown and challenging. First, the catalyst needs to differentiate a pair of enantiomers (intermolecular recognition) instead of different π faces (e.g. olefins) or different sides of ketones (intramolecular recognition). Another issue is that cleavage of the less sterically hindered C–C bonds (the unproductive pathway) is generally more favorable.[2j] Hence, the desired reaction would have to address regio- and enantioselectivity problems simultaneously. Moreover, this type of reactions typically

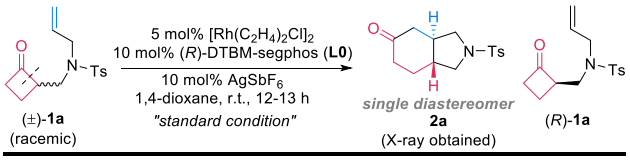
Scheme 2. Enantioselective "Cut-and-Sew" Reactions between Cyclobutanones and Unsaturated Bonds



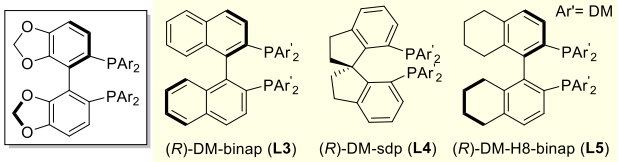
need high reaction temperatures (≥ 120 °C),[5] which makes it difficult to control enantioselectivity. In this communication, we describe our preliminary results of a highly selective kinetic resolution of cyclobutanones via a Rh-catalyzed "cut-and-sew" reaction (Scheme 2b). Surprisingly, the reaction can operate at *room temperature* with the selectivity factor up to 785. This approach provides an asymmetric entry to the 5,6-fused bicycles[6] often found in chiral bioactive compounds,[7] as well as α-substituted cyclobutanones that are nontrivial to prepare enantioselectively without stoichiometric chiral auxiliaries.

To explore the feasibility of the kinetic resolution approach, cyclobutanone **1a** with a tethered olefin was chosen as the model substrate. After extensive studies, it was ultimately found that a combination of a cationic Rh complex and DTBM-segphos permitted a room temperature carboacylation of **1a** (Table 1). The kinetic resolution was highly selective: both product **2a** and cyclobutanone **1a** were obtained in nearly theoretical yields and excellent optical purity (98% ee) with selectivity factor[8] of 458. The reaction is also diastereoselective: the *trans*-5,6-fused ring (**2a**) was observed as a single diastereomer. The absolute stereochemistry of product **2a** was confirmed through X-ray crystallography, which shows that the *S*-enantiomer of the substrate reacted selectively. The cationic rhodium catalyst can be smoothly generated *in situ* from $[Rh(C_2H_4)_2Cl]_2$, (*R*)-DTBM-segphos and $AgSbF_6$ in 1,4-dioxane. It is noteworthy that fused ring formation via a cut-and-sew reaction between cyclobutanones and olefins has not been reported previously.[6]

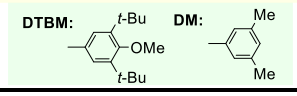
Table 1. Selected Condition Optimization[a]



entry	modification from "standard condition"	yield of **2a** (ee)[b]		+ **1a** (ee)[b]		*s* (conv.)[c]
1	**None**	**46%**	**(98%)**	**47%**	**(98%)**	**458** (50%)
2	w/o $AgSbF_6$	10%	N/D	89%	N/D	N/D
3	w/o (*R*)-DTBM-segphos	0%	N/A	81%	N/A	N/A
4	w/o $[Rh(C_2H_4)_2Cl]_2$/ $AgSbF_6$	0%	N/A	99%	N/A	N/A
5	$[Rh(coe)_2Cl]_2$ instead of $[Rh(C_2H_4)_2Cl]_2$	44%	(99%)	48%	(95%)	747 (49%)
6	$[Rh(cod)Cl]_2$ instead of $[Rh(C_2H_4)_2Cl]_2$	0%	N/A	99%	N/A	N/A
7	$[Rh(CO)_2Cl]_2$ instead of $[Rh(C_2H_4)_2Cl]_2$	10%	N/D	90%	N/D	N/D
8	$AgBF_4$ instead of $AgSbF_6$	44%	(98%)	45%	(96%)	392 (49%)
9	$AgNTf_2$ instead of $AgSbF_6$	45%	(98%)	45%	(95%)	371 (49%)
10	**L1** instead of **L0**	12%	N/D	40%	N/D	N/D
11	**L2** instead of **L0**	10%	N/D	67%	N/D	N/D
12	**L3** instead of **L0**	0%	N/A	49%	N/A	N/A
13	**L4** instead of **L0**	0%	N/A	95%	N/A	N/A
14	**L5** instead of **L0**	0%	N/A	95%	N/A	N/A
15	THF instead of 1,4-dioxane	36%	(99%)	52%	(94%)	713 (49%)
16	toluene instead of 1,4-dioxane	0%	N/A	90%	N/A	N/A
17	5 mol% [Rh]	41%	(99%)	50%	(86%)	556 (46%)



