(4) The final option is slow addition plus acetate at room temperature.[12] For all these variations, stir the mixtures for the entire reaction period.[3] We now always recommend investigating slow addition—it may not help much in some cases, but it will never hurt.

Enzymes and the asymmetric dihydroxylation catalyst are at the opposite ends of the spectrum with respect to dependence on binding to achieve selectivity, and even the titanium-catalyzed asymmetric epoxidation and the various asymmetric hydrogenation catalysts all rely on a tethering group to achieve high ee's and rates. With the above improvements, the asymmetric dihydroxylation becomes the first catalytic process to achieve good enantioselectivity across an enormous range of substrates and without requiring prior binding of the substrate to the catalyst.

Acknowledgment. Financial support was provided by the National Science Foundation (CHE-8303355) and Eli Lilly & Co. We are very grateful to the following members of our laboratory for helpful discussions and/or experimental results that aided the discovery and rapid appreciation of the phenomena described herein: Christopher J. Burns, Pui Tong Ho, Thomas H. Kalantar, Bhushan Lohray, and Paul R. Fleming. J.S.S., E.N.J., and K.B.S. respectively thank the Royal Norwegian Council for Scientific and Industrial Research, the National Institutes of Health, and the John Simon Guggenheim Memorial Foundation for fellowships.

(12) A caveat: in the case of α,β-unsaturated esters and allylic alcohols, the presence of acetate results in lower ee's.

Nickel-Catalyzed Cross-Couplings of Alkenyl and α-Metalated Alkenyl Sulfoximines with Organometallics: Stereoselective Synthesis of Carbacyclins

Irene Erdelmeier and Hans-Joachim Gais*

Institut für Organische Chemie und Biochemie der Universität Freiburg, Albert-Strasse 21 D-7800 Freiburg, Federal Republic of Germany

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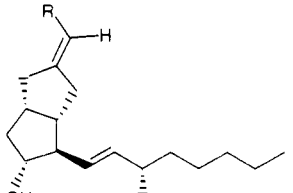
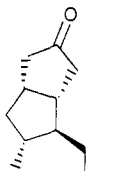
Asymmetric synthesis of alkyl- and/or aryl-substituted exocyclic alkenes from ketones[1] (e.g., **11c** from 4-*tert*-butylcyclohexanone) still constitutes a challenge despite some success achieved recently through Wittig-type olefinations.[2,3] The synthesis of carbacyclins **1** from the key intermediate **2**[2b] represents a most sought after



1

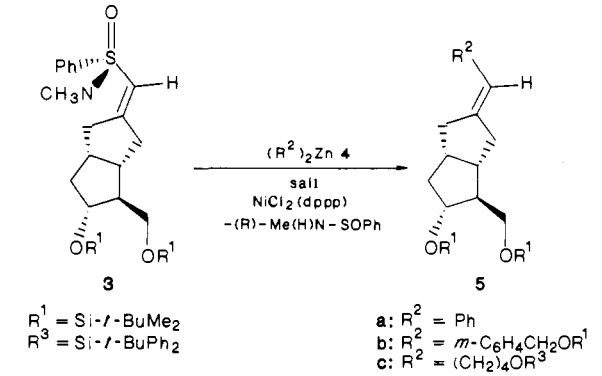


2

a: R = *m*-C_6H_4COOH
b: R = $(CH_2)_3COOH$
c: R = CH_2OCH_2COOH

case where such a method would be of considerable practical importance.[4] Previous syntheses of **1** from **2**[2b,c,4a,b] have failed to stereoselectively effect the geometry of the exocyclic double bond.[5] Transition-metal-catalyzed cross-coupling of alkenyl halides,[6] sulfones,[7a] sulfides,[6] selenides,[6] phosphates,[7b] ethers,[6,7c] or triflates[6] with suitable organometallics ought to be a most promising method therefore, given such derivatives can be prepared from ketones, e.g., **2**, in a stereocontrolled manner which is, unfortunately, not the case.[8] However, alkenyl sulfoximines **3** and **6**, e.g., are obtained with high diastereoselectivity (ds) from **2** (protected OH groups) and 4-*tert*-butylcyclohexanone, respectively, and enantiomerically pure $LiCH_2SO(NMe)Ph$[9] via asymmetric elimination.[10]

Scheme I

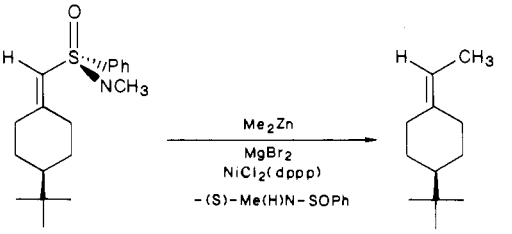


3 **5**

R^1 = Si-*t*-BuMe$_2$
R^3 = Si-*t*-BuPh$_2$

a: R^2 = Ph
b: R^2 = *m*-$C_6H_4CH_2OR^1$
c: R^2 = $(CH_2)_4OR^3$

Scheme II



6 **7**

Here we report an *E*-selective synthesis of exocyclic alkenes **5**, ultimate precursors for **1**,[11,12] from **3** by Ni-catalyzed cross-

