Asymmetric Alkylation of Allylic *gem*-Dicarboxylates

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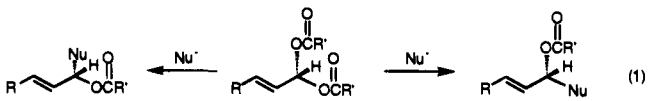
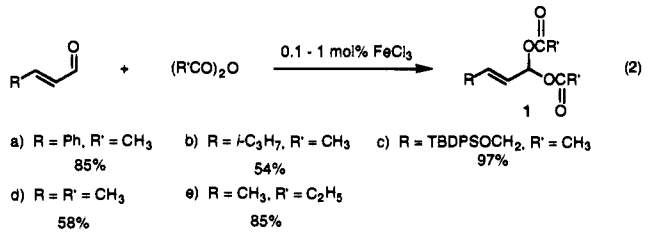
Asymmetric additions to carbonyl groups recognize that the two faces are enantiotopic. While enantioselective formation of C−C bonds by simple additions has been slow to evolve, Oguni's observation of the ability of (*S*)-leucinol to catalyze the asymmetric addition of organozinc reagents to aldehydes initiated a spectacular development of this process for addition of alkyl, vinyl, and aryl groups, but not stabilized nucleophiles.[1,2] An alternative concept recognizes that the two C−O bonds of an acetal are enantiotopic.[3] Thus, asymmetric induction can be achieved by enantioselective substitution of one of the two oxygen functions of such a derivative as shown in eq 1.



(1)

Pd(0)-catalyzed reactions should permit asymmetric additions of stabilized nucleophiles. Chiral recognition in such an alkylation catalyzed by a chiral Pd(0) complex is complicated by the fact that the substrate contains two prochiral structural elements: the double bond and the *gem*-dicarboxylate. For satisfactory levels of asymmetric induction, good molecular recognition of both elements must be achieved in the ionization step. Furthermore, the initial complex must react with the nucleophile faster than it racemizes. In this communication, our initial observations regarding the desymmetrization of achiral *gem*-dicarboxylates with a chiral catalyst are recorded.

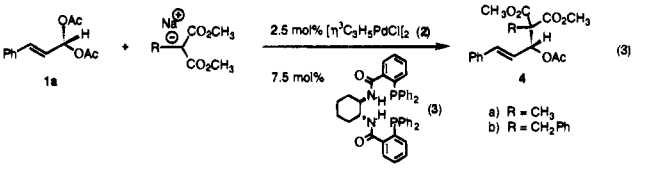
gem-Dicarboxylates **1** are readily available by addition of an acid anhydride to an aldehyde catalyzed by 0.1−1 mol % ferric chloride neat or in a minimal amount of acetonitrile (eq 2).[3] Such compounds are chemically quite robust. They are readily purified by either distillation or column chromatography and appear much more stable toward acid hydrolysis than normal acetals.



(2)

a) R = Ph, R' = CH_3 85% b) R = *i*-C_3H_7, R' = CH_3 54% c) R = TBDPSOCH$_2$, R' = CH_3 97%
d) R = R' = CH_3 58% e) R = CH_3, R' = C_2H_5 85%

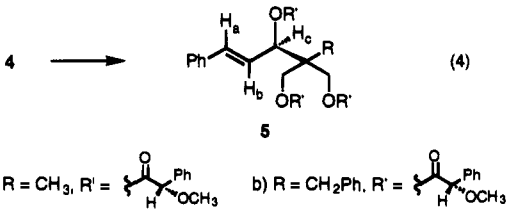
Initial studies centered on **1a**.[4] Exposure of a mixture of dimethyl sodiomethylmalonate and **1a** in THF to a catalyst derived from (π-allyl)palladium chloride dimer (**2**) and ligand **3** (P:Pd, 3:1) at ambient temperature (eq 3) produced the monoalkylation product **4a**[4] in 92% yield. Chiral shift studies