Ar = DTBM, (*R*)-DTBM-segphos (**L0**)
Ar = DM, (*R*)-DM-segphos **L1**
Ar = Ph, (*R*)-segphos **L2**



[a] The reaction was run on a 0.1 mmol scale at room temperature for 12-13 h and all the yields are isolated yields. [b] Determined by chiral HPLC. [c] Calculated conversion (C) = $ee_{SM}/(ee_{SM} + ee_{PR})$; selectivity (*s*) = $\ln[(1 - C)(1 - ee_{SM})]/\ln[(1 - C)(1 + ee_{SM})]$.

To gain more insights into this reaction, a series of control experiments were performed. Unsurprisingly, the rhodium, silver salt and the phosphine ligand are all essential for this transformation (Table 1, entries 2-4). The existing ligands on the rhodium precatalysts were found to be critical (entries 5-7). Ethylene and cyclooctene (COE) ligands, which undergo easier ligand substitution reactions, can both provide excellent yields and enantioselectivity; in contrast, stronger 1,5-cyclooctadiene (COD) and electron-deficient CO ligand led to much lower conversions. The counter-ions for the *in situ* generated cationic rhodium catalysts can be extended to BF_4 and NTf_2, although the ees for the recycled cyclobutanone were slightly diminished with these catalysts (entries 8 and 9). DTBM-segphos was found to be crucial for this transformation. Based on the segphos backbone, switching the DTBM group to other aryl substituents significantly decreased the reactivity (entries 10 and 11). Chiral backbones other than segphos did not provide the desired product at room temperature (entries 12-14). Regarding the solvent used, 1,4-dioxane was superior, while THF gave some decomposition and toluene afforded no desired product (entries 15 and 16). Lastly, comparably results could still be obtained with a halved catalyst loading (entry 17).

Next, we performed density functional theory (DFT) calculations to elucidate the origin of the unexpected high reactivity and enantioselectivity and the unique role of DTBM-segphos. The calculated energy profiles of the reaction with both enantiomers of **1a** (Figure 1) indicated the rate- and enantioselectivity-determining step is the irreversible C–C oxidative addition because transition states in subsequent steps have lower energy barriers. This step has a relatively low activation barrier of 22.0 kcal/mol for the more reactive enantiomer (*S*)-**1a**, which is consistent with the experimental reactivity at room temperature. The most favorable oxidative addition transition state (**TS1**) involves the cleavage of the more substituted C–C bond in (*S*)-**1a** and is stabilized by the weak coordination of the *N*-tosyl oxygen to the Rh center.[6] The oxidative addition of the less substituted C–C bond (**TS3**) is kinetically disfavored due to the lack of such *N*-tosyl coordination. The C–C oxidative addition with the (*R*)-enantiomer of **1a** (**TS2**) requires a much higher barrier, in agreement with the high selectivity factor observed in experiment. The origin of the enantioselectivity can be rationalized by the quadrant diagrams shown in Figure 2. The (*S*)-selective transition state (**TS1**) places the cyclobutanone moiety and the *N*-tosyl group on the substrate in quadrants **I** and **III**, which are less occupied by the C2-symmetric (*R*)-DTBM-segphos ligand. By contrast, in **TS2**, the cyclobutanone moiety is placed in the more occupied quadrant (**II**) and the *N*-Ts coordination cannot be achieved because the coordination site is blocked by the ligand in quadrant **IV**. The diastereoselectivity is determined in the subsequent alkene migratory insertion. This step strongly favors the formation of the *trans*-substituted pyrrolidine via **TS4**-*trans*. **TS4**-*cis* leading to the *cis*-diastereomer is 4.0 kcal/mol less stable because of the unfavorable steric repulsions about the forming C–C bond. The resulting seven-membered rhodacycle intermediate **8** undergoes facile C–C reductive elimination to yield product **2a** and regenerate the Rh(I) catalyst.