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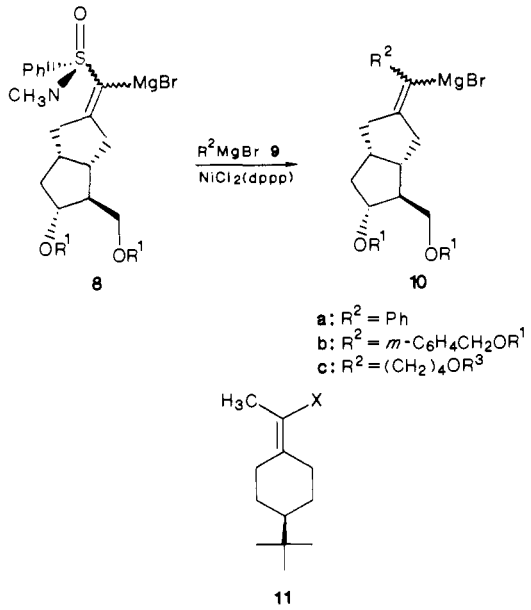
Scheme III[a]



[a] For R^1 and R^3 see Scheme I.

coupling with diorganozinc reagents **4** (+ salt) and the synthesis of optically active alkenes **7** and **11c** from **6** and **11a**, respectively. In the course of these investigations we have uncovered a *Ni-catalyzed cross-coupling between α-magnesio alkenyl sulfoximine **8** and organomagnesiums **9** giving alkenyl magnesium derivatives **10***.

Cross-coupling of **3** with pure **4a** in the presence of $MgBr_2$ (1 equiv), LiBr (1 equiv), or $ZnCl_2$ (2 equiv) and $NiCl_2$(dppp), dppp = $Ph_2P(CH_2)_3PPh_2$, as catalyst proceeded in ether at reflux (24 h) to give the aryl alkene **5a**[13] in 83% yield and 99:1 ds (Scheme I).[14] *It is to be noted that without magnesium, lithium, or zinc salts as cocatalysts practically no coupling occurs.*[15] Starting from pure **4a** and adding one of the above salts is no prerequisite to the success of the coupling reaction. An ethereal solution of **4a** (+2MgX_2), prepared in situ from Grignard reagent **9a** and $ZnCl_2$·Et_2O (molar ratio of 2:1), may be used instead with equal success. In like manner the aryl carbacyclin precursor **5b**[13] was synthesized from **3** and the diaryl zinc derivative **4b** (+2MgX_2) in 89% yield and 99:1 ds.

Extending the coupling of **3** with arylzinc derivatives **4a,b** to that with dialkylzinc derivative **4c** was also met with success. Thus, reaction of **3** with **4c** (+2MgX_2) in ether in the presence of $NiCl_2$(dppp) at 0 °C for 5 days gave a 70% yield of alkyl carbacyclin precursor **5c**[13] in 99:1 ds. Here as byproduct formally hydrogenated **3**, **3**(+H_2), easily separable from **5c** by chromatography, was formed in 20% yield. Attempted coupling of **3** with salt free **4c**[16] led to **3**(+H_2) in 74% yield without formation of **5c**. *Z* isomers of **5a–c** were obtained stereoselectively from the *Z*,*S*(S) isomer of **3**[10] and **4a–c** by the above protocol. In comparison of **5a–c** with their *Z* isomers, the ds of the coupling reactions was unequivocally ascertained.[17] The cross-coupling was further applied to the synthesis of enantiomerically pure alkene **7**[8b,13] from (+)-**6**[10] and Me_2Zn in the presence of $MgBr_2$ (2 equiv) which could be accomplished in 74% yield (Scheme II). *Besides **5a–c** and **7** optically active MeN(H)-SO-Ph*[18] (≥98% *ee*) *is formed in high yields with retention of configuration.* The role of the metal salts in the above cross-couplings with diorganozincs is not clear at present.[15] However, that even $ZnCl_2$ causes a dramatic rate enhancement is noteworthy.

Coupling of **3** with more basic organomagnesiums or -lithiums takes a different and surprising course. From **3** (1 equiv) and an excess of **9a–c** (3 equiv, ether, 0 °C, 3–48 h) in the presence of $NiCl_2$(dppp) (8 mol %) **5a** (74%), **5b** (75%), and **5c** (27%) were isolated with complete loss of olefinic stereochemistry (Scheme III).[19] Deuteriation experiments[20a] revealed that (a) **3** is rapidly and quantitatively metalated at 0 °C at C-8 by **9a** and presumably also by **9b** and **9c** (Cl instead of Br) furnishing α-metalated alkenyl sulfoximine **8** which isomerizes at 0 °C to a 1:1 mixture of **8** and its *Z* isomer[21] and (b) a *facile Ni-catalyzed cross-coupling of **8** (*E*:*Z* = 1:1) with **9a–c** (ether, 0 °C, 3–48 h) occurs to give the alkenyl metal derivatives **10a–c** and their Z isomers (1:1)*.

