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A Practical, General Three-Component Coupling Approach to Prostaglandin and Non-Prostaglandin-Related Skeleta

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Abstract: Starting with a terminal alkyne, a one-pot, six-step sequence has been developed which results in prostaglandin and related skeleta in high yields. The method involves a transmetalation between organozirconium and cuprate species, as well as another between a copper enolate and organozincate reagent. Only catalytic amounts of the cuprate are needed. A variety of cyclic and acyclic enones participate in these multiple couplings, demonstrating that the methodology applies to far more than just the prostaglandin nucleus.

Introduction

For decades, prostaglandins (PG's) have been the focus of extensive efforts in synthetic chemistry.[1] Monographs devoted entirely to their syntheses have been written,[2] and while their promise as panaceas for a variety of human ailments has not materialized, they are still very much in demand.[3] One of the more attractive routes to the natural PG carbon skeleton, as well as a multitude of synthetic analogs, relies on the superior Michael acceptor properties of the cyclopent-2-enone nucleus. Conjugate addition of a vinylic organometallic,[4] most commonly involving an organocopper reagent,[5] introduces the β-chain with concomitant enolate generation. In principle, trapping of such an intermediate with an electrophile (E^+) should allow for regiospecific attachment of the required α-chain, thereby completing the 20 carbon backbone (Figure 1). Early work on this particular one-pot, three-component strategy, while demonstrating feasibility,[6] met with limited success until Noyori described an efficient procedure in 1988 using a phosphine-stabilized vinylic organocopper species as Michael donor (Scheme 1).[7] Unfortunately, as has now come to be more fully appreciated, copper/lithium enolates are notoriously unreactive relative to those bearing most other gegenions,[8] and it was therefore essential for such an intermediate to be initially converted to its triphenyltin derivative prior to attachment of the α-side chain. Although elegant, certain features such as the presence of a phosphine, stoichiometric copper and tin, and the presence of HMPA to assist with the alkylation encouraged this school to subsequently develop[9] a related process based on mixed triorganozincates.[10] Selective transfer of a vinyl ligand from a species such as **2** results in a far more reactive zinc enolate, which is now highly amenable to coupling with an α-chain precursor (Scheme 1).

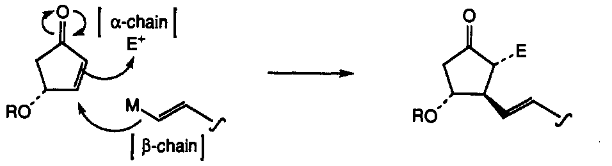
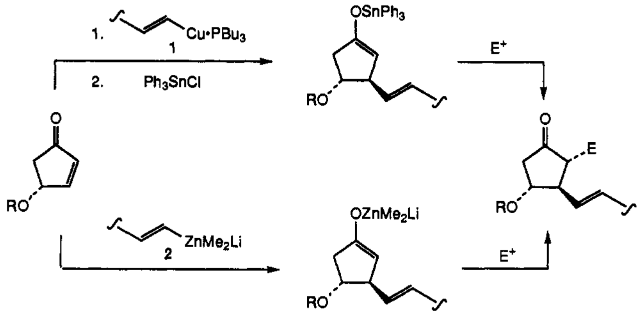


Figure 1. 3-Component coupling strategy.

Scheme 1. Noyori's Approaches Based on $RCu{\cdot}PBu_3$ and Me_3ZnLi Reagents



Ostensibly, each of the above two organometallic pathways provides a solution to the rapid construction of PG's, natural or otherwise. At issue here, however, is the preparation of the individual organocopper or zincate reagents which ultimately participate in these three-component couplings (3-CC's). In other words, from where do the vinylic copper and vinylic zincates derive? The answer, in both cases, comes in the form

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⊛ Abstract published in *Advance ACS Abstracts,* September 1, 1994.

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(6) Patterson, J. W.; Fried, J. H. *J. Org. Chem.* **1974**, *39*, 2506.

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(8) Chapdelaine, M. J.; Hulce, M. *Org. React.* (N.Y.) **1990**, *38*, 227.

(9) Suzuki, M.; Koyano, H.; Noyori, R. *Synlett.* **1989**, 22; Morita, Y.; Suzuki, M.; Noyori, R. *J. Org. Chem.* **1989**, *54*, 1785. See also, Takahashi, T.; Nakazawa, M.; Kanoh, M.; Yamamoto, K. *Tetrahedron Lett.* **1990**, *31*, 7349.

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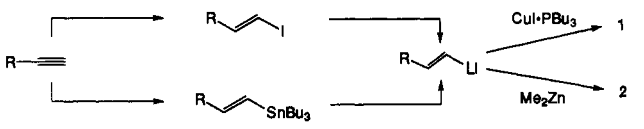
Scheme 2. Routes to Vinyllithium Precursors **1** and **2**.



of a precursor vinyllithium,[11] which is either treated with the Whitesides complex[12] CuI·PBu$_3$ to form **1**, or Me$_2$Zn to arrive at **2** (Scheme 2). The vinylic lithium, in turn, is prepared from either a vinylic iodide or stannane *via* low-temperature (−95 °C) metal−halogen exchange with 2 *t*-BuLi, or lithium−tin exchange with MeLi, respectively. Each of these precursors comes from yet another educt, a terminal alkyne, which must be converted to the iodide or stannane by standard protocols. Since the latter method which proceeds by way of an organotin is preferred,[11] it is important to note that hydrostannylation of 1-alkynes is neither stereo- nor regiospecific for *E*-vinylstannane formation,[13] with both the *Z*- and 1,1-isomers expected in nontrivial amounts which are difficult to separate.[14] Thus, prior to the actual 3-CC, a number of additional steps are involved, each relying on intermediates that require isolation and purification. Given that a 1-alkyne is the common ground shared by both of these potent reagents (*i.e.*, **1** and **2**), ideally it should be possible to completely bypass the intermediacy of a vinyllithium and any of its precursors and proceed directly to an *E*-vinylic organometallic (such as **2**) capable of effecting 1,4-addition followed by enolate trapping. We now report on just such a process carried out in a single flask which combines three fundamental elements of a PG illustrated in Figure 2: (1) a cyclopentenone; (2) an *E*-vinylic organometallic prepared *in situ* from a 1-alkyne; (3) an α-chain precursor, in a true 3-CC sense.

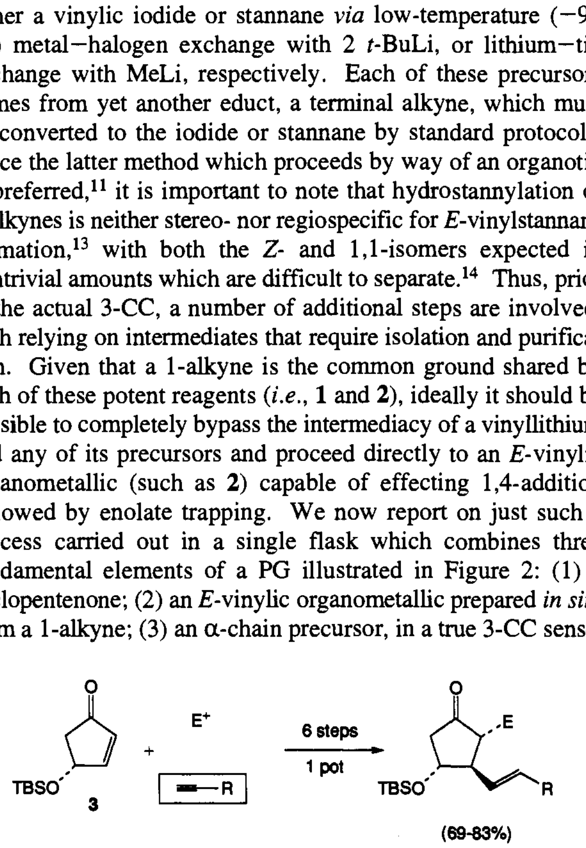


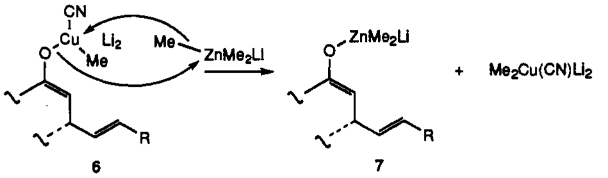
Figure 2. 3-CC using three basic components.

Results and Discussion

The original concept, as alluded to above, was to parlay a 1-alkyne directly to an *E*-vinylic organometallic such as mixed zincate **2** *via* transmetalation of an intermediate vinyl zirconocene (Scheme 3). Hence, hydrozirconation of an alkyne with Schwartz' reagent [Cp$_2$Zr(H)Cl][15] readily affords **4**, which upon exposure to Me$_3$ZnLi (from 3MeLi + ZnCl$_2$·TMEDA)[16] in THF at −78 °C does effect transmetalation to the desired mixed zincate.[17] Unfortunately, the extent of transmetalation appears to be variable, being highly dependent upon the nature of R in the 1-alkyne. Moreover, although mixed zincates react nicely with cyclopentenones,[9] this enone is especially reactive toward soft nucleophiles. In most other cases of mixed zincate conjugate additions, yields tend to drop considerably. With enones that offer any hint of steric hindrance at the *β*-position, zincates are not acceptable ligand donors.[10]

As an alternative to zincate-induced transmetalation, we had previously shown that a trivial higher order (HO) cyanocuprate, Me$_2$Cu(CN)Li$_2$, quantitatively effects ligand exchange with vinyl zirconocenes **4** at −78 °C in minutes.[18] When combined with the knowledge that mixed vinyl cuprates **5** selectively transfer vinyl rather than alkyl groups to enones at −78 °C[19] the possibility of using a *catalytic* amount of Me$_2$Cu(CN)Li$_2$ was raised, assuming a method could be developed for regeneration of this cuprate following its consumption in the transmetalation/1,4-addition steps (Scheme 4).

Although, formally, the elements of MeLi are needed to complete the catalytic cycle, clearly there exists a compatibility problem for this source of methyl anion ("Me$^-$ M$^+$") with the enone. The breakthrough came when it was recognized that the corresponding zincate, Me$_3$ZnLi, is not particularly competitive with a HO cuprate in its 1,4-addition chemistry and yet is effective at donating a methyl group to copper present in enolate **6** at −78 °C (eq 1).[20] It may well be that the "MeCu(CN)Li" portion of a modified *lithium* enolate[21] is quite willing to accept a methyl ligand from zinc in return for a strong Zn−O bond, given the general ease with which ligand exchange occurs among copper *ate* complexes.[22] In essence, therefore, it is the Me$_3$ZnLi which supplies a methyl carbanion in mild form, acting as a "shuttle" between hard MeLi and soft Me$_2$Cu(CN)Li$_2$. Realization of this multimetal, sequential transmetalation−1,4-addition−transmetalation scenario not only provides a novel method for *E*-vinyl ligand 1,4-delivery using catalytic quantities of a cuprate,[23] but may well result in a 1,4-adduct (*e.g.*, **7**) similar in composition to that involved in the Noyori zincate route[9] and of equal reactivity toward a second coupling which would introduce the α-chain (*cf.* Scheme 1).



(1)

The generality of this new catalytic cuprate protocol for conversion of a 1-alkyne to the product of *E*-vinyl ligand delivery to an α-*β*-unsaturated ketone is demonstrated by the examples shown in Table 1. A variety of alkynes appear to

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(20) It should be mentioned that eq 1 is simply a working hypothesis with respect to the nature of the gegenion present following the Michael addition step (*i.e.*, a balanced equation).

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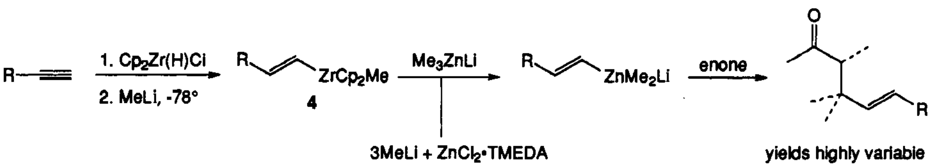
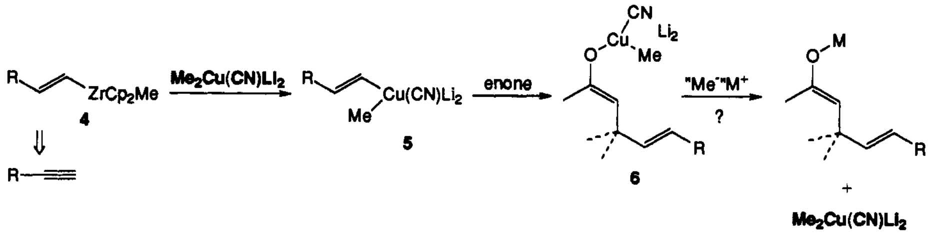
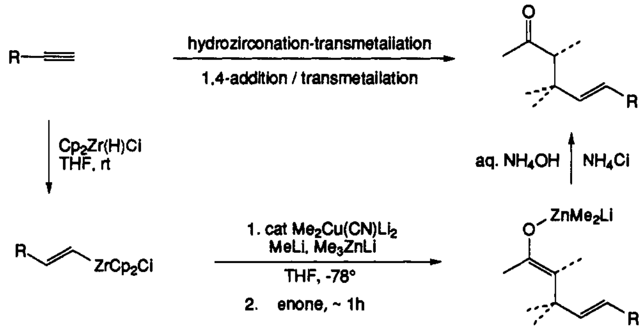
Scheme 3. Transmetalation of Vinyl Zirconocenes with Lithio Zincates



Scheme 4. Regeneration of the Catalytic Cyanocuprate Me$_2$Cu(CN)Li$_2$



Scheme 5. Overall Sequence for Catalytic Cuprate-Induced Vinyl Ligand 1,4-Addition



readily participate, including those which are heavily oxygenated. Tolerance to sulfide functionality is noteworthy, as are additions to β,β-disubstituted enones. The sequence calls for the room temperature hydrozirconation of a 1-alkyne in THF, followed by cooling the resulting solution to −78 °C. An equivalent of MeLi is then added to replace the chloride ligand on zirconium. Although the essential 1,4-addition proceeds without this modification at Zr,[24] yields tend to be 20−30% lower. Addition of the HO cuprate and then the zincate is followed by the slow-dropwise addition of an enone over the course of *ca.* 1 h. Usual aqueous "cuprate quench"[25] affords the 1,4-product ketone (Scheme 5).

Three-Component Couplings. The intermediate zinc enolate **7** resulting from the 1,4-addition−transmetalation[26] is now in a position to react further in two types of C—C bond-forming processes normally used for installation of a PG α-chain.[11] That is, both aldol and alkylation reactions should be realizable. Of course, with 1 equiv of Cp$_2$ZrMe$_2$ in the pot, an outgrowth of the vinyl zirconocene−cuprate transmetalation, it is entirely possible that several enolate species (*i.e.*, of zinc, zirconium, or less likely copper) could be present, although those bearing zirconium as gegenion are known to be equally reactive.[27] Introduction of an aldehyde to the initial 1,4-adduct does indeed afford a product of 3-CC in remarkably high yield. These 1,2-additions, as expected, are rapid at −78 °C and produce a mix of diastereomers at the newly generated stereogenic center. Diastereoselectivity tends to be low,[28] although in terms of target PG structures, this is of no consequence. Table 2 illustrates several examples of these 3-CC's, the yields of which are uniformly good, especially considering that six discrete steps are involved which include (originally) four dissimilar organometallics (*i.e.*, a vinyl zirconocene, MeLi, Me$_2$Cu(CN)Li$_2$, and Me$_3$ZnLi).

Highlighted in Table 3 are related cases which address the more challenging aspect of 3-CC reactions: enolate alkylations. In the Noyori systems,[11] propargylic iodides are recommended together with HMPA or HMPT as cosolvent. Highly controlled conditions are required [*e.g.*, warming the reaction mixture from −78 to −30 °C for long periods of time (between 19−39 h)]. In light of more recent developments in PG alkylations described by Gooding,[29] where the corresponding *in situ* derived triflates have been found to be of greater reactivity, we have utilized these intermediates with good success. Thus, upon addition of excess alkylating agent at −78 °C and in the *absence* of HMPA, a <5 min reaction time is all that is needed for generation of the 3-CC product! Attempts to apply this strategy to *unactivated* primary triflates, which would allow for direct formation, *e.g.*, of PGE$_1$, were not successful. Apparently, the temperatures required to effect alkylation with these electrophiles are too high, which allow for enolate equilibration leading to competing silyl oxide elimination as well as 1,2-additions.

