References and Notes

(1) O. Makovcova, L. Sindelar, and P. Vaculik, *Biol. Plant.*, **10**, 360 (1968).
(2) R. A. Abramovitch and J. G. Saha, *Adv. Heterocycl. Chem.*, **6**, 229 (1966).
(3) L. D. Goodhue, U.S. Patent 3 325 355 (1967); cf. *Chem. Abstr.*, **67**, 63301 (1967).
(4) B. R. Keney, U.S. Patent 3 404 094 (1968); cf. *Chem. Abstr.*, **70**, 6146 (1969).
(5) K. C. Agrawal, B. A. Booth, S. M. Denuzzo, and A. C. Sartorelli, *J. Med. Chem.*, **18**, 368 (1975).
(6) (a) K. Schofield, "Hetero-Aromatic Nitrogen Compounds", Plenum Press, New York, N.Y., 1967, p 163; (b) C. S. Giam and S. D. Abbott, *J. Am. Chem. Soc.*, **93**, 1294 (1971); (c) C. S. Giam and J. L. Stout, *Chem. Commun.*, 478 (1970).
(7) E. B. Sanders, H. V. Secor, and J. I. Seeman, *J. Org. Chem.*, **41**, 2658 (1976).
(8) P. G. Gassman and C. T. Huang, *J. Chem. Soc., Chem. Commun.*, 685 (1974).
(9) M. Ryang, I. Rhee, and S. Tsutsumi, *Bull. Chem. Soc. Jpn.*, **37**, 341 (1964).
(10) Y. Sawa, M. Ryang, and S. Tsutsumi, *J. Org. Chem.*, **35**, 4183 (1970).
(11) (a) J. P. Collman, *Acc. Chem. Res.*, **8**, 342 (1975), and references cited therein; (b) M. Yamashita, Y. Watanabe, T. Mitsudo, and Y. Takegami, *Tetrahedron Lett.*, 1585 (1976).
(12) All elemental analyses reported were within the accepted limit of ±0.4%.
(13) New naming for this compound is 1-(6-phenyl-3-pyridinyl)ethanone according to "Selection of Index Names for Chemical Substances", *Chem. Abstr.*, **76** (1972), Index Guide.
(14) C. S. Giam and J. L. Stout, *Chem. Commun.*, 142 (1969).
(15) H. Gilman and S. M. Spatz, *J. Org. Chem.*, **16**, 1485 (1951).
(16) A. Schoenberg and R. F. Heck, *J. Am. Chem. Soc.*, **96**, 7761 (1974), and references herein.

Choo-Seng Giam,* Keiyu Ueno
Department of Chemistry, Texas A&M University
College Station, Texas 77843

Received November 2, 1976

Hydrogen vs. Deuterium Transfer in Asymmetric Reductions: Reduction of Phenyl Trifluoromethyl Ketone by the Chiral Grignard Reagent from (*S*)-2-Phenyl-1-bromoethane-*1,1,2-d*$_3$

Sir:

We wish to report on an asymmetric reduction by a Grignard reagent that is chiral by virtue of a hydrogen and deuterium disparity at the asymmetric β-carbon. We find that (S)-PhCHDCD$_2$MgBr(**5**) not only reduces a prochiral ketone asymmetrically, but shows a higher asymmetric induction for deuterium transfer than for hydrogen transfer.

The chiral Grignard reagent **5** was synthesized[1] from (R)-($-$)-mandelic acid **1** according to Scheme I, and used to reduce phenyl trifluoromethyl ketone, **6**, to the mixture of chiral carbinols, **8**.

Composition of 8:

S_H-**8**	R_H-**8**	S_D-**8**	R_D-**8**
45.8 ± 0.8%	16.5 ± 0.5%	8.6 ± 0.5%	29.1 ± 0.6%
62.3 ± 0.6% H transfer		37.7 ± 0.6% D transfer	
47.1 ± 1.6% ee S_H-**8**		54.4 ± 2.2% ee R_D-**8**	

Product analysis of the enantiomeric and isotopic four-component carbinol mixture **8** was achieved by conversion to the mixture of the α-methoxy-α-trifluoromethyl phenylacetates **9** (MTPA derivatives).[2] At 254 MHz, the ^{19}F NMR spectrum[3] of the diasteromeric esters **9** showed completely resolved resonance signals of the carbinyl CF$_3$ group for the four components, shown in Figure 1.