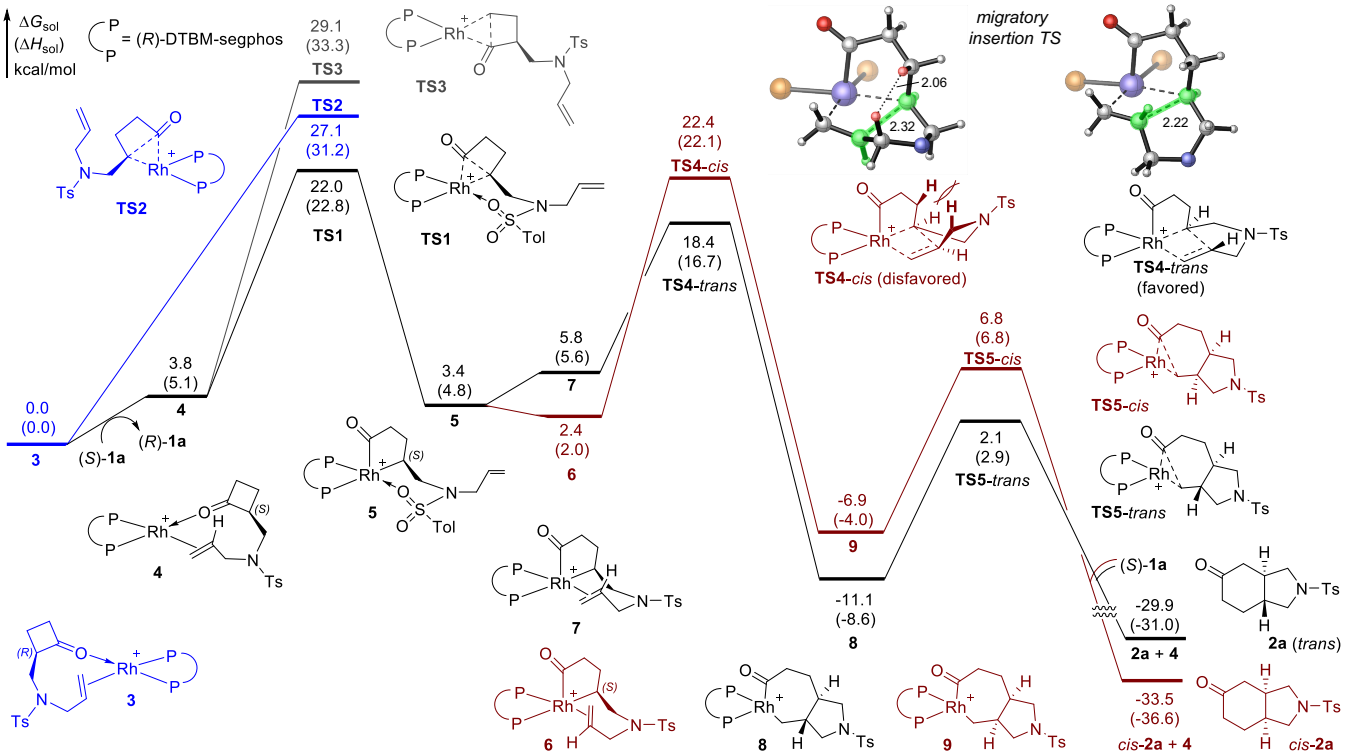
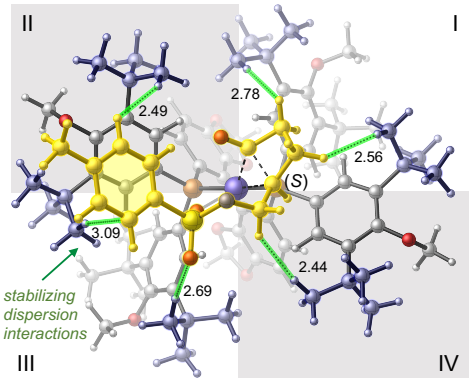
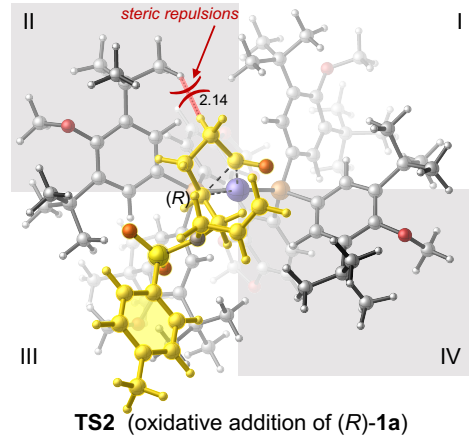


