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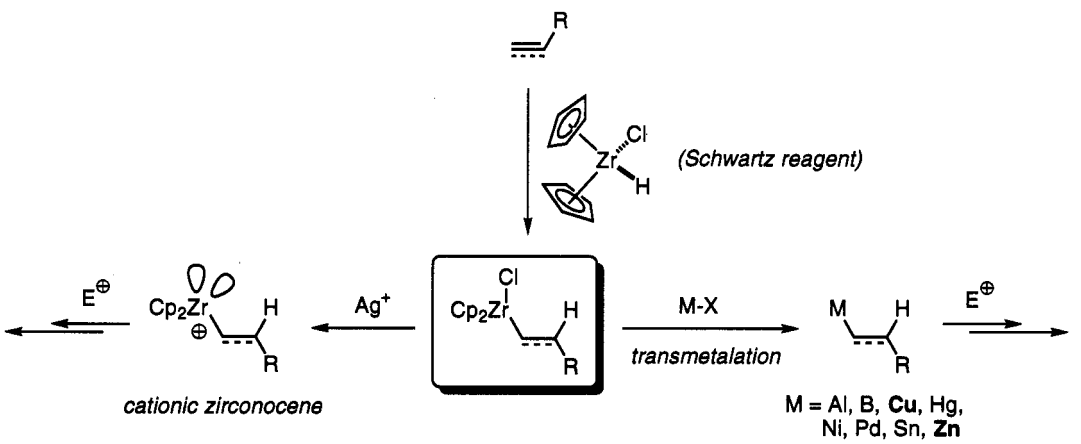
Synthetic applications of organozirconocenes

Peter Wipf,* Wenjing Xu, Hidenori Takahashi, Heike Jahn, and Philip D. G. Coish

Department of Chemistry, University of Pittsburgh, Pittsburgh, PA 15260, USA

Abstract - Alkenyl- and alkylzirconocenes are readily available by hydrozirconation of alkynes and alkenes, respectively. Due to the relatively low nucleophilicity of the carbon-zirconium bond in these organometallics, transmetalation schemes have been developed for carbon-carbon bond formations. Especially, *in situ* transmetalation to copper(I) and zinc(II) species can be used for selective alkylation reactions with organic electrophiles. Alternatively, conversion of organozirconocenes to the corresponding cationic complexes enhances their reactivity considerably. Synthetic applications include protocols for orthoester formations and Diels-Alder catalysis as well as natural products (Curacin A, Manumycin) synthesis.