Conceivable alternative routes to **10** from **8** such as substitution of **8** with **9** without invoking the transition-metal catalyst by a mechanism like the one described for the substitution of α-metalated vinyl halides by organometallics[22] or a Ni-catalyzed coupling of **8** and **9** to give **5** but having instead of an H-atom at C-8 a sulfoximine group, and its subsequent cleavage by **9** can be excluded.[20b] Under the conditions listed above without $NiCl_2$(dppp) no coupling occurs between **8** and **9**, and alkenyl sulfoximine **11a**, which served as a model compound, is not converted to the alkenyl Grignard derivative **11b** upon t .tment with **9a**. Instead, in the presence of $NiCl_2$(dppp) a cross-coupling between **11a** and **9a** took place which led to the isolation of optically active disubstituted exocyclic alkene **11c**[13] in 80% yield.

To our knowledge, the above described Ni-catalyzed cross-coupling of an α-functionalized alkenyl metal derivative with organometallics to give substituted alkenyl metal derivatives is without precedent.[6]

Further studies and applications of the cross-couplings of alkenyl and α-metallo alkenyl sulfoximines, especially focusing on the synthesis of 3-oxacarbacyclins **1c**,[2b,c] from **3** are now in progress in our laboratory.

Acknowledgment. This research was generously supported by the Deutsche Forschungsgemeinschaft, the Schering AG, Berlin, and the Fonds der Chemischen Industrie (fellowship to I.E.). We thank Professor M. Julia, Paris, for stimulating discussions.

Supplementary Material Available: Synthesis and NMR and MS data for **3**(+H_2), **5a**, *Z*-**5a**, **5b**, *Z*-**5b**, **5c**, *Z*-**5c**, **7**, **8**, and **11c** (11 pages). Ordering information is given on any current masthead page.

(13) Optical rotations, $[\alpha]_{365}^{20}$, for compounds prepared in this study are as follows: **5a**, +20.5° (*c* 0.20, *n*-hexane); **5b**, +81.9° (*c* 0.5, *n*-hexane); **5c**, +7.9° (*c* 0.7, *n*-hexane); **7**, +18.7° (*c* 0.7, $CHCl_3$) (λ = 546 nm); **11c**, +149.6° (*c* 0.8, $CHCl_3$).

(14) With $PdCl_2(PPh_3)_2$ under identical conditions no coupling occurred.

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(16) Salt free **4c** in ether was prepared from **9c** (Cl instead of Br) and $ZnCl_2$·Et_2O (molar ratio 2:1), precipitation of the salts by addition of *n*-hexane, filtration, evaporation, and dissolution of the residue in ether.

(17) *E*/*Z* ratios were determined by HPLC (two 10 cm × 0.8 cm 4μ-C_{18} columns (waters): solvent, 97:3 methanol/water; flow rate, 1.7 mL/min; detection, UV (225 nm)) (for **5c**) and ^1H NMR (400 MHz) using the signals of the Si-*t*-$BuMe_2$ groups (**5a**: 0.83, 0.89, *Z* isomer: 0.84, 0.86; **5b**: 0.84, 0.90, 0.93, *Z* isomer: 0.85, 0.87; **5c**: 0.850, 0.900, *Z* isomer: 0.847, 0.897).

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(19) Cross-coupling of **3** with **9a–c** (THF, 0 °C, 30 min) in the presence of stoichiometric amounts of $Fe(acac)_3$[7a] gave **5a** (74%, *E*:*Z* = 4:1), **5b** (75%, *E*:*Z* = 3:1), and **5c** (34%, *E*:*Z* = 7:1), respectively.

(20) (a) (D)-**3** (95%, 100% D, *E*:*Z* = 1:1) and (D)-**5a** (80%, 100% D, *E*:*Z* = 1:1) were isolated from **8** and **10a**, respectively, through CF_3COOD quench followed by usual workup. (b) **10a** is not formed from **5a** and **9a**.

(21) α-Metalated alkenyl sulfoximines, e.g., **8**, accessible by metalation of corresponding alkenyl sulfoximines with organomagnesiums (−20 °C) or -lithiums (−78 °C) are configurationally stable at −78 °C in ether and can be alkylated (ether/HMPA) with retention of configuration (e.g., **11a**, 83%, $[\alpha]^{27}_D$ +22.5° (*c* 1.3, acetone), mp 102.5 °C): Gais, H.-J.; Erdelmeier, I.; Diederichsen, U., manuscript in preparation.

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