Acknowledgment. We thank the Natural Sciences and Engineering Research Council of Canada for support of this work.

Supplementary Material Available: Complete experimental details (7 pages). Ordering information is given on any current masthead page.

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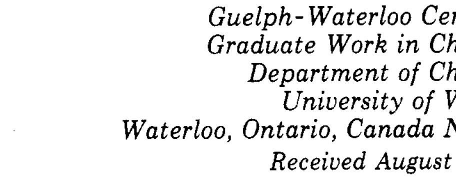
Carboxamide and Carbalkoxy Group Directed Stereoselective Iridium-Catalyzed Homogeneous Olefin Hydrogenations

Summary: Carboxamide and carbalkoxy substituents are capable of directing the stereochemical course of homogeneous [Ir(cod)py(PCy_3)]PF_6/CH_2Cl_2-catalyzed hydrogenation (1 atm) of cyclohexenes.

Sir: In studies directed at total syntheses of the pumiliotoxins,[1] we desired a stereoselective method for effecting the conversion of 1 into 2. Hydrogenation of 1 under



1 2, >99:1(1:9)

heterogeneous conditions with 5% palladium on carbon gave an unfavorable 1:9 ratio of 2 and its diastereoisomer, presumably as a result of steric approach control. Indeed, molecular models of 1 show that the tertiary amide carbonyl group very effectively shields the β-face of the C(2)–C(3) double bond.

We then considered the possibility of directing the course of the hydrogenation of 1 by catalyst coordination with the amide carbonyl group. Support for this proposition came from the work of Halpern and co-workers concerning the mechanism of homogeneous rhodium-catalyzed hydrogenations of α-(acylamino)acrylic acid derivatives.[2] Furthermore, several research groups have demonstrated impressive stereochemical control by hydroxyl group coordination with rhodium and iridium catalyst systems.[3] We now report that excellent stereochemical control can be obtained by hydrogenation of 1, and related olefins (Table I), with the catalyst system [Ir(cod)py(PCy_3)]PF_6/CH_2Cl_2 described by Crabtree and co-workers.[4]

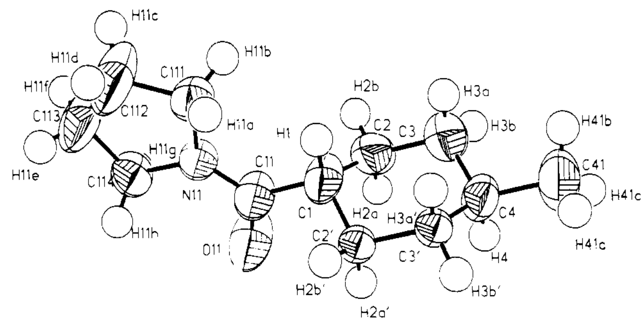


Figure 1. Molecular structure of **4**.

Hydrogenation of **1**[5] in CH_2Cl_2 with ~5 mol % of the iridium catalyst at atmospheric pressure gives **2** with better than 99:1 diastereoselectivity in quantitative yield.[6] Stereochemical configuration of the cyclohexane ring in **2** was determined by conversion to a derivative of an intermediate in the Overman synthesis of *dl*-pumiliotoxin C[7] and to the enantiomer of natural pumiliotoxin C.[8]

Table I shows that the carboxamide group is a superior stereocontrol agent for the iridium-catalyzed hydrogenation of cyclohexene rings. Also included in the table are product ratios for the hydrogenation of each substrate with palladium on carbon. Conversion of **3** to **4** is highly stereoselective with the iridium catalyst (130:1) but is nearly stereorandom with palladium on carbon. Stereochemistry in **4** has been established by single-crystal X-ray structure determination.[9] The molecular structure of **4** is shown in Figure 1. This X-ray diffraction analysis coupled with chemical interconversions and spectroscopic comparisons provides unambiguous stereochemical assignments within the product series **4**, **6**, **8**, and **10** (vide infra).