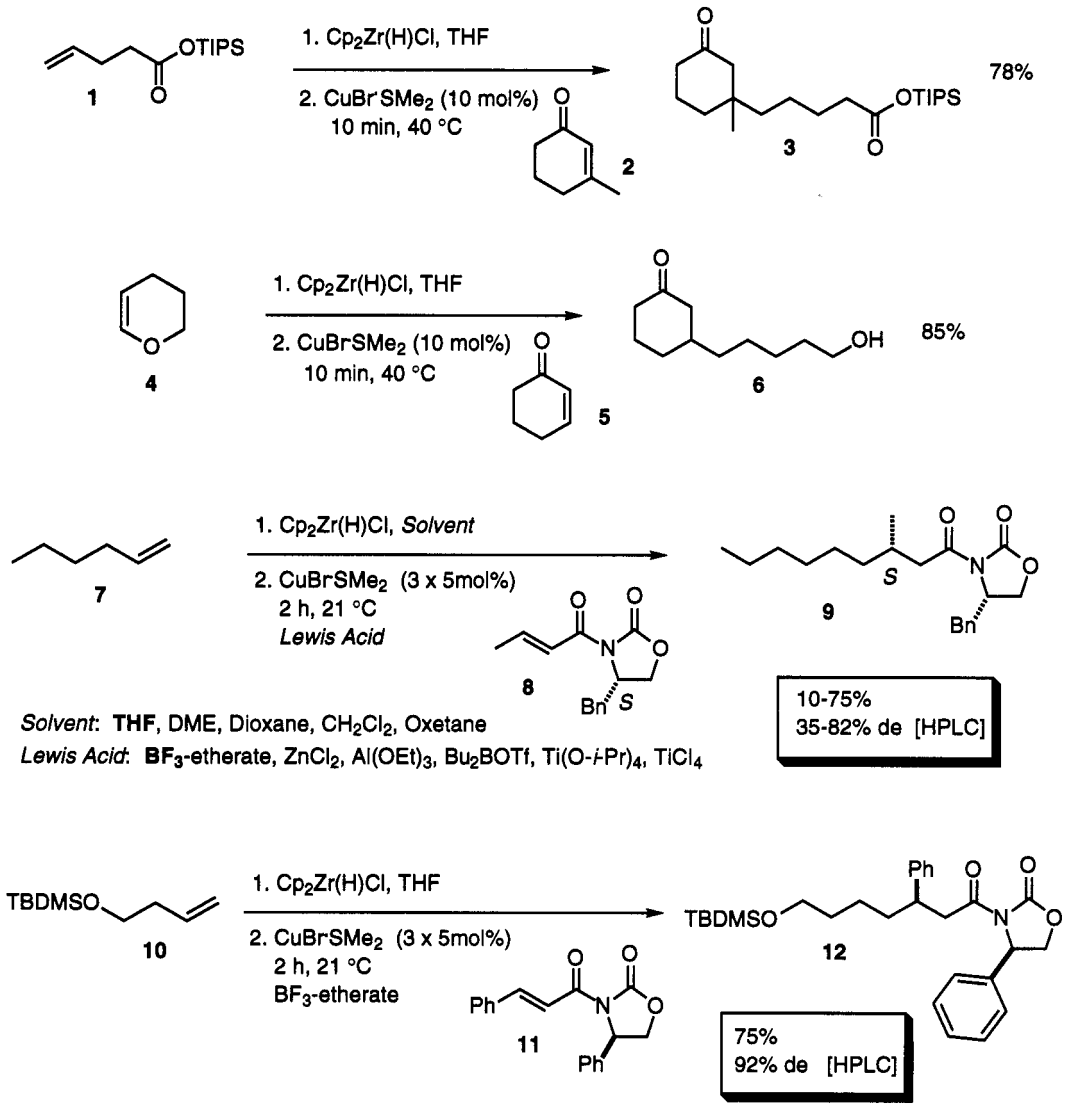
Since the preparation of the first organochlorobis(cyclopentadienyl)zirconium(IV) complex by Wailes, Weigold and Bell 25 years ago (ref. 1), the application of these organometallics for carbon-carbon and carbon-heteroatom bond formations has become an important aspect of synthetic strategy and tactics. Clearly, this is due to the relative ease of preparation of alkenyl- and alkylzirconocenes by hydrozirconation of alkynes and alkenes with $Cp_2Zr(H)Cl$ (Schwartz reagent) (ref. 2). In spite of a polarization of the carbon-zirconium bond similar to Grignard reagents, the bulky cyclopentadienyl groups sterically prevent the attack of many organic electrophiles. The resulting functional group tolerance of organozirconocenes is useful for the preparation of the organometallic species, but this low reactivity must be overcome for subsequent selective carbon-carbon bond formations. Much of the development of the chemistry of organozirconocenes has therefore focused on indirect reaction pathways involving transmetalation or activation by ligand abstraction.



In our work, we have been especially interested in the chemo-, regio-, and stereoselectivity of the hydrozirconation process, the transmetalation of alkyl- and alkenylzirconocenes to copper(I)- and zinc(II)-derivatives, and the organic chemistry of cationic zirconocene complexes (ref. 3-10). In addition to our studies, several other research groups have contributed to recent advances in these fields (ref. 11).

