A Catalytic Asymmetric Wagner−Meerwein Shift

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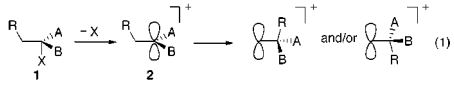
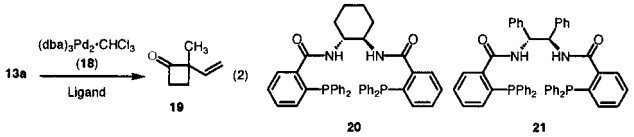
The Wagner−Meerwein rearrangement,[1] a carbon-to-carbon 1,2-migration, typically of an alkyl, vinyl, or aryl group to an adjacent carbocationic center, as depicted in eq 1, requires



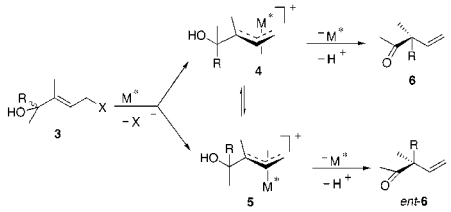
differentiation of the prochiral faces of the sp^2 migration terminus in **2** to proceed asymmetrically. To the extent that migration of R and departure of X in **1** are concerted to any degree instead of proceeding through a free carbocation, then the reaction becomes asymmetric if the starting material can be available enantiomerically pure. Synthetically, it would be valuable to impose chirality upon the carbocation **2** using a catalyst that may differentiate the prochiral faces of the sp^2 carbon. Scheme 1 outlines a possibility to effect such a process. A chiral catalyst can initiate ionization by preferential complexation to one of the two prochiral faces of the alkene **3** to generate preferentially **4** or **5** and subsequently **6** or *ent*-**6**. In this communication, we realize what we believe to be the first catalytic asymmetric Wagner−Meerwein shift not involving chiral substrates which has led to asymmetric syntheses of cyclobutanones, cyclopentanones, γ-butyrolactones, and δ-valerolactones.

We chose to examine a ring expansion protocol[1−4] for which the substrates were easily accessed via cuprate additions, as shown in Scheme 2 and Table 1.[5,6] By this protocol, only the *Z* geometrical isomers were obtained.[7] The methyl substrate **13a**[7] was initially examined to test the feasibility of the reaction as shown in eq 2. Exposing **13a** to 2.5 mol % of the Pd(0) complex

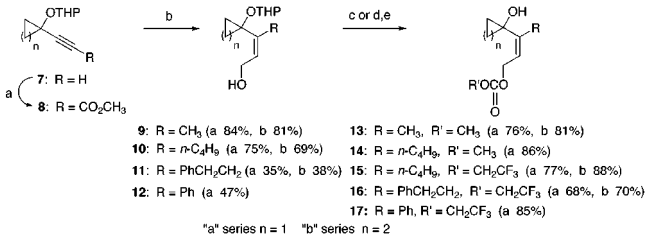


18 and 7 mol % dppb led to smooth ring expansion product **19**[8] in THF at room temperature. The low isolated yield of 36% appears to derive from the volatility of the product. Using a chiral ligand like BINAP[9] or DIOP[9] led to a very slow reaction and only produced very low yields of product (2−11%) of very low ee (5−16%). On the other hand, our standard chiral ligand **20**[10] promoted the reaction with even higher efficiency than dppb since it gave a quantitative yield of **19** (by GC) after only 2 h at room temperature. Gratifyingly, the ee was already a respectable 64%. Changing the solvent had little effect except for acetonitrile in which the ee plummeted to 15%. A very slight increase to 67% occurred in toluene which led to the latter being adopted as our solvent of choice. Changing the ligand to the stilbene diamine derived one **21**[11] significantly increased the ee to 85%. Other ligands gave mainly lower ee's. The final boost in ee came upon the addition of base. While adding inorganic bases such as lithium or cesium carbonate had little effect, tetramethylguanidine (TMG) had a notable effect. Adding 1 equiv had an extremely deleterious effect on both the conversion and the enantioselectivity. On the

Scheme 1. Catalytic Asymmetric Wagner−Meerwein Shift



Scheme 2. Synthesis of Substrates[a]



[a] (a) *n*-C_4H_9Li, THF, $ClCO_2CH_3$, 56%. (b) i. RLi (for **9**, **10** and **12**) or RMgCl (for **11**), CuI (for **9** and **12**) or CuBr•DMS (for **10** and **11**), ether, −70°; ii. DIBAL-H, ether, −70°. (c) $ClCO_2CH_3$, C_5H_5N, CH_2Cl_2, room temperature. (d) $CCl_3OCO_2CCl_3$, CF_3CH_2OH, C_5H_5N, CH_2Cl_2, room temperature. (e) CH_3OH, TsOH, room temperature.