By contrast with the above results, use of stoichiometric HO cuprate to effect vinyl zirconocene transmetalation/1,4-addition followed by quenching with an aldehyde afforded only a modest yield of this 3-CC. Clearly in this case, the lower reactivity of the intermediate copper/lithium enolate, now in the absence of zincate, is not as effective as a zinc enolate even toward a simple

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(26) For a spectroscopic study establishing the presence of a zinc enolate as the major species in solution from these 1,4-additions, see Lipshutz, B. H.; Wood, M. R. *Tetrahedron Lett.* **1994**, *35*, 6433.

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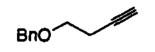
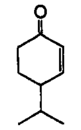
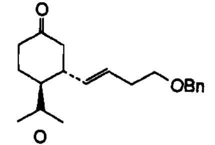
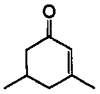
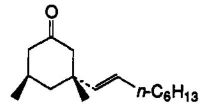
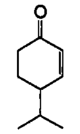
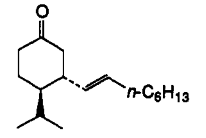
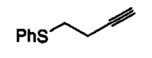
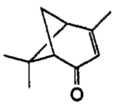
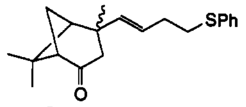
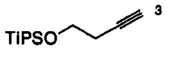
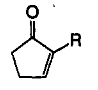
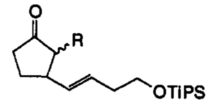
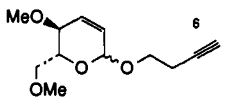
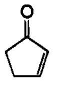
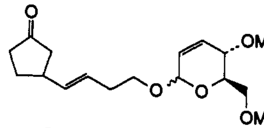
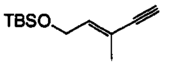
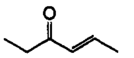
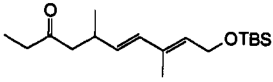
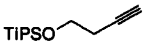
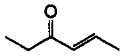
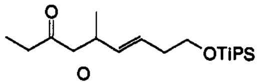
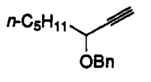
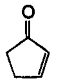
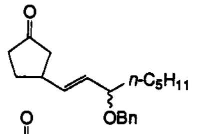
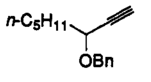
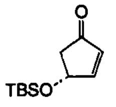
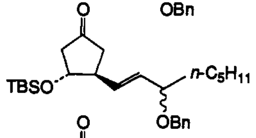
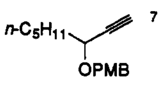
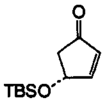
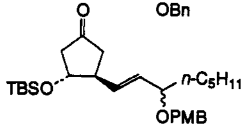
Table 1. Conjugate Addition Reactions of Catalytically Generated *E*-Vinylic Cyanocuprates

entry	1-alkyne	educt	mol % cuprate[1]	product	yield (%)[2]
1			20		81
2	n-C_6H_{13}—≡		20		84
3 4 5	n-C_6H_{13}—≡		5 10 20		81 90 89
6			10		71
7 8	 [3]		20 20		81[4] 88[5]
9	 [6]		10		87[6]
10			20		86
11			20		85
12			10		93
13 14 15			10 20 30		71 87 92
16	 [7]		20		85

[1] Cuprate = reagent **5** following hydrozirconation–transmetalation of the 1-alkyne. [2] Isolated. [3] TIPS = $(i\text{-Pr})_3Si$. [4] R = Me; 9:1 mix of isomers. [5] R = H. [6] 8:1 Mix of anomers. [7] PMB = *p*-methoxybenzyl.

aldehyde (Scheme 6). The corresponding comparison in terms of alkylation chemistry led to an even bigger yield differential.[30]

One final example (Scheme 7) makes the point that these catalytic cuprate-initiated 3-CC's are also amenable to *non*-PG-related frameworks. Indeed, this is, perhaps, one of the most cogent arguments in favor of this new methodology, given the limitations associated with the use of mixed zincates alone.[10] No work as yet; however, has been carried out in an effort to control the diastereoselectivity in either the conjugate or aldol addition steps.

Preparation of Me_3ZnLi. The preferred reagent, Me_3ZnLi, is normally prepared from $ZnCl_2$ and 3 equiv of MeLi. Since $ZnCl_2$ is very hygroscopic, its TMEDA complex was initially used in this work, since it is a beautifully crystalline, stable, white solid.[16] This preparation of Me_3ZnLi, however, brings between 10–20% Et_2O and LiCl into the sequence (*i.e.*, MeLi comes in Et_2O), which could discourage large scale use. Fortunately, switching to FMC Lithco's reagent, MeLi in THF/cumene, is a safe and equally effective alternative in these 3-CC's. Still simpler, however, is use of commercial Me_2Zn in heptane, to which only 1 equiv of MeLi need be added. Yields for the latter protocol also tended to be slightly higher (*cf.* Table 4, entries 1–3).

Other Sources of "Me^- Me^+". Although the zincate Me_3ZnLi appears to function especially well in this chemistry, it was of interest to determine whether other metals bearing methyl ligands ("Me^- Me^+") would act similarly and whether a yet

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(30) For example, treatment of vinyl zirconocene **i** under both catalytic and stoichiometric cuprate conditions in the presence of cyclopentenone followed by alkylation with propargylic triflate **ii** gave the product ratios of **iii** to **iv** shown below.

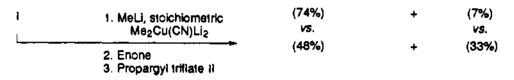
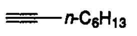
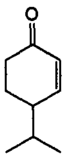
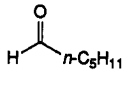
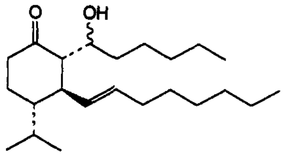
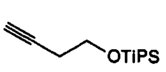
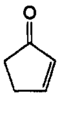
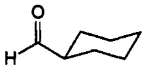
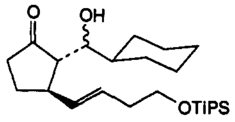
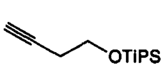
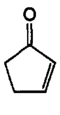
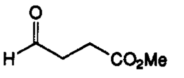
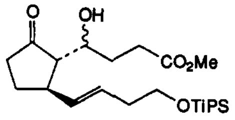
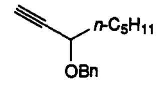
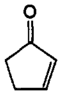
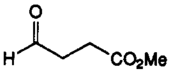
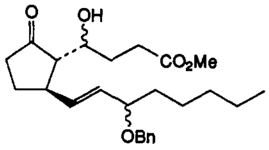
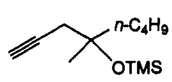
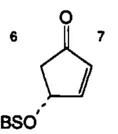
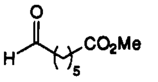
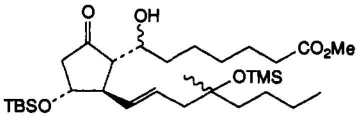
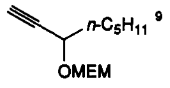
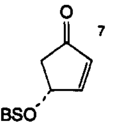
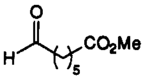
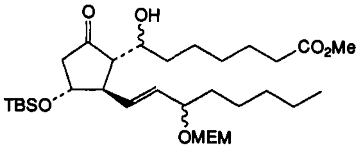


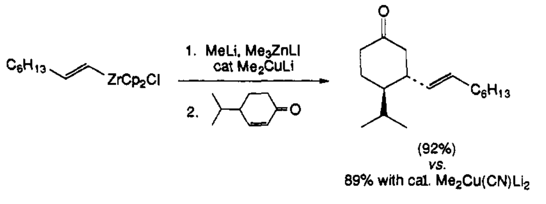
Table 2. Examples of 3-CC Related to PG's Using Aldehydes as the α-Chain Precursor

entry	1-alkyne	enone	electrophile	product	yield (%)[1]
1					82[2]
2					80[3]
3					74[4]
4					75[5]
5		[6]  [7]			79[8]
6	 [9]	 [7]			83[10]

[1] Isolated. [2] A mixture of two isomers as determined by ^{1}H NMR. [3] One isomer by ^{1}H NMR. [4] Two isomers by ^{1}H NMR. [5] Five isomers by ^{1}H NMR. [6] Provided by G. D. Searle; racemic material. [7] Provided by Teijin industries; nonracemic educt. [8] Four isomers by ^{1}H NMR. [9] MEM = (methoxyethoxy)methyl ($MeOCH_2CH_2OCH_2-$). [10] Two isomers by ^{1}H NMR.

more attractive species could be identified. Table 4 lists those that were examined, solely from the standpoint of their effect on the 1,4-addition portion of the 3-CC sequence, according to Scheme 8. Clearly, of those studied, only the nickelate (Me_3NiLi)[31] and manganate (Me_3MnLi)[31,32] approach the efficiency of Me_3ZnLi. The former is not a likely replacement in terms of large scale use, although the latter (which derives from very inexpensive $MnCl_2$)[32] could be a candidate with yield optimization.

Other Cuprate Catalysts. To date, most transmetalations between organometallics and cuprates have fallen under the domain of cyanocuprate ($R_2Cu(CN)Li_2$) technology.[22,34] The list of organometallics includes stannanes,[35] alanes,[36] tellurides,[37] and zirconocenes.[18,24] In these ligand exchanges, Gilman reagents (Me_2CuLi) are seemingly not nearly as effective, at least with respect to yields obtained. Thus, it was with considerable surprise that the outcome from a comparison reaction afforded *identical* results upon substituting Me_2CuLi for $Me_2Cu(CN)Li_2$ (eq 2). Such a finding imparts an additional element of flexibility, for although CuCN as a source of Cu(I) is far less expensive than all traditional Gilman precursor salts (*e.g.*, CuI, $CuBr{\cdot}SMe_2$, CuOTf) and requires no special handling or purification, it might in certain circumstances be less desirable due to the cyanide ligand (and hence the potential for generation of HCN under acidic conditions).



(2)

Stoichiometries. Relative to a starting enone, the stoichiometric requirements for vinyl zirconocene, zincate and cuprate have all been investigated. Most of the examples in Table 1 were conducted using 20 mol % $Me_2Cu(CN)Li_2$. While lesser amounts (*i.e.*, 5–10 mol %) are acceptable in many cases insofar as the 1,4-addition step is concerned, the yields of 3-CC were reproducibly better using 10 mol % of the cuprate. With the (silyloxy)cyclopentenone **3**, 20 mol % HO cuprate was essential in order to obtain the yields sited in Tables 1–3. Lesser

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(31) Corey, E. J.; Posner, G. H. *Tetrahedron Lett.* **1970**, 315.

(32) Kauffmann, T.; Bisling, M. *Tetrahedron Lett.* **1984**, *25*, 293.

(33) Cahiez, G.; Marquais, S. *Synlett* **1993**, *45*. Cahiez, G.; Laboue, B. *Tetrahedron Lett.* **1992**, *33*, 4439. Cahiez, G.; Alami, M. *Ibid.* **1990**, *31*, 7423.

(34) Lipshutz, B. H. *Synlett* **1990**, 119. *Synthesis* **1987**, 3250. Wipf, P. *Synthesis* **1993**, 537.

(35) Behling, J. R.; Babiak, K. A.; Ng, J. S.; Campbell, A. L.; Moretti, R.; Koerner, M.; Lipshutz, B. H. *J. Am. Chem. Soc.* **1988**, *110*, 2641.

(36) Wipf, P.; Smitrovich, J. H.; Moon, C.-W. *J. Org. Chem.* **1992**, *57*, 3178. Ireland, R. E.; Wipf, P. *Ibid.* **1990**, *55*, 1425. Lipshutz, B. H.; Dimock, S. H. *J. Org. Chem.* **1991**, *56*, 5761.

(37) Marino, J. P.; Tucci, F.; Comasseto, J. V. *Synlett* **1993**, 761.

Table 3. Three-Component Couplings Involving Enolate Alkylations with Propargylic Triflates

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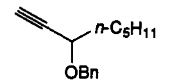
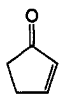
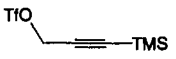
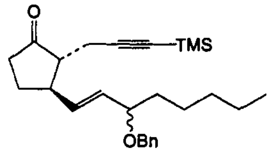
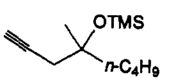
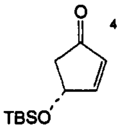
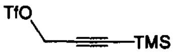
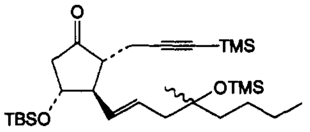
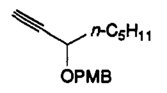
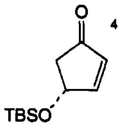
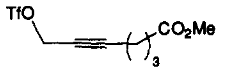
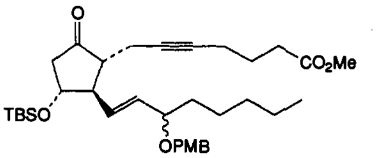
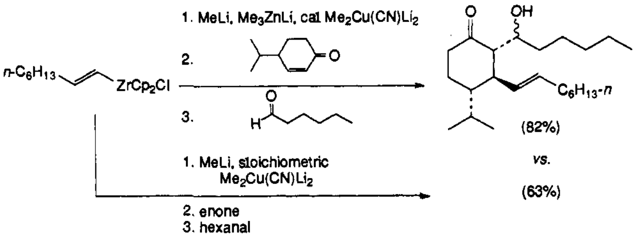
1					74^3
2					69^5
3					71^6

[1] Prepared *in situ*; see Experimental Section. [2] Isolated. [3] A mixture of two isomers as determined by ^{1}H NMR. [4] Nonracemic educt. [5] Two isomers by ^{1}H NMR. [6] Two isomers by ^{1}H NMR.

Scheme 6



quantities of Me$_2$Cu(CN)Li$_2$ tended to increase the amount of polar products, believed to arise from competitive 1,2-addition of the intermediate zinc enolate to the incoming enone. With respect to vinyl zirconocene, it is important that ≥1.7 equiv be used, as yields tend to drop off substantially if this level is not present at the outset. As for Me$_3$ZnLi, only 1.05 equiv are necessary.

3-CC Reaction Workup. Products from these 3-CC's, in particular those from the α-chain-inserting aldol reactions, are quite sensitive to the pH of the aqueous phase present during workup. Yields using the standard "cuprate quench" (pH 10) were typically diminished by *ca.* 20%. Switching to a 5% aqueous HCl quench raised the outcome by 10−15%, although best results were obtained with a pH 7 buffer quench at −78 °C followed by immediate processing and isolation.

Anomalies. In testing a variety of PG β-side chains, propargyl alcohol **11** (the precursor to the naturally occurring C-13 to C-20 unit) was screened in terms of protecting group compatibility. Unexplicably, no silyl ether was found which allowed for a clean transmetalation of the corresponding *in situ*-derived vinylic organometallic **12** (Figure 3). Competitive transfer of the methyl ligand from copper to the enone was observed (to the extent of *ca.* 30−40%), the implication being that complete transmetalation from zirconium to copper had not taken place. This was true with silyl ethers ranging from TMS and TBS, to TBDPS. Even the TIPS derivative, which had served flawlessly in our transmetalations of functionalized vinyl zirconocenes,[24] failed to negate the allylic ether's inhibitory effects. A related phenomenon was also seen with THP and dimethyl MOM derivatives. Thus, notwithstanding the structural similarities between the THP, dimethyl MOM, and MEM moieties (Figure 4), only the latter among this triad, in our hands, is well-disposed toward these transmetalations. On the other hand, both benzyl and *p*-methoxybenzyl moieties are excellent choices for this specific β-chain.

