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Cooperative Titanocene and Phosphine Catalysis: Accelerated C–X Activation for the Generation of Reactive Organometallics

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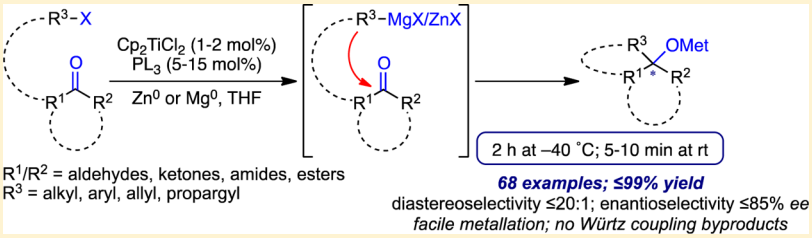
Supporting Information



ABSTRACT: The study presented herein describes a reductive transmetalation approach toward the generation of Grignard and organozinc reagents mediated by a titanocene catalyst. This method enables the metalation of functionalized substrates without loss of functional group compatibility. Allyl zinc reagents and allyl, vinyl, and alkyl Grignard reagents were generated in situ and used in the addition to carbonyl substrates to provide the corresponding carbinols in yields up to 99%. It was discovered that phosphine ligands effectively accelerate the reductive transmetalation event to enable the metalation of C–X bonds at temperatures as low as −40 °C. Performing the reactions in the presence of chiral diamines and amino alcohols led to the enantioselective allylation of aldehydes.

INTRODUCTION

Organozinc and organomagnesium intermediates have become increasingly essential to the development of new synthetic methods and in the assembly of biologically active natural products.[1] Although generally useful for constructing a diverse array of carbon–carbon and carbon-heteroatom bonds, these reagents have become fixtures in the transition metal-catalyzed cross-couplings.[2] As a result, establishing new methods to prepare these synthetically versatile compounds is paramount to the construction of structurally complex molecular architectures.[3] Pioneered over a century ago, the oxidative insertion of Zn^0 or Mg^0 into C–X bonds is still the most direct way to generate these organometallics[4] despite the challenges associated with their use.[5,6] Therefore, recent studies have focused on the clean and mild activation of these readily available metals to generate the corresponding organometallics without resorting to less attractive conventional activating agents such as I_2,[7] $TMSCl/Br(CH_2)_2Br$,[8] or the expensive and highly reactive Rieke metals.[5b,9] Of these, the accelerating effect of LiCl on metal C–X insertion, discovered by Knochel and co-workers,[8,10] is one of the most widely used methods for the generation of organozinc and Grignard reagents due to its operational simplicity.[11] Alternatively, Cu^{I},[12] Pd^{II},[13] Ni^{II},[14] Mn^{II},[15] In^{III},[16] Fe^{III},[17] Al^{III}[18] and Co^{II}[19] complexes can facilitate organozinc formation while the combination of $FeCl_2$ (5 mol %), $MgBr_2$ (5 mol %), and EtBr (10 mol %) will catalyze the formation of aryl Grignard reagents derived from 2-chloropyridines.[20] In contrast, we sought a universal method for the formation of both organozinc and organomagnesium reagents under ambient conditions using an inexpensive, shelf-stable catalyst. To achieve this objective, we hypothesized that commercially available Cp_2TiCl_2 would enable the insertion of unactivated Zn dust or magnesium turnings from readily available alkyl halides via a reductive transmetalation event.[21] Herein, we present the successful implementation of this substrate activation approach, for the generation of organozinc and organomagnesium reagents.

In recent years, a number of prominent research groups have studied the catalytic behavior of titanocene catalysts[22] to enable some truly remarkable C–C bond constructions.[23] Ding,[21b] Roy,[24] and Oltra/Cuerva,[25] independently showed that the slow addition of allyl bromide to stoichiometric Cp_2TiCl (2.5 equiv) and benzaldehyde afforded the corresponding homoallylic alcohols in good yields (eq 1).[26] A catalytic variant employing Mn(0) as the stoichiometric reductant was later discovered to facilitate the allylation event.[27] Although the allylation of aldehydes proceeded smoothly under these conditions, the addition to ketones and esters proved less effective.[26l] Reports from Umani-Ronchi,[28] Robles and Oltra,[29] Little,[21h] and Shimizu[30] highlight the use of Cp_2TiCl_2 (cat.)/Mn(0) in the addition of α-halo carbonyl derivatives to aldehydes. Ding has proposed that the corresponding titanocene-catalyzed Reformatsky reaction with Zn(0) dust proceeds through a zinc enolate in the C–C bond-forming event.[31] To complement these studies, we discovered that the combination of Cp_2TiCl_2 (1 mol %) and phosphine (5 mol %) promoted the formation and subsequent carbonyl addition of

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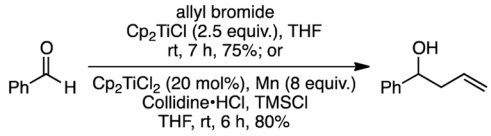
Y. Ding (1992), S. Roy (2004) and A. Gansäuer (2009):



(1)

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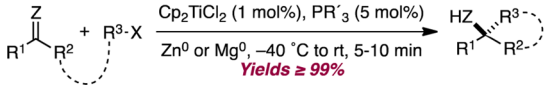


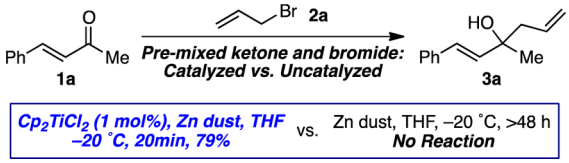
(2)

$R^1C(=Z)R^2$ = aldehydes, ketones, esters, amides
R^3 = alkyl, benzyl, allyl, propargyl, vinyl, aryl; X = Br, Cl, I

organozinc and Grignard reagents at temperatures as low as −40 °C and in as little as 5 min (eq 2).[21c,d]

RESULTS AND DISCUSSION

The allylation of carbonyl derivatives is of fundamental importance to the field of organic synthesis, as it constitutes one of the principal methods for constructing the ubiquitous β-hydroxy carbonyl motif.[32] Thus, we initially evaluated our hypothesis that Cp_2TiCl_2 will catalyze the activation of C−X bonds for Zn or Mg insertion, in the generation of allylzinc and allyl Grignard reagents from their corresponding allyl halides.[21d] The metalation of allyl bromide (**2a**) in the presence of enone **1a**, zinc dust, and Cp_2TiCl_2 (1 mol %) afforded alcohol **3a** in 79% yield at −20 °C and 99% in a mere 5 min at room temperature (eq 3). Interestingly, enone **1a** was

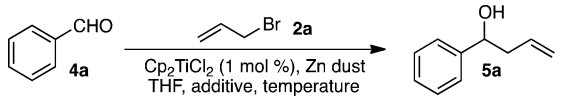


(3)

recovered quantitatively in the absence of Cp_2TiCl_2 at −20 °C. Although Cp_2TiCl_2 is clearly playing a role in the formation of homoallylic alcohol **3a**, we were uncertain as to the nature of the nucleophilic allyl reagent involved in the C−C bond-forming event. Based on the sluggish reactivity of (η^3-allyl)$TiCp_2Cl$ with ketones,[25a,33] we speculated that the rapid allylation of **1a** indicated involvement of an allylzinc species.[34] It is noteworthy that no Cp_2TiCl-catalyzed Würtz, McMurry, or pinacol coupling products were detected.[35] Encouraged by this preliminary result, we sought to gain further insight into the role of titanocene in the metalation event.

Effect of Phosphine Additives. We initially chose to further probe this temperature dependence on the efficiency of allylzinc formation from allyl bromide (**2a**) using benzaldehyde (**4a**) as the terminal electrophile (Table 1). Although excellent yields of the resulting homoallylic alcohol **5a** were obtained in 5−10 min at temperatures as low as −20 °C in the allylation of benzaldehyde (**4a**) with Cp_2TiCl_2 (1 mol %) and Zn(0) dust, performing the reaction at lower temperatures resulted in a significant decrease in yield (entries 1−5). Whereas allylzinc reagents are known to react readily with aldehydes at temperatures as low as −78 °C, the titanocene-catalyzed metalation of **2a** failed to occur at −40 °C and lower, leading to a quantitative recovery of aldehyde **4a** (entries 4 and 5). We discovered that upon addition of 5 mol % PPh_3, the rate of metalation increased to provide alcohol **5a** in 96% yield at −40 °C (entry 6). The addition of trialkyl phosphines and bisphosphines (PCy_3, dppp, dppe, dppb, dppf, and

Table 1. Temperature and Phosphine Effects[a]



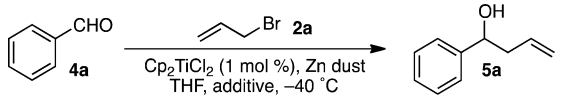
entry	additive	temperature	yield[b] (%)
1	–	rt	98
2	–	0 °C	95
3	–	−20 °C	91
4	–	−40 °C	NR[c]
5	–	−78 °C	NR[c]
6	5 mol % PPh_3	−40 °C	96
7	5 mol % PCy_3	−40 °C	95
8	5 mol % dppe	−40 °C	>99
9	5 mol % dppp	−40 °C	>99
10	5 mol % dppb	−40 °C	50
11	5 mol % dppf	−40 °C	99
12	5 mol % (±)-BINAP	−40 °C	98
13	1 equiv PCy_3	−78 °C	10

[a]Reactions conducted in THF using 0.4 mmol of benzaldehyde **4a**, 1.0 mmol of allyl bromide **2a**, 1 mol % Cp_2TiCl_2, 1.0 mmol zinc dust and the phosphine indicated (see Supporting Information for details). [b]Isolated yields. [c]Reaction was run for ≥48 h.

(±)-BINAP) similarly increased the yield of **5a** at low temperatures (entries 7−12). However, at −78 °C the reaction proved inefficient even in the presence of a stoichiometric amount of phosphine (entry 13). Additionally, the enhanced metalation efficiency was observed irrespective of the phosphine cone angle as illustrated by the excellent yields of **5a** obtained with dppe (125°) and PCy_3 (170°). These results would indicate that Cp_2TiCl_2 can serve as a catalyst for the formation of organozinc intermediates in the absence of an electrophile at low temperatures.

To compare phosphines of disparate size and basicity, we examined PPh_3 and $^nBu_3P$ at varying concentrations (Table 2). Although, PPh_3 provided excellent yields of alcohol **5a** in 2−50 mol % (entries 1−5), the addition of 2 or 5 mol % of $^nBu_3P$ failed to facilitate metalation at low temperatures (entries 6 and 7). The addition of 10, 20, and 50 mol % $^nBu_3P$ provided

Table 2. Comparison of PPh_3 and P^nBu_3 at Various Loadings[a]



entry	additive	yield[b] (%)
1	2 mol % PPh_3	91
2	5 mol % PPh_3	96
3	10 mol % PPh_3	96
4	20 mol % PPh_3	93
5	50 mol % PPh_3	>99
6	2 mol % P^nBu_3	trace
7	5 mol % P^nBu_3	trace
8	10 mol % P^nBu_3	29
9	20 mol % P^nBu_3	42
10	50 mol % P^nBu_3	33

[a]Reactions conducted in THF using 0.4 mmol of benzaldehyde **4a**, 1.0 mmol of allyl bromide **2a**, 1 mol % Cp_2TiCl_2, 1.0 mmol zinc dust and the phosphine indicated (see Supporting Information for details). [b]Isolated yields.

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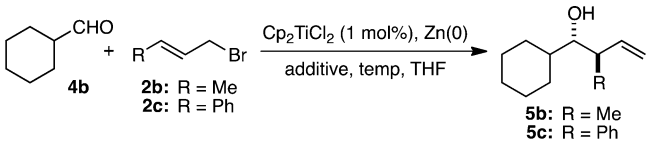
alcohol **5a**, albeit in low yield (entries 8−10). In each case, the starting material could be recovered with excellent mass recovery. Examination of the titanocene-catalyzed metalation with Mg(0) turnings likewise provided alcohol **5a** in excellent yields at temperatures as low as −40 °C. Recent work from our group on the role of phosphines in zinc acetylide additions to aldehydes corroborate these findings, and indicate that phosphine is likely involved in the metalation event and present in the transition state leading to the new C−C bond.[21a,c,36] Although the exact role of phosphine is unclear at this time, this modification appears quite general when performing the metalation of allyl halides at low temperatures.

While certainly playing a role in the formation of alcohol **5a** at lower temperatures, it was unclear whether the added phosphine was simply affecting the efficiency of allylzinc formation, involved in the C−C bond-forming event, or both. Speculating that if phosphine were involved in the transition state leading to homoallylic alcohol formation,[36,37] examining the diastereoselectivity in the crotylation of aldehydes would shed light on the nature of this unusual phosphine effect. Thus, we targeted homoallylic alcohols **5b** and **5c** resulting from the crotylation of cyclohexyl carboxaldehdye **4b** with crotyl bromide (**2b**) and cinnamyl bromide (**2c**) respectively (Table 3).[38] The addition of **2b** to aldehyde **4b** using Cp_2TiCl_2 (1 mol %) and zinc dust led to an excellent yield (90%) of homoallylic alcohol **5b** in a 4:1 diastereomeric ratio favoring the *anti* stereoisomer (entry1). That diastereoselectivity was nominally increased to 5:1 when the temperature was reduced to −20 °C (entry 2). Although, further attempts to lower the reaction temperature to −40 °C proved futile, the addition of PPh_3 (5 mol %) restored the combined reactivity of Cp_2TiCl_2 and zinc dust and improved the ratio of *anti-syn* adducts to 9:1 (entry 3). Employing dppe in place of PPh_3 led to only a slight decrease in diastereoselectivity (entry 4). The addition of cinnamyl bromide **2c** to aldehyde **4b** at room temperature provided homoallylic alcohol **5c** in a 14:1 *anti-syn* ratio (entry 5). Whereas, the addition of 5 mol % PPh_3 permitted a −40 °C reaction temperature leading to an increase in diastereoselectivity favoring *anti*-**5c** in 21:1 dr (entry 6). Unlike crotyl bromide **2b**, the addition of dppe at −40 °C with **2c** provided alcohol **5c** in comparable stereoselectivity to PPh_3 (entry 7).

Table 3. Diastereoselective Crotylation and Cinnamylation[a]

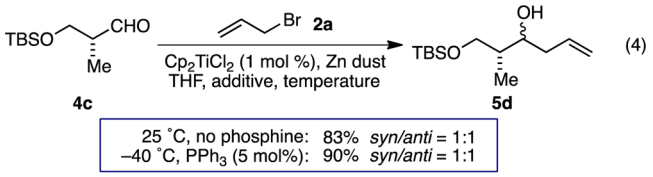


entry	2	temperature	additive	yield (%)[b]	anti:syn[c]
1	**2b**	rt	–	90	4:1
2	**2b**	−20 °C	–	83	5:1
3	**2b**	−40 °C	PPh_3	59	9:1
4	**2b**	−40 °C	dppe	51	6.5:1
5	**2c**	rt	–	90	14:1
6	**2c**	−40 °C	PPh_3	88	21:1
7	**2c**	−40 °C	dppe	87	20:1

[a]Reactions conducted in THF using 0.4 mmol of cyclohexanecarboxaldehyde **4b**, 1.0 mmol of appropriate bromide, 1 mol % Cp_2TiCl_2, 1.0 mmol zinc dust and the phosphine indicated (see Supporting Information for details). [b]Isolated yields. [c]Ratios determined by 500 MHz ^{1}H NMR.

Although the added phosphine appears to affect the stereochemical outcome, the observed increase in diastereoselectivity may be simply a kinetic effect resulting from a broader temperature profile available for the metalation event. We are continuing to examine the role of phosphines in these and similar reactions to more fully understand this enhancement.

Although the addition of phosphine enhanced the diastereoselection in the crotylation of aldehydes under the titanocene reductive metalation conditions, the stereoselective allylation of α-chiral aldehydes proved more challenging. Treatment of enantioenriched aldehyde **4c** with allyl bromide **2a** under our standard conditions yielded homoallylic alcohol **5d** in good yield as a 1:1 mixture of diastereomers (eq 4).[39] Likewise, when



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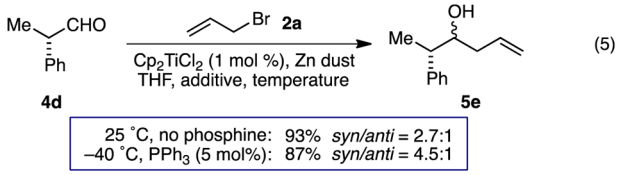

(5)

the allylation of **4c** was performed in the presence of PPh_3 (5 mol %) at −40 °C, no appreciable 1,2-stereoinduction was observed in the formation of alcohol **5d**. Allylation of aldehyde **4d** bearing an α-phenyl substituent at 25 °C in the absence of phosphine provided alcohol **5e** in 93% yield and 2.7:1 ratio favoring the *anti* stereoisomer. A modest increase in the diastereoselectivity to 4.5:1 was observed in the presence of PPh_3 (5 mol %) at −40 °C (eq 5). Although dependent on the size of the α-substituent, 1,2-stereoinduction is observed in the allylation of α-chiral aldehydes when paired with an *in situ* generated allylmetal species.

Enantioselective Allylations. The enantioselective addition of highly reactive organometallic reagents is a major challenge in organic synthesis due to their propensity for rapid, uncontrolled carbonyl additions even at low temperatures.[40] As a result, a stoichiometric amount of chiral ligand is often required for useful levels of selectivity.[41] Our observation that phosphine additives facilitated low temperature metalation led us to hypothesize that an enantioselective allylation with a highly reactive allylmetal reagent could be performed with a catalytic amount of chiral agent. By controlling the temperature and rate of metalation with the addition of phosphine, the effective concentration of chiral ligand-bound reagent is maximized while minimizing the amount of unligated organometallic intermediate. Using a series of well-established chiral diols, diamines and β-amino alcohols **L1**−**L9** in asymmetric organozinc additions to aldehydes, we began evaluating our hypothesis by examining the allylation of benzaldehyde (**4a**) with allyl bromide (**2a**) at −40 °C in the presence of dppe (15 mol %) and chiral ligand (Table 4). Employing the salen-derived ligand **L1**[42] and Schiff base **L2**[43] provided alcohol (+)-**5a** in excellent yield and 18 and 8% *ee*, respectively (entries 1 and 2). Indene-derived amino alcohol **L3**[44] gave alcohol (+)-**5a** in 67% *ee*, and chiral β-amino alcohols **L4**[45] and **L5**[46] proceeded in 12 and 67% *ee*, respectively (entries 3−5).[47] Likewise, diamine **L6** underwent allylation in 68% *ee* (entry

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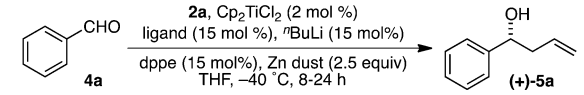
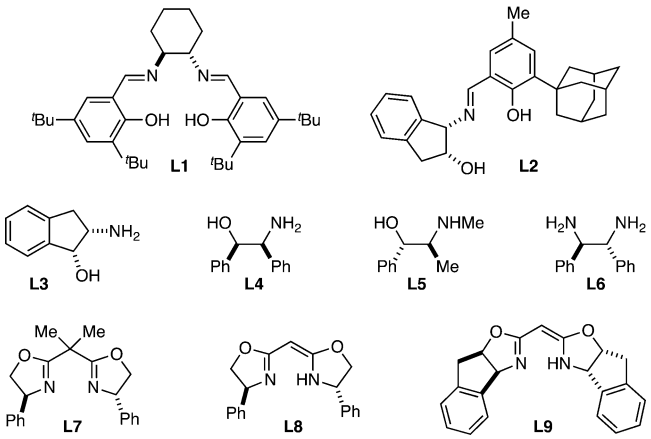
Table 4. Asymmetric Allylation of Benzaldehyde[a]





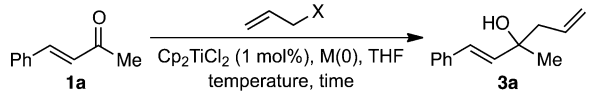
entry	ligand	yield[b]	% *ee*[c]
1	**L1**	92	18
2	**L2**	97	8
3	**L3**	22	67
4	**L4**	99	12
5	**L5**	22	67
6[d]	**L6**	28	68
7	**L7**	5	85
8	**L8**	95	21
9[d]	**L9**	97	8

[a]Reactions conducted in THF using 0.4 mmol of benzaldehyde **4a**, 1.0 mmol of allyl bromide **2a**, 1 mol % Cp_2TiCl_2, 1.0 mmol zinc dust, 0.06 mmol dppe and deprotonated ligand as indicated (see Supporting Information for details). [b]Isolated yield after chromatographic purification. [c]Ratios determined by chiral HPLC. [d]50 mol % of ligand used.