This difference in stereoselectivity between hydrogen vs. deuterium transfer cannot be ascribed to any differences in reagents or conditions in contrast to previous incidental studies[5,6] since the competing reactions are taking place simultaneously and internally within the same mixture. Reduction by a single electron transfer process (SET) or by a magnesium hydride species giving rise to only S_H-**8** and R_H-**8** seems remote.[4]

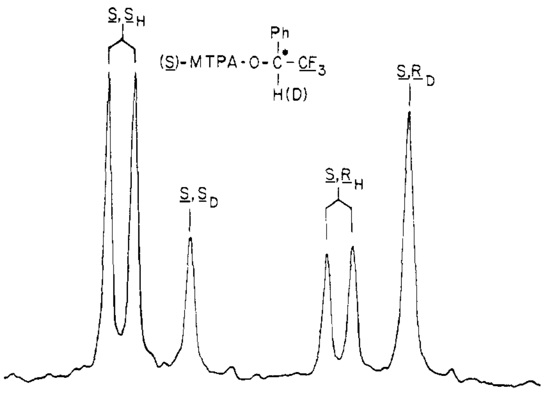
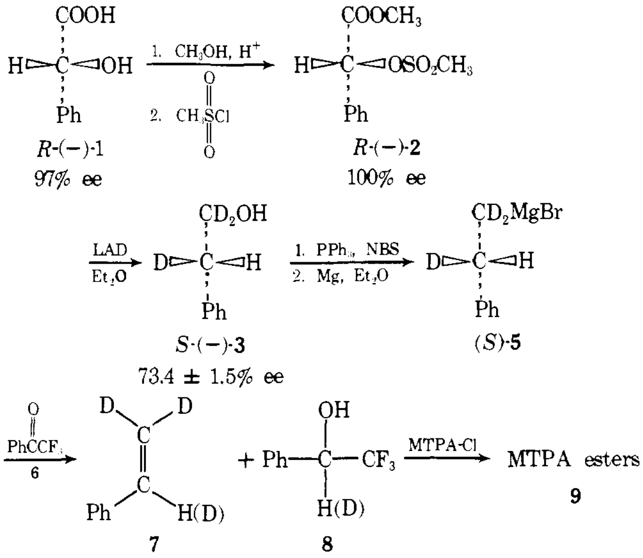
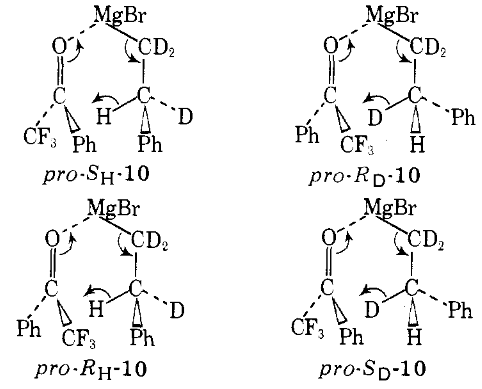


Figure 1. A 254-MHz ^{19}F NMR spectrum in the carbinyl CF$_3$ region of **9**.

Scheme I



Scheme II



The mechanistic situation can be conceptualized in terms of four models for the competing transition states (Scheme II). Two of these models (*pro*-S_H-**10** and *pro*-R_D-**10**) involve transfer of hydrogen from the reagent **5** to the prochiral faces of the ketone **6** to give enantiomeric protio carbinols (S_H-**8** and R_H-**8**) and two (*pro*-S_D-**10** and *pro*-R_D-**10**) involve transfer of deuterium to give enantiomeric deuteriocarbinols (S_D-**8** and R_D-**8**). The preferred transition state for hydrogen transfer is represented by *pro*-S_H-**10** and that for deuterium transfer by *pro*-R_D-**10** as anticipated.[7] The differences in stereoselectivity can be viewed as the sum of at least two effects—namely, the differences associated with the transfer of hydrogen vs. deuterium and the differences due to the nonbonding interactions of H vs. D with CF_3 and Ph. Deuterium has a slightly smaller steric requirement than hydrogen which is manifest only under conditions of severe steric overcrowding.[8] We believe that this effect would be barely perceptible in the present case. The observed difference in stereoselectivity then must be a direct consequence of the hydrogen vs. deuterium transfer.

Three factors, not necessarily unrelated, associated with the direct transfer of hydrogen vs. deuterium may account for the observed stereochemical differences: (1) bond distance; the average C–H bond distance is about 0.008 Å longer than the C–D bond distance;[9] (2) the difference in rate of transfer per se; (3) tunneling. Evidence bearing on the second and third points can be obtained by a temperature study and this is in progress.[10] It may be that the stereoselectivity is extremely susceptible to the proximity of approach of the carbon centers in the C--H--C vs. C--D--C transition states. Hydrogen (hydride), with a de Broglie wavelength greater than that of deuterium, may be able to transfer from reagent to substrate from a greater distance than can deuterium (deuteride). The logical presumption is that the closer the proximity of the two carbon centers, the greater the steric compression in the transition state. This should lead to greater stereoselectivity for deuterium transfer, as observed.