Iridium-catalyzed hydrogenation of the methyl ester analogue of **3** occurs with decreased diastereoselectivity (**5** → **6**; 41:1).[10] Extending the distance of the amide carbonyl group from the olefinic center by one methylene unit results in negligible erosion of the stereoselectivity of hydrogenation (e.g., **7** → **8**; >100:1), but with the methyl ester analogue **9a** conversion to **10a** is stereorandom.

The absence of stereoselectivity in hydrogenations of olefinic ester **9a** is consistent with Stork's observation[3c] that hydrogenation of acetate derivatives of homoallylic alcohols with structures similar to **9a** (e.g., **9b**) proceeds with essentially no selectivity under the homogeneous iridium conditions. These reactivity patterns must be a result of more effective coordination between the amide carbonyl group and iridium than is obtainable with the ester carbonyl group. Interestingly, the nitrile analogue **9c** failed to undergo hydrogenation with the iridium catalyst.[11]

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(1) Warnick, J. E.; Jessup, P. J.; Overman, L. E.; Eldefrawi, M. E.; Nimit, Y.; Daly, J. W.; Albuquerque, E. X. *Mol. Pharm.* **1982**, *22*, 565 and references cited therein.

(2) Halpern, J. *Pure Appl. Chem.* **1983**, *55*, 99.

(3) (a) Brown, J. M.; Naik, R. G. *J. Chem. Soc., Chem. Commun.* **1982**, 348. (b) Crabtree, R. H.; Davis, M. W. *Organometallics* **1983**, *2*, 681. (c) Stork, G.; Kahne, D. E. *J. Am. Chem. Soc.* **1983**, *105*, 1072. (d) Evans, D. A.; Morrissey, M. M. *J. Am. Chem. Soc.* **1984**, *106*, 3866.

(4) Crabtree, R. H.; Felkin, H.; Fellebeen-Khan, T.; Morris, G. E. *J. Organomet. Chem.* **1979**, *168*, 183. The catalyst was prepared as described in ref 3c, footnote 4.

(5) Heterocycle 1 is obtained in enantiomerically pure form by a modification of the Birch reduction–alkylation method described by: Schultz, A. G.; McCloskey, P. J.; Sundararaman, P. *Tetrahedron Lett.* **1985**, *26*, 1619.

(6) After our work was nearly completed, a report concerning the stereochemistry of rhodium- and iridium-catalyzed hydrogenation of several cyclohexenecarboxylic acids and their esters appeared; see: Brown, J. M.; Hall, S. A. *J. Organomet. Chem.* **1985**, *285*, 333.

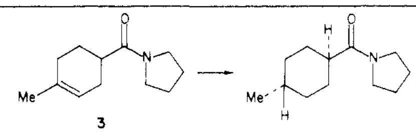
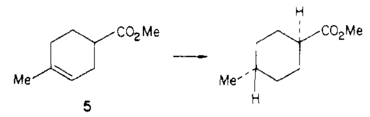
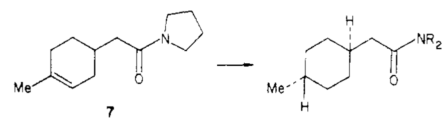
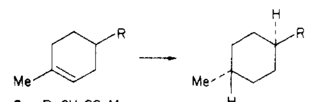
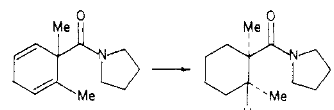
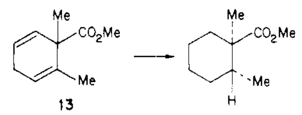
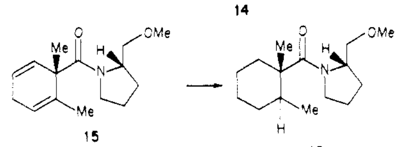
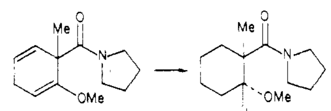
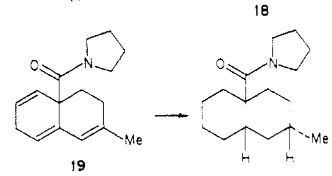
(7) Overman, L. E.; Jessup, P. J. *J. Am. Chem. Soc.* **1978**, *100*, 5179.