Spinoffs. The facility with which zincate Me$_3$ZnLi interacts with a copper enolate (*e.g.*, *cf.* **6**) to regenerate a HO cuprate offers an opportunity to devise a method for utilizing organozinc reagents, *e.g.*, RZnX, as precursors to HO *dilithio* cuprates. That is, while Rieke,[38] Knochel,[39] and Nakamura/Kuwajima[40] have provided a wealth of valuable cuprate chemistry based on reagents derived from RZnX in the presence of a Cu(I) source (*e.g.*, RCu(CN)ZnX), the reduced reactivity of these zinc cuprates (due to the gegenion [ZnX]$^+$) relative to Grignard and especially lithio cuprates has oftentimes necessitated coadministration of additives (such as BF$_3$•OEt$_2$[41] and Me$_3$SiCl[42]). Using the zincate−copper enolate transmetalation concept, it was envisioned that organozinc R$_T$ZnX (from R$_T$X + Zn^0) could be converted into a mixed zincate R$_T$Th$_2$ZnLi (from R$_T$ZnX + 2 ThLi; Th = 2-thienyl) and then *via* ligand transfer of R$_T$ to ThCu(CN)Li[43] into R$_T$(Th)Cu(CN)Li$_2$.[44] The resulting HO cuprate would then deliver the desired group (R$_T$) to a subsequently introduced enone (see "proposal", Scheme 9). Thus, in effect, a dilithio cuprate would be formed from a zinc precursor. Moreover, once the cuprate delivered the R$_T$ ligand to the enone, it would be regenerated by the zincate R$_T$(Th)$_2$ZnLi present, again translating into a catalytic-in-copper scenario.

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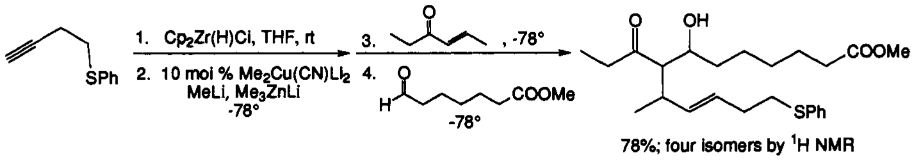
Scheme 7. 3-CC on an Acyclic Enone



78%; four isomers by ^{1}H NMR

Scheme 8. Sequence Used to Test for Alternative Sources of "Soft" MeLi

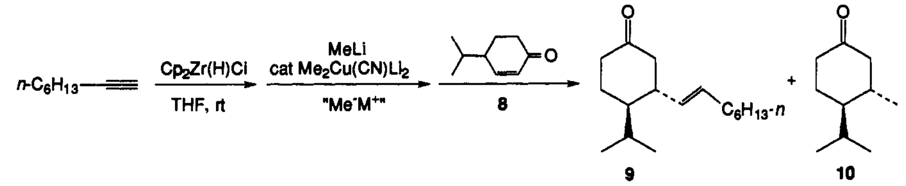


Table 4. Comparison between Me_3ZnLi and Other Sources of "Soft" MeLi

entry	"Me^- M^+"	yield (%) of **9** or GC ratio of **8**:**9**:**10**[a]	comments
1	Me_3ZnLi	81	$ZnCl_2$·TMEDA + 3MeLi
2	Me_3ZnLi	89	Me_2Zn + MeLi (in Et_2O)
3	Me_3ZnLi	91	Me_2Zn + MeLi (in THF/cumene)
4	Me_3NiLi	77	$NiCl_2$ + 3MeLi
5	Me_3MnLi	76	$MnCl_2$ + 3MeLi
6	MeMnCl	6:35:1	$MnCl_2$ + MeLi
7	MeMgBr	1:20:10	commercial reagent
8	MeLi	2:5:1	low halide MeLi
9	$Me_2Ti(O\text{-}Pr\text{-}i)_3Li$	1:0:0	2MeLi + $Ti(O\text{-}Pr\text{-}i)_3Cl$
10	$MeTi(O\text{-}Pr\text{-}i)_4Li$	24:10:0	MeLi + $Ti(O\text{-}Pr\text{-}i)_4$
11	Me_3CoLi	6:2:10	3MeLi + $CoCl_2$
12	Me_5SnLi	25:25:10	MeLi + Me_4Sn
13	$Me_3ZnMgBr$	2:11:1	MeMgBr + Me_2Zn
14	$Me_3NiMgBr$	13:26:1	3MeMgBr + $NiCl_2$

[a] Cf. Scheme 8.

To test the concept, *n*-BuZnCl was prepared[45] and treated with 2 equiv of thienyllithium[43] at −78 °C and then 5 mol % ThCu(CN)Li together with BF_3·OEt_2 (1 equiv). Addition of 3,5-dimethylcyclohexenone led, after 3 h at −78 °C, to the 1,4-adduct in 72% yield. Increasing the amount of cuprate to 20 mol % under otherwise identical conditions raised the yield to 86% (Scheme 10). Control experiments based on R_TTh_2ZnLi, with and without BF_3·OEt_2 (*i.e.*, no cuprate present), resulted in no consumption of educt, thereby revealing the cuprate as the reactive species responsible for the conjugate addition. The scope of these and related processes are currently under active investigation in our laboratories.[46]

Conclusions

Three-component, one-pot couplings which involve conjugate addition of an *in situ*-derived, *E*-vinylic organometallic to an α,β-unsaturated ketone followed by enolate trapping with an aldehyde or propargylic triflate are described. This new method, which is extremely efficient, is applicable to a variety of structurally diverse enones, as well as to cyclopentenones *en route* to prostanoids. Advantage is taken of the regio- and stereoselectivity of 1-alkyne hydrozirconations, facile transmetalation between a HO cyanocuprate and vinylic zirconocene, and the novel use of a trivial zincate to effect ligand exchange with a copper enolate, thereby rendering the process catalytic in cuprate.

Experimental Section

General Methods. Flash chromatography was performed on ICN BioMedical's, ICN Silica, 32-63, 60 Å. THF and ether were distilled from sodium/benzophenone ketyl prior to use. CH_2Cl_2 was distilled from CaH_2. Hexanes were distilled from and stored over sodium. Thin layer chromatography was carried out on precoated silica gel 60 F_{254} plates (EMx Science), 0.25 mm layer thickness. ^{1}H NMR spectra were run on a General Electric GN-500 (at 500 MHz, with *J* values in hertz), in $CDCl_3$ unless noted otherwise. ^{13}C spectra were run on a Varian Gemini-200 Spectrometer (at 50 MHz), also in $CDCl_3$. IR spectra were run on one of the following: 2020 Galaxy FTIR spectrometer, or a Perkin-Elmer Model 283, or a Perkin Elmer 1330 infrared spectrophotometer. Mass spectra were run on either a VG-Autospec at the UCLA campus or an analytical VG 70-250 HF instrument. Gas chromatographic analyses were performed on a Hewlett-Packard 5890A gas chromatograph equiped with a 60 m fused silica J & W DB-5 capillary column. Flame ionization detection was employed with H_2 as the carrier gas. All reactions were carried out under an inert atmosphere of argon using oven-dried glassware (at least 8 h, at 120 °C) and standard syringe/septa techniques. Dimethylzinc was purchased for Texas Alkyls as a 1.25 M solution in heptane. Methyllithium (low halide) was abtained from Aldrich as a 1.4 M solution in ether.

***trans*-4-Isopropyl-3-((*E*)-1-octenyl)cyclohexanone (Table 1, entry 5).** A representative procedure used for the preparation of all products in Table 1 is as follows. To a 10 mL round bottom flask equipped with a stir bar and septum and having been cooled under a stream of argon was added $Cp_2Zr(H)Cl$ (301 mg, 1 mmol), followed by 3.5 mL of THF and octyne (155 μL, 1 mmol). The two-phase reaction mixture was shielded from light by wrapping in aluminum foil and allowed to stir for 30 min, after which the reaction was judged to be complete as evidenced by a homogeneous solution. This mixture was then cooled to −78 °C, and at this temperature was added MeLi in ether (0.65 mL, 1 mmol), dropwise over 1 min. At the same time, to another 10 mL round bottom flask, equipped with a stir bar and septum having been cooled under argon, was added CuCN (9.2 mg, 0.1 mmol), followed by 0.5 mL of THF. The mixture was cooled to −78 °C, and Me_2Zn in heptane (0.44 mL, 0.53 mmol) was added dropwise to the stirred slurry, followed quickly by dropwise addition of MeLi in ether (0.46 mL, 0.74 mmol). After 5 min this three-phase slurry was placed in an ice bath for 10 min during which time both remaining liquid phases became clear and homogeneous. This solution was then cooled back to −78 °C and the solution containing the methyl vinyl zirconocene, still at −78 °C, was transferred *via* canula into the flask containing the zincate/catalytic cuprate mixture. After 5 min of stirring, 4-isopropylcyclohexenone (77 μL, 0.5 mmoL) was added portionwise *via* microliter syringe over 75 min. After 1 h of additional reaction time the reaction was quenched at −78 °C with 1 mL a of 9:1 saturated aqueous NH_4Cl/concentrated NH_4OH solution. The reaction mixture was then transferred to a separatory funnel containing an additional 14 mL of the 9:1 quench and 25 mL of ether, with the help of an additional 25 mL of ether. The combined organic layers were washed three times with 20 mL of brine and then dried over $MgSO_4$. After concentration *in vacuo*, flash chromatography on silica gel using 40:1 (petroleum ether/ethyl acetate) afforded 111.1 mg (89%) of the produce as a clear

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(45) For simplicity, *n*-BuZnCl was prepared from *n*-BuLi + $ZnCl$·TMEDA rather than *via* *n*-BuI + Zn^0, the latter route being required for all cases where the organolithium precursors are not readily available.

(46) Lipshutz, B. H.; Wood, M. R.; Tirado, R.; Chang, V., unpublished.

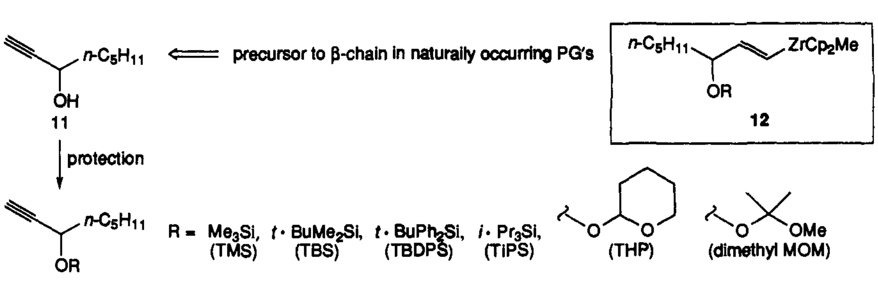


Figure 3. Protecting groups in propargylic alcohol **9** which partially inhibit transmetalation.

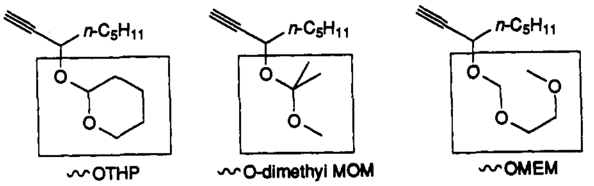


Figure 4. Structural relationships between selected protecting groups in **11**.

oil: TLC [petroleum ether/ethyl acetate, 10/1]R_f 0.41; ^{1}H NMR δ 5.39 (dt, J = 15, 7, 1H, vinylic), 5.18 (ddt, J = 15, 8, 1, 1H, vinylic), 2.4−2.2 (m, 4H, adjacent to ketone), 1.97 (dt, J = 7, 7 2H, allylic CH$_2$), 1.94−1.2 (m, 13H, aliphatic), 0.94 (d, J = 7, 3H, isopropyl CH$_3$), 0.86 (t, J = 7, 3H, CH$_3$), 0.72 (d, J = 7, 3H, isopropyl-CH$_3$); ^{13}C NMR δ 211.41, 132.34, 131.20, 48.01, 46.31, 45.25, 40.92, 32.29, 31.57, 29.21, 28.59, 27.51, 24.22, 22.56, 21.47, 15.25, 13.99; IR (neat) cm^{-1} 2920−2970 (b, s), 2910 (s), 2895 (s), 2878 (s), 2860 (s), 1718 (s), 1465 (m), 1458 (m), 1462 (w), 1420 (w), 1388 (w), 1369 (m), 1339 (w), 1324 (w), 1295 (w), 1245 (w), 1200 (m), 1180 (w), 1057 (w), 1030 (w), 992 (w), 968 (s), 945 (w); EIMS, m/e (rel. intensity) 250 (M$^+$, 58.2), 207 (22.2), 189 (24.7), 165 (40.5), 139 (25.3), 138 (27.2), 137 (27.2), 123 (22.8), 111 (67.7), 110 (47.5), 109 (38.1), 97 (27.2), 96 (33.5), 95 (65.2), 93 (22.8), 83 (67.7), 81 (48.1), 69 (100), 67 (50.6), 55 (88.0), 43 (62.0); HREIMS calcd (M$^+$) 250.2297, found 250.2287.

***trans*-3-[(*E*)-4-(Benzyloxy)butenyl]-4-isopropylcyclohexanone (Table 1, entry 1)** was prepared as in the case above, using Cp$_2$Zr(H)Cl (286 mg, 1 mmol), 3.5 mL of THF, 3-butyn-1-ol benzyl ether (172 μL, 1 mmol), and MeLi in ether (0.64 mL, 1 mmol) in the first round bottom flask. CuCN (9.6 mg, 0.11 mmol) and ZnCl$_2$·TMEDA (130.3 mg, 0.52 mmol) were placed in the second round bottom flask, followed by 1 mL of THF, it was cooled to −78 °C, and MeLi in ether was added (1.14 mL, 1.77 mmol). After the standard warming and cooling cycle the procedure continued as stated in the representative example above. 4-Isopropylcyclohexenone (77 μL, 0.5 mmol) was added over 75 min, followed by a 1 h reaction time. Workup and flash chromatography using 20:1 (petroleum ether:ethyl acetate) afforded 121.3 mg (81%) as a clear oil; TLC [petroleum ether/ethyl acetate, 10/1] R_f 0.22; ^{1}H NMR δ 7.4−7.2 (m, 5H, aromatic), 5.44 (dt, J = 16, 7, 1H, vinylic), 5.40 (dd, J = 16, 8, 1H, vinylic), 4.48 (s, 2H, benzylic), 3.47 (t, J = 7, 2H), 2.4−1.4 (m, 9H, aliphatic) 2.21 (dt, J = 7, 7, 2H, allylic CH$_2$), 0.92 (d, J = 7, 3H, CH$_3$), 0.71 (d, J = 7, 3H, CH$_3$); ^{13}C NMR δ 211.17, 134.39, 128.25, 127.44, 127.24, 72.79, 69.86, 47.73, 46.16, 45.13, 40.87, 32.88, 27.46, 24.17, 21.46, 15.30; IR (neat) cm^{-1} 3030 (m), 2960 (s), 2870 (s), 1710 (s), 1453 (m), 1375 (m), 1203 (m), 1102 (b, m), 715 (s), 700 (m); EIMS, m/e (rel. intensity) 300 (3.0, M$^+$), 162 (8.4), 95 (7.4), 91 (100), 83 (8.6), 69 (16.5), 57 (10.1), 55 (16.6), 43 (16.0); HREIMS calcd (M$^+$) 300.2089, found 300.2081.

3,5-Dimethyl-3-((*E*)-1-octenyl)cyclohexanone (Table 1, entry 2) was prepared according to the representative procedure above using Cp$_2$Zr(H)Cl (284.1 mg, 0.99 mmol), 3.5 mL of THF, 1-octyne (152 μL, 0.99 mmol), and MeLi in ether (0.64 mL, 1 mmol) in the first 10 mL round bottom flask. CuCN (9.1 mg, 0.1 mmol), ZnCl$_2$·TMEDA (128.7 mg, 0.51 mmol), 1 mL of THF, and MeLi (1.12 mL, 1.74 mmol) were used to prepare the zincate/catalytic cuprate mixture. 3,5-Dimethyl-2-cyclohexen-1-one (71 μL, 0.5 mmol) was added over 50 min, followed by 1 h at −78 °C and then 1 h at 0 °C. Workup and flash chromatography using 40:1 (petroleum ether:ethyl acetate) afforded 99.0 mg (84%) as a clear oil: TLC [petroleum ether/ethyl acetate, 10/1] R_f 0.43; ^{1}H NMR δ 5.27 (dt, J = 16, 7, 1H, vinylic), 5.16 (d, J = 16, 1H, vinylic), 2.45−1.16 (m, 15H, aliphatic), 1.89 (dt, J = 7, 7, 2H, allylic CH$_2$), 1.03 (s, 3H, CH$_3$), 0.93 (d, J = 7, 3H, CH$_3$), 0.82 (t, J = 7, 3H, CH$_3$); ^{13}C NMR δ 211.23, 136.45, 129.67, 51.02, 49.14, 46.69, 40.10, 32.73, 31.57, 30.85, 29.30, 29.12, 28.65, 22.56, 22.14, 14.00; IR (neat) cm^{-1} 3030 (w), 2958 (s), 2921 (s), 2870 (s), 1720 (s), 1455 (m), 1420 (m), 1380 (m), 1360 (m), 1345 (m), 1275 (s), 1230 (s), 980 (m); EIMS, m/e (rel intensity) 236 (15.5, M$^+$), 221 (27.8), 179 (42.4), 151 (62.5), 137 (25.7), 123 (86.9), 109 (56.7), 95 (65.1), 81 (56.4), 69 (79.2), 55 (100), 43 (48.9); HREIMS calcd (M$^+$) 236.2140, found 236.2153.