Table 1. Catalytic Asymmetric Wagner−Meerwein Shift

entry	substrate	mol % TMG	°C	time (h)	cycloalkanone	% yield	% ee
1	**13a**	0	rt	2	**19**	quant.[b]	85
2	**13a**	2	rt	3	**19**	quant.[b]	92
3	**14a**	2	60	5	**22**	58	91
4	**15a**	20	0	5	**22**	quant.[b]	85
5	**15a**	50	0	8	**22**	quant.[b]	90
6	**16a**	50	rt	0.67	**23**	quant.[b]	92
7	**17a**	50[a]	rt	24	**24**	62	70
8	**28**	2	0	8	**25**	91	89
9	**30**	2	rt	2	**32**	quant.[b]	77
10	**30**	20	rt	2.5	**32**	94	81
11	**30**	50	rt	5	**32**	90	87
12	**30**	100	rt	24	**32**	52	89
13	**15b**	50	60	3	**33**	90	82
14	**16b**	50	60	6	**34**	57	69
15	**31**	50	60	4	**35**	73	93

[a] In this case, 50 mol % *N*,*N*-diisopropylethylamine was used instead of TMG. [b] Quantitative yield.

(1) For an overview of Wagner−Meerwein rearrangements and related reactions, see: Hanson, J. R. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Pattenden, G., Eds.; Pergamon Press: Oxford, 1991; Vol. 3, Chapter 3.1, pp 705−720; Ricknorn, B., idem.; Chapter 3.2, pp 721−732, and Chapter 3.3, pp 733−776; Covency, D.; Chapter 3.4, pp 777−802.

(2) For asymmetric synthesis of cyclobutanones based upon a pinacol rearrangement of chiral scalemic cyclopranol substrates, see: Miyata, J.; Nemoto, H.; Ihara, M. *J. Org. Chem.* **2000**, *65*, 504; Yoshida, M.; Ismail, M. A.-H.; Nemoto, H.; Ihara, M. *J. Chem. Soc., Perkin I* **2000**, 2629 and earlier references therein.

(3) For Pd(0)-catalyzed rearrangements of vinyloxaspirohexanes, see: Kim, S.; Uh, K. H.; Lee, S.; Park, J. H. *Tetrahedron Lett.* **1991**, *32*, 3395.

(4) For leading references to various Pd-catalyzed ring expansion reactions, see: Larock, R. C.; Reddy, C. K. *Org. Lett.* **2000**, *2*, 3325; Yoshida, M.; Sugimoto, K.; Ihada, M. *Tetrahedron Lett.* **2000**, *41*, 5089; Nishimura, T.; Uemura, S. *J. Am. Chem. Soc.* **1999**, *121*, 11010; Nemoto, H.; Miyata, J.; Yoshida, M.; Raku, N.; Fukumoto, K. *J. Org. Chem.* **1997**, *62*, 7850; Jeong, I.-Y.; Nagao, Y. *Synlett* **1999**, 576; Liebeskind, L. S.; Bombrun, A. *J. Org. Chem.* **1994**, *59*, 177; Demuth, M.; Pandey, B.; Wietfield, B.; Said, H.; Viader, J. *Helv. Chim. Acta* **1988**, *71*, 1392; Clark, G. R.; Thiensathit, S. *Tetrahedron Lett.* **1985**, *26*, 2503; Boontanonda, P.; Grigg, R. *Chem. Commun.* **1977**, 583.

(5) Substrate **7** available by acetylide addition to the hemiacetal of cyclopropanone. Cf. Salaün, J.; Bennani, F.; Compain, J.-C.; Fadal, A.; Ollivier, J. *J. Org. Chem.* **1980**, *45*, 4129; Wasserman, H. H.; Cochoy, R. E.; Baird, M. S. *J. Am. Chem. Soc.* **1969**, *91*, 2375.