(3)

a) R = CH_3 b) R = CH_2Ph

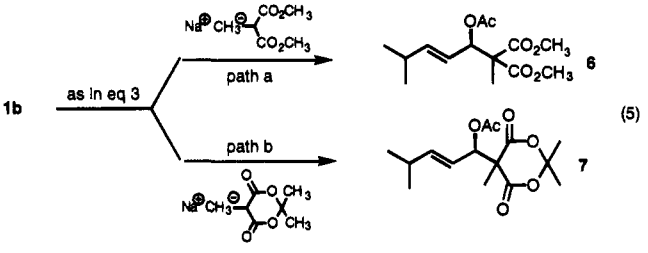
with Eu(hfc)$_3$ revealed only a single enantiomer. This conclusion was reinforced by converting the triester to the triol with LAH (ether, 0 °C) and derivatizing the triol with (*S*)-*O*-methylmandelic acid (DCC, DMAP, CH_2Cl_2, room temperature) (eq 4). The signals for H_a, H_b, and H_c were completely resolved



(4)

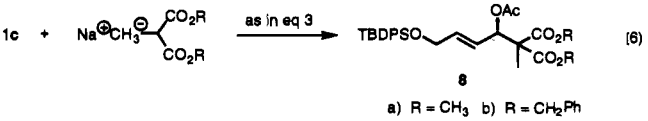
in the two diastereomers from racemic **4**. The appearance of only one set of signals indicates the de to be >95% for **5a**, and thus the ee of the alkylation was determined to be >95%. Furthermore, using the NMR correlations previously established for *O*-methylmandelate esters,[5] the absolute configuration may be assigned as depicted in eq 3. The size of the substituent on the malonate had little effect. Thus, alkylation of **1a** with dimethyl sodiobenzylmalonate under the same conditions gave **4b**[6] in 75% yield with >95% ee, analyzing **4b** in the same fashion as for **4a**.

The isopropyl substrate gave an analogous result with dimethyl sodiomethylmalonate as illustrated in eq 5a wherein the alkylated product **6**[6] was obtained in 75% yield with 95% ee. Some dependence on the nucleophile was observed since alkylation with a Meldrum's acid analogue gave the product **7**[6] in 58% yield with 90% ee.



(5)

Using the straight chain derivative **1c** also gave satisfactory results with dimethyl sodiomethylmalonate (eq 6) wherein the alkylated product **8a**[6] was obtained in 76% yield and 89% ee at ambient temperature. Performing the same reaction at 0 °C



(6)

a) R = CH_3 b) R = CH_2Ph

(1) Oguni, N.; Omi, T.; Yamamoto, Y.; Nakamura, A. *Chem. Lett.* **1983**, 841. Oguni, N.; Omi, T. *Tetrahedron Lett.* **1984**, *25*, 2823. Oguni, N.; Matsuda, Y.; Kaneko, T. *J. Am. Chem. Soc.* **1988**, *110*, 7877. Also see: Noyori, R.; Suga, S.; Kawai, K.; Okada, S.; Kitamura, M.; Oguni, N.; Hayashi, M.; Kaneko, T.; Matsuda, Y. *J. Organomet. Chem.* **1990**, *382*, 19. Seebach, D.; Beck, A. K.; Schmidt, B.; Wang, Y. M. *Tetrahedron* **1994**, *50*, 4363. For reviews, see: Soai, K.; Niwa, S. *Chem. Rev.* **1992**, *92*, 833. Noyori, R. *Asymmetric Catalysis in Organic Synthesis*; John Wiley & Sons, Inc.: New York, 1994; Chapter 5, pp 255−297.

(2) For use of chiral acetals as chiral auxiliaries, see: Johnson, W. S.; Harbert, C. A.; Stipanovic, R. D. *J. Am. Chem. Soc.* **1968**, *90*, 5279. Johnson, W. S.; Harbert, C. A.; Ratcliffe, B. E.; Stipanovic, R. D. *J. Am. Chem. Soc.* **1976**, *98*, 6188. For leading references, see: Sammakia, T.; Smith, R. S. *J. Am. Chem. Soc.* **1992**, *114*, 10998. Ishihara, K.; Hanaki, N.; Yamamoto, H. *J. Am. Chem. Soc.* **1993**, *115*, 10695. For a review, see: Alexakis, A.; Mangeney, P. *Tetrahedron: Asymmetry* **1990**, *1*, 477.