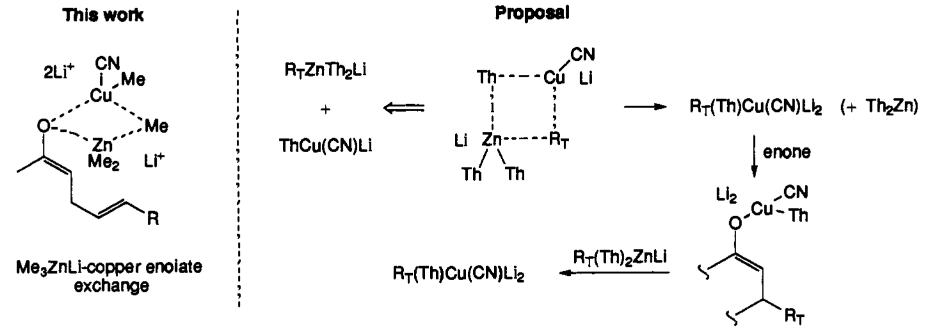
***trans*-4-Isopropyl-3-((*E*)-1-octenyl)cyclohexanone (Table 1, entry 3)** was prepared according to the representative procedure above with the exception that 5 mol % copper was used (2.3 mg, 0.026 mmol), with the appropriate reduction in MeLi to afford 101.8 mg (81%) of product.

***trans*-4-Isopropyl-3-((*E*)-1-octenyl)cyclohexanone (Table 1, entry 4)** was prepared according to the representative procedure above, with the exception that 10 mol % copper was used (4.8 mg, 0.05 mmol), with the appropriate reduction in MeLi to afford 112.7 mg (90%) of product.

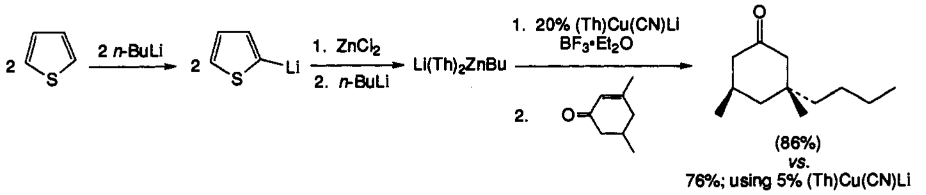
(1*S*)-4-(4-Thiophenoxy-((*E*)-1-butenyl)-4,6,6-trimethylbicyclo-[3.1.1]heptan-2-one (Table 1, entry 6) was prepared according to the representative procedure above using Cp$_2$Zr(H)Cl (414.2 mg, 1.5 mmol), 3.5 mL of THF, 3-butynyl phenyl sulfide (235 μL, 1.5 mmol), and MeLi in ether (0.715 mL, 1.5 mmol) in the first round bottom flask. CuCN (7.5 mg. 0.08 mmol), 0.75 mL of THF, Me$_2$Zn in heptane (0.92 mL, 0.78 mmol) and MeLi (0.45 mL, 0.95 mmol) were used to prepare the zincate/catalytic cuprate mixture. Prior to the addition of the enone, BF$_3$·Et$_2$O (0.1 mL, 0.82 mmol) was added at −78 °C. (1*S*)-(−)-Verbenone (123 μL, 0.75 mmol) in 0.75 mL of ether was added over 40 min, followed by an additional 3 h of reaction time. Workup and flash chromatography using 6:1 (petroleum ether:ethyl acetate) afforded 168.4 mg (71%) as a clear oil: TLC [petroleum ether/ethyl acetate, 4/1] R_f 0.40; ^{1}H NMR δ 7.4−7.2 (m, 5H, aromatic), 5.49 (d, J = 16, 1H, vinylic), 5.38 (dt, J = 16, 7, 1H, vinylic), 2.98 (t, J = 7, 2H, CH$_2$), 2.74 (d, J = 20, 1H, CH$_2$ adjacent to ketone), 2.57 (dd, J = 5, 5, 1H, CH$_2$), 2.49 (ddd, J = 11, 5, 5, 1H, CH$_2$), 2.38 (d, J = 20, 1H, CH$_2$ adjacent to ketone), 2.34 (dt, J = 7, 7, 2H, allylic CH$_2$), 2.03 (dd, J = 5, 5, 1H, CH), 1.60 (d, J = 11, 1H, CH), 1.41 (s, 3H, CH$_3$), 1.26 (s, 3H, CH$_3$), 1.09 (s, 3H, CH$_3$); ^{13}C NMR δ 213.72, 142.49, 136.47, 129.22, 128.85, 125.90, 124.01, 57.57, 51.62, 45.69, 40.63, 37.71, 33.73, 32.37, 27.95, 27.36, 25.91, 25.56; IR (neat) cm^{-1} 3070 (w), 3050 (w), 2985 (s), 2953 (s), 2942 (s), 2871 (s), 1709 (s), 1583 (m), 1479 (m), 1439 (m), 1412 (m), 1371 (m), 1286 (m), 1267 (m), 1248 (m), 1201 (m), 1090 (m), 1026 (m), 976 (m), 741 (m), 692 (m); EIMS, m/e (rel intensity) 314 (M$^+$, 9.6), 163 (9.0), 149 (7.1), 135 (5.4), 123 (100), 107 (23.1), 83 (160), 69 (13.3), 55 (15.5), 45 (18.3); HREIMS calcd (M$^+$) 314.1704, found 314.1686.

3-[(*E*)-4-[(Triisopropylsilyl)oxy]-1-butenyl]-2-methylcyclopentanone (Table 1, entry 7) was prepared according to the representative procedure above using Cp$_2$Zr(H)Cl (302.3 mg, 1 mmol), 4 mL of THF, 3-butyn-1-ol triisopropylsilyl ether (293 μL, 1 mmol), and MeLi in ether (0.67 mL, 1 mmol) in the first round bottom flask. CuCN (9.7 mg, 0.11 mmol), ZnCl$_2$·TMEDA (132.3 mg, 0.52 mmol), 1 mL of THF, and MeLi (1.17 mL, 1.79 mmol) were used to prepare the zincate/catalytic cuprate mixture. 2-Methyl-2-cyclopenten-1-one (50 μL, 0.5 mmol) was added over 80 min, followed by a 1 h reaction time. Workup and flash chromatography using 40:1 (petroleum ether:ethyl acetate) afforded 131.5 mg (81%) as a 9:1 mixture of isomers as determined by GC: TLC [petroleum ether/ethyl acetate, 10/1] R_f 0.41;

Scheme 9. Extension of Zincate-Induced Transmetalations



Scheme 10



^{1}H NMR δ 5.53 (dt, J = 16, 7, 1H, vinylic), 5.40 (dd, J = 16, 8, 1H, vinylic), 3.67 (t, J = 7, 2H, CH$_2$), 2.3−1.5 (m, 8H, aliphatic), 1.04 (hept, J = 4, 3H, silyl CH), 1.01 (d, J = 4, 18H, silyl isopropyl CH$_3$), 0.90 (d, J = 7, 3H, CH$_3$); ^{13}C NMR δ 220.23, 133.63, 128.18, 63.18, 50.04, 48.38, 43.75, 37.11, 35.76, 27.79, 17.93, 11.89; IR (neat) cm^{-1} 2960 (s), 2950 (s), 2948 (s), 2900 (s), 2890 (s), 2865 (s), 1744 (s), 1465 (m), 1410 (w), 1385 (m), 1250 (w), 1161 (m), 1109 (s), 1070 (m), 1013 (m), 997 (m), 970 (m), 935 (w), 920 (w), 882 (s), 790 (w), 734 (m), 677 (s), 656 (m); EIMS, *m/e* (rel intensity) 282 (M$^+$ − *i*-Pr + H, 21.6), 281 (M$^+$ − *i*-Pr, 100), 145 (12.5), 133 (12.5), 131 (15.4), 105 (11.1), 103 (18.2), 81 (12.5), 75 (27.3), 67 (22.2), 61 (18.6), 59 (16.8), 55 (14.2); HREIMS calcd (M − *i*-Pr) 281.1937, found 281.1966.

3-[(*E*)-4-[(Triisopropylsilyl)oxy]-1-butenyl]cyclopentanone (Table 1, entry 8) was prepared according to the representative procedure above using Cp$_2$Zr(H)Cl (288.9 mg, 1 mmol), 4 mL of THF, 3-butyn-1-ol triisopropylsilyl ether (290 μL, 1 mmol), and MeLi in ether (0.65 mL, 1 mmol) in the first round bottom flask. CuCN (10 mg, 0.11 mmol), ZnCl$_2$·TMEDA (131.7 mg, 0.52 mmol), 1 mL of THF, and MeLi (1.15 mL, 1.78 mmol) were used to prepare the zincate/catalytic cuprate mixture. 2-Cyclopenten-1-one (43 μL, 0.5 mmol) was added over 50 min, followed by a 2 h reaction time. Workup and flash chromatography using 40:1 (petroleum ether:ethyl acetate) afforded 136.5 mg (88%) as a clear oil: TLC [petroleum ether/ethyl acetate, 10/1] R_f 0.34; ^{1}H NMR δ 5.48 (m, 2H, vinylic), 3.66 (t, J = 6, 2H, CH$_2$), 2.75 (m, 1H, allylic CH), 2.21 (dt, J = 6, 6, 2H, allylic CH$_2$), 2.4−1.6 (m, 6H, aliphatic), 1.02 (hept, J = 5, 3H, isopropyl CH), 1.01 (d, J = 5, 18H, isopropyl-CH$_3$); ^{13}C NMR δ 219.05, 133.86, 127.10, 63.10; 44.80, 39.87, 38.18, 36.18, 29.82, 17.95, 11.89; IR (neat) cm^{-1} 3040 (w), 2945 (s), 2935 (s), 2898 (s), 2870 (s), 1740 (s), 1464 (s), 1406 (m), 1382 (m), 1245 (w), 1155 (m), 1100 (b, s), 1012 (m), 995 (m), 967 (m), 919 (w), 881 (m), 785 (w), 735 (m), 678 (s), 655 (s), 638 (m); EIMS, *m/e* (rel intensity) 268 (M$^+$ − *i*-Pr + H, 21.3), 267 (M$^+$ − *i*-Pr, 100), 225 (13.1), 145 (11.8), 131.1 (20.1), 119 (13.1), 105 (11.3), 103 (23.9), 91 (13.5), 77 (10.9), 75 (37.1), 67 (47.4), 61 (25.7), 59 (21.3), 55 (11.0), 45 (11.4); HREIMS calcd (M$^+$ − *i*-Pr) 267.1780, found 267.1763.

1-[4-(3-Oxocyclopentyl)-(*E*)-3-butenyl]-4,6-dimethyl-D-glucal (Table 1, entry 9) was prepared according to the representative procedure above using Cp$_2$Zr(H)Cl (277.9 mg, 1 mmol), 3 mL of THF, an 8:1 mix of α and β anomers of 1-(3-butynyl)-4,6-dimethyl-D-glucal (225 μL, 1 mmol), and MeLi in ether (0.49 mL, 1 mmol) in the first round bottom flask. CuCN (5.2 mg, 0.06 mmol), 0.5 mL of THF, Me$_2$Zn in heptane (0.61 mL, 0.52 mmol), and MeLi in ether (0.3 mL, 0.63 mmol) were used to prepare the zincate/catalytic cuprate mixture. 2-Cyclopenten-1-one (43 μL, 0.5 mmol) was added over 35 min as a solution in 1 mL of THF, followed by a 1 h additional reaction time. Workup and flash chromatography using 2:1 (petroleum ether:ethyl acetate) afforded 135.4 mg (87%) as an 8:1 mixture of α and β anomers as determined by ^{1}H NMR: TLC [petroleum ether/ethyl acetate, 4/1] R_f 0.12; ^{1}H NMR δ 6.04 (d, J = 11, 1H, vinylic), 5.73 (ddd, J = 11, 2, 2, 1H, vinylic), 5.49 (m, 2H, vinylic), 4.97 (d, J = 2, 1H, anomeric H), 3.9−3.4 (m, 6H, aliphatic, adjacent to oxygen), 3.40 (s, 3H, OCH$_3$), 3.37 (s, 3H, OCH$_3$), 2.8−1.6 (m, 9H, aliphatic); ^{13}C NMR δ 219.10, 134.08, 130.10, 126.66, 126.49, 94.58, 71.82, 71.61, 68.78, 68.01, 59.34, 56.51, 44.82, 39.84, 38.21, 32.88, 29.84; IR (neat) cm^{-1} 2929 (s), 2890 (s), 1741 (s), 1525 (m), 1460 (m), 1300 (m), 1135 (s) 1120 (s), 1099 (s), 1062 (s), 1038 (s), 1005 (s), 976 (s); EIMS, *m/e* (rel intensity) 236 (M$^+$ − C$_3$H$_6$O$_2$, 35.8), 157 (70.6), 125 (26.6), 109 (19.3), 100 (100), 97 (33.9), 95 (33.9), 81 (30.3), 71 (54.1), 69 (20.6), 67 (41.3), 57 (34.4), 55 (56.0), 53 (19.3), 45 (56.4), 43 (24.8); HREIMS calcd (M$^+$ − C$_3$H$_6$O$_2$) 236.1412, found 236.1394.

3,6-Dimethyl-8-oxo-(*E*,*E*)-deca-2,4-dien-1-ol *tert*-butyldimethylsilyl ether (Table 1, entry 10) was prepared according to the representative procedure above using Cp$_2$Zr(H)Cl (298.5 mg, 1 mmol), 4 mL of THF, (*E*)-3-methyl-2-penten-4-yn-1-ol *tert*-butyldimethylsilyl ether (251 μL, 1 mmol), and MeLi in ether (0.66 mL, 1 mmol) in the first round bottom flask. CuCN (8.9 mg, 0.1 mmol), 1.5 mL of THF, Me$_2$Zn in heptane (0.43 mL, 0.52 mmol), and MeLi in ether (0.47 mL, 0.71 mmol) were used to prepare the zincate/catalytic cuprate mixture. (*E*)-4-Hexene-3-one (58 μL, 0.5 mmol) was added over 50 min followed by a 1 h additional reaction time. Workup and flash chromatography using 50:1 (petroleum ether:ethyl acetate) afforded 134 mg (86%): TLC [petroleum ether/ethyl acetate, 10/1] R_f 0.51; ^{1}H NMR δ 5.99 (d, J = 16, 1H, vinylic), 5.48 (dd, J = 16, 8, 1H, vinylic), 5.44 (t, J = 7, 1H, vinylic), 4.24 (d, J = 7, 2H, CH$_2$), 2.8−2.3 (m, 5H, aliphatic), 1.65 (s, 3H, allylic CH$_3$), 0.98 (d, J = 7, 3H, CH$_3$), 0.98 (t, J = 7, 3H, CH$_3$), 0.85 (s, 9H, *tert*-butyl on Si), 0.013 (s, 6H, CH$_3$ on Si); ^{13}C NMR δ 210.46, 133.77, 133.01, 132.81, 130.21, 60.10, 49.54, 36.49, 32.73, 25.89, 20.37, 18.31, 12.56, 7.59, −5.21; IR (neat) cm^{-1} 3035 (w), 2959 (s), 2940 (s), 2885 (s), 2860 (s), 1718 (s), 1461 (m), 1380 (m), 1363 (m), 1255 (m), 1110 (m), 1055 (m), 967 (w), 837 (w), 775 (w); EIMS, *m/e* (rel intensity) 310 (M$^+$, 0.6), 253 (28.1), 197 (13.5), 181 (12.1), 178 (12.2), 161 (27.9), 157 (34.2), 129 (16.6), 121 (44.9), 107 (86.4), 91 (20.0), 75 (100), 73 (47.4), 57 (60.4); HREIMS calcd (M$^+$) 310.2328, found 310.2302.

