Stereoselective Borylative Ketone-Diene Coupling
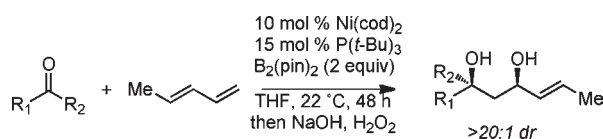
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ABSTRACT

In the presence of catalytic Ni(cod)$_2$ and P(t-Bu)$_3$, ketones, dienes, and B$_2$(pin)$_2$ undergo a stereoselective multicomponent coupling reaction. Upon oxidation, the reaction furnishes 1,3-diols as the major reaction product.

Tertiary alcohols are common motifs in natural products and in medicinally active agents. Indeed, roughly 20% of the top 50 pharmaceuticals bear tertiary alcohols or their derivatives.[1] While construction of these functional groups is readily accomplished by nucleophilic additions to ketones, such reactions can be challenging, particularly when stereocontrol is a required element.[2]

Scheme 1. Borylative Diene−Carbonyl Coupling

Recent studies in our laboratory have focused on the development of stereoselective borylative aldehyde−diene coupling reactions (Scheme 1).[3−6] These reactions occur with exceptionally high levels of diastereoinduction when aldehydes are employed as substrates and it was of interest to ascertain whether these processes might also apply to ketone electrophiles and to determine whether high levels of stereocontrol could be maintained.[7] In this report, we show that borylative ketone−diene coupling reactions can be accomplished in high yields and with excellent levels of diastereocontrol. Importantly, this reaction extends to aryl

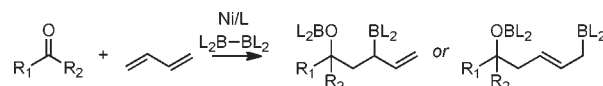(1) See http://cbc.arizona.edu/njardarson/group/top-pharmaceuticals-poster.

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alkyl ketones as well as to dialkyl ketones. Also of note, this reaction occurs in a predictable fashion, yet with regioselection that is distinct from related aldehyde−diene coupling reactions.

To initiate studies in ketone−diene coupling reactions, acetophenone was treated with (E)-1,3-pentadiene under conditions similar to those employed for aldehyde coupling reactions (10 mol % Ni(cod)$_2$, 15 mol % P(t-Bu)$_3$, 2 equiv B$_2$(pin)$_2$) and the reaction mixture was treated to oxidative workup. As depicted in Scheme 2 (eq 1), this reaction occurred in good yield and > 20:1 diastereoselectivity. Surprisingly, the reaction of acetophenone followed a different regiochemical course compared to the analogous reaction with benzaldehyde. As depicted in Scheme 2 (eq 2), when benzaldehyde was subjected to similar reaction conditions, 1,5-diol **2** was produced, not the 1,3-diol **1** that predominates with acetophenone. Not only is the hydroxyl-positioning different between the two products, but the diene is also incorporated into the product with opposite connectivity in the case of the ketone relative to the aldehyde electrophile.

Scheme 2. Borylative Coupling of Acetophenone Compared to Benzaldehyde
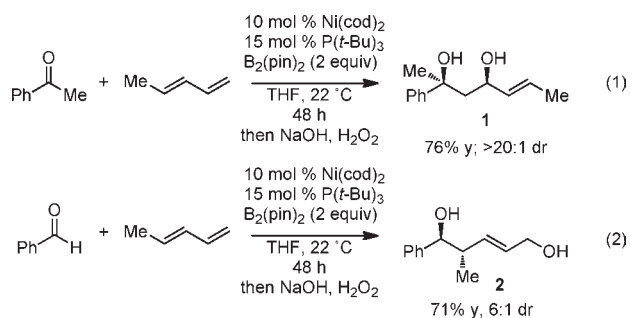
To learn whether the reactivity observed with acetophenone is unique to this substrate, a number of other ketone electrophiles were employed in the coupling reaction. This survey of the reaction revealed that many other ketones are processed in a similar manner as acetophenone. Importantly, a variety of functional groups and substitution patterns are tolerated in the ketone electrophile. As

