Organic LETTERS

Letter

pubs.acs.org/OrgLett

$Cp_2ZrMeCl$: A Reagent for Asymmetric Methyl Addition

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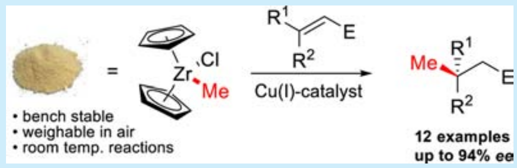
Ⓢ *Supporting Information*

ABSTRACT: The use of $Cp_2ZrMeCl$ is described as a source of nucleophilic methyl in asymmetric catalysis. This easily prepared reagent is bench stable, weighable in air, and generally useful in highly enantioselective copper-catalyzed addition reactions at room temperature. Methyl is successfully (generally >90% ee) added in 1,4-additions to cyclic and acyclic α,β-unsaturated ketones to provide tertiary and quaternary centers. Examples of catalyst controlled diastereoselective 1,6-addition and dynamic kinetic asymmetric allylic alkylation reactions are also reported. The reagent is used in the catalytic asymmetric synthesis of naturally occurring fragrance (*R*)-(−)-muscone (82% yield, 91% ee).



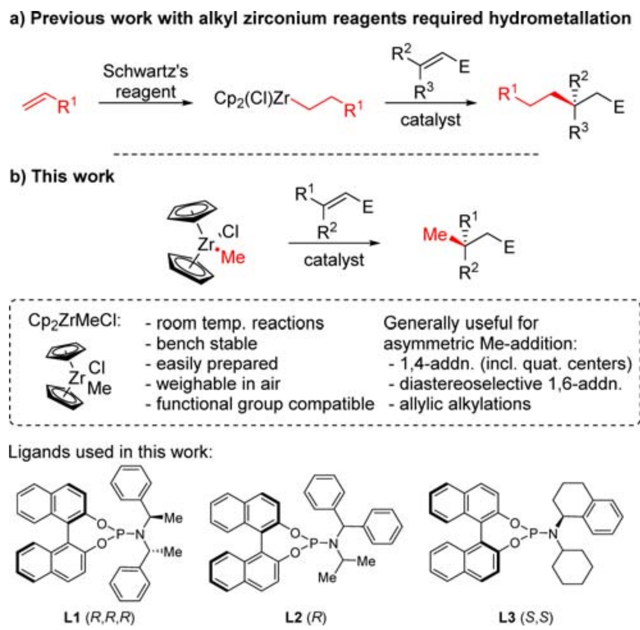
Many biologically active compounds feature stereocenters bearing methyl groups, making methods for the asymmetric addition of Me nucleophiles extremely important. Both tertiary and quaternary centers containing methyl groups are widely represented in natural products[1] and clinically used medicines.[2] Asymmetric conjugate additions (ACAs) of alkyl groups to electron-deficient α,β-unsaturated systems have been widely developed.[3−7] ACAs to add methyl rely on Cu catalysis, and asymmetric methods developed for addition of other alkyl nucleophiles (for example, ethyl) are sometimes suitable, but very often problematic, with methyl nucleophiles.[3]

While Me_3Al can be used to effectively add a methyl group in ACAs,[8,9] the reactivity profile of the reagent presents real safety concerns.[10] Additionally, asymmetric additions with Me_3Al must be performed at cryogenic temperatures, and the reagents Lewis acidity renders it incompatible with many functional groups, limiting applications in complex molecule synthesis.

Other organometallic sources of nucleophilic Me also have limitations. Dimethylzinc spontaneously combusts upon exposure to air and reacts violently in a number of common laboratory situations. Conversely, methyl Grignard reagents tend to have less aggressive reactivity profiles than other Grignard reagents, attributed to aggregation of MeMgX species.[11] However, the importance of asymmetric Me addition has led to several useful procedures using Me Grignard reagents to acyclic enones,[12] a variety of electrophilic thioester acceptors,[13−15] and Loh's protocol which may be used with unsaturated esters.[16,17] Despite high reactivity to air and water, Me_2Zn also shows sluggish reactivity in ACAs, requiring an excess of reagent and long reaction times; designed acceptors have recently been reported to address these issues.[18]