(8) Schultz, A. G.; McCloskey, P. J., manuscript in preparation.

(9) Suitable crystals of 4 (mp 97–98 °C) for X-ray diffraction studies were obtained from ethyl acetate solution.

(10) Brown and Hall report[6] that iridium-catalyzed hydrogenation of 5 gives 6 "in excess of 90%". These workers do not indicate how product stereochemistry was determined. Our assignment rests on chemical interconversions between 4 and 6.

Table I. Iridium-Catalyzed Homogeneous Olefin Hydrogenation

reaction[a]	diastereoisomeric excess (de)[b]	yield,[c] %
 3 → 4	130:1 (1.6:1)	89
 5 → 6	41:1 (1.7:1)	87
 7 → 8	>100:1 (4:1)	90
 9a, R = CH_2CO_2Me; b, R = OCOMe; c, R = CH_2CN → 10	a, 1.2:1 (1.9:1); b, no selectivity;[3c] c, no reaction	
 11 → 12	170:1 (1:2.8)	82
 13 → 14	105:1 (1:5)	67[d]
 15 → 16	530:1 (1:2.5)	92
 17 → 18	170:1 (1.6:1)	82
 19 → 20	>1000:1 (1:1:11.6)	91

[a] Reaction conditions are as described in the text for the hydrogenation of **1**. Complete reaction required 2-4 h. [b] Product ratios were determined by quantitative gas chromatography. For details of the analysis procedure, see ref 13. The ratios in parentheses refer to reduction with 5% palladium on carbon in methanol or ethyl acetate. [c] Yields refer to isolated mixtures of diastereoisomers. [d] The low isolated yield in this example appears to be a result of the volatility of **14**.

Alkyl-substituted 1,4-cyclohexadienes also undergo highly stereoselective homogeneous hydrogenation (e.g., **11** → **12**; 170:1); the methyl ester analogue is somewhat less selective (**13** → **14**; 105:1).[12] The preparation of **16** (530:1) highlights the fact that enantiomerically pure cyclohexane derivatives may now be obtained from *o*-toluic acid by (1) the enantioselective Birch reduction–alkylation procedure[13] and (2) carboxamide-directed homogeneous catalytic hydrogenation.

The related conversion of **17** to **18** (170:1) is especially noteworthy[14] because it demonstrates that carboxamide-directed enol ether hydrogenation should provide a useful alternative to a potentially problematic carbonyl group reduction. This unprecedented hydrogenation of an enol

(11) For the preparation of complexes of the type $[Ir(cod)(PPh_3)(RCN)]BF_4$ and $[IrH_2(cod)(PPh_3)(RCN)]BF_4$, see: Crabtree, R. H.; Morehouse, S. M. *Inorg. Chem.* **1982**, *21*, 4210.

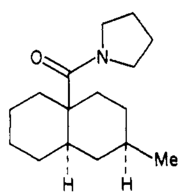
(12) The constitution of **12** and **14** was determined by comparison to authentic *cis*-1,2-dimethylcyclohexanecarboxylic acid previously characterized from the Diels–Alder reaction of tiglic acid and butadiene, followed by hydrogenation; see: Stork, G.; Borowitz, I. J. *J. Am. Chem. Soc.* **1960**, *82*, 4307.

(13) Schultz, A. G.; Sundararaman, P.; Macielag, M.; Lavieri, F. P.; Welch, M. *Tetrahedron Lett.* **1985**, *26*, 4575.