(*E*)-5-Methyl-7-oxo-3-nonen-1-ol triisopropylsilyl ether (Table 1, entry 11) was prepared according to the representative procedure above using Cp$_2$Zr(H)Cl (291.6 mg, 1 mmol), 4 mL of THF, 3-butyn-1-ol triisopropylsilyl ether (292 μL, 1 mmol), and MeLi in ether (0.655 mL, 1 mmol) in the first round bottom flask. CuCN (9.4 mg, 0.1 mmol), ZnCl$_2$·TMEDA (131 mg, 0.52 mmol), 1.5 mL of THF, and MeLi (1.14 mL, 1.77 mmol) were used to prepare the zincate/catalytic cuprate mixture. (*E*)-4-Hexen-3-one (58 μL, 0.5 mmol) was added over 50 min, followed by a 1.5 h additional reaction time. Workup and flash chromatography using 50:1 (petroleum ether:ethyl acetate) afforded 138.2 mg (85%): TLC [petroleum ether/ethyl acetate, 10/1]

R_f 0.57; ^{1}H NMR δ 5.36 (m, 2H, vinylic), 3.61 (t, J = 7, 2H, ether CH$_2$), 2.62 (m, 1H, CH), 2.4−2.2 (m, 4H, aliphatic), 2.16 (q, J = 8, 2H, CH$_2$ adjacent to ketone), 1.02 (hept, J = 5, 3H, isopropyl CH), 1.01 (d, J = 5, 18H, isopropyl CH$_3$), 0.99 (t, J = 8, 3H, CH$_3$), 0.96 (d, J = 7, 3H, CH$_3$); ^{13}C NMR δ 210.74, 136.67, 125.47, 63.34, 49.54, 36.52, 36.29, 32.69, 20.26, 17.95, 11.92, 7.58; IR (neat) cm^{-1} 2960 (s), 2955 (s), 2930 (s), 2920 (s), 2895 (s), 2870 (s), 1720 (s), 1465 (s), 1415 (m), 1380 (m), 1365 (m), 1250 (w), 1105 (s), 1070 (m), 1012 (m), 995 (m), 970 (m), 930 (w), 920 (w), 880 (s), 790 (w), 735 (m), 680 (s), 655 (w); EIMS, *m/e* (rel intensity) 283 (M$^+$ − *i*-Pr, 100), 284 (M$^+$ − *i*-Pr + H, 22.7), 215 (78.9), 185 (37.2), 173 (46.5), 157 (25.7), 145 (27.8), 131 (31.4), 81 (31.4), 75 (51.1), 61 (37.2), 59 (33.2), 57 (63.4), 43 (21.5); HREIMS calcd (M$^+$ − *i*-Pr) 283.2072, found 283.2093.

3-[(*E*)-3-(Benzyloxy)-1-octenyl]cyclopentanone (Table 1, entry 12) was prepared according to the representative procedure above using Cp$_2$Zr(H)Cl (272.1 mg, 1 mmol), 3.5 mL of THF, 1-octyn-3-ol benzyl ether (246 μL, 1 mmol), and MeLi in ether (0.63 mL, 1 mmol) in the first round bottom flask. CuCN (4.8 mg, 0.05 mmol), 0.5 mL of THF, Me$_2$Zn in heptane (0.42 mL, 0.52 mmol), and MeLi (0.39 mL, 0.62 mmol) were used to prepare the zincate/catalytic cuprate mixture. 2-Cyclopenten-1-one (43 μL, 0.5 mmol) was added over 40 min, followed by 30 min of additional reaction time. Workup using pH 7 buffer as the quench rather than the usual basic workup and flash chromatography using 10:1 (petroleum ether:ethyl acetate) afforded 139.5 mg (93%): TLC [petroleum ether/ethyl acetate, 10/1] R_f 0.19; ^{1}H NMR δ 7.30 (m, 5H, aromatic), 5.62 (dd, J = 16, 7, 1H, vinylic), 5.40 (dd, J = 16, 8, 1H, vinylic), 4.53 (dd, J = 12, 5, 1H, benzylic CH$_2$), 4.33 (dd, J = 12, 4, 1H, benzylic CH$_2$), 3.69 (ddd, J = 8, 8, 8, 1H, allylic CH), 2.87 (m, 1H, allylic CH), 2.5−2.0 (m, 4H, CH$_2$ adjacent to ketone), 1.8−1.2 (m, 10H, aliphatic), 0.85 (t, J = 7, 3H, CH$_3$); ^{13}C NMR δ 218.62, 138.79, 135.07, 130.94, 128.29, 127.65, 127.38, 79.77, 69.92, 44.64, 39.32, 38.09, 35.61, 31.68, 29.76, 25.06, 22.56, 14.02; IR (neat) cm^{-1} 3030 (w), 2954 (s), 2931 (s), 2860 (s), 1743 (s), 1454 (m), 1155 (m), 1090 (s), 1068 (s), 974 (m), 737 (m), 698 (m); EIMS, *m/e* (rel intensity) 300 (M$^+$, 0.5), 229 (39), 209 (3), 194 (4), 186 (s), 137 (2), 99 (9), 92 (23), 91 (100); HREIMS calcd (M$^+$) 300.2089, found 300.2083.

***trans*-3-Hydroxy-4-[(*E*)-3-(benzyloxy)-1-octenyl]cyclopentanone *tert*-butyldimethylsilyl ether (Table 1, entry 13)** was prepared according to the representative procedure above, with the exception that 10 mol % copper was used (4.4 mg, 0.05 mmol), with the appropriate reduction in MeLi to afford 162.1 mg (71%) of product.

***trans*-3-Hydroxy-4-[(*E*)-3-(benzyloxy)-1-octenyl]cyclopentanone *tert*-butyldimethylsilyl ether (Table 1, entry 14)** was prepared according to the representative procedure above using Cp$_2$Zr(H)Cl (271.2 mg, 1 mmol), 3.5 mL of THF, 1-octyn-3-ol benzyl ether (245 μL, 1 mmol), and MeLi in ether (0.62 mL, 1 mmol) in the first round bottom flask. CuCN (8.9 mg, 0.1 mmol), 1 mL of THF, Me$_2$Zn in heptane (0.42 mL, 0.52 mmol), and MeLi (0.435 mL, 0.72 mmol) were used to prepare the zincate/catalytic cuprate mixture. (4*R*)-4-Hydroxy-2-cyclopenten-1-one *tert*-butyldimethylsilyl ether (**3**) (110.3 mg, 0.509 mmol) in 1 mL of THF was added at −78 °C over 55 min, followed by 5 min of additional reaction time. Workup using pH 7 buffer as the aqueous quench and flash chromatography using 16:1 (petroleum ether:ethyl acetate) afforded 190.5 mg (87%) as a mixture of two diastereomers: TLC [petroleum ether/ethyl acetate, 10/1] R_f 0.33, 0.35; ^{1}H NMR δ 7.30 (m, 5H, aromatic), 5.63, 5.59 (dd, J = 16, 7, 1H, vinylic), 5.43 (dd, J = 16, 8, 1H, vinylic), 4.54, 4.51 (d, J = 12, 1H, benzylic), 4.33, 4.32 (d, J = 12, 1H, benzylic), 4.13 (m, 1H, CH), 3.70 (m, 1H, allylic CH), 2.84 (m, 1H, allylic CH), 2.60−2.46 (m, 2H, CH$_2$ adjacent to ketone), 2.18 (dd, J = 19, 6, 1H, CH$_2$ adjacent to ketone), 2.08 (dd, J = 19, 8, 1H, CH$_2$ adjacent to ketone), 1.7−1.1 (m, 8H, aliphatic), 0.87 (s, 9H, *tert*-butyl), 0.85, 0.86 (t, J = 7, 3H, CH$_3$), 0.07, 0.05 (s, 3H, CH$_3$ on Si), 0.06, 0.04 (s, 3H, CH$_3$ on Si); ^{13}C NMR δ 215.20, 138.76, 132.81, 132.63, 132.39, 132.29, 128.32, 127.63, 127.42, 79.86, 79.79, 74.67, 74.61, 70.16, 70.09, 47.90, 47.68, 47.23, 47.13, 42.53, 42.18, 35.67, 31.68, 25.71, 25.13, 25.04, 22.58, 17.98, 14.04, −4.63, −4.80; IR (neat) cm^{-1} 3032 (w), 2954 (s), 2929 (s), 2858 (s), 1749 (s), 1462 (m), 1402 (m), 1390 (m), 1377 (m), 1361 (w), 1253 (w), 1201 (m), 1116 (m), 1070 (w), 1028 (m), 1007 (w), 976 (m), 906 (m), 860 (m), 839 (w), 779 (w), 744 (w), 698 (w); EIMS, *m/e* (rel intensity) 373 (M$^+$ − *t*-butyl, 1.3), 227 (5.2), 137 (3.4), 92 (9.8), 91 (100), 75 (30.7), 67 (7.5); HREIMS calcd (M$^+$ − *tert*-butyl) 373.2193, found 373.2199.

***trans*-3-Hydroxy-4-[(*E*)-3-(benzyloxy)-1-octenyl]cyclopentanone *tert*-butyldimethylsilyl ether (Table 1, entry 15)** was prepared according to the representative procedure above, with the exception that 30 mol % copper was used (13.4 mg, 0.15 mmol), with the appropriate increase in MeLi to afford 205.9 mg (92%) of product.

***trans*-3-Hydroxy-4-[(*E*)-3-[(4-methoxybenzyl)oxy]-1-octenyl]cyclopentanone *tert*-butyldimethylsilyl ether (Table 1, entry 16)** was prepared according to the representative procedure above using Cp$_2$Zr(H)Cl (274.2 mg, 1 mmol), 3.5 mL of THF, 1-octyn-3-ol *p*-methoxybenzyl ether (269 μL, 1 mmol), and MeLi in ether (0.69 mL, 1 mmol) in the first round bottom flask. CuCN (9.2 mg, 0.1 mmol), 1 mL of THF, Me$_2$Zn in heptane (0.42 mL, 0.52 mmol), and MeLi (0.49 mL, 0.73 mmol) were used to prepare the zincate/catalytic cuprate mixture. Enone **3** (108.5 mg, 0.5 mmol) in 1 mL of THF was added at −78 °C over 50 min, followed by 5 min of additional reaction time. Workup using pH 7 buffer as the aqueous quench, drying over sodium sulfate (rather than magnesium sulfate), and flash chromatography using 10:1 (petroleum ether:ethyl acetate) afforded 194.9 mg (85%) as an equal mixture of two diastereomers: TLC [petroleum ether/ethyl acetate, 10/1] R_f 0.17, 0.20; ^{1}H NMR δ 7.21, 7.20 (d, J = 9, 2H, aromatic, *meta* to OMe), 6.84 (d, J = 9, 2H, aromatic, *ortho* to OMe), 5.59 (m, 1H, vinylic), 5.43 (m, 1H, vinylic), 4.47, 4.44 (d, J = 11, 1H, benzylic), 4.25, 4.24 (d, J = 11, 1H, benzylic), 4.12 (m, 1H, ring CH), 3.78 (s, 3H, OCH$_3$), 3.69 (ddd, J = 7, 7, 7, 1H, allylic CH), 2.84 (m, 1H, allylic CH), 2.6−2.4 (m, 2H, CH$_2$ adjacent to ketone), 2.2−2.1 (m, 2H, CH$_2$ adjacent to ketone), 1.7−1.1 (m, 8H, aliphatic), 0.87 (s, 9H, *tert*-butyl), 0.85, 0.84 (t, J = 7, CH$_3$), 0.07, 0.05 (s, 3H, CH$_3$ on Si), 0.06, 0.04 (s, 3H, CH$_3$ on Si); ^{13}C NMR δ 215.20, 215.02, 163.82, 159.03, 132.90, 132.72, 132.25, 132.15, 129.19, 133.70, 79.47, 79.39, 74.66, 69.80, 69.7, 55.23, 47.88, 47.68, 47.20, 47.10, 42.52, 42.18, 35.67, 31.68, 25.70, 25.13, 25.04, 22.56, 17.91, 14.03, −4.63, −4.80; IR (neat) cm^{-1} 2954 (s), 2931 (s), 2858 (s), 1749 (s), 1612 (m), 1513 (s), 1464 (m), 1250, (s) 1117 (s), 1082 (m), 860 (m), 837 (s), 777 (m); CIMS, *m/e* (rel intensity) 478 (M + NH$_4^+$, 56), 137 (6), 121 (PMB$^+$, 100); HRCIMS calcd (M + NH$_4^+$) 478.3353, found 478.3360.

***trans,trans*-2-(1-Hydroxyhexyl)-3-((E)-1-octenyl)-4-isopropylcyclohexanone (Table 2, entry 1).** A representative procedure used for the preparation of all products in Table 2 is as follows. To a 10 mL round bottom flask equipped with a stir bar and septum and having been cooled under a stream of argon was added Cp$_2$Zr(H)Cl (266.9 mg, 1 mmol), followed by 2.5 mL of THF and octyne (152 μL, 1 mmol). The two-phase reaction mixture was shielded from light by wrapping in aluminum foil and allowed to stir for 30 min, after which time the reaction was judged to be complete as evidenced by a homogeneous solution. This mixture was then cooled to −78 °C and at this temperature was then added MeLi in ether (0.63 mL, 1 mmol) dropwise over 1 min. At the same time, to another 10 mL round bottom flask, similarly cooled and equipped, was added CuCN (4.7 mg, 0.05 mmol), followed by 0.5 mL of THF. After the mixture was cooled to −78 °C, Me$_2$Zn in heptane (0.43 mL, 0.52 mmol) was added to the stirred slurry, followed quickly by dropwise addition of MeLi (0.39 mL, 0.62 mmol). After 5 min this three-phase slurry was placed in an ice bath for 10 min, during which time both remaining phases became homogeneous. This solution was then cooled back to −78 °C and the solution containing the methyl vinyl zirconocene, also at −78 °C, was transferred *via* cannula into the flask containing the zincate/catalytic cuprate mixture. After 5 min of stirring, 4-isopropyl-2-cyclohexen-1-one (77 μL, 0.5 mmol) was added portionwise *via* microliter syringe over 70 min, followed by an additional 1 h of reaction time. After this period, hexanal (250 μL, 2 mmol), in 1 mL of THF and cooled to −78 °C, was added rapidly *via* cannula to the reaction mixture, still at −78 °C. After 10 min the reaction was quenched at −78 °C with 1 mL of pH 7 buffer. The two-phase mixture was then transferred to a separatory funnel containing an additional 10 mL of pH 7 buffer and 25 mL of ether, using an additional 25 mL of ether to aid in this transfer. The aqueous layer was extracted twice with 25 mL of ether. The combined organic layers were washed three times with 25 mL of brine and then dried over sodium sulfate. After concentration *in vacuo*, flash chromatography on silica gel using 20:1 (petroleum ether:ethyl acetate) afforded 80:8 mg (46%) of the higher R_f diastereomers and 63.7 mg (36%) of lower R_f diastereomers TLC [petroleum ether/ethyl acetate, 10/1] R_f 0.38, 0.22. Major diastereomers: ^{1}H NMR δ 5.52 (dt, J = 16, 7, 1H, vinylic), 5.02 (dd, J = 16, 10, 1H, vinylic), 3.62 (m, 1H, CH geminal with OH), 2.91 (d, J = 12, 1H, CH), 2.52 (ddd, J = 11, 11, 11, 1H, allylic CH), 2.34 (m, 2H, aliphatic), 2.2−1.2 (m, 23H, aliphatic + O*H*), 0.92 (d, J = 7, 3H, isopropyl CH$_3$), 0.86 (t, J = 7, 3H, CH$_3$), 0.85 (t, J = 8, 3H, CH$_3$), 0.69 (d, J = 7, 3H, isopropyl CH$_3$); ^{13}C NMR δ 215.45, 134.08, 131.13, 70.66, 57.66, 49.71, 46.82, 43.01, 36.42, 32.45, 31.75, 31.68, 29.31, 28.84, 27.71, 26.39, 25.43, 22.65, 21.84, 14.81, 14.06; IR (neat) cm^{-1} 3543 (br m), 2956 (s), 2927 (s), 2870 (s), 2856 (s), 1699 (s), 1466 (m), 1410 (m), 1377 (m), 1352 (m), 1171 (m), 1128 (m), 1061 (m), 971 (m); CIMS, *m/e* (rel intensity) 351 (M + H$^+$, 13), 333 (27), 252 (18), 251 (100), 250 (19), 233 (39), 139 (13), 111 (14), 83 (80), 55 (28); HRCIMS calcd (M + H$^+$) 351.3263, found 351.3238. Minor diastereomers: ^{1}H NMR δ 5.37 (dt, J = 16, 7, 1H, vinylic), 5.05 (dd, J = 16, 10, 1H, vinylic), 3.55 (m, 1H, CH geminal to OH), 3.06 (br m, 1H, OH), 2.5−1.2 (m, 27H, aliphatic), 0.92 (d, J = 7, 3H, isopropyl CH$_3$), 0.862, 0.860 (t, J = 7, 6H, CH$_3$), 0.68 (d, J = 7, 3H, isopropyl CH$_3$); ^{13}C NMR δ 214.59, 133.08, 130.45, 71.64, 58.23.47.86, 46.02, 41.89, 32.44, 31.77, 31.68, 31.07, 29.39, 28.86, 27.37, 26.23, 2334, 22.70, 22.62, 21.60, 14.70, 14.07; IR (neat) cm^{-1} 3508 (br m), 2956 (s), 2957 (s), 2872 (s), 2858 (s), 1703 (s), 1616 (w), 1466 (m), 1178 (m), 1232 (m), 1126 (m), 1045 (m), 972 (w), 725 (w); CIMS, *m/e* (rel intensity) 351 (M + H$^+$, 25), 350 (M$^+$, 11), 333 (100), 279 (18), 251 (61), 233 (35), 139 (11), 109 (11), 95 (13), 83 (79), 69 (11), 55 (31); HRCIMS calcd (M$^+$) 350.3185, found 350.3197.