Alkylzirconium reagents can be used in ACAs (Scheme 1a) to acyclic[19] and cyclic[20−24] enones, lactones,[25] 1,4- and 1,6-additions to functionalized steroid derivatives,[26,27] in the formation of quaternary centers, and remote asymmetric C−H activations sequences initiated by alkene isomerization.[28] These highly enantioselective reactions generally proceed at room temperature although in some cases better results are obtained at 0 °C. Recently, alkylzirconium species have been shown to undergo dynamic kinetic asymmetric kinetic transformations to allow highly enantioselective allylic alkylations.[29,30] These methods generally work in a variety of solvents and have wide functional group tolerance. In all cases, the nucleophilic zirconium species were prepared by hydrometalation of alkenes using Schwartz's reagent (Cp_2ZrHCl), so the use of methyl nucleophile was not possible.

Scheme 1. Asymmetric Addition of Me Groups



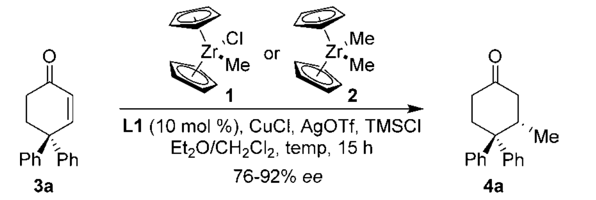
Recognizing the potential importance of a nucleophilic Me reagent that could operate at room temperature in a variety of solvents, we hoped that the reactivity profile of $Cp_2ZrMeCl$ **1**

Received: June 22, 2016
Published: July 26, 2016

DOI: 10.1021/acs.orglett.6b01829
Org. Lett. 2016, 18, 3814−3817

would be similar to the zirconocenes described above. We examined readily available zirconocenes **1** and **2** (Scheme 2) and began by applying conditions previously developed for hydrozirconated alkenes to cyclohexenones. Enone **3a** was used for testing because the product is nonvolatile.

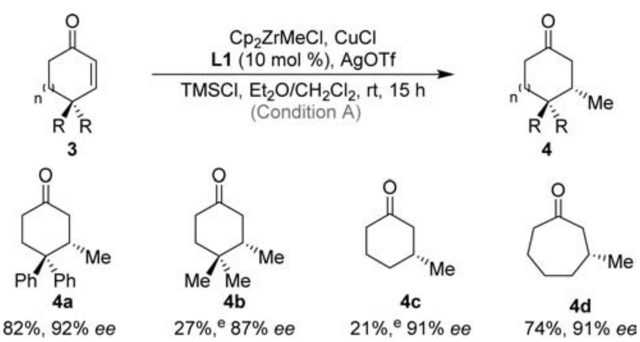
Scheme 2. Examining Readily Available Me-zirconocenes



Dimethyl zirconocene **2** gave encouraging preliminary results (ee's over 75%) for the room-temperature ACA shown in Scheme 2, but we found that **2** slowly degrades when stored at room temperature, even under an inert atmosphere. In contrast, chloro(methyl)zirconocene **1** is stable for at least 6 months on the bench without any noticeable changes. Control experiments showed that $Cp_2ZrMeCl$ is unreactive to enone **3a** in the absence of a catalyst, and no traces of 1,2- nor 1,4-addition products were observed after 4 days at room temperature in Et_2O/CH_2Cl_2. $Cp_2ZrMeCl$[31] is readily prepared on a 10 g scale from Cp_2ZrCl_2 (see the SI for the protocol), although this current procedure is straightforward it uses Me_3Al as the source of methyl.

Reported conditions[24] for the asymmetric addition of alkyl zirconocenes to **3a** were highly effective with $Cp_2ZrMeCl$, and screening temperatures and solvents only gave moderate improvement. Optimized conditions use 1.6 equiv of $Cp_2ZrMeCl$ with 10 mol % of copper(I)triflate and **L1** (10 mol %) in a mixture of Et_2O and CH_2Cl_2 at room temperature (**4a** obtained in 82%, 92% ee, Scheme 3). The role of silver salts

Scheme 3. ACAs To Form Tertiary Centers[a–d]