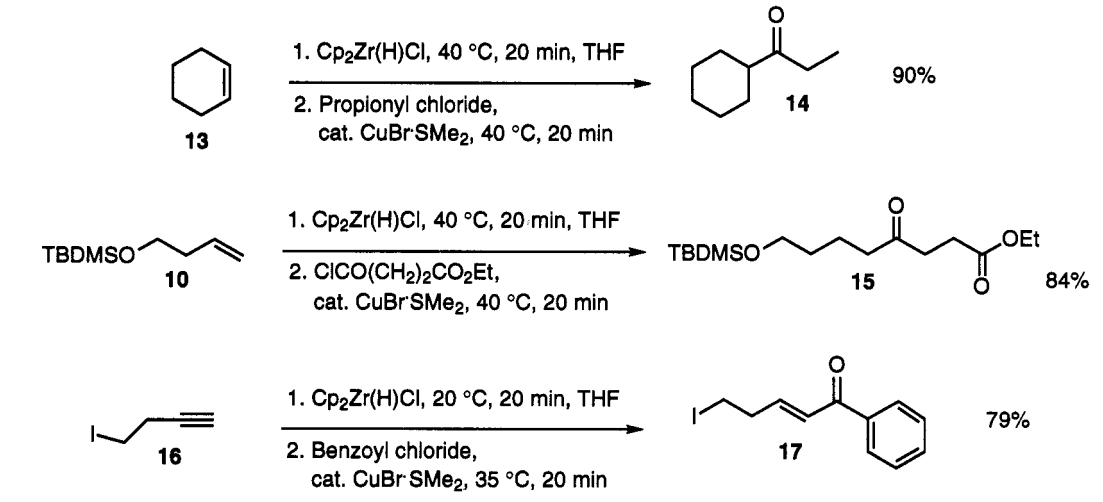
The copper-catalyzed conjugate addition of alkylzirconocenes allows an *in situ* addition of terminal alkenes to enones and vinyl sulfones in 60-90% overall yield (ref. 4,8). This reaction is formally equivalent to a hydrocupration-conjugate addition sequence and tolerates various functionality. In contrast to the copper(I)-mediated reactions of alkenylzirconocenes, however, an actual transmetalation probably does not

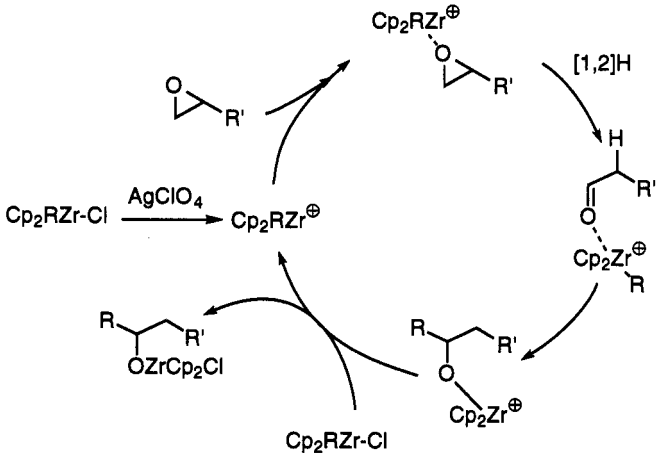
occur due to the poorer exchange properties of alkyl vs. alkenyl metal substituents. In an asymmetric version of this process, we have recently investigated the conjugate addition to acyl oxazolidinones. With the chiral benzyl oxazolidinone **8** (ref. 12), an optimal choice of solvent (THF) and Lewis acid additive (BF_3-etherate) provided the β-branched carboxylic acid derivative **9** in 75% yield and 82% de. In the absence of suitable Lewis acids, the %de of this reaction was very low. Whereas several other chiral auxiliaries including Oppolzer's sultam failed to give a significant level of diastereocontrol, %de's of up to 92% could be obtained with phenyl oxazolidinone **11** (ref. 13).