***trans*-3-[(*E*)-4-[(Triisopropylsilyl)oxy]-1-butenyl]-2-(1-cyclohexyl-1-hydroxymethyl)cyclopentanone (Table 2, entry 2)** was prepared according to the representative procedure above using Cp$_2$Zr(H)Cl (268.1 mg, 1 mmol), 3 mL of THF, 3-butyn-1-ol triisopropylsilyl ether (277 μL, 1 mmol), and MeLi in ether (0.52 mL, 1 mmol) in the first round bottom flask. CuCN (4.7 mg, 0.05 mmol), 0.5 mL of THF, Me$_2$Zn in heptane (0.61 mL, 0.52 mmol) and MeLi (0.315 mL, 0.63 mmol) were used to prepare the zincate/catalytic cuprate mixture. 2-Cyclopenten-1-one (43 μL, 0.5 mmol) was added over 50 min, followed by 10 min of additional reaction time. Cyclohexanecarboxaldehyde (0.25 mL, 2 mmol) was added in 1 mL of ether *via* cannula. After 10 min the reaction was quenched and worked up as previously described. Flash chromatography using 20:1 (petroleum ether:ethyl acetate) afforded 169.3 mg (80%) as a clear oil; TLC [petroleum ether/ethyl acetate, 4/1] R_f 0.47; ^{1}H NMR δ 5.59 (dt, J = 16, 7, 1H, vinylic), 5.42 (dd, J = 16, 8, 1H, vinylic), 3.69 (t, J = 7, 2H, CH$_2$OSi), 3.38 (ddd, J = 5, 5, 5, 1H, CH geminal to OH), 2.97 (d, J = 5, 1H, OH), 2.61 (m, 1H, allylic CH), 2.33 (dd, J = 19, 9, 1H, aliphatic), 2.26 (dt, J = 7, 7, 2H, allylic CH$_2$), 2.2−1.1 (m, 15H, aliphatic), 1.05 (hept, J = 5, 3H, silyl CH), 1.04 (d, J = 5, 18H, silyl isopropyl CH$_3$); ^{13}C NMR δ 222.08, 134.04, 128.44, 75.63, 63.20, 55.93, 43.92, 40.34, 38.50, 36.25, 30.04, 28.44, 27.13, 26.33, 25.82, 18.01, 11.95; IR (neat) cm^{-1} 3498 (br m), 2929 (s), 2864 (s), 1728 (s), 1462 (m), 1450 (m), 13749 (w), 1106 (s), 1007 (w), 883 (m), 683 (m); EIMS, *m/e* (rel intensity) 361 (M$^+$ − *i*-Pr − H$_2$O, 12.8), 267 (100), 237 (16.4), 145 (20.3), 131 (32.3), 119 (20.3), 103 (44.0), 91 (20.7), 83 (41.3), 75 (70.7), 68 (25.8), 67 (97.7), 55 (93.7), 43 (20.3); HREIMS calcd (M$^+$ − *i*-Pr − H$_2$O) 361.2563, found 361.2544.

***trans*-2-[3-(Methoxycarbonyl)-1-hydroxypropyl]-3-[(*E*)[(triisopropylsilyl)oxy]-1-butenyl]cyclopentanone (Table 2, entry 3)** was prepared according to the representative procedure above using Cp$_2$Zr(H)Cl (260.2 mg, 1 mmol), 3 mL of THF, 3-butyn-1-ol triisopropylsilyl ether (267 μL, 1 mmol), and MeLi in ether (0.5 mL, 1 mmol) in the first round bottom flask. CuCN (4.9 mg, 0.05 mmol), 0.5 mL of THF, Me$_2$Zn in heptane (0.61 mL, 0.52 mmol), and MeLi (0.32 mL, 0.63 mmol) were used to prepare the zincate/catalytic cuprate mixture. 2-Cyclopenten-1-one (43 μL, 0.5 mmol) was added over 50 min, followed by 10 min of additional reaction time. Methyl 4-oxobutanoate (215 μL, 2 mmol) in 1 mL ether was added at −78 °C. After 10 min the reaction was quenched in the hood using 5% aqueous HCl rather than pH 7 buffer. Flash chromatography using 6:1 (petroleum ether:ethyl acetate) afforded 158.3 mg (74%) of a clear oil consisting of two isomeric products (12:1 ratio of isomers). Major isomer: TLC [petroleum ether/ethyl acetate, 80/20], R_f 0.30; ^{1}H NMR δ 5.60 (dt, J = 16, 7, 1H, vinylic), 5.54 (dd, J = 16, 9, 1H, vinylic), 3.68 (t, J = 7, 2H, CH$_2$), 3.63 (s, 3H, ester CH$_3$), 3.37 (br d, J = 4, 1H, OH), 2.43 (t, J = 7, 2H, CH$_2$), 2.25 (dt, J = 7, 7, 2H, CH$_2$), 2.7−1.6 (m, 9H, aliphatic), 1.04 (hept, J = 5, 3H, isopropylsilyl CH), 1.02 (d, J = 5, 18H); ^{13}C NMR δ 221.29, 174.22, 134.10, 128.96, 70.71, 63.03, 58.90, 51.57, 43.54, 38.35, 36.24, 30.16, 28.40, 28.25, 17.99, 11.93; IR (neat) cm^{-1} 3525 (br m), 2942 (s), 2866 (s), 1739 (s), 1461 (m), 1437 (m), 1250 (s), 1165 (s), 1014 (s), 970 (m), 681 (m); EIMS, *m/e* (rel intensity) 383 (M$^+$ − *i*-Pr, 2.1), 365 (13.6), 351 (14.6), 268 (22.3), 267 (100), 239 (15.7), 231 (12.6), 157 (14.6), 145 (25.6), 131 (39.4), 119 (35.7), 105 (16.7), 103 (43.7), 91 (22.5), 88 (27.6), 87 (18.6), 85 (33.9), 79 (16.5), 77 (18.3), 75 (66.4), 73 (16.1), 67 (72.0), 61 (43.0), 59 (46.4), 57 (19.1), 55 (24.6), 45 (19.9); HREIMS calcd (M$^+$ − *i*-Pr) 383.2254, found 383.2218; Minor isomer: TLC [petroleum ether/ethyl acetate, 80/20], R_f 0.24; ^{1}H NMR δ 5.61 (dt, J = 15, 7, 1H, vinylic), 5.46 (dd, J = 15, 8, 1H vinylic), 3.92 (m, 1H, OH), 3.68 (t, J = 7, 2H, CH$_2$), 2.25 (dt, J = 7, 7, 2H, CH$_2$), 2.8−1.2 (m, 11H, aliphatic), 1.05 (hept, J = 5, 3H, isopropylsilyl CH), 1.03 (d, J = 5, 18H); ^{13}C NMR δ 220.74, 174.20, 134.06, 128.53, 70.05, 63.07, 59.46, 51.66, 41.68, 38.68, 36.26, 30.94, 28.99, 28.33, 18.00, 11.94; IR (neat) cm^{-1} 3525 (br m), 2942 (s), 2866 (s), 1739 (s), 1461 (m), 1437 (m), 1250 (s), 1165 (s), 1014 (s), 970 (m), 681 (m); EIMS, *m/e* (rel intensity) 383 (M$^+$ − *i*-Pr, 1.7), 365 (28.8), 351 (45.7), 268 (21.8), 267 (100), 203 (24.2), 175 (17.8), 157 (21.3), 145 (36.0), 131 (58.6), 119 (51.3), 117 (18.7), 115 (16.6), 105 (23.4), 103 (56.9), 91 (31.5), 88 (25.9), 87 (21.2), 85 (41.0), 81 (19.0), 79 (25.1), 77 (22.5), 75 (85.6), 73 (21.0), 67 (75.3), 61 (55.2), 59 (52.4), 57 (18.9), 55 (24.2), 45 (16.3), 43 (15.5); HREIMS calcd (M$^+$ − *i*-Pr) 383.2254, found 383.2238.

***trans*-2-[3-(Methoxycarbonyl)-1-hydroxypropyl]-3-[(*E*)-3-(benzyloxy)-1-octenyl]cyclopentanone (Table 2, entry 4)** was prepared according to the representative procedure above using Cp$_2$Zr(H)Cl (272.9 mg, 1 mmol), 3.5 mL of THF, 1-octyn-3-ol benzyl ether (247 μL, 1 mmol), and MeLi in ether (0.63 mL, 1 mmol) in the first round bottom flask. CuCN (4.8 mg, 0.05 mmol), 0.5 mL of THF, Me$_2$Zn in heptane (0.42 mL, 0.52 mmol), and MeLi (0.39 mL, 0.62 mmol) were used to prepare the zincate/catalytic cuprate mixture. 2-Cyclopenten-1-one (43 μL, 0.5 mmol) was added over 50 min, followed by 20 min additional reaction time. Methyl 4-oxobutanoate (120 μL, 1.1 mmol) in 1 mL ether was added at −78 °C. After 10 min the reaction was quenched and worked up. Flash chromatography using 6:1 (petroleum ether:ethyl acetate) afforded 156.4 mg (75%) of a mixture of four isomers by ^{1}H NMR: TLC [petroleum ether/ethyl acetate, 4/1] R_f 0.14, 0.10. Major diastereomers: ^{1}H NMR δ 7.29 (m, 5H, aromatic), 5.60, 5.58 (dd, J = 16, 8, 1H, vinylic), 5.51, 5.49 (dd, J = 16, 8, 1H, vinylic), 4.54 (d, J = 12, 1H, benzylic), 4.34, 4.32 (d, J = 12, 1H, benzylic), 3.70 (m, 2H, CH geminal to O), 3.65, 3.62, 3.57 (s, 3H, methyl ester), 3.47 (br m, 1H, OH), 2.67 (m, 1H, allylic CH), 2.44 (t, J = 7, 2H, CH$_2$ adjacent to ester), 2.4−1.2 (m, 15H, aliphatic), 0.85 (t, J = 7, 3H, CH$_3$); ^{13}C NMR δ 220.95, 174.04, 138.73, 135.18, 132.84, 132.58, 128.27, 127.63, 127.56, 127.38, 79.51, 70.67, 69.98, 58.99, 58.81, 51.53, 43.05, 38.25, 35.61, 31.67, 30.28, 30.16, 28.49, 27.63, 25.07, 22.55, 14.01; IR (neat) cm^{-1} 3485 (br s), 3030 (w), 2953 (s), 2931 (s), 2860 (s), 1728 (s), 1454 (m), 1439 (m), 1365 (m), 1275 (m), 1257 (m), 1201 (m), 1169 (m), 1090 (m), 1068 (m), 739 (w), 698 (w); EIMS, *m/e* (rel intensity) 417 (M + H$^+$, 2), 399 (M + H$^+$ − H$_2$O, 4), 367 (6), 309 (48), 292 (22), 291 (100), 277 (56), 259 (43), 237 (9), 193 (74), 175 (13), 117 (9), 91 (49), 85 (21); HRCIMS calcd (M + H$^+$ − H$_2$O) 399.2535, found 399.2530. Minor diastereomers: ^{1}H NMR δ 7.30 (m, 5H, aromatic), 5.61, 5.60 (dd, J = 16, 8, 1H, vinylic), 5.53, 5.51 (dd, J = 16, 8, 1H, vinylic), 4.54 (d, J = 12, 1H, benzylic), 4.34, 4.32 (d, J = 12, 1H, benzylic), 3.97 (m, 1H, CH), 3.70 (m, 1H, CH), 3.63, 3.60 (s, 3H, methyl ester), 2.9−1.2 (m, 19H, aliphatic), 0.850, 0.847 (t, J = 7, 3H, CH$_3$); ^{13}C NMR δ 220.18, 174.08, 138.76, 135.41, 135.28, 132.54, 132.29, 128.32, 127.68, 127.42, 79.68, 79.61, 70.09, 69.99, 69.90, 59.48, 51.68, 40.92, 38.60, 35.64, 31.71, 30.95, 29.21, 28.47, 25.10, 22.59, 14.05; IR (neat) cm^{-1} 3485 (br s), 3030 (w), 2953 (s), 2931 (s), 2860 (s), 1728 (s), 1454 (m), 1439 (m), 1365 (m), 1275 (m), 1257 (m), 1201 (m), 1169 (m), 1090 (m), 1068 (m), 739 (w), 698 (w); CIMS, *m/e* (rel intensity) 399 (M + H$^+$ − H$_2$O, 2), 373 (4), 309 (16), 291 (41), 277 (46), 259 (52), 193 (79), 175 (13), 117 (19), 91 (100), 85 (66), 79 (15); HRCIMS calcd (M + H$^+$ − H$_2$O) 399.2535, found 399.2531.