(3) Saucy, G.; Marbet, R.; Lindlar, H.; Isler, O. *Helv. Chim. Acta* **1959**, *6*, 1945. Scriabine, I. *Bull. Soc. Chim. Fr.* **1961**, 1194. Michie, J. K.; Miller, J. A. *Synthesis* **1981**, 824. Kochhar, K. S.; Bal, B. S.; Deshpande, R. P.; Rajadhyaksha, S. N.; Pinnick, H. W. *J. Org. Chem.* **1983**, *48*, 1765.

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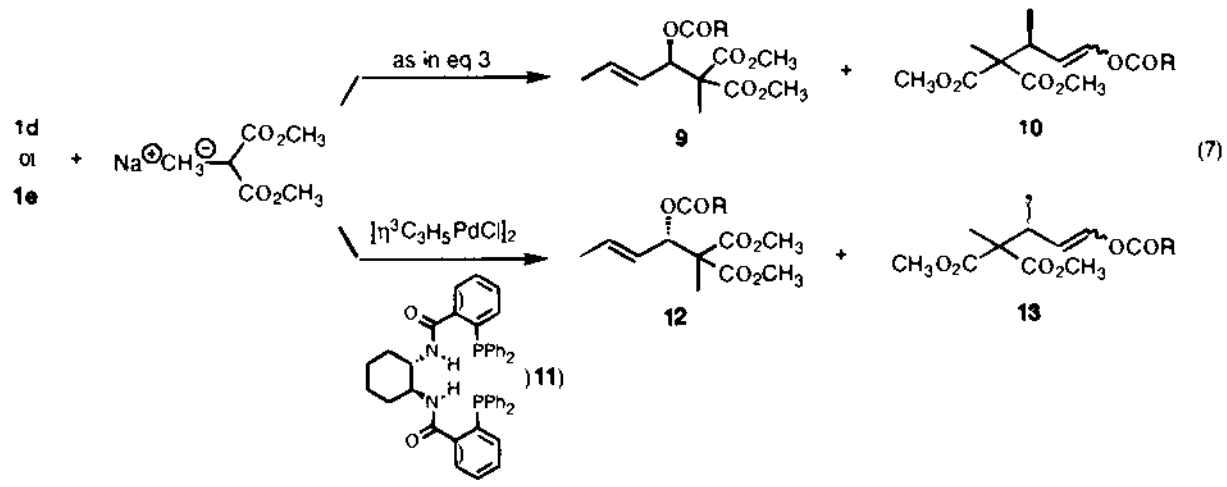
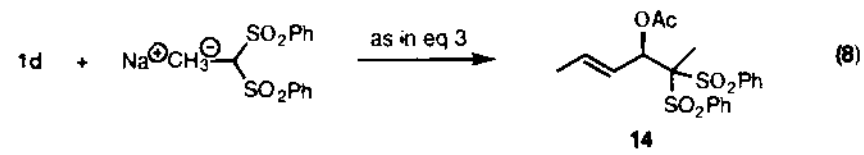
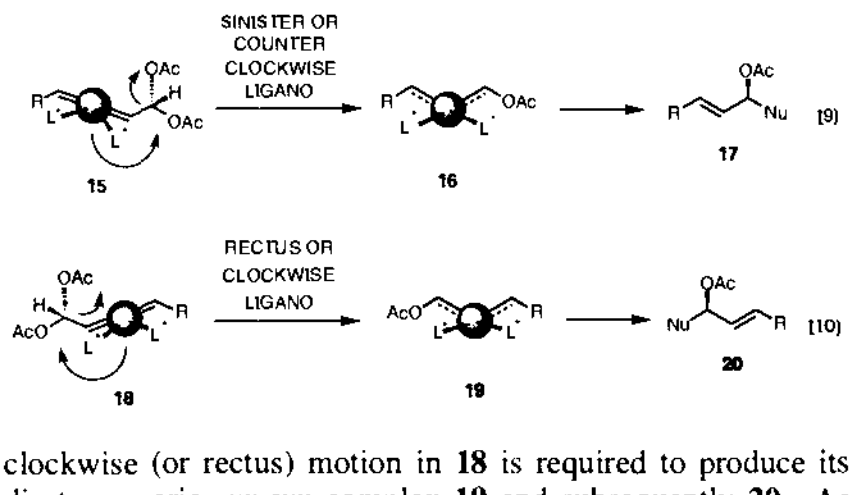


increased the yield to 85% and the ee to 91%. A number of reaction parameters were tested in this case. The reaction did show a dependence on the nature of the cation associated with the nucleophile.[7] Using lithium, potassium, cesium, or tetraalkylammonium cations gave inferior results. Other solvents including methylene chloride, dioxane, acetonitrile, DMF, and DMSO also proved inferior to THF. Switching the malonate ester from methyl to benzyl had little effect. The alkylation product **8b**[6] was obtained in 76% yield and 87% ee.