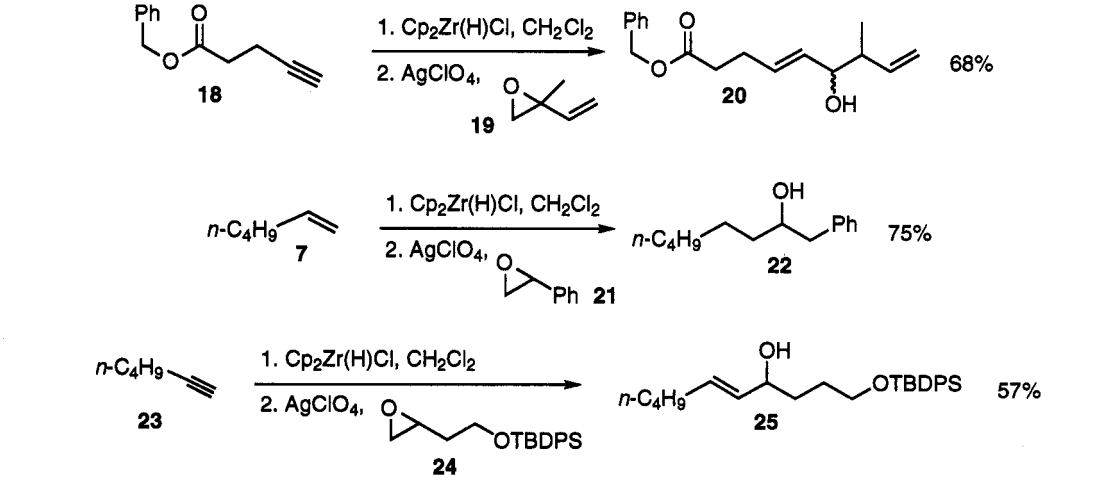
Cu(I)-catalyzed activation of organozirconocenes can also be used for the preparation of highly functionalized ketones from acid chlorides (ref. 5). No over-addition or base-promoted elimination reactions were observed for **15** and **17**. The δ-iodo enone **17** is extremely sensitive and decomposes within a few hours when stored at room temperature. Nonetheless, it can be obtained in 79% yield by hydrozirconation of alkyne **16** and copper(I)-catalyzed acylation.

In spite of its success in carbonyl additions, this protocol cannot be used for epoxide openings, quite possibly because no actual transmetalation occurs under the reaction conditions. We have therefore developed the use of cationic zirconocenes in epoxide additions (ref. 6,7).



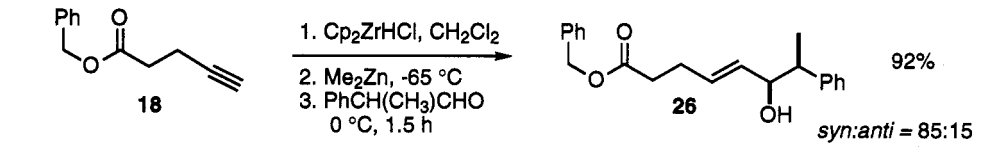


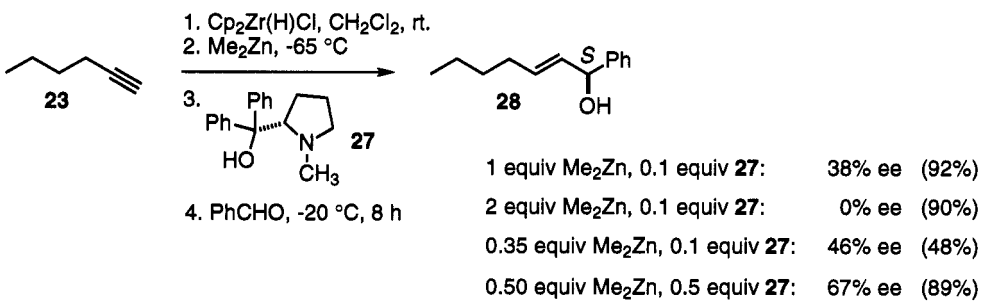
In the presence of catalytic amounts of silver perchlorate, a chloride ligand is abstracted from the *in situ* prepared zirconocene and the resulting formally cationic complex induces a [1,2]hydrogen shift in the epoxide substrate. The resulting aldehyde is subsequently alkylated by ligand transfer from the organozirconocene to yield a secondary alkoxy zirconocene. Abstraction of a chloride ligand from unreacted organochlorobis(cyclopentadienyl)zirconium(IV) complex closes the catalytic cycle. *In situ* prepared cationic zirconocene complexes can also be used for acetal and orthoester formations and in Diels-Alder reactions (ref. 7,10).



