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Enantioselective Synthesis of Cyclopentenones via Rhodium-Catalyzed Kinetic Resolution and Desymmetrization of 4-Alkynals

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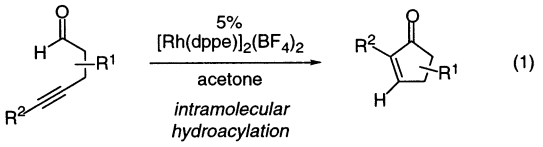
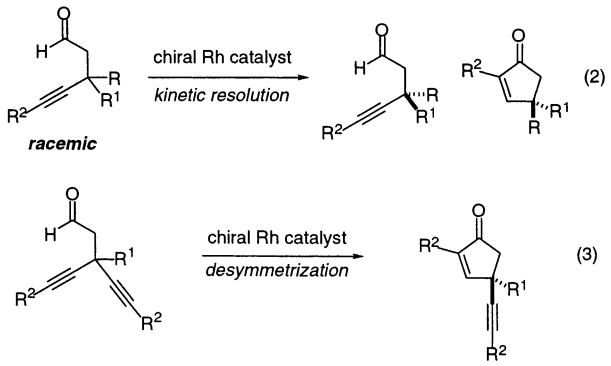
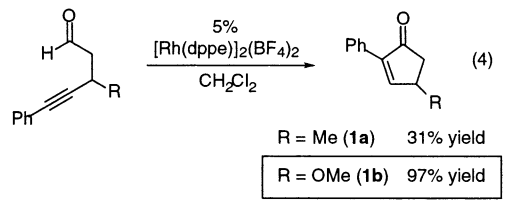
We have recently described a new method for synthesizing cyclopentenones via the rhodium-catalyzed cyclization of 4-alkynals (eq 1; Scheme 1).[1] With regard to asymmetric catalysis of this



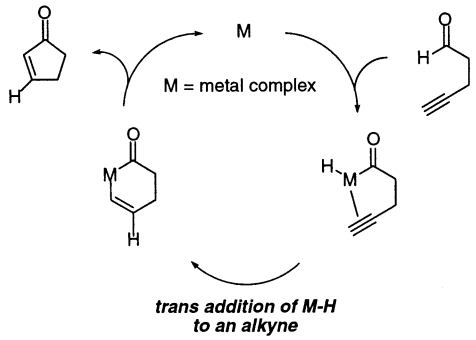
transformation, for simple substrates, no stereocenter is generated in the process. Nevertheless, one can envision that a chiral catalyst could be applied to kinetic resolution (e.g., eq 2) and/or desymmetrization (e.g., eq 3) reactions.[2]



The data illustrated in eq 4 provided the stimulus for our efforts to pursue these possibilities. In early work, we had determined that the use of a coordinating solvent such as acetone (eq 1) is usually critical for obtaining a good yield of the desired cyclopentenone. For example, for the methyl-substituted substrate (**1a**) depicted in eq 4, the cyclization proceeds in only 31% yield when the reaction is run in CH_2Cl_2,[3] versus an 88% yield in acetone. We were surprised, therefore, to discover that closely related methoxy-substituted 4-alkynal **1b** cyclizes in CH_2Cl_2 in essentially quantitative yield (eq 4).



Scheme 1



In view of the well-known propensity of 12-electron $[RhL_2]^+$-based catalysts to participate in hydroxy- and alkoxy-directed reactions,[4] perhaps most notably hydrogenation processes, we postulated that the anomalously efficient cyclization of **1b** might be attributable to coordination of the methoxy group to rhodium. Because two-point (more generally, multi-point) complexation of a substrate to a catalyst often provides a level of organization conducive to high selectivity,[4] we decided to attempt to capitalize on this observation by developing an enantioselective cyclization. Enantiopure 4-hydroxycyclopent-2-enones are of interest due to their utility as intermediates in the synthesis of natural products such as prostaglandins[5] and pentenomycins.[6,7]

We are pleased to report that rhodium/(chiral bisphosphine) catalysts can indeed achieve intramolecular hydroacylation reactions of 4-alkynals with high levels of stereoselection. For example, Rh/(*i*-Pr-DUPHOS) serves as an efficient catalyst for the kinetic resolution[8] of substrates in which the β carbon is a tertiary stereocenter (Table 1, entries 1−3).[9] Selectivity factors (s = [rate of fast-reacting enantiomer]/[rate of slow-reacting enantiomer]) of ~20−40 can be obtained, values that are sufficiently high to allow the unreacted aldehyde or the cyclopentenone to be isolated in good enantiomeric excess.[10] If the β carbon is a quaternary stereocenter,[11] then Tol-BINAP is the ligand of choice,[12] providing very good selectivity factors when the β position bears a methyl group ($s \approx$ 20; entries 4 and 5), although the presence of a bulky isopropyl substituent leads to lower enantioselection (entry 6).