The reaction of the very simply substituted *gem*-diacetate **1d** was the first occasion where both regioisomeric products **9**[6] and **10** were observed in a 2.9:1 ratio (99% yield). The ee of **9** was still excellent, 92%. Switching the leaving group to propionate enhanced the regioselectivity while maintaining the excellent yield and ee. Thus, using the *S,S*-ligand **11** at 0 °C, a 99% yield of a 5.5:1 ratio of **12**[6] and **13** was obtained wherein the ee of **12** was 92%. It is interesting to note that the chiral ligand not only provided asymmetric induction but also improved the yield and regioselectivity relative to an achiral ligand. Thus, triphenylphosphine gave the racemic products in only 38% yield with a 2.5:1 ratio of regioisomers. The bulkier sodium salt of 1,1-bis(phenylsulfonyl)ethane gave only a single regioisomer **14**[6] in its alkylations with **1d** (99% yield) but in diminished ee, 67% (eq 8).



The stereochemistry of the reaction can be understood on the basis of the following mnemonic. Assuming that ionization will occur preferentially to produce the *syn,syn*-(π-allyl)-palladium complex, formation of the initial alkene–palladium complex as in **15** requires a counterclockwise (or sinister) motion of the palladium with respect to substrate to give **16**, which upon combination with the nucleophile produces **17**. A



clockwise (or rectus) motion in **18** is required to produce its diastereomeric *syn,syn* complex **19** and subsequently **20**. As defined previously,[8] the *R,R*-ligand is a "counterclockwise" ligand and follows the path outlined in eq 9 and the *S,S*-ligand, being a "clockwise" type, follows the path depicted in eq 10. This method constitutes the first report of the equivalent of addition of a stabilized nucleophile to a carbonyl group with high asymmetric induction.[9]

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Supporting Information Available: Characterization data for **4b**, **6**–**9**, **12**, and **14** (3 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

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(4) Trost, B. M.; Vercauteren, J. *Tetrahedron Lett.* **1985**, *26*, 131. Also see: Gravel, D.; Benoît, S.; Kumanovic, S.; Sivaramakrishnan, H. *Tetrahedron Lett.* **1992**, *33*, 1403.

(5) Trost, B. M.; Belletire, J. L.; Godleski, S.; McDougal, P. G.; Balkovec, J. M.; Baldwin, J. J.; Christy, M. E.; Ponticello, G. S.; Varga, S. L.; Springer, J. P. *J. Org. Chem.* **1986**, *51*, 2370.

(6) This compound has been fully characterized spectroscopically and its elemental composition established by combustion analysis and/or high-resolution mass spectrometry. In the case of **8a** and **8b**, full characterization was obtained after desilylation.

(7) Cf.: Trost, B. M.; Bunt, R. C. *J. Am. Chem. Soc.* **1994**, *116*, 4089.

(8) Trost, B. M.; Van Vranken, D. L.; Bingel, C. *J. Am. Chem. Soc.* **1992**, *114*, 9327.

(9) A typical experimental procedure follows (see eq 5). A mixture of dimethyl methylmalonate (150 mg, 1.03 mol) and sodium hydride (60% dispersion, 35 mg, 0.87 mmol) in 1 mL of THF was stirred at room temperature until evolution of hydrogen gas ceased. The mixture was cannulated into a 1.5 mL THF solution of **1b** (105 mg, 0.52 mmol) and preformed catalyst generated by mixing dimer **2** (3.5 mg, 0.0096 mmol) and ligand 3 (18.0 mg, 0.026 mmol). After stirring 5 h at room temperature, the reaction mixture was poured into aqueous sodium bisulfate and extracted with ether. The organic extracts were washed with brine, dried ($MgSO_4$), concentrated *in vacuo*, and flash chromatographed (15% ethyl acetate in hexane) to give 112 mg (75% yield) of **6**. See supplementary material for characterization.