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Parallel Kinetic Resolution of 4-Alkynals Catalyzed by Rh(I)/Tol-BINAP: Synthesis of Enantioenriched Cyclobutanones and Cyclopentenones

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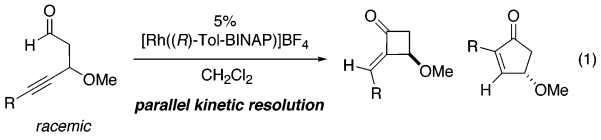
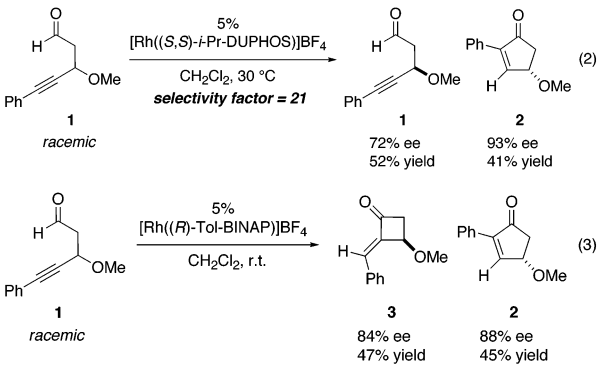
Kinetic resolution is a powerful, widely used strategy for obtaining nonracemic compounds.[2] In most kinetic resolutions, one enantiomer is transformed into a product relatively rapidly, while the other enantiomer reacts slowly to form the enantiomeric product (Figure 1). In contrast, in a parallel kinetic resolution, both enantiomers react efficiently, but they are converted into nonenantiomeric products (Figure 1).[3] Not surprisingly, parallel kinetic resolutions—especially catalytic processes that form carbon−carbon bonds[3a,4]—are much less common than conventional kinetic resolutions. In this communication, we describe an intriguing new example of a parallel kinetic resolution: a rhodium-catalyzed cyclization that furnishes enantioenriched cyclobutanones and cyclopentenones (eq 1).



We have recently reported that Rh(I)/(*i*-Pr-DUPHOS) can efficiently kinetically resolve 4-alkynals (eq 2).[5] During the course of that study, we determined that Rh(I)/(Tol-BINAP) is not effective for this process, providing a poor mass balance of unreacted 4-alkynal **1** and cyclopentenone **2**. However, a careful examination of the reaction mixture revealed that an unanticipated product, cyclobutanone **3**, is generated in good yield by Rh(I)/(Tol-BINAP) (eq 3).



This observation is noteworthy for a number of reasons, including the scarcity of metal-catalyzed methods for the synthesis of cyclobutanones[6] and the dramatic dependence of the fate of the starting material on the structure of the ligand (eq 2 vs eq 3). Equally exciting was our discovery that both of the cycloalkanones are produced in very good enantiomeric excess (eq 3)! To the best of our knowledge, all previously described catalytic methods for the synthesis of enantioenriched cyclobutanones are based on chiral, nonracemic starting materials.[7,8]

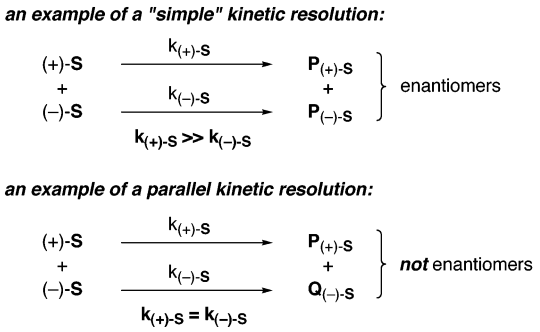


Figure 1. Examples of kinetic resolutions.

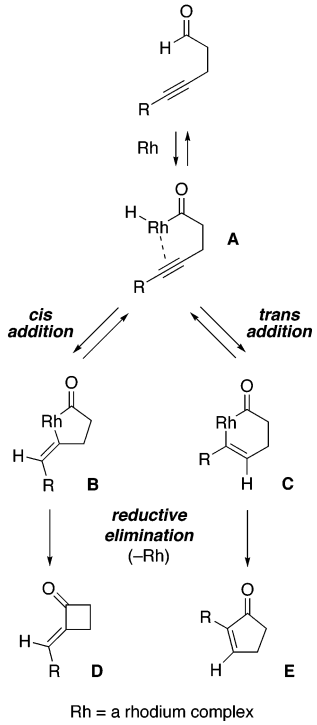


Figure 2. Possible pathways for the rhodium-catalyzed formation of cyclobutanones and cyclopentenones from 4-alkynals.