Our successful kinetic resolutions with Rh/(Tol-BINAP) of 4-alkynals in which the β carbon is a quaternary stereocenter (Table 1, entries 4 and 5) suggested to us that we might also be able to effect catalytic enantioselective desymmetrizations of prochiral diynes. As illustrated in Table 2, this has proved to be possible. Thus, Rh/(Tol-BINAP) catalyzes the cyclization of an array of diynes to generate the desired cyclopentenones in excellent yield and enantioselectivity.[13]

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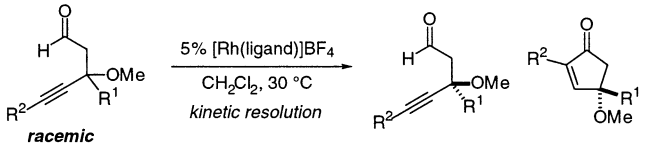
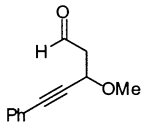
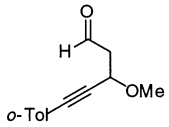
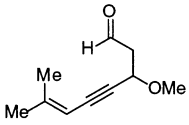
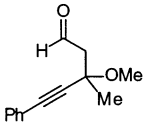
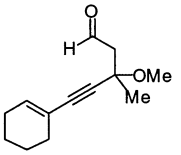
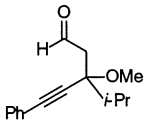
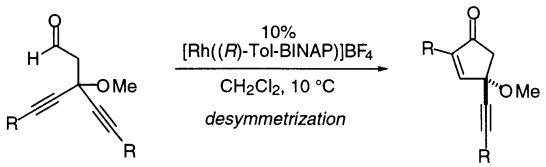
Table 1. Rhodium-Catalyzed Kinetic Resolution of 4-Alkynals



entry	substrate	ligand	% ee of unreacted aldehyde (% conv.)[a]	s[b]
1		(*S*,*S*)-*i*-Pr-DUPHOS	93 (56)	**22**
2[c]		(*S*,*S*)-*i*-Pr-DUPHOS	90 (56)	**19**
3		(*S*,*S*)-*i*-Pr-DUPHOS	93 (53)	**41**
4		(*R*)-Tol-BINAP	99 (60)	**22**
5		(*R*)-Tol-BINAP	99 (63)	**18**
6		(*R*)-Tol-BINAP	95 (76)	**5.4**

[a] Value for a specific run. [b] Average of two runs. [c] Carried out at 40 °C.

Table 2. Rhodium-Catalyzed Desymmetrization of 4-Alkynals[a]



entry	R	yield (%)[b]	ee (%)
1	*n*-C_5H_{11}	95	**92**
2	Cy	94	**95**
3	$(CH_2)_3Cl$	91	**91**
4	CH_2OMe	93	**82**

[a] All data are the average of two runs. [b] Isolated yield.

In conclusion, we have developed two new catalytic asymmetric processes that provide efficient access to interesting chiral building blocks, cyclopentenones that bear tertiary and quaternary stereocenters, in high enantiomeric excess. Future work will include additional studies of the scope and mechanism of this and related transformations.

Acknowledgment. We thank Dr. Bruce A. Pearlman (Pharmacia), Dr. James R. Gage (Pharmacia), and Ryo Shintani (MIT) for assistance in determining the absolute configuration of the reaction products, Ivory D. Hills for help in preparing the manuscript, and Johnson Matthey Inc. for supplying $[Rh(nbd)_2]BF_4$. Support has been provided by Bristol-Myers Squibb, Mitsubishi Chemical (postdoctoral fellowship to K.T.), and Novartis. Funding for the MIT Department of Chemistry Instrumentation Facility has been furnished in part by NSF CHE-9808061 and NSF DBI-9729592.