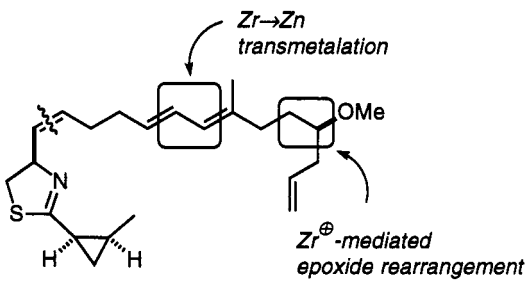
Suzuki and co-workers have shown that silver(I) salts can catalyze the addition of organozirconocenes to aldehydes (ref. 11). An alternative protocol for aldehyde additions is the Zr→Zn transmetalation (ref. 9). In the presence of stoichiometric amounts of dimethyl- or diethylzinc, rapid ligand exchange occurs at temperatures between -65 and 0 °C, and the resulting mixed organozinc species readily

add to carbonyl compounds. An advantage of this process is its greater level of diastereocontrol. Whereas the allylic alcohol **20** was obtained as a 1:1 mixture of diastereomers in the cationic addition with epoxide **19**, alcohol **26** was produced as an 85:15 *syn/anti* mixture. This route is also amenable to asymmetric catalysis. In the presence of 10 mol% of amino alcohol **27** (ref. 14), allylic alcohol **28** was isolated in 38% ee. Interestingly, an increase in the Me_2Zn:**27** ratio led to no asymmetric induction, and a reduction of the Me_2Zn:zirconocene ratio increased the %ee but halved the yield. At 0.50 equiv of Me_2Zn and a Me_2Zn:**27** ratio of 1, a 67% ee and 89% yield resulted. This strong dependence on reaction parameters can be explained by a competition between zirconocene and zinc derivatives for the chiral ligand and background racemic additions of mixed zinc species to the aldehyde catalyzed by achiral zirconocene halide.





We have recently started to apply organozirconocene chemistry for key transformations in the synthesis of complex natural products. In our retrosynthetic analysis of the antimitotic *Lyngbya majuscula* metabolite curacin A, we envisioned the use of Zr→Zn transmetalation and cationic zirconocene-induced epoxide rearrangement for the preparation of the lipophilic carbon chain of this molecule.