6).[48] In contrast, bis-oxazoline **L7** resulted in the highest level of enantioselectivity (85% *ee*), but unfortunately also gave alcohol (+)-**5a** in the lowest yield (entry 7).[49] However, oxazoline derivatives **L8** and **L9** proceeded in excellent yields but only 21 and 8% *ee*, respectively (entries 8 and 9).[50] It should be noted that the addition of chiral phosphines alone failed to provide any measurable enantioselectivity in the allylation, and that prolonged reaction times did not lead to an increase in yield or enantioselectivity. These results support our hypothesis that the enantioselective addition of an allyl organozinc reagent is attainable through a kinetically controlled metalation event at low temperatures in the presence of phosphine.

Formation of Allylzinc and Allylmagnesium Reagents. We next turned our attention toward evaluating the affect the halogen on the allyl substrate would have on the metalation event (Table 5). Although, bromide **2a** provided alcohol **3a** in excellent yield with unactivated Zn(0) dust or Mg(0) turnings (entries 1 and 2), this was not found to be a general trend for other allyl halides. Subjection of allyl iodide provided the homoallylic alcohol **3a** in slightly diminished yield with zinc dust at room temperature, but the use of magnesium turnings required slightly elevated temperatures to provide the product in 56% yield (entries 3 and 4). In contrast, allyl chloride failed to undergo any reaction in the presence of zinc dust, but gave

Table 5. Metallation of Allyl Halides[a]



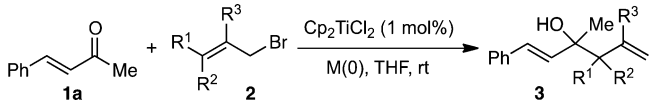
entry	X	M(0)	temperature	yield[b] (%)
1	Br	Zn	rt	99
2	Br	Mg	rt	99
3	I	Zn	rt	78
4	I	Mg	50 °C	56
5	Cl	Zn	rt	NR
6	Cl	Mg	50 °C	88

[a]Reactions conducted in THF using 0.4 mmol of enone **1a**, 1.0 mmol of appropriate halide, 1 mol % Cp_2TiCl_2, 1.0 mmol zinc dust or magnesium turnings at room temperature (see Supporting Information for details). [b]Isolated yields.

3a in 88% yield using Mg(0) at 50 °C (entries 5 and 6). It warrants mention that in comparison to the allyl halides mentioned, the corresponding acetate, methyl carbonate, and trifluoroacetate were unreactive.

With the appropriate halide identified, we turned our attention toward examining the effect of C2 and C3 allyl substitution using a series of allyl bromides with enone **1a** (Table 6). In general, excellent yields of alcohol **3** were

Table 6. Titanium-catalyzed Metallation of Substituted Allyl Bromides[a]



entry	M(0)	R^1	R^2	R^3	2	3	yield[b] (%)
1	Zn	CH_3	H	H	**2b**	**3b**	85[c]
2	Mg	CH_3	H	H	**2b**	**3b**	89[c]
3	Zn	Ph	H	H	**2c**	**3c**	90[c]
4	Mg	Ph	H	H	**2c**	**3c**	91[c]
5	Zn	CH_3	CH_3	H	**2d**	**3d**	95
6	Mg	CH_3	CH_3	H	**2d**	**3d**	91
7	Zn	H	H	CH_3	**2e**	**3e**	64
8	Mg	H	H	CH_3	**2e**	**3e**	95

[a]Reactions conducted in THF using 0.4 mmol of enone **1a**, 1.0 mmol of appropriate bromide, 1 mol % Cp_2TiCl_2, 1.0 mmol zinc dust or magnesium turnings at room temperature (see Supporting Information for details). [b]Isolated yields. [c]*syn*:*anti* = 1:1.

obtained within 5−10 min following treatment with either zinc dust or magnesium turnings in the presence of 1 mol % Cp_2TiCl_2. Crotyl and cinnamyl bromides **2b** and **2c** underwent allylation in an S_E2' fashion to provide a 1:1 mixture of *syn* and *anti* alcohols **3b** and **3c** respectively in 85−91% (entries 1−4).[34d,51] Likewise, prenyl bromide **2d** underwent addition in comparable fashion to yield alcohol **3d** containing congruent quaternary centers in excellent yields (entries 5 and 6). Methallyl bromide **2e** also underwent metalation and carbonyl addition in the presence of Zn and Mg to yield the desired alcohol **3e** in good yields (entries 7 and 8). Most notably, the allylation reaction proceeded smoothly at room temperature without the formation of Würtz coupling byproducts common in allyl Grignard generation.[52]

Application to the Reductive Transmetalation of Non-Allyl Substrates. Although the formation of allylzinc and allyl

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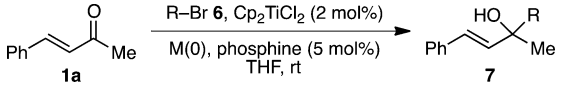
Grignard reagents proved exceptionally facile and efficient, we discovered that the activation/metalation of less activated alkyl bromides, and their subsequent addition to ketone **1a**, proved more difficult (Table 7). Consistent with our earlier findings

Table 7. Metallation of Non-allyl Halides[a]

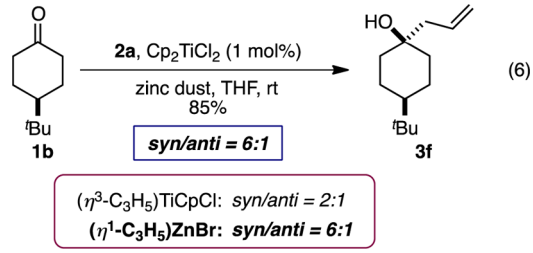


entry	M(0)	R–Br	additive	7	yield[b] (%)
1	Mg	^{n}BuBr (**6a**)	dppp	**7a**	41
2	Zn	^{n}BuBr (**6a**)	dppe	**7a**	17
3	Mg	$PhCH_2Br$ (**6b**)	dppp	**7b**	65
4	Zn	$PhCH_2Br$ (**6b**)	dppe	**7b**	44
5	Mg	Ph_2CHBr (**6c**)	dppe	**7c**	39
6	Mg	PhBr (**6d**)	dppp	**7d**	73
7	Mg	$(CH_3)_2CHBr$ (**6e**)	dppe	**7e**	24
8	Mg	$H_2C{=}CHBr$ (**6f**)	dppp	**7f**	49

[a]Reactions conducted in THF using 0.4 mmol of enone **1a**, 1.0 mmol of appropriate bromide, 1 mol % Cp_2TiCl_2, 1.0 mmol zinc dust or magnesium turnings at room temperature (see Supporting Information for details). [b]Isolated yields.

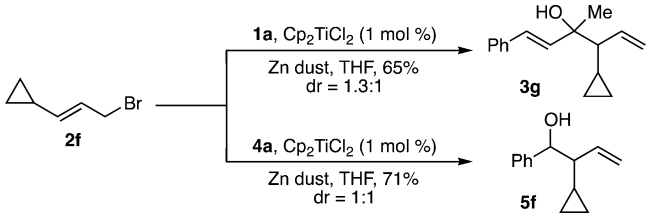
that added phosphines led to improved metalation/alkylation efficiency, we discovered that the presence of a bidentate phosphine (5 mol %) led to overall better yields of **7**. In general, magnesium turnings performed better than zinc dust in the reductive transmetalation, leading to better yields of alcohols **7a** and **7b**, while dppp and dppe gave comparable results under the same conditions (entries 1–4). The metalation and addition of *n*-butyl bromide (**6a**) and benzyl bromide (**6b**) proceeded in 41% and 65% yield, respectively in the presence of magnesium turnings (entries 1 and 3), whereas alcohols **7a** and **7b** were obtained in 17% and 44% using zinc dust as the reducing metal (entries 2 and 4). Treatment of diphenyl methyl bromide (**6c**) in the presence of Cp_2TiCl_2 (2 mol %) and Mg(0) was less effective than **6b**, providing alcohol **7c** in 39% yield (entry 5). However, bromobenzene (**6d**) readily underwent metalation and addition to ketone **1a** to give alcohol **7d** in 73% yield (entry 6). The titanocene-catalyzed metalation protocol also proved effective in the metalation of 2-bromopropane (**6e**) and vinyl bromide (**6f**) to provide alcohols **7e** and **7f** respectively, albeit in diminished yields (entries 7 and 8). Conventional methods of generating reactive organometallics, Grignard reagents in particular, are well described and would likely give higher yields in a direct comparison. However, given the difficultly of generating some reactive alkyl carbanions under comparably mild conditions using conventional strategies,[9a,b,53] these results highlight the utility of this titanocene-catalyzed reductive transmetalation protocol.

Mechanism of the Reductive Transmetalation. To gain insight into the mechanism of the titanocene-catalyzed reductive transmetalation and subsequent carbonyl addition event, we began by examining the role of titanium and zinc in the allylation of benzaldehyde (**4a**). No reaction was observed without the initial reduction of Cp_2TiCl_2, and full conversion to the corresponding alcohol took substantially longer (>6 h) in the absence of Cp_2TiCl. Additionally, we observed no reaction with stoichiometric Cp_2TiCl in the absence of zinc dust after prolonged reaction times (>24 h). Therefore, it would appear that both titanium and zinc are participating in the allylation. Although the *in situ* generated $ZnCl_2$ may act as a Lewis acid in the carbonyl addition step,[54] the addition of $ZnCl_2$ and stoichiometric Cp_2TiCl failed to provide alcohol **7a**. These results support our hypothesis that although an allyltitanium reagent is formed, a transmetalation to zinc is likely occurring prior to allylation.[55] The involvement of an allylzinc species is further corroborated by the addition of allylzinc chloride to enone **1a** to yield alcohol **2a** in reaction times comparable to those obtained in the presence of Cp_2TiCl_2 (cat.) and zinc dust.[34f,56] Finally, the diastereoselectivity observed in the allylation of 4-*t*-butylcyclohexanone (**1b**) gave a 6:1 ratio favoring the *syn* alcohol **3f**, which is more consistent with the addition of allylzinc bromide (dr = 6:1)[57] as compared to a 2:1 ratio of diastereomers observed with (η^3-allyl)TiCpCl (eq 6).[25a]



Although these results provide compelling support for the general mechanism described above,[58] further evidence for two rapid single electron reductions of allyl bromide by $Cp_2Ti^{III}Cl$ was obtained by utilizing vinylcyclopropane **2f** as the allylmetal precursor (Scheme 1).[59] If the substrate were to demonstrate

Scheme 1. Metallation of Cyclopropyl Allyl Bromide



radical character en route to metalation, we would expect to see strain-driven ring expansion of the cyclopropane. However, if titanium induces an inner sphere reduction of the allylbromide followed by rapid radical–radical annihilation, the cyclopropane ring should remain intact throughout the metalation process.[60] Treatment of **2f** and either enone **1a** or aldehyde **4a** to Cp_2TiCl_2 (1 mol %) and Zn(0) cleanly provided alcohols **3g** and **5f** respectively, absent any evidence of cyclopropane ring-opening.

On the basis of these findings, it appears that the Lewis acidic properties of *in situ* generated $M^{II}X_2$ and titanocene are not solely responsible for the overall efficiency of the metalation, and that Cp_2TiCl is likely participating in the formation of the organometallic intermediate responsible for the ultimate C–C bond formation. Taking into account the results obtained thus far, our working hypothesis involves initial reduction of the precatalyst Cp_2TiCl_2 followed by metalation of halide **2** or **6** to yield R-$Ti^{IV}Cp_2Cl$ **8** (Scheme 2).[24,26h] Reduction of the titanocene complex **8** provides R-$Ti^{III}Cp_2$ **9** to facilitate transmetalation to $M^{II}X_2$ leading to the formation of reagent **10** and the regeneration of $Cp_2Ti^{III}X$.[61] Subsequent addition of **10** to the carbonyl derivative ketone **1** or aldehyde **4** provides

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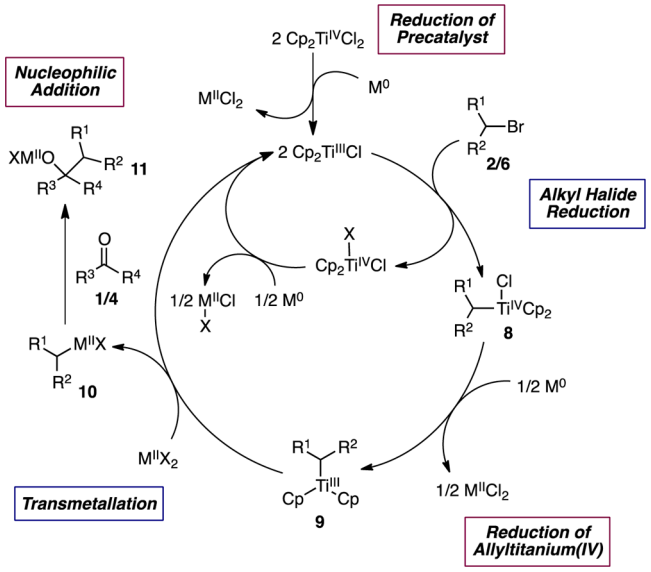
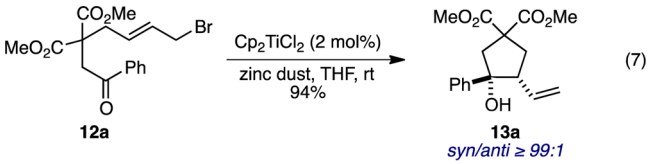
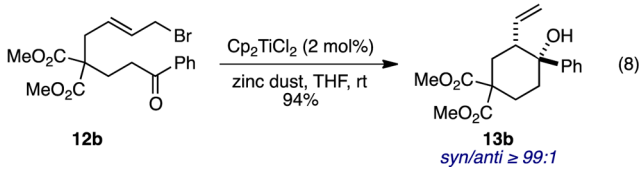
Scheme 2. Proposed Catalytic Cycle



the alkoxide **11**. The nature of X (e.g., Cl^-, RO^-, Br^-) ligated to titanocene at various stages of the catalytic cycle remains unclear at the present time. It bears mention that catalyst turnover is facilitated by transmetalation from titanocene to zinc. Although the exact role of phosphine is purely speculative at this stage, based on our previous work[21a,c,36] we postulate that it serves to stabilize low valent titanocene intermediates in the catalytic cycle, while increasing the reactivity of **10** through an unusual $P-M^{II}$ ligation.[62] This method constitutes a general way to prepare these versatile reagents in a mild and stoichiometric fashion.

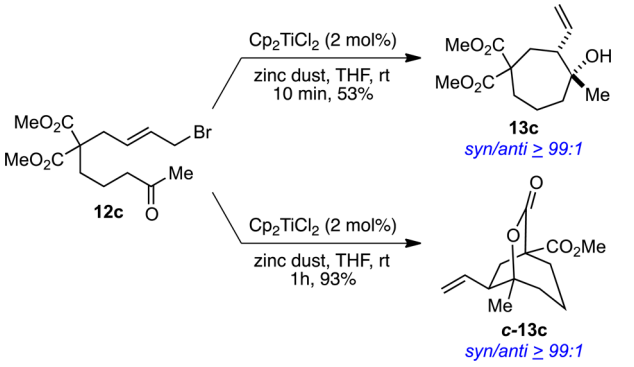
Highly Diastereoselective Intramolecular Carbonyl Additions. Given the preponderance of small carbocyclic ring systems in biologically active natural products,[63] we next examined the utility of the titanocene-catalyzed metalation-carbonyl addition protocol in the formation of 5- and 6-membered carbocycles. To that end, treatment of allylbromide **12a** with Cp_2TiCl_2 (2 mol %) and zinc dust provided cyclopentanol **13a** in 94% exclusively as the *syn* diastereomer after a mere 10 min at room temperature (eq 7).[64]





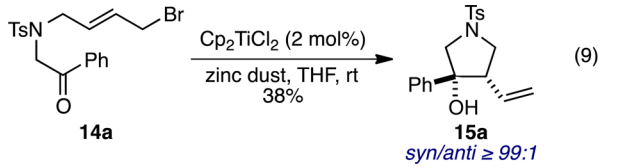
Interestingly, when polar aprotic solvents, such as acetonitrile and NMP, were employed the yield of **13a** was substantially reduced to 48% and 36% respectively, and chlorinated solvents led to little formation of the expected homoallylic alcohol. Using Mg(0) turnings in place of zinc dust provided only recovered ketone **12a**, whereas indium metal gave the cyclopentanol in 60% yield. Access to 6-membered carbocycles in a similar fashion was achieved by the intramolecular allylation of ketone **12b** to provide homoallylic alcohol **13b** in 94% yield (eq 8).[65] Likewise, cycloheptanol **13c** was obtained in 53% yield after only 10 min by subjection of ketone **12c** to our optimized conditions (Scheme 3).[66] However, when

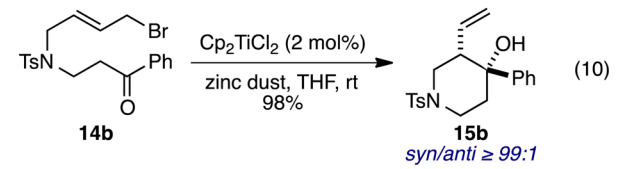
Scheme 3. Synthesis of Cycloheptanols



the reaction was stirred for 1 h, bridged bicycle ***c*-13c**, resulting from intramolecular transesterification of the methyl ester residing *syn* to the newly formed homoallylic alcohol, is produced in 93% yield.[67] It bears mentioning that the diastereoselectivity was excellent in each case, providing the *syn* diastereomer in ≥99:1 even in the case of the 7-membered carbocycle **13c**.[68]

Our next set of experiments focused on establishing the titanocene-catalyzed intramolecular metalation/allylation in the construction of nitrogen heterocycles.[69] Thus, treatment of ketone **14a**, bearing a sulfonamide linker between the carbonyl and allylbromide motifs, with Cp_2TiCl_2 (2 mol %) and zinc dust at room temperature provided pyrrolidine **15a** with complete selectivity for the *syn* diastereomer, albeit in diminished yield (eq 9). However, extending this method to





the construction of 6-membered heterocycles led to sulfonyl piperdine **15b** from ketone **14b** in 98% yield (eq 10). As in each example thus far, we observed an exceptionally high level of diastereoselectivity in the formation of **15b**. These results complement the modest stereoselectivity in intramolecular allylation of ketones using conventional methods.[64b,65a]

Recently, allenes have attracted the attention of the synthetic community due to their versatility as functional handles in a wide assortment of transition metal-catalyzed carbocyclization reactions.[70] Expanding the intramolecular carbonyl addition reaction to include propargyl bromides would provide the corresponding carbinols bearing an exocyclic allene moiety.[71] Thus, subjection of propargyl bromide **16a** to the titanocene-catalyzed metalation conditions that proved effective for the intramolecular propargylation reaction, yielded allene **17a** in

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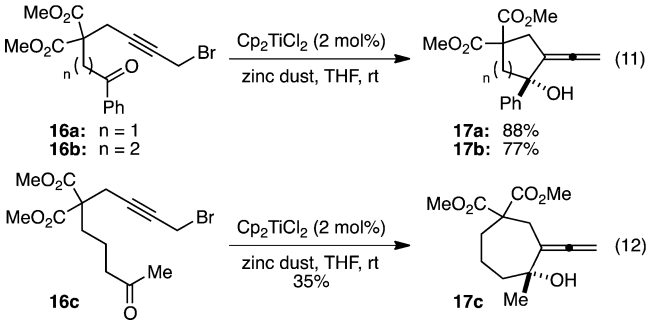
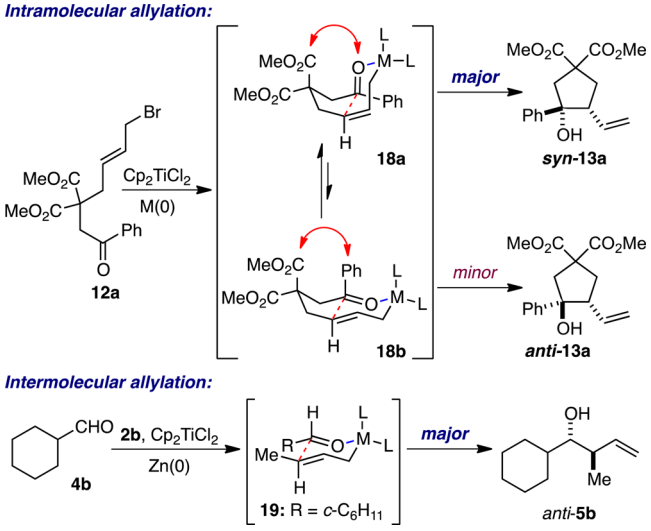
88% yield after only 10 min at room temperature (eq 11). As anticipated, the alkylation reaction proceeded with exclusive



S_E2' selectivity. Lengthening the carbon tether to access the cyclohexyl-substituted allene **17b** from propargyl bromide **16b** proceeded in 77% yield. In contrast to allyl bromide **12c**, the metalation of methyl ketone **16c** provided the 7-membered allene-bearing carbocycle **17c** in only 35% yield (eq 12). The addition of ZnX_2 salts, $TiCl_4$, $BF_3{\cdot}OEt_2$, or Brønsted acids to the reactions of **16b** and **16c** failed to improve the yields of **17b** and **17c**. In addition, the corresponding intermolecular addition of propargyl bromides to aldehydes and ketones led to an inseparable mixture of allenic and homopropargylic alcohol.[72]

The diastereoselectivity in the cyclic and acyclic cases can be readily understood by invoking a chairlike transition state similar to that which is generally accepted in the allylation of carbonyl substrates (Scheme 4).[73] The *anti*-selectivity in the

Scheme 4. Possible Transition States for Diastereoselective Allylations



intramolecular allylations for the formation of cyclopentanols is rationalized by examining the envelope-chair transition states **18a** and **18b** wherein the R group of the carbonyl resides in the more favorable pseudoequatorial position in **18a** to avoid the transannular diaxial interactions present in **18b**.[64b] Similarly, the intermolecular crotylations of aldehyde **4b** likely proceed through a chairlike transition state **19** where the crotyl methyl substituent resides pseudoequatorial, again to minimize unfavorable 1,3-diaxial interactions, leading to the *anti*-homoallylic alcohol **5b**.[74]

Examination of the Carbonyl Electrophile. The titanocene-catalyzed reductive transmetalation for the formation of allylzinc reagents derived from allylbromide and prenyl bromide proved compatible with a wide array of substitution patterns within the carbonyl substrates (Table 8). In general, good to excellent yields of the corresponding homoallylic alcohols, derived from the allylation of ketones and aldehydes, were obtained. Aryl aldehydes gave their respective alcohols in excellent yields, regardless of whether they were electron rich (entries 1−5), electron deficient (entries 6−10), or heteroaromatic (entry 11). Interestingly, the presence of a free phenol moiety did not hinder the allylation reaction, as exemplified by the conversion of aldehydes **4h** and **4i** to their respective homoallylic alcohols **5j** and **5k** (entries 4 and 5). However, the presence of the nitro group in aldehyde **4n** prevented the formation of alcohol **5p** leading to complete recovery of starting material (entry 10).[24,75] The allylation of unsaturated aldehydes proved highly regioselective, leading to exclusive 1,2-addition without any of the conjugate addition products observed (entries 12 and 13). Finally, aliphatic aldehydes, characterized by cyclohexyl carboxaldehyde (**4b**) and *n*-hexanal (**4r**), underwent allylation to yield homoallylic alcohols **5t** and **5u** in 79% and 91% yield, respectively (entries 14 and 15). The reactivity of prenyl bromide **2d** in the allylation of aldehydes proved comparable to that observed with **2a** for aryl and aliphatic aldehydes (entries 16−18). It is important to note that the allylzinc reagent derived from **2d** underwent exclusive S_E2' carbonyl addition to yield the homoallylic alcohol containing a vicinal quaternary center.