(14) Enol ether **17** is obtained from Birch reduction–alkylation of an *o*-anisic acid derivative; see: Schultz, A. G.; Dittami, J. P.; Lavieri, F. P.; Salowey, C.; Sundararaman, P.; Szymula, M. B. *J. Org. Chem.* **1984**, *49*, 4429.

ether by a cationic catalyst system is all the more remarkable in light of the well-known sensitivity of enol ethers toward Lewis acids.[15]

Perhaps the most dramatic entry in the table is the conversion **19** → **20**, with a diastereoisomeric excess of >1000:1.[16] In contrast, hydrogenation with palladium on carbon produces the other three possible diastereoisomers in a ratio of 1:1:11.6. Because of the steric bulk of the carboxamido group in **19**, we assume that the major diastereoisomer from the Pd/C reaction is trans fused **21**. We expect that hydrindanes and other fused ring systems will be similarly available in either cis or trans modification by these complimentary hydrogenation procedures.



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Acknowledgment. We thank the National Institutes of Health (GM 33061) for their support of this work. The purchase of the Nicolet R3m X-ray Diffractometer by Rensselaer Polytechnic Institute is gratefully acknowledged. We thank Dr. Rudolf Kullnig for the X-ray diffraction analysis of **4**.

Supplementary Material Available: Complete listings of positional parameters, bond angles and distances, and thermal parameters for structure **4** (6 pages). Ordering information is given on any current masthead page.

(15) We have found that under carefully defined conditions the enol methyl ether of cyclohexanone is hydrogenated by the iridium catalyst system to give methyl cyclohexyl ether. Although this result requires more detailed study, it does demonstrate that bidentate substrate catalyst coordination is not required for successful enol ether hydrogenation.

(16) Triene **19** is prepared from *o*-anisic acid by the Birch reduction-alkylation procedure, followed by the Lewis acid catalyzed ene methodology described by Snider and co-workers; see: Jackson, A. C.; Goldman, B. E.; Snider, B. B. *J. Org. Chem.* **1984**, *49*, 3988. Details of this synthesis will be published elsewhere.

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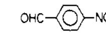
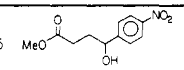
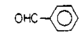
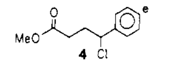
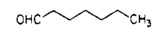
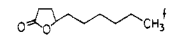
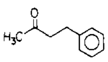
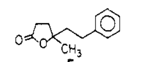
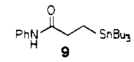
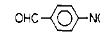
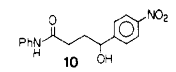
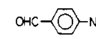
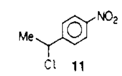
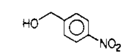
A New Method for Generating Trichlorotitanium(IV) Ester Homoenolates. Direct Tin-Titanium Exchange

Summary: Treatment of the β-tri-*n*-butylstannyl derivatives of esters with titanium tetrachloride in dichloromethane effects tin-titanium exchange to generate trichlorotitanium(IV) homoenolate derivatives of the esters, which may then be used in further reaction with electrophiles.

Sir: Functionalization of β-carbon atoms of carbonyl compounds via carbanion (homoenolate anions) **1** has been of considerable interest to synthetic organic chemists. Many approaches to generate useful homoenolate anion equivalents have been reported.[1] It is well-known that certain types of carbon-tin σ-bonds can be activated by various catalysts to form carbon-carbon bonds with electrophiles.[2] This fact, coupled with the ease with which trialkyltin moieties can be introduced at the β-carbon atoms of carbonyl compounds,[3] prompted us to investigate the possibility of using such β-trialkyltin-substituted carbonyl derivatives as latent homoenolate anions. We report here the generation of trichlorotitanium(IV) ester homoenolate derivatives via direct tin-titanium exchange.