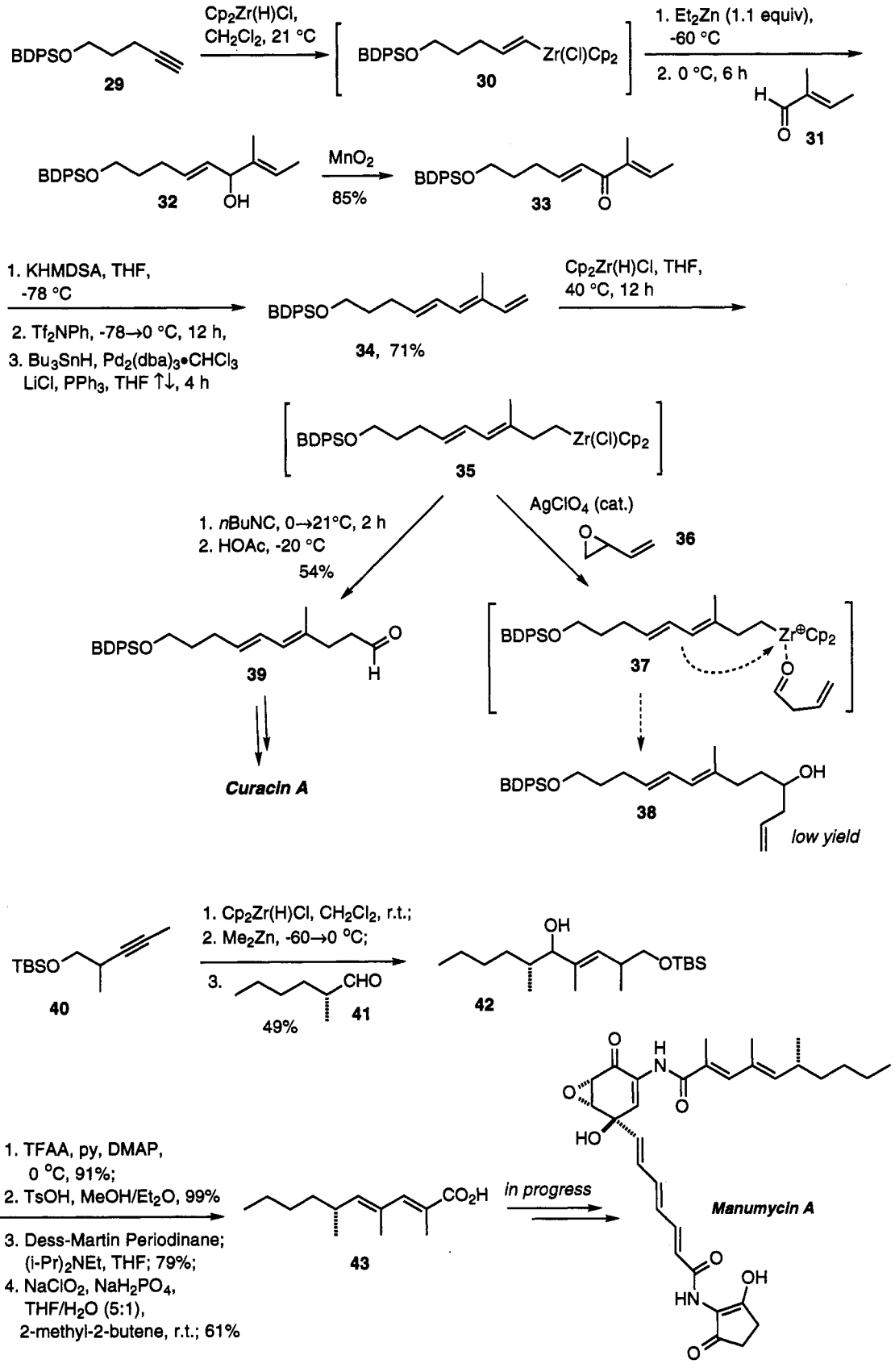


Curacin A

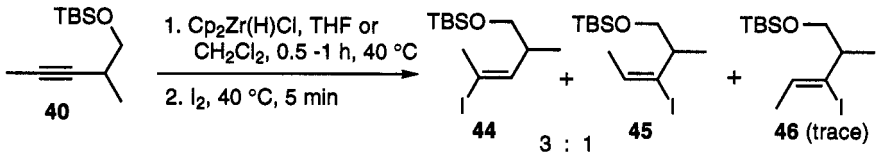
Hydrozirconation-transmetalation of alkyne **29** followed by 1,2-addition to aldehyde **31** and oxidation provided the cross-conjugated dienone **33** in 85% overall yield. Selective hydrozirconation of triene **34**, which was obtained by enolization, enolate trapping, and Pd-catalyzed Stille reduction of the enoltriflate, led to zirconocene intermediate **35**. However, neighboring group participation of the diene moiety reduced the reactivity of the cationic zirconocene **37**, and, accordingly, only traces of the desired homoallylic alcohol **38** were obtained besides **36**-derived polymer.