The corresponding homoallylic tertiary alcohols derived from ketone electrophiles under the titanocene-catalyzed conditions were obtained in good to excellent yields. The allylation of acetophenone provided alcohol **3h** in 89% yield (entry 19). Both electron rich and electron poor cinnamyl derivatives **1d**−**1j** yielded the corresponding alcohols **3i**−**3o** in yields as high as 97% (entries 20−26). As with the phenols **4g** and **4h**, the free phenol in ketone **1g** did not impede either the metalation or subsequent carbonyl addition events (entry 23). However, the presence of the nitro group in enone **1k** again prevented formation of the corresponding homoallylic alcohol **3p** (entry 27). Most notably, the cyclopropane-substituted allylic alcohol **3q** was obtained in 97% yield while leaving the cyclopropane ring intact (entry 28).[76] Unsaturated ketones **1m** and **1n**, and aliphatic enones **1o**−**1s** underwent smooth allylation to provide homoallylic alcohols **3r**−**3x** resulting from exclusive 1,2-addition in excellent yields (entries 29−35). The allylation of benzophenone (**1t**) proceeded in excellent yield (97%) to provide the corresponding homoallylic tertiary alcohol **3y** without elimination, even under the Lewis acidic conditions of the reaction (entry 36). Not surprisingly, the reaction proved chemoselective for the more electrophilic carbonyl functionality (entries 6 and 26). Even in an excess allyl bromide and reducing metal, homoallylic alcohols **5l** and **3o** were obtained in 90% and 81% respectively by carefully monitoring for the consumption of aldehyde **4j** and ketone **1j**.

Less electrophilic carbonyl derivatives also proved reactive under the titanocene-catalyzed reductive transmetalation conditions when in the absence of aldehydes and ketones (Table 9). The allylation of esters **20a**−**d** with allyl bromide (**2a**) proceeded smoothly in the presence of Cp_2TiCl_2 (1 mol %) and Zn(0) dust to yield the corresponding tertiary alcohols resulting from the addition of two equivalents of allylzinc (entries 1−4). Methyl benzoate **20a** and cinnamate derivatives **20b**−**20d** underwent bisallylation to yield the corresponding tertiary alcohols **21a**−**d** in 75−87% yield. Attempts to isolate

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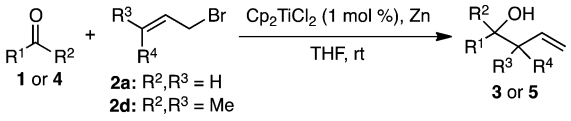
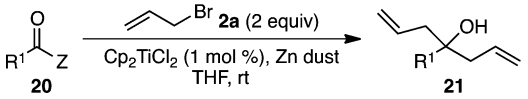
Table 8. Allylation of Aldehydes and Ketones[a]



entry	R^1	R^2	2	yield[b] (%)	entry	R^1	R^2	2	yield[b] (%)
1	4-Me-C_6H_4 (**4e**)	H	**2a**	84 (**5g**)	19	Ph (**1c**)	Me	**2a**	89 (**3h**)
2	4-MeO-C_6H_4 (**4f**)	H	**2a**	89 (**5h**)	20	*trans*-(*c*-C_6H_{11})CH=CH (**1d**)	Me	**2a**	83 (**3i**)
3	4-Me_2N−C_6H_4 (**4g**)	H	**2a**	91 (**5i**)	21	*trans*-(4-MeO-C_6H_4)CH=CH (**1e**)	Me	**2a**	91 (**3j**)
4	2-HO-C_6H_4 (**4h**)	H	**2a**	97 (**5j**)	22	*trans*-(4-Me_2N−C_6H_4)CH=CH (**1f**)	Me	**2a**	91 (**3k**)
5	3-HO-4-MeO-C_6H_3 (**4i**)	H	**2a**	99 (**5k**)	23	*trans*-(4-HO-3-MeO-C_6H_4)CH=CH (**1g**)	Me	**2a**	97 (**3l**)
6	4-MeO_2C−C_6H_4 (**4j**)	H	**2a**	90 (**5l**)	24	*trans*-(4-F_3C−C_6H_4)CH=CH (**1h**)	Me	**2a**	92 (**3m**)
7	4-F_3C−C_6H_4 (**4k**)	H	**2a**	90 (**5m**)	25	*trans*-(4−Cl-C_6H_4)CH=CH (**1i**)	Me	**2a**	92 (**3n**)
8	4−Cl-C_6H_4 (**4l**)	H	**2a**	93 (**5n**)	26	*trans*-(4-MeO_2C−C_6H_4)CH=CH (**1j**)	Me	**2a**	81 (**3o**)
9	4-NC-C_6H_4 (**4m**)	H	**2a**	85 (**5o**)	27	*trans*-(4-O_2N−C_6H_4)CH=CH (**1k**)	Me	**2a**	NR (**3p**)
10	4-O_2N−C_6H_4 (**4n**)	H	**2a**	NR (**5p**)	28	*trans*-(*c*-C_3H_5)CH=CH (**1l**)	Me	**2f**	97 (**3q**)
11	2-furyl (**4o**)	H	**2a**	88 (**5q**)	29	Me_2C=CH (**1m**)	Me	**2f**	98 (**3r**)
12	*trans*-PhCH=CH (**4p**)	H	**2a**	91 (**5r**)	30	-$CH_2CH_2CH_2CH$=CH- (**1n**)	-	**2a**	98 (**3s**)
13	*trans*-MeCH=CH (**4q**)	H	**2a**	83 (**5s**)	31	-$CH_2CH_2CH_2CH_2$− (**1o**)	-	**2a**	76 (**3t**)
14	*c*-C_6H_{11} (**4b**)	H	**2a**	79 (**5t**)	32	-$CH_2CH_2CH_2CH_2CH_2$− (**1p**)	-	**2a**	89 (**3u**)
15	*n*-C_5H_{11} (**4r**)	H	**2a**	91 (**5u**)	33	*c*-C_6H_9 (**1q**)	Me	**2a**	64 (**3v**)
16	Ph (**4a**)	H	**2d**	99 (**5v**)	34	*t*-C_4H_9 (**1r**)	Me	**2a**	82 (**3w**)
17	4-MeO-C_6H_4 (**4f**)	H	**2d**	88 (**5w**)	35	$PhCH_2CH_2$ (**1s**)	Me	**2a**	98 (**3x**)
18	*n*-C_5H_{11} (**4r**)	H	**2d**	83 (**5x**)	36	Ph (**1t**)	Ph	**2a**	97 (**3y**)

[a]Reactions conducted in THF using 0.4 mmol of aldehyde or ketone, 1.0 mmol of appropriate bromide, 1 mol % Cp_2TiCl_2, 1.0 mmol zinc dust at room temperature (see Supporting Information for details). [b]Isolated yields.

Table 9. Allylation of Less Electrophilic Carbonyl Derivatives[a]



entry	R^1	Z	21	yield[b] (%)
1	2-Me-C_6H_4 (**20a**)	OMe	**21a**	87
2	*trans*-(4-MeO-C_6H_4)CH=CH (**20b**)	OEt	**21b**	87
3	*trans*-(4-Me_2N−C_6H_4)CH=CH (**20c**)	OEt	**21c**	75
4	*trans*-(4−Cl-C_6H_4)CH=CH (**20d**)	OEt	**21d**	83
5[c]	Me (**20e**)	NHPh	**21e**	NR

[a]Reactions conducted in THF using 0.4 mmol of ester or amide **20**, 1.0 mmol of appropriate bromide, 1 mol % mmol Cp_2TiCl_2, 1.0 mmol zinc dust or magnesium turnings at room temperature (see Supporting Information for details). [b]Isolated yield after chromatographic purification. [c]Reaction was run for ≥48 h.

the incipient ketones by adding one equivalent of allylzinc provided only the tertiary alcohol and unreacted ester (~1:1). In contrast, amides proved unreactive to the allylation conditions, as illustrated by the reaction with phenyl acetimide **20e** (entry 5).

CONCLUSION

In summary, this study describes a complementary approach toward the generation of highly reactive organometallic reagents under mild conditions through the titanocene-catalyzed reductive transmetalation of alkyl halides. In contrast to metal activation employed by conventional methods of organometallic reagent generation, this strategy utilizes titanocene as a catalytic substrate activator to facilitate the overall metal insertion into C−X bonds. The use of commercially available and inexpensive Cp_2TiCl_2 makes this process attractive from a practical standpoint. Implementation of this controlled reagent generation strategy affords enhanced regio-, chemo-, and stereocontrol in the construction of functionalized synthetic intermediates.

EXPERIMENTAL SECTION

Solvents and reagents were ACS grade and used without purification unless noted below. Tetrahydrofuran (THF) was passed through a column of molecular sieves and stored under argon. Benzaldehyde and *p*-anisaldehyde were distilled under vacuum over molecular sieves and stored under nitrogen. $Zn^{(0)}$ dust was rinsed with 1 M HCl, filtered and washed thoroughly with water, acetone and diethyl ether and dried under vacuum. Phosphines and ligands **L1**, **L2**, **L3**, **L4**, **L5**, **L6**, **L7**, **L8** and **L9** were obtained from commercial sources taking any precautions for storage and handling as noted by manufacturer. Substrates **1d**[77], **1e**[78], **1f**[79], **1g**[80], **1h**[81], **1i**[82], **1j**[83], **1k**[82], **1l**[84], **4c**[85], **4d**[86a], **20b**[87], **20c**[81] and **20d**[81] were synthesized following literature procedures. ^{1}H nuclear magnetic resonance (NMR) spectra were obtained at either 300, 400, 500, or 600 MHz. ^{13}C NMR were obtained at 100, 125, or 150 MHz. Chemical shifts are reported in parts per million (ppm, δ), and referenced from the solvent or tetramethylsilane (TMS). Flash column chromatography was performed according to Still's procedure.

Representative Allylation Procedure. A clean, oven-dried 4 dram screw cap vial was charged with Cp_2TiCl_2 (1 mg, 4 μmol) and zinc dust (66 mg, 1 mmol) under an atmosphere of N_2 at room temperature. THF (2.0 mL) was added via syringe and the reaction stirred for 10 min or until the solution had turned from red to green. A solution of aldehyde (0.4 mmol) and appropriate allyl bromide (1.0 mmol) in THF (2.0 mL) was then added via syringe. The reaction was stirred for 20 min or until all starting material was consumed as monitored by TLC (*p*-anisaldehyde). The mixture was diluted with saturated aqueous NH_4Cl (10 mL) and Et_2O (10 mL) and the layers were separated. The aqueous layer was extracted with Et_2O (3 × 10 mL), and the combined organic fractions were washed with saturated aqueous NaCl (30 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The crude residue was purified by flash

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chromatography, eluting with hexanes/EtOAc to give the homoallylic alcohol.

1-Phenyl-3-buten-1-ol (5a). Purified by flash chromatography eluting with hexanes/EtOAc (5:1) to provide 58 mg (98%) as a clear, colorless oil. Spectral data (^{1}H NMR and ^{13}C NMR) consistent with literature values.[88]

1-Cyclohexyl-2-methyl-3-buten-1-ol (5b). Purified by flash chromatography eluting with hexanes/EtOAc (10:1) to provide 45 mg (90%) of a clear, colorless oil and a 4:1 mixture of *anti/syn* diastereomers. Spectral data (^{1}H and ^{13}C NMR) consistent with literature values.[73,89]

1-Cyclohexyl-2-phenyl-3-buten-1-ol (5c). Purified by flash chromatography eluting with hexanes/EtOAc (4:1) to provide 63 mg (90%) of a clear, colorless oil and a 14:1 mixture of *anti/syn* diastereomers. Spectral data (^{1}H NMR and ^{13}C NMR) consistent with literature values.[73,86]

2-Methyl-3-hydroxy-1-tertbutyldimethylsiloxy-5-hexene (5d). Purified by flash chromatography eluting with hexanes/EtOAc (4:1) to provide 61 mg (83%) of a clear, colorless oil and a 1:1 mixture of *anti/syn* diastereomers. Spectral data (^{1}H NMR and ^{13}C NMR) consistent with literature values.[39a,90]

2-Phenyl-3-hydroxy-5-hexene (5e). Purified by flash chromatography eluting with hexanes/EtOAc (4:1) to provide 57 mg (93%) of a clear, colorless oil and a 2.7:1 mixture of *syn-anti* diastereomers. Spectral data (^{1}H NMR and ^{13}C NMR) consistent with literature values.[91]

***(R)*-1-Phenyl-3-buten-1-ol [(+)-5a].** A clean, oven-dried 4 dram screw cap vial was charged with Cp_2TiCl_2 (2 mg, 8 μmol), zinc dust (66 mg, 1 mmol) and 1,3-bis(diphenylphosphino)propane (dppp, 24.7 mg, 0.06 mmol) under an atmosphere of N_2 at room temperature. THF (2.0 mL) was added via syringe and the reaction stirred for 10 min or until the solution had turned from red to green before being cooled to −78 °C. In a separate 2 dram vial a solution of (1*S*,2*S*)-(−)-1,2-diphenylethylenediamine (42.5 mg, 0.2 mmol) in THF (1.0 mL) was deprotonated with ^{n}BuLi (0.38 mmol, 2.0 M in hexanes, 0.19 mL) at room temperature and then added via syringe to the reduced titanium/zinc/dppp solution and stirred for 10 min. A solution of benzaldehyde (42.4 mg, 0.4 mmol, 40.2 μL) and allyl bromide (121 mg, 1.0 mmol, 87 μL) in THF (1.0 mL) was then added via syringe. The reaction was allowed to warm from −78 to −40 °C over a period of 3 h and then kept at −40 °C for 8 h. The mixture was diluted with saturated aqueous NH_4Cl (10 mL) and Et_2O (10 mL), filtered through Celite eluting with Et_2O and the layers separated. The aqueous layer was extracted with Et_2O (3 × 10 mL), and the combined organic fractions were washed with saturated aqueous NaCl (30 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The crude residue was purified by flash chromatography, eluting with hexanes/EtOAc (4:1) to give (+)-**5a** as a clear, colorless oil. The enantiomeric excess was determined by HPLC (4.6 × 250 mm ChiralCel OD, hexanes/^{i}PrOH = 98/2, flow rate =1 mL/min) and absolute stereochemistry determined in comparison to reported literature values.[92]

***(E)*-1-Phenyl-3-methyl-1,5-hexadien-3-ol (3a).** Purified by flash chromatography eluting with hexanes/EtOAc (4:1) to provide 74 mg (99%) of a clear, colorless oil. Spectral data (^{1}H NMR and ^{13}C NMR) consistent with literature values.[93]

***(E)*-1-Phenyl-3,4-dimethyl-1,5-hexadien-3-ol (3b).** Purified by flash chromatography eluting with hexanes/EtOAc (4:1) to provide 72 mg (85%) of a clear, colorless oil and a 1.3:1 ratio of diastereomers as determined by ^{1}H NMR. Differentiating peaks: δ 1.81 (Diastereomer A, integration 1.04) and 1.72 (Diastereomer B, integration 0.78) gives *dr* = 1.33; δ 1.09 (Diastereomer A, integration 3.98) and 1.07 (Diastereomer B, integration 2.98) gives *dr* = 1.30. ^{1}H NMR (300 MHz, $CDCl_3$) δ (Diastereomer A) 7.41−7.21 (m, 5 H), 6.61 (dd, *J* = 16.2, 1.8 Hz, 1 H), 6.31 (dd, *J* = 16.2, 3.9 Hz, 1 H), 5.93−5.72 (comp, 1 H), 5.18−5.15 (comp, 1 H), 5.12 (app br t, 1 H), 2.44−2.28 (comp, 1 H), 1.81 (br s, 1 H), 1.36 (d, *J* = 4.5 Hz, 3 H), 1.09 (d, *J* = 7.2 Hz, 3 H); (Diastereomer B) 7.41−7.21 (m, 5 H), 6.61 (dd, *J* = 16.2, 1.8 Hz, 1 H), 6.31 (dd, *J* = 16.2, 3.9 Hz, 1 H), 5.93−5.72 (comp, 1 H), 5.18−5.15 (comp, 1 H), 5.12 (app br t, 1 H), 2.44−2.28 (comp, 1 H), 1.72 (br s, 1 H), 1.36 (d, *J* = 4.5 Hz, 3 H), 1.07 (d, *J* = 6.9 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (Diastereomer A) 140.8, 138.0, 136.2, 129.5, 129.0, 128.3, 127.3, 117.9, 75.3, 50.3, 27.2, 16.3; (Diastereomer B) 140.8, 138.0, 135.5, 129.5, 128.9, 128.3, 127.3, 117.5, 75.3, 49.4, 26.2, 15.3; IR (neat) 3464, 3451, 3430, 3402, 3090, 3026, 2975, 2933, 1491, 1445, 1386 cm^{-1}; HRMS (FAB-TOF) *m*/*z* = 185.1328 [$C_{14}H_{17}$ (M−OH) requires 185.1330].

***(E)*-1,4-Diphenyl-3-methyl-1,5-hexadien-3-ol (3c).** Purified by flash chromatography eluting with hexanes/EtOAc (4:1) to provide 107 mg (90%) of a clear, colorless oil and a 1:1.6 ratio of diastereomers as determined by ^{1}H NMR. Differentiating peaks: δ 6.56 (Diastereomer A, integration 0.66) and 6.51 (Diastereomer B, integration 1.06) gives *dr* = 1.61; δ 1.76 (Diastereomer A, integration 0.64) and 2.00 (Diastereomer B, integration 1.04) gives *dr* = 1.62. ^{1}H NMR (300 MHz, $CDCl_3$) δ (Diastereomer A) 7.42−7.21 (comp, 10 H), 6.56 (d, *J* = 7.5 Hz, 1 H), 6.36−6.32 (comp, 1 H), 5.29−5.12 (comp, 2 H), 3.53−3.45 (comp, 1 H), 1.76 (br s, 1 H), 1.37 (s, 3 H); (Diastereomer B) 7.42−7.21 (comp, 10 H), 6.51 (d, *J* = 7.8 Hz, 1 H), 6.36−6.32 (comp, 1 H), 5.29 − 5.12 (comp, 2 H), 3.53−3.45 (comp, 1 H), 2.00 (br s, 1 H), 1.35 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (Diastereomer A) 139.9, 137.4, 137.0, 135.0, 129.5, 128.3, 128.1, 127.4, 127.0, 126.9, 126.4, 118.2, 74.9, 61.7, 26.9; (Diastereomer B) 140.3, 137.1, 137.0, 134.3, 129.2, 128.6, 128.3, 127.4, 127.0, 126.9, 126.4, 118.8, 74.4, 62.2, 26.6; IR (neat) 3567, 3546, 3481, 3081, 3060, 3028, 2974, 2925, 1610, 1502, 991 cm^{-1}; HRMS (FAB-TOF) *m*/*z* = 265.1606 [$C_{19}H_{21}O$ (M+1) requires 265.1592].