7-Hydroxy-11-*O*-(*tert*-butyldimethylsilyl)-15-dehydroxy-16-methyl-16-[(trimethylsilyl)oxy] PGE_1 methyl ester (Table 2, entry 5) was prepared according to the representative procedure above using $Cp_2Zr(H)Cl$ (274.8 mg, 1 mmol), 3.5 mL of THF, 4-methyl-1-octyn-4-ol trimethylsilyl ether (271 μL, 1 mmol), and MeLi in ether (0.606 mL, 1 mmol) in the first round bottom flask. CuCN (8.9 mg, 0.1 mmol), 1 mL of THF, Me_2Zn in heptane (0.42 mL, 0.52 mmol), and MeLi (0.43 mL, 0.72 mmol) were used to prepare the zincate/catalytic cuprate mixture. Enone **3** (109.4 mg, 0.5 mmol) in 1 mL of THF was added over 70 min, followed by 5 min of additional reaction time. Methyl 7-oxoheptanoate (242 μL, 1.5 mmol) in 1 of mL of THF was added at −78 °C. After 5 min the reaction was quenched and worked up. Flash chromatography using 8:1 (petroleum ether:ethyl acetate) afforded 171.8 mg (59%) of a top set of diastereomers and 57.7 mg (20%) of a lower R_f set of diastereomers, for a total of four isomers by ^1H NMR; TLC [petroleum ether/ethyl acetate, 4/1] R_f 0.37, 0.30; Major diastereomers: ^1H NMR δ 5.58 (dt, $J = 15, 7$, 1H, vinylic), 5.32 (ddd, $J = 15, 19, 1$ 1H, vinylic), 4.02 (m, 1H, CH geminal to OTBS), 3.73 (br m, 1H, OH), 3.64 (s, 3H, methyl ester), 3.29 (dd, $J = 9, 4$, 1H, CH geminal to OH), 2.27 (t, $J = 8$, 2H, CH_2 adjacent to ester), 2.60−2.05 (m, 6H, aliphatic), 1.6−1.2 (m, 14H, aliphatic), 1.14, 1.13 (s, 3H, CH_3 geminal to OTMS), 0.87 (t, $J = 7$, 3H, CH_3), 0.86 (s, 9H, *tert*-butyl CH_3), 0.08 (s, 9H, $SiMe_3$), 0.034 (s, 3H, TBS CH_3), 0.025 (s, 3H, TBS CH_3); ^{13}C NMR δ 217.83, 132.32, 132.25, 130.04, 75.87, 73.32, 71.94, 58.18, 52.56, 51.44, 47.84, 45.68, 42.18, 35.14, 33.99, 29.04, 27.59, 26.16, 25.68, 25.34, 24.93, 23.24, 17.99, 14.20, 2.66, −4.76; IR (neat) cm^{-1} 3458 (br m), 2954 (s), 2933 (s), 2858 (s), 1740 (s), 1462 (m), 1375 (m), 1252 (s), 1198 (s), 1159 (s), 1113 (w), 1020 (m), 975 (m), 885 (s), 777 (m), 669 (w); CIMS, *m/e* (rel intensity) 602 ($M + NH_4^+$, 20), 585 ($M + H^+$, 5), 530 (100), 513 (38), 512 (23), 495 (32), 363 (21), 176 (31), 159 (9); HRCIMS calcd ($M + NH_4^+$) 602.4272, found 602.4264. Minor diastereomers: ^1H NMR δ 5.42 (m, 1H, vinylic), 5.27 (m, 1H, vinylic), 4.21 (br m, 1H, OH), 4.01 (m, 1H), 3.88 (m, 1H), 3.64 (s, 3H, methyl ester), 2.4−1.2 (m, 22H, aliphatic), 1.13, 1.12 (s, 3H, CH_3 geminal to OTMS), 0.87 (t, $J = 7$, 3H, CH_3), 0.84 (s, 9H, *tert*-butyl CH_3), 0.08 (s, 9H, TMS CH_3), −0.011 (s, 3H, TBS CH_3), −0.014 (s, 3H, TBS CH_3); ^{13}C NMR δ 217.64, 173.82, 134.62, 134.56, 133.32, 75.95, 73.45, 71.91, 55.06, 53.90, 51.48, 45.83, 42.06, 34.28, 33.92, 33.82, 28.94, 28.63, 26.11, 25.79, 25.17, 24.54, 18.04, 14.25, 2.68, −4.60, −4.72; IR (neat) cm^{-1} 3504 (br m), 2953 (s), 2933 (s), 2858 (s), 1738 (s), 1462 (m), 1437 (m), 1373 (m), 1363 (m), 1252 (s), 1198 (s), 1173 (s), 1118 (m), 1088 (m), 1065 (m), 1007 (m), 864 (m), 839 (s), 777 (m), 671 (w); CIMS, *m/e* (rel intensity) 602 ($M + NH_4^+$, 20), 585 ($M + H^+$, 7), 530 (100), 513 (27), 512 (17), 495 (38), 363 (24), 176 (47), 159 (11), 142 (10); HRCIMS calcd ($M + NH_4^+$) 602.4272, found 602.4270.

7-Hydroxy-11-*O*-(*tert*-butyldimethylsilyl)-15-*O*-[(2-methoxyethoxy)methyl] PGE_1 methyl ester (Table 2, entry 6) was prepared according to the representative procedure above using $Cp_2Zr(H)Cl$ (274.9 mg, 1 mmol), 3.5 mL of THF, 1-octyn-3-ol (2-methoxyethoxy)methyl ether (243 μL, 1 mmol), and MeLi in ether (0.606 mL, 1 mmol) in the first round bottom flask. CuCN (9.0 mg, 0.1 mmol), 1 mL of THF, Me_2Zn in heptane (0.42 mL, 0.52 mmol), and MeLi (0.43 mL, 0.72 mmol) were used to prepare the zincate/catalytic cuprate mixture. Enone **3** (111.4 mg, 0.51 mmol) in 1 mL of THF was added over 60 min, followed by 5 min of additional reaction time. Methyl 7-oxoheptanoate (162 μL, 1 mmol) in 1 mL of THF was added at −78 °C. After 3 min the reaction was quenched and worked up. Flash chromatography using 3:1 (petroleum ether:ethyl acetate) afforded 249.9 mg (83%) as a mixture of at least two isomers; TLC [petroleum ether/ethyl acetate, 1/1] R_f 0.47, 0.54. Higher R_f diastereomers (major): ^1H NMR δ 5.50 (m, 2H, vinylic), 4.70 (d, $J = 7$, 1H, acetal CH_2), 4.61 (d, $J = 7$, 1H, acetal CH_2), 4.02 (m, 2H, CH_2), 3.74 (m, 2H, CH × 2), 3.64 (s, 3H, CO_2Me), 3.60 (m, 1H, CH), 3.53 (m, 2H, CH_2), 3.37 (s, 3H, OCH_3), 3.14 (d, $J = 5$, 1H, OH), 2.64 (m, 2H), 2.27 (t, $J = 8$, 2H, CH_2 adjacent to ester), 2.24 (m, 1H), 2.08 (m, 1H), 1.7−1.2 (m, 16H, aliphatic), 0.87 (t, $J = 7$, 3H, CH_3), 0.85 (s, 9H, *tert*-butyl CH_3), 0.03 (s, 3H, silyl CH_3), 0.02 (s, 3H, silyl CH_3); ^{13}C NMR δ 217.36, 173.52, 133.01, 132.75, 92.62, 73.18, 71.75, 66.95, 59.05, 57.92, 51.47, 47.95, 35.59, 35.09, 33.98, 31.69, 29.02, 25.67, 25.39, 25.21, 24.91, 11.61, 17.92, 14.05, −4.58, −4.84; IR (neat) cm^{-1} 3488 (br m), 2858 (s), 2931 (s), 2951 (s), 1741 (s), 1464 (m), 1408 (m), 1363 (m), 1252 (m), 1200 (s), 1173 (s), 1155 (s), 1109 (m), 1041 (w), 976 (m), 885 (s), 850 (m), 839 (m), 777 (m); CIMS, *m/e* (rel intensity) 604 ($M + NH_4^+$, 6), 586 (M^+, 3), 472 (10), 446 (14), 426 (14), 379 (7), 350 (26), 349 (100), 331 (21), 307 (13), 265 (12), 208 (13), 191 (42), 176 (31), 159 (24), 133 (22); HRCIMS calcd ($M + NH_4^+$) 604.4245, found 604.4239. Lower R_f diastereomers (minor): ^1H NMR δ 5.57 (dd, $J = 16, 8$, 1H, vinylic), 5.45 (dd, $J = 16, 8$, 1H, vinylic), 4.73 (d, $J = 7$, 1H, acetal CH_2), 4.61 (d, $J = 7$, 1H, acetal CH_2), 4.03 (m, 2H, CH_2), 3.77 (m, 1H, CH), 3.71 (m, 1H, CH), 3.64 (s, 3H, CO_2Me), 3.59 (m, 1H, CH), 3.53 (t, $J = 5$, 2H, CH_2), 3.37 (s, 3H, OCH_3), 3.25 (d, $J = 4$, 1H, OH), 2.61 (m, 2H), 2.27 (t, $J = 8$, 2H, CH_2 adjacent to ester), 2.23 (m, 1H), 2.08 (m, 1H), 1.7−1.2 (m, 16H, aliphatic), 0.86 (t, $J = 7$, 3H, CH_3), 0.85 (s, 9H, *tert*-butyl CH_3), 0.04 (s, 3H, TBS CH_3), 0.03 (s, 3H, silyl CH_3); ^{13}C NMR δ 216.83, 133.68, 132.85, 92.68, 71.76, 71.53, 66.92, 59.00, 58.35, 52.02, 51.46, 47.94, 25.56, 25.19, 33.98, 31.73, 28.99, 25.68, 25.53, 25.03, 24.91, 22.58, 17.96, 14.20, 14.07, −4.63, −4.83; IR (neat) cm^{-1} 3488 (br m), 2858 (s), 2931 (s), 2951 (s), 1741 (s), 1464 (m), 1408 (m), 1363 (m), 1252 (m), 1200 (s), 1173 (s), 1155 (s), 1109 (m), 1041 (w), 976 (m), 885 (s), 850 (m), 839 (m), 777 (m); CIMS, *m/e* (rel intensity) 604 ($M + NH_4^+$, 6), 586 (M^+, 3), 472 (10), 446 (14), 426 (14), 379 (7), 350 (26), 349 (100), 331 (21), 307 (13), 265 (12), 208 (13), 191 (42), 176 (31), 159 (24), 133 (22); HRCIMS calcd ($M + NH_4^+$) 604.4245, found 604.4239.

***trans*-3-[(*E*)-3-(Benzyloxy)-1-octenyl]-2-[3-(trimethylsilyl)-2-propynyl]cyclopentanone (Table 3, entry 1).** A representative procedure used for the preparation of all products given in Table 3 is as follows. Both the enolate and the propargyl triflate need to be ready for the final step at the same time. Hence, the triflate preparation was started just slightly before (~10 min) the hydrozirconation. To a 50 mL round bottom flask, equipped with a stir bar and septum and having been cooled under a stream of argon, was added trifluoromethanesulfonic anhydride (0.534 mL, 3.14 mmol). This flask was then cooled to −24 °C. In a 5 mL flask similarly cooled under a stream of argon was placed 2.6 mL of CH_2Cl_2, 3-(trimethylsilyl)propargyl alcohol (0.45 mL, 3.0 mmol) and 2,6-di-*tert*-butylpyridine (0.74 mL, 3.2 mmol). This solution was then added dropwise *via* cannula to the stirred triflic anhydride, followed by a 1 mL CH_2Cl_2 wash to insure complete transfer. After about 15 min of stirring at −24 °C, 17.6 mL of dry hexanes were added dropwise over 15 min, during which time a white precipitate formed. After the addition of hexanes was complete, the flask was placed in a −78 °C bath and stirred at this temperature for 10 min. While still at −78 °C this two-phase slurry was filtered through a 5 mm pad of anhydrous sodium sulfate into a dry 50 mL double necked flask cooled to −78 °C, equipped with a stir bar and septum. After a 5.2 mL rinse of hexanes (also at −78 °C) was passed through the sodium sulfate pad a vacuum was slowly applied and most of the solvent was stripped off over about 1 h, bumping being avoided by applying the vacuum at −78 °C with rapid stirring, and after ~10 min the −78 °C bath was removed. Solvent evaporation was the only source of cooling, but with rapid enough evaporation the temperature of the flask stayed below −20 °C. After most of the hexanes was removed, the solution was cooled to −78 °C and 3 mL of THF were run down the side of the flask. This clear, water-white solution now waited at −78 °C for enolate formation to be complete.

Zinc enolate preparation was carried out according to the representative procedure for Table 1 using $Cp_2Zr(H)Cl$ (265.6 mg, 1 mmol), 4.0 mL of THF, 1-octyn-3-ol benzyl ether (250 μL, 1 mmol), and MeLi in ether (0.65 mL, 1 mmol) in the first 10 mL round bottom flask. CuCN (8.8 mg, 0.1 mmol), 1 mL of THF, Me_2Zn in heptane (0.42 mL, 0.52 mmol), and MeLi (0.45 mL, 0.72 mmol) were used to prepare the zincate/catalytic cuprate mixture in a 25 mL round bottom flask. 2-Cyclopenten-1-one (43 μL, 0.5 mmol) was added portionwise over 50 min, followed by an additional 10 min of reaction time. The triflate solution was then transferred *via* cannula into the 25 mL round bottom flask containing the 1,4-addition product, both at −78 °C. A rapid color change was observed, usually from red/brown to yellow. The reaction was then quenched after 5 min with 1 mL of pH 7 buffer. The two-phase mixture was then transferred to a separatory funnel containing an additional 14 mL of pH 7 buffer and 25 mL of ether, using 25 mL of ether as a rinse to aid in the transfer. The aqueous layer was extracted twice with 25 mL of ether. The combined organic layers were washed 3 times with 25 mL of brine and then dried over sodium sulfate. After concentration *in vacuo*, flash chromatography on silica gel using 15:1 (petroleum ether:ethyl acetate) afforded 148.9 mg (74%) of a clear oil: TLC [petroleum ether/ethyl acetate, 10/1] R_f 0.26; ^{1}H NMR δ 7.31 (m, 5H, aromatic), 5.61 (m, 1H, vinylic), 5.50 (m, 1H, vinylic), 4.56 (d, $J = 12$, 1H, benzylic), 4.36, 4.34 (d, $J = 12$, 1H, benzylic), 3.71 (m, 1H, allylic CH), 2.83 (m, 1H, allylic CH), 2.7−1.3 (m, 11H, aliphatic), 1.25 (m, 4H, CH_2), 0.86 (t, $J = 7$, 3H, CH_3), 0.10 (s, 9H, $SiMe_3$); ^{13}C NMR δ 217.01, 138.76, 134.31, 132.45, 128.30, 127.68, 127.41, 103.33, 86.59, 79.86, 69.98, 53.16, 43.71, 37.94, 35.66, 31.70, 27.55, 25.13, 22.60, 177.74, 14.05, 0.08; IR (neat) cm^{-1} 3029 (w), 2956 (s), 2931 (s), 2860 (s), 2175 (m), 1745 (s), 1497 (m), 1454 (m), 1406 (m), 1333 (w), 1250 (s), 1092 (m), 1068 (m), 1028 (w), 974 (s), 847 (m), 760 (m), 698 (w); CIMS, *m/e* (rel intensity) 428 ($M + NH_4^+$, 100), 411 ($M + H^+$, 5), 339 (39), 319 (11), 303 (40), 167 (7), 108 (8), 91 (26), 90 (15); HRCIMS calcd ($M + NH_4^+$) 428.2985, found 428.2979.

***trans*,*trans*-4-Hydroxy-3-[(*E*)-4-methyl-4-[(trimethylsilyl)oxy]-1-octenyl]-2-[3-(trimethylsilyl)-2-propynyl]cyclopentanone *tert*-butyldimethylsilyl ether (Table 3, entry 2)** was prepared according to the representative procedure above. The triflate was generated exactly as described above in the same quantity. $Cp_2Zr(H)Cl$ (245.8, 0.9 mmol), 3 mL of THF, 4-methyl-1-octyn-4-ol trimethylsilyl ether (261 μL, 0.9 mmol), and MeLi in ether (0.60 mL, 0.9 mmol) were used to make the methyl vinyl zirconocene. CuCN (7.0 mg, 0.078 mmol), 1 mL of THF, Me_2Zn in heptane (0.34 mL, 0.42 mmol), and MeLi (0.37 mL, 0.58 mmol) were used to prepare the zincate/catalytic cuprate mixture. Enone **3** (86.9 mg, 0.40 mmol) in 1 mL of THF was added *via* syringe over 45 min. After 5 min the triflate solution was added *via* cannula, and the reaction was quenched in the usual manner after stirring for 6 min. Workup and flash chromatography using 30:1 (petroleum ether:ethyl acetate) afforded 148.5 mg (69%) as a 1:1 mixture of isomers by ^{1}H NMR: TLC [petroleum ether/ethyl acetate, 4/1] R_f 0.59; ^{1}H NMR δ 5.61 (m, 1H, vinylic), 5.31 (m, 1H, vinylic), 4.06 (ddd, $J = 7, 7, 7$, 1H, ring CH), 2.8−2.0 (m, 8H, aliphatic), 1.40 (m, 2H, aliphatic), 1.27 (m, 4H, aliphatic), 1.151, 1.147 (s, 3H, CH_3), 0.87 (t, $J = 7$, 3H, CH_3), 0.86 (s, 9H, *tert*-butyl CH_3), 0.11 (s, 9H, $OSiMe_3$), 0.08 (s, 9H, $CSiMe_3$), 0.04 (s, 3H, TBS CH_3), 0.02 (s, 3H, TBS CH_3); ^{13}C NMR δ 213.89, 131.41, 131.27, 130.54, 130.43, 103.49, 86.77, 75.80, 72.89, 52.75, 52.62, 47.75, 45.74, 42.05, 27.43, 26.13, 25.69, 23.23, 18.12, 18.00, 14.21, 2.66, 0.06, −4.70; IR (neat) cm^{-1} 2958 (s), 2931 (s), 2900 (s), 2860 (s), 2175 (m), 1749 (s), 1250 (s), 1155 (s), 1119 (m), 1063 (m), 1030 (w), 883 (m), 849 (s), 777 (m), 760 (m); CIMS, *m/e* (rel intensity) 554 ($M + NH_4^+$, 55), 537 ($M + H^+$, 5), 464 (10), 447 (59), 354 (11), 315 (14), 205 (11), 173 (100), 90 (71); HRCIMS calcd ($M + H^+$) 537.3616, found 537.3615.