(6) For cuprate additions, see: Kozlowski, J. A. In *Comprehensive Dynamic Synthesis*; Trost, B. M., Fleming, I., Semmelhack, M. F., Eds.; Pergamon: Oxford, 1991; Vol. 4, Chapter 1.4.8.8, pp 185−187.

(7) New compounds have been characterized spectroscopically, and elemental composition was performed by combustion analysis or high-resolution mass spectrometry.

(8) Trost, B. M.; Keeley, D. E.; Arndt, H. C.; Bodganowicz, M. J. *J. Am. Chem. Soc.* **1977**, *99*, 3088.

(9) Ohkuma, T.; Kitamura, M.; Noyori, R. In *Catalytic Asymmetric Synthesis*, 2nd ed.; Ojima, I., Ed.; Wiley-VCH: New York, 2000; Chapter 1.

(10) Trost, B. M. *Acc. Chem. Res.* **1996**, *29*, 355.

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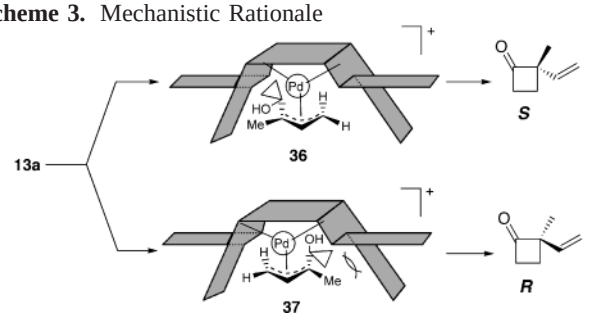
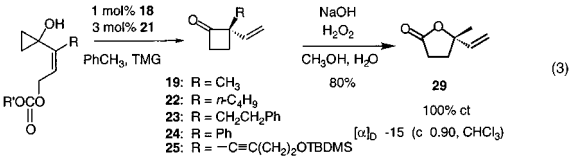
Scheme 3. Mechanistic Rationale



other hand, adding 20 mol % TMG saw some deterioration in rate but the ee increased to 92%. Decreasing the mol % to 10, 5, 2, and 1 saw a corresponding increase in rate (i.e. reaction times decreased from 7 to 5, 3, and 2 h, respectively, for quantitative conversion and yield) and a maintaining of the ee at 92%. While we generally adopted 2 mol %, subsequent work showed that the preferred amount varied with substrate.

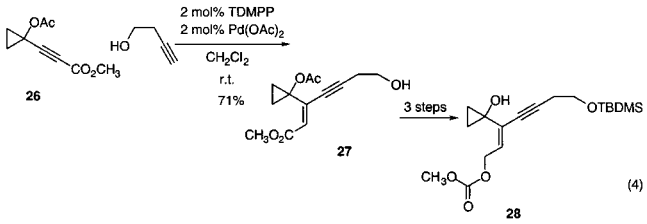
Given the success of the rearrangement, Table 1 (entries 1−8) summarizes the results of the ring expansion to form chiral cyclobutanones according to eq 3. In going from methyl to



(3)

n-butyl, a significant slowing of the reaction occurred. Thus, even at 60° (entry 3), the reaction was still incomplete after 5 h. A significant improvement occurred by switching to the better leaving group trifluoroethyloxycarboxylate. Even at 0° (entry 4), the reaction went to completion to form cyclobutanone **22**[7] in 5 h. Increasing the amount of TMG to 50 mol % saw an increased reaction time of 8 h, but the ee increased to 90% (entry 5). The phenethyl substrate **16a** required only 40 min at room temperature to give a quantitative yield of **23** of 92% ee (entry 6). The phenyl substrate **17a** posed the most difficulty as revealed in entry 7.

On the other hand, the alkyne substrate **28** proved interesting. The substrate was readily available from alkynoate **26** (eq 4).

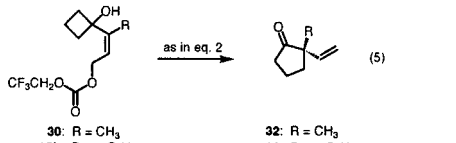


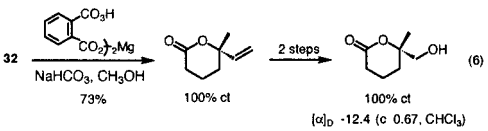
(4)

Pd-catalyzed addition of 3-butyn-1-ol to alkynoate[11] **26** produced directly the *Z*-alkenoate **27**[7] exclusively. Silylation, DIBAL-H reduction, and esterification completed the sequence to the substrate **28**.[7] The catalytic asymmetric rearrangement occurred facilely at 0° to give the desired ring expansion product chemo- and enantioselectively (entry 8).