***(E)*-1-Phenyl-3,3-dimethyl-1,5-hexadien-3-ol (3d).** Purified by flash chromatography eluting with hexanes/EtOAc (4:1) to provide 84 mg (95%) of a clear, colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41−7.20 (comp m, 5 H), 6.60 (d, *J* = 15.9 Hz, 1 H), 6.42 (d, *J* = 15.9 Hz, 1 H), 6.03 (dd, *J* = 17.4, 0.6 Hz, 1 H), 5.16−5.08 (comp m, 2 H), 1.67 (br s, 1 H), 1.34 (s, 3 H), 1.11 (s, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 145.8, 138.1, 135.4, 129.5, 129.0, 128.2, 127.3, 115.0, 77.3, 45.3, 24.7, 23.5, 22.8; IR (neat) 3512, 3495, 3486, 3463, 3082, 3027, 2991, 2940, 1504, 1462, 1377 cm^{-1}; HRMS (FAB-TOF) *m*/*z* = 199.1499 [$C_{15}H_{19}$ (M−OH) requires 199.1487].

***(E)*-1-Phenyl-3,5-dimethyl-1,5-hexadien-3-ol (3e).** Purified by flash chromatography eluting with hexanes/EtOAc (4:1) to provide 77 mg (95%) of a clear, slightly yellow oil. Spectral data (^{1}H NMR and ^{13}C NMR) consistent with literature values.[94]

1-Phenyl-3-methyl-3-hydroxy-1-heptene (7a). Purified by flash chromatography eluting with hexanes/EtOAc (10:1) to provide 33 mg (41%) of a clear, colorless oil. Spectral data (^{1}H NMR and ^{13}C NMR) consistent with literature values.[95]

1,4-Diphenyl-3-methyl-3-hydroxy-1-butene (7b). Purified by flash chromatography eluting with hexanes/EtOAc (4:1) to provide 62 mg (65%) of a clear, colorless oil. Spectral data (^{1}H NMR and ^{13}C NMR) consistent with literature values.[96]

1,4,4-Triphenyl-3-methyl-3-hydroxy-1-butene (7c). Purified by flash chromatography eluting with hexanes/EtOAc (4:1) to provide 49 mg (39%) of a clear, pale yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.55 (app dt, *J* = 8.0, 1.5 Hz, 2 H), 7.44 (app dt, *J* = 8.0, 1.5 Hz, 2 H), 7.33 − 7.15 (m, 11 H), 6.52 (d, *J* = 16.0 Hz, 1 H), 6.37 (d, *J* = 16.0 Hz, 1 H), 4.11 (s, 1 H), 1.85 (br s, 1 H), 1.41 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 141.2, 141.1, 137.4, 136.4, 130.3, 130.0, 128.8, 128.7, 128.4, 128.2, 127.6, 127.0, 126.8, 126.7, 75.7, 63.2, 28.8; IR (neat) 3442, 3059, 3026, 2975, 2927, 2894, 2868, 1598, 1493, 1449, 1371, 1116, 969 cm^{-1}; HRMS (FAB-TOF) *m*/*z* = 337.1585 [$C_{23}H_{22}ONa$ (M+Na) requires 337.1563].

1,3-Diphenyl-3-hydroxy-1-butene (7d). Purified by flash chromatography eluting with hexanes/EtOAc (4:1) to provide 65 mg (73%) of a clear, colorless oil. Spectral data (^{1}H NMR and ^{13}C NMR) consistent with literature values.[97]

1-Phenyl-3-hydroxy-3,4-dimethyl-1-pentene (7e). Purified by flash chromatography eluting with hexanes/EtOAc (4:1) to provide 18 mg (24%) of a clear, colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40−7.38 (m, 2 H), 7.33−7.30 (m, 2 H), 7.27−7.21 (m, 1 H), 6.60 (d, *J* = 16.5 Hz, 1 H), 6.30 (d, *J* = 16.0 Hz, 1 H), 1.81 (m, *J* = 2.0 Hz, 1 H), 1.50 (br s, 1 H), 1.35 (s, 3 H), 0.97 (d, *J* = 4.5 Hz, 3 H), 0.95 (d, *J* = 4.5 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.4, 136.0, 128.8,

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127.9, 127.6, 126.6 75.8, 38.5, 25.7, 17.9, 17.4; IR (neat) 3431, 3062, 3027, 2963, 2929, 2873, 1705, 1494, 1448, 1369, 1176, 1204, 1068 cm^{-1}; HRMS (ESI-TOF) m/z = 213.1282 [$C_{13}H_{18}ONa$ (M+Na) requires 213.1274].

1-Phenyl-3-hydroxy-3-methyl-1,4-pentadiene (7f). Purified by flash chromatography eluting with hexanes/EtOAc (5:1) to provide 34 mg (49%) of a clear, colorless oil whose ^1H NMR and ^{13}C NMR spectral data was consistent with literature values.[98]

1-(2-Propene)-4-tertbutyl-cyclohexan-1-ol (3f). Purified by flash chromatography eluting with hexanes/EtOAc (2:1) to provide 56 mg (71%, 85% overall) of ***syn*-3f** as a pale yellow oil and 11 mg (14%, 85% overall) of ***anti*-3f** in a 6:1 ratio of *syn/anti* diastereomers. Spectral data (^1H and ^{13}C NMR) was consistent with literature values.[99]

Cyclopropylallyl Bromide (2f). Was prepared according to laboratory procedures kindly provided by Professor Peter Wipf[59]; PPh_3 (1.16 g, 4.4 mmol) was dissolved in dry CH_2Cl_2 (11 mL), cooled on ice and treated with Br_2 (0.22 mL, 4.4 mmol). The mixture was stirred at 0 °C for 10 min, followed by imidazole (0.37 g, 5.5 mmol) and a solution of alcohol (0.27 g, 2.75 mmol) in CH_2Cl_2 (11 mL). The mixture was stirred at 0 °C for 25 min, poured into hexanes and filtered through a pad of silica, washing the pad with CH_2Cl_2. The solvent was evaporated and the crude material (~80%) was used in the next step. This bromide is very unstable and it decomposes in a matter of min/h. Initial attempts at isolation for the purpose of characterization resulted in decomposition and ring opened products therefore the crude mixture was immediately transferred to the subsequent reaction flask and used without further purification.

***(E)*-1-Phenyl-3-methyl-4-cyclopropyl-1,5-hexadien-3-ol (3g).** Purified by flash chromatography eluting with hexanes/EtOAc (4:1) to provide 59 mg (65%, 94% based on recovered starting material) of a clear, colorless oil in a 1.12:1 ratio of diastereomers as determined by ^1H NMR. The diastereomers have a ratio of Differentiating peaks: δ 5.91 − 5.83 (m, 1H) − Diastereomer A, integration 1.00 and 5.78−5.71 (m, 1H) − Diastereomer B, integration 1.11 gives dr = 1.11; δ 2.19 (s, 1H) − Diastereomer A, integration 0.87 and 2.57 (s, 1H) − Diastereomer B, integration 0.98 gives dr = 1.13. ^1H NMR (500 MHz, $CDCl_3$) δ (Diastereomer A) 7.41−7.21 (comp, 2 H), 7.36−7.31 (comp 2H), 7.25−7.21 (comp, 1H), 6.66 (d, J = 16 Hz, 1 H), 6.44 (d, J = 16 Hz, 1H), 5.91−5.83 (comp, 1 H), 5.19−5.11 (comp, 2H), 2.19 (s, 1H), 1.61 (t, J = 9 Hz, 1H), 1.45 (s, 3H), 0.89−0.79 (comp, 1H), 0.68−0.59 (comp, 1H), 0.51−0.44 (m, 2 H), 0.11−0.07 (m, 1H); (Diastereomer B) 7.41−7.21 (comp, 2 H), 7.36−7.31 (comp 2H), 7.25−7.21 (comp, 1H), 6.63 (d, J = 16 Hz, 1 H), 6.41 (d, J = 16 Hz, 1H), 5.78−5.71 (comp, 1H), 5.17−5.08 (comp, 2H), 2.06 (s, 1H), 1.53 (t, J = 9 Hz, 1H), 1.41 (s, 3H), 0.89−0.79 (comp, 1H), 0.68−0.59 (comp, 1H), 0.36−0.30 (m, 2H), 0.06−0.02 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (Diastereomer A) 138.0, 135.9, 128.8, 128.7, 127.7, 118.4, 75.7, 60.0, 27.0, 11.4, 6.5; (Diastereomer B) 137.6, 135.4, 128.01, 127.8, 127.12, 117.8, 75.4, 59.9, 26.4, 10.6, 6.0; IR (neat) 3435, 3078, 3026, 3002, 2975, 2931, 2872, 1494, 1449, 1373, 1333, 1271, 1071, 1021, 1001, 971, 910 cm^{-1}; HRMS (FAB-TOF) m/z = 251.1382 [$C_{16}H_{20}ONa$ (M+Na) requires 251.1406].

1-Phenyl-3-cyclopropyl-3-buten-1-ol (5f). Purified by flash chromatography eluting with hexanes/EtOAc (4:1) to provide 53 mg (71%, 91% based on recovered starting material) of a clear, colorless oil in 1.2:1 ratio of diastereomers as determined by ^1H NMR. Differentiating peaks: 2.33 (d, J = 4 Hz, 1H) − Diastereomer A, integration 0.87 and 2.18 (d, J = 3 Hz, 1H) − Diastereomer B, integration 1.04 gives dr = 1.19; δ 0.22−0.17 (m, 1 H) − Diastereomer A, integration 1.05 and −0.11 to −0.16 (m, 1H) − Diastereomer B, integration 1.22 gives dr = 1.16. ^1H NMR (500 MHz, $CDCl_3$) δ (Diastereomer A) 7.35−7.25 (comp, 5H), 5.81 − 5.74 (comp, 1H), 5.22−5.06 (comp, 2 H), 4.78 (dd, J = 4.0, 6.0 Hz, 1H), 2.33 (d, J = 4 Hz, 1H), 0.74−0.64 (comp, 2 H), 0.56−0.51 (comp, 1H), 0.44 − 0.39 (comp, 1H), 0.22 − 0.16 (m, 1H); (Diastereomer B) 7.35−7.25 (comp, 5H), 5.72−5.65 (comp, 1H), 5.22−5.06 (comp, 2 H), 4.67 (dd, J = 7.0, 3.0 Hz, 1H), 2.18 (d, J = 3 Hz, 1H), 0.50−0.45 (comp, 1H), 0.31−0.25 (comp, 1H), 0.09−0.04 (m, 2H), −0.11 to −0.16 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (Diastereomer A) 143.2, 137.8, 128.3, 128.1, 127.6, 118.3, 77.4, 56.7, 12.5, 4.9, 4.8; (Diastereomer B) 142.3, 137.7, 127.1, 126.9, 126.2, 117.2, 75.0, 56.0, 11.7, 3.2, 3.1; IR (neat) 3400, 3076, 3028, 3003, 2957, 2930, 2871, 1638, 1494, 1454, 1424, 1382, 1299, 1196, 1108, 1019, 915 cm^{-1}; HRMS (FAB-TOF) m/z = 211.1082 [$C_{13}H_{16}ONa$ (M+Na) requires 211.1093].

***(E)*-Dimethyl 2-(4-Bromobut-2-en-1-yl)-2-(2-oxo-2-phenylethyl)malonate (12a).** Dimethyl 2-(2-oxo-2-phenylethyl)-malonate[100] (400 mg, 1.6 mmol) was added to a slurry of NaH (64 mg, 1.6 mmol) in THF (6 mL, 0.25 M) at 0 °C. The mixture was allowed to warm to room temperature by removal of the ice bath, stirred for 15 min, then 1,4-dibromo-2-butene (1.03 g, 4.8 mmol) was added in one portion. The resulting solution was stirred for 4 h then diluted with saturated aqueous NH_4Cl (10 mL) and DCM (10 mL) and the layers were separated. The aqueous phase was extracted with CH_2Cl_2 (3 × 15 mL), and the combined organic fractions were washed with saturated aqueous NaCl (30 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The crude residue was purified by flash chromatography, eluting with hexanes/EtOAc (3:1) to give 387 mg (1.0 mmol, 62%) of a clear, colorless oil. ^1H NMR (400 MHz, $CDCl_3$) δ 7.98 (d, J = 8 Hz, 2 H), 7.61 (t, J = 7.6 Hz, 2 H), 7.50 (t, J = 7.2 Hz, 1 H), 5.70 (m, 2 H), 3.84 (d, J = 2 Hz, 2 H), 3.78 (s, 6 H), 3.69 (s, 2 H), 2.90 (d, J = 2 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.6, 170.8, 136.4, 133.6, 131.2, 130.0, 128.7, 128.2, 55.4, 53.0, 41.5, 36.0, 32.1; IR (neat) 3059, 3029, 2953, 2844, 1737, 1687, 1597.5, 1448, 1281, 1207, 1058, 973 cm^{-1}; HRMS (ESI-TOF); Calcd for $C_{17}H_{20}BrO_5$: 383.0489; found: 383.0461 (M+1).

***(E)*-Dimethyl 2-(4-Bromobut-2-en-1-yl)-2-(3-oxo-3-phenylpropyl)malonate (12b).** Following a similar allylation procedure listed above for the synthesis of **12a**, utilizing dimethyl 2-(3-oxo-3-phenylpropyl)malonate[101] (206 mg, 0.78 mmol) yielded 150 mg (48%) of a clear oil. ^1H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, J = 8 Hz, 2 H), 7.59 (t, J = 7.2 Hz, 1 H), 7.48 (t, J = 8 Hz, 2 H), 5.76 (m, 2 H), 3.91 (d, J = 7.2 Hz, 2 H), 3.75 (s, 6 H), 3.03 (t, J = 7.6 Hz, 2 H), 2.72 (d, J = 7.2 Hz, 2 H), 2.33 (t, J = 6.8 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.9, 171.4, 136.8, 133.4, 131.1, 129.6, 128.8, 128.2, 57.3, 52.8, 37.1, 33.9, 32.4, 27.7; IR (neat) 3003, 2954, 1731, 1687, 1448, 1210, 1079, 973.7, 740 cm^{-1}; HRMS (ESI-TOF); Calcd for $C_{18}H_{22}BrO_5$: 397.0645; found: 397.0640 (M+1).

***(E)*-Dimethyl 2-(4-Bromobut-2-en-1-yl)-2-(4-oxopentyl)-malonate (12c).** To a cold solution of pent-4-yn-1-ol (1.48 g, 17.6 mmol, 1.64 mL) and triethylamine (2.18 g, 21.4 mmol, 3.0 mL) in CH_2Cl_2 (60 mL, 0.3 M) was added methanesulfonyl chloride (2.46 g, 21.4 mmol, 1.66 mL) dropwise at 0 °C. The mixture was allowed to warm to room temperature by removal of the cooling bath and stirred for 4 h. The resulting solution was diluted with saturated aqueous NH_4Cl (50 mL) and CH_2Cl_2 (40 mL) and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL), and the combined organic fractions were dried ($MgSO_4$) and concentrated under reduced pressure. The crude residue was added slowly to a solution of NaH (1.43 g, 35.7 mmol) and dimethyl malonate (5.89 g, 44.6 mmol, 5.1 mL) in THF (71 mL, 0.25 M) at room temperature and stirred for 8 h. The resulting solution was quenched with saturated aqueous NH_4Cl (80 mL), the layers were separated and the aqueous phase extracted with CH_2Cl_2 (3 × 90 mL). The combined organic fractions were dried ($MgSO_4$) and concentrated under reduced pressure. Lindlar's catalyst (195 mg, 10 mg/mmol) was added to the crude residue and EtOAc (65 mL) was added to the flask at room temperature. The solution was sparged with H_2 then placed under 1 atm of H_2 and stirred for 8 h at room temperature. The heterogeneous mixture was filtered, washed with EtOAc (120 mL), and the filtrate concentrated under reduced pressure. The crude material was then diluted with DMF (5 mL) and added to a mixture of CuCl (800 mg, 8.1 mmol) and $PdCl_2$ (238 mg, 1.34 mmol) in DMF/H_2O (6.3:1, 0.2 M) that was stirred under 1 atm of O_2 for 30 min. The mixture was stirred at 45 °C for 14 h then diluted with water (100 mL), the layers separated, and the aqueous phase extracted with CH_2Cl_2 (3 × 50 mL). The combined organic fractions were washed sequentially with water (3 × 30 mL) and saturated aqueous NaCl (100 mL), then dried ($MgSO_4$) and concentrated under reduced pressure. The crude residue was purified by flash chromatography, eluting with hexanes/EtOAc

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(1:1) to give 756 mg (20%) of dimethyl 2-(4-oxopentyl)malonate as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.75 (s, 6 H), 3.38 (t, J = 7.6 Hz, 1 H), 2.48 (t, J = 7.2 Hz, 2 H), 2.15 (s, 3 H), 2.00−1.80 (m, 2 H), 1.60 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 208.2, 169.9, 52.8, 51.7, 43.3, 30.1, 28.4, 21.6; IR (neat) 2957, 1735, 1437, 1251, 1153 cm^{-1}; HRMS (ESI-TOF); Calcd for $C_{10}H_{17}O_5$: 217.1071; found: 217.1057 (M+1).

Following a similar allylation procedure listed above for the synthesis of **12a**, utilizing dimethyl 2-(4-oxopentyl)malonate (294 mg, 1.36 mmol) 421 mg (89%) of **12c** was prepared as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.77 (m, 2 H), 3.91 (d, J = 7.2 Hz, 2 H), 3.73 (s, 6 H), 2.67 (s, J =7.2 Hz, 2 H), 2.45 (t, J = 7.2 Hz, 2 H), 2.14 (s, 3 H), 1.84 (m, 2 H), 1.47 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 208.1, 171.5, 130.9, 129.8, 57.8, 52.8, 43.5, 35.5, 32.6, 32.2, 30.2, 18.3; IR (neat) 3000, 2954, 1734, 1436, 1205, 1090, 973 cm^{-1}; HRMS (ESI-TOF); Calcd for $C_{14}H_{22}BrO_5$: 349.0645; found: 349.0641 (M +1).

(*E*)-*N*-(4-Bromobut-2-en-1-yl)-4-methyl-*N*-(2-oxo-2-phenylethyl)benzenesulfonamide (14a). To an oven-dried vial was added 4-methyl-*N*-(2-oxo-2-phenylethyl)benzenesulfonamide[102] (400 mg, 1.38 mmol), K_2CO_3 (580 mg, 4.14 mmol), 1,4-dibromo-2-butene (1.18 g, 5.52 mmol), and acetonitrile (9.2 mL, 0.15 M) before being capped and heated to reflux for 2−3 h. The soution was cooled to room temperature before addition of water (20 mL). The aqueous layer was extracted with DCM (3 × 30 mL), and the combined organic fractions were dried ($MgSO_4$) and concentrated under reduced pressure. The crude residue was purified by flash chromatography, eluting with hexanes/EtOAc (2:1) to give 214 mg (0.506 mmol, 37%) of a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, J = 3.2 Hz, 2 H), 7.77 (d, J = 3.2 Hz, 2 H), 7.61 (t, J = 6.8 Hz, 1 H), 7.48 (t, J = 8 Hz, 2 H), 7.30 (d, 2 H), 5.70 (m, 2 H), 4.74 (s, 2 H), 3.93 (d, J = 6.4 Hz, 2 H), 3.82 (d, J = 6.4 Hz, 2 H), 2.44 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.9, 143.7, 136.8, 134.9, 133.9, 131.4, 129.7, 129.5, 128.9, 128.0, 127.6, 52.1, 49.2, 31.1, 21.7; IR (neat) 3062, 2974, 2867, 1702, 1598, 1340, 1158, 1066, 990 cm^{-1}; HRMS (ESI-TOF); Calcd for $C_{19}H_{21}BrNO_3S$: 422.0420; found: 422.0407 (M+1).