Figure 1. Computed energy profiles of the Rh-catalyzed C–C activation of (*R*)-**1a** (in blue) and (*S*)-**1a** (in black) at the M06/SDD-6-311+G(d,p), SMD(1,4-dioxane)//B3LYP/LANL2DZ-6-31G(d) level of theory. Distances are in angstrom.



TS1 (oxidative addition of (*S*)-**1a**)
Δ*G*‡ = 22.0 kcal/mol



TS2 (oxidative addition of (*R*)-**1a**)
Δ*G*‡ = 27.1 kcal/mol

Figure 2. Oxidative addition transition states with the (*R*)-DTBM-segphos-supported Rh catalyst. The *N*-allyl group in **TS1** is not shown for clarity.

In agreement with the low reactivity with the segphos-supported Rh catalyst, the rate-determining oxidative addition (**TS6**) requires a 3.3 kcal/mol higher barrier when the segphos ligand is employed in place of DTBM-segphos (Figure 3). To investigate the origin of the ligand effects on reactivity, we computed the dispersion interactions (ΔE_{disp})[9] between substrate (*S*)-**1a** and the bisphosphine ligand in the oxidative addition transition states (**TS1** and **TS6**) and the catalyst resting states (**3** and **10**) using Grimme's DFT-D3 method[10] (see SI for details). Because **TS1** is stabilized by various C–H/C–H and C–H/π interactions between the (*R*)-DTBM-segphos ligand and the substrate (Figure 2), the ΔE_{disp} of **TS1** is 5.6 kcal/mol more favorable than that of the resting state **3**, indicating a significant dispersion effect that promotes the oxidative addition.[11] In the reaction with the smaller (*R*)-segphos ligand, the ΔE_{disp} of **TS6** is only 3.6 kcal/mol more favorable than in the resting state **10**. The weaker dispersion effects with (*R*)-segphos diminish the stabilization effects in the oxidative addition transition state, and thus lead to lower reactivity than in reactions with the (*R*)-DTBM-segphos ligand.

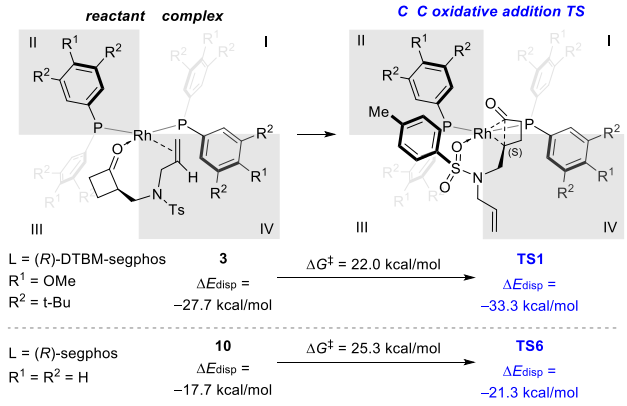
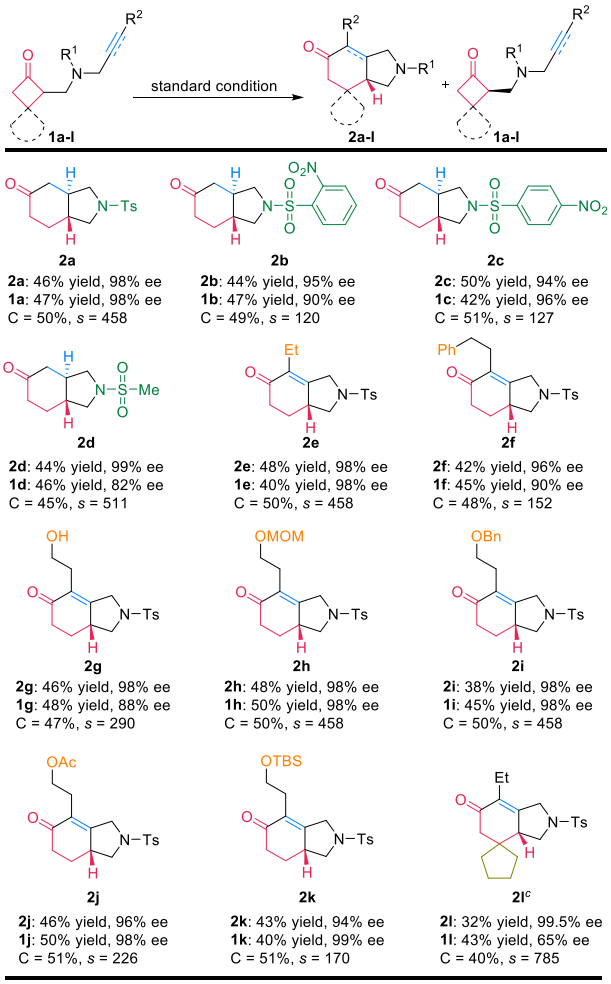