The overall low kinetic isotope effect is consistent with a nonlinear hydride transfer. However, a larger kinetic isotope effect ($k^H/k^D = 1.92 \pm 0.04$) was found for the formation of R_H-**8** and S_D-**8** (the least favored products arising from *pro*-R_H-**10** and *pro*-S_D-**10**) compared to that ($k^H/k^D = 1.58 \pm 0.04$) for the favored products (S_H-**8** and R_D-**8** arising from *pro*-S_H-**10** and *pro*-R_D-**10**). These observations are qualitatively consistent with proton tunneling arguments.

(*R*)-(−)-Mandelic acid, **1,** was converted via the methyl ester, 70.5 g, mp 54–55 °C, $[\alpha]^{20}{}_D$ −174.2 (*c* 4.05, $CHCl_3$), >99% enantiomerically pure, into (*R*)-(−)-methyl *O*-mesylmandelate, **2,** mp 115–116 °C $[\alpha]^{20}{}_D$ −113.6 (*c* 6.67 $CHCl_3$), 77.6 g. Treatment of **2** (63 g in 800 mL of THF) with LAD (10.8 g in 600 mL of ether) for 4 h at room temperature gave crude **3** (73% crude yield of a 9–91 mixture of 1- and 2-phenylethanols). Fractionation through a 28-plate glass-helices column gave **3,** $\alpha^{20}{}_D$ −1.10 (neat, *l* = 1). Analysis by GLC showed 99.8% 2-phenylethanol and by NMR indicated 99 ± 1% 2-phenylethanol-*1,1,2*-d_3. This alcohol, 4.5 mg in $CDCl_3$ in the presence of 43 mg of the chiral shift reagent $Eu(dcm)_3$,[1a] showed signals for the benzylic protons of the *S* and *R* enantiomers at 1492 and 1520 Hz in the ratio of 86.8 to 13.1 (73.7 ± 1.5% ee). The enantiomer NMR chemical shift differences with the chiral $Eu(hfbc)_3$[11] reagent were observable but the signals were not completely separated.

S-(−)-**3,** 13 g, was converted into *S*-(+)-**4** (PPh_3, 7.7 g, NBS, 19.8 g, benzene, 65 mL, 0 °C) to give 13.7 g, 63.5%, of redistilled **4,** $\alpha^{20}{}_D$ +0.855° (neat *l* = 1), from which the Grignard reagent **5** was prepared (sublimed Mg, Et_2O). An aliquot was oxidized (O_2, −78 °C) to regenerate **3** which was purified by preparative GLC and shown[1] to be an 86.7:13.3 mixture of *S* and *R* enantiomers (73.4 ± 2% ee, i.e., no racemization in **3** → **4** → **5** → **3**). An aliquot of the same Grignard solution was treated at 0 °C with **6,** to give a 66% yield of **8** (purified by GLC 20 ft × ⅜ in. Carbowax, 215 °C). The MTPA derivatives **9** were analyzed by ^{19}F NMR (Figure 1). Identity of signals and quantitative analysis were determined by samples of known configuration and composition.

References and Notes

(1) (a) The enantiomeric purity of **3** was determined by use of Whitesides' chiral shift reagent, $Eu(dcm)_3$. M. D. McCreary, D. W. Lewis, D. L. Wernick, and G. M. Whitesides, *J. Am. Chem. Soc.*, **96,** 1038 (1974). We wish to thank Dr. Whitesides for the sample of $Eu(dcm)_3$ used in these studies. (b) The absolute configuration of **3** is assigned assuming an S_N2 displacement of mesylate by deuteride. C. H. DePuy, F. W. Breitbeil, and K. R. DeBruin, *J. Am. Chem. Soc.*, **88,** 3347 (1966); P. K. Wong, K. S. Y. Lou, and J. K. Stille, *ibid.*, **96,** 5956 (1974); R. O. Hutchins, D. Kandasamy, C. A. Maryanoff, D. Masilamani, and B. E. Maryanoff, *J. Org. Chem.*, **42,** 82 (1977); L. M. Stephenson and D. L. Mattern, *ibid.*, **41,** 3614 (1976).