(*E*)-*N*-(4-Bromobut-2-en-1-yl)-4-methyl-*N*-(3-oxo-3-phenylpropyl)benzenesulfonamide (14b). Following a similar allylation procedure for the synthesis of **14a**, 220 mg (0.50 mmol, 35%) of **14b** was prepared as a clear, colorless oil.[103] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (d, J = 7.2 Hz, 2 H), 7.21 (d, J = 8.4 Hz, 2 H), 7.60 (t, J = 7.6 Hz, 1 H), 7.49 (t, J = 6.4 Hz, 2 H), 7.32 (d, J = 8 Hz, 2 H), 5.75 (m, 2 H), 3.86 (comp, 4 H), 3.51 (t, J = 4.4 Hz, 2 H), 3.38 (t, J = 3.2 Hz, 2 H), 2.46 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.5, 143.8, 136.6, 136.5, 133.7, 130.7, 130.4, 130.1, 128.9, 128.3, 127.4, 50.8, 43.9, 39.3, 31.5 21.8; IR (neat) 3062, 2922, 1681, 1449, 1339, 1209, 1156, 1093 cm^{-1}; HRMS (ESI-TOF); Calcd for $C_{20}H_{23}BrNO_3S$: 436.0577; found: 436.0566 (M+1).

Dimethyl 2-(4-Bromobut-2-yn-1-yl)-2-(2-oxo-2-phenylethyl)malonate (16a). To a slurry of NaH (17 mg, 0.42 mmol) in THF (2 mL, 0.2 M) at 0 °C was added slowly dimethyl 2-(2-oxo-2-phenylethyl)malonate (100 mg, 0.4 mmol) before warming to room temperature. The solution was stirred for 15 min followed by a dropwise addition of silyl protected proparygyl bromide (105 mg, 4 mmol). The mixture was stirred for 8 h before being diluted with saturated aqueous NH_4Cl (4 mL) and DCM (4 mL). The layers were separated, and the aqueous layer was extracted with DCM (3 × 10 mL) before the organic fractions were combined, dried ($MgSO_4$) and concentrated under reduced pressure. The crude residue was purified by flash chromatography, eluting with hexanes/EtOAc (2:1) to give 146 mg (92%) of dimethyl 2-(4-((*tert*-butyldimethylsilyl)oxy)but-2-yn-1-yl)-2-(2-oxo-2-phenylethyl)malonate as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (d, J = 6.4 Hz, 2 H), 7.58 (t, J = 6 Hz, 1 H), 7.49 (t, J = 6.4 Hz, 2 H), 4.22 (t, J = 2 Hz, 2 H), 3.91 (s, 2 H), 3.76 (s, 6 H), 3.16 (t, J = 2 Hz, 2 H), 0.86 (s, 9 H), 0.05 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.8, 169.9, 136.4, 133.6, 128.7, 128.2, 82.4, 79.8, 77.4, 77.1, 76.8, 54.8, 53.2, 51.8, 41.2, 25.8, 23.8, 18.4, −4.8; IR (neat) 2955, 2931, 2858, 1743, 1688, 1598, 1436, 1207, 1079 cm^{-1}; HRMS (ESI-TOF); Calcd for $C_{23}H_{33}O_6Si$: 433.2041; found: 433.2014 (M+1).

A solution of dimethyl 2-(4-((*tert*-butyldimethylsilyl)oxy)but-2-yn-1-yl)-2-(2-oxo-2-phenylethyl)malonate (200 mg, 0.46 mmol) in DCM (14 mL, 0.03 M) was cooled to 0 °C before portionwise addition of triphenylphosphine dibromide (215 mg, 0.50 mmol). The solution was then allowed to warm up to room temperature slowly and stirred for 8 h before being diluted with saturated aqueous NH_4Cl (15 mL) and separation of the layers. The aqueous layer was extracted with DCM (3 × 20 mL) and the combined organic fractions were dried ($MgSO_4$) then concentrated under reduced pressure. The crude residue was purified by flash chromatography, eluting with hexanes/EtOAc (3:1) to give 83 mg (47%) of **16a** as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (d, J = 8.4 Hz, 2 H), 7.61 (t, J = 7.6 Hz, 1 H), 7.50 (t, J = 8 Hz, 2 H), 3.91 (s, 2 H), 3.83 (t, J = 2.4 Hz, 2 H), 3.77 (s, 6 H), 3.19 (t, J = 2 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.0, 170.2, 136.7, 133.7, 128.8, 128.3, 83.1, 79.3, 55.1, 53.3, 41.4, 24.6 14.9; IR (neat) 3008, 2954, 2923, 1740, 1686, 1435, 1208 cm^{-1}; HRMS (ESI-TOF); Calcd for $C_{17}H_{17}BrO_5Na$: 403.0152; found: 403.0154 (M +Na).

Dimethyl 2-(4-Bromobut-2-yn-1-yl)-2-(3-oxo-3-phenylpropyl)malonate (16b). Following a similar procedure listed above for the formation of 2-(4-((*tert*-butyldimethylsilyl)oxy)but-2-yn-1-yl)-2-(2-oxo-2-phenylethyl)malonate, 548 mg (1.23 mmol, 77% yield) of dimethyl 2-(4-((*tert*-butyldimethylsilyl)oxy)but-2-yn-1-yl)-2-(3-oxo-3-phenylpropyl)malonate was produced as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (d, J = 7.2 Hz, 2 H), 7.57 (t, J = 5.6 Hz, 1 H), 7.46 (t, J = 8 Hz, 2 H), 4.25 (t, J = 2 Hz, 2 H), 3.74 (s, 6 H), 3.04 (m, 2 H), 2.96 (t, J = 2 Hz, 2 H), 2.50 (m, 2 H), 0.92 (s, 9 H), 0.08 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.7, 170.6, 136.7, 133.2, 128.7, 128.1, 82.4, 79.1, 56.4, 52.9, 51.8, 33.8, 27.2, 25.9, 24.4, 18.3, −5.1; IR (neat) 2955, 2930, 2858, 1738, 1690, 1448, 1254, 1207, 1079, 838 cm^{-1}; HRMS (ESI-TOF); Calcd for $C_{24}H_{35}O_6Si$: 447.2197; found: 447.2197 (M+1).

Following a similar alkylation procedure for the synthesis of **16a**, 141 mg (0.36 mmol, 79%) of **16b** was prepared as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, J = 8 Hz, 2 H), 7.57 (t, J = 7.2 Hz, 1 H), 7.47 (t, J = 7.6 Hz, 2 H), 3.84 (t, J = 2.4 Hz, 2 H), 3.74 (s, 6 H), 3.06 (t, J = 6.4 Hz, 2 H), 2.95 (t, J = 2.4 Hz, 2 H), 2.48 (t, J = 7.6 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.6, 170.5, 136.6, 133.3, 128.7, 128.2, 82.0, 78.8, 56.4, 53.0, 33.8, 27.4, 24.6, 14.7; IR (neat) 3060, 3006, 2955, 2869, 2237, 1734, 1686, 1598, 1448, 1211, 1072 cm^{-1}; HRMS (ESI-TOF); Calcd for $C_{18}H_{20}BrO_5$: 395.0489; found: 395.0478 (M+1).

Dimethyl 2-(4-Bromobut-2-yn-1-yl)-2-(4-oxopentyl)-malonate (16c). Following a similar alkylation procedure listed above for 2-(4-((*tert*-butyldimethylsilyl)oxy)but-2-yn-1-yl)-2-(2-oxo-2-phenylethyl)malonate, dimethyl 2-(4-((*tert*-butyldimethylsilyl)oxy)-but-2-yn-1-yl)-2-(4-oxopentyl)malonate (185 mg, 0.46 mmol) was produced as a clear oil in 48% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.24 (t, J = 2 Hz, 2 H), 3.72 (s, J = 6 H), 2.86 (t, J = 2 Hz, 2 H), 2.44 (t, J = 7.6 Hz, 2 H), 2.12 (s, 3 H), 1.99 (m, 2 H), 1.45 (m, 2 H), 0.88 (s, 9 H), 0.08 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.9, 170.6, 81.9, 79.3, 56.9, 52.8, 51.8, 43.5, 31.6, 29.9, 25.8, 23.2, 18.3, 18.3, −4.9; IR (neat) 2955, 2931, 2857, 1743, 1689, 1599, 1436, 1207, 1091 cm^{-1}; HRMS (ESI-TOF); Calcd for $C_{20}H_{34}O_6SiNa$: 421.2017; found: 421.2012 (M+Na).

Following a similar allylation procedure for the synthesis of **16a**, 41.3 mg (0.119 mmol, 35%) of **16c** was prepared as a clear oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.87 (t, J = 2.4 Hz, 2 H), 3.75 (s, 6 H), 2.90 (t, J = 2.4 Hz, 2 H), 2.48 (t, J = 7.2 Hz, 2 H), 2.15 (s, 3 H), 2.00 (m, 2 H), 1.47 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 208.1, 170.6, 82.3, 78.5, 57.1, 53.1, 43.6, 31.8, 30.1, 23.5, 18.4, 15.0; IR (neat) 2955, 2373, 2345, 1736, 1719, 1439, 1205 cm^{-1}; HRMS (ESI-TOF); Calcd for $C_{14}H_{20}BrO_5$: 347.0489; found: 347.0484 (M+1).

Representative General Procedure for the Intramolecular Allylation of Ketones. A clean, oven-dried 4 dram screw cap vial was charged with Cp_2TiCl_2 (1.2 mg, 5 μmol, 5 mol %) and zinc dust (16.3 mg, 0.25 mmol, 2.5 equiv) under an atmosphere of N_2 at room temperature. THF (0.9 mL) was added via syringe and the slurry

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stirred for 10 min or until the solution had turned from red to green. A solution of ketone (0.1 mmol, 1 equiv) in THF (0.2 mL) was then added via syringe dropwise. The reaction was stirred for 20 min or until all starting material was consumed as monitored by TLC (*p*-anisaldehyde or $KMnO_4$). The mixture was diluted with saturated aqueous NH_4Cl (2 mL) and DCM (2 mL) and the layers were separated. The aqueous layer was extracted with DCM (3 × 4 mL), and the combined organic fractions were washed with saturated aqueous NaCl (15 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The crude residue was purified by flash chromatography, eluting with hexanes/EtOAc to give the homoallylic alcohol.

Dimethyl-3-hydroxy-3-phenyl-4-vinylcyclopentane-1,1-dicarboxylate (13a). Purified by flash chromatography eluting with hexanes/EtOAc (3:1) to provide 28.6 mg (94%) of a white solid (mp 96−97 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (d, J = 8.8 Hz, 2 H), 7.38 (t, J = 7.6 Hz, 2 H), 7.29 (t, J = 7.4 Hz, 1 H), 5.67 (m, 1 H), 5.11 (m, 2 H), 3.80 (s, 3 H), 3.78 (s, 3 H), 3.14 (m, 1 H), 2.69 (comp, 4 H), 2.28 (s, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.17, 143.4, 134.1, 128.3, 127.2, 125.2, 118.6, 83.3, 53.8, 53.2, 53.1, 50.1, 36.8; IR (neat) 3520, 3027, 2954, 2925, 1732, 1446, 1264 cm^{-1}; HRMS (ESI-TOF); Calcd for $C_{17}H_{20}O_5Na$: 327.1203; found: 327.1191 (M+Na). ^{1}H NMR and ^{13}C NMR spectra for opposite diastereomer do not match the isolated compound leading to determination of opposite syn/anti stereochemistry.

Dimethyl-4-hydroxy-4-phenyl-3-vinylcyclohexane-1,1-dicarboxylate (13b). Purified by flash chromatography eluting with hexanes/EtOAc (3:1) to provide 29.9 mg (94%) of a clear crystalline white solid (mp 84−85 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40−7.15 (comp, 5 H), 5.52 (m, 1 H), 5.08 (m, 2 H), 3.76 (s, 3 H), 3.72 (s, 3 H), 2.92 (m, 1 H), 2.40−2.15 (comp, 4 H), 1.95 (m, 1 H), 1.90−1.75 (comp, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.7, 171.9, 147.4, 137.2, 128.5, 127.0, 124.8, 117.7, 73.9, 53.0, 52.9, 44.4, 37.0, 30.3, 29.9, 26.8; IR (neat) 3525, 3024, 2954, 1731, 1446, 1251 cm^{-1}; HRMS (ESI-TOF); Calcd for $C_{18}H_{22}O_5Na$: 341.1359; found: 341.1359 (M+Na).

Dimethyl-4-hydroxy-4-methyl-3-vinylcycloheptane-1,1-dicarboxylate (13c). Purified by flash chromatography eluting with hexanes/EtOAc (2:1) to provide 15.8 mg (53%) of a viscous colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.92 (m, 1 H), 5.07 (m, 2 H), 5.08 (m, 2 H), 3.74 (s, 3 H), 3.70 (s, 3 H), 2.49 (m, 1 H), 2.25−1.95 (m, 4 H), 1.80−1.50 (comp m, 4 H), 1.16 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.2, 172.8, 139.72, 115.5, 73.1, 57.1, 52.7, 52.4, 48.3, 44.5, 34.9, 32.2, 30.1, 19.8; IR (neat) 3535, 2955, 2929, 1731, 1456, 1233 cm^{-1}; HRMS (ESI-TOF); Calcd for $C_{14}H_{23}O_5$: 271.1540; found: 271.1563 (M+1).

Methyl-5-methyl-7-oxo-9-vinyl-6-oxabicyclo[3.2.2]nonane-1-carboxylate (*c*-13c). Purified by flash chromatography eluting with hexanes/EtOAc (2:1) to provide 24.3 mg (93%) of a white solid (mp 97−98 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.83 (m, 1 H), 5.05 (m, 2 H), 3.79 (s, 6 H), 2.57 (m, 1 H), 2.38 (comp, 2 H), 2.20−1.70 (comp m, 6 H), 1.29 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.8, 171.8, 138.6, 116.0, 84.0, 77.3, 53.0, 43.4, 39.6, 32.4, 30.6, 28.1, 20.4; IR (neat) 2979, 2952, 1744, 1729, 1450, 1272, 1054 cm^{-1}; HRMS (ESI-TOF); Calcd for $C_{13}H_{18}O_4Na$: 261.1097; found: 261.1079 (M+Na).

3-Phenyl-1-tosyl-4-vinylpyrrolidin-3-ol (15a). Purified by flash chromatography eluting with hexanes/EtOAc (2:1) to provide 29.9 mg (38%) of an off-white solid whose ^{1}H NMR and ^{13}C NMR spectral data was consistent with literature values.[82]

4-Phenyl-1-tosyl-3-vinylpiperidin-4-ol (15b). Purified by flash chromatography eluting with hexanes/EtOAc (2:1) to provide 35 mg (98%) of a white solid (mp 143−144 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, J = 6.8 Hz, 2 H), 7.45−7.15 (comp, 7 H), 5.43 (m, 1 H), 5.08 (d, J = 10.8 Hz, 1 H), 4.95 (d, J = 17.6 Hz, 1 H), 3.85−3.70 (comp m, 2 H), 3.04 (m, 1 H), 2.80−2.60 (comp, 2 H), 2.47 (s, 3 H), 2.18 (m, 1 H), 1.80 (dt, J = 14, 2.4 Hz, 1 H), 1.65 (d, J = 2 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.1, 146.0, 143.8, 134.4, 133.6, 130.0, 128.7, 127.9, 127.4, 124.7, 119.0, 73.0, 47.2, 45.6, 42.3, 39.4, 21.8; IR (neat) 3509, 3059, 3030, 2925, 2864, 1339, 1162, 925 cm^{-1}; HRMS (ESI-TOF); Calcd for $C_{20}H_{24}NO_3S$: 358.1471; found: 358.1461 (M+1).

Dimethyl-3-hydroxy-3-phenyl-4-vinylidenecyclopentane-1,1-dicarboxylate (17a). Purified by flash chromatography eluting with hexanes/EtOAc (2:1) to provide 26.6 mg (88%) of a viscous colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (d, J = 7.2 Hz, 2 H), 7.36 (t, J = 8.4 Hz, 2 H), 7.27 (m, 1 H), 4.81 (m, 2 H), 3.83 (s, 3 H), 3.73 (s, 3 H), 3.58 (m, 1 H), 3.14 (m, 1 H), 2.87 (d, J = 14 Hz, 1 H), 2.75−2.50 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.6, 173.2, 144.5, 128.2, 127.4, 125.9, 109.6, 83.6, 80.5, 58.7, 53.4, 53.2, 51.2, 37.9; IR (neat) 3509, 3001, 2955, 2924, 1957, 1739, 1687, 1448, 1207 cm^{-1}; HRMS (ESI-TOF); Calcd for $C_{17}H_{18}O_5Na$: 325.1046; found: 325.1067 (M+Na).

Dimethyl-4-hydroxy-4-phenyl-3-vinylidenecyclohexane-1,1-dicarboxylate (17b). Purified by flash chromatography eluting with hexanes/EtOAc (2:1) to provide 24.4 mg (77%) a white solid (mp 120−121 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (d, J = 8.8 Hz, 2 H), 7.45 (t, J = 6.4 Hz, 2 H), 7.30 (m, 1 H), 4.76 (m, 2 H), 3.78 (s, 3 H), 3.73 (s, 3 H), 3.11 (d, J = 13.6 Hz, 1 H), 2.68 (m, J = 14 Hz, 1 H), 2.60−2.30 (m, 2 H), 2.20−1.85 (m, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.7, 171.3, 143.5, 128.3, 127.7, 126.1, 104.1, 78.1, 73.8, 55.3, 52.8 52.7, 35.8, 33.9, 28.1; IR (neat) 3504, 3057, 2955, 2373, 2245, 1961, 1736, 1439, 1254 cm^{-1}; HRMS (ESI-TOF); Calcd for $C_{18}H_{20}O_5Na$: 339.1203; found: 339.1201 (M+Na).

Dimethyl-4-hydroxy-4-phenyl-3-vinylidenecycloheptane-1,1-dicarboxylate (17c). Purified by flash chromatography eluting with hexanes/EtOAc (2:1) to provide 11.6 mg (35%) of a white solid (mp 46−47 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.83 (m, 2 H), 3.71 (s, 6 H), 2.99 (d, J = 14 Hz, 1 H), 2.61 (d, J = 14 Hz, 1 H), 2.20 (m, 1 H), 1.85 (comp m, 3 H), 1.76 (s, 1 H), 1.64 (m, 2 H), 1.35 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.7, 172.5, 106.9, 78.0, 73.2, 57.6, 52.4, 52.2, 41.7, 35.8, 32.3, 30.0, 20.14; IR (neat) 3510, 2953, 1953, 1732, 1436, 1244, 1203 cm^{-1}; HRMS (ESI-TOF); Calcd for $C_{14}H_{20}O_5Na$: 291.1203; found: 291.1216 (M+Na).

1-(*p*-Methyl)phenyl-3-buten-1-ol (5g). Purified by flash chromatography eluting with hexanes/EtOAc (2:1) to provide 54 mg (84%) of a yellow oil whose ^{1}H NMR and ^{13}C NMR spectral data was consistent with literature values.[88]

1-(*p*-Methoxy)phenyl-3-buten-1-ol (5h). Purified by flash chromatography eluting with hexanes/EtOAc (2:1) to provide 63 mg (89%) of clear, colorless oil whose ^{1}H NMR and ^{13}C NMR spectral data was consistent with literature values.[88]

1-(*p*-Dimethylamino)phenyl-3-buten-1-ol (5i). Purified by flash chromatography eluting with hexanes/EtOAc (2:1) to provide 69 mg (91%) of a yellow oil whose ^{1}H NMR and ^{13}C NMR spectral data was consistent with literature values.[104]

1-(*o*-Hydroxy)phenyl-3-buten-1-ol (5j). Purified by flash chromatography eluting with hexanes/EtOAc (1:1) to provide 64 mg (97%) of a clear, colorless oil whose ^{1}H NMR and ^{13}C NMR spectral data was consistent with literature values.[105]

1-(*p*-Hydroxy-*o*-methoxy)phenyl-3-buten-1-ol (5k). Purified by flash chromatography eluting with hexanes/EtOAc (1:1) to provide 77 mg (99%) of a white solid (mp 51−53 °C). ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.91 (d, J = 1.5 Hz, 1 H), 6.87 (d, J = 8.0 Hz, 1 H), 6.82 (dd, J = 8.0, 2.0 Hz, 1 H), 5.85−5.76 (m, 1 H), 5.63 (s, 1 H), 5.18−5.12 (comp m, 2 H), 4.66 (dt, J = 7.0, 2.5 Hz, 1 H), 3.86 (s, 3 H), 2.51−2.48 (comp m, 2 H), 2.06 (br d, J = 3.0 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 146.8, 145.2, 136.2, 134.9, 119.1, 118.6, 114.4, 108.5, 73.5, 56.2, 44.1; IR (neat) 3418, 3079, 3007, 2995, 2981, 2940, 2899, 1614, 1519, 1440, 1354, 1330, 1272, 1249, 1155, 1126, 1051, 1037 cm^{-1}; HRMS (FAB-TOF) m/z = 176.0823 [$C_{11}H_{12}O_2$ (M−H_2O) requires 176.0837].