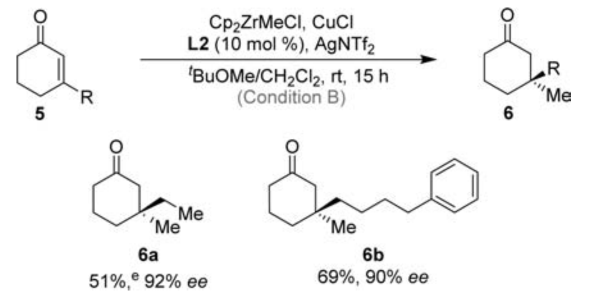


[a]Reactions performed on 0.4 mmol scale. [b]Isolated yields. [c]ee determined by chiral GC or chiral HPLC. [d]Conditions A: $Cp_2ZrMeCl$ (1.6 equiv), **L1** (10 mol %), CuCl (0.10 equiv), AgOTf (0.11 equiv), TMSCl (5.0 equiv), 5:1 Et_2O/CH_2Cl_2, rt, 15 h. [e]Volatile product.

in these reactions appears to be limited to counterion exchange with CuCl. These conditions (conditions A) were applied to other cyclic enones **3** (Scheme 3). 6-Membered ring substrates **3b** and **3c** (R = Me or H) gave ACA products **4b** and **4c** with high ee's (87% and 91%, respectively). Low isolated yields (27% and 21%, respectively) are due to product volatility, but complete conversion (TLC control) and clean crude NMR spectra were obtained. Cyclopentenone gave a complex mixture of products as expected,[6,32] and the 7-membered ring enone **3d** gave **4d** (74% yield, 91% ee).

On more challenging all-carbon quaternary centers, applying conditions B (Scheme 4) to 3-substituted enones **5** gave excellent results.[20,21] Cyclohexanones **6a** and **6b** were obtained in good yield (51% and 69%, respectively) with high ee (92% and 90%).

Scheme 4. ACAs To Form Quaternary Centers[a–d]



[a]Reactions performed on 0.4 mmol scale. [b]Isolated yields. [c]ee determined by chiral GC or chiral HPLC. [d]Conditions B: $Cp_2ZrMeCl$ (1.6 equiv), **L2** (10 mol %), CuCl (0.10 equiv), $AgNTf_2$ (0.05 equiv), 5:1 $^tBuOMe/CH_2Cl_2$, rt, 15 h. [e]Volatile product.

Other substrates were then assessed (Table 1). ACA of methylzirconocene **1** to 5-membered protected-acetal **7**[22] using related conditions (condition C) and ligand **L3** at 0 °C cleanly afforded methyl adduct **8** in 57% yield with excellent (94%) ee.

Linear enones such as **9** and **10**[19] can also be used, with far shorter reaction times (~45 min) than cyclic enones. TLC monitoring is essential to avoid byproducts, but quenching at the appropriate time gave very clean crude reaction mixtures and β-methyl ketones **10** and **12** with high ee's (92% and 94%). The yield of **12** was excellent (84%), while **10** suffers from volatility (29%).

We next tested the compatibility of the reagent with complex molecules using commercially available steroid **13**.[26] Compound **13** bears a number of stereogenic centers as well as an acetate and is capable of 1,2-, 1,4-, and 1,6-additions. In the event, using conditions E gave a separable mixture (5.1:1 crude dr) of two diastereomers where **14** could be isolated as a pure single isomer in 61% yield.

We also examined $Cp_2ZrMeCl$ in an asymmetric allylic alkylation reaction with racemic allyl chloride **15**.[29] This Cu-catalyzed dynamic kinetic asymmetric transformation gave excellent results with 72% yield (based on an NMR standard) and 94% ee (GC analysis of epoxidized crude material).

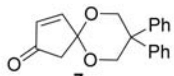
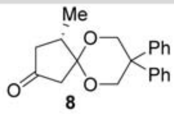
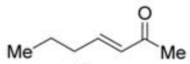
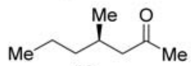
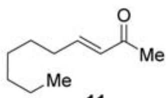
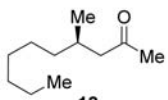
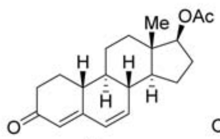
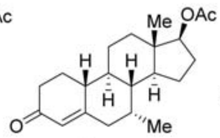
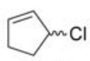
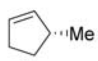
Finally, we synthesized (*E*)-enone **17** from commercially available cyclopentadecanone[33] and applied conditions D due to the low rigidity of the 15-membered macrocycle (Scheme 5).[34] These conditions, developed for linear substrates, gave a quick (45 min) and clean reaction to afford natural product (*R*)-(−)-muscone **18** (82% yield, 91% ee) which compares favorably with previous catalytic asymmetric approaches to this fragrance.[34−39]