(7) For diene−carbonyl couplings that employ ketones, see: (a) Sato, Y.; Takimoto, M.; Hayashi, K.; Katsuhara, T.; Takagi, K.; Mori, M. *J. Am. Chem. Soc.* **1994**, *116*, 9771. (b) Sato, Y.; Takimoto, M.; Mori, M. *Tetrahedron Lett.* **1996**, *37*, 887. (c) Kimura, M.; Fujimatsu, H.; Ezoe, A.; Shibata, K.; Shimizu, M.; Matsumoto, S.; Tamaru, Y. *Angew. Chem., Int. Ed.* **1999**, *38*, 397. (d) Kimura, M.; Matsuo, S.; Shibata, K.; Tamaru, Y. *Angew. Chem., Int. Ed.* **1999**, *38*, 3386. (e) Sato, Y.; Takimoto, M.; Mori, M. *J. Am. Chem. Soc.* **2000**, *122*, 1624. (f) Ezoe, A.; Kimura, M.; Inoue, T.; Mori, M.; Tamaru, Y. *Angew. Chem., Int. Ed.* **2002**, *41*, 2784. (g) Kimura, M.; Kojima, K.; Tamaru, Y. *Synthesis* **2004**, 3089. (h) Kimura, M.; Ezoe, A.; Mori, M.; Tamaru, Y. *J. Am. Chem. Soc.* **2005**, *127*, 201. (i) Kimura, M.; Ezoe, A.; Mori, M.; Iwata, K.; Tamaru, Y. *J. Am. Chem. Soc.* **2006**, *128*, 8559. (j) Saito, N.; Yamazaki, T.; Sato, Y. *Chem. Lett.* **2009**, *38*, 594.

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depicted in Scheme 3, halogen substitution in the form of chloro and fluoro groups is accommodated in the reaction (compounds **3**, **4**, **5**, **7**) as is the presence of both electron-donating (compounds **10**, **11**) and electron-withdrawing substituents (compound **8**). In all cases surveyed, > 20:1 syn:anti diastereoselectivity was observed in the reaction products.
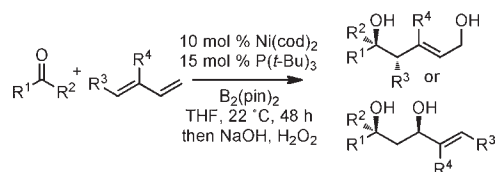
Scheme 3. Borylative Coupling of Methyl Ketones[a]
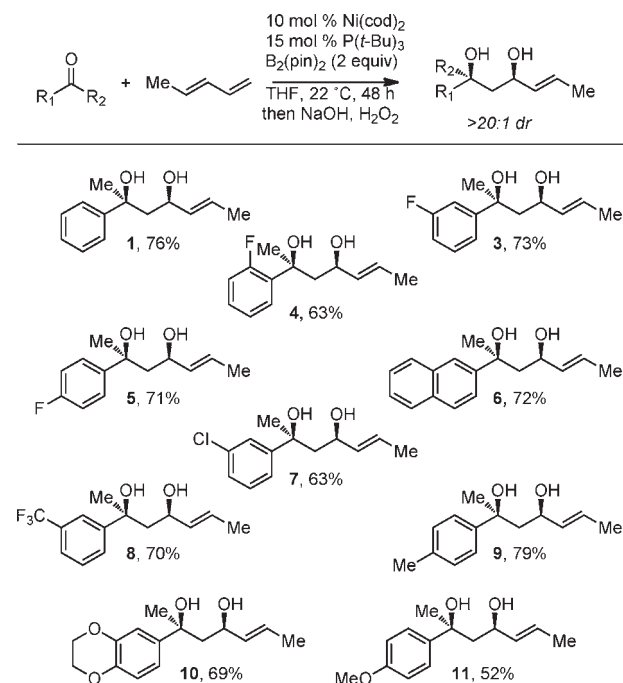
[a] (a) Stereoselectivity determined by ^{1}H NMR analysis. Yields refer to isolated yield of purified material; value is an average of two or more experiments.