1-(*p*-Carboxymethyl)phenyl-3-buten-1-ol (5l). Purified by flash chromatography eluting with hexanes/EtOAc (2:1) to provide 73 mg (90%) of a clear, colorless oil whose ^{1}H NMR and ^{13}C NMR spectral data was consistent with literature values.[88]

1-(*p*-Trifluoromethyl)phenyl-3-buten-1-ol (5m). Purified by flash chromatography eluting with hexanes/EtOAc (2:1) to provide 78 mg (90%) of a clear, colorless oil whose ^{1}H NMR and ^{13}C NMR spectral data was consistent with literature values.[88]

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1-(*p*-Chloro)phenyl-3-buten-1-ol (5n). Purified by flash chromatography eluting with hexanes/EtOAc (2:1) to provide 68 mg (93%) of a clear, colorless oil whose ^{1}H NMR and ^{13}C NMR spectral data was consistent with literature values.[88]

1-(*p*-Cyano)phenyl-3-buten-1-ol (5o). Purified by flash chromatography eluting with hexanes/EtOAc (2:1) to provide 55 mg (85%) of a clear, colorless oil whose ^{1}H NMR and ^{13}C NMR spectral data was consistent with literature values.[88]

1-(2-Furyl)-3-buten-1-ol (5q). Purified by flash chromatography eluting with hexanes/EtOAc (4:1) to provide 48 mg (88%) of a clear, colorless oil which is volatile when placed under vacuum. Spectral data (^{1}H and ^{13}C NMR) was consistent with literature values.[106]

(*E*)-1-Phenyl-1,5-hexadien-3-ol (5r). Purified by flash chromatography eluting with hexanes/EtOAc (2:1) to provide 70 mg (91%) of a pale yellow oil whose ^{1}H NMR and ^{13}C NMR spectral data was consistent with literature values.[84]

(*E*)-2,6-Heptadien-4-ol (5s). Purified by flash chromatography eluting with hexanes/EtOAc (4:1) to provide 37 mg (83%) of a clear, colorless oil which is volatile when placed under vacuum. Spectral data (^{1}H and ^{13}C NMR) was consistent with literature values.[107]

1-Cyclohexyl-3-buten-1-ol (5t). Purified by flash chromatography eluting with hexanes/EtOAc (5:1) to provide 48 mg (79%) of a clear, colorless oil which is volatile when placed under vacuum. Spectral data (^{1}H and ^{13}C NMR) was consistent with literature values.[84]

1-Nonen-4-ol (5u). Purified by flash chromatography eluting with hexanes/EtOAc (4:1) to provide 51 mg (91%) of a clear, colorless oil which is volatile when placed under vacuum. Spectral data (^{1}H and ^{13}C NMR) was consistent with literature values.[84]

1-Phenyl-2,2-dimethyl-3-buten-1-ol (5v). Purified by flash chromatography eluting with hexanes/EtOAc (4:1) to provide 70 mg (99%) of a clear, slightly yellow oil whose ^{1}H NMR and ^{13}C NMR spectral data was consistent with literature values.[89]

1-(*p*-Methoxy)phenyl-2,2-dimethyl-3-buten-1-ol (5w). Purified by flash chromatography eluting with hexanes/EtOAc (2:1) to provide 72 mg (88%) of a clear, pale yellow oil whose ^{1}H NMR and ^{13}C NMR spectral data was consistent with literature values.[108]

3,3-Dimethyl-1-nonen-4-ol (5x). Purified by flash chromatography eluting with hexanes/EtOAc (5:1) to provide 54 mg (83%) of a clear, colorless oil whose ^{1}H NMR and ^{13}C NMR spectral data was consistent with literature values.[6]

1-Methyl-1-phenyl-3-buten-1-ol (3h). Purified by flash chromatography eluting with hexanes/EtOAc (4:1) to provide 58 mg (89%) of a clear, colorless oil whose ^{1}H NMR and ^{13}C NMR spectral data was consistent with literature values.[94]

(*E*)-1-Cyclohexyl-3-methyl-1,5-hexadien-3-ol (3i). Purified by flash chromatography eluting with hexanes/EtOAc (4:1) to provide 66 mg (83%) of a clear, colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.85−5.71 (comp, 1 H), 5.56 (dd, J = 15.6, 6.0 Hz, 1 H), 5.47 (dd, J = 15.9, 0.6 Hz, 1 H), 5.14−5.12 (comp, 1 H), 5.11−5.06 (comp, 1 H), 2.34−2.19 (comp, 2 H), 1.99−1.88 (m, 1 H), 1.69 (app br d, 2 H), 1.62 (app br s, 1 H), 1.25 (s, 3 H), 1.21−1.03 (m, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 134.2, 133.9, 133.8, 118.8, 71.9, 74.3, 33.1, 33.0, 27.9, 26.2, 26.0; IR (neat) 3387, 2976, 2926, 2852, 1449 cm^{-1}; HRMS (FAB-TOF) m/z = 193.1602 [$C_{13}H_{21}O$ (M−1) requires 193.1592].

(*E*)-(1-(*p*-Methoxy)phenyl)-3-methyl-1,5-hexadien-3-ol (3j). Purified by flash chromatography eluting with hexanes/EtOAc (2:1) to provide 40 mg (91%) of a clear, colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31 (dt, J = 8.4, 2.7 Hz, 2 H), 6.85 (dt, J = 8.7, 3.0 Hz, 2 H), 6.54 (d, J = 16.2 Hz, 1 H), 6.16 (d, J = 16.2 Hz, 1 H), 5.91−5.77 (comp, 1 H), 5.18 (app br t, 1 H), 5.15−5.11 (comp, 1 H), 3.80 (s, 3 H), 2.47−2.31 (comp, 2 H), 1.85 (br s, 1 H), 1.38 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.0, 134.9, 130.5, 128.5, 127.7, 120.2, 114.9, 73.2, 56.2, 48.3, 29.0; IR (neat) 3440, 3007, 2976, 2934, 1607, 1512, 1248, 1175 cm^{-1}; HRMS (FAB-TOF) m/z = 218.1325 [$C_{14}H_{18}O_2$ (M^+) requires 218.1307].

(*E*)-(1-(*p*-Dimethylamino)phenyl)-3-methyl-1,5-hexadien-3-ol (3k). Purified by flash chromatography eluting with hexanes/EtOAc (2:1) to provide 84 mg (91%) of a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28 (dt, J = 9.0 Hz, 2 H), 6.68 (dt, J = 9.0 Hz, 2 H), 6.50 (d, J = 15.9 Hz, 1 H), 6.11 (d, J = 16.2 Hz, 1 H), 5.92−5.78 (comp, 1 H), 5.17 (app br t, 1 H), 5.13−5.12 (comp, 1 H), 2.95 (s, 6 H), 2.47−2.31 (comp, 2 H), 1.75 (br s, 1 H), 1.38 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.2, 151.0, 132.9, 128.2, 128.1, 126.3, 120.0, 113.5, 73.3, 48.4, 41.5, 29.0; IR (neat) 3474, 3412, 3046, 2976, 2929, 2806, 1610, 1521, 1354, 1166 cm^{-1}; HRMS (FAB-TOF) m/z = 231.1638 [$C_{15}H_{21}NO$ (M^+) requires 231.1623].

(*E*)-(1-(*p*-Hydroxy-*o*-methoxy)phenyl)-3-methyl-1,5-hexadien-3-ol (3l). Purified by flash chromatography eluting with hexanes/EtOAc (1:1) to provide 63 mg (97%) of a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.91−6.85 (comp m, 3 H), 6.51 (d, J = 16.5 Hz, 1 H), 6.14 (d, J = 16 Hz, 1 H), 5.89−5.80 (m, 1 H), 5.66 (s, 1 H), 5.18−5.14 (comp m, 2 H), 3.91 (s, 3 H), 2.44 (dd, J = 13.5, 6.5 Hz, 1 H), 2.35 (dd, J = 13.5, 8.0 Hz, 1 H), 1.80 (br s, 1 H), 1.39 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 146.9, 145.6, 134.2, 133.9, 129.7, 127.5, 120.3, 119.6, 114.7, 108.6, 72.6, 56.1, 47.6, 28.3; IR (neat) 3396, 3287, 3073, 2975, 2933, 2868, 1596, 1514, 1427, 1372, 1271, 1233, 1155, 1119, 1034, 968 cm^{-1}; HRMS (FAB-TOF) m/z = 216.1182 [$C_{14}H_{16}O_2$ (M−H_2O) requires 216.1150].

(*E*)-(1-(*p*-Trifluoromethyl)phenyl)-3-methyl-1,5-hexadien-3-ol (3m). Purified by flash chromatography eluting with hexanes/EtOAc (2:1) to provide 92 mg (92%) of a clear, slightly yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.56 (app dt, J = 4.8 Hz, 2 H), 7.46 (appt dt, J = 4.8 Hz, 2 H), 6.65 (d, J = 9.6 Hz, 1 H), 6.39 (d, J = 9.6 Hz, 1 H), 5.87−5.79 (comp, 1 H), 5.21 − 5.15 (comp, 2 H), 2.46 (app ddt, 1 H), 2.37 (app ddt, 1 H), 1.94 (br s, 1 H), 1.40 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 141.3, 139.7, 134.1, 127.5, 127.5, 127.2, 126.4, 126.4, 120.7, 73.3, 48.1, 28.9; IR (neat) 3431, 3398, 3002, 2979, 1617, 1325, 1165, 1125, 1108, 1068 cm^{-1}; HRMS (FAB-TOF) m/z = 239.1069 [$C_{14}H_{14}F_3$ (M−OH) requires 239.1048].

(*E*)-(1-(*p*-Chloro)phenyl)-3-methyl-1,5-hexadien-3-ol (3n). Purified by flash chromatography eluting with hexanes/EtOAc (2:1) to provide 82 mg (92%) of a clear, colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29 (m, 4 H), 6.56 (d, J = 15.9 Hz, 1 H), 6.27 (d, J = 16.2 Hz, 1 H), 5.89−5.75 (comp, 1 H), 5.19 (app br t, 1 H), 5.17−5.13 (comp, 1 H), 2.40 (ddt, J = 27.0, 6.6, 1.2 Hz, 2 H), 1.82 (br s, 1 H), 1.38 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.7, 136.3, 134.3, 133.9, 129.6, 128.5, 127.2, 120.5, 73.2, 50.1, 28.9; IR (neat) 3468, 3447, 3374, 3076, 2977, 2929, 1491, 1092 cm^{-1}; HRMS (FAB-TOF) m/z = 221.0728 [$C_{13}H_{14}OCl$ (M−1) requires 221.0733].

(*E*)-(1-(*p*-Carboxymethyl)phenyl)-3-methyl-1,5-hexadien-3-ol (3o). Purified by flash chromatography eluting with hexanes/EtOAc (2:1) to provide 82 mg (81%) of a clear, colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.98 (dd, J = 8.5, 1.5 Hz, 2 H), 7.42 (dd, J = 8.0, 2.0 Hz, 2 H), 6.64 (d, J = 16.0 Hz, 1 H), 6.41 (dd, J = 16.5, 2.0 Hz, 1 H), 5.87−5.78 (comp, 1 H), 5.20−5.16 (comp, 2 H), 3.91 (d, J = 2.0 Hz, 3 H), 2.47−2.34 (comp, 2 H), 1.89 (br s, 1 H), 1.40 (d, J = 1.5 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.1, 141.6, 139.1, 133.5, 130.1, 129.0, 126.8, 126.5, 119.9, 72.6, 52.3, 47.4, 28.1; IR (neat) 3527, 3503, 3480, 3074, 3032, 2977, 2953, 2930, 1719, 1608, 1436, 1284, 1179, 1111 cm^{-1}; HRMS (FAB-TOF) m/z = 247.1324 [$C_{15}H_{19}O_3$ (M+1) requires 247.1334].

(*E*)-(1-(*o*-Hydroxy)phenyl)-3-methyl-1,5-hexadien-3-ol (3p). Purified by flash chromatography eluting with hexanes/EtOAc (2:1) to provide 77 mg (94%) of a white solid (mp 86−88 °C). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 (dd, J = 8.0, 1.5 Hz, 1 H), 7.12 (td, J = 7.5, 1.5 Hz, 1 H), 6.90 (app td, J = 7.5, 0.5 Hz, 1 H), 6.81−6.79 (m, 2 H), 6.28 (d, J = 16.0 Hz, 1 H), 5.90−5.81 (m, 1 H), 5.39 (s, 1 H), 5.19−5.15 (comp m, 2 H), 2.46 (dd, J = 13.5, 6.5 Hz, 1 H), 2.38 (dd, J = 13.5, 8.0 Hz, 1 H), 2.00 (br s, 1 H), 1.41 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.9, 138.0, 133.6, 128.6, 127.4, 124.0, 121.9, 120.9, 119.4, 115.9, 72.8, 47.3, 28.0; IR (neat) 3306, 3074, 2977, 2932, 2864, 2804, 2776, 2742, 1603, 1488, 1455, 1390, 1297, 1228, 1122, 1076, 1043 cm^{-1}; HRMS (FAB-TOF) m/z = 186.1060 [$C_{13}H_{14}O$ (M−H_2O) requires 186.1045].

1-Cyclopropyl-3,4,4-trimethyl-1,5-hexadien-3-ol (3q). Purified by flash chromatography eluting with hexanes/EtOAc (4:1) to provide 70 mg (97%) of a clear, slightly yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.99 (dd, J = 10.5, 6.3 Hz, 1 H), 5.71 (dd, J = 9.3, 0.3 Hz, 1 H), 5.13 (dd, J = 9.3, 5.1 Hz, 1 H), 5.09 (dd, J = 6.6, 0.9 Hz, 1

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H), 5.05 (dd, J = 10.5, 0.9 Hz, 1 H), 1.44 (br s, 1 H), 1.43−1.33 (comp, 1 H), 1.20 (s, 3H), 1.03 (s, 6H), 0.69 (dt, J = 6.3, 2.7 Hz, 2 H), 0.36 (dt, J = 5.4, 2.7 Hz, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 146.1, 133.7, 132.8, 114.4, 75.5, 44.9, 24.6, 23.4, 22.8, 14.5, 7.6; IR (neat) 3468, 3449, 2969, 2930, 2874, 1632 cm^{-1}; HRMS (ESI-TOF) m/z = 203.1430 [$C_{12}H_{20}ONa$ (M+Na) requires 203.1406].

(*E*)-2,4,5,5-Tetramethyl-2,6-heptadien-4-ol (3r). Purified by flash chromatography eluting with hexanes/EtOAc (5:1) to provide 66 mg (98%) of a clear, colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.02 (dd, J = 17.1, 11.1 Hz, 1 H), 5.34−5.32 (comp, 1 H), 5.10 (dd, J = 3.3, 1.8 Hz, 1 H), 5.06 (dd, J = 9.6, 1.8 Hz, 1 H), 1.87 (d, J = 1.2 Hz, 3 H). 1.72 (d, J = 1.5 Hz, 3 H), 1.47 (br s, 1 H), 1.27 (s, 3 H), 1.05 (d, J = 2.4 Hz, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 145.3, 133.9, 128.2, 113.5, 65.9, 45.3, 27.9, 24.5, 19.0; IR (neat) 3567, 3510, 3490, 2972, 2930, 2878, 1374 cm^{-1}; HRMS (ESI-TOF) m/z = 191.1387 [$C_{11}H_{20}ONa$ (M+Na) requires 191.1406].

1-Cyclohexenyl-1-methyl-3-buten-1-ol (3s). Purified by flash chromatography eluting with hexanes/EtOAc (5:1) to provide 65 mg (98%) of a colorless oil that is volatile under reduced pressure. Spectral data (^{1}H and ^{13}C NMR) was consistent with literature values.[109]

1-(2-Propene)-1-cyclopentanol (3t). Purified by flash chromatography eluting with hexanes/EtOAc (4:1) to provide 38 mg (76%) of a colorless oil that is volatile under reduced pressure. Spectral data (^{1}H and ^{13}C NMR) was consistent with literature values.[110]

1-(2-Propene)-1-cyclohexanol (3u). Purified by flash chromatography eluting with hexanes/EtOAc (4:1) to provide 50 mg (89%) of a colorless oil that is volatile under reduced pressure. Spectral data (^{1}H and ^{13}C NMR) was consistent with literature values.[94]

1-(2-Propene)-2-cyclohexen-1-ol (3v). Purified by flash chromatography eluting with hexanes/EtOAc (4:1) to provide 56 mg (98%) of a colorless oil that is volatile under reduced pressure. Spectral data (^{1}H and ^{13}C NMR) was consistent with literature values.[94]

2,2,3-Trimethyl-5-hexen-1-ol (3w). Purified by flash chromatography eluting with hexanes/EtOAc (4:1) to provide 57 mg (82%) of a colorless oil that is volatile under reduced pressure. Spectral data (^{1}H and ^{13}C NMR) was consistent with literature values.[111]

1-Phenyl-3-methyl-5-hexen-3-ol (3x). Purified by flash chromatography eluting with hexanes/EtOAc (4:1) to provide 70 mg (98%) of a clear, pale yellow oil that is volatile under reduced pressure. Spectral data (^{1}H and ^{13}C NMR) was consistent with literature values.[89]

1,1-Diphenyl-3-buten-1-ol (3y). Purified by flash chromatography eluting with hexanes/EtOAc (5:1) to provide 87 mg (97%) of a white solid whose ^{1}H NMR and ^{13}C NMR spectral data was consistent with literature values.[94]

4-(2-Methylphenyl)-1,6-heptadien-4-ol (21a). Purified by flash chromatography eluting with hexanes/EtOAc (4:1) to provide 85 mg (87%) of a clear, colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43−7.41 (m, 1 H), 7.18−7.13 (m, 3 H), 5.67−5.59 (comp, 2 H), 5.14−5.07 (comp, 4 H), 2.86 (ddt, J = 14, 6.5, 1.5 Hz, 2 H), 2.56 (dd, J = 14.0, 8.0 Hz, 2 H), 2.54 (s, 3 H), 2.25 (s, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.0, 135.2, 134.0, 132.9, 127.3, 127.2, 125.9, 119.3, 76.5, 45.4, 23.0; IR (neat) 3554, 3516, 3483, 3075, 3017, 2978, 2932, 1639, 1486, 1444, 1340, 1038, 999, 916 cm^{-1}; HRMS (FAB-TOF) m/z = 203.1447 [$C_{14}H_{19}O$ (M+1) requires 203.1436].

(*E*)-4-(4-Methoxystyryl)-1,6-heptadien-4-ol (21b). Purified by flash chromatography eluting with hexanes/EtOAc (2:1) to provide 87 mg (87%) of a clear, colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35 (app dt, 2 H), 6.89 (app dt, 2 H) 6.57 (d, J = 16 Hz, 1 H), 6.15 (d, J = 16 Hz, 1 H), 5.92−5.83 (comp, 2 H), 5.20−5.16 (comp, 4 H), 3.84 (s, 3 H), 2.49−2.38 (comp, 4 H), 1.98 (s, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.36, 133.72, 132.80, 129.90, 128.18, 127.82, 119.39, 114.24, 74.02, 55.58, 45.90; IR (neat) 3567, 3524, 3487, 3074, 3004, 2978, 2935, 2907, 2837, 1606, 1512, 1303, 1249, 1174, 1035 cm^{-1}; HRMS (FAB-TOF) m/z = 245.1558 [$C_{16}H_{21}O_2$ (M+1) requires 245.1542].

(*E*)-4-(4-Dimethylaminostyryl)-1,6-heptadien-4-ol (21c). Purified by flash chromatography eluting with hexanes/EtOAc (2:1) to provide 77 mg (75%) of a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29 (dt, J = 9.0, 3.0 Hz, 2 H). 6.70 (dt, J = 8.7, 3.0 Hz, 2 H), 6.52 (d, J = 15.9 Hz, 1 H), 6.07 (d, J = 16.2 Hz, 1 H), 5.94−5.80 (comp, 2 H), 5.19−5.17 (comp, 2 H), 5.15−5.12 (comp, 2 H), 2.96 (s, 6 H), 2.49−2.33 (comp, 4 H), 1.92 (s, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 150.3, 133.9, 130.7, 128.5, 127.6, 125.6, 119.2, 112.8, 74.1, 46.0, 40.8; IR (neat) 3550, 3493, 3459, 3075, 3008, 2978, 2928, 2858, 2802, 1639, 1610, 1522, 1443, 1353, 1266, 1220, 1187, 1165 cm^{-1}; HRMS (FAB-TOF) m/z = 257.1785 [$C_{17}H_{23}NO$ (M+) requires 257.1780].