In conclusion, we have shown that $Cp_2ZrMeCl$ can be used as a methylating agent in a wide variety of copper-catalyzed asymmetric reactions. Excellent levels of enantioselectivity (87−94% ee) were obtained in all cases. These procedures occur by a variety of mechanisms, tolerate acid-labile functional groups such as acetals and esters, and have been used in the short synthesis of a natural product. $Cp_2ZrMeCl$ was easily synthesized on a 10 g

DOI: 10.1021/acs.orglett.6b01829
Org. Lett. 2016, 18, 3814−3817

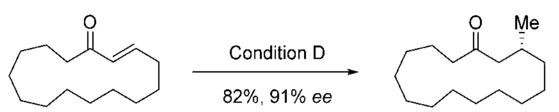
Table 1. Other Substrates[a]

substrate $\xrightarrow[\text{up to 94\% } ee]{\text{conditions}}$ product

entry	substrate	product	conditions[b]	yield, %[c] ee, %
1	 7	 8	C	57 94[d]
2	 9	 10	D	29[e] 92[f]
3	 11	 12	D	84 94[f]
4	 13	 14	E	61[g] 5.1:1 crude *dr*
5	 (±)-15	 16	F	72[h] 94[i]

[a]Reactions performed on 0.4 mmol scale. [b]Conditions C: $Cp_2ZrMeCl$ (2.5 equiv), **L2** (22 mol %), CuCl (0.20 equiv), AgOTf (0.20 equiv), TMSCl (5.0 equiv), 5:1 Et_2O/CH_2Cl_2, 0 °C, 15 h. Conditions D: $Cp_2ZrMeCl$ (1.6 equiv), **L3** (10 mol %), CuCl (0.10 equiv), AgOTf (0.11 equiv), TMSCl (5.0 equiv), 5:1 Et_2O/CH_2Cl_2, 0 °C, 45 min. Conditions E: $Cp_2ZrMeCl$ (1.6 equiv), *ent*-**L1** (10 mol %), CuCl (0.10 equiv), AgOTf (0.11 equiv), TMSCl (5.0 equiv), 1:1 Et_2O/CH_2Cl_2, rt, 15 h. Conditions F: $Cp_2ZrMeCl$ (1.6 equiv), **L1** (10 mol %), CuI (0.10 equiv), $CDCl_3$, rt, 15 h. [c]Isolated yield unless stated otherwise. [d]Determined by chiral HPLC. [e]Volatile product. [f]Determined by chiral GC. [g]Pure major isomer only. [h]NMR yield against internal standard. [i]Determined by chiral GC analysis of epoxidised crude mixture of **16**.

Scheme 5. Synthesis of Natural Muscone[a,b]



(*E*)-**17** (*R*)-(−)-muscone **18**

[a]Isolated yield. [b]ee determined by GC analysis of crude material reduced to the corresponding alcohols.

scale in our laboratory, and presumably this scale can be increased. The reagent is a readily manipulated crystalline powder that can be weighed out in air and is stable for at least 6 months when stored on the bench under inert gas.

Ongoing studies in our laboratory aim to expand the range of asymmetric reactions alkyl zirconocene species can be used in and will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01829.

All procedures, characterization data, NMR spectra, and GC and HPLC traces (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

E. Rideau (Oxford Chemistry) is acknowledged for stimulating discussions and valuable assistance. K.G. is supported by EPSRC Centre for Doctoral Training in Synthesis for Biology and Medicine (EP/L015838/1). S.P.F. is supported by the EPSRC (EP/M002144/1, EP/M025241/1, EP/N022246/1).

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(2) For example: (a) Afinitor (everolimus), Novartis; (b) Advair Diskus (fluticasone propionate), GSK; (c) Vyvanse (lisdexamfetamine), Shire Pharmaceuticals Group; (d) Symbicort (budesonide), AstraZeneca; (e) Xeloda (capecitabine), Roche.
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DOI: 10.1021/acs.orglett.6b01829
Org. Lett. 2016, 18, 3814−3817