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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(1) Tanaka, K.; Fu, G. C. *J. Am. Chem. Soc.* **2001**, *123*, 11492−11493.
(2) (a) For a single example of an analogous kinetic resolution of a 4-alkenal that bears an α stereocenter, see: James, B. R.; Young, C. G. *J. Chem. Soc., Chem. Commun.* **1983**, 1215−1216. James, B. R.; Young, C. G. *J. Organomet. Chem*. **1985**, *285*, 321−332. (b) For a single example of an analogous kinetic resolution of a 4-alkenal that bears a β stereocenter, see: Barnhart, R. W.; Bosnich, B. *Organometallics* **1995**, *14*, 4343−4348. The moderate selectivity is probably due to the reversibility of a number of steps in the catalytic cycle. (c) For analogous desymmetrizations of 4-alkenals, see: Wu, X.-M.; Funakoshi, K.; Sakai, K. *Tetrahedron Lett.* **1993**, *34*, 5927−5930. Tanaka, M.; Imai, M.; Fujio, M.; Sakamoto, E.; Takahashi, M.; Eto-Kato, Y.; Wu, X. M.; Funakoshi, K.; Sakai, K.; Suemune, H. *J. Org. Chem.* **2000**, *65*, 5806−5816.
(3) The major product is a cyclohexenone derived from a [4 + 2] annulation/dimerization. See: Tanaka, K.; Fu, G. C. *Org. Lett.* **2002**, *4*, 933−935.
(4) For an overview of directed reactions, see: Hoveyda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev.* **1993**, *93*, 1307−1370.
(5) For reviews, see: (a) Noyori, R.; Suzuki, M. *Science* **1993**, *259*, 44−45. (b) Straus, D. S.; Glass, C. K. *Med. Res. Rev.* **2001**, *21*, 185−210.
(6) For leading references to pentenomycins, see: Seepersaud, M.; Al-Abed, Y. *Tetrahedron Lett.* **2000**, *41*, 4291−4293.
(7) For leading references to jasmone and its derivatives, see: (a) Dobbs, D. A.; Vanhessche, K. P. M.; Brazi, E.; Rautenstrauch, V.; Lenoir, J.-Y.; Genêt, J.-P.; Wiles, J.; Bergens, S. H. *Angew. Chem., Int. Ed.* **2000**, *39*, 1992−1995. (b) Fràter, G.; Bajgrowicz, J. A.; Kraft, P. *Tetrahedron* **1998**, *54*, 7633−7703.
(8) For reviews of kinetic resolution, see: (a) Kagan, H. B.; Fiaud, J. C. *Top. Stereochem.* **1988**, *18*, 249−330. (b) Hoveyda, A. H.; Didiuk, M. T. *Curr. Org. Chem.* **1998**, *2*, 489−526. (c) Keith, J. M.; Larrow, J. F.; Jacobsen, E. N. *Adv. Synth. Catal.* **2001**, *1*, 5−26.
(9) Notes: (a) Other ligands (e.g., CHIRAPHOS and JOSIPHOS) furnish lower enantioselection. For Table 1, entry 1, Et-DUPHOS provides a selectivity factor of 14; the reaction rate is faster than with *i*-Pr-DUPHOS. (b) We obtain more modest selectivity factors in more coordinating solvents (e.g., acetone or THF). (c) Substrates that lack a methoxy group are not effectively resolved.
(10) For a kinetic resolution that proceeds with a selectivity factor of 30, one can obtain a 48% (out of 50%) yield of aldehyde of 90% enantiomeric excess (ref 8a). To generate the cyclopentenone in very high ee, the best approach is to carry out the kinetic resolution to the conversion that provides aldehyde with the target enantiomeric excess, and then to cyclize the aldehyde to the cyclopentenone with a catalytic amount of $[Rh(dppe)]_2(BF_4)_2$.
(11) The development of catalytic, enantioselective methods for generating quaternary stereocenters is one of the more difficult challenges in stereoselective organic synthesis. For leading references, see: Corey, E. J.; Guzman-Perez, A. *Angew. Chem., Int. Ed.* **1998**, *37*, 388−401. See also: Fuji, K. *Chem. Rev.* **1993**, *93*, 2037−2066.
(12) (*S*,*S*)-*i*-Pr-DUPHOS furnishes higher enantioselectivity (and the same sense) as (*R*)-Tol-BINAP, but the reactions proceed very slowly.
(13) The use of other chiral phosphines (e.g., the DUPHOS family, BINAP, and JOSIPHOS) leads to lower enantioselectivity.

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