(*E*)-4-(4-Chlorostyryl)-1,6-heptadien-4-ol (21d). Purified by flash chromatography eluting with hexanes/EtOAc (4:1) to provide 81 mg (83%) of a clear, colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31−7.26 (m, 4 H), 6.57 (d, J = 16 Hz, 1 H), 6.23 (d, J = 16 Hz, 1 H), 5.87−5.77 (comp, 2 H), 5.19−5.14 (comp, 4 H), 2.46−2.35 (comp, 4 H), 1.94 (s, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 135.64, 135.62, 133.41, 133.27, 128.96, 127.90, 127.71, 119.67, 74.02, 45.78; IR (neat) 3565, 3498, 3481, 3460, 3078, 3009, 2979, 2930, 2906, 1639, 1491, 1091, 1012, 972, 997 cm^{-1}; HRMS (FAB-TOF) m/z = 249.1046 [$C_{15}H_{18}OCl$ (M+1) requires 249.1046].

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Spectra (^{1}H NMR and ^{13}C NMR) of new compounds and observed nOE values for compounds **13a, 13b, 13c, *c*-13c** and **15b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Erdik, E. *Tetrahedron* **1992**, *48*, 9577. (b) Knochel, P.; Singer, R. D. *Chem. Rev.* **1993**, *93*, 2117. (c) Knochel, P.; Perea, J. J. A.; Jones, P. *Tetrahedron* **1998**, *54*, 8275. (d) Negishi, E. In *Organozinc Reagents: A Practical Approach*; Knochel, P., Jones, P., Eds.; Oxford University Press: New York, 1999; Ch. 1. (e) Knochel, P.; Millot, N.; Rodriguez, A. L.; Tucker, C. E. *Org. React* **2001**, *58*, 417. (f) Knochel, P. In *Science of Synthesis*; Thieme Medical Publisher, 2003; Vol. 3, p 5. (g) Knochel, P.; Kopp, F. In *Handbook of Functionalized Organometallics*; Knochel, P., Ed.; Wiley-VCH: Weinheim, 2005. (h) *Handbook of Grignard Reagents*; Silverman, G. S., Rakita, P. E., Eds.; Marcell Dekker: New York, 1996. (i) Richey, H. G., Jr. *Grignard Reagents: New Developments*; Wiley & Sons: New York, 1999. (j) *Main Group Metals in Organic Synthesis*; Yamamoto, H., Oshima, K., Eds.; Wiley-VCH: Weinheim, Germany, 2004. (k) Seyferth, D. *Organometallics* **2009**, *28*, 1598.

(2) (a) Negishi, E.; King, A. O.; Okukado, N. *J. Org. Chem.* **1977**, *42*, 1821. (b) Negishi, E.; Valente, L. F.; Kobayashi, M. *J. Am. Chem. Soc.* **1980**, *102*, 3298. (c) Wang, G.; Yin, N.; Negishi, E.-i. *Chem.—Eur. J.* **2011**, *17*, 4118. (d) Milne, J. E.; Buchwald, S. L. *J. Am. Chem. Soc.* **2004**, *126*, 13028. (e) Han, C.; Buchwald, S. L. *J. Am. Chem. Soc.* **2009**, *131*, 7532. (f) Çalimsiz, S.; Sayah, M.; Mallik, D.; Organ, M. G. *Angew. Chem., Int. Ed.* **2010**, *49*, 2014. (g) Negishi, E.-i. *Bull. Chem. Soc. Jpn.* **2007**, *80*, 233. (h) Johnson, J. B.; Rovis, T. *Acc. Chem. Res.* **2008**, *41*, 327. (i) Terao, J.; Kambe, N. *Acc. Chem. Res.* **2008**, *41*, 1545. (j) Phapale, V. B.; Cardenas, D. J. *Chem. Soc. Rev.* **2009**, *38*, 1598. (k) Netherton, M. R.; Fu, G. C. *Adv. Synth. Catal.* **2004**, *346*, 1525. (l) Shinokubo, H.; Oshima, K. *Eur. J. Org. Chem.* **2004**, *2004*, 2081. (m) Frisch, A. C.; Beller, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 674.

(3) (a) Courtois, G.; Miginiac, L. *J. Organomet. Chem.* **1974**, *69*, 1. (b) Negishi, E.-i. *Organometallics in Organic Synthesis*; Wiley: New

York, 1980. (c) Weidmann, B.; Seebach, D. *Angew. Chem.* **1983**, *95*, 12.
(4) (a) Grignard, V. *Hebd. Séances Acad. Sci.* **1900**, *130*, 1322. (b) Ashby, E. C. *Q. Rev. Chem. Soc.* **1967**, *21*, 259. (c) Tamura, M.; Kochi, J. *Synthesis* **1971**, 303. (d) Lai, Y.-H. *Synthesis* **1981**, 585. (e) Fürstner, A. *Angew. Chem., Int. Ed.* **1993**, *32*, 164. (f) Boudier, A.; Bromm, L. O.; Lotz, M.; Knochel, P. *Angew. Chem., Int. Ed.* **2000**, *39*, 4414. (g) Knochel, P.; Dohle, W.; Gommermann, N.; Kneisel, F.; Kopp, F.; Korn, T.; Sapountzis, I.; Vu, V. *Angew. Chem., Int. Ed.* **2003**, *42*, 4302. (h) Seyferth, D. *Organometallics* **2006**, *25*, 2. (i) Piller, F. M.; Metzger, A.; Schade, M. A.; Haag, B. A.; Gavryushin, A.; Knochel, P. *Chem.—Eur. J.* **2009**, *15*, 7192. (j) Seyferth, D. *Organometallics* **2009**, *28*, 2. (k) Blümke, T. D.; Piller, F. M.; Knochel, P. *Chem. Commun.* **2010**, *46*, 4082.
(5) (a) Ramsden, H. E.; Balint, A. E.; Whitford, W. R.; Walburn, J. J.; Cserr, R. *J. Org. Chem.* **1957**, *22*, 1202. (b) Burns, T. P.; Rieke, R. D. *J. Org. Chem.* **1987**, *52*, 3674.
(6) (a) Zhu, L.; Wehmeyer, R. M.; Rieke, R. D. *J. Org. Chem.* **1991**, *56*, 1445. (b) Jubert, C.; Knochel, P. *J. Org. Chem.* **1992**, *57*, 5425.
(7) Huo, S. *Org. Lett.* **2003**, *5*, 423.
(8) Krasovskiy, A.; Malakhov, V.; Gavryushin, A.; Knochel, P. *Angew. Chem., Int. Ed.* **2006**, *45*, 6040.
(9) (a) Rieke, R. D.; Hudnall, P. M. *J. Am. Chem. Soc.* **1972**, *94*, 7178. (b) Rieke, R. D.; Uhm, S. J.; Hudnall, P. M. *J. Chem. Soc., Chem. Commun.* **1973**, 269. (c) Rieke, R. D. *Acc. Chem. Res.* **1977**, *10*, 301. (d) Rieke, R. D.; Li, P. T.-J.; Burns, T. P.; Uhm, S. T. *J. Org. Chem.* **1981**, *46*, 4323. (e) Rieke, R. D. *Science* **1989**, *246*, 1260.
(10) (a) Boudet, N.; Sase, S.; Sinha, P.; Liu, C.-Y.; Krasovskiy, A.; Knochel, P. *J. Am. Chem. Soc.* **2007**, *129*, 12358. (b) Metzger, A.; Schade, M. A.; Knochel, P. *Org. Lett.* **2008**, *10*, 1107. (c) Piller, F. M.; Appukkuttan, P.; Gavryushin, A.; Helm, M.; Knochel, P. *Angew. Chem., Int. Ed.* **2008**, *47*, 6802.
(11) (a) Gong, H.; Gagné, M. R. *J. Am. Chem. Soc.* **2008**, *130*, 12177. (b) Manolikakes, G.; Schade, M. A.; Hernandez, C. M. o.; Mayr, H.; Knochel, P. *Org. Lett.* **2008**, *10*, 2765. (c) Ochiai, H.; Jang, M.; Hirano, K.; Yorimitsu, H.; Oshima, K. *Org. Lett.* **2008**, *10*, 2681. (d) Sase, S.; Jaric, M.; Metzger, A.; Malakhov, V.; Knochel, P. *J. Org. Chem.* **2008**, *73*, 7380. (e) Murakami, K.; Yorimitsu, H.; Oshima, K. *Org. Lett.* **2009**, *11*, 2373. (f) Metzger, A.; Bernhardt, S.; Manolikakes, G.; Knochel, P. *Angew. Chem., Int. Ed.* **2010**, *49*, 4665. (g) Schade, M. A.; Manolikakes, G.; Knochel, P. *Org. Lett.* **2010**, *12*, 3648. (h) Sumida, Y.; Yorimitsu, H.; Oshima, K. *Org. Lett.* **2010**, *12*, 2254. (i) Thaler, T.; Haag, B.; Gavryushin, A.; Schober, K.; Hartmann, E.; Gschwind, R. M.; Zipse, H.; Mayer, P.; Knochel, P. *Nat. Chem.* **2010**, *2*, 125. (j) Yoshida, Y.; Murakami, K.; Yorimitsu, H.; Oshima, K. *J. Am. Chem. Soc.* **2010**, *132*, 8878.
(12) Knochel, P.; Rozema, M. J.; Tucker, C. E.; Retherford, C.; Furlong, M.; AchyuthaRao, S. *Pure Appl. Chem.* **1992**, *64*, 361.
(13) Stadtmüller, H.; Lentz, R.; Tucker, C. E.; Stüdemann, T.; Doerner, W.; Knochel, P. *J. Am. Chem. Soc.* **1993**, *115*, 7027.
(14) Vaupel, A.; Knochel, P. *Tetrahedron Lett.* **1994**, *35*, 8349.
(15) Klement, I.; Knochel, P.; Chau, K.; Cahiez, G. *Tetrahedron Lett.* **1994**, *35*, 1177.
(16) Blümke, T. D.; Groll, K.; Karaghiosoff, K.; Knochel, P. *Org. Lett.* **2011**, *13*, 6440.
(17) Melzig, L.; Diene, C. R.; Rohbogner, C. J.; Knochel, P. *Org. Lett.* **2011**, *13*, 3174.
(18) Barbot, F.; Miginiac, P. *J. Organomet. Chem.* **1979**, *170*, 1.
(19) Gosmini, C.; Rollin, Y.; Nedelec, J. Y.; Perichon, J. *J. Org. Chem.* **2000**, *65*, 6024.
(20) Bogdanović, B.; Schwickardi, M. *Angew. Chem., Int. Ed.* **2000**, *39*, 4610.
(21) (a) Campos, C. A.; Gianino, J. B.; Pinkerton, D. M.; Ashfeld, B. L. *Org. Lett.* **2011**, *13*, 5680. (b) Ding, Y.; Zhao, G. *J. Chem. Soc., Chem. Commun.* **1992**, 941. (c) Fleury, L. M.; Ashfeld, B. L. *Org. Lett.* **2009**, *11*, 5670. (d) Fleury, L. M.; Ashfeld, B. L. *Tetrahedron Lett.* **2010**, *51*, 2427. (e) Kablaoui, N. M.; Buchwald, S. L. *J. Am. Chem. Soc.* **1996**, *118*, 3182. (f) Kosal, A. D.; Ashfeld, B. L. *Org. Lett.* **2010**, *12*, 44. (g) Lenoir, D. *Synthesis* **1989**, *1989*, 883. (h) Parrish, J. D.; Shelton, D. R.; Little, R. D. *Org. Lett.* **2003**, *5*, 3615.
(22) (a) Klei, E.; Teuben, J. H. *J. Organomet. Chem.* **1982**, *224*, 327. (b) Marek, I. *Titanium and Zirconium in Organic Synthesis*; Wiley-VCH: Weinheim, 2002. (c) Reetz, M. T. *Organotitanium Reagents in Organic Synthesis*; Springer-Verlag: New York, 1986. (d) Sato, F.; Iijima, S.; Sato, M. *Tetrahedron Lett.* **1981**, *22*, 243. (e) Seebach, D.; Beck, A. K.; Schiess, M.; Widler, L.; Wonnacott, A. *Pure Appl. Chem.* **1983**, *55*, 1807. (f) Wilkinson, G.; Birmingham, J. M. *J. Am. Chem. Soc.* **1954**, *76*, 4281.
(23) (a) Daasbjerg, K.; Gansäuer, A. *Angew. Chem., Int. Ed.* **2006**, *45*, 2041. (b) Beller, M.; Bolm, C.; Duthaler, R. O.; Bienewald, F.; Hafner, A. *Transition Met. Org. Synth.* (2nd ed.) **2004**, *1*, 491. (c) Friedrich, J.; Walczak, K.; Dolg, M.; Piestert, F.; Lauterbach, T.; Worgull, D.; Gansäuer, A. *J. Am. Chem. Soc.* **2008**, *130*, 1788. (d) Gansäuer, A. *Synlett* **1998**, 801. (e) Gansäuer, A.; Behlendorf, M.; von Laufenberg, D.; Fleckhaus, A.; Kube, C.; Sadasivam, D. V.; Flowers, R. A. *Angew. Chem., Int. Ed.* **2012**, *51*, 4739. (f) Gansäuer, A.; Bluhm, H. *Chem. Rev.* **2000**, *100*, 2771. (g) Gansäuer, A.; Bluhm, H.; Pierobon, M. *J. Am. Chem. Soc.* **1998**, *120*, 12849. (h) Gansäuer, A.; Bluhm, H.; Rinker, B.; Narayan, S.; Schick, M.; Lauterbach, T.; Pierobon, M. *Chem.—Eur. J.* **2003**, *9*, 531. (i) Gansäuer, A.; Fleckhaus, A.; Lafont, M. A.; Okkel, A.; Kotsis, K.; Anoop, A.; Neese, F. *J. Am. Chem. Soc.* **2009**, *131*, 16989. (j) Gansäuer, A.; Otte, M.; Shi, L. *J. Am. Chem. Soc.* **2011**, *133*, 416. (k) Gansäuer, A.; Pierobon, M. In *Radicals in Organic Synthesis*; Renaud, P., Sibi, M. P., Eds.; Wiley-VCH: Weinheim, 2001; Vol. 2, p 207. (l) Gansäuer, A.; Rinker, B. In *Titanium and Zirconium in Organic Synthesis*; Marek, I., Ed.; Wiley-VCH: Weinheim, 2002; p 435. (m) Ladipo, F. T. *Curr. Org. Chem.* **2006**, *10*, 965. (n) Ramon, D. J.; Yus, M. *Chem. Rev.* **2006**, *106*, 2126.
(24) Jana, S.; Guin, C.; Roy, S. C. *Tetrahedron Lett.* **2004**, *45*, 6575.
(25) (a) Estévez, R. E.; Justicia, J.; Bazdi, B.; Fuentes, N.; Paradas, M.; Choquesillo-Lazarte, D.; García-Ruiz, J. M.; Robles, R.; Gansäuer, A.; Cuerva, J. M.; Oltra, J. E. *Chem.—Eur. J.* **2009**, *15*, 2774. (b) Estévez, R. E.; Oller-López, J. L.; Robles, R.; Melgarejo, C. R.; Gansäuer, A.; Cuerva, J. M.; Oltra, J. E. *Org. Lett.* **2006**, *8*, 5433. (c) Rosales, A.; Oller-López Juan, L.; Justicia, J.; Gansäuer, A.; Oltra, J. E.; Cuerva, J. M. *Chem. Commun.* **2004**, 2628.
(26) (a) Campaña, A. G.; Bazdi, B.; Fuentes, N.; Robles, R.; Cuerva, J. M.; Oltra, J. E.; Porcel, S.; Echavarren, A. M. *Angew. Chem., Int. Ed.* **2008**, *47*, 7515. (b) Kasatkin, A.; Nakagawa, T.; Okamoto, S.; Sato, F. *J. Am. Chem. Soc.* **1995**, *117*, 3881. (c) Kaur, P.; Singh, P.; Kumar, S. *Tetrahedron* **2005**, *61*, 8231. (d) Klei, B.; Teuben, J. H.; De Liefde Meijer, H. J. *J. Chem. Soc., Chem. Commun.* **1981**, 342. (e) Klei, E.; Telgen, J. H.; Teuben, J. H. *J. Organomet. Chem.* **1981**, *209*, 297. (f) Klei, E.; Teuben, J. H.; De Liefde Meijer, H. J.; Kwak, E. J.; Bruins, A. P. *J. Organomet. Chem.* **1982**, *224*, 327. (g) Reetz, M. T.; Sauerwald, M. *J. Org. Chem.* **1984**, *49*, 2292. (h) Riediker, M.; Duthaler, R. O. *Angew. Chem., Int. Ed.* **1989**, *28*, 494. (i) Sato, F.; Iida, K.; Iijima, S.; Moriya, H.; Sato, M. *J. Chem. Soc., Chem. Commun.* **1981**, 1140. (j) Spencer, R. P.; Schwartz, J. *Tetrahedron* **2000**, *56*, 2103. (k) Tanaka, H.; Inoue, K.; Pokorski, U.; Taniguchi, M.; Torii, S. *Tetrahedron Lett.* **1990**, *31*, 3023. (l) Yatsumonji, Y.; Nishimura, T.; Tsubouchi, A.; Noguchi, K.; Takeda, T. *Chem.—Eur. J.* **2009**, *15*, 2680.
(27) Gansäuer, A.; Bluhm, H.; Lauterbach, T. *Adv. Synth. Catal.* **2001**, *343*, 785.
(28) Sgreccia, L.; Bandini, M.; Morganti, S.; Quintavalla, A.; Umani-Ronchi, A.; Cozzi, P. G. *J. Organomet. Chem.* **2007**, *692*, 3191.
(29) Estévez, R. E.; Paradas, M.; Millan, A.; Jimenez, T.; Robles, R.; Cuerva, J. M.; Oltra, J. E. *J. Org. Chem.* **2008**, *73*, 1616.
(30) Shimizu, M.; Kobayashi, F.; Hayakawa, R. *Tetrahedron* **2001**, *57*, 9591.
(31) Chen, L.; Zhao, G.; Ding, Y. *Tetrahedron Lett.* **2003**, *44*, 2611.
(32) (a) Arefolov, A.; Panek, J. S. *J. Am. Chem. Soc.* **2005**, *127*, 5596. (b) Bode, J. W.; Gauthier, D. R., Jr.; Carreira, E. M. *Chem. Commun.* **2001**, 2560. (c) Meng, D.; Bertinato, P.; Balog, A.; Su, D.-S.; Kamenecka, T.; Sorensen, E. J.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1997**, *119*, 10073. (d) Roush, W. R. *Actual. Chim.* **2004**, 21.