(2) (a) J. A. Dale, D. L. Dull, and H. S. Mosher, *J. Org. Chem.*, **34,** 2543 (1969); J. A. Dale and H. S. Mosher, *J. Am. Chem. Soc.*, **95,** 512 (1973).

(3) We would like to thank Dr. Brian Sykes of the University of Alberta, Edmonton, Alberta, for determining these spectra.

(4) Our preliminary studies have shown that these processes if present are operative to less than 1%. H. S. Mosher, E. R. Larson, and R. L. Elsenbaumer, unpublished results. See E. C. Ashby, J. D. Buhler, I. G. Lopp, T. L. Wiesemann, J. S. Bowers, Jr., and J. T. Laemmle, *J. Am. Chem. Soc.*, **98,** 6561 (1976).

(5) (a) V. E. Althouse, K. Ueda, and H. S. Mosher, *J. Am. Chem. Soc.*, **82,** 5938 (1960); (b) research by A. Horeau, H. Lapin, D. Mea, and A. Nouaille as quoted by J. Mathieu and J. Weill-Raynal, *Bull. Soc. Chim. Fr.*, 1211 (1968); (c) S. Yamaguchi and H. S. Mosher, *J. Org. Chem.*, **38,** 1870 (1973); (d) H. Weber, J. Seible, and D. Arigoni, *Helv. Chim. Acta*, **49,** 741 (1966); (e) L. Verbit and P. F. Heffron, *J. Org. Chem.*, **32,** 3199 (1967); (f) D. Seebach and H. Daum, *Chem. Ber.*, **107,** 1748 (1974); D. Nasipuri et al., *J. Org. Chem.*, **35,** 657 (1970).

(6) J. D. Morrison and H. S. Mosher, "Asymmetric Organic Reactions", Prentice-Hall, Englewood Cliffs, N.J., 1970, pp 201–202, 215–216, 228–230.

(7) J. L. Schmiegel, Ph.D. Thesis, Stanford University, 1967; D. M. Feigl, Ph.D. Thesis, Stanford University, 1965. cf. ref 6, pp 190–194.

(8) K. Mislow, R. Braeve, A. J. Gordon, and G. H. Wahl, *J. Am. Chem. Soc.*, **86,** 1638 (1964), and references therein.

(9) (a) V. W. Laurie and D. Herschbach, *Bull. Am. Phys. Soc.*, **5** (11), 500 (1960); (b) L. S. Bartell, K. Kuchitsu, and R. J. deNeui, *J. Chem. Phys.*, **33,** 1254 (1960).

(10) See E. F. Caldin, *Chem. Rev.*, **69,** 135 (1969); M. D. Harmony, *Chem. Soc. Rev.*, **1,** 211 (1972); R. P. Bell, *ibid.*, **3,** 513 (1974).

(11) R. R. Fraser, M. A. Petit, and J. K. Saunders, *Chem. Commun.*, 1450 (1971).

J. D. Morrison, J. E. Tomaszewski

Department of Chemistry, University of New Hampshire
Durham, New Hampshire 93824

H. S. Mosher,* James Dale
Delores Miller, R. L. Elsenbaumer

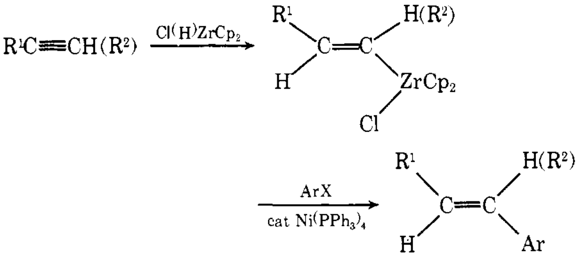
Department of Chemistry, Stanford University
Stanford, California 94305

Received December 13, 1976

Selective Carbon–Carbon Bond Formation via Transition Metal Catalysis. 4.[1] A Novel Approach to Cross-Coupling Exemplified by the Nickel-Catalyzed Reaction of Alkenylzirconium Derivatives with Aryl Halides

Sir:

We wish to report a novel approach to the selective cross-coupling which involves the reaction of organozirconium derivatives with organic halides under the influence of nickel complexes, such as $Ni(PPh_3)_4$. Although the scope of the present discussion is restricted to the alkenyl-aryl coupling represented by eq 1, the applicability of the methodology presented below appears general.



(1)

Within the past few years, hydrozirconation[2a] has emerged as a unique hydrometalation with some attractive features, such as the facile formation of terminally Zr-substituted derivatives from internal alkenes[2b] and high regioselectivity observed with alkynes[2c] and dienes.[2d] Moreover, our preliminary study indicates that the reaction can tolerate certain