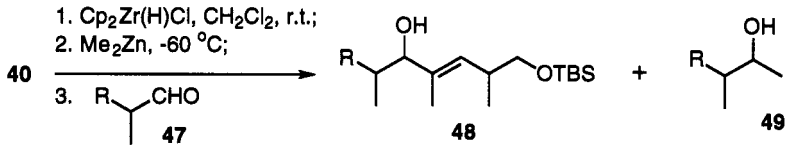
Accordingly, an alternative route that avoided the use of cationic zirconocene intermediates was used. Insertion of terminal zirconocene **35** into isocyanide (ref. 15), followed by hydrolysis of the intermediate iminoacyl zirconocene gave aldehyde **39** which was successfully converted to curacin A.

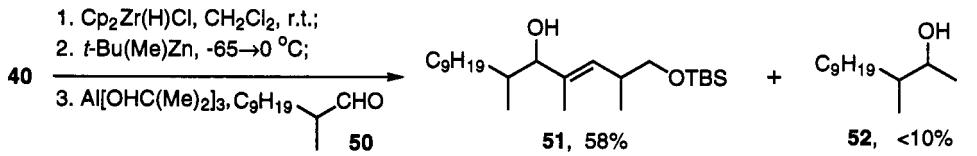
A Zr→Zn transmetalation was also the key step in the synthesis of the manumycin carboxylic acid moiety **43**. Hydrozirconation of alkyne **40** and zinc-mediated addition to chiral aldehyde **41** provided the allylic alcohol **42** which was readily converted to the dienoic acid **43**. This convergent strategy avoids the repetitive use of Wittig reagents for the preparation of the dienoate moiety and is especially useful for rapid analog synthesis. The enantiomeric purity of acid **43** was determined to be >95% by Mosher ester analysis. In order to improve the yield in the addition to **41**, we have studied the regioselectivity of the hydrozirconation of alkyne **40**. Under standard conditions, a 3:1 ratio of isomers **44** and **45** was isolated upon iodination of the vinylzirconocene. Modifications in the nature of the alcohol protective group did not significantly alter the regioselectivity of hydrozirconation. In addition, we observed that upon transmetalation


Cp2Zr(H)Cl, CH2Cl2, 21 °C
BDPSO
29
Zr(Cl)Cp2
30
1. Et2Zn (1.1 equiv), -60 °C
2. 0 °C, 6 h
H
O
31
OH
32
MnO2
85%
33
1. KHMDSA, THF, -78 °C
2. Tf2NPh, -78→0 °C, 12 h,
3. Bu3SnH, Pd2(dba)3•CHCl3 LiCl, PPh3, THF ↑↓, 4 h
34, 71%
Cp2Zr(H)Cl, THF, 40 °C, 12 h
35
1. nBuNC, 0→21°C, 2 h
2. HOAc, -20 °C
54%
AgClO4 (cat.)
36
39
Curacin A
37
38
low yield
TBSO
40
1. Cp2Zr(H)Cl, CH2Cl2, r.t.;
2. Me2Zn, -60→0 °C;
3.
CHO
41
49%
OH
OTBS
42
1. TFAA, py, DMAP, 0 °C, 91%;
2. TsOH, MeOH/Et2O, 99%
3. Dess-Martin Periodinane; (i-Pr)2NEt, THF; 79%;
4. NaClO2, NaH2PO4, THF/H2O (5:1), 2-methyl-2-butene, r.t.; 61%
CO2H
43
in progress
Manumycin A

to dimethylzinc, alkene transfer to the aldehyde competed with methylation, and various ratios of allylic alcohol **48** and secondary alcohol **49** were formed. The use of the mixed zinc reagent *t*-Bu(Me)Zn (ref. 16) solved this problem, and in an unoptimized model reaction with aldehyde **50**, the desired product **51** was obtained in 58% yield with <10% of the methyl alcohol **52**. We are continuing our studies to improve the regioselectivity of hydrozirconation of internal alkynes such as **40**.







The preparations of curacin A and manumycin segments demonstrate that a zirconocene-based strategy can successfully be used for critical carbon-carbon bond formations in natural product synthesis.

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