(e) Rychnovsky, S. D. *Chem. Rev.* **1995**, *95*, 2021. (f) Zacuto, M.; Leighton, J. L. *Tetrahedron* **2003**, *59*, 8889.
(33) Ding, Y.; Zhao, G. *Tetrahedron Lett.* **1992**, *33*, 8117.
(34) (a) Gao, Y.; Urabe, H.; Sato, F. *J. Org. Chem.* **1994**, *59*, 5521. (b) Killinger, T.; Wolinsky, J. *J. Organomet. Chem.* **1977**, *124*, 131. (c) Marek, I.; Sklute, G. *Chem. Commun.* **2007**, 1683. (d) Petrier, C.; Luche, J. L. *J. Org. Chem.* **1985**, *50*, 910. (e) Ruppert, J. F.; White, J. D. *J. Org. Chem.* **1976**, *41*, 550. (f) Zhang, Y.; Wang, J.-X. *Eur. J. Org. Chem.* **2009**, *2009*, 2983.
(35) (a) Gansäuer, A.; Bauer, D. *Eur. J. Org. Chem.* **1998**, *1998*, 2673. (b) Gansäuer, A. *J. Org. Chem.* **1998**, *63*, 2070. (c) Gansäuer, A. *Chem. Commun.* **1997**, 457.
(36) Wilson, E. E.; Oliver, A. G.; Hughes, R. P.; Ashfeld, B. L. *Organometallics* **2011**, *30*, 5214.
(37) (a) Ara, I.; El Bahij, F.; Lachkar, M.; Ben Larbi, N. *Transition Met. Chem.* **2003**, *28*, 908. (b) Darensbourg, D. J.; Zimmer, M. S.; Rainey, P.; Larkins, D. L. *Inorg. Chem.* **2000**, *39*, 1578. (c) Fey, N.; Harvey, J. N.; Lloyd-Jones, G.; Murray, P.; Orpen, A. G.; Osborne, R.; Purdie, M. *Organometallics* **2008**, *27*, 1372. (d) Vongtragool, S.; Gorshunov, B.; Dressel, M.; Krzystek, J.; Eichhorn, D. M.; Telser, J. *Inorg. Chem.* **2003**, *42*, 1788.
(38) (a) Sancho-Sanz, I.; aMiguel, D.; Millán, A.; Estévez, R. E.; Oller-López, J. L.; Álvarez-Manzaneda, E.; Robles, R.; Cuerva, J. M.; Justicia, J. *J. Org. Chem.* **2011**, *76*, 732. (b) Tan, K.-T.; Chng, S.-S.; Cheng, H.-S.; Loh, T.-P. *J. Am. Chem. Soc.* **2003**, *125*, 2958. (c) Xia, G.; Yamamoto, H. *J. Am. Chem. Soc.* **2006**, *128*, 2554.
(39) (a) Hoffman, T. J.; Kolleth, A.; Rigby, J. H.; Arseniyadis, S.; Cossy, J. *Org. Lett.* **2010**, *12*, 3348. (b) Kim, H.; Ho, S.; Leighton, J. L. *J. Am. Chem. Soc.* **2011**, *133*, 6517. (c) Rauniyar, V.; Hall, D. *Angew. Chem., Int. Ed.* **2006**, *45*, 2426. (d) Roush, W. R.; Banfi, L. *J. Am. Chem. Soc.* **1988**, *110*, 3979. (e) Roush, W. R.; Grover, P. T. *J. Org. Chem.* **1995**, *60*, 3806. (f) Roush, W. R.; Hoong, L. K.; Palmer, M. A. J.; Straub, J. A.; Palkowitz, A. D. *J. Org. Chem.* **1990**, *55*, 4117. (g) Roush, W. R.; Palkowitz, A. D.; Palmer, M. J. *J. Org. Chem.* **1987**, *52*, 316.
(40) (a) Dosa, P. I.; Ruble, J. C.; Fu, G. C. *J. Org. Chem.* **1997**, *62*, 444. (b) Harada, T.; Kanda, K. *Org. Lett.* **2006**, *8*, 3817. (c) Hong, B.-C.; Hong, J.-H.; Tsai, Y.-C. *Angew. Chem., Int. Ed.* **1998**, *37*, 468. (d) Kitamura, M.; Suga, S.; Kawai, K.; Noyori, R. *J. Am. Chem. Soc.* **1986**, *108*, 6071. (e) Noyori, R.; Kitamura, M. *Angew. Chem., Int. Ed.* **1991**, *30*, 49. (f) Pu, L.; Yu, H.-B. *Chem. Rev.* **2001**, *101*, 757. (g) Soai, K.; Niwa, S. *Chem. Rev.* **1992**, *92*, 833.
(41) (a) Denmark, S. E.; Fu, J. *Chem. Rev.* **2003**, *103*, 2763. (b) Mukaiyama, T.; Soai, K.; Sato, T.; Shimizu, H.; Suzuki, K. *J. Am. Chem. Soc.* **1979**, *101*, 1455. (c) Muramatsu, Y.; Harada, T. *Angew. Chem., Int. Ed.* **2008**, *47*, 1088. (d) Nakajima, M.; Tomioka, K. *Tetrahedron* **1993**, *49*, 9751. (e) Weber, B.; Seebach, D. *Angew. Chem., Int. Ed.* **1992**, *31*, 84. (f) Weber, B.; Seebach, D. *Tetrahedron* **1994**, *50*, 6117. (g) Yong, K. H.; Taylor, N. J.; Chong, J. M. *Org. Lett.* **2002**, *4*, 3553.
(42) (a) Cozzi, P. G. *Angew. Chem., Int. Ed.* **2003**, *42*, 2895. (b) Jacobsen, E. N.; Zhang, W.; Muci, A. R.; Ecker, J. R.; Deng, L. *J. Am. Chem. Soc.* **1991**, *113*, 7063. (c) Ramón, D. J.; Yus, M. *Angew. Chem., Int. Ed.* **2004**, *43*, 284.
(43) (a) Gademann, K.; Chavez, D. E.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2002**, *41*, 3059. (b) Li, Z.; Fernández, M.; Jacobsen, E. N. *Org. Lett.* **1999**, *1*, 1611.
(44) Corey, E. J.; Roper, T. D.; Ishihara, K.; Sarakinos, G. *Tetrahedron Lett.* **1993**, *34*, 8399.
(45) Hirayama, L.; Singaram, B. *Tetrahedron Lett.* **2005**, *46*, 2315.
(46) (a) Kinnaird, J. W. A.; Ng, P. Y.; Kubota, K.; Wang, X.; Leighton, J. L. *J. Am. Chem. Soc.* **2002**, *124*, 7920. (b) Palomo, C.; Oiarbide, M.; Laso, A. *Angew. Chem., Int. Ed.* **2005**, *44*, 3881. (c) Soai, K.; Hayase, T.; Takai, K.; Sugiyama, T. *J. Org. Chem.* **1994**, *59*, 7908.
(47) (a) Mazet, C.; Kohler, V.; Pfaltz, A. *Angew. Chem., Int. Ed.* **2005**, *44*, 4888. (b) Salvi, L.; Jeon, S.-J.; Fisher, E. L.; Carroll, P. J.; Walsh, P. J. *J. Am. Chem. Soc.* **2007**, *129*, 16119.
(48) (a) Corey, E. J.; Imwinkelried, R.; Pikul, S.; Xiang, Y. B. *J. Am. Chem. Soc.* **1989**, *111*, 5493. (b) Gennari, C.; Ceccarelli, S.; Piarulli, U.; Montalbetti, C. A. G. N.; Jackson, R. F. W. *J. Org. Chem.* **1998**, *63*, 5312. (c) Oppolzer, W.; Radinov, R. N. *Tetrahedron Lett.* **1991**, *32*, 5777.
(49) (a) Evans, D. A.; Kozlowski, M. C.; Murry, J. A.; Burgey, C. S.; Campos, K. R.; Connell, B. T.; Staples, R. J. *J. Am. Chem. Soc.* **1999**, *121*, 669. (b) Ghosh, A. *Tetrahedron: Asymmetry* **1998**, *9*, 1.
(50) (a) Corey, E. J.; Zhe, W. *Tetrahedron Lett.* **1993**, *34*, 4001. (b) Cozzi, P. G.; Umani-Ronchi, A. *Tetrahedron Lett.* **1997**, *38*, 145. (c) Nakamura, M.; Hirai, A.; Nakamura, E. *J. Am. Chem. Soc.* **1996**, *118*, 8489. (d) Nakamura, M.; Hirai, A.; Sogi, M.; Nakamura, E. *J. Am. Chem. Soc.* **1998**, *120*, 5846. (e) Saito, S.; Tsubogo, T.; Kobayashi, S. *J. Am. Chem. Soc.* **2007**, *129*, 5364.
(51) Jones, P.; Knochel, P. *J. Org. Chem.* **1999**, *64*, 186.
(52) (a) DeWolfe, R. H.; Young, W. G. *Chem. Rev.* **1956**, *56*, 753. (b) Hill, E. A.; Boyd, W. A.; Desai, H.; Darki, A.; Bivens, L. *J. Organomet. Chem.* **1996**, *514*, 1. (c) Hutchison, D. A.; Beck, K. R.; Benkeser, R. A.; Grutzner, J. B. *J. Am. Chem. Soc.* **1973**, *95*, 7075.
(53) (a) Guijarro, A.; Rieke, R. D. *J. Am. Chem. Soc.* **1999**, *121*, 4155. (b) Noller, C. R. *J. Am. Chem. Soc.* **1929**, *51*, 594.
(54) Motoyama, Y.; Nishiyama, H. *Lewis Acids Org. Synth.* **2000**, *1*, 59.
(55) Rele, S.; Chattopadhyay, S.; Nayak, S. K. *Tetrahedron Lett.* **2001**, *42*, 9093.
(56) Maeda, H.; Ohmori, H. *Chem. Pharm. Bull.* **1994**, *42*, 1808.
(57) Shono, T.; Ishifune, M.; Kashimura, S. *Chem. Lett.* **1990**, *19*, 449.
(58) (a) Kim, J. G.; Camp, E. H.; Walsh, P. J. *Org. Lett.* **2006**, *8*, 4413. (b) Waltz, K. M.; Gavenonis, J.; Walsh, P. J. *Angew. Chem., Int. Ed.* **2002**, *41*, 3697. (c) Wooten, A. J.; Kim, J. G.; Walsh, P. J. *Org. Lett.* **2007**, *9*, 381.
(59) Wipf, P.; Walczak, M. A. A. *Angew. Chem., Int. Ed.* **2006**, *45*, 4172.
(60) (a) Griller, D.; Ingold, K. U. *Acc. Chem. Res.* **1980**, *13*, 317. (b) Newcomb, M.; Toy, P. H. *Acc. Chem. Res.* **2000**, *33*, 449.
(61) Fiorelli, C.; Maini, L.; Martelli, G.; Savoia, D.; Zazzetta, C. *Tetrahedron* **2002**, *58*, 8679.
(62) (a) Clegg, W.; García-Álvarez, J.; García-Álvarez, P.; Graham, D.; Harrington, R.; Hevia, E.; Kennedy, A.; Mulvey, R.; Russo, L. *Organometallics* **2008**, *27*, 2654. (b) Fedushkin, I.; Eremenko, O.; Skatova, A.; Piskunov, A.; Fukin, G.; Ketkov, S.; Irran, E.; Schumann, H. *Organometallics* **2009**, *28*, 3863. (c) Gutschank, B.; Schulz, S.; Bläser, D.; Boese, R.; Wölper, C. *Organometallics* **2010**, *29*, 6133. (d) Kahnes, M.; Görls, H.; Westerhausen, M. *Organometallics* **2010**, *29*, 3490. (e) Wooten, A.; Carroll, P. J.; Maestri, A. G.; Walsh, P. J. *J. Am. Chem. Soc.* **2006**, *128*, 4624.
(63) (a) Boonsombat, J.; Zhang, H.; Chughtai, M. J.; Hartung, J.; Padwa, A. *J. Org. Chem.* **2012**, *73*, 3539. (b) Deak, H. L.; Stokes, S. S.; Snapper, M. L. *J. Am. Chem. Soc.* **2001**, *123*, 5152. (c) Nörret, M.; Sherburn, M. S. *Angew. Chem., Int. Ed.* **2001**, *40*, 4074. (d) Poulin, J.; Grise-Bard, C. M.; Barriault, L. *Chem. Soc. Rev.* **2009**, *38*, 3092.
(64) (a) Millan, A.; Campaña, A. G.; Bazdi, B.; Miguel, D.; Alvarez de Cienfuegos, L.; Echavarren, A. M.; Cuerva Juan, M. *Chem.—Eur. J.* **2011**, *17*, 3985. (b) Paquette, L. A.; Mendez-Andino, J. L. *J. Org. Chem.* **1998**, *63*, 9061.
(65) (a) Campaña, A. G.; Bazdi, B.; Fuentes, N.; Robles, R.; Cuerva Juan, M.; Oltra, J. E.; Porcel, S.; Echavarren, A. M. *Angew. Chem., Int. Ed.* **2008**, *47*, 7515. (b) Estévez, R. E.; Justicia, J.; Bazdi, B.; Fuentes, N.; Paradas, M.; Choquesillo-Lazarte, D.; García-Ruiz, J. M.; Robles, R.; Gansäuer, A.; Cuerva Juan, M.; Oltra, J. E. *Chem.—Eur. J.* **2009**, *15*, 2774.
(66) (a) Justicia, J.; Oller-Lopez Juan, L.; Campaña, A. G.; Oltra, J. E.; Cuerva Juan, M.; Bunuel, E.; Cárdenas, D. J. *J. Am. Chem. Soc.* **2005**, *127*, 14911. (b) Nguyen, V. C.; Kim, Y.-T.; Yu, Y.-K.; Kang, H.-Y. *Bull. Korean Chem. Soc.* **2005**, *26*, 711.
(67) (a) Szarek, W. A.; Adams, K. A. H.; Curcumelli-Rodostamo, M.; MacLean, D. B. *Can. J. Chem.* **1964**, *42*, 2584. (b) Tashkhodzhaev, B. *Chem. Nat. Compd.* **2010**, *46*, 421.

(68) Relative stereochemistry was assigned based on comparison of 1D NOE data and ^{1}H NMR spectra to values for identical or similar compounds previously reported in the literature.
(69) (a) Duan, J.-A.; Williams, I. D.; Che, C.-T.; Zhou, R.-H.; Zhao, S.-X. *Tetrahedron Lett.* **1999**, *40*, 2593. (b) O'Hagan, D. *Nat. Prod. Rep.* **2000**, *17*, 435. (c) Padwa, A.; Sheehan, S. M.; Straub, C. S. *J. Org. Chem.* **1999**, *64*, 8648. (d) Trost, B. M.; Oslob, J. D. *J. Am. Chem. Soc.* **1999**, *121*, 3057. (e) Watson, A. A.; Fleet, G. W. J.; Asano, N.; Molyneux, R. J.; Nash, R. J. *Phytochemistry* **2001**, *56*, 265.
(70) (a) López, F.; Mascareñas, J. L. *Chem.—Eur. J.* **2011**, *17*, 418. (b) Yu, S.; Ma, S. *Angew. Chem., Int. Ed.* **2012**, *51*, 3074.
(71) (a) Justicia, J.; Sancho-Sanz, I.; Álvarez-Manzaneda, E.; Oltra, J. E.; Cuerva Juan, M. *Adv. Synth. Catal.* **2009**, *351*, 2295. (b) Lee, P. H. *Bull. Korean Chem. Soc.* **2007**, *28*, 17.
(72) Muñoz-Bascón, J.; Sancho-Sanz, I.; Álvarez-Manzaneda, E.; Rosales, A.; Oltra, J. E. *Chem.—Eur. J.* **2012**, *18*, 14479−14486.
(73) Takahara, J. P.; Masuyama, Y.; Kurusu, Y. *J. Am. Chem. Soc.* **1992**, *114*, 2577.
(74) (a) Allinger, N. L.; Miller, M. A. *J. Am. Chem. Soc.* **1961**, *83*, 2145. (b) Gundertofte, K.; Liljefors, T.; Norrby, P.-O.; Pettersson, I. *J. Comput. Chem.* **1996**, *17*, 429.
(75) Tan, X.-H.; Liu, L.; Guo, Q.-X. *Tetrahedron* **2004**, *60*, 6129.
(76) (a) Donohoe, T. J.; Kershaw, N. M.; Orr, A. J.; Wheelhouse, K. M. P.; Fishlock, L. P.; Lacy, A. R.; Bingham, M.; Procopiou, P. A. *Tetrahedron* **2008**, *64*, 809. (b) Franz, A.; Woerpel, K. A. *Angew. Chem., Int. Ed.* **2000**, *39*, 4295. (c) Hatano, M.; Mizuno, T.; Ishihara, K. *Chem. Commun.* **2010**, *46*, 5443. (d) Reynolds, K. A.; Dopico, P. G.; Brody, M. S.; Finn, M. G. *J. Org. Chem.* **1997**, *62*, 2564. (e) Tamaki, T.; Ogoshi, S. *Chem.—Eur. J.* **2009**, *15*, 10083.
(77) Wang, W.; Mei, Y.; Li, H.; Wang, J. *Org. Lett.* **2005**, *7*, 601−604.
(78) McConville, M.; Saidi, O.; Blacker, J.; Xiao, J. *J. Org. Chem.* **2009**, *74*, 2692−2698.
(79) Cui, M.; Ono, M.; Kimura, H.; Liu, B.; Saji, H. *J. Med. Chem.* **2011**, *54*, 2225−2240.
(80) Guanti, E. M.; Ncokazi, K.; Egan, T. J.; Gut, J.; Rosenthal, P. J.; Bhampidipati, R.; Kopinathan, A.; Smith, P. J.; Chibale, K. *J. Med. Chem.* **2011**, *54*, 3637−3649.
(81) Zumbansen, K.; Dohring, A.; List, B. *Adv. Synth. Catal.* **2010**, *352*, 1135−1138.
(82) Pedrosa, R.; Andrés, C.; Rosón, C. D.; Vicente, M. *J. Org. Chem.* **2003**, *68*, 1852−1858.
(83) Stern, T.; Ruckbrod, S.; Czekelius, C.; Donner, C.;; Brunner, H. *Adv. Synth. Catal.* **2010**, *352*, 1983−1992.
(84) Collins, P. W.; Gasiecki, A. F.; Perkins, W. E.; Gullikson, G. W.; Bianchi, R. G.; Kramer, S. W.; Ng, J. S.; Yonan, E. E.; Swenton, L.; Jones, P. H.; Bauer, R. F. *J. Med. Chem.* **1990**, *33*, 2784−2793.
(85) Rink, C.; Navickas, V.; Maier, M. E. *Org. Lett.* **2011**, *13*, 2334−2337.
(86) (a) Vogt, M.; Ceylan, S.; Kirschning, A. *Tetrahedron* **2010**, *66*, 6450−6456. (b) Matsumoto, K.; Oshima, K.; Utimoto, K. *J. Org. Chem.* **1994**, *59*, 7152−7155.
(87) El-Batta, A.; Jiang, C.; Zhao, W.; Anness, R.; Cooksy, A. L.; Bergdahl, M. *J. Org. Chem.* **2007**, *72*, 5244−5259.
(88) Dam, J. H.; Fristrup, P.; Madsen, R. *J. Org. Chem.* **2008**, *73*, 3228−3235.
(89) Kobayashi, S.; Nishio, K. *J. Org. Chem.* **1994**, *59*, 6620−6628.
(90) White, J. D.; Blakemore, P. R.; Gren, N. J.; Hauser, E. B.; Holoboski, M. A.; Keown, L. E.; Nylund, L. E.; Kolz, B.; Phillips, W. *J. Org. Chem.* **2002**, *67*, 7750−7760.
(91) (a) Heathcock, C. H.; Kiyooka, S.-i.; Blumenkopf, T. A. *J. Org. Chem.* **1984**, *49*, 4214−4223. (b) Davis, A. P.; Jaspers, M. *J. Chem. Soc., Perkin Trans. I* **1992**, 2111−2118.
(92) Wu, T. R.; Shen, L.; Chong, J. M. *Org. Lett.* **2004**, *6*, 2701−2704.
(93) Schneider, U.; Kobayashi, S. *Angew. Chem., Int. Ed.* **2007**, *46*, 5909−5912.
(94) Roman, J. G.; Soderquist, J. A. *J. Org. Chem.* **2007**, *72*, 9772−9775.
(95) Pace, V.; Castoldi, L.; Hoyos, P.; Sinisterra, J. V.; Pregnolato, M.; Sanchez-Montero, J. M. *Tetrahedron* **2011**, *67*, 2670−2675.
(96) Taniguchi, T.; Zaimoku, H.; Ishibashi, H. *Chem.−Eur. J.* **2011**, *17*, 4307−4312.
(97) (a) Zeng, H.; Hua, R. *J. Org. Chem.* **2008**, *73*, 558−562. (b) Hou, Z.; Fujiwara, Y.; Jintoku, Y.; Mine, N.; Yokoo, K.; Taniguchi, H. *J. Org. Chem.* **1987**, *52*, 3524−3528.
(98) Ndungu, J. M.; Larson, K. K.; Sarpong, R. *Org. Lett.* **2005**, *7*, 5845−5848.
(99) Kataoka, Y.; Makihira, I.; Yamagata, T.; Tani, K. *Organometallics* **1997**, *16*, 4788−4795.
(100) Miura, K.; Fujisawa, N.; Saito, H.; Wang, D.; Hosomi, A. *Org. Lett.* **2001**, *3*, 2591−2594.
(101) Crossland, I.; Bock, K.; Norrestam, R. *Acta Chem. Scand.* **1985**, *39*, 7−14.
(102) Loughlin, W. A.; Murphy, M. E.; Elson, K. E.; Henderson, L. C. *Aust. J. Chem.* **2004**, *57*, 227−232.
(103) Chang, M.; Lin, C.; Pai, C. *Tetrahedron Lett.* **2006**, *47*, 2565−2568.
(104) Chretien, J.-M.; Zammattio, F.; Gauthier, D.; Le Grognec, E.; Paris, M; Quintard, J.-P. *Chem.−Eur. J.* **2006**, *12*, 6816−6828.
(105) Zhang, T.; Shi, M.; Zhao, M. *Tetrahedron* **2008**, *64*, 2412−2418.
(106) Li, G.-L.; Zhao, G. *J. Org. Chem.* **2005**, *70*, 4272−4278.
(107) Zhang, X. *Synlett* **2008**, *1*, 65−68.
(108) Bower, J. F.; Skucas, E.; Patman, R. L.; Krische, M. J. *J. Am. Chem. Soc.* **2007**, *129*, 15134−15135.
(109) Kim, H. Y.; Choi, K. I.; Pae, A. N.; Koh, H. Y.; Choi, J. H.; Cho, Y. S. *Synth. Commun.* **2003**, *33*, 1899−1904.
(110) Shen, K.-H.; Yao, C.-F. *J. Org. Chem.* **2006**, *71*, 3980−3983.
(111) Nowrouzi, F.; Thadani, A. N.; Batey, R. A. *Org. Lett.* **2009**, *11*, 2631−2634.