Whereas aromatic methyl ketones were found to react with good yield and selectivity providing the 1,3 diol regioselectively, reactions of aliphatic ketones delivered the regioisomeric 1,5 diol. For example, 4-phenyl-2-butanone (entry 1, Table 1) underwent smooth coupling with pentadiene but, in contrast to reactions of aromatic ketones, was converted to the derived 1,5-diol in a manner similar to that observed for reactions of benzaldehyde (Scheme 2, eq 2). Suspecting that the steric encumbrance surrounding the reacting carbonyl may determine the regiochemical outcome, we examined constrained cyclic ketones and found that these also deliver the 1,5-diol product (entries 2−4, Table 1). It should be noted that the product of entry 4 appears to arise by preferred equatorial attachment of the diene to the carbonyl carbon of the substrate. Lastly, isoprene was found to react in a regioselective manner as well.

Diene−carbonyl coupling reactions have been extensively studied by Tamaru and Mori, both of whom executed these transformations under reducing conditions with silane, organozinc reductants, and organoborane reductants.[4,7] Related alkylative reactions are known with

Table 1. Borylative Coupling of Ketones and Dienes[a]

| entry	ketone	diene	product	dr	% yield
1		Me⌿⌿	**12**	7:1	69
2		Me⌿⌿	**13**	N/A	56
3		Me⌿⌿	**14**	N/A	52
4	t-Bu	Me⌿⌿	**15**	>20:1	53
5		Me	**16**	N/A	39

[a] Stereoselectivity determined by ^{1}H NMR analysis. Yields refer to isolated yield of purified material; value is an average of two or more experiments.

organoboronate reagents.[7j,8] These processes are thought to occur by conversion of the diene and aldehyde to metallacyclic intermediates. The identity of this intermediate was secured by Ogoshi and Kurosawa who isolated such structures from stoichiometric reactions of Ni(cod)$_2$, PCy$_3$, a 1,3-diene, and benzaldehyde.[9] Considering the similar reaction conditions, it is considered likely that such mechanisms also operate in the borylative carbonyl-diene coupling reactions and these can be used to understand the regiochemical course of the coupling processes with hindered and nonhindered carbonyl substrates. As depicted in Scheme 4, with nonhindered electrophiles, reaction with pentadiene may occur to give nickellacycle **17**. Subsequent σ-bond metathesis with B$_2$(pin)$_2$ would then deliver π-allyl **18**, a compound that may engage in π−σ−π isomerization prior to reductive elimination to afford **19**. With more hindered carbonyls, it is tenable that steric effects retard C−C bond formation with the substituted terminus of the diene and, instead, the less hindered end of the diene adds to the carbonyl. Subsequent σ-bond metathesis delivers a
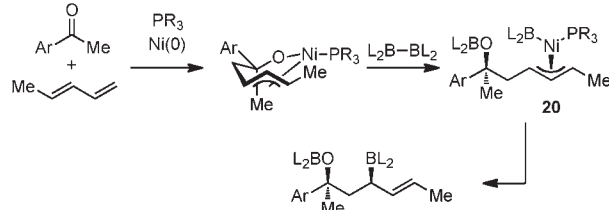
π-allyl **20**, which undergoes reductive elimination to furnish the 1,3-diol. It is conceivable that with a substituted π-allyl the π−σ−π isomerization is retarded relative to reductive elimination and the geometry of the initial σ-bond metathesis product dictates the regiochemical outcome of the reaction.

Scheme 4

A. *non-hindered carbonyls*
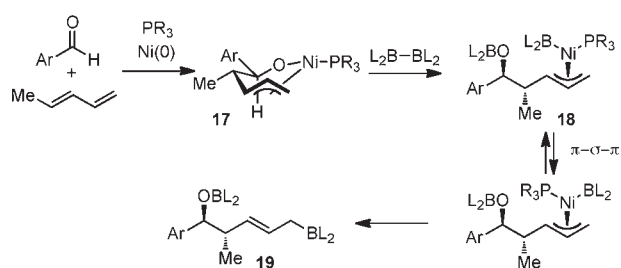
B. *hindered carbonyls*

In conclusion, we have demonstrated that the borylative carbonyl-diene coupling reaction can extend to ketone substrates and that it occurs in a regio- and stereoselective fashion. While the outcome of the reaction is distinct from that which is observed with aldehyde substrates, it is consistent with known features of this class of transformations. Further studies on the utility of these processes are in progress.

Supporting Information Available. Complete experimental procedures and characterization data (^{1}H and ^{13}C NMR, IR, and mass spectrometry). This material is available free of charge via the Internet at http://pubs.acs.org.