Methyl 3-(tri-*n*-butylstannyl)propionate (**2**, R = Me) can be prepared easily in large quantities by treating tri-*n*-butyltin hydride with methyl acrylate (80 °C, 4 h, 75% yield).[4] Treatment of this methyl ester (**2**, R = Me) with

Table I. Reactions of Tin Compounds with Electrophiles in the Presence of $TiCl_4$[8]

entry	tin substrate	electrophile	reactn condn[a] temp,[b] °C	reactn condn[a] time,[c] h	product	yield,[d] %
1	**2** (R = Me)		0	2.5		75
2			20	5.0	 **4** [e]	64
3			-10	5.0	 [f]	61
4	**2** (R = Me)[g]		-10	24.0	 **5**	(50)[h]
5	**2** (R = Me)[i]		-10	24.0		54[j]
6	 **9**		-10	7.0	 **10**	(60)[k]
7	**9**[l]		-10	16.0		83
8	Me_4Sn[l]		-10	48.0	 **11**	47
9	Bu_4Sn[l]		-10	48.0		26[m]

[a] CH_2Cl_2 solvent; unless otherwise mentioned, 1.0 equiv of $TiCl_4$ was used. [b] The initial -78 °C cooling bath was replaced by the specified-temperature bath, and the reaction mixture was allowed to warm to room temperature gradually. [c] The reaction mixture was quenched after the specified time. [d] Unless otherwise mentioned, yield refers to isolated yield of the pure compound. [e] Even at a lower temperature (-30 °C, 20 h), the chloro compound was the major product. [f] Product after lactonization (refluxing in toluene with PTSA as catalyst, 4 h). [g] 2.0 equiv of tin ester and 1.0 equiv of $TiCl_4$ were used in this reaction. [h] A 1:1 mixture of the product and the unreacted ketone was obtained, according to ^1H NMR analysis. [i] 4.0 equiv of tin ester and 2.0 equiv of $TiCl_4$ were used in this reaction. [j] The crude product contained no unreacted ketone, by ^1H NMR analysis. [k] Crude reaction product contained 60% hydroxy amide and 40% *N*-phenylpropionamide; 40% of the aldehyde was unreacted. [l] 2.0 equiv of tin substrate and 2.0 equiv of $TiCl_4$ were used. [m] Much of the unreacted *p*-nitrobenzaldehyde was recovered from the reaction mixture. Based on the recovered *p*-nitrobenzaldehyde, the yield of *p*-nitrobenzyl alcohol was 52%.

(1) For a recent review, see: Werstiuk, N. H. *Tetrahedron* **1983**, *39*, 205.

(2) (a) Allyltin compounds: Yamamoto, Y.; Yatagai, H.; Naruta, Y.; Maruyama, K. *J. Am. Chem. Soc.* **1980**, *102*, 7107. Naruta, Y. *Ibid.* **1980**, *102*, 3774. (b) Trialkyltin enolates: Trost, B. M.; Keinan, E. *Tetrahedron Lett.* **1980**, *21*, 2591. Noltes, J. G.; Verbeek, F.; Creemers, H. M. J. C. *Organomet. Chem. Synth.* **1971**, *1*, 57. (c) Intramolecular carbocyclizations: Macdonald, T. L.; Mahalingam, S.; O'Dell, D. E. *J. Am. Chem. Soc.* **1981**, *103*, 6767. (d) Pd(0)-catalyzed reactions: Milstein, D.; Stille, J. K. *J. Am. Chem. Soc.* **1979**, *101*, 4992. Logue, M. W.; Teng, K. *J. Org. Chem.* **1982**, *47*, 2549.

(3) Still, W. C. *J. Am. Chem. Soc.* **1977**, *99*, 4836 and references cited therein.

(4) (a) VanDerkerk, G. J. M.; Noltes, J. G.; Luijten, J. G. A. *J. Appl. Chem.* **1957**, *7*, 356. (b) Hayashi, K.; Iyoda, J.; Shiihara, I. *J. Organomet. Chem.* **1967**, *10*, 81.