Figure 3. Ligand effects on reactivity. Dispersion interaction energies (ΔE_{disp}) between the bisphosphine ligand and the substrate were calculated with the DFT-D3 method.[11]

The substrate scope of the kinetic resolution was then investigated (Table 2). Given the importance of the sulfonyl oxygen coordination, the linkage can be changed to nosyl and methylsulfonyl groups with good yields and excellent enantioselectivity maintained (**2b**-**2d**).[12] More substituted olefins were not reactive under the current conditions likely due to a slow migratory insertion step (the second highest energy barrier, Figure 1). Gratifyingly, alkyne-tethered cyclobutanones proved to be excellent substrates (**2e** to **2l**). Owing to the mild and redox-neutral reaction condition, a number of labile groups were tolerated, including MOM (**2h**), benzyl (**2i**), acyl (**2j**) and TBS-protected alcohols (**2k**), giving both good yields and excellent selectivity. Remarkably, free primary alcohol (**2g**) was well compatible. Substitution at the 3-position of cyclobutanone reduced the reactivity; however, at slightly elevated temperature (40 °C), the kinetic resolution still occurred with a good yield and excellent selectivity (**2l**). Substrate with a homopropargyl group on the NTs linker failed to deliver the 6,6-fused bicyclic product.[13]

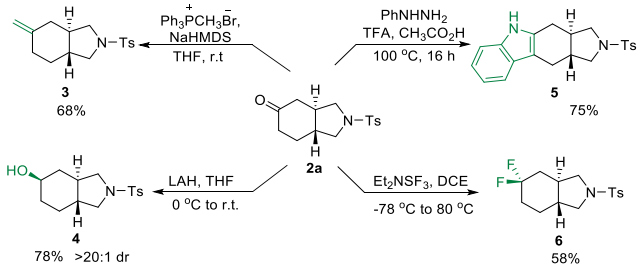
Table 2. Substrate Scope[a,b]



[a] The reaction was run on a 0.1 mmol scale. [b] All yields are isolated yields; ee was determined by chiral HPLC; selectivity (s) = $\ln[(1 - C)(1 - ee_{SM})]/\ln[(1 - C)(1 + ee_{SM})]$, calculated conversion (C) = $ee_{SM}/(ee_{SM} + ee_{PD})$. [c] Reaction was carried out with $[Rh(CH_2{=}CH_2)_2Cl]_2$ (10 mol %), (*R*)-DTBM-segphos (20 mol%), $AgSbF_6$ (20 mol%), THF (1 mL) at 40 °C.

The enantio-enriched *trans*-5,6-fused bicyclic product (**2a**) can be conveniently transformed to a variety of other structural motifs (Scheme 3).[14] For example, the ketone moiety underwent smooth olefination to give alkene **3** in 68% yield. LAH reduction afforded the secondary alcohol (**4**) with excellent diastereoselectivity. In addition, Fischer indole synthesis could be employed to efficiently generate tetracycle **5** in a good yield. Moreover, the *gem*-difluoro compound (**6**) was obtained upon treatment of **2a** with (diethylamino)sulfur trifluoride (DAST).