5,6-Didehydro-11-*O*-(*tert*-butyldimethylsilyl)-15-*O*-(4-methoxybenzyl) PGE_2 methyl ester (Table 3, entry 3) was prepared according to the representative procedure above. The propargyl triflate was generated on the same scale, the only difference being that methyl 7-hydroxy-5-heptynoate (477.5 mg, 3.00 mmol) was used to generate the electrophile.[29] Next, $Cp_2Zr(H)Cl$ (268.9 mg, 1 mmol), 3.5 mL of THF, 1-octyn-3-ol 4-methoxybenzyl ether (263 μL, 1 mmol), and MeLi in ether (0.68 mL, 1 mmol) were used to prepare the methyl vinyl zirconocene. CuCN (10.2 mg, 0.1 mmol), 1 mL of THF, Me_2Zn in heptane (0.42 mL, 0.52 mmol), and MeLi (0.50 mL, 0.74 mmol) were used to prepare the zincate/catalytic cuprate mixture. Enone **3** (109.1 mg, 0.5 mmol) in 1 mL of THF was added over 45 min. After 10 min the triflate solution was added *via* cannula, and the reaction was quenched and worked up after 5 min. Flash chromatography using 10:1 (petroleum ether:ethyl acetate) afforded 213.3 mg (71%) as a 1:1 mixture of isomers; TLC [petroleum ether/ethyl acetate, 4/1] 0.16, 0.18; Higher R_f diastereomer: ^{1}H NMR δ 7.22 (m, 2H, aromatic *meta* to OMe), 6.84 (m, 2H, aromatic *ortho* to OMe), 5.56 (m, 2H, vinylic), 4.51 (d, $J = 12$, 1H, benzylic), 4.26 (d, $J = 12$, 1H, benzylic), 3.78 (s, 3H, $ArOCH_3$), 3.72 (ddd, $J = 6, 6, 6$, 1H, allylic CH), 3.64 (s, 3H, CO_2Me), 2.8 (m, 1H, allylic CH), 2.39 (t, $J = 8$, 2H, CH_2 adjacent to the ester), 2.7−1.1 (m, 17H, aliphatic), 0.87 (s, 9H, *tert*-butyl CH_3), 0.85 (t, $J = 7$, 3H, CH_3), 0.06 (s, 3H, TBS CH_3), 0.05 (s, 3H, TBS CH_3); ^{13}C NMR δ 213.50, 173.64, 159.01, 134.59, 131.61, 130.86, 129.20, 113.70, 81.00, 79.57, 72.93, 69.86, 55.26, 52.78, 52.10, 51.53, 47.71, 35.87, 32.74, 31.70, 25.72, 25.27, 24.10, 22.60, 20.17, 18.16, 17.99, 16.62, 14.04, −4.49, −4.70; IR (neat) cm^{-1} 2954 (s), 2929 (s), 2856 (s), 2220 (w), 1738 (s), 1707 (s) 1612 (m), 1585 (m), 1512 (s), 1439 (m), 1244 (m), 1034 (m); CIMS, *m/e* (rel intensity) 616 ($M + NH_4^+$, 52), 598 (M^+, 5), 541 (5), 446 (8), 330 (3), 194 (3), 137 (14), 121 (PMB^+, 100); HRCIMS calcd ($M + NH_4^+$) 616.4033, found 616.4021. Lower R_f distereomer: ^{1}H NMR δ 7.21 (m, 2H, aromatic *meta* to OMe), 6.85 (m, 2H, aromatic *ortho* to OMe), 5.54 (m, 2H, vinylic), 4.49 (d, $J = 12$, 1H, benzylic), 4.25 (d, $J = 12$, 1H, benzylic), 3.78 (s, 3H, $ArOCH_3$), 3.71 (ddd, $J = 6, 6, 6$, 1H, allylic CH), 3.64 (s, 3H, CO_2Me), 2.78 (m, 1H, allylic CH), 2.39 (t, $J = 8$, 2H, CH_2 adjacent to the ester), 1.76 (tt, $J = 8, 8$, 2H, CH_2), 2.7−1.1 (m, 15H, aliphatic), 0.87 (s, 9H, *tert*-butyl CH_3), 0.86 (t, $J = 7$, 3H, CH_3), 0.05 (s, 3H, TBS CH_3), 0.04 (s, 3H, TBS CH_3); ^{13}C NMR δ 213.45, 173.62, 159.06, 134.74, 131.81, 130.78, 129.22, 113.74, 81.01, 79.39, 72.76, 69.71, 55.27, 53.00, 52.39, 51.53, 47.69, 25.79, 32.77, 31.79, 25.72, 25.09, 24.11, 22.59, 20.18, 18.17, 18.03, 16.71, 14.09, −4.50, −4.73; IR (neat) cm^{-1} 2954 (s), 2929 (s), 2856 (s) 2220 (w), 1738 (s), 1707 (s), 1612 (m), 1585 (m), 1512 (s), 1439 (m), 1244 (m), 1034 (m); CIMS, *m/e* (rel intensity) 616 ($M + NH_4^+$, 25), 599 ($M + H^+$, 4), 541 (9), 137 (16), 121 (PMB^+, 100); HRCIMS calcd ($M + NH_4^+$) 616.4033, found 616.4015.

***trans*,*trans*-2-(1-Hydroxyhexyl)-3-((*E*)-1-octenyl)-4-isopropylcyclohexanone (Scheme 6, use of stoichiometric cuprate)** was prepared according to the representative procedure for Table 2, with the exception being that stoichiometric $Me_2Cu(CN)Li_2$, generated from CuCN (88.9 mg, 1 mmol) and MeLi in ether 1.24 mL, 2 mmol), was used to effect the 1,4 addition and enolate trapping, as a control experiment, to afford 110.6 mg (63%) of product.

Methyl 7-hydroxy-9-methyl-8-(1-oxopropyl)-13-thiophenoxy-(*E*)-10-tridecenoate (Scheme 7) was prepared according to the representative procedure above using $Cp_2Zr(H)Cl$ (260.8 mg, 1 mmol), 3.5 mL of THF, 3-butynyl phenyl sulfide (158 μL, 1 mmol), and MeLi in ether (0.635 mL, 1 mmol) in the first round bottom flask. CuCN (8.2 mg, 0.1 mmol), 1 mL of THF, Me_2Zn in heptane (0.42 mL, 0.52 mmol), and MeLi (0.45 mL, 0.72 mmol) were used to prepare the zincate/catalytic cuprate mixture. (*E*)-4-Hexen-3-one (59 μL, 0.5 mmol) was added neat *via* syringe over 60 min, followed by 50 min of additional reaction time. Methyl 7-oxoheptanoate (121 μL, 0.75 mmol) in 1 mL of THF was added at −78 °C. After 5 min the reaction was quenched in the hood with 3% HCl, rather than pH 7 buffer. Workup and flash chromatography using 4:1 (petroleum ether:ethyl acetate) afforded 121.4 mg (58%) of two higher R_f diastereomers and 41.4 mg (20%) of two lower R_f diastereomers, for a total of four isomers by ^{1}H NMR: TLC [petroleum ether/ethyl acetate, 4/1] R_f 0.25, 0.19. Major isomers: ^{1}H NMR δ 7.22, 7.11 (m, 5H, aromatic), 5.51 (dt, $J = 15, 7$, 1H, vinylic), 5.26 (ddt, $J = 15, 9, 2$, 1H, vinylic), 3.64 (m, 1H, CH geminal to OH), 3.59, 3.58 (s, 3H, CO_2Me), 2.95−2.25 (m, 9H, aliphatic + O*H*), 2.21 (t, $J = 8$, 2H, CH_2 adjacent to ester), 1.6−1.2 (m, 8H, aliphatic), 0.97 (d, $J = 7$, 3H, CH_3), 0.86 (d, $J = 7$, 3H, CH_3); ^{13}C NMR δ 214.31, 175.80, 135.04, 129.01, 128.84, 128.30, 125.97, 125.85, 71.06, 60.86, 51.45, 40.41, 37.04, 36.29, 33.93, 33.46, 32.09, 28.97, 28.85, 26.01, 24.78, 18.95, 6.89; IR (neat) cm^{-1} 3508 (br m), 3072 (w), 2933 (s), 2860 (m), 1738 (s), 1695 (m), 1583 (w), 1458 (m), 1439 (m), 1375 (w), 1365 (m), 1254 (m), 1205 (m), 1173 (m), 1024 (k), 976 (m), 740 (m), 692 (m); CIMS, *m/e* (rel intensity) 438 ($M + NH_4^+$, 14), 421 ($M + H^+$, 21), 311 (9), 280 (27), 263 (100), 229 (8), 205 (10), 176 (84), 159 (31), 123 (14); HRCIMS calcd ($M + NH_4^+$) 438.2678, found 438.2691, calcd ($M + H^+$) 421.2413, found 421.2419. Minor isomers: ^{1}H NMR δ 7.15, 7.27 (m, 5H, aromatic), 5.44 (m, 2H, vinylic), 3.80 (m, 1H, CH geminal to OH), 3.64, 3.63 (s, 3H, CO_2Me), 3.0−2.1 (m, 11H, aliphatic + O*H*), 1.4−1.2 (m, 8H, aliphatic), 1.0−0.9 (m, 6H, overlapped CH_3); ^{13}C NMR δ 214.15, 174.19, 136.39, 134.93, 129.19, 128.88, 128.38, 127.95, 125.96, 71.99, 71.24, 62.42, 62.11, 51.48, 39.99, 36.89, 36.42, 33.93, 33.68, 33.48, 31.97, 31.83, 28.94, 25.76, 24.83, 18.51, 7.15; IR (neat) cm^{-1} 3498 (br m), 3055 (w), 2935 (s), 2860 (s), 1738 (s), 1695 (s), 1583 (m), 1460 (m), 1439 (s), 1375 (m), 1365 (m), 1252 (s), 1203 (s), 1173 (m), 1024 (m), 740 (s); CIMS, *m/e* (rel intensity) 438 ($M + NH_4^+$, 26), 421 ($M + H^+$, 72), 403 (12), 313 (21), 311 (16), 280 (18), 264 (29), 263 (100), 262 (20), 229 (20), 205 (14), 176 (93), 159 (55), 123 (33), 110 (25), 99 (10); HRCIMS calcd ($M + NH_4^+$) 438.2678, found 438.2668, calcd ($M + H^+$) 421.2413, found 421.2416.

***trans*-4-Isopropyl-3-((*E*)-1-octenyl)cyclohexanone (Table 4, entry 1)** was prepared according to the representative procedure for Table 1, with the exception that $ZnCl_2$·TMEDA (128.9 mg, 0.51 mmol) and MeLi in ether (1.0 mL, 1.53 mmol) were used to generate the $LiMe_3Zn$, to afford 102.5 mg (81%) of product.

Table 4, entry 2 *cf.* Table 1, entry 5.

Table 4, entry 3 was prepared according to the representative procedure for Table 1, with the exception that all MeLi was used as a solution in THF/cumene (1.14 M) to afford 114.5 mg (91%) of product.

Table 4, entry 4. Prepared according to the representative procedure for Table 1, with the exception that Me_3NiLi, generated from $NiCl_2$ (68.0 mg, 0.52 mmol) and MeLi in ether (0.98 mL, 1.57 mmol), was used as the source of "soft" MeLi to afford 97.1 mg (77%) of product.

Table 4, entry 5. Prepared according to the representative procedure for Table 1, with the exception that Me_3MnLi, generated from $MnCl_2$ (67.8 mg, 0.54 mmol) and MeLi in ether (1.10 mL, 1.61 mmol), was used as the source of "soft" MeLi to afford 95.6 mg (76%) of product.

Equation 2. The product was prepared according to the representative procedure for Table 1, with the exception that 20 mol % Me_2CuLi, generated from CuI (20.7 mg, 0.1 mmol) and MeLi in ether (0.14 mL, 0.2 mmol), was used as the source of catalytic cuprate to afford 115.3 mg (92%) of product.

3-Butyl-3,5-dimethylcyclohexanone (Scheme 10). In a 10 mL pear-shaped flask, equipped with a stir bar and having been cooled under a stream of argon, was placed 1 mL of ether and thiophene (146 μL, 1.8 mmol). After cooling to −78 °C, *n*-BuLi in hexanes (0.81 mL, 1.8 mmol) was added slowly *via* syringe. The reaction mixture was stirred for 15 min before being warmed to −25 °C for 40 min. After recooling to −78 °C this solution was then transferred *via* cannula to another dry 10 mL round bottom flask containing solid $ZnCl_2$ (from 1.8 mL of a 0.5 M solution in THF, the THF having been removed under high vacuum, 0.9 mmol), followed by a 0.5 mL ether wash. While still at −78 °C, *n*-BuLi (0.405 mL, 0.9 mmol) was added prior to warming to 0 °C for 10 min. A small amount of white precipitate was observed which increased when the solution was cooled back to −78 °C. ThCu(CN)Li (0.56 mL of a 0.25M solution, 0.14 mmol) was then added followed by $BF_3 \cdot Et_2O$ (86 μL, 0.7 mmol). After 5 min at −78 °C, 3,5-dimethyl-2-cyclohexen-1-one (100 μL, 0.7 mmol) was added neat all at once. The reaction was stirred for 3 h at −78 °C, during which time the white precipitate dissolved. The mixture was quickly poured into a separatory funnel containing 50 mL of ether and 20 mL of a 9:1 saturated aqueous NH_4Cl/concentrated NH_4OH solution. The aqueous layer was extracted once with 25 mL ether. The combined organics were washed three times with 25 mL of brine and then dried over magnesium sulfate. Concentration *in vacuo* followed by flash chromatography on silica gel using 20:1 (petroleum ether:ethyl acetate) afforded 110.2 mg (86%) as a yellow liquid: TLC [petroleum ether/ethyl acetate, 10/1] R_f 0.39; ^{1}H NMR δ 2.28 (dm, J = 13, 1H, CH_2), 2.11 (ddd, J = 14, 3, 3, 1H, CH_2), 2.06 (d, J = 13, 1H, CH_2), 1.92 (m, 1H, CH), 1.84 (m, 1H, CH_2), 1.67 (dm, J = 14, 1H, CH_2), 1.25−1.05 (m, 7H, aliphatic), 0.97 (d, J = 6, 3H, CH_3), 0.94 (s, 3H, CH_3), 0.84 (t, J = 8, 3H, CH_3); ^{13}C NMR δ 212.13, 53.58, 49.22, 44.84, 37.59, 37.38, 28.96, 28.33, 25.59, 23.28, 22.52, 14.03; IR (neat) cm^{-1} 2956 (s), 2929 (s), 2872 (s), 1713 (m), 1458 (w), 1421 (w), 1379 (w), 1363 (w), 1336 (w), 1273 (w), 1227 (w), 1082 (w); EIMS, *m/e* (rel intensity) 182 (M^+, 2) 167 (5), 125 (64), 83 (61), 69 (100), 55 (86), 43 (15); HREIMS calcd (M^+) 182.1671, found 182.1674.

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