The absolute configuration of **19** was established by the Baeyer−Villiger reaction[13] to form γ-butyrolactone **29** with high chemoselectivity (eq 3). The ee of the product is identical to that of the starting material indicating a 100% chirality transfer (ct). Comparison of the observed rotation to that of a known sample[14] demonstrates the absolute configuration as *S*.

The success of the ring expansion of vinylcyclopropanols led us to investigate the reactions of vinylcyclobutanols. The substrates were made in analogous fashion, as shown in Scheme 2 for **15**, **16** and **30**, and eq 4 for **31**. The preparation of **8** ($n = 2$, $R = CO_2C_2H_5$) involved the direct addition of ethyl 3-lithiopropiolate to cyclobutanone followed by THP protection. The slower rates of reaction led to the use of the trifluoroethyl carbonates, as shown in eq 5. The behavior of **30** paralleled the behavior of





13b with respect to the effect of TMG. As the amount of TMG was increased from 2 to 100 mol %, the ee increased from 77 to 89% but at the expense of conversion from Q down to 52% (see Table, entries 9−12). In all the remaining cases (entries 13−15) the reactions were performed using 50 mol % TMG at 60° as a compromise between rate and ee. The absolute configuration of **32** was established by correlation to a compound of known configuration as shown in eq 6.[15]

The observations to date support the notion that the enantiodiscriminating step is the initial ionization as depicted in Scheme 3.[16] The effect of base on ee supports this interpretation. Addition of base should increase the rate of the 1,2-shift relative to interconversion of the two diastereomeric complexes **36** and **37** by $\pi-\sigma-\pi$ mechanisms. If the enantiodiscriminating step were the bond migration, the equilibration would have to be fast compared to the 1,2-shift. Thus, base should have decreased not increased the ee if the 1,2-shift was enantiodetermining. Additional support for this interpretation derives from the effect of the addition of tetra-*n*-butylammonium chloride or TBAT. These additives are known[16] to enhance $\pi-\pi$ interconversion and, therefore, should increase ee if the 1,2-shift is enantiodetermining. However, in both cases, the opposite effect is seen—that is, the ee decreases upon their addition. Scheme 3 reveals that, using the cartoons to represent the π-allylpalladium intermediates previously developed,[16] structures **36** and **37** are the two possible diastereomeric complexes. Due to the unfavorable steric interactions present in **37** but not **36**, ionization to diastereomer **36** should be preferred and the *S* product formed—as observed. Thus, the chiral complexes developed previously for asymmetric additions of nucleophiles to π-allylpalladium complexes are excellent in controlling enantioselectivity in a Wagner−Meerwein shift—validating the premise that preferential complexation of enantiotopic faces of a carbocation can induce asymmetry. Furthermore, the versatility of the access to the requisite substrates and the functionality of the obtained products should make this approach an attractive asymmetric synthetic strategy.

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Supporting Information Available: Experimental procedures for **13a−b, 14a, 15a−b**, **16a−b**, **17a**, **19**, **22−25**, **28−35** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) Trost, B. M.; Van Vranken, D. L.; Bingel, C. *J. Am. Chem. Soc.* **1992**, *114*, 9327.
(12) Trost, B. M.; Sorum, M.; Chan, C.; Harms, A. E.; Rühter, G. *J. Am. Chem. Soc.* **1997**, *119*, 698.
(13) Trost, B. M.; Bogdanowicz, M. J. *J. Am. Chem. Soc.* **1973**, *95*, 5321.
(14) Okazaki, T.; Ohsuka, A.; Kotake, M. *Nippon Kagaku Kaishi* **1973**, 359; Felix, D.; Melera, A.; Seibl, J.; Kovats, E. *Helv. Chim. Acta* **1963**, *46*, 1513.
(15) Sato, T.; Maeno, H.; Noro, T.; Fujisawa, T. *Chem. Lett.* **1988**, 1739.
(16) Cf. Trost, B. M.; Toste, F. D. *J. Am. Chem. Soc.* **1999**, *121*, 4545.