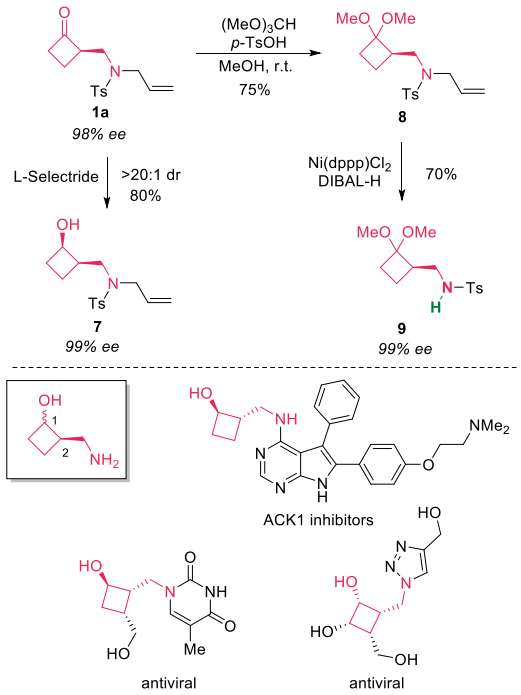
Scheme 3. Transformations of Bicyclic Product 2a



On the other hand, the obtained enantio-enriched cyclobutanone (**1a**) could serve as a versatile precursor to access other chiral four-membered ring scaffolds (Scheme 4). For example, the ketone moiety

could be reduced to an alcohol (**7**) diastereoselectively. In addition, after the ketal protection, the allyl moiety can be removed via a Ni-catalyzed isomerization. Notably, no loss of enantio-purity was observed in these reactions. The 2-aminomethyl-1-cyclobutanol moiety has been found in a number of pharmaceutical agents.[15]

Scheme 4. Transformations of Enantio-enriched Cyclobutanone 1a



In summary, we describe the discovery of kinetic resolutions/asymmetric transformations of cyclobutanones with existing stereocenters via a Rh-catalyzed "cut-and-sew" reaction. The reaction takes place at room temperature tolerating many functional groups. High efficiency and excellent enantio- and diastereoselectivity have been obtained. The enantio-enriched *trans*-5,6-fused ring products and C2-substituted cyclobutanones could serve as useful building blocks for the asymmetric synthesis of bioactive compounds. Elucidated by the DFT study, the reaction mechanism and the origin of the ligand effect for enhanced reactivity and enantioselectivity could have implications for other C–C activation reactions. The development of related stereo-convergent reactions is ongoing in our laboratory.[16]

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS publications website.
Experimental procedures; spectral data
Crystallographic data for **2a**
Computational details, additional computational results, and Cartesian coordinates

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Notes

The authors declare no competing financial interests.

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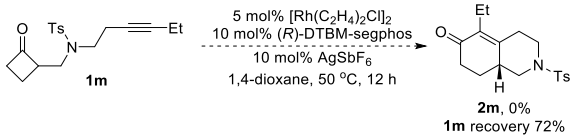
(12) Carbon and oxygen linkers were unsuccessful with this catalytic system.

(13) Substrate **1m** failed to deliver the 6,6-fused bicyclic product **2m** even at elevated temperature.



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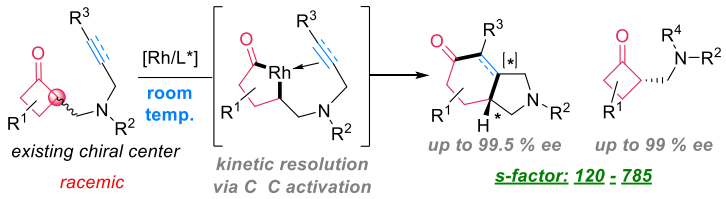
(16) Attempts to realize the dynamic kinetic asymmetric transformation through adding a base or acid to epimerize the C2 stereocenter were not fruitful under the current conditions.


[Rh/L*]
room temp.
existing chiral center
racemic
kinetic resolution
via C C activation
up to 99.5 % ee
up to 99 % ee
s-factor: 120 - 785