Possible pathways for the formation of the two cycloalkanones are illustrated in Figure 2. Initially, the Rh(I) catalyst oxidatively inserts into the aldehyde C−H bond, affording rhodium hydride **A**. Cis addition of the Rh−H to the alkyne provides rhodacycle **B**, which reductively eliminates to generate strained cyclobutanone **D**.[9] Cyclopentenone **E** can also be produced from rhodium hydride **A**, via a (net) trans addition of the Rh−H to furnish a six-membered metalacycle (**C**), which reductively eliminates to afford **E**.[10]

We have explored the scope of the Rh(I)/(Tol-BINAP)-catalyzed parallel kinetic resolution of 4-alkynals (Table 1).[11,12] Electron-rich (entry 2) and electron-poor (entry 3) aromatic groups are

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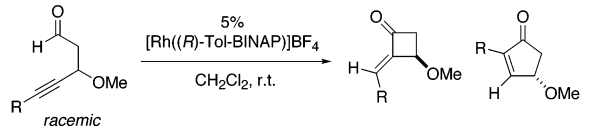
Table 1. Parallel Kinetic Resolution of 4-Alkynals To Generate Enantioenriched Cyclobutanones and Cyclopentenones

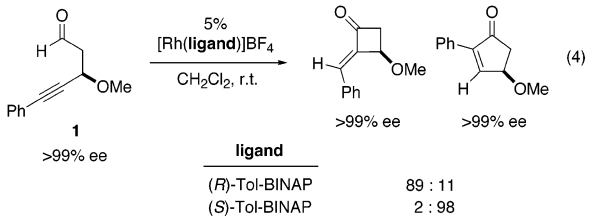


		cyclobutanone		cyclopentenone	
entry	R	ee (%)	yield (%)	ee (%)	yield (%)
1	Ph	**84**	47	**88**	45
2	4-MeO(C_6H_4)	**81**	43[a]	**81**	36[a]
3[b]	4-CF_3(C_6H_4)	>**99**	32	**62**	58
4[b]	*o*-tol	>**99**	27	**85**	41
5	2-furyl	**98**	26	**46**	66
6	Cy	>**99**	25	**84**	41

All yields are isolated yields. [a] Isolated as a mixture of cyclobutanone and cyclopentenone (the yields are distributed according to the ^{1}H NMR spectrum). [b] The reaction was carried out at 40 °C.

tolerated in the 5 position, as are sterically demanding (entry 4) and heteroaryl (entry 5) substituents. Furthermore, efficient resolution does not require an aromatic group—alkynes that bear an aliphatic substituent are also suitable substrates (entry 6).

To provide additional evidence that the matched or mismatched nature of the catalyst versus substrate configurations determines the partitioning between cyclobutanone and cyclopentenone formation, we treated enantiopure **1** with rhodium catalysts derived from (*R*)- and from (*S*)-Tol-BINAP (eq 4). In the case of (*R*)-Tol-BINAP,



ligand	
(*R*)-Tol-BINAP	89 : 11
(*S*)-Tol-BINAP	2 : 98

the alkynal reacts to generate the cyclobutanone preferentially, whereas for (*S*)-Tol-BINAP, the cyclopentenone is produced with excellent selectivity. *Thus, simply by choosing the appropriate enantiomer of Tol-BINAP, one can dictate whether a cyclobutanone or a cyclopentenone is formed.*[13]

In conclusion, we have discovered a Rh(I)/Tol-BINAP-catalyzed parallel kinetic resolution of 4-alkynals that generates cyclobutanones and cyclopentenones in good enantiomeric excess. In view of the scarcity of examples of parallel kinetic resolutions (particularly, catalyzed processes that involve carbon−carbon bond formation) and of catalytic methods for the synthesis of cyclobutanones, we believe these observations are noteworthy. We hope that future work will elucidate the origin of the remarkable dependence of the course of the reaction on the structure of the ligand.

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Supporting Information Available: Experimental procedures and compound characterization data (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) The stereochemistry of the olefin has been assigned in analogy with: Iwasawa, N.; Matsuo, T.; Iwamoto, M.; Ikeno, T. *J. Am. Chem. Soc.* **1998**, *120*, 3903−3914.
(10) Essentially no cyclobutanone is generated when CHIRAPHOS, DUPHOS, BPE, and JOSIPHOS are employed as ligands.
(11) Notes: (a) Use of BINAP leads to lower enantiomeric excess. (b) When reactions are stopped at partial conversion, significant quantities of both the cyclobutanone and the cyclopentenone are observed, indicating that the enantiomeric 4-alkynals are reacting in parallel, not sequentially. (c) To date, we have only observed effective parallel kinetic resolutions for 4-alkynals that bear a methoxy group in the 3 position.
(12) Sample procedure (Table 1, entry 1): In the air, [Rh(nbd)((*S*)-Tol-BINAP)]-BF_4 (19.4 mg, 0.0199 mmol) was placed into a Schlenk tube, which was then flushed with argon. CH_2Cl_2 (1.0 mL) was added, and then H_2 was introduced into the Schlenk tube. The mixture was stirred at rt for 0.5 h, and then the H_2 was removed by flushing with argon. 3-Methoxy-5-phenylpent-4-ynal (75.0 mg, 0.398 mmol) and CH_2Cl_2 (1.0 mL) were added, and then the mixture was stirred at rt for 21 h. Next, the solution was concentrated, and the residue was purified by preparative TLC (hexanes:EtOAc = 4:1), which furnished (*S*)-2-benzylidene-3-methoxycyclobutanone (35.2 mg, 0.187 mmol, 47%; 84% ee) and (*R*)-4-methoxy-2-phenylcyclopent-2-enone (33.8 mg, 0.180 mmol, 45%; 88% ee).
(13) Thus, as an alternative to a parallel kinetic resolution, one can generate a cyclobutanone in very high ee through a two-step process: kinetic resolution of a 4-alkynal (ref 5), followed by cyclization with the appropriate enantiomer of Rh(I)/Tol-BINAP.

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